Biomedical Signal Processing and Control 44 (2018) 270–278

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

# Creating smooth SI. B-spline basis function representations of insulin sensitivity

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ARTICLE INFO

*Article history:*
Received 6 August 2017
Received in revised form 22 March 2018
Accepted 5 May 2018

*Keywords:*
Insulin sensitivity
B-spline
Basis function
Glucose-insulin model
Glycaemic control
Intensive care unit

ABSTRACT

In the intensive care unit (ICU), stress-induced insulin resistance leading to hyperglycemia is commonplace. If safe and effective glycemic control (GC) can be provided, a significant reduction in the negative effects of dysglycemia can be achieved. The Intensive Control Insulin-Nutrition-Glucose (ICING) model has worked particularly well in guiding patient-specific GC. The current method to identify patient- and time- specific insulin sensitivity (SI) with this model employs a discrete stepwise hourly function, which is effective, but not physiologically representative at hourly transitions.

2nd Order B-spline basis functions (BF) are investigated as a more continuous and physiologically relevant alternative for two different cohorts of patient data (Benchmark, 20 patients; Stochastic TARgeted (STAR) sub-cohort, 72 patients). Various knot-widths (KW) of 2nd Order B-spline BFs were investigated and compared to the currently used step function BF in terms of physiological relevance, identifiability, robustness to false measurements, and susceptibility to noise to ensure the most physiologically realistic representation of SI.

The 180 min KW 2nd Order B-spline BFs provided the most physiologically realistic fit to the blood glucose (BG) measurements in both cohorts (Standard Deviation of relative fitting error: Benchmark 8.7% vs. 9.35% BG meter, STAR sub-cohort 6.0% vs. 6.0% BG meter), while also having significantly less susceptibility to false BG measurements compared to the current BF.

The 180 min 2nd Order B-spline BF provides a smooth second order continuous, more physiologically representative, and identifiable model of the dynamics of SI, and a more realistic resulting BG solution. The outcome provides a promising new addition to the ICING model and STAR GC protocol, while also opening up several new potential continuous time analyses of SI dynamics, not previously possible.



## 1. Introduction

In the intensive care unit (ICU) stress-induced insulin resistance, leading to hyperglycemia is commonplace [1–3]. Hyperglycemia has been linked to increased morbidity and mortality [1,2,4]. However, if safe, effective glycemic control (GC) can be provided, a significant reduction in the negative effects of dysglycemia can be achieved [5–10]. Safe, effective GC has been associated with reductions in the rate and severity of organ failure [11], mortality [5] and cost of care [12,13].

Some of the most effective and safe GC techniques used currently are model-based [14–17], where treatment decisions are based on model identified physiological markers and forward prediction of insulin-glucose response to care. A model that has worked particularly well in guiding GC is the Intensive Control Insulin-Nutrition-Glucose (ICING) model [18,19], which is used in the Stochastic TARgeted (STAR) framework [14,20–22]. The STAR model-based framework is able to provide patient-specific, safe control using models of time-varying patient metabolic dynamics [23,24], with discrete, hourly-identified stepwise jumps of model-based insulin sensitivity (SI) values [25]. However, the current identification of SI has multiple issues:

- Constant, hourly stepwise jumps in SI are not strictly physiologically accurate. As BG and thus SI is a physiological signal, changes are continuous and smooth [26–33], even if rapid, and not discrete step wise jumps.

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https://doi.org/10.1016/j.bspc.2018.05.001
1746-8094/

- Frequent (Hourly) SI changes require assumed intermediate blood glucose (BG) dynamics to be identifiable [34,35]. As the median measurement interval for STAR is 1.8 h [14], and 2 BG measurements (1 Change in BG equation) are required to identify each step in SI, linear interpolation is used to assume extra data points required [36].
- The identified SI is very susceptible to noise, capturing both measurement error and modelling error [25]. Rapid SI changes, caused by large errors, negate any relevant dynamics in the model and capture all of the measurement error.

Therefore, representing SI with a continuous, identifiable function which is less susceptible to measurement error would significantly improve the physiological representation of this parameter, in this already clinically proven model [14,20,21,37].

In many physiological models, basis functions (BFs) have proven to be effective in reproducing physiological signals [38–40]. In particular, B-spline BFs have been shown to represent many time varying natural phenomena [41,42]. Hence, B-spline BFs offer a means of parameterizing a time-varying signal like SI, in a more physiologically relevant and continuous manner, without adding significant complexity or identifiability issues [34,35].

This paper investigates the identification of the current, zeroth order B-spline, technique and alternative 2nd Order B-spline technique, in modelling patient-specific time-varying SI. The BFs are compared in terms of physiological relevance, identifiability, and susceptibility to noise and error. The goal is a more physiologically relevant and less over fitted SI function that also provides potential for greater physiological insight into metabolic dynamics.

## 2. Methods

### 2.1. Glucose-insulin model

A variant of the clinically evaluated ICING model [18,37] is used to describe glucose-insulin metabolic system dynamics:

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

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

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

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

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

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

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

The model presented is a compartment model, accounting for the appearance of insulin and glucose in blood and interstitial fluid volumes. Key variables are described in Table 1, while the remaining model parameters, rates and constants are described in Table 2 and [18,43].

### 2.2. Identification of insulin sensitivity (SI)

The model-based insulin sensitivity, $S_I(t)$ (SI) seen in Eq. (1), represents the whole body balance of insulin and carbohydrate from all sources, and has been shown to be independent of both insulin and nutrition inputs. Thus, SI can be used to calculate the likely BG response to treatments other than those given clinically.

**Table 1**
Key variables of the ICING 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 |

SI(t) is identified as the linear combination of BFs, $\phi_i(t)$, minimizing the error between modelled and clinically measured BG, given the clinical interventions:

$$\begin{bmatrix}\phi_1(t) & \phi_2(t) & \cdots & \phi_n(t)\end{bmatrix}\begin{bmatrix}\gamma_1(t)\\ \gamma_2(t)\\ \vdots\\ \gamma_n(t)\end{bmatrix} = S_I(t) \quad (8)$$

Where $\gamma_i(t)$ = basis function fitted coefficients

Integral-based identification of SI, for the current BF technique, can be found in [18,25]. The modelled BG solution, G(t) Eq. (1), can then be simulated using the ICING model, Eqs. (1)–(7), with the identified SI(t) trace and the same clinical interventions. The shapes of the BFs restrict dynamics in the identified SI(t) profile, directly influencing the modelled BG solution's goodness-of-fit to the clinical BG data.

Given the nature of SI within the ICING model, 2 BG measurements (1 Change in BG equation) per BF are required to identify each BF. A new BF occurs every KW. Therefore, to ensure identifiability, 2 BG measurements per KW are needed. As the measurement intervals offered by STAR are 1–3 h [20,21], a KW greater than or equal to 180 min (3 h) is required to ensure BF identifiability without having to assume BG measurements as is done currently with the zeroth order BFs.

### 2.3. Physiological representation

In non-critically ill patients, SI is often assumed to be approximately constant over long periods of time [44,45], but within critically ill patients the stress-heightened state after injury/illness can result in a highly dynamic counter-regulatory hormone and cytokine response, inducing frequent changes in the BG [27–29,31] and thus effective SI [23,46,47]. However, as SI is a physiological signal it is generally considered to occur in a continuous manner. In this study we consider a physiologically realistic signal to be continuous and 2nd order differentiable, as generally considered. The continuous differentiability criteria ensures a smooth curve and smoothly changing first derivative of the SI trace, which would match the dynamics of all observed metabolic processes, which are not discrete or step-wise in their behaviors. As a result, the current Zeroth order and preceding 1 st order B-spline BF do not meet this criterion and thus are not considered to be physiologically representative. Thus, a 2nd Order B-spline BF is chosen to represent SI as a smooth continuous trace.