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Computational modelling suggests complex interactions between interstitial flow and tumour angiogenesis

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Our theory is composed by a set of discrete agents, a continuous model for angiogenesis defined by

$$\frac{\partial c}{\partial t} = \nabla \cdot \left(M \nabla \left(\mu \left(c \right) - \lambda^2 \Delta c \right) \right) + \mathcal{B} \left(f \right) c \mathcal{H} \left(c \right), \tag{1}$$

$$\frac{\partial f}{\partial t} = \nabla \cdot \left(D \nabla f \right) - \nabla \cdot \left(\mathbf{u} f \right) + \mathcal{P} \left(d \right) \left(f_{\text{HYC}} - f \right) - \mathcal{U} \left(c \right) f, \tag{2}$$

and a continuous model for the fluid flow defined by

$$\nabla \cdot \mathbf{u} = 0, \tag{3}$$

$$\mathbf{u} = -\mathcal{K} \nabla p \tag{4}$$

In this document we first explain the algorithms for the discrete rules and the continuous equations. Then, we detail the numerical methods of the full model. Finally, we show the stability analysis for equation (2).

The discrete component

TECs form the discrete part of this theory. They are modelled as circular agents centred at $\mathbf{x}^j_{\text{TEC}} \in \Omega$ with radius R, where Ω is the computational domain and j stands for the jth-TEC. For the activation of a new discrete agent we test whether the following conditions are met at any Gauss integration point: 1) $c > c_{\text{act}}$, 2) $f > f_{\text{act}}$, and 3) the distance to the closest TEC is greater than δ_4. If all of them are satisfied we create a new TEC at that location. If more than one point meets the conditions, we randomly select one, update condition 3) and search for new TECs until no more activations are possible. Each time step we move TECs with velocity $\mathbf{v}_{\text{TEC}} = \chi \frac{\nabla f}{|\nabla f|}$. If the TEC has travelled the equivalent of two diameters from its inception point, we also perform checks at points that represent the location of filopodia. These points are distributed in an annular sector centred around the direction of velocity with angle $\frac{2\pi}{3}$, and with internal and external radii $2R$ and $4R$, respectively. In particular, we use 408 points per TECs evenly spaced in the annular sector. If at any of these points we find a value $c > -0.9$, then the velocity direction is fixed towards the point. Finally, we also check the conditions for TEC deactivation each time step. TECs are deactivated and its associated agent is removed from the computation when condition 2) is not satisfied at the centre of the TEC. In addition, TECs are also deactivated when they anastomose, that is, when $c > 0.9$ in its close vicinity. We check this condition at 51 points equispaced along a circular arc with angle $\frac{2\pi}{3}$ and radius R centred around the migration direction.

The continuous equations

Equations (1) to (4) form the continuous formulation of our problem. Let $\Omega \subset \mathbb{R}^d$ be an open set, where $d = 2$ or 3, and let $\partial\Omega = \Gamma = \Gamma_N \cup \Gamma_D$ be the Lipschitz boundary of this domain, composed of two complementary parts Γ_N and Γ_D, such that $\overline{\Gamma_D \cap \Gamma_N} = \emptyset$. Let also $\mathbf{n}$ be the unit outward normal of Ω. Introducing equation (4) into equations (2) and (3) yields the following strong form of this problem: find c, p, f such that

$$\frac{\partial c}{\partial t} = \nabla \cdot \left(M \nabla \left(\mu\left(c\right) - \lambda^2 \Delta c \right) \right) + \mathcal{B}\left(f\right) c \mathcal{H}\left(c\right) \tag{5}$$

$$\frac{\partial f}{\partial t} = \nabla \cdot \left(D \nabla f \right) - \nabla \cdot \left(-\mathcal{K} \nabla p f \right) + \mathcal{P}\left(d\right) \left(f_{\text{HYC}} - f \right) - \mathcal{U}\left(c\right) f \tag{6}$$

$$0 = \nabla \cdot \left(-\mathcal{K} \nabla p \right) \tag{7}$$

in $\Omega \times (0, T)$ and satisfying the following boundary conditions

$$M \nabla \left(\mu\left(c\right) - \lambda^2 \Delta c \right) \cdot \mathbf{n} = 0 \qquad \text{on} \quad \Gamma \times (0,T) \tag{8}$$

$$M \lambda^2 \Delta c = 0 \qquad \text{on} \quad \Gamma \times (0,T), \tag{9}$$

$$\nabla f \cdot \mathbf{n} = 0 \qquad \text{on} \quad \Gamma \times (0,T) \tag{10}$$

$$\mathcal{K} \nabla p \cdot \mathbf{n} = 0 \qquad \text{on} \quad \Gamma_N \times (0,T) \tag{11}$$

$$p = p_g\left(\mathbf{x}\right) \qquad \text{on} \quad \Gamma_D \times (0,T) \tag{12}$$

where p_g is a given function. In order to solve the above problem we first derive an equivalent variational formulation and then approximate the problem with a space and time discretization.

Variational formulation Let $\mathcal{V}$ denote the trial and weighting function spaces, which are assumed to be equal. After multiplying by test functions and integrating by parts, we obtain the following weak form: find $c, f, p \in \mathcal{V}$ such that $\forall q, w, r \in \mathcal{V}$:

$$\begin{aligned} 0 =& \left(q, \frac{\partial c}{\partial t} \right)_\Omega + \left(\nabla q, M \nabla \mu\left(c\right) \right)_\Omega \\ &+ \left(\Delta q, M \lambda^2 \Delta c \right)_\Omega - \left(q, \mathcal{B}\left(f\right) c \mathcal{H}\left(c\right) \right)_\Omega, \end{aligned} \tag{13}$$

$$\begin{aligned} 0 =& \left(w, \frac{\partial f}{\partial t} \right)_\Omega + \left(\nabla w, D \nabla f \right)_\Omega + \left(\nabla w, \mathcal{K}\left(c, \|\nabla c\|\right) \nabla p f \right)_\Omega \\ &- \left(w, \mathcal{P}\left(d\right) \left(f_{\text{HYC}} - f \right) \right)_\Omega + \left(w, \mathcal{U}\left(c\right) f \right)_\Omega \end{aligned} \tag{14}$$

$$0 = \left(\nabla r, \mathcal{K}\left(c, \|\nabla c\|\right) \nabla p \right)_\Omega \tag{15}$$

where $(\cdot, \cdot)_\Omega$ denotes the $\mathcal{L}^2$ inner product in Ω. The weak form is equivalent to the strong formulation of the problem under the assumption that functions living in the space $\mathcal{V}$ are sufficiently smooth. In particular, because of the second order derivatives present in the weak form, $\mathcal{V}$ is a subset of $\mathcal{H}^2$, the Sobolev space of square integrable functions with square integrable first and second derivatives.

Spatial discretization We obtain the spatial discretization of the weak form making use of the Galerkin method. The above system of equations can thus be approximated by the following variational problem: find $c^h, f^h, p^h \in \mathcal{V}^h \subset \mathcal{V}$ such that $\forall q^h, w^h, r^h \in \mathcal{V}^h \subset \mathcal{V}$:

$$\begin{aligned} 0 =& \left(q^h, \frac{\partial c^h}{\partial t}\right)_\Omega + \left(\nabla q^h, M\nabla\mu\left(c^h\right)\right)_\Omega \\ &+ \left(\Delta q^h, M\lambda^2\Delta c^h\right)_\Omega - \left(q^h, \mathcal{B}\left(f^h\right)c^h\mathcal{H}\left(c^h\right)\right)_\Omega . \end{aligned} \tag{16}$$

$$\begin{aligned} 0 =& \left(w^h, \frac{\partial f^h}{\partial t}\right)_\Omega + \left(\nabla w^h, D\nabla f^h\right)_\Omega + \left(\nabla w^h, \mathcal{K}\left(c^h, \|\nabla c^h\|\right)\nabla p^h f^h\right)_\Omega \\ &- \left(w^h, \mathcal{P}\left(d\right)\left(f_{\mathrm{HYC}} - f^h\right)\right)_\Omega + \left(w^h, \mathcal{U}\left(c^h\right)f^h\right)_\Omega \end{aligned} \tag{17}$$

$$0 = \left(\nabla r^h, \mathcal{K}\left(c^h, \|\nabla c^h\|\right)\nabla p^h\right)_\Omega \tag{18}$$

Here, everything is defined except for the particular finite element space $\mathcal{V}^h = \mathrm{span}\{N_A\}$, $A = 1, \ldots, n_b$, being N_A the basis functions and n_b the number of basis functions. Note that because we are using a conforming discretization this subspace needs to fulfil the same smoothness properties as $\mathcal{V}$. The discrete space needs also to capture the smooth but steep phase-field interfaces. What is more, as suggested by Fig. 2 in the main manuscript, the pressure will have even steeper transitions at the transvascular region than the phase-field, which also need to be reproduced. Thus, in this model the pressure field is one of the major restrictions for the numerical method. We also need a method able to deal with the high-order term of the phase-field equation. For these reasons we make use of isogeometric analysis [1], specially due to its high-order basis functions and smoothness, variation diminishing property, and proven accuracy. In particular we choose second-order B-splines as our basis functions N_A and we define c^h, f^h, and p^h as

$$c^h\left(\mathbf{x}, t\right) = \sum_{A=1}^{n_b} c_A\left(t\right) N_A\left(\mathbf{x}\right), \tag{19}$$

$$f^h\left(\mathbf{x}, t\right) = \sum_{A=1}^{n_b} f_A\left(t\right) N_A\left(\mathbf{x}\right), \tag{20}$$

$$p^h\left(\mathbf{x}, t\right) = \sum_{A=1}^{n_b} p_A\left(t\right) N_A\left(\mathbf{x}\right), \tag{21}$$

where p_A, f_A, and c_A are the control variables.

Temporal discretization We use the notation $\dot{c}_n^h, c_n^h, \dot{f}_n^h, f_n^h, p_n^h$ for the space and time discrete solutions of the variables of the problem and their corresponding time derivatives. Here we perform a finite-difference-type temporal discretization of the spatially discretized problem. This problem derives, however, from a steady state equation for the fluid flow and two transient equations for the continuous angiogenesis model. We detail them separately and show afterwards how we incorporate them in our numerical scheme.

The problem for the fluid flow is defined as: given c_n^h and the time step $\Delta t_n = t_{n+1} - t_n$, find p_{n+1}^h such that:

$$0 = \left(\nabla r^h, \mathcal{K}\left(c_n^h, \|\nabla c_n^h\|\right)\nabla p_{n+1}^h\right)_\Omega . \tag{22}$$

We integrate the continuous angiogenesis model in time using the generalised-α method. The discrete angiogenesis problem can thus be stated as: given $\dot{f}_n^h, f_n^h, \dot{c}_n^h, c_n^h, p_{n+1}^h$, and the time step $\Delta t_n = t_{n+1} - t_n$, find $\dot{c}_{n+1}^h, c_{n+1}^h, \dot{f}_{n+1}^h, f_{n+1}^h$ such that:

$$\begin{aligned}
0 =& \left(q^h, \dot{c}_{n+\alpha_m}^h\right)_\Omega + \left(\nabla q^h, M\nabla\mu\left(c_{n+\alpha_f}^h\right)\right)_\Omega \\
&+ \left(\Delta q^h, M\lambda^2\Delta c_{n+\alpha_f}^h\right)_\Omega - \left(q^h, \mathcal{B}\left(f_{n+\alpha_f}^h\right) c_{n+\alpha_f}^h \mathcal{H}\left(c_{n+\alpha_f}^h\right)\right)_\Omega, \qquad (23)\\
0 =& \left(w^h, \dot{f}_{n+\alpha_m}^h\right)_\Omega + \left(\nabla w^h, D\nabla f_{n+\alpha_f}^h\right)_\Omega \\
&+ \left(\nabla w^h, \mathcal{K}\left(c_{n+\alpha_f}^h, \|\nabla c_{n+\alpha_f}^h\|\right)\nabla p_{n+1}^h f_{n+\alpha_f}^h\right)_\Omega \\
&- \left(w^h, \mathcal{P}(d)\left(f_{\mathrm{HYC}} - f_{n+\alpha_f}^h\right)\right)_\Omega \\
&+ \left(w^h, \mathcal{U}\left(c_{n+\alpha_f}^h\right) f_{n+\alpha_f}^h\right)_\Omega, \qquad (24)
\end{aligned}$$

where

$$\dot{f}_{n+\alpha_m}^h = \dot{f}_n^h + \alpha_m\left(\dot{f}_{n+1}^h - \dot{f}_n^h\right), \qquad (25)$$

$$f_{n+\alpha_f}^h = f_n^h + \alpha_f\left(f_{n+1}^h - f_n^h\right), \qquad (26)$$

$$f_{n+1}^h = f_n^h + \Delta t_n \dot{f}_n^h + \gamma\Delta t_n\left(\dot{f}_{n+1}^h - \dot{f}_n^h\right), \qquad (27)$$

$$\dot{c}_{n+\alpha_m}^h = \dot{c}_n^h + \alpha_m\left(\dot{c}_{n+1}^h - \dot{c}_n^h\right), \qquad (28)$$

$$c_{n+\alpha_f}^h = c_n^h + \alpha_f\left(c_{n+1}^h - c_n^h\right), \qquad (29)$$

$$c_{n+1}^h = c_n^h + \Delta t_n \dot{c}_n^h + \gamma\Delta t_n\left(\dot{c}_{n+1}^h - \dot{c}_n^h\right), \qquad (30)$$

$$\gamma = \frac{1}{2} + \alpha_m - \alpha_f, \qquad (31)$$

$$\alpha_m = \frac{1}{2}\left(\frac{3-\rho_\infty}{1+\rho_\infty}\right), \qquad (32)$$

$$\alpha_f = \frac{1}{1+\rho_\infty}, \qquad (33)$$

and ρ_∞ is the spectral radius of the amplification of the matrix as $\Delta t \to \infty$. In addition, the generalised-α method can be easily implemented within an adaptive time step framework.

Numerical scheme for the discrete–continuum coupling

Because of the modular nature of the model we have chosen to implement a staggering numerical scheme to reduce its computational cost. Each time step, first we update the discrete component, checking the discrete rules, moving those TECs that are active and updating the field c. We want to highlight the role of the seamless coupling between TECs and the continuous variables in this theory. The definition of the permeability relies heavily on the smoothness of the vascular wall, which is *a priori* guaranteed by the phase-field equation. However, in the coupling process, TECs modify the phase field by overwriting c with a constant value. If not properly handled, this could create sharp

interfaces in the phase field in the transvascular region surrounding TECs. This would result in high gradients, which, in turn, would produce a non-smooth permeability. Our implementation of the coupling with template functions (see [2]) circumvents this potential problem, as they are based on the multidimensional generalisation of an exact one-dimensional solution to the Cahn-Hilliard equation. The templates provide the required smoothness in the TECs transvascular region and, thus, a smooth permeability function.
The next step in our numerical scheme is to solve the flow problem and update the pressure field. Finally, we solve the equations for the angiogenesis model. At the end of every time step, making use of an adaptive time step (see [2]) we check if the error (e_{n+1}) is smaller than a given tolerance ($\Upsilon_{\Delta t}$). If the error is greater than the tolerance, we reduce the time-step size and repeat the iteration until this condition is satisfied. The algorithm continues until all the VEGF of the domain has been consumed and there are no active TECs.

Stability analysis of the convection-diffusion equation

Under certain conditions, spurious oscillations may appear in convection-diffusion equations such as equation (2). These conditions are well represented by the elemental Peclet number, Pe, defined as

$$\mathrm{Pe} = \frac{\|\mathbf{u}\| h}{2D}, \tag{34}$$

where h is the element side. This dimensionless number is a measure of convective over the diffusion effects. When $\mathrm{Pe} > 1$ the problem is said to be convection-dominated and may produce boundary layers that the numerical method may be unable to capture. Otherwise, the problem is said to be diffusion-dominated. A large elemental Peclet number indicates that an instability may arise during a simulation. However, other factors such as reaction terms, nonlinearities or boundary conditions also influence whether the instability appears or not, even for a convection-dominated problem. In our problem, in the intravascular region, we can assume that there will be not enough VEGF to form boundary layers because of the tumour angiogenic consumption by endothelial cells. In the extravascular region we can approximate $\mathcal{K}$ by κ^e and further assume a constant pressure drop, which using a 512×512 mesh, yields an estimated $\mathrm{Pe} = 2.44 \times 10^{-3}$, suggesting no spurious oscillations in that region. We conclude then that the potential location of instabilities is within the transvascular region. We have to study our specific problem through simulations and, in the eventuality of spurious oscillations in the solution, address the issue.
There are several alternatives to correctly solve boundary layers. The first and more direct is to reduce the element size enough to be able to capture smaller scales. This method is effective, but implies a higher computational cost. Another alternative is to implement one of the existent stabilisation techniques, such as streamline upwind/Petrov–Galerkin (SUPG, [3]) or variational multiscale (VMS, [4]). Both of them involve the incorporation of an extra term in the variational formulation of equation (2). We simulated the model with and without the SUPG stabilisation technique (results not shown) with a 512×512 mesh and found that there is no need to use SUPG on the mesh that we employed. We also checked the appearance of spurious oscillations in all simulations performed in this work and found none.

References

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