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MetaSpread: A cancer growth and metastatic spread simulation program in Python

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Summary

We develop and provide MetaSpread, an open-source simulation package and interactive program in Python for tumor growth and metastatic spread, based on a mathematical model by Franssen et al. (2019). This paper proposed a hybrid modeling and computational framework where cellular growth and metastatic spread are described and simulated in a spatially explicit manner, accounting for stochastic individual cell dynamics and deterministic dynamics of abiotic factors. This model incorporates several key processes such as the growth and movement of epithelial and mesenchymal cells, the role of the extracellular matrix, diffusion, haptotaxis, circulation and survival of cancer cells in the vasculature, and seeding and growth in secondary sites. In the software that we develop, these growth and metastatic dynamics are programmed using MESA, a Python Package for Agent-based modeling (Masad & Kazil, 2015).

Keywords: cancer, growth, metastatic spread, multi-scale dynamics, simulation

Statement of need

Models of tumor growth and metastatic spread are critical for understanding the key underlying biological processes and clinical evolution in patients. Mathematical models can be of different levels of detail, computational or theoretical, spatial or non-spatial in nature, and can have several mechanisms explicit or implicitly embedded in them, including interaction with resources, biomechanical signals, cellular competition, mutation and migration (Chaplain, 2020; Franssen et al., 2021; Macnamara et al., 2020; Opasic et al., 2020; Waclaw et al., 2015). While theoretical and analytical advances remain crucial in mathematical models of cancer, computational approaches that offer direct simulation platforms for efficient numerical exploration, focused study and hypothesis testing are also very much needed. Here, we contribute to this aspect, by offering an open source simulation framework in Python for spatio-temporal progression of tumor and metastatic spread. We build the simulation framework on a hybrid mathematical model developed by Franssen et al. (2019), extending the previous work (Anderson & Chaplain, 1998), in close agreement with empirical data (Newton et al., 2015; Sabeh et al., 2009). This contribution aims to bridge gaps between mathematicians, oncologists, biologists, computer scientists and interested researchers working in the field of cancer metastatic progression.

Cancer growth and spread model

A 2-dimensional multigrid hybrid spatial model of cancer dynamics is developed in Python (see Figure 1 for a snapshot illustration), where the first grid represents the primary tumor site, and the secondary grids represent metastatic sites, connected via the vasculature compartment. Here we combine the stochastic individual-based dynamics of single cells with deterministic dynamics

of the abiotic factors. In the tumor site we consider two different cancer cell phenotypes: epithelial (epithelial-like) and mesenchymal (mesenchymal-like) cells. The epithelial-like (E) cancer cells reproduce at a higher rate, but diffuse more slowly than mesenchymal (M) cells, which reproduce at a lower rate but diffuse more rapidly. Furthermore, epithelial cells require the presence of mesenchymal cells to be able to intravasate into normal vessel entry-points. The exception to this are ruptured vessels, that allow for the intravasation of any type of cancer cell. The cellular growth and movement in space is modeled considering 2 partial differential equations, where diffusion and haptotaxis movement are implemented. The model includes two additional equations: one for the spatio-temporal dynamics of matrix metalloproteinase 2 (MMP-2), a chemical that favors the spread of cancer cells, and another for the degradation of the extracellular matrix (ECM), which also favors the haptotactic movement of the cancer cells. We follow the equations and discretization of PDEs as described by Franssen et al. (2019) for the spatial densitites of different populations:

$$\begin{aligned}
\frac{\partial c_E}{\partial t} &= D_{\mathrm{E}}\nabla^2 c_{\mathrm{E}} - \Phi_{\mathrm{E}}\nabla\cdot(c_{\mathrm{E}}\nabla w)\\
\frac{\partial c_{\mathrm{M}}}{\partial t} &= D_{\mathrm{M}}\nabla^2 c_{\mathrm{M}} - \Phi_{\mathrm{M}}\nabla\cdot(c_{\mathrm{M}}\nabla w)\\
\frac{\partial m}{\partial t} &= D_m\nabla^2 m + \Theta c_{\mathrm{M}} - \Lambda m\\
\frac{\partial w}{\partial t} &= -(\Gamma_1 c_{\mathrm{M}} + \Gamma_2 m)w
\end{aligned} \tag{1}$$

With c_E, c_M, m, and w the concentrations of epithelial cells, mesenchymal cells, MMP-2, and ECM, respectively. Parameters: D_k, diffusion coefficients; Φ_k, haptotactic sensitivities; Θ, MMP-2 expression rate; Λ, MMP-2 decay rate; Γ_1, ECM degradation by MT1-MMP; Γ_2, ECM degradation by MMP-2.

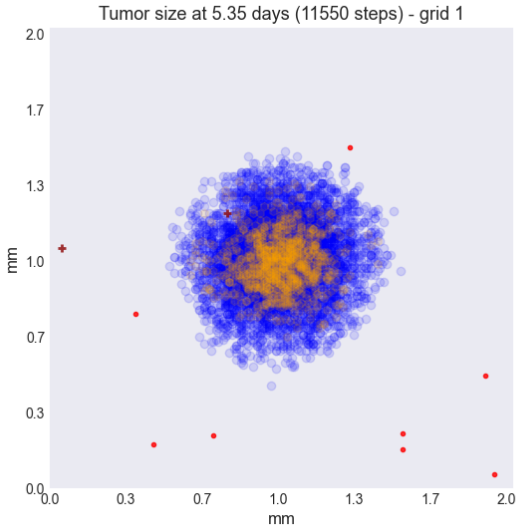

Figure 1: Early snapshot of our simulations for cancer cell spread in the primary tumour (grid 1) after approximately 5 days. Parameters set as default with initial distribution centered around (1 mm, 1 mm) with radius of about ~0.1 mm, and total initial size = 388 cells. The blue color denotes mesenchymal cells, the orange color denotes epithelial cells. The intensity of the color represents the number of cells (from 0 to 4, the maximum amount of cells allowed in each unit of space) in that particular grid point. The red grid points represent entry-points to the vasculature, with circles intact vessels and crosses representing ruptured vessels. See the documentation (Hernandez-Inostroza & Gjini, 2024).

Implementation

For the simulation of the spatio-temporal growth dynamics, and metastatic spread, the system of PDE's is non-dimensionalized and discretized. Each cell on every grid at location (x_i, y_j) is modeled as an individual agent, which obeys probability rules for growth and movement. Only the primary site is seeded with an initial number and distribution of cells. In order for the cells to migrate to another site, they must travel through the vasculature, which they do if they intravasate by one of the several randomly selected points in the grid that represent entrances to the vasculature system. The cellular processes in the vasculature are modeled through probabilistic rules according to Franssen et al. (2019). The dynamics of the MMP-2 and the extracellular matrix are modeled deterministically from the PDE's.

For more details on the implementation, API, interactive CLI, mathematical model, and data analysis tools refer to the original publication by Franssen et al. (2019) and MetaSpread's documentation (Hernandez-Inostroza & Gjini, 2024).

Future directions for extension and links with other existing packages

There are other packages that simulate cancer processes in the literature. For example, CancerSim (Opasic et al., 2020) is a software that simulates somatic evolution of tumors. It produces virtual spatial tumours with variable extent of intratumour genetic heterogeneity and realistic mutational profiles. By applying multi-region sampling to simulated tumors to obtain mutation profiles, one can later match them with sequencing data. This makes CancerSim a useful tool for studying various sampling strategies in clinical cancer diagnostics. Although there are some parallels of CancerSim with our software MetaSpread, like the agent-based formulation for individual cells, there are also several differences. For example, CancerSim does not address metastatic processes, nor does it account explicitly for the cancer cell interaction with the extracellular matrix or MMP2, or the specificities of cell movement like diffusion and haptotaxis that our hybrid model based on (Franssen et al., 2019) includes. The objectives being different, CancerSim focuses on cell heterogeneity and evolutionary processes and their effects on tumor growth, while MetaSpread focuses on cell population processes (deterministic and stochastic) leading to metastatic spread. We believe both of these frameworks can be complementary, and used in parallel or combined to study and integrate distinct aspects of cancer dynamics.

There are several directions for extensions of the algorithm and simulation package. On the computational side, the main challenge relies on making the code flexible for parallel computing, so that both the spatial and temporal resolution can be increased. Furthermore, we could implement a 3D version of the dynamics and improve the computational efficiency and speed of the simulation, which now requires about 24 hours for 28.000 time steps (~12 days). On the biological side, we could include the immune system, interaction of the cancer cells with healthy cells, implement the effect of treatment, for example adaptive therapies (West et al., 2023), mutations and EMT transition. In the current formulation the metastatic spread is captured only by the biases in arrival probabilities (Newton et al., 2015). A novelty would be to consider heterogeneity in different grids, allowing for differential suitability for growth and colonization by arriving cancer cells.

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