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AN OVERVIEW OF COMPUTATIONAL STUDIES CONCERNING THE DEVELOPMENT OF TUMORS

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ABSTRACT:

The study of cancer biology entails intricate and ever-changing interactions between cancer cells and the tissue microenvironments in which they are located. The consequences of a single cell on the clinical development are of crucial importance. It is possible for normal physiological processes to be co-opted by chemical and mechanical communication between tumour and stromal cells in order to enhance growth and invasion. The heterogeneity of cancer cells enhances the disease's capacity to try out new tactics for coping with the pressures of its immediate environment. Both hypoxia and therapy have the potential to select for cancer stem cells, which then drives both invasion and resistance. Cell-based computational models, which are also known as discrete models, agent-based models, or individual-based models, are used to simulate individual cells as they interact in virtual tissues. This enables us to investigate how single-cell behaviours contribute to the dynamics that we observe and work to control in cancer systems. Within the scope of this study, we will go through a wide variety of approaches that are currently accessible for cell-based computational modelling. The techniques may vary from extremely detailed models of just a few cells and their morphologies to models consisting of millions of simpler cells arranged in three-dimensional tissue. The modelling of individual cells enables us to immediately transform discoveries made in biological research into simulation rules. In many situations, individual cell agents contain molecular-scale models. We are able to relate the development of cancer to the circumstances of the microenvironment because to the majority of models' ability to mimic the movement of oxygen, medicines, and growth factors. Examples from cancer hypoxia,

angiogenesis, invasion, stem cells, and immunosurveillance are used throughout this article to highlight the various strategies.
Keywords: Computational analysis, Growth, Tumor

INTRODUCTION:

Cancer is a difficult problem to solve because it entails complicated interactions between cancer cells and the tissue microenvironments in which they are located. Therapeutic techniques that concentrate only on cancer cells typically result in unsatisfactory results, such as therapy ineffectiveness, cancer cell resistance, and invasion of surrounding tissues. These failures may be attributed, at least in part, to the unexpected behaviours that manifest themselves from the dynamical systems of cancer tissues. Therapies exert a selection pressure, even as cancer cells take use of the increased genetic diversity available to them in order to test a variety of survival strategies and adapt. Chronic hypoxia is another kind of selective pressure that may cause metabolic alterations, the selection of cancer stem cells that are resistant to therapy, invasion, and angiogenesis. Because of their ability to interact both biochemically and biomechanically with the surrounding stromal cells, tumour cells are able to hijack normally occurring physiologic processes. Mathematical models can serve as "virtual laboratories" with fully controlled conditions, allowing scientists and clinicians to investigate the emergent clinical behaviours that result from basic cell hypotheses and to evaluate new therapeutic strategies. In these "virtual laboratories," scientists and clinicians can investigate the emergent clinical behaviours that result from basic cell hypotheses.

This article provides an overview of the cell-based techniques that are used to simulate cancer. Cell-based models are a kind of model that simulates the actions of individual cells within their respective tissue contexts. These models are also known as discrete models, agent-based models, or individual-based models. These devices provide a number of distinct benefits. Each cell agent is capable of tracking a totally autonomous state with distinct characteristics that represent the heterogeneity that is present in cancer. Run simulation experiments that explore the emergent behaviours of these hypotheses. Compare against new data to confirm, reject, or iteratively improve the underlying hypotheses. Modelers can directly implement cell rules that

reflect observations of single-cell behaviour and cell-cell interactions. This allows us to translate biological hypotheses to mathematical rules quickly.

A SURVEY OF CELL-BASED MODELING METHODS:

Cell-based models may be broken down into two basic paradigms: lattice-based models, which monitor cells along a rigid grid, and off-lattice models, which do not have this limitation. Both of these models represent individual cells. The majority of cell-based modelling methodologies are broken out in Figure 1. The most popular open-source modelling software are outlined.

Lattice-Based Methods:

Both regular structured meshes (such as Cartesian11 [two- or three-dimensional [2D/3D], dodecahedral [3D]) and unstructured meshes may be used in lattice-based models. Structured meshes are easier to design, display, and integrate with partial differential equation (PDE) solvers than unstructured meshes, however the structure of structured meshes may lead to grid biases. Unstructured meshes provide a potential solution to these problems13, but at the expense of increased complexity.

We are able to further classify lattice-based approaches depending on the spatial resolution that they provide. The cellular automaton (CA) modelling technique allows for a single cell to occupy each lattice location. 14-17 Each cell is given an update based on discrete lattice-based rules at each time step. These rules may be summarised as follows: stay, migrate to an adjacent lattice site, die (free a lattice site), or divide to deposit a daughter cell in a nearby site. The lattice sites are often updated in a randomised sequence using these approaches in an effort to eliminate grid artefacts.

Instead of tracking the movements of each individual cell, LGCA models count the number of cells that pass through channels between individual lattice locations. This makes analysis easier and offers a bridge to continuum approaches that represent cell densities or populations rather than single cells. They are able to simulate extremely large numbers of cells effectively over extended periods of time while also relating to the theory of statistical mechanics.

The resolution of some issues may involve an examination of the morphology of individual cells. Cellular Potts models, often known as CPMs, depict each cell by using a number of different attice sites. CPMs go to each pixel

(2D) or voxel (3D), try a random swap with an adjacent pixel/voxel, then approve or reject the swap (probabilistically) based on whether it would lower a global energy. This process occurs at each time step. CPMs are much more computationally demanding than CA models despite the fact that they can represent cell morphologies and mechanics that cannot be integrated in CA models. In addition, the process of calibrating Monte Carlo steps to actual physical time may be difficult.

Off-Lattice Methods:

Off-lattice models may be broken down into two categories: center-based models (CBMs), which concentrate on cell volumes (or masses), and models, which concentrate on cell borders. These methods may be further categorised based on the amount of morphologic information they include.CBMs monitor the location of the centre of mass or volume of each cell, often via the use of a single software agent for each cell.

There are many different CBMs, and some of them depict cell volumes directly, while others just show cells as dots. In most cases, CBMs will update the locations of the cells by stating explicitly the adhesive, repulsive, locomotive, and drag-like forces that are transferred between cell centres. The vast majority of CBMs model cells as spheres; however, other models model cells as deformable ellipsoids in order to more accurately portray the morphologies of the cells. By dividing cells up into their constituent subcellular pieces, CBMs are able to mimic the shape of cells in more detail. Multiple center-based agents, which may interact with both adhesive and repulsive forces, are used to represent each cell. These models provide a closer approximation of the biomechanics of cells; however, this comes at the expense of increasing computing cost. On the other hand, cells may be grouped together into clusters or functional units (such as breast glands or colon crypts), which can then be mimicked as agents that interact with one another via the use of mechanical forces or other rule-based movements. Modelers are now able to include diverse information into individual clusters of cells while yet achieving higher levels of computing efficiency than was previously possible with conventional CBMs.

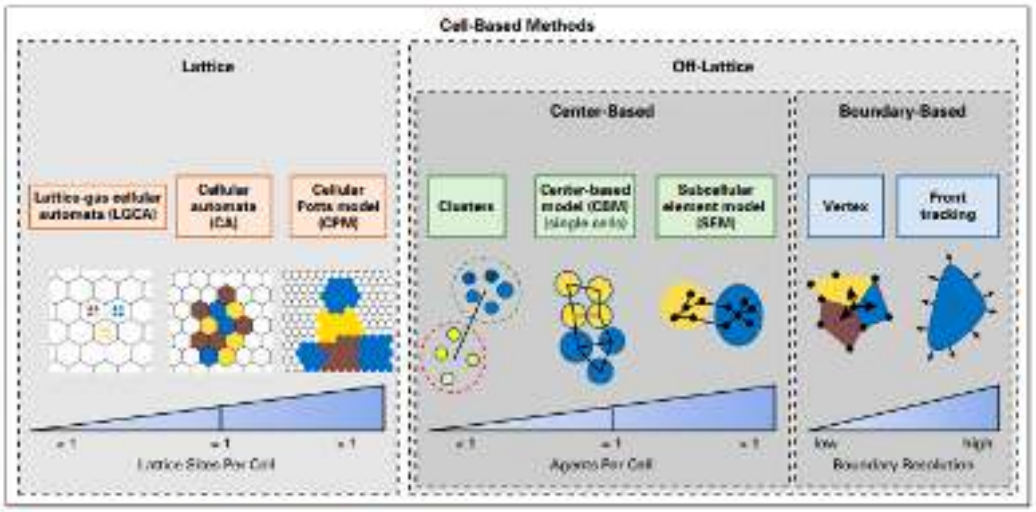


FIG 1. A schematic classification of cell-based modeling approaches.

Boundary-tracking models:

Vertex-based approaches (for example, Fletcher et al28) describe cells as polygons (2D) or polyhedra (3D) and calculate the forces that act on their vertices. These methods are especially helpful for modelling confluent tissues. 29 Front-tracking approaches, such as the immersed boundary method (IBM), solve partial differential equations (PDEs) for fluid flow within and between cells, and then advect boundary points along the membranes of the cells in response to this flow. This allows for increased spatial resolution. 30 Level set approaches have been employed to implicitly monitor the movement of cell boundaries31, and VCell (see Connecting to Molecular Effects) has recently introduced front-tracking capabilities. Both of these techniques have been applied. 32,33 These cell-based approaches are among the most computationally costly, yet they are helpful for linking precise cell mechanics to fluid and solid tissue mechanics.

Connecting to Molecular Effects:

The vast majority of cell-based models are of the hybrid discrete-continuum kind; that is, they marry a discrete cell model with continuum models of the microenvironment. In general, these models replicate the biotransport of oxygen, growth hormones, and medications via the use of reaction-diffusion PDEs. BioFVM was created by Ghaffarizadeh et al. in order to address the diffusive transport of tens to hundreds of chemical substrates in three-dimensional tissues. It is the fundamental PDE solver for PhysiCell (a center-based simulation framework). 21 Modelers will construct rules within this framework to tie the phenotypes of individual cells to the circumstances of the local chemical substrate.

Ordinary differential equations (ODEs) are a component of many discrete models, which are used to simulate the molecular processes that occur in individual cells.

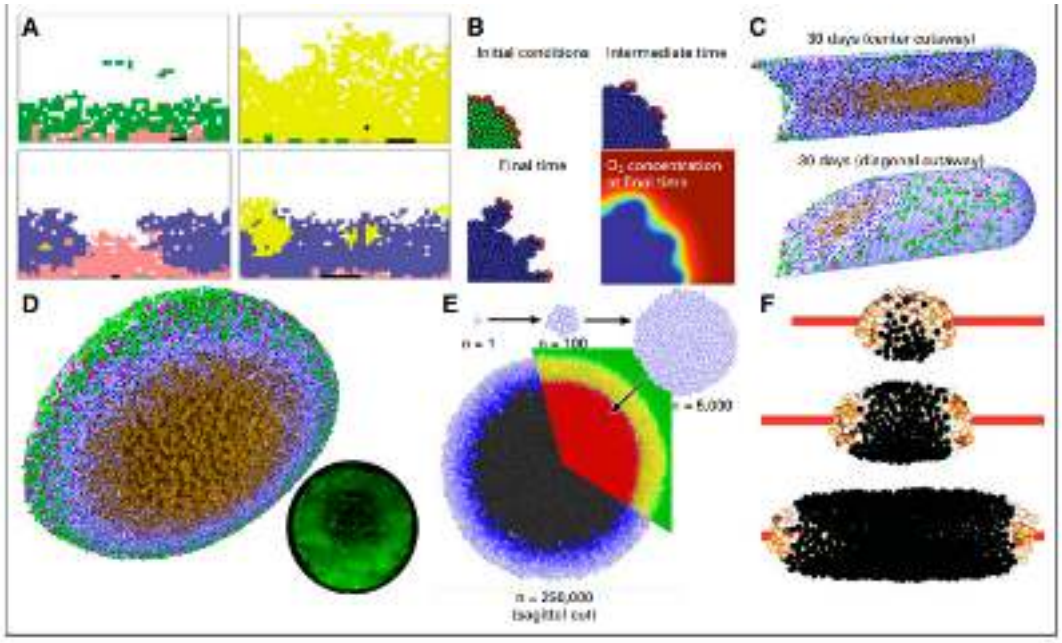
VCellis able to simulate the reacting flows of many proteins within a single detailed cell and many modelling packages support systems biology markup language (SBML) to include systems of ODEs that simulate molecular effects in individual cells. Others use discrete models within individual agents. Gerlee and Anderson used small neural networks to simulate individual cell phenotypic "decisions" on the basis of microenvironmental inputs. On the other hand, PhysiBoSS combines the Boolean network modelling approach of MaBoSSwith PhysiCell to simulate molecular processes in individual cells.

EXAMPLES OF CELL-BASED MODELING IN CANCER BIOLOGY:

Moving further, we will investigate a number of modeling topics that exemplify the use of cell-based modeling in cancer biology. Despite the fact that we are unable to conduct a comprehensive review of all cell-based modeling in cancer (or even sample all major use cases for cell-based modeling), these themes have been compiled from a variety of research areas to illustrate scientific problems that have significant effects at the cell scale and for which cell-based models have the potential to provide novel insights.

In order to examine tumour development in hypoxic tissues and, more broadly, the influence of diffusive transport constraints, a number of different groups have developed cell-based models. CAs were used in the studies by Gatenby et al. and Small bone et al. in order to investigate hypoxia-driven shift to invasive phenotypes in ductal cancer in situ (DCIS). They integrated metabolic adaptations of cells to hypoxia, which made it possible for them to investigate early stages of tumour invasion. Anderson and colleagues expanded prior CA results by adapting IBCell30 (an IBM) to mouse mammary (EMT6/Ro) tumour cell proliferation in hypoxic tissues. This was done in order to extend earlier CA findings. They discovered, just as they had previously, that hypoxic gradients might promote tissue invasion. However, because to IBCell's enhanced modeling of cell adhesion and biomechanics, they expected more rounded invasive points. (Fig 2B) Macklin et al.50 and Hyun and Macklin51 used a CBM to analyse oxygen-driven proliferation and necrosis in solid-type DCIS with comedonecrosis. Both groups found that the CBM was effective in their research.

They were able to simulate comedonecrosis and micro calcifications as emergent properties of the simulations along with realistic, constant rates of tumour advancement along the breast ducts after calibrating to individual patient pathology data (tissue specimens immunostained for the Ki protein to detect cycling cells, cleaved caspase 3 to detect apoptosis, and annotated with viable rim sizes and cell density). This was accomplished by simulating comedonecrosis Ghaffarizadeh et al. improved the DCIS model by extending it to three dimensions and simulating the hypoxic interiors of hanging drop spheroids while calibrating their parameters to match the birth and death dynamics of MCF-10A cells in culture (Figs 2C and D). They hypothesised that the cells would have a layered structure, with an outside proliferative ring enclosing a quiescent perinecrotic zone and an internal necrotic core, similar to the early 3D work that Drasdo and Hohme 48 had done on EMT6/Ro cells (Fig 2E). They were the first to predict networks of fluid-filled pores in the necrotic cores, which emerge from the competing effects of necrotic cell shrinking and adhesion; these structures are observed in experimental models. Necrotic cell shrinkage and adhesion are two effects that compete with one another (Fig 2D inset). The researchers Szymanska et al. 49 employed a cultured biological model (CBM) consisting of EMT6 cells to imitate a developing tumour cord. A tumour cord is a solid tumour that forms around a blood artery. They hypothesised that there would be a similar three-layer structure, but in the opposite order: a necrotic outer, a quiescent interior, and a growing core close to the blood artery (Fig 2F).



TUMOR-INDUCED ANGIOGENESIS AND DRUG DELIVERY:

Sprouting angiogenesis was modelled by colleagues using a CA model of vessel tip movement, which included the following: Sprout tip agents migrated in the direction of hypoxic tumour locations by following chemotactic and haptotactic signals, leaving behind a trail of functioning vasculature as they did so. They used this framework to investigate the possibility of therapeutic delivery from vasculatures associated with tumours. This framework included the incorporation of a detailed vascular network flow model, which included dynamic wall shear stress rules for vessel branching and anastomosis (vessel looping) (Fig 3A).

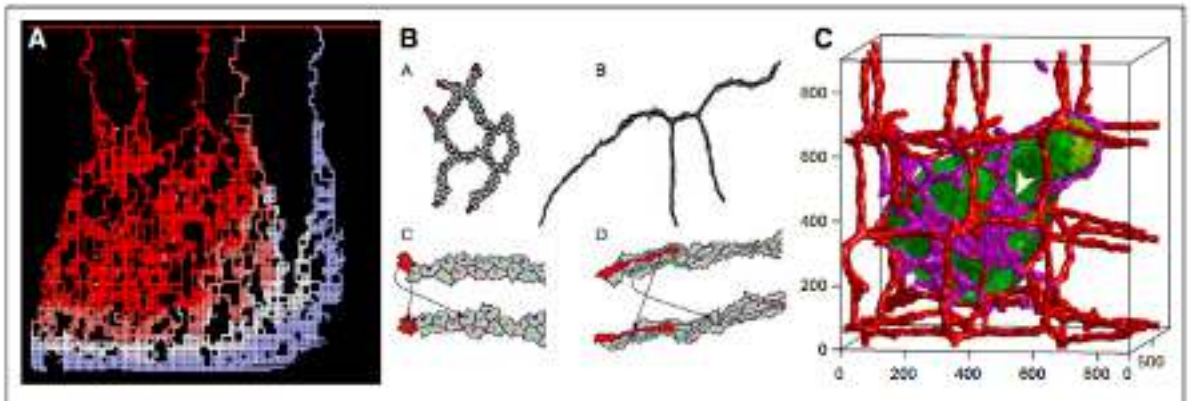


Fig. 2: Cancer Stem Cells

Models of cancer stem cells, often known as CSCs, provide very useful insights into the factors that are driving the biology of cancer. In order to investigate the involvement of stem cells (which are located at the bottom of the crypt) in the development of colorectal cancer, Fletcher and colleagues constructed a 3D CBM of colonic crypts. The division of stem cells and their differentiation were directed by Wnt gradients that ran down the crypt axis. Neighboring cells were linked to one another by linear springs. An overall base-to-top proliferative cell flow was produced as a result of the architecture of the stem-cell hierarchy, which consisted of proliferation at the crypt base, expansion and differentiation along the middle, and differentiation at the top. Unless the mutation takes place in a stem-cell niche, this flux exerts an anticancer preventive effect by expelling any mutant cell and its children from a crypt before they are able to spread throughout the crypt. This is the case even if the mutation takes place in a stem-cell niche.

In order to investigate the dynamic relationship that exists between triple-negative breast cancer and stromal cells, Norton et al. developed a 3D CA model. Cancer cells exchanged chemical signals with invading macrophages and fibroblasts while stem cells proliferated and differentiated into progenitor cells. Stem cells also proliferated and differentiated into progenitor cells. They observed, among other things, that increasing the stromal influence on cancer cell proliferation led to a smaller overall tumour size, but increasing the stromal effect on cancer cell migration led to a larger tumour size. This was one of their findings.

CONCLUSION:

Cancer invasion is critical to metastatic progression. In order to flee primary tumours and infiltrate neighbouring tissues (as theoretically portrayed in epithelial-to-mesenchymal transition [EMT]), penetrate and migrate through blood and lymphatic arteries, and eventually populate distant metastatic habitats, cancer cells develop a motile phenotype. Due to the importance of single-cell effects, several cell-based models have been developed to examine cancer invasion, either with or without the inclusion of explicit modelling of EMT. The LGCA model was developed to mimic the consequences of heterogeneous cell-cell adhesion in an epithelial layer. One of the outcomes of epithelial-to-mesenchymal transition (EMT) is a reduction in cell-cell adhesion. To mimic cell-cell adhesion, we varied both the starting number and the maximum number of adhesion receptors that were present in each virtual cell. They discovered that higher adhesion heterogeneity led to enhanced dispersion, as did decoupling receptor number from environmental signals (cell-cell interaction).

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