



Control-oriented modeling of glucose insulin dynamics with dynamic insulin sensitivity [★]

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ABSTRACT

This work proposes a physiologically interpretable, control-oriented model of glucose–insulin dynamics that explicitly accounts for time-varying insulin sensitivity. The proposed model combines a single-compartment glucose subsystem, two-compartment insulin pharmacokinetics, two-compartment meal absorption, and a dynamic state for insulin sensitivity driven by circadian modulation. Under basal, fasting conditions, the model predicts two basal operating regimes: (i) one in which a constant basal insulin infusion leads to a periodic glucose trajectory, and (ii) one in which a periodic basal insulin infusion is used to maintain a constant basal glucose level. Structural identifiability and sensitivity analyses are used to define a practically estimable parameter subset for personalization. The model is validated both in silico on the commercial UVA/Padova adult cohort and on free-living data from thirteen subjects of the TAILOR/3 study. Compared with a previous control-oriented linear formulation, the proposed model provides improved prediction accuracy, with higher goodness of fit and lower root mean squared error. On clinical data, the improvement holds for every subject over the identification period, while over a two-day open-loop validation horizon the proposed model yields a positive fit on eleven subjects out of thirteen, against nine for the linear benchmark and without ever failing on a subject on which the benchmark remains usable, with performance markedly lower than in silico, as expected given real-life uncertainties. These results indicate that explicitly modeling dynamic insulin sensitivity can improve physiological fidelity and prediction performance, supporting the development of more personalized model-based strategies for automated insulin delivery.

1. Introduction

Type 1 Diabetes Mellitus (T1DM) is characterized by the autoimmune destruction of pancreatic β -cells, resulting in the loss of endogenous insulin production and the need for lifelong exogenous insulin therapy (Katsarou et al., 2017). The primary therapeutic objective is to maintain Blood Glucose (BG) levels within the euglycemic range (70–180 mg/dL), as both hypoglycemia and chronic hyperglycemia are associated with severe complications. In particular, hypoglycemia can lead to acute events such as confusion, loss of consciousness,

seizures, and death. On the other hand, chronic hyperglycemia is associated with long-term complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy (American Diabetes Association, 2021). Although progress has been achieved through approaches such as Functional Insulin Treatment (FIT) (Howorka, 2012) and continuous glucose monitoring (Walsh & Roberts, 2017), accurately matching insulin delivery to metabolic needs remains challenging due to the non-linear and time-varying nature of glucose–insulin interactions.

Among the main sources of variability, Insulin Sensitivity (S_I) plays a central role, as it determines how effectively insulin promotes

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glucose uptake and suppresses endogenous glucose production (Bloomgarden & Accili, 2025). In practice, S_I varies both within and across days due to multiple factors, including hormonal fluctuations, stress, sleep, and physical activity (Petersen & Shulman, 2018). In addition, temporal patterns, such as circadian modulation and the dawn phenomenon, can lead to recurrent changes in insulin requirements (Gibson & Jarrett, 1972; Peng et al., 2022). Clinically, these variations are typically managed through manual adjustment of basal insulin profiles, carbohydrate-to-insulin ratios (CR), and correction factors (CF) (Carroll & Schade, 2005). However, this approach transfers the burden of adaptation to the user and provides only an indirect way to account for the underlying physiological changes.

The emergence of hybrid closed-loop Automated Insulin Delivery (AID) systems, also known as the artificial pancreas, has shifted the focus from manual therapy adjustment to algorithm-driven glucose regulation (Cobelli & Kovatchev, 2023; Haidar, 2016). In model-based control frameworks, such as Model Predictive Control (MPC), the accuracy and structure of the underlying glucose–insulin model directly affect prediction quality, control action, and overall clinical safety (Deshpande et al., 2023; Messori et al., 2018). This makes the representation of S_I variability a key modeling issue: if S_I is inadequately represented, predictions may become biased and insulin delivery suboptimal, particularly during periods in which glycemic disturbances are more pronounced, such as the early morning hours (Carroll & Schade, 2005; Pretty et al., 2012).

Several strategies have been proposed to address S_I variability in the modeling and control literature. Model-based approaches (Hovorka et al., 2004; Magdelaine et al., 2015; Ruan et al., 2017) provide physiologically grounded and interpretable descriptions, and in some cases incorporate S_I as a time-varying quantity (Abuin et al., 2022a,b; Moscoso-Vasquez et al., 2023); however, these profiles are often imposed *a priori* from external information (e.g., predefined circadian schedules or literature-based patterns), rather than being generated endogenously by the model or estimated from subject-specific data. This limits adaptability and complicates parameter identification. Data-driven approaches (Aiello et al., 2024; De Carli et al., 2026; Sonzogni et al., 2025), on the other hand, can capture variability more flexibly, but often at the expense of interpretability and with increased computational burden, which may be undesirable in safety-critical real-time applications. Furthermore, personalizing such models remains highly challenging when clinical datasets present incomplete or noisy inputs (Ozslan et al., 2025). Others include stochastic formulations (Lin et al., 2008) and step-wise representations aligned with meals (Visentin et al., 2015), which capture relevant temporal variations in S_I , but do not provide a continuous, physiologically structured mechanism suitable for identifiability analysis and control design. Therefore, a key open challenge is to reconcile: (i) *physiological interpretability*, to support personalization and reasoning about safety-relevant behaviors; (ii) *time-varying insulin sensitivity modeling*, to capture predictable circadian variations affecting fasting glycemia and basal insulin needs; and (iii) *computational tractability* for real-time prediction, estimation, and control.

This work addresses this gap by proposing a nonlinear, control-oriented glucose–insulin model in which S_I is represented as an *endogenous, continuously evolving state* driven by a circadian reference profile parameterized through a truncated Fourier series, extending the Linear Time Invariant (LTI) framework of Abuin et al. (2020), Ruan et al. (2017). Treating S_I as a dynamic state, rather than a fixed parameter or an externally prescribed time-varying profile, is the key structural novelty of the proposed formulation. The resulting model is compact and physiologically interpretable, while remaining amenable to identifiability and sensitivity analysis and to direct integration into MPC-based AID systems (Abuin et al., 2024; Hovorka et al., 2004). Basal (fasting) operating trajectories are analytically characterized under two clinically relevant configurations: constant basal insulin infusion leading to periodic glucose dynamics, and periodic basal insulin delivery designed to maintain a constant basal glucose level. A structural identifiability and sensitivity analysis support practical parameter estimation and person-

alization. Finally, the model is validated both in silico on the commercial version of the FDA-accepted UVA/Padova adult cohort (Dalla Man et al., 2014) (accepted as a substitute for pre-clinical trials of AID systems), and on real subject data, showing improved prediction accuracy with respect to the established LTI control-oriented formulation.

2. Preliminaries: the LTI control-oriented model

The proposed work extends the control-oriented glucose–insulin linear model introduced in Ruan et al. (2017) and further developed in Abuin et al. (2020). To provide the necessary context, this section reviews the original formulation, emphasizing its limitations and the rationale for the developments introduced in this study.

2.1. Glucose dynamics

A single compartment describes the evolution of glycemia:

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

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 model parameters include θ_1 , i.e., the glucose effectiveness [1/min], which represents the rate of glucose uptake by peripheral tissues and the suppression of hepatic glucose release. This is also referred to as the glucose self-regulation effect to promote its own metabolism. S_I is the insulin sensitivity [mg/(dL·U)], 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_b) at basal levels [mg/(dL·min)].

2.2. Insulin absorption dynamics

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

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

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

where $Q_{i_{sub}}(t)$ 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/bolus infusion rates, can be derived from Eqs. (2) and (3) as:

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

considering $u(0) = 0$ and $Q_i(0) = 0$ as initial condition in (2) and (3) (Abuin et al., 2020).

2.3. Meal absorption dynamics

The following two compartments similarly describe the meal absorption subsystem:

$$\frac{dQ_g(t)}{dt} = -\frac{1}{\theta_4} Q_g(t) + \frac{1}{\theta_4} Q_{sto}(t) \quad (4)$$

$$\frac{dQ_{sto}(t)}{dt} = -\frac{1}{\theta_4}Q_{sto}(t) + \frac{1}{\theta_4}r(t) \quad (5)$$

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

2.4. Basal operating point and model limitations

Under basal conditions, i.e., constant insulin infusion ($u(t) = U_b$) and in a fasting scenario ($r(t) = 0$), the LTI model admits a unique equilibrium at which all state derivatives vanish. In particular, the basal glucose level, from (1), is determined by:

$$G_b = \frac{\theta_0 - S_I U_b}{\theta_1}, \quad (6)$$

which is a time-invariant operating point. This structure implies that, for a given constant basal infusion, the predicted fasting glucose is constant over time. However, clinical observations and physiological studies indicate that insulin sensitivity exhibits systematic circadian variations, particularly in individuals with T1DM. A well-known manifestation is the *dawn phenomenon*, whereby reduced S_I during the early morning hours increases insulin requirements and contributes to elevated glucose levels (Carroll & Schade, 2005; Gibson & Jarrett, 1972). Since the LTI model assumes a constant value of S_I , it cannot reproduce these time-varying metabolic conditions. As a consequence, the model not only predicts a constant fasting glucose operating point under constant basal insulin, but also fails to adapt the glucose response to insulin throughout the day. This limitation may lead to systematic under- or overestimation of glucose excursions, reducing the accuracy of predicted hyperglycemic and hypoglycemic events when S_I deviates from its nominal value. Over multi-hour or multi-day prediction horizons, these errors accumulate and manifest as a slowly varying prediction bias, crucial in control-oriented applications. A quantitative comparison between the LTI model and the formulation proposed in this paper is provided in Section 6.

3. Methods: modeling insulin sensitivity as a dynamic state

The proposed model addresses the structural limitation of the LTI formulation by replacing the constant insulin sensitivity parameter with a dynamic state $S_I(t)$, whose evolution is governed by a physiologically motivated circadian target. The following subsections describe the rationale for the circadian representation and the full model structure.

3.1. Circadian insulin sensitivity profiles from the literature

Several research groups have proposed mathematical representations of the circadian variation of S_I in T1DM, based on physiological studies and clinical data. To inform the design of the circadian variability used in this work, four reference daily S_I profiles from the literature are considered:

- Fabietti et al. (2006) used a simple sinusoidal model to reproduce the periodic effect of S_I ;
- Toffanin et al. (2013) collected several literature references to define fixed points for a multiplicative factor $y(t)$, then interpolated (t, y) with a cyclic piecewise cubic Hermite interpolating polynomial. This pattern is implemented in the commercial version of the UVA/Padova simulator by TEG (The Epsilon Group, 2016);
- Mansell et al. (2015) used a series of linear basis functions, i.e., three overlapping triangular basis functions, motivated by the typical three meals per day and the corresponding three main glycemic disturbances used for parameter identification;
- Visentin et al. (2015) identified seven classes of variability by integrating diurnal patterns over the three main periods of the day, each associated with a main meal. This pattern is implemented in the full version of the UVA/Padova simulator (Visentin et al., 2018).

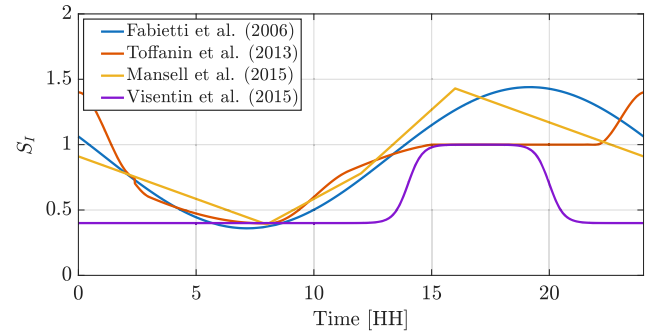


Fig. 1. Reference circadian S_I patterns (dimensionless) built as daily multipliers of nominal sensitivity, generated from four literature models Fabietti et al. (2006), Mansell et al. (2015), Toffanin et al. (2013), and Visentin et al. (2015), plotted over one 24 h period. The first three profiles are consistent with the dawn phenomenon (reduced S_I in the early morning); the profile by Visentin et al. (2015) instead depends on the selected variability class.

These four profiles are shown in Fig. 1. These profiles all reflect a 24 h modulation of S_I consistent with circadian physiology (Carroll & Schade, 2005; Gibson & Jarrett, 1972), while differing substantially in amplitude, phase, and waveform because of differences in the underlying data and modeling assumptions: Fabietti et al. (2006) sought a minimal sinusoidal representation as a control-oriented simple structure; Mansell et al. (2015) aimed to reflect the three main postprandial disturbances; while both Toffanin et al. (2013) and Visentin et al. (2015) derived more detailed diurnal patterns from physiological data and literature-reported time points. This variability highlights that intraday S_I modulation is not uniquely defined; for this reason, the goal of the proposed formulation is to introduce a *general and compact* representation of circadian variability that can reproduce a broad class of periodic S_I trajectories, while remaining suitable for identification and predictive control. In the following, this is achieved by driving the new state $S_I(t)$ toward a periodic target $S_{I,Tar}(t)$ described through a low-order harmonic representation. The selection of the harmonic structure is designed to balance expressiveness and parsimony, and is detailed in Appendix A.

3.2. Proposed insulin sensitivity dynamics

The proposed physiological long-term model is an extension of the physiological model originally proposed by Ruan et al. (2017) and subsequently adopted in Abuin et al. (2020). The parameter S_I is now introduced as a dynamic state in the glucose Eq. (1), described by the following single-compartment model:

$$\frac{dS_I(t)}{dt} = -\frac{1}{\theta_5}S_I(t) + \frac{1}{\theta_5}S_{I,Tar}(t) \quad (7)$$

where θ_5 is the time constant [min] that governs the rate of change for $S_I(t)$.

The state is driven toward a time-varying target, $S_{I,Tar}(t)$, which represents a generic circadian modulation.

The target trajectory is parameterized through a low-order harmonic representation, implemented by a set of auxiliary differential equations.

To avoid explicit time dependencies in the model and maintain it in an autonomous formulation, for each harmonic component k ($k = \{1, 2, 3\}$), a pair of state variables, $z_{k,1}(t)$ and $z_{k,2}(t)$, is introduced, which behave as a linear harmonic oscillator. The algebraic equation for the insulin sensitivity target, $S_{I,Tar}(t)$, is defined as a baseline modulated by the sum of the state variables $z_k(t)$:

$$S_{I,Tar}(t) = A_{SI} \left[1 + \sum_{k=1}^3 \alpha_k z_{k,1}(t) \right] \quad (8)$$

where A_{S_I} represents the basal (average) S_I , and α_k is the relative amplitude of the k -th harmonic. The additional differential equations are:

$$\frac{dz_{k,1}(t)}{dt} = \omega_k \cdot z_{k,2}(t) \quad z_{k,1}(0) = \sin(\varphi_k) \quad (9)$$

$$\frac{dz_{k,2}(t)}{dt} = -\omega_k \cdot z_{k,1}(t) \quad z_{k,2}(0) = \cos(\varphi_k) \quad (10)$$

where φ_k is the phase of the k -th harmonic, and ω_k is the angular frequency of the k -th harmonic, defined as:

$$\omega_k = k \cdot \frac{2\pi}{T_0}$$

with $T_0 = 1440$ min (24 hours) being the fundamental period.

HARMONIC SELECTION. In the proposed implementation, the circadian target for $S_I(t)$, $S_{I,Tar}(t)$, is represented by a truncated Fourier series with harmonics at integer multiples of the 24-h fundamental frequency. To assess the harmonic order required to capture the range of daily profiles reported in the literature, (i) the reference S_I patterns in [Fabietti et al. \(2006\)](#), [Mansell et al. \(2015\)](#), [Toffanin et al. \(2013\)](#), [Visentin et al. \(2015\)](#) were reconstructed, and (ii) the Root Mean Squared Error (RMSE) obtained with increasing harmonic order was computed. This analysis showed that three harmonics provide a satisfactory trade-off between reconstruction accuracy and model complexity. The reconstruction error decreases in the same manner for all four profiles, and three harmonics are adequate for each of them despite their substantially different waveforms; the representation is therefore not tuned to any specific profile. Since the profile by [Toffanin et al. \(2013\)](#) is the variability scenario implemented in the commercial UVA/Padova simulator, it is the profile that generates the in silico data, and is used as the reference of that benchmark for consistency with the data-generating process; however, the proposed representation is introduced to accommodate a broader class of circadian S_I patterns.

The full rationale for selecting three harmonics in the circadian target representation is detailed in [Appendix A](#).

MODEL SUMMARY. A summary of all model parameters is provided in [Table 1](#), and [Fig. 2](#) illustrates the overall structure of the system.

4. Equilibria, basal operating trajectories, and control-oriented interpretation

Classical equilibria of nonlinear systems are defined as state-input pairs (x_b, u_b) for which all state variables remain constant over time. In

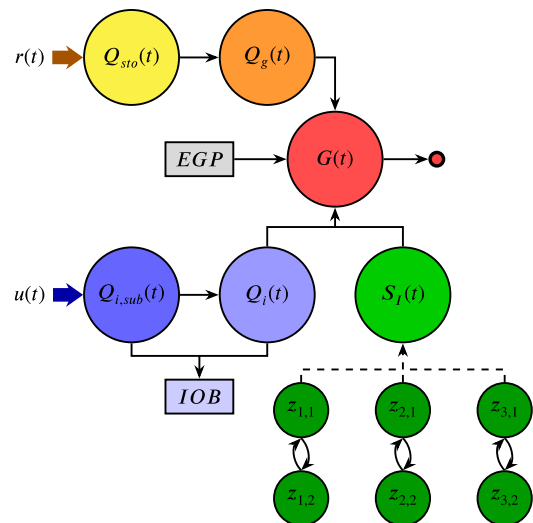


Fig. 2. Schematic representation of the proposed model. The inputs are meal $r(t)$ and insulin $u(t)$, while the measurable output is glycemia $G(t)$.

Table 1

Model parameters description.

Parameter	Description
θ_0 [mg/(dL·min)]	Endogenous glucose production (EGP)
θ_1 [1/min]	Glucose effectiveness
θ_2 [mg/(dL·g)]	Carbohydrate factor
θ_3 [min]	Insulin absorption time constant
θ_4 [min]	Meal absorption time constant
θ_5 [min]	S_I rate of change time constant
α_k	Harmonic relative amplitude
φ_k	Harmonic relative phase shift
A_{S_I} [mg/(dL·U)]	Basal insulin sensitivity

the proposed model, however, $S_I(t)$ is a *dynamic state* driven by the circadian target $S_{I,Tar}(t)$ through (7). Since $S_{I,Tar}(t)$ is T_0 -periodic by construction and the corresponding dynamics are stable, $S_I(t)$ converges to a unique T_0 -periodic closed orbit, denoted by $S_{I,b}(t)$ (see [Appendix B](#) for the derivations and closed-form expressions). As a consequence, when $S_I(t)$ evolves periodically, a constant input cannot generally maintain *all* states at constant values; therefore, the system admits *no equilibrium* in the usual sense. Rather, under fasting conditions, basal operation is described by the convergence to a stable limit cycle. In the following, basal conditions are assumed to correspond to fasting, i.e., $r(t) = 0$.

Clinically, fasting glycemia may still exhibit day–night trends because S_I varies over the circadian cycle. Accordingly, the model naturally operates around periodic trajectories: after the meal-related transients have decayed, the meal absorption states vanish, while glucose and insulin dynamics remain influenced by the periodic evolution of $S_{I,b}(t)$. This leads to two clinically meaningful basal regimes, illustrated in [Fig. 3](#) and analytically characterized in [Appendix B](#).

In the first regime, a constant basal insulin infusion gives rise to a periodic fasting glucose trajectory because the circadian modulation of insulin sensitivity induces a time-varying glucose utilization.

In the second regime, a constant basal glucose level is maintained by a time-varying insulin delivery $u_b(t)$ (given that insulin $u(t)$ is the sum of the basal $u_b(t)$ and bolus $u_B(t)$ insulin, i.e., $u(t) = u_b(t) + u_B(t)$) that compensates for the oscillation of $S_{I,b}(t)$. In particular, imposing $G(t) \equiv G_b$ under fasting conditions yields

$$Q_{i,b}(t) = \frac{\theta_0 - \theta_1 G_b}{S_{I,b}(t)}, \quad (11)$$

which provides a direct physiological interpretation: when insulin sensitivity decreases, a proportionally larger insulin effect is required to maintain the same glucose level, and vice versa. The full derivation of the corresponding basal insulin infusion rate $u_b(t)$ is provided in [Appendix B](#).

This analysis clarifies the role of dynamic S_I in shaping basal behavior. In models with constant S_I , fasting operation is typically associated with an equilibrium; here, instead, the natural basal regime is a periodic trajectory induced by circadian modulation. This distinction is relevant not only from a physiological viewpoint, but also for model initialization, personalization, and prediction, since it shows that basal behavior cannot, in general, be represented by a single time-invariant operating point.

Remark 2. A third regime, not considered here, arises under periodic insulin delivery and periodic BG. In this setting, insulin profiles can be designed to induce specific BG limit cycles of interest. For instance, one may target a limit cycle in which BG is intentionally maintained at higher levels during periods of increased hypoglycemia risk (e.g., physical activity or the dawn phenomenon) and lower otherwise.

5. Identifiability and practical estimation

This section summarizes the analyses used to support parameter estimation. First, an *a priori* structural identifiability study was performed

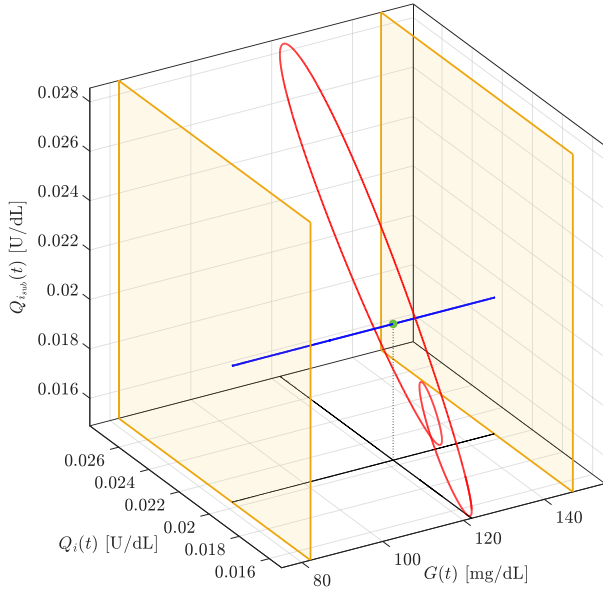


Fig. 3. Basal operating trajectories of the glucose-insulin model in the $(G(t), Q_i(t), Q_{i,sub}(t))$ coordinates. The blue curve represents the constant-basal-insulin regime that leads to periodic fasting glycemia, while the red curve represents the time-varying-basal-insulin regime designed to maintain glycemia close to a constant basal target. The green dot denotes the intersection of the two trajectories, corresponding simultaneously to a time instant t^* at which the system states coincide, $x(t^*, u_b, G_b(\cdot)) = x(t^*, u_b(\cdot), G_b)$, and to the equilibrium of the LTI system associated with the pair (G_b, u_b) . The analytical characterization of both trajectories is reported in Appendix B. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to verify whether the model parameters are, in principle, recoverable from ideal input–output data. Then, an *a posteriori* sensitivity analysis was carried out to rank parameter influence on glucose and to define a practically estimable parameter set under physiological constraints.

5.1. A priori - structural identifiability

Structural identifiability was assessed with the MATLAB toolbox GenSSI (Chiş et al., 2011), to determine whether model parameters are structurally globally, locally, or non-identifiable. The analysis considered $G(t)$ as the measured output and $u(t)$ and $r(t)$ as known inputs. Here, *ideal input–output data* refers to the theoretical setting of noise-free, continuous-time observation of $G(t)$ with persistently exciting inputs $u(t)$ and $r(t)$; this establishes parameter recoverability in principle, independently of noise or finite-sampling constraints.

Because a full analysis of the complete parameter set is computationally demanding, a block-wise strategy was adopted. The analysis was first applied to the subset of kinetic and basal sensitivity parameters $\{\theta_0, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, A_{SI}, \alpha_1, \alpha_2, \alpha_3\}$. For this subset, GenSSI showed full-rank identifiability and established *Structural Global Identifiability* (SGI), meaning that these parameters can be uniquely recovered in the ideal noise-free continuous-time setting. The corresponding identifiability tableaux are reported in Fig. S1 of the Supplementary Material.

The analysis was then extended to include the circadian phase parameters ϕ_k . In this case, GenSSI indicated at most local identifiability, consistently with the intrinsic periodicity of the harmonic representation: different phase shifts can generate equivalent input–output behavior. Therefore, the loss of global uniqueness is attributable to the circadian phase component, whereas the kinetic subset remains structurally well posed. The corresponding tableaux are reported in Fig. S2 of the Supplementary Material.

Overall, the *a priori* analysis confirms that the proposed model is structurally suitable for parameter estimation and that the main source of non-uniqueness is the expected phase ambiguity of the periodic S_I representation.

5.2. A posteriori - sensitivity analysis

Since structural identifiability does not guarantee reliable estimation under noisy and finite data, a global sensitivity analysis was performed *a posteriori* with AMIGO2 (Balsa-Canto et al., 2016). The analysis was based on input profiles generated through simulations with the commercial UVA/Padova T1DM simulator, including the variability scenario proposed in Toffanin et al. (2013). To reproduce realistic daily-life conditions, these profiles included meal intake and basal/bolus therapy. In particular, two experiments of four days each were considered for training-oriented analysis. These input profiles are used only for the sensitivity analysis and parameter-selection study; the final in silico validation results reported in Section 6.1 are instead obtained on a separate three-day validation scenario. Parameter influence was quantified through the normalized mean-square-root sensitivity index:

$$\delta_{\theta_p}^{\text{msqrt}} = \frac{1}{n_D} \sqrt{\sum_{l=1}^{n_{\text{lhs}}} \sum_{e=1}^{n_e} \sum_{j=1}^{n_o} \sum_{t_s=1}^{n_s} \left(s_{\theta_p, j}^{l, e}(t_s) \right)^2}, \quad (12)$$

where $s_{\theta_p, j}^{l, e}(t_s)$ denotes the local sensitivity function of the j -th observable with respect to parameter θ_p , evaluated at time t_s , for the l -th Latin Hypercube Sampling (LHS) sample (Iman et al., 1980), and the e -th experiment. It is defined as $s_{\theta_p, j}^{l, e}(t_s) = \frac{\partial y_j^{l, e}(t_s)}{\partial \theta_p}$, where $y_j^{l, e}(t_s)$ is the model output corresponding to the j -th observable. Moreover, $n_o = 1$ is the number of observables (glycemia), $n_e = 2$ is the number of experiments, and $n_{\text{lhs}} = 10000$ is the number of LHS draws, generated by the AMIGO2 toolbox. The quantity n_s is the number of sampling times per experiment-observable pair; given each experiment spans 4 days, it is computed as $n_s = 4 \cdot 24 \cdot 60 / T_s$, where T_s [min] is the sampling time. Consequently, the total number of data is $n_D = n_e \cdot n_o \cdot n_s$.

The analysis was repeated for each subject, and the cohort-level summary is reported in Fig. 4 (results are by means of the median and 95% bounds of $\delta_{\theta_p}^{\text{msqrt}}$ over subjects, with parameters sorted left-to-right from most to least influential on glucose). Color coding distinguishes high (green), intermediate (blue), and low (red) sensitivity levels. Among the parameters related to the circadian component, the basal insulin sensitivity A_{SI} and the first harmonic amplitude α_1 showed the largest influence on glucose. In contrast, the second α_2 and the third α_3 harmonic amplitudes were consistently less sensitive. Based on these results, these latter two were fixed to population values, computed as the median estimates from a preliminary identification run, while the remaining parameters were estimated on a subject-specific basis. This choice reduces

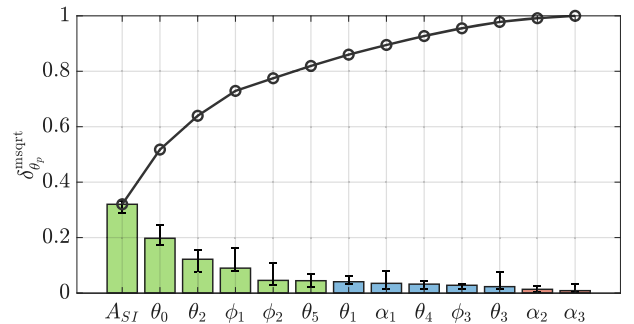


Fig. 4. Cohort-aggregated parameter sensitivity (10 subjects): median [2.5th – 97.5th] of $\delta_{\theta_p}^{\text{msqrt}}$, with parameters sorted by decreasing influence on glucose. The solid curve indicates the cumulative contribution of median parameter sensitivities.

Table 2
A-priori parameters for 10 in silico adult patients.

Patient	001	002	003	004	005	006	007	008	009	010
θ_3^0 [min]	56.0	40.0	52.5	59.5	45.5	52.5	47.5	50.0	47.5	50.0
θ_5^0 [min]	340.0	244.5	225.0	81.5	27.0	359.0	346.0	85.5	155.0	13.0
RF [mg/(dL·g)]	19.161	22.484	14.552	19.703	13.469	8.995	18.145	8.793	19.763	13.773
CF [mg/(dL·U)]	43.854	42.101	35.151	53.204	48.019	25.890	42.604	37.062	53.445	39.503

the effective dimension of the estimation problem and alleviates practical identifiability issues without changing the structural conclusions of the model.

PRACTICAL CONSTRAINTS. Beyond structural identifiability, practical estimation requires encoding physiological constraints to ensure well-posedness and robustness under noise and finite sampling. The following constraints were therefore enforced: (i) state nonnegativity, consistent with the compartmental nature of the model and with nonnegative inputs and initial conditions; and (ii) parameter regularization via box constraints, to confine weakly informed directions, preventing optimizer drift into flat, noninformative regions.

It is important to remark that these constraints do not alter the structural identifiability conclusions (SGI remains an a priori property), but they are essential for robust estimation under realistic noise and sampling conditions, affecting practical identifiability. Taken together, the sensitivity analysis and the practical constraints define a parameterization that is both expressive and estimable, and directly lead to the constrained optimization problem formulated in the next section.

5.3. Parameter estimation

The a priori analysis in Section 5.1 establishes SGI for the kinetic and harmonic-amplitude subset, while the inclusion of the phase parameters yields only local identifiability because of the intrinsic periodic ambiguity of the harmonic representation. The final subject-specific identification was then carried out with α_2 and α_3 fixed and the remaining parameters estimated individually (Section 5.2). Together, these results support estimating the full parameter set, provided that experimental inputs $u(t)$ and $r(t)$ are sufficiently informative and that estimation accounts for noise and model mismatch.

Let $\xi \in \mathbb{R}^p$ denote the vector of identified parameters $\xi = [\theta_0 \ \theta_1 \ \theta_2 \ \theta_3 \ \theta_4 \ \theta_5 \ \alpha_1 \ \varphi_1 \ \varphi_2 \ \varphi_3 \ A_{SI}]^T$, with $p = 11$. Parameter identification is formulated as a regularized nonlinear least-squares problem and solved using the *fmincon* routine in MATLAB:

$$\min_{\xi \in \Xi} \frac{\|y(k) - \hat{y}(k)\|^2}{\|y(k) - \bar{y}\|^2} + \|\rho(\xi)\|_W^2 \quad (13)$$

where $y(k)$ and $\bar{y}$ denote the measured glucose concentration and its average, respectively, while $\hat{y}(k)$ is the predicted subcutaneous glucose profile. The regularizer kernel is defined as $\rho(\xi) = [A_{SI} - CR \cdot \theta_2 \ \theta_3 - \theta_3^0 \ \theta_4 - \theta_4^0 \ \theta_5 - \theta_5^0]^T$ with weighting matrix $W = \text{diag}(1, 1, 1/(\theta_3^0)^2, 10^{-4})$, where θ_3^0 and θ_4^0 denote the parameters' nominal (initial) values as in Abuin et al. (2020). The additional kernel term, compared with Abuin et al. (2020), is a subject-specific regularization term on θ_5 , described below.

The admissible parameter set is defined by box constraints:

$$\Xi = \{\xi \in \mathbb{R}^p : \xi^L \leq \xi \leq \xi^U\}, \quad (14)$$

where lower and upper bounds are given by scaled nominal values, $\xi^L = k_L \cdot \xi^0$ and $\xi^U = k_U \cdot \xi^0$, with element-wise scaling factors k_L and k_U .

For each subject, this vector is set from a common population prior ξ^0 as follows:

- $\theta_0^0 = 0.004$ [1/min] (Ruan et al., 2017);
- $\theta_4^0 = 40$ [min] (Abuin et al., 2020);

- $(\alpha_1^0, \alpha_2^0, \alpha_3^0) = (0.50, 0.2487, 0.0878)$, maintaining the amplitudes of the second and third harmonics fixed to population values, in agreement with the sensitivity analysis;
- $(\varphi_1^0, \varphi_2^0, \varphi_3^0) = (0, 0, 0)$ (i.e., neutral alignment at the start of the simulation).

The remaining parameters are initialized using subject-specific data summarized in Table 2; in particular:

- θ_2^0 is initialized from the carbohydrate raise factor $RF = CF/CR$ of each subject in the studied cohort;
- θ_3^0 is individualized through a subject-dependent prior obtained by minimizing the least-squares error between the estimated IOB (Remark 1) and the corresponding reference from the subject, a choice aimed at avoiding insulin stack artifacts (Abuin et al., 2020);
- A_{SI}^0 is individualized from the subject's insulin correction factor CF , guaranteeing that, at initialization, the overall gain from insulin to glucose is compatible with the subject's therapy settings.
- θ_5^0 is estimated from the multi-start analysis described below;

The last parameter is the endogenous glucose production at basal levels θ_0^0 , chosen to satisfy the basal equilibrium relation between glucose production and insulin-mediated uptake. Specifically, for each subject $\theta_0^0 = G_b \theta_0^0 + U_b CF$, so that the model is initially consistent with the nominal basal operating point, where G_b and U_b denote the subject-specific basal glucose concentration and basal insulin infusion rate, respectively.

MULTI-START ANALYSIS AND SUBJECT-SPECIFIC REGULARIZATION OF θ_5 . To assess the robustness of the identified solution against local minima, a multi-start LHS strategy was adopted: for each subject, $N_{\text{LHS}} = 500$ optimization runs were performed with starting points sampled across $[\xi^L, \xi^U]$. Convergence was assessed via two metrics computed from the distribution of optimal parameter values across runs: (i) the dominant mode fraction, defined as the proportion of runs whose converged parameter values clustered around the most frequently attained solution, identified through kernel-density-based mode detection; and (ii) the within-mode Coefficient of Variation (CV), computed across runs belonging to that dominant cluster.

For subjects 1, 2, 3, 6, 7, and 9, all parameters excluding the circadian phases converged consistently across initializations, with dominant mode fraction (median 94.3%, min 82.4%) and within-mode CV (median 0.07%, max 3.45%). Phase parameters $(\varphi_1, \varphi_2, \varphi_3)$ showed instead the expected bimodal distribution at $\pm\pi$, consistent with the structural local identifiability established by GenSSI in Section 5.1: both modes produce identical model outputs due to the periodicity of the cosine representation.

For subjects 4, 5, 8, and 10, the cost landscape was ambiguous prior to regularization of θ_5 (dominant mode fraction median 50.1%, min 27.7%), caused by a multimodality of this parameter's landscape that induced correlated ambiguity across all parameters simultaneously, with θ_5 exhibiting a high run-to-run variability (CV across all runs: 88.0%, computed as the median over the four subjects). A subject-specific prior θ_5^0 , estimated as the median of the dominant LHS convergence mode (reported in Table 2), was therefore incorporated into the cost function (13) as a soft penalty with weight 10^{-4} . A second LHS run ($N_{\text{LHS}} = 500$) incorporating this regularization confirmed that the ambiguity had been resolved. The variability of all non-phase parameters dropped from a

Table 3Estimated parameters of 10 in silico adult patients. Amplitude parameters α_2 and α_3 were fixed to population values (Section 5.2).

Patient	001	002	003	004	005	006	007	008	009	010
θ_0 [mg/(dL·min)]	2.2161	2.1803	1.5541	1.6565	1.1073	2.2511	2.3000	1.2482	1.6040	1.6202
θ_1 [1/min]	0.0059	0.0055	0.0037	0.0057	0.0037	0.0073	0.0021	0.0049	0.0044	0.0072
θ_2 [mg/(dL·g)]	3.6811	2.9239	2.8084	2.8734	2.8006	4.6395	5.4034	3.4945	3.3824	2.5048
θ_3 [min]	56.0022	40.0065	52.5021	59.5011	45.5018	52.5041	47.5031	50.0024	47.5038	50.0022
θ_4 [min]	36.4388	30.2846	37.0573	38.2602	38.3403	34.9016	35.7582	38.3269	34.6422	36.8318
θ_5 [min]	339.2148	244.5193	226.3833	81.7582	26.8434	358.5627	346.3608	84.9640	154.7163	13.0310
α_1	0.1974	0.1477	0.1616	0.1855	0.2565	0.1443	0.1805	0.2373	0.1668	0.2687
α_2	0.2487	0.2487	0.2487	0.2487	0.2487	0.2487	0.2487	0.2487	0.2487	0.2487
α_3	0.0878	0.0878	0.0878	0.0878	0.0878	0.0878	0.0878	0.0878	0.0878	0.0878
φ_1	-2.8402	3.2643	-2.9925	2.0242	1.7469	3.3336	3.3614	2.2358	2.7460	2.2965
φ_2	2.1495	2.2773	2.0906	1.2192	0.3744	2.2619	2.2028	1.1195	1.3997	0.8504
φ_3	3.7596	2.9471	-2.6313	1.7044	1.3834	3.3023	-2.3797	1.7446	2.6798	1.1218
A_{SI}	70.5334	65.7398	40.8659	56.6138	37.7188	41.7289	98.0412	30.7242	66.8448	34.4951

median CV of 4.3% to a median of 2.41% (max 15.95%), with θ_5 itself collapsing from 88.0% to below 2.20% across all four subjects. The complete distributions of the converged parameter values across the LHS runs, for all parameters and all subjects, together with the cost landscape of θ_5 before and after regularization, are reported in Sec. S2 of the Supplementary Material.

5.4. Performance metrics

The quality of the model predictions was quantified using the following indices:

$$\text{COD} = 100 \left(1 - \frac{\|\hat{y}(k) - y(k)\|^2}{\|y(k) - \bar{y}\|^2} \right) \in (-\infty, 100], \quad (15)$$

$$\text{GoF} = 100 \left(1 - \frac{\|\hat{y}(k) - y(k)\|}{\|y(k) - \bar{y}\|} \right) \in (-\infty, 100], \quad (16)$$

$$\text{PME} = \max\{\max\{\hat{y}(k) - y(k), 0\}, 0\}, \quad (17)$$

$$\text{NME} = |\min\{\min\{\hat{y}(k) - y(k), 0\}, 0\}|, \quad (18)$$

$$\text{RMSE} = \sqrt{\frac{\|\hat{y}(k) - y(k)\|^2}{N_s}}, \quad (19)$$

where N_s is the total number of samples in the testing protocol. The Coefficient of Determination (COD) and Goodness-of-Fit (GoF) indices express the degree of agreement between model predictions and reference data, while Positive and Negative Max Error (PME and NME) quantify the extreme overestimation and underestimation errors, respectively. Finally, RMSE provides an overall measure of the mean prediction accuracy across the entire simulation horizon.

6. Model validation

This section evaluates the proposed model through progressively more realistic validation scenarios. First, an in silico study on the commercial UVA/Padova simulator (Dalla Man et al., 2014) is used to assess the capability of the model to reproduce glucose dynamics under controlled conditions and to compare it against the baseline LTI formulation. Subsequently, the identification procedure is applied to clinical data from the TAILOR/3 study to assess performance under real-world conditions. Finally, rolling-horizon prediction results are presented to evaluate the suitability of the proposed model for MPC applications.

6.1. In silico validation

The proposed model was evaluated through in silico simulations using the commercial version of the UVA/Padova T1DM simulator (Dalla Man et al., 2014), built upon the nonlinear model by Dalla Man et al. (2007) and including the variability scenario described in Toffanin et al. (2013). The evaluation comprised a training phase

for parameter identification and a separate validation phase for performance assessment. The data are generated by including dedicated error models for CGM sensing (Breton & Kovatchev, 2008) and insulin pump delivery (MiniMed, 2018), both increasing the level of model mismatch involved in this experiment.

The training dataset, used both to conduct the sensitivity analysis (Section 5.2) and to identify the model (Section 5.3), consisted of two four-day simulated experiments per subject. Each experiment included three daily meals with variable timing and sizes, together with standard basal/bolus insulin therapy. The validation dataset consisted of a separate three-day scenario with variable meal timing and sizes, designed to reproduce realistic daily-life conditions. In both cases, carbohydrate intake and insulin delivery profiles were provided to the model as known inputs. Glucose predictions were generated as open-loop simulations over the entire three-day validation horizon.

The individualized parameter estimates obtained after solving the optimization problem (13) are summarized in Table 3. The prediction performance obtained with the proposed nonlinear model for each subject is reported in the first ten rows of Table 4. The lower part of the table summarizes the cohort statistics for both the proposed nonlinear model (NLTI) and the LTI benchmark. The cohort-level glucose trajectories are shown in Fig. 5.

Across the adult cohort, the proposed nonlinear model outperforms the LTI baseline of Abuin et al. (2020), identified here under the same variability scenario.

As reported in Table 4, all the considered performance indices improve: the median COD increases from 50.88% to 82.57%, and the median GoF from 29.94% to 58.25%. At the same time, the error metrics decrease from 55.46 to 39.14 mg/dL for PME, from 81.54 to 55.02 mg/dL for NME, and from 28.33 to 16.55 mg/dL for RMSE. These results are consistent with Fig. 5, where the nonlinear model more accurately captures both postprandial excursions and slower glycemic drifts across the cohort.

6.2. Real-data validation

To assess the model under clinical conditions, the same identification procedure was applied to free-living data from the TAILOR/3 study (U. S. National Library of Medicine, 2025).

SUBJECT SELECTION. The study enrolled fifteen Real Subjects (RS) with T1DM, and free-living data preceding the trial were collected for only fourteen of them. Since the proposed model is driven by the announced carbohydrate intake and the recorded insulin delivery and is fitted to the CGM record, subjects were included only when these three signals were available and sufficiently complete over at least four consecutive days, allowing the available data to be divided into identification and validation periods. Following these inclusion criteria, the subject RS3 was excluded because no meal was recorded over the entire monitoring period, leaving thirteen subjects for the analysis. Physical activity is not

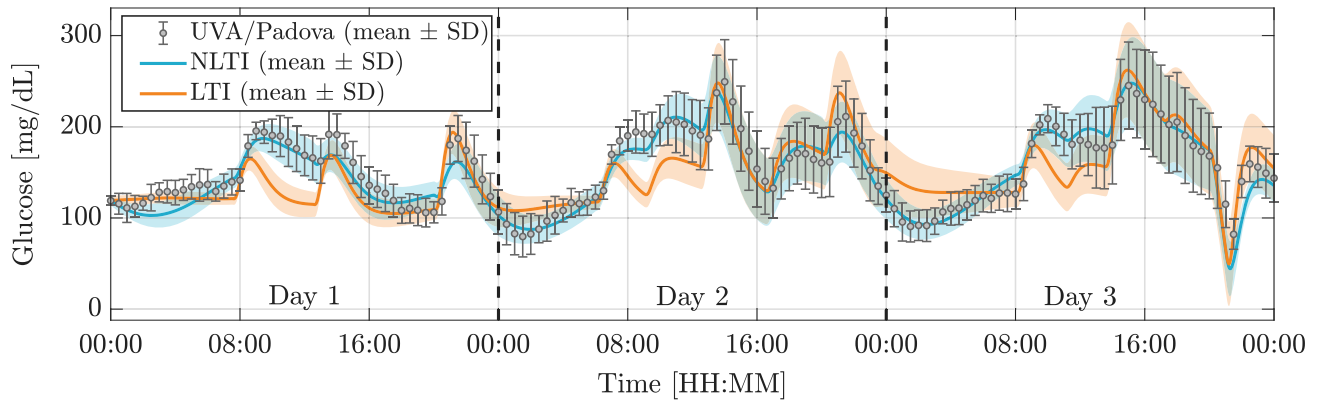


Fig. 5. Validation scenario for the 10 adult patients of the UVA/Padova in silico cohort. The comparison is between glucose predictions in terms of mean and standard deviation: gray dots indicate the reference trajectory generated by the UVA/Padova simulator, blue lines correspond to the proposed non-linear model, and orange lines to the linear model from [Abuin et al. \(2020\)](#). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4

Prediction performance metrics of 10 in silico adult patients, with comparison in median [25th – 75th] of the proposed nonlinear model (NLTI) and the linear model (LTI) in [Abuin et al. \(2020\)](#). The first ten rows report the individual results obtained with the proposed NLTI, while the remaining rows summarize the cohort statistics for both the NLTI and the LTI benchmark.

	Patient	COD	GoF	PME	NME	RMSE
	001	79.43	54.65	35.65	67.63	16.60
	002	65.45	41.22	32.22	71.76	19.38
	003	84.33	60.42	34.57	54.86	15.19
	004	83.21	59.03	55.03	42.19	16.32
	005	90.36	68.96	35.63	35.46	14.28
	006	70.81	45.98	43.67	94.27	20.80
	007	83.17	58.97	46.54	100.62	31.77
	008	85.17	61.49	45.79	46.68	16.49
	009	81.97	57.53	42.62	55.17	20.35
	010	79.12	54.30	35.15	51.81	16.10
NLTI	median	82.57	58.25	39.14	55.02	16.55
	25th prc	79.12	54.30	35.15	46.68	16.10
	75th prc	84.33	60.42	45.79	71.76	20.35
LTI	median	50.88	29.94	55.46	81.54	28.33
	25th prc	34.95	19.35	49.06	76.42	26.42
	75th prc	61.87	38.25	58.87	86.77	32.01

used as an inclusion criterion: this element was annotated by one subject only (RS7), so it cannot be evaluated across the cohort. It is therefore treated as an unmodeled disturbance for every subject, RS7 included, and for the remaining twelve the absence of an annotation must not be read as the absence of physical activity.

For each subject, the identification period comprised the days satisfying the above criteria and preceding the validation period. Its duration therefore varied across subjects, ranging from two to five days depending on the amount of available data. The validation period was fixed to two days for all subjects, ensuring a consistent prediction task for model comparison. Glucose trajectories were obtained by open-loop simulation over the entire two-day validation interval, initialized from the estimated model state at the beginning of the validation period. The Prediction Horizon (PH) of the real-data validation therefore coincides with the whole validation interval, i.e., $ph = 2$ days (2880 min) for every subject, and the model state is never re-initialized with the measured glucose within it. It should be noted that the data used in this study were collected during the free-living period. As expected in a free-living protocol, announced meal information may be affected by timing delays and errors in portion estimation. In addition, because the raw

CGM signal was affected by sensor noise, glucose measurements were first processed using the Bayesian denoising method proposed in [Camerlingo et al. \(2023\)](#). To account for these sources of uncertainty and reduce overfitting, a stronger regularization term was adopted during identification to improve model generalization over the validation interval. The complete set of identification and validation profiles, with one figure per subject, is reported in Sec. S3 of the Supplementary Material.

COHORT RESULTS. The results over the thirteen subjects are collected in [Table 5](#). On the identification period, the proposed model improves on the LTI benchmark for *all* thirteen subjects: the median GoF increases from 10.42% to 20.62%, and the median RMSE decreases from 38.5 to 33.3 mg/dL.

On the validation period, i.e., an open-loop simulation over two days, the proposed model attains a positive GoF for eleven subjects out of thirteen, with a median of 8.91% [2.76, 22.58], against nine subjects for the LTI benchmark, with a median of 5.37% [−1.48, 15.48].

Although the median paired difference is only 2.86 percentage points of GoF in favor of the proposed model, the evidence that the free-living data provide in validation is more about robustness than about accuracy: over a two-day open-loop horizon the dynamic S_I enlarges the set of subjects for which a usable model is obtained. The subjects on which the benchmark remains usable are in fact a subset of those on which the proposed model is: there is no subject for which the LTI benchmark attains a positive validation GoF and the proposed model does not, whereas on RS11 and RS12 the proposed model remains positive while the benchmark falls below zero, that is, becomes less accurate than the mean of the validation record itself.

Two subjects returned negative validation GoF, i.e., RS2 and RS13. For RS2, the identification fit is itself essentially null, with negative validation GoF for both models. This suggests that the subject's glucose-insulin dynamics are not adequately described by either constant-parameter model. A possible explanation is the inconsistency between recorded meals and insulin delivery. Over the whole monitoring period, announced carbohydrates amount to only 45% of those implied by the delivered bolus insulin through the individual insulin-to-carbohydrate ratio. Moreover, during identification, 4.2 out of 7.2 daily boluses are not associated with an announced meal, compared with a cohort median of 2.0. These boluses may represent correction boluses due to underestimated or unannounced carbohydrate intake, suggesting substantial meal under-reporting. For RS13 the identification fit is instead among the highest of the cohort (28.80%), and what fails is the extrapolation: its validation period departs from the identification one more than for

Table 5

Real-data identification and validation results over the TAILOR/3 cohort. The identification period of each subject is the usable record that precedes the validation period and lasts from two to five days; the validation period is two days for every subject. Validation is an open-loop simulation over the whole validation period, initialized at the end of the identification period and never re-initialized, so that the prediction horizon is $ph = 2$ days (2880 min) for every subject. GoF and RMSE are defined in (16) and (19). The last two columns quantify the physiological distance between the identification and the validation period, as the absolute difference of the mean glucose $|\Delta\bar{G}|$ and of its standard deviation $|\Delta\sigma_G|$ over the two periods. Subjects are labeled RS1–RS14 (RS: real subject) after the identifiers of the study; RS3 is the excluded subject and does not appear. RS7 and RS11 are the two reported in Fig. 6. The complete profiles of all the subjects are reported in Sec. S3 of the Supplementary Material.

Subject	Num. days		Proposed model (NLTI)				Benchmark LTI (Abuin et al., 2020)				Id.–val. distance	
			GoF [%]		RMSE [mg/dL]		GoF [%]		RMSE [mg/dL]		$ \Delta\bar{G} $	$ \Delta\sigma_G $
	Id.	Val.	Id.	Val.	Id.	Val.	Id.	Val.	Id.	Val.	[mg/dL]	[mg/dL]
RS1	3	2	7.73	9.41	34.8	64.7	−4.80	1.12	39.5	70.6	5.4	33.7
RS2	4	2	−0.42	−17.35	53.2	38.9	−3.07	−11.74	54.6	37.1	11.8	19.8
RS4	2	2	16.14	2.76	37.5	50.3	14.06	3.98	38.4	49.6	0.1	7.0
RS5	4	2	13.71	22.58	33.3	26.7	5.90	15.48	36.3	29.1	3.9	4.1
RS6	5	2	2.69	8.87	30.4	36.3	−2.01	5.37	31.9	37.7	12.1	8.7
RS7	2	2	35.13	31.24	42.3	33.5	24.94	23.30	49.0	37.4	17.7	16.6
RS8	3	2	9.24	11.19	26.8	19.9	6.72	11.94	27.5	19.7	3.2	7.1
RS9	2	2	24.88	8.91	32.3	34.6	10.42	11.37	38.5	33.7	20.6	5.0
RS10	2	2	31.85	4.55	20.4	46.4	19.13	22.10	24.2	37.8	18.7	18.6
RS11	2	2	33.39	29.45	24.4	34.8	20.82	−1.48	29.1	50.1	6.6	12.7
RS12	3	2	20.62	1.53	33.0	40.3	3.26	−18.06	40.2	48.3	7.7	0.7
RS13	2	2	28.80	−17.93	43.4	100.3	19.18	−4.79	49.3	89.1	21.1	24.1
RS14	3	2	34.85	32.17	48.1	50.3	30.04	29.31	51.7	52.4	3.4	0.3
Median	3	2	20.62	8.91	33.3	38.9	10.42	5.37	38.5	37.8	7.7	8.7
25th prc			9.24	2.76	30.4	34.6	3.26	−1.48	31.9	37.1	3.9	5.0
75th prc			31.85	22.58	42.3	50.3	19.18	15.48	49.0	50.1	17.7	18.6

any other subject in mean glucose, and is by far the most variable of the cohort ($\sigma_G = 85.1$ mg/dL against a cohort median of 48.6 mg/dL). This subject is also the one whose inputs are least informative during identification: its diary reports 3.0 meals, 95 g of carbohydrates and 10.1 U of bolus insulin per day over the identification period, against 4.0 meals, 165 g and 17.2 U per day over the two validation days, i.e. an increase of about 70% in both carbohydrates and insulin, the largest of the cohort. The model is therefore identified on a period that excites the meal and insulin channels considerably less than the one over which it is then asked to predict. In both cases, the LTI benchmark is negative as well, so neither failure is attributable to the circadian representation; they delimit, rather, the conditions under which a model identified once and then held constant can be expected to extrapolate, which is the subject of Section 7.

Two observations are needed to read Table 5 correctly. First, GoF and RMSE must be read together, because they respond in opposite ways to the variability of the validation period: subject RS8 has the lowest validation RMSE of the whole cohort, 19.9 mg/dL, and yet a GoF of only 11.19%, because its glucose record is the flattest ($\sigma_G = 22.4$ mg/dL). Second, the last two columns of the table quantify how far the validation period of each subject departs from its identification period, in mean glucose and in its standard deviation; as discussed in Section 7, this is the quantity that accompanies the loss of accuracy between the two periods.

Subjects RS7 and RS11 are reported in Fig. 6 as representative cases. For RS7, the model achieved a GoF of 35.13% on the training interval and 31.24% on the validation interval (blue and red lines in the figure). The LTI benchmark model yields lower performance, with a GoF of 24.94% on the training set and 23.30% on the validation set (purple and green lines), indicating that the proposed model provides a clear improvement in both identification and validation. For RS11, the separation is larger still: the proposed model attains 33.39% and 29.45% of GoF on identification and validation, whereas the benchmark, with an identification fit of 20.82%, degrades to −1.48% in validation, i.e. it becomes less accurate than the mean of the validation record itself.

Over the whole cohort, as expected, the values obtained are *lower* than those observed in the *in silico* cohort. There, meal intake and insulin delivery are known exactly, and the model mismatch, although present and not negligible, is limited to the structural differences with respect to the simulator and to its CGM and pump error models (Section 6.1). The real-data setting adds to these the uncertainty of the meal information, which may be over- or under-announced, and unmodeled disturbances such as physical activity, stress, or illness, all of which degrade long-horizon open-loop predictive performance. However, it is worth noting that Fig. 6 reports open-loop glucose predictions over the entire two-day validation interval (PH = 2880 min), normally referred to in the literature as *infinite horizon* prediction. The next section evaluates the performance of the proposal as a *finite horizon* predictor, suitable for MPC.

6.3. Rolling-horizon prediction on real data

This last analysis is reported as a *proof of concept* on the single subject RS7. A cohort-wide rolling-horizon evaluation, together with the closed-loop assessment, is left to future work.

Despite the limitations highlighted in the previous section, it is important to emphasize that the proposed model is not intended as an open-loop predictor over very long horizons, but rather as an internal simulation model for MPC. In this context, the clinically relevant quantity is not the error accumulated over an entire multi-day validation interval, but the prediction accuracy over a finite receding horizon, typically up to 6 hours (Abuin et al., 2020; Licini et al., 2026). For this reason, prediction performance was also evaluated in a rolling-horizon setting. At each validation step, the model was initialized from the current state estimate provided by an Extended Kalman Filter (EKF), implemented according to the augmented observer structure in Abuin et al. (2020) (using a linearized version of the nonlinear model in this work), and then simulated over different finite PHs, ranging from 5 to 360 min. The prediction error was computed over these horizons before the window was shifted forward and the procedure repeated.

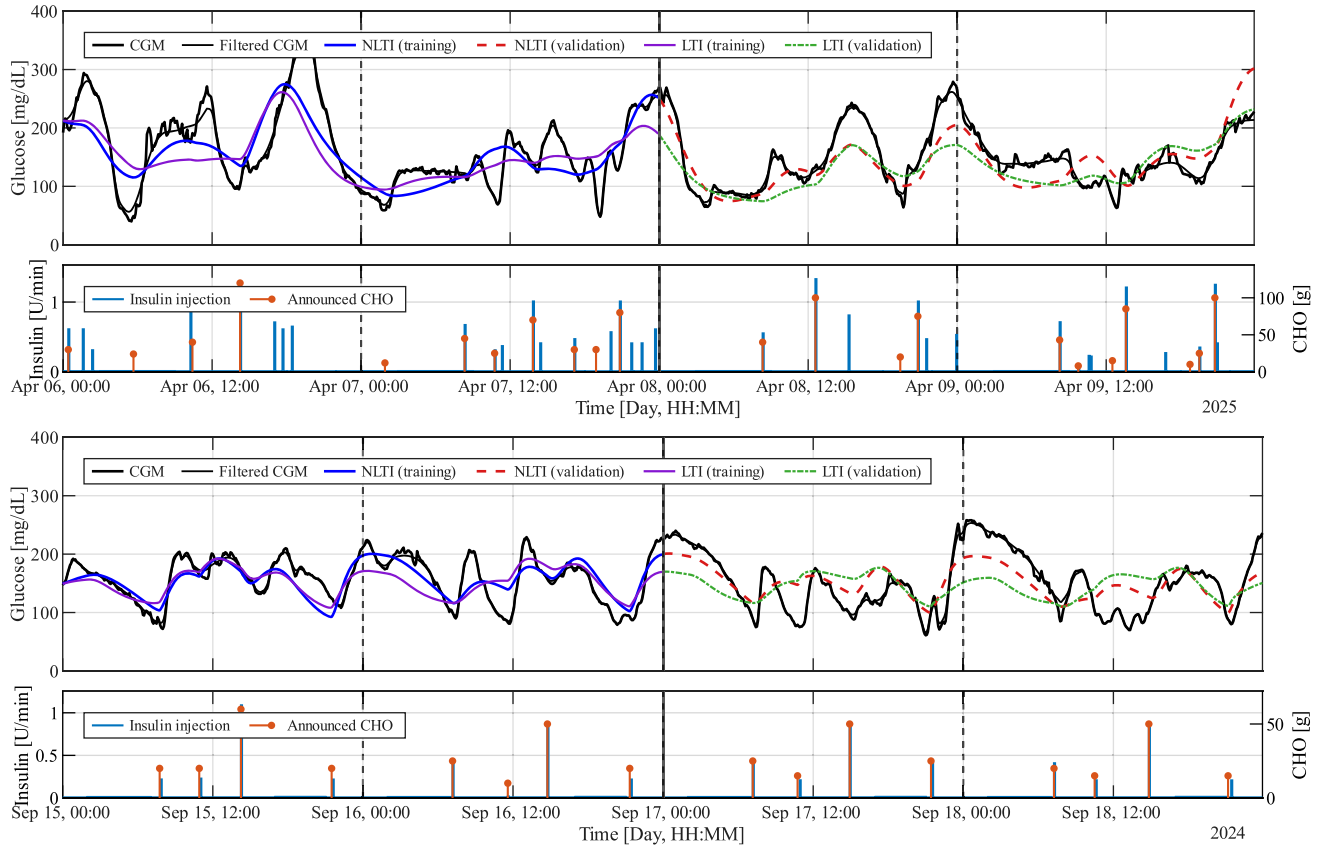


Fig. 6. Real-data identification and validation results for two representative subjects (top: RS7; bottom: RS11) from the TAILOR/3 study (U. S. National Library of Medicine, 2025). The corresponding figures for all the thirteen subjects of the cohort are reported in Sec. S3 of the Supplementary Material. The upper panel of each subject compares the CGM signal, its Bayesian-filtered version (Camerlingo et al., 2023), and the glucose trajectories predicted by both the proposed model and the LTI benchmark model over the training (blue/purple) and validation (red/green) intervals. The lower panel reports the corresponding insulin delivery and announced carbohydrate intake profiles used as model inputs. For both subjects, two days of data were used for parameter identification and the following two days for validation. Validation is an open-loop simulation over the whole two-day interval, initialized at the end of the identification period and never re-initialized, so that the prediction horizon is $ph = 2$ days (2880 min). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

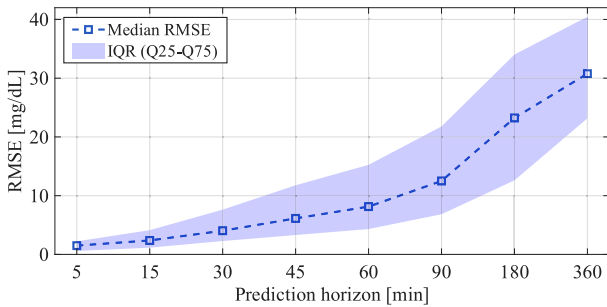


Fig. 7. Rolling-horizon prediction accuracy on real data (subject RS7) as a function of the prediction horizon, obtained by initializing the nonlinear model with the current state estimate of an Extended Kalman Filter. The plot reports the median and interquartile RMSE computed across all rolling windows for ph ranging from 5 to 360 min. Prediction error increases progressively with the horizon length, while remaining comparatively low over the initial portion of the horizon, which is the most relevant region for receding-horizon MPC. The detailed values of the median and interquartile RMSE for each ph are reported in Table S2 of the Supplementary Material.

Note that, in the rolling-horizon setting, the GoF index defined in (16) is not used as a performance metric. Since GoF is normalized by the variance of the reference signal within each prediction window, it

becomes unstable for short horizons (e.g., 5–15 min), where the glucose profile can be nearly flat and the normalization denominator approaches zero. RMSE is therefore the appropriate metric for this analysis, as it provides a direct and stable measure of prediction accuracy across all horizon lengths.

The corresponding RMSE statistics are reported in Fig. 7, and their detailed values in Table S2 of the Supplementary Material. As expected, prediction accuracy decreases as the horizon increases. The median RMSE increases from 1.50 mg/dL at 5 min to 8.14 mg/dL at 60 min and to 30.77 mg/dL at 360 min; these results indicate that, once reinitialized through state estimation, the model retains good predictive accuracy over the short and medium horizons, while the uncertainty naturally accumulates at longer horizons.

From a control perspective, this result is particularly relevant. In receding-horizon MPC, the initial portion of the prediction horizon has the greatest influence on the optimization and the resulting insulin delivery decision, since the horizon is reinitialized at every control step. Therefore, the relatively low prediction errors near the initialization point support the model's suitability as an internal predictor for closed-loop control, even though long-horizon open-loop forecasts on real data remain challenging. In other words, the real-data analysis suggests that, when combined with EKF-based state estimation, the proposed model can still provide prediction accuracy that is meaningful for MPC, especially over the time scales that matter most for the receding-horizon strategy.

7. Discussion

IN SILICO RESULTS. The in silico improvement over the LTI baseline on the UVA/Padova cohort is substantial across all performance indices. The harmonic order was selected on the four literature profiles reviewed in Section 3.1; the profile of Toffanin et al. (2013) enters the experimental setup only as the variability scenario implemented in the simulator that generates the data, and therefore the harmonic amplitudes and phases are estimated from these data for each subject. The in silico improvement primarily demonstrates that the estimation procedure correctly identifies patient-specific parameters and that the harmonic approximation accurately captures the simulator's circadian dynamics. The insulin sensitivity trajectories recovered by the identification, for the ten in silico subjects and for each of the thirteen subjects of the clinical cohort, are reported in Sec. S4 of the Supplementary Material, the latter against the four reference profiles of Section 3.1. They illustrate the property that motivates the proposed formulation: the reference profiles are fixed population-level shapes that must be selected a priori, whereas amplitude, phases and tracking time constant are here estimated from each subject's own records, so that the resulting trajectory is subject-specific and is not constrained to resemble any of the four. In silico the timing of the modulation is recovered accurately, while its amplitude is underestimated, which is a consequence of the first-order lag that drives $S_I(t)$ rather than of the identification.

REAL-DATA RESULTS. To contribute as an independent validation of the proposed circadian structure against diverse real-world physiology, the real-subject validation on TAILOR/3 (U. S. National Library of Medicine, 2025) data provides complementary, independent evidence. The subjects' actual S_I dynamics are unknown and not constrained to match the simulator's profile, making this a more challenging test. Over the thirteen subjects of the cohort, the dynamic S_I formulation improves the identification fit for every subject, indicating that the additional degree of freedom describes structure that is present in the data of all of them. In validation, over a two-day open-loop horizon, the advantage is better read in terms of robustness than of accuracy: the proposed model attains a positive GoF on eleven subjects against nine for the benchmark, and the subjects on which the benchmark remains usable are a subset of those on which the proposed model is. There is no subject on which the benchmark works and the proposed model does not, whereas on two subjects the proposed model stays positive while the benchmark falls below zero, that is, becomes less accurate than the mean of the validation record itself. However, the absolute GoF values are lower relative to the in silico case. This result is expected and attributable to sensor noise, meal announcement uncertainty (i.e., meals that are announced with time delay, over-/under-estimated, or non-announced, a well known problem in T1DM literature (Reiterer & Freckmann, 2019; Roversi et al., 2020)), and unmodeled disturbances inherent to free-living conditions (e.g., physical activity or stress).

DAY-TO-DAY VARIABILITY. The last two columns of Table 5 report how far the validation period of each subject departs from its identification period, in mean glucose and in glucose variability, and they accompany the behavior observed in validation: the subjects whose validation period resembles the identification one retain their accuracy, whereas the largest losses occur for the subjects whose glucose statistics shift the most between the two periods. The quality of the identification fit does not anticipate this, which is the expected signature of a generalization problem rather than of a fitting one. The LTI benchmark degrades on the same subjects, so this is not a limitation of the circadian representation but a property of any constant-parameter model identified on free-living data: its parameters describe the physiological condition of the identification period, and in free-living conditions that condition changes from one day to the next. This is precisely the argument for the recursive state estimation of Section 6.3, in which the model is re-initialized at

every control step and is therefore never required to extrapolate two days ahead from a condition that has since changed.

The rolling-horizon analysis (Section 6.3) further shows that, when combined with EKF-based state estimation, the model achieves clinically meaningful prediction accuracy over the short horizons (median RMSE of 1.50 mg/dL at 5 min and 8.14 mg/dL at 60 min). This supports the primary intended use of the model as an internal predictor for MPC, rather than as a multi-day open-loop forecaster.

LIMITATIONS. Several limitations should be acknowledged. First, although the real-data validation covers thirteen subjects, the cohort remains small, single-center and observational; the identification and validation periods are limited by the length of the usable record of each subject, and the rolling-horizon assessment of Section 6.3 is a proof of concept on a single subject. Moreover, these are genuinely free-living data collected before the controlled inpatient trial: no clinical protocol constrains what the subjects do (other than reporting carbohydrate content), and there is no supervised, systematic data collection as in a laboratory setting, so the model inputs rely entirely on the accuracy of the entries reported by the subjects themselves. Second, the harmonic circadian target does not model transient S_I perturbations due to physical activity, stress, or illness, which are prominent sources of variability in free-living conditions. Third, the model has only been evaluated in open-loop prediction; closed-loop performance in an MPC framework remains to be demonstrated. Addressing these limitations constitutes the primary direction for future work.

8. Conclusion

This work presented a compact, physiologically interpretable, control-oriented model of glucose–insulin dynamics in which insulin sensitivity is treated as a dynamic state driven by a circadian target. The proposed formulation extends the established long-term model in Ruan et al. (2017) by replacing constant insulin sensitivity with a first-order dynamic linked to a truncated harmonic representation of circadian modulation. In this way, a structure suitable for analysis, parameter estimation, and integration into model-based control schemes is preserved.

The model was analytically characterized under fasting conditions, showing that circadian variability naturally induces basal operating trajectories (limit cycles) rather than static equilibria. Two clinically relevant basal regimes were derived: constant basal insulin infusion leading to periodic glucose dynamics, and periodic basal insulin delivery required to maintain constant basal glucose.

The identification study showed that the main kinetic and basal sensitivity parameters are structurally globally identifiable, while the expected non-uniqueness introduced by the harmonic phase parameters remains confined to the circadian component. In addition, sensitivity analysis supported a reduced and practically estimable parameterization.

Validation on the UVA/Padova adult cohort showed that the proposed nonlinear model improves prediction accuracy with respect to the previous linear control-oriented formulation. Validation on free-living data from thirteen subjects of the TAILOR/3 study showed that the dynamic insulin sensitivity improves the identification fit for every subject of the cohort, and yields a positive validation goodness of fit for eleven of them over a two-day open-loop horizon, against nine for the linear benchmark, without ever failing on a subject on which the benchmark remains usable. The residual loss between the two periods follows the day-to-day change of the glucose statistics of each subject, which delimits the validity of a constant-parameter model on free-living data. Consistently with this, the rolling-horizon analysis, reported as a proof of concept on a single subject, showed that prediction accuracy remains satisfactory over the short and medium horizons that are most relevant for receding-horizon MPC, where the model is re-initialized at every control step.

These results suggest that the harmonic formulation could be used to analyze and assess the presence of variability classes suggested by the literature (Visentin et al., 2015).

Finally, while the present analysis focused on prediction and identifiability, a natural next step of the work is the embedding of this model within advanced closed-loop strategies, considering also potential links between the insulin sensitivity and other relevant states of a general insulin-glucose nonlinear model.

CRediT authorship contribution statement

Nicola Licini: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization; **Jorge Bondia:** Writing – review & editing, Supervision; **Clara Furió-Novejarque:** Writing – review & editing, Supervision; **Iván Sala-Mira:** Writing – review & editing, Supervision; **Pablo Abuin:** Writing – review & editing, Supervision; **Beatrice Sonzogni:** Writing – review & editing, Supervision; **Fabio Previdi:** Writing – review & editing, Supervision, Funding acquisition; **José-Luis Díez:** Writing – review & editing, Supervision; **Alejandro H. González:** Writing – review & editing, Supervision, Conceptualization; **Antonio Ferramosca:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

Supplementary material associated with this article can be found in the online version at [10.1016/j.conengprac.2026.107309](https://doi.org/10.1016/j.conengprac.2026.107309).

Appendix A. Harmonic representation and selection of the circadian insulin sensitivity target

The circadian target for insulin sensitivity, $S_{I, Tar}(t)$, developed in this work, is modeled as a truncated Fourier series with harmonics at integer multiples of the 24-h fundamental frequency. The choice of three

harmonics is therefore not arbitrary but is supported by (i) an *a priori* spectral analysis of four representative $S_I(t)$ profiles from the literature (Section 3.1), and (ii) an *a posteriori* assessment of model performance and complexity. This appendix details the procedure used to design and select the harmonic representation of $S_{I, Tar}(t)$.

A.1. Fourier analysis of reference insulin sensitivity patterns

For each reference profile $S_I^{(j)}(t)$, $j = \{1, \dots, 4\}$ (i.e., Fabietti et al., 2006; Mansell et al., 2015; Toffanin et al., 2013; Visentin et al., 2015), its Discrete Fourier Transform (DFT) was computed, retaining the spectral components at integer multiples of the fundamental daily frequency $\omega_0 = 2\pi/24 \text{ h}^{-1}$. The results are depicted in Fig. A.1, where the top row shows the four reference $S_I(t)$ multipliers over a single day, and the bottom row the corresponding one-sided Fourier amplitude spectra.

The magnitude spectra demonstrate that the dominant energy is concentrated in the first few harmonics, with rapidly decaying amplitudes for higher-order components, suggesting that a low-order harmonic representation should be sufficient.

A.2. Truncated harmonic reconstruction

To assess how many harmonics are required for an accurate yet parsimonious description, each reference pattern was approximated using a truncated Fourier series:

$$\hat{S}_I^{(j)}(t) = a_0^{(j)} + \sum_{k=1}^N (a_k^{(j)} \cos(k\omega_0 t) + b_k^{(j)} \sin(k\omega_0 t)),$$

where N is the number of retained harmonics ordered by increasing frequency ($k = 1, \dots, N$), and the coefficients $\{a_k^{(j)}, b_k^{(j)}\}$ are obtained from the DFT of $S_I^{(j)}(t)$.

For each reference pattern j and truncation order N , the reconstruction error was quantified via the RMSE between $S_I^{(j)}(t)$ and $\hat{S}_I^{(j)}(t; N)$, and the evolution of $\text{RMSE}^{(j)}(N)$ was examined as N increased from 1 to 10. The resulting RMSE curves are reported in Fig. A.2. Across all four reference profiles, the RMSE decreases markedly when increasing N from 1 to 2 and from 2 to 3, with only modest improvement when moving from $N = 3$ to $N = 4$. The only exception is the Fabietti shape, which is already sinusoidal and is therefore represented exactly by a single harmonic. These results indicate that the first three harmonics capture the dominant circadian structure of $S_I(t)$ for a broad set of reported patterns, while higher-order components mainly refine fine-scale details. Fig. A.3 shows this evidence for the first 3 harmonics; it is clear from the plots that 3 harmonics follow all four waveforms with comparable fidelity, although the four differ substantially in shape, confirming that the representation accommodates the whole range of circadian S_I shapes reported in the literature rather than one particular waveform.

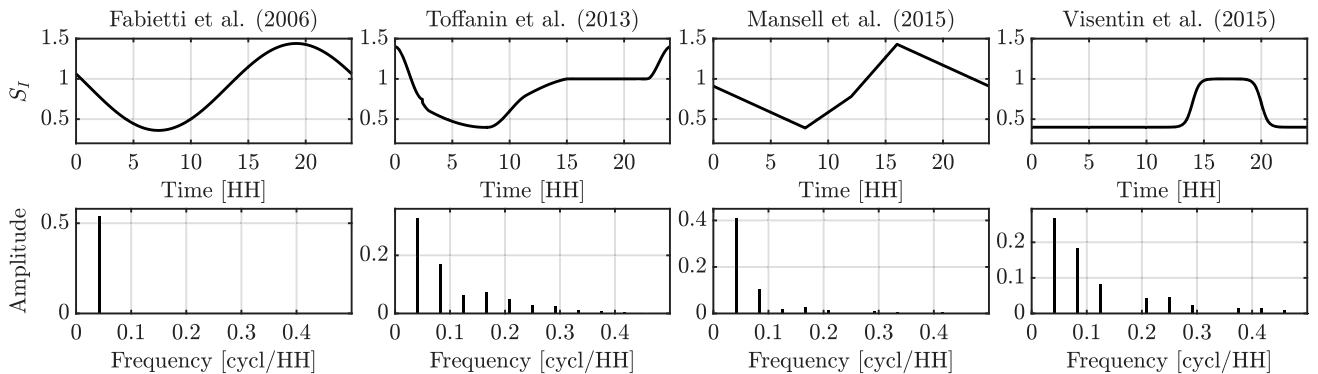


Fig. A.1. Reference circadian insulin sensitivity patterns and corresponding Fourier amplitude spectra. *Top row:* daily multipliers of insulin sensitivity, $S_I(t)$, generated from four literature models (Fabietti et al., 2006; Mansell et al., 2015; Toffanin et al., 2013; Visentin et al., 2015), plotted over one 24 h period. *Bottom row:* corresponding one-sided Fourier amplitude spectra, with frequency expressed in cycles per hour. The circadian fundamental frequency appears at approximately 1/24 cycles/hour, and most of the spectral energy is concentrated in the lowest harmonics.

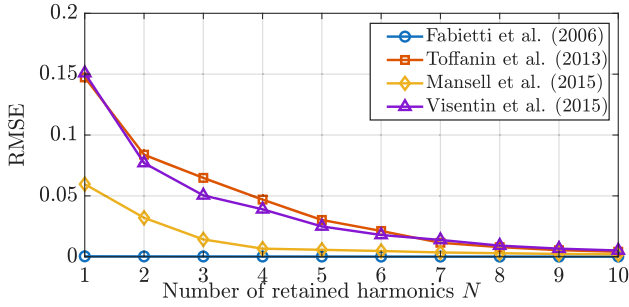


Fig. A.2. Reconstruction accuracy as a function of the number of harmonics. Each curve reports the RMSE between the original reference profile $S_I^{(j)}(t)$ and its truncated Fourier reconstruction $\hat{S}_I^{(j)}(t; N)$ as a function of N , using the N most energetic harmonic components of the spectrum. Across all reference patterns, the RMSE decreases substantially from $N = 1$ to $N = 2$ and from $N = 2$ to $N = 3$, while further reductions for $N \geq 4$ are comparatively modest. For the Fabietti profile, which is already sinusoidal, the RMSE is minimal for $N = 1$ and shows negligible improvement with additional harmonics.

A.3. Selection of the number of harmonics

The number of harmonics was chosen as a trade-off between reconstruction accuracy, model performance, and complexity. Fourier analysis of representative insulin sensitivity profiles shows that most spectral energy is concentrated in the first few harmonics, suggesting that a low-order representation is sufficient.

The following analysis is conducted on *in silico* data generated with the commercial version of the UVA/Padova T1DM simulator, which adopts the variability scenario proposed in Toffanin et al. (2013). Hence, for $N \in \{1, 2, 3, 4\}$ a corresponding model variant was instantiated in which $S_{I,Tar}(t)$ is generated by N coupled harmonic oscillators. For each value of N , the model was calibrated on *in silico* data, and the following aspects were evaluated: (i) standard error- and fit-based metrics (i.e., RMSE and GoF), and (ii) the qualitative temporal regularity of the predicted $S_I(t)$ trajectories, with particular attention to the appearance of spurious fast oscillations or unrealistic shape distortions when higher-order harmonics are included.

Reconstruction results in Fig. A.4 indicate that increasing the number of harmonics from $N = 1$ to $N = 3$ significantly improves glucose prediction metrics (i.e., RMSE and GoF), while additional harmonics ($N = 4$) provide only marginal improvements. These findings are further illustrated in Fig. A.5, which reports representative simulated trajectories of the circadian target $S_{I,Tar}(t)$ and the corresponding dynamic insulin sensitivity $S_I(t)$ for $N = \{1, 2, 3, 4\}$ harmonics under the same experimental protocol. With one and two harmonics, the model captures the main diurnal modulation but tends to oversimplify the dawn-related changes and intra-day variability. Three harmonics reproduce the key circadian features with smooth and physiologically plausible profiles, whereas four harmonics introduce only minor refinements and, in some cases, additional small-amplitude oscillations. Moreover, each additional harmonic increases the number of parameters and states, worsening identifiability and sensitivity to noise, since insulin sensitivity is not directly measurable. Therefore, selecting three harmonics provides a good trade-off: (i) it captures the main circadian features (including dawn effects), (ii) ensures smooth and physiologically plausible behavior, and (iii) keeps the parameter space sufficiently restricted to remain structurally and practically identifiable under realistic excitation and noise conditions.

Appendix B. Basal analysis derivations

Under fasting conditions ($r(t) = 0$) and in the absence of exogenous insulin variations, glycemia and insulin remain at their basal steady-state values. In this setting, the $S_I(t)$ state evolves according to the lin-

ear non-homogeneous dynamics (7), whose forcing term $S_{I,Tar}(t)$ is T_0 -periodic by construction of the harmonic oscillators. Because a linear system with a periodic input admits a unique T_0 -periodic steady-state solution, the basal trajectory $S_{I,b}(t)$ converges asymptotically to a unique T_0 -periodic orbit, independently of the initial condition $S_{I,b}(0)$.

The solution of (7) is obtained by the standard integrating factor method, yielding

$$S_{I,b}(t) = e^{-t/\theta_5} S_{I,b}(0) + \frac{1}{\theta_5} e^{-t/\theta_5} \int_0^t e^{\tau/\theta_5} S_{I,Tar}(\tau) d\tau. \quad (B.1)$$

The first term in (B.1), $e^{-t/\theta_5} S_{I,b}(0)$, decays exponentially to zero as $t \rightarrow \infty$, since $\theta_5 > 0$. Thus, the long-term behavior of $S_{I,b}(t)$ is fully determined by the second term:

$$S_{I,b}^*(t) = \frac{1}{\theta_5} e^{-t/\theta_5} \int_0^t e^{\tau/\theta_5} S_{I,Tar}(\tau) d\tau, \quad (B.2)$$

which represents the asymptotic (steady) basal trajectory.

To make (B.2) more transparent, a change of variables is performed. Let $\sigma = t - \tau$, i.e., $\tau = t - \sigma$ and $d\tau = -d\sigma$. Then

$$\begin{aligned} S_{I,b}^*(t) &= \frac{1}{\theta_5} e^{-t/\theta_5} \int_0^t e^{\tau/\theta_5} S_{I,Tar}(\tau) d\tau \\ &= \frac{1}{\theta_5} e^{-t/\theta_5} \int_t^0 e^{(t-\sigma)/\theta_5} S_{I,Tar}(t-\sigma) (-d\sigma) \\ &= \frac{1}{\theta_5} \int_0^t e^{-\sigma/\theta_5} S_{I,Tar}(t-\sigma) d\sigma. \end{aligned} \quad (B.3)$$

Since the exponential kernel $e^{-\sigma/\theta_5}$ decays for large σ , the integral in (B.3) converges as t grows, and it is natural to extend the upper limit to $+\infty$ in the steady-state sense:

$$S_{I,b}^*(t) = \frac{1}{\theta_5} \int_0^\infty e^{-\sigma/\theta_5} S_{I,Tar}(t-\sigma) d\sigma. \quad (B.4)$$

Eq. (B.4) shows that the basal insulin sensitivity state is a weighted (exponentially decaying) average of past values of the circadian target $S_{I,Tar}(\cdot)$.

The integral expression (B.4) can also be used to give an intuitive, purely time-domain interpretation of how the circadian harmonics are reshaped by the basal dynamics. To see this, recall that the circadian target is defined as

$$S_{I,Tar}(t) = A_{SI} \left[1 + \sum_{k=1}^3 \alpha_k z_{k,1}(t) \right], \quad (B.5)$$

where, at steady state, each oscillator satisfies

$$z_{k,1}(t) = \sin(\omega_k t + \varphi_k), \quad \omega_k = k \frac{2\pi}{T_0}, \quad k = \{1, 2, 3\}. \quad (B.6)$$

Thus,

$$S_{I,Tar}(t) = A_{SI} + \sum_{k=1}^3 A_{SI} \alpha_k \sin(\omega_k t + \varphi_k). \quad (B.7)$$

Now, consider the response of (7) to a single sinusoidal component of the target. Let

$$S_{I,Tar}^{(k)}(t) = A_{SI} \alpha_k \sin(\omega_k t + \varphi_k), \quad (B.8)$$

and denote by $S_{I,b}^{(k)}(t)$ the corresponding steady-state contribution in (B.4). From (B.4), it follows that

$$S_{I,b}^{(k)}(t) = \frac{1}{\theta_5} \int_0^\infty e^{-\sigma/\theta_5} S_{I,Tar}^{(k)}(t-\sigma) d\sigma. \quad (B.9)$$

Using the trigonometric identity

$$\sin(\omega_k(t-\sigma) + \varphi_k) = \sin(\omega_k t + \varphi_k) \cos(\omega_k \sigma) - \cos(\omega_k t + \varphi_k) \sin(\omega_k \sigma), \quad (B.10)$$

substitution into (B.9) gives

$$\begin{aligned} S_{I,b}^{(k)}(t) &= \frac{A_{SI} \alpha_k}{\theta_5} \int_0^\infty e^{-\sigma/\theta_5} \left[\sin(\omega_k t + \varphi_k) \cos(\omega_k \sigma) \right. \\ &\quad \left. - \cos(\omega_k t + \varphi_k) \sin(\omega_k \sigma) \right] d\sigma \\ &= A_{SI} \alpha_k \left[\sin(\omega_k t + \varphi_k) I_{c,k} - \cos(\omega_k t + \varphi_k) I_{s,k} \right], \end{aligned} \quad (B.11)$$

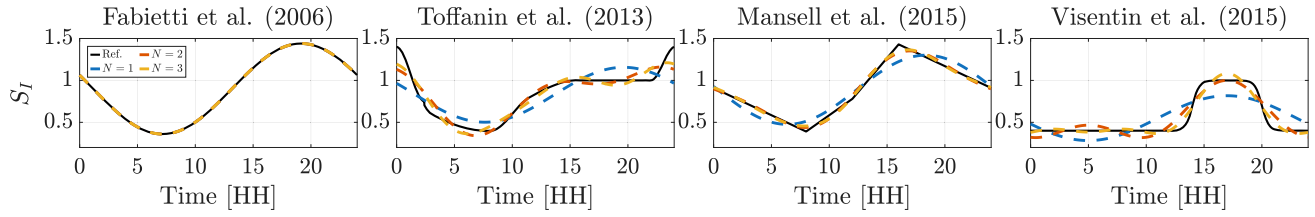


Fig. A.3. Least-squares approximation of the four reference circadian S_I profiles with the parameterization adopted for $S_{I,Tar}(t)$ in the proposed model. Each panel reports one reference profile over a single 24 h period (black, solid) together with its approximation obtained with $N = 1, 2, 3$ harmonics of the 24-h fundamental frequency (dashed).

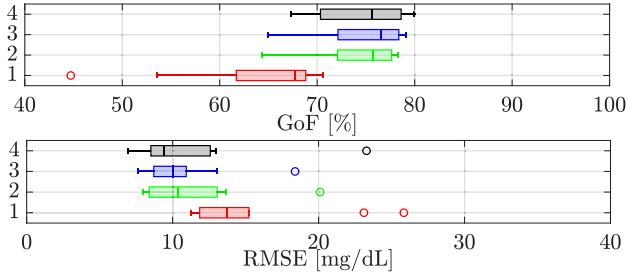


Fig. A.4. Comparison of identification performance for models with $N = 1, 2, 3, 4$ harmonics in the circadian target $S_{I,Tar}(t)$. Bars summarize representative fit indices, with GoF in the top plot and RMSE in the bottom one, both computed on common identification and validation datasets. Moving from $N = 1$ to $N = 3$ yields progressively improved fits for the corresponding glucose trajectories, whereas the additional fourth harmonic provides only marginal gains.

where

$$I_{c,k} = \frac{1}{\theta_5} \int_0^\infty e^{-\sigma/\theta_5} \cos(\omega_k \sigma) d\sigma, \quad (\text{B.12})$$

$$I_{s,k} = \frac{1}{\theta_5} \int_0^\infty e^{-\sigma/\theta_5} \sin(\omega_k \sigma) d\sigma. \quad (\text{B.13})$$

The integrals (B.12) and (B.13) can be evaluated in closed form. Standard formulas for exponentially weighted sines and cosines give

$$I_{c,k} = \frac{1}{1 + (\omega_k \theta_5)^2}, \quad (\text{B.14})$$

$$I_{s,k} = \frac{\omega_k \theta_5}{1 + (\omega_k \theta_5)^2}. \quad (\text{B.15})$$

Substituting (B.14) and (B.15) into (B.11) yields

$$S_{I,b}^{(k)}(t) = A_{SI} \alpha_k \left[\frac{1}{1 + (\omega_k \theta_5)^2} \sin(\omega_k t + \varphi_k) - \frac{\omega_k \theta_5}{1 + (\omega_k \theta_5)^2} \cos(\omega_k t + \varphi_k) \right]. \quad (\text{B.16})$$

Expression (B.16) already shows that the output harmonic is a linear combination of sin and cos with the same frequency ω_k . This combination can be rewritten as a single sinusoid with modified amplitude and phase. Let

$$S_{I,b}^{(k)}(t) = \tilde{A}_k \sin(\omega_k t + \tilde{\varphi}_k), \quad (\text{B.17})$$

for some effective amplitude $\tilde{A}_k$ and phase $\tilde{\varphi}_k$. Matching (B.16) and (B.17) term by term, and using the identity

$$\sin(\omega_k t + \tilde{\varphi}_k) = \sin(\omega_k t) \cos \tilde{\varphi}_k + \cos(\omega_k t) \sin \tilde{\varphi}_k, \quad (\text{B.18})$$

it follows that

$$\tilde{A}_k = A_{SI} \alpha_k \sqrt{I_{c,k}^2 + I_{s,k}^2} = A_{SI} \alpha_k \frac{1}{\sqrt{1 + (\omega_k \theta_5)^2}}, \quad (\text{B.19})$$

$$\tilde{\varphi}_k = \varphi_k - \arctan(\omega_k \theta_5). \quad (\text{B.20})$$

Therefore, higher-frequency harmonics (larger ω_k) are attenuated more strongly by the factor $1/\sqrt{1 + (\omega_k \theta_5)^2}$ and experience a larger phase delay $\arctan(\omega_k \theta_5)$.

Finally, summing over all harmonics and including the constant term, the steady basal insulin sensitivity trajectory can be written as

$$S_{I,b}^*(t) = A_{SI} + \sum_{k=1}^3 A_{SI} \alpha_k \frac{1}{\sqrt{1 + (\omega_k \theta_5)^2}} \sin(\Phi), \quad (\text{B.21})$$

with $\Phi = \omega_k t + \varphi_k - \arctan(\omega_k \theta_5)$.

At this point, two possible solutions of the model under basal conditions are proposed.

Remark 3. The derivation in (B.8)–(B.20) is exactly the sinusoidal steady-state, frequency-response result, for the first-order stable subsystem (7), when $S_{I,Tar}(t)$ is viewed as a periodic input term. In particular, (B.19) and (B.20) provide the gain attenuation and phase lag for each harmonic, while (B.17) is the corresponding single-sinusoid representation.

B.1. Periodic basal glucose

In this framework, depicted in Fig. B.1, insulin injection is maintained constant at a basal value (U_b). In this way, due to insulin sensitivity oscillations caused by circadian modulation, glycemia $G(t)$ cannot be fixed; hence, it varies following a periodic trajectory.

From the insulin compartment dynamics at equilibrium $\dot{Q}_i(t) = 0$, $\dot{Q}_{i,sub}(t) = 0$, with $u(t) = U_b$:

$$0 = -\frac{1}{\theta_3} Q_{i,b}(t) + \frac{1}{\theta_3} Q_{i,sub,b}(t) \quad (\text{B.22})$$

$$0 = -\frac{1}{\theta_3} Q_{i,sub,b}(t) + \frac{1}{\theta_3} U_b \quad (\text{B.23})$$

hence it follows that $Q_{i,b} = Q_{i,sub,b} = U_b$.

General solution. It is now possible to analytically solve the glucose equation with $Q_g(t) = 0$ (no meal intake at basal levels):

$$\dot{G}_b(t) = \theta_0 - \theta_1 G_b(t) - U_b S_{I,b}(t). \quad (\text{B.24})$$

The basal glucose dynamics satisfy the first-order linear ODE

$$\dot{G}_b(t) + \theta_1 G_b(t) = \theta_0 - U_b S_{I,b}(t). \quad (\text{B.25})$$

Since (B.25) is a standard first-order linear equation, the solution can be found through the integrating factor method as

$$G_b(t) = e^{-\theta_1 t} G_b(0) + e^{-\theta_1 t} \int_0^t e^{\theta_1 \tau} [\theta_0 - U_b S_{I,b}(\tau)] d\tau. \quad (\text{B.26})$$

As $t \rightarrow \infty$, the homogeneous term $e^{-\theta_1 t} G_b(0)$ vanishes because $\theta_1 > 0$. The asymptotic (steady) basal glucose trajectory is therefore

$$G_b^*(t) = e^{-\theta_1 t} \int_0^t e^{\theta_1 \tau} [\theta_0 - U_b S_{I,b}(\tau)] d\tau. \quad (\text{B.27})$$

Convolution form. To emphasize the dependence on past values of $S_{I,b}(t)$, the change of variables $\sigma = t - \tau$ is performed (so that $\tau = t - \sigma$, $d\tau = -d\sigma$):

$$G_b^*(t) = e^{-\theta_1 t} \int_0^t e^{\theta_1 \tau} [\theta_0 - U_b S_{I,b}(\tau)] d\tau$$

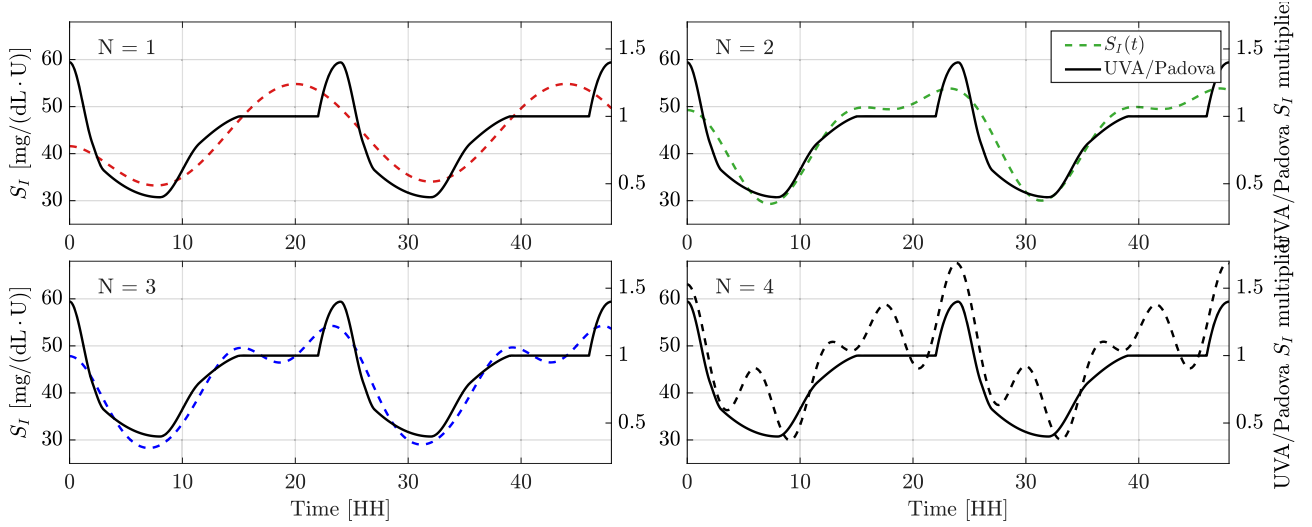


Fig. A.5. Example simulated insulin sensitivity trajectories for different numbers of harmonics. Representative simulations of the dynamic $S_I(t)$ are reported for $N = 1, 2, 3, 4$ harmonics under the same protocol. Note that the comparison between $S_I(t)$ (left axis, [mg/(dL·U)]) and the UVA/Padova reference (right axis, dimensionless multiplier) is intended as a qualitative shape comparison only: the two curves share the same time axis but have different units and different physical interpretations, and their absolute magnitudes should not be compared directly. Using $N = 2$ harmonics captures the gross diurnal trend but under-represents some circadian features, particularly around dawn. Adding a fourth harmonic ($N = 4$) produces only minor visible refinements and may introduce superfluous fast oscillations.

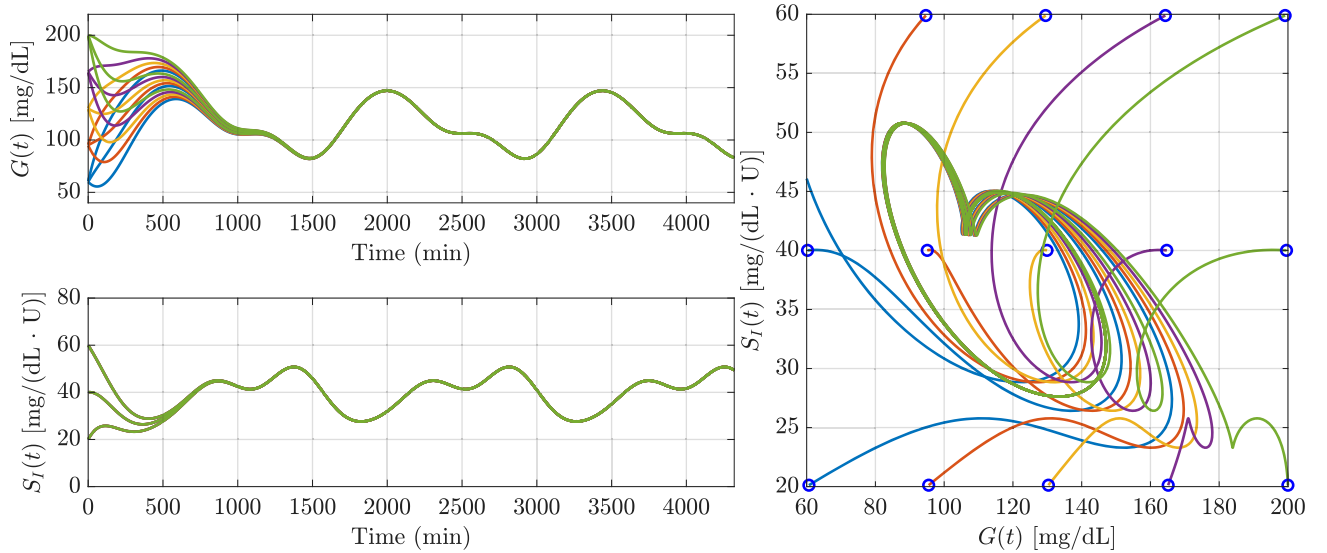


Fig. B.1. Equilibrium under constant basal insulin injection. Left plots show glycemia (upper) and insulin sensitivity (lower) periodic trajectories. The multiple lines represent free evolutions from different initial conditions; all trajectories converge to the same periodic basal limit cycle, regardless of starting point. The right plot shows the phase portrait of the two states, highlighting a domain of attraction.

$$\begin{aligned}
 &= e^{-\theta_1 t} \int_t^0 e^{\theta_1(t-\sigma)} [\theta_0 - U_b S_{I,b}(t-\sigma)] (-d\sigma) \\
 &= \int_0^t e^{-\theta_1 \sigma} [\theta_0 - U_b S_{I,b}(t-\sigma)] d\sigma.
 \end{aligned} \tag{B.28}$$

Since $e^{-\theta_1 \sigma}$ decays for large σ , the upper limit can be extended to $+\infty$ in the steady-state sense:

$$G_b^*(t) = \int_0^\infty e^{-\theta_1 \sigma} [\theta_0 - U_b S_{I,b}(t-\sigma)] d\sigma. \tag{B.29}$$

The first term in (B.29) can be evaluated explicitly:

$$\int_0^\infty e^{-\theta_1 \sigma} \theta_0 d\sigma = \frac{\theta_0}{\theta_1}, \tag{B.30}$$

so that

$$G_b^*(t) = \frac{\theta_0}{\theta_1} - U_b \int_0^\infty e^{-\theta_1 \sigma} S_{I,b}(t-\sigma) d\sigma. \tag{B.31}$$

Because $S_{I,b}(t)$ is T_0 -periodic (see previous subsection), the convolution term in (B.31) is also T_0 -periodic, and hence $G_b^*(t)$ is periodic with period T_0 . Thus, under a constant basal insulin infusion U_b and in fasting conditions, the model admits a unique periodic basal glucose trajectory $G_b^*(t)$.

Mean basal glucose. The average value of $G_b^*(t)$ over one period can also be characterized. With the period average denoted by

$$\langle z \rangle := \frac{1}{T_0} \int_{t_0}^{t_0+T_0} z(\tau) d\tau, \tag{B.32}$$

averaging both sides of (B.25) in steady state gives:

$$\langle \dot{G}_b^* \rangle + \theta_1 \langle G_b^* \rangle = \theta_0 - U_b \langle S_{I,b}^* \rangle. \tag{B.33}$$

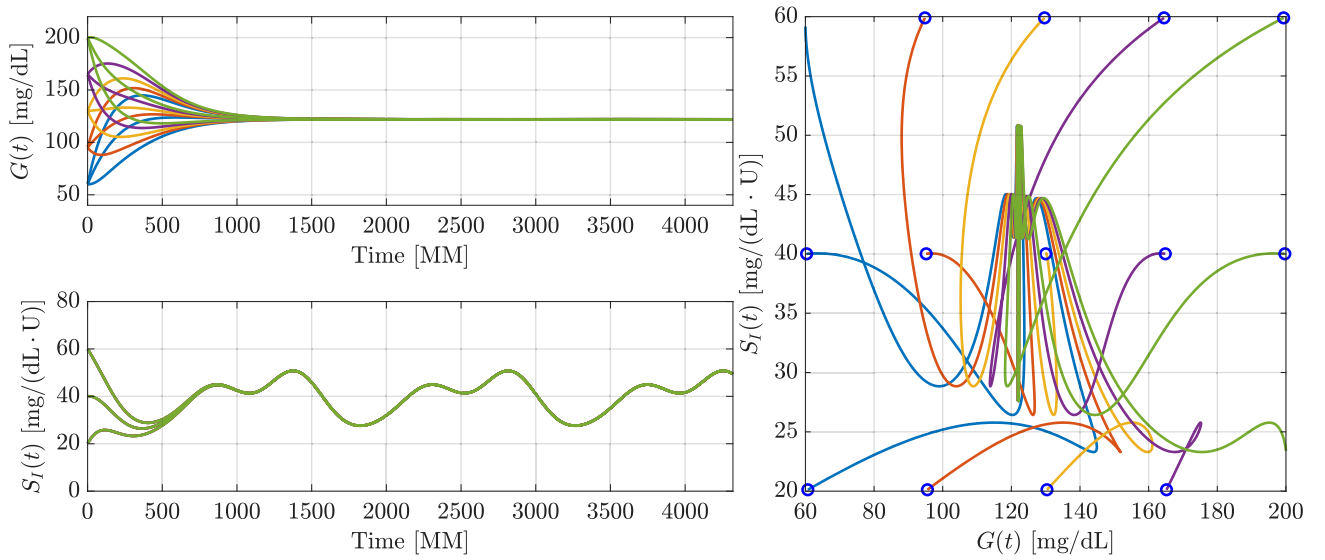


Fig. B.2. Equilibrium under periodic basal insulin injection. Left plots show glycemia (upper) and insulin sensitivity (lower) trajectories. The multiple lines represent free evolutions from different initial conditions; the time-varying basal infusion $u_b(t)$ is designed so that the required insulin effect $Q_{i,b}(t) = (\theta_0 - \theta_1 G_b)/S_{I,b}(t)$, Eq. (11), exactly compensates for the circadian oscillation of $S_{I,b}(t)$, which is a direct algebraic consequence of the model structure. All trajectories converge to the same periodic orbit. The right plot shows the phase portrait of the two states, highlighting a domain of attraction.

Since $G_b^*(t)$ is periodic, $\langle \dot{G}_b^* \rangle = 0$, and from (B.21) it follows that $\langle S_{I,b}^* \rangle = A_{SI}$. Therefore,

$$\theta_1 \langle G_b^* \rangle = \theta_0 - U_b A_{SI}, \quad (\text{B.34})$$

which gives

$$\langle G_b^* \rangle = \frac{\theta_0 - U_b A_{SI}}{\theta_1}. \quad (\text{B.35})$$

Expression (B.35) shows that the mean basal glucose level depends only on the parameters $(\theta_0, \theta_1, A_{SI})$ and on the chosen basal infusion U_b , but not on the circadian modulation amplitudes α_k nor on the time constant θ_5 . In particular, if the basal insulin infusion is chosen as

$$U_b = \frac{\theta_0 - \theta_1 G_{ref}}{A_{SI}}, \quad (\text{B.36})$$

then the mean basal glucose equals the desired reference level G_{ref} , i.e. $\langle G_b^* \rangle = G_{ref}$.

Explicit harmonic decomposition. To obtain a fully explicit expression for $G_b^*(t)$, the harmonic expansion of $S_{I,b}^*(t)$ derived previously is exploited. From (B.21), it follows that

$$S_{I,b}^*(t) = A_{SI} + \sum_{k=1}^3 \hat{A}_k \sin(\omega_k t + \psi_k), \quad (\text{B.37})$$

where, for compactness,

$$\hat{A}_k := A_{SI} \alpha_k \frac{1}{\sqrt{1 + (\omega_k \theta_5)^2}}, \quad \psi_k := \varphi_k - \arctan(\omega_k \theta_5). \quad (\text{B.38})$$

Substituting (B.37) into (B.25) gives

$$\dot{G}_b^*(t) + \theta_1 G_b^*(t) = \theta_0 - U_b A_{SI} - U_b \sum_{k=1}^3 \hat{A}_k \sin(\omega_k t + \psi_k). \quad (\text{B.39})$$

The right-hand side of (B.39) consists of a constant term plus a finite sum of sinusoids. By linearity, the steady-state glucose trajectory is the superposition of the individual responses. The constant term

$$(\theta_0 - U_b A_{SI}) \quad (\text{B.40})$$

yields the mean level $(\theta_0 - U_b A_{SI})/\theta_1$, (B.35). Each sinusoidal term $-U_b \hat{A}_k \sin(\omega_k t + \psi_k)$ produces, by standard first-order frequency response (which can also be verified by the integrating-factor technique used above), a steady-state contribution with attenuation factor

$1/\sqrt{\theta_1^2 + \omega_k^2}$ and phase lag $\phi_k = \arctan(\omega_k/\theta_1)$. Summing over all harmonics, the explicit steady-state basal glucose trajectory is

$$G_b^*(t) = \frac{\theta_0 - U_b A_{SI}}{\theta_1} - \sum_{k=1}^3 U_b \hat{A}_k \frac{1}{\sqrt{\theta_1^2 + \omega_k^2}} \sin(\omega_k t + \psi_k - \phi_k). \quad (\text{B.41})$$

Eq. (B.41) provides an explicit closed-form expression for the periodic basal glucose trajectory. The results are depicted in Fig. B.1, where the free evolutions of G and S_I from different starting points under constant insulin injection U_b are shown. This shows that:

- The average basal glucose level is given by (B.35) and can be tuned via the choice of U_b .
- The circadian modulation of insulin sensitivity induces glucose oscillations at the same harmonics ω_k present in $S_{I,b}^*(t)$.
- Each harmonic is attenuated by the glucose time constant through the factor $1/\sqrt{\theta_1^2 + \omega_k^2}$ and is phase-lagged by $\phi_k = \arctan(\omega_k/\theta_1)$, so that the glucose oscillations are a delayed and smoothed version of the underlying circadian modulation.

B.2. Periodic basal insulin

In this second framework, depicted in Fig. B.2, glucose levels are maintained at their desired basal state (G_b), while insulin sensitivity oscillates due to intrinsic circadian modulation. This is implemented by making basal insulin delivery, $u_b(t)$, a periodic trajectory dependent on $S_{I,b}$ variations.

From the glucose equation with $\dot{G}(t) = 0$ and $Q_g(t) = 0$:

$$\theta_0 - \theta_1 G_b - S_{I,b}(t) Q_{i,b}(t) = 0, \quad (\text{B.42})$$

Therefore, the required basal insulin effect is:

$$Q_{i,b}(t) = \frac{\theta_0 - \theta_1 G_b}{S_{I,b}(t)}, \quad (\text{B.43})$$

For the insulin compartment dynamics at equilibrium:

$$\dot{Q}_{i,b}(t) = -\frac{1}{\theta_3} Q_{i,b}(t) + \frac{1}{\theta_3} Q_{i,sub,b}(t), \quad (\text{B.44})$$

$$\dot{Q}_{i,sub,b}(t) = -\frac{1}{\theta_3} Q_{i,sub,b}(t) + \frac{1}{\theta_3} u_b(t), \quad (\text{B.45})$$

From the first equation:

$$\dot{Q}_{i,b}(t) = \dot{Q}_{i,b}(t) + \theta_3 \dot{Q}_{i,b}(t), \quad (\text{B.46})$$

where:

$$\dot{Q}_{i,b}(t) = -\frac{(\theta_0 - \theta_1 G_b) \dot{S}_{I,b}(t)}{[S_{I,b}(t)]^2}, \quad (\text{B.47})$$

From the second equation, the required basal insulin input is:

$$u_b(t) = \dot{Q}_{i,b}(t) + \theta_3 \dot{Q}_{i,b}(t), \quad (\text{B.48})$$

Substituting and simplifying:

$$u_b(t) = \dot{Q}_{i,b}(t) + 2\theta_3 \dot{Q}_{i,b}(t) + \theta_3^2 \ddot{Q}_{i,b}(t), \quad (\text{B.49})$$

This analytical solution provides the time-varying basal insulin infusion rate $u_b(t)$ that maintains constant glucose levels despite circadian variations in insulin sensitivity. Applied to the model's free evolution, the result depicted in Fig. B.2 is obtained.

Finally, the basal $IOB_b(t)$ trajectory is then given by:

$$IOB_b(t) = \theta_3 (\dot{Q}_{i,b}(t) + \dot{Q}_{i,b}(t)), \quad (\text{B.50})$$

which varies over time to maintain glucose homeostasis, confirming that constant glucose requires time-varying insulin delivery patterns.

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