Optimal Input Design for Network Reverse Engineering

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Background

- Network Reverse Engineering addresses the question of finding the structure of a (unknown) network given input/output data (e.g. metabolic concentrations, transcription data, etc)
- Not much research has been conducted in experimental and input design for this problem in an attempt to maximize the information content of the experimental data (Fisher Information) w.r.t. parameter estimation

We suggest
- a careful design of the experiments
- better parameter estimation results
- a more reliable reconstruction of the network structure

Method

1. Perform an arbitrary experiment and use the input-output data as a first guess for determination of the parameters in the Jacobi matrix $A = \frac{df}{dx}(x(t),u(t))$
2. Analyse the resulting linear system, where the primary goal is now to maximize information content w.r.t. the Jacobi matrix parameters, using input or state perturbations
$$\frac{d(\delta x(t))}{dt} = A\delta x + B\delta u$$
3. The results of the second step yield an ‘optimal’ perturbation that can now be used in an improved new experiment
4. If necessary, repeat step (2) with the new parameter estimates as to further improve the condition number of the Fisher Information Matrix

This method yields an adaptive optimal input design

Future work

1. Refinement of parameter estimation method, i.e. include prediction-error methods (L. Ljung) that naturally include constraints on the parameter estimates
2. Test this method on a larger network

Test Cases

Laub-Loomis metabolic network

The Laub-Loomis model describes a metabolic interaction underlying cAMP oscillation observed in Dicyostelium discoideum cells. The figure below shows convergence to a steady oscillation behavior after an ‘optimal’ initial perturbation

Our method yields the interaction matrix (see figure below). The blue dots indicate a direct interaction between nodes.

Four gene network model (Kholodenko et al.)

The figure below shows the mRNA concentrations due to an ‘optimal’ (constant) input perturbation, i.e. a change in the maximal enzyme rates appearing in the non-linear relations for synthesis and degradation of mRNA.

Our method yields the interaction matrix (see figure below). The blue dots indicate a direct interaction between nodes.

References