Spatial patterns in a population model structured by cell size, quiescence and sensing radius

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EVERYTHING DISPERSES TO MIAMI
THE ROLE OF MOVEMENT AND DISPERsal IN SPATIAL ECOLOGY, EPIDEMIOLOGY AND ENVIRONMENTAL SCIENCE

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Multi-drug resistance is a phenomenon by which tumor cells exhibit resistance to a variety of chemically unrelated chemotherapeutic drugs. The classical form of multidrug resistance is connected to overexpression of membrane P-glycoprotein (P-gp), which acts as an energy dependent drug efflux pump.
Direct immunodetection of P-gp transfers in co-cultures of sensitive (MCF-7) and resistant (MCF-7/Doxo) variants of the human breast cancer cell line. Mixtures of 50:50 ctgMCF-7:MCF-7/Doxo were co-cultured on glass coverslips during periods varying from 0 to 7 days (D0-D7). P-gp was immunodetected with phycoerythrin-conjugated (PE)-UIC2 mAb (red fluorescence) by confocal laser scanning microscopy in non-dispersed. From D3 to D7, sensitive ctgMCF-7 show an increasing P-gp-specific red membrane staining (arrows), restricted to the plasma membrane, in non-dispersed as well as in dissociated cells.

Pasquier, Galas, Boulangé-Lecomte, Rioult, Bultelle, Magal, Webb and Le Foll (’12).
**Pattern & Proliferation**

*B*, flow cytometry histogram in representative medulloblastoma tumor cells, with the first peak (gate M1) representing cells negative for CD133- phycoerythrin expression, and the second peak (gate M2) representing CD133 positive cells. Tumor cells were then sorted for CD133 expression by magnetic bead cell sorting. CD133+ and CD133- populations were collected, checked for purity by flow cytometry, and cultured separately in TSM for stem cell assays. Purity was found to range from 46.9 to 79.8% in CD133+ populations, and 92.6 to 97.3% in CD133- populations.

*C*, CD133+ tumor cells proliferated in culture as nonadherent spheres, whereas CD133- tumor cells adhered to culture dishes, did not proliferate and did not form spheres.

Singh, Clarke, Terasaki, Bonn, Hawkins, Squire, & Dirks ('03).
Pressure for growth (Nonlocal pressure)

\[ \bar{p}(t, x) = \int_{\Omega} K(x, y)p(t, y)dy. \]

- Contact inhibition of growth
- Supply and demand for Nutrition or Oxygen

**Remark. Angiogenesis**

- Numerical simulation for Nutrition-Absorption relation
- A function given by the nonlocal reaction (defined below)
A model incorporating **Cell size, Fission, Quiescence & Sensing radius.**

\[ u(t, x, s) : \text{population density of proliferating cells.} \]
\[ v(t, x, s) : \text{population density of quiescent cells.} \]
\[ m(t, x) = \int_0^{+\infty} s \left[ u + v \right] (t, x, s) ds : \text{density of mass.} \]
\[ p(t, x) = m(t, x): \text{pressure for motility,} \quad \bar{p}(t, x) = \int_{\Omega} K(x, y)m(t, y)dy : \text{pressure for growth.} \]

\[
\begin{align*}
  u_t = & \text{div}_x \left( u \nabla_x p \right) - \frac{\partial}{\partial s} \left[ g(s) u \right] - \beta_u \left( \bar{p}(t, x), s \right) u + \beta_v \left( \bar{p}(t, x), s \right) v \\
  & + 4b(2s)u(t, x, 2s) - b(s)u(t, x, s) - \mu(s)u(t, x, s), \\
  v_t = & \text{div}_x \left( v \nabla_x p \right) + \beta_u \left( \bar{p}(t, x), s \right) u - \beta_v \left( \bar{p}(t, x), s \right) v - \mu(s)v(t, x, s).
\end{align*}
\]

\[ g(s) : \text{cell size growth rate,} \quad \mu(s) : \text{mortality rate,} \]
\[ \beta_u(p, s) : \text{non-decreasing function for transition form proliferation to quiescence,} \]
\[ \beta_v(p, s) : \text{non-increasing function for transition form quiescence to proliferation,} \]
\[ b(s) : \text{division rate s.t.} \quad b(s) = \begin{cases} 
  0 & \text{if } s \leq s_f, \\
  \geq 0 & \text{if } s_f < s.
\end{cases} \]

The cells cannot divide before they have reached a size \( s_f \).
We assume that the dynamics of transition to and from quiescence and proliferation are fast compared to the other dynamics.

\[
\begin{align*}
    u_t &= \text{div}_x (u \nabla x p) - \partial_s \left[ g(s)u - \varepsilon^{-1} \beta_u (\bar{p}(t, x), s) u + \varepsilon^{-1} \beta_v (\bar{p}(t, x), s) v + 4b(2s)u(t, x, 2s) - (b(s) + \mu(s))u(t, x, s) \right] \\
    v_t &= \text{div}_x (v \nabla x p) + \varepsilon^{-1} \beta_u (\bar{p}(t, x), s) u - \varepsilon^{-1} \beta_v (\bar{p}(t, x), s) v - \mu(s)v(t, x, s),
    \end{align*}
\]

where \(0 < \varepsilon \ll 1\).

Taking a formal limit as \(\varepsilon \searrow 0\),

\[\beta_u (\bar{p}(t, x), s) u = \beta_v (\bar{p}(t, x), s) v.\]

\[u(t, x, s) = G (\bar{p}(t, x), s) n(t, x, s).\]

Set 
\[n(t, x, s) := (u + v)(t, x, s), \quad \text{population density of total cells of size } s.\]

\[G (\bar{p}(t, x), s) := \frac{\beta_v (\bar{p}(t, x), s)}{\beta_u (\bar{p}(t, x), s) + \beta_v (\bar{p}(t, x), s)}.\]

\[n_t = \text{div}_x (n \nabla x p) - \partial_s \left[ g(s)G (\bar{p}(t, x), s) n(t, x, s) \right] + 4b(2s)G (\bar{p}(t, x), 2s) n(t, x, 2s) - b(s)G (\bar{p}(t, x), s) n(t, x, s) - \mu(s)n(t, x, s).\]
Equation for density of mass

\[ n_t = \text{div}_x (n \nabla_x p) - \partial_s [g(s)G(\bar{p}(t, x), s) n(t, x, s)] \\
+ 4b(2s)G(\bar{p}(t, x), 2s) n(t, x, 2s) - b(s)G(\bar{p}(t, x), s) n(t, x, s) \\
- \mu(s)n(t, x, s). \]

We assume that

\[ g(s) = gs, \quad G(\cdot, s) = G(\cdot), \quad \mu(s) = \mu. \]

Multiply both sides by \( S \) and integrate over \((0, +\infty)\) w.r.t. \( S \) to obtain

\[ m(t, x) = \int_0^{+\infty} s [u + v] (t, x, s) ds \]

Note \( m(t, x) = \int_0^{+\infty} A(\cdot, \cdot, s) ds \)

\[ m_t = \text{div} (m \nabla m) + G(\bar{m}) \int_0^{+\infty} A(\cdot, \cdot, s) ds - \mu m. \]

Here,

\[ A(t, x, s) := -s\partial_s [g(s)n(t, x, s)] + 4sb(2s)n(t, x, 2s) - sb(s)n(t, x, s). \]
Equation for density of mass

\[ A(t, x, s) := -s \partial_s [g(s)n(t, x, s)] + 4sb(2s)n(t, x, 2s) - sb(s)n(t, x, s). \]

Note \( b(s) = \begin{cases} 0 & \text{if } s \leq s_f, \\ \geq 0 & \text{if } s_f < s. \end{cases} \)

\[
\int_0^{s_f} A(s)ds = -gs_f^2n(s_f) + g \int_0^{s_f} sn(s)ds + \int_{s_f}^{2s_f} sb(s)n(s)ds.
\]

\[
\int_{s_f}^{\infty} A(s)ds = gs_f^2n(s_f) + g \int_{s_f}^{\infty} sn(s)ds + \left( \int_{s_f}^{\infty} - \int_{s_f}^{2s_f} \right) sb(s)n(s)ds.
\]

We assume \( \lim_{s \to +\infty} s^2n(s) = 0. \) (Then \( m < \infty. \))

Therefore,

\[
\int_0^{\infty} A(s)ds = gm.
\]

### Simplified Model

\[ m_t = \text{div} (m \nabla m) + \left( gG \left( \int_{\Omega} K(\cdot, y)m(t, y)dy \right) - \mu \right) m. \]
Assumptions

(P) \[
\begin{aligned}
&m_t - \Delta \phi(m) = F(\overline{m})m & \text{in} & (0, \infty) \times \Omega, \\
&\frac{\partial \phi(m)}{\partial \nu} = 0 & \text{on} & (0, \infty) \times \partial \Omega, \\
&m(0, \cdot) = m_0 & \text{in} & \Omega,
\end{aligned}
\]

where \( \phi(s) = \frac{1}{2}s^2, \ F(s) = gG(s) - \mu, \ g, \mu > 0: \) const.

\[
\overline{m}(t, x) = \int_{\Omega} K(x, y)m(t, y)dy.
\]

- \( m_0 \in L^1_+(\Omega), \)
- \( K \in L^\infty(\Omega \times \Omega), \)
- \( G : [0, \infty) \to [0, 1] \) is Lipschitz continuous.
**Definition.** (Weak energy solution) A measurable function \( m : [0, \infty) \times \Omega \to \mathbb{R}_+ \) is said to be a weak energy solution of (P) if for each \( T > 0 \)

(i) \( m \in L^2(Q_T) \) and \( w = \phi(m) \in L^2(0, T; H^1(\Omega)) \),

(ii) \( m \) satisfies for each \( \eta \in C^1(\overline{Q_T}) \) s.t. \( \eta(T, \cdot) \equiv 0 \)

\[
\int_{Q_T} (\nabla w \cdot \nabla \eta - m \eta_t) \, dt \, dx = \int_{\Omega} m_0(x) \eta(0, x) \, dx + \int_{Q_T} \eta F(\overline{m}) m \, dt \, dx.
\]
Theorem (Ducrot-Le Foll-Magal-M-Pasquier-Webb ('11))

For each $m_0 \in L^3_+(\Omega)$ there exists a unique energy solution $m \equiv m(t, x; m_0)$ of (P) such that

$$m \in L^\infty_{loc}([0, \infty); L^3(\Omega)) \cap C([0, \infty); L^1(\Omega)).$$

Moreover for each $M > 0$ and each $T > 0$ there exists $\delta = \delta(T, M) > 0$ such that for each $m_0, m_1 \in L^3_+(\Omega)$, if $\|m_0\|_{L^1} \leq M$ and $\|m_1\|_{L^1} \leq M$, then

$$\|m(t, ..; m_0) - m(t, ..; m_1)\|_{L^1} \leq \delta(T, M)\|m_0 - m_1\|_{L^1}, \quad \forall t \in [0, T].$$
Finite speed of propagation

Theorem (Ducrot-Le Foll-Magal-M-Pasquier-Webb ('11))

If $m_0 \in L^3_+(\Omega)$ satisfies that there exists $x_0 \in \Omega$, $\rho_0 \in (0, \text{dist} (x_0, \partial \Omega)$, $m_0(x) = 0$, a.e. $x \in B(x_0, \rho_0)$, then there exists $T^* > 0$ and a mapping $\rho : [0, T^*] \rightarrow [0, \rho_0]$ such that $m = m(t, x; m_0)$ satisfies

$$m(t, x) = 0 \quad \text{for} \quad t \in [0, T^*], \ x \in B(x_0, \rho(t)).$$
Numerical experiments

\[ m_t = \frac{1}{2} \Delta m^2 + \left( gG \left( \int_{\Omega} K_r(\cdot, y)m(t, y)dy \right) - \mu \right) m. \]

with periodic b.c.

\[ \Omega = (0, 20)^2. \]

\[ G(p) := \frac{\beta_v(p)}{\beta_u(p) + \beta_v(p)}. \]

\[ K_r(x, y) = \begin{cases} 
1/(\pi r^2) & \text{if } |x - y| < r, \\
0 & \text{otherwise.} 
\end{cases} \]
Numerical experiments

g=15, \mu=5, r=0.2.

\[ m, \quad u = G(\overline{m})m. \]

at \( t = 2, y=6, x \in (10,20). \)
Effect of sensing radius  \( g = 15, \mu = 5 \).

- \( r = 0.2 \)
- \( r = 1 \)
- \( r = 2 \)
- \( r = 4 \)
Effect of growth rate

$r = 2, \mu = 5.$

Singh, Clarke, Terasaki, Bonn, Hawkins, Squire, & Dirks ('03).

Proliferate Not proliferate
Effect of growth rate

$r = 2, \mu = 5.$

$g = 6$

$g = 5.5$

$g = 5.1$

$g = 5.01$
Effect of mortality rate

\[ r = 2, \ g = 15. \]

\[ \mu = 5 \quad \mu = 2 \quad \mu = 0.5 \]
Conclusion

A model incorporating Cell size, Fission, Quiescence & Sensing radius.

- Contact inhibition,
- Supply and demand for Nutrition or Oxygen.

\[
\begin{align*}
    u_t &= \text{div}_x (u \nabla x p) - \partial_s [g(s)u] - \beta_u (\bar{p}(t, x), s) u + \beta_v (\bar{p}(t, x), s) v + 4b(2s)u(t, x, 2s) - b(s)u(t, x, s) - \mu(s)u(t, x, s), \\
v_t &= \text{div}_x (v \nabla x p) + \beta_u (\bar{p}(t, x), s) u - \beta_v (\bar{p}(t, x), s) v - \mu(s)v(t, x, s),
\end{align*}
\]

Simplified Model

\[
m_t = \frac{1}{2} \Delta m^2 + \left( gG \left( \int_{\Omega} K_r(\cdot, y) m(t, y) dy \right) - \mu \right) m.
\]

Theoretical results

- Unique existence of the solution.
- Finite speed of propagation.

Numerical results

<table>
<thead>
<tr>
<th></th>
<th>Large</th>
<th>Small</th>
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</thead>
<tbody>
<tr>
<td>Sensing radius</td>
<td>colonies</td>
<td>uniform distribution</td>
</tr>
<tr>
<td>growth rate</td>
<td></td>
<td></td>
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<tr>
<td>mortality rate</td>
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</tbody>
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Future work (Co-cultured cells)

\[
\begin{align*}
\frac{\partial m_1}{\partial t} &= \text{div} \left( m_1 \nabla (a_{11} m_1 + a_{12} m_2) \right) \\
&\quad + \left[ g_1 G_1 \left( \int_{\Omega} K_{r_1} (\cdot, y) \left( b_{11} m_1 (\cdot, y) + b_{12} m_2 (\cdot, y) \right) dy \right) - \mu_1 \right] m_1, \\
\frac{\partial m_2}{\partial t} &= \text{div} \left( m_2 \nabla (a_{21} m_1 + a_{22} m_2) \right) \\
&\quad + \left[ g_2 G_2 \left( \int_{\Omega} K_{r_2} (\cdot, y) \left( b_{21} m_1 (\cdot, y) + b_{22} m_2 (\cdot, y) \right) dy \right) - \mu_2 \right] m_2.
\end{align*}
\]

Pasquier, Magal, Boulangé-Lecomte†, Webb & Le Foll (‘11).