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Editorial

New approaches to modelling and analysis of biochemical reactions, pathways and networks

One of the most profound observations arising from the genome sequencing of different species is the similarity, rather than the differences, apparent in the various sequences. This similarity is reflected not only in the numbers of protein-coding genes (Claverie, 2001), but also in the degree of homology between the genes belonging to different species (Boguski, 2002). What are we to make of this observation? Functional genomics aims to make biological sense of this genome information: to go from a list of components to an operational wiring diagram for an organism. This is of course a major challenge, and there is a growing acceptance that mathematical and computational approaches are needed to make progress.

One possible outcome of the functional genomics programme would be the finding that similar sets of genes in different developmental programmes or in different organisms are hooked up in different ways, and that biological complexity will be explained by the huge combinatorial possibilities for networks of interactions between genes. There is much current interest in the structure of biological networks of various types, in particular focusing on their topology (Barabási and Oltvai, 2004). Certain organisational properties appear to be a recurrent feature of biological systems. For example, a scale-free probability distribution for network connectivity has been reported in systems as diverse as protein folding (Koonin et al., 2002), networks of metabolic reactions (Jeong et al., 2000; Wagner and Fell, 2001) and ecological food webs (Solé et al., 2003), and might point to a common evolutionary mechanism: preferential attachment according to the number of existing connections. Network topology is implicated in conferring robustness of network properties, for example in setting up patterns of cellular differentiation in gene regulatory networks in the early development of the fruit fly (von Dassow et al., 2000; Albert and Othmer, 2003).

This static picture cannot tell us everything, however, and it is difficult to predict functional properties of networks from topological information alone (Bray, 2003). Biological systems are characterised by their regulatory and adaptive properties, from homeostatic mechanisms which maintain constant output levels to switching between alternative substrates or developmental pathways. Regulatory mechanisms including thresholds, allosteric interactions and feedback in gene transcription networks, metabolic pathways, signal transduction and intercellular interactions are defining biological characteristics—almost everything that happens in life boils down to enzymatic catalysis and biochemical kinetics. Another possibility, then, is that the kinetic properties of biological pathways and networks, which we know to be necessary to understand much of their functionality, are also important determinants in conferring the differences among

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the products of different genomes. In other words, variations in kinetic mechanisms and parameter values alone may be sufficient to give rise to qualitative differences in biological outcomes.

While the modelling approach has a long history in biochemical reactions and enzyme kinetics, the importance of modelling complex reactions, biochemical pathways and networks has only recently begun to be appreciated by the wider community of biochemical researchers. During the late 1960s to early 1980s, the foundations for a model-based analysis of biochemical systems were developed. There are now many excellent reviews on the subject. In the late 1970s Reinhart Heinrich and coauthors S.M. Rapoport and T.A. Rapoport published a review entitled "Metabolic regulation and mathematical models" in this journal (Heinrich et al., 1977). This classic paper sets down a number of the basic concepts for the application of the theory of dynamical systems to the study of biochemical pathways which, along with the work of Kacser and Burns (1973) amongst others, set the stage for the development of flux-oriented sensitivity analysis of reaction pathways, which has come to be called metabolic control analysis.

It is timely, therefore, some 25 years later, to reconsider progress on modelling and analysis of biochemical pathways and networks in view of the enormous changes to the biological landscape which have taken place over that time. This issue of Progress in Biophysics and Molecular Biology contains four papers concerned with modelling and analysis of biochemical pathways and networks, in each case considering their dynamical properties. One of the important ideas to emerge is modularity in the organisation of biological systems. Using comparisons with man-made and engineered devices, Sauro and Kholodenko (this volume) explore the computational properties of signal transduction pathways, drawing edifying parallels between basic analog processes and signalling cascades. If biological systems have indeed evolved in a modular fashion (which remains very much an open question) then it might be expected that similar motifs would reoccur in different surroundings, performing in each different context the same basic function (integrating several input signals, providing rapid switching and so forth). Sauro and Kholodenko provide examples of such motifs in different biological systems and show how more complex functions can be built up from basic building blocks.

While this discussion is presented in reference to signal transduction, the organisational principals may be common to all regulatory networks. Indeed, the traditional division into signalling, metabolic and gene transcription networks can to some extent be discarded in current systems-oriented approaches. Mariani et al. (this volume) discuss the control of gene transcription with reference to the differentiation of helper T lymphocytes in the immune system. In this regard, the different qualitative forms of gene regulation which they discuss (the rapid rise to a stable expression level for simple autoinhibitory regulation; bistability and switching behaviour characteristic of autoactivatory and certain cross-regulatory interactions, for example) might also be interpreted as functional motifs for gene regulatory networks, likely to crop up again and again in different gene networks in different developmental programmes. Indeed, there is now evidence from Uri Alon and coworkers (Shen-Orr et al., 2002; Milo et al., 2002) to suggest that this is in fact the case.

It is to be hoped that these ideas, which represent a form of "functional reductionism" may provide some help in making sense of the functional genomic data sets, by looking for recognisable network motifs and patterns of modular organisation. As useful as these approaches are, however, Heinrich et al. pointed out in 1977 that the "precondition" for modelling is the

correct identification of both topological and kinetic properties, which is also identified by Sauro and Kholodenko as one of the most acute problems facing the analysis of signalling pathways. Crampin et al. (this volume) present a survey of mathematical and computational techniques for identifying the mechanisms of complex biochemical reactions from data, for determining both the connectivity and the reaction kinetics. It should be apparent that if progress is to be made with the rapidity anticipated in the functional genomics community then a degree of automation of the process of modelling and data analysis must become an important area of focus.

The importance of kinetic studies does not of course stop at the regulation of intracellular processes. The kinetics of cellular networks are, similarly, just as important to the study of tissue development, movement and functionality as reaction pathways are to sub-cellular processes.[1] Roussel and Roussel (this volume) have revisited the classical reaction–diffusion models for intercellular signalling and pattern formation to show that various explicit models for intercellular signalling lead to reaction–diffusion models, averaged over the spatial scale of the cell, with the inclusion of spatially varying diffusion coefficients. Many of the results of classical reaction–diffusion models should now be reinterpreted in terms of the dynamic properties of signalling and transport in tissues, potentially with important implications for the role of cellular communication in establishing the spatial and temporal patterns of differentiation during development.

As much as the papers in this collection present advances in our understanding of the functional properties of biological pathways and networks, they also reveal just how much of the molecular detail of life remains to be understood. It is interesting to note that it is the success of gene-centric molecular biology which is ultimately likely to drive mainstream biological research to rely on systematic mathematical and computational analyses of biochemical kinetics, just as it currently relies on informatics databases and algorithms for the management and analysis of genomic and proteomic data.

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[1] Many examples of integrative kinetic approaches in the physiological setting can be found in another recent focused issue of this journal on "Modelling Cellular and Tissue Function", N.P. Smith and E.J. Crampin (Eds.), Volume 85, Issues 2–3, 2004.

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