IEEE Control Systems Letters paper presented at
2023 62nd IEEE Conference on Decision and Control (CDC)
December 13-15, 2023. Marina Bay Sands, Singapore

The long-term effects of physical activity on blood glucose regulation: a model to unravel diabetes progression

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***Abstract*— Physical activity plays a key role in the prevention of type 2 diabetes. However, despite the numerous clinical evidences, there are still no mathematical models that satisfactorily describe the effects of physical activity on the progression of diabetes, preventing its onset or slowing down its course. Instead, there are models describing the influence of single training sessions of physical activity on blood glucose and insulin levels in the short term. In this article we propose a novel model for the long term effects of physical activity on diabetes progression, by exploiting and adapting an existing short-term model of physical activity. A pivotal role in the proposed model is played by interleukin-6 released during physical activity and known to be fundamental in maintaining pancreatic beta cells production and therefore satisfactory insulin secretion. The proposed simulation scenarios show how a modeling approach of physical activity that neglects the interleukin-6 action is not sufficient to capture the cumulative effects of physical exercise on disease progression. Indeed, preliminary results pave the way to natural extensions of the model to account for model-based control techniques for the long-term control of diabetes through personalized lifestyle interventions, properly accounting for the effects of physical activity on the long-term dynamics of blood glucose.**

I. Introduction

Type 2 diabetes, the most common type of diabetes mellitus, is a disease characterized by alterations in the glucose-insulin regulation mechanism, eventually leading to sustained hyperglycemia, strongly related to a wide range of diabetic complications including retinopathy, neuropathy, nephropathy, etc. Type 2 diabetes occurs as a combination of insulin resistance and gradual beta-cells decrease, a decline arising through years, usually related to unhealthy habits including nutrition and lack of physical activity [1]. In light of its high prevalence, the serious social implications and the non-negligible draining of the national healthcare budgets [2], [3], in recent years a new line of research has emerged, usually named as Artificial Pancreas, aiming at developing control techniques for the regulation of the glucose-insulin feedback-loop. Within this framework, a model-based approach has shown indisputable advantages, since it allows to properly account for the physiological machinery underlying the equations describing the glucose-insulin homeostasis, therefore providing meaningful different scenarios according to which control algorithms could be efficiently tested.

Besides, model-based approaches allow to resort to a large variety of classical or up-to-date control techniques: we may cite, among the others, Model Predictive Control [4] [5], nonlinear control [6]–[8], robust control [9], and symbolic control [10]. All these closed-loop control approaches have been focused, so far, on the short-term treatment of diabetes.

On the other hand, dealing with type 2 diabetes prevention, there is ample evidence in the literature that type 2 diabetes progression can be slowed down or also prevented through lifestyle intervention, for example physical activity, diet, and stress management, whereas lack of prevention can lead to significant burden of illness, multi-morbidity, and excess health system utilization [11] [12]. However, mathematical models able to explain the long-term benefits of physical activity are lacking. Motivated by these considerations, the work presented here proposes a novel model, capable of simulating the effects of physical activity on blood glucose control *in the long term*, by introducing the effect of variables that can be used to design the glucose feedback control in closed loop also for the long term.

We remark that defining a proper model of physical activity and its long-term effects on the progression of type 2 diabetes is certainly a complex problem, in light of the numerous physiological variables involved. The approaches reported in the literature concern explanatory models of the effect of physical activity on the glucose dynamics in the short term [13]–[18]. Among these, one of the most popular models is the model by *Roy and Parker* [19], which in turn adapts and extends the minimal model by *Bergman et al.* [20], to include the effect of physical activity on short-term dynamics. These models of physical activity describe how the variables glucose and insulin concentration behave in response to single bouts of physical exercise in a time span of hours. For what concerns the modelling of the long-term effects of physical activity on type 2 diabetes progression, few attempts have been done. An example is the one proposed in [21] to describe the overall long-term effects of lifestyle

This work was supported in part by the European Union, Grant Agreement n. 101095672 (project PRAESIIDIUM "Physics informed machine learning-based prediction and reversion of impaired fasting glucose management", call HORIZON-HLTH-2022-STAYHLTH-02). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. The European Union can not be held responsible for them. This work was also partially supported by the European Union Next-GenerationEU (PNRR) – MISSIONE 4 COMPONENTE 1, INVESTIMENTI 3.4 e 4.1 – Decreto MIUR n.351 del 09/04/2022 within the Italian National Ph.D. Program in Autonomous Systems (DAuSy).

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interventions (a combination of diet and physical activity) in patients enrolled in a diabetes prevention program. It should be pointed out, however, that the literature does also include models of general progression of type 2 diabetes, such as the model by *Topp et al.* [22] and its extensions [23]–[25], that consider also the slow dynamics of beta cells: these models allow to simulate the trends of the variables over a time span of years. The methodology proposed in this work exhibits two fundamental features: on the one hand, it proposes a multiple time-scale model, through the integration of minimal models of physical activity and progression models; on the other hand, it introduces the effects of a particular protein with anti-inflammatory action [26]–[28], which is produced during training sessions: Interleukin-6 (IL-6), on the dynamics of beta cells replication and death. With respect to the existing literature, our contribution is two-fold. First, we show that the simulation of the short-term effects of single bouts of exercise sessions, repeated over a time span of years, is not sufficient to capture the benefits of physical activity in delaying the progression of the disease: to do this, we merged a short-term model of physical activity with a progression model of type-2 diabetes in a two-timescale model. Second, we formalize the effect of IL-6 (by adding new state variables, new parameters and reformulating the long-term dynamics) and show how, with this new mathematical formulation, the two-timescale model is able to explain the benefits produced by physical activity on diabetes progression. The most important result of the work is to show that the benefits produced by physical exercise on the progression of diabetes are mediated by the key action of this involved protein. We finally remark again that the dynamics of low grade systemic inflammation are very complex, and they are mediated by many proteins, of which IL-6 represents indeed a key component, but surely not the only one. To this regard, IL-6 can be seen as a way, in our model, to mathematically represent this cumulative effect in a simple-enough manner to render the model amenable to control purposes. In fact, the one we propose is the first model formulation that takes into account the role of IL-6, possibly paving the way to novel model-based control techniques.

The remainder of the paper is organized as follows: Section II illustrates the development of the work, clarifying the methodology followed for the definition of the model and highlighting the original contribution achieved. Section III and IV show, respectively, the simulation scenarios and the results we obtained in the different stages of implementation and, finally, in Section V we summarize our results and mention further extension of the proposed work.

II. Model formulation

As discussed in the Introduction, with the aim of deriving a control-oriented dynamical model, we propose a two-timescale model. The proposed two-timescale approach is defined by integrating the fast dynamics of physical activity described by the model by *Roy and Parker* [19] and the glucose-insulin slow dynamics, suitably modified from the model by *Ha et al.* [25]. With respect to [19], which adapts and extends the minimal model by *Bergman et al.* [20], we consider only those variables that are specifically introduced to take into account the effect of physical activity, through the oxygen consumption variable $PVO_2^{\max}$, that is

$$\dot{G}_{prod} = a_1 PVO_2^{\max} - a_2 G_{prod}, \tag{1a}$$

$$\dot{G}_{up} = a_3 PVO_2^{\max} - a_4 G_{up}, \tag{1b}$$

$$\dot{I}_e = a_5 PVO_2^{\max} - a_6 I_e, \tag{1c}$$

$$\dot{PVO}_2^{\max} = -0.8 PVO_2^{\max} + 0.8u, \tag{1d}$$

where:

- G_{prod} represents the rate of incremental hepatic glucose production due to glucogenesis promoted to contribute the increased glucose uptake by working tissues G_{up} [mg/kg/min]; I_e represents the rate of incremental insulin removal from the circulatory system induced by physical activity [μU/ml/min];
- $PVO_2^{\max}$ is the istantaneuos oxygen consumption during exercise expressed as a fraction of the maximum oxygen consumption;
- u represents the exercise intensity above the basal level;
- a_1, a_3, a_5, a_2, a_4, a_6 are parameters whose values are taken from [19], and are respectively 0.00158 [mg/kg/min^2], 0.00195 [mg/kg/min^2], 0.00125 [μU/ml/min], 0.056 [1/min], 0.0485 [1/min], 0.075 [1/min].

For what concerns the model by *Ha et al.* [25], it is described by the following equations

$$\dot{G} = R_0 - (E_{g0} + S_I I)\, G, \tag{2a}$$

$$\dot{I} = \frac{\beta}{V} ISR - kI, \tag{2b}$$

$$\dot{\beta} = \frac{P(ISR) - A(M)}{\tau_\beta}\beta, \tag{2c}$$

$$\dot{\gamma} = \frac{\gamma_\infty(G) - \gamma}{\tau_\gamma}, \tag{2d}$$

$$\dot{\sigma} = \frac{\sigma_\infty(ISR, M) - \sigma}{\tau_\sigma}, \tag{2e}$$

$$\dot{S}_I = \frac{-S_I + S_{I,target}}{\tau_{SI}}, \tag{2f}$$

which involve the following state variables:

- G is the plasma glucose concentration [mg/dl];
- I is the serum insulin concentration [μU/ml];
- β is the beta cell mass [mg]; $P(\cdot)$ and $A(\cdot)$ represent beta cells replication and death as sigmoidal functions of the Insulin Secretion Rate (ISR) and of the beta cell Metabolism (M), respectively, see [25] for the details;
- γ is dimensionless and models the shift of the glucose dependence of insulin secretion;
- σ represents the insulin secretion capacity per unit of mass [μU/μg/ d];
- S_I is the insulin sensitivity [ml/μU/d].

For what concerns the parameters, we have

- R_0 is the basal hepatic glucose production ($R_0 = 864$ [mg/dl/d]);

- E_{g0} is the glucose effectiveness at zero insulin ($E_{g0} = 1.44$ [1/d]);
- V is the insulin distribution volume ($V = 5000$ [mL]);
- k is the insulin clearance rate ($k = 432$ [1/d]);
- τ_γ is gamma time constant ($\tau_\gamma = 2.14$ [d]);
- τ_σ is sigma time constant ($\tau_\sigma = 250$ [d]);
- τ_β is beta cells time constant ($\tau_\beta = 7000$ [d]);
- τ_{SI} is the insulin sensitivity time constant ($\tau_{SI} = 250$ [d]).

We remark that the two models above are well accepted and have been validated by clinical data [19], [25]. Our idea is to stem from these models, and couple the fast dynamics of (1) with the slow one of (2), to simulate training sessions over a span of years. To this end, we propose a new dynamics of beta cells by introducing a new state variable, in order to consider the dependence of beta cells replication and death on the total volumes of IL-6 produced during training sessions. In this way, a mathematical formalization of the alteration of the mass of beta cells induced by physical exercise is reached thanks to the intermediate role played by IL-6.

In more detail, we merge the equations (1) of the model by *Roy and Parker* [19] with a modified version of the equations of the model (2) by *Ha et al.* [25], which leads to the following original formulation, involving two new state variables and a new definition of beta cells dynamics:

$$\dot{G} = R_0 + \frac{W}{V_g}\left(G_{prod} - G_{up}\right) - \left(E_{g0} + S_I I\right) G, \tag{3a}$$

$$\dot{I} = \frac{\beta}{V} ISR - kI - I_e, \tag{3b}$$

$$\dot{\beta} = \frac{\bar{P}(ISR) - \bar{A}(M)}{\tau_\beta}\beta, \tag{3c}$$

$$\dot{\gamma} = \frac{\gamma_\infty(G) - \gamma}{\tau_\gamma}, \tag{3d}$$

$$\dot{\sigma} = \frac{\sigma_\infty(ISR, M) - \sigma}{\tau_\sigma}, \tag{3e}$$

$$\dot{S}_I = \frac{-S_I + S_{I,target}}{\tau_{SI}}, \tag{3f}$$

$$\dot{IL}_6 = SR \cdot PVO_2^{\max} - K_{IL6} \cdot IL_6, \tag{3g}$$

$$\dot{Vl} = IL_6 - k_s Vl, \tag{3h}$$

where

- the glucose, insulin and IL_6 dynamics are driven by physical activity by means of the u variable, as explained below, thus allowing to couple the short-term dynamics (1) with the long-term progression (2);
- W is the average body weight of the subject ($W = 70$ [kg]), V_g is the glucose distribution volume ($V_g = 117$ [dl]), from [19];
- IL_6 represents the concentration of IL-6 in the muscle compartment expressed in [pg/ml], due to the short-term IL-6 release induced by physical exercise; for Eq. (3g) reference is made to [28];
- Vl is a new state variable to describe the integral effect of IL-6 released during exercise sessions [(pg/ml)min];
- parameter k_s was set equal to $2.76 \cdot 10^{-6}$ [1/min] to account for the typical times needed for the training induced benefits to decline progressively. Specifically, as described in [29], it has been supposed a 20% decline in the first 8 weeks (80640 in minutes) of detraining and then a complete reversal after long-term inactivity. As a consequence $k_s = -\frac{\ln(0.8)}{80640}$.

As described in [19], u represents the set point for the *sovrabasal* oxygen consumption. It is a *continuous* variable describing a percent value that can span from 0 to 0.92. By varying u, different exercise levels can be simulated: from less intensive training to more intensive ones (for instance $u = 0.3$ for mild exercise like walking, $u > 0.5$ for intensive exercise sessions like intense running). When $u = 0$, no *sovrabasal* oxygen consumption is required to the individual. More precisely, when $u = 0$ basal oxygen consumption for routine activities is experienced by the individual but it does not contribute to fast dynamics in [19] as its contribution is negligible. When $u > 0$ (i.e., during exercise), the fast variables associated with physical activity (i.e. G_{prod}, G_{up}, I_e) perturb the slow dynamics, whereas when the exercise session is over ($u = 0$) those variables, after a transient, go to zero. This allows to couple a fast dynamics of minutes associated with single bouts of exercise session with the overall slow progression. With u switching from 0 to a given continuous value (and vice versa) for each of the exercise sessions, the dynamics of the involved variables is governed by the *continuous* transient of $PVO_2^{\max}$, which takes into account all the intermediate phases of adaptation of the individual to the physical activity.

Dealing with beta cells, a new dynamics is introduced, by modifying the equations of the auxiliary functions $P(ISR)$ and $A(M)$ as described in the original formulation [25] to take into account the integral effect of IL-6 on beta cell replication and death in the following way:

$$\bar{P}(ISR) = P(ISR) + \zeta_1 \frac{Vl^2}{k_n^2 + Vl^2} \tag{4a}$$

$$\bar{A}(M) = A(M) - \zeta_2 \frac{Vl^2}{k_n^2 + Vl^2} \tag{4b}$$

where $P(ISR)$ and $A(M)$ are inherited from [25], as well as γ, σ and S_I dynamics. The use of Hill functions is motivated by the fact that these functions allow to represent a saturation of the effect of the benefit produced by physical exercise in the long term. Due to this property, these functions are widely employed in modeling of biological systems and, in particular, of the glucose regulation [22], [23]. Parameters ζ_1, ζ_2 and k_n have been set equal to 0.5, 0.5 and 3500 [(pg/dl)min], respectively, based on preliminary simulations. These parameters quantify the rate and time of acquisition of the benefits of physical activity on beta cells and could be linked to the individual. These parameters, together with the parameter W, can be used for a more accurate characterization of the individualized response to exercise.

The proposed model represents the formalization of the long-term effect of physical activity on diabetes progression

and it is, to the best of our knowledge, the first model in the literature to take into account this effect.

TABLE I
OUTLINE OF SIMULATIONS

Case	Physical activity	Model
1	No	Ha et al. [25] (HSS)
2	Yes	Ha et al. [25] + Roy-Parker [19] (HSS+RP)
3	Yes	Proposed model (HSS+RP+IL6)

The proposed formulation of equations (4) is linked to the "memory" and benefits that physical activity exerts on beta cells in the long term, promoting their replication and reducing their death, due to the "cumulative" anti-inflammatory effect produced by the total volumes of IL-6 released during training sessions.

III. SIMULATION SCENARIOS

Using the model structure defined in the previous section, it is possible to simulate recurrent sessions of physical activity at varying frequency, over a given range of five-year progression. The simulations are performed under the assumption that at time $t = 0$ conditions predisposing to type 2 diabetes arise, with a significant and progressive reduction of insulin sensitivity, which passes from an initial value of 0.8 to a final value in the five years of 0.3 following an exponential decay, as in [25], with time constant $\tau_{SI} = 250$ [d]. Physical activity is introduced in the simulations in terms of periodic training sessions performed every four days, each lasting two hours, with an exercise intensity $u = 0.7$, corresponding to the 70% of the maximum oxygen consumption, thus simulating exercise sessions performed at intensive level. Initial conditions for glucose concentration, insulin concentration and beta cell mass are set equal to 100 [mg/dl], 5.7 [μU/ml] and 1533.91 [mg], respectively [25]. Simulations have been performed in three different cases described in the following and summarized in Table I.

- **Case 1.** The first case concerns the natural progression of the disease as described by the model *by Ha et al.* (2) [25] without any intervention of physical activity.
- **Case 2.** It includes regular training sessions by modeling only their short-term effect in the course of the five years. That means, the model equations (1) by *Roy and Parker* [19] merged to the model equations (2) by *Ha et al.* [25], with the input u different from zero (specifically, $u = 0.7$) during exercise sessions and u set to zero otherwise, but without IL_6 and Vl dynamics, i.e. both set equal to zero. This case is aimed at showing how the simulation of regular training sessions, reported on a progression of years using the two-timescale model through the coupling of Eqs. (1) and (2), is not sufficient to capture the effects of physical exercise.
- **Case 3.** It concerns the simulations obtained by the proposed model, introducing the modification due to IL-6 and its effects on the dynamics of beta cells on the model described in Case 2.

IV. SIMULATION RESULTS

The results of the simulations carried out assuming a progressive reduction in insulin sensitivity, as described in Section III, are shown in Fig. 1-4.

Fig. 1 shows the observed dynamics of G obtained with the three models here used. The model by *Ha et al.* (HSS), due to the fact that it does not reproduce physical activity, represents only the trend of the basal glucose concentration during the five-year progression. Vice versa, the other two models, with physical activity, show the oscillating effect produced by repeated exercise sessions in the fast-slow dynamics. The sessions of physical activity locally disturb the progression and generate oscillations, that are more distinctly observable in Fig. 1, right-hand panel. Specifically, during each session, glucose concentration drops and, at the end of the exercise, after a transient, it approximately returns to its quasi-stationary value.

The glycemic trends, sampled before each exercise session, are shown in Fig. 2. During the progression, the basal glucose concentration in *Ha et al.* + *Roy and Parker* (HSS+RP) substantially overlaps with the basal glucose concentration of HSS, out of the transient provided by physical activity, exceeding the diabetic threshold of 126 [mg/dl] [30] before the end of the third year of simulation. Therefore, the scenario including only the short-term dynamics of physical activity (HSS+RP) does not seem to capture the progressive, long-term beneficial effects of physical exercise. On the contrary, the basal glucose concentration curve associated with the proposed model (HSS+RP+IL6) remains at normoglycemic levels for almost the entire duration of the simulation, approaching the hyperglycemia threshold of 126 [mg/dl] only in the fifth year. By modeling the action of IL-6 on the dynamics of beta cells, the simulation suggests that physical activity can significantly delay the progression of diabetes, as reasonably expected from a real-world scenario. Similar results, regarding the action of physical activity in delaying the progression of the disease, are found in [21].

For what concerns insulin concentration, it is also subject to the oscillating effect of physical activity in the fast-slow dynamics. However, for the sake of clarity, only the basal trends (i.e., sampled pre-exercise), are illustrated in Fig. 3. The results in Fig. 3 confirm what has already been observed in the glycemic curves in Fig. 2 and they can be explained by also observing the trends of beta cells, as shown in Fig. 4. In the proposed model (HSS+RP+IL6), the increased proliferation and the reduced apoptosis of cells promoted by the effect of IL-6 allow the mass of cells to grow, thus increasing the production of insulin and preventing the onset of glucotoxicity, which, in the first two models, is conversely at the basis of the progressive death of the cells and consequently of the reduced insulin production [22]. It is to note that the beta cell mass obtained at the end of the simulation of model HSS+RP+IL6 (i.e., approximately 2000 [mg]) represents a reasonable mass for the human pancreas, which can have a total beta cell mass, depending on individuals, up to 8000 mg, as explained in [23].

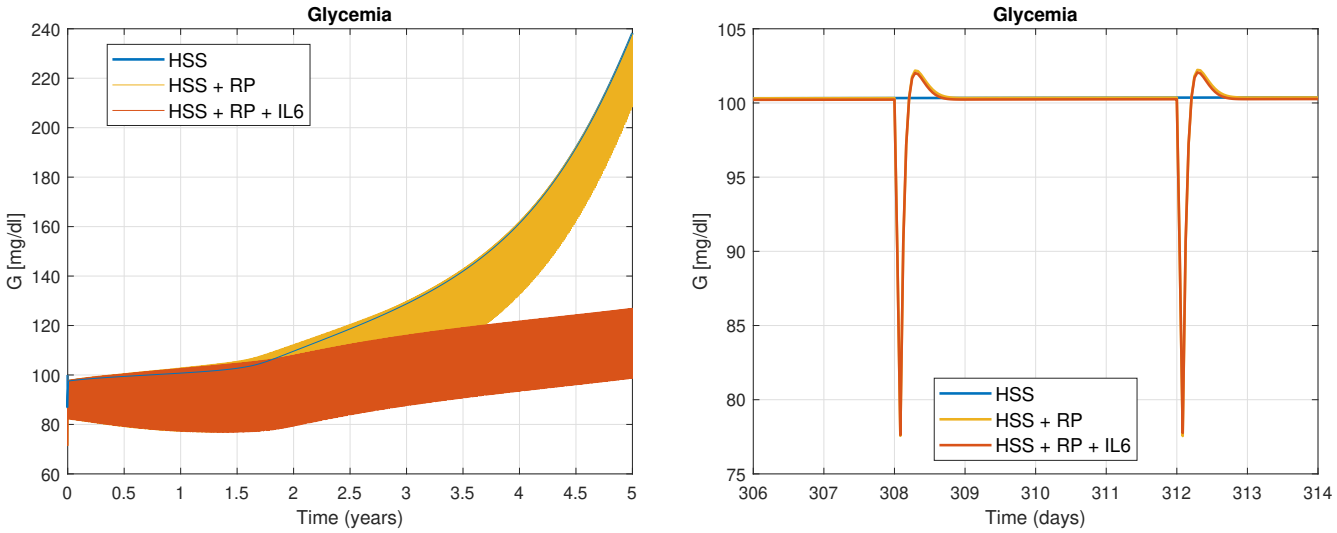

Fig. 1. Left-hand panel: plasma glucose concentration in the fast-slow dynamics as a function of time observed in *Ha et al.* (HSS, blue), in *Ha et al.* + *Roy and Parker* (HSS+RP, yellow) and in the model proposed in this paper (HSS+RP+IL6, red). Right-hand panel: zoom showing the effect of single training sessions in the same models.

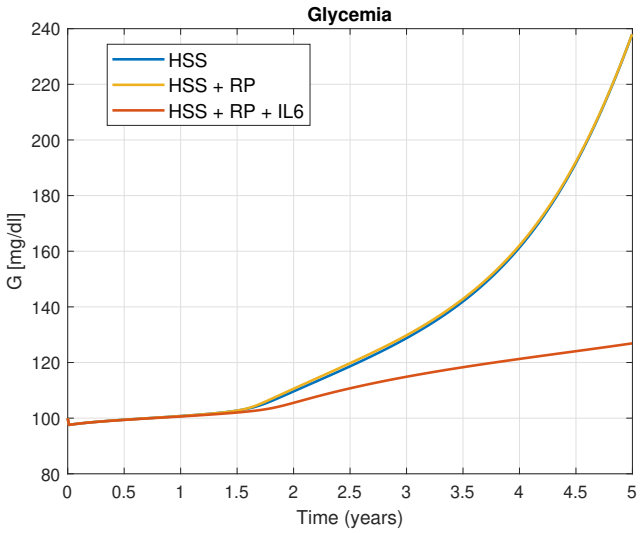

Fig. 2. Plasma basal glucose concentration as a function of time observed in *Ha et al.* (HSS, blue), in *Ha et al.* + *Roy and Parker* (HSS+RP, yellow) and in the model proposed in this paper (HSS+RP+IL6, red).

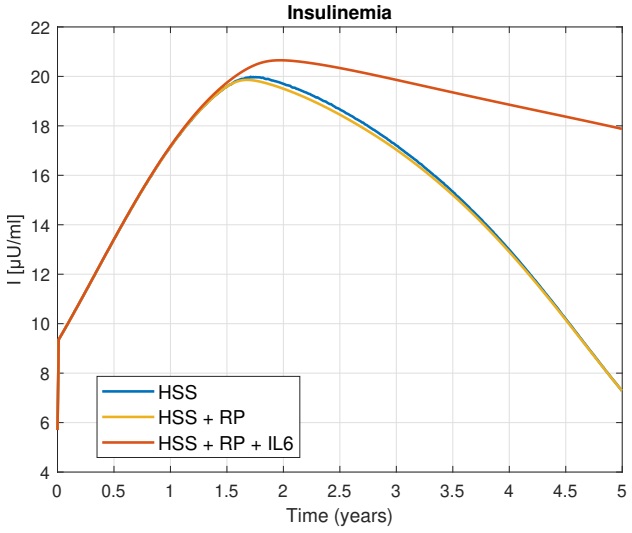

Fig. 3. Serum basal insulin concentration as a function of time observed in *Ha et al.* (HSS, blue), in *Ha et al.* + *Roy and Parker* (HSS+RP, yellow) and in the model proposed in this paper (HSS+RP+IL6, red).

V. Conclusions and Open Issues

The model proposed in this study is the first, to the best of our knowledge, which links the long-term benefits of physical activity to a specific protein, IL-6, so introducing a completely new player in the control of diabetes progression. The results here shown are preliminary but encouraging as they suggest that the proposed model may be used to describe the progressive benefits of physical activity on diabetes progression. Indeed, the next and immediate development of the work will be to implement model-based control techniques based on the model presented here and the validation of the model through data (e.g. Diabetes Prevention Program data [31]). Moreover, it would be interesting in our context to express the dependence on IL-6 of the reduction of insulin resistance, since the already cited clinical literature [26], [27] suggests the beneficial action of physical activity and IL-6 also on insulin sensitivity. Ultimately, it will be useful to characterize the benefit under different scenarios: for example different levels of insulin sensitivity decay, different oxygen consumption dynamics, as suggested in [32]–[34], and also for varying physical activity programs, such as for different frequency, duration, and intensity of exercise.

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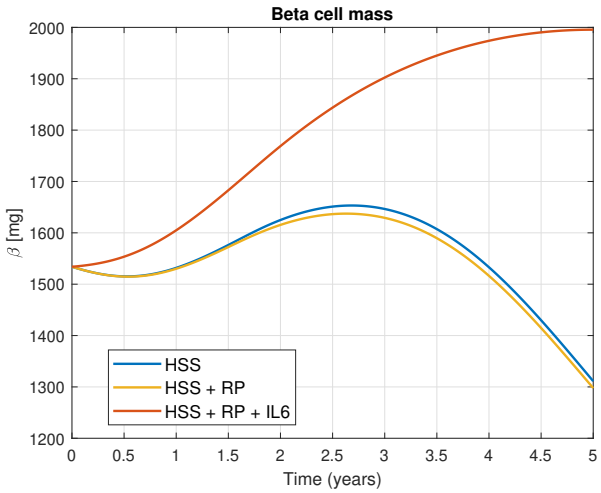

Fig. 4. Beta cell mass as a function of time observed in *Ha et al.* (HSS, blue), in *Ha et al. + Roy and Parker* (HSS+RP, yellow) and in the model proposed in this paper (HSS+RP+IL6, red).

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