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Analysis of Stochastic Noise of Blood-Glucose Dynamics

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Abstract:
Introduction of the stochastic noise in the modelling of blood-glucose dynamics becoming more and more acceptable because of the high complexity of the physiological processes. The representation of the stochastic noise term in the phenomenological as well as in data-driven models until now limited to stationary Gaussian process. In this paper the statistical nature of the stochastic blood-glucose system model noise is investigated to prove or disprove this general assumption. To ensure the generalization of the noise term a Wiener process ($W(t)$) with time depending diffusion coefficient ($\sigma(t)W(t)$) was considered. This stochastic term was embedded into the phenomenological *ICING* (*Intensive Control Insulin-Nutrition-Glucose*) model and then $\sigma(t)$ was identified by using clinical measurements from nine patients. The mean value, the standard deviation, as well as the covariance of the slide distributions of the stochastic glucose trajectories generated by the Ito type process were investigated. We have found that this stochastic term is Gaussian process but not stationary. Our final goal is to find general representation of the stochastic noise term by a parametric time series processes.

Keywords: blood-glucose dynamics, stochastic noise, stochastic differential equation, stationary Gaussian process, Intensive Control Insulin-Nutrition-Glucose (ICING) model

1. INTRODUCTION

Development of an accurate model of human blood glucose regulatory system that captures the relationship between blood glucose changes, nutrition intake and insulin delivery represent major challenge. Modelling approaches may be categorized as i) phenomenological models and ii) data-driven models (Zhang et al. (2014)). The phenomenological models use a priori knowledge of the physiology to describe the underlying processes (e.g. internal insulin secretion, glucose uptake by different organs, etc.) by compartments (Bergman (1989); Palumbo et al. (2013); De Gaetano and Arino (2000); Dalla Man et al. (2006)). These models generally contain relatively high number of differential equations and system parameters that makes hard to map these models to measurement data with low-dimension and thus validate them.

Data-driven models are created by exploiting the information hidden in the data. These models are constructed without close relationship between the model elements - i.e. differential equations and their parameters - and physiological processes (Zhang et al. (2014); Florian and Parker (2005); De Gaetano and Arino (2000)). Thus the interpretation of these models are rather challenging.

Most of the published models in both of these categories are deterministic models, i.e. ordinary differential equations (ODE) are used for the description of the models (Bergman (1989); Palumbo et al. (2013)). However, it is known that these models are imperfect in the sense that modelling uncertainties, frequently stochastic nature of the physiological system, and measurement noise cannot be taken consideration (Georga et al. (2011)). Stochastic modelling, i.e. description of the system by stochastic differential equations can overcome on these shortcomings as it has been successfully applied in several pharmacokinetic / pharmacodynamic systems (Donnet and Samson (2013)).

Tornøe et al. (Tornøe et al. (2004)) revealed that stochastic terms could take into consideration unknown or incorrectly modelled dynamics of the system. After describing the methodology of the stochastic modelling and parameter estimation, they employed a simplified form of *Bergman's minimal model* Bergman (1989) to compare stochastic and deterministic modelling and found that the system noise parameter in the glucose equation is significant. However, this model, now well-known does not capture system dynamics well and may have mis-estimated the stochastic features of the system.

Duun-Henriksen et al. (Duun-Henriksen et al. (2013)) systematically analysed a grey-box variant of an *extended minimal model* and found two diffusion-terms are enough to compensate error in the model equations. Although it

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may not be physically realistic since two diffusion terms versus one implies a non-existent compartment. They could demonstrate significant improvement in reducing model error via stochastic modelling. To carry out computations they used a statistical software CTSMR package (Continuous Time Stochastic Modelling in R).

Vilhjálmsdóttir (Vilhjálmsdóttir (2013)) employed deterministic as well as stochastic *minimal model* to investigate insulin sensitivity. She added diffusion terms only to the insulin and glucose equations and used the results of the deterministic model as initial guess for the parameter estimation of the stochastic model. She found that stochastic approach could give better estimate of the insulin sensitivity than the deterministic one. Finally, Kristensen et al. also described the methodology of the parameter estimation of stochastic differential equations and illustrated software tools CTSMR as well as MoCaVa which runs under MATLAB (Kristensen et al. (2004)).

The stochastic model allows not only the reduction of the model error but also enables characterizing the noise integrated into the stochastic term. The representation of the stochastic term in the phenomenological as well as in data-driven models for blood glucose dynamics until now limited to a stationary Gaussian process. In this paper the statistical nature of the noise is investigated to prove or disprove this general assumption. For this study our previously published stochastic differential equation (SDE) based blood glucose system model is used (Paláncz et al. (2016b)). Ensuring the generalization of the noise term a Wiener process with time depending diffusion coefficient ($\sigma(t)W(t)$) was considered (Paláncz et al. (2016a)). This stochastic term embedded into the *ICING* (*Intensive Control Insulin-Nutrition-Glucose*) (Evans et al. (2012)) model was identified by using clinical measurements. The mean value, the standard deviation, as well as the covariance of the slide distributions of the stochastic glucose trajectories generated by the Ito type processes were investigated.

2. METHODS

2.1 ICING model and its stochastic extension

ICING is a highly sophisticated deterministic model developed for critically ill patients. It has been successfully used as a tool for in silico design of patient treatment protocols and integrated into a real-time glycemic control advisory system (Lin et al. (2011); Evans et al. (2012); Fisk et al. (2012); Le Compte et al. (2012)).

The deterministic, white-box model is represented by the following equations (Pretty (2012)),

$$\frac{dG(t)}{\mathrm{dt}} = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G}, \tag{1}$$

$$\frac{dQ(t)}{\mathrm{dt}} = n_I(I(t)-Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)}, \tag{2}$$

$$\frac{dI(t)}{\mathrm{dt}} = -n_K I(t) - n_L\frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{\mathrm{ex}}(t)}{V_I} + (1-x_L)\frac{u_{\mathrm{en}}(t)}{V_I}, \tag{3}$$

$$\frac{dP_1(t)}{\mathrm{dt}} = -d_1 P_1(t) + D(t), \tag{4}$$

$$\frac{dP_2(t)}{\mathrm{dt}} = -\min\left(d_2 P_2(t), P_{\max}\right) + d_1 P_1(t), \tag{5}$$

$$P(t) = \min\left(d_2 P_2(t), P_{\max}\right) + P_N(t), \tag{6}$$

$$u_{\mathrm{en}}(t) = \min\left(\max\left(u_{\min}, k_1 G(t) + k_2\right), u_{\max}\right). \tag{7}$$

The model parameters values, their descriptions as well as the exogenous input variables - functions of time - can be found in Fisk (2014); Pretty (2012).

Model parameters were estimated and identification of the insulin sensitivity profile, $S_I(t)$ was achieved employing an integral-based method Hann et al. (2005). To account for future variability a non-parametric stochastic model based on clinical measurements is employed (Lin et al. (2006); Le Compte et al. (2010)). However, in this way all of the dynamic errors were lumped into the $S_I(t)$ profile, which caused potentially unacceptable high frequency changes in the blood glucose concentration profile.

To regularize the $S_I(t)$ profile an additional stochastic term was suggested in the glucose equation, which can capture unmodelled dynamics and measurement noise, but is not to be incorporated in the $S_I(t)$ profile (Fisk (2014)). It also suggested a non-parametric method to extend the glucose equation with a stochastic term. The noise of the residual $r_G(t)$ of the glucose equation Eq. (1), defined in Eq. (8) is found to be a Gaussian-type noise (Fisk (2014)).

$$r_G(t)|_{t=\tau} \approx \mathcal{N}(\tau). \tag{8}$$

The blood glucose noise related to different measurement intervals can be seen on Fig. 1. Blood glucose values measured in mmol/l are represented on the vertical axes and the figure shows the difference between the blood glucose measurements and the calculated blood glucose value by the ICING model based simulation. These differences - considered as a noise - are distributed on the horizontal axes by the actual measurement interval of the current measurement.

Using these results stochastic Ito version of the ICING model equations with *parametric* stochastic noise term is suggested in Paláncz et al. (2016b). The computations of the system trajectories and their statistical features like mean value, standard deviation, and slice distribution were carried out using a stochastic Runge-Kutta method in the presence of Wiener-type diffusion process term. Parameter estimation of the resulting stochastic model is achieved via a maximum likelihood technique. The global optimization problem was solved using global methods like genetic algorithms, simulated annealing and Nelder-Mead procedures. The parameter computation has been carried out at different system noise levels, and the optimal