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Feature Article

The Virtual Human: Towards a Global Systems Biology of Multiscale, Distributed Biochemical Network Models

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Summary

There is an emerging recognition of the importance of modelling large-scale biochemical systems, with the 'digital human' an obviously desirable goal. This will then permit researchers to analyse the behaviour of such systems *in silico* so as to be able to perform 'what-if?' experiments prior to determining whether they are actually worthwhile or not, and for understanding whether a particular model does in fact describe or predict experimental observations. Existing and developing standards such as SBML are beginning to permit the principled storage and exchange of biochemical network models, while environments for effecting distributed workflows (such as Taverna) will allow us to link together these models and their behaviour. This allows the local experts to work on those parts of cellular or organellar biochemistry on which they have most expertise, while making their results available to the community as a whole. This kind of architecture permits the distributed yet integrated goal of an evolving 'digital human' model to be realized.

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INTRODUCTION

Most laboratories of biochemistry have and display a copy of the celebrated wallcharts illustrating the major metabolic 'pathways' (see http://www.expasy.ch/cgi-bin/show_thumbnails.pl and (*1*)). These networks are logical graphs that have as nodes the metabolites that are transformed and as edges the agents (normally enzymes) that catalyse their transformation or translocation. In addition there are links describing the allosteric or other interactions of effectors that serve to modulate the kinetics of the enzymes with which they interact. Similar charts describe the various signalling pathways that are known.

Since the above is a commonplace, what then is 'new' about the rising interest in what has come to be called Systems Biology (*2 – 6*)? One answer lies in the *bringing together* of the antecedent tracks of molecular biology and systems modelling (*7*) (see also Fig. 1). Another (*8 – 12*) is the recognition that it is time to move from simple qualitative models that merely represent interactions, to models that are integrative and quantitative. Further, we need to recognize that it is hard to make hypotheses when you do not know about the existence of a particular molecule or activity or set of interactions, and that data-driven approaches are consequently likely to deliver more useful advances (*13, 14*). A particular kind of example of interactions in metabolism involves metabolic channelling (*15 – 17*), where very particular kinds of experiment are needed to discriminate the different possible kinetic mechanisms involved (*18, 19*), each of which leads to a very different kind of biology.

At the metabolic level, on which this paper concentrates, we are starting to witness a revolution (*11*), in which we can begin to bring together the increasing knowledge of the human metabolic network (*20*) with experimental measurements (*21 – 26*) of the metabolites that it is considered to contain (*27*). The metabolic level or metabolome (*21, 23, 28*) is appropriate since (i) unlike signalling pathways there are thermodynamic and stoichiometric constraints that make it easier to relate models to experiments, and (ii) for fundamental reasons connected with metabolic control analysis (*29 – 31*), small changes in the amount or activity of individual enzymes have little effect on fluxes but can have large effects on metabolite concentrations (*19, 32*), such that the metabolome is typically amplified relative to the transcriptome and the proteome. It is also and consequently closer to the phenotype of the organism. Since regulatory molecules such as transcription factors are normally assumed to change the concentrations but not the kinetic constants of the proteins whose expression they induce, it is easy to add a regulatory layer later.

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Molecular → Systems Biology

Traditional molecular biology	The new systems biology
Study molecules in isolation	Study systems as a whole
Qualitative	Quantitative
Reductionist	Holistic/synthetic
Largely hypothetico-deductive	Largely inductive
Little need for computation	Computation and modelling at the core
The importance of technology development is barely recognised	The importance of technology development is explicit

Figure 1. Some of the differences between molecular biology and systems biology.

WHY MODEL?

Since there will be readers who wonder why the use of mathematical models might be of any value at all, rather than concentrating solely on the 'real thing' (i.e., 'wet' biology), it is probably worth rehearsing some of the arguments (*9*). The main reasons why one would wish to have a mathematical model of a complex (biological) system include:

- Giving us the ability to test whether the model is accurate, in the sense that it reflects – or can be made to reflect – known experimental facts.
- Allowing us to analyse the model in order to understand which parts of the system contribute most to some desired (or indeed in the case of diseases or pharmacodynamics *undesired*) properties of interest.
- Hypothesis generation and testing, allowing one rapidly to analyse the effects of manipulating experimental conditions *in the model* without having to perform complex and costly experiments (or to restrict the number that are performed).
- Testing what changes in the model would improve the consistency of its behaviour with experimental observations.

In addition, quantitative description of the properties of the complex network(s) allow one to predict molecular mechanism, macromolecular interactions, the role of 'external factors' (e.g., interactions with effectors from 'other' pathways), pathological 'hot spots' in the network, sites of action of perturbations, the effect of combinations of potential drugs at a system level (*33, 34*), and effects of interfering locally on the behaviour at a systems level (e.g., whether there are compensatory mechanisms using related pathways).

Underlying all of this is the recognition that biological systems, because of the many nonlinear interactions they possess, are too complex to understand simply by eyeballing them, and that it is a lot better and easier to work on a representation of the system then on the poorly specified system itself. Clearly, too, there are ethical and practical limitations to the manipulations that one can do *in vivo* anyway!

REPRESENTATION OF BIOCHEMICAL NETWORKS IN A STANDARD MANNER ALLOWING INTEROPERABILITY

Although the wallchart representation conveys much useful information, it is hard to reason about it computationally, and the representation of a biochemical network used by most systems biologists encodes it in the Systems Biology Markup Language (SBML; www.sbml.org; (*35, 36*)). This is an eXtensible Markup Language (XML) representation that encodes the representation in a well-defined and standard manner, that consequently allows one to exchange such models and to analyse them using appropriate software. We note too that further standards are emerging for annotating a model sufficiently to allow others to reproduce it (*37*).

CREATING, USING AND ANALYSING SBML MODELS

The next issue is that there are many things that one might wish to do with a biochemical network model in SBML, for instance creating it automatically using text mining (*38*), editing it (*39*), merging sub-models (*40*), coverting it to a system of ODEs and integrating them (usually referred to as 'running the model') (*41*), performing parameter estimation (*42–46*), sensitivity analysis, e.g., (*47, 48*), the analyses of fluxes (*49*) and flux balances (*50*) under constraints (*51*), and many other kinds of analyses that we cannot do at all well, especially on models of any scale. However, even integrated environments such as Cell Designer (*52*) (www.celldesigner.org), COPASI (*41*) (www.copasi.org), Cytoscape (*53*) (www.cytoscape.org) and the SBW (*54*) (http://sbw.kgi.edu/) do only a small fraction of what one might wish to do, and in particular they do not (yet?) use modern community standards for interoperability and extensibility. In addition, many of them were not necessarily designed with very large scale models in mind and cannot deal sensibly with their visualization (although, importantly, it is now possible to mark up visualizations in the more recent versions of SBML (*55, 56*)). Not only are the elements of software distributed but so are the data that they might use (Fig. 2).

DEALING WITH DISTRIBUTED DATA AND TOOLS

Our view of the way to deal with this (*10–12*) is to recognize that provided that each of these elements expose themselves as Web Services with suitable semantics (*57–59*),

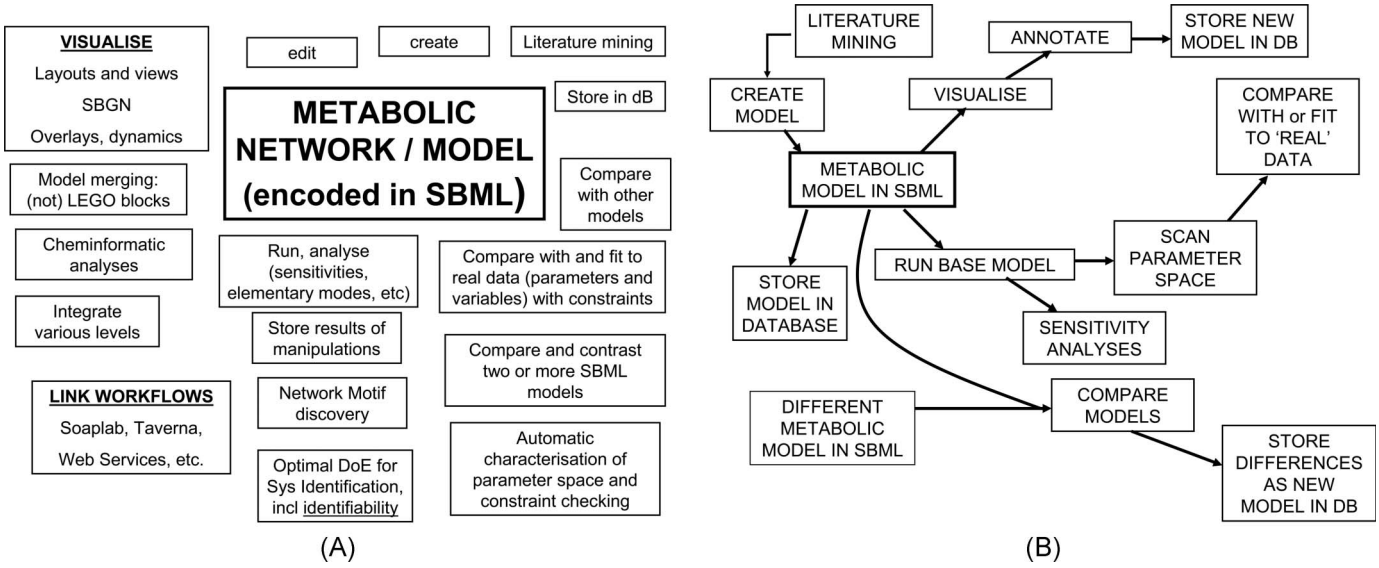

Figure 2. Some examples of activities that one might wish to perform on a metabolic (or other biochemical) model encoded in SBML. Items of software that perform one or more of these 'modules' or processes (A) sometimes exist somewhere but do only a fraction of what one might wish. Preferably one would stitch them together into an automated workflow such as that in (B) that would carry out the analyses serially. One such environment for doing this is Taverna.

the problem is then reduced (or at least transformed) into (a) one of ensuring that the interfaces between the elements do obey recognized standards with suitable semantic content, and (b) of providing a software environment in which one can effect integration by joining together the elements into suitable workflows (Fig. 2). One such environment is Taverna (see e.g., *59–63*) and www.taverna.sf.net).

TAVERNA, UTOPIA AND ARCADIA: SOFTWARE FOR DISTRIBUTED NETWORK MODELLING

A major attraction of an environment such as Taverna is that its elements are *loosely coupled*. This enables it to be largely neutral about what these individual elements actually do (i.e., it is entirely general), provided that they explain themselves in terms of their interfaces and make their resources (whether data or tools) available appropriately. This provides a win-win for all those who are developing such data resources or tools since any developer can then make their resources available in a manner that does not require one to load complex programs with obscure dependencies, and that they can be run on any platform. The utility or otherwise of such resources is then simply reflected in the use to which they are put by the community.

The latest versions of Taverna also allow one to configure them in a way that enables access to more specialized resources. Thus SBML is itself supported by libSBML http://sbml.org/software/libsbml/, a software library that has been developed to read, write, manipulate and validate SBML files and data streams. libSBML has been implemented in C and C++ but is also provided with language bindings in, e.g., Python, Matlab and Java. In recent work (*64*) we have enabled Taverna to work with libsbml, allowing the automation and integration of systems biology modelling (of models encoded in SBML) within Taverna workflows (Fig. 3).

In a similar vein, UTOPIA (e.g., *65–67*) and www.utopia.cs.manchester.ac.uk) is an architecture and software environment that allows the high-level visualization of *in silico* experiments and models, and can work seamlessly with Taverna and with other software that makes its resources available as Web Services. We are strongly engaged in the integration of Systems Biology models into these environments as the ARCADIA project.

LINKING SBML SUB-MODELS

The idea, then, is that if the different groups with specific expertise in particular areas of cell or organ(ellar) biology can develop sub-models, we can eventually merge them into more complete and complex models of the whole, provided that we describe them properly in a way that forces them to obey a standardized set of semantics (*37, 40*). Both the models themselves, and the results of running the models (e.g., if they both share the same compartment such as 'serum'), can be merged together given the appropriate architecture. This is again a win-win for both developers and

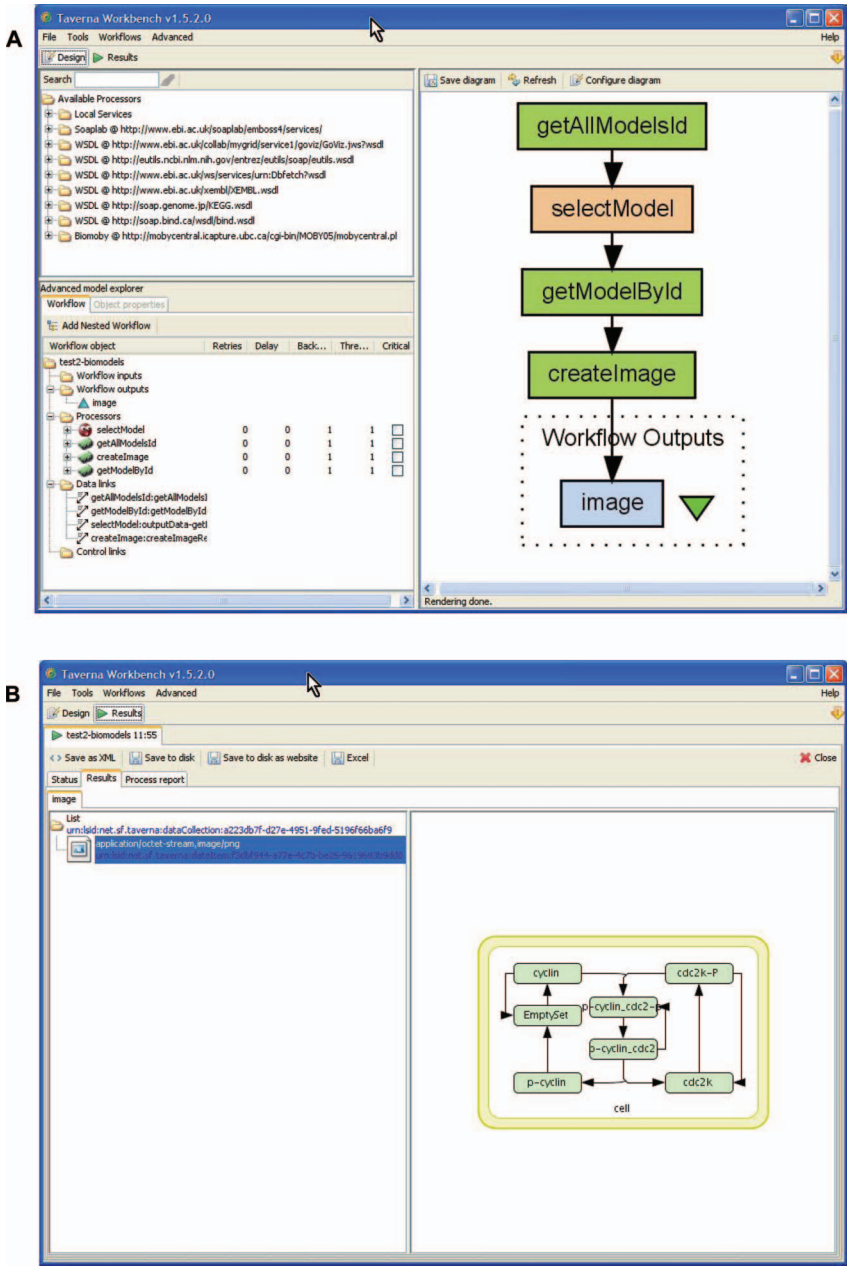

Figure 3. The Taverna workflow system, showing (A) available services, the 'advanced model explorer' and a particular workflow (created by Peter Li) that allows one to download and visualize a Systems Biology model from the www.biomodels.net database. (B) The results of running the workflow (after choosing a particular model).

users, since everyone gets to contribute their expertise to the whole. Emerging data compilations on biochemical kinetic parameters (*68*) and the availability of detailed data on protein concentrations (*69*) (www.proteinatlas.org) will greatly enhance the ease of populating these models. Similarly, upcoming social workflow sites such as ^{my}Experiment (www.myexperiment.org) will allow the principled sharing of the models, as well as the workflows and submodels used in their generation, whether as work-in-progress or (as with the curated repositories such as www.biomodels.net (*70*)) when published formally.

CONCLUDING REMARKS

Although modern systems biology is in its infancy, it has a clear agenda, and one that strikes at the heart of what

biochemists wish to do, i.e., to understand the biochemical workings of biological *systems*. However, to quote Henrik Kacser (*71*), ''But one thing is certain: to understand the whole you must look at the whole''. This means that we must integrate the efforts of the entire community who wish to participate in this great endeavour. The 'digital human' (in various flavours – see, e.g., http://europhysiome.org/ and (*72*) for a couple) will in time come to be seen as more significant than the human genome sequence in terms of the new biology it brings. Now is the time to start preparing it.

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Note

A larger and more comprehensive model of the human metabolic network has just been published by Goryanin and colleagues Ma H, Sorokin A, Mazein A, Selkov A, Selkov E, Demin O and Goryanin I (2007). The Edinburgh human metabolic network reconstruction and its functional analysis. Mol. Syst. Biol., **3**, 135.

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