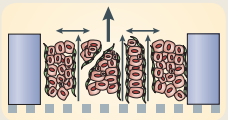
FOREWORD



Computational cellular dynamics: a network–physics integral

Computational models that reproduce and predict the detailed behaviours of cellular systems form the Holy Grail of systems biology. They require decades of work to integrate mathematical-modelling efforts, data on molecular-interaction networks and information on the physics of cellular structures. The challenges are formidable, but recent advances indicate that this endeavour looks increasingly feasible.

The modelling of cellular systems is one of the key challenges in systems biology. Sophisticated models with molecular details that can predict cellular behaviours under various conditions are crucial for elucidating system-level properties of cellular systems, such as their robustness and the underlying principles of cellular functions. In the past, progress in computational technologies has provided answers to numerous scientific questions, and has transformed the design process in various industry sectors. The expectations are high that similar technologies will provide important advances in our understanding of biological systems, and transform drug design and biotechnology in the process. However, even the most successful computational approach so far, computational fluid dynamics (CFD), took decades of research to become practically useful. So, it is perhaps too optimistic to expect such a technology to be easily obtainable, although there is no need to think that it will never be realized.

There are numerous opinions as to what constitutes 'modelling', a 'model' and 'simulation', and each describes a different level of abstraction that depends on the scientific question. For understanding the principles that underlie cellular functions, the model has to reproduce the dynamic behaviours of cells computationally, not just at the level of interaction networks but also at the level of the physical dynamics of cellular structures. The integration of interaction networks with cell-system biophysics is essential for the realistic reproduction of cellular dynamics for most cellular processes (as discussed by Kholodenko in his Review). I would like to describe this type of modelling as computational cellular dynamics (CCD).

CCD requires the integration of heterogeneous computational models that are on different spatial and temporal scales, and the basic equations still need to be defined. Most interaction-network simulations use the Michaelis–Menten equation or a similar equation that assumes a certain ideal condition. However, these assumptions might be unwarranted in a crowded molecular environment in which reactions and molecular movements are constrained in space. The challenging issue of the integration of different computational models for interaction networks and cellular structures, macroscopic dynamics at the cellular and molecular levels and processes with different timescales has to be resolved.

Computational technologies for CCD have to use data-collection and verification techniques that improve the accuracy of the models further; they remain a significant challenge for CCD. The structural, spatial and temporal dynamics of both interaction networks and cellular structures have to be identified in order to define CCD models. Interaction networks might be identified through the integration of various experimental data (as argued by Joyce and Palsson in their Review), including those obtained by structure-based approaches (see the Review by Aloy and Russell) and RNA-interference-based screening methods (see the Review by Moffat and Sabatini). The dynamics of cellular structure and interaction networks need to be measured by taking comprehensive, high-resolution quantitative measurements of intracellular status, such as the concentrations, interactions, modifications and localizations of molecules, and of cellular structures at each coordinate in four dimensions under various conditions (Baumeister and colleagues discuss one of these technologies in their Innovation article). Finally, bioengineering techniques that can reproduce 3D tissue enable us to maintain cells in a physiological context (as discussed in the Review by Griffith and Swartz).

CCD has the potential to become a truly integrated technology of computational science and biological measurements, which might change the way biological science is pursued. Early pioneers have strived towards these goals, but now, emergent technologies should allow us to undertake this essential endeavour. The journey is going to be long, but it is likely to be a fruitful one.

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