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Impact of variation in patient response on model-based control of glycaemia in critically ill patients

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ABSTRACT

Critically ill patients commonly experience stress-induced hyperglycaemia, and several studies have shown tight glycaemic control (TGC) can reduce patient mortality. However, tight control is often difficult to achieve due to conflicting drug therapies and evolving patient condition. Thus, a number of studies have failed to achieve consistently safe and effective TGC possibly due to the use of fixed insulin dosing protocols over adaptive patient-specific methods. Model-based targeted glucose control can adapt insulin and dextrose interventions to match identified patient insulin sensitivity. This study explores the impact on glycaemic control of assuming patient response to insulin is constant, as many protocols do, versus time-varying. Validated virtual trial simulations of glucose control were performed on adult and neonatal virtual patient cohorts. Results indicate assumptions of constant insulin sensitivity can lead to six-fold increases in incidence of hypoglycaemia, similar to literature reports and a commonly cited issue preventing increased adoption of TGC in critical care. It is clear that adaptive, patient-specific, approaches are better able to manage inter- and intra-patient variability than typical, fixed protocols.

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1. Introduction

Critically ill patients, both adult and infant, often experience hyperglycaemia and high levels of resistance to insulin [1]. Hyperglycaemia worsens outcomes, increasing the risk of severe infection [2], myocardial infarction [3] and critical illness such as polyneuropathy and multiple organ failure [4]. The occurrence of hyperglycaemia is associated with increased morbidity and mortality in adults. Glycaemia variability, and thus poor control, is also independently associated with increased mortality [5].

An increasing body of recent literature links hyperglycaemia in preterm neonates to worsened outcomes in a parallel of the adult case. Studies have demonstrated an increased risk of further complications such as sepsis, increased ventilator dependence, retinopathy of prematurity, hospital length of stay and mortality associated with high levels of blood glucose [6–8].

Hyperglycaemia as a response to the stress of critical illness is a common origin of this altered metabolic state in both adults and neonates. The counter-regulatory response to stress increases the level of circulating catecholamines, resulting in increased endogenous glucose production and

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reduced sensitivity to insulin. Hyperglycaemia in the neonate is unique in that in addition to manifestation as a response to stress, several patho-physiologies are directly related to the immaturity of the glucose regulatory system, including impaired beta-cell secretion of insulin [9], limited number of insulin-dependent tissues [10] and hepatic unresponsiveness to glucose infusions [11].

Tight glycaemic control has been shown to reduce mortality by 18–45% in adult patients [4,12]. There is also evidence of significant reductions in the need for dialysis, bacteraemia testing and blood transfusions with tight glycaemic control (TGC) using intensive insulin therapy [4]. Further studies have shown reduced excess inflammation and reduction immune system performance with insulin therapy in animal models [13], as well as myocardial protection and reduced inflammation in neonatal cardiac surgery patients [14]. All of these results point towards the conclusion that the control of blood glucose levels in adult critical care has a significant clinical impact.

Although it is now becoming an unacceptable practice to allow hyperglycaemia and its associated effects [15], moderately elevated blood glucose levels are tolerated or recommended [16] because of the fear of hypoglycaemia and higher nursing effort frequently associated with TGC [15]. Thus, despite the potential benefits, there is no universal standard algorithm or method for controlling blood glucose in critical care. Real-time model-based control may offer a glucose regulation method that is adaptable across cohorts and clinical practices [17].

In general, any glycaemic control protocol must reduce elevated blood glucose levels with minimal hypoglycaemia, while accounting for inter-patient variability, conflicting drug therapies and dynamically evolving physiological condition. Ideally, it must titrate glucose control interventions based on some estimate of patient metabolic state. Model-based control can adapt control interventions by quantifying the level of insulin response directly from data [18]. However, many insulin therapy regimes employ fixed dosing protocols [19], or dosing schemes adjusted by patient weight or other factors [20], ignoring inter- and/or intra-patient variability in metabolic response [21], and thus implicitly assume that the patient response to insulin is constant in some form.

In this study, the effects of intra- and inter-patient variability in sensitivity to insulin are explored in the context of simulations of glucose control using a clinically validated glucose–insulin system model [22]. Adaptive, model-based control is modified in simulation to test the relative importance of tracking metabolic state between patients and over time by comparing adaptive control results with simulations assuming the patient response to insulin is constant across patients and/or over time. These assumptions mirror the implicit assumptions in (1) absolute fixed insulin sliding scales (assumes response to insulin is the same across all patients and at all times), and (2) protocols which dose insulin based on a fixed patient metric such as weight (assumes insulin response changes between patients, but remains constant within a patient over time).

Cohorts of adult and neonatal virtual patients, fitted from clinical retrospective data, are used to determine the impact of not adequately addressing inter- or intra-patient variability

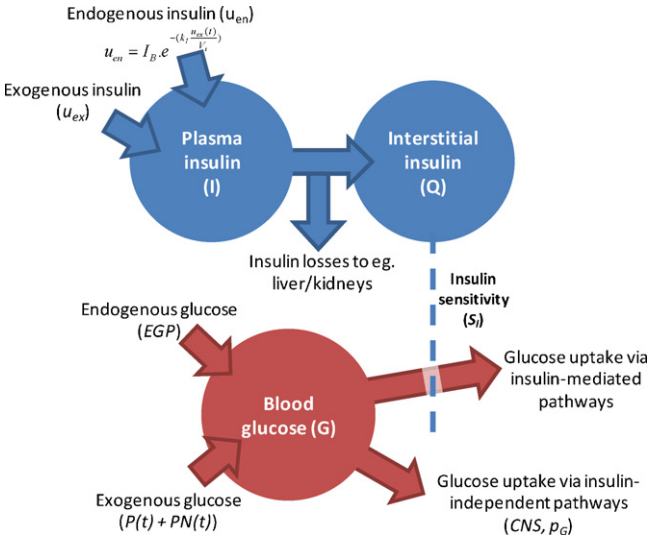

Fig. 1 – Major components of the glucose–insulin model.

on glycaemic control. The distributions of sensitivity to insulin are compared between adults and neonates to identify any potential differences in the glycaemic management between the cohorts. Clinically validated virtual trial simulations are performed to highlight the potential for model-based control to better adapt to significantly different clinical situations. Thus, exploring the relative importance of model-based control to account for inter- vs. intra-patient variabilities and the differences in variability between adults and neonates can indicate the magnitude by which model-based control can provide more robust and safer control of glucose levels.

2. Methods

2.1. Models

Blood glucose system models clinically validated in both adults [22] and neonates [23] are used in this study [24]. The overall form of the models is presented in Eqs. (1)–(3). Major components of the model are displayed in Fig. 1.

$$\dot{G} = -p_G G - S_I G \frac{Q}{1+\alpha_G Q} + \frac{P(t) + (P_{END} \times m_{body}) - (CNS \times m_{brain})}{V_{G,frac}(t) \times m_{body}} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{V_{I,frac} \times m_{body}} + I_B e^{-(k_I(u_{ex}(t)/V_I))} \quad (3)$$

where $G(t)$ [mmol/L] is plasma glucose, $I(t)$ [mU/L] is plasma insulin, $u_{ex}(t)$ [mU/min] is exogenous insulin input, basal endogenous insulin secretion is I_B [mU/L/min], with k_I representing suppression of basal insulin secretion by exogenous insulin. Interstitial insulin is $Q(t)$ [mU/L], with k [1/min] accounting for losses and transport. Body weight and brain

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