

Reconstructing Signalling Pathways using Nested Effects Models

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Abstract

Functional genomics has a long tradition of inferring the inner working of a cell through analysis of its response to various perturbations. Observing cellular features after knocking out or silencing a gene reveals which genes are essential for an organism or for a particular pathway. A key obstacle to inferring genetic networks from perturbation screens is that phenotypic profiles generally offer only indirect information on how genes interact.

I will discuss an algorithm to infer pathway features based on differential gene expression in silencing assays. In this approach, I distinguish two kinds of genes: the candidate pathway genes, which are silenced by RNAi, and the genes, which show effects of such interventions in expression profiles. I call the first S-genes (S for "silenced" or "signaling") and the second E-genes (E for "effects"). Because large parts of signaling pathways are non-transcriptional, there will be little or no overlap between S-genes and E-genes. Elucidating relationships between S-genes is the focus of our analysis; the E-genes are only needed as reporters for signal flow in the pathway. E-genes can be considered as transcriptional phenotypes. S-genes have to be chosen depending on the specific question and pathway of interest. E-genes are identified by comparing measurements of the stimulated and non-stimulated pathway; genes with a high expression change are taken as E-genes. Our approach models how interventions interrupt the information flow through the pathway. Thus, S-genes are silenced while the pathway is stimulated to see which E-genes are still reached by the signal. I will show the applicability of our methodology for two real world datasets, an RNAi study of immune response in *Drosophila melanogaster* and a study on BCR signalling in immature B-cells in mice.