The Systems Biology Cycle: Computational Workflow & Uncertainty Quantification

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Centrum Wiskunde & Informatica
Amsterdam

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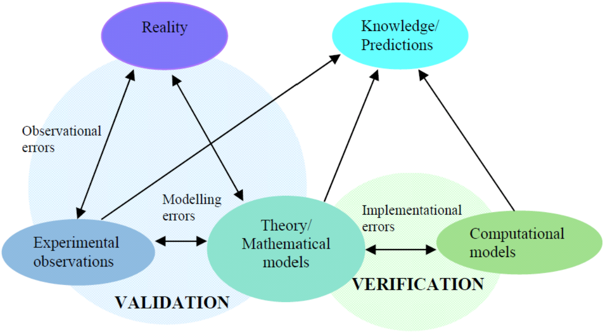
INTRODUCCTION

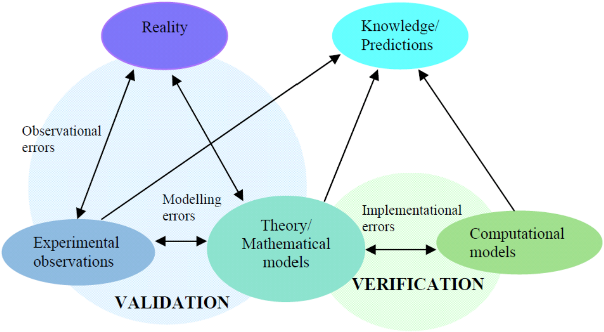
- Postdoc in the Scientific Computing for Systems Biology / Life Science (LS)
- **BioPreDyn:** From Data to Models (European project, FP7,#289434) with J.G. Blom and A.T. Valderrama

Outline

Errors


Reality
Knowledge/ Predictions
Observational errors
Modelling errors
Implementational errors
Experimental observations
Theory/ Mathematical models
Computational models
VALIDATION
VERIFICATION

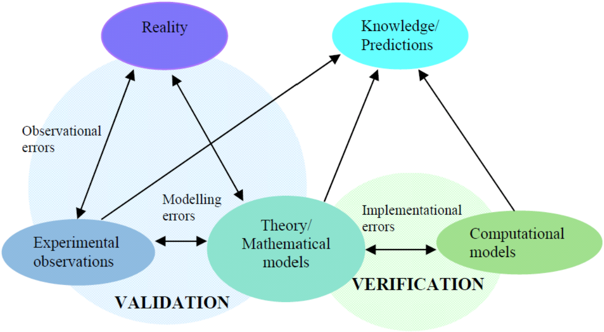
Errors



Experimental models: controlled version of reality

model organisms, synthetic biology

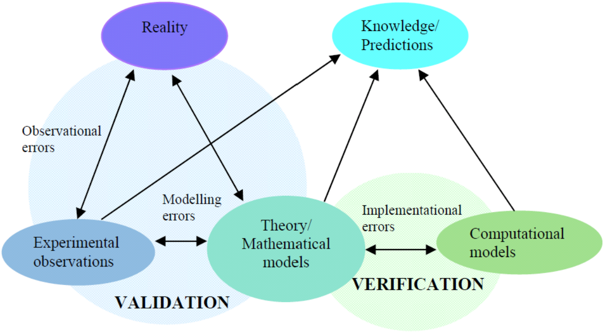
Errors



Mathematical models: *precise* description of an *approximation* of reality

assumptions, equations

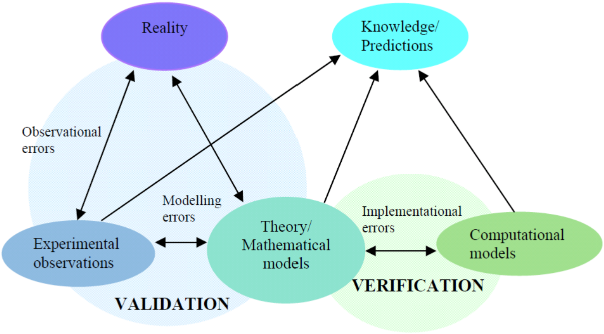
Errors



Computational models: implementation of mathematical model

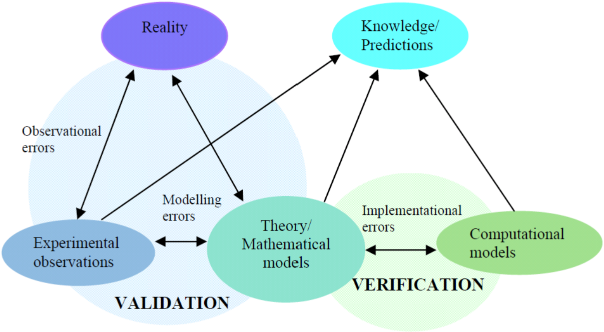
equation-based, model identification, verification, validation

Errors

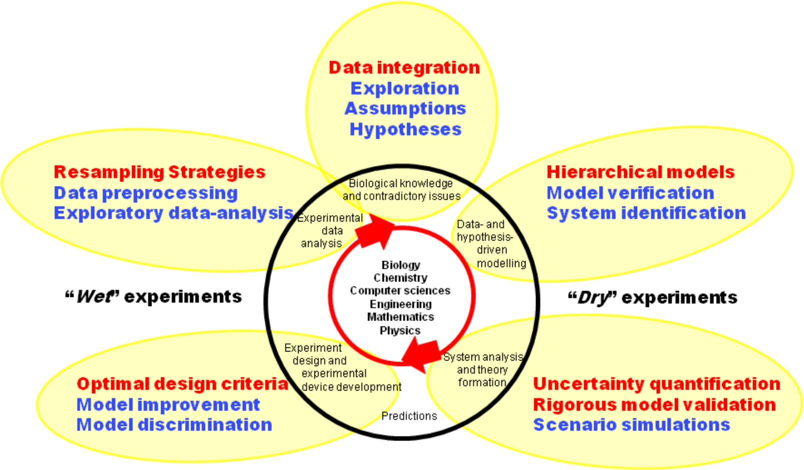


(Controllable) errors everywhere

Errors

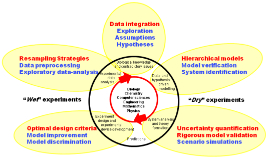


(Controllable) errors everywhere
THINK before you do


Data integration
Exploration
Assumptions
Hypotheses
Resampling Strategies
Data preprocessing
Exploratory data-analysis
Hierarchical models
Model verification
System identification
Biological knowledge and contradictory issues
Experimental data analysis
Data- and hypothesis-driven modelling
Biology
Chemistry
Computer sciences
Engineering
Mathematics
Physics
"Wet" experiments
"Dry" experiments
Experiment design and experimental device development
System analysis and theory formation
Predictions
Optimal design criteria
Model improvement
Model discrimination
Uncertainty quantification
Rigorous model validation
Scenario simulations

"Dry": Mathematical / Computational Model

Experimental data for some observables
(data analysis: exp. error, exploratory)



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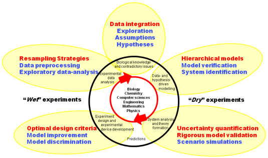

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2. Analyze model and parameter identifiability (math. analysis + structural ident.)

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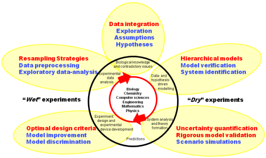

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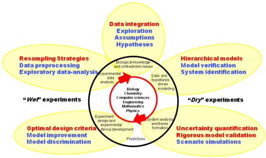

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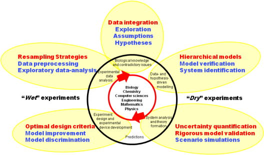

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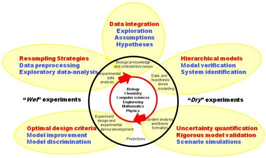

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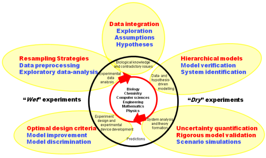

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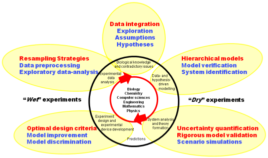

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7. Optimal Experimental Design (experimental options, aim)
8. Model predictions

Uncertainty Quantification

1 Why Uncertainty Quantification?

2 The Systems Biology Cycle

3 Polynomial Chaos Expansion

4 PCE for correlated inputs

Deterministic mathematical model

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t)), \qquad \mathbf{y}(0) = \mathbf{y}_0$$

Uncertainty in *initial values* or *parameters* (e.g. from error in data)

ξ (multi-variate) random variable, $\mathbf{y}(t, \xi)$ random process:

Stochastic mathematical model

$$\mathbf{y}'(t, \xi) = \mathbf{f}(t, \mathbf{y}(t, \xi), \xi), \qquad \mathbf{y}(0, \xi) = \mathbf{y}_0(\xi)$$

How to compute $\mathbf{y}(t, \xi)$?

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How to compute $\mathbf{y}(t, \xi)$? **Polynomial Chaos Expansion**

PCE: decomposition of random process y (cf Fourier, Taylor)

Wiener (1938) separation of variables

$$y(t,\xi) = \sum_{p=0}^{\infty} y_p(t)\Psi_p(\xi), \qquad \xi \text{ RV}$$

Ψ polynomials; orthogonal wrt **pdf** $\rho(\xi)$

$$< \Psi_i, \Psi_j >= \int_S \Psi_i(\xi)\Psi_j(\xi)\rho(\xi)d\xi = 0, \quad i \neq j$$

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Solution: response surface, pdf $y(t,\xi) \approx \sum_{p=0}^{\hat{p}} y_p(t)\Psi_p(\xi)$

Basics

Response surface, pdf $y(t,\xi) \approx \sum_{p=0}^{\hat{p}} y_p(t)\Psi_p(\xi)$

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Explicit mean, variance, Sobol indices; higher moments: cheap integrals

Mean $\mu_y(t) = \int_S y(t,\xi)\rho(\xi)d\xi = y_0(t)$

Response surface, pdf $y(t,\xi) \approx \sum_{p=0}^{\hat{p}} y_p(t)\Psi_p(\xi)$
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Mean $\mu_y(t) = \int_S y(t,\xi)\rho(\xi)d\xi = y_0(t)$

Variance $\sigma_y^2(t) = \int_S (y(t,\xi))^2\rho(\xi)d\xi - \mu_y^2(t) = \sum_{p=1} y_p(t)^2||\Psi_p||^2$

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Sobol indices $S_l(t) = \frac{y_l(t)^2||\Psi_l||^2}{\sigma_y^2(t)}$ first order, independent random variables

- $n > 1$ RVs: multidimensional pdf's
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  # expansion terms: $N = \frac{(n+\hat{p})!}{n!\,\hat{p}!} - 1$
- arbitrarily distributed independent RVs
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- **arbitrarily multivariate distribution (2014)**
  incl. correlations between RVs
  In collaboration with J. Witteveen - Scientific Computing

Stochastic mathematical model

$$\mathbf{y}'(t,\xi) = \mathbf{f}(t,\mathbf{y}(t,\xi),\xi), \qquad \mathbf{y}(0,\xi) = \mathbf{y}_0(\xi)$$

ξ CORRELATED multi-variate random variable and $\rho(\xi)$ its pfd

How to compute $\mathbf{y}(t,\xi)$ taking correlations into account?

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How to compute $\mathbf{y}(t,\xi)$ taking correlations into account?
multivariate arbitrarily distributed PCE

Orthogonal polynomials for correlated inputs

The polynomials have to be orthogonal with respect to the inner product $<,>$ with $\rho(\boldsymbol{\xi})$

$$\langle \Phi_i(\boldsymbol{\xi}), \Phi_j(\boldsymbol{\xi}) \rangle = \int_{\Xi} \Phi_i(\boldsymbol{\xi}) \Phi_j(\boldsymbol{\xi}) \rho(\boldsymbol{\xi}) \mathrm{d}\boldsymbol{\xi} = ||\Phi_i||^2 \delta_{ij},$$

A) For **independent** random variables: Φ_i's are tensor products of one-dimensional polynomials, $\Phi_i(\boldsymbol{\xi}) = \prod_{j=1}^{n} \tilde{\Phi}_i(\xi_j)$

B) For **correlated** random variables: By applying GRAM-SCHMIDT orthogonalization to a set of of linearly independent polynomials $\{e_j(\boldsymbol{\xi})\}_{j=0}^{N}$ given by

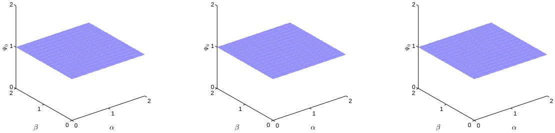
$$e_j(\boldsymbol{\xi}) = \prod_{l=1}^{n} \xi_l^{j_l}, \quad j = 0, \ldots, N, \; j_l \in \{0, \ldots, p\}, \text{ and } \sum_{l=1}^{n} j_l \leq p,$$

E.g., if $n = p = 2$ then $N + 1 = 5$ and the set of linearly independent polynomials $\{e_j(\xi_1, \xi_2)\}_{j=0}^{5}$ equals $\{1, \xi_1, \xi_2, \xi_1^2, \xi_2^2, \xi_1\xi_2\}$

Orthogonal polynomials for correlated inputs

Order 0:

$\varrho = -0.5$ $\varrho = 0$ $\varrho = 0.5$



Order 1:

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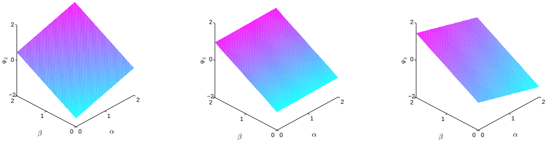

Order 2:

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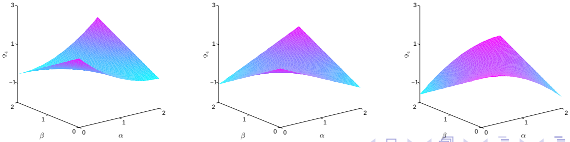

Explicit mean, variance, Sobol indices

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Sobol indices $\mathrm{S}_{\boldsymbol{I}}(t) = \frac{\mathrm{Cov}[M_{\boldsymbol{I}}(t,\boldsymbol{\xi}_{\boldsymbol{I}}),\boldsymbol{y}]}{\sigma^2_{\boldsymbol{y}}(t)} = S^u_I(t) + S^c_I(t)$, with

$$S^u_I(t) = \frac{\mathrm{Var}[\mathrm{E}_{\boldsymbol{\xi}_{\neg I}}[\boldsymbol{y}|\boldsymbol{\xi}_I]]}{\sigma^2_{\boldsymbol{y}}(t)},\ \text{and}$$

$$S^c_I(t) = \frac{\mathrm{Cov}[\mathrm{E}_{\boldsymbol{\xi}_{\neg I}}[\boldsymbol{y}|\boldsymbol{\xi}_I],\boldsymbol{y}-\mathrm{E}_{\boldsymbol{\xi}_{\neg I}}[\boldsymbol{y}|\boldsymbol{\xi}_I]]}{\sigma^2_{\boldsymbol{y}}(t)}$$

CWI

Example

$$\mathrm{E} + \mathrm{S} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{C},$$

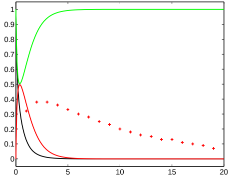
$$\mathrm{C} \overset{k_3}{\rightarrow} \mathrm{E} + \mathrm{P}$$

Example

$$E + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} C,$$

$$C \xrightarrow{k_3} E + P$$

Parameter estimation



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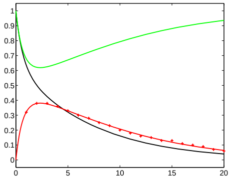

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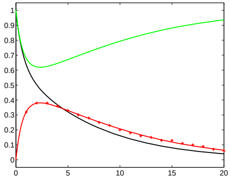
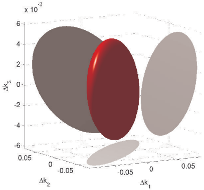


Uncertainty in parameters



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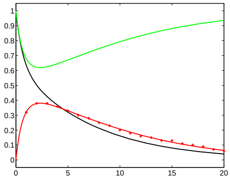


Uncertainty in parameters

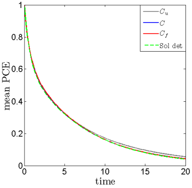
$\Delta^I(k_1)$	$\Delta^I(k_2)$	$\Delta^I(k_3)$
0.295	0.169	0.008

$$R_{20} = \begin{pmatrix} 1 & 0.9 & -0.37 \\ 0.9 & 1 & -0.45 \\ -0.37 & -0.45 & 1 \end{pmatrix}$$

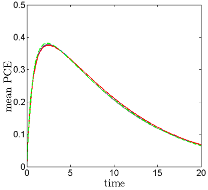
Correlations effect?

Example

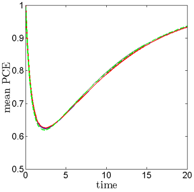
FIGURE : Means



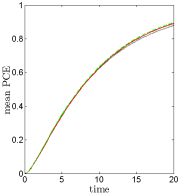
(A) Substrate S



(B) Complex C

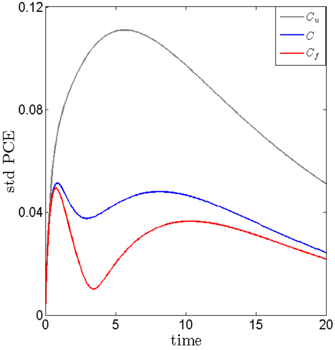


(C) Enzyme E

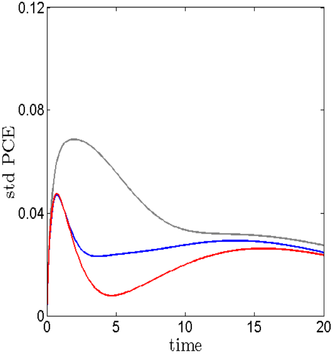


(D) Product P

FIGURE : Significant qualitative effect of correlation on standard deviation



(A) Substrate S



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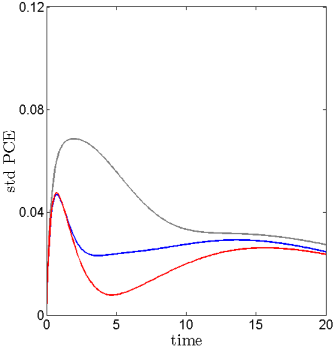

FIGURE : Significant qualitative effect of correlation on standard deviation

(A) Enzyme E

(B) Product P

Conclusions and Future works

- Study the UQ of the QoIs helps us to know the quality of the model predictions
- Sobol indices: ranking influence of RVs (uncertain parameters) $\rightarrow$ reduction
- Take correlations into account
- Develop Gauss quadrature based on new polynomials

Thank you