Enhanced Physics-Informed Neural Networks for collective cancer invasion

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Introduction

Aggressive attempts to eliminate cancer often lead to drug resistance and tumor recurrence, while strategies that aim to control tumor growth may be more sustainable in the long term. Collective invasion—where clusters of cancer cells move together while maintaining cell–cell connections—allows them to survive better than individual cells, partly because they are more resistant to immune attacks and treatments. Leader cells guide this movement by reshaping the surrounding environment and directing follower cells. By targeting the interactions between leader and follower cells, therapies could shift toward containment and reduce the risk of metastasis [1].

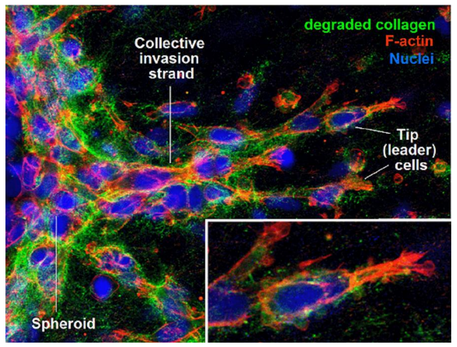


Fig. 1. The figure shows part of the tumor sphere. The tumor has both single cells and clusters of cancer cells (including leader cells and follower cells) separating from it. Figure is modified from [2].

Collective invasion refers the leader-follower coordination leading to the forming of protruding, finger-like clusters Leaders, highly motile and invasive cells, can move, while followers proliferate and reinforce the cluster by adhering strongly to the leaders. This cooperation is critical for cancer metastasis, as isolated cells are largely ineffective in spreading the disease [3].

Methods

We model collective cancer cell invasion as a two-species system consisting of the density of leader (ρ_l) and follower (ρ_f) cells evolving over space and time. The model is derived from the effects of diffusion, cell-cell adhesion, and chemotaxis. Thus, the dynamics are governed by the following final coupled partial differential equations (PDEs):

$$\frac{\partial \rho_l}{\partial t} = (D_l - 2\kappa_l\alpha_l\rho_l)\nabla^2\rho_l - 2\alpha_l\kappa_l(\nabla\rho_l)^2 - \kappa_l\alpha_{fl}\nabla\rho_l\nabla\rho_f - \kappa_l\alpha_{fl}\rho_l\nabla^2\rho_f - \chi\nabla(\rho_l\nabla C)$$

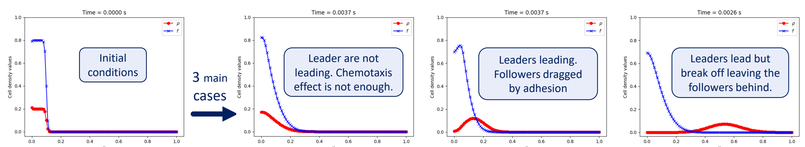
$$\frac{\partial \rho_f}{\partial t} = \left(D_f - 2\kappa_f\alpha_f\rho_f\right)\nabla^2\rho_f - 2\alpha_f\kappa_f\left(\nabla\rho_f\right)^2 - \kappa_f\,\alpha_{fl}\nabla\rho_f\nabla\rho_l - \kappa_f\alpha_{fl}\rho_f\nabla^2\rho_l$$

Our model assumptions include: (1) Invasion is initiated by pre-existing leaders and followers. (2) Leaders undergo chemotaxis, responding to external chemical gradients; followers do not. (3) Strong adhesive interactions bind followers to leaders which enables their movement and thus the collective cancer invasion.

The model incorporates no-flux and Dirichlet boundary conditions to constrain cell movement within the domain. The initial conditions are of a hyperbolic tangent type, and the boundary conditions are defined as,

$$\left[(D_l - 2\kappa_l\alpha_l\rho_l)\nabla\rho_l - \kappa_l\alpha_{fl}\rho_l\nabla\rho_f - \chi\rho_l\right]\Big|_{x=0} = \vec{0}$$
$$\left[\left(D_f - 2\kappa_f\alpha_f\rho_f\right)\nabla\rho_f - \kappa_f\alpha_{fl}\rho_f\nabla\rho_l\right]\Big|_{x=0} = \vec{0}$$
$$\rho_l|_{x=L} = 0, \quad \rho_{fl}\Big|_{x=L} = 0$$

Considering $\boldsymbol{\kappa = \kappa_l = \kappa_f}$, $\boldsymbol{\varepsilon = \frac{D_f}{D_l} < 1}$, and $\boldsymbol{\alpha_l < \alpha_f < \alpha_{fl}}$, our final model is in dimensionless form with six key parameters corresponding to physical properties of the system. To evaluate the accuracy of our approach, we compute a reference solution using the Finite Difference Method (FDM) applied to the dimensionless form of the governing equations. This FDM solution serves as a benchmark for comparison. Some solutions are as,



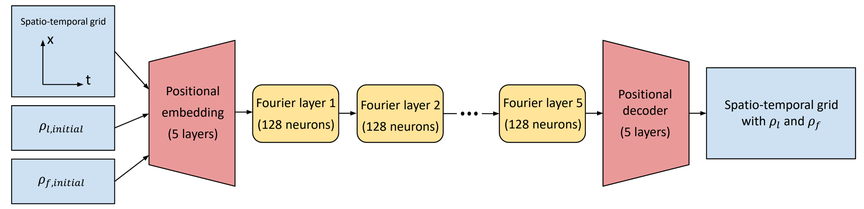
Modified PINN Architecture

To solve the equations in a data-efficient, mesh-free manner, we use a family of Physics-Informed Neural Operators (PINOs) [4]. These models avoid reliance on labeled data by encoding physical constraints (PDEs, initial and boundary conditions) directly into the learning process via the loss function. Our implementation is based on the Tensorized Fourier Neural Operator (TFNO), which learns mappings from input spatio-temporal coordinates and initial conditions to the densities of leader and follower cells, $\boldsymbol{\rho_l(x,t)}$ and $\boldsymbol{\rho_f(x,t)}$, respectively. The model takes as input the space-time grid (x,t), along with the initial density fields for both species, and predicts their evolution over time. We explored two distinct variants of this architecture: one enforcing the strong form of the PDE using automatic differentiation, and the other using a weak form of the residuals. Training is guided by a composite loss function:

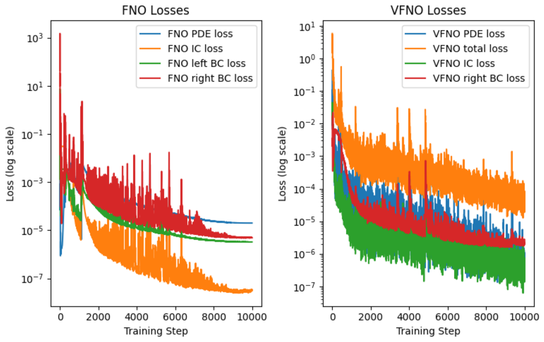
$$\boldsymbol{\mathcal{L}(\theta) = \lambda_f\mathcal{L}_f(\theta) + \lambda_{ic}\mathcal{L}_{ic}(\theta) + \lambda_{bc}\mathcal{L}_{bc}(\theta)}$$

All derivatives required for the residuals are computed with PyTorch's autograd engine [5].

Preliminary Tests and Results



Our initial models failed to learn the solution of the PDE System by falling into one of the many failure modes of PINOs, the vanishing gradients. This is evident in our training as the PDE loss drops close to zero, however our solution shows no movement of the cells across the x-axis.



Conclusions/Future Directions

We aim to improve accuracy and stability, we are exploring a sequence-to-sequence (Seq2seq) PINO approach and Augmented Lagrangian (AL) to imposing IC and BCs [6]. The first method decomposes the time domain into discrete time snapshots and trains the model sequentially, using the output of one snapshot as the initial condition for the next. The latter, imposes the boundary and initial conditions in some numerical examples since it has a better performance compared to the original PINN.

References

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