

# An *in vitro* cell population dynamics model incorporating cell size, quiescence, and contact inhibition

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## 1 Introduction

The objective of this paper is to analyze a population dynamics model of a proliferating cell culture in *in vitro* settings with respect to spatial movement, cell-cell interaction, cell cycle phase, and proliferative status of individual cells in the culture. Specifically, we consider a monolayer of cells occupying a two-dimensional geometry, proliferating over a time course from an initial seeding to confluence. We are particularly focused on the formation of cell colonies, or clusters of a small number of cells, that arise as a consequence of contact inhibition. We incorporate cell heterogeneity in the population by tracking the size of individual cells, which is correlated to the cell cycle. We incorporate proliferative status by tracking transition to and from quiescence of individual cells in the population.

Non-senescent replicative cells can be found in two fundamental conditions, a growing state when they progress within the cell cycle to undergo a cell division, and a quiescent state when they undertake specialized functions during periods separating consecutive mitosis. Transitions between growing and quiescent states are under complex control by cell extrinsic and intrinsic signals, and among these signals, contacts with surrounding boundaries play a central role. For decades, establishment of cell-to-cell interactions has been known to constitute a strong anti-growth signal, called Contact Inhibition of Growth (CIG) [21, 34]. This phenomenon is of first importance for organ size control during development and

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tissue regeneration after injury. Loss of this function is also recognized as a key step towards uncontrolled cell proliferation in cancer [29].

Intracellular transductions pathways coupling neighbour cell sensing to cell cycle arrest have only recently emerged [55]. It becomes therefore apparent that CIG is distinct from contact inhibition of locomotion, a process by which a motile cell changes its direction of migration upon collision with another cell [35]. CIG can be affected by the cell environment, as shown in the hormone-sensitive MCF-7 human breast cancer cell line. In this cell model, nodules of postconfluent cellular overgrowth occur under estrogen stimulation [26]. By contrast, when grown in a culture medium deprived of estrogenic-activity, MCF-7 form a regular monolayer containing only quiescent cells at confluence. MCF-7 can therefore be viewed as tumoural contact-sensitive cell lines that proliferates under constraint of CIG-induced quiescence in culture. This behavior has been recently proposed to have severe consequences on interactions between cells and on spatial organization of the monolayer population [39].

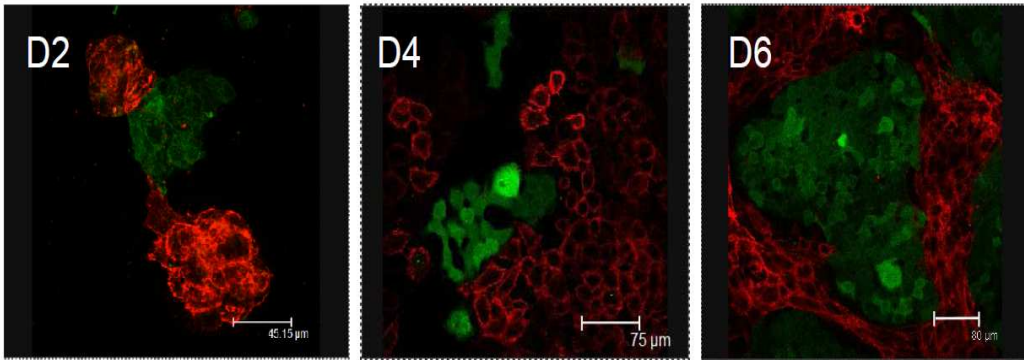


Figure 1: *Confocal imaging of cell-to-cell interactions in the human breast cancer cell line, MCF-7. MCF-7 were cytosol-tagged with the persistent probe CellTracker Green (green fluorescence, ctgMCF-7) or membrane-tagged with a phycoerythrin-conjugate antibody directed against a specific surface protein (red fluorescence, peMCF-7). A mixture of 50:50 of ctgMCF-7 and peMCF-7 was co-cultured over 6 days. Images were obtained by confocal laser scanning microscopy. Photos were taken at day 2 (D2) (scale=45.15 $\mu$ m), day 4 (D4) (scale=75.0 $\mu$ m), and day 6 (D6) (scale=80.0 $\mu$ m). Note that cells become organized into well-delimited islets over the 6-day time course.*

In [39], MCF-7 cells acquired resistance to chemotherapeutic treatments by direct transfer of a protein called *P-glycoprotein* (*P-gp*) from resistant to sensitive cells in vitro. Figure 1 shows the complexity of the spatial distribution of these cells in co-culture. The red cells correspond to resistant cells, and the green cells correspond to sensitive cells. From these experiments, it is clear that cell movement is not a linear diffusion process. Our future goal is to describe the acquired resistance of sensitive cells from resistant cells by such cell-to-cell transfer, and other direct and indirect transfer processes. Recent experiments [40] show that these transfer processes may occur at the frontiers of colonies (or islets). Therefore, in order to model general cell transfer processes, we first develop in this paper models that provide a better understanding of colony formation.

We will derive the following model for the spatial density  $m(x, t)$  of cells in mono-layer culture by

using a heuristic method to simplify the size structured - proliferative/quiescent state spatial model:

$$m_t = \kappa \operatorname{div}_x (m \nabla_x m) + b G \left( \int_{\Omega} K(x, y) m(t, y) dy \right) m(t, x) - \mu m(t, x)$$

with Neumann boundary conditions

$$\vec{\nu}(x) \cdot \nabla (m(t, x))^2 = 0, \text{ for } x \in \partial\Omega, t > 0, \Omega \subset \mathbb{R} \times \mathbb{R},$$

where  $\kappa > 0$ ,  $b > 0$ ,  $\mu > 0$ ,  $\vec{\nu}(x)$  is the outward pointing normal vector at  $x \in \partial\Omega$ ,  $G$  is a bounded locally Lipschitz continuous scalar function,  $K \in L^{\infty}_+(\Omega \times \Omega)$  is a Boltzmann kernel, and where the initial distribution is

$$m(0, \cdot) = m_0 \in L^1_+(\Omega).$$

As background references for our work here we mention that recent surveys of spatial models of cancer cell population dynamics including [2, 5, 6, 7, 10, 11, 33, 42, 43]. Recent mathematical models of contact inhibition include [1, 3, 4, 14, 18, 25, 38, 41, 45, 46, 48, 49, 50, 51]. Size structured cell population models have been studied in [13, 16, 17, 36, 22, 30, 31], and size structured models with quiescent compartments in [19, 27, 28, 44, 54]. Recent models of porous media equations related to our work here include [9, 11, 23, 24, 37, 45, 47, 32, 53, 56].

The organization of this paper is as follows: In Section 2 we present a two compartment space and size structured model consisting of proliferating and quiescent cell densities. An individual cell transitions between these compartments by sensing the total cell-mass nearby. Cell motility is modeled by nonlinear diffusion in each compartment. Individual cell growth is modeled by linear transport dependent on cell size. In Section 3 we reduce the two compartment model to one compartment through a singular perturbation of the two compartment model, under the assumption that the proliferation/quiescence transition rates are relatively fast compared to the average cell cycle time. The resulting single equation is of porous media type, but with a nonstandard nonlocal nonlinearity. In Sections 4 and 5 we provide a mathematical analysis of the porous media equation of the reduced model, using the techniques of nonlinear semigroup theory. In Section 6 we provide numerical simulations of the model applicable to *in vitro* experiments involving the formation of cell islets. In Section 7 we give a summary and discussion of our results.

## 2 The two compartment model

We define  $u(t, x, s)$ ,  $v(t, x, s)$  to be the density of proliferating (quiescent) cells at time  $t$ , spatial position  $x$ , and cell size  $s$ , respectively. Cells are located in a spatial region  $\Omega \subset \mathbb{R} \times \mathbb{R}$ . Cell proliferation in the proliferating compartment is modeled under the assumptions that cell mass is conserved during division and each daughter cell inherits exactly half the size of the mother cell. We interpret  $\Omega$  to be a micro-subregion of the well, and impose Neumann boundary conditions on its boundary. We assume that there is a finite range of division sizes  $(s_{\min}, s_{\max})$ , where  $s_{\min} > 0$ , and consequently, the minimum size of any cell is  $s_{\min}/2$ . We assume that  $2s_{\min} < s_{\max} (\Leftrightarrow s_{\min} < \frac{1}{2}s_{\max})$ . The equations of the model are

$$\begin{cases}
u_t = \underbrace{\operatorname{div}_x (u \nabla_x p)}_{\text{cell motility}} - \underbrace{\partial_s [g(s)u]}_{\text{cell size growth}} - \underbrace{\beta_u(\bar{p}(t, x), s)u}_{\text{to quiescence}} + \underbrace{\beta_v(\bar{p}(t, x), s)v}_{\text{from quiescence}} \\
\quad + 4b(2s)u(t, x, 2s) - (b(s) + \mu(s))u(t, x, s), \\
v_t = \underbrace{\operatorname{div}_x (v \nabla_x p)}_{\text{cell motility}} + \underbrace{\beta_u(\bar{p}(t, x), s)u}_{\text{birth and mortality from proliferation}} - \underbrace{\beta_v(\bar{p}(t, x), s)v}_{\text{to proliferation}} - \underbrace{\mu(s)v(t, x, s)}_{\text{mortality}}, \\
s \in (s_{\min}, s_{\max}), \quad x \in \Omega, t > 0
\end{cases} \tag{1}$$

with a non-flux boundary condition at the cell size-boundary  $s = 0$ ,

$$u(t, x, s) = 0 \text{ for } s = 0, t > 0, \text{ and } x \in \Omega,$$

and with Neumann boundary condition on  $\partial\Omega$ ,

$$\begin{cases} u(t, x, s) \vec{\nu}(x) \cdot \nabla p(t, x, s) = 0, \\ v(t, x, s) \vec{\nu}(x) \cdot \nabla p(t, x, s) = 0, \end{cases} \text{ for } s \in (s_{\min}, s_{\max}), x \in \partial\Omega, t > 0,$$

where  $\vec{\nu}(x)$  is the outward pointing normal vector at  $x \in \partial\Omega$ .

The size-dependent division function  $b$  satisfies

$$b(s) = \begin{cases} 0, & \text{if } s \geq s_{\max} \text{ and } s \leq 2s_{\min} \\ \geq 0, & \text{if } 2s_{\min} \leq s \leq s_{\max}. \end{cases}$$

the size-dependent cell growth function  $g$  is a Lipschitz continuous function satisfying

$$\begin{cases} g(s) > 0, & \text{if } s \in [s_{\min}, s_{\max}), \\ g(s) = 0, & \text{if } s = s_{\max} \text{ (whenever } s_{\max} < +\infty) \end{cases}$$

the density of cells at position  $x$  and time  $t$  is

$$m(t, x) = \int_{s_{\min}}^{s_{\max}} (u(t, x, s) + v(t, x, s)) ds,$$

the pressure on cell motility due to the density of cells at position  $x$  and time  $t$  is

$$p(t, x) = \kappa m(t, x),$$

the pressure for contact inhibition of cells due to surrounding cells modulated by a nonlocal kernel function  $K(x, y)$  is

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

$\beta_u : [0, +\infty) \times [s_{\min}, s_{\max}] \rightarrow [0, +\infty)$  is a Lipschitz continuous nondecreasing function for transition from proliferation to quiescence satisfying

$$\beta_u(0, s) = 0,$$

and  $\beta_v : [0, +\infty) \times [s_{\min}, s_{\max}] \rightarrow [0, +\infty)$  is a Lipschitz continuous nonincreasing function for transition from quiescence to proliferation satisfying

$$\begin{cases} \beta_v(p, s) > 0, & \text{if } p < p^* \\ \beta_v(p, s) = 0, & \text{if } p \geq p^*. \end{cases}$$

We summarize the variables and parameters of the model in Table 1.

Symbol	Interpretation
$x$	spatial position
$s$	cell size
$t$	time
$g(s)$	growth rate of proliferating cells
$b(s)$	division rate of proliferating cells
$\mu(s)$	mortality rate of proliferating and quiescent cells
$\beta_u(p, s)$	rate at which growing cells become quiescent cells
$\beta_v(p, s)$	rate at which quiescent cells become growing cells
$u(t, x, s)$	spatial and size density of growing cells
$v(t, x, s)$	spatial and size density of quiescent cells
$m(t, x) = \int_0^{+\infty} [u + v](t, x, s) ds$	spatial density of all cells
$p(t, x) = \kappa m(t, x)$	spatial density motility pressure
$\int_0^{+\infty} s [u + v](t, x, s) ds$	spatial density of total cell mass
$\bar{p}(t, x) = \int_{\Omega} K(x - y) m(t, y) dy$	spatial density contact inhibition pressure

**Table 1.** List of parameters of the models

### 3 The one compartment porous media model

We now assume that the dynamics of transition to and from quiescence and proliferation are fast compared to the other dynamics of the model. We can then rewrite the two compartment system equations (1) as follows:

$$\begin{cases} u_t = \operatorname{div}_x (u \nabla_x p) - \partial_s [gu] - \varepsilon^{-1} \beta_u (\bar{p}(t, x), s) u + \varepsilon^{-1} \beta_v (\bar{p}(t, x), s) v \\ \quad + 4b(2s) u(t, x, 2s) - (b(s) + \mu(s)) u(t, x, s) \\ v_t = \operatorname{div}_x (v \nabla_x p) + \varepsilon^{-1} \beta_u (\bar{p}(t, x), s) u - \varepsilon^{-1} \beta_v (\bar{p}(t, x), s) v - \mu(s) v(t, x, s) \end{cases} \quad (2)$$

where  $0 < \varepsilon \ll 1$ .

By taking a formal limit when  $\varepsilon \searrow 0$  in the second equation of system (2), we obtain

$$\beta_u (\bar{p}(t, x), s) u - \beta_v (\bar{p}(t, x), s) v = 0 \Leftrightarrow u = \frac{\beta_v (\bar{p}(t, x), s)}{\beta_u (\bar{p}(t, x), s)} v,$$

and thus

$$u + v = \left( 1 + \frac{\beta_u (\bar{p}(t, x), s)}{\beta_v (\bar{p}(t, x), s)} \right) u.$$

Therefore we formally obtain

$$u = \frac{\beta_v (\bar{p}(t, x), s)}{\beta_u (\bar{p}(t, x), s) + \beta_v (\bar{p}(t, x), s)} (u + v). \quad (3)$$

Now set

$$n(t, x, s) := (u + v)(t, x, s),$$

and

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

By using (3) we obtain

$$u(t, x, s) = G(\bar{p}(t, x), s) n(t, x, s), \quad (4)$$

and by summing the two equation of system (2) we obtain formally

$$n_t = \operatorname{div}_x (n \nabla_x p) - \partial_s [gu] + 4b(2s) u(t, x, 2s) - bu - \mu n.$$

Thus, by using (4) we obtain

$$\begin{aligned} n_t = & \operatorname{div}_x (n \nabla_x p) - \partial_s [g(s)G(\bar{p}(t, x), s) n(t, x, s)] \\ & + 4b(2s) G(\bar{p}(t, x), 2s) n(t, x, 2s) - b(s)G(\bar{p}(t, x), s) n(t, x, s) \\ & - \mu(s)n(t, x, s). \end{aligned} \quad (5)$$

We observe that the function  $G : [0, +\infty) \times [s_{\min}, +\infty) \rightarrow [0, +\infty)$

$$G(p, s) = \frac{\beta_v(p, s)}{\beta_u(p, s) + \beta_v(p, s)} \in [0, 1] \quad (6)$$

can be interpreted as the growth fraction of cells, that is, the ratio of proliferating to quiescent cells in the culture. Thus, whenever the transfer rate from proliferation to non-proliferation is a relatively fast process compared to the growth rate of cells, we can reduce the two compartment model to a one compartment model.

In order to derive a porous media equation, we make the following simplifying assumptions:

**Assumption 3.1** *We assume that*

$$s_{\min} = 0, \text{ and } s_{\max} = +\infty,$$

*and we assume that*

$$\mu(s) = \mu, b(s) = b, G(\cdot, s) = G(\cdot)$$

*are constant function of  $s \geq 0$ .*

Under the above assumption, we obtain

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

with the boundary condition

$$n(t, x, 0) = 0.$$

By integrating  $s \rightarrow n(t, x, s)$  over  $(0, +\infty)$ , we obtain

$$m_t = \kappa \operatorname{div}_x (m \nabla_x m) + b G \left( \int_{\Omega} K(x, y) m(t, y) dy \right) m(t, x) - \mu m(t, x)$$

with Neumann boundary conditions

$$\vec{\nu}(x) \cdot \nabla (m(t, x))^2 = 0, \text{ for } x \in \partial\Omega \text{ and } t > 0.$$

## 4 Existence of global weak solutions

In this section, let  $\Omega \subset \mathbb{R}^N$ , a bounded and regular (at least  $C^2$ ) domain, and consider the following problem:

$$\begin{aligned} p_t - \Delta \phi(p) &= pF(\bar{p}(t, x)), \quad t > 0, \quad x \in \Omega, \\ \vec{\nu}(x) \cdot \nabla \phi(p) &= 0 \text{ on } \partial\Omega, \\ p(0, \cdot) &= p_0(\cdot) \in L^1_+(\Omega) \geq 0, \end{aligned} \tag{7}$$

where we have set

$$\phi(p) = \frac{1}{2}p^2, \text{ and } F(s) = G(s) - \mu,$$

where  $\mu > 0$  is a given constant, and by using the same notation for  $K$  and  $K/\kappa$  we have

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

and

$$K \in L^{\infty}_+(\Omega \times \Omega).$$

We will assume that

**Assumption 4.1**  $G : [0, \infty) \rightarrow [0, \infty)$  is bounded and locally Lipschitz continuous.

In the sequel, for each  $T > 0$  consider the cylinder  $Q_T \subset \mathbb{R} \times \mathbb{R}^N$  defined by

$$Q_T = [0, T] \times \Omega.$$

Moreover for each  $0 < \tau < T$  we set  $Q(\tau, T)$  to be the cylinder defined by  $Q(\tau, T) = (\tau, T) \times \Omega$ .

**Definition 4.2 (Weak solution)** A measurable function  $p : [0, \infty) \times \Omega \rightarrow \mathbb{R}^+$  is a global weak solution of (7) if for each  $T > 0$

- (i)  $p \in L^1(Q_T)$  and  $w = \phi(p) \in L^1(0, T; W^{1,1}(\Omega))$ ,
- (ii)  $u$  satisfies for each  $\eta \in C^1(\overline{Q_T})$  such that  $\eta(T, \cdot) \equiv 0$

$$\int_{Q_T} (\nabla w \cdot \nabla \eta - p\eta_t) dt dx = \int_{\Omega} p_0(x)\eta(0, x)dx + \int_{Q_T} \eta p F(\bar{p}) dt dx.$$

**Definition 4.3 (weak energy solution)** A global weak solution  $p$  of (7) is said to be a weak energy solution if  $w = \phi(p)$  satisfies

$$\nabla w \in L^2((0, T) \times \Omega), \quad \forall T > 0.$$

**Theorem 4.4** For each  $p_0 \in L^3_+(\Omega)$  there exists a unique global weak energy solution  $p \equiv p(t, x; p_0)$  of (7) such that

$$p \in L^{\infty}_{loc}([0, \infty); L^3(\Omega)), \quad p \in C([0, \infty); L^1(\Omega)).$$

Moreover for each  $M > 0$  and each  $T > 0$  there exists  $\delta = \delta(T, M) > 0$  such that for each  $p_0, p_1 \in L^3_+(\Omega)$ , if  $\|p_0\|_{L^1} \leq M$  and  $\|p_1\|_{L^1} \leq M$ , then

$$\|p(t, \cdot; p_0) - p(t, \cdot; p_1)\|_{L^1} \leq \delta(T, M)\|p_0 - p_1\|_{L^1}, \quad \forall t \in [0, T]. \tag{8}$$

**Corollary 4.5** *There exists a unique continuous semiflow  $\{U(t)\}_{t \geq 0}$  acting from  $L^1_+(\Omega)$  into itself such that for each  $p_0 \in L^3_+(\Omega)$  the map  $t \rightarrow U(t)p_0$  is the unique energy solution of (7).*

The proof of this result follows directly from (8) by using a simple classical extension argument. The solutions constructed above correspond to limit solutions constructed by Vásquez in [52].

**Proof of Theorem 4.4.** Let  $\{p_{0,n}\} \subset \mathcal{D}_+(\Omega)$  be a sequence such that

$$p_{0,n} \rightarrow p_0 \text{ in } L^3(\Omega).$$

For each  $k > 0$ , consider the sequence  $\{p_{0,n}^k := \min\{p_{0,n}, k\}\}_{n \geq 0} \subset C(\overline{\Omega})$ , so that

$$\begin{aligned} p_{0,n}^k &\rightarrow p_0^k := \min\{p_0, k\} \text{ in } L^1(\Omega), \\ \sup_{n \geq 0, k > 0} \int_{\Omega} (p_{0,n}^k)^3(x) dx &< \infty \end{aligned}$$

For each  $k > 0$  and each  $n \geq 0$ , we consider the regularized problem:

$$\begin{aligned} p_t - \Delta \phi_n(p) &= pF(\overline{p}(t, x)), \quad t > 0, \quad x \in \Omega, \\ \frac{\partial \phi_n(p)}{\partial \nu} &= 0 \text{ on } \partial\Omega, \\ p(0, \cdot) &= p_{0,n}^k(\cdot) \geq 0, \end{aligned} \tag{9}$$

where we have set for each  $n \geq 1$ :  $\phi_n(s) = \phi(s + \frac{1}{n})$ .

From standard results for non-degenerate quasilinear parabolic equation, (9) has a globally defined classical solution, denoted by  $p_n^k$ , for each  $n \geq 0$  and each  $k > 0$ . We aim to pass to the limit first as  $n \rightarrow \infty$  and then as  $k \rightarrow \infty$  to obtain a global weak energy solution of (7).

Let us first fix the value of  $k > 0$ , and notice that integrating (9) over  $\Omega$  leads to

$$\int_{\Omega} p_n^k(t, x) dx \leq \int_{\Omega} p_{0,n}^k(x) dx e^{Mt}. \tag{10}$$

where  $M > 0$  is such that

$$F(s) \leq M, \quad \forall s \in \mathbb{R}.$$

On the other hand, from a standard comparison principle, one has

$$p_n^k(t, x) \leq \sup_{x \in \Omega} p_{0,n}^k(x) e^{Mt}. \tag{11}$$

We will now omit explicitly writing the dependence with respect to  $k$ , that is,  $p_n \equiv p_n^k$ .

Next, multiplying (9) by  $\phi_n(p_n)$  and integrating over  $\Omega$  leads to

$$\frac{d}{dt} \int_{\Omega} \Psi_n(p_n) dx + \int_{\Omega} |\nabla \phi_n(p_n)|^2 dx = \int_{\Omega} \phi_n(p_n) p_n F(\overline{p}_n(t, x)) dx,$$

where we have set

$$\Psi_n(s) = \int_0^s \phi_n(l) dl.$$



Note now that for each  $n \geq 1$  and each  $s \geq 0$  we have

$$s\phi_n(s) \leq \frac{1}{2} \left( s + \frac{1}{n} \right)^3 \leq \frac{1}{2} \left( 6\Psi_n(s) + \frac{1}{n} \right).$$

Therefore we obtain

$$\frac{d}{dt} \int_{\Omega} \Psi_n(p_n) dx + \int_{\Omega} |\nabla \phi_n(p_n)|^2 dx \leq 3M \int_{\Omega} \left( \Psi_n(p_n) + \frac{1}{6n} \right) dx.$$

This implies from Gronwall's inequality that for each  $t \geq 0$  and each  $n \geq 0$ :

$$\int_{\Omega} \Psi_n(p_n(t, x)) dx + \frac{1}{6n} \leq \int_{\Omega} \Psi_n(p_{0,n}(x)) dx e^{3Mt}, \quad (12)$$

and therefore that for each  $t \geq 0$  and each  $n \geq 0$ .

$$\int_0^t \int_{\Omega} |\nabla \phi_n(p_n(t, x))|^2 dx \leq \int_{\Omega} \Psi_n(p_{0,n}(x)) dx e^{3Mt}. \quad (13)$$

We will now obtain estimates of the time derivative. Consider a time cut-off function  $\zeta \in \mathcal{D}_+(0, \infty)$  and the function  $w_n = \phi_n(p_n)$ . Multiplying (9) by  $\zeta(t)w_{nt}$  and integrating over  $\Omega$  leads to

$$\zeta(t) \int_{\Omega} w_{nt} p_{nt} + \int_{\Omega} \zeta(t) \frac{d}{dt} |\nabla w_n|^2 = \zeta(t) \int_{\Omega} w_{nt} p_n F(\bar{p}_n(t, x)).$$

Integrating this last equality over  $(0, \infty)$  leads to

$$\int_0^{\infty} \zeta(t) \int_{\Omega} w_{nt} p_{nt} - \int_0^{\infty} \int_{\Omega} \zeta'(t) |\nabla w_n|^2 = \int_0^{\infty} \int_{\Omega} \zeta(t) w_{nt} p_n F(\bar{p}_n).$$

Recalling from (11) that for each  $T > 0$  there exists some constant  $C_T = C_T(k)$  such that

$$p_n(t, x) \leq C_T \quad \forall t \in (0, T], \quad x \in \Omega,$$

we have

$$w_{nt} p_{nt} = \phi'_n(p_n) |p_{nt}|^2, \quad |w_{nt}|^2 = |\phi'_n(p_n) p_{nt}|^2.$$

Thus for each  $T > 0$  there exists some constant  $M_T$  such that

$$M_T |w_{nt}|^2 \leq w_{nt} p_{nt} \quad t \in (0, T].$$

Let  $\tau \in (0, T)$  are given and let  $\zeta \in \mathcal{D}_+(0, \infty)$  be given such that

$$\zeta(t) = \begin{cases} 1 & \text{if } t \in (\tau, T) \\ 0 & \text{if } t < \tau/2 \text{ and } t > 2T \end{cases}.$$

Then we get

$$M_{2T} \int_Q \zeta(t) |w_{nt}|^2 dt dx \leq \int_Q \zeta'(t) |\nabla w_n|^2 + C_{2T} M \int_Q \zeta(t) |w_{nt}|.$$

Recalling (13), there exists some constant  $M(\tau, T) > 0$  such that for each  $n \geq 1$

$$\int_Q \zeta'(t) |\nabla w_n|^2 dt dx \leq M(\tau, T).$$

This leads us to

$$\frac{M_{2T}}{2} \int_Q \zeta(t) |w_{nt}|^2 dt dx \leq M(\tau, T) + \frac{M_{2T}^{-1} C_{2T}^2 M^2}{2} \int_Q \zeta(t) dt dx,$$

which implies that for  $0 < \tau < T$ , there exists  $\widehat{M}(\tau, T) = \widehat{M}^k(\tau, T)$  such that for each  $n \geq 1$

$$\int_\tau^T \int_\Omega |w_{nt}|^2 \leq \widehat{M}(\tau, T).$$

Before passing to the limit as  $n \rightarrow \infty$  we mention the following  $L^1$ -contraction principle that will be used in the sequel: From the results in [52], Chapters 5 and 11, for each  $k, k' > 0$ , each  $n \geq 1$  and each  $t \geq 0$ , one has

$$\|p_n^k(t) - p_n^{k'}(t)\|_{L^1(\Omega)} \leq \|p_{n0}^k(\cdot) - p_{n0}^{k'}(\cdot)\|_{L^1(\Omega)} + \int_0^t \|f_n^k(t) - f_n^{k'}(t)\|_{L^1(\Omega)}, \quad (14)$$

where we have set for each  $k > 0$  and  $n \geq 1$

$$f_n^k(t, x) = p_n^k F(\overline{p_n^k}).$$

Let  $k > 0$  be given. The sequence  $\{w_n := \phi_n(p_n)\}$  is bounded in  $L^2(Q_T)$  for each  $T > 0$  and in  $H^1(Q(\tau, T))$  for each  $0 < \tau < T$ . Therefore, up to a subsequence, one may assume that

$$w_n \rightarrow w \text{ when } n \rightarrow \infty,$$

almost everywhere, for the strong topology of  $L^2(Q(\tau, T))$  and weakly in  $H^1(Q(\tau, T))$  for each  $0 < \tau < T$ . As a consequence,  $p_n$  converges almost everywhere to some function  $p$  and (since uniformly bounded) strongly in  $L^p(Q_T)$  for each  $T > 0$  and each  $p \in [1, \infty)$ . As a consequence, we obtain

$$w = p^2 \text{ a.e..}$$

In addition, since  $K \in L^\infty(\Omega \times \Omega)$  we have

$$\overline{p_n} \rightarrow \overline{p} \text{ in } L^\infty(Q_T) \quad \forall T > 0,$$

and therefore

$$p_n F(\overline{p_n}) \rightarrow p F(\overline{p}) \text{ in } L^1(Q_T), \quad \forall T > 0.$$

Let  $T > 0$  be given and let  $\eta \in C^1([0, T] \times \overline{\Omega})$  such that  $\eta(T, \cdot) = 0$  be given. Then for each  $n \geq 0$  we have

$$\int_{Q_T} \eta p_{0,n}^k - \int_{Q_T} \eta_t p_n^k + \int_{Q_T} \nabla \eta \nabla w_n^k = \int_{Q_T} \eta p_n^k F(p_n^k).$$

Passing to the limit  $n \rightarrow \infty$  leads to

$$\begin{aligned} \int_{Q_T} \eta p_0^k - \int_{Q_T} \eta_t p^k + \int_{Q_T} \nabla \eta \nabla w^k &= \int_{Q_T} \eta F(p^k) \\ w^k &= (p^k)^2. \end{aligned}$$

Moreover from the  $L^1$ -contraction principle (see (14)) one gets for each  $k, k' > 0$  and each  $t \geq 0$  that

$$\|p^k(t) - p^{k'}(t)\|_{L^1(\Omega)} \leq \|p_0^k(\cdot) - p_0^{k'}(\cdot)\|_{L^1(\Omega)} + \int_0^t \|f^k(t) - f^{k'}(t)\|_{L^1(\Omega)}.$$

where we have set

$$f^k(t, x) = p^k F(\overline{p^k}).$$

Next we get that for each  $k > 0$  and each  $t \geq 0$ :

$$\begin{aligned} \int_{\Omega} (p^k)^3(t, x) dx &\leq \int_{\Omega} (p_0^k)^3(x) dx e^{3Mt}, \\ \int_0^t \int_{\Omega} |\nabla w^k|^2 dx &\leq \int_{\Omega} (p_0^k)^3(x) dx e^{3Mt}. \end{aligned} \tag{15}$$

Therefore for  $T > 0$  given, since  $K$  is bounded and  $F$  is locally Lipschitz continuous, there exists some constant  $M_T$  such that for each  $k, k' > 0$

$$\|f^k(t) - f^{k'}(t)\|_{L^1(\Omega)} \leq M_T \|p^k(t, \cdot) - p^{k'}(t, \cdot)\|_{L^1(\Omega)}.$$

Then, due to Gronwall's inequality, we obtain for each  $T > 0$  that

$$\|p^k(t) - p^{k'}(t)\|_{L^1} \leq \|p_0^k(\cdot) - p_0^{k'}(\cdot)\|_{L^1(\Omega)} e^{M_T t}.$$

Since  $p_0^k \rightarrow p_0$  in  $L^1$ , for each  $T > 0$ , the family  $\{p^k\}$  satisfies the Cauchy criteria in  $L^\infty(0, T, L^1(\Omega))$  and thus converges to some function  $p$ . Moreover due to (15) and Fatou lemma we get that  $p \in L^\infty(0, T, L^3(\Omega))$  while  $\nabla w^k$  converges weakly in  $L^2(Q_T)$  to some function  $W$ . Recalling that  $w^k = (p^k)^2 \rightarrow p^2$  a.e., we obtain that

$$\nabla p^2 \in L^2(Q_T) \text{ and } W = \nabla p^2 \text{ a.e..}$$

Then one can pass to the limit as  $k \rightarrow \infty$  into the weak formulation in order to obtain the existence of a global weak energy solution.

The uniqueness claim follows from the  $L^1$ -contraction principle for energy solutions of the porous medium equation. If we consider two solutions  $p$  and  $q$  corresponding to the same initial data  $p_0 \in L^3_+(\Omega)$  then  $p$  and  $q$  are weak energy solution of the problems

$$\begin{aligned} p_t &= \Delta \frac{p^2}{2} + f_p(t, x), \\ q_t &= \Delta \frac{q^2}{2} + f_q(t, x), \\ \nu(x) \cdot \nabla p(t, x)^2 &= \nu(x) \cdot \nabla q(t, x)^2 = 0, \\ p(0, \cdot) &= q(0, \cdot) = p_0, \end{aligned}$$

where we have set

$$f_p(t, x) = p(t, x)F(\bar{p}(t, x)), \quad f_q(t, x) = q(t, x)F(\bar{q}(t, x)),$$

which belong to  $L^1(Q_T)$  for each  $T > 0$ . Then the  $L^1$ -contraction principle implies that  $p \equiv q$  and the uniqueness follows. Moreover, using once again the regularity results given in [52], we obtain that  $p \in C([0, \infty); L^1(\Omega))$ . Finally, using the same argument, coupled together with Lipschitz continuity of  $F$ , the estimate (8) follows, and the proof of Theorem 4.4 is complete. ■

**Remark 4.6 (Finite time propagation and free boundary)** *We observe that the local vanishing property of the solutions of (7) holds true for weak energy solutions. Indeed, it is easily checked, using the comparison principle, that for each  $p_0 \in L^1_+(\Omega)$  we have*

$$0 \leq U(t)p_0 \leq S(t)p_0, \quad \forall t \geq 0, \quad (16)$$

where  $\{S(t)\}_{t \geq 0}$  is the semiflow associated with the following problem:

$$\begin{aligned} p_t - \Delta \phi(p) &= p(\|G\|_\infty - \mu), \quad t > 0, \quad x \in \Omega, \\ \frac{\partial \phi(p)}{\partial \nu} &= 0 \quad \text{on } \partial\Omega, \\ p(0, \cdot) &= p_0(\cdot) \in L^1_+(\Omega) \geq 0. \end{aligned}$$

On the other hand, if  $p_0 \in L^3_+(\Omega)$  satisfies the condition that there exists  $x_0 \in \Omega$ ,  $\rho_0 \in (0, \text{dist}(x_0, \partial\Omega))$ ,  $p_0(x) = 0$ , a.e.  $x \in B(x_0, \rho_0)$ , then from Theorem 3.1 in [15], there exists  $T^* > 0$  and a mapping  $\rho : [0, T^*] \rightarrow [0, \rho_0]$  such that  $p(t, x) = S(t)p_0$  satisfies

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

Thus, the finite time propagation of energy solutions for (7) holds true due to (16). This leads to the propagation of a free boundary  $\{x \in \Omega : (U(t)p_0)(x) = 0\}$ , at least for weak energy solutions.

## 5 Dissipation for the one dimensional case

In this section, we prove the  $L^1$ -boundedness property of the solutions of equation (7) in the one dimensional setting. More precisely we consider the following problem

$$\begin{cases} \frac{\partial p}{\partial t} = d \frac{\partial^2 p^2}{\partial x^2} + p(G(\bar{p}) - \mu), \quad t > 0, \quad x \in (0, 1), \\ \frac{\partial p^2(t, x)}{\partial x} = 0, \quad t > 0, \quad x = 0, 1, \\ p(0, \cdot) = p_0(\cdot) \in L^1_+(0, 1), \end{cases} \quad (17)$$

where  $d > 0$  is some given constant taking into account a possible rescaling due to the choice of the interval  $(0, 1)$ . We assume that

**Assumption 5.1**  $K \in L^\infty_+((-1, 1)^2)$  and there exist  $m > 0$  and  $c \in (\frac{1}{2}, 1)$  such that

$$K(x, y) \geq m \mathbf{1}_{(-c, c)}(x - y), \quad \forall (x, y) \in (0, 1)^2.$$

**Assumption 5.2**  $G : [0, \infty) \rightarrow [0, \infty)$  is locally Lipschitz continuous and bounded with  $\inf_{s \in [0, \infty)} G(s) < \mu$ . For each  $0 < \tilde{s} < \hat{s}$  large enough, there exists  $\widehat{G} : [0, \infty) \rightarrow \mathbb{R}$  decreasing and concave such that

$$\begin{aligned} G(s) &\leq \widehat{G}(s) \quad \forall s \in [0, \hat{s}], \\ \widehat{G}(\tilde{s}) &= \mu. \end{aligned}$$

**Remark 5.3** We observe that  $G$  defined in (6) satisfies the above assumption.

**Theorem 5.4** Let Assumption 5.1 and 5.2 be satisfied. For each  $p_0 \in L^1_+(0, 1)$ , there exists some constant  $\kappa > 0$  such that the global solution  $p$  of (17) satisfies

$$\int_0^1 p(t, x) dx \leq \kappa, \quad \forall t \geq 0.$$

We note that a similar result has been obtained by Perthame and Génieys [24] for a nonlocal Fisher equation. Here we prove such a result for a general nonlinear function  $G$ .

**Proof.** Consider some constant  $M > 0$  such that

$$(a^2 + b^2)^{\frac{1}{2}} \geq M(|a| + |b|), \quad \forall (a, b) \in \mathbb{R}^2. \quad (18)$$

Consider the map  $N(t) = \int_0^1 p(t, x) dx$  defined for  $t \geq 0$ . Let  $s_1 > 0$  be given such that

$$N(0) < \max(\|K\|_\infty, 1) \frac{s_1}{mM}.$$

Let  $s_2 := \max(1, \|K\|_\infty) \frac{s_1}{mM}$  and, according to Assumption 5.2, consider a map  $\widehat{G} : [0, \infty) \rightarrow \mathbb{R}$  decreasing and concave such that

$$\begin{aligned} G(s) &\leq \widehat{G}(s) \quad \forall s \in [0, s_2], \\ \widehat{G}(s_1) &= \mu. \end{aligned}$$

Then we aim to show that for each  $t \geq 0$

$$N(t) < \frac{s_1}{mM}, \quad \forall t \geq 0. \quad (19)$$

To do so, we shall argue by contradiction by assuming that there exists  $T > 0$  such that

$$\begin{aligned} N(t) &< \frac{s_1}{mM}, \quad \forall t \in [0, T], \\ N(T) &= \frac{s_1}{mM}. \end{aligned}$$

Next for all  $t \in [0, T]$  we have

$$\int_0^1 K(x, y) p(t, y) dy \leq \|K\|_\infty \frac{s_1}{mM} \leq s_2.$$

Therefore we obtain that for all  $t \in [0, T]$

$$\begin{aligned} N'(t) &= -\mu N(t) + \int_0^1 p(t, x) G \left( \int_0^1 K(x, y) p(t, y) dy \right) dx \\ &\leq -\mu N(t) + \int_0^1 p(t, x) \widehat{G} \left( \int_0^1 K(x, y) p(t, y) dy \right) dx. \end{aligned}$$

Then since  $\widehat{G}$  is decreasing we obtain that

$$N'(t) \leq -\mu N(t) + \int_0^1 p(t, x) \widehat{G} \left( m \int_0^1 1_{[-c, c]}(x - y) p(t, y) dy \right) dx.$$

Now let us notice that for each function  $f \in L_+^1(0, 1)$ , from Jensen inequality for concave maps, we have

$$\int_0^1 f(x) \widehat{G} \left( m \int_0^1 1_{[-c, c]}(x - y) f(y) dy \right) dx \leq I(f) \widehat{G} \left( \frac{m}{I(f)} \int_0^1 f(x) \int_0^1 1_{[-c, c]}(x - y) f(y) dy dx \right),$$

where we have set  $I(f) = \int_0^1 f(s) ds$ . On the other hand we have

$$\begin{aligned} \int_0^1 f(x) \int_0^1 1_{[-c, c]}(x - y) f(y) dy dx &= \int_0^1 f(x) \int_{(x-c)^+}^{(x+c)^{\wedge 1}} f(y) dy dx \\ &\geq \int_0^c f(x) \int_0^{(x+c)^{\wedge 1}} f(y) dy dx + \int_{1-c}^1 f(x) \int_{(x-c)}^1 f(y) dy dx \\ &\geq \left( \int_0^c f(x) dx \right)^2 + \left( \int_{1-c}^1 f(x) dx \right)^2. \end{aligned}$$

Due to the definition of  $M$  given in (18) we get

$$\left( \int_0^c f(x) dx \right)^2 + \left( \int_{1-c}^1 f(x) dx \right)^2 \geq M \left( \int_0^c f(x) dx + \int_{1-c}^1 f(x) dx \right)^2$$

and recalling that  $c \in (\frac{1}{2}, 1)$  leads to

$$\left( \int_0^c f(x) dx \right)^2 + \left( \int_{1-c}^1 f(x) dx \right)^2 \geq M \left( \int_0^1 f(x) dx \right)^2$$

Therefore one obtains that for each  $f \in L_+^1(0, 1)$  that

$$\int_0^1 f(x) \int_0^1 1_{[-c, c]}(x - y) f(y) dy dx \geq M \left( \int_0^1 f(x) dx \right)^2,$$

As a consequence, since  $\widehat{G}$  is decreasing, we obtain that

$$\int_0^1 f(x) \widehat{G} \left( \int_0^1 K(x, y) f(y) dy \right) \leq I(f) \widehat{G} (mMI(f)).$$

Finally we obtain that for each  $t \in [0, T]$

$$N'(t) \leq N(t) \left( \widehat{G}(mMN(t)) - \mu \right),$$

together with  $N(0) < s_1$ . From the comparison principle we obtain that

$$N(t) < s_1 \quad \forall t \in [0, T],$$

a contradiction, and the proof of Theorem 5.4 is complete. ■

## 6 Numerical simulations

Numerical simulations are given for the following simplified model of cell contact inhibition:

$$p_t = \operatorname{div}_x (p \nabla_x p) + \left[ bG \left( \int_{\Omega} K_r(x-y)p(t,y)dy \right) - \mu \right] p(t,x)$$

with periodic boundary conditions, and with

$$K_r(x) = \begin{cases} 1 & \text{if } |x| < r, \\ 0 & \text{otherwise.} \end{cases}$$

Here we fix  $\Omega = (0, L)^2$ ,  $L = 20$ ,  $\mu = 5$ ,  $b = 15$ , and we use  $r$  as a sensitivity parameter for the radius of contact inhibition pressure. We use periodic boundary conditions as approximations for Neumann boundary conditions for numerical simplicity, taking advantage of symmetry in the  $x$  and  $y$  directions. We employ the nonlinear Chernoff formula to discretize in time (see Berger et al. [8]). Moreover, we use

$$\beta_u(x) = x, \quad \beta_v(x) = 1 - \operatorname{erf}(10x),$$

$$G(x) = \frac{1 - \operatorname{erf}(10x)}{x + 1 - \operatorname{erf}(10x)}.$$

In the figures below, we use green to plot  $p(t, x)$ , and we use red to plot  $m(t, x)$ . The figures demonstrate the importance of the radius  $r$  of contact inhibition pressure. In Fig. 2 ( $r = 0.5$ ) the initial seeding does not result in the formation of colonies, but instead yields a mostly uniform spatial distribution to final confluence. In Fig. 3 ( $r = 1$ ) colonies begin to develop on the edges of the spatial regions growing from the initial seeding, but do not maintain as the population becomes confluent. In Fig. 4 ( $r = 2.0$ ) colonies develop throughout the spatial regions spreading from the initial seeding. The development of colonies in the simulations in Fig. 4 agree very well with the experimental data in Fig. 1, particularly at days 2,4,6. The importance of the sensing radius of contact inhibition pressure is clearly demonstrated. Movies of the numerical simulations are available at <http://www.math.u-bordeaux1.fr/~pmagal/cancer/cancer.htm> .

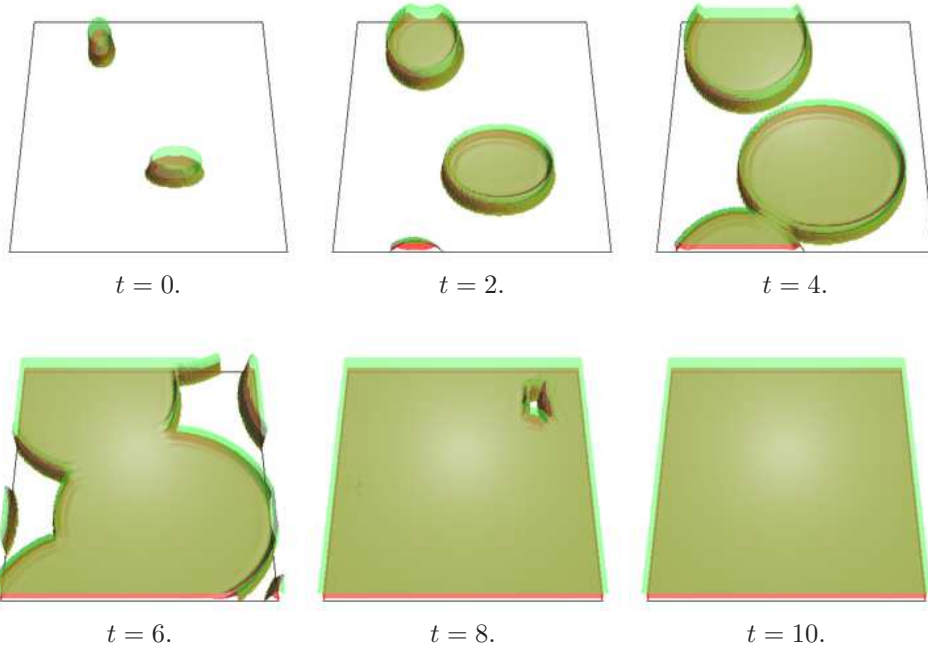


Figure 2:  $r = 0.5$ . No colonies are formed over the 10-day time course of the simulation.



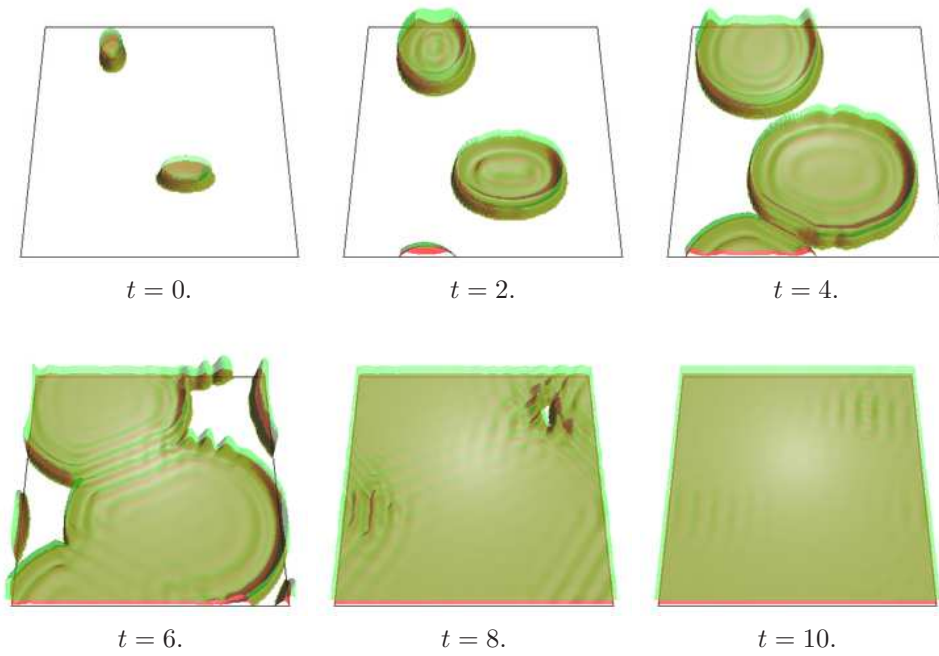


Figure 3:  $r = 1.0$ . We observe the formation of damped oscillations at the moving boundaries, but colonies are not maintained over the 10-day time course of the simulation.

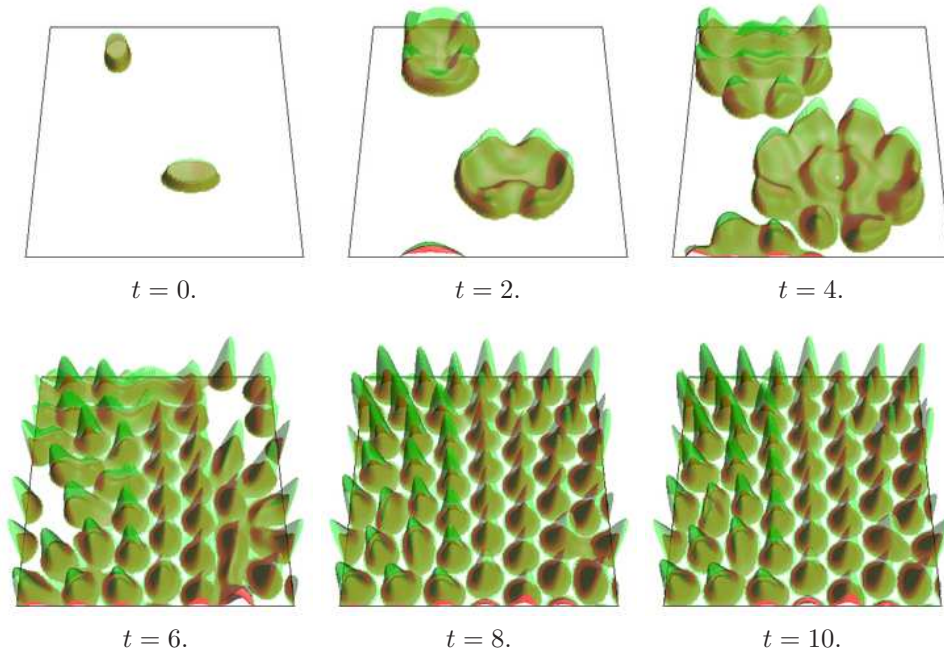


Figure 4:  $r = 2.0$ . Colonies form abundantly throughout the region after day 2 of the simulation (compare to Fig. 1).

## 7 Discussion

In this article we have developed a mathematical model describing the growth, proliferation, and spatial movement of an *in vitro* cell population using a nonlinear diffusion process (namely, the porous media term  $\operatorname{div}_x(p\nabla_x p)$ ). The growth of individual cells is constrained in the model via a nonlinear and spatially nonlocal cell proliferation process (namely, the Boltzmann term  $bG(\int_{\Omega} K_r(x-y)p(t,y)dy)$ ). Porous media equations have been used extensively in the context of cells population dynamics. The main originality of the model presented here is that we formally derive our model as a limiting case of a model incorporating quiescence and individual cell size, which are important considerations in models of cell population dynamics. Thus, we bridge more complex nonlinear models with quiescence and cell size terms to simpler models without these elements, but still including technically difficult nonlinear diffusion terms.

The main feature of the model is that due to the presence of nonlinear diffusion, we can produce spatial colonies or islets of cells with finite time propagation and free boundaries by controlling the radius contact inhibition pressure of the nonlocal proliferation term (see remark 4.6 for a theoretical explanation of this phenomenon). The formation of these clusters is demonstrated in our numerical simulations (Fig. 2, 3, 4), and compare well with what is observed in laboratory experiments (Fig. 1). In models with linear diffusion the initial data is instantaneously propagated to infinity in space, so that true clusters with compact support do not form from initial data with compact support. Another important technical

element of our analysis is that we derive the boundedness of solutions in the one dimensional case, at least in certain parameter regimes. The boundedness of solutions remains open in more general cases. As mentioned in this introduction, two types of inhibition are identified in proliferating cells lines - contact inhibition of cell motility and contact inhibition of cell growth and division. In this article we neglected the contact inhibition of locomotion, which will be considered in future work. The main challenge to cell model development is to derive models which contain the complex phenomena present in the cell biology, but are simple enough to be theoretically analyzed. An issue for future work concerns the nonlinear motility term, which should be a function of the density of mass  $m(t, x) = \int_{s_{\min}}^{s_{\max}} s (u(t, x, s) + v(t, x, s)) ds$ , and not the density of individuals. Here our choice for the population pressure on motility is motivated in the reduced model by choosing  $m(t, x) = \int_{s_{\min}}^{s_{\max}} (u(t, x, s) + v(t, x, s)) ds$ . Also left for future work is generalization of the model to describe colony formation with two classes of co-cultured cells - cells resistant to treatment and cells sensitive to treatment - a topic of major importance in optimizing cancer chemotherapy.

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