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An Intraoperative Glucose Control Benchmark for Formal Verification

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Abstract: Diabetes associated complications are affecting an increasingly large population of hospitalized patients. Since glucose physiology is significantly impacted by patient-specific parameters, it is critical to verify that a clinical glucose control protocol is safe across a wide patient population. A safe protocol should not drive the glucose level into dangerous low (hypoglycemia) or high (hyperglycemia) ranges. Verification of glucose controllers is challenging due to the high-dimensional, non-linear glucose physiological models which contain both unobservable states and unmeasurable patient-specific parameters. This paper presents a hybrid system model of a closed-loop physiological system that includes an existing FDA-accepted high-fidelity physiological model tailored to intraoperative settings and a validated improvement to a clinical glucose control protocol for diabetic cardiac surgery patients. We propose the closed-loop model as a physiological system benchmark for verification and present our initial results on verifying the system using the SMT-based hybrid system verification tool dReach.

Keywords: Formal verification; Medical applications; Safety analysis; Closed-loop Controllers; Glucose control;

1. INTRODUCTION

For the more than 29 million Americans who have diabetes, the risk of death is nearly twice as high when compared to age-matched non-diabetic individuals (Xu et al. (2010)). Those suffering from this disease, especially Type 1 diabetics, depend on insulin self-injections to manage their blood glucose level. As such, glucose regulation is a safety-critical control task: too much insulin causes life-threatening hypoglycemia (low glucose levels) and too little insulin causes hyperglycemia (high glucose levels), a condition that has potential outcomes such as blindness and nerve damage.

While outpatient glucose management has been the primary focus of recent diabetes research (e.g., the artificial pancreas (AP) Cobelli et al. (2011)), mounting evidence suggests that diabetes associated complications among hospitalized patients are increasing (Wallymahmed et al. (2005)); thus, methods for inpatient glycemic control are important (Bruno et al. (2008); McAlister et al. (2005)). During surgeries, patients can suffer from stress-induced glucose fluctuations (Bochicchio et al. (2005)). Data suggests that specialized inpatient glucose level management within a safe range can minimize the hypoglycemia risk and improve clinical outcomes (Subramaniam et al. (2009); Lazar et al. (2004)). Clinicians currently follow rule-based protocols to administer insulin and glucose during surgeries (e.g., see Kohl et al. (2013)), but those protocols are still far from foolproof (Meijering et al. (2006)). Thus, verifying that intraoperative glycemic controllers avoid severe hypoglycemia/hyperglycemia events across a diabetic population is imperative.

Recently, the United States (US) Food and Drug Administration (FDA) has accepted the UVa/Padova Type 1 Diabetes Mellitus Metabolic Simulator (T1DMS) as a substitute for animal testing in certain pre-clinical trials of glucose controllers (Kovatchev et al. (2009); Dalla Man et al. (2014)). The T1DMS utilizes a high-dimensional, multi-modal, and non-linear model with over 30 patient-dependent parameters that are (mostly) unobservable in ordinary T1D patients through standard medical tests. Existing work on evaluating controllers using T1DMS relies on simulating the physiological models with a finite set (typically 300, see Kovatchev et al. (2009)) of "virtual subjects", which are discrete realizations of the model parameters identified through invasive experiments (Basu et al. (2003)). However, there is no formal guarantee that the "virtual subject" set covers the entire T1D population. To this end, formal verification of controllers can provide a new level of safety assurance to clinical practitioners before performing human clinical trials. [1]

This paper makes the following contributions towards formal verification of intraoperative glycemic control. First,

[1] Currently, model-based trials are only approved to replace pre-clinical testing. It is unclear whether model-based trials will ever be approved to replace clinical (human) testing due to unmodeled physiology and comorbidity inherent in all models.

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we introduce the model of the closed-loop intraoperative glycemic control system as a case study verification benchmark: the model contains both an FDA-accepted high-fidelity physiological model and a validated intraoperative glycemic control protocol. We also provide over-approximated value ranges of all model states and parameters whose ranges are supported by extensive clinical studies. Second, we implement the benchmark in a recently proposed SMT-based hybrid system verification tool, dReal/dReach (Gao et al. (2013a)). Third, we present a proof-of-concept safety verification of the intraoperative glycemic control benchmark over a non-scalar subspace of each physiological parameter/state.

The rest of this paper is organized as follows: Section 2 presents the problem formulation; Section 3 introduces the diabetes model in the intraoperative setting; Section 4 presents the hybrid system model of the closed-loop physiological system; Section 5 describes the case study of verifying an intra-operative glycemic controller on the surgical physiological model using dReach and includes a presentation of our initial verification results in a subspace of the entire parameter and initial condition range; Section 6 discusses our future work.

2. PROBLEM FORMULATION

In this section, we define the safety verification problem considered in this work. We represent the combined intraoperative glucose control protocol and physiological dynamics (defined in Section 3) as a standard hybrid system,

$$\mathcal{H} = \langle \mathcal{X}, \mathcal{Q}, \mathcal{X}_{init}, \mathcal{X}_{inv}, \mathcal{F}(\mathcal{P}), T \rangle , \tag{1}$$

where $\mathcal{X}$ represents the continuous states, $\mathcal{Q}$ denotes the discrete modes, $\mathcal{X}_{init} \in \mathcal{R}_{\mathcal{X}}$ specifies the initial condition space, $\mathcal{F}(\mathcal{P})$ captures the flows parameterized by a vector $\mathcal{P} \in \mathcal{R}_P$, $\mathcal{X}_{inv}$ identifies invariants mapping modes to flows, and T relates the transitions between modes. A measurable output $y = \phi(t; \mathcal{X}_{init})$ denotes the glucose value, with $\phi(t, \mathcal{X}_{init})$ describing the measurement at time $t \in [0, t_{\max}]$ [2], having evolved from initial condition $\mathcal{X}_{init}$. In this paper, we aim to solve the following safety verification problem:

$$\forall t \in [0, t_{\max}] , \ \forall \mathcal{P} \in \mathcal{R}_P, \ \forall \mathcal{X}_{init} \in \mathcal{R}_{\mathcal{X}}, \quad y \notin \mathcal{R}_{unsafe},$$

where $\mathcal{R}_{unsafe}$ is a region representing unsafe blood glucose content (i.e., hypoglycemia and hyperglycemia).

3. MODELING OF SURGICAL GLUCOSE CONTROL

In this section, we introduce the FDA-accepted T1DMS model (Man et al. (2007); Dalla Man et al. (2014)) modified for the intraoperative clinical scenario and a clinically validated glucose control protocol (Kohl et al. (2013)).

3.1 Glucose-Insulin System Model

The full T1DMS model contains three sub-models (insulin, glucose, and carbohydrate-ingestion) with 13 states and 32 parameters. The original publications (e.g., Man et al. (2007); Kovatchev et al. (2009)) discuss the details of physiological modeling and our previous paper (Chen et al. (2015)) summarizes the model equations from the literature. Since intraoperative patients receive insulin and glucose via intravenous infusion, the two subcutaneous insulin compartment states and the entire carbohydrate-ingestion sub-system can be neglected, resulting in a 7-state intraoperative model, as described in the remainder of this subsection.

The intraoperative model contains an insulin sub-model and a glucose sub-model. The insulin system is a 5-state linear model driven by the insulin input, $u(t)$, written as

$$\dot{I}_p(t) = -(m_2 + m_4) I_p(t) + m_1 I_l(t) + u(t) * 10^2 / BW \tag{2a}$$
$$\dot{X}(t) = P_{2U}/V_i I_p(t) - P_{2U} X(t) - P_{2U} * I_b \tag{2b}$$
$$\dot{I}_1(t) = k_i/V_i I_p(t) - k_i I_1(t) \tag{2c}$$
$$\dot{I}_d(t) = k_i I_1(t) - k_i I_d(t) \tag{2d}$$
$$\dot{I}_l(t) = m_2 * I_p(t) - (m_1 + m_3) I_l(t). \tag{2e}$$

The $I_p(t)$ and $I_l(t)$ states represent insulin mass in the plasma and liver, respectively. $I_1(t)$ and $I_d(t)$ represent a delayed insulin transportation process. $X(t)$ represents an insulin signal in the remote tissue that governs glucose concentration in the interstitial compartment. The model contains a set of parameters that are patient dependent: $m_{1...4}$ and P_{2u} are rates of insulin mass diffusion among different compartments, V_i is the insulin distribution volume, and BW is the body weight.

The glucose system has two states and is written as

$$\begin{aligned} \dot{G}_p(t) = &- k_1 * G_p(t) + k_2 * G_t(t) - F_{snc} + m(t) * 10^3 / BW \\ &+ \max(0, k_{p1} - k_{p2} * G_p(t) - k_{p3} * I_d(t)) \\ &- 1 - \max(0, k_{e1} * (G_p(t) - k_{e2})) \end{aligned} \tag{3a}$$

$$\dot{G}_t(t) = - \frac{(V_{m0} + V_{mx} * X(t)) * G_t(t)}{K_{m0} + G_t(t)} + k_1 * G_p(t) - k_2 * G_t(t) \tag{3b}$$

where, $G_p(t)$ and $G_t(t)$ represent the glucose concentration in plasma and interstitial fluids, respectively. The $G_p(t)$ derivative (Equation 3a) contains two saturation switches $\max(0, k_{p1} - k_{p2} * G_p(t) - k_{p3} * I_d(t))$ and $\max(0, k_{e1} * (G_p - k_{e2}))$, which represent the endogenous glucose production (EGP) and renal glucose clearance, respectively. These two max switches yield four discrete modes in the hybrid system representation of the model, and transitions among the four modes are governed by saturations of the two max terms. The G_t derivative contains a non-linear term $-\frac{(V_{m0} + V_{mx} * X(t)) * G_t(t)}{K_{m0} + G_t(t)}$ that represents the remote insulin signal $X(t)$'s impact on glucose dynamics. The model contains two population static parameters k_{e1} (glomerular filtration rate) and k_{e2} (renal threshold of glucose). All other parameters are patient dependent: k_1 and k_2 are the mass exchange rate between the G_p and G_t compartments; k_{p1} is the extrapolated EGP; k_{p2} is the liver glucose effectiveness; k_{p3} is the insulin action on liver; V_{m0}, V_{mx}, and K_{m0} are model parameters that govern the insulin action on G_t; V_g is the glucose distribution volume. $m(t)$ is the intravenous glucose input into the plasma compartment.

The 7-state intraoperative glucose control model is observed through $y(t) = G_p(t)/V_g$, corresponding to the plasma glucose measurement (in mg/dL). Most of the patient-dependent parameters, except for a few such as the body weight, are not measurable in standard hospital tests. Estimating those parameters on individual patients involves invasive and costly procedures such as the triple-

[2] $t_{\max}$ represents the maximum time the patient is in surgery.