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Blood glucose level reconstruction as a function of transcapillary glucose transport

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ABSTRACT

A diabetic patient occasionally undergoes a detailed monitoring of their glucose levels. Over the course of a few days, a monitoring system provides a detailed track of their interstitial fluid glucose levels measured in their subcutaneous tissue. A discrepancy in the blood and interstitial fluid glucose levels is unimportant because the blood glucose levels are not measured continuously. Approximately five blood glucose level samples are taken per day, and the interstitial fluid glucose level is usually measured every 5 min. An increased frequency of blood glucose level sampling would cause discomfort for the patient; thus, there is a need for methods to estimate blood glucose levels from the glucose levels measured in subcutaneous tissue. The Steil–Rebrin model is widely used to describe the relationship between blood and interstitial fluid glucose dynamics. However, we measured glucose level patterns for which the Steil–Rebrin model does not hold. Therefore, we based our research on a different model that relates present blood and interstitial fluid glucose levels to future interstitial fluid glucose levels. Using this model, we derived an improved model for calculating blood glucose levels. In the experiments conducted, this model outperformed the Steil–Rebrin model while introducing no additional requirements for glucose sample collection. In subcutaneous tissue, 26.71% of the calculated blood glucose levels had absolute values of relative differences from smoothed measured blood glucose levels less than or equal to 5% using the Steil–Rebrin model. However, the same difference interval was encountered in 63.01% of the calculated blood glucose levels using the proposed model. In addition, 79.45% of the levels calculated with the Steil–Rebrin model compared with 95.21% of the levels calculated with the proposed model had 20% difference intervals.

1. Introduction

Let us consider a human diabetic patient who receives regular insulin doses. From time to time, the patient undergoes a detailed monitoring of his/her glucose levels using a continuous glucose monitoring system (CGMS). Over the course of a few days, the CGMS provides a detailed track of the interstitial fluid glucose levels measured in the patient's subcutaneous tissue. A physician reviews the interstitial fluid glucose levels measured. A difference between the blood and interstitial fluid glucose levels is considered to be unimportant because the blood glucose levels are not measured continuously. Approximately five blood glucose-level samples are taken per day, while the interstitial fluid glucose levels are usually measured every 5 min.

As another example, let us consider a critically ill human patient with stress-induced hyperglycemia. Instead of having the patient tolerate the hyperglycemia, intensive insulin infusion therapy could be administered to the patient with the aim of reducing mortality [1,2]. To control the insulin dosage, the patient's glucose levels must be monitored. Once again, it is the CGMS that measures the patient's interstitial fluid glucose levels.

Glucose is primarily distributed throughout the body by blood vessels. The maintenance of normal blood glucose levels is accomplished by a network of hormones, neural signals and substrate effects that regulate endogenous glucose production and glucose utilization by tissues other than the brain [3]. From the blood, glucose is transported through the blood capillary membrane into the interstitial fluid. The interstitial fluid, which is found in the intercellular spaces between tissue cells, supplies the cells with nutrients such as glucose. In the interstitial fluid, the glucose is either utilized or leaves the interstitial fluid to eventually return to the blood. The lymphatic system represents an accessory route through which the fluid can flow from the interstitial spaces into the blood [4].

Interstitial fluid glucose levels then vary, reflecting changes in blood glucose levels. However, the change in interstitial fluid glucose levels exhibits both a delay and a magnitude difference. Different compartments may have different glucose levels; this

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difference is because capillaries in different compartments have different permeabilities [4]. Subsequently, the cells of different tissues have different glucose utilization rates depending on the tissue's metabolic needs and the levels of available glucose. Thus, as blood glucose levels change, subcutaneous tissue glucose levels cannot be assumed to be equivalent to those in different compartments. Describing the relationship between plasma glucose and interstitial fluid glucose dynamics is an important but challenging open problem.

The two-compartment model developed by Steil and Rebrin [5–7], assumes that interstitial fluid glucose levels are a convolution of blood glucose levels and the impulse response of the system with only one unknown parameter. However, a one-parameter model cannot fully describe a complex system.

Another approach used experiments involving glucose tracers. Researchers [8] measured the concentrations of three different glucose tracers in both plasma and the interstitium. Similarly, other studies [9–11] have used an approach based on fluorodeoxyglucose and positron emission tomography. Such studies are intended to elucidate a particular aspect of plasma-interstitium dynamics and are not well suited for everyday use by patients. One has to consider that a diabetic patient will need to wear a CGMS taking five blood samples a day in practice. In addition, a radioactive component (the tracer) is required to perform a positron emission tomography scan, and this is a risk factor for pregnant and breastfeeding women.

Another approach treats measured glucose levels as noisy time series and applies a Kalman filter [12,13]. It estimates future glucose measurements using a systems dynamics model and present glucose measurements. To estimate the model's parameters, one can change the parameters until the estimated glucose levels match the measured glucose levels to a satisfactory degree of accuracy. In this paper, we present an alternative to the Steil–Rebrin model of systems dynamics.

2. Materials and methods

2.1. Experimental setup

Very frequent blood glucose level sampling is the only way to understand if the newly proposed method is able to correctly reconstruct blood glucose dynamics. While other studies [12–14] measure blood glucose levels every 15 min, we measured blood glucose levels every 5 min. The work presented herein was tested on hereditary hypertriglyceridemic rats because this allowed for a frequency of blood glucose level measuring and a longer experiment period than would be acceptable with humans.

First, the experimenter tried to achieve a steady blood glucose level, preferably at 6 mmol/l, using a manually corrected glucose infusion and a constant insulin infusion. After 15 min of the steady state, a bolus of glucose was administered to initiate a rapid rise of blood glucose levels. The experimenter then continued to maintain the steady state at the new blood glucose levels for 60 min. Next, the experimenter administered a short-action insulin bolus to create a rapid fall of blood glucose levels and continued measuring glucose levels for only the next 80 min.

During the experiment, glucose levels were measured simultaneously every 5 min in arterial blood (± 0.2 mmol/l tolerance), subcutaneous tissue, skeletal muscle tissue and visceral fat (15% tolerance for the three latter compartments). For example, when a rat was given a bolus of glucose, the successive glucose levels could be increased by more than 15%. This was not due to an improper calibration of the measuring device but to an inability to further increase glucose level sampling frequencies—see Ref. [15].

This study extends our previous work as we derive an improved model of plasma-interstitium glucose dynamics. Therefore, we reused our previously conducted set of experiments to compare the previous model with the presently proposed model on the same data sets. See Ref. [16] for full details of the experimental setup.

2.2. The Steil–Rebrin model

Using the Steil–Rebrin model, we reviewed the differences between blood glucose levels and CGMS-measured interstitial fluid glucose levels [17,18]. According to Ref. [18], $C_1(t)$ and $C_2(t)$ represent the plasma, i.e., the blood and interstitial fluid glucose levels, respectively, V_1 and V_2 represent the plasma and the interstitial fluid volumes, respectively, and k_{ij} denotes the transfer rate from compartment j to compartment i. Ref. [18] gives Eq. (1).

$$\frac{dC_2(t)}{dt} = -\frac{1}{\tau}C_2(t) + \frac{g}{\tau}C_1(t), \text{ where } g = \tau \times \frac{k_{21} \times V_1}{V_2} \quad \tau = \frac{1}{k_{02} + k_{12}} \tag{1}$$

Ref. [18] assumes the existence of a steady state with no change in interstitial fluid glucose levels. Thus, Eq. (1) transforms into the boundary condition (2).

$$0 = -\frac{1}{\tau}C_2(t) + \frac{g}{\tau}C_1(t) \tag{2}$$

Ref. [18] assumes the following regarding the parameter g: If the blood and interstitial fluid glucose levels are equal, the expected value of g is 1 with respect to Eq. (2). τ is treated as an unknown parameter and is estimated from the data. However, it has been shown that a recalibration of the measured interstitial fluid glucose levels is needed to get the calculated g close to 1. Ref. [18] concludes with a need for developing more sophisticated recalibration procedures with time-varying modulation.

There are three effects on interstitial fluid glucose levels that cannot be covered with a single change in glucose levels: the exchange of glucose between the blood and interstitial fluid across the capillary membrane, the glucose utilization by cells and the accessory route of the lymphatic system by which the glucose returns to the blood after a delay. In laboratory experiments with frequent glucose level sampling, such patterns of glucose levels were observed, which are in conflict with Eq. (1). The interstitial fluid glucose levels were steady for at least 15 min while the blood glucose levels changed. For example, see the original measured glucose levels in Fig. 1. This suggests that either the interstitial fluid glucose levels were sub-sampled or the Steil–Rebrin model is

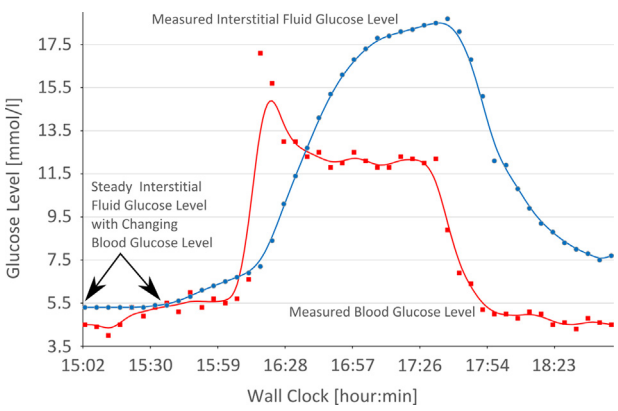

Fig. 1. Blood and interstitial fluid glucose level courses.