Tailoring the Padova Type 2 Diabetes Simulator for Treatment Guidance in Target Populations

Roberto Visentin, *Member, IEEE*, Michele Schiavon, Jacopo Bonet, Michela Riz, Britta Wagenhuber, and Chiara Dalla Man

Abstract*—*Objective: **The Padova type 2 diabetes (T2D) simulator (T2DS) has been recently proposed to optimize T2D treatments including novel long-acting insulins. It consists of a physiological model and an in silico population describing glucose dynamics, derived from early-stage T2D subjects studied with sophisticated tracer-based experimental techniques. This limits T2DS domain of validity to this specific sub-population. Conversely, running simulations in insulin-naïve or advanced T2D subjects, would be more valuable. However, it is rarely possible or cost-effective to run complex experiments in such populations. Therefore, we propose a method for tuning the T2DS to any desired T2D sub-population using published clinical data. As case study, we extended the T2DS to insulin-naïve T2D subjects, who need to start insulin therapy to compensate the reduced insulin function. *Methods:* T2DS model was identified based on literature data of the target population. The estimated parameters were used to generate a virtual cohort of insulin-naïve T2D subjects (inC1). A model of basal insulin degludec (IDeg) was also incorporated into the T2DS to enable basal insulin therapy. The resulting tailored T2DS was assessed by simulating IDeg therapy initiation and comparing simulated vs. clinical trial outcomes. For further validation, this procedure was reiterated to generate a new cohort of insulin-naïve T2D (inC2) assuming inC1 as target population. *Results:* No statistically significant differences were found when comparing fasting plasma glucose and IDeg dose, neither in clinical data vs. inC1, nor inC1 vs. inC2. *Conclusions:* The tuned T2DS allowed reproducing the main findings of clinical studies in insulin-naïve T2D subjects. *Significance:* The proposed methodology makes the Padova T2DS usable for supporting treatment guidance in target T2D populations.**

***Index Terms*—Physiological modeling, in silico clinical trial, in silico patient, glucose variability, insulin therapy, decision support.**

I. Introduction

IN SILICO trials aim to recreate the concept of clinical trials using a simulation approach, where a large number of virtual patients is used for initializing a disease intervention strategy. In diabetes field, *in silico* experiments contribute to accelerate technology and drug development [1]. In fact, the use of a computer simulator, consisting of a mathematical model and a cohort of virtual patients spanning the variability of a desired population, represents a time- and cost-effective approach to de-risk and optimize drug discovery and development, and allows to assess a large variety of scenarios which could be difficult, dangerous, or unethical to perform *in vivo*.

An example of such *in silico* tools is the UVA/Padova type 1 diabetes (T1D) simulator [2], [3], [4] that has been accepted and widely used as decision support system for testing several diabetes technology treatments, such as artificial pancreas prototypes (e.g., [5], [6], [7]) and, more recently, glucose monitoring systems and novel insulin formulations (e.g., [8], [9], [10], [11]). In addition to T1D, particular interest has been recently raised also on supporting treatments for type 2 diabetes (T2D), given that individuals with T2D represent 90% of the global population with diabetes, and may benefit from a variety of treatments specific for different stages of disease progression.

We recently developed a T2D simulator (T2DS) [12], consisting of a large-scale simulation model and a population of 100 *in silico* T2D subjects. The virtual patients were generated based on glucose, insulin, C-peptide concentrations and estimated glucose rate of appearance, endogenous production, utilization, and insulin/C-peptide secretion available in 204 healthy [13] and 51 early-stage T2D subjects [14], [15], [16], who underwent a triple-tracer mixed-meal tolerance test [17]. As such, this simulator is able to reliably describe the glucose-insulin-C-peptide dynamics in early-stage T2D subjects (like those in [14], [15], [16]), but it is not suitable to test treatments in subjects with advanced insulin-dependent T2D or belonging to different age or ethnic groups. This limited the usability of this promising tool to a particular subgroup of the diverse T2D population.

Theoretically, specific T2D subpopulations should be studied as highlighted in [12], in order to be properly simulated. However, these complex multiple-tracer experiments needed to

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estimate the metabolic fluxes and therefore are very burdensome for patients, expensive and time consuming, so the benefit of running the *in silico* trial would be lost. Rather, the commonly available information for a specific population is limited, usually consisting of population average, sometimes its variability, and rarely individual data.

To overcome this limitation, we propose a method for tailoring the Padova T2DS to the specific characteristics of a desired T2D subpopulation, even in case of limited available data. The T2DS is briefly described first. Then, the pipeline to get a tailored simulator is presented. This includes i) the adaptation of the virtual patients to the target population using data available in the literature, ii) the incorporation of possible additional modules needed for running the appropriate virtual trial, and iii) the validation of the tailored simulator. A case study is provided to illustrate how to perform these steps in practice to tailor the T2DS to an insulin-naïve T2D population. Finally, the method is re-applied to the newly generated insulin-naïve virtual population, now considered the target to be virtually recreated, and a second insulin-naïve T2D virtual population is generated. This allowed a robust validation of the method since, in the simulated target population, not only sparsely sampled but continuous plasma glucose and hormone data can be used to compare simulated vs target outcomes.

II. Methods

A. The Padova Type 2 Diabetes Simulator

The Padova T2DS consists of a set of 14 nonlinear differential equations (described in the online Supplementary Material), defining the physiological system behavior (glucose absorption by the intestinal tract, endogenous glucose production, glucose utilization, and a description of the impaired endogenous insulin secretion in T2D), an infrastructure to set up the simulation scenarios (duration of the simulation, time and amount of the meals, etc.), and a set of virtual patients, defining the population on which the user wants to run the *in silico* trial [12].

The i-th virtual subject is represented in the simulator by a vector $\mathbf{p_i}$ containing the N model parameters**:**

$$\boldsymbol{p_i} = [p_1,\ p_2,\ \ldots, p_N]^T \tag{1}$$

randomly extracted from a log-normal joint parameter distribution $LN(\mu_\mathbf{p}, \Sigma_\mathbf{p})$, originally obtained by identifying the T2DS model on data of both early-stage T2D and healthy subjects studied with a triple-tracer mixed meal protocol [13], [14], [15], [16], [17].

B. Pipeline for Tailoring the T2D Simulator

We propose a pipeline to virtually recreate any T2D population using data usually available in the literature, i.e., plasma glucose and hormone concentration measurements, either at average or individual level (Fig. 1). The pipeline constis of five steps:

1) Model Identification: To tailor the T2DS to the specific populations of interest, appropriate data are required for model identification. This usually consists of average demographic characteristics, fasting and post-prandial time courses of plasma glucose, insulin and C-peptide concentrations.

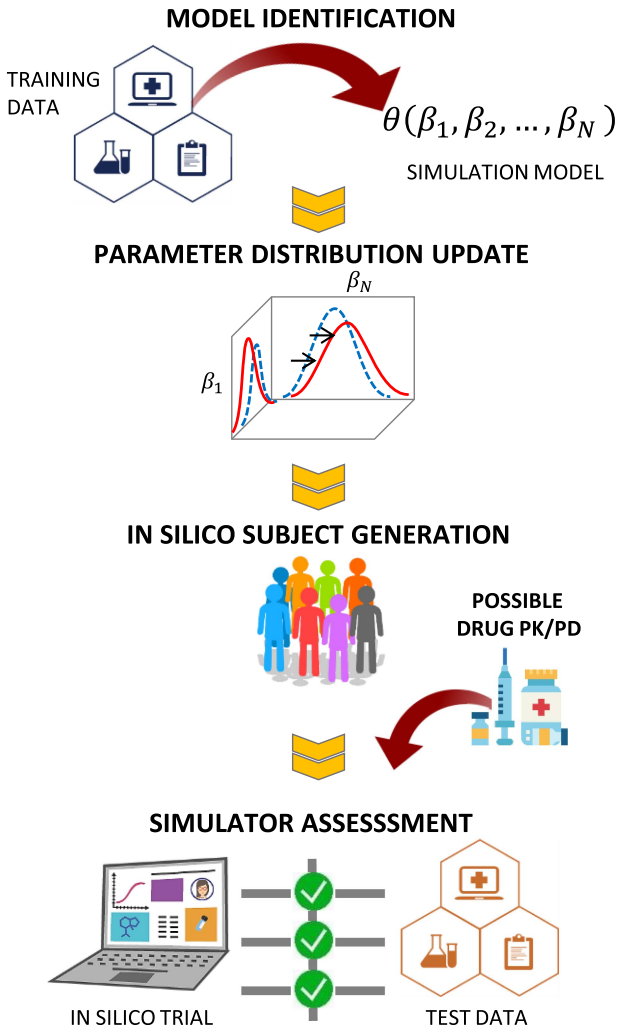

Fig. 1. Flowchart describing the pipeline to tune the simulator to a target population. A training database (e.g., available from literature or study record) is used to identify the simulation model and, if needed, to develop/incorporate a PK/PD model of the drug to be tested in the simulator. Then, the joint distribution of simulation model parameters is updated based on the estimated model parameters (available from the previous step), and the in silico target population can be generated. Finally, the simulator is assessed by exploiting clinical study data. Specifically, the clinical protocol is replicated in silico, and the simulations are compared with the clinical results.

Here, we assume that the available information on a target population consists of average demographic parameters (age, body weight (BW), body mass index (BMI), etc.) and glucose, insulin, and C-peptide time courses (e.g., sampled during a mixed meal tolerance test). These data are used to identify the T2DS model using a Bayesian Maximum a Posteriori (MAP) Estimator [18], and provide the parameter estimates, $\hat{\boldsymbol{\mu}}_\mathbf{p}$, describing the average dynamics of the target population.

2) Parameter Distribution Update: Assuming that only average data are available, the new parameter distribution is $LN(\hat{\boldsymbol{\mu}}_\mathbf{p}, \Sigma_\mathbf{p})$ with covariance matrix $\Sigma_\mathbf{p}$ of the original T2D population. If the data allow to estimate the target population

variability (i.e., individual data are available), the new parameter distribution becomes $LN(\hat{\boldsymbol{\mu}}_{\mathbf{p}}, \hat{\sum}_{\mathbf{p}})$.

3) In Silico Subject Generation: The *in silico* population is generated by randomly extracting a certain number of model parameter vectors ($\mathbf{p_i}$), each one representing an *in silico* subject, from the joint parameter distribution $LN(\hat{\boldsymbol{\mu}}_{\mathbf{p}}, \hat{\sum}_{\mathbf{p}})$ obtained at step 2. Similarly to [4], [12], parameter vectors with Mahalanobis distance greater than the 95$^{\text{th}}$ percentile are discarded, so implausible parameter combinations are avoided.

In particular, in order to get an *in silico* population of M subjects $\mathbb{M} : \{\boldsymbol{p}_1, \boldsymbol{p}_2, \ldots, \boldsymbol{p}_M\}$, a set of $L>M$ subjects (defined as $\mathbb{L} : \{\boldsymbol{p}_1, \boldsymbol{p}_2, \ldots, \boldsymbol{p}_L\}$) is generated, each of them undergoing the same experiment as the target population (likely, an oral glucose or mixed meal tolerance test). Among the possible combinations of M subjects taken from L, the optimal set $\hat{\mathbb{M}}$, corresponding to the tailored population, is selected as the one that maximizes the following similarity score (S):

$$S = (FIT_G + FIT_I + FIT_{Cp})/3 \tag{2}$$

where each *FIT* index is calculated with respect to the average glucose (G), insulin (I), C-peptide (Cp) curves. For example,

$$FIT_G = 1 - \sqrt{\frac{\sum_{i=1}^{N}\left(G^{target}(i) - G^{tailored}(i)\right)^2}{\sum_{i=1}^{N}\left(G^{target}(i) - \overline{G^{target}}\right)^2}} \tag{3}$$

where G^{target} and $G^{tailored}$ are the average glucose curves of the target and tailored populations, respectively, $\overline{G^{target}}$ is the G^{target} sample mean, N is the number of time points and i is the time point index. In addition, in the case that variability data (e.g., standard deviation) also are available, a refined similarity score S^* can be evaluated to better match the target population variability:

$$\begin{aligned} S^* = (&FIT_G + FIT_{G,lo} + FIT_{G,hi} \\ &+ FIT_I + FIT_{I,lo} + FIT_{I,hi} \\ &+ FIT_{Cp} + FIT_{Cp,lo} + FIT_{Cp,hi})/9 \end{aligned} \tag{4}$$

where subscripts *lo* and *hi* refer to average $\mp$ standard deviation curves, respectively.

4) Incorporation of Additional Modules (Optional): If needed, additional modules simulating a specific treatment (e.g., a model of long- or short-acting subcutaneous insulin kinetics, or the PK/PD model of an antidiabetic drug to be tested) can be incorporated into the simulator at this step. If no additional modules are needed, this step can be skipped.

5) Simulator Assessment: The resulting tailored simulator is finally validated by comparing clinical data (preferably not derived in the same cohort used for model identification) to the simulations, in which the *in silico* scenario matches the reference clinical trial.

C. Case Study: Creating a Virtual Insulin-Naïve T2D Population

As case study, we present the application of the described pipeline to create a T2DS for testing basal insulin therapy initiation in insulin-naïve T2D subjects, i.e., patients who start basal insulin therapy to compensate the impairment in insulin secretion and action.

1) Model Identification:

a) Database: Data used to tune the T2DS to the insulin-naïve population are taken from [19]. Briefly, a total of 260 European American insulin-naïve T2D patients (122 female, age = 55±9 years, BMI = 32.4±4.5 kg/m^2) were randomized to three treatment arms (IDeg, Liraglutide, or IDegLira) and underwent two mixed meal tolerance tests (MMTT), before (*visit 1*) and at the end of a 26-week period of once-daily treatment administration (*visit 2*). In both visits, subjects consumed a single, standardized, mixed meal containing 96 g of carbohydrates (CHO). Plasma glucose, insulin and C-peptide concentrations were measured at $t = -10$, 15, 30, 45, 60, 90, 120, 180, and 240 min, with 0 indicating the start of the meal.

b) Model identifiability and parameter estimation: The T2DS model [12] was fitted to plasma glucose, insulin and C-peptide average data available from [19]. Only data from *visit 1* (i.e., before treatment) were used to fit the baseline characteristics of the target population.

It is worth noting that the T2DS model is not a priori identifiable from the available data. Indeed, given the complexity of the model, the sole availability of plasma glucose, insulin and C-peptide makes it impossible to estimate a unique combination of model parameters by using standard identification techniques, such as nonlinear least squares or maximum likelihood. Hence, T2DS model parameters describing insulin sensitivity (V_{mx}, k_{p3}), insulin secretion (Φ_b, Φ_s, Φ_d) and hepatic extraction (HE_b) were identified using a Maximum A Posteriori (MAP) estimator implemented in MATLAB R2021b [20], while the remaining parameters were fixed to population values [12]. In particular, the a *priori* information was taken from [12], and corresponded to the original joint parameter distribution derived from triple-tracer data [13], [14], [15], [16]. This strategy was proposed and validated in a previous work [18]. To note, insulin sensitivity, secretion and hepatic extraction are known to be the key parameters that mostly characterize T2D pathophysiology and differ among populations, as already found in previous analysis [21].

Measurement error on average plasma glucose data was assumed to be independent, Gaussian, with zero mean and known coefficient of variation (CV = 2%). Measurement error on plasma insulin (I) and C-peptide (Cp) data were assumed to be independent, Gaussian, with zero mean and known variance linked to insulin and C-peptide measurements (in pmol/L), i.e., $\text{Var}(I) = 6 + 0.0055 \times I^2$ and $\text{Var}(Cp) = 2000 + 0.001 \times Cp^2$, as described in [22]. The precision of parameter estimates was expressed by the coefficient of variation (CV, defined as the ratio between the standard deviation of the estimated parameter and the parameter value), which is related to how much variation of a specific parameter influences the model prediction (the lower the CV, the higher the sensitivity of model prediction to the parameter).

2) Joint Parameter Distribution Update: The estimated model parameters and the demographic characteristics (i.e., age, BW, BMI) were used to update $\hat{\boldsymbol{\mu}}_{\mathbf{p}}$ to insulin-naïve average

TABLE I
TITRATION ALGORITHM

FPG target: [70-90] mg/dL
Starting dose: 10 U

FPG (mg/dL)	Dose adjustment (U)
<56	-4
[56-70)	-2
(90-180]	+2
(180-270]	+4
>270	+6

Dose adjustments were done every 3 days, based on the last 3-day FPG. FPG: fasting plasma glucose. U: units of insulin.

($\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$). Since here we lacked individual subject data, $\Sigma_{\mathbf{p}}$ was kept identical to the early-stage T2D population [12].

3) In Silico Subject Generation: *In silico* insulin-naïve T2D subjects were generated from the joint parameter distribution $LN(\hat{\boldsymbol{\mu}}_{\mathbf{pC}},\Sigma_{\mathbf{p}})$ and underwent a 4-hour MMTT with 96 g of CHO. The final simulated insulin-naïve T2D population of 100 subjects was selected based on S^* of (4), as the one best matching the average and variability of glucose, insulin and C-peptide time courses of the reference data set.

4) Incorporation of Additional Module: Long-Acting Insulin Pharmacokinetics: A model of subcutaneous absorption of long-acting insulin degludec (IDeg), was incorporated into the simulator to enable the simulation of basal insulin therapy in the simulated tailored population, as previously described [11]:

$$\begin{cases} \dot{I}_{q1}(t) = -k_d \cdot I_{q1}(t) + F \cdot D & I_{q1}(0) = 0 \\ \dot{I}_{q2}(t) = -k_d \cdot I_{q2}(t) + k_d \cdot I_{q1}(t) & I_{q2}(0) = 0 \\ \dot{I}_{q1}(t) = -k_a \cdot I_{q3}(t) + k_d \cdot I_{q2}(t) & I_{q3}(0) = 0 \\ Ra_I(t) = k_a \cdot I_{q3}(t) \end{cases} \quad (5)$$

where D (mU/kg/min) is the insulin dose administered into the subcutis, F (dimensionless) is the bioavailability, k_d (min^{-1}) is the rate constant of molecular complex conversion, k_a (min^{-1}) is the rate constant of insulin absorption to plasma, and Ra_I is the insulin rate of appearance in plasma.

In a previous work [23], this model was identified on average IDeg serum concentrations measured in 49 [23] and 63 insulin-dependent T2D subjects [25] receiving 0.4 U/kg or 0.6 U/kg IDeg once-daily injections, respectively. This provided a good description of IDeg therapy in T2D individuals.

5) Assessment of the Insulin-Naïve T2DS:

a) Database: A set of 773 European American T2D subjects (302 female, age = 59±10 years, BMI = 30.9±4.8 kg/m^2), reported in [26], underwent a 52-week trial, in which they were up-titrated to their individual optimal once-daily IDeg dose following the titration rule reported in Table I. The IDeg starting dose was 10 U. In the 52 treatment weeks, each subject-specific IDeg dose was adjusted every 3 days on the basis of the average fasting plasma glucose (FPG) of the last 3 days, ensuring titration towards a predefined FPG target of 70-90 mg/dL.

FPG and IDeg daily dose were recorded throughout the trial to evaluate the efficacy of the treatment.

b) In silico trial: The *in silico* 100 insulin-naïve T2D subjects performed the same experimental scenario described in [26]. Specifically, each *in silico* subject underwent a 52-week 3-meal/day IDeg titration trial. Simulated meal times and amounts were distributed during the days as implemented in [10], [11], to mimic real-life habits: three meals per day were randomly generated for each subject assuming mealtime uniformly distributed in the intervals 06:30 am–08:00 am (breakfast), 11:30 am–01:00 pm (lunch), 06:30 pm–08:00 pm (dinner); meal amounts were randomly sampled from a uniform distribution with mean ± standard deviation of 58.2 ± 22.5 g (breakfast), 77.7 ± 27.0 g (lunch), 83.9 ±32.3 g (dinner). Subjects were up-titrated to their individual optimal IDeg dose following the titration rule reported in Table I. An inter-occasion variability in IDeg bioavailability was generated by randomly modulating the subject-specific nominal value with Gaussian noise with zero mean and coefficient of variation equal to 8.5% [11].

Simulated continuous glucose monitoring (CGM) data, FPG, IDeg doses and number of severe hypoglycemic events (classified as plasma glucose < 54 mg/dL) were collected during the entire trial.

The insulin-naïve T2DS was assessed against clinical data by comparing the distributions of simulated and real FPG, its final deviation from baseline (Δ_{BSL}), IDeg dose, and the cumulative number of severe hypoglycemic events.

Outcome distributions were reported as mean ± standard deviation if normally distributed, as median and [25$^{\mathrm{th}}$ – 75$^{\mathrm{th}}$] percentiles, otherwise. The normality of outcome distributions was assessed by the Lilliefors test, and unpaired comparison (*in silico* vs. *in vivo*) was performed based on outcome distribution: t-test for normally distributed values, Mann-Whitney U-test otherwise. Significance level was set to $P = 0.05$ for all the statistical tests.

D. In Silico Validation

In order to provide a robust validation of the tailoring method, we tested if we were able to reproduce the in silico insulin-naïve population generated in the previous section C. In fact, using the simulated population as target, not only sparse concentration data but continuous variables are available for performance assessment.

The 100 *in silico* insulin-naïve T2D subjects, generated in Section C, were randomized in two groups of 50 subjects, one (*training*) used as target for T2DS tuning and the other one (*test*) used for the assessment steps.

Specifically, the training data set consists of individual plasma glucose, insulin and C-peptide concentrations obtained in 50 *in silico* subjects undergoing a 4-hour MMTT with 96 g of CHO. Despite the availability of individual data, we supposed availability of average and variability measurements only. Thus, the T2DS model [12] was fitted to the MMTT glucose, insulin and C-peptide average data, as in Section II-C-1. This allowed to update $\hat{\boldsymbol{\mu}}_{\mathbf{p}}$ to a new average ($\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$) and to generate a new cohort of 100 *in silico* subjects from the joint parameter distribution $LN(\hat{\boldsymbol{\mu}}_{\mathbf{pC2}},\Sigma_{\mathbf{p}})$ following the same procedure described in Sections II-C-2, II-C-3.

The new *in silico* population was then validated by running the same 52-week IDeg titration trial described in Section II-C-5,

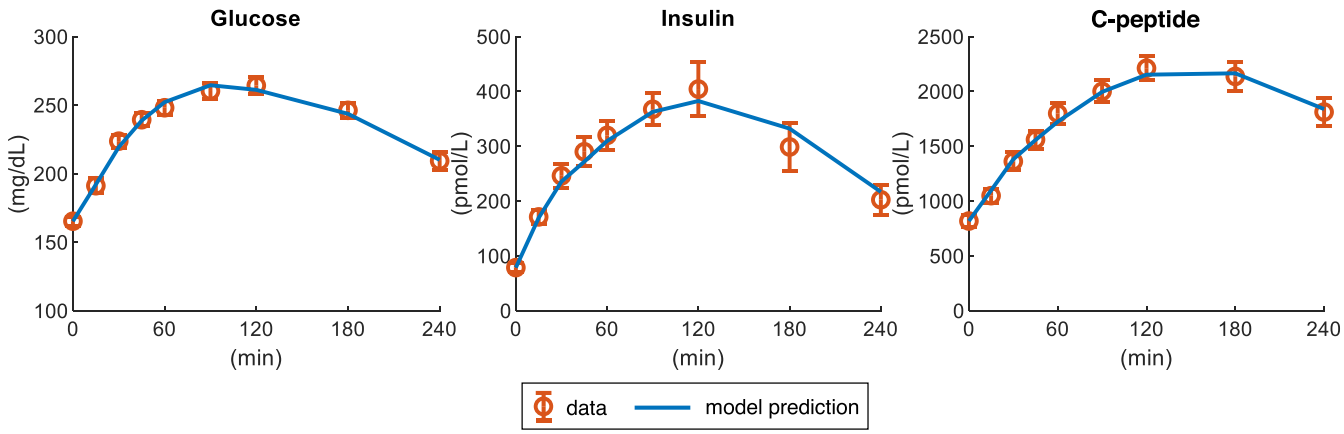

Fig. 2. Model predictions (blue line) of plasma glucose (*left*), insulin (*center*), and C-peptide (*right panel*) compared to the respective average clinical data (orange dots) [19]. Vertical bars represent standard deviation of the measurement error.

and comparing the simulated individual CGM data, FPG, IDeg doses and number of severe hypoglycemic events to the respective counterparts available for the test set, i.e., the second group of 50 simulated subjects. Besides the distributions of FPG, Δ_{BSL}, IDeg dose, and cumulative number of severe hypoglycemic events, the statistical comparison also involved the CGM-based glucose control metrics [28], i.e., glucose average (Mean), standard deviation (SD), coefficient of variation (CV), percent time in range 70-180 mg/dL (TIR), below range <70 mg/dL (TBR70), below range <54 mg/dL (TBR54), above range >180 mg/dL (TAR180) and above range >250 mg/dL (TAR250).

III. Results

A. Insulin-Naïve T2D Simulator

1) T2DS Model Identification: The T2DS model well fits average glucose, insulin and C-peptide concentrations of clinical study [19], as shown in Fig. 2. Model parameters describing insulin sensitivity, secretion and hepatic extraction were estimated with good precision and reported in Table II ($\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$). Consistently with the more severe disease condition of advanced insulin-naïve vs. early-stage T2D, estimated V_{mx}, k_{p3}, Φ_b, Φ_s, Φ_d, and HE_b were lower than the respective values in the original prior $\hat{\boldsymbol{\mu}}_{\mathbf{p}}$ (estimated in early-stage T2D subjects).

2) In Silico T2D Subject Generation and IDeg Incorporation: Based on the results obtained at the previous step, the joint parameter distribution was updated according to $\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$ reported in Table II, and a cohort of 100 *in silico* insulin-naïve T2D subjects was generated as described in Sections II-C-3. The resulting tailored population, undergoing the same 4-hour MMTT with 96 g of CHO, satisfactorily matched the measured glucose, insulin, and C-pepetide data, in terms of both average and variability, as proven by the similarity score ($S^* = 0.87$), with the lowest (but still acceptable) similarity index obtained for the average + standard deviation insulin curve ($FIT_{I,hi} = 0.80$).

In order to compare the ability of the original early-stage T2D *in silico* population vs. the tailored one in reproducing the available data, Table III reports the root mean square error (RMSE) and mean absolute error (MAE) calculated from mean and mean ± SD curves of glucose, insulin and C-peptide: as it can be observed, the quality of the model prediction is substantially improved (meant as reduced RMSE and MAE) with the tailored population vs. the original one.

Each subject was then equipped with an individual set of IDeg therapy parameters as described in Section II-C-4. By doing so, the tailored T2DS implementing insulin therapy was created.

3) T2DS Assessment: The progression of FPG and IDeg dose during the 52-week titration is shown in Fig. 3. The titration algorithm mostly acts in the first 10-12 weeks, increasing the IDeg dose to lower FPG towards the glucose target, as observed in study [26]. At the end of the trial, *in silico* results were similar to clinical outcomes: final FPG was 102 ± 22 mg/dL ($\Delta_{\mathrm{BSL}} =$

TABLE II
Model Parameter Estimates

Process	Parameter	Unit	$\hat{\boldsymbol{\mu}}_{\mathbf{p}}$	$\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$ (CV%)	$\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$ (CV%)
Insulin Sensitivity	V_{mx}	mg/kg/min per pmol/L	0.045	0.018 (19%)	0.024 (35%)
	k_{p3}	mg/kg/min per pmol/L	0.009	0.005 (37%)	0.006 (87%)
Insulin Secretion	Φ_b	10^{-9} min^{-1}	6.7	4.9 (-)	5.8 (-)
	Φ_s	10^{-9} min^{-1}	20.1	15.4 (3%)	14.9 (4%)
	Φ_d	10^{-9}	294.8	276.1 (14%)	299.4 (15%)
Hepatic Extraction	HE_b	dimensionless	0.48	0.34 (39%)	0.44 (36%)

Estimated model parameters compared to the original early-stage T2DS prior ($\hat{\boldsymbol{\mu}}_{\mathbf{p}}$) [12] by fitting the T2DS model on average clinical data [19] ($\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$) or average *in silico* training set ($\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$). Precision of parameter estimates is reported in parenthesis as percent coefficient of variation (CV, defined as the ratio between the standard deviation of the estimated parameter and the parameter value). CV is missing for basal β-cell responsivity (Φ_b) since it is calculated and not estimated from data [22].

TABLE III
PREDICTION INDEXES

	Data vs. Simulation (original population)		Data vs. Simulation (tailored population)	
	RMSE	*MAE*	*RMSE*	*MAE*
Glucose (mg/dL)				
Mean	24.9	22.1	6.1	5.3
Mean+SD	46.0	39.8	14.5	12.0
Mean-SD	37.9	35.4	17.0	16.1
Insulin (pmol/L)				
Mean	59.9	53.2	31.9	27.0
Mean+SD	53.9	47.4	33.5	29.3
Mean-SD	79.4	68.4	61.6	51.4
C-peptide (pmol/L)				
Mean	380.1	312.9	40.1	32.8
Mean+SD	506.3	379.4	134.9	121.5
Mean-SD	382.4	365.3	106.3	101.1

Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) for glucose, insulin and C-peptide mean and mean ± standard deviation (SD) data vs. simulation obtained using both the original and the tailored *in silico* populations.

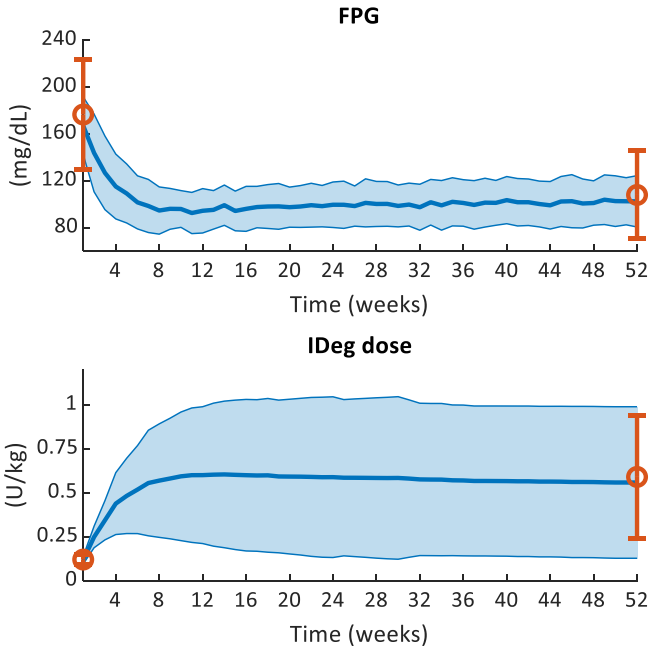

Fig. 3. *Upper panel*: Simulated fasting plasma glucose (FPG) progression during the insulin degludec (IDeg) titration period of 52 weeks. *Lower panel*: IDeg dose distribution during the 52-week titration period. In silico data are reported as mean (thick line) ± standard deviation (shaded area), while in vivo data are reported as mean (circles) ± standard deviation (vertical bars).

−64 ± 27 mg/dL) *in silico* vs. 106 ± 37 mg/dL ($\Delta_{\mathrm{BSL}} = -68$ ± 45 mg/dL) *in vivo*, $P = 0.335$; final IDeg dose was 0.56 ± 0.43 U/kg *in silico* vs. 0.59 ± 0.35 U/kg *in vivo*, $P = 0.434$. To note, inter-individual FPG variability, described by standard deviation, was lower in the *in silico* vs. *in vivo* cohort.

The cumulative number of severe hypoglycemic events per patient/year also was comparable among studies: 1.81 *in silico* vs. 1.52 *in vivo*. A similar difference was found between two subject groups in [26], and resulted neither statistically nor clinically significant.

B. In Silico Validation

1) T2DS Model Identification: The T2DS model well fits average glucose, insulin and C-peptide concentrations of the simulated training set, as shown in Fig. 4. Model parameters describing insulin sensitivity, secretion and hepatic extraction were estimated with precision and reported in Table II ($\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$). V_{mx}, k_{p3}, Φ_b, Φ_s, and HE_b were comparable with the $\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$ estimates. To note, although Φ_d was higher, the total β-cell responsiveness (Φ_{tot}) was similar (16.3 and 15.9 . 10^{-9} min^{-1}, for $\hat{\boldsymbol{\mu}}_{\mathbf{pC}}$ and $\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$, respectively) and lower than $\hat{\boldsymbol{\mu}}_{\mathbf{p}}$ (19.9 . 10^{-9} min^{-1}).

2) In Silico T2D Subject Generation and IDeg Incorporation: The joint parameter distribution was updated according to $\hat{\boldsymbol{\mu}}_{\mathbf{pC2}}$, and a cohort of 100 in silico insulin-naïve T2D subjects has been generated as described in Sections II-C-3. The obtained distributions of key metabolic parameters were statistically identical to both training and test sets (see Fig. S1 in the online Supplementary Material). The resulting tailored population, undergoing the same 4-hour MMTT with 96 g of CHO, well matched the training set glucose, insulin, and C-pepetide curves, in terms of both average and variability (Fig. 5), resulting in a similarity score $S^* = 0.93$, with the lowest similarity obtained for average + standard deviation insulin curve ($FIT_{I,hi} = 0.89$).

Again, individual sets of IDeg model parameters were added to each subject to enable insulin therapy.

3) T2DS Assessment: The progression of FPG and IDeg dose during the 52-week titration is shown in Fig. 6. No statistically significant differences were found when comparing both FPG and IDeg doses in the two populations throughout the 52 weeks. In particular, at the end of the trial, final FPG was 102 ± 19 mg/dL ($\Delta_{\mathrm{BSL}} = -67 \pm 29$ mg/dL) in the tailored population vs. 100 ± 21 mg/dL ($\Delta_{\mathrm{BSL}} = -63 \pm 25$ mg/dL) in the simulated test set, $P = 0.269$, final IDeg dose was 0.61 ± 0.50 U/kg in the tailored population vs. 0.60 ± 0.42 U/kg in the simulated test set, $P = 0.879$.

The increase in the cumulative number of severe hypoglycemic events (Fig. 7) was comparable among the studies, with a final rate of 1.85 and 1.68 episodes per patient/year, for tailored population and test set, respectively.

Finally, no statistically significant differences were found when comparing the distributions of CGM-based glucose control outcomes (Table IV).

IV. DISCUSSION

Given the progressive nature of T2D, therapies differ depending on the stage of disease progression. Based on this consideration, we aimed to maximize the applicability of the Padova T2DS, to support drug development and therapeutic decisions in a given target population with T2D. Since multiple-tracer data (necessary for an optimal estimation of all T2DS model parameters) usually are not available, we developed an alternative method to tailor the T2DS to a specific population of interest (Fig. 1). The idea was to exploit data available in the target population (usually average plasma glucose and hormone profiles and possibly their variability) and capture, by T2DS

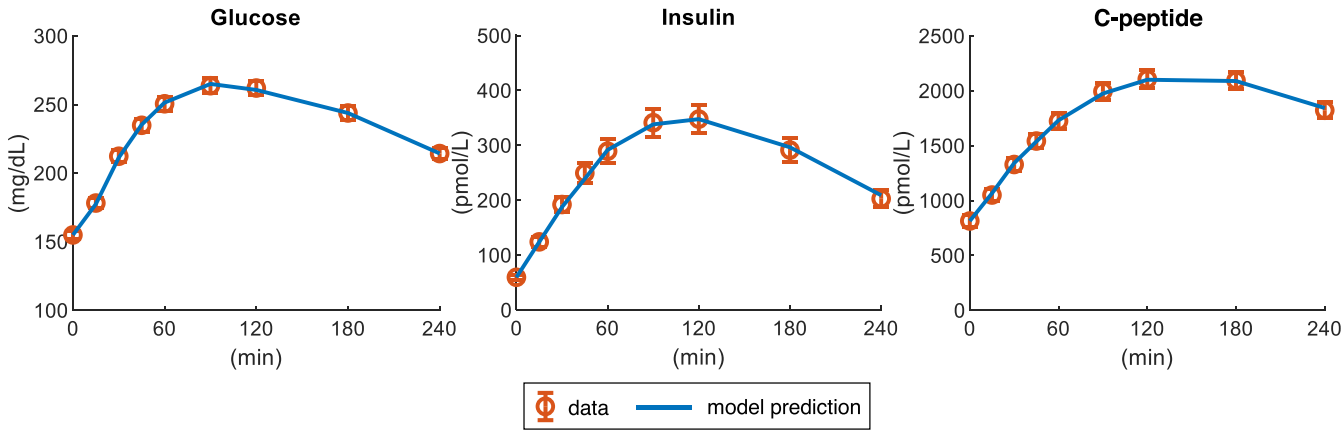

Fig. 4. Model predictions (blue line) of plasma glucose (*left*), insulin (*center*), and C-peptide (*right panel*) compared to the respective average training set data (orange dots). Vertical bars represent standard deviation of the measurement error.

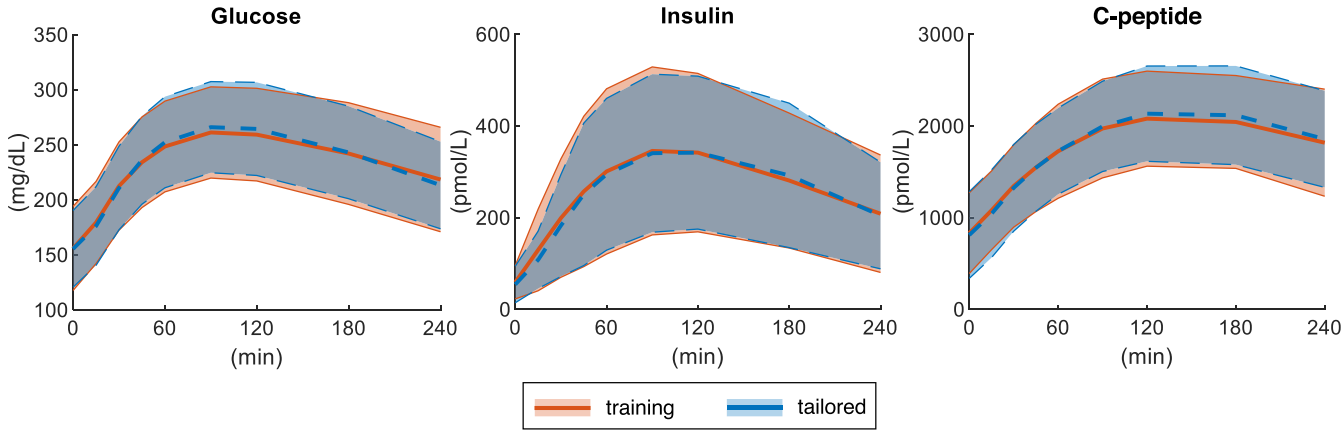

Fig. 5. Mean (continuous or dashed lines) ± intersubject variability (i.e., standard deviation, shaded areas) of plasma glucose (*left*), insulin (*center*), and C-peptide (*right panel*) obtained by simulating a 4-hours mixed meal tolerance test with 96 g of carbohydrates in the training set (orange) and tailored population (blue).

model identification, possible differences in key metabolic parameters with respect to the original early-stage population [12]. This result, merged into the available statistical information (i.e., the joint distribution of T2DS model parameters [12]), allowed generating a new cohort of virtual patients, tailored to the T2D target population.

As a case study, we presented the set up of a T2DS for testing basal insulin therapy initiation in advanced insulin-naïve T2D patients. In particular, after fitting the T2DS model to average clinical data of the target population, we generated a tailored cohort of virtual subjects. Interestingly, the tailored population was able to satisfactorily predict the target population dynamics, much better than what achievable with the early-stage population originally included in the T2DS (Table III). This further underlines the utility of the proposed methodology to provide reliable simulations in a target population.

Then, we equipped the T2DS with a model of IDeg [11], [23] to enable basal insulin therapy, and simulated basal insulin therapy initiation in the tailored population. We showed that the tailored population satisfactorily predicted clinical trial outcomes, in terms of FPG, IDeg dose progressions (both average and, to a lesser extent, variability) and rate of hypoglycemic episodes.

Despite these positive results, it is important to discuss the observed differences in FPG variability at the end of the titration period, which was higher *in vivo* vs. *in silico*. This can be attributed to several factors in the clinical study [26], including subject compliance to the titration rule and trial drug handling, which resulted in an ineffective insulin titration in the 7% of the population (data obtained from Clinical Trial Report no. NN1250-3579, available at www.novonordisk-trials.com). On the contrary, the *in silico* trial granted the optimal adherence to insulin titration by design. This represents the main limitation of the current simulator, therefore future developments will include the possibility to simulate more realistic patient behavior, including imperfect adherence to insulin therapy. However, it is important to point out that the possibility of performing an ideal comparison is the intrinsic value of running simulation.

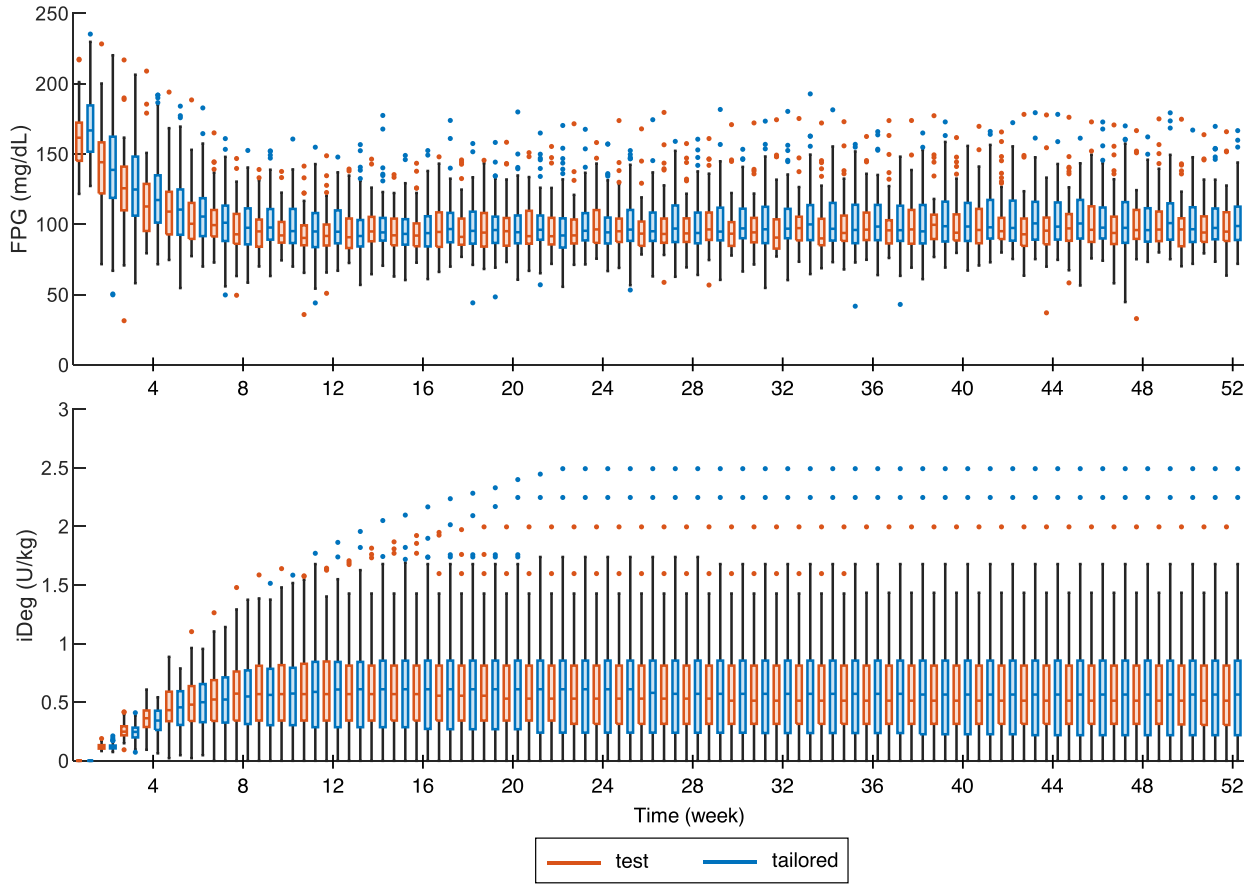

Fig. 6. *Upper panel*: Distribution (boxplot) of simulated fasting plasma glucose (FPG) during the insulin degludec (IDeg) titration period of 52 weeks, in the test set (orange) and tailored population (blue), respectively. *Lower panel*: Simulated IDeg dose distribution (boxplot) during the 52-week titration period, in the test set (orange) and tailored population (blue), respectively. Each boxplot reports the outcome median value (central tick), the interquartile range (colored box), minimum and maximum values (whiskers), and outliers (dots).

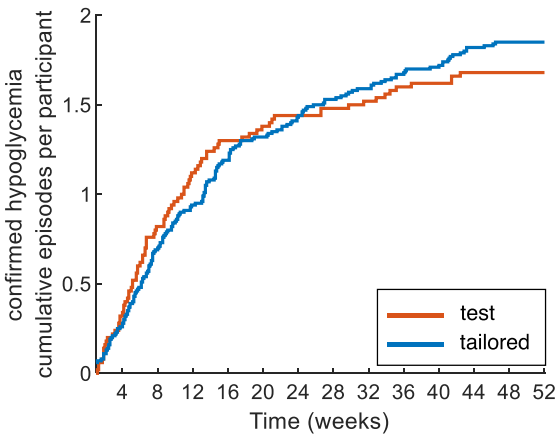

Fig. 7. Cumulative number of hypoglycemic episodes during the 52-week IDeg titration trial in the test set (orange) and tailored population (blue).

TABLE IV
CGM-BASED METRICS

Outcome	Tailored	Test set	*P*
Mean (mg/dL)	161.4 ± 20.4	156.5 ± 19.8	0.168
SD (mg/dL)	48.0 ± 14.4	46.5 ± 15.5	0.566
CV (%)	29.5 ± 6.5	29.6 ± 7.4	0.596
TIR (%)	65.5 ± 14.5	67.9 ± 13.7	0.317
TBR70 (%)	1.7 [0.9 - 2.3]	1.9 [1.1 - 3.2]	0.121
TBR54 (%)	0.3 [0.1 - 0.5]	0.4 [0.2 - 0.8]	0.080
TAR180 (%)	32.7 ± 14.3	29.6 ± 13.6	0.201
TAR250 (%)	5.0 [1.2 - 12.5]	2.3 [0.9 - 8.9]	0.128

Values are reported as mean ± standard deviation and statistical *P* obtained by unpaired t-test for normally distributed outcome, as median and [25th – 75th] percentiles and statistical *P* obtained by Mann-Whitney U-test, otherwise.

In addition, it is worth mentioning that no IDeg PK data was available for the target insulin-naïve T2D population. Therefore we assumed that the iDeg PK variability in insulin-naïve T2D subjects was the same of the T2D patients of studies [23], [25]. This aspect might have potentially contributed to the observed different FPG variability. However, it is to note that the above limitations are related to the case study and do not invalidate the proposed methodology.

In order to provide further validation of the methodology, we re-applied it to match the newly generated *in silico* insulin-naïve population, now considered as target. By doing so, we generated

a second insulin-naïve T2D cohort, so we could perform a robust statistical comparison, also including the analysis of the most common glucose control outcome metrics based on CGM data. The performance of the method achieved in simulation was similar to those obtained on real data, even increasing the match of FPG variability.

Finally, it is important to underline the potential benefit of using a tailored simulator, that is the possibility to test a certain treatment in a population with specific characteristics. Indeed, in the present work, we focused on optimally titrating IDeg in European American T2D subjects, quantifying the insulin need for optimal glycemic control (0.56 ± 0.43 U/kg). The same insulin amount might be uneffective or, even worse, dangerous if administered in a different, i.e., more insulin resistant or more insulin sensitive population, respectively. Therefore, working with a tailored simulator is fundamental to provide optimal treatment dose guidance to the target population, before perfoming clinical trials in humans.

V. Conclusion

We developed a method for tuning the Padova T2DS from early-stage to advanced insulin-naïve T2D subjects, by exploiting commonly available plasma glucose and hormones concentrations taken from clinical meal-test studies. This methodology has the potential to develop virtual populations representative for the T2D subpopulations of interest and that can be used to perform *in silico* clinical trials to guide the development of novel T2D treatments, including basal insulin therapies.

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No other potential conflict relevant to this article was reported.

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