

Verified Solution and Propagation of Uncertainty in Physiological Models

Joshua A. Enszer and Mark A. Stadtherr

Department of Chemical and Biomolecular Engineering
University of Notre Dame, Notre Dame, IN 46556, USA



13th GAMM - IMACS International Symposium on Scientific Computing, Computer Arithmetic and
Verified Numerical Computations, University of Texas at El Paso, 29 September – 3 October 2008

Overview

- Motivation–Physiological Models
- Background
 - Representing Uncertainty
 - Problem Statement
- Solution Procedure
- Examples
 - Diabetes Model
 - Long-term Starvation Model
- Concluding Remarks

Motivation–Physiological Models

- Models can be developed to simulate the dynamics of the human body
 - Often “compartment” based
 - Unsteady material and/or energy balances
 - Lumped or distributed parameter
- Models can be used to investigate physiological processes under circumstances that would be unsafe or impractical to simulate with physical experiments
 - Pharmacokinetics and drug delivery
 - Treatment plans and dosing
 - Operation and control policies for devices (e.g. insulin delivery)
- Parameters and initial states in these models may be determined based on limited empirical investigation, so are not precisely known, but bounds and imprecise probability distributions may be available
- Need procedure to rigorously propagate the uncertainty to the model outputs

Example–Diabetes Model

- The Bergman “minimal” model (Bergman et al., 1981) represents the effect of insulin infusion (U) and glucose inputs (G_{meal}) on blood glucose concentration (G) in a diabetic patient:

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

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

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

- I is blood insulin concentration; X is “remote” (effective) insulin concentration
- Given uncertainties in parameters and initial states, what uncertainties result in G and X ?

Representing Uncertainty: Intervals

- Uncertainty in a parameter or initial state can be bounded by a real interval

$$X = [a, b] = \{x \in \mathbb{R} \mid a \leq x \leq b\}$$

- An interval provides upper and lower bounds only and gives no information about the distribution of uncertainties

- An interval vector $\mathbf{X} = [X_1, X_2, \dots, X_n]^T$ can be thought of as an n -dimensional rectangle

- Basic interval arithmetic for intervals X and Y is

$$X \text{ op } Y = \{x \text{ op } y \mid x \in X, y \in Y\}$$

- Interval elementary functions, e.g. $\exp(X)$, $\sin(X)$, are also available

Representing Uncertainty: Intervals

- An interval extension $F(\mathbf{X})$ encloses $f(\mathbf{x})$ for every $\mathbf{x} \in \mathbf{X}$:

$$F(\mathbf{X}) \supseteq \{f(\mathbf{x}) \mid \mathbf{x} \in \mathbf{X}\}$$

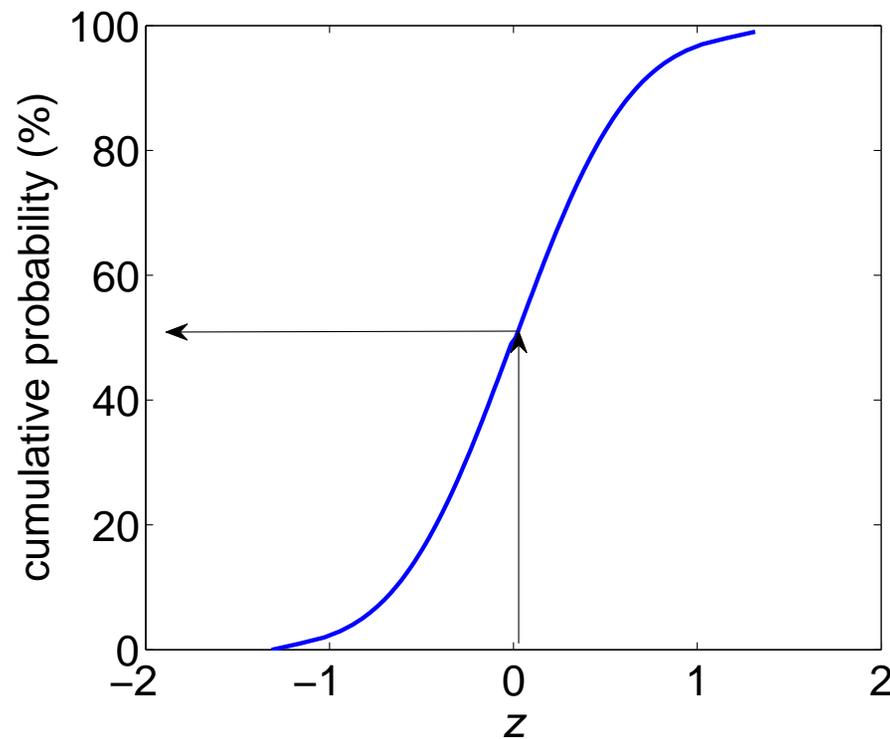
- If the function calls an interval-valued variable more than once, direct substitution (natural interval extension) may lead to overestimation (the “dependency” problem)
- If an interval is used to enclose (wrap) a nonrectangular set of values, then overestimation occurs (the “wrapping effect”)
- Repeated applications of such overestimations can quickly lead to the loss of any meaningful interval enclosure

Representing Uncertainty: Taylor Models

- Taylor Model $T_f = (p_f, R_f)$: Bounds $f(\boldsymbol{x})$ over \boldsymbol{X} using a q -th order Taylor polynomial p_f and an interval remainder bound R_f
- One way to obtain T_f is directly from Taylor's theorem
- Can also compute Taylor models by using Taylor model (TM) operations (Makino and Berz, 1996)
 - Beginning with Taylor models of simple functions (e.g., constant, identity) and using TM operations, one can compute the TM of a complicated function
- Compared to other methods, Taylor models often yield sharper bounds for modest to complicated functional dependencies

Representing Uncertainty: CDF's

- For a quantity x , the cumulative distribution function (CDF) $F_x(z)$ gives the probability that $x \leq z$
- Example: in the CDF below, $P(x \leq 0) = 0.5$



Representing Uncertainty: P-boxes

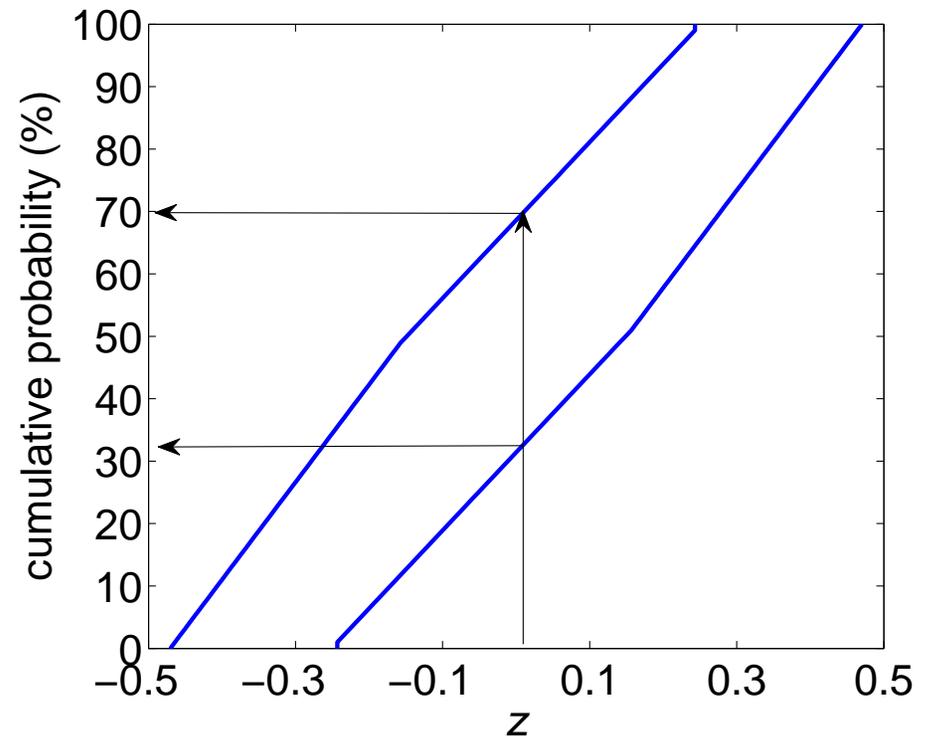
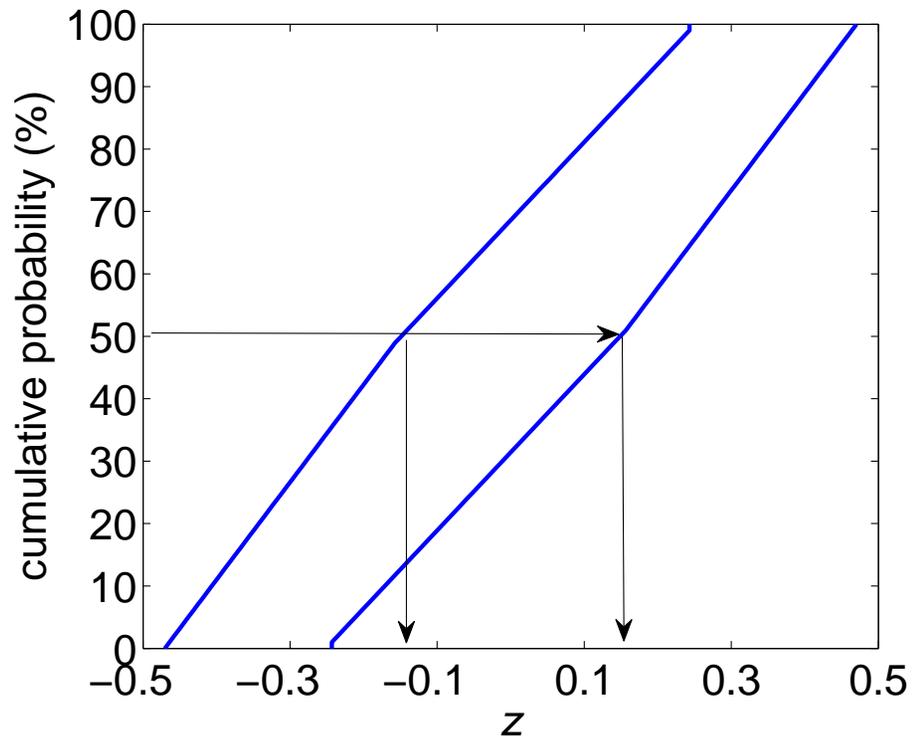
- A probability box (p-box) bounds a set of probability distributions, much like an interval bounds a set of real numbers
- A p-box is the set of all CDFs enclosed by two bounding functions $F(z)$ and $G(z)$:

$$(F, G) = \{H(z) \mid F(z) \geq H(z) \geq G(z) \quad \forall z \in \mathbb{R}\}$$

- P-boxes may be formulated from
 - Known distributions with uncertain parameters (e.g., mean, standard deviation)
 - Any bounds consistent with available information
- Arithmetic operations can be defined in a manner analogous to intervals
- P-box operations are implemented in RAMAS Risk Calc (Ferson, 2002). We also use a “bare bones” Matlab implementation.

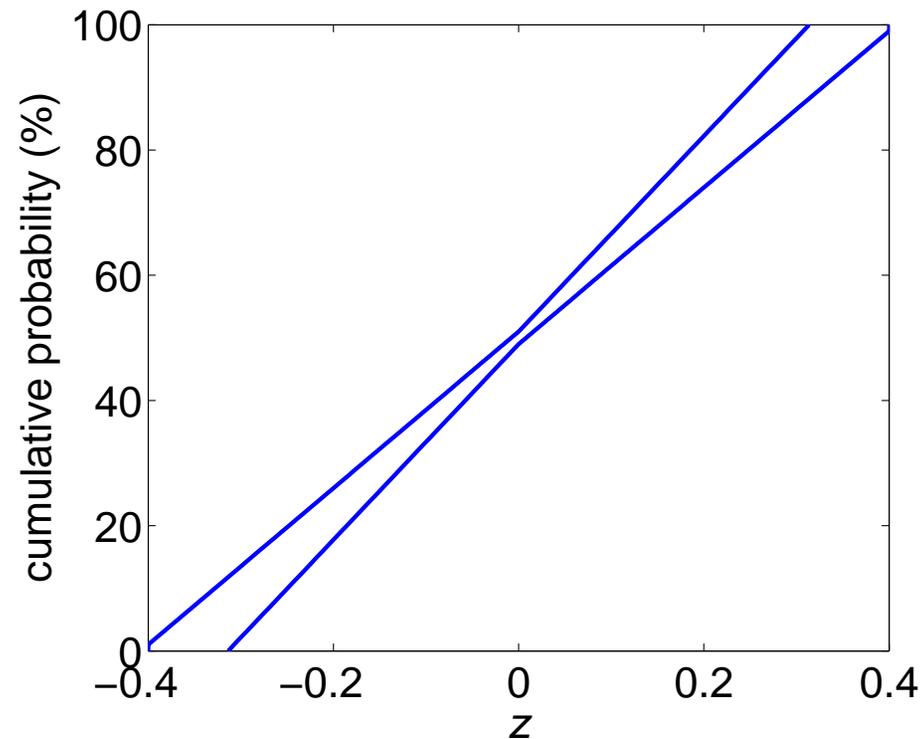
Representing Uncertainty: P-boxes

- P-boxes provide an interval of probabilities for a corresponding value or an interval of values for a corresponding probability



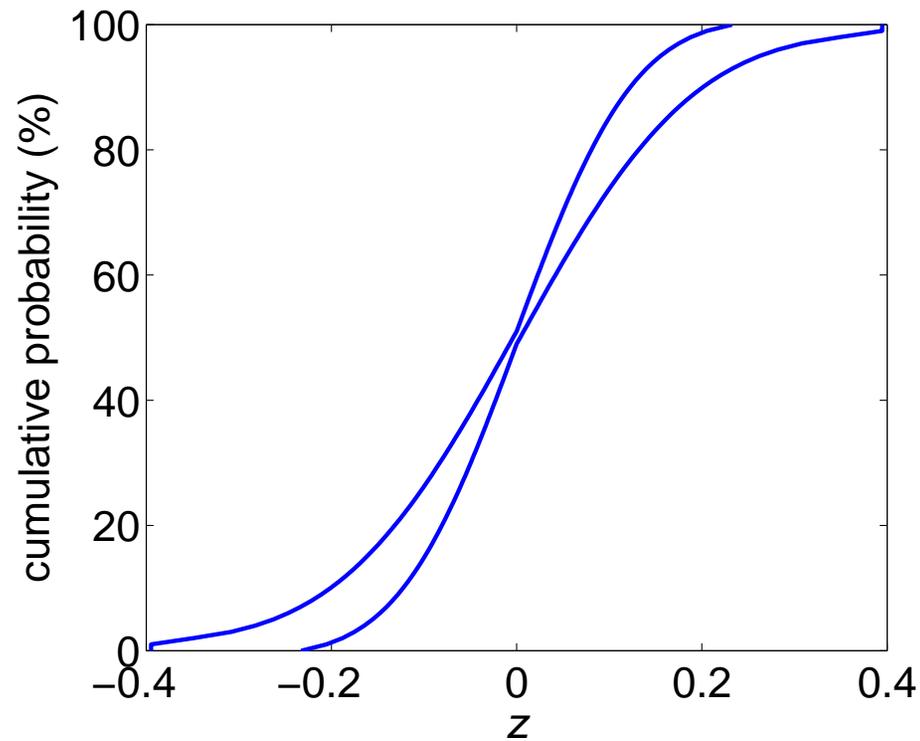
Representing Uncertainty: P-boxes

- Example of a p-box from a known distribution and uncertain parameter:
 - A “uniform” p-box obtained from a uniform distribution with uncertain outer bounds $[-0.4, -0.32]$ and $[0.32, 0.4]$ and fixed midpoint 0
 - This p-box can be enclosed in the interval $[-0.4, 0.4]$



Representing Uncertainty: P-boxes

- Another example of a p-box from a known distribution / uncertain parameter:
 - A “normal” p-box with bounds obtained from a truncated normal distribution with fixed mean 0 and interval standard deviation $[0.10, 0.15]$
 - This p-box can be enclosed in the interval $[-0.3947, 0.3947]$



Problem Statement

- We consider physiological models that can be formulated as ODE initial value problems,

$$\frac{dy}{dt} = f(y, \theta), \quad y(t_0) = y_0 \in Y_0, \quad \theta \in \Theta,$$

in which at least one of the initial states y_0 or one of the time-invariant parameters θ is uncertain (contained in Y_0 and/or Θ)

- There may be information about the distribution of this uncertainty that can be represented by a p-box
- **Goal 1:** Obtain a rigorous, verified enclosure of all possible solutions to this uncertain, parametric IVP over a time horizon of interest
- **Goal 2:** Obtain rigorous, verified bounds (p-boxes) on the probability distribution of the states at times of interest

Solution Procedure–Goal 1

- **Goal 1:** Obtain a rigorous, verified enclosure of all possible solutions to this uncertain, parameter IVP over a time horizon of interest
- Use a method for verified (validated) solution of IVP
 - Guarantees there exists a unique solution y in the interval $[t_0, t_f]$, for each $\theta \in \Theta$ and $y_0 \in Y_0$
 - At time step j , computes an interval Y_j that encloses all solutions of the ODEs system at t_j for $\theta \in \Theta$ and $y_0 \in Y_0$
- Tools are available – AWA, VNODE, COSY VI, ValEncIA-IVP, **VSPODE**, etc.

Summary of VSPODE

- Use interval Taylor series to represent dependence on time
- Use Taylor models to represent dependence on uncertain quantities (parameters and initial states)
- Assuming Y_j is known, then
 - Phase 1: Compute a coarse enclosure \tilde{Y}_j and prove existence and uniqueness using fixed point iteration with Picard operator and high-order interval Taylor series (as in VNODE)
 - Phase 2: Refine the coarse enclosure to obtain Y_{j+1} using Taylor models in terms of the uncertain parameters and initial states
- Implemented by Lin and Stadtherr (2007)

Phase 2 of VSPODE

- Represent uncertain initial states and parameters using Taylor model identity functions T_{y_0} and T_θ
- Bound the interval Taylor series coefficients $f^{[i]}$ by Taylor models $T_{f^{[i]}}$
 - Use mean value theorem
 - Evaluate using Taylor model operations
- Reduce “wrapping effect” by using a new type of Taylor model

$$T_{y_j} = \hat{T}_{y_j} + \mathcal{P}_j, \quad \text{where } \mathcal{P}_j = \{A_j v_j \mid v_j \in V_j\}$$

- The result: a Taylor model $T_{y_{j+1}}$ in terms of the initial states y_0 and parameters θ ; then $Y_{j+1} = B(T_{y_{j+1}})$ (interval bound on $T_{y_{j+1}}$)

Solution Strategy–Goal 2

- **Goal 2:** Obtain rigorous, verified bounds (p-boxes) on the probability distribution of the states at times of interest
- For a time of interest t_j (end of j -th time step), VSPODE has computed a Taylor model representation $T_{y_j} = T_{y_j}(y_0, \theta)$ of the state variables as a function of the initial states y_0 and parameters θ
- This Taylor model is valid for all $y_0 \in Y_0$ and $\theta \in \Theta$
- Substitute distributions (p-boxes) for y_0 and θ into $T_{y_j} = T_{y_j}(y_0, \theta)$ and use p-box arithmetic to compute p-boxes of state variables $y_j = y(t_j)$
- To reduce overestimation in p-box arithmetic, subinterval reconstitution (SIR) can be used (Ferson and Hajagos, 2004).

Example: Diabetes Model

- The Bergman “minimal” model (Bergman et al., 1981) represents the effect of insulin infusion (U) and glucose inputs (G_{meal}) on blood glucose concentration (G) in a diabetic patient:

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

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

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

- I is blood insulin concentration; X is “remote” (effective) insulin concentration
- Consider “open loop” simulation of effect on G and X of a “slow” meal ($G_{\text{meal}} = 100$ g/hr)
- Uncertain initial states $G(0)$ and $X(0)$

Example: Diabetes Model

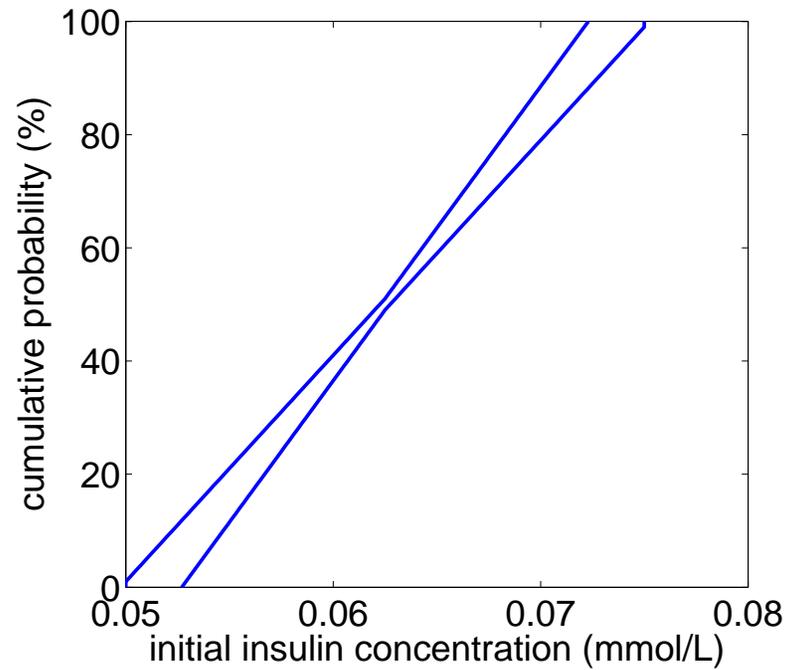
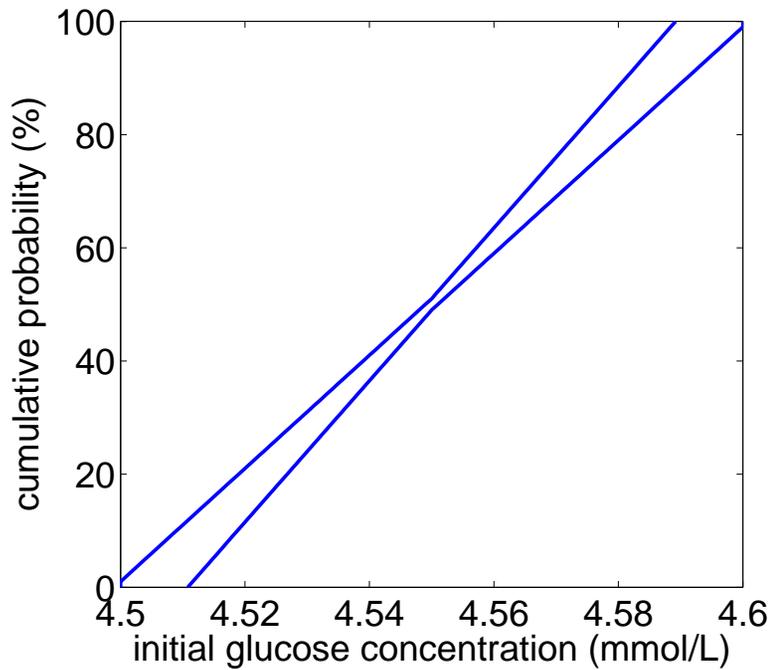
- Parameters (Lynch and Bequette, 2001) and initial conditions:

	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

- Assume imprecise uniform distributions for $G(0)$ and $X(0)$

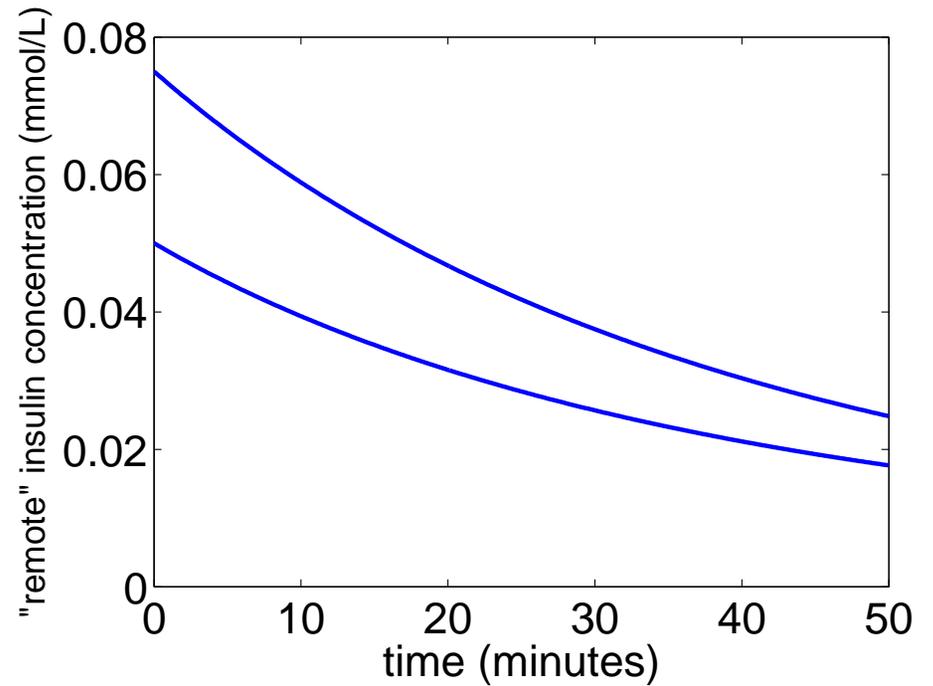
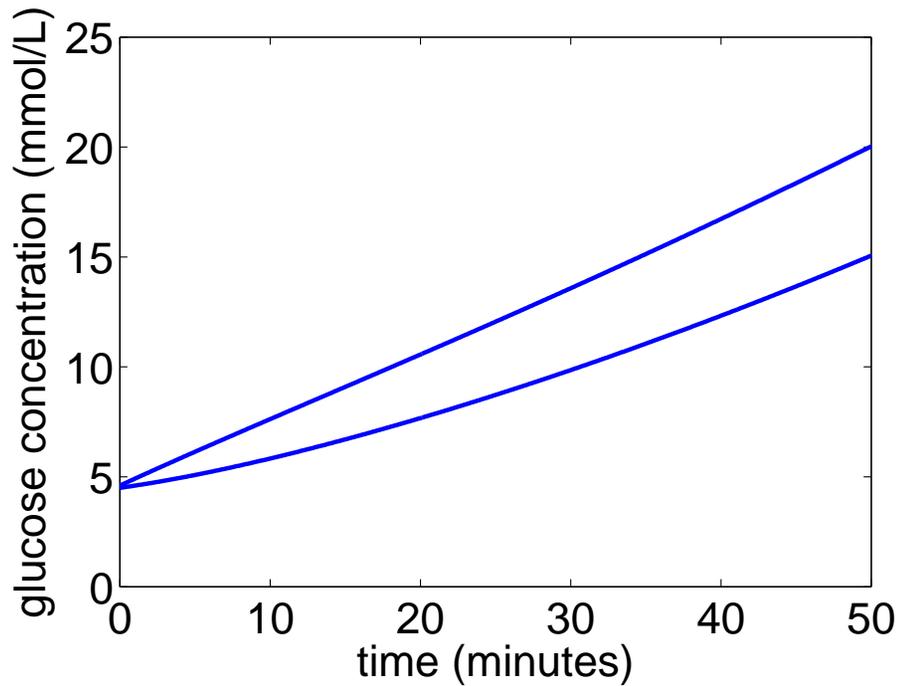
Example: Diabetes Model

- P-box representation of uncertain initial states $G(0)$ and $X(0)$



Example: Diabetes Model

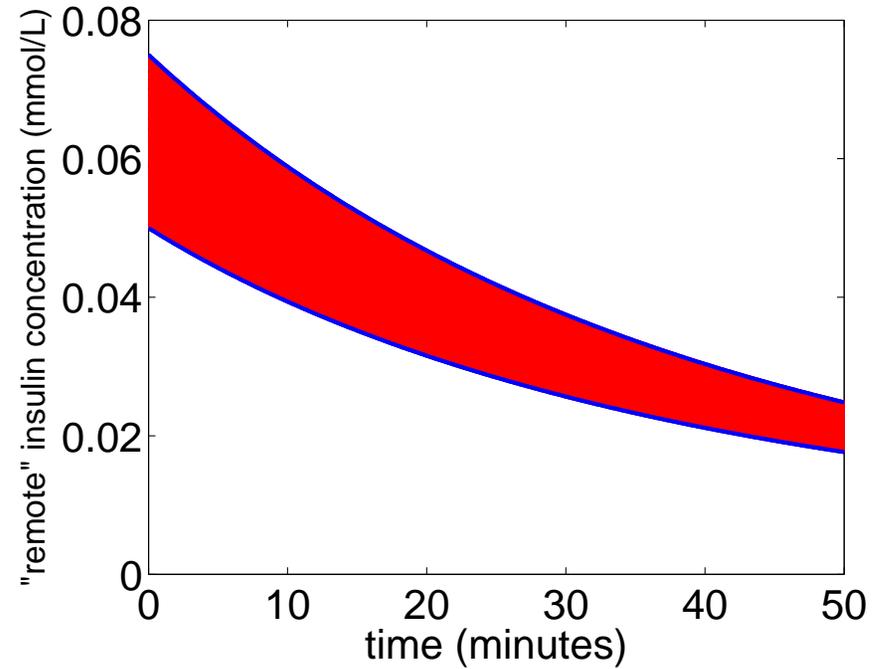
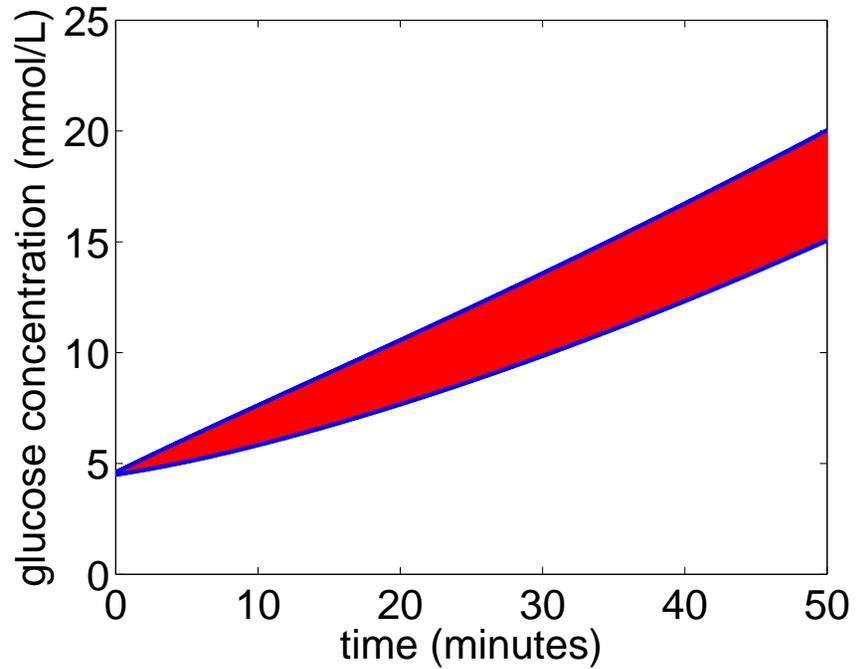
- VSPODE enclosures of $G(t)$ and $X(t)$ over $t = [0, 50]$ min



- How tight are these bounds?

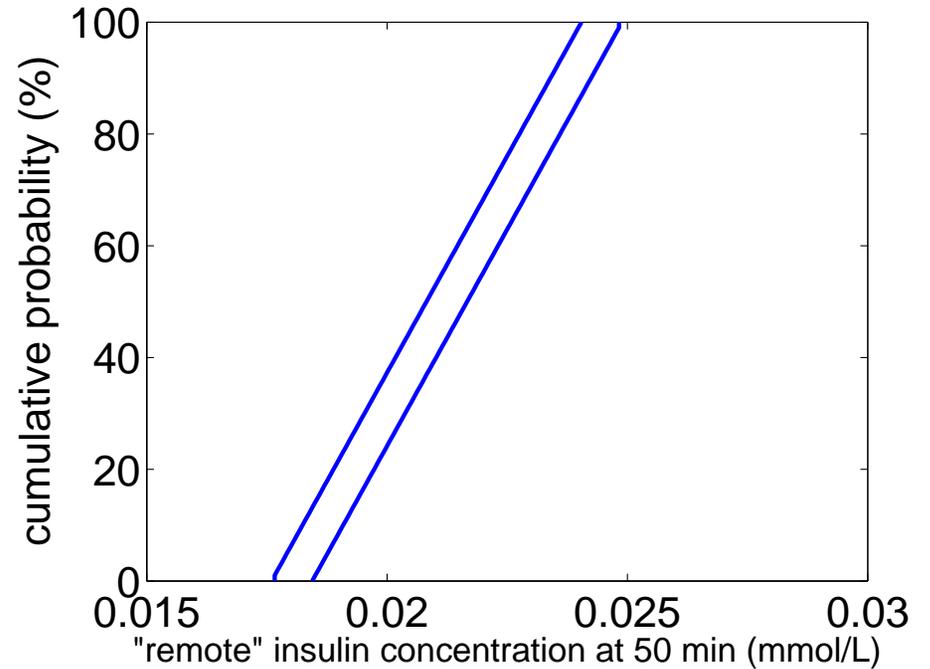
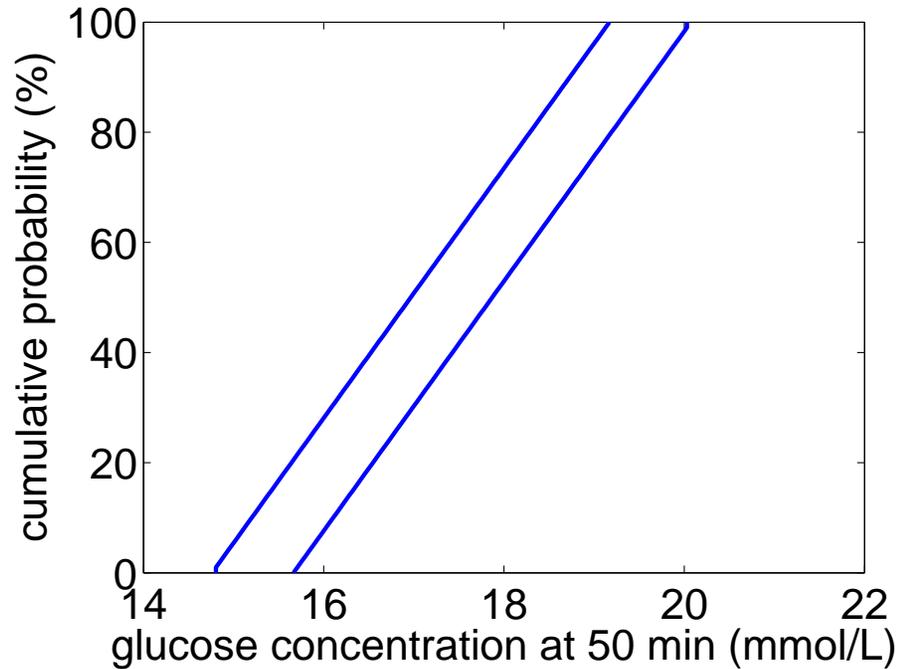
Example: Diabetes Model

- Comparison of VSPODE bounds to Monte Carlo simulations



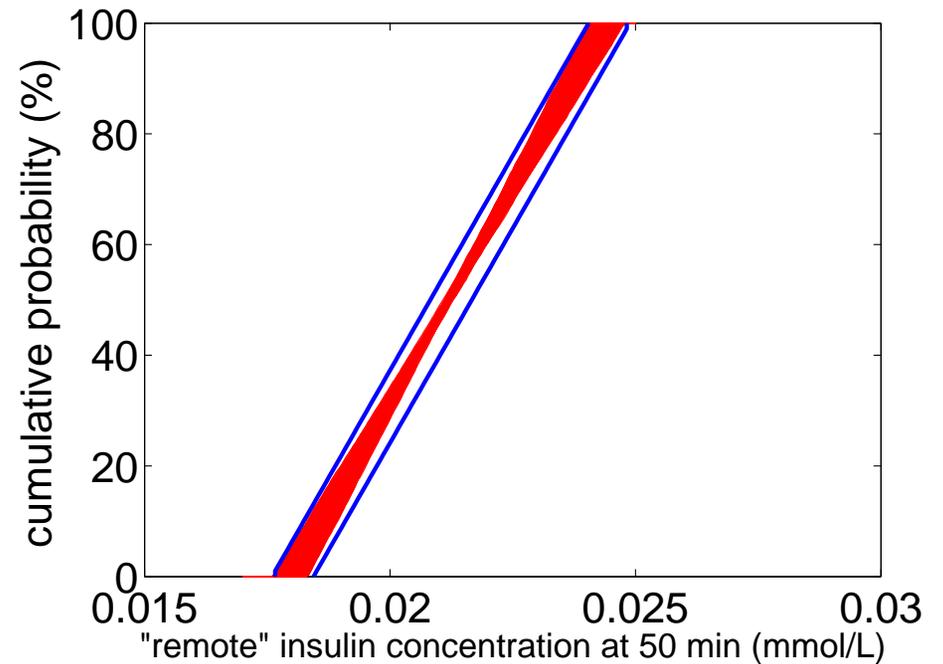
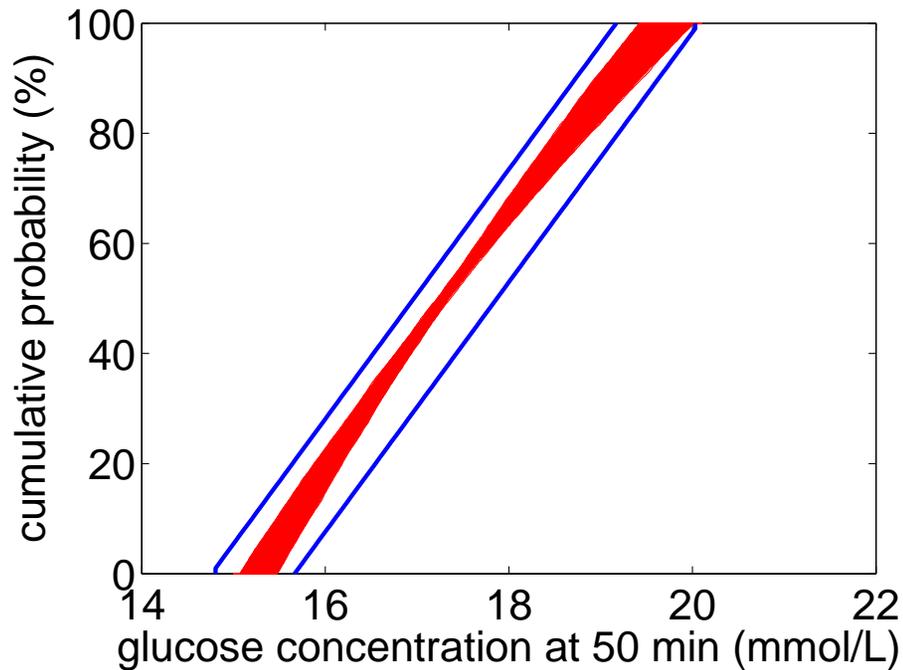
Example: Diabetes Model

- Probability distributions (p-boxes) for G and X at $t = 50$ min



Example: Diabetes Model

- Comparison with Monte Carlo simulations: 500 simulations, each with probability distributions for $G(0)$ and $X(0)$ sampled from the input p-boxes; each simulation consisting of 10000 trials



Example: 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 (acetone, AcAc, BHB) $K(t)$
- From this starting point, balance equations can be developed for a physiological simulation of long-term starvation (Song and Thomas, 2007):

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

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

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

- All parameters taken from literature studies, except for κ (effect of body mass on basal metabolic rate) and b (rate of ketone use by brain)

Example: Long-term Starvation Model

- Parameters and initial conditions:

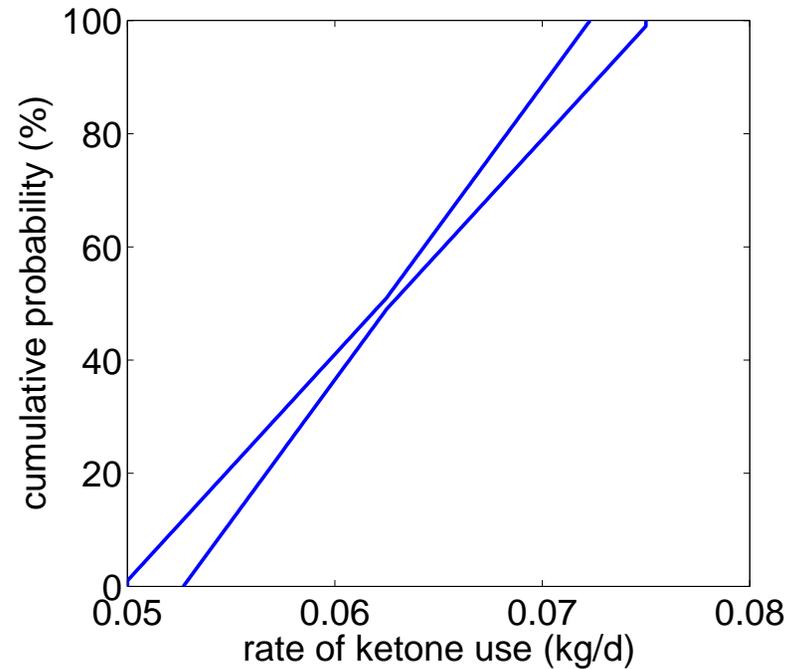
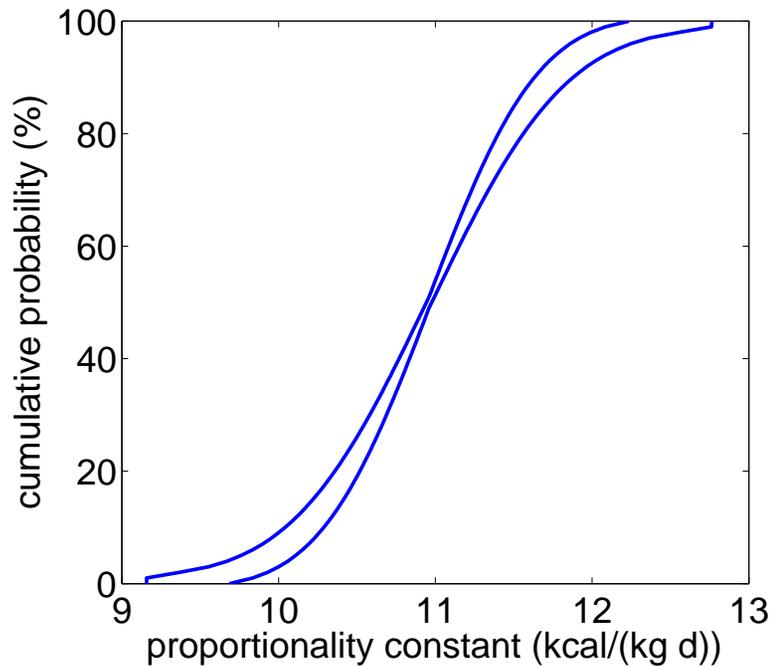
	Value	Units		Value	Units
a	0.013	kg/d	V	0.9	(kg fat)/(kg ketone)
C	772.3	kcal/d	$F(0)$	25	kg
L_0	30.4	kg	$M(0)$	43.6	kg
λ_F	7777.8	kcal/kg	$K(0)$	0.02	kg
λ_M	1400	kcal/kg			
κ	[8.22, 13.7]	kcal/(kg d)	b	[0.05, 0.075]	kg/d

Example: Long-term Starvation Model

- The parameter κ is the proportionality constant accounting for the effect of body mass on the basal metabolic rate.
 - Standard literature value does not apply since it is an average over normal individuals
 - Song and Thomas (2007) assume a normal distribution for κ with mean of 10.96 kcal/(kg d)
 - We assume a standard deviation in [0.548, 0.685]
- The parameter b is the rate of ketone body use by the brain
 - Song and Thomas (2007) estimate this to be in [0.05, 0.075] and assume a uniform distribution
 - We assume imprecision in bounds, with lower bound in [0.05, 0.0525] and upper bound in [0.0725, 0.075]

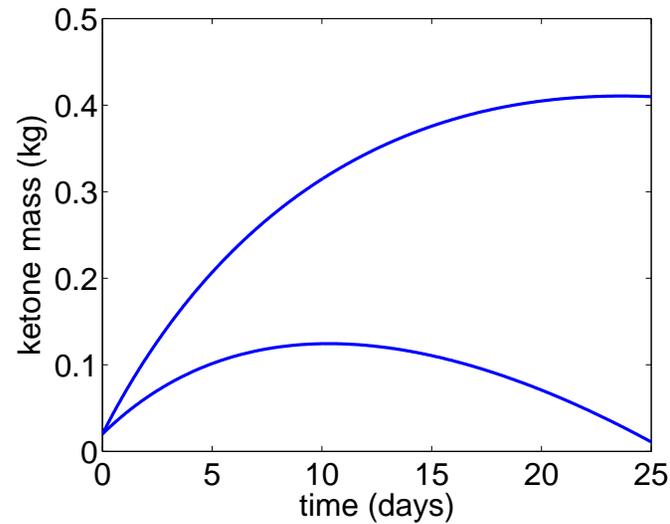
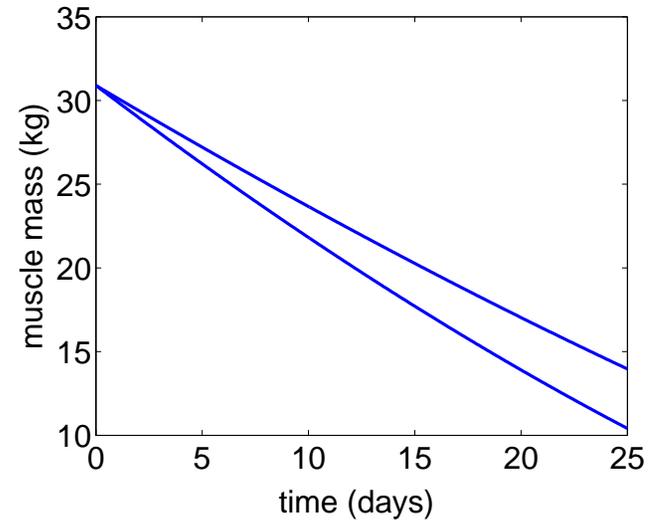
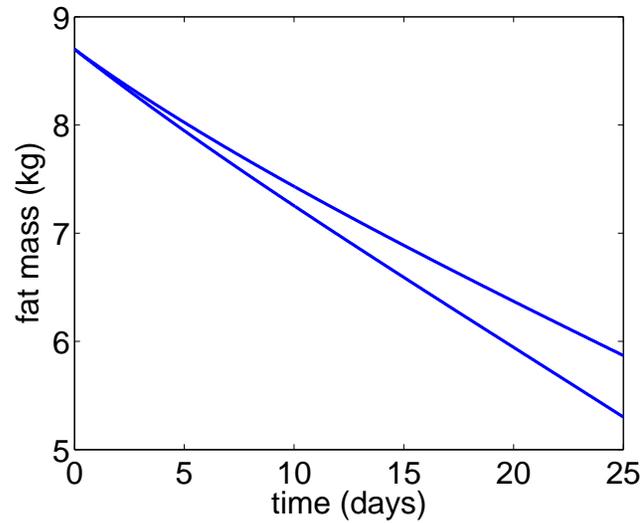
Example: Long-term Starvation Model

- P-box representation of uncertain parameters κ and b



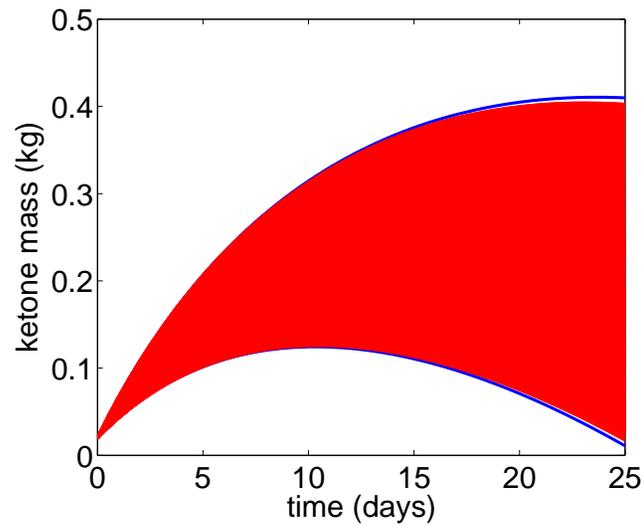
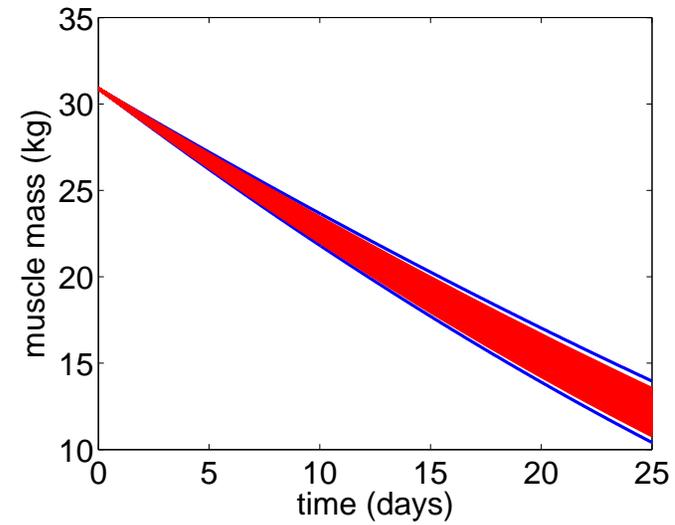
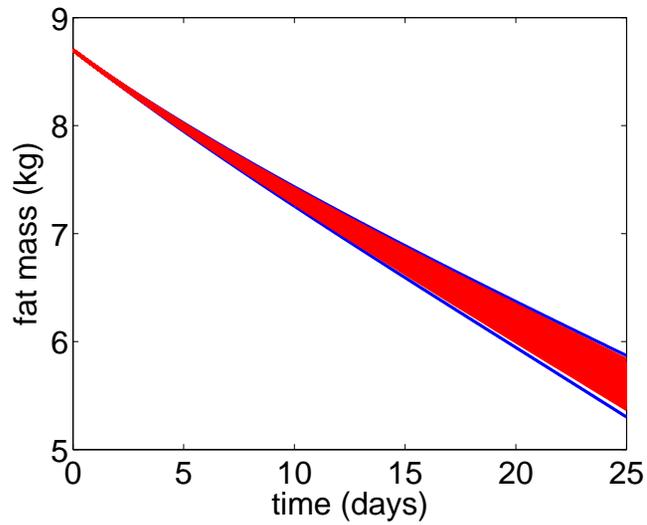
Example: Long-term Starvation Model

- VSPODE enclosures of $F(t)$, $M(t)$, $K(t)$ over $t = [0, 25]$ days



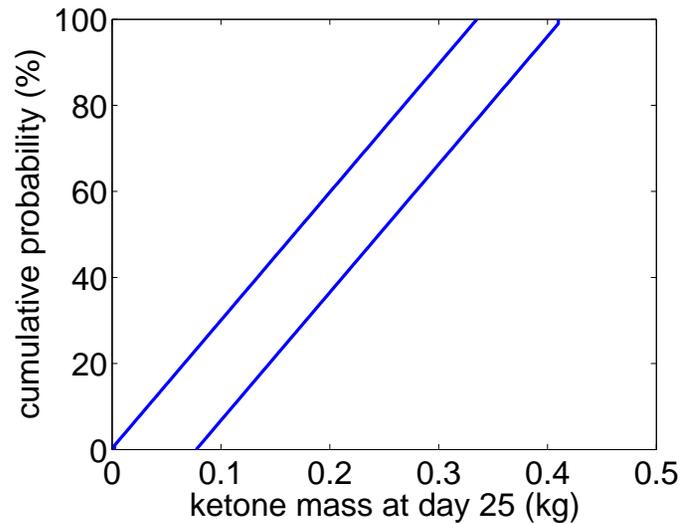
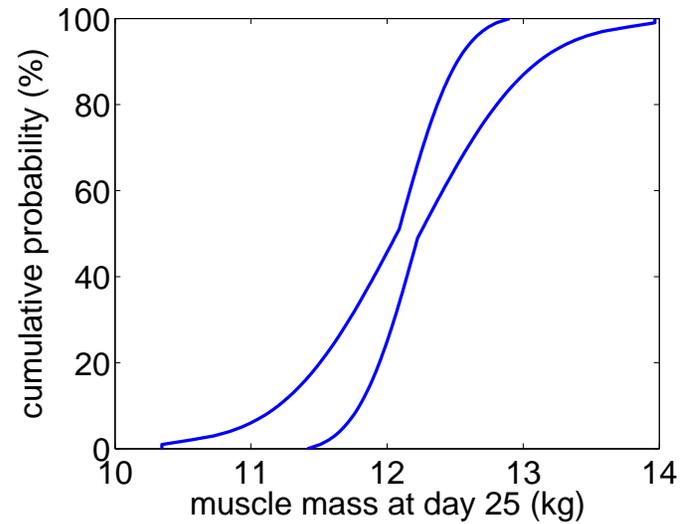
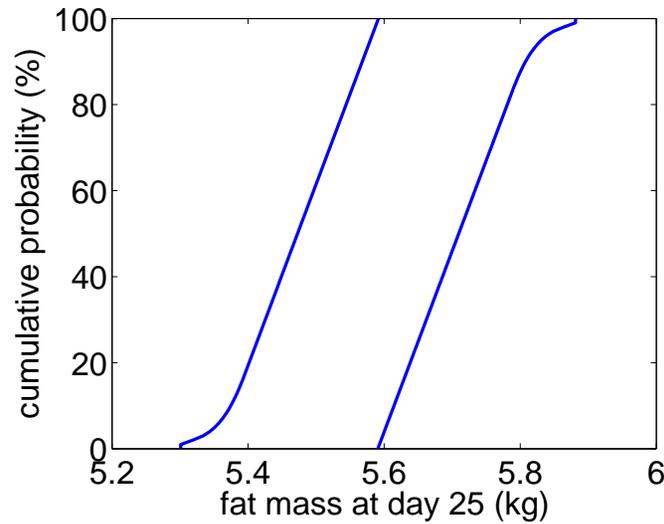
Example: Long-term Starvation Model

- Comparison of VSPODE bounds to Monte Carlo simulations



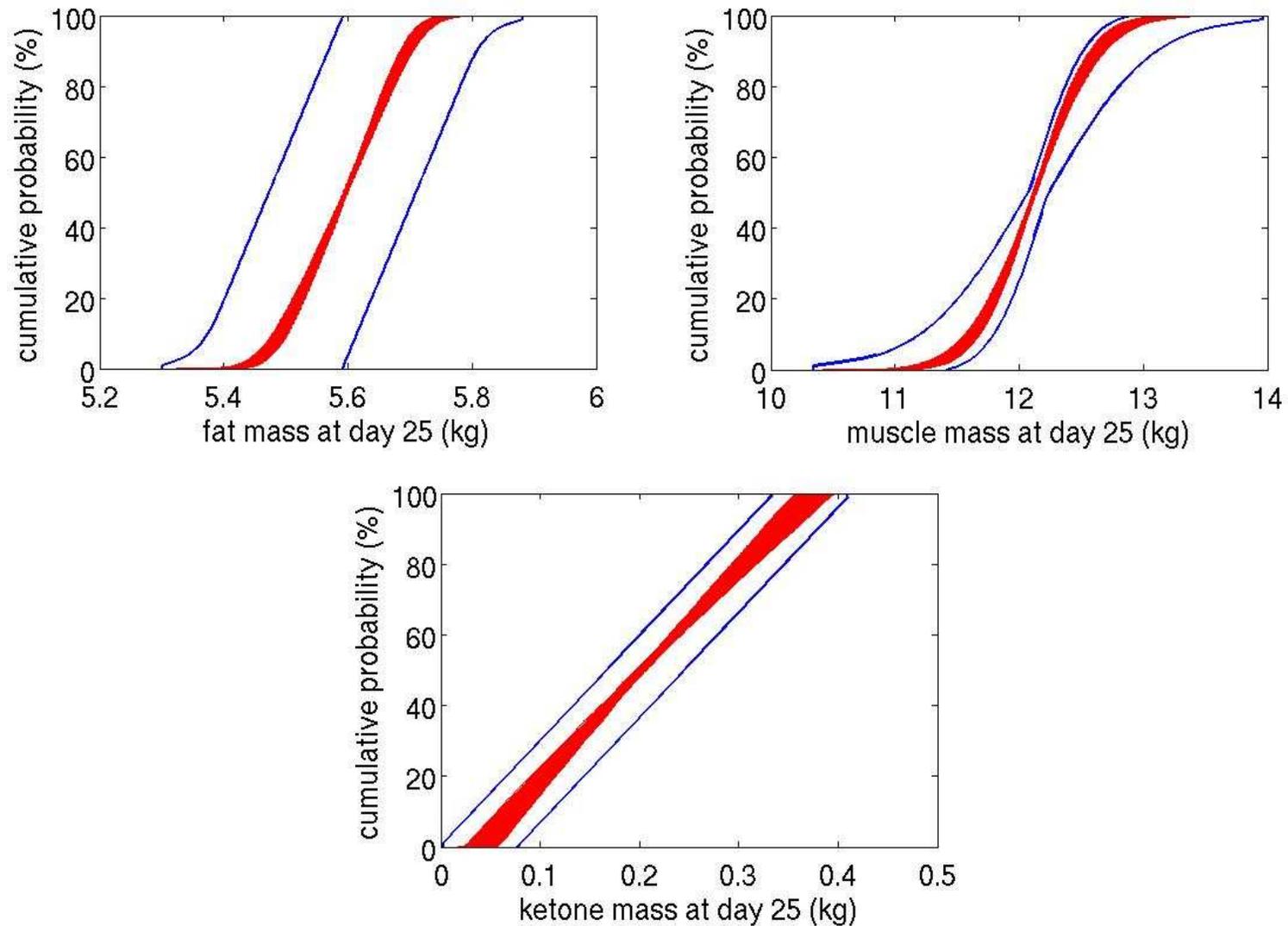
Example: Long-term Starvation Model

- Probability distributions (p-boxes) for F , M and K at $t = 25$ days



Example: Long-term Starvation Model

- Comparison with Monte Carlo simulations: 500 simulations, each 10000 trials



Concluding Remarks

- ODE models may be required to simulate physiological phenomena when physical experimentation is impractical or impossible
- Physiological models incorporate parameters that cannot be precisely known but are bounded by intervals or probability boxes
- VSPODE (Lin and Stadtherr, 2007) is a powerful tool to propagate interval uncertainties in initial conditions and parameters through nonlinear ODEs
- Taylor Models can be used to propagate both interval and p-box uncertainties through a dynamic system

References

- R. N. Bergman, L. S. Phillips, C. Cobelli, Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man: Measurement of Insulin Sensitivity and Beta-Cell Glucose Sensitivity from the Response to Intravenous Glucose. *J. Clin. Invest.*, 68, 1456–67, 1981.
- S. Ferson, *RAMAS Risk Calc 4.0: Risk Assessment with Uncertain Numbers*. Lewis Press, 2002
- S. Ferson and J. G. Hajagos, Arithmetic with Uncertain Numbers: Rigorous and (Often) Best Possible Answers. *Reliability Engineering and System Safety*, 85, 135–152, 2004.
- S. M. Lynch and B. W. Bequette, Estimation-based Model Predictive Control of Blood Glucose in Type I Diabetics: A Simulation Study. *Proceedings of the IEEE 27th Annual Northeast Bioengineering Conference*, pp. 79-80, 2001.
- K. Makino and M. Berz, Remainder Differential Algebras and their Applications. In Berz, M., Bishof, C., Corliss, G., Griewank, A. (Eds.), *Computational Differentiation: Techniques, Applications, and Tools*. SIAM, Philadelphia, pp. 63–74, 1996.
- B. Song and D. M. Thomas. Dynamics of Starvation in Humans. *J. Math. Biol.*, 54, 27–43, 2007.
- Y. Lin and M. A. Stadtherr. Validated Solutions of Initial Value Problems for Parametric ODEs. *Appl. Numer. Math.*, 57, 1145–1162, 2007.