Prediction and Exploitation of Uncertainty in Dynamic Processes

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OMEGA Optimization Methods For Green Applications

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Outline

Quality by Design (QbD)

- The FDA encourages the pharmaceutical industry to design (and validate) their processes for a range of process conditions that results in acceptable products for the patient: Design Space

  [ICH Guideline Q8 on Pharmaceutical Development, 2004]

↳ Need to understand and quantify complex interactions between material, processes and products

Quality by Design (QbD)

- The FDA encourages the pharmaceutical industry to design (and validate) their processes for a range of process conditions that results in acceptable products for the patient: Design Space

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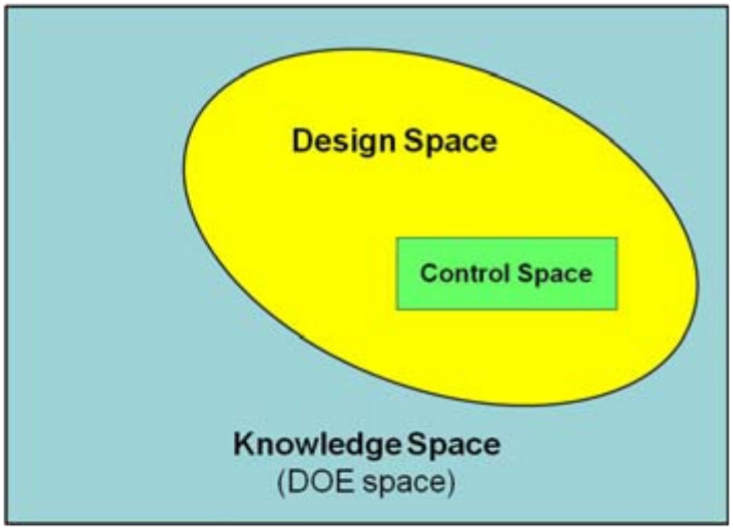
Robust Approach:
Identify all possible combinations of process parameters that yield acceptable product quality for all possible variations in raw materials

- Carry out a well-designed set of experiments (DOE)
- Use response surface methodology



Use of Mechanistic Models in QbD

Advantages of a Model-Centric Strategy:

- Ability to study of a very large number of parameters simultaneously
- Ability to adjust operating conditions to compensate for materials variability leading to larger design space (robust $\rightarrow$ reactive)

↳ Empowered by mathematical tools developed by the PSE community

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- Ability to study of a very large number of parameters simultaneously
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↳ Empowered by mathematical tools developed by the PSE community

But...

- Need to account for and carefully quantify modeling inaccuracies, alongside other types of uncertainty

Organic Process Research & Development

Article

pubs.acs.org/OPRD

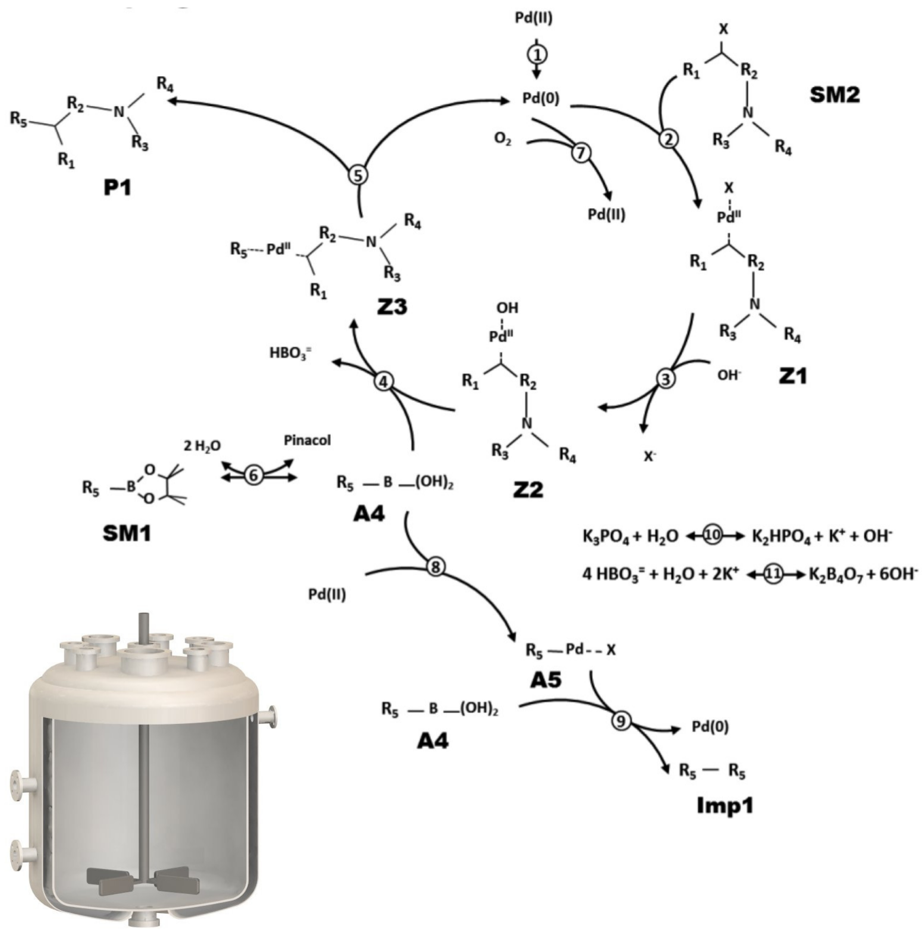
Definition of Design Spaces Using Mechanistic Models and Geometric Projections of Probability Maps

Salvador García-Muñoz,* Carla V. Luciani, Shankar Vaidyaraman, and Kevin D. Seibert

Small Molecule Design and Development, Lilly Research Laboratories, Eli Lilly & Company, 1400 West Raymond Street, Indianapolis, Indiana 46221, United States

Example: Suzuki Coupling Model

Gas-liquid reaction system in batch mode:



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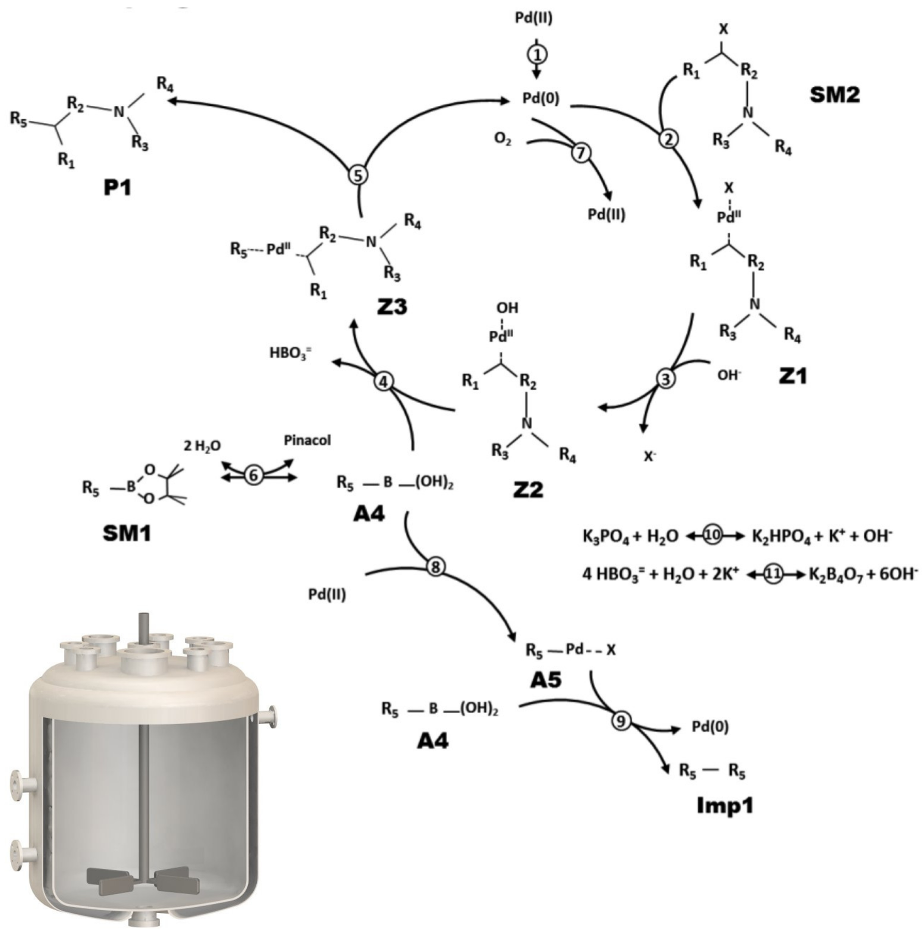


Quality Attributes:

- Max. amount of unreacted **SM2** (reaction completion)
- Max. amount of produced **Imp1** (downstream purif.)

Process Parameters:

- ratio of starting materials
- reaction volume
- solvent composition
- reaction temperature
- catalyst loading
- initial Pd speciation
- O_2 level in head-space
- reaction time
- potassium phosphate charged amount

Example: Suzuki Coupling Model

Kinetic Model Formulation:

$$\frac{d\{[Pd(0)]V\}}{dt} = \{-k_{s2}[Pd(0)][SM2] - k_{s7}[Pd(0)][O_2]_L^{1/2} + k_{s9}[A5][A4] + k_{s5}[Z3]\}V \quad (1)$$

$$\frac{d\{[Pd(II)]V\}}{dt} = \{k_{s7}[Pd(0)][O_2]_L^{1/2} - k_{s8}[Pd(II)][A4]\}V \quad (2)$$

$$y_{O_2}P = [O_2]_{L,sat}H_{O_2} \quad (3)$$

$$H_{O_2} = \exp\left(\sum_{j=\text{water,THF}} x_j \ln H_{O_2,j} - x_{THF}\ln\left(\frac{H_{O_2,THF}}{H_{O_2,water}}\right) - \ln\left(x_{water} + x_{THF}\frac{H_{O_2,water}}{H_{O_2,THF}}\right)\right) \quad (4)$$

$$\frac{d\{[O_2]_L V\}}{dt} = \{k_{s12}([O_2]_{L,sat} - [O_2]_L)\}V \quad (5)$$

$$\frac{d\{[SM2]V\}}{dt} = \{-k_{s2}[Pd(0)][SM2]\}V \quad (6)$$

$$\frac{d\{[Z1]V\}}{dt} = \{k_{s2}[Pd(0)][SM2]_L - k_{s3}[Z1][OH^-]\}V \quad (7)$$

$$\frac{d\{[Z2]V\}}{dt} = \{k_{s3}[Z1][OH^-] - k_{s4}[A4][Z2]\}V \quad (8)$$

$$\frac{d\{[Z3]V\}}{dt} = \{k_{s4}[A4][Z2] - k_{s5}[Z3]\}V \quad (9)$$

$$\frac{d\{[A4]V\}}{dt} = \{k_{s6}[SM1] - k_{s-6}[A4] - k_{s4}[A4][Z2] - k_{s8}[Pd(II)][A4] - k_{s9}[A5][A4]\}V \quad (10)$$

$$\frac{d\{[A5]V\}}{dt} = \{k_{s8}[Pd(II)][A4] - k_{s9}[A4][A5]\}V \quad (11)$$

$$\frac{d\{[SM1]V\}}{dt} = \{-k_{s6}[SM1] + k_{s-6}[A4]\}V \quad (12)$$

$$\frac{d\{[Imp1]V\}}{dt} = \{-k_{s9}[A4][A5]\}V \quad (13)$$

$$\frac{d\{[K_3PO_4]V\}}{dt} = \{-k_{s10}[K_3PO_4] + k_{s-10}[K_2HPO_4][OH^-]\}V \quad (14)$$

$$\frac{d\{[K_2HPO_4]V\}}{dt} = \{k_{s10}[K_3PO_4] - k_{s-10}[K_2HPO_4][OH^-]\}V \quad (15)$$

$$\frac{d\{[HBO_3^-]V\}}{dt} = \{k_{s4}[A4][Z2] - k_{s11}[HBO_3^-] + k_{s-11}[K_2B_4O_7][OH^-]\}V \quad (16)$$

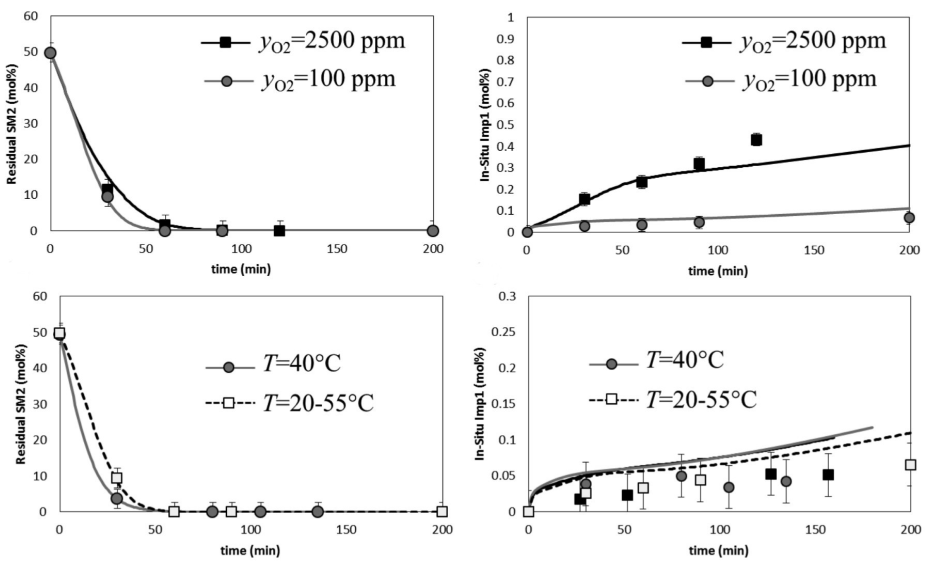
$$\frac{d\{[OH^-]V\}}{dt} = \{k_{s10}[K_3PO_4] - k_{s-10}[K_2HPO_4][OH^-] + k_{s11}[HBO_3^-] - k_{s-11}[K_2B_4O_7][OH^-]\}V \quad (17)$$

$$\frac{d\{[K_2B_4O_7]V\}}{dt} = \{k_{s11}[HBO_3^-] - k_{s-11}[K_2B_4O_7][OH^-]\}V \quad (18)$$

$$\frac{d\{[P1]V\}}{dt} = \{k_{s5}[Z3]\}V \quad (19)$$

Example: Suzuki Coupling Model

Kinetic Model Calibration:

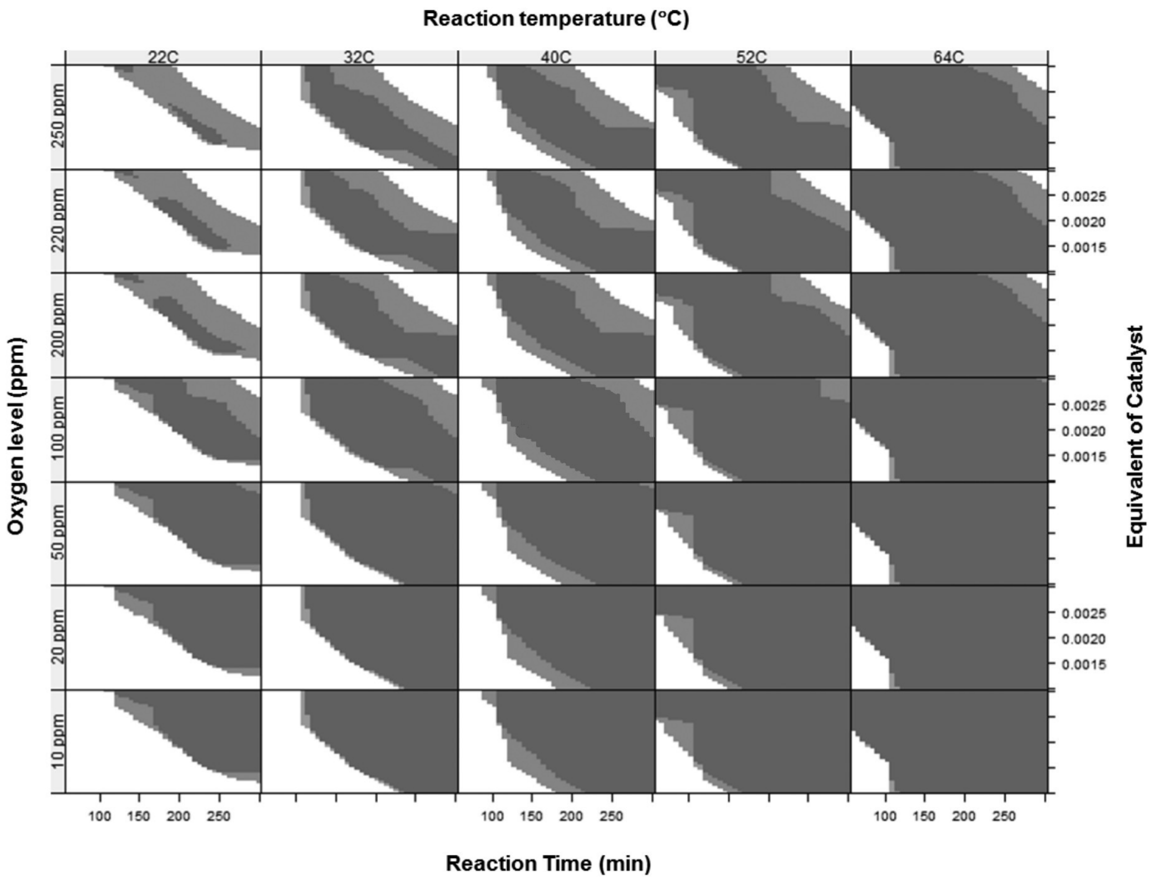


parameter	value
Suzuki Coupling[a]	
$k_{s2,\mathrm{ref}}$ (L mol^{-1} min^{-1})	1.74×10^2
$k_{s3,\mathrm{ref}}$ (L mol^{-1} min^{-1})	7.14×10^3
$k_{s4,\mathrm{ref}}$ (L mol^{-1} min^{-1})	4.37×10^3
$k_{s5,\mathrm{ref}}$ (min^{-1})	2.49×10^3
$k_{s6,\mathrm{ref}}$ (min^{-1})	2.94
$K_{eq,6} = k_{s6,\mathrm{ref}}/k_{s-6,\mathrm{ref}}$ (—)	2.08
$k_{s7,\mathrm{ref}}$ (L$^{0.5}$ mol$^{-0.5}$ min^{-1})	1.04×10^1
$k_{s8,\mathrm{ref}}$ (L mol^{-1} min^{-1})	7.54
$k_{s9,\mathrm{ref}}$ (L mol^{-1} min^{-1})	3.84×10^2
$k_{s10,\mathrm{ref}}$ (min^{-1})	5.50
$K_{eq,10} = k_{s10,\mathrm{ref}}/k_{s-10,\mathrm{ref}}$ (L^{-1} mol)	3.96×10^{-2}
$k_{s11,\mathrm{ref}}$ (min^{-1})	2.34
$K_{eq,11} = k_{s11,\mathrm{ref}}/k_{s-11,\mathrm{ref}}$ (L^{-1} mol)	5.00×10^{-4}
$k_{s12,\mathrm{ref}}$	2.74×10^{-3}

[a] $k_i(T) = k_{si,\mathrm{ref}} \exp(-E_{ai}/R(1/T - 1/T_{\mathrm{ref}}))$ with $T_{\mathrm{ref}} = 303.15$ K; activation energies are as follows (kJ/mol): $E_{a2} = 27.4$, $E_{a3} = 0.0$, $E_{a4} = 15.3$, $E_{a5} = 22.4$, $E_{a6} = 30.0$, $E_{a,eq6} = -65$, $E_{a,7} = 0.0$, $E_{a,8} = 20.1$, $E_{a,9} = 0.0$, $E_{a,10} = 30$, $E_{a,eq10} = 50$, $E_{a11} = 30.0$, $E_{a,eq11} = 139.0$, and $E_{a,12} = 15.0$.

Example: Suzuki Coupling Model

Design space estimated via griding of process parameters and running numerous simulations:



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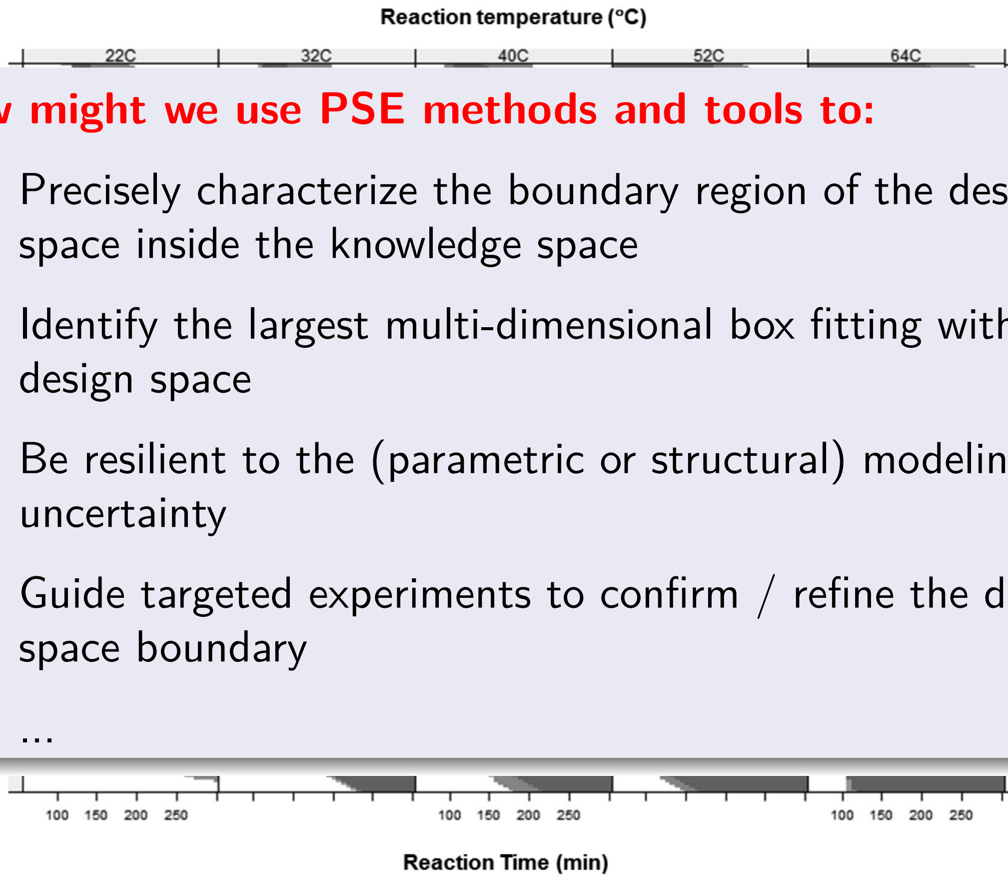


How might we use PSE methods and tools to:

- Precisely characterize the boundary region of the design space inside the knowledge space
- Identify the largest multi-dimensional box fitting within the design space
- Be resilient to the (parametric or structural) modeling uncertainty
- Guide targeted experiments to confirm / refine the design space boundary
- ...

Computational Systems Biology

BIOLOGICAL ROBUSTNESS

Hiroaki Kitano

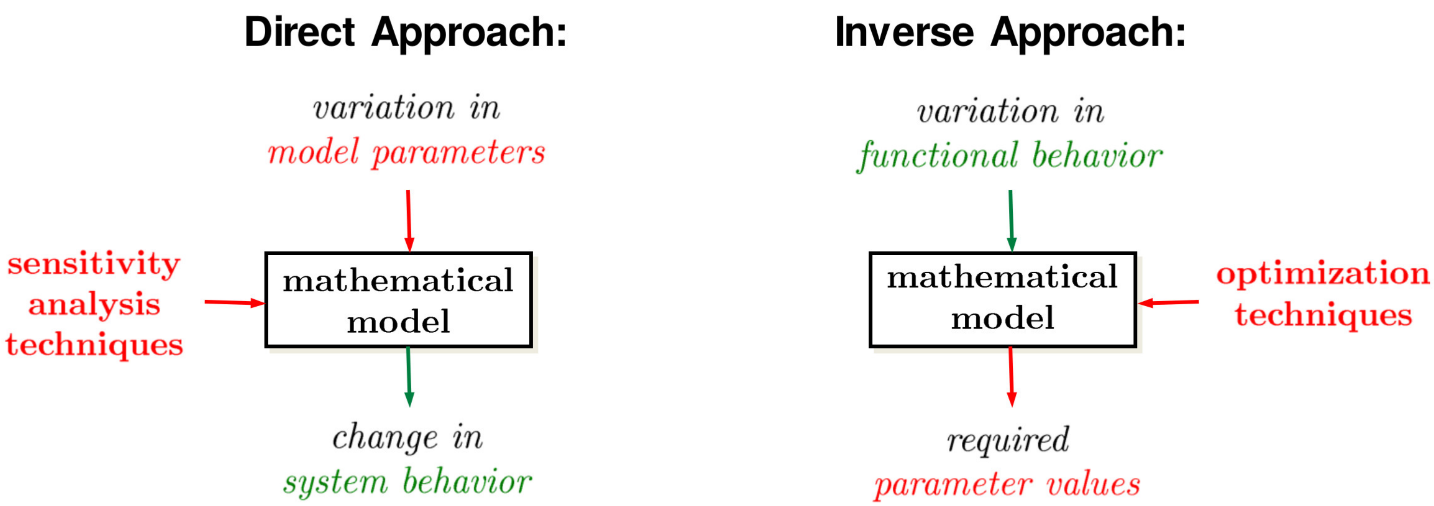
Abstract | Robustness is a ubiquitously observed property of biological systems. It is considered to be a fundamental feature of complex evolvable systems. It is attained by several underlying principles that are universal to both biological organisms and sophisticated engineering systems. Robustness facilitates evolvability and robust traits are often selected by evolution. Such a mutually beneficial process is made possible by specific architectural features observed in robust systems. But there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure. Insights into inherent properties of robust systems will provide us with a better understanding of complex diseases and a guiding principle for therapy design.

826 | NOVEMBER 2004 | VOLUME 5 www.nature.com/reviews/genetics

- Identify and understand the basic architecture for a robust system, and the associated trade-offs and faults: Reverse Engineering
- Develop counter-measures, such as targets for new drugs: Therapeutic Design

Approaches in Computational Systems Biology

How large a perturbation can a system tolerate before loosing a specific behavior?

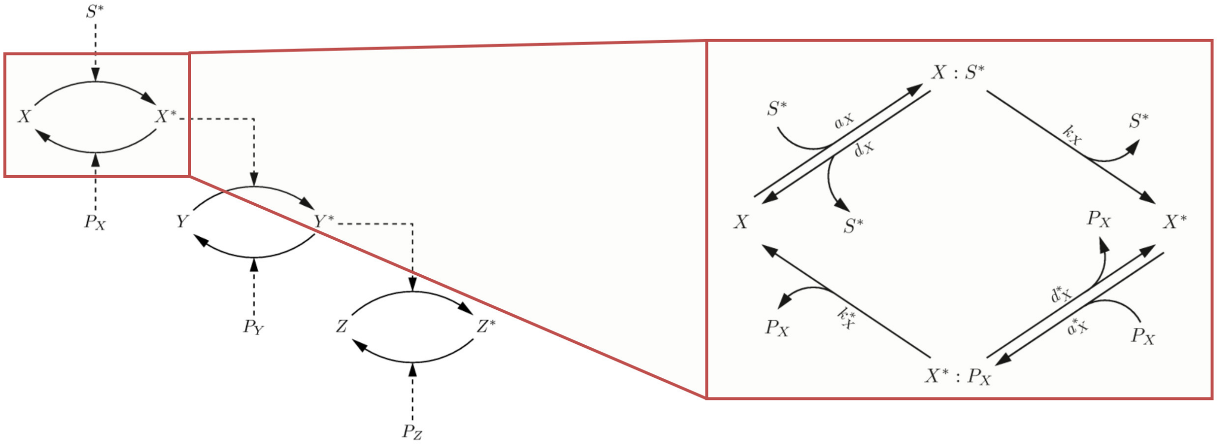


Examples of Qualitative Functional Behaviors:

Oscillation, Bistability, Switch-like activation, Perfect adaptation, Amplification, *etc.*

Example: Covalent Modification Cycle

MAP cascades: a ubiquitous "signaling module" in Eucaryotes



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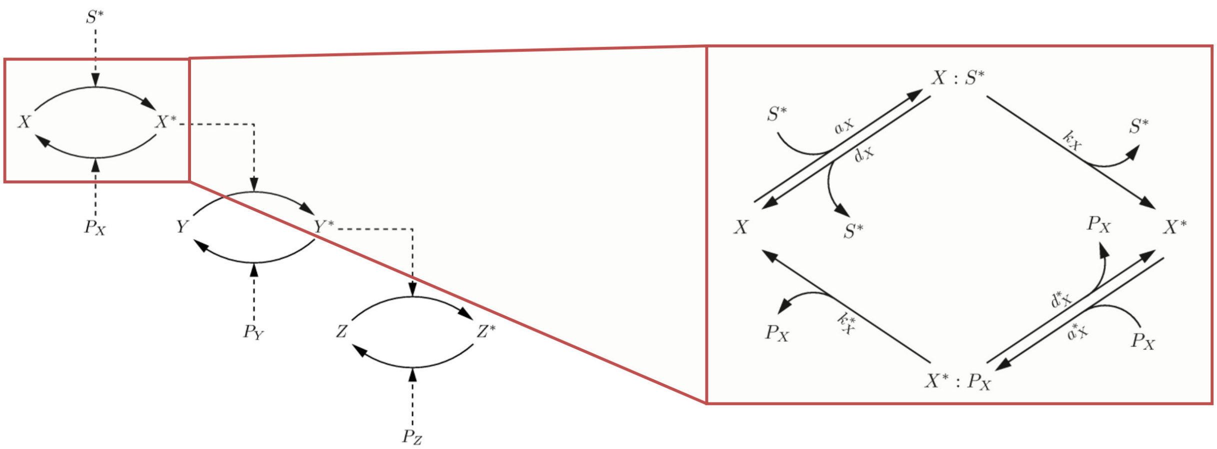

DAE Model:

$$
\begin{aligned}
\frac{\mathrm{d}[X^*]}{\mathrm{d}t} &= -a_X^*[X^*][P_X] + k_X[X:S^*] + d_X^*[X^*:P_X]\\
\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} &= a_X[X][S^*] - (k_X + d_X)[X:S^*]\\
\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} &= a_X^*[X^*][P_X] - (k_X^* + d_X^*)[X^*:P_X]\\
[X]_{\mathrm{tot}} &= [X] + [X^*] + [X:S^*] + [X^*:P_X]\\
[S]_{\mathrm{tot}} &= [S] + [S^*] + [X:S^*]\\
[P_X]_{\mathrm{tot}} &= [P_X] + [X^*:P_X]
\end{aligned}
$$

Example: Covalent Modification Cycle

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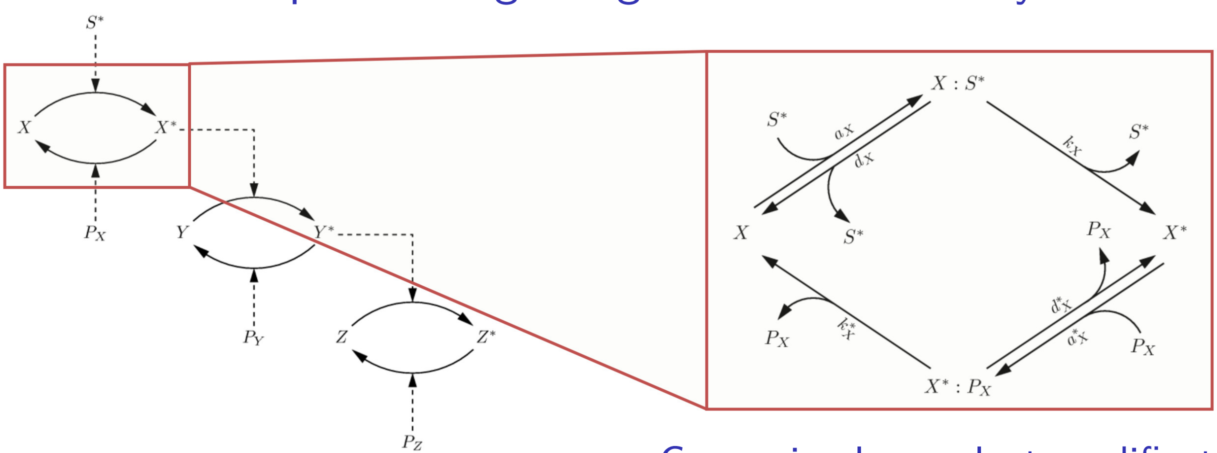


DAE Model:

$$\frac{\mathrm{d}[X^*]}{\mathrm{d}t} = -a_X^*[X^*][P_X] + k_X[X:S^*] + d_X^*[X^*:P_X]$$

$$\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} = a_X[X][S^*] - (k_X + d_X)[X:S^*]$$

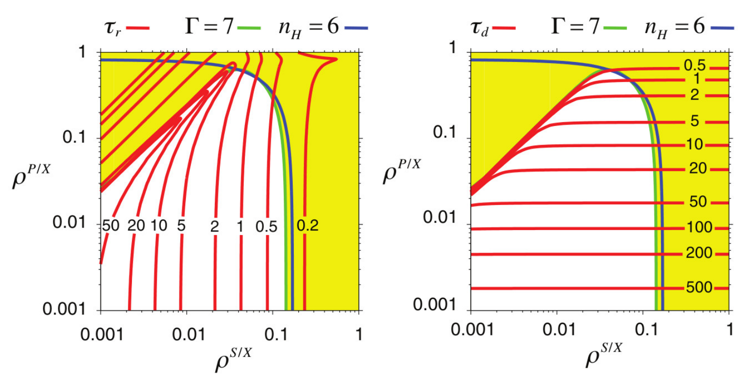
$$\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} = a_X^*[X^*][P_X] - (k_X^* + d_X^*)[X^*:P_X]$$

$$[X]_{\mathrm{tot}} = [X] + [X^*] + [X:S^*] + [X^*:P_X]$$

$$[S]_{\mathrm{tot}} = [S] + [S^*] + [X:S^*]$$

$$[P_X]_{\mathrm{tot}} = [P_X] + [X^*:P_X]$$

Can a simple covalent modification cycle feature both a high gain and switch-like activation in a wide operating window?



Trends in Computational Systems Biology

The second wave of synthetic biology: from modules to systems

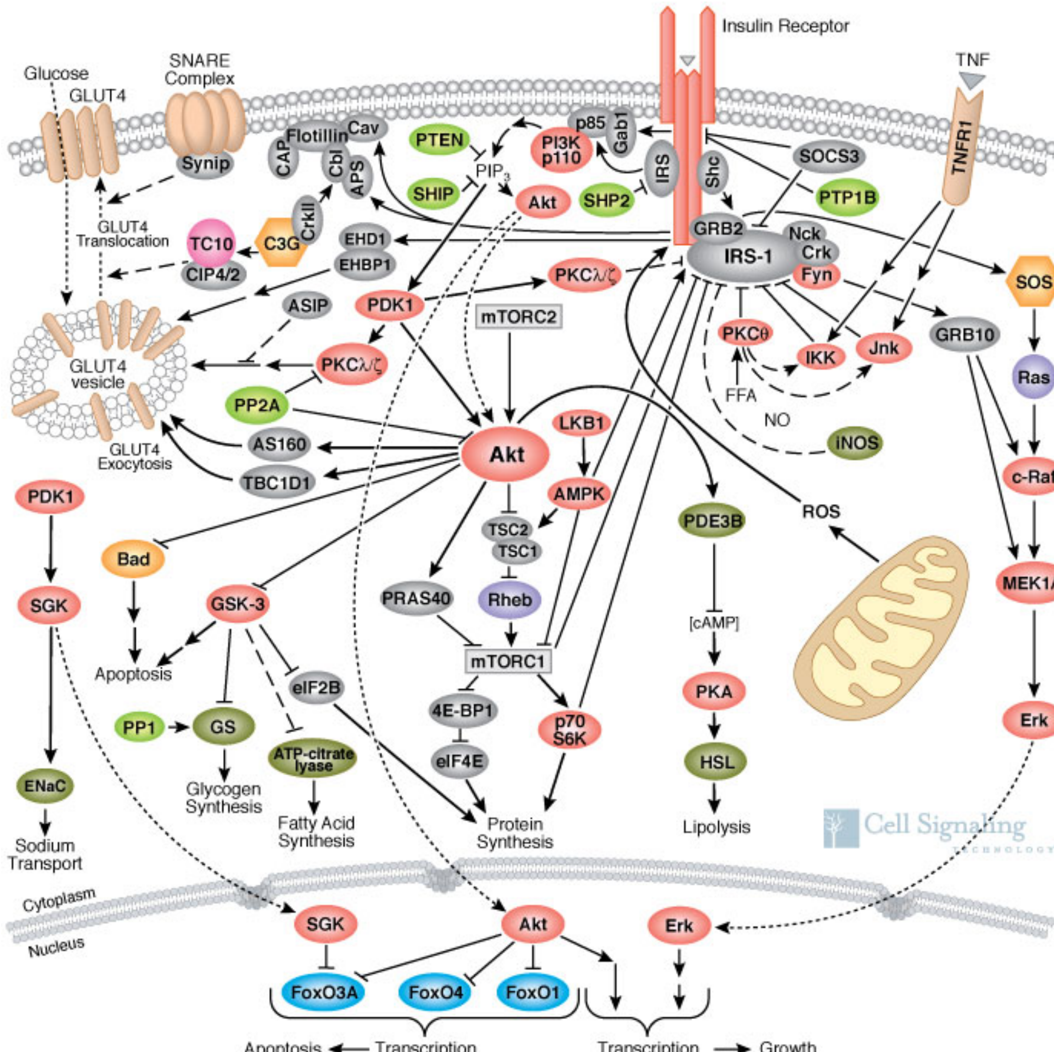
Priscilla E. M. Purnick and Ron Weiss

Abstract | Synthetic biology is a research field that combines the investigative nature of biology with the constructive nature of engineering. Efforts in synthetic biology have largely focused on the creation and perfection of genetic devices and small modules that are constructed from these devices. But to view cells as true 'programmable' entities, it is now essential to develop effective strategies for assembling devices and modules into intricate, customizable larger scale systems. The ability to create such systems will result in innovative approaches to a wide range of applications, such as bioremediation, sustainable energy production and biomedical therapies.

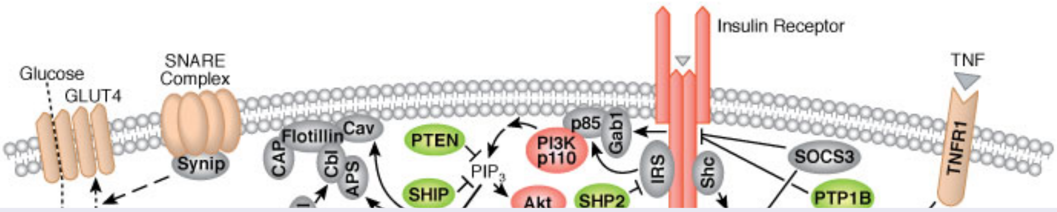
410 | JUNE 2009 | VOLUME 10 **www.nature.com/reviews/molcellbio**

- First Wave – Development and understanding of basic elements and modules
- Second Wave – Integration of basic elements and modules to create system-level circuitry

A More Complex Signaling Pathway



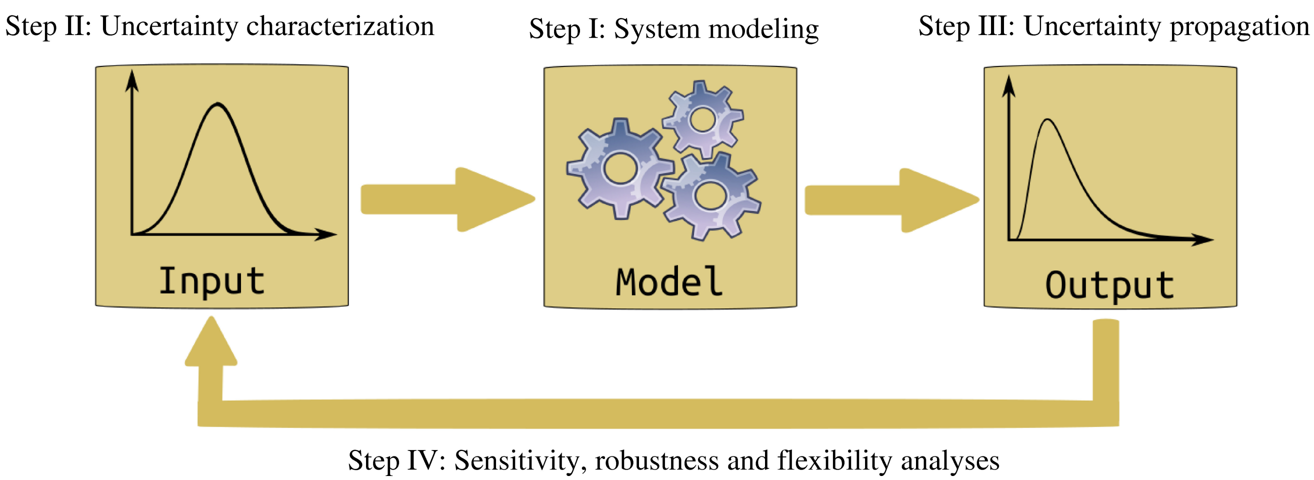
A More Complex Signaling Pathway



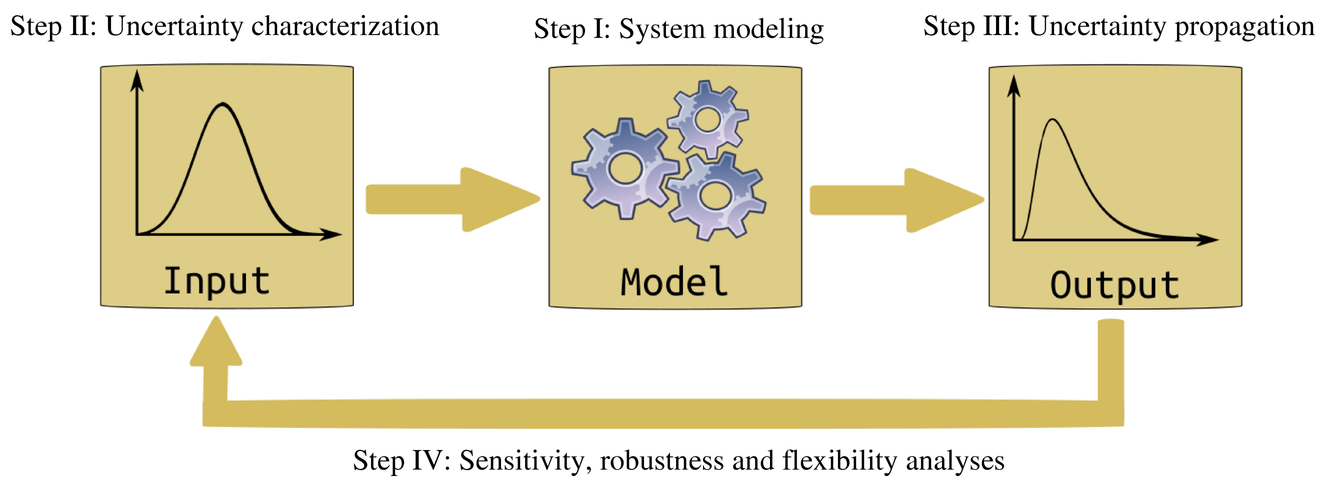
How might we use PSE methods and tools to:

- Characterize the stability, oscillations, and other dynamical properties of such complex systems
- Control these cellular systems through drugs or genetic modifications
- Develop models with suitable algebraic forms for the reactions and values for the kinetic parameters
- Estimate time-varying internal states, such as the concentrations of proteins and other chemical substances, from input/output experiments
- ...

Workflow

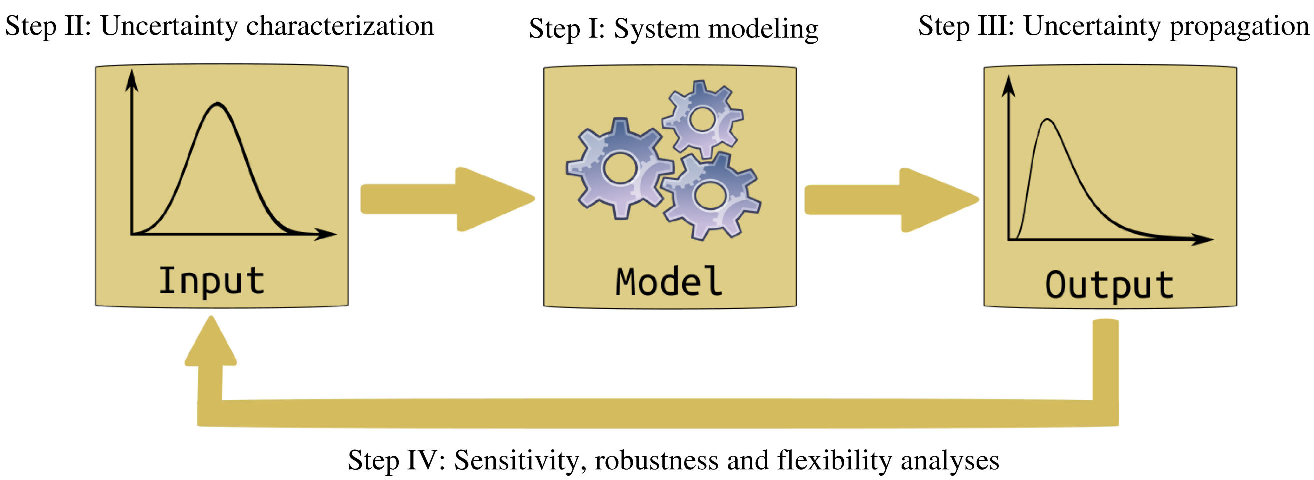

Step II: Uncertainty characterization
Step I: System modeling
Step III: Uncertainty propagation
Input
Model
Output
Step IV: Sensitivity, robustness and flexibility analyses

Workflow



1. **Prediction of Uncertainty:**
   Characterizing the uncertainty under which a system must be resilient
   - external perturbations; uncertain measurement data
   - structural / parametric modeling uncertainties

Workflow



1. **Prediction of Uncertainty:**
   Characterizing the uncertainty under which a system must be resilient
   - external perturbations; uncertain measurement data
   - structural / parametric modeling uncertainties
2. **Exploitation of Uncertainty:**
   Applying methods and tools for design and analysis of resilient systems
   - uncertainty quantification; robust design; flexibility analysis; *etc*

Uncertainty Descriptions: The Role of Data

Extreme Variability of Data across the Process and Biotechnology Industries

"Big" data	$\overset{vs.}{\longleftrightarrow}$	Scarce data
Quantitative data	$\longleftrightarrow$	Qualitative data and expert knowledge
Precise data	$\longleftrightarrow$	Noisy data

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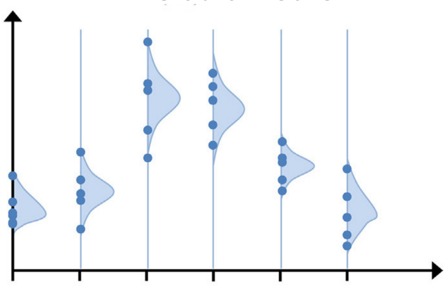
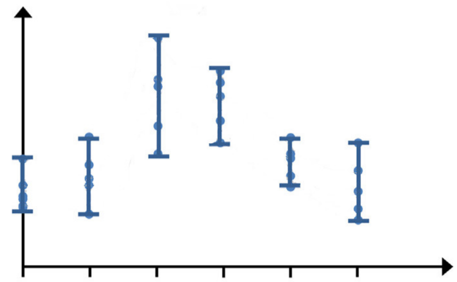
Two Main Paradigms for Uncertainty Description in Model Development:

Probabilistic



Set-membership



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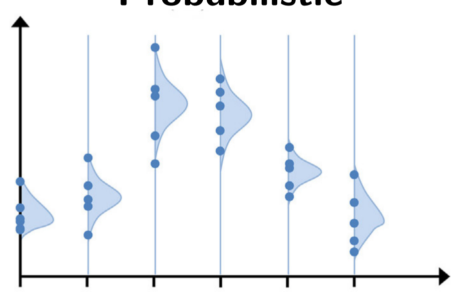

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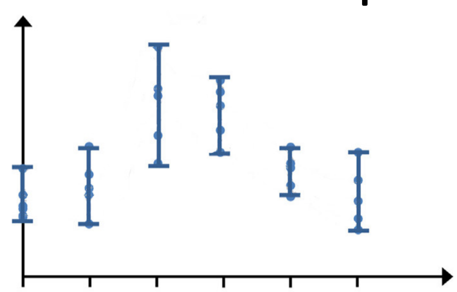


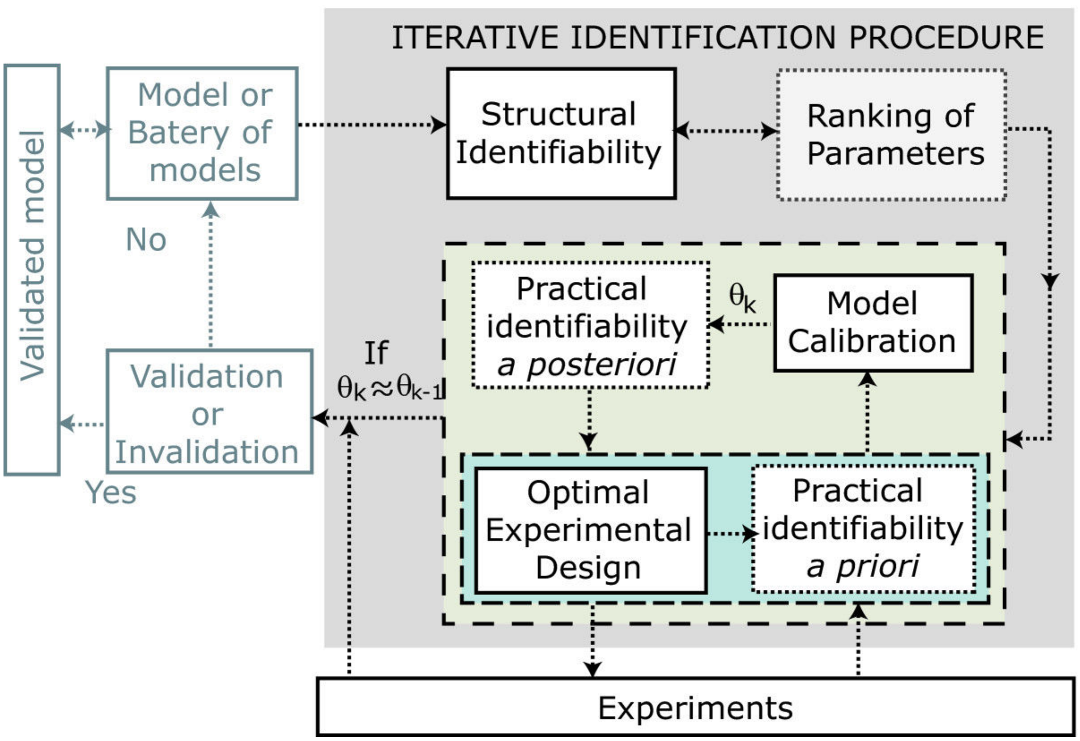
Frequentist inference
Determine a fixed value for the parameters

Bayesian inference
Determine a probability distribution for the parameters

Set-membership inference
Determine a range of consistent parameter values

Classical Model Development Framework: Frequentism

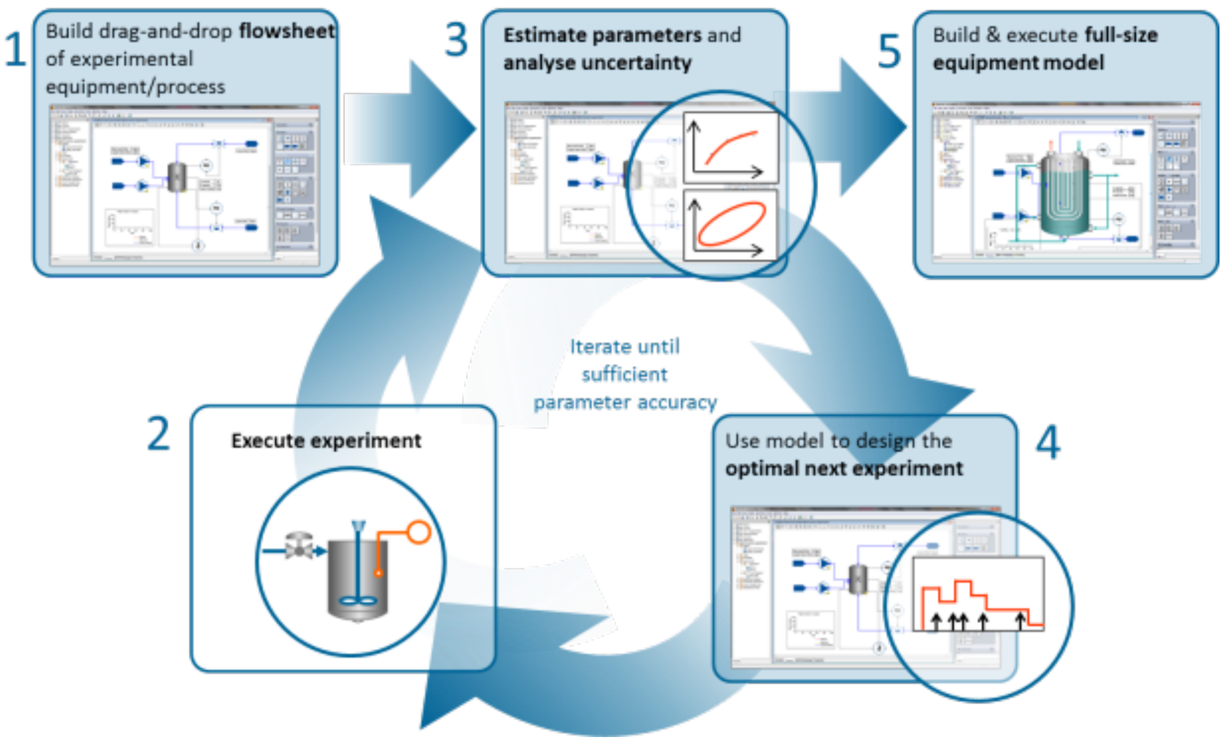
How to best use data to validate or invalidate a mathematical model?



[Balsa-Canto et al., *BMC Systems Biology*, 2010]

Classical Model Development Framework: Frequentism

Also implemented in commercial process simulators like gPROMS



[source: https://www.psenterprise.com/concepts/mbe]

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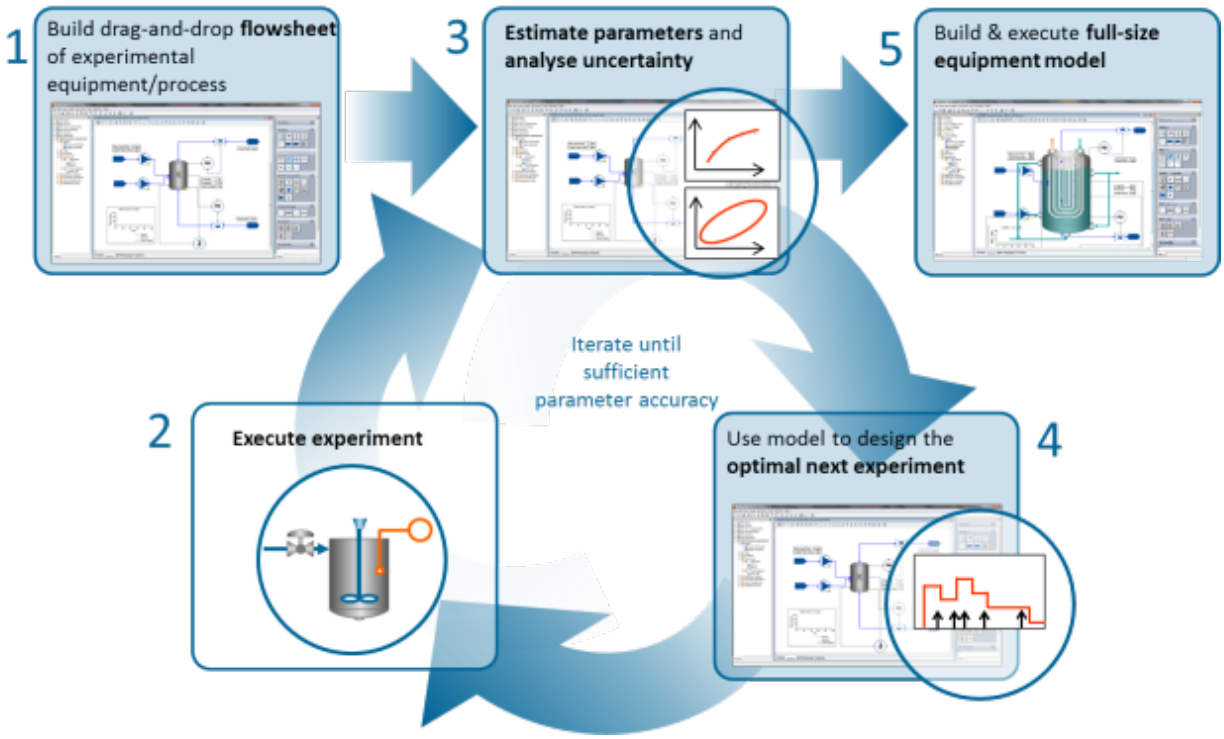

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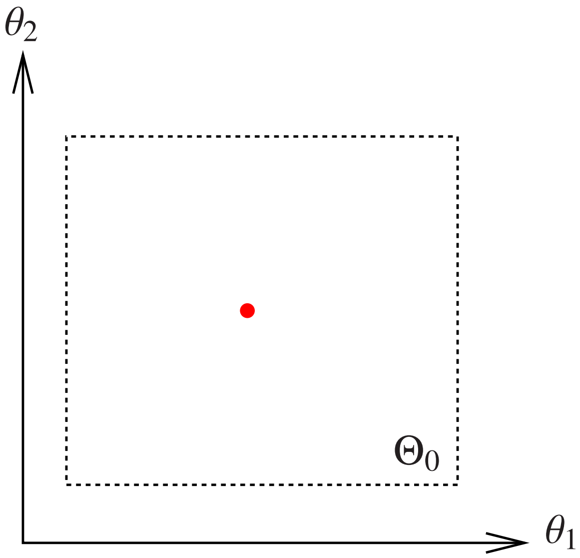
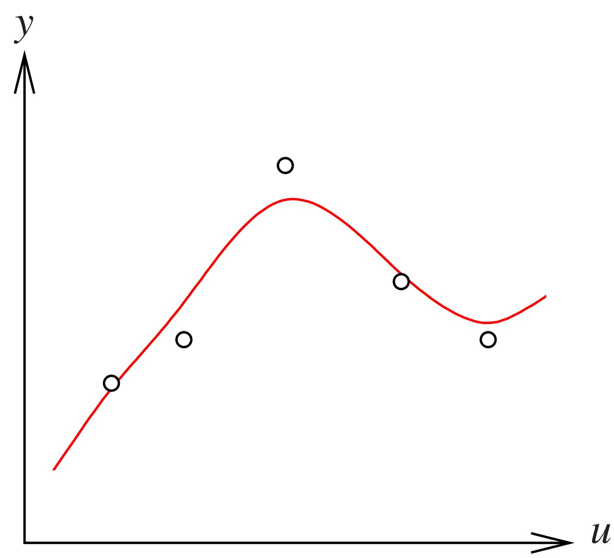
↳ Is frequentism appropriate for model development and validation?

Review of Frequentist Inference

- **Step 1:** Formulate and solve a regression problem

$$\hat{\boldsymbol{\theta}} \in \arg\max \mathcal{L}(\boldsymbol{\theta}|\mathbf{u}^{\mathrm{m}}, \mathbf{y}^{\mathrm{m}})$$

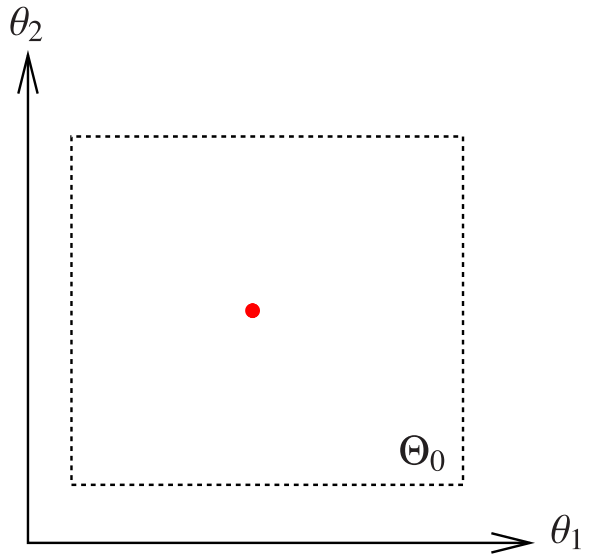


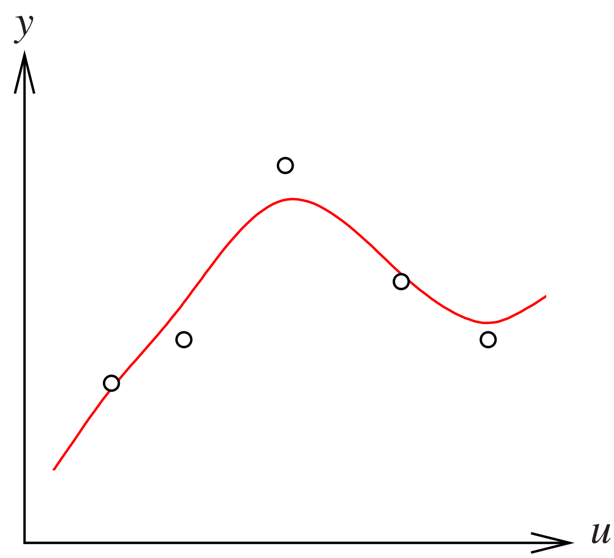


Review of Frequentist Inference

- **Step 1:** Formulate and solve a regression problem; e.g., ℓ_2 regression

$$\hat{\boldsymbol{\theta}} \in \arg\min \sum_{k=1}^{n_m} \left(\sum_{i=1}^{n_u} \frac{\left(u_{k,i} - u_{k,i}^{\mathrm{m}}\right)^2}{\sigma_{u_k,i}^2} + \sum_{i=1}^{n_y} \frac{\left(y_i(t_k, \mathbf{u}_k, \boldsymbol{\theta}) - y_{k,i}^{\mathrm{m}}\right)^2}{\sigma_{y_k,i}^2} \right)$$





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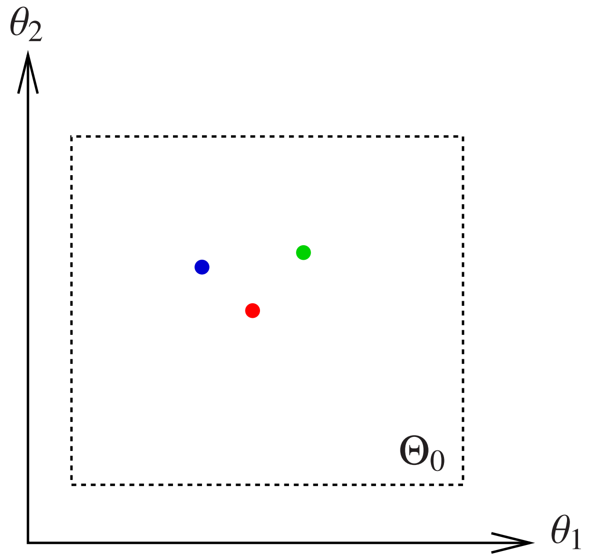
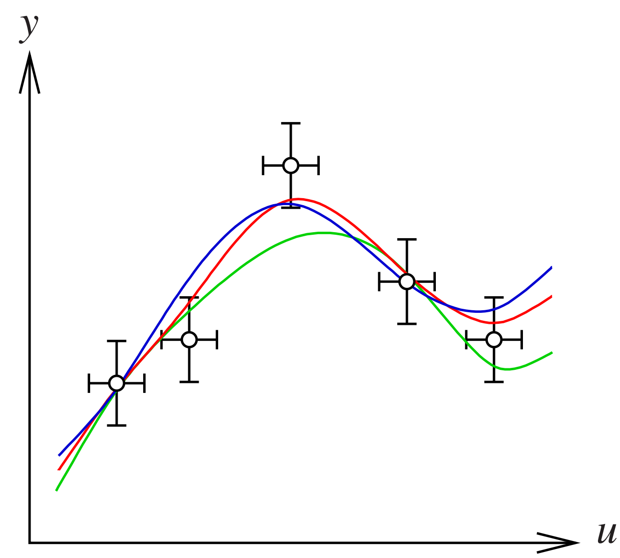
- **Step 2:** Construct (frequentist) confidence regions





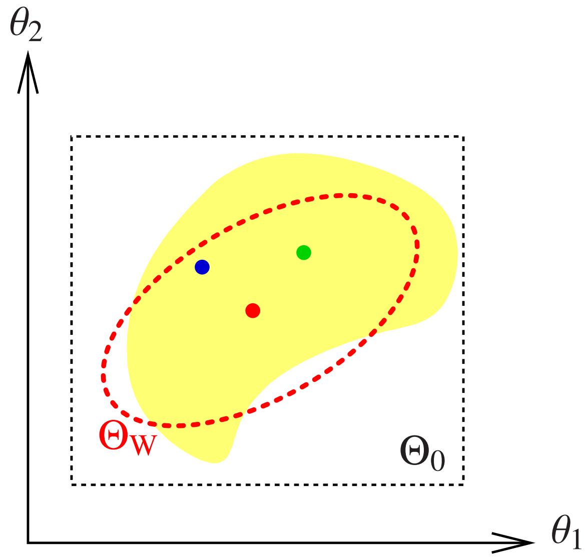
Review of Frequentist Inference

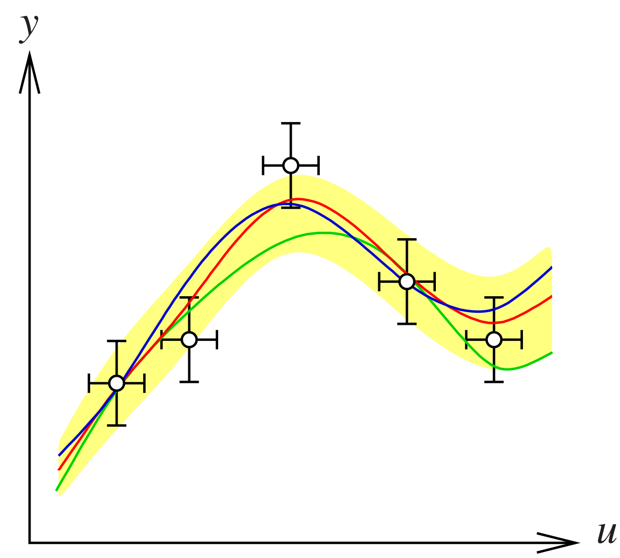
- **Step 1:** Formulate and solve a regression problem; e.g., ℓ_2 regression

$$\hat{\boldsymbol{\theta}} \in \arg\min \sum_{k=1}^{n_m} \left(\sum_{i=1}^{n_u} \frac{\left(u_{k,i} - u_{k,i}^{\mathrm{m}}\right)^2}{\sigma_{u_k,i}^2} + \sum_{i=1}^{n_y} \frac{\left(y_i(t_k, \mathbf{u}_k, \boldsymbol{\theta}) - y_{k,i}^{\mathrm{m}}\right)^2}{\sigma_{y_k,i}^2} \right)$$

- **Step 2:** Construct (frequentist) confidence regions

$$\Theta_{\mathrm{W}} := \left\{ \boldsymbol{\theta} \in \Theta_0 \;\middle|\; \left(\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}\right)^{\mathsf{T}} \mathbf{V}_{\hat{\boldsymbol{\theta}}}^{-1} \left(\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}\right) \leq \chi_{n_\theta}^2(1-\alpha) \right\}$$





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\+ Approach may be applied to very large-scale models

But...

— Solution of the regression problem needs global optimization

— Construction of inference regions assumes mismatch due to (Gaussian) measurement noise only – no structural mismatch

— Wald regions assume unimodality – nonlinear inference regions (likelihood-ratio test) are much harder to describe

— Confidence regions often confused with parameter regions including $(1-\alpha)\%$ of the probability distribution

Review of Bayesian Inference

Construct a posterior distribution of the parameters, based on:
(i) a likelihood function; (ii) a prior distribution; and (iii) available observations

$$\pi(\boldsymbol{\theta}|\mathbf{u}^{\mathrm{m}}, \mathbf{y}^{\mathrm{m}}) \;\propto\; \mathcal{L}(\boldsymbol{\theta}|\mathbf{u}^{\mathrm{m}}, \mathbf{y}^{\mathrm{m}})\; \pi(\boldsymbol{\theta})$$

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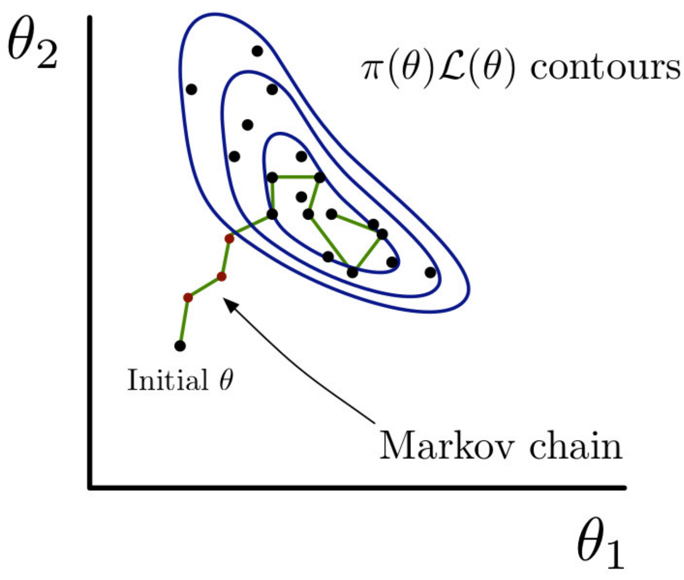
- **Step 1:** Generate samples from the (conditional) joint posterior distribution



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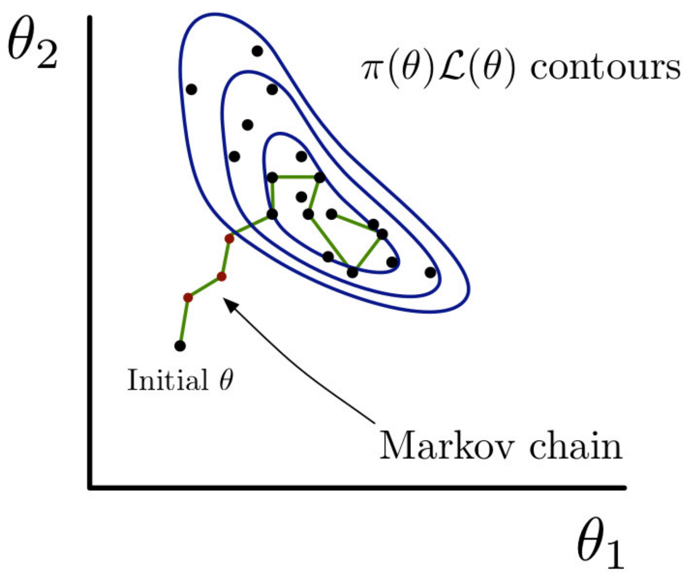
- **Step 1:** Generate samples from the (conditional) joint posterior distribution
- **Step 2:** (Re)construct highest posterior density (HPD) credibility regions

$$\Theta_{\mathrm{B}} := \{\boldsymbol{\theta} \,|\, \pi(\boldsymbol{\theta}|\mathbf{u}^{\mathrm{m}}, \mathbf{y}^{\mathrm{m}}) \geq \pi_\alpha\} \quad \text{such that} \quad \int_{\Theta_{\mathrm{B}}} \pi(\boldsymbol{\theta}|\mathbf{u}^{\mathrm{m}}, \mathbf{y}^{\mathrm{m}})\, d\boldsymbol{\theta} = 1 - \alpha$$



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+ Impressive developments by the Machine Learning community: MCMC algorithms (Metropolis-Hasting, nested sampling, affine-invariant stretch move, *etc.*)

But...

– Difficulty dealing with problems having $\geq$ 10 parameters in general

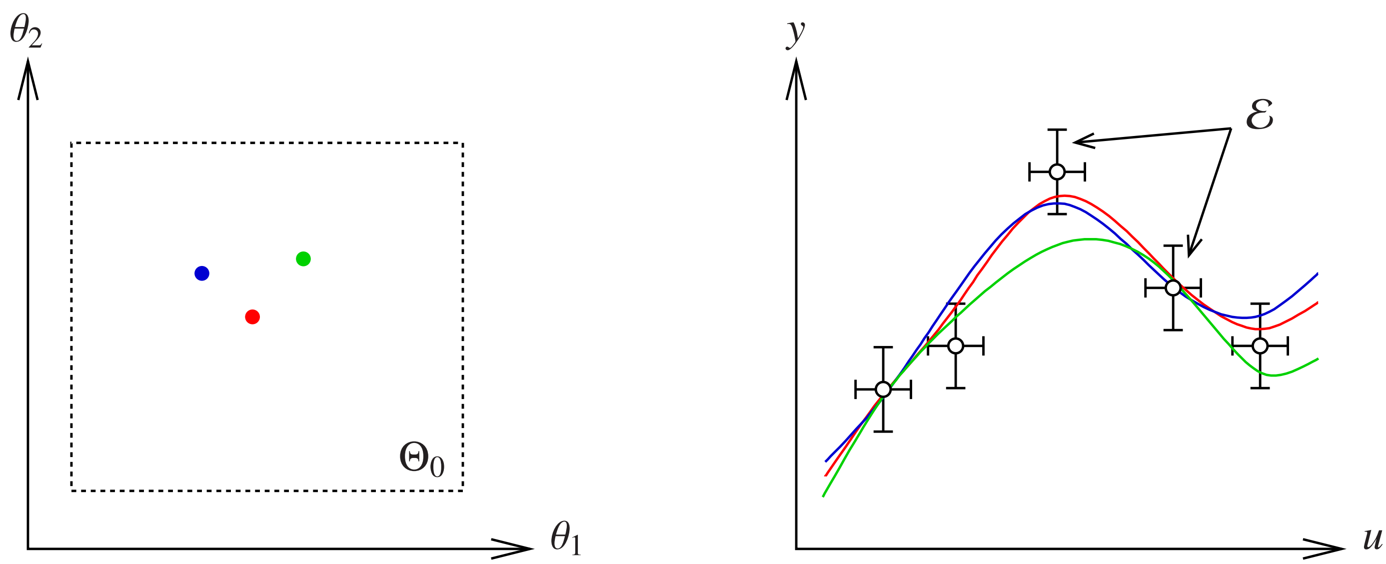
– Difficulty dealing with multimodal posteriors

– MCMC algorithms need (sometimes many) tuning parameters (rejection test, burning length, *etc.*) – Need for the chains to converge to their equilibrium distributions

Review of Set-Membership Inference

- Determine a parameter region such that the model predictions are consistent with the measurements within a given error set $\mathcal{E}$:

$$\Theta_{\mathrm{G}} := \left\{ \boldsymbol{\theta} \in \Theta_0 \;\middle|\; \begin{array}{l} \exists \mathbf{u}_1, \ldots, \mathbf{u}_{n_m} : \\ [\;\ldots\; \mathbf{u}_k - \mathbf{u}_k^{\mathrm{m}},\; \mathbf{y}(t_k, \mathbf{u}_k, \boldsymbol{\theta}) - \mathbf{y}_k^{\mathrm{m}} \;\ldots\;] \in \mathcal{E} \end{array} \right\}$$



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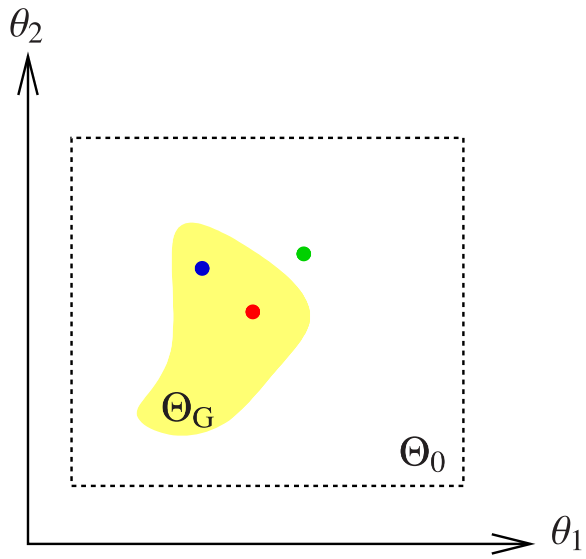

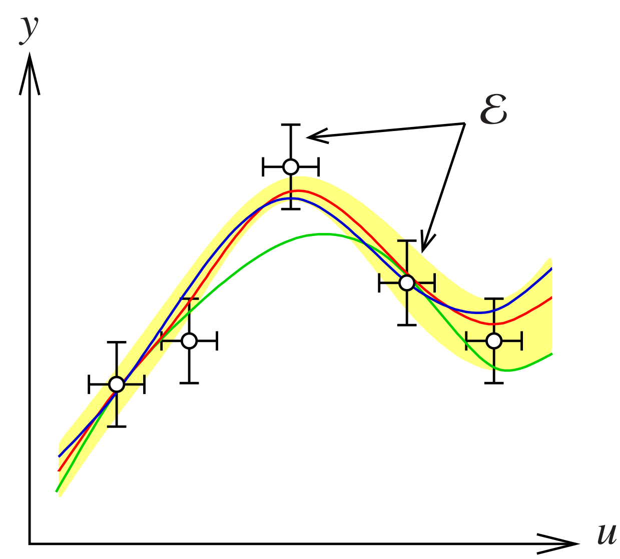

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+ Natural approach when lacking information about the measurement error
+ Approach may also provide certificates for invalidating candidate models

But...

– Difficulty dealing with problems having $\geq$ 10 parameters in general
– Current algorithms rely on complete search methods (branch-and-prune)
– Parameter region very sensitive to measurement noise – risk of false conclusions

Challenges in Model-Based Inference

Various approaches developed / promoted by different communities:

	Frequentist	Bayesian	Set-membership
stochastic search	✓	✓	**?**
complete search	✓	**?**	✓

↳ Can Bayesian and set-membership estimation efficiently handle larger-scale problems? Multimodal estimation problems?

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New approaches combining existing inference frameworks

- E.g., set-membership regression approach:

$$\Theta_{\rm R} := \left\{ \boldsymbol{\theta}^* \in \Theta_0 \;\middle|\; \begin{array}{l} \exists \mathbf{e} \in \mathcal{E} : \\ \boldsymbol{\theta}^* \in \arg\max \mathcal{L}(\boldsymbol{\theta} | \mathbf{y}^{\rm m}, \mathbf{e}) \end{array} \right\}$$

[Perić et al., *J Proc Cont*, 2018]

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[Perić et al., *J Proc Cont*, 2018]

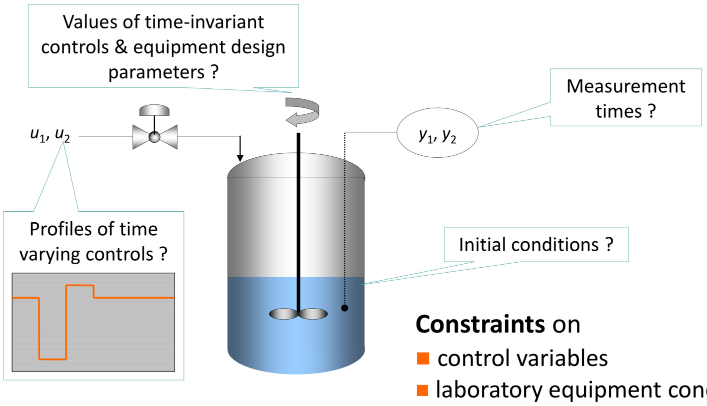
New approaches taking advantage of multiple information sources – "Big Data":

- Fuse quantitative data with qualitative data and expert opinions
- Handle a very large volume of data

Challenges in Model-Based Inference

Design an experiment to:

- ↳ Improve parameter confidence
- ↳ Discriminate model structures
- ↳ Improve information content
- ↳ …



Constraints on
- control variables
- laboratory equipment conditions

Challenges in Model-Based Inference

Design an experiment to:

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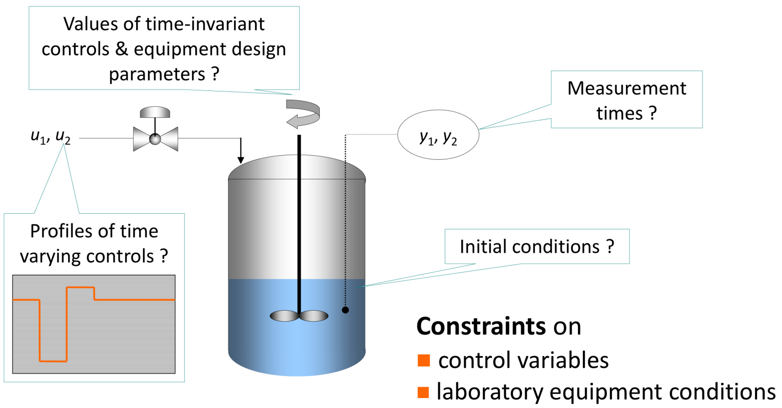
↳ Discriminate model structures

↳ Improve information content

↳ ...



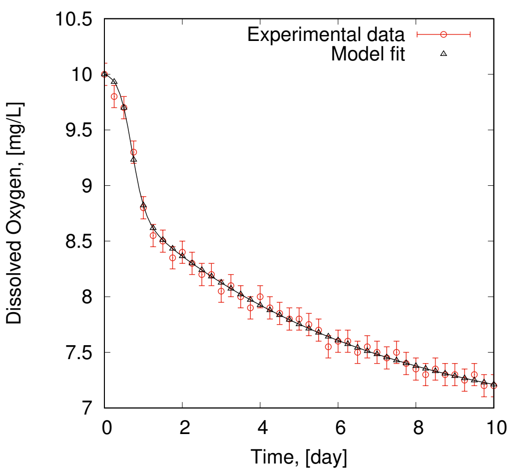
Challenges:

- Optimal experiment design problems are notoriously hard to solve – complex, typically nonconvex, objectives
- "Chicken-and-egg" problem: model-based inference using an inaccurate model!
  ↳ Need for robust optimal design of experiments
- Bayesian and set-membership approaches to experiment design
  ↳ Will these approaches ever be able to handle large-scale problems?

Example: BOD Abatement

$$\dot{B}(t) = \mu S(t)B(t) - \beta B(t)$$
$$\dot{S}(t) = -\frac{\mu}{Y}S(t)B(t) + f\beta B(t)$$
$$\dot{D}(t) = -\frac{1-Y}{Y}\mu S(t)B(t)$$

- $S(0) = 4$ mg/L, $D(0) = 10$ mg/L
- Constant $Y = 0.67$ and $f = 0.9$
- Estimated μ, β, and $B(0)$



Model Parameters

- Probability of parameter lying between (Final Value -α% Confidence Interval) and (Final Value +α% Confidence Interval) = α%
- The t-value shows the percentage accuracy of the estimated parameters, with respect to the 95% confidence intervals.

Model Parameter		Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval 90%	95%	99%	95% t-value	Standard Deviation
bod_test.b		0.407326	0.300000	0.00000	1.00000	0.0245700	0.0295000	0.0395200	13.81	0.0145700
bod_test.m		1.56126	2.00000	0.00000	4.00000	0.553100	0.664000	0.889500	2.351	0.328000
bod_test.X0	[mg/L]	0.0405593	0.100000	0.000100000	1.00000	0.0652400	0.0783200	0.104900	0.5179 **	0.0386900
								Reference t-value (95%):	1.68604	

Click here to use above final values in future calculations

** an individual 95% t-value smaller than the reference t-value indicates that the available data from these experiments may not be sufficient to estimate the parameter precisely

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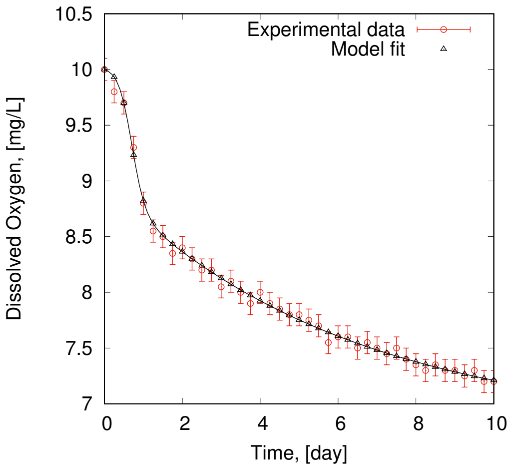
Design one extra experiment for a more precise parameter estimation. Consider the same (unknown) biomass inoculum $B(0)$ in the flask and the same sensor; and optimize the concentration of the sample $S(0) \in [2, 6]$ mg/L, the duration of the experiment in $[1, 4]$ days, and the measurement times with $\Delta t_k \geq 30$ min



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Example: BOD Abatement

Initialization: 2-day horizon, with 20 equidistant measurement times

Model Parameters

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bod_test. b		0.407326	0.407326	0.0217100	0.0260000	0.0346000	15.66	0.0129900
bod_test. m		1.56126	1.56126	0.155100	0.185700	0.247100	8.407	0.0927900
bod_test. X0	[mg/L]	0.0405593	0.0405593	0.0195900	0.0234600	0.0312200	1.729	0.0117200

Reference t-value (95%): 1.6714

Experiment: extra (designed)

Duration

	Final Value	Initial Guess	Lower Bound Value	Lower Bound Lagrange Multiplier	Upper Bound Value	Upper Bound Lagrange Multiplier
	1.53616	2.00000	1.00000	0	4.00000	0

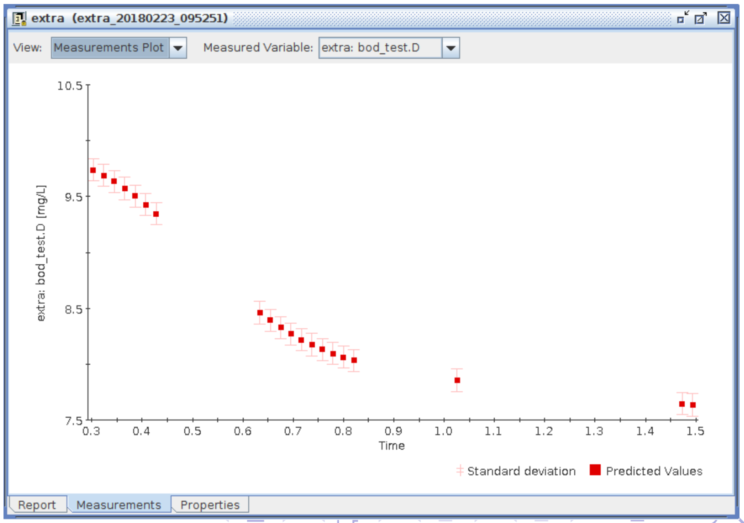
Initial Conditions

Name	Final Value	Initial Guess	Lower Bound Value	Lower Bound Lagrange Multiplier	Upper Bound Value	Upper Bound Lagrange Multiplier
bod_test.D [mg/L]	10.0000	10.0000	10.0000 *	-1×10^{30}	10.0000 *	1×10^{30}
bod_test.S [mg/L]	6.00000	4.00000	2.00000	0	6.00000 *	0.006467

Control Intervals

Name	Final Value	Initial Guess	Lower Bound Value	Lower Bound Lagrange Multiplier	Upper Bound Value	Upper Bound Lagrange Multiplier
Interval # 1	1.53616	0.00000	1.00000	0	4.00000	0

* active bound



Example: BOD Abatement

Initialization: 1-day horizon, with 20 equidistant measurement times

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bod_test.D [mg/L]	10.0000	10.0000	10.0000 *	-1×10^{30}	10.0000 *	1×10^{30}
bod_test.S [mg/L]	6.00000	4.00000	2.00000	0	6.00000	0

Control Intervals

Name	Final Value	Initial Guess	Lower Bound Value	Lower Bound Lagrange Multiplier	Upper Bound Value	Upper Bound Lagrange Multiplier
Interval # 1	4.00000	0.00000	1.00000	0	4.00000	0

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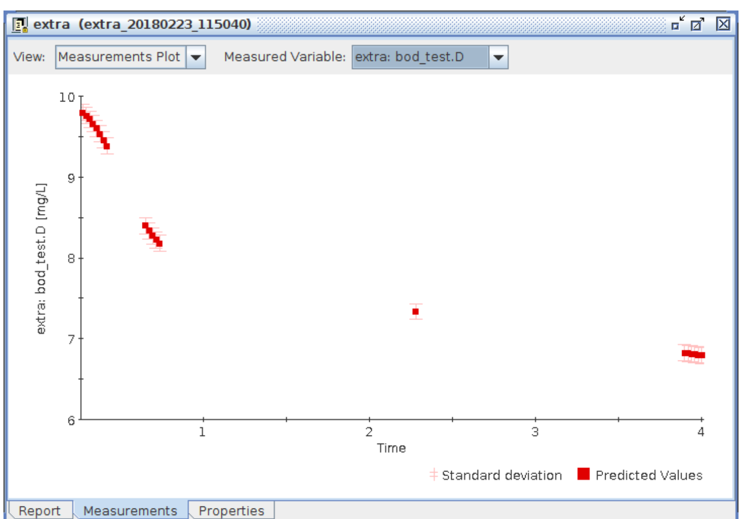
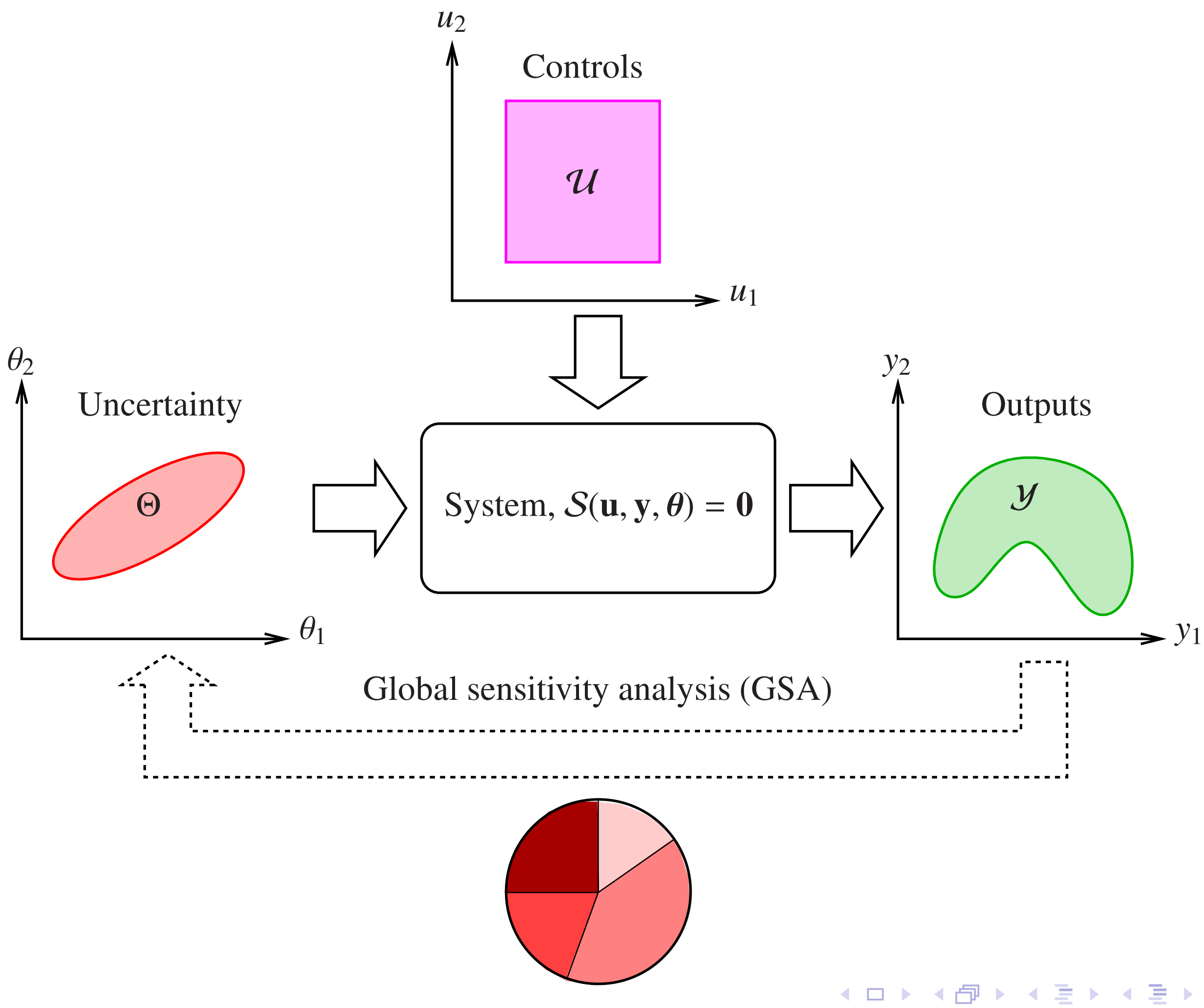
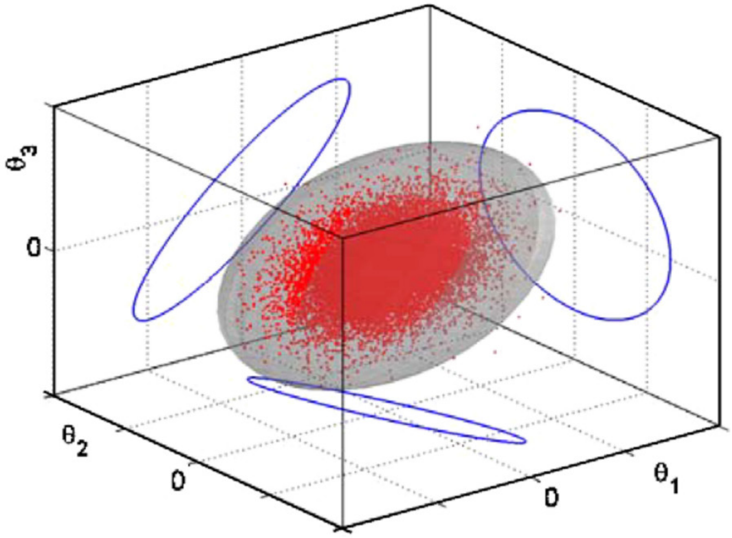


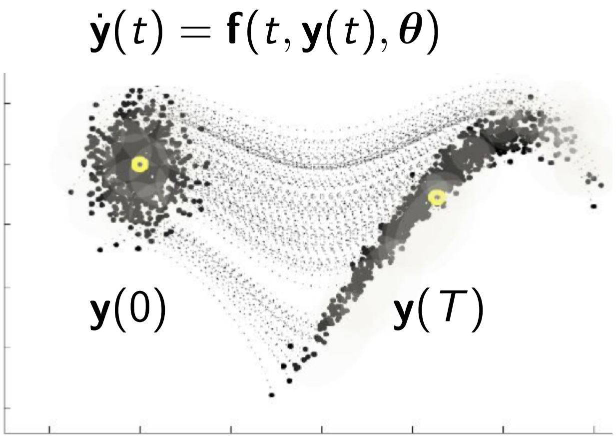
(Forward) Uncertainty Propagation



Review of Uncertain Dynamic Systems

Classical Monte Carlo Approach:





- Inner-approximation of reachable set
- Approximation of state joint probability distribution

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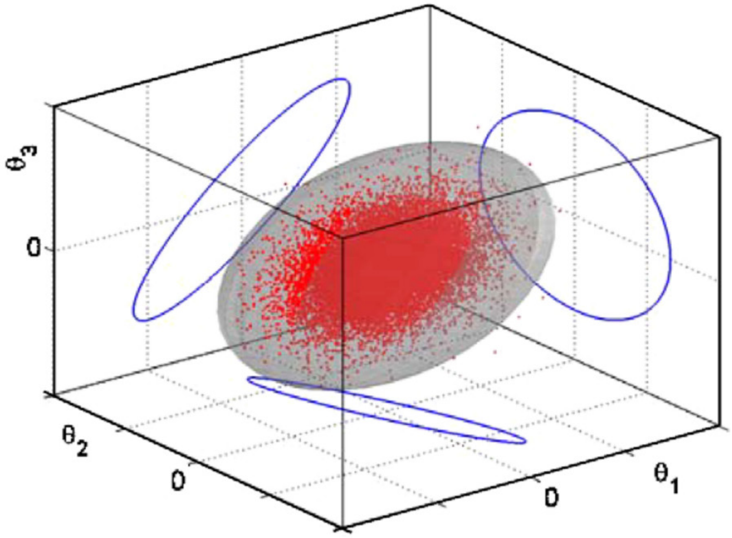

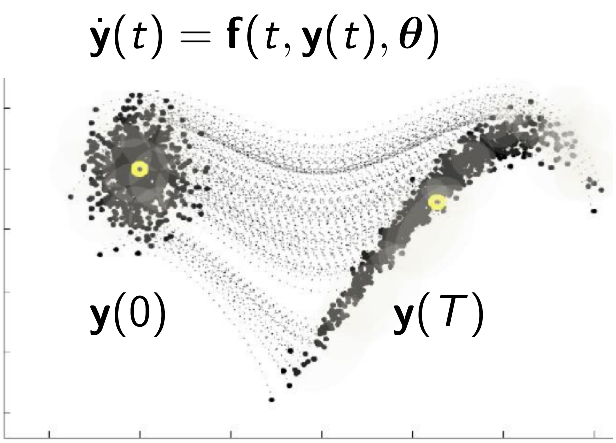

- Inner-approximation of reachable set
- Approximation of state joint probability distribution

+ Non-intrusive approach, readily implemented and parallelizable

− Slow convergence, accuracy $\propto N^{-\frac{1}{2}}$
(quasi-random low-discrepancy sequences $\propto N^{-1}$; importance sampling; *etc*)

Review of Uncertain Dynamic Systems

Spectral Approach:

Approximate functional dependence of outputs $\mathbf{y}(t,\cdot)$ w.r.t. random parameters $\boldsymbol{\theta}$

Set-Based Approach:

Enclose all possible outputs $\mathbf{y}(t,\cdot)$ w.r.t. parameter bounds $\boldsymbol{\theta} \in \Theta$

Review of Uncertain Dynamic Systems

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Polynomial chaos (PC) expansion:

$$\mathbf{y}(t,\boldsymbol{\theta}) \approx \sum_k \boldsymbol{\xi}_k(t)\phi_j(\boldsymbol{\theta})$$

Set-Based Approach:

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$$\mathbf{y}(t,\boldsymbol{\theta}) \in \left\{ \sum_k \boldsymbol{\xi}_k(t)\phi_j(\boldsymbol{\theta}) \right\} \oplus \mathbf{r}(t)$$

↳ Both approaches entail the construction of (polynomial) surrogates

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Determine coefficients $\boldsymbol{\xi}$ using Galerkin scheme (intrusive); stochastic colloc., projection, or regression (non-intrusive)

Propagate reachable-set parameterization $\boldsymbol{\xi}$ through continuous-time or discretized ODEs (intrusive)

↳ Both approaches handle small parameter dimensions only

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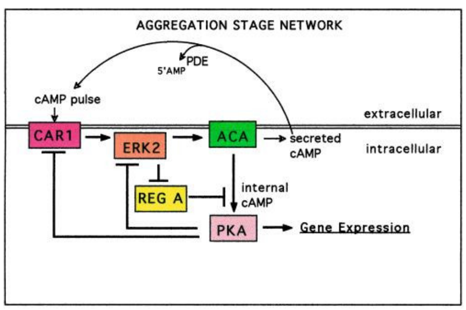
Accuracy can degrade along time

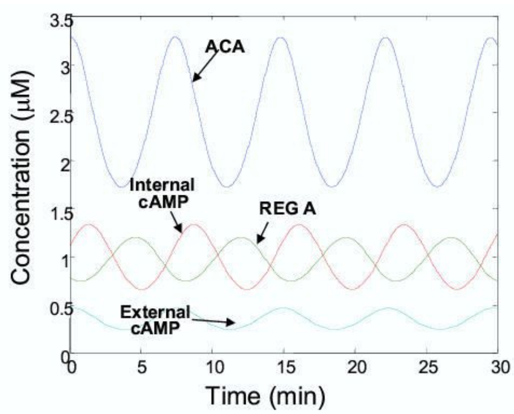
Bounds can explode in finite time

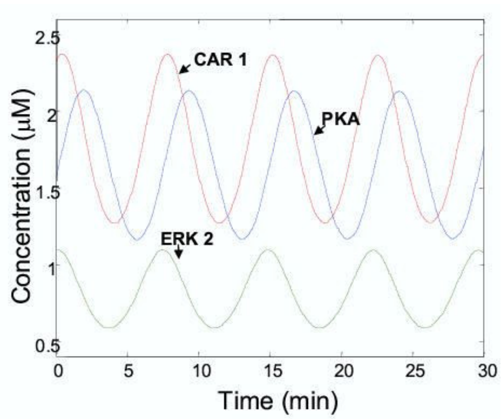
Example: cAMP Oscillations

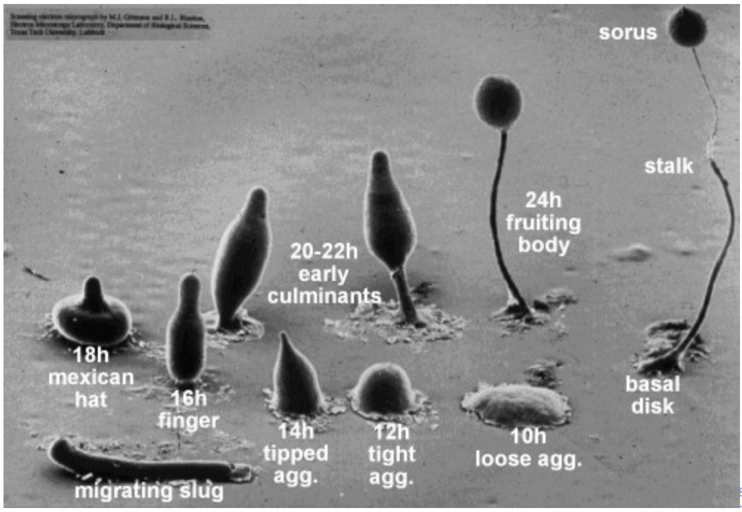
Oscillations in cAMP observed during the early development of *D. discoideum*



[Laub & Loomis, *Mol Biol Cell*, 1998]

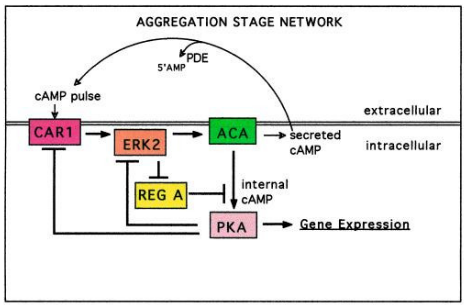






Example: cAMP Oscillations

Oscillations in cAMP observed during the early development of *D. discoideum*



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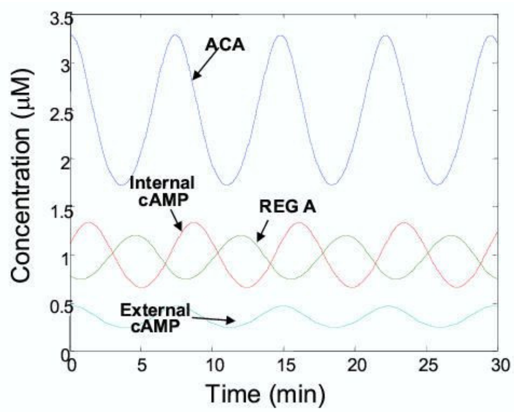

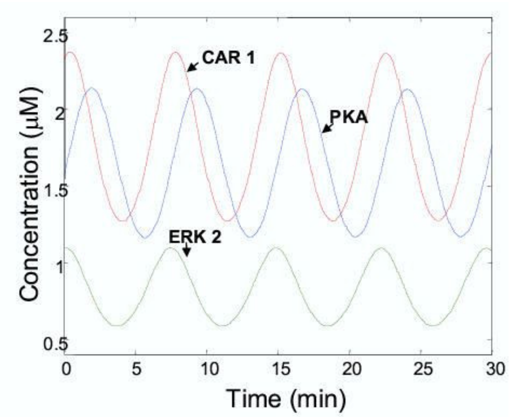

$$\dot{x}(t) = \begin{bmatrix} k_1 x_7(t) - k_2 x_1(t) x_2(t) \\ k_3 x_5(t) - k_4 x_2(t) \\ k_5 x_7(t) - k_6 x_2(t) x_3(t) \\ k_7 - k_8 x_3(t) x_4(t) \\ k_9 x_1(t) - k_{10} x_4(t) x_5(t) \\ k_{11} x_1(t) - k_{12} x_6(t) \\ k_{13} x_6(t) - k_{14} x_7(t) \end{bmatrix}$$

- 14 kinetic rate constants, k_i
- 7 states,
  $x_1 = [\text{ACA}]$,
  $x_2 = [\text{PKA}]$,
  $x_3 = [\text{ERK2}]$,
  $x_4 = [\text{REGA}]$,
  $x_5 = [\text{Internal cAMP}]$,
  $x_6 = [\text{External cAMP}]$,
  $x_7 = [\text{CAR1}]$

Example: cAMP Oscillations

- Single uncertain parameter $k_6 \in 0.8 \pm 0.1$
- Set-propagation using a Chebyshev polynomial approximant and an ellipsoidal remainder bound

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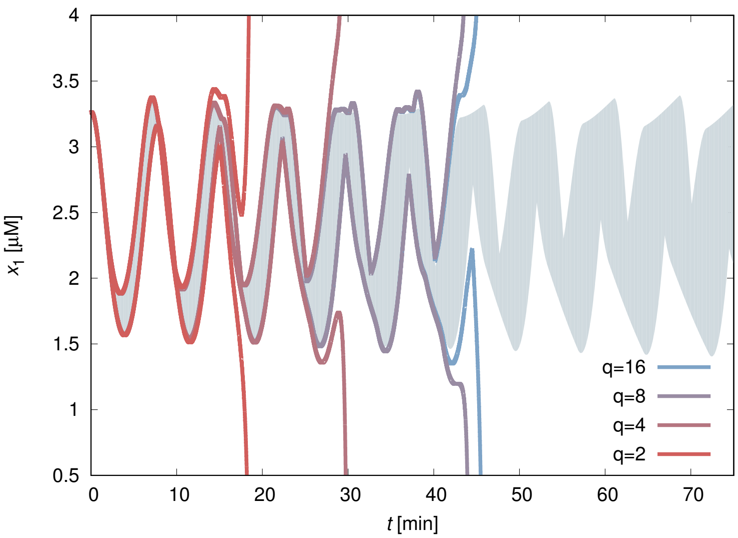

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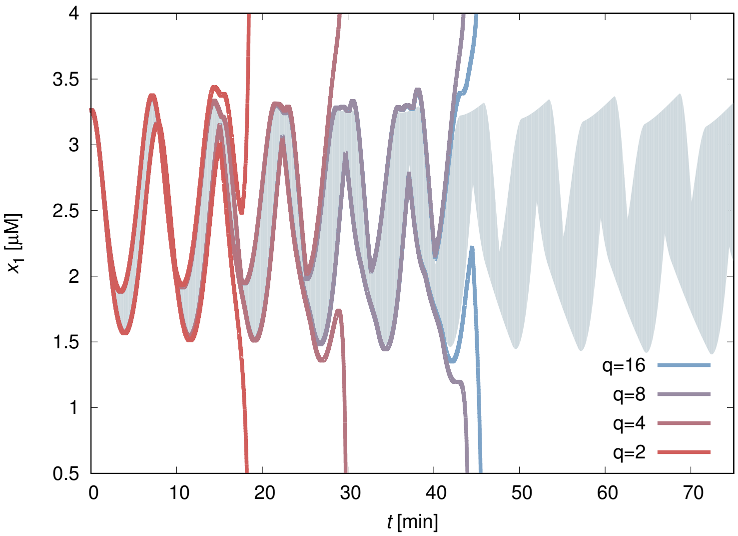

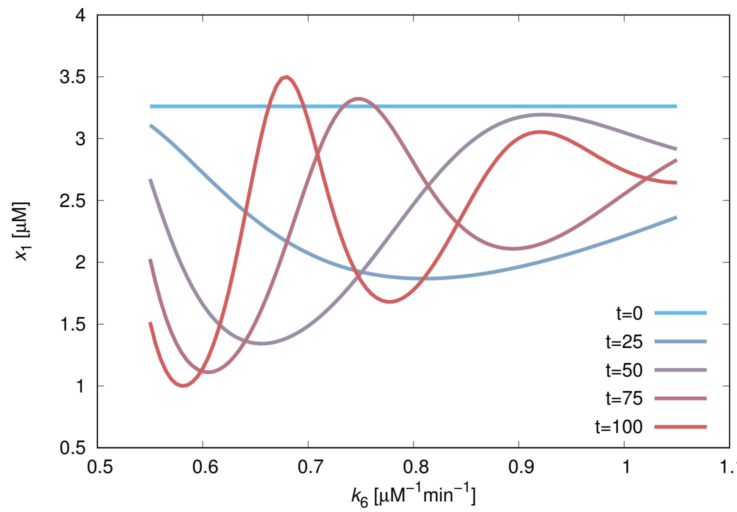

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↳ State dependence in parameter increasingly nonlinear as time increases

Example: cAMP Oscillations

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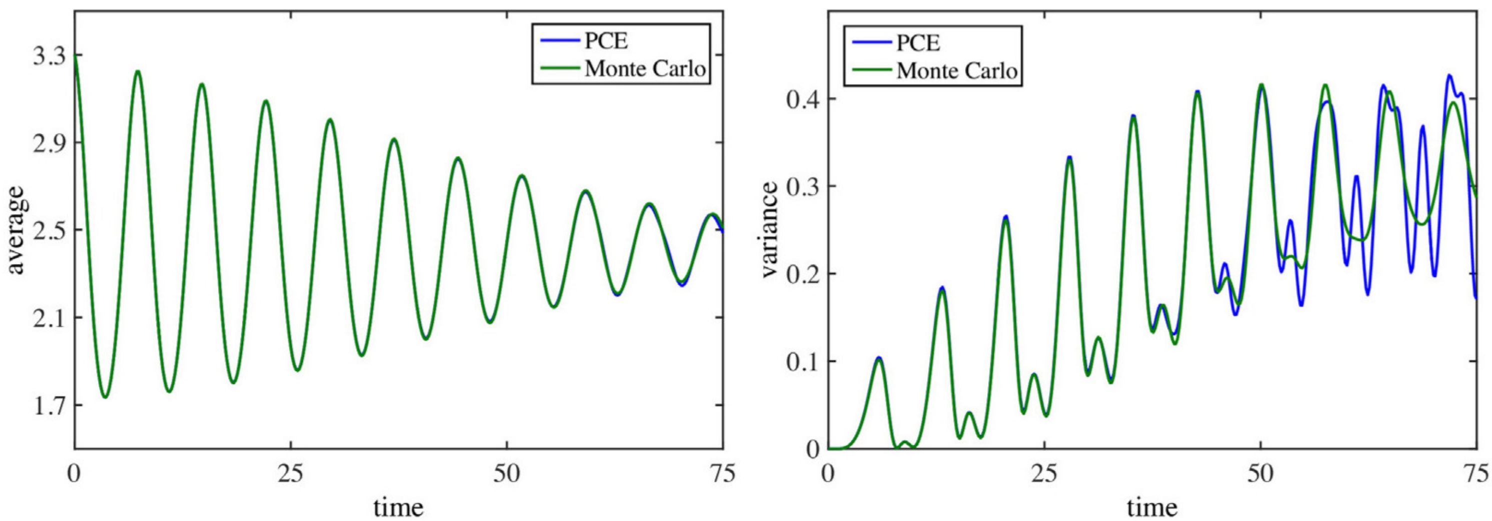

[Streif *et al.*, *J Proc Cont*, 2016]

↳ PCE is in agreement with Monte Carlo on short horizons

↳ Large discrepancy in variance predictions for $t > 50$

Challenges in Uncertain Dynamic Systems

	Sampling	Spectral	Set-based
non-intrusive	✓	✓	**?**
intrusive		✓	✓

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Improve Existing Methods

- Solve faster / more accurately by exploiting structure (e.g., sparsity, simplifications) and properties (e.g., periodicity)
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Develop New Methods

- Exploit underlying theories (e.g., Kolmogorov equations, Hamilton-Jacobi-Isaacs equations)
- Combine non-intrusive approaches synergistically (e.g., PC-Kriging)
- Combine non-intrusive approaches (black-box components) with intrusive approaches (glass-box components)
- Exploit model reduction and multi-fidelity modeling techniques

Challenges in Uncertain Dynamic Systems

Big data holds promises to better characterize uncertainty in process and biological systems

- Historical data; Process analytical chemistry (PAC) tools; DNA micro-arrays; *etc*

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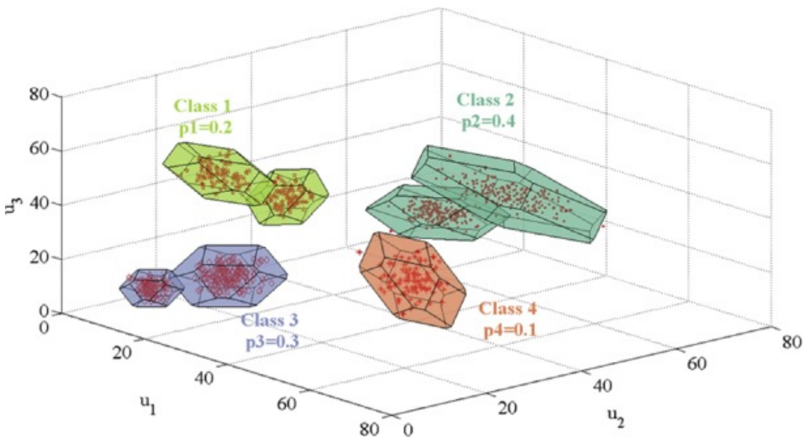
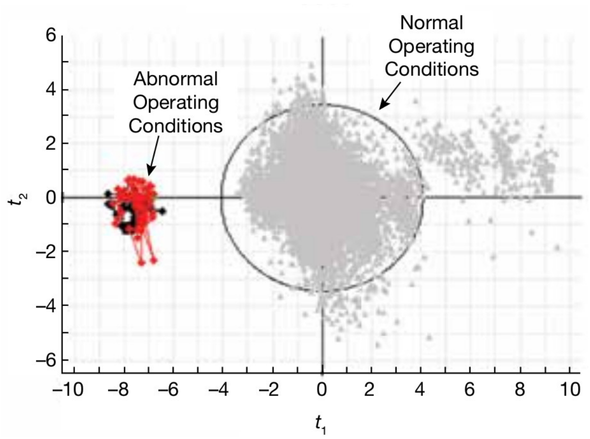


[Ning & You, *Comp Chem Eng*, 2018]



[García-Muñoz & MacGregor, *Chem Eng Prac*, 2016]

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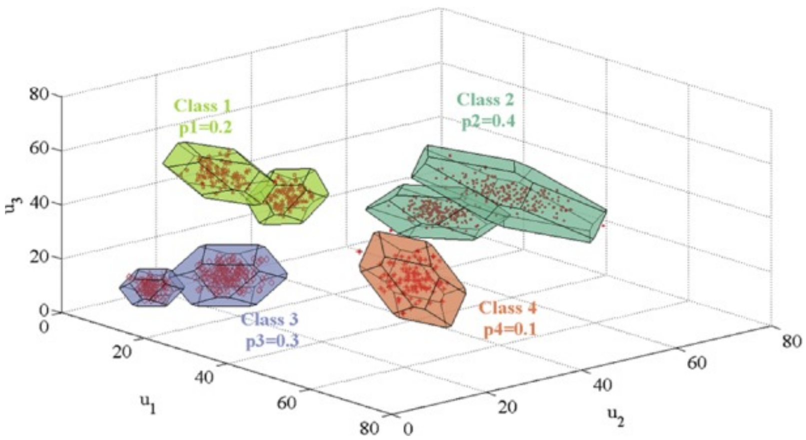

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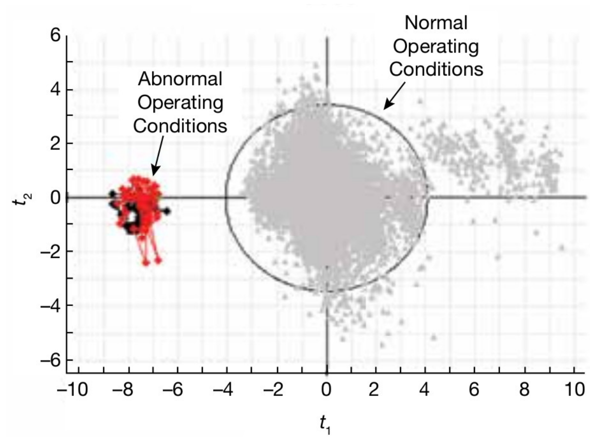

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↳ Take advantage of refined uncertainty descriptions to reduce conservatism

Reverse Uncertainty Propagation

How Might We ...

- Assess robustness in biochemical networks?
- Characterize a design space in QbD?
- Design safe operating regions in chemical plants?
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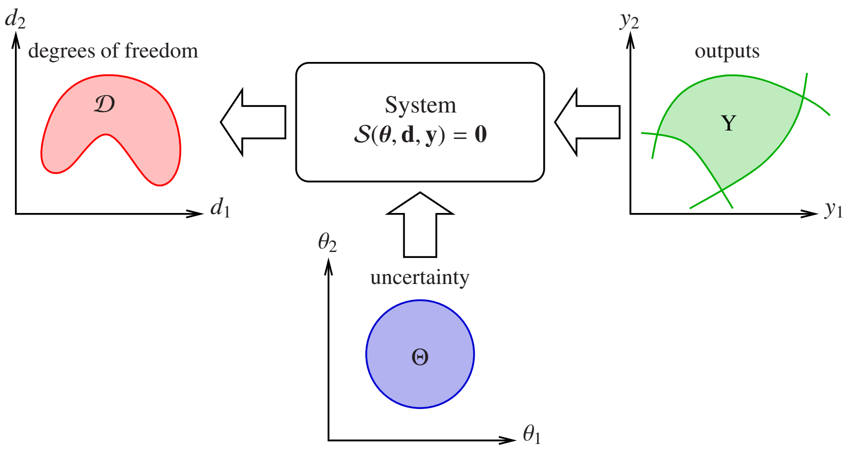

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Find $\mathbf{d} \in \mathcal{D}$ such that the output constraints $\mathbf{y} \in \mathcal{Y}$ are met for all uncertainty $\boldsymbol{\theta} \in \Theta$

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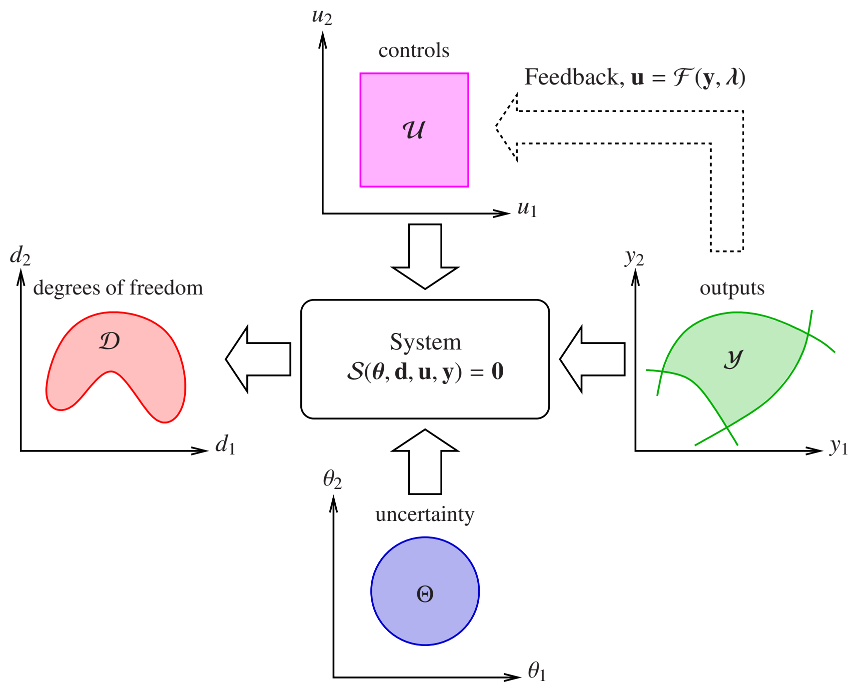

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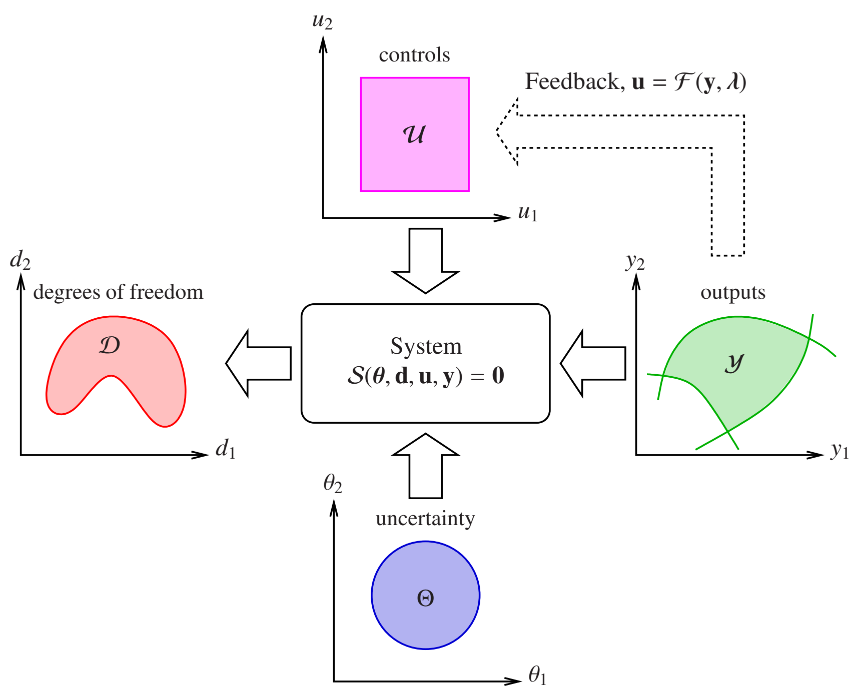

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Integrated Design & Control

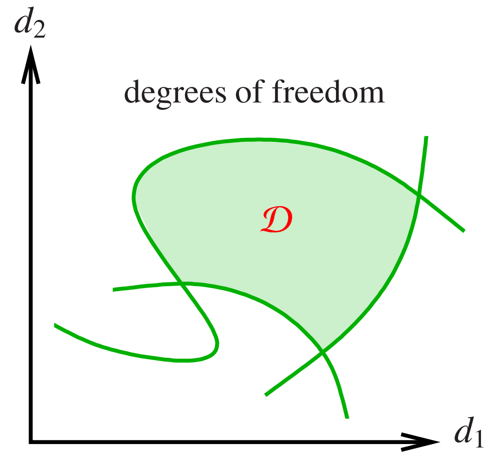
Find $\mathbf{d} \in \mathcal{D}$ such that the output constraints $\mathbf{y} \in \mathcal{Y}$ are met for all uncertainty $\boldsymbol{\theta} \in \Theta$ and a feedback control $\mathbf{u} = \mathcal{F}(\mathbf{y}, \boldsymbol{\lambda})$

Robust Feasibility Analysis

Feasibility Set

$$\mathcal{D} := \left\{ \mathbf{d} \;\middle|\; \begin{array}{l} \forall \boldsymbol{\theta} \in \Theta,\ \exists \mathbf{y}: \\ \mathbf{0} = \mathcal{S}(\boldsymbol{\theta}, \mathbf{d}, \mathbf{y}) \\ \mathbf{0} \geq \mathbf{g}(\boldsymbol{\theta}, \mathbf{y}) \end{array} \right\}$$

- Probabilistic counterpart, with chance constraints instead of worst-case



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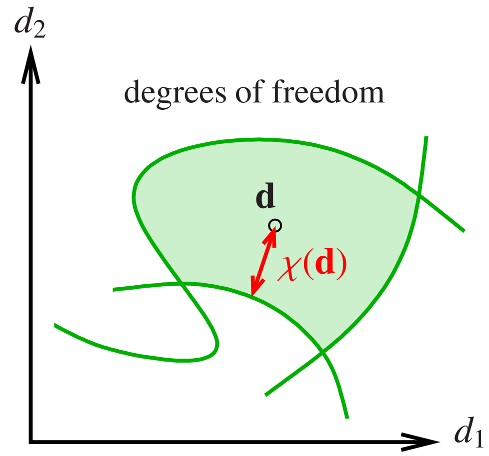

Feasibility Test

$$\chi(\mathbf{d}) := \max_{\boldsymbol{\theta} \in \Theta, \mathbf{y}} \|\mathbf{g}(\boldsymbol{\theta}, \mathbf{y})\|_\infty$$
$$\text{s.t.} \quad \mathbf{0} = \mathcal{S}(\boldsymbol{\theta}, \mathbf{d}, \mathbf{y})$$

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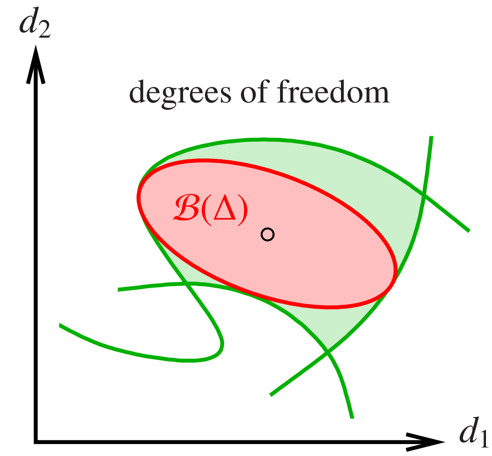

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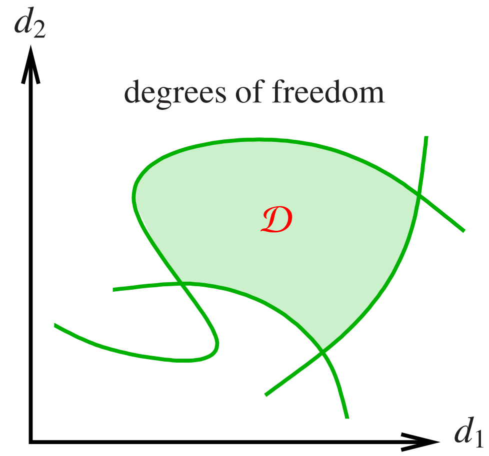

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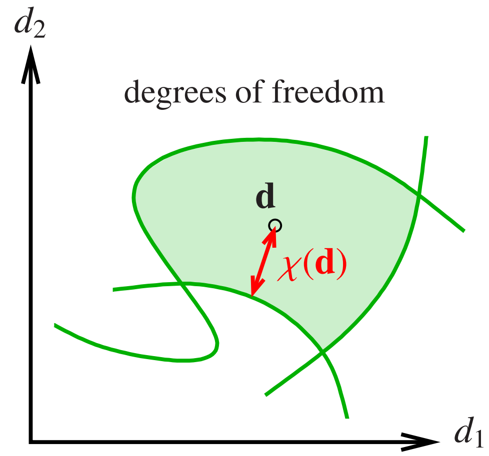

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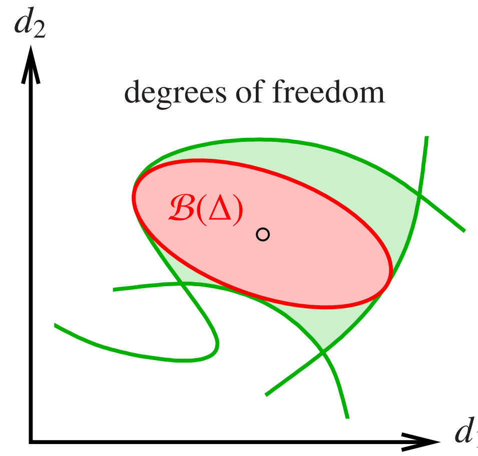

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Challenges in Robustness and Flexibility Analyses

How to solve bi-level or multi-level nonconvex optimization formulations with embedded dynamic systems?

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How to handle time-varying uncertainty?

How to devise effective computational platforms?

- Both modeling and numerical solution

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A framework for modeling and optimizing dynamic systems under uncertainty

CrossMark

Bethany Nicholson*, John Siirola

Center for Computing Research, Sandia National Laboratories, Albuquerque, NM 87185, United States

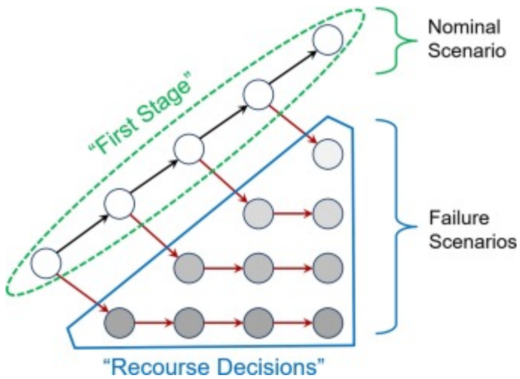
Challenges in Robustness and Flexibility Analyses

Scenario-Integration Optimization

[Abel & Marquardt, *AIChE J*, 2000]

- Account for possible failure scenarios alongside a nominal scenario
- Scenarios may have different dynamics, constraints, objectives, degrees of freedom
- Scenarios may be triggered at any time

↳ Multi-level dynamic optimization problems



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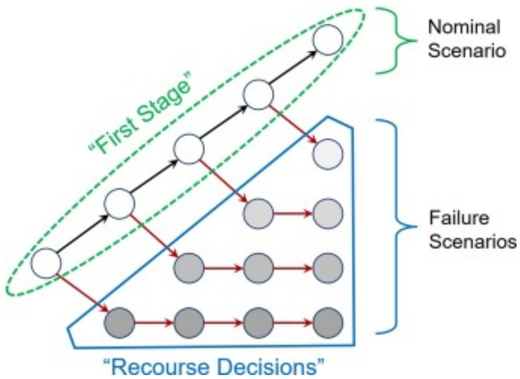
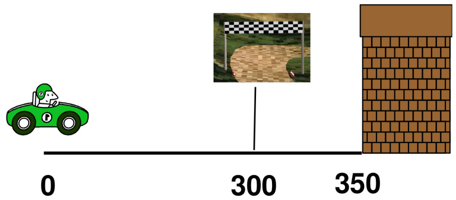


◦ Cover 300m in minimum time

◦ Do not hit the wall at 350m in case of break failure to 10% of nominal breaking capability



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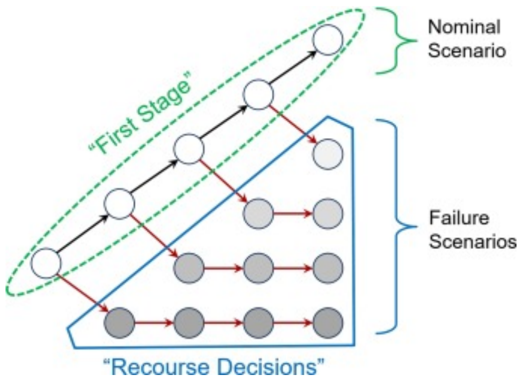

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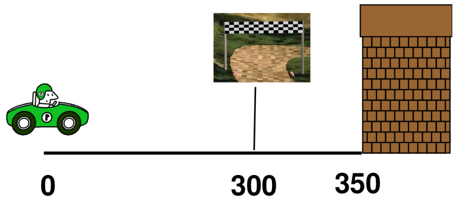

Robust-to-Dynamic Optimization

[Ahmadi & Günlük, *ArXiv*, 2018]

- Policy should remain feasible at all times despite dynamic drift:

$$\min_{\mathbf{x}_0} \left\{ f(\mathbf{x}_0) \;\middle|\; \begin{array}{l} \mathbf{x}(t,\mathbf{x}_0) \in \Omega, \forall t \geq 0 \\ \text{u.t.d.} \;\; \dot{\mathbf{x}}(t) = \mathbf{g}(\mathbf{x}(t)) \end{array} \right\}$$

"To be uncertain is to be uncomfortable, but to be certain is to be ridiculous." – Chinese proverb

Thank you very much for your attention!