Electronic supplementary material T1

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A mathematical model of tumour angiogenesis: Growth, regression, and regrowth

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1 Discretization of the continuous equations

Here, we show the discretization of the partial differential equations of the mathematical model proposed in the main text. The strong form of the problem is: find f, c such that:

$$\frac{\partial f}{\partial t} = \nabla \cdot (D \nabla f) + \mathcal{P}(d)(f_{\text{hyc}} - f) - \mathcal{U}(c) f \tag{1a}$$

$$\frac{\partial c}{\partial t} = M\left(\lambda^2 \Delta c - \mu(c, f)\right), \tag{1b}$$

with natural boundary conditions. We first show the spatial discretization followed by the temporal discretization.

1.1 Spatial discretization

The spatial discretization is based on the Galerkin method and on isogeometric analysis [1, 2]. Let Ω be the problem domain and $[0, T]$ the time interval of interest. We start by deriving the weak form of the strong problem. Let $\mathcal{V}$ denote the trial solution space for c and f. The test function spaces are assumed to be the same as their corresponding trial spaces. We denote $\mathcal{L}^2$ the space of square integrable functions. $\mathcal{H}^1$ is the Sobolev space of square integrable functions with square integrable first derivatives. After multiplying with smooth functions, integrating over the domain, and applying integration by parts, we obtain the variational formulation of the problem, which may be stated as follows: find $f(t) \in \mathcal{L}^2([0,T]; \mathcal{V}) \cap \mathcal{H}^1([0,T]; \mathcal{L}^2(\Omega))$ and $c(t) \in \mathcal{L}^2([0,T]; \mathcal{V}) \cap \mathcal{H}^1([0,T]; \mathcal{L}^2(\Omega))$ such that:

$$\int_\Omega w_1 \frac{\partial f}{\partial t} \,\mathrm{d}\Omega + \int_\Omega \nabla w_1 D \nabla f \,\mathrm{d}\Omega - \int_\Omega w_1 \mathcal{P}(d)(f_{\text{hyc}} - f) \,\mathrm{d}\Omega + \int_\Omega w_1 \mathcal{U}(c) f \,\mathrm{d}\Omega = 0 \quad \forall w_1 \in \mathcal{V} \tag{2a}$$

$$\int_\Omega w_2 \frac{\partial c}{\partial t} \,\mathrm{d}\Omega + \int_\Omega \nabla w_2 M \lambda^2 \nabla c \,\mathrm{d}\Omega + \int_\Omega w_2 M \mu(c, f) \,\mathrm{d}\Omega = 0 \quad \forall w_2 \in \mathcal{V} \tag{2b}$$

We make use of the Galerkin method to perform the spatial discretization. Let us define the discrete space $\mathcal{V}^h$, which is a subset of $\mathcal{V}$. We approximate the previous weak problem by the following variational problem over the finite dimensional space: find $f^h(t) \in \mathcal{L}^2([0,T]; \mathcal{V}^h) \cap \mathcal{H}^1([0,T]; \mathcal{L}^2(\Omega))$ and $c^h(t) \in \mathcal{L}^2([0,T]; \mathcal{V}^h) \cap$

$\mathcal{H}^1([0,T];\mathcal{L}^2(\Omega))$ such that:

$$\int_\Omega w_1^h \frac{\partial f^h}{\partial t}\,\mathrm{d}\Omega + \int_\Omega \nabla w_1^h D \nabla f^h\,\mathrm{d}\Omega - \int_\Omega w_1^h \mathcal{P}(d)\left(f_{\mathrm{hyc}} - f^h\right)\,\mathrm{d}\Omega + \int_\Omega w_1^h \mathcal{U}\left(c^h\right) f^h\,\mathrm{d}\Omega = 0 \quad \forall w_1 \in \mathcal{V}^h \tag{3a}$$

$$\int_\Omega w_2^h \frac{\partial c^h}{\partial t}\,\mathrm{d}\Omega + \int_\Omega \nabla w_2^h M\lambda^2 \nabla c^h\,\mathrm{d}\Omega + \int_\Omega w_2^h M\mu\left(c^h, f^h\right)\,\mathrm{d}\Omega = 0 \quad \forall w_2 \in \mathcal{V}^h \tag{3b}$$

Here, f^h is defined as

$$f^h(\mathbf{x},t) = \sum_{A=1}^{n_b} f_A(t)\, N_{A,p}(\mathbf{x}) \tag{4}$$

where n_b is the dimension of the discrete space $\mathcal{V}^h$, the coefficients f_A are the so-called control variables, and $N_{A,p}$ are the basis functions. The subindex p in $N_{A,p}$ denotes the polynomial degree. The rest of the variables, namely c^h, w_1^h, and w_2^h, are defined analogously to f^h. We use

The multivariate spline functions $N_{A,p}$ are constructed from univariate B-splines using tensor products. Univariate B-splines may be defined from a knot vector, that is, a non-decreasing set of coordinates in the parameter space. Since the paper deals with simulations on squares only, the parameter space and the physical space may be considered identical. Let $\Xi = \{\xi_1, \xi_2, \ldots, \xi_{n+p+1}\}$ be the knot vector, where $\xi_i \in \mathbb{R}$ is the ith knot, i is the knot index, $i = 1, 2, \ldots, n+p+1$, $n \in \mathbb{N}$ is the number of basis functions, and p the polynomial order or degree. A univariate B-spline basis, $N_{i,p}$, is defined recursively given some degree $p \in \mathbb{N}$ and a knot vector Ξ[1]. Starting with piece-wise constants ($p = 0$):

$$N_{i,0}(\xi) \begin{cases} 1 & \text{if } \xi_i \le \xi < \xi_{i+1}, \\ 0 & \text{otherwise.} \end{cases} \tag{5}$$

For higher degrees $p = 1, 2, \ldots$ the basis is defined using the Cox-de Bor recursion formula:

$$N_{i,p}(\xi) = \frac{\xi - \xi_i}{\xi_{i+p} - \xi_i} N_{i,p-1}(\xi) + \frac{\xi_{i+p+1} - \xi}{\xi_{i+p+1} - \xi_{i+1}} N_{i+1,p-1}(\xi)\,. \tag{6}$$

1.2 Temporal discretization

We integrate in time using the generalized-α method [3] which can be applied to a first-order in time differential equations following [4]. The generalized-α method is a second-order accurate, unconditionally A-stable method with controllable high-frequency dissipation that can be easily implemented within an adaptive time step framework. These features make it a good choice for the resolution of the model, as we are able compute nonlinear stiff problems with large time steps.

In the following we use $\dot{f}_n^h, f_n^h, \dot{c}_n^h$, and c_n^h for the fully discrete solutions of the tumour angiogenic factor time derivative, the tumour angiogenic factor, the order parameter time derivative, and the order parameter, respectively. The problem can be stated as: given $\dot{f}_n^h, f_n^h, \dot{c}_n^h, c_n^h$ and $\Delta t_n = t_{n+1} - t_n$, find $\dot{f}_{n+1}^h, f_{n+1}^h, \dot{c}_{n+1}^h, c_{n+1}^h$ such that:

$$\int_\Omega w_1^h \dot{f}_{n+\alpha_m}^h\,\mathrm{d}\Omega + \int_\Omega \nabla w_1^h D \nabla f_{n+\alpha_f}^h\,\mathrm{d}\Omega - \int_\Omega w_1^h \mathcal{P}(d)\left(f_{\mathrm{hyc}} - f_{n+\alpha_f}^h\right)\,\mathrm{d}\Omega + \int_\Omega w_1^h \mathcal{U}\left(c_{n+\alpha_f}^h\right) f_{n+\alpha_f}^h\,\mathrm{d}\Omega = 0 \tag{7a}$$

$$\int_\Omega w_2^h \dot{c}_{n+\alpha_m}^h\,\mathrm{d}\Omega + \int_\Omega \nabla w_2^h M\lambda^2 \nabla c_{n+\alpha_f}^h\,\mathrm{d}\Omega + \int_\Omega w_2^h M\mu\left(c_{n+\alpha_f}^h, f_{n+\alpha_f}^h\right)\,\mathrm{d}\Omega = 0 \tag{7b}$$

[1]The standard in CAD are open knot vectors, defined as those whose first and last knot values appear $p+1$ times.

where

$$f^h_{n+1} = f^h_n + \Delta t_n \dot{f}^h_n + \gamma \Delta t_n \left(\dot{f}^h_{n+1} - \dot{f}^h_n \right), \tag{8}$$

$$c^h_{n+1} = c^h_n + \Delta t_n \dot{c}^h_n + \gamma \Delta t_n \left(\dot{c}^h_{n+1} - \dot{c}^h_n \right), \tag{9}$$

$$\dot{f}^h_{n+\alpha_m} = \dot{f}^h_n + \alpha_m \left(\dot{f}^h_{n+1} - \dot{f}^h_n \right), \tag{10}$$

$$\dot{c}^h_{n+\alpha_m} = \dot{c}^h_n + \alpha_m \left(\dot{c}^h_{n+1} - \dot{c}^h_n \right), \tag{11}$$

$$f^h_{n+\alpha_f} = f^h_n + \alpha_f \left(f^h_{n+1} - f^h_n \right), \tag{12}$$

$$c^h_{n+\alpha_f} = c^h_n + \alpha_f \left(c^h_{n+1} - c^h_n \right), \tag{13}$$

$$\gamma = \frac{1}{2} + \alpha_m - \alpha_f, \tag{14}$$

$$\alpha_m = \frac{1}{2} \left(\frac{3 - \rho_\infty}{1 + \rho_\infty} \right), \tag{15}$$

$$\alpha_f = \frac{1}{1 + \rho_\infty}, \tag{16}$$

and ρ_∞ is the spectral radius of the amplification of the matrix[2] as $\Delta t \to \infty$. If the condition $\gamma = \frac{1}{2} + \alpha_m - \alpha_f$ is satisfied we obtain second-order accuracy and provided that $\alpha_m \geq \alpha_f \geq \frac{1}{2}$ we obtain unconditional stability for a linear problem.

After space and time discretization, we obtain a non-linear system which is solved using a predictor multi-corrector algorithm based on the Newton-Raphson method following [6].

2 Estimation of f_{act}

In order to estimate the value of the parameter f_{act} we study the following one-dimensional problem in the domain $\Omega = [0, L]$:

$$\frac{\partial f}{\partial t} = D \frac{\partial^2 f}{\partial x^2} - U_d f, \tag{17}$$

subject to the initial and boundary conditions

$$f(x, 0) = e^{-mx}, \qquad f(0, t) = f_{\text{hyc}} = 1, \qquad f(L, t) = e^{-mL}$$

for large values of L and m. This problem is a simplification of the equation that governs the dynamics of tumour angiogenic factor, that is, equation (1a). Here, we replaced the production term by a Dirichlet boundary condition at $x = 0$ and used the parameter value of f_{hyc} given in table 1 in the main text. The right-hand side boundary condition imposes a small value of f far away from the production of TAF. We have also defined an initial condition compatible with the problem. This configuration may be thought as a hypoxic cell located at $x = 0$ that releases tumour angiogenic factor which diffuses and decays at a rate proportional to D and U_d, respectively.

This problems allows us to study the time evolution of the distance d_{act} at which $f = f_{\text{act}}$; that is the distance at which a hypoxic cell can activate a tip endothelial cell. As the objective is to estimate an order of magnitude for f_{act}, we neglect the uptake rate of endothelial cells. Using separation of variables we obtain the solution to this problem in the form of the following Fourier series

$$f(x, t) = \sum_{n=1}^{\infty} a_n(t) \sin\left(\frac{n \pi x}{L} \right) + e^{-mx} \tag{18}$$

[2] The amplification matrix establishes the relation between the vector of unknowns in two consecutive time steps for a linear model problem. The eigenstructure of the amplification matrix defines the stability of the algorithm (see [5]).

where,

$$a_n(t) = \frac{q_n}{\left(\frac{n\pi}{L}\right)^2 + \frac{U_d}{D}} \left(1 - \exp\left\{-D\left(\left(\frac{n\pi}{L}\right)^2 + \frac{U_d}{D}\right)t\right\}\right), \tag{19}$$

$$q_n = \frac{\left(m^2 - U_d\right)\int_0^L e^{-ms}\sin\left(\frac{n\pi s}{L}\right)\,\mathrm{d}s}{\int_0^L \sin^2\left(\frac{n\pi s}{L}\right)\,\mathrm{d}s} \tag{20}$$

We show in figure 1a the solution for $L = 300$ at several times. We observe in the figure that f_{act} needs to be small for a hypoxic cell to activate a tip endothelial cell in less than one day at a distance of $d_{\text{act}} = 200\,\mu\text{m}$. As shown in figure 1b, for $f_{\text{act}} = 0.001$, d_{act} grows in time but is always below $300\,\mu\text{m}$ within the timescale of angiogenesis.

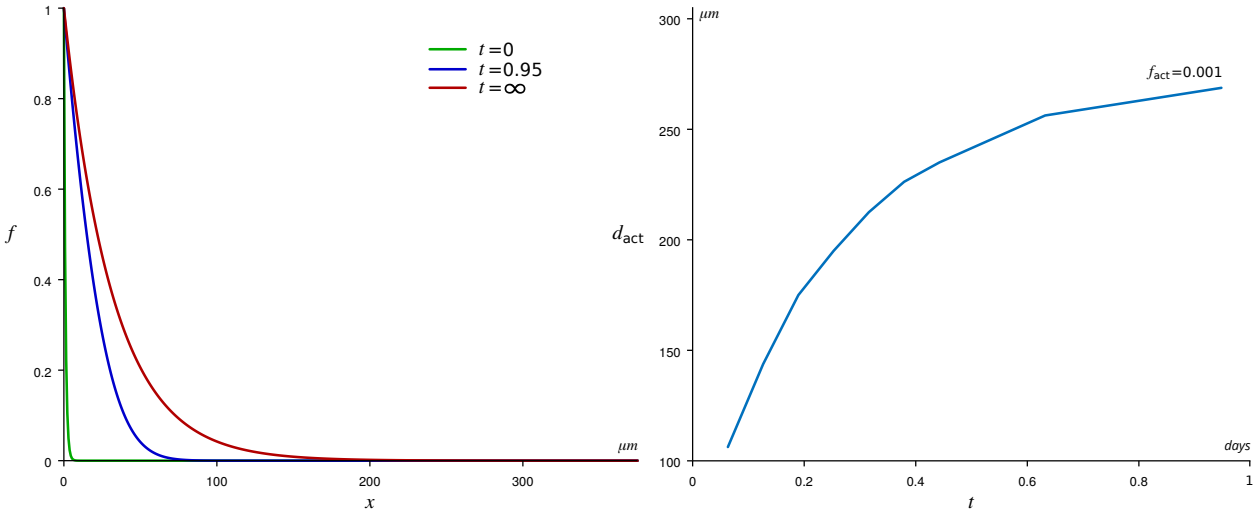

Figure 1. Estimation of f_{act}. (a) Plot of the solution to the one-dimensional problem in equation (17) for $t = 0$, $t = 0.3$, and $t = \infty$. (b) Plot of d_{act} at different times for $f_{\text{act}} = 0.001$.

References

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