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Guaranteed computation methods for compartmental in-series models under uncertainty

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Abstract

The pattern of some real phenomenona can be described by compartmental in-series models. Nevertheless, most of these processes are characterized by their variability, which produces that the exact values of the model parameters are uncertain, although they can be bounded by intervals.

The aim of this paper is to compute tight solution envelopes that guarantee the inclusion of all possible behaviours of such processes. Current methods, such as monotonicity analysis, enable us to obtain guaranteed solution envelopes. However, if the model includes non-monotone compartments or parameters, the computation of solution envelopes may produce a significant overestimation.

Our proposal consists in performing a change of variables in which the output is unaltered, and the model obtained is monotone with respect to the uncertain parameters. The monotonicity of the new system allows us to compute the output bounds for the original system without overestimation. These model transformations have been developed for linear and non-linear systems. Furthermore, if the conditions are not completely satisfied, a novel method to compute tight solution envelopes is proposed. The methods exposed in this paper have been applied to compute tight solution envelopes for two different models: a linear system for glucose modelling and a non-linear system for an epidemiological model.

Keywords: Compartmental models, Uncertainty, Parametric uncertainty, Interval simulations

1. Introduction

Compartmental systems have been widely used to simulate processes from many different real situations emerging from biology, economics, engineering, medicine, human sciences and many other research fields. When studying a real process with a mathematical system, there is always some mismatch between the model and reality, caused because mathematical models are usually a simplified version of the actual processes. Furthermore, a common characteristic of any real phenomenon is variability, leading to parametric uncertainty. Therefore, the exact values for the initial conditions and model parameters are unknown, although they can be bounded

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by intervals. While there is a single possible behaviour for a model with constant parameters, parametric uncertainty produces a set of different possible solutions. Hence, the computation of solution envelopes acquires importance.

Monte Carlo approaches have been used to implement these kinds of systems. They consist in performing a large number of different simulations by the variation of the parameter values [1]. These methods have been widely used to deal with uncertainty due to their easy computation. However, the computational cost of Monte Carlo approaches increases proportionally to the number of simulations executed and, moreover, they never guarantee that the bounds obtained include all the possible solutions, independently to the number of simulations [2]. This inclusion guarantee is needed for error-bounded parametric identification and constraint-satisfaction problems.

Trajectory-based approaches have been also applied to obtain solution envelopes [3–5]. Compared with Monte Carlo simulations, monotonicity analysis guarantees that the actual response is inside the envelopes. However, if the model analysed includes any non-monotone state or parameter, the computation of solution envelopes may produce a significant overestimation. If the overestimation is high, it could not be useful from a practical point of view, for instance, in an insulin therapy for diabetes patients [6].

This work is an extension of the paper [7], which aims to compute tight solution envelopes for compartmental in-series models under parametric uncertainty. The solution envelopes computed must guarantee the inclusion of all possible solutions and minimize the overestimation. The proposal consists in performing a change of variables of the original model to obtain a monotone system with respect to its states and parameters, and keeping the output unaltered. As all the states and parameters of the new model are monotone, output bounds can be computed without overestimation. In [7], these model transformations were formulated in a lemma for bidirectional chains. In this work, we propose an additional lemma for unidirectional chains that requires fewer conditions. Furthermore, when the system does not completely satisfy the lemma conditions, we propose a new method to compute tight solution envelopes that consists in the application of an upper and a lower bounding model.

This work has been organised as follows: In Section 2, uncertain systems are introduced. In Section 3, compartmental in-series models are presented. In Section 4, several new methods are proposed for the analysis of the system monotonicity with respect to the parameters. In Section 5, a novel technique is proposed for near-monotone systems. In Section 6, the proposed methods are applied to compute the output bounds for linear and non-linear models. Finally, Section 7 outlines the conclusions of this study.

2. Uncertain systems

Continuous-time compartmental systems are described by an initial-value problem (IVP):

$$\begin{aligned} &\dot{x}(t,p) = f(t,x,p,u), \quad x(t_0) = x_0, \\ &x \in \mathbb{R}^n,\ t \in \mathbb{R},\ p \in \mathbb{R}^{n_p},\ u \in \mathbb{R}^n \end{aligned} \tag{1}$$

where f is the vector function with components f_i, x is the state vector, p is the parameter vector, n_p is the number of parameters, and u is the input vector. The solution of (1) is denoted by $x(t; t_0, x_0, p, u)$.

As parametric uncertainty is considered, initial conditions and parameter values are unknown, but they can be bounded by intervals. Representing intervals in bold, interval vectors $\mathbf{p}$, $\mathbf{u}$ and $\mathbf{x_0}$ include all possible values for the parameters p, for the input vector u and for the initial conditions x_0 of the model, respectively. The set of possible solutions derived from parametric uncertainty is denoted by $\mathbf{x}(t; t_0, \mathbf{x_0}, \mathbf{p}, \mathbf{u})$:

$$\mathbf{x}(t; t_0, \mathbf{x_0}, \mathbf{p}, \mathbf{u}) = \{x(t; t_0, x_0, p, u) \mid x_0 \in \mathbf{x_0}, p \in \mathbf{p}, u \in \mathbf{u}\}.$$

The computation of solution envelopes plays a key role in the simulation of systems under parametric uncertainty. Such a computation can be performed by one-step-ahead iteration based on previous approximations of a set of point-wise trajectories generated by the selection of particular values of the parameters $p \in \mathbf{p}$, the input vector $u \in \mathbf{u}$ and the initial conditions $x_0 \in \mathbf{x_0}$ by using heuristics such as a monotonicity analysis of the system [8].

Monotone systems have very robust dynamical characteristics, since they respond to perturbations in a predictable way. The interconnection of monotone systems may be studied in an analytical way [9], by considering a flow $\mathbf{x}(t) = \phi(\mathbf{x_0}, t)$. A system is monotone with respect to the states, or simply monotone, if $\mathbf{x_0} \preceq \mathbf{y_0} \Rightarrow \phi(\mathbf{x_0}, t) \preceq \phi(\mathbf{y_0}, t)$ for all $t \geq 0$, where $\preceq$ is a given order relation. Cooperative systems form a class of monotone dynamical systems [4] in which

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad \text{for all } i \neq j,\ t \geq 0.$$

An upper bounding model and a lower bounding model are computed to obtain solution envelopes for the original model. The cooperative states take their upper (lower) bound value in an upper (lower) bounding model, while the monotone but non-cooperative states, known as competitive states, take their lower (upper) bound value in an upper (lower) bounding model. Nevertheless, in both cases non-monotone states have to be computed as intervals that produce a significant overestimation in the computation of solution envelopes.

The monotonicity of the system with respect to the parameters of the model can be analysed by considering the parameters as system states in an extended model [3], that is, by performing a monotonicity analysis of a new system with $n + n_p$ states given by:

$$\begin{aligned}
\dot{x}_1(t) &= f_1(t, x_1(t), x_2(t), ..., x_n(t), p_1(t), p_2(t), ..., u_1(t)) \\
&\vdots \\
\dot{x}_n(t) &= f_n(t, x_1(t), x_2(t), ..., x_n(t), p_1(t), p_2(t), ..., u_n(t)) \\
\dot{p}_i(t) &= 0 \quad \forall i \in \{1, \ldots, n_p\}
\end{aligned} \tag{2}$$

Thus, a system (1) is monotone with respect to a parameter if the extended system (2) is monotone with respect to the corresponding extended model states.

3. Compartmental in-series models

Compartmental systems consist of a finite number of interconnected subsystems called compartments. The interactions among compartments are transfers of material according to the law of conservation of mass [10]. The state variables of these systems represent the amount of material contained in each compartment. For this reason, compartmental systems belong to the broader class of *non-negative* systems [11]:

Definition 3.1. *A non-linear dynamical system* $\dot{x}(t) = f(x(t)) + G(x(t))u(t)$ *is non-negative if for every non-negative initial state and non-negative control vector, the solution* $x(t)$, $t \geq 0$, *is non-negative.*

A general compartmental in-series model composed of n compartments is shown in Figure 1.

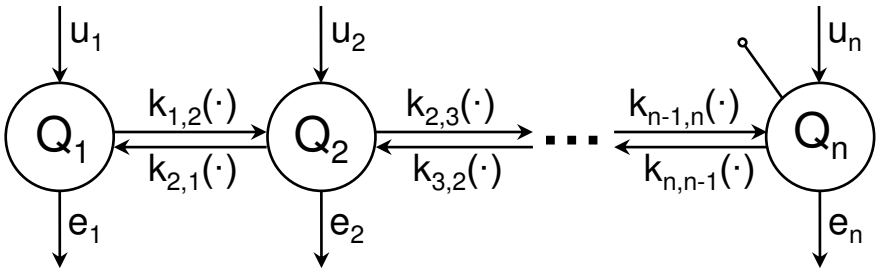

Figure 1: *Diagram of a compartmental in-series model.*

If the fluxes among the compartments of an in-series model go forward and backward, the model is called bidirectional. However, if the fluxes just go forward, the in-series model is named unidirectional. Bidirectional in-series models are given by the following equations:

$$\begin{aligned}
\dot{Q}_1(t) &= u_1(t) - (k_{1,2}(\cdot) + e_1)Q_1(t) + k_{2,1}(\cdot)Q_2(t) \\
\dot{Q}_i(t) &= u_i(t) + k_{i-1,i}(\cdot)Q_{i-1}(t) + k_{i+1,i}(\cdot)Q_{i+1}(t) - (k_{i,i-1}(\cdot) + k_{i,i+1}(\cdot) + e_i)Q_i(t) \\
\dot{Q}_n(t) &= u_n(t) + k_{n-1,n}(\cdot)Q_{n-1}(t) - (k_{n,n-1}(\cdot) + e_n)Q_n(t) \\
Q_1(0) &= Q_{1_0}, \quad Q_i(0) = Q_{i_0}, \quad Q_n(0) = Q_{n_0}
\end{aligned} \tag{3}$$

for $i \in \{2, ..., n-1\}$, where the states of the model $Q_j(t) \geq 0$, $j \in \{1, ..., n\}$, are the in-series compartments. Furthermore, $u_j(t) \geq 0$, $j \in \{1, ..., n\}$, represent the inputs, $e_j \geq 0$, $j \in \{1, ..., n\}$, are parameters that denote the elimination rates for each compartment, while $k_{i,j}(\cdot) \geq 0$, $i, j \in \{1, ..., n\}$, are non-negative scalar functions that represent the flux from the compartment i to the compartment j and they may depend on the states of the model and on a parameter $\alpha_{i,j}$, i.e., $k_{i,j}(\cdot) = k_{i,j}(Q_1(t), \ldots, Q_n(t), \alpha_{i,j}) \geq 0$, such that $\frac{\partial k_{i,j}}{\partial \alpha_{i,j}} \geq 0$. The system will be linear if the fluxes among the compartments are constant, i.e. $k_{i,i+1}(\cdot) = \alpha_{i,i+1}$ and $k_{i+1,i}(\cdot) = \alpha_{i+1,i}$, $i \in \{1, ..., n-1\}$. From now on, we consider that $Q_n(t)$ is the output of the model.

The extended system (including parameters as constant states) is given by adding the following equation to the previous system (3):

$$\dot{p}(t) = 0, \quad p(0) = p_0 \tag{4}$$

where p encompasses the parameters of the model, i.e., e_i, $\alpha_{j,j+1}$, $\alpha_{j+1,j} \in p$, $\forall i \in \{1, ..., n\}$, $\forall j \in \{1, ..., n-1\}$.

4. Analysis of the system monotonicity

In this section, we analyse compartmental in-series models by focusing on the monotonicity of the dynamical system with respect to the states and the parameters of the model.

Let us consider a non-linear bidirectional in-series system (3) and its extended system given by (4). Note that it is not possible to determine the exact sign of the partial derivatives $\frac{\partial \dot{Q}_i(t)}{\partial Q_j(t)}$, $i, j \in \{1, ..., n\}, i \neq j$. Here we have an example:

$$\frac{\partial \dot{Q}_1(t)}{\partial Q_2(t)} = -\frac{\partial k_{1,2}(\cdot)}{\partial Q_2(t)} Q_1(t) + k_{2,1}(\cdot) + \frac{\partial k_{2,1}(\cdot)}{\partial Q_2(t)} Q_2(t)$$

Consequently, some states of the model may be non-monotone. Therefore, the system monotonicity cannot be analysed with respect to the compartments or the parameters of the model through the extension given in (2). We propose to transform in-series system (3) by performing a change of variables, keeping unaltered the output compartment. This new system is given by:

$$\begin{aligned}
\dot{S}_1(t) &= \textstyle\sum_{j=1}^{n} u_j(t) - \sum_{j=1}^{n-1} e_j(S_j(t) - S_{j+1}(t)) - e_n S_n(t) \\
\dot{S}_i(t) &= \textstyle\sum_{j=i}^{n} u_j(t) + k_{i-1,i}(\cdot)(S_{i-1}(t) - S_i(t)) - k_{i,i-1}(\cdot)(S_i(t) - S_{i+1}(t)) \\
&\quad - \textstyle\sum_{j=i}^{n-1} e_j(S_j(t) - S_{j+1}(t)) - e_n S_n(t) \\
\dot{S}_n(t) &= u_n(t) + k_{n-1,n}(\cdot)(S_{n-1}(t) - S_n(t)) - (k_{n,n-1}(\cdot) + e_n) S_n(t) \\
\dot{p}(t) &= 0
\end{aligned} \tag{5}$$

for $i \in \{2, ..., n-1\}$, where $S_i = \sum_{j=i}^{n} Q_j(t)$, $\forall i \in \{1, ..., n\}$. It is worth mentioning that all the fluxes $k_{i,j}$ in this new system may depend on the new states S_i, due to the fact that $k_{i,j}(\cdot) = k_{i,j}(Q_1(t), \ldots, Q_n(t), \alpha_{i,j})$ where $Q_i(t) = S_i(t) - S_{i+1}(t)$, $i \in \{1, ..., n-1\}$ and $Q_n(t) = S_n(t)$. Now we have that, for $i \in \{2, ..., n-1\}$:

$$\begin{cases}
\frac{\partial \dot{S}_1(t)}{\partial S_j(t)} = e_{j-1} - e_j & (2 \leq j \leq n), \\
\frac{\partial \dot{S}_i(t)}{\partial S_j(t)} = \frac{\partial k_{i-1,i}(\cdot)}{\partial S_j(t)}(S_{i-1}(t) - S_i(t)) - \frac{\partial k_{i,i-1}(\cdot)}{\partial S_j(t)}(S_i(t) - S_{i+1}(t)) & (j < i-1), \\
\frac{\partial \dot{S}_i(t)}{\partial S_{i-1}(t)} = \frac{\partial k_{i-1,i}(\cdot)}{\partial S_{i-1}(t)}(S_{i-1}(t) - S_i(t)) - \frac{\partial k_{i,i-1}(\cdot)}{\partial S_{i-1}(t)}(S_i(t) - S_{i+1}(t)) + k_{i-1,i}(\cdot), & \\
\frac{\partial \dot{S}_i(t)}{\partial S_{i+1}(t)} = \frac{\partial k_{i-1,i}(\cdot)}{\partial S_{i+1}(t)}(S_{i-1}(t) - S_i(t)) - \frac{\partial k_{i,i-1}(\cdot)}{\partial S_{i+1}(t)}(S_i(t) - S_{i+1}(t)) + k_{i,i-1}(\cdot) + (e_i - e_{i+1}), & \\
\frac{\partial \dot{S}_i(t)}{\partial S_j(t)} = \frac{\partial k_{i-1,i}(\cdot)}{\partial S_j(t)}(S_{i-1}(t) - S_i(t)) - \frac{\partial k_{i,i-1}(\cdot)}{\partial S_j(t)}(S_i(t) - S_{i+1}(t)) + (e_{j-1} - e_j) & (j > i+1), \\
\frac{\partial \dot{S}_n(t)}{\partial S_j(t)} = \frac{\partial k_{n-1,n}(\cdot)}{\partial S_j(t)}(S_{n-1}(t) - S_n(t)) - \frac{\partial k_{n,n-1}(\cdot)}{\partial S_j(t)} S_n(t) & (j < n-1), \\
\frac{\partial \dot{S}_n(t)}{\partial S_{n-1}(t)} = \frac{\partial k_{n-1,n}(\cdot)}{\partial S_{n-1}(t)}(S_{n-1}(t) - S_n(t)) - \frac{\partial k_{n,n-1}(\cdot)}{\partial S_{n-1}(t)} S_n(t) + k_{n-1,n}(\cdot) &
\end{cases}$$

For $i \in \{1, ..., n\}$:

$$\begin{cases} \frac{\partial \dot{S}_i(t)}{\partial e_j(t)} = 0 & (1 \leq j < i), \\ \frac{\partial \dot{S}_i(t)}{\partial e_j(t)} = -(S_j(t) - S_{j+1}(t)) \leq 0 & (i \leq j \leq n-1), \\ \frac{\partial \dot{S}_i(t)}{\partial e_n(t)} = -S_n(t) \leq 0 \end{cases}$$

$$\begin{cases} \frac{\partial \dot{S}_i(t)}{\partial \alpha_{j-1,j}(t)} = 0 & (i \neq j, 2 \leq j \leq n), \\ \frac{\partial \dot{S}_i(t)}{\partial \alpha_{j,j-1}(t)} = 0 & (i \neq j, 2 \leq j \leq n), \\ \frac{\partial \dot{S}_i(t)}{\partial \alpha_{i-1,i}(t)} = \frac{\partial k_{i-1,i}(\cdot)}{\partial \alpha_{i-1,i}(t)}(S_{i-1}(t) - S_i(t)) & (i \geq 2), \\ \frac{\partial \dot{S}_i(t)}{\partial \alpha_{i,i-1}(t)} = -\frac{\partial k_{i,i-1}(\cdot)}{\partial \alpha_{i,i-1}(t)}(S_i(t) - S_{i+1}(t)) & (2 \leq i \leq n-1), \\ \frac{\partial \dot{S}_n(t)}{\partial \alpha_{n,n-1}(t)} = -\frac{\partial k_{n,n-1}(\cdot)}{\partial \alpha_{n,n-1}(t)} S_n(t) \end{cases}$$

As $\dot{p} = 0$, all the partial derivatives of $\dot{p}$ are always null. Now, let us look for to ensure the monotonicity of model (5). For that, the elimination rates and the fluxes among compartments must satisfy certain conditions. In addition to the relation $e_j \geq e_{j+1}$, $\forall j \in \{1, ..., n-1\}$, among the elimination rates, it is also necessary that $\frac{\partial k_{i,i+1}(\cdot)}{\partial S_j} \geq 0$ and $\frac{\partial k_{i+1,i}(\cdot)}{\partial S_j} \leq 0$, $\forall i, j : i \in \{1, ..., n-1\}$, $j \in \{1, ..., n\}$.

If the above conditions are satisfied, the system is monotone with respect to all the states of the model. The system is cooperative with respect to the states S_i, $i \in \{1, ..., n\}$, the inputs $u_j(t)$, $j \in \{1, ..., n\}$, and the parameters $\alpha_{j,j+1}$, $j \in \{1, ..., n-1\}$, while the system is competitive with respect to the elimination rates e_j, $j \in \{1, ..., n\}$ and the parameters $\alpha_{j+1,j}$, $j \in \{1, ..., n-1\}$.

If the conditions are satisfied, the computation of the bounds for all the new system states is performed without overestimation because the new system is monotone with respect to all the states (states and parameters in the original model). Thus, some specific values of the parameters and the initial conditions are used to compute the upper bound and the lower bound, values that are usually different in each bound. Notice that during the combination of equations, the output compartment remains unchanged because $S_n(t) = Q_n(t)$. Thus, the output of the original system has the same value as the output of the new system. Then, if the same parameters values and initial conditions are applied for the original model, the computation of its output bounds is performed without overestimation. Therefore, the conclusions obtained by the monotonicity analysis of system (5) can be applied to original in-series system (3). Taking into account the correspondence among the flux derivatives[1], all these relations can be formulated in the following lemma:

[1]

$$\frac{\partial k(\cdot)}{\partial S_1} = \sum_{s=1}^{n} \frac{\partial k(\cdot)}{\partial Q_s} \frac{\partial Q_s}{\partial S_1} = \frac{\partial k(\cdot)}{\partial Q_1}$$

$$\frac{\partial k(\cdot)}{\partial S_j} = \sum_{s=1}^{n} \frac{\partial k(\cdot)}{\partial Q_s} \frac{\partial Q_s}{\partial S_j} = \frac{\partial k(\cdot)}{\partial Q_j} - \frac{\partial k(\cdot)}{\partial Q_{j-1}} \quad \forall j \in \{2, ..., n\}$$

where $k(\cdot)$ represents both $k_{i,i+1}(\cdot)$ and $k_{i+1,i}(\cdot)$, $i \in \{1, ..., n-1\}$.

Lemma 4.1. *Consider a non-linear in-series model (3) characterized by:*

(a) The elimination rate for each compartment is greater than or equal to the elimination rate for the next compartment, i.e. $e_j \geq e_{j+1},\ \forall j \in \{1, ..., n-1\}$.

(b) The forward fluxes among the compartments satisfy that $\frac{\partial k_{i,i+1}(\cdot)}{\partial Q_j} - \frac{\partial k_{i,i+1}(\cdot)}{\partial Q_{j-1}} \geq 0$, *whereas the backward fluxes satisfy that* $\frac{\partial k_{i+1,i}(\cdot)}{\partial Q_j} - \frac{\partial k_{i+1,i}(\cdot)}{\partial Q_{j-1}} \leq 0$, $\forall i, j : i \in \{1, ..., n-1\}$, $j \in \{2, ..., n\}$, *where* $\frac{\partial k_{i,i+1}(\cdot)}{\partial Q_0} = \frac{\partial k_{i+1,i}(\cdot)}{\partial Q_0} = 0$.

Then, system (5), with the same output value as (3), satisfies the following properties:

(i) System (5) is cooperative with respect to the states S_i, $i \in \{1, ..., n\}$, *the inputs* $u_j(t)$, $j \in \{1, ..., n\}$, *and the parameters* $\alpha_{j,j+1}$, $j \in \{1, ..., n-1\}$.

(ii) System (5) is competitive with respect to the elimination rates e_j, $j \in \{1, ..., n\}$, *and the parameters* $\alpha_{j+1,j}$, $j \in \{1, ..., n-1\}$.

Let us set the fluxes among compartments to be constants, i.e. $k_{i,i+1}(\cdot) = \alpha_{i,i+1}$ and $k_{i+1,i}(\cdot) = \alpha_{i+1,i}$. This kind of systems is called linear in-series systems. In this case, the partial derivatives of the fluxes are always equal to zero and the conditions of Lemma 4.1 can be simplified.

Note that, by definition, every linear system is cooperative with respect to all its states in the non-extended system, where the parameters are not considered as system states. However, the analysis of the system monotonicity with respect to the parameters is performed in the extended system (2). As the parameters are considered as extra states, the system is not linear anymore and its monotonicity is not proven.

Corollary 4.2. *Consider a linear in-series system. If the elimination rate for each compartment is greater than or equal to the elimination rate for the next compartment, i.e.* $e_j \geq e_{j+1},\ \forall j \in \{1, ..., n-1\}$, *then system (5) satisfies the following properties:*

(i) System (5) is cooperative with respect to the states S_i, $i \in \{1, ..., n\}$, *the inputs* $u_j(t)$, $j \in \{1, ..., n\}$, *and the parameters* $\alpha_{j,j+1}$, $j \in \{1, ..., n-1\}$.

(ii) System (5) is competitive with respect to the elimination rates e_j, $j \in \{1, ..., n\}$, *and the parameters* $\alpha_{j+1,j}$, $j \in \{1, ..., n-1\}$.

In the particular case of unidirectional linear in-series systems, where $k_{i,i+1}(\cdot) = \alpha_{i,i+1}$ and $k_{i+1,i}(\cdot) = 0$, $i \in \{1, ..., n-1\}$, the conditions can be simplified even more. Let us consider a single-input single-output (SISO) system [12] with $u_i(t) = 0$, $i \in \{2, ..., n\}$. Its transfer function is given by:

$$H(s) = \frac{1}{e_n + s} \prod_{i=1}^{n-1} \frac{\alpha_{i,i+1}}{e_i + \alpha_{i,i+1} + s} \tag{6}$$

The transfer function (6) will be maintained unaltered [13] if the values of the binomial ($\alpha_{i,i+1}$, e_i) are exchanged with the values of the binomial ($\alpha_{j,j+1}$, e_j) for $i, j \in \{1, ..., n-1\}$. In consequence, the output value does not change. Therefore, a compartmental model where $e_j \geq e_n\ \forall j \in \{1, ..., n-1\}$, can be transformed in a new in-series model, with the same transfer function, where the elimination rates satisfy

$$e_j \geq e_{j+1},\ \forall j \in \{1, ..., n-1\}.$$

This new model satisfies the conditions of Corollary 4.2. Therefore, the compartments, the inputs $u_j(t),\ j \in \{1, ..., n\}$, and the parameters $\alpha_{i,i+1}$ of the new system are cooperative for all $i \in \{1, ..., n-1\}$, while the elimination rates $e_j,\ j \in \{1, ..., n\}$, are competitive parameters. Hence, the following result is straightforward:

Lemma 4.3. *Consider a SISO unidirectional linear in-series model with input in the first compartment. If the elimination rate for each compartment is greater than or equal to the elimination rate for the output compartment, i.e.* $e_j \geq e_n,\ \forall j \in \{1, ..., n-1\}$, *then system (5) satisfies the following properties:*

(i) System (5) is cooperative with respect to the states $S_i,\ i \in \{1, ..., n\}$, *the inputs* $u_j(t),\ j \in \{1, ..., n\}$, *and the parameters* $\alpha_{j,j+1},\ j \in \{1, ..., n-1\}$.

(ii) System (5) is competitive with respect to the elimination rates $e_j,\ j \in \{1, ..., n\}$.

5. The computation of near-monotone compartmental in-series models

We have just seen that by a change of variables, a new system is obtained with the same output. If Lemma 4.1 or Lemma 4.3 conditions are satisfied, the new system is monotone with respect to the states and the parameters of the model. In consequence, the computation of output bounds for this new system is performed without overestimation and hence, the output bounds for the original system.

When none of the above lemmas is completely satisfied, the computation of output bounds has to be performed directly for the original system. As the non-monotone states and parameters have to be considered as intervals, the output bounds will include a significant overestimation.

However, some systems nearly satisfy the lemma conditions. These kinks of systems are known as near-monotone system [5]. In these cases, based on the theory exposed in [14], we propose a novel method for the computation of a solution envelope that consists in obtaining an upper bounding model and a lower bounding model of the original model that satisfy the lemma conditions. Then, the computation of the output bounds is performed without overestimation. The area delimited between the lower bound for the lower bounding model and the upper bound for the upper bounding model will guarantee the inclusion of all possible solutions for the original model, and it will minimize the overestimation.

The conditions for Lemma 4.1 and Lemma 4.3 include special requirements on the elimination rates of the compartmental in-series models. As the elimination rates are competitive parameters, an upper bounding model is obtained at the lower bounds for the elimination rates. Similarly, a lower bounding model is obtained at the upper bounds for the elimination rates.

For example, Lemma 4.3 includes the condition $e_j \geq e_n,\ \forall j \in \{1, ..., n-1\}$. If our model does not satisfy this requirement, an upper bounding model can be computed such that the elimination rates are given by $\tilde{e}_j = e_j,\ j \in \{1, ..., n-1\}$, and $\tilde{e}_n = min(e_1, ..., e_n)$. A lower bounding model is computed by increasing the elimination rate values to $\tilde{e}_j = max(e_j, e_n),\ j \in \{1, ..., n-1\}$, and $\tilde{e}_n = e_n$. In both models the lemma condition $\tilde{e}_j \geq \tilde{e}_n,\ \forall j \in \{1, ..., n-1\}$ is satisfied.

6. Examples

In the sequel, we illustrate the results presented in the previous section through two different models. The first example is a linear system for glucose modelling, while the second one is a non-linear system for an epidemiological model. Furthermore, a death rate is added to the second example to analyse a near-monotone model. Namely, we perform a change of variables of the non-monotone systems to obtain new monotone systems, in which output bounds are easily computed without overestimation. Results obtained for both examples are compared with the computation of output bounds following the traditional monotonicity approach [9].

6.1. Linear glucose model

Insulin is a hormone secreted by the pancreas with the role of reducing glucose concentration in blood. Under normal circumstances, insulin secretion helps to maintain plasma glucose concentration in blood within a narrow range. A decrease in plasma glucose concentration is followed by a decrease in insulin secretion, while insulin secretion increases when plasma glucose concentration increases, for instance after an ingestion. The analysis of glucose kinetics is essential to analyse the insulin secretion by the pancreas.

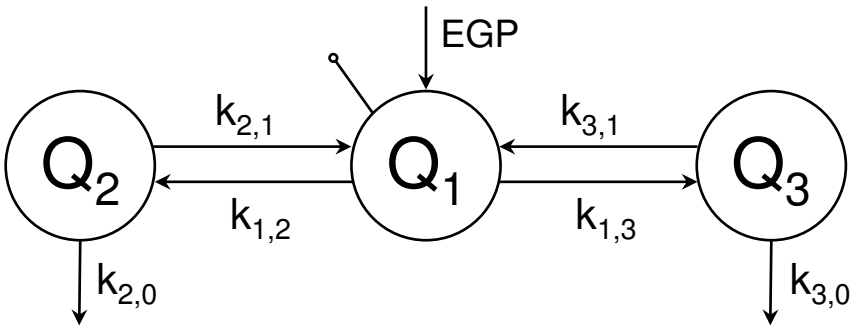

Figure 2: *Diagram of the linear glucose model developed by Cobelli et al.*

Cobelli et al. [15, 16] developed a physiological model to analyse insulin secretion. This model is composed by three compartments that describe the non-accessible portion of insulin system, as seen in Figure 2. The central compartment represents the insulin concentration of the accessible pool. It is the output compartment. The mass balance and measurement equations are given by:

$$\begin{aligned}
\dot{Q}_1(t) &= -(k_{1,2} + k_{1,3})Q_1(t) + k_{2,1}Q_2(t) + k_{3,1}Q_3(t) + EGP \\
\dot{Q}_2(t) &= k_{1,2}Q_1(t) - (k_{2,1} + k_{2,0})Q_2(t) \\
\dot{Q}_3(t) &= k_{1,3}Q_1(t) - (k_{3,1} + k_{3,0})Q_3(t) \\
G(t) &= \tfrac{Q_1(t)}{V_I}
\end{aligned} \tag{7}$$

where $Q_1(t)$ is the accessible pool of the plasma glucose, $Q_2(t)$ and $Q_3(t)$ illustrate peripheral compartments in rapid and slow equilibrium with the accessible pool, respectively, and the output

of the model is given by the plasma glucose concentration $G(t)$, which depends on the central compartment $Q_1(t)$. The parameter V_I is the volume of plasma in the accessible compartment, the parameter EGP denotes the input, the constant parameters $k_{1,2}$, $k_{1,3}$, $k_{2,1}$ and $k_{3,1}$ are the fluxes among the compartments, while the parameters $k_{2,0}$ and $k_{3,0}$ stand for the elimination rates of the peripheral compartments. In this model there is no elimination rate in the accessible pool.

Performing a monotonicity analysis of the corresponding extended model, it is deduced that system (7) is cooperative with respect to the compartments. Furthermore, the input EGP is also a cooperative parameter, while V_I, and the elimination rates $k_{2,0}$ and $k_{3,0}$ are competitive parameters. However, the system is non-monotone with respect to the fluxes $k_{1,2}$, $k_{1,3}$, $k_{2,1}$ or $k_{3,1}$, because the partial derivatives of the compartments with respect to the fluxes take different signs. For instance:

$$\frac{\partial \dot{Q}_1(t)}{\partial k_{1,2}} = -Q_1(t) < 0 \quad \text{while} \quad \frac{\partial \dot{Q}_2(t)}{\partial k_{1,2}} = Q_1(t) > 0$$

However, *Cobelli et al.* model (7) can be analysed as two compartmental in-series models interconnected, where the central compartment is the output of both in-series models. Following the same idea of the change of variables presented in the lemmas, we can find a new monotone model:

$$\begin{aligned}
\dot{S}_1(t) &= -(k_{1,2} + k_{1,3})S_1(t) + k_{2,1}(S_2(t) - S_1(t)) + k_{3,1}(S_3(t) - S_1(t)) + EGP \\
\dot{S}_2(t) &= -k_{1,3}S_1(t) - k_{2,0}(S_2(t) - S_1(t)) + k_{3,1}(S_3(t) - S_1(t)) + EGP \\
\dot{S}_3(t) &= -k_{1,2}S_1(t) - k_{3,0}(S_3(t) - S_1(t)) + k_{2,1}(S_2(t) - S_1(t)) + EGP \\
\dot{p}(t) &= 0 \\
G(t) &= \tfrac{S_1(t)}{V_I}
\end{aligned} \tag{8}$$

where $S_1 = Q_1$, $S_2 = Q_1 + Q_2$, $S_3 = Q_1 + Q_3$, and all the parameters are included in the parameter vector p, i.e., $p = [k_{1,2},\ k_{1,3},\ k_{2,1},\ k_{3,1},\ k_{2,0},\ k_{3,0},\ V_I]$.

Now, we can study the monotonicity of system (8):

$$\frac{\partial \dot{S}_1(t)}{\partial S_2(t)} = k_{2,1} \geq 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial S_3(t)} = k_{3,1} \geq 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial k_{1,2}(t)} = -S_1(t) \leq 0$$

$$\frac{\partial \dot{S}_1(t)}{\partial k_{1,3}(t)} = -S_1(t) \leq 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial k_{2,1}(t)} = S_2(t) - S_1(t) \geq 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial k_{3,1}(t)} = S_3(t) - S_1(t) \geq 0$$

$$\frac{\partial \dot{S}_1(t)}{\partial k_{2,0}(t)} = 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial k_{3,0}(t)} = 0 \qquad \frac{\partial \dot{S}_1(t)}{\partial V_I(t)} = 0$$

$$\frac{\partial \dot{S}_2(t)}{\partial S_1(t)} = k_{2,0} - k_{3,1} - k_{1,3} \qquad \frac{\partial \dot{S}_2(t)}{\partial S_3(t)} = k_{3,1} \geq 0 \qquad \frac{\partial \dot{S}_2(t)}{\partial k_{1,2}(t)} = 0$$

$$\frac{\partial \dot{S}_2(t)}{\partial k_{1,3}(t)} = -S_1(t) \leq 0 \qquad \frac{\partial \dot{S}_2(t)}{\partial k_{2,1}(t)} = 0 \qquad \frac{\partial \dot{S}_2(t)}{\partial k_{3,1}(t)} = S_3(t) - S_1(t) \geq 0$$

$$\frac{\partial \dot{S}_2(t)}{\partial k_{2,0}(t)} = -(S_2(t) - S_1(t)) \leq 0 \qquad \frac{\partial \dot{S}_2(t)}{\partial k_{3,0}(t)} = 0 \qquad \frac{\partial \dot{S}_2(t)}{\partial V_I(t)} = 0$$

$$\frac{\partial \dot{S}_3(t)}{\partial S_1(t)} = k_{3,0} - k_{2,1} - k_{1,2} \qquad \frac{\partial \dot{S}_3(t)}{\partial S_2(t)} = k_{2,1} \geq 0 \qquad \frac{\partial \dot{S}_3(t)}{\partial k_{1,2}(t)} = -S_1(t) \leq 0$$

$$\frac{\partial \dot{S}_3(t)}{\partial k_{1,3}(t)} = 0 \qquad \frac{\partial \dot{S}_3(t)}{\partial k_{2,1}(t)} = S_2(t) - S_1(t) \geq 0 \qquad \frac{\partial \dot{S}_3(t)}{\partial k_{3,1}(t)} = 0$$

$$\frac{\partial \dot{S}_3(t)}{\partial k_{2,0}(t)} = 0 \qquad \frac{\partial \dot{S}_3(t)}{\partial k_{3,0}(t)} = -(S_3(t) - S_1(t)) \leq 0 \qquad \frac{\partial \dot{S}_3(t)}{\partial V_I(t)} = 0$$

As $\dot{p} = 0$, the partial derivatives of $\dot{p}$ are always null. Therefore, system (8) is monotone if the conditions $k_{2,0} - k_{3,1} - k_{1,3} > 0$ and $k_{3,0} - k_{2,1} - k_{1,2} > 0$ are satisfied. If these conditions are satisfied, the system is cooperative with respect to the states S_1, S_2 and S_3. Furthermore, the input EGP, and the parameters $k_{2,1}$ and $k_{3,1}$ are also cooperative, while the parameters $k_{1,2}$ and $k_{1,3}$, the elimination rates $k_{2,0}$ and $k_{3,0}$, and the volume V_I are competitive parameters.

The black dashed lines in Figure 3 display the computed output bounds, while the light grey lines represent several numerical simulations executed by the variation of the parameters and initial conditions values. First of all, the computation of output bounds is performed following the traditional monotonicity approach [9], where system (7) is non-monotone with respect to the parameters $k_{1,2}$, $k_{1,3}$, $k_{2,1}$ and $k_{3,1}$. The lower (upper) bound is computed by considering the minimum (maximum) value for the cooperative states and parameters, while the maximum (minimum) value for the competitive states and parameters. However, the values of the non-monotone parameters $k_{1,2}$, $k_{1,3}$, $k_{2,1}$ and $k_{3,1}$ that minimize (maximize) $\dot{Q}_1(t)$, $\dot{Q}_2(t)$ and $\dot{Q}_3(t)$, inside their intervals, are considered to compute the lower (upper) bound:

$$\begin{cases} \underline{\dot{Q}_1}(t) &= -(\overline{k_{1,2}} + \overline{k_{1,3}}) \cdot \underline{Q_1}(t) + \underline{k_{2,1}} \cdot \underline{Q_2}(t) + \underline{k_{3,1}} \cdot \underline{Q_3}(t) + \underline{EGP} \\ \underline{\dot{Q}_2}(t) &= \underline{k_{1,2}} \cdot \underline{Q_1}(t) - (\overline{k_{2,1}} + \overline{k_{2,0}}) \cdot \underline{Q_2}(t) \\ \underline{\dot{Q}_3}(t) &= \underline{k_{1,3}} \cdot \underline{Q_1}(t) - (\overline{k_{3,1}} + \overline{k_{3,0}}) \cdot \underline{Q_3}(t) \end{cases}$$

$$\begin{cases} \overline{\dot{Q}_1}(t) &= -(\underline{k_{1,2}} + \underline{k_{1,3}}) \cdot \overline{Q_1}(t) + \overline{k_{2,1}} \cdot \overline{Q_2}(t) + \overline{k_{3,1}} \cdot \overline{Q_3}(t) + \overline{EGP} \\ \overline{\dot{Q}_2}(t) &= \overline{k_{1,2}} \cdot \overline{Q_1}(t) - (\underline{k_{2,1}} + \underline{k_{2,0}}) \cdot \overline{Q_2}(t) \\ \overline{\dot{Q}_3}(t) &= \overline{k_{1,3}} \cdot \overline{Q_1}(t) - (\underline{k_{3,1}} + \underline{k_{3,0}}) \cdot \overline{Q_3}(t) \end{cases}$$

where $\underline{A}$ and $\overline{A}$ represent the lower bound and the upper bound for A. As parameters $k_{1,2}$, $k_{1,3}$, $k_{2,1}$ and $k_{3,1}$ appear in several differential equations with different effects, these parameters take

different values to minimize (or maximize) $\dot{Q}_1(t)$, $\dot{Q}_2(t)$ and $\dot{Q}_3(t)$. For example, $k_{1,2}$ assumes different values to minimize $\dot{Q}_1(t)$ and to minimize $\dot{Q}_2(t)$. This technique ensures the inclusion of all the possible solutions, but it may produce an overestimation in the computation of solution envelopes, as Figure 3a illustrates.

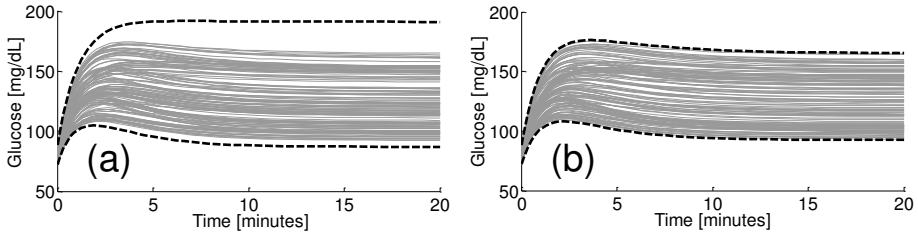

Figure 3: *Output bounds for the linear glucose model developed by Cobelli et al., where* $Q_1(0) = 40$, $Q_2(0) = 90$, $Q_3(0) = 90$, $EGP = 22$, $V_I = 0.5$, $k_{2,0} = 0.6$ *and* $k_{3,0} = 0.55$ *under 5% uncertainty, and* $k_{1,2} = 0.3$, $k_{2,1} = 0.1$, $k_{1,3} = 0.15$, $k_{3,1} = 0.25$ *under 15% uncertainty. (a) Monotonicity approach. (b) Using system (8) when the monotonicity conditions are satisfied.*

Nevertheless, if the monotonicity conditions are satisfied, the system obtained by a change of variables is monotone with respect to all the states and parameters of the model, thus none of them have to be considered as intervals. Therefore, as shown in Figure 3b, the computation of output bounds is performed without overestimation:

$$\begin{cases} \dot{\underline{S}}_1(t) &= -(\overline{k_{1,2}} + \overline{k_{1,3}}) \cdot \underline{S}_1(t) + \underline{k_{2,1}} \cdot (\underline{S}_2(t) - \underline{S}_1(t)) + \underline{k_{3,1}} \cdot (\underline{S}_3(t) - \underline{S}_1(t)) + \underline{EGP} \\ \dot{\underline{S}}_2(t) &= -\overline{k_{1,3}} \cdot \underline{S}_1(t) - \overline{k_{2,0}} \cdot (\underline{S}_2(t) - \underline{S}_1(t)) + \underline{k_{3,1}} \cdot (\underline{S}_3(t) - \underline{S}_1(t)) + \underline{EGP} \\ \dot{\underline{S}}_3(t) &= -\overline{k_{1,2}} \cdot \underline{S}_1(t) - \overline{k_{3,0}} \cdot (\underline{S}_3(t) - \underline{S}_1(t)) + \underline{k_{2,1}} \cdot (\underline{S}_2(t) - \underline{S}_1(t)) + \underline{EGP} \end{cases}$$

$$\begin{cases} \dot{\overline{S}}_1(t) &= -(\underline{k_{1,2}} + \underline{k_{1,3}}) \cdot \overline{S}_1(t) + \overline{k_{2,1}} \cdot (\overline{S}_2(t) - \overline{S}_1(t)) + \overline{k_{3,1}} \cdot (\overline{S}_3(t) - \overline{S}_1(t)) + \overline{EGP} \\ \dot{\overline{S}}_2(t) &= -\underline{k_{1,3}} \cdot \overline{S}_1(t) - \underline{k_{2,0}} \cdot (\overline{S}_2(t) - \overline{S}_1(t)) + \overline{k_{3,1}} \cdot (\overline{S}_3(t) - \overline{S}_1(t)) + \overline{EGP} \\ \dot{\overline{S}}_3(t) &= -\underline{k_{1,2}} \cdot \overline{S}_1(t) - \underline{k_{3,0}} \cdot (\overline{S}_3(t) - \overline{S}_1(t)) + \overline{k_{2,1}} \cdot (\overline{S}_2(t) - \overline{S}_1(t)) + \overline{EGP} \end{cases}$$

6.2. Non-linear epidemiological SIS model

Epidemiological models have been widely used to assist the decision-making process by helping to evaluate the consequence of choosing one of the alternate strategies available [17]. Furthermore, epidemic systems have also been used in non-medical areas to study processes that follow an epidemiological behaviour. Here, we have analysed a SIS model [18] composed by a susceptible population, denoted by $S(t)$, and an infected population, denoted by $I(t)$, as shown in Figure 4. Two different cases for the SIS model will be studied depending on whether death by the disease is considered in the system or not. The dynamics of the first model are given by the following equations, in which no disease death rate is considered:

$$\begin{aligned}\dot{S}(t) &= \gamma - \beta S(t)I(t) + \alpha I(t) - \nu S(t)\\ \dot{I}(t) &= \beta S(t)I(t) - \alpha I(t) - \nu I(t)\end{aligned} \tag{9}$$

where the infected population $I(t)$ is the output of the model. The birth rate of the population is represented by the parameter γ, while the death rate is ν. The parameters β and α denote the infection rate and the recuperation rate, respectively.

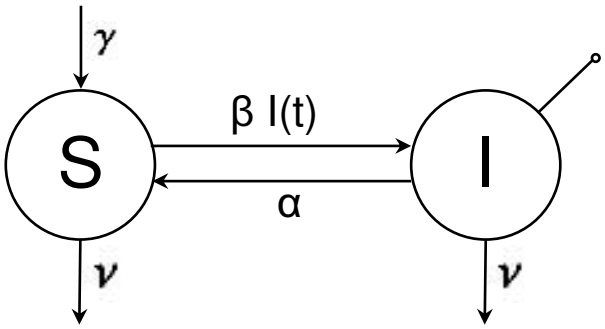

Figure 4: *Diagram of the non-linear epidemiological SIS model without disease death rate.*

Performing a monotonicity analysis of the corresponding extended model, it is deduced that system (9) is non-monotone with respect to the states, as the sign of the partial derivative $\frac{\partial \dot{S}(t)}{\partial I(t)} = -\beta S(t) + \alpha$ cannot be determined. Consequently, the system monotonicity with respect to the parameters cannot be evaluated.

Nevertheless, a change of variables can be performed for system (9) to obtain a monotone system with the same output, given by:

$$\begin{aligned}\dot{N}(t) &= \gamma - \nu N(t)\\ \dot{I}(t) &= \beta(N(t) - I(t))I(t) - \alpha I(t) - \nu I(t)\\ \dot{p}(t) &= 0\end{aligned} \tag{10}$$

where $N(t) = S(t) + I(t)$, and all the parameters are included in the parameter vector p, i.e., $p = [\gamma,\ \beta,\ \alpha,\ \nu]$. As the output is unaltered, the conclusions achieved by the computation of the output bounds of (10) can also be applied to system (9). System (10) is cooperative with respect to the compartments, the parameter β and the input γ, while it is competitive with respect to α and the elimination rate ν.

System (10), with the same monotonicity properties, can also be obtained applying Lemma 4.1, as the lemma conditions are satisfied. The elimination rates of both compartments of the original model are equal to ν. Furthermore, the fluxes between the compartments are given by the function $\beta I(t)$ and the constant parameter α, whose partial derivatives satisfy that $\frac{\partial \beta I(t)}{\partial I(t)} - \frac{\partial \beta I(t)}{\partial S(t)} = \beta - 0 = \beta \geq 0$ and $\frac{\partial \alpha}{\partial I(t)} - \frac{\partial \alpha}{\partial S(t)} = 0 - 0 = 0 \geq 0$.

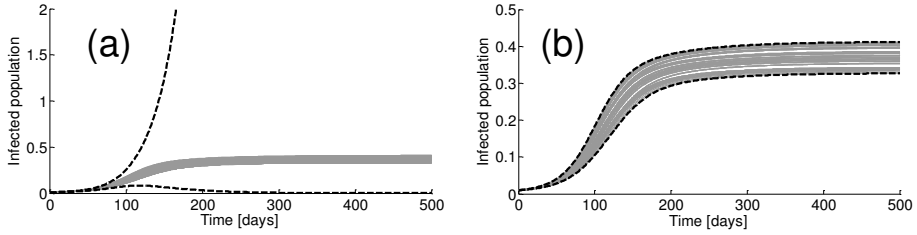

Figure 5: *Improvements on the computation of bounds for the proportion of infected individuals during a 500 days period, where* $I(0) = 0.01$, $S(0) = 1 - I(0)$, $\gamma = \nu = 0.012$, $\beta = 0.15$ *and* $\alpha = 0.12$ *under 1% uncertainty. A) Monotonicity approach. B) Using Lemma 4.1.*

Figure 5 shows two different computations of the output bounds. The starting point is performed following the traditional monotonicity approach. Figure 5a shows that the solution envelope grows exponentially, producing a considerable overestimation over the numerical simulations. Nevertheless, the overestimation disappears when Lemma 4.1 is applied, as shown in Figure 5b. Output bounds are computed without overestimation, as all the states and parameters of the system (10) are monotone.

From now on, a different SIS model will be analysed, in which a death by the disease rate θ is considered. The dynamic of this model is given by the following equations:

$$\begin{aligned} \dot{S}(t) &= \gamma - \beta S(t)I(t) + \alpha I(t) - \nu S(t) \\ \dot{I}(t) &= \beta S(t)I(t) - \alpha I(t) - \nu I(t) - \theta I(t) \end{aligned} \tag{11}$$

Unfortunately Lemma 4.1 cannot be applied to this system, because the lemma conditions are not completely satisfied, due to the fact that the elimination rates of the compartments $S(t)$ and $I(t)$ are ν and $\nu + \theta$, respectively. To overcome this trouble we compute upper and lower bounding models. The upper bounding model is computed by reducing the elimination rate of $I(t)$ to ν, while the lower bounding model is obtained by increasing the elimination rate of $S(t)$ to $\nu + \theta$. Thus, both the upper and the lower bounding models satisfy the Lemma 4.1 conditions and guarantee the inclusion of all possible solutions for the system (11).

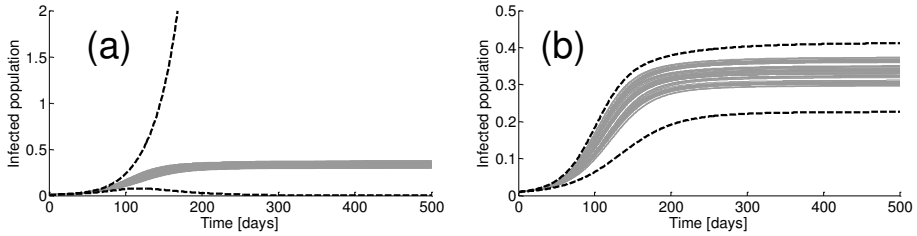

Figure 6: *Improvements on the computation of bounds for the proportion of infected individuals during a 500 days period considering a death by the disease rate, where* $I(0) = 0.01$, $S(0) = 1 - I(0)$, $\gamma = 0.015$, $\nu = 0.012$, $\theta = 0.001$, $\beta = 0.15$ *and* $\alpha = 0.12$ *under 1% uncertainty. A) Monotonicity approach. B) Computing an upper bounding model and a lower bounding model, and applying Lemma 4.1 on them.*

Again, the solution envelope computed following the traditional monotonicity approach grows exponentially, producing a significant overestimation, as seen in Figure 6a. The upper bound for the upper bounding model and the lower bound for the lower bounding model will guarantee the inclusion of all possible solutions of the system (11) and minimize the overestimation, as seen in Figure 6b.

7. Discussion and Conclusion

The problem of computing tight solution envelopes under parametric uncertainty for ordinary differential equations has been tackled in the literature applying different approaches. Monte Carlo methods are not considered valid methods because they do not guarantee the inclusion of all possible solutions. The most common method used in the literature is to perform a monotonicity analysis for a trajectory-based approach. This method allows us to compute tight solutions envelopes that guarantee the inclusion of all possible solutions. However, non-monotone states or parameters have to be computed as intervals, which produce a significant overestimation in the computation of output bounds.

Our proposal consists in performing a combination of the equations of the original model to obtain a new model in which the output compartment is unaltered. This new system is monotone with respect to all the compartments and parameters of the model. Therefore, the computation of its output bounds is performed without overestimation. As the output of the original model is preserved in the new model, the computed solutions bounds for the new model can be applied to the original model. These model transformations were formulated in Lemma 4.1 for bidirectional non-linear chains in [7]. In this work, we present Lemma 4.3 for unidirectional linear chains, with more relaxed conditions.

Furthermore, in this work, a novel method to compute tight solution envelopes when the lemma conditions are not completely satisfied by the models involved. This method consists in computing an upper bounding model and a lower bounding model such that these new models satisfy the lemma conditions. Thus, the computation of their solution envelopes is performed without overestimation. As the original model is inferior to the upper bounding model and superior to the lower bounding model, combining both solution envelopes a tight solution envelope is obtained for the original system that guarantees the inclusion of all possible solutions, and minimizes the overestimation.

In this work, our proposal has been compared with the last techniques in two different examples: a linear system for glucose modelling and a non-linear system for a SIS epidemiological model. In both cases, the solution envelopes have been computed using a monotonicity approach, and applying the ideas and lemmas presented in this paper. Our proposed techniques outperform the previous approaches for the computation of solution envelopes on compartmental in-series models, as they compute the output bounds without overestimation. Furthermore, if the lemma conditions are not completely satisfied, we can compute tight solution envelopes in which the overestimation is minimized compared with the most recent techniques.

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Conflict of interest

No competing financial interests exist.

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