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IFAC PapersOnLine 51-1 (2018) 289–294

Physiological Models and Control for Type 1 Diabetes Mellitus: A Brief Review

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Abstract: The regulation of blood glucose in Type-1 Diabetes Mellitus (T1DM) patient is being extensively investigated by researchers. This research, therefore, has contributed to the development of many glucose-insulin mathematical models, which at some level successfully mimic the physiological behaviour of the human body. These mathematical models describe the dynamics of glucose in the presence of insulin in the body. One the most important factors affecting the glucose-insulin dynamics is meal intake. Hence, augmenting glucose-insulin dynamics with meal dynamics is very important. Augmented mathematical models have many patient specific physiological parameters which are difficult to estimate. Thus, there is a need to check for the identifiability of the parameters and hence there is a need to identify and estimate these parameters. The most fundamental research, which goes into automation of insulin infusion into the T1DM patient is the development of control algorithms. In this paper, a brief review on some of the important augmented models, identification, parameter estimation and existing control algorithms are presented. For the development of Artificial Pancreas System (APS) integration of glucose sensor is an important issue which in turn introduces sensor noise in the measurement, thereby leading to model imperfection. This paper further discusses the design of control algorithms in the presence of such noises and various other disturbances.

Keywords: T1DM, Glucose-Insulin models, parameter estimation of glucose-insulin dynamics, glucose-insulin control, Glucose sensor error.

1. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) occurs due to the autoimmune destruction of the pancreatic beta cells and consequently, the T1DM subjects rely on mandatory external insulin infusions for survival as mentioned in Daneman (2006). Glucose levels are tightly regulated within a normal range of $70 - 110 mg/dl$ in a healthy individual. However, in T1DM subjects the glucose level remains at a very high value due to a small amount of insulin in the body. Serious health problems related to diabetes were highlighted in Arnold (2005) which mentions that negligibly small amount of insulin secretion in the body causes hyperglycemia (blood glucose level above the normal range), which leads to long-term health complications, such as loss of vision, neural disorders, renal failure, etc. Contrarily, an excess of insulin causes severe hypoglycemia (blood glucose level below the normal range) that may lead to coma and other serious health complications. Hence it is of utmost importance to maintain acceptable insulin and blood glucose levels in T1DM subjects. The problem of blood glucose regulation in insulin-dependent diabetic patients is categorized as the open-loop control that comprises of multiple daily insulin injections and closed-loop control via Artificial Pancreas System (APS) as stated in Krzymien et al. (2016). The APS, as reviewed in Haidar (2016), is a wearable device that comprises of a continuous glucose measuring (CGM) sensor, a control algorithm, and a continuous subcutaneous insulin infusion (CSII) pump, required for accomplishment of tight glucose control in T1DM subjects as depicted in Fig. 1. Based on the glucose measurements provided by the CGM sensors, the control algorithm calculates the required insulin dosage which is infused via the CSII pump in the blood. Some of the important advantages of APS over open-loop control are as follows: (i) Improvement in glycemic control in terms of glycated haemoglobin A1c (HbA1c) concentration, and a reduction in hypoglycemia. (ii) Automatic changes in the basal insulin infusion rate at the time of exercise without any extra high-carbohydrate intake.

This paper aims to review important mathematical models and control algorithms currently being used for APS. Section 2 throws light on four important gluco-regulatory models and their major variants. Section 3 discusses structural identifiability and parameter estimation required for the mathematical models. Section 4 presents a brief survey the different control algorithms used in APS.

2. GLUCO-REGULATORY SYSTEM MODELS

The endocrine hormones: insulin and glucagon, are the primary regulators of the blood glucose regulatory system

⋆ This work was supported by funding from IMPRINTS, MHRD, Government of India.

10.1016/j.ifacol.2018.05.077

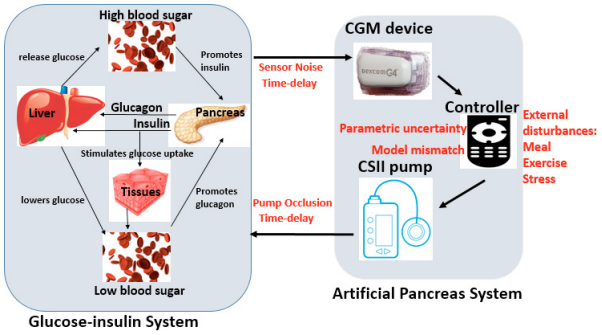

Fig. 1. Graphical representation of glucose-insulin regulatory system integrated with Artificial pancreas system

illustrated in Fig. 1. An increase in the blood glucose level stimulates insulin secretion by the pancreatic beta cells that enhances the glucose utilization in the liver and tissues. In the reverse case, when blood glucose level falls below the basal value, glucagon is released into blood plasma as glucose as mentioned in Farmer et al. (2008). This physiological process has been mathematically modelled and many of these control-oriented mathematical models prove to be helpful in visualizing this complex system.

This section aims to review the important features of different control-oriented models used in APS. A majority of these mathematical models are essentially compartmental models, that describe various physiological events in terms of a series of interconnected compartments. The single-hormone pharmacokinetic (PK) models (only insulin is considered), comprise of the absorption and clearance kinetics as well as compartments related to the elimination and absorption of glucose and insulin. The glucose-insulin regulatory system dynamics can be decomposed into various sub-dynamics such as: (i) plasma-glucose dynamics, (ii) insulin action dynamics, (iii) insulin absorption dynamics and (iv) meal absorption dynamics. The intravenous models include only the plasma-glucose dynamics,the insulin action dynamics and the meal absorption dynamics, while the subcutaneous models include all of them.

2.1 Minimal Model and its Variants:

One of the most widely used nonlinear models describing the glucoregulatory system based on IVGTT, was developed by Bergman et al. (1979) and is popularly known as the Bergman Minimal Model. It comprises of the plasma glucose dynamics represented by equation (1) that accounts for the glucose kinetics, the insulin action dynamics given by equation (2) representing the delayed action of insulin on glucose(remote compartment insulin), and the plasma insulin dynamics given by equation (3).The meal absorption dynamics given by equation (4), represents the appearance of glucose in the plasma after ingestion of a meal.

$$\dot{G}_p(t) = -p_1[G_p(t) - G_b] - R(t)G_p(t) + D(t) \quad (1)$$

$$\dot{R}(t) = -p_2 R(t) + p_3[I_p(t) - I_b] \quad (2)$$

$$\dot{I}_p(t) = -p_4[I_p(t) - I_b] + \gamma[G_p(t) - h]^+ t \quad (3)$$

$$\dot{D} = -p_5 D(t) \quad (4)$$

where G_p, R and I_p represent the plasma glucose,the remote insulin and, the plasma insulin concentrations, respectively. G_b and I_b represent the basal glucose and basal insulin concentrations which correspond to the G_p and I_p values at steady-state.D represents the rate of glucose appearance in the plasma. p_1,p_2,p_3 and p_4 represent the model parameters whose details are provided in Bergman et al. (1979). The term $\gamma[G_p(t) - h]^+ t$ in equation (3) refers to the internal self regulatory pancreatic action, that is negligible in T1DM subjects. Several modifications have been made to the minimal model. One of the most significant modifications was the addition of glucose infusion or meal disturbance input in the glucose kinetics and replacing the pancreatic function term by exogenous insulin infusion, $u(t)$ in the plasma insulin dynamics, as reported by Ollerton (1989). The subcutaneous glucose dynamics was introduced in Lynch and Bequette (2002) by inserting an additional subcutaneous glucose dynamics to the modified minimal model by Fisher. The subcutaneous glucose dynamics is given as:

$$\dot{G}_{sc} = \frac{G_p - G_{sc}}{5} - R_{ut} \quad (5)$$

where G_{sc} represents the subcutaneous glucose concentration and R_{ut} represents the glucose utilization rate in tissues. Roy and Parker (2006) further modified the model to account for the effects of free fatty acids and exercise. Several models have also been developed to describe the dynamics of the subcutaneous infusion of insulin. The delay in the transfer of insulin from the subcutaneous tissue to the plasma was described using compartmental models developed by Kobayashi et al. (1983), Kraegen and Chisholm (1984) and Puckett and Lightfoot (1995).

Hovorka's Model: Another nonlinear compartmental model that finds importance in the development of control algorithms was reported in Hovorka et al. (2002). It consists of a glucose subsystem (glucose absorption, distribution, and disposal), insulin subsystem (insulin absorption kinetics, distribution, and disposal dynamics) and insulin action subsystem. The core glucoregulatory system is represented by (i) plasma glucose dynamics represened by the masses of glucose in the accessible and non-accessible compartments and (ii) insulin action dynamics represented by the effect of insulin on glucose transport, disposal and endogenous glucose production (EGP) respectively. The important nonlinear functions involved in this model represent the insulin-independent glucose fluxes and the renal clearance respectively.

2.2 Dalla Man's Model and its Variants:

A similar pharmacokinetic model with twelve state variables and thirty-five model parameters was developed to describe the sequel of physiological events that occur following meal administration, for both non-diabetic and diabetic patients undergoing a triple tracer meal protocol. The entire dynamics is divided into several sub-systems: (i) glucose subsystem, (ii) insulin subsystem, (iii) liver, (iv) gastrointestinal tract, (v) muscle and adipose tissues, and (vi) β-cells.

The plasma glucose dynamics is represented by a two-compartmental model representing glucose masses in the plasma and rapidly equilibrating tissues. Similarly, the insulin subsystem is represented by two ODEs representing the insulin masses in the plasma and liver. Further, unit process models and forcing function strategies were employed to derive the mathematical equations representing the physiological connections for endogenous glucose production (EGP), glucose rate of appearance (meal disturbance), glucose utilization, and insulin secretion dynamics.A detailed explanation of the dynamics can be found in Dalla Man et al. (2007b).

This model has proven to be a very successful model till date as it has been fit to a large database of normal as well as T1DM subjects.Dalla Man et al. (2007a) have included the model for development of a software named GIM.The model was also incorporated in the popular T1DM simulator (UVA/Padova Simulator), developed by Kovatchev et al. (2009). This simulator was approved by the Food and Drug Administration (FDA) and is widely used as a substitute for animal trials. León-Vargas et al. (2015) included sinusoidal variations of 20% amplitude and time period of 19 and 29 hours, to account for intra-patient variability in the UVA/Padova simulator model.

Sorensen's Model and its Variants: Foster et al. (1973) developed a physiological model considering glucose-compartment for blood, muscle, and liver, and considering different compartments each for insulin, glucagon, and free fatty acids.It comprises of twenty-one state variables with twenty-two metabolic functions as well as six compartments for different organs including the lungs, heart, brain, gut, liver, kidney and peripheral tissues. The model was modified by Guyton et al. (1978), where a central organs compartment is added to the glucose sub-system, that includes diffusion in glucose transport, and an advanced insulin secretion dynamics.Sorensen (1985) further updated the model by providing a detailed mathematical explanation.Parker et al. (1999) modified the model by including (i) meal disturbance, and (ii) parameters for uncertainty analysis, resulting in a nineteenth order model wherein the glucose sub-system is divided into six more sub-systems while the insulin sub-system has a similar structure as before.

3. STRUCTURAL IDENTIFIABILITY AND PARAMETER ESTIMATION

Knowledge-driven lumped minimal models do not essentially resemble the glucoregulatory system at various levels of body such as tissues and/or organs. To mimic the complex glucoregulatory system, comprehensive knowledge driven models are required, which generally possess many parameters relating to physiological process. These parameters must be physiologically defined and determined (or estimated) in order to practically apply the model for further analysis. Identifiability analysis is the most critical step in parameter estimation process. This analysis focuses on the possibility of uniquely identifying model parameters with the help of given data. Once the details of identifiability of model parameters are known, parameter estimation can be carried out. Unique identification of model parameters depends on various factors such as (i) model formulation, (ii) data collection of various physiological states (like blood glucose level, plasma insulin concentration, rate of meal digestion etc.),(iii) type of clinical test incorporated (like IVGTT, OGTT, euglycemic hyperinsulinemic clamp test etc) and (iv) time sampling of data or observations.

Identification of various type-1 diabetic models has been carried with data such as blood glucose concentration and/or plasma insulin concentration, obtained from various clinical tests. These clinical test must be performed (with possible modification in clinical test procedure) in such a way that obtained data is adequate in estimating parameters uniquely. As mentioned by Galvanin et al. (2009), physiological parameters in Bergman minimal model are uniquely identifiable with a modification of IVGTT clinical test procedure. Yang et al. (1987) suggests that continuous intravenous insulin infusion as opposed to insulin bolus in IVGTT improves estimates of the model parameters. Galvanin et al. (2009) using modified test protocol estimated Hovorka-Wilinska model. Chin and Chappell (2011) using concepts in structural identifiability on the original minimal model and extended minimal model reported that extended minimal model is globally structurally identifiable when both insulin and blood glucose concentration levels are known.

Watson et al. (2011) proposed a general glucose homeostatic model on an argument that insulin secretion takes place in three phases, resembling proportional-integral-derivative (PID) type controller used in applied control theory. And the model successfully relates to the biological mechanism of the gluco-regulatory system. Structurally identifiability analysis on this model showed that two parameters are unidentifiable i.e. rate of glucose production and rate proportional gain coefficient when IVGTT was conducted. And it was also suggested that glucose production rate can be identified from tracer experiment and proportional control gain can be identified as mentioned in Watson et al. (2011).

4. CONTROL ALGORITHMS

Automation of insulin infusion into the T1DM patient is the main aim for the development of control algorithms. The specific features of the control algorithms and controller tuning strategies in APS are discussed in De Nicolao et al. (2011). Here we highlight the challenges in algorithm development for APS, along with a brief review of all the control algorithms reported in the literature. The significant challenges that controllers used in APS face are stated as follows:

4.1 Proportional Integral Derivative Controllers

Proportional-Integral-Derivative (PID) controller accounts for the most dominant linear control strategy in APS that has been designed both in in-silico and in-vitro environment. Steil et. al developed PID controllers for APS in Steil et al. (2002) and Steil et al. (2004). In Renard (2002) and Renard et al. (2002), PD control algorithm is designed for T1DM subjects where three meal disturbances are considered. Chee et al. developed PI and PID controllers for critically ill patients in Chee et al. (2003a) and Chee et al. (2003b) respectively where insulin was infused intravenously based on subcutaneous glucose measurements. A

robust PID was designed in Ramprasad et al. (2004) based on Sorensen's and Parker's models where both single and multiple meals are considered.

Advanced PID technique with a switching strategy, time-varying reference and noise and derivative filters for sensor noise attenuation were reported in Marchetti et al. (2008). The safety and efficacy of the PID with insulin feed-back strategy were tested in Ly et al. (2017) that is used in the Medtronic hybrid closed-loop system. A model-free intelligent PID controller was designed and validated on UVA/Padova metabolic simulator in MohammadRidha et al. (2017).

4.2 Model Predictive Controllers

The inherent properties of the model predictive control (MPC) such as constraint handling, an optimal control signal, and flexibility to include different types of objectives, make it one of the most preferred controllers for incorporation in APS. Various developments in MPC applied to APS can be found in Bequette (2013), and hence only some recent works are discussed here. A novel zone-MPC approach with the introduction of asymmetric input costs in the objective function was reported in Gondhalekar et al. (2016). In Messori et al. (2016), MPC was employed to two patient-specific linearized model from UVA/Padova simulator data via two novel identification procedures (i) kernel-based non-parametric approach, and (ii) a constrained optimization based grey-box identification technique. A comparative study of single-hormone and dual-hormone MPC was conducted in Resalat et al. (2016), where the authors developed a switching dual-hormone MPC that avoided continuous glucagon delivery causing nausea.

A robust MPC for automatic glucose control was developed in Schaller et al. (2016), where the robustness to uncertainties was introduced via PID-based offset control. A novel methodology combining individualized MPC, a state estimator and an open-loop optimization problem subjected to constraints was proposed in Zavitsanou et al. (2015).

4.3 Robust Controllers

An output feedback based robust H-∞ controller was proposed in Mandal et al. (2014) in an LMI framework where meal disturbances were considered deterministic while the actuator and sensor were considered stochastic. A novel approach of H-∞ control based on an identified control-relevant model, along with an insulin feedback loop and a safety mechanism was proposed in Colmegna et al. (2014) to avoid hyperglycemia and hypoglycemia in the presence of parametric uncertainty and meal disturbance.

An internal-model based SMC with feed-forward meal compensation was proposed in Abu-Rmileh et al. (2010) where identification of a first order transfer function with delay was done using data from Dalla Man's model. A similar control configuration, based on SMC with Smith predictor structure was reported in Abu-Rmileh and Garcia-Gabin (2011), and wienner-SMC was proposed in Abu-Rmileh and Garcia-Gabin (2012). A fusion of nonlinear back-stepping and SMC approach was adopted in Parsa et al. (2014) was designed based on the minimal model. To address the problems related to chattering in the control signal in classical SMC, a super-twisting controller was proposed in Ahmad et al. (2017) for the minimal model of T1DM subjects.

4.4 Adaptive controllers

Most of the adaptive control algorithms are based on empirical models and have parameter estimation schemes inherent to their control design. As discussed in Turksoy and Cinar (2014), the important variants of adaptive control schemes ranging from minimum variance control and self-tuning regulator (STR) that had been designed mostly rely on a linear model identification and recursive parameter estimation strategy. A comparative study of STR with MPC and PID were reported in Goh et al. (2008), where STR proved to be superior to the other controllers due to the indirect adaptive algorithm incorporated in it. In order to take to account for the large fluctuations in G_p due to meal, stress, and exercise, a change detection method to conduct the unknown model parameter estimation using RLS for STR with a forgetting factor was proposed in Eren-Oruklu et al. (2008). An adaptive method to vary the forgetting factor was incorporated in the RLS based STR control scheme in Turksoy et al. (2014).

Generalized Predictive Control (GPC) based on dual-hormone subcutaneous T1DM models where the outputs are predicted for a future time horizon and the control actions are taken via minimization of an objective function, were designed and validated through clinical trials in pigs El-Khatib et al. (2007) and humans in El-Khatib et al. (2010). GPC designed on subcutaneous ARMA model that comprised of smith-predictor for delay compensation outperformed LQG controllers as reported in Eren-Oruklu et al. (2009).

5. CONCLUSION

Advancements in development of knowledge-driven blood glucose dynamic models have been reviewed briefly in this article. An overview of the important control oriented meal models and a brief discussion on insulin dynamics has been provided. Developed mathematical models posses various physiological parameters, hence these parameters must be checked for their unique identifiability and subsequently estimated using parameter estimation techniques. This paper has also touched upon various work that has been carried on identifiability and parameter estimation. This is followed by a detailed review of the recent control algorithm development specific to APS. The review shows that in many cases, the development of control algorithms involve realization of control-oriented models from the physiological model either by linearization or using the model data. It can be inferred from the discussion that a successful control algorithm for APS requires a good control oriented model from which the control law can be easily derived, a state/parameter estimation scheme for updating the control law to cope with various uncertainties. The control-oriented model should provide a good trade-off between accuracy and complexity involved in the physiological models, whereas the control algorithms must

have a high degree of robustness against parametric uncertainties. Future research must be done to include more sophisticated and advanced control algorithms that have additional features like fault detection, noise cancellation, and other safety schemes.

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