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Addition of New Therapeutic Agents to an Established Type 2 Diabetes Simulation Platform for Therapy Optimization: A Bayesian Model-Based Approach

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Abstract: Patients with type 2 diabetes mellitus (T2DM) typically take blood glucose level lowering oral or injectable therapeutic agents to treat their condition. Titration and timing of administration of these agents can be difficult under optimal conditions. Largely because of these challenging tasks, less than half of patients with T2DM under therapy are reaching desired glycemic targets. Computer simulations have been shown in both types of diabetes to be powerful tools to design and test optimal therapies. However, the diversity of available therapeutic agents makes the construction of such a platform challenging. In this manuscript, we present a methodology to integrate pharmacokinetics (PK) and pharmacodynamics (PD) of anti-diabetic drugs into an existing T2DM population simulation platform to optimize therapy dosage and timing, and inform clinical trial designs; the mixture of insulin glargine and a glucagon-like peptide 1 receptor agonist (GLP1-RA) was used as an example. The platform was augmented with several drug-specific new/modified sub-models and the associated parameter distributions were derived from various blood measurements collected during clinical studies. The joint model parameter distribution of the augmented platform was obtained by fitting simulated glucose profiles on 2000 days of glucose sensor data in a novel Bayesian framework. The resulting platform was then validated by reproducing glucose distributions from a large clinical study, originally excluded from the training data. Finally, simulation experiments of optimal administration timing of the studied mixture were run.

Keywords: Modeling, Identification, Optimization, Simulation, Type 2 Diabetes Mellitus.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a disease characterized by resistance of body cells to the action of insulin - a pancreatic secreted hormone responsible for enhancing glucose entering the cells - resulting in high blood glucose (BG) values or hyperglycemia, whose consequences has been shown in previous studies to be long term micro- and macrovascular complications such as neuropathy, nephropathy, and retinopathy Nathan DM (1993). A wide range of therapeutic options aiming at reducing glycemia is available for T2DM treatment. Typically, patients with advanced T2DM start with oral agents and a daily long-acting exogenous insulin injection. However, low BG levels or hypoglycemia can be induced by therapies if overdosed, putting patients at risk for seizure and death. This condition prevents patients with T2DM from intensifying therapies which, coupled with postmeal hyperglycemic excursions forbid American diabetes association (ADA) recommended glycemic targets to be reached in 50% to 60% of cases Raccah D (2007).

Glucagon-like peptide 1 (GLP1) receptor agonist (GLP1-RA) is a category of injectable therapeutic agents, recently receiving significant attention. These agents bind to the receptors of a gut-derived hormone called GLP1, which stimulates insulin secretion in a glucose-dependent fashion, inhibits gastric emptying, reduces appetite and suppresses the secretion of glucagon, a pancreatic hormone promoting the increase of glycemia Drucker DJ (2006), without impacting its natural secretion response to hypoglycemia. Through these mechanisms, they dampen postmeal hyperglycemia without inducing hypoglycemia and thus, are good candidates to overcome the aforementioned obstacles. In the present study, we will specifically focus on an injectable fixed-ratio combination of GLP1-RA lixisenatide and long-acting insulin glargine (iGlar). The mixture has been shown to be safe and efficacious in the treatment of patients with T2DM Riddle MC (2013), Rosenstock J (2016).

Dosing glucose-lowering agents is a challenging task. Overdosing leads to the life-threatening condition of hypoglycemia and the underdosing to hyperglycemia and its aforementioned consequences. The timing of injection has also proven to be difficult. As those agents have prolonged actions with peaks, adequate injection timing would match action peaks with hyperglycemia zones and nadirs with hypoglycemia ones, which in practice is hardly feasible without extensive knowledge on the mechanism of action. Simulation platforms were used broadly to help with this

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Table 1. Lixisenatide Pharmacokinetic Parameter Estimates

	Average value	Units
k_1	0.0045	min^{-1}
k_2	$8.3 \cdot 10^{-4}$	min^{-1}
k_3	0.0024	min^{-1}
k_d	1	$pg/ml/min$
k_p	0.018	ml/pg
k	18.4	ml^{-1}

difficult task. In this context, the UVA/Padova type 1 diabetic simulation platform was approved by the FDA for testing insulin dosing algorithms as a substitute for animal trials Kovatchev BP (2009).

The present study describes the augmentation of a previously published type 2 diabetic simulation platform Dalla Man C (2007) with new drug sub-models to enable simulation scenarios, with an application on determining the best injecting time for the combination drug.

2. METHODS

2.1 Constructing Dynamic Models Modules from Pharmacokinetics and Pharmacodynamics Experiments

In this section, new sub-models incorporated into the existing simulation platform are discussed. All models presented below are built on data from two previously published studies Becker RH (2014), Becker RH (2015), providing measurements of blood hormonal and glucose responses to respectively intravenous and oral glucose challenges. These measurements were used to fit the built models on or as input forcing functions. Linear models with one compartment or linearized pre-existing ones (if available) were first considered. They were then augmented by up to 2 compartments after which non-linearities were considered and were selected or rejected based on the fit residuals and coefficient of variation (CV) of the associated parameter estimates. Residuals were used to assess the accuracy and the CV the posteriori identifiability and over-fitting risks. Parameter CV were required to be less than 100% and residuals to have the x-axis (0) within the interval mean ± standard deviation (SD).

The three following models were built on blood concentration data from a study where 22 subjects with T2DM were given an intravenous glucose dose two hours following the injection of lixisenatide or placebo Becker RH (2014).

GLP1-RA Model A non-linear triangular shaped three compartment model was selected to describe the evolution of lixisenatide in blood from a subcutaneous injection Eqs.(1)-(4). Depletion rate of the 3rd compartment was modeled with a second order Michaelis-Menten like formula Eq.(4) to obtain satisfactory residuals. Average model fit and average data is shown Fig. 1 and parameter estimates are listed Table 1.

$$\dot{L}_{sc1}(t) = -(k_1 + k_3)L_{sc1}(t) + SCI(t) \tag{1}$$

$$\dot{L}_{sc2}(t) = -k_2 L_{sc2}(t) + k_3 L_{sc1} \tag{2}$$

$$Ra_{lixi}(t) = k_1 L_{sc1} + k_2 L_{sc2} \tag{3}$$

$$\dot{L}_p(t) = -k_d \frac{(k_p \cdot L_p(t))^2}{1 + (k_p \cdot L_p(t))^2} + k \cdot Ra_{lixi} \tag{4}$$

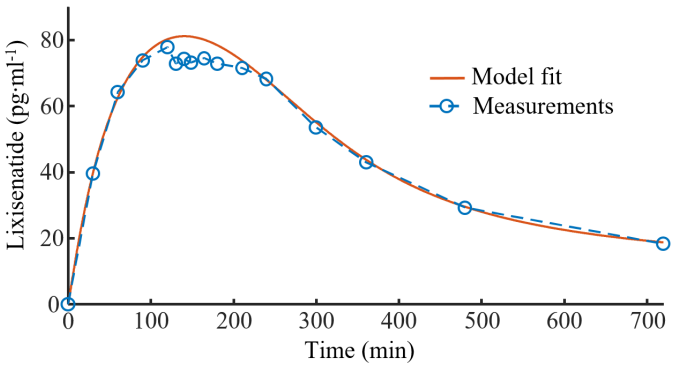

Fig. 1. Lixisenatide average model fit on blood measurements following a subcutaneous injection of 20 μg Becker RH (2014).

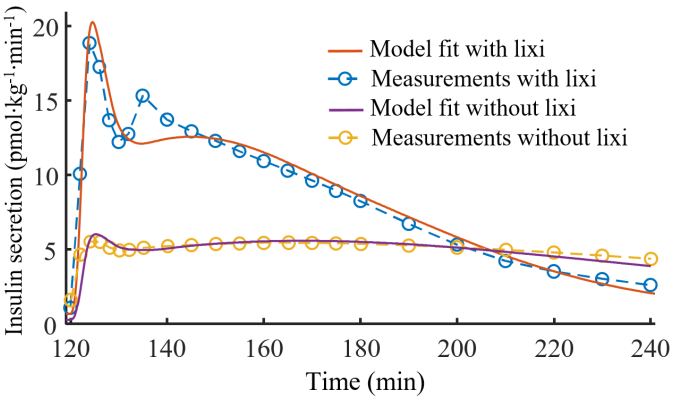

Fig. 2. Insulin secretion model fit on insulin secretion rates derived from c-peptide measurements following an intravenous glucose injection Becker RH (2014).

with, $SCI(\mu g/min)$ the lixisenatide injection rate; L_{sc1} and $L_{sc2}(\mu g)$, states describing lixisenatide mass evolution in rapidly and slowly equilibrating tissues respectively; $k(ml^{-1})$, the gain term accounting for volume of distribution and change of units; $L_p(pg/ml)$, lixisenatide plasma concentration; k_1, k_2, and $k_3(min^{-1})$, rates of exchange between compartments; $k_d(pg/ml/min)$, maximum depletion rate and $k_p(ml/pg)$, a Michaelis-Menten constant like parameter.

Insulin Model A modified version of the insulin secretion model presented in Dalla Man C (2007) with additional compartments to obtain satisfactory residuals was selected. Glucose stimulated insulin secretion Eq.(5) is the sum of the 1st phase dynamic response Eq.(6) and the 2nd phase static response Eq.(8). Fit with and without lixisenatide are shown Fig. 2. Table 2 lists the obtained parameter estimates.

$$S_{po} = Y_I(t) + Y_{II}(t) + S_b \tag{5}$$

where $S_{po}(t)(pmol/kg)$ is the insulin secretion; S_b, the basal secretion; $Y_I(t)$ and $Y_{II}(t)$ are 1st and 2nd phase secretion responses.

$$\dot{Y}_I(t) = \begin{cases} -q \cdot [Y_I(t) - K \cdot Z(t)] & \text{for } Z > 0 \\ -q \cdot Y_I(t) & \text{otherwise} \end{cases} \tag{6}$$

$$\dot{Z}(t) = -p \cdot [Z(t) - \dot{G}(t)]. \tag{7}$$

Table 2. Insulin Secretory Parameter Estimates

	Baseline	With lixisenatide	Units
S_b	0.16	0.28	$pmol/kg/min$
K	0.08	0.53	$pmol \cdot dl/mg/kg$
q	0.71	0.61	min^{-1}
p	0.30	0.30	min^{-1}
α_1	0.07	0.10	min^{-1}
α_2	0.01	0.02	min^{-1}
α_d	0.06	0.33	min^{-1}
β	0.29	0.90	$pmol \cdot dl/mg/kg/min$

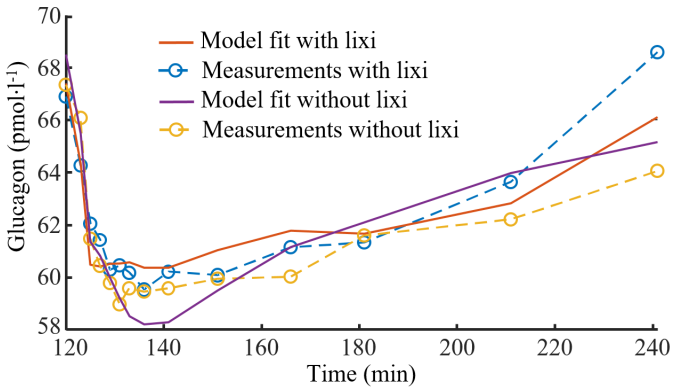

Fig. 3. Glucagon secretion model fit on blood glucagon concentration measurements following an intravenous glucose injection Becker RH (2014).

here, $K(pmol \cdot dl/mg/kg)$ is the pancreatic sensitivity to glucose rate-of-change $\dot{G}(t)$; q and $p(min^{-1})$, delays between glucose rate-of-change and 1st phase response.

$$Y_{II}(t) = \alpha_1 \cdot Y_1(t) + \alpha_2 \cdot Y_2(t) \tag{8}$$

$$\dot{Y}_1(t) = \begin{cases} -(\alpha_1 + \alpha_d) \cdot [Y_1(t) - \beta \cdot (G(t) - G_b)] \\ \text{if } \beta \cdot (G(t) - G_b) \geq -S_b \\ -(\alpha_1 + \alpha_d) \cdot [Y_1(t) + S_b] \text{ otherwise,} \end{cases} \tag{9}$$

$$\dot{Y}_2(t) = \alpha_d \cdot Y_1(t) - \alpha_2 \cdot Y_2(t). \tag{10}$$

here, α_1, α_2 and $\alpha_d(min^{-1})$ are the delays between glucose signal and insulin secretion; $\beta(pmol \cdot dl/mg/kg/min)$, pancreatic sensitivity to glucose $G(t)$ and $G_b(mg/dl)$, basal glucose concentration.

Glucagon Model Glucagon models were proposed in a previously published paper Man CD (2014), the non-linear version was selected. As with the insulin model, a dynamic Eq.(12) and a static secretion Eq.(11) component are described, sensitive to both insulin and glucose blood concentrations. A one-compartment model was used to represent the pharmacokinetics Eq.(13). This model is fit on measurements from the same study Becker RH (2014). Model fits are shown in Fig. 3, and associated parameters listed in Table 3.

$$\dot{SR}^s_H(t) = -\rho \left[SR^s_H(t) - max\left(\sigma \frac{G_b - G(t)}{max(I(t) - I_b, 1)} + SR^b_H, 0 \right) \right] \tag{11}$$

where $SR^s_H(pmol/l/min)$ represent the static secretion component; $SR^b_H(pmol/l/min)$, basal secretion; $I(pmol/l)$, blood insulin concentration; $I_b(pmol/l)$, basal insulin value; $\rho(min^{-1})$ delay of the static secretion component; $\sigma(pmol^2/mg/l/min)$ and σ_2 $(pmol/mg/min)$, the

Table 3. Glucagon Secretory Parameter Estimates

	Baseline	With lixisenatide	Units
SR^b_H	8.82	9.60	$pmol/l/min$
I_b	7.40	12.92	$pmol/l$
ρ	0.54	0.45	min^{-1}
σ	1.23	2.21	$pmol^2/mg/l/min$
δ	0.21	0.16	$pmol/mg$
n	0.13	0.15	min^{-1}

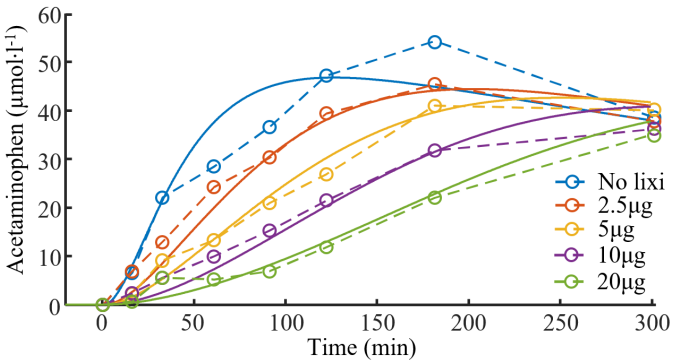

Fig. 4. Gastric emptying model fit on acetaminophen blood concentration measurements following a meal and subcutaneous injection dose of lixisenatide or placebo Becker RH (2015).

Table 4. Gastric Emptying Parameter Estimates

	Baseline	With lixisenatide (20 μg)	Units
k_{empt}	0.048	0.0084	min^{-1}
k_{abs}	0.048	0.0085	min^{-1}
k_{dep}	0.0013	0.0013	min^{-1}
K	0.051	0.051	$\mu mol/mg/l$

glucagon static secretory sensitivities to insulin and/or glucose concentration.

$$SR^d_H(t) = \delta \cdot max\left(-\dot{G}(t), 0\right) \tag{12}$$

where $SR^d_H(pmol/l/min)$ is the dynamic secretion component and $\delta(pmol/mg)$, glucagon dynamic secretory sensitivity to glucose rate-of-change.

$$\dot{H}(t) = -n \cdot H(t) + SR^d_H(t) + SR^s_H(t) \tag{13}$$

here, $H(pmol/l^{-1})$ is blood glucagon concentration and $n(min^{-1})$, its depletion rate.

Gastric Emptying Model A linearized version Eqs.(14)-(16) of the pre-existing platform meal model Dalla Man C (2007) was selected and fitted on data from the oral challenge study Becker RH (2015). In this study, subjects underwent subcutaneous injections of lixisenatide in different doses (0, 5, 15 and 20 μg) two hours prior to the ingestion of a meal mixed with acetaminophen. Glucose appearance in blood from the ingested meal was assessed through acetaminophen blood concentrations. Fitted acetaminophen concentrations are shown in Fig. 4, and the associated parameters are given in Table. 4.

$$\dot{Q}_{sto}(t) = -k_{empt} \cdot Q_{sto}(t) + ACT(t) \tag{14}$$

$$\dot{Q}_{gut}(t) = -k_{abs} \cdot Q_{gut}(t) + k_{empt} \cdot Q_{sto}(t) \tag{15}$$

$$\dot{Acet}_p(t) = -k_{dep} \cdot Acet_p(t) + K \cdot k_{abs} \cdot Q_{gut}(t) \tag{16}$$

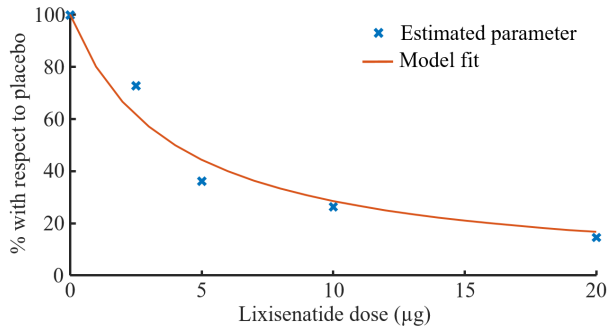

Fig. 5. Average evolution of k_{abs} with lixisenatide dose

where, $ACT(mg/min)$ represents the acetaminophen ingestion; Q_{sto} and $Q_{gut}(mg)$ the acetaminophen mass in stomach and gut; $Acet_p(\mu mol/l)$, acetaminophen blood concentration; k_{empt}, k_{abs}, $k_{dep}(min^{-1})$, exchange and depletion rates and $K(\mu mol/mg/l)$, a gain representing volume of distribution and change of unit.

2.2 Sub-Models Integration into the pre-existing Platform

Sub-model Parameter dependence on Lixisenatide In all models presented above, estimated parameters were assumed to be distributed either normally or log-normally, making the estimated averages and covariance matrices sufficient to completely describe their distributions. They are determined for with and without lixisenatide and for different lixisenatide doses. Any significant differences in parameters between with and without lixisenatide are assumed to follow a drift depending on lixisenatide concentration described by the relationship given in Eq.(17) and shown Fig. 5. Parameter p_1 is estimated from the extent of the drift and p_2 is identified using data from the multi-dose study Becker RH (2015).

$$e\% = 1 + p_1 \frac{p_2 \cdot L_p}{1 + p_2 \cdot L_p} \tag{17}$$

where $e\%$ is the multiplicative drift; p_1 (%), the saturated change; $p_2(mL/pg)$, the Michaelis-Menten parameter and $L_p(\mu g)$ the lixisenatide dose. Described sub-models were integrated into the simulation platform presented in Dalla Man C (2007) as illustrated by Fig. 6. Although the augmented platform models are all determined, before running experimental studies, different covariance matrices from identified sub-models and the pre-existing simulation platform must be merged.

Estimating Joint Parameter Distribution The joint parameter distribution is determined by fitting simulated traces to continuous glucose measurements (CGM) from Bergenstal RM (2017) while imposing Bayesian priors derived from sub-models and original platform parameter distributions. The 24-week study allowed the collection of 14 days of CGM data both before and after introducing lixisenatide in 69 subjects with T2DM. In the study data, no information on mealtime and amount was available. As a result, meals were detected from CGM traces with a threshold-based method using first and second CGM derivatives. Meal amounts are further optimized, concurrently with the parameter joint distribution, imposing tight Bayesian priors on total daily meal size reported in Saslow LR (2014). Parameters and meals were estimated

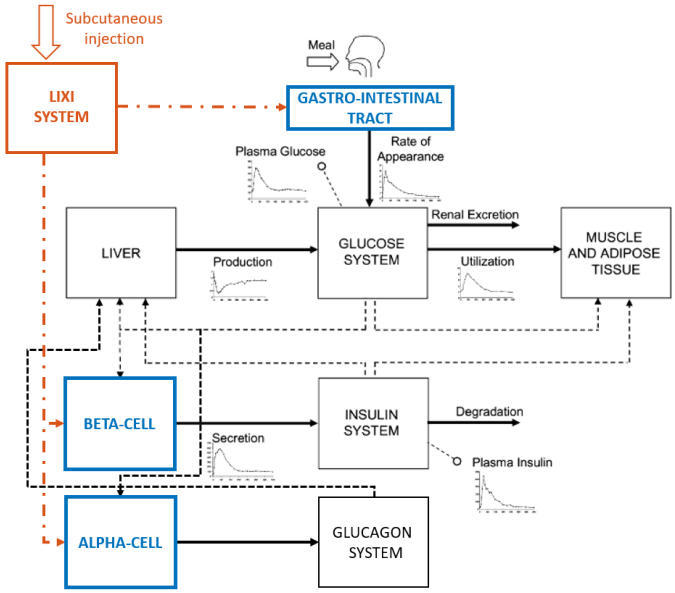

Fig. 6. Augmented simulation platform. Modified from Dalla Man C (2007).

using a multi-initialization optimization process, sampling from the prior distributions. Maximum a posterior estimator was obtained by minimizing the following cost function:

$$\begin{aligned} J(p) = (G_{mes} - G(p)) \cdot W^{-1} \cdot (G_{mes} - G(p)) \\ + (p - p_{prior}) \cdot R^{-1} \cdot (p - p_{prior}) \end{aligned} \tag{18}$$

here, $G_{mes}(mg/dl)$ is a vector of CGM measurements; $G(p)(mg/dl)$, a vector of simulated glucose; W, the covariance matrix of CGM measurements; p, the vector of estimated parameters of both models and meals; p_{prior} and R, the average and covariance matrix from prior distributions. A trust reflective region algorithm was used for the optimization procedure. For each patient, the best fit of each day is kept to build a personalized parameter distribution (assumed normal or log-normal). The fitting process is then repeated, using the personalized parameter distribution as a prior and its average as initial condition for all days. Meal amounts are simultaneously estimated in both of these optimization steps. A representative result of this fitting procedure by day is given in Fig. 7.

The rationale behind a two-step optimization using personalized priors is to account for variability in individual patients' responses to therapy and behaviors across days. Imposing a personalized prior will allow some, although limited variance within-subject (across days) compared to variance within population (across subjects). These personalized parameter distributions then form the joint parameter distribution matrices, allowing for some correlation between parameters originating from independently identified models. We refer to this joint distribution as *in-silico* population.

2.3 Validation of the new Simulation Platform using Drug Efficacy Trials

The *in-silico* population was validated on an independent data set previously unseen by the built models. The data were collected in a large study of 736 insulin-treated patients randomized 1:1 to insulin iGlar/GLP1-

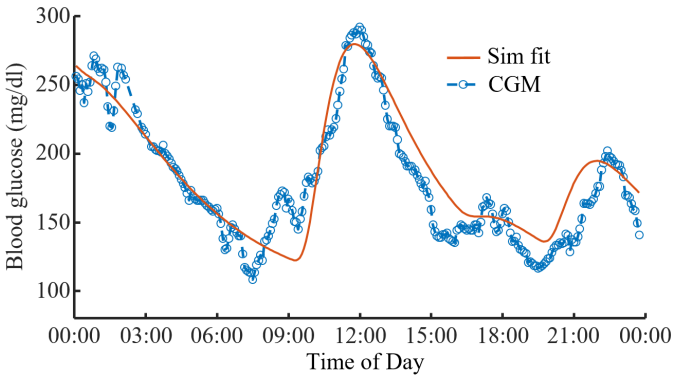

Fig. 7. A representative example of one day CGM data fit to type 2 diabetes simulator generated trace.

RA combination or iGlar only, administered once daily in the morning within an hour before breakfast Aroda VR (2016). To assess the quality of glucose control, seven-point self-monitored BG (SMBG) profiles - BG measurements performed prior to, and two hours after, each main meal (breakfast, lunch, and dinner) and at bedtime - were obtained at baseline (before the studied intervention) and after 26 weeks of intervention (endpoint).

A cohort of 100 virtual subjects was constructed by sampling from the *in-silico* population. Simulated subjects were randomized 1:1 to receive either insulin glargine or the combination during the simulated trial; to match the previous protocol, injections were simulated within an hour of breakfast every day and titrated to match average doses of the study Aroda VR (2016). As no meal information was available in the collected dataset, we built a probabilistic meal-generator from Bergenstal RM (2017) to construct the meal sequence in the simulated trial. From the simulation BG output, baseline and endpoint seven-point profiles were extracted and compared against the ones given by the validation study data Aroda VR (2016) with a two-sample χ^2 test and the null hypothesis H_0 : the two samples are from the same distribution.

2.4 In-silico Study of the Optimal iGlar & GLP1-RA combination Administration Time

A cohort of 100 subjects with T2DM was sampled from the *in-silico* population. Daily administration of the combination drug was simulated after titration. The same cohort underwent two different studies: one with pre-breakfast injections and one with pre-dinner ones. Identical meals, generated by the probabilistic meal generator were given across studies.

3. RESULTS AND DISCUSSIONS

3.1 Sub-Models Identification

Fits of identified sub-models on average data and associated parameters have already been presented above. All measurement errors were assumed independent, normally distributed with 10% coefficient of variation. Average weighted squared residuals for all fits were < 1 and all contained the x-axis in the interval mean $\pm$ SD, which was considered satisfactory. In addition, all CV of

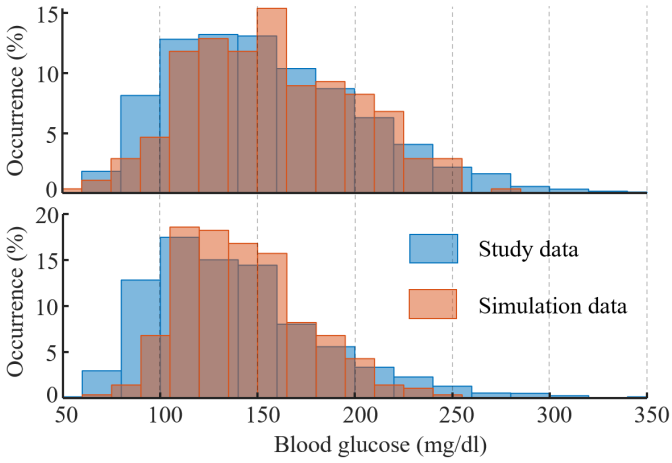

Fig. 8. Validation of the built platform against the Lixilan-L study Aroda VR (2016). Top panel displays SMBG distributions at baseline, and bottom panel, SMBG distributions after stabilisation of combination treatment.

parameter estimates were below 100%. Evolution of the parameter estimates with and without lixisenatide are in line with what is found in the literature: lixisenatide increases glucagon inhibition (reflected as increase in σ in Table 3); augments insulin secretion both in a glucose-dependent fashion (reflected as an increase in β and K in Table 2); and slows gastric emptying (reflected as decreases in k_{empt} and k_{abs} in Table 4) Drucker DJ (2006).

The use of acetaminophen as a marker of gastric emptying has been criticized for its lack of accuracy in the following papers Bartholomé R (2015). This and the fact that in the gastric emptying study, concentration measurements stop 300 min after the food intake (too early to observe the decay in acetaminophen concentration) should be noted as a limitation of the presented research. Additionally, the relationship between parameter distributions and lixisenatide concentrations were all assumed to be the same as Eq. 17, as observed in the multi-dose study Becker RH (2015). However, no published study on lixisenatide dynamics are available for more precise modeling.

3.2 Validation of In-silico Population

Clinical and in-silico SMBG histograms are compared in Fig. 8. In both cases, the variances of distributions decrease between baselines and endpoints, with an average shift towards lower (healthier) glycemic values ($\approx$ 100 mg/dl). Two sample χ^2 test between clinical and in-silico SMBG distributions for both baseline and endpoint did not reject the null hypothesis at 95% confidence level, demonstrating the similarity in glucose profiles and validating the ability of the built platform to accurately predict clinical glucose outcomes. Although the potential interaction between iGlar and lixisenatide was neglected, it does not seem to hurt the glucose prediction.

3.3 Optimal Administration Time

In-silico population median, quartiles, 10th and 90th percentiles of simulated BG with the combination being administrated before breakfast vs before dinner is shown

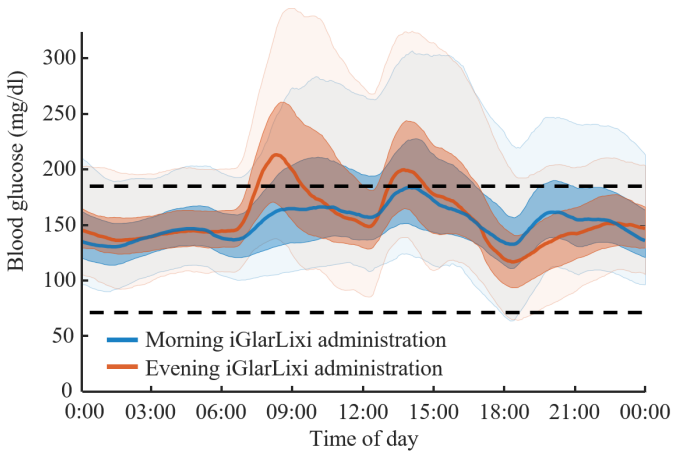

Fig. 9. Daily in-silico population simulated blood glucose median, quartiles, 10th and 90th percentiles. The 70 - 180 mg/dl range bounded by dashed black lines is considered healthy.

Fig. 9. Decrease of post-breakfast and post-lunch hyperglycemia is achieved by the breakfast group compared to the dinner group while a further decrease of post-dinner hyperglycemia is achieved by the dinner group. No important increase in hypoglycemia is seen in either group. Understandably, these results are dependent on meal eating habit, and further investigation is required to quantify its impact.

4. CONCLUSION

A methodology for integrating pharmacokinetics (PK) and pharmacodynamics (PD) models of new drugs into a pre-existing type 2 diabetes simulation platform for the determination of optimal therapy dosing and timing was proposed. The PK-PD models of the GLP1-RA lixisenatide were built and identified using multiple data sets derived from blood samples collected during clinical trials on a limited amount of subjects Becker RH (2014), Becker RH (2015). These sub-models were then integrated into the pre-existing type 2 diabetic simulation platform Dalla Man C (2007), and the joint *in-silico* population parameter distributions of the unified model was tuned fitting CGM data Bergenstal RM (2017) with Bayesian priors. The resulting platform was validated with sparse BG measurements from an independent larger study Aroda VR (2016). *In-silico* subjects, sampled from the newly identified *in-silico* population, underwent the same study design as Aroda VR (2016). Resulting distributions of simulated glycemic outcomes were non-significantly different from the ones of the clinical study both for baseline and endpoint. The augmented type 2 diabetes simulation platform was then used to determine the best administration time of the combination drug. In this *in-silico* experiment, it appears that administration before breakfast is beneficial for post-breakfast and lunch hyperglycemia control compared to an evening administration.

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