Sensitivity Analysis and Uncertainty Quantification for Pharmacokinetic Models

Ralph C. Smith
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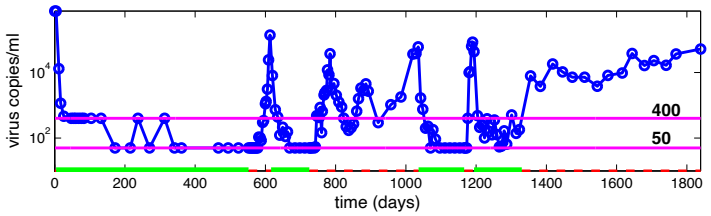
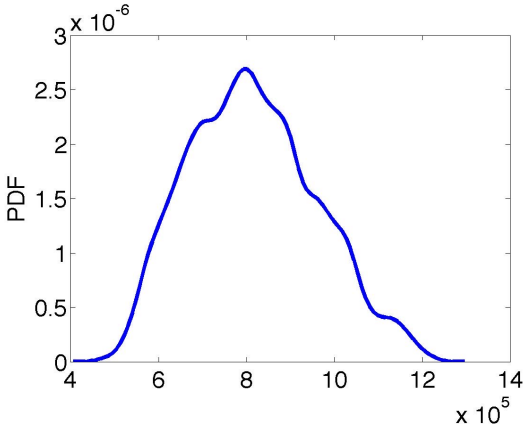
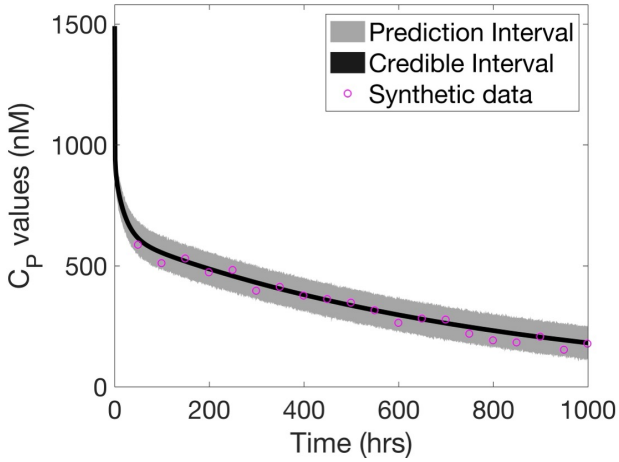


Experimental Errors



Parameter Uncertainty



Response Uncertainty

Support: Statistical and Mathematical Sciences Institute (SAMSI)

Essentially, all models are wrong, but some are useful, George E.P. Box, Industrial Statistician

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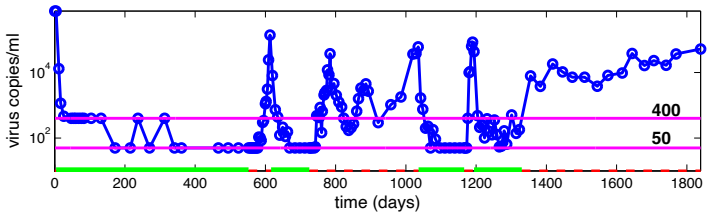

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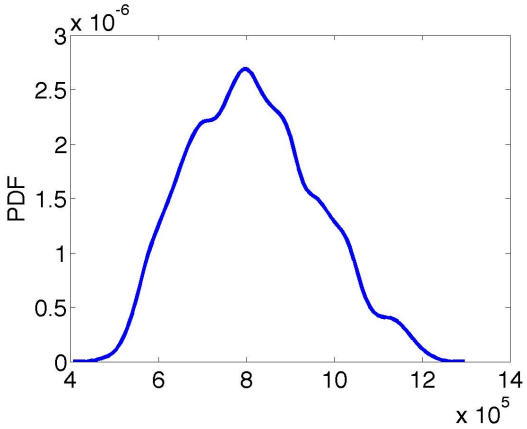

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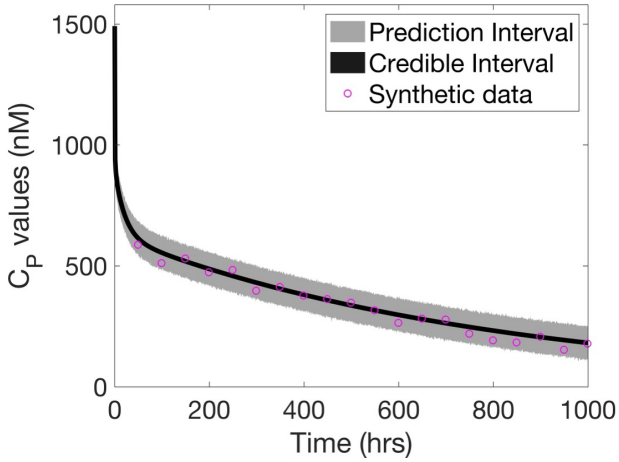


Response Uncertainty

"We": Kamala Dadashova, Mansoor Haider, Brian Reich (NCSU)

Example 1: SIR Model for Disease Dynamics

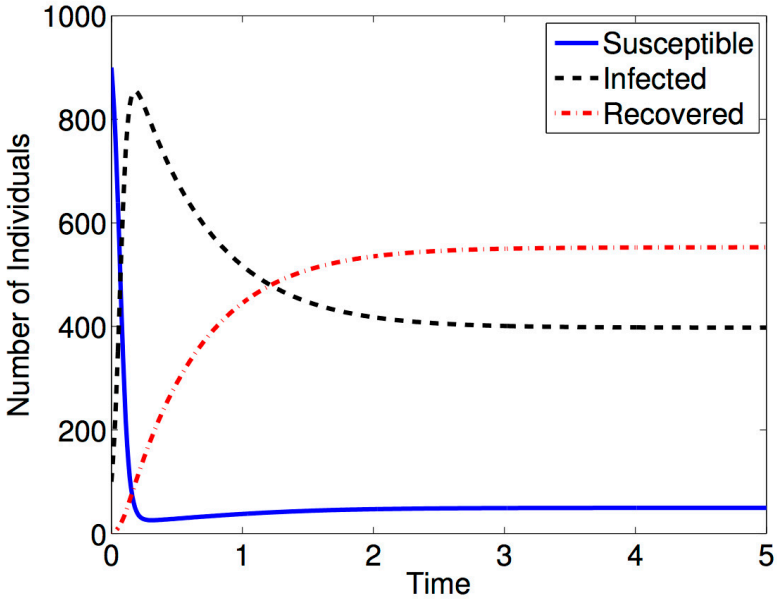
SIR Model: Population N

$$\frac{dS}{dt} = \delta N - \delta S - \gamma k I S \quad , \; S(0) = S_0$$

$$\frac{dI}{dt} = \gamma k I S - (r + \delta) I \quad , \; I(0) = I_0$$

$$\frac{dR}{dt} = rI - \delta R \quad , \; R(0) = R_0$$

Typical Realization



Parameters:

- γ: Infection coefficient
- k: Interaction coefficient
- r: Recovery rate
- δ: Birth/death rate

Response:

$$y = \int_0^5 R(t, \theta)\, dt$$

Note: Parameters $\theta = [\gamma, k, r, \delta]$ not uniquely determined by data y

Goal: Use sensitivity or identifiability analysis to isolate subset of influential or identifiable parameters

SIR Model for Disease Dynamics

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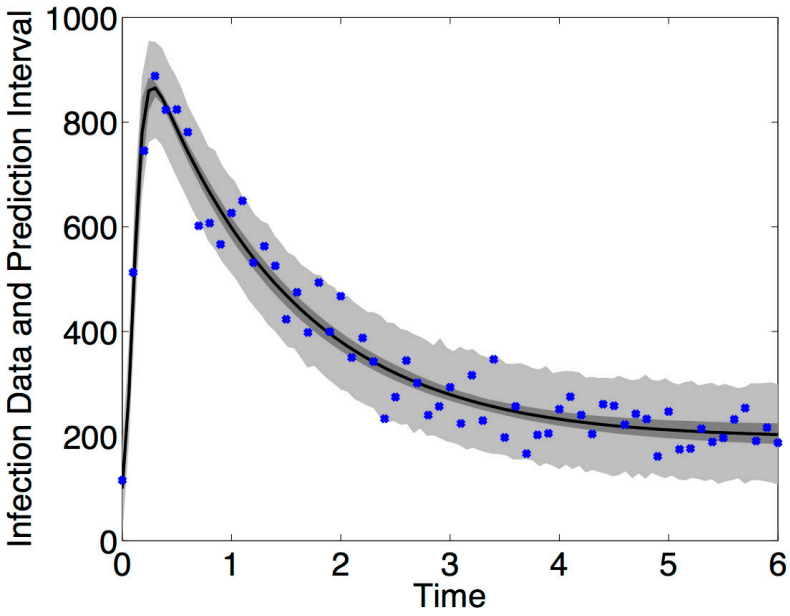

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Uncertainty Quantification Goal: Predict I(t) with prediction intervals

Example 2: Minimal PBPK Model for Brain

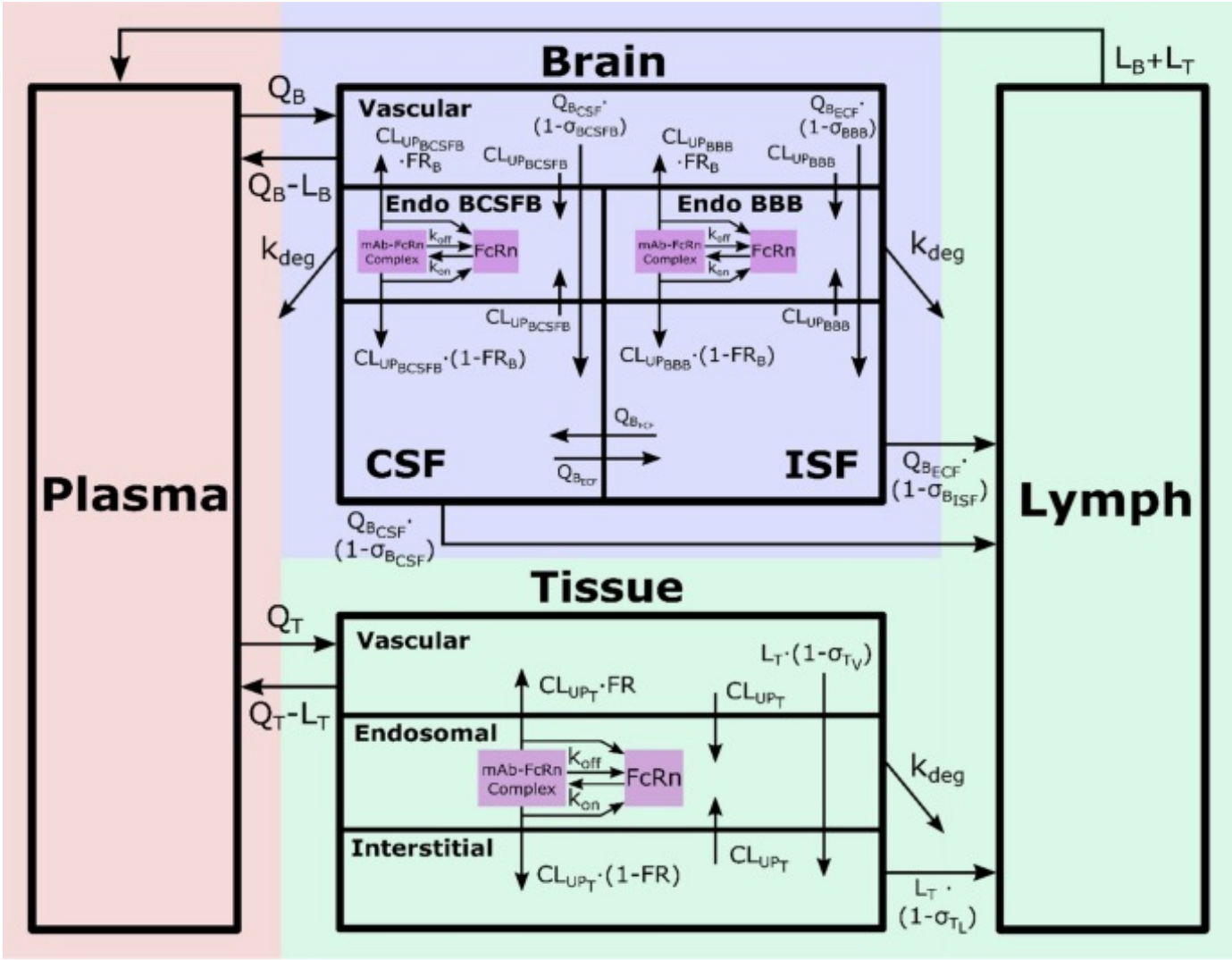
Model: Minimal Physiologically-Based Pharmacokinetic (mPBPK) of brain for antibody therapeutics [Bloomingdale, Bakshi, Maass, et al., 2021]

Note:

- 16 ODE
- 31 Parameters

Current Research:

- Digital Twins
- Virtual Populations



Objective: Isolate parameters that are informed by concentrations of interest

Minimal PBPK Model for Brain

Representative Differential Equation:

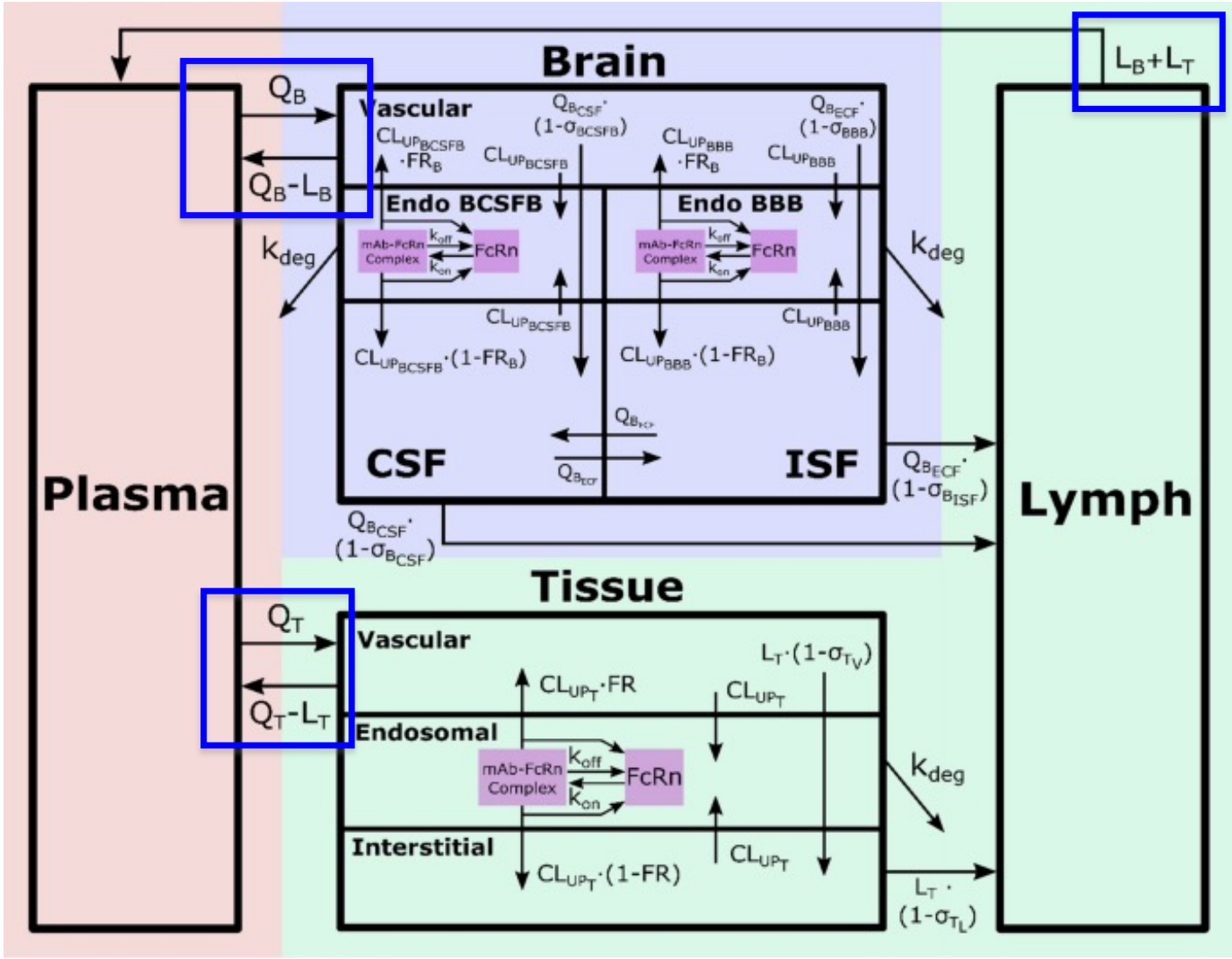
$$V_P \frac{dC_P}{dt} = (Q_T - L_T)C_{T_V} + (Q_B - L_B)C_{B_V} + (L_T + L_B) \cdot C_L - Q_T C_P - Q_B C_P$$

Note: C is antibody concentration

- C_P: Plasma
- C_{T_V}: Tissue Vascular
- C_{B_V}: Brain Vascular
- C_L: Lymph

Parameters:

- Q_T: Tissue Blood flow
- Q_B: Brain blood flow
- L_T: Tissue lymphatic flow
- L_B: Brain lymphatic flow



Example 3: HIV Model to Guide Treatment Regimes

HIV Model: 7 coupled differential equations

E.g., $$\frac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1-\varepsilon_1) k_1 V_I T_1$$

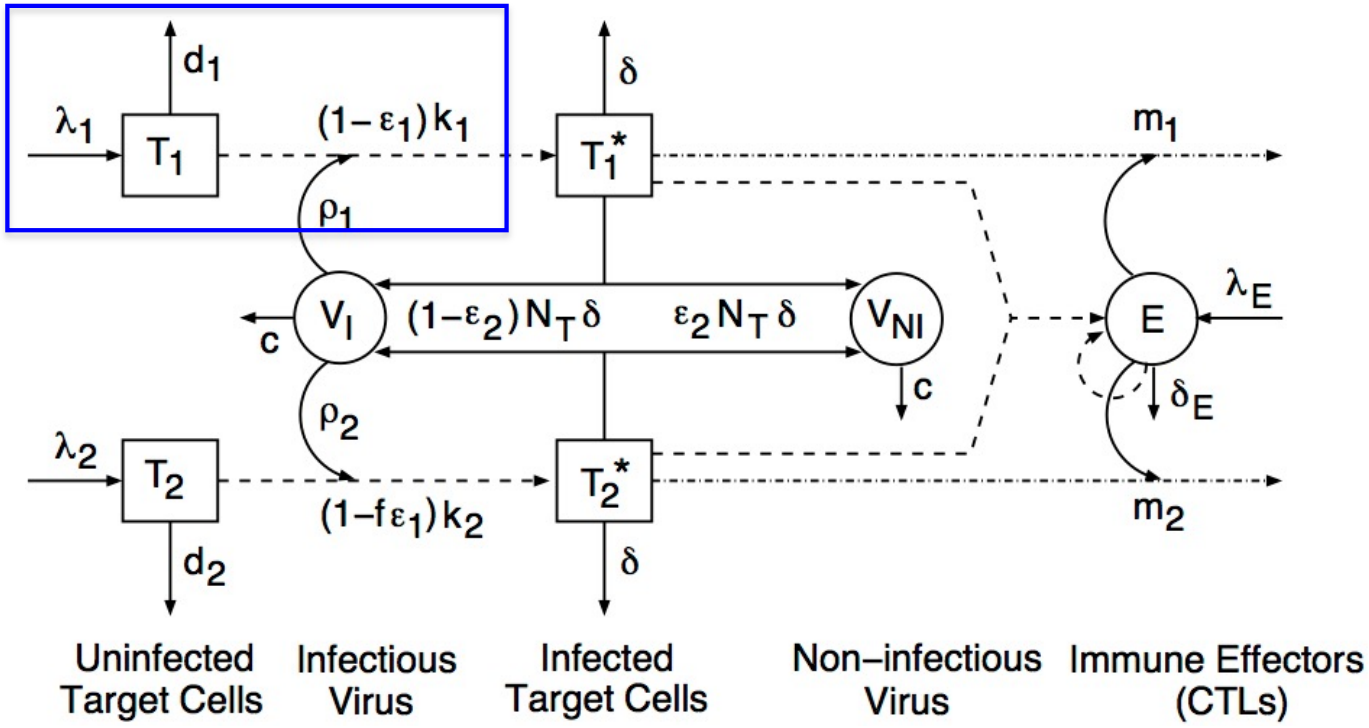
Note: Similar differential equations for

$$T_2(t),\ T_1^*(t),\ T_2^*(t),\ V_I(t),\ V_{NI}(t),\ E(t)$$

Note: 21 parameters

Reference: B.M. Adams, H.T. Banks, M. Davidian and E.S. Rosenberg, "Model fitting and prediction with HIV treatment interruption data," *Bulletin of Mathematical Biology*, 69(2), pp. 563-584, 2007.

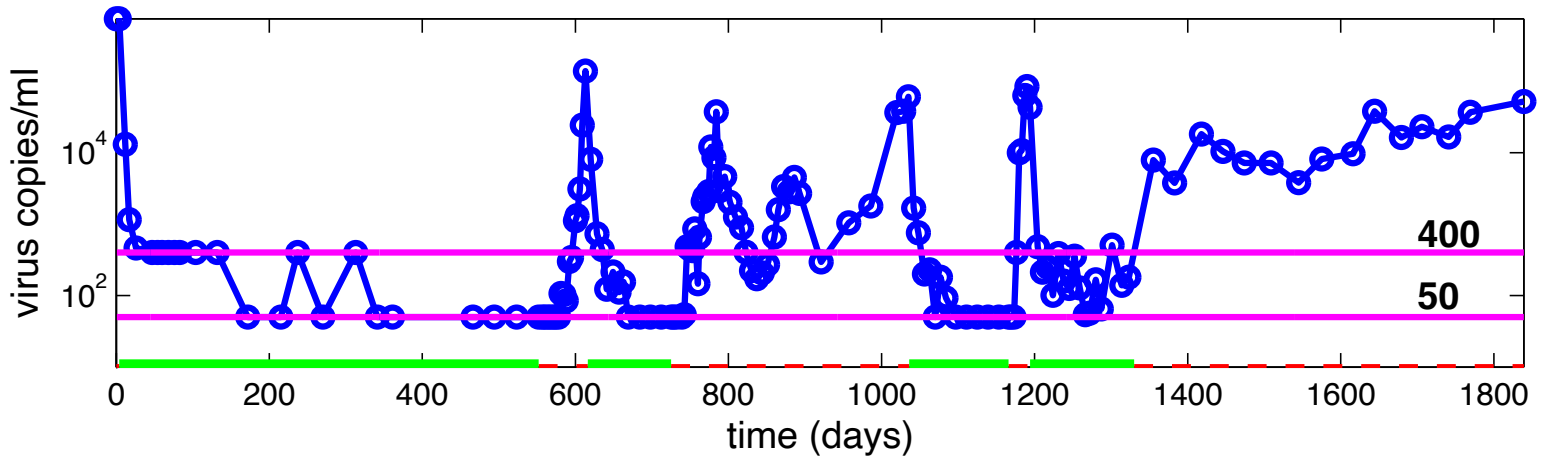
Compartments:



Model for Characterization and Treatment Regimes

Model: Several sources of uncertainty including viral measurement techniques

Example: Upper and lower limits to assay sensitivity



UQ Questions:

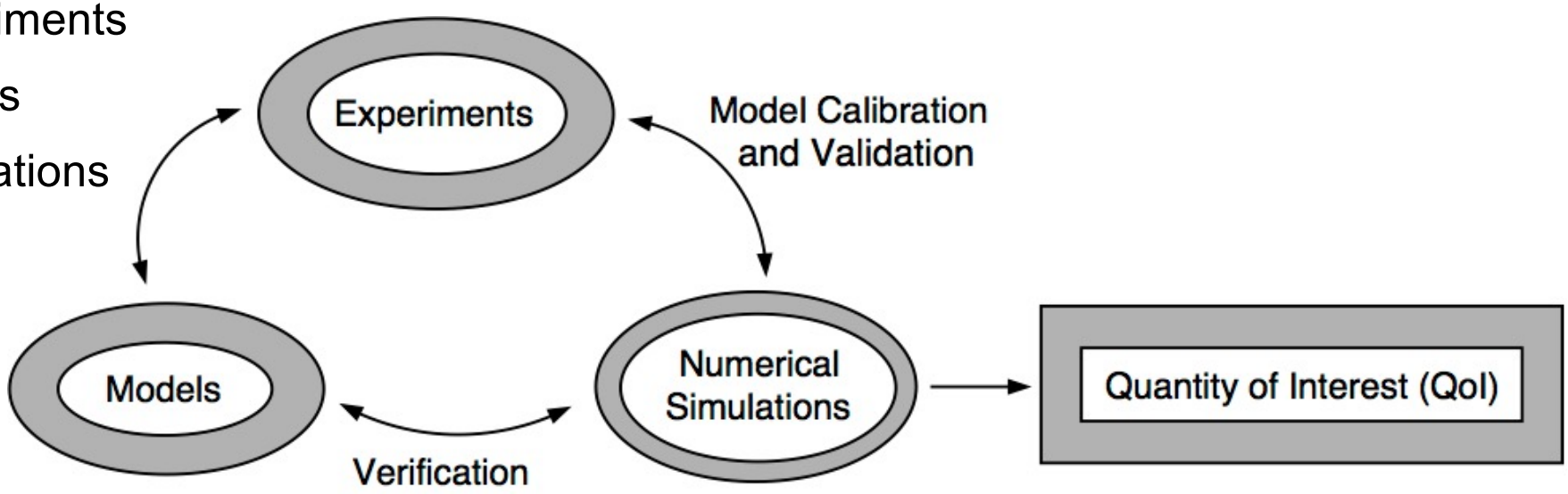
- What are uncertainties in parameters which cannot be directly measured?
- What is optimal treatment regime which is “safe” for patient?
- What is expected viral load? Issue: very often requires high-dimensional integration!
- e.g.,

$$\mathbb{E}[V(t)] = \int_{\mathbb{R}^{21}} V(t,\theta)\rho(\theta)d\theta$$

Predictive Science

Components: All involve uncertainty and errors

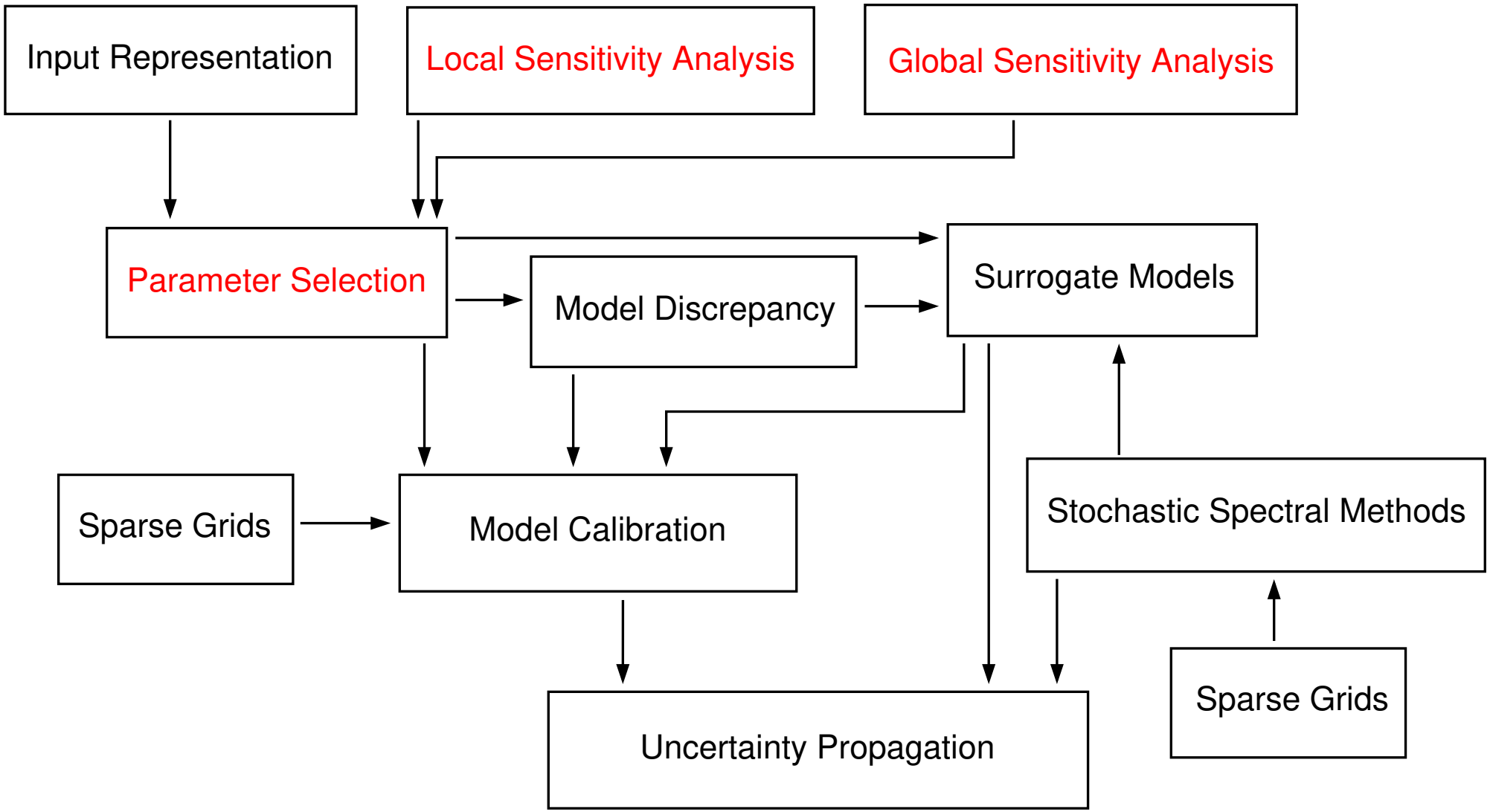
- Experiments
- Models
- Simulations



- *Essentially, all models are wrong, but some are useful,* George E.P. Box, Industrial Statistician.
- *Experimental results are believed by everyone, except for the person who ran the experiment*, source anonymous, quoted by Max Gunzburger, Florida State University.
- *Computational results are believed by no one, except the person who wrote the code*, source anonymous, quoted by Max Gunzburger, Florida State University.
- *I have always done uncertainty quantification. The difference now is that it is capitalized.* Bill Browning, Applied Mathematics Incorporated.

Steps in Uncertainty Quantification for Large-Scale Models

Note: Uncertainty quantification requires synergy between mathematics, statistics, engineering, and sciences



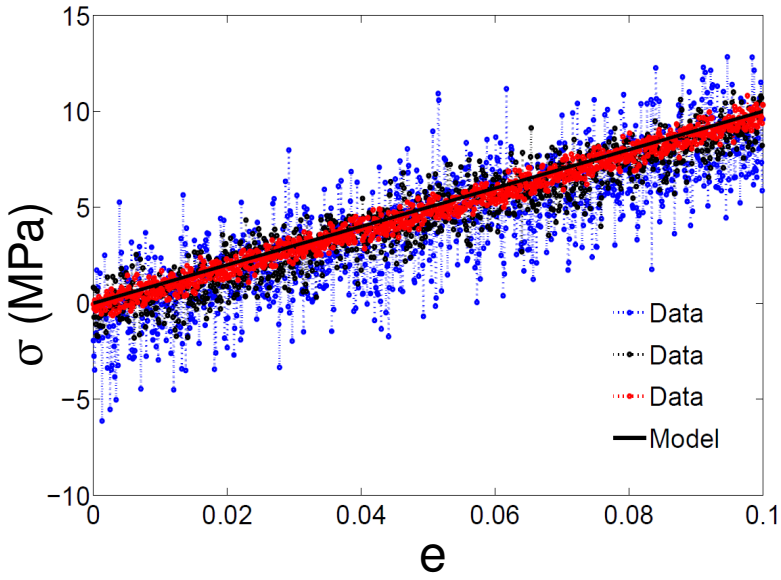
Sensitivity Analysis: Motivation

Example: Linear constitutive relation

$$\sigma = Ee + c\frac{de}{dt}$$

Nominal Values: $E = 100$, $c = 0.1$

$$e = 0.001 \text{ , } \frac{de}{dt} = 0.1$$



Question: To which parameter E or c is stress most sensitive?

Local Sensitivity Analysis:

$$\frac{\partial \sigma}{\partial E} = e = 0.001$$

$$\frac{\partial \sigma}{\partial c} = \frac{de}{dt} = 0.1$$

Conclusion: Model most sensitive to damping parameter c

Limitations:

- Does not accommodate potential uncertainty in parameters.
- Does not accommodate potential correlation between parameters.
- Sensitive to units and magnitudes of parameters.

Global Sensitivity Analysis

Example: Linear constitutive relation

$$\sigma = Ee + c\frac{de}{dt}$$

Nominal Values: $E = 100,\ c = 0.1$

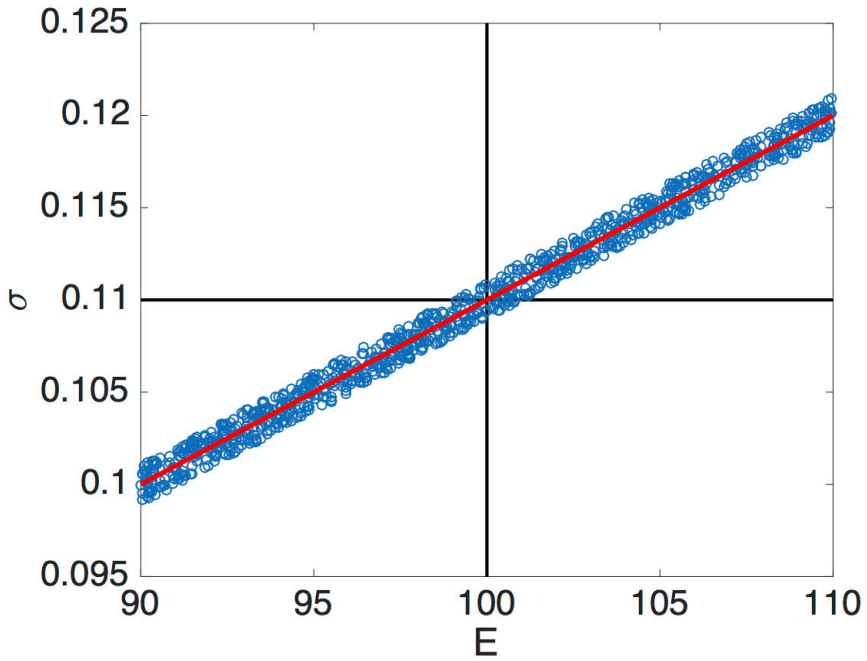
Uncertainty: 10% of nominal values

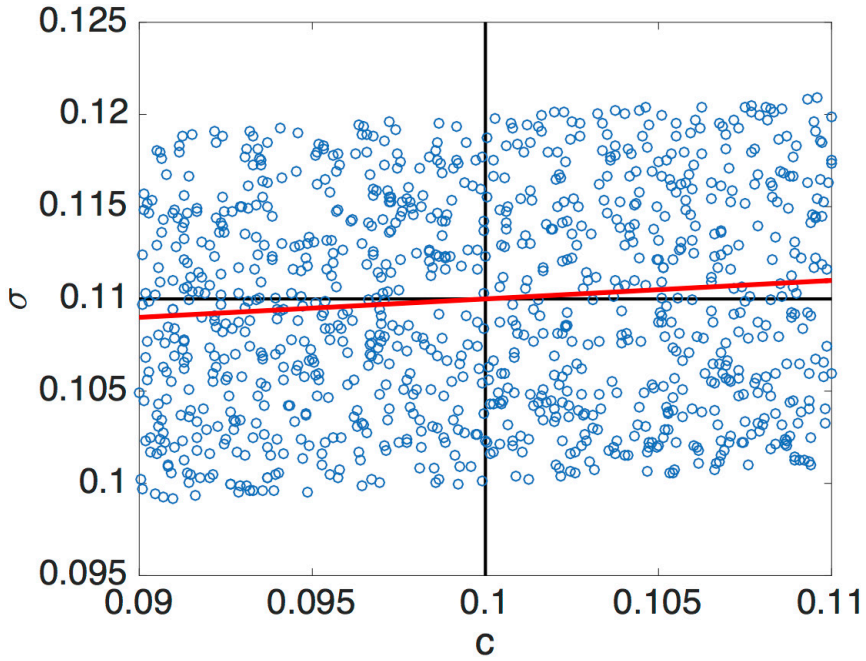
$$E \sim \mathcal{U}(90, 110)\ ,\ c \sim \mathcal{U}(0.09, 0.11)$$

Local Sensitivities:

$$\frac{\partial \sigma}{\partial E} = e = 0.001$$

$$\frac{\partial \sigma}{\partial c} = \frac{de}{dt} = 0.1$$





Global Sensitivity: E is more influential

Variance-Based Methods

Sobol Representation: For now, take $Q_i \sim \mathcal{U}(0,1)$ and $\Gamma = [0,1]^p$

Take

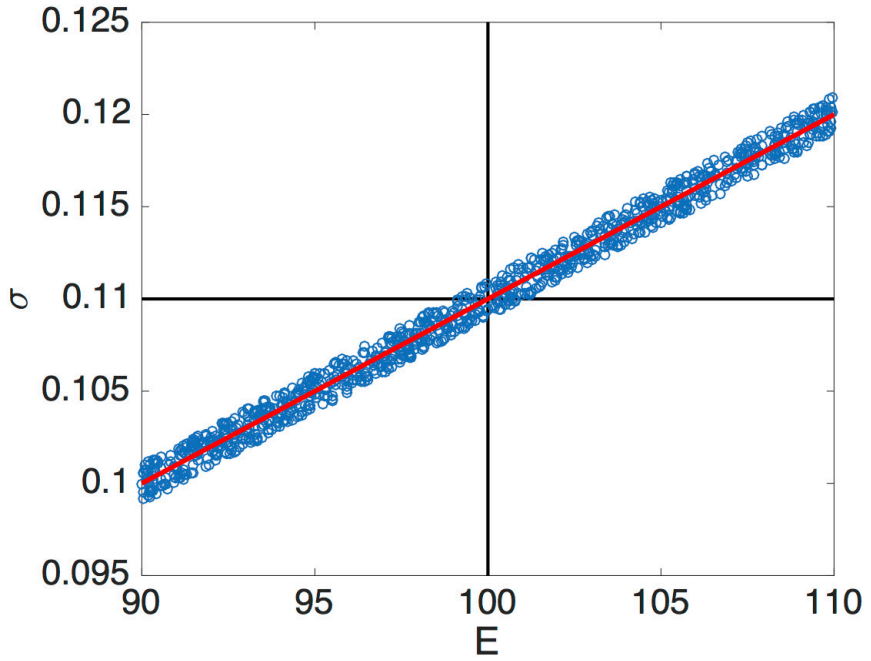
$$Y = f(q) = f_0 + \sum_{i=1}^{p} f_i(q_i) + \sum_{1 \leqslant i < j \leqslant p} f_{ij}(q_i, q_j)$$

Analogy: Taylor or Fourier series

Here

$$f_0 = \int_\Gamma f(q)\,dq$$

$$f_i(q_i) = \int_{\Gamma^{p-1}} f(q)\,dq_{\sim i} - f_0$$



Variances:

$$D_i = \int_0^1 f_i^2(q_i)\,dq_i$$

$$D = \mathrm{var}(Y)$$

Sobol Indices: $S_i = \dfrac{D_i}{D}$

Statistical Interpretation:

$$D_i = \mathrm{var}[\mathbb{E}(Y|q_i)] \Rightarrow S_i = \frac{\mathrm{var}[\mathbb{E}(Y|q_i)]}{\mathrm{var}(Y)}$$

Global Sensitivity Analysis: Analysis of Variance

Sobol' Representation: $Y = f(q)$

$$f(q) = f_0 + \sum_{i=1}^{p} f_i(q_i) + \sum_{i \leqslant i < j \leqslant p} f_{ij}(q_i, q_j) + \cdots + f_{12\cdots p}(q_1, \ldots, q_p)$$

$$= f_0 + \sum_{i=1}^{p} \sum_{|u|=i} f_u(q_u)$$

Typical Assumption: $q_1, q_2, \ldots, q_p$ independent. Then

$$\int_\Gamma f_u(q_u) f_v(q_v) \rho(q) dq = 0 \quad \text{for } u \neq v$$

$$\Rightarrow \text{var}[f(q)] = \sum_{i=1}^{p} \sum_{|u|=i} \text{var}[f_u(q_u)]$$

Sobol' Indices:

$$S_u = \frac{\text{var}[f_u(q_u)]}{\text{var}[f(q)]} \quad , \quad T_u = \sum_{v \subseteq u} S_v$$

Note: Magnitude of S_u, T_u quantify contributions of q_u to var$[f(q)]$

Global Sensitivity Analysis

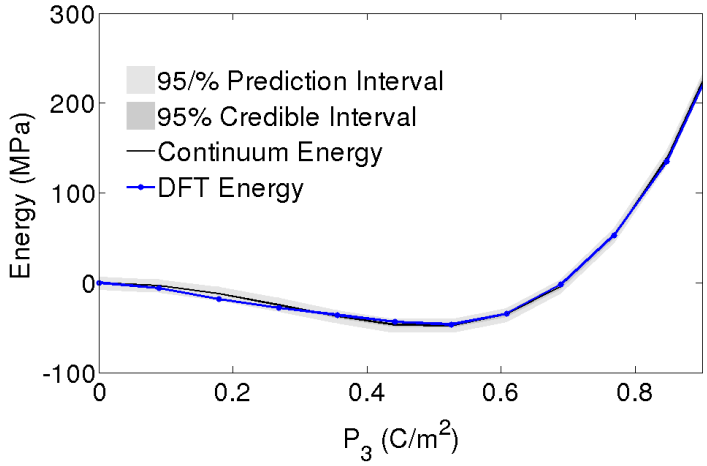
Example: Quantum-informed continuum model

Question: Do we use 4th or 6th-order Landau energy?

$$\psi(P, q) = \alpha_1 P^2 + \alpha_{11} P^4 + \alpha_{111} P^6$$

Parameters:

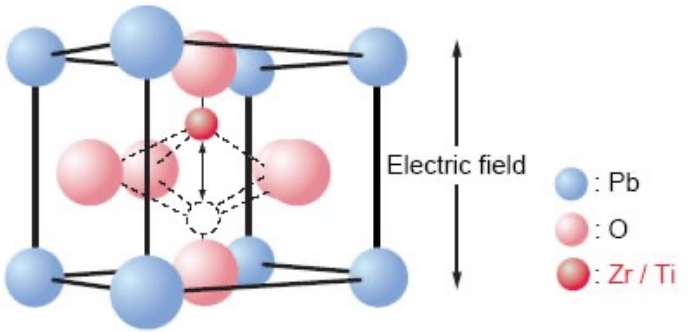
$$q = [\alpha_1, \alpha_{11}, \alpha_{111}]$$



Landau energy

Global Sensitivity Analysis:

	α_1	α_{11}	α_{111}
S_k	0.62	0.39	0.01
T_k	0.66	0.38	0.06
μ_k^*	0.17	0.07	0.03



Lead Titanate Zirconate (PZT)

Conclusion:

α_{111} insignificant and can be fixed

Global Sensitivity Analysis

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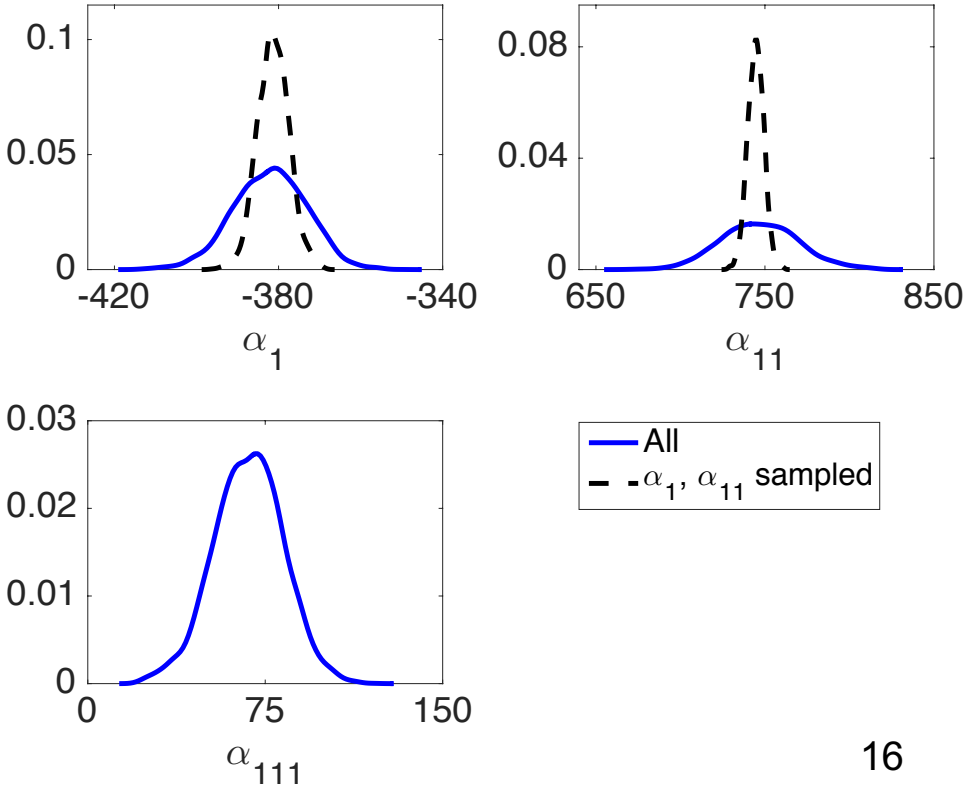
Problem: We obtain different distributions when we perform Bayesian inference with fixed non-influential parameters



Global Sensitivity Analysis

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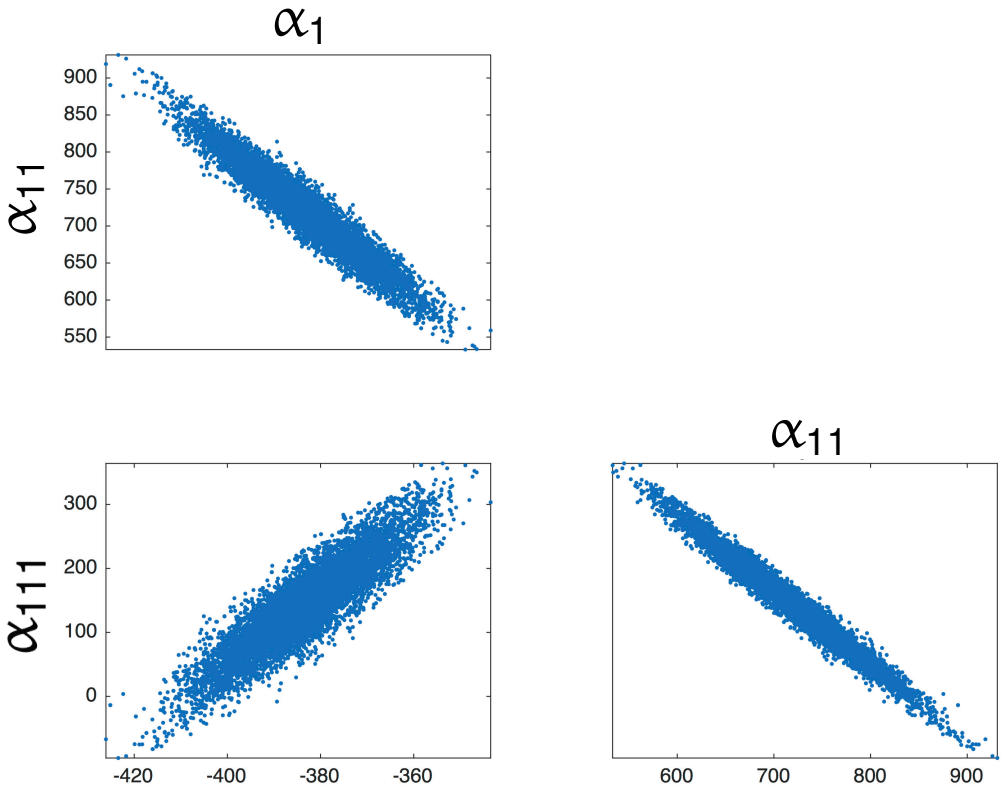
Note: Must accommodate correlation

Problem:

- Parameters correlated
- Cannot fix α_{111}



Global Sensitivity Analysis: Analysis of Variance

Sobol' Representation:

$$f(q) = f_0 + \sum_{i=1}^{p} \sum_{|u|=i} f_u(q_u)$$

One Solution: Take variance to obtain

$$\text{var}[f(q)] = \sum_{i=1}^{p} \sum_{|u|=i} \text{cov}[f_u(q_u), f(q)]$$

Sobol' Indices:

$$S_u = \frac{\text{cov}[f_u(q_u), f(q)]}{\text{var}[f(q)]}$$

Alternatives:

- Parameter subset selection
- Active subspace techniques
- Both accommodate parameter correlation

Pros:

- Provides variance decomposition that is analogous to independent case

Cons:

- Indices can be negative and difficult to interpret
- Often difficult to determine underlying distribution
- Monte Carlo approximation often prohibitively expensive.

Parameter Subset Selection -- Motivation

Motivation: SIR model

$$\frac{dS}{dt} = \delta N - \delta S - \gamma k I S \quad , \; S(0) = S_0$$

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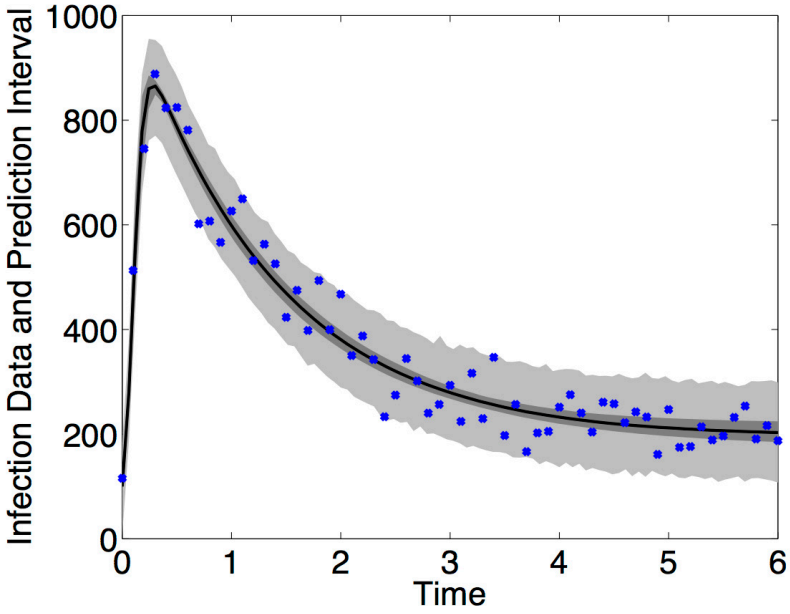

Parameters:

- γ: Infection coefficient
- k: Interaction coefficient
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Note: Parameters $\theta = [\gamma, k, r, \delta]$ not uniquely determined by data

Observation Model:

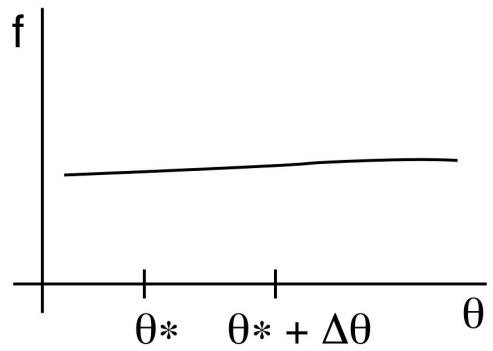
$$y_i = I(t_i, \theta) + \varepsilon_i \quad , \; i = 1, \ldots, n$$

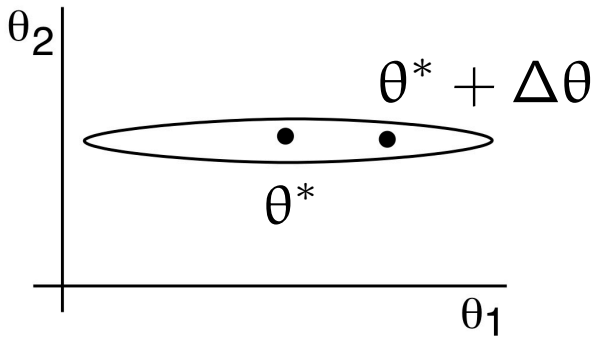
Parameter Subset Selection

Motivation: Consider statistical observation model

$$y_i = f(t_i, \theta^*) + \varepsilon_i \ , \ i = 1, \ldots, n$$

Note: Nonidentifiable or noninfluential parameters have minimal influence on f





Taylor Expansion: Consider

$$f(t_i, \theta^* + \Delta\theta) \approx f(t_i, \theta^*) + \nabla_\theta f(t_i, \theta^*) \cdot \Delta\theta$$

about nominal value θ^* and the functional

$$J(\theta) = \frac{1}{n} \sum_{i=1}^{n} [y_i - f(t_i, \theta)]^2$$

Note: Often based on optimization but does not require it; e.g., m-PBPK model

Parameter Subset Selection – Theoretical Motivation

Taylor Expansion: Consider

$$f(t_i, \theta^* + \Delta\theta) \approx f(t_i, \theta^*) + \nabla_\theta f(t_i, \theta^*) \cdot \Delta\theta$$

Issue: Requires efficient gradient approximations

about nominal value θ^* and the functional

$$J(\theta) = \frac{1}{n} \sum_{i=1}^{n} [y_i - f(t_i, \theta)]^2$$

Since $y_i \approx f(t_i, \theta^*)$,

$$\begin{aligned} J(\theta^* + \Delta\theta) &\approx \frac{1}{n} [\nabla_\theta f(t_i, \theta^*) \cdot \Delta\theta]^2 \\ &= \frac{1}{n} \Delta\theta^T \boldsymbol{S}^T \boldsymbol{S} \Delta\theta \end{aligned}$$

$$\boldsymbol{S} = \begin{bmatrix} \frac{\partial f}{\partial \theta_1}(t_1, \theta^*) & \cdots & \frac{\partial f}{\partial \theta_p}(t_1, \theta^*) \\ \vdots & & \vdots \\ \frac{\partial f}{\partial \theta_1}(t_n, \theta^*) & \cdots & \frac{\partial f}{\partial \theta_p}(t_n, \theta^*) \end{bmatrix}$$

Sensitivity Matrix

Scaled Fisher Information Matrix

- Incorporates parameter correlation

Strategy: Take $\Delta\theta$ to be eigenvector of $\boxed{\boldsymbol{S}^T \boldsymbol{S}}$

$$\Rightarrow \boldsymbol{S}^T \boldsymbol{S} \Delta\theta = \lambda \Delta\theta$$

$$\Rightarrow J(\theta^* + \Delta\theta) \approx \frac{\lambda}{n} \|\Delta\theta\|_2^2$$

Note:

$\lambda \approx 0 \Rightarrow$ Perturbations $J(\theta^* + \Delta\theta) \approx 0$

$\Rightarrow$ Nonidentifiable

Parameter Subset Selection – Numerical Algorithm

Computational Algorithm: Employ SVD or QR of $\boldsymbol{S}$ rather than eigenvalues of $\boldsymbol{S}^T\boldsymbol{S}$

History: [Reid, *Transactions on Automatic Control*, 1977]

Parameters θ sensitivity identifiable at θ^* if and only if $\boldsymbol{S}(\theta^*)$ is one-to-one

Unidentifiable Subspace: $\mathcal{N}(\boldsymbol{S}) = \mathcal{N}(\boldsymbol{S}^T\boldsymbol{S})$

Example:

$$\frac{dS}{dt} = \delta N - \delta S - \gamma k I S \quad , \; S(0) = S_0$$

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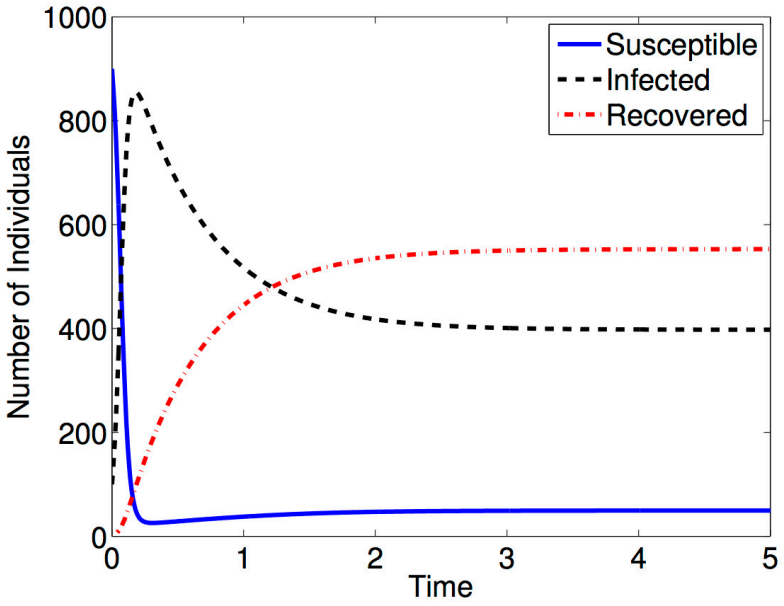


Parameters: $\theta = [\delta, \gamma, k, r]$

Result:

- $\text{rank}(\boldsymbol{S}^T\boldsymbol{S}) = 3$
- γ, k not jointly identifiable

Issues:

- Requires efficient gradient approximations
- Identifiable parameters based on threshold
- Local about a nominal value

Complex-Step Derivative Approximation

A Bit of History: Discussed in

- J.N. Lyness and C.B. Moler, *SIAM Journal on Numerical Analysis*, 1967.

Derivation: For sufficiently smooth f, consider

$$f(x+ih) = f(x) + ihf'(x) - \frac{h^2}{2!}f''(x) - i\frac{h^3}{3!}f^{(3)}(x) + \mathcal{O}(h^4)$$

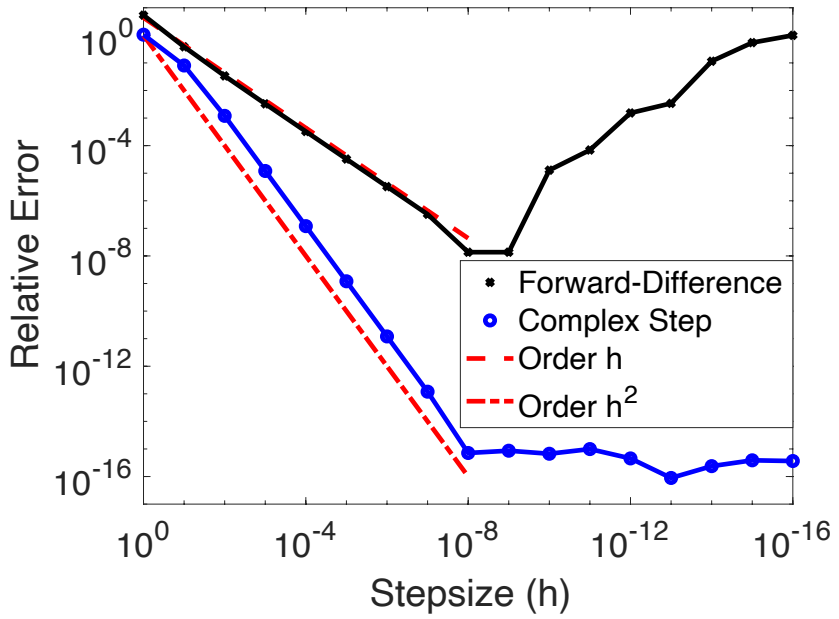
Complex-Step Approximation:

$$f'(x) = \frac{\mathrm{Im}[f(x+ih)]}{h} + \mathcal{O}(h^2)$$

Note:

- Avoids subtractive cancellation; e.g., can use h=1e-14!

Example



Role of Threshold Value

Computational Parameter Subset Selection Algorithm:

Inputs: Nominal $p \times 1$ parameter vector $\boldsymbol{\theta}^*$, $\theta_j^* > 0$, and $n > p$ values t_i

Output: Subset $\boldsymbol{\theta}_{id} \subseteq \boldsymbol{\theta}$ of identifiable parameters

1. Set threshold $0 < \widehat{\eta} \ll 1$ in the manner noted for Algorithm 8.20.
2. Construct $n \times p$ scaled sensitivity matrix $\widehat{\boldsymbol{S}}(\boldsymbol{\theta}^*)$, which we denote by $\widehat{\boldsymbol{S}}$.
3. For $k = 1$ to p
   - (i) Set $r = p - k + 1$. Compute singular value decomposition $\widehat{\boldsymbol{S}} = \boldsymbol{U}\boldsymbol{\Sigma}\boldsymbol{V}^T$, where the $r \times r$ diagonal matrix $\boldsymbol{\Sigma}$ contains the singular values $\sigma_1 \geq \cdots \geq \sigma_r \geq 0$ of $\widehat{\boldsymbol{S}}$, and the $r \times r$ orthogonal matrix $\boldsymbol{V}^T$ contains the right singular vectors.
   - (ii) If $(\sigma_r/\sigma_1)^2 > \widehat{\eta}$, then
     Return $\boldsymbol{\theta}_{id} = \boldsymbol{\theta}$; all parameters are identifiable for threshold $\widehat{\eta}$.
     else
     - (a) For singular vector $\boldsymbol{v}_r \in \boldsymbol{V}^T$, determine index j of component with largest magnitude. This specifies least identifiable parameter.
     - (b) Remove j^{th} column of $\widehat{\boldsymbol{S}}$ and θ_j from $\boldsymbol{\theta}$.

     end

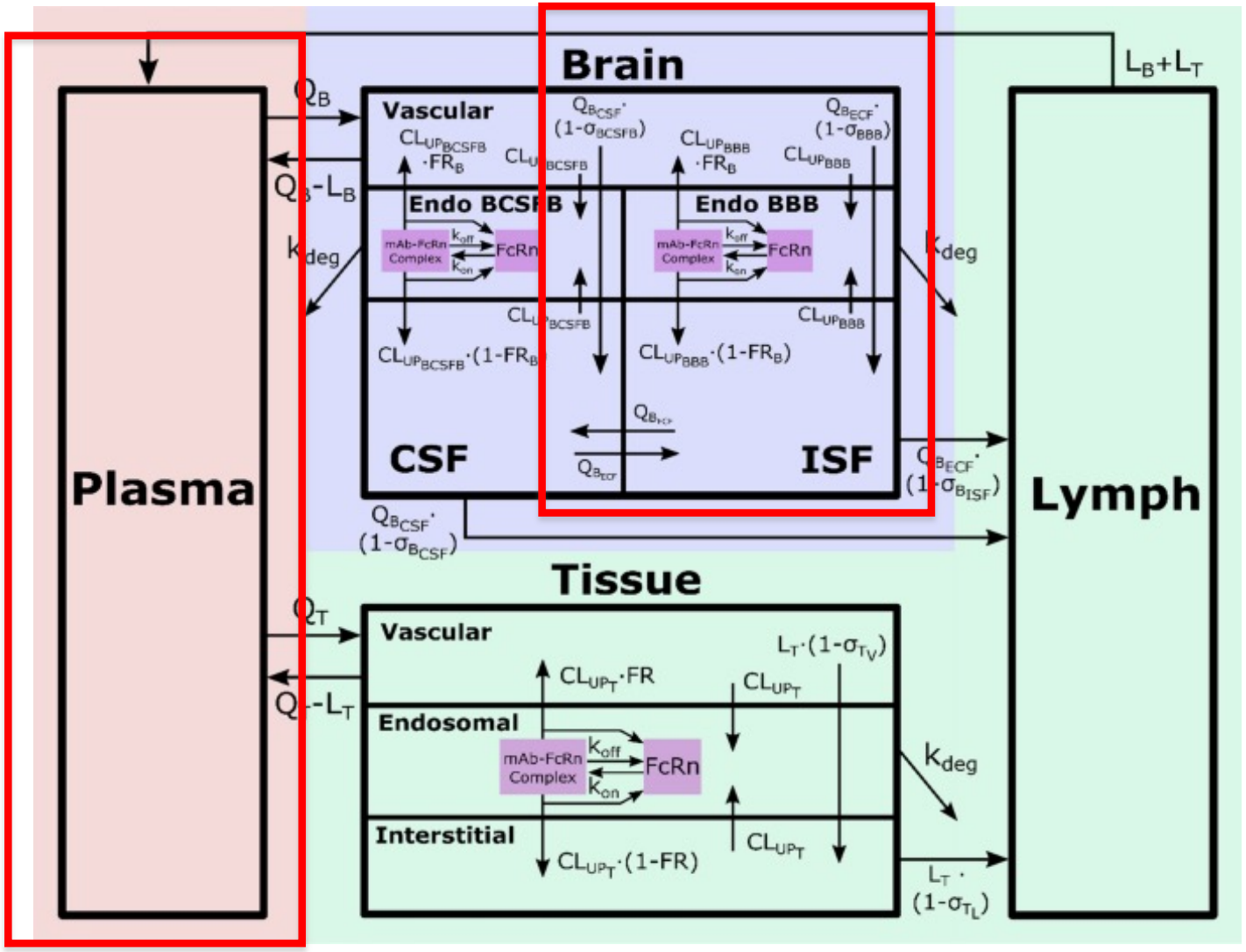
end

Parameter Subset Selection for Minimal PBPK Model

Model: Minimal Physiologically-Based Pharmacokinetic (mPBPK) of brain for antibody therapeutics [Bloomingdale, Bakshi, Maass, et al., 2021]

Note:

- 16 ODE
- 31 Parameters

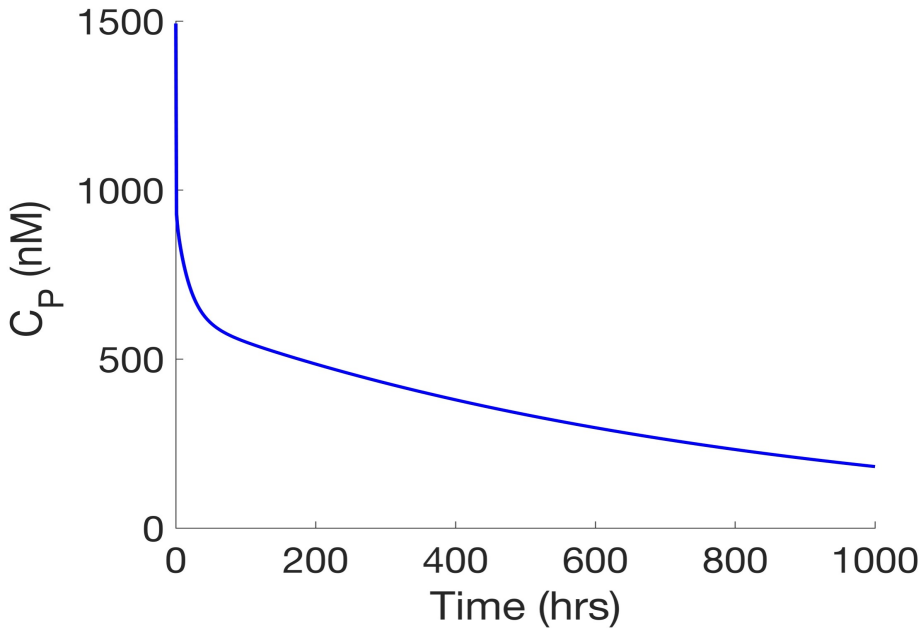


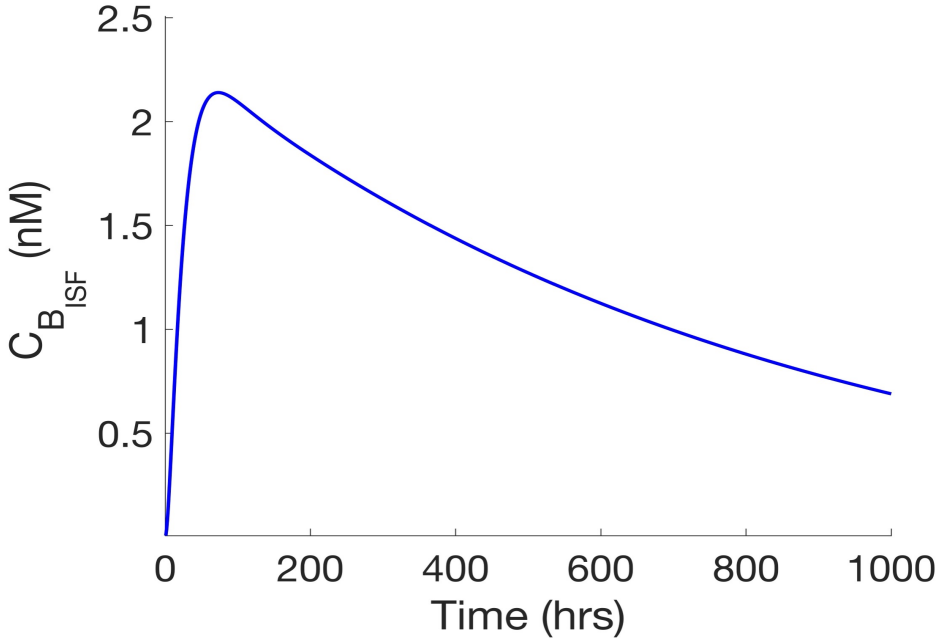
Results: Kamala Dadashova, North Carolina State University

Specific Model Responses

Responses:

- Concentration in Plasma (C_P) and Brain ISF (C_{ISF})

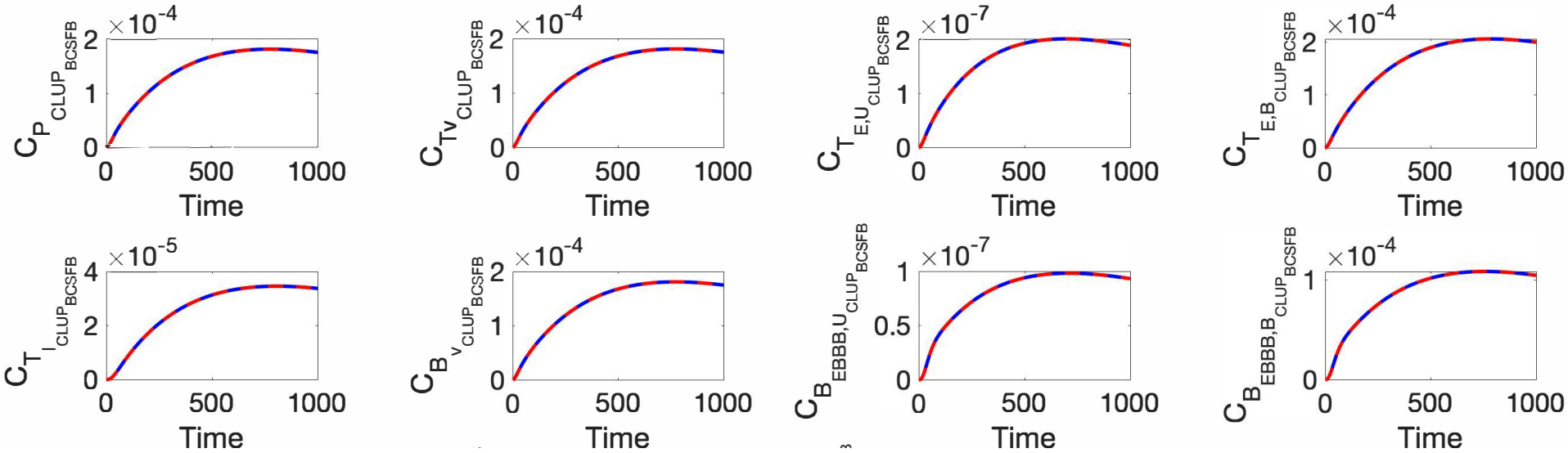




Note: Units and/or scaling important!

Sensitivities for Minimal PBPK Model

Example: Verify by comparing complex-step and sensitivity equations



Note: Complex-Step

Sensitivity Equations

Notes:

- Complex-step required modification of two lines of MATLAB code:

  S0_complex = complex(S0,h); S_S0 = imag(Y(:,1))/h

- Accuracy dictated by accuracy of ODE solver
- Significantly easier to code than sensitivity equations!

Parameter Subset Selection for Minimal PBPK Model

Impact of Threshold: Concentration in Plasma

$\hat{\eta}$ Values	Subsets of Identifiable Parameters									
10^{-6}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}					
10^{-8}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}			
10^{-10}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}	LT	σ_{BBB}	
10^{-12}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}	LT	σ_{BBB}	V_{T_V}

Notes:

- Important when performing Bayesian inference to quantify parameter and response uncertainties;
- Subsets of identifiable parameters differ for other concentrations.
- Tissue volumes: V_P, V_{T_E}, V_{T_v}

Parameter Subset Selection for Minimal PBPK Model

Setting: Considered doses (mg/kg) of 1, 3, 10, 30 100

Concentration in Plasma: 7 nonidentifiable parameters

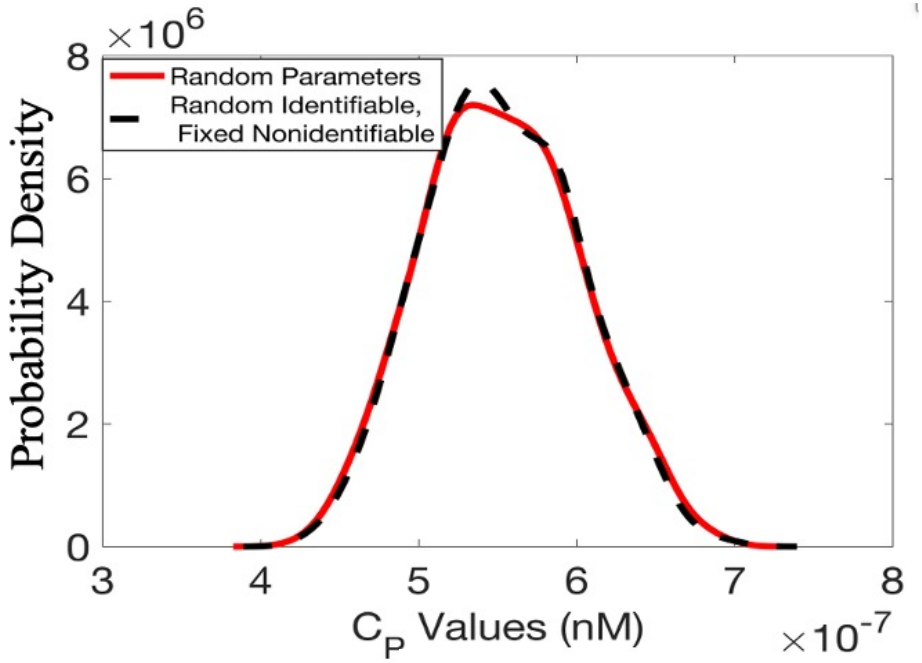
$$V_P \ , \ \sigma_{T_V} \ , \ k_{deg} \ , \ V_{T_E} \ , \ V_{T_I} \ , \ FR \ , \ \sigma_{BCSFB}$$

Qualitative Verification:

- Randomly sample all 31 parameters from uniform distribution
- Randomly sample 7 identifiable parameters and fix 24 nonidentifiable

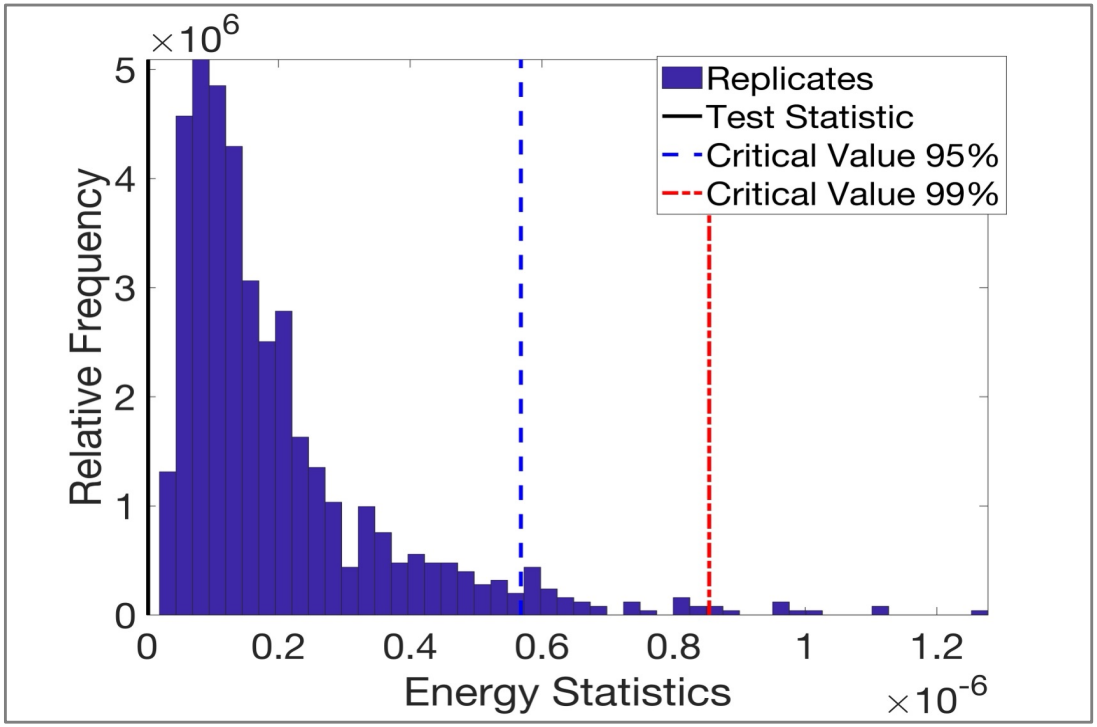
Results:

- Response density at t=100
- Note units



Parameter Subset Selection for Minimal PBPK Model

Quantitative Verification: Hypothesis testing using “Energy Statistics”



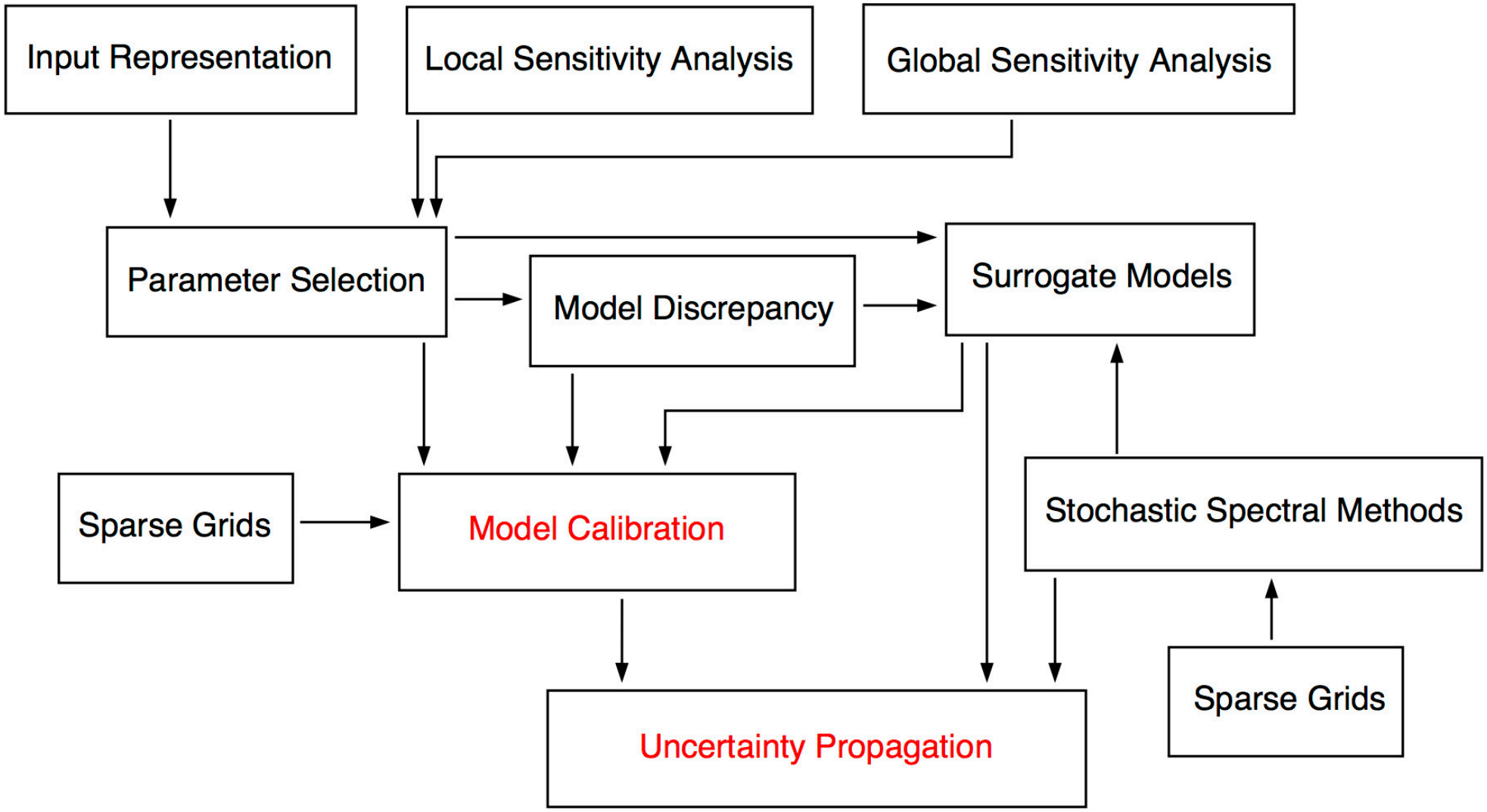
Null Hypothesis: Two sets of samples come from same distribution

Conclusion: Test statistic less than both critical values so we do not reject null hypothesis at either 95% or 99% confidence levels

Reference: G.J. Székely and M.L. Rizzo, *The Energy of Data and Distance Correlation*, CRC Press, 2023.

Steps in Uncertainty Quantification for Large-Scale Models

Note: Uncertainty quantification requires synergy between mathematics, statistics, engineering, and sciences

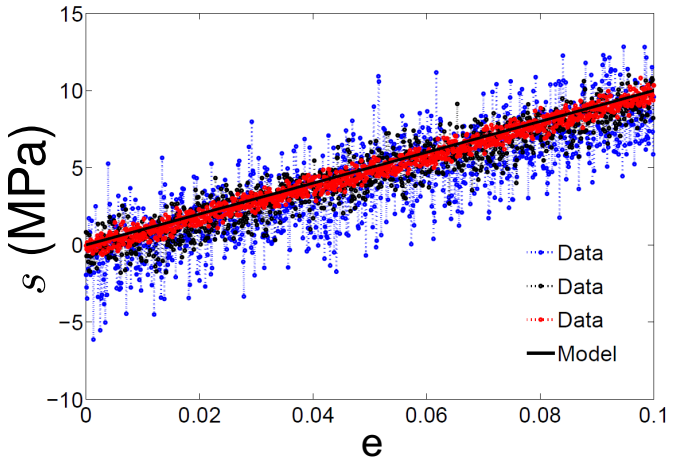


Bayesian Inference: Motivation

Example: Displacement-force relation (Hooke's Law)

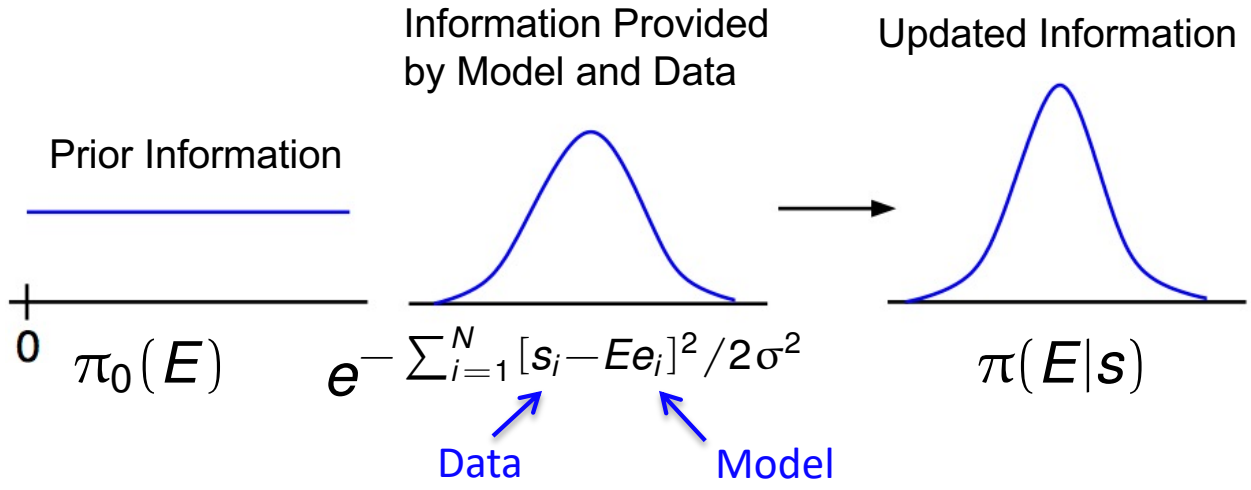
$$s_i = Ee_i + \varepsilon_i \ , \ i = 1, \ldots, N$$

$$\varepsilon_i \sim N(0, \sigma^2)$$



Parameter: Stiffness E

Strategy: Use model fit to data to update prior information

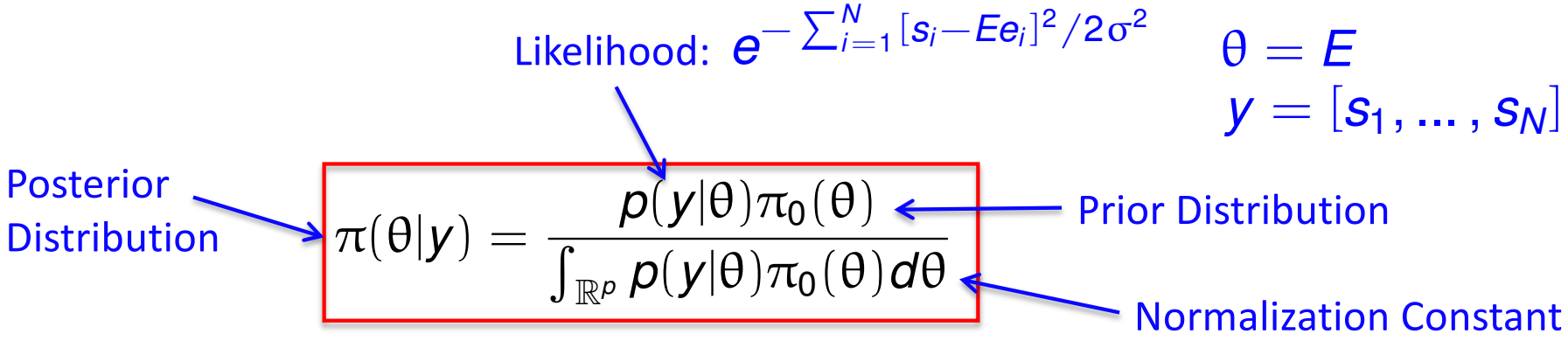


Non-normalized Bayes' Relation:

$$\pi(E|s) = e^{-\sum_{i=1}^{N}[s_i - Ee_i]^2/2\sigma^2}\pi_0(E)$$

Bayesian Inference

Bayes' Relation: Specifies posterior in terms of likelihood and prior



Problem: Can require high-dimensional integration

- e.g., m-PBPK Model: p = 31
- One solution: Sampling-based Markov Chain Monte Carlo (MCMC) algorithms
- Current applications: Delayed Rejection Adaptive Metropolis (DRAM)
- MATLAB, Python, R, Dakota
- **Reference:** H. Haario, M. Laine, A. Mira and E. Saksman, "DRAM: Efficient adaptive MCMC," *Statistics and Computing*, 16(4), pp. 339-354, 2006

Bayesian Model Calibration – HIV Example

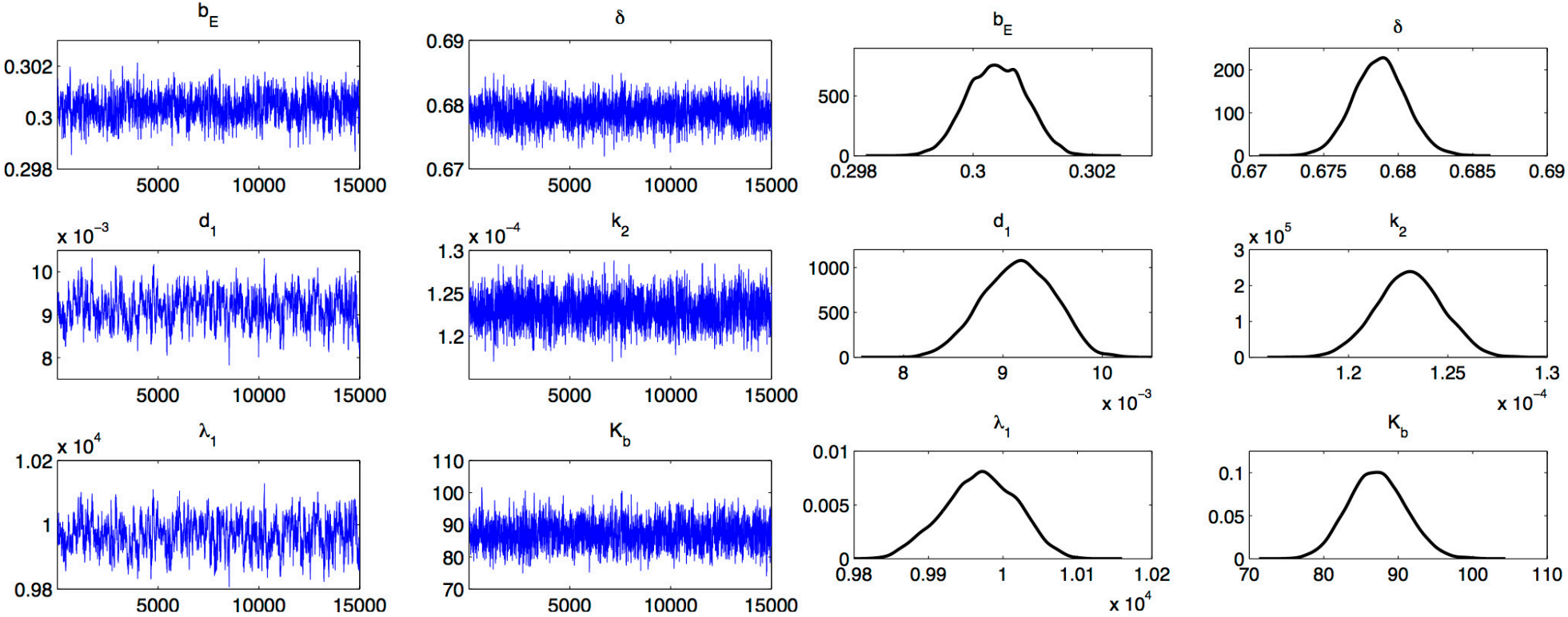
Model: First equation

$$\frac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1 - \varepsilon_1) k_1 V_I T_1$$

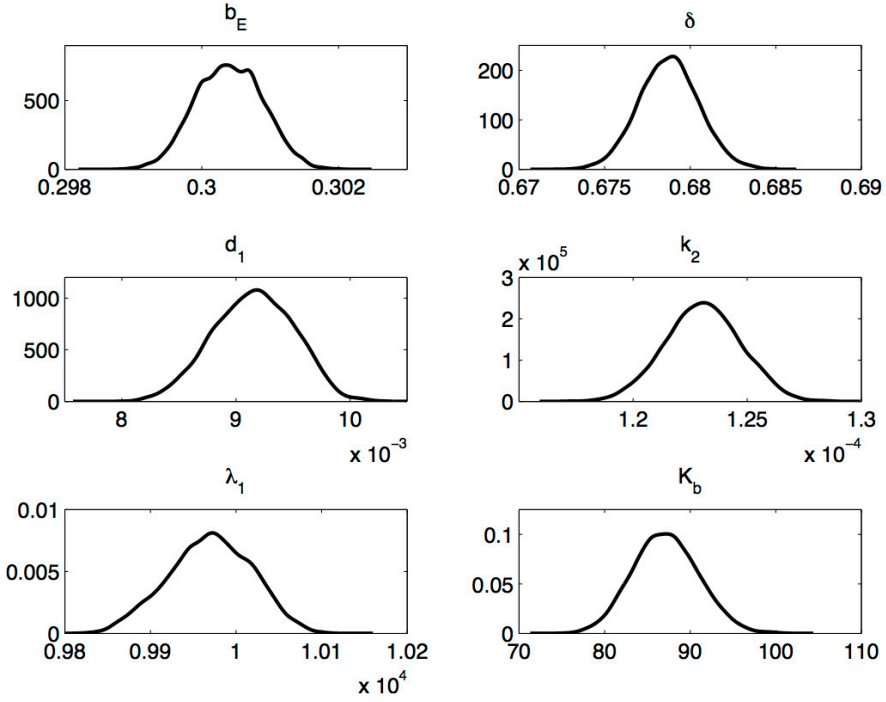
Verification: Why do we trust results??

- Compare results from different algorithms; e.g., DRAM and DREAM

Parameter Chains and Densities: $\theta = [b_E, \delta, d_1, k_2, \lambda_1, K_b]$



Propagation of Uncertainty in Models



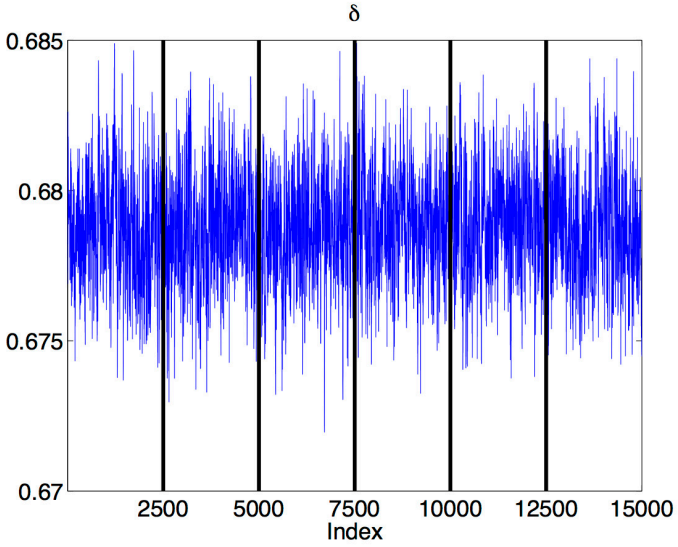
HIV Model: First equation

$$\frac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1 - \varepsilon_1) k_1 V_I T_1$$

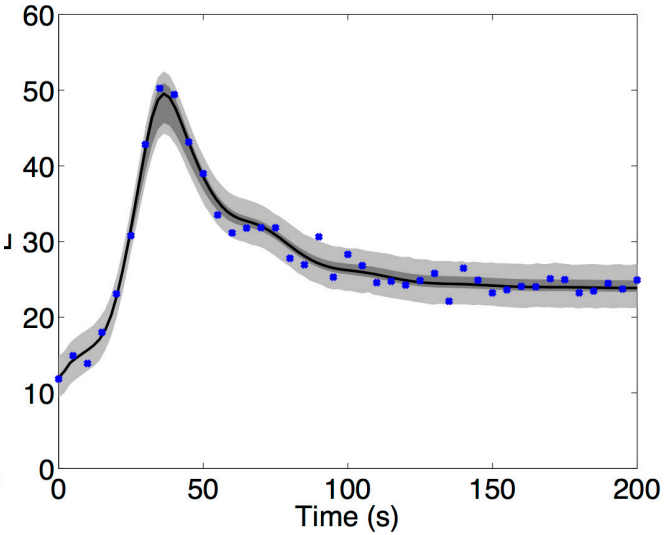
Techniques:

- Sample from parameter densities to construct prediction intervals for QoI
- Provides formal validation framework

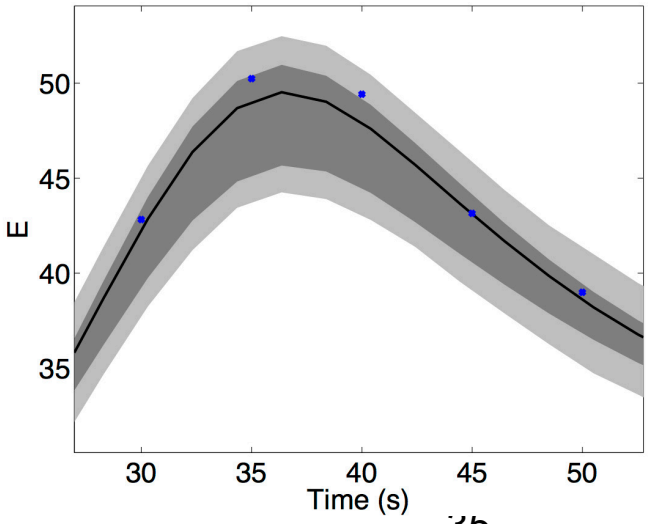
Response: Immune effector cells



Samples from Chain



Data and Prediction Intervals



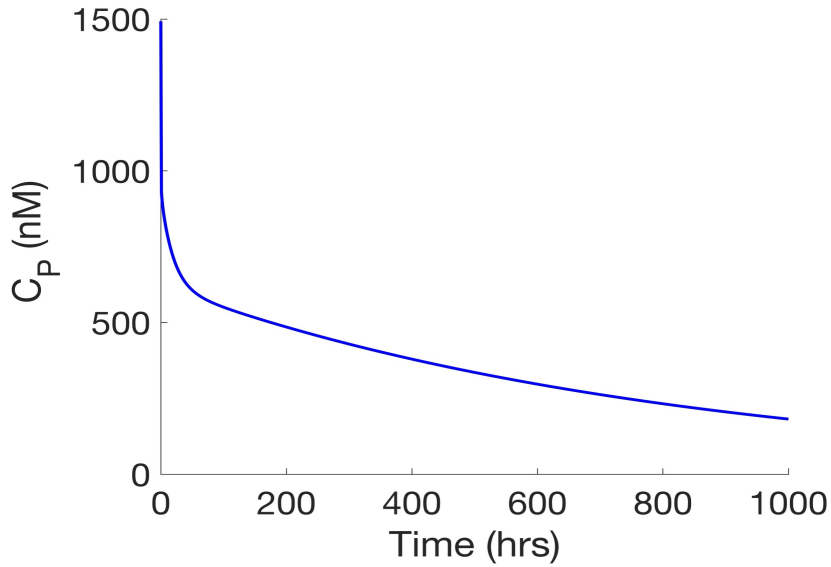
Data and Prediction Intervals

Combined role of PSS and Bayesian Inference

Response: Concentration in Plasma

$\hat{\eta}$ Values	Parameter Candidates									
2.5×10^{-8}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR				
1×10^{-8}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}			
2.5×10^{-10}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}	σ_{BBB}		
1×10^{-10}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}	σ_{BBB}	L_T	
1×10^{-12}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	σ_{BCSFB}	σ_{BBB}	L_T	V_{T_V}

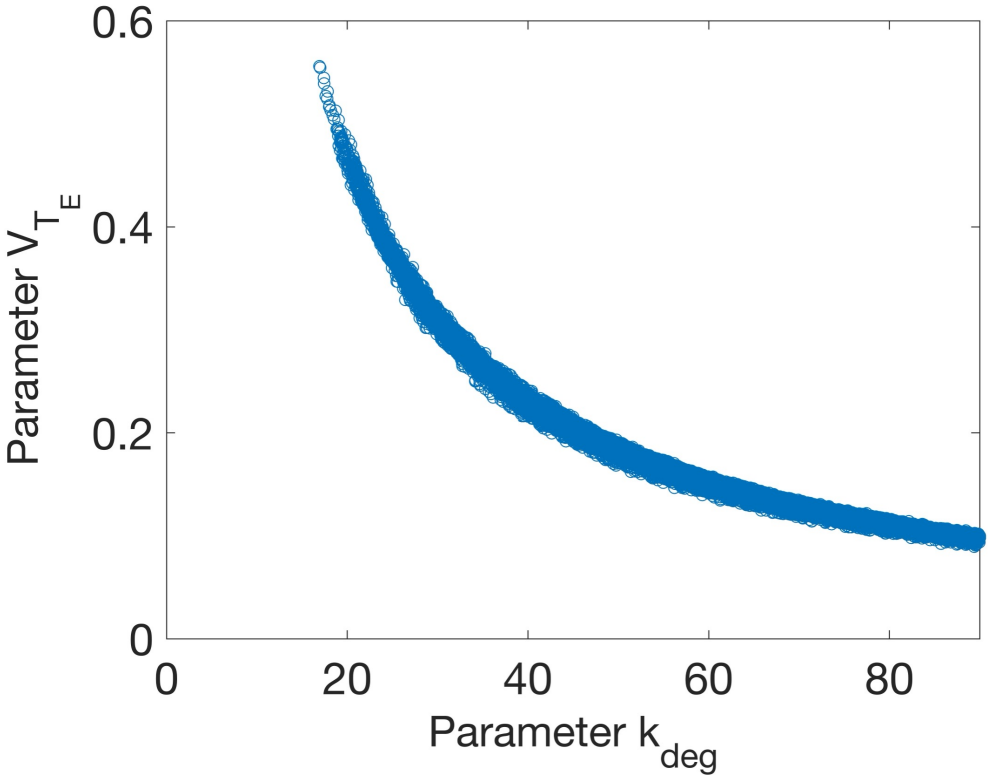
Response: Concentration in Plasma

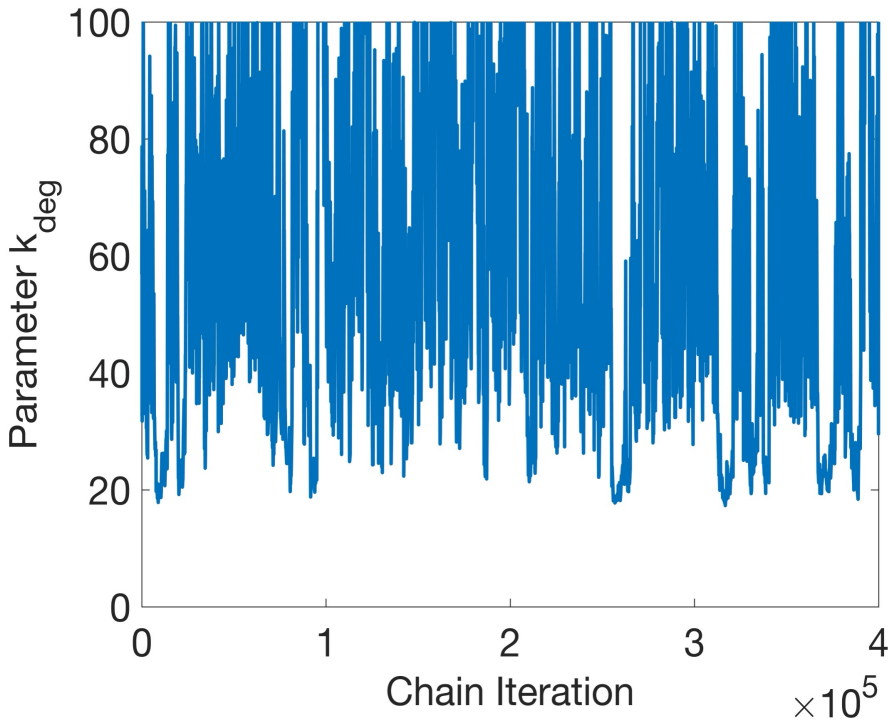


Combined role of PSS and Bayesian Inference

Set 1: $\hat{\eta} = 2.5 \times 10^{-8}$

$\{V_P, \sigma_{T_V}, k_{deg}, V_{T_E}, V_{T_I}, FR\}$





Result:

- Algebraic dependence between parameters
- Differs from statistical dependence

Refined Parameter Set

Response: Concentration in Plasma

$\hat{\eta}$ Values	Refined Parameter Candidates						C1	C2	C3	Excluded Parameter
2.5×10^{-8}	V_P	σ_{T_V}	k_{deg}	V_{T_E}	V_{T_I}	FR	$\times$	✓	$\times$	V_{T_E}
1×10^{-8}	V_P	σ_{T_V}	k_{deg}	V_{T_I}	FR	σ_{BCSFB}	✓	X	✓	σ_{BCSFB}
2.5×10^{-10}	V_P	σ_{T_V}	k_{deg}	V_{T_I}	FR	σ_{BBB}	✓	$\times$	✓	σ_{BBB}
1×10^{-10}	V_P	σ_{T_V}	k_{deg}	V_{T_I}	FR	L_T	✓	$\times$	✓	L_T
1×10^{-12}	V_P	σ_{T_V}	k_{deg}	V_{T_I}	FR	V_{T_V}	✓	✓	✓	–

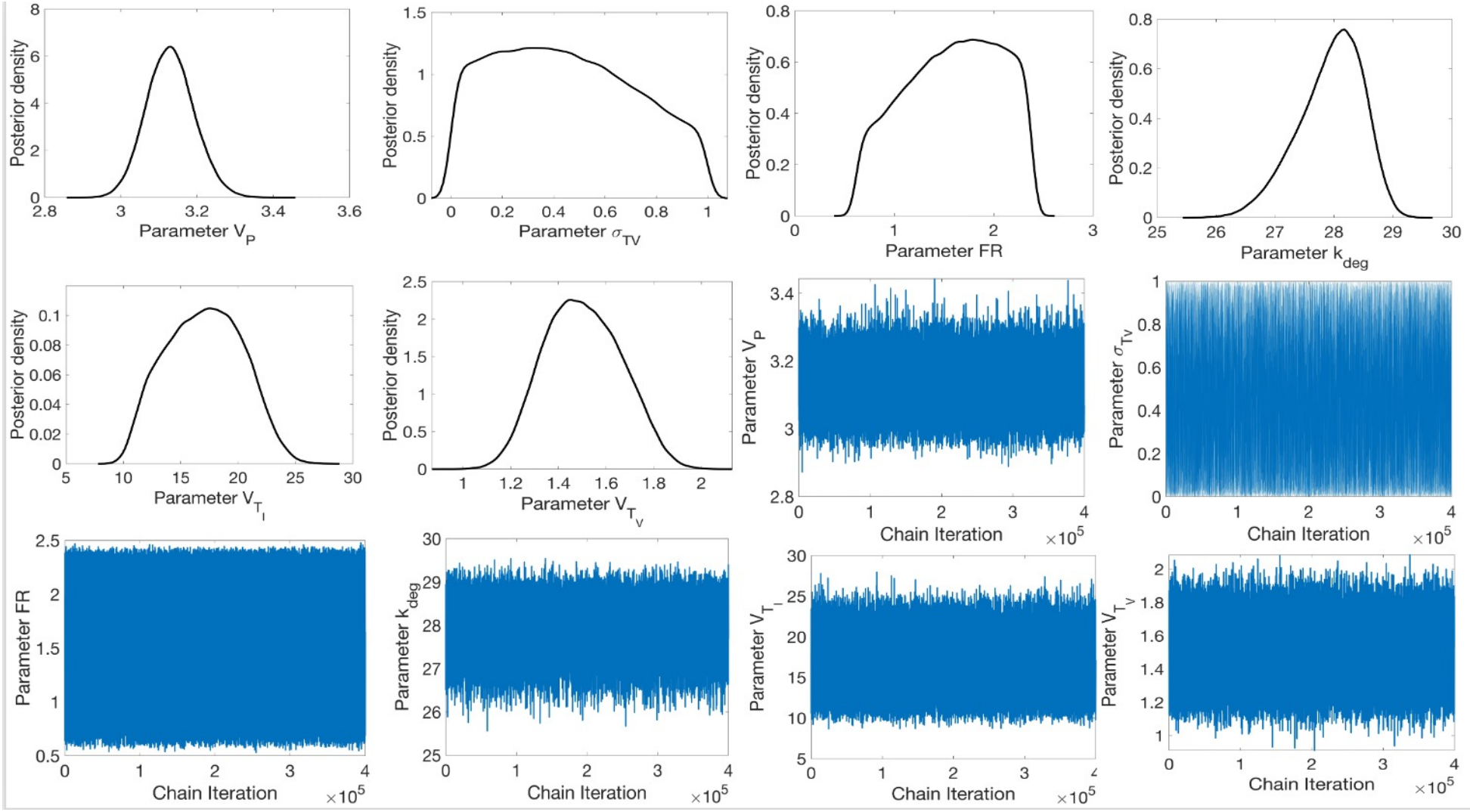
Criteria:

- C1: No algebraic relations in joint posterior plots
- C2: Prior distribution informed by likelihood (data and model)
- C3: Chains adequately mix and converge

Final Parameter Set

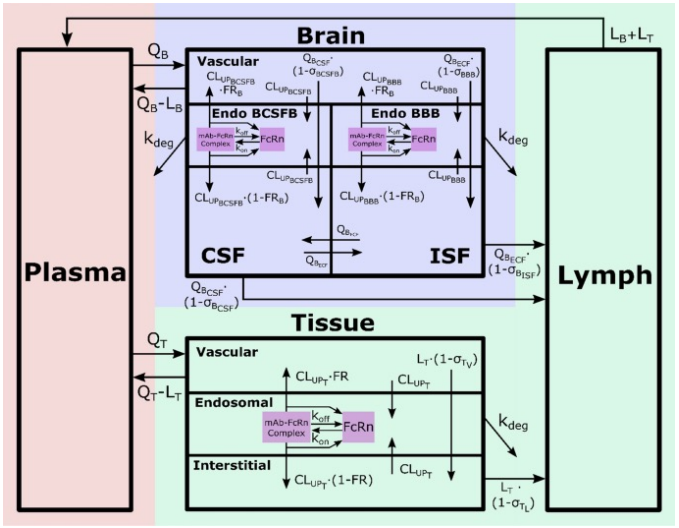
Final Set: $\hat{\eta} = 1.0 \times 10^{-12}$

$$\{V_P, \sigma_{T_V}, k_{deg}, V_{T_I}, FR, V_{T_V}\}$$

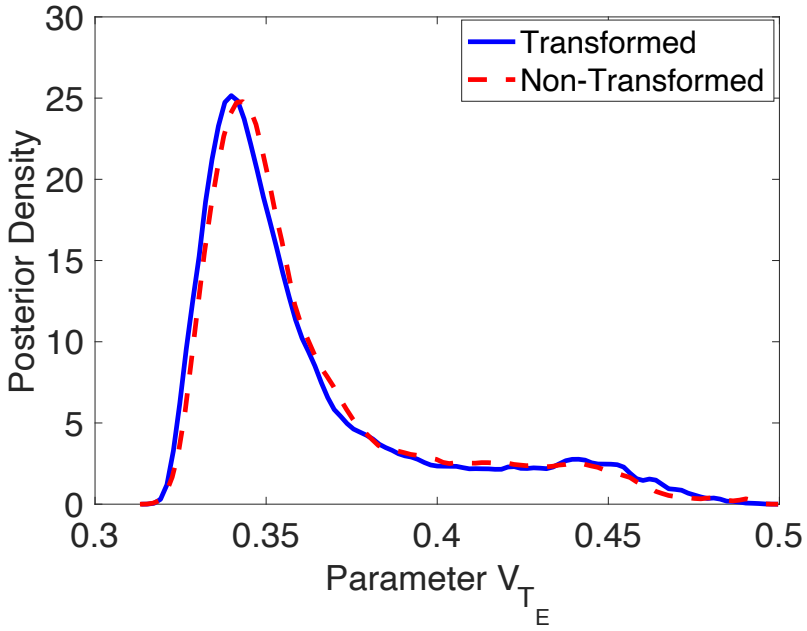


Bayesian Inference and Uncertainty Propagation

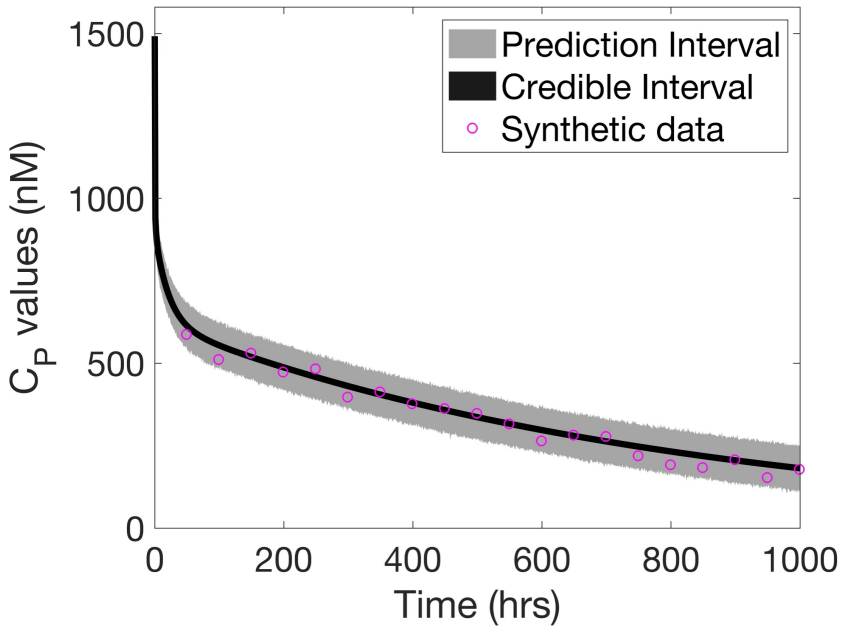
m-PBPK Model:



Parameter Posterior Distribution



Prediction Interval for Response



UQ Application Field: Digital Twins

Early Example: Apollo 13: NASA Mission Control employed spacecraft data to update simulation models to inform strategies to bring spacecraft back to earth.

Present Application Areas:

- Semiautonomous nuclear power plant monitoring: NCSU Nuclear Engineering
- Aerospace/aeronautic health monitoring
- Medical treatment and surgery strategies (NIH)
- See later presentations

Roles of Sensitivity Analysis/Uncertainty Quantification:

- Sensitivity analysis required to determine subsets of influential parameters;
- Experimental design necessary to guide where to collect future data to best inform models;
- Uncertainty quantification required to guide design and validation;
- Uncertainty analysis often required to assess risk, increase profits, and inform policy.

UQ Application Field: Virtual Populations

Example: Minimal PBPK Model

- 16 ODE, 31 Parameters

Goal: Determine parameter distributions so that distribution for model response reflects that of population under consideration

Objective: Employ virtual population to guide:

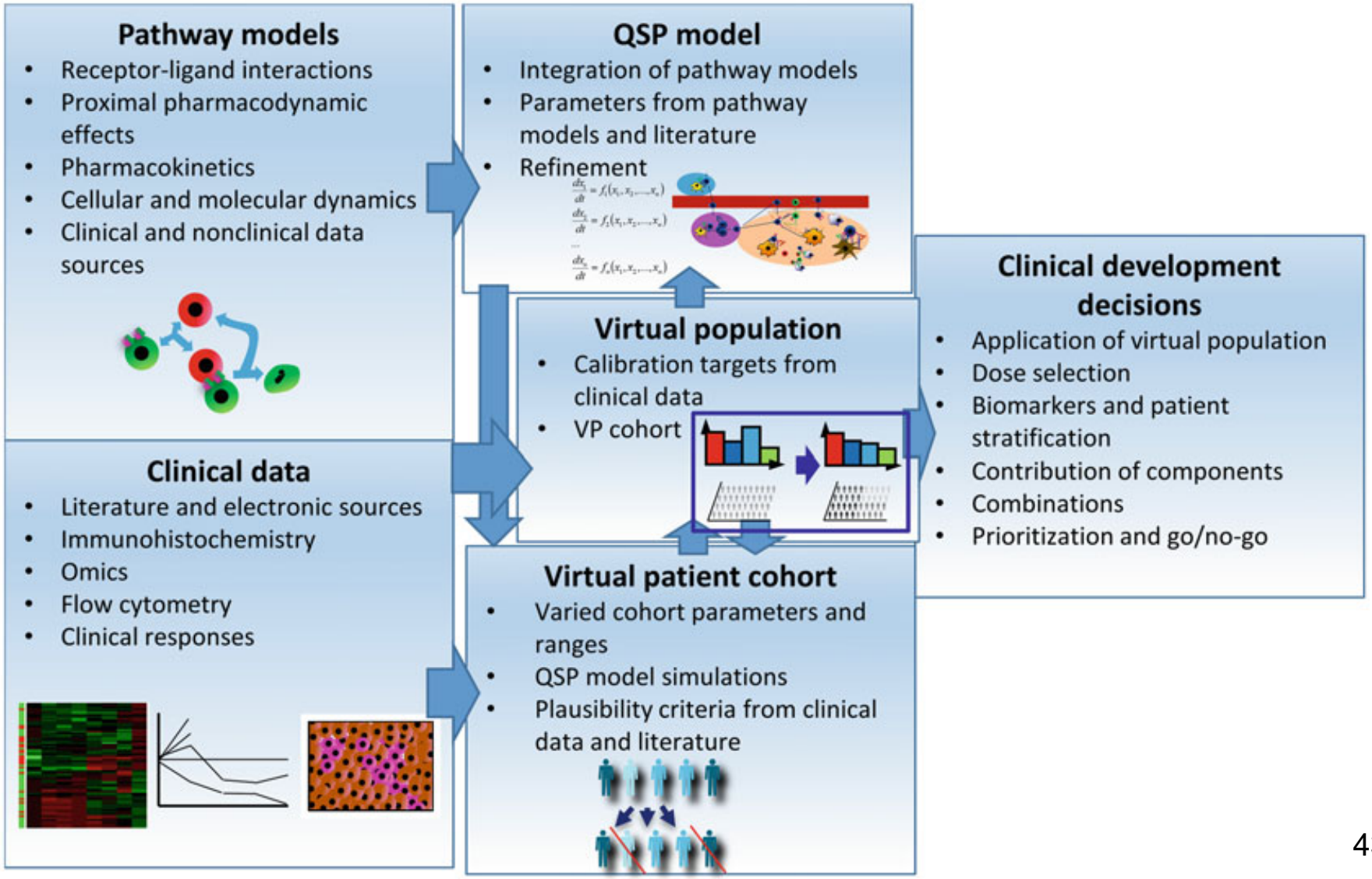
- Drug discovery
- Develop safe and effective treatment regimes
- Guide clinical decisions and dose selection

Recent Reference:

- R. Rao, C.J. Musante and R.J. Allen, ``A quantitative systems pharmacology model of the pathophysiology and treatment of COVID-19 predicts optimal timing of pharmacological interventions,'' *NPJ Syst Biol Appl*., 9(1): 13, 2023.

UQ Application Field: Virtual Populations

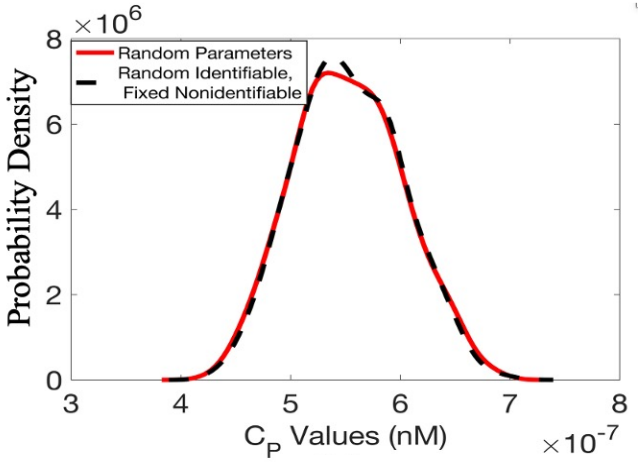
Example: Cheng et al, "Virtual populations for Quantitative Systems Pharmacology Models," in *Systems Medicine*, 2022.

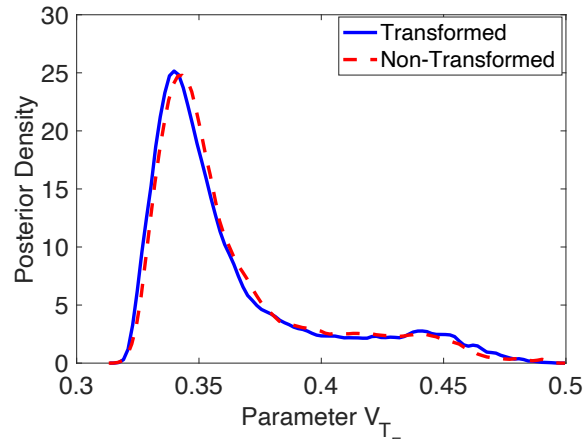


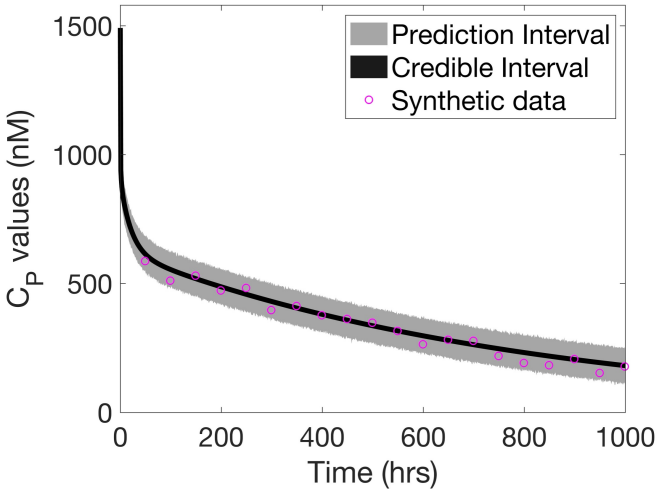
Concluding Remarks

Notes:

- UQ requires a synergy between statistics, applied mathematics, engineering and science.
- Model calibration, model selection, uncertainty propagation and experimental design natural in a Bayesian framework.
- Goal: Predict model responses with quantified and reduced uncertainties.
- Parameter selection critical to isolate identifiable and influential parameters.
- Surrogate models critical for computationally intensive simulation codes.
- Codes and packages: MATLAB, Python, R, UQLab, Sandia Dakota.
- Significant role of UQ for Digital Twins and Virtual Populations
- *Prediction is very difficult, especially if it's about the future*. Niels Bohr.







References

- K. Dadashova, R.C. Smith and M.A. Haider, “Local identifiability analysis, parameter subset selection, and verification for a minimal brain PBPK model, Bulletin of Mathematical Biology, 86(2), 2024.
- K. Dadashova, R.C. Smith, M.A. Haider and B.J. Reich, “Bayesian inference informed by parameter subset selection for a minimal brain PBPK model, Philosophical Transactions of the Royal Society A, 2025.