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A Model of Glucose Evolution in Type 1 Diabetes Patients

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A Model of Glucose Evolution in Type 1 Diabetes Patients

Bachelor Thesis, 23 April 2012

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Abstract

We have analyzed a model proposed by Steil et al. [1] for glucose metabolism. The model consists of 5 differential equations describing the change of a patient's blood glucose concentration to his/her basal and bolus insulin pump data. This relatively simple model of 8 parameters was analyzed using measured plasma insulin and blood glucose concentrations from a study by the Amsterdam Medical Centre of 10 patients of the span of approximately 43 hours. In this study almost continuous blood insulin measurements were taken, in addition to insulin pump data and blood glucose measurements. This is quite difficult to measure, so this gave us a unique opportunity to individually analyze sections of the model.

We have obtained relatively good fits for the insulin plasma submodel on most patients. Our optimisation remained inconclusive on the remaining blood glucose submodel, and alternative formulations to solve this also gave insufficient results. In conclusion, the linear submodel for insulin plasma concentrations described the data, while the remaining submodel for glucose and alternative formulations of it are still in need of further study.

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1. Introduction

The idea of developing an 'artificial endocrine pancreas', which would be used to aid type 1 diabetes patients, has been an area of increasing interest since the 1970's. This idea of closed-loop blood glucose control was pioneered by a number of researchers, such as Albisser et al. [2] and Pfeiffer et al. [3], leading to the production of the first glucose controlled insulin infusion system. This approach has been successful, but is in general too invasive due to the equipment and measurement apparatus necessary to make it function.

As a promising alternative to these approaches, the idea of model predictive glucose control has become an increasingly popular methodology among researchers and practitioners in the field over the past years. Instead of being only reactive, model predictive control uses a mathematical model of the underlying biological dynamics to try and anticipate changes in a patients glucose levels and try to rectify this accordingly.

In this paper we aim to test the validity of a model concerning insulin dynamics in type 1 diabetes patients, which was previously proposed and studied by Steil et al. He examined a model describing a patient's insulin pharmacokinetics and blood glucose appearance following meals. This model is of interest as it contains only five equations and eight identifiable parameters. Furthermore, this model stays relatively simple by allowing for intraday variation in certain model parameters. Previously studied models typically contain a much larger number of equations and parameters, eg. Hovorka et al. [4], Cobelli et al. [5]. If we can find a more simple model which could describe the same behaviour in a satisfactory manner, this would naturally be preferred.

The data we will be using was obtained from a clinical observational study of 10 patients[6]. Usually only the insulin pump data is measured and not the blood insulin concentration, thus this gives us a unique opportunity to test different sections of the model. Such measurements can give better insight into what parts of the pharmacokinetics and -dynamics of this model are well described, and which parts are in need of further research.

In the following sections we will give a brief introduction to type 1 diabetes for those not familiar with it, introduce the mathematical model in question, show how the parameters were identified, and finally discuss our results.

2. Diabetes

Diabetes, formally referred to as diabetes mellitus, is the general term for a disease which manifests itself in different ways, all of which cause high glucose concentration in the blood. Each manifestation has slightly different mechanics, but all interfere with the bodies natural closed-loop system for regulating free blood sugar. Due to this glucose builds up in the blood, and is then disposed of by the body through the urine. The greeks were somewhat aware of this, as the name diabetes mellitus comes from the greek words *diabainein* and *mel* which respectively mean to *pass through* and *sweet*. As this study restricts itself to type 1 diabetes, I shall only explain the dynamics of this form of diabetes.

2.1. Insulin Feedback Loop

The disrupted closed-loop system I mentioned above starts in the stomach, where ingested foods are digested and sugars are released into the blood for further use by cells throughout the body. From this point two substances take over the job, insulin and glucagon. Insulin is

responsible for the storage of glucose, and it also allows cells to use it for energy which they need to function.

Insulin is released when blood glucose levels are high (known as hyperglycaemia) to reduce this surplus. Glucagon on the other hand, is responsible for the release of stored glucose and is released when glucose levels are low (hypoglycaemia) to compensate for the shortage. These two together form part of a feedback loop which keeps blood glucose at healthy levels.

In a type 1 diabetic patient this cycle is broken due to an auto-immune reaction in the body which kills off beta-cells in the pancreas, which are responsible for producing insulin during hypoglycaemia. Blood glucose builds up in the blood, and cells are unable to get the required energy for their metabolic reactions. This has short term effects such as fatigue, increased urination, increased hunger and thirst, but also serious long term effects such as multiple organ failure, damage to the nervous system and brain, and death if not treated. At the moment there is no known cure, so the only option now is to try and simulate the insulin production of the pancreas.

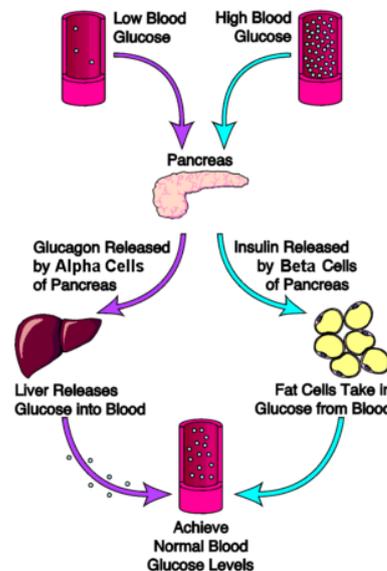


Figure 1: Insulin-glucagon feedback loop. [13]

2.2. Treatment

What we are trying to simulate, namely how insulin is released from the pancreas of a healthy person, is a complex mechanism. When blood glucose rises, for example after a meal, the beta-cells rapidly release insulin in response, followed by a slower extended release. Blood sugar levels naturally oscillate due to the nature of the feedback loop, and meals can cause these oscillations to be quite large. In addition, this behaviour is determined by highly personal factors and differs from person to person, and even in the same person biological factors can vary from day-to-day. Although challenging, ideally we would like to imitate this natural behaviour in diabetic patients.

Currently two methods of insulin administration are used. Patients can make use of manual injections, or they can have an insulin pump implanted in the body which can continuously inject insulin. Although injections are often used, they provide much less thorough control of blood glucose levels as users typically inject only 3-4 times a day. This means large oscillations in blood sugar levels and a larger deviation from the bodies' natural concentrations. Frequent sampling of glucose levels would allow for much better control using a pump and a sensor, but this requires an algorithm to administer insulin based on the measurements.

2.3. Closed Loop Control Algorithm

In general these algorithms designed for closed loop control fall into one of two categories, proportional-integral-derivative control and model predictive control. Proportional-integral-derivative control algorithms are reactive in nature, responding to changes in glucose levels

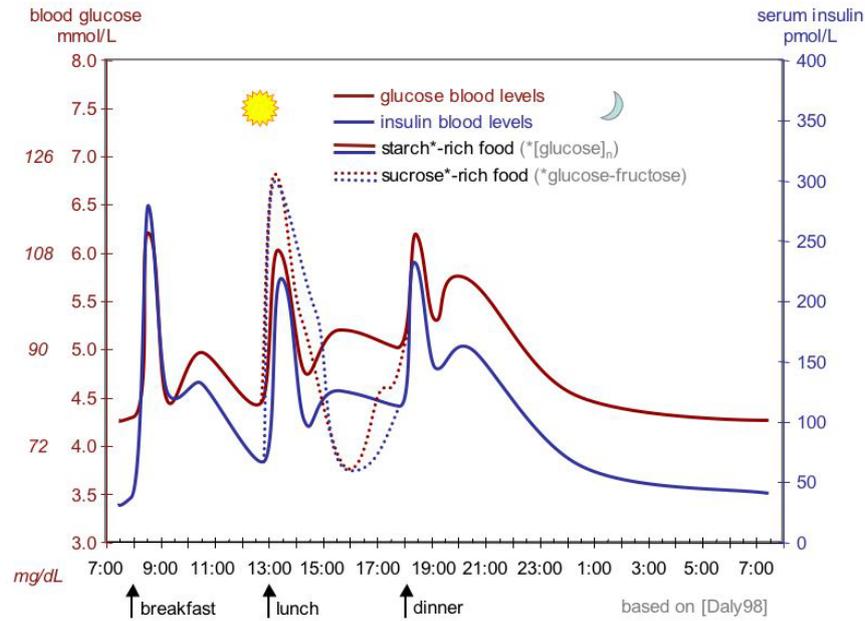


Figure 2: Glucose and insulin levels in a non-diabetic person. [14]

with adjustment in insulin delivery. This causes time delays due to measurements being discrete instead of continuous like a real pancreas, and is obviously not ideal.

Model predictive control algorithms are based on mathematical models of the human pancreas, and because of this can anticipate changes in glucose level. These algorithms are proactive, and are clearly preferable because of how this better mimics the human body. Having an accurate mathematical model of the behaviour of this feedback loop is an important piece of the puzzle in making an effective artificial pancreas.

3. Model

The model in question we will be studying is a modified version of the model suggested by Bergman et al. [7], with other parts being taken from a number of other models proposed by Sherwin et al. [8] and from work done R. Hovorka[4] and associates. It is a compartmental model, with the following physiological quantities we are interested in:

- $ID(t)$ [U/min] = insulin pump rate which is used as an input function for the model (U represents units of insulin);
- $I_{sc}(t)$ [$\mu U/ml$] = subcutaneous insulin concentration, signifying the area of insulin injection;
- $I_p(t)$ [$\mu U/ml$] = concentration of insulin the patient's blood plasma;
- $I_{eff}(t)$ [dimensionless] = how strong the effect of the plasma insulin concentration is on the blood glucose level;
- $G(t)$ [mg/dl] = blood glucose concentration in the patient;
- $R_A(t)$ [$mg/(dl \cdot min)$] = increase in blood glucose due to meals consumed.

The model in question makes use of a form of model commonly used in mathematical biology, namely *compartmental analysis*. Each of the circles below represents an idealized compartment in which one could imagine the relevant substances being stored. The arrows between these compartments are then the equations which give the relationships between them as a function of time. The amounts denoted next to each arrow represents the rate of change at which these relations occur.

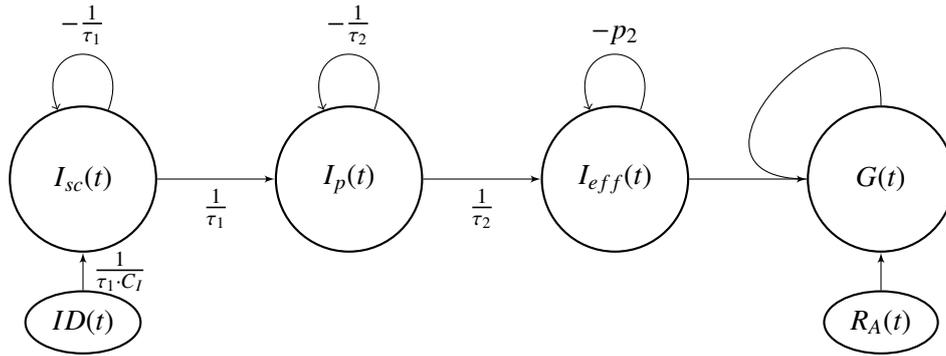


Figure 3: A schematic representation of Steil's model.

With this in mind the model is represented by the equations below:

$$\frac{d}{dt}I_{sc}(t) = -\frac{1}{\tau_1}I_{sc}(t) + \frac{1}{\tau_1} \frac{ID(t)}{C_1}$$

$$\frac{d}{dt}I_p(t) = -\frac{1}{\tau_2}I_p(t) + \frac{1}{\tau_2}I_{sc}(t)$$

$$\frac{d}{dt}I_{eff}(t) = -p_2 \cdot I_{eff}(t) + p_2 \cdot S_I \cdot I_p(t)$$

$$\frac{d}{dt}G(t) = -\left(GEZI + I_{eff}(t)\right) \cdot G(t) + EGP + R_A(t)$$

$$R_A(t) = \sum_i \frac{C_i}{V_G \cdot \tau_{m,i}^2} \cdot t \cdot e^{-\frac{t}{\tau_{m,i}}}$$

Note that in the equation for $R_A(t)$ we take the sum over the i meals consumed during the time patients are monitored.

The parameters involved are the following:

- $\tau_{1,2} [min]$ = the time constants related to insulin movement between the subcutaneous delivery site and the blood plasma;
- $C_I [ml/min]$ = insulin clearance from the injection to the subcutaneous injection site;
- $p_2 [min^{-1}]$ = delay in insulin action following an increase in plasma insulin;
- $S_I [ml/\mu U]$ = insulin sensitivity;
- $GEZI [min^{-1}]$ = the influence the glucose level itself has on the glucose uptake into cells and on the endogenous glucose production at zero insulin;

- $EGP [mg/(dl \cdot min)]$ = endogenous glucose production estimated at zero insulin.

The parameters involving glucose absorption from meals have the following interpretation:

- $C_i [g]$ = the amount of carbohydrates consumed during meal i ;
- $V_G [dl]$ = relates to the distribution volume in which glucose equilibrates;
- $\tau_{m,i} [min]$ = peak time of absorption for meal i .

This is model clearly a simplification of how these processes actually function in the body, but what we want to find out is if the above model is sufficiently accurate for our needs.

We will also consider an alternative formulation for the initial plasma insulin model, namely the one proposed in Steil's paper. He introduces a so called 3-compartment model which can be formulated as follows:

$$\begin{aligned}\frac{d}{dt}I_{sc}(t) &= -\frac{1}{\tau_1}I_{sc}(t) + \frac{1}{\tau_1} \frac{ID(t)}{C_1} \\ \frac{d}{dt}I_2(t) &= -\frac{1}{\tau_2}I_2(t) + \frac{1}{\tau_2}I_{sc}(t) \\ \frac{d}{dt}I_p(t) &= -\frac{1}{\tau_3}I_p(t) + \frac{1}{\tau_3}I_2(t)\end{aligned}$$

which introduces an extra variable I_2 combined with parameter τ_3 which both relate to insulin movement as with the other two already existing variables. This extra equation governs I_2 in the exact same fashion as the first equation governs I_{sc} , so can be seen as an extra identical compartment being added to the model. We will investigate whether this offers any improvement to the 2-compartment formulation, but will use the first model if possible as this would give a simpler description method.

4. Problem Description

What we want to achieve in this thesis is to test the validity of the mathematical model against patient medical data obtained by the AMC (Academisch Medisch Centrum) in Amsterdam [6]. In order to do this we must first estimate the unknown model parameters for each patient, as these parameters are patient-specific. We will do this by minimizing the sum square error (SSE) between the model predicted values and measured concentrations:

$$\arg \min_{p_j} \{\text{SSE}\} = \arg \min_{p_j} \left\{ \sum_i (y_i - y(t_i, p_j))^2 \right\},$$

with p_j representing our unknown parameters, (t_i, y_i) our data points, and $y(t, p_j)$ being the insulin plasma predicted by the model. The above expression gives us a fairly good idea of how close the values predicted are to the ones in our data, so at the same time this also tells us how close our estimated parameters are to the ideal ones we seek (where the SSE is zero).

At this point we need to make a distinction between model parameters and optimisation parameters. As we've seen the system of differential equations has 8 unknown parameters we want to estimate. We call these the model parameters. In order to estimate these, we also need the initial values of each quantity which are only used during the optimisation procedure. Since we need an initial value for each quantity we have $8 + 4 = 12$ optimisation parameters.

4.1. Patient Data

Patients were hospitalized on day 1 at 6.00 PM. A subcutaneous glucose sensor was placed in the abdomen and a venous catheter was inserted in the forearm. The administered insulin was insulin aspart. At 8.00 PM the measurements started. On day 2, three meals with known carbohydrate content were served at 8.00 AM, 12.00 AM and at 6.00 PM. On day 3 breakfast was served at 7.30 AM, three hours later followed by an exercise of 30 minutes. After the exercise lunch was served at 12.00 AM. Three hours after lunch the patients were discharged home. Venous glucose and insulin concentration were measured during the observation: at rest every hour, every 10 minutes after a meal the first hour and the last two hours every 20 minutes. During exercise, the measurements were performed every 5 minutes. The exercise of 30 minutes was made by home trainer with an average intensity of $75 \pm 5\%$ of the theoretical heart rate reserve frequency. Heart rate reserve frequency is calculated by the formula $(220 - \text{age} - \text{heart rate at rest})$ multiplied by 75% . Furthermore the amount of administered insulin was noted. The basal rate of the insulin pump and the mealtime boluses were recorded.

The relevant measurements for our model are the measured insulin pump rate ($ID(t)$), the plasma insulin concentration ($I_p(t)$), the blood glucose concentration ($G(t)$), and the amount of carbohydrates consumed during each meal time (C_i). The insulin pump rate $ID(t)$ consists of the basal rate of the insulin pump and the mealtime boluses combined. For the blood glucose concentration, measurements were made using two different methods. One method was a monitor on the patient in question, which could then measure this quantity in a continuous fashion. The other method was taking discrete blood samples and then analyzing them in the lab. Since the lab measurements generally agreed with the glucose monitor data, we used monitor data as this gave us much more information about the quality of the model fit.

As the measurements were taken in SI units and the model is formulated in terms of Conventional (US) units, the data received was converted from SI to Conventional quantities according to values given by the Society for Biomedical Diabetes Research [10].

4.2. Splitting into subsystems

One useful fact about the model is that the dependence of our differential equations is unidirectional. To put this into more precise terms, the equation for variable i is independent of $i + 1$ and greater. This means we can evaluate the model sequentially in the form of subsystems, and we will do this in the following manner. The first subsystem is:

$$\begin{aligned}\frac{d}{dt}I_{sc}(t) &= -\frac{1}{\tau_1}I_{sc}(t) + \frac{1}{\tau_1} \frac{ID(t)}{C_1} \\ \frac{d}{dt}I_p(t) &= -\frac{1}{\tau_2}I_p(t) + \frac{1}{\tau_2}I_{sc}(t).\end{aligned}$$

Since we have recorded insulin pump values of each patient, we can identify all the unknown parameters in this subsystem per patient by minimizing the SSE between what the above model predicts and the measured blood insulin concentrations. The second subsystem consists of the remaining equations, namely:

$$\begin{aligned}\frac{d}{dt}I_{eff}(t) &= -p_2 \cdot I_{eff}(t) + p_2 \cdot S_I \cdot I_p(t) \\ \frac{d}{dt}G(t) &= -(GEZI + I_{eff}(t)) \cdot G(t) + EGP + R_A(t) \\ R_A(t) &= \sum_i \frac{C_i}{V_G \cdot \tau_{m,i}^2} \cdot t \cdot e^{-\frac{t}{\tau_{m,i}}}\end{aligned}$$

and for this we can use the recorded C_i and I_p values as input, and fit this to the lab measured blood glucose concentrations.

There are many advantages to this subsystem approach. Since we split one optimisation attempt into two separate ones, we also cut the parameters space for each of these attempts in half. Since the problem of finding a global minimum becomes significantly harder in larger dimensional parameter spaces, this greatly increases our chances of finding good fits.

A second advantage is in the case we run into difficulties finding the optimum parameters. Let us imagine we cannot find good parameters for one fit of the whole model. If we assume the model is incorrect, we would like to know which part of the model is causing problems. By splitting it up into subsystems and using measured data as input for subsystem two (instead of simulated data from subsystem 1) we essentially make their fitting processes independent, and we can then study them independently.

This does have a negative side as well, since an implementation of this model would be as a whole system and not as two subsystems. This means that we ideally want to study the fit of the entire system, therefore any discrepancies between simulated and measured I_p would result in differences in a fit of the whole system and the fit of the second subsystem. Therefore we have also kept that in mind during this study.

5. Finding solutions analytically

Although not always possible, solving such problems analytically has numerous advantages to numerical options. Having exact solutions is obviously more accurate, but the path to finding these solutions often gives us insight into the nature of the problem and grants us a better understanding of the underlying mechanics involved.

5.1. Existence of optimum parameters

Recall that our current formulation of the problem of finding the "true" parameters is to minimize the following function cost function $C : [0, c_1] \times [0, c_2] \times \dots \times [0, c_5] \rightarrow \mathbb{R}$,

$$C(\mathbf{c}) = \int_{T \subset \mathbb{R}} (y_i - y(t, \mathbf{c}))^2 dt$$

which is integrated over the relevant time interval T . Since we are integrating over a set of discrete data points in time, namely (t_i, y_i) , this integral can be written as the following sum:

$$C(\mathbf{c}) = \sum_i (y_i - y(t_i, \mathbf{c}))^2 \tag{1}$$

with respect to the parameter vector $\mathbf{c} \in \mathbb{R}^5$ with $y(t, \mathbf{c})$ being the second component of the solution of a differential equation of the form:

$$\mathbf{y}'(t) = f(t, \mathbf{y}(t), \mathbf{c}) \quad \text{with } \mathbf{y} \in \mathbb{R}^2 \quad (2)$$

where we limit the parameter vector to some $[0, c_1] \times [0, c_2] \times \cdots \times [0, c_5] \subset \mathbb{R}^5$. With this in mind consider the following theorem, which we will use to show that there exists a unique solution to our problem. Note that we use the notation $B_\varepsilon(x_0) := \{x \in X : d(x, x_0) < \varepsilon\}$.

Theorem. (Picard-Lindelöf Existence Theorem). *Let $f : B_\alpha(t_0) \times B_\beta(y_0) \rightarrow \mathbb{R}^n$, and consider the following initial value problem:*

$$y'(t) = f(t, y(t)) \quad y(t_0) = y_0 \quad y \in \mathbb{R}^n.$$

If f is uniformly Lipschitz continuous in y and continuous in t , then there exists a solution to the above initial value problem on $[t_0, t_0 + b]$, with $b = \min\{\alpha, \beta/M\}$ and $M = \max_{y \in B_\beta(y_0), t \in B_\alpha(t_0)} |f(t, y)|$, and that solution is unique.

We should first note that the form stated in Picard-Lindelöf is exactly the form of our model. Also considering that (2) is linear in y in our case, this also implies that it is Lipschitz continuous in y and in particular for any β such that $y \in B_\beta(y_0)$. It is also continuous in t , under the reasonable assumption that $ID(t)$ is continuous. Thus there exists a unique solution to (2) on $[t_0, t_0 + b]$ with $b = \min\{\alpha, \beta/(\max_{y \in B_\beta(y_0), t \in B_\alpha(t_0)} |f(t, y)|)\}$.

Now we will show that this solution is continuously dependent on its parameters.

Theorem. (Continuous Dependence on Parameters [11]). *Suppose $f : B_b(y_0) \times B_r(\mu_0) \rightarrow \mathbb{R}^n$ is uniformly Lipschitz dependent on $y \in B_b(y_0)$ and is a uniformly continuous function of parameters $\mu \in B_r(\mu_0)$. Then the ODE $y' = f(y, t, \mu)$ has a unique solution that is a uniformly continuous function of μ on some interval T .*

Since we have already shown that (2) is Lipschitz with respect to y , we only have to show that it is also uniformly continuous function of μ . Since (2) is not linear with respect to its parameters, we must be careful how we choose our r . All of the parameters are of the form $1/\tau_1$, so we must choose r and μ_0 such that $B_r(\mu_0) \cap \{0\} = \emptyset$. Then f is indeed uniformly continuous with respect to its parameters on $B_r(\mu_0)$. From this we have that the solution to (2) is uniformly continuous with respect to its parameters.

Now we have a solution to (2) which is continuous with respect to its parameters. Due to the form of the cost function (1), which is polynomial in nature, we now have that this too is continuous with respect to the same parameters.

Then according to the extreme value theorem, any continuous function $f : K \rightarrow \mathbb{R}$ attains a minimum on K , if K is compact. We are now dealing with the continuous function $C : [0, c_1] \times [0, c_2] \times \cdots \times [0, c_5] \rightarrow \mathbb{R}$, and since $[0, c_1] \times [0, c_2] \times \cdots \times [0, c_5]$ is a bounded subset of \mathbb{R}^5 and therefore compact, we know that C will attain a minimum value on this subspace.

5.2. Integrating factor

Since we are dealing with an array of differential equations, we have a number of solution techniques available to us to tackle these problems. As we mentioned previously, the system can be split into two sets of two equations. The first set of equations is then linear, while the second set is non-linear. For the first set I used the method of the integrating factor, which can then be used multiple times as the differential equation for I_{sc} contains no I_p terms.

For ease of notation, we take $1/\tau_1 = c_1$ and $1/(\tau_1 \cdot C_I) = c_2$, giving the following first-degree differential equation:

$$I'_{sc} + c_1 I_{sc} = c_2 ID(t).$$

This form of differential equation has a known solution, which is as follows:

$$I_{sc} = e^{-\frac{t}{\tau_1}} \int_0^t e^{\frac{\tau}{\tau_1}} \cdot \frac{ID(\tau)}{\tau_1 C_I} d\tau + e^{-\frac{t}{\tau_1}} I_{sc}(0).$$

Since the equation for I_p is of the same form, we can iterate this process to get the following expression for I_p :

$$I_p(t) = e^{-\frac{t}{\tau_2}} \int_0^t e^{\frac{\tau}{\tau_2}} \frac{1}{\tau_2} \left(e^{-\frac{\tau}{\tau_1}} \int_0^\zeta e^{\frac{\zeta}{\tau_1}} \cdot \frac{ID(\zeta)}{\tau_1 C_I} d\zeta + e^{-\frac{\tau}{\tau_1}} I_{sc}(0) \right) d\tau + e^{-\frac{t}{\tau_2}} I_p(0)$$

which can then be expanded to

$$I_p(t) = \frac{1}{\tau_1 \tau_2 C_I} e^{-\frac{t}{\tau_2}} \int_0^t \int_0^\tau e^{\left(\frac{\tau}{\tau_2} - \frac{\tau}{\tau_1} + \frac{\zeta}{\tau_1}\right)} \cdot ID(\zeta) d\zeta d\tau + \frac{1}{\tau_2} e^{-\frac{t}{\tau_2}} \int_0^t e^{\left(\frac{\tau}{\tau_2} - \frac{\tau}{\tau_1}\right)} I_{sc}(0) d\tau + e^{-\frac{t}{\tau_2}} I_p(0)$$

Then we interchange the order of integration of τ and ζ and evaluate the single integral on the right to obtain

$$I_p(t) = \frac{1}{\tau_1 \tau_2 C_I} e^{-\frac{t}{\tau_2}} \int_0^t \int_\zeta^\tau e^{\left(\frac{\tau}{\tau_2} - \frac{\tau}{\tau_1} + \frac{\zeta}{\tau_1}\right)} \cdot ID(\zeta) d\tau d\zeta + \frac{\tau_1 - \tau_2}{\tau_1 \tau_2^2} \left(e^{-\frac{t}{\tau_1}} + e^{-\frac{t}{\tau_2}} \right) I_{sc}(0) + e^{-\frac{t}{\tau_2}} I_p(0)$$

and then the integral over τ can be evaluated to give

$$I_p(t) = \frac{\tau_1 - \tau_2}{\tau_1^2 \tau_2^2 C_I} e^{-\frac{t}{\tau_2}} \int_0^t \left(e^{\left(\frac{t}{\tau_2} - \frac{t}{\tau_1} + \frac{\zeta}{\tau_1}\right)} - e^{\frac{\zeta}{\tau_2}} \right) \cdot ID(\zeta) d\zeta + \frac{\tau_1 - \tau_2}{\tau_1 \tau_2^2} \left(e^{-\frac{t}{\tau_1}} + e^{-\frac{t}{\tau_2}} \right) I_{sc}(0) + e^{-\frac{t}{\tau_2}} I_p(0).$$

This expression can then be used to find extra information about the optimal solution of our original problem. Using the shorthand notation $A(\tau_1, \tau_2, t) := \frac{\tau_1 - \tau_2}{\tau_1^2 \tau_2^2 C_I} e^{-\frac{t}{\tau_2}} \int_0^t \left(e^{\frac{t}{\tau_2} - \frac{t}{\tau_1} + \frac{\zeta}{\tau_1}} - e^{\frac{\zeta}{\tau_2}} \right) \cdot$

$ID(\zeta) d\zeta$, $B(\tau_1, \tau_2, t) := \frac{\tau_1 - \tau_2}{\tau_1 \tau_2^2} \left(e^{-\frac{t}{\tau_1}} + e^{-\frac{t}{\tau_2}} \right)$ and $C' := 1/C_I$ we can write the sum square error as

$$\begin{aligned} L &= \sum_{i=1}^N (y_i - I_p(t_i))^2 \\ &= \sum_{i=1}^N \left(y_i - C' A(\tau_1, \tau_2, t_i) - I_{sc}(0) B(\tau_1, \tau_2, t_i) + I_p(0) e^{-\frac{t_i}{\tau_2}} \right)^2 \end{aligned}$$

Now since we want to minimise L with respect to its parameters, we know that such a set of parameters must satisfy $(\partial L)/(\partial \mu) = 0$ for all parameters μ . Consider the following:

$$\begin{aligned}\frac{\partial L}{\partial C'} &= -2 \sum_{i=1}^N \left(y_i - C' A(\tau_1, \tau_2, t_i) - I_{sc}(0) B(\tau_1, \tau_2, t_i) + I_p(0) e^{-\frac{t_i}{\tau_2}} \right) \cdot A(\tau_1, \tau_2, t_i) \\ \frac{\partial L}{\partial I_{sc}(0)} &= -2 \sum_{i=1}^N \left(y_i - C' A(\tau_1, \tau_2, t_i) - I_{sc}(0) B(\tau_1, \tau_2, t_i) + I_p(0) e^{-\frac{t_i}{\tau_2}} \right) \cdot B(\tau_1, \tau_2, t_i) \\ \frac{\partial L}{\partial I_p(0)} &= -2 \sum_{i=1}^N \left(y_i - C' A(\tau_1, \tau_2, t_i) - I_{sc}(0) B(\tau_1, \tau_2, t_i) + I_p(0) e^{-\frac{t_i}{\tau_2}} \right) \cdot e^{-\frac{t_i}{\tau_2}}\end{aligned}$$

By setting each of these derivatives to zero we get the an array of equations.

$$\begin{aligned}C' \sum_{i=1}^N A(\tau_1, \tau_2, t_i)^2 + I_{sc}(0) \sum_{i=1}^N A(\tau_1, \tau_2, t_i) B(\tau_1, \tau_2, t_i) + I_p(0) \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A(\tau_1, \tau_2, t_i) &= \sum_{i=1}^N y_i A(\tau_1, \tau_2, t_i) \\ C' \sum_{i=1}^N A(\tau_1, \tau_2, t_i) B(\tau_1, \tau_2, t_i) + I_{sc}(0) \sum_{i=1}^N B(\tau_1, \tau_2, t_i)^2 + I_p(0) \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B(\tau_1, \tau_2, t_i) &= \sum_{i=1}^N y_i B(\tau_1, \tau_2, t_i) \\ C' \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A(\tau_1, \tau_2, t_i) + I_{sc}(0) \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B(\tau_1, \tau_2, t_i) + I_p(0) \sum_{i=1}^N \left(e^{-\frac{t_i}{\tau_2}} \right)^2 &= \sum_{i=1}^N y_i e^{-\frac{t_i}{\tau_2}}\end{aligned}$$

In order to solve this we can convert this to matrix notation. To save space we use $A_i := A(\tau_1, \tau_2, t_i)$ and $B_i := B(\tau_1, \tau_2, t_i)$ giving us

$$\begin{pmatrix} \sum_{i=1}^N A_i^2 & \sum_{i=1}^N A_i B_i & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A_i \\ \sum_{i=1}^N A_i B_i & \sum_{i=1}^N B_i^2 & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B_i \\ \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A_i & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B_i & \sum_{i=1}^N \left(e^{-\frac{t_i}{\tau_2}} \right)^2 \end{pmatrix} \begin{pmatrix} C' \\ I_{sc}(0) \\ I_p(0) \end{pmatrix} = \begin{pmatrix} \sum_{i=1}^N y_i A_i \\ \sum_{i=1}^N y_i B_i \\ \sum_{i=1}^N y_i e^{-\frac{t_i}{\tau_2}} \end{pmatrix}$$

which is then solvable if the matrix on the left is invertible, which is the case when its determinant $\mathbf{det} \neq 0$. If it is not equal to zero, then we can express $C', I_{sc}(0)$ and $I_p(0)$ in terms of τ_1 and τ_2 in the following manner:

$$\begin{pmatrix} C' \\ I_{sc}(0) \\ I_p(0) \end{pmatrix} = \frac{1}{\mathbf{det}} \begin{pmatrix} \sum_{i=1}^N A_i^2 & \sum_{i=1}^N A_i B_i & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A_i \\ \sum_{i=1}^N A_i B_i & \sum_{i=1}^N B_i^2 & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B_i \\ \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} A_i & \sum_{i=1}^N e^{-\frac{t_i}{\tau_2}} B_i & \sum_{i=1}^N \left(e^{-\frac{t_i}{\tau_2}} \right)^2 \end{pmatrix}^T \begin{pmatrix} \sum_{i=1}^N y_i A_i \\ \sum_{i=1}^N y_i B_i \\ \sum_{i=1}^N y_i e^{-\frac{t_i}{\tau_2}} \end{pmatrix}$$

which now reduces the amount of parameters we have to optimise for from 5 to 2, which should greatly simplify the process.

Unfortunately this process cannot be emulated for the second set of equations, as there are non-linear terms in the equation for $G(t)$. For such non-linear differential equations there often no solutions in analytical form, and for those that do have them they are often extremely complicated. Therefore we will have to solely rely on numerical solution procedures for the problem at hand.

6. Finding solutions numerically

In this section we try to estimate the optimum parameters by minimizing the SSE, but here we do it using numerical methods and algorithms. This approach is often advantageous for such biological problems as their differential equations are often non-linear, complicated, and they contain many parameters. We sacrifice some accuracy in our parameter estimates in order to make the problem of fitting easier.

For these numerical simulations MATLAB® [12] was used, and any command mentioned in the form `command` will refer to the corresponding function or command in MATLAB.

6.1. Step-by-step approach

With the techniques used in this paper, namely Levenberg-Marquardt and Nelder Mead optimisation techniques, the value at which the optimisation is started has a large impact on what minimum is found, and how optimal this point is. The second model in particular has a substantially larger parameter space, which exacerbates this problem considerably. To minimize this, we tried to hand-tune each parameter to get as close to a reasonable starting point as possible, and varied around this point. Such hand-tuning is also very limited in larger parameter spaces, but by doing this we try to reduce the chance of falling into local minima.

Unfortunately this varying of parameters has inherent limitations in larger parameters spaces. If we would want to evaluate just 3 points per dimension, this would lead to having to optimise for $3^{12} = 531,441$ different starting points, which is clearly not feasible. We try to still have some variance in initial points, so we evaluated $\lambda \cdot p_0$, with λ taking different values in the interval $[0, 2]$. Since the plasma insulin model has a five-dimensional parameter space, we can with some confidence say we avoid local minima, but since the blood glucose model contains 12 or more parameters, there is a much larger chance of getting stuck in local minima.

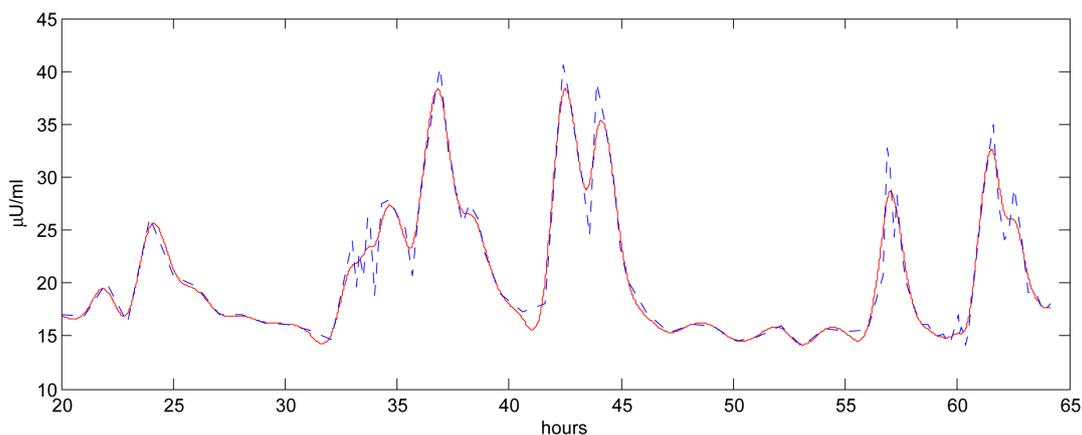


Figure 4: An example of the smoothing algorithm used. Blue: unchanged data from insulin sensor. Red: Insulin data after smoothing.

We started by smoothing the measured blood insulin and blood glucose data using smoothing splines. This was done using the `csaps` function with a smoothing parameter $p = 0.0005$. This was needed as there was noticeable noise in the measurements, which can have any number of reasons such as measurement errors. This can significantly lower the fit of otherwise ideal parameters, and is therefore unwanted. Smoothing in this fashion assumes the error caus-

ing the noise is one which is centered around the actual (error-free) value, and is not biased. Considering such an error would be caused by measuring equipment, such as measurement inaccuracies and not be systematically done, it is valid to assume this error is unbiased. The results of this smoothing can be seen in figure 4.

First subsystem of equations

Since the insulin pump data was given as two sets of data, the basal insulin rate and the size of administered insulin boli, these were combined into one data set for insulin delivery. Since the boluses were given as discrete amounts, these were added to the basal rate as $b_i \cdot \Gamma(5, 7)$ with b_i the value of the insulin bolus and $\Gamma(k, \theta)$ the gamma distribution with shape k and scale θ . This is justified in that the area under such a curve is equal to the size of its respective insulin bolus.

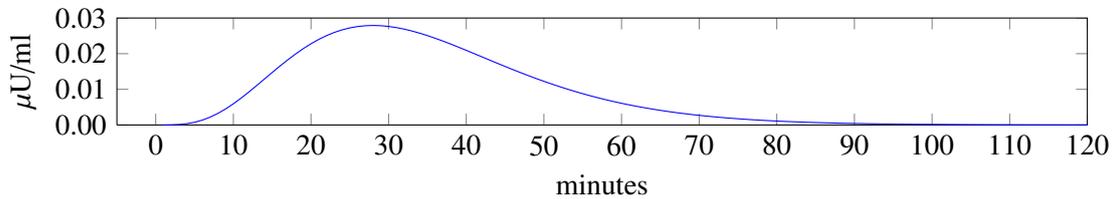


Figure 5: The resulting pump insulin rate from a single bolus of $1U$.

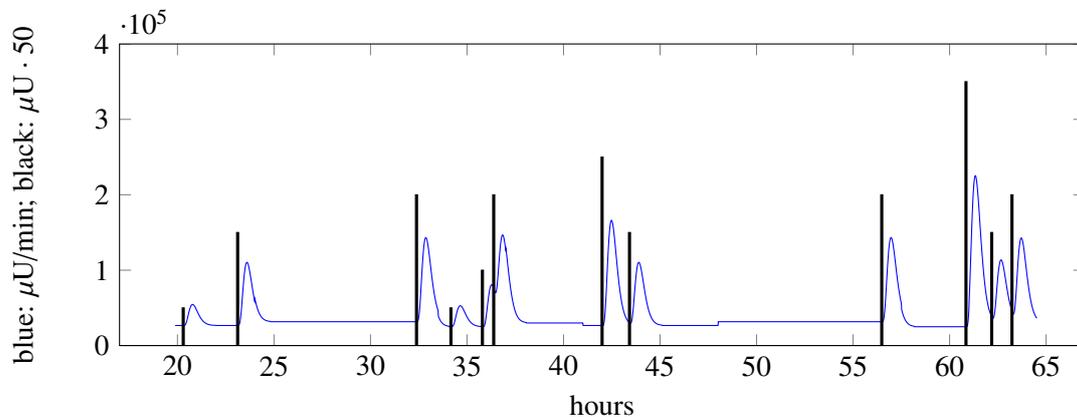


Figure 6: Blue: The combined basal and bolus data used as equation input.
Black: Bolus pump data.

The first subsystem was then made into a function callable by the ordinary differential equation solver `ode45`, using the insulin pump rate as input. This in conjunction with the measured plasma insulin data was used to calculate the SSE. This could then be called on by a minimization algorithm, since it is a function of our set of parameters $\tau_1, C_I, \tau_2, I_{sc}(0)$ and $I_p(0)$. For this we used the Levenberg-Marquardt non-linear least square fitting (`lsqnonlin`) algorithm, which combines the Gauss-Newton algorithm and that of gradient descent. If this failed to give a satisfactory fit, we also tried the Nelder-Mead optimisation technique (`fminsearch`) to see if this gave improved results, which is a downhill simplex method.

Second subsystem of equations

For the second subsystem the plasma insulin concentration was required as input. For this we chose to use the measured concentration in contrast to the one predicted by the first subsystem. This has the advantage that any inaccuracies or errors made during the first fitting process are not carried over to this one. This improves the chances of finding a good optimisation for the second subsystem, and allows us to judge its individual accuracy. We however should note that in any practical situation this model would be applied, one would use the insulin concentration predicted from the first model as an input for the second model. We use the measured value only to be able to assess the individual models.

The second system was set up in the same fashion as the first one, using the measured blood insulin concentration as input to calculate the SSE as a function of the parameters p_2 , S_I , $GEZI$, EGP , V_G , $I_{eff}(0)$, $G(0)$ and $\tau_{m,i}$ for each meal i . Just as the first subsystem, the relevant data was smoothed using a smoothing algorithm. Since we are now dealing with two sets of noisy data, we smoothed both the input plasma insulin, and the blood glucose concentrations. For the glucose smoothing, we used a smoothing parameter $p = 0.00005$.

We then interpolated the input plasma insulin data to 1 minute intervals, and used the same ode45 solver to output the function values for $G(t)$. Then the sum squared error of this and the measured blood glucose was minimized using the Levenberg-Marquardt, Nelder-Mead and Simulated Annealing least square fitting algorithms.

If the fits found this way were not deemed satisfactory, we tried the alternative model proposed in Steil's paper. First we tried allowing the parameters S_I , $GEZI$ and EGP to vary during different times of the day. This was modelled using two extra model parameters $t_1, t_2 \in [0, t_{max}]$ which split the time window our model is simulated on into $[0, t_1] \cup [t_1, t_2] \cup [t_2, t_{max}]$. We then introduced 2 new copies of S_I , $GEZI$, EGP , totalling a pair of each for each time window. As a necessary requirement we made sure that the $I_{sc}(t)$ and $G(t)$ were both continuous and differentiable at the meeting point of the time windows.

Although this form of intraday variation is interesting to examine, it introduces many extra parameters which cause the fitting process to be very difficult. As an alternative approach which tries to remedy this problem, we will also examine a model where each of the parameters S_I , $GEZI$ and EGP are defined as a time dependent $p(t)$ in the manner

$$p(t) = p_0 + p_1 \cdot t + p_2 \cdot t^2$$

or using a sine function to capture such oscillatory behaviour as

$$p(t) = p_0 + p_1 \cdot t + p_2 \cdot \sin(\omega t)$$

which offers the same flexibility of the parameters being able to change throughout the day, but with the advantage of introducing less extra parameters compared to the intraday model proposed by Steil. Then instead of having the single parameter p we now have p_0, p_1, p_2 and possibly ω .

Seeing as these models, although allowing more flexibility into the model also increase the parameter space considerably, we also proposed one with a reduced parameters space. In this we take the non-intraday model and chose to, instead of having a $\tau_{m,i}$ for each meal, take one time parameters τ_m for all the meals and see if this would simplify the fitting process.

7. Results

In this section we will discuss subjects such as how well each of the subjects measurements fit each model, and this will be approached both qualitative and quantitative point of view.

7.1. Plasma Insulin fits

The methods used to minimize the sum squared error gave good results for the first two equations. If we look from a qualitative point of view, 6 out of the 9 patients' plasma insulin was well described, mimicking the general behaviour of the data. In only one of the six patients does the model properly predict the peak insulin level, but with the rest of the patients the model does come quite close, with a maximum difference of only $6.6 \mu\text{U}/\text{ml}$ in 6 of the 9 subjects. We can see an example of this described behaviour in the figure below.

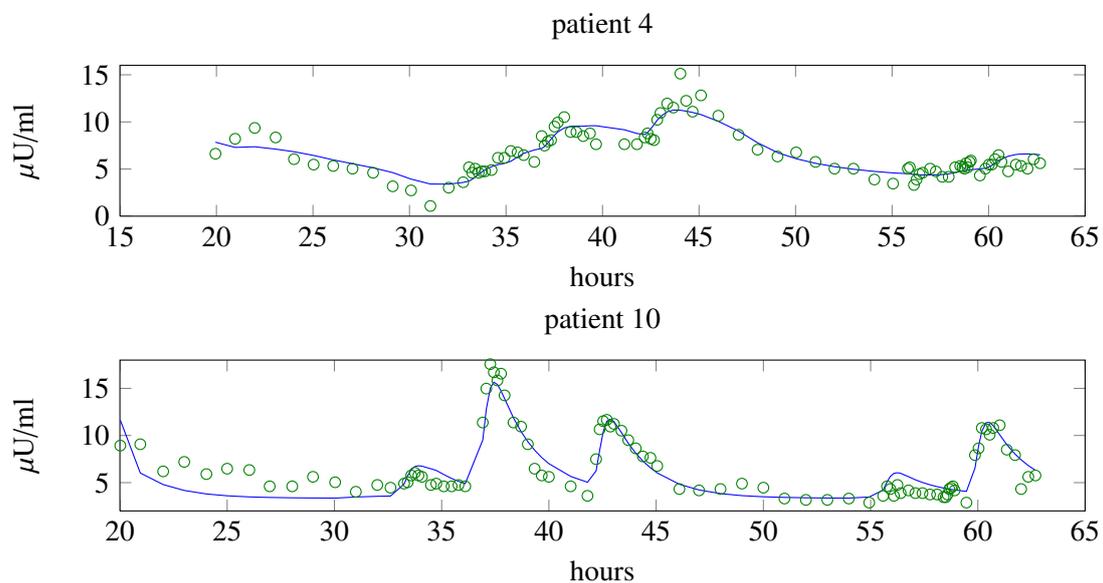


Figure 7: Plots of the fitted plasma insulin model of subjects 4 and 10 respectively.
Green: Measured plasma insulin data; Blue: model predicted plasma insulin.

The three patient for which we weren't able to find a satisfactory fit for, we also tried Steil's proposed 3-compartment model to see if this would offer any improvements. These patients failed to show any improvement from the alternative model, either in terms of the sum squared error or in terms of the behaviour of the model prediction.

A full summary of the parameters found for each subject, and the related evaluation of fit can be found in figure 8. Subject 7 was not included due to the fact that the patient data was corrupt.

Patient	τ_1 (min)	τ_2 (min)	C_I (ml/min)	$I_{sc}(0)$ (μ U/ml)	$I_p(0)$ (μ U/ml)	max. residual (μ U/ml)	SSE
1	290	16	$1.97 \cdot 10^3$	18	25	17.6	$3.92 \cdot 10^3$
2	118	18	$1.79 \cdot 10^4$	1	1	5.0	173
3	108	9	$6.60 \cdot 10^3$	2	17	15.5	$1.57 \cdot 10^3$
4	235	55	$3.73 \cdot 10^3$	7	8	2.3	63
5	328	10	$3.44 \cdot 10^3$	5	5	2.9	101
6	75	2	$1.28 \cdot 10^4$	8	5	15.9	$1.15 \cdot 10^3$
8	743	3	$3.03 \cdot 10^3$	2	22	15.2	$2.67 \cdot 10^3$
9	63	4	$1.30 \cdot 10^4$	0	1	3.0	87
10	104	5	$5.48 \cdot 10^3$	8	12	3.0	142

Figure 8: This table shows the parameters found in the fitting process of the first two equations. The two most right columns show the largest residual out of all the data points and the total sum squared error respectively.

7.2. Fitting Glucose Levels

The results for second subsystem were not nearly as successful as the first. The fitting of the non-intraday plasma glucose model gave largely unsatisfactory results on all the subjects. As we can see with in figure 9, the model fails to mimick the peaks and nadirs of the data, and we have large residuals in the fits of all the subjects. There are intervals where the residuals are relatively small, such as in (timespan in figure) on the right, but on the whole the model fails to describe the data.

After this the intraday variation model proposed by Steil was tried, although this failed to give any improvements. The peaks and nadirs of the data were less apparent in the model predictions, and the total residuals were actually larger than those in the non-intraday model.

In addition to Steil's version of intraday variation, we also tested our own variations. Defining the three concerning parameters as second order polynomial or as a combined polynomial and sine function also failed to offer any improvement on the basic model.

8. Discussion

From this research it was quickly clear what the inherent limitations are of trying to solve such complex biological models analytically. Even in the simple case of the first model, where

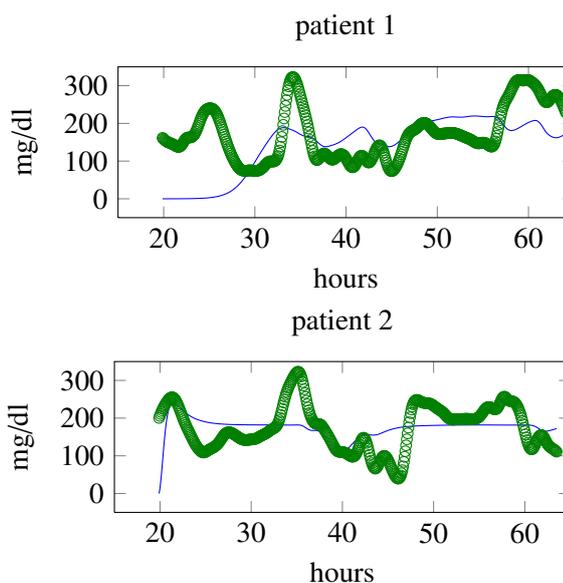


Figure 9: Two simulations of the glucose submodel.

we can find the exact solution to our differential equation, trying to then implement this in the framework of finding optimal parameters which minimize the sum squared error quickly shows limitations of such an approach. This is especially true for the blood glucose model, in which we can't find an exact form for the solution of differential equation.

Fortunately numerical methods are better developed and aimed towards solving such problems. As stated in the methodology, the problem of numerically fitting the first model was far less problematic than the fitting of the second model. This is partially due to the fact that the first model describing the plasma insulin is a system of linear ordinary differential equations, which is much easier to solve for numeric algorithms. The other factor which plays a role here, as we stated earlier, is that the first model has a five-dimensional optimisation parameter space, compared to the 12 dimensions and upwards we had to wrestle with in the second model.

The first model shows that the insulin dynamics can be modelled accurately using a second order ODE, and the higher order model proposed as an alternative seems to be unnecessary, failing to improve the results found from the first model. This agrees with the results posted by Steil, who also reports this model to describe the data properly. The difference is that Steil found the three-compartment model to give improved results on two of the ten patients, whereas we did not.

Moving to the model for predicting blood glucose, our results were much less conclusive. With the parameters we found there were large residuals, and the peaks and nadirs of the data were not emulated either. The problem herein is it is difficult to pinpoint what is the cause of these bad fits.

One of the possible causes is that the optimisation algorithms we utilized struggled with the dimensionality of the parameter space, and quickly got stuck in local minima. Especially with such non-linear differential equations as the second model, the cost as a function of the parameters often has a very chaotic landscape and is full of such local minima. Since our curve fitting algorithms converge to local minima, this is probably the cause of our unsatisfactory fits.

If we compare our results of the blood glucose subsystem model to what Steil found, his results for the non-intraday model largely agree with ours. He found satisfactory fits in only 3 of the 10 patients he analyzed, which clearly indicates problems fitting the model. Where our results differ, is that he found large improvements by moving to the intraday model he used. This increased the amount of satisfactory fits to 7 of the 10 patients.

9. Conclusion

Finding positive results gives further evidence for the accuracy of this second-order model for describing plasma insulin concentrations. We can also conclude that a third-order model is unnecessary in this case. This model is not a new one to the field of model predictive glucose control, but such reassuring results will further justify its use in the future.

What we also hoped to achieve in this paper was to provide additional evidence for the need of implementing intraday variance in blood glucose modelling. Modelling the intraday parameters according to time dependant functions is a promising concept as it introduces few extra parameters and allows continuous variation of these parameters over the span of the day. Unfortunately we could not give compelling evidence to support this, or to support the glucose subsystem at all. This also shows that the problem of estimating such parameters in highly dimensional parameter space ($12 >$) is a non-trivial one, as such biological problems often have very chaotic cost functions.

References

- [1] Sami S. Kanderian, M.S., Stu Weinzimer, M.D., Gayane Voskanyan, Ph.D., and Garry M. Steil, Ph.D.; "Identification of Intraday Metabolic Profiles during Closed-Loop Glucose Control in Individuals with Type 1 Diabetes"; *Journal of Diabetes Science and Technology*, vol. 3, no. 5, pp. 1047-1057, September 2009.
- [2] A.M. Albisser, B.S. Leibel, T.G. Ewart, Z. Davidovac, C.K. Botz, and W. Zingg; "An Artificial Endocrine Pancreas"; *Diabetes May 1974 vol. 23 no. 5*, pp. 389-396, May 1974.
- [3] E.F. Pfeiffer, C. Thum, A.H. Clemens; "The Artificial Beta Cell - A Continuous Control of Blood Sugar by External Regulation of Insulin Infusion (Glucose Controlled Insulin Infusion System)"; *Horm. Metab. Res.* 6, pp. 339-342, 1974.
- [4] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M.O. Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering, and M.E. Wilinska; "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes"; *Physiological Measurement no. 25*, pp. 905-920, 2004.
- [5] C. Cobelli, G. Federspil, G. Pacini, A. Salvan, C. Scandellari; "An integrated mathematical model of the dynamics of blood glucose and its hormonal control"; *Mathematical Biosciences vol. 58, no. 1*, pp. 27-60, 1982.
- [6] A.C. van Bon, E. Verbitskiy, G. von Basum, J.B.L. Hoekstra, J.H. de Vries; "DADS, Diabetes Algorithmic Decision Support project; Decision support for glucose regulation in daily life in diabetes mellitus, data collection and analysis".
- [7] R.N. Bergman, D.T. Finegood, M. Ader; "Assessment of insulin sensitivity in vivo", *Endocrine Reviews vol. 6 no. 1* pp. 45-86.
- [8] R.S. Sherwin, K.J. Kramer, J.D. Tobin, P.A. Insel, J.E. Liljenquist, M. Berman, R. Andres; "A model of the kinetics of insulin in a man"; *Journal of Clinical Investigation vol. 53 no.5* pp. 1481-1492.
- [9] The Merck manual for health care professionals, *accessed 4 May 2012* <http://www.merckmanuals.com>
- [10] The Society for Biomedical Diabetes Research, *accessed 24 January 2012*, <http://www.soc-bdr.org>.
- [11] J.D. Meiss, *Differential Dynamical Systems*, p.97 Theorem 3.16
- [12] MATLAB[®] version 7.11; Mathworks Inc., Natick, Massachusetts, U.S.A.

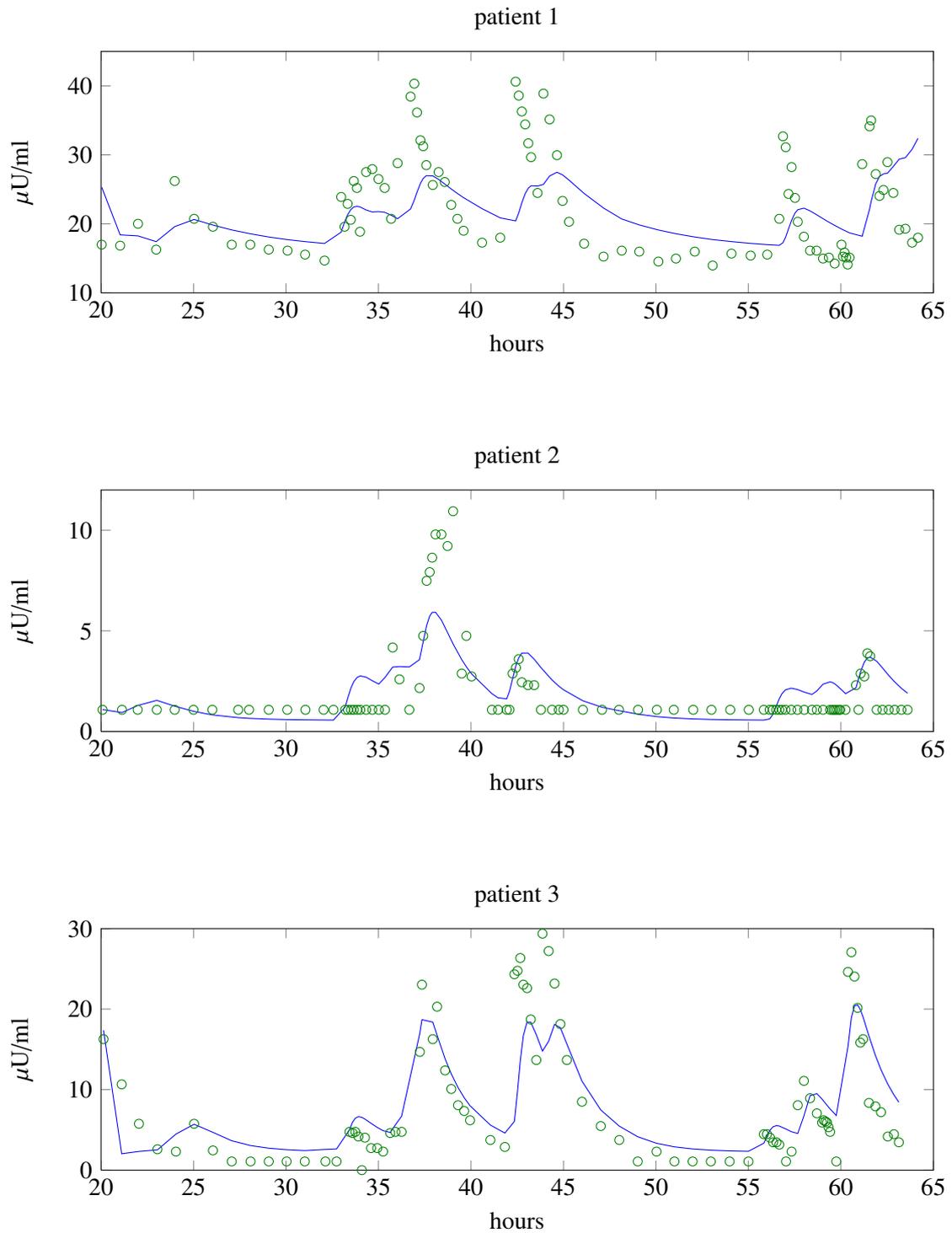
9.1. Figures

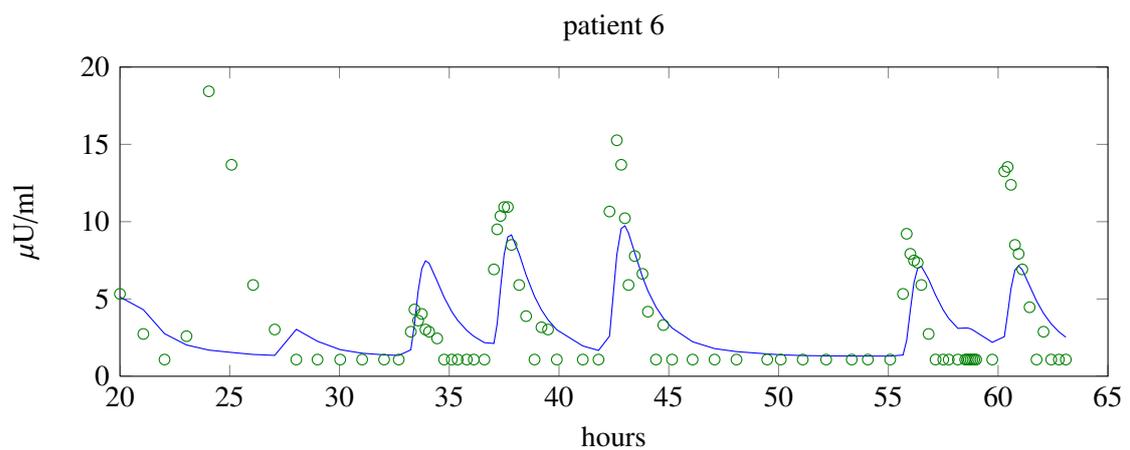
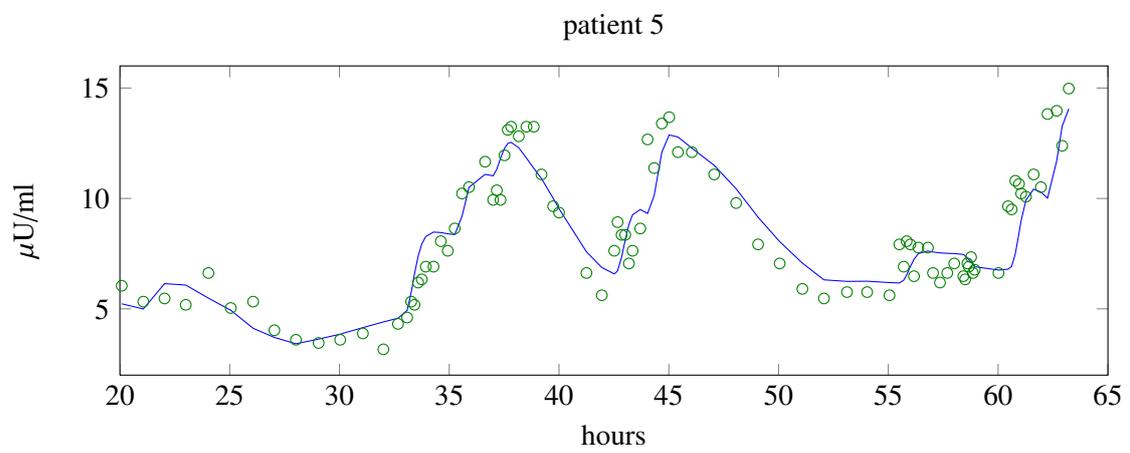
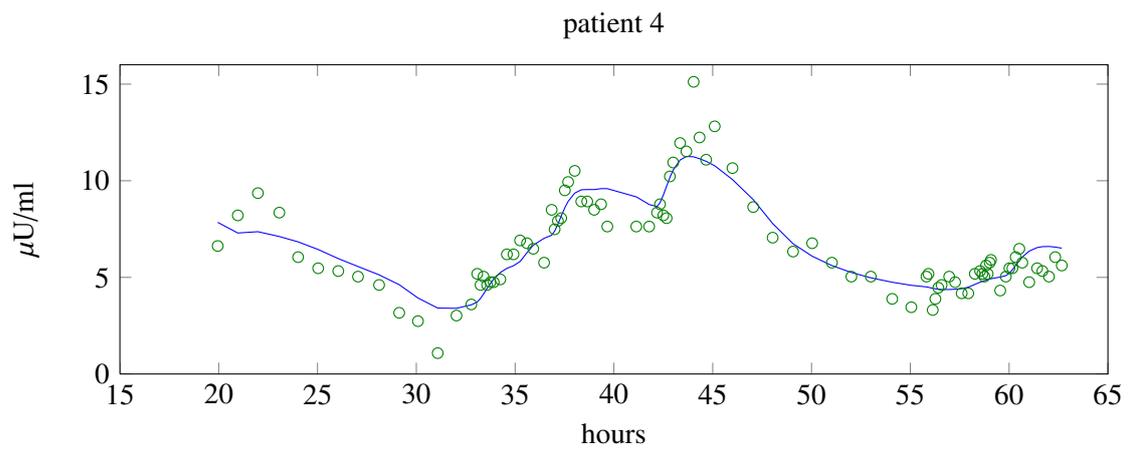
- [13] Brown University, Division of Biology and Medicine, *accessed 26 April 2012*, <http://biomed.brown.edu>
- [14] Jakob Suckale, Michele Solimena, *Solimena Lab and Review Suckale Solimena 2008 Frontiers in Bioscience*

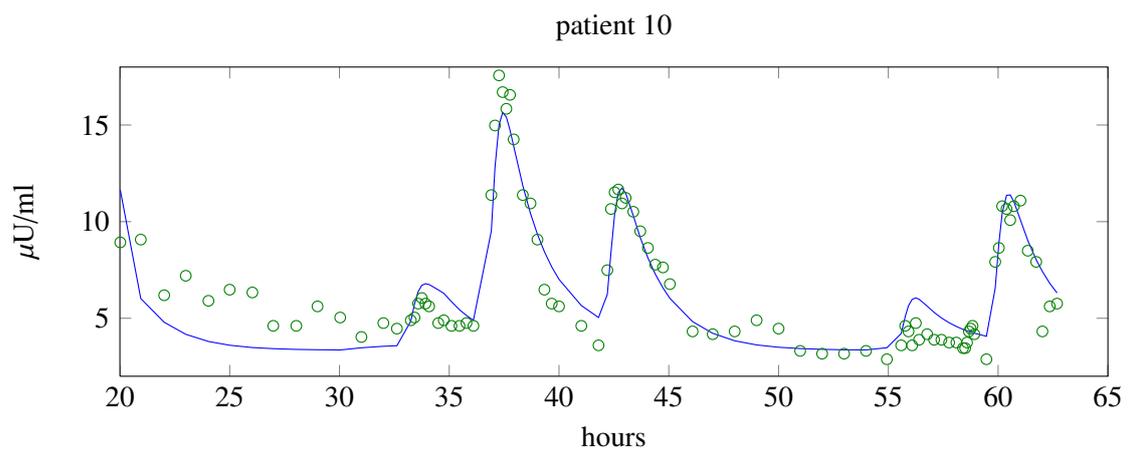
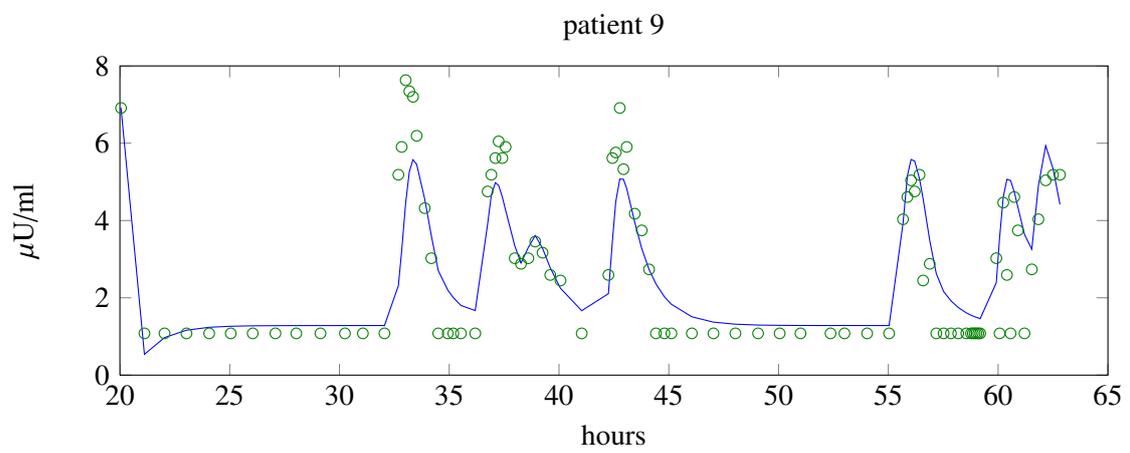
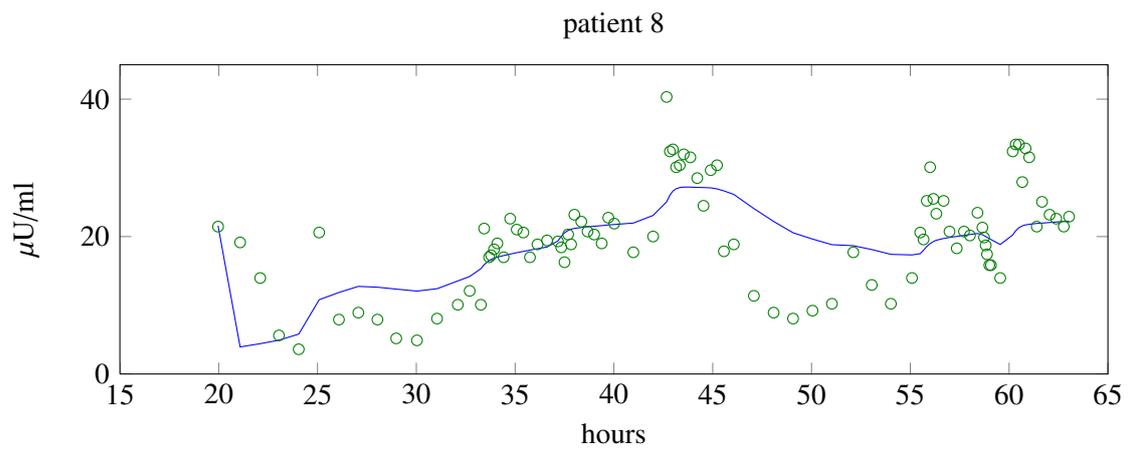
10. Appendix

10.1. Model predicted Blood Insulin

Blue: Model predicted blood insulin; Green: Measured blood insulin.







10.2. Model predicted Blood Glucose

Blue: Model predicted blood glucose; Green: Measured blood glucose.

