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Accurate and precise prediction of insulin sensitivity variance in critically ill patients

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ABSTRACT

Background: Glycaemic control (GC) in critical care can reduce mortality and improve clinical outcomes. Model based GC allows personalised and effective predictive control. Improving accuracy and precision of patient specific models, parameter identification, and resulting blood glucose predictions would enable more effective model-based GC algorithms.
Methods: Glycaemic data from 30 critically ill patient episodes was used to fit a model of glucose dynamics. In this model, insulin sensitivity (*SI*) is identified through time using b-spline basis functions. The number of basis functions, *M*, relative to the number of data points in each data set, *N*, determines the level of parameterisation of the model. By fitting the model to all 30 data sets, the identified *SI* profiles could be used to build stochastic maps of *SI* changes over time. These maps show how *SI* is expected to change based on the current *SI* and the overall behaviour of this cohort. Thus, for a given time step into the future, *SI* prediction distributions can be found. Stochastic maps were made for varying basis function degree (d) ($d \in \{0, 1, 2\}$), and ratio of M to N ($M{:}N \in \{0.3, 0.65, 0.85, 1\}$). Using small subsets of each data set, many trials were carried out to compare *SI* prediction distributions to the distribution of the true *SI* values at the next measurement, for each combination of M and d. The main aim was to observe how the model parameterisation affected the predictive ability of the model. Outcomes from an Akaike Information Criterion (AIC) analysis were compared to the prediction analysis. AIC is a method of model comparison that assesses which of the given models provides the best trade-off between goodness-of-fit and model complexity, based on the expected measurement noise. For each basis function order, an AIC analysis was used to select the best $M{:}N$ ratio of the four options tested.
Results: Increasing the parameterisation of the model resulted in lower model-data residuals and thus wider stochastic maps, as *SI* changed at a faster rate to enable the model to more closely fit to the data. Therefore, increasing $M{:}N$ resulted in wider prediction distributions. In all cases, when $M{:}N = 1$, the prediction distributions were too wide, and when $M{:}N = 0.3$ the prediction distributions were too narrow. Increasing the basis function order resulted in tighter prediction distributions, and allowed more accurate predictions to be made with a higher $M{:}N$ ratio. The ratios that gave the most accurate predictions were $M{:}N = 0.65$ when $d = 0$, $M{:}N = 0.85$ when $d = 1$, and $M{:}N = 1$ when $d = 2$. In contrast, the AIC analysis found that an $M{:}N$ ratio of approximately 0.45 was optimal in all cases.
Conclusions: This study presented a new strategy for observing how the level of parameterisation and basis function order affects accuracy of future predictions of *SI* variability. Applications based on the findings of this research with a larger cohort could lead to improved predictive capability in GC algorithms. Accurate predictions would ultimately allow model-based GC algorithms to be implemented more effectively, increasing clinician confidence and improving patient outcomes.

1. Introduction

Hypoglycaemia, hyperglycaemia and glycaemic variability in critical care are each individually associated with increased mortality and morbidity [1–6]. Many critically ill patients present are admitted to the intensive care unit (ICU) with hyperglycaemia, very high insulin resistance, and often exhibit very high glycaemic

Abbreviations: AIC, Akaike information criterion; GC, glycaemic control; ICU, intensive care unit; SI, insulin sensitivity.

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metabolic variance, which can be exacerbated by sepsis [7–9]. This combination of dysfunctions requires blood glucose to be intensively monitored and controlled. Glycaemic control (GC) algorithms have been proven to reduce blood glucose levels, variability, and the risk and incidence of hypoglycaemia [10–16]. GC can therefore reduce the rate and severity of organ failure. GC can also reduce mortality, if it controls all patients well, which can be more readily achieved with model-based approaches [11,14,17–19].

Clinical data and models can be used retrospectively to determine the variability of insulin sensitivity (*SI*) in cohorts of critically ill patients [20–23]. Such analyses lead to stochastic differential equations that can predict the patient *SI* or glucose likelihood distributions, or ordinary differential equations that determine the most likely outcome with *SI* variance added *a posteriori*. Regardless of the strategy, it is critical that the resulting prediction distribution for a given intervention is accurate. If the predicted likelihood distribution is too tight, the GC may be overly aggressive and risk unexpected hypoglycaemia. If the distribution is too wide, the GC may be too conservative, and, while safe, not as tight as possible.

The Akaike Information Criterion (AIC) assesses whether the level of model parameterisation is appropriate by considering goodness-of-fit against expected measurement errors. The AIC cannot determine if any single model is over-parameterised. However, AIC generally implies that fitting N parameters to N data points means that the data is over-fitted, indicating that measurement error may be falsely attributed to the underlying behaviour of the identified system dynamics. For GC, this issue could ultimately mean the algorithm will expect more variability in *SI* and glucose than might actually occur. A model that is not over-fitted, but catches the true underlying behaviour of the patient would yield the best prediction outcomes.

The aim of this paper is to present a new method of observing the effect of parameterisation on the predictive ability of a model of blood glucose. The model is fit to retrospective data from 30 patient episodes to determine overall insulin sensitivity (*SI*) variability for the cohort at different levels of model parameterisation. Distributions of future *SI* are able to be predicted using this measure of variability. The predictions are compared with the true *SI* identified at future glucose measurements. The prediction analysis is compared with an AIC analysis.

2. Materials and methods

2.1. Data

This study uses 30 data sets covering 6785 h of GC from patients treated using the Specialised Relative Insulin Nutrition Table (SPRINT) protocol for GC in critically ill patients [11]. Data was collected between August 2005 and May 2007. Measurements were usually hourly (2420 samples) or two hourly (1365 samples). There were occasional gaps of three hours (222 samples) or more (202 samples) between measurements. The patient age range was 37–86 years, with a mean of 65. Diagnoses included sepsis, respiratory failure and pneumonia. Baseline blood glucose varied between 3.3 and 19.7 mmol L^{-1}, with a mean of 8.3 mmol L^{-1}. Each patient's data spanned multiple days, and had a differing number of data points (N). Further details on SPRINT and its development can be found in [11,15,24,25]. Ethics approval to collect, audit, and present these data was obtained from the South Island Regional Ethics Committee, New Zealand.

2.2. The glucose model

Linear differential equations were used to model the insulin and glucose kinetics of the patients. The insulin model was a two compartment approach with clearance from both plasma and interstitial compartments [26]. The glucose model was a linear adaptation of a clinically validated single compartment approach [27]. The linear adaptation allowed analytical forward simulations, and thus enabled quicker computational simulation compared with iterative time stepping or error stepping methods.

Table 1
Constant model parameters.

Variable	Description	Value
p_G	Non-insulin mediated glucose uptake	0.004 min^{-1}
V_G	Glucose distribution volume	9 L
V_P	Plasma insulin distribution volume	4 L
E_{GP}	Endogenous glucose production	1.5 mU min^{-1}
G_b	Basal glucose	5 mmol L^{-1}
k_1	Linear clearance of plasma insulin	0.05 min^{-1}
k_2	Transfer rate of insulin from interstitium to plasma	0.025 min^{-1}
k_3	Transfer rate of insulin from plasma to interstitium	0.025 min^{-1}
k_4	Clearance rate of insulin from interstitium	0.033 min^{-1}

$$\dot{I}(t) = -k_1 I(t) + k_2 Q(t) + \frac{U}{V_p} \tag{1}$$

$$\dot{Q}(t) = k_3 I(t) - k_4 Q(t) \tag{2}$$

$$\dot{G}(t) = p_G (G_b - G(t)) + \frac{P_x(t) + E_{GP}}{V_G} - SI(t) G(t) Q(t) \tag{3}$$

where $G(t)$ is the total plasma glucose (mmol L^{-1}), $I(t)$ is the plasma insulin (mU L^{-1}), $Q(t)$ is the interstitial insulin (mU L^{-1}), $P_x(t)$ is exogenous glucose (mmol min^{-1}), U is the insulin input to plasma (mU min^{-1}), and $SI(t)$ is the identified insulin sensitivity profile (L mU^{-1} min^{-1}). The model constants are given in Table 1.

Insulin sensitivity is modelled with a series of b-spline basis functions:

$$SI(t) = \sum_{i=1}^{M} SI_i \phi_{i,d}(t) \tag{4}$$

where $\varphi_{i,d}$ are basis functions of degree d though time, and SI_i are the identified basis function coefficients. M is the number of basis functions, and determines the level of parameterisation of the model. The basis functions [28] ($\varphi_{i,d}$) are defined:

$$\phi_{i,0}(t) = \begin{cases} 0, & t < t_i \\ 1, & t_i \le t < t_{i+1} \\ 0, & t_{i+1} \le t \end{cases} \tag{5}$$

$$\phi_{i,d}(t) = \frac{t - t_i}{t_{i+d} - t_i} \phi_{i,d-1}(t) + \frac{t_{i+d+1} - t}{t_{i+d+1} - t_{i+1}} \phi_{i+1,d-1}(t) \tag{6}$$

where t_i are knots on the interval $[t_0, t_{max}]$. All basis functions sum to one for all time. Basis functions of zeroth ($d = 0$), first ($d = 1$), and second ($d = 2$) order were used in this analysis (Fig. 1).

Since blood glucose sampling rates were not always consistent, the basis function knots were evenly distributed across the sample times. For example, when $M = N$, each basis function knot corresponds exactly to the time of each glucose measurement. When $M = 0.5N$ the basis function knots corresponded with every second data point. This protocol removes the possibility of a large gap between samples bridging one or more basis functions and thus inducing non-identifiability in the coefficients of those basis functions. Fig. 2 shows zeroth, first, and second order basis functions with a dataset containing a higher frequency of measurements in the later stages of the measurement window.

Fig. 3 shows an example of the *SI* profiles and corresponding glucose model output, plotted at the time of each measurement. While the parameterisation is the same for a given M:N regardless of d, the added complexity of higher order basis functions allows $SI(t)$ to