Predictability Assessment in Stochastic Reaction Networks

Khachik Sargsyan, Bert Debusschere, Habib Najm

Sandia National Laboratories
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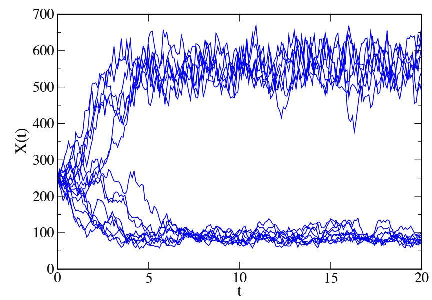
Stochastic Reaction Networks

- Reaction networks involving small number of molecules necessitate the use of *stochastic* modeling instead of the *deterministic* one. E.g.
  - Microbial processes (bioenergy, bioremediation)
  - Surface catalytic reactions (fuel cells, batteries)
  - Immune system signaling reactions



- SRNs are modeled as Jump Markov Processes
  - Governed by Chemical Master Equation $\dot{P}(X(t)=n)=\sum_m A_{nm}P(X(t)=n)$
  - Reduces to deterministic Rate Equations in the large volume limit
  - Trajectories simulated by Gillespie's Stochastic Simulation Algorithm (SSA, Gillespie, 1977)

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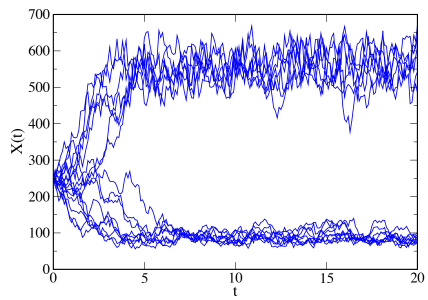

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Objective: predictability in high-d

$$X(t, \boldsymbol{\theta}, \boldsymbol{\lambda})$$

- Develop tools for *predictability*($\boldsymbol{\lambda}$) and *dynamical analysis*(t) of SRNs accounting for
  - Inherent stochasticity ($\boldsymbol{\theta}$)
  - Model/parameter uncertainty ($\boldsymbol{\lambda}$)
  - Limited data

$$\mathcal{D} = \{(\lambda_i, X_i)\}_{i=1}^{N}$$

- Predictability assessment
  - Fix t, focus on λ dependence
  - Statistical properties $Y(\lambda) = \langle f(X(\theta, \lambda)) \rangle$ have sampling noise
  - How uncertainty in λ affects uncertainty in $Y(\lambda)$ given limited data
- High dimensionality of λ

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High-dimensional parametric uncertainty in stochastic systems

- Statistical property $Y(\boldsymbol{\lambda}) = \langle f(X(\boldsymbol{\theta}, \boldsymbol{\lambda}))\rangle$ of interest.
  - High-dimensional parametric uncertainty ($\boldsymbol{\lambda}$)
  - Sampling noise due to limited data $\{X_i\}$
- Expectation $\langle \cdot \rangle$ filters intrinsic noise.
  - Averaging over sample realizations of X
  - Still leftover noise, width $\sim 1/\sqrt{N}$
- Polynomial Chaos expansion to represent input-output relationship
  - Sensitivity analysis
  - Surrogate model for optimization or inverse problems
  - Identify key reaction mechanisms

Polynomial Chaos expansion represents a random variable as a polynomial of a standard random variable

- Truncated PCE: finite dimension n and order p

$$Y \simeq \sum_{k=0}^{P} c_k \Psi_k(\boldsymbol{\eta})$$

  with the number of terms $P+1 = \frac{(n+p)!}{n!p!}$.

- $\boldsymbol{\eta} = (\eta_1, \cdots, \eta_n)$ standard i.i.d. r.v.
  Ψ_k standard orthogonal polynomials
  c_k spectral modes.

- Most common standard Polynomial-Variable pairs:
  (continuous) Gauss-Hermite, Legendre-Uniform,
  (discrete) Poisson-Charlier.

[Wiener, 1938; Ghanem & Spanos, 1991; Xiu & Karniadakis, 2002]

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Alternative methods to obtain PC coefficients

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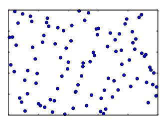
The integral $\langle Y(\boldsymbol{\eta})\Psi_k(\boldsymbol{\eta})\rangle = \int Y(\boldsymbol{\eta})\Psi_k(\boldsymbol{\eta})\pi(\boldsymbol{\eta})d\boldsymbol{\eta}$ can be estimated by

- Monte-Carlo

$$\frac{1}{K}\sum_{j=1}^{K} Y(\boldsymbol{\eta}_j)\Psi_k(\boldsymbol{\eta}_j)$$



many samples from $\pi(\boldsymbol{\eta})$

- Quadrature

$$\sum_{j=1}^{Q} Y(\boldsymbol{\eta}_j)\Psi_k(\boldsymbol{\eta}_j)w_j$$

samples at quadrature

- *Bayesian inference*

$$P(c_k|Y(\boldsymbol{\eta}_j)) \propto P(Y(\boldsymbol{\eta}_j)|c_k)P(c_k)$$

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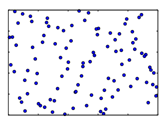

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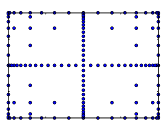

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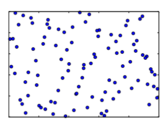

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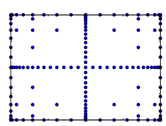

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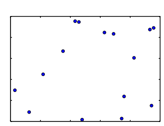

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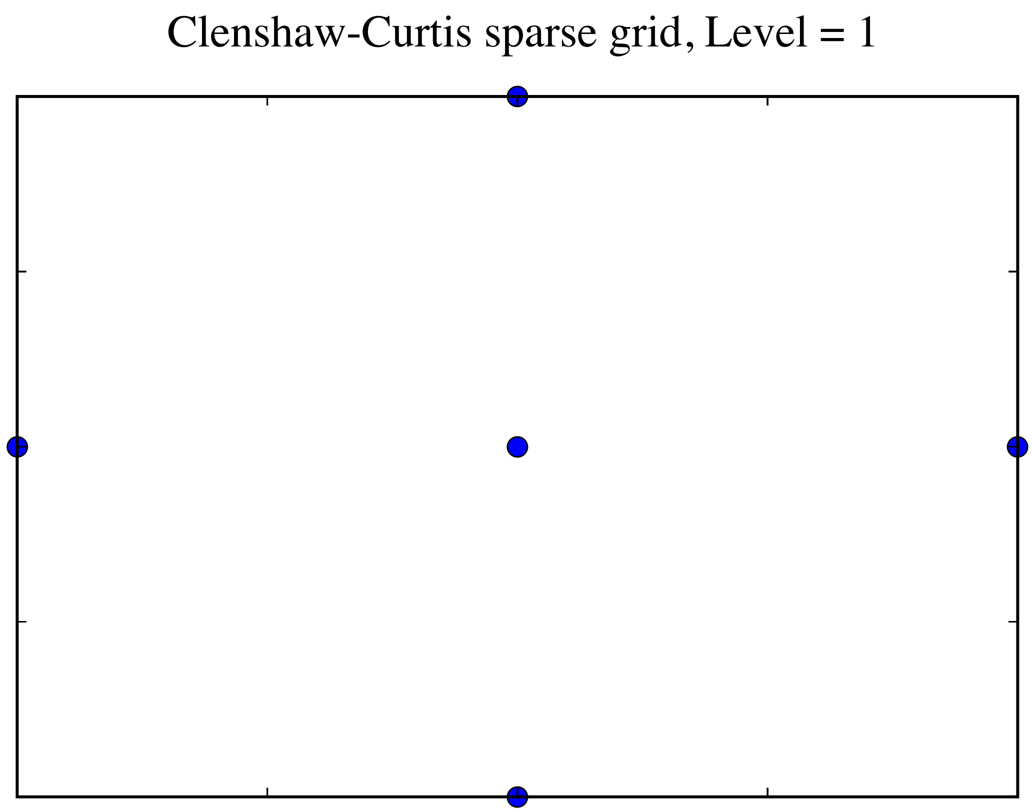
Sparse quadrature integration well-suited for high-dimensional *smooth* integrands



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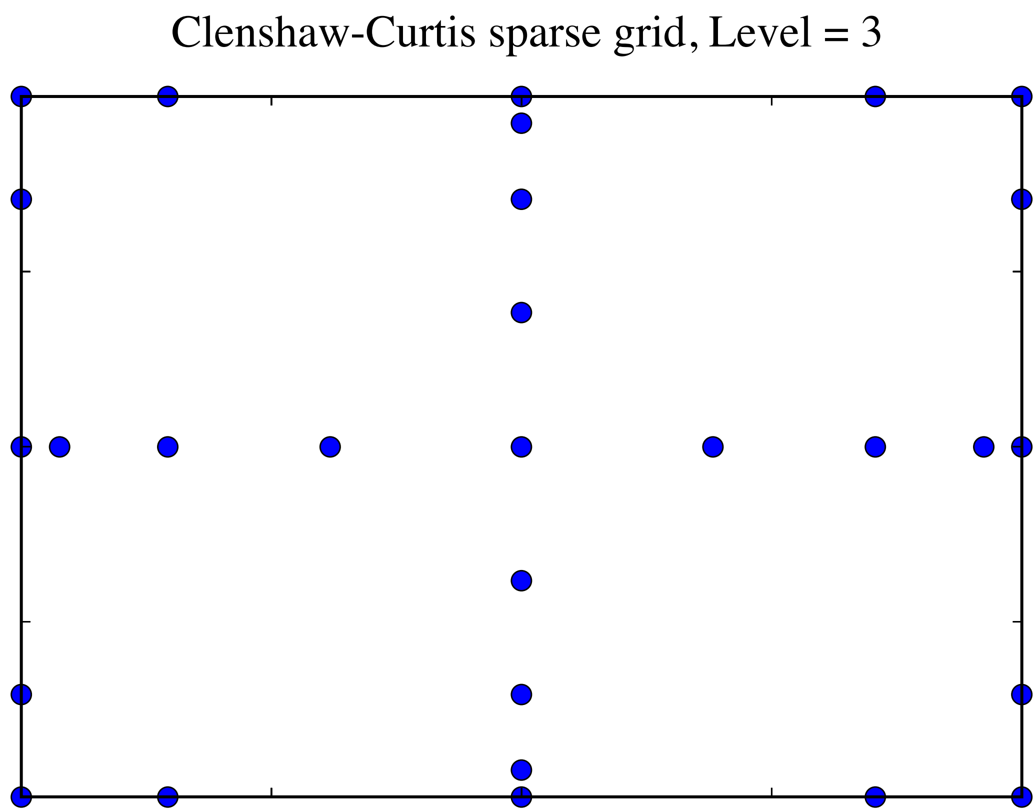

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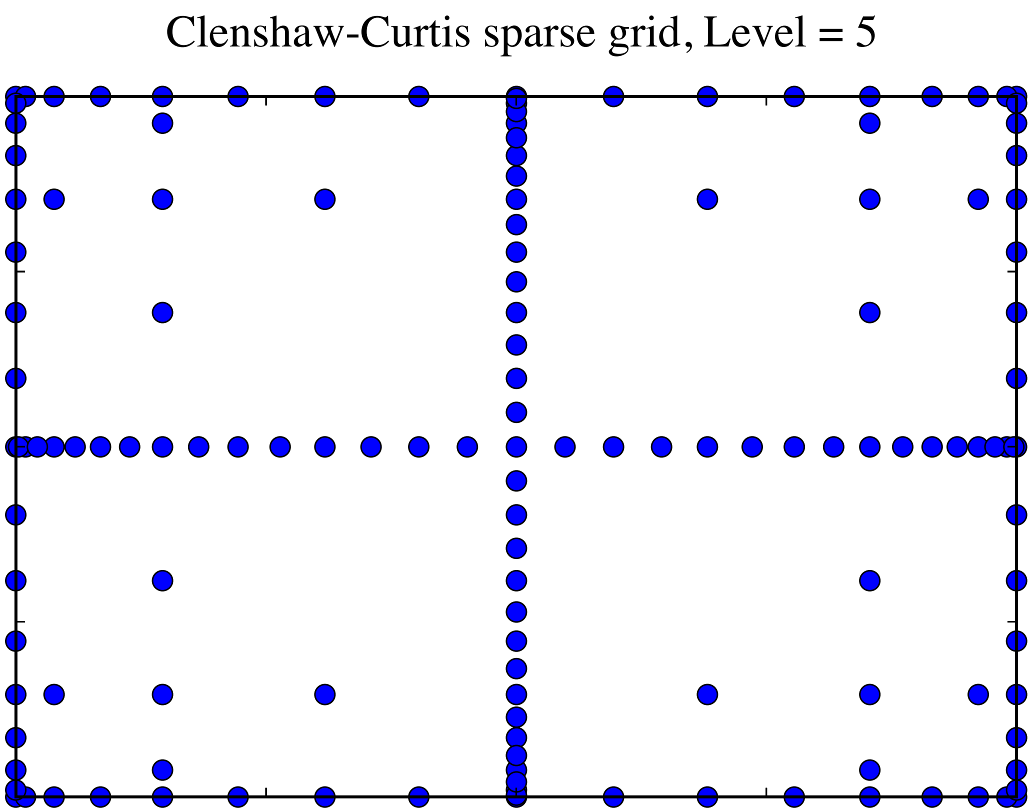

Sparse quadrature integration fails for noisy integrands

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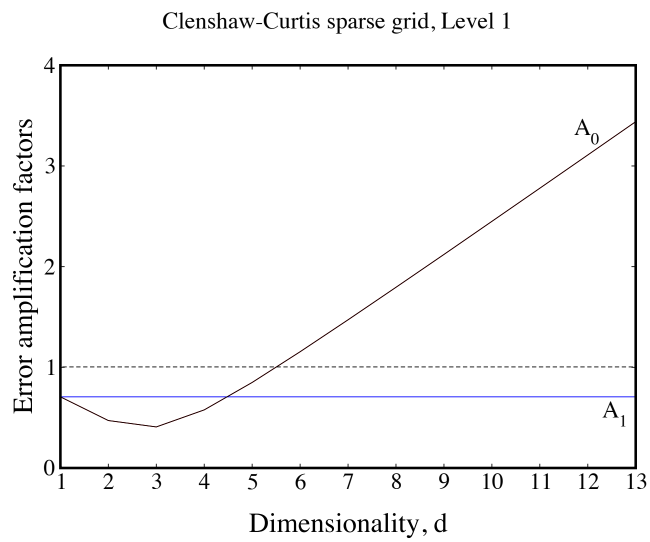
$\text{Noise}_Y \sim \sigma \Longrightarrow \text{Error}_{c_k} \sim A_k \sigma$



- amplification factor A_k grows with dimensionality
  - CC, level 1: $A_0 = \frac{1}{3}\sqrt{(d-3)^2 + \frac{d}{2}}, \qquad A_1 = \frac{1}{\sqrt{2}}$.
- blame the negative weights.
- for full quadrature, $\frac{1}{n^{d/2}} \leq A_0 \leq 1$, no amplification!

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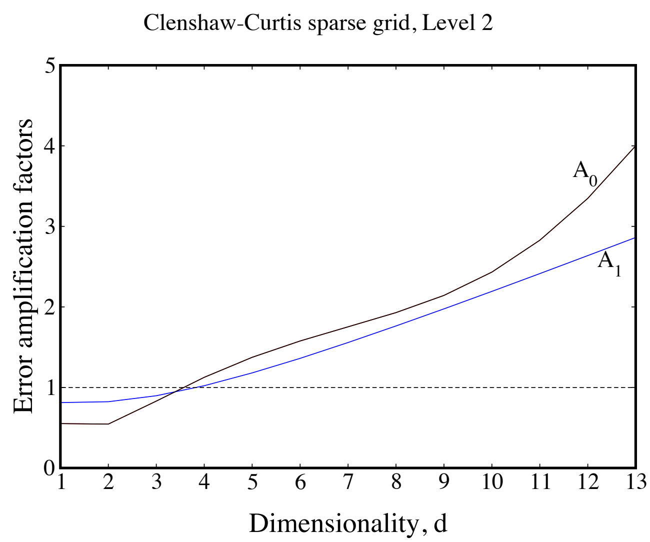

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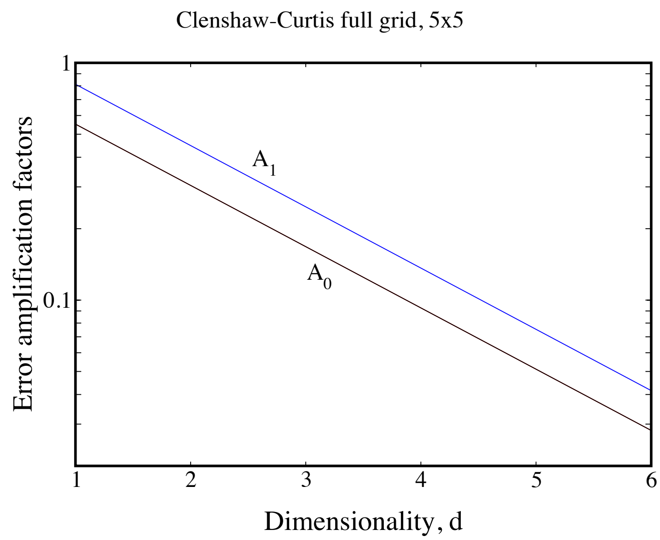

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Bayesian inference handles the intrinsic stochasticity well

$$Y = \langle X \rangle \simeq \sum_{k=0}^{P} c_k \Psi_k(\boldsymbol{\eta}) \qquad \overbrace{P(\boldsymbol{c}|\mathcal{D})}^{\text{Posterior}} \propto \overbrace{P(\mathcal{D}|\boldsymbol{c})}^{\text{Likelihood}} \overbrace{P(\boldsymbol{c})}^{\text{Prior}}$$

$$\text{Data} \qquad \mathcal{D} \equiv \{(\tilde{\boldsymbol{\eta}}_1, X_1), \ldots, (\tilde{\boldsymbol{\eta}}_N, X_N)\} = (\tilde{\boldsymbol{\eta}}, \boldsymbol{X})$$

$$L(\boldsymbol{c}) = P(\mathcal{D}|\boldsymbol{c}) = \left(\frac{1}{\sigma\sqrt{2\pi}}\right)^N \prod_{i=1}^{N} \exp\left(-\frac{(X_i - \sum_{k=0}^{P} c_k \Psi_k(\tilde{\boldsymbol{\eta}}_i))^2}{2\sigma^2}\right)$$

- Noise model is assumed gaussian with σ fixed or inferred
- Uniformly distributed priors
- Posterior exploration using Markov Chain Monte Carlo (MCMC)
- The whole posterior distribution is accessible,
  i.e. uncertain response surface
- Input parameters can have arbitrary values

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- Posterior is *a multivariate normal*

$$\boldsymbol{c} \quad \in \quad \mathcal{N}(\underbrace{(\boldsymbol{P}^T\boldsymbol{P})^{-1}\boldsymbol{P}^T\boldsymbol{X}}_{\boldsymbol{\mu}}, \underbrace{\sigma^2(\boldsymbol{P}^T\boldsymbol{P})^{-1}}_{\boldsymbol{\Sigma}}), \qquad \text{where } \boldsymbol{P}_{ik} = \Psi_k(\tilde{\boldsymbol{\eta}}_i)$$

- The response surface is *a gaussian process*

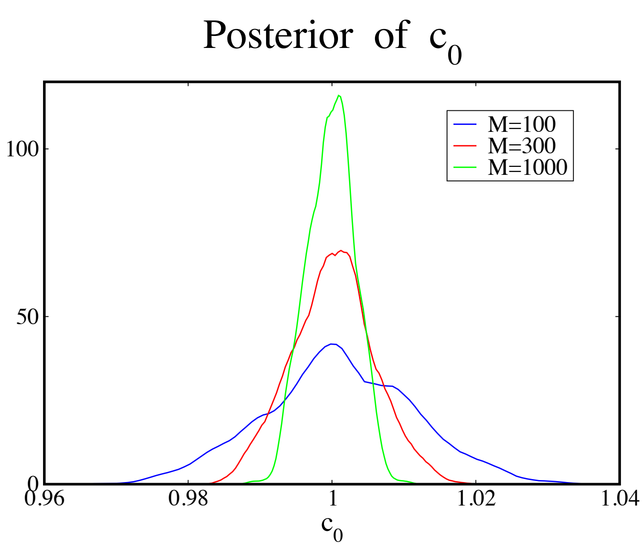
$$\sum_{k=0}^{P} c_k \Psi_k(\boldsymbol{\eta}) = \boldsymbol{\Psi}(\boldsymbol{\eta})^T \boldsymbol{c} \quad \in \quad \mathcal{GP}(\boldsymbol{\Psi}(\boldsymbol{\eta})^T\boldsymbol{\mu}, \boldsymbol{\Psi}(\boldsymbol{\eta})\boldsymbol{\Sigma}\boldsymbol{\Psi}(\boldsymbol{\eta}')^T)$$

Posterior narrows around the true value as more samples are taken

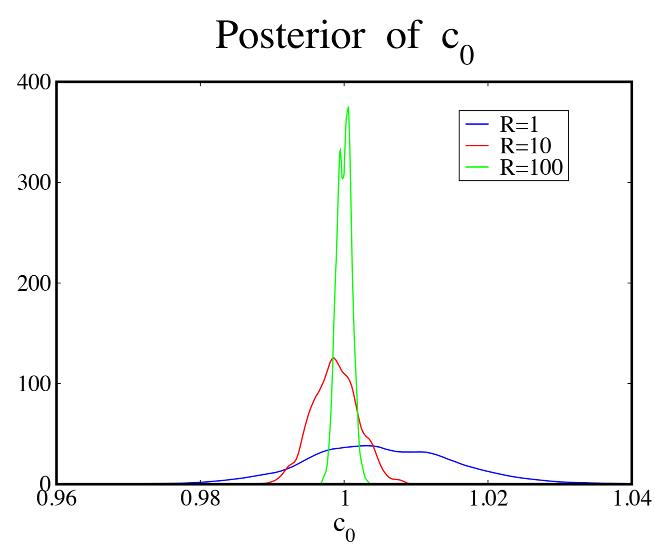
- M parameter locations
- R replicas per parameter

- Second order Legendre polynomial expansion with unit coefficients.

No noise in function evaluations, $R = 1$



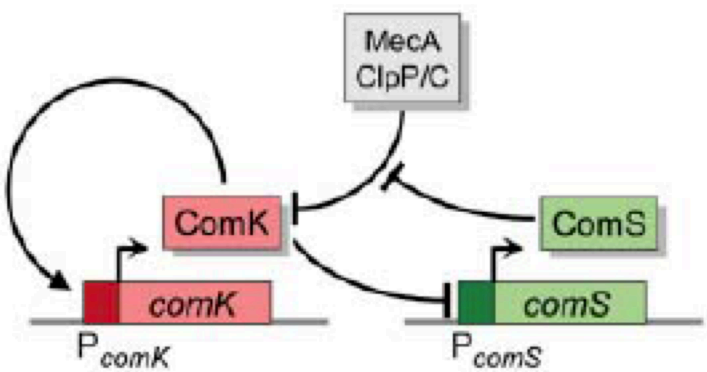
Noisy function evaluations, $M = 100$



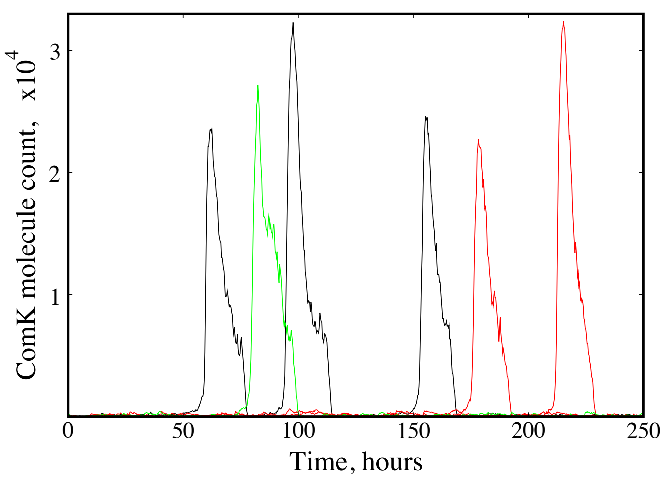
Bacillus subtilis is a soil bacterium

relevant to bioenergy and bioremediation

- 16 reactions, 11 species
- Competence in *B. Subtilis* allows uptake of external DNA
- Rapid rise in transcription factor comK molecules
- Vegetative $\rightarrow$ Competent state transition is driven by stochasticity
- Input parameters: rate constants of underlying reactions (high-d)
- Output observable: probability of competence $P_c = P(X_\infty > 5000)$



Süel et al., Science, 2007



Intrinsic stochasticity induces transition to competence

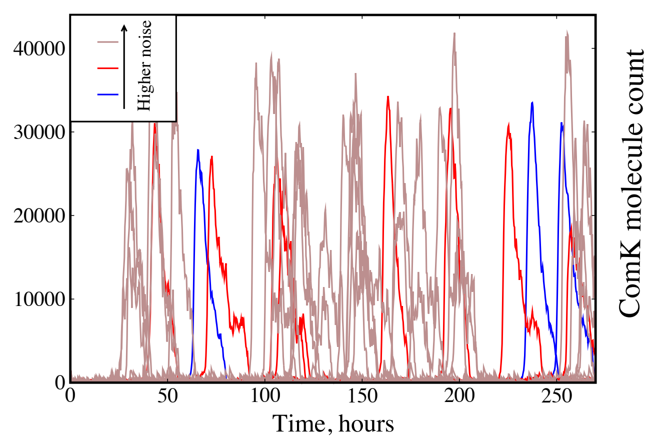
Chemical Master Equation (CME):

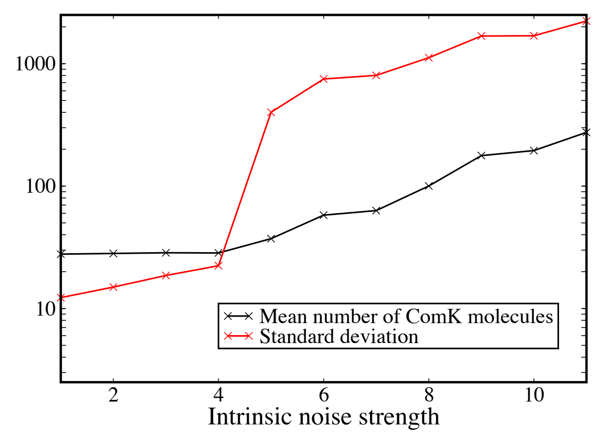
$$\frac{d}{dt}P(X(t)=n)=\sum_m A_{nm}P(X(t)=n)$$

Rate equation (ODE):

$$\frac{d}{dt}X(t)=\tilde{A}(X)$$

- No-noise or large volume limit (ODE) does not produce competence
- Many parameter combinations lead to the same ODE limit, but correspond to different effective volumes, i.e. intrinsic noise strength
- Increasing intrinsic noise leads to more frequent transitions





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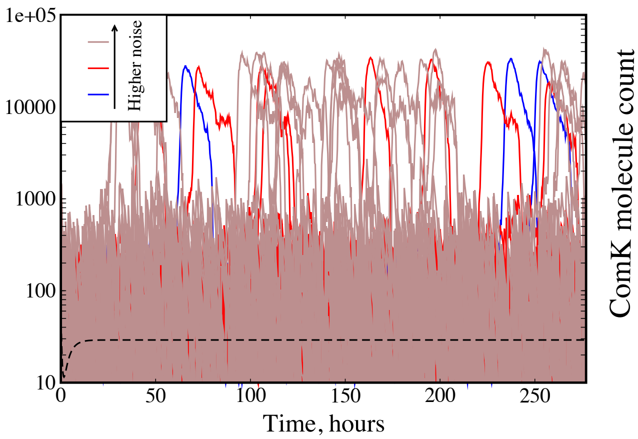
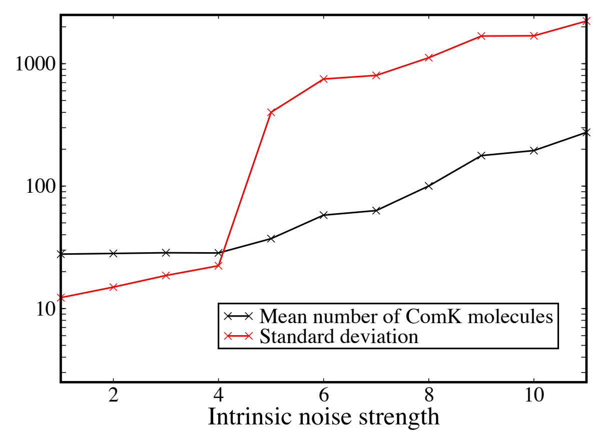
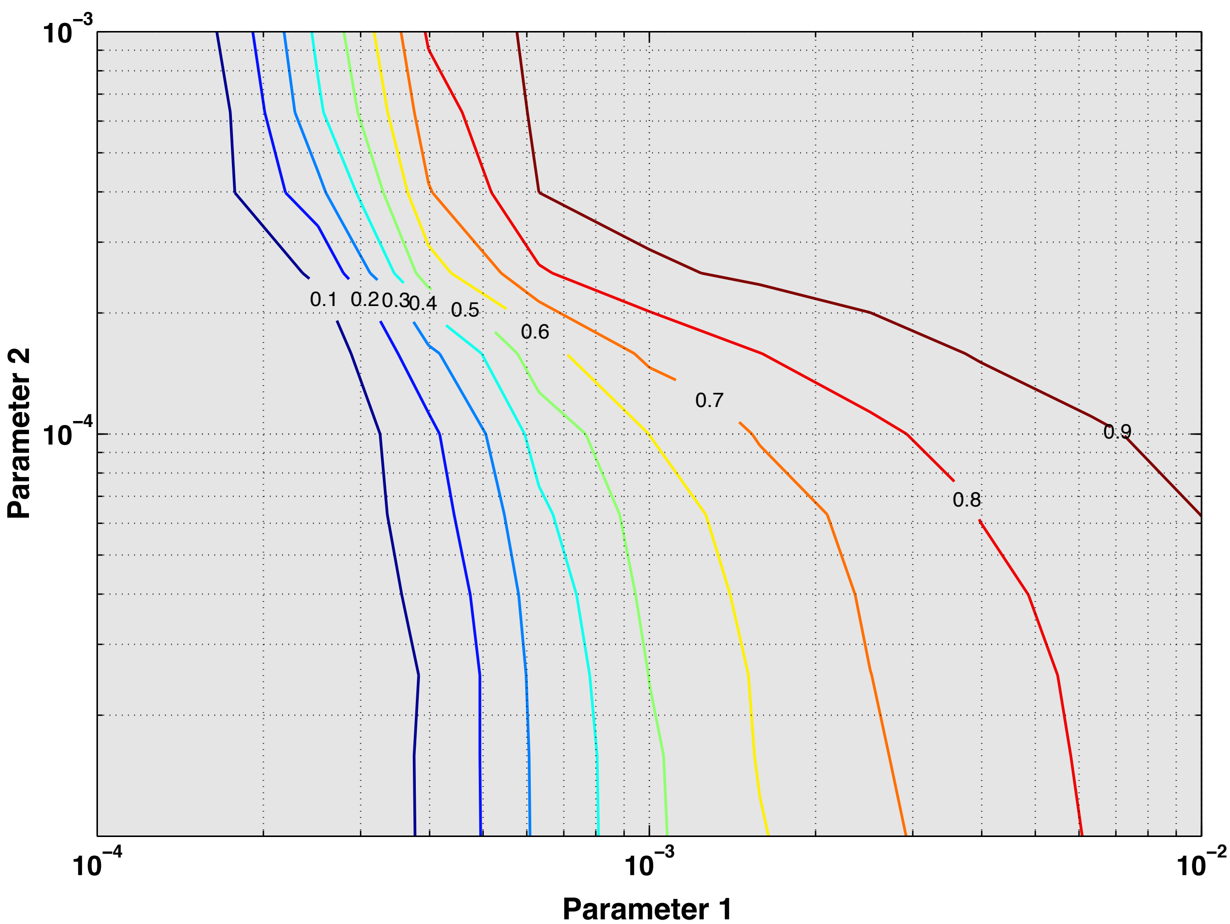




Various dynamical regimes revealed by exploring parameter space

Contours of probability of competence P_c



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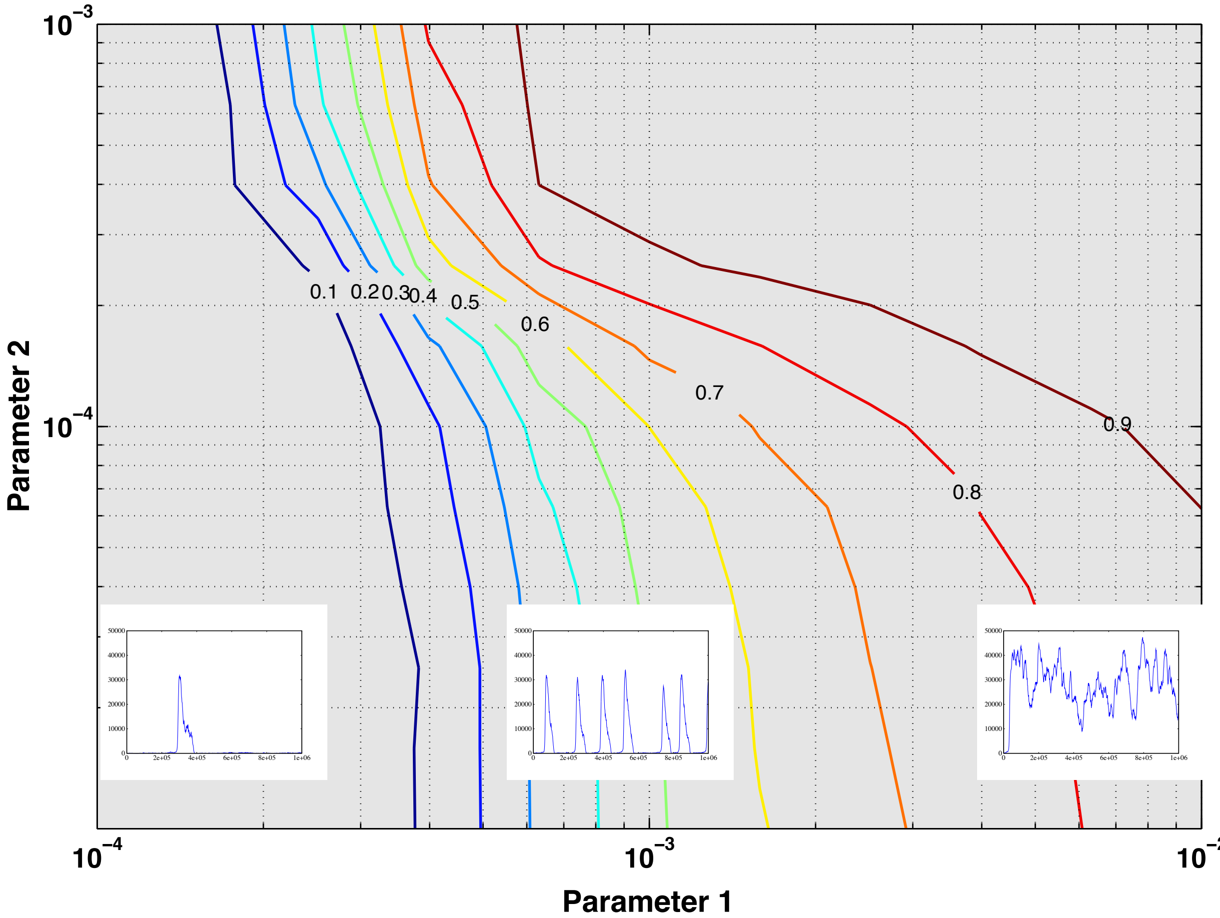
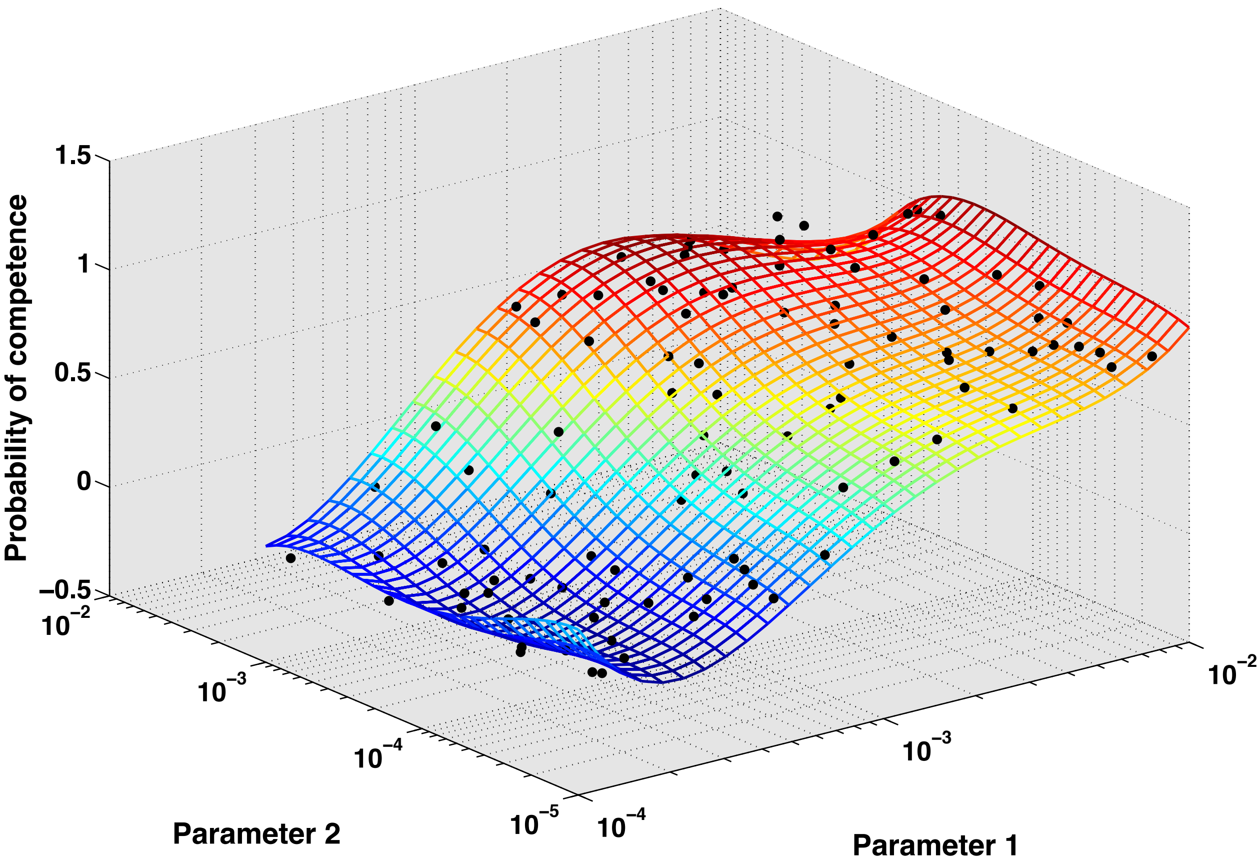
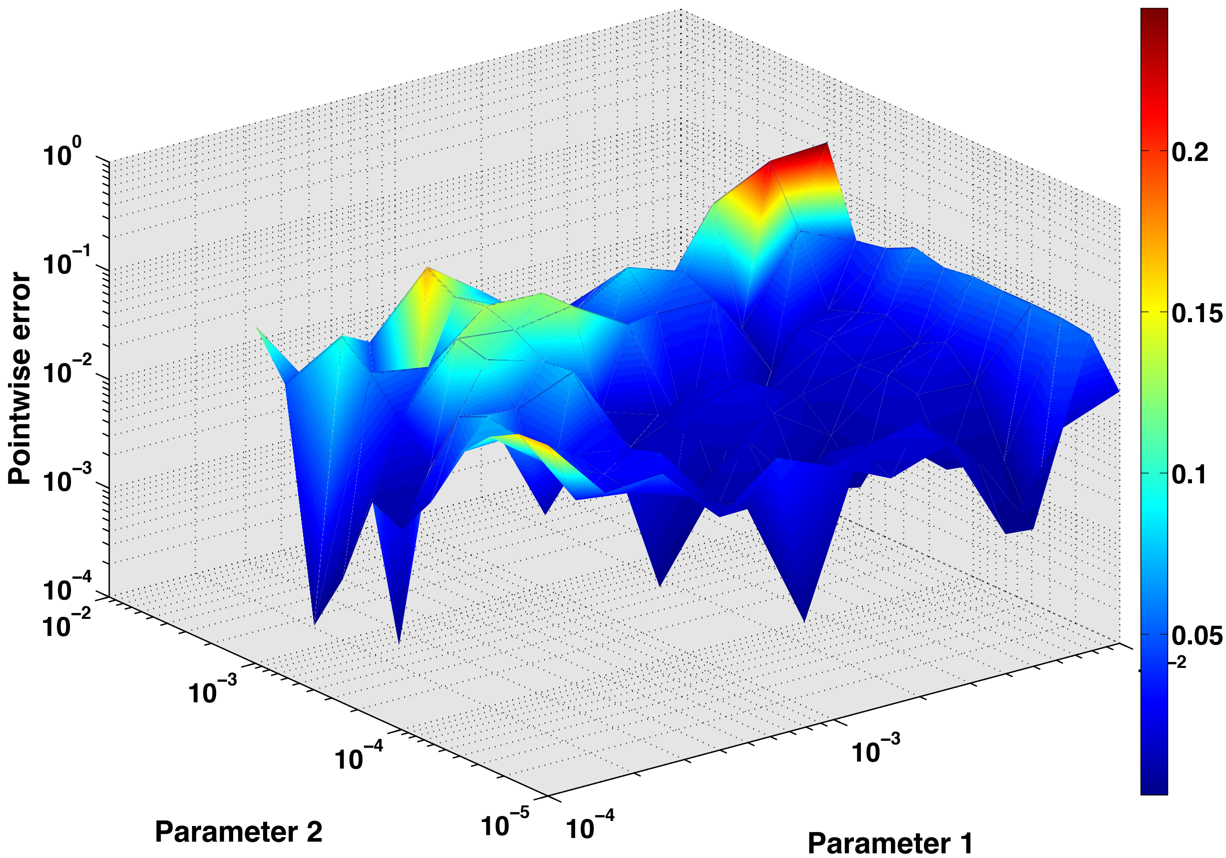


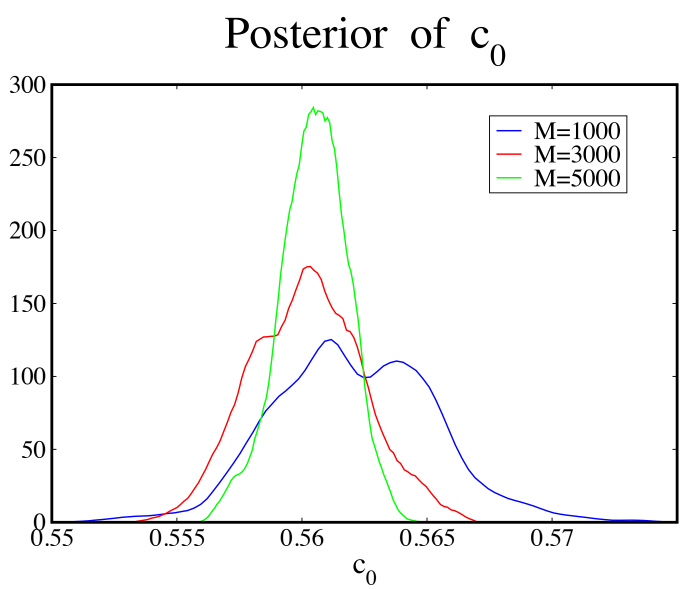

1.5
1
0.5
0
−0.5
Probability of competence
10^{-2}
10^{-3}
10^{-4}
10^{-5}
Parameter 2
10^{-4}
10^{-3}
10^{-2}
Parameter 1

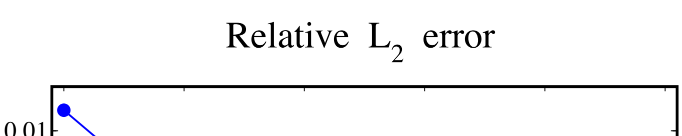
Pointwise error in MAP estimate of 4th order PC



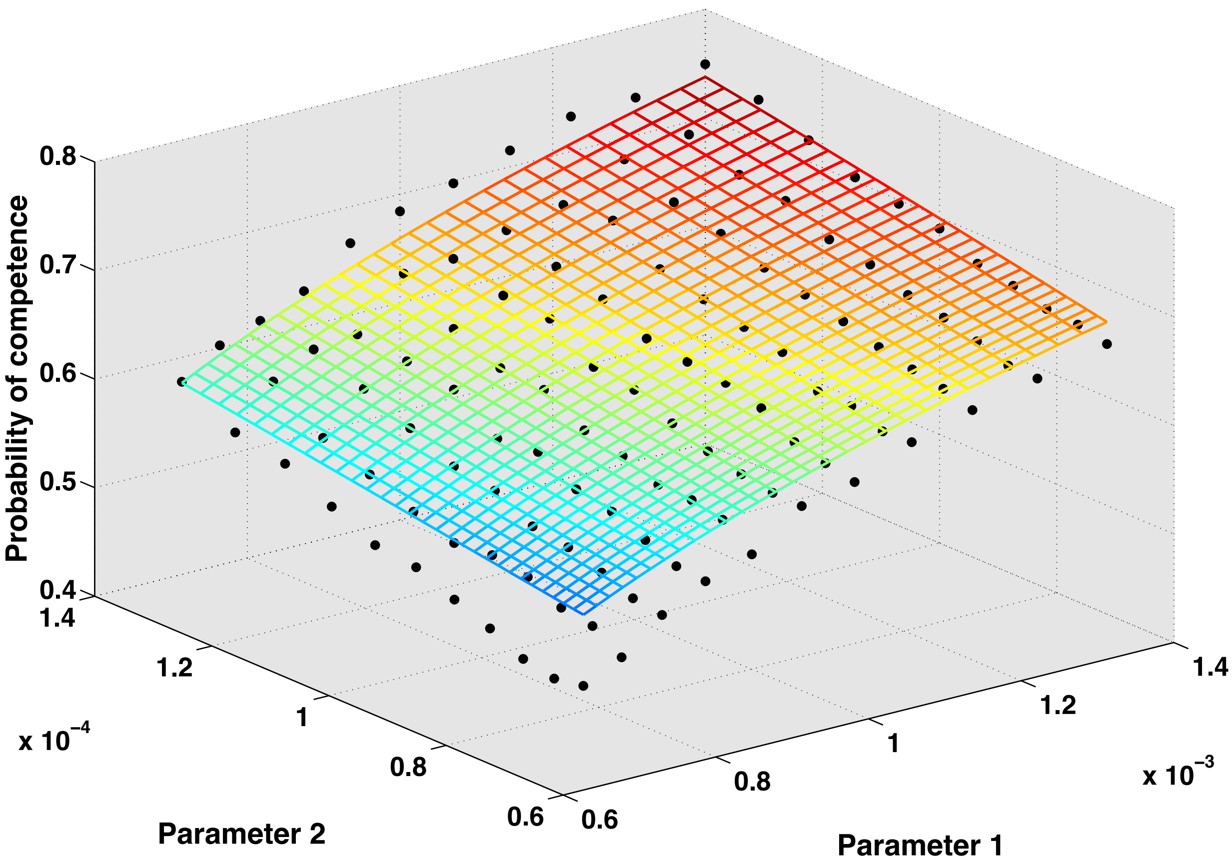
Convergence both in posterior width and order

- With more input parameter samples, posterior narrows around the true value
- Convergence in PC order is established





2-nd order response surface in 10-d case: 2-d slice



High Dimensional Model Representation (HDMR)

breaks the function into group-wise contributions of input variables

$$f(\boldsymbol{\lambda}) = f(\lambda_1, \ldots, \lambda_d) = f_0 + \sum_i f_i(\lambda_i) + \sum_{i<j} f_{ij}(\lambda_i, \lambda_j) + \sum_{i<j<k} f_{ijk}(\lambda_i, \lambda_j, \lambda_k) + \cdots$$

Component functions are found by

$$f_0 = \int_{R^d} f(\boldsymbol{\lambda}) d\boldsymbol{\lambda}, \qquad f_i(\lambda_i) = \int_{R^{d-1}} f(\lambda_i, \boldsymbol{\lambda}_{\bar{i}}) d\boldsymbol{\lambda}_{\bar{i}} - f_0$$

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- Component function $f_{i_1 \ldots i_s}(\lambda_{i_1}, \ldots, \lambda_{i_s})$ is found by a $(d-s)$-dimensional integral. Still too high-dimensional.
- Otherwise called ANOVA decomposition (analysis of variance)
- Exact in the limit, but not unique.

High Dimensional Model Representation (HDMR)

breaks the function into group-wise contributions of input variables

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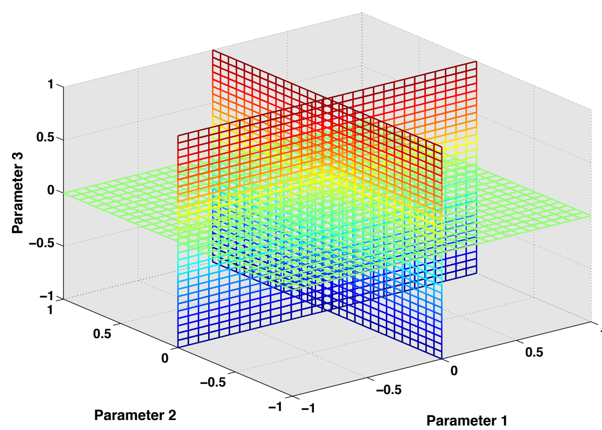
- Two major variants:
  - Cut-HDMR
  - RS-HDMR



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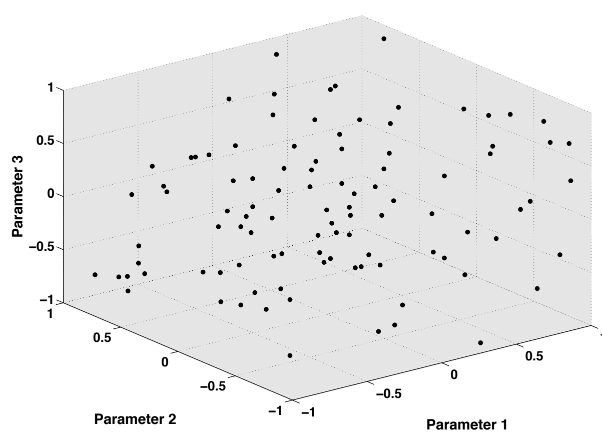

cut-HDMR disregards corners in the parameter space and does not guarantee accuracy in general

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- Relies on values at lower-dimensional hyperplanes
- Depends on the anchor point $\boldsymbol{\lambda}^a$
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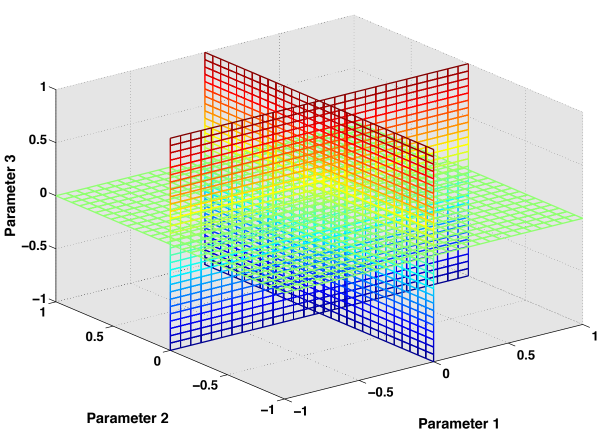

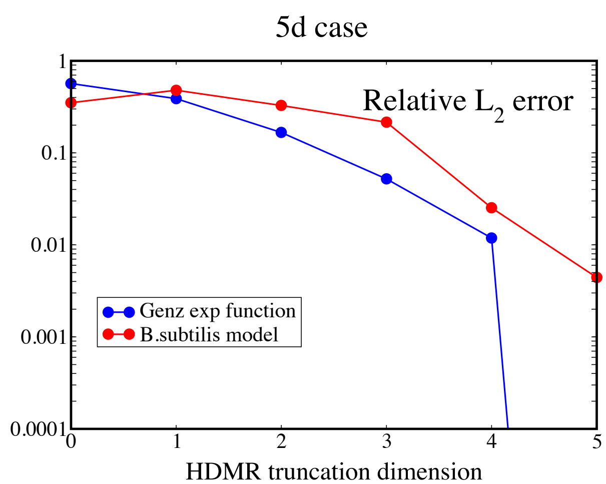

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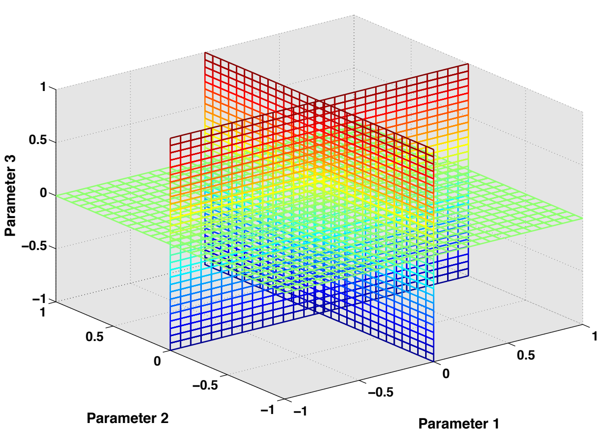

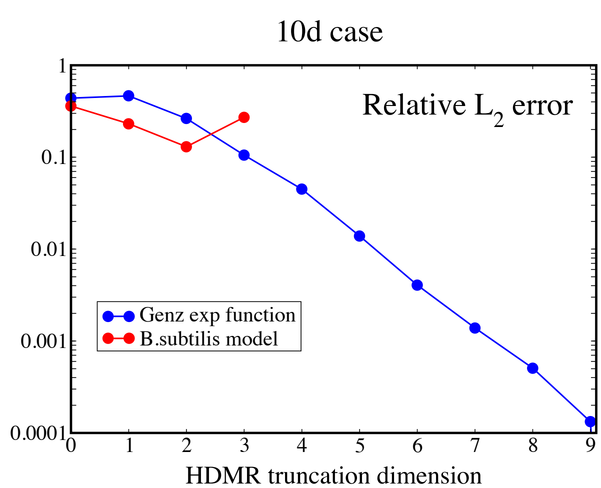

Random Sampling (RS) HDMR in principle equivalent to PC expansion with Monte-Carlo integration

$$f(\boldsymbol{\lambda}) = f(\lambda_1,\ldots,\lambda_d) = f_0 + \sum_i f_i(\lambda_i) + \sum_{i<j} f_{ij}(\lambda_i,\lambda_j) + \sum_{i<j<k} f_{ijk}(\lambda_i,\lambda_j,\lambda_k) + \cdots$$

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- MC integrals still too expensive (new random samples needed for each hyperplane)
- Represent component functions with a polynomial expansion and use same set of samples
- Equivalent to Monte-Carlo PC with reordered multiindices!
  - PC (total order): $f(\xi_1,\xi_2) = 1 + [\xi_1+\xi_2] + [(\xi_1^2-1) + \xi_1\xi_2 + (\xi_2^2-1)] + \ldots$
  - RS-HDMR: $f(\xi_1,\xi_2) = 1 + [\xi_1 + (\xi_1^2-1)] + [\xi_2 + (\xi_2^2-1)] + \xi_1\xi_2\ldots$
- In future: employ Bayesian inference on component functions.

Summary

- Polynomial Chaos expansions represent effects of uncertainties of input parameters to output statistical properties
  - Sensitivity analysis
  - Uncertainty quantification
  - Response surface construction

- Noise in function evaluations hampers quadrature methods
  - Sparse integration of noisy functions useless in high-d !
- HDMR constructions do not always guarantee accuracy with small computational effort
  - Generally still require high-d integrals
  - cut-HDMR overcomes this requirement but is not accurate enough
- Bayesian inference well-suited to handle noisy data

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