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Sampled-Data Dynamic Output Feedback Controller for the Plasma Glucose Regulation in Type 2 Diabetic Patients

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Content

Abstract

- We deal with the problem of tracking a desired plasma glucose concentration by means of intra-venous insulin administration, for Type 2 diabetic patients (see [1]).
- A nonlinear time-delay model is used to describe the glucose-insulin regulatory system (see [2], [3]), according to which a model-based approach is exploited to design a glucose control therapy.
- By the use of the results provided in [4], it is shown that emulation, by Euler approximation, of a proposed continuous-time dynamic output feedback controller ensures semi-global practical stability of the glucose-insulin system, with arbitrarily small steady-state tracking error.
- A pre-clinical *in-silico* validation is performed.

[1] M. Di Ferdinando, P. Pepe, P. Palumbo, S. Panunzi, A. De Gaetano, Semi-Global Sampled-Data Dynamic Output Feedback Controller for the Glucose-Insulin System, *IEEE Transactions on Control Systems Technology, Special Issue on System Identification and Control in Biomedical Applications*, Vol. 28, pp. 16 - 32, 2020.
[2] S. Panunzi, P. Palumbo, and A. De Gaetano, A discrete single delay model for the intra-venous glucose tolerance test, *Theor. Biol. Med. Model.*, Vol. 4, pp. 35, Sep. 2007.
[3] P. Palumbo, S. Panunzi, and A. De Gaetano, Qualitative behavior of a family of delay differential models of the glucose insulin system, *Discrete Continuous Dynam. Syst. B*, Vol. 7, no. 2, pp. 399–424, 2007.
[4] M. Di Ferdinando, P. Pepe, Sampled-Data Emulation of Dynamic Output Feedback Controllers for Nonlinear Time-Delay Systems, *Automatica*, Vol. 99, pp. 120-131, 2019.

Glucose-Insulin Model

Let us consider a glucose-insulin system described by (see [2], [3])

$$\begin{aligned}
\dot{G}(t) &= -K_{xgi} G(t)\, I(t) + \frac{T_{gh}}{V_G}, \\
\dot{I}(t) &= -K_{xi} I(t) + \frac{T_{iGmax}}{V_I} \varphi\left(G(t-\tau_g)\right) + \frac{u(t)}{V_I}, \\
y(t) &= G(t), \quad G(\tau) = G_0(\tau), \quad I(\tau) = I_0(\tau), \quad \tau \in [-\tau_g, 0],
\end{aligned} \tag{1}$$

where:

- $G(t)$, [mmol/L], and $I(t)$, [pmol/L] are the plasma glucose and insulin concentrations;
- K_{xgi}, T_{gh}, V_G, V_I, K_{xi}, τ_g are parameters involved in the model;
- $\varphi\left(G(t-\tau_g)\right) = \dfrac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}$, with γ, G^* related parameters, is the function modeling the endogenous pancreatic IDR which cannot be neglected in T2DM patients;
- $(G_0(\tau), I_0(\tau))$ is the initial condition of the model, corresponding to the plasma glucose/insulin concentrations before the control input is applied;
- $y(t)$ [mmol/L], is the continuous-time glucose measurement i.e., the output signal;
- $u(t)$, [(pmol/kgBW)/min], is the exogenous intra-venous insulin delivery rate, i.e., the control input.

Glucose-Insulin Model

- Let G_{ref} be the desired glucose reference, the one to be tracked by the control law. The choice of a desired glucose level G_{ref} leads to the definition of the insulin and input references, I_{ref} and u_{ref}, respectively

$$I_{ref} = \frac{T_{gh}}{V_G G_{ref} K_{xgi}}, \quad u_{ref} = V_I I_{ref} K_{xi} - T_{iGmax} \varphi\left(G_{ref}\right). \tag{2}$$

  The pair (G_{ref}, I_{ref}) refers to the steady state solution achieved by fixing: $u(t) \equiv u_{ref}$, $t \geq 0$, $G_0(\tau) \equiv G_{ref}$, $I_0(\tau) \equiv I_{ref}$, $\tau \in [-\tau_g, 0]$.

- Notice that, since it is usually assumed that the plasma glycemia and insulinemia are fixed at their constant basal values before the insulin administration therapy starts, there exists a positive real q such that the following inequality holds:

$$\operatorname{ess} \sup_{\theta \in [-\tau_g, 0]} \left| \frac{d}{d\theta} \begin{bmatrix} G_0(\theta) - G_{ref} \\ I_0(\theta) - I_{ref} \end{bmatrix} \right| \leq q. \tag{3}$$

Sampled-data Control

In the vast literature on model-based control design, an area that has involved many researchers in the last years is sampled-data control.

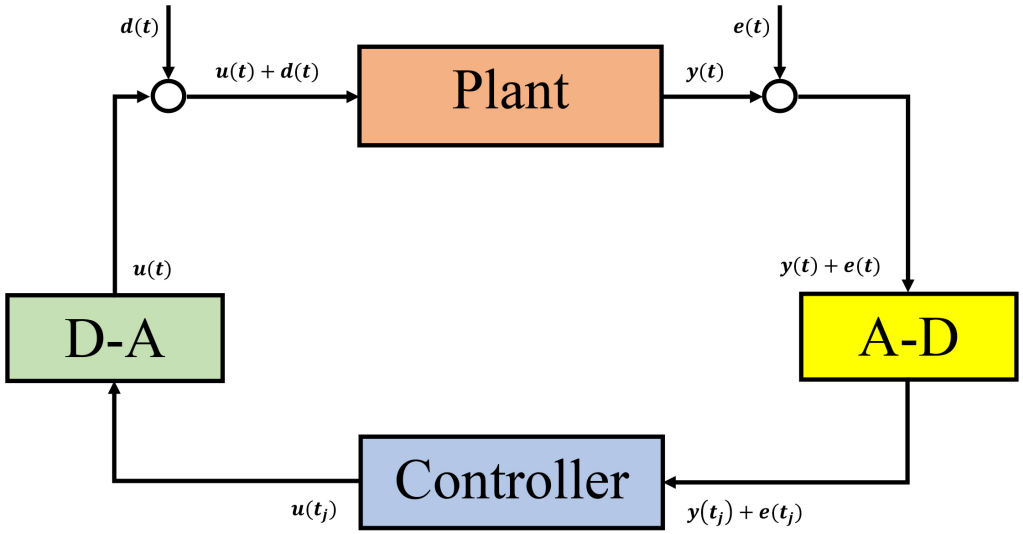

Figure: Sampled-data control system configuration.

In this contest, a continuous time plant is typically controlled by a discrete-time feedback algorithm (a practical engineering situation).

Sampled-data Control

Sampled-data stabilization has been studied in the literature by many approaches, such as:

- **Approximate system discretization:** see, e.g., [5];
- **Emulation:** see, e.g., [6] (Time-varying delay), [7] (Dissipation method), [8] (Hybrid system), [9] (Stabilization in the sample-and-hold sense);
- **Sampled-data:** see, e.g., [10].

[5] S. Monaco, D. Normand-Cyrot, M. Mattioni, Sampled-data stabilization of nonlinear dynamics with input delays through immersion and invariance, *IEEE Transactions on Automatic Control*, Vol. 62, pp. 2561-2567, 2017.
[6] E. Fridman, Introduction to time-delay systems: Analysis and control, *Birkhauser*, 2014.
[7] D. S. Laila, D. Nesic, A. R. Teel, Open and closed loop dissipation inequalities under sampling and controller emulation, *Europ. J. Control*, Vol. 18, pp. 109-125, 2002.
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[10] Y. Yamamoto, A function space approach to sampled data control systems and tracking problems, *IEEE Transactions on Automatic Control*, Vol. 39, pp. 703–713, 1994.

Emulation Approach

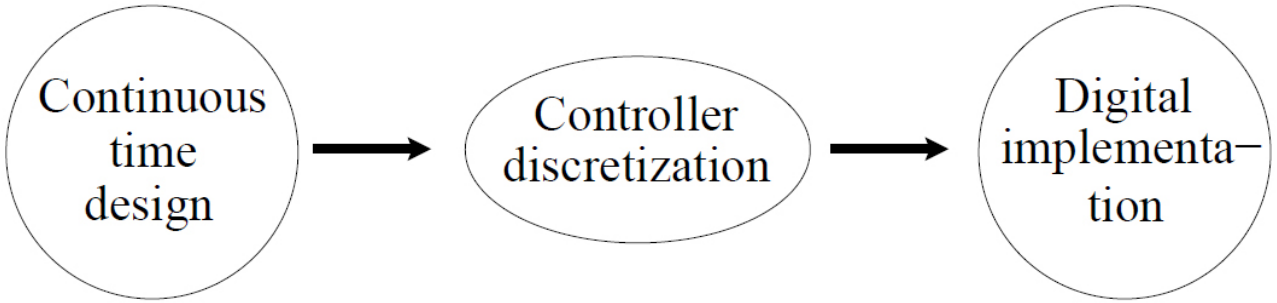


Figure: Emulation of controller

1) a continuous time controller for the system at hand is firstly designed, ignoring sampling;
2) the continuous time controller is discretized and implemented using sample and hold devices;
3) a maximum allowable inter-sampling time is selected in order to ensure/preserve a certain stability property of the sampled-data closed-loop system.

Dynamic Output Feedback Regulator

In the spirit of emulation approach, we first propose the following continuous time dynamic output feedback controller for (1):

$$
\begin{aligned}
\dot{\widehat{G}}(t) &= -K_{xgi}\widehat{G}(t)\widehat{I}(t) + \frac{T_{gh}}{V_G} + H_1(y(t) - \widehat{G}(t)),\\
\dot{\widehat{I}}(t) &= -K_{xi}\widehat{I}(t) + \frac{T_{iGmax}}{V_I}\varphi(y(t-\tau_g)) + \frac{u(t)}{V_I} + H_2(y(t) - \widehat{G}(t))\\
&\quad + \frac{K_{xgi}}{\rho}\left((\widehat{G}(t) - G_{ref})^2 - (y(t) - G_{ref})^2\right),\\
u(t) &= V_I\Bigg(K_{xi}\widehat{I}(t) - \frac{T_{iGmax}}{V_I}\varphi(y(t-\tau_g)) + \frac{K_{xgi}}{\rho}(y(t) - G_{ref})^2\\
&\quad - H_2(y(t) - G_{ref}) - H_3(\widehat{I}(t) - I_{ref})\Bigg),\\
\widehat{G}(\tau) &= \widehat{G}_0(\tau), \quad \widehat{I}(\tau) = \widehat{I}_0(\tau), \quad \tau \in [-\tau_g, 0],
\end{aligned}
\tag{4}
$$

where $H_1, H_2, H_3, \rho \in \mathbb{R}$ are scalar control tuning parameters.

Controller Emulation

The Euler emulation of the output dynamic controller provided in (4) is described, by the following equations

$$
\begin{aligned}
\widehat{G}(t_{j+1}) &= \widehat{G}(t_j) + (t_{j+1} - t_j)\Big(- K_{xgi}\widehat{G}(t_j)\widehat{I}(t_j) + \frac{T_{gh}}{V_G} + H_1(y(t_j) - \widehat{G}(t_j))\Big), \\
\widehat{I}(t_{j+1}) &= \widehat{I}(t_j) + (t_{j+1} - t_j)\Big(- K_{xi}\widehat{I}(t_j) + \frac{T_{iGmax}}{V_I}\varphi(y(t_j - \tau_g)) + \frac{u(t_j)}{V_I} \\
&\quad + H_2(y(t_j) - \widehat{G}(t_j)) + \frac{K_{xgi}}{\rho}\Big((\widehat{G}(t_j) - G_{ref})^2 - (y(t_j) - G_{ref})^2\Big)\Big), \\
u(t) &= V_I\Big(K_{xi}\widehat{I}(t_j) - \frac{T_{iGmax}}{V_I}\varphi(y(t_j - \tau_g)) + \frac{K_{xgi}}{\rho}(y(t_j) - G_{ref})^2 \\
&\quad - H_2(y(t_j) - G_{ref}) - H_3(\widehat{I}(t_j) - I_{ref})\Big), \qquad t_j \le t < t_{j+1},
\end{aligned}
\tag{5}
$$

where t_j, $j = 0, 1, ...,$ are the sampling instants.

Assumptions

There exist a scalar H_2, and positive scalars H_1, H_3, ρ, p_1, p_2, q_1, q_2, q_3, q_4, ω_1, ω_2, ω_3, ω_4, η, μ such that:

$$\begin{aligned} \Xi_1 + \eta\mu p_1 < 0, \qquad & \Xi_2 + \eta\mu\rho p_1 < 0, \\ \Xi_3 + \eta\mu p_2 < 0, \qquad & \Xi_4 + \eta\mu\rho p_2 < 0, \end{aligned} \tag{6}$$

with

$$\Xi_1 = p_1|K_{xgi}G_{ref} + \rho H_2|\omega_1 - 2p_1K_{xgi}I_{ref} + \frac{p_2H_1}{\omega_4} + q_1, \tag{7}$$

$$\Xi_2 = \frac{p_1|K_{xgi}G_{ref} + \rho H_2|}{\omega_1} - 2\rho p_1K_{xi} + \frac{\rho p_1|K_{xi} - H_3|}{\omega_2} + q_2, \tag{8}$$

$$\begin{aligned} \Xi_3 = {} & p_2|K_{xgi}G_{ref} + \rho H_2|\omega_3 - 2p_2K_{xgi}I_{ref} + p_2H_1\omega_4 \\ & -2p_2H_1 + q_3, \end{aligned} \tag{9}$$

$$\Xi_4 = \rho p_1|K_{xi} - H_3|\omega_2 + \frac{p_2|K_{xgi}G_{ref} + \rho H_2|}{\omega_3} - 2\rho p_2H_3 + q_4. \tag{10}$$

Main Result

Theorem

Let the above Assumptions hold. Let $a \in (0, 1]$. Then, for any positive scalars $\bar{q}$, R, r with $r < R$, there exist positive scalars δ (*sampling period*), T (*settling time*), E (*overshoot*) such that, for any partition $\pi_{a,\delta} = \{t_j,\ j = 0, 1, ...\}$, for any initial condition such that

$$\left|\begin{matrix} G_0(\tau) - G_{ref} \\ I_0(\tau) - I_{ref} \\ \widehat{G}_0(\tau) - G_{ref} \\ \widehat{I}_0(\tau) - I_{ref} \end{matrix}\right| \leq R, \quad ess \sup_{\theta \in [-\tau_g, 0]} \left| \frac{d}{d\theta} \begin{bmatrix} G_0(\theta) - G_{ref} \\ I_0(\theta) - I_{ref} \\ \widehat{G}_0(\tau) - G_{ref} \\ \widehat{I}_0(\tau) - I_{ref} \end{bmatrix} \right| \leq \bar{q}, \quad \tau \in [-\tau_g, 0],$$

the corresponding solution of the sampled-data closed-loop system, described by (1)-(5) exists for all $t \in \mathbb{R}^+$, $t_j \in \pi_{a,\delta}$, and, furthermore, satisfies:

$$\left|\begin{matrix} G(t) - G_{ref} \\ I(t) - I_{ref} \\ \widehat{G}(t_j) - G_{ref} \\ \widehat{I}(t_j) - I_{ref} \end{matrix}\right| \leq E,\ \forall t \in \mathbb{R}^+,\ \forall t_j \in \pi_{a,\delta}, \qquad \left|\begin{matrix} G(t) - G_{ref} \\ I(t) - I_{ref} \\ \widehat{G}(t_j) - G_{ref} \\ \widehat{I}(t_j) - I_{ref} \end{matrix}\right| \leq r,\ \forall t \geq T,\ \forall t_j \in \pi_{a,\delta},\ t_j \geq T. \tag{11}$$

Pre-clinical validation

- In order to perform a pre-clinical validation concerning the safety and the efficacy of the proposed glucose control law, we consider a virtual environment very used in the literature.
- A pivotal role in the proposed benchmark is played by the comprehensive mathematical model used to build up the population of virtual subjects upon which the control law is applied: such model [12] allows to deal with healthy subjects as well as T2DM patients and, along with [11] provides the base for the in silico subjects of the UVA/Padua Type 1 Diabetes Simulator (see [13], [14]), accepted by the Food and Drug Administration (FDA) as a substitute to animal trials to test insulin administration therapies for Artificial Pancreas (AP).

[11] C. Dalla Man, D. M. Raimondo, R. A. Rizza, C. Cobelli, GIM, simulation software of meal glucose-insulin model, *J. Diabetes Sci. Technol.*, Vol. 1, no. 3, pp. 323–330, 2007.
[12] C. D. Man, R. A. Rizza, C. Cobelli, Meal simulation model of the glucose-insulin system, *IEEE Trans. Biomed. Eng.*, Vol. 54, no. 10, pp. 1740–1749, Oct. 2007.
[13] B. P. Kovatchev, M. D. Breton, C. Dalla Man, C. Cobelli, In silico model and computer simulation environment approximating the human glucose/insulin utilization, in *Food and Drug Administration Master File MAF 1521*, 2008.
[14] R. Visentin, E. Campos-Náñez, M. Schiavon, D. Lv, M. Vettoretti, M. Breton, B. Kovatchev, C. D. Man, C. Cobelli, The UVA/Padova Type 1 Diabetes Simulator Goes From Single Meal to Single Day, *J. Diabetes Sci. Technol.*, Vol. 12, pp. 273-281, 2018.

Pre-clinical validation

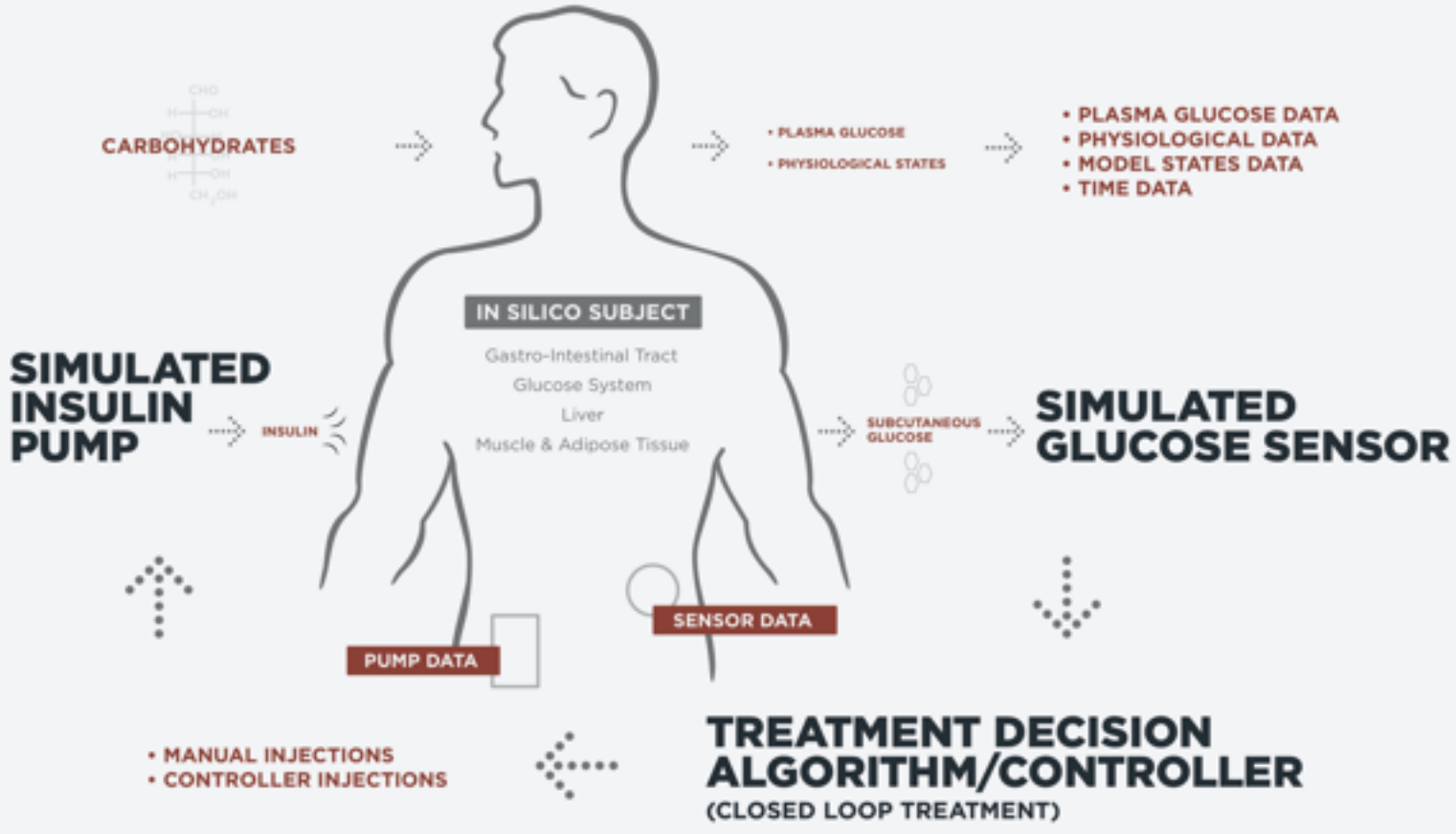


Figure: UVA/Padua Simulator

Pre-clinical validation

Setup of the virtual environment

As in [15], the virtual environment is achieved according to the following steps.

1) The comprehensive model [12] provides a set of parameters allowing to build a T2DM average Virtual Patient (VP).
2) According to a virtual clinical experiment (IVGTT), the model parameters (1) are estimated in order to best fit the compact model onto the comprehensive one (see [15]).
3) The control law parameters are set for the compact model (1) identified at Step 2), properly accounting for the constraints required by the Assumptions.
4) A population of T2DM VPs is sampled by randomly varying the comprehensive model parameters.
5) The proposed control law, tuned for the average VP (according to step 3)), is applied to the population of VPs and performances are assessed.

[15] P. Palumbo, G. Pizzichelli, S. Panunzi, P. Pepe, A. De Gaetano, Model-based control of plasma glycemia: Tests on populations of virtual patients, *Math. Biosci.*, Vol. 257, pp. 2-10, Nov. 2014.

Pre-clinical validation

- The first three Steps of the aforementioned procedure are purely related to the synthesis of the control law, whilst the last two ones are related to the building of the virtual environment.
- In the spirit of a personalized medicine, we could imagine to substitute Step 1) with a real T2DM subject, undergoing a real clinical noninvasive experiment (like the IVGTT, usually exploited for such aim [2]) in order to identify the compact model parameters (1).
- The performed simulations consider the case of a general control law, designed upon an average VP that could be the representative of a rather heterogeneous class of T2DM subjects: a unique control law applied in closed loop to different individuals, each belonging to the same class of patients.

Pre-clinical validation

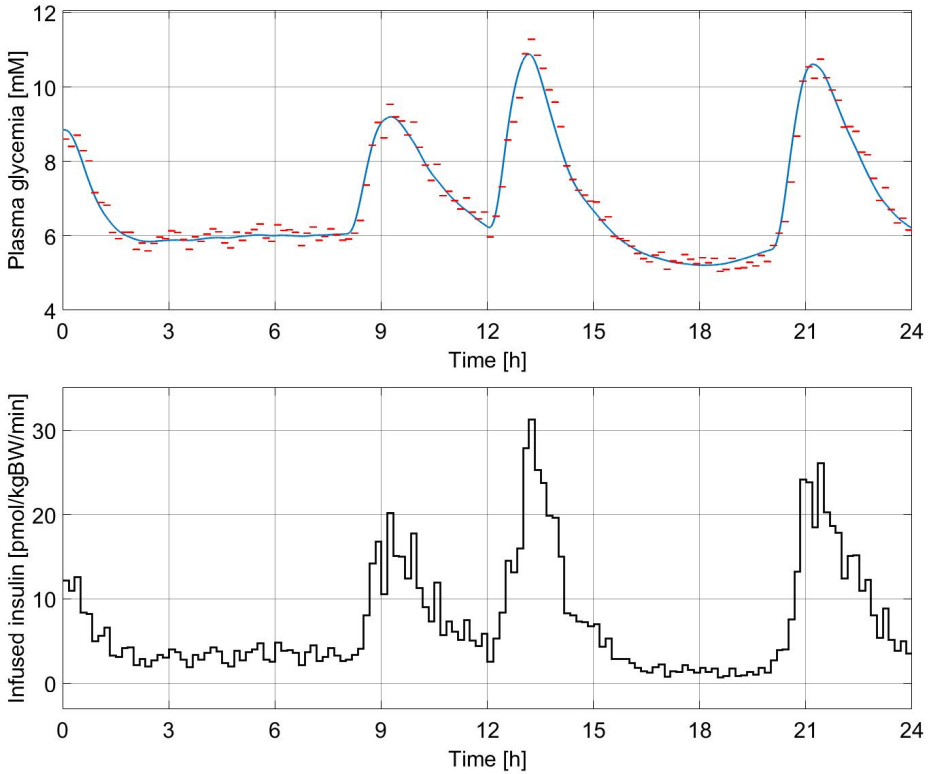
In performed simulations, the following clinical constraints have been also taken into account:

- errors in blood glucose measurements;
- malfunctioning of the insulin delivery pumps;
- presence of health monitoring systems (HMS) (used in order to comply with safety clinical requirements).

Data analysis have been carried out according with well-known standard methodologies proposed in [16], [17] and very used in the literature for the evaluation of glucose control therapies (see, for instance, [15], [18], [19], [20]).

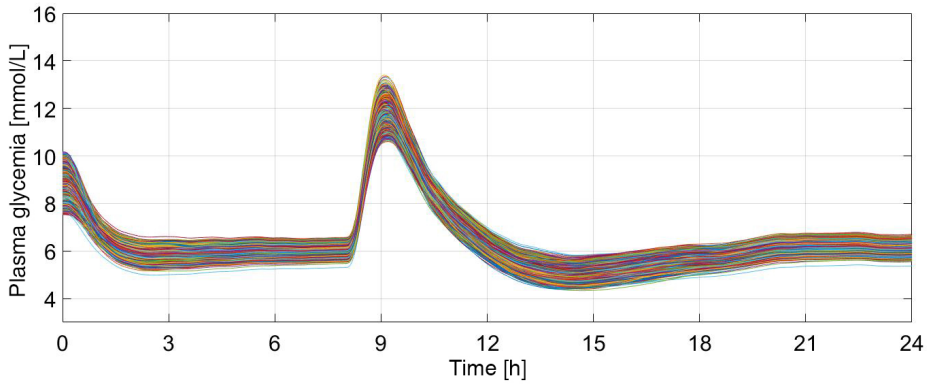
[16] L. J. Chassin, M. E. Wilinska, R. Hovorka, Evaluation of glucose controllers in virtual environment: Methodology and sample application, *Artif. Intell. Med.*, Vol. 32, no. 3, pp. 171-181, 2004.
[17] D. M. Maahs et al., Outcome measures for artificial pancreas clinical trials: A consensus report, *Diabetes Care*, Vol. 39, no. 7, pp. 1175-1179, 2016.
[18] R. Gondhalekar, E. Dassau, H. C. Zisser, and F. J. Doyle, III, Periodic-zone model predictive control for diurnal closed-loop operation of an artificial pancreas, *J. Diabetes Sci. Technol.*, Vol. 7, no. 6, pp. 1446-1460, 2013.
[19] R. Gondhalekar, E. Dassau, and F. J. Doyle, III, Periodic zone-MPC with asymmetric costs for outpatient-ready safety of an artificial pancreas to treat type 1 diabetes, *Automatica*, Vol. 71, pp. 237-246, Sep. 2016.
[20] R. Gondhalekar, E. Dassau, and F. J. Doyle, III, Velocity-weighting & velocity-penalty MPC of an artificial pancreas: Improved safety & performance, *Automatica*, Vol. 91, pp. 105-117, May 2018.

Average Virtual Patient

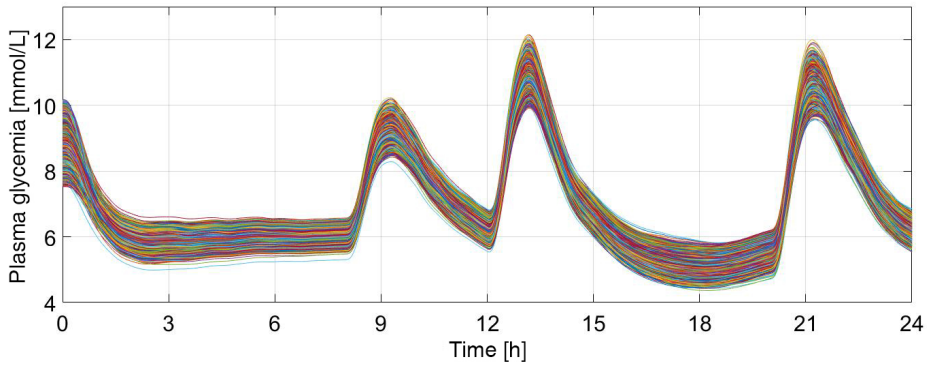


Plasma glycemia and insulin infusion rate for the average VP during the whole 24 [h] of the virtual experiment (three meals of 45, 70, and 70 [g] of CHO are administered at 8, 12, and 20 [h], respectively). The piecewise-constant red line refers to the noisy glucose samples measurements in each sampling interval and the blue continuous is the controlled VP glycemia. The piecewise-constant black line is the control input with uniform sampling period equal to 10 [min].

Population of Virtual Patients



Controlled glycemia of a population of 10000 VPs during the whole 24 [h] of the virtual experiment (a single meal of 90 [g] of CHO is administered at 8 [h]).



Controlled glycemia of a population of 10000 VPs during the whole 24 [h] of the virtual experiment (three meals of 45, 70, and 70 [g] of CHO are administered at 8, 12, and 20 [h], respectively).


THANK
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BOLZÏN
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BÏYAN
SHUKRIA
TINGKI
YAQHANYELAY
TASHAKKUR ATU
SUKSAMA
EKHMET
MEHRBANI
GRAZIE
MAAKE
KOMAPSUMNIDA
JUSPAXAR
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