Verified Solution and Propagation of Uncertainty in Physiological Models*

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Abstract

We demonstrate here a method for the verified solution of nonlinear ODE models in physiology, computing rigorous bounds on the trajectories of the state variables, based on the ranges of the uncertain parameters. We also demonstrate an approach for the propagation of uncertain probability distributions in one or more model parameters and/or initial conditions. Assuming an uncertain probability distribution (p-box) for each parameter and/or initial condition of interest, we propagate these distributions through the dynamic model to the state variables. As a result, we obtain a p-box describing the probability distribution for each state variable at times of interest. As test problems, we use two physiological models. The first model simulates the metabolism of glucose in diabetic patients. The second is a simulation of long-term starvation that models the human body over time given uncertain metabolic rates. In both problems, comparisons are made with results obtained from Monte Carlo analysis.

Keywords: uncertainty, verified solutions, differential equations, physiology, p-box
AMS subject classifications: 65G20, 65L70, 92C30

1 Introduction

Physiological models are used to simulate the dynamics of the human body, especially in cases where experiments on humans is not a viable option. Such simulations can allow for a large number of numerical experiments to be performed, by adjustment and control of specific model parameters. Our focus here is on continuous-time physiological models expressed by systems of ordinary differential equations (ODEs) and formulated as initial value problems (IVPs). Of particular interest is the verified (i.e., mathematically and computationally guaranteed) solution of such systems of ODEs, especially systems that involve uncertainty in initial conditions and/or model parameters. Accounting for such uncertainties is particularly important in the context of physiological models, since in most, if not all, cases, initial values and model parameters are not known exactly. We will assume that, for such uncertain quantities, bounds

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on their true probability distribution are available. That is, uncertain quantities will be represented by probability boxes (p-boxes), as described in Section 2.3. Since this implies that there are infinitely many possible values for the uncertain quantities, it follows that, even for fixed initial conditions, we have infinitely many possible solutions of the underlying ODE system, corresponding to different values of the uncertain quantities. Therefore, we seek rigorous, verified bounds on all the possible trajectories.

For determining rigorous bounds on the solution of an ODE system, with or without uncertainties, the use of interval methods (also called validated or verified methods) is a natural approach, as computations with intervals, as opposed to floating-point numbers, can provide both mathematically and computationally guaranteed enclosures. Excellent reviews of interval methods for IVPs are available in the literature [15, 17]. For addressing interval-based ODE problems, there are various packages available, including AWA [9], VNODE [16], COSY VI [3], and ValEncIA-IVP [19]. In the work described here, we will use a recently developed solver [8] for parametric ODEs called VSPODE (Verifying Solver for Parametric ODEs), which is used to produce guaranteed bounds on the solutions of nonlinear dynamic systems with interval-valued initial states and parameters. Both COSY VI and VSPODE use Taylor models [11, 12, 13], though in different ways, to deal with the uncertain quantities (parameters and initial values). In this paper, we propose the use of Taylor-model methods, specifically VSPODE, for propagating uncertainties through nonlinear ODE models in physiology.

This paper is divided as follows. The next section will provide background on the tools used here to treat uncertainty. Section 3 describes the general ODE problem to be addressed, and in Section 4 we outline the specific method that is used to solve this problem. In Section 5, we present examples and highlight the results of using this solution method.

2 Background

2.1 Interval Analysis

The real interval vector $\boldsymbol{x} = [\underline{x}, \overline{x}]$ provides bounds on the real vector $x = [x_1, \ldots, x_n]^{\mathrm{T}}$, $n \geq 1$. The real vectors $\underline{x} = [\underline{x}_1, \ldots, \underline{x}_n]^{\mathrm{T}}$ and $\overline{x} = [\overline{x}_1, \ldots, \overline{x}_n]^{\mathrm{T}}$ provide the lower and upper bounds, respectively, on the components of x. That is, $\underline{x}_i \leq x_i \leq \overline{x}_i$ or $x_i \in [\underline{x}_i, \overline{x}_i]$. An n-dimensional interval vector can be interpreted geometrically as an n-dimensional rectangle or box. Basic arithmetic operations are defined on interval scalars according to $\boldsymbol{x} \circ \boldsymbol{y} = \{x \circ y \mid x \in \boldsymbol{x}, y \in \boldsymbol{y}\}, \circ \in \{+, -, \times, \div\}$, with division in the case of $\boldsymbol{y}$ containing zero allowed only in extensions of interval arithmetic [7]. Addition and multiplication are commutative and associative but only subdistributive. Interval versions of the elementary functions can also be defined.

For a real function $f(x) : \mathbb{R}^n \to \mathbb{R}$ that can be evaluated using an expression $\mathsf{f}(x)$ that is a composition of arithmetic operations and elementary functions, the range of $f(x)$ over $x \in \boldsymbol{x}$ can be bounded by substituting $\boldsymbol{x}$ into $\mathsf{f}(x)$ and evaluating with interval operations. That is, $\mathsf{f}(\boldsymbol{x}) \supseteq \{f(x) \mid x \in \boldsymbol{x}\}$. The tightness of these bounds depends on the form of the expression $\mathsf{f}(x)$. If $\mathsf{f}(x)$ is a single-use expression, in which no variable appears more than once, then the exact function range is obtained. However, if any variable appears more than once in $\mathsf{f}(x)$, then overestimation of the function range may occur, due to the "dependency" problem [7] of interval arithmetic. Another source of overestimation that may arise in the use of interval methods is the

"wrapping" effect. This occurs when an interval vector is used to enclose (wrap) a set of results that is not an interval vector. If this type of overestimation is propagated from step to step in an integration procedure for ODEs, it can quickly lead to the loss of a meaningful enclosure.

2.2 Taylor Models

Makino and Berz have described a remainder differential algebra (RDA) approach for bounding function ranges and control of the dependency problem of interval arithmetic [11, 12]. In this method, a function is represented using a model consisting of a Taylor polynomial and an interval remainder bound. Such a model is called a Taylor model.

One way of forming a Taylor model of a function is by using the Taylor theorem. Consider a real function $f(x) : \mathbb{R}^n \to \mathbb{R}$ that can be evaluated using the expression $\mathsf{f}(x)$. Assume that $\mathsf{f}(x)$ is $(q+1)$ times partially differentiable on $\boldsymbol{x}$ and let $x_0 \in \boldsymbol{x}$. The Taylor theorem states that for each $x \in \boldsymbol{x}$, there exists a real ζ with $0 < \zeta < 1$ such that

$$\mathsf{f}(x) = \mathsf{p}_\mathsf{f}(x - x_0) + \mathsf{r}_\mathsf{f}(x - x_0, \zeta), \tag{1}$$

where p_f is a q-th order polynomial (truncated Taylor series) in $(x - x_0)$ and r_f is a remainder, which can be quantitatively bounded over $0 < \zeta < 1$ and $x \in \boldsymbol{x}$ using interval arithmetic or other methods to obtain an interval remainder bound $\boldsymbol{r}_\mathsf{f}$. A q-th order Taylor model $\mathsf{T}_\mathsf{f} = \mathsf{p}_\mathsf{f} + \boldsymbol{r}_\mathsf{f}$ for $\mathsf{f}(x)$ over $\boldsymbol{x}$ then consists of the polynomial expression p_f and the interval remainder bound $\boldsymbol{r}_\mathsf{f}$ and is denoted by $\mathsf{T}_\mathsf{f} = (\mathsf{p}_\mathsf{f}, \boldsymbol{r}_\mathsf{f})$. The expression $\mathsf{f}(x)$ can now be bounded for $x \in \boldsymbol{x}$ by seeking bounds on the Taylor model $\mathsf{T}_\mathsf{f}(x - x_0)$ for $x \in \boldsymbol{x}$. This could be done using the interval evaluation $\mathsf{T}_\mathsf{f}(\boldsymbol{x} - x_0)$, but usually tighter bounds can be obtained using other methods [8, 14, 18].

In practice, it is more useful to compute Taylor models of functions by performing Taylor model operations. Arithmetic operations with Taylor models can be done using RDA operations, which include addition, multiplication, reciprocal, and intrinsic functions [11, 12, 13]. Using these, it is possible to start with simple expressions such as the constant $\mathsf{f}(x) = k$, for which $\mathsf{T}_\mathsf{f} = (k, [0, 0])$, and the identity $\mathsf{f}(x_i) = x_i$, for which $\mathsf{T}_\mathsf{f} = (x_{i0} + (x_i - x_{i0}), [0, 0])$, and then to compute Taylor models for very complicated expressions. It has been shown that, compared to other rigorous bounding methods, the Taylor model often yields sharper bounds for expressions that are even modestly complicated [11, 12, 18]. The uses and limitations of Taylor models are discussed in more detail elsewhere [18].

2.3 Probability Boxes (P-boxes)

For some quantity (variable or parameter) x, the cumulative distribution function (CDF) $F(z)$ gives the probability that $x \leq z$. In practice, knowledge of the probability distribution describing an uncertainty is often itself uncertain. To deal with imprecise probability distributions, we use probability boxes (p-boxes) [5, 6]. A p-box, as defined below, is a way to bound probability distributions, in much the same way that an interval is used to bound real numbers. Furthermore, arithmetic operations with p-boxes can be performed, again in much the same way as done with intervals. Computations with p-boxes allow for more information about the uncertainty of a quantity to be utilized in modeling and analysis.

Formally, a p-box (F, G) is the set of all CDFs enclosed by two bounding CDFs $F(z)$ and $G(z)$; that is, $(F, G) = \{H(z) | F(z) \geq H(z) \geq G(z)\}$. Less formally, a

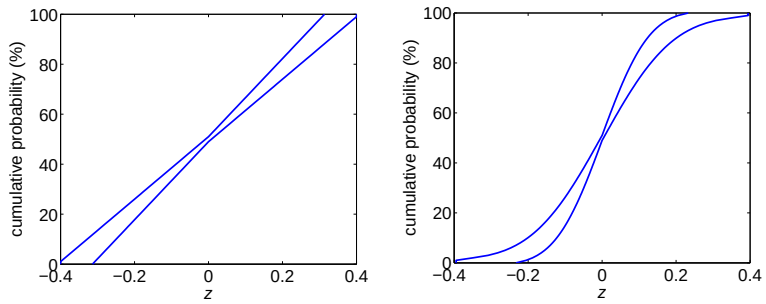

Figure 1: Examples of p-boxes based on uniform and normal distributions, respectively.

p-box can be thought of as a set of interval bounds on a cumulative distribution function, and thus, in practice, computation with p-boxes and intervals are analogous [5]. The bounding functions $F(z)$ and $G(z)$ are decomposed into interval-mass pairs, and interval arithmetic is then applied. Therefore, computation with p-boxes involves the same issues of dependency and wrapping that occur in computations with intervals. For a p-box represented as n interval-mass pairs, a single arithmetic operation with another independent p-box provides a result with n^2 interval-mass pairs, and a p-box with n interval-mass pairs must then be used to condense (wrap) this result.

A p-box may be constructed from any available information about an uncertain quantity, including, but not limited to, any combination of its maximum, minimum, mean, median, or standard deviation. An interval is the special case of a p-box for which only the maximum and minimum are known. P-boxes may also be created by assuming a particular form of probability distribution for the bounding functions $F(z)$ and $G(z)$. Two such p-boxes are shown in Figure 1. The first is a "uniform" p-box, constructed using uniform distributions with median 0 but uncertain outer bounds $[-0.4, -0.32]$ and $[0.32, 0.4]$. The second is a "normal" p-box, constructed by bounding all normal distributions (truncated at 99% confidence) with mean of zero and standard deviation in the interval $[0.1, 0.15]$. It is important to note that the true probability distribution simply lies between the bounding functions and does not necessarily take the same form as a bounding function; that is, a distribution within a p-box bounded by uniform distributions is not necessarily also uniform. Also, all p-boxes may be bounded by intervals that include all possible values of z.

3 Problem Statement

We investigate physiological models of the form

$$y'(t) = f(y, \theta), \quad y(t_0) = y_0 \in \boldsymbol{y}_0, \quad \theta \in \boldsymbol{\theta}, \tag{2}$$

where $t \in [t_0, t_m]$ for some $t_m > t_0$. Here $y \in \mathbb{R}^n$ is a vector of state variables with initial value y_0, and $\theta \in \mathbb{R}^p$ is a vector of time-invariant parameters. The intervals $\boldsymbol{y}_0$ and $\boldsymbol{\theta}$ enclose p-boxes that bound probabilistic uncertainties in the initial states and parameters, respectively. We treat $f(y, \theta)$ as a general nonlinear function, which we assume can be represented by an expression $\mathsf{f}(y, \theta)$ that is a composition of a finite

number of standard functions. It is also assumed that $\mathsf{f}(y,\theta)$ is $(k-1)$ times continuously differentiable with respect to y and $(q+1)$ times continuously differentiable with respect to θ. Here, k is the order of the truncation error in the interval Taylor series (ITS) method used by VSPODE, and q is the order of the Taylor model used in VSPODE to represent dependence on parameters and initial values. Our specific goals are (1) to obtain a rigorously guaranteed enclosure of the state variables y at all times of interest from t_0 to t_m, and (2) to obtain an enclosure (p-box) of the probability distribution for the values of y within these enclosures.

4 Solution Procedure

In this section, we outline the method used by VSPODE for solving the problem described in the previous section. Specifically, it is desired to determine a rigorously verified enclosure of all possible solutions to the IVP expressed in Eq. (2). We denote by $y(t;t_j,\boldsymbol{y}_j,\boldsymbol{\theta})$ the set $\{y(t;t_j,y_j,\theta) \mid y_j \in \boldsymbol{y}_j, \theta \in \boldsymbol{\theta}\}$, where $y_j = y(t_j)$ and $y(t;t_j,y_j,\theta)$ denotes a solution of $y'(t) = f(y,\theta)$ for the initial condition $y = y_j$ at $t = t_j$. We will summarize a method for determining enclosures $\boldsymbol{y}_j$ of the state variables at each time step $j = 1,\ldots,m$, such that $y(t_j;t_0,\boldsymbol{y}_0,\boldsymbol{\theta}) \subseteq \boldsymbol{y}_j$.

Assume that at t_j we have an enclosure $\boldsymbol{y}_j$ of $y(t_j;t_0,\boldsymbol{y}_0,\boldsymbol{\theta})$, and that we want to carry out an integration step to compute the next enclosure $\boldsymbol{y}_{j+1}$. Then, in the first phase of the method, the goal is to find a step size $h_j = t_{j+1} - t_j > 0$ and a rough enclosure $\widetilde{\boldsymbol{y}}_j$ of the solution such that a unique solution $y(t;t_j,y_j,\theta) \in \widetilde{\boldsymbol{y}}_j$ is guaranteed to exist for all $t \in [t_j,t_{j+1}]$, all $y_j \in \boldsymbol{y}_j$, and all $\theta \in \boldsymbol{\theta}$. We apply a traditional interval method, with high order enclosure, to the parametric ODEs by using an interval Taylor series (ITS) with respect to time. That is, we determine h_j and $\widetilde{\boldsymbol{y}}_j$ such that for $\boldsymbol{y}_j \subseteq \widetilde{\boldsymbol{y}}_j^0$,

$$\widetilde{\boldsymbol{y}}_j = \sum_{i=0}^{k-1} [0,h_j]^i \mathsf{f}^{(i)}(\boldsymbol{y}_j,\boldsymbol{\theta}) + [0,h_j]^k \mathsf{f}^{(k)}(\widetilde{\boldsymbol{y}}_j^0,\boldsymbol{\theta}) \subseteq \widetilde{\boldsymbol{y}}_j^0. \tag{3}$$

Here k denotes the order of the Taylor series, $\widetilde{\boldsymbol{y}}_j^0$ is an initial estimate of $\widetilde{\boldsymbol{y}}_j$, and the $\mathsf{f}^{(i)}$ are the Taylor coefficients of $y(t)$ with respect to time, which can be obtained recursively in terms of $y'(t) = \mathsf{f}(y,\theta)$ using automatic differentiation. When Eq. (3) is satisfied, it demonstrates [4] that there exists a unique solution $y(t;t_j,y_j,\theta) \in \widetilde{\boldsymbol{y}}_j$ for all $t \in [t_j,t_{j+1}]$, all $y_j \in \boldsymbol{y}_j$, and all $\theta \in \boldsymbol{\theta}$.

In the second phase of the method, we compute a tighter enclosure $\boldsymbol{y}_{j+1} \subseteq \widetilde{\boldsymbol{y}}_j$ such that $y(t_{j+1};t_0,\boldsymbol{y}_0,\boldsymbol{\theta}) \subseteq \boldsymbol{y}_{j+1}$. This is done by using an ITS approach to compute $\mathsf{T}_{y_{j+1}}(y_0,\theta)$, a Taylor model of y_{j+1} in terms of the initial values y_0 and parameters θ, and then obtaining the enclosure $\boldsymbol{y}_{j+1}$ by bounding $\mathsf{T}_{y_{j+1}}(y_0,\theta)$ over $y_0 \in \boldsymbol{y}_0$ and $\theta \in \boldsymbol{\theta}$. For the Taylor model computations, we begin by representing the interval initial states and parameters by the Taylor models (identity functions) T_{y_0} and T_θ, respectively. Then, we can determine Taylor models $\mathsf{T}_{\mathsf{f}^{(i)}}$ of the Taylor series coefficients $\mathsf{f}^{(i)}(y_j,\theta)$ by using RDA operations to compute $\mathsf{T}_{\mathsf{f}^{(i)}} = \mathsf{f}^{(i)}(\mathsf{T}_{y_j},\mathsf{T}_\theta)$. Using an interval Taylor series for y_{j+1} with coefficients given by $\mathsf{T}_{\mathsf{f}^{(i)}}$, and using the mean value theorem, one can obtain $\mathsf{T}_{y_{j+1}}(y_0,\theta)$, the desired Taylor model of y_{j+1} in terms of the parameters θ and initial states y_0. To control the wrapping effect, the state enclosures are propagated using a new type of Taylor model consisting of a polynomial and a *parallelepiped* (as opposed to an interval) remainder bound. Complete details of the computation of $\mathsf{T}_{y_{j+1}}(y_0,\theta)$ using VSPODE are given by Lin and Stadtherr [8].

Table 1: Parameter values and initial states for diabetes model.

	Value	Units		Value	Units
p_1	0	min^{-1}	V_1	12	L
p_2	0.025	min^{-1}	n	5/54	min^{-1}
p_3	0.000013	mU/L	G_{meal}	9.259	mmol/min
G_b	4.5	mmol/L	U	50/3	mU/min
I_b	4.5	mU/L	$I(0)$	0.02	mmol/L
$G(0)$	$[4.5, 4.6]$	mmol/L	$X(0)$	$[0.05, 0.075]$	mmol/L

Using the method summarized above, we can obtain, for a specified time of interest t_k, a Taylor model $\mathsf{T}_{y_k}(y_0, \theta)$ that gives the state variables $y_k = y(t_k)$ as a polynomial $\mathsf{p}_{y_k}(y_0, \theta)$ in terms of the initial states $y_0 \in \boldsymbol{y}_0$ and the parameters $\theta \in \boldsymbol{\theta}$, plus a small remainder bound. If probability distributions (p-boxes) are available for y_0 and for θ, then these can be substituted directly into $\mathsf{T}_{y_k}(y_0, \theta)$, and a p-box giving bounds on the probability distribution for y_k can be computed using standard p-box operations. For this purpose, we use our own skeletal Matlab implementation of p-box arithmetic.

5 Examples

As test problems, we will apply the method outlined above to two physiological models. The first simulates the metabolism of glucose in diabetic patients, and the second models the effects of long-term starvation on the human body. For both examples, VSPODE was used with its default ITS order $k = 17$ and default Taylor model order $q = 5$. When Monte Carlo (MC) simulations are run for purposes of comparison, they are done in Matlab, using the ode45 routine with default tolerances.

5.1 Diabetes Model

This physiological model for blood glucose in diabetic patients is an example of a model that investigates biological feedback control systems. The Bergman "minimal" model [2] represents the effects of insulin infusion U in response to a glucose input G_{meal} for a diabetic patient. The model is

$$\frac{dG}{dt} = -p_1 G - X(G + G_b) + \frac{G_{\text{meal}}}{V_1},$$

$$\frac{dX}{dt} = -p_2 X + p_3 I,$$

$$\frac{dI}{dt} = -n(I + I_b) + \frac{U}{V_1}.$$

I is the blood insulin concentration and X is the "remote" (or effective) insulin concentration. Here we will do an "open-loop" simulation to determine the effects on G and X of a slow meal of $G_{\text{meal}} = 100$ g/hr begun at $t = 0$ with uncertain initial states $G(0)$ and $X(0)$. Model parameter values [1, 10] are given in Table 1. The intervals given in Table 1 for $G(0)$ and $X(0)$ enclose the p-boxes that represent the uncertainty

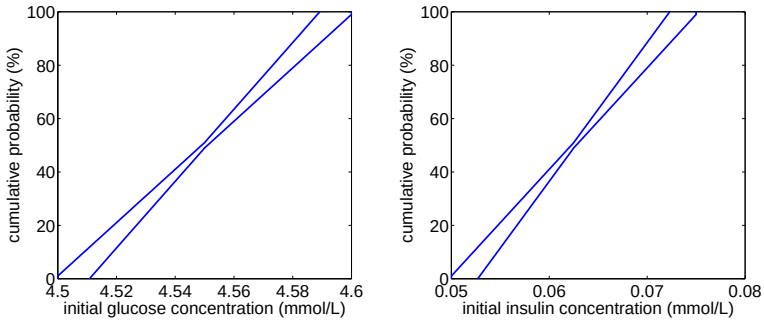

Figure 2: P-boxes for uncertainty in $G(0)$ and $X(0)$ in diabetes model.

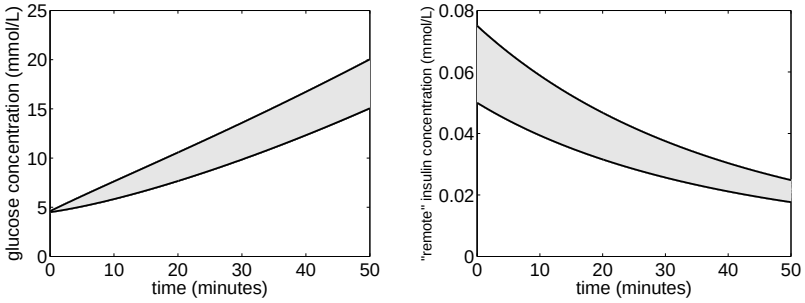

Figure 3: VSPODE enclosures (solid curves) for G and X over $t = [0, 50]$ min, with comparison to MC simulation results (shaded areas).

on these initial conditions. For both quantities, we will assume p-box bounds based on uniform distributions, as shown in Figure 2.

VSPODE was first used to determine rigorous enclosures of the trajectories for G and X from $t_0 = 0$ to $t_m = 50$ min. These results (solid curves) are shown in Figure 3. We checked the tightness of the VSPODE bounds by comparison to the results of an MC simulation with 50000 trials. For each trial, real values of $G(0)$ and $X(0)$ were selected at random from within their specified interval bounds. Bounds obtained from MC analysis are not guaranteed and in general will yield an inner estimate of the true bounds (the rigorous VSPODE bounds represent an outer estimate). The MC simulation results are shown by the shaded areas in Figure 3. Clearly, VSPODE provides very tight bounds on these trajectories.

The Taylor model from VSPODE at $t = t_m$ was then used to compute bounds on the probability distributions for $G(t_m)$ and $X(t_m)$. These are shown as p-boxes (solid curves) in Figure 4. This shows, for example, that the probability of $G(t_m)$ being less than 16 mmol/L is rigorously bounded by the interval $[0.076, 0.281]$. For comparison, probability bounds were also determined using MC simulation, as shown by the shaded areas in Figure 4. These are the results of 500 MC simulations consisting of 10000 trials each. For each simulation, uniform probability distributions were chosen randomly from within the input p-boxes for the initial conditions (Figure 2), and then

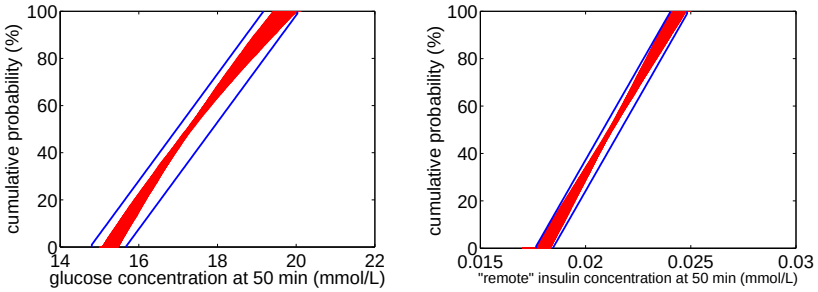

Figure 4: P-box enclosures (solid curves) of probability distributions for G and X at $t = 50$ min, with comparison to MC simulation results (shaded areas).

the ODE model was integrated for 10000 different inputs chosen according to these probability distributions. The results obtained from the Taylor model are clearly consistent with the MC results. It is important to note: (1) Probability bounds obtained from MC analysis are not rigorous, but those obtained from the Taylor model analysis are. For the number of MC trials done here, which is relatively many to ensure meaningful results, the computation time was quite large, about 4 hours (vs. about 5 seconds for the rigorous Taylor model approach). (2) The probability bounds from MC become quite narrow at the median, less so than those obtained from the Taylor model analysis. This reflects the use of only uniform distributions in the MC analysis. A p-box with uniform bounds also contains non-uniform distributions, and this is accounted for in the bounds from Taylor model analysis. (3) There is likely to be significant overestimation of the probability bounds obtained from the Taylor model, due to mostly to the dependency problem that occurs when p-box operations are done. This problem can be greatly ameliorated by using subinterval reconstitution [6], which we will apply to this example in future work.

5.2 Long-Term Starvation Model

After depletion of glucose reserves (3-4 days fasting), energy to sustain the human body comes from fat, $F(t)$, protein stored in muscle mass, $M(t)$, and (for brain function) ketone bodies, $K(t)$. The long-term starvation model proposed by Song and Thomas [20] uses material and energy balances to model the dynamics of these three components. This model is given by

$$\frac{dF}{dt} = F\Big(-\frac{a}{1+K} - \frac{1}{\lambda_F}\Big(\frac{C+\kappa L_0}{F+M} + \kappa\Big)\Big),$$

$$\frac{dM}{dt} = -\frac{M}{\lambda_M}\Big(\frac{C+\kappa L_0}{F+M} + \kappa\Big),$$

$$\frac{dK}{dt} = \frac{VaF}{1+K} - b.$$

Song and Thomas [20] set all parameters and initial values (Table 2) at standard literature values, except for κ, a proportionality constant for the effect of body mass on metabolic rate, and b, the rate of ketone use in the brain. The standard literature value for κ does not apply as it is an average over "normal" (not starving) individuals, and

Table 2: Parameter values and initial states for starvation model.

	Value	Units		Value	Units
a	0.013	kg/d	V	0.9	(kg fat)/(kg ketone)
C	772.3	kcal/d	$F(0)$	25	kg
L_0	30.4	kg	$M(0)$	43.6	kg
λ_F	7777.8	kcal/kg	$K(0)$	0.02	kg
λ_M	1400	kcal/kg	b	$[0.05, 0.075]$	kg/d
κ	$[8.22, 13.7]$	kcal/(kg d)			

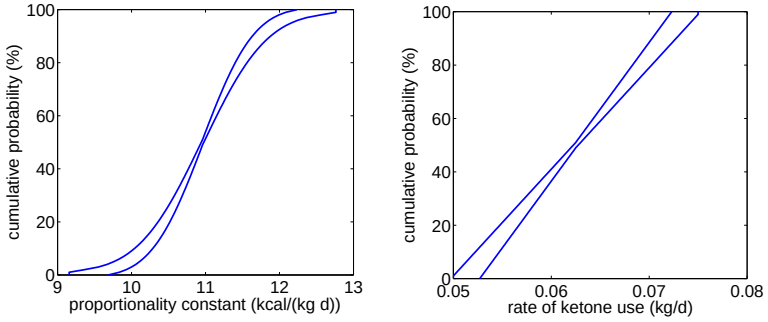

Figure 5: P-boxes for uncertainty in κ and b in starvation model.

only rough estimates are available for b. For these two parameters, Song and Thomas [20] considered values in the intervals shown in Table 2, assuming a normal distribution of values for κ and a uniform distribution for b. We have introduced uncertainty in these distributions by taking the standard deviation for κ to be $[0.548, 0.685]$, and the upper and lower bounds for b to be $[0.0725, 0.075]$ and $[0.05, 0.0525]$, respectively. The resulting p-boxes for κ and b are shown in Figure 5.

The results of using VSPODE to rigorously bound the trajectories for $M(t)$ and $K(t)$ for $t_m = 25$ days are shown in Fig. 6, again with comparison to results obtained by MC simulation. Since death is certain when the ketone mass becomes zero, this shows that the individual being modeled would potentially be near death at day 25. Figure 7 gives the results of using the VSPODE Taylor model at $t_m = 25$ days to determine p-boxes for $M(t_m)$ and $K(t_m)$, along with results of MC analysis (500 simulations consisting of 10000 trials each). As noted previously, we anticipate that the use of subinterval reconstitution [6] will result in significantly less overestimation in the p-box bounds.

6 Concluding Remarks

Mathematical models of physiological dynamics often involve uncertain parameters and/or initial states. We have demonstrated here an approach for dealing rigorously with this uncertainty. With this approach, guaranteed bounds on the state trajectories

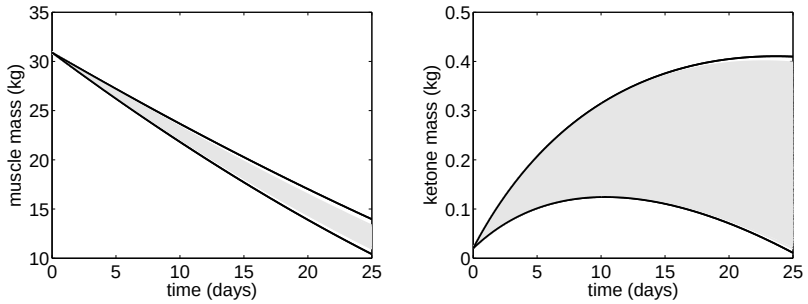

Figure 6: VSPODE enclosures (solid curves) for M and K over $t = [0, 25]$ days, with comparison to MC simulation results (shaded areas).

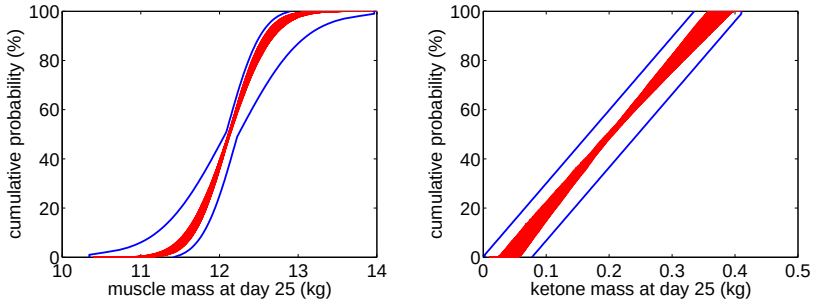

Figure 7: P-box enclosures (solid curves) of probability distributions for M and K at $t = 25$ days, with comparison to MC simulation results (shaded areas).

can be determined, as well as guaranteed bounds on the probability distributions of the states. In future work, we will reduce overestimation of the probability bounds by using subinterval reconstitution.

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