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Modeling cellular signaling: taking space into the computation

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Abstract

In living systems, chemical reactions and the geometry of cells feed back on each other. Methods for computational modeling are beginning to take this complexity into account.

We often describe cellular signaling networks in terms of circuits or wiring diagrams, but that view is incomplete. In a computer, computation takes place on a static network of electric wires. In biological systems, computation takes place in networks of biochemical reactions. A key difference is that biochemical reactions actively change the shape of cells and organelles over time, directly affecting the spatial position of molecules and the possible biochemical reactions that can occur. In other words, cells and tissues constantly remodel the structure of the computing networks—the ‘wires’—by altering the spatial organization of the reactants. Hence, in biology the remodeling of the network is as important to the computation as the reactions taking place. A new computational method described in this issue of *Nature Methods*¹ now makes it easier for biologists to model such feedback between chemical reactions and geometry.

Taking into account this feedback in computational models requires addressing two key challenges. First, one must track the effects of chemical reactions on the mechanics and geometry of cells and tissues². Second the network of possible biochemical reactions must be locally reconstructed as the cellular geometry changes, a task that is computationally expensive because of the combinatorial complexity of signaling networks³.

Angermann *et al.*¹ describe a new computational approach that addresses these challenges by combining advanced spatial simulation techniques with a rule-based description of molecular interactions (Fig. 1). They implement this hybrid approach in the general-purpose software platform Simmune⁴, which provides a flexible graphical interface for constructing and simulating such models. Together, the new methods and graphical modeling

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environment of Simmune should expand the scope of spatial models of cellular signaling and accelerate the construction of new models.

One of the standard methods for modeling the spatial localization of biochemical reactions is partial differential equations (PDEs). With this approach, three-dimensional (3D) spatial compartments, such as cells and organelles, are subdivided into small volumes, called voxels. PDEs are then used to compute how the average concentration of every molecular species in each voxel changes over time. As the shape of the compartment changes, voxels can be deformed, added or removed. Some simulation tools are starting to provide these spatial capabilities, such as CompuCell3D (ref. 5) and Virtual Cell⁶. A fundamental limitation of PDE models is that a separate equation and variable is required for every potential molecular species. Taking protein complexes and post-translational modifications into account typically creates an overwhelming number of possible molecular species. This difficulty has been termed the problem of combinatorial complexity³.

The new methods implemented in Simmune address the problem of combinatorial complexity by using an established rule-based approach^{3,7,8} to define the biochemistry of the system. Rules describe only the minimal conditions required for a reaction to occur. Thus, a small set of interaction rules can succinctly represent, without approximation, a much larger reaction network composed of many distinct molecular species. Rules also facilitate incremental model building because molecular details can be incorporated as they become available from new experimental results, without major revisions of the model⁹.

Software such as BioNetGen and Kappa can then convert a set of rules into the complete set of reactions^{7,8}. However, generating the full reaction network for spatial simulations is not required because many reactions can only occur in certain cellular locations. The key advance of Simmune is a new reaction network generator that intelligently decides which voxels require which subset of reactions (Fig. 1). For instance, if a molecular interaction can never occur on the membrane surface, then the reaction is not added to the membrane voxels. This provides two important advantages: first, the burden of constructing a new spatial model is reduced because researchers only need to specify a relatively small set of rules. Second, simulations run more efficiently because molecular interactions that do not occur in a particular cellular location are never considered during the simulation.

Angermann *et al.*¹ demonstrate these advantages by constructing a model of the mitogen-activated protein kinase (MAPK) signaling pathway involved in the pheromone response of yeast. Like many eukaryotic signaling networks, the MAPK response is inherently a spatial process in which a localized signal generates an internal concentration gradient of activated kinase. Additionally, signaling molecules in the pathway can form large complexes and can be phosphorylated on multiple sites, requiring a model that accounts for more than 150 reactions in some voxels. The model of Angermann *et al.*¹ reproduced the complex spatial pattern of intracellular kinase activation observed in recent experiments.

Using rules to automatically assign reactions to specific voxels has yet another key advantage: it allows voxels to be efficiently added during simulation (because a computationally costly step of creating new voxels is in deciding which reactions should be

modeled within each new voxel). This feature allows the shape of a cell to change dynamically during simulation. To correctly model changes in cell morphology based on physical forces, Angermann *et al.*¹ use a 3D cellular Potts model¹⁰, a type of model created by defining an energy cost for adding new connected voxels or removing existing voxels on the cell surface. If adding or removing a voxel is energetically favorable, then the action is carried out with some probability. The energy function can be defined both in terms of physical forces and the biochemical state of the system, which allows the signaling network to feed back on cellular morphology.

One important application of this method is the study of cellular adhesion, a process that remains challenging to simulate in detail because of the complexity of adhesion complexes and the dynamic shape of the cell. With Simmune, Angermann *et al.*¹ built a model of E-cadherin-mediated cell adhesion that demonstrated the importance of considering the dynamic feedback between the biochemistry and the shape of the cell. Only a dynamic cellular geometry could properly account for the distribution of E-cadherin complexes on the surface of the interacting cells.

The new features of Simmune are a welcome addition to the computational modeling toolbox, but there are still many unresolved challenges in building spatial models of cellular signaling. For instance, in many situations, such as when details of receptor aggregation are considered, particle-based approaches^{11,12}—which track the individual 3D location of each molecule and simulate rules directly to avoid full network generation—are needed to properly account for system dynamics. Future research is necessary to determine how exactly to combine PDE-based methods with existing rule-based particle methods^{7,9}. Additionally, as the interpretation of new experiments requires larger and more complicated computational models, simulation efficiency of spatial models becomes a key bottleneck. Much work is still required to devise efficient methods for running spatial simulations of cellular signaling on multicore processors and parallel supercomputers.

The methods implemented in Simmune signify a growing trend toward multiscale, hybrid approaches that combine the features of multiple modeling methods. We expect that this trend will greatly expand the scope and accessibility of biological models in the near future but will require continued development and support of advanced software applications such as Simmune.

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Figure 1. Combination of rule-based modeling with dynamic cellular geometries. Existing network generators yield the full reaction network given a set of interaction rules, typically without spatial information. A spatial reaction network generator uses rules to map possible reactions to specific cellular locations. The reactions can then be simulated and voxels added or removed to model changes in cellular geometry.