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# Robust insulin estimation under glycemic variability using Bayesian filtering and Gaussian process models

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ABSTRACT

The ultimate goal of an artificial pancreas (AP) is finding the optimal insulin rates that can effectively reduce high blood glucose (BG) levels in type 1 diabetic patients. To achieve this, most autonomous closed-loop strategies continuously compute the optimal insulin bolus to be administrated on the basis of the estimated plasma concentrations for glucose and insulin. Unlike subcutaneous glucose levels which can be measured in real-time, unavailability of insulin sensors makes it essential the use of mathematical models so as to fully estimate plasma insulin concentrations. For model-based estimation, GP-Bayesian filters have been recently proposed to incorporate probabilistic non-parametric Gaussian process (GP) models of dynamic systems into Kalman filtering techniques. As a result, model uncertainty can explicitly be incorporated into the prediction step and in the filtering processes, which is usually not the case for more traditional filtering strategies that resort to parametric models for state estimation. More specifically, the question arises as to whether glycemic variability is properly taken into account in model formulations and whether it would compromise proper estimation of plasma insulin concentration. To tackle this, a stochastic glycemic model including variability was incorporated into different parametric and nonparametric filtering techniques to provide an estimate of the plasma insulin levels. In particular, we compared density representation against using knowledge about the parameterization of the transition dynamics and the observation function. We found that, as glycemic variability increases, filtering techniques based on parametric models rapidly degrades their performance as a consequence of large nonlinearities. Results show that Bayes' filtering techniques increase predictability of the patient state, and thus, boost safety and performance in the AP control and monitoring tasks.



## 1. Introduction

With existing sensing and pump technologies, widespread acceptance and use of an AP is steadily increasing and hopefully it will soon take part of routine clinical care [1]. The key control goal of an AP is the real-time calculation of the optimal insulin rates to be infused in type 1 diabetic patients so as to mimic the body's natural regulatory mechanism, i.e. BG levels between 70 and 140 [mg/dl]. To this aim, a number of control and monitoring strategies [2–6] has been proposed to compute optimal exogenous insulin infusion profiles on the basis of plasma glucose and plasma insulin estimation. For BG determination this is achieved by a continuous glucose monitor (CGM) that senses the glucose concentration in the interstitial area, and later on by considering the dynamics between this determination and the actual plasmatic concentration [7]. However, unlike plasma glucose which can be measured in real-time, the lack of specific sensors to determine plasma insulin levels makes the use of mathematical or inductive models for inferring insulin concentration the alternative of choice.

For obtaining plasma insulin estimations, a minimal parametric glucose-insulin dynamic model can be used in an open-loop configuration [8]. The main limitation of this state estimation strategy is that available CGM data are not taken into account to adapt the parameters of the model employed, despite these adjustments are mandatory in a dynamic system exhibiting significant levels of variability and complex regulatory behavior. To improve state

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estimation of a diabetic patient, plasma insulin concentration has recently been estimated from BG data using Bayesian filtering techniques which allow improving the estimation of glycemic conditions in real-time [9,10]. Filtering techniques are based on the proper combination of a dynamic model of the system and a state observer and have enjoyed remarkable success in the estimation of hidden states for different types of biomedical systems [11,12].

A number of Bayesian filtering techniques for nonlinear dynamic systems have been proposed and extensively studied [13,14]. The key issue in a Bayesian filter operation is the propagation of a Gaussian density function through the system dynamics. In the Extended Kalman Filter (EKF) the state distribution is represented by a Gaussian, which is then fully propagated through the first-order Taylor series expansion, that is, linearization of a nonlinear system dynamics [15]. In turn, the Unscented Kalman Filter (UKF) addresses state estimation by using a deterministic sampling approach, where the probability distribution of states is represented using a set of sample points. Noteworthy, the foregoing Kalman filters for state estimation are based on known parametric models of the state transition and measurement functions. However, for most nonlinear systems accurate parametric models are never readily available to describe all the (hidden) aspects of their dynamics. A feasible solution when facing nonlinear dynamics is the use of an approximated model in a nonparametric approach based on Gaussian processes (GP) models [16]. The so-called GP-Bayesian filters incorporate probabilistic non-parametric GPs models for states into the design EKF and UKF techniques[17]. In this manner, model uncertainty can explicitly be incorporated into the state prediction and the filtering steps.

Poor predictability of the glucose-insulin dynamics in a diabetic patient is a key issue that any control and monitoring strategy, to be implemented in an AP, should be able to address. Therefore, it is of significance and concern whether excessive variability might affect the estimation of plasma insulin concentration and, in consequence, compromise safety and performance of an AP operation. In this work, a stochastic version of the well-known Hovorka glucose-insulin model [18] was incorporated into parametric and nonparametric Bayesian filtering techniques to provide a real-time estimate of the plasma insulin concentration. Better understanding the effect of BG variability on the error between a given model, describing glucose-insulin interactions, and the real and complex physiologic system is of great significance for accelerating the acceptance of an AP.

This article is structured as follows. Section 2 introduces a stochastic model for describing the glucose-insulin dynamics in diabetic patients. Section 3 provides an overview of Bayesian filtering and GP regression models used to capture the underlying latent function for state transitions. In Section 4 different Bayesian filtering techniques are presented. In particular, we evaluate whether the filter propagates the full densities on the system dynamics (EKF and GP-ADF) or resorts to a sampling approach (UKF and GP-UKF). Also, it is analyzed whether the filter has full knowledge of the parameterization of the transition and measurement functions (EKF and UKF) or it uses a Gaussian approximation (GP-UKF and GP-ADF). In Section 5, results obtained for plasma insulin estimation in a simulation environment are shown and discussed. Finally, in Section 6 some remarks and future research efforts are outlined.

## 2. Stochastic model of the glucose-insulin dynamics

In this section, the reference deterministic model of the glucose-insulin dynamics based on the work of Hovorka et al. [18] is first presented. Later on, a stochastic diffusion process to model glycemic variability in synthetic diabetic patients is discussed. The Hovorka glucose-insulin model is a nonlinear compartmental numerical model with two inputs, insulin and glucose intake, and one output, glycemia. Particularly, the insulin-glucose interaction is nonlinear and it is given as

$$\begin{aligned}\frac{dQ_1(t)}{dx} &= -\left[\frac{F_0}{V_G G(t)} + x_1(t)\right] Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP \quad [1 - x_3(t)] \\ \frac{dQ_2(t)}{dx} &= x_1(t)Q_1(t) - [k_{12} + x_2(t)] \quad Q_2(t)\end{aligned} \tag{1}$$

where $Q_1(t), Q_2(t)$ represent the amounts of glucose in the accessible and non-accessible compartments, respectively, whereas $k_{12}$ is the transfer rate constant and $EGP$ is the parameter for endogenous glucose production; $F_0$ is a parameter that represents the total non-insulin dependent glucose flux and $F_R$ represents renal glucose clearance above the glucose concentration threshold of 9 [mmol/l]. In turn, $U_G(t)$ is carbohydrate absorption rate, $x_1(t)$ is the remote effect of insulin on the rate of glucose transport, while $x_2(t)$ and $x_3(t)$ account for the elimination and endogenous glucose production, respectively. For space consideration, the remaining subsystems are not given, but they are fully described in [18]. BG measurements are then given as

$$G(t) = \frac{Q_1(t)}{V_G} \tag{2}$$

where $V_G$ is glucose distribution volume. Table 1 shows the parameters used in the glucose-insulin interaction model of a type 1 diabetic patient, as given in [18]. The current patient state can be summarized in the vector $\mathbf{x}(t)$ in Eq. (3), where the entries are different state variables.

$$\mathbf{x}(t) = [S_1(t), S_2(t), I(t), x_1(t), x_2(t), x_3(t), Q_1(t), Q_2(t), G(t)] \tag{3}$$

As CGM determines BG levels in the interstitial fluid and the glucose exchange across the capillary walls occurs, by a simple but not instantaneous diffusion across a concentration gradient with a time-lag $\tau_{lag}$, we have that the interstitial concentration is given as

$$\frac{dIG(t)}{dx} = \frac{1}{\tau_{lag}}(G(t) - IG(t)) \tag{4}$$

Finally, the obtained glucose profile is multiplied by a random time-varying calibration error $\xi(k)$ and later corrupted by an additive noise sequence sampled from a zero mean white Gaussian noise process $v(k)$, that is:

$$CGM(t) = \left(1 + \xi(t)\right) IG(t) + v(t) \tag{5}$$

For the development of efficient control and monitoring strategies of an AP, the deterministic glucose-insulin model might be enhanced by taking into account the variable behavior of patient metabolism [19–21]. An effective, yet simple alternative way to describe such fluctuating behavior is modeling temporal variability through a stochastic diffusion process. Ito [22] provided an alternative to ordinary numerical rules of calculus by defining a particular kind of uncertainty representation based on the Wiener diffusion process. Accordingly, the system transition function is described as a controlled Ito's diffusion process of the form

$$\dot{\mathbf{x}}(t) = \mathrm{a}\left(\mathbf{x}(t), u(t)\right) + \sigma d\omega \tag{6}$$

**Table 1**
Set of model parameters.

| Parameter | Value | Unit |
|---|---|---|
| $k_{12}$ | 0.066 | [min−1] |
| $V_G$ | 0.16*BW | [l] |
| $EGP$ | 0.0161 | [mmol/min] |
| $F_0$ | 0.8507 | [mmol/min] |
| $F_R$ | $0.003(G(t) - 9)V_G$ | [mmol/min] |
| $\tau_{lag}$ | 5 | [min] |
| $\xi(k)$ | 2 | % |