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# A simulator with realistic and challenging scenarios for virtual T1D patients undergoing CSII and MDI therapy

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ABSTRACT

In silico simulations have become essential for the development of diabetes treatments. However, currently available simulators are not challenging enough and often suffer from limitations in insulin and meal absorption variability, which is unable to realistically reflect the dynamics of people with type 1 diabetes (T1D). Additionally, T1D simulators are mainly designed for the testing of continuous subcutaneous insulin infusion (CSII) therapies. In this work, a simulator is presented that includes a generated virtual patient (VP) cohort and both fast- and long-acting Glargine-100 U/ml (Gla-100), Glargine-300 U/ml (Gla-300), and Degludec-100 U/ml (Deg-100) insulin models. Therefore, in addition to CSII therapies, multiple daily injections (MDI) therapies can also be tested. The Hovorka model and its published parameter probability distributions were used to generate cohorts of VPs that represent a T1D population. Valid patients are filtered through restrictions that guarantee that they are physiologically acceptable. To obtain more realistic scenarios, basal insulin profile patterns from the literature have been used to identify variability in insulin sensitivity. A library of mixed meals identified from real data has also been included. This work presents and validates a methodology for the creation of realistic VP cohorts that include physiological variability and a simulator that includes challenging and realistic scenarios for in silico testing. A cohort of 47 VPs has been generated and in silico simulations of both CSII and MDI therapies were performed in open-loop. The simulation outcome metrics were contrasted with literature results.

## 1. Introduction

Diabetes mellitus is a chronic condition that has become a pandemic affecting 537 million people worldwide [1]. T1D, with a prevalence of approximately 10% of all diabetes cases, is characterized by the self-destruction of the insulin producing beta cells in the pancreas. This leads to a permanent lack of insulin that causes an abnormal glucose homeostasis state of high blood glucose levels, known as hyperglycemia, which eventually leads to chronic complications. Diabetes complications are both microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (coronary artery, peripheral artery and cerebrovascular conditions), as well as other acute complications [2,3]. People with T1D rely on exogenous insulin to lower blood glucose levels back to normoglycemia (70–180 mg/dl), which has been established as a control objective [4]. To this end, either MDIs, CSII, and more recently artificial pancreas (AP) have been prescribed to them.

Although much progress has been made on the subject, many researchers are still working on more effective methods for its diagnosis and treatment. Mathematical models that contain different sets of parameters and nonlinear equations to describe the behavior of insulin and glucose dynamics in patients with T1D [5–8], are a widely used tool for creating, testing, and optimizing diagnostic and treatment methodologies. Several studies have shown that simulators containing the Hovorka [8] and Dalla Man models [7,9–11] are useful in developing MDI therapies and closed-loop control systems, also known as the AP [12–18].

The Hovorka model [8] is a compartmental model of glucose kinetics and insulin action that represents the input–output relationship between subcutaneous insulin infusion (as the input) and intravenous glucose concentration (as the output) [19]. The Dalla Man model [7] is also a compartmental model, however, this model links together

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glucose and insulin plasma concentrations with glucose fluxes (endogenous glucose production, glucose rate of appearance, glucose utilization, renal extraction) and insulin fluxes (rate of insulin appearance from the subcutaneous tissue and insulin degradation). The latest version of the Dalla Man model [20] also incorporates glucagon kinetics, secretion, and action models.

Simulation tools based and defined by mathematical models are a fundamental instrument to the investigation of diabetes treatments, as they provide a safe and economical platform to validate treatment strategies and control algorithms via in silico tests. A number of simulation environments exist and are available in the literature [9,12,21–23]. The basic characteristics that define diabetes simulators are its ability to: (1) create varied scenarios in which food intake can be defined by the time of ingestion and the amount of carbohydrates (CHO) consumed, (2) simulate physical exercise using a model that can adjust exercise schedules, frequency, and intensity, (3) simulate blood glucose control strategies that manipulate insulin and/or glucagon or suggest rescue CHO, and (4) identify the dynamic behavior of glucose considering a variety of variables and provide a series of results that allow the performance of the strategy used to be evaluated.

All these simulators use VP cohorts to evaluate open and closed-loop glycemic control strategies. For this reason, generating a physiologically adequate VP is key to effective in silico testing. Simulators can incorporate a simple set of parameters that represent an 'average patient' or multiple sets of parameters that represent a VP population [24].

The main limitations of these simulation tools are: (1) physiological variability of insulin absorption and meals that do not reflect real patients, (2) scenarios that do not replicate real-life characteristics which makes the current scenarios easy to control, and (3) simulators that are not designed for trials with MDI therapy.

In [25] it is stated that most of the studies in the literature have investigated meals or beverages containing glucose and, for methodological reasons, very few studies have included other simple sugars or complex CHO. They conclude that large evening meals containing complex CHO provide different challenges to the management of T1D, depending on the composition of the meals. A meal with a high glycemic load results in a pronounced, but shorter, absorption pattern, whereas a meal with a low glycemic load results in sustained and prolonged absorption and a higher overall glucose appearance. Although published simulators may incorporate some degree of variability in the rate of glucose appearance profiles, they are not able to simulate the variety of mixed meals found in real-life conditions due to limitations in the data they were built upon [26].

The consequence of these limitations is that most of today's simulators result in scenarios that provide blood glucose dynamics that are very easy to control. Reported results in the literature using such simulators show that blood glucose control strategies are able to obtain 90% or higher time in the euglycemic range, and times in hyperglycemia or hypoglycemia are close or equal to zero [13,14,27–29] and these results are obtained regardless of the scenario used. However, it is later demonstrated that this behavior is not replicated in clinical trials [30–33].

During the past 15 years, there have been changes and advancements in long-acting insulin formulations. Models describing the pharmacokinetics of long-acting insulin [34–36] model the effect of the injected basal insulin dose. In [35], an absorption model of insulin glargine is proposed and in [37], this model is incorporated into the UVA/Padova simulator for simulations with MDI therapy. In [18], the incorporation of the insulin degludec model into the UVA/Padova simulator is described.

The objective of this work is to minimize the limitations of the simulators present in the literature, bringing in silico simulations closer to real-life conditions and creating a greater challenge for the design of controllers aimed at blood glucose control in patients with T1D. For this, a methodology to generate VP cohorts that include physiological variations and realistic scenarios incorporating basal insulin patterns identified in the literature and adding a library of challenging mixed meals is presented. Additionally, the incorporation of insulin glargine and degludec absorption subsystems into the Hovorka model to evaluate different MDI therapies is validated.

## 2. Methods

### 2.1. Generation and validation of VP

The generation of VPs for the Hovorka model is based on public data contained in a series of publications [21,38,39]. From these publications, it is known that $V_G$, $R_{th}$, $R_{CL}$, $V_I$, $k_a$, $k_e$, $BIO$, $t_{max}$, $k_{aint}$ have univariate distributions, whereas the two groups of parameters $\{EGP_0, F_{01}, S_{ID}, S_{IE}, S_{IT}\}$ and $\{k_{12}, k_{a1}, k_{a2}, k_{a3}\}$ have multivariate distributions, in this case covariance matrices were calculated using the patient data presented in [39]. The probability distribution of the parameters of the Hovorka model and covariance matrices are included in Appendix B Supplementary data 1.

The first step for the creation of VPs includes randomly generating multiple sets of parameters using the Matlab commands *mvnrnd* for multivariate parameters (uses the covariance matrix), and *normrnd* or *lognrnd* (depending on the type of distribution) for univariate parameters.

Next, if a randomly sampled VP does not behave in a physiologically acceptable manner, it is discarded from the final cohort. This is determined by the following conditions: (1) all sampled parameters for each VP have to be included within the minimum and maximum allowed values [39]; (2) a glucose–insulin model must reflect an insulin-independent consumption of glucose that is always lower than the endogenous glucose production, in the Hovorka model, this is fulfilled by verifying the following relationship: $EGP_0 > F_{01}$; (3) VPs, in the absence of insulin, must have glucose levels at steady state that exceed 300 mg/dl [12]; (4) VPs without external disturbances nor variability, e.g. meals or exercise, must have an input–output relation such that for some input basal insulin infusion, the resulting output model basal glucose stays in the 90–160 mg/dl band; and (5) variations of 0.01 U/h in the basal insulin infusion rate cannot cause a change in basal glucose greater than 20 mg/dl.

The VPs that meet all the established restrictions are each assigned a 24 h circadian pattern of insulin sensitivity, a set of adjusted carbohydrate ratios (CR), correction factors (CF) and a basal insulin pattern. The basal insulin for CSII therapy is adjusted in U/h, and is calculated depending on the desired basal glucose and for MDI therapy is adjusted in mU and is dependent upon the time of day it will be administered. The CR (g/U) is generally known in clinical practice as "Insulin to Carbohydrate Ratio" and represents how many grams of CHO are covered by 1 unit of insulin, three values of CR are calculated for three different time periods, 6:00 h–12:00 h, 12:00 h–17:00 h, and 18:00 h–24:00 h, different meals from the meal library are randomly selected and simulated for each (breakfast, lunch, dinner), then we iteratively adjust the CR such that the resulting infused bolus insulin ensures minimization of hyperglycemia, trying not to cause postprandial hypoglycemia. The CF (mg/dl/U), which is defined as the amount of blood glucose that falls with 1 unit of insulin, is calculated following the test protocols detailed in [40] and consists of choosing a CF that brings glucose within ±30 mg/dl of the target value in 5 h without falling below this limit.

### 2.2. Mixed meal library

The Micelab group has a mixed meal library, described in [41], that has been incorporated into the current T1D simulator to create more realistic scenarios. This library, see Appendix A Supplementary data 1, can be employed to test and optimize the design of closed-loop insulin delivery systems, insulin bolus calculators, hypoglycemia prediction algorithms, and fault detection and supervision systems for

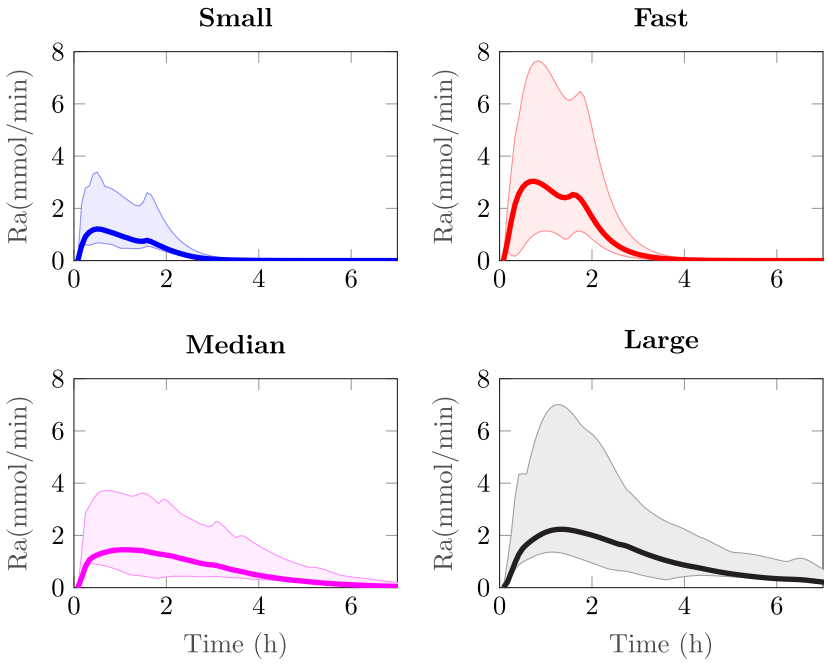


**Fig. 1.** Classification of meals in the library.

an AP. This library contains $Ra$ profiles from a total of 54 different meal compositions. The mixed meals are defined by their composition (fat, protein, fiber, and energy), amount of CHO, and classified according to the Kolmogorov–Smirnov distance into large (10), medium (26), small (12), and fast (6). Fig. 1 shows the mean, maximum, and minimum of the 4 classified groups. Each meal has a time profile of 84 values taken with a sampling time of 5 min, which represents the glucose rate of appearance of 7 h after the moment of the meal. For its implementation, the term $U_g(t)$ from Eq. (A.1) of the glucose subsystem (Appendix A.1) is replaced by the parameter $Ra(t)$ according to the time profile corresponding to each meal.

### 2.3. Circadian variability of insulin sensitivity

Insulin sensitivity variability is a phenomenon identified as one of the main challenges in the treatment of diabetes. In 2005 [42] and 2007 [43], two clinical studies presented 24-hour basal insulin patterns identified with data from insulin pump patients. In the first study [42], an analysis is made of the characteristics of basal insulin requirements by age and gender in patients with T1D. In the second study [43], the same analysis was performed, but only for children and adolescents. In this work, we include hourly insulin sensitivity variability from randomly sampled basal insulin patterns according to the results presented in Table 1 in [42], for patients between 21–60 years of age. The procedure for generating multiple basal insulin profiles is detailed in Appendix B.1.

Fig. 2 shows the average of 100 generated basal insulin patterns, and it can be noted that the curve has similar behavior to that shown in [42]. Every single basal insulin pattern is next used to accordingly generate a unique insulin sensitivity pattern that will be given to a VP.

Insulin sensitivity is introduced into the model, in the equations in Appendix A.2, as an hourly time-varying multiplicative factor of the original sensitivity parameters of the Hovorka model ($S_{ID}$ $S_{IE}$, $S_{IT}$), see Eq. (1).

$$\begin{aligned} S_{ID}(t) &= \alpha(t) S_{ID} \\ S_{IE}(t) &= \alpha(t) S_{IE} \\ S_{IT}(t) &= \alpha(t) S_{IT} \end{aligned} \tag{1}$$

where $\alpha(t)$ is a picewise constant function with 24 steps representing the factor for each hour in a day that affects the model's insulin sensitivity. To obtain $\alpha(t)$, the steady-state of a VP is solved using a generated basal profile u, this procedure is detailed in Appendix B.2.

### 2.4. Long-acting insulin glargine and degludec

The insulin glargine and degludec, both second-generation insulin analogs, aim to achieve stable glucose profiles with fewer peaks, while minimizing the amount of nocturnal hypoglycemia in patients with T1D. The UVA/Padova research group has developed and clinically validated a compartmental model that describes the subcutaneous absorption of insulin glargine and degludec (Appendices A.5–A.7) [18, 35].

#### 2.4.1. Glargine model

In [35], pharmacokinetic (PK) data from 3 different clinical studies have been used to model the subcutaneous (sc) absorption of insulin glargine. In each study, euglycemic clamp protocols were conducted in patients with T1D and a validated radio immunoassay. The sc absorption model of both, Gla-100 and Gla-300 is a two-compartment structure proposed in [37] and incorporated in the UVA/Padova Simulator and validated for the Dalla Man model [37].

#### 2.4.2. Degludec model

Second-generation insulin Deg-100 provides new basal insulin therapies for the treatment of T1D. In [18], a three-compartment PK model is presented describing subcutaneous absorption of Deg-100 based on clinical data and incorporated into the UVA/Padova simulator.

Fig. 3 shows the incorporation of both models into the Hovorka model. In both analogs, active plasma insulin ($I_t$) is considered as the sum of the long-acting insulin concentration ($I_{l_a}$) and the fast-acting insulin concentration ($I_{f_a}$) (Eq. (2)). Eq. (3)–(6), shows the modifications of the insulin absorption subsystem (Appendix A.3) and the insulin action subsystem (Appendix A.2) of the Hovorka model [8]. The parameters of both long-acting models are the same as reported in [18,35] and do not vary between VPs, except for the $V_I$ parameter, which is identified individually for each VP.

$$I_t(t) = I_{f_a}(t) + I_{l_a}(t) \tag{2}$$

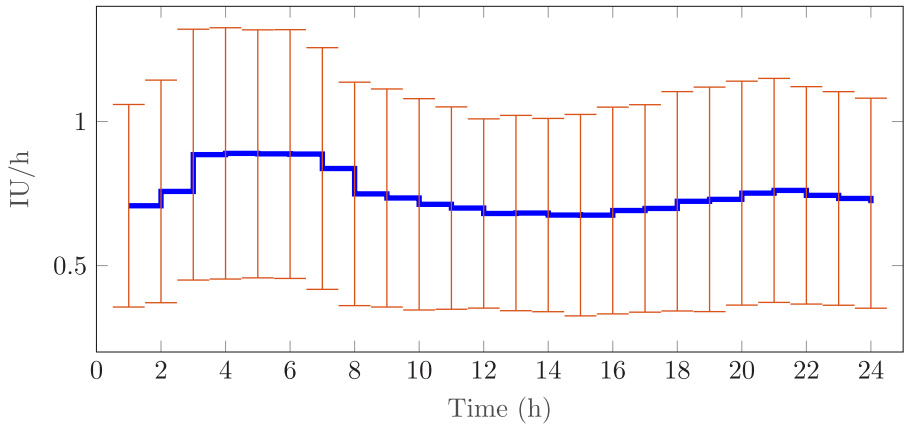


**Fig. 2.** Mean and SD of the generated basal insulin profiles.

$$\frac{dI_{f_a}(t)}{dt} = \frac{S_2(t)}{T_{maxI} * V_I} - k_e I_{f_a}(t) \tag{3}$$

$$\frac{dx_1(t)}{dt} = -k_{a1}x_1(t) + k_{a1}S_{IT}I_t(t) \tag{4}$$

$$\frac{dx_2(t)}{dt} = -k_{a2}x_2(t) + k_{a2}S_{ID}I_t(t) \tag{5}$$

$$\frac{dx_3(t)}{dt} = -k_{a3}x_3(t) + k_{a3}S_{IE}I_t(t) \tag{6}$$

### 2.5. Simulation protocol

The proposed simulator was implemented in Matlab R2021a and simulations were performed using an Intel(R) Core(TM) i7-4770 CPU @ 3.40 GHz processor with 16 GB RAM. The initial cohort size was 100 VPs for the Hovorka model, of which 47 VPs met the requirements set and were taken as valid. The Supplementary data 1. Appendix B presents a table with all parameters of the Hovorka model of the generated cohort.

For the generated cohort CSII therapy, a vector is created from 0.02 to 4 with a variation of 0.01 that represents the input of basal insulin (U/h) to the model and the one that guarantees glucose at a steady-state (basal glucose) around 160 mg/dl is selected. For MDI therapy, basal insulin was adjusted based on two defined injection times at 9:00 h or 20:00 h. The insulin bolus, given at the time of the meal, is calculated with Eq. (7) presented in [44] where $CR$ (g/U), $CF$ (mg/dl/U) and $G_{Target}$ (mg/dl) are specific parameters individually adjusted for each VP. The $IOB$, which is defined as the amount of insulin delivered that is still active, was modeled as proposed in [45].

$$Bolus = \frac{CHO}{CR} + \frac{G - G_{Target}}{CF} - IOB \tag{7}$$

The considered scenario consists of a 60 day simulation protocol with meals of 40, 85, and 75 grams of CHO were given at 7:30 h, 13:00 h, and 19:00 h, respectively, with a variability of 30 min in the scheduled intake times and 10% in the CHO content. To simulate these meals, the amount of CHO defined in the initialization of the scenario was used to select a meal with similar characteristics from the mixed meal library. To model continuous glucose monitoring (CGM), we follow the same procedure as in [11] where starting from the calibration error of the sensor they generate measurement noise additive to the simulated blood glucose concentration.

A low frequency term of intra-patient variability is also included by using a sinusoidal pattern, on some parameters of the Hovorka model ($EGP_0$, $F_{01}$, $k_{12}$, $t_{maxI}$, $k_e$) and on the long-acting insulin glargine and degludec models ($m_4$, $k_a$). Each parameter affected by intra-patient variability becomes a time-varying parameter, and a specific $\beta(t)$ function is generated individually. For example, $EGP_0$ becomes time varying by applying $EGP_0(t) = EGP_0\beta(t)$. The procedures to generate the $\beta(t)$ signal is detailed in Appendix C.

## 3. Results

Using the previously described simulator, generated VP cohort and scenario, we proceeded to test how adding the meal library and circadian variability affects the simulations, and compared CSII and MDI results with real reported outcomes. In silico simulations of both therapies were always performed in open-loop therapy.

### 3.1. Simulator complexity analysis

Table 1 shows the effects of combining the mixed meal library and circadian variability on insulin sensitivity versus the base Hovorka model. The outcomes for the base Hovorka model resulted in 87.6% of the time in range (TIR) (70–180 mg/dl) and low values of hypoglycemia (< 70 mg/dl) and hyperglycemia (> 180 mg/dl). The same table shows how this behavior is affected by incorporating both factors separately; it is important to note that these cause a decrease in TIR metrics and a notable increase in hyperglycemia values. This behavior is shown in Fig. 4. The results suggest that the inclusion of the mixed meal library and circadian variability resulted in more physiologically realistic outcomes.

### 3.2. Outcomes for CSII and MDI therapies

To assess the performance of both therapies, Table 2, 3, 4, and 5 show the standardized CGM metrics [46] (these values are reported as a percentage of time in the specified range), for CSII and MDI therapies. Some of the clinical trials used in this work for comparison purposes do not report the metrics as suggested in [46], that is, less severe hypoglycemia (70–54 mg/dl) and severe (< 54 mg/dl) and less severe hyperglycemia (180–250 mg/dl) and severe (> 250 mg/dl). They are presented as a single category, including less severe and severe. Therefore, the clinical outcomes presented in Tables 2, 3, and 4 span to different ranges as compared to the 'in silico' outcomes. The results are presented as the median (25th, 75th percentile). Fig. 5 shows the glucose outcomes per day for both therapies. We can verify the physiological plausibility of the glucose trajectories in the simulations. In addition, Supplementary data 2 shows the AGP report of two representative patients with CSII and MDI therapy.

Table 2 shows the CSII therapy results for the nominal Hovorka model and with the inclusion of the meal library and circadian variability. Comparing the results with the clinical trial it can be seen that mixed meals library and circadian variability result in more physiologically feasible VPs. Comparing the results obtained with the clinical

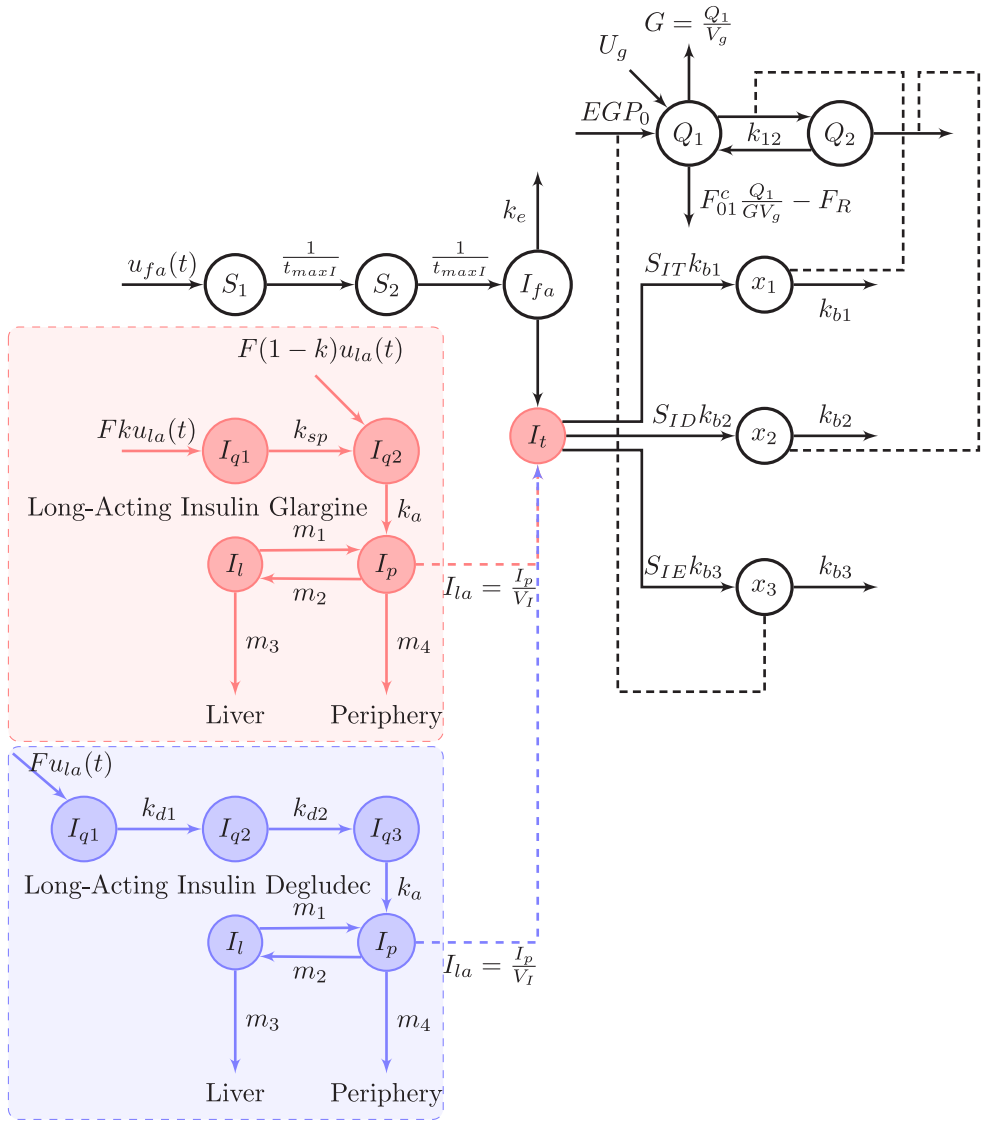


**Fig. 3.** Glucose–insulin compartment model with the addition of the long-acting insulin glargine (red) and degludec model (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

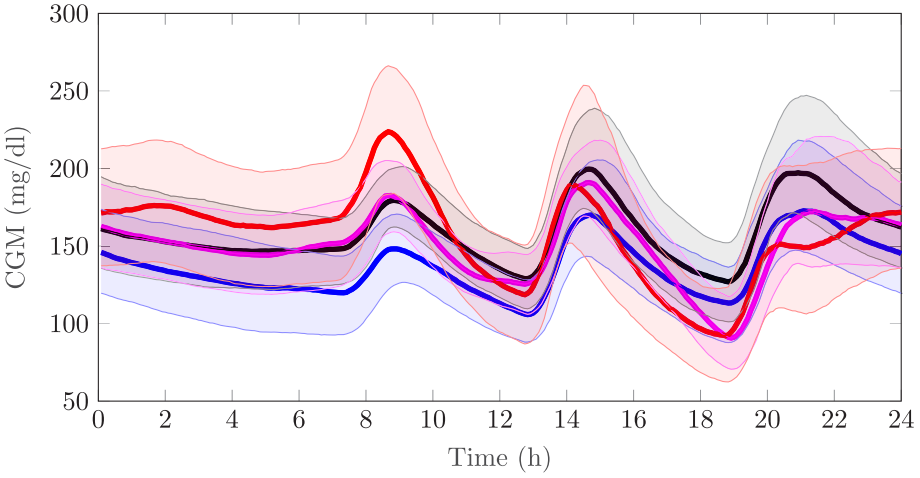


**Fig. 4.** Daily aggregated CGM of the cohort of Table 1 (median + IQR). The blue curve shows the Hovorka model, the black curve the Hovorka model using the meal library, the magenta curve the Hovorka model including circadian variability, and the red curve the Hovorka model with the meal library and circadian variability. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
Effects caused by the addition of the mixed meal library and circadian variability of insulin sensitivity in the outcomes for CSII.

| Performance indicator | Nominal Hovorka model[a] | Hovorka model with mixed-meal library[a] | Hovorka model with circadian variability[a] |
|---|---|---|---|
| *CGM* (mg/dl) | 136.4 (120.1–150.8) | 158.1 (143.9–180.1) | 153.3 (140–160) |
| %CV | 22.9 (16.7–31) | 20.6 (15–30) | 23.9 (18.1–30.1) |
| % time CGM > 250 mg/dl | 0 (0–0.6) | 0 (0–8.7) | 0.1 (0–4.7) |
| % time CGM 180–250 mg/dl | 5.7 (2–25) | 19.6 (9.6–35.1) | 18.6 (9.3–28.4) |
| % time CGM 70–180 mg/dl | 87.6 (63.2–96.8) | 77.4 (47.1–87.4) | 77.5 (60.3–89.8) |
| % time CGM 54–70 mg/dl | 0.5 (0–3.2) | 0 (0–0.5) | 0.1 (0–2.7) |
| % time CGM < 54 mg/dl | 0 (0–0.1) | 0 (0–0) | 0 (0–1) |

[a]Values are reported as median, interquartile range (25th, 75th percentile).

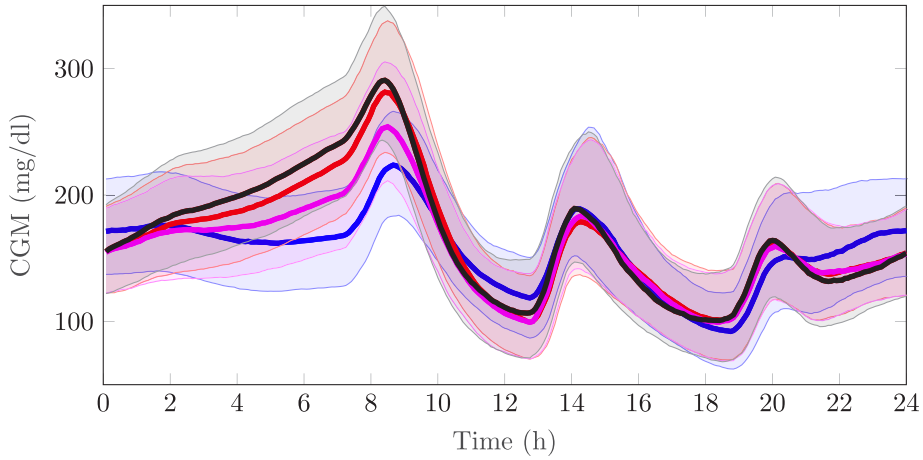


**Fig. 5.** Daily aggregated CGM of the generated cohort (median + IQR) for different therapies: CSII (blue), Gla-100 9 h (black), Gla-300 9 h (magenta) and Degludec 9 h (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 2**
Outcomes for CSII therapy and clinical trial.

| Performance indicator | Nominal Hovorka model[a] | Hovorka model with variability and mixed meals[a] | Clinical trial [30][b] |
|---|---|---|---|
| Median *CGM* (mg/dl) | 136.4 (120.1–150.8) | 159.9 (147.1–172.1) | 174 (18) |
| %CV | 22.9 (16.7–31) | 35.4 (32.5–41.7) | 40 (4) |
| % time CGM > 250<br>% time CGM 180–250 mg/dl | 0 (0–0.6)<br>5.7 (2–25) | 5.8 (3–11.9)<br>26 (19.5–30.4) | 42 (10) |
| % time CGM 70–180 mg/dl | 87.6 (63.2–96.8) | 62 (47.5–68.9) | 54 (9) |
| % time CGM 54–70<br>% time CGM < 54 mg/dl | 0.5 (0–3.2)<br>0 (0–0.1) | 2.9 (2.2–4.2)<br>1.6 (0.7–3) | 3.9 (1.7–5.3) |
| Insulin | | | |
| Basal (U/day) | 23 (16.9–32.5) | 22.1 (15.9–31.6) | – |
| Basal (U/kg) | 0.33 (0.23–0.44) | 0.32 (0.22–0.42) | 0.32 (0.10) |
| Bolus (U/day) | 18.7 (14.4–26.2) | 18.7 (14.4–26.2) | – |
| Bolus (U/kg) | 0.29 (0.18–0.37) | 0.29 (0.18–0.37) | 0.39 (0.13) |
| Total (U/day) | 45.2 (32.3–55.9) | 44.2 (31.3–55) | – |
| Total (U/kg) | 0.58 (0.47–0.81) | 0.57 (0.46–0.79) | 0.71 (0.19) |

[a]Values are reported as median, interquartile range (25th, 75th percentile).
[b]Values are reported as mean, SD.

targets for CGM presented in [4], it can be noted that the TIR has a median of 62% which is less than the 70% that represents the target value. In the case of time in hypoglycemia and hyperglycemia the target value is 5% and 25%, respectively and the results obtained have a median of 4.5% and 31.8%, respectively. The glycemic variability has a median of 35.4% and the target value is $\leqslant$ 33%.

Tables 3 and 4 present the results for MDI therapy with insulin glargine. Comparing the results with the clinical trial it is also confirmed for this therapy that the inclusion of mixed meals and circadian variability causes a more realistic behavior in VPs. The in silico TIR for Gla-100 and Gla-300 was 54% vs. 57.1% in the morning and 65% vs. 60.3% at night, very similar to the values obtained of 53.6% and 56.2% respectively, in figure 1 of [47]. The hypoglycemic for Gla-100 6.2% and 5.4% and for Gla-300 6.1% and 6.8%. The glycemic variability for Gla-100 was greater than for Gla-300 in the morning, which coincides with the characteristics reported in clinical trials on these parameters for both analogs [37,47].

Table 5 shows the results obtained from the incorporation of insulin degludec into the Hovorka model. It was first simulated with a fixed dose of 0.4 U/kg or 0.6 U/kg as reported in [49–51] the adequacy of the 0.4 U/kg dose was confirmed as it was close to the normal daily dose of basal insulin observed. A lower glycemic variability can be observed

**Table 3**
Outcomes for MDI therapy with insulin Gla-100, in silico and clinical trial [47,48].

| Performance indicator | Injection time | Nominal Hovorka model[a] | Hovorka model with variability and mixed meals[a] | Clinical trial Gla-100[b] |
|---|---|---|---|---|
| *CGM* (mg/dl) | 9 h<br>20 h | 137.5 (112.6–152.7)<br>117.4 (106.3–132.7) | 166.8 (154.5–185.5)<br>151.3 (136.2–165.3) | 152.1 (32.8)[d]<br>169.3[c] |
| %CV | 9 h<br>20 h | 25.7 (20–37.5)<br>29.9 (22.8–40) | 40.4 (36–47)<br>38.6 (32.9–45.3) | –<br>– |
| % time CGM > 250 mg/dl | 9 h<br>20 h | 0.1 (0–2.4)<br>0 (0–1.3) | 12.9 (5.7–18.1)<br>5.5 (2.9–12.5) | 16.1[c] |
| % time CGM 180–250 mg/dl | 9 h<br>20 h | 9.6 (3.1–22.2)<br>6.9 (2–16.4) | 24.4 (18.7–30.3)<br>19.7 (15.4–23.9) | 22.8[c] |
| % time CGM 70–180 mg/dl | 9 h<br>20 h | 78.8 (57.2–87.5)<br>73.4 (61.1–89.8) | 54 (46.8–65.1)<br>65 (52.8–73.9) | 53.6[c] |
| % time CGM 54–69 mg/dl<br>20 h<br>% time CGM<br>9h<br>< 54 mg/dl<br>20 h | | 2.3 (0–9)<br>5.1 (0.7–15.2)<br>0.2 (0–4)<br>0.3 (0–3.7) | 3.7 (2.3–4.6)<br>3.8 (2.4–5.8)<br>2.5 (1.2–4)<br>1.6 (0.8–3.6) | 8.2[c] |
| Insulin | | | | |
| Basal (U/day) | 9 h<br>20 h | 39.9 (29.1–52.6)<br>37.5 (28.8–50.9) | 30.7 (22.4–40.5)<br>28.9 (22.1–39.2) | –<br>– |
| Basal (U/kg) | 9 h<br>20 h | 0.55 (0.41–0.7)<br>0.53 (0.39–0.66) | 0.42 (0.32–0.54)<br>0.41 (0.3–0.51) | 0.45 (0.19)[d]<br>0.36 (0.16)[d] |
| Bolus (U/day) | 9 h<br>20 h | 24.3 (17.5–34.9)<br>24.9 (19.3–36.4) | 24.3 (17.5–34.9)<br>24.9 (19.3–36.4) | –<br>– |
| Total (U/day) | 9 h<br>20 h | 66.2 (47–84.1)<br>66.4 (48.2–83.9) | 59 (40.5–71.8)<br>58.7 (42–73.3) | –<br>– |
| Total (U/kg) | 9 h<br>20 h | 0.91 (0.71–1.11)<br>0.95 (0.72–1.12) | 0.77 (0.61–0.94)<br>0.81 (0.6–1) | 0.73 (0.27)[d]<br>0.63 (0.18)[c] |

[a]Values are reported as median, interquartile range (25th, 75th percentile).
[b]Values are reported as mean, SD.
[c][47].
[d][48].

**Table 4**
Outcomes for MDI therapy with insulin Gla-300, in silico and clinical trial [47,48].

| Performance indicator | Injection time | Nominal Hovorka model[a] | Hovorka model with variability and mixed meals[a] | Clinical trial Gla-300[b] |
|---|---|---|---|---|
| *CGM* (mg/dl) | 9 h<br>20 h | 128.8 (109–139.5)<br>123.2 (106.6–139.5) | 161.7 (147.9–176)<br>154.2 (141.1–173.2) | 158 (38)[d]<br>165.0[c] |
| %CV | 9 h<br>20 h | 26.1 (19–34.1)<br>26.8 (20.4–37.5) | 37.9 (33.5–46.8)<br>39.4 (35.2–47.5) | –<br>– |
| % time CGM > 250 mg/dl | 9 h<br>20 h | 0 (0–0.3)<br>0 (0–0.5) | 7.8 (4–13.2)<br>7.5 (3.6–13.2) | 13.6[c] |
| % time CGM 180–250 mg/dl | 9 h<br>20 h | 6.2 (1–15.4)<br>5.9 (0.8–18.2) | 23.3 (18–30.1)<br>22.4 (17.3–27) | 24[c] |
| % time CGM 70–180 mg/dl | 9 h<br>20 h | 82.9 (62.1–93.7)<br>78.2 (54.3–92.8) | 57.1 (49.1–64.4)<br>60.3 (47.7–69) | 56.2[c] |
| % time CGM 54–69 mg/dl<br>20 h<br>% time CGM<br>9 h<br>< 54 mg/dl<br>20 h | | 3.7 (0.1–9.3)<br>3 (0–7.4)<br>0.2 (0–2.8)<br>0.1 (0–5.5) | 3.7 (2.4–5)<br>4.1 (2.3–5.4)<br>2.4 (1.1–5.1)<br>2.7 (0.8–4.7) | 7.3[c] |
| Insulin | | | | |
| Basal (U/day) | 9 h<br>20 h | 42.4 (31.7–54.4)<br>34.6 (26.2–48.1) | 32.6 (24.4–41.8)<br>26.6 (20.2–37) | –<br>– |
| Basal (U/kg) | 9 h<br>20 h | 0.59 (0.43–0.72)<br>0.49 (0.36–0.64) | 0.45 (0.33–0.56)<br>0.37 (0.27–0.49) | 0.49 (0.22)[d]<br>0.45 (0.21)[d] |
| Bolus (U/day) | 9 h<br>20 h | 23.8 (17–32.4)<br>27 (19.3–39.7) | 23.8 (17–32.4)<br>27 (19.3–39.7) | –<br>– |
| Total (U/day) | 9 h<br>20 h | 71 (48.8–85.9)<br>67.8 (46.2–85.3) | 62.2 (41.5–71.5)<br>57.2 (40.3–73.2) | –<br>– |
| Total (U/kg) | 9 h<br>20 h | 0.96 (0.75–1.13)<br>0.92 (0.72–1.14) | 0.8 (0.63–0.96)<br>0.78 (0.61–0.98) | 0.81 (0.32)<br>0.67 (0.23)[c] |

[a]Values are reported as median, interquartile range (25th, 75th percentile).
[b]Values are reported as mean, SD.
[c][47] .
[d][48].

**Table 5**
Outcomes for MDI therapy with Deg-100.

| Performance indicator | Injection time | In silico-Basal insulin of 0.4 U/kg[a] | In silico- Basal insulin of 0.6 U/kg[a] | Individually adjusted basal insulin[a] |
|---|---|---|---|---|
| *CGM* (mg/dl) | 9 h | 170.1 (151.4–187.9) | 158.4 (142.7–169.2) | 166.3 (153.6–198.1) |
| | 20 h | 165.8 (147.8–191.1) | 150.3 (141–171.6) | 171.4 (153–191.5) |
| %CV | 9 h | 45 (34.5–49.2) | 39.8 (35.9–45.2) | 41.2 (35.9–47.5) |
| | 20 h | 38.1 (33.2–45.2) | 36.2 (32.9–41.7) | 37.8 (34.3–42) |
| % time CGM > 250 mg/dl | 9 h | 15.4 (8.7–21.8) | 8.8 (3.5–13.4) | 13.4 (7.2–26.6) |
| | 20 h | 12.9 (5.7–19.8) | 5.4 (2–10.2) | 11.2 (6.4–26.7) |
| % time CGM 180–250 mg/dl | 9 h | 24.8 (19.5–28.2) | 23.5 (17.3–30.4) | 25.2 (19.3–29.1) |
| | 20 h | 26.6 (19–32.3) | 20.8 (17.4–27.4) | 30.7 (23–35) |
| % time CGM 70–180 mg/dl | 9 h | 48.4 (41.4–56.1) | 56.4 (46.1–67.4) | 52.3 (39.6–61.6) |
| | 20 h | 49.8 (41.4–65.1) | 61.8 (49.4–69.5) | 45.8 (38.2–54.4) |
| % time CGM 54–69 mg/dl | 9 h | 4 (2–5.9) | 4.1 (3.1–5.5) | 3.5 (2.2–5) |
| | 20 h | 3.1 (1.3–5.4) | 4 (2.1–5.5) | 3.4 (1.9–4.7) |
| % time CGM < 54 mg/dl | 9 h | 2.9 (1.1–6.9) | 3.7 (1.8–5.1) | 2.4 (0.8–4.9) |
| | 20 h | 1.5 (0.4–4.3) | 1.9 (1–4.2) | 2.6 (0.7–4.6) |
| Insulin | | | | |
| Basal (U/kg) | 9 h | 0.4 (0.4–0.4) | 0.6 (0.6–0.6) | 0.39 (0.31–0.55) |
| | 20 h | 0.4 (0.4–0.4) | 0.6 (0.6–0.6) | 0.47 (0.35–0.6) |
| Bolus (U/kg) | 9 h | 0.4 (0.27–0.62) | 0.34 (0.2–0.51) | 0.38 (0.28–0.6) |
| | 20 h | 0.41 (0.28–0.62) | 0.33 (0.21–0.53) | 0.36 (0.26–0.53) |
| Total (U/kg) | 9 h | 0.8 (0.67–1.02) | 0.94 (0.8–1.11) | 0.85 (0.64–1.06) |
| | 20 h | 0.81 (0.68–1.02) | 0.93 (0.81–1.13) | 0.87 (0.68–1.06) |

[a]Values are reported as median, interquartile range (25th, 75th percentile).

in the nocturnal injection, 38.1 (33.2–45.2)% and 36.2 (32.9–41.7)% for 0.4 U/kg and 0.6 U/kg, respectively. In addition, a basal insulin adjustment was made and 0.39 (0.31–0.55) U/kg and 0.47 (0.35–0.6) U/kg were obtained at 9:00 h and 20:00 h, respectively, which is similar to that reported in the literature. Mean glucose, TIR, or insulin requirements are presented in [52–55]. Particularly in [52], patients who received either insulin glargine or insulin detemir twice daily were instead given insulin degludec. The median results obtained were 166.3 (153.6–198.1) mg/dl vs. 171.4 (153–191.5) mg/dl for 9:00 h vs. 20:00 h in silico and 168.6 (±23.9) mg/dl in vivo [52]. For a basal insulin of 0.39 (0.31–0.55) U/kg vs. 0.47 (0.35–0.6) U/kg in silico and 0.4 (±0.2) U/kg in vivo. The percentage of time in the range 70–180 mg/dl obtained was 52.3 (39.6–61.6)% vs. 45.8 (38.2–54.4)% in silico and 57.5 (±13.3)% in vivo (Table 3 of [52]). There were also similarities in glycemic variability of 41.2 (35.9–47.5)% vs. 37.8 (34.3–42)% in silico and 35.9 (±6.4)% in vivo (See Table 5).

## 4. Discussion

Treating diabetes remains a challenge today and although insulin pumps and CSII are gaining ground, MDI therapy remains the most popular treatment for T1D with slow-acting insulin formulations used to satisfy insulin daily needs [36,56]. Simulators are an indispensable tool to test different treatments of CSII and MDI and therefore, more challenging scenarios are required.

This paper presents a methodology to generate a physiologically valid VP cohort. The simulation tools referenced in this paper have a CHO absorption model to represent the action of meals and a mixed meal library that allows the simulation of a variety of realistic meals, which represents a greater challenge when testing control strategies. Regarding the variability of insulin sensitivity, it is generally represented with a sinusoidal function of the parameters that influence this phenomenon. In this paper, we add circadian patterns of insulin sensitivity identified through basal insulin patterns reported in clinical trials. The addition of the mixed meal library and circadian variability results in outcomes that more accurately reflect real-life conditions. This is shown in Tables 1, 2, 3, and 4 where it can be seen that these phenomena make the VPs more realistic compared to the nominal Hovorka model. Another advantageous feature of this work is that it allows the simulation of both CSII and MDI therapies within a single simulation tool.

To validate the results obtained with CSII therapy, they were compared with trials reported in the literature. In [30], the authors conducted a 12-week study with patients of both genders and of average age of 21 years. The study outcomes report a mean glucose of 174 mg/dl, slightly higher when compared to the median of 154.3 mg/dl from our in silico simulation. However, the insulin requirement obtained in both cases is noticeably similar, 0.32 U/kg vs. 0.33 U/kg reported in [57]. Glucose control in [30] was slightly better for VPs, which is reflected in the differences of 54% vs. 62% in normoglycemia, 3.9% vs. 4.5% in hypoglycemia and, 42% vs. 31.8% in hyperglycemia. This may be caused by the fact that patients were free to eat any food and do any physical activity at any time in the clinical trial unlike our simulation protocol.

The incorporation of the insulin glargine and degludec into the Hovorka model allows for the simulation of MDI therapies. The results were validated by comparing them to those reported in clinical trials, [31,32,47,48] for glargine and [49–55,58–61] for degludec. The behavior of the plasma insulin concentration (Figs. 6 and 7) was similar to those reported in the literature for both analogs.

In [48], a multicenter, randomized, four-arm, parallel-group study with T1D including 275 patients for Gla-100 and 274 for Gla-300 was conducted. Morning injection of insulin glargine time was between prebreakfast and prelunch (inclusive) and evening at the diner until bedtime, while participants continued using fast acting insulin to cover meals. The insulin requirements, reported as mean (SD) for Gla-100 was 0.45 (±0.19) U/kg in the morning and 0.36 (±0.16) U/kg at night. For Gla-300 was 0.49 (±0.22) U/kg in the morning and 0.45 (±0.21) U/kg at night. These results are similar to those obtained our simulations, reported as median (25th, 75th percentile), for Gla-100 0.42 (0.32–0.54) U/kg in the morning and 0.41 (0.3–0.51) U/kg at night. For Gla-300 was 0.45 (0.33–0.56) U/kg in the morning and 0.37 (0.27–0.49) U/kg at night. The mean glucose was 152.1(±32.8) and 158.8(±38) mg/dl for Gla-100 and Gla-300, respectively, in vivo, remarkably comparable with the results obtained in silico of 166.8 (154.5–185.5) mg/dl and 161.7 (147.9–176) mg/dl for Gla-100 and Gla-300.

Degludec is an ultra-long-acting insulin analog with a flat and reproducible pharmacodynamic profile. In [52], 29 patients with a

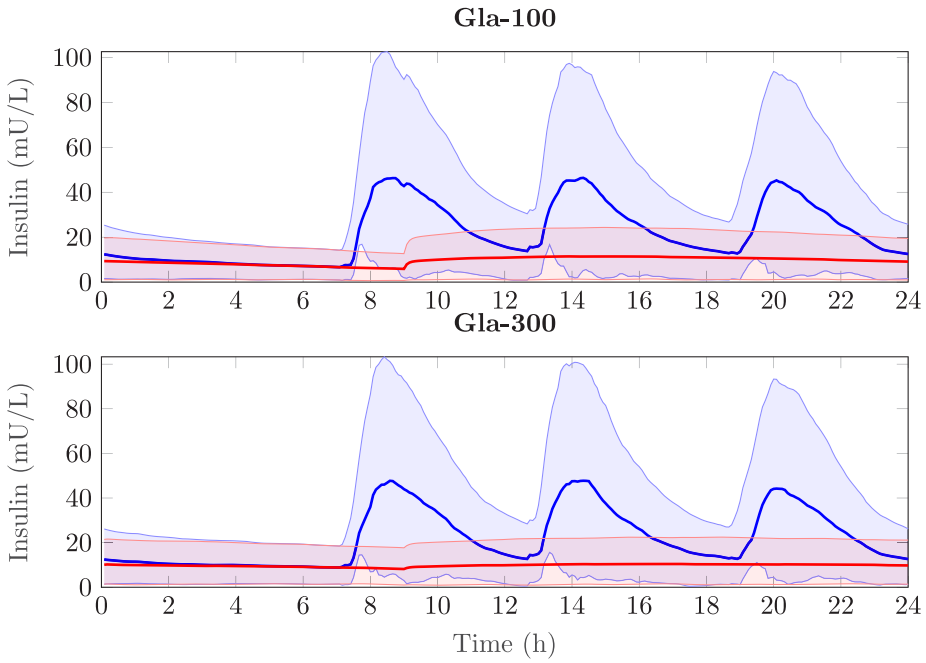


**Fig. 6.** Median (IQR) of plasma insulin concentration total (blue), Gla-100, and Gla-300 (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

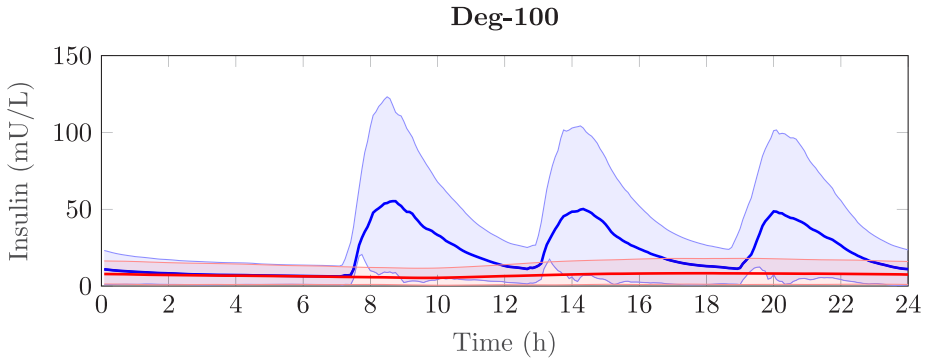


**Fig. 7.** Median (IQR) of plasma insulin concentration total (blue) and Deg (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mean age of 34.8 (±11.4) years with T1D who did not achieve 24 h coverage with glargine or detemir were chosen and the effect of changing the treatment to degludec was studied. The resulting basal insulin was 0.39 (0.31–0.55) vs. 0.47 (0.35–0.6) U/kg in our simulations and 0.3 (±0.1) U/kg in the clinical trial after 12 weeks. The TIR obtained was 52.3 (39.6–61.6)% vs. 45.8 (38.2–54.4)% in silico and 57.5 (±13.3)% in vivo. The times above 180 mg/dl were 38.8 (±14.4) in vivo and 25.2 (19.3–29.1)% in the range 180–250 mg/dl vs. 13.4 (7.2–26.6)% > 250 mg/dl in silico (See Table 3 of [52]). The hypoglycemia time provided in [52] is defined by time below < 70 mg/dl and was 3.6 (±3.7)% and for our simulations it was 5.9 (3–9.9)%.

It should be noted that there are some differences in the results of clinical trials and in silico results. This is mainly because the simulation does not include any disturbances related to free-living conditions such as physical activity, stress, or hormonal changes such as the menstrual cycle. Another factor that influences the differences found are the different eating habits of each patient, which is not taken into account in the simulator. Furthermore, the same clinical attributes of the study and the insulin titration algorithms were not implemented. However, the in silico study showed similar trends to those obtained in clinical studies, especially regarding insulin requirements.

This study presents an approach that improves upon current simulation tools, yielding results that more closely reflect real-life conditions. However, more research is still required to improve the simulators available in the literature. The main limitations of this study are given by: (1) although 24 h patterns of variability of insulin sensitivity are identified and implemented into the simulator, a model that represents it is not defined, and (2) glucagon, a hormone that is becoming more important for the treatment of T1D, was not included in the experiments.

## 5. Conclusion

The inclusion of the identified insulin sensitivity variability and a mixed meal library into a T1D simulator provides challenging scenarios that is better able to mimic real-life behavior, an important feature for evaluating treatments through in silico tests. The incorporation of the pharmacokinetic model of long-acting insulin glargine and degludec to the Hovorka model reproduces the main characteristics observed in the literature for these analogs, which demonstrates its validity for the testing of MDI therapies.

## CRediT authorship contribution statement

**Ernesto Estremera:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Funding acquisition. **Alvis Cabrera:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Funding acquisition. **Aleix Beneyto:** Conceptualization, Methodology, Software, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Josep Vehi:** Conceptualization, Methodology, Software, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

## 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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## Appendix A. Model equations

### A.1. Glucose subsystem of the Hovorka model

$$\frac{dQ_1}{dt} = -[\frac{F_{01}^c}{V_G G(t)} + x_1(t)] + k_{12}Q_2(t) - F_R + U_g(t) + EGP_0[1 - x_3(t)] \quad (A.1)$$

$$\frac{dQ_2}{dt} = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t) \quad (A.2)$$

$$G(t) = \frac{Q_2(t)}{V_G} \quad (A.3)$$

$$F_{01}^c = \begin{cases} F_{01} & \text{if } G \geq 4.5 \text{ mmolL}^{-1} \\ \frac{F_{01}G}{4.5} & \text{otherwise} \end{cases} \quad (A.4)$$

$$F_R = \begin{cases} 0.003(G - R_{th})V_G & \text{if } G \geq R_{th} \text{ mmolL}^{-1} \\ 0 & \text{otherwise} \end{cases} \quad (A.5)$$

### A.2. Insulin action subsystem of the Hovorka model

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + k_{a1}S_{IT}(t) \quad (A.6)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{a2}S_{ID}(t) \quad (A.7)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{a3}S_{IE}(t) \quad (A.8)$$

### A.3. Insulin absorption subsystem of the Hovorka model

$$\frac{dS_1}{dt} = u(t) - k_a S_1(t) \quad (A.9)$$

$$\frac{dS_2}{dt} = k_a S_1(t) - k_a S_2(t) \quad (A.10)$$

$$\frac{dI}{dt} = \frac{k_a S_2(t)}{V_I} - k_e I(t) \quad (A.11)$$

### A.4. Gut absorption subsystem of the Hovorka model

$$\frac{dG_1}{dt} = -\frac{G_1(t)}{t_{maxG}} + Bio * D(t) \quad (A.12)$$

$$\frac{dG_2}{dt} = \frac{G_1(t)}{t_{maxG}} - \frac{G_2(t)}{t_{maxG}} \quad (A.13)$$

$$U_g(t) = \frac{G_2(t)}{t_{maxG}} \quad (A.14)$$

### A.5. Glargine insulin model

$$\frac{dI_{q1}}{dt} = -k_{sp}I_{q1}(t) + k * F * u_{la}(t) \quad (A.15)$$

$$\frac{dI_{q2}}{dt} = -k_a I_{q2}(t) + k_{sp}I_{q1}(t) + (1 - k) * F * u_{la}(t) \quad (A.16)$$

$$R_{ai}(t) = k_a I_{q2}(t) \quad (A.17)$$

### A.6. Degludec insulin model

$$\frac{dI_{q1}}{dt} = -k_{d1}I_{q1}(t) + F * D \quad (A.18)$$

$$\frac{dI_{q2}}{dt} = -k_{d2}I_{q2}(t) + k_{d1}I_{q1}(t) \quad (A.19)$$

$$\frac{dI_{q3}}{dt} = -k_a I_{q3}(t) + k_{d2}I_{q2}(t) \quad (A.20)$$

$$R_{ai}(t) = k_a I_{q3}(t) \quad (A.21)$$

### A.7. Insulin subsystem model glargine and degludec

$$\frac{dI_p}{dt} = -(m_2 + m_4)I_p(t) + m_1 I_l(t) + R_{ai}(t) \quad (A.22)$$

$$\frac{dI_l}{dt} = -(m_1 + m_3)I_l(t) + m_2 I_p(t) \quad (A.23)$$

$$I(t) = \frac{I_p(t)}{V_I} \quad (A.24)$$

## Appendix B. Procedures to generate the circadian variability of insulin sensitivity

### B.1. Procedure for generation of basal insulin profile

Probability distributions are formulated how $N(\mu, \sigma^2)$ where $\mu$ represents the mean and $\sigma$ is the standard deviation. For the generation of basal insulin profile the following terms are introduced.

1. The number of daily insulin basal rates $n_r \in \mathrm{N}^+$ is sampled and rounded to the nearest integer following the normal distribution $N(5.04, 3.35)$.
2. The array of insulin basal rates $\mathbf{u} = \{u_{np} \cup u_p\} \in \mathrm{R}^{n_r}$ in U/h. Each basal insulin profile contains one peak basal insulin infusion, $u_p$, which is the highest infusion throughout the day and an array of non-peak basal infusions, $u_{np} \in \mathrm{R}^{(n_r-1)}$. Here, the peak basal rate is sampled from $N(0.92, 0.13)$ U/h. Then, the non-peak basal rates can be computed taking into account that the average of $u_{np}$ is at least 25% lower than $u_p$ [42], as shown in Eq. (B.1).

$$\overline{u_{np}} = \frac{\sum \mathbf{u} - u_p}{n_r - 1} < \frac{u_p}{1 + \frac{v}{100}} \quad (B.1)$$

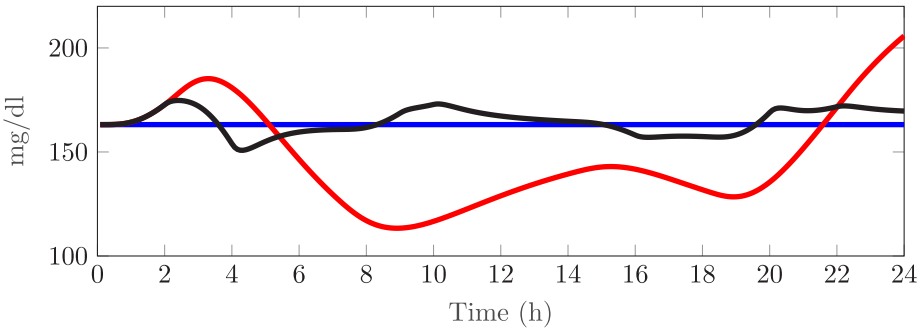


**Fig. B.8.** Representative blood glucose concentration $Q_1(t)/V_g$. The blue curve is the Hovorka model response with $\alpha = 1$ and using $u_b$, the red curve is the Hovorka model response with $\alpha = 1$ and using $\tilde{\mathbf{u}}_b$ and the black curve is the Hovorka model response with the obtained $\alpha(t)$ and using $\tilde{\mathbf{u}}_b$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Where $\upsilon \sim N(30, 2.25)\%$ is the variation percentage that ensures, at least with a 99.7% probability, that $\overline{u_{np}}$ will be a 25% lower than $u_p$. After that, we randomly generate $u_{np} = \left\{u \in (0.4u_p, 0.8u_p) \forall u \in u_{np} | \overline{u_{np}} = \frac{\upsilon}{100} * u_p\right\}$ with $u_{np} \in \mathrm{R}^{(n_r-1)}$.

3. The array of the duration of each basal rate $\mathbf{d} = \left\{d_{u_{np}} \cup d_{u_p}\right\} \in \mathrm{R}^{n_r}$ in $h$. The duration of the peak basal insulin, $d_{u_p}$, follows $N(5.2, 11.29)$ hours. Then, we randomly generate the non-peak basal rates duration $d_{u_{np}} = \left\{\forall d \in d_{u_{np}} | \sum d_{u_{np}} = 24 - d_{u_p}\right\}$ with $d_{u_{np}} \in \mathrm{R}^{(n_r-1)}$.

Once generated **u** and **d** each basal rate is matched to its corresponding duration. To generate the basal insulin profile each glucose rate is distributed in the 24 h. We known that $u_p$ is distributed 80% of the times between 2:00 h–8:00 h and 20% time CGM between 20:00 h–2:00h [42]. The $d_{up}$ is then centered at either 5:00 h or 24:00 h. After that, $d_{\mathbf{u}_{np}}$ is concatenated to the ending time of the up basal rate.

### B.2. Procedure for $\alpha(t)$ generation

$\alpha(t)$ is the day hourly-varying factor affecting the model's insulin sensitivity. To obtain the array $\alpha$, the steady state of a VP is solved using a generated basal profile **u**. Then, a maximization problem is iteratively solved, hour by hour, such that the daily steady state glucose remains in a 30 mg/dl band.

$$\begin{aligned} \min \quad & -\alpha \\ \text{s.t.} \quad & f(\mathbf{x}, \tilde{\mathbf{u}}_b, \alpha) = 0 \\ & \frac{Q_1}{V_g} \in \left[\frac{-0.3Q_{1,basal}}{V_g}, \frac{0.3Q_{1,basal}}{V_g}\right] \\ & \tilde{\mathbf{u}}_b = u_b \frac{\mathbf{u}}{\overline{\mathbf{u}}} \end{aligned} \tag{B.2}$$

Where $\mathbf{x} \in \mathrm{R}^8$ is the state vector of the Hovorka model, $f(\mathbf{x}, \tilde{\mathbf{u}}_b, \alpha)$ represents the nonlinear Hovorka model with the time-varying $\alpha$ factor, $Q_{1,basal}$ is the steady state value of $Q_1$ when $u_b$ is used, $u_b$ is the basal insulin obtained when solving for $f(\mathbf{x}, u_b) = 0$ with $Q_1/V_g = 160$ mg/dl and a constant $\alpha = 1$, **u** is a basal pattern generated using the previous described methodology, $\overline{\mathbf{u}}$ is the average basal insulin of **u** and $\tilde{\mathbf{u}}_b$ is the basal insulin pattern scaled based on the VP original basal insulin $u_b$. Basically, we introduce the scaled basal insulin to the model to provoke variability and then we solve for $\alpha$ such that the variability in the glucose concentration state is physiologically plausible. Fig. B.8 shows the different steps involved. First, the blue trajectory shows the base steady state of the Hovorka model without variability. Then, using one of the scaled generated basal profiles we show in the red curve that the variability on glucose is significantly more complex compared to the original case. Then, we translate this effect into the $\alpha$ time-varying parameter such that glucose concentration is constrained to a ±30 mg/dl band [42].

**Table C.6**
Period and phase for the time-varying $\alpha(t)$ for each parameter.

| Parameters | P (Period) | $\varphi$ (Phase) |
|---|---|---|
| $EGP_0$ | 61 | 0.1152 |
| $F_{01}$ | 71 | 0.9324 |
| $k_{12}$ | 59 | 0.2936 |
| $t_{maxI}$ | 31 | 0.5737 |
| $k_c$ | 37 | 0.8423 |
| $m_4$ | 41 | 0.7567 |
| $k_6$ | 39 | 0.1491 |

## Appendix C. Procedures to generate $\beta(t)$

Intra-patient variability is introduced in model parameters by applying the following product:

$$p(t) = p_0\beta(t) \tag{C.1}$$

where $p(t)$ represents the new time-varying parameter, $p_0$ represents the constant nominal parameter from the VP and $\beta(t)$ is a time-varying sinusoidal function of the form (C.2).

$$\beta(t) = 1 + \frac{A}{100}\sin\left(\frac{2\pi}{P \cdot 60}t + 2\pi\varphi\right) \tag{C.2}$$

where the period $P$, in hours, is different for each parameter and is represented by prime numbers randomly assigned between 31 and 71 to avoid periodicity between the parameters, the phase $\varphi$ is randomly selected between 0 and 1 (Table C.6 shows P and $\varphi$ selected for each parameter), the amplitude $A$ was set to 20 following [62]. A total of 7 model parameters can include intra-patient circadian variability.

## Appendix D. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.jbi.2022.104141.

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