Assessing the impact of tissue vascularisation on intratumour heterogeneity using a formal Hamilton-Jacobi approach

Chiara Villa, Mark A.J. Chaplain, Tommaso Lorenzi

cv23@st-andrews.ac.uk, majc@st-andrews.ac.uk, tl47@st-andrews.ac.uk

St Andrews Mathematical Biology Research Group (StAMBio), School of Mathematics and Statistics, University of St Andrews

Summary

Background. Phenotypic heterogeneity of cancer cells within solid tumours poses a major obstacle to therapy and management of disease relapse. Accumulating evidence indicates that the emergence of intratumour phenotypic heterogeneity is an eco-evolutionary process driven by spatial variations in the distribution of abiotic factors, including oxygen, which support the creation of distinct local niches whereby cells with different phenotypic characteristics can be selected.

Methods. We present a space- and phenotype-structured model for the eco-evolutionary dynamics of cancer cells within solid tumours. Our model consists of a system of nonlinear partial differential equations (PDEs) for the local cell population density and the local oxygen concentration. Integrating our model with clinical data from malignant melanoma patients, we use a formal Hamilton-Jacobi approach to assess the impact of tissue vascularisation on intratumour phenotypic heterogeneity.

Main results. The results of our formal analysis and numerical simulations demonstrate how cells in different phenotypic states can be selected within the same solid tumour depending on the distance from the blood vessels. Moreover, our results establish a relation between the degree of tissue vascularisation and the level of intratumour phenotypic heterogeneity, measured either as the equitability index or the Simpson diversity index, which could be used to inform targeted anticancer therapy.

Model description

Independent and dependent variables

- Spatial position: $\mathbf{r} \in \Omega \subset \mathbb{R}^2$, with Ω representing the 2D cross-section of a vascularised tumour tissue.
- Cell phenotypic state: $x \in [0,1] \subset \mathbb{R}$ modelling the normalised level of expression of a hypoxia-responsive gene.
- Local cell population density at time $t \geq 0$: $n(t,\mathbf{r},x) \geq 0$.
- Cell density and local mean phenotypic state:

$$I(t,\mathbf{r}) = \int_0^1 n(t,\mathbf{r},x)\,\mathrm{d}x \quad \text{and} \quad X(t,\mathbf{r}) = \frac{1}{I(t,\mathbf{r})}\int_0^1 x\,n(t,\mathbf{r},x)\,\mathrm{d}x\,.$$

- Total cell number and fraction of cells in the phenotypic state x:

$$N(t) = \int_\Omega I(t,\mathbf{r})\,\mathrm{d}\mathbf{r} \quad \text{and} \quad F(t,x) = \frac{1}{N(t)}\int_\Omega n(t,\mathbf{r},x)\,\mathrm{d}\mathbf{r}\,.$$

- Local concentration of oxygen: $s(t,\mathbf{r}) \geq 0$.

Model equations

- The evolution of the local population density, $n(t,\mathbf{r},x)$, and the local oxygen concentration, $s(t,\mathbf{r})$, is governed by the following coupled parabolic PDEs

$$\partial_t n = \underbrace{R\big(x, I(t,\mathbf{r}), s(t,\mathbf{r})\big)\,n}_{\text{cell proliferation and competition}} + \underbrace{\alpha\,\partial^2_{xx} n}_{\substack{\text{phenotypic}\\ \text{variations}}} + \underbrace{\beta\,\Delta_{\mathbf{r}} n}_{\text{cell dispersal}} \tag{1}$$

$$\partial_t s = \underbrace{\beta_s \Delta_{\mathbf{r}} s}_{\text{diffusion}} - \underbrace{\eta_s \int_0^1 g(x,s) n(t,\mathbf{r},x)\,\mathrm{d}x}_{\text{consumption by the cells}} - \underbrace{\lambda_s s}_{\text{decay}} + \underbrace{\sigma(t)\chi(\mathbf{r})}_{\substack{\text{influx from}\\ \text{blood vessels}}} \tag{2}$$

  complemented with zero Neumann boundary conditions (NBCs).

- The function $\chi(\mathbf{r}) \geq 0$ represents the map of the blood vessels in the tumour tissue, while the function $\sigma(t) \geq 0$ models the oxygen inflow rate.
- The cell fitness function $R\big(x, I(t,\mathbf{r}), s(t,\mathbf{r})\big)$ is defined as

$$R\big(x, I(t,\mathbf{r}), s(t,\mathbf{r})\big) = \underbrace{f(x) + g\big(x, s(t,\mathbf{r})\big)}_{\text{proliferation}} - \underbrace{\kappa\, I(t,\mathbf{r})}_{\text{competition}}\,.$$

- The function $f(x)$ models the cell proliferation rate in the absence of adequate oxygen supply (i.e. in hypoxic conditions), while the function $g(x,s)$ is the cell proliferation rate in oxygenated environments (i.e. in normoxic conditions).
- To ensure analytical tractability of the model, we consider the following biologically realistic definitions

$$f(x) = \varphi\left[1-(1-x)^2\right] \quad \text{and} \quad g(x,s) = \gamma\frac{s}{\theta_s + s}\left(1-x^2\right) \quad \text{with} \quad \varphi \ll \gamma\,.$$

Parameter	Biological meaning
α	Rate of spontaneous phenotypic variations
β	Cell motility coefficient
κ	Death rate due to cell competition
φ	Maximum rate of cell proliferation in hypoxic conditions
γ	Maximum rate of cell proliferation in normoxic conditions
θ_s	Michaelis-Menten constant of oxygen
β_s	Diffusion coefficient of oxygen
η_s	Conversion factor for cell consumption of oxygen
λ_s	Natural decay rate of oxygen

Formal asymptotic analysis

- We consider a stationary oxygen distribution $s(\cdot,\mathbf{r}) = \bar{s}(\mathbf{r})$. To capture the fact that phenotypic variations and cell dispersal occur on slower time scales compared to cell proliferation and competition, we define $\alpha = \beta = \varepsilon^2$ for some small $\varepsilon > 0$.
- To explore the evolutionary dynamics of the population over many cell generations, we consider the hyperbolic time scaling $t \to t/\varepsilon$ and study the asymptotic behaviour of the solution to the following rescaled equation for $\varepsilon \to 0$

$$\varepsilon\,\partial_t n_\varepsilon = R\big(x, I_\varepsilon(t,\mathbf{r}), \bar{s}(\mathbf{r})\big)\,n_\varepsilon + \varepsilon^2\,\partial^2_{xx} n_\varepsilon + \varepsilon^2\,\Delta_{\mathbf{r}} n_\varepsilon\,.$$

- If the initial cell population is locally monomorphic, i.e. under the assumption

$$n^0_\varepsilon(\mathbf{r},x) = I^0(\mathbf{r})\,e^{u^0_\varepsilon(\mathbf{r},x)/\varepsilon} \quad \text{with} \quad u^0_\varepsilon(\mathbf{r},x) \ \text{ s.t. } \ n^0_\varepsilon(\mathbf{r},x) \xrightarrow[\varepsilon\to 0]{} I^0(\mathbf{r})\,\delta(x-\bar{x}^0(\mathbf{r})),$$

  in the asymptotic regime $\varepsilon \to 0$ the population remains locally monomorphic, i.e.

$$I_\varepsilon(t,\mathbf{r}) \xrightarrow[\varepsilon\to 0]{} I(t,\mathbf{r}), \quad n_\varepsilon(t,\mathbf{r},x) \xrightarrow[\varepsilon\to 0]{} I(t,\mathbf{r})\delta(x-\bar{x}(t,\mathbf{r}))\,.$$

- The locally selected phenotypic state $\bar{x}(t,\mathbf{r})$ satisfies the canonical equation

$$\partial_t \bar{x} = -(\partial^2_{xx} u(t,\mathbf{r},\bar{x}))^{-1}\,\partial_x R(\bar{x}(t,\mathbf{r}), I(t,\mathbf{r}), \bar{s}(\mathbf{r})),$$

  where the function $u(t,\mathbf{r},x)$ satisfies the constrained Hamilton-Jacobi equation

$$\begin{cases} \partial_t u = R(x, I(t,\mathbf{r}), \bar{s}(\mathbf{r})) + (\partial_x u)^2 + |\nabla_{\mathbf{r}} u|^2 \\ \max\limits_{x\in[0,1]} u(t,\cdot,x) = 0 = u(t,\cdot,\bar{x}) \end{cases} \qquad \text{(with NBCs)}$$

  and the pair $(\bar{x}(t,\mathbf{r}), I(t,\mathbf{r}))$ is such that $R\big(\bar{x}(t,\mathbf{r}), I(t,\mathbf{r}), \bar{s}(\mathbf{r})\big) = 0$.
- At equilibrium, the local cell density and the locally selected phenotypic state depend on the local oxygen concentration, i.e.

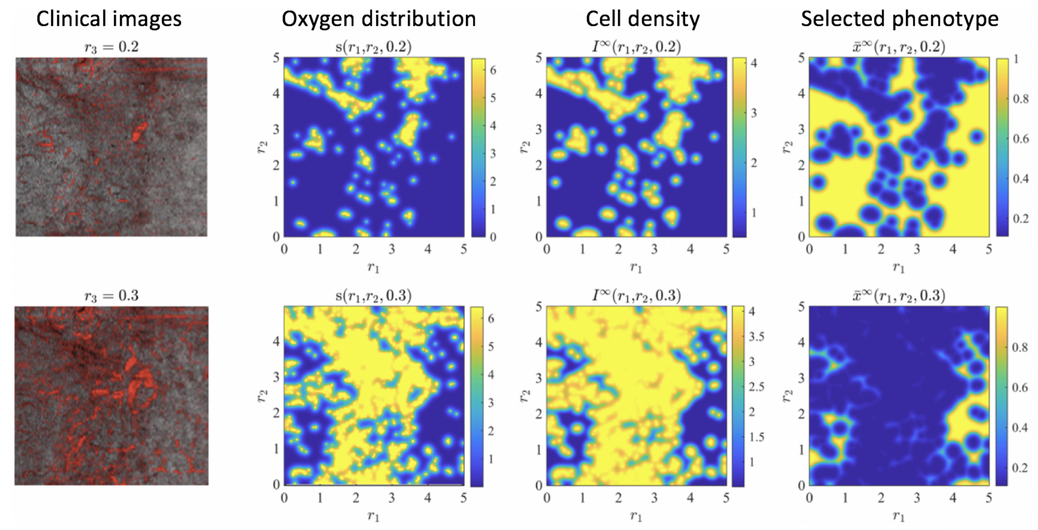
$$I(t,\mathbf{r}) \xrightarrow[t\to\infty]{} I^\infty(\bar{s}(\mathbf{r})) \quad \text{and} \quad \bar{x}(t,\mathbf{r}) \xrightarrow[t\to\infty]{} \bar{x}^\infty(\bar{s}(\mathbf{r}))$$

  with

$$I^\infty(\bar{s}(\mathbf{r})) = \frac{1}{\kappa}\left(\gamma_s\frac{\bar{s}(\mathbf{r})}{\theta_s+\bar{s}(\mathbf{r})} + \frac{\varphi^2}{\varphi+\gamma_s\frac{\bar{s}(\mathbf{r})}{\theta_s+\bar{s}(\mathbf{r})}}\right),\ \bar{x}^\infty(\bar{s}(\mathbf{r})) = \frac{\varphi}{\varphi+\gamma_s\frac{\bar{s}(\mathbf{r})}{\theta_s+\bar{s}(\mathbf{r})}} \tag{3}$$

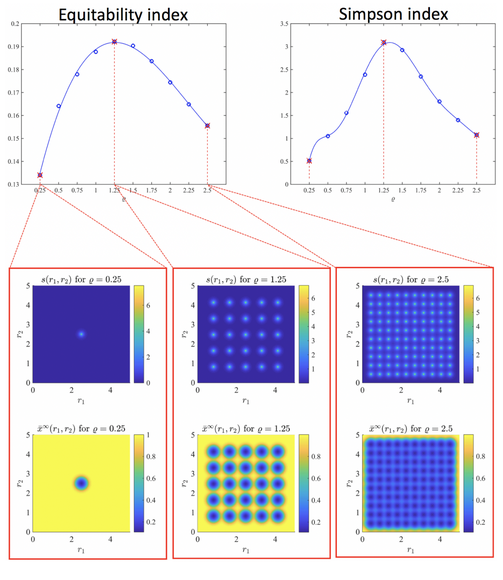
Numerical solutions

Integration of the model with clinical data



The clinical images [Schuh *et al.* Dermatol Ther., 7:187-202, 2017] show the blood vessel distribution in two different cross sections of a malignant melanoma. These images were used to define the blood vessel map $\chi(\mathbf{r})$. The other panels display the oxygen distribution (in units of 10^{-6}), the cell density (in units of 10^8) and the locally selected phenotypic state obtained by solving numerically the PDEs (1) and (2). The cell density and the phenotypic state match exactly with the asymptotic values given by equation (3).

Impact of tissue vascularisation on intratumour heterogeneity



Equitability index

$$E(t) = -\int_0^1 \frac{F(t,x)\,\log F(t,x)}{\log\big(N(t)\big)}\,\mathrm{d}x$$

and Simpson diversity index

$$S(t) = \left(\int_0^1 F^2(t,x)\,\mathrm{d}x\right)^{-1}$$

as functions of the blood vessel density

$$\varrho = \frac{1}{|\Omega|}\int_\Omega \chi(\mathbf{r})\,\mathrm{d}\mathbf{r}.$$

The plots in the red boxes show the oxygen distribution (top panels) and the selected phenotypic state (bottom panels) for three sample values of ϱ.