DDT Vol. 8, No. 6 March 2003

Systems biology unplugged

Eric Werner, Cellnomica, Fort Myers, Florida, USA; email: eric.werner@cellnomica.com

The *International Conference on Systems Biology 2002* (ICSB 2002; 13–15 December 2002, Karolinska Institute, Stockholm, Sweden), despite being held in the dark of winter was warm and intellectually active, filled with lively debate and discussion. Here, a few of the many interesting and new presentations are summarized (see http://www.ki.se/ICSb2002 for full details).

What is systems biology?

Many speakers defined systems biology as building mathematical, computational models based on biological data to predict and retrodict future and past data. The speakers were divided roughly into biologists (data gatherers), model builders, theory builders and tool providers. Of course, many did several of these activities simultaneously. The model builders made up the overwhelming majority of speakers and posters. In addition, there appears to be a split in the approach to building models. The level of ontology and abstraction ranging from low level differential equation modeling, to automata, all the way to Boolean logic. Another dimension is what to model: chemical pathways, genomic regulatory networks, cell signaling [1], whole cells, cell pattern formation by way of gradients [2].

Theory builders and data gatherers

The talk by Mark Ptashne (Memorial Sloan-Kettering Cancer Center; http://www.mskcc.org), in the role of the theorist, seemed to influence many at the conference with the idea of regulated recruitment. Ptashne is no formalist and so the idea of regulated recruitment was not precisely defined. Instead he used examples to illustrate what he meant. The basic idea seems to be that the cellular machinery that runs transcription and translation is general and common to most, if not all cells. It can not account for the specificity of regulation. However, small molecules recruit the large, common machinery to specific locations on the genome. These are recruiters and they are regulated. Thus, it is not the massive and multicomponent ribosomal molecule that is directly regulated, rather it is recruited to start transcription as particular DNA promoters through recruiters [3].

Forward engineering cis-regulatory logic and nanobiotechnology

Terence Hwa (University of California, San Diego; UCSD, ttp://www.ucsd.edu), gave an insight into how to develop cis-regulatory logics that emulate what computer logic gates do. One example was to model an OR-gate using simple cis-regulatory logic using promoters and activators. The goal is to be able to model any logical circuit *in vitro* or *in vivo* using basic modules. It is known in computer science that any complex logic circuit can be built out of a few basic components. This can have practical applications, such as smart nanosensors in the cell that react only under specific conditions.

The potential for such research in pharma industry, as well as in basic research, is evident. For example, a DNA logic circuit might be able to report when and only when a certain cancer gene becomes active. More generally, this type of work points the way toward an integration of systems biology with nanotechnology. One problem with this approach is that it is still not certain whether cis-regulatory logic components can be combined without interference to produce more complex logic circuits. For example, it could turn out that such regions interfere with one another. Hwa is now in the process of trying to construct more of these basic components and, by a combination of simulation and *in vivo* experiment, to discover stable components that can be combined without interference.

George Church (Harvard Medical School, http://www.hms.harvard.edu) took this to a higher level of abstraction by talking about modeling a minimal cell and also nanobiotechnology. However, his talk did not include any specifics as to how these fields were to be integrated.

Space and time

Spatial location could be just as important as regulation in controlling the cell cycle. This was one of the main points made by biologist Lucy Shapiro (Stanford University, http://www.stanford.edu). Shapiro's topic was about the processes and proteins that are involved in the control of the cell cycle. She said that the cell cycle could not be explained by transcriptional mechanisms alone. Instead, regulatory pathways must be supplemented by non-transcriptional mechanisms. Where the proteins are located in the cell is just as important as when the protein is expressed. Thus, there is a spatial component that is crucial to the cell cycle. She suggested that the control of regulation of the chromosome could, in part, be caused by its spatial configuration and position in the cell [4]. The work on multicellular simulations at Cellnomica (http://www.cellnomica.com) concurs

  PII: S1359-6446(03)02631-X

with Shapiro's view of the importance of spatial information in the process of development.

Martin Howard (Leiden University, http://www.leidenuniv.nl) followed the classical approach to pattern formation started by Turing and refined by Meinhardt to develop a model that generates a gradient that gives a standing wave in the middle of a cell. His point was that you only get this standing wave if you have noise and not if there is no noise. Thus, he claimed noise is essential to accurate cell division in *Escherichia coli*. One problem with this approach is that it takes no account of the internal structure of the cell and it avoids questions of spatial localization and regulation of localization.

Networks

Uri Alon (Weizmann Institute, http://www.weizmann.ac.il) introduced the notion of network motifs. These are simple networks that occur in many parts of genomes. He developed an algorithm that can find such motifs, which are then modeled, and their dynamic signature studied. Network motifs combine to form more complex networks. A question is, why are most such network motifs shallow? Alon's answer: Quick reaction time and fast signaling.

In silico drug discovery?

It was surprising that only one speaker (David Fell, Oxford Brookes University, http://www.brookes.ac.uk) related systems biology to drug discovery. He stressed the potential of taking a systems view in the discovery of targets in complex cellular, genomic and signaling networks.

It was, however, discussed that systems biology is still a hard sell to upper management in big pharma, who think it is too immature and do not appear to understand the need to integrate this field with the drug discovery process. The reason for this is perhaps that big pharma is under pressure to produce the next big winner, taking a short rather than a longer term view. However, it means that this is an opportunity for forward looking pharmaceutical and biotech companies to gain a significant competitive advantage and future market share.

Birthing problems with the European and German Initiative

Following the US initiative, Germany now has an initiative to fund systems biology, with 50 million Euros for an initial period of five years, with much more expected after that. The focus of the German initiative is the hepatocyte or liver cell. It is true that it has important pharmacological applications but there is not enough data on the liver cell to start simulating it. Hence, it looks as if much of the funding will go to doing basic biology of the liver cell, and not to systems biology. This could hinder the speedy development of this area in Germany. The argument for the liver cell is that Germany could thus leap ahead of the USA, by taking on something that has not been tackled as yet. The risk of this end-run strategy is that nothing could come out of it for a long time, if at all.

What is even more surprising is that Hans Westerhoff (Vrije Universiteit, http://www.vu.nl), who heads the European initiative, suggested that the European version will be heavily influenced by the German initiative. This could mean that they might also overspecialize too early and thus hinder the development of systems biology in Europe as well.

The engineering perspective

Many at the conference were using modeling techniques for biological phenomena that previously have been used by engineers to model non-biological processes. John Doyle (Caltech, http://www.caltech.edu) gave a talk about the properties of systems that engineers consider to be important. He focussed on two properties of systems, robustness and scalability. For a system to be robust it must be able to take the bumps and scratches of reality and still be able to achieve the specified goals. Scalability refers a characteristic of models and the theories underlying those models. A model is scalable if an increase in complexity does not result in the model's dynamic behavior becoming computationally intractable (i.e. practically impossible). Doyle's talk was rather ambitious; he tried to motivate new mathematical theories that would enable the construction of scalable models [5]. There are, however, some inherent limitations when modeling complex biological systems that have to do with the complexity conservation principle [6].

Small is beautiful

The small but beautiful and practical successes of many at the conference (including the impressive work of Palsson [7], Ideker [8] and Tomita [9]) show that systems biology is the 'new kid on the block'. The field is revolutionizing biology. It is an extremely dynamic growing field that will have many new surprises in store. And, even if not all of Mother Nature is conquered, we might gain enough of an understanding that will enable us to benefit mankind. There will be applications in medicine, agriculture, manufacturing control, the pharmaceutical industry, biocomputers and nanobiotechnology. In addition, we are gaining a deeper understanding of some of the most fundamental questions about ourselves, namely our development and evolution. After all, the focus of systems biology really is the logic and complexity of life.

References

1 Werner, E. (2003) *In silico* cell signaling underground. Science STKE, p.8 (http://www.stke.org)
2 Kitano, H. (2002) Computational systems biology. *Nature* 420, 206–210
3 Ptashne, M. and Gann, A. (2002) *Genes and Signals*. Cold Spring Harbor Laboratory Press

4 Shapiro, L. *et al.* (2002) Generating and exploiting polarity in bacteria. *Science* 298, 1942–1946
5 Csete, M.E. and Doyle, J.C. (2002) Reverse engineering of biological complexity. *Science* 295, 1664–1669
6 Werner, E. (1996) *What Ants Cannot Do.* Distributed Software Agents and Applications, (Perram, J.W. and Müller, J.P., eds), Springer Verlag
7 Palsson, B. (2002) *In silico* biology through 'omics'. *Nat. Biotechnol.* 20, 649–650
8 Ideker, T. *et.al.* (2001) Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. *Science* 292, 929–934
9 Tomita, M. (2001) Whole-cell simulation: a grand challenge of the 21st century. *Trends Biotechnol.* 19, 205–210

Biodiversity and Natural Product Diversity: Tetrahedron Organic Chemistry Series Volume 21

By Francesco Pietra, Pergamon Press, 2002, Price US$45.00, 368 pages in paperback, ISBN 0-0804-3707-0

Defining and cataloguing biodiversity is a difficult task, and explaining how the diversity of natural products relates to the diversity of living organisms is also challenging. That is what the author sets out to do in this monograph. Although the book contains many examples of natural product diversity, both in terms of chemistry and biological activity, it is less successful in providing a clear and compelling explanation of how biodiversity leads to chemical diversity.

The book is made up of six sections of varying lengths: the concept of biodiversity; the relationship between biodiversity and natural product diversity; natural product diversity at the ecosystem level; natural product diversity at the functional level; biotechnology and chemical synthesis of natural products; and threatening and management of natural product diversity.

The opening chapters briefly explore various concepts and definitions of biodiversity and possible changes in biodiversity throughout evolution. The next section moves on to consider possible ways to relate the diversity of natural products to levels of biodiversity. Various problems are highlighted, in particular the fact that estimates of the diversity of natural products are hampered because the numbers of many species, particularly of micro-organisms, are not known. Also, many bacteria are not readily grown in culture so that it is difficult to isolate their secondary metabolites for study.

So far, it seems impossible to correlate genetic approaches to taxonomy with chemical approaches. The author introduces a numerical system for comparing the size and complexity of different chemical compounds. Because this system is used subsequently in detailed comparisons of individual structures from different sources, it would be helpful to have a more extensive discussion on the strengths and weaknesses of the chosen system.

In the following section, natural product diversity is considered at the level of major ecosystems. The detailed information is presented in maps and charts. The maps are too small for easy comprehension and the charts are too densely packed for easy reading. It seems that only rather broad conclusions can be reached about the levels of biodiversity in different ecosystems, and caution needs to be applied because not all systems are equally researched. One chapter attempts to summarize the molecular complexity of the different chemical classes (alkaloids, peptides, and so on) that are known to exist in different environments. Although this is a valuable attempt to classify and condense important information, the complex 3D multicoloured graphs are difficult to decipher.

The largest section in the book is given over to 'functional diversity', for example, a consideration of the variety of natural products with different biological activities, such as signalling and defense compounds, antifeedants and toxins. The uses to which natural products have been put are also discussed, with examples being given of the diversity of chemical structures. Because this is a massive area to review, some of the coverage is understandably sketchy and some of the examples are misleading (e.g. α-bungarotoxin is not an anticholinesterase, and ω-conotoxin does not block acetylcholine receptors).

The functional diversity section is followed by consideration of the roles of biotechnology and chemical synthesis. Although the topic of synthetic developments from natural products is obviously relevant to drug discovery, it is not clear why it is relevant to a book that is relating natural product diversity to biodiversity.

Finally, there are two short general chapters on threats to biodiversity and how biodiversity can be conserved or managed.

Overall, the book contains some interesting information. However, it is unlikely to be particularly useful to scientists concerned with drug discovery. Factual errors about drug types and uses have crept in, probably because of the need to condense so much information in a small volume. The dense format also makes the book a little hard to read, and parts of the text needed the touch of a sympathetic editor.

Alan Harvey
Strathclyde Institute for Drug Research
27 Taylor Street
Glasgow, UK G4 0NR
e-mail: a.l.harvey@strath.ac.u

  PII: S1359-6446(03)02640-0