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Using meta-differential evolution to enhance a calculation of a continuous blood glucose level

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ABSTRACT

We developed a new model of glucose dynamics. The model calculates blood glucose level as a function of transcapillary glucose transport. In previous studies, we validated the model with animal experiments. We used analytical method to determine model parameters. In this study, we validate the model with subjects with type 1 diabetes. In addition, we combine the analytic method with meta-differential evolution. To validate the model with human patients, we obtained a data set of type 1 diabetes study that was coordinated by Jaeb Center for Health Research. We calculated a continuous blood glucose level from continuously measured interstitial fluid glucose level. We used 6 different scenarios to ensure robust validation of the calculation. Over 96% of calculated blood glucose levels fit A+B zones of the Clarke Error Grid. No data set required any correction of model parameters during the time course of measuring. We successfully verified the possibility of calculating a continuous blood glucose level of subjects with type 1 diabetes. This study signals a successful transition of our research from an animal experiment to a human patient. Researchers can test our model with their data on-line at https://diabetes.zcu.cz.

1. Introduction

Glucose is primarily distributed in the blood through which it is transported across capillary membrane into the interstitial fluid of subcutaneous tissue [1,2]. In subcutaneous tissue, the interstitial fluid glucose level (IG) can be monitored continuously with a sensor of continuous glucose monitoring system (CGMS). The sensor comprises a needle that measures electrical current produced by glucose oxidase reaction in the subcutaneous tissue [3–5]. This current is mathematically filtered and wirelessly sent to the CGMS receiver, where it is converted to glucose level unit and downloaded to a computer [4,5]. Downloaded data comprise time series of IG with 5 minute interval between each two levels.

There is an immune response as the CGMS sensor is a foreign body [3,6]. Because of physiological interference, manufacturing tolerances and imperfections, the sensor must be repeatedly calibrated using blood glucose level (BG) [3–5]. To avoid calibration errors, IG should be steady so that it could be assumed that BG is steady as well and thus both levels agree. As sensor's precision degrades continually, despite the calibration procedure, the sensor must be replaced eventually.

Using a finger-stick, the patient draws a drop of capillary blood onto a test strip [7]. Then, a glucometer applies an electric voltage on the terminals of the strip so that an electric

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current flows through the strip. This electric current is quantified, scaled and reported as glucose level [7].

Using a finger-stick, BG can only be monitored sporadically to avoid increasing the discomfort of the patient [8]. Minder et al. [9] pin-pointed 3 and 4 self-monitored blood glucose (SMBG) measurements a day. Petry et al. [10] reported SMBG increase from 2 to 5 measurements a day, if the patients earned monetary reinforcers. Beck et al. [11] explicitly state this: "requiring patients to do 6–8 SMBG a day at specified intervals for long periods of time will be too burdensome for most patients, and compliance with frequent middle-of-the-night measurements is likely to be low".

When self-measuring the blood glucose level, the patient could introduce an error as he could assign a wrong time to measured BG. Olansky and Kennedy [12] further reviewed the SMBG accuracy. In addition, Del Favero et al. [13] discussed human errors, erroneous data entry, and incorrect blood sampling/processing in the section on data pre-processing.

Inpatient closed-loop studies rely on BG measurements [11]. While CGMS solves the problem of sporadic BG measurements, it does not replace them. CGMS does not measure nor calculate BG. With outpatient studies, feasibility of SMBG is limited too [11]. Frequent and accurate reference BG is key for modeling and computing outcome metrics in clinical trials, but it is difficult, invasive, and costly to collect [13]. Continuous glucose monitoring (CGM) is a minimally-invasive technology that has the requested temporal resolution to substitute BG references for such a scope, but still lacks of precision and accuracy [13]. Therefore, we are motivated to calculate continuous BG from continuously measured IG. In this study, we validate our model of continuous BG calculation with subjects with type 1 diabetes. In addition, we present an extension to the original analytic method to determine model parameters.

1.1. *Related work*

Before we conducted this study, we considered other models of glucose dynamics. Only SMBG and CGMS are available in outpatient study. Therefore, we had to exclude models, which required additional measured quantities (e.g. insulin [14], rate of oxygen consumption [15,16], [18F]fluorodeoxglucose tracer [17]), from the consideration. Then, we excluded models which capture no physiological knowledge—e.g. Volterra–Wiener framework [18] and autoregressive model [19].

To the best of our knowledge, only the Steil–Rebrin model meets the required criteria. Equation (1) denotes this model; $b(t)$ and $i(t)$ symbols denote BG and IG respectively at time t.

$$\frac{\tau}{g}\times\frac{di(t)}{dt}+\frac{1}{g}\times i(t)=b(t) \tag{1}$$

Accordingly to References [20, 21], the g-parameter is steady-state gain and the τ-parameter is IG equilibration time constant. Considering steady state with no change of IG, the g-parameter should equal 1 as there would be zero concentration gradient between IG and BG. Nevertheless, estimating both parameters improves precision of the model [20,22].

Recently, Del Favero et al. [13] considered the g-parameter as 1 while adding a calibration-error model to restore a "true" IG, $i_t(t)$, using Equation (2). The α, β, and γ parameters are considered as calibration parameters, which must be re-determined whenever the CGMS sensor is calibrated. $\Delta t(t)$ is the time difference with respect to the last calibration time – t_{cal}.

$$i_t(t)=\frac{i(t)-\beta-\gamma\times\Delta t(t)}{\alpha};\quad \Delta t(t)=t-t_{cal} \tag{2}$$

From Equation (1), by substituting $i(t)$ with $i_t(t)$ of Equation (2), we obtain Equation (3). In Equation (3), $i(t)$ represents CGMS measured IG.

$$\frac{\tau}{g}\times\frac{\frac{di(t)}{dt}-\gamma}{\alpha}+\frac{1}{g}\times\frac{i(t)-\beta-\gamma\times\Delta t}{\infty}=b(t) \tag{3}$$

As Del Favero et al. [13] considered $g=1$, the α-parameter overtook the role of the g-parameter in Equation (1). Hence, we obtain Equation (4) that shows that Del Favero et al. [13] actually improve precision of the Steil–Rebrin model by adding simple linear regression with time as the explanatory variable. This variable is supposed to capture CGMS sensor degradation since last calibration. Therefore, α, β, and γ must be re-calculated with each calibration.

$$\frac{\tau}{\alpha}\times\frac{di(t)}{dt}+\frac{1}{\alpha}\times i(t)=b(t)+\left[\frac{\gamma}{\alpha}\times\Delta t(t)+\frac{\beta+\tau\times\gamma}{\alpha}\right] \tag{4}$$

Reference [8] queried diabetic type-1 patients' wishes and expectations on artificial pancreas. The patients asked for, i.a., minimal patient intervention, low maintenance, and ease of use. Therefore, we do not expect the patient to collect more BGs than those BGs that are required to keep CGMS calibrated, especially if these additional BGs would be used to re-determine model parameters until the next calibration only. Instead, we are going to meet patients' wishes by designing such a model whose parameters hold over several calibrations, possibly over the entire lifetime of the sensor.

2. Materials and methods

We developed a model that calculates BG from IG [22–25]. The model is based on a system of glucose dynamics and relates present BG and IG to future IG. We devised the physiological foundation of this model in Koutny [23]. Then, we further elaborated this physiological foundation in Koutny [24], where we have shown that model parameters correlate with glucose uptake rates of subcutaneous, skeletal muscle and visceral fat tissues. These rates correspond with other studies, which were conducted using different methods and experimental setups.

Fig. 1 depicts glucose flow in a selected part of glucose dynamics that is directly related to the model. Glucose may appear in the blood, e.g., due to consumed carbohydrates, the breakdown of liver glycogen or an infusion. From the blood, glucose is transported across the capillary membrane into the interstitial fluid. The rate of such a transport is limited by the size of capillary membrane surface, membrane permeability and concentration gradient between BG and IG [2]. In addition, this causes a delay in transport of glucose from blood into interstitial fluid. In the interstitial fluid, the glucose is either utilized