

I DEFINE AS A SYSTEM

anything consisting of entities that can interact with each other. These can then be described in terms of graphs (networks) of 'nodes' (the entities) interacting via 'edges'. This rather general definition recognizes that tools for describing and understanding biochemical networks can equally well be applied to problems of ecology and population biology in which there are fluxes of matter, energy and information.

To describe properly the properties of such a system – I use metabolic networks as an example – requires four steps, in order: (i) determining the qualitative or topological structure of the network in terms of 'who talks to whom' – these are the kinds of networks observed on laboratory wall charts, and the reconstruction relies on genomic, biochemical and literature data; (ii) determining whether the interactions are direct (as in an actual reaction that transforms substances chemically) or indirect (such as where an entity modifies that step, e.g. by activating or inhibiting it); (iii) adding the kinetic rate equations for each of the steps; (iv) determining their parameters (mainly kinetic and binding coefficients). The first two steps are qualitative, the last two quantitative.

Given such information, preferably encoded using a standard such as the Systems Biology Markup Language SBML (www.sbml.org), it is then possible to provide a stochastic or ordinary differential equation model of the entire metabolic network of interest, and to 'run' that model to provide the time evolution of the system variables (typically metabolic fluxes and concentrations). There are then many other things one might do with such a model, including comparing the predicted variables with those measured experimentally, seeking to estimate the parameters from the measured variables ('system identification' or 'solving the inverse problem') or seeing which changes in the network might beneficially change the system, e.g. for biotechnological purposes. A particularly

Systems microbiology

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How can the principles and techniques of systems biology be applied to microbiology?

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important set of techniques known as sensitivity analysis seeks to determine the relative importance or contribution of all the various steps in the network to the variables measured, since this allows experimenters to concentrate on those that matter.

Imagine a network with 1,000 enzymes. If knocking out just three of them would give a huge increase in a desirable flux, it should be a simple piece of molecular biology to effect this. The problem is that there are more than 100 million ways of choosing three from 1,000. However, the combination of sensitivity analysis and 'what if?' modelling allows one to search huge areas of the search space of possible networks *in silico* when seeking rational improvements in bioprocesses, and 100 million is not then a large number. This is the way to do business.

To conclude, systems methods are at the heart of modern microbiology, and are already revolutionizing how we work. The needs are user-friendly bioinformatics tools to integrate the many kinds of data, including high-throughput sequencing data, 'omics data and biochemical network properties that together will help us solve the problems of systems microbiology.

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FURTHER READING

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