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Model Predictive Control of Type 1 Diabetes ⋆

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Abstract: The paper presents an overview of the most important elements for the synthesis of a Model Predictive Control (MPC) algorithm for the development of an Artificial Pancreas (AP). Three possible control schemes for meal compensation are described and compared. MPC individualization is discussed through different solutions. Of paramount importance, for a realistic in-silico test, is the use of the population simulator, that has been accepted by the Food and Drug Administration (FDA) as a substitute of the preclinical animals studies. The concepts and techniques described in the paper are the core of the AP algorithm that has been used in the last 4 years during about 4000h of clinical experiments.

Keywords: Model Predictive Control, Diabetes, Simulator, Individualization

1. INTRODUCTION

Diabetes is a pathology that involves glucose regulation and can be divided in two main types: type 1, or insulin dependent, and type 2 or insulin resistant. The first one is characterized by the destruction of the beta cells in the pancreas, responsible for the insulin production, and, as a consequence, by the complete dependency of the patient on external insulin administration. In type 2 diabetic patients, there are an alteration of insulin secretion and a reduction of sensitivity to this hormone. A good glucose regulation, with glucose levels in the range $70-140$ mg/dl, is mandatory for both types of diabetes because low blood glucose levels, *hypoglycaemia*, can lead to coma and, if not treated, to death. Conversely, high blood glucose levels, *hyperglycaemia*, maintained for too long can lead to the long term problems such as cardiovascular diseases, chronic renal failures and retinal damages.

A patient with type 1 diabetes faces a life long behavior-controlled optimization problem: the administration of external insulin to control glycemia enters a stochastic scenario where hyperglycemia and hypoglycemia may not be easily prevented by open-loop therapy. The adjustment of therapy, i.e. basal insulin delivery and pre-meal boluses, on the basis of a few daily fingerstick blood glucose measurements, can be seen as rudimentary way to close the loop. Clearly, the few daily measurements, even if very important, considerably limit the effectiveness of the feedback action. Closed-loop glucose control uses in contrast frequent measurements. This subject has been discussed by numerous research papers since the sixties, and several surveys are now available Bequette [2005], Cobelli et al. [2009].

A new era for the development of the AP starts few years ago with the introduction of commercial subcutaneous (sc) Continuous Glucose Monitoring (CGM) and sc pumps that allow for a noninvasive closed-loop control. The problem of maintaining glucose levels within a predefined range by acting on insulin delivery is a control problem with a number of more or less specific features. The controlled variable is glucose utilization, the measured output is the sc glucose provided by the CGM, and the clinical criterion for success is plasma glucose. There is one control variable, namely the insulin delivered by the sc pump that can be acted upon by either the patient or the control systems to regulate plasma glucose. The system is subjected to disturbances, the most important one being the meals. It is important to note that this disturbance may be announced, approximately known, or even predictable. Such knowledge is routinely exploited in conventional insulin therapy in order to compute pre-meal boluses. Among other disturbance inputs, one may mention physical exercise that is known to acutely increase glucose utilization and chronically modify insulin sensitivity. The dynamics of the system linking sc insulin to sc glucose consist of a cascade of three subsystems: the sc insulin having plasma insulin as output, the insulin-glucose metabolism nonlinear model having plasma glucose as output, and the sc glucose subsystem having sc glucose as output. As a result, sc insulin infusion poses major challenges to control algorithms due to the significant time needed for insulin absorption, diffusion, and action. Such large time delays are relatively inconsequential in a steady (fasting) state, but have a major impact during system disturbances (e.g. meals, exercise). Recently, it has been found that, due to the "smoothing" inherent with sc insulin transport, small 15-minute insulin boluses are indistinguishable from continuous basal rate Chan et al. [2008], which allows designing control algorithms with up

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to a 15-minute actuation rate, an approach that may be superior to the traditional bolus+continuous basal rate in terms of both computational and insulin pump energy efficiency. Further, the effect of meals on plasma glucose is characterized by an absorption delay whose time constant is in the order of hours. Overall, the sc system dynamics is nonlinear and affected by substantial delays, making the design of effective sc closed-loop control algorithms all but a trivial task. In addition, control must also face the significant inter- and intra- patient variability, meaning that it may be virtually impossible to apply the same controller to different patients and that even the same patient may show large variations at different days. Another issue is the presence of intrinsic input constraints, in that the manipulated input variable, e.g. insulin, is nonnegative. Moreover, there are also output constraints on the controlled variable in that plasma glucose should never go below a hypoglycaemia threshold, e.g. 60 or 70 mg/dl. On the other hand, in order to prevent long-term complications, hyperglycemia should be avoided as well. Finally, it is important to realize that closed-loop control is not without risks. For instance, in presence of hyperglycemia following a meal the regulator is likely to react by delivering more insulin, whose effect will not be immediately apparent due to intrinsic system delays. Then, insulin given in excess and too late may act when meal effect has ceased, so that hypoglycemia becomes unavoidable even if the insulin pump is shut off.

The paper presents an overview of the most important elements for the synthesis of a MPC algorithm for the development of an AP. After a brief description of the conventional therapy for a type 1 diabetes that is the starting point for the development of an AP, different MPC control schemes are discussed. Then three possible control schemes for meal compensation are described and compared. In Section 5 a simulator of a population of type 1 diabetes, that has been accepted by the FDA as a substitute of the preclinical animals studies, is described. Finally the key point of MPC individualization is discussed through different solutions. The concept and techniques described in the paper are the core of the AP algorithm that has been used in the last 4 years during about 4000h of clinical experiments inside the projects promoted and founded by the JDRF, NIH, MIUR and EU.

2. CONVENTIONAL THERAPY

The conventional therapy addresses glucose regulation by a mix of piecewise constant insulin infusion, also called *basal insulin*, and impulse-like injections that are made just before meals to prevent excessive rises of blood glucose also called *insulin bolus*. In absence of meals, the basal insulin, which varies from patient to patient, would eventually bring blood glucose to a steady-state value, called *basal glucose*. Pre-meal boluses are self administered assuming that occurrence and size of the upcoming meal are known in advance (meal announcement). The amount of the insulin bolus is scaled to the meal size through a constant, specific to each individual, called carbo-ratio.

3. MODEL PREDICTIVE CONTROL

In recent years MPC has emerged as the most promising approach to glucose control. Different approaches are characterized by the model, the cost function, and the constraints. The model can be linear or nonlinear, continuous-time or discrete-time, state-space or input-output, black-box, grey-box or white-box. The cost function usually, but not necessarily, is a quadratic penalty on future deviations of the output from the setpoint y_0 and includes also a quadratic penalty on future control actions that can be the difference of the input u with respect to a reference u_0 or the variation along the time $u = u(k) - u(k-1)$. Finally, there may be constraints on the manipulated variables (insulin delivery rates by the pump is greater or equal than zero and less than some maximal value) and also on the controlled ones (glycemia in the admissible range).

Nonlinear Model Predictive Control can rely directly on insulin-glucose complex models or minimal models (nonlinear black-box models, e.g. Nonlinear ARMAX, can be considered as well). Significant inter and intra variability and the limited information available of the patient under control are an important limitation for the use of complex nonlinear models. This and the inherent computation complexity, at the moment, preclude the adoption of NMPC within commercial devices, for both engineering and regulatory reasons. NMPC is however of particular interest as a touchstone for other simpler MPC schemes. A study has indeed demonstrated a distinct improvement over linear MPC Magni et al. [2009b]. Few experiments on real patients using NMPC have also been performed Hovorka et al. [2004], Schaller et al. [2006]. The need for an individual model has been overcome, in this case, by on-line recursive identification of model parameters within a Bayesian setting. Given that experimental data alone may not guarantee parameter identifiability, the Bayesian priors play a key role.

Linear Model Predictive Control (LMPC) uses an approximate linear model of the insulin-glucose dynamics, which produces a substantial algorithmic simplification. The linear model can have different sources. For instance, it may be obtained from the linearization of a more complex nonlinear average patient model around a suitable working point; however such an approach would suffer from the lack of individualization. To overcome this limitation, one possibility is to resort to black-box identification of an individual patient model from data collected on the same individual subject to conventional therapy. In practice, time series of insulin, CGM data and meal information are used to identify an ARMAX model with two inputs (sc insulin and meals) and one output (sc glucose). A necessary condition to ensure good identifiability properties of ARMAX models is the so-called persistent excitation property of input signals, which should not be collinear between each other and whose spectrum should excite an adequate number of frequencies. Unfortunately, the meals and insulin boluses of the conventional therapy turn out to be collinear and, due to this lack of excitation, the identification algorithm may even fail to correctly estimate the sign of the gains from insulin and meals to sc glucose Finan et al. [2009]. As a remedy, it has been proposed to use splitted and/or delayed insulin boluses so as to improve

the joint excitation properties of the inputs Finan et al. [2009], Magni et al. [2009a]. Conversely, in Soru et al. [2012], the possibility of identifying an individual model from everyday's real life data is investigated. Even if the model is linear the control law can be linear or nonlinear if constraints are explicitly considered or not. The improvement that can be obtained by considering the constraints in the optimization problem is related to the quality of the model. In fact if the model is not accurate then nominal state constraints satisfaction does not guarantee the same property for the real system and on the contrary unfeasible optimization problem can occur even if a feasible solution exist for the real patients. Unconstrained MPC has the advantage to have an explicit linear closed-loop solution. If justified by a relevant performance improvement however also constrained LMPC could be considered for a commercial embedded solution either with an explicit solution or by computing on line the optimal solution via quadratic programming methods. It is unlikely that the first commercial realizations of an artificial pancreas will include overly complex computational algorithms. This motivates the interest for the simplest possible LMPC scheme, which is input-output unconstrained LMPC complemented with a safety layer where some constraints, based on future glucose or Insulin-On-Board, are added to the MPC control law a posteriori Ellingsen et al. [2009], Lee et al. [2009]. The use of an input-output model, instead of state-space model, alleviates the need for a state observer, which is a further simplification. A clinical trial on 20 patients has been carried out using the unconstrained LMPC proposed in Magni et al. [2007], showing a five-fold reduction of nocturnal hypoglycemia episodes and an improvement of overnight percent time within the target range of 70-140 mg/dl, with respect to conventional open-loop control Kovatchev et al. [2010]. Generalized Predictive Control (GPC) has been experimented on diabetic swines using both insulin and glucagon as inputs El-Khatib et al. [2007], El-Khatib et al. [2010].

3.1 Unconstrained Linear Model Predictive Control

In this section the MPC control algorithm described in Soru et al. [2012] is presented. It is a Linear Model Predictive Controller (LMPC) law that uses a linear discrete time model to predict future outputs (subcutaneous glucose) as a function of an input (subcutaneously injected insulin) and a disturbance (meal consumption). This model can be written in the following form:

$$\begin{cases} x(k+1) = Ax(k) + Bu(k) + Md(k) \\ y(k) = Cx(k) \end{cases} \tag{1}$$

where

- $x(k) \in R^n$, is the state;
- $y(k) = CGM(k) - G_b$ (mg/dl), is the difference between the subcutaneous glucose and the basal value (G_b);
- $u(k) = i(k) - u_b(k)$ (pmol/kg), is the difference between the injected insulin and its basal value, that could be time varying. The insulin is normalized by the patient weight;
- $d(k)$ (mg), represents the meal.

Thereafter, it is assumed that the triplet (A, B, C) is both stabilizable and detectable.

The LMPC algorithm uses this model to predict the future glucose profile given the carbohydrates and insulin taken in by the patient. Based on this prediction it is possible to find the optimal profile of the future insulin administration, according to the following cost function

$$\begin{aligned} & J\left(x(k), u(\cdot), k\right) \\ & = \sum_{i=0}^{N-1} \Big(q\left(y(k+i) - y_o(k+i)\right)^2 \\ & \quad + \left(u(k+i) - u_o(k+i)\right)^2 \Big) + \|x(k+N)\|_P^2 \end{aligned} \tag{2}$$

where q is a positive scalar weight to be tuned by the user, N is the prediction horizon. Moreover, $||x(k+N)||_P = x(k+N)'Px(k+N)$, where P is a nonnegative definite matrix, e.g the unique nonnegative solution of the discrete time Riccati equation

$$P = A'PA + qC'C - A'PB\left(1 + B'PB\right)B'PA$$

and

- $y_o(k) = \tilde{y}(k) - G_b$ (mg/dl), is the difference between the reference value ($\tilde{y}$) of the subcutaneous glucose and the glucose and the basal value (G_b);
- $u_o(t) = \tilde{u}(k) - u_b(k)$(pmol/kg), is the difference between the reference value ($\tilde{u}$) of the insulin profile and the insulin basal value (u_b).

In order to avoid on-line optimization or the computational and memory burden of an explicit MPC for constraints systems, the proposed algorithm does not include constraints. Hence, it is possible to calculate the following closed form solution exploiting the Lagrange formula and the Receding Horizon principle:

$$\begin{aligned} u^{MPC}(k) = & \left[\, 1 \;\; 0 \;\cdots\; 0 \,\right] \\ & \left(-K_x x(k) - K_d D(k) \right. \\ & \left. + K_{Y_o} Y_o(k) + K_{U_o} U_o(k)\right) \end{aligned}$$

where the reference vectors are

$$Y_o(k) = \left[\, y_o(k+1) \ldots y_o(k+N-1) 0 \quad \right]'^{1\times(N-1+n)}$$

$$U_o(k) = \left[\, u_o(k) \ldots u_o(k+N-2) u_o(k+N-1) \quad \right]'$$

and the vector of future meals

$$D(k) = \left[\, d(k) \;\ldots\; d(k+N-2) \;\; d(k+N-1) \,\right]'$$

The state $x(k)$ of the model in general is not measurable. To circumvent this problem, in Magni et al. [2007] the use of a non minimal state-space realization of the input-output model was proposed, whose state is made by past input and output values. However, also in this case, just noisy measures of the output (the subcutaneous glucose concentration) would be available with the consequent impact of sensor noise on the closed-loop performance. The use of a Kalman Filter, exploiting the knowledge included in the model and the past injected insulin, can help to improve the quality of the information provided to the LMPC algorithm.

4. MEAL COMPENSATION

An essential feature of glucose control in diabetic patients is the need of compensating large external disturbances given by the meals. On one side, nocturnal glucose control

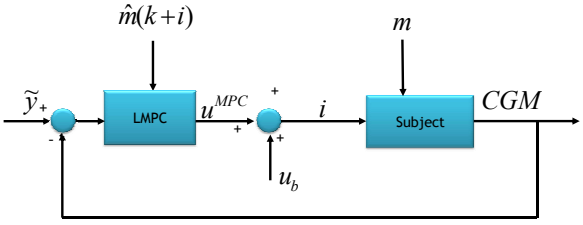

Fig. 1. Basic closed-loop scheme

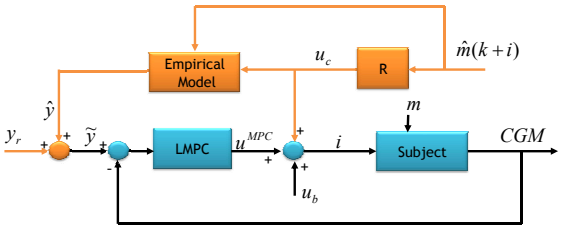

Fig. 2. Closed-loop scheme: MPC with open-loop meal compensation

is a rather standard regulation problem where a constant or slowly varying set-point is to be tracked. On the other hand, meals produce substantial excursions of glycemic values that can be handled only by injecting sufficient insulin in a relatively short time window. The conventional therapy considers these two different situations by means of the basal insulin administration throughout the day and with the insulin boluses at meal times. The boluses are computed on the predicted meal amount. The use of knowledge on an external disturbance in order to compensate in advance for its effects is a feedforward action. In real life, however, because both the patient dynamics and presence and size of external disturbances are far from being perfectly known, there is the need of corrections that must be based to the actual patient state. In the conventional therapy, occasional fingerstick glucose measurements are used to trigger corrective actions in order to react to deviations from the nominal profile that the open-loop control is expected to produce. This gives rise to a kind of feedback control scheme. However, few daily measurements are insufficient to change the nature of a control strategy which relies heavily on feedforward compensation. With the commercial availability of CGM, it has become possible to design minimally invasive closed-loop control schemes based on frequent output measurements. The sc delays present a major stumbling block on the way to a purely closed-loop control strategy: the action of insulin on plasma glucose is subject to significant delays so that effects of reactions to undesired glucose level may arrive too late to prevent hyper- or hypo-glycemic episodes. This problem is further exacerbated by the inherent delay between plasma glucose and the CGM signal.

In principle, if the patient dynamics was perfectly known, the MPC control law should be able to optimize both the feedback and the feedforward control components in the basic control architecture of the artificial pancreas displayed in Fig. 1, where an MPC module uses real time CGM readings and future predicted meals to decide the control action, combining in an automatic way the feedback and feedforward actions. Note that m is the real meal affecting patient's glycemic profile, while $\hat{m}$ is a presumed meal signal, known in advance by the patient, whose knowledge is forwarded to the controller as an announced disturbance d. The inherent delays of the physiological system, the saturation constraints on the insulin pump and the lack of a reliable individual patient model impose intrinsic limitations to the achievable time constant of the closed-loop, so that prompt controller responses may be not compatible with closed-loop stability and avoidance of hypo glycemic events. As a consequence, for the controller it may be impossible to generate the large insulin boluses needed for an effective meal compensation. In particular the availability of an individual meal absorption model is essential for a correct optimization of the feedforward component. A possible alternative, when the model is not sufficiently accurate is to better consider the individual knowledge of the patient included in the conventional therapy. For example, the feedback and feedforward actions can be split Patek et al. [2012], letting the latter be handled by an open-loop scheme inspired by conventional insulin therapy followed by the patient, see Fig. 2. In this scheme, the meals are compensated by the signal u_c generated by the therapeutic rules represented by means of the block R yielding the usual pre-meal boluses. An explicit or implicit patient model is used to compute the expected effect of meal and pre-meal boluses on the glucose profile. The MPC is in charge of feedback compensation so as to track the basal glucose profile, far from meals, and the expected glucose profile $y_r + \hat{y}$, immediately after meals. The feedback action is essential in order to handle exogenous disturbances as well as model and meal uncertainties. This scheme has the merit of incorporating valuable individual knowledge embedded in the consolidated therapeutic practice but suffers from several drawbacks. In fact, the pre-meal boluses are essentially decided according to empirical and static rules and delivered irrespective of real time and historical information coming from CGM measures and past delivered insulin. Another drawback has to do with the need of providing an approximation of the response $\hat{y}$ to the pre-meal bolus u_c. This is usually accomplished by some empirical and rough patient model that might give barely acceptable predictions. When a reliable model of the meal effect on glucose response were available, a possible way to optimize pre-meal boluses without losing the knowledge available in the conventional therapy, would become possible, as illustrated in Fig. 3. The main difference of this last scheme with respect to the one of Fig. 1, is that the conventional pre-meal bolus u_0 acts as a reference for the administration of insulin profile. The other two inputs of the LMPC are the error e between the prescribed set point $\tilde{y}$ and the measured output CGM and the signal d representing a prediction of the next meal. Due to inter- and intra-patient variability, it can happen that scheme 2 (MPC with open-loop meal compensation) may preform better than scheme 3 (MPC with open-loop insulin reference) or vice-versa. Therefore, there is scope for a further hybrid scheme 4, where meal compensation combines the two previous schemes, using the scalar weight α to control the balance between open-

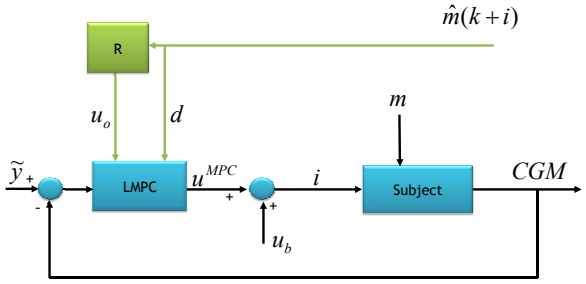

Fig. 3. Closed-loop scheme: MPC with open-loop insulin reference

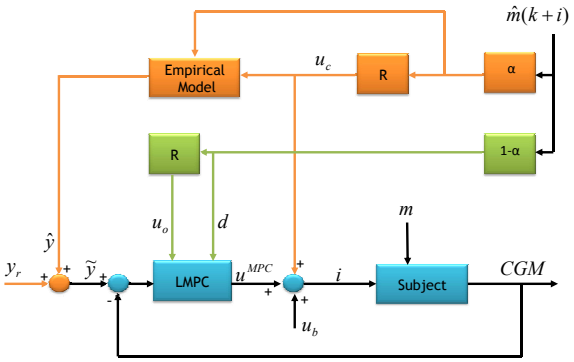

Fig. 4. Closed-loop scheme: mixed open-loop and closed-loop meal compensation

loop compensation and MPC compensation informed by the open-loop reference. In particular, scheme 2 is a particular case of scheme 4 for $\alpha = 1$ whereas scheme 3 is obtained for $\alpha = 0$.

5. SIMULATOR OF A POPULATION OF TYPE I DIABETES

A number of simulation models have been proposed in the last decades and used to assess performance of different control algorithms and different insulin infusion routes (Srinivasan et al. [1970], Cobelli et al. [1982], Cobelli and Mari [1983], Salzsieder et al. [1985], Carson and Cobelli [2001], Lehmann and Deutsch [1992], Andreassen et al. [1994], Hovorka et al. [2004]. However, all the above models are average population models and as a result they are only able to predict the average population dynamics, but not the inter-individual variability. The average-model approach is not realistic for in silico experimentation. To this purpose, it is necessary to have a diabetes simulator equipped with a cohort of in silico subjects that spans sufficiently well the observed inter-person variability of key metabolic parameters in the type 1 diabetes population. The knowledge on the variability is indeed crucial to design robust controllers and provide valuable information about their safety and limitations.

Recently, and building on the large scale model developed in the healthy state Dalla Man et al. [2007], a type 1 diabetes simulator have developed which, thanks to its ability to realistically describe inter-subject variability, has been recently accepted by FDA as a substitute of pre-clinical animal trials for certain insulin treatments Kovatchev et al. [2008].

5.1 The Model

The model has a glucose and an insulin subsystems linked by control signals. The glucose subsystem consists of a two compartment model of glucose kinetics: insulin-independent utilization occurs in the first compartment representing plasma and fast equilibrating tissue, while insulin-dependent utilization occurs in a remote compartment which represents peripheral tissues. Insulin subsystem also consists of two compartments, the first representing the liver and the second the plasma. The most important model unit processes are endogenous glucose production, gastro-intestinal absorption and utilization. Suppression of endogenous glucose production is assumed to be linearly dependent on plasma glucose concentration, portal insulin concentration and a delayed insulin signal. To describe glucose transit through the stomach and intestine, the model assumes that the stomach is represented by two compartments (one for solid and one for triturated phase), while a single compartment is used to describe the gut; the rate constant of gastric emptying is a nonlinear function of the amount of glucose in the stomach. Glucose utilization during a meal (both insulin-independent and -dependent) is made up of two components. Insulin-independent utilization in the brain and erythrocytes takes place in the first compartment and is constant; insulin-dependent utilization in muscle and adipose tissue takes place in the remote compartment and depends nonlinearly (Michaelis-Menten) from glucose in the tissues. Since in type 1 diabetes insulin is only exogenously administered by a subcutaneous (sc) injection of insulin analogues, a model of subcutaneous (sc) insulin kinetics and absorption is also incorporated. The model includes a two-compartment model approximating nonmonomeric and monomeric insulin fractions in the subcutaneous space, which can serve as a base for the translation of the insulin signal from the pump to insulin in the circulation. Finally, if glucose is measured using a CGM systems, the delay introduced by the plasma-to-interstitium dynamics can be described by a single compartment model. Sensor error is also described to provide realistic CGM measurements. In summary, the model consists of 13 differential equation and 35 parameters (26 of which are free and 9 derived from steady state constraints).

5.2 The Population of Virtual Patients

The above described model is rather complex and its identification requires the availability of plasma glucose and insulin concentrations and of major metabolic fluxes, measurable with multiple tracer protocols. However, even single-tracer studies in type 1 diabetes are scarce. Data from triple tracer meal experiments exist in 204 healthy adults Basu et al. [2006]. Therefore, the sub-models describing glucose kinetics and utilization, production and transit through the gastrointestinal tract, and insulin kinetics have been identified in the healthy state by a system

decomposition and forcing function strategy Dalla Man et al. [2007]. In order to obtain parameter joint distributions in type 1 diabetes from those in the adults healthy state, it is assumed that the inter-subject variability was the same (same covariance matrix), but certain clinically-relevant modifications were introduced in the average parameter vector, for instance basal endogenous glucose production is higher in type 1 diabetic compared to normal subject. Similarly, parameter distribution in different populations, such as type 1 diabetic children and adolescents can be obtained from that of type 1 diabetic adults by introducing certain clinically-relevant modifications in the average parameter vector, for instance insulin sensitivity is higher in children and lower in adolescents compared to adults. A large number of subjects can be generated in each population, by randomly extracting different realizations of the parameter vector from the appropriate joint parameter distribution.

5.3 The Simulator

The type 1 diabetes simulator is equipped with 100 virtual adults, 100 adolescents and 100 children, spanning the variability of the T1DM population observed in vivo. In January 2008 the simulator has been accepted by the FDA as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas studies, and has been adopted by the JDRF Artificial Pancreas Consortium as a primary test bed for new closed-loop control algorithms.

6. MPC INDIVIDUALIZATION

When controlling physiological systems, two major issues are the inherent inter-individual variability and the limited amount of information that can be gathered on the single subject under control. Hence, the importance but also the difficulty of controller individualization, that should ensure the needed flexibility without compromising simplicity and robustness. For this reasons, attention is focused on few but essential design choices, keeping fixed the less critical ones. The control horizon N is a value compatible with the maximum time constants of the insulin-glucose system for all patients. Controller individualization is obtained by tailoring the model and/or the cost function to the patient. As a matter of fact there are three main elements that can be individualized. First of all, there is the linear model used for synthesizing the MPC regulator. Ideally, such model should reflect the individual patient dynamics although sufficient information to derive an accurate individual model may be difficult to obtain. The second element is given by the reference signals u_o and y_o appearing in the cost function. With reference to scheme 4, a suitable choice, adopted in Soru et al. [2012], is to select profiles associated with the nominal/desired courses obtained under conventional pre-meal boluses. A third element that can be individualized is given by the weights of the cost function. For the sake of simplicity, only the scalar q is hereafter considered since it directly affects the aggressiveness of the controller and, hence, the trade-off between sluggish control and the risk of hypoglycemic episodes induced by insulin spikes delivered by an exceedingly sensitive regulator.

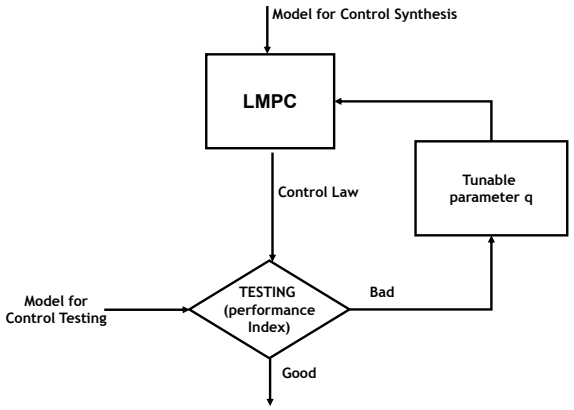

Fig. 5. Control Design Procedure

6.1 Calibration Procedure

The tuning of q is done through the iterative procedure described by the flow chart in Fig. 5. The main ingredients are: a performance index, a model for the control synthesis and a model for performance testing.

Concerning the performance index, the goal is to keep the glucose profile close to the reference 110 mg/dl. The testing is performed on an *in silico* experiment following a protocol that specifies meal times and amounts. Larger values of q yields aggressive control that, in view of uncertainty and disturbances, may trigger hypoglycemic episodes. Conversely, small values of q may be insufficient to counter glycemic rises subsequent to meals so that hyperglycemic episodes are more likely. When assessing performance, attention is focused on the worst hypoglycemic episode and the worst hyperglycemic one (without considering the first two hours after a meal). The error associated with the minimum glucose value is defined as $\epsilon_{MIN} = 110 - G_{MIN}$ while the one associated with the maximal glucose value is $\epsilon_{MAX} = G_{MAX} - 110$. Only these two errors are considered and combined to obtain a single index characterizing the whole glucose profile.

The weight given to ϵ_{MIN} is higher with respect to the one given to ϵ_{MAX} because it is more important to avoid hypo than hyper glycemia Kovatchev et al. [2005]. A good metrics can be derived from the Control Variability Grid Analysis (CVGA) Magni et al. [2008] where each profile collapses to a point whose x coordinate is a function of the minimal glucose value and whose y coordinate is a function of the maximal one. It is important to acknowledge that the risk associated with different hypoglycemic states is a linear function of blood glucose whereas the risk associated to hyperglycemic states is a nonlinear function of blood glucose.

Once the performance index has been defined, it is possible to implement the iterative calibration procedure shown in the flow chart of Fig. 5 to obtain the optimal weight.At each iteration the weight q is increased or decreased depending on previous results. As a consequence, at each iteration it is necessary to recalculate the MPC gains and assess the corresponding performance using the model for control testing.

7. FROM *IN SILICO* TO REAL PATIENTS

Mathematical models of glucose metabolism enter the flow chart of Fig. 5 in two distinct steps: control synthesis and control testing. Several control design strategies can be obtained by different combination of models. In Soru et al. [2012], for example, the following models are considered: (i) a non linear and time varying model associated with one particular *in silico* patient, drawn from the 100 patients provided by the Padova-Virginia simulator Kovatchev et al. [2008]; (ii) a linear individual model obtained by linearizing a non linear and time varying model Kovatchev et al. [2008] associated with the average patient, i.e. the patient whose physiological parameters coincide with the average values in the population of patients, around the basal; (iii)a linear model for an individual patient identified from either *in silico* of clinical experimental data.

7.1 Controlling real patients: average model design

In the control synthesis step, the linear individual model obtained by linearizing a non linear and time varying model Kovatchev et al. [2008] associated with the average patient is used for all patients. In view of the remarkable patient inter variability, individual tuning, carried out through the individualization of the cost function, is particularly important.

Unfortunately, the calibration procedure described in the previous section cannot be applied to real patients neither via clinical experiments nor via *in silico* tests. In fact, the former solution would require lengthy and expensive experiments on the patients, while the latter would rely on an individual model of the patient which, as just said, is hardly available. A feasible individualization method, introduced in Patek et al. [2012], is to find a function $f(\vartheta_1, \cdots, \vartheta_2)$ that, given a set of parameters $\{\vartheta_1, \cdots, \vartheta_2\}$ derived from the patient screening questionnaire, returns a scalar value q that approximates the weight q_o, according to some suitable metric.

7.2 Controlling real patients: individualized model design

For individualized model design, we mean a control design procedure based on a linear model identified from individual experiments. For the approach to be widely usable, it is essential that such experiments are as close as possible to real life conditions, involving just CGM collection and insulin and meal recordings. As discussed in Section 3.1 there different approaches for the identification of the model. The drawback of this approach with respect to the one based on a unique model is that the same model is considered both for control synthesis and testing so that it could be less robust to model uncertainty. Moreover, the individual information about well known clinical parameters are not considered. In silico trials clearly show that the individual models must be significantly better than the mean one in order to reach better performance with the individualized model than with the mean one.

7.3 Run-to-run control

An off-line module may be in charge of adapting the control strategy on a daily or weekly basis through the monitoring of the outcomes achieved by the real-time control module. This corresponds to a further closed-loop working on a coarser time scale. This type of problem, called run-to-run (R2R) control, has been extensively studied in the control of chemical and manufacturing processes Moyne et al. [2001]. The rationale of R2R control is rather simple: the parameter to be adjusted is corrected on the basis of the outcome of the last run. The first applications to glucose control regarded the iterative adjustment of the basal and boluses forming the conventional open-loop therapy Owens et al. [2006], Palerm et al. [2007], Palerm et al. [2008]. It goes without saying that if the glucose controller includes a feedforward action, it may still benefit from this kind of R2R control. More recently, R2R control has been applied also to the tuning of the controller parameters Magni et al. [2009a] where adjustment of the controller aggressiveness is considered. An iterative tuning based on the last 24 hours may also be performed continuously via iterative learning control techniques Wang et al. [2010].

8. CONCLUSION

In this paper the MPC control algorithm used for the development of an Artificial Pancreas has been considered. The individual tuning of the controller is the most critical step. The first clinical trials have been performed with a Matlab code. The first outpatient experiment has been done with a Java derision of the algorithm loaded an Adroid cell phone. A C++ version will be ready soon to be incorporated in an STMicroelectronics processor for an embedded platform.

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