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

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joint work with

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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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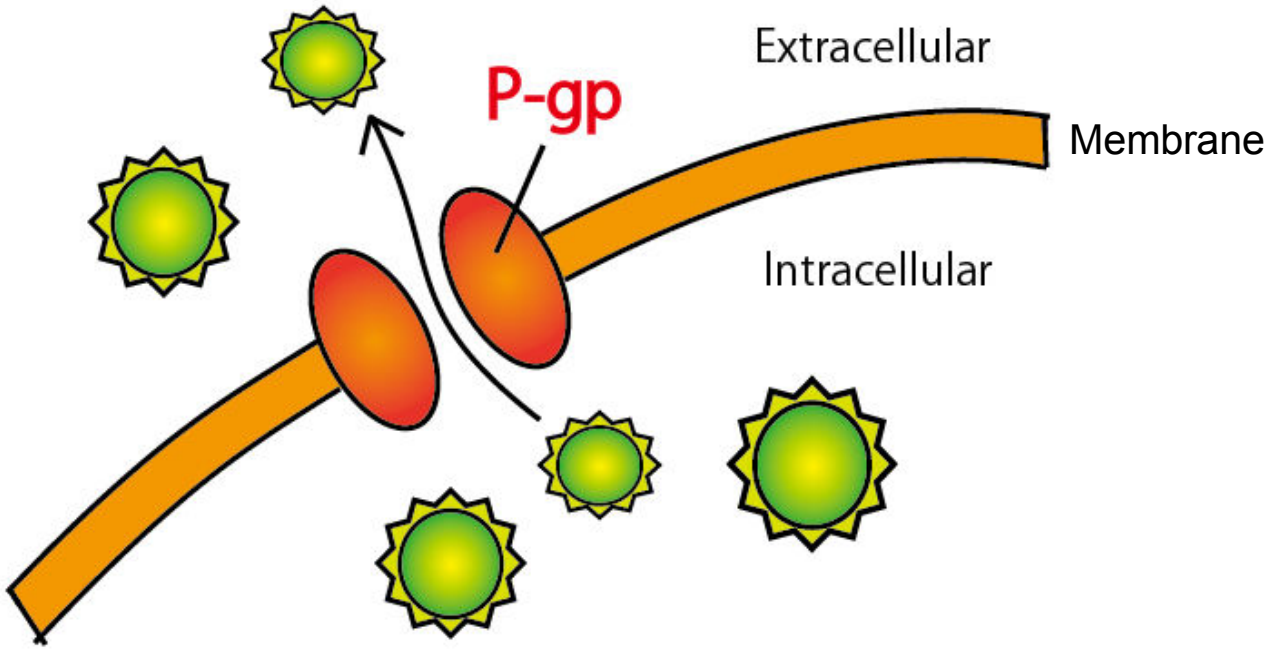
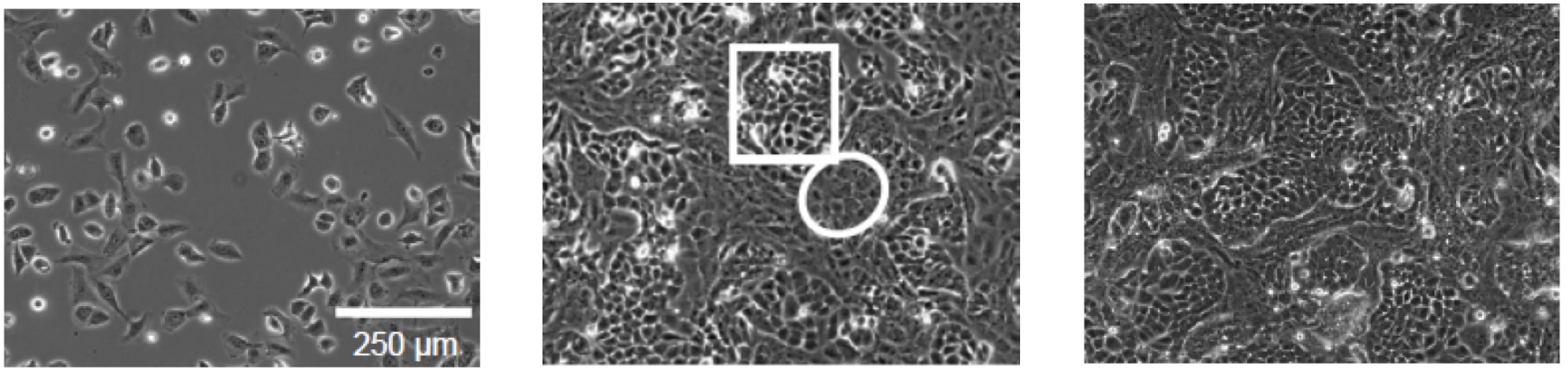
Multidrug resistance, P-glycoprotein

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.

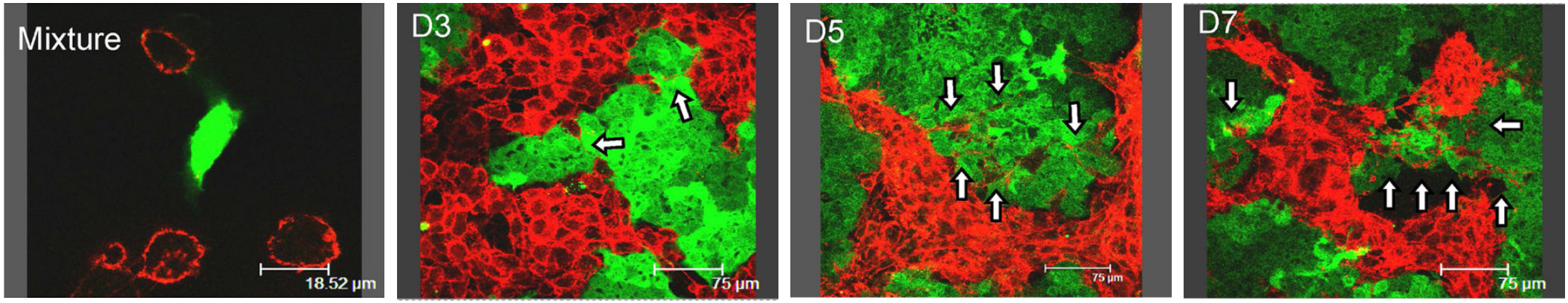


Spatial behavior and P-gp transfers



To obtain phase contrast micrographs of growing MCF-7 variants in co-cultures, dishes were seeded with a 50:50 mixture of MCF-7:MCF-7/DOXO at day 0. Morphological differences permit an immediate identification of each cell subpopulation. MCF-7 appeared birefringent and round (boxes) whereas MCF-7/DOXO are more flat and spread (ellipses). Note that the cells remained organized in well-delimited islets.

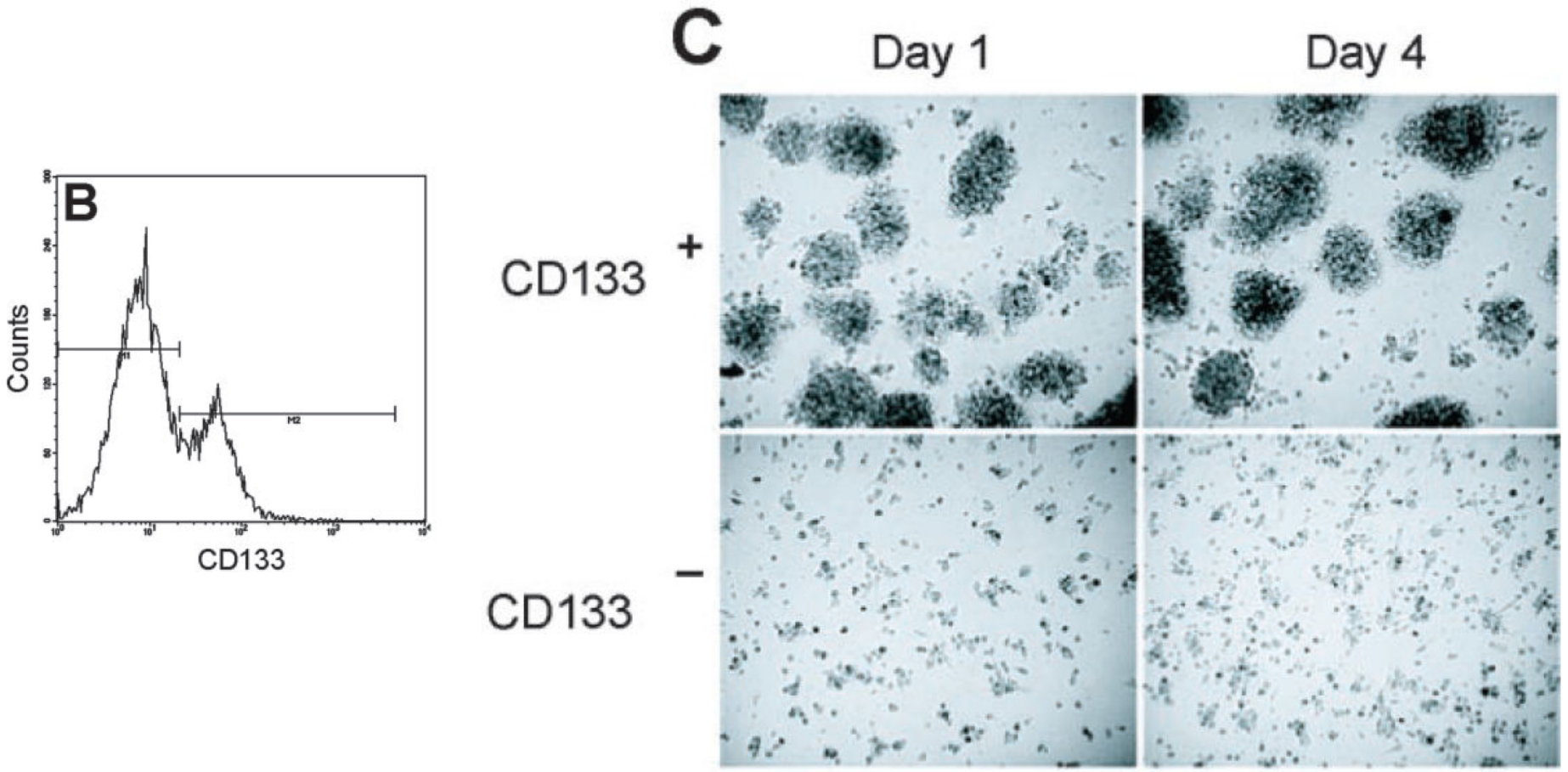
Pasquier, Magal, Boulangé-Lecomte†, Webb & Le Foll ('11).



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.

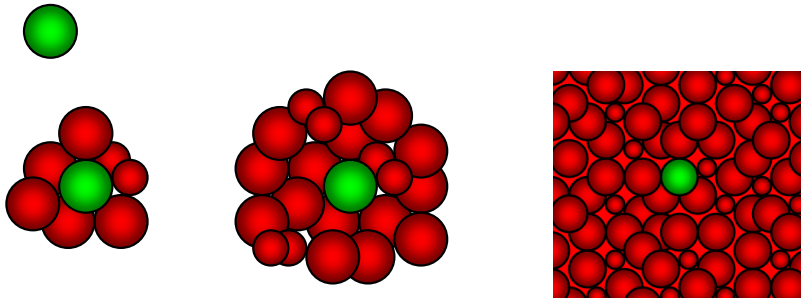
C, CD133+ tumor cells proliferated in culture as nonadherent spheres, whereas CD133- tumor cells adhered to culture dishes, did not proliferate and did not form spheres.

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

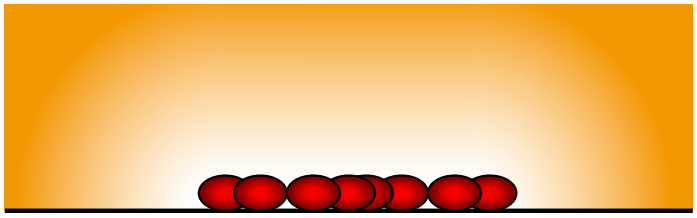
Pressure for growth (Nonlocal pressure)

$$\overline{p}(t,x) = \int_\Omega K(x,y)p(t,y)dy.$$

•Contact inhibition of growth

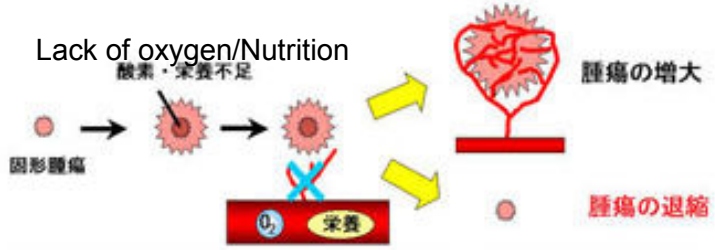


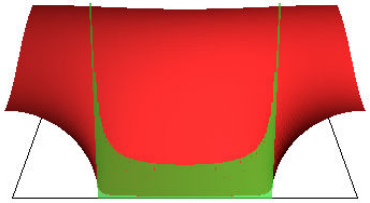
•Supply and demand for Nutrition or Oxygen



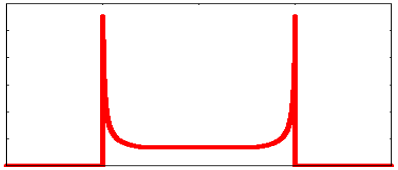
Sufficient supply ⟷ Excess of demand over supply

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.

$u(t,x,s)$: population density of proliferating cells.

$v(t,x,s)$: population density of quiescent cells.

t : time,

x : spatial position,

s : cell size.

$m(t,x) = \int_0^{+\infty} s\,[u+v]\,(t,x,s)ds$: density of mass.

$p(t,x) = m(t,x)$: pressure for motility, $\overline{p}(t,x) = \int_\Omega K(x,y)m(t,y)dy$: pressure for growth.

$$\begin{cases} u_t = \underbrace{\mathrm{div}_x\left(u\nabla_x p\right)}_{\text{cell motility}} - \underbrace{\partial_s\left[g(s)u\right]}_{\text{cell size growth}} - \underbrace{\beta_u\left(\overline{p}(t,x),s\right)u}_{\text{to quiescence}} + \underbrace{\beta_v\left(\overline{p}(t,x),s\right)v}_{\text{from quiescence}} \\ \qquad + \underbrace{4b\left(2s\right)u(t,x,2s) - b(s)u(t,x,s)}_{\text{fission}} - \underbrace{\mu(s)u(t,x,s)}_{\text{mortality}}, \\ v_t = \underbrace{\mathrm{div}_x\left(v\nabla_x p\right)}_{\text{cell motility}} + \underbrace{\beta_u\left(\overline{p}(t,x),s\right)u}_{\text{from proliferation}} - \underbrace{\beta_v\left(\overline{p}(t,x),s\right)v}_{\text{to proliferation}} - \underbrace{\mu(s)v(t,x,s)}_{\text{mortality}}. \end{cases}$$

$$t>0,\ x\in\Omega,\ s>0.$$

$g(s)$: cell size growth rate, $\mu(s)$: mortality rate,

$\beta_u(p,s)$: non-decreasing function for transition form proliferation to quiescence,

$\beta_v(p,s)$: non-increasing function for transition form quiescence to proliferation,

$b(s)$: division rate s.t. $b\left(s\right) = \begin{cases} 0 & \text{if } s \le s_f, \\ \geq 0 & \text{if } s_f < s. \end{cases}$

The cells cannot divide before they have reached a size s_f .

Fast transition

We assume that the dynamics of transition to and from quiescence and proliferation are fast compared to the other dynamics.

$$\begin{cases} u_t = \mathrm{div}_x\left(u\nabla_x p\right) - \partial_s\left[g(s)u\right] - \varepsilon^{-1}\beta_u\left(\overline{p}(t,x),s\right)u + \varepsilon^{-1}\beta_v\left(\overline{p}(t,x),s\right)v \\ \qquad + 4b\left(2s\right)u(t,x,2s) - \left(b(s)+\mu(s)\right)u(t,x,s) \\ v_t = \mathrm{div}_x\left(v\nabla_x p\right) + \varepsilon^{-1}\beta_u\left(\overline{p}(t,x),s\right)u - \varepsilon^{-1}\beta_v\left(\overline{p}(t,x),s\right)v - \mu(s)v(t,x,s), \end{cases}$$

where $0 < \varepsilon << 1$.

Taking a formal limit as $\varepsilon \searrow 0$, $\quad \beta_u\left(\overline{p}(t,x),s\right)u = \beta_v\left(\overline{p}(t,x),s\right)v.$

$$u(t,x,s) = G\left(\overline{p}(t,x),s\right)n(t,x,s).$$

Set $\quad n(t,x,s) := (u+v)\,(t,x,s),$: population density of total cells of size s .

$$G\left(\overline{p}(t,x),s\right) := \frac{\beta_v\left(\overline{p}(t,x),s\right)}{\beta_u\left(\overline{p}(t,x),s\right) + \beta_v\left(\overline{p}(t,x),s\right)}.$$

$$\begin{aligned} n_t = {} & \mathrm{div}_x\left(n\nabla_x p\right) - \partial_s\left[g(s)G\left(\overline{p}(t,x),s\right)n(t,x,s)\right] \\ & + 4b\left(2s\right)G\left(\overline{p}(t,x),2s\right)n(t,x,2s) - b(s)G\left(\overline{p}(t,x),s\right)n(t,x,s) \\ & - \mu(s)n(t,x,s). \end{aligned}$$

Equation for density of mass

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

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

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

$$m_t = \mathrm{div}\left(m \nabla m\right) + G\left(\overline{m}\right) \int_0^{\infty} A(\cdot, \cdot, s) ds - \mu m.$$

Here,

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

Equation for density of mass

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

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

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

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

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

Therefore, $$\int_0^{\infty} A(s)ds = gm.$$

Simplified Model

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

Assumptions

$$(\mathrm{P}) \quad \begin{cases} m_t - \Delta\phi(m) = F\left(\overline{m}\right) m & \text{in} \quad (0,\infty)\times\Omega, \\ \dfrac{\partial\phi(m)}{\partial\nu} = 0 & \text{on} \quad (0,\infty)\times\partial\Omega, \\ m(0,\cdot) = m_0 & \text{in} \quad \Omega, \end{cases}$$

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

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 $w = \phi(m) \in L^2\left(0, T; H^1(\Omega)\right)$,

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

$$\int_{Q_T} \left(\nabla w \cdot \nabla \eta - m\eta_t\right) dtdx = \int_\Omega m_0(x)\eta(0, x)dx + \int_{Q_T} \eta F\left(\overline{m}\right) mdtdx.$$

Existence and Uniqueness

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*

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

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* $\|m_0\|_{L^1} \le M$ *and* $\|m_1\|_{L^1} \le M$, *then*

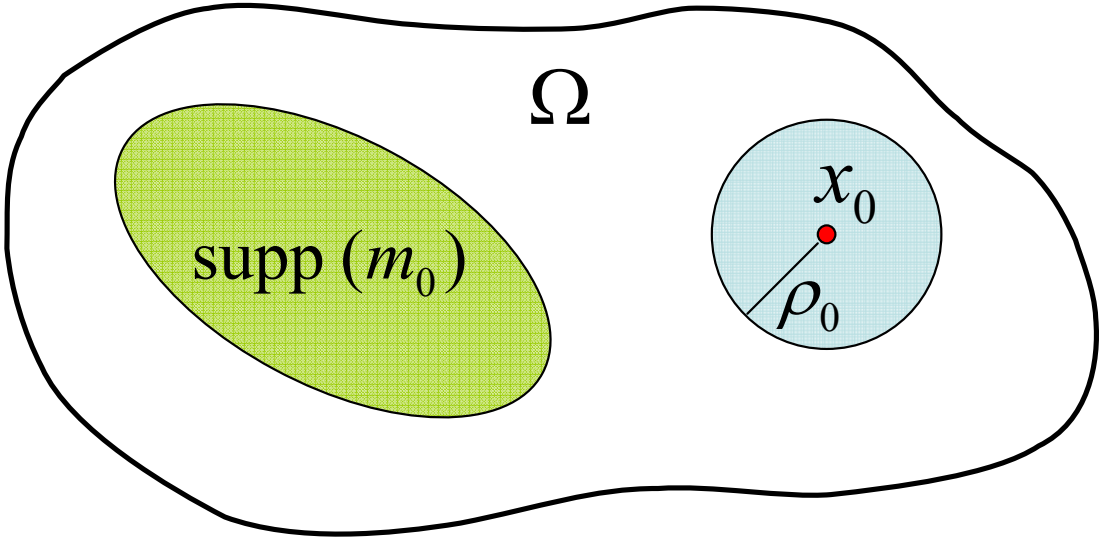
$$\|m(t,.;m_0) - m(t,.;m_1)\|_{L^1} \le \delta(T,M)\|m_0 - m_1\|_{L^1}, \quad \forall t \in [0,T].$$

Finite speed of propagation

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

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

$$m(t, x) = 0 \quad for \quad t \in [0, T^*],\ x \in B\left(x_0, \rho(t)\right).$$



Numerical experiments

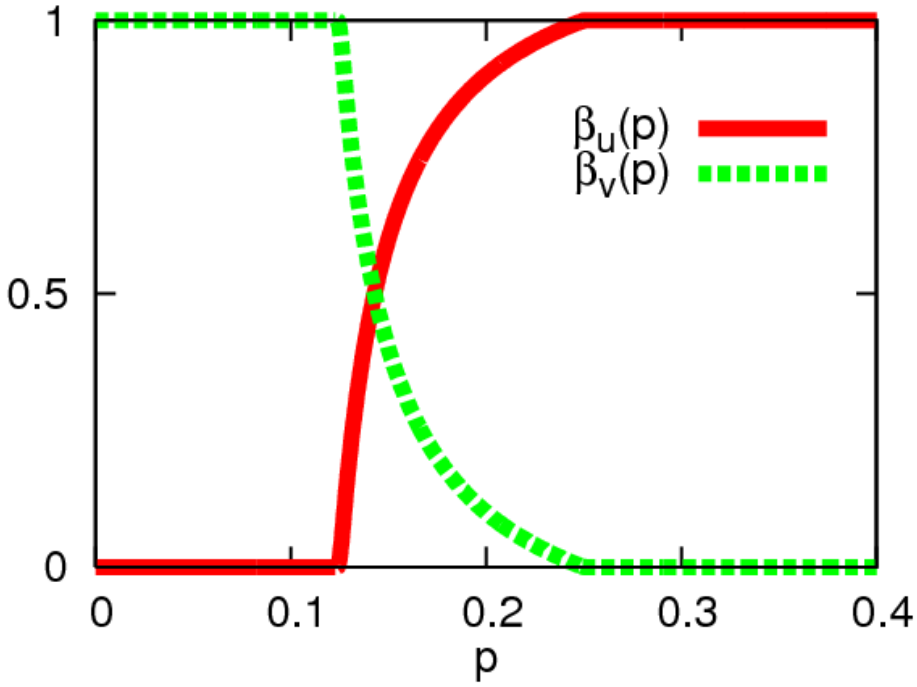
$$m_t = \frac{1}{2}\Delta m^2 + \left(gG\left(\int_\Omega K_r(\cdot, y) m(t, y) dy \right) - \mu \right) m.$$

with periodic b.c.

$$\Omega = (0, 20)^2.$$

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

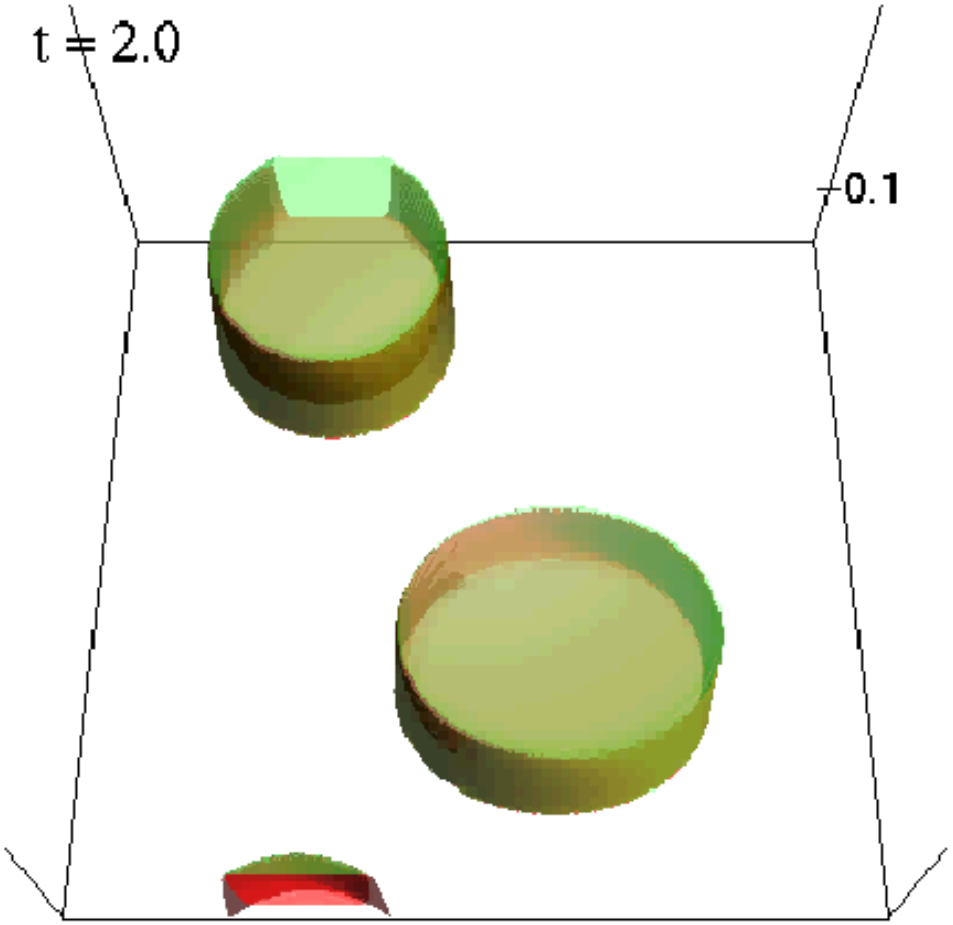
$$K_r(x, y) = \begin{cases} 1/(\pi r^2) & \text{if } |x - y| < r, \\ 0 & \text{otherwise.} \end{cases}$$



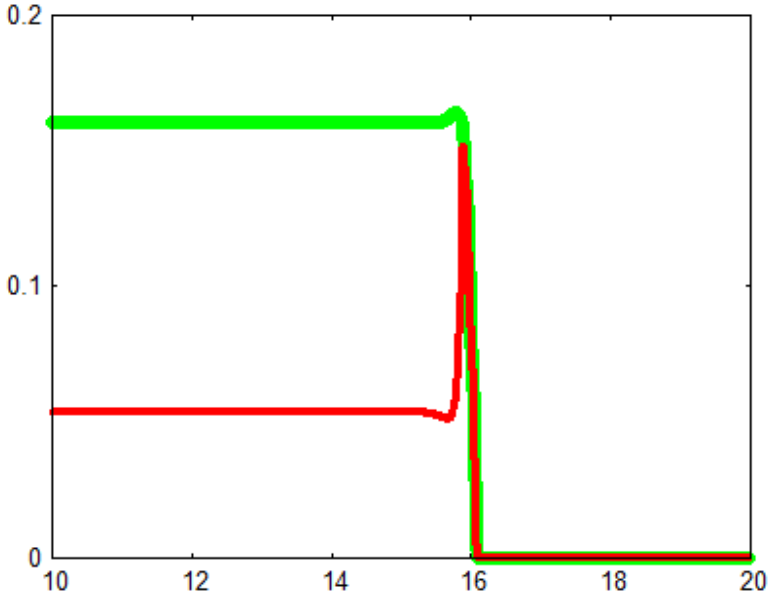
Numerical experiments

g=15, μ =5, r=0.2.

m. $u = G(\overline{m})\, m$.



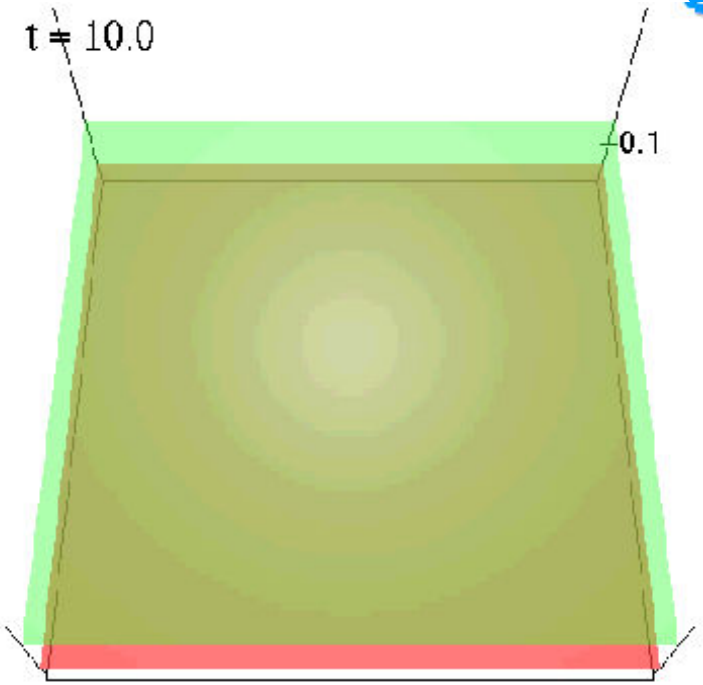
at t = 2, y=6, x∈(10,20).



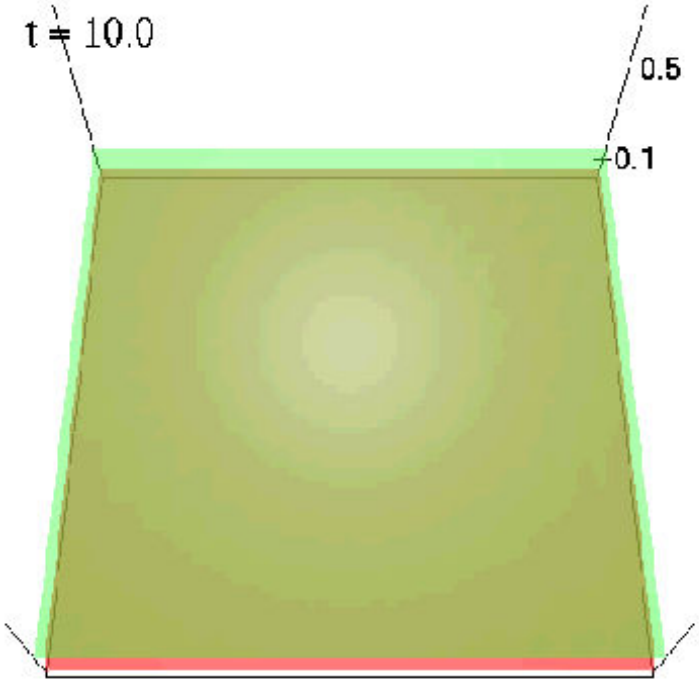
Effect of sensing radius

g = 15, μ = 5.

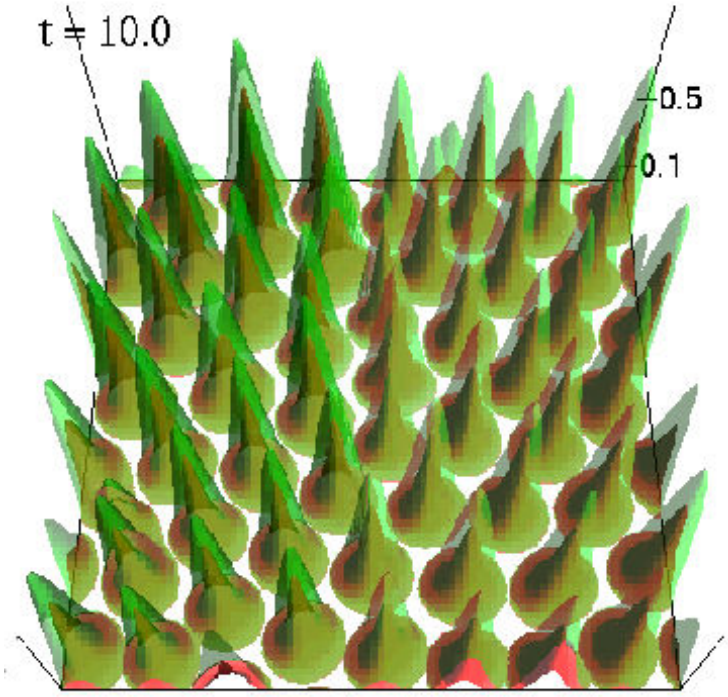
r = 0.2



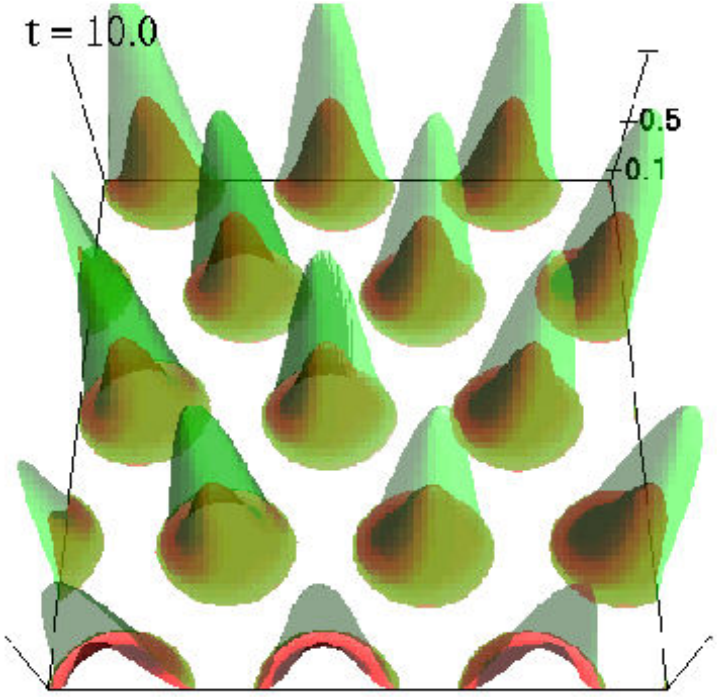
r = 1



r = 2



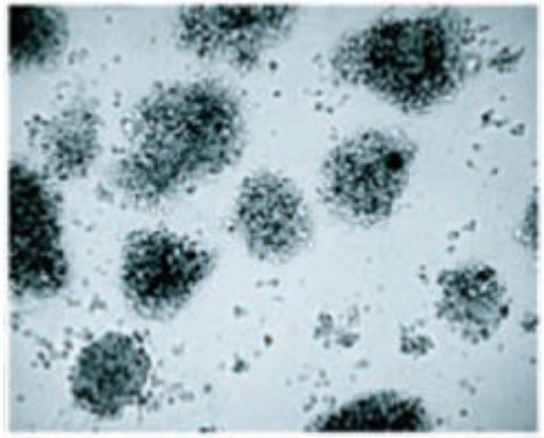
r = 4



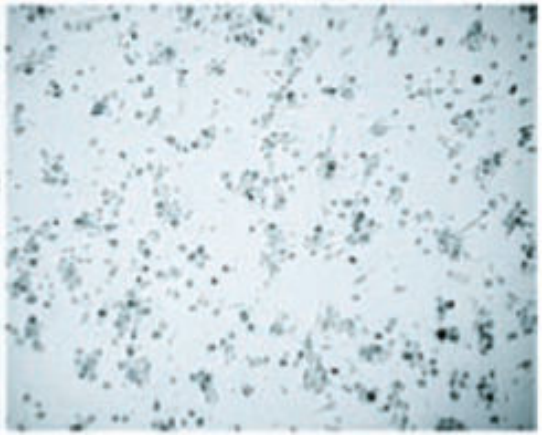
Effect of growth rate

r = 2, μ = 5.

Proliferate

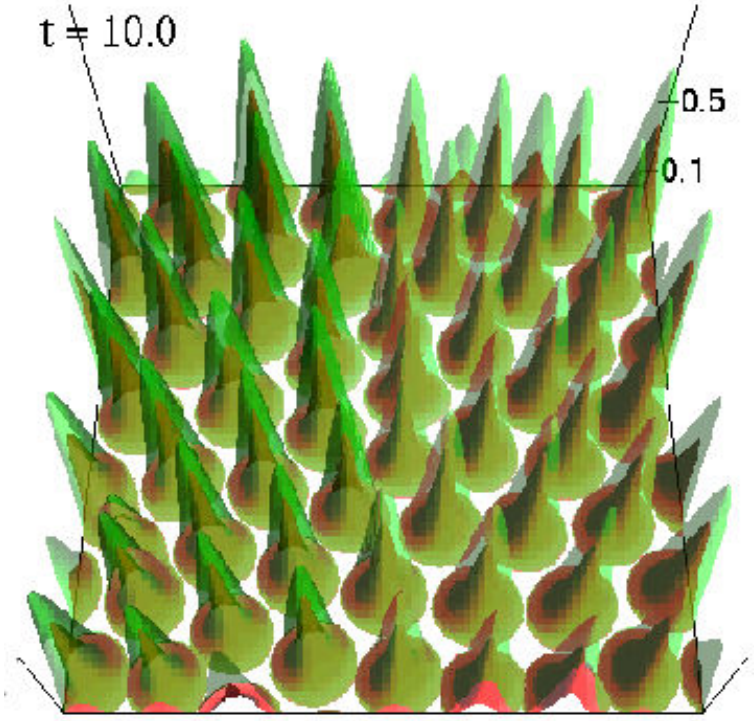


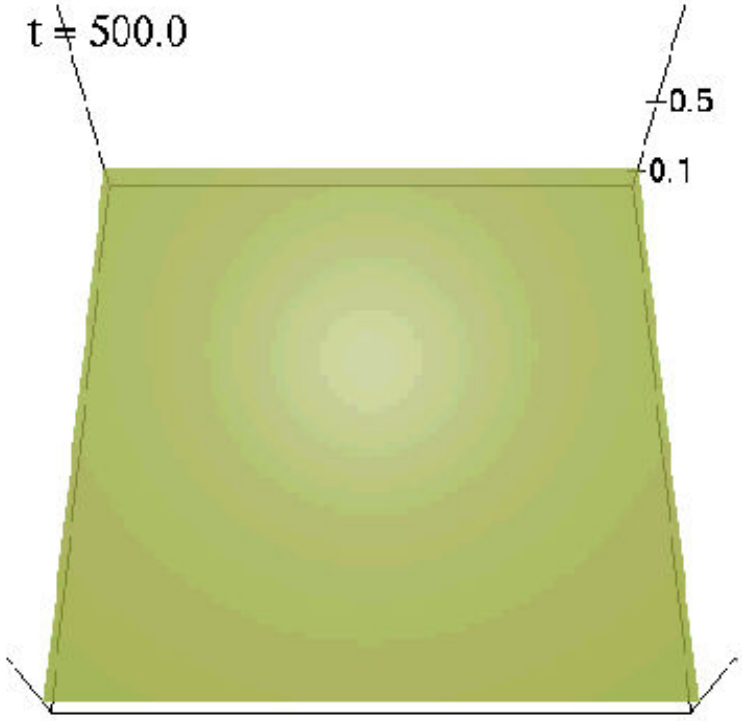
Not proliferate



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

g= 15



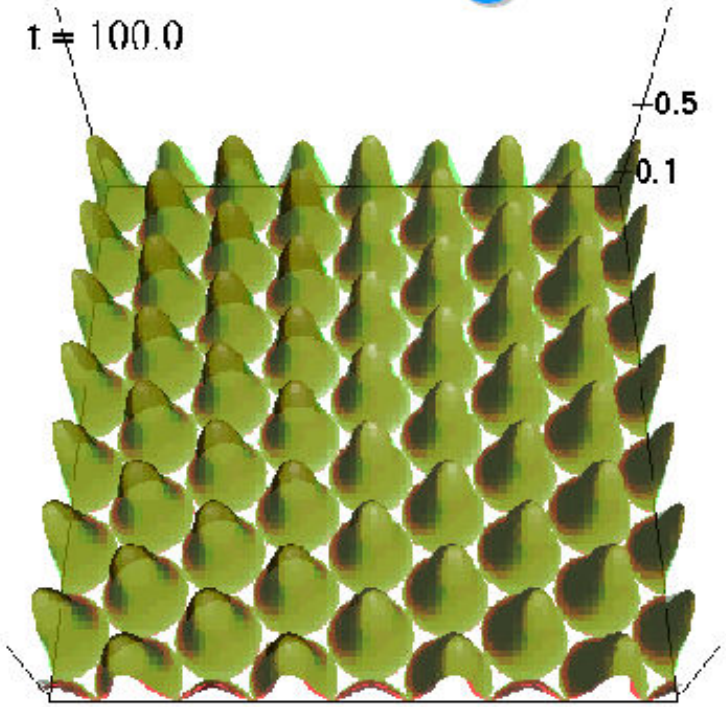


g = 5.01

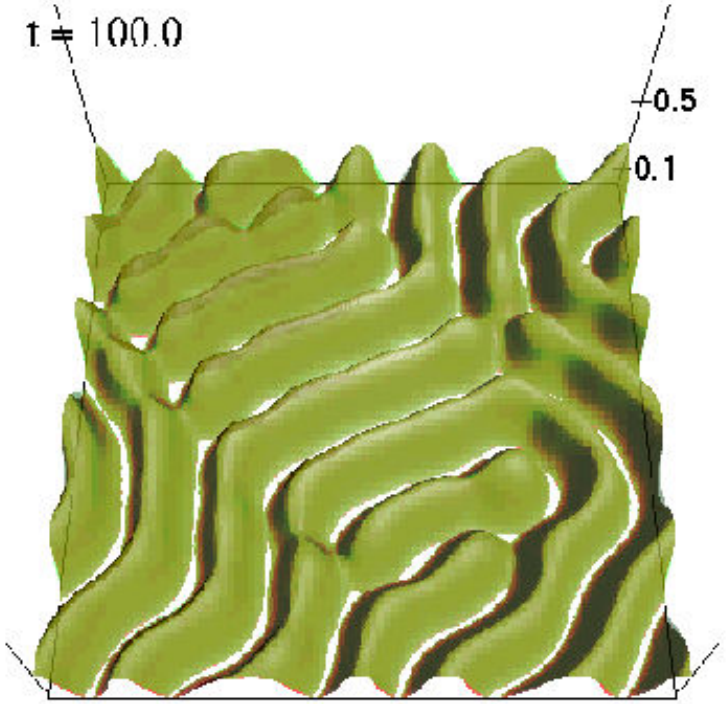
Effect of growth rate

r = 2, μ = 5.

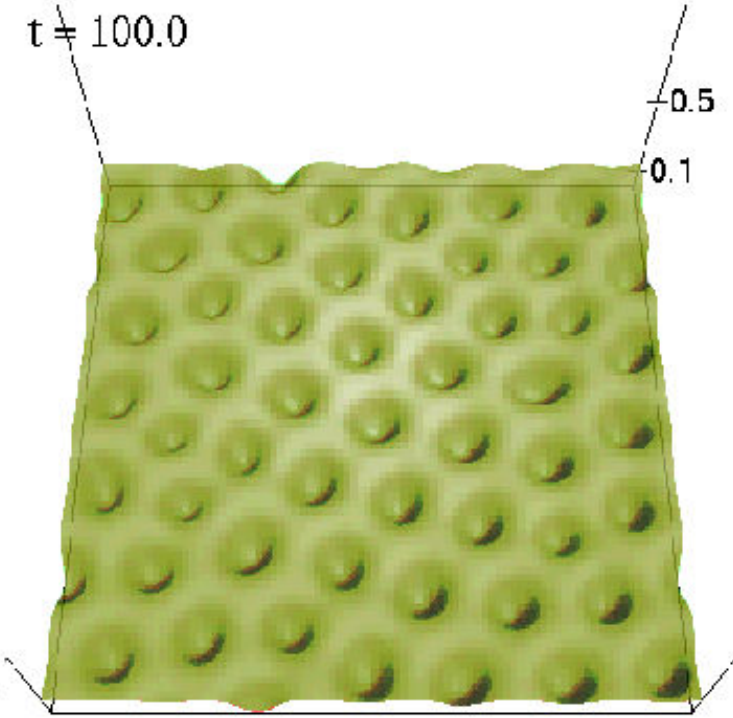
g = 6



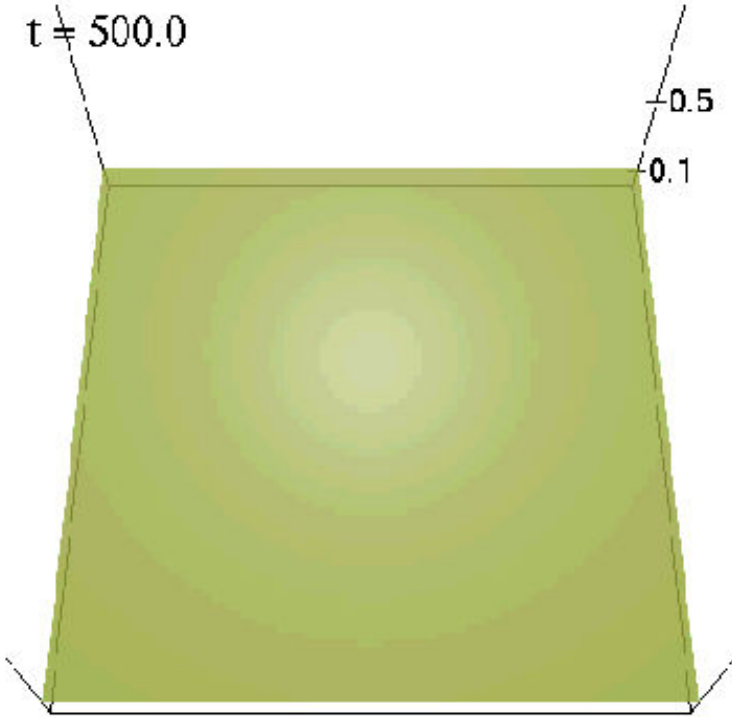
g = 5.5



g= 5.1



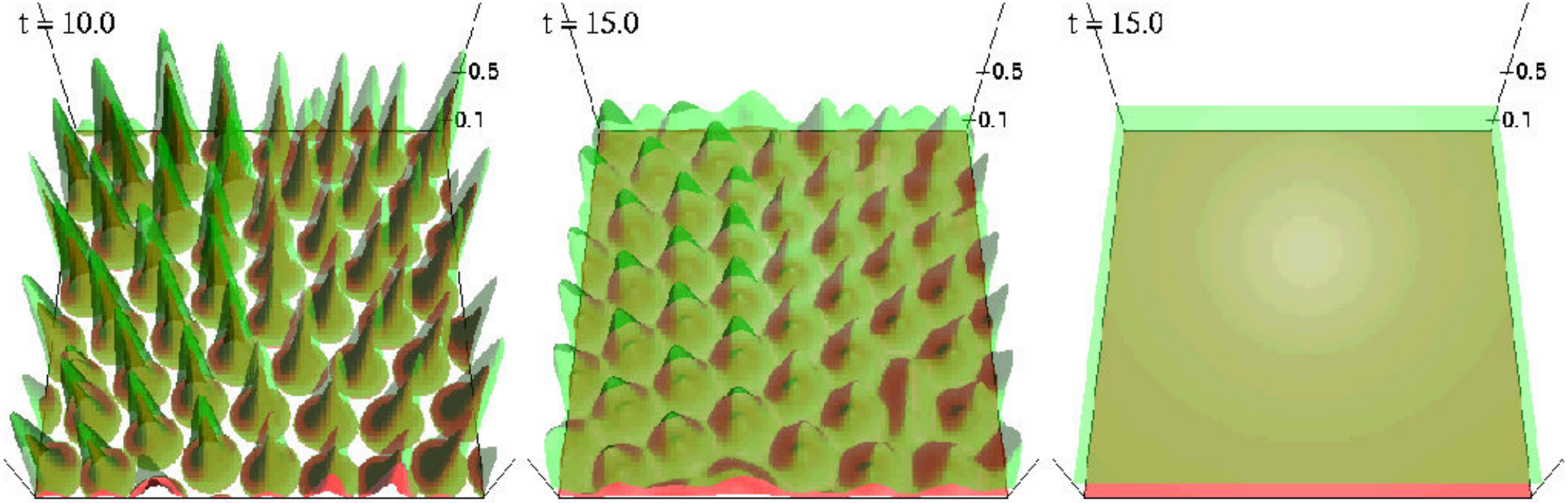
g = 5.01



Effect of mortality rate

r = 2, g = 15.

$\mu = 5$ $\mu = 2$ $\mu = 0.5$



Conclusion

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

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

$$\begin{cases} u_t = \underbrace{\mathrm{div}_x\left(u\nabla_x p\right)}_{\text{cell motility}} - \underbrace{\partial_s\left[g(s)u\right]}_{\text{cell size growth}} - \underbrace{\beta_u\left(\overline{p}(t,x),s\right)u}_{\text{to quiescence}} + \underbrace{\beta_v\left(\overline{p}(t,x),s\right)v}_{\text{from quiescence}} + \underbrace{4b\left(2s\right)u(t,x,2s) - b(s)u(t,x,s)}_{\text{fission}} - \underbrace{\mu(s)u(t,x,s)}_{\text{mortality}}, \\ v_t = \underbrace{\mathrm{div}_x\left(v\nabla_x p\right)}_{\text{cell motility}} + \underbrace{\beta_u\left(\overline{p}(t,x),s\right)u}_{\text{from proliferation}} - \underbrace{\beta_v\left(\overline{p}(t,x),s\right)v}_{\text{to proliferation}} - \underbrace{\mu(s)v(t,x,s)}_{\text{mortality}}, \end{cases}$$

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

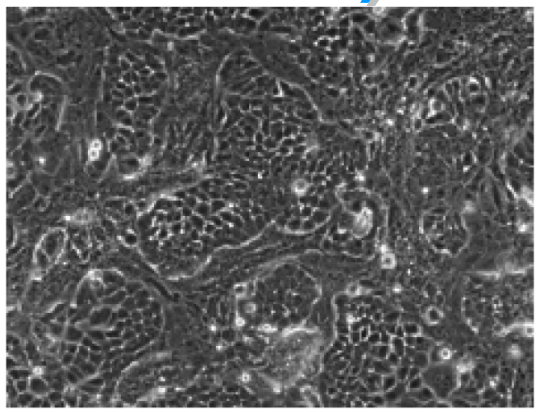
- Unique existence of the solution.
- Finite speed of propergation.

Numerical results

	Large	Small
Sensing radius	colonies	uniform distribution
growth rate		
mortality rate		

Future work (Co-cultured cells)

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



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