PAPER

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Effective pressure and cell area distribution in a confined monolayer

Evgeniy Khain[1,3] **and Lev S Tsimring**[2]

[1] Department of Physics, Oakland University, Rochester, MI 48309, United States of America
[2] BioCircuits Institute, UCSD, 9500 Gilman Drive, La Jolla, CA 92093-0328, United States of America

E-mail: khain@oakland.edu and ltsimring@ucsd.edu

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Abstract

Contact inhibition limits cell growth and division after they form a monolayer and make lasting contact with each other. It has been shown, however, that the cell proliferation does not stop instantaneously upon forming contacts. The newborn daughter cells continue to grow after division, however to a smaller equilibrium size; thus the average cell size dramatically decreases with time. It has also been found that the dispersion in cell sizes decreases as well. In this paper we argue that these observations can be reproduced and explained by introducing an effective pressure that affects cell growth. We present a mathematical model that predicts the temporal evolution of cell size distribution in a closed system; the theoretical predictions are in a good agreement with recent experimental observations.

Keywords: cell monolayer, effective pressure, tissue growth

(Some figures may appear in colour only in the online journal)

1. Introduction

The key feature of biological systems is their ability to adjust to the changing environment. This adaptive behavior on a microscopic (single cell) level leads to various emergent macroscopic phenomena, such as adaptive immune response (Iwasaki and Medzhitov 2010) or collective cell migration (Serra-Picamal *et al* 2012, Lee *et al* 2013, Cochet-Escartin

[3] Author to whom any correspondence should be addressed.

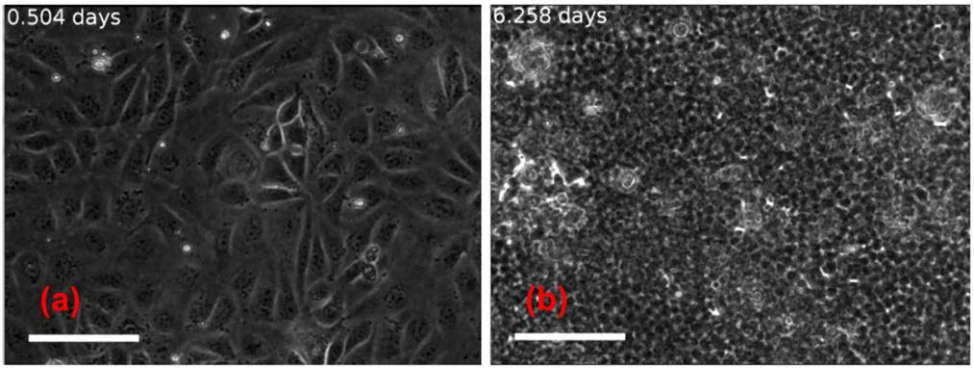

Figure 1. Epithelial cells on a substrate (Puliafito *et al* 2012), images were captured from above. Initially, cells are large ((a), half a day after the beginning of the experiment). Cells divide, their number increases, and their size dramatically decreases ((b), six days after the beginning of the experiment). The scale bar is 100 μm. Time instances are shown in the panels. These two snapshots were extracted from the movie (supplementary materials) of Puliafito *et al* (2012). Reproduced with permission from Puliafita *et al* (2012).

et al 2014, Li and Sun 2014, Zaritsky *et al* 2014, Kopf 2015, Loeber *et al* 2015, Segerer *et al* 2015) (for example, during morphogenesis (Shraiman 2005, Chiou *et al* 2012) and wound healing (Brugues *et al* 2014)). Understanding this connection between microscopic adaptivity and emergent macroscopic behavior is central to investigation of active systems. Here we focus on the cellular adaptivity to a changing mechanical environment: a cell in a dense monolayer adjusts its area due to mechanical stresses from the pushing neighboring cells.

Mechanical stresses are very important in developing tissues (Heisenberg and Bellaiche 2013, Legoff *et al* 2013). Cells both generate and respond to epithelial stresses during morphogenesis (Etournay *et al* 2015). Cell divisions generate forces that can determine flow patterns in expanding monolayers (Mather *et al* 2010, Boyer *et al* 2011, Doostmohammadi *et al* 2015). Living and growing cells in a dense monolayer may contact each other. It has been usually assumed that once cells form a monolayer, they stop dividing due to the lack of space (Eagle and Levine 1967). Experimental evidence suggests, however, that contact inhibition of growth does not occur immediately upon forming a contact with neighboring cells, but sets in gradually after a certain delay (Martz and Steinberg 1972). Recent experiments with Madin–Darby canine kidney cells have shown that cells continued dividing for a while, but the daughter cells were not able to grow to their mother cell size due to mechanical constraints (Puliafito *et al* 2012); in addition, the rate of proliferation dropped dramatically for smaller cells. As a result, the average cell size substantially decreased with time (Puliafito *et al* 2012), see figure 1, and the width of the distribution of cell sizes also decreased. A qualitatively similar behavior was observed for glioma cells (Rouzaire-Dubois *et al* 2004). Importantly, in these experiments, culture medium was frequently changed to ensure that cells had sufficient nutrients and growth factors. We hypothesize therefore, that the decrease in the average cell size can be attributed to the increase in mechanical stresses from other cells.

In this paper, however, we will not examine the detailed microscopic mechanobiology such as cellular deformations, mechanotransduction, the microscopic details of cell division and interactions between the neighboring cells. Instead, we introduce a purely phenomenological model that captures just a few basic features of the complex biological processes, see

below. In particular, we introduce the effective pressure between cells that arises in a dense monolayer when a cell growing after division pushes its neighbors. This effective pressure mimics the mechanical stresses in the system and affects cell growth. Therefore, the two crucial questions we pose in this paper are (1) whether or not this effective pressure exists in a densely packed collection of cells and (2) if yes, whether or not it affects the time evolution of the cell size distribution in the system. Puliafito *et al* (2012) considers the late stages of a long experiment, when the typical cell area is already small (smaller than 200 μm^2). Streichan (2013, 2014) presents experimental observations for the entire duration of the experiment. It was observed that for late stages of the experiment, cells did not grow after division. In this case, mechanical pressure might be less important, and so it was not taken into account in the modeling of Puliafito *et al* (2012). However, when cells are still big (at early and intermediate stages of the experiment), cells do grow after division (Streichan 2013, 2014), pushing the neighboring cells. It is clear, therefore, that the effective pressure does exist in a densely packed monolayer. Here we show that it is not only present in the system, but also significantly affects the time evolution of cell area distribution in a closed system.

This collective cell behavior becomes even more complex when the dense cell monolayer is expanding: cells near the edges are larger and migrate faster, while cells deep inside the colony are smaller and move slower (Reffay *et al* 2011, Silberzan 2014). As a first step, however, we will focus on a closed system, and assume that the cells live in a statistically uniform environment. In Puliafito *et al* (2012) and Zehnder *et al* (2015), the area distribution of cells in a monolayer was measured experimentally and the single cell dynamics was analyzed. Here we present a mathematical model for the time evolution of cell area distribution in a closed system and compare the theoretical results with experimental observations. As we discussed above, our modeling generalizes the continuum model of Puliafito *et al* (2012), taking into account pressure dependent cell growth, and thus can describe a much broader range of conditions within the tissue. The key feature of the model is the assumption that mechanical stresses equilibrate very fast over the system, so every cell 'feels' the same pressure (specifically prepared closed inhomogeneous systems are analyzed elsewhere). However, small cells (for example, daughter cells right after the division) have a stronger tendency to grow, compared to bigger cells. As a result, bigger cells in the system may shrink, to allow the newborn cells to grow.

2. The model

Consider a collection of cells that just formed a dense monolayer. The system is closed, so the overall area available to cells is fixed. We will describe the system in terms of cell area distribution function $f = f(a, t)$, which is the number of cells of area a at time t. Since the system is assumed statistically homogeneous, f does not depend on coordinates. Let us write down the continuity equation for f:

$$\frac{\partial f}{\partial t} + \frac{\partial}{\partial a}\left(f\,\frac{\mathrm{d}a}{\mathrm{d}t}\right) = -\alpha(a)f(a) + 4\,\alpha(2a)f(2a). \tag{1}$$

The left-hand side of this equation describes the evolution of the distribution due to individual cell size dynamics (specified by the $\mathrm{d}a/\mathrm{d}t$ function, see below). The right-hand side of this equation describes cell proliferation, where $\alpha(a)$ is the proliferation rate. The first term on the right-hand side represents the outflux of cells in the infinitesimal interval of cell areas $(a - \mathrm{d}a/2, a + \mathrm{d}a/2)$ due to division, and the second term on the right-hand side represents the influx of cells in the area interval $(a - \mathrm{d}a/2, a + \mathrm{d}a/2)$ due to division of cells in the area

interval $(2a - \mathrm{d}a, 2a + \mathrm{d}a)$. The factor of 4 comes from the fact that (1) for each dividing cell of area $2a$ we gain two cells of area a, and (2) cells from the interval $(2a - \mathrm{d}a, 2a + \mathrm{d}a)$ are 'mapped' into the interval $(a - \mathrm{d}a/2, a + \mathrm{d}a/2)$ which is two times smaller. The rate of cell proliferation, $\alpha(a)$, decreases as cell size becomes smaller (Puliafito *et al* 2012); we assume the following dependence: $\alpha(a) = \gamma_1(a - a_0)/(a_d - a_0)$ for $a_0 < a < a_d$. Experimental observations show that below a certain cell size ($a < a_0$), a cell can not divide ($a_0 \simeq 120\,\mu\mathrm{m}^2$, Puliafito *et al* 2012) $\alpha = 0$; above a certain size ($a > a_d$), the rate of proliferation is constant, $\alpha = \gamma_1$.

A conceptually similar continuum model for the temporal dynamics of the cell area distribution function was introduced in Puliafito *et al* (2012); however, it assumed that cells did not grow after division, $\mathrm{d}a/\mathrm{d}t = 0$. This assumption is expected to work only in the late stages of the tissue growth, when cells are so compressed that they do not have any room to grow. We are also interested in the description of earlier stages of monolayer dynamics, when cells do grow after they divide (Streichan 2013, 2014). The two models (with and without cell growth after cell division) are compared with experimental observations in figure 3, see below. Taking into account cell growth, we have to augment equation (1) by the equation describing the growth dynamics of a single cell, which we write in the following form:

$$\frac{\mathrm{d}a}{\mathrm{d}t} = c(a^*(P) - a)H(a^*(P) - a) - \delta\, P(a - a^*(P))H(a - a^*(P)). \tag{2}$$

Here H is the Heaviside step function and P is the effective dimensionless pressure in the system (a single scalar variable, because of the spatial homogeneity). The first term in the rhs of this equation describes cell growth towards a certain pressure dependent value of cell area $a^*(P)$. The second term describes cell shrinkage due to pressure if its size is greater than $a^*(P)$. It is easy to see that $a^*(P)$ is the fixed point of equation (2). This equation describes an interplay between the tendency of a cell to grow and a cell to shrink due to pressure. Since cell growth and shrinkage are controlled by different biophysical mechanisms, the rates of growth c and shrinkage δ are generally different. We assume a simple linear relationship between a^* and P, $a^*(P) = \bar{a} - s\,P$, where $\bar{a}$ is a typical cell area of individual cells without any mechanical stresses and s is a constant characterizing cell sensitivity to mechanical pressure. Although the (unknown *a priori*) pressure P is the same over the entire system, it may change with time due to cell growth. At the very early stage when cells do not touch each other, the pressure is zero, but as soon as cells form lasting contacts, the pressure begins to grow. Since our system is closed, as soon as the cells cover the substrate completely, the total area of cells remains constant. Thus, at this stage the pressure developing in the tissue can be determined by the integral constraint, namely the requirement that the total area occupied by the cells remains constant at all times,

$$\frac{\mathrm{d}}{\mathrm{d}t}\int f(a, t)a\ \mathrm{d}a = 0. \tag{3}$$

This type of modeling with an integral conservation law arises in different areas of science, for example, in phase ordering dynamics (Peleg *et al* 2001, Conti *et al* 2002).

Equations (1)–(3) do not take into account fluctuations in cell area. However, it was recently shown (Zehnder *et al* 2015) that these fluctuations are quite substantial, on average of the order of 20% (Zehnder *et al* 2015). One way of incorporating these experimental observations in the modeling would be by adding a noise term to equation (2). But in order to keep the model deterministic, we will take a different (although qualitatively similar) approach and add a linear diffusion term to the left-hand side of equation (1):

$$\frac{\partial f}{\partial t} + \frac{\partial}{\partial a}\left(f\,\frac{\mathrm{d}a}{\mathrm{d}t}\right) - D\frac{\partial^2 f}{\partial a^2} = -\alpha(a)f(a) + 4\,\alpha(2a)f(2a). \tag{4}$$

Equations (2)–(4) are solved numerically by using the following procedure. Suppose the initial cell area distribution function is given, so we know how many cells of each area there are in the system as well as the total area A_0 occupied by these cells. At the next time step, we need to find the value of the effective pressure and the new cell area distribution function. First, we find the effective pressure by solving equation (2) iteratively. Guessing some pressure value P_1, we obtain the corresponding value a_1^* and advance equation (2) by a single time step, during which some cells grow and some shrink. Then, we compute the new overall area occupied by the cells. If it is larger than A_0, the guessed pressure value was too small; if it is smaller than A_0, P_1 was too large. This procedure is performed many times until the new area after this time step becomes equal to the original area A_0. Notice that in our model, cell proliferation does not change the overall cell area. Once the correct value of P is found, equation (4) is advanced for a single time step by using third-order Runge–Kutta method, no-flux boundary conditions are implemented. The next section shows the results of computational modeling of equations (2)–(4) and their comparison with experimental observations.

3. Time evolution of cell area distribution

The model described above includes several parameters. Most of them are taken from experimental observations. The proliferation (division) rate for cells under normal conditions (without mechanical stresses) is assumed to be $\gamma_1 = 1/(18\,\mathrm{h})$ (Puliafito *et al* 2012) (although there is a broad range of proliferation rates in the literature Zehnder *et al* 2015); cells under area of $a_0 = 120\,\mu\mathrm{m}^2$ do not divide. The analysis of a single cell dynamics shows that cell growth rate is of the order of $c = 1/(5\,\mathrm{h})$ (Streichan 2013, 2014), which means that cells typically reach 'equilibrium' size well before they divide. The rate of cell shrinkage is not well known, so we assume a small value $\delta = 1/(15\,\mathrm{h})$, i.e. cells shrink due to pressure much slower than they grow toward pressure-controlled size. The diffusion coefficient (in the cell area space) D is chosen to fit the final width of experimental cell area distribution (Streichan 2013, 2014) after 6.5 d; in our simulations, $D = 50\,\mu\mathrm{m}^4\,\mathrm{h}^{-1}$. Other parameters of the model are specified in figure 2 caption.

Initially, the cell area distribution is wide, in agreement with Streichan (2013, 2014). As time goes on, $f(a, t)$ becomes much narrower, see figure 2. Also, the average cell area decreases dramatically from approximately $600\,\mu\mathrm{m}^2$ to about $120\,\mu\mathrm{m}^2$ after 6.5 d, see figure 3, again, in a good agreement with Streichan (2013, 2014). The coefficient of variation (standard deviation over the mean) first decreases and then remains nearly constant. Figure 3 also shows the total number of cells in the system as a function of time. Clearly, for a smaller value of a_d (describing the cell area below which the proliferation goes down), the total number of cells is larger, and the average cell area is smaller. At large times, all the cells become smaller than a_0, so the total number of cells in the system and the optimal single cell area, a^*, saturate at some constant values.

Figure 3 also presents a comparison between the models with and without cell growth after division. If cell growth after division is not incorporated in the modeling, one can see a very sharp decrease in the average cell size (squares in figure 3), a much faster decrease than the one observed experimentally. In contrast, the model presented in equations (2)–(4) agrees well with experimental observations. The final values of average cell sizes in both models are

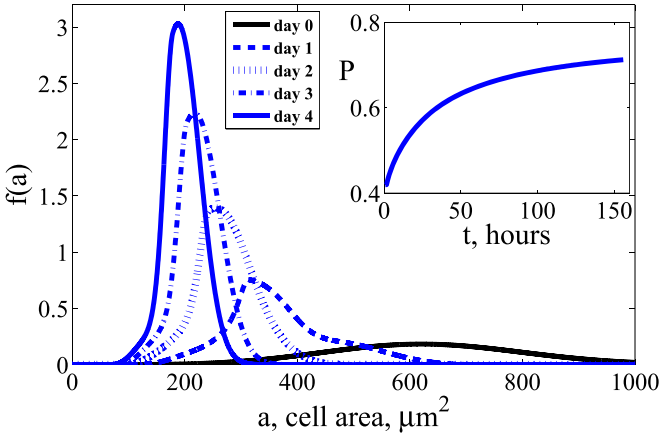

Figure 2. Time evolution of cell area distribution $f(a, t)$; time instances are labeled. The average cell size substantially decreased with time (compare with figure 1), and the dispersion in cell sizes decreased, too. The inset shows the dimensionless pressure as a function of time. The parameters are: $\gamma_1 = 0.056\,\mathrm{h}^{-1}$, $a_0 = 120\,\mu\mathrm{m}^2$, $a_d = 1000\,\mu\mathrm{m}^2$, $\bar{a} = 1000\,\mu\mathrm{m}^2$, $s = 1200\,\mu\mathrm{m}^2$, $c = 0.2\ \mathrm{h}^{-1}$, $\delta = 0.066\,\mathrm{h}^{-1}$. This series of cell area distribution functions matches the experimental observations of Streichan (2013, 2014).

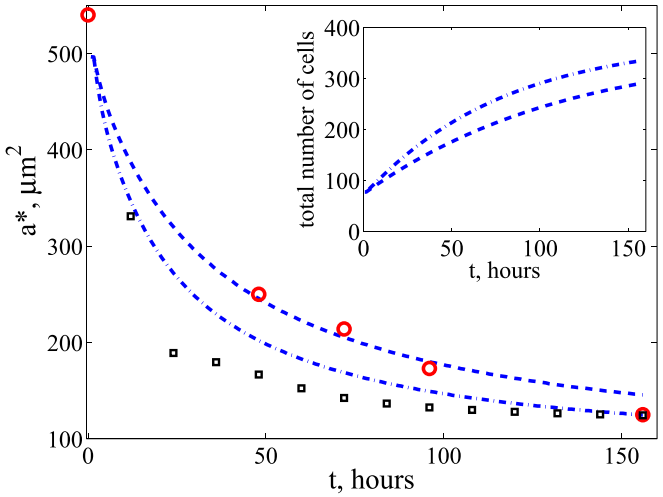

Figure 3. The optimal cell area as a function of time. Circles represent the peaks of the experimental cell area distributions (Streichan 2013, 2014). The inset shows the total number of cells in the system as a function of time. In both plots, the dashed lines correspond to $a_d = 1000\,\mu\mathrm{m}^2$, the dashed-dotted lines correspond to $a_d = 700\,\mu\mathrm{m}^2$; other parameters are the same as in figure 2. The squares correspond to simulations of the model without cell growth/shrinking (Puliafito *et al* 2012).

close since both models assume that cell proliferation stops at approximately $a_0 = 120\,\mu\mathrm{m}^2$ (as was experimentally shown).

We also analyzed the time evolution of an initially narrow cell area distribution $f(a, t)$, figure 4. The main result remains the same; however, one can observe two peaks at early

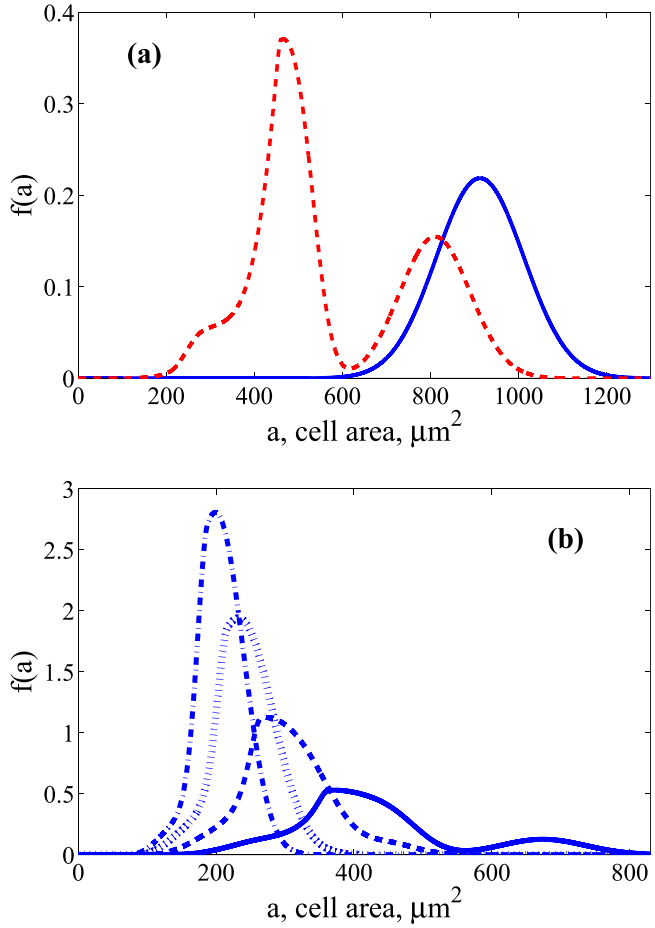

Figure 4. Time evolution of initially narrow cell area distribution $f(a, t)$. The upper panel shows f at time 0 (blue solid line) and after 12 h (red dashed line). The lower panel shows $f(a)$ after day 1 (solid line), day 2 (dashed line), day 3 (dotted line), and day 4 (dashed-dotted line) respectively. The parameters are the same as in figure 2.

times (see the upper panel). The peak of $f(a,\ t = 12\,\mathrm{h})$ at a smaller cell area is due to proliferation of cells forming the peak of $f(a, t = 0)$, while the second peak of $f(a, t = 12\,\mathrm{h})$ (at a larger cell area) is due to shrinking of cells forming the peak of $f(a, t = 0)$. Eventually, the second peak disappears, see the lower panel.

4. Summary and discussion

We formulated a theoretical model of cell dynamics in a monolayer focusing on the role of effective pressure that mimics the mechanical stresses. This purely phenomenological model assumes that the effective pressure builds up when a cell grows after division and pushes the neighboring cells. It also considers a geometrical constraint: in a closed system the overall area occupied by cells must remain constant. As a result, big cells must shrink due to the effective pressure to allow small cells to grow. We analyzed the resulting time evolution of

the system in terms of the cell area distribution function. Although the theoretical results agree with the experimental observations, the systems are not exactly the same. Theoretically, we considered a homogeneous setting, as if cells were initially placed at high density in a closed system, so that they cannot move away. Experimentally, cells were placed in the middle of an open system, so the colony started expanding. Next, cell size distribution in the middle region was measured as a function of time. In this setting, the system was initially non-uniform (cells are bigger near the edges of the colony), which is why the initial experimental cell size distribution is so wide. But as time goes on and the size of the colony becomes much larger than the size of the middle square, this middle square becomes more and more spatially uniform. Therefore, the presented modeling captures the experimentally observed features. However, we would like to suggest two possible experiments that would examine a simpler system, i.e. a system that would be spatially homogeneous from the very beginning. Here, the comparison with experimental observations would help to tune the parameters of the theoretical model before expanding it to spatial situations of cell invasion.

The first idea might be to put a high density suspension of cells in a closed system. Initially, cells should occupy the entire system; there should be no empty spaces. This way, the system remains uniform, so cell size distribution in one part of a system is exactly the same as in other parts. It should be noted that in this case, the initial cell size distribution will already be quite narrow. The difference in cell sizes between various cells can not be larger than a factor of 2. Still, one will be able to follow the average cell size versus time, see the theoretical prediction in figure 4. The second idea would be to prepare a collection of cells of very different sizes and then put them at high density in a closed system as before. So, the system remains closed and spatially uniform, but the initial cell size distribution is wide. One can think of various ways of preparing an initially wide cell area distribution. One way can be to put cells in the middle of the system, wait a bit and then collect all the cells (both from the middle and from the edges) and put them into a closed system. Another way is to put cells in different systems with delay: for example, let one system to evolve for one day, let another system to evolve for two days etc. Then again, collect all the cells from these systems and put everything in a closed system. As before, the density should be high, so the cells should occupy the entire system from the very beginning.

In our modeling we assumed that in a closed system every cell 'feels' the same pressure. This is reasonable when the effective pressure in the system quickly equilibrates, faster than the typical time for cell growth/shrinking. Serra-Picamal *et al* (2012) describes the phenomenon of wave propagation in the expanding colony. These mechanical waves originate at the growing cells that push their neighbors. In our closed system, the typical time for cell growth after division is of the order of 5 h, while the typical time between cell division events is of the order of 18 h (Streichan 2013, 2014). This means that at a given time roughly one quarter of the cells are growing. Since the dividing cells are distributed uniformly over the closed system, the typical distance between the growing cells is of the order of two cell diameters. According to the work by Serra-Picamal *et al* (2012), the typical speed for wave propagation is about 60 μm h^{-1}, so the information between the sources (the growing cells) is exchanged much faster than the typical time for cell growth/shrinking. Also, the waves should not affect the mean cell size due to the spatial averaging over a large system. Our current model is not suited to describe pressure waves, since it neglects the inertia term (the second derivative of cell area with respect to time), but we plan to address this phenomenon in the future.

Recently, a promising concept of homeostatic pressure was introduced (Basan *et al* 2009, Podewitz *et al* 2015). This is the pressure at which a balance between cell death and cell division is achieved. It seems that in the experiments we are describing, the rate of cell death

is negligible, so it is not taken into account in the modeling. However, the experimental observation that a cell cannot divide if its size is smaller than some minimal size a_0 also leads to a steady state, and the pressure reaches a plateau, figure 2.

We see two promising extensions of this modeling approach. First, one can test the theoretical predictions of the continuum model in molecular dynamics simulations where cells are represented by soft disks or spheres. There are several numerical methods used for modeling cell migration and tissue growth. One can investigate migration and proliferation of adhesive cells on a lattice, employing a stochastic approach (Khain *et al* 2007, 2009, 2011, Johnston *et al* 2012, Charteris and Khain 2014, Simpson *et al* 2014). One can perform off-lattice simulations investigating cell monolayers and three-dimensional tumor spheroids using Metropolis-like algorithms to model stochastic dynamics driven by physical interactions (Drasdo and Hoehme 2005). We plan to employ molecular dynamics simulations of soft disks; such methods are widely used in granular physics (see, for example, Volfson *et al* 2004), and were recently employed in modeling of collective behavior of bacteria (Volfson *et al* 2008).

Second, one can extend the model to open systems with non-spatially-uniform pressure and cell size distribution, investigating expansion of the monolayer (Reffay *et al* 2011, Silberzan 2014), tumor cell invasion in surrounding non-cancerous tissue and possible fingering (Mather *et al* 2010, Basan *et al* 2011, Boyer *et al* 2011, Khain *et al* 2012, Risler and Basan 2013, Doostmohammadi *et al* 2015, Tarle *et al* 2015). In the case of an expanding cell monolayer, certain regions of tissue might be under tension (Zimmermann *et al* 2016), which must be taken into account in the continuum modeling. Work in both directions is in progress.

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