Generating T1DM Virtual Patients for In Silico Clinical Trials via AI-Guided Statistical Model Checking

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Abstract. The availability of a representative population of virtual patients, *i.e.*, a population large enough to represent all relevant human patient behaviours, is a *key enabler* for the design of In Silico Clinical Trials (ISCTs), that is trials following simulation-based approaches for the safety and efficacy assessment of pharmacological treatments and biomedical devices. This involves the development of Virtual Physiological Human (VPH) models able to represent the *whole* phenotypes spectrum of the human physiology of interest. Usually, such models are open-loop models, *i.e.*, their behaviour depends also on exogenous inputs (such as, *e.g.*, pharmacological drugs).

In this paper, we propose a methodology to convert an open-loop VPH model into a *closed-loop* model. As a case study, we apply our methodology to a state-of-the-art VPH model defining the human glucose regulation system of individuals with Type 1 Diabetes Mellitus (T1DM), and show how we generate a representative population of T1DM virtual patients.

Keywords: In Silico Clinical Trials · VPH models · AI Global search · Model Checking · Simulation.

1 Introduction

The advance of biomedical engineering has promoted the design of new, revolutionary, biomedical devices. The purpose of such devices is to improve the quality of life in different kinds of patients by making the treatments they follow completely, or partially, automated. An In Silico Clinical Trial (ISCT), in opposition to the more traditional *in vivo* clinical trial, is used in the development of products such as drugs and biomedical devices. More specifically, a clinical trial is performed by means of computer simulations over a population of virtual patients (see, *e.g.*, http://paeon.di.uniroma1.it).

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1.1 Motivation

In order to generate virtual patients, a Virtual Physiological Human (VPH) model is required. A VPH model is a mathematical *mechanistic* model of the (patho-) physiology of interest and reactions to drugs (Pharmaco-Kinetics/Dynamics, PKPD) in the form of a parametric system of, *e.g.*, Ordinary Differential Equations (ODEs). Many of the parameters in the system usually model inter-subject variability, which means that different assignments to these parameters determine the behaviour of different patients. Unfortunately, many assignment to the parameters can lead to model evolutions that are not coherent with the laws of biology. As a consequence, the population of virtual patients can not be built by picking assignments arbitrarily, but a smart search in the parameter space is needed.

Given a VPH model M, we can define the corresponding population of Virtual Patients (VPs) as the set $S = \{\lambda | \lambda$ is an assignment to the parameters in M and λ defines a behaviour that is coherent with the laws of biology$\}$ [56].

Thanks to the use of *in silico* clinical trials, risky and costly experiments on humans can be reduced and postponed to when a deeper knowledge of the side-effects of the product has been acquired (http://paeon.di.uniroma1.it). ISCTs basically entail the following steps. First, generate a set of VPs whose predictions are in agreement with (patho-) physiology, PKPD, and *in vivo* clinical data. Second, use the above *in vivo* validated VPs to assess, through simulation, safety and efficacy of a candidate drug or biomedical device.

1.2 Contribution

In this paper, we consider, as a case study, patients with Type 1 Diabetes Mellitus (T1DM), and generate a population of VPs by exploiting the VP generator developed by the Model Checking Laboratory (MCLab) (http://mclab.di.uniroma1.it) and originally presented in [56,41]. This phase is preliminary to the verification of safety-critical devices such as artificial pancreas devices used for blood glucose levels monitoring and regulation.

For our case study, we implemented the Medtronic VPH model of the human glucose regulation system [22] into Modelica. However, the Medtronic VPH model could not be used directly within our VP generator, because it requires, as mandatory external inputs, the time functions defining the daily carbohydrates intake and insulin administration. Indeed, without such inputs, the model time evolutions are not significant.

To overcome this obstruction, we set up a methodology which allows us to use our VP generator tool [56,41] also in the case of VPH models that require external inputs (*open-loop* VPH models). In particular, we extend the Medtronic VPH model with a new module that, given some information on the patient (*e.g.*, their body weight), generates (using standardised formulas) the amounts of carbohydrates and insulin that are recommended for that patient. As the extended model is *closed-loop* (*i.e.*, it does not require any external input), we

could finally use our VP generator to compute a population of T1DM VPs. The generation of the population is a time consuming activity requiring clever AI-based exploration strategies of the search space on High Performance Computing (HPC) resources.

1.3 Paper Outline

The paper is organised as follows. After recalling the state of the art on VPH models and ISCTs (Section 2), in Section 3 we introduce the Medtronic VPH model of the human glucose regulation system and outline how we implemented it in Modelica. Then, in Section 4 we describe how we extended our VPH model to enable the computation of a representative population of T1DM VPs, by computing and providing proper input patterns for carbohydrates intake and insulin injections. Finally, in Section 5 we analyse the results of our computation and in Section 6 we draw conclusions.

2 State of the art

A key enabler to carry out an ISCT is the availability of a suitable cohort of VPs. Such a cohort must be *complete*, *i.e.*, large enough to represent all relevant human patient phenotypes. In hormonal regulatory systems (as is our case), the whole spectrum of possible phenotypes can be quite large, since such systems typically occur within a complex network of endocrinological, neurological, and psychological factors (see, *e.g.*, [18,27,26]). On the other hand, we also need such a cohort of VPs to be *minimal*, *i.e.*, to not include behaviours that are not compatible with the human (patho-) physiology of interest.

It is worth noting that achieving simultaneously completeness and minimality is presently out of reach. For this reason, usually, completeness is privileged. This way, an adequate *in silico* representation of all human patient phenotypes is guaranteed.

In the following we briefly review the state of the art on VPs generation methods.

VPH models are usually developed using medical knowledge from the literature and from pathway databases such as KEGG (Kyoto Encyclopedia of Genes and Genomes) or Reactome. Open formats, such as the Systems Biology Markup Language (SBML), allow exchange of computational models across different platforms and their integration within open-standard general-purpose simulation ecosystems [30].

Unfortunately, physiology knowledge is often qualitative. As a result, the model behaviour is hard to define and is not uniquely determined. To overcome such an obstacle, many qualitative as well as quantitative approaches have been devised. An overview is in [48].

Qualitative approaches, often referred to as *logic based*, discretise the values of interest. For example, using a Boolean approach, a gene up-regulation (respectively down-regulation) may be represented with a logical 1 (respectively 0).

Boolean models have been widely studied (see, *e.g.*, [20] and citations thereof). Logical models are very useful for a qualitative analysis, but are quite difficult to use within a compositional framework where quantitative models from physiology or pharmacology are present. Since in an ISCT quantitative aspects are extremely relevant (*e.g.*, drug dosage) we will focus on quantitative models.

Quantitative models typically focus on representing dynamics of chemical reactions through ODEs with stoichiometric parameters and reaction rates estimated from clinical data using model identification techniques, as, *e.g.*, in [58]. Such models are typically used to support ISCTs, as, *e.g.*, in [29]. The main obstacle to overcome in using quantitative models is the lack of knowledge about the values for their parameters. In fact, very few model parameter values can be estimated using clinical data (see, *e.g.*, [55] for a survey). As a result, most parameter values have to be estimated through computational methods, typically using *model identification* techniques (see, *e.g.*, [60,58]).

In such a setting, two approaches are typically used, respectively based on *optimisation* and *statistical* techniques.

Both global and local *optimisation*-based approaches, relying on AI as well as on numerical methods, have been widely studied. Global optimisation–based approaches are computationally heavy, however convergence is guaranteed to a global optimum (see, *e.g.*, [31,59,46]). On the other hand, local optimisation approaches (*e.g.*, [32,38,42]) are in general computationally lighter than global ones, but convergence is only guaranteed towards a local optimum (*e.g.*, [23,24,44]). An in-depth comparison among the two approaches can be found in [47], whereas an example of the use of AI-based optimisation techniques for computing personalised treatments is presented in [34].

Typically, both global as well as local optimisation approaches rely on model identifiability, *i.e.*, different values for the model parameters lead to different model behaviours (see, *e.g.*, [28]). In such a case, different model identification techniques can be used. Examples are in [10,49,12,57,1,53].

When clinical data are scarce, *e.g.*, when clinical assays are costly, risky and invasive, identification approaches can be applied by averaging data coming from different patients. However, in this case the resulting parameter value only yields an *inter-patient* model behaviour (see, *e.g.*, [50]).

Since the goal of the above mentioned approaches is to generate a model parameter value that fits available experimental data, a huge amount of data per patient is needed in order to generate a virtual population that is representative of all human phenotypes. As a result, generating a complete set of VPs using model identification techniques would require considering a large amount of patients (ideally at least one for each relevant phenotype) along with a huge amount of clinical data for each of such patients. Unfortunately, this is exactly one of the obstacles ISCTs aim at overcoming. Thus, while model identification techniques are essential to validate models against clinical data and to develop *patient-specific* models, they can be hardly used to generate a complete set of VPs.

Moreover, VPH models are often globally or partially unidentifiable, *i.e.*, wide ranges of parameter values lead to very similar model behaviours (see, *e.g.*, [8]). However, being able to generate VPs (*i.e.*, parameter values) which yield clearly distinguishable model behaviours is of crucial importance for ISCTs.

Statistical approaches are also widely used. In such approaches a parameter probability distribution, rather than a single value, is inferred (see, *e.g.*, [19,25,52]). They are typically used for physiology-based PKPD models (see, *e.g.*, [51]), *i.e.*, quantitative VP models where parameter values are measurable physiological quantities (such as blood flow, organ volumes, etc). Unfortunately, most VP models have hard-to-measure parameters such as stoichiometric constants and reaction rates. In fact, probability distribution functions for them are typically unknown.

Limited knowledge about VPH model parameters calls for methods that handle models whose parameters are partially unknown. This guarantees completeness, possibly at the price of minimality. In other words, we use an over-approximation of the set of all *physiologically admissible* (*i.e.*, whose behaviour is plausible with respect to physiology) VPs.

Since model-checking techniques enable exploration of all possible behaviours of a model, it is not surprising that such approaches have been investigated in order to generate VPs for both qualitative as well as quantitative VPH models. In particular, for qualitative models (*e.g.*, Boolean models) the problem of finding parameter values yielding a biological meaningful behaviour is reduced to the problem of finding stable states of the model, *i.e.*, attractors. In such a setting, symbolic model checking is widely used (see, *e.g.*, [45,15,2,21]). There, *physiological admissibility* can be defined using a *temporal logic*, such as CTL or LTL. Some examples are in [7,6,5,13,4] or in [17], where a probabilistic model-checking approach is used.

Unfortunately, even using model approximation techniques like those in [3,43], the above mentioned approaches cannot be used to generate VPs from quantitative ODE-based models, *i.e.*, those sought to support ISCTs. Indeed, in such a setting only simulation-based approaches are viable. This suggests to investigate use of model checking–driven simulation-based techniques to support VP generation.

3 Virtual Physiological Human Model of the Human Glucose Regulation System

VPH models of human glucose regulation give a quantitative description of pancreatic hormones-glucose interactions. These models can be used to predict the evolution of the species of interest (*e.g.*, blood glucose concentration) under certain conditions (*e.g.*, the amount of ingested carbohydrates), and are usually validated by comparing the results with data collected during clinical trials. In this paper, we use the Medtronic VPH model described in [22]. This model is simpler than the models in [11,9], but not less effective in predicting the evolution of blood glucose and plasma insulin concentrations.

We implemented the Medtronic VPH model using the Modelica language, by organising it in 4 compartments: glucose, insulin action, gastrointestinal absorption, subcutaneous insulin absorption. Also, we validated our Modelica implementation by comparing our simulation outcomes with the results shown in [22]. In order to collect data comparable to those available in that paper, we used the parameter values estimated by the authors and supplied the subjects with the same meals and the same insulin dosage specified by the protocol of the clinical trial [54] (*i.e.*, the same input used in [22]). As an example, Figure 1 shows the curves generated by our experiments for Subject 7, which are to be compared to those provided in [22]. Our simulation outcome is very similar to the model fit curves provided in that paper. There are indeed minor numerical differences, which are however justified by the fact that the glucose profile in [22] was fit using *actually measured* plasma insulin profiles, and *not* the model-predicted amounts, as obtained from the corresponding equations. This of course leads to limited error accumulation. Overall, the high qualitative similarity of *all* our predictions with respect to the corresponding model fit curves of [22] allows us to regard our Modelica porting of the Medtronic VPH model correct.

4 Generating T1DM Virtual Patients

In order to study the behaviour of the patients, an individualisable VPH model in an executable form is fundamental. Parametric ODE systems are usually employed to define individualisable VPH models. Changes in the parameter values entail the definition of patients with different behaviours. One way to generate VPs could be to instantiate the VPH model by choosing the parameter values at random. Unfortunately, this strategy usually leads to modelling the behaviour of a patient which is incompatible with respect to the physiological knowledge, *i.e.*, is not Biologically Admissible (BA). Behaviours that are not BA are typically obtained by choosing parameter values ignoring inter-dependency constraints among them. This might happen since such constraints are usually not explicitly known [56].

In order to compute a population of patients representative of the real population, we need to define a *global search* strategy that filters out all the virtual subjects with a non-BA behaviour. The criterion proposed in [56] defines the concept of BA behaviour as a behaviour which is *similar enough* to that of a known real patient. Our algorithm performs an AI-guided randomised search in the space of the model parameters, building on our Model Checking tools in, *e.g.*, [35,16,36,37,33]. It is important to note that, in most cases, the size of the parameter space is such that, even if we discretise it, an exhaustive search would be infeasible. To counteract this issue, our algorithm leverages on statistical hypothesis rejection approaches (see, *e.g.*, [14,40,39]), thus computing a set of BA virtual patients which is complete with an arbitrarily high statistical confidence.
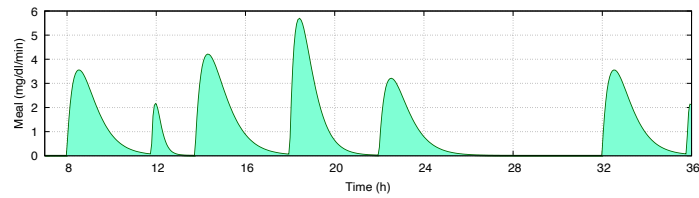
In the following, we describe the tool we used to generate the population of patients with T1DM (Section 4.1), and present a new methodology that applies in the case of VPH models that require inputs (Section 4.2).
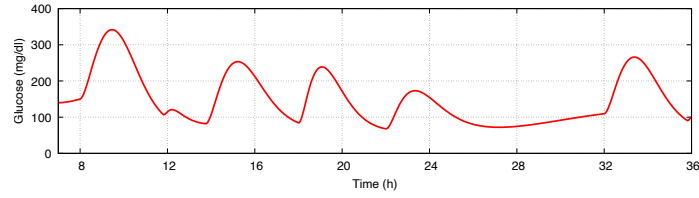
(a) Glucose
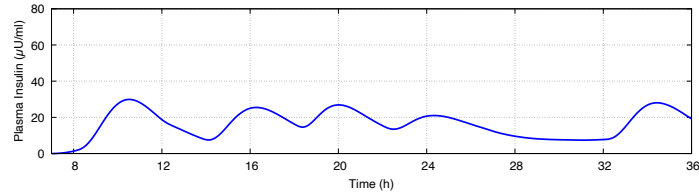
(b) Insulin

(c) Glucose plasma appearance

Fig. 1: Predictions of our Modelica model on the parameter assignment defining Subject 7 in [22].

4.1 VP Generator

We compute the population of T1DM patients using the tool presented in [56,41], which combines AI-based global search and statistical model checking. The system takes as input a VPH model in the form of a parametric ODE system and reference values for the parameter vector (*i.e.*, the parameter values that model the behaviour of one, real, patient), and computes the set of the parameter values that lead to time evolutions of the species of interest (*e.g.*, in our case study, blood glucose concentration and insulin among the others) that are *qualitatively similar* to those of the reference patient. This is done by computing a set S of BA parameter values (*i.e.*, the population of virtual patients) which is complete with an arbitrarily high statistical confidence [56].

In order to identify the elements of S, the tool iteratively selects a random parameter λ (*i.e.*, the model parameter vector) from the search space and, if λ passes the BA-test, adds λ to S.

Search effectiveness is achieved by sampling the parameter space using a (AI-based) strategy that conjugates *exploration* of the search space and *exploitation* of the knowledge acquired from the VPs already generated.

Search efficiency is achieved by using a HPC infrastructure in a master-slave architecture, where a single master process (Orchestrator) is responsible of intelligent sampling, storage of set S, and bookkeeping, and many slaves (BA Verifiers) are devoted to simulation of candidate VPs and assessment of their admissibility [41].

Assessment of biological admissibility (BA) of a parameter vector λ is performed by checking whether the predicted time evolution obtained using λ is qualitatively similar to the evolution obtained using the reference parameter vector λ_0. The concept of similarity is quantified by the use of signal processing Key Performance Indicators (KPIs) such as cross-correlation, normalised average differences, and normalised squared norm differences [56].

The algorithm termination condition is based on statistical hypothesis rejection techniques. Namely, given two user-defined values δ (*confidence ratio*) and ε (*error bound*) in $(0, 1)$, the algorithm, at any state of the search (when the current population is stored in set S), formulates the following *null hypothesis* $H_0(S)$: "the probability to find, by further sampling, a VP not in S is at least ε". When the algorithm *fails* to find such a new VP within $N = \left\lceil \frac{\log(\delta)}{\log(1-\varepsilon)} \right\rceil$ consecutive attempts, it rejects the current null hypothesis $H_0(S)$, thus inferring that the probability to find, by further sampling, a new VP is actually $< \varepsilon$, and terminates. Our algorithm implements a *one-sided error procedure*, in that it might reject $H_0(S)$ when it holds. However, the probability of committing such an error (which is called a *type-II error*) is upper-bounded by δ [56].

4.2 A New Methodology for Open VPH Models

In this section, we present a new methodology to exploit our VP generator, even in the presence of open VPH models, *i.e.*, models that require external inputs. Then, we apply such a methodology to generate a population of VPs for the Medtronic VPH model.

To do so, we need to take into account the effect of inputs when performing the BA-test. First, we define a portfolio U of representative input patterns suitable for the open VPH model at hand, M. Then, for each input pattern $u \in U$, we instantiate the given VPH model by feeding it with u. This leads to $|U|$ instances of the model M, denoted m_u, $u \in U$. Last, we create a new VPH model, M', defined as the composition of such instances. Model M' is closed, *i.e.*, no external inputs are required. In this way, by giving M' as input to the tool, the BA-test implicitly checks whether the behaviour entailed by a parameter vector λ is qualitatively similar to the behaviour entailed by λ_0, for *all* model instances m_u, $u \in U$.

Input Generators. The input to the model are the daily dose of insulin and the daily amount of ingested carbohydrates, together with meal times and time-

of-maximum appearance rate of glucose. In order to enable the simulation of the behaviour of T1DM VPs, we define the two input generators, describing daily dose of injected insulin and the amount of daily ingested carbohydrates, respectively.

Insulin Dose Generator. In order to get analysable results, we need an element in the model with the capability to supply each patient with the recommended dose of insulin. According to the Diabetes Teaching Center at the University of California (https://dtc.ucsf.edu), the correct dose can be calculated with the following formula:

$$\text{dose} = 0.55 \times \text{body\_weight} \times \text{insulin\_factor}$$

where dose is measured in units of insulin per day (U/day) and body_weight is in kilograms. Therefore, we introduce the body weight in the set of patient-specific parameters. Moreover, to enable the study of behaviour of subjects who received too much or too little insulin, we add a multiplication factor, namely the insulin_factor, having its nominal value equal to 1.

Meals Generator. Our meals generator is based on the assumption that a subject with T1DM has to follow a balanced diet, or at least does not eat an amount of carbohydrates which significantly deviates from the recommended dose. For this reason, we feed the VPs with 5 meals a day, each one at a fixed time.

The time-of-maximum appearance rate of glucose (τ_m) characterising a meal depends on the complexity of the ingested carbohydrates, and can vary from 10 minutes to more than 2 hours. We set τ_m to a different fixed value for each meal, and we add a multiplication factor in order to model inter-subject variability of time-of-maximum glucose absorption.

Finally, we define the percentage of carbohydrates in each meal as follows.

Our meals generator includes three different functions for calculating the recommended daily calories, and when invoked chooses the best (*i.e.*, more precise) formula according to the available information about the patient. The simplest function in the generator has been proposed by Harvard Medical School (https://hms.harvard.edu) and takes in input only the body weight and the level of physical activity (*e.g.*, sedentary, moderate, active) of the subject.

When further information, such as age and sex, are available, the generator computes the daily calories amount using the World Health Organization (http://www.who.int/en) equation.

The most precise formula in our meals generator is known as the Mifflin - St. Jeor equation and requires 5 inputs: body weight, level of physical activity, age, sex and height. The Mifflin - St. Jeor equation was judged by the American Dietetic Association as the most reliable formula in predicting actual energy expenditure.

Since subjects with diabetes are suggested to consume carbohydrates in the amount of 45–65% of the total calories intake (as estimated by the American Diabetes Association, http://www.diabetes.org) and 1 gram of carbohydrates

provides 4 kCal, we define the daily amount of carbohydrates using the following equation:

$$\text{daily\_carbos} = \frac{\text{carbo\_factor} \times 55 \times \text{daily\_calories}}{400}$$

In the equation above, carbo_factor is used to alter the amount of carbohydrates provided to subjects in order to simulate the behaviour of over- and under-eating patients.

Data. In order to provide a reference parameter vector value, λ_0, (*i.e.*, a reference BA VP) to our VP generator, we use the values of the subjects shown in [22]. For each component of the model parameter vector, we define a discrete domain (along the lines of [56]). This is not a rough approximation, since small deviations in values are meaningless from a biological point of view [41].

According to our methodology presented above, to perform a closed-loop simulation of the model we combine the VPH model together with our input generator. In particular, we define a portfolio of inputs, U, containing the following three elements:

Input 1 The recommended amount of carbohydrates and the recommended insulin dose (with respect to the patient in exam).

Input 2 An excessive amount of carbohydrates and an insufficient insulin dose (with respect to the patient in exam).

Input 3 An insufficient amount of carbohydrates and an excessive insulin dose (with respect to the patient in exam).
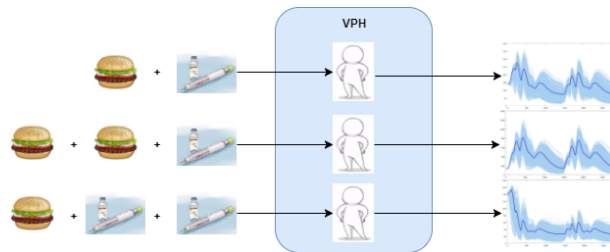

Fig. 2: Medtronic VPH model extended with our input generator.

In order to compute a population of VPs whose admissibility condition is based on qualitative similarity with respect to the reference patient under all our inputs (*i.e.*, normal, hyperglycemic, and hypoglycemic conditions), we define an outer Modelica model which encapsulates three instances of the Medtronic VPH model, one for each input. The three Medtronic model instances where configured with insulin_factor and patient_carbo_factor set to, respectively: $(1, 1)$ (normal conditions); $(0.5, 3)$ (hyperglycemic conditions); $(3, 0.5)$ (hypoglycemic conditions). Figure 2 shows our extended Medtronic VPH model.

5 Results

In this section we show the outcome of the execution of our VP generator on the input described in Section 3. Simulations have been executed on 16 nodes, each with 16 cores, of partition A1 of the Marconi CINECA cluster (located in Bologna, Italy). We set both our confidence ratio δ and error bound ε to 10^{-3}. In other words, our algorithm terminates when, with statistical confidence at least 99.9%, the probability to find, via further sampling, a *new* VP is less than 0.1%. The overall computation took 5 days.

The importance of the obtained computed population resides in its size. For example, the population computed using Subject 7 from [22] as the initial reference comprises 16 082 all-different VPs. This has to be contrasted with the size of the cohorts of *in vivo* clinical trials, which typically involve at most a few dozens of volunteers (see, for example, [11,54]).
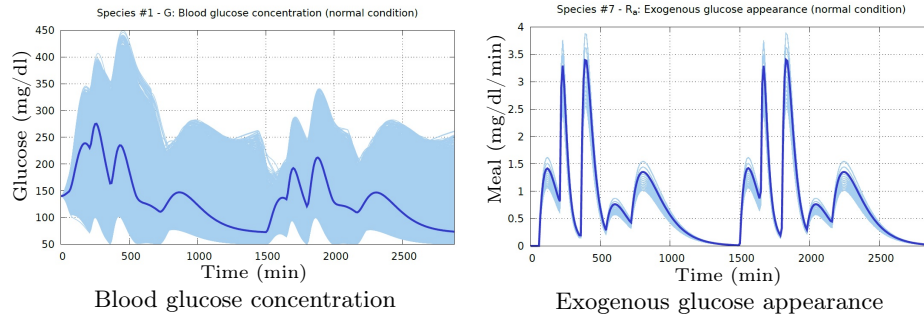
Figure 3 shows the time evolution of blood glucose concentration (left) and exogenous glucose appearance (right) in the three different scenarios (*i.e.*, normal, hyperglycemic, and hypoglycemic conditions) in the VPs found by our generator using Subject 7 as the initial reference. It can be seen that our computed population covers a wide spectrum of behaviours, with glucose concentrations assuming values in a much larger range than Subject 7 (physiological thresholds are part of our tool configuration), although keeping a clear qualitative similarity with respect to the time evolutions of the reference behaviour. On the other hand, excursions of the exogenous glucose appearance in the population (right plots of Figure 3) are way more limited. This is expected, as our input generator was indeed explicitly designed to generate input patterns properly *individualised* on the needs of each of the VPs (*e.g.*, carbohydrates intake computation considers information such as the body weight of each VP). Populations of VPs generated starting from the other subjects of [22] have a similar size and outlook.
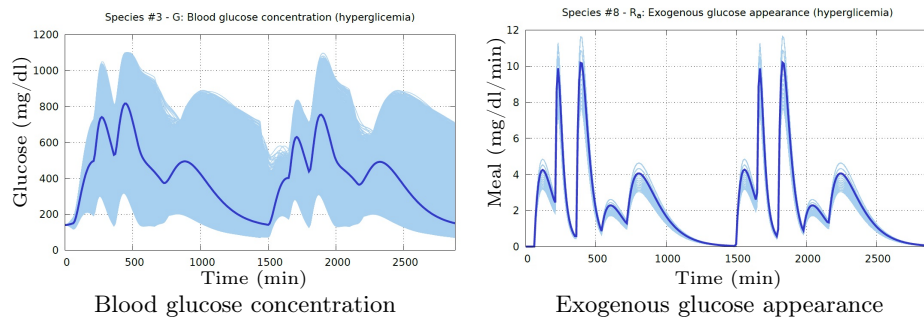
6 Conclusions

To make ISCTs effective, the first step to perform is the generation of a representative population of VPs, whose predictions are in agreement with (patho-) physiology, PKPD, and *in vivo* clinical data.

In this paper, we consider, as a case study, patients with T1DM, and compute a representative population of VPs exploiting the Medtronic VPH model of the glucose regulation mechanism [22] and the VP generation tool originally presented in [56,41]. Our tool leverages AI-driven global search and Statistical Model Checking techniques to deal with the huge search space stemming from the parameter space of the input VPH model.
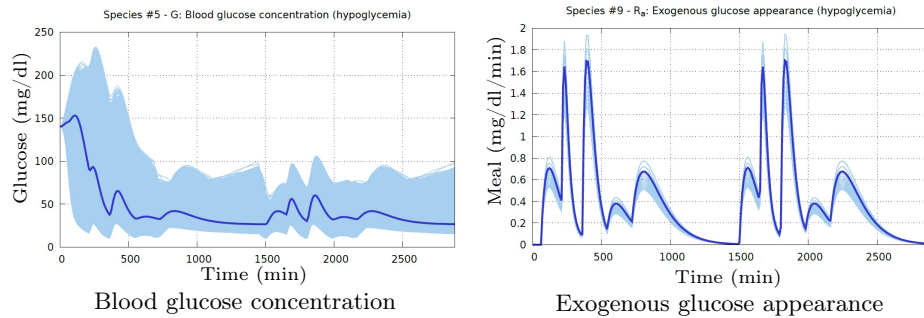
Since the Medtronic VPH model requires a time profile for carbohydrates intake and insulin injection as inputs, we equipped it with a new module that produces such inputs in a principled-yet-individualised way, by defining both normal conditions (proper carbohydrates and proper insulin intake for the VP

Blood glucose concentration   Exogenous glucose appearance

Normal conditions

Blood glucose concentration   Exogenous glucose appearance

Hyperglycemic conditions

Blood glucose concentration   Exogenous glucose appearance

Hypoglycemic conditions

Fig. 3: Blood glucose concentration and exogenous glucose appearance in normal, hyperglycemic, and hypoglycemic conditions for the 16 082 VPs found by our VP generator using Subject 7 from [22] as initial reference.

at hand) and pathological conditions (hyperglycaemic and hypoglycaemic conditions). Our approach is general, as it can be employed to transform any open-loop VPH model (*i.e.*, a model requiring inputs to function properly) into a closed-loop model.

The computed population of VPs defines a starting point for ISCTs of new insulin-injection patterns as well as new medical devices (*e.g.*, autonomous insulin pumps or artificial pancreas devices).

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