

A quantitative method for reverse engineering gene networks from microarray experiments using regulatory strengths

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ABSTRACT

Functioning of living systems is orchestrated by selective expression of genes. Expression of genes is modulated by specific proteins (activators and/or inhibitors) and metabolite effectors, which are gene products themselves. One can thus consider networks of genes in which some genes modulate the expression of others – gene regulatory networks. Uncovering such networks is essential to the understanding how the biological machinery of cells works and consequently to manipulate it to our advantage.

We propose a method for reverse engineering gene regulatory networks from microarray gene expression data. The method is based on metabolic control analysis [1] [2] and requires data from microarray gene expression experiments where the rate of change of a single gene has been perturbed. Gene regulatory interactions are quantified through “regulatory strengths” [3], which are determined from co-responses of messenger RNA to a common perturbation.

The method is comprised of several steps. First perturbations are made in the transcription rate of genes, one gene at a time, and changes in all mRNA concentrations are measured. From these measurements matrices of co-control coefficients [4] can be calculated. These matrices are inverted to yield regulatory strength matrices that contain quantitative information about the regulatory structure of the gene network. The elements of these matrices, regulatory strengths, quantify direct and indirect effects of one gene on another. By taking the regulatory strengths that describe direct interactions between genes and combining them in a single matrix we obtain the ‘gene regulation matrix’. This matrix represents the genetic network. The diagram can be drawn according to the matrix’ elements: positive regulatory strengths indicate activation influences, negative, -- inhibition effects, and a zero value means that there is no direct interaction.

A global gene regulatory network can be uncovered by this method if applied systematically to all genes in a genome. Alternatively, the method can be applied to a subset of genes in which case it identifies a phenomenological gene network that contains, beside direct interactions, contributions from indirect interactions (via the genes that were not considered). This

indicates that we can start applying the method on a subset of genes of the whole genome first to get a more phenomenological, but quantitative, view on the regulatory structure of genetic networks of living organisms and then increase the resolution by increasing the number of perturbations.

The application of the method is illustrated by analyzing data produced with computer simulations of model gene regulatory networks using the biochemical simulator Gepasi [5]. The analysis we employed is based on infinitesimal changes, but performed well even when perturbations were as large as two-fold.

Supplementary materials are available at
<http://www.vbi.vt.edu/~mendes/icsb01-supp.html>

REFERENCES

- [1] Kacser, H. and J.A. Burns, *The control of flux*. Symp. Soc. Exp. Biol., 1973. 27: p. 65-104.
- [2] Heinrich, R. and T.A. Rapoport, *A linear steady-state treatment of enzymatic chains. Critique of the crossover theorem and a general procedure to identify interaction sites with an effector*. Eur. J. Biochem., 1974. 42: p. 97-105.
- [3] Kahn, D. and H.V. Westerhoff, *The Regulatory strength: how to be precise about regulation and homeostasis*. Acta Biotheoretica, 1993. 41: p. 85-96.
- [4] Hofmeyr, J.H.S., A. Cornish-Bowden, and J.M. Rohwer, *Taking enzyme kinetics out of control - putting control into regulation*. European Journal of Biochemistry, 1993. 212(3): p. 833-837.
- [5] Mendes, P., *Biochemistry by numbers: simulation of biochemical pathways with Gepasi 3*. Trends in Biochemical Sciences, 1997. 22: p. 361-363.