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Individual-based and continuum models of phenotypically heterogeneous growing cell populations

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Abstract: Existing comparative studies between individual-based models of growing cell populations and their continuum counterparts have mainly been focused on homogeneous populations, in which all cells have the same phenotypic characteristics. However, significant intercellular phenotypic variability is commonly observed in cellular systems. In light of these considerations, we develop here an individual-based model for the growth of phenotypically heterogeneous cell populations. In this model, the phenotypic state of each cell is described by a structuring variable that captures intercellular variability in cell proliferation and migration rates. The model tracks the spatial evolutionary dynamics of single cells, which undergo pressure-dependent proliferation, heritable phenotypic changes and directional movement in response to pressure differentials. We formally show that the continuum limit of this model comprises a non-local partial differential equation for the cell population density function, which generalises earlier models of growing cell populations. We report on the results of numerical simulations of the individual-based model which illustrate how proliferation-migration tradeoffs shaping the evolutionary dynamics of single cells can lead to the formation, at the population level, of travelling waves whereby highly-mobile cells locally dominate at the invasive front, while more-proliferative cells are found at the rear. Moreover, we demonstrate that there is an excellent quantitative agreement between these results and the results of numerical simulations and formal travelling-wave analysis of the continuum model, when sufficiently large cell numbers are considered. We also provide numerical evidence of scenarios in which the predictions of the two models may differ due to demographic stochasticity, which cannot be captured by the continuum model. This indicates the importance of integrating individual-based and continuum approaches when modelling the growth of phenotypically heterogeneous cell populations.

Keywords: growing cell populations; phenotypic heterogeneity; individual-based models; continuum models; non-local partial differential equations; travelling waves

Supplementary Material

This supplementary material file is organised as follows. In Section S1, we provide the details of the formal derivation of the continuum model from the individual-based model. In Section S2, we carry out formal travelling-wave analysis of the continuum model. Finally, in Section S3 we describe the methods used to solve numerically the continuum model.

S1. Formal derivation of the continuum model

Building on the methods that we previously employed in [1–5], here we show that the non-local PDE (3.2) can be formally derived as the appropriate continuum limit of the IB model developed in this paper.

In the case where, between time-steps k and $k+1$, each cell in phenotypic state $y_j \in (0, Y)$ at position $x_i \in \mathbb{R}$ can first move, next undergo phenotypic changes and then die or divide according to the rules described in Section 2, the principle of mass balance gives the following difference equation

$$
\begin{aligned}
n_{i,j}^{k+1} \;=\;& n_{i+1,j+1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i+1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i-1,j+1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i-1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i+1,j-1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i+1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i-1,j-1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i-1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i,j+1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \left[1 - \frac{\nu\mu(y_j)}{2p_M} \left[\left(p_i^k - p_{i+1}^k\right)_+ + \left(p_i^k - p_{i-1}^k\right)_+\right]\right] \right\} \\
&+ n_{i,j-1}^{k} \left\{ \frac{\lambda}{2} \left[1 + \tau R(y_j, p_i^k)\right] \left[1 - \frac{\nu\mu(y_j)}{2p_M} \left[\left(p_i^k - p_{i+1}^k\right)_+ + \left(p_i^k - p_{i-1}^k\right)_+\right]\right] \right\} \\
&+ n_{i+1,j}^{k} \left\{ (1-\lambda) \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i+1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i-1,j}^{k} \left\{ (1-\lambda) \left[1 + \tau R(y_j, p_i^k)\right] \frac{\nu\mu(y_j)}{2p_M} \left(p_{i-1}^k - p_i^k\right)_+ \right\} \\
&+ n_{i,j}^{k} \left\{ (1-\lambda) \left[1 + \tau R(y_j, p_i^k)\right] \left[1 - \frac{\nu\mu(y_j)}{2p_M} \left[\left(p_i^k - p_{i+1}^k\right)_+ + \left(p_i^k - p_{i-1}^k\right)_+\right]\right] \right\}.
\end{aligned}
\tag{S1.1}
$$

Using the fact that for τ, χ and η sufficiently small the following relations hold

$$
n_{i,j}^k \approx n(t,x,y), \quad n_{i,j}^{k+1} \approx n(t+\tau,x,y), \quad n_{i\pm1,j}^k \approx n(t,x\pm\chi,y), \quad n_{i,j\pm1}^k \approx n(t,x,y\pm\eta)
$$

$$
\rho_i^k \approx \rho(t,x) := \int_0^Y n(t,x,y)\,\mathrm{d}y, \quad p_i^k \approx p(t,x) = \Pi[\rho](t,x), \quad p_{i\pm1}^k \approx p(t,x\pm\chi) = \Pi[\rho](t,x\pm\chi),
$$

equation (S1.1) can be formally rewritten in the approximate form

$$
n(t+\tau,x,y) \;=\; n(t,x+\chi,y+\eta) \left\{ \frac{\lambda}{2} \left[1 + \tau R(y,p)\right] \frac{\nu\mu(y)}{2p_M} \left(p(t,x+\chi) - p\right)_+ \right\} \tag{S1.2}
$$

$$+n(t,x-\chi,y+\eta)\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}$$
$$+n(t,x+\chi,y-\eta)\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+n(t,x-\chi,y-\eta)\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}$$
$$+n(t,x,y+\eta)\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}$$
$$+n(t,x,y-\eta)\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}$$
$$+n(t,x+\chi,y)\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+n(t,x-\chi,y)\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}$$
$$+n\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left(p-p(t,x+\chi)\right)_+ - \frac{\nu\mu(y)}{2p_M}\left(p-p(t,x-\chi)\right)_+\right]\right\},$$

where $n \equiv n(t,x,y)$ and $p \equiv p(t,x)$. If the function $n(t,x,y)$ is twice continuously differentiable with respect to the variables y and x, for η and χ sufficiently small we can then use the Taylor expansions

$$n(t,x,y\pm\eta) = n \pm \eta\frac{\partial n}{\partial y} + \frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2} + \text{h.o.t.}\,, \quad n(t,x\pm\chi,y) = n \pm \chi\frac{\partial n}{\partial x} + \frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2} + \text{h.o.t.}\,,$$

$$n(t,x+\chi,y\pm\eta) = n + \chi\frac{\partial n}{\partial x} \pm \eta\frac{\partial n}{\partial y} + \frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2} + \frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2} \pm \chi\eta\frac{\partial^2 n}{\partial x \partial y} + \text{h.o.t.}$$

and

$$n(t,x-\chi,y\pm\eta) = n - \chi\frac{\partial n}{\partial x} \pm \eta\frac{\partial n}{\partial y} + \frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2} + \frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2} \mp \chi\eta\frac{\partial^2 n}{\partial x \partial y} + \text{h.o.t.}\,,$$

which allow us to rewrite equation (S1.2) as

$$n(t+\tau,x,y) = n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\} \tag{S1.3}$$
$$+\chi\frac{\partial n}{\partial x}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$
$$+\chi\eta\frac{\partial^2 n}{\partial x \partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}$$

$$
\begin{aligned}
&+n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&-\chi\frac{\partial n}{\partial x}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&-\chi\eta\frac{\partial^2 n}{\partial x\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+\chi\frac{\partial n}{\partial x}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&-\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&-\chi\eta\frac{\partial^2 n}{\partial x\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&-\chi\frac{\partial n}{\partial x}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&-\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\chi\eta\frac{\partial^2 n}{\partial x\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[\left(p-p(t,x+\chi)\right)_+ +\left(p-p(t,x-\chi)\right)_+\right]\right]\right\}
\end{aligned}
$$

$$
\begin{aligned}
&+\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}\\
&+n\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}\\
&-\eta\frac{\partial n}{\partial y}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\frac{\lambda}{2}\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right]\right\}\\
&+n\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+\chi\frac{\partial n}{\partial x}\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x+\chi)-p\right)_+\right\}\\
&+n\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&-\chi\frac{\partial n}{\partial x}\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left(p(t,x-\chi)-p\right)_+\right\}\\
&+n\left\{(1-\lambda)\left[1+\tau R(y,p)\right]\left[1-\frac{\nu\mu(y)}{2p_M}\left(p-p(t,x+\chi)\right)_+ - \frac{\nu\mu(y)}{2p_M}\left(p-p(t,x-\chi)\right)_+\right]\right\} + \text{h.o.t.}\,.
\end{aligned}
$$

Collecting terms that contain the same derivative of n we can further simplify equation (S1.3) to obtain

$$
\begin{aligned}
n(t+\tau,x,y) \;=\; & n\left[1+\tau R(y,p)\right] \qquad \text{(S1.4)}\\
&+n\left\{\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p(t,x+\chi)-p)_+ + (p(t,x-\chi)-p)_+\right]\right\}\\
&-n\left\{\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right\}\\
&+\chi\frac{\partial n}{\partial x}\left\{\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p(t,x+\chi)-p)_+ - (p(t,x-\chi)-p)_+\right]\right\}\\
&+\frac{\chi^2}{2}\frac{\partial^2 n}{\partial x^2}\left\{\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p(t,x+\chi)-p)_+ + (p(t,x-\chi)-p)_+\right]\right\}\\
&+\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\lambda\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p(t,x+\chi)-p)_+ + (p(t,x-\chi)-p)_+\right]\right\}\\
&-\frac{\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left\{\lambda\left[1+\tau R(y,p)\right]\frac{\nu\mu(y)}{2p_M}\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right]\right\}
\end{aligned}
$$

$$+\frac{\lambda\eta^2}{2}\frac{\partial^2 n}{\partial y^2}\left[1+\tau R(y,p)\right]+\text{h.o.t.}\,.$$

Rewriting the above equation by using the fact that

$$\begin{aligned}&\left[(p(t,x+\chi)-p)_+ + (p(t,x-\chi)-p)_+\right]\\ &\qquad -\left[(p-p(t,x+\chi))_+ + (p-p(t,x-\chi))_+\right] = p(t,x+\chi)+p(t,x-\chi)-2\,p,\end{aligned}$$

dividing both sides of the resulting equation by τ, rearranging terms and then multiplying and dividing the terms on the right-hand side by either χ^2 or χ we find

$$\begin{aligned}\frac{n(t+\tau,x,y)-n}{\tau} \;=\;& R(y,p)\,n+\frac{\lambda\eta^2}{2\tau}\frac{\partial^2 n}{\partial y^2}\left[1+\tau R(y,p)\right]\\ &+\frac{\nu\chi^2}{2\tau}\,n\left\{\left[1+\tau R(y,p)\right]\frac{\mu(y)}{p_M}\left[\frac{p(t,x+\chi)+p(t,x-\chi)-2\,p}{\chi^2}\right]\right\}\\ &+\frac{\nu\chi^2}{2\tau}\frac{\partial n}{\partial x}\left\{\left[1+\tau R(y,p)\right]\frac{\mu(y)}{p_M}\left[\left(\frac{p(t,x+\chi)-p}{\chi}\right)_+-\left(\frac{p(t,x-\chi)-p}{\chi}\right)_+\right]\right\}\\ &+\frac{\chi}{2}\,\frac{\nu\chi^2}{2\tau}\frac{\partial^2 n}{\partial x^2}\left\{\left[1+\tau R(y,p)\right]\frac{\mu(y)}{p_M}\left[\left(\frac{p(t,x+\chi)-p}{\chi}\right)_++\left(\frac{p(t,x-\chi)-p}{\chi}\right)_+\right]\right\}\\ &+\frac{\eta^2}{2}\,\frac{\nu\chi^2}{2\tau}\frac{\partial^2 n}{\partial y^2}\left\{\lambda\left[1+\tau R(y,p)\right]\frac{\mu(y)}{p_M}\left[\frac{p(t,x+\chi)+p(t,x-\chi)-2\,p}{\chi^2}\right]\right\}\\ &+\text{h.o.t.}\,.\end{aligned}$$

If the function $n(t,x,y)$ is also continuously differentiable with respect to the variable t and the function $p(t,x)$ is twice continuously differentiable with respect to the variable x, letting $\tau\to 0$, $\chi\to 0$ and $\eta\to 0$ in such a way that conditions (3.1) are met, from the latter equation we formally obtain

$$\frac{\partial n}{\partial t}=R(y,p)\,n+\beta\frac{\partial^2 n}{\partial y^2}+\alpha\,\frac{\mu(y)}{p_M}\left\{n\frac{\partial^2 p}{\partial x^2}+\frac{\partial n}{\partial x}\left[\left(\frac{\partial p}{\partial x}\right)_+-\left(-\frac{\partial p}{\partial x}\right)_+\right]\right\}.$$

Hence, using the definition $\hat{\mu}(y):=\dfrac{\mu(y)}{p_M}$ along with the fact that $\left(\dfrac{\partial p}{\partial x}\right)_+-\left(-\dfrac{\partial p}{\partial x}\right)_+=\dfrac{\partial p}{\partial x}$, and recalling that $(x,y)\in\mathbb{R}\times(0,Y)$, we find the following non-local PDE for the cell population density function $n(t,x,y)$

$$\frac{\partial n}{\partial t}=R(y,p)\,n+\beta\frac{\partial^2 n}{\partial y^2}+\alpha\,\hat{\mu}(y)\left[n\frac{\partial^2 p}{\partial x^2}+\frac{\partial n}{\partial x}\frac{\partial p}{\partial x}\right],\quad (x,y)\in\mathbb{R}\times(0,Y),$$

which can easily be rewritten as the non-local PDE (3.2). Finally, zero-Neumann (*i.e.* no-flux) boundary conditions at $y=0$ and $y=Y$ follow from the fact that the attempted phenotypic variation of a cell is aborted if it requires moving into a phenotypic state that does not belong to the interval $[0,Y]$.

S2. Formal travelling-wave analysis for $\varepsilon \to 0$

Adopting a method analogous to those that we used [6, 7], which build on the Hamilton-Jacobi approach developed in [8–12], we make the real phase WKB ansatz [13–15]

$$n_\varepsilon(t,x,y) = e^{\frac{u_\varepsilon(t,x,y)}{\varepsilon}}, \tag{S2.1}$$

which gives

$$\partial_t n_\varepsilon = \frac{\partial_t u_\varepsilon}{\varepsilon} n_\varepsilon, \quad \partial_x n_\varepsilon = \frac{\partial_x u_\varepsilon}{\varepsilon} n_\varepsilon, \quad \partial^2_{yy} n_\varepsilon = \left(\frac{1}{\varepsilon^2}\left(\partial_y u_\varepsilon\right)^2 + \frac{1}{\varepsilon}\partial^2_{yy} u_\varepsilon\right) n_\varepsilon.$$

Substituting the above expressions into the non-local PDE (4.2) gives the following Hamilton-Jacobi equation for $u_\varepsilon(t,x,y)$

$$\partial_t u_\varepsilon - \hat{\mu}(y)\left(\partial_x u_\varepsilon\, \partial_x p_\varepsilon + \varepsilon\, \partial^2_{xx} p_\varepsilon\right) = R(y, p_\varepsilon) + \left(\partial_y u_\varepsilon\right)^2 + \varepsilon\, \partial^2_{yy} u_\varepsilon, \quad (x,y) \in \mathbb{R} \times (0, Y). \tag{S2.2}$$

Letting $\varepsilon \to 0$ in (S2.2) we formally obtain the following equation for the leading-order term $u(t,x,y)$ of the asymptotic expansion for $u_\varepsilon(t,x,y)$

$$\partial_t u - \hat{\mu}(y)\, \partial_x p\, \partial_x u = R(y,p) + \left(\partial_y u\right)^2, \quad (x,y) \in \mathbb{R} \times (0, Y), \tag{S2.3}$$

where $p(t,x)$ is the leading-order term of the asymptotic expansion for $p_\varepsilon(t,x)$.

Constraint on u. Consider $x \in \mathbb{R}$ such that $\rho(t,x) > 0$, that is, $x \in \mathrm{Supp}(\rho)$, and let $\bar{y}(t,x)$ be a non-degenerate maximum point of $u(t,x,y)$, that is, $\bar{y}(t,x) \in \underset{y \in [0,Y]}{\arg\max}\, u(t,x,y)$ with $\partial^2_{yy} u(t,x,\bar{y}) < 0$. Letting $\varepsilon \to 0$ in (S2.1) formally gives the following constraint for all $t > 0$

$$u(t,x,\bar{y}(t,x)) = \max_{y \in [0,Y]} u(t,x,y) = 0, \quad x \in \mathrm{Supp}(\rho), \tag{S2.4}$$

which also implies that

$$\partial_y u(t,x,\bar{y}(t,x)) = 0 \quad \text{and} \quad \partial_x u(t,x,\bar{y}(t,x)) = 0, \quad x \in \mathrm{Supp}(\rho). \tag{S2.5}$$

Remark 1. *When $n_\varepsilon(t,x,y)$ is in the form* (S2.1)*, if $u(t,x,y)$ is a strictly concave function of y with maximum point $y = \bar{y}(t,x)$ then the constraint* (S2.4) *implies that*

$$n_\varepsilon(t,x,y) \underset{\varepsilon \to 0}{\longrightarrow} \rho(t,x)\, \delta_{\bar{y}(t,x)}(y) \quad \textit{weakly in measures},$$

where $\delta_{\bar{y}(t,x)}(y)$ is the Dirac delta centred at $y = \bar{y}(t,x)$.

Relation between $\bar{y}(t,x)$ and $p(t,x)$. Assumptions (2.3) ensure that $\mathrm{Supp}(p) \subseteq \mathrm{Supp}(\rho)$. Hence, evaluating (S2.3) at $y = \bar{y}(t,x)$ and using (S2.4) and (S2.5) we find

$$R(\bar{y}(t,x), p(t,x)) = 0, \quad x \in \mathrm{Supp}(p). \tag{S2.6}$$

The monotonicity assumptions ensure that $p \mapsto R(\cdot, p)$ and $\bar{y} \mapsto R(\bar{y}, \cdot)$ are both invertible. Therefore, relation (S2.6) gives a one-to-one correspondence between $\bar{y}(t,x)$ and $p(t,x)$.

Transport equation for $\bar{y}$. Differentiating (S2.3) with respect to y, evaluating the resulting equation at $y = \bar{y}(t,x)$ and using (S2.4) and (S2.5) yields

$$\partial^2_{yt}u(t,x,\bar{y}) - \hat{\mu}(\bar{y})\,\partial_x p\,\partial^2_{yx}u(t,x,\bar{y}) = \partial_y R(\bar{y},p), \quad x \in \mathrm{Supp}(p). \tag{S2.7}$$

Moreover, differentiating (S2.5) with respect to t and x we find, respectively,

$$\partial^2_{ty}u(t,x,\bar{y}) + \partial^2_{yy}u(t,x,\bar{y})\,\partial_t\bar{y}(t,x) = 0 \;\Rightarrow\; \partial^2_{yt}u(t,x,\bar{y}) = -\partial^2_{yy}u(t,x,\bar{y})\,\partial_t\bar{y}(t,x)$$

and

$$\partial^2_{xy}u(t,x,\bar{y}) + \partial^2_{yy}u(t,x,\bar{y})\,\partial_x\bar{y}(t,x) = 0 \;\Rightarrow\; \partial^2_{yx}u(t,x,\bar{y}) = -\partial^2_{yy}u(t,x,\bar{y})\,\partial_x\bar{y}(t,x).$$

Substituting the above expressions of $\partial^2_{yt}u(t,x,\bar{y})$ and $\partial^2_{yx}u(t,x,\bar{y})$ into (S2.7) and using the fact that $\partial^2_{yy}u(t,x,\bar{y}) < 0$ gives the following transport equation for $\bar{y}(t,x)$

$$\partial_t\bar{y} - \hat{\mu}(\bar{y})\,\partial_x p\,\partial_x\bar{y} = \frac{1}{-\partial^2_{yy}u(t,x,\bar{y})}\partial_y R(\bar{y},p), \quad x \in \mathrm{Supp}(p). \tag{S2.8}$$

Travelling-wave problem. Substituting the travelling-wave ansatz

$$\rho(t,x) = \rho(z), \quad p(t,x) = p(z), \quad u(t,x,y) = u(z,y) \quad \text{and} \quad \bar{y}(t,x) = \bar{y}(z) \quad \text{with} \quad z = x - c\,t, \quad c > 0$$

into (S2.3)-(S2.6) and (S2.8) gives

$$-\,(c + \hat{\mu}(y)p')\,\partial_z u = R(y,p) + (\partial_y u)^2, \quad (z,y) \in \mathbb{R}\times(0,Y),$$

$$u(z,\bar{y}(z)) = \max_{y\in[0,Y]} u(z,y) = 0, \quad \partial_y u(z,\bar{y}(z)) = 0, \quad \partial_z u(z,\bar{y}(z)) = 0, \quad z \in \mathrm{Supp}(\rho),$$

$$R(\bar{y}(z),p(z)) = 0, \quad z \in \mathrm{Supp}(p), \tag{S2.9}$$

$$-\,(c + \hat{\mu}(\bar{y})p')\,\bar{y}' = \frac{1}{-\partial^2_{yy}u(z,\bar{y})}\partial_y R(\bar{y},p), \quad z \in \mathrm{Supp}(p). \tag{S2.10}$$

We consider travelling-front solutions $\bar{y}(z)$ that satisfy (S2.10) subject to the following asymptotic condition

$$\lim_{z\to-\infty}\bar{y}(z) = 0, \tag{S2.11}$$

so that, since $R(0,p_M) = 0$, relation (S2.9) gives $\lim_{z\to-\infty} p(z) = p_M$.

Monotonicity of travelling-front solutions. Differentiating (S2.9) with respect to z gives

$$\partial_y R(\bar{y}(z),p(z))\bar{y}'(z) + \partial_p R(\bar{y}(z),p(z))p'(z) = 0, \quad z \in \mathrm{Supp}(p). \tag{S2.12}$$

Substituting the expression of p' given by (S2.12) into (S2.10) yields

$$-c\,\bar{y}' + \hat{\mu}(\bar{y})\,\frac{\partial_y R(\bar{y},p)}{\partial_p R(\bar{y},p)}\,(\bar{y}')^2 = \frac{1}{-\partial^2_{yy}u(z,\bar{y})}\,\partial_y R(\bar{y},p),$$

that is,

$$\bar{y}' = \frac{-\partial_y R(\bar{y},p)}{c}\left(\frac{1}{-\partial^2_{yy}u(z,\bar{y})} + \frac{\hat{\mu}(\bar{y})\,(\bar{y}')^2}{-\partial_p R(\bar{y},p)}\right), \quad z \in \mathrm{Supp}(p). \tag{S2.13}$$

Since $\partial^2_{yy}u(z,\bar{y}) < 0$ and $\partial_y R(y,\cdot) < 0$ for $y \in (0,Y]$, using (S2.13) and the expression of p' given by (S2.12) we find

$$\bar{y}'(z) > 0 \quad \text{and} \quad p'(z) < 0, \quad z \in \mathrm{Supp}(p). \tag{S2.14}$$

Position of the edge of the travelling front $p(z)$. Relation (S2.9) and monotonicity results (S2.14) along with the fact that $R(Y, 0) = 0$ [*cf.* assumptions (2.7)] imply that the position of the edge of the travelling front $p(z)$ coincides with the unique point $\ell \in \mathbb{R}$ such that $\bar{y}(\ell) = Y$ and $\bar{y}(z) < Y$ on $(-\infty, \ell)$. Hence, $\mathrm{Supp}(p) = (-\infty, \ell)$.

Minimal wave speed. In the case where $R(y, p)$ is defined via (2.8), relation (S2.9) yields

$$p(z) = p_M\, r(\bar{y}(z)), \quad z \in \mathrm{Supp}(p).$$

Therefore, $\mathrm{Supp}(p) = \mathrm{Supp}(r(\bar{y}))$. Moreover, we have

$$\partial_p R(\cdot, p) = -\frac{1}{p_M} \quad \text{and} \quad \partial_y R(\bar{y}, \cdot) = \frac{\mathrm{d}}{\mathrm{d}y} r(\bar{y}).$$

Hence, recalling that $\hat{\mu}(y) := \dfrac{\mu(y)}{p_M}$, from equation (S2.13) we find

$$\mu(\bar{y})\, \partial^2_{yy} u(z, \bar{y})\, \frac{\mathrm{d}}{\mathrm{d}y} r(\bar{y})\, \left(\bar{y}'\right)^2 + c\, \partial^2_{yy} u(z, \bar{y})\, \bar{y}' - \frac{\mathrm{d}}{\mathrm{d}y} r(\bar{y}) = 0, \quad z \in r(\bar{y}(z)). \tag{S2.15}$$

The following condition has to hold for the roots of (S2.15), seen as an algebraic equation for $\bar{y}'(z)$, to be real

$$c \geq 2 \left| \frac{\mathrm{d}}{\mathrm{d}y} r(\bar{y}) \right| \sqrt{\frac{\mu(\bar{y})}{\left| \partial^2_{yy} u(z, \bar{y}) \right|}}, \quad z \in r(\bar{y}(z)).$$

This gives condition (4.4) on the wave speed.

S3. Methods used to solve numerically the non-local PDE (4.2)

Adopting a time-splitting approach, which is based on the idea of decomposing the original problem into simpler subproblems that are then sequentially solved at each time-step, we decompose the non-local PDE (4.2) posed on $\Omega := (0, T] \times (0, X) \times (0, Y)$, with $T = 8$, $X = 25$ and $Y = 1$, into two parts – *i.e.* the diffusion-advection part corresponding to the following non-local PDE

$$\begin{cases} \partial_t n_\varepsilon - \hat{\mu}(y)\, \partial_x (n_\varepsilon\, \partial_x p_\varepsilon) = \varepsilon\, \partial^2_{yy} n_\varepsilon, \\ p_\varepsilon = \Pi(\rho_\varepsilon), \quad \rho_\varepsilon(t, x) = \int_0^Y n_\varepsilon(t, x, y)\, dy. \end{cases} \tag{S3.1}$$

and the reaction part corresponding to the following integro-differential equation

$$\begin{cases} \varepsilon\, \partial_t n_\varepsilon = R(y, p_\varepsilon)\, n_\varepsilon, \\ p_\varepsilon = \Pi(\rho_\varepsilon), \quad \rho_\varepsilon(t, x) = \int_0^Y n_\varepsilon(t, x, y)\, dy. \end{cases} \tag{S3.2}$$

We complement (S3.1) with zero Neumann boundary conditions at $x = 0$ (we expect a constant step), $y = 0$ and $y = Y$. With the ansatz $n_\varepsilon(t, x, y) = e^{\frac{u_\varepsilon(t,x,y)}{\varepsilon}}$, the integro-differential equation (S3.2) can be rewritten in the following alternative form

$$\begin{cases} \partial_t u_\varepsilon = R(y, p_\varepsilon), \\ p_\varepsilon = \Pi(\rho_\varepsilon), \quad \rho_\varepsilon(t, x) = \int_0^Y e^{\frac{u_\varepsilon(t,x,y)}{\varepsilon}}\, dy. \end{cases} \tag{S3.3}$$

Preliminaries and notation We denote by $[\![k_1, k_2]\!]$ the set of integers between k_1 and k_2. We discretise Ω via a uniform structured grid of steps Δt, Δx, Δy whereby $t_h = h\Delta t$ and the (j,k)-th cell is

$$K_{j,k} = (x_{j-1}, x_j) \times (y_{k-1}, y_k) \quad \text{with} \quad x_j = j\Delta x, \quad y_k = k\Delta y,$$

where $j \in [\![1, m_x]\!]$ and $k \in [\![1, m_y]\!]$, $\Delta x = \frac{X}{m_x}$, $\Delta y = \frac{Y}{m_y}$ and $m_x, m_y \in \mathbb{N}$. In particular, given $\Omega := (0,T] \times (0,X) \times (0,Y)$, with $T = 8$, $X = 25$ and $Y = 1$, we choose $\Delta t = 10^{-4}$, $\Delta x = 0.01$ and $\Delta y = 0.02$. Moreover, we let $N^h_{\varepsilon j,k}$ be the numerical approximation of the average of $n_\varepsilon(t_h, x, y)$ over the cell $K_{j,k}$ and

$$\rho^h_{\varepsilon j} = \Delta y \sum_{k=1}^{m_y} N^h_{\varepsilon j,k}.$$

be the average of $\rho_\varepsilon(t_h, x)$ over the interval (x_{j-1}, x_j). For simplicity of notation, in the remainder of this section we drop the subscript ε.

Numerical scheme

Step 1 We first solve numerically (S3.1) by using the following implicit-explicit scheme

$$\frac{N^*_{j,k} - N^h_{j,k}}{\Delta t} - \hat{\mu}_k \frac{\delta_x P^h_{j+\frac{1}{2}} N^*_{j+\frac{1}{2},k} - \delta_x P^h_{j-\frac{1}{2}} N^*_{j-\frac{1}{2},k}}{\Delta x} = \varepsilon \frac{N^*_{j,k+1} - 2N^*_{j,k} + N^*_{j,k-1}}{(\Delta y)^2}. \tag{S3.4}$$

where $\hat{\mu}_k = \hat{\mu}(y_k)$, $\delta_x P^h_{j+\frac{1}{2}} = (P^h_{j+1} - P^h_j)/\Delta x$ and

$$N^*_{j+\frac{1}{2},k} = \begin{cases} N^*_{j,k}, & \text{if } \delta_x P^h_{j+\frac{1}{2}} \leq 0, \\ N^*_{j+1,k}, & \text{if } \delta_x P^h_{j+\frac{1}{2}} > 0. \end{cases}$$

Zero-flux/Neumann boundary conditions are implemented at $x = 0$, $y = 0$ and $y = Y$.

Step 2 Starting from $U^*_{j,k} = \varepsilon \ln\left(N^*_{j,k}\right)$, where $N^*_{j,k}$ is obtained via (S3.4), we solve numerically (S3.3) using the following implicit scheme

$$\begin{cases} U^{n+1}_{j,k} = U^n_{j,k} + \Delta t\, R(y_{k-\frac{1}{2}}, P^{n+1}_j), \\ P^{h+1}_j = \Pi(\rho^{h+1}_j), \quad \rho^{h+1}_j = \Delta y \sum_{k=1}^{m_y} e^{\frac{U^{h+1}_{j,k}}{\varepsilon}}. \end{cases} \tag{S3.5}$$

Substituting the first equation in (S3.5) into the second equation yields

$$\rho^{h+1}_j = \Delta y \sum_{k=1}^{m_y} \exp\left(\frac{U^*_{j,k} + \Delta t\, R\left(y_k, P^{h+1}_j\right)}{\varepsilon}\right),$$

from which ρ^{h+1}_j and P^{h+1}_j are computed. Straightforward calculations then lead to $U^{n+1}_{j,k}$ and $N^{n+1}_{j,k}$.

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