Stochastic Simulation and Parameter Estimation of the ICING Model ⋆

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Abstract: This paper develops a novel gray-box form of the ICING (Intensive Control Insulin-Nutrition-Glucose) model (Lin et al. (2011)) used both for glycemic control of Intensive Care patients and implementation of virtual trials. 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 drift term. Parameter estimation of the resulting stochastic model is achieved via maximum likelihood technique. The global optimization problem was solved using genetic algorithms, simulated annealing and Nelder-Mead procedures. The parameter estimation has been carried out at different system noise levels, and the optimal parameters corresponding to the maximum of the likelihood function were selected. While the gray-box model yielded improvement, it was not significant according to the likelihood ratio test in the case of the examined model parameters. Further investigations including estimation of more parameters simultaneously, adding drift terms to more equations, would be necessary to yield a definitive improvement on this deterministic baseline model. The *Mathematica* code used is transparent and can be easily applied to develop other similar stochastic system models.

Keywords: Biomedical control, Stochastic modelling, Differential equation, Runge-Kutta method, Glucose control

1. INTRODUCTION

Inter and intra patient variability in the appearance and action of therapeutic drugs provides a solid reason to model their Pharmaco-kinetics and dynamics as partly stochastic processes. There are some research papers dealing with stochastic differential equations applied to pharmacokinetic/pharmacodynamic processes published in the last decade. Recently Leander et al. (2015) used one-compartment pharmacokinetic model in preclinical study of nicotinic acid kinetics in obese Zucker rats. Using stochastic model they could separate measurement noise from uncertainty in model dynamics. Also Leander et al. (2014) provide examples for stochastic modelling and parameter estimation using *in silico* data from the *FitzHugh-Nagumo* model for excitable media and Lotka-Volterra predator-prey system. They proposed regularization of the objective function that can lead fewer local minima and can be solved by efficient gradient based methods instead of global minimization.

Concerning blood glucose-insulin kinetics, 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* to compare stochastic and deterministic modelling and found that the system noise parameter in the glucose equation is significant.

Duun-Henriksen et al. (2013) systematically analysed a gray-box variant of an *extended minimal model* and found two drift-terms are enough to compensate error in the model equations. 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 (2013) employed deterministic as well as stochastic *minimal model* to investigate insulin sensitivity. He 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. He found that stochastic approach could give better estimate of the insulin sensitivity than the deterministic one. Finally, Kristensen et al. (2004) also described the methodology of the parameter estimation of stochastic differential equations and illustrated software

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tools CTSMR as well as MoCaVa which runs under MATLAB.

The interested reader can find a comprehensive overview in Donnet and Samson (2013) about the application of stochastic pharmacokinetic/pharmacodynamic modelling.

ICING is a highly sophisticated model developed for critically ill patients as a tool for in silico design and real-time application of glycemic control (Lin et al. (2011); Evans et al. (2012); Fisk et al. (2012); Le Compte et al. (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 unacceptable high frequency changes in the 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 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. However, until now the stochastic Ito version of the ICING model equations with parametric stochastic noise term have been not investigated.

In this contribution we illustrate the methodology of the stochastic simulation and parameter estimation for this gray-box variant of the ICING model. We demonstrate how to get optimal noise level term when parameter estimation take places using the stochastic model. In particular the first Section, the white-box ICING model and its stochastic variant, the gray-box ICING model are presented. In the second Section the stochastic simulation of the process is considered. In the third Section the parameter estimation of the stochastic model is developed. In this study only two parameters were re-estimated with the stochastic model, namely V_G and $V_I$distribution volumes that govern key insulin and glucose concentration. Finally the deterministic model - with zero system noise - is compared to the optimal stochastic model using a likelihood-ratio test to asses improvements and/or errors.

2. MODELLING

2.1 White-box model

White-box models are mainly constructed on the basis of knowledge of physics about the system and are the PI/PD modelling used clinically. Solutions to ODE's are deterministic functions of time, and thus these models are built on the assumption that the future value of the state variables can be predicted exactly despite the fact that no model is perfect and there is always measurement error.

The *ICING*(*Intensive Control Insulin-Nutrition-Glucose*) pharmacokinetic-pharmacodynamic model (Lin et al. (2011)) defines glucose-insulin kinetics and dynamics in critically ill patients. The deterministic, white-box model is well validated (Chase et al. (2010b)), and represented by the following equations,

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

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

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

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

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

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

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

The values of the model parameters and their descriptions for the ICING model and the exogenous input variables, functions of time can be found in Fisk (2014).

2.2 Gray-box model

An essential part of model validation is the analysis of residual errors defined as the deviation between the true observations and the one-step predictions provided by the model. This validation method is based on the fact that a correct model with all necessary dynamics leads to uncorrelated residuals. This outcome is rarely obtainable for white-box models. Hence, in these situations, it is not possible to validate ODE models using standard statistical tools.

However, by using a slightly more advanced type of equations, this problem can be solved by replacing ODEs with stochastic-differential equations (SDEs) representing a gray-box model and incorporating stochastic behaviour of the system, like modelling error, unknown disturbances, system noise and any other relevant variabilities. The stochastic SDE model (gray-box model) can be considered as an extension of the ODE model by introducing system noise in the form of a Wiener process.

The application of the gray-box model was motivated directly by the fact that the noise of the residual of the glucose equation Eq.(1), see Fig. 1. It was found to be a Wiener process (Fisk (2014)) thus defined:

$$G_X(t)|_{t=\tau} \approx \mathcal{N}(0, \sigma). \tag{8}$$

Therefore, it is reasonable to compensate the simulation error in the equation of $G(t)$ by an additional stochastic term that should be added, namely a Wiener process.

The resulted gray-box model will be differ from the white-box model in the first differential equation describing the

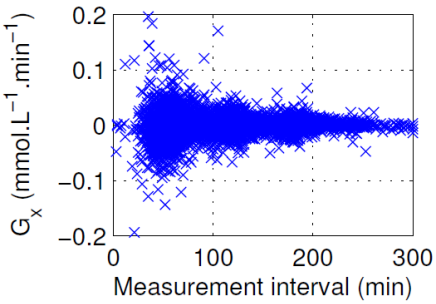

Fig. 1. Noise in the residual of Eq. (1) (Fisk (2014))

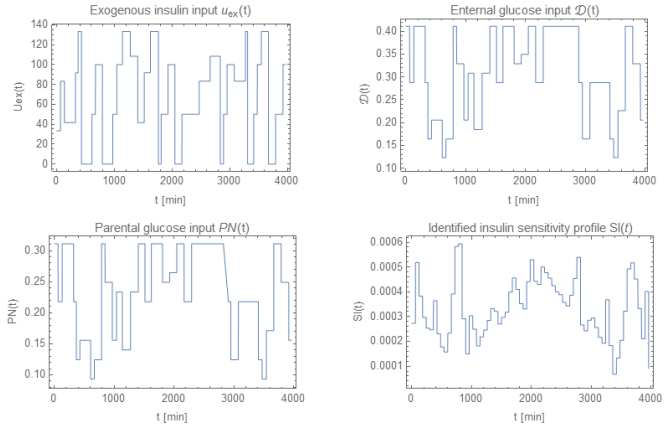

Fig. 2. Input functions of the ICING model from the clinical data

glucose dynamics (Eq. (1)). The SDE form of the equation looks like:

$$\frac{dG(t)}{\mathrm{dt}} = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} + \sigma\, dW(t), \tag{9}$$

where σ is the diffusion constant and $W(0, 1, \mathrm{t})$ is a Wiener process also known as Brownian motion, a continuous-time random walk. Practically, it is an integrated white noise process.

3. SIMULATION

Input functions of the model can be seen on Fig. 2. They are based on clinical data from a major clinical study (Chase et al. (2008, 2010a)).

Eq. (1) and Eq. (2)-Eq. (7) represent an Ito-process which can be simulated by *Mathematica* using stochastic Runge-Kutta method. The simulated blood glucose trajectories and a slice distribution of these trajectories at time t = 2700 min can be seen in Fig. 3 and Fig. 4, where they clearly match typical glucose profile in this cohort.

4. PARAMETER ESTIMATION

Parameter estimation is the critical phase of the modelling since it will determine how good the model can match the measurement data. It goes without saying that the

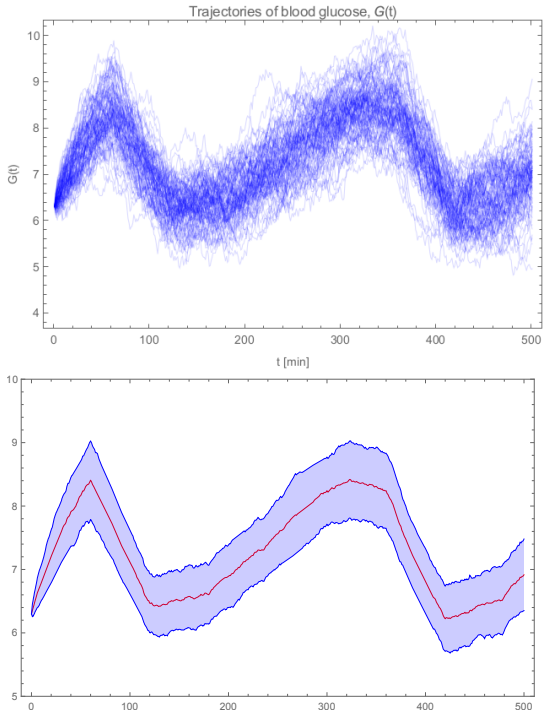

Fig. 3. Trajectories of the simulated blood glucose $G(\mathrm{t})$, in case of 100 realizations of the Ito process

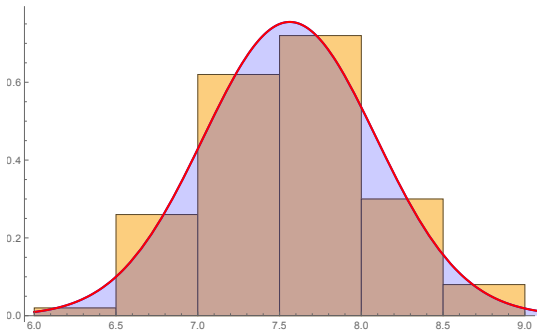

Fig. 4. A slice distribution of G(t) at $t = \tau$ in case of 100 realizations of the Ito process, at time $\tau = 2700$

measurement process itself also has error representing the serially uncorrelated error occurring due to imperfect accuracy and precision of the analysing equipment. However, if the identified model matches the data well, then it could also be effective in real-time control and in-silico design (Chase et al. (2011)).

A concrete realization of $G(\mathrm{t})$ is shown on Fig. 5. It is clear the identified model captures the measured data well over the 3 days shown. Equally, there are still some errors, particularly at sharp peaks or troughs, where it cannot capture these changes.

4.1 Likelihood function

As we have seen the solutions to SDEs are stochastic processes that are described by probability distribution. This property allows for maximum likelihood estimation. Let the deviation of the measurements from the model as

$$\epsilon_k(\theta) = G_k - \mu\left(G\left(t_k\right), \theta\right) \tag{10}$$

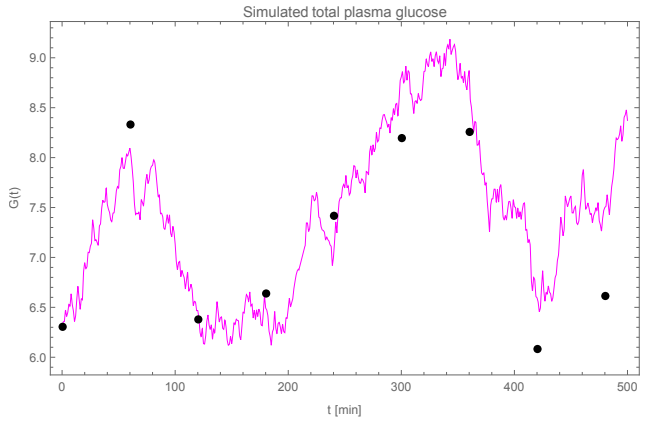

Fig. 5. A single realization of $G(t)$ (continuous purple line), and G_k is the measured values of $G(t)$ at $t{=}t_k$ (black dots)

where $\theta = \{V_G,\ V_I\}$ and $\mu(G(t))$ is the mean value of the simulated trajectories, G_k is the measured values of $G(t)$ at $t{=}t_k$. Assuming that the density function of ϵ_k can be approximated reasonably well by Gaussian density, the likelihood function to be maximized is defined

$$\mathcal{L}(\theta) = \frac{1}{2\pi} \exp\left(-\sum_{k=1}^{N} \epsilon_k(\theta)^2 \right). \tag{11}$$

For computation we use its logarithm. Now, two model parameters, V_G and V_I will be re-estimated in the SDE model employing maximum likelihood method. These distribution volumes are approximate values, but directly determine concentrations of glucose, V_G, and insulin, V_I. Therefore, stochastic error in these one size fits all approximations is justified.

4.2 Maximization of the Likelihood function

To optimize the likelihood function is not an easy task, due to flat objective function, non-differentiable terms, more local optimums adds computational effort. In addition a long evaluation time of the model. Instead of using direct global optimization, first we compute the values of the objective function on a 25 × 25 grid, as shown in Fig. 6. In this way, one can easily employ parallel computation to decrease the running time. We are looking parameters in a range $10 \leq V_G \leq 16$ and and $2 \leq V_I \leq 5$, based on physiology (Lin et al. (2011)).

Different methods were employed to carry out global maximization of the likelihood function, namely genetic algorithm, simulated annealing, Nelder- Mead method and random search technique. Genetic algorithms and random search proved to be the most reliable. The optimization has been carried out at different noise levels, at different values of the σ drift parameter, as defined in Table 2. The optimum, the maximum value of -Log$\mathcal{L}$ was found at $\sigma = 0.1$ and the corresponding optimal patient specific parameters are $V_G = 12.9684$ and $V_I = 3.7357$. The parameters for the example patient were $V_G = 13.3$ and $V_I = 4$ in the deterministic model ($\sigma = 0$), which are relatively close to this patient, but not optimal.

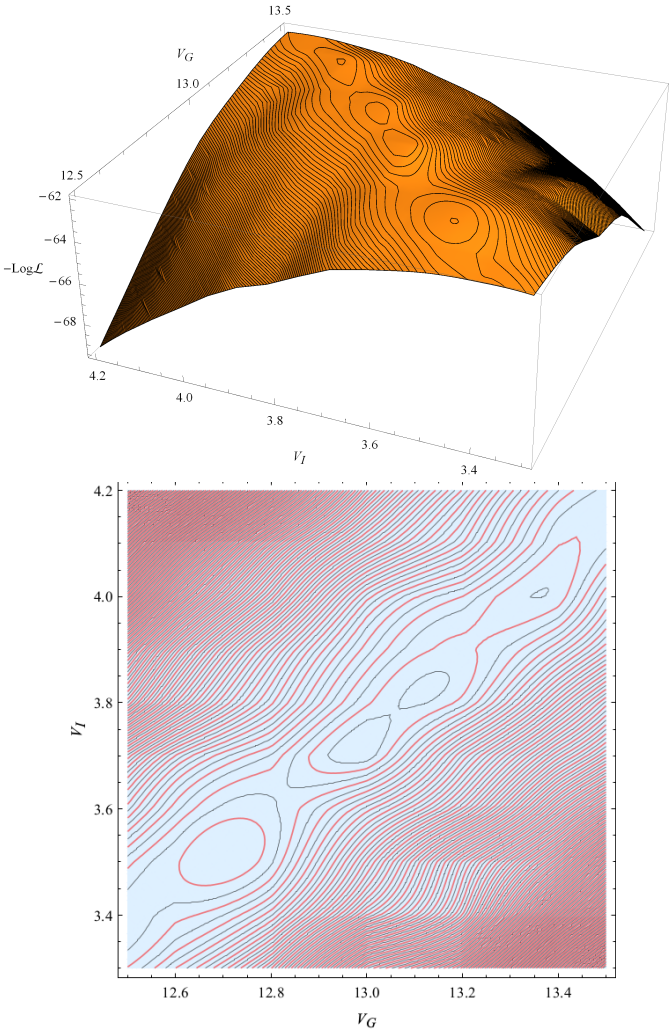

Fig. 6. The likelihood function with local maximums

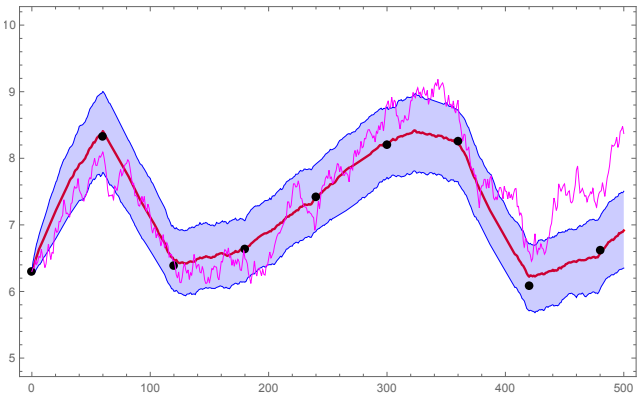

Fig. 7. The average of the simulated blood glucose trajectories and their ± standard deviation with the measured data points

5. SIMULATION WITH THE ESTIMATED PARAMETERS

Fig. 7 shows the result of the stochastic simulation of the blood glucose trajectories and their mean with these new parameters. The width of the band around the mean trajectory is 2σ contains all measurement data points. Hence, the model and fit are improved.

6. DETERMINISTIC VS. STOCHASTIC MODELLING

To compare the efficiency of the deterministic and stochastic modelling we should handle σ as a free parameter in the stochastic model to be fitted. This approach yields three free parameters to be estimated: V_G, V_I and σ. Carrying out the parameter estimation for different values of σ for the model, yields different results. The results can be seen in Table 2 where $\sigma = 0$ corresponds to the deterministic model.

Table 1. The results of the parameter estimation for different system noises

σ	-Log $\mathcal{L}(V_G, V_I)$	V_G	V_I
0.00	62.0712	13.3	4.0
0.05	61.9243	12.8828	3.6645
0.10	61.9042	12.9684	3.7357
0.15	62.0140	12.7485	3.5307

To demonstrate that stochastic model can provide significant improvement compared with the deterministic one, a likelihood-ratio test can be applied Allen (2007). The test statistic is defined:

$$\mathcal{R} = 2\left((\text{- Log}\mathcal{L}(\alpha,\beta))_{\mathcal{D}} - (\text{- Log}\mathcal{L}(\alpha,\beta))_{\mathcal{S}}\right) \qquad (12)$$

where indexes $\mathcal{D}$ and $\mathcal{S}$ stand for the deterministic and stochastic model, respectively.

$\mathcal{R}$ is $\chi^2(f)$ distributed where f is the difference in the number of parameters between the two models, in our case $f = 3 - 2 = 1$. The critical value for $\chi^2(1)$ at confidence level of 95 % is 3.84176. In our case, the difference is 62.0712-61.9042 = 0.167, which is smaller than the threshold value. Therefore the gray-box modelling has not proved to be significantly better than the deterministic one despite better results in Fig. 7. However, there is significant improvement, and over many patients, the modelling could improve.

The value of the likelihood function alone does not describe the error distribution in the sampling points ($t = t_k$). On Fig. 8 shown the error distributions in case of the ODE and SDE respectively.

In stochastic modelling case the mean value as well as the value of the maximum error are smaller, but the standard deviation is somewhat greater than in case of deterministic modelling, see Table 2.

Table 2. The results of the parameter estimation for different system noises

Error ϵ_k	σ=0	σ= 0.1
Mean	-0.0102	0.0021
Standard Deviation	0.1086	0.1112
Max Absolute Value	0.5584	0.4589

7. CONCLUSION

An initial step has been taken toward to applying parametric stochastic variant of the ICING model. However this numerical experiment was not successful it is advisable to continue the investigation via involving more parameters as well as implementing drift terms into other equations, too. *Mathematica* proved to be a handy vehicle for carrying out the stochastic numerical simulation.

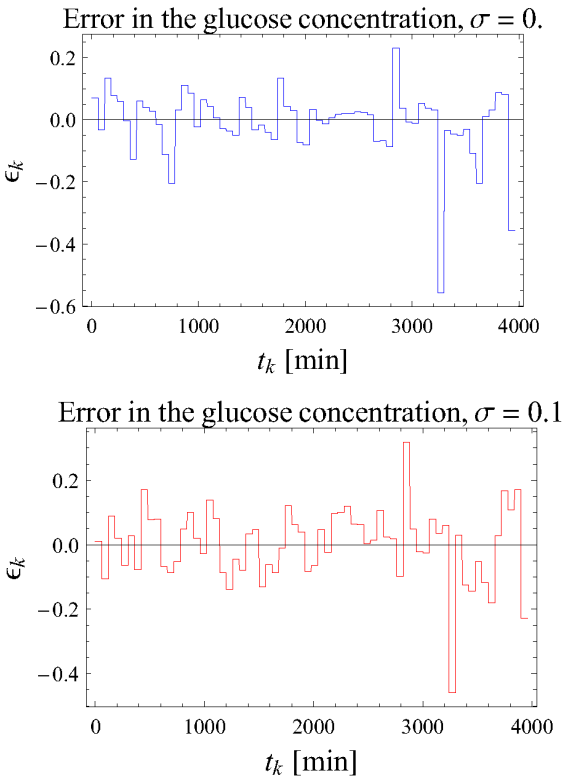

Fig. 8. Error distributions in the case of the ODE (above) and SDE (below)

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