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Potential Use Of The Stochastic ICING Model In STAR Protocol

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Abstract

The model of the human glucose-insulin system plays an important role in several clinical treatment methods and protocols, like tight glycemic control of intensive care patients. The Intensive Control Insulin-Nutrition-Glucose (ICING) model is one of these protocols that was used for the development of the Stochastic Targeted glucose control (STAR) protocol applied as a standard of care in New Zealand and Hungary. The original ICING model uses an ordinary differential equations (ODE) for the description of the glucose-insulin metabolic system.Recent studies attempted the extension of the original ICING model with stochastic terms resulting a new stochastic differential equations model(SDE). By using the resulted of this new model (SDE) we may have the chance to improve the accuracy of ICING modeling (reduce the modelling error) which can results a better clinical treatment using STAR. In the study presented in this paper, the potential use and implementation of the stochastic version of the ICING model (SDE), was analysed and the moddeling error was compared with the original version of the model using a large clinical data set including treatment records of 60 patients from Belgium, Hungary and New Zealand. The results show that the SDE model gives a smaller modeling error compared to the ICING model in most of patients.These results suggest that SDE model may be used to improve the prediction process of the blood glucose level of the ICU patients which will be an important step of the STAR protocol.

1. Introduction

Intensive care patients often experience hyperglycemia (high blood glucose levels) and high levels of insulin resistance caused by stress, which have been linked to increased morbidity and mortality in intensive care units (ICU) [1].Controlling blood glucose proved to be difficult due the risk of hypoglycemia (low blood glucose levels) and the highly variable state of the patient. It has been shown that tight glycemic control (TGC) was able to reduce the negative outcomes related to poor control with 17-45% reductions in mortality by controlling BG to normal levels [3],also Managing and quantifying hyper/hypoglycemia risk as a function of inter/intra-patient metabolic state variability which considered to be an important step in TGC by minimizing the risk of unintended harmful.

Stochastic Targeted (STAR) protocol is a model based TGC framework which can be applied in a wide range of clinical scenarios and approaches, it uses deterministic and stochastic models to regulate and control BG levels, workload and patient safety within a predefined risk management approach.STAR is a patient specific controller that manage inter/intra-patient variability using a stochastic forecasting of patients potential metabolic variability in conjunction with ICING model (Intensive Care Insulin-Nutrition-), a mathematical model used to simulate the fundamental metabolic dynamics of the human body [3456].

ICING is a deterministic models that uses an ordinary differential equation to describe the physiological system to help the STAR controller select the optimal glucose /insulin inputs in order to manage BG levels. These kind of models known as imperfect in the sense that modeling the uncertainty, system noise and the stochastic nature of the physiological system are not taken into consideration [7].ICING Models parameters was estimated and the identification of the insulin sensitivity SI (SI is representative of whole body metabolic state condition as a single parameter) was achieved via an integral based method. In this way all the dynamic error were lumped into the SI profile which caused unacceptable high variability in the blood glucose

levels. To solve this problem and try to regularize the SI profile, an additional stochastic term was suggested in the glucose equation, which can captures the unmodulated dynamics and measurement noise [8].

Palancz et al in [8] investigated the stochastic Ito version of the ICING model (SDE) equations with parametric stochastic noise term. The computation of the system trajectories and their statistical futures were carried out using Runge-Kutta method in the presences of Wiener-type diffusion process term. Parameter estimation is achieved via maximum likelihood technique. The stochastic model allows not only the characterization of the noise integrated in the stochastic term but also enables the reduction of the modeling error.

The aim of this work is to Analyses the potential use and implementation of the new stochastic differential equation ICING (SDE) model in STAR protocol by analyzing the modeling error and comparing it to the original ordinary differential equation version using a large clinical data set of 60 patient from 3 different ICUŠs in Belgium, Hungary, and New Zealand.

2. Physiological models

2.1. ICING

The Intensive Care Insulin-Nutrition-Glucose (ICING) model used in this study to simulate the fundamental metabolic dynamics of the human body which relies on a deterministic ordinary deferential equation model (ODE) that describes the physiological system to help select glucose and insulin inputs in order to facilitate control[9]. The ICING model is represented by the following equations:

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

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

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

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

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

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

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

The model parameters, the inputs variables, and their detailed description can be found in [10].

2.2. Stochastic ICING

In the stochastic version of the ICING model (SDE) an additional stochastic term was suggested in the glucose equation incorporating a stochastic behavior of the human metabolic system, like modelling error, unmodulated dynamics and system noise etc. [8]. SDE can be considered as an extension of the ICING model by introducing a system noise in form of Wiener processes in Eq(1):

$$dG(t) = -\left(p_G G(t) + S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)}\right)dt + \left(\frac{P(t)+EGP-CNS}{V_G}\right)dt + \sigma(t)dW(t) \quad (8)$$

Where $\sigma(t)$ is a so called diffusion term depending on time and W(t) is a Wiener process, also known Brownian motion, a continuous time random walk, practically it is integrated white noise process:

$$\frac{dW}{dt}(t) = \mathcal{N}(t). \quad (9)$$

3. Clinical data

The clinical data used in this study was collected from three independent cohorts of 60 critically ill patients, The patients are from 3 different ICUs: Belgium, Hungary, and New Zealand (20 patients from each hospital).

Belgian (BE) cohort: This cohort is From the Centre Hospitalier Universitaire of Lige (CHU) ICU, Belgium. The protocol applied at CHU of Lige targets the 5.6- 8.3 mmol/L (100-150 mg/dL) band, and is characterized by an insulin infusion-only approach with a 1- or 4- hour time interval between BG measurements[11].

New Zealand (NZ) cohort: This cohort is from the Christchurch Hospital ICU, New Zealand, which uses the stochastic model-based STAR glycemic control protocol. The STAR protocols adjust both insulin and nutrition levels, measurements taken hourly when outside the 4.4-8.0 mmol/L (80-144 mg/dL) band, and up to 3-hourly within the band based on nursing choice[5][12][13].

Hungarian (HU) cohort: This cohort is from Klmn Pndy Hospital ICU, Hungary, which also uses their own STAR version. The insulin delivered as an intravenous infusion with a higher carbohydrate nutrition formula than the New Zealand ICU.It has a similar 5 risk of BG<4.4 mmol/L, with different delivery of insulin and nutrition [14].

4. Parameter identification (Virtual patient)

In the ICING model in order To generate virtual patients: clinical data, Real BG measurements and insulin/nutrition inputs, are used with model Equations (1),(7) to identify a model-based SI(t) profile for each patient using integral-based methods in half-hourly bases [14].

SDE can generate unlimited numbers of blood glucose trajectories for a given SI(t) profile. Thus, it is more difficult to estimate the model parameters based on experimental observations which represent only one trajectory of the stochastic model. For this The Maximum likelihood estimation (MLE) method was used to identify both SI and $\sigma(t)$ [8].

SI(t) and $\sigma(t)$ were considered as stepwise functions, that are constant in each half-hourly intervals. The parameter estimation was achieved on the basis of the linear approximation of the not equidistant blood glucose measurements. The total treatment time has been divided into half-hourly sections $\sigma(t)$ and in every section a new insulin sensitivity value SI(i) and diffusion term value $\sigma(t)$ were estimated. The identification method in details with the equations can be found in [8].

5. Simulation (Virtual trail)

Also known as in-silico simulation, virtual trails is a stage where performance is verified before clinical testing .Numerical simulations of the both models with the estimated parameter profiles and the virtual patient data weer carried out using ordinary deferential equation solver for ICING and Runge-Kutta method for SDE with a fix step size of one minute.

During the simulation in case of SDE the number of the realizations of the stochastic trajectories varied between 100to500. The analysis considers the mean of the simulated trajectories.

6. Results

As mentioned in the previous section, SI identification is the first step in forming the virtual patients. The $\sigma(t)$ profiles are also identified for the SDE model. The result of the identification of a typical patient is shown in Figure 1, Figure 2.

The simulation of the BG values using the two models solvers for three times 20 patients will result in two BG trajectories for each patients. The two BG trajectories are plotted as a time series function together with the real BG values extracted from the clinical data in order to visually analyze and spot the differences and similarities on BG levels. The plot of one typical patient can be seen in Figure 3.

In order to convert the observational results into a numerical evaluation, the relative and absolute error were calculated. This numerical evaluation can be used to determine

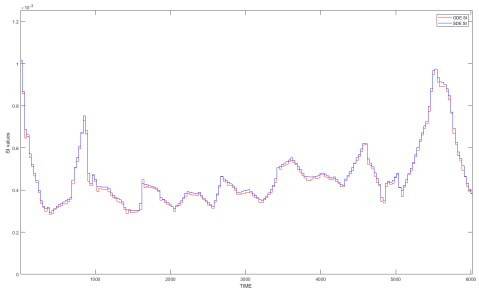

Figure 1: *Stepwise time series function of the identified SI by ICINC vs. SDE*

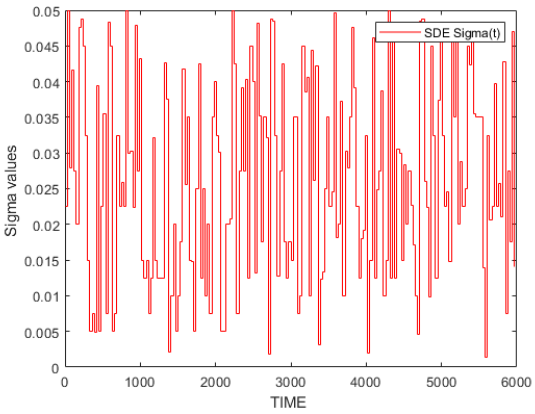

Figure 2: *Stepwise time series function of the identified $\sigma(t)$ by SDE*

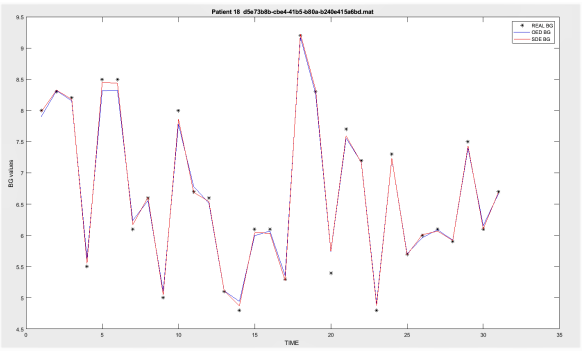

Figure 3: *The mean of trajectories of SDE (red) vs. the trajectory of ICING (blue) with the measurements points*

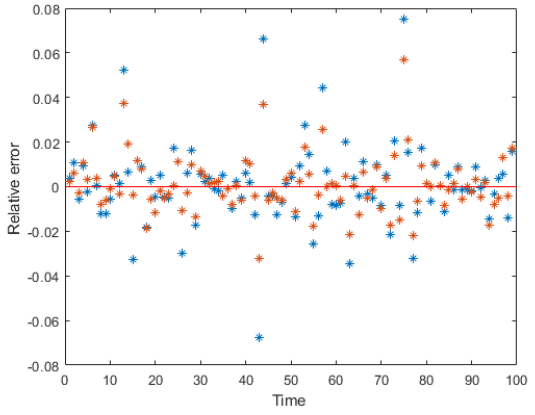

Figure 4: *The relative error of ICING (blue) vs. SDE (red) for one typical patient*

the model with lower modelling error and it provides the possibility for better clinical treatment.

The relative error was used to consider the under/overestimation of the BG levels which can lead to hyper/hypoglycemia in the clinical application of the models. The relative error in each measurement points of one typical patient can be seen in Figure 4. beginfigure

Both of the models absolute error was compared for all the three cohorts in every single measurement point (real BG) , The results of the statistical analysis using Median IQR for the three cohorts are graphically presented in Figure 5 ,Figure 6 ,Figure 7 .

7. Discussion

The stochastic version model allows not only the characterization of the noise integrated in the stochastic term but also can show a reduction in the modeling error, and by reducing the error we may get a presumed improvement under the STAR protocol using this new stochastic model.

As a first step in this analyses, SI was obtained using the two models with their different identification methods for the 3 times 20 patients. This basically leaded to the same physiological parameter and description of the patient state with slightly small differences noticed.

Figure 3 shows the time series of the ODE model BG trajectory and the mean of the SDE trajectories together with the real BG measurements points. It can be seen that the SDE is more flexible in approaching the real measurement points in a closer way than the SDE model(smaller error), also Figure 4 confirms the previous observation, and clearly shows that the SDE relative error is smaller especially in cases where the error is big (highly variable patient states).

The Median IQR error statistics results confirms also the superiority of the SDE model in term of better results with smaller values (smaller Q1,Q2,Q3 error) in each cohort.

8. Conclusions

The goal of this work was to analyze the potential use of the stochastic version of the ICING model which is an extension of the original ordinary differential equation based ICING model under the STAR protocol using a large clinical data set. The patient records were collected from three geographically distinct cohorts treated in Belgium, Hungary and New Zealand. The Method was to analyze the modeling error that was calculated creating a virtual patients at first then using in-silico simulation where the blood glucose trajectories were simulated by the two versions of the ICING model and then compared to the real measurements. The results show that modeling error of the SDE was smaller compared to the original model in the 3 different cohorts.

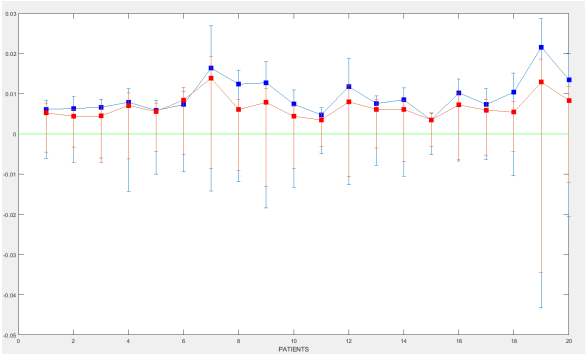

Figure 5: *The median IQR of SDE(red) vs ICING(blue) of Hungarian (HU) cohorts*

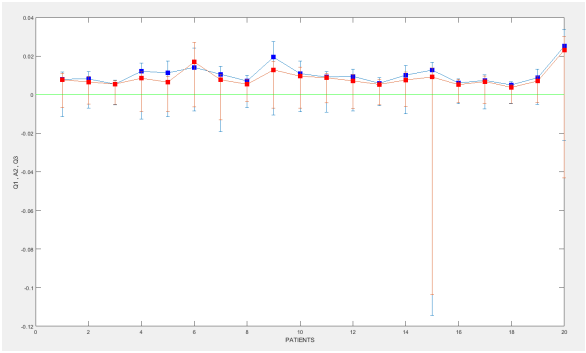

Figure 6: *The median IQR of SDE(red) vs ICING(blue) of New Zealand (NZ) cohorts*

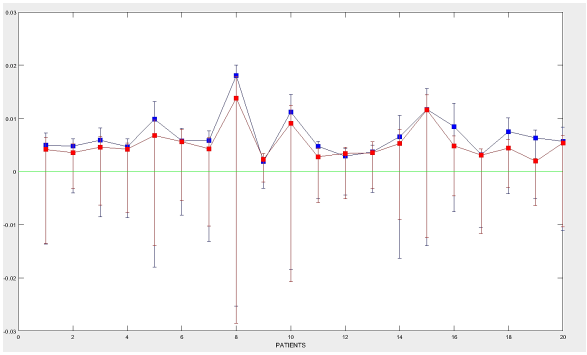

Figure 7: *The median IQR of SDE(red) vs ICING(blue) of Belgium (BE) cohorts*

This study provided encouraging results and the question now: is this reduction in error provided by SDE can lead to the point where it may be used to improve the prediction process of the blood glucose level of the ICU patient under the STAR protocol ? this question can be investigated and answered in a future work.

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