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Modeling glucose and subcutaneous insulin dynamics in critical care

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ABSTRACT

Model-based decision support could be used to tailor insulin treatment to patients suffering from stress hyperglycemia, while avoiding hypoglycemia. This work combines a previously published glucose and insulin model with a subcutaneous insulin delivery model, herein simplified using Markov Chain Monte Carlo optimization and Kullback–Liebler distance, to capture fast-acting and regular insulin using two shared and one type-specific fitted parameter. Glucose data from a critical care population ($N=48$) receiving subcutaneous insulin are fit to within finger stick glucose measurement error of 5% using a regularized, time-varying parameter. The resulting virtual patient cohort provides a basis on which automated insulin delivery systems can be tested.

1. Introduction

Stress hyperglycemia occurs frequently in critical care patients and many of the harmful repercussions may be mitigated by maintaining glucose within a glucose target zone (GTZ) using insulin and glucose administration. Since the landmark publication of the first Leuven study in 2001 (Van den Berghe et al., 2001), showing a decrease in mortality from 8% to 4.6% in over 1500 patients where a GTZ was maintained, there have been many attempts to create improved paradigms for treatment of stress hyperglycemia (Krinsley, 2004; Preiser, Devos, & Van den Berghe, 2002). Despite the literature supporting a GTZ (Umpierrez et al., 2002), several follow-up studies to the 2001 Leuven study showed limited benefit: morbidity but not mortality reduction in the case of the Leuven follow-up study in 2006 (Van den Berghe et al., 2006), or no change in outcome whatsoever as seen in both Glucontrol (Preiser et al., 2009) and CREATE-ECLA (Mehta, 2005). The waning potential for controlling stress hyperglycemia was exacerbated in 2009 when a multicenter prospective study (The NICE-SUGAR Study Investigators, 2009) of over 6000 patients showed an increase in mortality in the group receiving intensive insulin treatment. Retrospective analysis of the NICE-SUGAR study (Finfer, 2012) indicates that improved outcomes from glycemic control are overwhelmed by the increased risk of hypoglycemia and the accompanying increase in mortality associated with hypoglycemia (Hermanides et al., 2010; Krinsley & Grover, 2007), when aggressive glucose control is employed. Inconsistencies in glycemic control protocols (Wilson, Weinreb, & Hoo, 2007), as well as variation in GTZ outcomes for different ICU subpopulations (Hirasawa, 2009; Tiruvoipati et al., 2012; Whitcomb, Pradhan, Pittas, Roghmann, & Perencevich, 2005), has contributed to the mixed success of GTZ and subsequent disagreement regarding treatment protocols using insulin in the ICU (Marik & Preiser, 2010; Parsons & Watkinson, 2007).

A more accurate, personalized treatment that is tailored to an individual may significantly improve patient outcome. The most promising method to achieve better control using a personalized strategy is through the use of a model-based decision support system (DSS), wherein a mathematical patient model is coupled with a controller and user interface that provides for closed-loop control under the supervision of a clinician. Such systems have been extensively investigated for use in managing Type 1 diabetes (Battelino et al., 2015; Breton et al., 2012; Russell et al., 2012; Wilinska & Hovorka, 2014). A critical aspect of a DSS is accurate understanding and modeling of the various underlying

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mechanisms leading to stress hyperglycemia, as increased biological resolution and more accurate modeling is a critical component of control (Morari, 1989). Creating a decision support system with semi-automated control architecture allows for GTZ consistency across many different ICUs, thereby reducing variability in treatment implementation. Decision support systems have shown promising results in the critical care population (Eslami, Abu-Hanna, Jonge, & Keizer, 2009; Leelarathna et al., 2013), however, much of the error and subsequent failure of control comes from the failure to resolve inter- and intra-patient variations in glucose dynamics following insulin administration. A predictive model of glucose dynamics following insulin delivery with a small number of fitted parameters provides a parameter-centric way to quantify patient variability.

Stress hyperglycemia and its accompanying deleterious effects are primarily treated via insulin infusion. Subcutaneously injected insulin is a less invasive form of delivery used preferentially when patients are deemed stable enough to transition from intravenous administration in the ICU. Therefore, a control-relevant, population-based mathematical model that describes the patient-scale dynamics of subcutaneously administered insulin for multiple insulin types is the focus of this work. While several mathematical models have been proposed to describe subcutaneous insulin delivery (Nucci & Cobelli, 2000; Wilinska et al., 2005; Wong et al., 2008), the present focus is a low-order (state and parameter dimension) model that was readily tailored to individual patients by changing a small number of practically-identifiable model parameters based on readily available clinical data. Previously published models of subcutaneous insulin (Nucci & Cobelli, 2000; Wilinska et al., 2005; Wong et al., 2008) also tend to use different mathematical structures for each type of infused insulin (e.g., rapid-acting, regular, lente, etc.). The present work included regular and rapid-acting insulin types, and focused on constructing a single-structure model with parameters specific to insulin-type.

To build a low-order, practically identifiable subcutaneous insulin model, a previously reduced model (Vilkhovoy, 2014), originally selected from a literature review of subcutaneous insulin models (Wilinska et al., 2005), was further analyzed using published human data (Hedman, Lindstrom, & Arnqvist, 2001; Kraegen & Chisholm, 1984; Kobayashi et al., 1983; Plank et al., 2002). The model was fit using a Markov Chain Monte Carlo (MCMC) parameter search to provide posterior distributions of the model parameters. Finally, the reduced model of subcutaneous insulin delivery was validated with patient data from an intensive care clinical database to construct a virtual patient cohort for *in silico* analysis and potential use in control system design.

2. Methods

2.1. Insulin absorption model and reduction

In our earlier work (Vilkhovoy, 2014), a subcutaneous insulin absorption model from literature (Wilinska et al., 2005) was

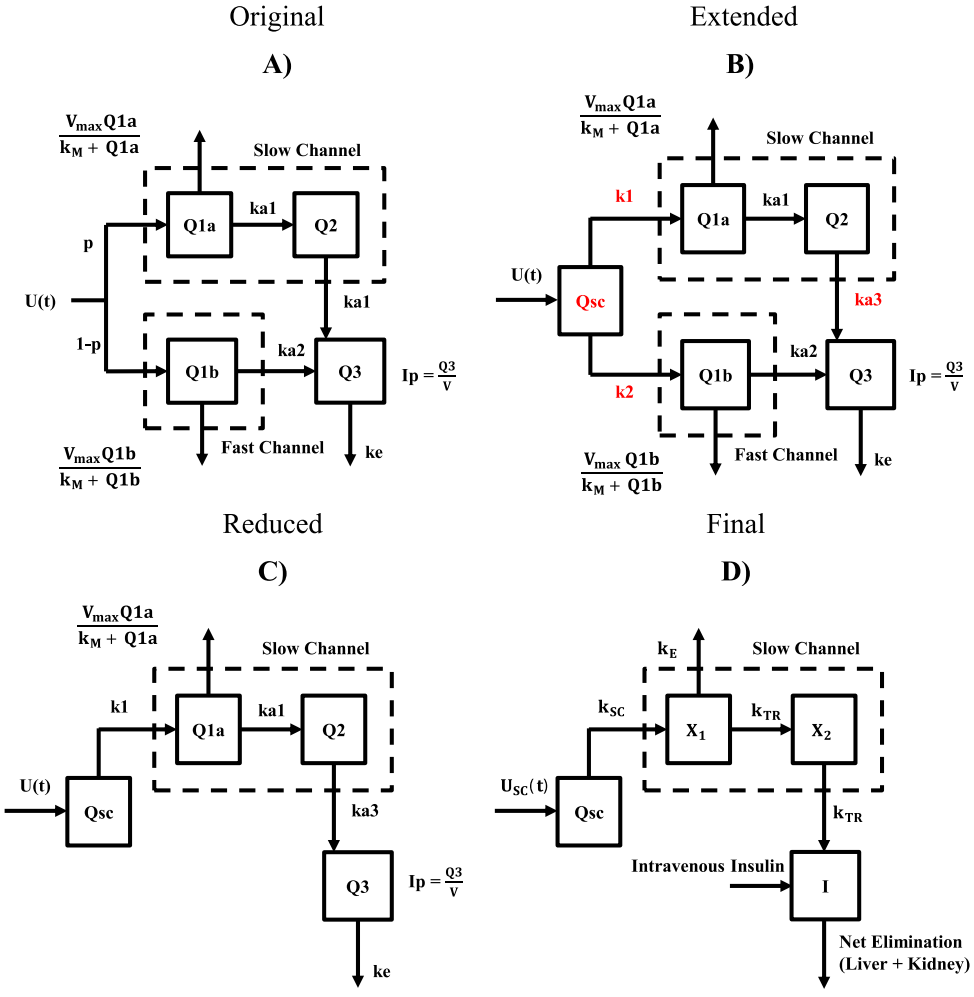

Fig. 1. Reduction of the originally published model by Wilinska et al. (2005) as described in Vilkhovoy (2014) with the addition of panel D showing the final model developed herein.