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Robust Parameter Estimation in a Model for Glucose Kinetics in Type 1 Diabetes Subjects

Cesar C. Palerm*†‡, *Senior Member, IEEE,* María Rodríguez-Fernández§, Wendy C. Bevier‡, Howard Zisser‡, Julio R. Banga§, Lois Jovanovič‡† and Francis J. Doyle, III*†‡, *Senior Member, IEEE*

*Department of Chemical Engineering, University of California Santa Barbara, Santa Barbara, CA 93106-5080

†Biomolecular Science and Engineering Program, University of California Santa Barbara, Santa Barbara, CA 93106-9611

‡Sansum Diabetes Research Institute, 2219 Bath St., Santa Barbara, CA 93105

§Process Engineering Group, IIM-CSIC, Spanish Council for Scientific Research, c/Eduardo Cabello 6, 36208 Vigo, Spain

Abstract— **There is a significant push to develop closed-loop control systems to deliver insulin for type 1 diabetic subjects. As part of this process, mathematical models are required to test and validate the proposed algorithms. There are several published physiology-based models of glucose and insulin dynamics in the literature, however, all of them were derived using data from subjects without diabetes. For this particular study we have selected one of the recently published models, by Hovorka *et al.* [1], replacing the subcutaneous insulin infusion model with the one described by Wilinska *et al.* [2]. Five subjects with type 1 diabetes underwent a hyperinsulinemic-euglycemic clamp with a meal challenge and corresponding subcutaneous insulin bolus. The data collected were used to fit the model parameters using global optimization methods. Our results show that the model is capable of describing the observed dynamics for type 1 subjects under the experimental conditions, and as such can be used to simulate subject behavior under the experimental conditions.**

I. Introduction

Diabetes mellitus is defined as a group of metabolic diseases which are characterized by high levels of blood glucose (hyperglycemia) [3]. This hyperglycemia results from defects in insulin secretion, insulin action, or both. In type 1 diabetes there is an absolute deficiency of insulin secretion, which is due to β cell destruction. People with type 1 diabetes are prone to ketoacidosis and fully depend on exogenous insulin for life support.

The chronic hyperglycemia in diabetes is associated with longterm complications due to damage, dysfunction and failure of various organs. The main complications are heart disease, stroke, retinopathy, nephropathy and neuropathy. These can eventually lead to renal failure, blindness, amputation and other types of morbidity. Subjects with diabetes are at higher risk of cardiovascular disease, and face increased morbidity and mortality when critically ill.

The efficacy of intensive treatment in preventing diabetic complications has been established by the Diabetes Control and Complications Trial (DCCT) [4] and the United Kingdom Prospective Diabetes Study (UKPDS) [5]. In both trials, the treatment regimens that reduced average glycosylated hemoglobin A_{1c} (a clinical measure of glycemic control, which reflects average blood glucose levels over the preceding 2–3 months) to approximately 7% (normal range is 4–6%) were associated with fewer long term microvascular complications. Recent evidence even suggests that these target levels might not be low enough [6].

Tight glucose control (*i.e.* as close to normal as possible) should be maintained for life in order to accrue the full benefits. Many factors influence the insulin dose requirements over time, including weight, physical condition, and stress levels. Due to this constantly changing insulin requirement, frequent blood glucose monitoring is mandated. Based on this monitoring the insulin dosage must be modified, dietary changes implemented (such as alteration in the timing, frequency and content of the meals), and activity and exercise patterns changed.

This need for frequently monitored glucose with adjustments to insulin dosage has spurred research to develop feedback control systems that will automatically adjust insulin dosing [7]–[9]. A critical component of these development efforts is a mathematical model that can be used to test the system's performance under different conditions. There are several physiology-based models in the literature; however, all of them were derived using data from subjects without diabetes (for a review, see [10]).

A particular experimental protocol of interest is the hyperinsulinemic-euglycemic clamp [11]. Picchini *et al.* [12] have modeled the clamp procedure for lean and obese subjects without type 1 diabetes. Their model allows for more information to be extracted from the procedure and thus gain more insight into the variations in insulin resistance. Their model is tailored exclusively for this protocol, thus it might not be applicable in other contexts.

For this particular study we have selected the model published by Hovorka *et al.* [1], replacing the subcutaneous insulin infusion model with the best one described by Wilinska *et al.* [2]. Five subjects with type 1 diabetes underwent a hyperinsulinemic-euglycemic clamp with a meal challenge

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Correspondence to: University of California Santa Barbara, Department of Chemical Engineering, Santa Barbara, CA 93106-5080. frank.doyle@icb.uscb.edu

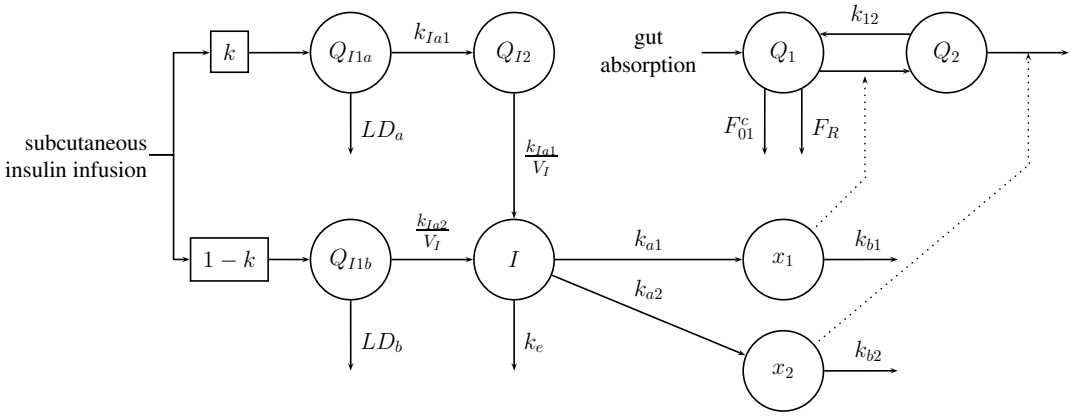

Fig. 1. Structure of the model as implemented for this study. Compartments Q_{I1a} and Q_{I2} correspond to the insulin absorption slow channel, Q_{I1b} to the insulin absorption fast channel, I is plasma insulin concentration, x_1 and x_2 mediate the effects of insulin on the glucose system, and Q_1 and Q_2 correspond to blood and tissue glucose respectively.

and corresponding insulin bolus [13]. All subjects signed an informed, witnessed consent approved by the Santa Barbara Cottage Health Systems Institutional Review Board. The data collected were used to fit the model parameters using global optimization methods. For two of these subjects the procedure was repeated, thus we have independent data to use for validation. Our results show that the model is capable of describing the observed dynamics for type 1 subjects under the experimental conditions, and as such can be used to simulate the subject behavior.

II. Methods

A. Experimental protocol and model description

The experimental protocol is detailed in a previous report [13]. The main objective of the protocol is to gather measurements of the blood glucose response to a mixed meal and the corresponding subcutaneous insulin bolus; the clamp procedure allows us to guarantee that the subject is in euglycemic steady state by the time the meal test begins. From a modeling perspective this is important, as without this clamp procedure additional dynamics might be present that are hard to identify, much less to quantify. For example, if the subject has a hypoglycemic event within a couple of hours before the meal test, this stimulates a counter-regulatory response that secretes stress hormones, which in turn induce insulin resistance. The high levels of plasma insulin during the clamp procedure serves to "turn off" this response. On the down side, the high insulin levels of this procedure also stops endogenous glucose production, thus model parameters corresponding to this effect cannot be estimated.

Blood glucose is measured every five minutes using a YSI 2300 STAT Plus™ (YSI Inc., Yellow Springs, Ohio) for the duration of the experiment. This glucose oxidase based assay is the clinical gold standard, and has an error specification of $\pm 2\%$ of the reading, or 2.5 mg/dl, whichever is higher, and a resolution of 1 mg/dl. The experimental data was preprocessed with a Hampel filter to remove outliers [14].

The model proposed by Hovorka *et al.* [1] is a compartmental model; two states describe plasma and tissue glucose, one is for plasma insulin and the remaining three describe various effects of insulin on glucose dynamics. In general, the model consists of mass-balance equations.

The model captures some aspects of physiology that other models do not address, including the variation of the effect of glucose concentration on the non-insulin-dependent glucose flux, renal glucose clearance, and endogenous hepatic glucose production. Under our experimental conditions we can assume there is no endogenous hepatic glucose production [11], [15], thus we remove this term from our model when estimating parameters, together with the corresponding $x_3(t)$ state.

In a subsequent paper the same group did more detailed modeling of the dynamics of insulin absorption for a subcutaneous infusion [2]. The model they highlight as the best performing divides the absorption into a slow and a fast channel, on the basis that the monomeric form of insulin will get absorbed faster than then dimeric form. The model also allows for local degradation of insulin in the tissue space. The model structure as implemented in this study is shown in figure 1.

B. Parameter estimation and identifiability analysis

Since most mathematical models considered for describing glucose metabolism involve coupled and highly nonlinear phenomena, the resulting parameter estimation problem can be very challenging to solve. In particular, complex nonlinearities might cause non-convexity, *i.e.* the optimization problem may contain several local minima in the area of interest [16]. Thus, if the initial guess is not in the basin of attraction of the global solution, traditional gradient-based methods, like Levenberg-Marquardt or Gauss-Newton, may fail to identify the global solution. Moreover, in the presence of a bad fit, there is no way of knowing if it is due to a wrong model formulation, or if it is simply a consequence of local convergence. Thus, there is an obvious motivation for using methods which provide more guarantees of converging to the globally optimal solution.

Moles *et al.* [17] reviewed the state of the art of global optimisation for parameter estimation and compared several

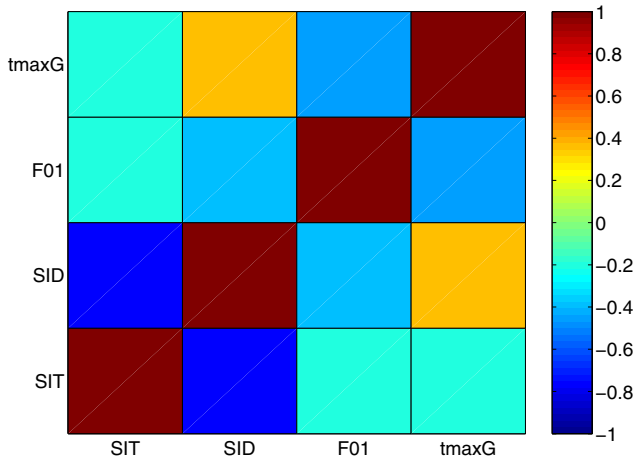

Fig. 2. Correlation matrix corresponding to the nominal parameters.

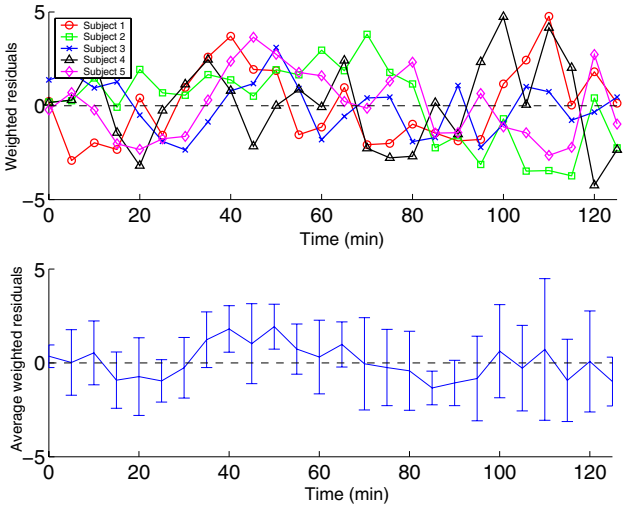

Fig. 3. Percentage of error between experimental and predicted data.

advanced deterministic and stochastic methods, concluding that current deterministic methods are too expensive (in terms of computational effort) for realistic problems. In contrast, stochastic methods can locate the parameter region containing the global solution in a relatively moderate computational time, although with only weak guarantees of global optimality. However, these methods present a rather slow convergence rate, particularly in the final stage of the search, resulting in excessive computation times.

In order to overcome such limitations, Rodríguez-Fernández *et al.* [18] proposed a hybrid methodology reducing significantly the computational effort by enhancing the convergence speed of global methods without losing reliability. The key idea is to combine global and local optimization methods in a sequential two-phase hybrid approach. The methods used were SRES (stochastic ranking for constrained evolutionary optimization) in the global phase and DN2GB (an adaptive nonlinear least-squares algorithm) in the local one, resulting in significantly improved performance.

Adopting the methodology proposed by Rodríguez-Fernández *et al.* [18], we have estimated the parameters corresponding to the glucose subsystem (F_{01}, S_{IT}, S_{ID}) and also $t_{max,G}$ considered to be a model constant by Hovorka *et al.* [1]. The parameters related to the insulin subsystem were kept at the nominal values. The notation is consistent with the original papers [1], [2].

In order to ensure that the parameter estimation problem is well posed, parameter identifiability tests should be performed [19]. Practical identifiability is here evaluated from the correlation matrix, computed from the Fisher Information Matrix as detailed in [18].

For our model, the correlation matrix (see figure 2) presented no off-diagonal elements equal to $+1$ or -1 (the highest correlation, for S_{ID} and S_{IT}, is at -0.774), meaning that all the parameters are *a priori* and *a posteriori* locally identifiable.

III. Results

It is known that parameters of the glucoregulatory system differ considerably between subjects, thus, parameter estimation was performed separately for each subject. Figure 3 shows the percentage error between experimental and predicted data for the glucose concentration as a function of time, showing good agreement for all five subjects.

TABLE I

AVERAGE PREDICTION ERRORS FOR THE GLUCOSE LEVEL

Subject	1	2	3	4	5
fitted data	4.41 %	3.71 %	3.07 %	4.19 %	4.79 %
cross-validation	16.99 %	N/A	N/A	N/A	11.09 %

TABLE II

ESTIMATED MODEL PARAMETER VALUES

	S_{IT} min^{-1}/(mU/L)	S_{ID} min^{-1}/(mU/L)	F_{01} mmol/(kg· min)	$t_{max,G}$ min
Original	5.12e-3	8.20e-4	9.70e-3	40.0
Mean	2.59e-3	6.87e-5	3.33e-2	65.0
Std Dev	1.67e-3	8.13e-5	9.03e-3	22.2

The mean values of the prediction errors for the glucose concentration are given in table I. It is observed that the estimates are fairly accurate and the system dynamics are captured. The average errors are less than 5% for all the subjects under study. The mean of the estimated parameter values and their standard deviation, together with the values in [1] are shown in table II.

For the two subjects that repeated the procedure the data from the second experiment was used to cross-validate the performance of the fitted model. Figures 4 and 5 show, for subject 1, the model fit based on the first experiment and the model prediction compared to the experimental results of the second clamp, respectively. For our purposes, the most important factor is the trend, and this is captured by the model when used to predict the results of the validation clamp. The error itself is not bad, considering that the two experiments were done more than three months apart, a time period sufficiently long that the subject's weight, fitness level and other factors that affect these dynamics most likely changed to some extent. The offset observed can easily be explained by an increase in the insulin sensitivity during the second clamp as compared to the first one.

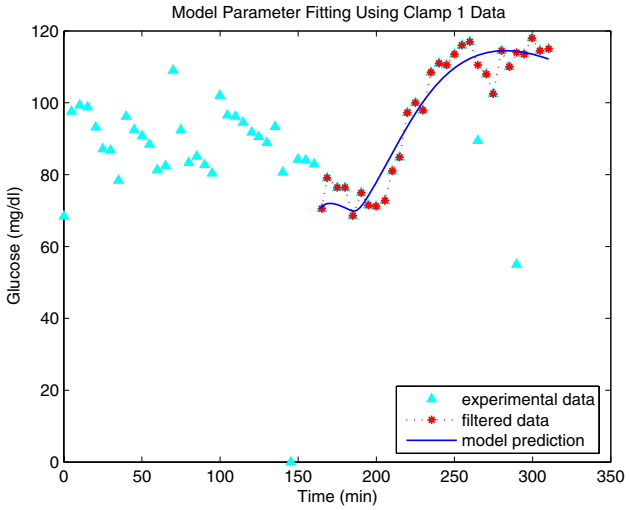

Fig. 4. Model prediction compared with experimental data used for fitting, subject 1.

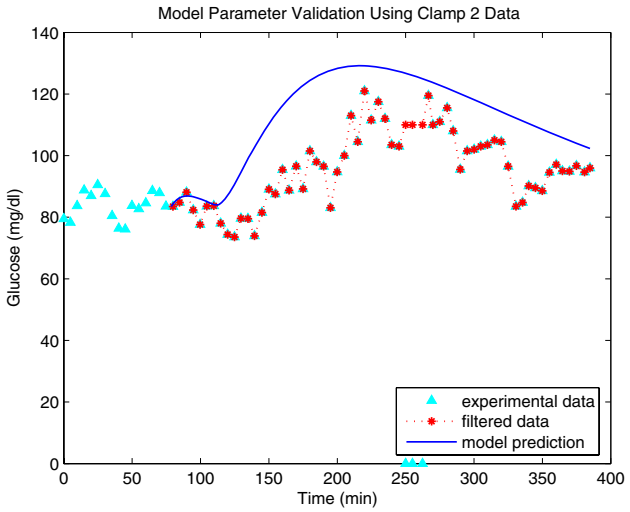

Fig. 5. Model prediction using estimated parameters based on first clamp compared with experimental data of second clamp, subject 1.

IV. Conclusions

The model evaluated is capable of describing the dynamics observed under the experimental protocol of the hyperinsulinemic-euglycemic clamp with meal challenge. This shows that the model in question can serve as a starting point to incorporate other effects that no other model currently describes. These other dynamics are related to the circadian variation in insulin sensitivity, changes to flux rates (insulin and non-insulin mediated) depending on physical activity levels, and counter-regulatory responses to hypoglycemia, stress and so on. Until such a platform is available we will not be able to make strong claims on the performance of any closed-loop control system based only on simulation studies.

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