Department of Control Engineering and Information Technology

Final report - OTKA K116574

Stochastic models for next generation accurate model-based glycemic control in intensive care: from all new models and methods to clinical validation

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1 Introduction

This report provides the summary of the main research achievements and other outcomes of the **OTKA K116574** research project titled *Stochastic models for next generation accurate model-based glycemic control in intensive care: from all new models and methods to clinical validation.*

The project successfully reached all the milestones planned, and the set of research outcomes is significantly more comprehensive than it was defined in the research proposal. This report briefly compares the proposed work plan and the achieved research result. Details of the scientific results are published in the referred research papers. However, the OTKA publications list is significantly longer than the referenced papers, as only the most significant ones are cited here. For the complete list of publications, please take a look at the publication list provided by the project management system.

2 Main research achievements and their relation to the work plan

According to the project proposal, the research plan aimed the achievement of the primary outcomes as follows:

- **O1**: Stochastic differential equation based metabolic model;
- **O2**: Next generation stochastic virtual patient methods and environment:
  - Patient state identification method using the new models;
  - New SDE model based patient simulation method.
- **O3**: Validated, next generation glycemic control protocol.

The outcomes will be introduced according to the above objectives defined in the project plan referencing the papers publishing the details of the actual results. In the subsequent section, the basic idea of the project is summarized in a nutshell providing an introduction to the research topic.

2.1 Stochastic differential equation based metabolic model

Glycaemic control (GC) of critical care patients with abnormal blood glucose (BG) level can reduce mortality and improve clinical outcomes. Model-based GC protocol, called Stochastic TARgeted Control (STAR) protocol (Evans et al. 2012; Fisk et al. 2012; Le Compte et al. 2012; Lin et al. 2011) allows personalized and effective control of BG level of the patients. STAR is used in several geographically distinct hospitals in Hungary (HU), New Zealand (NZ), Belgium (BE), and Malaysia (MA).

Intensive Control Insulin-Nutrition-Glucose (ICING) model (Lin et al. 2011), used by STAR is a well validated (Chase et al. 2010; Dickson et al. 2017; Pretty et al. 2012) classical ordinary differential equations (ODE) based white-box model describing the metabolic processes of human glucose-insulin system. ICING, developed simultaneously with STAR in the last few decades, is represented by the following equations (Dickson et al. 2017; Lin et al. 2011):

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

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

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

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

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

The model parameter values, their descriptions, and the exogenous input variables - functions of time - can be found in Fisk 2014; Pretty et al. 2012.

Even though the STAR protocol using ICING model can provide safe and efficient treatment for most of the patients, there is a small group of patients where the STAR performance is significantly below the average Dickson et al. 2017; Knopp et al. 2019; Stewart et al. 2016 motivating the development of a novel and more accurate physiological model. The stochastic extension of the ICING (ICING_SDE) is a stochastic differential equation (SDE) based grey-box model. It is an extension of the original ICING (ODE) model, where Eq. (1) is modified: In ICING_SDE the system noise is introduced in the form of Wiener process. Accordingly, the final form of the modified equation (Eq. (1)):

$$dG(t) = -\left(p_G G(t) + S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)}\right)dt + \left(\frac{P(t)+EGP-CNS}{V_G}\right)dt + \sigma(t)\mathrm{dW}(t) \tag{6}$$

where σ(t) is the diffusion term depending on time and W(t) is a Wiener process, also known as Brownian motion, a continuous-time random walk, practically is integrated white noise process:

$$\frac{\mathrm{dW}}{\mathrm{dt}}(t) = \mathcal{N}(t). \tag{7}$$

Further details of the stochastic model are given in Benyó et al. 2016; Benyó et al. 2018; Paláncz et al. 2016a,b.

2.2 Next generation stochastic virtual patient methods and environment

Using the stochastic grey-box model extension of the ICING (ICING_SDE) the in-silico simulation environment of the ICING model was rebuilt to enable the model validation and implementation of a series of research tasks. The research results are collected according to the objectives as follows:

- Patient state identification method using the new models;
- New SDE model based patient simulation method.

2.2.1 Patient state identification method using the new models

In the case of the original ICING model the 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. In the stochastic extension of the model a new σ(t) diffusion term is introduced into the model, as it can be seen in Eq. (1), describing the system noise during the treatment (Paláncz et al. 2016b).

The computation 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 (Olsson and Nelson 1975). The results were validated by statistical evaluation.

The parameter computation has been carried out at different system noise levels, and the optimal parameters corresponding to the maximum of the likelihood function were selected. While this grey-box model yielded improvement, it was not significant according to the likelihood ratio test in the case of the examined model parameters.

The most important research outcomes related to the stochastic-model-based patient state identification methods are as follows:

- Insulin sensitivity identification using ICING_SDE defining the patient's state trajectory and virtual patient definition:
  - Stochastic Simulation and Parameter Estimation of the ICING Model (Paláncz et al. 2016b)
- Stochastic model validation:
  - Clinical Data Based Validation of the Stochastic Version of ICING Model (Benyó et al. 2016)
  - Specific validation analysis of stochastic ICING model based estimation of insulin sensitivity profile using clinical data (Benyó et al. 2016)

2.2.2 New SDE model based patient simulation method

Due to the introduction of the new $\sigma(t)$ diffusion term the patient history is changed. Thus, a new simulation method had to be implemented dealing with the system noise term. The most important research outcomes achieved by using the SDE model based patient simulation method are as follows:

- Clinically relevant analysis tasks: System noise analysis and classification of patient behavior based on the insulin sensitivity profile of the patient:
  - Unsupervised Classification based Analysis of the Temporal Pattern of Insulin Sensitivity and Modelling Noise of Patient Groups under Tight Glycemic Control (Benyó et al. 2018)
  - Characterisation of the system noise using the stochastic term of the model (Benyó et al. 2016)

2.3 Validated, next generation glycemic control protocol

According to the research outcomes of the project the stochastic extension enabled significant improvement in the modeling accuracy and enabled several clinically relevant analysis task the clinical outcomes reflected only moderate improvement in the STAR treatment based on the in-silico simulation experiments.However, these research results are focused our attention to other steps of the calculation of the clinical treatment. These step7s are the **prediction of the future insulin sensitivity** of the patient and the **accurate definition of the endogenous glucose production**. The related research results are as follows:

- Methods predicting the future insulin sensitivity of the patient:

  - 3D model to forecast patient-specific insulin sensitivity
  - Artificial Intelligence bases insulin sensitivity prediction
- Patient specific definition of the endogenous glucose production parameter of the patient

2.3.1 3D model to forecast patient-specific insulin sensitivity

STAR uses a 2D stochastic model to predict distributions of likely future changes in model-based insulin sensitivity (SI) based on its current value, and determines the optimal intervention. A novel 3D model is proposed to forecast patient-specific insulin sensitivity variability and investigates the impact of a new 3D stochastic model on the ability to preHdict more accurate future SI distributions, which would allow more aggressive insulin dosing and improved glycaemic control. Details of the results are published in Uyttendaele et al. 2018, 2019

2.3.2 Artificial Intelligence bases insulin sensitivity prediction

Several versions of Artificial Intelligence (AI), especially Neural Network (NN) based methods, are developed to create an alternative stochastic model for the STAR protocol. The primary aim of this part of the research was to develop and validate an alternative methodology for S_I prediction and asses its accuracy for use in similar patient treatment, where the stochastic model has generalized over several countries and cohorts. The potential benefits of using a NN based method are the flexibility of the method to involve further patient parameters into the prediction and the opportunity to incrementally modify the stochastic model based on the results of recent patient treatments. The benefits of involving further patient parameters into the S_I prediction have been already shown by the development of a higher-dimensional, 3D stochastic model (Uyttendaele et al. 2018, 2019), which remains limited to other clinical variables by its structure, where a NN is much less limited. There is thus the opportunity to significantly expand the capability and accuracy of these prediction using readily available clinical data.

The option of regularly modifying the stochastic model by using data from the most recently treated patients is logical and may have the benefit to follow the trends of general behaviour of the patient. It is particularly important as cohorts evolve over time and no single patient provides enough data to create a patient-specific predictive model. The NN based stochastic model creation approach used here fits this opportunity as well. However, the prerequisite of the development of these opportunities is the development of the methodology providing an equally, or more, accurate S_I prediction than the 2-D model used in the original version of the STAR protocol.

Using the unique data set of insulin sensitivity trajectory of several thousands of patients many alternative solutions are developed. Details of the novel approaches are published in Benyó et al. 2020; Szabó et al. 2021, 2022

2.3.3 Patient specific endogenous glucose production parameter definition

Critically ill ICU patients frequently experience acute insulin resistance and increased endogenous glucose production, manifesting as stress-induced hyperglycemia and hyperinsulinemia. STAR (Stochastic TARgeted) is a glycemic control protocol, which directly manages inter- and intra-patient variability using model-based insulin sensitivity (SI). The model behind STAR assumes a population constant for endogenous glucose production (EGP), which is not otherwise identifiable. In this part of the research the effect of estimating EGP for ICU patients with very low SI (severe insulin resistance) is analyzed and its impact on identified, model-based insulin sensitivity identification, modeling accuracy, and model-based glycemic clinical control. The most relevant details of methods using patient specific EGP are published in Anane et al. 2019; Yahia et al. 2020, 2022 among others.

3 Indirect outcomes of the research project

The project achieved significant and valuable research results with a major impact on the scientific field of biomedical engineering, especially model-based clinical diagnostics and therapy. However, the additional outcomes of the OTKA project, such as the initialization of further research projects and embedding the research team into the scientific community of the given field of science, have similar importance as the direct research results since they provide longer-term sustainability of the research team and opportunity to disseminate the direct outcomes.

3.1 Granted and submitted research project proposals enabled by the OTKA project

The OTKA project was carried out with the collaboration of colleagues from the University of Canterbury, New Zealand, the University of Liege, Belgium, and the University of Furtwangen, Germany. The list of research projects directly connected to the scientific field of the OTKA project with the participation of the above consortium is as follows:

- Financed research projects initiated by the OTKA project:
  - H2020 RISE project (Grant ID: 872488) DCPM - Digital Clone for Personalized Medicine (consortium coordinator: Balázs Benyó/Budapest University of Technology and Economics)
  - OTKA K137995 – Models and Methods for Personalized Intensive Care (principal investigator: Balázs Benyó/Budapest University of Technology and Economics)
  - HORIZON EUROPE ERA PerMed JTC2021 - PerFluid: Personalised perfusion guided fluid therapy (consortium coordinator: Thomas Desaive, University of Liege; Budapest University of Technology and Economics principal investigator: Balázs Benyó)
- Submitted but not financed or under evaluation (almost all the projects were either invited to the second evaluation stage or were above the granting threshold):
  - HORIZON-HLTH-2022-TOOL-12-two-stage HORIZON-RIA (Grant ID: 101080141) PERS-MV: PERSONALISED STRATIFICATION IN MECHANICAL VENTILATION: DIGITAL TWIN PERSONALISATION, STRATIFICATION, AND OPTIMISATION OF CARE
  - HORIZON-EIC-2022-PATHFINDEROPEN-01 HORIZON-EIC (Grant ID: 101099438) AI4AMD: Artificial Intelligence for Additive Manufacturing Design of the Customized Craniofacial Bone
  - HORIZON EUROPE ERA PerMed JTC2021 - PER-MV: Personalized Mechanical Ventilation in ARDS
  - H2020-SC1-2020-Single-Stage-RTD (Grant ID: RIA 965445) PERFoRM: Personalized Fluid Responsiveness/Resuscitation Modelling and Management
  - H2020-SC1-2019-Two-Stage-RTD IA (Grant ID: 847953) STAR-PILOT: Large-scale pilots of the stochastic targeted protocol for personalised glycemic control of critically-ill patients
  - H2020-MSCA-RISE-2018 MSCA-RISE (Grant ID: 824041) PersonalICU: Personalized prediction of patient response: Decision Support and Automation for ICU
  - H2020-MSCA-RISE-2017 MSCA-RISE (Grant ID: 777688) PICoMED: Personalised Intensive Care Medicine
  - H2020-MSCA-RISE-2016 MSCA-RISE (Grant ID: 734244) PRIME-I2I: Partnering Researchers across Industry-Medicine-Engineering: Ideas to Innovations

3.2 Contribution to major international conferences of the related field of science

The OTKA project provided the opportunity to participate in the organization of several highly recognized international conferences in the given scientific field. The most relevant contributions are as follows:

- 11th IFAC Symposium on Biological and Medical Systems (BMS2021), Ghent, Belgium, September 19-22, 2021 (Proceeding's Chief Editor, Session organiser)
- 21st IFAC World Congress, July 12-17, 2020, Berlin, Germany (Associate Editor for 8.2. Bio- and Ecological Systems - Modeling and Control of Biomedical Systems / Reviewer. Involved in two Open Invited Tracks: "Control, Mechatronics, and Imaging for Medical Devices and Systems in Medicine" and "Physiological Control Systems in Medicine" - comprising 23 sessions and 110 articles.)
- 10th IFAC Symposium on Biological and Medical Systems, Sao Paulo, Brazil, September 2-5, 2018, a major triennial IFAC conference ()Associate Editor for Contributed Papers / Associate Editor for Invited Sessions / Referee / Chair or co-chair of 3 sessions. Sessions involved: "Identification and Personalized Care,"; "Modeling and Clinical Applications,"; "Clinical Validation and Implementation,"; "Clinical Potential of Modeling and Non-invasive Imaging in Pulmonary Care," – 4 session symposium of 24 papers organised with Geoffrey Chase (U of Canterbury), T Desaive (Univ of Liege), Thomas Schauer (TU Berlin), Knut Moeller (Furtwangen Univ), Marcos Tszuzuki (Sao PauloUniv), and several other.)
- 20th IFAC World Congress, July 9-15, 2017 Toulouse, France, a major triennial IFAC conference (Associate Editor for 8.2. Bio- and Ecological Systems - Modeling and Control of Biomedical Systems / Associate Editor for Invited Session / Associate Editor for Open Invited Track / Chair or co-chair of 2 session (session organizer/associate editor: "Control and Imaging for Devices and Systems in Medicine: Models, Identification and Clinical Application")
- 4th IFAC conference on Intelligent Control and Automation Sciences (ICONS 2016), June 1-3, 2016 (session co-organizer: "Biomedical Control: Clinical Applications, Systems and Methods")

4 Summary

As is summarized in this final report, the OTKA project led to high-quality research achievements relevant to biomedical engineering, especially model-based clinical diagnostics and therapy. The project outcomes not only met the proposed outcomes, but several new research problems have been found and solved in the project. Even though the project published a high number of publications, and several of them are published highly-ranked D1 (Chase et al. 2019; Stewart et al. 2016) and Q1 (Dickson et al. 2017; Knopp et al. 2019; Yahia et al. 2022) journals a part of the research results is still under publication. Several papers have been drafted, especially those related to artificial intelligence-based insulin sensitivity prediction. Due to the long paper development phase with the foreign partners, the manuscript version under submission could be attached only to this current research report. Still, their final version will be assigned to the project report as soon as they are published. Submission of a new PhD dissertation (by Yahia Anane) is expected in the near future.

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