# An event-based point of view on the control of insulin-dependent diabetes

Brigitte Bidégaray-Fesquet

# An event-based point of view on the control of insulin-dependent diabetes

Brigitte Bidegaray-Fesquet*
*Univ. Grenoble Alpes, CNRS, Grenoble INP, LJK, 38000 Grenoble, France
Email: Brigitte.Bidegaray@univ-grenoble-alpes.fr

***Abstract*—The treatment of insulin-dependent diabetes can be interpreted as a control problem. This control is continuous with an artificial pancreas, but more classical treatments involve a sporadic control that can be interpreted as an event-based control, both event- and self-triggered. The mathematical analysis can be performed on ordinary differential systems that have been developed in the last decade.**

***Keywords–Type 1 Diabetes; Event-based control; Self-triggered control.***

## I. Introduction

The treatment of insulin-dependent diabetes involves the artificial control of the patient's plasma glucose rate via insulin infusion. Some of todays research aims at developing integrated closed-loop systems [1] including a sensor and an insulin pump which control continuously the glucose rate. These systems, however, called artificial pancreas, are still under development and there are still, and there will be for some time, many patients over the world which are treated "classically" with isolated in time glucose-rate measures and insulin infusion.

These insulin infusions take place non regularly in time, and the decision may depend on external events to the patients (meals for example), internal ones (if a glucose rate sensor is on alarm mode for example). In this case the control is an *event-triggered control*. It may also take place at times which have been decided by the patients, or people taking care of him, at the moment when the last event took place, and then this type of control is related to *self-triggered control*.

The aim of this paper is to give a precise interpretation of the classical treatment of insulin-dependent diabetes in terms of nonuniform control. The discussion and numerical illustrations will make use of Cobelli's model [2].

The paper is organized as follows. In Section II we give the structure of Cobelli's model, identifying precisely which are the parameters and the measured variables, which inputs of the system are relatively well known and which are very difficult to identify. We illustrate the model with simulations for a healthy and a diabetic *in silico* subject. In Section III we interpret this model as an event-based controlled system and make precise what is controlled, when and which event-based paradigms are applied. Since it is work-in-progress, we give in a conclusion the future directions for work, to be able to make this analysis a really useful tool for the patient's better control of glycemia.

## II. Models for diabetes

Model for diabetes are relatively large systems subdivided in many sub-systems consisting in one or more compartments: the gastro-intestinal system, the glucose system (in plasma, liver, muscles,...), the insulin system, possibly the glucagon system. These systems are in natural interaction in a healthy subject, but some retractions are missing in an insulin-dependent subject. This induces the needs for an artificial retraction. From a modeling point of view, the lack of retroaction makes in a sense things simpler since the different compartments can be treated relatively sequentially. But the difficulty is that the measure is made on the "last" compartment of these cascading models.

### A. Model

We have implemented a model which includes all the features described in [2] and some of [3]. It describes the time evolution of there main variables, the plasma insulin $I$, glucagon $H$, and glucose $G$ concentrations. In usual life (not clinical) situations, only the glucose concentration can be measured. The system is however more complex since it involves about 15 auxiliary differential equations, which we cannot describe here, but refer to [2], [3].
The main inputs for this system are meals, and the stomach kinetics is part of the auxiliary model, and insulin infusions. They can be roughly considered as exactly known or with low uncertainty. The insulin infusion is the main control which is applied to the "system" (the subject). There are also more than 40 physiological parameters, more or less easy to evaluate, to which the system is also more or less sensitive.

To sum up, very coarsely, we face a relatively large differential system

$$\dot{Y} = f(Y,P,U), \quad (1)$$
$$y = CY, \quad (2)$$

where the vector $Y$ gather all the variables (main and auxiliary), $P$ are all the parameters (discussed a little more in detail below), including meals, and $U$ is the control (insulin infusions and extra carbohydrate ingestions). The output $y$ is usually only the plasma glucose concentration, which is one of the entries in $Y$. The function $f$ is complex. Many equations contain a natural clearance rate, and linear or nonlinear interactions of the various variables.

### B. Parameters

The model's parameters can be classified in many categories.

- known, and constant, subject parameters, such as weight;
- not exactly known and/or variable subject parameters, such as rate constants for intestinal glucose absorption or liver responsiveness to glucagon, to name only two;
- difficult to evaluate time-dependent inputs, such as physical activity, emotions, growth hormones for children...

A complete model should of course be able to take into account these variety of parameters, when given, constant or not, in

direct simulations of *in silico* subjects. We should also be able to estimate these parameters and possibly their time evolution from measures on real subjects.

### C. Direct simulations

Although the system is complex a very welcomed feature is that is can be easily simulated using simple methods (the direct Euler schemes works fine) with a very reasonable time step, typically 1 min. This period is also the one which can be obtained from usual glucose subcutaneous sensors, so that comparisons of the numerical results with real measures can be relatively simple, in particular in the context of parameter estimations.

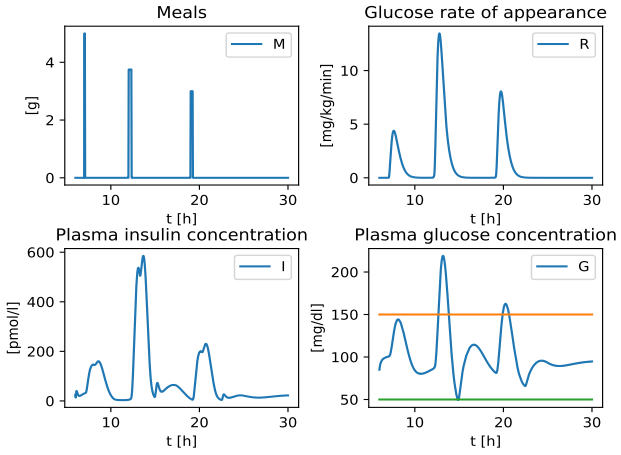


Figure 1. 30 hour numerical simulation of meals, glucose rate of appearance (out of the stomach), plasma insulin, and glucose concentrations, for a healthy *in silico* subject.

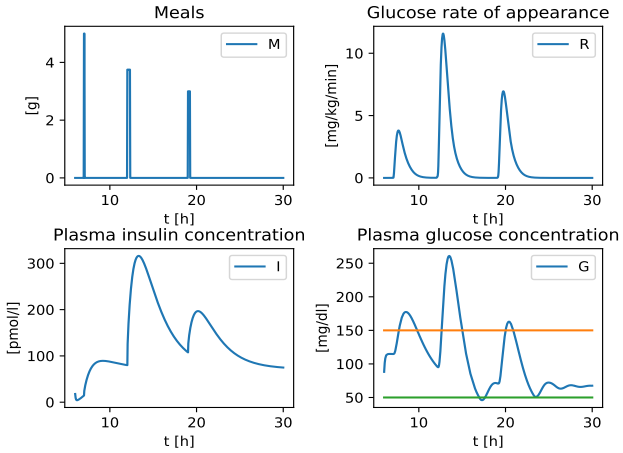


Figure 2. 30 hour numerical simulation of meals, glucose rate of appearance (out of the stomach), plasma insulin, and glucose concentrations, for a type 1 diabetic *in silico* subject.

Figures 1 and 2 display the time evolution of main variables for a healthy and a type 1 diabetic subject respectively. These simulations for a type 1 diabetic subject include the event-based control described in the next Section, while the simulation for a healthy subject include the natural retroactions but of course no external control.

In these simulations, the main inputs are the meals, which are the same for both the healthy and the diabetic subjects, and are displayed in the top-left sub-pictures. They induce a glucose rate of appearance in plasma, displayed in the top-right sub-pictures, following the same dynamics for both subjects with slightly different parameters characterizing the stomach sub-system. The profile of the insulin response is very different, and displayed in the bottom-left sub-pictures. For the healthy subject, the pancreas reacts very quickly to the increase in the glucose plasma concentration and releases insulin quickly in blood which regulates quickly the whole system. In the diabetic case, insulin is infused, sometimes after a meal inducing a first delay, and not directly in the blood but in the interstitial tissues. In the type 1 diabetic subject model, there are two delay equations involving interstitial insulin concentrations and the plasma insulin concentration is therefore delayed, with a much smoother dynamics and a much lower maximum value. The effect of plasma insulin on the plasma glucose concentration, displayed in the bottom-right sub-pictures, is of course more efficient for a healthy subject. The peaks are less high and a with a smaller duration than for a diabetic subject.

## III. Event-based and self-triggered controls

Interpreting external patient control in an event-based framework is not specific to diabetes. We can also cite the case of anesthesia control [4]. A rough parallel between the two situations can be done, since in both cases the issue is to maintain physiological characteristics within a predefined range. The case of anesthesia is however a bit simpler since the patient is at rest, and there are no complex inputs to take into account, such as meals, physical activity, etc.

The control goal is to keep the plasma glucose rate within a $R_1 \equiv [G_{\min}, G_{\max}] = [50, 150]$ mg/dl range (displayed on Figures 1 and 2). This should ensure a good present and future life quality to the patient. This is the target range, out of which events can be triggered. There is also a larger range, say $R_2 = [40, 350]$ mg/dl, out of which the subject is in immediate danger.

*Event-triggered control.* Even if some sensors allow it, patients very often disable alarms when measures are out of the $R_1$ target range. When it is enabled, it can allow an event-triggered control, with a few minutes delay (since subcutaneous glucose rate is captured by sensors, and not plasma glucose rate). Other events, that are taken into account, are symptoms of hypo-/hyper-glycemia, and also meals, sporting activities or other events that can strongly impact the glucose rate. Then a measure of glycemia is done, and the proper control is applied (insulin infusion or carbohydrate ingestion). The control algorithm is very simple and only depends on the measured glycemia, and the quantity of ingested carbohydrates if a meal is involved.

The control is modeled by an insulin infusion rate (IIR). It is the sum of a constant, $\mathrm{IIR}_c$ —induced by a constant insulin infusion by an insulin pump or by slow insulin, infused once a day and delivered progressively (in which case it is only almost constant)—, and of a time dependent term. This last term is active around meal times and proportional to the carbohydrate ingestion $M$ and takes also into account the fact that the glucose plasma rate is in the $R_1$ range or not. The IIR

takes therefore the form

$$\mathrm{IIR} = \mathrm{IIR}_c + \alpha(t)M + \beta(t)\lfloor\frac{G - G_{\max}}{50}\rfloor^+ - \beta(t)\lfloor\frac{G_{\min} - G}{50}\rfloor^+,$$

where $\lfloor\cdot\rfloor^+$ denotes the positive part of the floor function. This may seem a bit coarse, but this makes it tractable for patients with no specific calculation skills. Besides IIR is then delivered in integer multiples of a given quantity, due to the technology of insulin pens of pumps.

The event-triggered nature of this control is due to the fact that functions $\alpha(t)$ and $\beta(t)$ are only nonzero close to meal times. The control is also very far from continuous in terms of its variables, $M$ and $G$. Besides it is delayed, since it is infused not directly in blood and modeled by many cascading sub-systems, e.g.:

$$\dot{I}_1 = -\gamma_1 I_1 + \mathrm{IIR}(t, M, G),$$
$$\dot{I}_2 = -\gamma_2 I_2 + \delta_1 I_1,$$
$$\dot{I} = -\gamma I + \epsilon_1 I_1 + \epsilon_2 I_2,$$

where all the coefficients involved in the previous equations are patient dependent. The effect of these successive delay equations is clear on the plasma insulin concentration plot of Figure 2.

*Self-triggered control.* Other controls have a self-triggered nature. Indeed, when a control is applied a decision is made on the next time the subcutaneous glucose rate will be measured. It is prescribed to measure glycemia typically three hours after an insulin infusion. In case of low glycemia, glucose is ingested, and glycemia is measured one our afterwards. Therefore the presence of a control and its type (insulin infusion or glucose ingestion) triggers the time of the next measure and possibly the next control. This prescribed time delay can of course can be interrupted by an other event, meal, worrying signs of hypoglycemia...

The difficulties in analyzing the control therefore lies in the fact that the control is both event- and self-triggered, and also by the fact that the value that is measured by sensors is not the one that we want to keep in a predefined range, but reflects its value a few minutes before. In the case when the measure is done directly on capillary blood, the measure is much closer to plasma glycemia at the same time, but such measures are done only a few times a day, which is of course not enough to ensure a proper control.

The main issues to address are the following: 1) under which conditions can the security range $R_2$ be ensured while using the target range $R_1$ to generate events; 2) for a specific patient (when parameter estimation has been carefully performed), can self-triggered control delays be designed to ensure that most time is spent in the target range $R_1$.

The comparison has to be done with what is possible to achieve with the continuous control performed with an artificial pancreas, and to have arguments to discuss the trade-off between less expensive devices used with event-based control and a very efficient control that allows quite a narrow target range.

## IV. Conclusion

The treatment of insulin-dependent diabetes can be modelled as a controlled ordinary differential system. This approach, contrarily to purely automation approaches, needs to carefully estimate the numerous parameters of the model. The analysis as an event-based control will help better calibrate the treatment of diabetic subjects.


## Acknowledgment

This work has been partially supported by the LabEx PERSYVAL-Lab (ANR-11-61 LABX-0025-01).


## References


[1] B. P. Kovatchev, M. Breton, C. Dalla Man, and C. Cobelli, "In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes," Journal of Diabetes Science and Technology, vol. 3, no. 1, Jan. 2009, pp. 44–55.

[2] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," IEEE Transactions on Biomedical Engineering, vol. 54, no. 10, Oct. 2007, pp. 1740–1749.

[3] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, and C. Cobelli, "The UVA/PADOVA type 1 diabetes simulator: New features," Journal of Diabetes Science and Technology, vol. 8, no. 1, 2014, pp. 26–34.

[4] L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, and A. Visioli, "Event based control of propofol and remifentanil coadministration during clinical anesthesia," in 3rd International Conference on Event-Based Control, Communication and Signal Processing (EBCCSP). Funchal, Portugal: IEEE, May 2017, pp. 1–8.