Dynamics of Biochemical Networks with Known Topology and Uncertain Parameters

Kinetic
Modeling
Group

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Problem

Functional properties of biochemical networks depend on both the network structure and the kinetic parameters. While extensive data on network topologies have been collected in databases like KEGG [1], much less information is available about the kinetic constants or metabolite concentrations. Depending on the values of these parameters, network variables (here: steady state fluxes, metabolite concentrations, or metabolic control coefficients) may vary within a wide range. We study [2] whether topological knowledge, together with uncertain or partial knowledge of the parameters, can be used to make probabilistic statements about the network variables. Assuming that the parameters follow statistical distributions, we calculate the resulting distributions of the network properties, applying Monte Carlo simulation and an approximation method based on Metabolic Control Analysis [3,4].

Biochemical Reaction Networks

Differential equation systems for change of metabolite concentrations c_i:

$$\frac{ds_i}{dt} = \sum_{j=1}^{r} n_{ij} v_j \qquad \vec{\boldsymbol{s}} = \boldsymbol{N}\vec{\boldsymbol{v}}(\vec{\boldsymbol{s}},\vec{\boldsymbol{\pi}})$$

$N = \{n_{ij}\}$ – stoichiometric coefficients,
v_j – rates, p – parameters

The dynamical/functional properties of a biochemical reaction network depend on both its structure and its parameters.

Network structure Q
- Reaction stoichiometry
- Irreversibility / Reversibility
- External metabolites
- Activation / Inhibition
- Feedback / Feedforward regulation

Network parameters *p*

Real positive numbers with units
- Concentrations of external metabolites
- Kinetic parameters: Rate constants k_i
  Inhibition constants
  K_m-values, V_{max}
- Equilibrium constants, from ΔG

Network properties *Z = Z*(Q,p)

Steady state properties: concentrations, fluxes, elasticities, control coefficients, ...

Dynamic behavior: bifurcations, oscillations, characteristic times ...

- Reaction systems can show steady states, oscillations, chaos
- Assume steady state $\boldsymbol{s}_{SS}$ with stationary fluxes $\vec{J} = \vec{\boldsymbol{v}}(\vec{\boldsymbol{s}}_{SS},\vec{\boldsymbol{\pi}})$

- Response coefficients quantify, in first order, the change of steady states after perturbation of the system.

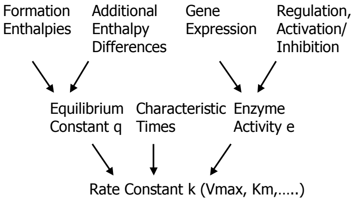
$$R^{Y_i}_{p_j} = \frac{\partial \ln Y_i}{\partial \ln p_j}$$

R – response coefficient,
Y – flux or concentration, resp.

Parameter Distributions

Quantify uncertain knowledge about kinetic parameters
- Measurement uncertainty
- Biological variability
- Choice of parameter values from a typical range

We use log-normal distributions in all these cases.


Formation Enthalpies
Additional Enthalpy Differences
Gene Expression
Regulation, Activation/ Inhibition
Equilibrium Constant q
Characteristic Times
Enzyme Activity e
Rate Constant k (Vmax, Km,…..)

To account for dependencies (e.g. imposed by thermo-dynamical constraints), we express the parameters by underlying independent parameters

Distributions of Variables

Monte Carlo sampling

Simulations with random parameters from the specified distribution yield samples from the true distribution of variables.

Analytical approximation

- Applicable to parameters of small variance
- Linearize system around standard parameter set (mean log. parameters)
- Variables are log-normal, with covariance matrix

$$\mathrm{cov}(\log \boldsymbol{y}) = \hat{\boldsymbol{R}}^{\boldsymbol{y}}_{\boldsymbol{p}}\, \mathrm{cov}(\log \boldsymbol{p}) \left(\hat{\boldsymbol{R}}^{\boldsymbol{y}}_{\boldsymbol{p}}\right)^{\mathrm{T}}$$

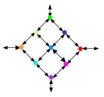
where $\hat{\boldsymbol{R}}^{\boldsymbol{y}}_{\boldsymbol{p}}$ denotes the matrix of normalized response coefficients.

The coefficients of variation for single variables read:

$$\sigma_i / \mu_i = \sqrt{\mathrm{e}^{\mathrm{var}(\log y_i)} - 1}$$

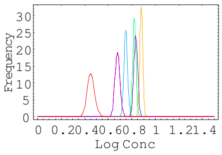
Example: Branched Reaction Networks

Branched reaction network with or without features like feedback inhibition or irreversibility: Upon varying parameters (chosen independently), steady state concentrations and fluxes are smeared over several orders of magnitude.



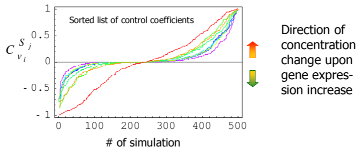
Concentrations

Lognormal distribution

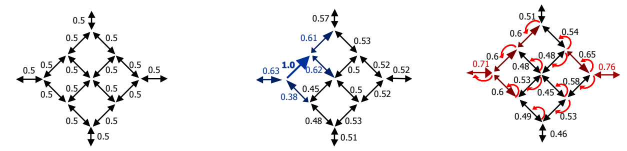


Concentration control coefficients

Change sign upon parameter variation



Sign of fluxes Relative number of positive fluxes in 10^4 simulation runs.



equal probabilities for all parameters
equal probabilities for all flux directions

with one irreversible reaction:
local effects

with feedback inhibition

The network structure has a probabilistic influence on the flux directions, without determining them strictly.

Conclusions

Using probability distributions of kinetic parameters, we could infer probabilistic statements about network variables. We propose to measure the robustness of dynamic quantities (steady state fluxes, concentrations etc.) with respect to the variability of kinetic parameters by the respective coefficients of variation. The investigation of networks structures must be accompanied or accomplished by studying the kinetics of the individual interactions.

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