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Modeling and Control of Diabetes: Towards the Artificial Pancreas

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Abstract: The paper offers a survey of some major simulation and control issues associated with the development of an Artificial Pancreas. The main topics include the role of large-scale simulation models used to carry out in silico trials, the discussion of the specific features of the glucose control problem, the layered architecture of the artificial pancreas, and the controller tuning strategies adopted to achieve individualization of the glucose control algorithm.

1. INTRODUCTION

The problem of regulating glycemia in diabetic patients represents one of the most challenging and socially important control problems in the field of biomedical systems. In absence of reliable glucose sensors, the therapeutic strategy cannot go beyond open-loop strategies, possibly improved by feedforward actions and episodic fingerstick measures. In recent years, the advent of minimally invasive subcutaneous (sc) CGM (Continuous Glucose Measurements) has opened the way to truly automated closed-loop control strategies. As a matter of fact, the ensemble of a CGM device, a control algorithm and an sc insulin pump constitutes a so-called Artificial Pancreas (AP), due to its potential to enforce glucose regulation as done by the pancreas in healthy subjects. On one side, the availability of sc sensing and actuation devices is important because the invasiveness of intravenous (iv) sensing and actuation devices was one of the major obstacles to the implementation of an artificial pancreas suitable for everyday's life. The Juvenile Diabetes Research Foundation (JDRF), recognized the changed technological scenario and in 2006 launched the Artificial Pancreas Project aimed to the rapid deployment to the market of commercial devices. On the other side, the sc to sc route introduces further delays within the loop that make the control problem even more challenging.

The aim of this paper is to provide a survey of the main control issues underlying the development of a sc-to-sc AP. First of all, it is recognized that the scenario has greatly changed not only due to the technological developments of sensors and pumps but also as a consequence of the possibility of carrying out extensive in silico experiments. In fact, it is often not possible, appropriate, convenient, or desirable to perform an experiment on type 1 diabetic subjects, because it cannot be done at all, or it is too difficult, too dangerous, or unethical. In such cases, simulation offers an alternative way of in silico experimenting on the system. In fact, large-scale simulations would account better for inter-subject variability than small-size animal trials and would allow for more extensive testing of the limits and robustness of control algorithms. Therefore, the first part of the paper will address the recent developments in the construction and use of large-scale simulators.

Then, we will proceed to analyze the control issues underlying the design of an AP. First, the specific features that make glucose regulation a nontrivial control problem will be illustrated. A hierarchical structure of the AP is also proposed in order to coordinate various functions, ranging from safety to real-time control and also supervision. The pros- and cons of PID ad MPC (Model Predictive Control) will be illustrated. Given the large inter-subject variability, an individualized control design based on an individualized patient model would be highly desirable. Given the difficulty of estimating such models, the practical solution is to design the controller on the basis of a linearization of the average patient, restricting individualization of the weight within the quadratic cost function cost function characterizing the NMPC (Nonlinear Model Predictive). In this context, the massive use of in-silico experiments can make the difference.

2. THE TYPE I DIABETES SIMULATOR

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 (Arleth et al., 2000, Srinivasan, et al. 1970, Cobelli, et al. 1982, Cobelli et al. 1983, Salzsieder, et al. 1985, Carson and Cobelli 2001, Lehmann et al. 1992, Andreassen et al. 1994,

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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. 2007a and b), we have developed a type 1 diabetes simulator 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).

2.1 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 continuous glucose monitoring (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).

2.2 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. 2007a).

In order to obtain parameter joint distributions in type 1 diabetes from those in the adults healthy state, we 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. Joint distribution of parameters describing sc insulin kinetics and plasma-to-interstium glucose dynamic has been also described following literature data (Dalla Man et al. 2007b). A large number of subjects can be generated in each population, by randomly extracting different realizations of the parameter

Table 1. Key Demographic and Metabolic Parameters of the In Silico Subjects

	Adults			Adolescents			Children		
Parameter	*Mean (SD)*	*Min*	*Max*	*Mean (SD)*	*Min*	*Max*	*Mean (SD)*	*Min*	*Max*
Mean Weight (kg) (SD)	79.7 (12.8)	52,3	118,7	54.7 (9.0)	37,0	88,7	39.8 (6.8)	27,6	60,7
Insulin (U/day)	47.2 (15.2)	21,3	98,4	53.1 (18.2)	22,6	141,5	34.6 (9.1)	17,6	56,1
CHO ratio (g/U)	10.5 (3.3)	4,6	21,1	9.3 (2.9)	3,2	19,9	14.0 (3.8)	8,0	25,5
Fasting plasma glucose (mg/dl)	143.4 (9.3)	122,1	167,1	144.0 (7.8)	124,0	166,3	142.9 (8.5)	125,5	168,4
Insulin sensitivity (10^{-2} mg/kg/min per pmol/liter)	3.8 (1.3)	1,1	8,08	3.1 (1.7)	1,0	40,9	12.6 (5.6)	3,6	35,4

vector from the appropriate joint parameter distribution.
The biometric characteristics of in silico subjects are reported in Table 1.

2.3 The Simulator

The type 1 diabetes simulator (Fig. 1) 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 Food and Drug Administration (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.

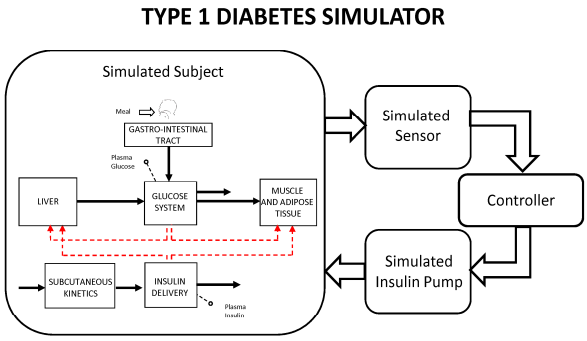

Fig. 1. Employment of the type 1 diabetes simulator for testing closed-loop control algorithms for insulin infusion.

2.4 Limitations and Further Developments

It is important to underline that model parameters are time-invariant. Therefore, the simulator does not account for circadian variation of patient metabolism, and provides reliable glucose traces only for a single meal time interval (6-hour). Recently, a NIH grant has been founded (DK 085516-01) to determine if a diurnal pattern of post prandial insulin action and meal glucose appearance occurs in type 1 diabetes and if so, whether it differs from nondiabetic healthy subjects. Preliminary results are reported in Dalla Man et al., 2010. These data are usable to introduce intra-subjects variability in the simulator.

3. CONTROL

3.1 Rationale

A patient with type 1 diabetes faces a lifelong behaviour-controlled optimization problem in which 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 a rudimentary closed loop control.
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 (Hovorka 2005, Bequette 2005, Cobelli et al. 2009). Herein, we focus on the subcutaneous (sc)-to-sc control route, relying on non-invasive sc insulin pumps and sc CGM devices. Another inclusion criterion is the validation platform that is restricted to control algorithms validated in clinical in-vivo trials or in advanced in silico experiments, providing accurate description of dynamic phenomena and/or incorporating inter-individual variability (Dalla Man et al. 2007a, Dalla Man et al. 2009, Wilinska et al. 2008, Hovorka et al. 2008, Wilinska et al. 2010). The importance of in silico validation is confirmed by the fact that the FDA has accepted in silico trials conducted with a large-scale in silico model as a substitute of the preclinical animals studies, which are usually needed to authorize clinical trials in humans (Kovatchev et al. 2008). In (Patek et al. 2009a, Kovatchev et al. 2009a) some guidelines for in silico proof-of-concept testing of artificial pancreas control algorithms are proposed.
In closed-loop glucose control, 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. The control variable is the insulin delivered by the sc pump. The system is subjected to disturbances, the most important one being the meals, which may be announced, approximately known, or even predictable. This knowledge is routinely exploited in conventional insulin therapy in order to compute pre-meal boluses. Another important disturbance is 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 is the 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. Using sc insulin as control variable poses major challenges to control algorithms due to the significant time needed for insulin absorption, diffusion, and action, even with the advent of new rapid-acting insulin analogues (e.g. lispro, aspart, glulisine). Further, the effect of meals on plasma glucose is characterized by an absorption delay whose time constant is in the order of hours. Not only the overall system dynamics is nonlinear and affected by substantial delays, but control must also cope with the significant inter- and intra-patient variability, meaning that the same controller cannot be applied to different patients and even the same patient may show large variations at different days. A further issue is the presence of input and output constraints: the manipulated input variable, e.g. insulin, is nonnegative and plasma glucose should never go below a hypoglycaemia threshold, e.g. 60 or 70 mg/dl, while avoiding also hyperglycemia in order to prevent long-term complications

3.2 The Architecture of Glucose Control

A recent paper has proposed a layered architecture for artificial pancreas systems (Kovatchev et al. 2009b) (Fig. 2), where the layers are characterized by the time-scale of their operations. At the bottom, the fastest layer is in charge of safety requirements. Possible algorithms include pump shutoff, insulin on board (IOB) and the so-called “brakes”. Immediately above, there is the real-time control layer deciding insulin delivery based on latest CGM data, previous insulin delivery, and meal information. Typical algorithms are either Proportional Integral Derivative (PID) or Model Predictive Control (MPC) regulators. The top layer (off-line control tuning) is in charge of tuning the real-time control

layer using clinical parameters and historical data. Possible methods include individual controller calibration strategies, run-to-run (R2R) control algorithms, and behavioural analysis of patient lifestyle. Each layer processes available information (experimental measurements and patient's inputs) in order to take decisions that are passed to a lower layer. If useful or necessary, commands from an upper layer can be overridden: a typical example may be given by the safety layer zeroing insulin administration decided by the real-time control module.

It is interesting to note that some layers may not be present in a particular technological implementation. For instance, within a traditional therapy consisting of basal insulin and meal-compensating boluses, use of the CGM information may be limited to safety interventions to prevent hypoglycemia

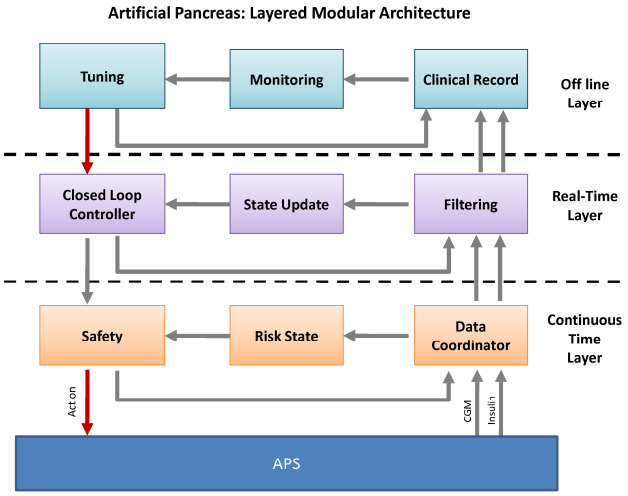

Fig. 2. Modular layered architecture of the artificial pancreas. The layers work on different time scales: the fastest one deal with safety maintenance, the middle one with real-time closed-loop control, and the top one with tuning and supervision on a daily or longer time scale. Three main functionalities are included in each layer: control, estimation, and data management. Decisions flow is from top to bottom and information flow from bottom to top. A layer can override decisions suggested by its upper layer, e.g. for safety reasons.

3.3 Safety Algorithms

Since the main short-term risk is hypoglycemia, safety algorithms are mainly concerned with discontinuing or reducing insulin delivery to prevent dangerous decreases of blood glucose level. They should rely on simple and physically grounded computations to offer a recovery strategy from physical or algorithmic failures of real-time controllers.

The simplest strategy is pump shut-off when hypoglycemia is predicted. This approach has been shown to reduce the risk of nocturnal hypoglycemia (Buckingham et al. 2009, Cengiz et al. 2009). A possible drawback is that the use of an on-off control law for basal insulin, similar to bang-bang or relay control, may induce undesired oscillations of plasma glucose.

An alternative approach uses insulin-on-board (IOB) computation (Zisser et al. 2009). The amount of IOB should never exceed a quantity that can cause future hyperglycemia. Remarkably, the IOB computation is simple enough to be used in a safety module that should act when upper layers have failed.

The third approach are the so called "brakes" (Patek et al. 2009b), which assess the risk associated with glucose values and reduce the delivered insulin accordingly.

3.4. Real-time Control

Feedback and feedforward control

The main difference between closed- and open-loop control is that the former does not employ real-time measurements in order to take decisions, whereas the latter exploits measurements correlated with the variable under control to react to uncertainties and disturbances.

A fully open-loop scheme corresponds to a fixed therapy, e.g. basal insulin administration throughout the day and insulin boluses at meal times, based on patient characteristics, without real-time plasma glucose measurements. The open-loop therapy may, however, include a feedforward action that anticipates external disturbances, e.g. adapting the boluses to the predicted meal amount. In nominal conditions (perfectly known patient dynamics and external disturbances) one could design an open-loop insulin profile ensuring the desired glycemic control. In real life, to compensate for uncertain dynamics and unpredictable disturbances, there is the need of corrections accounting for the actual patient state. Also in the conventional therapy, occasional fingerstick glucose measurements are used to trigger corrective actions in order to react to deviations from the nominal profile. This gives rise to a kind of partially closed-loop control scheme, whose feedback action relies only on few daily measurements.

With the commercial availability of CGM, the effect of external disturbances (e.g. meal and exercise, but also changes of insulin sensitivity) can be corrected based on their effect on glucose levels. When the CGM signal reports an excessive rise of glucose, the controller is alerted and can increase insulin delivery. Conversely, an undesired decrease of glycemia will trigger the reduction of basal insulin delivery.

A purely closed-loop control scheme would decide instantaneous insulin delivery on the basis of CGM signal alone. For example, an unexpected meal would be dealt with by reacting to the consequent rise of glucose. Unfortunately, the action of insulin on plasma glucose is subject to significant delays so that control decision may arrive too late to prevent hyper- or hypo-glycemic episodes. This problem is even more critical in view the inherent delay between plasma glucose and the CGM signal. For example, an excessive closed-loop insulin administration following post-prandial hyperglycemia is likely to cause a hypo-glycemic episode. This performance limitation is well known in control: in presence of significant delays in the route from manipulated (s.c. insulin) to the controlled variable (plasma glucose), the designer must settle for a relatively slow response time (i.e. the time needed for desired glycemia to be restored).

As pointed out in (Magni et al. 2009a), there exists the problem of finding a trade-off between nocturnal regulation, well suited to mild control actions, and postprandial regulation, calling for prompt and powerful correction. For instance, in previous closed-loop trials (Kovatchev et al. 2009c, Bruttomesso et al. 2009, Clarke et al. 2009) good nocturnal regulation went to the detriment of breakfast control

quality. This dilemma can be answered by a control scheme that combines feedforward and feedback actions (Magni et al. 2009, Lee et al. 2009). Feedback control actions are applied only as corrections that are summed to a "conventional" insulin administration (feedforward action) made of a basal profile and pre-meal boluses calibrated on the presumed meal amount. The closed-loop regulator bases its actions on the difference between the CGM signal and this nominal profile, representing the expected consequence of the conventional therapy. This approach offers the opportunity of combining prompt and powerful compensation of meals (through the feedforward bolus) together with the robustness of closed-loop control capable of coping with unpredicted events, disturbances and changes in patient's dynamics.

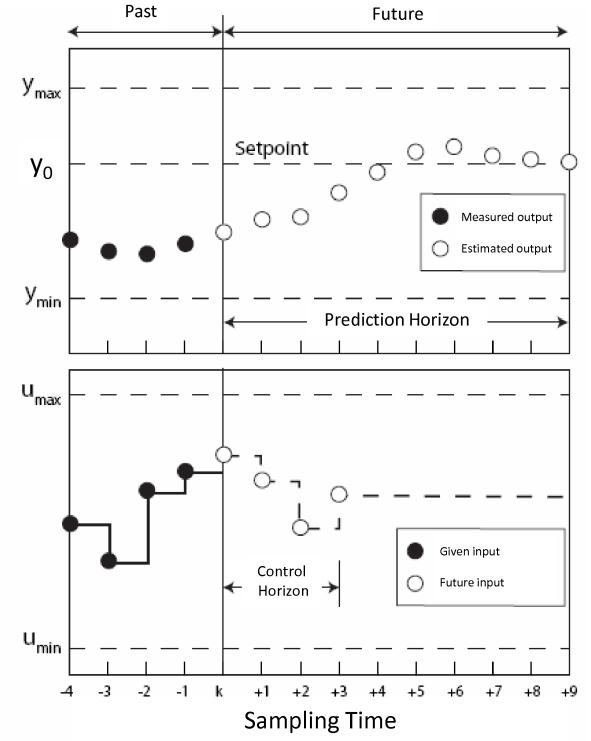

Fig. 3: Illustration of Model Predictive Control

MPC

In recent years MPC (Magni et al. 2009b) has emerged as the most promising approach to glucose control. The main ingredients of MPC are: the model, the cost function, and the constraints. The model is needed in order to be able to predict the future states and outputs of the system as a function of the current state, future values of the manipulated variables, and future values of measurable or predictable disturbances (Fig. 3). It 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 measures the quality of closed-loop control. Usually, but not necessarily, it is a quadratic penalty

$$J(k) = \sum_{i=0}^{N} \left(q\left(y_o(k+i) - y(k+i)\right)^2 + \left(u_o(k+i) - u(k+i)\right)^2 \right) \quad (1)$$

on future deviations (whose number is a design parameter called prediction horizon) of the output from the setpoint y_0 and may include 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 $\Delta u = u(k) - u(k-1)$. Finally, there may be constraints on the manipulated variables (insulin delivery rates by the pump is greater than zero and less than some maximal value)

$$u_{\min} \le u \le u_{\max} \quad (2)$$

$$\Delta u_{\min} \le \Delta u \le \Delta u_{\max} \quad (3)$$

and also on the controlled ones (glycemia in the admissible range)

$$y_{\min} \le y \le y_{\max} \quad (4)$$

The rationale behind MPC is simple: at each time point we compute the sequence of future input moves optimizing the cost function subject to the constraints. Then, only the first control move is applied. At the next step, the procedure is repeated by translating the predictions and control horizons: an optimization is again performed and only the first input move is applied. The principal merit of MPC is that it reduces the control design problem to a sequence of finite-horizon optimization problems, which makes it possible to deal with nonlinear system models, input and output constraints, multiple inputs and outputs. Finally, the tuning of the regulator is relatively straightforward: if the control action is sluggish, it suffices to increase the weight on the controlled output, i.e. glycemia. In the simplest implementation, after finding reasonable values for the control and prediction horizons (e.g. a unique value covering the duration of typical post-meal transients), the tuning reduces to the calibration of a scalar aggressiveness parameter (Magni et al. 2007).

Nonlinear Model Predictive Control (NMPC) assumes a nonlinear patient model and can keep into account input and output constraints. As a rule, the finite-horizon optimization problem does not admit an explicit solution, and the price to pay for an accurate description of the nonlinear dynamics is the need for on-line iterative optimization within the algorithm, which may preclude the adoption of NMPC within commercial devices, for both engineering and regulatory reasons. A further problem is the difficulty of obtaining reliable individual nonlinear models of insulin-glucose dynamics.

NMPC can also be used as a touchstone for other MPC schemes. In fact, an improvement over linear MPC (Magni et al. 2009c) on the average in silico patient of the insulin-glucose in silico model has been observed. Experiments on real patients using NMPC have also been performed (Hovorka et al. 2004a-b, Shaller et al. 2006). Individualization has been achieved by on-line recursive identification of model parameters within a Bayesian setting. In that context, the Bayesian priors play a key role in order to overcome possible identifiability issues. Note that a formal demonstration of stability and robustness properties of the closed-loop system is obstructed by the complex interplay between on line recursive identification and nonlinear control.

Linear Model Predictive Control (LMPC) uses an approximate linear model of the insulin-glucose dynamics, which yields an algorithmic simplification. The linear model may be obtained by linearizing a more detailed nonlinear average patient model. To obtain an individualized model, one may resort to black-box identification performed on data collected on the same individual subject to conventional therapy. In practice, an ARMAX model with two inputs (sc insulin and meals) and one output (sc glucose) is identified. In order to have good identifiability properties, the input signals should be persistently exciting. In particular they should not be collinear between each other. Unfortunately, the meals and insulin boluses of the conventional therapy are more or less collinear and so that 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). The use of split and/or delayed insulin boluses has been proposed to improve the joint excitation properties of the inputs (Finan et al. 2009, Magni et al. 2009a) (see also (Galvanin et al 2009) for further optimal design issues in the identification of insulin-glucose models).

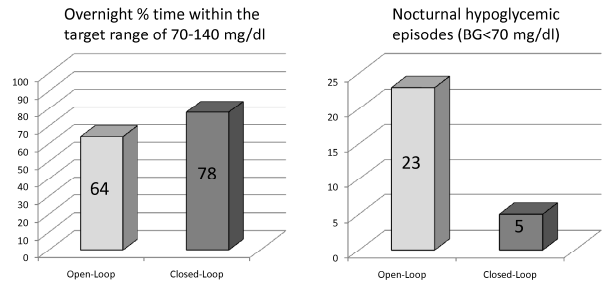

Fig. 4. Results of a recent clinical trial that compared conventional open-loop therapy to closed-loop glucose control using LMPC. Closed-loop control achieved an increase of overnight percent time within the target range and an almost five-fold reduction of the number of nocturnal hypoglycemic episodes.

Constrained LMPC admits a closed-form solution under the form of a piecewise constant control law that can be computed off line, see e.g. (Dua et al. 2006, Parker et al. 1999) for an application to simulated patients. The main drawback of explicit multiparametric MPC is the need of retrieving the appropriate control gain for the current state searching among a possibly very high number of regions in the state space. Alternatively, the optimal solution can be computed on line via quadratic programming methods, which may be computationally advantageous (Lee et al. 2009), A constraint on IOB could be included among the constraints of the optimization problem, so as to incorporate some safety already within the real-time control module (Ellingsen et al. 2009, Lee et al. 2009).

It is likely that the first commercial realizations of an artificial pancreas will avoid overly complex computational algorithms. Hence the interest for the simplest possible LMPC scheme, that is input-output unconstrained LMPC. This MPC scheme does not include constraints and uses a linear model in input-output form, e.g. an ARMAX- or ARX-type model. On-line optimization is avoided, because the unconstrained optimization problem admits a closed-form solution yielding the insulin rate as a simple linear combination of previous insulin rates, previous CGM values, and meal amounts (when known). A further simplification deriving from the use of an input-output model is the possibility of doing without a state-space model. A clinical trial on 20 patients has been recently carried out using unconstrained LMPC (Kovatchev et al. 2009c, Bruttomesso et al. 2009, Clarke et al. 2009a), 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. 2009c) (Fig. 4).

The LMPC controller relied on an average patient model and its aggressiveness was individualized on the basis of easy-to-measure individual clinical parameters. To improve breakfast regulation, which was slightly worse than open-loop one, an unconstrained LMPC with feedforward action has been proposed (Kovatchev et al. 2009b). Generalized Predictive Control (GPC), another example of input-output unconstrained LMPC, has been tested on diabetic swines using both insulin and glucagon as inputs. A first study used adaptive GPC employing insulin or glucagon depending on the sign of the difference between measured glycemia and its target value (El-Khatib et al. 2007). In a second study, to speed up glucagon administration, its regulation was decided by a PD controller; this has been tested in diabetic swine (El-Khatib et al. 2009) and more recently in humans (F. H. El-Khatib et al 2010). A multi-model LMPC based on the algorithm described in (Mazor et al. 1998) has been adopted in (Hovorka et al. 2010) in order to cope with inter- and intra-subject variability. The main drawbacks of unconstrained LMPC are: (i) a simplified linear model is used (this can be partially overcome by multi-model approaches), and (ii) constraints are neglected, especially the one on minimal admissible glycemia. These drawbacks are compensated by a very simple implementation, which may be appealing especially if this real-time controller is part of a modular architecture including a safety module responsible for hyperglycemia prevention.

Real-time detection and estimation Since the full state vector is not available, real time algorithms for state observation are needed (see Gillis et al. 2007, Wilinska et al. 2009, Patek et al. 2007). In fact, state estimation is important not only for control purposes, but can also be easily extended to prediction, for instance in order to predict hypoglycemia (Palerm et al. 2005, Palerm et al. 2009).

An ideal artificial pancreas would be completely automatic, without the need of receiving meal information from the patient. For this purpose, meal detection and estimation (Dassau et al. 2008, Lee et al. 2009, Cameron et al. 2009), can help the controller countering the glucose rise after a meal. However, the delay introduced by meal detection and estimation adds to the intrinsic delays in the sc-to-sc route, which may worsen meal compensation compared to an appropriate pre-meal bolus.

3.5 Strategies for Control Tuning

Models for control

The deployment of a controller, especially a closed-loop one, relies heavily on mathematical models. It is worth noting that

the requirements posed to models may vary depending on the different phases: design, tuning, and validation.
Most control design methods make use of compact models, whose main task is capturing system dynamics on the time scale regulation is concerned with. In this respect, linear time-invariant models may be obtained by linearization of either the average insulin-glucose in silico model or the minimal model (Bergman and Cobelli, 1980). In the former case, order reduction methods may be employed to eliminate redundant state variables. Another way to obtain a linear time-invariant model is by black-box identification techniques applied to patient's data, e.g. to identify ARMAX models. Some nonlinear control strategies such as Nonlinear Model Predictive Control, see below, can rely directly on nonlinear models such as the insulin-glucose in silico model or the minimal model (nonlinear black-box models, e.g. Nonlinear ARMAX, can be considered as well).
In the tuning and validation stages, it is convenient to run simulations that mimic the real system dynamics as faithfully as possible, so that large scale simulation models are particularly useful. In control engineering, it is a common practice to design a controller on some simple model (low-order linear time-invariant, for instance) and validate it on a detailed simulator of the system under control. Recalling that the insulin-glucose in-silico model characterizes a population of virtual patients it is even possible to tune the controller parameters through in silico trials that compare the performances of different parameters values on the whole in silico population.
In the following review of glucose control strategies, the role and type of associated models will be pinpointed for each control method. In any case, a common feature of models for control design is being instrumental to the achievement of satisfactory regulation performances rather than striving for the best possible description of all physiological phenomena.

Measuring control performance on a population

Although several classic control metrics exist for assessing the quality of glycemic control (Clarke et al. 2009b), some additional issues emerge. In particular, it does not suffice to develop an algorithm that performs satisfactorily on a single subject either real or simulated. As a matter of fact, given the great inter-individual variability, it is of paramount importance to guarantee satisfactory performance on the entire population of patients. This motivated the introduction of the so-called CVGA (Control Variability Grid Analysis) (Magni et al. 2008), which associates to each patient a point in a plane. The two coordinates correspond, via a nonlinear transformation, to the minimal and maximal glucose value in the considered time interval. The lower left corner is associated with ideal glycemic control while high x-values correspond to hypoglycemic episodes and high y-values to hyperglycemic episodes. The plane is partitioned into nine regions corresponding to different levels of glycemic control quality, from A (best) to E (worst). In this way, the results from a real or simulated trial can be visualized by plotting the patients as a cloud of points onto the CVGA and summarized by counting the percentage of points in the nine regions. Using the CVGA, comparison with either conventional open-loop control or another closed-loop controller is immediate. Of course, a good controller will bring as many patients as possible in the A and B regions. Preliminary to a clinical study, the controller can be applied to an in silico population, representative of the real population, and the performance assessed on the CVGA. If they are unsatisfactory, the controller can be modified and tested again by repeating the in silico trial. The procedure is iterated until glycemic control is acceptable for all the virtual patients.

Robustness vs. personalization of controller parameters

The ideal artificial pancreas should perform safely and satisfactorily in all patients. To achieve this, the designed controller should be highly robust against uncertainties in the system dynamics, either due to inter-individual or intra-individual variability. Experiments conducted in in silico patients have shown that, a fixed controller yields largely disparate performances when applied to different patients; hence, the need for a personalization of the control algorithm. Given the difficulty of identifying accurate individual models, the direct tuning of controller parameters has been investigated on the basis of few biometric and clinical parameters (body weight, total daily insulin, basal insulin delivery, carb ratio etc) characterizing the physiology of each individual. This can be done for both PID regulators (Marchetti et al. 2008) and MPC ones (Wilinska et al. 2009, Kovatchev et al. 2009c, Bruttomesso et al. 2009, Clarke et al. 2009a). In particular, for MPC the relation between biometric and physiological patient's parameters and the optimal scalar aggressiveness parameter of the controller can be determined through a sequence of in silico trials (Wilinska et al. 2009, Kovatchev et al. 2009c, Bruttomesso et al. 2009, Clarke et al. 2009a).

Run-to-run control and behavioral analysis

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. Proportional and Proportional-Integral control schemes are the most widely used ones. The first applications to glucose control regarded the iterative adjustment of the basal and boluses forming the conventional open-loop therapy (Zisser et al. 2005, 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).
Finally, stochastic models of patient's behaviour may be very helpful in order to design and recursively update the parameters (basal and boluses) of the conventional therapy. A formal stochastic model of the process of self-treatment in diabetes (e.g. regular meals, exercise, as well as random treatment deviations) and its potential to generate system

challenges can be very useful in that regard, giving a probabilistic interpretation of the observed patterns (Gonder-Frederick et al. 1997, Kovatchev et al. 1998). These studies have demonstrated a quantifiable relationship between stochastic patterns of self-treatment behavior and subsequent occurrence of hypoglycemic episodes (Clarke et al. 1999, Cox et al. 1999).

6. CONCLUSIONS

The simulator was immediately put to its intended use with the in silico testing of a new Model Predictive Control algorithm (Magni et al., 2007), and in April 2008, an investigational device exemption (IDE) was granted by the FDA for a closed-loop control clinical trial (see section on Control). This IDE was issued solely on the basis of in silico testing of the safety and effectiveness of the proposed artificial pancreas algorithm, an event that sets a precedent for future preclinical studies. Thus the following paradigm has emerged: (i) in silico modeling could produce credible preclinical results that could substitute certain animal trials, and (ii) in silico testing yields these results in a fraction of the time and the cost required for animal trials. However, one needs to emphasize that good in silico performance of a control algorithm does not guarantee in vivo performance; it only helps to test extreme situations and the stability of the algorithm and to out-rule inefficient scenarios. Thus computer simulation is only a prerequisite to, but not a substitute for, clinical trials. Another innovative use of computer simulation regards the individualization of the closed loop controller: extensive simulated experiments on populations of in silico patients have been used to learn the relationship between patient's clinical parameters and the key tuning knobs entering controller design. Recently, it has been shown that the nontrivial challenges posed by sc-to-sc real-time glucose control can be addressed by a Linear Model Predictive Control strategy, exploiting both knowledge embedded in conventional therapy, for feedforward action, and the information provided by large-scale simulation, for design and individualization. A clinical trial, conducted on 20 real patients, showed 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. 2009c).

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