



Impact of Lung Pathologies on Bioimpedance Spectroscopy Measurements – An Experimental Study

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Abstract. The early detection of lung pathologies is crucial to improve the outcome of the patient, especially in critically ill, ventilated patients. For this, a continuous monitoring tool available at the bedside would be appreciated. One possible modality for this is Bioimpedance Spectroscopy (BIS), which measures the complex bioimpedance in a frequency range, typically from a few kHz up to 1 MHz.

In this paper, we present the results of an experimental validation study in 17 animals to use bioimpedance measurement for the detection and identification of lung pathologies. Three different groups are investigated: in the first two groups, acute respiratory distress syndrome (ARDS) was induced using either an infusion of lipopolysaccharide or repetitive lavages, respectively. The third group served as the control group, where no additional intervention took place. The results of the statistical analysis show that the distribution of impedance magnitude features is significantly different in the two pathological groups compared to the control group. Furthermore, the separation between the two pathological groups seems to be possible by feature combination. Hence, the results indicate that bioimpedance spectroscopy is a promising modality to enable bedside monitoring for lung pathology detection.

Keywords: Bioimpedance Spectroscopy, Bioimpedance Measurement, Lung Pathologies, ARDS, Animal Trial

1. Introduction

Lung pathologies, such as atelectasis, edema, or pneumonia are often life-threatening conditions, especially in critically ill, ventilated patients at the intensive care unit. If not detected and treated at an early stage, these can develop into an acute respiratory distress syndrome (ARDS), which is a life-threatening condition [Thompson et al., 2017]. Currently, these pathologies are detected by arterial blood gas test, x-ray, computed tomography (CT), sonography, or a combination of these modalities [American Thoracic Society and Infectious Diseases Society of America, 2005; Khan et al., 2009; Marquette et al., 1995]. However, all these techniques do not provide continuous results. Furthermore, depending on the patients' condition, they may be difficult to conduct as, for example, in CT, the patient has to be transported and would be exposed to radiation. Thus, early detection of the respective pathology is not guaranteed as the tests are either performed in a fixed interval or only if symptoms are already present. Hence, continuous monitoring able to detect those pathologies would be highly recommended. One possible modality for this is the measurement of bioimpedance.

Bioimpedance measurements as a monitoring tool showed promising results in various medical applications. One modality based on bioimpedance measurements is Electrical Impedance Tomography (EIT), where conductivity changes inside the body are mapped onto an image from repetitive bioimpedance measurements at different positions on the body surface. Applications for this are widely ranged covering lung monitoring [Aguiar Santos et al., 2018; Trepte et al., 2016], perfusion monitoring

[Hentze et al., 2018], brain monitoring [Malone et al., 2014], breast cancer detection [Akhtari-Zavare and Latiff, 2015] or bladder volume estimation [Schlebusch et al., 2014]. A different technique is Bioimpedance Spectroscopy (BIS), where, in contrast to classical EIT, impedance measurements are not only performed at a single current injection frequency but in a frequency range, typically from a few kHz to 1 MHz. Here, typical applications are the analysis of body composition [Kyle et al., 2004] and the measurement of body fluid volumes [Jaffrin and Morel, 2008; Moissl et al., 2006]. Additionally, BIS showed promising results as a fluid management system in heart failure [Weyer et al., 2014] and as a monitoring technique in dialysis [Ismail et al., 2014]. Both modalities and applications have the considerable advantage of being inexpensive, available at the bedside, and non-invasive. These properties would also be desirable in the context of lung pathology identification.

In this paper, we aim to investigate if bioimpedance spectroscopy measurements can help to detect and identify different lung pathologies. In previous work, we showed in simulations, that lung pathologies have a significant impact on the measured impedance data at specific electrode positions [Orschulik et al., 2018c]. Now, we present the results of an experimental validation study in a total of 17 animals (pigs).

This paper is structured as follows: in Section 2, Materials and Methods, we give the medical background. The concept of bioimpedance spectroscopy is introduced with an emphasis on the effect of adjusted electrode configurations on the measurement result. Furthermore, the animal trial setup is shown and the measurement strategy presented. In Section 3, we give both the medical and technical results and present a statistical analysis of the impedance data. In Section 4, the results are discussed and the limitations of the study are addressed. Finally, we draw our conclusions in Section 5.

Preliminary findings related to this article have been previously published at the 11th International Conference on Bioelectromagnetism (ICBEM2018) [Orschulik et al., 2018b].

2. Materials and Methods

2.1 Medical Background

The general idea of this work is to inspect if specific lung pathologies can be identified and detected using bioimpedance spectroscopy measurements. If not treated in an early stage, these pathologies might develop into an acute respiratory distress syndrome (ARDS), which is a severe condition. According to the Berlin definition, the severity of ARDS can be divided into four stages of severity using the Horovitz index, which is defined as the ratio of the partial pressure of oxygen in blood (P_{a,O_2} [mmHg]) and the fraction of oxygen in inhaled air (F_{i,O_2}) [Horovitz et al., 1974; Ranieri et al., 2012]:

- 300 mmHg < $P_{a,O_2}/F_{i,O_2}$: *no* ARDS
- 200 mmHg < $P_{a,O_2}/F_{i,O_2}$ < 300 mmHg : *mild* ARDS
- 100 mmHg < $P_{a,O_2}/F_{i,O_2}$ < 200 mmHg : *moderate* ARDS
- $P_{a,O_2}/F_{i,O_2}$ < 100 mmHg : *severe* ARDS

In practice, the Horovitz index can only be calculated by arterial blood gas analysis. Unfortunately, this is not possible continuously and is potentially harmful to the patient. Bioimpedance spectroscopy, in contrast, allows a continuous measurement, which might be especially beneficial in mechanically ventilated, critically ill patients at the intensive care unit. Thus, continuous detection of the severity and an identification of the underlying pathology using BIS would be highly appreciated.

2.2 Bioimpedance Spectroscopy

The general idea of Bioimpedance Spectroscopy (BIS) is to determine the complex impedance in a given frequency range, typically in the range between a few kHz to 1 MHz. This is done using a tetrapolar measurement setup, where a small, alternating current is injected into the body at two electrodes while the resulting voltage drop is measured across two different electrodes. The tetrapolar measurement setup has the advantage of widely eliminating the electrode skin impedance.

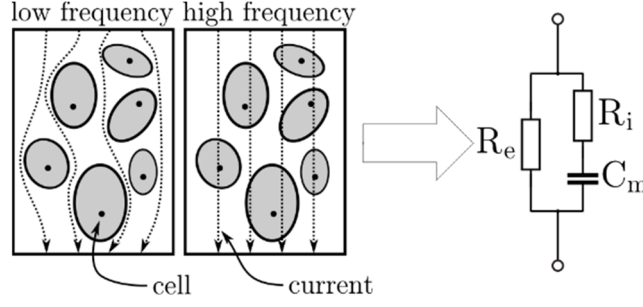


Figure 1: Current flow through biological tissue at low and high frequencies and electrical equivalent circuit [Schlebusch et al., 2010].

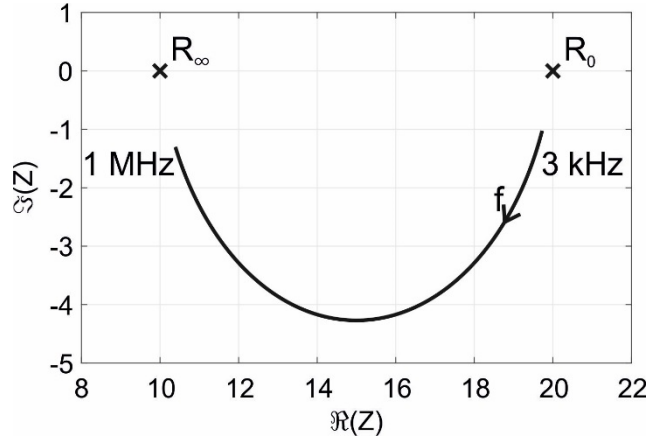


Figure 2: Sample shape of an impedance spectrum based on the Cole equation from Equation (1).

In the given frequency range, bioimpedance spectroscopy seeks to determine the effect of the cells, especially of the cell membrane, on the measured impedance. At low frequencies, the majority of the current flows through the extracellular space around the cells. As the cell membrane has a capacitive behavior, this changes at higher frequencies where the current flows through both the extra- and intracellular space. This characteristic is known as β -dispersion and is depicted in Figure 1, left.

Most commonly, this behavior is modeled by a three-component electrical equivalent circuit consisting of two resistors and one capacitor, which is known as the Debye model and depicted in Figure 1, right [Debye, 1929; Grimnes and Martinsen, 2005]. Later, this model was adjusted by an empirical constant leading to an equation for the frequency-dependent, complex tissue impedance known as the Cole equation [Cole, 1940]:

$$Z(f) = R_{\infty} + \frac{R_0 - R_{\infty}}{1 + (j \cdot 2\pi f \cdot \tau_z)^{\alpha}} \quad (1)$$

where R_0 is the resistivity at $f = 0$ Hz, R_{∞} the resistivity at $f \rightarrow \infty$ Hz, τ_z the characteristic time constant of the system and α an empirical constant. This equation results in a semicircular shaped impedance spectrum in the complex plane. Figure 2 shows a sample impedance spectrum derived from the Cole equation using the parameters $R_0 = 20 \Omega$, $R_{\infty} = 10 \Omega$, $\tau_z = 4 \mu s$ and $\alpha = 0.9$ in a frequency range from $f = 3$ kHz to $f = 1$ MHz. It should be noted that, due to the frequency range and the empirical constant α , the impedance spectrum does not intersect with the real axis. However, by analyzing and fitting the impedance spectrum to the model, the tissue parameters R_0 , R_{∞} , τ_z and α can be determined. For $\alpha = 1$, the Cole equation represents the Debye-model with the relation $R_e = R_0$, $R_i = R_0 || R_{\infty}$ and $\tau_z = R_i \cdot C_m$ [Simini and Bertemes-Filho, 2018].

Depending on the tetrapolar measurement setup, the measured impedance spectrum may vary from the actual tissue impedance. In particular, even though, typically, only resistive and capacitive

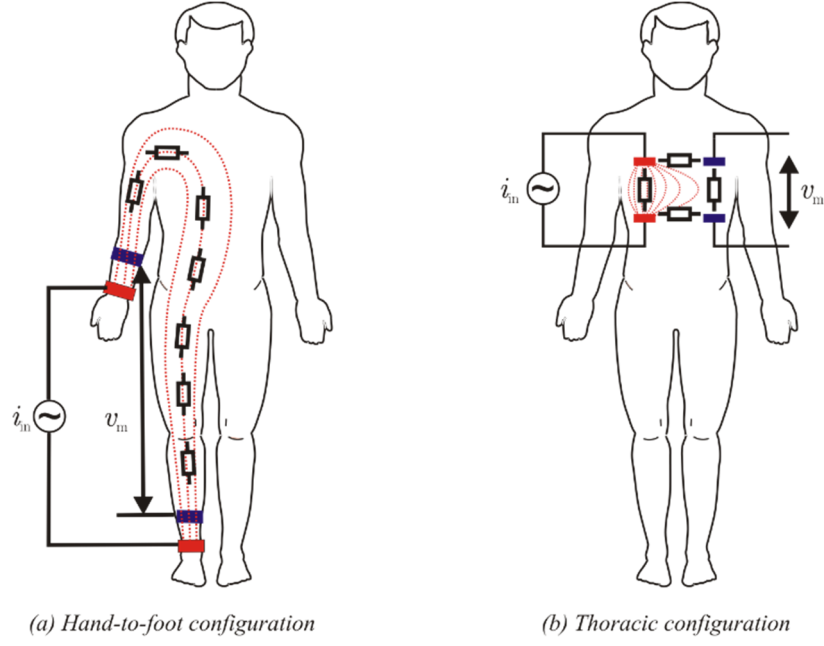


Figure 3: Exemplary electrode positions for hand-to-foot (left) and other thoracic configurations (right). Current injecting electrodes are depicted in red, voltage sensing electrodes in blue. Exemplary current density paths are shown in red dots.

components are present as tissue properties, impedance values representing inductive properties (positive phase value) may be present in the measured data. Commonly, these properties are taken as a sign of measurement and instrumentation errors, which certainly are a significant contributor to such unexpected behavior. However, these properties can additionally be explained by the fact that in the tetrapolar measurement setup, parts of the injected current do not flow through the measurement path but are bypassed through different regions [Callaghan et al., 2010; Grimnes and Martinsen, 2007].

In Figure 3, two different tetrapolar configurations are shown: a hand-to-foot configuration (Figure 3a), where two electrodes are placed on the hand and two electrodes are placed on the foot and a thoracic

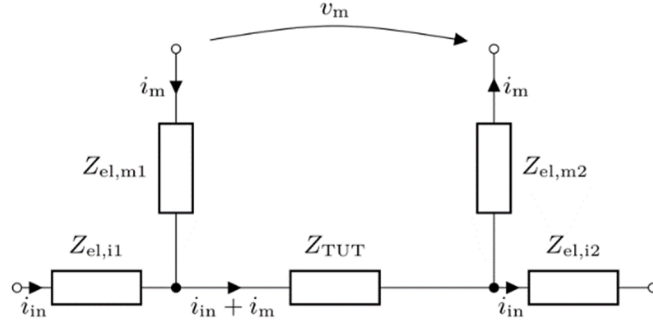


Figure 4: Tetrapolar measurement setup in hand-to-foot configuration with electrode impedances. The impedance of interest is Z_{TUT} (TUT = Tissue Under Test).

configuration (Figure 3b), where the electrodes are placed at the thorax. The current injection electrodes are depicted in red and the voltage sensing electrodes in blue. In the hand-to-foot configuration, almost the complete injection current flows through the measurement path. This configuration can be transferred to an equivalent circuit as shown in Figure 4, where Z_{TUT} is the impedance between the voltage sensing electrodes (TUT = Tissue Under Test) and Z_{el} the respective electrode skin impedance.

From this, the measured impedance Z can be derived as:

$$Z = \frac{v_m}{i_{in}} = \frac{i_{in} \cdot (Z_{TUT}) + i_m \cdot (Z_{el,m1} + Z_{TUT} + Z_{el,m2})}{i_{in}} \quad (2)$$

$\xrightarrow{i_m \ll i_{in}} Z_{TUT}$

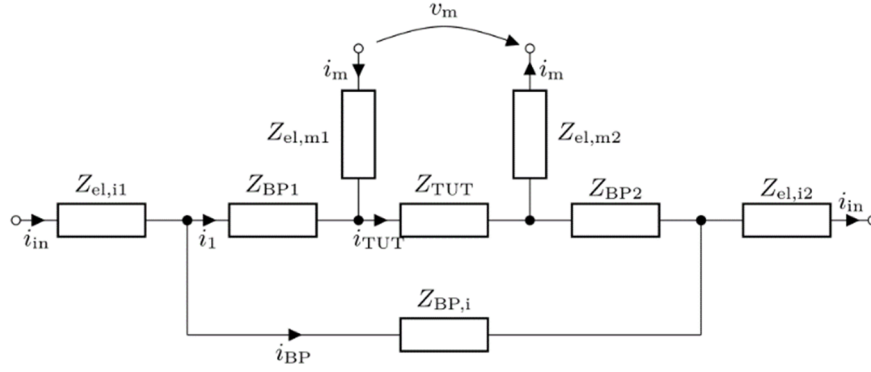


Figure 5: Tetrapolar measurement setup in the thoracic configuration with electrode impedances.

where i_{in} is the injected current and i_m is the necessary current to measure the voltage drop. It is apparent that, in this typical tetrapolar measurement setup, the impact of the electrode skin impedances is reduced and that the measured impedance is the actual impedance between the voltage sensing electrodes.

In the case of the thoracic configuration, however, a different scenario is present. Here, the appropriate equivalent circuit is shown in Figure 5. In addition to the impedance between the voltage sensing electrode pair Z_{TUT} and the electrode skin impedances Z_{el} , the impedance between the current injecting electrodes $Z_{BP,i}$ and the impedances between each respective current injecting and voltage sensing electrode $Z_{BP,1,2}$ are present. This leads to a different *measured* transfer function Z :

$$Z = \frac{v_m}{i_{in}} = \frac{Z_{TUT}}{i_{in}} \cdot \left(\frac{Z_{BP1} + Z_{BP,i} + Z_{BP2}}{Z_{TUT} + Z_{BP1} + Z_{BP,i} + Z_{BP2}} \cdot i_m + \frac{Z_{BP,i}}{Z_{TUT} + Z_{BP1} + Z_{BP,i} + Z_{BP2}} \cdot i_{in} \right) \quad (3)$$

$\xrightarrow{i_m \ll i_{in}} \frac{Z_{TUT} \cdot Z_{BP,i}}{Z_{TUT} + Z_{BP1} + Z_{BP,i} + Z_{BP2}}$

It is apparent that the *measured* transfer function Z is different from the impedance Z_{TUT} . Furthermore, if the phase of the denominator $\angle(Z_{TUT} + Z_{BP1} + Z_{BP,i} + Z_{BP2})$ is smaller than the phase of the numerator $\angle(Z_{TUT} \cdot Z_{BP,i})$, the measured phase will become positive, even though no inductive properties in the individual impedances exist. In practice, this may be the case when large capacities between current injecting and voltage sensing electrode pairs are present. Thus, it is likely that errors in measurement and instrumentation, together with the effect of electrode placement may cause quasi-inductive properties in bioimpedance spectroscopy measurements.

2.3 Animal trial

The data analyzed in this trial is based on an animal study. The experiments were performed in accordance with the German legislation governing animal studies following *The Principles of Laboratory Animal Care* and were approved by the North Rhine-Westphalia State Agency for Nature, Environment, and Consumer Protection (Germany; 84-02.04.2013.A200).

A total of 21 female pigs (German landrace) weighing 32.6 - 40.6 kg were investigated in this trial, of which 17 animals were included in this study. 4 animals were not included due to a premature ending of the trial or problems in instrumentation. The remaining animals were randomized into three different groups:

- ARDS induced by an infusion of lipopolysaccharides (LPS) (n=5)
- ARDS induced by bronchoalveolar lavage (LAV) (n=7)
- Control group with no intervention (CO) (n=5)

The initial procedure was similar in all three groups. All animals were mechanically ventilated in a volume-controlled mode using a tidal volume of 6–8 ml/kg bodyweight. The inspiratory-expiratory ratio was set to 1:1. A PEEP of 5 cm H₂O was maintained during the entire trial. The breathing rate was adjusted to maintain partial pressure of carbon dioxide in the range of $P_aCO_2 = 35\text{--}45$ mmHg.

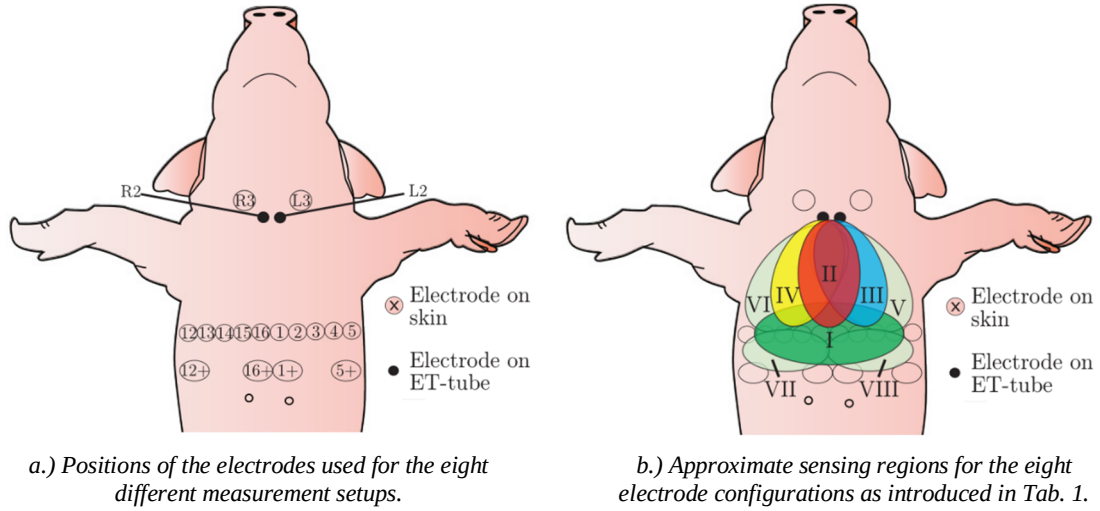


Figure 6: Positions of electrodes (a) and approximate sensing region (b) of the different measurement configurations used in the animal trial. Internal electrodes were places on the endotracheal tube (ET-Tube)

After initial preparations, a baseline measurement was performed. Then, F_{i,O_2} was set to 1.0 so that the measured P_{a,O_2} value is equal to the Horovitz index (see Section 2.1). Depending on the group, different interventions followed.

In the lipopolysaccharides group (LPS), ARDS was established by the infusion of 200 $\mu\text{g}/\text{kg}$ LPS (Escherichia coli, Sigma 055:B5) for one hour. Typically, three hours after infusion, a stable ARDS ($P_{a,O_2}/F_{i,O_2} < 300$ mmHg) was reached. The infusion led to a damage of the endothelial cells and an inflammatory response, as it would be present in pneumonia.

In the lavage group (LAV), lavages with 30 ml/kg bodyweight saline solution 0.9 % were performed every 10 min, followed by arterial blood gas test. ARDS was considered established, when P_{a,O_2} was below 100 mmHg one hour after the last lavage. This was typically the case after three hours of repeated lavages. This intervention led to atelectasis and edema.

In the control group (CO), no additional intervention was performed. All animals were ventilated with a F_{i,O_2} of 1.0 for three hours.

Medical parameters were recorded hourly simultaneously to the impedance measurements. The results and medical evaluation of the animal trial are published in [Hochhausen et al., 2019].

2.4 Measurement strategy

During the trials, measurements were performed hourly using a total of 16 external and two internal electrodes. The positions of the electrodes are depicted in Figure 6 a). Electrodes 1 – 5 and 12 – 16 were placed in a similar way as the electrodes of an EIT belt at approx. the height of the 5th intercostal space. Electrodes 12+, 16+, 1+ and 5+ were placed approx. 10 cm below the respective electrodes 12, 16, 1, and 5. Electrodes L2 and R2 were internal electrodes, which are integrated on the cuff on the endotracheal tube (ET-tube) used for mechanical ventilation. Electrodes L3 and R3 are surface electrodes at the same height as the internal electrodes. Using these electrode positions, tetrapolar impedance measurements were performed using eight different injection- and sensing patterns as shown in Table 1.

Table 1: Electrode configurations used in this study.

Config #	i_+	i_-	v_+	v_-
I	4	13	5	12
II	L2	2	R2	15
III	L2	2	R3	3
IV	R2	15	L3	14
V	L2	5	L3	4
VI	R2	12	R3	13
VII	16	12	16+	12+
VIII	1	5	1+	5+

In [Orschulik et al., 2016; Orschulik et al., 2018a], we showed in simulations that proper placement of electrodes can focus measurements on specific regions of interest. Furthermore, we demonstrated that the addition of internal electrodes might be beneficial for focused impedance measurements in the lung. In the given setup, the focus regions for the eight configurations I – VIII are:

- I. External, transthoracic measurement, central focus region,
- II. Two internal electrodes, central focus region,
- III. One internal electrode, central-left focus region,
- IV. One internal electrode, central-right focus region,
- V. One internal electrode, wide-left focus region,
- VI. One internal electrode, wide-right focus region,
- VII. External electrodes, bottom right focus region,
- VIII. External electrodes, bottom left focus region.

Figure 6 b) shows an approximation of the appropriate sensing regions. The exact measurement sensitivity is dependent on the internal conductivity distribution and the exact electrode position.

During the trials, bioimpedance spectroscopy measurements were recorded hourly using the BIS device *Sfb7* by Impedimed (Carlsbad, USA). Impedance was measured at 256 frequencies between 4 kHz and 1 MHz. The duration of one spectroscopic impedance measurement took less than 1 second. Data was recorded and processed in Matlab (MathWorks Inc., USA).

2.5 Data validity and filtering

In order to test the validity of the data, the Kramers-Kronig transformation was applied. Specifically, the conformity was verified using the linear Kramers-Kronig validity test as introduced in [Boukamp, 1995] using both a real-fit and complex fit as suggested in [Schönleber et al., 2014; Schönleber and Ivers-Tiffée, 2015].

Next, to reduce noise, the data was filtered. For this, a third-order Savitzky-Golay filter with a frame length of 41 was applied to the raw data of single impedance spectroscopy measurements [Savitzky and Golay, 1964]. Figure 7 shows an exemplary bioimpedance measurement before filtering (red) and after applying the filter (blue). It is apparent that the filter is able to eliminate the noise while the shape of the spectrum is maintained. All subsequent calculations and processing steps were henceforth based on the filtered data.

2.6 Data normalization

In general, the measured impedance of each individual subject is dependent on many different factors such as body height, body weight, or body composition. This is utilized by various applications such as Bioimpedance Analysis (BIA), where important parameters such as extra-, intracellular, and total body water are extracted from impedance measurements [Jaffrin and Morel, 2008; Kushner and Schoeller, 1986; Moissl et al., 2006]. The aim of this study was to investigate the effect of lung pathologies on the impedance spectrum. Thus, in order to cancel out other effects, all measurements were normalized to the baseline measurement at each measured frequency:

$$Z_{norm}(f, t) = \frac{Z(f, t)}{Z(f, 0)}, \quad (4)$$

with $Z(f, t)$ being the measured complex impedance at frequency f at time t and $Z(f, 0)$ the baseline measurement.

This means that, for the baseline measurements, all values were normalized to 1. At later measurements, the magnitude of each element directly showed if the measurement result at the specific frequency increased ($|Z_{norm}| > 1$) or decreased ($|Z_{norm}| < 1$). This normalization procedure was performed for all features except for the extracted tissue parameters, as such a normalization eliminates information on the shape of the spectrum. For the tissue parameters, each respective parameter was normalized on the baseline measurement. For example, the parameter $R_{e,norm}(t)$ was derived as:

$$R_{e,norm}(t) = \frac{R_e(t)}{R_e(0)}. \quad (5)$$

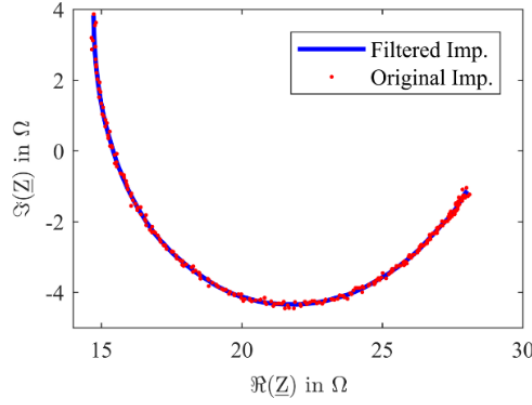


Figure 7: Exemplary bioimpedance measurement before (red) and after (blue) filtering with the third order Savitzky-Golay filter.

3. Results

In this chapter, the results of the animal study and the data analysis will be presented. In particular, we aim to answer three questions:

1. Does the presence of a lung pathology have a significant impact on the measured impedance spectrum compared to the control group?
2. Is the impact on the measured impedance spectrum dependent on the type of the pathology (Lavage or LPS group)? Is there a significant difference between the two pathologic groups?
3. Are configurations utilizing internal electrodes superior to configurations using only external electrodes?

First, the medical results will be briefly presented. Then, the features will be introduced. Finally, the best features will be displayed in boxplots, compared to the medical reference, and the results of a statistical significance analysis will be shown.

3.1 Medical results

In this paper, the medical results will only be presented in the form of the Horovitz index, which is the key medical reference parameter for the identification and classification of ARDS (see Section 2.1). For a complete analysis of the medical results and a comparison to Electrical Impedance Tomography, the reader is referred to [Hochhausen et al., 2019].

In Figure 8, boxplots of the Horovitz index for the three groups at the time points baseline, 4 h after baseline, 7 h after baseline, and 11 h after baseline are presented. In the LPS group, lipopolysaccharides was injected after baseline measurement, which resulted in ARDS. Specifically, 4 hours after the baseline measurement, mild ARDS was reached ($P_{a,O_2}/F_{i,O_2} < 300$ mmHg). At later time points, the Horovitz index even dropped further so that a stable moderate or severe ARDS ($P_{a,O_2}/F_{i,O_2} < 200$ mmHg) was achieved. In the LAV group, ARDS was induced by repetitive lavages. This led to a moderate or severe ARDS 4 h after baseline measurement. At later time points, however, the variance in the Horovitz index was found to be higher than in the LPS group. In some trials, at $t=7$ h and $t=11$ h the criterion for mild ARDS was not even fulfilled any more ($P_{a,O_2}/F_{i,O_2} > 300$ mmHg) while in other trials a severe ARDS was still present ($P_{a,O_2}/F_{i,O_2} < 100$ mmHg), indicating that in some cases, the lung recovered significantly. Thus, in this trial, the LPS method provided a more stable ARDS than the LAV method. In the CO group, no additional intervention was performed. Thus, it is not surprising that the Horovitz index stayed in the healthy range throughout the full trial.

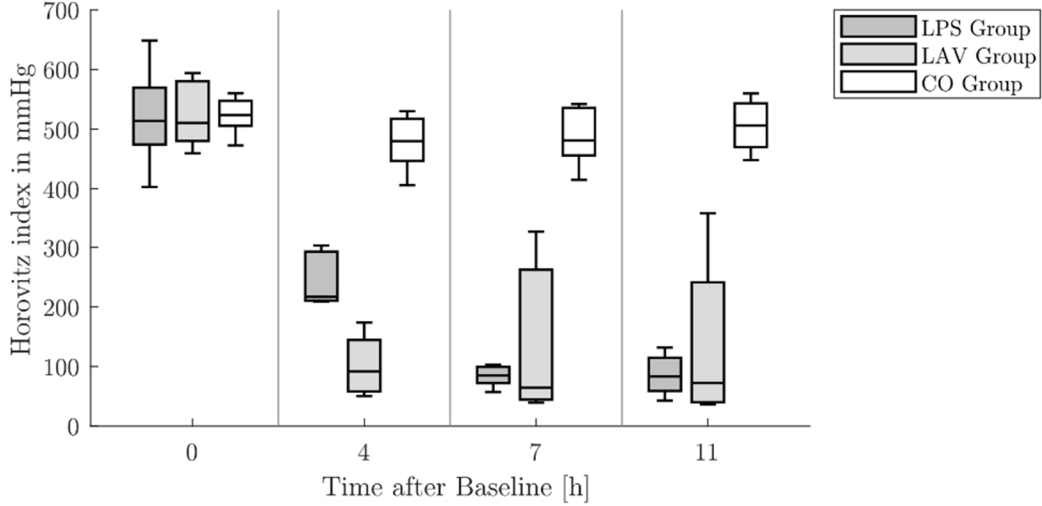


Figure 8: Medical results of the animal trial. Boxplots of the Horovitz index are shown for each group, individually. In the LPS and LAV group, ARDS is established at $t=4$ h after baseline measurement (Horovitz index < 300 mmHg). In the CO group, no ARDS is present.

3.2 Impedance features

In the given setup, impedance data was recorded hourly at 8 different electrode configurations. As only 17 animals were investigated in this study, a simple *fitting* of the impedance data to the medical reference would probably be successful. However, due to the small sample size, the validity would be questionable. Thus, in order to avoid *overfitting*, two meaningful feature sets were investigated: the impedance magnitude and the spectroscopic tissue parameters.

As introduced in Section 2.6, the impedance data was normalized to the baseline measurement. Thus, the value $|Z_{norm}(f, t)|$ represents the amplification or drop of the magnitude of the impedance at frequency f and time t with respect to the baseline measurement. This magnitude was analyzed at the frequencies of 4 kHz, 57 kHz, and 550 kHz in order to represent low, medium, and high frequencies.

The analysis of the spectroscopic measurements was performed taking into account the adjusted tetrapolar model as described in Section 2.2. For this, eq. (3) was applied, as in Section 2.2. However, adding three additional, independent *bypass* impedances Z_{BP1} , $Z_{BP,i}$ and Z_{BP2} would, depending on the modeled complexity of the respective impedances, introduce multiple parameters and thus additional degrees of freedom, which would make a potential fitting algorithm unstable and the results difficult to compare. Hence, the analysis was performed using various assumptions in four distinct steps: The simplification of eq. (3), the fitting of the baseline measurement to the simplified equation and the calculation of the *bypass* impedance for the baseline measurement, the decomposition of the measured impedance into the impedance of the *TUT* for each time step, and the extraction of tissue parameters and normalization of each extracted tissue parameter on the baseline measurement.

First, as mentioned above, a parameter fitting to eq. (3) would increase the degrees of freedom of the fitting algorithm, which could result in unstable results as the impedance at the 256 different frequency points are not independent of each other, but could be, in the best case, modeled using one single Cole equation. Hence, the number of parameters was reduced by two assumptions: Firstly, the impedance between the current injecting electrodes was assumed to be equal to the impedance between the voltage sensing electrodes: $Z_{TUT} = Z_{BP,i}$. Secondly, the two impedances between current injecting and voltage sensing electrodes were also assumed to be equal: $Z_{BP1} = Z_{BP2}$. In Figure 3 b.), for example, a typical thoracic electrode setup is shown. It can be seen that, in this example, both the respective impedance between the two current injecting and the two voltage sensing electrode pair is derived from a similar region and orientation, while the impedance between one single current injecting and voltage sensing electrode is perpendicularly orientated. After applying the simplifications above, eq. (3) was modified to

$$Z(f) = \frac{Z_{TUT}^2(f)}{2 \cdot Z_{TUT}(f) + 2 \cdot Z_{BP1}(f)}. \quad (6)$$

In the second step, the baseline measurement was fitted to the simplified model in eq. (6). For this, the impedance $Z_{TUT}(f)$ was modeled using the Cole equation as introduced in eq. (1). The impedance between a single current injecting and voltage sensing electrode $Z_{BP1}(f)$, however, was modeled as a parallel RC-circuit with an empirical constant:

$$Z_{BP1}(f) = \frac{R_b}{1 + (j \cdot 2\pi f \cdot R_b C_b)^{\alpha_b}}. \quad (7)$$

This modeling takes into account both capacitive effects between the current injecting and voltage sensing system due to electrode placement as well as errors due to instrumentation and was previously used in a comparable compensation approach in [Callaghan et al., 2010]. The curve fitting was realized in Matlab using the Nelder-Mead simplex algorithm, as described in [Lagarias et al., 1998]. After this step, the baseline measurement was decomposed into the Cole-shaped part $Z_{TUT,BL}(f, t = BL)$ and the bypass part $Z_{BP1,BL}(f, t = BL)$. This is visualized in the top row of *Figure 9*, where the complete decomposition chain is shown.

In the third step, the Cole-shaped part $Z_{TUT,t_i}(f, t = t_i)$ was derived for all subsequent measurements by decomposing the measured impedance $Z(f, t_i)$ using the baseline bypass impedance $Z_{BP1,BL}(f, t = BL)$:

$$Z(f, t_i) = \frac{Z_{TUT,t_i}^2(f, t = t_i)}{2 \cdot Z_{TUT,t_i}(f, t = t_i) + 2 \cdot Z_{BP1,BL}(f, t = BL)}. \quad (8)$$

In general, the procedure described in step 2 for the baseline could be repeated for each subsequent measurement, which would result in an individual Cole-shaped impedance and an individual bypass impedance for each time point. This, however, has the problem of, again, adding additional degrees of freedom to each measurement, which could introduce significant differences in the individual fitted results between the different measurement points. In order to avoid this, the bypass impedance was modeled to stay constant throughout each individual trial, which assumes that it is mainly dependent on the measurement setup itself and that the pathology purely affects the Cole-shaped impedance. The result of the decomposition is then the Cole-shaped part for each time point $Z_{TUT,t_i}(f, t = t_i)$.

The fourth and final step was the derivation and normalization of the tissue parameters from the impedance $Z_{TUT,t_i}(f, t = t_i)$. For this, the Cole equation as introduced in eq. (1) was applied to $Z_{TUT,t_i}(f, t = t_i)$ at all time points. This results in the parameters R_0, R_∞, τ_Z and α . From this, the extra- and intracellular resistance R_e and R_i were calculated based on the extracted parameters R_0 and R_∞ . The normalization of the derived parameters was based on the parameters of the baseline measurement, as shown in eq. (5). In total, five tissue parameters were extracted, normalized and analyzed: The extracellular resistance $R_{e,norm}$, the intracellular resistance $R_{i,norm}$, the ratio between extra- and intracellular resistance $(R_e/R_i)_{norm}$, the time constant $\tau_{Z,norm}$ and the empirical Cole parameter α_{norm} .

In *Figure 9*, the extraction method for the tissue parameters is visualized. At the baseline measurement (BL), both the impedance of the TUT $Z_{TUT,BL}(f, BL)$ and the *bypass* impedance $Z_{BP1,BL}(f, t = BL)$ was extracted. This *bypass* impedance was then used as an input in order to decompose the measured impedance into the impedance of the TUT for the subsequent time steps $Z_{TUT,t_i}(f, t_i)$, which is represented by the blue curve on the right side. The red dotted curve shows the result of the Cole-fit to the decomposed impedance.

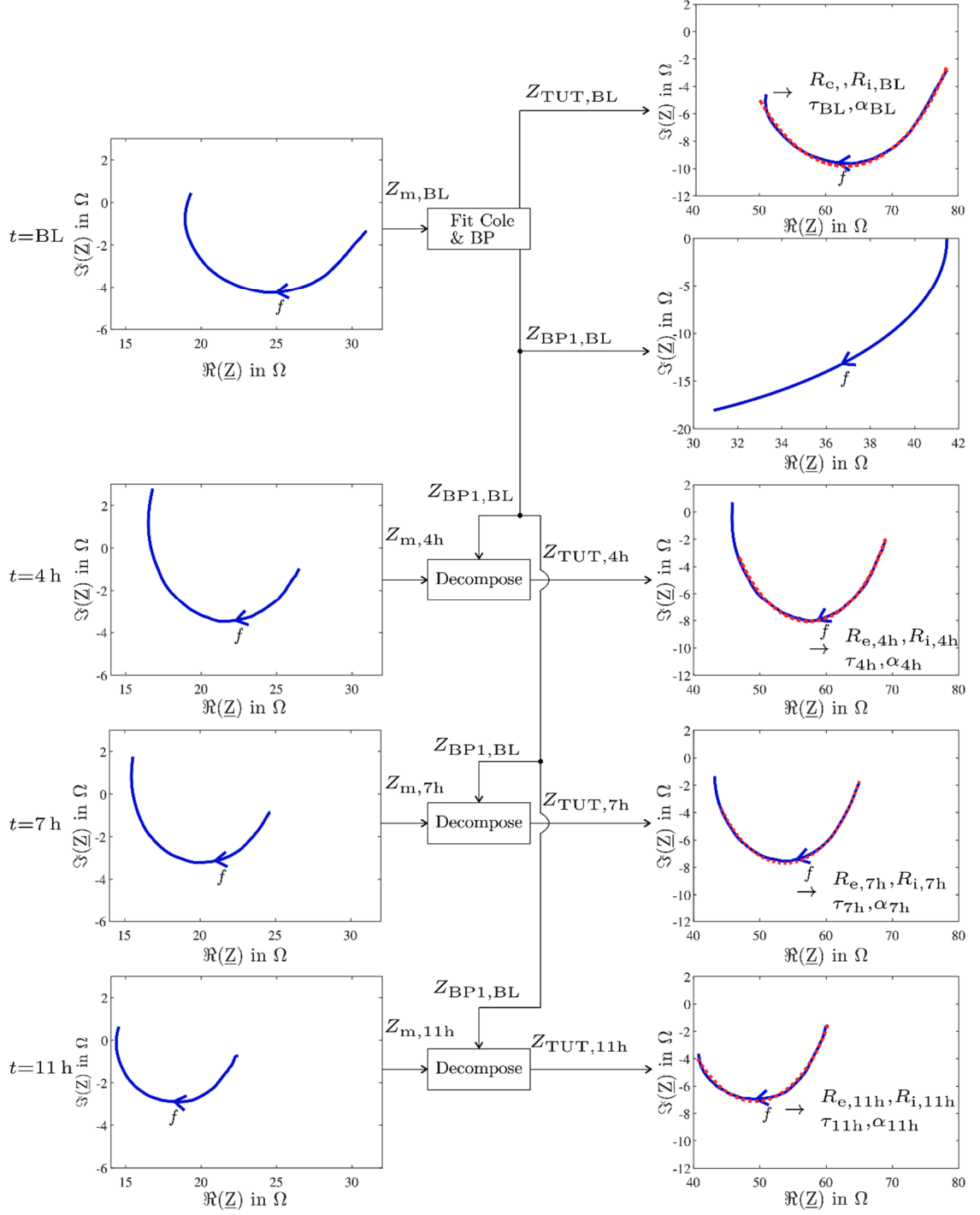


Figure 9: Fitting and decomposition of the measured impedance Z_m for tissue parameter extraction. Due to the adjusted electrode positions as introduced in Section 2.2, the measurement was assumed to consist of the Cole-shaped impedance Z_{TUT} and the bypass impedance Z_{BP1} . The initial fitting into the two impedances was done at the baseline measurement. The extracted bypass impedance at this time point was assumed to be valid for all subsequent measurements as well, so that a decomposition was performed at later time points. From the Cole-shaped impedance, the tissue parameters were extracted using curve fitting.

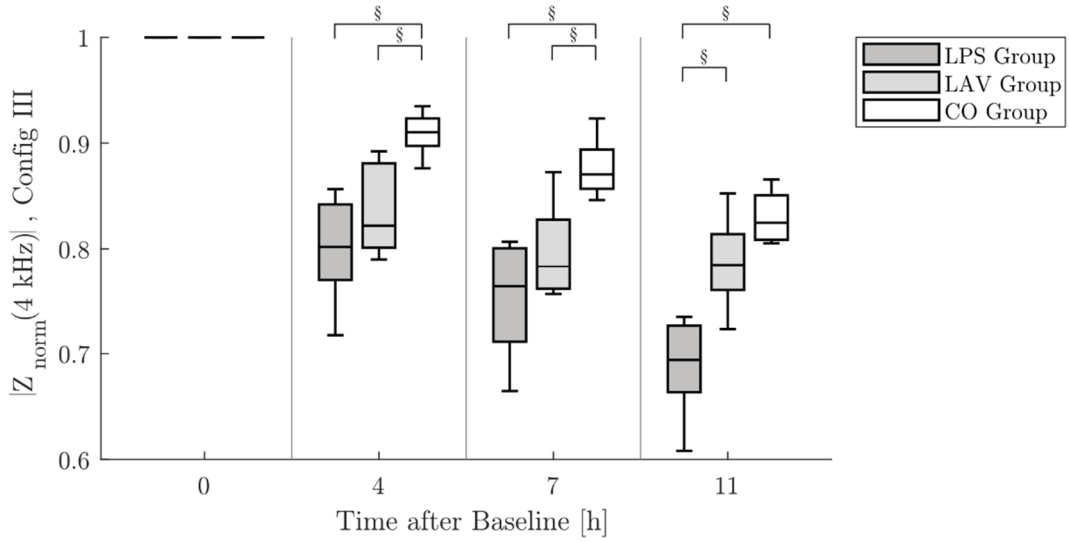


Figure 10: Boxplots of the feature $|Z_{\text{norm}}(4 \text{ kHz}, t)|$ of config. III at baseline, 4 h, 7 h and 11 h after baseline measurement. Pairwise significant differences between groups are marked with § ($p < 0.05$).

3.3 Results and Statistical evaluation

In this section, the results and statistical evaluation will be presented. The statistical evaluation was performed using the software SPSS (IBM SPSS Statistics for Windows, Version 23). The significance level was set at $p < 0.05$. Not-normal distribution was confirmed using the Shapiro-Wilk-test [Shapiro and Wilk, 1965]. The pairwise differences between the three groups (LPS and CO group, LAV and CO group, LPS, and LAV group) were analyzed using the Mann-Whitney-U-Test [Mann and Whitney, 1947].

In Figure 10, the distribution of the impedance magnitude feature $|Z_{\text{norm}}(4 \text{ kHz})|$ at configuration III, which was focusing on the central left focus region and utilized one internal electrode, is presented at 4 kHz (low frequency). Similar to the Horovitz index in Figure 8, the results are shown at baseline and 4 h, 7 h, and 11 h after baseline measurement. Significant pairwise differences between groups are marked with §. First, it is apparent that in all three groups, the normalized impedance magnitude dropped over the course of the study. At $t = 4 \text{ h}$, however, this drop was significantly higher in the two pathological groups (LPS and LAV group) than in the control group. This was also the case at $t = 7 \text{ h}$ after baseline measurement. At $t = 11 \text{ h}$ after baseline measurement, the difference between the LAV group and the CO group became smaller so that no significant difference was present any more between these two groups. In the LPS group, in contrast, the impedance magnitude dropped even further so that the distribution of the feature was significantly different between the LPS group and both the LAV and CO group at this time point.

In Figure 11, the results for another impedance magnitude feature, $|Z_{\text{norm}}(57 \text{ kHz})|$ at configuration IV at 57 kHz, are given. This time, the central right region was focused by the electrode configuration. The results obtained in this configuration are similar to the one of configuration III at 4 kHz above. Again, in all groups, the impedance magnitude dropped during the trial. Furthermore, at 4 h and 7 h after baseline measurement, the LPS and LAV groups had significant differences in the distribution of the feature compared to the CO group. At $t = 11 \text{ h}$ after baseline measurement, the distribution inside the

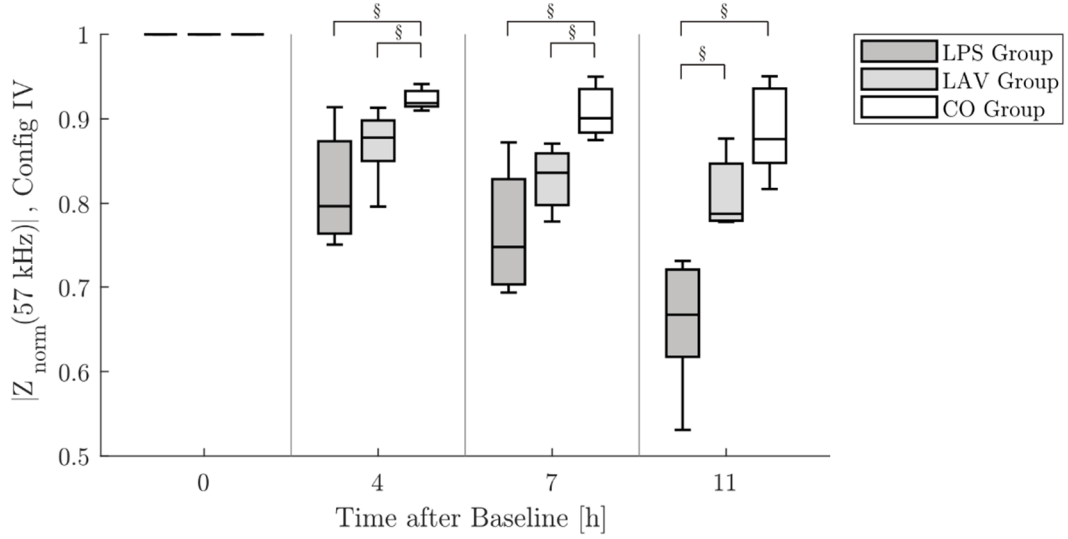


Figure 11: Boxplots of the feature $|Z_{\text{norm}}(57 \text{ kHz}, t)|$ of config. IV at baseline, 4 h, 7 h and 11 h after baseline measurement. Pairwise significant differences between groups are marked with § ($p < 0.05$).

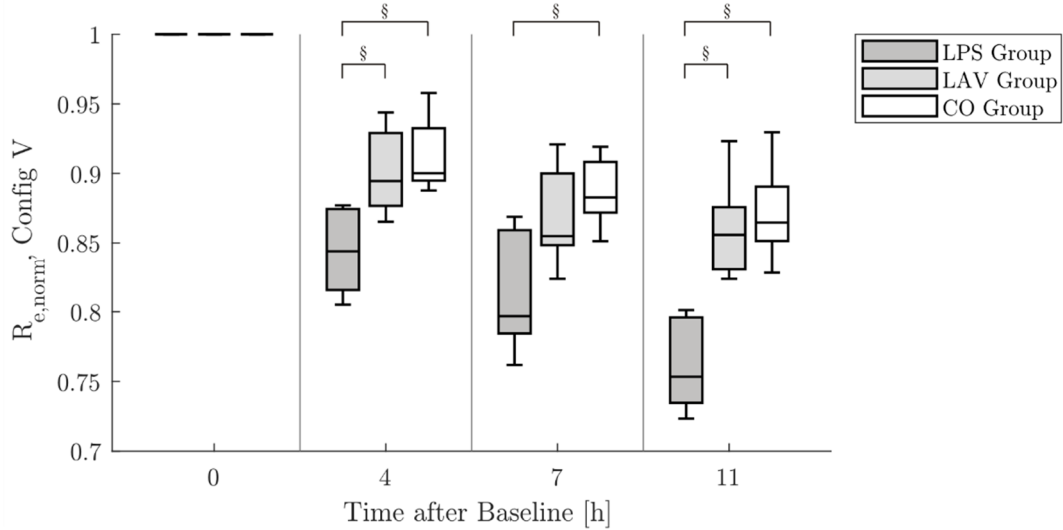


Figure 12: Boxplots of the feature $R_{e, \text{norm}}$ of config. V at baseline, 4 h, 7 h and 11 h after baseline measurement. Pairwise significant differences between groups are marked with § ($p < 0.05$).

LPS group was different from both the LAV and CO group, while the LAV and CO group did not show a significantly different pairwise distribution.

When comparing both impedance magnitude features to the Horovitz index in Figure 8, analogies and differences can be observed. For instance, the ARDS induced in the LPS group was more stable and more severe in the medical results at later time points than in the LAV group. This is also confirmed in the two presented impedance magnitude features, as the difference between the LPS group and the CO group grew throughout the trial. In the LAV group, however, this difference to the CO group became smaller at later time points. Notably, at $t = 11$ h after baseline measurement, the distribution of the feature inside the LAV and the CO group was not significantly different anymore. This is different from the medical result, in which the LAV and CO group showed different distributions in the Horovitz value throughout the complete trial. However, when applying the classification criteria of ARDS to the Horovitz index as introduced in Section 2.1, it is apparent that at $t = 11$ h after baseline measurement, ARDS was no longer present in some animals of the LAV group (Horovitz index > 300 mmHg). Hence, the rapprochement in the impedance magnitude features is in accordance with the medical reference measurement.

The overall drop of the impedance magnitude, which can also be observed in the CO group, is not visible in a similar way in the Horovitz index, where the control group remained in the same range during the full trial. The reason for this impedance magnitude drop is not apparent. However, it can be assumed that it was caused by the anesthetic procedure and fluid management, which was equal inside all three

groups. Overall, the results of the distribution in the two presented impedance magnitude features match the distribution in the medical reference data.

In Figure 12, the distribution of the extracted tissue parameter $R_{e, norm}$ at configuration V, is shown. This configuration had a wide left focus region and utilized one internal electrode. In contrast to the two features presented earlier, which were calculated based on the magnitude of the raw data, the tissue parameters are the result of the application of the adjusted tetrapolar model, as described in Section 3.2. Similar to the previous results, the value of the feature dropped in all three groups. The biggest difference to the magnitude feature is visible in the LAV group. In contrast to the impedance magnitude features, the distribution of the Cole feature was almost identical in the LAV and the CO group. In the LPS group, in contrast, the value of the feature dropped throughout the course of the study. As a result, the distribution of the LPS group was significantly different from the CO group at 4 h, 7 h, and 11 h after baseline measurement and significantly different to the LAV group at 4 h and 11 h after baseline measurement. Especially at 4h after baseline measurement, this is in contrast to the medical Horovitz index, where it was lowest in the LAV group. The reason for this is unclear. One possible explanation, however, is the underlying mechanism of the interventions which caused ARDS: While in the LPS group, ARDS was induced by injection of lipopolysaccharide leading to damage of the endothelial cells and an inflammatory response (pneumonia), the repetitive lavages in the LAV group caused atelectasis and edema. This might have led to different dielectric properties, which could be observed in the tissue parameters, as the shape of the impedance spectrum is taken into account [Ballard-Croft et al., 2012; Bannerman and Goldblum, 2003; Russ et al., 2016; Wang et al., 2008].

The complete results of the pairwise statistical analysis between the three groups are given in *Appendix 1 - Appendix 3*. For each electrode configuration (Config # I – VIII), the features introduced in Section 3.2 are analyzed. Again, the results are presented at the time points 4 h, 7 h, and 11 h after baseline measurement. The values show the p-value if $p < 0,05$ or “n.s.” if not significant.

Specifically, in *Appendix 1*, the results of the pairwise Mann-Whitney-U analysis between the CO and the LPS group are shown. It is apparent that in most cases, the distribution of the normalized impedance magnitude $|Z_{norm}(f, t)|$ was significantly different in the control group than in the LPS group. This difference becomes even stronger over the course of the trial, which is in accordance with both the medical results as well as the observation of three demonstrated features above. For the tissue parameters, the feature $R_{e, norm}$ showed the most significant differences, while the distribution in the other tissue parameters was not significantly different between the two groups.

In *Appendix 2*, the results of the pairwise analysis between the CO and LAV group are given. Here, at 4 h and 7 h after baseline measurement, the distributions of the measurement results from configurations III, IV, and VI, which all utilized both internal and external electrodes, showed significant differences between the two groups for the magnitude-based features. However, 11 h after baseline measurement, the difference between the two groups got smaller, as fewer features showed significant differences. This, again, is in accordance with the medical reference data and the observations in the boxplots. For the tissue parameters, almost no significant differences were present between the CO and the LAV group.

Finally, the results of the pairwise comparison between the LPS and the LAV group are presented in *Appendix 3*. At $t = 4$ h and $t = 7$ h after baseline measurements, almost no significant differences in the distribution of the features were observed. At $t = 11$ h, however, more features showed a significant difference in their distribution, especially in configuration IV, V, and VI, which all utilized both internal and external electrodes. Overall, only the feature $|Z_{norm}(4\text{ kHz}, t)|$ at configuration V, which was a configuration using internal and external electrodes, showed significant differences in all three time points.

4. Discussion

At the beginning of Chapter 3, three questions were asked:

1. Does the presence of a lung pathology have a significant impact on the measured impedance spectrum compared to the control group?
2. Is the impact on the measured impedance spectrum dependent on the type of the pathology (Lavage or LPS group)? Is there a significant difference between the two pathologic groups?
3. Are configurations utilizing internal electrodes superior to configurations using only external electrodes?

Based on the results, these questions can be answered as follows:

1. Depending on the feature, the distribution of the features in the pathological LPS and LAV groups was significantly different than in the control group.
2. The dependency of the extracted features on the type of the pathology has to be analyzed for each feature individually. In the impedance magnitude features, the behavior was similar in both pathologies: the impedance drop in the pathological groups was significantly higher than in the control group. In some Cole based features, the type of pathology had an impact on the feature value. Hence, one way to differentiate the two pathological groups from each other could be the combination of multiple features to create a strong separator.
3. The configurations with the most significant differences were the electrode configurations II, III, IV, V, and VI. All these configurations used both internal and external electrodes. Especially when comparing these configurations to the configurations I, VII, and VIII, which only used external electrodes, a benefit from internal electrodes can be observed.

It should be noted that, for most time points and configurations, the *simple* magnitude drop features produced more significant differences between the groups than the comparatively *complex* tissue parameters. One possible reason for this is that the tissue parameters were determined based on the adjusted tetrapolar model and the decomposition introduced in Section 2.2 and 3.2. While the comparison between the extracted tissue parameters and the decomposed impedance showed a good agreement (blue and red curve in *Figure 9, right*), the impact of the *bypass* impedance on the measurement is still unclear. In particular, assumptions on the size and shape of the *bypass* impedance were made, which might have caused an oversimplification of the underlying mechanisms. Nevertheless, the adjusted tetrapolar model and the decomposition strategy demonstrate that, especially when using electrode configurations in which the voltage sensing current does not match the injecting current, parameter extraction such as Cole-fitting should be used with care.

Despite this, the results of the study indicate in total that bioimpedance spectroscopy is a promising approach to detect and distinguish lung pathologies. However, multiple limitations apply to the study itself. First, the sample size is quite small. In total, the data of 17 animal trials was analyzed. Due to the small amount of data, one crucial question cannot be addressed: *Can the type and severity of lung pathologies be classified using bioimpedance spectroscopy measurements?* Based on the data, it could be assumed that, for example, a normalized impedance magnitude in configuration III at 4 kHz below 0,8 ($|Z_{norm}(4 \text{ kHz}, t)| < 0,8$) would be an indicator of acute respiratory distress syndrome. Such a statement, however, would be invalid as it is a result of overfitting. For a robust classification, the dataset has to be divided into a training, validation, and test set. This, however, is not possible in the given dataset size.

Second, all features were normalized on the baseline measurement. In a potential clinical scenario, however, a baseline measurement may not be available. This is problematic as all features are different in magnitude and scale due to interindividual differences in body height, body weight, or body fat percentage. Additionally, the time point of the baseline measurement is important as even in the control group, where no additional intervention took place, a variation of the impedance spectrum was observed. In a large dataset, however, a baseline definition based on external anatomical parameters might be possible as it is, for example, successfully performed in the field of bioimpedance analysis [Kyle et al., 2004].

Third, measurements were only performed for eight hours after ARDS establishment. In clinical scenarios, especially in the intensive care unit, patients will be ventilated and monitored for much longer times. It has to be investigated if significantly different distributions of the features also hold in long term experiments. Furthermore, if more data is available, more complex features could be extracted, potentially allowing a better distinguishability and classification of the three groups.

Despite the limitations, the results show that the distribution of the extracted features is significantly different in the pathological groups than in the control group. The fact that simple features, such as the impedance magnitude drop and tissue parameters, were used instead of more complex features adapted to the dataset increases the relevance of the results. While it is unlikely that impedance measurements will replace blood gas analysis, they could be used as an indicator of a worsened lung state. Especially as impedance measurement can be performed continuously and do not cause additional harm in ventilated patients, they can help to detect lung pathologies in an earlier stage which is a key factor in improving the patients' outcome.

Config #	I	II	III	IV	V	VI	VII	VIII
t=4 h								
Z _{norm} (4 kHz, 4 h)	0,028	0,009	0,009	n.s.	0,009	n.s.	n.s.	n.s.
Z _{norm} (57 kHz, 4 h)	0,047	0,009	0,009	0,009	0,009	0,009	0,028	n.s.
Z _{norm} (550 kHz, 4 h)	0,047	0,028	n.s.	0,009	0,016	0,028	0,047	n.s.
R _{e,norm}	0,028	0,028	n.s.	n.s.	0,009	n.s.	n.s.	n.s.
R _{i,norm}	n.s.	n.s.	n.s.	n.s.	0,009	n.s.	n.s.	n.s.
(R _e /R _i) _{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
τ _{Z,norm}	n.s.	n.s.	n.s.	n.s.	0,028	n.s.	n.s.	n.s.
α _{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
t=7 h								
Z _{norm} (4 kHz, 7 h)	0,028	0,009	0,009	n.s.	0,009	0,028	n.s.	0,016
Z _{norm} (57 kHz, 7 h)	0,016	0,009	0,009	0,009	0,009	0,016	n.s.	0,028
Z _{norm} (550 kHz, 7 h)	0,028	0,028	0,009	0,009	0,016	0,009	n.s.	n.s.
R _{e,norm}	0,009	0,009	n.s.	0,047	0,028	n.s.	n.s.	0,047
R _{i,norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
(R _e /R _i) _{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
τ _{Z,norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α _{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
t=11 h								

$ Z_{norm}(4 \text{ kHz}, 11 \text{ h}) $	0,016	0,009	0,009	0,009	0,009	0,009	n.s.	0,028
$ Z_{norm}(57 \text{ kHz}, 11 \text{ h}) $	0,016	0,009	0,009	0,009	0,009	0,009	n.s.	0,028
$ Z_{norm}(550 \text{ kHz}, 11 \text{ h}) $	0,028	0,009	0,009	0,009	0,009	0,009	n.s.	n.s.
$R_{e, norm}$	0,009	0,009	n.s.	0,009	0,009	0,028	n.s.	0,047
$R_{i, norm}$	n.s.	n.s.	0,047	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e/R_i)_{norm}$	n.s.	0,047	0,047	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Appendix 2: Results of the pairwise Mann-Whitney U analysis of different features between the control group (CO) and the lavage group (LAV) at $t=4 \text{ h}$, 7 h , and 11 h after baseline measurement. Values show the p -value if $p < 0.05$ or “n.s.” if not significant.

Config # Feature	I	II	III	IV	V	VI	VII	VIII
t=4 h								
$ Z_{norm}(4 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	0,012	0,012	n.s.	0,042	n.s.	n.s.
$ Z_{norm}(57 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	0,012	0,012	n.s.	0,012	n.s.	n.s.
$ Z_{norm}(550 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	0,007	0,007	n.s.	0,028	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e/R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
t=7 h								
$ Z_{norm}(4 \text{ kHz}, 7 \text{ h}) $	n.s.	n.s.	0,028	0,016	n.s.	n.s.	n.s.	n.s.
$ Z_{norm}(57 \text{ kHz}, 7 \text{ h}) $	n.s.	0,047	0,009	0,009	n.s.	0,047	n.s.	n.s.
$ Z_{norm}(550 \text{ kHz}, 7 \text{ h}) $	n.s.	n.s.	0,009	0,009	n.s.	0,047	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e/R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	0,028	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
t=11 h								
$ Z_{norm}(4 \text{ kHz}, 11 \text{ h}) $	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$ Z_{norm}(57 \text{ kHz}, 11 \text{ h}) $	n.s.	n.s.	0,028	n.s.	n.s.	0,047	n.s.	n.s.
$ Z_{norm}(550 \text{ kHz}, 11 \text{ h}) $	n.s.	n.s.	0,016	n.s.	n.s.	0,047	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e/R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	0,028	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Appendix 3: Results of the pairwise Mann-Whitney U analysis of different features between the Lavage group (LAV) and the LPS group (LPS) at $t=4 \text{ h}$, 7 h , and 11 h after baseline measurement. Values show the p -value if $p < 0.05$ or “n.s.” if not significant.

Config #	I	II	III	IV	V	VI	VII	VIII
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Feature								
t=4 h								
$ Z_{norm}(4 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	n.s.	n.s.	0,042	n.s.	n.s.	n.s.
$ Z_{norm}(57 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0,028	n.s.
$ Z_{norm}(550 \text{ kHz}, 4 \text{ h}) $	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	n.s.	0,028	n.s.	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e / R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	n.s.	n.s.	n.s.	0,028	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	0,028	n.s.	n.s.	n.s.	n.s.	n.s.
t=7 h								
$ Z_{norm}(4 \text{ kHz}, 7 \text{ h}) $	0,047	n.s.	n.s.	n.s.	0,047	n.s.	n.s.	n.s.
$ Z_{norm}(57 \text{ kHz}, 7 \text{ h}) $	n.s.	n.s.	n.s.	n.s.	0,047	n.s.	n.s.	n.s.
$ Z_{norm}(550 \text{ kHz}, 7 \text{ h}) $	n.s.	n.s.	n.s.	0,047	n.s.	n.s.	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	0,047	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e / R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	0,047	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
t=11 h								
$ Z_{norm}(4 \text{ kHz}, 11 \text{ h}) $	0,047	n.s.	0,016	0,009	0,009	0,016	0,028	n.s.
$ Z_{norm}(57 \text{ kHz}, 11 \text{ h}) $	n.s.	n.s.	n.s.	0,009	0,009	0,016	n.s.	n.s.
$ Z_{norm}(550 \text{ kHz}, 11 \text{ h}) $	n.s.	n.s.	n.s.	0,009	0,028	0,028	n.s.	n.s.
$R_{e, norm}$	n.s.	n.s.	n.s.	0,009	0,009	0,009	n.s.	n.s.
$R_{i, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$(R_e / R_i)_{norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\tau_{Z, norm}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
α_{norm}	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

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