Closed-loop Proportional-Integral Control of Physiological Systems

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***Abstract*— This work presents a general methodology to design Proportional-Integral (PI) controllers for negative feedback physiological control systems (NFPCS). It is shown that the resulting closed-loop system preserves the NFPCS structure and admits a unique equilibrium point. A local linearization around the equilibrium is then employed to derive general gains selection criteria guaranteeing closed-loop stability and convergence to the healthy physiological state. The proposed methodology is validated on the insulin-glucose regulatory system, where the proposed PI controller is able to drive the system back to the desired physiological equilibrium after a perturbation, achieving zero steady-state error.**

I. Introduction

Physiological processes, in both healthy and pathological conditions, are regulated by mechanisms that maintain key variables within bounded ranges, a principle formalized by homeostasis [1]. From a control-theoretic perspective, homeostasis is associated with the behavior of physiological systems in the neighborhood of equilibrium points, whose characterization is essential for understanding regulation mechanisms and designing strategies to restore equilibrium under perturbations. Physiological systems exhibit nonlinear dynamics, multiscale interactions, and coupling among multiple state variables. Therefore, mathematical modeling plays a central role in describing system dynamics and temporal evolution [2]–[5], while system and control theory provides a rigorous framework for analyzing the existence, uniqueness, and stability of homeostatic equilibria. In healthy conditions, regulation is primarily ensured by intrinsic negative feedback mechanisms that counteract deviations from equilibrium [6]. Pathological conditions may compromise these mechanisms, leading to altered or unstable equilibria and motivating the introduction of external control actions. Such artificial control strategies typically operate alongside endogenous feedback loops, resulting in a closed-loop system where biological dynamics and external inputs interact and whose equilibrium properties require a unified mathematical analysis. The contributions of this study are threefold: (i) to show that the closed-loop system obtained by introducing a Proportional Integral (PI) controller preserves the NFPCS structure; (ii) to prove the uniqueness of the closed-loop equilibrium point; and (iii) to derive general PI tuning conditions that ensure asymptotic stability of the equilibrium. The proposed framework is finally applied to the insulin–glucose regulatory system as a representative case study, demonstrating the effectiveness of control-theoretic tools in the analysis of physiologically relevant homeostatic dynamics.

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II. Methods

A. Reference Model for a Physiological Control System

In [7] we have defined the reference model for a NFPCS.

Definition 1 (NFPCS): Let us consider the following nonlinear system

$$\dot{y}(t) = A_a y(t) + B_a u^y(t) + f\big(y(t), x(t)\big) \tag{1a}$$

$$\dot{x}(t) = A_i x(t) + B_i u^x(t) + g\big(y(t), x(t)\big)\,, \tag{1b}$$

where $A_a \in \mathbb{R}^{m\times m}$, $A_i \in \mathbb{R}^{n\times n}$, $B_a \in \mathbb{R}^{m\times u}$, $B_i \in \mathbb{R}^{n\times v}$, $u^y(\cdot)$ and $u^x(\cdot)$ are nonnegative time functions defined in $[0, +\infty)$, $f : \mathbb{R}^m \times \mathbb{R}^n \mapsto \mathbb{R}^m$, and $g : \mathbb{R}^m \times \mathbb{R}^n \mapsto \mathbb{R}^n$ are piecewise continuously differentiable mappings. Given a compact connected set $\mathcal{O}_y \subseteq \mathbb{R}^m$, and a compact connected set $\mathcal{O}_x \subseteq \mathbb{R}^n$, we say that system (1) is a NFPCS in $\mathcal{O} := \mathcal{O}_y \times \mathcal{O}_x$, if the following conditions are satisfied:

i) The matrices A_a and A_i are diagonal with nonpositive elements.

ii) The functions f and g are continuously differentiable in $\mathcal{O}$, and for all $(x, y) \in \mathcal{O}$

   a) $\frac{\partial f_i(y,x)}{\partial x_j} \geq 0$, $i = 1, \ldots, m$, $j = 1, \ldots, n$; moreover, there exist $i \in \{1, \ldots, m\}$, and $h \in \{1, \ldots, n\}$, such that $\frac{\partial f_i(y,x)}{\partial x_h} > 0$;

   b) $\frac{\partial g_j(y,x)}{\partial y_i} \leq 0$, $j = 1, \ldots, n$, $i = 1, \ldots, m$; moreover, there exist $j \in \{1, \ldots, n\}$, and $k \in \{1, \ldots, m\}$, such that $\frac{\partial g_j(y,x)}{\partial y_k} < 0$. ■

The set $\mathcal{O}$ is, in practice, a suitable neighborhood of the equilibrium point; in the following it will be referred to as the operating envelope of the NFPCS. It is worth noting that the set $\mathcal{O}$ does not coincide, in general, with the Domain of Attraction of the equilibrium point [8]; rather, it is a compact subset of the state space where, if the assumptions

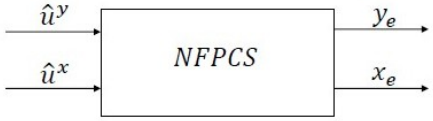

Fig. 1: The NFPCS described by (2) at the healthy equilibrium $(y_e,\, x_e)^T \in \mathcal{O}$.

are satisfied, the homeostatic equilibrium point is located. The problem of estimating the DA of such points will be investigated in future works (for more details on the role of the operating envelope, the interested reader is referred to [9]). The following comments elucidate the rationale behind Definition 1.

Remark 1: Recent papers (see [7], [9], [10]) have shown that model (1) captures the structure of several physiological systems at different scales, e.g. genic circuits, glucose regulation system, reflex arc dynamics, chemostat regulation, etc. ■

Remark 2: The first equation, (1a), is referred as the *activation chain* of the model; for this reason, the involved matrices are labeled with the subscript a. The sub-model (1a) is characterized by the action of the activation species, namely $x(t) \in \mathbb{R}^n$, versus the inhibition species $y(t) \in \mathbb{R}^m$, which represent the output of the sub-model itself. In the same way, the second equation (1b), is related to the *inhibition chain* of the model, which explains the use of the subscript i for the matrices of this sub-model. The sub-model (1b) is characterized by the action of the inhibition species, namely $y(t) \in \mathbb{R}^m$, versus the activation species $x(t) \in \mathbb{R}^m$, which represent the output of the sub-model itself. ■

Remark 3: The (possible) nonlinear terms f and g, are responsible for the negative feedback action of the whole model. More comments on these key parts of the proposed model can be found in the paper [9]. ■

Remark 4: In (1a), the input function u^y represents the production rate of the inhibition species y, while the activation function $f(\cdot,\cdot)$ describes the mechanism of activation of the species x against y. On the other hand, in (1b), u^x indicates the rate of production of x, while the inhibition function $g(\cdot,\cdot)$ accounts for the mechanism of inhibition of y against x. ■

Remark 5: Condition i) in Definition 1 is needed to guarantee the presence of a linear consumption term of the involved species, which has a stabilizing effect on the closed-loop system; some eigenvalues of A_a and/or A_i may be located at the origin of the complex plane, due to the presence of integral actions. ■

Remark 6: A consequence of Assumption 1-iii) is that, in the simplest case of second order systems (one activation and one inhibition variable), $\partial f/\partial x$ ($\partial g/\partial y$) must be strictly positive (negative) in the operating envelope. ■

B. Second Order Physiological Systems

In this section we shall consider system (1) when only one activation and one inhibition variable are present, that is

$$\dot{y}(t) = -\alpha y(t) + b_a u^y(t) + f\big(y(t), x(t)\big) \tag{2a}$$
$$\dot{x}(t) = -\beta x(t) + b_i u^x(t) + g\big(y(t), x(t)\big)\,, \tag{2b}$$

where, according to Definition 1, α, β, b_a and b_i are nonnegative scalars, $u^y(\cdot)$ and $u^x(\cdot)$ are nonnegative scalar time functions defined in $[0, +\infty)$, and $f : \mathbb{R}\times\mathbb{R} \mapsto \mathbb{R}$, and $g : \mathbb{R}\times\mathbb{R} \mapsto \mathbb{R}$ are piecewise continuously differentiable scalar functions. In this case, the sets $\mathcal{O}_y$ and $\mathcal{O}_x$ in Definition 1 reduce to compact intervals in $\mathbb{R}$, $\mathcal{O} = \mathcal{O}_y \times \mathcal{O}_x$ turns out to be a compact box in $\mathbb{R}^2$ and, according to Remark 6, we have that $\partial f/\partial x$ is strictly positive in $\mathcal{O}$, and $\partial g/\partial y$ is strictly negative in $\mathcal{O}$.

When the physiological system described by (2) is in a healthy state, the input functions set to steady-state values, namely $\hat{u}^y$ and $\hat{u}^x$, which lead the system to the homeostatic equilibrium $(y_e\, x_e)^T \in \mathcal{O} \subset \mathbb{R}^2$ (see Figure 1). The following result, provided in [9], establishes the conditions which guarantee existence, uniqueness and stability of the homeostatic equilibrium point for system (2).

Theorem 1: Assume that system (2) is a NFPCS in $\mathcal{O} := \mathcal{O}_y \times \mathcal{O}_x$, according to Definition 1, and that

i) at least one between α and β is strictly positive;
ii) for $(y\ x)^T \in \mathcal{O}$,

$$f_y(y,x) \le 0\,, \quad g_x(y,x) \le 0\,; \tag{3}$$

then, if an equilibrium point $(y_e\, x_e)^T \in \mathcal{O}$ exists, under the constant input $(\hat{u}^y\, \hat{u}^x)^T \in \mathbb{R}_+ \times \mathbb{R}_+$, it is asymptotically stable and unique in $\mathcal{O}$. △

In the following section we shall clarify the above discussion through a real world example.

C. Case study – Glucose concentration regulation

In order to illustrate our approach, we shall consider the second-order dynamic model describing the interactions among glucose and insulin [4], [11]. Understanding the physiological interactions between glucose and insulin is essential for developing accurate mathematical models that describe their dynamic behavior in health and disease. The dynamics of insulin and glucose is described by the following differential equations [12] (the time argument is omitted for brevity)

$$\dot{y} = -\frac{k_\alpha}{C_I} y + \frac{1}{C_I} u^y + f(y,x) \tag{4a}$$
$$\dot{x} = -\frac{\lambda}{C_G} x + \frac{1}{C_G} u^x + g(y,x)\,, \tag{4b}$$

where y and x represent the concentrations of insulin in the plasma and glucose in the blood, respectively; the parameter values are reported in Table I. The glucose concentration acts as the activation variable, whereas the insulin serves as

inhibition variable; moreover

$$f(y,x) = \begin{cases} 0 & x \leq \phi \\ \dfrac{k_\beta}{C_I}(x-\phi) & x > \phi\,, \end{cases} \tag{5a}$$

$$g(y,x) = \begin{cases} -\dfrac{1}{C_G}\nu x y & x \leq \theta \\ -\dfrac{1}{C_G}(\nu x y + \mu(x-\theta)) & x > \theta\,. \end{cases} \tag{5b}$$

Since x and y are intrinsically nonnegative variables, it is simple to verify that system (4)-(5) is a NFPCS, according to Definition 1 (see also [4]), with an operating envelope $\mathcal{O}$ defined as

$$\mathcal{O} := \left\{ (y\ x)^T : y \in [0, H], x \in [0.52, 2.49] \right\}\,, \tag{6}$$

with H any positive scalar.

Such system admits a unique equilibrium point

$$\begin{pmatrix} y_e \\ x_e \end{pmatrix} = \begin{pmatrix} 0.056 \\ 0.81 \end{pmatrix} \begin{bmatrix} mU/ml \\ mg/ml \end{bmatrix} \in \mathcal{O}\,, \tag{7}$$

under the constant inputs $\hat{u}^y$ and $\hat{u}^x$ (see Table I).

Since the hypothesis of Theorem 1 are satisfied in $\mathcal{O}$, we can conclude that the equilibrium point (7) is unique and asymptotically stable.

D. The PI Controller

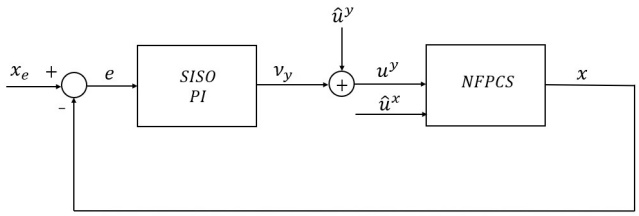

Fig. 2: Block diagram of the physiological control system regulated by a Proportional Integral (PI) controller.

The aim of this paper is to show how an artificial feedback controller can improve the resilience of NFPCSs in presence of perturbations; in particular, we focus on regulators possessing a PI structure. The control action will ensure that the system remains close to the healthy equilibrium even under parameter perturbations.

Current techniques typically focus on glucose regulation rather than insulin control, due to the inherent difficulty in accurately measuring insulin concentration. For this reason, only the x variable is measured.

Therefore, in the following, we shall assume the following general structure for the PI controller (see Figure 2)

$$\begin{aligned} u^y(t) &= \hat{u}^y + \nu_y(t) \\ &= \hat{u}^y + h_{yx} e(t) + k_{yx} \int_0^t e(\tau) d\tau \end{aligned} \tag{8a}$$

$$u^x(t) = \hat{u}^x\,, \tag{8b}$$

where (see Figure 2)

$$e := x_e - x\,, \tag{9}$$

represents the regulation error.

It is worth noting that the integral action in (8) requires one further state variable to be introduced; therefore, the vector of the state variables of the whole closed loop system, given by the connection of (4) and (8), belongs to $\mathbb{R}^3$.

E. Problem statement

The problem we shall consider in this paper is to design a PI controller for the glucose regulation according to the scheme in Figure 2.

Remark 7: In Figure 2, the output of the PI controller, $\nu_y(t)$, represents the rate of drug administered to the patient. Therefore, to guarantee the physical realizability of the proposed control scheme, it is necessary that, at each time instant, the function $\nu_y(t)$ be nonnegative. ■

The solution of the following problem aims to design an artificial PI controller to restore the steady-state conditions corresponding to the healthy state of the physiological system, following a possible deviation from it caused by a pathology.

It is worth noting that we require the closed-loop system retaining the physiological characteristics of the open-loop system. Although this requirement is not mandatory in the context of classical control, the authors believe that it can provide added value when considering the context of physiological systems.

Problem 1: Assume that system (2) is a NFPCS in $\mathcal{O} := \mathcal{O}_y \times \mathcal{O}_x \subset \mathbb{R}^2$, according to Definition 1, admitting the equilibrium $(y_e,\, x_e)^T \in \mathcal{O}$ under the constant inputs $\hat{u}^y$ and $\hat{u}^x$; then design a PI controller in the form (8), according to the scheme in Figure 2, where (9) represents the regulation error, such that the closed-loop system in Figure 2:

i) is a NFPCS in a suitable compact set $\hat{\mathcal{O}} \subset \mathbb{R}^3$;
ii) the closed-loop in Figure 2 admits the unique asymptotically stable equilibrium point $(y_e,\, x_e,\, 0) \in \hat{\mathcal{O}}$. ■

It is worth noting that the PI controller proposed in (8) depends on two gains; such parameters are left free for optimization purposes. By introducing the state variable v, a state-space representation of the integral operator in the PI block in Figure 2 is given by

$$\dot{v}(t) = x(t)\,; \tag{10}$$

therefore, the closed-loop connection of system (2), (8), (9) (with $x_e = 0$), (10), takes the following form

$$\begin{aligned} \dot{y}(t) = &-\alpha y(t) + b_a \hat{u}^y - b_a h_{yx} x(t) \\ &- b_a k_{yx} v(t) + f(y(t), x(t)), \end{aligned} \tag{11a}$$

$$\dot{x}(t) = -\beta x(t) + b_i \hat{u}^x + g(y(t), x(t)), \tag{11b}$$

$$\dot{v}(t) = x(t). \tag{11c}$$

As said above, the first question to answer is whether the closed-loop system (11) is still a NFPCS, according to Definition 1. The following result answers such question.

TABLE I: Parameters and their numerical values.

Parameter	Value	Description
$\hat{u}_x$	8400	Endogenous glucose inflow rate $[mg \cdot h^{-1}]$
$\hat{u}^y$	0	Endogenous insulin inflow rate $[mU \cdot h^{-1}]$
λ	2470	Tissue glucose utilization rate independent of insulin $[ml \cdot h^{-1}]$
k_α	7600	Insulin degradation rate $[ml \cdot h^{-1}]$
k_β	1430	Insulin production rate by the pancreas $[mU \cdot ml \cdot mg^{-1} \cdot h^{-1}]$
ν	139000	Tissue glucose utilization rate dependent on insulin $[ml^2 \cdot mU^{-1} \cdot h^{-1}]$
μ	7200	Renal glucose excretion rate constant $[ml \cdot h^{-1}]$
ϕ	0.51	Pancreatic threshold for insulin secretion $[mg \cdot ml^{-1}]$
θ	2.5	Renal threshold for glucose excretion $[mg \cdot ml^{-1}]$
C_G	15000	Glucose capacitance in the extracellular space $[ml]$
C_I	15000	Insulin capacitance in the extracellular space $[ml]$

Lemma 1: Given a pair of compact intervals $\mathcal{O}_y$ and $\mathcal{O}_x$, let system (2) be a NFPCS in $\mathcal{O} := \mathcal{O}_y \times \mathcal{O}_x$, according to Definition 1; assume there exists a set $\hat{\mathcal{O}}_x \subseteq \mathcal{O}_x$ such that

$$h_{yx} < \frac{1}{b_a}\frac{\partial f}{\partial x}(y,x)\,, \quad (y,x) \in \mathcal{O}_y \times \hat{\mathcal{O}}_x\,; \tag{12}$$

then the closed-loop system (11), rewritten in the form (the time argument is omitted for brevity)

$$\begin{pmatrix}\dot{y}\\ \dot{v}\end{pmatrix} = \begin{pmatrix}-\alpha & 0\\ 0 & 0\end{pmatrix}\begin{pmatrix}y\\ v\end{pmatrix} + \begin{pmatrix}b_a\\ 0\end{pmatrix}\hat{u}^y + \begin{pmatrix}\tilde{f}(y,v,x)\\ \tilde{h}(y,v,x)\end{pmatrix} \tag{13a}$$

$$\dot{x} = -\beta x + \hat{u}^x + \tilde{g}(y,v,x)\,, \tag{13b}$$

where

$$\tilde{f}(y,v,x) := f(y,x) - b_a k_{yx} v - b_a h_{yx} x \tag{14a}$$

$$\tilde{h}(y,v,x) := x \tag{14b}$$

$$\tilde{g}(y,v,x,) = g(y,x)\,, \tag{14c}$$

is an NFPCS in $\hat{\mathcal{O}} := \mathcal{O}_y \times [-M, M] \times \hat{\mathcal{O}}_x$, where M is an arbitrarily large positive number, with x being the activation variable and y, v the inhibition variables.

Proof. The proof follows from the direct computation of the derivatives of the functions $\tilde{f}$, $\tilde{h}$ and $\tilde{g}$, showing that, under the assumptions of the lemma, they verify Definition 1. △

Now, let us come back to the question concerning the existence and uniqueness of the equilibrium point.

Lemma 2: Under the assumptions of Lemma 1, the closed-loop system in Figure 2 admits the unique equilibrium point $(y_e\, 0\, x_e)^T \in \hat{\mathcal{O}}$.

Proof. Let us consider the closed-loop system in Figure 2, and set

$$\dot{v}(t) = e(t)\,. \tag{15}$$

The closed-loop is described by the following equations (time is omitted for brevity)

$$\dot{y} = -\alpha y + b_a \hat{u}^y + b_a h_{yx}\big(x_e - x\big) + b_a k_{yx} v + f(y,x) \tag{16a}$$

$$\dot{v} = x_e - x \tag{16b}$$

$$\dot{x} = -\beta x + \hat{u}^x + g(y,x)\,. \tag{16c}$$

Letting to zero the derivatives in (16), it is readily seen that the vector

$$\begin{pmatrix}y\\ v\\ x\end{pmatrix} := \begin{pmatrix}y_e\\ 0\\ x_e\end{pmatrix} \tag{17}$$

is an equilibrium point for system (16); moreover $(y_e, x_e, 0) \in \hat{\mathcal{O}}$.

As for the proof of the uniqueness of the equilibrium point (17), it is rather long and technical and is omitted for the sake of brevity. △

Lemmas 1 and 2 show under what conditions the closed-loop system (11) is a NFPCS and there exists a unique equilibrium point; the important question to be discussed in the following concerns its asymptotic stability. This fundamental issue is investigated in the following section together with the description of the approach followed for the controller design.

F. Controller design

The PI controller (8) is synthesized according to the properties described in Section II-E.

Procedure 1: The design strategy consists of the following steps:

1) Linearization of the NFPCS (2) around the equilibrium point $(y_e,\, x_e)^T$;
2) Computation of the transfer functions of the linearized NFPCS and of the PI controller, denoted by $G_P(s)$ and $G_C(s)$ respectively, and definition of the loop transfer function $L(s) := G_P(s) \cdot G_C(s)$;
3) Selection of the controller gains h_{yx} and k_{yx} in compliance with the constraint (12) of Lemma 1, so as to guarantee: (a) asymptotic stability of the equilibrium point $(y_e, 0, x_e) \in \hat{\mathcal{O}}$; and (b) nonnegativeness of the control input, as discussed in Remark 7. ■

We shall see that a controller designed according to Procedure 1 guarantees the satisfaction of point ii) in Problem 1. According to Procedure 1, the NFPCS is linearized about the equilibrium point, and the partial derivatives are evaluated locally. Since, in our case, $\delta u_x = 0$, because we only provide feedback on the y-channel, measuring the x variable, we obtain (in the following the time variable is omitted for

brevity)

$$\begin{pmatrix}\delta\dot{y}\\ \delta\dot{x}\end{pmatrix} = \begin{pmatrix}-\alpha+\frac{\partial f}{\partial y} & \frac{\partial f}{\partial x}\\ \frac{\partial g}{\partial y} & -\beta+\frac{\partial g}{\partial x}\end{pmatrix}\begin{pmatrix}\delta y\\ \delta x\end{pmatrix} + \begin{pmatrix}b_a\\ 0\end{pmatrix}\delta u^y$$
$$=: A_{lin}\begin{pmatrix}\delta y\\ \delta x\end{pmatrix} + B_{lin}\delta u^y\,, \tag{18a}$$
$$\delta y = \begin{pmatrix}0 & 1\end{pmatrix}\begin{pmatrix}\delta y\\ \delta x\end{pmatrix} =: C_{lin}\begin{pmatrix}\delta y\\ \delta x\end{pmatrix}\,. \tag{18b}$$

Therefore, a Single Input Single Output (SISO) configuration is assumed. This structure allows for the systematic derivation of general tuning rules for the controller gains, that guarantee the stability of the closed-loop system. The next one is the main result of the paper.

Theorem 2: Assume that

i) the hypothesis of Theorem 1 are satisfied;
ii) system (2) admits an equilibrium point $(y_e,\, x_e)^T \in \mathcal{O}$;
iii) there exists a set $\hat{\mathcal{O}}_x$ such that (12) holds;

then whenever the gains of the PI controller satisfy the conditions

$$k_{yx} < 0 \tag{19a}$$
$$h_{yx} < \frac{k_{yx}}{\phi_1} - \frac{\phi_2}{b_a\partial g/\partial y}\,, \tag{19b}$$

where

$$\phi_1 = \alpha + \beta - \frac{\partial g}{\partial x} - \frac{\partial f}{\partial y} \tag{20a}$$
$$\phi_2 = \alpha\beta - \alpha\frac{\partial g}{\partial x} - \beta\frac{\partial f}{\partial y} + \frac{\partial f}{\partial y}\frac{\partial g}{\partial x} - \frac{\partial f}{\partial x}\frac{\partial g}{\partial y}\,, \tag{20b}$$

the PI controller (8) solves Problem 1.

Proof. Conditions i) and iii) allow to apply Lemma 1 which guarantees that the closed-loop system in Figure 2 is a NFPCS in $\hat{\mathcal{O}} = \mathcal{O}_y \times [-M, M] \times \hat{\mathcal{O}}_x$, with M an arbitrary positive scalar. Moreover, Lemma 1 implies Lemma 2 which, together with condition ii), in turn implies that $(y_e\, 0\, x_e)^T \in \hat{\mathcal{O}}$ is the unique equilibrium point in $\hat{\mathcal{O}}$ of the closed-loop system in Figure 2. Now, to conclude the proof, we have to show that the PI (8), under conditions (19), guarantees the asymptotic stability of the equilibrium $(y_e\, 0\, x_e)^T$. To this end, we shall exploit the Lyapunov First Method, based on linearization arguments. Thus, based on point 2) of Procedure 1, the loop function $L(s)$ is defined as

$$L(s) = G_P(s)\cdot G_C(s) = \frac{b_a\partial g/\partial y\,(h_{yx}s + k_{yx})}{s\,(s^2 + \phi_1 s + \phi_2)}\,, \tag{21}$$

where $s^2 + \phi_1 s + \phi_2$ is the characteristic polynomial of the linearized open loop NFPCS (2).

Stability requires that the poles of the closed loop transfer function $L(s)/\big(1 + L(s)\big)$ lie in the left half of the complex plane; such poles coincide with the roots of the complex polynomial

$$s^3 + \phi_1 s^2 + (\phi_2 + b_a\partial g/\partial y\, h_{yx})s + b_a\partial g/\partial y\, k_{yx}\,. \tag{22}$$

For a third-order polynomial, the Routh-Hurwitz criterion provides necessary and sufficient conditions for asymptotic stability, which, in this case, requires

$$\phi_1 > 0 \tag{23a}$$
$$\phi_2 + b_a\partial g/\partial y\, h_{yx} > 0 \tag{23b}$$
$$b_a\partial g/\partial y\, k_{yx} > 0 \tag{23c}$$
$$\phi_1(\phi_2 + b_a\partial g/\partial y\, h_{yx}) > b_a\partial g/\partial y\, k_{yx}\,. \tag{23d}$$

Due to the assumption i) of the Theorem, the open loop NFPCS (2) is such that the equilibrium point $(y_e,\, x_e)^T$ is asymptotically stable; this last consideration guarantees that the coefficients ϕ_1 and ϕ_2 are strictly positive. Therefore, condition (23a) is satisfied.

Now, note that (19b) coincides with

$$h_{yx} < \frac{b_a\partial g/\partial y k_{yx} - \phi_1\phi_2}{\phi_1 b_a\partial g/\partial y}, \tag{24}$$

that, since the product $\phi_1 b_a\partial g/\partial y$ is strictly negative, can be rewritten

$$\phi_1 b_a\partial g/\partial y h_{yx} > b_a\partial g/\partial y k_{yx} - \phi_1\phi_2\,, \tag{25}$$

which can be finally rewritten as (23d); therefore condition (19b) implies (23d).

In turn, condition (23d) implies

$$\phi_2 + b_a\partial g/\partial y\, h_{yx} > \frac{b_a\partial g/\partial y\, k_{yx}}{\phi_1}\,. \tag{26}$$

The right hand side in (26), due to condition (19a), is strictly positive, therefore (23b) follows.

Finally, it is readily seen, due to (19a), that (23c) is satisfied. From this last consideration the proof follows. △

III. Results

By taking the general loop function form in (21), considering Table I, it follows that

$$b_a\partial g/\partial y = -\frac{\nu x_e}{C_G}\frac{1}{C_I} = -8.34\cdot 10^{-6}\,, \tag{27a}$$
$$\phi_1 = \frac{k_\alpha}{C_I} + \frac{\lambda}{C_I} + \frac{\nu y_e}{C_G} = 1.98\cdot 10^{-2}\,, \tag{27b}$$
$$\phi_2 = \frac{k_\alpha\lambda}{C_I^2} + \frac{k_\alpha\nu y_e}{C_I C_G} + \frac{\nu x_e k_\beta}{C_I C_G} = 2.95\cdot 10^{-4}. \tag{27c}$$

Therefore, by substituting these values in the general loop function expression in (21), we have

$$L(s) = \frac{-8.34\cdot 10^{-6}(h_{yx}s + k_{yx})}{s^3 + 1.98\cdot 10^{-2}s^2 + 2.95\cdot 10^{-4}s}\,. \tag{28}$$

Under the constraints derived in Theorem 2, the gain k_{yx} is necessarily negative. Conversely, the gain h_{yx} may be either positive or negative, depending on the numerical values of the parameters defining its upper bound. The optimal gain values were identified through *in silico* simulations under the stability constraints. The selected values are

$$k_{yx} = -0.1\,, \tag{29a}$$
$$h_{yx} = -1\,. \tag{29b}$$

Under healthy conditions, the equilibrium point is located at $(0.056\,\mathrm{mU/ml},\, 0.81\,\mathrm{mg/ml})$, as shown in Figure 3. The

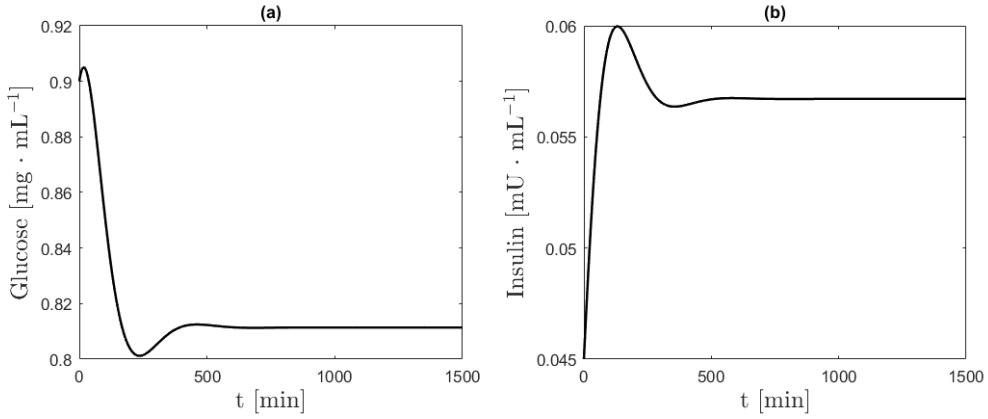

Fig. 3: Trends of state variables over time for a healthy patient. Panel (a) represents blood glucose concentration, whereas panel (b) represents insulin concentration.

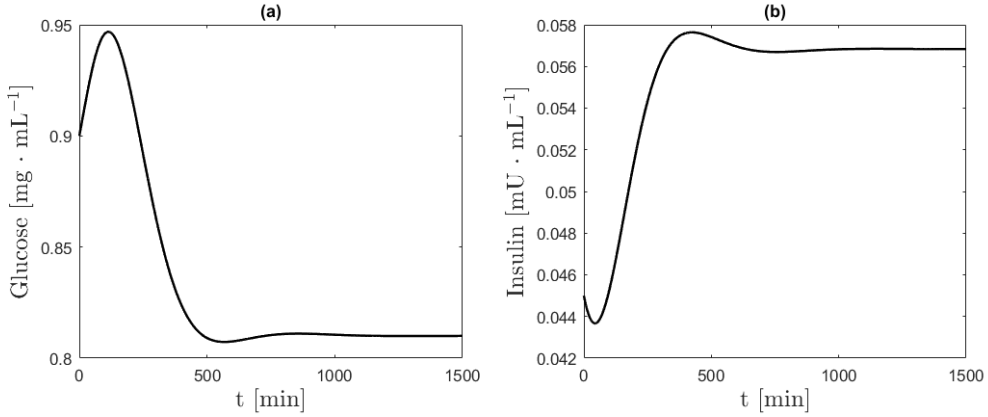

Fig. 4: Trends of state variables over time when the k_β parameter is varied by 50% with respect to its nominal value. Panel (a) represents the blood glucose concentration, whereas panel (b) represents the insulin concentration.

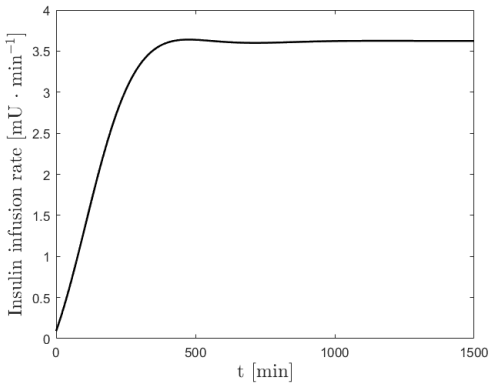

Fig. 5: Insulin infusion rate (control input) trend in time.

control objective is to preserve this equilibrium even in the presence of parameter perturbations. To model the onset of a pathological condition, a 50% perturbation of the parameter k_β is introduced. In this scenario, the PI controller, representing insulin delivery through an insulin pump, is designed according to the proposed methodology. Simulation results show that the controller successfully maintains the healthy equilibrium with zero steady-state error despite the parameter perturbation. The reference is reached with a 5% settling time of approximately 700 minutes (about 11 hours), as shown in Figure 4. Moreover, the control input remains bounded within physiologically plausible limits, ranging from 0.2 to 3.6 $\mathrm{mU\,min^{-1}}$, without excessive actuation effort, as reported in Figure 5.

IV. Discussion and Conclusions

Variations in the system parameters may shift the equilibrium point away from its healthy operating condition. Therefore, the control objective is to drive the system back to the healthy equilibrium while ensuring zero steady-state error. Lemmas 1 and 2 guarantee that the closed-loop system obtained by introducing a PI controller preserves the NFPCS structure and admits a unique equilibrium point. The analysis is carried out under a SISO configuration, in which the activation variable x is measured and the inhibition variable y is manipulated. To achieve the control objective, a general PI tuning methodology based on system linearization is proposed. The linearized plant is combined with the PI controller, leading to a general expression of the loop transfer function for an asymptotically stable NFPCS

under PI control. The closed-loop characteristic equation is then analyzed using the Routh–Hurwitz stability criterion, from which explicit conditions on the PI gains are derived. The proposed methodology is applied to the insulin–glucose regulatory system. The robustness of the PI controller is assessed by perturbing one of the system parameters, namely k_β, in order to emulate the onset of type 1 diabetes. This case study shows that the controller effectively compensates for reduced endogenous insulin production while maintaining bounded and physiologically realistic control inputs (see Figure 5). These results confirm that appropriately tuned PI controllers can achieve reliable regulation objectives in physiologically relevant systems.

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