

“Digital PET/MRI for Preclinical Applications”

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH
Aachen University zur Erlangung des akademischen Grades eines Doktors der
Ingenieurwissenschaften genehmigte Dissertation

vorgelegt von

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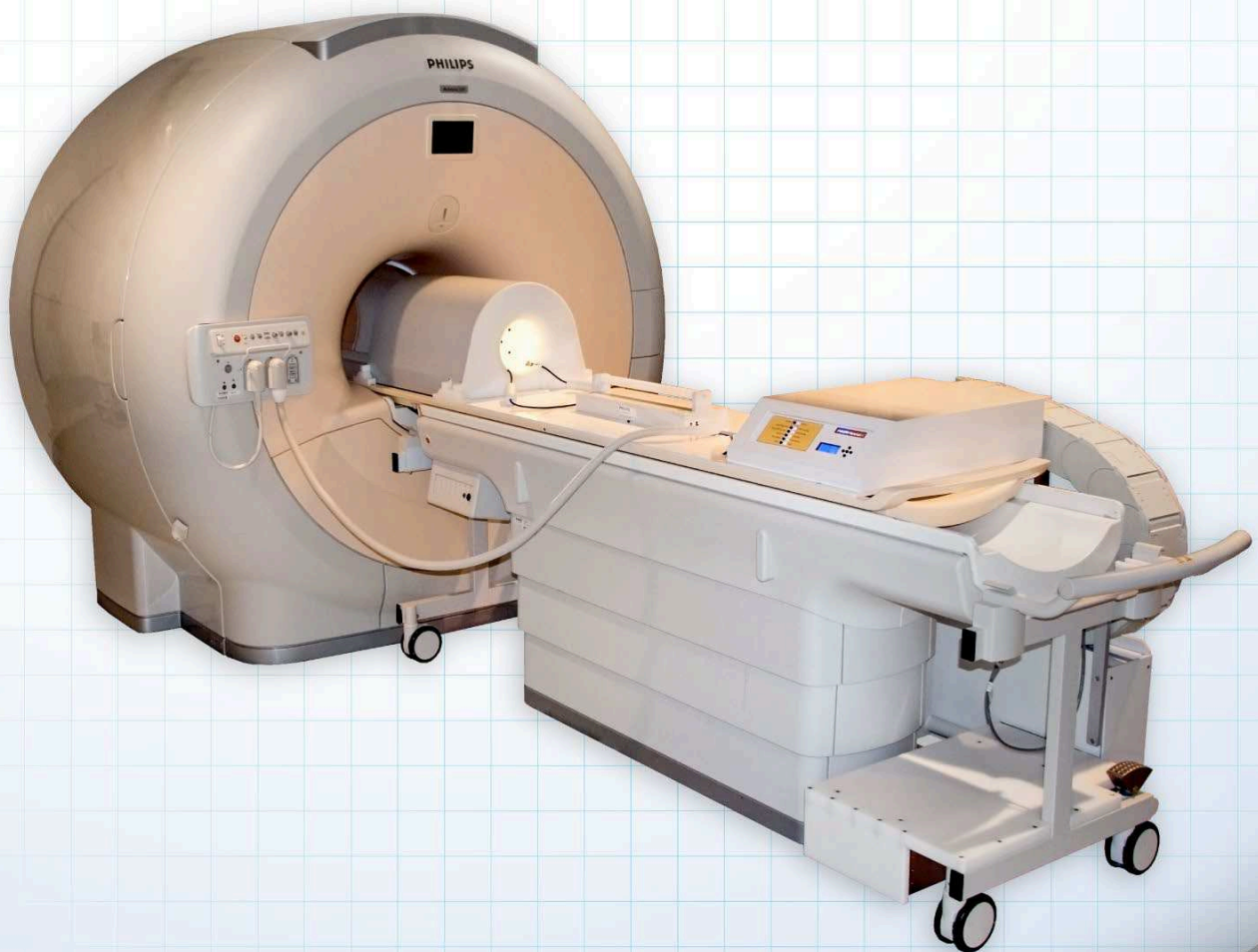
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Tag der mündlichen Prüfung: 25.04.2016

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DIGITAL PET/MRI INSERTS

FOR PRECLINICAL APPLICATIONS



Aachen, 2016

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Feedback

“Let me just share that I really enjoy seeing this progress! I have followed over the 1.5 year the evolution of this project, which is/was not an easy one. I appreciate the persistence, entrepreneurship and innovation competence at work here by all involved.”

François Adrianus "Frans" van Houten, CEO of Royal Philips Electronics.
Comment after the presentation on the IEEE NSS/MIC conference (Weissler et al., 2012a).

“... it's a research system that gave spectacular pre-clinical results.”

Homer Pien, Senior VP and CTO of Philips Healthcare
Comment about the publication in IEEE TMI (Weissler et al., 2015a)

“Pretty impressive video and outcome of this project. Congratulations to Björn and the entire team for the great work.”

Rene Botnar, Professor of Cardiovascular Imaging at King' College London
Comment about the publication in IEEE TMI (Weissler et al., 2015a)

“We were impressed by the performance of the pre-clinical insert technology.”

**Kees van Kuijk, Head of the Radiology Department at the VU University Medical Center
Amsterdam**
Written statement after a presentation of the results of (Weissler et al., 2015a)

Table of Contents

1. Introduction.....	8
2. Fundamentals.....	10
2.1 Positron Emission Tomography	10
2.1.1 Positron-Emitting Radioactive Decay.....	10
2.1.2 Interaction of the Gamma Photons with Matter.....	11
2.1.3 PET Scanner	12
2.1.4 Tracer and Applications.....	13
2.2 Magnetic Resonance Imaging	14
2.2.1 Nuclei, Spins and the Static Magnetic Field B_0	14
2.2.2 Magnetic Resonance and the RF Field B_1	15
2.2.3 Relaxation and Receiving the MR Signal.....	17
2.2.4 Image Generation and Gradients	18
2.2.5 MRI Sequences.....	20
2.2.6 K-Space, Sampling, Field Of View (FOV), Spatial Resolution, and Bandwidths	23
2.2.7 Contrasts and Applications.....	26
2.3 Hybrid Imaging	27
2.3.1 PET/CT.....	28
2.3.2 PET/MRI.....	28
2.4 Conclusion and Summary	31
3. Requirements, Interferences, and Verifications.....	32
3.1 PET and the Influence from MRI.....	32
3.1.1 Requirements on PET Performance Parameters	32
3.1.1.1 Energy Resolution	33
3.1.1.2 Time Resolution.....	36

3.1.1.3	Spatial Resolution	39
3.1.1.4	Sensitivity	41
3.1.1.5	Tracer Activity and Scan Time	42
3.1.1.6	Other Performance Parameters	43
3.1.2	Interferences from MRI	43
3.1.2.1	Static Magnetic Field	43
3.1.2.2	RF Excitation and Coils	45
3.1.2.3	Gradient Switching	46
3.1.3	Combined Verification Experiment	48
3.2	MRI and the Influence from PET	49
3.2.1	B_0 Homogeneity	49
3.2.2	Spurious Signals, SNR and Image Uniformity	52
3.2.3	Geometric distortions	56
3.2.4	Ghosting	58
3.2.5	Temporal Stability	63
3.3	PET/MR Imaging	64
3.3.1	Phantom studies	64
3.4	Preclinical Applications	66
3.4.1	Animal Handling	66
3.4.2	Temporal Synchronization	67
3.5	Conclusion and Summary	68
4.	Solid-State Detectors in PET/MRI: Components, History and Existing Systems	70
4.1	Avalanche Photo Diodes (APDs)	70
4.2	Silicon Photomultiplier (SiPMs)	71
4.3	Existing Systems	73
4.3.1	Preclinical PET Systems	73
4.3.2	Preclinical PET/MRI Systems	74
4.3.3	Clinical Systems	76
4.4	Conclusion and Summary	76
5.	Step I: Analog SiPMs and Integrated Digitization	77
5.1	The System	77
5.1.1	Singles Detection Module (SDM)	77
5.1.1.1	Detector Stack	78
5.1.1.1.1	Scintillator Array and Light Guide	78
5.1.1.1.2	SiPMs and Sensor Board	78
5.1.1.1.3	ASIC and Digitization Board	79

5.1.1.1.4	FPGA and Interface Board.....	81
5.1.1.2	Singles Processing Unit (SPU).....	82
5.1.1.2.1	Detector Stack Support	82
5.1.1.2.2	Firmware Configuration and Debugging.....	84
5.1.1.2.3	Communication.....	85
5.1.1.2.4	B ₀ Homogeneity Optimization.....	86
5.1.1.3	Module Power Supply.....	88
5.1.1.4	Module Cooling	88
5.1.1.5	RF Screen.....	89
5.1.1.6	Assembly.....	90
5.1.2	Synchronization	90
5.1.2.1	Synchronization of SDMs	90
5.1.2.2	Synchronization Between PET and MRI	91
5.1.3	Gantry	92
5.1.4	Power Supply	93
5.1.5	RF Coil.....	95
5.1.6	Insert	96
5.1.7	Cooling.....	97
5.1.8	Communication and Control.....	97
5.1.9	Processing, Calibration, and Reconstruction	100
5.1.9.1	Processing and Calibration	100
5.1.9.2	Image Reconstruction.....	100
5.2	Results	101
5.2.1	Performance of the Detector Stack.....	101
5.2.2	MRI Performance and the Influence of PET on MRI.....	102
5.2.2.1	B ₀ Distortion	102
5.2.2.2	Spurious Signals, SNR and Image Uniformity.....	103
5.2.2.3	Geometric Distortion	107
5.2.2.4	Temporal Stability.....	109
5.2.3	PET Performance and the Influence of MRI on PET.....	111
5.2.3.1	PET Performance Parameters	111
5.2.3.2	Maximum Activity.....	113
5.2.4	PET/MRI Synchronization by Detection of Switching Gradients.....	113
5.2.4.1	Threshold Scan	114
5.2.4.2	Slew Rate Scans.....	114
5.2.4.3	Time Accuracy and Precision	117
5.2.4.4	Recognition of Sequence Phases.....	118

5.2.5	PET/MR Imaging.....	119
5.2.5.1	Hot-Rod Phantom.....	119
5.2.5.2	In Vivo Measurement.....	121
5.3	Conclusion and Summary.....	122
6.	Step II: Digital SiPMs and Optical Synchronization	125
6.1	The System.....	125
6.1.1	Singles Detection Module (SDM)	126
6.1.1.1	Detector Stack	126
6.1.1.1.1	Scintillator Array and Light Guide	126
6.1.1.1.2	DSiPMs and Sensor Board.....	126
6.1.1.1.3	FPGA and Interface Board	128
6.1.1.2	Singles Processing Unit (SPU).....	129
6.1.1.2.1	Detector Stack Support.....	129
6.1.1.2.2	B ₀ Homogeneity Optimization	130
6.1.1.3	Module Power Supply	133
6.1.1.4	Module Cooling.....	134
6.1.1.5	RF Screen	135
6.1.1.6	Assembly	136
6.1.2	Synchronization	137
6.1.2.1	Synchronization of SDMs.....	137
6.1.2.2	Synchronization to Other Equipment.....	139
6.1.2.3	Remote Trigger Unit (RTU)	141
6.1.3	Power Supply	142
6.1.4	Gantry.....	145
6.1.5	RF Coils.....	146
6.1.6	Insert.....	147
6.1.7	PET System Back End.....	149
6.1.7.1	Data Acquisition and Processing Unit.....	149
6.1.7.2	Alternative Hardware Coincidence Unit.....	150
6.1.7.3	Image Reconstruction	151
6.1.7.4	Calibration and Processing.....	151
6.1.7.5	Control.....	151
6.2	Results.....	154
6.2.1	Performance of the Detector Stack.....	154
6.2.2	MRI Performance and the Influence of PET on MRI.....	155
6.2.2.1	B ₀ Distortion.....	155
6.2.2.2	Spurious Signals, SNR and Image Uniformity	158

6.2.2.3	Geometric Distortion	160
6.2.2.4	Temporal Stability.....	162
6.2.3	PET Performance and the Influence of MRI on PET	164
6.2.3.1	Sensitivity Degradation by the RF Coils	164
6.2.3.2	PET Performance Parameters	165
6.2.3.3	Maximum Activity	167
6.2.3.4	Time-Of-Flight (TOF) PET	168
6.2.4	PET/MR Imaging	169
6.2.4.1	Hot-Rod Phantom	170
6.2.4.2	MN $^1\text{H}/^{19}\text{F}$ Coil.....	173
6.2.4.3	In Vivo Measurement	174
6.3	Conclusion and Summary	179
7.	Comparison and Conclusion	181
7.1	Comparison.....	181
7.2	Conclusion	183
Appendix		184
	History, Acknowledgements, and Contributions	184
	Abbreviations	189
	Publications and Patents	190
	Publications from this Thesis.....	193
	Peer-reviewed Research Articles.....	193
	Presentations at International Research Conferences	194
	Patents and Patent Applications	194
	Related Publications.....	196
	Peer-reviewed Research Articles.....	196
	Presentations at International Research Conferences	198
	Patents and Patent Applications	201
	Related PhD Theses	202
	References.....	203

1. Introduction

Combining different medical imaging modalities into a single device is a promising way to attain comprehensive and complementary information. Hybrid imaging modalities thus enable new research methods, improve diagnostic accuracy, and improve clinical workflow. One successful example is the combination of Positron Emission Tomography (PET) and Computer Tomography (CT) in a single device. PET/CT enables one to obtain both the high sensitivity in vivo images of molecular processes using PET and the high-quality anatomical information from CT (Beyer *et al.*, 2000). At the end of 1990s, initial experiments had already begun seeking to combine PET and Magnetic Resonance Imaging (MRI) into a new hybrid system (Shao *et al.*, 1997). In comparison to PET/CT, this combination provides a better soft-tissue contrast and additional functional information at a lower overall lower radiation dosage (Torigian *et al.*, 2013). The seamless integration additionally leads to excellent spatial and temporal registration capabilities and reduces the overall scan time.

One of the main technological challenges is to develop a scalable PET detector architecture that is capable of supplying, controlling, cooling, synchronizing, and reading out a high number of detector channels, while at the same time keeping its interference with the MRI operation low. Multiple research groups worldwide are working on solutions to enable simultaneous PET/MR imaging (Vandenberghe and Marsden, 2015). Ideas range from using optical fibers to transport the scintillation light of each detector crystal to the PET detector electronics placed far away from the MRI gantry (Shao *et al.*, 1997) to battery-powered detector modules modulating analog laser-light signals (Olcott *et al.*, 2013). Unfortunately, such methods are often unable to be scaled to larger systems, face MRI compatibility problems, and suffer from degraded PET performance. The approach followed in this thesis is to digitize the PET sensor signals as closely to the sensors as possible in order to maximize the PET Signal-to-Noise Ratio (SNR). The digitization thus occurs directly within the PET detector modules, which are placed inside the bore of the MRI scanner. In a second step, the sensors measure the signals directly digitally. The downside of this approach is that it has the highest risk of influencing the MRI scanner. Digital electronics are known to disturb the MRI system in several ways: the homogeneity of the static magnetic field (B_0) becomes distorted by electronic components (Schenck, 1996), the gradient fields are influenced by induced eddy currents in conductive areas (Le Bihan *et al.*, 2006), and the RF system receives spurious signals from the switching circuits (Hornak, 2011).

In translational research, preclinical animal studies are required for both fundamental research and legally required tolerability studies (e.g., in pharmaceutical drug development). Compared to conventional invasive studies, which require the dissection of a new animal for each point in time of a longitudinal study, preclinical imaging allows studying the same subject multiple times. Additionally, observing the development of a single object results in more meaningful data than measuring the different stages from different objects. Therefore, preclinical imaging has the ability to improve the significance of preclinical studies, as well as the potential to drastically reduce the costs and the number of animals sacrificed (Yao *et al.*, 2012). Preclinical imaging – from mice to rabbits – was thus chosen as a meaningful targeted application.

This thesis covers the research on the PET hardware chains for both integration steps, with a focus on PET/MRI compatibility. The required performance parameters for a hybrid preclinical imaging modality are derived in chapter 3 on the basis of the fundamentals of the two single imaging modalities PET and MRI presented in chapter 2. Possible means of interaction between the two modalities and how they degrade the performance parameters are discussed. Reference examples – estimating calculations and measurements – provide an insight into the impact and magnitude of each interaction. Methods to verify whether the requirements are met are described in the same chapter. They were extensively used in the development phases of all subcomponents and serve to quantify the PET/MR compatibility of the final inserts. The history of PET/MRI research is closely linked to the developmental steps in solid-state scintillation light detectors. Chapter 4 thus presents these different detector technologies in combination with their usage in PET/MRI systems and discusses the advantages and reported problems. Beginning with the newest and most promising detector technology, Chapter 5 covers the developed hardware chain and the MRI compatibility measures taken for the first developed system in which the digitization of the analog sensor signals is integrated into the PET detector modules. The level of PET/MR compatibility attained is measured, discussed, and used as input for the second step (chapter 6), in which newly available, purely digital, sensors are used as scintillation light detectors. Additionally, the PET/MR compatibility is improved to match the requirements stipulated at the beginning of the thesis. Both chapters about the systems end with measurements demonstrating the quality and in vivo capabilities of the respective system. At the end of the thesis, the results are compared with the findings of the other research groups, which allows drawing a conclusion about the success of the early-digitization approach.

The two inserts and results from the MRI compatibility measurements are published, as condensed extractions from this thesis, in (Weissler *et al.*, 2014b, © 2014 IPPEM) and (Weissler *et al.*, 2015a, © 2015 IEEE). Additionally, PET/MRI synchronization attained by detecting the switching MRI gradients, as presented in section 5.1.2.1, is published in (Weissler *et al.*, 2015b, © 2015 IEEE). Additional related presentations at international research conferences, as well as journal and patent publications, are listed in the appendix.

2. Fundamentals

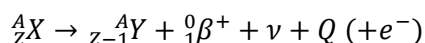
This chapter introduces the two single imaging modalities PET and MRI, their applications, and the idea of hybrid imaging modalities. The level of information is gauged to the needs of this thesis. More details are provided in the preceding chapter and references are made to other studies with further information when the topic is related, but not directly relevant, to this thesis.

2.1 Positron Emission Tomography

PET is a molecular imaging modality: A tracer that, after application to the patient, binds to targeted molecules is radioactively marked. The radioactive decay emits a positron that, in an annihilation process with an electron, results in two high-energy gamma photons that are emitted in (almost) exactly opposite directions. By detecting both gammas of many of such events, it is possible to reconstruct an image displaying the distribution of the tracer in the body.

2.1.1 Positron-Emitting Radioactive Decay

Only a minority (about 270) of the known nuclei are stable. The others (more than 2800) are radionuclides that decay with the time due to their unsuitable combinations of protons and neutrons and the resulting excess energy. As only a few of the radionuclides are found in nature, most are produced in reactors or cyclotrons. There are different decay processes. If a nucleus has too many protons (and the radionuclide has a transition energy of at least 1.022 MeV – see below) a proton can convert to a neutron by emitting a positron (β^+) and an (electron-) neutrino (ν). The general equation describing this process for an atom is:



The atom A_ZX decays to an atom ${}^A_{Z-1}Y$, having the same mass number (or nucleon number) A , but one less proton ($Z-1$): as such, e.g., ${}^{18}_9\text{F}$ decays to ${}^{18}_8\text{O}$ (the atomic number is often omitted in written form, as it is equivalent to the symbol X). To balance the charge of the new atom Y (the resulting atomic number is reduced by one), an electron (e^-) is emitted. A neutron is

one electron mass heavier than a proton, and, therefore, the radionuclide must have a transition energy of at least 1.022 MeV (two times 511 keV, the energy of an electron mass at rest). The rest of the transition energy is partly emitted by the neutrino (ν), and partly (Q) given to the positron. Therefore, the positron has an initial kinetic energy after its emission. By multiple (elastic and inelastic) interactions with electrons and nuclei of the surrounding matter, the positron loses its energy and thus travels in a zigzag-path through the tissue (for ^{18}F in water, the positron travels an average distance of about 0.46 mm). When this energy is almost used up, the positron is absorbed by an atom and combines with an electron. In human tissue, in about one-third of the cases, a positronium with a mean lifetime of about 10^{-7}s is formed first. A positronium is a non-nuclear, hydrogen-like element, having a positron instead of a proton (although, due to their similar mass, positrons and electrons rather tumble around each other). The relevance of positronium formation for PET is being debated (Harpen, 2004) (Ganguly *et al.*, 2009). In the annihilation process, a matter-antimatter reaction, the mass is converted to two gamma photons, each having the energy of an electron mass (i.e., 511 keV). Due to the conservation of energy and momentum, the two gamma photons are emitted in almost exactly opposite directions with a small angle caused by the positron's (and the electron's) rest momentum when hitting the electron (see section 3.1.1.3).

The rate of the decay is defined by the half-life, which is the time it takes the initial activity to be halved (this basic introduction neglects successive decays as well as biological processes, such as urinating, which also has to be calculated into (pre)clinical PET imaging). The activity A_t after the time t is calculated from the original activity A_0 as:

$$A_t = A_0 e^{-\lambda t}$$

The decay constant λ is related to the half-life $t_{1/2}$ as:

$$\lambda = \frac{\log_e(2)}{t_{1/2}}$$

^{18}F , for instance, has a half-life of about 110 minutes. The higher the transition energy is above 1.022 MeV, the more likely positron decay will be the decaying mechanism. Nevertheless, other types of decays (and cascades of decays) are possible. The branching ratio expresses the fraction that decays by the particular mechanism. For ^{18}F , the branching ratio is 0.969, meaning that 96.9 % of the decays produce positrons, whereas the other atoms decay – in this case – by electron capture: in the electron-capture decay process, an electron is captured by a proton of the nucleus and produces a neutron (and a neutrino to conserve the energy). Since activity and half-life are defined for the decaying nuclei, branching has to be taken into account when calculating the quantity of emitted positrons and, thus, the quantity of emitted gamma photons.

2.1.2 Interaction of the Gamma Photons with Matter

There are mainly two mechanisms in which the annihilation photons with the energy of 511 keV react with matter: the photoelectric effect and Compton scattering. Other mechanisms are found at lower (e.g., Rayleigh scattering) or higher energies (e.g., pair production).

- Photoelectric Effect

The gamma photon transfers all its energy to an electron (usually of the inner electron shells), which is ejected from the atom (leaving it ionized). The ejected electron is called a photoelectron. The vacated inner position is then taken by an electron from the outer shells. The binding energy from that electron is either emitted as another (X-ray) photon or transferred to another outer electron, by being ejected from the atom.

- Compton Scattering

In Compton scattering, the gamma photon transfers a part of its energy to an outer electron of the interacting atom. The transferred energy is used to overcome the binding energy of the electron and the rest is converted to kinetic energy. The ejected electron is called a Compton scatter electron. As a result, the photon with the rest energy leaves the interaction at a changed angle (see section 3.1.1.1). The maximum energy loss possible (341 keV) results in a complete backscatter of the photon.

More detailed information about the physical principles in PET are described in (Townsend, 2004).

2.1.3 PET Scanner

Due to the high energy of the gamma photons, they travel through the patient's body without interacting (although many photons are attenuated – see section 3.1.1.1). When these two gammas are simultaneously detected as a coincidence by the PET scanner, a line between the locations of the two detected singles can be drawn. With multiple such Lines Of Response (LOR) it is possible to reconstruct a tomographic image. Figure 1 illustrates this by overlaying the detected LORs: to improve image quality, modern PET reconstruction uses more sophisticated techniques, employing iterative expectation maximization algorithms, prior knowledge of the detector geometries, and Monte Carlo simulations.

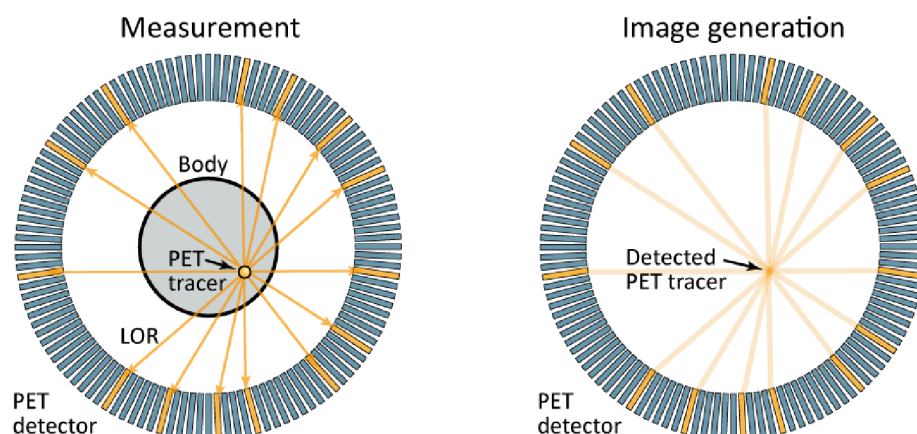


Figure 1: In the PET measurement, LORs are detected by detecting the coincident gamma photons (left). The resulting image is then generated from these LORs (right).

The PET detectors are normally built by surrounding the patient with solid scintillation detector crystals. These are made from materials that are optimized for high stopping power (stopping the gamma photons with a high density and effective atomic number (Z_{eff})), high

photon yield (high scintillation light output), short scintillation decay times, and good energy resolutions. Commonly used materials are bismuth germanate BGO ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$), LSO (cerium-doped lutetium oxyorthosilicate $\text{Lu}_2\text{SiO}_5:\text{Ce}$), GSO (cerium-doped gadolinium oxyorthosilicate $\text{Gd}_2\text{SiO}_5:\text{Ce}$), or LYSO (cerium-doped lutetium yttrium oxyorthosilicate $\text{LuYSiO}_5:\text{Ce}$). The gamma photon interacts with the crystal by Compton scattering and/or by the photoelectric effect. As described above, the vacated low-energetic positions are occupied either by electrons from outer shells or by free electrons in the conduction band of the crystal structure, and the energy is often radiated as X-rays or UV-photos. The doping of the scintillator crystals results in new energy states between the conduction band and the valence band of the crystal, which allows the energy of the emitted photons to be adjusted. As such, the crystals convert the single gamma photons into thousands of photons with a lower energy in the optical range.

These optical photons have to be detected by the PET detector electronics. In standard commercial PET scanners this is done by Photo Multiplier Tubes (PMTs). They convert incident photons to electrons, multiply them in a cascade of high-voltage dynodes, and, as such, create an output current that can be measured by the detector electronics. The PMTs normally have a much higher diameter than the scintillation crystals. Therefore, the light emitted from the crystals is often spread over multiple PMTs, and the crystal originally hit is determined by calculating the ratios of energy detected by the different PMTs (Figure 2).

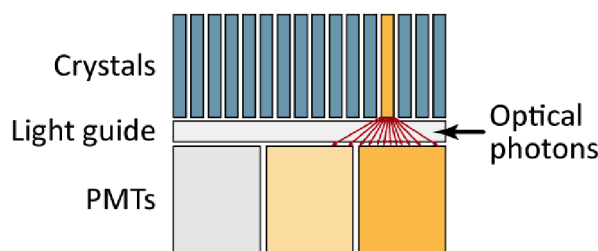


Figure 2: Anger method: The scintillation light from the crystal, hit by the gamma photon, is spread through a light guide over multiple PMTs. The crystal position can be reconstructed using the ratios of detected energy by the different PMTs.

Further details about PET scanner technology is given in chapter 3.1. A history and overview of current developments in PET detector technologies is given in (Lewellen, 2008) and (focused on solid-state detectors) in chapter 4.

2.1.4 Tracer and Applications

The PET tracer generally consists of the positron-emitting radionuclide attached to a ligand. This ligand is an analog in the targeted biomedical processes. The PET tracer, or radiopharmaceutical, thus behaves (to a certain extent) like the normal molecule after administration (e.g., injection). ^{18}F -Fluorodeoxyglucose (^{18}F -FDG), for instance, is an analog of glucose and is taken into the cells together with normal glucose. As it is not actual glucose, the cell cannot use it, and the tracer accumulates in the cells with high metabolic rates. ^{18}F -FDG is thus a marker for cellular metabolism. There are many combinations of radionuclides and ligands for many different applications. Nevertheless, only few (such as ^{18}F -FDG and ^{18}F -FLT) are currently routinely utilized for clinical purposes. Table 1 lists a few example

tracers used in tumor characterization and treatment monitoring. Another example are tracers used in cardiology – an overview can be found in (Acampa *et al.*, 2000).

Tracer	Biological property	Example applications
¹⁸ F-Fluorodeoxyglucose (FDG)	Glucose metabolism	Tumor detection
¹³ F-Fluorothymidine (FLT)	Cellular proliferation	Tumor characterization
¹⁷ O-Water	Perfusion	Vascularity, blood flow
¹⁸ F-Fluoromisonidazole (MISO)	Hypoxia	Tissue oxygenation
¹⁸ F-Fluoroethyltyrosine (FET)	Amino acid metabolism	Proliferation activity
¹⁸ F-Choline, ¹¹ C-Choline	Cellular proliferation	Cell membrane synthesis

Table 1: Example PET tracers used in tumor assessment.

PET is very sensitive – even pico-molar concentrations can be detected. A second, very interesting, aspect of PET is that the statistics about the detection processes from tracer decay to detection probability are known, and therefore PET can, in principle, be used as a quantitative imaging modality.¹

2.2 Magnetic Resonance Imaging

MRI is an imaging modality that excites nuclei in the body by deploying multiple magnetic fields of different strengths, directions, and frequencies. After excitation, the nuclei return to their state of equilibrium. The excited nuclei create an RF field that can be measured by an antenna. The frequency and phase of the excited nuclei are changed by the MRI scanner over space and time. As such, the received signal contains spatial information, and an image can be reconstructed.

The contrast that the images show depends on the exact sequence (timing, amplitude, frequency, direction) of the magnetic fields. It can be anatomical (e.g., showing the distribution of water and fat) or functional (e.g., showing blood oxygenation levels in the brain). Many other methods are available for using the MRI to, e.g., conduct spectroscopy, measure temperature, or visualize water diffusion.

There are many scholarly introductions to MRI available, some good examples are even available on free websites (Hornak, 2011). Therefore, the level of detail in this introduction is adapted to the needs of this thesis (topics such as preparation pulses or mathematical discussions of the Bloch equations are thus not covered).

2.2.1 Nuclei, Spins and the Static Magnetic Field B_0

Nuclei with an odd number of protons, neutrons, or both, have a magnetic dipole moment. Most important for clinical MRI is the proton (¹H), due to its abundance in the human body, mainly bound in fat and water (a human with a weight of 70 kg has about 7×10^{27} atoms, of

¹ MRI, for instance, is normally not quantitative, since the amount of received energy depends on many unknown parameters (although some techniques, such as T_1 mapping, are).

which about 4.7×10^{27} are ^1H). In the absence of a magnetic field, their quantum-mechanic spin property, which is responsible for the magnetic dipole, point randomly in every direction (Figure 3).²

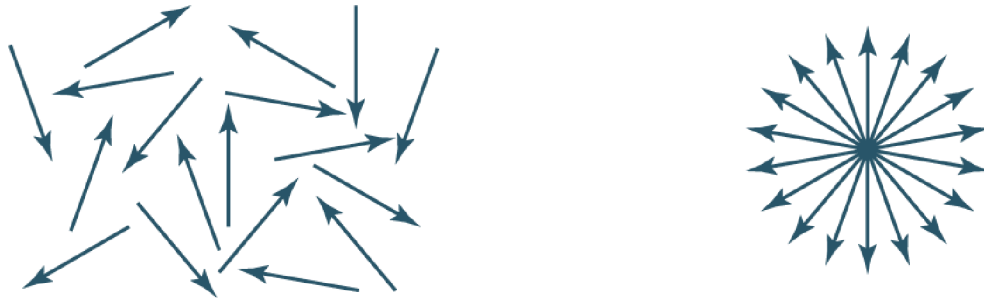


Figure 3: 2-D sketch of the spins in the absence of a magnetic field. Pointing in random directions (left), they produce no net magnetization (right: all vectors placed in the same origin).

An applied static magnetic field has a polarizing effect, but the orientation-energy of a single spin is much smaller than the thermal energy, so that overall the spins only have a slight tendency to point in the same direction as the magnetic field. Nevertheless, this skew results in a longitudinal equilibrium magnetization (Figure 4).

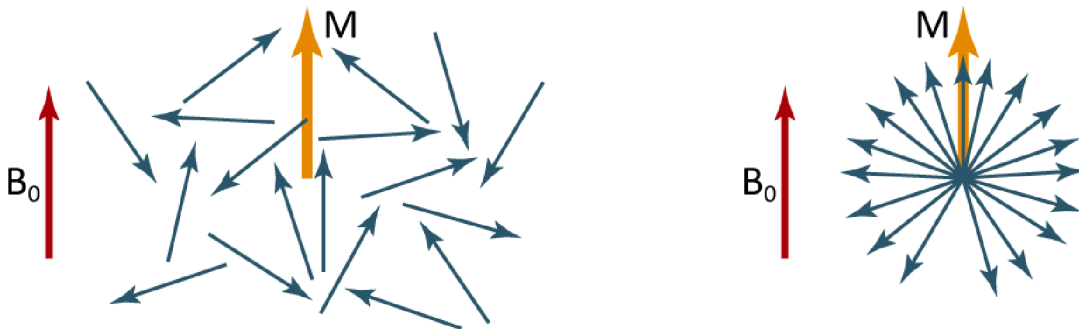


Figure 4: 2-D sketch of the spins in the presence of an external magnetic field B_0 at room temperature. The spins are slightly turned towards B_0 and produce a net magnetization (M).

In a common clinical MRI scanner, this external magnetic field (B_0) is applied by a superconducting magnet around the patient with field strengths of 1.5 T or 3 T. More details are given in sections 3.1.2.1 and 3.2.1.

2.2.2 Magnetic Resonance and the RF Field B_1

In the presence of the external magnetic field, the individual spins are, furthermore, precessing (Figure 5) around the axis of that field. As all spins are precessing out of phase, the resulting net equilibrium magnetization is not precessing (stationary without RF emission). The frequency of the precession depends on the magnetic field and is described by the Larmor equation $\omega = \gamma B_0$.

² As MRI is never able to measure single protons, their energy eigenstates, aligning parallel or anti-parallel to a magnetic field, are irrelevant for understanding MRI (Hanson, 2008).

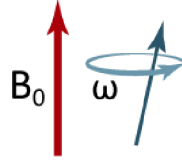


Figure 5: Sketch of a single spin precessing with the Larmor frequency ω in the presence of an external magnetic field B_0 .

The gyromagnetic ratio, γ , depends on the nuclei. Table 2 lists the ratios for the most common nuclei used in MRI.

Nucleus	γ [10^6 rad/s/T]	$\gamma/2\pi$ [MHz/T]
^1H	267.513	42.576
^{13}C	67.262	10.705
^{17}O	36.264	5.772
^{19}F	251.662	40.052
^{23}Na	70.761	11.262

Table 2: Gyromagnetic ratios of the most commonly used nuclei in MRI.

When an external RF field (B_1) is applied, the spins pick up energy from that field and start to increase their angle of rotation. When this field is combined with additional inhomogeneous fields associated with nuclear interactions,³ it results in a coherent excitation of the spins, leading to a transverse net magnetization. The net magnetization vector thus spirals around the axis of B_0 with an increasing Flip Angle (FA) (Figure 6). Seen from a point that rotates according to the RF frequency, the spins rotate into the transverse plane (Figure 7, left).

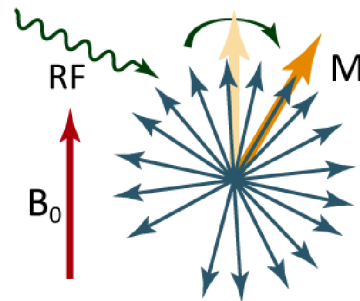


Figure 6: 2-D sketch of the excitation: The spins pick up energy from the RF field and start precessing coherently.

The exciting RF field is generated by the RF coil of the MRI scanner. Further details are presented in section 3.1.2.2.

³ Despite being often stated in MRI introductions, the RF field alone cannot bring the spins into phase (otherwise 180° pulses would not be able to produce echoes). The real source of coherence can be seen as a field-assisted T_1 -relaxation, although relaxations are normally associated with loss of coherence (Hanson, 2008).

2.2.3 Relaxation and Receiving the MR Signal

When the exciting RF field is switched off, the net magnetization relaxes and returns to the state of equilibrium (Figure 7, right). This is done by slowly (up to seconds) transferring the energy to the surrounding lattice. This longitudinal relaxation is thus also called spin-lattice relaxation, and the time constant describing it is named T_1 . This time constant (among others) depends on how efficient the energy is transferred, and is thus lattice dependent. Therefore, it is one of the contrasts imaged in MRI.

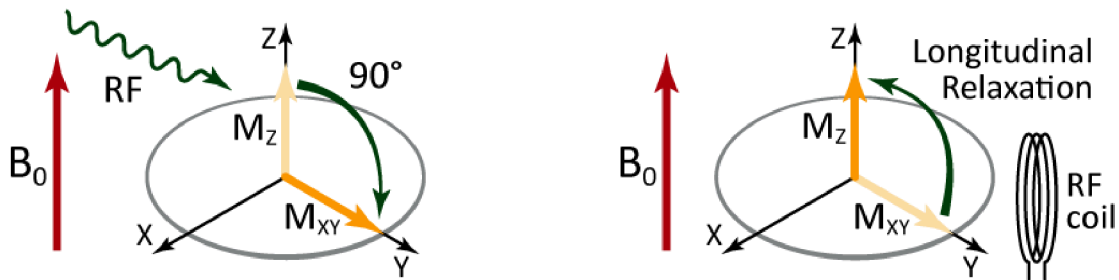


Figure 7: Sketch of the excitation (left) in the rotating frame: The longitudinal net magnetization (M_z) is flipped for 90° into the transverse plane. The RF field caused by transverse magnetization (M_{xy}) can be measured by receiving RF coils (right). After the excitation, the spins return to their state of equilibrium (right).

When the relaxing spins are in phase, they also produce a net magnetic field that rotates at the Larmor frequency. This field is the MR signal that can be received with RF antennas: the RF coils. The signal is very weak – the coils and the complete receiving RF chain is thus designed to be very sensitive (more details are presented in section 3.2.2).

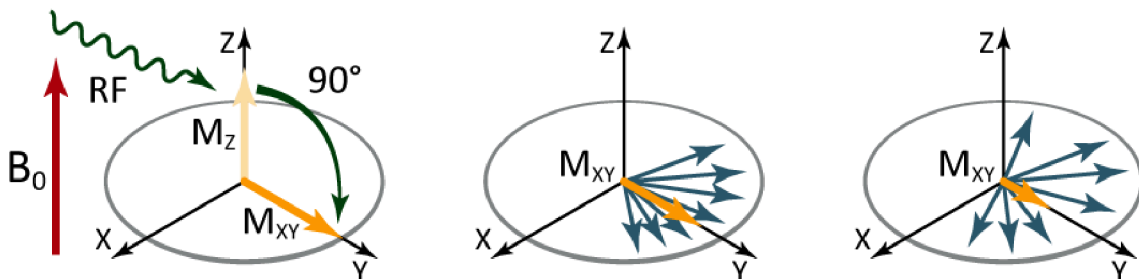


Figure 8: Sketch of the transverse relaxation: The RF excitation pulse turns the longitudinal magnetization into the transverse plane (left). The single spins start to go out of phase (middle), resulting in a vanishing net transverse magnetization (right).

A second relaxation mechanism is the interaction between the spins. By transferring energy between them, the spins lose their coherence, and thus lose the transverse net magnetization (Figure 8). This spin-spin relaxation is described by the time constant T_2 . Just as T_1 , it is tissue-related, but due to the different mechanism it results in different values, and thus into a different contrast. Some example values for T_1 and T_2 of different tissues are listed in Table 3.

Tissue	T ₁ [ms]	T ₂ [ms]
Liver	812	42
Skeletal muscle	1412	50
Heart	1471	47
Kidney	1194	56
White matter	1084	69
Gray matter	1820	99
Spinal cord	993	78
Blood	1932	275

Table 3: Average T₁- and T₂- values for different tissues at 3 T, as measured in (Stanisz *et al.*, 2005).

A third, and the fastest, mechanism for destroying the coherence is caused by local field inhomogeneity. Following the gyromagnetic ratio, the spins get out of phase very quickly. This Free Induction Decay (FID) is expressed by the T₂^{*} time constant. As this effect is relatively constant over time, the dephasing can be reversed, which is used in the spin echo sequences (see section 2.2.5).

In general, the magnetization over time can be described using the Bloch equations and its solutions. The magnetization (in liquids and excluding diffusion) over time $\vec{M}(t) = (M_x(t), M_y(t), M_z(t))$ can be calculated by the Bloch equations (Bloch, 1946). In vector notation, for the stationary frame of reference this is:

$$\frac{d\vec{M}(t)}{dt} = \gamma \vec{M}(t) \times \vec{B}(t) - \vec{e}_x \frac{M_x(t)}{T_2^*} - \vec{e}_y \frac{M_y(t)}{T_2^*} - \vec{e}_z \frac{M_z(t) - M_0}{T_1}$$

The first term on the right side of the equation describes the Larmor precession in an external magnetic field. The right term describes how the longitudinal magnetization is regained by transferring the energy with the time constant T₁ to the surrounding lattice. The two remaining terms describe the transverse spin-spin relaxation with the time constant T₂^{*}. A further detailed mathematic description can be found in (Wehner, n.d.).

2.2.4 Image Generation and Gradients

As described above, the frequency of the spin precession always depends on the magnetic field. When the patient is placed into the homogeneous B₀ field, all spins are excited simultaneously and produce a simultaneous MR signal. By superimposing a gradient field, the field strength of the static magnetic field is spatially altered in a known way, which is then used for the image encoding. These gradients are generated by the gradient coils (see section 3.1.2.3 for more details). Generally, the three dimensions can be resolved by means of the following three techniques used in the standard Cartesian image acquisition (different and hybrid forms exist):

- Slice Selection

Since the excitement of the spins is a resonance phenomenon, it only occurs at the exact Larmor frequency and thus depends on the field strength. When a gradient is applied during the excitation pulse, only a certain slice of the body is excited, depending on the gradient strength and the bandwidth of the B₁ pulse (Figure 9). The pulse shape also plays a role: Since the slice should have sharp edges, the complete

frequency range of the slice should be covered, but no other frequencies should be present. The required pulse shape is thus a Fourier-transformed rectangular function: a sinc pulse shape. During the excitement, the gradient already has a de-phasing effect on the net magnetization (see gradient echo in section 2.2.5). Therefore, a slice-rephasing lobe with the opposite direction (and half the strength-time product) has to either follow the excitation, or precede it as a dephasing lobe.

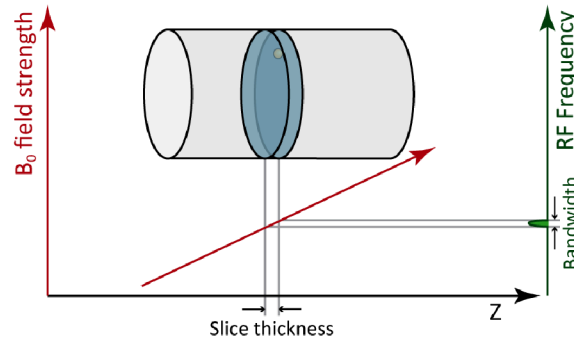


Figure 9: Slice selection: The B_0 field is overlaid with a spatial gradient. The RF excitation pulse thus only excites a slice with a thickness dependent on its bandwidth.

- Frequency Encoding (Readout Gradient)

During the relaxation, the spins also turn with the frequency relative to the magnetic field. When a spatial gradient is superimposed at the time, the MR signal is received, and the spins emit their signal with a slightly different (now spatial-dependent) frequency. The Fourier transformation of the received signal is thus a projection through the imaged slice (Figure 10). As the gradient is active during readout, the frequency-encoding direction is also called readout direction. Similarly to the slice-selecting gradient, a dephasing lobe (with half the strength $\times$ time product) has to be applied before the actual readout.

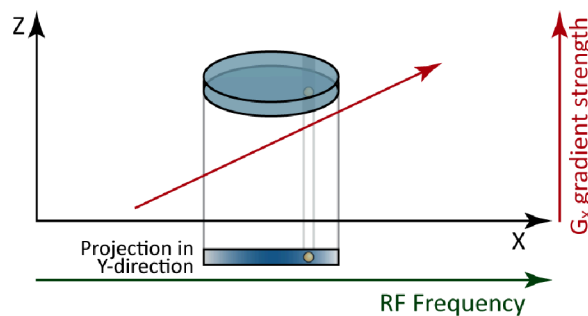


Figure 10: Frequency encoding using a readout gradient. The spectrum of the received signal represents a projection through the slice.

- Phase Encoding

Applying a gradient between slice selection and readout results for a short time in a faster turning of the net magnetization, which is spatially dependent on the gradient. Once the gradient is switched off, the spins continue with the original frequency, but now there is a phase difference between them. Signals from spins with the same phase add up, whereas signals from spins with a phase difference of 180° will be subtracted (Figure 11).

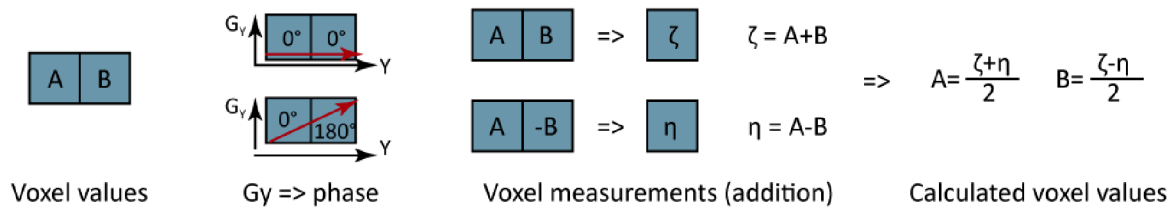


Figure 11: Phase-encoding example: The two example voxels (of the same tissue) have the proton densities A and B. They are measured twice: with no gradients and with a gradient changing the phase of B for 180°. The measurement adds both voxels each time. The original voxel values can be calculated with the resulting linear equation system.

Repeated measurements with changed spatial phase differences result in sets of linear equations, and thus in the second dimension of the Fourier-encoded image (Figure 12).

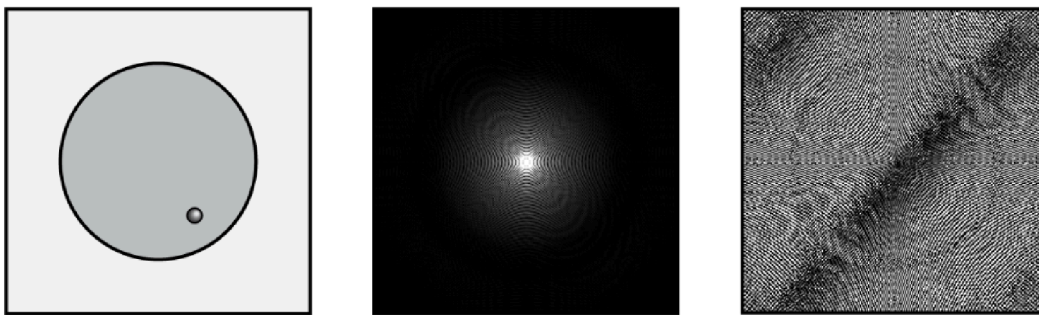


Figure 12: Original image (left) and Fourier-transformed version of the grayscaled original. The brightness of the magnitude image (middle) was greatly intensified, as the main intensity is concentrated in the center. The phase information (right) has values from $-\pi$ (black) to $+\pi$ (white).

2.2.5 MRI Sequences

As described above, in normal Cartesian MRI sequences, MR signal generation has to be repeated multiple times in order to cover all the phase-encoding steps. MRI sequences describe the chronologic pattern of RF pulses, gradient switching, and data acquisition. They define the imaging technique used, the contrast to be displayed, the scan time, and the image quality. Examples of imaging techniques are:

- Spin Echo (SE)

As stated in section 2.2.3, the influence of the local magnetic field differences, leading to the fast T_2^* decay, can be reversed. With an RF pulse having twice the energy as the excitation pulse, the spins are flipped 180° (Figure 13).

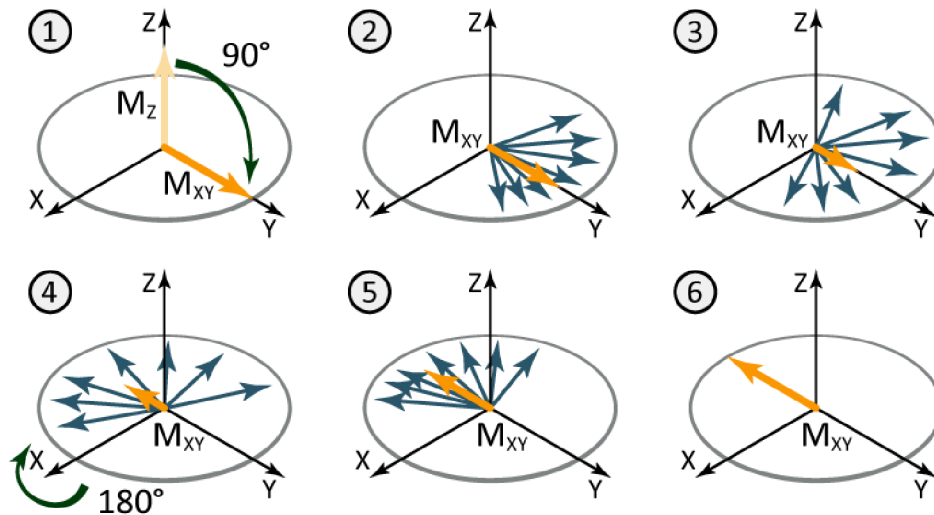


Figure 13: Sketch of the spin echo generation in the rotating frame: After the 90° pulse (1), the spins dephase (2), losing the transverse net magnetization (3). A 180° RF pulse flips the spins (4). The phase between the spins continues to change with the same speed and direction (5), restoring the transverse magnetization (6).

As a result, the slow- and fast-turning spins are all in phase again after twice the time between the 90° excitation pulse and the 180° pulse. The resulting echo signal (with a height dependent on T_2 and not T_2^*) is measured in the spin echo sequence (Figure 14).



Figure 14: Simplified sequence diagram of a SE sequence

- Turbo Spin Echo (TSE)

Although the signal height depends on T_2 , the T_2^* -effect will again cause dephasing after the short echo. The signal can be brought back multiple times with repeated 180° pulses – always with a slightly loss of intensity, depending on T_2 (and on the phase-encoding step). With further phase-encoding steps between the echoes, the scan time is reduced. Since the 180° pulses inverse the dephasing, the rephrasing slope in frequency direction only has to be made once per TR. The phase-encoding gradients, on the other hand, are reversed after each echo in order to start with zero phase difference for each echo. The sequence diagram in Figure 15, moreover, illustrates that this sequence uses higher RF power.

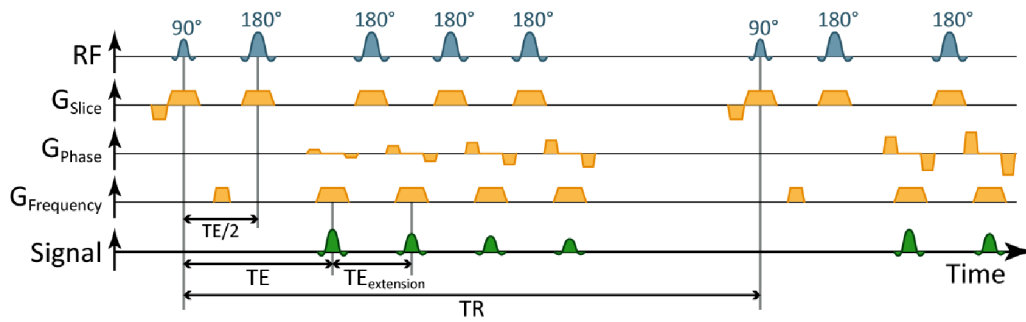


Figure 15: Simplified sequence diagram of a TSE sequence

- Gradient Echo (GE) or Fast Field Echo (FFE)

Applying a gradient during readout is necessary for spatial encoding. Similarly to the effect that causes the T_2^* -dependent signal decay, this gradient causes the spins to dephase, and thus loss of the signal. By applying the gradient in the opposite direction, the dephasing is reversed and a gradient echo (with a signal height of T_2^*) is generated. This echo can be provoked earlier than spin echoes, and TR is often shorter. FFE sequences are thus, in general, faster, as illustrated by the sequence diagram in Figure 16.

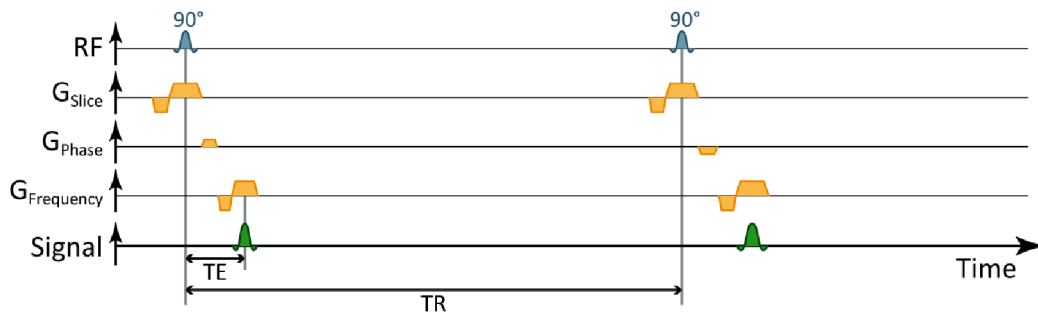


Figure 16: Simplified sequence diagram of an FFE sequence.

- Echo Planar Imaging (EPI)

Similarly to TSE sequences, multiple gradient echoes can be generated with a single RF excitation. The number of echoes (the echo train length) defines the speed-up of the sequences. The extreme version is a single-shot EPI sequence, making all phase-encoding steps with a single RF excitation. The sequence diagram in Figure 17 shows, that this type of sequence can produce the most echoes in the same time span and is thus the fastest sequence. The first echo does not produce the highest signal, since the sequence starts with a relatively large dephasing lobe in the phase-encoding direction and the net magnetization only gets back into phase after a few phase-encoding steps (see also section 2.2.6, Figure 19). It becomes apparent, furthermore, that the EPI sequence results in the highest amount of gradient switching, whereas the amount of RF power used is rather low.

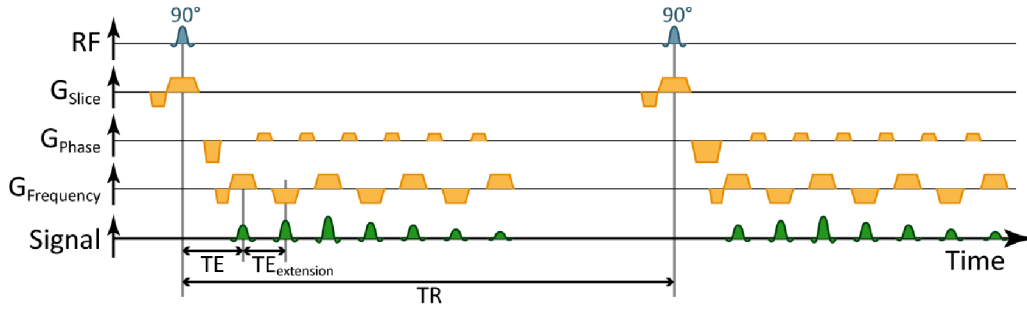


Figure 17: Simplified sequence diagram of an EPI sequence.

2.2.6 K-Space, Sampling, Field Of View (FOV), Spatial Resolution, and Bandwidths

The Fourier-encoded image, which can be measured with the above-described methods, is further known as the k-space, where k is the wavenumber: the reciprocal of the wavelength. Although less intuitive, the concept of k-space provides a more comprehensive representation of how the spatial encoding works and the sampling of data is realized. It furthermore provides insights into the relationships between FOV, data sampling, and pixel and image bandwidths.

The wavenumber k , or 3-dimensionally as k -vector, is defined as

$$k = \gamma \int_0^t G(t) dt$$

In this equation, γ is the gyromagnetic ratio (as frequency), $G(t)$ is the gradient strength, and t is the duration of the gradient. According to the Larmor equation, this describes the phase advance of the net magnetization as the integral of the gradient field over time. By applying the gradients with defined directions, strengths, and durations, it is possible to navigate freely through the k-space. Consequently, there are only practical differences between frequency- and phase- encoding.

Figure 18 shows the k-space trajectories as produced by the simple SE sequence (sequence diagram shown in Figure 14).

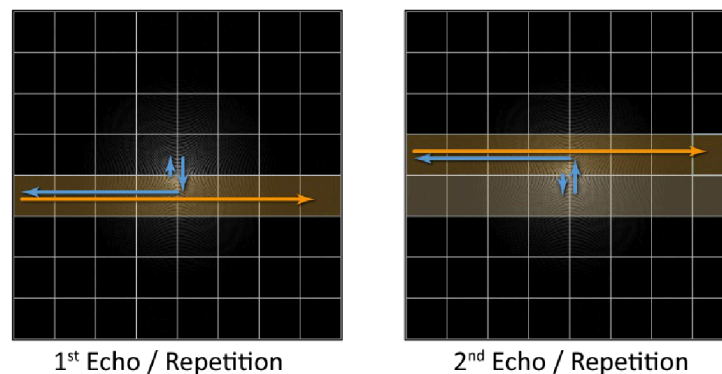


Figure 18: K-space trajectories as produced by the simple SE sequence (sequence diagram shown in Figure 14). Dephasing lobes and 180° RF pulse are shown in blue, readout gradients in orange.

The trajectory starts, after the excitation, in the center of the k-space. The phase-encoding gradient moves it in a phase-encoding direction (upwards in the example of Figure 18). The 180° RF pulse turns the trajectory (point symmetrically) to the opposite position, since this rotating inverses all accumulated phase differences. The dephasing lobe (in frequency-encoding direction) moves the trajectory to the side of the k-space. Now, the sampling of data – the filling of the k-space – starts. The signal of interest (magnitude and phase of the net magnetization) is modulated with the Larmor frequency. In a quadrature detector, the Larmor frequency is subtracted (by mixing and filtering) from the received signal. This is done once with a cosine and once with a sine (90° phase shift) signal. As such, the real and imaginary components are obtained, which allows the magnitude and phase of the signal to be calculated. During the readout of data, the frequency-encoding gradient moves the trajectory to the other side (to the right side in Figure 18) of the k-space. During the readout, the net magnetization gets in phase (in readout direction) when the phase-encoding axis is crossed. There, the signal has the highest amplitude, and the moment in time is thus the echo time TE.

Figure 19 shows the k-space trajectories as produced by a multishot EPI sequence (the sequence diagram would be similar to Figure 17, although only four echoes are used per repetition here). It is a good example of how a sequence can navigate through k-space, as it samples data for the majority of the time. It also visualizes why the first echo (in the sequence diagram of Figure 17) does not have the largest signal: it is generated far away from the center of the k-space and thus the net magnetization is mostly of phase. The concept of spins being in phase and out of phase points, furthermore, to the duality of phase and frequency encoding and explains why the data can be sampled as described above: In the center of the k-space, all spins with the same tissue properties are in phase, resulting in the DC component of the signal. Moving further along the frequency-encoding axis, only the spins (with similar tissue properties) that are distributed with the according spatial frequency are able to become in phase. The k-space thus shows the image in the spatial frequency domain.

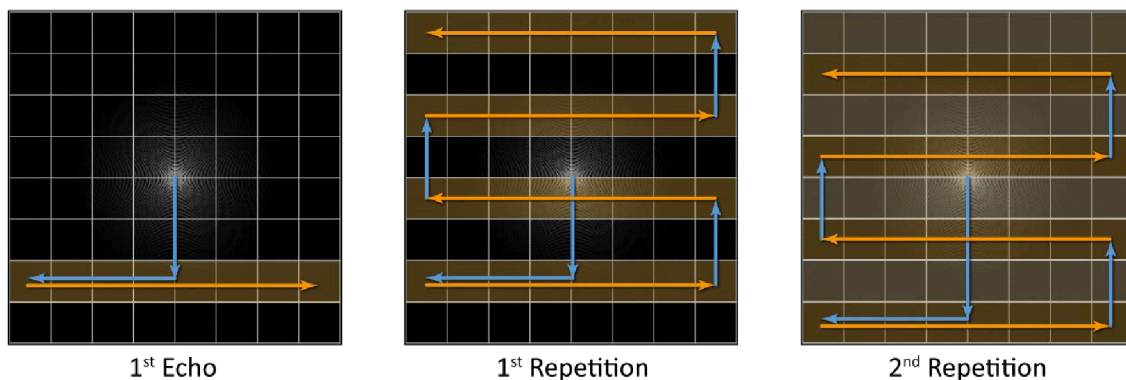


Figure 19: K-space trajectories as produced by a multishot EPI sequence (sequence diagram would be similar to Figure 17, although only four echoes are used per repetition here). Dephasing lobes are shown in blue, readout gradients in orange.

This free navigating through the k-space is, furthermore, used by non-Cartesian sequences that fill the k-space as well: e.g., in spiral trajectories, or by 3D sequences, which excite the complete imaging volume and similarly fill the three-dimensional k-space.

Although the trajectory moves continuously during readout (as the time advances continuously), the MRI signal is sampled in discrete time steps with sampling interval (or

dwell time) ΔT_s . To avoid aliasing, a scanner usually samples at least at the Nyquist frequency, and thus ΔT_s defines the receiver bandwidth of a sequence as $BW = 1/\Delta T_s$. Since the relationship between frequency and magnetic field is described by the linear Larmor equation, it also describes the relationship between the bandwidth, the gradient strength, and the FOV. The difference in magnetic field in a frequency encoding direction (assuming X-direction) over the FOV is $\Delta B_X = G_X \times FOV_X$, and thus the difference in frequency – the bandwidth – is:

$$BW_X = \frac{1}{\Delta T_s} = \gamma G_X \times FOV_X$$

The connection to the k-space can be made using the definition for k (as shown above):

$$\frac{1}{FOV_X} = \gamma G_X \times \Delta T_s = \Delta k_X$$

For spatial resolution, the FOV_X is divided in N_X pixels of the width Δx . The same subdivision, with the number of sampling points N_X , is made for the k-space (spanning in k_x -direction from $-k_{x_max}$ to $+k_{x_max}$), and therefore, the pixel size is defined by the number of samples taken:

$$\Delta X = \frac{FOV_X}{N_X} = \frac{1}{N_X \times \Delta k_X} = \frac{1}{2k_{x_max}}$$

A further combination of these relationships used in this thesis is the bandwidth of a single pixel in the image. This pixel bandwidth is calculated by dividing the total bandwidth of the image with the number of pixels in the frequency-encoding direction (or, in practice: the number of entries of the acquisition matrix).

$$Pixel\ bandwidth = \frac{BW_X}{N_X} = \gamma G_X \times \Delta X$$

Due to the similarity of both directions in k-space, the same relationships are, in principle, true for the phase-encoding direction. The presented relations are visualized in Figure 20.

The bandwidth in the phase-encoding direction is, in practice, very different for the two example sequences. In the SE sequence, all lines are sampled with the same delay (TR), and thus the bandwidth is infinite. In a single-shot EPI sequence, the period between two samples in the phase-encoding direction is, for $k_x=0$, a complete sampling of a line in the phase-encoding direction, plus the time needed for the phase-encoding gradient t_{GP} :

$$BW_{Y_SshEPI} = \frac{1}{N_X \times \Delta T_s + t_{GP}}$$

This bandwidth is much smaller than the bandwidth in X-direction, and thus for EPI sequences the bandwidth in the phase-encoding direction is the important parameter when discussing artifacts and image distortions (as will be done in chapter 3.2).

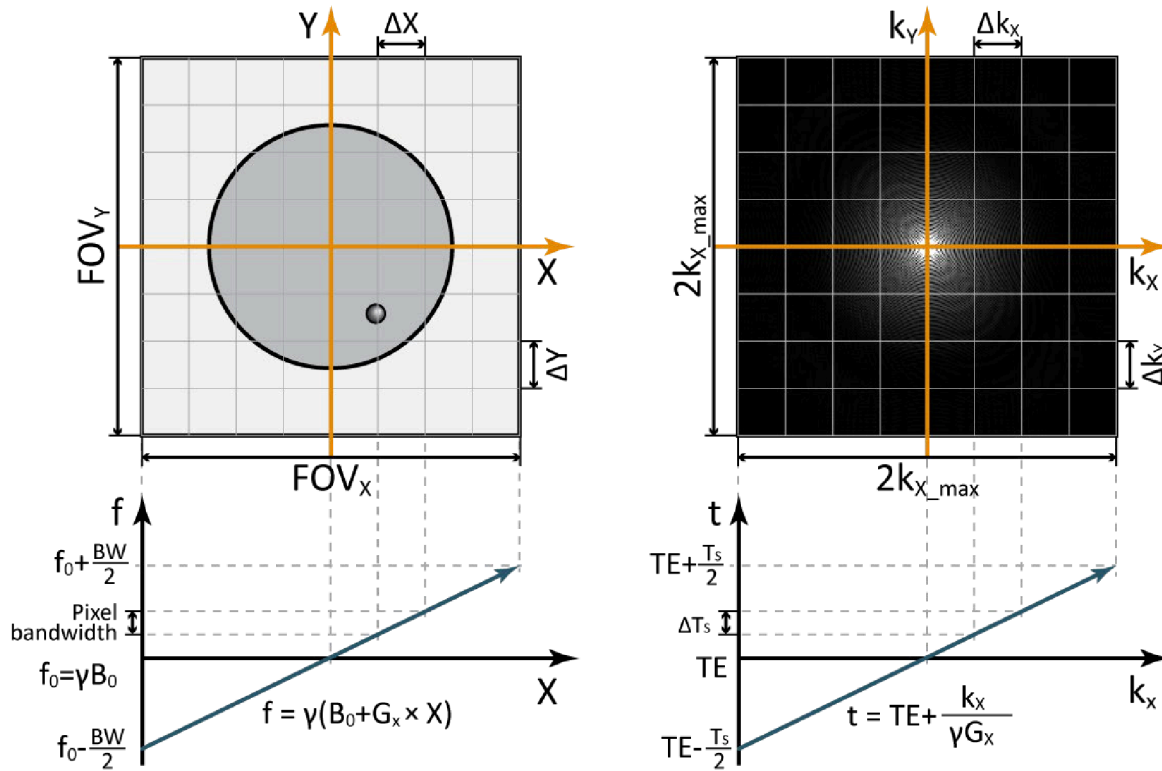


Figure 20: Image (left) and k-space (right) dimensions sketched in an example with $N_x=8$ pixels and samples per direction (the underlying image and k-space have higher resolutions in order to remain recognizable). The bottom row shows the relationship between spatial position and frequency (left), and the relationship between wavenumber and time (right).

2.2.7 Contrasts and Applications

All the imaging techniques presented are able to reveal different contrasts. This is mainly achieved by choosing different values for TE and TR (and by adding pre-pulses). As described above, the MR signal decays with the time constant T_2 or T_2^* . Waiting a long time before the echo is produced, tissues with short T_2 values contribute less to the signal, and the difference in T_2 dominates the contrast. When measuring shortly after the excitation, this effect is relatively low and the contrast is dominated by the amount of spins in the tissue. As only the already relaxed longitudinal magnetization can be excited again, when the longitudinal magnetization is not yet restored the signal will be smaller with each repeated excitation. Therefore, by choosing short TR values (i.e., in the range of the average T_1) it is possible to produce a contrast, which is primarily influenced by T_1 . With a longer TR, T_1 has less influence on the contrast.

Contrast	TE	TR	Practical Comments
T₁-weighted	Short	Short	A short TR is usually around T_1 , < 500 ms
T₂-weighted	Long	Long	A long value is about three times longer than a short, $TE > 90$ ms, $TR > 1500$ ms
PD-weighted	Short	Long	A short TE is usually < 90 ms

Table 4: Value combinations for TE and TR resulting in different contrasts.

Table 4 lists combinations of TE and TR, resulting in T_1 -, T_2 -, and Proton-Density (PD) weighted images, which will be used in later chapters. Having long values for both TE and TR results in a poor contrast, and this combination is thus normally not used. Figure 21 illustrates the influences of TE and TR on the image contrast graphically.



Figure 21: Graphical representation of the TE/TR - influences on the MRI image contrasts (qualitative color coding: blue: T_1 -weighted, orange: T_2 -weighted, black: PD-weighted).

The presented sequences are merely examples for standard sequences that are used throughout this thesis. The amount of techniques, variations, combinations, and achievable contrasts is almost endless. The possible applications of MRI in research and clinical applications are as manifold as the contrasts. They range from morphology imaging (as in the presented sequences) to special applications, such as cerebral fiber tracking or brain activity imaging (Table 5).

Biological property	Imaging technique
Anatomy / morphology	Spin echo, gradient echo, etc.
Water diffusion capacity	Diffusion weighted imaging
Vascular anatomy	MR angiography, Time-Of-Flight MRI
Cerebral blood flow	Arterial spin labelling
Perfusion	Perfusion weighted imaging
Tissue metabolites	Magnetic resonance spectroscopy
Vascularity and vascular permeability	Contrast agent take-up and T_1 mapping
Temperature	MR temperature mapping
Tissue characterization	Chemical shift imaging
Brain activation (functional MRI)	Blood oxygenation level dependent contrast

Table 5: Examples for biological properties that can be imaged with MRI, and the respective imaging techniques used.

2.3 Hybrid Imaging

In research and in clinical applications, patients are regularly imaged with multiple imaging modalities, insofar as one modality alone often does not reveal sufficient information for a complete diagnosis. The idea of multimodality imaging is, therefore, to combine two or more systems into a single hybrid imaging system. As such, the scan time is reduced, the images can be perfectly registered to each other, and, often, the complementary strengths of the systems enable completely new applications.

There are many possible combinations, such as Ultrasound with MRI (Piron *et al.*, 2003), X-ray with MRI (Fahrig *et al.*, 2003), or X-ray with optical luminescence (Carpenter *et al.*, 2010). Some, such as SPECT/CT (Mariani *et al.*, 2010), are already widely established in clinical practice. In accordance with the topic of the thesis, this chapter focuses on the combinations of PET with CT and PET with MRI.

2.3.1 PET/CT

As PET images in general have a low spatial resolution and do not show much anatomical detail, the information is often insufficient for a clinical diagnosis. Small lesions, for example, can be detected but not precisely localized. PET scanners were thus combined with CT scanners into single systems (Beyer *et al.*, 2000), allowing the PET information to be displayed alongside, or overlaid upon, the CT images. As both modalities are based on photons traveling through the body, this hybrid imaging modality has a further technical advantage: The attenuation of the lower energy X-rays for CT imaging can be used to estimate the attenuation of the gamma photons in PET imaging. As such, the attenuation can be corrected without the need for transmission scans with additional radioactive sources that were formerly used (Kinahan *et al.*, 1998). The success of the PET/CT combination was so successful that about six years later PET scanners were only sold in combination with CT scanners (Townsend, 2009).

Although preliminary detectors for combined PET and X-ray detection (for CT) are being developed (Bergeron *et al.*, 2015), PET/CT is usually a sequential hybrid modality constructed from two subsequent gantries for a single patient table (the Philips GEMINI and Ingenuity PET/CT series even allow a separation of the two gantries to provide better patient access). As a result, the patient can still move slightly between the images, and these movements and involuntarily motions, such as breathing, lead to artifacts forwarded from one modality to the other (Osman *et al.*, 2003).

2.3.2 PET/MRI

The hybrid imaging modality PET/MRI does more than simply combine the information that can be obtained by using the two single systems. Simultaneous PET/MRI data acquisition has many further advantages, as the following list outlines:

- Reduced Space Requirements

Unless newly built, available space is usually sparse in large hospitals. Therefore, saving the space required by a complete imaging system with its examination, control, technical, and patient preparation rooms is an often underestimated advantage. Additionally, due to the radiation involved, PET systems cannot be placed in an arbitrary free room, but need to be in a controlled region (often in the basement for evacuation and weight reasons).⁴ This is also an argument against sequential systems

⁴ For example, the GE MINItace cyclotron for PET tracer generation weights over 50 t.

that need especially large rooms, which are sometimes not available in the nuclear medicine department.⁵

- Reduced Scan Time and Increased Patient Comfort

PET and MRI examinations require roughly the same time, lasting up to an hour. Measuring the information from both simultaneously thus reduces the scan time substantially. The reduction of costs for the medical personnel during the measurements is not the only advantage: The patients often have to lie down in a prone position with raised arms, which is uncomfortable and for the patients (often being in poor health condition) impossible to maintain for such long periods of time. An even more drastic example can be found in epilepsy applications, where seizures have to be provoked while the measurements are taken: the simultaneous PET/MRI scan spares the patient a complete epileptic seizure. For preclinical imaging, not only the scan time, but also the total time of anesthesia is reduced by about 50 %, which is an important advantage (Wehrl *et al.*, 2015). The same advantage is also significant for pediatric patients, as children often have to be sedated for PET and MRI measurements.

- Dose Reduction

The overall radiation dose of a PET/CT examination is relatively high, ranging from about 14 mSv to 32 mSv. By comparison, the average effective radiation dose of a person living in Germany is 2.4 mSv per year. The maximum allowed job-related dose in Germany is 20 mSv per year. The CT part of PET/CT contributes around 54 % to 81 % of the overall radiation (Huang *et al.*, 2009). Although the high radiation dose might be justified for many patients with life-threatening illnesses, there are many reasons to reduce the amount of radiation (Hall and Brenner, 2008). For example, in oncology staging applications the response to a treatment is monitored multiple times, and, in that case, the radiation dose accumulates to very high levels. A second very important example are pediatric applications, where “lifetime radiation risks for children undergoing CT are quantitatively not negligible” (Brenner *et al.*, 2001). Dose reduction even plays a role in preclinical applications, since the applied radiation can alter the outcome of the studies by, e.g., influencing the immune response or other biological pathways (Boone *et al.*, 2004). A further opportunity for dose reduction in simultaneous PET/MRI is to use the complete MRI measurement time for the PET measurement. When the planned MRI measurement time is longer than a normal PET scan, it is possible to reduce the tracer activity injected into the patient (Oehmigen *et al.*, 2014).

- Optimal Temporal Registration

Dynamic studies follow the chronological events in the patient’s body after stimulation or the injection of agents. When carried out in separate experiments for PET and MRI, the events do not necessarily occur at the same place/time offsets from the

⁵ One of the first installations of a sequential system was actually built into a container with a total weight of 40 t, which was attached to the outside wall of the “Hôpitaux Universitaires de Genève”.

stimulation. It is also possible that the experiment cannot be repeated for the separate imaging modalities as, e.g., in preclinical infarction studies.

- Optimal Spatial Registration

In many applications, separate PET and MRI exams are made to diagnose patients. The scanners are often not directly next to each other as one is in the radiology- and the other in the nuclear medicine department. For the same reason, it is not guaranteed that both scans can be made on the same day and by the same personnel. Patients are thus positioned slightly differently for both scans. The resulting images can then not be exactly aligned with one another. Even in PET/CT and sequential PET/MRI, the patients, or the inner organs, can move between the images. With simultaneous imaging, the problem of misalignment is nonexistent.

- Motion Compensation

As stated above, the patient often moves involuntarily during the long PET measurements. Some motions, such as bowel movements, breathing, or the beating of the heart cannot even be paused. The MRI can track these motions with fast temporal (and low spatial) resolution image sequences or, e.g., with pencil-beam navigator techniques. The detected motion fields can then be used to remove the motion from the PET data during the reconstruction (Furst *et al.*, 2015).

- Partial Volume Effect Compensation

The extremely complementary properties of the two modalities can be further used to compensate for the shortcomings of a single modality (similar to the motion compensation). Compared to MRI, PET has very low spatial resolution. Small active regions (e.g., small lesions) and the borders of larger structures (e.g., the heart muscle) are often only partially inside a reconstructed voxel volume. The voxel intensities, and, therefore, the quantitative Standardized Uptake Values (SUV) results, are averaged over the voxel, and thus underestimated. This partial volume effect might be compensated for by using the higher spatial resolution of MRI (Evans *et al.*, 2015).

Of course, there are also downsides in comparison to PET/CT that have to be overcome. Aside from the high price of a PET/MRI system, there is also the difficulty of generating attenuation maps (Berker *et al.*, 2012), where CT is (due to similar transaxial FOV and similar photon-based image generation) much more suitable (Boss *et al.*, 2015).

Combining PET with MRI reveals comprehensive and complementary information (Wehrl *et al.*, 2013), and thus promises to be a valuable tool for research (Judenhofer and Cherry, 2013). Multiple clinical applications have already been suggested (Torigian *et al.*, 2013). They are mostly found in the field of neurology (e.g., dementia and other neurodegenerative diseases (Barthel *et al.*, 2015)) and oncology (e.g., in cancers of the head and neck (Queiroz and Huellner, 2015)), but also in cardiology (e.g., (Rischpler *et al.*, 2015)), in basic research (e.g., (Wehrl *et al.*, 2009)), or in the field of drug development (e.g., (Wolf, 2011)). The increasing global interest in PET/MR is also reflected in the high number of publications each year related to this topic (see Figure 22).

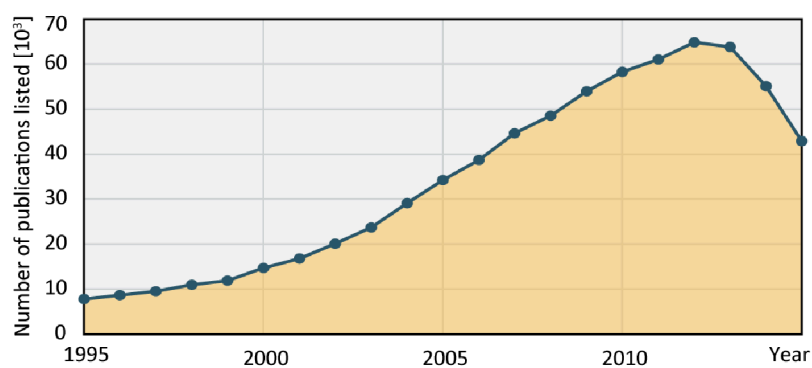


Figure 22: Number of publications over the years listed by Google Scholar for the search term “PET MR OR MRI”. It usually takes multiple years until the values stabilize, which can explain the downwards trend in the last three years (displayed data collected in March 2016).

2.4 Conclusion and Summary

PET is a molecular imaging modality, creating a visual image of the distribution of an applied tracer in the body. It accomplishes this by detecting the two annihilation (gamma) photons, which result from the positron-emitting decay process of the tracer’s radionuclide. MRI, on the other hand, uses magnetic resonance effects to visually represent the anatomy and physiologic contrast of the body. The combination of both PET and MRI provides comprehensive and complementary information and thus promises to be a valuable tool for research. Multiple clinical applications have already been suggested.

3. Requirements, Interferences, and Verifications

Both modalities have certain parameters that describe their performance. Examples for PET are spatial resolution and sensitivity, and for MRI the B_0 homogeneity and the image SNR. This chapter discusses these parameters and defines the requirements for preclinical applications. Combining the two systems and operating them at the same time will inevitably lead to interferences between them and, thus, to deteriorations of the performance parameters. The expected ways of interaction between the modalities and the impacts on the systems performances are explained in this chapter.

For an engineer, designing an MRI-compatible device, it is, furthermore, essential to have a quantitative understanding of the interactions. For each type of interaction, a reference example is presented that allows the impacts and limits to be estimated. From these estimations, a set of rules and measures can be derived that help to mitigate the interactions and remain within the specifications.

Finally, verification methods are defined at the end of each subsection. They will be used throughout the thesis to verify that the interferences have been reduced to a level that meets the requirements.

The targeted applications in preclinical imaging impose further requirements on the final system, ranging from animal handling to temporal synchronization. These will be discussed in the last section of this chapter.

3.1 PET and the Influence from MRI

3.1.1 Requirements on PET Performance Parameters

The performance of a PET system can be evaluated on different levels. On a clinical level, this would involve, e.g., the contrast between abnormal and normal tissue, which is influenced by factors such as count densities, scattered radiation, size of the lesions, up to

patient motions and the visualization on a monitor or a film. On a technical level, the performance of a PET detector is mainly defined by its energy-, time-, and spatial-resolutions, as well as its sensitivity.

3.1.1.1 Energy Resolution

When the gamma photons travel through matter, they can undergo Compton scatter, which entails that the photon loses some energy to an outer electron of the matter and the direction of the photon is changed (see section 2.1.2). These scattered events have a different LOR than the true events and, thus, result in increased image background noise (Figure 23).

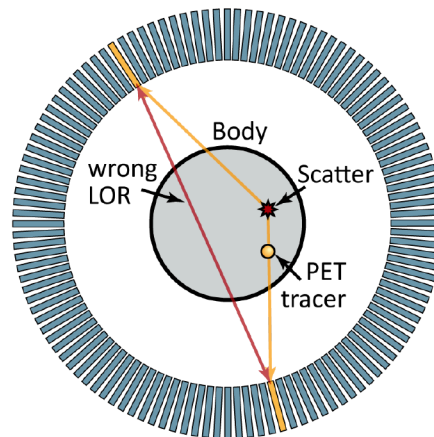


Figure 23: Scattered gamma photons result in wrongly assumed LORs that increase the image background noise.

By measuring the energy of the gamma, it is possible to determine whether the detected gamma was scattered. Figure 24 shows a typically measured energy spectrum of a positron emission source: The photopeak is found at around an energy of 511 keV. Scattered gamma photons (with lower residual energy) are mostly found around the Compton plateau. The plateau reaches from the Compton edge (maximum energy loss by the incident photon through Compton scattering) to the backscatter peak (caused by gamma photons scattered back from surrounding material before detection). The histogram, furthermore, shows some counts with higher energy than the photopeak⁶, which are caused by detecting energy from more than one gamma photon.

The energy resolution describes how well the energy can be measured, and it thus represents the sharpness of the measured photopeak. An energy window can be set and a part of the scattered gammas can thus be rejected (then counting to the attenuated gammas). The mean path for a 511 keV photon in water is about 70 mm, so in clinical PET, most of the gammas are scattered. In preclinical applications, this depends on the size of the scanned animal: while for rabbits (with diameters around 160 mm) many gammas are scattered, this is not the case for mice (with a diameter around 30 mm). Nevertheless, the mouse-sized phantom studies (presented in chapter 6.2.4.1) have shown that a narrower energy window still

⁶ Additionally, the energy spectrum of ^{22}Na actually has a second small photopeak around 1.274 MeV. It is a single gamma photon, which is emitted when the nucleus decays from an excited state.

reduces the background noise of the images. Compton scatter also happens in the detector crystal array, where just a part of the gamma's energy is detected. The scattered gamma can either exit the scintillator area without further detection, or possibly be scintillated in a different crystal. In that case, it is not possible to calculate which crystal was hit first (and which represents the right crystal for the LOR). The probability function for the angle of the scattered gamma is a function of the energy from the photon to be scattered. It can be calculated by the Klein–Nishina formula (Klein and Nishina, 1929). For 511 keV, the main direction is still forward. Due to the long crystals (and previous scatter in the patient that reduced the gamma's energy), detector scatter is quite a problem for clinical scanners. In preclinical scanners, the probability is very high that a detector-scattered photon leaves the detector and is not detected a second time. Since these detections are thus valid, it makes sense to open the energy window further to lower energies (gaining sensitivity, but slightly increasing the background noise).

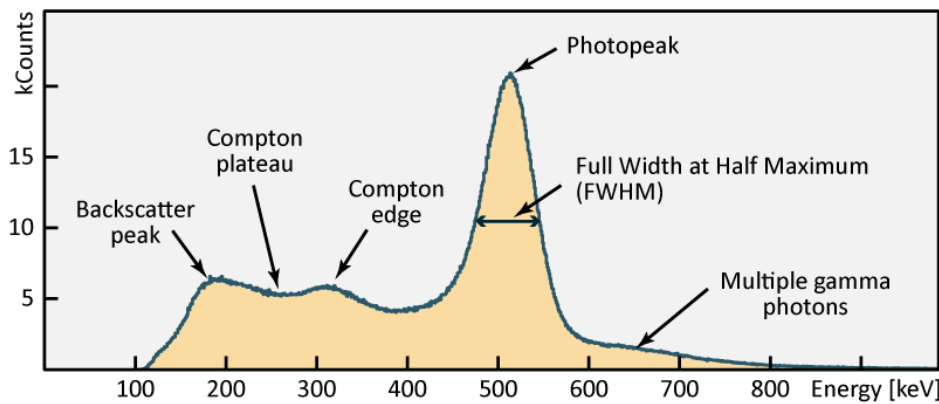


Figure 24: Energy spectrum of a ^{22}Na point source, measured with a detector stack of Hyperion II^D

A requirement on the energy resolution could be calculated from the angular error that is made when a scattered event is not rejected. The energy of a photon after Compton scattering is calculated from the Compton equation ($m_0c^2 = 511 \text{ keV}$ is the electron rest energy).

$$E'_\gamma = \frac{E_\gamma}{1 + \frac{E_\gamma}{m_0c^2}(1 - \cos \theta_c)} = \frac{511 \text{ keV}}{2 - \cos \theta_c}$$

Using this formula, which energy resolution is needed to detect that the photon was scattered can be calculated. Figure 25 plots this energy resolution over the scatter angle. Vice versa, this plot shows the minimum Compton scatter angle that can be detected, relative to the energy resolution of the system.

Limiting the undetectable scatter angle to the value with the unavoidable error produced by the noncolinearity (see section 3.1.1.3) would result in unachievably low energy resolutions. The lowest possible energy resolution is determined by the energy resolution of the scintillator material (see below). Standard values for complete preclinical systems are around 15 % to 20 % (see chapter 7.1). Even when reducing the energy resolution to 10 %, the resulting minimum detectable scatter angle would be 19° . Due to these for the most part undetectable angles, improving the energy resolution will have the effect of reducing the background noise, rather than directly deblurring the images. A requirement is thus not

fixed, but the target should be lower than the above stated standard values, thus lower than 15 %.

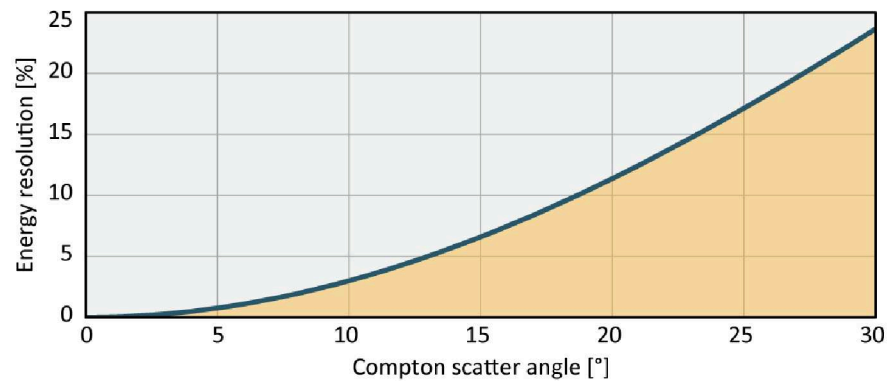


Figure 25: Energy resolution that is needed to detect that a 511 keV photon was Compton-scattered, over the scatter angle (and respectively: the Compton scatters that can be detected, relative to the energy resolution).

The energy resolution is influenced by the following factors (among others):

- Intrinsic Scintillator Energy Resolution

The intrinsic scintillator energy resolution for LYSO this is around 7.5 % to 9.5 % (Pidol *et al.*, 2004). It is furthermore affected by inhomogeneity in the crystal structure, and it thus depends on the optical quality of the crystal.

- Crystal Surfaces and Light Coupling

The energy resolution is reduced by lost scintillation light. The treatment of the crystal walls (e.g., polishing, roughening, or chemical etching) is thus as important as the reflective coating or wrapping (usually with aluminum foil or Teflon tape). In addition, the optical coupling to the sensor is prone to light losses, e.g., due to reflections when the fraction indices of the optical media change.

- Photo-Detection Efficiency (PDE)

The probability of detecting an optical photon hitting the sensor is described by the PDE. It is influenced, e.g., by the probability of generating a photoelectron (which is influenced by design parameters, such as the optical windows, the spectral sensitivity, and the doping layer order of solid-state detectors, but also by operational parameters, such as the bias voltage). For solid-state Geiger-mode devices, the number and sizes of the micro-cell play an important role, since they balance fill factor versus saturation effects (see chapter 4.2).

The singles energy resolution (also abbreviated as dE/E) is determined in a measurement by placing the energy of all the detected singles of a point source in a histogram and determining the FWHM value of the photopeak. The value is expressed in % of energy resolution (with respect to the 511 keV). Fitting a Gaussian curve over the peak to achieve noise-cleaned values is possible, but since the scattered events alter the tails of the peak in a non-Gaussian form, the fit is usually only made around the top part of the peak.

3.1.1.2 Time Resolution

Since the moment in time of the radioactive decay is only of a statistical nature, it is possible that two (or more) decays happen so quickly after each other that they are both within the coincidence acceptance window of the PET system. When all four, or three, of the gammas are detected, this situation is recognized and can be rejected (triple or multiple coincidences), even though both decays were not then detected. A different situation is even worse for the image quality: When single gammas are attenuated or a decay occurs outside the FOV, which directs one gamma towards the detector, the two remaining single gammas might accidentally be detected as a random coincidence (Figure 26).

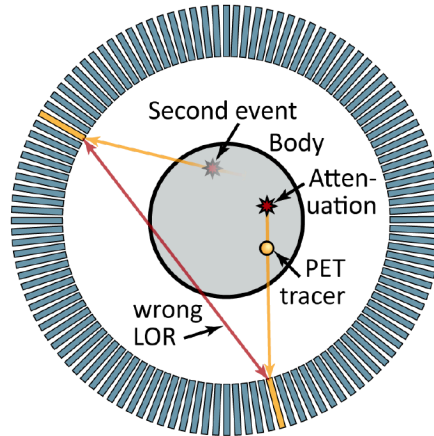


Figure 26: Random coincidence: Two single gammas of different events (the others are e.g., attenuated or the second event was outside the FOV) are detected simultaneously as a wrong LOR.

The Coincidence Resolution Time (CRT) describes how precisely the PET scanner can determine the point in time at which a gamma photon arrives at the detector. A good timing resolution allows for a short coincidence time window. This keeps the number of randoms low and is thus important when measuring higher activities.

When very high time resolutions (below 1 ns) are reached, it is useful to measure the Time-Of-Flight (TOF) difference between the two coincident gammas. As such, the position of the annihilation on the LOR can be localized (Figure 27). The uncertainty of the TOF measurement (described by the CRT) can be directly translated into the uncertainty of the position (by multiplying the speed of light). Further benefits include the possibility to separate the gammas originating out of the FOV, e.g., the LYSO background radiation. Another idea is to use this information to separate LORs from an additional transmission source around the patient for attenuation correction (Mollet *et al.*, 2014). The main benefit is not an increase in resolution, but a decrease of statistical noise in the reconstructed image. A theoretical discussion of the benefits of improved time resolution can be found in (Moses, 2003), and practical results are shown in (Karp *et al.*, 2008). The positive impact on tumor detection is reported in (Kadrmas *et al.*, 2009).

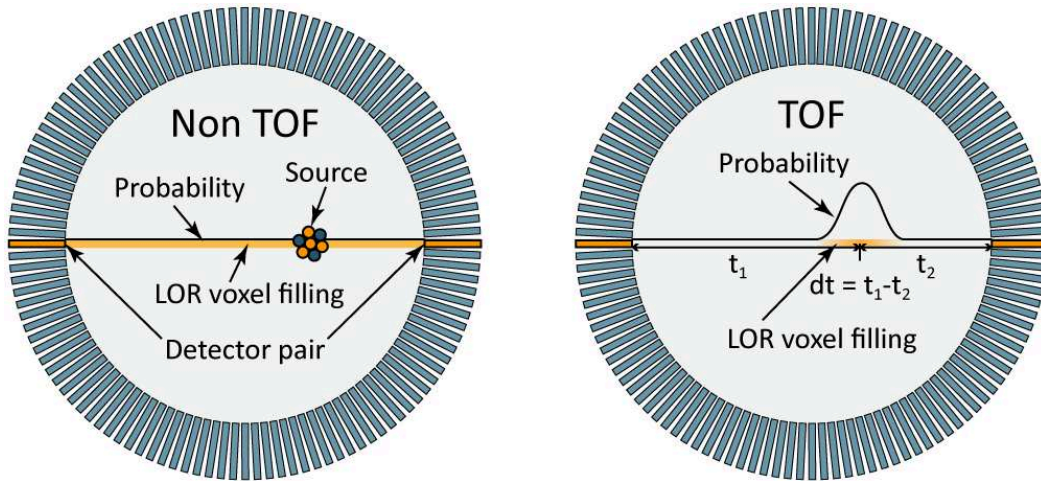


Figure 27: TOF-based image noise reduction: Normally (left), all voxels in a detected LOR, have the same probability and are thus filled equally. With TOF (right), the probability is defined by the uncertainty of the time difference measurement.

Requirements for the time resolution can be derived from the desired benefits. To be able to detect LYSO background, the CRT has to resolve the distance between the FOV and the scintillator. For benefits involving the image quality (by restricting the location of the detected decay along the LOR), the diameter of the measured subject is of importance. Statistical noise reduction from TOF information can be calculated as a multiplicative factor from the diameter D of the subject divided by the uncertainty Δx of the measured position (Moses, 2003):

$$f = \frac{D}{\Delta x} = \frac{2D}{c \times \Delta t}$$

In this formula, c is the speed of light and Δt the uncertainty in timing – the CRT. A different representation of the same formula is that a benefit from TOF can be expected when the uncertainty is less than twice the dimension of the origin of radiation. Light travels 10 cm in 330 ps. In clinical imaging, with patient diameters around $D=35$ cm, the TOF benefit thus theoretically starts ($f>1$) with CRTs shorter than $2D/c \approx 2.3$ ns. For rabbits with a diameter of around 16 cm, the needed CRT, where TOF theoretically starts is 1.1 ns. Nevertheless, in practice, values about twice as high ($f>2$) are needed to see subjective benefits from TOF. Therefore, for a rabbit with a diameter of 16 cm and a targeted noise reduction factor of 2, a CRT of 535 ps would be needed. Figure 28 plots the needed time resolution over the object diameter for $f=1$ and $f=2$.

For mice with a diameter of approximately 3 cm, the benefit starts at 200 ps, and 100 ps would be needed to reach the noticeable noise reduction factor of 2. CRTs in the range of 100 ps have so far only been demonstrated in single-crystal experiments with very short and hydroscopic scintillation crystals (Schaart *et al.*, 2010). It is thus not realistic to reach this target at the same time as fulfilling all other requirements (especially an adequate sensitivity, which forbids the use of very short crystals). The CRT requirements for TOF are thus only set for rabbit-sized imaging.

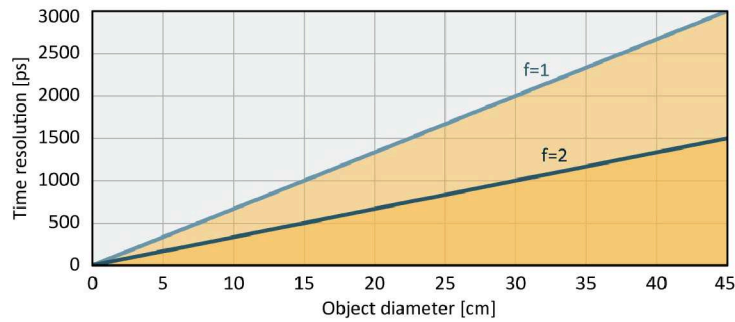


Figure 28: Needed CRT over the object diameter, where the benefit of TOF information theoretically starts ($f=1$) and where a difference becomes practically visible ($f=2$).

The timing resolution of a system is influenced by all the components involved in the measurement of the time difference. These primarily include:

- Scintillator Pulse Shape

The scintillator is the first component in the detector chain, and there are many attributes influencing the time resolution (Lecoq *et al.*, 2010). Most important is the scintillator material itself, including its doping, defects, and impurities. In addition, the length and surface treatments play a large role. When the photons travel through the crystal, they take different paths: whereas some photons exit directly, others undergo multiple reflections (resulting in longer time to exit and higher loss probability).

- Detector Time Resolution

The conversion from light to an electric signal and its amplification are subject to statistical variations, and thus influence the timing. In a PMT, e.g., the photoelectrons travel different distances to the first dynode, resulting in different delays. In APDs (chapter 4.1), the avalanche process forbids its use for TOF applications in PET, and a lot of effort is put into the optimization of SiPMs (chapter 4.2) for TOF (Gundacker *et al.*, 2012). The same is true for the operation of the SiPMs, as, for example, the overvoltage influences the PDE, and thus the timing resolution. Furthermore, the detection circuits influence the timing, e.g., by the way the timestamps are generated, with different amplifications, trigger thresholds, or noise on the electronic lines.

- Infrastructure

The infrastructure for the detector plays an important role, as the distributed timestamp-generating circuits need a reference clock to run synchronously. All jitter between the different clocks will add to the uncertainty of the time measurement. Furthermore, ripples on the supply voltages can influence the Time-to-Digital Converter (TDC) circuits (see section 3.1.2.3).

The CRT can be measured with a point source in the center of the FOV. All measured coincidence time differences are placed in a histogram, and the CRT is expressed as the FWHM value. When multiple point sources are used, the detected LORs have to be assigned to their originating source in order to count for the distance between them. The calculations are then made for each source individually and the results are averaged afterwards.

3.1.1.3 Spatial Resolution

The spatial resolution describes how well two voxels in an image can be separated. The spatial resolution is affected by multiple factors, and the most important are listed as follows and sketched in Figure 29:

- Position Estimation Accuracy:

For pixelated detectors the intrinsic resolution is given by the detector crystal pitch d . Close to the axis of the scanner it is generally $d/2$, gradually changing to d close to the detector.

- Positron Range:

The positron range depends on the decaying nucleus (following a certain distribution due to the emission energy) and on the matter it travels through (see section 2.1.1). Since the position of the annihilation, and not the position of the decaying atom, is imaged, this effect contributes to the spatial resolution with an error. In water the effective positron range for ^{82}Rb ($E_{\beta^+, \text{max}} = 3.35 \text{ MeV}$) is 15.5 mm. For ^{18}F ($E_{\beta^+, \text{max}} = 640 \text{ keV}$) it is 2.2 mm. The resulting errors R_p are 2.6 mm for ^{82}Rb , and 0.2 mm for ^{18}F (Tarantola *et al.*, 2003). The path of the positron can be influenced by a magnetic field, since it is inherently present in a PET/MRI application, but positive effects on the positron range are only expected at field strength higher than 7 T (Raylman, 1996).

- Noncolinearity:

At the end of the positron range, the momentum of the positron is not zero, when it annihilates with an electron (which also has a kinetic energy greater than zero). Due to the conservation of energy and impulse, the two gammas are not emitted at exactly 180° . The maximum deviation is 0.5° FWHM. The resulting angular error depends on the diameter D of the PET detector ring: $R_a = 0.0022 \times D$ (Saha, 2010).

- Depth-Of-Interaction (DOI):

Also known as radial elongation, parallax error, or radial astigmatism. A pixelated detector with long, thin crystals is normally not able to determine where the gamma was scintillated on the long axis of the crystal. This uncertainty between the top and bottom of the crystal degrades the spatial resolution towards higher radii of the FOV. Depending on the position, this effect influences all dimensions differently, and the point spread function is, thus, no longer homogenous. Measurements on multiple clinical (BGO-based) PET scanners have shown that the spatial resolution deteriorates on average from 4.5 mm in the center of the FOV to 8.5 mm at a radius of 20 cm (Adam *et al.*, 1997).

- Localization:

Normally, the light from the crystals is sensed by a few detectors, and the position of the crystal is calculated, for example, using the Anger method. With inexact input data, due, e.g., to different gains of the detectors, the position is calculated wrongly. A difference between the real mechanical positions of the crystals and their intended positions, assumed by the reconstruction, also has an influence (Salomon *et al.*, 2013).

Since the spatial resolution is influenced by so many parameters, ET scanner geometries should be simulated before it is built. This can be done, e.g., by performing a Monte Carlo

analysis with GATE, a Gant4-based simulation platform for PET and SPECT systems (Jan *et al.*, 2004). As such, it is also possible to simulate the limits for a certain scanner geometry: For ^{18}F and a scanner diameter of 20 cm, the system spatial resolution limit (in FWHM) is ~ 1 mm for 1.3 mm crystals (Levin and Hoffman, 1999). Furthermore, it is possible to simulate the fundamental limits for the spatial resolution, which is around 0.4 mm for ^{18}F (Cherry, 2006).

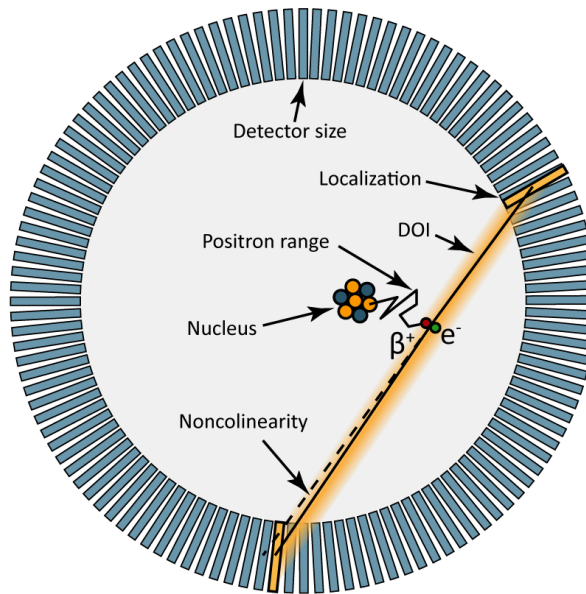


Figure 29: Factors influencing the spatial resolution of a PET detector: detector size, positron range, noncolinearity, and the DOI effect.

The spatial resolution is usually expressed as a one-dimensional point source resolution in the center of the FOV, or slightly off-center to stay out of regions with extreme positive or negative influences of the detector symmetries. The three-dimensional equivalent is the volumetric resolution in mm^3 : a multiplication of the one-dimensional resolution off all three spatial directions. Requirements for the spatial resolution can be defined by the size of the geometries to be measured. The heart of a mouse has a diameter of 5 mm with an intraventricular septum thickness of 1.3 mm to 1 mm (Doevendansa *et al.*, 1998). The spatial resolution requirement is thus 1 mm, or, expressed as volumetric spatial resolution, 1 mm^3 ($1 \mu\text{l}$).

The spatial resolutions are measured as FWHM values by fitting Gaussian functions in three dimensions over high-resolution point sources with a diameter of $250 \mu\text{m}$. The National Electrical Manufacturers Association (NEMA) ⁷ conform measurement demands the use of a Filtered Back Projection (FBP) reconstruction to exclude resolution-improving features of the reconstruction algorithm (such as point spread function resolution recovery). Nevertheless, using the normal reconstruction for imaging gives a more meaningful result of the spatial resolution achieved in real life. Therefore, this value is often stated in the literature and should be confirmed, as described in section 3.3.1, with hot-rod-phantom experiments.

⁷ <http://www.nema.org>

3.1.1.4 Sensitivity

The sensitivity describes how many radioactive decays of the tracer are correctly detected by the PET system and used for the reconstruction of the image. The values are normally displayed in percentages for a point source in the center of the FOV. Since the sensitivity depends highly on the position of the source (due to the solid angle towards the detector), the NEMA protocols include a sensitivity profile along the center axis. Apart from this point sensitivity, further representations exist, such as line- and volume sensitivity.

It is difficult to set strict requirements for the sensitivity, as it depends on the image quality of the final scanner. The question to answer would be how many counts are necessary to produce the needed contrast for the targeted application. This depends, e.g., on the decay time of the tracer, how much activity can be injected into a subject, the uptake in the organ of interest, or the available scan time (see section 3.1.1.3). The sensitivity of currently commercially available and experimental prototype preclinical PET scanners is reported to be between 0.1 % and 10 %. The average of all the systems presented in chapter 7.1 (excluding the quadHiDAC, which has no energy discrimination at all) is 3 %. This value can thus be considered as a target requirement.

The sensitivity is mainly influenced by the following efficiencies and settings:

- Geometric Efficiency

The geometric efficiency is defined by the percentage of the solid angle of the PET detector that covers the source of radiation. Long, thin scanners thus have a higher efficiency than short scanners with a large diameter.

- Detection Efficiency

The detection efficiency describes how well a gamma ray is detected when it hits the detector. This value is mainly influenced by the stopping power of the scintillator material, its fill factor, and its length. A design specification for the crystal length can be derived by the attenuation length, where the probability has dropped to $1/e$ that the gamma has not been stopped (≈ 63 % of the gammas were stopped). That is, e.g., 21.3 mm in LaBr₃, 14.2 mm in GSO and 11.2 mm in LYSO.

- Energy Windows

The gamma rays are scattered in the subject itself as well as in the detector. A small energy window can be used to reject the scattered events. This, however, also reduces the sensitivity, since, for instance, valid events (that have been scattered once in the detector and then escaped) are also cut.

- Dead Time

Once a sensor detects a signal it has to be read out and then reset afterwards. During this time, the detector is “dead” in a certain area, and a second signal during this time cannot be detected. There are many origins of dead time in a system (e.g. SiPM cells hit (see chapter 4.2), Application-Specific Integrated Circuits (ASICs) processing a channel, or data lines busy transporting hit information), and thus the dead time is highly dependent on the architecture. Additionally, the time resolution of the scanner has a direct influence on the dead time.

The point sensitivity can be measured with a small and weak point source in the center of the FOV. As such, scatter- and random-coincidences and detector dead time can be neglected. The sensitivity is the ratio of the coincidence count rate divided by the real activity of the source (taking the electron capture to positron branching ratio of $e^-/\beta^+ = 0.1079$ into account). Since the scintillator material LYSO is slightly radioactive and able to produce valid coincidences, this background has to be subtracted first (by measuring the count rate without the point source). As the sensitivity is directly proportional to the coincidence count rate, changes of the sensitivity (due to e.g. MRI activity) can be seen over time in the count rates curves, which is the representation most often used in compatibility studies.

3.1.1.5 Tracer Activity and Scan Time

Directly connected to the requirements of the sensitivity are the activities of the tracer used and the scan time. The used tracer activity depends on the subject scanned, the uptake in the organ of interest, the tracer, and the available scan time. The upper limit is often given by the maximum quantity of fluid that can be injected. For mouse imaging and ^{18}F -FDG, that limit can be estimated from the available tracer: When the hospital or research facility does not have its own cyclotron, the tracer has to be produced by a third party and delivered to the place of the measurement. During delivery, the tracer is already decaying. A production activity concentration of 500 MBq/ml and 80 minutes delivery time will result in a concentration of about 300 MBq/ml (this is already a research purpose concentration, delivered for the measurements in this thesis, which is much higher than the normal clinical concentration). If the tracer is injected two hours after delivery, the concentration will have dropped to 140 MBq/ml. The maximum volume that can be injected into a mouse is about 10 % of the blood volume, which is roughly 8 % of the weight. For a mouse with a weight of 19 g, this results in a volume of 150 μl (significantly higher volumes can even be lethal). The resulting maximum activity is thus 21 MBq. On the other hand, the activity is often lower, as the tracer should not change the metabolism itself (a maximum receptor occupation by the tracer of 1 % should not be exceeded, leading to activities as low as 0.1 MBq (Hume *et al.*, 1998)). The typical activity applied to mice is about 10 MBq. For rats it is 30 MBq (Mackewn *et al.*, 2015b). Imaging of rabbits is often performed with maximum activities of 30 MBq to 150 MBq. The average of 90 MBq can thus be perceived as a target requirement for rabbit imaging.

The scan time faces similar dependencies. In relatively simple oncology studies using ^{18}F -FDG as a tracer, it is possible to scan for hours. For mice imaging, the time under anesthesia, which is about four hours, is the limiting factor. An example of the opposite – short scan times – would be a dynamic cardiac study using ^{15}O with a half-life of 2.03 minutes: in (Herrero *et al.*, 2006), 40 data points are taken within 2 minutes, resulting in a scan time of 3 seconds per data point.

Additionally, the maximum scan time per day has to be taken into account, as this defines the minimum time the system needs to be running, before pauses (e.g., to process, compress or move the data) are allowed. This could be a complete workday of 8 hours. Much higher scan times per day are not expected, as the experiments need additional time for preparation, and ethics forbid a too dense (and thus risky) schedule. Additionally, the availability of radioactive tracer is a limiting factor, as it decays throughout the day.

3.1.1.6 Other Performance Parameters

There exist further, more detailed performance parameters that characterize a PET system. Some of them are defined by the NEMA protocols. They are not measured or calculated throughout this thesis, since an influence from the MRI can already be studied according to the parameters described above and no further influence on these parameters has been thus far described.

Examples are:

- Nose Equivalent Count Rate (NECR)

The NECR characterizes the image noise, which is proportional to the SNR in the final reconstructed image. It can be calculated as $NECR = T^2/(T+S+R)$, where T are the true counts, S the scattered coincidence counts, and R the random coincidence counts. The NECR (or the linearity of the NECR over the activity) is often used to compare the performance of PET scanners. TOF capabilities are normally (especially in the NEMA definitions) not integrated into this value. Modifications, such as a factor of $\sqrt{D/\Delta x}$ are discussed (Conti, 2006).

- Scatter Fraction (SF)

The SF is the ratio between scattered and prompt count rates. Lower values indicate better image quality.

- Recovery Coefficient (RC)

The ratio between measured and real activity in an image.

- Contrast Recovery Coefficient

Shows how well activity can be revealed in backgrounds. The contrast recovery coefficient is defined for hot and for cold spheres.

3.1.2 Interferences from MRI

3.1.2.1 Static Magnetic Field

The static magnetic field of standard clinical MRIs has a field strength of 1.5 T to 3 T. As a reference: The earth's magnetic field has a field strength of 48 μ T at 50° of latitude. Standard horseshoe magnets have a flux density of around 100 mT. The maximum flux density of a neodymium magnet (NdFeB) is 1.61 T. Most modern MRI magnets are actively shielded (by outer counter-windings) to reduce the fringe field outside the bore. The result is a lower field strength far away from the magnet, but also higher fields (up to double the nominal field strength) close to the magnet. Especially the spatial gradients of the static magnetic field are increased, and these are responsible for torque forces on magnetic material and for pulling them into the bore. Although this effect seems trivial, it has an impact on all components that are brought into the MRI examination room: if the component is not stationary, it can become a safety hazard (especially when used by different personnel during time-pressured measurements).

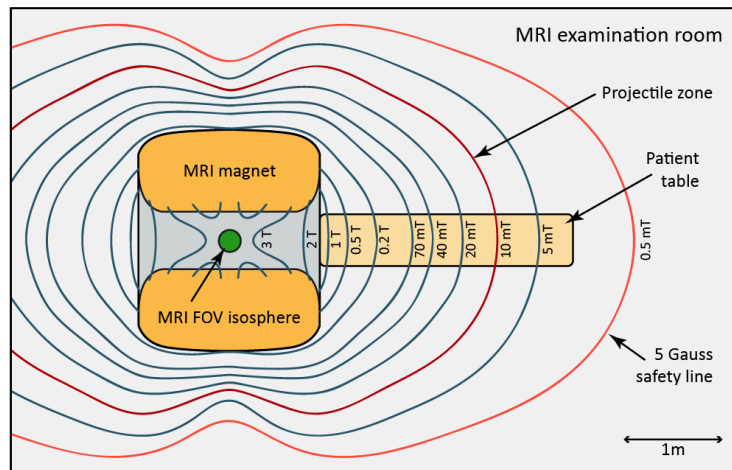


Figure 30: Fringe field of Philips 3T Achiva MRI, shown as isolines of magnetic flux density. The 0.5 mT line is defined as the 5 Gauss safety line: only special MRI equipment is allowed inside this area. Around 10 mT the “projectile zone” begins, where ferromagnetic parts can be dangerously accelerated toward the magnet.

The static magnetic field itself has an influence on the behavior of many electronic components, as the Lorentz force acts on the moving charges in them. This is the reason, for instance, why Gallium Arsenide (GaAs) transistors, despite having superior noise performance than silicon-based transistors, are seldom used in MRI RF receive coils. Due to their high electron mobility, the gain changes with the orientation to the magnetic field of the scanner. A different example are ferrite materials: They already saturate at a field strength around 0.5 T (Chikazumi, 1997), and thus lose their function. Ferrite material is often used as cores for inductors > 500 nH, or in Electromagnetic Interference (EMI) filters, and all the electronic components and circuits based on them can thus not be used. Secondary effects of the magnetic field are already noticeable at low magnetic fields (even lower than 0.5 mT (5 Gauss)): For example, electric motors begin to wobble, which results, among other things, in a lower lifetime of all electric ventilators in the MRI examination room. The same lower lifetime is noticed for incandescent light bulbs (often used inside the MRI examination rooms for their low electromagnetic emissions), where the 50 Hz or 60 Hz of the power net inside the magnetic field results in small vibrations of the lighting filaments.

The Lorentz force also affects the main component currently used in all commercially available PET/CT scanners: the PMT. PMTs convert the light from the scintillation crystals to electrons and amplify them to a measurable current. Photons hitting the photocathode layer at the front of these tubes release electrons, and the electrons are accelerated in electrical fields between a series of dynodes where they release more and more secondary electrons. The PMT is very sensitive to magnetic fields, since the electrons traveling multiple cm through the vacuum of the tube and the usage of PMTs inside the MRI is thus not at all possible.



Figure 31: Photomultiplier tube for scintillation counting applications (420 nm peak sensitivity), such as PET (Hamamatsu, Japan). Diameter: 38mm. Anode to cathode supply voltage: 1500 V.

3.1.2.2 RF Excitation and Coils

The RF coil sends B_1 pulses at frequencies of around 128 MHz for proton imaging at 3 T to excite the spins. With peak flux densities of up to 35 μT , the pulses can have a peak power of several kW (the maximum amplifier output for the standard Philips 3T Achieva is specified as ≥ 18 kW). The high voltages induced by these fields can lead to the destruction of electronic devices. A reference estimation for the RF induction can be made using values from the targeted system: The voltage induced in a circle with a diameter of 65 mm (width of the SPU, see chapter 5.1.1.2) by a B_1 of 35 μT (maximum power of the used RF coil, see chapter 6.1.5):

$$V = A \frac{\partial B}{\partial t} = A \omega B_1 = 3318 \text{ mm}^2 \times 2\pi \times 128 \text{ MHz} \times 20 \mu\text{T} \approx 93 \text{ V}$$

In a circle with a diameter of 40 cm (width of the gantry – see section 5.1.3) the same field would induce a voltage of 3.5 kV (the dielectric strength of air is around 3 kV/mm). It is thus important to keep the electronics away, or shielded, from these fields. When long cables (e.g. power supply cables) are placed into the RF field, common-mode currents can be generated on these cables. This effect not only deteriorates the strength and homogeneity of the B_1 field (see section 3.2.2), it also transports the power to other electronics outside the bore (e.g., the respective power supply). Furthermore, depending on the transfer impedance of the used cable, this can also result in differential mode currents able to destroy the electronics on both ends of the cable. Ferrite beads and baluns are normally used in such cases to suppress common-mode currents. They are effective common-mode suppressors, as they can be used in broad frequency ranges and convert large portions of the energy to heat, thereby reducing resonances on the cables. Unfortunately, they do not work in close proximity to the magnet (the ferrite material gets saturated), and therefore large, expensive alternatives, such as “bazookas” (quarter-wave sleeve baluns), have to be used. They also have further disadvantages, e.g., that they have to be tuned to the right frequency and that they are exposed to risks of cable resonances and coupling through RF stray fields.

Placing the transmitting coil inside the PET gantry reduces many of these problems, although it gives rise to others. At least the receiving RF coil has to be placed close to the patient (to achieve a good SNR), and thus inside the PET gantry. As a result, the gammas to be detected by the PET detector have to travel through the coil. The gammas can get scattered and attenuated by dense parts of the coil (e.g. ceramic capacitors, or metal rods), which may lead to image artifacts and incorrect tracer uptake quantitation (MacDonald *et al.*, 2011). A reference estimation can be calculated for the γ attenuation: The intensity of a γ ray, when it passes through matter is calculated as:

$$I(x) = I_0 \times e^{-n\sigma x} = I_0 \times e^{-\mu x}$$

where n = the number of atoms per volume, and σ is the absorption cross section per surface. The total absorption coefficient μ is depending on the energy of the γ . At 500 keV, e.g., this is $\mu_{\text{Air}} = 11.2 \text{ km}^{-1}$, $\mu_{\text{Water}} = 97 \text{ m}^{-1}$, and $\mu_{\text{Copper}} = 730 \text{ m}^{-1}$. Expressed as Half Value Layer (HVL), the length after half the intensity is left (equivalent to the half life value used for radioactive decays), this is $\text{HVL}_{\text{Air}} = 61.89 \text{ m}$, $\text{HVL}_{\text{Water}} = 71.5 \text{ mm}$, and $\text{HVL}_{\text{Copper}} = 9.5 \text{ mm}$. The value for copper is close to the thickness of the copper rods used in the build-in body coil of the MRI systems used. The HVL of lead is 4.2 mm - approximately the thickness of the solder joints for the large high-voltage ceramic capacitors used in the RF coils (see Figure 86).

3.1.2.3 Gradient Switching

The gradient amplifier of the MRI system drives the gradient coils, depending on the availability of the dual amplifier option and their configuration, with several hundreds of volts and amperes. In the parallel amplifier configuration (mode 1), the fields of up to 0.040 T/m can be built up with slew rates of up to 200 T/m/s on one axis (346 T/m/s effectively). The spectrum is in the kHz-range, and it is thus difficult to shield electronics from these fields – especially without disturbing the intended field pattern. The gradients are supposed to alter the static magnetic field, and thus should produce only fields in the axial direction of the scanner. Nevertheless, there are always transaxial field components, because magnetic field lines have to be closed. More precisely, magnetic fields are source free, as described by Gauss's law for magnetism $\vec{\nabla} \cdot \vec{B} = 0$. Consequently, magnetic flux lines have no beginning and no end, and they thus either form closed loops or extend to infinity. Figure 32 sketches the field lines of the different gradients (more precise 2-dimensional drawings based on simulations are shown in Figure 106 of chapter 0).

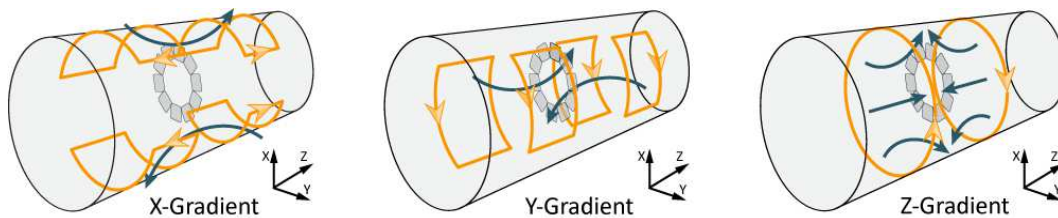


Figure 32: Sketch of gradient coil windings (orange) and the resulting field lines (blue). A cross section of the intended PET gantry is indicated in dark gray to illustrate the impact on the PET electronics.

Consequently, unless placed exactly in the isocenter, electronics in the MRI bore will always experience magnetic flux changes, which leads to induced voltages in the circuits. The results can be lost data in digital communication, wrong triggers, or false values in analog circuits. The consequences for PET would be degradations of all performance parameters. E.g., too high or too low analog values can influence the energy resolution. As a secondary effect, the sensitivity can be decreased when valid detections are pushed out of the energy window. A different example of an influence on the sensitivity would be false signals triggering the readout of the sensors: Although this trigger would be rejected by the validation thresholds, it imposes a dead time for the detector, leading to a reduced sensitivity. A reference example can be calculated by placing a printed circuit board (PCB) 15 cm away from the center of the FOV. The magnetic flux change at that position using the slew rate of 200 T/m/s is:

$$\frac{\partial B}{\partial t}(r = 15\text{cm}) = 200 \frac{T}{m \times s} \times 15\text{cm} = 30 \frac{T}{s}$$

A single-ended signal line over a ground plane that connects an analog sensor to the digitizing chip is now considered. These lines are normally not directly straight connections, but mostly laid out in 45° or 90° angles. The return current in the ground plane for low frequency signals does not follow that path, but instead takes the straight path. A line with 50 mm upwards and 50 mm to the side would span a triangular area of 1250 mm², resulting in an induced voltage of:

$$V = A \frac{\partial B}{\partial t} = 1250\text{mm}^2 \times 30 \frac{T}{s} \approx 37.5 \text{ mV}$$

Careful PCB routing is thus very important. From an EMI point of view, a differential line would be advantageous: On a standard 4-layer PCB with a distance of 350 µm between the tracks and a length of 10 cm, the line would pick up a voltage of 1 mV. For analog signals, this might still be too much, so techniques, such as twisting the tracks, might have to be used.

Voltages can also be induced in the power supply networks and ground planes, which can lead to ground bounces and ripples on the supply voltages. A reference estimation can be made with a circle with a diameter of 65 mm (again the diameter of the SPU, which is introduced later in this thesis). Placed normal to the axis of the MRI, at a distance of 15 cm from the isocenter, the large slew rate of 200 T/m/s will induce a voltage of 100 mV. When not filtered properly, these ripples can have the same effects on the signal lines as induced voltages, e.g., through a provoked jitter on circuits such as Voltage Controlled Oscillator (VCO), Phase-Locked Loop (PLL), or Delay-Locked Loop (DLL).

In conductive structures, the induced voltages result in eddy currents. Especially prone are large structures, such as heat sinks, RF-shielded housings, and ground loops, for instance, in power supply cablings. In low-ohmic supply and ground planes of PCBs these currents can become very high, which results in the direct heating of the electronic devices soldered to them. The reference example given above can be extended to gradient-induced eddy currents and heating: Assuming a circular shaped PCB with a ground plane placed on the axis of the MRI bore, perpendicular to the axis, and at a distance of ΔZ away from the center ($Z=0$) of the FOV (Figure 34).

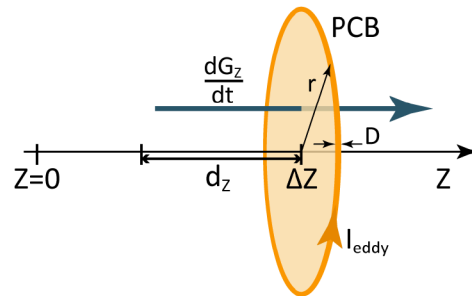


Figure 33: Geometry (left) of a circular PCB plane with thickness D , placed at a distance ΔZ of on the Z -axis. The switching gradient dG_z/dt induces an eddy current I .

The induced voltage U is derived from the law of induction, and the sheet resistance of the circle can be calculated with the circumference C , the thickness D and the conductivity of copper σ . The dissipated power P is then described as:

$$U = \frac{dB}{dt} A = \frac{dB}{dt} \pi r^2, R' = \frac{C}{\sigma D} = \frac{2\pi r}{\sigma D} \Rightarrow P = \frac{U^2}{R'} = \frac{\sigma D \pi r^3}{2} \left(\frac{dB}{dt} \right)^2$$

The total dissipated power during gradient switching can be calculated by integrating over the radius of the PCB:

$$P(R) = \int_0^R P(r) dr = \frac{\sigma D \pi}{8} \left(\frac{dB}{dt} \right)^2 R^4$$

A standard copper ($\sigma=5.96E7$ S/m) ground plane with a thickness of $D=35 \mu\text{m}$ (1 oz/ft²) and the SPU diameter of $R=65$ mm thus result in a power dissipation of 8.2 W. The gradients do not switch all the time. A duty cycle of 10 % can be assumed (see example values in Table 7 of section 3.1.3). Taking into account that the PCB has three ground planes, the total extra power dissipation during the MRI scan would be around 2.5 W. The PCB will thus heat up during the MRI activity, and, as a result, e.g., the operational points of transistors or the gains of sensors can change over time.

A secondary effect is the mechanical forces caused by the high alternating currents in the magnetic field. The resulting vibrations can be coupled mechanically to the PET detector (e.g. from the gradient coil) or can originate from the eddy currents inside the detector electronics. These mechanical forces and vibrations can influence the lifetime of the detector.

3.1.3 Combined Verification Experiment

The PET performance parameters are tested in a single combined test. Seven ²²Na point sources, together amounting to an activity that would be injected in a typical ¹⁸F-FDG mouse study, are placed in a horizontal row and measured for more than 20 minutes. During that scan, three MRI sequences are executed: a T₁-weighted (T₁w) TSE (using RF pulses for the echo trains), T₁w 3D FFE (using gradients for the echoes), and an EPI sequence (using gradients with very high slew rates). Apart from small changes, such as Number of Signals Averaged (NSA) to make them all about three minutes long (TSE/FFE: NSA6; EPI 7: 10 slices, NSA 12), they do not differ from the sequences that will be used in the SNR measurements (see section 3.2.2). Details of the sequences are listed in Table 6 and Table 7.

MRI sequence	ETL/ES ^a [ms]	TR/TE ^b [ms]	NSA ^c	FA ^d	pixel bandwidth	slices	ST ^e [mm]	scan time
T₁w aTSE	6 / 5.7	612 / 20	6	90°	640 Hz	1	2	3:12 min
T₁w 3D-FFE	1 / -	11 / 2.3	6	35°	434 Hz	20	2	3:14 min
EPI 7	7 / 1.9	34.9 / 9.1	12	20°	656 Hz	1	4	2.55 min
^a) Echo Train Length / Echo Spacing					Image size : 160 mm × 160 mm			
^b) Repetition Time / (effective) Echo Time					Pixel size: 500 μm × 500 μm			
^c) Number of Signals Averaged					Acquisition matrix: 320 × 319 pixels			
^d) Flip Angle					Slice selection gradient direction: Z (head-feed)			
^e) Slice Thickness								

Table 6: MRI sequences to test the influence of MRI on PET.

Table published in the supplemental material of (Weissler *et al.*, 2015a) ©2015 IEEE.

MRI sequence	Slew Rates, Duty Cycle (X-gradient: phase)	Slew Rates, Duty Cycle (Y-gradient: frequency)	Slew Rates, Duty Cycle (Z-gradient: slice)
T₁w aTSE	58.8 T/m/s, 0.7 %	193.78 T/m/s, 1 %	94.4 T/m/s, 0.6 %
T₁w 3D-FFE	101.8 T/m/s, 6.6 %	98.68 T/m/s, 5.7 %	58.1 T/m/s, 7.3 %
EPI 7	203.8 T/m/s, 9.6 %	203.8 T/m/s, 12 %	121.6 T/m/s, 3.6 %

Table 7: Slew rates and duty cycles of the MRI sequences to test the influence of MRI on PET.
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3.2 MRI and the Influence from PET

3.2.1 B₀ Homogeneity

The static magnetic field has to be very homogeneous in the range of about a few ppm. A distortion by the PET detector leads to signal loss, wrong flip angles (Wang *et al.*, 2006a), and spatial displacement of voxels in the MR image (Schenck, 1996). The maximum distortion permitted in a certain volume Region Of Interest (ROI) depends on the targeted application. The limit can be estimated by calculating the displacement of a pixel caused by the distortion. Assuming a maximum allowed displacement of 0.5 mm (half the spatial resolution requirement for PET) and a low readout gradient of $G_R = 6$ mT/m (lowest readout gradient is limited by the receiver bandwidth). The resulting limit is $\Delta B_0 = \Delta X \times G_R = 3$ mT. Expressed as peak-to-peak value in parts per million (ppm) for 3 T, this would result in a requirement of 2 ppm. The same value is stated by the “Magnetic Resonance Imaging Quality Control Manual” (American College of Radiology, 2004) as a typical value, which can be measured over a 30 to 40 cm diameter sphere in clinical MRIs.

Magnetic Resonance Spectroscopy (MRS) has much stricter requirements, although it has to be kept only within a small ROI (e.g., in 2² cm³ of the human brain). Frequently used metabolites in MRS of the human brain are choline (Cho), a cell membrane metabolism marker at 3.2 ppm frequency difference to ¹H in water, and creatine/phosphocreatine (Cr), an energy metabolism marker, which is often also used as a reference peak at 3.0 ppm frequency difference. To distinguish the two peaks, being 0.2 ppm apart, a B₀ homogeneity of 0.1 ppm is needed in single voxel spectroscopy. Since the signal is the integral over the volume, the Volume Root Mean Square (VRMS) value (Havens *et al.*, 2002) has to be judged in this case. It is defined as:

$$V_{rms} = \sqrt{\frac{1}{V} \int_V (B_z(\vec{r}) - B_z(\vec{0}))^2 dV}$$

Where $B_z(\vec{r})$ and $B_z(\vec{0})$ are the z components of the magnetic field and the center of the FOV. The VRMS values are often used by the industry to specify their systems – e.g., the typical homogeneity within a 30³ cm³ ROI from a Philips 3T Achieva is guaranteed to be below 0.16 ppm VRMS (Philips Healthcare, n.d.).

To mitigate B_0 distortion, all components brought into the MRI bore have to be tested for magnetic material. First checks involved a simple test of attraction to a neodymium bar magnet. These experiments give an indication, but they are not precise enough for small electronic components, since the size and weight of the components have a large influence. Therefore, a device was built to measure field distortions caused by small components. Four 3-D magnetometer Integrated Circuits (ICs) (HMC5883L, Honeywell International Inc.) were placed on a PCB, together with completely non-magnetic supporting capacitors. A coil, made from PCB traces around the ICs, allows a known magnetic field to be produced (although the earth's magnetic field was sufficient for all the experiments conducted). The device being tested, placed on top of the sensors, deforms this magnetic field, which is then measured by the magnetometers (see Figure 34).

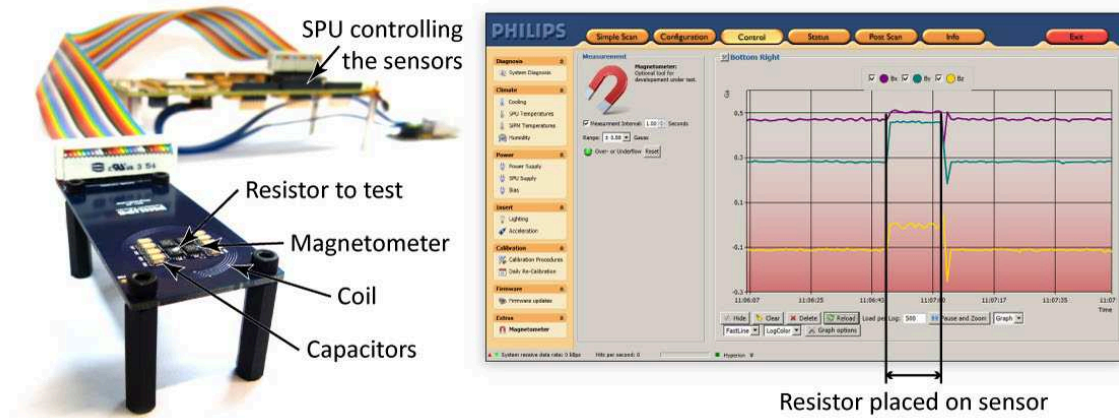


Figure 34: Test for magnetic material using the magnetometer-PCB: A standard resistor in an 0402 package (1 mm × 0.5 mm × 0.3 mm) is placed on a magnetometer (left). The result (right) is 50 %-change of the measured B -field in y -direction (short side of the PCB).

The final acceptance test and selections are made with an MRI scanner. That method is very sensitive and directly measures the effects that need to be minimized – including saturation effects. A gradient echo imaging sequence with activated B_0 -field-map feature is used. The sequence measures two images with slightly different echo times. The phase differences $\Delta\Phi$ in each voxel is calculated as follows:

$$\Delta B_0 = \frac{\Delta\phi}{2\pi\gamma\Delta TE}$$

ΔTE , also named $TE_{\text{extension}}$, is the difference in echo time between the two images. To avoid phase wrappings, but to maximize the SNR, this value has to be chosen in a way that a phase wrapping is visible slightly outside the ROI. The method is further discussed in (Funai *et al.*, 2008)).

The distortion caused by small objects, such as electronic components, can be evaluated by placing them, e.g., on a coronal body phantom (400 mm diameter, 100 mm height) filled with mineral oil (Figure 35). The B_0 map of the almost homogeneous field in the center of that phantom shows the distortion by the component. Subtraction of a Gaussian-blurred (to reduce noise) reference scan of the phantom reduces the influence of distortions from the magnet and the phantom. The components to be tested can be compared by measuring the distance needed to remain below a certain distortion.

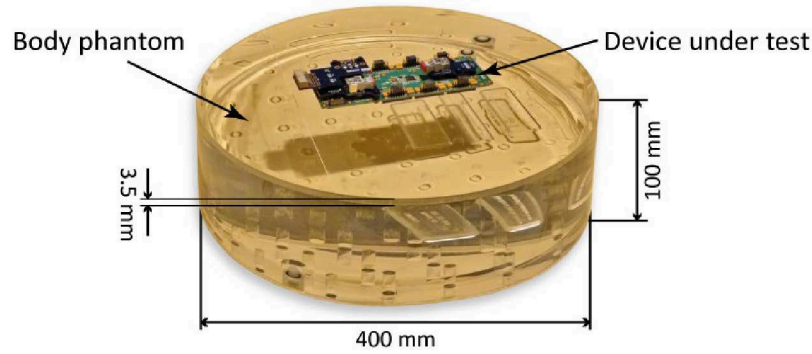


Figure 35: Test setup to determine the B_0 distortion caused by single devices or subunits. The device being tested is placed on a coronal body phantom, which is moved to the center of the FOV in the MRI bore.

Using a similar measurement, it is possible to show the phase image (besides the normally used magnitude image, it is also possible to calculate real-, imaginary-, or phase images from the k-space data). As the phantom is filled homogeneously, the phase image should be homogenous as well. As a reference example for B_0 distortions caused by electronic components, Figure 38 shows the distortion caused by a single standard Surface-mounted device (SMD) ceramic capacitor placed on the phantom. Its influence is noticeable to roughly about 40 mm below the capacitor.

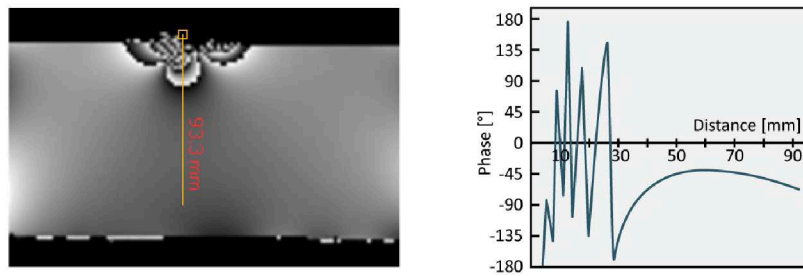


Figure 36: Distortion in the phase image of homogeneously filled phantom (left) caused by a single standard ceramic capacitor (10 μF , 16V, 1206 SMD housing), placed at the position of the yellow square. Transitions from black to white are phase wraps from -180 to $+180^\circ$. The profile along the yellow line (right) indicates an influence to about 40 mm from the capacitor.

The fields produced by the static currents in the PET electronics itself can be a second source of B_0 distortion. Its impact can be estimated by calculating the B_0 distortion caused by a DC current in a loop with the size of the intended electronics: A current of 8 A (roughly the supply current of an SDM – see section 5.1.1) in a transverse circle with a diameter of $2R=65$ mm at a distance of $z=15$ cm from the isocenter would cause a B_0 distortion of:

$$B(z) = \frac{\mu_0}{2} \frac{R^2 I}{\sqrt{(R^2 + z^2)^3}} \approx 1.5 \mu\text{T} \Rightarrow \text{Distortion@3T} \approx 0.5 \text{ ppm}$$

The described distortion thus has an impact on the design of power supply circuits and power cabling. As a reference example for the influence of the cabling, Figure 37 shows the distortion caused by a standard power supply cable. It has about 30 twists per meter and, due to the isolation, for 300 V the conductors are 2 mm apart from each other. The cable was placed on the phantom described above, and 10 A of DC current were driven through the cable. The twisted structure of the cable results in repetitive distortions with alternating

sign. The higher distortion on the left side is caused by a slightly larger loop, where the (coaxial) supply line is soldered to the sample cable.

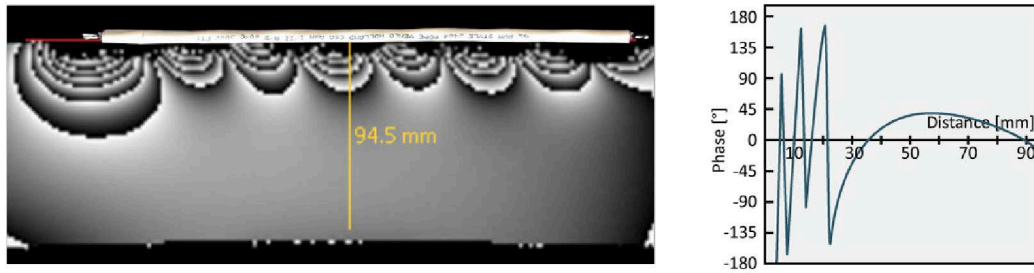


Figure 37: Distortion in the phase image of homogeneously filled phantom (left), caused by 10 A DC current through a twisted pair power supply cable. A photo of the cable was overlaid on the image. Transitions from black to white are phase wraps from -180° to $+180^\circ$. The profile along the yellow line (right) indicates an influence that extends to about 35 mm from the cable.

This reference experiment, furthermore, illustrates that it is important to make the final acceptance tests while the scanner is at full operation. To assess the distortion of the finalized insert, a bottle-phantom (3 l mineral oil, diameter 140 mm) is placed into the scanner. It covers almost the complete FOV. B_0 maps, as described above, are measured with an isotropic voxel size of 2^3 mm^3 . The maximum B_0 -difference as peak-to-peak values in a spherical ROI, limited by the hybrid FOV, is then plotted over the ROI diameter. As described above, the largest diameter, staying below the 2 ppm peak-to-peak value, serves as the figure of merit.

3.2.2 Spurious Signals, SNR and Image Uniformity

The quality of the spin-exciting RF field (B_1) has a direct influence on the image quality, as its magnitude, integrated over time, determines the achieved flip angle of the spins. Whereas the overall magnitude can be calibrated by a flip angle measurement procedure, the homogeneity of the field is determined by the RF coil, and how the coil is electromagnetically loaded. Conductive structures, such as cables, directly distort the field. The normal patient already distorts the B_1 field due to the conductive and dielectric properties of the body. Measures against these problems include, e.g., a multi-Tx system, which allow the shape of the B_1 field to be controlled using two or more separate transmission channels (Katscher and Börnert, 2006). At higher field strengths, such as 7 T or 9.4 T, where the wavelength is even shorter than the body itself, resonance effects inside also come into play. It is beneficial to build the RF coil with its own RF screen inside the PET detector. As such, the B_1 -field is separated (to a certain extent) from the influence of the PET system. Detailed B_1 -mapping experiments (for the second system with digital SiPMs and the small ^1H coil), supporting this assumption, are presented in (Wehner *et al.*, 2014b).

After the spins are excited by the B_1 field, and the echo is generated, the MRI signal is received by the RF coil. The frequency used is around 128 MHz for a 3-T scanner with a maximum bandwidth of around 1.5 MHz. The power of the echo from the tissue is very low, and, to achieve a good SNR, the RF coils are optimized to detect even signals close to the thermal noise floor (and with a high dynamic range of up to 150 dB). Consequently, every additionally received electromagnetic noise will reduce the SNR, or will even lead to image artifacts, such as dotted lines (Hornak, 2011). These artifacts are also termed zipper artifacts,

although some articles use this term solely for RF-feed-through artifacts, where RF power from the excitation pulse leaks into the RF receive chain and causes a single centered line with a similar appearance. An example is shown in Figure 38: a High-Definition Multimedia Interface (HDMI) cable was slightly loose at the synchronization unit (see section 5.1.2), which resulted in the emission of spurious signals that were received by the RF coil. They show up as spurious noise artifacts in the image on the left, which is not acceptable.

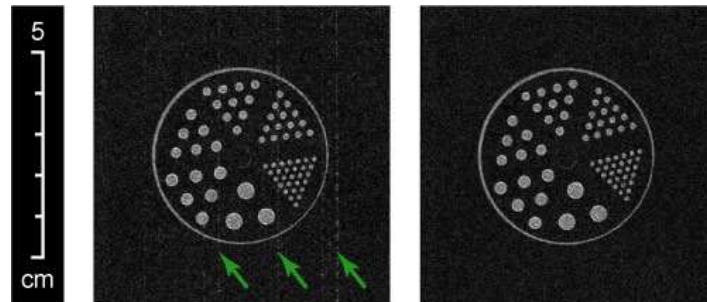


Figure 38: Two MR images of a hot-rod phantom measured with “Hyperion I”. During the acquisition of the image on the left, a synchronization cable was slightly loose at the connection to the synchronization unit, which resulted in spurious signals that are visible as dotted lines (arrows).

To measure these unwanted spurious emissions from the PET detector electronics, a quality control batch scan, called a “spurious scan”, which is available on the MRI systems used, is employed. It measures multiple images covering a large total bandwidth of 730 kHz (180 Hz/pixel). Although there is very little RF transmission ($FA = 1^\circ$), the coil has to be empty to avoid any real MRI signal and to prevent any additional thermal noise pickup from the phantom. Since the amplitude of the displayed MR images is always scaled (see example in Figure 39), the processing is performed on absolute values (called Floating Point (FP) values on Philips MRI systems). These can be retrieved by exporting the data in the “par/rec-research” format. The frequency-encoding direction directly represents the measured frequencies. The phase-encoding direction shows the magnitude of the Fourier transformation of multiple measurements, which are averaged to generate the final plots.

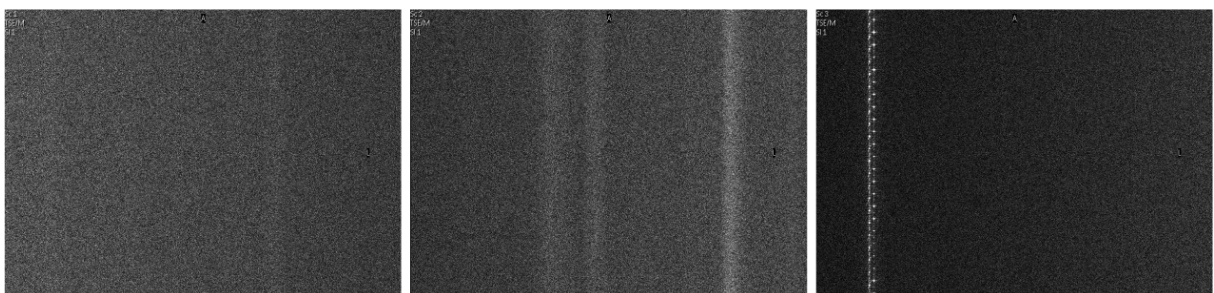


Figure 39: Spurious scan result (three subsequent images) from experiments with an external shielded housing for the optical transceivers connected via shielded twinax cables. The image on the left mostly shows background noise and only some (probably acceptable) broadband features (vertical stripes). In the middle image (higher frequencies), the intensity is higher. On the image on the right (even higher frequencies), spurious signals are visible with an intensity much higher than the background noise. The dotted structure is caused by a periodical signal that is sampled by the phase-encoding in a vertical direction. The test result required discarding the idea of external transceivers, although they would have been beneficial for the B_0 homogeneity (see chapter 5.1.1.2.4).

Apart from artifacts having a low bandwidth, the spurious signals can increase the background noise in a broadband manner. It is very difficult to quantify requirements for the SNR, as it depends on the clinical application and the physician is more interested in malignancy detectability, which depends on the contrast-to-noise ratio and on the detectability of low contrasts (American College of Radiology, 2004). Additionally, the SNR depends on many different parameters defined by the hardware (e.g., the used RF coil, its tuning, and its loading), as well as the imaging sequence (e.g., voxel volume, the receiver bandwidth, the sequence timing, the flip angle, and the echo train lengths). Accordingly, it is also difficult to determine limits for the maximum allowed degradations of the SNR. Similar debates are held with regard to the clinical relevance of 3-T MRI over 1.5-T MRI (Willinek and Schild, 2008). The 3-T system theoretically offers twice the SNR – although, due to the increase in susceptibility effects in most tissues, the SNR gain is limited to about 50 %. An SNR deterioration of 33 % thus roughly degrades the performance of a 3-T MRI system to the performance of 1.5-T scanner. With a third of the SNR, it is thus still possible to perform decent imaging. Nevertheless, the target should stay at a magnitude below that change.

The change in MRI image SNR due to the PET system is quantified using method four of the NEMA standards publication (NEMA MS 1, 2008). It was chosen, because it defines the sequence parameters, the boundary conditions, and the calculation method in a useful manner and was created in a consensus standards development process. A 1 l bottle-phantom (water, CuSO₄, Arquad (a preserving agent), H₂SO₄) with a diameter of 93 mm is scanned with a SE sequence (TR / TE = 612 ms / 20 ms, voxel size = 500² μm² × 2 mm, 320² pixel, pixel bandwidth = 640 Hz, 3:17 min measurement time). The SNR is calculated as:

$$SNR = \frac{\text{signal}}{\text{image noise}} = \frac{\text{Mean of signal ROI}}{\text{SD of Rayleigh distribution of 4 noise ROIs}} \sqrt{\frac{4 - \pi}{2}}$$

The signal value is the mean value of a ROI covering 23217 pixels. The image noise is determined from the standard deviation of a fitted Rayleigh distribution over the pixel values of four ROIs in the corners with 6724 pixels in total. Here, the distribution is calculated from the magnitude image and not from a complex noise. As the real and imaginary components of the noise are independent with equal variance and a mean value of zero, the magnitude is Rayleigh-distributed. Therefore, the standard deviation of the Rayleigh distribution $\sqrt{((4 - \pi)/2)} \approx 0.655$ has to be used as a correction factor (Henkelman, 1985). The size and orientation of the ROIs are shown in Figure 40.

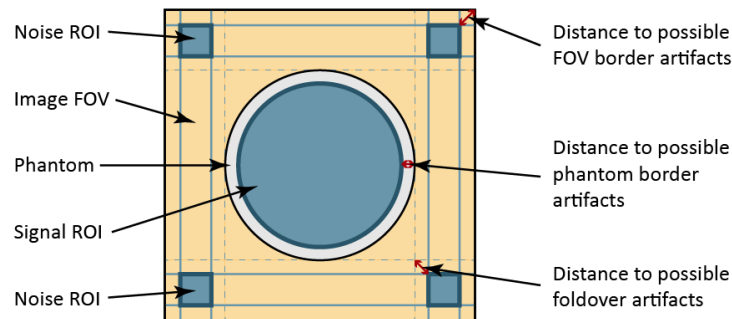


Figure 40: Schematic illustrating the signal and noise measurement regions in a transverse slice of a bottle-phantom

In addition to the SNR, it is important that the signal is uniform throughout the image. This is influenced, e.g., by B_0 inhomogeneity altering the intended flip angle, or by geometric distortions (see next section). A large factor is B_1 non-uniformities: When the spin-exciting field is not homogeneous, some areas will have larger or lower flip angles, which will cause different signal intensities (see example in Figure 41). The same result is also caused by a non-uniform sensitivity profile of the receiving coil, if not corrected.

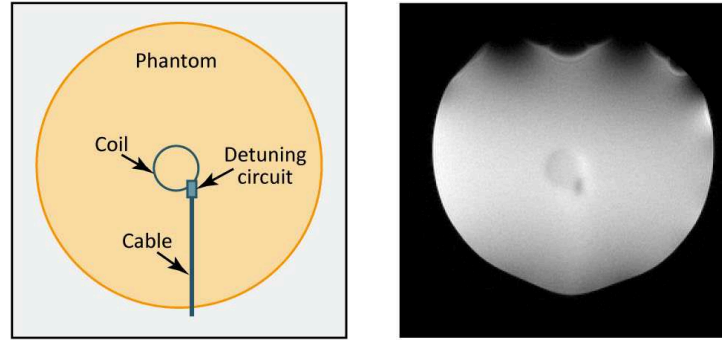


Figure 41: Example of image non-uniformities of about -9 % caused by local changes of the B_1 fields: In the center of the phantom, a circular MRI receive coil with a diameter of 5 cm, which was placed on the phantom (sketch on the left), is visible. It is detuned by a resonant detuning circuit, which again locally changes the field near it. Additionally, signal increments are visible along the power cable, caused by B_1 pickup from the cable. The outer distortions of the phantom are unrelated B_0 inhomogeneities.

MRI image uniformity is computed using a method from the “ACR MR Accreditation Procedure” described in the NEMA standards publication (NEMA MS 3, 2008). Firstly, a low-pass filter against noise influence is applied. Then, small areas around the maximum and minimum intensity are defined, and the pixel values are averaged. “Percent Image Uniformity” (PIU) is calculated as:

$$PIU = \left(1 - \frac{S_{max} - S_{min}}{S_{max} + S_{min}}\right) \times 100 \%$$

Unfortunately, this measurement is not very precise, as for instance S_{min} is often found close to the border of the phantom, where it is likely to be influenced by border-effects itself. On the other hand, defects of the coil or B_1 shielding effects lead to relatively large changes, and thus changes around 5 % can still be seen as a normal.

Although not defined in the NEMA standards, the SNR and Image Uniformity measurements are repeated with a wide range of standard MR sequences. 2D TSE sequences, 3D FFE gradient echo sequences, and EPI sequences were taken from the pre-installed example sequences (knee and brain), and were only slightly modified to show similar images. Details for all sequences are listed in Table 8.

MRI sequence	ETL/ES ^a	TR/TE ^b [ms]	NSA ^c	FA ^d	pixel bandwidth	slices	ST ^e	scan time
T₁w SE	1 / -	612 / 20	1	90°	640 Hz	1	2 mm	3:18 min
T₁w aTSE	6 / 5.7 ms	612 / 20	4	90°	640 Hz	1	2 mm	2:09 min
T₂w TSE	19 / 10 ms	2400 / 100	4	90°	291 Hz	1	2 mm	2:36 min
T₁w 3D-FFE	1 / -	11 / 2.3	8	35°	434 Hz	20	2 mm	4:19 min
T₂w 3D-FFE	1 / -	13 / 8.1	8	45°	217 Hz	20	2 mm	5:06 min
EPI 3	3 / 1.8 ms	26.1 / 6.8	8	20°	663 Hz	1	4 mm	22.3 s
EPI 5	5 / 1.8 ms	28.4 / 7.4	8	20°	665 Hz	1	4 mm	14.8 s
EPI 7	7 / 1.8 ms	31.6 / 9.1	8	20°	656 Hz	1	4 mm	11.6 s
EPI 11	11 / 1.8 ms	37.9 / 12.3	8	20°	657 Hz	1	4 mm	9.1 s
EPI 19	19 / 1.8 ms	51.2 / 19.1	8	20°	658 Hz	1	4 mm	6.9 s
EPI 25	25 / 1.8 ms	61.6 / 24.2	8	20°	658 Hz	1	4 mm	9.1 s
EPI 33	33 / 1.8 ms	75.4 / 32.2	8	20°	658 Hz	1	4 mm	5.9 s
^a) Echo Train Length / Echo Spacing ^b) Repetition Time / (effective) Echo Time ^c) Number of Signals Averaged ^d) Flip Angle ^e) Slice Thickness								
Image size : 160 mm × 160 mm, Pixel size: 500 µm × 500 µm Acquisition matrix: 320 × 319 pixels Slice selection gradient: Z (axial) Phase encoding: X (top-down), anterior- posterior (AP) Slew rate: dB/dt: ~98 T/m/s								

Table 8: MRI sequences for SNR, image uniformity, and geometric distortion tests.
Table partly published in the supplemental material of (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

3.2.3 Geometric distortions

Geometric distortions in the MR images can have multiple origins – the main causes are B_0 inhomogeneities (as explained in chapter 2.2.6) and gradient distortions. In (American College of Radiology, 2004), it is stated that most modern MRI systems can achieve a geometric distortion of less than 1 %. This value is normally achieved in spin echo sequences that can compensate for minor B_0 distortions through use of the inverting 180° RF pulse (see chapter 2.2.5).

In Cartesian EPI, the bandwidth in the phase-encoding direction is very low (compared to the readout direction). Therefore, although the frequency shift is similar, the spatial shift is larger than in the readout direction. The bandwidth in the phase-encoding direction is defined by the minimum time steps of the rows in the k-space, or the time needed for all phase-encoding steps in one echo train divided by the number of steps. Table 9 shows the pixel bandwidths of the EPI sequences used in frequency- and phase-encoding directions, and depicts the water-fat shift as an example for a pixel displacement of 3.5 ppm (as – in contrast to spin echo sequences – the lowest bandwidth is in phase-encoding direction, the water-fat shift also appears in that direction). The most distortions are therefore expected at EPI sequences with high EPI factors.

MRI sequence	Pixel bandwidth phase-encoding direction	Water-fat shift (3.5 ppm, 440 Hz @ 3T)
EPI 3	117.4 Hz	3.4 pixel, 1.7 mm
EPI 7	67 Hz	6.5 pixel, 3.25 mm
EPI 19	28.6 Hz	15.2 pixel, 7.6 mm
EPI 25	22.1 Hz	19.7 pixel, 9.9 mm
EPI 33	16.9 Hz	25.7 pixel, 12.85 mm

Table 9: Pixel bandwidths of the EPI used to scan the distortion phantom. The last column lists the water-fat shift as an example for a pixel displacement caused by 3.5 ppm B_0 distortion.

As the gradient fields are needed for the spatial encoding of the MRI scanner, their distortions in space and time consequently lead to distortions in the image. Spatial nonlinearities in the gradient field can shear, bend, expand, and squeeze the images (Figure 42). As the gradients superimpose on the static magnetic field, the effect is similar to those caused by B_0 distortions.

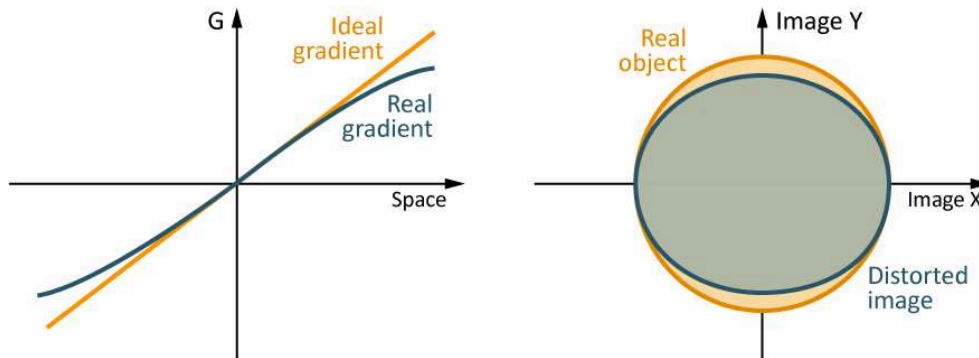


Figure 42: Spatial diversion from the ideal gradient field in space (left) results in geometrically distorted images of the actual object (right)

A second form of non-linearity is caused by eddy currents that are induced by the switching gradients in conductive structures. These eddy currents produce their own magnetic field, and, as a result, the ideal trapezoid shape of the gradient field is distorted over time, as shown in Figure 43.

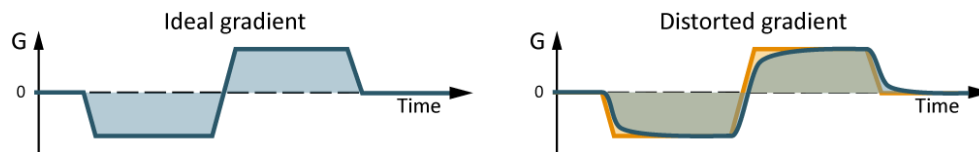


Figure 43: Sketch of the ideal gradient waveform (left) and its distortion by eddy currents (right).

The manifestations of the distortions depend on the directions of the gradients and on the (positions and directions of the) eddy currents. Typically, these consist of (similar to gradient non-linearity) contracting, stretching, shearing, and overall shifting of the images (Le Bihan *et al.*, 2006).

A phantom was designed to measure geometric distortions (Figure 44). The phantom is imaged with the set of standard imaging sequences, also used in the SNR determination experiments (Table 8).

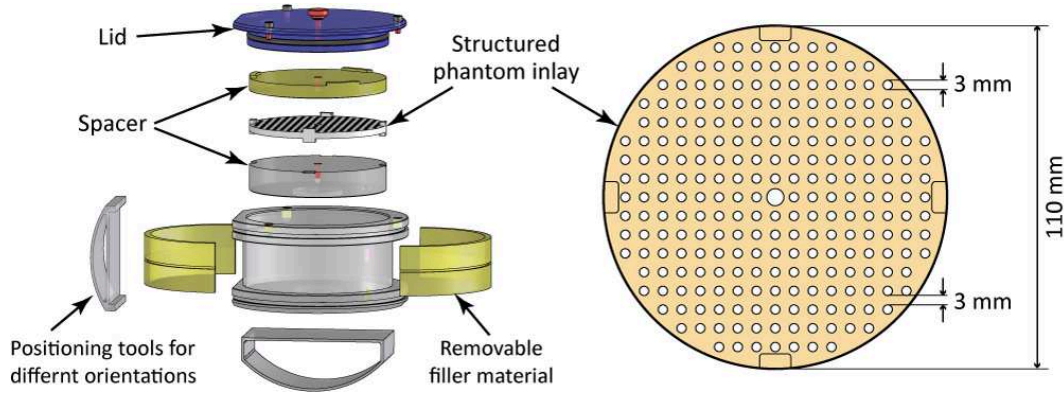


Figure 44. Phantom for measuring the geometric image distortion. Exploded-view drawing (left), and sketch of the structured phantom inlay, whose holes are to be filled with a liquid tracer (left).

The phantom inlay, made from rapid prototyping, has 3-mm-wide holes that are arranged in a Cartesian pattern. The distances of these holes to the center of the phantom are measured in the images and are compared to the real distances (according to the (NEMA MS 2, 2008) standard protocol for determining two-dimensional geometric distortions in MRI, example 3). The distortion is expressed in terms of percentage from the maximum distortion that could be determined (L_m : measured length, L_a : actual length in the phantom):

$$geometric\ distortion = MAX \left(\frac{|L_m - L_a|}{L_a} \right) \times 100 \%$$

3.2.4 Ghosting

Distorting the intended magnetic field over space and time with eddy currents results in a second type of MRI artifact: ghosting. In EPI sequences, the k-space is often filled in a zigzag trajectory, meaning, that the odd and even lines are measured with opposite readout gradients. With distorted gradients, the odd and even lines (in phase-encoding direction) are thus shifted in opposite directions. In the image (Fourier-transformed k-space), this results in “Nyquist ghosts” in the phase-encoding direction, overlaid over the normal image (see Figure 45).

Their appearance and intensity (as well the geometric and intensity distortions) depend on a complex combination of parameters influencing amplitude-, phase-, and time discontinuities. Among them are the EPI factor (the echo train length), TR, TE, the gradient strengths, directions, and slew rates. Additionally, B_0 homogeneity, shimming, timing mismatches, and the used artifact suppression techniques play a role in the formation of ghosting effects (Hennel, 1998). A theoretical discussion about EPI ghosting can be found in (Reeder *et al.*, 1997), where (among others), a formula is derived to estimate the maximum allowed phase error depending on the maximum allowed ghost-to-noise ratio α , the SNR, and the number of shots of the EPI sequence. As the number of shots equals the acquisition matrix size ($2k_{Y_max}$) in the phase-encoding direction divided by the EPI factor, the maximum allowed phase error is calculated as:

$$\Delta\phi = \frac{2\alpha(2k_{x_max}) \sin\left(\frac{\pi \times EPIfactor}{2(2k_{y_max})}\right)}{EPIfactor \times SNR}$$

A reference estimation can be made, e.g., for the EPI 11 sequence (example for medium aggressive speed-up) from Table 8 and the SNR measured with that sequence (chapter 6.2.2.2, Table 30). Allowing for ghosts with twice the intensity of the background noise results in a maximum allowed phase error of $\Delta\Phi = 6^\circ$. For single-shot EPI and ghosts with the same intensity as the background noise, $\Delta\Phi$ would have to be less than 2° .

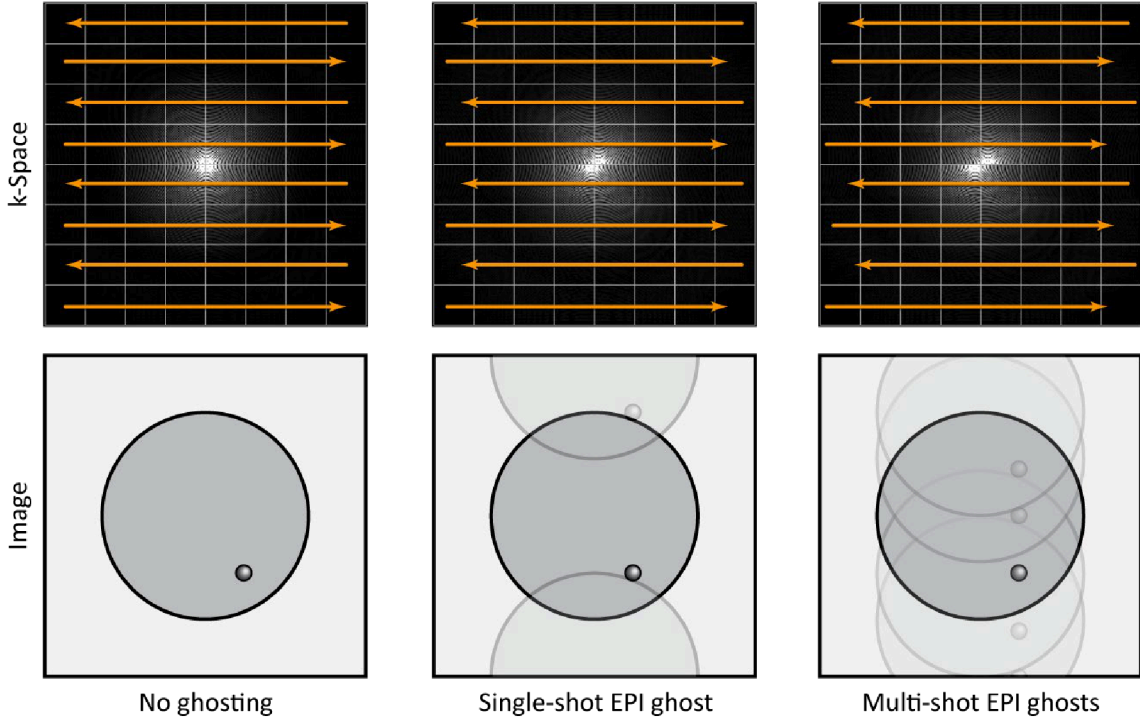


Figure 45: Sketches for ghosting in EPI sequences: shifted k-space trajectories (only readout gradients are shown in orange) result in alternating patterns in the phase-encoding direction. These patterns manifest as ghost images, overlaid over the normal image (additional sinusoidal intensity changes in the readout direction are omitted in the presented sketches).

It is now possible to make a reference calculation to estimate the amount of conductive material that would cause this phase error. Similarly to the calculation of heat dissipation by eddy currents (chapter 3.1.2.3), a circular shaped PCB with a ground plane is placed on the axis of the MRI bore. It is perpendicular to the axis and at a distance of ΔZ away from the center ($Z=0$) of the FOV (Figure 46, left).

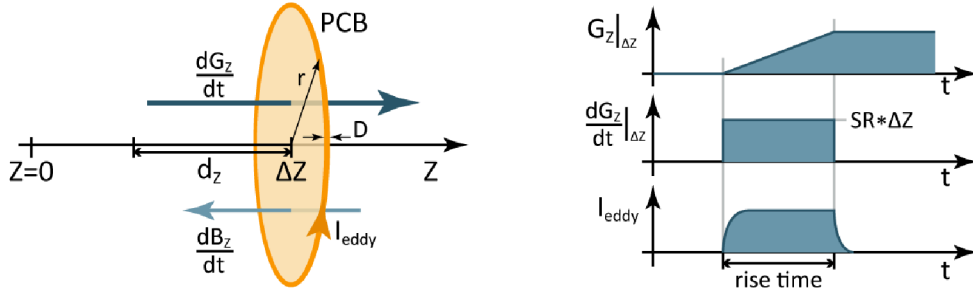


Figure 46: Geometry (left) of a circular PCB plane with thickness D , placed at a distance ΔZ on the Z -axis. The switching gradient dG_z/dt induces an eddy current I , which causes a magnetic field in the opposite direction. The waveforms are sketched on the right.

The induced eddy current can be calculated as current density J in a ring of the PCB ground plane. The induced voltage U is derived from the law of induction, and the sheet resistance of the circle can be calculated with the circumference C , the thickness D and the conductivity of copper σ .

$$U = \frac{dB}{dt} A = \frac{dB}{dt} \pi r^2, R' = \frac{C}{\sigma D} = \frac{2\pi r}{\sigma D} \Rightarrow J = \frac{U}{R'} = \frac{\sigma D r}{2} \times \frac{dB}{dt}$$

The magnetic field change at a distance z on the axis of the PCB can be calculated by integrating the formula for the field of a current in a loop over the radius:

$$\Delta B(z, R) = \int_0^R \frac{\mu_0 r^2 J}{2\sqrt{(r^2 + z^2)^3}} dr = \frac{\mu_0 \sigma D}{4} \times \frac{dB}{dt} \times \frac{R^2 + 2z^2 - 2z\sqrt{R^2 + z^2}}{\sqrt{R^2 + z^2}}$$

The final phase error of the net magnetization can be calculated by integrating the Larmor equation at the magnetic field error (with dB/dt being the slew rate at that position) over the rise time of the gradient. The trapezoid gradient shape (Figure 46, right) simplifies this, as dB/dt is constant over the rise time, and the integral is the rise time multiplied with the slew rate. Since the slew rate is the gradient strength divided by the rise time, the integral is the field strength from the gradient at the position of the PCB (and this is the gradient strength multiplied with the distance ΔZ from the center of the FOV ($Z=0$)). The waveform of the eddy current, sketched in Figure 46 on the right, indicates an exponential rising and falling edge. This is caused by the self-inductance of the copper disc, but it can be neglected in this case, as the relaxation constant is much smaller than the rise time of the gradient. Since the phase error of the net magnetization is caused by both the positive and negative slopes of the gradient switching, a factor of two has to be added. The error in phase, at the distance d_z from the PCB, is thus:

$$\Delta\phi(d_z, R) = \gamma \frac{\mu_0 \sigma D}{2} G \Delta Z \frac{R^2 + 2d_z^2 - 2d_z\sqrt{R^2 + d_z^2}}{\sqrt{R^2 + d_z^2}}$$

Assuming a standard copper ($\sigma=5.96E7$ S/m) ground plane with a thickness of $35 \mu\text{m}$ (1 oz/ft^2), a gradient of 15 mT/m (as used in that sequence in Z -direction), and a PCB with a diameter of 65 mm at a distance of 10 cm from the isocenter, it is possible to plot the resulting phase error over the distance from the plate (Figure 47).

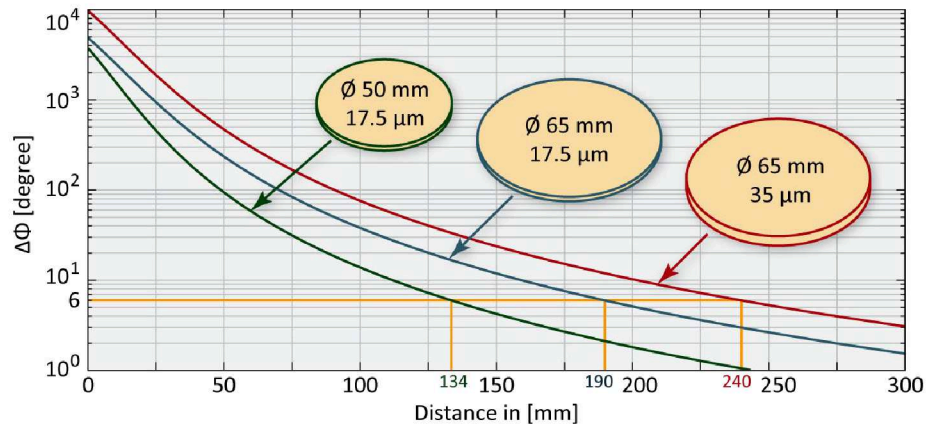


Figure 47: Calculated phase errors, caused by circular ground planes with different diameters and thicknesses (horizontal diameter drawn in scale of the plot), plotted on a logarithmic scale over the distance from the plate (see test for further boundary conditions). The orange line marks the target of 6° , which is reached at distances between 134 mm and 240 mm.

To stay below the phase error of 6° , a distance of 240 mm from the PCB has to be maintained. Thinning the ground plane thickness to $17.5 \mu\text{m}$ (0.5 oz/ft^2) reduces the necessary distance to 190 mm. Additionally shrinking the ground plane, e.g., to a diameter of 5 cm, reduces the needed distance to 134 mm.

The above calculated reference example is, on the other hand, constructed with a worst-case position, as a current through a ring produces a dipole-field. Furthermore, only the Z-component of the resulting field is relevant, since it alters the B_0 field. Therefore, a position that is not on the axis of the FOV will have far less influence (Figure 48, left).

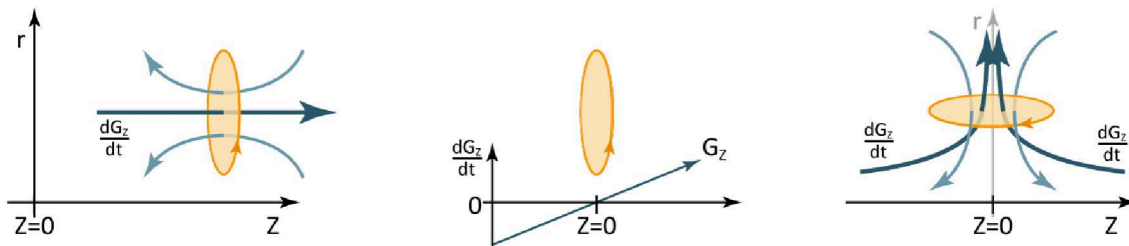


Figure 48: Sketch of eddy currents and resulting fields induced by the Z-gradient on conductive planes in different positions: normal to the Z-axis but shifted in radial direction (left), additionally centered on the Z-axis (middle), and parallel to the Z-axis but shifted in radial direction (right).

As described above, the gradient field increases with distance to the isocenter. Close to the isocenter, the field is low – and so are the induced eddy currents (Figure 48, middle). To reduce them, it is thus beneficial to build the electronics close to the isocenter, or into the isoplanes (see patent “Magnetic Resonance Gradient Coil Iso-Plane Backbone for Radiation Detectors of 511 keV” in the appendix). For this reason, it is favorable to design the PET insert in a way that the axis of the PET gantry is similar to the axis of the MRI bore. Rotating the conductive area parallel to the Z-axis leads to induction from the transaxial components of the Z-gradient. On the other hand, the resulting field from the eddy current has a low Z-component underneath (and above) the conductive plate (Figure 48, right).

The estimation given above was made for the rotational symmetric Z-gradient. The orthogonal X- and Y-gradients have a different field pattern (see Figure 32 in chapter 2.2.4

and Figure 106 in chapter 5.2.4.2) and thus have different eddy current distributions (Figure 49), resulting in gradient field distortions.

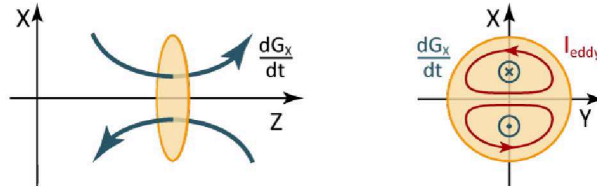


Figure 49: Sketch of eddy currents (red) induced by the X-gradient on a conductive plane normal to the Z-direction.

Additionally, not all conductive structures are straight plains – some are bent in three dimensions (e.g., screened housings). It is thus very difficult to predict the final resulting field distortions in a complete system, and simulations are needed (Kroot, 2005). Furthermore, the MRI scanner is able to perform a one-dimensional, non-linear phase correction using a dedicated step in the preparation phase of each scan. For all these reasons, the final phase error produced by a PCB ground plane is about one to two magnitudes lower. On the other hand, in a complete PET system, there are multiple detector modules with housings and multi-layer PCBs, which will result in approximately the same magnitude higher number of conductive planes. Therefore, the presented reference example can indeed be used as a rough design limit for single conductive planes in the system with regard to size, thicknesses, and distance to the FOV.

Similar to the SNR discussion, the level of acceptable ghosting depends on the application, because often a compromise between spatial resolution, scan time, SNR, and artifact level has to be found. Nevertheless, when ghosts fold into the ROI to be examined by the physician, they might mask existing structures or mimic malignant tissue if they are not recognized as a ghosting artifact. Therefore, the goal is to produce no additional ghosting, and to have a similar ghosting level as reference scans without the PET insert.

The amount of ghosting is experimentally determined by imaging, e.g., bottle or hot-rod phantoms (see section 3.3.1). If object and ghost can be clearly recognized, and there are areas where they do not overlap (as for instance in the single-shot EPI example of Figure 45), the ghost-to-noise ratio (as described above) can be used as a measure. Alternatively, a ghosting level can be calculated, including the signal magnitude as described in (American College of Radiology, 2004):

$$\text{Percent signal ghosting} = \left| \frac{\text{Ghost Signal} - \text{Background Signal}}{2 \text{ Mean Signal}} \right| \times 100 \%$$

If there is no possibility to distinguish with certainty between object and ghost artifact, and the ghosting changes from image to image (although the scan parameters were not changed), the amount of ghosting can be estimated over series with a large amount of images. During experiments, it became apparent that by visually inspecting all images, it is easy to discriminate three levels of ghosting: almost no ghosting (ghosts hardly visible), normal ghosting (ghosts present but, due to the low intensity, clearly distinguishable from the object), and severe (where the ghosts have a similar intensity to that of the object itself, and the image is thus not usable). The phase-error contribution from the eddy currents to EPI sequences is quantified in (Wehner *et al.*, 2015) by fitting a model to the phase advance in subsequent echoes, measured with the second insert and the small ^1H coil.

3.2.5 Temporal Stability

Functional MRI (fMRI) used to visualize brain activity, often uses the Blood Oxygenation Level Dependent (BOLD) contrast (Ogawa *et al.*, 1990). In relatively large voxels (about 3^3 mm^3 in human brain studies), it is followed over time (usually over multiple minutes with a temporal resolution of a few seconds). Changes in that contrast are determined and correlated to external stimuli. Since the change in BOLD contrast is normally only in the order of a few percent, the MRI system has to deliver stable signal levels, with fluctuations much lower than the change to be measured.

The multicenter fMRI consortium FIRST-BIRN⁸ developed a test protocol (Glover *et al.*, 2012) that is used in weekly quality assessments to compare the quality of scanners in the different imaging centers (Friedman and Glover, 2006). In this thesis, the protocol is slightly adapted to the preclinical PET/MRI situation. Similarly to the MRI SNR determination experiments (section 3.2.2), a 1 l bottle-phantom is scanned with the MRI, while the PET system acquires data from seven ^{22}Na point sources, radially orientated around the bottle-phantom, a single-shot EPI sequence with an echo train length of 63, and a TE of 16.6 ms is used (FA=90°, pixel bandwidth = 3037 Hz). Within 2 seconds, it images a volume of $160 \text{ mm} \times 160 \text{ mm} \times 32 \text{ mm}$ (complete hybrid FOV of the first system) in 7 slices (pixel size of $2.5 \text{ mm} \times 2.5 \text{ mm}$, 4 mm slice thickness, 1 mm interslice gap). For 10 minutes, the complete volume is scanned every 2 seconds, resulting in 2100 images (300 repetitions, 7 slices, 64×64 pixels per slice).

Unless stated otherwise, data analysis is performed only on the center slices of 198 time steps (from 53 to 250), following the original protocol. A signal image is generated as a simple voxel by voxel average. A Signal-to-Fluctuation-Noise Ratio (SFNR) map is calculated by dividing the signal image by a temporal fluctuation noise image. The latter is an image of the standard deviation (voxel by voxel, of the residuals after a detrending step with a second-order polynomial). Values for SNR and SFNR are determined as mean values from a ROI of 20×20 pixels around the center of the phantom. Both values should be within a few percent of each other.

The same ROI and second-order polynomial fit is used to calculate percent fluctuation and drift:

$$\text{Percent fluctuation} = \frac{\text{SD of the residuals}}{\text{mean signal intensity}} \times 100 \%$$

$$\text{Percent drift} = \frac{\text{maximum fit value} - \text{minimum fit value}}{\text{mean signal intensity}} \times 100 \%$$

Finally, a Fourier analysis of the residuals is performed, which allows detecting low-frequency oscillations in the image intensity.

The data from multiple fMRI sites, presented in (Friedman and Glover, 2006), indicates that a value of ~0.10 % percent fluctuation is a typical lower level, and that all stable scanners are below 0.2 % on average. For the drift values (absolute value), the best sites reached a value of ~0.4 %, and stable scanners generally stay on average around 1.0 % or less. SNR and SFNR values in this measurement are typically around 200 for 3-T systems.

⁸ <http://www.birncommunity.org>

3.3 PET/MR Imaging

When all the performance parameters described above are within the specification, one can assume that the systems work as designed. Nevertheless, beside these quantitative measurements, it is important to perform qualitative imaging studies. These studies demonstrate that the complete imaging chain works, visualize the performance in real-life examples, and prove that no other artifacts and influences are present.

3.3.1 Phantom studies

Phantom imaging is performed to measure and control the image quality for all kinds of imaging modalities. They make use of known geometrical structures that have to be recognized in the images. Depending on the exact purpose, many different phantoms have been designed. For PET and SPECT these often have tubes and spheres of different sizes to be filled with different activities. Some phantoms with exactly described shapes, sizes, and materials are named after their inventor, e.g. “Derenzo”, “Defrise”, “Esser”, or “Jaszczak”.

The phantoms used in this thesis to evaluate the combined PET/MR image quality, are self-designed hot-rod phantoms. The base is a watertight, closable tube with small extra inlets to fill it with a liquid radioactive tracer with few residual air bubbles. Different inlays can be placed inside the tube with structures that are seen in the image. The tube and most inlays are made from polymethyl methacrylate (PMMA), also known as acrylic glass, or Plexiglas. The material is often used for MRI phantoms (e.g., see Figure 35) because it generates almost no signal and causes low B_0 disturbance due to its low density. The design, including the filling procedure, has to be well thought through: due to the radioactivity of the liquid, splashes have to be avoided, and only one attempt to fill them is allowed per day.

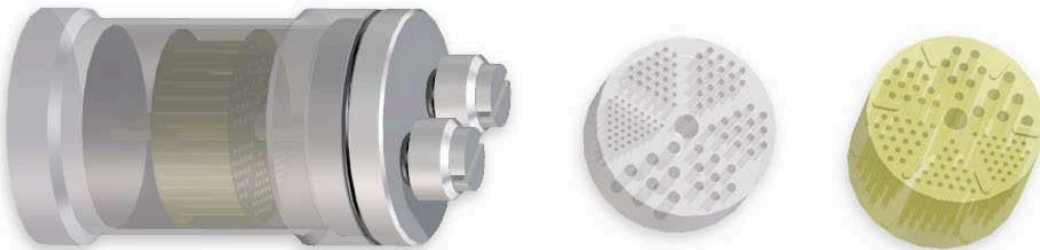


Figure 50: 3D models of the micro hot-rod phantom used in section 6.2.4.1: PMMA container (left) with large lit and two screws to fill the phantom (each sealed with rubber gaskets). Two hot-rod inserts (29 mm diameter) made from drilled plastics (middle) and FullCure (right).

The solid hot-rod inlays have holes that have to be filled with the liquid tracer. Since ^{18}F -FDG is a solution in water, it is also visible in the MRI, and it is thus suitable as a phantom filling for a combined PET/MRI phantom. The inlays are either made from a material having a z -value close to tissue (to model scatter right) or are made in stereolithographic rapid prototyping (Park *et al.*, 2008). Unlike PMMA, the used material “FullCure 720” (Objet Geometries Ltd, Rehovot, Israel) has the additional advantage of being hydrophilic, which helps to fill the small rods by increased capillary forces. Since the spatial resolution is defined as the distance between two volumes that can still be differentiated, the hot-rod inlays have regions with different rod sizes. The distance between the centers of the rods in one region is

always twice the diameter of the rod itself, which results in an equidistant hot-cold pattern. The length of the rods is used to increase the statistics by displaying large slice thicknesses. This is a valid and commonly used method, since a longer measurement time would result in similar statistics. An intensity profile plotted through the centers of the rods demonstrates the ability to separate the rods (which might be expressed as a peak-to-valley ratio). The rods are positioned in a way that permits one profile to go through the centers of the rods of two regions. The inlay is smaller than the phantom tube and centered by an axis, so it is surrounded by a ring of tracer. This ring is useful for visualizing image distortions and artifacts.

Phantoms have intentionally artificial geometric structures. The cold- and hot-rod phantoms, for instance, have repetitive rungs, which can align with the detector geometry. This often results in biased results: either too positive, when optimally aligned; or too negative, when the alignment results in artifacts. As mentioned, the length of the rods is also used to display very large slice thicknesses, which, although allowed, does not reflect a normal imaging situation. To be free from all these geometric issues, images from organically grown structures are often presented. Fruits and vegetables are available in all kinds of sizes, have interesting contrasts and very fine structures. The sizes and features, moreover, are generally known, so that a broader audience is able to judge the results (see examples Figure 51). A further advantage is that they can be imaged without ethical considerations.

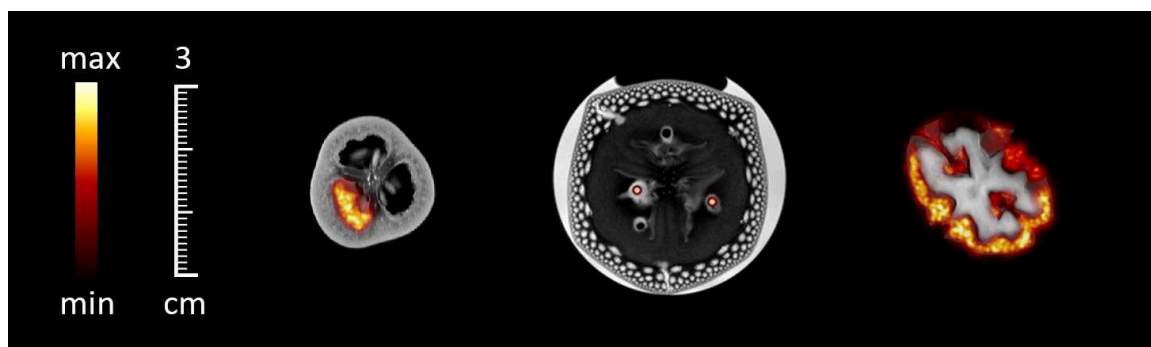


Figure 51: Example transverse ^{18}F -FDG PET/MR images of generally known organic structures measured with Hyperion II^D: A chili (left) with one chamber tracer-filled (T_{1w} aTSE MRI sequence). A banana (middle, T_{2w} TSE sequence) with three glass capillaries of tracer (top one has an air bubble at this slice). A fourth hole was made by a capillary taken out (note how the compression of the tissue around the capillaries changed the T_2 value.) A walnut was filled with tracer⁹ and imaged with a T_{1w} TSE sequence (note the water-fat-shift artifact on the top right, between the water-based tracer and the fatty nut core.)

⁹ Within minutes, dry nuts soak up injected liquids. The core expands and cracks the nut from the inside. Since spilling of the radioactive tracer has to be avoided, the nut was first punctuated and equipped with tracer inlet and air outlet tubes, and was then molded in a pressure-withstanding glass-fiber/epoxy coating.

3.4 Preclinical Applications

The size (volume and weight) of animals used in preclinical applications is around 2 to 3 orders less than human patients. This work focuses on small animals from rodents, such as mice, to rabbits. The axial FOV shall allow a whole-body scan of a mouse (excluding the tail), and thus has to be at least 7 cm long. As the sensitivity is very low at the ends of the FOV (due to the small solid angle for coincidences), the axial FOV should extend an additional cm on both sides. This length will also cover complete organs of larger animals, such as the rabbit brain (full body coverage for rabbits is not possible in this project due to cost restrictions). New Zealand white rabbits, intended for use, e.g., in studies of vulnerable aortic plaque, have a diameter of around 150 mm. They define the requirement for the diameter of the FOV.

3.4.1 Animal Handling

Anesthesia is needed to keep the animal calm and motionless during the measurements, although this changes the metabolism (an alternative is to attach the scanner to the awake animal, which was tested in (Woody *et al.*, 2007), although this approach is, of course, not directly possible for MRI). The anesthesia is usually made with a mixture of isoflurane and oxygen gases that have to be brought to the animal. The ventilation might be restricted in small tube-like bores for imaging. In that case, the exhaled gases need to be removed with an additional vacuum pump. The amount of applied gas has to be regulated carefully to the extent of the anesthesia. Applying too little gas risks awakening the animal, which will then move and become stressed. The comfort of the animal is not only an ethical question: stress is known to alter the outcome of experiments (e.g., do muscle movements, cramps, or hypothermal shivering result in ^{18}F -FDG uptake) (Fueger *et al.*, 2006). Even animals escaping is not a seldom occurrence, which is problematic as their urine is not only a biohazard, but also radioactive. For the same reason, all system parts where the animal might be (and below that) have to be water tight, cleanable, able to be disinfected, and/or removable. Too much anesthesia gas, on the other hand, can also be critical for the animal. Therefore, the breathing rhythm of the animal should be monitored during the experiments, and the anesthesia has to be set accordingly.

During longer measurements of smaller animals, such as mice, the core temperature can drop as a result of the anesthesia, and hypothermia can even become a lethal problem. It is thus important to heat the animal during the measurement. On the other hand, the RF excitation pulses of the MRI can deposit quite large amounts of energy into the body, which might cause the animal to overheat. The optimal solution, therefore, is to measure the core temperature of the animal with a rectal thermometer and to warm or cool it accordingly. In MRI applications, both measuring and regulating the temperature are problematic, since no conductive material should be placed underneath, or inserted into, the mouse (B_0 and B_1 distortion). Additionally, the idea of circulating water next to the animal for temperature regulation is problematic for both modalities: for PET it attenuates the gamma photos, and for MRI it generates additional thermal noise and MR signals.

The imaging tracer for PET and the contrast media for MRI have to be injected. Usually, an intravenous cannula is inserted into the tail vein. Depending on the type of study, the time of injection might be during or directly at the beginning of the measurement. Therefore, the

cannula and the tubes have to stay in place during the measurement and have to be accessible from the outside.

The complete infrastructure has to fit into the scanner, and fast access is required at all times in order to react to complications. As all these requirements have to be fulfilled in a practical manner, and initial in vivo measurements have to be performed (and are often demanded by the ethical committees before studies with statistical relevant animal quantities are permitted).

3.4.2 Temporal Synchronization

Having both PET and MRI data from exactly the same time enables new applications, such as dynamic studies or motion compensation (Judenhofer and Cherry, 2013). The motivation behind PET motion compensation arises from the fact that moving regions (during the long PET measurement) can become blurry in the image, or might be reconstructed with motion artifacts. This reduces, for instance, the detectability of small lesions in oncology applications (Figure 52), or hinders the comparison between systole and diastole in cardiac examinations.

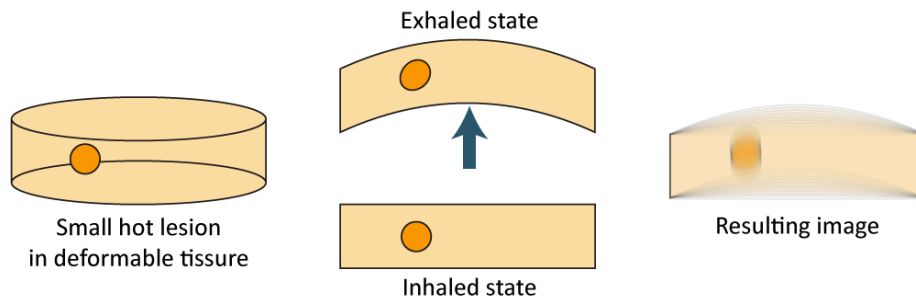


Figure 52: Example of a hot lesion in a homogeneous background (left). With breathing deformation applied during PET data acquisition (middle), the resulting image is blurred (right).

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Repetitive physiological motions in the body can be tracked, to a certain extent, by external devices. Cameras can follow the motion of a patient, air cushions can detect breathing, and an Electrocardiography (ECG) can register the electric stimulation of heart muscles during its contraction. The motion can then be corrected retrospectively, or gated images that show frozen states of the movement can be reconstructed. It is also possible to control the image acquisition directly from that physiological data, which makes particular sense for MRI, where data is not measured continuously but rather in discrete echoes. In that situation, one might want to gate the PET data accordingly, and thus the beginning and end of MRI activity has to be detected, as shown in Figure 53.



Figure 53: Breath gated MRI sequence: The MRI decides with a breathing monitor when to scan. The PET system needs to know the beginning and end of each scanning period (orange arrows).

Figure published in (Weissler *et al.*, 2015b) ©^{3.0} 2015 IEEE.

A variation of the same idea is to track movements and deformation with the MRI, while the PET data is acquired (Tsoumpas *et al.*, 2011). This yields direct information about the movements inside the body, rather than interpreting the indirect information from outer body movements (as for inhaling) or ECG data. Furthermore, it allows tracking other internal motions, such as bowel movements. In rather advanced scenarios, it is even possible to mix navigator sequences for motion detection with a normal imaging sequence. For instance, the MRI can switch seamlessly between two interleaved sequences (Henningsson *et al.*, 2014).

For all these techniques of combining PET and MRI, the data has to be temporally synchronized. Although the timing of the MRI sequence (once it has begun and does not use external steering as described above) is known precisely, the actual moment in time when it starts depends on multiple uncontrollable factors. Firstly, the operator starts the scan manually in the graphical user interface of the MRI console. Then it takes time to calculate the sequence and to send it to the real-time control of the scanner. Subsequently, the hardware has to be brought into the correct operating points, which depends on the sequence (e.g., whether the cryopump needs to be switched off) and on the previous scans (e.g., whether components still need to warm up). The length of the subsequently following preparation phase of the MRI scan is also undetermined, especially when some iterative optimizations, such as automatic shimming, are included. When the timing of the MRI sequence is not predetermined, e.g., due to steering by a respiratory monitor, the synchronization has to be repeated during the data acquisition.

Most of the described applications can be realized by obtaining temporal trigger information from external equipment. These can be respiratory monitors, ECGs, and even the MRI scanner itself. As galvanic connections between different electronic equipment are often sources of Electromagnetic Compatibility (EMC) problems, and these have to be avoided, especially for MRI applications (see section 3.1.2.2), it is advantageous to realize the triggering without these galvanic connections. Once a trigger signal is received by the PET system, it has to be stored with a valid PET timestamp for the current measurement. The necessary precision for the synchronization is determined by the physiological signal to follow, and is in the range of half a second for human breathing. A mouse has a heart rate of about 450 to 750 beats per minute, resulting in a minimum heart cycle of 80 ms. To produce eight images during a cycle requires a precision of $80 \text{ ms} / 8 \text{ images} / 2 = 5 \text{ ms}$.

3.5 Conclusion and Summary

The most important performance parameters for PET and MRI were explained, and quantitative requirements specifications were derived. Although the system will work for many applications if the requirements are not met, they nevertheless constitute the targets for a high-performance system with a very good PET/MRI compatibility. The requirements for the PET scanner are summarized in Table 10. The final requirements for the MRI system are listed in Table 11. Numerical requirements for the combined hybrid system are repeated in Table 12.

Parameter	Requirement
Energy resolution	15 % FWHM
Time resolution	1 ns FWHM
Time resolution for TOF (rabbit imaging)	535 ps FWHM
Spatial resolution	1 mm FWHM
Sensitivity	3 %
Maximum activity for mouse imaging	21 MBq
Average activity for rat imaging	30 MBq
Average maximum activity for rabbit imaging	90 MBq

Table 10: PET system requirements summary

Parameter	Requirement
B ₀ homogeneity (anatomical imaging)	2 ppm peak-to-peak (over the whole FOV)
B ₀ homogeneity (spectroscopy)	0.1 ppm VRMS (over single MRS voxel size)
Spurious signals	No spikes in spectrum
Spurious signal image artifacts	Not visible in background noise
SNR degradation	3.3 %
Percent Image Uniformity degradation	± 5 %
Ghosting	No difference to reference
Geometric distortion	1 %
Temporal fluctuation	0.2 %
Temporal drift	1 %
FBIRN test SNR	200
FBIRN test SFNR	200

Table 11: MRI system requirements summary

Parameter	Requirement
Axial hybrid FOV	9 cm
Diameter (transaxial) hybrid FOV	15 cm
Maximum scan time (mouse imaging)	4 hours
Maximum total scan time per day	8 hours
Temporal synchronization accuracy	5 ms

Table 12: PET/MRI system requirements summary

Multiple means of interaction between the two modalities have been described, and how they are expected to deteriorate the performance. Whether the requirement specifications are met has to be determined using the verification methods presented above. The subjective image quality and in vivo capabilities have to be demonstrated in phantom- and with in-vivo experiments.

4. Solid-State Detectors in PET/MRI: Components, History and Existing Systems

Several technological challenges present themselves when combining PET and MRI into a single system. Firstly, PMTs, the main element of standard PET detectors, do not work in strong magnetic fields. They need to be kept at a certain distance from an MRI scanner as done for the since 2010 available sequential clinical PET/MR systems (Maniawski, 2011). By using a rotating table, they allow the patient to be moved into the two gantries without being repositioned between the subsequent scans.

The first approach for simultaneous PET/MR used optical fibers to transport the light from the scintillating crystals to PMTs outside the MRI (Shao *et al.*, 1997). Due to the large number of fibers needed and the optical losses in those, that approach is limited with respect to system size and performance.

4.1 Avalanche Photo Diodes (APDs)

The operation of PET detectors inside the MRI bore became possible by replacing PMTs with solid-state detectors (Pichler *et al.*, 2006). APDs have a structure that is close to P-I-N-diodes, but have an additional highly doped p^+ layer next to the n^+ (Figure 54, left). As in P-I-N-diodes built for light detection, photons are absorbed in the intrinsic (π) layer and generate an electron-hole pair. Due to the electrical field across the layer (Figure 54, right), the electrons drift towards the anode. At the highly doped p^+/n^+ -junction, the field is very high (bias voltage is around 100 V), causing a multiplication of electrons in an avalanche process.

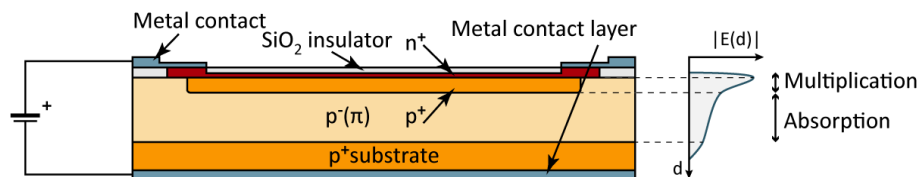


Figure 54: Sketch of a cross section through an APD (left) and the resulting electrical field (right).

APDs were built into several preclinical research inserts (Judenhofer *et al.*, 2008) and are used in the only currently commercially available simultaneous PET/MRI system (Delso *et al.*, 2011). A further development of APDs are Position Sensitive Avalanche Photo Diodes (PSAPDs), which allow determining the position of the avalanche by adding a resistive layer to the backside of the APD. The signal is read out in the four corners, whereas the resistive layer acts as a position-dependent voltage divider (Shah *et al.*, 2004).

4.2 Silicon Photomultiplier (SiPMs)

A further development of APDs are SiPMs, which are well suited for PET applications (Roncali and Cherry, 2011). The avalanche in an APD becomes self-sustaining, when the bias voltage over the diode is increased over the breakdown voltage. In that case, termed Geiger-mode, the gain of such a device is very high, but the avalanche has to be stopped by reducing the bias voltage under the breakdown voltage. This can be achieved by using a quenching resistor in series with the diode: The avalanche current provokes a voltage drop over the quenching resistor, thereby reducing the voltage over the diode. The resulting device, a Single Photon Avalanche Diode (SPAD) is digital and can only detect whether at least one photon was triggering the device. During the avalanche, it is blind to further photons. To detect more than one photon, thousands of small SPADs are connected in parallel (Figure 55).

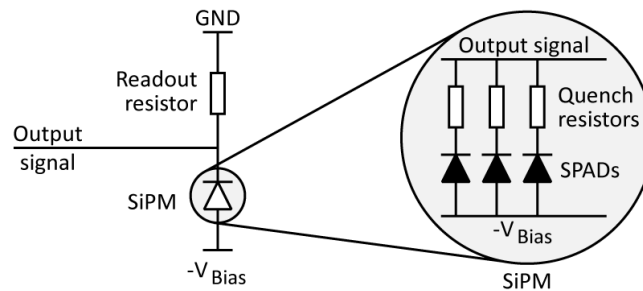


Figure 55: SiPM circuits: An SiPM is constructed from SPADs in series with individual quench resistors, connected in parallel (right). In series with a readout resistor, they produce an analog output signal.

As such, each SPAD can detect a single photon of the scintillation light, and the output signal is almost proportional to the number of photons. It can be read out as a voltage drop on a further readout resistor in series with the SiPM (Figure 55, left), or, e.g., with a current amplifying circuit (Corsi *et al.*, 2007). It is also possible that two or more photons hit the same SPAD, resulting in non-linear response (Figure 56). Therefore, the number and size of the SPADs have to be optimized to the light output of the scintillator.

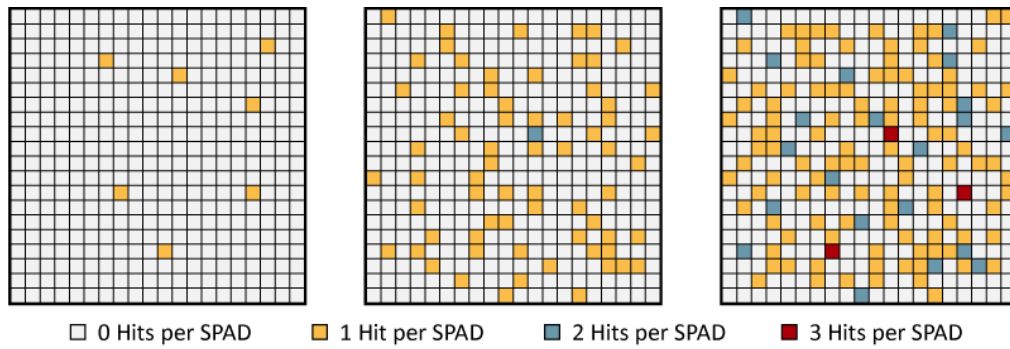


Figure 56: Sketch of photons from a single scintillation event, hitting a SiPM with 400 SPADs: At first (left), only a few SPADs are triggered. With more incident photons, the SPAD are hit by two (middle) or more (right) photons.

Production of SiPMs became possible in the early 1990s, when adequate resistors (metal-resistor-semiconductors) could be implemented in silicon. A sketch of a cross section through a SiPM is shown in Figure 57.

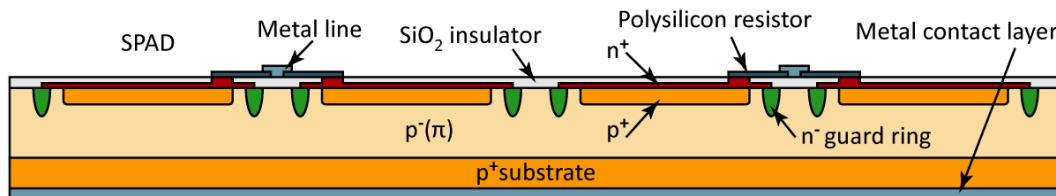


Figure 57: Sketch of a cross section through a SiPM: Multiple small SPADs are connected with an integrated quenching resistor to a common cathode.

Due to the operation in Geiger-mode, SiPMs have a higher gain, a lower temperature dependency, and a faster response time than APDs. Their fast response time allows for measuring TOF information, which can be used to increase the image SNR (as described in chapter 3.1.1.2). SiPMs were, henceforth, used to build the first PET/MRI inserts. For instance, in (Maramraju *et al.*, 2011) and in (Hong *et al.*, 2013), long cables were used to connect SiPM-based detectors to the electronics outside the magnet bore.

As described in chapter 1, long cables are a potential source of signal degradation and interaction with the MRI scanner. The problems have been known for a long time (Timms, 1992), and thus interference problems are frequently reported with these designs. Furthermore, the amount of cables required becomes extremely high as the systems become larger. The experimental systems referenced above thus have very small FOVs (more details are shown below). Therefore, analog compression circuits, e.g., summing up signals with resistor networks, are often used. These, however, result in a loss of PET SNR (Lau *et al.*, 2010).

4.3 Existing Systems

4.3.1 Preclinical PET Systems

As discussed in chapter 1, the performance of a PET scanner depends on several design choices that have to be balanced. Standard clinical scanners are not optimal for preclinical applications, since small animals have different sizes, the injected activities are different, and spatial resolution is more important than sensitivity. For example, with an 800-mm wide clinical PET gantry, the noncolinearity effect (described in section 3.1.1.3) already limits the resolution of a PET scanner to about 2 mm (FWHM), which is not suitable for the imaging of small animals, such as rodents (Cherry, 2006). The development of dedicated preclinical PET scanners thus began around the early 1990s with experimental systems such as those presented in (Watanabe *et al.*, 1992). Table 13 provides an overview of the most important existing preclinical PET-only (or PET/CT and PET/SPECT) systems and the technology they employ.

System	References	Technology and Comment
UC Davis microPET	(Cherry <i>et al.</i> , 1997)	PMT
Concorde microPET P4	(Tai <i>et al.</i> , 2001)	MC PMT, Primate size
Concorde microPET R4	(Knoess <i>et al.</i> , 2003)	MC PMT, Rodent size
UC Davis microPET II	(Tai <i>et al.</i> , 2003)	MC PMT
quadHiDAC (32 Module)	(Schäfers <i>et al.</i> , 2005)	High Density Avalanche Chamber
Siemens Focus 220	(Lehnert <i>et al.</i> , 2006)	
GE eXplore Vista	(Wang <i>et al.</i> , 2006b)	PMT, 2-layer DOI
CrystalClearCollaboration ClearPET	(Roldan <i>et al.</i> , 2007)	PMT, Different configurations
Siemens Focus 120	(Kim <i>et al.</i> , 2007)	
Philips MOSAIC	(Huisman <i>et al.</i> , 2007)	
Siemens Inveon	(Bao <i>et al.</i> , 2009)	PMT
GammaMedica Flex Triumph X-PET	(Prasad <i>et al.</i> , 2010)	PMT, Company renamed to Trifoil
Oncovision Albira	(Sánchez <i>et al.</i> , 2012)	MC PMT, monolithic crystals
MILabs VECTOR	(Goorden <i>et al.</i> , 2012)	Pinhole collimator for PET/SPECT

Table 13: Overview of existing preclinical PET-only (or PET/CT and PET/SPECT) systems and their technology. The reference-columns show a suitable characterization paper. The resulting timeline has a certain error of a few years, because the different groups published at different stages of their work. In addition, the quality of publication ranges from conference abstracts to full characterization papers. For example, the HiDAC technology has been known and used since 1982.

Sketches of crystal arrangement of the preclinical PET gantries and the scintillation crystals used are illustrated in Figure 58. To facilitate comparison, all single-crystal dimensions and all gantry sizes are visualized in comparable scales.

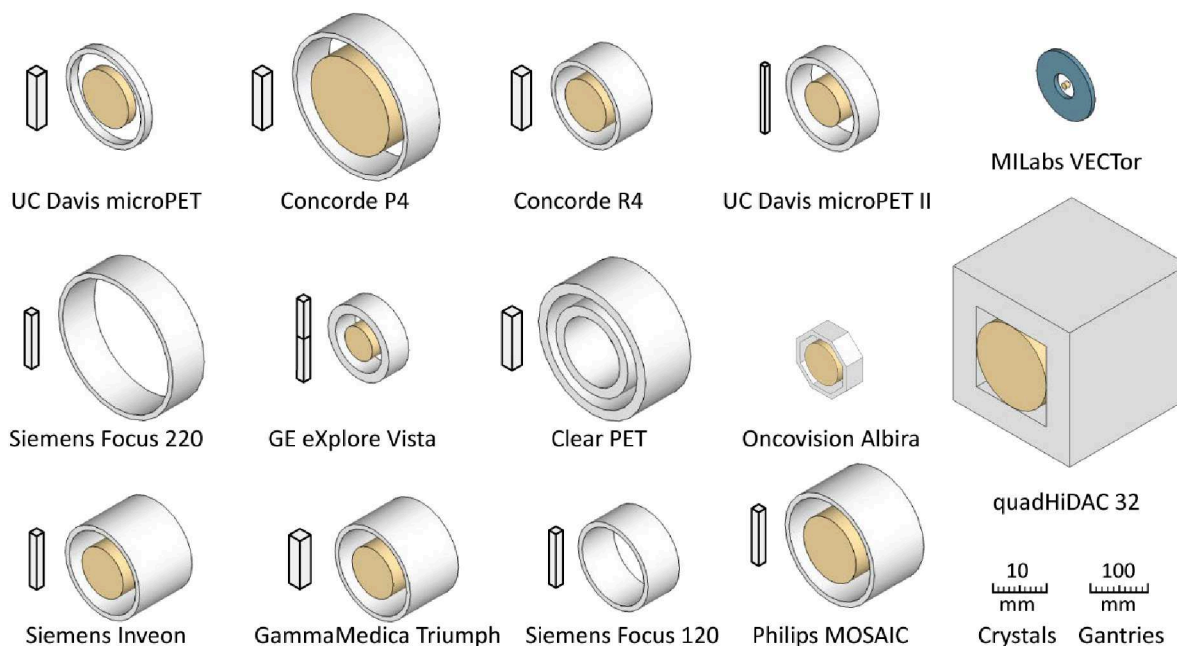


Figure 58: Sketches of existing preclinical PET gantries and the scintillation crystals used: All single crystals and all crystal arrangements are drawn in comparable sizes (gray). If a resulting FOV is given in the literature, it is drawn in orange. Exceptions: The quadHiDAC-based scanner does not use scintillation crystals, the Albira system uses eight monolithic crystals, and a slice through the collimator of the VECTOR system is shown with the same thickness as the resulting FOV (in blue).

4.3.2 Preclinical PET/MRI Systems

Towards the end of the same decade, the first hybrid combinations for simultaneous PET/MR image acquisition were built. A few were already mentioned in the beginning of this chapter, when the different detector technologies were introduced. A detailed history of PET/MRI challenges, solutions and systems can be found in (Vandenberghe and Marsden, 2015). Table 14 gives an overview of the most important existing preclinical PET/MRI systems, the targeted MRI field strengths, and the technology used to realize the system.

System	References	Field Strength	Technology and Comment
McPET II	(Shao <i>et al.</i> , 1997)	0.2 T	4-m long fibers to MC PMT
West Virginia University	(Raylman <i>et al.</i> , 2006)	3 T	Only two modules, 2.5-m fibers to MC PMT
UC Davis PET/MR	(Catana <i>et al.</i> , 2006)	7 T	110-mm long fibers to PS APD
University of Tübingen PET/MR	(Judenhofer <i>et al.</i> , 2007)	7 T	APD
Cambridge PET/MR	(Hawkes <i>et al.</i> , 2008)	1 T	110-mm long fibers using focus 120 hardware, split-magnet design
KC London Panda (Mackewn)	(Mackewn <i>et al.</i> , 2010)	3 T	3.5-m long fibers to MC PMT Four-layer DOI
Kobe City College iPET/MRI	(Yamamoto <i>et al.</i> , 2010)	0.3 T	750-mm long fibers to MC PMT Dual-layer DOI
RatCAP PET/MR	(Maramraju <i>et al.</i> , 2011)	9.4 T	APD, 1:1 coupling, ASIC in module
UC Davis PET/MR Generation II	(Judenhofer <i>et al.</i> , 2011)	7 T	PS APD
Kobe City College iPET/MRI II	(Yamamoto <i>et al.</i> , 2011)	0.15 T	1.2-m long cables from SiPMs Dual-layer DOI
Seoul National University	(Yoon <i>et al.</i> , 2012)	3 T	Long cables from SiPM
Mediso NanoScan PET/MR	(Nagy <i>et al.</i> , 2013)	1 T	Only sequential system

Table 14: Overview of existing preclinical PET/MRI systems, the MRI field strengths used, and the technology employed.

When comparing the crystal sizes and the dimensions of the gantries from these hybrid systems (Figure 59) to the sizes of the PET-only scanners (Figure 58), it becomes apparent that the gantries are much smaller. Additionally, the crystal size does not scale in equal measure. The reasons for this are mainly the restricted space in the often-used preclinical MRI scanners. Additionally, as described above, the solutions developed to achieve MRI compatibility, such as using optical fibers to transport the scintillation light or long analog cables for each sensor, result in unscalable architectures. The performance of these systems is thus often much lower than the performance of preclinical PET systems not subject to the PET/MRI restrictions (see chapter 7.1 for a performance comparison).

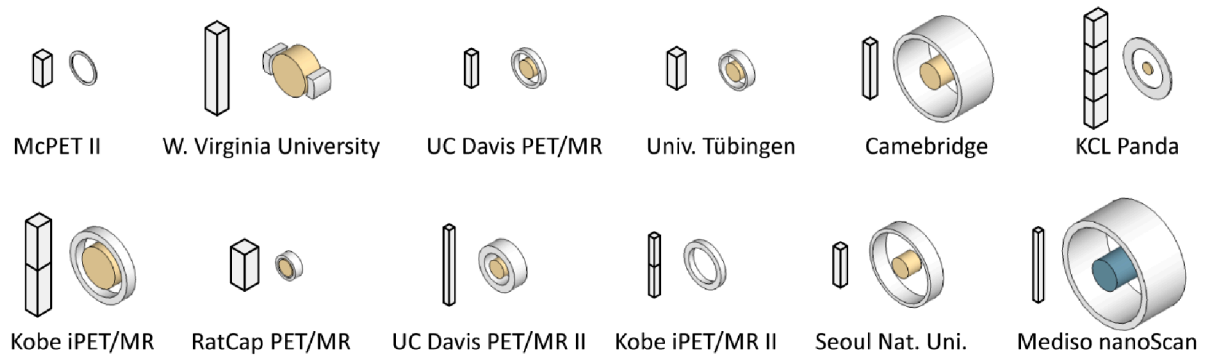


Figure 59: Sketches of existing preclinical PET/MRI gantries and the scintillation crystals used: All single crystals and all crystal arrangements (gray) are drawn in sizes comparable to Figure 58. The hybrid FOV for simultaneous imaging is drawn in orange, when its diameter is stated in the respective papers. The “Mediso nanoScan PET/MR” is a sequential system, and its hybrid FOV is thus drawn in blue.

4.3.3 Clinical Systems

The existing clinical PET/MRI systems all use slightly different technologies, and they were thus already introduced in the beginning of this chapter. An overview with references, field strengths, and used technologies is listed in Table 15.

System	References	Field Strength	Technology and Comment
Siemens BrainPET Insert	(Schlemmer <i>et al.</i> , 2008)	2.8 T	APD-based head insert
Philips Ingenuity TF	(Ojha <i>et al.</i> , 2010)	3 T	PMT, TOF-PET, sequential system
Siemens Biograph mMR	(Delso <i>et al.</i> , 2011)	2.8 T	APD, whole-body system
Sogang University Seoul	(Hong <i>et al.</i> , 2013)	3 T	Insert, 3-m long cables from SiPMs
GE Signa PET/MR	(Levin <i>et al.</i> , 2013)	3 T	SiPM, TOF, no publication available

Table 15: Overview of existing clinical PET/MRI systems, the MRI field strengths used, and the technology employed.

Due to the different optimization, the sizes of the used scintillation crystals, as well as the gantry sizes, are different from the dedicated preclinical systems (see Figure 60).

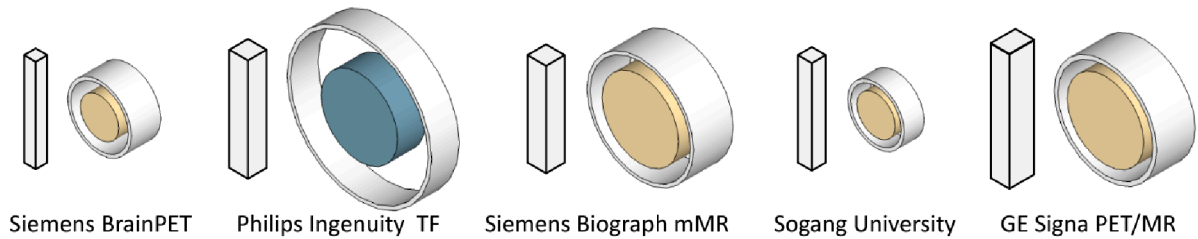


Figure 60: Sketches of existing clinical PET/MRI gantries and the scintillation crystals used: All single crystals are drawn in sizes comparable to Figure 58 and Figure 59. The sizes of the crystal arrangements (gray) and the hybrid FOVs (orange and blue) are shown in comparable scales for this figure. The “Philips Ingenuity TF” is a sequential system and its hybrid FOV is thus drawn in blue.

4.4 Conclusion and Summary

Early attempts to combine PET with MRI were already made in the late 1990s with a single-slice PET insert. About a decade later, solid-state photo detectors were used to build the first more complex hybrid systems. However, the technologies used to achieve MRI compatibility, such as optical fibers to transport the scintillation light for each crystal, both limit the FOV and reduce the PET performance of these systems.

5. Step I: Analog SiPMs and Integrated Digitization

PET signal degradation is best avoided by digitizing the signal as close as possible to the sensors. The approach followed here is, thus, to move the digitization directly into the PET detector module. This promises higher PET SNR and keeps the vulnerable region (where MRI can interfere with the PET detector) small. On the other hand, the entire PET detector electronics are placed directly into the bore of the MRI, which poses a high risk of interaction between the two modalities.

As a first step in using such an architecture to test and reduce the interactions between PET and MRI, a preclinical PET/RF insert with integrated digitization was built as an insert for clinical 3T MRI systems. The concept was first presented in (Schulz *et al.*, 2009). The finalized insert and the respective MRI compatibility measurements are partly, as extractions from this chapter, published in (Weissler *et al.*, 2014b, © 2014 IPEM) and in (Weissler *et al.*, 2015b, © 2015 IEEE). Further publications are referenced in the text and listed in the appendix.

5.1 The System

The PET/RF system is constructed with individually RF-shielded Singles Detection Modules (SDM). Ten SDMs form a PET ring around a dedicated PET-compatible MRI RF transmit/receive (Tx/Rx) coil. The RF coil is based on a birdcage resonator. The orientation inside the MRI bore is chosen to be coaxial with the MRI system. A perpendicular orientation would allow a solenoid RF coil around the subject with a potentially higher MRI SNR, but the coaxial orientation is beneficial to reduce eddy currents, and the resulting image artifacts, as described in chapter 3.2.4.

5.1.1 Singles Detection Module (SDM)

The gamma detector on the SDM is organized in six (almost) similar detector stacks of PCBs, which are connected to a mainboard.

5.1.1.1 Detector Stack

The detector stacks contain five layers: scintillation crystal array, light guide, and sensor-, digitization-, and interface board (Figure 61). Their functions are described in the following sections.

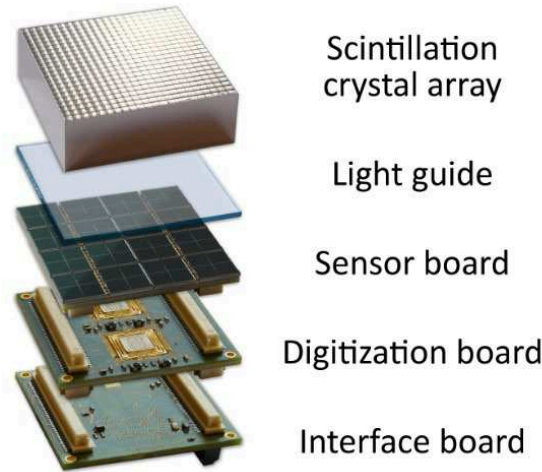


Figure 61: SiPM/ASIC-based detector stack (right, scintillation crystal array shown upside down to emphasize the individual crystals).
Figure published in (Weissler *et al.*, 2014b).

5.1.1.1.1 Scintillator Array and Light Guide

The scintillation arrays have 22×22 (22×24 for the inner stacks of the module) 10-mm long cerium-doped LYSO crystals (Agile, Knoxville, USA). The length is thus only slightly shorter than the absorption length of 11.2 mm (see chapter 3.1.1.4). The single crystals are optically isolated by 67 μm Vikuity™ ESR films (3M, St. Paul, USA). Array dimensions are 30.1 mm × 30.1 mm × 10 mm (and 30.1 mm × 32.9 mm × 10 mm for the planned inner stacks – see Figure 79 in section 5.1.1.6). A glass plate of 1.5 mm thickness is used to spread the light over the sensor array. Meltmount™ (Cargille, Cedar Grove, USA) is used for optical interfacing and for gluing that light guide to the crystal and to the sensor array.

5.1.1.1.2 SiPMs and Sensor Board

The SiPMs used are based on the first prototypes of SiPMs (Piemonte *et al.*, 2007) at Fondazione Bruno Kessler (FBK, Trento, Italy). For this project, the SiPMs were optimized with 3080 microcells per SiPM (Zorzi *et al.*, 2011), and produced as monolithic 2×2 SiPM arrays (see Figure 62). The geometric coverage of the SiPM is ~85 %. The monolithic array has a common ground, which is connected on the backside of the sensor chip.

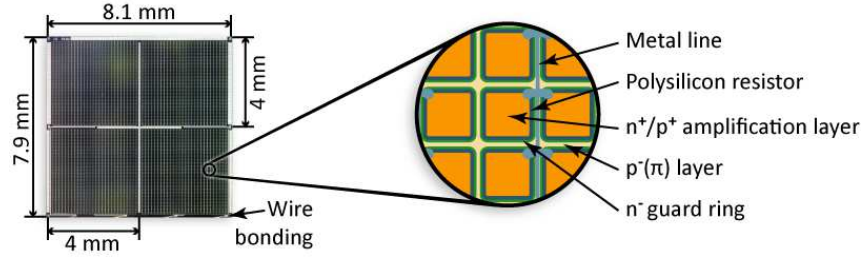


Figure 62: Microscopic photo of a monolithic 2×2 SiPM array from FBK as it was used on the sensor board (left) with magnified sketch (right) of the sensor structure (similar colors used as in Figure 57).

Sixteen of these arrays are mounted and bonded to the sensor board, resulting in an overall tile fill factor of $\sim 92\%$. The readout circuit is designed in a pseudo-differential way (Figure 63). As such, the sensitive analog connections between the SiPMs and the ASICs on the digitization board can make use of differential pair lines (ground and signal), which are less prone to Electromagnetic Interference (EMI) originating from the MRI. The backside of the PCB contains the readout resistors and Alternating Current (AC)-coupling capacitors for all 64 SiPMs. Resistor and capacitor arrays were used to save space. The two boards are each composed of two completely galvanically separated sides. This keeps conductive areas small and avoids forming a large loop over the connectors, where eddy currents could have been induced.

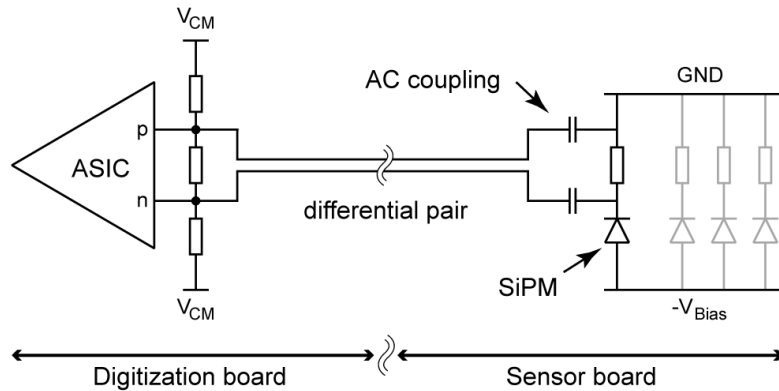


Figure 63: SiPM connection circuit. The SiPMs (one monolithic quad SiPM with a common anode is shown) are biased with a negative bias voltage and connected via quench resistors to ground. Detected light results in a current through the quench resistor. This signal is AC-coupled to a differential pair and transported to the ASIC. The ASIC, powered with a single positive voltage, provides a differential input, whose inputs thus need a centered common-mode voltage (V_{CM}).

Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.1.1.1.3 ASIC and Digitization Board

The connected digitization board contains two dedicated ASICs, each with 40 independent channels for amplification and digitization (Heidelberg University, Heidelberg, Germany). Every channel provides an independent time- and energy-measurement of the detected light pulses. Figure 64 sketches the function in a simplified block diagram. The input channels have fully differential analog input stages in order to achieve high noise immunity and to reject common-mode ripples induced by the MRI. A trigger discriminator compares the input voltage against a differential analog trigger threshold. This reference is made by a dual-channel Digital-to-Analog-Converter (DAC) on the interface board. The trigger logic latches

the timestamp taken from a common TDC. Due to the actual implementation, there are multiple synchronous TDCs on the ASIC (furthermore divided into coarse- and fine-counting). The trigger logic also starts the digitally controlled Analog-to-Digital Converter (ADC), which integrates the voltage over time (measuring the energy of the detected photons). A digital logic decides whether the data was valid, preprocesses TDC data, and shifts the data to a common digital readout register. More details about the ASIC are presented in (Fischer *et al.*, 2009).

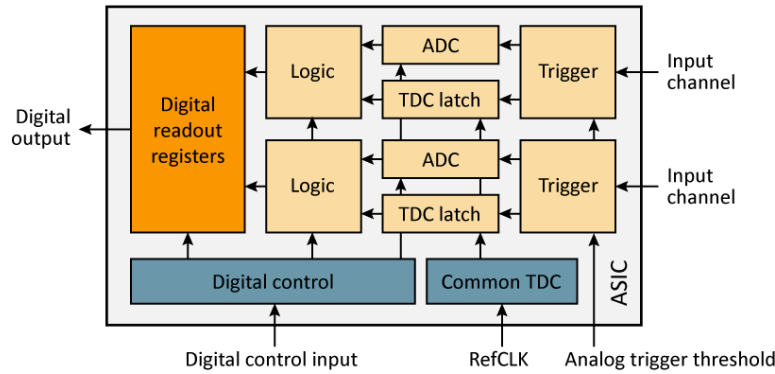


Figure 64: Simplified block diagram of the ASIC with two input channels (description: see text)

Fast circuits on the ASICs are realized in constant-current-mode logic to reduce RF emission from internal switching (and from the respective noisy currents on the power supply lines). Additionally, the power dissipation is constant, which reduces the risk of influencing the SiPMs temperature depending on activity. The drawback of the constant-current-mode logic is the high current uptake. In normal operation it is around 1.3 A per ASIC, and thus stitch wire bonds to the middle of the chip are needed to supply the current (see Figure 65). The ASICs are produced by United Microelectronics Corporation (UMC, Hsinchu, Taiwan) in a standard 180-nm-Complementary metal-oxide-semiconductor (CMOS) process.

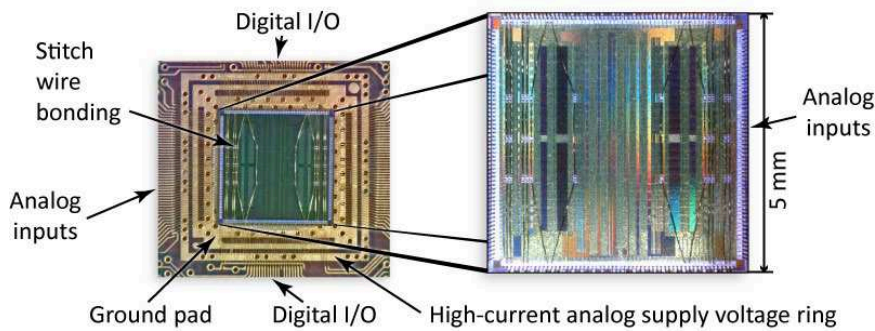


Figure 65: ASIC soldered and bonded the PCB (left), and microscopic photo of the ASIC itself (right). The ASIC is built up symmetrically, thus having twenty analog input channels on the left and on the right, whereas the digital I/O circuits are placed in the center of the chip, and are thus bonded to the top and to the bottom.

The TDCs of the ASICs are synchronized to a system-wide 625-MHz Reference Clock (RefCLK). The signal is transported to the digitization board with a single Low Voltage Differential Signaling (LVDS) line. Short stub-lines forward the signal from the single LVDS termination resistor to the differential CMOS inputs (with a high impedance) of the ASIC. Having two ASICs on one board results in a total of 80 input channels (the amount of

channels per ASIC is determined by the size of the silicon die, which is – in the shared production process used for universities and research – only available in certain steps). As only 64 channels are used by the SiPMs, eight channels (one for each TDC on the chip) are connected to system-wide synchronization pulse (Sync.). A further eight channels are used as spare channels and can replace broken channels, although this requires re-bonding before the chip and the bond wires are secured with a glob top.

5.1.1.1.4 FPGA and Interface Board

Real-time readout of the ASICs and pre-processing of the data are performed by a Field-Programmable Gate Array (FPGA) (Spartan-3, Xilinx, San Jose, USA) on the next PCB layer. It forms the interface between the detector stacks and the mainboard of the module. The stack hierarchy and its interconnections are displayed in Figure 66.

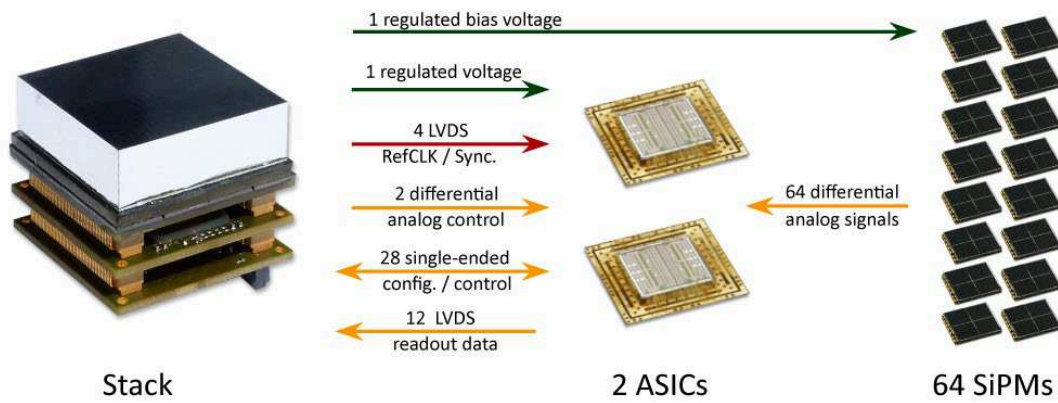


Figure 66: Detector stack hierarchy: The light from 484 crystals is detected by 16 2×2 SiPM arrays. Their signals are transported to two ASICs via analog differential pair lines. RefCLK, Sync., and all communication between the ASICs and the interface board are realized as LVDS pairs.

Figure published in the supplemental material of (Weissler *et al.*, 2014b) © 2014 IPEM.

The interface board, furthermore, contains two dual-channel DACs to create the required analog reference voltages. It additionally contains a linear regulator to supply the analog supply voltage (1.8 V) of the ASICs. Being close to the ASICs, this is able to filter ripples on the power supply line, originating from other digital circuits and from inductions of the MRI's gradients. Each ASIC of the board is only routed to one connector towards the sensor board. Although this complicates the layout of the PCB, it is important for ensuring the galvanic separation of the two connectors, as described in the section above.

Detailed numbers of the detector stack are summarized in Table 16.

Parameter	Value
Scintillation crystal size	$1.3 \times 1.3 \times 10 \text{ mm}^3$
SiPM sensor size	$4 \times 4 \text{ mm}^2$
Microcells per SiPM sensor	3080
Amount of individual readout channels	$8 \times 8 + 8^a + 8^b$
a) 8 channels are used for synchronization	
b) 8 spare channels	

Table 16: Details of the detector stack.
Table published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.1.2 Singles Processing Unit (SPU)

The mainboard of the SDM supports up to 3×2 stacks (Figure 68). It provides the processing power that is intended to process the raw data into qualified single events before they are transmitted to the data acquisition server. The mainboard of the SDM is, thus, the Singles Processing Unit (SPU). Parts of this chapter were published as a Conference Record, introducing the SPU (Weissler *et al.*, 2012b, © 2012 IEEE)

5.1.1.2.1 Detector Stack Support

The stacks are supplied with five regulated and three unregulated voltages, which are always stabilized with large tantalum capacitors. In the beginning of the project, the final SiPM connection circuit was still part of the ongoing research (e.g., a test sensor board with four different circuits was built and used). To adapt to the requirements of different SiPM types and connection circuits (e.g., positive or negative bias voltage), the bias voltage is controlled on a separate, exchangeable PCB on the backside of the SPU (Figure 67). Per stack, they regulate either positive or negative voltages and provide overcurrent-protection. The resulting bias currents are translated to voltages that are measured with an ADC on the SPU. Although standard ICs exist especially for APD bias current regulation (e.g., LT3905 from Linear Technologies, Milpitas, USA), they cannot be used because they employ switched-mode power supplies with ferrite-based inductors. Therefore, the circuits have to be made from other components, which is especially difficult for negative bias voltage: no IC with the necessary functionality could be found, and thus a (partly) discrete regulation circuit had to be developed.

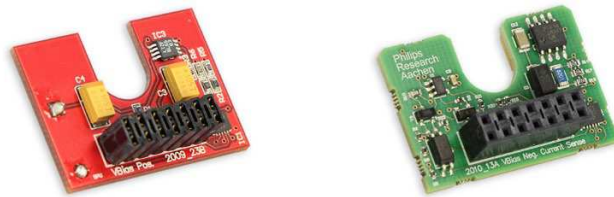


Figure 67: Vbias control boards for positive (left) and negative (right) voltages up to ± 40 V.
Circuit design by M. Zinke.

To measure the temperature of the sensors without producing any digital noise and with only one component on the (already filled-up) sensor board, a 4-wire PT100 temperature measurement-system is provided by the SPU at each stack connector.

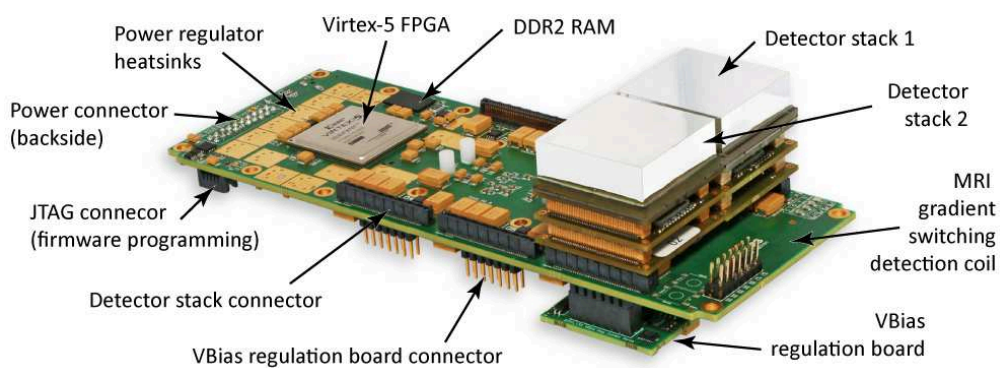


Figure 68: SPU v1.3 (top view) with two detector stacks and negative Vbias regulation boards

Multiple additional sensors are placed on the SPU to monitor and to control the function of the SDM:

- Input voltages (4-times) + one ADC for each stack to measure the bias current
- Temperatures (9-times) + one 4-wire PT100-system for each detector stack
- Humidity and dew point to enable maximum cooling
- Acceleration sensor to detect and quantify vibrations
- MRI gradient switching for wireless PET/MR synchronization (see section 5.1.2.1)

All communication from the ASICs down to the SPU (Figure 66 and Figure 70) is realized in shielded LVDS in order to reduce electromagnetic emission and to be resistant against electromagnetic induction from the outside (NationalSemiconductor, 2004). Communication with the stacks and most processing clock domains run at 100 MHz. Reference clock (RefCLK) (625 MHz) and synchronization signals (Sync.) are distributed by a high-speed (DC to 3 GHz), low-jitter fanout chip. The circuit is powered by its own local Low-Dropout Regulator (LDO) and power plane section to filter power supply ripples that might be induced by the MRI gradients. Aside from the magnetic properties, the LDO type was thus chosen on the Power Supply Rejection Ratio (PSRR) in the frequency range of the gradient switching. The RefCLK and Sync. LVDS transmission lines to the stack connectors all have the same length (difference < 1 mm), which serves to keep the skew between the stacks small (see section 5.1.1.6).

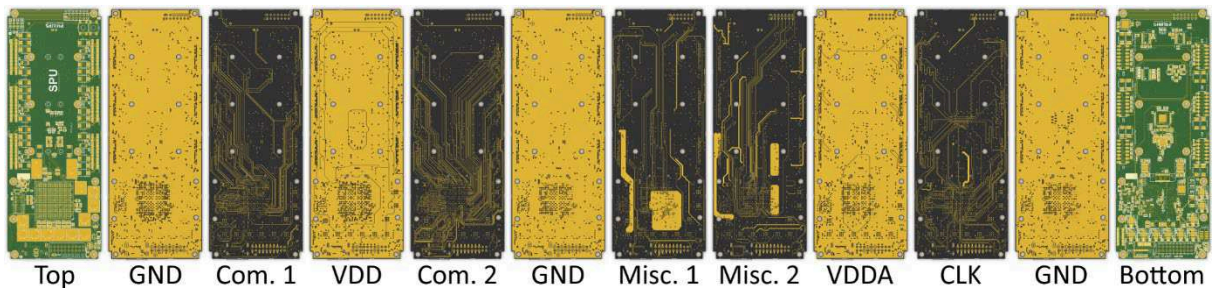


Figure 69: The 12-layer SPU PCB layer stack (from left to right): To reduce electromagnetic interferences the high-speed communication (Com) and clock (CLK) lines are embedded between grounds (GND) and power supply (VDD and VDDA) planes.

The layer stack of the 12-layer PCB (see Figure 69) is optimized for low electromagnetic interferences: ground layers were placed directly underneath the top and bottom layer, serving as a shield against radiation. Furthermore, all high-speed-communication lines are routed on three dedicated layers, each covered by two planes (ground and/or supply voltage).

A Virtex-5 FPGA (LXT Platform, 665-ball flip-chip fine-pitch ball-grid-array package, Speed Grade 1, 360 user I/Os) from Xilinx (San Jose, USA) provides the main processing power. Unlike the Spartan FPGAs used on the interface board, the packaging of the Virtex-5 comprises an integrated heat spreader, a fanout PCB, and discrete substrate capacitors. Although these capacitors result in a relatively large B_0 distortion, they help to keep the electromagnetic interferences low, as they decouple very close to the FPGA silicon (without the extra inductance of PCB traces and vias).

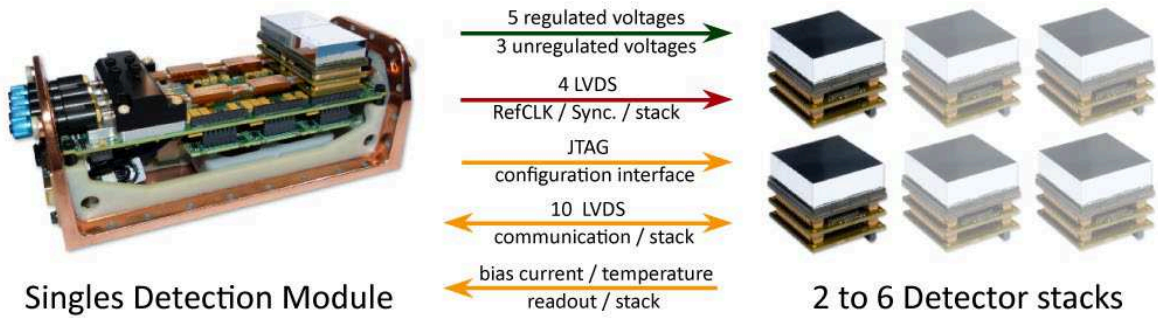


Figure 70: Module hierarchy: The stacks are supplied with regulated and unregulated voltages. Differential signaling is used for RefCLK/Sync and communication to reduce electromagnetic emission and to be resistant against noise from the outside.

Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.1.1.2.2 Firmware Configuration and Debugging

The firmware on the FPGA (Gebhardt *et al.*, 2012) collects and further processes the data from the detector stacks. It is automatically loaded to the FPGA from a Serial Peripheral Interface (SPI) flash chip after the implemented local power-up sequence has finished. Once the FPGA is configured, it can communicate with a PC via Ethernet or Universal Serial Bus (USB). Using this communication connection, the firmware in the flash chip can be programmed, allowing firmware updates without additional physical access to the SPU. The FPGAs on the interface boards are also programmed via this communication link: their configuration is sent from the control PC to the SPU FPGA in the Serial Vector Format (SVF) – a Joint Test Action Group (JTAG) data stream. The SPU FPGA has a JTAG-player module, which forwards the data to the FPGAs on stacks (see Figure 71).

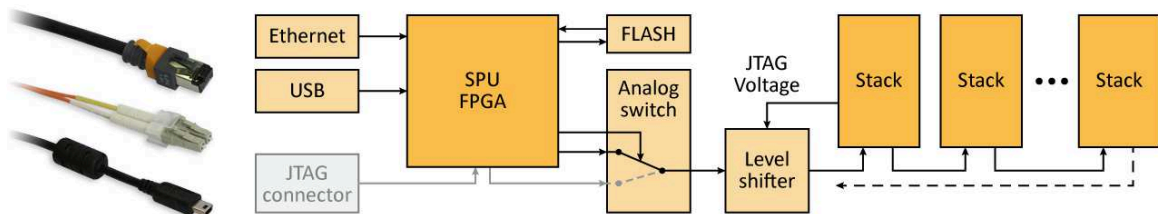


Figure 71: Configuration of all FPGAs through the standard communication of the SPU: Ethernet and USB (only until SPU version v.1.2). During power-up, the SPU FPGA is configured by the SPI flash. Once booted, the SPU can communicate and the SPI flash and the other stack FPGAs are configured by the control software.

The JTAG-voltage required by the FPGA on the detector stack is determined by a control pin on the stack connector. A level-shifter circuit converts the JTAG signals accordingly. Additionally, this circuit has an R-C low-pass filter, which is implemented to reduce the slew rates of the outgoing signals to reduce cross talk and ringing on the lines. To control the JTAG chain, the SPU FPGA actively toggles an analog switch circuit. By default, the switch connects the complete chain to a connector on the SPU (see Figure 72).

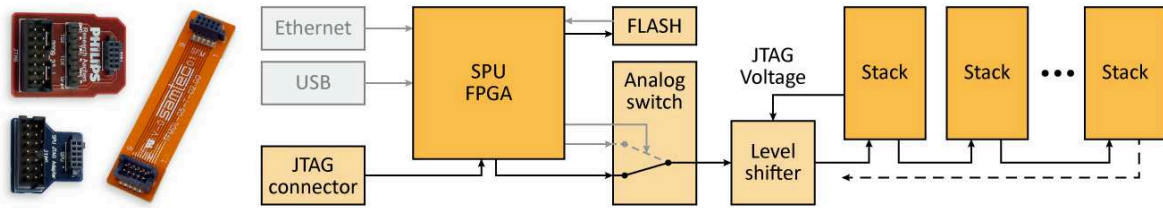


Figure 72: Configuration of all FPGAs through a JTAG connector: With adaptors and flexible extension cables (left), the complete JTAG chain can be used with standard JTAG software (only one direction of the chain is shown in the schematic view).

By using an adaptor (for this small and non-magnetic connector), the JTAG chain can be controlled by a standard USB-to-JTAG device (available, e.g., from Xilinx or Digilent Inc, Pullman, USA). In the same way, the SPI flash chip is programmed before it can be used to boot the SPU. The external control of the JTAG chain with standard JTAG software has a further important role: it can be used to connect to special firmware cores for debugging (e.g., the Xilinx ChipScope firmware logic analyzer). Debugging solutions are very important in the system integration phase: Without the possibility to connect almost every electrical line to a logic analyzer and an oscilloscope, larger projects are almost impossible to realize. As all electronics in the SDM are very densely packed, multiple PCBs were designed and dedicated to the debugging purposes of the SPU – a few of them are shown in shown in Figure 73 (debugging PCBs dedicated to the stack are presented in Figure 119 of chapter 6.1.1.2).



Figure 73: Debugging PCBs to connect the oscilloscopes and logic analyzer (header pins and Matched Impedance ConnectOR (Mictor)) to a small, non-magnetic, connector on the SPU. A third PCB (center) contains an RS-232 interface.

The RS-232 interface board (Figure 73, center) allows a terminal window to the integrated PowerPC processor on the Virtex-5 FPGA to be opened. By using this, e.g., the 128 MByte of DDR2 memory on the SPU was successfully tested. This memory is henceforth available for buffering data and for the singles processing.

5.1.1.2.3 Communication

The 100 MHz clock for the communication with the stacks and for most FPGA-internal firmware modules was chosen, since it equates – after an 8B/10B encoding – to the 125 MHz clock used by Ethernet Media Access Controller core of the FPGA. Early versions of the SPU (until version v1.2) supported USB for communication with a PC using an FTDI FT2232D IC (Future Technology Devices International, Glasgow, United Kingdom). This allowed for a simple connection to every PC, and thus a fast development and debugging of every component. Furthermore, long USB extension cords using optical communication are available off-the-shelf. In a non-conductive version, they can be routed through waveguides

into the RF shielding of the examination room, which made early MRI experiments possible. Since the 12 Mbit/s maximum data rate of the USB 1.0 Full Speed used is much too low, it was replaced by an optical Gigabit Ethernet communication (1000BASE-SX). This communication standard was chosen as beneficial to the project for the following reasons:

- Gigabit Ethernet provides the needed bandwidth to transport the raw data from a complete SDM.
- Optical communication maintains galvanic isolation and does not interfere with the electromagnetic fields of the MRI. Furthermore, passive optical connecting of multiple cables is possible without any metal components.
- The optical version of Gigabit Ethernet allows a direct connection of the transceiver to the FPGA, without an additional physical layer chip (aside from additional B_0 distortion, they employ communication through inductively coupled coils at 125 MHz, which is relatively close to the 128 MHz of the 3-T MRI RF system).
- Using media converter to copper-based Ethernet (10 Mbit/s / 100 Mbit/s) it can connect to almost every PC.
- As a mass product, various mature components are available, which are still very cost effective¹⁰.
- A standard network switch with a 10GbE backplane connector might be used as data concentrator to one Ethernet adaptor.
- The Virtex-5 FPGA has a built-in Ethernet Media Access Controller core that handles the media communication layer, and the implementation of a UDP-Internet Protocol (IP) in firmware is relatively simple.
- Ethernet sockets are available on all Windows and Linux operational systems (x86 and x64) without the installation of external drivers. Access to the sockets is built into all common programming languages.

In the final insert, the data are sent using the User Datagram Protocol (UDP) to the data acquisition server outside the examination room (see Figure 89 in section 5.1.8).

5.1.1.2.4 B_0 Homogeneity Optimization

All electronic components of the SDM were tested with respect to the presence of magnetic material and were selected in experiments as described in section 3.2.1. Some devices (e.g., tantalum capacitors) were found in low- or non-magnetic versions with similar electrical properties. In some cases, completely different technology was needed: Figure 74 shows the distortion caused by a single quartz oscillator, which was used to generate the high frequency clocks on the first SPU designs. It was replaced by Micro-Electro-Mechanical Systems (MEMS) that became available in small, plastic housings.

¹⁰ A standard 10-m long multi-mode duplex cable (50/125 μ m, OM3) is currently available with overnight-shipping for 16 €.

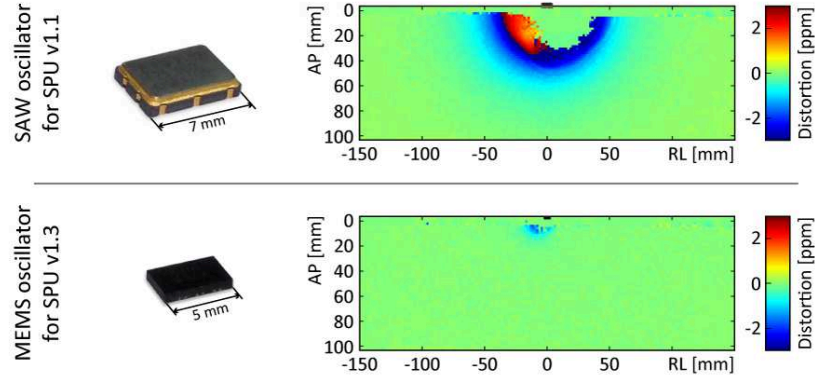


Figure 74: B_0 component testing in the MRI: The distortion caused by a standard quartz oscillator (top) is lower than 0.5 ppm only at a distance of 55 mm. In close proximity to the device (up to 30 mm radius), the distortion is so high that phase is wrapped over 2π to positive values (left part), or the signal gets completely lost (right side). From the alternative oscillator, using MEMS technology, only a distance of 15 mm has to be maintained for the same distortion.

Other components, e.g., many connectors, were especially manufactured for this project in non-magnetic versions. A few devices, such as ferrite beads, coils with ferrite cores, and ceramic capacitors with high capacity were completely rejected, and alternatives had to be found. The ASICs of the digitization boards are directly bonded to the PCBs in house, since lead frames are often very magnetic and influencing packaging companies appeared to be very difficult. The highly magnetic gigabit transceiver was placed on a separate PCB to move it to a larger distance from the FOV. The resulting B_0 disturbance of a single SPU is shown in Figure 75. The maximum FOV (inner diameter of the RF coil) of the targeted system starts about 53 mm from the SPU. At that distance, one of the first test models of the SPU (version v1.1) still causes disturbances with complete signal loss, whereas the disturbance of the used version v1.3 is significantly reduced.

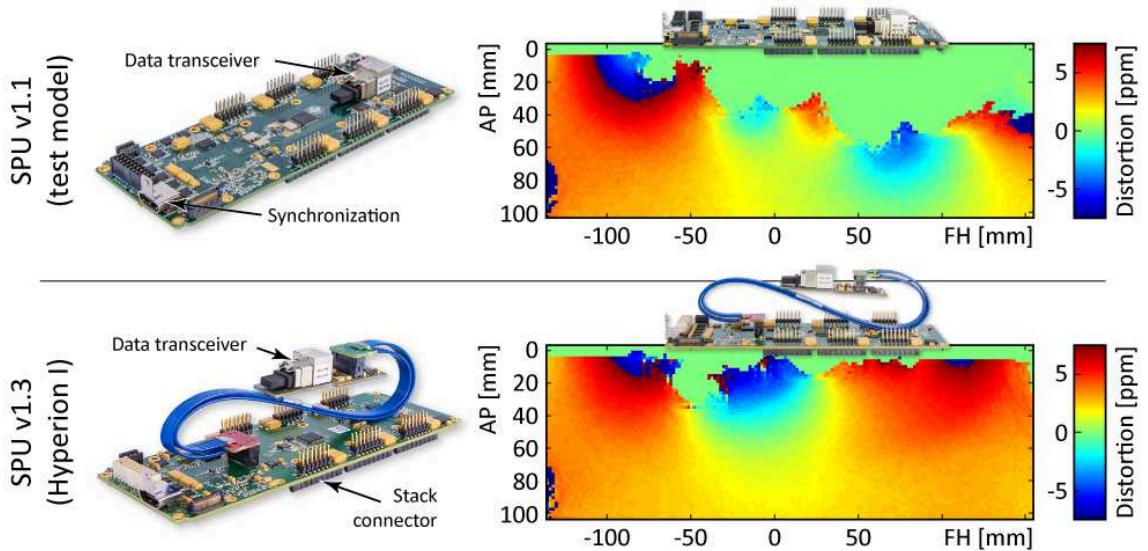


Figure 75: B_0 distortion caused by one of the first test models of the SPU (top), and the SPU v1.3 (bottom) that was used to build the Hyperion I insert. Equivalent to Figure 74, the regions close to the SPU, depicted with 0 ppm, have too high of a distortion to be measured. The negative values are caused by the phase, wrapped over 2π , and are thus even higher values than the already unacceptable 5 ppm. The devices used in the scan, and their size and position, are indicated in the field plots.

5.1.1.3 Module Power Supply

The power supply concept for the insert begins inside the SDMs, where all voltages are generated close to the loads by linear low-dropout (LDO) regulators. These were chosen according to their power supply ripple rejection capabilities in the frequency bandwidth of the MRI's gradient system, their magnetic properties, and their requirements with respect to stabilizing capacitors. Standard switched-mode power supply circuits for multiple amperes of output current use coils with ferrite cores, and they can thus not be used in the magnetic field. To keep the power dissipation in the linear regulators at moderate levels, the SDMs are fed with four different voltages, which are specified at the entrance of the module: 1.7 V (2 A) to generate the voltages of the FPGAs cores and their transceiver circuits, 3 V (8 A) to generate the supply voltages for the ASIC and the inter-FPGA communication, and 4.5 V (2 A) to generate power for the optical communication and some circuits based on 3.3 V electronics. Finally, -39 V (20 mA) is applied to generate the bias voltage for the SiPMs.

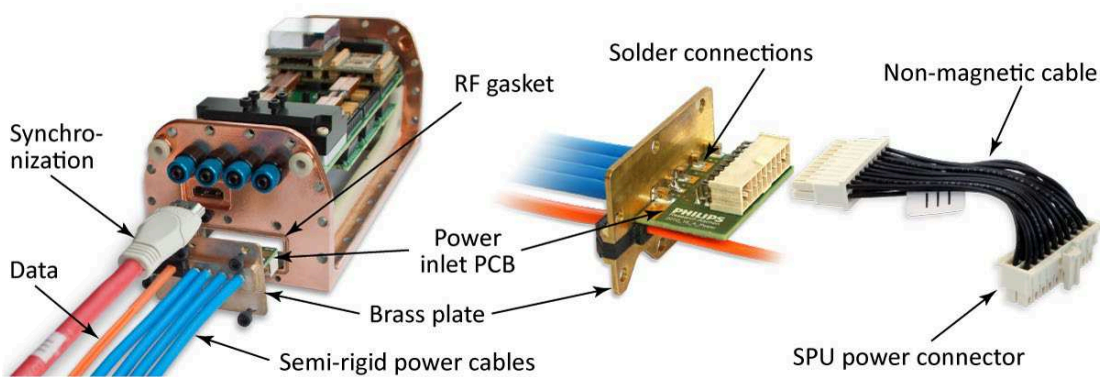


Figure 76: RF-tight power inlets into the SDM. The screens of the semi-rigid cables are soldered to a power inlet PCB and brass plate, which is screwed to the SDM housing. A flexible non-magnetic cable connects to the SPU power connector (see Figure 124).

Figure partly (left part) published in (Weissler *et al.*, 2014b) © 2014 IPPEM.

Semi-rigid coaxial cables are used close to the gantry for their superior RF shielding and their low static magnetic stray fields (compared, e.g., to twisted pair cables, as shown in Figure 37 of chapter 3.2.1). They enter the SDMs through a brass plate, which forms an RF-tight power connector (see Figure 76). Inside the SDM, the power is transported to the SPU using a flexible cable with twenty wires. Current directions on the cable are interleaved to keep the combined B_0 disturbance, caused by DC supply currents, low.

5.1.1.4 Module Cooling

The SDMs, with an approximate power dissipation of 37 W each, are cooled via a combined water (15° C) and air (available air supply at the MRI examination room: 18° C, 29 % relative humidity) chilling system. ASICs, FPGAs and regulators are water cooled through two independent counter flow systems to achieve equal temperature across all stacks (Figure 77). The copper pipes are electrically insulated, and a non-conductive plastic part feeds the water through the module screen. In doing so, the RF shield is not penetrated, nor are any loops formed where large eddy currents can flow. The power regulators and the FPGA on the SPU are thermally coupled to the liquid cooling pipes via an aluminum heat sink, which is split into two parts to reduce the electrically conductive area spanned.

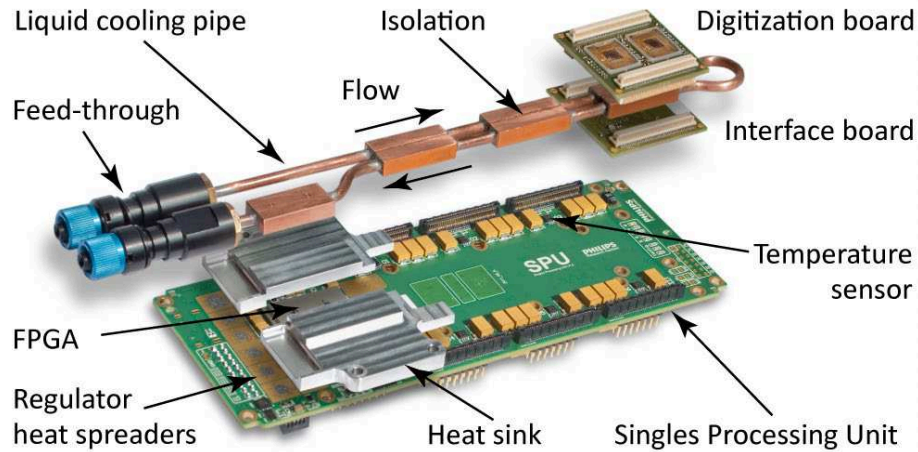


Figure 77: Exploded view of the liquid cooling system inside the SDMs (only one of two cooling pipes and one ASIC- and interface board are shown). The parts are thermally coupled via non-conductive thermal pads.

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.1.5 RF Screen

The module housing was manufactured from a liquid resin with ceramic particles using stereolithographic technology. It is capable of producing very smooth surfaces. A copper layer for light- and RF tightness was electro-galvanized onto the layer. To increase the resistance for eddy currents (induced by the gradient fields) while ensuring sufficient RF shielding, the copper layer should be around three times the skin depth at the MRI RF frequency (Carlson, 1994). The resulting 18 μm could be produced reliably on average on the intended housing shape. The galvanization process demands a slight conductivity, which was realized by applying a silver-based lacquer. This 15 μm to 20 μm thick layer has an approximately fifteen times higher sheet resistance (14.3 mOhm/sq) than the copper layer (0.9 mOhm/sq), and can thus be neglected (see Figure 78). To further increase the resistance to eddy currents, the two parts of the housing plus the PCB lit on the backside are connected via RF gaskets with a high-pass characteristic (Ag/Cu coated foam cord, Neuhaus, Berlin, Germany).

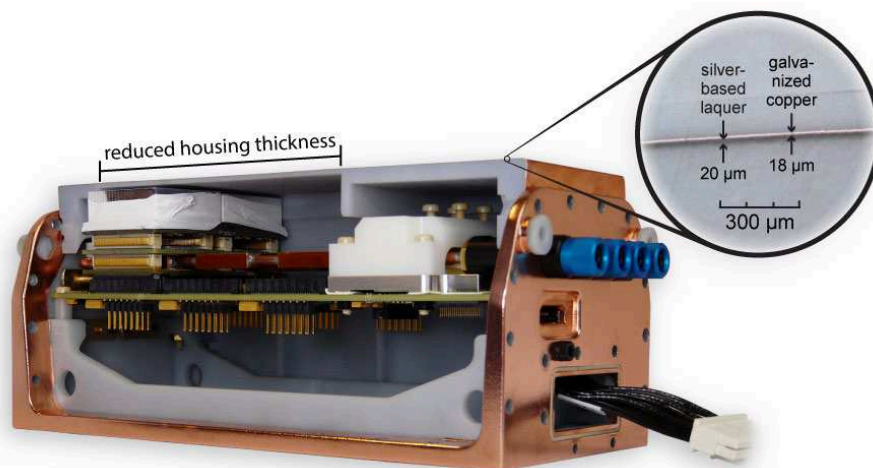


Figure 78: The SDM housing. The area covering the crystals is relatively thin to reduce scattering of the gammas. A copper layer of 18 μm thickness was electro-galvanized on the outside of the housing as an RF shield.

Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.1.1.6 Assembly

As described above, an SDM can be equipped with 3 x 2 detector stacks. The axial FOV can thus be varied depending on the number of used stacks (Figure 79). Stack 1 and 2 were assembled on 10 SDMs to form a complete PET ring.

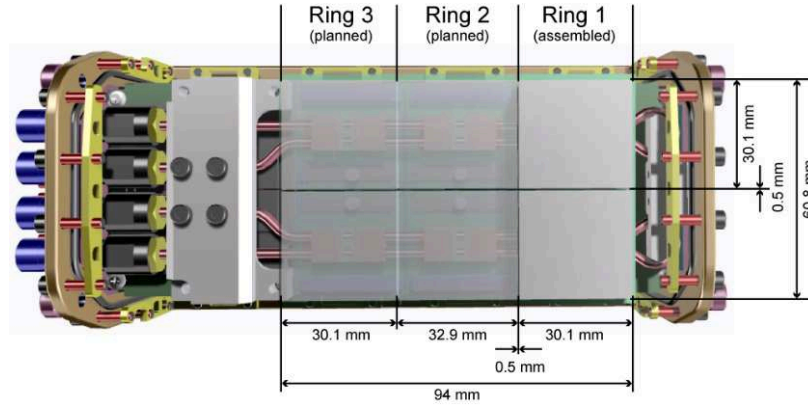


Figure 79: 3D model of the open Singles Detection Module. The dimensions given describe the size of the crystal arrays – the active detection area. The sensor boards (visible in light green underneath the crystal arrays) are slightly larger than the crystal arrays.

Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.1.2 Synchronization

Two kinds of temporal synchronization are needed for the completed system: A synchronization of the otherwise independent SDMs and a synchronization between PET and MRI as explained in chapter 3.4.2.

5.1.2.1 Synchronization of SDMs

The independent SDMs need to be synchronized to measure the time of arrival of the gammas with sub ns accuracy over the whole system. A centralized unit generates a low-jitter reference clock of 625 MHz with a custom-made Surface Acoustic Wave (SAW) filtered quartz oscillator (Epson Toyocom, Tokyo, Japan). Eleven signals are derived using a low-jitter LVDS fanout-buffer IC (Micrel, San Jose, USA). While ten of the signals are directly sent to the ten SDMs, one of the signals is divided by a programmable clock divider and fed as a trigger signal (156.25 MHz) to the SPU FPGA. The FPGA can now generate software-controlled Sync pulses that are linked to the reference clock. The Sync signal is distributed over the same (dual-channel) fanout buffer as the RefCLK. Together, they are sent to the SDMs, where again a fanout IC is used to distribute the signals to the detector stacks. To keep the signal delay similar, all PCB traces have approximately the same length. Signal transmission from the synchronization unit to the SDMs is realized over 2-m long HDMI cables (see Figure 80 and Figure 89). These cables come with an additional RF screen (continuously connected to the metal housing of the plugs) around multiple high-quality shielded differential pairs, and thus promise very good EMI properties. The synchronization unit itself also has an RF shield, which is directly connected to the screen of the cables (Figure 80). Relatively large and thick copper walls (compared to the SDMs) are used here, since the unit is placed outside the influence of the gradient coils.

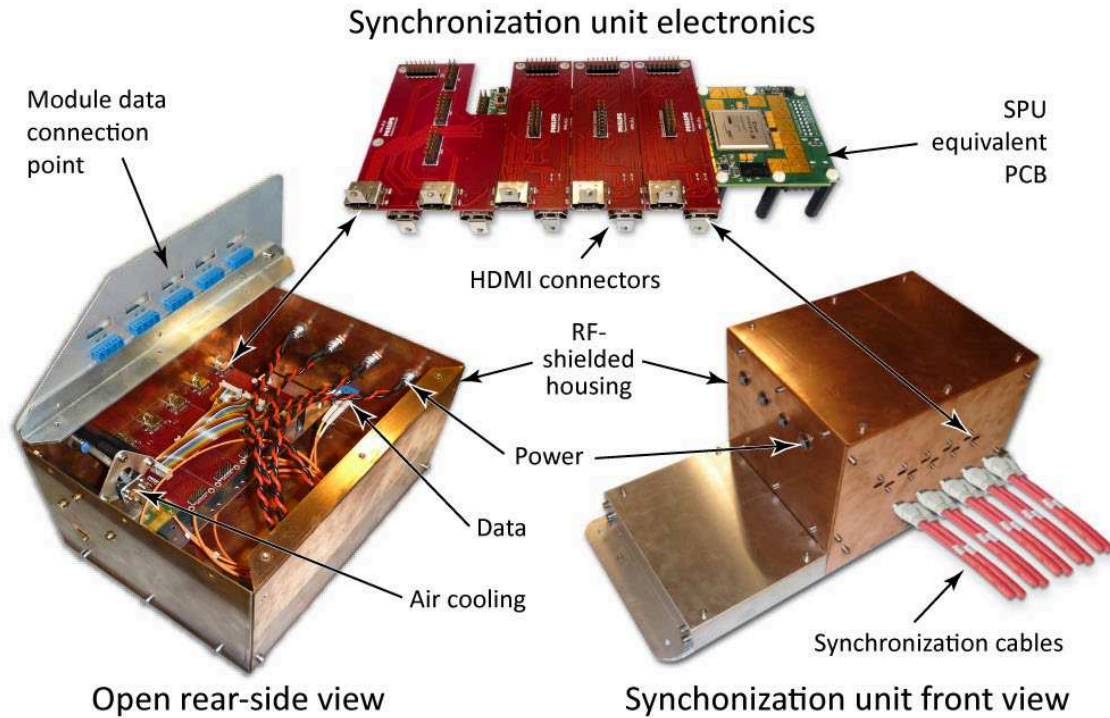


Figure 80: Centralized synchronization unit: The electronics (top), realized with piggyback boards on an SPU-equivalent PCB, generating and distributing reference clocks and software-controlled synchronization pulses for the SDMs.

Figure partly (top and right part) published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.2.2 Synchronization Between PET and MRI

As described in chapter 5.1.1.5, the SDMs are shielded against RF fields from the MRI scanner (and the MRI scanner from the fields generated by the SDM electronics), but the gradient fields penetrate that shielding due to their relatively low frequency. The normally unwanted effect of induced voltages in the electronics caused by these switching fields (see section 3.1.2.3) is used to realize a synchronization between the PET and MRI systems. Two coils from PCB traces and vias were deliberately constructed on the SPU of each SDM: one in axial and one in transaxial direction (Figure 81). The two coils are connected in series, so that voltages induced by changing fields of the Z-gradient add up.

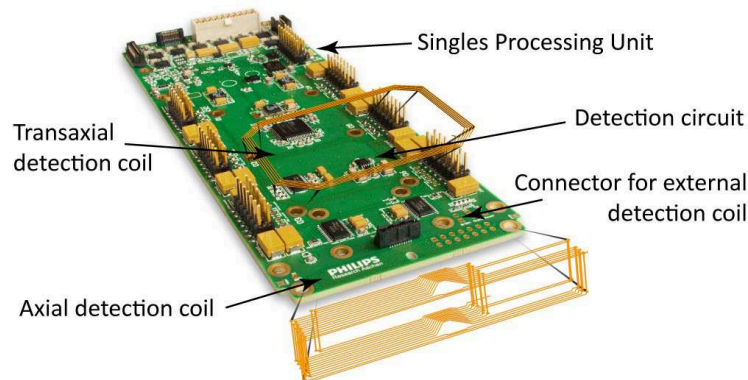


Figure 81: Transaxial and axial detection coils, made from PCB traces and vias on the SPU (coils shown as exploded-view drawing).

The coils are connected to a detection circuit (Figure 82, top row). A voltage is induced by the changing flux through the windings when the gradients of the MRI switch. The coil is AC-coupled to a voltage divider. It shifts positive and negative pulses into the positive voltage range that can be used by standard electronics. A software-controlled DAC sets a threshold voltage, which is compared against the voltage at the voltage divider by a comparator. The output is a 1-bit digital signal, and the firmware in the SPU FPGA generates a message with a PET timestamp when this signal changes.

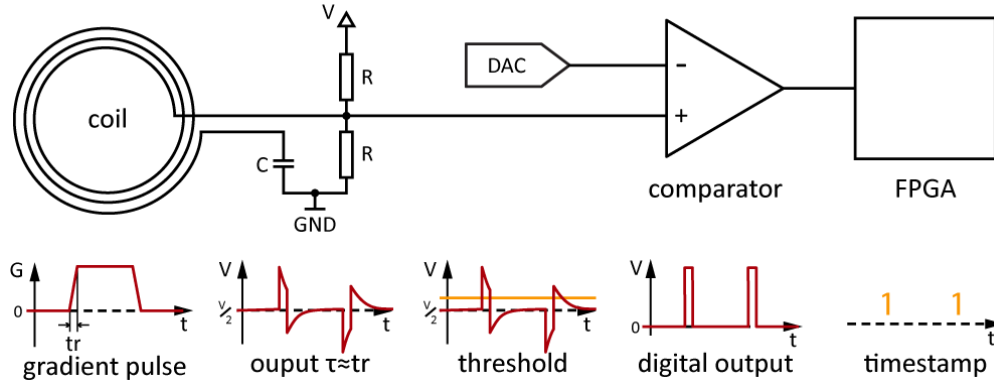


Figure 82: Gradient switching detection circuit (from left to right): pick-up coil, AC-coupling to voltage divider, threshold-defining DAC, comparator, and time stamp generation in the FPGA. The lower row indicates the shape of the gradient intensity (left) and the signal over time at each stage of the circuit.

Figure published in (Weissler *et al.*, 2015b).

The simulated (SPICE) voltage curves over time in (Figure 82, bottom row) depict that positive and negative slopes can be detected, since the AC-coupling capacitor C and the resistors R in the voltage divider are chosen in such a way that the time constant of the RC-circuit τ is close to the rise time t_r of the gradients. More details about the synchronization attained through the detection of the switching gradients are presented in (Weissler *et al.*, 2014a).

5.1.3 Gantry

The preclinical PET gantry is built from 10 SDMs around the MRI RF Tx/Rx coil. The gantry mechanics are built from polyoxymethylene copolymer (POM-C), which was chosen for its mechanical properties (stiffness, low water absorption, good machinability), its chemical properties (resistance against cleaning and disinfection agents), and its good results from the MRI compatibility tests (low conductance, low B_0 distortion). The gantry provides the infrastructure (power, cooling, data, and synchronization) and the mechanical alignment (Figure 83, left). Its outer diameter is roughly 40 cm.

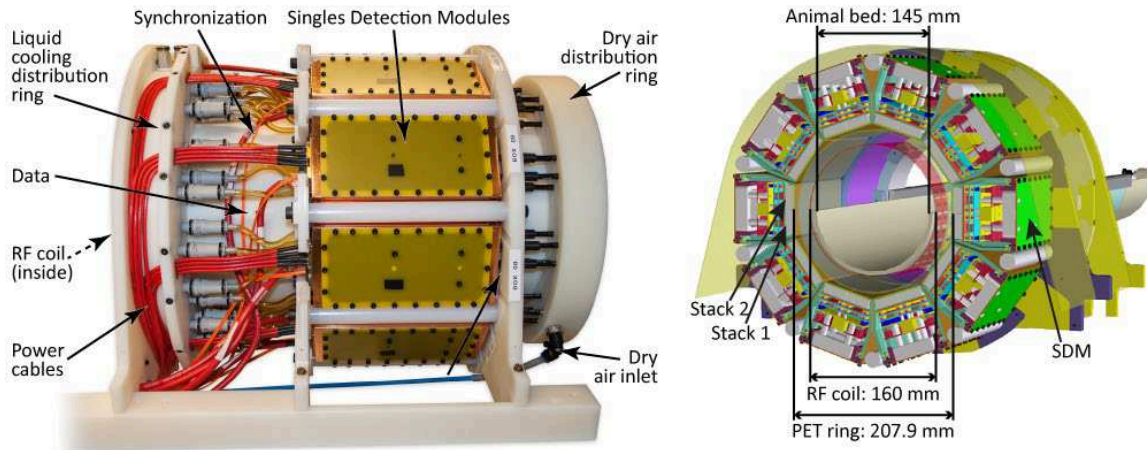


Figure 83: Preclinical PET/RF gantry formed by 10 SDMs (left). A 3D model of the gantry, shown from the backside and cut at the position of the detector stacks (right), depicts the dimensions.

Right part of the figure published in the supplemental material of (Weissler *et al.*, 2014b).

An animal bed was built from Plexiglas. It slides into the gantry and snaps into place when the center of FOV is reached. Table 17 and the 3D model shown in Figure 83 (right) display the resulting dimensions and system defining details.

Parameter	Value
Total amount of detector stacks	20 (60) ^a
Total amount of crystals	9680 (29992) ^a
Total amount of independent sensor channels	1280 (3840) ^a
PET FOV (pixel-to-pixel transaxial × axial)	207.9 mm × 30 mm (94 mm) ^a
MRI FOV (transaxial × axial)	160 mm × 160 mm
Hybrid PET/MR FOV (transaxial × axial)	160 mm × 30 mm (94.1 mm) ^a
Animal bed diameter	145 mm

^a) Values in brackets stand for a fully equipped system

Table 17: System details of the PET/RF insert.
Table published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.4 Power Supply

As described in section 5.1.1.3, semi-rigid coaxial cables are used close to the gantry for their superior RF shielding and almost vanishing static magnetic stray fields.

The power supply itself is placed inside the MR examination room and uses a standard filtered AC wall outlet. Placing it outside the RF cage of the MRI (as, for instance, is done for the RF coil power supply of the MRI scanner) would cause two problems: Firstly, the long cables would be very heavy, expensive, and cause too high voltage drops. Secondly, each conductor that penetrates the RF cage has to be filtered. Not only would that be very expensive (every standard filter costs about 80 € and two are needed per power supply line), it would also require a modification of each MRI examination room, where the insert would be used.

Inside an RF-shielded housing of the power supply, eleven iMP4 power supplies units (Emerson, St. Louis, USA) generate 43 galvanically separated DC voltages (Figure 84). As

their output current can go up to 35 A, an additional current-measuring and overcurrent-shutdown circuit was developed and added to each output.

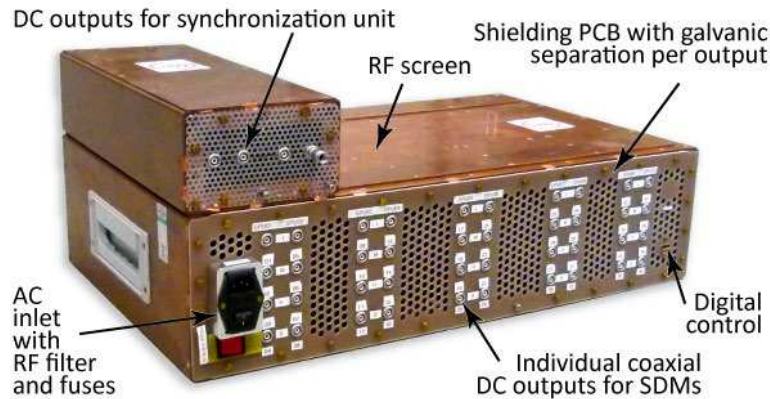


Figure 84: Power supply with 43 galvanically separated, coaxial DC outputs in an RF screened housing.

All eleven power supplies are digitally controllable. They are connected to two Inter-Integrated Circuit (I²C) busses that are connected via an HDMI cable to the synchronization unit (see section 5.1.2.1). As such, the power supplies can be switched on by software in a controlled manner (e.g., enabling the high bias voltage only after the SDMs are completely booted).

A schematic view of the grounding concept is shown in Figure 85. The screen of the SDMs serves as a combined ground for the module. RefCLK / Sync are transported to the modules from a central synchronization unit via HDMI cables. The screens of these cables are galvanically connected to the modules as well as to the synchronization unit, which, therefore, forms the single star point of the ground for the system. The screens of the coaxial power supply cables are only connected with capacitors to the housing of the power supply. Without that galvanic separation, a loop with the ground star point at the modules would be formed, and the return currents would not be forced to take the same cable as they came from. All cables are equipped with additional ferrite cores to suppress residual high-frequency common-mode currents from the switched-mode power supply.

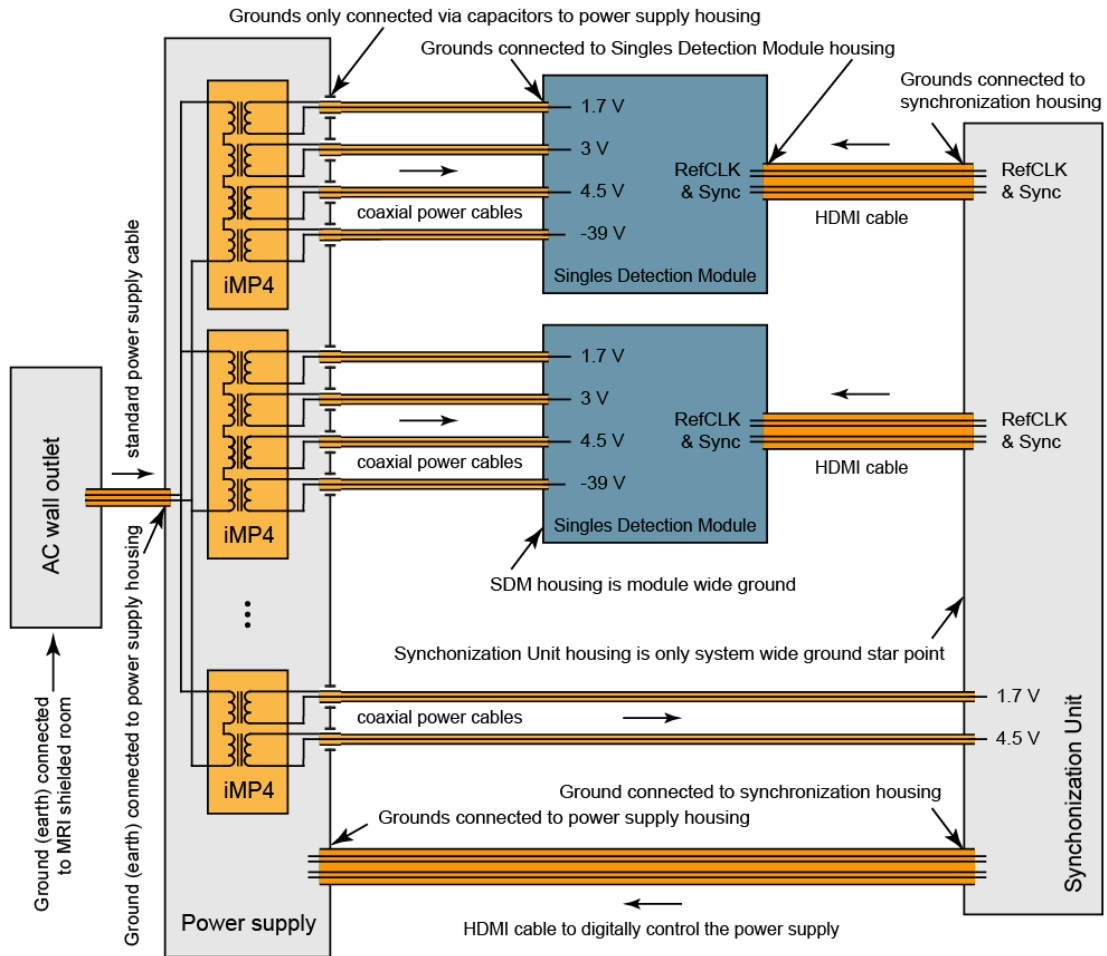


Figure 85: Power supply concept (see text for detailed description).
 Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.1.5 RF Coil

The MRI RF transmit/receive coil (16-rod birdcage resonator) is permanently mounted inside the PET ring. Being outside the RF screen of the coil, the SDMs do not disturb the transmitted fields of the coil, and the sensitivity of the coil to noise from the PET electronics is lower. Furthermore, the SDMs are not directly exposed to the RF fields, and the excitation of common-mode currents on the cables is reduced. The drawback of that choice is that the gammas have to travel through the entire RF coil. Therefore, the coil uses thin copper layers as conductors for rods, and all electronic components are moved outside the PET FOV (Figure 86). The coil electronics (coil identification, power splitter, and preamplifier) are taken from the Philips Transmit Receive Head coil.

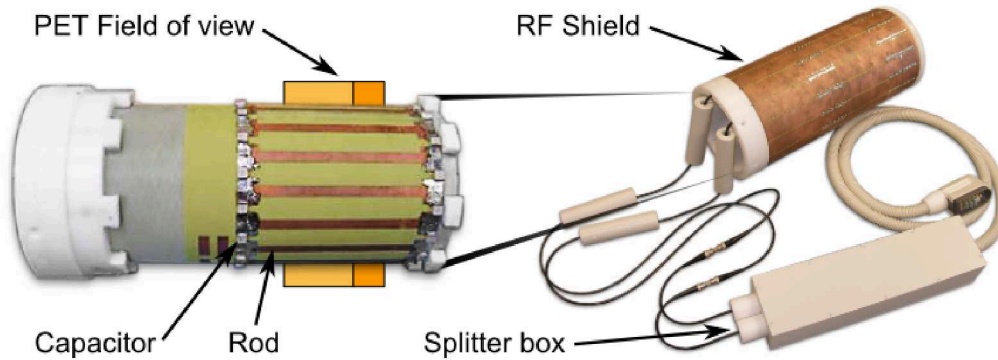


Figure 86: PET compatible RF coil with connecting cables and coil electronics (right). The interior of the coil is shown on the left (current PET FOV with one PET ring indicated in dark orange, the planned full PET FOV with three rings in light orange).

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.6 Insert

The PET/RF insert is mounted on a fixed frame, which snaps into the patient table of a clinical MRI scanner, providing the rest of the MR imaging chain (Figure 87). The infrastructure (power, data and cooling) is brought to the insert via a detachable cable carrier, so that the insert can be installed inside the MRI examination room from three separate parts. The cable carrier (cable slab) supports the controlled movement of the insert into the MRI bore, which is carried out by the normal patient table control.

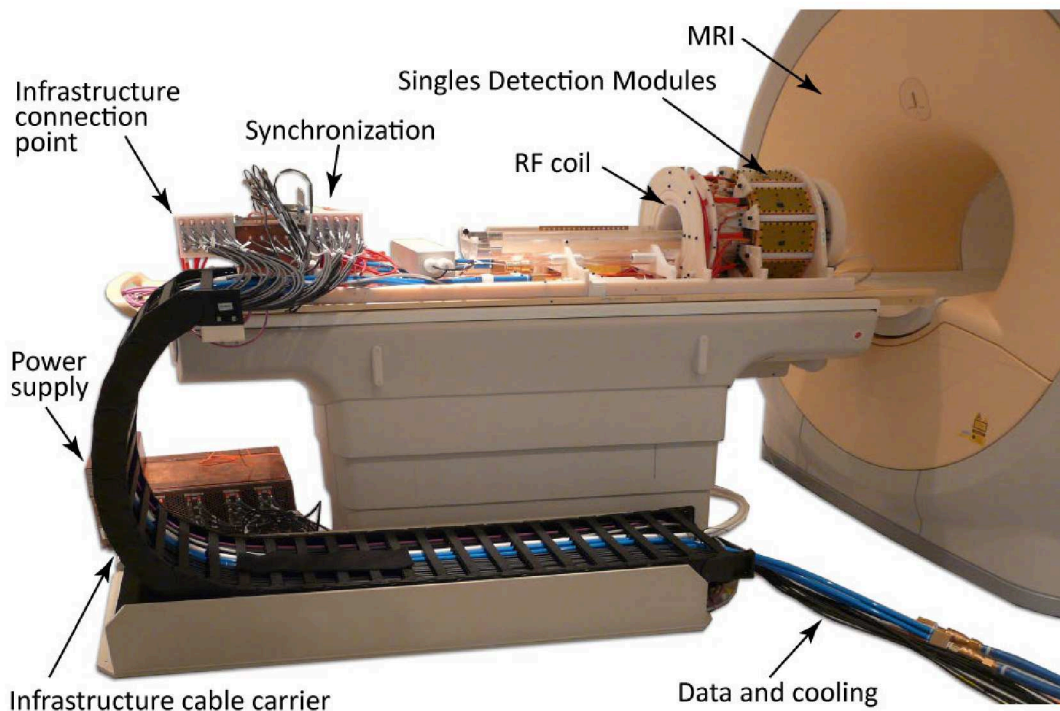


Figure 87: The PET/RF insert "Hyperion I" mounted on the patient table of a clinical 3-T MRI system.

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

5.1.7 Cooling

Liquid cooling is provided by a transportable Integral XT 150 process thermostat (Lauda, Lauda-Königshofen, Germany) in the technical room (Figure 88). Compared to simpler (and less expensive) heat exchanger systems, it can hold the outflow temperature with a precision of ± 0.05 K. This is an important characteristic, as early lab experiments, monitoring the stability of the photo peak for single SiPMs, already showed the influence of the laboratory air conditioning, which regulated the room temperature only within ± 0.5 K. The maximum cooling power of the Integral XT 150 is about 1.2 kW at 15° C (1kW at -10°C), which is about twice the expected power dissipation and thus well dimensioned for the scanner. The temperature of the cooling liquid is normally set to 15° C and the pump pressure to 1 bar. An ethylene glycol / water combination (Kryo 30, Lauda) is used as the cooling agent, which allows for cooling temperatures to reach as low as -20° C. The electrical conductance of 2 Ohm $\times$ cm is about ten times lower than normal tap water. This is important to avoid corrosion from the buildup of galvanic voltages and to prevent forming a large conductive loop (against induction from the MRI gradient system). Although material incompatibilities are not known to the vendor, multiple long-time tests were made with the plastic tubes and rubber gaskets used.

A malfunction of the cooling system is dangerous to the PET detector hardware, and there are many ways that possible failures can occur: Freezing of the chiller, low level of cooling agent, incorrect connection of cooling tubes, or simply forgetting to switch it on. Therefore, a safety mechanism is needed for its daily use. The process thermostat can be controlled with a serial interface (RS-232), which was implemented into the systems control software (presented in chapter 6.1.7.5). As such, the cooling system can be switched on by the software, and its proper functioning is checked automatically before the system is started. Additionally, the cooling temperature can be set by the software that is used to program temperature profiles, thereby shortening the time to a stable system temperature and preventing condensation after system shutdown.



Figure 88: Liquid cooling system: transportable Lauda Integral XT 150 process thermostat.

5.1.8 Communication and Control

The insert is controlled on a workstation next to the MR console in the MRI control room. This workstation is connected to a Data Acquisition and Processing Server (DAPS) (Dell

Poweredge R910 server with 4× Intel Xeon X7560 CPUs and 256 GByte RAM) in the MR technical room. It routes control and status communication to the control workstation, while PET data coming from the SDMs are directly pre-processed and stored on a RAM disc (Figure 89).

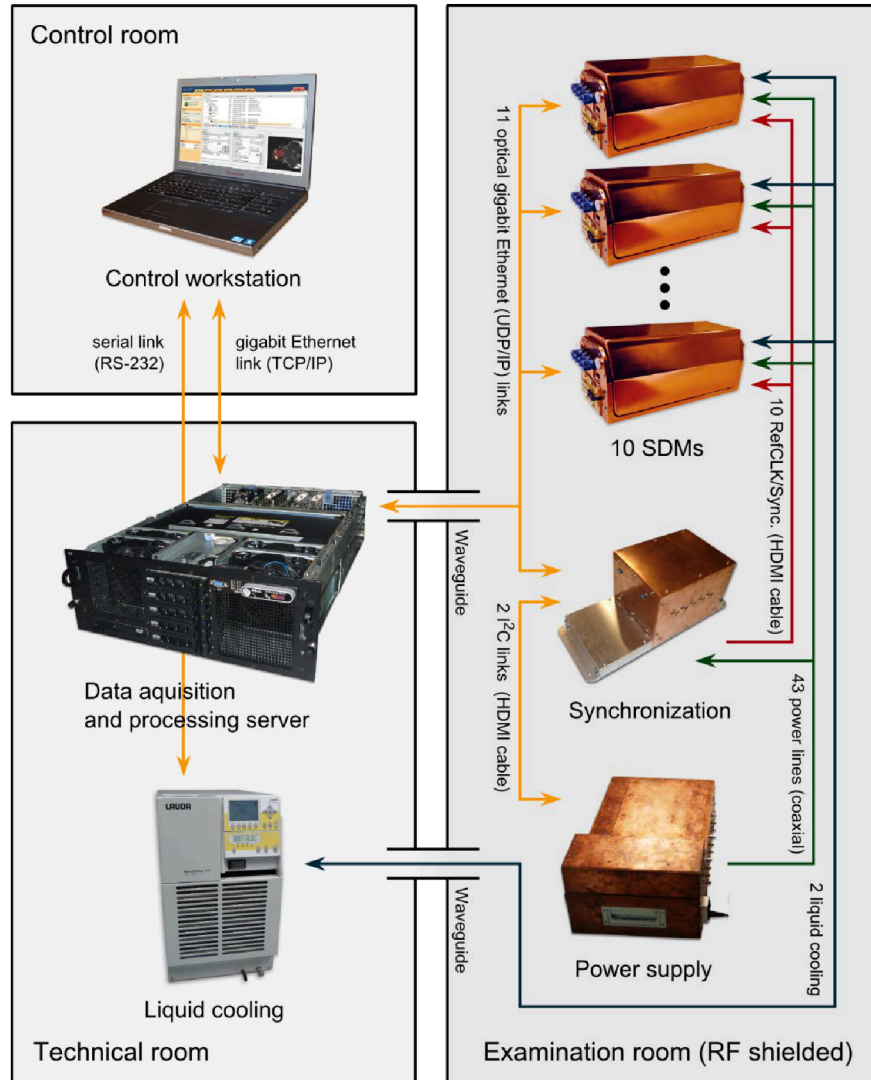


Figure 89: PET system hierarchy: The PET system is controlled with a workstation connected to the DAPS. Between the DAPS and the SDMs (and the centralized synchronization unit), the communication uses optical Gigabit Ethernet. The optical fibers and the plastic tubes for the liquid cooling system penetrate the RF-shielded examination room through waveguides. Figure published in the supplemental material of (Weissler *et al.*, 2014b).

The communication between the control workstation and the DAPS is realized by a Gigabit Ethernet connection using the Transmission Control Protocol (TCP) / IP standard. It provides a reliable link, ensuring that all data sent is also received. Between the DAPS and the SDMs, UDP/IP links are employed, as these allow higher data rates (due to less protocol overhead). Furthermore, UDP limits the downstream transmission time to known delay (in case there is too much data at a given point in time, the data is lost instead of delaying all the subsequent data to come). Additionally, as described in the SPU section, it can be implemented with fewer resources in the FPGA firmware (e.g., no data has to be stored for possible resending after data loss, as needed when implementing the TCP protocol). The

downside of UDP is that data are allowed to be lost. Therefore, critical data (mostly configuration data sent upstream to the detector) has to be manually secured on the session layer of the communication protocol.

The developed communication protocol allows for communication between the control software (see section 6.1.7.5) and the hardware through the hierarchical tree of the PET system. To have flexibility, on one hand, but a performant and stable system on the other, the communication adheres to the following ground principles:

- The hardware is organized in a hierarchical manner: A parent always has a configurable number of children (for instance, an SPU has up to six detector stacks).
- The FPGA firmware in the hardware is organized in modules per component (which is, for example, an electronic IC to control).
- The control software rebuilds the hardware hierarchy with the firmware modules as software objects.
- The communication always takes place between a software module in the control software and a firmware module in the hardware (or a software module in the DAPS).
- The communication is always straight upstream (towards the detector hardware) or downstream (which forbids communication between two children of the same parent).
- The protocol structure is reciprocal (i.e., upstream similar to downstream).
- A parent of the hierarchy knows only its children, but not its parents, nor its siblings (e.g., an SPU can route to its detector stacks, but downstream behaves the same, whether it is connected with other SPUs to the DAPS, or directly to a control workstation on its own).
- When a communication is passed from a parent to a child, the ID of the parent is removed by the parent (to be compliant with the rule stated above). When a communication is passed by a parent from its child to the child's grandparent, the ID of the child is added by the parent.
- To address a parent instead of a child, the child ID in the address is set to 0 (consequently, children's IDs always start at 1).
- Each message should contain enough information to be completely interpreted on its own. This enables the parallelization of threads in the control workstation and results in robustness against lost messages. Furthermore, it includes a feature that makes it possible for information not only to be pulled by the control software, but also to be pushed by the hardware itself, causing the same reactions.

The communication protocol is sketched in detail in Figure 90. Each message can be split over multiple UDP packages. Since some of these can get lost, the receiver has to check whether a complete, valid message is available, before it processes it: The receiver first checks the Cyclic Redundancy Check (CRC) code of the header. Then it decodes the number of bytes

field in the header, collects this amount of payload data, and finally checks the CRC or trailer bytes at the end of the message. If any check fails, the header is discarded, and a search is conducted for the beginning of a new header in the following data by searching for the common preamble. A continuous sequence number per (firmware/software) module allows for the detection of lost data.

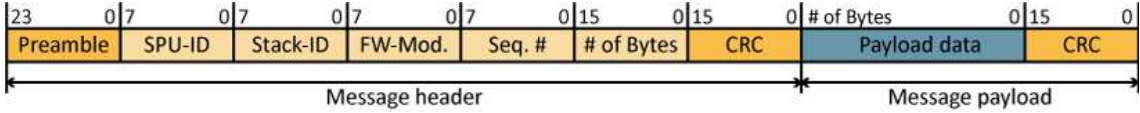


Figure 90: Communication protocol details. The message header is formed by a preamble, SPU-ID (depending whether multiple SPUs are connected via a DAPS), stack-ID, firmware-module-ID, sequence number, number of payload bytes, and a CRC over the header. The payload ends by a CRC over the payload or a common trailer code.

To increase overall communication performance and robustness, the communication to some critical firmware modules requiring large amounts of data (which are currently the JTAG configuration of the interface boards, the programming of the flash memory with the boot configuration of the SPU, and the sensor configuration) is secured with a generic First In – First Out (FIFO) front-end. It communicates its status by pushed and pulled information about being empty, or memory of a complete chunk of data being recently freed. As such, the control software always knows how much data can be sent safely, without losing substantial idle time.

5.1.9 Processing, Calibration, and Reconstruction

Once the raw data is stored on the DAPS, it can be processed and used for the system calibration or for reconstructing the final images.

5.1.9.1 Processing and Calibration

Singles and coincidences processing are performed in post-processing steps on the DAPS using a sliding window technique (Goldschmidt *et al.*, 2013). A Maximum-Likelihood Positioning Estimation (ML-PE) algorithm is used to estimate the gamma/crystal interaction position. It employs the normalized mean light distributions of around 511 keV for all crystals that have been measured on a bench setup before system assembly (Lerche *et al.*, 2011). The gain of each channel is determined roughly every three months through a dedicated calibration procedure. Time alignment of all channels is realized with synchronization pulses at the dedicated input channels of all ASICs. This procedure takes about 10 seconds and has to be conducted after each system power-up (Lerche *et al.*, 2012).

5.1.9.2 Image Reconstruction

Image reconstruction is performed with a list-mode algorithm that uses Maximum-Likelihood Expectation Maximization, including self-normalization and Resolution Modelling (MLEM-RM) (Salomon *et al.*, 2012). All images presented in this chapter are reconstructed with this technique by using an energy window of $\pm 3 \sigma$ (per detector stack), a singles time window of 25 ns, and a coincidence window of 3 ns (except for the in vivo images). The isotropic reconstruction voxel size is usually a third of the crystal pitch (0.46^3 mm^3). A

fourth of the crystal pitch (0.34^3 mm^3) is only used for the determination of the spatial resolution.

5.2 Results

The PET/MRI compatibility and the performances, which are achieved by the complete system, are accessed by the methods presented in chapter 1.

5.2.1 Performance of the Detector Stack

A detailed PET performance analysis of the detector stack is presented in (Solf *et al.*, 2009). It uses $4 \text{ mm} \times 4 \text{ mm} \times 22 \text{ mm}$ crystals without a light guide (configuration mend for clinical PET scanner), as this results in a one-to-one coupling between scintillator crystals and SiPMs. The paper shows, that a single detector stack can reach a time resolution of around 678 ps and a total energy resolution of around 15 %. With the small crystals and the light guide used here, the results are different, since the light from a single event is distributed over multiple channels. Differences in gain of the SiPMs and ASIC channels, as well as the noise of multiple channels, add to the calculated single event. Furthermore, some channels far away from the hit crystal even stay below their trigger or validation thresholds and do not contribute to the single event. These effects also have an influence on the identification of the crystal that was hit. Figure 91 shows flood histograms (histograms of the positions of all detected singles) of two detector stacks, measured with a ^{22}Na point source.

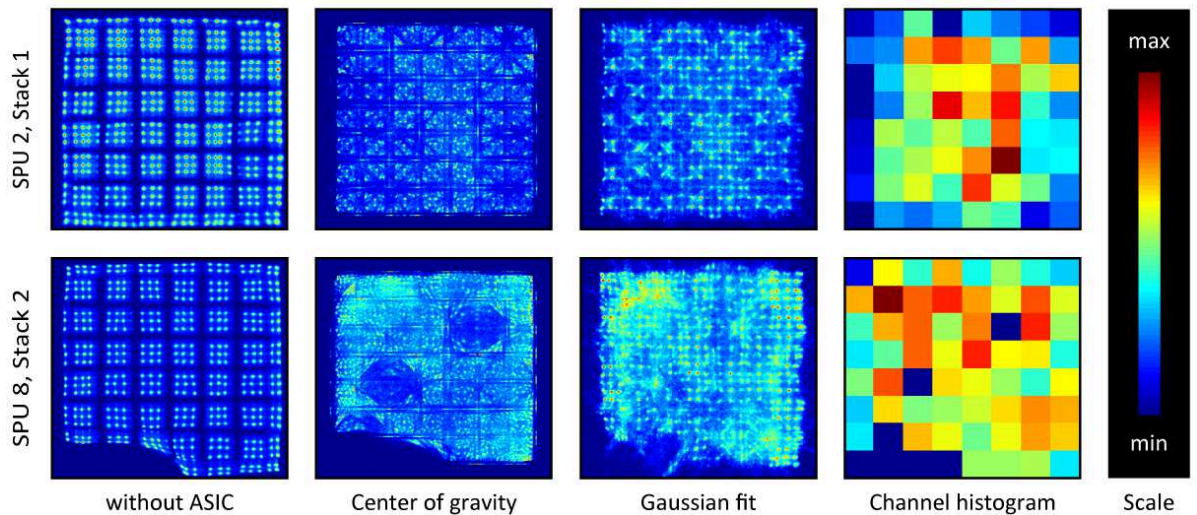


Figure 91: Flood histograms of two detector stacks: measured without the ASIC (the sensor board connected to a QDC system), calculated with a center-of-gravity (Anger) method, and with a Gaussian-fit method. A channel histogram (right) shows how many hits were detected by the ASICs.

Measurement and analysis performed by T. Solf.

To exclude the influence of the ASICs, the sensor boards are first read out with a VME-based Energy-to-Digital-Converter (QDC) system (Costruzioni Apparecchiature Elettroniche Nucleari S.p.A. (CAEN), Viareggio, Italy). The results are clear flood histograms in which all

crystals are distinguishable, although some SiPMs, or their connections, are defective, as in the bottom left of Figure 91. When using the ASICs to read out the SiPMs, the flood histograms become distorted, as the different gains and threshold levels of the digitizing channels influence the measurement. Dead channels of the ASIC board (clearly noticeable as additional dark blue squares in the channel histogram on the right) are also visible as two holes in the center-of-gravity calculated map on the bottom row. Missing parts of the energy can partly be completed by fitting the pattern of a single to a Gaussian distribution (Goldschmidt *et al.*, 2013). As described in section 5.1.9.1, the processing used for the final insert is an ML-based algorithm, which is calibrated with light matrices that are measured on a bench setup before system assembly (Lerche *et al.*, 2011).

The problem with the trigger dispersion was solved in a newer version of the ASIC, where the trigger threshold can be programmed individually per channel. Furthermore, a neighbor logic allows the integration of all channels to begin, when one channel triggers. This resolves the problem of missing small fractions of light on the sides of the light spot. Additionally, some logic parts of the ASIC were redesigned from constant-current-logic to CMOS-logic in order to reduce power consumption. The new ASIC version “PETA3” was successfully tested with the infrastructure presented, but (due to lack of time) could not be implemented for the complete ring. The results are presented in (Mlotok *et al.*, 2011).

5.2.2 MRI Performance and the Influence of PET on MRI

5.2.2.1 B_0 Distortion

The homogeneity of the static magnetic field was determined as described in section 3.2.1. The measurements were taken while the PET was on, while the PET was switched off, and – as an additional reference – completely without the PET/RF insert (using the build-in body coil of the MRI). In a separate experiment, the standard automatic volume-shimming feature of the MRI was enabled to compensate for the distortion in the hybrid FOV.

The relevant central slices of the B_0 map scans are displayed in Figure 92. They show a considerable rotational symmetry due to the symmetry of the PET gantry. The distortions on the sides are probably caused mainly by the detector stacks and transceiver boards. Compared to the scan using the body coil, the total field is decreased by 6.3 ppm (the value was calculated from the automatic f_0 determination in the preparation phase of each scan, which adjusts f_0 according to the B_0 field in the FOV). The plots of the maximum distortion over the ROI diameter (Figure 92, d) show linear increasing values almost up to the diameter where the spherical shapes of the ROIs become limited by the PET FOV. The map in Figure 92b indicates the large B_0 gradient in the head-feed direction as the reason for the large values. This relatively smooth distortion can be pushed out of the hybrid FOV by the shimming mechanism. The resulting ROI with a distortion < 2 ppm peak-to-peak is marked in Figure 92 and has a diameter of 90 mm (56 mm without shimming). The maximum distortion in the complete measured FOV (96 mm × 130 mm diameter) is below 5 ppm or 1.76 ppm calculated VRMS value. The large increments in ppm values for diameters > 120 mm are caused by local distortions at the border of the phantom, as described, for instance, in (Delso *et al.*, 2011).

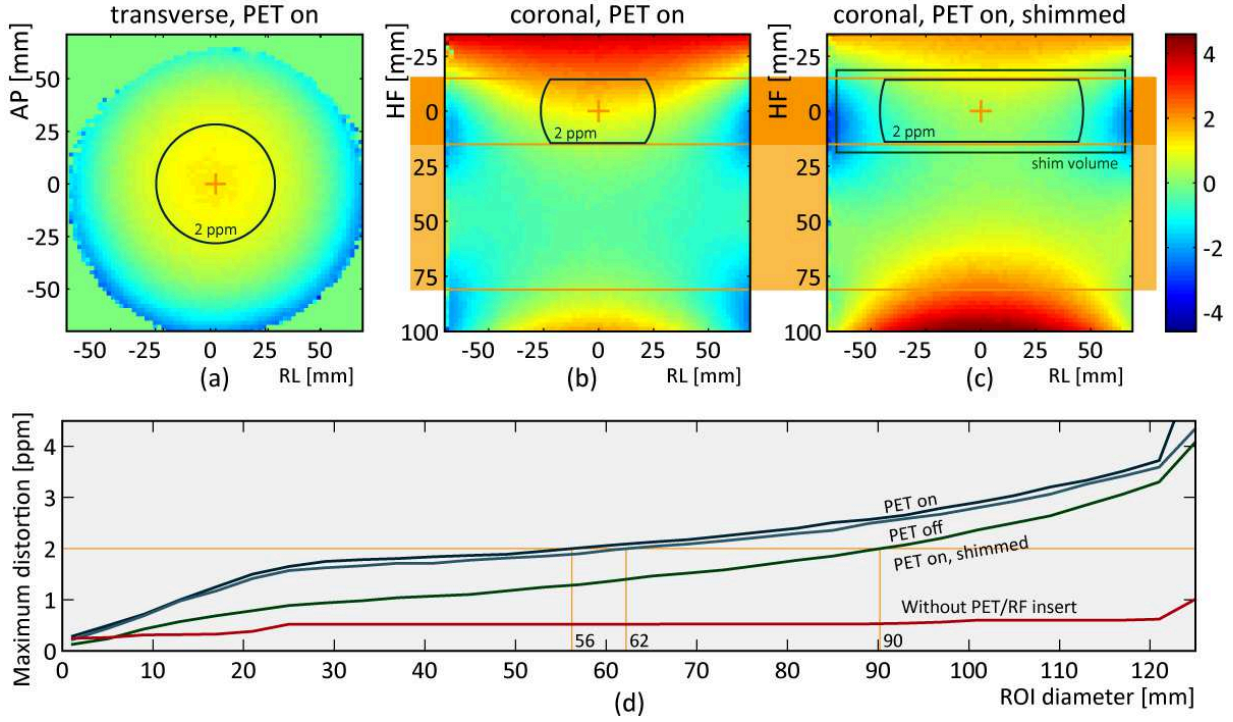


Figure 92: B_0 maps (peak-to-peak values) with PET on: transverse center slice (a), coronal center slice (b) and coronal center slice with shimming (shim volume is indicated) (c). Current PET FOV and its center are shown in dark orange (top). The light orange region (bottom) indicates the extended FOV for a system equipped with three detector rings. The maximum distortion for a spherical ROI, limited by the PET FOV, is shown in (d). ROIs with distortions less than 2 ppm (orange lines) are indicated in all plots.

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

The 2-ppm peak-to-peak value, defined as the requirement for anatomical imaging in section 3.2.1, is not exceeded in the hybrid ROI of 56 mm diameter. Through shimming, the diameter could be increased to 90 mm. Calculated as VRMS values (not shown in the plots), the maximum value is 1.63 ppm VRMS (1.76 ppm VRMS for the extended PET FOV for three rings). This shows that the B_0 homogeneity is good enough for standard imaging sequences within a large portion of the FOV, but not throughout the whole of it. For more demanding sequences, such as EPI, this is at least the case for the hybrid FOV with a diameter of 55 mm. For spectroscopy, the 0.1 ppm VRMS border is reached at a diameter of 8 mm with the shim technique used. Larger corrected diameters might be achieved with different (smaller) shim volumes, although the shim system also needs to shim the inhomogeneity introduced by the subject to be scanned. Keeping in mind the almost 10000 components of the gantry and the ~7 A current feeding per module, this is already a good result. On the other hand, adding the extra 40 detector stacks for a fully equipped system will change the distortion, so that in future systems the amount of ferromagnetic material should be further reduced.

5.2.2.2 Spurious Signals, SNR and Image Uniformity

The spurious signal analysis was performed as described in chapter 3.2.2. A reference was measured with the PET system completely disconnected from the power, and the experiment was then repeated with the PET system measuring seven ^{22}Na point sources (~9.3 MBq in total, approximately the activity used in mouse imaging – see chapter 3.1.1.5).

Figure 93 shows the average MR signal over frequency. The mean value over the complete bandwidth is 242 ± 4 for the PET system switched off and 292 ± 26 when the point sources are measured. This is an increase of 21 % on average, with a slight dependency on the frequency. Above the noise floor, increased values appear at discrete frequencies, which is typical for signals emitted from digital electronic circuits. Their height is slightly dependent on the activity: the maximum value with point sources is 637, whereas it is 542 when only measuring the LYSO background. These values give a hint of the expected intensity of the artifact in the images (although not directly comparable, especially since the automatic gain setting of the RF receiver chain lowers the mean values by about 24 %: With a bottle-phantom and only 1° flip angle, the highest value is around 6000 (at the center frequency representing the DC component of the image)). The orange curve in Figure 93 shows the result of an early measurement, before improvements on the cabling and shielding of the power supply were made and before ferrites were added to the cables.

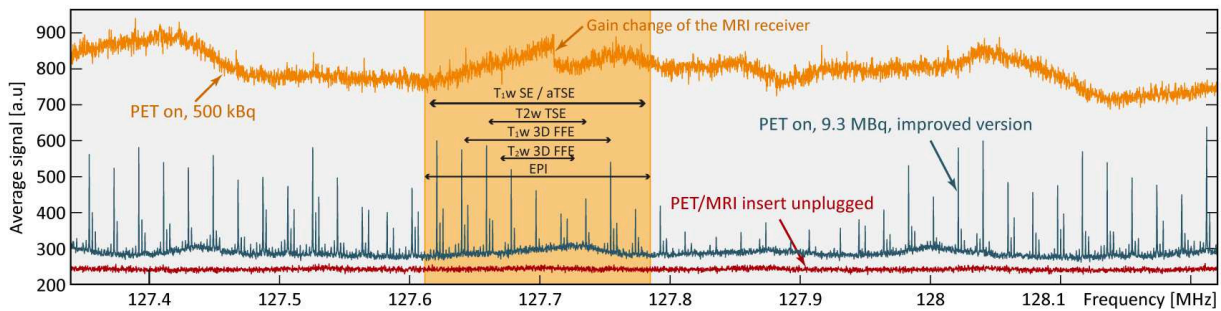


Figure 93: Averaged MRI signal over frequency while the PET system was measuring seven ^{22}Na point sources with an activity of about 9.3 MBq (blue). The baseline (red) was measured with a completely unplugged PET system. The orange curve shows an early measurement without optimized power supply (an automatic change of the MRI receiver gain is visible as a step around 127.7 MHz – the real values right from that step are thus shown too low). The bandwidths used by sequences for the SNR measurements of this section are indicated – the orange area represents the bandwidth of the SE sequence.

Figure party published in (Weissler *et al.*, 2014b) © 2014 IPEM.

The increased mean noise floor (factor 1.2) directly translates into a lower image SNR, which was measured as described in section 3.2.2. A decrease of 14 %, from 24.7 to 21.2 (factor $1/1.2$), in image SNR was calculated from the spin echo image presented in Figure 94. The spurious signals from the PET detector electronics are not directly visible in the image, but when brightness and contrast are scaled to reveal the background noise, they can be seen as RF-noise artifacts in the phase-encoding direction (Figure 94, right).

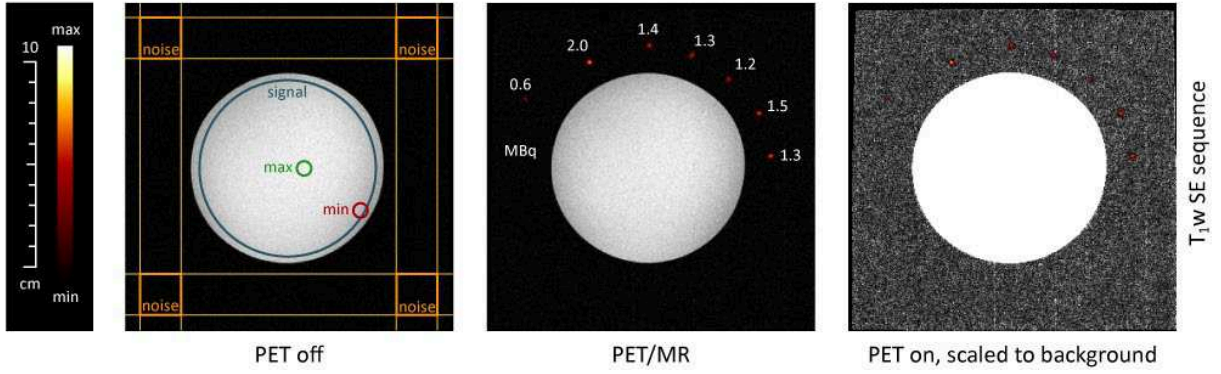


Figure 94: MRI SNR and image uniformity measurements (spin echo sequence). The ROI for the calculations are overlaid in the MRI-only image (left). The PET/MR images (middle and right) show the bottle-phantom (MRI) and the seven ^{22}Na point sources (PET). The spurious signals from the PET electronics are visible as RF-noise artifacts in the background of the MR image (right).

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

Since the noise is slightly frequency-dependent, the final SNR loss also depends on the bandwidth an MRI scan uses. Figure 95 shows the MRI-only and the PET/MR images for six other sequences (detailed scan parameters are listed in Table 8). The mean SNR degradation is 13 % and the image uniformity changed -0.6 % on average. Separate results for all sequences are displayed in Table 18. In 3D sequences the RF-noise artifacts are not visible, due to averaging of the signal in the second phase-encoding direction. With higher EPI factors, typical artifacts are visible in the bottle-phantom.

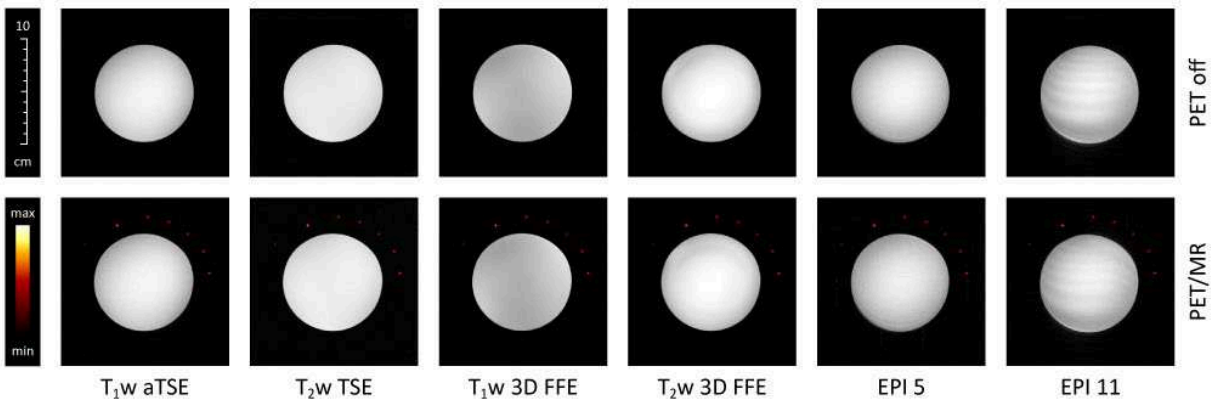


Figure 95: MRI SNR and image uniformity measurements with different sequences: TSE sequences for good image quality (1 slice, ~ 2:30 min scan time), fast 3D FFE sequences (20 slices, ~ 5 min scan time) and very fast EPI sequences (1 slice, 14.8 s scan time for EPI 5 and 9.1 s for EPI 11).

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MRI sequence	SNR	SNR difference	PIU	PIU difference
T₁w SE	21	-14 %	85	-1.3 %
T₁w aTSE	46	-15 %	83	-2.9 %
T₂w TSE	31	-2 %	93	-0.8 %
T₁w 3D-FFE	67	-15 %	87	0.5 %
T₂w 3D-FFE	308	-14 %	80	0.3 %
EPI 5	36	-16 %	79	-1.1 %
EPI 11	37	-17 %	80	0.8 %

Table 18: MRI SNR and image uniformity results for all MRI sequences.
Table published in the supplemental material of (Weissler *et al.*, 2014b).

The problem of increased noise is also reported by other research groups digitizing outside the MRI bore: (Hong *et al.*, 2013), for instance, indicate a decrease in SNR between 53 % and 80 %, while vertical stripes in the images are reported in (Yamamoto *et al.*, 2011). The main source of the increased noise seems to be common-mode currents from the power supply. These have been reduced through multiple measures over the years. Early measurements required sequences with very high intrinsic SNR. For instance, the rat image shown in Figure 112 of section 5.2.5.2 used a high numbers-of-averages value, which results in a long scan time. Adding ferrite common-mode filters on the supply lines reduced the noise level in the spurious signal scans from 800 to 430 (Lerche *et al.*, 2012). Adding more filters, closing holes in the power supply housing and removing unneeded cables resulted in a further reduction of more than 40 %. This allows for scanning with sequences that have a much lower intrinsic SNR, e.g., with increased spatial resolution or decreased scan time. The downside is that spurious signals from the PET electronics that were previously covered by the increased noise level now become visible when the SNR becomes too low (see Figure 96, where simultaneous PET/MR images of a pepper filled with ¹⁸F-FDG are shown, which was measured with a loose synchronization cable). These RF-noise artifacts are typical for noise emitted by electronic circuits, and similar effects were reported, for instance, in (Wehrl *et al.*, 2011), where a housing was left open for purposes of demonstration. Since the intensity of these signals depends on the data rate, an increment can be expected when the system is populated with the two additional detector rings.

The image uniformity changed about -1.3 % from 93.6 % to 92.9 % when the PET system was switched on. The change is below the requirement in the same region: as reported, for instance, by (Catana *et al.*, 2006) or (Wehrl *et al.*, 2011).

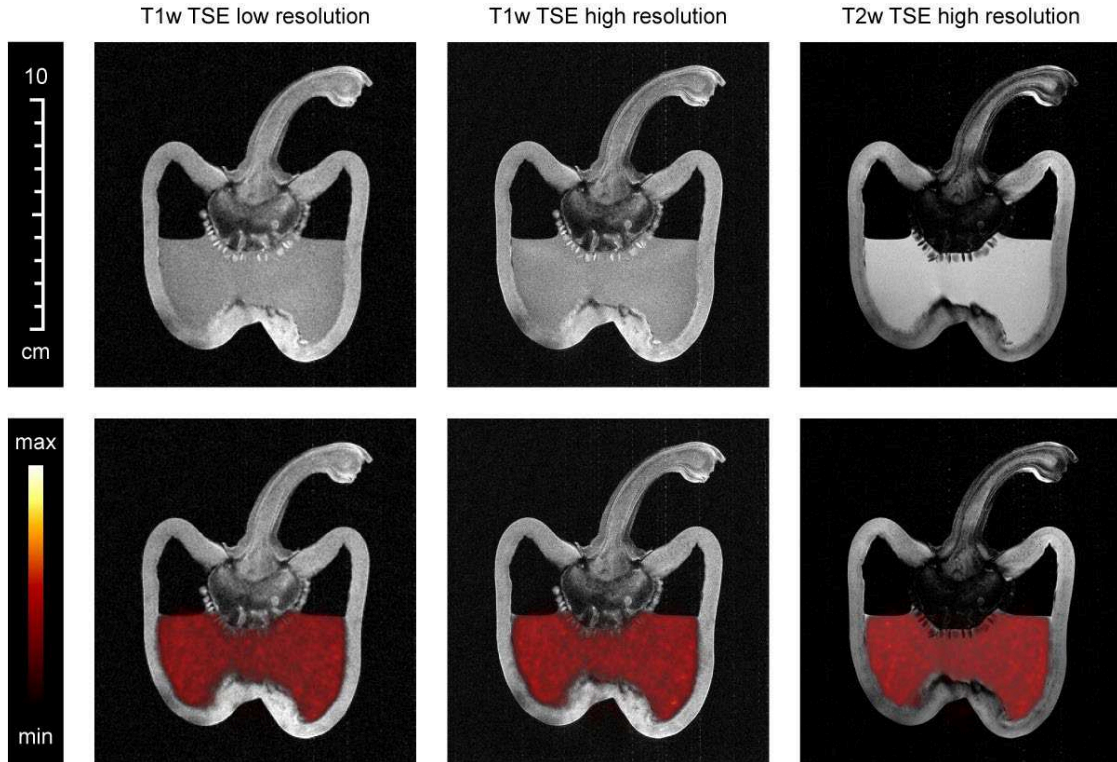


Figure 96: Simultaneous PET/MR measurements of a pepper filled with ~ 15 MBq of ^{18}F -FDG, with one out of ten synchronization cables slightly loose. The spurious signals emitted become visible as vertical dotted lines (RF-noise artifacts) in the MR images with a low SNR and low pixel bandwidth (center and right). T₁w TSE 6 low resolution: TR/TE: 612 ms / 20 ms, acquisition matrix: 320×320 pixels, pixel size: $0.5 \text{ mm} \times 0.5 \text{ mm}$, NSA 4, pixel bandwidth: 640 Hz/pixel, 2:09 minutes scan time. T₁w TSE 6 high resolution: TR/TE: 612 ms / 20 ms, acquisition matrix: 640×640 pixels, pixel size: $250 \mu\text{m} \times 250 \mu\text{m}$, NSA 8, pixel bandwidth: 322 Hz/pixel, 8:41 minutes scan time, SNR 67 % of low-resolution image. T₂w TSE 19 high resolution: TR/TE: 2400 ms / 100 ms, acquisition matrix: 640×640 pixels, pixel size: $250 \mu\text{m} \times 250 \mu\text{m}$, NSA 8, pixel bandwidth: 291 Hz/pixel, 10:36 minutes scan time. All: slice thickness: 2 mm, FA: 90°.

Figure published in the supplemental material of (Weissler *et al.*, 2014b).

5.2.2.3 Geometric Distortion

The phantom used to measure geometric distortions was filled with ^{18}F -FDG (activity of approximately 22 MBq). It was placed in the center of the scanner's FOV, with the structured inlay in transverse direction. While PET data was being acquired, it was simultaneously measured with the set of standard MRI sequences used in the SNR experiments (Table 8). The resulting MR images are shown in Figure 97.

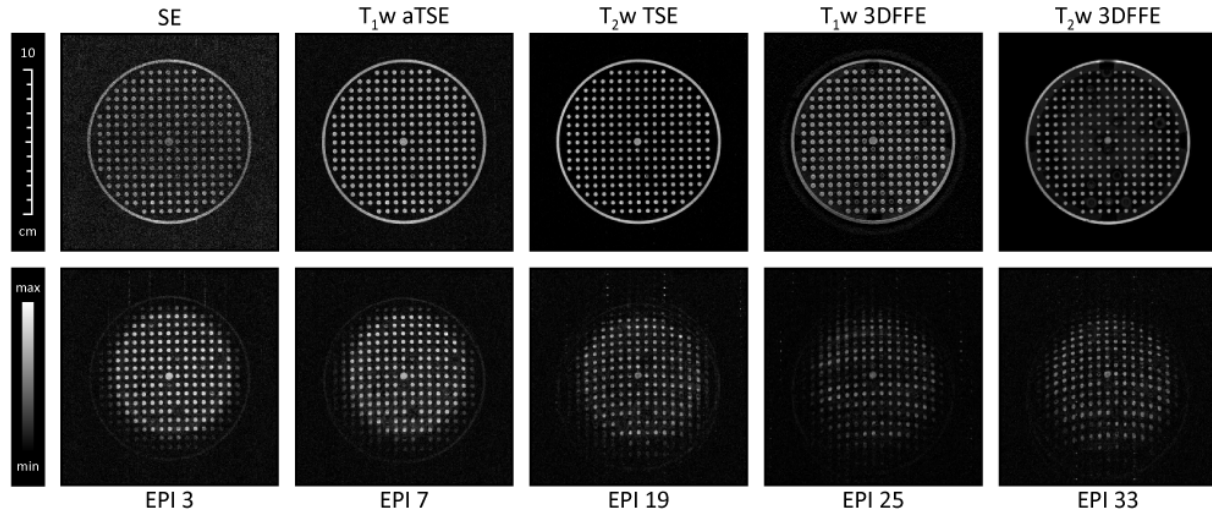


Figure 97: Distortion phantom imaged with different imaging sequences.

Unlike the spin echo and 3D gradient echo images, which all stay below the requirement, the EPI images show significant geometric distortions. The calculated values for the distortions are listed in Table 19. Reference values are measured with a separate RF coil (large ^1H coil, introduced in chapter 6.1.5) without a PET insert (images shown in chapter 6.2.2.3, Figure 159, top row). Compared to the references, the PET insert clearly worsens the geometric distortion between 23 % and 83 %. Whether the level is still acceptable depends on the application. As the distortion is relatively constant when multiple images are made, the images can be mapped to a low-distortion image and the high temporal resolution can still be used, e.g., in dynamic or fMRI studies.

MRI sequence	Geometric distortion	Reference
EPI3	2 %	1.1 %
EPI7	5.5 %	3 %
EPI19	11 %	8 %
EPI25	14 %	11.3 %
EPI33	21 %	15.2 %

Table 19: Geometric distortions in EPI images

Besides the distortion, the outer ring and rods are already almost invisible in the EPI 3 image. This is most likely caused by the larger B_0 distortions at higher radii, which is consistent with the B_0 maps shown in Figure 92. The shape of the geometric distortion (which appears melted from the outside) is consistent with the B_0 map depicted: The outer regions with slightly lower B_0 are shifted downwards in the phase-encoding direction. The local B_0 distortions caused by small air bubbles in the rods become apparent in the gradient echo images. The images seem to be slightly sheared, which is a typical sign of eddy currents (see chapter 3.2.3). Spurious signal artifacts are visible, especially in the EPI images with lower intrinsic SNR (for instance, in the EPI 19 image above the phantom). These were caused by a slightly loose synchronization cable, which was later fixed (see Figure 38).

A PET image, reconstructed from data measured outside the MRI (8:45 min scan time, starting with 22 MBq) and during the EPI sequences (15: 38 min scan time, starting at 11 MBq), is shown in Figure 98. It is relatively noisy, as most of the activity is not in the hot

rods, but underneath the lid and in the homogeneous regions (intended to improve the filling of the phantom) next to the 5-mm-long rods. A geometric distortion of the image is not visible.

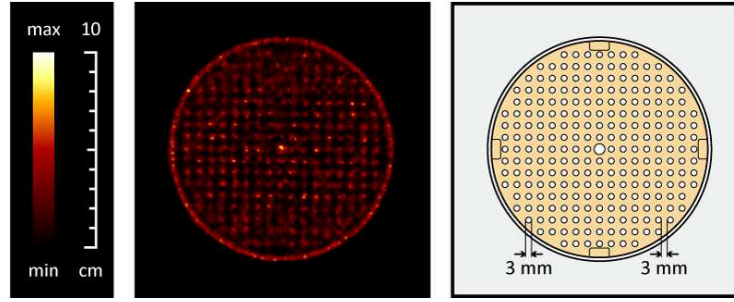


Figure 98: PET image (left) with 4 mm slice thickness (same as the MR images) and a sketch of the distortion phantom inlay with 241 hot rods.

5.2.2.4 Temporal Stability

The measurements for the temporal stability were performed with the PET system measuring the seven ^{22}Na point sources (~ 9.3 MBq) and with the PET system switched off, but still being plugged in. Since the RF coil cannot be removed for a reference scan, the measurement was repeated with the built-in Quadrature Body Coil (QBC). The resulting mean images and SFNR maps are shown in Figure 99.

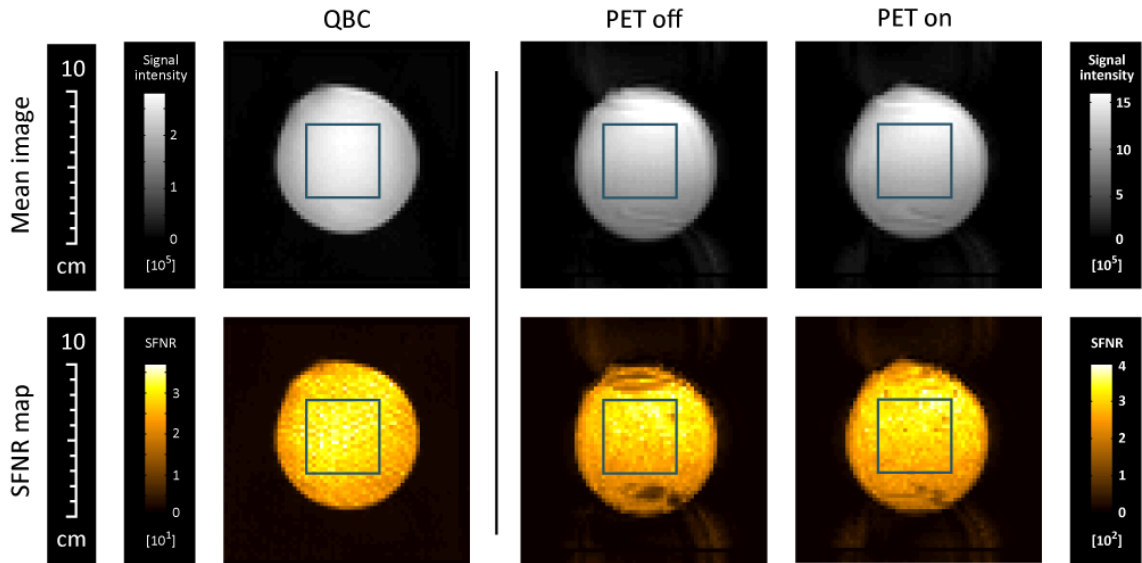


Figure 99: Mean images (top row) and SFNR maps (bottom row) of the temporal stability measurements, performed with the QBC (left) and the PET/MRI insert (right). The ROI to calculate the numerical results is indicated in blue.

Although the QBC (due to its size and wrong loading) has a much lower signal intensity and SNR, the only apparent artifacts are caused by the two point sources at the top left of the phantom (as also seen in Figure 158, right). With the PET system, the Nyquist artifacts, already reported in section 3.2.2, are visible and influence the signal fluctuation over time, as they are especially visible in the SFNR maps. Since the MRI sequence is a single-shot EPI sequence, only one ghost, shifted by half the size of the FOV (and wrapped around from top to bottom) is visible. The signal regions of these ghosts do not reach the ROI, which is used to calculate the signal stability over time, which is plotted in Figure 100.

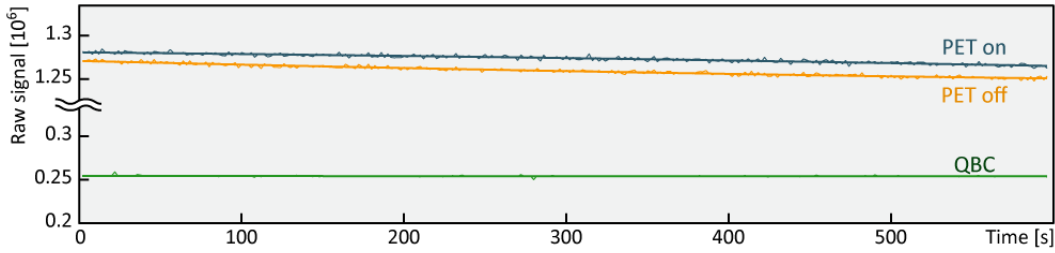


Figure 100: Raw signal intensity, averaged inside the ROI, over time (all 300 2-s-long repetitions are shown). The fitted second-order polynomial trend is overlaid.

Table 20 lists the numerical results of the measurements. With PET on and PET off, the fluctuation stays between the typical lower level of 0.10 % and the maximum value of 0.2 %, which is described as the target. In addition, the drift stays below the targeted average of 1.0 %. The calculated values for the QBC measurement are not comparable, as the SNR is far too low in that measurement (the QBC is too large for the small phantom). Looking carefully at the series of images produced reveals a geometrical drift effect: During the 10 minutes of the scan from image 2 to 300, the FOV shifts continuously upwards about a complete pixel (2.5 mm). Between the first and the second image, the FOV shifts about four pixels toward the top (a common and known effect, which is why the first two images, plus images from an additional warm-up phase, are normally discarded in the analysis).

Measurement	SNR	SFNR	Fluctuation	Drift
QBC	32	30	0.22 %	0.09 %
PET on	363	302	0.14 %	0.76 %
PET off	340	299	0.12 %	0.99 %

Table 20: Numerical results of the temporal stability measurements

The SFNR values are about 12 % to 17 % lower than the SNR values, which, according to (Friedman and Glover, 2006), is often caused by low-frequency phase instabilities in the gradient or the RF subsystem. Nevertheless, there is no hard border between a normal and broken system. The spectral analysis (Figure 101), on the other hand, reveals a clear peak around 0.22 Hz, equivalent to a period of 4.5 s.

This peak is visible whether the PET system is on or off, but not in the QBC measurements. It is, thus, likely, that the cause of the instability is the insert itself, or that MRI gets unstable by the presence of the insert (e.g., by picking up noise from the outside).

Since fluctuation and drift values are within specification, they do not hinder fMRI studies. Nevertheless, the fluctuations around 0.22 Hz should be kept in mind, when analyzing the results of such studies.

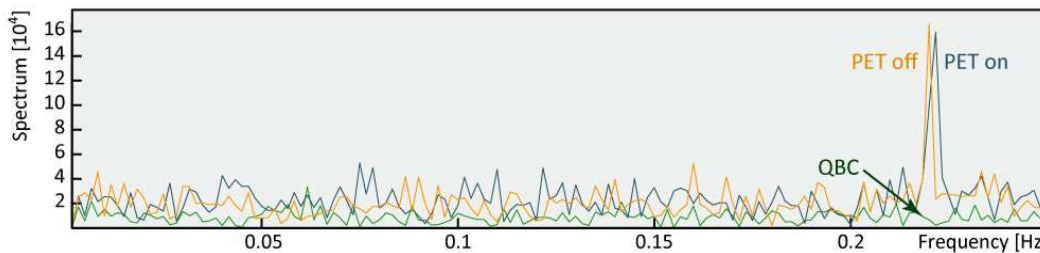


Figure 101: Spectrum analysis from the signals inside the complete ROIs in all 300 images.

5.2.3 PET Performance and the Influence of MRI on PET

5.2.3.1 PET Performance Parameters

The results of the point source measurements during MRI sequences are displayed in Figure 102. PET photopeak position is averaged in 2 s bins over the ADC values from the ASIC. The count rates of singles and coincidences are calculated in 1 s bins. Energy- and timing-resolutions were determined by fitting Gaussian functions in histograms over 2 s measurement times. The electronic jitter on the synchronization input channel of the ASICs was calculated to determine the TOF capabilities of the electronic readout infrastructure.

During the gradient-intense EPI sequence, a mean increase of the SPU temperature of 0.09° was measured. The sensor boards heat up to about 0.03 K on average. After the sequence has stopped, the temperature seems to continue increasing with a very low time constant until it reaches an additional 0.01 K after 6 minutes. This heat could have been transferred from the environment, such as from the SPU or the housing. Furthermore, it is possible that the heating of the SPU has an effect on the bias voltage regulation PCB. It had to be built from discrete analog components (see section 5.1.1.2), and has a transistor in regulation loop, which was not temperature compensated. Nevertheless, the change is so low that errors, drifting effects of the sensors, and even completely different reasons cannot be excluded. On the other hand: The gain of the SiPMs decreases with the temperature, which results in a consistent maximum bias current reduction of 24 μA (-6 %) per sensor board at the same time. Consequently, the photopeak shifts about 4 ADC values (of 12 bit, thus approximately 0.5 %), and the singles rate drops around 1.2 %. At about 2 %, the effect on the coincidences rate is hardly noticeable. 24 minutes after the EPI sequence stopped, the temperature and bias currents are back to the values they had before the start of the sequence. The EPI sequence, with its high gradient duty cycle and slew rate, thus clearly has a heating effect on the detector electronics. Nevertheless, the tested scan, with a duration of 3 minutes, heats the sensor boards only about 0.04 K, and the effect on the coincidences count rate is very low. Direct influences during gradient switching, as shown in (Weirich *et al.*, 2012), are not visible. Changes in count rates during RF pulses, as reported, for instance, by (Maramraju *et al.*, 2011), could also not be observed.

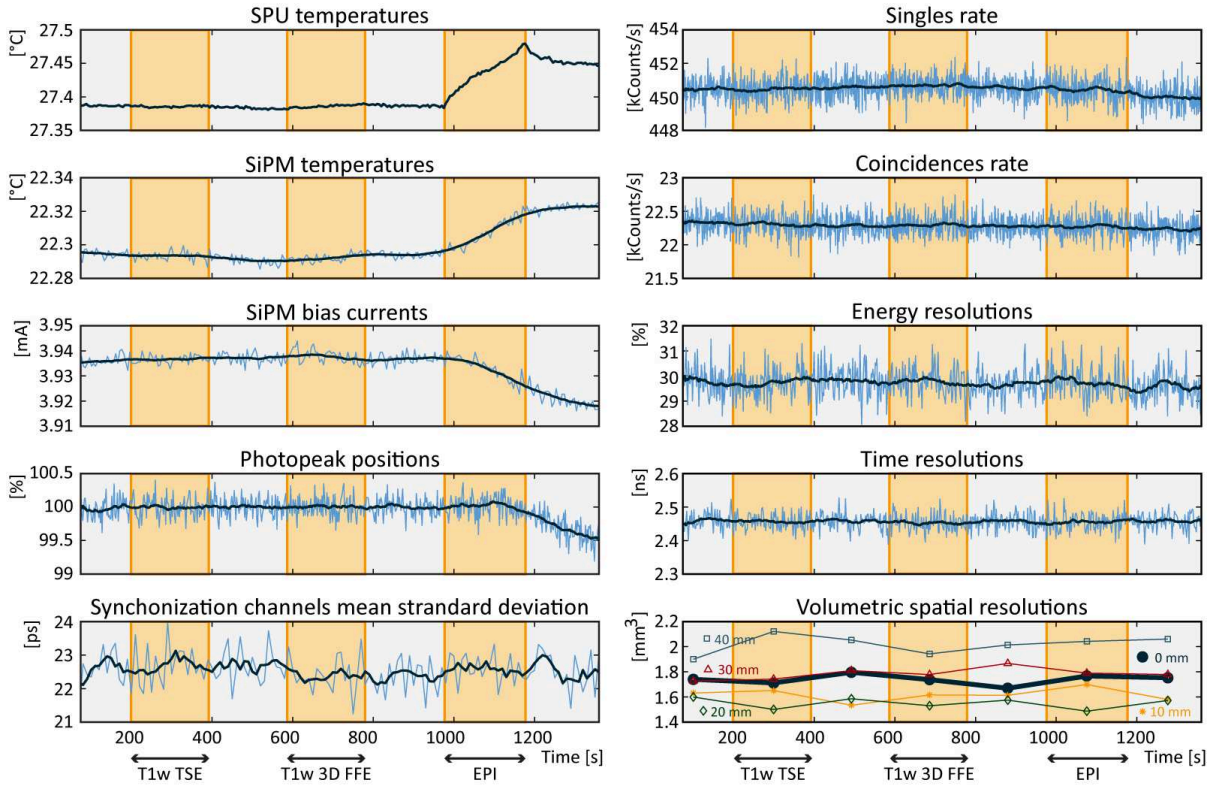


Figure 102: Important parameters during a 23-minute-long PET measurement of seven ^{22}Na point sources while three different MR imaging sequences were executed (orange areas). The dark, thick curves are filtered with a 1-minute-moving-average filter to visualize the tendencies. The volumetric spatial resolutions are plotted for five different transaxial radii from the isocenter to 60 mm.

Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.

The energy resolution of 29.7 % seems to be unaffected by the MR sequences. It is a bit lower than previous measurements that showed 23 % (Lerche *et al.*, 2012). Reasons for that could be slightly shifted crystal arrays (and thus suboptimal ML positioning and energy correction) due to having the wrong climate during storage and transport. The light coupling between crystals and SiPMs is based on Meltmount™, and the system is now more than 3 years old and has been moved eight times in a van.

The timing resolution of 2.5 ns remains unaffected by the tested MRI sequences and is below the targeted requirement for a non-TOF-system. The 112 synchronization channels used for the measurement show an unaffected jitter (average of the standard deviations) of 22.5 ps. As the time binning of the ASICs is 50 ps, this value shows that the synchronization pulses mostly hit the same time bin. It thus seems that the electronic architecture with a centralized synchronization system is TOF-capable – even under the MRI test conditions presented.

The volumetric spatial resolution is below 1.8 mm³ (transaxial: 1.2 mm × 1.3 mm, axial: 1.15 mm) in the center of the FOV. Due to the gaps between the SDM, the spatial resolution is better slightly off-center. At radii > 45 mm the DOI effect reduces the spatial resolution to values lower than in the center. There are no signs indicating an effect of the MRI activity on the spatial resolution.

In summary, the observations described above indicate that early digitization close to the sensors and the measures that were taken, such as differential signaling for the analog signals, result in a good MR hardness.

5.2.3.2 Maximum Activity

As described in chapter 3.1.1.6, the NECR curve, plotted over different activities, shows (among others), how sensitive a system is and how well it can handle high activities. A measurement of the curve was presented in (Mackewn *et al.*, 2015a): A 140-mm long ^{18}F -FDG-filled line source was placed in a rat-sized scatter cylinder with a diameter of 50 mm and a length of 150 mm. It was constructed according to the specifications of (NEMA NU 4, 2008). The result of a measurement from 40 MBq down to 1 MBq is shown in Figure 103.

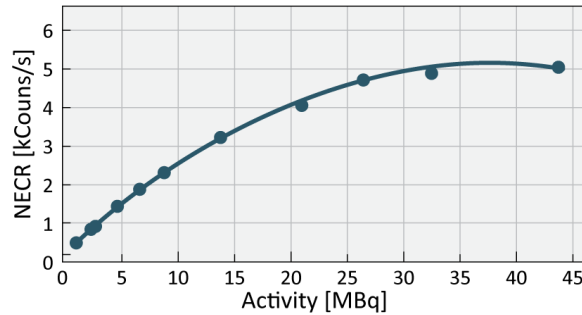


Figure 103: NECR curve over activity in a rabbit-sized scatter phantom.
Measurement performed and analyzed by J. Mackewn. Data was published in (Mackewn *et al.*, 2015a).

The NECR curve reaches a plateau at around 35 MBq. The system is thus fine for mouse and rat imaging, but less suitable for rabbits – especially as large amount of activity would be outside the FOV and would further increase the multiple and random counts. The NECR values seem to vary around the fitted curve (even more visible in the other curves of the cited paper). The reason is a problem in the off-line processing software, which lost data when reading them in multiple threads. The issue was solved before the measurements for this thesis were made. The actual sensitivity might thus be slightly higher than the 0.6 %, stated in the same paper. Additionally, a three-fold increase of point source sensitivity can be expected when upgrading the modules to six detector stacks resulting in three detector rings (volume sensitivity would improve by a factor of almost 9). Further improvements are anticipated from a firmware-update that is able to read out the ASICs four times more often per time frame.

5.2.4 PET/MRI Synchronization by Detection of Switching Gradients

The gradient detection sensors (described in section 5.1.2.1) were characterized inside the MRI to determine the influence of the programmable thresholds on the sensitivity to different slew rates, and their time accuracy and precision.¹¹ A patched MRI software allows for creating single gradient pulses with a known direction, strength, duration, rise time, and slew rate. More detailed measurements and an application example are presented in (Weissler *et al.*, 2014a).

¹¹ Due to availability of the inserts, the sensors were characterized on the second generation of the PET/RF insert (chapter 1) in which the gradient detection circuits are built in identically to this insert.

5.2.4.1 Threshold Scan

The slew rate for the Z-gradient is set to the highest possible value of 200 T/m/s. The exact gradient waveform and a sketch of the fields produced by the Z-gradient are shown in Figure 104, top left. The trigger thresholds are varied from +80 mV to -80 mV (relative to the equilibrium of the voltage divider) and the location and number of the sensors triggered are evaluated.

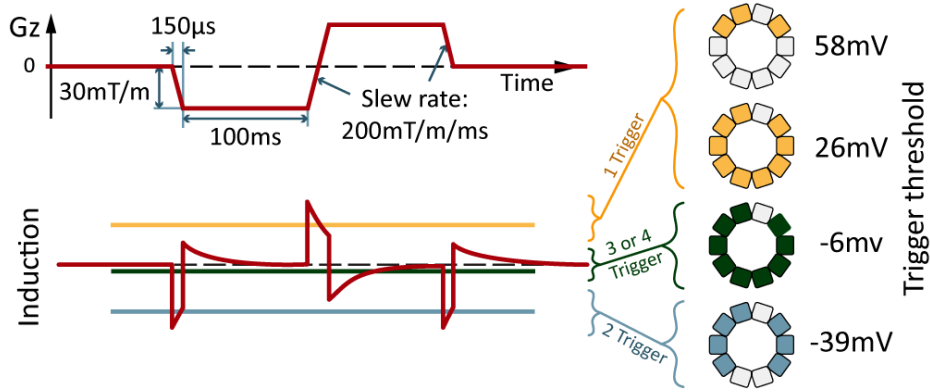


Figure 104: Gradient waveform and simulated induced voltage at the output of the voltage divider (left) and the resulting triggers (right).
Figure published in (Weissler *et al.*, 2015b) © 2015 IEEE.

Figure 104 also shows the gradient waveform over time, the (simulated) voltage at the input of the comparators, and how many triggers are counted in which detector module for four different threshold voltages. Threshold values larger than +74 mV disable the sensors, since no gradients are detected. With high, positive trigger thresholds, the first detector modules on the top of the insert (the isocenter of the PET insert is shifted 45 mm upwards in comparison to the MRI system) count one trigger. One module at the top has a defect circuit and is not triggered. Reduction of the threshold results in detected gradients in lower modules as well. When the threshold voltage reaches 0 mV, three or four triggers are counted. Negative thresholds below a certain level (blue line in the graph of the simulated voltage at the comparator in Figure 104) yield to two triggers per module. The amount of triggers (from one to three) detected per module corresponds to the theory that the capacitor of the AC-coupling is significantly charged and discharged during the rise time. When the threshold voltage is further lowered, modules at the bottom cease to trigger. At threshold voltages lower than -70 mV, no sensor triggers any more.

5.2.4.2 Slew Rate Scans

By changing the rise time, the slew rate of the gradients is varied, and the lowest trigger threshold at which at least one sensor triggers is determined. Furthermore, the three gradient directions X, Y, and Z (as defined in Figure 32 of chapter 3.1.2.3) are tested separately. The lowest slew rate of the gradients, where the first gradient sensor triggers, is plotted over different threshold voltages in Figure 105.

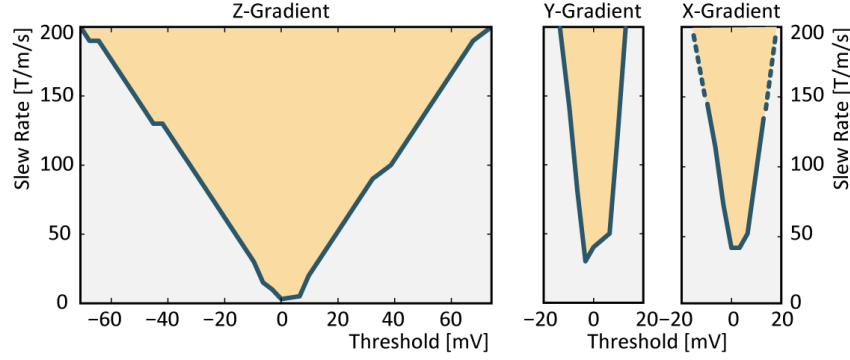


Figure 105: Lowest slew rate at which the first sensor triggers over threshold voltage. The scales are similar for the Z-gradient (left), and Y- and X-gradients (right).

Figure similarly published in (Weissler *et al.*, 2015b) ©^{3.0} 2015 IEEE.

From lower negative thresholds (for the Z-gradient greater than -70 mV) to 0 mV, the needed slew rate to trigger decreases almost linearly. For positive thresholds, it also decreases (almost) linearly with the same slope. At a gradient strength of 30 mT/m, the first sensor already triggers at a slew rate of 3 T/m/s (0 mV threshold level). The sensors are much less sensitive to gradients in the X- and Y-direction: For the X-gradient, the lowest slew rate is 40 T/m/s, and for the Y-gradient it is 30 T/m/s. In addition, the threshold voltage, where triggering requires the maximum available slew rate, is lower: for the Y-gradient, it is ± 15 mV. The same seems to be true for the X-gradient, although with the software patch it could only be driven to 140 T/m/s (graph extrapolated as dotted lines). The behavior can be explained by the field pattern of the different gradients. Figure 106 sketches the gradient fields for the Z-gradient and the X-gradient.

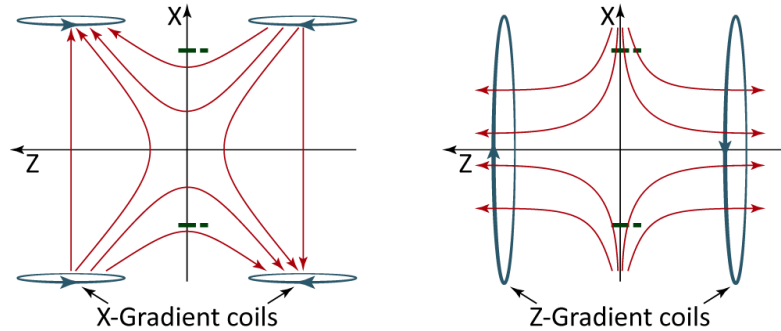


Figure 106: Sketch of currents in the gradient coils (blue) and the gradient fields in the Y-plane (red) of the X-gradient (left) and the Z-gradient (right). The cross sections of the detector coils are indicated as green lines (longer lines are the transaxial coils). The center of the PET gantry is slightly higher than the axis of the MRI scanner (Z-axis).

Figure published in (Weissler *et al.*, 2015b) ©^{3.0} 2015 IEEE.

Whereas the field lines of the X-gradient are rather parallel to large transaxial gradient detection coil, the Z-gradient fields go right through the coil. This is the reason for the higher sensitivity for the Z-gradient coil. The Y-gradient is similar to the X-gradient, only turned 90°, which explains the comparable sensitivity in those directions.

The experiments have shown that even at very low gradient strengths of 1 mT/m, the sensor triggers reliably at a minimum slew rate of 15 mT/m/s, which is 7.5 % of the maximum available slew rate. Increasing the number of windings or the area of the coil can even lower that value. The sensor thus triggers reliably at almost every MRI sequence. Exceptions might

be very exotic sequences that apply only very small steps in gradient strength, such as zero TE imaging with the SWIFT technique (Idiyatullin *et al.*, 2006). These would require a preceding gradient pulse that can definitely be detected (e.g., a crusher gradient – see section 5.2.4.4).

The result from the slew rate scan can now be used to enable triggering selectively on certain MRI sequences by setting the threshold level accordingly. The maximum slew rate of a sequence can be set manually or by changing gradient mode settings: Whereas “maximum” uses the maximum available gradient strength and slew rate (for fast scans), “regular” restricts the value (to achieve a better signal to noise ratio). The “default” setting chooses balanced values in between. These gradient modes are used for two different example MRI sequences: A TSE sequence and a single-shot EPI sequence (sagittal single-slice, no preparation phases). Details are listed in Table 21.

Sequence	Gradient Mode	TR / TE [ms / ms]	Scan Time	Gradient Strength ^a	Rise Time ^a	Slew Rate ^a
T₁w aTSE ^b	regular	611 / 20	2:09 min	10 mT/m	600 μ s	17 T/m/s
T₁w aTSE ^b	default	612 / 20	2:09 min	21 mT/m	210 μ s	99 T/m/s
T₁w aTSE ^b	maximum	612 / 20	2:09 min	30 mT/m	155 μ s	194 T/m/s
SSh-EPI ^c	regular	120 / 53	1.1 s	10 mT/m	600 μ s	17 T/m/s
SSh-EPI ^c	default	56 / 23	508 ms	21 mT/m	210 μ s	100 T/m/s
SSh-EPI ^c	maximum	42 / 16	379 ms	31 mT/m	156 μ s	198 T/m/s
^a) Data shown for the Z-gradient in each echo						
^b) Echo train length: 6, FOV: 160 mm $\times$ 160 mm, Voxel Size: 0.5 mm $\times$ 0.5 mm $\times$ 2 mm						
^c) Single-Shot (SSh) EPI Echo train length: 64, FOV: 160 mm $\times$ 160 mm, Voxel Size: 2.5 mm $\times$ 2.5 mm $\times$ 4 mm						

Table 21: Detailed sequence information for the selective triggering tests.

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The trigger thresholds are set to the standard value of 0 mV, to 42 mV, and to 58 mV. For each combination whether the sensors trigger or not is recorded, and the results are shown in Table 22.

Sequence	Gradient Mode	Trigger at 0 mV	Trigger at 42 mV	Trigger at 58 mV
T₁w aTSE	regular	yes	-	-
T₁w aTSE	default	yes	yes	-
T₁w aTSE	maximum	yes	yes	yes
SSh-EPI	regular	yes	-	-
SSh-EPI	default	yes	yes	-
SSh-EPI	maximum	yes	yes	yes

Table 22: Results of the selective triggering tests.

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All sequences cause triggers at the standard trigger threshold of 0 mV. At 42 mV, only the sequences with the gradient mode set to “default” or “maximum” trigger. A threshold voltage of 58 mV selects the sequences with a “maximum” gradient mode. This demonstrates that selective triggering on sequences with high slew rates is possible. With the two tested sequences, it is even possible to choose the triggering sequence by selecting the gradient mode used. Both sequences show a similar trigger behavior, since the gradient mode settings result in similar slew rates. Although these are just two sequences, they represent very different

applications: As described in chapter 2.2.5, TSE sequences are frequently used for anatomical imaging with a high spatial resolution, whereas EPI sequences are used for very fast imaging. They are thus good examples for the combination of sequences, as might be used in a motion compensation application (chapter 3.4.2): Multiple short EPI images for motion detection can be interleaved with a long anatomic TSE imaging sequence. In this case, the synchronization would only trigger on the generation of the motion detection frames.

5.2.4.3 Time Accuracy and Precision

A 13-minute-long standard T_2 -weighted (T_2w) spin-echo sequence with a long repetition time, $TR = 2.4$ s ($TE = 50$ ms), and a slew rate of 59 T/m/s (unchanged setting with normal Peripheral Nerve Stimulation (PNS) level) is executed. The threshold is left at the default value of 0 mV and the number of triggers for a detector module is plotted over time. The sequence generates echoes with a time difference of exactly TR . Since TR is very long, the generated gradient triggers can easily be assigned to the different repetitions. The error in detection timing is calculated as the time difference between the first detected gradient of each repetition, minus the repetition time TR . The result, displayed in Figure 107, shows that during the T_2w spin echo sequence, the sensors trigger very regularly: messages (with multiple counted triggers) are generated for each echo. The mean time difference to TR is (20 ± 120) μ s, which can be interpreted as accuracy and precision of the measurement.

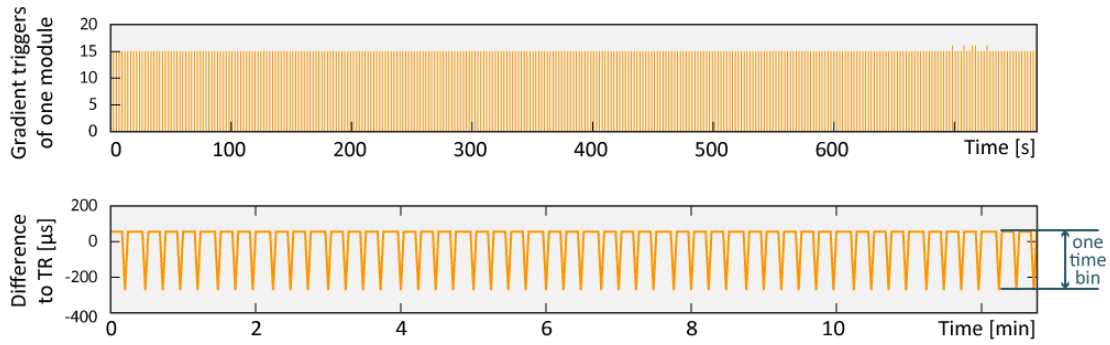


Figure 107: Timing of gradient triggers for one module (top) and the difference to the repetition time $TR=2.4$ s (bottom) of the MRI sequence.

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The high standard deviation of 120 μ s results from the current time binning of 327.68 μ s. It is higher than the mean value, because about every 15 s the accumulated time-binning errors result in an additional counted time bin (see Figure 108). The lower row of Figure 108 shows that the time bins could be made smaller to increase the precision. Nevertheless, the required precision of milliseconds for PET motion compensation is clearly met.

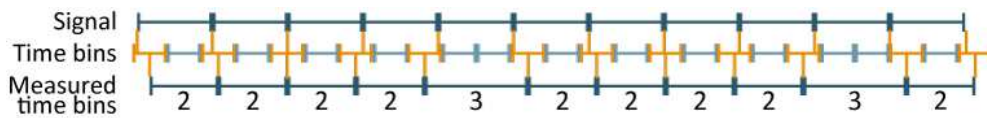


Figure 108: Example for accumulated time-binning error resulting in repetitive additional counted time bins.

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5.2.4.4 Recognition of Sequence Phases

A scout scan sequence (gradient echo, $TR / TE = 9.9 \text{ ms} / 1.25 \text{ ms}$), normally used as a first scan to plan other detailed MRI scans, is used in this experiment. As every other standard sequence (see chapter 2.2.5), it consists of a preparation phase, followed by the k-space filling (in this sequence, for three orthogonal stacks with seven, five, and five images each). The preparation phase itself has different parts, such as f_0 determination, power optimization, and RF-noise level determination. The latter part is very distinct, as it uses crusher gradients (with a rise time of $389 \mu\text{s}$ and slew rate of 25 T/m/s) in all directions to dipphase residual net magnetizations. They are followed by 150 ms of absolute silence during which the system measures the RF noise. In this sequence, the noise level determination is executed three times. The pulse diagram in Figure 109, top row, shows the direction and gradient strength of all three gradients at the end of the preparation phase and the beginning of the k-space filling phase of the scout sequence (the exact shape of the gradients is not visible, since the time-zoom-factor is too low). The measured triggers (trigger threshold is the default 0 mV) are shown on the bottom row of Figure 109.

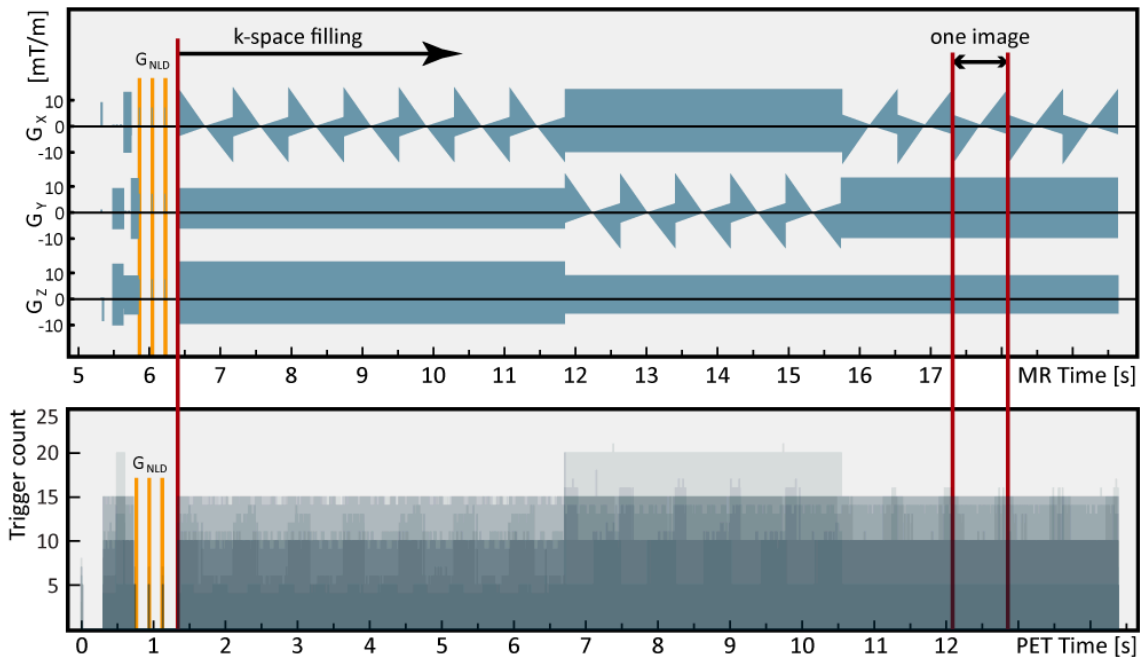


Figure 109: Pulse diagram (top) of the survey sequence (only end of the preparation phase shown). The trigger count of the gradient sensors are shown with transparency for the different modules (bottom). Clearly recognizable are the three crusher gradients (G_{NLD}) of the noise level determination and the structure of the k-space filling.

Figure published in (Weissler *et al.*, 2015b) ©^{3.0} 2015 IEEE.

The structure of the sequence with the three orthogonal stacks of images (with seven images for the first stack and five images for the other orientations) is clearly recognizable. The time between the noise level determination and the k-space filling is slightly longer than shown in the pulse diagram. Furthermore, the length of the receiver optimization phase (preceding the noise level determination) is longer than in the diagram (as explained in chapter 3.4.2). It thus makes sense to determine the beginning of the k-space filling and synchronize accordingly. The three crusher gradients of the noise level determination (preceding the k-space filling) are also distinguishable, which would even allow for this distinct pattern in the

data stream to be found automatically. The synchronization would, in that case, be realized on the next following detect gradient, which is, consequently, the first gradient of the k-space filling.

5.2.5 PET/MR Imaging

5.2.5.1 Hot-Rod Phantom

To visualize the spatial distortions and resolutions, a 20 mm thick hot-rod phantom inlay (rod diameters = 1, 1.5, 2, 2.5, 3, and 4 mm) was built for a phantom container and filled with ^{18}F -FDG. A reference PET scan was made outside the MRI using an activity of 24 MBq. Then, inside the MRI, 5 PET scans were made beginning with 16.7 MBq and progressing down to 8 MBq. To keep the number of coincidences roughly the same, the scan time was chosen as $200 \text{ MBq} \times \text{min}$ divided by the start activity of the scan (reference scan: 50 % more to ensure good statistics for the baseline). Details are listed in Table 23.

MRI sequence	start activity	scan time
PET-only	24.7 MBq	12 min
T¹w aTSE	16.7 MBq	12 min
T₂w TSE	14.4 MBq	14 min
T₁w 3D-FFE	12.3 MBq	16 min
T₂w 3D-FFE	10.3 MBq	19 min
EPI	8 MBq	25 min

Table 23: Hot-rod phantom PET scan details.
Table published in the supplemental material of (Weissler *et al.*, 2014b).

During each PET scan, a single type of MRI sequence was executed. The sequences are similar to the ones for the SNR measurements, but the FOV was reduced, the spatial resolution increased to $250^2 \mu\text{m}^2$, and the NSA values and slice thicknesses were partly increased in order to improve the intrinsically lower SNR at this resolution (for details see Table 24).

The RF coil is not correctly loaded because it was designed and tuned for much larger objects. In order to still be able to scan with the normal automatic RF power determination, a one-liter-bottle-phantom was placed next to the hot-rod phantom. This loads the coil and brings it closer to the situation in that its resonance frequency and matching circuits were tuned. The shorter MRI scans were repeated until the PET scan time was over. Due to the short scan time of the EPI sequences (down to 2 s), they were varied from EPI factor 3 to EPI factor 19, 1 slice / 10 slices and NSA 4, 8 and 16. As such, 184 EPI images were taken during the PET scan (1184 images counting each NSA).

MRI sequence	ETL ^a	TR/TE ^b [ms]	NSA ^c	FA	pixel bandwidth	slices	acquisition voxel size [mm ³] ^d	scan time
T₁w aTSE	6	612 / 20	8	90°	328 Hz	1	0.25 × 0.26 × 2	4:16 min
T₂w TSE	19	2400 / 100	8	90°	291 Hz	1	0.25 × 0.26 × 2	5:10 min
T₁w 3D-FFE	1	11 / 2.3	16	35°	433 Hz	10	0.4 × 0.4 × 4	2:34 min
T₂w 3D-FFE	1	13 / 8.1	8	45°	217 Hz	10	0.25 × 0.25 × 4	2:27 min
EPI 19	19	51.2 / 19.1	4	20°	658 Hz	1	0.5 × 0.5 × 4	2.0 s
^a) Echo Train Length					^c) Number of Samples Averaged			
^b) Repetition Time / Echo Time					^d) Image size : 80 mm × 80 mm			

Table 24: MRI sequences for the hot-rod phantom measurements.
Table published in the supplemental material of (Weissler *et al.*, 2014b).

The images are displayed in Figure 110. The MR images are neither resized nor filtered, nor are brightness and contrast adjusted manually. As described above, the MR images have a relatively low SNR. Therefore, the noise floor is visible in the background of some images and the slight decrease of SNR due to the active PET electronics is also visible there. Since the SNR is especially low in the EPI images, the RF-noise artifacts (see SNR measurements, chapter 3.2.2) are visible in the background of 6.5 % of the 184 taken images. Nevertheless, the SNR is good enough to show the small details of the phantom – even in the 2 s short EPI sequence.

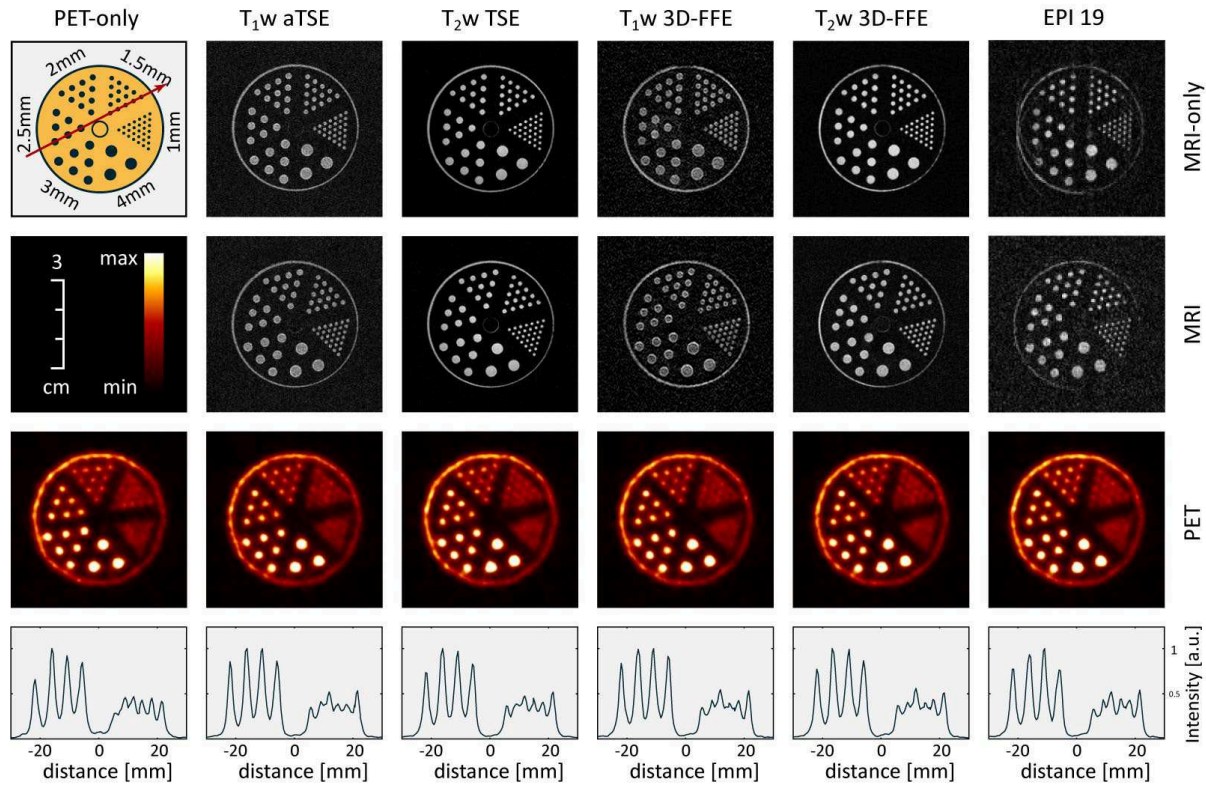


Figure 110: PET-only (left column), MRI-only (first row) and simultaneous PET/MR measurements of a hot-rod phantom (rod diameter = 1, 1.5, 2, 2.5, 3 and 4 mm, 20 mm length).

The orientation of the profiles through the PET images (bottom row, intensity scaled individually) is shown in the schematic of the phantom (top left).

Figure published similarly in (Weissler *et al.*, 2014b) © 2014 IPEM.

Upon visual inspection, about 26 % of the EPI images show ghosting artifacts, which can be seen in the top right image of Figure 110 – in 7.6 %, the ghosting is severe (meaning that the

real rods are not clearly distinguishable from the ghosts). Although the artifacts seem less with lower EPI factors, a clear correlation of scan parameters and the appearance of ghosts was not yet observed. Nevertheless, 74 % of the EPI images seem to be free from these artifacts. In the MRI-only image of the T_{1w} 3D-FFE sequence, a mild fold-back artifact is visible around the 2.5 mm rods. This is normal in 3D imaging and unrelated to the PET/RF insert. All other images are free from visual artifacts.

The outer ring of the phantom is somewhat angular in all PET images (also the PET-only image), and resembles the shape of PET detector built from 10 modules. There are no visual differences between the reference PET image and the image during the MRI sequences. While the 1-mm rods are blurred, the 1.5-mm rods are separable. The differences in the profiles are very small and probably caused by the different profile angle, since the phantom was slightly turned when the PET system was moved into the MRI. Figure 111 shows a PET image, reconstructed from a combined dataset with all data measured during the MRI scans.

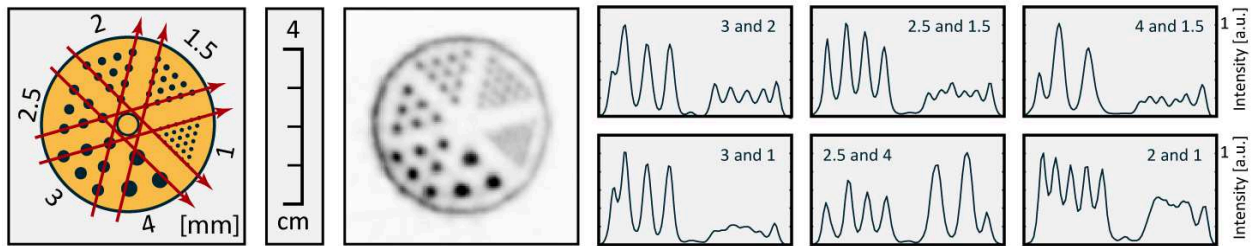


Figure 111: Reconstructed PET image from a combined list-mode file, containing all data measured during the MRI sequences. Profiles are displayed through all hot-rod areas (right).

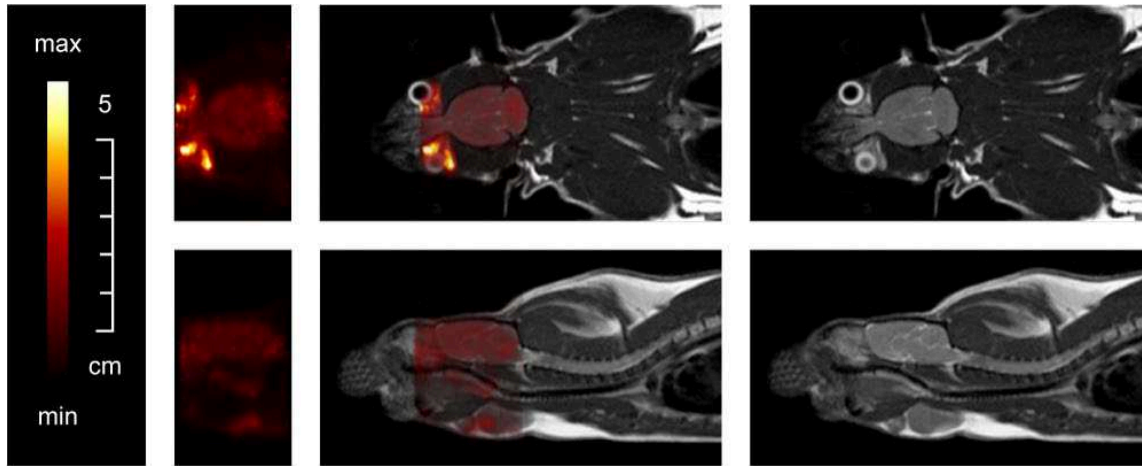
The phantom study illustrates that the spatial resolution does not deteriorate, nor do other artifacts appear in the images during MRI operation, which matches the results from the point source measurements (chapter 5.2.3). Effects related to the presence of the static magnetic field (such as reported in (Chaudhari *et al.*, 2009)) were also not observed.

5.2.5.2 In Vivo Measurement

A simultaneous PET/MRI measurement of a living rat (Wistar strain, male, 240 g) was performed by the clinical partner King's College London to demonstrate the in vivo measurement capability of the system. The measurements were operated under the project license reviewed by the Ethical Review Panel at King's College London and the UK Home Office. After being anaesthetized with isoflurane, the rat was injected in the tail with approximately 7 MBq of ^{18}F -FDG. The PET scan was started one hour after injection. Several MR sequences (T_{2w} 3D TSE, balanced Turbo Field Echo (TFE), and 3D Steady-State Free Precession (SSFP)) were executed during the 50-minute-long PET data acquisition.

Figure 112 shows the resulting images. The time alignment (see section 5.1.9.1) was not available at the acquisition, and thus the singles and coincidences windows were chosen to be 25 ns. 16 ML-EM iterations (1 subset) were used to reconstruct the image. At the time of the measurement, the MRI SNR was relatively low due to emissions from the PET system. Therefore, a high NSA was used in the TSE sequence (echo train length 18, FA 90° , voxel size $500^2 \mu\text{m}^2 \times 2 \text{ mm}$, acquisition matrix 240^2 , TR/TE = 1000 ms/51.6 ms, NSA 30, 2:30 min scan time, pixel bandwidth 445 Hz/pixel). The noise level of the system was improved and is now 3.3 times lower (see section 5.2.2.2). Therefore, three equal MR images were averaged

to demonstrate the MRI SNR that can now be obtained using only an NSA value of 8 (40 s scan time). The MR images were manually fused with the PET images by calculating the opacity of each PET pixel from its brightness.



**Figure 112: Simultaneous PET/MR measurement of a rat brain with ~ 5 MBq ^{18}F -FDG. Coronal slices (top) and sagittal slices (bottom). PET-only (left), fused PET/MR (middle) and MR images (right) (T_2w TSE 18, FA 90° , voxel size $500^2 \mu\text{m}^2 \times 2$ mm TR/TE = 1000 ms/51.6 ms, NSA 90 – equivalent to NSA 8, 40 s scan time with current system).
Figure published in (Weissler *et al.*, 2014b) © 2014 IPEM.**

The respiration, pulse, and temperature of the rat remained normal during the measurements. Together with the successful image generation, this confirms the systems simultaneous in vivo PET/MR capability.

Beside the uptake in the brain (which naturally shows high ^{18}F -FDG uptake due to its high metabolic activity), an increased uptake is visible behind the eyes in the Harderian glands. The glands can be found in animals that have a nictitating membrane (a transparent or translucent third eyelid). The increased ^{18}F -FDG uptake is a known phenomenon in the preclinical PET imaging of rodents. Due to high values compared to the brain, it was even suggested to remove them to reduce partial volume errors (Brammer *et al.*, 2007).

5.3 Conclusion and Summary

Since the insert is only populated with one PET detector ring, the axial PET FOV is only 30.1 mm long, which is sufficient for single organ measurements, as shown for the rat brain, but too small for whole-body mouse imaging. With an energy resolution of 29.7 % and a time resolution of 2.5 ns, it achieved a spatial resolution of 1.3 mm and a peak sensitivity of 0.6 %. These values are already better than all other PET/MRI inserts presented in the benchmark (see chapter 7.1), but do not yet meet the targeted requirements for the high-performance system. B_0 distortion is kept below 2 ppm peak-to-peak (without shimming) in a diameter of 56 mm within the hybrid FOV. However, 0.1 ppm VRMS homogeneity, important for advanced MR sequences such as spectroscopy, can only be maintained within a diameter of 8 mm (automatic shimming). Spurious signal scans revealed RF noise originating from the PET electronics, which appeared as dotted lines in some of the MR images. Further

experiments indicated that these signals leaked out of connections between the PET detector modules and the synchronization cables. During long EPI sequences, induced eddy currents resulted in a heating of the PET electronics and, consequently, in a slight adjustment of its count rates (influencing sensitivity and thus quantification capabilities). Additionally, the eddy currents appear as ghosting effects in the MR images: 48 of the 184 taken EPI images show ghosting; in 14 images, ghosting is severe. The NECR curve reaches a plateau at around 35 MBq. The system is thus fine for mouse and rat imaging, but less suitable for rabbit imaging – especially as large amounts of activity would be outside the FOV and would further increase the multiple and random counts. Since the data is initially stored on the RAM, the maximum measurement time is limited (and activity depending). With 10 MBq, a scan can take about 35 minutes. Copying the data on the hard drives takes about the same time, which limits the maximum scan time per day to half the available time. Simultaneously measured PET and MR images of a living rat demonstrate the in vivo capability of the system, and, in (Mackewn *et al.*, 2015b), a dynamic study is shown, using a dual-labeled PET/MR probe with ⁶⁴Cu as the radionuclide. Nevertheless, as a first prototype, the insert has a few deficits that hinder advanced in vivo imaging: the system is complicated to set up, the integrated MRI RF coil is not exchangeable (often resulting in suboptimal MRI SNR), and it does not have inputs for external trigger signals.

The measured performance parameters are summarized in Table 25 to Table 27. The results are mostly a factor of two away from the target set for a high-performance system, but never a complete magnitude. The numerical results thus support the outcomes from the imaging experiments: the system is well suited for simple imagining in small rodents, but has deficits for rabbit imaging and more advanced studies such as MRS experiments.

Parameter	Requirement	Result
Energy resolution	15 % FWHM	29.7 % FWHM
Time resolution	1 ns FWHM	2.5 ns FWHM
Time resolution for TOF (rabbit imaging)	535 ps FWHM	-
Spatial resolution	1 mm FWHM	1.7 mm / 1.8 mm ³ FWHM
Sensitivity	3 %	0.6 %
Maximum activity (mouse / rat / rabbit)	(21 / 30 / 90) MBq	35 MBq

Table 25: PET system performance parameter summary for Hyperion I

Parameter	Requirement	Result
B₀ homogeneity (anatomical imaging)	2 ppm peak-to-peak (over the whole FOV)	Ø 56 mm in FOV Ø 90 mm (shimming)
B₀ homogeneity (spectroscopy)	0.1 ppm VRMS (single voxel)	Ø 8 mm (shimming)
Spurious signals	No spikes in spectrum	Spikes visible
Spurious signal image artifacts	Not visible in background noise	Visible if SNR is too low
SNR degradation	3.3 %	14 %
Percent Image Uniformity degradation	± 5 %	- 1.3 %
Ghosting	No difference to reference	Visible at high EPI factors
Geometric distortion	1 %	Only exceeded at EPI (maximal 5.8 % worse than reference)
Temporal fluctuation	0.2 %	0.14 %
Temporal drift	1 %	0.769 %
FBIRN test SNR	200	363
FBIRN test SFNR	200	302

Table 26: MRI system performance parameter summary for Hyperion I

Parameter	Requirement	Result
Axial hybrid FOV	90 mm	30.1 mm
Diameter (transaxial) hybrid FOV	150 mm	160 mm
Maximum scan time (mouse imaging)	4 hours	35 min
Maximum total scan time per day	8 hours	4 hours
Temporal synchronization accuracy	5 ms	140 µs

Table 27: PET/MRI system performance parameter summary for Hyperion I

These results indicate that direct in-bore digitization and processing is possible without severe influences between the two modalities. Due to the extended incorporation of electronics, a TOF-capable infrastructure for a high number of channels at a small form-factor is facilitated, and this is necessary for improved PET/MRI system integration. In the next step, the PET performance, as well as the PET/MRI compatibility, has to be improved.

6. Step II: Digital SiPMs and Optical Synchronization

The next evolutionary step in solid-state light sensor design was introduced by Philips in 2009 ((Frach *et al.*, 2009) and (Degenhardt *et al.*, 2009)): The digital SiPM (dSiPM), also named Digital Photon Counters (DPCs), have digital electronics integrated into the sensor silicon die and count the number of detected photons directly. This promises high sensitivity, excellent timing and improved robustness – in particular against electromagnetic fields (PDPC, 2013). In the second step of this thesis, where the PET/MRI compatibility will be improved, this new sensor technology will also be integrated. The resulting design concept of the world's first preclinical PET/RF insert using fully digital silicon photomultiplier technology was first presented in (Weissler *et al.*, 2012a). The finalized insert and results are published as extractions from this chapter in (Weissler *et al.*, 2015a, ©^{3.0} 2015 IEEE).

6.1 The System

The PET/MRI insert is based on the system presented in the first step. The results from the previous chapter, as well as all the detected shortcomings and lessons learned, are used to improve the design and meet the targeted requirement specifications for a high-performance system.

The dimensions of the insert are kept similar to previous insert and, where possible, the interfaces between the system components were kept compatible. This includes the hardware (e.g., the interface between the detector stack and the SPU) as well as the software (i.e., the communication protocol, the control software and partly the DAPS software). As such, it is possible to develop and test single components – as well as firmware and software – independently using the old hard and software.

6.1.1 Singles Detection Module (SDM)

6.1.1.1 Detector Stack

The new digital sensors have two advantages when it comes to system integration. Firstly, the entire digitization board is no longer needed. Secondly, the sensor diodes are biased with a positive voltage, which can be regulated with an off-the-shelf IC. Consequently, the detector stack (Figure 113) contains only four layers: scintillation crystal array, light guide, sensor- and interface- board.

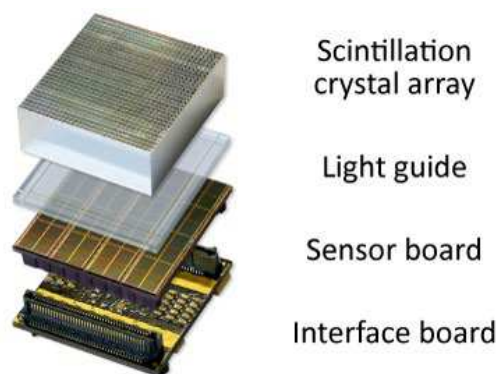


Figure 113: DSIPM-based detector stack scintillation crystal array shown upside down to emphasize the individual crystals.

Figure published as part of a figure in (Weissler *et al.*, 2015a) ©2015 IEEE.

6.1.1.1.1 Scintillator Array and Light Guide

The scintillation arrays are made from 30×30 12-mm long cerium-doped lutetium yttrium orthosilicate (LYSO) crystals (Agile, Knoxville, USA); optically isolated by 67 μm Vikuity™ ESR films (3M, St. Paul, USA). Compared to the previous insert, the smaller crystal pitch of 1 mm (drawing with dimensions: Figure 129) will increase the spatial resolution. The crystals were also chosen to be 2 mm longer to increase the sensitivity. Scintillation light is coupled to the sensor board through a borosilicate glass light guide. It is 2 mm thick and has 1.3-mm deep slits, filled with white paint, that partly optically isolate the outer crystal rows. As such, less light from the outer crystals is shared with the inner sensors, and thus the calculated position in the flood histogram is shifted outwards. This will increase the ability to separate the outer crystal rows. Optical interfacing between the crystal array, the light guide, and the sensor board is realized with a two-component silicon glue (Scionix, Utrecht, the Netherlands). Unlike the previously used Meltmount, it also ensures the connection at temperatures higher or lower than room temperature. The gluing process itself is difficult, as high precision and two gluing steps are required: between the scintillator array and the light guide, and between the latter and the sensor board. A special gluing-rig was built for this purpose. Furthermore, the silicon needs to cure for 12 hours and the glued parts need to be kept in position during that time. An alternative solution is an optical glue that hardens under ultraviolet light, but then the connection is permanent and the glue cannot be removed.

6.1.1.1.2 DSIPMs and Sensor Board

The single microcells of a SiPM are operated in Geiger-mode (similar to the SiPM as described in chapter 4.2). As such, each cell is an intrinsic digital device that detects single photons. By

connecting all cells in parallel, the signals are summed up in a SiPM and produce the analog output signal. This has to be re-digitized by the detector electronics. The dSiPM has digital electronics integrated¹² that directly count the number of detected photons, and thus the intermediate analog step is omitted completely. By rendering the concept of gain and amplifier-noise meaningless, this concept promises very high SNR for PET applications.

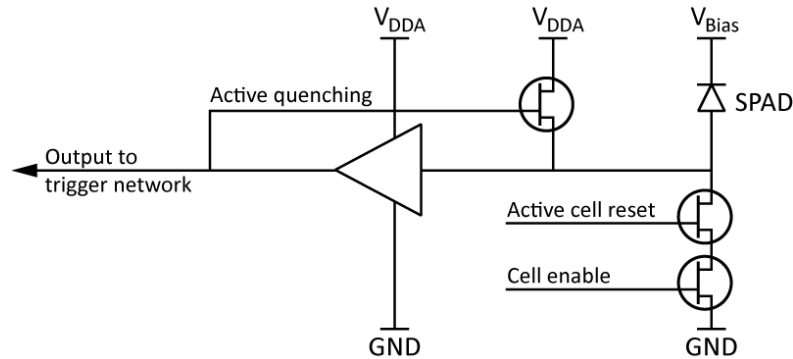


Figure 114: Simplified circuit of a micro-cell in a dSiPM: Each SPAD can be actively quenched, reset, and disabled.

Similar to analog SiPMs, not all microcells function exactly as designed. Impurities or defects created in the production process or due to handling or aging, can result in cells that trigger with a higher probability. The result is avalanches in SPADs without any incident photons: the dark counts. Unlike analog SiPMs, the dSiPM can shut down these cells down by means of an additional transistor (Figure 114). Once the dark-count rate of all cells is measured, the overall dark-count rate can be reduced by disabling a certain percentage of the cells with the highest rate. Currently, usually between 10 % and 25 % of the SPADs are inactivated.

Quenching the avalanche in a SPAD can be realized much faster than in a normal SiPM. In the latter, the voltage over the cell is slowly reduced by the current through the diode and the series quenching resistor. In the dSiPM, the digital circuit of the cell actively quenches the avalanche with a fast transistor (Figure 114) once the avalanche is detected. As such, the time of the single cell, and thus the dead time of the complete sensor, is significantly reduced.

¹² Actually, the design was made the other way round: To keep the production price affordable, the SPAD was designed in a way that permits it to be realized in an almost-standard CMOS process.

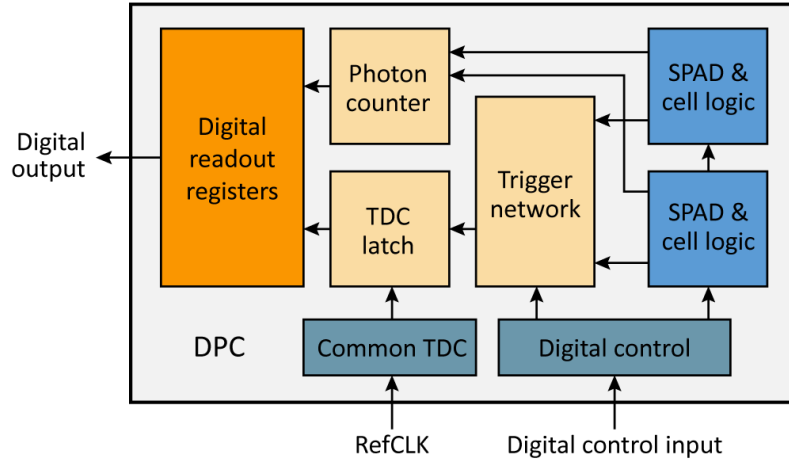


Figure 115: Simplified block diagram of a dSiPM: The SPADs (only two shown) have digital outputs to the photon-counting circuit (to measure the energy) and, via a programmable trigger network, to the TDC circuit (to measure the time of arrival).

When a photon is detected by the SPAD, digital signals are given to a programmable trigger network (see Figure 115). Depending on its settings, the triggers are discarded (as dark counts) or validated as an event. In the latter case, the time of arrival is generated from a common TDC and, together with the value of counted photons, placed into the readout registers. More detailed information about the dSiPM, its functions, and its settings can be found in (Frach *et al.*, 2009), (Haemisch *et al.*, 2012), and (Tabacchini *et al.*, 2014).

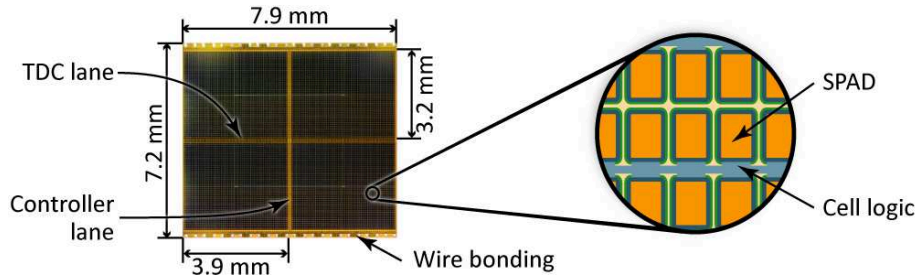


Figure 116: Microscopic photo of a monolithic 2×2 dSiPM array (left) with magnified sketch (right) of the sensor structure.

The standard dSiPMs used, namely the DLS 3200-22 (Philips Digital Photon Counting, Aachen, Germany), have 3,200 microcells per sensor channel (often also called sensor pixel), each with a size of $59.4 \mu\text{m} \times 64 \mu\text{m}$. Every monolithic sensor die has 2×2 dSiPM channels with a single interface for all four channels (see Figure 116).

Sixteen of these dies are mounted on a custom-made sensor board that was designed for MRI compatibility. The backside of the board bears non-magnetic decoupling capacitors to support the supply voltages. Similarly to the sensor board made for the analog SiPMs, the PCB is electrically split into two sides, thereby avoiding conductive loops over the two connectors towards the interface board.

6.1.1.1.3 FPGA and Interface Board

Every sensor die is provided with a single-ended RefCLK and a Sync signal. The stack FPGA is used for the distribution of the signals. As such, the Sync signal lines can also be used to realize a neighbor logic (as described in section 5.2.1). The sensors are configured and

controlled in two JTAG chains (one for each side), counting ten lines all together. Data are transmitted over two single-ended lines per die to the interface FPGA (Figure 117).

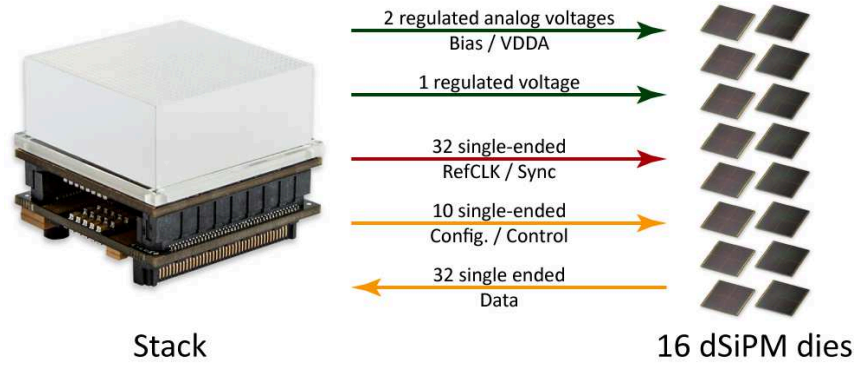


Figure 117: Detector stack hierarchy: The light from 900 crystals is detected by sixteen monolithic sensor dies containing each 2×2 dSiPM channels. They are powered by one digital supply and two analog voltages. Communication to the interface FPGA is realized in single-ended CMOS lines.

Data from the dSiPMs are read out and pre-processed by a Spartan-6 FPGA (Xilinx, San Jose, USA). It is the direct successor of the previously used Spartan-3 FPGA. Similarly to the old design, it forms the interface to the SPU and is the main component of the interface board. The bias voltage for the dSiPMs and the quenching supply voltage (V_{DDA} in Figure 114) are regulated on the interface board. The respective currents are measured by additional ADCs. Detailed numbers and dimensions of the detector stack are displayed in Table 28 and Figure 129. A comprehensive description of the detector stack is given in (Dueppenbecker *et al.*, 2012b) and (Dueppenbecker *et al.*, 2016).

Parameter	Value
Scintillation crystal pitch / size	1 mm / $0.933 \times 0.933 \times 12 \text{ mm}^3$
Sensor type	PDPC DLS 3200-22
dSiPM sensor channel (pixel) pitch / size	4 mm / $3.9 \times 3.2 \text{ mm}^2$
Microcells per dSiPM channel	3200

Table 28: Details of the digital detector stack.
Table published in (Weissler *et al.*, 2015a) ©2015 IEEE.

6.1.1.2 Singles Processing Unit (SPU)

The SPU was upgraded in two steps from version v1.3 to v1.5. Although remaining backwardly compatible (mechanically and electronically) with the old version of the SPU, many improvements have been made.

6.1.1.2.1 Detector Stack Support

The SPU still supplies and controls 3×2 stacks. Details of the used communication and clock lines, as well as the supply voltages, are shown in Figure 118.

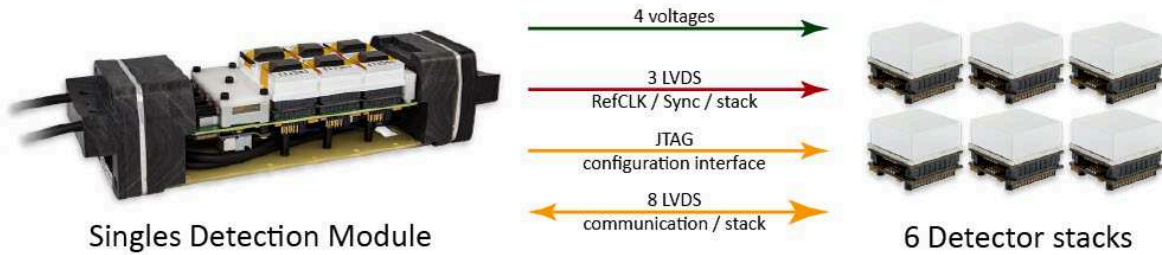


Figure 118: Module hierarchy: The stacks are supplied with two regulated and two unregulated voltages. RefCLK / Sync and communication are realized as differential LVDS pairs.

Multiple extender PCBs and adaptors were built to connect the detector stack to the SPU (Figure 119). A debugging adaptor routes all pins of the connection to header pins (as discussed in chapter 5.1.1.2, debugging possibilities are vital in the system integration phase, where the hardware is brought to life with firm- and software). Other PCBs allow the stack to be shifted horizontally and turned 90°, which is used both for MRI compatibility studies of the stack and in a testing rig to test all sensor tiles. In addition, flexible stack connector PCBs were built for further research studies. Besides removing the mechanical stress, they allow tilting the stacks so that they can be positioned more precisely and exactly aligned to the gantry radius (see patent in chapter 0).



Figure 119: Different adaptors to connect a detector stack to the SPU: A debugging adaptor (left, red) routing all pins to headers, two adaptors displacing the stack horizontally (blue and green), and a flexible PCB allowing the stack to be tilted and turned in multiple dimensions.

6.1.1.2.2 B₀ Homogeneity Optimization

The results from chapter 5.2.2.1 revealed that the amount of magnetic material has to be further reduced to improve B₀ homogeneity. The main disturbance was caused by the optical data transceiver (Figure 120, top, shows the disturbance caused by a single device). The housing of the laser transmitting and receiving diodes are normally made from a ferromagnetic alloy that has the same thermal expansion coefficient as the diode semiconductors. In the extensive research for a solution (other research groups, confronted with the same problem, started to develop their own diode housings (Olcott *et al.*, 2009)), a new transceiver with plastic housings for the diodes was found. Since the Small Form-factor Pluggable (SFP) housing still causes a significant B₀ distortion (Figure 120, second row), a new housing, milled from aluminum was designed (Figure 120, third row). The modified transceiver was successfully tested inside the MRI bore. Nevertheless, the manufactured aluminum housings are very expensive, and modifying a component always bears the risk of destroying it. Therefore, it was decided to use a different technology, developed in parallel: In cooperation with the manufacturer, a non-magnetic version of their newly developed transceiver for optical Gigabit Ethernet communication was designed. The 650-nm light is emitted from Resonant Cavity Light Emitting Diodes (RCLED) and is transported through

Plastic Optical Fibers (POF). By replacing an internal capacitor, the contact leads, and the coating of the shielded housing, it became almost completely non-magnetic (Figure 120, bottom row). The SPU v.1.5, used for Hyperion II^D, is equipped with two optical transceiver modules: one for data transfer and one used as a receiver for synchronization signals (see section 6.1.2).

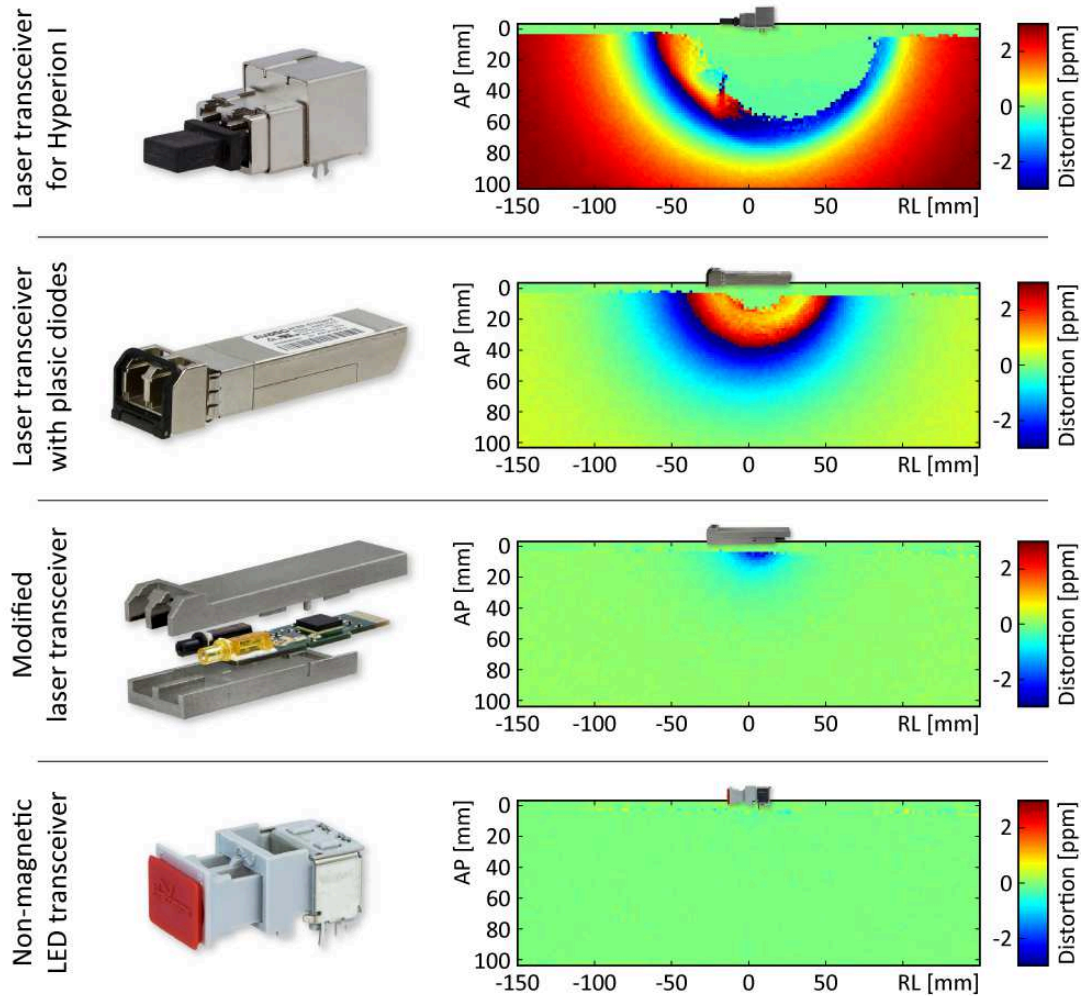


Figure 120: Optical transceivers for communication and synchronization of the SPU: The standard laser transceiver distorts the B_0 field of the complete phantom. The laser transceiver with plastic diode housings still causes a strong distortion, even showing signal loss and a phase wrap close to the component. The modified laser transceiver has a much smaller distortion radius, and the specially designed LED transceiver is invisible in terms of the static magnetic field.

The transceivers were placed on piggyback boards, which allows for using different technologies for different situations (Figure 121). Whereas the POF transceiver is used inside the SDMs, a direct laser transceiver board (1000BASE-SX optical Gigabit Ethernet standard) is used in the synchronization unit (which is based on the SPU electronics – see section 6.1.2). During the development phase of the electronics, the firmware, and the software, a copper-based Ethernet module (1000BASE-T) that was plugged into a SFP cage, allowed direct connection with every standard PC or laptop. A special module with two SFP transceivers was made to test double maximum data rates, or the daisy-chaining of SPUs.

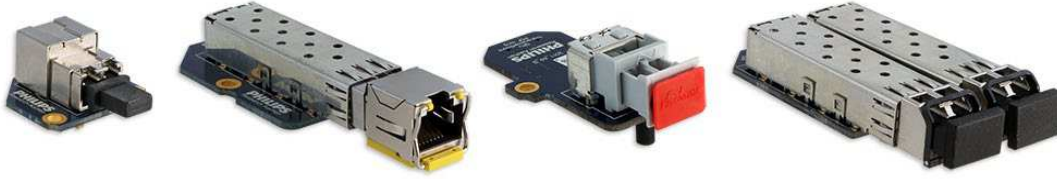


Figure 121: Transceiver piggyback boards for the SPU from left to right: 1000BASE-SX optical Gigabit Ethernet, 1000BASE-T copper-based Ethernet SFP, non-magnetic POF, and double SFP module, equipped with two optical 1000BASE-SX transceivers.

The data sheets off all transceivers demand the use of filter circuits using inductors or ferrite beads, which decouple the high-speed transceiver from noise and ripples of the power supply network (especially important, since induced ripples on the power supply chain are expected from inductions by the MRI's gradient switching – see section 3.1.2.2). Since ferrites lose their capabilities in the high static magnetic fields of the MRI, a local LDO power regulator circuit, which was chosen for its PSRR in the frequency range of the switching gradients, is placed on the piggyback boards. Media-conversion boards (Figure 122) that translate between POF and glass fiber communication, as well as from POF to copper-based Ethernet with an RJ45 connector (although multiple media-conversion steps are possible but not advisable with respect to reliability and bit-error rates) had to be designed.



Figure 122: Active media converters from for Gigabit Ethernet from POF to copper-based RJ45 and laser-based LC glass fiber connector (custom-made) and passive couplers for POF, LC, and RJ45 (of-the-shelf components).

The amount of magnetic material on the SPU was further reduced, in comparison to version v1.3 (section 5.1.1.2), by replacing more and more devices (mainly capacitors, connectors, and ICs) with carefully selected, or extra manufactured, versions. The resulting B_0 distortion caused by the SPU (Figure 123) was thus significantly reduced compared to the older versions. The overlay of the SPU in the B_0 map, furthermore, indicates that the residual distortion is mainly caused by the Virtex-5 FPGA.

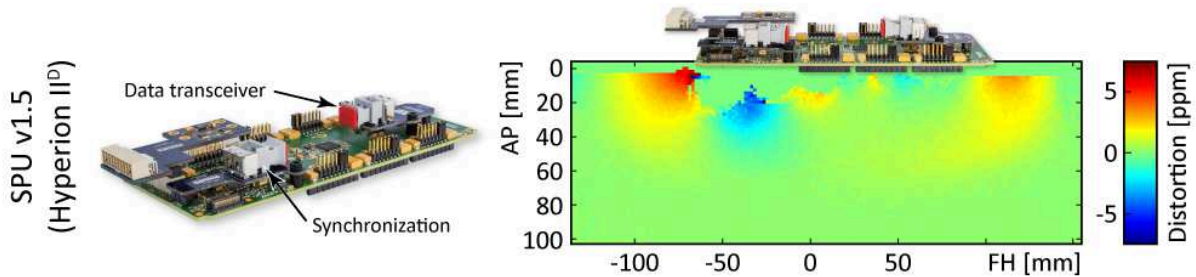


Figure 123: Backside of SPU v1.5 (left), including transceiver boards for communication and synchronization, and the power supply conversion board (see section 6.1.1.3). The resulting B_0 distortion map is shown on the right (to allow a comparison, it uses the same colormap as in the measurements shown in Figure 75 for the older version of the SPU).

This process of replacing components to optimize B_0 homogeneity was continued for the SDM mechanics: The screws used, for instance, are either made from aluminum, brass, or glass-

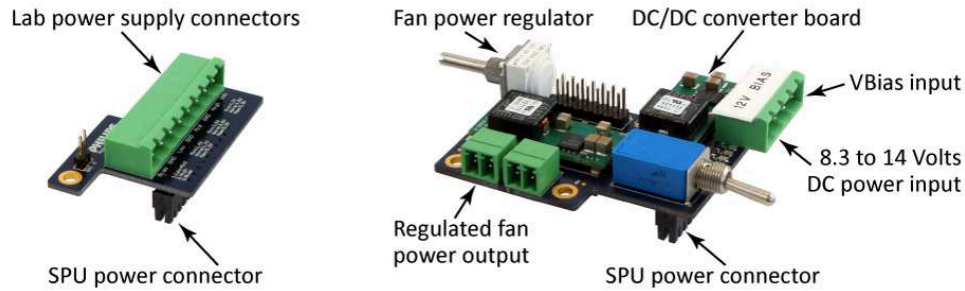


Figure 125: Example power supply boards for the SPU: A simple board (left) to connect lab power supplies with screwable connectors (Phoenix Contact), and a switched-mode power supply that can operate the SPU with a standard wall power supply.

Locally, the SPU v1.5 has eleven linear regulators for different voltages and supply domains (e.g., to separate digital communication supply from clock distribution and ADCs). The necessary voltages are set with feedback resistor networks at the regulator circuit, but problems in the production process are both common and dangerous: Wrong or broken resistors, bad connections (tombstones), or short circuits can result in output voltages that can destroy the SPU. Therefore, a service connector was added to the last version of the SPU, giving direct access to all local voltages. For the first power-up of each SPU, a 16-channel DAC system (NI USB-6210, National Instruments) is connected. As such, all voltages are monitored with a LabView program (National Instruments), when the input voltages are risen in defined steps with adequate current limitations.

6.1.1.4 Module Cooling

Similar to the previous version, the SDM is cooled with a combined liquid and dry air chilling system. The sensor boards and interface boards are directly cooled by four cooling pipes (Figure 126) that have a square cross section. The pipes are electrically insulated from the PCBs of the stacks by thermal pads. The linear voltage regulators and the FPGA on the SPU are thermally connected, via an aluminum heat spreader, to the cooling pipes. Although the pipes are electrically connected to the heat spreader, they do not form conductive loops, as the 180° curves are made from rubber. For the same purpose of reducing the eddy currents (induced by the MRI system's gradients), the heat spreader has a slit, thus decreasing the effective conductive cross section. The dry air is taken from the MR examination room and is blown into the SDM via a distribution ring (see Figure 141). The air leaves the SDMs on the inside of the gantry and is guided by covers through the complete insert. This reduces condensation problems and allows the low liquid cooling temperatures. A humidity sensor on the SPU measures the dew point of the atmosphere inside the SDM, and thus allows for safely choosing the cooling temperature. The temperature of the liquid cooling was planned to be 10° C, as this is the lowest temperature specified by the mechanical components (e.g., rubber gaskets). Nevertheless, the system is normally operated at 0° C liquid cooling temperature. It was also operated at -5° C, but this causes mechanical stress on all components. It is furthermore a good practice to increase the temperature to normal operation temperatures before switching the system (and the dry air supply) off, in order to reduce mechanical stress and condensation after operation. Dangerous situations can arise for the hardware if the liquid cooling system is not switched on or is broken (or frozen). Although the local regulator ICs have a temperature protection built in, which switches the output off in the event of a too high temperature, this point in time might be too late for other

parts of the electronics and the dSiPMs (especially since the regulators are thermally connected to large heat sinks). Therefore, not only was a temperature sensor placed close to the regulators with the highest power dissipation, but two thermostat ICs (LM56, National Semiconductor) with two thermostats each were additionally placed on the SPU. They constantly survey the SPU surface temperature and provoke the sending of an error message once 55° C are reached. At 61° C, they autonomously shut down the SPU by disabling all (but its own) voltage regulators until the SPU is cooled down to 5°.

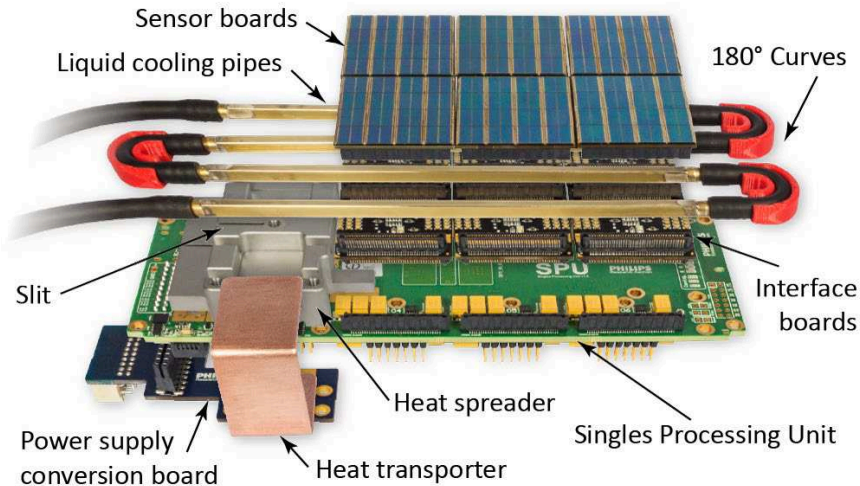


Figure 126: Exploded-view photo of the liquid cooling system inside the SDMs: four brass cooling pipes are thermally, but not electrically, coupled to all the sensor- and interface boards, to the SPU, and to a power supply conversion board.

Figure published in the supplemental material of (Weissler *et al.*, 2015a) ©2015 IEEE.

6.1.1.5 RF Screen

Two problems of the old insert were probably caused by the shielding concept of the SDMs. Ghosting artifacts were visible in EPI images (possibly related to eddy currents in the shielding) and spurious signals were visible in low SNR images (probably caused by electromagnetic noise, leaking out of the SDMs). The copper-coated housings of the SDMs were thus replaced by carbon fiber composites. They promise good shielding properties at high frequencies, while having a reduced conductivity at the lower frequencies of the gradient switching (Chung, 2001). The carbon fiber RF screens (details are published in (Dueppenbecker *et al.*, 2012a)) are formed as a tube and pushed over the modules. The shielding is closed on both sides by PCBs, placed between two glass-fiber-reinforced plastic parts (see Figure 127). Tightening the closing screws presses the RF gaskets (Amucor Shield 6833-01-N, Holland Shielding Systems, Dordrecht, the Netherlands) on the PCBs and on the carbon fiber tube in order to reduce possible leakages. Furthermore, connectors can be placed on both sides of the PCB, and thus the power input of the SDM is realized with RF-tight SMA connectors on the outside and a connector to the power conversion board on the inside.

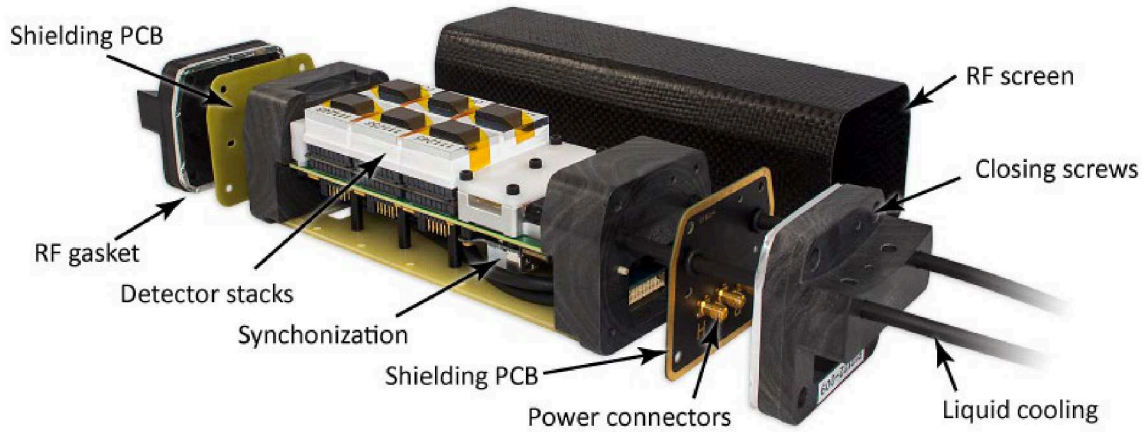


Figure 127: Exploded-view photo of the SDM shielding concept: The carbon fiber RF screen is pushed over the module and the RF shield is closed on both sides by shielding plates, manufactured as PCBs.

Figure published as part of a figure in (Weissler *et al.*, 2015a) ©2015 IEEE.

A second possible source of leakage source in the previous design was the usage of HDMI cables for synchronization. Although the cables themselves have good Electromagnetic Compatibility (EMC) properties, the entry point of the cable into the SDM is vulnerable. This gap in the shielding concept is now closed by using an optical reference clock and synchronization method (see section 6.1.2).

6.1.1.6 Assembly

The SDMs are equipped with all six detector stacks (Figure 128), which results in the maximum axial FOV of 96.6 mm.

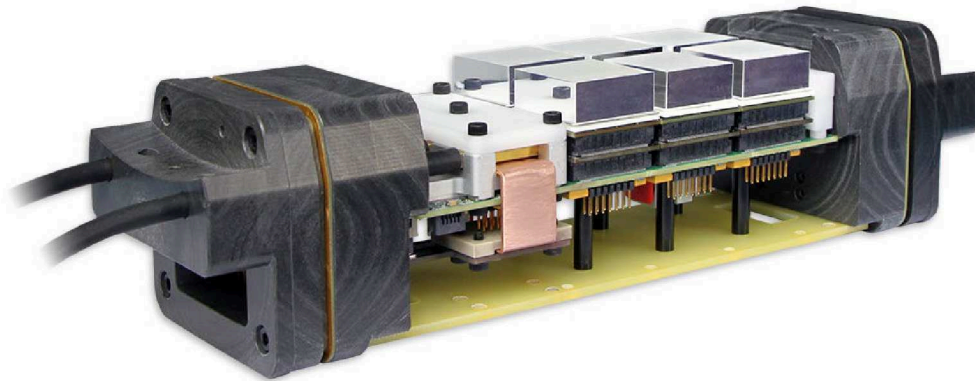


Figure 128: SDM, fully equipped with six detector stacks (view from the power supply board side).

All dimensions of the active detection areas and the gaps between the detector crystals are drawn in the 3D model of the SDM, shown in Figure 129.

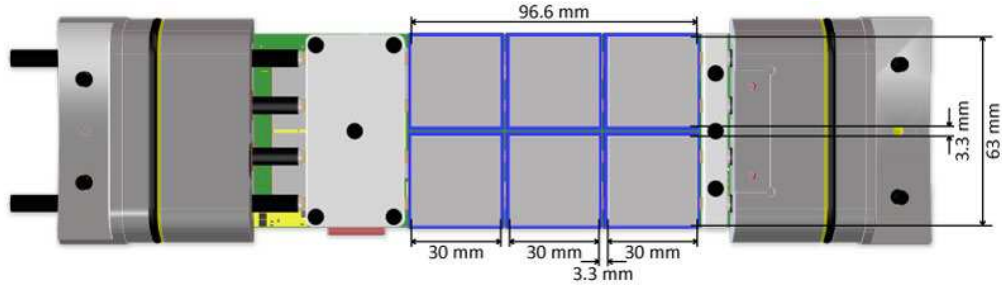


Figure 129: 3D model of the SDM. The dimensions are the size of the crystal arrays. The sensor boards (visible in blue underneath the crystal arrays) are slightly larger than the crystal arrays.

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6.1.2 Synchronization

6.1.2.1 Synchronization of SDMs

Similarly to the previous SDMs, the independent modules are synchronized with a RefCLK and a Sync pulse (used, e.g., for a common counter reset and the data acquisition start), and an optional gate (Gate) signal (to coordinate data acquisition). The synchronization is realized as an optical system to improve the SDM shielding and to remove the galvanic connection at the synchronization unit (see section 5.1.1.6). Optical high-speed (and thus low-jitter) communication systems have a minimum operation frequency, which means that they are not capable of transporting single pulses of different lengths, as is necessary for Sync and Gate. Therefore, these signals are encoded into the continuous RefCLK of 100 MHz by skipping single or double clock pulses. The combined signal is generated by the FPGA in the synchronization unit (based on the same hardware as the SPU). It is distributed over ten POF transmitters to the SDMs (see Figure 130, left). An eleventh signal is transmitted from the synchronization unit over glass fiber to the RTU outside the MR examination room (see section 6.1.2.3).

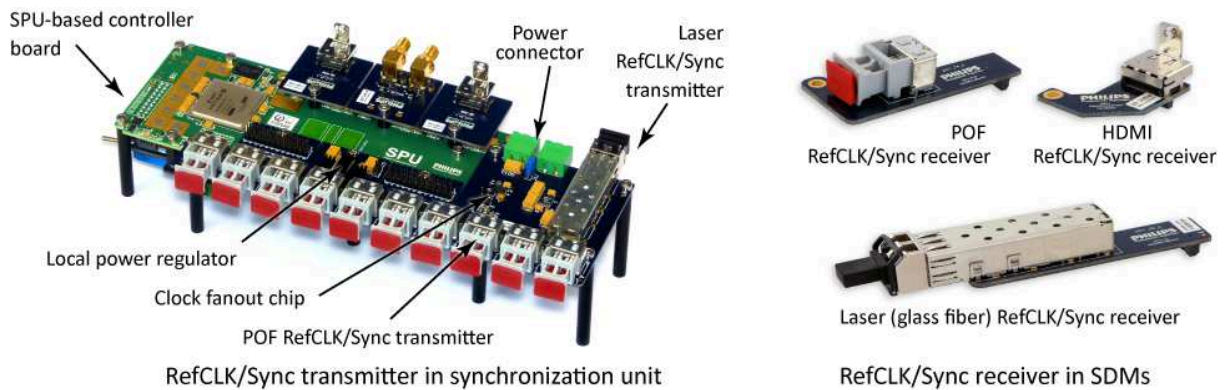


Figure 130: Optical RefCLK/Sync generation and distribution PCB (left), and different piggyback boards for the SPU to receive the signals via POF, glass fiber, or an HDMI cable (right).

Figure published partly (left part) and without descriptions in (Weissler *et al.*, 2012b) © 2012 IEEE.

On the SPUs, the missing clock pulses are detected by the FPGA firmware, and separated Sync- and Gate signals are generated. The missing clock pulses are regenerated by a PLL circuit in the FPGA. Since a missing clock pulse causes the PLL to change its frequency for

a short time, a cascade of two PLLs is used. Analogously to the communication, the receiver hardware on the SPU is realized as a piggyback board. As such, different media can be used: The connector on the SPU has multiple differential LVDS lines to clock-capable pins of the FPGA and directly to the clock fanout chip on the SPU to the detector stacks. It is thus also possible to build and test other RefCLK receiving hardware, such as clock recovery from data or synchronization signals transmitted over the power supply lines (see section 6.1.1.3). Figure 130, right, shows boards for POF (inside the SDMs), laser-based glass fiber (used in the RTU), and copper-based HDMI cabled (to ensure backwards compatibility to the synchronization unit presented in chapter 5.1.2.1). The central RefCLK itself is generated on the SPU-based electronics in the synchronization unit: A special piggyback board, connected where the normal SPUs in the SDMs have the RefCLK-receiver board, generates the signal with a high-quality clock generator. The used oscillator (Epson, Japan) has a quartz, a controlling ASIC, and a SAW filter built in, resulting in a frequency tolerance of 50 ppm and a phase jitter lower than 1 ps.

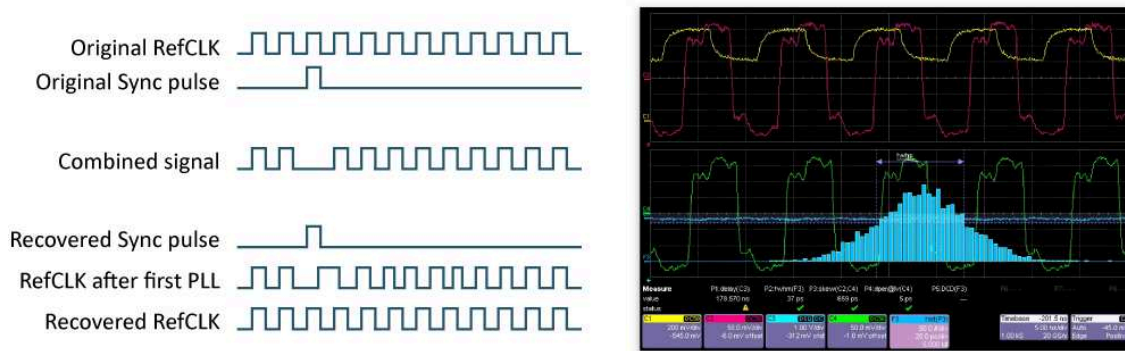


Figure 131: Optical RefCLK/Sync transmission: The original RefCLK and Sync signals are combined for transmission. The missing pulse is detected and recovered by a cascade of three PLLs (left). The resulting jitter, measured between two stacks of two synchronized SPUs, has a FWHM of only 37 ps (right) (yellow: signal at synchronization unit, red and green: signals at detector stack connectors of the SPUs, blue: skew histogram between them).

Figure published partly (right part) (Weissler *et al.*, 2012b) © 2012 IEEE.

The complete synchronization setup was tested with an oscilloscope connected to detector stack connectors on two synchronized SPUs. The jitter was determined as 37 ps FWHM by a histogram over the skew between the two resulting reference clocks (Figure 131, right).

Different actions can be performed when a Sync signal is sent to all SDMs (and thus also to the detector stacks). This can involve, e.g., resetting counters, synchronous starting or stopping of clocks. The firmware of all FPGAs is prepared upfront by the control software using the normal communication. Since this communication is asynchronous and the delay is undetermined, the system waits a few hundred milliseconds between sending all commands and provoking the synchronization unit to send the Sync pulse. Alternatively, the upstream communication could be realized synchronously, when a dedicated hardware with full control over the outgoing data is used (e.g., using the alternative hardware coincidence unit presented in section 6.1.7.2). In that case, synchronization and gating can be realized purely by communication. Additionally, the RefCLK can be encoded into the data stream. This would allow removing the separate RefCLK/Sync line completely. The idea is published in a respective patent application (see chapter 0).

The gate signal has the purpose to pause data acquisition synchronously throughout the whole system. This is necessary when the activity inside the scanner is too high for the system. In that case, single elements in the complete data acquisition chain will start to lose data. As the information from multiple sensors on a detector stack (for singles processing) and the information from the coincident SDM are needed to result in a valid event, all the other data generated by the event becomes useless. Additionally, this data might contribute to jamming other pipelines, which then can lose data when the original pipeline works again. The result of such phenomena contributes to frequently published NECR curves that, after their peak value, show a negative slope (less numbers of detected counts with increasing activity). By pausing the data generation synchronously, it is possible to ensure that no generated data is lost, and that all data can lead to valid coincidences. The gating signal can be generated by a manually-set, duty-cycle generator in the synchronization unit. As such, the overall sensitivity of the scanner will be reduced, but the maximum usable activity and linearity toward higher activities will be increased. An automatic solution can be realized, when every component in the data chain is able to send a fast busy signal when data is (or is about to be) lost. The signal has to be sent downstream to the synchronization unit. In order to travel rapidly, it bypasses all communication and processing (except for being combined (logical OR) with other busy signals). The synchronization unit then raises the gate signal until the busy signal is taken away. Although planned, the complete busy/gate concept was not yet implemented in the firmware, but the gating functionality was already successfully used: By gating the clock of the dSiPMs when the MRI is receiving the MR signal it became possible to reduce the received electromagnetic noise from the detector, and thus to improve MRI compatibility (Gebhardt *et al.*, 2014).

6.1.2.2 Synchronization to Other Equipment

The synchronization unit (Figure 132) provides an interface for the operator next to the gantry. A software-controlled panel provides interaction with the operator: LEDs indicate system states and pushbuttons place time stamps in log files or start scripts. A display informs about count rates, the total amount of measured coincidences, or the current scan progress.

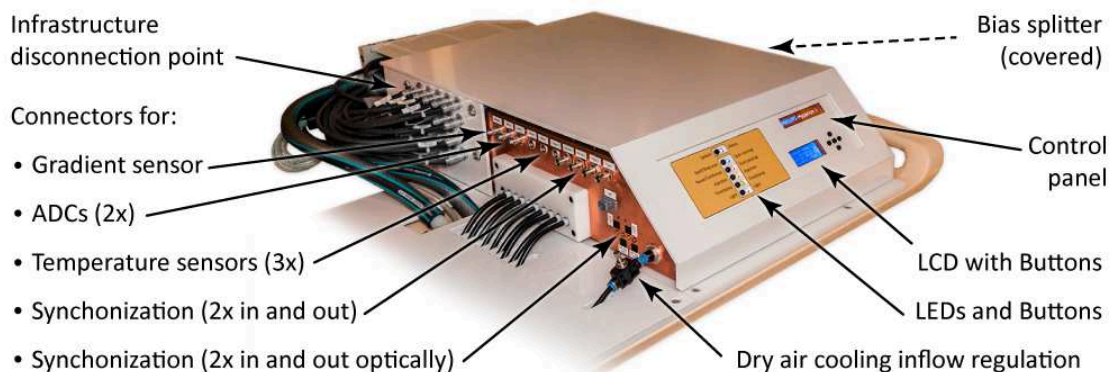


Figure 132: The centralized synchronization unit provides user control and connections to external sensors and devices.

Figure published as part of a figure with different descriptions in (Weissler *et al.*, 2015a) ©2015 IEEE.

The unit also provides multiple possibilities to get trigger signals to and from other devices. This can be done either galvanically (two times trigger in and out, compatible from

3.3 LVCMOS to ± 10 V signals) or optically (two times trigger in and out using Versatile Link (Avago, San Jose, USA) without a minimum frequency). Furthermore, two ADC channels, one input for a MRI gradient switching detection coil (see section 5.1.2.1) and three PT100 temperature sensor ports (four-wire interfaces) are available.

The synchronization unit comprises 19 PCBs in total (Figure 133). It is placed on the patient table of the MRI. As such, it is inside the examination room but not directly inside the MRI bore. MRI compatibility thus still has to be taken into account, but in a different way than in the gantry. The components used can be slightly magnetic because distorting influences reaching into the FOV are unlikely. On the other hand, when the insert is moved into the MRI, the unit is directly in front of the MRI bore and attraction to the magnet still has to be avoided. The static magnetic field at this position is around 0.5 T (see Figure 30 of chapter 3.1.2.1) and ferrite material is still saturated, and has thus lost its function. Moving metallic parts, such as in cooling fans, also cannot be used. The distance to the RF coil is more than a meter and there are no direct galvanic connections from the synchronization unit to the coil, but the power cables to the SDMs and the unshielded box containing the RF coil electronics, including the low-noise preamplifiers, are close. The synchronization unit thus still has to be shielded, but this can be achieved with a copper housing, since the box is far enough away from the FOV and the MRI's gradient coils.

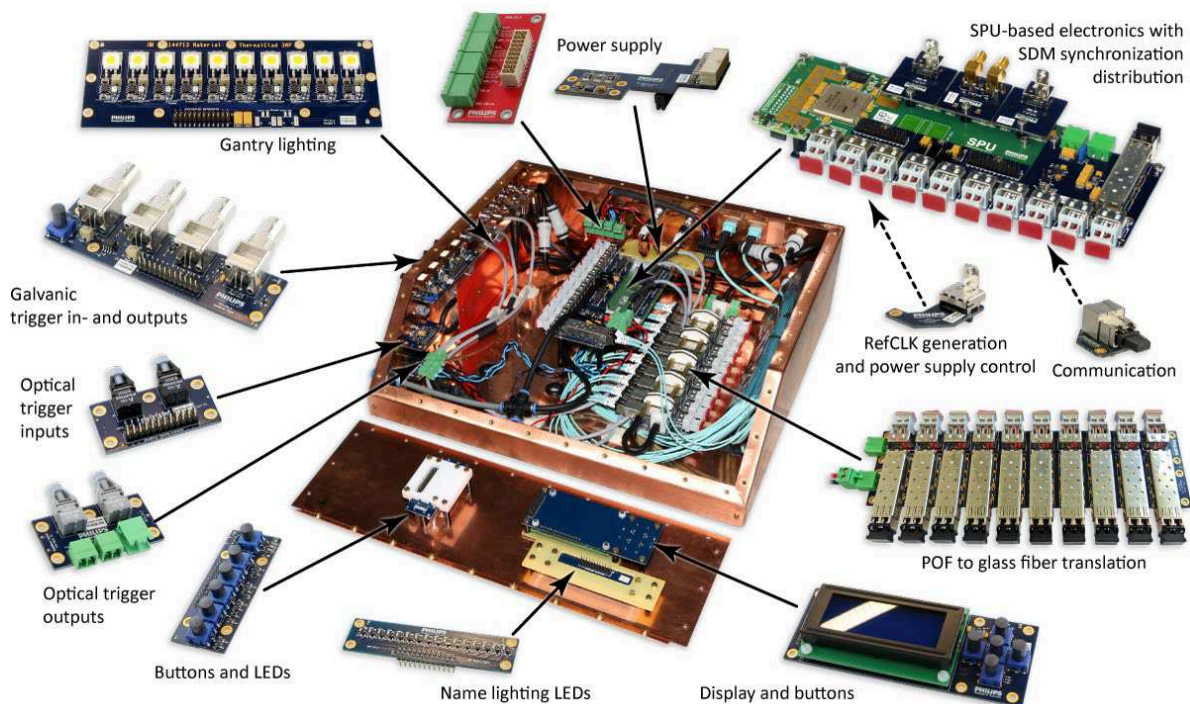


Figure 133: Interior of the synchronization unit: 19 PCBs provide functions, such as, synchronization of the SDMs and synchronization to external equipment. Furthermore, it houses the translation from POF to glass fiber for the complete communication.

The synchronization unit also contains the conversion from POF to glass fiber communication, which is needed to connect to the standard optical Gigabit Ethernet adaptors (Intel) in the DAPS. The twenty communication fibers from the SDMs, along with two communication fibers from the synchronization unit itself and two RefCLK/Sync signals for the RTU, are combined into one cable. Connected with two MTP connectors, this cable exits the examination room through a waveguide (a diagram is provided in Figure 134).

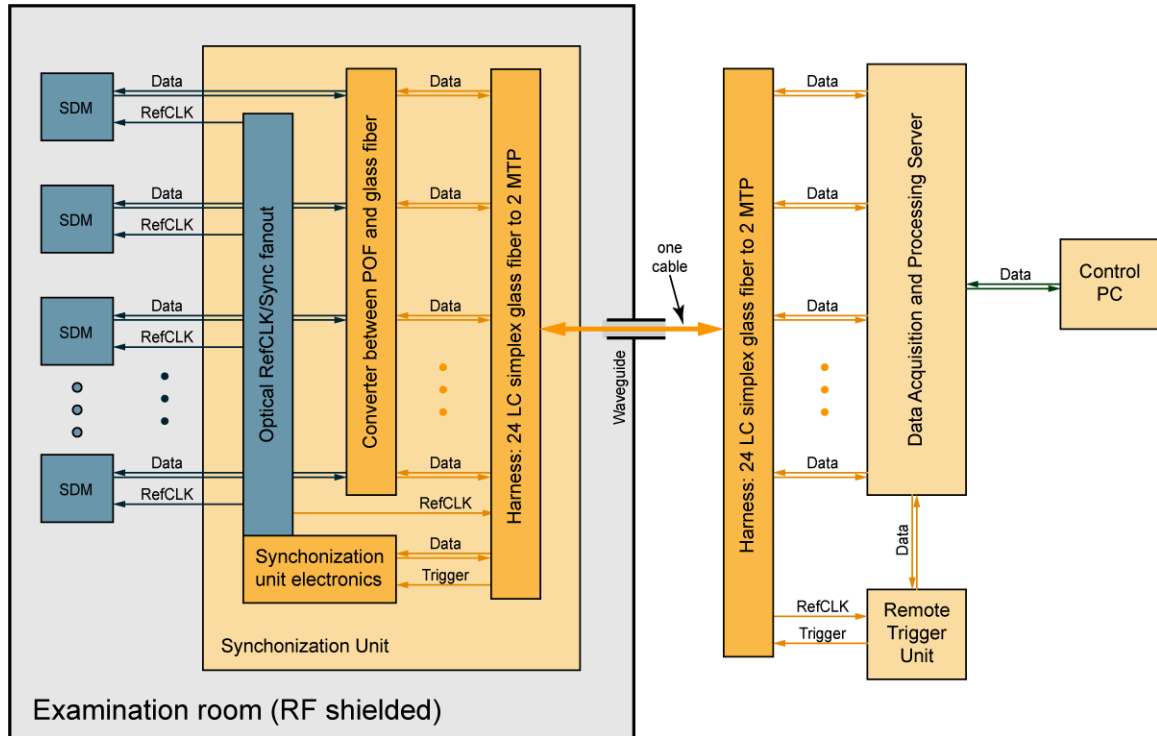


Figure 134: Optical communication and synchronization: The SDMs are synchronized with a combined RefCLK / Sync over POF (blue). These signals, plus a further RefCLK / Sync signal for the RTU (transmitted over glass fiber) (orange), are generated in the synchronization unit. The fiber cable leaves the examination room through a waveguide. At the server rack, the fibers are split to the DAPS and the RTU.

Figure published in the supplemental material of (Weissler *et al.*, 2015a) ©2015 IEEE.

6.1.2.3 Remote Trigger Unit (RTU)

The RTU (Figure 135) provides the same synchronization functionality to external equipment as the synchronization unit does. It is placed outside the MRI examination room and is synchronized to the PET system by the laser-based RefCLK/Sync connection made over the 23rd glass fiber from the synchronization unit to the RTU (see Figure 134, bottom right). The 24th glass fiber is used as a trigger signal back to synchronization unit. The RTU is housed in a standard 19" rack housing and can be placed, e.g., in the PET server rack (Figure 146). When it is placed in the technical room, it can be connected to the trigger outputs of the MRI (3.3 V / 50 Ohm Bayonet Neill–Concelman (BNC) connectors of the CDAS clock board). In the operating room, it can be connected to other equipment, such as patient monitors.

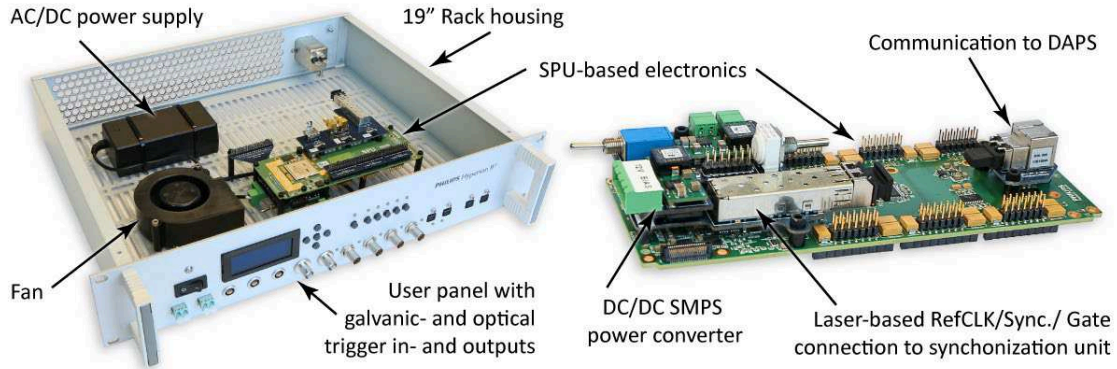


Figure 135: Remote Trigger Unit (left, inner cabling removed where possible) and the SPU-based electronics used (right).

6.1.3 Power Supply

The current is, similarly to the previous insert, brought to the SDMs with coaxial, partly semi-rigid, cables. To ensure that the current flowing to the SDMs in the cores of the cables is returned on the screens of the same cables, only one ground star point is used for the complete system. This star point is formed by the VBias splitter (Figure 136), where all bias supply lines are connected in parallel to the same power supply module. Splitting is realized on a simple PCB (hidden behind the top flap of the cover) with one input and ten SMA outputs. The screened housing was built much larger than the required PCB, as other experimental PCB are foreseen: Having a direct connection to all SDMs with high-quality RF cables, this star point can be used to superimpose a RefCLK signal on the supply lines. This could then replace the rather expensive optical RefCLK/Sync system.

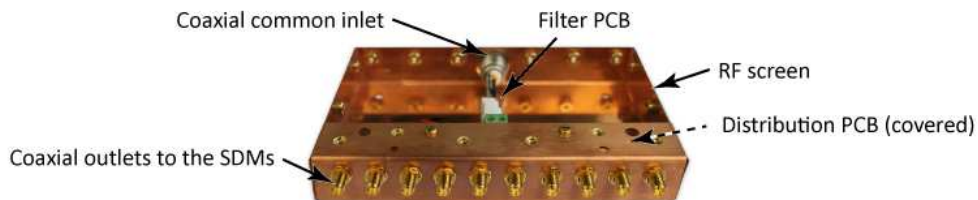


Figure 136: VBias splitter: The incoming bias voltage (rear side) is filtered and split to ten outputs for the SDMs.

Figure published as part of a figure in (Weissler *et al.*, 2015a) ©2015 IEEE.

This and the removal of a power line for each SDM, facilitated realizing the power supply system with a single IEC 60601-1-compliant power supply unit, which is important for safety certifications (IEC 60601-1: medical electrical equipment – part 1: general requirements for basic safety and essential performance). A diagram of the complete power supply concept is displayed in Figure 137: An AC wall outlet in the MRI examination room is used to power one digitally controllable iVS3 power supply unit. The supply lines exit the power supply housing through coaxial connectors whose screens are electrically connected only via capacitors to the housing of the power supply. As described, the bias voltage for the dSiPMs is distributed in the VBias splitter, which is the ground star point for the system. The grounds of a module are connected at the entrance of the power supply cables. Reference clock and synchronization signals are transported optically to the modules, and thus do not connect the grounds.

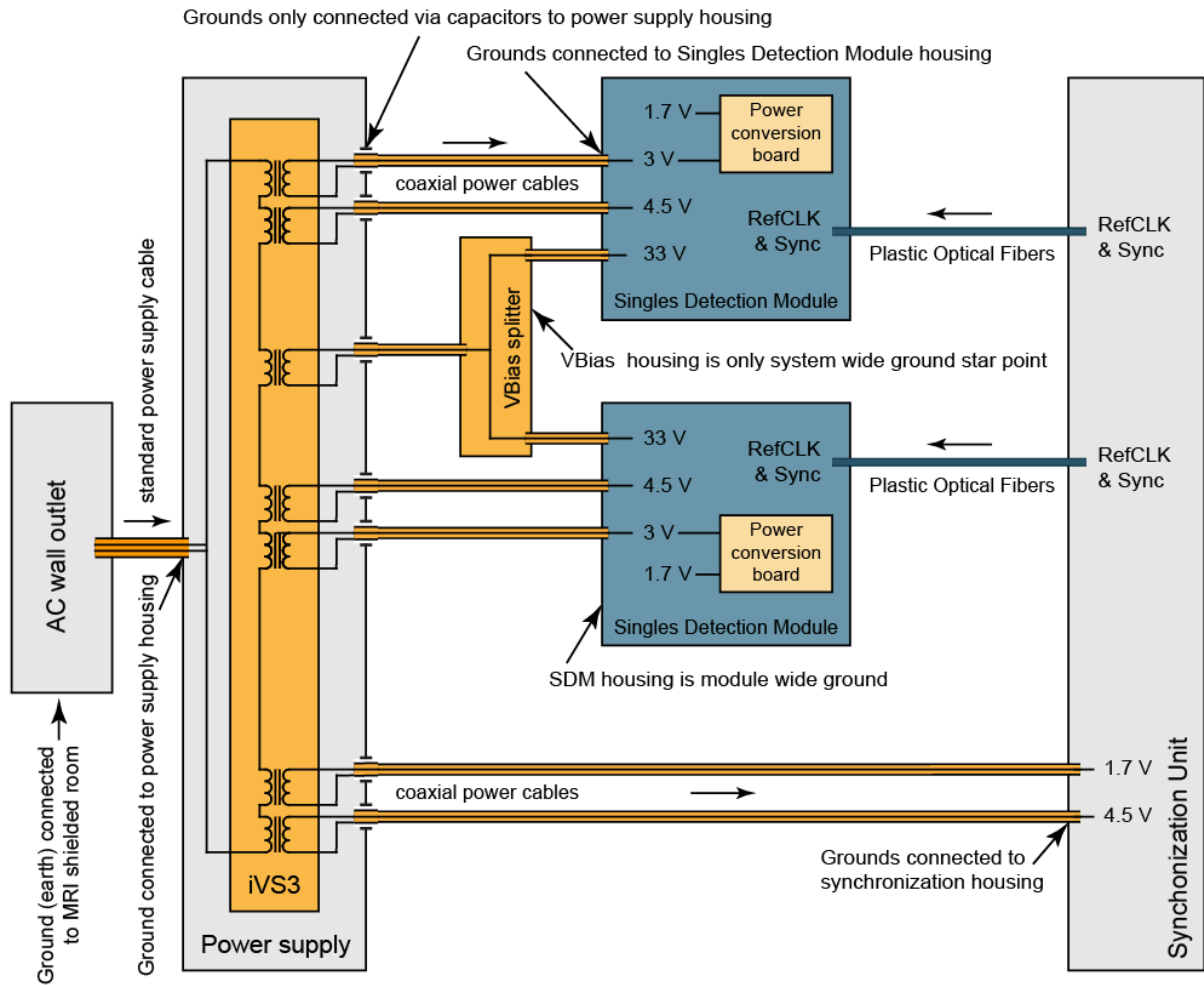


Figure 137: Power supply concept (see text for description).

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The power supply itself (Figure 138) is placed on the insert trolley underneath the patient table. It is fully RF screened, which is important for keeping the common-mode currents on the power cables low. The fan outlets of the housing were designed in a changeable way, since RF leakages were predicted at this position. As expected, the outlets had to be double screened (including RF gaskets), and the fans themselves were displaced about 1 cm inwards from the outlets (a further reduction of RF leakages might be achieved with honeycomb vent panels).

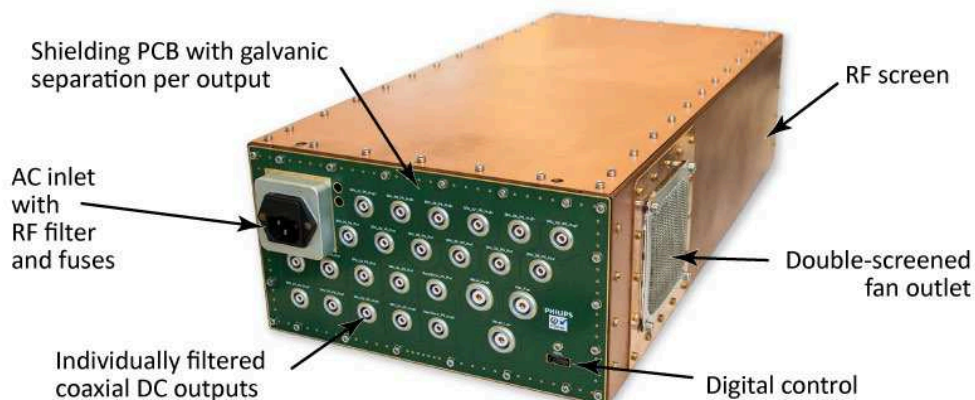


Figure 138: Power supply unit: The power supply itself is placed together with two extra fans and filter PCBs in an RF-screened housing.

Figure published as part of a figure in (Weissler *et al.*, 2015a) ©2015 IEEE.

To keep the grounds of the outgoing supply lines separated for low frequencies (in order not to disturb the static magnetic field or interact with the MRI gradient system), but at the same time to screen against high frequencies (so as not to interfere with the MRI RF system), the connectors are fed through a shielding plate. This PCB has separate ground islands (Figure 139) for each connector, which are RF-wise coupled to the screen by a ring of capacitors (on the inside) and overlapping copper planes with a prepreg-distance of only $50\text{ }\mu\text{m}$. All outputs are filtered on separate PCBs (Figure 139) with combined differential/common-mode filters (Murata, Nagaokakyō, Japan).

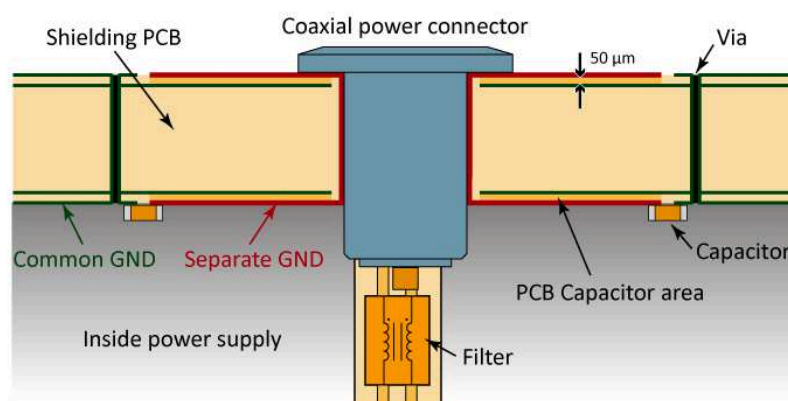


Figure 139: Cross section through the shielding plate of the power supply. The coaxial DC power connectors are connected to separate ground islands that are capacitively coupled to the common ground. Each line is filtered with a combined differential/common-mode filter.

The AC inlet and all connections enter the case on one side of the power supply to prevent forming a dipole-structure with a center feed. All cables, connected to the power supply unit, have additional ferrite cores to suppress residual common-mode currents, placed close to the connectors. This is the furthest position away from the static magnetic field. Additionally, for a standing wave at 128 MHz, beginning at the far end of the power supply, this is the position with a current-maximum, where ferrites are most effective in suppressing common-mode currents.

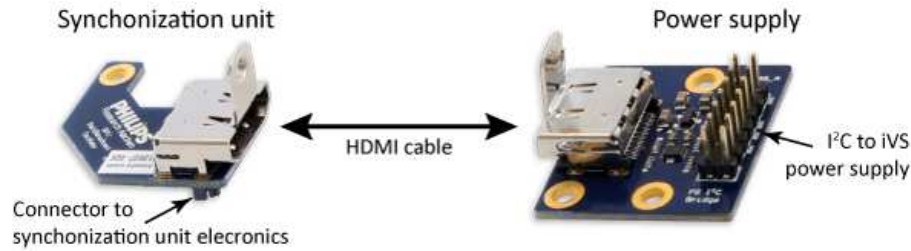


Figure 140: Connection between the Synchronization unit and the power supply, which is used to program and control it during operation.

The power supply itself, an iVS (Emerson, St. Louis, USA), is digitally controllable to set the output voltages. This is important, as the amount of current drawn by the SDMs varies largely according to the number of detector stacks installed. As a result, the voltage drop over the long power cable changes and the input voltage at the SDM can either be too low (unreliable operation) or too high (too high power dissipation in the local linear regulators). Programming (and surveillance of all parameters during operation) can be done via the synchronization unit. Through an HDMI cable, this unit can be connected to the power supply, which contains an adaptor needed for the I²C interface (Figure 140). The software counterpart is implemented in the control software (see section 6.1.7.5).

6.1.4 Gantry

The gantry mechanics are made from polyoxymethylene (POM-C) by standard manufacturing techniques, such as turning and milling. All female screw threads in the gantry are realized as aluminum or brass threaded inserts. The screws themselves are made from aluminum or glass-fiber-reinforced plastics.

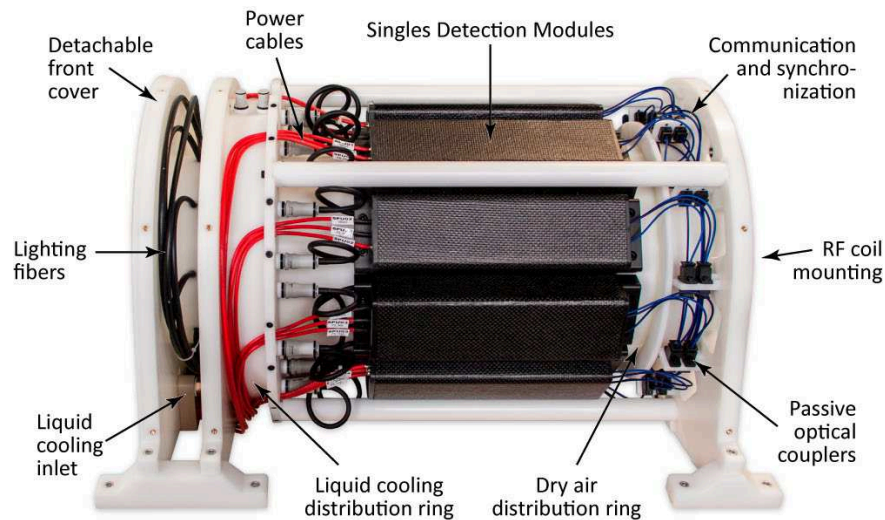


Figure 141: Side view of the preclinical PET gantry.
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The SDMs are mounted on two cooling distribution rings: liquid cooling (Figure 141, left) and dry air (Figure 141, right). There is no further material between the SDMs and the RF coil to keep the attenuation of the gamma photons low. At the gantry, the infrastructure is connected to the SDMs: power (red semi-rigid cables) with SMA connectors, liquid cooling

with no-spill connectors (gray), and communication/synchronization (blue POF) with passive optical couplers.

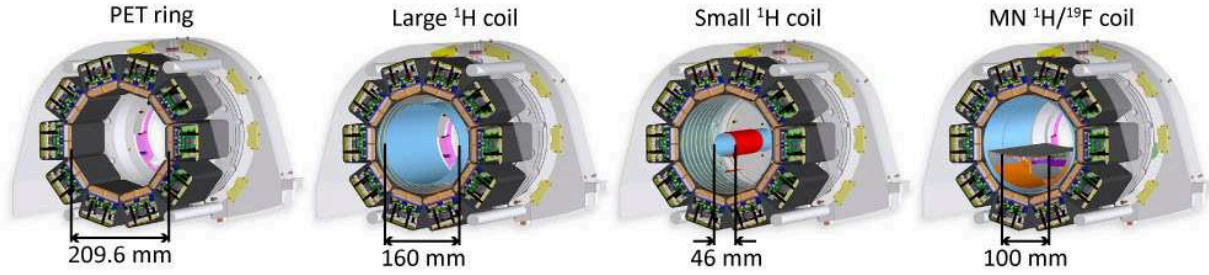


Figure 142: 3D models of the PET/RF insert, shown from the backside and cut off. Dimensions are given for the inner diameter of the PET ring and the inner diameter of all three RF coils. Figure published in the supplemental material of (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

The RF coil (see next section) is inserted from the rear side and positioned with a key-and-slot system. The final hybrid FOV thus changes according to the coil used. The resulting dimensions are shown in Figure 142 and Table 29.

Parameter	Value
Total amount of detector stacks	60
Total amount of crystals	54000
Total amount of dSiPM dies / channels (pixel)	960/3840
PET FOV (crystal-to-crystal transaxial × axial)	209.6 mm × 96.6 mm
MRI FOV Large ¹ H coil (transaxial × axial)	160 mm × 200 mm
MRI FOV Small ¹ H coil (transaxial × axial)	46 mm × 120 mm
MRI FOV MN ¹ H/ ¹⁹ F coil (transaxial × axial)	100 mm × 100 mm

Table 29: System details of the PET/RF insert Hyperion IIP. Table published in (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

6.1.5 RF Coils

The RF coil is now easily exchangeable, and thus far three different dedicated PET compatible RF coils have been built (Figure 143). The large ¹H coil is a 16-rung high-pass birdcage resonator with a diameter of 160 mm and a length of 200 mm. It generates a maximum B_1 field of 35 μ T. The small ¹H coil, dedicated to mouse imaging, is made from a 12-rod-birdcage resonator with a diameter of 46 mm and a length of 120 mm (maximum B_1 field is 30 μ T). Exchangeable flanges in the front and back of the resonator bore enable the precise positioning of phantom holders or animal beds (Figure 176). The third coil is a double-resonant Multi-Nuclei (MN) ¹H/¹⁹F coil (maximum B_1 field of 20 μ T for both frequencies: 127.728 MHz and 120.3 MHz). Unlike the other two coils, it is realized as an inductively-coupled surface coil with a length and width of 100 mm (Findekle *et al.*, 2013).

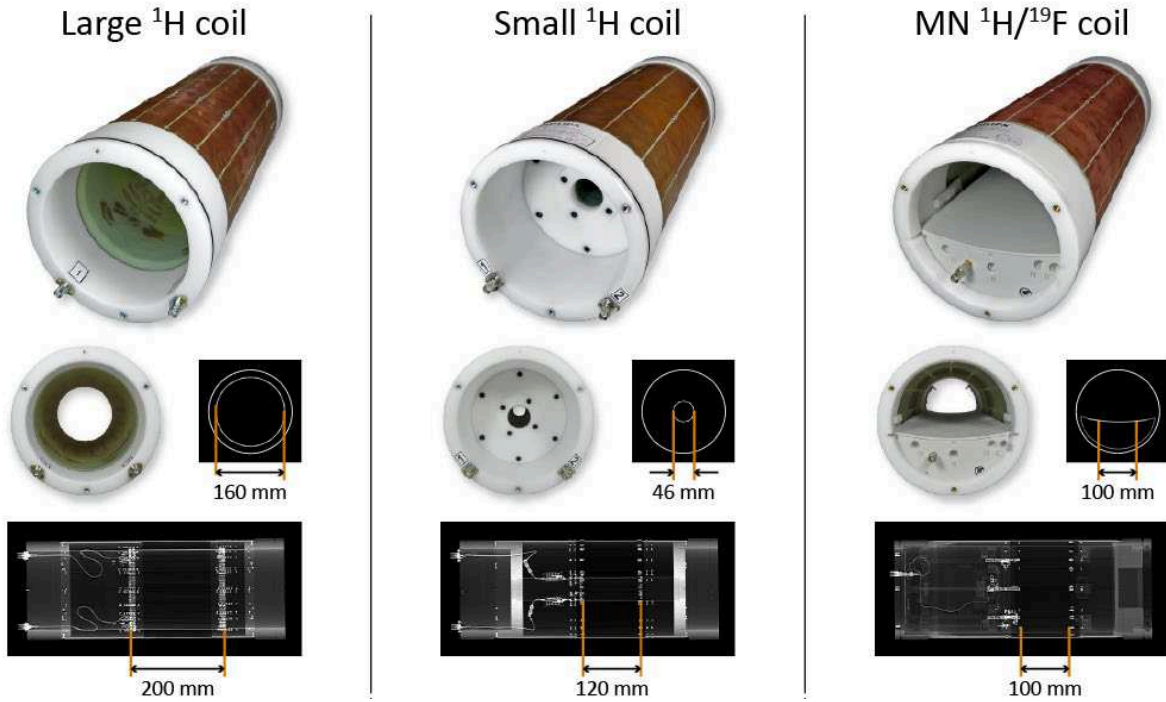


Figure 143: Gamma-transparent Tx/Rx RF coils, built for the insert: A large ^1H volume coil with a 160 mm diameter (left); a small ^1H volume coil with a 46 mm inner diameter (middle), dedicated to mouse imaging; and a double-resonant MN $^1\text{H}/^{19}\text{F}$ surface coil (right) with a 100 mm length and width. CT scans (transverse slice and coronal X-ray image) indicate the gamma transparency.

Figure published in (Weissler *et al.*, 2015a) © 2015 IEEE.

All coils have an RF screen (400 mm length, 40 mm off-center to the front) around the outer glass-fiber-composite cylinder. The screen is made from copper stripes (18 μm thick semi-flexible, glueable PCBs) that are high-pass-coupled with capacitors to reduce eddy currents induced by the MRI gradients. For improved gamma transparency in the region of the hybrid FOV, the wall of the cylinder (3 mm thick) was thinned from the inside to 1 mm. Figure 143 also shows sagittal CT scans and coronal X-ray images (made with a Brilliance CT 16, Philips, the Netherlands) of the coils that visually display the gamma transparency.

The coil electronics (responsible for coil identification, power splitting, and pre-amplification) of all coils are modified with an optical transmitter that can signal the receive state of the RF coils to the synchronization unit (see section 6.1.2). This makes it possible to align the PET data to the times of MRI data acquisition, e.g., for dynamic studies or gated MR imaging. It also enables techniques, such as pausing the PET data acquisition while the MRI is receiving, to reduce cross talk between PET and MRI (Gebhardt *et al.*, 2014).

Although these coils were directly built for the insert and optimized for PET/MRI, it is also possible to use other Tx/Rx RF coils, as long as they fit into the bore.

6.1.6 Insert

The PET/RF insert is mounted on an MR-compatible trolley, together with all components needed in the MR examination room (Figure 144).

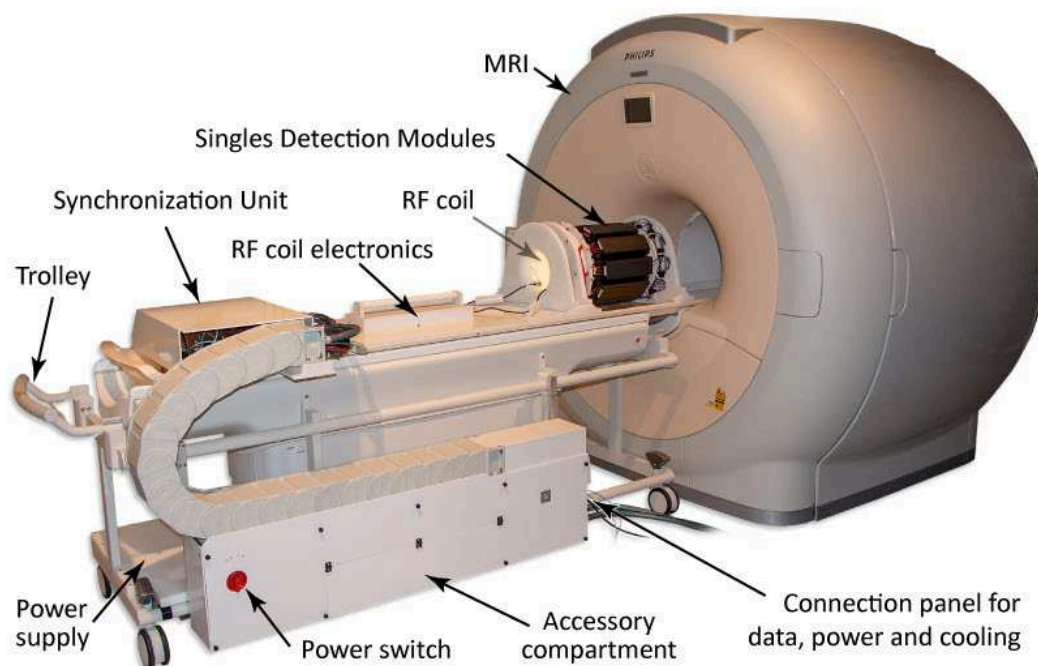


Figure 144: The PET/RF insert “Hyperion II” mounted on the patient table of a clinical 3T MRI system (gantry cover removed).

Figure published as part of a figure in (Weissler *et al.*, 2015a) © 3.0 2015 IEEE.

The patient tabletop of the clinical MRI scanner can be removed by hand. The patient table is then lowered and the insert is rolled over the table. When the patient table is lifted up again, it picks up the insert and moves it into the MRI bore. Power (one cable), cooling (two hoses for liquid, one for air), and data (one cable with two connectors) are plugged into a connection panel on the backside of the trolley (Figure 145). Power is taken from an outlet in the MR examination room – all other infrastructure cables and hoses are not conductive and exit the shielded room through waveguides.

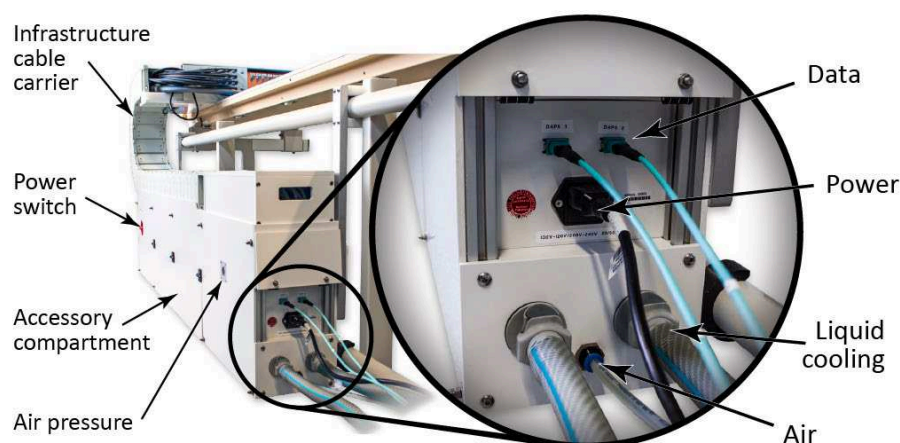


Figure 145: Backside of the trolley: Data (one cable, split to two MTP connectors), power (IEC-60320), liquid cooling (in and out), and dry air are plugged in at a connection panel.

6.1.7 PET System Back End

DAPS, Reconstruction Server (Recon), and a Network Attached Storage (NAS) are mounted in a movable server rack (Figure 146). They are connected with a network switch that allows data to be transferred over multiple Gigabit Ethernet connections.

6.1.7.1 Data Acquisition and Processing Unit

The DAPS (Dell Poweredge R910, $4 \times$ Intel Xeon X7560 CPUs, 256 GByte RAM, Linux (Ubuntu) operating system) collects the data from the insert with six optical dual-port Ethernet adapters (Intel X520 DA2). Singles and coincidences processing are performed online in software, and list-mode data is saved (Goldschmidt *et al.*, 2015). Alternatively, the raw data is saved directly on six hard drives in parallel (RAID 0), while the RAM is used as a buffer. This drastically improves the maximum scan time restriction of the previous insert (only storing data in the RAM). Using the RAM as a buffer is still necessary in that case, as only about 340 MB/s can be saved directly. Even when saving raw data, the RAID system has enough space for a complete measurement day, and the data can be moved over night. All measurements in this thesis make use of storing the raw data, as the parameter of the processing and the performed analysis can be controlled and changed in the post-processing steps. Singles and coincidences processing use sliding window techniques. The hits reported by the dSiPMs are first sorted and clustered. Gamma crystal interaction position is then determined by a center-of-gravity automatic-corner-extrapolation (COG-ACE) Anger algorithm (Schug *et al.*, 2014a). Alternatively, a Maximum-Likelihood (ML) method (Lerche *et al.*, 2013a) with ML filtering (removing 30 % of the LOR with the lowest likelihood values) is employed. In this paper, either a narrow energy window from 411 keV to 561 keV (to keep the number of random and Compton-scattered events low), or a wide energy window from 250 keV to 625 keV (to include events that were Compton-scattered in the detector crystals) is used. The coincidence window is set to 1 ns.

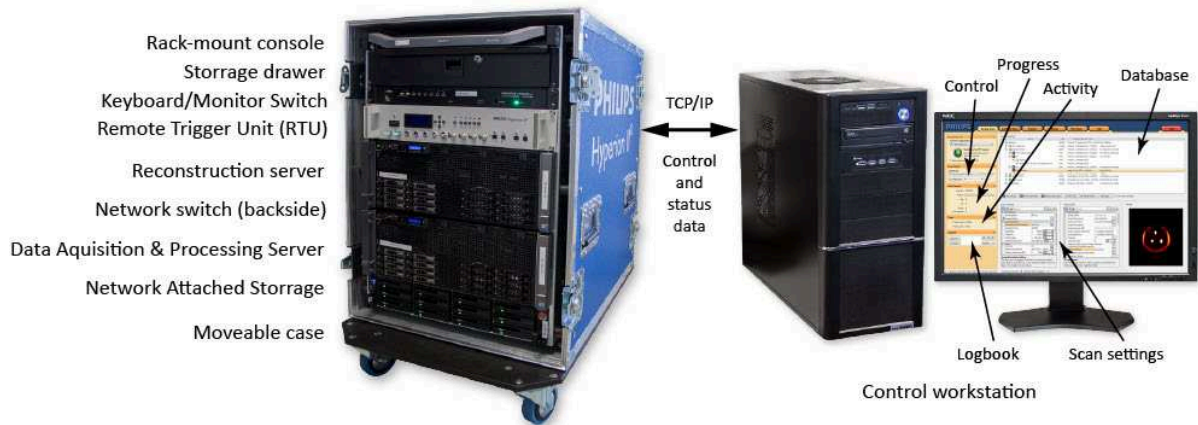


Figure 146: Server rack (left): DAPS, Recon server and NAS are connected to each other with an integrated network switch. The insert is remotely (TCP/IP) controlled on the control workstation (right). The simple scan interface (shown on the monitor) provides complete control of the scanner on one screen.

All data can be saved on the integrated NAS (RS2414+, Synology, Taipei, Taiwan), which provides a storage capacity of 40 TB (secured with RAID 6 redundancy). Data can be transported on external hard drives, connected to the USB 3 ports of the NAS, or sent over

the local intranet. To ensure stand-alone functionality (when scanning), as well as remote access through the intra- and internet, a managed network switch is integrated. It provides an internal network for all components in the rack (and the control PC) with fixed local IP addresses and two aggregated Gigabit Ethernet connections per device (except the control PC) to increase data transmission speed. Separated from that local network, the switch allows controlled remote access to all components though a single network cable, which is connected, e.g., to a hospital network.

6.1.7.2 Alternative Hardware Coincidence Unit

Using an off-the-shelf server and software-based coincidence search has the advantages of fast algorithm development and very good debugging capabilities. The disadvantages are limitations in the possible parallelization performance and a high hardware price per unit (the DAPS including the optical Network Interface Cards (NICs) has an approximate price of 26000 €, not including VAT, installation, and service). An alternative solution is a hardware-based coincidence unit. To investigate in this direction, a solution for less than 10 % of the price was developed. It is based on a Virtex-6 FPGA demo board (Xilinx ML605). The PCB comprises the FPGA, DDR3 RAM and the complete power supply and cooling infrastructure. An on-board SFP port can be used as a downstream connection to the control workstation. Since only processed coincidences have to be transported, the data rate of this single Gigabit Ethernet connection would be sufficient for the whole insert. Twelve upstream connections are needed for the ten SDMs, the synchronization unit, and the RTU. The demo board has a FPGA Mezzanine Card (FMC) connector, which enables connecting to eight GTX transceiver hardcores of the FPGA. An FMC communication board was thus designed with eight optical transceivers. The demo board is built as a PCIe PC card. The PCIe interface is realized with the same GTX transceiver hardcores of the FPGA, which enables the remaining four necessary optical transceivers to be connected via a 180° PCIe extender PCB (Figure 147).

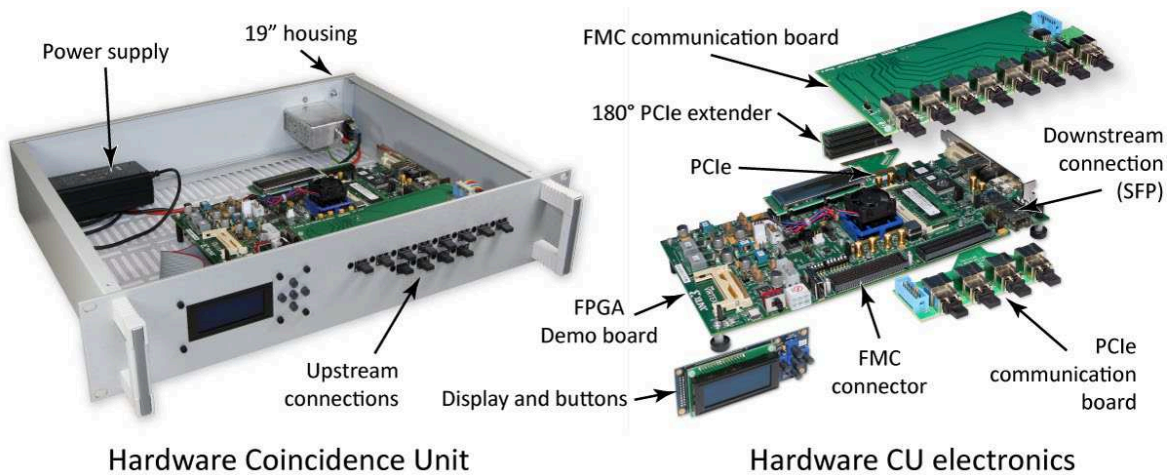


Figure 147: Alternative hardware coincidence unit, based on an FPGA demo board.
PCB layout by G. Aydos

The firmware was designed to communicate via Gigabit Ethernet and the protocol used by the SPUs was implemented. Routing data was successfully tested. The communication protocol is not limited to Gigabit Ethernet: when the SPUs use the laser-based SFP

transceiver (see section 6.1.1.2), an inter-FPGA communication of up to four gigabit per SDM can be realized, e.g., by employing the Xilinx Aurora protocol.

A further advantage of a hardware coincidence unit is the full control over the communication. As the exact timing of every bit sent to the SPUs is determined, it can be used to encode the RefCLK into the data stream by means of standard clock recovery mechanisms. Moreover, sending synchronization or gating pulses can be realized completely by this communication, eliminating the need for separate RefCLK/Sync lines (see patent applications, chapter 0).

6.1.7.3 Image Reconstruction

Image reconstruction is performed on the second server (Dell Poweredge R910, 2× Intel Xeon X7560 CPUs, 128 GByte RAM, Windows Server 2008 R2 operating system). A list-mode algorithm is used with MLEM-RM (Salomon *et al.*, 2012). The self-normalization can be performed directly on the measured data if the complete active area is included in the FOV (as is the case here), or, alternatively, an additional arbitrary scan satisfying the aforementioned criteria can be used. Resolution modeling is achieved in a similar manner as in (Autret *et al.*, 2013). Intra-crystal scattering has not been considered. In this paper, unless stated otherwise, the images are reconstructed in 32 iterations (16 for the in vivo images) with eight subsets per iteration, and an isotropic voxel resolution of 0.25^3 mm^3 . Although the reconstruction software is capable of attenuation- and scatter-correction, it was not used for the images presented (for accurate PET quantification, attenuation corrections should be employed (Prasad and Zaidi, 2014)). Image fusion is achieved either manually or with AMIDE (Loening and Gambhir, 2003).

6.1.7.4 Calibration and Processing

Calibration of the system is performed at different times: for instance, a map showing the dark counts for all individual 12 million dSiPM cells is measured once after assembly. A calibration of time stamps (TDC of the dSiPMs) and crystal energy calibration factors was conducted every time the system configuration was changed. The needed calibration steps and chosen parameters depend on the optimization goal (e.g., highest sensitivity vs. highest possible activity) and are discussed in (Schug *et al.*, 2014a). Throughout this thesis, conservative settings were used: 20 % of the cells are deactivated, 0° C or 5° C liquid cooling temperature, 2.5 V SiPM cell overvoltage, trigger scheme 3, validation network 0x54 or 0x55 (Tabacchini *et al.*, 2014).

6.1.7.5 Control

The insert is controlled on a workstation next to the MRI system console with an object-orientated and multithreading control software. Every hardware and firmware module has its software-counterpart object: from the sensor die configuration to the cooling system, data acquisition, and reconstruction. Every object possesses “settings”, “commands”, and “logs”. The “settings” are values for parameters, e.g., the bias voltage to be set for a detector stack. A “command” is made from executable code, which, e.g., takes the demanded bias voltage, calculates the bitstream for the DAC-IC, and sends it to the hardware. A different “command” would send the bitstream needed to start an ADC measurement on the hardware, and read

out the result. The answer from the hardware is placed in a “log”, which stores the data in the RAM and in log files. Receiving log-data can, furthermore, trigger the execution of other commands, e.g., to react at certain values. When possible, the communication is realized in a request-answer style, but with questions and answers handled completely independently. As such, the system is more robust against lost data and the firmware can decide to send data autonomously, for instance, sending temperature data when the temperature is too hot. Additionally, “chronjobs” execute “commands” periodically in the background, e.g., permanently requesting the current bias currents.

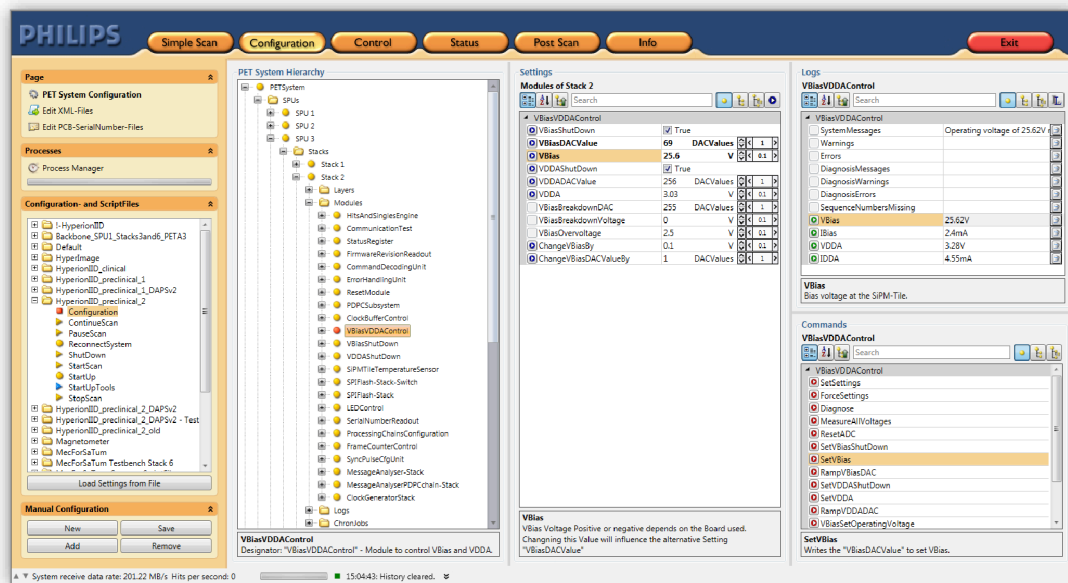


Figure 148: Configuration page of the control software. Configuration- and script-files can be chosen and executed in the left column. Next to it, the hierarchy of the PET system can be browsed. Settings, commands, and logs of the selected item or items are displayed on the right. This screen allows interaction with the system on a very detailed level.

A Graphical User Interface (GUI) allows hierarchical access to all these parameters (Figure 148). As such, all parameters of one kind can be changed at the same time, while also allowing for differentiating, for example, between the stacks or even according to detected hardware serial numbers. The GUI and logic code are strictly separated, and the same hierarchical access to all “settings”, “commands”, and “chronjobs” is given to an XML-based script language. XML was chosen because it is based on a hierarchical concept, is machine- and human-readable, and multiple editors are available. Additionally, these scripts define the hardware configuration (Figure 149). As such, the same software is used for the complete inserts (both, analog and digital) and for simple bench tests (e.g., an SPU directly connected to the PC or for setups to test new ASICs as mentioned in chapter 5.2.1).

The scripts also allow the execution of commands and have additional scripting language features, such as variables and loops. These scripts thus facilitate complicated system performance measurements and calibration procedures. They are also employed by the simple scan interface, which hides all complicated settings and commands, and allows for concentrating on the current measurement (Figure 150).

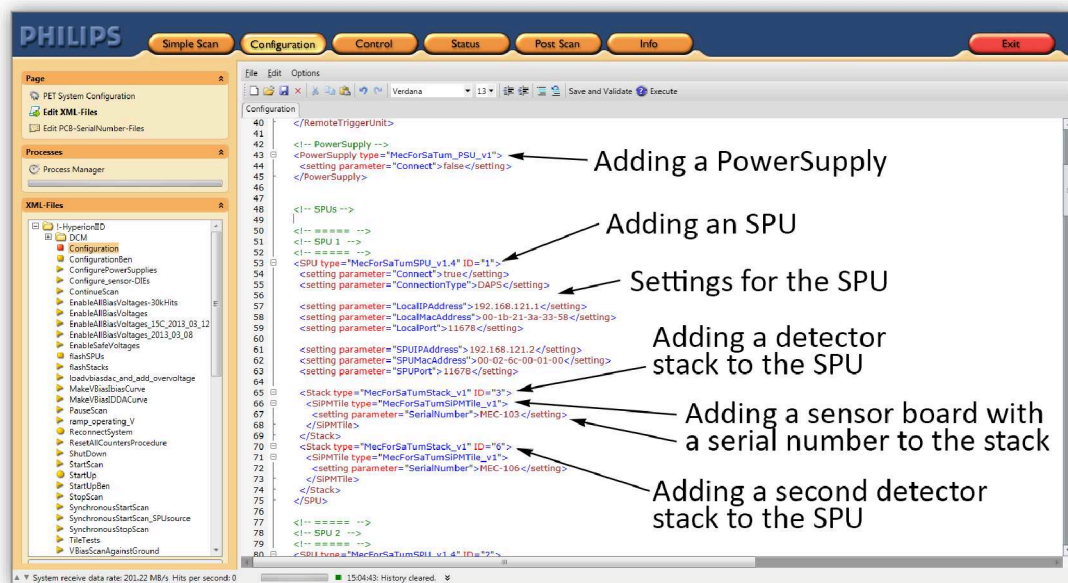


Figure 149: Example of an XML-based configuration file in the build-in editor. In this section, first a power supply is added, which is also controllable via this software. Then an SPU is added, and settings such as the IP addresses are set. The SPU, furthermore, gets two detector stacks of the digital type.

This end user interface also presents a simple file-based database to organize the scans and the data, and to label them with tags in a manner consistent with the Digital Imaging and Communications in Medicine (DICOM) standard.

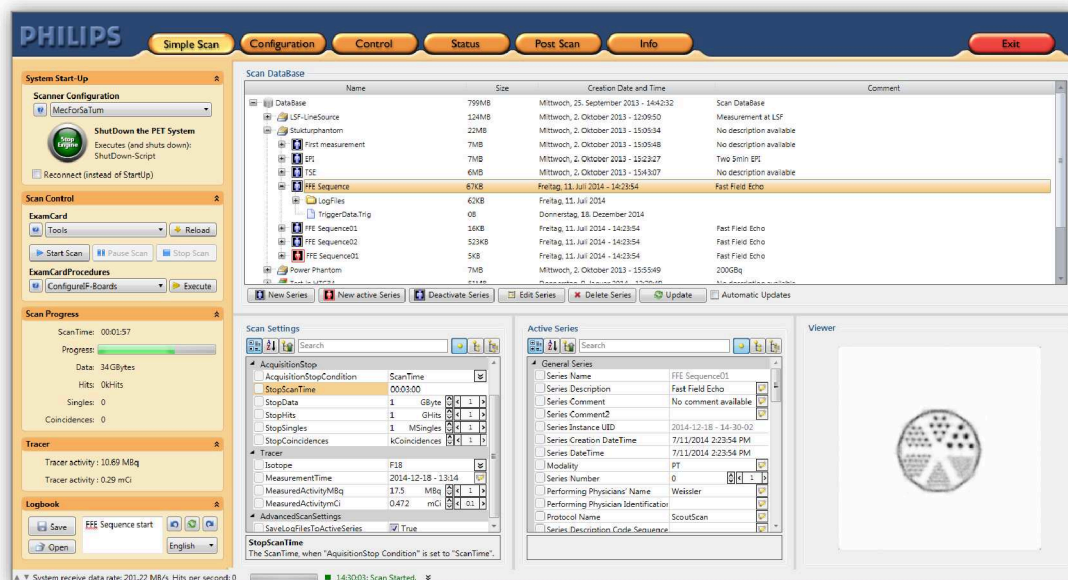


Figure 150: SimpleScan page of the control software: The left column (at the top) allows one to choose a system configuration and to execute the corresponding system-start-up script. Below that, the scan is controlled: An ExamCard can be chosen and the scan can be started. Scan progress (according to the scan settings, middle of lower row) is monitored underneath that. The scan database is displayed on the top right of the window.

The same data structure is automatically generated on the DAPS, so that the data can always be retrieved. By choosing an “ExamCard”, it is possible to use a dedicated set of settings for the entire system, including the DAPS and reconstruction server (e.g., for a fast scout scan it would set the DAPS to online processing, the reconstruction server to fast low-resolution reconstruction and define a short scan time).

The status of the system can be checked during operation in several ways. For development, all communication data can be stored and displayed. System messages, organized in normal-, warning-, and error-levels, give an overview of the system status and allow an overview of the history of events. Measurement values that whose stability has to be checked over time to ensure a perfect status for performance analysis, e.g., a stabilized sensor temperature, can be monitored graphically (Figure 151).



Figure 151: Control-page of the control software displaying the (d)SiPM temperatures for all 60 sensor tiles of the complete PET system. The graphs can be detached and continue in separate windows, as shown with the temperature-graphs of the humidity sensors the SPUs.

6.2 Results

The results for the improved insert are measured similarly to those of the first insert. Except for a few adaptations to the new possibilities (e.g., changing the RF coil), the tests are executed with the same parameters and the resulting graphs are shown with the same scales (often underlying the previous data).

6.2.1 Performance of the Detector Stack

Figure 152 presents flood- and energy histograms of a randomly chosen detector stack (Scanner 3, SPU 3, Stack 2) from the ^{22}Na measurement, presented in section 6.2.3.1. The

energy resolution of the chosen stack is 13.2 % (FWHM). It improves to 12.3 % (FWHM) when only the singles from completely detected coincidences are taken into account.

The flood histogram (Figure 152, left) shows that all 900 scintillator crystals are clearly separable – although it was calculated, using the relatively simple center-of-gravity algorithm (compared to the more sophisticated crystal identification algorithms using Gaussian fits or ML optimizations). The PET performance of the digital detector stack is presented in detail in (Dueppenbecker *et al.*, 2016).

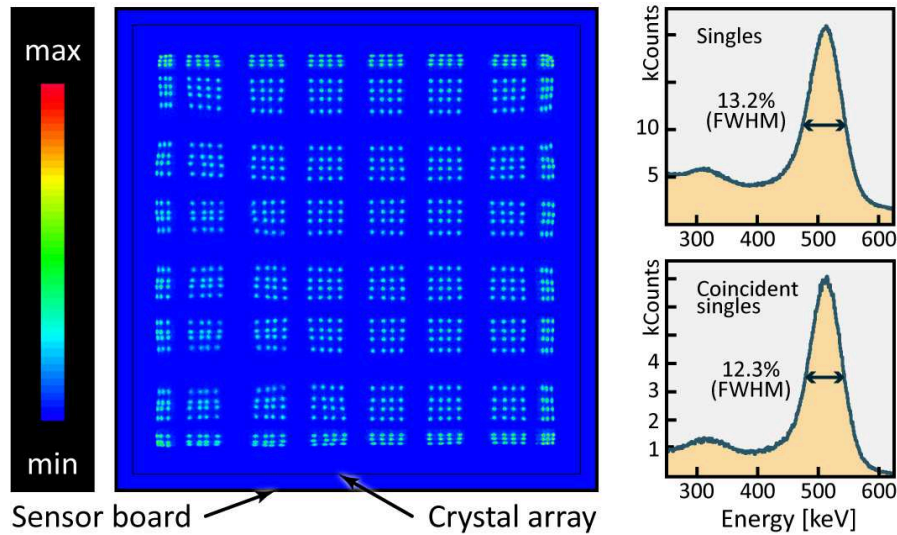


Figure 152: Flood histogram of a digital detector stack (left) and the energy histograms for singles and coincident singles.

Compared to the performance of the analog detector stack with the used ASIC (chapter 5.2.1), this is a large improvement. Since the distance between the peaks in the flood histogram are larger than the diameter of the peaks themselves, it is very likely that the detector stack can be enhanced to (at least) a two-layer DOI detector (Tsuda *et al.*, 2004): By cutting the crystal array in half and displacing the top part half a crystal pitch in both directions, the light from a top-layer crystal will be spread over the four lower crystals and generate new peaks between the peaks of the lower array half. As such, the DOI effect (chapter 3.1.1.3) can be taken into account.

6.2.2 MRI Performance and the Influence of PET on MRI

6.2.2.1 B_0 Distortion

The homogeneity of the static magnetic field was determined as described in section 3.2.1. The measurements were done with the large ^1H RF coil: once while the PET was on and once without the PET insert (only with the RF coil). No shimming was used in the first experiments.

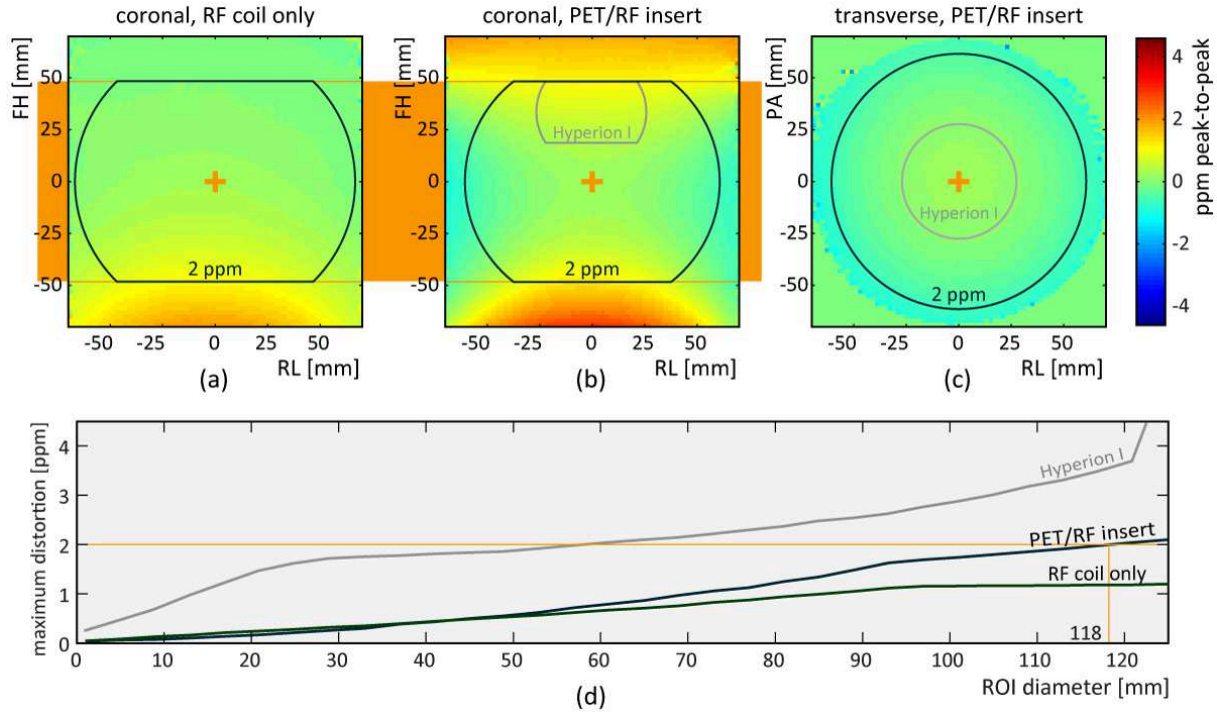


Figure 153: B_0 maps (peak-to-peak values) of Hyperion II^D without shimming: Coronal center slice measured with the large RF-coil only (a) and the operating PET/RF insert (b and c). The PET FOV is indicated in orange. The transverse center slice is shown in (c). The maximum peak-to-peak distortions for spherical ROIs, which are limited by the PET FOV, are plotted in (d) over the diameter. The smallest ROIs with a maximum distortion of 2 ppm are indicated in all plots. For comparison, the results of the previous insert Hyperion I are overlaid in gray.

Figure published partly as parts of a figure in (Weissler *et al.*, 2015a) ©©_{3.0} 2015 IEEE.

With the PET/RF insert, the total B_0 field is decreased by 5.7 ppm in comparison to the RF-coil-only case. This decreases the field in comparison to the integrated body coil by 0.2 ppm. Although this value is slightly lower than for the Hyperion I insert (6.9 ppm), it is of less relevance because the resulting imaging frequency is calibrated in the preparation phase of each scan. The plots in Figure 153, d show almost linear increasing values from the center up to the diameter, where the spherical shapes of the ROIs become limited by the PET FOV. A maximum distortion of 2 ppm peak-to-peak is reached at a transaxial diameter of 118 mm (RF-coil-only: 132 mm). For purely spherical ROIs, this border is reached at 102 mm (RF-coil-only: 129 mm). Calculated as a VRMS value, the measured cylindrical volume in the hybrid FOV stays below 1.5 ppm and below 1.7 ppm in the complete volume depicted in Figure 153. The volume with a distortion lower than 2 ppm peak-to-peak is large enough to image animals up to the size of rabbits. Even though 60 rather than twenty detector stacks are now installed, the diameter of the hybrid ROI with a distortion below 2 ppm without shimming was enlarged from 56 mm to 118 mm. This demonstrates the positive impact of the measures described in section 6.1.

The coronal and transverse central slices of the B_0 map (Figure 153, b, and c) indicate that the homogeneity is mainly altered by a second-order distortion. This perception is supported by the orthogonal profiles through the centers, shown in Figure 154.

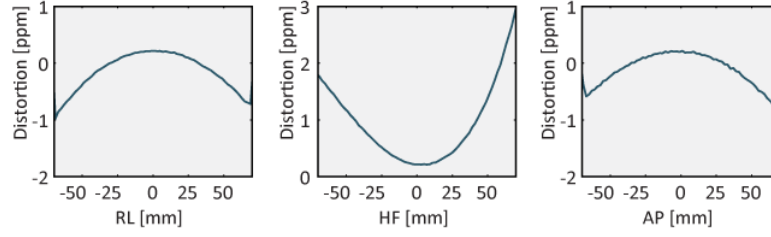


Figure 154: Distortion profiles (ppm peak-to-peak) in the three dimensions right-left (RL, X), head-feed (HF, Z), and anterior-posterior (AP, Y)

Since the MRI scanner that was used is capable of dynamic first and second (high) order shimming, it should be possible to shim these components from the distortion, unless the magnitude of the distortion is too high to be compensated by the shim field. The experiments were thus repeated using automatic pencil-beam volume shimming. The shim volume was set to the size of the hybrid FOV fitting into the bottle ($100 \times 100 \times 100 \text{ mm}^3$ around the center of the FOV). The results are shown in Figure 155.

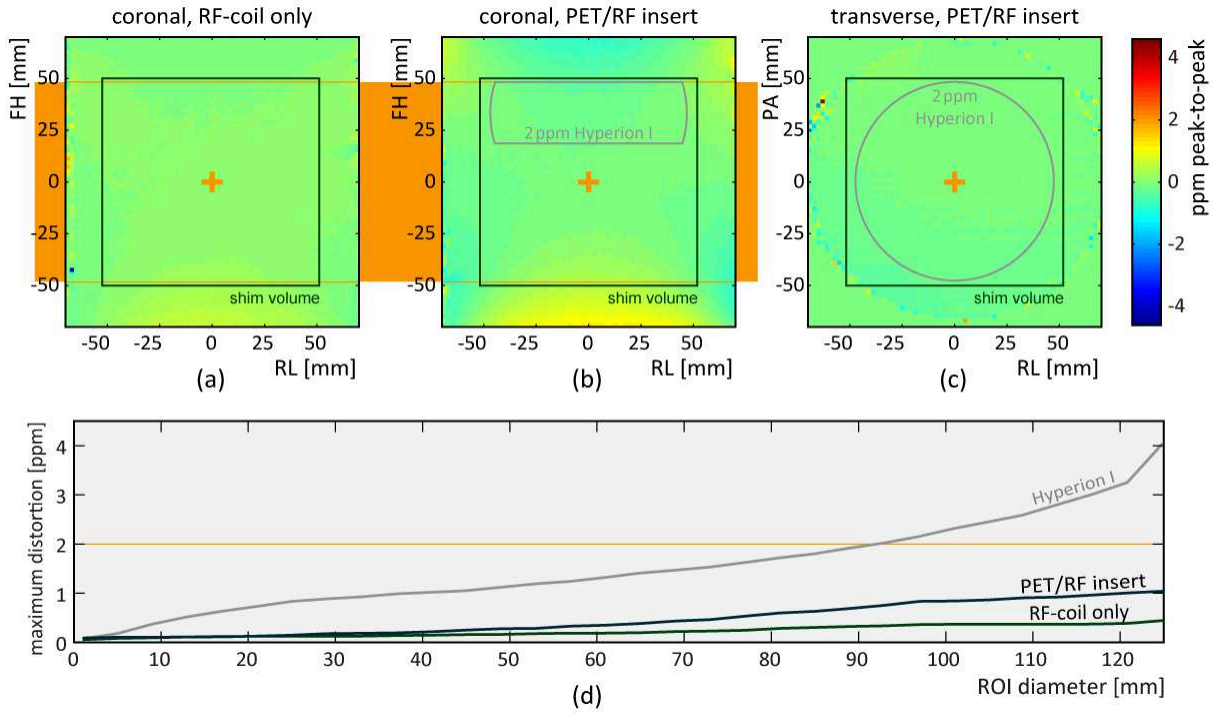


Figure 155: B_0 maps (peak-to-peak values) of Hyperion II^D with shimming (shim volume indicated in dark green): Coronal center slice measured with the large RF-coil only (a) and the operating PET/RF insert (b and c). The PET FOV is indicated in orange. The transverse center slice is shown in (c). The maximum peak-to-peak distortions for spherical ROIs, which are limited by the PET FOV, are plotted in (d) over the diameter. The 2-ppm border is never reached, using shimming, and is thus not drawn in the field maps. For comparison, the results of the previous insert “Hyperion I”, also using shimming, are overlaid in gray.

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As expected, the field was homogenized by the shimming. The system never reaches the 2-ppm border, and thus fulfills the requirement specification. At a diameter of 124 mm, the maximum distortion is 1 ppm peak-to-peak, compared to 0.4 ppm without the PET insert. Calculated as VRMS values (not shown in the graphs), the 0.1-ppm VRMS border, defined as the requirement for spectroscopy (see section 3.2.1), is reached at a diameter of 96 mm. This value is even larger than a rabbit brain (with a length of approximately 5 cm).

6.2.2.2 Spurious Signals, SNR and Image Uniformity

The spurious signal analysis was performed with the large and the small ^1H RF coils as described in section 3.2.2, while the PET system measured seven ^{22}Na point sources (~ 8.9 MBq in total). References were measured without the PET insert, using only the RF coils.

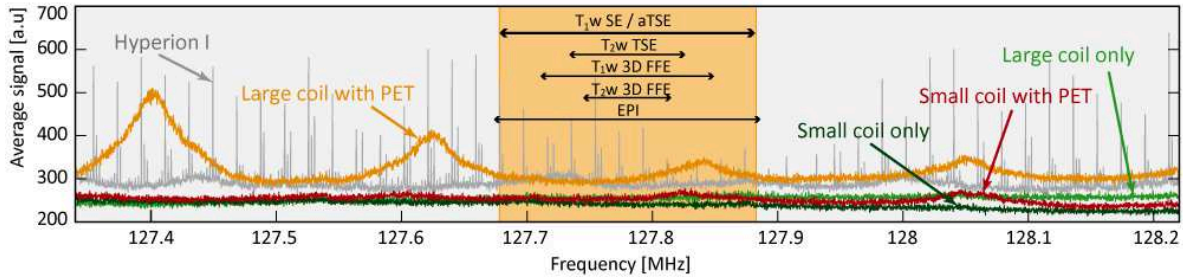


Figure 156: Averaged MRI signal received by the ^1H RF coils over frequency. Large (orange) and small (red) coil while the PET system measured seven ^{22}Na point sources with an activity of about 8.9 MBq. Baselines are represented by measurements with the coils only. The bandwidth of the SNR sequences are indicated by arrows – the bandwidth of the SE sequence is emphasized by the orange area. The result of the old insert is repeated in dark gray for purposes of comparison.

Figure published in (Weissler et al., 2015a) ©2015 IEEE.

The average MR signal over frequency received by the two ^1H coils without any MR phantom is shown in Figure 156. The (orange) plot for the large coil shows distinct spurious signals at multiples of around 215 kHz, whereas the exact frequencies are not fixed, but seem to shift according to temperature and activity. The origin of these spurious signals is the switched-mode power supply, which uses different switching frequencies in that range. For instance, the switching frequency of 220 ± 20 kHz, is used by a flyback converter for the auxiliary voltage. The buck converters of all the modules inside the power supply use frequencies of 250 ± 13 kHz (first stage) and $200 - 215$ kHz (output stages). Mixtures of these are most likely also the cause of the different amplitudes of the spurious signals. The pattern, repeating at about 215 kHz, is also visible with the old insert, but less distinctly. In that insert, eleven power supplies work asynchronously, which distributes the peaks over the bandwidth. The mean received signal is increased by 28 %, from 253 ± 7 to 323 ± 39 (maximum value increased from 273 to 510). For the small coil the increase is 5 %, from 240 ± 9 to 253 ± 9 (maximum value from 264 to 278). Compared to the previous insert (292 ± 26 instead of 242 ± 4 for PET off) these values are slightly higher, but high amplitudes at localized frequencies (seen as spikes with a maximum value of 637 in the plot for Hyperion I) are not visible. The amplitude of the measured signal depends on the used RF coil: compared to the old insert, the new large ^1H coil is more sensitive, which results in a higher increase (28 % instead of 21 % at the old insert), but also in higher overall SNR. The small ^1H coil is less sensitive to signals coming from the outside (5 % increase instead of 28 %), which is a consequence of its smaller dimensions. The RF-coupling between the screen and the birdcage resonator is particularly lower due to the large distance between them.

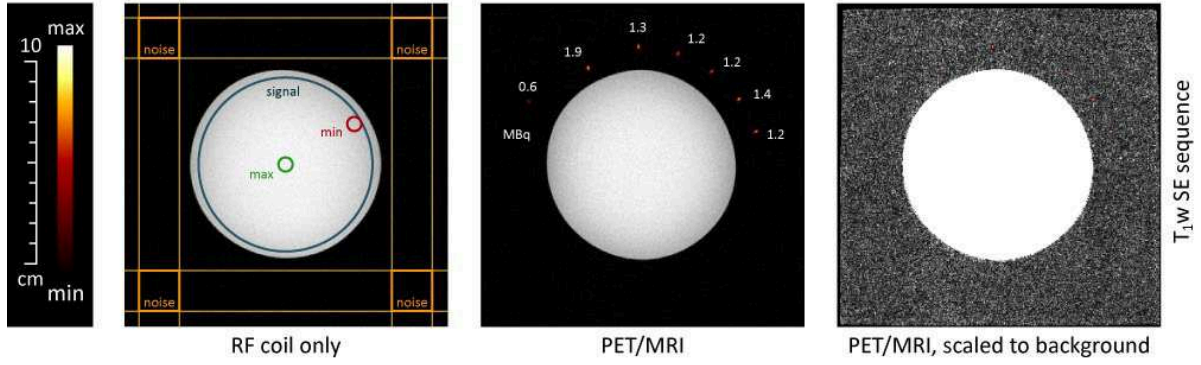


Figure 157: MRI SNR and image uniformity measurements (spin echo sequence). In the RF-coil-only image (left) the ROIs for SNR and PIU calculations are indicated. PET/MRI images (middle and right) show the 1-l bottle-phantom (MRI) and the seven ^{22}Na point sources (PET). In the right image, brightness and contrast are scaled to show the background noise of the MR image.

Figure published partly as parts of a figure in (Weissler *et al.*, 2015a) ©©3.0 2015 IEEE.

The increased noise floor results in a lower image SNR, which was measured analogously to the measurements with the previous insert presented in section 5.2.2.2. A decrease of 13 %, from 44.2 to 38, was calculated in the spin echo image of Figure 157. Although relative to the MRI-only, the SNR decreases about the same factor as for the old insert (14 %), the total SNR for this measurement increases by 80 % (comparable SNR result for Hyperion I: 21.2). Therefore, the result represents a large improvement.

Vertical stripes (RF-noise artifacts) that were visible in some images from the old insert (and that were dominant in the spurious scan) are no longer noticeable. Also, the amplified background of the MR image seems free from any artifacts. Their disappearance demonstrates that the improvements made to the SDM screens, and the introduction of the optical synchronization, were successful.

The image uniformity changed by around a factor of -1.9 %, from 89.8 % (RF-coil-only) to 88.2 % (PET/MRI). The difference is in the same order of magnitude as for the old insert (-0.6 %) and matches the results reported, for instance, in (Catana *et al.*, 2006) (1.5 % to 6.5 %) or (Wehrl *et al.*, 2011) (0 % to -3.6 %).

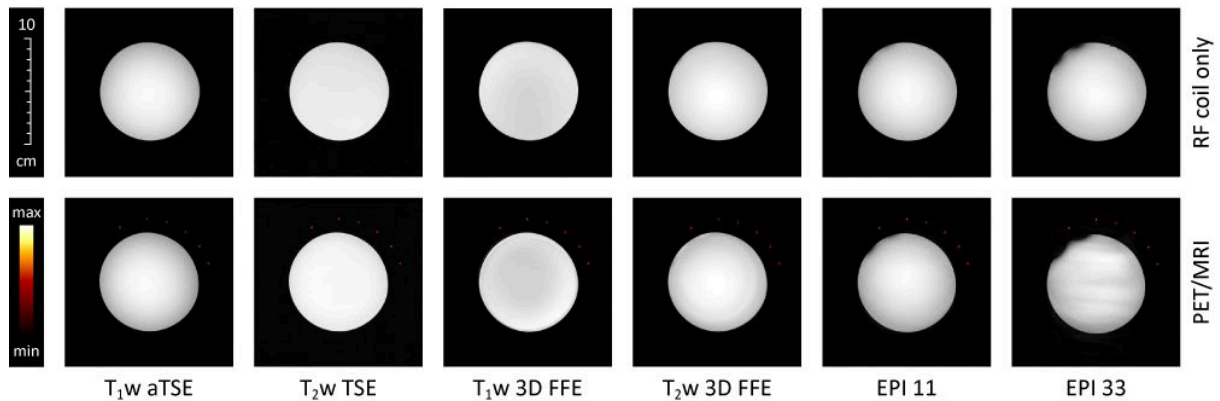


Figure 158: MRI SNR and image uniformity measurements with different sequences. TSE sequences for good image quality (1 slice, 2:30 min scan time), faster 3D FFE sequences (20 slices, 5 min scan time), and very fast EPI sequences (1 slice, 9.1 s scan time for EPI 5 and 5.9 s for EPI 33).

Figure published partly as parts of a figure and in the supplemental material of (Weissler *et al.*, 2015a) ©©3.0 2015 IEEE.

The images produced by the six other sequences are shown in Figure 158. A slight increase of background noise is visible in the PET/MR images, mainly in the EPI images. The average SNR loss is 14 % and the image uniformity changed by -1.7 %. Separate results for all sequences are displayed in Table 30. No RF-noise artifacts are noticeable in the images. EPI-typical Nyquist artifacts are visible in the images with higher echo train length. They are reduced compared to the old insert, where they were already clearly visible with EPI factors of eleven. The two B_0 artifacts at the top left of the EPI images are caused by the two point sources having a different package than the others.

MRI sequence	SNR	SNR difference	PIU	PIU difference
T₁w SE	38	-13 %	88	-1.9 %
T₁w aTSE	80	-15 %	83	-3.5 %
T₂w TSE	33	-1 %	96	-0.3 %
T₁w 3D-FFE	107	-16 %	91	-3.7 %
T₂w 3D-FFE	578	-1.6 %	89	-0.2 %
EPI 11	59	-23 %	84	-3.0 %
EPI 33	64	-27 %	86	0.6 %

Table 30: SNR and image uniformity rate the results for all MRI sequences.
Table published in the supplemental material of (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

The point sources in the PET images are depicted as rather needle-shaped in a radial direction. The top point source was reconstructed with a transaxial length of 1.9 mm (FWHM) and widths of 0.8 mm $\times$ 0.9 mm (axial). This DOI effect at large radii (point sources in Figure 157 and Figure 158 are located at a radius of about 6 cm) is greater than for the previous insert. Whereas Hyperion I depicted the top point source in the same experiment as rather round, with FWHM-dimensions of 1.6 mm $\times$ 1.8 mm $\times$ 1.3 mm (X $\times$ Y $\times$ Z), the new insert shows it with a size of 0.8 mm $\times$ 1.9 mm $\times$ 0.9 mm. Whereas the slight transaxial elongation of 0.1 mm can be explained by the 20 % longer scintillation crystals, the spatial resolutions perpendicular to the radius are (compared to Hyperion I) improved by a factor of 1.7, which leads to the thinning of the depicted point source in the other two directions.

6.2.2.3 Geometric Distortion

The structured insert of the distortion phantom was modified to have longer rods (20 mm instead of 5 mm) and to improve the distinguishability in the PET images. Filled with ^{18}F -FDG (~ 10 mBq), it was placed into the center of the FOV and scanned for about 12 minutes. For MRI, only the EPI sequences from Table 8 were used, as only they show significant geometric distortions. As a reference, the images were also taken without the PET insert, using only the large ^1H coil. The images are shown in Figure 159.

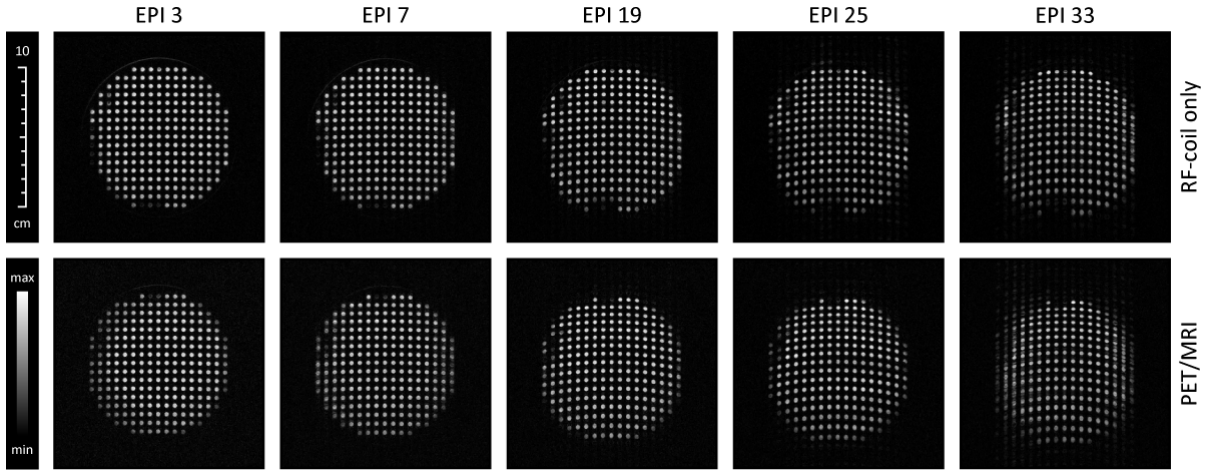


Figure 159: Distortion phantom in transverse direction, scanned without the PET insert (top row), and in simultaneous PET/MRI measurements (phantom was flipped upside down between the measurements; therefore, the positions of the air bubbles are mirrored).

Just as in the experiment with the previous insert, the outer rods show a reduced intensity, shifted downwards in the phase-encoding direction. Nevertheless, the effect is much smaller, which is mainly a result of the improved B_0 homogeneity. Although the EPI sequences deploy automatic shimming per default, the mechanism fails in this case, as the amount of MR signal is too low in this phantom. The amount of ghosting artifacts is reduced, and the geometric distortion has clearly improved. For the EPI 33 sequence, the geometric distortion deteriorates only by about 10 %, whereas it was 38 % with the old insert. Detailed values are listed in Table 31. The impact of the PET insert is of the same order as the impact of a higher EPI factor. Therefore, the distortion caused by the insert can be compensated for by only slightly longer scan times.

MRI sequence	Transverse geometric distortion	Transverse Reference	Sagittal geometric distortion	Sagittal Reference
EPI3	1.8 %	1.1 %	0.9 %	0.3 %
EPI7	4.3 %	3 %	1.8 %	1 %
EPI19	9.7 %	8 %	4.2 %	3.2 %
EPI25	13.2 %	11.3 %	6.5 %	4.5 %
EPI33	16.7 %	15.2 %	8.6 %	6.7 %

Table 31: Two-dimensional geometric distortion in MR images

The experiments were repeated with the phantom placed in a sagittal direction, and the Z-gradient (axial) was chosen as the readout gradient, as this causes the highest eddy currents and the largest effect in the images (Wehner *et al.*, 2015). The PET scan was also 12 minutes long (about 8.8 MBq start activity). As the MR images in Figure 160 show, when the scans were performed with the PET insert the Nyquist ghosts are clearly visible in the outer regions of the phantom. Additionally, the shearing of the image is increased, which supports the theory, since this effect is often caused by eddy currents (see chapter 3.2.3) and cannot be explained by measured B_0 distortion maps. Therefore, when possible, the readout gradient should be switched to a direction other than Z. Although the geometric distortion is much lower in the sagittal direction, the deterioration caused by the PET insert is worse than that

of the transverse direction (for instance, the distortion of EPI 33 is increased by 28 %). Details are listed in Table 31.

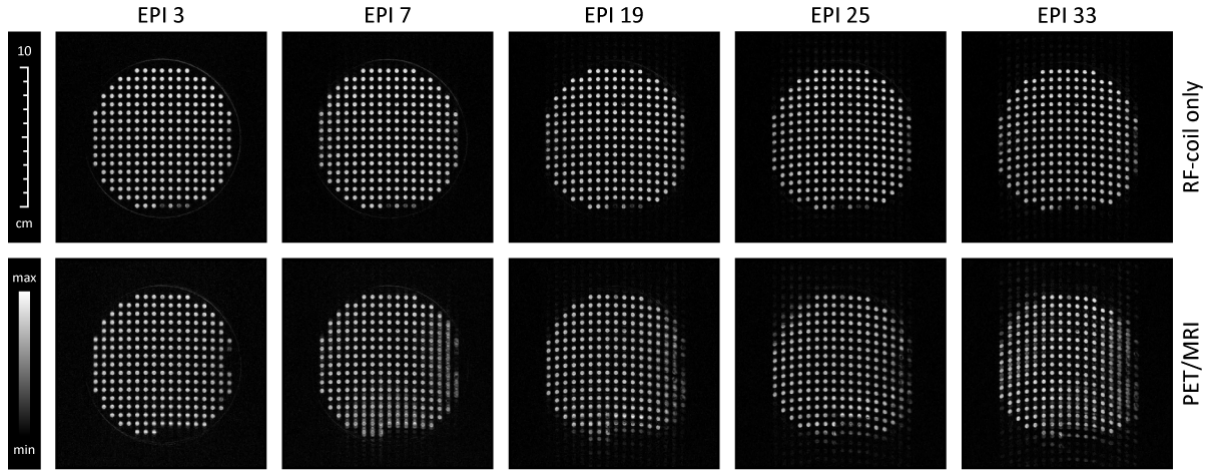


Figure 160: Distortion phantom in sagittal direction scanned using the Z-gradient as the readout gradient. The reference (top row) was scanned only with the large ^1H coil.

The PET images for both directions are shown in Figure 161. Neither the transverse nor the sagittal image gives any indication of geometric distortion. The transverse position is unfavorable for this kind of phantom, as most gamma photons have to travel a long way through the phantom before they are detected (which increases the SF). In addition, the gaps between the detector modules add up to two slightly blurred regions about 40 mm above and below the center of the FOV (this can be partly compensated by using the scanner in TOF mode (trigger scheme 1), as demonstrated in (Schug *et al.*, 2015a)). The image in sagittal direction is therefore much sharper. It gets noisier at the (head and feed) edges, where the sensitivity is lower (due to the geometric coverage with detectors).

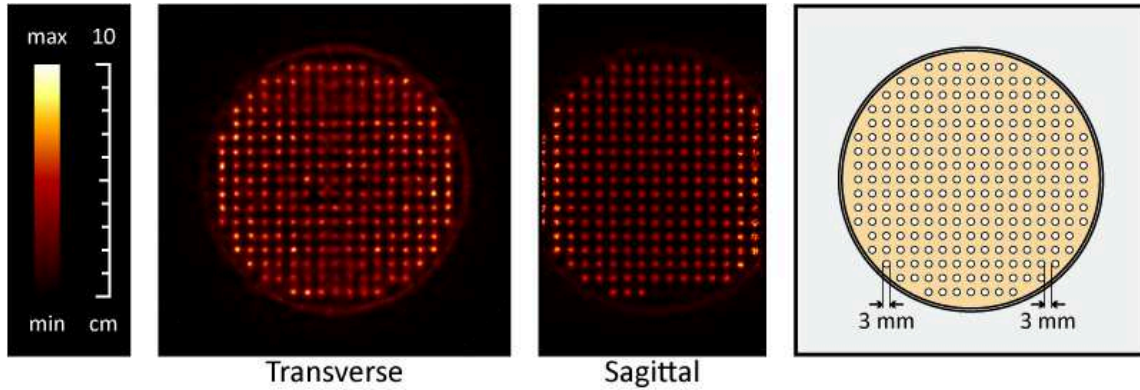


Figure 161: PET images of the distortion phantom placed and imaged in transverse and sagittal direction.

6.2.2.4 Temporal Stability

The measurements for the temporal stability were performed only with the large ^1H coil, with the PET system present but switched off, and with PET system measuring the seven ^{22}Na point sources (~ 8.9 MBq). The resulting mean images and SFNR maps are shown in Figure 162.

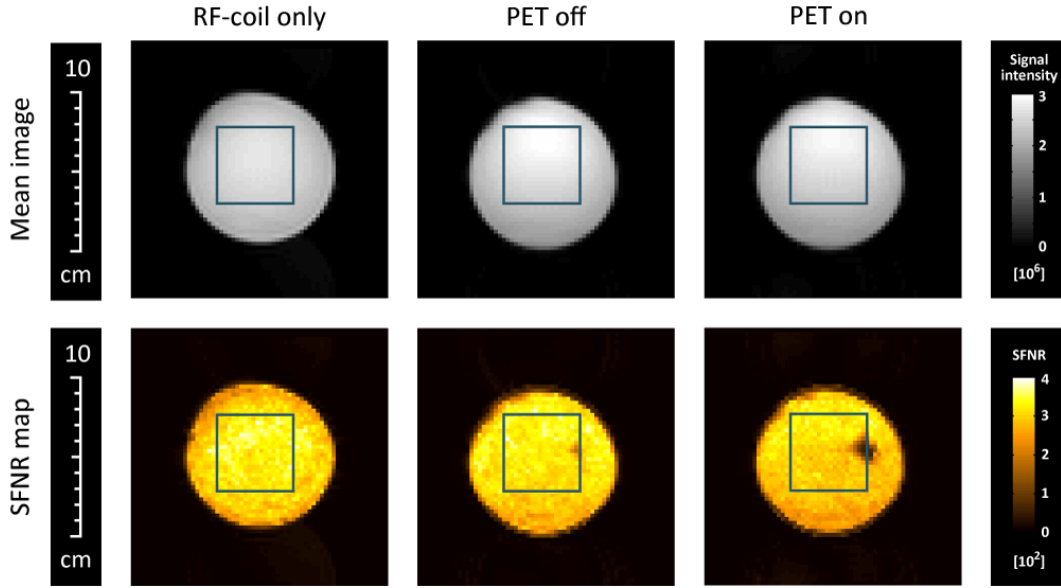


Figure 162: Mean images (top row) and SFNR maps (bottom row) of the temporal stability measurements, performed using only the RF coil (left) and with the PET/MRI insert (center and right). The ROI to calculate the numerical results is indicated in blue.

The B_0 -distortion artifacts from the two point sources at the top left are visible in all cases, although the effect is inverted by the presence of the PET insert: Whereas the phantom is depicted enlarged near the sources when using only the coil, parts of the phantom seem to be cut off by the sources when the PET system is nearby. Very dominant is a hole in the SFNR map in the case where the PET system was measuring. With less intensity it is also visible in the PET-off case (and was probably also present with the first insert, shown in Figure 99). By looking at the produced images in fast-forward (for instance, 10 minutes in 10 seconds), a ringing artifact becomes visible in that area, which changes its phase over time. This time lapse also shows the same geometrical upward drift of nearly a pixel over the 10 minutes time, as it was visible with the old insert and the QBC (see section 5.2.2.4). Additionally, it shows that the Nyquist ghost slightly, but continuously, gains intensity over time. Nevertheless, that ghost is barely visible, and it is also present without the PET insert, which marks a large improvement from the previous system. This effect does not seem to influence the signal intensity, as the fluctuations plotted in Figure 163 are similar for the cases with and without the PET insert.

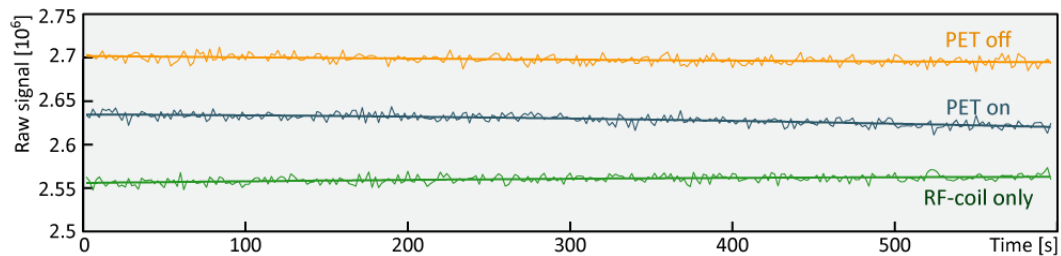


Figure 163: Raw MRI signal intensity, averaged inside the ROI, over time (all 300 2-s-long repetitions are shown). The fitted second-order polynomial trend is overlaid.

This perception is confirmed by the numerical values listed in Table 32, as there is no significant difference in percentage fluctuation between the cases. The drift value seems to

have improved compared to the old insert: from the reference average value listed in (Friedman and Glover, 2006), it improved to the lower reference value of 0.4 %.

Measurement	SNR	SFNR	Fluctuation	Drift
RF-coil only	386	330	0.16 %	0.14 %
PET on	335	292	0.16 %	0.37 %
PET off	414	320	0.15 %	0.21 %

Table 32: Numerical results of the temporal stability measurements

The differences between SFNR values and SNR values are similar to the values of the old insert, and the spectral analysis (Figure 164) also shows peaks at around 0.22 Hz that are not present when measured without the PET insert. Further peaks seem to be visible at around 0.01 Hz and 0.03 Hz, but their exact position changes and they become insignificant, when the number of images for evaluation is only changed slightly (p-value calculated according to (Meigen and Bach, 1999)).

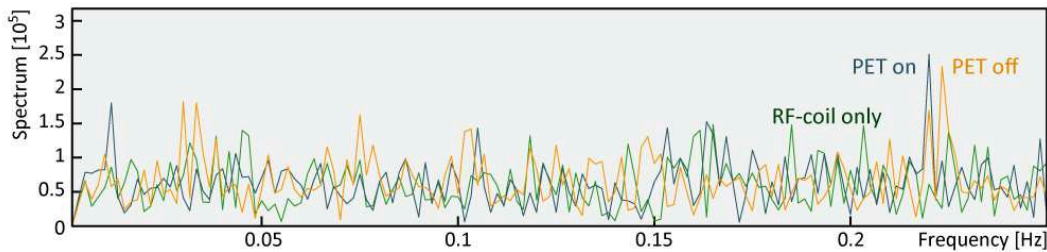


Figure 164: Spectrum analysis from the signals inside the complete ROIs in all 300 images.

Although the new insert improved almost all values concerning the temporal stability, the fluctuations around 0.02 Hz are still present, and they have to be taken into account when fMRI studies are made.

6.2.3 PET Performance and the Influence of MRI on PET

6.2.3.1 Sensitivity Degradation by the RF Coils

The gamma transparency of the RF coils was assessed by measuring a cylindrical ^{22}Na source (activity of 3.3 MBq, active volume of 4 mm diameter $\times$ 4 mm length, in a metal container with 6.3 mm diameter $\times$ 9 mm length). This was held in the center of the FOV by a 1-mm thick carbon fiber holder, which was attached to the outside of the insert. As such, the RF coils could be exchanged without moving the ^{22}Na source. Subsequent 3-minute-long PET measurements were made with and without all three RF coils. The closest distance of each detected LOR to the center of the source was determined, and the differences in count rates (introduced by the coils) were calculated as a function of the distance. To estimate the loss in sensitivity caused by the coils, all LORs through a spherical volume-ROI around the source were counted. The selected ROI radius was 12 mm (10 mm as defined by NEMA NU 4 (NEMA NU 4, 2008) for sensitivity calculations of point sources, plus 2 mm accounting for the active source diameter). The detected count rates and differences compared to the coil-only case are plotted in Figure 165.

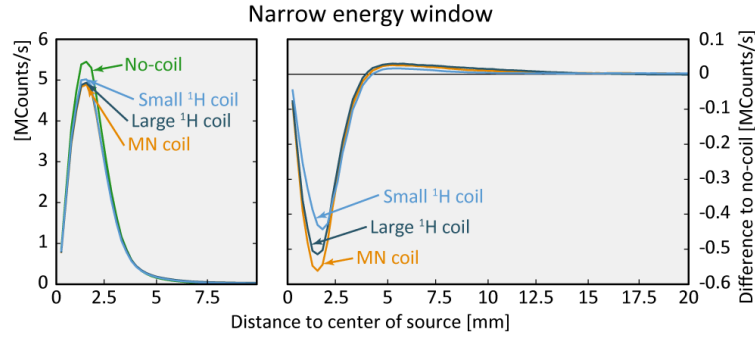


Figure 165: Count rates and change in count rates, caused by the three RF coils, as a function of distance to the center of the ^{22}Na source (processed with the narrow energy window).
Figure published in (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

They show that the count rates are reduced inside a radius of 4 mm, whereas they are increased outside. This is a clear indication of scatter introduced by the coils, as LORs seem to be shifted from the inside (less counts) to the outside (more counts) of that radius (consistent with the theory, explained in chapter 3.1.1.1). More of these scattered events are accepted by the wider energy window, since Figure 166 shows increased count rates at higher radii than for the narrow window.

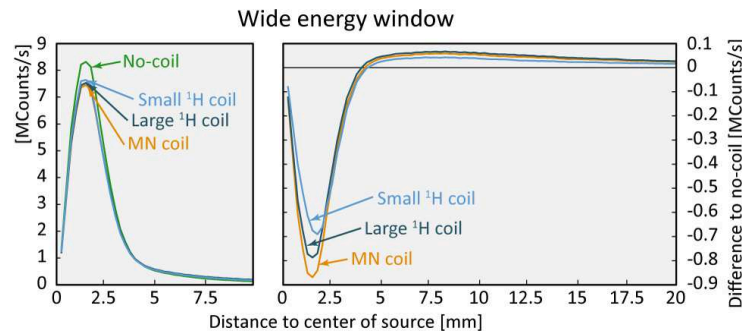


Figure 166: Count rates and change in count rates, caused by the three RF coils, over the distance to the center of the ^{22}Na source. The wide energy window, which accepts more scattered photons with lower energies, was employed. These events were scattered in larger angles and the detected LORs are thus further away from the real active area of the source.
Figure published in the supplemental material of (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

Although these additional LORs decrease the loss in sensitivity, they also cause blurring of the PET image. Using the small energy window, the calculated sensitivity is reduced by a factor of 7.2 % with the two ^1H coils and 8.4 % with the MN coil. When the wide energy window is employed, the sensitivity reduction factor is 5.6 % for the large ^1H coil, 5.9 % for the small ^1H coil, and 6.9 % for the MN coil. These sensitivity reduction factors are significant, but quantification of PET images is not affected, as the coils are always placed in the exact same position, and attenuation maps can thus be used.

6.2.3.2 PET Performance Parameters

The combined PET performance measurement was realized according to the verification method described in chapter 3.1.3, and is thus similar to the measurement with the previous insert.

Temperatures on the SPU and the temperatures of the dSiPMs were monitored with the built-in digital sensors on the PCBs. Bias currents through the detector diodes were measured with ADCs on the interface boards. Count rates for singles and coincidences were calculated in 0.1 s bins. Anger algorithm and the small energy window were used, as they are potentially more sensitive to influences from the MRI. The cooling liquid temperature was set to 0° C for the same reason. PET photopeak position, energy, and time resolution were determined by fitting Gaussian functions in histograms over 5 s scan time.

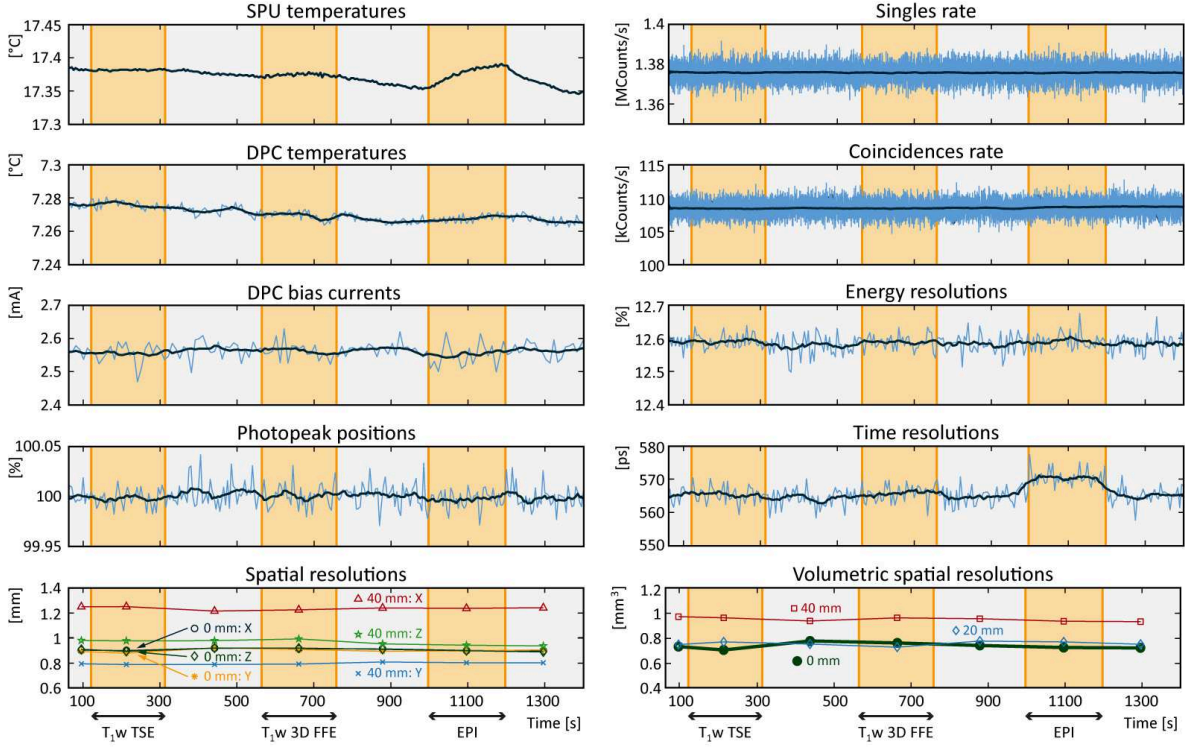


Figure 167: Performance parameters of the PET insert during a 23-minute-long measurement of seven ^{22}Na point sources while three different MR imaging sequences were executed (orange areas). The dark, thick curves are filtered with a 1-minute-moving-average filter to visualize tendencies. Spatial resolutions are plotted for a point source in the isocenter and a point source at a horizontal distance of 40 mm, or half the hybrid FOV. Additionally, the volumetric spatial resolution is given for a point source at a radius of 20 mm.

Figure published similarly in (Weissler *et al.*, 2015a) © 3.0 2015 IEEE.

The results of the point source measurements during MRI sequences are displayed in Figure 167. The averaged measured SPU temperature increases slightly during the gradient-intense EPI sequence. This heating of the SPU during the long and gradient-intense EPI sequence was also observed with the previous insert (chapter 5.2.3). Due to the improved cooling system with larger cooling pipes and greater contact surfaces, (the SPU itself did not change much in that respect), the observed heating is about 50 % lower. After the sequence has stopped, the SPU cools back down to its starting value in two minutes, which is twelve times faster. If there is an increase in dSiPM sensor board temperature at the same time, it is lower than the normal fluctuations and total temperature drift during this long measurement. Moreover, the temperature of the dSiPMs seems to be stabilized, since the bias voltage regulation circuits and the sensor boards themselves are now directly connected to the cooling pipes. The bias currents, photopeak position, and count rates likewise do not show apparent changes during MRI activity. Drops in count rates and changes in energy resolutions were

observed with higher PDE settings of the insert (e.g., high bias voltage) and artificially higher duty cycles and slew rates of the MRI gradients ((Wehner *et al.*, 2014b) and (Schug *et al.*, 2014b)). Nevertheless, they are not visible in these experiments with standard settings and the real imaging sequences that were used. The energy resolution is around 12.6 % (FWHM), and no indications were found that the applied MRI sequences lead to noticeable degradations. Although the average time resolution of 565 ps (FWHM) only changes about 6 ps during the EPI sequence, it is more than 2.5 times the average standard deviation during the times without MRI activity, and can thus be seen as an effect of the MRI on the PET system. The loss of time resolution has been reported before (Wehner *et al.*, 2014a) and is caused by induced voltages on the power supply network. After further investigation, the problem could be solved by using updated interface board (Dueppenbecker *et al.*, 2016). Nevertheless, the measured effect is only 1 %.

The spatial resolutions in X- (transaxial left-right), Y- (transaxial top-down), and Z- (axial) direction are 0.9 mm in the center of the FOV. Displaced 40 mm in X-direction, the spatial resolutions were determined as 1.24 mm (X), 0.8 mm (Y) and 0.97 mm (Z). The average measured volumetric spatial resolution in the center FOV is $0.73 \text{ mm}^3 \pm 7 \%$. At higher radii, the volumetric spatial resolution decreases: at 40 mm it is $0.95 \text{ mm}^3 \pm 2 \%$. The spatial resolution does not change during MRI activity and outperforms the predecessor Hyperion I (transaxial: $1.2 \text{ mm} \times 1.3 \text{ mm}$, axial: 1.15 mm, volumetric: 1.8 mm^3).

6.2.3.3 Maximum Activity

An NECR measurement, comparing multiple different settings for the scanner, is presented in (Schug *et al.*, 2016). There, a mouse-sized scatter phantom (built according to (NEMA NU 4, 2008)) with a length of 70 mm and a diameter of 25 mm was filled with an activity of 110 MBq ^{18}F -FDG and was measured until the activity decayed to 500 kBq. The results for the settings used in this thesis are shown in Figure 168.

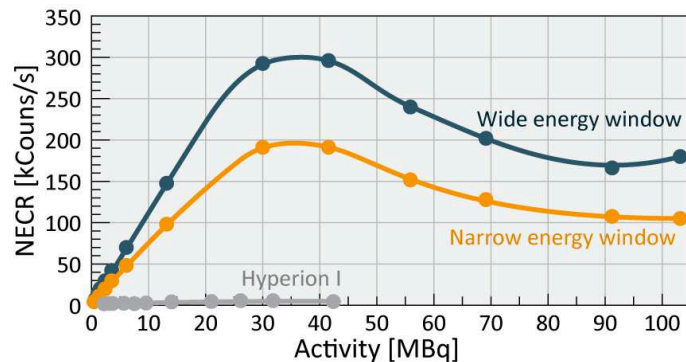


Figure 168: NECR curves over activity using a mouse-sized scatter phantom. The data are processed once using the wide, and once using the narrow energy window. The curve for Hyperion I (using a rat-sized phantom) is overlaid in grey.

Measurement performed and analyzed by D. Schug. Data was published in (Schug *et al.*, 2016) ©2015 IPEM.

The peaks of the NECR curves are around 35 MBq. This seems to be no improvement over the previous insert (35 MBq), but the sensitivity of the new insert is more than four times higher. Additionally, the measurements use different phantoms and are thus not directly comparable. Using higher trigger schemes and validation thresholds (already reducing the sensitivity slightly), the peak of the NECR curve can be at values as high as 50 MBq. The

NECR peak can probably be pushed to higher activities, when the prepared technologies, such as data compression and online hardware singles processing are implemented, as currently the GBit Ethernet connection seems to be the bottleneck for the generated raw data. The busy/gate and the duty cycle gating concept (presented in section 6.1.2.1) are also intended to extend the linear part of the curves to allow higher activities. A different, hardware-based solution, would be the hardware coincidence unit (see section 6.1.7.2) in combination with the laser-based transceiver modules (section 6.1.1.2.2), theoretically allowing up to four times the data-rate for each SDM. First measurements of the peak point source sensitivity currently indicate values around 2.6 %. Disabling all filters, it can even be pushed to 3.2 % (on the expense of image quality).

6.2.3.4 Time-Of-Flight (TOF) PET

As described before, the PET performance is influenced by numerous settings, which can be chosen to optimize the system for the demands of the actual application. Whereas a tumor characterization study might need a high spatial resolution, a dynamic tracer study might rather need a high sensitivity. Other situations demand higher count rates or a linearity of the NECR curve in a certain activity range (see section 6.2.3.3). Additionally, the used tracer and the type of object (e.g., mouse versus rabbit) have an influence on the system settings. All system settings can thus be changed by sets of settings (ExamCards – see section 6.1.7.5) and the influences of these parameters are examined in detail in (Schug *et al.*, 2016).

One of the optimization choices is, whether the system should have a higher sensitivity or a higher CRT resulting in TOF-PET. As explained in chapter 3.1.1.2, for mice, it is unlikely to achieve improvements with TOF, but for rabbits, it might make sense. To optimize the PET system for TOF, the trigger scheme is set to one and -5° C liquid cooling temperature is used. Using these settings, CRTs of 260 ps were measured with a single point source, as shown in Figure 169.

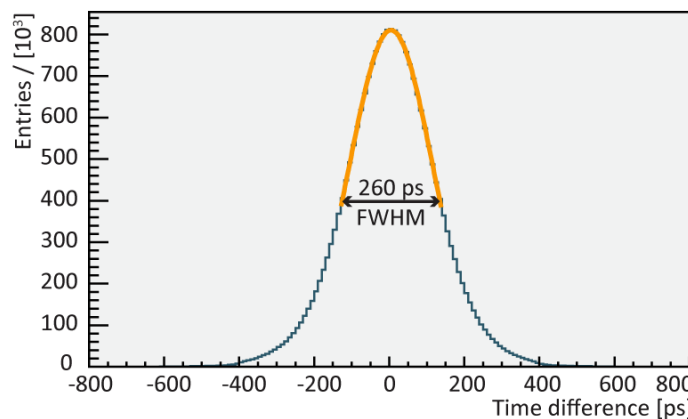


Figure 169: PET CRT, measured with the insert using timing-optimized settings. A single ^{22}Na point source (1.3 MBq) was placed in the center of the FOV for the scan. Fitting parameters for the analysis are described in detail in (Schug *et al.*, 2014a).

Figure published in the supplemental material of (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

Although this demonstrates already, that the system – including the optical synchronization method – is suitable for TOF-PET, the interesting question is, whether this is visible in the images. It is still possible, that the optimization causes the system to loose on other performance parameters (e.g., reducing the sensitivity), outweighing the TOF advantage. To

investigate this, the distortion phantom measurement, presented in section 6.2.2.3, was afterwards repeated to compare the TOF-optimized settings. As the ^{18}F -FDG is decaying during the experiments, the measurement times were made slightly different to have an equal amount of about 2.8×10^9 decays during the scans: With the standard settings, the scan has a length of 13 minutes (starting at 3.8 MBq), and with TOF settings it was scanned for 17 minutes (starting at 3 MBq). The results, compared to the standard settings used in the rest of this thesis, are shown in Figure 170.

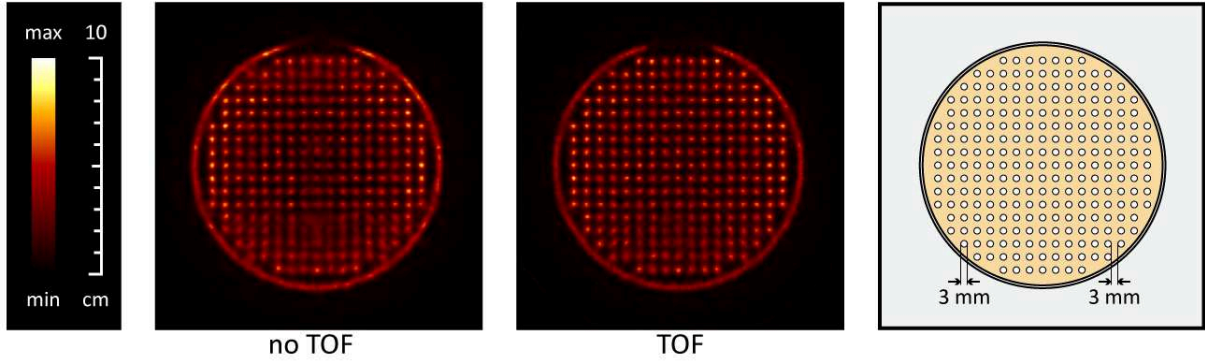


Figure 170: TOF influence in PET images of the distortion phantom in transverse direction (16 mm slice thickness).

Dataset published in (Schug *et al.*, 2016) ©^{3.0} 2015 IPEM.

The TOF image is clearly sharper and TOF was even able to (partly) compensate the blurred regions at the bottom (caused by the symmetry and the gaps of the detector). With this result, Hyperion II^D is the first PET scanner, being able to demonstrate a TOF benefit for pre-clinical applications. A further investigation of the TOF performance using even TOF-optimized crystals and testing the respective MRI compatibility under these more vulnerable settings is presented in (Schug *et al.*, 2015a).

6.2.4 PET/MR Imaging

PET/MR imaging examples with the large ^1H coil are shown in Figure 171: a pepper was filled with ~ 15 MBq of ^{18}F -FDG using the large ^1H RF coil. The MRI sequences used are a $T_1\text{w}$ aTSE 6 sequence (TR/TE: 612 ms / 20 ms, pixel size: $250 \mu\text{m} \times 250 \mu\text{m}$, slice thickness: 2 mm, NSA 6, pixel bandwidth: 322 Hz/pixel, FA: 90° , 10 slices, 13:02 minutes scan time) and a $T_2\text{w}$ TSE 19 sequence (TR/TE: 2400 ms / 2100 ms, pixel size: $250 \mu\text{m} \times 250 \mu\text{m}$, slice thickness: 2 mm, NSA 6, pixel bandwidth: 291 Hz/pixel, FA: 90° , 10 slices, 16:19 minutes scan time). The PET images were reconstructed with a resolution of $500 \mu\text{m} \times 500 \mu\text{m}$ and have the same slice thickness as the MR images (2 mm).

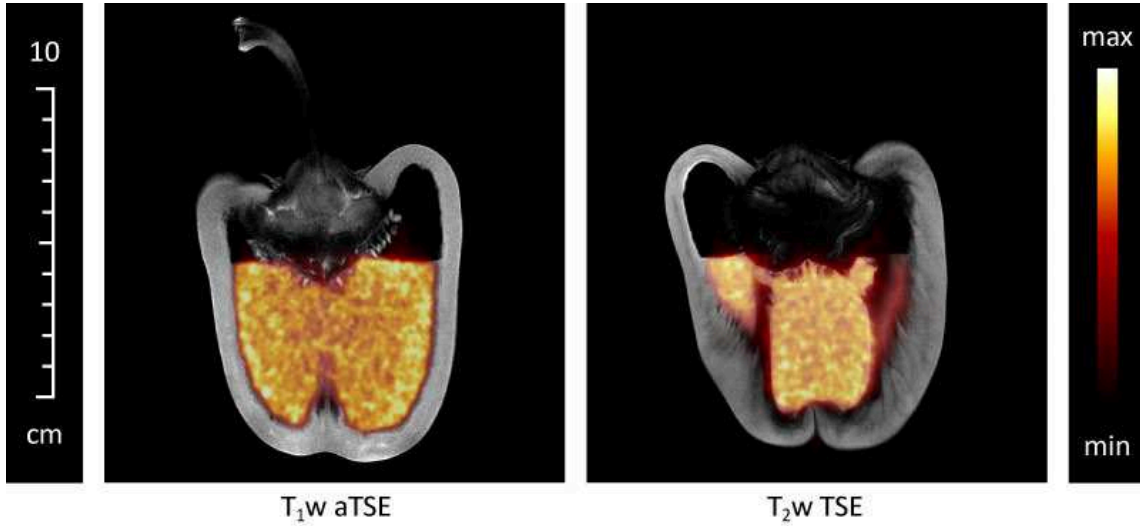


Figure 171: Simultaneous PET/MRI measurements (large ^1H RF coil) of a pepper filled with approximately 15 MBq of ^{18}F -FDG.

Figure published in the supplemental material of (Weissler *et al.*, 2015a) © $\text{O}^{3.0}$ 2015 IEEE.

Compared to the images made with the previous insert (Figure 96), these show a higher SNR and no RF-noise artifacts.

6.2.4.1 Hot-Rod Phantom

PET/MR images of a mouse-size hot-rod phantom were acquired using the small ^1H coil. The hot-rod insert of the phantom (shown in chapter 3.3.1, Figure 50, right) has a height of 20 mm and a diameter of 28 mm. The rods have diameters and gaps of 2, 1.5, 1.2, 1.0, 0.9, and 0.8 mm. The phantom was filled with ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) with a total activity of 20.3 MBq (about 25 % of the activity is in the rods) when a PET-only scan started. Directly after the reference scan, the PET insert was moved into the MRI and five subsequent PET/MRI scans were made. All PET measurements were stopped automatically once 150 GByte of raw data were acquired (5:26 min for PET-only and 8:05 min for the last scan having a start activity of 12.3 MBq – details are listed in Table 33). The narrow energy window and the ML algorithm with ML filtering were applied for singles processing, since they seem to result in higher spatial resolutions. PET reconstruction was performed with an isotropic voxel size of $250^3 \mu\text{m}^3$.

MRI sequence	start activity	scan time
PET-only	20.3 MBq	05:26 min
T₁w aTSE	29.0 MBq	05:42 min
T₂w TSE	18.0 MBq	05:58 min
T₁w 3D-FFE	17.1 MBq	06:15 min
T₂w 3D-FFE	16.0 MBq	06:38 min
EPI	12.6 MBq	08:05 min

Table 33: Activities and scan times for the hot-rod phantom measurements.

Table published in the supplemental material of (Weissler *et al.*, 2015a) © $\text{O}^{3.0}$ 2015 IEEE.

The MRI sequences are based on the sequences used in the SNR measurements. The acquisition pixel size was changed to $200^2 \mu\text{m}^2$ for all imaging sequences (except for the T₁w 3D-FFE sequence that requires $300^2 \mu\text{m}^2$ to maintain the short echo time). Compared to the

sequences used for the old insert, not only was the spatial resolution was increased (acquisition pixel size for Hyperion I: $250^2 \mu\text{m}^2$ and $300^2 \mu\text{m}^2$ for T₁w 3D-FFE, $500^2 \mu\text{m}^2$ for EPI), but the NSA was also halved to reduce the scan time. Details for all sequences are listed in Table 34. The MRI scans were repeated until the PET scan time was over. Due to the short scan time of the EPI sequences (from 3.3 s to 2 s), they were varied from EPI factor 3 to EPI factor 33 and repeated with an NSA value of 4.

MRI sequence	ETL / ES ^a [ms]	TR/TE ^b [ms]	NSA ^c	FA	pixel BW ^d	slices	acquisition matrix	acqu. voxel size [mm]	scan time
T ₁ w aTSE	6 / 9	612 / 20	4	90°	263 Hz	1	320 × 312	0.2 × 0.2 × 2	2:09 min
T ₂ w TSE	18 / 10.5	2400/100	4	90°	263 Hz	1	320 × 306	0.2 × 0.2 × 2	2:49 min
T ₁ w 3D-FFE	1 / -	11 / 2.3	8	35°	389 Hz	20	214 × 214	0.3 × 0.3 × 4	2:52 min
T ₂ w 3D-FFE	1 / -	13.4 / 8.1	4	45°	217 Hz	20	320 × 320	0.2 × 0.2 × 4	2:37 min
EPI 3	3 / 5.1	29 / 13	1	20°	263 Hz	1	320 × 318	0.2 × 0.2 × 4	3.3 s
EPI 19	19 / 4.1	89 / 43	1	20°	263 Hz	1	320 × 304	0.2 × 0.2 × 4	2.0 s

^a) Echo Train Length / Echo Spacing
^b) Repetition Time / (effective) Echo Time
^c) Number of Signals Averaged
^d) Pixel Bandwidth
Image size: 64 mm × 64 mm
Slice selection gradient direction: Z (head-feed)

Table 34: MRI sequences to image the hot-rod phantom.

Figure 172 shows the images of the hot-rod phantom, taken as simultaneous PET/MRI and with the small ¹H RF-coil-only. The shown MR images are centered, but neither filtered nor resized (possible visual improvement of resolution by interpolation); nor are brightness and contrast manually adjusted.

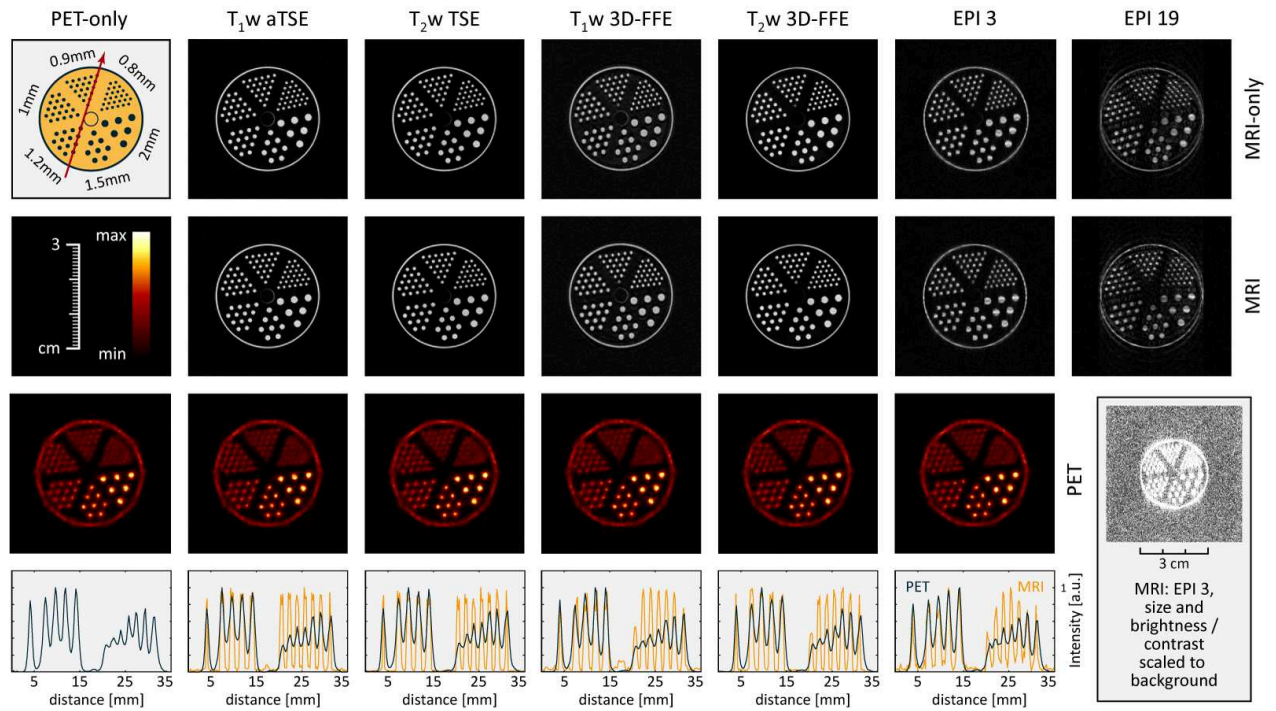


Figure 172: PET-only (left column), RF-coil-only (first row) and simultaneous PET/MRI measurements of the hot-rod phantom (rod diameter = 0.8, 0.9, 1, 1.2, 1.5, and 2 mm, 20 mm length). The orientation of the profiles (last row) through the PET images (second last row) is shown in the schematic of the phantom (top left). The image on the bottom right shows the MR image of the EPI 3 sequence with size and brightness/contrast scaled to show the background noise.

Figure published in (Weissler *et al.*, 2015a) © 2015 IEEE.

Visual differences between the MR images taken with and without PET are not noticeable. Slight Nyquist ghosting artifacts, which increase with higher EPI factors, are visible in all EPI images, both with and without the PET insert. Severe ghosting (where the ghosts have a similar intensity as the object) appeared in 15 of the 266 images measured. The exact cause of the effect is unknown, but the effect is independent of the presence of the PET insert (an example is shown in Figure 173). Despite the high spatial resolution of $195\text{ }\mu\text{m}$, the EPI 19 sequence has a scan time of only 2 s (the EPI 3 needs 3.3 s), which shows that high-speed imaging (as needed, e.g., for fMRI applications) is possible.

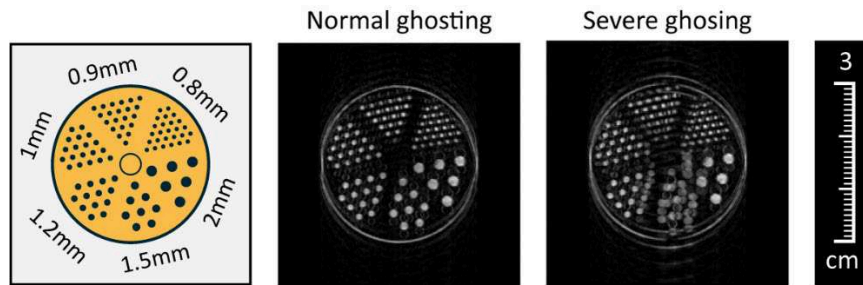


Figure 173: Example for the occasional severe ghosting effect with EPI sequences (only the RF coil was used, without the PET insert): unlike the left MR image, the image on the right suffers from a ghosting artifact that has, around the 1.5-mm rods, almost the same intensity as the original image. Both images were taken with the exact same MRI sequence (EPI 15, NSA 4, TR/TE = 73 ms / 35 ms, voxel size = $200\text{ }\mu\text{m} \times 200\text{ }\mu\text{m} \times 4\text{ mm}$, 6.7 s scan time).

Figure published in the supplemental material of (Weissler *et al.*, 2015a) © $\text{O}^{3.0}$ 2015 IEEE.

The EPI3 image (with PET) is shown again in the bottom right of Figure 172, but with size and brightness/contrast scaled to the background noise. RF-noise artifacts are visible neither in any of the images nor in the scaled background. As a result of the exchangeable RF coil, and by using the small ^1H coil, the SNR was largely improved in comparison to the previous insert (due to the mouse-sized phantom, the images shown in Figure 172 have a different scale than in Figure 110).

In the PET images, the polygonal shape of the detector geometry can be seen in the shape of the outer ring of the phantom. Almost all rods (including the 0.8-mm wide rods) are separable in all images. Aside from some statistical variations, there are neither differences between PET-only images and PET/MRI images, nor are artifacts visible. The line profiles through the 1.2-mm and 0.9-mm rods support this perception. As the PET images do not show any differences, the PET data from all scans could be combined and then reconstructed with a high-resolution voxel volume of $180^3\text{ }\mu\text{m}^3$ (almost three times smaller voxel volume than $250^3\text{ }\mu\text{m}^3$). In Figure 174, the image is shown in grayscale (as is usually done for PET-only images), together with profiles through all hot-rod areas. It confirms that all hot rods are distinguishable. Resolving the 0.8-mm hot rods in the PET images constitutes a large improvement over the previous insert, where even 1 mm rods were blurred. The ability to separate 0.8 mm hot rods with PET was only shown once before with a preclinical sequential 1-T MRI and PET system (Nagy *et al.*, 2013) using position-sensitive photomultiplier tubes, which cannot be used in a simultaneous configuration.

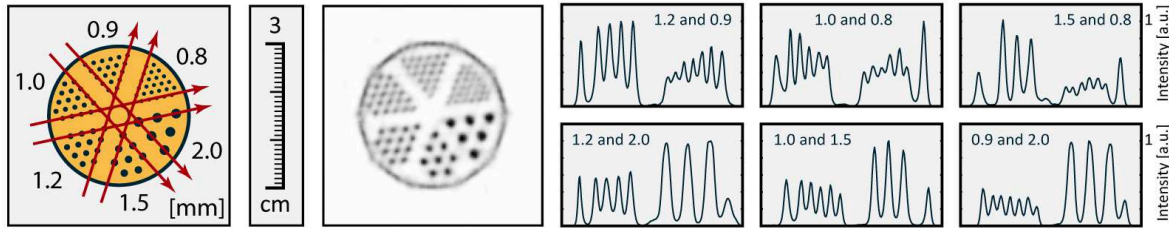


Figure 174: Reconstruction with an isometric voxel size of $180^3 \mu\text{m}^3$ from a combined list-mode file, measured as PET-only and during the different MRI sequences. All rods are clearly separable. Profiles are shown through all hot-rod areas from 2.0 mm to 0.8 mm.

Figure published partly as parts of a figure in (Weissler *et al.*, 2015a) © 3.0 2015 IEEE.

6.2.4.2 MN $^1\text{H}/^{19}\text{F}$ Coil

To test the operation of the MN $^1\text{H}/^{19}\text{F}$ coil, a phantom for coronal orientation (82 mm outer diameter) was built (see Figure 175a). It is split in two compartments by a sagittal wall. One compartment and the outer ring (3 mm thickness) were filled with water (approximately 20 mm high). Six vials, each with 1.8 ml of different content, were placed into both compartments. They contain isopropyl alcohol (IPA), standard phantom fluid (PhF) (same as used in the SNR experiments), air or water (depending on the compartment), ^{18}F -FDG with an activity of approximately 5 MBq, perfluoro-15-crown-5-ether ($\text{C}_{10}\text{F}_{20}\text{O}_5$) and olive oil. While PET data were acquired, multiple MR sequences (e.g., ^1H T₁w, ^1H T₂w, PDw) TSE and ^{19}F FFE) were executed. Fat suppression was used (Spectral Presaturation pulse with Inversion Recovery (SPIR)) to generate a water-weighted image. From the available data, a fat-weighted image was calculated as the absolute difference from the PDw image. Details of the sequences are listed in Table 35. The PET image was reconstructed from a five-minute long data acquisition with MRI activity. PET and MR images have a pixel size of $500\text{ }\mu\text{m} \times 500\text{ }\mu\text{m}$ and a slice thickness of 2 mm.

Different coronal images of the phantom, sketched in Figure 175, a, are shown in Figure 175, d. The contrasts in the T_{1w} 1H image (TR/TE: 600 ms/31.5 ms) and T_{2w} 1H (TR/TE: 2400 ms/100 ms) image are as expected: While the phantom fluid brightens up in both images, fat (short T_1 and a long T_2) is bright in the T_{1w} image, and water (long T_1 and T_2) and ^{18}F -FDG (solute in water) are bright in the T_{2w} scan. The water-fat-shift of about one pixel (pixel bandwidth 445 Hz) is visible for the oil and the isopropyl. The SPIR fat saturation works, and the small susceptibility artifacts (in the water around the air vial and on the sides of the phantom) are most likely caused by the phantom itself. ^{18}F -FDG PET and ^{19}F MR are free of visible artifacts.

MRI sequence	ETL ^a	TR/TE ^b [ms]	NSA ^c	FA ^d	scan time	f ₀ [MHz]
PDw TSE	8	2400 / 31.5	1	90°	1:17 min	127.78
T₁w TSE	8	600 / 31.5	8	90°	2:26 min	127.78
T₂w TSE	8	2400 / 100	4	90°	4:53 min	127.78
FatSat SPIR TSE	32	2400 / 114	1	90°	21.06 s	127.78
¹⁹F FFE	19	51.2 / 19.1	4	20°	2.0 s	120.21

^{a)} Echo Train Length ^{c)} Number of Signals Averaged
^{b)} Repetition Time / effective Echo Time ^{d)} Flip Angle

Voxel size: 500 μm × 500 μm × 2 mm, Acquisition matrix: 240 × 240 pixels, Water-fat-shift: minimum (0.977 pixel), Pixel bandwidth: 445 Hz (419 Hz for ¹⁹F FFE)

Table 35: MRI sequences for the MN $^1\text{H}/^{19}\text{F}$ measurements.

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For the combined image (Figure 175, b), PET, ^{19}F and fat-weighted image were color-mapped differently and overlaid (transparency according to brightness) over the water-weighted image. The normalized profiles in Figure 175, c demonstrate that the four different substances can be clearly separated.

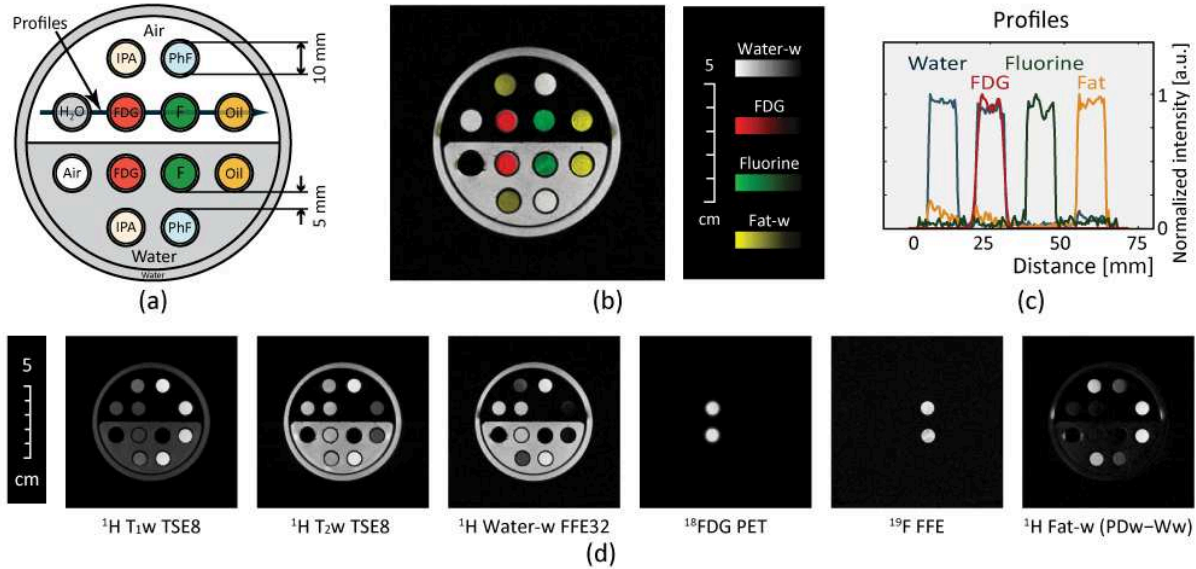


Figure 175: MN phantom (a) filled with water and twelve 1.8 ml vials of isopropyl alcohol (IPA), standard phantom fluid (PhF), air or water (depending on the compartment), ^{18}F -FDG with an activity of approximately 5 MBq, perfluoro-15-crown-5-ether ($\text{C}_{10}\text{F}_{20}\text{O}_5$) and olive oil. Coronal PET and MR images (measured by the MN $^1\text{H}/^{19}\text{F}$ coil with different MR sequences) are shown in (d). The four images on the bottom right are fused to the combined image (b). Intensity profiles through a row of vials (orientation indicated in (a)) are plotted in (c).

Figure published in (Weissler *et al.*, 2015a) ©2015 IEEE.

Although not quantitative, the images presented in Figure 175 demonstrate that the combination of the PET insert with the MN $^1\text{H}/^{19}\text{F}$ coil works as designed. Neither PET nor MR images show visible artifacts. This indicates that the shielding of all components is not limited to the MR frequency of ^1H at 3 T, but is also sufficient at the MR frequency of ^{19}F . The profiles shown in Figure 175c demonstrate the differentiability between the scanned fluids, and thus the adequate SNR of the methods used.

6.2.4.3 In Vivo Measurement

To study the image quality of both modalities in vivo, a longitudinal study that showed the development of a subcutaneous tumor in a mouse model was conducted. Furthermore, cardiac cinematic (CINE) images of the mouse heart were acquired. All animal procedures were approved by the Maastricht University ethical review committee and were performed according to Dutch national law and the institutional animal care committee guidelines. Furthermore, approval from the Philips Internal Committee for Biomedical Experiments (ICBE) was acquired prior to the measurements.

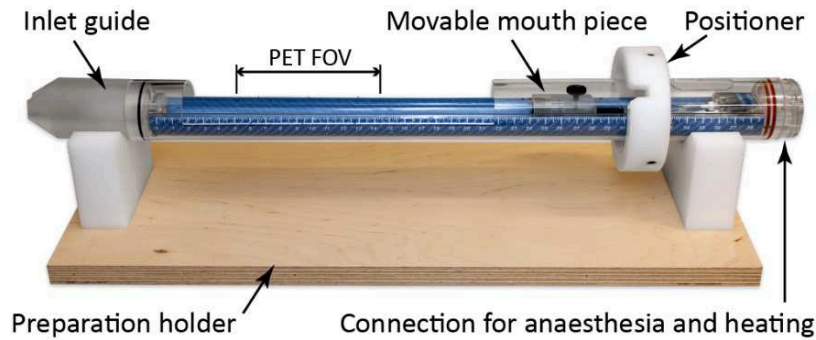


Figure 176: Adaptor with mouse bed (blue) to be inserted into the small ^1H coil. The MR-compatible animal bed (Minerve, France) is inserted into a Plexiglas tube with an opening for the mouse. The system provides anesthesia and animal heating with hot air circulating underneath the bed. A positioner, screwed to the tube, ensures grip and a defined position in the small ^1H coil.

Human breast tumor cells (MDA-MB-231, 5×10^6 cells in 100 μl Phosphate-Buffered Saline (PBS)) were injected subcutaneously in the hind leg of an 8 weeks old female Balb/c mouse (Charles River, Burlington, MA USA) with a weight of 18.9 g. The tumor size was monitored weekly with a caliper. The mouse was measured three times: 4, 16, and 37 days after the implantation. Each time, the mouse was anesthetized with isoflurane (3 % induction, 1-2 % maintenance) and placed in the animal setup (Minerve, Esternay, France), shown in Figure 176. The mouse was kept warm by circulating hot air inside the animal bed and its core temperature was surveyed during the experiment with an optical rectal temperature sensor (Neoptix, Québec, Canada). Respiration was likewise monitored with a sensor (Rapid Biomedical, Rimpf, Germany). During the experiments, the mouse was monitored and the level of anesthesia and body temperature were controlled. Three vials with small droplets of ^{18}F -FDG (~ 500 kBq in total) were additionally placed next to the mouse as fiducial markers to facilitate and verify MRI and PET image fusion.

Measurement	injected activity	Uptake time ^a	Start activity ^a	scan time ^b	Energy window	Processing	Measured coincidences ^b
Day 4	14 MBq	167 min	4.9 MBq	16 min	wide	COG-ACE	98.8 Mcounts
Day 16	15.1 MBq	51 min	11 MBq	64 min	narrow	ML	185.6 Mcounts
Day 37	11.2 MBq	41 min	8.6 MBq	44 min	wide	COG-ACE	463.3 Mcounts
^a) Before data was used to reconstruct the shown images							
^b) Of data used for the shown images							

Table 36: Detailed PET scan information for the in vivo measurements.
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Before inserting the animal setup into the scanner, approximately 13 MBq of ^{18}F -FDG (~ 100 μl) were injected intravenously via the tail vein. The PET/MRI insert was equipped with the small ^1H coil. PET data was acquired directly after insertion, and the total measurement time varied from 75 minutes to 190 minutes. The shown PET images were reconstructed from PET data recorded after an uptake time of at least half an hour – detailed information is listed in Table 36. Multiple MRI sequences with different contrasts were executed during the experiments. A list with detailed parameters of the images shown is given in Table 37.

MRI sequence	ETL ^a	TR/TE ^b [ms]	Pixel size	ST [mm]	Acq. matrix [pixel]	slices	NSA ^c	FA ^d	scan time	Pixel BW
T₂w TSE multi-slice	16	2400 / 100	195 μm^2	1	400 $\times$ 400	24	2	90°	10:12 min	295 Hz
T₂w TSE single-slice	16	2400 / 100	195 μm^2	2	400 $\times$ 400	1	4	90°	5:03 min	329 Hz
T₁w aTSE	9	612 / 20	195 μm^2	1	400 $\times$ 396	24	4	90°	5:34 min	329 Hz
CINE 15	32	7.46 / 2.754	300 μm^2	1	112 $\times$ 112	1	20	10°	5.03 s	396 Hz
^a) Echo Train Length					^c) Number of Signals Averaged					
^b) Repetition Time / effective Echo Time					^d) Flip Angle					

Table 37: MRI sequences for the in vivo measurements.

Figure 177 shows the images resulting from the longitudinal study. Four days after cell injection, the tumor had a volume of approximately 28 mm³, measured with a caliper. The tumor is visible in the T₂w MR image, but shows relatively low activity in the PET image. 12 days later, a tumor with a size of ~37 mm³ had grown. It is clearly visible in the MR and in the PET image. Three weeks later, the mouse was imaged for the last time after the tumor had grown within three days to approximately 42 mm³. Aside from the tumor, the PET image slice from day 16 shows higher uptake in the kidneys, brain, and Harderian glands behind the eyes. The PET images have a high level of detail over the complete body of the mouse: from the tumor in the leg up to structures in the kidneys. Although the brain is rather on the edge of the FOV (where the PET sensitivity is lower due to the solid angle towards the detectors), some structure of the brain is already recognizable. As the same animal was successfully measured three times, the in vivo capabilities of the insert are demonstrated, as is its usability for longitudinal studies.

In the last measurement of this longitudinal study, self-made ECG leads were connected to the front paws of the mouse. To improve the ECG signal, EEG paste (Weaver and Co., Aurora, Colorado USA) was added between the electrode and the feeds. Great attention was paid to reducing the loop size of the open leads, as the signal is measured inside the RF coil. The cable to the ECG monitor was a double-shielded cable that was routed through a waveguide to the ECG monitor outside the examination room.

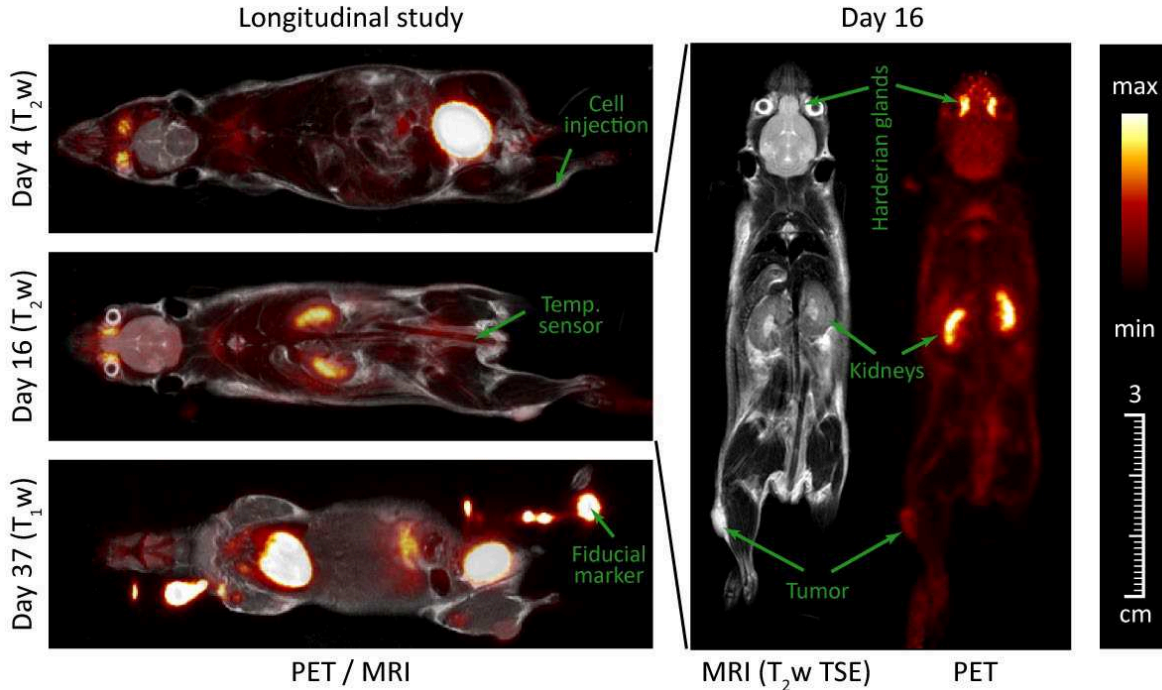


Figure 177: Longitudinal study of a human breast cancer tumor growing subcutaneously on the left hind leg of a mouse. Left column shows simultaneously measured whole-body PET/MR images at 4 days after the subcutaneous cell injection (1 mm slice of 24 multislice T2w TSE16 sequence, NSA2, 10:12 min scan time); after 16 days (2 mm single-slice, NSA4, 5:03 min scan time); and after 37 days (1 mm single-slice of 24 multislice T1w TSE9 sequence). On the right, PET and MR images are shown separately for day 16.

Figure published similarly in (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

This construction would have turned the waveguide into a coaxial structure, which is more of a broadband transmission line than the intended high-pass filter. Therefore, the rubber insulator of the cable was removed and the shielding braid around the cable was connected with copper wire wool to the waveguide, thereby closing the transmission line structure. The ECG signal and the respiratory signal were analyzed with a preclinical ECG trigger unit (Rapid Biomedical, Rimpär, Germany). Both the ECG trigger and the respiratory gating signals were converted to optical signals and were fed through a waveguide back into the MRI examination room, where they were then transmitted to the MRI scanner and the PET system. For PET, this was achieved by converter PCBs (Figure 178) that were designed to convert, among other things, TTL-signals to the optical POF input provided by the synchronization unit as described in section 6.1.2 (the RTU (see section 6.1.2.3), though designed for these tasks, was not finalized at the time of the measurement.).

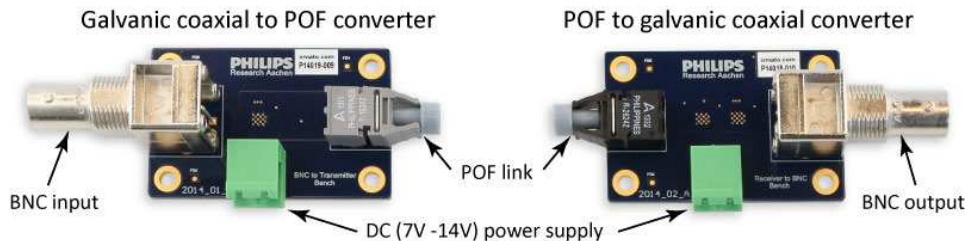


Figure 178: Converter PCBs between galvanic signals (e.g., TTL-compatible) and POF links. PCB layout by J. Mustafa.

The heart rate was relatively constant ($\pm 3.8\%$) at around 506 beats per minute, resulting in 119 ms per heart cycle. 47.6 % of the 463.3 million coincidences were retrospectively discarded due to breathing and cardiac cycles reaching into the breathing movements. The data was binned once into eight time bins. The images were reconstructed independently (Figure 179). As such, prospectively ECG triggered MRI CINE images of the mouse heart (acquisition time ~ 5 min, details see Table 37) were fused with retrospectively dual-gated PET CINE images, as described in (Lee *et al.*, 2012) and (Judenhofer and Cherry, 2013), as a preclinical PET/MRI application. PET and MRI clearly show the contraction of the heart. Both ventricles are visible in the PET images and are depicted without holes. Furthermore, an animation with all 15 MRI time frames and respectively interpolated PET images was created.

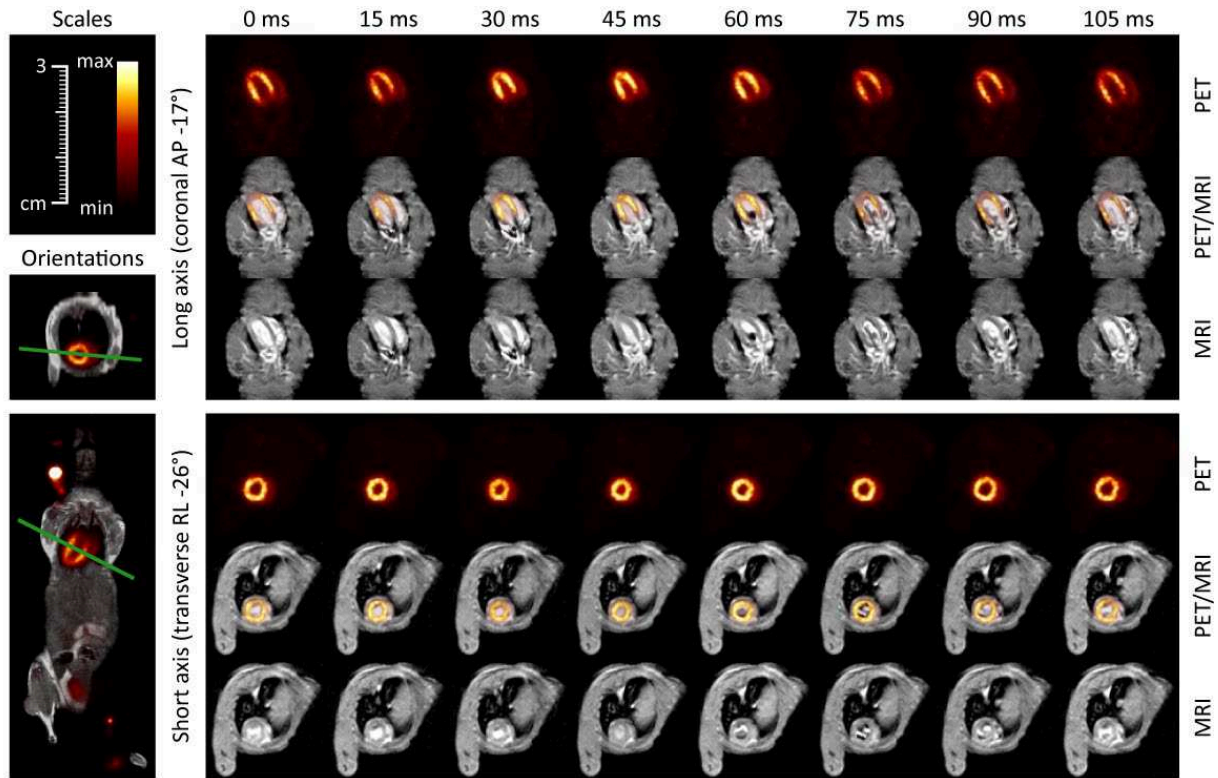


Figure 179: Retrospective dual-gated (respiratory and ECG) simultaneous CINE PET/MRI measurement of a mouse heart. Eight time bins are shown. The slices are orientated along the long (top) and short axis (bottom) of the heart. The MR images (gradient echo CINE sequence with $300^2 \mu\text{m}^2$ pixel size and 1 mm slice thickness, $\text{TR}/\text{TE} = 7.46 \text{ ms}/2.754 \text{ ms}$, $\text{FA}=10^\circ$) show one of fifteen time frames representing the time bin from the PET data.

Figure published similarly in (Weissler *et al.*, 2015a) ©^{3.0} 2015 IEEE.

This measurement demonstrates that the insert is suitable for more advanced preclinical research applications, for which foreign equipment has to be connected.

6.4 Conclusion and Summary

The preclinical PET/RF insert “Hyperion II^D” is the world’s first PET/MRI system that uses digital silicon photomultiplier technology. Many improvements have been made with respect to its predecessor with analog SiPMs and a digitization ASICs in the detector stack: By fully populating the detector modules, the hybrid FOV was enlarged by a factor of three, to 160 mm × 96.6 mm (transaxial × axial). The diameter of a spherical ROI within that FOV, with a B_0 disturbance lower than 2 ppm, was increased to 118 mm (even though three times more detector stacks are installed). With shimming, the system never reaches the 2-ppm limit. The 0.1-ppm VRMS border, defined as the requirement for spectroscopy, is reached at a diameter of 96 mm (using shimming). MRI Tx/Rx RF coils are now changeable, and three different dedicated coils were built. Although the relative MRI SNR degradation of 13 % using the large ^1H coil is almost the same as for the previous insert, the total MRI SNR was improved by 80 %. Still, the degradation is significant and larger than the set requirement specification. The small ^1H coil is much less sensitive to spurious signals, and thus the noise floor is only increased by 5 %. Dotted lines (RF-noise artifacts) are visible neither in the unscaled MRI images nor in their amplified backgrounds. The detector stacks do not show significant heating during a three-minutes-long, gradient-intense EPI sequence. Moreover, changes in bias currents, photopeak position, or count rates were not apparent with the standard imaging sequences used. The energy resolution of 12.6 % (FWHM) seems to be unaffected by the MRI sequences that were tested, with possible changes remaining below normal fluctuations. The measured average time resolution of 565 ps (FWHM, trigger scheme three and seven point sources in transaxial direction) only deteriorated by 5 ps during the EPI sequence. The peak NECR can reach up to 50 MBq. Spatial PET resolutions of 0.9 mm (FWHM, 0.73 mm³ FWHM isotropic volumetric resolution, iterative reconstruction) in the isocenter are not altered by the MRI. These values are supported by phantom measurements where the 0.8 mm rods are resolved. Due to the high SNR of the small ^1H coil, it became possible to increase the spatial resolution of the EPI images by a factor of five. This revealed slight ghosting artifacts, which were similarly present when measured with the RF coil alone. The effect of severe ghosting (visible in 3.8 % of the EPI images of that phantom) is also independent of the PET insert.

The results are summarized in Table 38 to Table 40, and almost all requirement specifications are met (except for a slightly too low sensitivity, the already mentioned SNR degradation, and the maximum activity (peak of the NECR curve), which can be increased when all the planned methods are implemented – see section 6.1.2.1).

Parameter	Requirement	Hyperion I	Hyperion II ^D
Energy resolution	15 % FWHM	29.7 % FWHM	12.6 % FWHM
Time resolution	1 ns FWHM	2.5 ns FWHM	565 ps (Trig. 3)
Time resolution for TOF (rabbit imaging)	535 ps FWHM	-	260 ps (Trig. 1)
Spatial resolution	1 mm FWHM	1.7 mm FWHM 1.8 mm ³ FWHM	0.9 mm FWHM 0.73 mm ³ FWHM
Sensitivity	3 %	0.6 %	2.6 %
Maximum activity (mouse / rat / rabbit)	(21 / 30 / 90) MBq	35 MBq	50 MBq

Table 38: PET system performance parameter summary for Hyperion I and Hyperion II^D

Parameter	Requirement	Hyperion I	Hyperion II ^D
B₀ homogeneity (anatomical imaging)	2 ppm peak-to-peak (over the whole FOV)	Ø 56 mm in FOV Ø 90 mm (shimming)	Ø 118 mm in FOV Full FOV with shimming
B₀ homogeneity (spectroscopy)	0.1 ppm VRMS (single MRS voxel)	Ø 8 mm (shimming)	Ø 96 mm (shimming)
Spurious signals	No spikes in spectrum	Spikes visible	No spikes in spectrum
Spurious signal image artifacts	Not visible in background noise	Visible if SNR is too low	Not visible in background noise
SNR degradation	3.3 %	14 %	13 %
Percent Image Uniformity degradation	± 5 %	- 1.3 %	- 1.6 %
Ghosting	No difference to reference	Visible at high EPI factors	Only visible at high EPI factors and with Z-readout gradient
Geometric distortion	1 %	Only exceeded at EPI (maximal 5.8 % worse than reference)	Only exceeded at EPI (maximal 2 % worse than reference)
Temporal fluctuation	0.2 %	0.14 %	0.16 %
Temporal drift	1 %	0.769 %	0.37 %
FBIRN test SNR	200	363	335
FBIRN test SFNR	200	302	292

Table 39: MRI system performance parameter summary for Hyperion I and Hyperion II^D

Parameter	Requirement	Hyperion I	Hyperion II ^D
Axial hybrid FOV	90 mm	30.1 mm	96.6 mm
Diameter (transaxial) hybrid FOV	150 mm	160 mm	160 mm
Maximum scan time (mouse imaging)	4 hours	35 min	no limit
Maximum total scan time per day	8 hours	4 hours	no limit
Temporal synchronization accuracy	5 ms	140 µs	140 µs

Table 40: PET/MRI system performance parameter summary for Hyperion I and Hyperion II^D

Initial $^1\text{H}/^{19}\text{F}/^{18}\text{F}$ images (shown in Figure 175) taken with the MN $^1\text{H}/^{19}\text{F}$ coil, demonstrate the versatility of the PET/RF insert, and show that the RF tightness is not limited to the ^1H frequency at 3 T. Repeated simultaneous whole-body mouse PET/MRI measurements show the usability of the insert in longitudinal in vivo studies. The dual-gated heart images illustrate that external equipment can be connected and that the insert is thus eligible for more advanced research applications.

The presented PET/RF insert demonstrates that digital silicon photomultipliers can be used to build high-resolution preclinical PET systems, and that, with an elaborated system design, they can also unfold their potential during simultaneous PET and MRI acquisitions.

7. Comparison and Conclusion

As stated in chapter 4, several research groups have used different detector technologies in recent decades to build and improve upon preclinical PET and hybrid PET/MR systems. To appraise the results of this work, the most important systems are listed here, and comparisons are made using the performance parameters introduced in chapter 1.

7.1 Comparison

Figure 180 plots the total number of scintillation crystals over the total crystal volume for multiple PET-only (or PET/CT or PET/SPECT) and PET/MRI systems. Whereas the total crystal volume is important for the size of the FOV and the stopping power (and thus for the sensitivity), the size of crystals – and thus the number of crystals – is important for the spatial resolution.

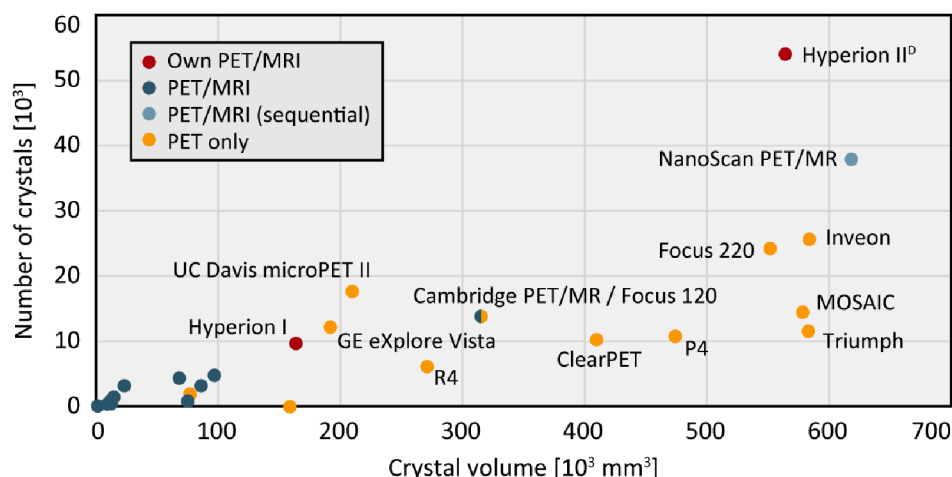


Figure 180: Comparison of different preclinical PET and PET/MRI systems: Number of crystals over total crystal volume.

The performance of the systems generally increases from the bottom left to the top right. Likewise, the size, price, and system complexity also increase. It thus becomes immediately

apparent that the PET/MRI combinations are at the lower end, far away from the normal PET system. As explained in section 4.3.2, the reason for this is mainly that the solutions to achieve MRI compatibility result in unscalable architectures. The systems presented in this thesis overcome these limitations by using direct digitization. The sizes of single crystals and the complete crystal arrangement (Figure 181) compared to the other systems (Figure 58 and Figure 59), and the positions of Hyperion I and II^D in Figure 180 visualize the advantages of this approach.



Figure 181: Sketches of the preclinical PET gantries that were built and the scintillation crystals used: The single crystals and the crystal arrangements (gray) are drawn in comparable sizes to those of Figure 58 and Figure 59 in chapter 0. The hybrid FOVs are drawn in orange (and blue for the small ¹H coil).

Aside from the scalability of the architecture, the thesis claimed in the preceding chapters that early digitization is advantageous for achieving the highest SNR for the PET signal. As Figure 182 shows, the Hyperion II^D system, which digitizes directly in the sensor die, has the highest energy resolution and the best time resolution of all comparable systems (the time resolution is even better than for clinical systems).

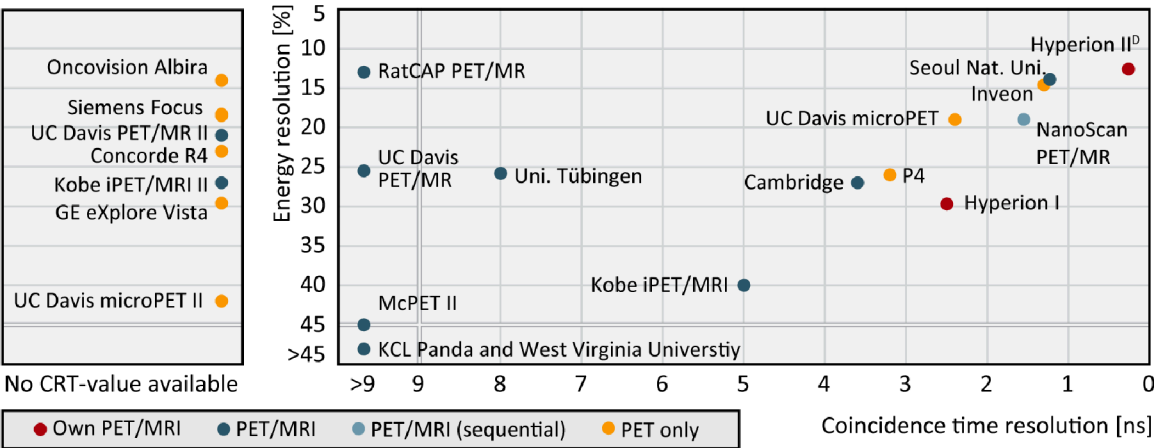


Figure 182: Comparison of different preclinical PET and PET/MRI systems: Energy resolution over time resolution (since smaller values for the energy resolution are better, the ordinate is swapped – the system performances thus increase from the lower left corner to the upper right). Systems without documented time resolution are plotted on the left.

The most important performance parameters for the end user are the sensitivity and the spatial resolution. A suitable representation is used in Figure 183, where both values are plotted against each other in a logarithmic scale. All values for the plot are taken from the available literature, and the measurements were not always performed under the same conditions: e.g., the spatial resolution is often determined using FBP reconstruction, which is correct with respect to the NEMA standard for performance analysis, but does not represent a realistic scenario. With regard to the sensitivity, the chosen energy window plays a large role, since, for instance, scattered events are counts as well, although they reduce the image quality. Factors of four and more are possible. The KCL Panda, e.g., uses an extremely

broad energy window of 170 keV to 1020 keV, and the quadHiDAC detector cannot even determine the energy. Nevertheless, this plot shows a clear indication of the scanner performances and allows a direct classification of the insert presented.

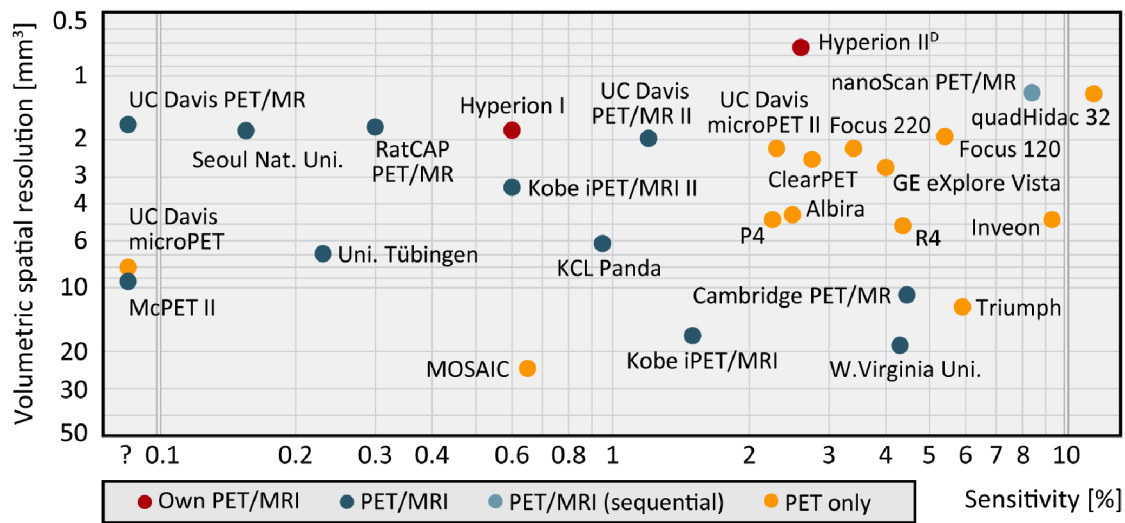


Figure 183: System comparison: Volumetric spatial resolution over sensitivity. The spatial resolution axis is turned around so that better performance values are thus plotted towards the upper right. All values are taken from the literature and are not measured under the same conditions (see text).

7.2 Conclusion

The thesis described the principles of PET and MR imaging, as well as the advantages of combining the two modalities into a single hybrid system. It furthermore explained the technical challenges that have to be solved, derived the requirements for performance parameters that have to be met, and defined how the fulfillment of these requirements is verified. The challenges were addressed in two steps: Firstly, using analog SiPMs and integrated digitization in the PET detector module, and secondly, using fully digital SiPMs. How the interactions between the two modalities are minimized within these two steps is described in detail. The measurements presented demonstrate the quality of the inserts, and that all requirements are met in the second step (except for a slightly too low sensitivity and the non-negligible SNR degradation). The result is the world's first digital preclinical PET scanner, which is also the world's first digital PET/MRI system. The PET spatial resolution is higher than all other simultaneous PET/MRI systems and is even similar to the best reference PET scanner that has been built to date. Furthermore, the achieved PET coincidence time resolution introduces TOF-PET to preclinical applications.

These results demonstrate that the described approach of early digitization results in highest PET performance, and that the resulting MRI compatibility challenges can be solved by means of an elaborate system design.

Appendix

History, Acknowledgements, and Contributions

This work has been supported by Philips Research (Philips GmbH Innovative Technologies) and five public research grants. This chapter describes these projects, the related work that preceded the thesis, and my personal role. It furthermore acknowledges the contributions of my colleagues (in addition to the references to their respective publications throughout the thesis).

The idea of digital PET, the dSiPM for highest PET performance, and its usage for TOF-PET/MRI arose around 2005 at Philips Research, Aachen. I joined the group (which at that time consisted of Thomas Frach, Carsten Degenhardt, Gordian Prescher, Andreas Thon, Torsten Solf, and Volkmar Schulz) at the beginning of 2007. In light of my MRI experience, gained at Philips Medical Systems (Best, the Netherlands), I started on the development of the first MRI compatible SPU for the first SDM (Figure 184). The module and a mockup of a complete gantry were used for the first PET/MRI compatibility tests at Philips Research, Hamburg.

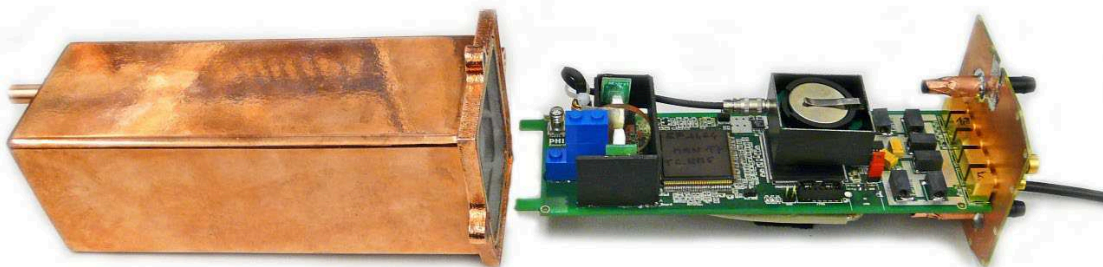


Figure 184: Setup for the first PET/MRI compatibility measurements involving coincidence measurements under MRI conditions: A point ^{22}Na point source (taped to blue Lego bricks) was measured with two crystals (enclosed in white Teflon tape) and two single SiPMs (on green upright PCBs). One of two ASICs is visible in the large housing with hand-written marks. The FPGA (Xilinx Spartan 2) of the SPU is partly visible underneath a battery-driven test-pulser (connected to another input of the ASIC). Together with an optical USB adapter, the setup was placed in the screened SDM housing (left).

In 2008, the EU FP7 project HYPERImage (Grant agreement no. 201651) began. Lead by Philips Research (Volkmar Schulz) it was intended to mature predevelopments from multiple academic and industrial partners, and to combine them into integrated PET/MRI systems. The idea was to build the complete imaging chain from SiPMs to complete systems in a modular way (the planned module with detector stacks are visualized in Figure 185).

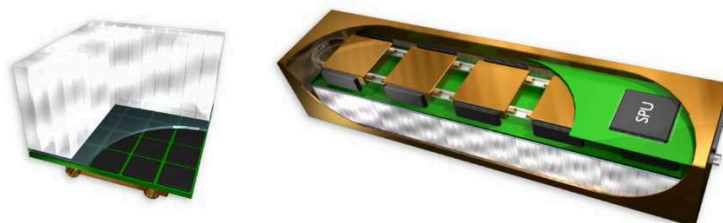


Figure 185: Concept sketch for a detector stack with crystals, light guide, SiPMs, and ASIC and cooling on the backside (left). Connected to an SPU they form a PET detector module (right).

The SiPMs were produced by FBK (Trento, Italy), mainly by Claudio Piemonte and Nicola Zorzi. The ASIC was designed by Peter Fischer, Ivan Peric, and Michael Ritzert from Heidelberg University (UH, Germany, formerly University of Mannheim). Viacheslav Mlotok and Michael Ritzert (from UH) designed the sensor-, the digitization-, and the interface board (under our guidance – especially for the MR compatibility aspects).

The task of the team in Aachen was to combine all parts into two PET/MR systems. The first system was a preclinical insert and the second a clinical scanner (later reduced to a 2-module demonstrator) built into a split gradient coil (Figure 186).

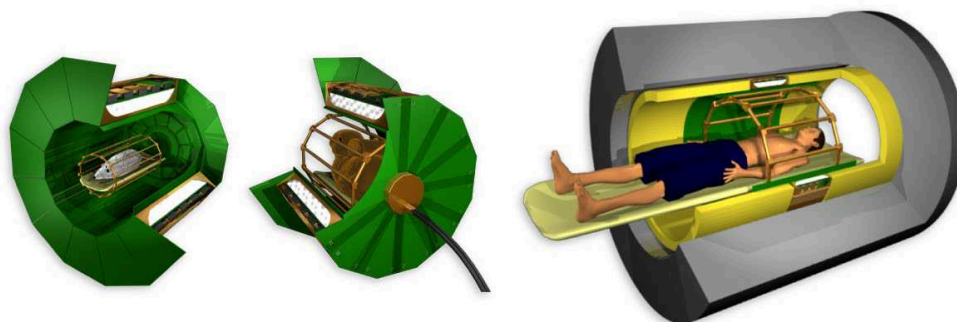


Figure 186: Concept sketches of the planned preclinical PET insert with coils for mice (left) and rabbits (middle, backside view), and a clinical ring mounted in the space of a split gradient coil (right).

My responsibility was to design the SPU, the synchronization of the SDMs, the power supply concept, the control software, and the overall MRI compatibility. In 2009, I took over the project coordination for the Aachen part of the preclinical insert. The firmware was programmed in Aachen by Pierre Gebhardt and Manfred Zinke, with the help of Stephan Borucki-Haefner and Eduard Buchnitzki. The insert mechanics were made under our guidance by the mechanical workshop, primarily Wolfgang Renz and Andreas Poqué. I programmed the control software, while the data acquisition and processing software were written by Benjamin Goldschmidt. The system calibration and PET performance analysis calculation were done by Christoph Lerche. The image reconstruction software was based on an existing package and programmed by André Salomon.

Outside Aachen, the system was simulated by the team of Stefaan Vandenberghe (Ghent University, Belgium). The electrical part of the RF coil was built by Daniel Wirtz from Philips Research, Hamburg.

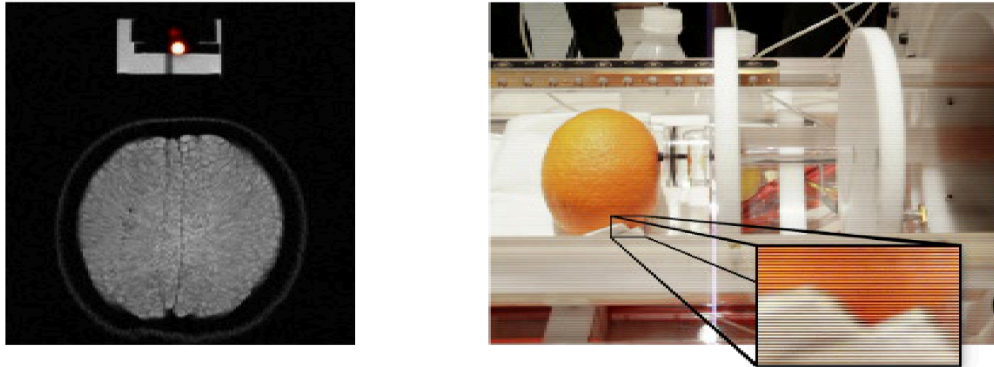


Figure 187: First simultaneous PET/MR image ever made with the Hyperion I system (left), and a photo of the setup (right), which is the last photo that camera ever took, since the camera (unlike the PET insert) was not MRI compatible (zoomed section shows the first defects as black and darkened lines).

After initial tests at Philips Medical Systems (Best, the Netherlands, see Figure 187) and the Uniklinik Aachen, the final preclinical insert was installed at King's College London (KCL, United Kingdom). There, a PET characterization of the system was performed by Jane E. Mackewn. Georgios M. Soultanidis used the system for motion compensation demonstrations, and the first in vivo measurements were made with the help of Kavitha Sunasse. At the end of 2013, the insert was transported to Philips Research, Eindhoven, where, after a phase of maintenance (repairs, updates, and improvements), I performed the final PET/MRI compatibility tests presented in this thesis.

In 2010/2011, three research projects that had a shared goal (among others) of developing a high-performance preclinical PET/MRI insert were begun: The ForSaTum project (grant number z0903ht014g), co-funded by the German federal state North Rhine Westphalia (HighTech.NRW) and the European Union (European Regional Development Fund: Investing In Your Future); the Sublima project (grant number 241711, successor of the HYPERImage project); and a project of the Center of Excellence in Medical Engineering (MEC) funded by the Wellcome Trust and EPSRC (grant number WT 088641/Z/09/Z). Again, as a project leader, it was my responsibility to develop the digital successor of the insert and to build three prototypes. This includes all system architecture and MR compatibility aspects presented in this thesis (e.g., power supply and synchronization). Aside from that, I personally designed all custom-made PCBs (excluding the two stack PCBs). The digital detector stack, including the new cooling pipes, was made by Peter Düppenbecker, who also developed the carbon fiber RF shield (Düppenbecker, n.d.). Integration of the digital sensors and all firmware designs were realized by Pierre Gebhardt (Gebhardt, n.d.) with the help of Lars Dues and Hubert Bessems (formally Irmato Industrial Solutions, Aachen, Germany), as well as Hennie van de Poel from Philips Research, Eindhoven. Christoph Lerche realized the optical interfaces.

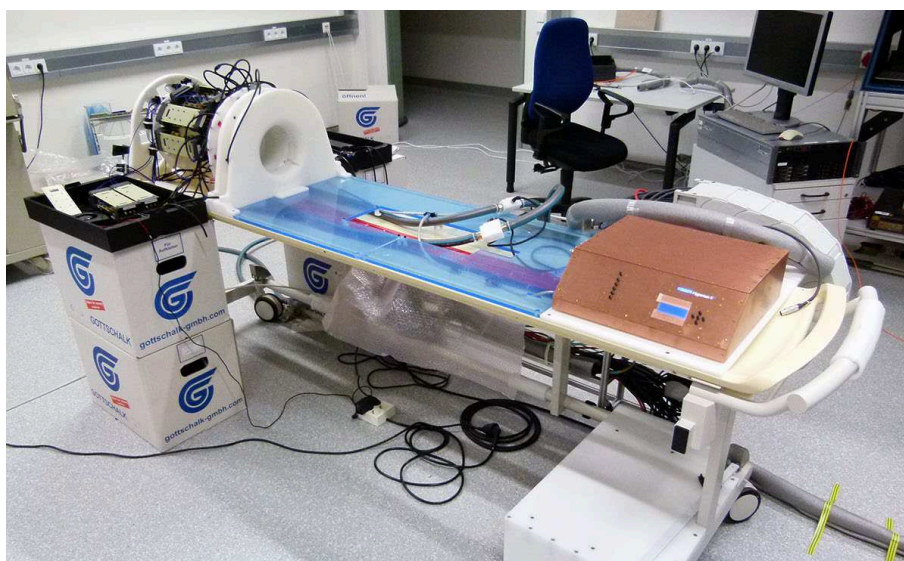


Figure 188: System integration phase of Hyperion II^D with all SDMs connected. The SDMs are open, and the lower modules are placed next to the gantry to have access for debugging.

The mechanical design and production was carried out under my guidance by Wolfgang Renz and Katharina Schumacher (both formerly Irmato Industrial Solutions). Daniel Wirtz (from Philips Research Hamburg) improved the electronics for the ^1H RF coils. The $^1\text{H}/^{19}\text{F}$ coil was built by Christian Findekle (Philips Research Hamburg), with funding from InnoMeT (grant number z0909im008a). The capacitor arrangement around the shielding plate of the power supply was optimized by Walter Ruetten. I continued to enhance the control software and Benjamin Goldschmidt improved the data acquisition software. PET data analysis, processing, calibration, and PET performance analysis was done by David Schug (Schug, n.d.). MRI optimizations (such as writing patches for the MRI used in the gradient detection measurements or enabling the ^{19}F -MRI measurement) were performed by Jakob Wehner. He also realized a more detailed analysis of the MRI compatibility, thereby extending the scope of this thesis (e.g., maps of phase errors in the FOV caused by eddy currents). The results are shown in (Wehner, n.d.).

Before the final installation of the systems in the Uniklinik Aachen and at the King's College London, the systems were installed at the former Life Science Facility (LSF) of the High Tech Campus in Eindhoven. There they were tested and improved, and there I performed all the system PET/MRI measurements here presented (components tests, such as in Figure 120, were made in the Uniklinik Aachen). I gratefully thank Suzanne Kivits (formerly of Philips Research, Eindhoven) for ^{18}F -FDG phantom filling. The in vivo experiments (and ethics committee approval) were organized by Iris Verel and executed with help in animal handling from Caren van Kammen (formerly Maastricht University). The MRI cardiac CINE measurements (Figure 189) of the mouse heart were realized with the help of Edwin Heijman. The cover backgrounds base on vector art from Freepik.com. Special thanks are due to Volkmar Schulz, who was the principle investigator of both inserts and guided the preparation of the scientific publications, as well as the completion of this thesis.

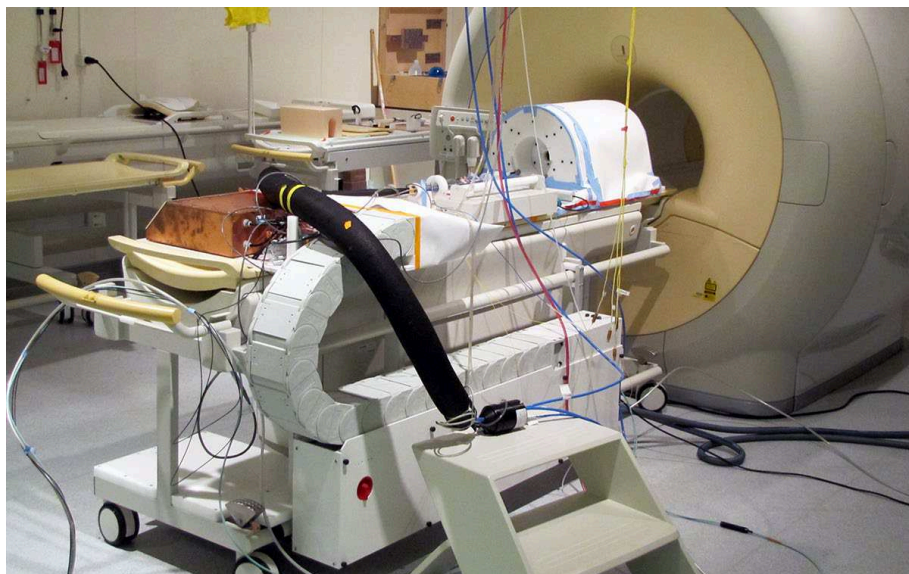


Figure 189: Photo of the system at the LSF before an in vivo measurement (with all additional cables and tubing needed for the animal handling and the dual-gated cardiac CINE images)

Additionally, I would like to thank my wife Ariane for her enduring patience, for her sympathy, and for her constant encouragements.

Abbreviations

The following table lists used and related abbreviations, acronyms, and names:

Abbreviation	Definition
¹⁸F-FDG	¹⁸ F-Fluorodesoxyglucose
ADC	Analog-to-Digital Converter
AMIDE	Amide's a Medical Imaging Data Examiner
APD	Avalanche Photo Diode
ASIC	Application-Specific Integrated Circuit
BackBone	Internal name for the central synchronization unit
BGO	Bismuth Germinate (Bi ₄ Ge ₃ O ₁₂)
BNC	Bayonet Neill Concelman (Coaxial FR connector)
BOLD	Blood Oxygenation Level Dependent
CAR	Department of Clinical Application Research
CDAS	C - Data Acquisition System (MRI data acquisition system)
CEO	Chief Executive Officer
CINE	CINEmatic imaging sequence producing frames of a repetition
CLK	Clock
CMOS	Complementary Metal-Oxide-Semiconductor
COG	Center-Of-Gravity
COG-ACE	COG - Automatic Corner Extrapolation
CRC	Contrast Recovery Coefficient
CRT	Coincidence Resolution Time
CT	Computer Tomography
CTO	Chief Technology Officer
DAC	Digital-to-Analog Converter
DAPS	Data Acquisition and Processing Server
DICOM	Digital Imaging and Communications in Medicine
DLL	Delay-Locked Loop
DOI	Depth-Of-Interaction
DOI	Digital Object Identifier
DPC	Digital Photon Counter (Philips name for dSiPM)
dSiPM	digital Silicon Photomultiplier
ECG	Electrocardiography
EMC	Electromagnetic compatibility
EMI	Electromagnetic Interference
EPI	Echo Planar Imaging
ExMI	Department of Experimental Molecular Imaging
FA	Flip Angle
FBK	Fondazione Bruno Kessler
FBP	Filtered Back Projection
FDG	Fluorodesoxyglucose

Abbreviation	Definition
FFE	Fast Field Echo (Philips term for a gradient echo MRI sequence)
FID	Free Induction Decay
FIFO	First In - First Out
FMC	FPGA Mezzanine Card
ForSaTum	Forschungssatellit für eine beschleunigte Umsetzung neuer Tumorbehandlungskonzepte
FOV	Field Of View
FP	Floating Point
FPGA	Field- Programmable Gate Array
FWHM	Full Width Half Maximum, related to the standard deviation σ of a Gaussian function as: $FWHM = \sqrt{8\log_e 2}\sigma$
G NLD	Crusher gradient (G) for the Noise Level Determination
GaA	Gallium Arsenide
GE	Gradient Echo
GND	Ground (in an electronic circuit)
GSO	Cerium-doped gadolinium oxyorthosilicate Gd ₂ SiO ₅ :Ce
GTX	Gigabit Transceiver - X (Xilinx gigabit transceiver hardcore)
GUI	Graphical User Interface
HDMI	High-Definition Multimedia Interface
HVL	Half Value Layer
Hyperion	A titan from the Greek mythology. Second generation after Chaos and father of Helios
IC	Integrated Circuits
ICBE	Internal Committee for Biomedical Experiments
IEEE	Institute of Electrical and Electronics Engineers
IP	Internet Protocol
IPA	India Pale Ale
ISMRM	International Society for Magnetic Resonance in Medicine
JTAG	Joint Test Action Group
KCL	King's College London
LC	Optical Gigabit Ethernet connector standard
LDO	Low-Dropout Regulator
LED	Light Emitting Diode
LOR	Lines Of Response
LSF	Life Science Facility
LSO	Cerium-doped lutetium oxyorthosilicate Lu ₂ SiO ₅ :Ce
LVDS	Low Voltage Differential Signaling
LYSO	Cerium-doped lutetium yttrium oxyorthosilicate LuYSiO ₅ :Ce
MEC	Center of Excellence in Medical Engineering
MEMS	Micro-Electro-Mechanical Systems
MIC	Medical Imaging Conference
ML	Maximum Likelihood

Abbreviation	Definition
MLEM	Maximum-Likelihood Expectation Maximization
MLEM-RM	MLEM Resolution Modelling
ML-PE	ML Positioning Estimation
MN	Multi-Nuclei
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRI	Repetition Time
MTP	An optical connector standard
NAS	Network Attached Storage
NECR	Nose Equivalent Count Rate
NEMA	National Electrical Manufacturers Association
NIC	Network Interface Cards
NSA	Number of Signals Averaged
NSS	Nuclear Science Symposium
PBS	Phosphate-Buffered Saline
PCB	Printed Circuit Boards
PD	Proton-Density
PDE	Photo-Detection Efficiency
PET	Positron Emission Tomography
PhF	Phantom Fluid
PIU	Percent Image Uniformity
PLL	Phase-Locked Loop
PMI	Physics of Molecular Imaging
PMI	Physics of Molecular Imaging
PMMA	PolyMethyl MethAcrylate (= acrylic glass or Plexiglas)
PMT	Photo Multiplier Tubes
PNS	Peripheral Nerve Stimulation
POF	Plastic Optical Fibers
POM-C	Polyoxymethylene Copolymer
PSAPD	Position Sensitive Avalanche Photo Diodes
PSRR	Power Supply Rejection Ratio
PVA	PolyVinyl Alcohol
QBC	Quadrature Body Coil
QDC	Energy-to-Digital Converter
RAID	Redundant Array of Independent Disks
RCLED	Resonant-Cavity Light Emitting Diode
RefCLK	Reference clock
RF	Radio Frequency
ROI	Region Of Interest
RTU	Remote Trigger Unit
RWTH	Rheinisch-Westfälische Technische Hochschule Aachen

Abbreviation	Definition
SAW	Surface Acoustic Wave
SDM	Singles Detection Module
SE	Spin Echo
SF	Scatter Fraction
SFNR	Signal-to-Fluctuation-Noise Ratio
SFP	Small Form-factor Pluggable (transceiver standard)
SI	Système international d'unités
SiPM	Silicon Photomultiplier
SMA	SubMiniature version A (RF connector standard)
SMD	Surface-Mounted Device
SNR	Signal to Noise Ratio
SPAD	Single Photon Avalanche Diode
SPECT	Single Photon Emission Computed Tomography
SPI	Serial Peripheral Interface
SPICE	Simulation Program with Integrated Circuit Emphasis
SPIR	Spectral Presaturation pulse with Inversion Recovery (MRI sequence)
SPU	Singles Processing Unit
SSFP	Steady-State Free Precession
SUV	Standardized Uptake Values
SWIFT	Method for zero TE imaging (MRI sequence)
Sync	Synchronization pulse
TCP	Transmission Control Protocol
TDC	Time-to-Digital Converter
TE	Echo Time
TF	True Flight
TFE	Turbo Field Echo
TOF	Time-Of-Flight
TSE	Turbo Spin Echo (MRI sequence)
UDP	User Datagram Protocol
UH	University of Heidelberg
UMC	United Microelectronics Corporation
USB	Universal Serial Bus
VCM	Common-Mode Voltage
VCO	Voltage Controlled Oscillator
VDD	Positive supply voltage
VDDA	Positive supply voltage for Analog circuits
VECSEL	Vertical-External-Cavity Surface-Emitting-Laser
VRMS	Volume Root Mean Square

Publications and Patents

During the work on the thesis, publications of the current state of the research were made. The first section lists publications and patents that were directly extracted from this thesis (i.e., I am the leading author). The second section lists publications related to this work (i.e. I am a co-author).

Publications from this Thesis

This chapter lists scientific research publications and patent publications that were directly extracted from this thesis (i.e., I am the leading author).

Peer-reviewed Research Articles

The following publications thus represent parts of this thesis. Although the publications list multiple co-authors due to their contributions (see chapter 1), there are no shared first authorships.

- MR Compatibility Aspects of a Silicon Photomultiplier-Based PET/RF Insert With Integrated Digitisation
Bjoern Weissler, Pierre Gebhardt, Christoph Lerche, Jakob Wehner, Torsten Solf, Benjamin Goldschmidt, Jane Mackewn, Paul Marsden, Fabian Kiessling, Michael Perkuhn, Dirk Heberling, and Volkmar Schulz
 Physics in Medicine and Biology (PMB), 2014, Vol. 59, Issue 17, pp. 5119–5139, (Weissler *et al.*, 2014b), 25 citations until April 2016.
 Featured article with additional publication in “Medical Physics Web”¹³ and “Aunt Minnie Europe”¹⁴
- PET/MR Synchronization by Detection of Switching Gradients
Bjoern Weissler, Pierre Gebhardt, Christoph Lerche, Georgios Soultanidis, Jakob Wehner, Dirk Heberling, and Volkmar Schulz
 IEEE Transactions on Nuclear Science (TNS), 2015, Vol. 62, Issue 3, pp. 650-657, Open Access publishing under a Creative Commons Attribution 3.0 License, (Weissler *et al.*, 2015b), 4 citations until April 2016.
- A Digital Preclinical PET/MRI Insert and Initial Results
Bjoern Weissler, Pierre Gebhardt, Peter Dueppenbecker, Jakob Wehner, David Schug, Christoph Lerche, Benjamin Goldschmidt, Andre Salomon, Iris Verel, Edwin Heijman, Michael Perkuhn, Dirk Heberling, Rene Botnar, Fabian Kiessling, and Volkmar Schulz
 IEEE Transactions on Medical Imaging (TMI), 2015, Vol. 34, Issue 11, pp.2258-2270, Open Access publishing under a Creative Commons Attribution 3.0 License, (Weissler *et al.*, 2015a), 13 citations until April 2016.

¹³ <http://medicalphysicsweb.org/cws/article/research/58345>

¹⁴ <http://www.auntminnieeurope.com/index.aspx?sec=prtf&sub=def&itemId=610391>

Featured article with additional publication on the journals website¹⁵.

Presentations at International Research Conferences

The following presentations were given at international research conferences:

- Design Concept of World's First Preclinical PET/MR Insert with Fully Digital Silicon Photomultiplier Technology
Bjoern Weissler, Pierre Gebhardt, Peter Dueppenbecker, Benjamin Goldschmidt, Andre Salomon, David Schug, Jakob, Wehner, Christoph Lerche, Daniel Wirtz, Wolfgang Renz, Katharina Schumacher, Ben Zwaans, Paul Marsden, Fabian Kiessling and Volkmar Schulz
 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2012, pp. 2113-2116, (Weissler *et al.*, 2012a), 22 citations until March 2016.
 Talk M02-3 in joint session, Nominated for Best Student Award
- An MR-Compatible Singles Detection and Processing Unit for Simultaneous Preclinical PET/MR
Bjoern Weissler, Pierre Gebhardt, Manfred Zinke, Fabian Kiessling and Volkmar Schulz
 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2012, pp. 2759-2761, (Weissler *et al.*, 2012a), 16 citations until March 2016.
 Poster M10-66
- World's First Preclinical 3T PET/MR Insert with Fully Digital Silicon Photomultiplier Technology
Bjoern Weissler, Peter Dueppenbecker, Pierre Gebhardt, Andre Salomon, Benjamin Goldschmidt, Paul Marsden, Fabian Kießling, Volkmar Schulz
 World Molecular Imaging Congress (WMIC), 2012
 Poster P365
- PET/MR Synchronization by Detection of Switching Gradients
Bjoern Weissler, Pierre Gebhardt, Christoph Lerche, Georgios Soultanidis, Jakob Wehner, Dirk Heberling, Volkmar Schulz
 Conference on PET/MR and SPECT/MR (PSMR), 2014, (Weissler *et al.*, 2014a)
 Talk 1-3, Price for Best Oral Presentation

Patents and Patent Applications

The following list shows granted patents and ongoing patent applications:

- Data Detection Device for Use in Combination with an MRI Apparatus
Bjoern Weissler, Manfred Zinke
 Koninklijke Philips N.V.

¹⁵ <http://www.ieee-tmi.org> and <http://www.ieee-tmi.org/fast-facts/featured-article.asp?id=10&title=A-Digital-Preclinical-PET/MRI-Insert-and-Initial-Results>

United States Patent Application Publication, US 20150002150 A1, Feb. 06, 2013, (Weissler and Zinke, 2015)

Further publications as: CN 104105979 A, EP 2812717 A1, WO 2013118060 1

Original invention disclosure title: “GradientSync”

- Method and System for Synchronizing Positron Emission Tomography (PET) Detector Modules

Bjoern Weissler, Pierre Gebhardt

Koninklijke Philips N.V.

United States Patent Application Publication, US 20150014545 A1, Jan. 15, 2015, (Weissler and Gebhardt, 2015)

Further publications as: CN 104136939 A, EP 2820450 A2, WO 2013128363 A2, WO 2013128363 A3

- Reducing Interference in a Combined Assembly for MRI and Nuclear Imaging System

Bjoern Weissler, Pierre Gebhardt, Jacob Wehner, Volkmar Schulz

Koninklijke Philips N.V., Kings College London

World Intellectual Property Organization Patent Application, WO 2015007593 A1, Jul. 09, 2014, (Weissler *et al.*, 2014c)

- Reducing Interference in a Combined System Comprising an MRI System and a Non-MR Imaging System

Bjoern Weissler, Volkmar Schulz, Pierre Gebhardt, Peter Dueppenbecker, Christoph Lerche

Koninklijke Philips N.V., Philips Deutschland GmbH

World Intellectual Property Organization Patent Application, WO 2014064286 A1, Oct. 28, 2013, (Weissler *et al.*, 2013)

- Thermally Stabilized PET Detector for Hybrid PET-MR System

Michael Morich, Gordon DeMeester, Jerome Griesmer, Torsten Solf, Volkmar Schulz, Bjoern Weissler

Koninklijke Philips Electronics N.V.

United States Patent, US 8378677 B2, Feb. 19, 2013, (Morich *et al.*, 2013)

Further publications as: CN 101688916 A, CN 101688916 B, CN 102749640 A, CN 104316953 A, EP 2176683 A2, US 2010018808 A2, WO 2009004521 A2, WO 2009004521 A3

Merged from invention disclosure “Heat Pipe Module for digital PET and PET/MR” of Bjoern Weissler, Torsten Solf, and Volkmar Schulz, in Oct. 24, 2007

- Flexible Connectors for PET Detectors

Jinling Liu, Bjoern Weissler, Steven R. Martin, Volkmar Schulz, Pierre Gebhardt, Peter Michael Dueppernbecker, Wolfgang Renz

Koninklijke Philips Electronics N.V.

United States Patent Application Publication, US 20140312238 A1, Oct. 23, 2014, (Liu *et al.*, 2014)

Further publications as: CN 104067146 A, EP 2798374 A2, WO 2013098725 A2, WO 2013098725 A3

Mainly based on the original invention disclosure “PET-FlexStack” of Bjoern Weissler, Volkmar Schulz, Pierre Gebhardt, Peter Michael Dueppenbecker, and Wolfgang Renz, in Jun. 14, 2011

Related Publications

This section lists publications related to this work (i.e. I am a co-author).

Peer-reviewed Research Articles

- Calibration and Stability of a SiPM-based Simultaneous PET/MR Insert
Christoph Lerche, Jane Mackewn, Benjamin Goldschmidt, Andre Salomona, Pierre Gebhardt, *Bjoern Weissler*, Richard Ayres, Paul Marsden, and Volkmar Schulz
Nuclear Instruments and Methods in Physics Research Section A (NIMA), 2013, Vol. 702, pp. 50-53, (Lerche *et al.*, 2013b)
- PET/MRI Insert Using Digital SiPMs: Investigation of MR-Compatibility
Jakob Wehner, *Bjoern Weissler*, Peter Dueppenbecker, Pierre Gebhardt, David Schug, Walter Ruetten, Fabian Kiessling, and Volkmar Schulz
Nuclear Instruments and Methods in Physics Research Section A (NIMA), 2014, Volume 734, pp. 116-121, (Wehner *et al.*, 2014b)
- Data Processing for a High Resolution Preclinical PET Detector Based on Philips dSiPM Digital SiPMs
David Schug, Jakob Wehner, Benjamin Goldschmidt, Christoph Lerche, Peter Michael Dueppenbecker, Patrick Hallen, *Bjoern Weissler*, Pierre Gebhardt, Fabian Kiessling, and Volkmar Schulz
IEEE Transactions on Nuclear Science (TNS), 2015, Volume 62, Issue 3, pp. 669-678, (Schug *et al.*, 2015c)
- RESCUE - Reduction of MR-SNR-Degradation by Using an MR-Synchronous Low Interfering PET Acquisition Technique
Pierre Gebhardt, *Bjoern Weissler*, Jakob Wehner, Thomas Frach, Paul Marsden, and Volkmar Schulz
IEEE Transactions on Nuclear Science (TNS), 2015, Volume 62, Issue 3, pp. 634-643, (Gebhardt *et al.*, 2015)
- ToF Performance Evaluation of a PET Insert with Digital Silicon Photomultiplier Technology During MR Operation
David Schug, Jakob Wehner, Peter Michael Dueppenbecker, *Bjoern Weissler*, Pierre Gebhardt, Benjamin Goldschmidt, Torsten Solf, and Volkmar Schulz
IEEE Transactions on Nuclear Science (TNS), 2015, Volume 62, Issue 3, pp. 658-663, (Schug *et al.*, 2015b)
- PET Performance Evaluation of a Pre-Clinical SiPM-Based MR-Compatible PET Scanner
Jane Mackewn, Christoph Lerche, *Bjoern Weissler*, Kavitha Sunassee, Rafael de Rosales, Alkystis Phinikaridou, Andre Salomon, Richard Ayres, Charalampos

Tsoumpas, Georgios Soultanidis, Pierre Gebhardt, Tobias Schaeffter, Paul Marsden, and Volkmar Schulz

IEEE Transactions on Nuclear Science (TNS), 2015, Volume 62, Issue 3, pp. 784-790, (Mackewn *et al.*, 2015a)

- PET Performance and MRI Compatibility Evaluation of a Digital, ToF-Capable PET/MRI Insert Equipped with Clinical Scintillators

David Schug, Jakob Wehner, Peter Dueppenbecker, *Bjoern Weissler*, Pierre Gebhardt, Benjamin Goldschmidt, Andre Salomin, Fabian Kiessling, and Volkmar Schulz

Physics in Medicine and Biology (PMB), 2015, Vol. 60, Issue 6, pp. 2231-2255, (Wehner *et al.*, 2015)

- MR-Compatibility Assessment of the First Preclinical PET-MRI Insert Equipped with Digital Silicon Photomultipliers

Jakob Wehner, *Bjoern Weissler*, Peter Dueppenbecker, Pierre Gebhardt, Benjamin Goldschmidt, David Schug, Fabian Kiessling, and Volkmar Schulz

Physics in Medicine and Biology (PMB), 2015, Vol. 60, Issue 6, pp. 2231-2255, (Wehner *et al.*, 2015)

- Software-based Real-Time Acquisition and Processing of PET Detector Raw Data

Benjamin Goldschmidt, David Schug, Christoph Lerche, Andre Salomon, Pierre Gebhardt, *Bjoern Weissler*, Jakob Wehner, Peter Dueppenbecker, Fabian Kiessling, and Volkmar Schulz

IEEE Transactions on Biomedical Engineering (TBME), 2015, Vol. 63, Issue 2, pp. 316-327, (Goldschmidt *et al.*, 2015)

- Development of an MRI-compatible digital SiPM detector stack for simultaneous PET/MRI

Peter Dueppenbecker, *Bjoern Weissler*, Pierre Gebhardt, David Schug, Jakob Wehner, Paul Marsden, and Volkmar Schulz

Biomedical Physics & Engineering Express, 2016, Vol. 2, Issue 1, (Dueppenbecker *et al.*, 2016)

- Maximum likelihood positioning and energy correction for scintillation detectors

Christoph Lerche, André Salomon, Benjamin Goldschmidt, Sarah Lodomez, *Bjoern Weissler*, and Torsten Solf

Physics in Medicine and Biology (PMB), 2016, Vol. 61, Issue 4, pp. 1650, (Lerche *et al.*, 2016)

- Initial PET Performance Evaluation of a Preclinical Insert for PET/MRI with Digital SiPM Technology

David Schug, Christoph Lerche, *Bjoern Weissler*, Pierre Gebhardt, Benjamin Goldschmidt, Jakob Wehner, Peter Dueppenbecker, Andre Salomon, Patrick Hallen, Fabian Kiessling, and Volkmar Schulz

Physics in Medicine and Biology (PMB), 2016, Vol. 61, Issue 7, pp. 2851-2878, (Schug *et al.*, 2016)

- FPGA-based RF interference reduction techniques for simultaneous PET-MRI

Pierre Gebhardt, Jakob Wehner, *Bjoern Weissler*, Rene Botnar, Paul Marsden, and Volkmar Schulz

Physics in Medicine and Biology (PMB), 2016, Vol. 61, Issue 9, pp. 3500-3526, (Gebhardt *et al.*, 2016)

Presentations at International Research Conferences

- A Preclinical PET/MR Insert for a Human 3T MR Scanner

Volkmar Schulz, Torsten Solf, *Bjoern Weissler*, Pierre Gebhardt, Peter Fischer, Michael Ritzert, Viacheslav Mlotok, Claudio Piemonte, Nicola Zorzi, Mirko Melchiorri, Stefaan Vandenberghe, Vincent Keereman, Tobias Schaeffter, and Paul Marsden

IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2009, pp. 2577-2579, (Schulz *et al.*, 2009)

- Solid-State Detector Stack for ToF-PET/MR

Torsten Solf, Volkmar Schulz, *Bjoern Weissler*, Andreas Thon, Peter Fischer, Michael Ritzert, Viacheslav. Mlotok, Claudio. Piemonte, Nicola. Zorzi

IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2009, pp. 2798-2799, (Solf *et al.*, 2009)

- SiPM Based Preclinical PET/MR Insert for a Human 3T MR: First Imaging Experiments

Volkmar Schulz, *Bjoern Weissler*, Pierre Gebhardt, Torsten Solf, Christoph Lerche, Peter Fischer, Michael Ritzert, Viacheslav Mlotok, Claudio Piemonte, Benjamin Goldschmidt, Stefaan Vandenberghe, Andre Salomon, Tobias Schaeffter, and Paul Marsden

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- Calibration and Stability of a SiPM-based Simultaneous PET/MR Insert

Christoph Lerche, Jane Mackewn, Benjamin Goldschmidt, Andre Salomona, Pierre Gebhardt, *Bjoern Weissler*, Richard Ayres, Paul Marsden, and Volkmar Schulz

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- First Evaluations of the Neighbor Logic of the Digital SiPM Tiles

David Schug, Peter Dueppenbecker, Pierre Gebhardt, *Bjoern Weissler*, Ben Zwaans, Fabian Kiessling, and Volkmar Schulz

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- Development of an MRI Compatible Digital SiPM based PET Detector Stack for Simultaneous Preclinical PET/MRI

Peter Dueppenbecker, *Bjoern Weissler*, Pierre Gebhardt, David Schug, Jakob Wehner, Paul Marsden, and Volkmar Schulz

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- FPGA-based Singles and Coincidences Processing Pipeline for Integrated Digital PET/MR Detectors
 Pierre Gebhardt, *Bjoern Weissler*, Manfred Zinke, Fabian Kiessling, Paul Marsden, and Volkmar Schulz
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- MR Image Quality and Timing Resolution of an Analog SiPM Based Pre-clinical PET/MR Insert
 Christoph Lerche, Jane Mackewn, Richard Ayres, *Bjoern Weissler*, Pierre Gebhardt, Torsten Solf, Benjamin Goldschmidt, Andre Salomon, Kavitha Sunassee, Paul Marsden and Volkmar Schulz
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- Demonstration of Motion Correction for PET-MR with PVA Cryogel Phantoms
 Georgios Soultanidis, Irene Polycarpou, *Bjoern Weissler*, Christoph Lerche, Jane Mackewn, Richard Ayres, Charalampos Tsoumpas, Volkmar Schulz, and Paul Marsden
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- First PET Performance Evaluation of the World's First Preclinical PET/MR Insert with Fully Digital Silicon Photomultiplier Technology
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- MR-Compatibility Study of a Preclinical, Fully Digital PET/MRI Insert
 Jakob Wehner, *Bjoern Weissler*, Peter Dueppenbecker, Pierre Gebhardt, Walter Ruetten, David Schug, Fabian Kiessling, and Volkmar Schulz
 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2013, Poster J2-7
- RF Interference Reduction for Simultaneous Digital PET/MR Using an FPGA-based, Optimized Spatial and Temporal Clocking Distribution
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- Data Processing Techniques and PET Performance Evaluation of a Preclinical PET/MR Insert with Digital Silicon Photomultiplier Technology
David Schug, Christoph Lerche, *Bjoern Weissler*, Pierre Gebhardt, Benjamin Goldschmidt, Jakob Wehner, Peter Dueppenbecker, Fabian Kiessling, Volkmar Schulz
IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2014, Poster M21-2
- Hybrid PET/MRI Insert: B₀ Field Optimization by Applying Active and Passive Shimming on PET Detector Level
Jakob Wehner, *Bjoern Weissler*, and Volkmar Schulz
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- ToF Performance Evaluation of a PET Insert with Digital Silicon Photomultiplier Technology During MR Operation
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- Hybrid PET/MRI Insert: B₀ Field Optimization by Applying Active and Passive Shimming on PET Detector Level
Jakob Wehner, *Bjoern Weissler*, and Volkmar Schulz
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- PET/MRI Insert Using Digital SiPMs: Investigation of MR-compatibility
Jakob Wehner, *Bjoern Weissler*, Peter Dueppenbecker, Pierre Gebhardt, David Schug, Walter Ruetten, Fabian Kiessling, and Volkmar Schulz
Conference on PET/MR and SPECT/MR (PSMR), 2013, (Wehner *et al.*, 2014b)
- RESCUE - Reduction of MR-SNR-Degradation by Using an MR-Synchronous Low Interfering PET Acquisition Technique
Pierre Gebhardt, *Bjoern Weissler*, Jakob Wehner, Thomas Frach, Paul Marsden, and Volkmar Schulz
Conference on PET/MR and SPECT/MR (PSMR), 2014, (Gebhardt *et al.*, 2014)
- PET Performance Evaluation of a Preclinical Digital PET/MRI Insert
David Schug, Christoph Lerche, Peter Dueppenbecker, Pierre Gebhardt, Benjamin Goldschmidt, Andre Salomon, Jakob Wehner, *Bjoern Weissler*, Fabian Kiessling, and Volkmar Schulz
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- Hyperion IIP^D - A Digital Preclinical PET/MRI Insert
Bjoern Weissler, David Schug, Pierre Gebhardt, Jakob Wehner, Benjamin Goldschmidt, Andre Salomon, Peter Dueppenbecker, Patrick Hallen, Fabian Kiessling, and Volkmar Schulz
 European Molecular Imaging Meeting (EMIM), 2015, Vortrag PS2/5
- Hyperion-IIP^D: A Preclinical PET/MRI Insert Using Digital Silicon Photomultipliers
 Jakob Wehner, *Bjoern Weissler*, David Schug, Peter Dueppenbecker, Pierre Gebhardt, Benjamin Goldschmidt, Andre Salomon, Rene Botnar, Fabian Kiessling, and Volkmar Schulz
 23rd International Society for Magnetic Resonance in Medicine Annual Meeting (ISMRM), Talk 0413

Patents and Patent Applications

- Apparatus and Method for the Evaluation of Gamma Radiation Events
 Christoph Lerche, Sarah Lodomez, Volkmar Schulz, *Bjoern Weissler*
 Koninklijke Philips N.V., Philips GmbH
 World Intellectual Property Organization Patent Application, Apr. 30, 2014, WO 2014180734 A3
- Inductively Powered Electric Component of an MRI Apparatus
 Eberhard Waffenschmidt, Achim Hilgers, Bert de Vries, *Bjoern Weissler*, Derk Reefman, Mark van Helvoort, Pieter Blanden
 Koninklijke Philips Electronics N.V.
 United States Patent, US 8866480 B2, Jun. 15, 2009, (Waffenschmidt *et al.*, 2014)
 Further publications as: CN 102066967 A, EP 2291672 A2, US 20110084694, WO 2009153727 A2, WO 2009153727 A3
- Magnetic Resonance Gradient Coil Iso-Plane Backbone for Radiation Detectors of 511keV
 Torsten Solf, Volkmar Schulz, *Bjoern Weissler*
 Koninklijke Philips Electronics N.V.
 United States Patent, US 8547100 B2, Oct. 01, 2013, (Solf *et al.*, 2013)
 Further publications as: CN 101960330 A, CN 101960330 B, EP 2247962 A2, EP 2247962 B1, US 20110018541, WO 2009107005 A2, WO 2009107005 A3
 Also published under the original name of the invention disclosure “Iso-Plane Backbone for PET/MR”
- Apparatus and Method for the Evaluation of Gamma Radiation Events
 Christoph Lerche, Sarah Lodomez, Volkmar Schulz, *Bjoern Weissler*
 Koninklijke Philips N.V., Philips GmbH
 World Intellectual Property Organization Patent Application, WO 2014180734 A3, May. 15, 2015, (Lerche *et al.*, 2015)

Related PhD Theses

- Development of a high-resolution, MRI-compatible PET detector using digital silicon photomultipliers
Peter Dueppenbecker, King's College London, intended for 2016.
- Design and Investigation of an FPGA-Based Data Acquisition and Control Architecture with MRI RF Interference Reduction Capabilities for Simultaneous PET/MRI Systems using Silicon Photo-multiplier Detectors
Pierre Gebhardt, Division of Imaging Sciences & Biomedical Engineering, King's College London, intended for 2016.
- About the Calibration and PET Performance of a preclinical PET/MRI insert equipped with digital Silicon Photomultipliers
David Schug, Department of Physics of Molecular Imaging (PMI) Institute of Experimental Molecular Imaging (ExMI), RWTH Aachen.
- About the MR compatibility of a preclinical PET/MRI insert equipped with digital Silicon Photomultipliers
Jakob Wehner, Department of Physics of Molecular Imaging (PMI) Institute of Experimental Molecular Imaging (ExMI), RWTH Aachen.

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Combining different medical imaging modalities into a single device is a promising way to attain comprehensive and complementary information. The seamless integration of Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) will additionally lead to excellent spatial and temporal registration capabilities and will reduce the overall scan time. The technical challenges that have to be solved are explained in this thesis, requirements for performance parameters are derived, and measuring methods to verify the achieved performances are defined. The challenges are addressed in two subsequently built preclinical PET/MRI inserts for clinical MRI scanner. The approach followed is to digitize the PET sensor signals as closely to the sensors as possible in order to maximize the PET signal-to-noise ratio. The digitization thus occurs directly within the PET detector modules, which are placed inside the MRI bore. In a second step, the sensors measure the signals directly digitally. The result is the world's first digital preclinical PET scanner, which is also the world's first digital PET/MRI system. The achieved spatial resolution in PET is higher than for all other simultaneous PET/MRI systems known, and is even similar to the best standalone PET scanners. Additionally, the accomplished PET coincidence time resolution introduces Time-Of-Flight-PET to preclinical applications. Undesired mutual influences between the two modalities are reduced to a minimum. The inserts demonstrate that the described approach of early digitization enables highest PET performance, and that the resulting MRI compatibility challenges can be solved by means of an elaborate system design.

