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On the computation of output bounds on parallel inputs pharmacokinetic models with parametric uncertainty

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Abstract

Pharmacokinetic models are of utmost importance in drug and medical research. The class of parallel inputs models consists of two or more linear chains connected together in parallel. It has been used to represent pharmacokinetic processes in which the input shows effects on the output with different delays in time.

Due to physiological variability, the exact values of the model parameters are uncertain, but they can be bounded by intervals. In this case, the computation of output bounds can be posed as the solution of an initial value problem (IVP) for ordinary differential equations (ODEs) with uncertain initial conditions. However, current methods may produce a significant overestimation.

In this paper, a new method to minimise overestimation when using the parallel inputs model is proposed and applied to two cases: subcutaneous insulin absorption for artificial pancreas research, and the study of the double-peak phenomenon observed for certain drugs. Our proposal consists in performing a model reduction in conjunction with analytical solutions of the input chains and a monotonicity analysis of model states and parameters. This method allows obtaining tighter output bounds with low computational cost compared to the latest techniques.

Keywords: Compartmental models, Parallel inputs, Uncertainty, Interval uncertainty, Bounded solutions
2000 MSC: 34B05, 34B08, 34B37, 65G40, 92B05

1. Introduction

Compartmental modelling is a common approach to simulate biological processes. Furthermore, these models are used in many diverse areas such as economics, engineering, medicine or human sciences. In particular, many models have been developed to study pharmacokinetic processes, such as the examples analysed in this paper.

This work is focused on the parallel inputs model [1], which is based on a suggestion given by *Jacquez*, who considered that the single-peak concentration-time response that usually follows the oral administration of a drug could be modelled using a single linear chain of identical compartments connected together in series. A similar approach is based on two or more parallel

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linear chains connected to the output compartment with elimination rate k_e. Each chain is formed by a number (that can vary for each chain) of identical compartments. Due to the possible different pathways to reach the output, this type of model is usually used to analyse pharmacokinetic processes in which inputs show effects on the output with different delays in time.

When studying a biological process with a compartmental model there is always some mismatch between the model and real life, caused because the mathematical models are a simplified version of the actual process. This mismatch yields non-modelled dynamics. Furthermore, a common characteristic of biological processes is variability, leading to parametric uncertainty. The exact values of the model parameters and initial conditions are unknown, but they can be bounded by intervals. There is just one solution for constant parameters, but parametric uncertainty yields a set of different possible solutions. The computation of an output envelope must guarantee the inclusion of all the possible solutions for the model.

Montecarlo methods have traditionally been used to deal with uncertainty [2]. However, they are not applicable for computing output bounds because, independently of the number of simulations executed, the bounds obtained do not guarantee the inclusion of all the possible solutions [3]. This inclusion guarantee is a priority when a model is used as part of a medical decision system, as is the case here, since the output bounds must ensure that all the possible responses by the patient are outside risk levels. Other areas where this is needed include error-bounded parametric identification and constraint-satisfaction problems. In the former, the range (or a tight overestimation) of the output trajectory must be computed and compared with measurements to estimate intervals for the model parameters guaranteeing data consistency. In the latter, the computed range must be compared with the constraints to be satisfied so as to obtain an inner and outer approximation of the solution set for the decision variables. Furthermore, the computational cost of Montecarlo methods increases proportionally to the number of simulations performed to cover the uncertain input space sufficiently. For these reasons, region-based and trajectory-based approaches [4] have been considered to compute output bounds based mainly on interval analysis [5] and monotone systems theory [6, 7]. However, current methods may lead to a significant overestimation when the uncertainty is high and some monotonicity properties are not fulfilled.

The aim of this work is to propose a new method to minimise the overestimation of output bounds on the class of parallel inputs models. This method is applied to two cases: subcutaneous insulin absorption for artificial pancreas research [8], and the study of the double-peak phenomenon observed for certain drugs [9]. Our proposal consists in performing a model reduction combining analytical solutions of the input chains with a monotonicity analysis of model compartments and parameters. This method allows computing tighter output bounds with low computational cost compared to latest techniques.

This work has been organised as follows: In Section 2, interval simulation for an initial value problem for parametric ordinary differential equations (ODEs) is introduced, and the two main approaches are listed. In Section 3, a new method for the computation of output bounds on the parallel inputs model is proposed. In Section 4, simulations for the two examples of pharmacokinetics models are executed, and the output bounds are computed using different methods. Finally, Section 5 outlines the conclusions of this study.

2. Initial Value Problems for Parametric ODEs

Systems in which the parameters and initial conditions are unknown but bounded are considered henceforth. A system modelled using interval parametric uncertainty is called an interval

dynamic system. The continuous-time system under study is described by an initial-value problem (IVP):

$$x'(t,p) = f(x,p), \quad x(t_0) = x_0, \quad x \in \mathbb{R}^n,\ t \in \mathbb{R} \tag{1}$$

where x is the state vector, p is the parameter vector and $x(t; t_0, x_0, p)$ is the solution of (1). The different initial conditions x_0 and parameters p analysed can be expressed as the interval vectors $\mathbf{x_0}$ and $\mathbf{p}$, respectively (intervals are represented in bold). The set of possible solutions obtained by considering parametric uncertainty is denoted by $\mathbf{x}(t; t_0, \mathbf{x_0}, \mathbf{p})$:

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

Computing output bounds plays a key role in the simulation of systems under uncertainty. Algorithms for computing output bounds can be classified according to whether the computation is performed using one-step-ahead iteration based on previous approximations of the reachable set (region-based approaches), or a set of point-wise trajectories generated by selecting particular values of $p \in \mathbf{p}$ using heuristics or optimisation (trajectory-based approaches) [4].

2.1. Region based approaches

Region-based approaches for computing output bounds consist of two phases [10, 11]. Supposing $\mathbf{x_i}$ has been computed at a given time instant t_i such that

$$\mathbf{x}(t_i; t_0, \mathbf{x_0}, \mathbf{p}) \subseteq \mathbf{x_i}$$

the first step consists in finding an a priori enclosure $\tilde{\mathbf{x}}_\mathbf{i}$ for an interval $[t_i, t_{i+1}]$. State vector $\mathbf{x}(t)$ has a unique solution for each $x_i \in \mathbf{x_i}$, $t \in [t_i, t_{i+1}]$, such that

$$\mathbf{x}(t; t_i, \mathbf{x_i}, \mathbf{p}) \subseteq \tilde{\mathbf{x}}_\mathbf{i} \quad \forall t \in [t_i, t_{i+1}]$$

The second step uses $\tilde{\mathbf{x}}_\mathbf{i}$ to enclose the truncation error of the method and computes a tighter enclosure $\mathbf{x_{i+1}}$ at t_{i+1} such that

$$\mathbf{x}(t_{i+1}; t_0, \mathbf{x_0}, \mathbf{p}) \subseteq \mathbf{x_{i+1}} \subseteq \tilde{\mathbf{x}}_\mathbf{i}.$$

In contrast to traditional ODE solvers, which compute approximate solutions, region-based solvers prove that a unique solution for the problem exists; afterwards rigorous bounds that guarantee the enclosure of the solution are computed.

The problem of wrapping appears when a raft approximation of the solution set is iterated with one-step-ahead recursion of the state space function $\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{p})$. At each iteration, the true solution set is wrapped into a region based on outer approximations. A significant overestimation is introduced since the regions must be feasible to be constructed and represented on a computer. The errors involved can quickly accumulate and the output bounds on the interval system can blow up. Since the wrapping effect was first observed in the early 1960s [12], several approaches have been proposed to avoid or reduce it. These approaches include the rotation of the state space of the interval system by a change of coordinates [12] or by a QR-factorisation [13]. Also, region-based approaches have been enhanced using ellipsoids [14] or zonotopes [15].

A state-of-the-art solver is VNODE-LP [5], developed by *N. Nedialkov*. This package is a successor of the VNODE [16] package, validated numerical ODE. A distinctive feature of the VNODE-LP solver is that it is implemented entirely using literate programming [17]. As a result, its correctness can be verified by a human expert, similarly to how mathematical results are certified.

2.2. Trajectory based approaches

In compartmental ODE models, the rate of change of each compartment can be expressed as a function of the rest of compartments at that time:

$$\begin{aligned}
\dot{x}_1(t,p) &= f_1(t, x_1(t), x_2(t), ..., x_n(t), p) \\
\dot{x}_2(t,p) &= f_2(t, x_1(t), x_2(t), ..., x_n(t), p) \\
&\vdots \\
\dot{x}_n(t,p) &= f_n(t, x_1(t), x_2(t), ..., x_n(t), p)
\end{aligned}$$

or $d\mathbf{x}/dt = \mathbf{f}(\mathbf{x})$, where $\mathbf{f}$ is the vector function with components f_i. It is assumed that all compartments x_i of the system take arbitrary non-negative values.

Monotone systems respond to perturbations in a predictable way, and they have very robust dynamical characteristics. Interconnection of monotone systems may be analysed in an analytical way [11] by considering a flow $\mathbf{x}(t) = \phi(\mathbf{x_0}, t)$. A system is 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 relation order. Cooperative systems form a class of monotone dynamical systems [6] in which

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

A monotone and cooperative study can also be performed using graph theory. In particular, the *species graph* [7] assigns a node for each model compartment. No edge is drawn from node x_i to node x_j if the partial derivative $\frac{\partial f_j}{\partial x_i}(x)$ equals zero, meaning that node x_i has no direct effect on node x_j. An activation arrow ($\rightarrow$) represents that the derivative is strictly positive, while an inhibition line ($\dashv$) denotes that it is strictly negative. However, if the derivative sign changes depending on the particular entries, both an activation arrow and an inhibition line are drawn from node x_i to node x_j.

A *spin assignment* is an assignment in which each node has a sign. Nodes connected by an activation arrow ($\rightarrow$) have the same sign, while nodes connected by an inhibition line ($\dashv$) have different sign. A dynamical system is monotone if there exists at least one consistent assignment. Furthermore, a system is cooperative if all nodes are connected by activation arrows ($\rightarrow$). Figure 1 shows an example of monotone and non-monotone systems.

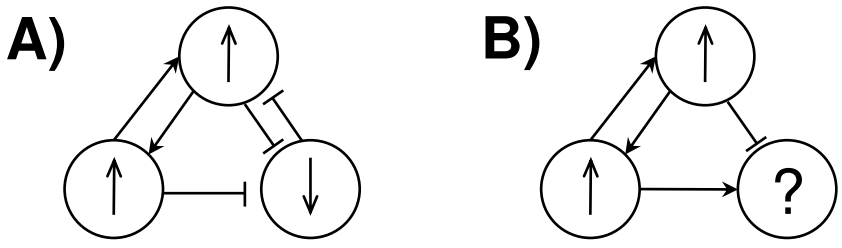

Figure 1: *Examples of graph monotonicity analysis. A) A monotone system. B) A non-monotone system.*

In order to calculate output bounds, two models are considered: an upper bounding model and a lower bounding model. In an upper bounding model, cooperative compartments with respect to

the solution take their maximum values, while monotone but non-cooperative compartments take their minimum values. On the other hand, a lower bounding model is obtained by considering the minimum value of cooperative compartments, and the maximum value of monotone but non-cooperative compartments. Despite parametric uncertainty, only interval endpoints of monotone compartments (cooperative or not) are needed for the computation of the upper and the lower output bounds. In both cases, non-monotone compartments are still considered as intervals, and these interval uncertainties will produce an overestimation on the computation of output bounds.

Analysis of monotone and cooperative parameters is performed by considering the parameters as invariant compartments, where

$$\begin{aligned} \dot{x}_1(t) &= f_1(t, x_1(t), x_2(t), ..., x_n(t), p_1(t), p_2(t), ...) \\ &\vdots \\ \dot{x}_n(t) &= f_n(t, x_1(t), x_2(t), ..., x_n(t), p_1(t), p_2(t), ...) \\ \dot{p}_i(t) &= 0 \end{aligned}$$

3. The computation of output bounds on the parallel inputs model

The parallel inputs model [1] consists of two or more parallel linear chains connected to the output compartment, represented by X, with a varying number of identical compartments per chain, as shown in Figure 2. This model has mostly been used to analyse biological processes in which inputs show different and separate effects on the output. The characteristics of the delays determine the number of compartments and the absorption rates of each chain. Longer chains are used for representing larger delays.

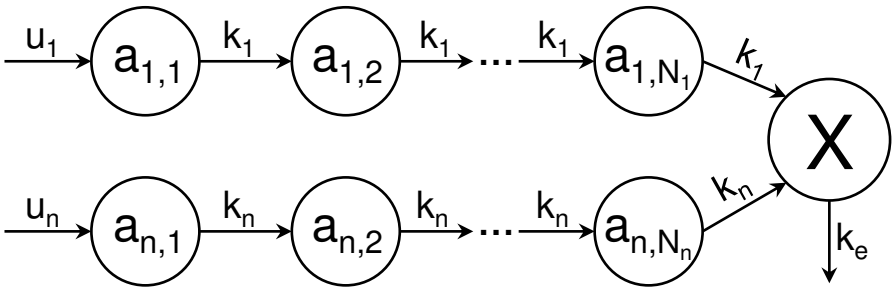

Figure 2: *Diagram of the parallel inputs model.*

The inputs of each chain can be considered as impulses, continuous functions, or both. As a general case, each chain has an impulsive input $D_i\delta(t)$, where $D_i = a_{i,1}(0)$ is the initial condition, and a continuous input u_i. Each chain is formed by N_i identical compartments, joined with the same absorption rate k_i.

The differential equations for the parallel inputs model composed of n chains are, for $i = 1, ..., n$,

$$
\begin{array}{rclrcl}
\dot{a}_{i,1} & = & u_i - k_i a_{i,1} & a_{i,1}(0) & = & D_i \\
\dot{a}_{i,2} & = & k_i a_{i,1} - k_i a_{i,2} & a_{i,2}(0) & = & 0 \\
\dot{a}_{i,3} & = & k_i a_{i,2} - k_i a_{i,3} & a_{i,3}(0) & = & 0 \\
 & \vdots & & & \vdots & \\
\dot{a}_{i,N_i} & = & k_i a_{i,(N_i-1)} - k_i a_{i,N_i} & a_{i,N_i}(0) & = & 0 \\
\dot{X} & = & \sum_{i=1}^{n} k_i a_{i,N_i} - k_e X & X(0) & = & X_0
\end{array}
\tag{2}
$$

One of the advantages of the parallel inputs model is that, despite the large number of compartments ($1 + \sum_{i=1}^{n} N_i$) that are included in the model, there are a few parameters under uncertainty ($3n + 2$).

Using graph theory to perform a monotonicity analysis, Figure 3 shows a spin assignment of the parallel inputs model in which the parameters are considered as invariant compartments ($\dot{u}_i = 0$, $\dot{k}_i = 0$ and $\dot{k}_e = 0$). The compartments X and $a_{i,j}$ are cooperative; thus the initial conditions D_i and X_0 are also cooperative. Furthermore, the parameters u_i are cooperative, while the parameter k_e is monotone but not cooperative. Finally, the parameters k_i are not monotone with respect to the system.

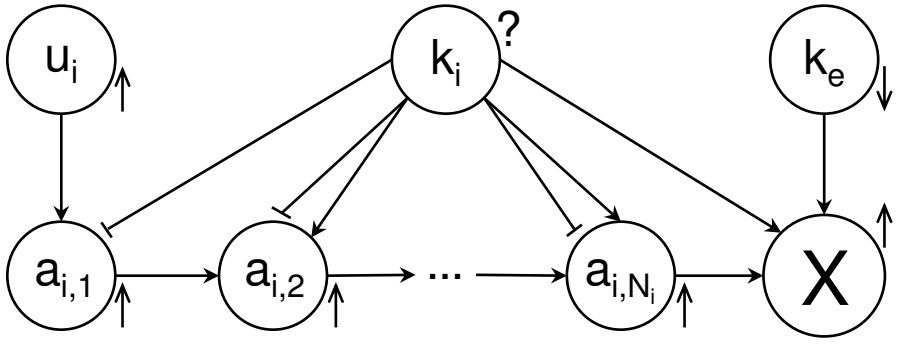

Figure 3: *Diagram of monotonicity of the parallel inputs model parameters. The parameters D_i are cooperative and the parameter k_e is monotone non-cooperative, while the parameters k_i are not monotone.*

When studying the upper (lower) bounds on the output of the parallel inputs model, the maximum (minimum) interval value for the cooperative parameters D_i, u_i, and X_0 is considered, while the minimum (maximum) interval value for the monotone non-cooperative parameter k_e is considered. In both cases, the non-monotone parameters k_i are still considered as intervals, and they will produce an overestimation on the the computation of output bounds.

3.1. Proposed method

As after a monotonicity analysis non-monotone compartments still cause an overestimation in the output bounds computation, a new method is proposed from now on based on using an equivalent model to the parallel inputs model. As the parallel inputs model is a linear ODE system with the form $Y'(t) = AY(t)$, where A is a nxn matrix, the solution is given by $Y(t) = e^{At}Y(0)$.

The output solution is not easy to deal with analytically in order to compute the envelopes. However, the solution a_{i,N_i} of the last compartment N_i of each chain can be studied more easily [18]:

$$a_{i,N_i}(t) = D_i e^{-k_i t} \frac{(k_i t)^{N_i-1}}{(N_i-1)!} + u_i \frac{1 - e^{-k_i t} \sum_{j=1}^{N_i-1} \frac{(k_i t)^j}{j!}}{k_i} \tag{3}$$

Analytical solutions of the last compartment of each chain and the ODE associated with the output compartment have been combined, transforming the parallel inputs model into an equivalent and simpler model with just one compartment where inputs are given by (3). The new model has thus one input for each chain of the parallel inputs model. The differential equation for the one-compartmental model with n inputs is

$$\dot{X}(t) = \sum_{i=1}^{n} k_i a_{i,N_i}(t) - k_e X(t) \qquad X(0) = X_0 \tag{4}$$

where the unique compartment is $X(t)$. As the one-compartment model is equivalent to the parallel inputs model, the monotonicity analysis shows that the parameters D_i, u_i, and X_0 are still cooperative and that the parameter k_e is monotone but not cooperative, while the parameters k_i are not monotone.

The parameters k_i are non-monotone in both models, and they produce an overestimation in the output bounds computation. In the parallel inputs model is not possible to analyse the critical points of these parameters because they are present in different equations with different signs. However, in the one-compartment model each k_i appears as a parameter for a unique input of the model. Studying the critical points of $\dot{X}(t)$ with respect to k_i, there is one non-trivial value:

$$\frac{\partial \dot{X}(t)}{\partial k_i} = 0 \quad \Rightarrow \quad k_i = 0 \quad \text{or} \quad k_i = \frac{N_i D_i + t u_i}{D_i t} \tag{5}$$

Analysing the second derivative with respect to k_i, stability of the non-trivial critical point is obtained:

$$-\frac{e^{-N_i - \frac{u_i t}{D_i}} t (N_i D_i + u_i t)^{N_i-1}}{(N_i-1)! D_i^3}$$

As the second derivative is negative, $\dot{X}(t)$ reaches a maximum at that point. If the critical point (5) belongs to the interval k_i, it is applied to obtain the upper bound on the solution. Otherwise, the endpoint of the interval k_i that maximises the output is considered. As there is no minimum, both endpoints of the interval k_i are analysed, and the value that minimises the output is considered to compute the lower bound.

4. Pharmacokinetic examples

Two examples, subcutaneous insulin absorption and the double-peak phenomenon, are studied to verify the effectiveness of the method proposed above. In both cases, 10% uncertainty is considered in all the parameters and the initial conditions of the model. The starting point is the result of computing output bounds using the VNODE-LP package [5] for interval analysis. The second computation is performed using a monotonicity analysis of the parallel inputs model.

Finally, the last computation is carried out evaluating the critical points for the non-monotone parameters of the one-compartment equivalent model. These last two computations are executed using Matlab with the toolbox IntLab [19] for interval analysis.

Each output bounds computation is compared with several possible numerical simulations executed by varying the parameter values inside the intervals. Each numerical simulation takes 0.01 s to be computed using an Intel(R) 3.2 GHz Pentium(R) processor. Computing the output bounds with our proposed method takes 0.02 s, as it is composed of two simulations, one for the upper bound and one for the lower bound.

4.1. Subcutaneous insulin absorption

Insulin is a hormone secreted by the pancreas with the role of reducing the glucose concentration in blood. Under normal circumstances, an increase in plasma glucose concentration, for instance after an ingestion, is followed by an increase in insulin secretion. On the other hand, insulin secretion decreases when the plasma glucose concentration decays. Indeed, insulin secretion maintains blood glucose concentrations in a narrow range.

Patients affected by type 1 Diabetes Mellitus suffer an autoimmune disease related to a low level of insulin in the blood. When this is untreated, it can cause hyperglycaemia, i.e. a high level of plasma glucose concentration. Insulin administration is necessary to maintain the plasma glucose concentration in a safe range, and to avoid severe symptoms related to hyperglycaemia or hypoglycaemia, i.e. a low level of plasma glucose concentration.

Technological progress has fuelled research on Artificial Pancreas, a project to develop closed-loop glucose control systems that automatically dispense insulin subcutaneously. Insulin therapy aims to mimic the pattern of endogenous insulin secretion present in healthy subjects. Several models of subcutaneous insulin kinetics have been proposed [20, 21], but here we focus on one of the most used models, formulated by *Wilinska et al.* [8].

This subcutaneous insulin absorption model is composed of two parallel chains of two and one compartments. The differential equations are given by (2) with $n = 2$, $N_1 = 2$ and $N_2 = 1$, with the initial conditions $D_1 = a_{1,1}(0) = 445\ mU$, $D_2 = a_{2,1}(0) = 120\ mU$, and $X_0 = 395\ mU$, and a continuous dose of $u_1 = 5\ mU/min$ and $u_2 = 2.5\ mU/min$. The absorption rates are $k_1 = 0.0112\ min^{-1}$ and $k_2 = 0.021\ min^{-1}$, while the elimination rate is given by $k_e = 0.0189\ min^{-1}$. In order to represent insulin concentration in blood, the output result is divided by $V_i = 0.5645\ L\ kg^{-1}$ and by the patient weight $BW = 70\ kg$.

To analyse a more general model, instead of assuming an impulse bolus at the initial time, it is supposed that the impulse bolus occurs at $t = t_b \geq 0$. While $t < t_b$, a model with two chains is considered. However, after the impulse bolus at $t = t_b$, two more chains are added to the model with the same absorption rates k_1 and k_2 and initial conditions $D_3 = 500\ mU$ and $D_4 = 250\ mU$. Figure 4 shows the new model structure with four chains.

The starting point is given by the VNODE-LP computation in Figure 5a, which shows that the output bounds give a considerable overestimation over the numerical simulations. The output bounds adjust much better after performing a monotonicity analysis of the parallel inputs model, but there is still place for improvements, as shown in Figure 5b. Finally, our proposed method is evaluated by computing output bounds on the equivalent one-compartment model, given by (3) and (4). Figure 5c shows that the output bounds adjust almost perfectly to the numerical simulations.

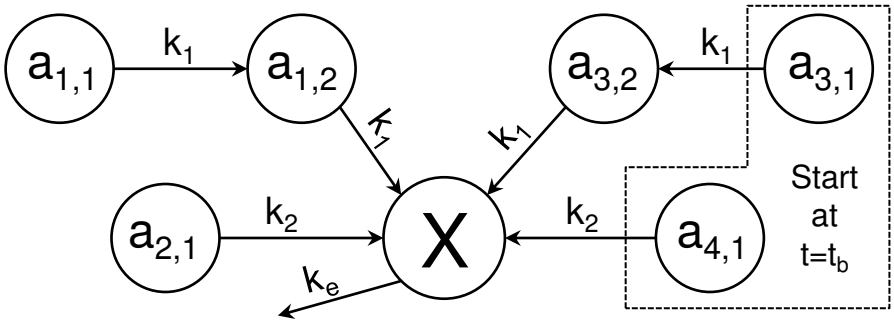

Figure 4: *Diagram of the parallel inputs model for the Wilinska model. Chains* 1 *and* 3 *share the parameter* k_1*, while chains* 2 *and* 4 *share the parameter* k_2*.*

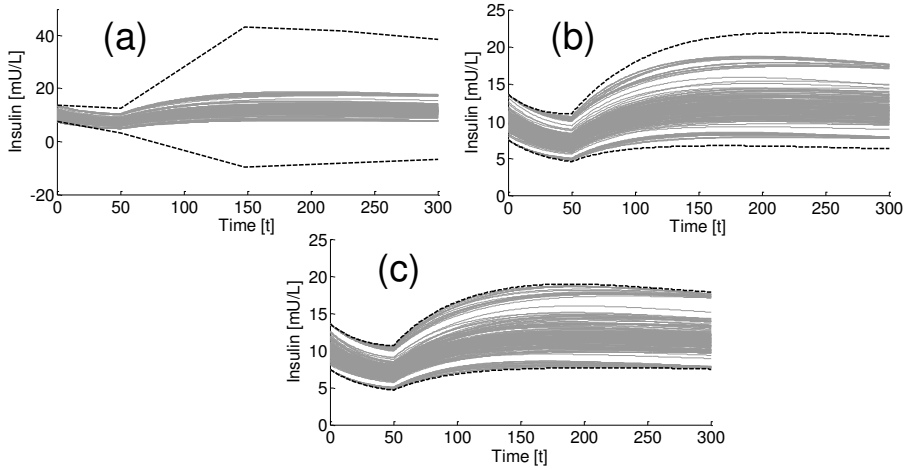

Figure 5: *Improvements computing subcutaneous insulin absorption bounds with impulse bolus at* $t_b = 50$*. (a) VNODE-LP computation. (b) Monotonicity analysis of the parallel inputs model. (c) Monotonicity analysis of the equivalent one-compartment model.*

4.2. Double-peak phenomenon

After the administration of a single dose of several drugs, there is normally a peak in the plasma concentration-time response, before it decays away. However, for certain drugs the plasma concentration rises to a peak, starts to decay, but then it rises again and a second peak is obtained before decaying away again. The second peak is usually higher than the first one, but its magnitude depends on the drug and the means of administration.

Several biological reasons can explain this behaviour, known as the double-peak phenomenon. The first one is *enterohepatic recirculation*, which refers to the process in which bile circulates from the liver to the small intestine and back to the liver, producing a smaller second peak [22]. The second possible reason affects drugs with high water solubility after oral administration, resulting in part of the dose being delayed in the stomach; this is known as *delayed gastric emp-*

tying [23]. Finally, the most common reason is *variability of absorption* within different regions of the gut [24].

The parallel inputs model has been used by *Godfrey et al.* [9] to model the double-peak phenomenon. Two chains are considered, one for each peak in plasma concentration. One chain is usually smaller and, indeed, faster than the other one, so both peaks are clearly differentiable.

In this paper, two chains of ten and five compartments with impulse bolus are considered. The number of compartments of each chain has been chosen arbitrarily to represent an example with longer chains than the subcutaneous insulin absorption example and to demonstrate the method's performance in high-order models. Their differential equations are given by (2) with $n = 2$, $N_1 = 10$, and $N_2 = 5$. As the dose is given as an impulse, $u_1 = u_2 = 0\ mU$, while the initial conditions are $X_0 = 0\ mU$, $D_1 = 30\ mU$, and $D_2 = 10\ mU$. The absorption rates for each chain are $k_1 = 0.15\ min^{-1}$ and $k_2 = 0.40\ min^{-1}$, while the elimination rate is given by $k_e = 0.20\ min^{-1}$.

The VNODE-LP computation, represented in Figure 6a, shows that the computed output bounds grow exponentially due to the high number (16) of model compartments, not providing any helpful information. Figure 6b shows that after performing a monotonicity analysis of the parallel inputs model there is still an overestimation, but the error is much smaller. Finally, a monotonicity analysis of the equivalent one-compartment model is carried out, given by (3) and (4), where the output bounds adjust almost perfectly to the numerical simulations, as shown in Figure 6c.

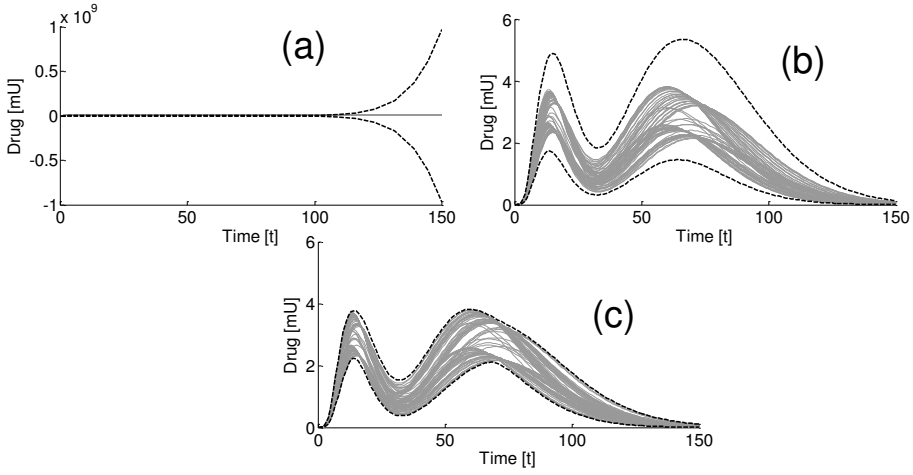

Figure 6: *Improvements computing double-peak phenomenon bounds. (a) VNODE-LP computation. (b) Monotonicity analysis of the parallel inputs model. (c) Monotonicity analysis of the equivalent one-compartment model.*

5. Discussion and Conclusion

Different approaches have been applied to compute the set of possible solutions when interval parametric uncertainty is considered. In this paper, a new method for the computation of output bounds on the class of parallel inputs models is proposed. This method has been compared with previous approaches in two cases: subcutaneous insulin absorption for artificial pancreas research, and the study of the double-peak phenomenon observed for certain drugs.

Montecarlo simulations have been used to measure the overestimation produced by the different methods. However, Montecarlo approaches have not been considered as valid methods to compute solution bounds, as they never guarantee the inclusion of all the solutions. Furthermore, a high number of simulations is needed to cover the uncertain input space sufficiently, with a computational cost of 0.01 s for each simulation in both cases. If five possible values are considered for each of the eight parameters that have uncertainty, the output computation would need 5^8 simulations, whereas our proposal just needs two simulations.

Region-based approaches have been considered for the output bounds computation, using VNODE-LP software. This C++ solver computes guaranteed output bounds, but the error seems to increase drastically depending on the number of model compartments: 4 in Figure 5a and 16 in Figure 6a. A large overestimation is produced in both cases.

The most common method in the literature to reduce overestimation is to perform a monotonicity analysis of a trajectory-based approach. After this analysis is performed, only non-monotone compartments or parameters produce an overestimation in the output bounds computation. In the parallel inputs model, the only non-monotone parameters are k_i. In both cases, an overestimation is produced due to these parameters, as seen in Figure 5b and Figure 6b, but this is much smaller than the error obtained with the VNODE-LP method.

Finally, our proposal consists in obtaining an equivalent model combining analytical solutions of the input chains with a monotonicity analysis. This approach allows computing critical points of the non-monotone parameter k_i, which helps to compute tighter output bounds, as seen in Figure 5c and Figure 6c. Furthermore, the computational cost is just 0.02 s to obtain the solution bounds.

Our proposed method outperforms previous approaches for the computation of output bounds on the parallel inputs model, as it minimises the overestimation produced, and also because of its low computational cost. To extend these results to nonlinear equations is still an open problem.

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Conflict of interest

No competing financial interests exist.

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