A Minimal Exercise Extension for Models of the Glucoregulatory System

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Abstract

For patients with type 1 diabetes mellitus, appropriate control of blood glucose concentrations is vital. Exercise is one of the disturbances that can affect these concentrations. Therefore, predictions in the presence of exercise are useful among others for model-based control methods, bolus calculators and educational tools. Although several models quantifying the effect of exercise are available, they generally include a high number of model parameters, which makes the identification a particularly challenging task, especially if only blood glucose measurements are available. In this paper, a new data-based minimal extension for existing models of the glucoregulatory system, which is able to account for the effect of exercise, is proposed. As observed from clinical data, for given exercise intensities and durations, the model does not depend on exercise intensity, making intensity measurements obsolete. Another main advantage is that this minimal extension involves the identification of only two additional scalar model parameters. The resulting model shows good agreement with the clinical data, and the obtained parameters are consistent between patients.

Keywords: Type 1 Diabetes Mellitus, Dynamical Model Extension, Exercise, Biomedical Systems

1. Introduction

Patients with type 1 diabetes mellitus (T1DM) need to maintain their blood glucose concentrations (BGs) within narrow bounds in order to avoid hypo- and hyperglycemia, which correspond to low and high BGs, respectively. Hypoglycemia may lead to a coma or even death, while high BGs over several years lead to complications such as retinal, neurological, renal or cardiovascular damage [1].

Exercise can have lowering and increasing effects on BGs and patients need to adapt their treatment to stay within the above mentioned bounds if they want to exercise [2]. However, the necessary adaptions are difficult to estimate and, thus, the risk of hypoglycemia is increased during exercise. In this context, models predicting the effect of exercise can be very useful tools for helping patients to adjust their treatment.

Only a few models for exercise are available in the literature [3-6]. Their level of complexity varies strongly, but the number of parameters is typically high, which makes their identification, using only BG measurements, difficult.

For this reason, we propose a minimal exercise extension for existing models of the glucoregulatory system that is based on observations from a clinical study. This extension introduces two additional parameters, that can be identified using only BG

measurements, and one intensity-independent exercise input. Patient specific parameters are shown to be necessary to account for the considerable inter-patient variability.

This paper is organized as follows: In Section 2, the clinical study is described and analyzed. The model extension and the parameter identification method are described in Section 3. Results are presented and discussed in Section 4, while conclusions are drawn in Section 5.

2. Clinical Study

2.1. Protocol

12 patients with T1DM using continuous subcutaneous insulin injection (CSII), 6 female, 6 male, ages 20-45, were monitored during a 2-day in-patient period. During this time, BGs were measured intravenously every 5 minutes and heart rate (HR) was recorded every 5 seconds. Insulin management was performed by the patients themselves. The protocol for both days was identical except for the exercise, which was executed at 65% of maximum HR for the first day and 75% for the second. These exercise periods, performed on cycle ergometers, started at 16h00 and lasted 30 minutes. Among the 12 patients recruited for this study, only 7 presented data that were not corrupted by low BG interventions.

2.2. Analysis

The drop in BG appears to be linear during the effort, as can be observed in Fig.1. For this reason, the most interesting parameter is the slope of the linear part, as illustrated in Fig.1. A linear regression is performed and its dependence on several factors, such as exercise intensity, gender, age, body mass index (BMI), insulin concentrations and initial BGs, is tested. The slope is calculated within a time frame of 30 minutes.
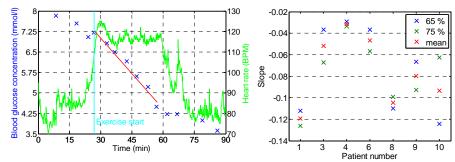

Fig.1. Blood glucose concentration and heart rate for patient 9 on day 2. Illustration of linear regression (red line).

Fig. 2. Comparison of slopes for different patients. Values for both exercise sessions and their mean are shown.

Intuitively one would expect that the drop in BG depends on exercise intensity. In fact, this assumption, which is used by nearly all existing exercise models is somehow contradicted by our clinical study, for the ranges of exercise intensities considered. Fig. 2 shows that the slopes for each patient, except patient 10, are nearly the same for both intensities, and the drop in BG will be considered to be independent of the intensity. Under this assumption, two equivalent datasets are available for each patient.

The results presented in Fig. 2 also show that the slope varies strongly between patients. Thus, individual identification will be performed, similarly to [7], for which individual identification was carried out for different meal types.

The analysis of the influence of the aforementioned factors on the slope does not give any statistically convincing result. Additional data would be necessary to draw more general conclusions.

3. Modeling and Parameter Estimation

3.1. Model Extension

According to [8], exercise leads to increases in several variables of the glucoregulatory system:

- *Insulin sensitivity*, which quantifies the effect of insulin on BGs.
- *Glucose effectiveness at zero insulin*, which gives the insulin independent glucose uptake.
- *Utilization of insulin*, i.e. the rate of elimination of insulin.

Trying to model all these effects simultaneously results in a model that is difficult to identify, as time constants of these effects are similar. Therefore, the effect of exercise is modeled as an increase in glucose effectiveness at zero insulin S_e, in accordance with observations of [9]. The proposed sub-model can, thus, be used as an extension for all models incorporating the concept of insulin independent glucose uptake.

S_e should be 0 when no exercise is performed and have a positive value in the opposite case. The effect of exercise is not instantaneous and therefore a time constant for S_e is introduced. The dynamic behavior of S_e is defined in equation (*1*).

$$\frac{dS_e(t)}{dt} = -a_e S_e(t) + K_e a_e U_e(t) \tag{1}$$

Where a_e (the inverse of the time constant in min^{-1}) and K_e (the exercise sensitivity in min^{-1}) are the two additional parameters that have been introduced.

As a consequence of the independence on exercise intensity, the new input $U_e = 0$ if no exercise is performed and 1 otherwise, and thus, K_e represents the amplitude of the increase in glucose uptake, while a_e shows how fast the effect appears and disappears.

3.2. Parameter Identification

An appropriate model of the glucoregulatory system is needed to identify the resulting new parameters. A modified version of the widely accepted Bergman *minimal model* [10] is used. During exercise, the insulin infusion is constant. Therefore, the effect of insulin is considered constant during this period and can be combined with the glucose effectiveness at zero insulin into the new parameter $S_{ins+zero}$. Endogenous glucose production is assumed to be constant during exercise [9]. The complete model extension corresponds to equations (*1*) and (*2*).

$$\frac{dG(t)}{dt} = -\left(S_{ins+zero} + S_e(t)\right)G(t) + S_{ins+zero}G_b \tag{2}$$

Where G is the BG in mmol/l and G_b is the basal BG chosen equal to 5.5 mmol/l. The term $S_{ins+zero}G_b$ is the endogenous glucose production.

Firstly, $S_{ins+zero}$ is identified for each day and each patient using the data collected before the exercise session, and a standard least squares approach. This allows taking into account differences in insulin infusion that may occur from one day to another.

Then, in a second step, a_e and K_e are identified using the Iterative Two Stage (ITS) method [11]. As the exercise effect is supposed to be identical for the two days, only one couple (a_e, K_e) is identified for each patient.

However, as the sensitivity for a_e is low, an empirical value can be chosen without loss of prediction capabilities, as shown in Fig. 3, and better coefficients of variation are obtained. A value of 0.1 min^{-1} is proposed.

4. Results and Discussion

4.1. Model Fits

Parameters for all patients are given in Table 1. These parameters are consistent as the coefficients of variation are below 100% for nearly all patients and the population mean's coefficient of variation is low. All model fits, as for example shown in Fig. 3 for patient 9, are acceptable. Nevertheless, high variability within some patients can still be observed.
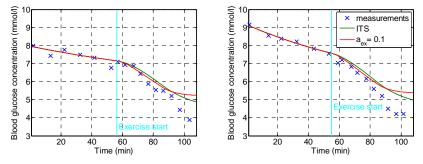

Fig. 3. Model fit for patient 9 for both days

Pat. N.	1	3	4	6	8	9	10	Mean
a_e (ITS)	0.0262	0.0173	0.0173	0.0289	0.0548	0.0508	0.0266	0.0317
	(66)	(120)	(126)	(62)	(42)	(46)	(66)	(47)
K_e (ITS)	0.0195	0.0089	0.0089	0.0231	0.0239	0.0206	0.0197	0.0178
	(45)	(96)	(101)	(40)	(25)	(28)	(45)	(35)
K_e ($a_e = 0.1$)	0.0097	0.0043	0.0042	0.0117	0.0183	0.0164	0.0100	0.0107
	(19)	(45)	(77)	(23)	(17)	(18)	(18)	(51)

Table 1 Identified parameters for all patients and respective coefficients of variation (%)

4.2. Model Limitations

The proposed model extension is strongly based on observations collected during a clinical study. However, this study only covers a small subset of possible exercise setups in terms of exercise duration or intensity and exercise types.

- Because exercise *duration* was 30 minutes, the extension is only applicable for exercise with limited durations. In fact, after about 90 minutes, the physiological processes change since the hepatic glycogen stocks are depleted [12]. Hence, the effects of exercise are no longer captured by the proposed extension after 90 minutes.
- The *exercise intensity* was set to 65 and 75% of the maximal heart rate, i.e. in the aerobic range. However, at higher intensities, the anaerobic threshold is passed and BG dynamics change as described in [13].
- The *type of exercise* that is performed might change the exercise parameters. As only data from cycling are available, this cannot be verified.
- The middle and long term effects of exercise on *insulin sensitivity* are not taken into account in this extension. However, it is shown that these changes in insulin sensitivity can be detected up to 2 days after the exercise session [14], but also over several weeks when regular exercise is performed [15].

5. Conclusion

A model extension for predicting the evolution of BGs during exercise has been proposed. This model was found to be identifiable and in accordance with the clinical study. Additionally, as the exercise input is independent of exercise intensity, no additional measurement device is necessary. Implementations should lead to an improved quality of life for patients suffering from T1DM. Future work will include an extension of the proposed model to longer durations and a broader range of exercise intensities. For this purpose, additional clinical studies will have to be carried out.

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