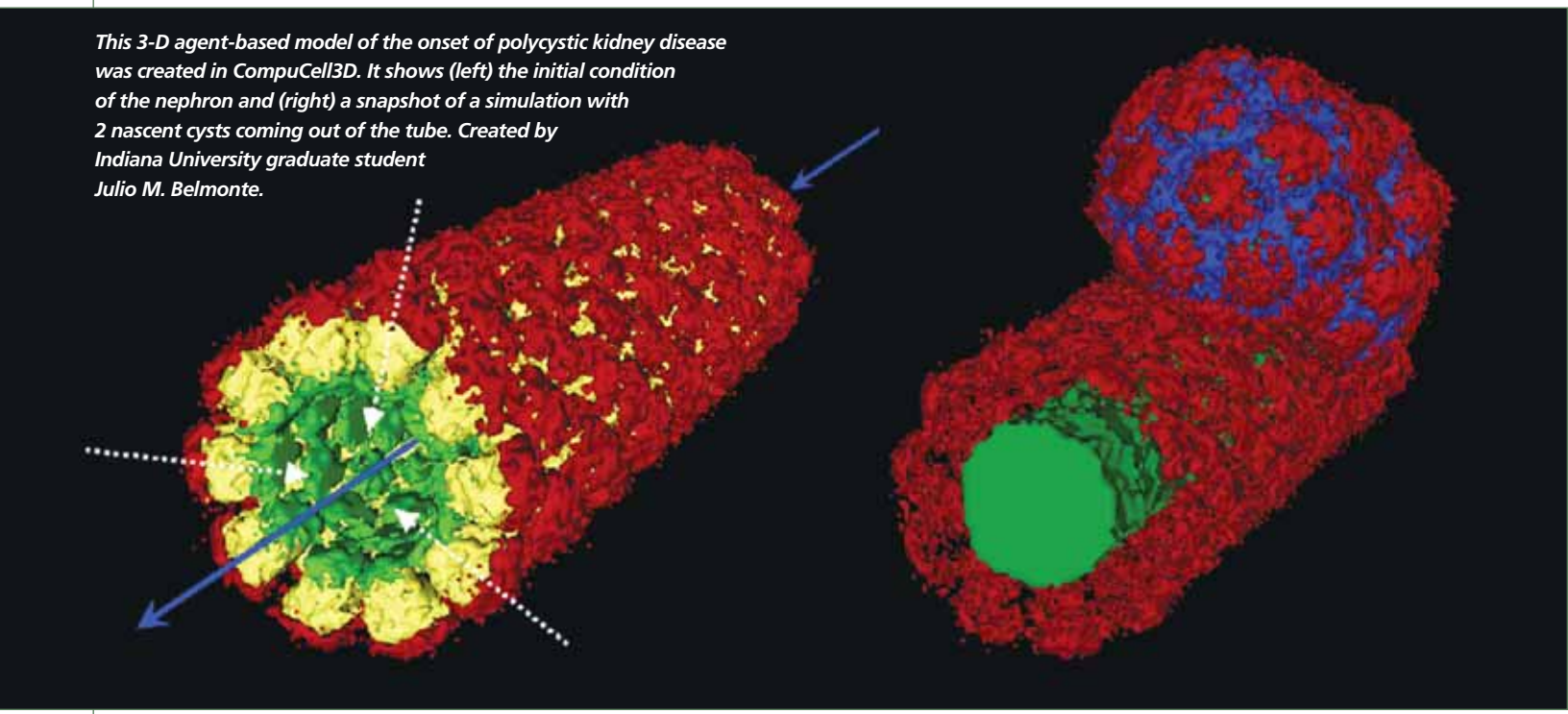
Under TheHood

BY MACIEJ SWAT AND JAMES A. GLAZIER

Agent-Based Virtual-Tissue Simulations

Cells have a limited repertoire of behaviors and interactions. They grow, divide, die, stick to each other, send and receive signals, change shape, polarize, differentiate (change behaviors), form sheets, secrete, absorb, pull on and remodel extracellular material, and migrate in response to signals in their environment. Despite their limits, cells nevertheless give rise to a wide range of tissue-level processes including embryonic development; wound healing; regeneration of a severed salamander limb; degeneration of bone in osteoporosis; cancer metastasis; and lethal over-growth of the kidney in polycystic kidney disease.



This 3-D agent-based model of the onset of polycystic kidney disease was created in CompuCell3D. It shows (left) the initial condition of the nephron and (right) a snapshot of a simulation with 2 nascent cysts coming out of the tube. Created by Indiana University graduate student Julio M. Belmonte.

Even the most detailed introspective examination of the properties of a single cell cannot reliably predict this variety of behaviors at the tissue- or organ-level. Moreover, cells themselves do not usually behave idiosyncratically, as the common biological definition of cell types indicates. And while the biochemical networks inside cells are capable of highly varied behavior *in principal*, the regulatory mechanisms active during particular developmental stages or diseases are often quite simple.

It turns out that emergent behaviors at the tissue level result from feedback—the way an agent (or cell) acts in response to its environment that in turn changes that environment. Indeed, it is the emergent interactions among classes of behaviors, rather than details of their control, that often leads to complexity of pattern formation.

These observations—that the interactions among simple cellular behaviors drive the emergent behaviors of tissues, organs and organisms—lie at the core of agent-based virtual tissues. Their empirical validity is the reason we can build predictive models using a limited number of relatively simple, universal biological mechanisms.

Agent-based models abstract key behaviors and interactions from the complexity of real biological components, embody them as computational agents and then run simulations to observe the emergent phenomena. They are especially useful in answering questions about the dependence of emergent properties on specific agent behaviors or environmental perturbations. For example, if we want to understand the factors determining the trajectories of birds in a flock, we can abstract the birds to motile *boids*, which attempt to maintain a fixed distance and angle with respect to their neighbors. To understand why antiangiogenic chemotherapies can lead benign tumors to metastasize, we can model tumor-cell agents that use nutrients to grow, mutate when they reproduce, and die when they starve. These agents also consume diffusible nutrients from the environment and, in the absence of sufficient oxygen supply, secrete diffusible signaling molecules to promote the proliferation of vascular endothelial cell agents, which in turn supply diffusible nutrients and oxy-

gen to their environment.

We might then compare how the velocities of boids in a flock correlate, or how the distribution of cell motilities in the tumor changes over time for an unperturbed tumor versus one in which we temporarily kill off the nutrient-supplying vasculature. Both simulations make useful, experimentally verifiable predictions: Increasing the inertia of the boids causes a transition from gnat-like swarming to goose-like smooth flight, while loss of vasculature causes a pattern of nutrient deprivation which favors motile, potentially metastatic tumor-cell phenotypes at the expense of the non-motile benign phenotypes favored by a steady nutrient supply.

It is important to keep in mind, however, that we may easily overlook important mechanisms—a successful model shows sufficiency of mechanism, not necessity. As a consequence, we are most likely to identify new mechanisms when simulation results differ from experiment.

Agent-based virtual tissues come in two main types—multi-cell and continuum—that serve different purposes. Multi-cell virtual tissues are useful for examining emergent behaviors resulting from the movement and reorganization of hundreds of thousands of individual cells over volumes of cubic millimeters, as in the organization of organs in embryos. Continuum virtual tissues, in which the agents are tissue volumes aggregating the behaviors of tens of thousands to millions of cells, are useful for treating larger volumes, such as an adult heart or a multi-centimeter brain tumor. Jump-up/jump-down (or hybrid) virtual tissues combine continuum models with periodic multi-cell simulations of representative tissue-volume agents to update continuum model parameters.

The various multi-cell simulation methodologies (and there are many) trade off the level of detail per cell against the number of cells per simulation. **Cellular automata**, for example, represent cells as single, fixed lattice points, allowing the largest simulations but limiting the possible cell movements and interactions. **Center models** represent cells as point particles in 3-D space interacting via potential-energy fields, much like molecular dynamics simulations, allowing cell movement, but neglecting cell shapes. **Sub-element models** build individual cell agents out of collections of tens or hundreds of center-model subcomponents at proportionally greater computational cost. **Cellular Potts Model** (or **Glazier-Graner-Hogeweg**) stochastic models approximate complex cell shapes as collections of pixels on a regular lattice and define their behaviors and interactions through the local minimization of effective energies depending on cell and pixel configurations. And **finite element** and **immersed boundary** models allow detailed geometrical representation of the shapes and surface properties and forces of cells, at much greater computational load per cell. Ultimately, each simulation method should give the same results for the same biologically determined classes of objects, behaviors and interactions.

Until recently, coding complex virtual-tissue simulations required the creation of custom low-level computer code for each model. Now, virtual-tissue simulation environments simplify the construction, execution and analysis of agent-based models by providing libraries of cells, subcellular components, extra-cellular materials, intracellular biochemical networks, and fluid and diffusing chemical agents. Just as Matlab made sophisticated mathematical modeling accessible to non-specialists, domain-specific multi-cell simulation environments such as CompuCell3D, Morpheus, Simmune and CellSys democratize virtual-tissue simulations. By reducing the model-specification code from tens of thousands to hundreds of lines, these environments allow researchers to concentrate on the difficult problem of understanding the biology rather than on computational details. In these environments, the modeler only needs to specify high-level parameters, such as the agents and their properties and how these properties change over time; the modeling software then iteratively evaluates all of the interactions present in the current model configuration and updates the parameters of each agent.

Just as Matlab made sophisticated mathematical modeling accessible to non-specialists, domain-specific multi-cell simulation environments such as CompuCell3D, Morpheus, Simmune and CellSys democratize virtual-tissue simulations.

Such agent-based simulations, like modern vital 3-D microscopy, produce cell-resolution 3-D time series results, which can then be compared against experimental results through the identification of characteristic metrics. While we are still learning how to extract biological meaning optimally from these simulations, they remain rich sources of information. □

DETAILS

Maciej Swat is an associate scientist and lead developer of CompuCell3D. James A. Glazier is professor of physics and director of the Biocomplexity Institute at Indiana University Bloomington. CompuCell3D (CC3D, www.compucell3d.org) is an open-source, cross-platform, multi-cell simulation environment that provides a platform for compact, high-level specification of simulation agents and behaviors using predefined Python templates in a language-aware template-supporting editor (Twedit++), as well as simulation execution, visualization, post-processing and results tracking.