A Closed-loop system for blood glucose level control

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Introduction

Diabetes mellitus type 1 is a metabolic disease characterized by chronic increase of blood glucose concentration (BG) that occurs when pancreas is no longer available to produce enough amount of insulin. Patients with diabetes mellitus need continuous control of BG.

One of the most widespread methods for type 1 diabetes compensation is pump insulin therapy based on the exogenous insulin infusion combined with special physical activity treatments.

Closed-loop system for BG control may improve efficiency of insulin therapy and, furthermore provides an opportunity to compensate diabetes mellitus automatically.

Almost all up-to-date commercial BG meters and monitoring systems are invasive. A portable noninvasive glucometer development is an important task for modern science.

In the paper, we present a closed-loop system for blood glucose level control on the basis of a noninvasive glucometer, an insulin pump and model predictive control.

Elements and applications

Closed-loop operation is in maintaining BG in physiological range and preventing hypo- and hyperglycemia. A continuous glucose monitor measures BG noninvasively. An analyzing system is based on model-predictive control.

An insulin pump (IP) provides precision subcutaneous insulin infusion and control of an actual infused dose. The IP experimental embodiment comprises of a control unit, a mechanical drive based on a micro motor with a reduction gear system 1:1024, and an infusion system with a 3 ml reservoir. Tab.1 presents main parameters of the developed pump.

The experimental embodiment of portable non-invasive glucometer (PNG) comprises of a control unit and an earlap clip, connected to each other by an opto-electrical cable. Noninvasive BG measurement is based on absorption spectroscopy method. Infrared radiation from a laser diode is transmitted through an earlap and is registered by a photodiode. Transmitted radiation is analyzed and BG is calculated. The algorithm for calculating the concentration is based on the iterative methods.

The clip consists of a housing, a transmitter, a receiver (InGaAs photodiode) and optical elements (lenses, mirrors, windows). Infrared radiation goes from the control unit to the earlap via the optical fiber. Tab.2 presents main parameters of the developed glucometer.

Table 1: Insulin Pump
Experimental Embodiment Parameters

Parameter	**Value**
Reservoir volume	3 ml (300 u)
Basal insulin discretization	0.025 u
Bolus insulin discretization	0.2 u (2 ml)
Amount of daily basal profiles	48
Infusion accuracy	±2,6%
Energy supply	1 AAA battery
Run time (continuous work time)	3 days
Connection	Bluetooth
Control	autonomous/ by smartphone
Indication	3.5″TFT resistive touch screen

Table 2: Glucometer Experimental
Embodiment Parameters

Parameter	**Value**
Measurement object	earlap
Laser power	30 mW
Time of a single measurement	5 min
Amount of measurements during monitoring	12 mes/h
Energy supply	2xICR18650
Run time (continuous work time)	> 6 h
Connection	Bluetooth
Control	by smartphone
Indication	LED

IP and PNG can be controlled by a smartphone connected to them via Bluetooth interface. Smartphone application allows user to:

– input data about food intake and calibration data;

– input of personal and physiological data affecting on BG dynamics;

– create of basal and bolus insulin patterns creation and launching;

– visualize current BG and its dynamics track;

– save and show statistics data of the patient by certain day, week or month;
– signalize on appearance of system messages, warnings or errors.

In order to organize an effective feedback between IP and PNG we propose a short-term prediction algorithm [1]. Tasks of the algorithm are the following:
– patient BG prediction;
– calculation of the required bolus insulin dose;
– infusion subsystem or glucometer faults alarms;
– detecting user incorrect information input;
– alarms for hypo- and hyperglycemia;
– correcting the mathematical model parameters;
– detecting wrong BG measure results;
– detecting the need of glucometer to be recalibrated.

The algorithm is based on mathematical model of BG dynamics [2, 3]. The model assumes that glucose dynamics is regulated by insulin, amylin, epinephrine and glucagon secretion. Ascents of BG are mainly caused by food intake as well as glycogenolysis and gluconeogenesis activated by glucagon and epinephrine. Descents of BG are caused by glycolisys and glycogenesis activated by insulin and amylin. Thus, the general equation of BG dynamics can be represented as follows:

$$G = G_0 + G_f(m_{carb}, \zeta) + G_{gls}(\nu_{gn}, \nu_{epn}) + \\ + G_{gng}(\nu_{gn}, \nu_{epn}) - G_{glg}(\nu_{ins}, \nu_{am}) - G_{gs}(\nu_{ins}, \nu_{am}) \quad (1)$$

where G is current BG, G_0 is initial BG, m_{carb} is meal carbohydrates mass, ζ is food glycemic index, ν_{gn}, ν_{epn}, ν_{ins}, ν_{am} are concentrations of glucagon, epinephrine, insulin and amylin.

The closed-loop system comprises of two data sets – the measured BG from PNG and the predicted BG. The difference between them determines its further operation.

When a patient enters meal/insulin data or bolus insulin data is received from the pump, the model and the prediction are recalculated. After the prediction is made, several intervals are calculated for the current prediction. These ranges are used to classify the measured value into one of the following categories: reliable, reasonable reliable and unreliable. They are taken into consideration for error determination if appeared.

Results

Experimental trials of the closed-loop system were performed using the special test bench [4]; the scheme of the one is presented in the Fig.1.The test bench allows adjusting necessary glucose concentration in a model solution circulating in a flowthrough cuvette. Glucose level increasing simulates food intake while decreasing simulates insulin infusion. Blood-model solution contained glucose, water and such blood plasma components as albumin, urea, creatinine etc. A controlled hydraulic system provides smooth and accurate setting of target concentration in the cuvette.

Current glucose concentration in the cuvette was measured by the developed noninvasive glucometer and HemoCue Glucose 201+ as a reference. For relative error estimation 20 experiments were performed (36 measurements/experiment with BG in range 75–400 mg/dl, step 5–10 mg/dl). An average error in hyperglycemia is 13,41 %, in normoglycemia is 17,85 %, in hypoglycemia is 24,89 %. Adequacy of glucose meters is acceptable to be estimated using Clarke Error Grid Analysis (EGA). EGA of developed noninvasive glucometer is represented on the Fig.2. On the X axis are reference measurements; on the Y axis are developed glucometer measurements.

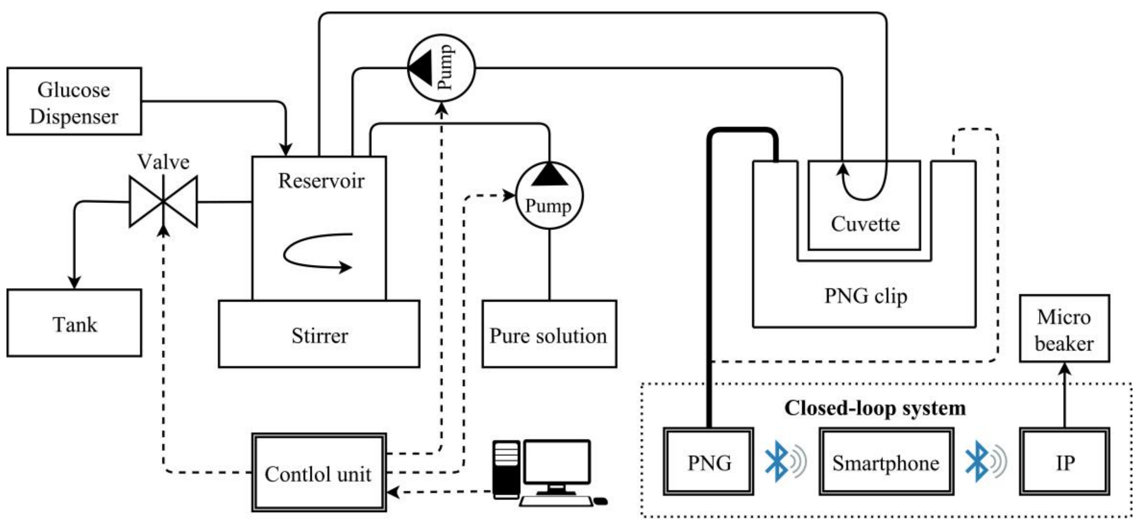

Figure 1: The scheme of the test bench for the closed-loop system experimental trails

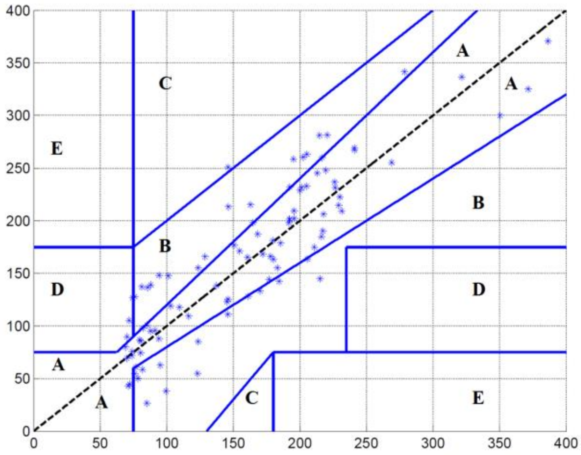

Figure 2: EGA of developed glucometer.
95.8% of measurements are in the A- and B-zone,
in C-zone is 1%, in D-zone – 3.1%, in E-zone – 0%

Series of experiments were performed in order to estimate the accuracy of the developed insulin pump. The amount of infusing insulin was changed from 0.1 ml to 2 ml, by 0.1 ml once an hour. Actually infused value was estimated by a micro beaker. As a result, the insulin infusion error averaged for one hour is 2.6%, while the maximum error is in the test range of 3.1%.

The short-term prediction algorithm was designed and tested *in silico* using Matlab. The input data sets for the algorithm were formed using the processed [5] DirecNet clinical protocols [6]. Two studies were performed: the accuracy study and the functional one. The functional study was aimed to test PNG and IP faults, incorrect data, hypo- and hyperglycemia alarms adequacy. During the study data from 30 patients was used. It included tracks for two consecutive days. For each patient, the day 1 track was used for mathematical model training and the day 2 track - for prediction system tests.

As measured BG in accuracy tests, we use actual patient track values with 5–25 % normal noise added. The algorithm was tested on every patient with different noise levels. Tests show that the difference between predicted values and patient BG values was less than 10%. During functional tests in every BG track, we deleted some data about food intake or insulin injections. As a result, the predicted track differed from real and measured ones. The algorithm analyzed the nature of the discrepancy of tracks and indicated relevant message. In every test the algorithm detected incorrect/absent data or displayed the necessary timely warnings.

The example of the prediction algorithm operation is presented in the Fig. 3.

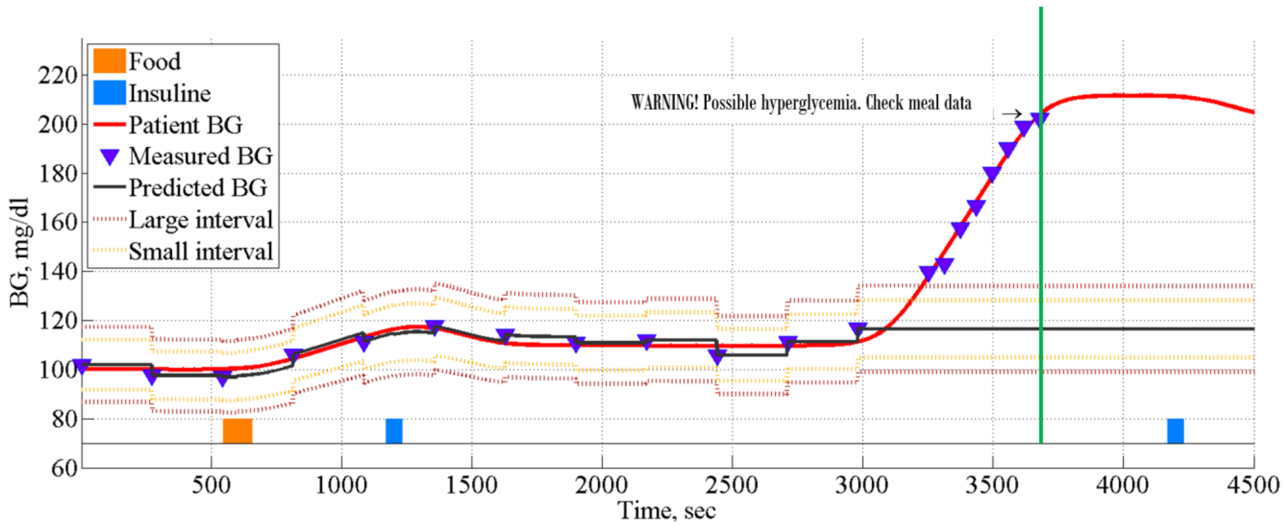

Figure 3: Prediction testing example. Patient BG is unknown for algorithm.
Predicted track is shifted to measured point if the latter is inside the reliable interval (small interval), measurement frequency 1 in 300s. If measured values are aside the reliable zone measurement frequency increased (1 in 60s).
If a divergent trend is detected, the algorithm cautions user.

Conclusions

The closed-loop system for BG level control is aimed to automate BG maintaining in physiological range with patient minimal involvement. The key feature of the system is a model predictive control and noninvasive BG measurements. The developed closed-loop elements (the optical noninvasive glucometer, the insulin pump and the model-based prediction algorithm) tests show high efficiency of proposed methods. The prediction algorithm detects incorrect data, faults of the glucometer and the pump. The implemented model predictive control allows reduction of measurement errors.

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