Patient-Specific Models from Inter-Patient Biological Models and Clinical Records

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***Abstract*—One of the main goals of systems biology models in a health-care context is to *individualise* models in order to compute patient-specific predictions for the time evolution of species (e.g., hormones) concentrations. In this paper we present a statistical model checking based approach that, given an *inter-patient* model and a few clinical measurements, computes a value for the model parameter vector (*model individualisation*) that, with high confidence, is a global minimum for the function evaluating the mismatch between the model predictions and the available measurements. We evaluate effectiveness of the proposed approach by presenting experimental results on using the *GynCycle* model (describing the feedback mechanisms regulating a number of reproductive hormones) to compute patient-specific predictions for the time evolution of blood concentrations of E2 (Estradiol), P4 (Progesterone), FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone) after a certain number of clinical measurements.**

I. Introduction

Systems biology models aim at providing quantitative information about time evolution of biological species. Depending on the system at hand, many modelling approaches are currently investigated. For example, see [21], [19] for an overview on discrete as well as continuous modelling approaches, and [43] for a survey on stochastic modelling approaches. In this paper we focus on biological networks modelled with a system of *Ordinary Differential Equations (ODEs)* depending on a set of parameters as in, e.g., [33], [44], [36].

A. Motivations

One of the main goals of systems biology models in a health-care context is to individualise models in order to compute patient-specific predictions (see, e.g., [23]) for the time evolution of species of interest (e.g., hormones). In our setting, this can be done by assigning suitable values to the model parameters.

Biological models typically depend on many (easily hundreds of) parameters, whose values cannot be chosen arbitrarily because of *inter-dependency* constraints among them (see, e.g., [25]). If model parameter values are chosen ignoring such constraints, then the resulting model behaviour is biologically meaningless. Unfortunately, such constraints are usually not explicitly known and thus are not modelled.

Model identification (see, e.g., [26]) techniques are typically used to estimate model parameters by minimising mismatch with respect to experimental data. In our setting, model identification is typically accomplished by computing a value for the model parameter vector (*parameter estimation*) so that a suitable error function measuring mismatch between model predictions and experimental data is minimised. If such a value exists and is unique the model (as well as its parameter vector univocally defining the model [26]) is said *identifiable*.

Model identification techniques require availability of many measurements (see, e.g., [7]). This is difficult to achieve in a scientific trial, let alone in a clinical setting. For example, model identification for our *GynCycle* case study has been done in [36] (with the approach described in [9]) using a Pfizer database comprising 20–25 measures for each of the 4 observed hormones for 12 healthy women. This amounts to more than 1000 overall measurements. This is a typical state of affairs: in order to gather enough experimental data, model identification is carried out using measurements from several patients. This leads to the computation of a value (*default value*) for the model parameters that averages among the behaviours of many patients (see, e.g., [7], [36]). As a result, although in principle model identification techniques could be used to compute *patient-specific* model parameters, in practice, because of the large amount of measurements needed, they are typically used to compute *inter-patient* model parameters.

In a clinical setting, for each patient, only a few (say, 3) measurements are available, since measurements can be costly, invasive and time-consuming. This is far from the hundreds of measurements used in model identification. Furthermore, a fast response time is needed, since decisions resting upon our patient-specific predictions must be taken within a time compatible with the health problem being addressed.

The above considerations motivate investigation on methods and tools that can support model individualisation in a clinical setting where measurements are at a premium and a fast response time is needed.

B. Main contributions

We present a statistical model checking based approach that given an ODE based model for a biological system and a few clinical measurements for a patient, computes a patient-specific model. This enables patient-specific predictions for the time evolution of each species of interest.

As discussed in Section I-A, the above cannot be done using *model identification* approaches, since we do not have enough measurements available to attain identifiability. *Parameter estimation* approaches cannot be used either, since with such a few data they would not take into due consideration inter-dependencies among model parameters [25], thereby leading to biologically meaningless model behaviours.

We overcome such an obstacle as well as that of getting a fast on-line response time, by splitting our computation into two phases. First, an *off-line* phase that accounts for

parameter inter-dependencies [25] and narrows our search space to vectors of parameter values leading to *biologically meaningful* model behaviours. Second, an *on-line* phase that computes a patient-specific model by selecting a vector of parameter values in our search space. Our contributions can be summarised as follows.

Formalisation of biological admissibility: In general, to decide if time evolution of species concentration is biologically meaningful takes a domain expert. However, our goal is to build a general purpose tool that can automatically search through millions of model parameter values. Thus, we need a criterion to automatically filter out (*most* of) the parameter values leading to time evolutions that are not biologically meaningful. We provide such a criterion by defining, as *Biologically Admissible (BA)* parameter values, those entailing time evolution with a second order statistics *close enough* to that of the model default parameter values.

Off-line computation of all Biologically Admissible (BA) parameters: Our goal is to compute a set of BA values for the model parameters that encompasses as many biologically meaningful behaviours as possible, but at the same time is not too large, in order to speed up our on-line computation. Thus, taking into account that differences in values below a certain threshold are meaningless from a biological point of view, we discretise the range of values for each model parameter. In such a framework, we present a statistical model checking based algorithm that computes a set S containing *only* and (with arbitrarily high confidence) *all* BA values for our model parameters. Note that such an algorithm does not depend on patient-specific data. Thus it can be run once and for all *off-line* and its output (the set S) can be stored for further processing.

On-line computation of patient-specific predictions: Given the set S computed by our off-line algorithm above and patient-specific clinical measurements, we compute a parameter λ^* that globally minimises the mismatch between species concentrations computed using parameter λ^* and those actually measured from the patient. Simulating our model with parameter λ^* yields the patient-specific predictions we are looking for. Note that, by looking at such predictions, a domain expert can easily disregard them (and thus λ^*) if they are not biologically meaningful. Thus, returning BA parameter values that do not yield biologically meaningful time evolutions is harmless, but returning too many of them makes our tool useless. Thanks to the off-line pre-computation of the set S, our on-line algorithm has a fast response time and allows us to compute a patient-specific model from very few (say, 3) patient measurements.

Experimental evaluation: We evaluate effectiveness of our approach by presenting experimental results on using it on the *GynCycle* model in [36]. The computation time of our off-line algorithm (computing set S above) ranges from about a week to more than a month, depending on the thresholds used to check biological admissibility of model parameters and on the degree of confidence required (0.999 in our case). Starting from the set S above and from clinical measurements for E2, P4, FSH and LH, our on-line algorithm computes in a matter of *minutes* patient-specific predictions for the concentrations of all 33 species in the model (that is, also for those for which no clinical measurements are available). Our results show that: 1) most patient-specific predictions stemming from our computed BA model parameters in S are biologically meaningful (*soundness*); 2) most of the measurements in our data sets (from Pfizer database logs, [36]) can be reproduced by selecting a suitable parameter in S (*completeness*); 3) the average error of our patient-specific predictions with respect to experimental data is smaller that the one yielded by predictions based on the default model parameter.

C. Overview of the paper

Biological systems as dynamical systems: We model (Section II) a biological system with a system of ODEs defining a dynamical system (see, e.g., [37]) whose state variables comprise species concentration and whose outputs are the species that we can actually measure. Our approach is *black-box*. Accordingly we use a solver (namely, *Limex* [11]) to compute a solution to the ODEs modelling our system.

Biologically Admissible (BA) model parameters: Section III gives our notion of *biological admissibility*. First, we note that a biological model is equipped with a default value λ_0 for the (vector of the) model parameters. Such a default value is provided by the model authors and summarises the biological behaviour of many patients (*inter-patient model*). We say that a model parameter λ is BA if the model behaviours that λ entails are *highly correlated* (in a signal processing sense, [41]) to the model behaviours entailed by the model default parameter λ_0. Our approach can be easily generalised to account for models which define multiple different admissible behaviours (modelling, e.g., both healthy patients and patients with different pathologies) by providing a *set* Λ_0 of default parameters (one per behaviour class) and by considering as BA any λ entailing a model behaviour highly correlated to the behaviour entailed by at least one default parameter $\lambda_0 \in \Lambda_0$. In this paper, for simplicity of presentation, we focus on models equipped with a single default parameter (as it happens in the *GynCycle* model).

Patient Logs and Parameter Fitness: Section IV describes how we model patient data (*clinical records* or just *logs*) and our measure of fitness. Given a patient log $\mathcal{L}$ and a model parameter λ, we define the error $\eta(\mathcal{L}, \lambda)$ as the mismatch between the species concentrations computed from our model using parameter λ and those in log $\mathcal{L}$.

Off-line computation of the set of BA parameters: Along the lines of [16], we use statistical hypothesis testing to compute off-line, with high statistical confidence, the set S of BA values for the model parameters. To this end, Section V first defines our sampling space and our sampling strategy. Our sampling space is the set $\hat{\Lambda}$ of discretised values for the model parameters. Our off-line algorithm initialises S to the singleton set $\{\lambda_0\}$ containing only the default parameter, and then samples $\hat{\Lambda}$ adding all found BA parameter values to S until S stays stable for *long enough*. Upon termination, we are guaranteed that, with high statistical confidence, all BA parameter values are in S.

Individualising a Biological Model: Section VI gives our main algorithm that computes, with arbitrarily high statistical confidence, a BA parameter value λ^* which globally minimises error $\eta(\mathcal{L}, \lambda)$ when λ is constrained to take BA values. Our algorithm consists of two phases: an *off-line* phase computing, as outlined above, the set S of BA parameter values, followed by an *on-line* phase, computing a value λ^* such that $\eta(\mathcal{L}, \lambda^*)$ attains its global minimum in S. The off-line phase is computationally quite heavy. However it has to be run only once and does not depend on the patient-specific data in $\mathcal{L}$. The on-line phase is our fast response time algorithm (since S is usually quite small) to be deployed in a clinical setting.

Experimental results: Section VII describes our case study, namely the *GynCycle* model described in [36], and presents experimental results evaluating effectiveness of our approach.

D. Related work

The input to our off-line algorithm consists of a system model along with the *default value* for its parameters. The *GynCycle* model considered in our case study has been presented in [36] and the default value for its parameters has been computed in [9] using model identification (often referred to as *parameter identification* in our setting) techniques [26].

A key feature of parameter identification approaches is their ability to give information about parameter *identifiability* (see, e.g., [7] and citations thereof). For example, the parameter identification approach in [9] provides information about parameter identifiability. Gradient-based methods, as, e.g., the classical one in [24], provide a local optimum solution to the parameter estimation problem, without giving any information about parameter identifiability. Global methods, such as [27], provide a global optimum solution without any information about parameter identifiability. Heuristic approaches as evolutionary algorithms (see, e.g., [5], [40]), provide near-global optimal solutions without information about parameter identifiability. When observations are scarce, parameters usually become non-identifiable. Studying the correlation among system parameters can reduce the number of data needed for identifiability (see, e.g., [34], [25]). Our goal here is to support model individualisation from clinical measurements. This means that we need to compute model parameters from a few (say, 3) observations about a small subset (4 in our case study) of the species occurring in the model (33 in our case). Unfortunately, as discussed in Section I-A, because of scarcity of measurements, neither model identification approaches nor parameter estimation approaches can be used in our setting.

Model checking based parameter estimation approaches have been investigated for example in [18], [10], [35], [20]. Such approaches differ from ours, since they do not address the problem of automatically restricting the search to parameters leading to biologically meaningful model trajectories. This is a fundamental step in complex models as ours.

The works closest to ours are those in [38], [6] and citations thereof, where the problem of computing all (discretised) model parameter values meeting given LTL properties has been investigated. We extend such works in two directions. First, the above mentioned papers focus on piecewise affine ODE systems, whereas we can handle any (possibly) non-linear ODE system (as is the case for our *GynCycle* model [36]). Second, the above mentioned papers aim at computing a maximal set of parameters satisfying a given LTL property describing the typical behaviour for the biological system at hand. Thus, when the model changes, a new LTL property has to be provided by domain experts. Our approach infers such a system property by the default value for the model parameters using the notion of biological admissibility of Section III. This decreases the amount of input needed from domain experts, thereby alleviating one of the main problems in such a framework: formalising the properties that biologically meaningful system trajectories must satisfy.

We note that computing the set of *all* model parameter values that satisfy a given property is closely related to that of computing *all* control strategies satisfying a given property. In a discrete time setting this problem has been addressed, for piecewise affine systems and safety properties, in [30], [2], [1], [31], [4], [3], [32], [8].

Model checking techniques have been widely used in systems biology, in order to verify time behaviours. Examples are in [22], [17], [12], [14], [33]. Such approaches focus on verifying a given property for the model trajectories, whereas our main problem here is to compute *all* biologically plausible values for the model parameters.

II. Parametric dynamical systems

We model biological systems using dynamical systems (see, e.g., [37]). In this section we give the formal background on which our approach rests. Throughout the paper, we denote with $[n]$ the set $\{1, 2, \ldots, n\}$ of the first n natural numbers and with $\mathbb{R}^+$, $\mathbb{R}^{\geq 0}$ and $\mathbb{R}$ the sets of, respectively, positive, non-negative and all real numbers. We also denote with $(\mathbb{R}^{\geq 0} \times \mathbb{R}^{\geq 0})^*$ the set of pairs $(a, b) \in \mathbb{R}^{\geq 0} \times \mathbb{R}^{\geq 0}$ such that $a \geq b$.

Definition 1 (Parametric Dynamical System): A *Parametric Dynamical System* (or, simply, a Dynamical System) $\mathcal{S}$ is a tuple $(\mathcal{X}, \mathcal{Y}, \Lambda, \varphi, \psi)$, where:

- $\mathcal{X} = X_1 \times \ldots \times X_n$ is a non-empty set of *states*, called the *state space* of $\mathcal{S}$;
- $\mathcal{Y} = Y_1 \times \ldots \times Y_p$ is a non-empty set of *outputs*, called the *output value space*;
- Λ is a non-empty set of *parameters*, called the *parameter value space*;
- $\psi : \mathbb{R}^{\geq 0} \times \mathcal{X} \to \mathcal{Y}$ is the *observation function* of $\mathcal{S}$;
- $\varphi : (\mathbb{R}^{\geq 0} \times \mathbb{R}^{\geq 0})^* \times \mathcal{X} \times \Lambda \to \mathcal{X}$ is the *transition map* of $\mathcal{S}$. Intuitively, $\varphi(t_2, t_1, x, \lambda)$ is the state reached by the system (with parameter values λ) at time t_2 starting from the state $x \in \mathcal{X}$ at time $t_1 \leq t_2$. Function φ must satisfy the following properties:
  - *semigroup*: for each $t_1, t_2, t_3 \in \mathbb{R}^{\geq 0}$ such that $t_1 < t_2 < t_3$, for each $\lambda \in \Lambda$, we have that $\varphi(t_3, t_1, x, \lambda) = \varphi(t_3, t_2, \varphi(t_2, t_1, x, \lambda), \lambda)$;
  - *consistency*: for each $t \in \mathbb{R}^{\geq 0}$, $x \in \mathcal{X}$ and $\lambda \in \Lambda$, we have $\varphi(t, t, x, \lambda) = x$.

Remark 1: Usually, a dynamical system comes equipped with a function space $\mathcal{U}$ that models both *controllable* inputs (e.g., treatments) as well as *uncontrollable* inputs (*disturbances*). In this paper, we do not address treatments or disturbances. Accordingly, for sake of simplicity, we omit inputs from Definition 1.

Remark 2: To simplify notation, unless otherwise stated, we assume that the set of parameters Λ has the form $\mathcal{X} \times \Gamma$ (where Γ is a non-empty set). Therefore, a parameter $\lambda = (x_0, \gamma) \in \Lambda$ embodies information about the initial state x_0 of a system trajectory. Such a system trajectory is a function of time $x(\lambda)(t)$, which, for each $t \in \mathbb{R}^{\geq 0}$, evaluates to $\varphi(t, 0, x_0, \gamma)$. In the following, abusing notation as usual, we write $x(\lambda, t)$ instead of $x(\lambda)(t)$. Analogously, we write $x_i(\lambda, t)$ $[y_i(\lambda, t)]$ for the time evolution $x_i(\lambda)(t)$ $[y_i(\lambda)(t)]$ of the i^{th} state [output] component with parameters γ starting in x_0 from time 0.

Example 1: Dynamical systems whose dynamics is described by a system of Ordinary Differential Equations (ODEs) depending on parameters are currently of great interest as a mathematical model for biological networks (see, e.g., [13], [36]). In this paper, we will use as a case study the *GynCycle* model presented in [36]. It is a differential equation

model for the feedback mechanisms between Gonadotropin-Releasing Hormone (GnRH), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), development of follicles and corpus luteum, and the production of Estradiol (E2), Progesterone (P4), Inhibin A (IhA), and Inhibin B (IhB) during the female menstrual cycle. The model aims at predicting blood concentrations of LH, FSH, E2, and P4 during different stages of the menstrual cycle. The model is intended as a tool to help in preparing and monitoring clinical trials with new drugs that affect GnRH receptors (*quantitative and systems pharmacology*). To get simulations of hormone concentrations, the system of differential equations is solved numerically.

In our *black-box* approach, the system transition map models our call to a solver (namely, *Limex* [11]) computing a solution to the ODEs defining dynamical systems in our context. This is along the lines of simulation based system level formal verification as in [42], [28], [29].

III. Biological admissibility

In general, given a value λ for the (vector of) model parameters, it takes a domain expert to decide if it holds that for each species x_i in the model, the time evolution $x_i(\lambda, t)$ is *biologically meaningful*. This stems from the fact that many parameter values lead to time evolutions for the model species that are not compatible with the laws of biology. However, our goal is to build a general purpose tool that automatically searches through millions of model parameter values. Thus, we need a criterion to automatically filter out parameter values leading to time evolutions that are not biologically meaningful. We provide such a criterion by asking that the time evolution of $x(\lambda, t)$ is *similar enough* (modulo bounded *stretch* and/or *time-shifts*) to that of $x(\lambda_0, t)$, that is the one entailed by the model default parameter value λ_0. To this end, in the following definition, we consider three measures of how similar two trajectories are (modulo bounded stretch and/or time-shift).

Given a function f from $\mathbb{R}$ to $\mathbb{R}$ and $\alpha, \tau \in \mathbb{R}$, we denote with $f^{\alpha,\tau}$ the function defined by $f^{\alpha,\tau}(t) = f(\alpha(t + \tau))$ for all t. Here, α and τ are used to model, respectively, a stretch and a shift of f. Given two functions f and g from $\mathbb{R}$ to $\mathbb{R}$, the *cross-correlation* (see, e.g., [41]) $\langle f, g\rangle(\xi)$ between f and g is a function of ξ (where $\xi \in \mathbb{R}$ is the *time lag*) defined as: $\langle f, g\rangle(\xi) = \int_{-\infty}^{+\infty} f(t)g(t + \xi)\mathrm{d}t$. We consider the *normalised zero-lag cross-correlation* function $\rho_{f,g}$, defined as $\rho_{f,g} = \frac{\langle f,g\rangle(0)}{\|f\|\|g\|}$, where $\|f\|$ and $\|g\|$ are the L^2 norms of f and g, i.e., $\sqrt{\langle f, f\rangle(0)}$ and $\sqrt{\langle g, g\rangle(0)}$. The higher $\rho_{f,g}$ the more *similar* are f and g (e.g., f and g have the same peaks). In particular, $\rho_{f,g}$ is 1 if f is equal to g up to an amplification factor.

Given a dynamical system $\mathcal{S}$ with n state variables, two parameter values λ, λ_0 for $\mathcal{S}$, and a finite horizon $h \in \mathbb{R}^{\geq 0}$, let $x_i(\lambda_0, t)$ and $x_i(\lambda, t)$ be the time evolutions of species x_i (for each $i \in [n]$) under parameters λ_0 and λ respectively. Being time evolutions, both $x_i(\lambda_0, t)$ and $x_i(\lambda, t)$ are defined for $0 \leq t \leq h$. Anyway, to easily match the above general definition of cross-correlation, we define such functions on the whole set of real numbers, as being 0 for any $t < 0$ or $t > h$.

In order to model biological admissibility, we define the following three functions (i ranges over $[n]$, $\alpha, \tau \in \mathbb{R}$):

1) normalised zero-lag cross-correlation:

$$\rho_{\lambda_0,\lambda,i}(\alpha, \tau) = \rho_{x_i(\lambda_0),x_i^{\alpha,\tau}(\lambda)}$$

2) normalised average differences:

$$\mu_{\lambda_0,\lambda,i}(\alpha, \tau) = \left| \frac{\int_0^h (x_i(\lambda_0, t) - x_i^{\alpha,\tau}(\lambda, t))\mathrm{d}t}{\int_0^h x_i(\lambda_0, t)\mathrm{d}t} \right|$$

3) normalised squared norm differences:

$$\chi_{\lambda_0,\lambda,i}(\alpha) = \left|(\|x_i(\lambda_0)\|^2 - \|x_i^{\alpha,\tau}(\lambda)\|^2)\right| \,/\, \|x_i(\lambda_0)\|^2.$$

The *normalised zero-lag cross-correlation* $\rho_{\lambda_0,\lambda,i}(\alpha, \tau)$ measures the similarity of the trajectories $x_i(\lambda_0, t)$ and $x_i(\lambda, t)$ as for qualitative aspects (for example, if they have the same peaks), when $x_i(\lambda, t)$ is subject to stretch α and time-shift τ. Analogously, the *normalised average differences* $\mu_{\lambda_0,\lambda,i}(\alpha, \tau)$ and the *normalised squared norm differences* $\chi_{\lambda_0,\lambda,i}(\alpha, \tau)$ are two measures of the average distance between $x_i(\lambda_0, t)$ and $x_i(\lambda, t)$, when $x_i(\lambda, t)$ is subject to stretch α and time-shift τ.

In the following, we use these functions to formalise the notion of Biologically Admissible (BA) parameter λ with respect to a default parameter λ_0. Intuitively, Definition 2 considers λ as BA if the three measures above are all above or below certain thresholds.

Definition 2 (Biologically Admissible parameter): Let λ_0, $\lambda \in \mathcal{X} \times \Lambda$ be two parameters. Let $\mathbb{A} \subseteq \mathbb{R}^+$, $\mathbb{B} \subseteq \mathbb{R}$ be two sets of real numbers such that $1 \in \mathbb{A}$ and $0 \in \mathbb{B}$. Given a tuple $\Theta = (\theta_1, \theta_2, \theta_3)$ of positive real numbers, we say that λ is Θ-*biologically admissible* with respect to λ_0, notation $adm_{\mathbb{A},\mathbb{B}}(\lambda_0, \lambda, \Theta)$, if there exist $\alpha \in \mathbb{A}$ and $\tau \in \mathbb{B}$ such that, for all $i \in [n]$: $(\rho_{\lambda_0,\lambda,i}(\alpha, \tau) \geq \theta_1) \wedge (\mu_{\lambda_0,\lambda,i}(\alpha, \tau) \leq \theta_2) \wedge (\chi_{\lambda_0,\lambda,i}(\alpha, \tau) \leq \theta_3)$.

IV. Patient logs and parameter fitness

In order to evaluate model predictions with respect to clinical records, we first formally define the notion of system log. System logs model experimental results that we get by taking system measurements. A system log consists of a sequence of time instants for each output under consideration, and, for each time instant, the corresponding measured value. This definition is motivated by the fact that, in clinical practice, different species may be measured in different time instants.

Definition 3 (System log): Let $\mathcal{S}$ be a dynamical system as in Definition 1, and $\mathcal{Y} = Y_1 \times \ldots \times Y_p$ be its p-component output value space.

An *output time set* T for $\mathcal{S}$ is the Cartesian product $T_1 \times \ldots \times T_p$, where each T_i is a finite subset (possibly empty) of $\mathbb{R}^{\geq 0}$. A T-*output log* is a map from T to $\mathcal{Y}$.

A *system log* $\mathcal{L}$ for $\mathcal{S}$ is a pair (T, z), where T is an output time set for $\mathcal{S}$, and z is a T-output log.

Example 2: As an example of system log, here we briefly describe a typical patient log for monitoring women menstrual cycle (see Example 1) that we use in our case study. Logs from 12 women from a Pfizer database considered in [36] contain measurements regarding only four hormones: Estradiol (E2), Progesterone (P4), Follicle-Stimulating Hormone (FSH), and Luteinizing Hormone (LH). These hormone concentrations are measured mostly every day from day 5 to day 28 of the menstrual cycle. In such a case, we have $T_{E2} = T_{P4} = T_{FSH} = T_{LH} = \{5, 6, 7, \ldots, 28\}$ (time here is in days). In everyday clinical practice, even a smaller set of measurements is taken. For example, in clinical treatments of fertility, only three to five blood samples (measurements) are performed during a cycle and some hormone concentrations are measured only twice. As an instance, the output time set for Estradiol could be $T_{E2} = \{1, 7, 9, 12, 23\}$ and the output time set for Progesterone could be $T_{P4} = \{1, 6\}$.

To evaluate how well a model prediction fits a system log, we consider an *error function* $\eta(\mathcal{S}, \mathcal{L}, \lambda)$, which is a real-valued map that measures to what extent predictions computed with the model $\mathcal{S}$ with parameter λ differ from measurements in the patient log $\mathcal{L}$. When the system $\mathcal{S}$ under consideration is clear from the context, we will write just $\eta(\mathcal{L}, \lambda)$ for $\eta(\mathcal{S}, \mathcal{L}, \lambda)$.

In our case study, we consider the *GynCycle* model as in Example 1 and a system log $\mathcal{L} = (T, z)$ as in Example 2. Our error function is defined as the average (over the $p = 4$ measured species) of the average error of model predictions $[y_i(\lambda, t)]$ with respect to all measurements in the patient log $[z_i(t)]$: $\eta(\mathcal{L}, \lambda) = \frac{1}{p} \sum_{i \in [p]} \frac{1}{|T_i|} \sum_{t \in T_i} \frac{|y_i(\lambda,t) - z_i(t)|}{\max\{|z_i(t)|, \zeta\}}$. Note that, as we need to average the errors for different species, we need *normalised* error functions. To this end, we consider the log observations as reference values (*relative* error), and to avoid abnormal situations, if an observation is 0, we normalise it with respect to a given small positive constant ζ. An alternative option would have been to normalise the error with respect to the length of the range of legal values for each species. Unfortunately, this option is unviable in our context, as the range of legal values for many (unobservable) species is unknown.

V. Computation of admissible parameters

The first phase of our procedure finds the set S of (with high confidence) all Biologically Admissible (BA) parameter values with respect to a default parameter λ_0 validated by the model designer as biologically meaningful. The set S is computed by checking parameter values in a finite (grid-shaped) subset $\hat{\Lambda}$ of Λ (*discretised parameter space*). This approach is justified by the fact that small differences in values are meaningless from a biological point of view.

Since the number of parameters to identify is large (75 in our case study), the discretised parameter space is huge (10^{75} if we consider 10 possible values for each parameter), thus making an exhaustive search on the discretised parameter space $\hat{\Lambda}$ unfeasible. To overcome such an obstruction, we follow an approach inspired by statistical model checking [16], [15].

A. Algorithm Outline

Algorithm 1 incrementally computes the set S of Biologically Admissible (BA) parameter values trying to find at each iteration of the **repeat** loop (lines 5–13) new BA parameter values. To do so, Algorithm 1 iteratively selects a random parameter value $\lambda \in \hat{\Lambda}$ (line 8), tests if it is BA (i.e., if $\mathit{adm}_{\mathbb{A},\mathbb{B}}(\lambda_0, \lambda, \Theta)$ holds) and, if this is the case, adds it to the set S of already computed BA parameter values (lines 10–11).

To check $\mathit{adm}_{\mathbb{A},\mathbb{B}}(\lambda_0, \lambda, \Theta)$ we compute the functions defined in Section III by numerical integration over a finite number of points. To do this, we invoke the simulator just once for any parameter value λ: given the requested output time set T and the sets $\mathbb{A}$ and $\mathbb{B}$ for the allowed stretch and time-shift factors, function $\mathit{simulate}(\mathcal{S}, T_{\mathbb{A},\mathbb{B}}, \lambda)$ in line 9 simulates the system $\mathcal{S}$ computing points $(t, x(\lambda, t))$ of the system trajectory for all time points in $T_{\mathbb{A},\mathbb{B}}$. Set $T_{\mathbb{A},\mathbb{B}}$ (line 4) contains all time instants for which function $\mathit{adm}_{\mathbb{A},\mathbb{B}}$ needs species values in order to evaluate whether parameter λ satisfies Definition 2. Function $\mathit{simulate}(\mathcal{S}, T_{\mathbb{A},\mathbb{B}}, \lambda)$ returns as a result a finite domain function L, such that, for any time instant $t \in T_{\mathbb{A},\mathbb{B}}$, $L_i(t)$ is the value of species x_i at time t.

Our sampling strategy selects a parameter value λ from $\hat{\Lambda} \setminus S$ with probability $\mathbf{Pr}^S[\lambda] > 0$. To speed up our procedure, we give a higher probability to parameter values "close" to those already in S (see Section V-C).

Algorithm 1 Computing the set S of BA parameters

Input: A dynamical system $\mathcal{S} = (\mathcal{X}, \mathcal{Y}, \Lambda, \varphi, \psi)$, a finite subset $\hat{\Lambda}$ of Λ, a default parameter λ_0, two real numbers $\varepsilon, \delta \in (0, 1)$, a tuple Θ of BA thresholds, two finite sets of real numbers $\mathbb{A}$ and $\mathbb{B}$ (with $1 \in \mathbb{A}$ and $0 \in \mathbb{B}$), and an output time set T

function *bioAdmPars*$(\mathcal{S}, \hat{\Lambda}, \lambda_0, \varepsilon, \delta, \Theta, \mathbb{A}, \mathbb{B}, T)$

1. $N \leftarrow \lceil \ln(\delta) / \ln(1 - \varepsilon) \rceil$
2. $S' = \{\lambda_0\}$
3. $L_0 \leftarrow \mathit{simulate}(\mathcal{S}, T, \lambda_0)$
4. $T_{\mathbb{A},\mathbb{B}} \leftarrow T \cup \{t' \mid t' = \alpha(t + \tau), t \in T, \alpha \in \mathbb{A}, \tau \in \mathbb{B}\}$
5. **repeat**
6. $\quad S \leftarrow S'$
7. $\quad$ **for** $i \leftarrow 1$ **to** N **do**
8. $\quad\quad \lambda \leftarrow \mathit{chooseNextParameter}(\hat{\Lambda}, S)$
9. $\quad\quad L \leftarrow \mathit{simulate}(\mathcal{S}, T_{\mathbb{A},\mathbb{B}}, \lambda)$
10. $\quad\quad$ **if** $\mathit{adm}_{\mathbb{A},\mathbb{B}}(L, L_0, \Theta) \wedge \lambda \notin S$ **then**
11. $\quad\quad\quad S' \leftarrow S' \cup \{\lambda\}$
12. $\quad\quad\quad$ **break**
13. **until** $S' = S$
14. **return** S

We use Statistical Hypothesis Testing to compute S, much along the lines of [16]. Let δ and ε be two real numbers in $(0, 1)$ and $N = \lceil \frac{\ln(\delta)}{\ln(1-\varepsilon)} \rceil$. The algorithm stops when N attempts fail to find a BA parameter. Our null hypothesis $H_0(S)$ states that the probability of selecting a BA parameter value outside S is greater than ε. In other words, $H_0(S)$ states that S does not contain *all* BA parameter values. Upon termination, the algorithm rejects H_0 with statistical confidence $1 - \delta$. This means that the probability of a Type-I error (i.e., to reject H_0 when it holds) is less than $1 - \delta$. Rejecting H_0 means that the probability of selecting a BA parameter value outside $S \subseteq \hat{\Lambda}$ is less than ε.

B. Algorithm Correctness

The above considerations are the key argument to prove the following.

Theorem 1: Given a dynamical system $\mathcal{S}$ as in Definition 1, a finite subset $\hat{\Lambda}$ of Λ, a value $\lambda_0 \in \hat{\Lambda}$, a tuple Θ of biological admissibility thresholds, two real numbers ε and δ in $(0, 1)$, and two finite sets of real numbers $\mathbb{A}$ and $\mathbb{B}$ (with $1 \in \mathbb{A}$ and $0 \in \mathbb{B}$), Algorithm 1 is such that:

1) it terminates in $\mathcal{O}(N|\hat{\Lambda}|)$ steps, where $N = \lceil \frac{\ln \delta}{\ln(1-\varepsilon)} \rceil$;

2) upon termination, it computes a set $S \subseteq \hat{\Lambda}$ of Θ-Biologically Admissible parameter values;

3) set S is such that, with confidence $1 - \delta$: $\mathbf{Pr}^S[\{\lambda \in \hat{\Lambda} \setminus S \mid \mathit{adm}_{\mathbb{A},\mathbb{B}}(\lambda_0, \lambda, \Theta)\}] < \varepsilon$.

The computational complexity of Algorithm 1 depends on the fact that, in order to find a BA parameter, we make at worst N attempts and, in principle, all discretised parameter values can be BA. As a consequence, the worst running time of Algorithm 1 is worse than an exhaustive search over $\hat{\Lambda}$. We remark, however, that the *average* running time is, in general, much better than that of an exhaustive search, since the set of BA parameters is very small compared with the size of the whole discretised parameter space. As a matter of fact, the algorithm stops with high probability in a reasonable time (see Section VII-B) by failing to find a new BA parameter value.

C. Parameter Probability Space

The probability distribution that we consider over the parameter space $\hat{\Lambda}$ is parametric to the set S of BA parameter values computed so far, and it is defined in such a way that parameter values that are close to values in S are most likely to be chosen. This speeds up (with respect to, e.g., uniform sampling) the finding of new BA parameter values.

Given a set S, we choose the next value λ to examine as follows:

1) We randomly choose $\lambda' \in S$ uniformly at random.

2) We randomly choose the maximum number h of components in which λ will differ from λ'. In this case, the set $[n]$ is considered distributed as a power-law of the form $\mathbf{Pr}[h] = ah^{-b}$, with $b > 1$ and a being a normalisation constant. This implies that, with high probability, λ will differ from λ' in a small number of components.

3) We randomly choose a subset of h different components in $[n]$, assuming a uniform distribution over the set of subsets of cardinality h, $\mathcal{P}_h([n])$, that is $\{X \subseteq [n] \mid |X| = h\}$.

4) For each component i, we choose a value $\lambda_i \in \hat{\Lambda}_i$ uniformly at random.

This sampling technique defines a probability space $(\hat{\Lambda}, \mathcal{P}(\hat{\Lambda}), \mathbf{Pr}^S)$ parametric with respect to a set $S \subseteq \hat{\Lambda}$. By multiplying the (conditional) probabilities of steps 1)–4) above, we have: $\mathbf{Pr}^S[\lambda] = \frac{1}{|S|} \sum_{\lambda' \in S} a\, |d(\lambda, \lambda')|^{-b} \binom{n}{|d(\lambda,\lambda')|}^{-1} \prod_{i \in d(\lambda,\lambda')} \frac{1}{|\hat{\Lambda}_i|}$, where $d(\lambda, \lambda')$ is the set of the components on which λ and λ' differ. Note that $\mathbf{Pr}^S[\lambda]$ is non-zero for all λ.

VI. Computation of patient-specific parameters

Once the set S of (almost) all Biologically Admissible (BA) parameters has been computed by the *off-line* procedure described in Section V, *patient-specific parameters* can be efficiently computed. Given a patient log $\mathcal{L}$, the patient-specific parameter for $\mathcal{L}$ is the parameter λ^* that minimises $\eta(\mathcal{L}, \lambda)$, that is the parameter that minimises model prediction errors with respect to the patient measurements in $\mathcal{L}$.

Since S contains with *arbitrary high confidence* all BA parameters, we just compute the value $\lambda^* = \mathit{argmin}_{\lambda \in S} \eta(\mathcal{S}, \mathcal{L}, \lambda)$ to get, with the same confidence, a BA parameter value λ^* that minimises $\eta(\lambda, \mathcal{L})$ over $\hat{\Lambda}$. This procedure is intended to be an *on-line* computation to be used in everyday clinical practice.

Theorem 2: Let S be the set of BA parameters computed by Algorithm 1 taking as input a dynamical system $\mathcal{S}$, a tuple Θ of biological admissibility thresholds, a finite subset $\hat{\Lambda}$ of the parameter space Λ, a default parameter value $\lambda_0 \in \hat{\Lambda}$, a probability threshold ε, a confidence level δ, and finite sets $\mathbb{A}$ and $\mathbb{B}$. Given a patient log $\mathcal{L} = (T, z)$, the parameter value $\lambda^* = \mathit{argmin}_{\lambda \in S} \eta(\mathcal{S}, \mathcal{L}, \lambda)$ is such that, with confidence $(1-\delta)$, $\mathbf{Pr}^S[\{\lambda \in \hat{\Lambda} \setminus S \mid \eta(\mathcal{L}, \lambda) < \eta(\mathcal{L}, \lambda^*)\}] < \varepsilon$.

Remark 3: Once the *off-line* set S of (almost) all BA parameters has been computed (once and for all), the computation of $\lambda^* = \mathit{argmin}_{\lambda \in S} \eta(\mathcal{L}, \lambda)$ is linear in the size of S, which in turn is very small with respect to $\hat{\Lambda}$.

VII. Experimental results

The effectiveness of our approach has been evaluated on the *GynCycle* model in [36]. Such a model has 114 parameters, 75 of which are patient-specific (at least for our purposes), and consists of 41 differential equations defining the time evolution of 33 species. We implemented our tool in the C programming language and connected it with the *Limex* solver [11] integrating the Ordinary Differential Equations (ODEs) defining our model.

A. Experimental setting

All experiments have been carried out on a cluster of Linux machines each one equipped with two Intel(R) Xeon(R) CPU @ 2.27GHz and 24GB of RAM.

We set the probability threshold ε and the confidence level δ to 10^{-3}. Set $\mathbb{A}$ (see Definition 2 in Section III) comprises all stretch factors α multiple of 0.1, from 0.9 to 1.1. Set $\mathbb{B}$ (see Definition 2 in Section III) comprises all time-shifts τ multiple of 2 hours, from -5 days to $+5$ days. We set constant ζ (see Section IV) to 10^{-4} to avoid division by zero during normalisation. The discretisation $\hat{\Lambda}$ of Λ has been obtained by uniformly discretising the range of each parameter into 10 or 3 values. Cross-correlations, averages and L^2 norms are computed on a discretisation of the time evolutions with values every 15 minutes. As for the individualisation of our model we used the very same Pfizer data in [36] about 12 women.

B. Experimental results

1) Off-line computation of admissible parameters: Table I shows the computation time and the size of the set S of computed Biologically Admissible (BA) parameters for different runs of our off-line algorithm, using different configurations for biological admissibility thresholds $\theta_1, \theta_2, \theta_3$ (see Section III).

run id	θ_1	θ_2	θ_3	discr. steps	|S|	CPU time
r1	0.6	0.5	0.5	10	3940	$\sim$ 31 days
r2	0.6	0.4	0.4	10	3504	$\sim$ 29 days
r3	0.5	0.7	0.7	10	6989	$\sim$ 147 days
r4	0.5	0.5	0.5	10	6406	$\sim$ 167 day
r5	0.7	0.3	0.3	3	126	$\sim$ 6 days

TABLE I: Off-line: Size of the set of BA parameters and computation time.

Parts of such runs have been executed with a parallel version of our algorithm, which is still under development. Other parts have been executed with our stable sequential algorithm. In order to allow comparisons, we ensure homogeneity by reporting in Table I all times as if we were running our sequential algorithm. Data in Table I should be read with some caution since, being generated by a probabilistic algorithm implementing the sampling process described in Section V, different runs may yield different results as for computation time and size of set S.

As we can see from Table I, the off-line computation may take several days of intensive computation. On the other hand, it only has to be run once, since it does not depend on the patient log being considered. The RAM usage is negligible and the disk storage requirements are perfectly reasonable (tens of GB) for today standards.

2) On-line computation of patient-specific parameters: To evaluate the improvement that we obtain in species predictions, we consider patient $p2$ in the Pfizer data set and its associated log $\mathcal{L}_2$. The average error $\eta(\lambda_0, \mathcal{L}_2)$ obtained by using the default parameter λ_0 is 61.9%.

Table II shows results when *only three* observations (at days 8, 11, and 15 of the patient menstrual cycle) are used to compute our predictions for patient $p2$.

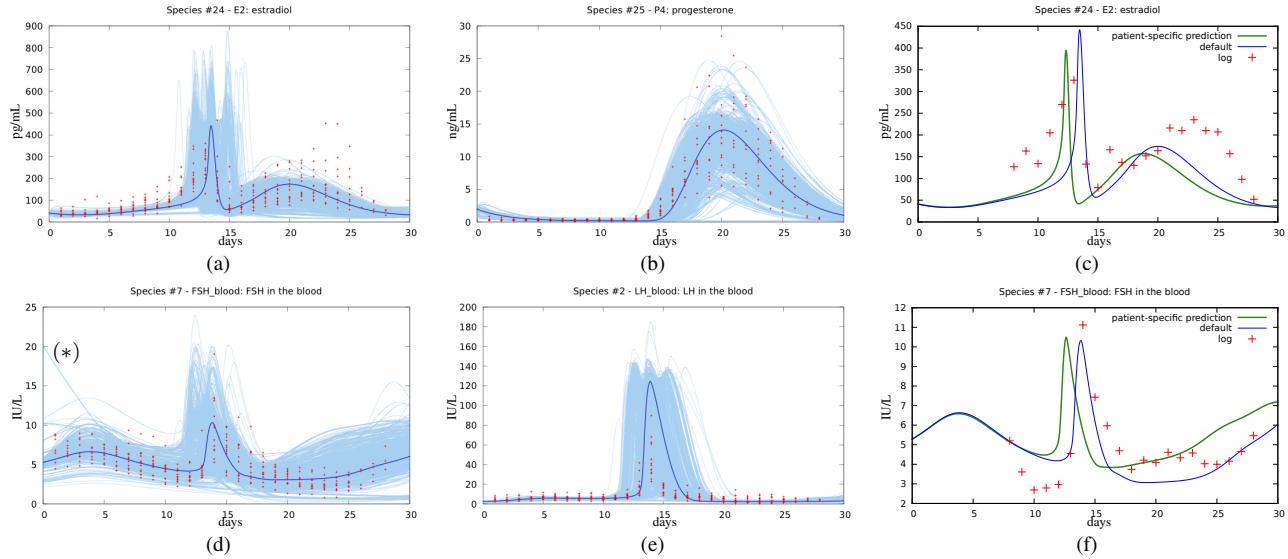

Fig. 1: (a), (b), (d), (e): all system trajectories under admissible parameters, as computed in run $r3$ for, respectively, E2, P4, FSH, LH (dark blue curves denote trajectories under default parameter). (c), (f): patient-specific prediction (green curves) for patient $p2$ vs. default prediction (blue curves) for, respectively, E2 and FSH.

run id	CPU time	avg. error	error red.	error red.%	biol. meaningful
r1	8m35s	56.0%	5.9	9.5%	yes
r2	5m06s	55.7%	6.1	9.9%	yes
r3	39m20s	55.0%	6.9	11.2%	yes
r4	36m5s	55.4%	6.5	10.5%	yes
r5	0m23s	61.9%	0.0	0.0%	yes

TABLE II: On-line: Error reduction using λ^* for patient $p2$.

The table shows CPU time and effectiveness of our on-line algorithm, when run with the same configurations for biological admissibility thresholds $\theta_1, \theta_2, \theta_3$ as in Table I. Column "average error" gives the minimum value of $\eta(\lambda, \mathcal{L}_2)$ for $\lambda \in S$, where S is the set of BA parameters computed by the off-line algorithm (as shown in the corresponding rows of Table I). Column "error reduction" shows the value of $(\eta(\lambda_0, \mathcal{L}_2) - \eta(\lambda, \mathcal{L}_2))\,/\eta(\lambda_0, \mathcal{L}_2)$. Column "biologically meaningful" shows always "yes", as all trajectories we found are biologically meaningful, even though we cannot ensure a priori that all BA parameters will yield biologically meaningful trajectories.

Results show that the on-line computation completes within minutes, thereby yielding a fast on-line response time as required in a clinical setting. Runs $r3$ and $r4$ have been executed on a machine with an external storage device: their longer computation times are due to slower I/O. RAM requirements are negligible.

C. Discussion

1) Experimental soundness and completeness of biological admissibility: We experimentally evaluate *soundness* and *completeness* of our notion of biological admissibility, using reference values from the literature (e.g., [39]). To this end, Figures 1a, 1b, 1d and 1e show the trajectories for hormones E2, P4, FSH and LH (for which measurements are available in our Pfizer data-set) obtained by running the *GynCycle* model on all parameter values computed by our *off-line* algorithm in run $r3$. We see that most of such trajectories are biologically meaningful, being in agreement with the trajectories in [39]. This shows (experimentally) *soundness* of our biological admissibility notion. Furthermore, most of our Pfizer measurement data (red crosses in Figures 1a, 1b, 1d and 1e) lie within the region covered by our trajectories. This shows (experimentally) *completeness* of our biological admissibility notion.

An example of biologically *not* meaningful trajectory is denoted with $(*)$ in Figure 1d. Also, Figure 1a shows that not all Pfizer data are covered by our trajectories. This state of affairs is to be expected, since both biological admissibility and our off-line algorithm are based on statistical notions (signal second order statistics and statistical model checking, respectively), and clinical measurements might be noisy.

2) Error reduction in patient-specific predictions: The error reductions reported in Table II show that our proposed approach enables effective patient-specific predictions even in a clinical setting, where the measurements are at a premium (we used only three observations). Figures 1c and 1f give an example of the predictions of, respectively, E2 (Estradiol) and FSH for patient $p2$, and compare them with the default predictions and actual measurements in the patient log. The achieved error reduction is of about 10%. This value has a relevant impact from a clinical standpoint, as it can move hormone peaks (which are among the main fertility/infertility indicators) by several days (see Figures 1a, 1b, 1d and 1e).

The lack of error reduction shown in the single case where the minimum cross-correlation is 0.7 is due to the fact that the only BA parameters found by our off-line algorithm are very close to the default parameter. On the other hand, the first row of Table I is more liberal in considering parameters as BA. As a result, that process was able to find more parameter values in less time (possibly including model parameters leading to model behaviours which are not biologically meaningful).

VIII. Conclusions

We have presented a method to effectively compute patient-specific predictions from an ODE-based biological model and

clinical records. We overcome the main obstacles in our clinical setting (scarcity of measurements and fast response time) with an approach resting on three main pillars: first, a formalisation of the notion of *biological admissibility* that allows us to automatically filter out most parameter values that do not lead to biologically meaningful system trajectories; second, a statistical model checking algorithm that, with arbitrarily high confidence, computes *off-line* the set S of *all* (discretised) Biologically Admissible parameter values; third, an *on-line* algorithm that computes from S the best prediction with the available data. We are currently developing a parallel version for the presented algorithms.

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