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Constraint reasoning in deep biomedical models

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Epidemiology

Summary

Objective: Deep biomedical models are often expressed by means of differential equations. Despite their expressive power, they are difficult to reason about and make decisions, given their non-linearity and the important effects that the uncertainty on data may cause. The objective of this work is to propose a constraint reasoning framework to support safe decisions based on deep biomedical models.
Method: The methods used in our approach include the generic constraint propagation techniques for reducing the bounds of uncertainty of the numerical variables complemented with new constraint reasoning techniques that we developed to handle differential equations.
Results: The results of our approach are illustrated in biomedical models for the diagnosis of diabetes, tuning of drug design and epidemiology where it was a valuable decision-supporting tool notwithstanding the uncertainty on data.
Conclusion: The main conclusion that follows from the results is that, in biomedical decision support, constraint reasoning may be a worthwhile alternative to traditional simulation methods, especially when safe decisions are required.

1. Introduction

Biomedical models provide a representation of the functioning of living organisms, making it possible to reason about them and eventually to take decisions about their state (diagnosis) or adequate actions (e.g. therapeutic) regarding some intended goals. Parametric differential equations are general and expressive mathematical means to model systems dynamics, and are suitable to express the deep modelling of many biomedical systems. However, reasoning with such models may be quite difficult, given their complexity. Analytical solutions are available only for the simplest models. Alternative numerical simulations require precise numerical values for the parameters involved, which are usually impossible to gather given the uncertainty on available biomedical data. This may be an important drawback, since, given the usual non-linearity of the models, small differences on the input parameters may cause important differences on the output produced.

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To overcome this limitation, Monte Carlo methods rely on a large number of simulations, that may be used to estimate the likelihood of the different options under study. However, given the various sources of errors that they suffer from, both input precision errors and round-of errors accumulated in the simulations, they cannot provide safe conclusions regarding these options. In the sequel, we use the term safe in a mathematical (not biomedical) sense—if a variable is bound (by reasoning with a certain model) within a certain interval, then it is not possible that it takes a value outside that interval.

In contrast with such methods, constraint reasoning assumes the uncertainty of numerical variables within given bounds (e.g. intervals of real numbers) and propagates such knowledge through a network of constraints on these variables, in order to decrease the underlying uncertainty (i.e. width of the intervals). To be effective, constraint reasoning methods must rely on advanced safe methods that sufficiently bound uncertainty to guarantee that safe decisions are made.

Lack of space prevents a full explanation of the constraint reasoning techniques that we developed to handle differential equations [1,2]. Nevertheless, a brief introduction in Section 2 shows the expressive power of the framework developed, and stresses the active use of certain constraints on actual, upper and lower values of the functions involved, on the time or the area under curve in which they exceed a certain threshold. These constraints can only be used passively, both on alternative constraint reasoning frameworks or more conventional numerical simulation methods.

This expressive power is illustrated in three biomedical applications, regarding the diagnosis of diabetes, the tuning of drug design and an epidemic study, presented in Sections 3—5, respectively. We show in these examples how the active use of constraints of the types above is sufficient to make safe decisions regarding the intended goals. The paper ends with a summary of the main conclusions.

2. Continuous constraint satisfaction problems

Many real world problems can be modelled as constraint satisfaction problems (CSPs) defined by a triple (X, D, C) where X is a set of variables, each with an associated domain of possible values in D, and C is a set of constraints on subsets of the variables [3]. A constraint specifies which values from the domains of its variables are compatible. A solution to the CSP is an assignment of values to all its variables, which satisfies all the constraints.

In continuous CSPs (CCSPs), variable domains are continuous real intervals and constraints are equality and inequality [4]. The interval constraints framework [5] combines propagation and search techniques from AI with methods from interval analysis [6] for solving CCSPs. Sound filtering algorithms are used to prune the domains of the CCSP variables guarantedly losing no possible solutions.

Partial information expressed by a constraint is used to eliminate incompatible values from the domain of its variables. Through a process known as constraint propagation, the reduction of a variable domain is propagated to all constraints on that variable, which may further reduce the domains of other variables. The process terminates when a fixed point is attained and the domains cannot be further reduced.

Consider the CCSP characterized by variables x and y, initially ranging in [-2, 2] and [-2, 10], respectively, and the following two constraints:

$$y = x^2, \qquad y \geq 2x + 4$$

Fig. 1a illustrates the problem, showing the box with the initial domains and the two constraints. Any solution of the CCSP must be within the box, above the straight line and on the curved line. The enforcement of local consistency on this example may be described by the following sequence of steps.

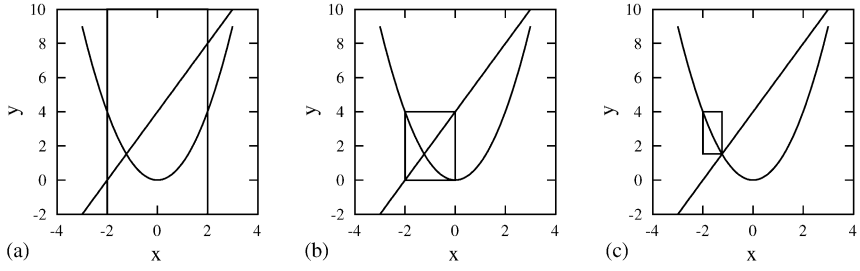


Figure 1 Solving a simple CCSP. (a) Initial domains box; (b) box obtained after constraint propagation; (c) enclosing box obtained by enforcing global hull consistency.

From the first constraint, and knowing that the x absolute value cannot exceed 2, the upper bound of y may be safely reduced to the square of 2, that is, 4. Similarly, the y lower bound may be safely increased to 0, since there is no possible x value with the square smaller than 0. Hence, by using only the partial information expressed by the first constraint, the domain of y can be safely narrowed from $[-2, 10]$ to $[0, 4]$.

The reduction of the y domain is then propagated to the other constraint allowing the safe reduction of the x domain. If y cannot exceed 4, then x cannot exceed 0 without violating the second constraint. The narrowing process terminates, since the domains cannot be further reduced by using the partial information of any constraint.

The result of constraint propagation on the original domains box is illustrated in Fig. 1b. The original domains box is narrowed onto a smaller box, with $x \in [-2, 0]$ and $y \in [0, 4]$, with the guarantee that such new box still contains all solutions contained in the original box.

Constraint propagation is a safe primary method used in CCSPs for narrowing the domains of its variables according to the (local) properties of its constraints; hence, it is said to enforce local consistency [7,8]. However, local consistency is partial, in that it is not sufficient to remove all inconsistent value combinations among the CCSP variables. As easily checked in Fig. 1b, the box obtained could be further narrowed without losing CCSP solutions, but constraint propagation alone does not achieve it.

In fact, the pruning of the domains obtained by enforcing local consistency is often insufficient to support safe decisions in many practical problems, especially those including differential equations.

To obtain better pruning, it is necessary to split the domains box and reapply constraint propagation to each subbox. The narrowing procedure is a branch and prune process which terminates when additional requirements establishing non-local properties on the variable domains are satisfied. Such higher order properties characterize the consistency criterion that is enforced by the narrowing procedure. Several alternative partial consistency criteria have been proposed [9] trying to offer the best trade-off between the computational cost of the enforcing algorithm and the pruning of the CCSP variable domains.

We have been developing global hull consistency, the strongest consistency criterion for pruning the initial CCSP variable domains into a single "box" (where each variable domain is represented by a single real interval) [10,11]. It narrows the original domains into the smallest box that contains all possible canonical solutions, a canonical solution being the smallest box that can be represented with some specified precision that cannot be proved inconsistent (notice that not all values in the box correspond to solutions, but only that there are no solutions outside the box). Being a computational expensive criterion, an important property of its enforcing algorithm is its any time nature (partial pruning results are provided at any time during the narrowing process).

Fig. 1c illustrates the single enclosing box that would be obtained by enforcing global hull consistency. Note that such box is the smallest box enclosing all the CCSP canonical solutions and any further pruning is prevented due to the canonical solutions placed in its upper left and lower right edges.

2.1. Constraint satisfaction differential problems

The behaviour of many systems is naturally modelled by a system of first-order ordinary differential equations (ODEs), often parametric. ODEs are equations that involve derivatives w.r.t. a single independent variable, t, usually representing time.

An ODE system O with n equations may be represented in vector notation as

$$y'(t) = f(y, t) \quad \text{with} \quad y'(t) = \begin{bmatrix} y_1' \\ \dots \\ y_n' \end{bmatrix} \quad \text{and}$$

$$f(y, t) = \begin{bmatrix} f_1(y_1, \dots, y_n, t) \\ \dots \\ f_n(y_1, \dots, y_n, t) \end{bmatrix}$$

where vector function f determines, for an instantiation of y and t, the evolution of y within an increment of t, and may be seen as a restriction on the sequence of values that y can take over t. A solution of O w.r.t. an interval of time T is a n-ary function $s(t)$ that satisfies the ODE system during that interval of time, $\forall\, t \in T : s'(t) = f(s(t), t)$.

Since an ODE system does not fully determine a solution function (but rather a family of such solution functions), initial/boundary conditions are usually provided with a complete/partial specification of y at some time point t.

Classical numerical approaches for solving ODE problems compute numerical approximations of the solutions and do not provide guarantees on their accuracy. In contrast, validated [12] and constraint methods [13] do verify the existence of unique solutions and produce guaranteed error bounds for the true trajectory.

In this paper, we use an extension of the interval constraints framework for including ODE systems as

constraints within CCSPs [1,14]. An ODE system and additional information is denoted a constraint satisfaction differential problem (CSDP). A CCSP that includes constraints defined as CSDPs is denoted an extended CCSP.

In a CSDP, there is a special variable (tr_{ODE}) for representing the solutions of O during T that satisfy all the additional restrictions (possible trajectories). A special constraint, denoted $ODE_{O,T}(tr_{ODE})$, associates the variable tr_{ODE} with the ODE system O during time interval T. The other variables of the CSDP, denoted restriction variables, are all real valued variables used to model a number of constraints of interest in many applications.

A value restriction, denoted $Value_{s_j,t}(x)$, associates a variable x with the value of a trajectory component s_j at a particular time t, and can be used to model initial and boundary conditions. A maximum restriction, $Maximum_{s_j,T}(x)$, associates x with the maximum value of a trajectory component s_j within a time interval T (minimum restrictions are similar). A time restriction $Time_{s_j,T,\geq\theta}(x)$ associates x with the time within time period T in which the value of a trajectory component s_j exceeds a threshold θ. Similarly, the area restriction $Area_{s_j,T,\geq\theta}(x)$ associates x with the area of a trajectory component s_j, within time period T, above threshold θ. A first time restriction $FirstValue_{s_j,T,\geq\theta}(x)$ associates x with the first time within period T in which the value of s_j exceeds θ. Restrictions $FirstMaximum_{s_j,T}(x)$ and $FirstMinimum_{s_j,T}(x)$ associate x with the first time within period T in which the value of component s_j is, respectively, a maximum or a minimum. Last time restrictions, $LastValue_{s_j,T,\geq\theta}(x)$, $LastMaximum_{s_j,T}(x)$ and $LastMinimum_{s_j,T}(x)$, are similar.

The solving procedure for CSDPs that we developed maintains a safe enclosure for the set of functions that are solutions of the ODE system and satisfy all the restrictions (the set of possible trajectories). Such trajectory enclosure is based on an interval Taylor series method [12] for solving ODE problems with initial conditions. A sequence of discrete time points $t_0, t_1, \ldots, t_i$ is considered within the whole interval of time T and enclosures are computed not only for the trajectory values at these time points but also for every time gap between two consecutive points. An enclosure at a time point is obtained from a Taylor series expansion around an adjacent time point with the error term bounded as a result of an a priory enclosure computed for the time gap between the two points. An a priory enclosure between two consecutive points is computed based on the interval Picard operator (see [12] for details).

Consider the following binary ODE system O defined for $t \in [0, 6]$:

$$x'(t) = -0.7x(t), \qquad y'(t) = 0.7x(t) - \frac{\ln(2)}{5}y(t)$$

with the initial condition $x(0) = 1.25$ and $y(0) \in [0.4, 0.7]$ specifying a trajectory enclosure at $t = 0$ and an additional restriction requiring the maximum value of component y between $t = 1$ and $t = 3$ to lie within interval $[0, 4]$.

This is represented by CSDP $P = (X, D, C)$ with:

$$\begin{aligned} X &= \langle tr_{ODE}, x_0, y_0, y_{max}\rangle \\ D &= \langle Dtr_{ODE}, Dx_0, Dy_0, Dy_{max}\rangle \\ C &= \{ODE_{O,[0,6]}(tr_{ODE}), Value_{x,0.0}(x_0), Value_{y,0.0}(y_0), \\ &\quad Maximum_{y,[1,3]}(y_{max})\} \end{aligned}$$

and initial domains $Dx_0 = [1.25], Dy_0 = [0.4, 0.7]$, $Dy_{max} = [0, 4]$.

Fig. 2 shows the set of real functions that satisfy the ODE system with the required initial condition. For keeping the illustration in two dimensions, each component of each real function is represented in a different graphic sharing the same time axis: a single line represents component x and the grey area component y.

A possible trajectory enclosure computed by the successive application of the interval Taylor series method is also presented in Fig. 2. The ODE trajectory is defined through a sequence of seven time points and the time gaps in between. For each component, the interval enclosures associated to each time point and time gap are represented, respectively, as a vertical line and a dashed rectangle. Such trajectory enclosure includes all functions whose components are continuous functions enclosed by the rectangles and crossing all the vertical lines; thus, it is a safe enclosing for the set of real functions that satisfy the ODE system and the initial condition.

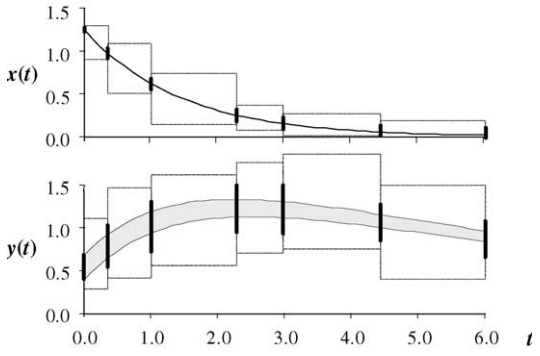


Figure 2 A trajectory enclosure for the set of real functions that satisfy the CSDP P.

The improvement of the quality of a trajectory enclosure is combined with the enforcement of the ODE restrictions through constraint propagation on a set of narrowing functions associated with the CSDP. Some are responsible for reducing the domain of a restriction variable according to the current trajectory enclosure. Others are responsible for reducing the uncertainty of the trajectory enclosure according to the domain of a restriction variable. Finally, there are narrowing functions responsible for reducing the uncertainty of the trajectory enclosure by the successive application of the validated method between consecutive time points.

In the previous example, and according to the trajectory enclosure, the maximum value of the x component between times 1 and 3 can be safely enclosed within the interval $[a, b]$ illustrated in Fig. 3. It cannot exceed b because such value is the maximum upper bound among the time gaps between times 1 and 3 (maximum of all enclosure upper bounds). It cannot be less than a because such value is the minimum possible value at one time point within that time period (maximum of all enclosure lower bounds). Such enclosure is safe as can be easily checked in the figure, where the correct bounds for the maximum value are represented by interval I.

Consequently, the current domain of the restriction variable y_{max} can be safely narrowed by intersecting it with the interval $[a, b]$. Moreover, with better trajectory enclosures, the same reasoning could be used for obtaining smaller domains for restriction variable y_{max} with the guarantee that if the trajectory enclosures are safe, then such domain is also a safe enclosure for the maximum property it represents.

Conversely, if the domain of the restriction variable y_{max} is upper bounded, for example, with value 1.3, then the trajectory enclosures within the time period 1−3 should also be upper bounded by the same value. Such local updates of the trajectory should then be propagated along the whole trajectory enclosure through the reapplication of the interval Taylor series method.

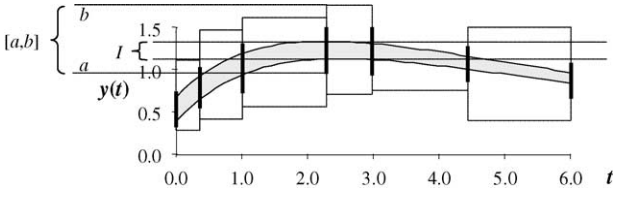


Figure 3 A safe enclosure for the maximum restriction.

2.2. Integration of a CSDP constraint in a CCSP

The full integration of a CSDP within an extended CCSP is accomplished by sharing the restriction variables of the CSDP. The CSDP solving procedure is used as a safe narrowing procedure for reducing the domains of the restriction variables. For example, the CSDP P could be included as a third constraint for the CCSP of Fig. 1 where y_{max} is variable y. The result would be the narrowing of y into $[a, b]$ and the propagation of such narrowing to the other constraints.

3. A differential model for diagnosing diabetes

Diabetes mellitus prevents the body from metabolising glucose due to an insufficient supply of insulin. A glucose tolerance test (GTT) is frequently used for diagnosing diabetes. The patient ingests a large dose of glucose after an overnight fast and in the subsequent hours, several blood tests are made. From the evolution of the glucose concentration, a diagnosis is made by the physicians.

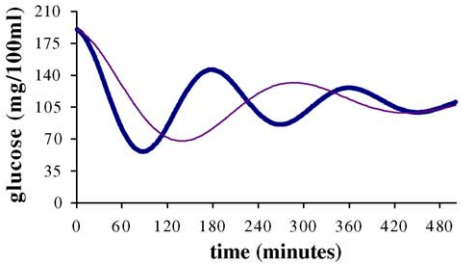
Ackerman et al. [15] proposed a well-known model for the blood glucose regulatory system during a GTT, with the following parametric differential equations:

$$\frac{dg(t)}{dt} = -p_1 g(t) - p_2 h(t),$$
$$\frac{dh(t)}{dt} = -p_3 h(t) + p_4 g(t)$$

where g is the deviation of the glucose blood concentration from its fasting level; h is the deviation of the insulin blood concentration from its fasting level; p_1, p_2, p_3 and p_4 are positive, patient-dependent parameters.

Let $t = 0$ be the instant immediately after the absorption of a large dose of glucose, g_0, when the deviation of insulin from the fasting level is still negligible. According to the model, the evolution of glucose and insulin blood concentrations is described by the trajectory of the above system of differential equations, with initial values $g(0) = g_0$ and $h(0) = 0$, and depends on the parameter values $p_1 - p_4$.

Fig. 4 shows the evolution of the glucose concentration for two patients with a glucose fasting level concentration of 110 mg glucose/100 ml blood. Immediately after the ingestion of an initial dose of glucose, the glucose concentration increases to 190 (i.e. $g_0 = 190 - 110 = 80$). The different trajectories are due to different parameters.



In case A (thick line), typical normal values were used:
p_1=0.0044 p_2=0.04
p_3=0.0045 p_4=0.03

In case B (thin line), parameters p_2 and p_4 were reduced:
p_2=0.033 p_4=0.018

Figure 4 Evolution of the blood glucose concentration.

The general behaviour of the glucose trajectory (and insulin trajectory as well) oscillates around, and eventually converges to, the fasting concentration level. The natural period T of such trajectory is given (in min) by:

$$T = \frac{2\pi}{\sqrt{p_1 p_3 + p_2 p_4}}$$

A criterion used for diagnosing diabetes is based on the natural period T, which is increased in diabetic patients. It is generally accepted that a value for T higher than 4 h is an indicator of diabetes, otherwise normalcy is concluded. We next show how the extended CCSP framework can be used to support the diagnosis of diabetes, possibly interrupting the sequence of blood tests if a safe decision can be made.

3.1. Representing the model and its constraints with an extended CCSP

The above decision problem may be modelled by an extended CCSP with two constraints. A first constraint, defined as a CSDP, relates the evolution of the glucose and insulin concentrations with the trajectory values obtained through the blood tests. A second constraint is a simple numerical constraint relating the natural period with the ODE parameters according to its defining expression.

The CSDP constraint is associated with the following ODE system O based on the original system of differential equations but with the parameters included as new components with null derivatives:

$$O \equiv \begin{cases} g'(t) = -p_1(t)g(t) - p_2(t)h(t) \\ h'(t) = -p_3(t)h(t) + p_4(t)g(t) \\ p_1'(t) = p_2'(t) = p_3'(t) = p_4'(t) = 0 \end{cases}$$

If n blood tests were made at times $t_1, \ldots, t_n$, the constraint is defined by the CSDP P_n, which includes the ODE constraint enforcing the trajectories to satisfy the ODE system O between $t = 0.0$ and $t = t_n$, together with value restrictions representing each known trajectory component value. Variables g_0, h_0, p_1, p_2, p_3 and p_4 are the initial values and variables $g_{t_1}, \ldots, g_{t_n}$, the glucose component values at times $t_1, \ldots, t_n$.

CSDP $P_n = (X_n, D_n, C_n)$ where:

$$\begin{aligned} X_n &= \langle \mathrm{tr}_{\mathrm{ODE}}, g_0, h_0, p_1, p_2, p_3, p_4, g_{t_1}, \ldots, g_{t_n}, T \rangle \\ D_n &= \langle D\mathrm{tr}_{\mathrm{ODE}}, Dg_0, Dh_0, Dp_1, Dp_2, Dp_3, Dp_4, Dg_{t_1}, \\ &\quad \ldots, Dg_{t_n}, DT \rangle \\ C_n &= \{\mathrm{ODE}_{O,[0.0,t_n]}(\mathrm{tr}_{\mathrm{ODE}}), \mathrm{Value}_{g,0.0}(g_0), \\ &\quad \mathrm{Value}_{h,0.0}(h_0), \mathrm{Value}_{p_1,0.0}(p_1), \mathrm{Value}_{p_2,0.0}(p_2), \\ &\quad \mathrm{Value}_{p_3,0.0}(p_3), \mathrm{Value}_{p_4,0.0}(p_4), \\ &\quad \mathrm{Value}_{g,t_1}(g_{t_1}), \ldots, \\ &\quad \mathrm{Value}_{g,t_n}(g_{t_n}), T = 2\pi/\sqrt{p_1 p_3 + p_2 p_4}\} \end{aligned}$$

3.2. Using the extended CCSP for diagnosing diabetes

By solving the extended CCSP P_n with the initial variable domains set up to the available information, the natural period T will be safely bounded, and a guaranteed diagnosis can be made if T is clearly above or below the threshold of 240 min.

In the following, we assume that the acceptable bounds for the parameter values are 50% above/below the typical normal values ($p_1 = 0.0044$, $p_2 = 0.04$, $p_3 = 0.0045$, $p_4 = 0.03$) and study two different patients, A and B, whose observed values for blood glucose concentration largely agree with Fig. 4.

The first blood test on patient A, performed 1 h after the glucose, indicates a glucose deviation from the fasting level concentration of -30 ± 1 mg/100 ml. The extended CCSP P_1 (with a single blood test) is solved by enforcing global hull consistency on the following initial variable domains:

$$\begin{aligned} &Dp_1 = [0.0022, 0.0066], \quad Dp_2 = [0.0200, 0.0600], \\ &Dp_3 = [0.0022, 0.0068], \quad Dp_4 = [0.0150, 0.0450], \\ &Dg_0 = [80.0], \quad Dh_0 = [0.0], \\ &Dg_{60} = [-31.0, -29.0], \quad DT = [-\infty, +\infty]. \end{aligned}$$

After 1 min of CPU time,[1] the natural period is proved to be within 167.5 and 191.8 min, hence smaller than 240 min, so a normal diagnosis can be guaranteed with no need of further examinations.

In patient B, the observed glucose deviation at the same first blood examination is 7 ± 1 mg/100 ml. The initial domains for the variables of P are thus the same of the previous case, except for the observed glucose value $Dg_{60} = [6.0, 8.0]$.

Enforcing global hull consistency on P with such information alone, no safe diagnosis can be attained before the next blood test. In fact, after 46 s, the bounds for the period were guaranteed to be outside the interval [239.6, 272.1], so the period is not guarantedly either below or above the critical threshold of 240 min (although irrelevant in this case, the time period is proved to be within 237.9 and 275.3 min in 13 CPU min). Both diagnoses, normal or diabetic, are still possible, though diabetes is quite likely.

Further information is required, and a second test is performed 1 h later, indicating a glucose concentration of -47 ± 1 mg/100 ml. The extended CCSP P_2 (two blood tests) is solved with the appropriate initial variable domains ($Dg_{60} = [6.0, 8.0]$, $Dg_{120} = [-48.0, -46.0]$, $DT = [237.9, 275.3]$) but still no safe decisions can be made, since in about 5 CPU min, the time period was proven to be within interval [237.9, 273.2].

A third test is thus necessary. After another hour, a -11 ± 1 mg/100 ml blood glucose concentration was measured. Solving again the extended CCSP P_3 with interval $Dg_{180} = [-12.0, -10.0]$, it is guaranteed (after 4 CPU min) that the time period is above 240 min, thus enabling a safe diagnosis of diabetes.

4. A differential model for drug design

Pharmacokinetics studies the time course of drug concentrations in the body, how they move around it and how quickly this movement occurs. Oral drug administration is a widespread method for the delivery of therapeutic drugs to the blood stream. This section is based on the following two-compartment model of the oral ingestion/gastro-intestinal absorption process (see [16] for details):

$$\frac{dx(t)}{dt} = -p_1 x(t) + D(t),$$
$$\frac{dy(t)}{dt} = p_1 x(t) - p_2 y(t)$$

where x is the concentration of the drug in the gastro-intestinal tract, y is the concentration of the drug in the blood stream, D is the drug intake regimen, p_1 and p_2 are positive parameters.

The model considers two compartments, the gastro-intestinal tract and the blood stream. The drug enters the gastro-intestinal tract according to a drug intake regimen, described as a function of time $D(t)$. It is then absorbed into the blood stream at a rate, p_1, proportional to its gastro-intestinal concentration and independently from its blood concentration. The drug is removed from the blood through a metabolic process at a rate, p_2, proportional to its concentration there.

The drug intake regimen $D(t)$ depends on several factors related with the production of the drug by the pharmaceutical company. We assume that the drug is taken on a periodic basis (every 6 h), providing a unit dosage that is uniformly dissolved into the gastro-intestinal tract during the first half hour. Consequently, for each period of 6 h, the intake regimen is defined as:

$$D(t) = \begin{cases} 2 & \text{if } 0.0 \le t \le 0.5 \\ 0 & \text{if } 0.5 \le t \le 6.0 \end{cases}$$

The effect of the intake regimen on the concentrations of the drug in the blood stream during the administration period is determined by the absorption and metabolic parameters, p_1 and p_2. Maintaining the above intake regimen, the solution of the ODE system asymptotically converges to a 6-h periodic trajectory called the limit cycle, shown in Fig. 5 for specific values of the ODE parameters.

In designing a drug, it is necessary to adjust the ODE parameters to guarantee that the drug concentrations are effective, but causing no side effects. In general, it is sufficient to guarantee some constraints on the concentrations over a limit cycle.

One constraint is to keep the drug concentration in the blood within predefined bounds, namely to prevent its maximum value (the peak concentration) to exceed a threshold associated with a side effect. Other constraint imposes bounds on the area under the curve of the drug blood concentration (known as AUC) guaranteeing that the accumulated dosage is high enough to be effective. Finally, bounding the total time that such concentration

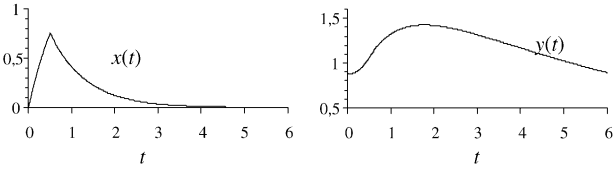


Figure 5 The periodic limit cycle with $p_1 = 1.2$ and $p_2 = \ln(2)/5$.

[1] In this paper, all experiments were made with a Pentium 4, 512 MB RAM, running at 3 GHz.

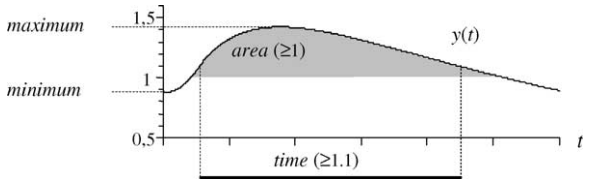


Figure 6 Maximum, minimum, area and time values at the limit cycle ($p_1 = 1.2$ and $p_2 = \ln(2)/5$).

remains above or under some threshold is an additional requirement for controlling drug concentration during the limit cycle. Fig. 6 shows maximum, minimum, area (≥ 1.0) and time (≥ 1.1) for the limit cycle of Fig. 5.

We show below how the extended CCSP framework can be used for supporting the drug design process. We will focus on the absorption parameter, p_1, which may be adjusted by appropriate time release mechanisms (the metabolic parameter, p_2, tends to be characteristic of the drug itself and cannot be easily modified). The tuning of p_1 should satisfy the above requirements during the limit cycle, namely

(1) the drug concentration in the blood bounded between 0.8 and 1.5;
(2) its area under the curve (and above 1.0) bounded between 1.2 and 1.3;
(3) it cannot exceed 1.1 for more than 4 h.

4.1. Representing the model and its constraints with an extended CCSP

The expressive power of the extended CCSP framework allows its use for representing the limit cycle and the different requirements illustrated in Fig. 6. Due to the intake regimen definition $D(t)$, the ODE system has a discontinuity at time $t = 0.5$, and is represented by two CSDP constraints, P_{O_1} and P_{O_2}, in sequence.

The first, P_{O_1}, ranges from the beginning of the limit cycle ($t = 0.0$) to time $t = 0.5$, and the second, P_{O_2}, is associated to the remaining trajectory of the limit cycle (until $t = 6.0$). O_1 and O_2 are the corresponding ODE systems, where p_1 and p_2 are included as new components with null derivatives and the intake regimen $D(t)$ is a constant:

$$O_1 \equiv \begin{cases} x\prime(t) = -p_1(t)x(t) + 2 \\ y\prime(t) = p_1(t)x(t) - p_2(t)y(t) \\ p_1'(t) = p_2'(t) = 0 \end{cases},$$

$$O_2 \equiv \begin{cases} x\prime(t) = -p_1(t)x(t) \\ y\prime(t) = p_1(t)x(t) - p_2(t)y(t) \\ p_1'(t) = p_2'(t) = 0 \end{cases}$$

Both CSDP constraints are defined as shown below for P_{O_1} (P_{O_2} is similar). Besides the ODE constraint, value, maximum value, minimum value, area and time restrictions associate variables with different trajectory properties relevant in this problem. Variables x_{init}, y_{init}, p_1 and p_2 are the initial trajectory values, and x_{fin} and y_{fin} are the final trajectory values of the x and y components. Variables $y_{\max}$ and $y_{\min}$ are the maximum and minimum trajectory values of the y component (drug concentration in the blood stream) for this period. Variables y_a and y_t denote the area above 1.0 and the time above 1.1 of the y component in this same period.

CSDP $P_{O_1} = (X_1, D_1, C_1)$ where:

$$\begin{aligned} X_1 &= \langle \text{tr}_{\text{ODE}}, x_{\text{init}}, y_{\text{init}}, p_1, p_2, x_{\text{fin}}, y_{\text{fin}}, y_{\max}, \\ &\quad y_{\min}, y_a, y_t \rangle \\ D_1 &= \langle D\,\text{tr}_{\text{ODE}}, Dx_{\text{init}}, Dy_{\text{init}}, Dp_1, Dp_2, Dx_{\text{fin}}, Dy_{\text{fin}}, \\ &\quad Dy_{\max}, Dy_{\min}, Dy_a, Dy_t \rangle \\ C_1 &= \{\text{ODE}_{O_1,[0.0,0.5]}(\text{tr}_{\text{ODE}}), \text{Value}_{x,0.0}(x_{\text{init}}), \\ &\quad \text{Value}_{y,0.0}(x_{\text{init}}), \text{Value}_{p_1,0.0}(p_1), \text{Value}_{p_2,0.0}(p_2), \\ &\quad \text{Value}_{x,0.5}(x_{\text{fin}}), \text{Value}_{y,0.5}(y_{\text{fin}}), \\ &\quad \text{Maximum}_{y,[0.0,0.5]}(y_{\max}), \text{Minimum}_{y,[0.0,0.5]}(y_{\min}), \\ &\quad \text{Area}_{y,[0.0,0.5],\geq 1.0}(y_a), \text{Time}_{y,[0.0,0.5],\geq 1.1}(y_t)\} \end{aligned}$$

The extended CCSP P connects in sequence the two ODE segments by assigning the same variables x_{05} and y_{05} to both the final values of P_{O_1} and the initial values of P_{O_2} (parameters p_1 and p_2 are shared by both constraints). Moreover, the 6-h period is guaranteed by the assignment of the same variables x_0 and y_0 to both the initial values of P_{O_1} and the final values of P_{O_2}. Besides considering all the restriction variables ($y_{\max}, \ldots, y_t$) of each ODE segment, new variables for the whole trajectory y_{area} and y_{time} sum the values in each segment.

CSDP $P = (X, D, C)$ where:

$$\begin{aligned} X &= \langle x_0, y_0, p_1, p_2, x_{05}, y_{05}, y_{\max 1}, y_{\max 2}, y_{\min 1}, \\ &\quad y_{\min 2}, y_{a_1}, y_{a_2}, y_{\text{area}}, y_{t_1}, y_{t_2}, y_{\text{time}} \rangle \\ D &= \langle Dx_0, Dy_0, Dp_1, Dp_2, Dx_{05}, Dy_{05}, Dy_{\max 1}, \\ &\quad Dy_{\max 2}, Dy_{\min 1}, Dy_{\min 2}, Dy_{a_1}, Dy_{a_2}, Dy_{\text{area}}, Dy_{t_1}, \\ &\quad Dy_{t_2}, Dy_{\text{time}} \rangle \\ C &= \{P_{O_1}(x_0, y_0, p_1, p_2, x_{05}, y_{05}, y_{\max 1}, y_{\min 1}, y_{a_1}, y_{t_1}), \\ &\quad P_{O_2}(x_{05}, y_{05}, p_1, p_2, x_0, y_0, y_{\max 2}, y_{\min 2}, y_{a_2}, y_{t_2}), \\ &\quad y_{\text{area}} = y_{a_1} + y_{a_2}, y_{\text{time}} = y_{t_1} + y_{t_2}\} \end{aligned}$$

4.2. Using the extended CCSP for parameter tuning

The tuning of drug design may be supported by solving P with the appropriate set of initial domains for its variables. We will assume p_2 to be fixed to a 5-h half live ($Dp_2 = [\ln(2)/5]$) and p_1 to be adjustable up to about 10-min half live ($Dp_1 = [0, 4]$). The initial value x_0, always very small, is safely bounded in interval $Dx_0 = [0.0, 0.5]$.

The assumptions about the parameter ranges together with the bounds imposed by the above requirements justify the following initial domains for the variables of P (all the remaining variable domains are unbounded):

$$Dx_0 = [0.0, 0.5], \quad Dy_0 = [0.8, 1.5],$$
$$Dp_1 = [0.0, 4.0], \quad Dp_2 = [\ln(2)/5],$$
$$Dy_{\min 1} = [0.8, 1.5], \quad Dy_{\max 1} = [0.8, 1.5],$$
$$Dy_{\text{area}} = [1.2, 1.3], \quad Dy_{\min 2} = [0.8, 1.5],$$
$$Dy_{\max 2} = [0.8, 1.5], \quad Dy_{\text{time}} = [0.0, 4.0].$$

Solving the extended CCSP P (enforcing global hull consistency), with a precision of 0.001, narrows the original p_1 interval to [1.191, 1.543] in about 1.5 min. Hence, for p_1 outside this interval, the set of requirements cannot be satisfied.

This may help to adjust p_1 but offers no guarantees on specific choices within the obtained interval. For instance, two canonical solutions for p_1, [1.191, 1.192] and [1.542, 1.543], contain no real solution, since when solving the problem with a higher precision (0.000001), the domain of p_1 is narrowed to [1.209233, 1.474630] that does not include the above canonical solutions (obtained with the lower 0.001 precision).

Nevertheless, using CCSP P with different initial domains may produce guaranteed results for particular choices of the p_1 parameter values. For example, for $p_1 \in [1.3, 1.4]$ (the manufacturing process prevents p_1 to be expressed with higher precision), and the following initial domains (the remaining are unbounded):

$$Dx_0 = [0.0, 0.5], \quad Dy_0 = [0.8, 1.5],$$
$$Dp_1 = [1.3, 1.4], \quad Dp_2 = [\ln(2)/5]$$

global hull consistency on P (with 0.001 precision) narrows the following, initially unbounded, domains to:

$$y_{\min 1} \in [0.881, 0.891], \quad y_{\max 1} \in [1.090, 1.102],$$
$$y_{\text{area}} \in [1.282, 1.300],$$
$$y_{\min 2} \in [0.884, 0.894], \quad y_{\max 2} \in [1.447, 1.462],$$
$$y_{\text{time}} \in [3.908, 3.967].$$

Notwithstanding the uncertainty, these results do prove that with p_1 within [1.3, 1.4], all limit cycle requirements are safely guaranteed (the obtained bounds are well within the requirements). Moreover, they offer some insight on the requirements showing, for instance, the area requirement to be the most critical constraint.

The above bounds were obtained in about 7 min. However, faster results may be obtained if the goal is simply to check whether the requirements are met. Since global hull consistency is enforced by an any-time algorithm, its execution may be interrupted as soon as the requirements are satisfied (5 min in this case).

A better approach in this case would be to prove that the CCSP P with the initial domains $Dx_0 = [0.0, 0.5], Dy_0 = [0.8, 1.5], Dp_1 = [1.3, 1.4]$ and $Dp_2 = [\ln(2)/5]$ together with each of the following domains cannot contain any solution (again, the remaining domains are kept unbound):

$$Dy_{\max 1} = [1.5, +\infty], \quad Dy_{\max 2} = [1.5, +\infty],$$
$$Dy_{\min 1} = [-\infty, 0.8], \quad Dy_{\min 2} = [-\infty, 0.8],$$
$$Dy_{\text{area}} = [1.3, +\infty], \quad Dy_{\text{area}} = [-\infty, 1.2],$$
$$Dy_{\text{time}} = [4.0, +\infty].$$

By independently proving that no solutions exist for the above problems, which cover all non-satisfying possibilities, it is proved that all the requirements are necessarily satisfied. This was achieved in less than 3 min.

5. The SIR model of epidemics

The time development of epidemics is the subject of many mathematical models that have been proved useful for the understanding and control of infectious diseases. The SIR model [17] is a well-known model of epidemics which divides a population into three classes of individuals and is based on the following parametric ODE system:

$$\frac{dS(t)}{dt} = -rS(t)I(t), \quad \frac{dI(t)}{dt} = rS(t)I(t) - aI(t),$$
$$\frac{dR(t)}{dt} = aI(t)$$

where S are the susceptibles, individuals who can catch the disease; I are the infectives, individuals who have the disease and can transmit it; R are the removed, individuals who had the disease and are immune or died; r and a are positive parameters.

The model assumes that the total population N is constant ($N = S(t) + I(t) + R(t)$) and the incubation period is negligible. Parameter r accounts for the efficiency of the disease transmission (proportional to the frequency of contacts between susceptibles and infectives). Parameter a measures the recovery (removing) rate from the infection.

Important questions in epidemic situations are: whether the infection will spread or not; what will be the maximum number of infectives; when will it start to decline; when will it end; and how many people will catch the disease.

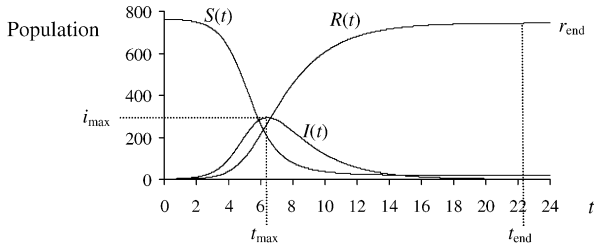


Figure 7 SIR model predictions with $S(0) = 762$, $I(0) = 1$, $R(0) = 0$, $r = 0.00218$ and $a = 0.44036$.

Fig. 7 shows the number of susceptibles, infectives and removed as a function of time, as predicted by the SIR model with $S(0) = 762$, $I(0) = 1$, $R(0) = 0$, $r = 0.00218$ and $a = 0.44036$. In this case, the infection will spread up to a maximum number of infected of about 294 individuals (i_{max}), starting to decline after 6.5 days (t_{max}), ending after 22.2 days (t_{end}) and affecting a total of 744 individuals (r_{end}).

Frequently, there is information available about the spread of a disease on a particular population. This is usually gathered as series of time-infectives (t_i, I_i) or time-removed (t_i, R_i) data points together with the values (t_0, S_0), (t_0, I_0) or (t_0, R_0) that initiated the epidemics on the population. An important problem is to predict the behaviour of a similar disease (with similar parameter values) when occurring in a different environment, namely with a different population size or a different number of initial infectives.

The following study is based on data reported in the British Medical Journal (4 March 1978) from an influenza epidemic that occurred in an English boarding school (taken from [17]): a single boy (from a total population of 763) initiated the epidemics and the evolution of the number of infectives, available daily, from day 3 to day 14, is shown in Table 1.

The goal of our study is to predict what would happen if a similar disease would occur in a different place, say a small town with a population of about 10,000 individuals. Moreover, if there is a vaccine to that disease, what would be the vaccination rate necessary to guarantee that the maximum number of infectives never exceeds some predefined threshold, for example, half of the total population.

5.1. Using the extended CCSP for characterizing an epidemic disease

The first step for solving the above problem is to characterize an epidemic disease which is similar to the one reported in the boarding school. The classical approach would be to perform a numerical best fit approximation to compute the parameter values r' and a' that minimize the residual:

$$\sum_{j=1}^{m} (I(t_j) - I_{t_j})^2$$

where $I_{t_1}, \ldots, I_{t_m}$ are the infectives observed at times $t_1, \ldots, t_m$, and $I(t_1), \ldots, I(t_m)$ their respective values predicted by the SIR model with $r = r'$ and $a = a'$. In [17], this method is used to compute $r = 0.00218$ and $a = 0.44036$ with a residual of 4221 (Fig. 7 shows the best fit solution).

Table 1 Infectives reported during an epidemics in an English boarding school

t	I_t
0	1
3	22
4	78
5	222
6	300
7	256
8	233
9	189
10	128
11	72
12	28
13	11
14	6

However, generating a single value for each parameter does not capture the essence of the problem which is not to determine the most similar disease but rather to reason with a set of similar enough diseases. Moreover, such approach does not provide any sensitive analysis about the quality of the data fitting, namely on the effects of small changes on the parameter values.

An alternative, possible in a constraints framework, is to relax the imposition of the "best" fit and merely impose a "good" fit. This can be achieved either by considering acceptable errors ε_j for each observed data and computing ranges for the parameters such that the distance between the model predictions and the observed data does not exceed these errors or by imposing some upper bound on the residual value (or any other measure of the unfitness of the model).

Neither the first approach, known as the data driven inverse problem, nor the second approach, denoted here as the maximum residual problem, can be solved by classical constraint approaches, since the epidemic model has no analytical solution form.

However, both problems can be represented as extended CCSPs, P_1 and P_2, respectively, which include a CSDP constraint P_O, representing the evolution of the susceptibles and infectives during the

reported period of time (the first 14 days). The associated ODE system O is composed by the first two components of the SIR model together with two extra components, with null derivatives, for representing the parameters:[2]

$$O \equiv \begin{cases} S'(t) = -0.01r(t)S(t)I(t) \\ I'(t) = 0.01r(t)S(t)I(t) - a(t)I(t) \\ r'(t) = a'(t) = 0 \end{cases}$$

CSDP P_O contains several value restrictions for associating variables with: the initial values of the susceptible (s_0) and infective (i_0); the parameter values (r and a); and the values of the infective at times $3, \ldots, 14$ ($i_3, \ldots, i_{14}$).

CSDP $P_O = (X, D, C)$ where:

$$\begin{aligned} X &= \langle \mathrm{tr}_{\mathrm{ODE}}, s_0, i_0, r, a, i_3, \ldots, i_{14} \rangle \\ D &= \langle D\mathrm{tr}_{\mathrm{ODE}}, Ds_0, Di_0, Dr, Da, Di_3, \ldots, Di_{14} \rangle \\ C &= \{\mathrm{ODE}_{O,[0.0,14.0]}(\mathrm{tr}_{\mathrm{ODE}}), \mathrm{Value}_{S,0.0}(s_0), \\ &\quad \mathrm{Value}_{I,0.0}(i_0), \mathrm{Value}_{r,0.0}(r), \mathrm{Value}_{a,0.0}(a), \\ &\quad \mathrm{Value}_{I,3.0}(i_3), \ldots, \mathrm{Value}_{I,14.0}(i_{14})\} \end{aligned}$$

The extended CCSP P_2, which represents the maximum residual problem, besides CSDP constraint P_O, contains also a numerical constraint defining the residual (R) from the variables $i_3, \ldots, i_{14}$ and the observed values (represented as constants $k_3, \ldots, k_{14}$).

CSDP $P_1 = (X_1, D_1, C_1)$ where:

$$\begin{aligned} X_1 &= \langle s_0, i_0, r, a, i_3, \ldots, i_{14} \rangle \\ D_1 &= \langle Ds_0, Di_0, Dr, Da, Di_3, \ldots, Di_{14} \rangle \\ C_1 &= \{P_O(s_0, i_0, r, a, i_3, \ldots, i_{14})\} \end{aligned}$$

CSDP $P_2 = (X_2, D_2, C_2)$ where:

$$\begin{aligned} X_2 &= \langle s_0, i_0, r, a, i_3, \ldots, i_{14} \rangle \\ D_2 &= \langle Ds_0, Di_0, Dr, Da, Di_3, \ldots, Di_{14} \rangle \\ C_2 &= \{P_O(s_0, i_0, r, a, i_3, \ldots, i_{14}), R = \textstyle\sum (i_j - k_j)^2\} \end{aligned}$$

Assuming very wide initial parameter ranges ($D_r = D_a = [0, 1]$), the "good" fit requirement can now be enforced by solving either P_1 or P_2 with appropriate initial domains for the remaining variables (the values of the susceptible and infective are initialized according to the report, $Ds_0 = [762]$ and $Di_0 = [1]$). In the case of P_1, each Di_j should be initialized with the interval $[\lfloor k_j - \varepsilon_j \rfloor, \lceil k_j + \varepsilon_j \rceil]$ (for example, with $\varepsilon_j = 30$). In the case of P_2, all Di_j are kept unbounded, but the residual initial domain DR must be upper bounded (for example, with $DR = [0, 4800]$).

Enforcing global hull consistency (with precision 10^{-6}) on P_1 with $\varepsilon_j = 30$, the parameter ranges are narrowed from [0, 1] to $r \in [0.214, 0.222]$ and $a \in [0.425, 0.466]$ in about 18 min. Identical narrowing would be obtained by enforcing global hull consistency (with precision 10^{-6}) on P_2 with $DR = [0, 4800]$: $r \in [0.213, 0.224]$ and $a \in [0.423, 0.468]$.

5.2. Using the extended CCSP for predicting the epidemic behaviour

Once obtained the parameter ranges that may be considered acceptable to characterize epidemic diseases similar to the one observed, the next step is to use them for making predictions in the new context of a population of 10,000 individuals.

In this case, a single CSDP constraint $P_{O'}$ represents the first two components of the model together with ODE restrictions associating variables with the predicted values (besides the value restrictions to associate variables with the parameter values r and a and the initial values s_0 and i_0). A maximum value restriction represents the infectives' maximum value $i_{\max}$ and a first maximum restriction represents the time of such maximum $t_{\max}$. A last value restriction represents the duration t_{end} of the epidemics as the last time that the number of infectives exceeds 1. Finally, a value restriction represents the number of people s_{25} that are still susceptible at a time (25) safely after the end of the epidemics.

CSDP $P_{O'} = (X, D, C)$ where:

$$\begin{aligned} X &= \langle \mathrm{tr}_{\mathrm{ODE}}, s_0, i_0, r, a, i_{\max}, t_{\max}, t_{\mathrm{end}}, s_{25} \rangle \\ D &= \langle D\,\mathrm{tr}_{\mathrm{ODE}}, Ds_0, Di_0, Dr, Da, Di_{\max}, Dt_{\max}, \\ &\quad Dt_{\mathrm{end}}, Ds_{25} \rangle \\ C &= \{\mathrm{ODE}_{O,[0.0,25.0]}(\mathrm{tr}_{\mathrm{ODE}}), \mathrm{Value}_{S,0.0}(s_0), \\ &\quad \mathrm{Value}_{I,0.0}(i_0), \mathrm{Value}_{r,0.0}(r), \mathrm{Value}_{a,0.0}(a), \\ &\quad \mathrm{Maximum}_{I,[0.0,25.0]}(i_{\max}), \\ &\quad \mathrm{FirstMaximum}_{I,[0.0,25.0]}(t_{\max}), \\ &\quad \mathrm{LastValue}_{I,[0.0,25.0],\geq 1.0}(t_{\mathrm{end}}), \mathrm{Value}_{S,25.0}(s_{25})\} \end{aligned}$$

Solving such problem with the parameters ranging within the previously obtained intervals (for example, $Dr = [0.213, 0.224]$ and $Da = [0.423, 0.468]$), the initial value domains $Ds_0 = [9999]$ and $Di_0 = [1]$, and all the other variable domains unbounded, the results obtained for these domains indicated that:

- $i_{\max} \in [8939, 9064]$ clearly suggesting the spread of a severe epidemics;
- $t_{\max} \in [0.584, 0.666]$ and $t_{\mathrm{end}} \in [20.099, 22.405]$ predicting that the maximum will occur during the first 14–16 h (0.584–0.666 days), starting then to decline and ending before the 10th hour of day 22;
- $s_{25} \in [0, 0.001]$ showing that everyone will eventually catch the disease.

[2] In the equations, r is multiplied by 0.01 rescaling it to the interval [0, 1] (its best fit value 0.00218 is rescaled to 0.218).

If the administration of a vaccine is considered at a rate λ proportional to the number of susceptibles, then the differential model must be modified into:

$$\frac{dS(t)}{dt} = -rS(t)I(t) - \lambda S(t),$$
$$\frac{dI(t)}{dt} = rS(t)I(t) - aI(t), \qquad \frac{dR(t)}{dt} = aI(t) + \lambda S(t)$$

The requirement that the maximum number of infectives cannot exceed half of the population is represented by adding the numerical constraint $i_{max} \leq 5000$. Solving this new CCSP with the λ initial domain [0, 1.5], its lower bound is raised up to 0.985 indicating that at least such vaccination rate is necessary to satisfy the requirement.

6. Conclusion

This paper presents a framework to make decisions with deep biomedical models expressed by differential equations, with a constraint reasoning approach. In contrast to Monte Carlo and other stochastic techniques that can only assign likelihoods to the different decision options, and despite the uncertainty of medical information and approximation errors during calculations, the enhanced propagation techniques developed (enforcing global hull consistency) allow safe decisions to be made. Whereas the traditional use of complex differential models for which there are no analytical solutions is currently unsafe, the constraint reasoning framework extends the possibility of practical introduction of this type of models in medical decision making, especially when safe decisions are required.

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