Variation of metabolic network properties for fixed network topology

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Abstract

Functional properties of metabolic networks depend on both the network structure and the kinetic parameters. Some of the properties may show little variation over a wide range of parameter values. Our aim is to calculate the distributions of network properties (such as stationary fluxes or control coefficients) for a given ensemble of parameter values, in order to determine weakly varying functional properties from the network structure. The distributions of network properties are estimated by Monte-Carlo simulations: the parameter values are drawn from statistical distributions, while the network structure is kept fixed. The parameter distributions chosen are supposed to describe prior knowledge: sharp distributions can account for the uncertainty of a known parameter value, while unknown parameter values may be characterised by broad distributions. We assume log-normal distributions for all positive parameters, such as external metabolite concentrations or rate constants. Due to the structural features of networks, some qualitative patterns are found with a high probability although they are not strictly forced by the network structure.

Metabolic systems

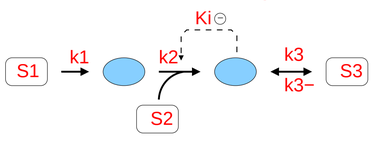
- Differential equations for metabolite concentrations $s(t)$.

$$\dot{s} = Nv(s, \pi)$$

N denotes the stoichiometric matrix, v the flux velocities, and π the system parameters.

- Metabolic systems can show steady states, oscillations, chaos.
- Assume steady state S with stationary fluxes $J = v(S, \pi)$. Metabolic control analysis [1] studies how the steady state depends, in first order, on perturbations of the system.

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



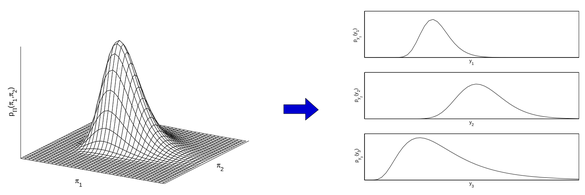
Network structure Σ
- Reaction stoichiometries
- Irreversible reactions
- External metabolites
- Activation/inhibition of enzymes

Network parameters π
(real or positive numbers)
- Concentrations of external metabolites
- Kinetic parameters, e.g. rate constants k^i_+, k^i_-, inhibition constants K_i, ...
- Free energies of metabolites $\rightarrow$ equilibrium constants

Network properties $y_i = y_i(\Sigma, \pi)$
(real, positive, or binary numbers or matrices)
- Qualitative behaviour: existence of steady state, oscillations, ...
- Steady-state properties: concentrations, fluxes, elasticities, control coefficients, ...
- Properties derived from the ones above: absolute values, signs, order relations, correlations, ...

Random parameters lead to property distributions

The values of network parameters are often uncertain or completely unknown. We treat them as random variables Π, distributed with a density $p_\Pi(\pi)$, and yielding a distribution of network properties Y with density $p_Y(y)$.



Due to the network structure, some network properties may be invariant, i.e., independent of the choice of parameters.
- Signs of some steady-state-fluxes (visible from elementary modes)
- Invariants due to theorems of metabolic control theory, e.g., $C^S K = 0$ and $C^J \epsilon L = 0$

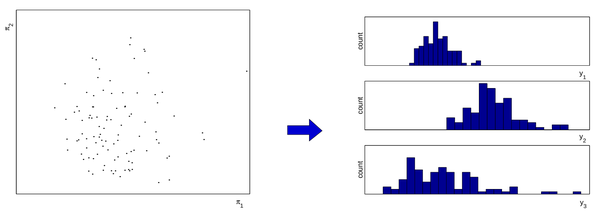
Our aim: Study the distributions of network properties for a given ensemble of parameter values, in particular those which show a finite but small variation, due to the network structure.

Distributions for the network parameters

- Unknowm positive parameters π:
  Log-normal distribution, i.e. $log_{10}(\pi)$ is normally distributed with mean 1 and standard deviation σ. Identical, independent distributions for the different parameters.
  A log-normal distribution can result from the multiplication of many independent random effects.
- Mass-action rate constants:
  The equilibrium constant fulfils $q = k_+/k_- = exp(-\beta \Delta F)$.
  Dicing the rate constants k independently would lead to inconsistencies. Dice (normal) free energies F and (log-normal) products $k_+ k_- \rightarrow$ solve for k_+ and k_-.

Monte-Carlo simulation

Aim: to estimate the distribution of a network property Y.
Use Monte-Carlo (MC) approach to draw samples y.

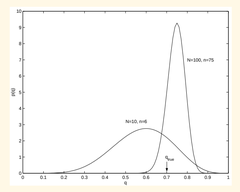


- Draw parameter values π according to density $p_\Pi(\pi)$
- Calculate network property $y = y(\Sigma, \pi)$
- The resulting values y are distributed according to $p_Y(y)$

Estimation error

A finite number of Monte Carlo samples allows to estimate the true distribution of Y. The number of samples needed does not depend on the size and complexity of the system.

Example:
- Binary property y with values ± 1 e.g., a flux direction.
- True distribution described by $q = p_Y(y = 1)$.
- Estimate q by sampling:
  Bayesian treatment with a flat prior
  If n out of Na samples were positive, q is estimated by $\langle q \rangle = (n+1)/(N+2)$, with an error $\sigma_q \leq \sqrt{1/(2(N+3))}$.



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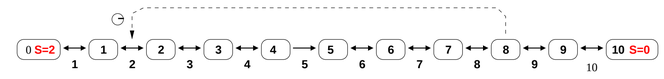
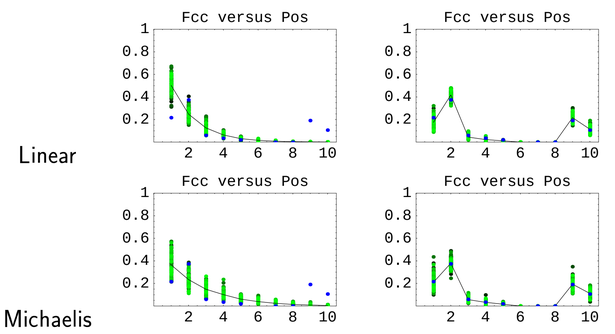
Example: flux control in a linear chain



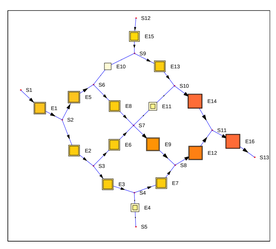
- Structural features:
  reaction 5 irreversible, enzyme 2 inhibited by metabolite 8
- Fixed external metabolites, equilibrium constants = 2
- "True" Michaelis-Menten kinetics for all reactions:
  $v^+_{max} = 4, v^-_{max} = 3, K^+_m = 2, K^+_m = 3$
- Random parameters: log-normal parameters with mean 1, standard deviation 0.25.



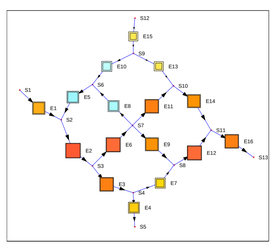
Example: flux directions on a square grid

- Fixed ext. metabolites $S_{ext} = (1, 0.5, 0.5, 0.1)^T \rightarrow$ concentration decline
- Gaussian free energies with $\sigma(log_{10}\, F) = 1$
  Log-normal products $(k_+ k_-)$ with $\sigma = \mathrm{Std}(log_{10}(k_+ k_-)) = 0.5$.
- Calculate probabilities of flux directions from 20 MC runs

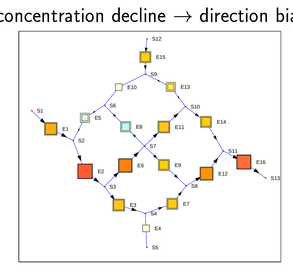
The squares dento the flux direction bias $b = \mathrm{Prob}(y > 1) - 0.5$
(color code: positive negative) Inner/outer square area: mean and standard deviation.



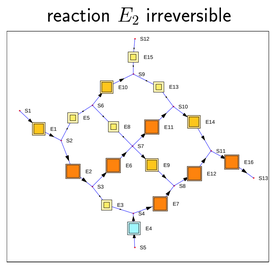
concentration decline $\rightarrow$ direction bias



reaction E_2 irreversible



E_2 irreversible, $\sigma = 1$



same, estimation from 5 MC runs

Discussion

- Obtain more functional information from the network structure: which functional properties can be determined with high probability?
- The approach may be useful where much more structural than kinetic information is available.
- The results depend strongly on the prior distributions. For sharp priors, properties vary according to their their linear sensitivities [2].
- The accuracy of the Monte-Carlo estimation does not depend on the system's complexity. The Monte-Carlo approach used is, of course, not restricted to metabolic systems.

References

[1] R. Heinrich and S. Schuster, The regulation of cellular systems, Chapman & Hall, 1996

[2] J. R. Small and D. Fell, Metabolic control analysis. Sensitivity of control coefficients to elasticities. Eur.J.Biochem. 191 (1990), 413-420