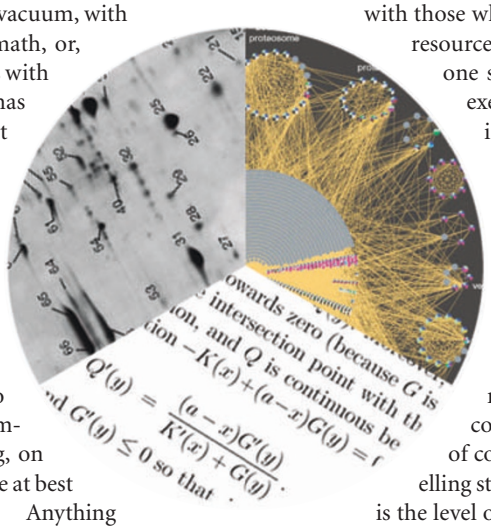
EDITORIAL

nature cell biology

Scaling cell biology: all systems go!

'Systems' and the related '-omics' are among the biggest buzzwords in cell biology at present. Nevertheless, 'systems biology' remains one of the less well-defined terms: some use it in the broadest sense to describe any approach for studying the underlying network structure of a biological system. This definition includes high-throughput approaches, bioinformatics to mine the resulting datasets, and modelling. Some narrow the definition to mathematical or *in silico* modelling of a network, separating it from large-scale approaches or 'systematics'. Others emphasize the study of the underlying physics of defined systems, or indeed the engineering of facilitating technologies.

Although systems biology has a significant history, molecular and cell biologists have only recently begun to embrace the subject with some vigour. In many ways, however, this late flowering is for the better: although the gap has left something of a vacuum, with biologists desperately scrambling to learn math, or, more realistically, attempting to make friends with people who speak the systems language, it has allowed technology to advance to a point where systems approaches to study complex molecular networks has become realistic.



Systems biology should not be denigrated as an interesting side-line to mainstream research: although traditional molecule-by-molecule approaches have been tremendously successful in building up a remarkably advanced knowledge base over the last four decades, it is impossible to derive real understanding of even the more simple pathways, say nuclear receptor signalling, on the basis of data that is often semi-quantitative at best and acquired in widely disparate settings. Anything approaching a real understanding of the dynamics of a regulatory circuit requires an accurate quantitative description of how all its components behave. This is information that large-scale approaches can provide. Advanced modelling evidently becomes more meaningful when based on such datasets. But is high-throughput biology a prerequisite for modelling in cell biology? Successful modelling of defined networks has been carried out for some time, based on literature-derived information or the construction of small engineered systems, such as defined transcriptional networks (see, for example, *Nature* **405,** 590–593 (2000), **403,** 335–338 (2000) and **403,** 339–342 (2000)). Although quantitative proteomics is the prerequisite for a golden era of holistic models that describe complex systems, advanced modelling on the basis of current knowledge is increasingly successful.

Following the trendsetting launch of the Institute of Systems Biology (http://systemsbiology.org) in 2000, many top research institutions, including Harvard (http://sysbio.med.Harvard.edu), MIT (http://csbi.mit.edu), Stanford (http://biox.stanford.edu) and Princeton (http://www.genomics.Princeton.edu), are founding new institutes, departments and undergraduate courses to cater for this emerging dimension of cell biology. Others have launched geographically distributive collaborative projects, such as the Alliance for Cellular Signaling (see January editorial), and many US funding agencies are looking to support systems research. Although Europe has begun to pull its own weight in high-throughput genomic, and in some cases post-genomic, approaches, cross-disciplinary research initiatives at the systems level are being led largely by the US.

High-throughput biology has been accepted readily by geneticists. The view in the cell biology community, however, is more polarized, with those who appreciate the tremendous emerging data resources and the increasing promise of modelling on one side, and on the other those who regard the exercise as descriptive or even intellectually inferior and not worthy of publication in top journals. With the coming of age of proteomics, the time is right for all cell biologists to accept systems biology into their fold in all its manifestations. *Nature Cell Biology* is certainly surveying the budding field with considerable interest and we welcome submissions of both large-scale studies related to cell biology and advanced modelling of cellular systems. We will, of course, hold these to our customary standards of conceptual advance and data quality. For modelling studies in particular, a general criterion applied is the level of its predictive power and indeed the level of experimental evidence for such predictions (for example, perturbation analysis). Two examples that exemplify this are the study from Tewis Bouwmeester and colleagues on page 97 of this issue (see also News and Views on page 87), and the study from Joseph Pomerening and colleagues (*Nature Cell Biol.* **5,** 346–351 (2003). Bouwmeester *et al.* utilize the TAP-tag approach, initially developed for global protein interaction analysis in yeast, to significantly enlarge our horizons of the TNFα/NFκB signalling map. Pomerering *et al.* presented a well-developed model and experimental support for bistability, as well as hysteresis, of the cell cycle oscillator Cdc2/cyclinB.

Although every cell biologist should be encouraged to delve into the systems world, it would be a serious mistake to trivialize more classical molecule-by-molecule studies, which remain by far the main source of conceptually striking breakthroughs and will consequently continue to populate the pages of this journal. □