

Development of a clinical Type 1 diabetes metabolic system model and *in silico* simulation tool

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Objectives:

To develop a system model of Type 1 diabetes for the purpose of *in silico* simulation for the prediction of long-term glycaemic control outcomes.

Methods:

The system model is created and identified on a physiological cohort of virtual Type 1 diabetes patients ($n=40$). Integral based identification is used to develop ($n=40$) insulin sensitivity profiles.

Results:

The $n=40$ insulin sensitivity profiles provide a driving input for virtual patient trials using this model. The identified models have a total median (90% range) absolute percentage error of 1.33% (0.08-7.20%). The total median (90% range) absolute error is 0.12mmol/l (0.01-0.56mmol/l). The model and integral based identification of S_I captures all patient dynamics with low error, which leads to more physiological behaviour simulation.

Conclusions:

A simulation tool incorporating $n=40$ virtual patient data sets to predict long-term glycaemic control outcomes from clinical interventions is developed based on a physiological Type 1 diabetes metabolic system model. The overall goal is to utilize this model and insulin sensitivity profiles to develop and optimise for self monitoring blood glucose and multiple daily injection therapy.

1. INTRODUCTION

Control of Type 1 diabetes is a widely studied and experimented research field. Previously published control methods are diverse, using different routes of insulin administration and glucose measurement. Since the 1970s, the closed loop artificial endocrine pancreas (AEP) has been heralded as the solution (as reviewed in [1]). While no commercial product currently exists, the systems in current clinical use that are likely to constitute the components of an extracorporeal artificial pancreas are the continuous subcutaneous insulin infusion (CSII) pump and a continuous glucose measurement (CGM) device. Advanced control algorithms and methods to ‘close the loop’ have also been widely studied (as reviewed in [2-4]) in spite of early and ongoing limitations in sensors and pumps. Currently, the use of open-loop CGM and/or CSII has resulted in at best, a modest *clinical* advantage over conventional methods of insulin administration or multiple daily injection (MDI) (as reviewed in [5, 6]). Additionally, these systems are only used by a small population of Type 1 diabetics due to high upfront costs, costs of consumables, complexity, and the extensive healthcare infrastructure and support required. Prevalence of CSII use is as low as 2% of the Type 1 diabetes population in the UK and up to 15-20% elsewhere and the US [7].

Hence, there is a more practical and urgent need to address the large majority of the Type 1 diabetes population using conventional glucose measurement i.e. self-monitoring blood glucose (SMBG) and insulin administration i.e. MDI methods, and for whom current conventional or intensive therapies are failing to deliver recommended levels of glycaemic control [8]. In the US, over 50% of diagnosed

diabetics aged 20-64 are deemed 'out of control' [9]. The higher accuracy of bedside capillary blood glucose meters [10, 11], and the latest insulin analogues for MDI therapy [12], coupled with better control methods have the potential to provide better care to the majority of outpatient or ambulatory Type 1 diabetics than currently observed. Such techniques must necessarily be simple to implement to ensure broad clinical uptake by the diabetes population.

This study reports the development of a system model of the Type 1 insulin-glucose regulatory system and its identification on a virtual patient cohort. The models utilised have several novel and unique features. In particular, the insulin model used is unique and captures the insulin kinetics of multiple insulin types in a single PK model for all shared physiological spaces. The pharmacodynamic model used has not been reported previously but bears components of similar nature to other such models used in this field due to the need to capture similar physiology. This study is the basis for a novel model-based application to develop a simple and practical adaptive method for clinical glycaemic control of Type 1 diabetes using multiple daily injection and self monitoring blood glucose measurements. In addition, the modelling of long term clinical outcomes of glycaemic control and their corroboration against clinical expectations and studies will be further explored in a subsequent *in silico* simulation on a virtual patient cohort which is also reported in this Journal. Later, the complex interaction of all quantifiable errors in protocol application is investigated in a **Monte Carlo study** to test the robustness of the developed protocol in effectiveness and safety [13].

2. MODEL DEVELOPMENT

The system model shown in Equation (1) is an evolution of the model of Chase et al. [14] and Wong et al. [15].

$$\dot{G}(t) = EGP_{0-G} - p_G G(t) - S_I G(t) Q(t) - RGC(t) - CNS + P(t) \quad \text{Eq. 1}$$

where:

$G(t)$ Plasma glucose concentration [mmol/l]

CNS Central nervous system glucose uptake [mmol/l.min]

EGP_{0-G} Endogenous glucose production extrapolated to zero plasma glucose concentration [mmol/l.min]

p_G Glucose effectiveness [min^{-1}]

S_I Insulin sensitivity [l/min.mU]

$Q(t)$ Interstitial (effective) insulin concentration [mU/l]

$RGC(t)$ Renal glucose clearance [mmol/l.min]

$P(t)$ Meal plasma glucose rate of appearance [mmol/l.min]

This glucose model differs mathematically from the model developed by Chase et al. [14] and Wong et al. [15] in removal of insulin effect saturation and the addition of renal glucose clearance rate, $RGC(t)$. These two studies were on highly dynamic, critically-ill patients with high effective insulin resistance and treated with intravenous insulin doses. The removal of the insulin effect saturation was deemed suitable for modelling more compliant, insulin sensitive and stable Type 1 diabetes patients treated with subcutaneously administered insulin.

$$RGC(t) = \begin{cases} \frac{GFR}{V_p m_b} (G(t) - RGT) & \text{if } G(t) > RGT \\ 0 & \text{if } G(t) \leq RGT \end{cases} \quad \text{Eq. 2}$$

where:

$RGC(t)$ Renal glucose clearance [mmol/l.min]

GFR Glomerular filtration rate [l/min]

$G(t)$ Plasma glucose concentration [mmol/l]

RGT Renal glucose threshold [mmol/l]

V_p Glucose distribution volume [l/kg]

m_b Body mass [kg]

Referring to Equation (2), the renal glucose clearance rate, $RGC(t)$, models glucose removal by the kidney above the renal glucose threshold, RGT , using a linear relationship proportional to the glucose concentration above RGT and the glomerular filtration rate, GFR . From the study by Johansen et al. [16], this linear approximation is acceptable. Linear models have also been used in AIDA [17] by Lehmann et al. [18] and by Arleth et al. [19].

Insulin absorption from subcutaneous injection or infusion has been widely studied since Binder [20]. A novel, compartmental model of subcutaneous insulin absorption kinetics specifically developed for diabetes decision support has been presented [21, 22]. The model accounts for the volume and concentration dependence of regular human insulin absorption, and models the absorption kinetics of 6 insulin types including monomeric insulin (MI) and insulin glargine. Additionally, insulin injected or infused subcutaneously or intravenously can also be modelled. A schematic of the model adapted from [22] is shown in Figure (1). This model is used in this study, which is the first application of the developed model in the control of Type 1 diabetes.

(Figure (1) here)

Modelling of meal glucose rate of appearance (R_a) including the digestion, absorption and transport of glucose is a complex process not widely studied [23]. Meal carbohydrate amount and type are the main factors affecting meal glucose R_a or $P(t)$ in Equation 1 and 6 [24, 25]. However, clinical models of glucose R_a almost universally accept input of meal glucose amount only [18, 26]. *Glucose equivalent carbohydrate* (GEC) introduced by Yates et al. [23] to express carbohydrate values as monosaccharide equivalents necessarily depends on an *a priori* known content of the carbohydrate type within the meal to be consumed which is typically unavailable. Carbohydrate counting is a technique [27-29] commonly taught by diabetes care providers to improve glycaemic management. Glycaemic index (GI), a measure of the effect of carbohydrate type, is not easily calculable for mixed meals [30] nor readily available like carbohydrate content.

The minimal models of meal glucose Ra by Worthington [31] and Lehmann et al. [17, 18] form the basis of the model used in this study. Referring to Figure (2) and Equations (3-5), the model consists of two compartments for the stomach and gut, with linear gastric emptying and gut-absorption rates to describe the plasma glucose Ra in Equation (6). Another simplification is the expression of meal carbohydrate content (in grams) as equivalent to the same mass of glucose monosaccharide regardless of the meal carbohydrate type [23]. Again, such meal data is typically unavailable in a clinical setting. As such, the complex digestion processes such as the hydrolysis of polysaccharides, are assumed linear and lumped into the simplified processes above.

$$\frac{dSTO(t)}{dt} = -k_6STO(t) + u_{CHO}(t) \quad \text{Eq. 3}$$

$$\frac{dGUT(t)}{dt} = GABS(t) + k_6STO(t) \quad \text{Eq. 4}$$

$$GABS(t) = -\min(k_7GUT(t), GABS_{\max}) \quad \text{Eq. 5}$$

$$P(t) = \frac{GABS(t)}{0.18(V_p m_b)} \quad \text{Eq. 6}$$

where:

STO(t)	Mass of carbohydrate/glucose in the stomach [g]
GUT(t)	Mass of carbohydrate/glucose in the gut [g]
GABS	Gut carbohydrate/glucose absorption rate [g/min]
GABS _{max}	Maximum gut carbohydrate/glucose absorption rate [g/min]
k ₆	Carbohydrate/glucose gastric emptying rate [min ⁻¹]
k ₇	Carbohydrate/glucose gut-absorption rate [min ⁻¹]

$u_{CHO}(t)$	Meal carbohydrate/glucose input [g/min]
$P(t)$	Meal plasma glucose rate of appearance [mmol/l.min]
V_p	Glucose plasma distribution volume [l/kg]
m_b	Body mass [kg]

(Figure (2) here)

Worthington [31] found the one-compartment model with time delay had the smallest fitting error. However, this result was obtained with a model fit to plasma glucose data and is dependent on the model of glucose kinetics used. Lehmann et al. [18] uses a ‘complex’ function to describe the gastric emptying rate from the stomach compartment. This study uses a linear transport rate, k_6 while the glucose input into the stomach compartment, $u_{CHO}(t)$ is described by a delta function. Similar to the saturable gastric emptying rate of Lehmann et al. [18], this study incorporates a saturable gut-absorption rate, $GABS_{max}$. Saturable gut-absorption has been postulated by Korach-Andre et al. [32] in experiments using relatively large starch meals. However, this difference is likely to be small considering the minimal nature of both models. Referring to Figure (3), the effective gut absorption rate is shown as a function of the mass of carbohydrate/glucose in the *GUT* compartment. The addition of the saturable term $GABS_{max}$ effectively makes the gut absorption rate nonlinear as a function of the amount of carbohydrate in the gut. This dynamic is similar to that of the nonlinear three compartment model of Dalla Man et al. [26]. The Dalla Man et al. model consists of dual stomach compartments with a nonlinear gastric emptying rate with 4 identified parameters. Nonlinear gastric emptying term is described by a hyperbolic tangent function as a function of the *proportion* of the consumed

carbohydrate remaining in the stomach. There is no saturation term considered for large, absolute meals.

(Figure (3) here)

Referring to Table (1), the values of patient-independent model population constants are *a priori* identified from literature. The renal glucose threshold, RGT has been shown to vary considerably in Type 1 diabetes [16] but median values of 10mmol/l have been widely reported. The glucose distribution volume, V_p is taken to be 0.22l/kg, the same value used by Lehmann et al. [18]. The glomerular filtration rate, GFR is taken as 0.12l/min or 120ml/min which reflects the average adult GFR of 125ml/min [33].

In a study by Dalla Man et al. [34], the maximum meal Ra (Ra_{meal}) was ~8-9mg/kg.min after an oral dose of 1g/kg glucose. In the study by Korach-Andre [32], the exogenous meal Ra (Ra_{exo}) was approximately 7-9mg/kg.min for a meal of 4g/kg of starch (~4.4g/kg glucose). Despite the fourfold increase in glucose load, the maximum Ra remains at ~9mg/kg.min or ~0.72g/min for an average adult. In a study by Noah et al. [35], a higher figure still of 11mg/kg.min is reported in a porcine model. The *maximum* value of the rate of gut absorption is taken as 1.1g/min using the Noah et al. study as a basis, assuming a 100kg body weight.

The proportion of glucose lost to first pass splanchnic uptake is still being debated with proportions from negligible [36, 37] to as high as 30% reported in some studies [38]. As there will be no tracer data in the intended application of the model, negligible

losses from first-pass splanchnic sequestration and complete absorption is assumed for simplicity [39] with complete absorption of meal glucose. The values of k_6 and k_7 are optimised using nonlinear least squares to model-independent mixed-meal tracer glucose Ra data [34] (results not shown).

(Table (1) here)

The values of CNS , EGP_{0-G} and p_G are derived from results of studies by Del Prato et al. [40, 41]. Like the minimal model of Bergman et al. [42], the model is unable to differentiate non-insulin mediated glucose uptake from production, which are lumped in a linear relationship with glucose. Referring to Figures (4-5), total body glucose uptake (TBGU) and hepatic glucose production (HGP) data from [40, 41] are used to identify CNS , EGP_{0-G} and p_G . Data at glucose exceeding the approximate RGT of 10mmol/l are ignored to eliminate the need to evaluate renal glucose clearance, RGC , and associated errors. Under fasting and insulinopenic conditions, the $P(t)$ and $S_I G(t)Q(t)$ terms of Equation (1) can be further eliminated. By the linear definition of the effect of hyperglycaemia on TBGU, CNS can then be derived as the ‘virtual’ y-intercept of the linear TBGU curve. The term ‘virtual’ is used as no glucose uptake is theoretically possible at zero glucose. The central nervous system glucose uptake CNS is saturated at 3.3mmol/l and is relatively insensitive to insulin and glucose [43, 44]. At euglycaemia, CNS accounts for ~70% of all non-insulin mediated glucose uptake [45] and this proportion is likely to increase with hypoglycaemia. Hence, the use of the term CNS for the virtual y-intercept of the linear TBGU curve is justified.

Similarly, by the linear definition of the effect of hyperglycaemia on HGP, EGP_{0-G} is the y-intercept of the linear HGP curve and p_G the slope of the combined TBGU and HGP curve. Hence, p_G is similar to the minimal model glucose effectiveness, S_G but defined under conditions of insulinopenia or sub-basal insulin, rather than basal insulin [46].

Unlike the minimal model, the insulin model in this study models the absolute insulin concentration, not insulin concentration above basal. In Type 1 diabetes, conditions of basal insulin are not necessarily met all the time. Using data from [41] for an insulinopenic normal cohort (Figure (4)), values of $CNS=1.4\text{mg/kg.min}$, $EGP_{0-G}=2.6\text{mg/kg.min}$ and $p_G=0.006\text{min}^{-1}$ are obtained compared $CNS=1.3\text{mg/kg.min}$, EGP_{0-G} of 3.0mg/kg.min and $p_G=0.009\text{min}^{-1}$ under basal insulin conditions (figure not shown). Compared to insulinopenia, the presence of basal insulin results in overestimation of p_G although this value is still approximately half that of published values of the minimal model S_G for a normal cohort $\sim 0.024\text{min}^{-1}$ [46].

(Figure (4) here)

Using the data of [40] for an IDDM cohort under basal insulin (Figure (5)), values of $CNS=1.7\text{mg/kg.min}$, $EGP_{0-G}=3.0\text{mg/kg.min}$ and $p_G=0.006\text{min}^{-1}$ are obtained. Hence, p_G of the normal, insulinopenic cohort [41] is similar to the IDDM cohort under basal insulin [40]. This result is logical since S_G is decreased in IDDM [46] while basal insulin increases S_G , either by increased glucose uptake [44] or suppression of endogenous glucose production [41]. In IDDM, the p_G obtained is also approximately half that of published S_G values of $\sim 0.013\text{min}^{-1}$ [46]. One explanation is the

elimination of the data at high glucose concentrations from the p_G analysis, which if unaccounted for would include the effect of urinary glucose excretion, thereby increasing the ‘effective’ glucose uptake. From this investigation, it can be deduced that for an IDDM cohort under conditions of insulinopenia, p_G must have an upper bound of 0.006min^{-1} , which is assumed in this study. The values of CNS obtained are in agreement with [45, 47, 48], and the assumption that CNS is approximately equal to the virtual y-intercept of the linear TBGU curve is valid. A summary of the values of the model constants are shown in Table 1.

(Figure (5) here)

3. METHODS

3.1 Patient cohort

The patient data used in this study is obtained from AIDA on-line², the web-based version of the AIDA educational diabetes program [49]. AIDA on-line² incorporates the physiological model developed by Lehmann et al. [18] and can simulate glycaemic levels for any insulin or meal stimuli over a period of one day. The patient data ($n=40$) for this study were obtained from sample diabetes case scenarios available with AIDA on-line². Referring to Table (2), each patient case is unique in body weight, meals/carbohydrates consumed, and insulin treatment. Each patient also has unique clinical variables of hepatic and peripheral insulin sensitivity, glucose renal threshold, and glomerular filtration rate. Hence, the AIDA on-line² cohort represents a broad range of patients and possible clinical behaviour. To retrieve the

blood glucose, plasma insulin and meal glucose absorption rate from AIDA on-line², the ‘Advanced’ display is selected to output the data in text format. A sample of this data is shown in Figure (6).

(Table (2) here)

(Figure (6) here)

3.2 Simulation method

For *in silico* simulation, the virtual patient method is used [50, 51]. This method has been utilised to develop effective glycaemic control protocols by simulating the physiological glycaemic response to glucose and insulin stimuli [50-52]. The glycaemic responses are generated with patient specific $S_I(t)$ profiles derived from retrospective data. This clinically validated method [50] enables extensive simulations to be performed in a short time for rapid development and testing of any control methodology. The *in silico* simulation was performed using MATLAB[®] (The Mathworks, Natick, MA, USA) implemented on a PC notebook (Pentium M 1.7Ghz).

To obtain the retrospective $S_I(t)$ patient data profiles, the model is first fitted to the data using the linear and convex, integral-based parameter identification method [53]. Equation (1) can be expressed in a generic integral form (Equation (7)) for period t_{i-1} to t_i , which is a set of linear equations (Equation (8-9)). All quantities in Equation (7) are modelled and as such, are known except for $G(t)$.

$$\begin{aligned}
\int_{t_{i-1}}^t \dot{G}(t) dt &= \int_{t_{i-1}}^t [EGP_{0-G} - p_G G(t) - \bar{S}_{I,i} G(t) Q(t) - RGC(t) - CNS + P(t)] dt \\
G(t_i) - G(t_{i-1}) &= \int_{t_{i-1}}^t [EGP_{0-G} - RGC(t) - CNS + P(t)] dt \\
&\quad - p_G \int_{t_{i-1}}^t G(t) dt \\
&\quad - \bar{S}_{I,i} \int_{t_{i-1}}^t G(t) Q(t) dt \\
\bar{S}_{I,i} \int_{t_{i-1}}^t G(t) Q(t) dt &= \int_{t_{i-1}}^t [EGP_{0-G} - RGC(t) - CNS + P(t)] dt \\
&\quad - p_G \int_{t_{i-1}}^t G(t) dt \\
&\quad - [G(t_i) - G(t_{i-1})]
\end{aligned}$$

Eq. 7

$$G(t) = \sum_{i=1}^N \left[\bar{G}_{i-1} + (\bar{G}_i - \bar{G}_{i-1}) \left(\frac{t - t_{i-1}}{t_i - t_{i-1}} \right) \right] (H(t - t_{i-1}) - H(t - t_i))$$

Eq. 8

AIDA on-line² uses a first-order Euler integration method with a 15min step-size to solve the plasma glucose model equation [54]. To determine $G(t)$ to solve Equation (7), the AIDA on-line² glucose data is linearly interpolated to obtain a piecewise linear $G(t)$ function (Equation (8)).

The $t_i - t_{i-1}$ time interval for the optimisation of $S_I(t)$ is chosen arbitrarily as 10mins. Equation (8) is solved using a proprietary MATLAB[®] linear solver. Referring to Figure (7) and Equations (9-10), a stepwise, time-variant $S_I(t)$ with a 10min step interval is obtained.

$$\bar{A}\{\bar{S}_{I,i}\} = b \quad \text{Eq. 9}$$

where:

$$\begin{aligned} \bar{A} &= \int_{t_{i-1}}^t G(t)Q(t) dt \\ \bar{b} &= \int_{t_{i-1}}^t EGP_{0-G} - RGC(t) - CNS + P(t) dt \\ &\quad - P_G \int_{t_{i-1}}^t G(t) dt \\ &\quad - [G(t_i) - G(t_{i-1})] \end{aligned}$$

$$S_I(t) = \sum_{i=1}^N \bar{S}_{I,i} (H(t - t_{i-1}) - H(t - t_i)) \quad \text{Eq. 10}$$

(Figure (7) here)

A proprietary MATLAB[®] numerical ode solver is used to solve the model equations with a 1min time step. Biphasic insulin preparations are treated as in AIDA with the insulin response assumed to be a superposition of the individual components of the preparation [18]. This is an acknowledged simplification considering the large variety and lack of data on such preparations.

The numerical solution to the model equations form the *in silico* simulation tool. With the set of 40 virtual patient $S_I(t)$ profiles, any meal or sc insulin input and its effect on glycaemia can be simulated with the assumption that S_I is independent of the inputs administered i.e. the virtual patient. This opens the possibility of simulating any glycaemic control protocol, even current clinical methods [55-57]. An initial validation would be to *replicate* long-term glycaemic control outcomes e.g. HbA_{1c}.

4. RESULTS

To gauge the model fit to data, the absolute and absolute percentage errors of the $G(t)$ model fit to the AIDA on-line² patient data cohort is shown in Table (3) and (4). In Table (3), per patient errors are shown while the total errors over the entire cohort is shown in Table (4). A sample $G(t)$ fit is also shown in Figure (8).

(Figure (8) here)

(Table (3-4) here)

From Table (3), the per patient median (95% range) absolute percentage error in $G(t)$ is 1.24% (0.09-4.85%) which translates into a per patient absolute error in $G(t)$ of 0.11mmol/l (0.01-0.43mmol/l). Over the entire cohort the figures are 1.33% (0.08-7.20%) and 0.12mmol/l (0.01-0.56mmol/l) which are similar. The errors reported are extremely low and within the measurement errors of clinical methods of glucose measurement in current use. This shows that the model and S_I identification method is capable of capturing all patient $G(t)$ dynamics, which will produce a more physiologically accurate simulation.

5. CONCLUSIONS

An *in silico* simulation tool is presented that utilises an extended model of glucose kinetics, a simple glucose rate of appearance model, and the novel application of a subcutaneous insulin pharmacokinetic model. Models are identified to a

physiological cohort of Type 1 diabetes virtual patients. To corroborate the approach initially, an *in silico* simulation with the data from the patient cohort using the virtual patient simulation method is planned.

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DISCLOSURES

None recorded.

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FIGURES

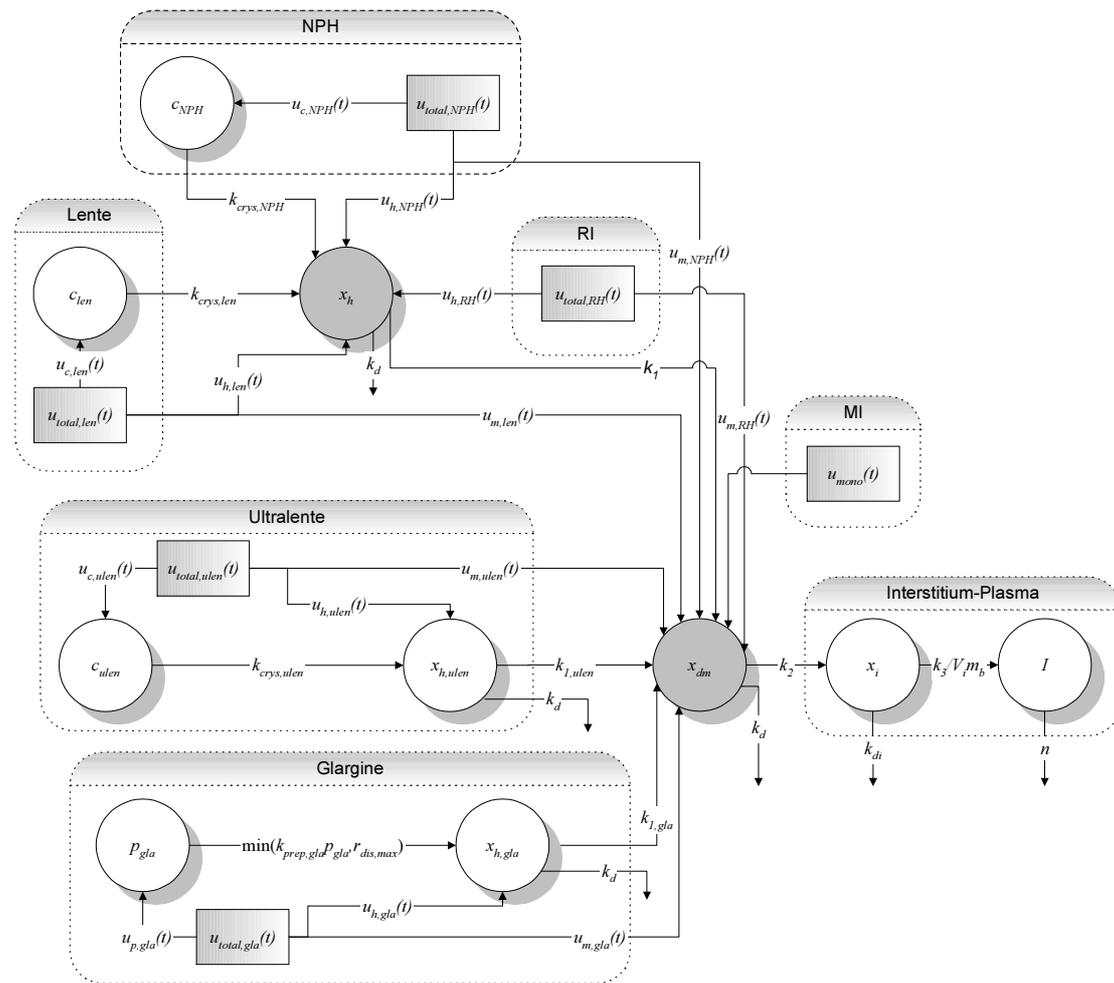


Figure 1: Structure of the sc insulin absorption kinetic model. Model is characterised by a common hexameric state compartment for RI, NPH and lente insulins (x_h) while those for insulin glargine and ultralente ($x_{h,ulen}$ and $x_{h,gla}$) are separate. A crystalline state compartment for NPH (c_{NPH}), lente (c_{len}) and ultralente (c_{ulen}) insulins, and a precipitate compartment for insulin glargine (p_{gla}) model these protraction mechanisms. All insulin flows through a common a dimeric-monomeric state compartment (x_{dm}), interstitium compartment (x_i), and finally into the plasma (I). Adapted from [22]

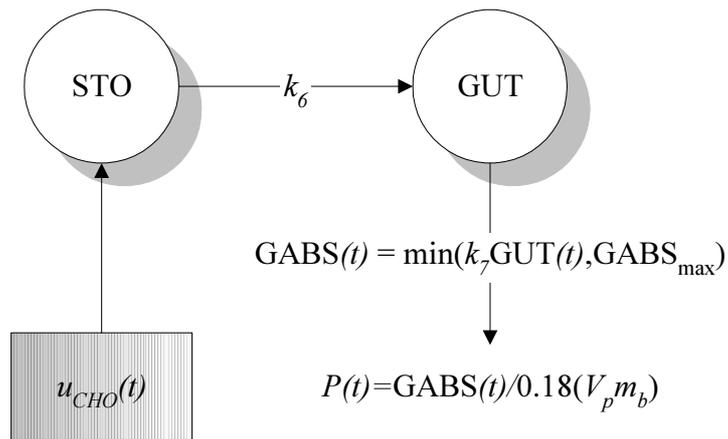


Figure 2: Structure of the meal glucose rate of appearance model. The model is characterised by a delta function to describe meal glucose input ($u_{CHO}(t)$), linear gastric emptying (k_6) and gut absorption (k_7) rates, and saturable gut absorption ($GABS_{\max}$)

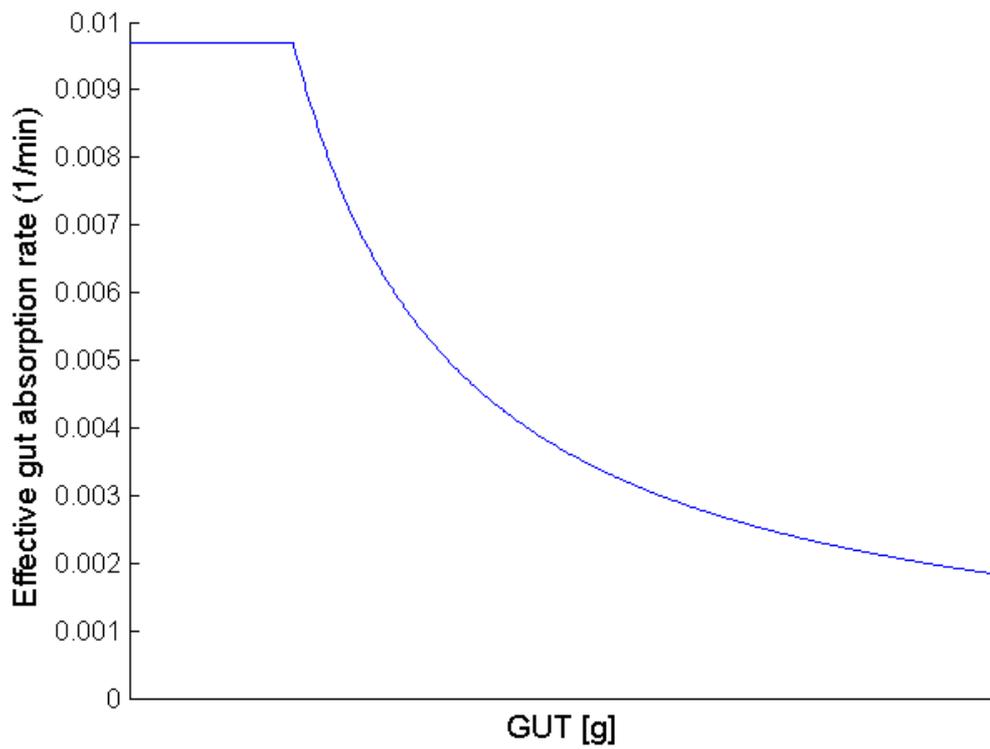


Figure 3: Qualitative plot of the *effective* gut absorption rate as a function of the mass of carbohydrate/glucose in the *GUT* compartment. While the processes of gastric emptying is linear, the addition of the saturable gut absorption term, $GABS_{max}$ of 1.1g/min effectively makes the process of gut absorption, and hence meal glucose Ra nonlinear. At low glucose levels in the gut, the effective gut absorption rate is 0.00971/min.

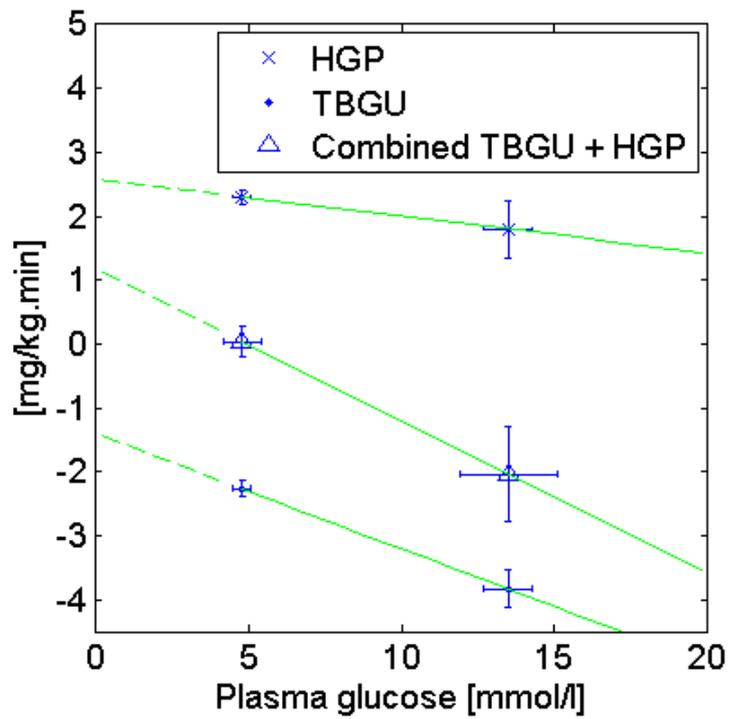


Figure 4: Using HGP and TBGU data from [41] for an insulinopenic normal cohort, values of $CNS=1.4\text{mg/kg.min}$, $EGP_{0-G}=2.6\text{mg/kg.min}$ and $p_G=0.006\text{min}^{-1}$ can be calculated by linear regression

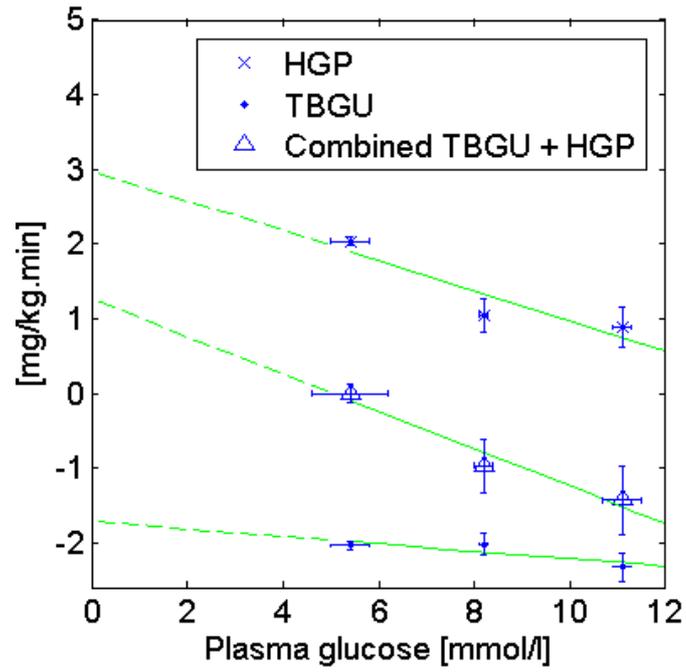


Figure 5: Using HGP and TBGU data of [40] for an IDDM cohort under basal insulin, values of $CNS=1.7\text{mg/kg.min}$, $EGP_{0-G}=3.0\text{mg/kg.min}$ and $p_G=0.006\text{min}^{-1}$ can be calculated by linear regression

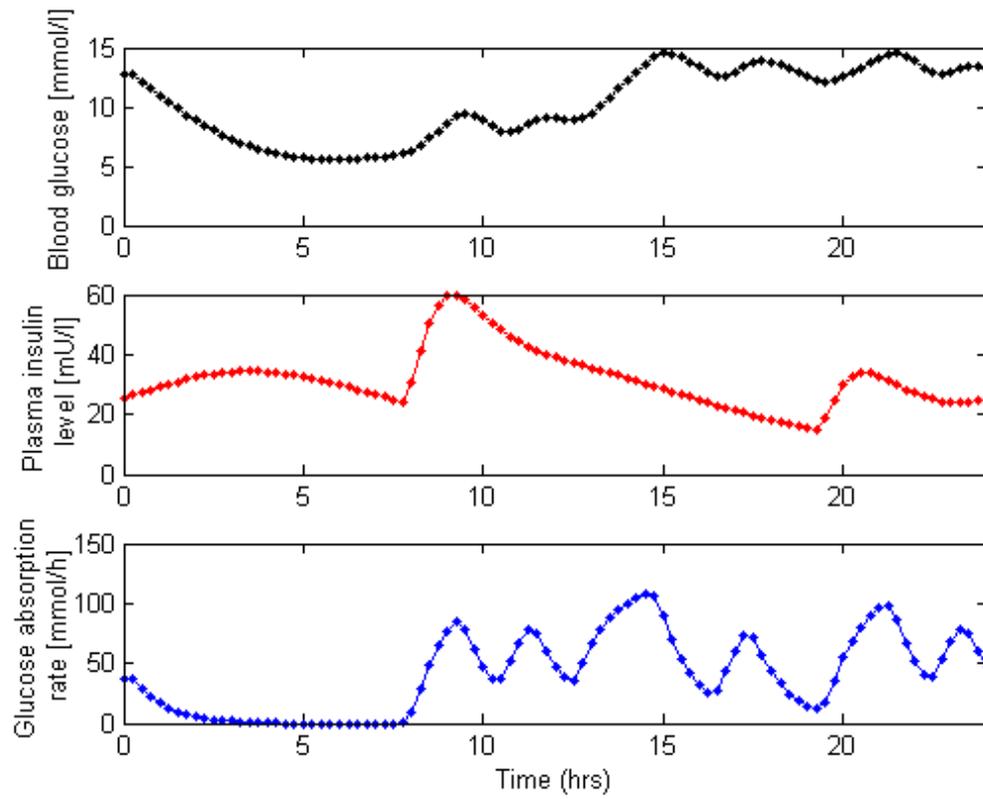


Figure 6: Sample raw blood glucose, plasma insulin level and glucose absorption rate data from AIDA² on-line [49]

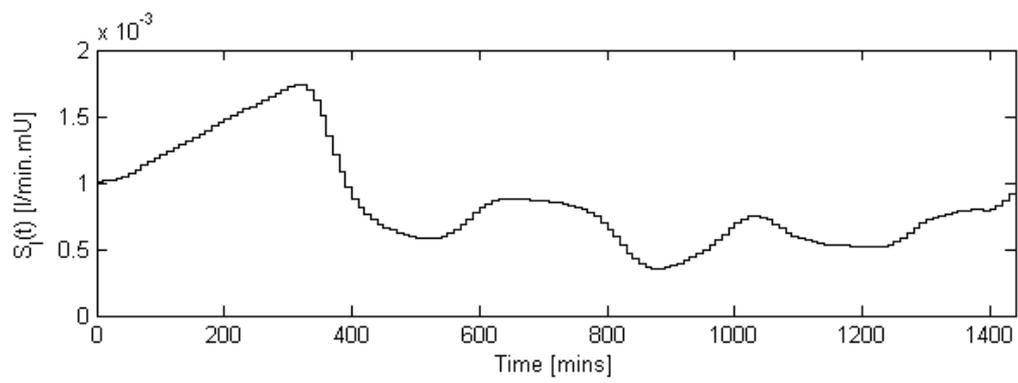


Figure 7: Sample patient $S_I(t)$ profile as obtained from model fit. Note the 10min interval for fitting the stepwise, time-variant $S_I(t)$

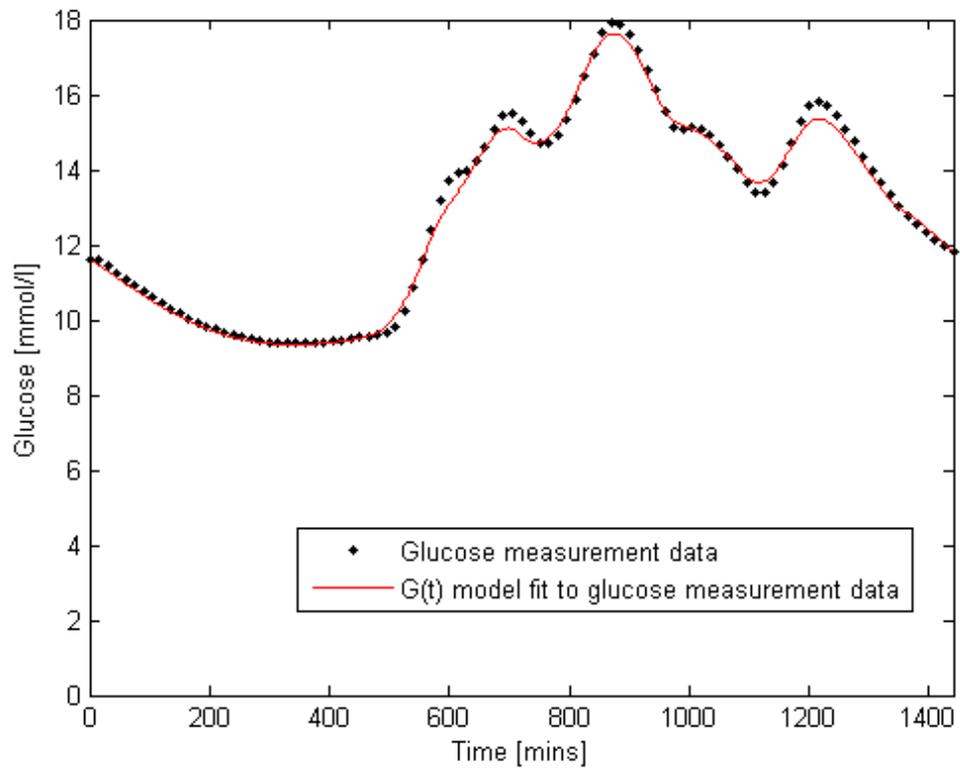


Figure 8: $G(t)$ model fit to glucose measurement data for Patient 1 shown with the glucose measurement data from AIDA on-line².

TABLES

Table 1: *A priori* identified model constants obtained from literature except the linear gastric emptying and gut absorption rates (k_6 and k_7 respectively) which are optimised using nonlinear least squares to model-independent, mixed-meal tracer glucose Ra data [34]

Model constants	Values [units]
$GABS_{\max}$	1.1 [g/min]
p_G	0.0060 [min^{-1}]
CNS	1.7 [mg/kg.min]
EGP_{0-G}	3.0 [mg/kg.min]
GFR	0.12 [l/min]
RGT	10 [mmol/l]
V_P	0.22 [l/kg]
k_6	0.0388 [min^{-1}]
k_7	0.0097 [min^{-1}]

Table 2: Details of the patient cohort ($n=40$) from AIDA² on-line showing body weight, total carbohydrate consumed, total prandial insulin dose, total basal insulin dose, and the unique clinical variables of hepatic and peripheral insulin sensitivity, glucose renal threshold, and glomerular filtration rate

Case number	Body weight [kg]	Total carbohydrate consumed [g]	Total prandial insulin dose [U]	Total basal insulin dose [U]	Renal threshold	Renal function	Hepatic insulin sensitivity	Peripheral insulin sensitivity
1	70	130	7	30	Normal	Normal	Reduced	Reduced
2	68	180	13	10	High	Normal	Increased	Increased
3	70	120	9	13	Normal	Normal	Normal	Increased
4	60	180	13	12	Normal	Normal	Increased	Increased
5	98	180	12	12	Normal	Normal	Normal	Normal
6	76	120	8	28	Normal	Normal	Reduced	Increased
7	70	90	7	24	Normal	Normal	Increased	Reduced
8	70	120	10	20	Normal	Normal	Reduced	Increased
9	70	180	12	12	High	Normal	Normal	Increased
10	70	120	15	8	Normal	Normal	Normal	Increased
11	70	205	16	22	Normal	Normal	Normal	Increased
12	70	185	24	20	Normal	Normal	Reduced	Increased
13	76	100	8	26	Normal	Normal	Normal	Increased
14	65	70	5	20	Normal	Normal	Reduced	Normal
15	99	115	6	42	Normal	Normal	Reduced	Normal
16	70	180	9	32	Normal	Normal	Reduced	Increased
17	70	110	10	24	Normal	Normal	Reduced	Increased
18	60	165	18	36	High	Normal	Reduced	Increased
19	60	180	12	12	Normal	Normal	Normal	Increased
20	70	105	8	36	Normal	Normal	Normal	Increased
21	98	295	34	40	Normal	Normal	Reduced	Reduced
22	75	70	Biphasic 40		Normal	Normal	Reduced	Reduced
23	87	177	38	12	Normal	Normal	Reduced	Increased

24	76	95	7	24	Normal	Normal	Normal	Increased
25	70	120	18	28	Normal	Normal	Reduced	Normal
26	80	170	Biphasic 20		Normal	Normal	Normal	Increased
27	70	120	9	13	Low	Normal	Normal	Normal
28	75	85	5	40	Normal	Normal	Normal	Increased
29	83	60	12	25	Normal	Normal	Reduced	Normal
30	80	165	16	36	Normal	Normal	Reduced	Increased
31	99	220	29	14	Low	Normal	Normal	Increased
32	90	70	0	28	Normal	Normal	Reduced	Reduced
33	98	180	0	18	Normal	Normal	Normal	Increased
34	60	175	17	13	High	Normal	Normal	Increased
35	60	170	22	10	Normal	Normal	Normal	Increased
36	70	100	8	32	Normal	Normal	Reduced	Increased
37	70	105	9	36	High	Normal	Reduced	Reduced
38	70	95	Biphasic 26		Normal	Normal	Normal	Reduced
39	70	110	12	35	High	Normal	Reduced	Increased
40	76	100	7	30	Normal	Normal	Normal	Normal

Table 3: Per patient absolute and absolute percentage $G(t)$ model fit error to the patient cohort data ($n=40$) from AIDA² on-line

Case number	Absolute % $G(t)$ fit error [%]			Absolute $G(t)$ fit error [mmol/l]		
	Median	5 th percentile	95 th percentile	Median	5 th percentile	95 th percentile
1	0.84	0.08	2.87	0.10	0.01	0.43
2	1.28	0.05	7.14	0.10	0.00	0.50
3	1.19	0.02	3.56	0.12	0.00	0.37
4	1.72	0.05	7.84	0.12	0.00	0.42
5	0.94	0.11	3.24	0.11	0.01	0.36
6	1.25	0.04	4.89	0.13	0.00	0.53
7	1.93	0.11	4.52	0.07	0.00	0.20
8	0.96	0.05	4.46	0.09	0.00	0.49
9	1.03	0.10	2.94	0.12	0.01	0.39
10	1.92	0.28	4.27	0.17	0.02	0.39
11	3.09	0.20	14.04	0.20	0.01	2.39
12	1.23	0.05	8.78	0.13	0.00	0.70
13	1.08	0.09	4.80	0.07	0.00	0.26
14	0.47	0.04	3.43	0.05	0.00	0.47
15	1.00	0.12	3.84	0.08	0.01	0.29
16	1.61	0.11	5.84	0.18	0.01	0.59
17	1.31	0.06	4.38	0.13	0.00	0.38
18	3.34	0.32	7.84	0.21	0.03	0.80
19	1.23	0.09	4.14	0.16	0.01	0.52
20	2.89	0.17	21.39	0.13	0.00	0.89
21	2.73	0.49	7.17	0.32	0.06	0.93
22	0.88	0.11	3.95	0.09	0.01	0.50
23	1.50	0.03	4.96	0.11	0.00	0.33

24	1.98	0.21	6.67	0.14	0.01	0.43
25	1.37	0.02	7.44	0.09	0.00	0.59
26	0.67	0.09	2.48	0.07	0.01	0.31
27	0.69	0.08	2.74	0.06	0.01	0.27
28	0.81	0.09	6.27	0.05	0.00	0.36
29	0.81	0.15	4.48	0.07	0.01	0.40
30	9.36	0.98	37.10	0.72	0.06	2.56
31	1.16	0.11	8.67	0.08	0.01	0.44
32	0.60	0.06	2.36	0.06	0.01	0.28
33	0.93	0.13	2.72	0.10	0.01	0.29
34	1.84	0.01	5.93	0.15	0.00	0.44
35	3.30	0.18	11.70	0.26	0.01	1.06
36	1.36	0.19	5.05	0.12	0.01	0.39
37	0.94	0.03	3.38	0.12	0.00	0.46
38	0.73	0.08	3.07	0.08	0.01	0.40
39	1.29	0.04	5.53	0.11	0.00	0.51
40	1.70	0.20	7.20	0.10	0.01	0.31
Median	1.24	0.09	4.85	0.11	0.01	0.43
Range	0.47-9.36	0.01-0.98	2.36-37.10	0.05-0.72	0.00-0.06	0.20-2.56

Table 4: Total absolute and absolute percentage $G(t)$ model fit error to the patient cohort data ($n=40$) from AIDA² on-line

Absolute % $G(t)$ fit error [%]			Absolute $G(t)$ fit error [mmol/l]		
Median	5th percentile	95th percentile	Median	5th percentile	95th percentile
1.33	0.08	7.20	0.12	0.01	0.56