A novel dynamic modeling of Insulin Sensitivity in the Blood Glucose Minimal Model

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***Abstract*— Type 1 Diabetes Mellitus (T1DM) is an autoimmune condition characterized by the destruction of pancreatic beta cells, leading to insulin deficiency and requiring lifelong exogenous insulin administration. Effective management of T1DM depends on accurate insulin dosing, a challenge due to the dynamic nature of glucose-insulin interactions, which varies both between and within individuals over time due to variation in insulin sensitivity (S_I). This paper presents an extension of the physiological long-term glucose-insulin model initially proposed by Ruan et al. [1], incorporating a novel nonlinearity in it. The new model reflects S_I variability as a function of both physiological variables and circadian rhythms. By capturing the temporal fluctuations in S_I, the model aims to enhance the predictive capability of glucose-insulin models without increasing complexity, facilitating future integration into real-time control systems like model predictive control (MPC) in artificial pancreas (AP) systems. Simulation scenarios with the UVA/Padova T1DM simulator validate the model, demonstrating improvements in blood glucose modeling compared to existing methods.**

I. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune condition characterized by the destruction of pancreatic beta cells, leading to an absolute deficiency in insulin production [2]. Patients with T1DM require lifelong exogenous insulin administration to regulate their blood glucose levels (BGL) and prevent both hypoglycemia and hyperglycemia, i.e., respectively, BGL $\leqslant$ 70 and $\geqslant$ 180 [mg/dL], and the related long-term complications affecting the cardiovascular, renal, and nervous systems [3]. Effective management of T1DM, the functional insulin treatment (FIT), relies on precise dosing of insulin, trying to mimic healthy pancreatic function [4]. Insulin administration must be carefully balanced during both mealtimes and fasting periods, requiring accurate computation of postprandial boluses and basal insulin levels. Although these doses can be directly estimated through the FIT support tools (i.e. correction factor, CF, insulin to carbs ration, CR, duration of insulin action, DIA) [5] according to BGL, this is inherently challenging because of the complex and dynamic nature of glucose-insulin interactions in the human body. Moreover, when considering traditional, patient-managed manual therapy the likelihood of over- or underestimation of required insulin levels increases, leading to the complications mentioned above. The development of advanced therapeutic strategies is crucial to avoid such scenarios; the artificial pancreas (AP), a hybrid closed-loop system, is the best strategy at the moment to implement automatic blood glucose control in T1DM patients. The core rate of AP is the control algorithm embedded, whose goal is to compute the right amount of insulin needed to steer glycemia to the *euglycemic* range, i.e. 70 $\leqslant$ BGL $\leqslant$ 180 [mg/dL] (normoglycemia). However, although the advent of AP, insulin management in T1DM individuals often remains suboptimal; effective glycemic control in T1DM requires the consideration of factors like circadian rhythms, physical activity, and psychological stress that affect insulin needs. This intra-day and inter-day variability is caused mainly by variations of insulin sensitivity (S_I), which reflects the body's responsiveness to insulin in terms of enhancing glucose uptake and reducing endogenous glucose production. S_I is not static; it fluctuates due to factors such as circadian rhythms, physical activity, stress, and hormonal variations [6]. Particularly, several studies evidenced the fact that S_I (often referred as its opposite, insulin resistance) varies according to two more scenarios, i.e. glycemia above the fasting basal levels and hyperinsulinemia (elevated insulin levels in the bloodstream) [7]. These have been shown to both initiate and exacerbate insulin resistance across various tissues. This diminished sensitivity impairs glucose uptake and utilization, further exacerbating hyperglycemia and creating a feedback loop that perpetuates metabolic dysfunction [8]. Similarly, even modest increases in basal insulin levels can significantly impair S_I, creating a vicious cycle where insulin resistance further drives hyperinsulinemia [9], [10]. To cope with this variability, physicians periodically review self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM) data to fine-tune FIT tools such as basal rates (i.e. insulin ground injections), CR and CF. Capturing the dynamic behavior of S_I would avoid this necessity, being possible to automatize this process through models, and so improving their predictive capability and, consequently, the safety and efficacy of insulin therapy. To address this challenge, (i) model-based control algorithms [1], [11], [12], offer a particularly effective solution, as they rely on mathematical models to replicate glucose-insulin

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interactions, providing a high degree of interpretability. Such approaches can capture systematic variations in S_I via time-varying parameters [13], [14]. However, identifying other S_I fluctuations, aligned with the underlying physiological mechanisms, remains challenging. In contrast, (ii) data-driven approaches [15], [16], [17] rely on large datasets to infer system dynamics, often using machine learning techniques. These methods can bypass some of the complexities involved in model identification, as they require less physiological knowledge. Despite this, they tend to lack in interpretability and are often computationally demanding.

Previous modeling efforts of S_I have still been made; Lin et al. [18] presented a stochastic model of S_I variability that defines probability density functions of S_I one hour ahead, to be used to find the glycemic distribution, i.e. BGL of the next hour. Moreover, Visentin et al. [19] studied the intra-day (circadian) variations of S_I, proposing a step-wise model that varies three times a day, according to the three main meals. In this study, we adopt a model-based approach (i) by introducing a more dynamic representation of insulin sensitivity. Building upon the physiological long-term glucose-insulin interaction model of Ruan et al. [1] (also extended in [20], Section 2), our model treats S_I as a continuously evolving state, influenced by physiological variables such as glucose levels and insulin on board (IOB), rather than a static or step-wise parameter. By incorporating these dynamics, we aim to better capture temporal fluctuations in S_I and provide a more realistic representation of its behavior, without significantly increasing model complexity. In this way it remains easy the integration of the model into real-time control systems, such as model predictive control (MPC) algorithms used in AP systems [21].

The remainder of this paper is organized as follows: Section II details the methods used to develop the extended model, including the formulation of glucose dynamics, insulin absorption, meal absorption, and the novel insulin sensitivity dynamics. Section III presents the results of parameter identification and model validation using simulation scenarios based on the UVA/Padova T1DM simulator [22]. Finally, Section IV discusses the implications of our findings and potential future applications in the management of T1DM.

II. METHODS

The proposed physiological long-term model is an extension of the Ruan proposal [20], that considers a new nonlinerity on the insulin sensitivity.

A. Glucose dynamics

The evolution of glycemia term is described by a single compartment:

$$\frac{dG(t)}{dt} = \theta_0 - \theta_1 G(t) - S_I(t) Q_i(t) + \theta_2 Q_g(t) \tag{1}$$

where $G(t)$ is the blood glucose concentration [mg/dL], $Q_i(t)$ is the insulin delivery rate in plasma [U/min] and $Q_g(t)$ is the rate of carbohydrate absorption from the gut [g/min]. The novelty of this proposal lies in considering the dynamic behavior of the insulin sensitivity, $S_I(t)$ [mg/(dL · U)], making it a new system state rather than a fixed parameter. Its formulation will be discussed later in this chapter.

The model parameters include θ_1, the glucose effectiveness [/min], which represents the rate of glucose uptake by peripheral tissues and the suppression of hepatic glucose release. This is also referred to as glucose self-regulation effect to promote its own metabolism. Moreover, θ_2 is the carbohydrate raise factor [mg/(dL · g)], being the glucose rate of appearance in plasma $Ra(t) = \theta_2 Q_g(t)$. Finally, θ_0 is the endogenous glucose production (EGP) at zero glucose and insulin levels [mg/(dL · min)], i.e. basal levels.

B. Insulin absorption dynamics

The insulin absorption subsystem is described by two compartments, representing pharmacokinetics of insulin in both the subcutaneous and blood compartments:

$$\frac{dQ_i(t)}{dt} = -\frac{1}{\theta_3} Q_i(t) + \frac{1}{\theta_3} Q_{i_{sub}}(t) \tag{2}$$

$$\frac{dQ_{i_{sub}}(t)}{dt} = -\frac{1}{\theta_3} Q_{i_{sub}}(t) + \frac{1}{\theta_3} u(t) \tag{3}$$

where $Q_{i_{sub}}$ is the insulin delivery rate in the subcutaneous compartment [U/min], θ_3 is the time constant for time-to-maximum effective insulin concentration [min] and $u(t)$ is the insulin infusion rate (including both bolus and basal) [U/min].

Remark 1 Insulin on Board (IOB) [U], i.e. the amount of insulin remaining in the body from previous basal/boluses injections, can be derived from equations (2)-(3) as:

$$\begin{aligned} IOB(t) :&= \int_0^t (u(\tau) - Q_i(\tau)) d\tau \\ &= \int_0^t \theta_3 (\dot{Q}_i(\tau) + \dot{Q}_{isub}(\tau)) d\tau \\ &= \theta_3 (Q_i(t) + Q_{i_{sub}}(t)) \end{aligned} \tag{4}$$

considering $u(0) = 0$ and $Q_i(0) = 0$ as initial condition in (2)-(3) [20].

C. Meal absorption dynamics

The meal absorption subsystem is similarly described by the following two compartments:

$$\frac{dQ_g(t)}{dt} = -\frac{1}{\theta_4} Q_g(t) + \frac{1}{\theta_4} Q_{sto}(t) \tag{5}$$

$$\frac{dQ_{sto}(t)}{dt} = -\frac{1}{\theta_4} Q_{sto}(t) + \frac{1}{\theta_4} r(t) \tag{6}$$

where Q_{sto} is the glucose delivery rate from the stomach [g/min], θ_4 is the time-to-maximum appearance rate of glucose in gut (time constant) [min] and $r(t)$ is the rate of oral ingested carbohydrate [g/min].

D. Insulin Sensitivity dynamics

The novel state of the model, S_I is described using a single-compartment dynamic model of which evolution is analytically computed as:

$$\dot{S}_I(t) = -\frac{1}{\theta_5} S_I(t) - \frac{1}{\theta_6} \Delta G(t) - \frac{1}{\theta_7} \Delta IOB(t) + \frac{1}{\theta_5} S_{I_{Tar}}(t) \quad (7)$$

where θ_5, θ_6 and θ_7 are time constant [min] that govern the rate of change for S_I, $\Delta G(t)$, and $\Delta IOB(t)$, respectively. Here, $\Delta G(t) = G(t) - \tilde{G}_b$ represents the deviation of glucose $G(t)$ from its basal, fasting level $\tilde{G}_b$, capturing the increase in insulin resistance due to hyperglycemia beyond basal rates [8]. Similarly, $\Delta IOB(t) = IOB(t) - IOB_b$ is the difference between the insulin on board and its basal value, which reflects the increase in insulin resistance due to hyperinsulinemia [9], [10]. The basal insulin on board, $IOB_b = 2\tilde{U}_b\theta_3$, is derived from solving Equation 4 assuming $u(t) = \tilde{U}_b$, the basal insulin delivery rate required to bring glucose levels to $\tilde{G}_b$.

The term $S_{I_{Tar}}(t)$ represents the baseline insulin sensitivity, which is subject to circadian variations. This baseline reflects insulin sensitivity at zero glucose and insulin deviation (i.e. at basal levels) and is modeled as a sinusoidal function with a 24-hour period, following the approach described in [23]. This function is given by:

$$S_{I_{Tar}}(t) = CF \cdot \left(1 + \theta_8 \cdot sin\left(\frac{2 \cdot \pi \cdot t}{60 \cdot 24} + 2 \cdot \pi \cdot \theta_9\right)\right) \quad (8)$$

where CF is the so-called "correction factor", which is estimated a priori using the 1700 rule [22]. The sinusoidal oscillation of $S_{I_{Tar}}(t)$ introduces a circadian rhythm into the insulin sensitivity, with θ_8 representing the amplitude of the oscillation and θ_9 the phase shift. As a result, the state $S_I(t)$ oscillates around CF due to the circadian modulation provided by $S_{I_{Tar}}(t)$.

It is important to note that both $\tilde{G}b$ and $\tilde{U}b$ (the basal glucose and insulin delivery, respectively) cannot remain constant simultaneously due to the oscillatory nature of insulin sensitivity driven by S_{ITar}. Therefore, these are denoted as $\tilde{G}_b$ and $\tilde{U}_b$ temporarily, with a revised basal condition to be introduced in Section II-E.

Remark 2 The system of ordinary differential equation (1)-(7) can be reordered in the following nonlinear system:

$$\dot{x}(t) = f\left(x(t), u(t), r(t), S_{I_{Tar}}(t), t\right) \quad (9)$$

where $x(t) = [G(t), Q_i(t), Q_{i_{sub}}(t), Q_g(t), Q_{sto}(t), S_I(t)]'$ is the system states vector and $f(\cdot)$ groups the respective ordinary differential equations.

E. Basal condition analysis

The condition in which there is no meal intake ($r(t) = 0$) is referred as "system under basal condition". In such a fasting scenario, it is called basal insulin value U_b the ground, constant insulin value that maintains fixed the blood glucose level, called basal G_b. This pair (U_b, G_b) represent the ground equilibrium condition in a linear minimal model, as presented in [20]. If the case of a non linear system is assumed, like the one proposed in this paper, the concept of equilibrium is lost. In such a fasting scenario insulin sensitivity is affected by the circadian variations, intrinsic in the state. This condition is biunivocally reflected on insulin and glucose basal levels: if a fixed (constant) insulin value is maintained, circadian variability of S_I is reflected on glucose levels, which will oscillate around a trajectory. On opposite, if a fixed (constant) glucose level is desired, variable and periodic values of insulin basal injections are needed. However, it is possible in both cases to assume the concept of equilibrium not as a single point, but as a trajectory, based on the element of the pair (u_s, G_s) desired to be maintained fixed.

In this sense, if a fixed input $u(t) = U_b$ is considered, the basal condition of $x(t)$, defined as $x_b(t)$ is obtained through a trajectory of period T, explicitally written as follows:

$$x_b(t) = \begin{bmatrix} \tilde{G}_b \\ Q_{i_b} \\ Q_{i_{sub}} \\ 0 \\ 0 \\ S_{I,b}(t) \end{bmatrix} = \begin{bmatrix} \frac{\theta_0 - S_{I_{Tar}}(t) \cdot U_b}{\theta_1} \\ U_b \\ U_b \\ 0 \\ 0 \\ S_{I_{Tar}}(t) \end{bmatrix}$$

Following this reasoning, Eq. 7 considers basal insulin value $\tilde{U}_b = U_b$ and glucose values $\tilde{G}_b(t) = \frac{\theta_0 - S_{I_{Tar}}(t) \cdot U_b}{\theta_1}$. Similar analysis considering a fixed value of glucose, G_b, can be found in [13]. However, for the sake of this paper, all the analysis have been conducted considering a fixed basal insulin value U_b.

F. Parameter Identification/Simulation scenario

Model parameters were identified using a cohort of 10 T1DM adult patients from the UVA/Padova simulator [22]. In addition, the commercial version by TEG (DMMS.R [24]) implements circadian variations in insulin sensitivity, following the work proposed by Toffanin et al. [25]. The identification protocol consists of a 4-day simulation, with the first 3 days dedicated to model parameter estimation and the final day reserved for validation purposes. The timing and sizes of both meals and insulin boluses were chosen based on the scenario outlined by Messori et al. [26] (Table 2, "Identification protocol for constrained optimization approach").

A critical consideration in identifying parameters for biological models is ensuring that the parameters remain physiologically plausible, i.e. they should accurately reflect the real physiological system. To achieve this, we employed a double regularized least-squares (RLS) technique. The first phase of parameter identification was based on initial estimates of the carbohydrate-to-insulin ratio (CR^0), time-to-maximum effective insulin concentration (θ_4^0), and time-to-maximum glucose appearance rate in the gut (θ_5^0), following the method proposed by Abuin et al. [20] (Eq. 7, Section 2.5). In this first scenario, the circadian variability in the UVA/Padova simulator was deactivated, and the model from [20] was used to estimate fixed S_I parameters. Once plausible parameters for the fixed S_I model were identified, a second RLS process

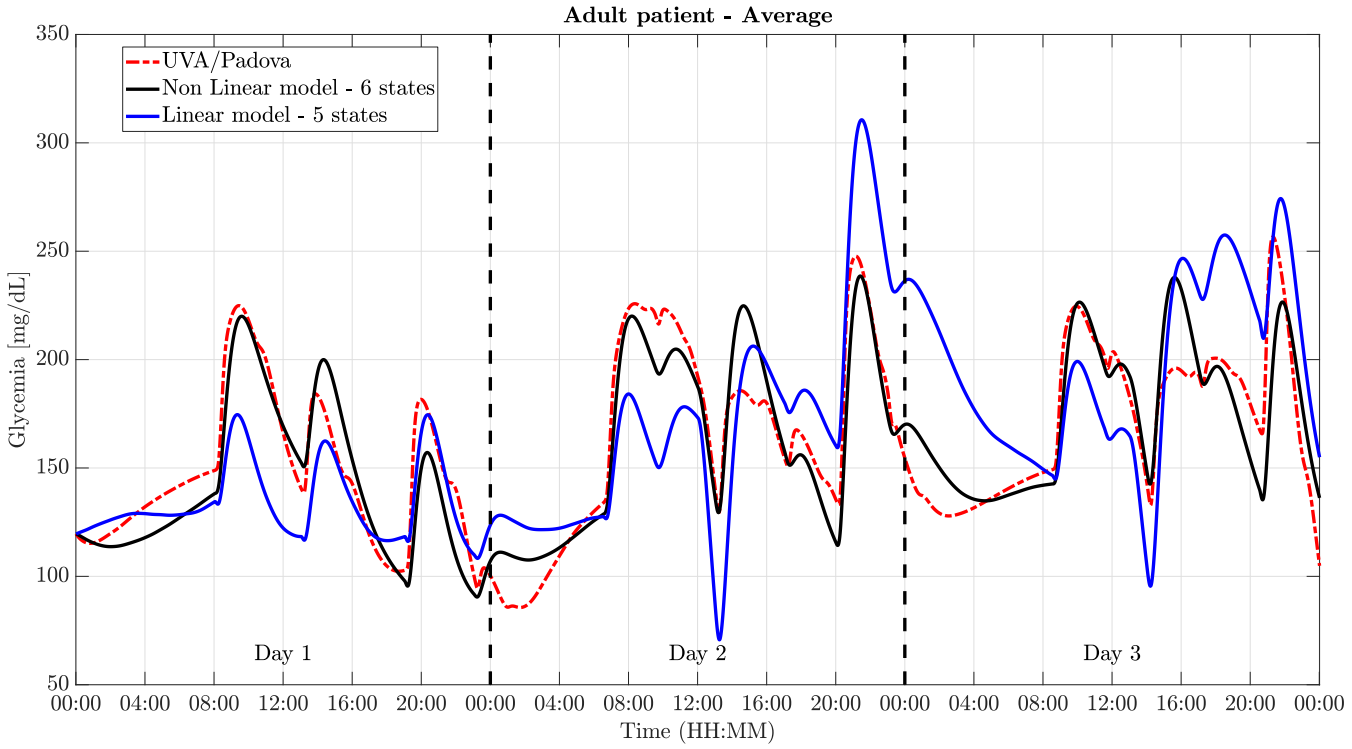

Fig. 1: Validation of the adult average patient of UVA/Padova. The red dotted line is the in-silico glucose data, considered as ground truth (nonlinear time variant model from UVA/Padova), that embeds circadian variability of insulin sensitivity. The black line is the prediction obtained by means of the nonlinear model proposed in this article. The blue line is the prediction obtained through the linear model proposed by [20], which considers S_I as a fixed parameter.

TABLE I: Estimated parameters of 10 in-silico adult patients

Patient	001	002	003	004	005	006	007	008	009	010
θ_0 [mg/(dL · min)]	1.933	1.8055	1.5381	1.4402	1.0664	1.9347	1.6855	1.2454	1.4662	1.4463
θ_1 [/min]	0.0085	0.0075	0.005	0.0051	0.0031	0.01	0.0065	0.0046	0.0063	0.0057
θ_2 [mg/(dL· g)]	3.4062	2.8165	2.7003	2.8965	3.5044	3.975	5.0279	3.2781	3.9508	2.8249
θ_3 [min]	56.0042	40.0139	52.2082	59.5082	45.5115	52.5075	47.5077	50.0108	50.5095	50.5091
θ_4 [min]	33.8452	23.4108	31.2135	32.132	33.4039	30.959	31.8087	33.3191	31.7201	30.5903
θ_5 [min]	20.0075	20.6461	20.5779	47.1303	59.2646	20.0007	34.976	52.1151	28.1193	38.5459
θ_6 [min]	236.0527	140.6553	143.8824	237.9891	239.4908	239.4273	190.3575	229.391	181.9385	220.7172
θ_7 [min]	15.0036	17.8467	15.7327	15.0008	15.0001	18.9189	270.1115	15.0013	15.1185	15.0009
θ_8	23.282	21.4315	16.5408	15.7272	15.6879	22.9181	29.8667	18.2776	21.094	21.8212
θ_9	40.9308	44.9974	42.1654	37.9537	41.582	38.9836	32.6753	41.7485	41.0704	46.2165

was conducted with circadian variability enabled, regularized around the parameters found. This approach ensured that the model maintained physiological plausibility gained by the first regularization, while capturing the dynamics of the new state S_I. The cost function minimization was performed using the Matlab *fmincon* routine.

After parameter identification, model validation was carried out using the second protocol proposed by Messori et al. [26] (Table 3, "Test protocol for individualized models"), applying the goodness of fit (GoF) metric to evaluate the model's performance:

$$GoF = 100\left(1 - \frac{||y(k) - \hat{y}(k)||}{||y(k) - \overline{y}(k)||}\right) \tag{10}$$

where $y(k)$ is the measured blood glucose from in-silico patient of UVA/Padova simulator, $\overline{y}(k)$ is its average, and $\hat{y}(k)$ is the model predicted output.

III. RESULTS

In view of utilizing the individualized model for control purposes ([21], [27]), its performance and quality have been evaluated through simulations (i.e., the validation scenario). In this sense, values of inputs $u(k)$ and $r(k)$ have been used in equations 3 and 6, without incorporating past glucose values $G(k)$. The results, presented in Figure 1, are compared with the average nonlinear adult patient model (regarded as the ground truth), whose values were obtained from the UVA/Padova simulator. Additionally, predictions from the linear model described in [20]—which assumes S_I as a fixed parameter—are also included for comparison with our extended proposal. The overall GoF, calculated by equation 10, obtained a median value and interquartile range of 54.44

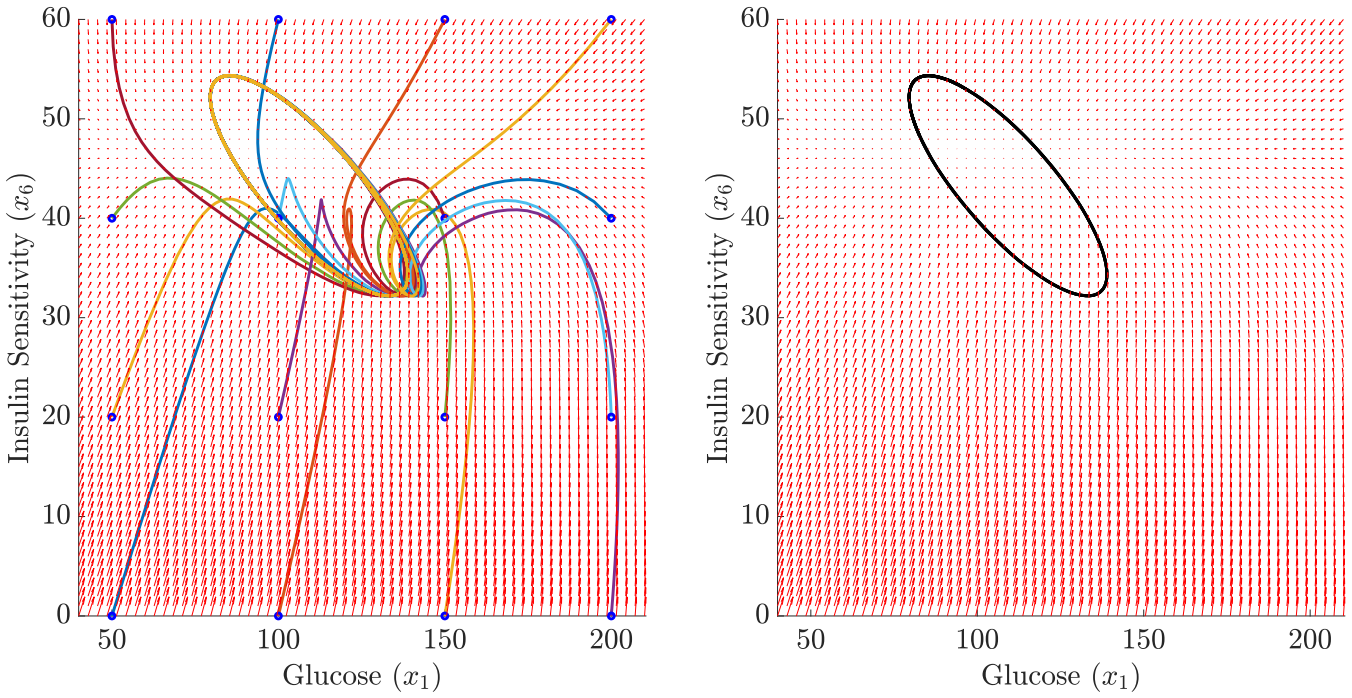

Fig. 2: Phase analysis of glycemia state (x_1, x-axis) versus the new insulin sensitivity state (x_6, y-axis). The trajectories are defined by different starting points, i.e., different (x_1, x_6) pairs depicted by blue circles, showing the fact they reach, in basal conditions and after a transient, a common domain of attraction, depicted in the right figure. Red arrows in the background show the areas where the gradients (first derivatives) decrease, highlighting a white area where the derivatives reach their minimum, i.e. where the trajectories go converging. This attraction domain could be exploited for control purposes.

[50.19, 62.79], similar to the result obtained by the model in [20]. This reflects the ability of the new approach to capture fluctuations in S_I while maintaining model plausibility. Moreover, the result remains acceptable compared to those obtained by Messori et al. in [26]. Table I presents the different parameters identified for the 10 in-silico patients. Of interest here is the differentiation among patients of the time constant devoted to S_I fluctuations; this as evidence of the intrinsic variability of this parameter among different subjects.

A. Attraction domain analysis

A phase portrait is the visual representation of the trajectories of a dynamical system in the state space. It depicts the behavior of system variables over time by showing how their values evolve, typically using streamlines or curves. In Figure 2, the portrait depicts a two-dimensional subsystem of the model proposed in this paper, illustrating how different initial conditions lead to distinct trajectories, converging toward equilibrium points. The scenario under analysis is the basal condition of the glucose-inuslin model, i.e. the scenario described in II-E; the trajectories represent glucose concentration (x_1, x-axis) versus insulin sensitivity (x_6, y-axis) evolution driven by the underlying dynamical equations. Superimposed on the streamlines are red arrows, representing the direction and magnitude of the vector field at different points. These arrows provide insight into how the system evolves locally—whether glucose levels and insulin sensitivity increase or decrease. Interestingly, the contour lines near the central region suggest an oscillatory or stable behavior, tending to form a quasi-elliptical curve; the system here shows signs of convergence to stable periodic behavior near the fixed points. This potential local attraction and stability area, better represented in Figure 2, right-hand side, is noteworthy in view of using the model on control purposes, with the controller devoted to steer the glucose at its equilibrium basal value.

IV. CONCLUSIONS

This study introduces a novel approach to modeling insulin sensitivity (S_I) in glucose-insulin dynamics, which plays a critical role in managing T1DM. The inclusion of dynamic S_I as a state influenced by physiological variables, along with circadian variability, represents a significant advancement over previous static or step-wise models of S_I. By incorporating temporal variability without significantly increasing model complexity, this approach strikes a balance between physiological accuracy and computational feasibility.

The results of the simulations, validated using the UVA/Padova T1DM simulator, suggest that the proposed work improves blood glucose modeling in patients. This improvement is critical for the safety and efficacy of insulin therapy, as better control of glycemia can reduce the risk of both hypoglycemic and hyperglycemic episodes, which are major concerns in diabetes management. These results,

alongside with the simplicity of the model structure, make it feasible to integrated it into control systems like MPC algorithms in artificial pancreas devices. This integration could lead to more robust AP systems that are capable of adapting to the complex and fluctuating nature of insulin sensitivity in daily life, providing a more individualized and precise therapy for patients.

Future work could focus on expanding the validation cohort to include a wider range of patients, including in-silico children and adolescents, and testing the model through real-world clinical data. Additionally, further refinement of S_I variability modeling, possibly integrating more environmental and behavioral factors such as stress or physical activity, could enhance the model's robustness and utility in T1DM treatment.

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