Computational Model Predicts Tissue-Specific Cell Activity Over Time

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NEW YORK – A new computational modeling method uses plain language to write its own code for predicting cellular activity over time and generating testable hypotheses.

The computational framework, called "cell behavior hypothesis grammar," is an application of a computational method called agent-based modeling. The method could open doors to creating complex simulations of cellular systems for precision cancer research, an application that its creators hope to advance. It was published late Friday in the journal *Cell*.

Agent-based modeling (ABM) is a computational modeling technique used to understand system behavior by analyzing the interactions of autonomous programs, or "agents," each of which obeys its own set of rules. In this case, the agents model individual cells whose behavioral rules are derived from prior multiomic research.

Paul Macklin, professor of intelligence systems engineering at Indiana University and one of the paper's corresponding authors, described ABM as a powerful tool for studying dynamic biological systems but one that has so far been somewhat unapproachable for many biologists without strong computational backgrounds.

"Ten years ago, as a brand new computational system, it was very [computer science] heavy," he said. "It was very hard to use, you had to program everything by hand in C++, and it was very difficult to build reusable models in particular and to train new people to use it."

To make ABM more approachable, Macklin and his colleagues programmed cell-type specific agents with reference behavior models that simulate key processes such as cell division, growth, death, migration, secreting chemical factors, and differentiation.

"We make this big palette of behaviors that are already built in under the hood, and each of those has been calibrated to prior experiments," Macklin said.

Key to the model is a plain language interface — the "behavior hypothesis grammar" — that takes inputs such as "oxygen decreases necrosis" and connects those behaviors to signals the cells see in their simulated environment, such as drugs and signaling factors.

"We can go out and make more detailed models, but this language gives us a way to shortcut around that, saying [that] if you have an observation from prior analysis or observation, you can create rules that relate a change in cell behavior to something that we see in our simulated environment," Macklin said.

As the wealth of knowledge in the scientific community improves, he continued, more rules can be added to give a more complete picture of how cells act.

The investigators used this framework to model immune processes such as macrophage plasticity, T-cell activation and expansion, antigen recognition, and inflammation through a series of virtual experiments that Macklin and his colleagues said could eventually lead to the creation of digital twins, which could aid clinicians in better personalizing cancer therapies.

The team used real-world genomics data from breast cancer patients to reproduce the tumor-promoting behavior that often arises during an immune response then adapted that modeling framework to simulate an immunotherapy trial in a pancreatic cancer setting.

Working with data from untreated pancreatic cancer tissue samples, the model predicted an array of responses that each virtual patient might have to various immune-targeted therapies. These therapies comprised Bristol Myers Squibb's (BMS) anti-CD137 agonist therapy urelumab, the allogeneic pancreatic cancer vaccine GVAX, and BMS's anti-PD-1 immune checkpoint inhibitor Opdivo (nivolumab).

While a combination of the three drugs converted the most simulated T cells to an optimal killing state, single or double combinations outperformed the triple combination for several tissue models, suggesting a new biological hypothesis that macrophage clearing of tumor cells is essential for lymphocyte trafficking and tumor cell killing in PDAC. The authors commented in their study that this hypothesis is consistent with clinical observations of increased TREM2+ macrophage signaling to tumor cells in response to the triple combination.

Finally, the team demonstrated the generalizability of their modeling method to systems beyond cancer by simulating the formation of tissue layers in brain development. By fitting rule parameters to datasets representative of the endpoint of the simulation when the brain regions have fully formed, they successfully reproduced the laminar structure of both the somatosensory and auditory cortices.

Elana Fertig, director of the Institute for Genome Sciences at the University of Maryland and one of the study's coauthors, said that she and her coauthors are now working to expand their findings to the precancer space and see if they can extend those to other cell types to figure out which lesions are more likely to grow, relative to the lesions that are more likely to be controlled naturally by the immune system.

Laura Heiser, professor of biomedical engineering at Oregon Health and Science University and another of the study's coauthors, said that she is excited to carry the results of this study forward to explore more aspects of breast cancer.

"I've become quite interested in understanding the role of the macrophage population in mediating tumor progression and also as a population of cells that may be co-opted therapeutically to reduce tumor outgrowth and provide therapeutic endpoints," Heiser said.

Fertig also commented that computational biology is experiencing a broad move towards predicting perturbations from virtual cells via artificial intelligence (AI) and that the new cell behavior hypothesis grammar provides a better approach for modeling more complex behaviors that arise from multiple cellular interactions.

"Predicting perturbations from virtual cells … is not mechanistic," Fertig said. "You don't necessarily know what happened in that perturbation, but even if you did, [the AI] considers each cell in isolation, whereas all these ecosystems are multicellular, and none of the AI approaches account for that."

Fertig said that this obstacle for AI stems from a lack of training data for all these cellular interactions.

"Even thinking about how you would generate training data of all the different cell-cell combinations and perturbations," she said, "it becomes a combinatorial impossibility in terms of the amount of data that would be needed for AI."

Another key advantage of the cell behavior hypothesis grammar may be the ability to see precisely which parameters within the model drive the observed results.

"The beauty of mechanistic modeling is that it's explainable," Macklin said. "Machine language starts being written in a human readable format and then put into a model, rather than just [being] a black box, which makes it a lot more interpretable."

Although the simulations carried out in the current study were all modeled in two dimensions, Macklin said that the team has been working to expand their modeling capabilities into three dimensions, initially working with the pancreatic cancer model they developed for this study.

"We took that 2D [model], made a 3D tumor sphere [with] the immune cells' initial conditions, left everything else alone, and the same predictions came out," Macklin said. "This is the kind of science that really comes about when you allow people to develop and have some creativity and then come together as a team."