MINISYMPOSIUM

RECENT TRENDS IN THE MODELING AND CONTROL OF THE GLUCOSE-INSULIN SYSTEM

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Mathematical modeling of the glucose-insulin feedback system is necessary for the understanding of the homeostatic control, to analyze experimental data, to identify and quantify relevant biophysical parameters, to design clinical trials and to evaluate diabetes prevention or disease modification therapies. During the last decades, several models describing specific external perturbations have been presented (such as the Intra-Venous Glucose Tolerance Test, the Oral Glucose Tolerance Test or the Euglycemic Hyperinsulinemic Clamp), therefore inevitably focusing on short-term periods, or detailing a single specific viewpoint of the larger phenomenon. Nowadays, motivated by the improvements in the technological devices providing more and more accurate Continuous Glucose Sensors and affordable insulin pumps, the design of artificial pancreas algorithms has further increased the interest in modeling the glucose-insulin system as a whole, in particular when the closed-loop insulin delivery control law requires the formal knowledge of the system model. Comprehensive reviews on the glucose-insulin models can be found (among others) in [1, 2].

The present Minisymposium aims at introducing very recent trends in the modeling of the glucose-insulin system, with a special focus on their possible applications to the artificial pancreas. Mathematical models have been extensively exploited in the abstract by György Eigner, "Blood glucose regulation possibilities by modern robust control methodologies", where robust model-based control laws need to cope with parameter uncertainties. In Claude Moog's abstract, "Clinical assessment of a new biomathematical model for decision making in functional insulin therapy", the model is also effectual in making decisions supporting the proper insulin therapy. Multi-scale modeling is discussed by Gunnar Cedersund in its abstract "Multi-level modelling of diabetes for improved treatments and understanding", where he presents an interactive dynamic model, evolving in the sense that new pieces of information can be added and replaced as soon as they show up, so that the model could be exploited to see how it responds to treatments, drugs, and diets, on the intracellular, organ, and whole-body level. The idea of the glucose-insulin system as a network of integrated submodels, properly accounting for the many delayed effects appearing in the submodels communication, is also developed by Jiaxu Li in "An integrated system towards artificial pancreas and its numerical trials". Finally, the abstract by Jorge Bondia, "Physiological modelling of counterregulatory response to hypoglycaemia in type 1 diabetes", is focused on hypoglycemic events, an important feature of any insulin infusion therapy, and presents a mathematical model aiming at properly describing the counterregulatory response to hypoglycemia in Type 1 diabetic patients.

All these researches support their theoretical results by means of clinical trials.

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BLOOD GLUCOSE REGULATION POSSIBILITIES BY MODERN ROBUST CONTROL METHODOLOGIES

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Keywords: Robust control, Type 1 diabetes mellitus, LPV modeling, Parameter uncertainty.

Diabetes mellitus (DM) is one of the most widespread disease connected to the human metabolic system. In case of DM, the gluco-regulatory system is not able to operate on a normal basis due to different conditions mostly regard to the insulin hormone [3]. More precisely, the diabetic condition is mostly caused by the lack of insulin (Type 1 DM – T1DM), the resistance against the hormone (Type 2 DM – T2DM) or both. In the recent years the effective handling of DM became more crucial due to the continuously increasing diabetic population. The age standardized size of the global population suffering from DM was around 422 million world wide in 2014. Unfortunately, the diabetic population has risen faster in the low- and mid-developed countries than the high-income ones in which the available treatment may not as advanced [4].

In the last decades the biomedical engineering and physiological control approaches demonstrated their benefit in DM treatment. Advanced mathematical modeling of the physiological glucose-insulin interaction, system identification and controller design solutions have appeared in order to provide the highest possible quality of treatment. The nature of the physiological process raises several challenges, which is needed to be handled during the application of the developed control techniques: parameter uncertainties, patient variability, nonlinearity of the model, time-delay of the glucose and insulin, strict control goals, lack of precise sensor and actuator models, and other challenges [5, 6].

In DM treatment two different approaches can be used: personalization and generalization. Personalized models and control solutions have the best performance in case of individuals from the treatment point of view. However, these solutions cannot be applied on larger population due to their uniqueness. Generalized solutions can be applied on larger population, although these do not provide the best treatment for individuals.

Due to the aforementioned challenges we propose the use of modern robust control methodologies with the primary goal to avoid hypoglycemia at any cases. The handling of parameter uncertainties, the estimation of internal states and the controller design requires the use of these techniques instead of the commercially used ones, such as regular Proportional-Integral-Derivative (PID) or Model Predictive Control (MPC) that have unquestionable advantages at individualized level [7, 8]. It is not possible to satisfy both of requirements by using these techniques – although combination of them is possible.

Handling the model parameters in order to use the above mentioned modern control methods is a challenging task as well. Linear Parameter Varying (LPV) framework has been demonstrated to be a suitable solution. By the use of LPV methodology the parameter uncertainties coming from the inter- and intra-variability of patients can be described and encapsulated. Hence, general robust control on linear matrix inequality (LMI) level, robust fixed point transformation based control (RFPT) or tensor product (TP) based control can be used. The lack of sensor models can be bridged by using advanced estimation techniques. In our research we focus to extend the capabilities of applicable treatment possibilities by using the aforementioned techniques for a better care [9, 10, 11, 12, 13].

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CLINICAL ASSESSMENT OF A NEW BIOMATHEMATICAL MODEL FOR DECISION MAKING IN FUNCTIONAL INSULIN THERAPY

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Keywords: Hypoglycaemia, Type-1 Diabetes, Modelling.

The model. Modelling glucose-insulin dynamics is a key factor to improve algorithm for automatic glycemia regulation. Maximal models attempt to use a full description of the metabolic regulation and are nonlinear models of high order, with a large number of parameters. This class of models cannot be identified from standard clinical measurements and their utility is mainly dedicated to system simulation. Minimal models are parsimonious and describe the key features of the system. These models are useful to estimate relevant physiological parameters such as insulin sensitivity. A minimal model of glucose-insulin dynamics of type 1 diabetes, dedicated to functional insulin therapy, has been developed. It is linear and includes five states and five parameters. Its static properties show that a unique value of a constant insulin delivery rate can maintain glycemia at any value when fasting; this is known in clinical practice as the basal rate. Moreover, tools for functional insulin therapy such as basal rate, correction factor, carb-to-insulin ratio and duration of insulin action are derived from the model parameters. The model also fits on standard clinical data (CGM, injections and CHO estimations) for two days whereas historical models are fitted on average over 6 hours using data from a glucose tolerance test. The model is named "long-term" with respect to these good static and dynamic properties.

The clinical trial. A clinical study has begun in October 2017 at Nantes University Hospital. The objective is to assess the relevance of the tools (basal rate, correction factor, carb-to-insulin ratio and duration of insulin action) computed from the long-term mathematical model. In this study, 40 type 1 diabetic patients in ambulatory conditions, wearing a Dexcom G4 CGM device, an insulin pump, and counting carbohydrates will be included. For this study, a linear parameter varying (LPV) algorithm has been developed in order to catch intraday patient variability. The algorithm can estimate circadian variability of the basal rate and a different value of the carb-to-insulin ratio for each meal. The correction factor and the duration of insulin action are assumed to be constant over the week and are identified as constant parameters. The determination of such tools from one week record of standard clinical data is used as a genuine tool for supporting decision-making in adjusting insulin therapy. When insulin adjustment proposed by the algorithm is approved by physicians, the patient will wear the CGM device for another week. Glycemic variability (time spent above 180 mg/dl, time spent below 70 mg/dl) is used to assess the quality of

the insulin adjustment. The clinical study is under progress and the forthcoming results will establish to which extend the biomathematical model estimates are helpful for decision making.

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AN INTEGRATED SYSTEM TOWARDS ARTIFICIAL PANCREAS AND ITS NUMERICAL TRIALS

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Keywords: Artificial pancreas, Diabetes, Numerical trials.

Millions of Americans suffer type 1 diabetes mellitus (T1DM) that is caused by the lack of insulin producing pancreatic beta-cells. Exogenous insulin or its analogues must be daily administered to utilize and lower the chronic high glucose level, ideally, though an artificial pancreas, an integrated system consisting of an insulin pump, a glucose monitoring system, and closed loop control (CLC) algorithms. An effective CLC algorithm is still lacking in handling the delayed effects of insulin in delivery mechanisms, GMS and the hepatic glucose production (HGP). The timing discrepancies and dose inaccuracies often cause undesired glucose fluctuations including both hyperglycemia and dangerous hypoglycemia. Our ultimate goal is to formulate an integrated system, consisting of several submodels, with the aims to develop and validate effective CLC algorithms for artificial pancreas.

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PHYSIOLOGICAL MODELLING OF COUNTERREGULATORY RESPONSE TO HYPOGLYCAEMIA IN TYPE 1 DIABETES

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Keywords: Hypoglycaemia, Type-1 Diabetes, Modelling.

Background: The risk of hypoglycaemia is still a limiting factor of achieving near-normoglycaemia in Type 1 Diabetes (T1D). Several glucose dynamic models have been proposed and proven to be useful in tackling various aspects and physiological responses in T1D research. However, counterregulatory response to hypoglycaemia has not been adequately addressed to date, although hypoglycaemia is a common scenario in T1D management. Dalla Man et al. [14] propose a grey-box approach by defining a risk function associated to a paradoxical auto-potentiation of hypoglycaemia, as part of the UVA/Padova v3.2 simulator's maximal model. In this work, physiological models describing counterregulatory response during hypoglycaemia through adrenaline and free fatty acid (FFA) dynamics are sought. Due to model tractability, minimal model approaches are considered, such as the extension of the widely-used Bergman minimal model [15], to which extensions considering meal intake [16], exercise [17] and FFA [18] are already available. Methods: Data from two eu-hypoglycaemic clamp studies (with different levels of insulinemia -low and high insulin-) of 12 subjects with T1D were used (total of 24 clamp studies). Bergman minimal model with FFA extension suggested by A. Roy [18] was considered. In the absence of glucagon response to hypoglycaemia in T1D, adrenaline remains as the first line of counterregulatory response. Thus, new model components representing adrenaline secretion and action face to hypoglycaemic levels of glucose were added, including a direct effect on glucose increase and an indirect effect though the influence of adrenaline in the FFA secretion. Regarding the identification process, the model was divided into three unit processes: adrenaline, FFA and glucose. For each of them, the parameters' values from individual data were estimated with a forcing function strategy. The global optimization algorithm CMA-ES [19, 20] was used for the parameters estimation of each unit. A least-square-error function was considered as the cost function to be minimized. The goodness-of-fit was assessed by the coefficient of determination (R2), MAPE and RMSE.

Results: The proposed extended model successfully captured the FFA, adrenaline and glucose dynamics during the eu-hypoglycaemic clamp. The goodness-of-fit of glucose profile during the whole clamp was R2(%)= 88.30±8.20%; and during hypoglycaemic range,

89.10±7.31%. Moreover, the average MAPE(%) of 5.65±2.06 and the average RMSE(mg/dL) of 5.25±1.83 demonstrate an accurate estimation results. Comparing the results of our approach with the Bergman minimal model, improvements have been proved during hypoglycaemic phase: average R2(%) across the subjects was 89.10±7.31%. vs 30.35±6.54% without the model extension. Indeed, this difference was statistically significant during hypoglycaemia (p=0.028).

Conclusions: A model of counterregulatory effects on plasma glucose dynamics was developed. Based on the eu-hypoglycaemic clamp, the extended model is able to reproduce the plasma glucose, FFA and adrenaline concentrations in response to hypoglycaemic glucose concentrations. Inclusion of the adrenaline effect in FFA secretion, which affects indirectly the glucose production; and, the direct influence of adrenaline concentrations in glucose level increase made it possible to capture the counterregulatory behaviour during hypoglycaemia and reproduce the glucose hypoglycaemic profiles.

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MULTI-LEVEL MODELLING OF DIABETES FOR IMPROVED TREATMENTS AND UNDERSTANDING

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Keywords: Diabetes, Multi-level modelling.

Type 2 diabetes and obesity are important precursors for a multitude of complications, perhaps most importantly in the cardiovascular system. These diseases are caused by malfunctions in a complex web of interacting factors. To bring order in this complexity, we have for the last 10+ years closely integrated experiments with mathematical modelling, to first test and refine mechanistic hypotheses for specific sub-systems, and then integrate the approved mechanisms as pieces in an ever-growing puzzle for the big picture. The resulting model is dynamic, evolving, and interactive, meaning that we can add and replace new pieces of information as they appear, and that we can probe patient-specific versions of our model to see how it responds to treatments, drugs, and diets, on both the intracellular, organ, and the whole-body level. The model has won awards in diabetes communities, and is used by several drug development companies. In the presentation, I will go through both the usage and structure of the model, as well as some of the methodological advances that has been necessary for acquiring the model's high usefulness.

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