New Software for Complex Multiscale Spatially-resolved Modeling and Simulation: A Focus on the Biology, Not the Math

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In recent years, major strides have been made in the technologies for discovery and qualitative / statistical analysis of pathways and networks in biological systems. However, the development of software tools that permit moving from the resulting descriptive maps of interacting components to multiscale, quantitative, spatially-faithful models and simulations of cell physiology remains a major technical challenge. This is especially true if these modeling and simulation tools are to be of wide utility to biologists lacking advanced computer programming or mathematical expertise. To address this need we have created 'Simmune', a software package that supports the facile development and testing of detailed computational representations of cellular behavior. Simmune allows creation and simulation of highly complex models that span the scale from bimolecular binding site interactions to biochemical networks to the behavior of multicellular systems, all without requiring direct user involvement with the underlying mathematics or the writing of scripted instructions. At the cellular scale, Simmune uses a rules-based, stimulus-response approach similar to, but substantially more realistic than, typical discrete-state cellular automaton models to simulate the action of individual cells. At the molecular scale, users sequentially define the binary binding site interactions that biologists understand as the basis for all signaling networks, using familiar dialog box entry to specify reaction rates and molecular concentrations. The software automatically translates this simple input into the emergent signaling network and produces spatially-resolved simulations accompanied by time-resolved, quantitative graphical representations of the network. A sophisticated browser feature enables facile examination of the encoded pathways at any user-selected scale of resolution, permitting visualization of the simulated dynamic behavior of the entire network or of selected submodules or reaction types. As an example of the utility of this new software suite, Simmune was used to create and evaluate a detailed model of the chemotactic signaling response of *Dictyostelium*. The resulting simulations made non-trivial predictions that would not have been possible with overly abstract models and that were subsequently experimentally verified by quantitative single-cell microscopy, including the unexpected existence of spatially asymmetrical, multi-phasic, cAMP-induced PIP_3 generation at the leading edge of the cell. This combination of computational and experimental studies led us to propose a new model for chemoattractant-induced biochemical polarization in *Dictyostelium*, illustrating the value of detailed quantitative modeling and computer simulation in advancing biological understanding and of Simmune in supporting such efforts.