Meeting report

Making systems biology work in the 21st century

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A report on the Biochemical Society meeting 'Systems biology: will it work?', Sheffield, UK, 5 January 2005.

The idea of systems biology is not new: as long ago as 1968, the mathematician and engineer Mihajlo Mesarovic regretted that "in spite of considerable interest and efforts, the application of systems theory in biology has not quite lived up to expectation". But what of systems biology today? Does it now look more likely to lead to the expected benefits? These questions are of particular urgency in the UK at a time when the Biotechnology and Biological Sciences Research Council (BBSRC) is planning to create six new centers for systems biology over the next two years, investing £6 million in each. It was in the hope of answering them that a one-day meeting exploring the nature of systems biology and its potential was organized by the Biochemical Society early this year.

In the 1950s the geneticist and biochemist Henrik Kacser was already urging biologists to take systems seriously: "The problem is ... the investigation of *systems,* i.e. components related or organised in a specific way. The properties of a system are in fact 'more' than (or different from) the sum of the properties of its components, a fact often overlooked in zealous attempts to demonstrate 'additivity' of certain phenomonena. It is with these 'systemic properties' that we shall be mainly concerned...".

To most people, however, 'systems biology' is still just a combination of words they encounter with increasing frequency in the literature - a search of PubMed on 3 January 2005 produced 11 hits for the new year, more than for all the years before 1998, suggesting that the total of 316 mentions in 2004 will easily be exceeded this year. The range of opinions expressed at the Sheffield meeting was enlightening, but might leave the outsider none the wiser. It would be an exaggeration to say that each speaker offered a distinct and incompatible opinion about what systems biology is, but there was certainly less unanimity about the nature of the subject matter than there is at most research meetings. One speaker even announced that "before I came to this meeting I didn't know what systems biology was", and answers to the question posed by the meeting's title ranged from scepticism to the unambiguous "Yes!" with which Hans Westerhoff (Free University of Amsterdam, The Netherlands) entitled his contribution.

To sceptics such as myself, systems biology sometimes appears to be little more than a new name for old-fashioned reductionist biology practised on an ever-larger scale, with ever-larger and more expensive machines. That is certainly not what Kacser meant. Nor did the theoretical biologist Ludwig von Bertalanffy, the founder of systems theory, who described what he saw as the analytical obsession of modern science, the splitting up of reality into smaller and smaller units, as a "malady".

In attempting to define systems biology, Olaf Wolkenhauer (University of Rostock, Germany) emphasized the need for a shift in focus away from molecular characterization towards understanding functional activity. He argued that systems biology must be different from genomics and bioinformatics, and the same point was later made by Alf Game (BBSRC, Swindon, UK), who gave "genomics plus computers" as an example of what systems biology is not. I argued for renewed attention to Erwin Schrödinger's famous question "What is Life?" and for serious attempts to build on the theoretician Robert Rosen's life's work in trying to answer it. Failure to do this will mean that genetic engineering will never become more than glorified tinkering.

Last year's Nobel prizewinner for physics, theoretical physicist Frank Wilczek, said in a recent interview that he still mainly uses pencil and paper in his work. Similarly, investigating complex biological systems does not necessarily need large financial investment but rather a significant investment in intellectual resources. Nevertheless, a genuinely

systemic view is not incompatible with gathering huge quantities of experimental data. This was well illustrated by Douglas Kell (University of Manchester, UK), who emphasized that studying bits of a system will not lead to understanding the whole. He argued that it is not a question of replacing a tried and true approach with an untried one, but of replacing an approach that is reaching the limits of its possibilities with one that will, if applied properly, allow continued advances towards understanding systems. Kell discussed his group's analysis of the transcription factor NF-κB that indicates the necessity of taking account not only of the amplitude of its oscillations of activity but also of the frequency of these oscillations. This may seem unduly complicated to those who hoped to see a simpler message in such signals, but frequency may well fulfill a necessary physiological function, as using it as well as amplitude allows a system to avoid undesirable cross-talk between signals that rely on the same chemical entities.

In some cases, the systems approach is already working at a sophisticated level. As Denis Noble (University of Oxford, UK) pointed out, models of heart function have now reached astonishing levels of detail, accuracy and predictive power. He illustrated this with realistic simulations of normal and abnormal hearts beating, based on real measurements, which were developed in collaboration with Peter Hunter (University of Auckland, New Zealand). Noble had predicted that about 10^{27} computers of the power of the IBM supercomputer Blue Gene would be needed to compute the behavior of a single cell in full. In practice, ordinary computers can tackle the task vastly better than this pessimistic calculation implies. As he pointed out, the better performance is due to a fair degree of modularity in nature: many separate functions are handled independently, and are only integrated into a single model at the end. Moreover, with sufficient understanding of the system under study one can select the data that need to be included in the model: despite the good results given by his heart model, Noble estimates that it includes only about 2% of the proteins that are believed to be expressed in the heart.

A systems approach to cell biology naturally needs to know where the system components are located in the cell. Bob Murphy (Carnegie-Mellon University, Pittsburgh, USA) discussed the degree of expertise needed to identify proteins by fluorescence microscopy. Machine-learning techniques can train a program to recognize the subcellular locations of proteins from the morphological features visible in fluorescence images, and now allow computers to do tasks that humans find difficult or impossible. For example, a trained program can distinguish between different Golgi proteins in such images with fair accuracy, even though expert humans can barely see any difference.

Putting the case for systems biology, Westerhoff described examples of how a systemic view has allowed not only a better understanding of how organisms behave, but also much better prediction of how they will respond to manipulation. For example, finding drugs to combat African trypanosomiasis means choosing the right potential drug target in the trypanosome parasite. This requires sufficient knowledge of the metabolism of the parasite and its host to predict what is likely to happen if a given enzyme in the parasite is inhibited. We will know how well this works in practice for treating the disease when studies become available that are currently carried out at the University of Washington in collaboration with Westerhoff's group.

In a striking image, Rob Beynon (University of Liverpool, UK) pointed out that a mouse has a new liver every day - virtually all its liver cells are replaced. For him, neither the transcriptome nor the metabolome are fixed entities; they need to be treated in terms of a dynamic exchange, with amino acids constantly being converted into proteins, and proteins being degraded into amino acids. His experiments with labeling leucine residues in proteins with deuterium and measuring how fast the labels disappear have allowed measurement of how fast particular proteins are degraded, and this shows that protein turnover is highly variable. Some proteins disappear in a matter of minutes, whereas others are effectively immortal, with no detectable loss during the duration of an experiment. The balance between synthesis and degradation is maintained by kinetic considerations, and this means that an organism must be treated as a dynamic system that is changing all the time.

The many aspects to consider when setting up even a highly simplified model imply, therefore, that making systems biology work will never be easy. However, difficult or not, there is no alternative. As Kell remarked, as his answer to the question in the meeting's title, "the *not-system* approach does *not* work".