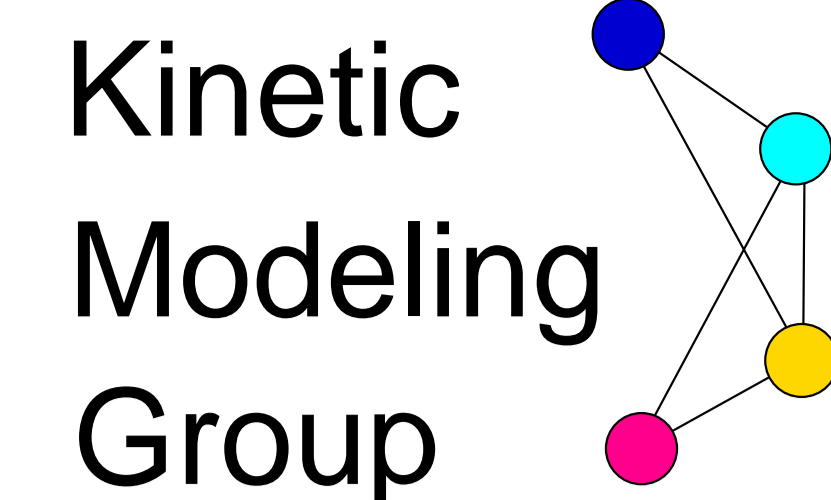




Metabolic control analysis with temporal parameter fluctuations

Wolfram Liebermeister lieberme@molgen.mpg.de

Max Planck Institute for Molecular Genetics, Ihnestr. 73, 14195 Berlin. www.molgen.mpg.de/~ag_klipp
BCB - Berlin Center for Genome Based Bioinformatics

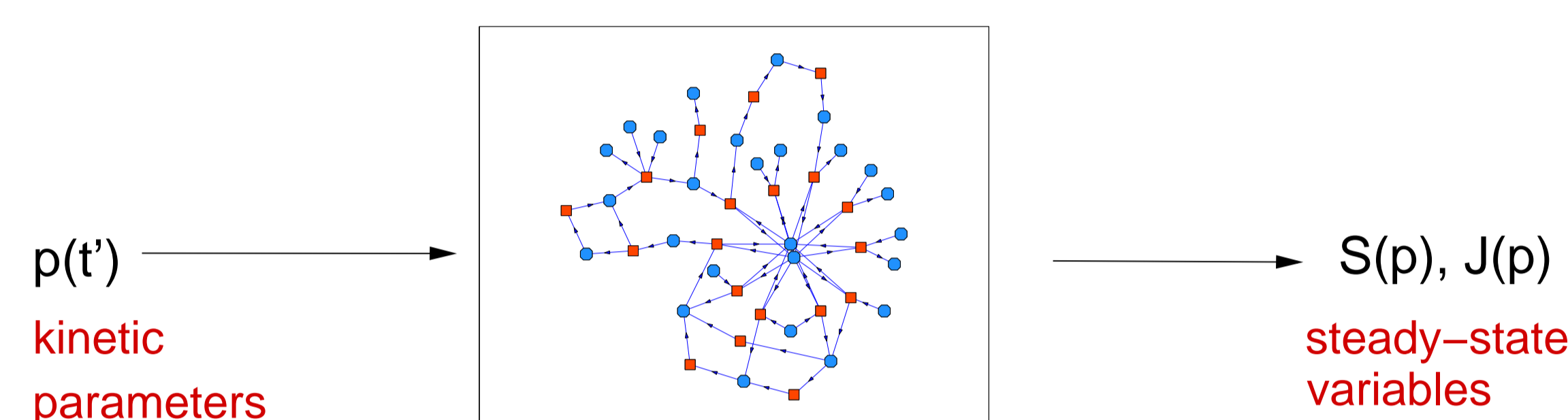


Abstract

Metabolic response coefficients describe how dynamic properties of metabolic systems - like steady state concentrations - respond to small, time-independent changes of the kinetic parameters. We extend this concept to temporal parameter fluctuations and define spectral response coefficients that relate Fourier components of concentration time courses to Fourier components of the underlying parameters. The spectral response coefficients describe forced oscillations of the concentrations and fluxes, caused by small harmonic oscillations of single parameters. They depend on the driving frequency and comprise the relative phases and amplitudes. To illustrate the basic idea, only first-order response coefficients for metabolic concentrations are addressed on this poster.

Metabolic control analysis of steady states

Stable metabolic system: Each choice of the kinetic parameters (enzyme activities, Michaelis constants, etc.) leads to certain steady state concentrations



Expand the stationary concentrations S_l after a parameter change Δp :
Metabolic response coefficients (see [2]):

$$S_l(\mathbf{p}^0 + \Delta \mathbf{p}) \approx S_l(\mathbf{p}^0) + \sum_m R_{lm}^S \Delta p_m \quad R_{lm}^S := \frac{\partial S_l(\mathbf{p})}{\partial p_m}$$

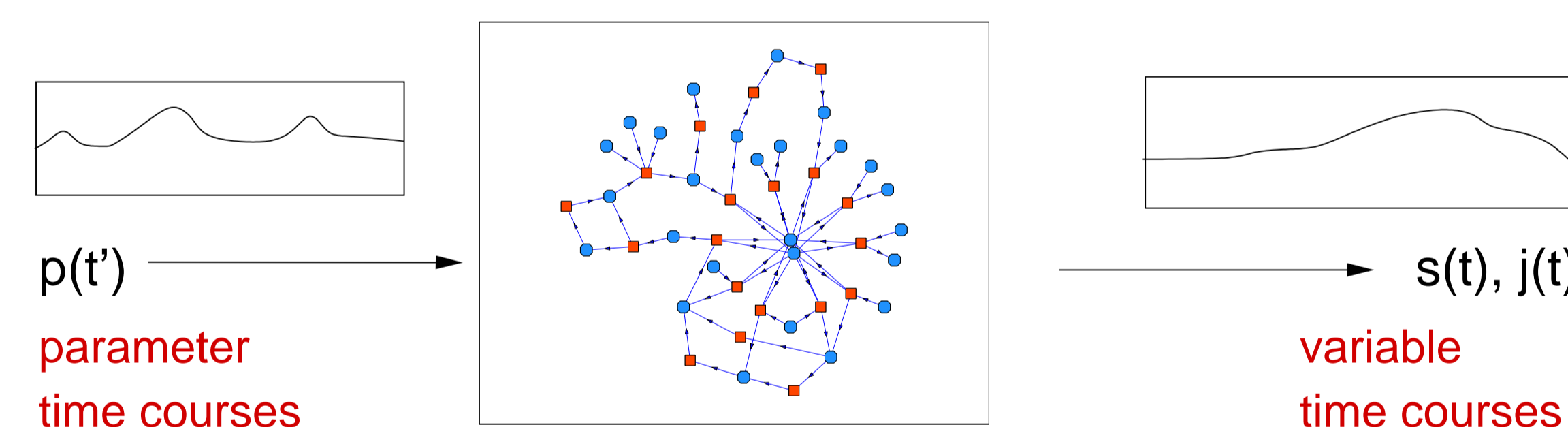
Computation:

- Consider the stationarity condition $0 = \dot{\mathbf{x}} = \mathbf{N}\mathbf{v}(\mathbf{x}, \mathbf{p})$ v_k : kinetics functions
 - Differentiation by \mathbf{p} yields $\mathbf{R}^S = -(\mathbf{N}\boldsymbol{\epsilon}_s)^{-1}\mathbf{N}\boldsymbol{\epsilon}_p$
- with stoichiometric matrix \mathbf{N} and reaction elasticities $(\epsilon_s)_{kl} := \frac{\partial v_k}{\partial x_l}$, $(\epsilon_p)_{km} := \frac{\partial v_k}{\partial p_m}$

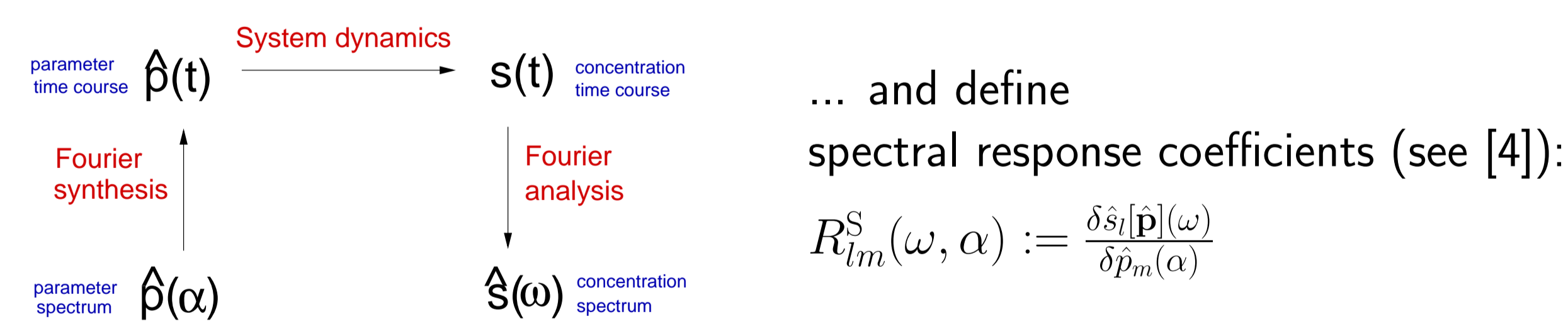
Spectral response coefficients

Parameter fluctuations:

Instead of parameter vectors, we now consider vectorial time courses



Describe the time courses by their Fourier spectrum...



Computation:

- Consider the system equation $\dot{\mathbf{x}} = \mathbf{N}\mathbf{v}(\mathbf{x}(t), \mathbf{p}(t))$
- Fourier transformation yields $i\omega \hat{\mathbf{s}}(\omega) = \mathbf{N}\hat{\mathbf{j}}(\omega)$ \mathbf{j} : fluxes
- Differentiation by \mathbf{p} yields $\mathbf{R}^S(\omega, \alpha) = -(\mathbf{N}\boldsymbol{\epsilon}_s - i\omega\mathbf{I})^{-1}\mathbf{N}\boldsymbol{\epsilon}_p\delta(\omega - \alpha)$

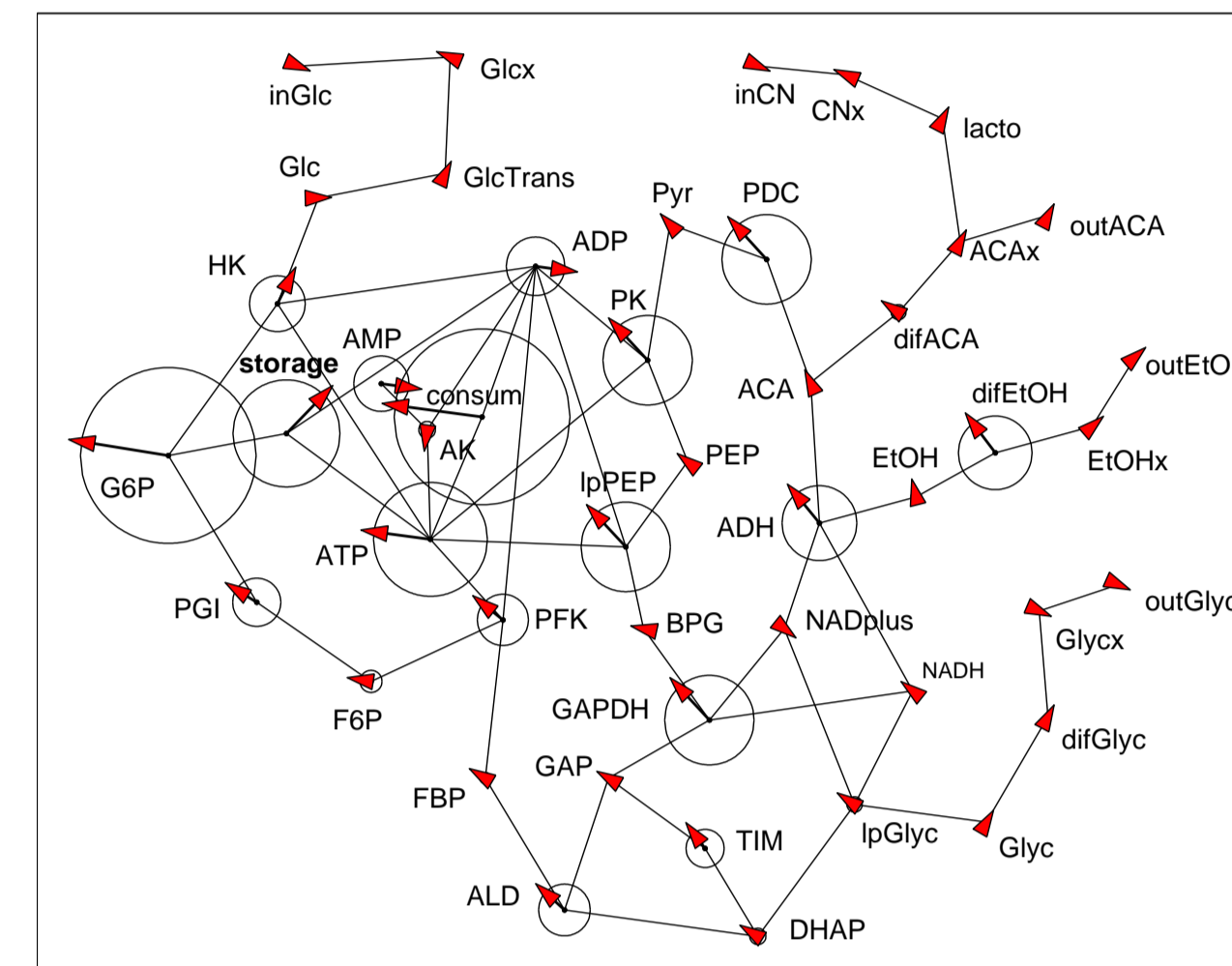
- The spectral response coefficients are complex and frequency-dependent.
- They describe the response to a harmonic oscillation of a parameter.
- They may show resonance near Hopf bifurcations.
- To account for conservation relations \Rightarrow Restriction to independent metabolites (see [5])

Example: Glycolysis model

We start with the glycolysis model from Hynne et al. (2001) (see [3]) at a stable steady state (low external glucose concentration $\text{Glc}_{\text{ext}}=5.0$).

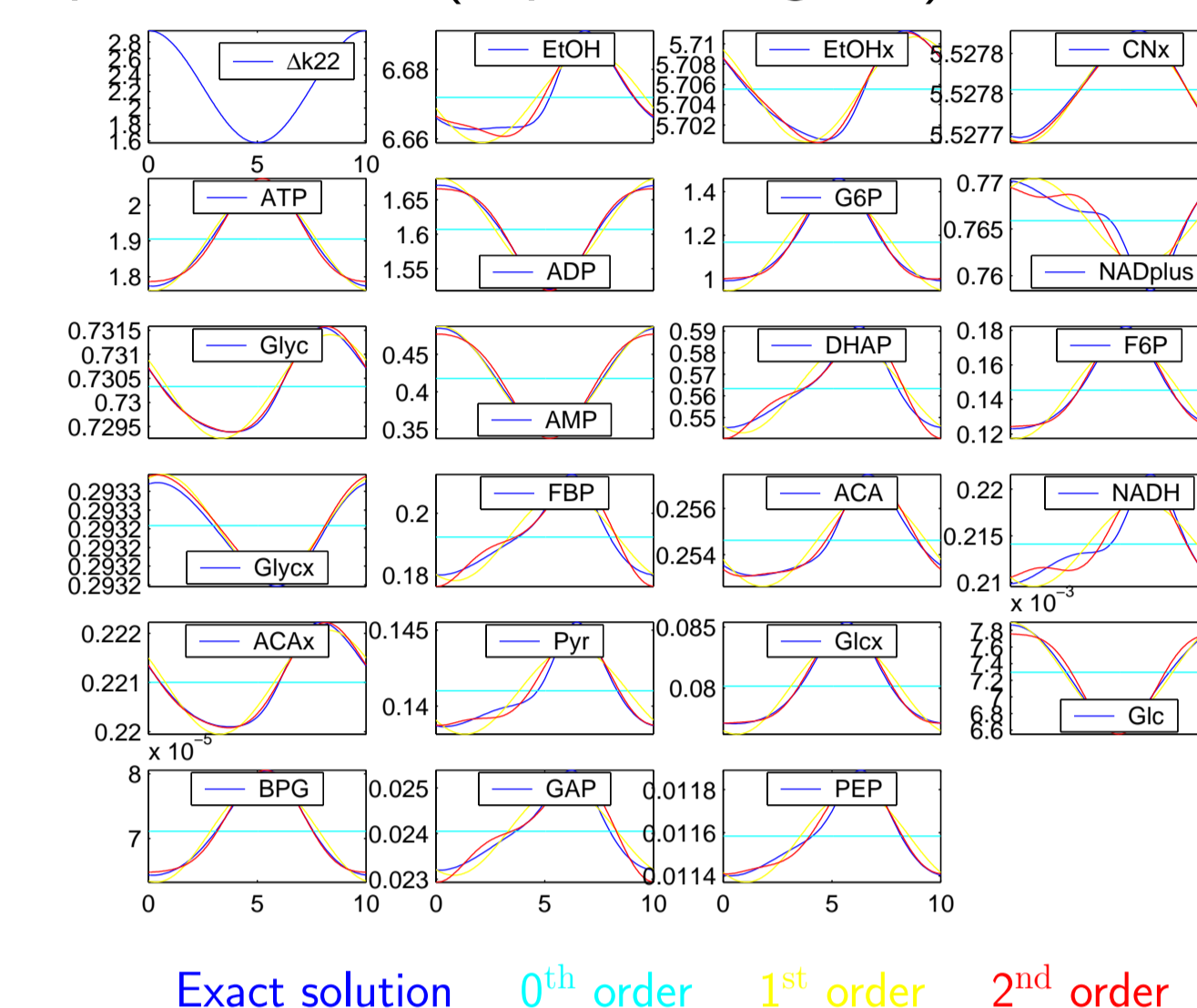
The storage reaction (parameter k_{22}) is perturbed by a harmonic oscillation of frequency $\alpha = 2\pi/(10 \text{ min}) \Rightarrow$ Forced oscillations of all concentrations.

Spectral response coefficients of concentrations and fluxes



Glycolysis network (shown by nodes and straight lines). Arrows represent the complex values of the response coefficients.

Temporal response to an oscillatory perturbation (top left diagram)



Time courses for general perturbations can be computed via Fourier synthesis.

Propagation of stochastic fluctuations

Stochastic fluctuations due to small particle numbers can be described by the chemical Langevin equation (see [1])

$$\frac{d}{dt}\bar{x}_i(t) = N_{ik} a_k(\bar{\mathbf{x}}(t)) + N_{ik} \sqrt{a_k(\bar{\mathbf{x}}(t))} \eta_k(t)$$

\bar{x}_i : molecule numbers
 a_k : propensity functions
 η_k : white standard noises

After linearisation around the mean concentrations $\bar{\mathbf{x}}^0$, the fluctuations can be described by virtual noise parameters with elasticities

$$\boldsymbol{\epsilon}_p := (n \text{ liters/mol})^{-1/2} \text{diag}(\mathbf{v}(\bar{\mathbf{x}}^0))^{1/2}$$

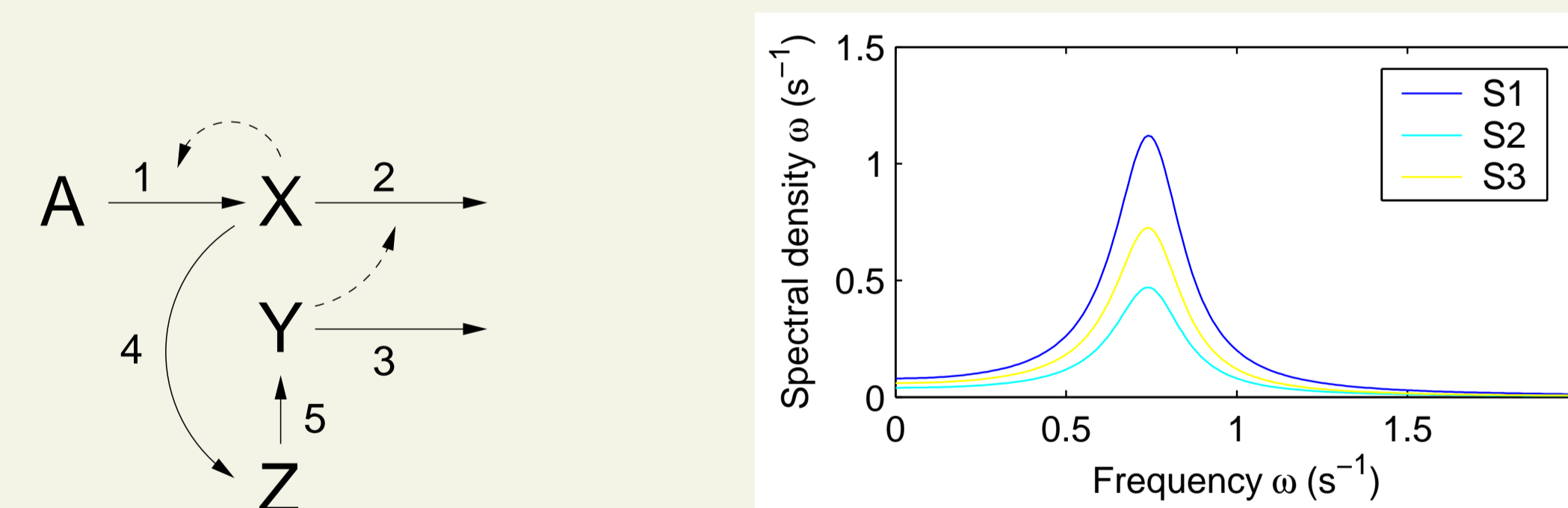
n : average molecule number at 1 mol/liter, n liters/mol = $N_A \Omega$
 Ω : system volume
 N_A : Avogadro's constant

Concentration fluctuations are quantified by their spectral densities:

$$S^S(\omega) = R^S(\omega) R^{S^T}(\omega) = n^{-1} (\mathbf{N}\boldsymbol{\epsilon}_s - i\omega)^{-1} \mathbf{N} \text{diag}(\mathbf{v}^*) \mathbf{N}^T (\mathbf{N}\boldsymbol{\epsilon}_s + i\omega)^{-1^T} \cdot \text{liters/mol.}$$

Example: Minimal reaction system (3 substances) with Hopf bifurcation [6]

Stable steady state in a cubic volume $(3.9 \text{ nm})^3$ containing, on average, $n = 100$ molecules of each substance \Rightarrow Spontaneous fluctuations of concentrations



Note the resonance - below the bifurcation- near the oscillation frequency $\omega_0 \approx 0.75 \text{ s}^{-1}$ of the bifurcation point.

Not shown here...

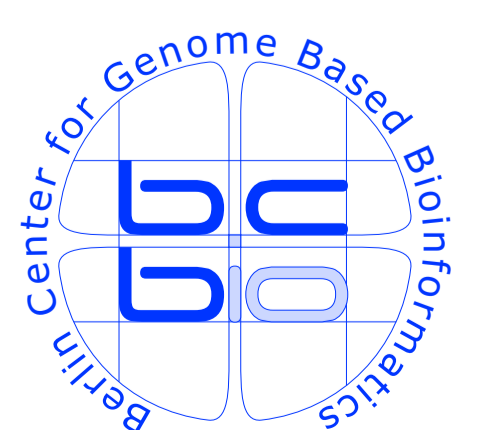
Based on the same idea, it is also straightforward to compute (see [4])

- Response coefficients for fluxes
- Second-order response coefficients
- Control coefficients (1st and 2nd order)
- Summation and connectivity theorems

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