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EDITORIAL

Proliferating dynamic modeling in systems biology studies†

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Systems biology integrates experimental and computational approaches in order to study the basic properties of biological networks and their dynamic behavior. It covers a wide range of areas: from computational analysis of biological systems to experimental technologies such as next-generation sequencing, synthetic biology, and proteomics. To discuss these topics, scientists gather annually at the International Conference for Systems Biology (ICSB) meetings. This series of annual conferences, launched in Tokyo in 2000, forms a major meeting place for the world-wide systems biology community. The annual meetings have alternated between the USA (2001 in CalTech, 2003 in St Louis, 2005 in Boston, 2007 in Long Beach, 2009 in Stanford), Europe (2002 in Stockholm, 2004 in Heidelberg, 2008 in Goteborg), and Japan (Tokyo in 2000 and Yokohama in 2006). In 2010 the researchers gathered in Edinburgh, UK to further interconnect the systems biology community.

Each ICSB meeting is usually accompanied by multiple workshops focusing on different aspects of systems biology research. One of the very important issues in the field is the dynamical analysis of the behavior of biological systems. The workshop on the 'Advanced Modeling and Simulation Techniques' held in Edinburgh last year acknowledged that some modeling techniques are becoming more and more popular and increasingly interrelated: rule-based, spatially-resolved, and stochastic models and simulations. The workshop brought together modelers and software developers that are using one or more of these modeling approaches.

The rule-based modeling approach is relatively new, but increasingly gaining popularity. In this approach, molecular interactions are represented as a system of rules—precise formal statements about the conditions under which interactions occur, and about the consequences of these interactions. Rule-based modeling is a natural way to model multicomponent, heterogeneous structures such as large protein aggregates.

Indeed, the number of protein modifications and protein complexes that can be generated through multiple binding site interactions is orders of magnitude larger than the number of proteins in the model (combinatorial complexity). Models marked by combinatorial complexity may include very large or potentially infinite numbers of species, and often cannot be formulated in terms of reaction networks. This fact is illustrated by two of the papers in this issue. The model of the post-synaptic proteome (Sorokina *et al.* DOI: 10.1039/C1MB05152K) describes interactions among 54 proteins, many of which are scaffolds. This model is capable of precise description of protein aggregates, including complexes consisting of 1580 protein molecules of 48 different types. The model of iron homeostatis (Ghosh *et al.*, DOI: 10.1039/C1MB05093A) is comprised of 92 biomolecules connected *via* 85 protein–protein or protein–metabolite interactions, which have been captured as a set of 194 rules. Operating with the set of rules, the authors are able to identify critical events in the systems dynamics, valid over wide parameter ranges.

As the rule-based models are gaining acceptance, the issue of convenient visualization and annotation of such models becomes an issue. The details captured in a rule-based model are of limited use unless they can be presented in a manner understandable by both modelers and experimental biologists. Chylek *et al.* (DOI: 10.1039/C1MB05077J) suggested a set of guidelines to enable efficient visualization and annotations of such models.

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Stochasticity has long played a significant role in biology, especially when systems with a small number of molecules and random molecular collisions were studied, *e.g.* including RNA. In the paper by Giampieri *et al.* (DOI: 10.1039/C1MB05086A), the authors study a toggle switch, involving a protein compound and an miRNA cluster, and compare the results of a stochastic *versus* deterministic analysis. A similar theme is discussed in the paper by Barberis *et al.* (DOI: 10.1039/C1MB05073G) who analyze cell cycle progression of budding yeast relating to the very low number (1–2) of mRNA copies generated per gene. The stochastic systems theory was used by Stys *et al.* (DOI: 10.1039/C1MB05083D) to describe the cell states and trajectories based on a novel image content descriptor.

An interesting approach combining spatial modeling with rules is employed in the paper by Dobay *et al.* (DOI: 10.1039/C1MB05060E). The authors use a Projective Activated-Bud-Mate (PABM) calculus, a formalism that operates on compartments. PABM uses rules that are very different from reaction rules described above. However, the basic ideas behind using rules are the same as in a rule-based approach: consider molecules as systems, formulate a certain biological description in a formal language and let the software generate a precise system of reactions, thus freeing the user from extensive bookkeeping.

Taken together, the talks at the workshop and the papers included in this issue have highlighted an important issue regarding modeling at large. Some talks and papers have described detailed models that integrate information about a large number of biomolecules, their components and interactions among them. Such models provide broad insights into the behavior of biological systems, but require measurements and details not yet available from experiments. Other talks and papers have given us small-scale models focusing on few biomolecules and interactions. These models provide deep insights into specific mechanisms. Thus, a lot of theoretical work and experimental studies will be required to bridge the gap between these types of models and able us to design large models on the level of precision and fine-tuning available currently for small scale models only.

