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Stochastic Model Predictive (STOMP) glycaemic control for the intensive care unit: Development and virtual trial validation

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ABSTRACT

Critically ill patients often experience stress-induced hyperglycaemia, which results in increased morbidity and mortality. Glycaemic control (GC) can be implemented in the intensive care unit (ICU) to safely manage hyperglycaemia. Two protocols SPRINT and STAR, have been implemented in the Christchurch ICU, and have been successful in treating hyperglycaemia while decreasing the risk of hypoglycaemia. This paper presents a new GC protocol that implements the probabilistic, stochastic forecasting methods of STAR, while formalizing the control methodology using model predictive control (MPC) theory to improve the ability to tune the dynamic response of the controller. This Stochastic Model Predictive (STOMP) controller predicts the response to a given insulin/nutrition intervention, and attributes weighted penalty values to several key performance metrics. The controller thus chooses an intervention at each hour that minimizes the sum of these penalties over a prediction window of 6 h, which is twice as long as the 3-h window used in STAR. Clinically validated virtual trials were used to evaluate the relative performance of STOMP. Results showed STOMP was able to obtain results very similar to STAR with both protocols maintaining approximately 85% of time within 4.4–8.0 mmol/L glycaemic band, and only 4–5 patients of the 149 patient STAR cohort having blood glucose (BG) <2.2 mmol/L. STOMP was able to attain similar results to STAR while further increasing ease of controller tuning for different clinical requirements and reducing the number of BG measurements required by 35%.

1. Introduction

Critically ill patients often experience stress-induced hyperglycaemia and high levels of insulin resistance [1–7]. The occurrence of hyperglycaemia, predominantly severe hyperglycaemia, is associated with an increase in morbidity and mortality in this group of patients [1,3]. Glycaemic variability, and thus poor control, is also independently associated with an increase in mortality [8,9].

It has been shown that effective glycaemic control (GC) can significantly reduce the number of negative outcomes associated with poor control by modulating nutrition and/or insulin administration [7,10,11]. Effective GC can also lead to a reduction in the rate and severity of organ failure [12] and the cost of care [13,14]. However, consistent, safe and effective GC remains elusive with several other studies achieving negative, or inconclusive outcomes [15–20]. In addition, there is little agreement on what constitutes desirable glycaemic performance [21–23], particularly with regard to how GC affects outcome.

The model-derived SPRINT protocol has been successful at reducing organ failure and mortality [10,12] with a patient-specific approach, providing the tightest control across all patients of several large studies [24,25]. As a series of interactive charts, the SPRINT protocol allowed nutrition and insulin interventions to be tailored to current patient condition. However, as a paper-based protocol, SPRINT was relatively inflexible to different desired blood glucose targets and clinical uses, and required a relatively high nurse workload with 1–2 hourly blood glucose (BG) measurements.

The Stochastic TARgeted (STAR) glycaemic control protocol was thus developed to address these issues [26,27]. STAR recommends an intervention based on a clinically specified maximum risk of mild hypoglycaemia (e.g. BG < 4.4 mmol/L), derived from stochastic model predictions of future insulin sensitivity [28,29]. With the ability to quantify the probability of hypoglycaemia, STAR allows aggressive yet safe control of blood glucose within a target band. STAR is flexible to different blood glucose targets [30,31] and nursing intervention frequency, and thus, addresses many of the areas

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for improvement with the SPRINT protocol. However, the intervention selection algorithm used by STAR is fixed and does not allow for dynamic tuning, which limits the capacity for the controller to be further optimized in real time.

Model predictive control (MPC) is an alternative control approach that allows the dynamic response of the controller to be easily tuned through a series of clinically pre-defined cost functions. MPC utilizes a mathematical model of a system to forecast the response to a given input, and control interventions are chosen to produce optimal forecasted results. Commonly, optimization will involve specifying weighted (cost) functions to key input and output performance metrics, and choosing an intervention that minimizes the sum of these values. The benefit of such a system is that the cost functions can be easily optimized to produce robust and consistent control outcomes from an intuitively easily understood clinical specification. This type of controller was chosen due to the flexibility of cost functions in allowing the dynamic response of the controller to be easily tuned. MPC has also been used for glycaemic control with a different model [32–35].

This article presents a Stochastic Model Predictive (STOMP) GC protocol that uses a low error, infrequently measured, BG signal to control the BG levels in adult ICU patients while providing greater flexibility than STAR. This research presents the protocol design and optimization for an adult ICU using clinically validated [36] virtual trials to amend safety and efficacy before clinical uptake.

2. Methods

2.1. Glucose–insulin model

A variant of the ICING model [37] was used to describe glucose–insulin metabolic system dynamics:

$$\dot{G}(t) = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G} \quad (1)$$

$$\dot{Q}(t) = n_I(I(t)-Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (2)$$

$$\dot{I}(t) = -n_K I(t) - n_L\frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}(G)}{V_I} \quad (3)$$

$$P(t) = \min(d_2P_2, P_{\max}) + PN(t) \quad (4)$$

Table 1
Key variables of metabolic glucose model.

Variable	Unit	Description
$G(t)$	mmol/L	Blood glucose concentration
$I(t)$	mU/L	Plasma insulin concentration
$Q(t)$	mU/L	Interstitial insulin concentration
$P(t)$	mmol/min	Glucose appearance in plasma from dextrose intake
$S_I(t)$	L/mU/min	Insulin sensitivity

$$\dot{P}_1(t) = -d_1P_1 + D(t) \quad (5)$$

$$\dot{P}_2(t) = -\min(d_2P_2, P_{\max}) + d_1P_1 \quad (6)$$

$$u_{en}(G) = min\,(\max(u_{\min}, k_1G(t)+k_2),\ u_{\max}) \quad (7)$$

The key variables are described in Table 1, while the remaining model parameters, rates and constants are described in [37,38].

This model-based insulin sensitivity, $S_I(t)$ (SI), has been shown to be independent of both insulin and nutrition inputs, and can be used to calculate the likely BG response to treatments other than those given clinically. This process is called a virtual trial, and has been clinically validated to describe both whole cohort and per-patient results [36].

2.2. Stochastic model

Forward prediction of BG is enabled by an estimate of the conditional probability density function of SI based on historical data (stochastic model). The stochastic model used by STAR is generated using kernel-density methods and model-based insulin sensitivity data from a large cohort of patients (43,000 SI values from approximately 400 patients). Given a value of SI (at time n), the stochastic model can be used to estimate the probability of future SI values (at time $n+1$).

STAR focuses on the 5th- and 95th-percentile values, as these values can be used to impose a 5% risk limit on hypoglycaemia for a given insulin/nutrition intervention. Fig. 2 indicates the relationship between the insulin sensitivity and the associated blood glucose trajectory. The model covers a broad medical ICU cohort over all the days of stay, but can be made specific to unique cohorts [39,40].

Using the insulin sensitivity stochastic model obtained from Fig. 1 the BG stochastic model, for a specific insulin and nutrition intervention, can be obtained through solving the glucose–insulin

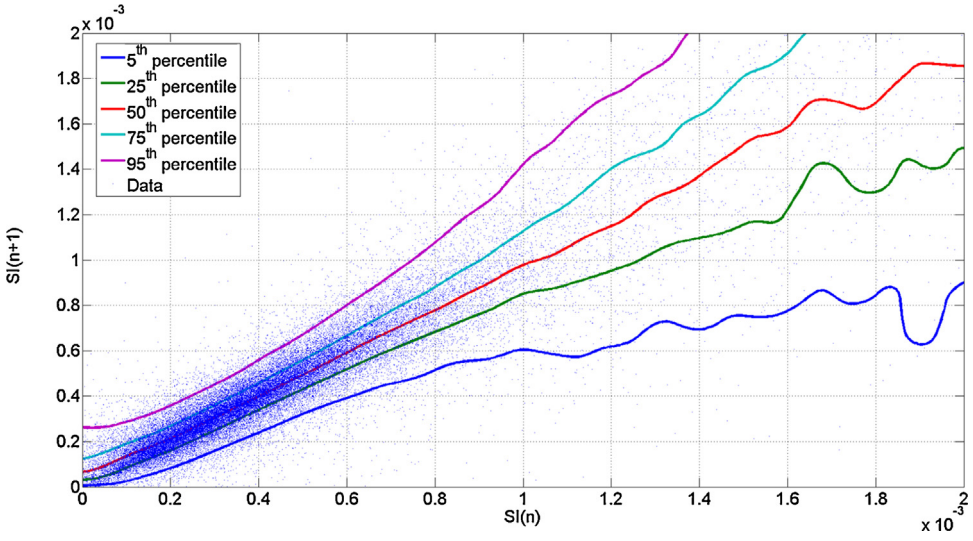

Fig. 1. Stochastic model of insulin sensitivity.