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Estimation of secondary effect parameters in glycaemic dynamics using accumulating data from a virtual type 1 diabetic patient

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ABSTRACT

Some individuals with type 1 diabetes mellitus find self-managed glycaemic control difficult due to the confounding influence of secondary effects. Stress and sleep deprivation temporarily lower insulin sensitivity (*SI*), often resulting in hyperglycaemia, while aerobic exercise depletes glucose, leading to hypoglycaemia if treatment is unchanged. This study tests the estimation of these factors and circadian rhythms of *SI* in noisy data. Sparse, irregular and noisy virtual blood glucose data, mimicking the glycaemic dynamics of an individual with type 1 diabetes, was created via adapted pharmacokinetic–pharmacodynamic models of glucose and insulin that included the impact of the secondary effects. A Gauss–Newton algorithm was used to recover the original model parameters for *SI*, stress, fatigue and exercise. During longer identification periods, compensation was made for drift in *SI*. Monte Carlo analyses were undertaken to validate the methods. The coefficient of variation (CV) in all parameters decreased as the data accumulated in proportion to the $1/\sqrt{n}$ rule ($R^2 > 99.9\%$). Relatively small biases from the original parameter values occurred (<1%). Long term drift trends in *SI* were captured and did not obscure estimation of the secondary effects (biases < 1%, CV approximately equivalent to drift free outcomes). Adherence to the $1/\sqrt{n}$ trend indicates a robust identification method and the ability of accumulating data to override the effect of measurement error. Compensation for *SI* drift allows viable observation of secondary effects and *SI* rhythms over longer time periods. Collectively, these outcomes indicate that quality results for identified parameters could be obtained during *in vivo* studies.

1. Introduction

Established type 1 diabetes mellitus is a metabolic disease characterised by an almost absolute lack of pancreatic insulin production. Individuals with this condition are dependent on exogenous insulin and generally take two or more doses a day [36]. They must carefully monitor blood glucose (*BG*) levels to avoid hypoglycaemia, or hyperglycaemia. Fear of hypoglycaemia frequently results in patients tending toward hyperglycaemia [42]. Increased incidences of hypo- and/or hyper-glycaemia are associated with reduced quality of life in diabetes [35] and a number of long-term complications [36,38,32,11].

There is significant potential benefit in developing effective glycaemic control mechanisms for individuals with type 1 diabetes similar to those used for the critically ill [7,29]. However, there are many social and psychological factors that confound the type of regimented glycaemic control used successfully in that cohort. In particular, some social situations induce over consumption. Furthermore, stress, anxiety and frustration can affect glycaemic behaviour and occur intermittently. Stress and related factors can be caused by self-monitored blood glucose, regimented lifestyles, and unpredictable glycaemic variability [36]. Thus, a further, necessary goal of glycaemic control algorithms for this cohort should be to mitigate the psychological impact of the control algorithm itself by allowing greater flexibility in daily activities.

There are many secondary effects that influence glycaemic control. It is well established that emotional (as well as medical) stress results in hyperglycaemia in individuals with type 1 diabetes [40,20]. This hyperglycaemia is due to insulin resistance caused by the endogenous release of corticosteroids and catecholamines [42]. Sleep deprivation is also responsible for changes in insulin sensitivity without significant changes in cortisol levels [14]. In contrast, moderate-intensity (aerobic) exercise can lower *BG* significantly, and eventually causes hypoglycaemia if care is not altered [39,49]. These factors provide challenges for self-managed glycaemic regulation. Furthermore, they are capable of confounding model-based control algorithms due to the lack of quantitative evidence or direct identification of their effect on glycaemia.

The use of physiological modelling has emerged in the field of glycaemic control for the critically ill [27,28,7]. Inter- and intra-patient

Abbreviations: SI, insulin sensitivity; CV, coefficient of variation; BG, blood glucose; CGM, continuous glucose monitor; DISST, dynamic insulin sensitivity and secretion test; SC, subcutaneous; CI, confidence interval; CHO, carbohydrate.

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Table 1
Parameter constants used to simulate the virtual patient glycaemic profiles in Eqs. (1)–(6). The * indicates parameters which were identified as variables from virtual data.

Parameter	Description	Value	Unit
n_I	Plasma to interstitium transport rate	0.02	min^{-1}
n_T	Plasma insulin clearance rate	0.1	min^{-1}
n_C	Cell metabolism of insulin	0.02	min^{-1}
v_P	Volume of distribution of plasma insulin	4.3	L
p_G	Glucose dependant balance	0.004	min^{-1}
V_G	Glucose distribution volume	12.4	L
k_1	Rate of glucose transfer from stomach to gut	0.05	min^{-1}
k_2	Rate of glucose absorption from gut	0.008	min^{-1}
k_X	Rate of insulin dispersed from injection site	0.01	min^{-1}
G_0*	Basal glucose level	4.5	mmol.L^{-1}
Q_0	Basal interstitial insulin level	4.23	mU.L^{-1}
ε_{max}*	Exercise coefficient	6.5	mmol.L^{-1}
σ_{max}*	Stress coefficient	0.3	
φ_{max}*	Fatigue coefficient	0.1	
SI_1*	Morning (8.30 am) SI peak	0.8×10^{-3}	$\text{L.mU}^{-1}\text{.min}^{-1}$
SI_2*	Midday (12 pm) SI peak	1.0×10^{-3}	$\text{L.mU}^{-1}\text{.min}^{-1}$
SI_3*	Afternoon (3.30 pm) SI peak	0.6×10^{-3}	$\text{L.mU}^{-1}\text{.min}^{-1}$

variability provides challenges to maintaining glycaemic control for individual patients. Thus, these modelling methods identify a number of patient-specific parameters as well as using *a priori* population-average parameters [7]. Recent developments have also been made in the field of automated treatments for out-patients with type 1 diabetes that are using continuous glucose monitors (CGMs) [16,4,8]. Some of these developments also include compensation for stress hyperglycaemia [42]. However, this type of treatment is still experimental and has high cost and complexity [17,4]. Hence, it may be more practical to improve upon conventional approaches such as self-monitored glucose with multiple daily insulin injections [46,47]. Knowledge of relevant patient-specific parameters would benefit model-based therapy support for insulin dosing information.

Sparse, irregular data provides challenges in uncovering clear trends. Thus the purpose of this research was to test parameter estimation in such data, identifying some of the key patient-specific secondary effects on glycaemic dynamics: stress, fatigue and exercise. The data was generated *in silico* to mimic self-reported, diary-style data with simulated self-monitored glucose measurement and omission errors. The results obtained from parameter identification were assessed in accumulating data-sets over a Monte Carlo (MC) population. Finally, the methods were tested for their ability to handle long-term changes in insulin sensitivity (*SI*) that occur due to changes in a patient's metabolism [24,1,48].

2. Methods

2.1. The virtual patient model

To test the estimation of factors affecting glycaemic dynamics, a virtual patient with type 1 diabetes was simulated *in silico*. The patient ingested regular meals and the occasional snack. They took insulin boluses with meals as well as a constant insulin infusion to mimic slow acting insulin. The virtual patient also participated in moderate exercise several times a week and experienced days of stress or fatigue several times per month.

The model used to simulate the glycaemic dynamics of the *in silico* patient is a variation of the clinically validated DISST model [21]. The adaptations include a nutrition model [19,44,45] and effects of exercise, stress, fatigue and *SI* drift. The model consists of *a priori* parameters (definitions in Table 1), time-dependent inputs (definitions in Table 2) and identified variables (Table 1). A flowchart showing the order of dependent species in the model can be seen in Fig. 2.

First, subcutaneous insulin concentration (U_S) was modelled as a kinetic delay from regular bolus doses and a basal infusion (U_X):

$$\dot{U}_S(t) = k_X(U_X(t) - U_S(t)) \tag{1}$$

Interstitial insulin concentration (Q) was modelled as being co-dependent with plasma insulin (I) which is a function of U_S:

$$\dot{I}(t) = -(n_T + n_I)I(t) + n_I Q(t) + \frac{k_X U_S(t)}{V_P} \tag{2}$$

$$\dot{Q}(t) = -(n_I + n_C)Q(t) + n_I I(t) \tag{3}$$

Glucose absorbed into the gut (P_S) was modelled as a kinetic delay from regular meals of varying glucose content (P_X) and randomly timed snacks (P_C) [19,44,45]:

$$\dot{P}_S(t) = \frac{P_X(t) + P_C(t)}{V_G} - k_1 P_S(t) \tag{4}$$

Table 2
Time-dependent vector inputs for used to simulate the virtual patient, noting that the simulation uses 1 min resolution.

Vector	Description	Value	Unit
$\mathbf{P_X}$	Meals	$\begin{cases}[400,\ 500] \text{ at } 0800,\ 1200 \text{ and } 1900 \text{ hrs daily}\\ 0 \text{ otherwise}\end{cases}$	mmol
$\mathbf{P_C}$	Snacks	$\begin{cases}160 \text{ at } 52 \text{ random } t \text{ per year}\\ 0 \text{ otherwise}\end{cases}$	mmol
$\mathbf{U_X}$	Insulin doses	$\begin{cases}1000 \text{ with meals}\\ 4 \text{ otherwise}\end{cases}$	mU
$\mathbf{f}_\varepsilon$	Exercise	$\begin{cases}\in [0.5,\ 0.6, \ldots,\ 1.0] \text{ at } 0830 \text{ to } 1030 \text{ hrs},\ 3 \text{ days/week}\\ 0 \text{ otherwise}\end{cases}$	
$\mathbf{f}_\sigma$	Stress	$\begin{cases}\in [0.5,\ 0.6, \ldots,\ 1.0] \text{ 3 days per 4 weeks}\\ 0 \text{ otherwise}\end{cases}$	
$\mathbf{f}_\varphi$	Fatigue	$\begin{cases}\in [0.5,\ 0.6, \ldots,\ 1.0] \text{ 5 days per 4 weeks}\\ 0 \text{ otherwise}\end{cases}$	
$\mathbf{g_1}$	Morning *SI* basis	$\begin{cases}0 \text{ 1200 to 1530 hours}\\ 1 \text{ 0830 hours}\\ 0 < g_1 < 1 \text{ otherwise}^a\end{cases}$	
$\mathbf{g_2}$	Midday *SI* basis	$\begin{cases}0 \text{ 1530 to 0830 hours}\\ 1 \text{ 1200 hours}\\ 0 < g_2 < 1 \text{ otherwise}^a\end{cases}$	
$\mathbf{g_3}$	Afternoon *SI* basis	$\begin{cases}0 \text{ 0830 to 1200 hours}\\ 1 \text{ 1530 hours}\\ 0 < g_3 < 1 \text{ otherwise}^a\end{cases}$	

[a] Triangular basis function forms are pictured in Fig. 1.