Entropy-driven cell decision-making predicts ‘fluid-to-solid’ transition in multicellular systems

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Abstract

Cellular decision making allows cells to assume functionally different phenotypes in response to microenvironmental cues, with or without genetic change. It is an open question, how individual cell decisions influence the dynamics at the tissue level. Here, we study spatio-temporal pattern formation in a population of cells exhibiting phenotypic plasticity, which is a paradigm of cell decision making. We focus on the migration/resting and the migration/proliferation plasticity which underly the epithelial-mesenchymal transition and the go or grow dichotomy. We assume that cells change their phenotype in order to minimize their microenvironmental entropy following the LEUP (Least microEnvironmental Uncertainty Principle) hypothesis. In turn, we study the impact of the LEUP-driven migration/resting and migration/proliferation plasticity on the corresponding multicellular spatio-temporal dynamics with a stochastic cell-based mathematical model for the spatio-temporal dynamics of the cell phenotypes. In the case of the go or rest plasticity, a corresponding mean-field approximation allows to identify a bistable switching mechanism between a diffusive (fluid) and an epithelial (solid) tissue phase which depends on the sensitivity of the phenotypes to the environment. For the go or grow plasticity, we show the possibility of Turing pattern formation for the ‘solid’ tissue phase and its relation with the parameters of the LEUP-driven cell decisions.

1. Introduction

Cellular decision making allows cells to respond to microenvironmental cues [1]. For instance, if an external ligand from the microenvironment binds to the cell membrane, it may trigger a chain of biochemical reactions inside the cell [2]. After the microenvironmental information has been processed, the cell may respond by changing its properties implying cell differentiation, proliferation, migration, apoptosis etc. Thus, cellular decision making depends on intrinsic signal transduction pathways, the genetic cell network [3], extrinsic stimuli, and molecular noise [4]. Cell-decision making plays a key role in cell fate determination and the maintenance of phenotypic plasticity. In the former, cells irreversibly acquire new fates by following a hierarchical lineage, where pluripotent stem cells in a proper microenvironment (stem cell niche) differentiate into e.g. bone, muscle, epithelial and further specialised cells. On the other hand, phenotypic plasticity allows a reversible adaptation to different microenvironmental stimuli [5].
cellular decision making is well-studied for single cells, it is an open question how individual cell decisions influence the dynamics at the tissue level.

In this paper, we analyze the implications of phenotypic plasticity on spatio-temporal pattern formation in the cell population and focus on the migration/resting and migration/proliferation plasticity. The migration/resting type of plasticity is observed during the epithelial-mesenchymal transition (EMT/MET) [6–8] while the migration/proliferation plasticity characterizes the go-or-grow (GoG) dichotomy found in different types of cancers, such as glioblastoma or breast cancer, but also during normal development [9–12]. Epithelial cells are immotile, connected by strong adhesion bonds, exhibit regular shapes and show strong apico-basal cell polarity. Epithelial and mesenchymal phenotypes can be interpreted as representing two migration modes, resting and motile, respectively. On the other hand, GoG refers to the mutual exclusion of cell migration and proliferation, leading to the existence of proliferative/immotile and nonproliferative/mobile cell phenotypes.

We assume that a Least microEnvironmental Uncertainty Principle (LEUP) dictates the phenotypic switching in both types of the considered phenotypic plastic behaviors. The Least microEnvironmental Uncertainty Principle idea is based on the idea of energy minimization in the context of cell decision making. In order to make phenotypic decisions, cells sense their surrounding by employing energetically expensive processes, such as polymerizing pseudopodia, translocating receptor molecules or modifying the cytoskeleton according to mechanical signals [13–15]. However, the cost can be minimized if cells build informative priors about their microenvironment, i.e. encoding persistent microenvironmental information [16]. At the same time, in many biological processes, such as development and wound healing, cell phenotypic decisions effectively promote the co-evolution of the cellular microenvironment into more organized states, leading to a decrease of the microenvironmental entropy from high to low. The assumption of microenvironmental entropy minimization is exploited by LEUP to define the dynamics of cell phenotypic decisions. The idea of viewing cells as Bayesian decision-makers under energetic constraints can be translated into a free-energy principle, implying a statistical mechanics theory for cell decision making [17]. According to this theory, cells try to optimize their phenotypic prior to reduce the joint entropy of their own phenotype and the microenvironmental state. Similar ideas using information theoretic measures have been proposed also in seminal works by W Bialek [14, 18]. Our LEUP-based low-dimensional mathematical model can be used to analyze collective effects of cell decision making which is the main goal of our paper. At this point, it is important to mention that LEUP is still a hypothesis which currently undergoes experimental validation.

The manuscript is structured as follows: in the next section, we define a LEUP-driven cell decision model based on the migration/resting plasticity. In section 3, we develop a stochastic individual-based model (IBM) for moving and resting cells where cells can change their phenotype according to the LEUP-driven cell decision model and show the formation of aggregates of resting cells in corresponding simulations. In section 4, we derive a macroscopic mean-field approximation of our microscopic model which allows to explain the formation of aggregates in the microscopic model. In section 5, we analyze the stability of the steady states and the pattern formation potential of the macroscopic go-or grow model. Finally, in section 6, we discuss the biological implications of our results in terms of multicellular growth and pattern control.

2. A minimal model of LEUP-driven cell migration plasticity

Here, we define a mathematical model for LEUP-based switching between moving and resting phenotypes. We assume that cells can sense their microenvironment and can change their own phenotype $X_i$ on a domain $\mathcal{L} \subseteq \mathbb{R}^2$ accordingly, where $X_i = 0,1$ corresponds to the resting and migrating state, respectively. We define the microenvironment of cell $i$ as the number $N_i^0$ of cells having phenotype $X_i = 0$ and by the number $N_i^1$ of cells having phenotype $X_i = 1$. By assuming a maximum cell capacity $N$ of the microenvironment, we can define

$$N = N_i^1 + N_i^0 + N_i^0,$$

where $N_i^0$ are the free spaces/slots. The total number of cells $N_T$ is defined as the sum of cells having phenotype ($X_i = 1$) and cells having phenotype ($X_i = 0$). So,

$$N_T = N_i^1 + N_i^0.$$

(2)

Cells will select their phenotype in a Bayesian fashion, i.e.

$$P (X_i | Y_i) = \frac{P (Y_i | X_i) P (X_i)}{P (Y_i)},$$

(3)
where \( P(Y_i|X_i) \) can be interpreted as the probability that the cell perceives all other cells in its surroundings, and \( P(X_i) \) is the prior probability distribution of the cell’s phenotypes. The former probability distribution models the microenvironmental sensing conditioned by the intrinsic state \( X_i \). However, sensing other cells and evaluating \( P(Y_i|X_i) \) entails an energy cost. It is reasonable to assume that the cell will try to optimize its prior \( P(X_i) \) for the sake of energetic frugality.

Here we define \( Y_i \) as the extrinsic random variable of the \( i \)th cell, where \( Y_i = N^X_i|N_T \), \( X_i = 0,1 \) represents the number of cells of phenotype \( X_i \) given the total local number of cells \( N_T \). The conditional probability of having \( N^X_i \) cells present in the microenvironment follows a binomial distribution \( (B) \) for the derivation details see S.I. (https://stacks.iop.org/10.1088/1367-2630/22/123034/mmedia):

\[
P(\{N^X_i|N_T\}) = P(Y_i = N^X_i|N_T) = B(N_T, p_i),
\]

where \( p_i \) is the probability of \( N^X_i \) cells having phenotype \( X_i = 1 \) out of \( N_T \) cells:

\[
p_i = \frac{N^X_i}{N_T}.
\]

Using statistical mechanical arguments [17], the problem of finding the probability of the cell’s phenotype is equivalent to finding the prior that minimizes the entropy of a cell’s phenotype and its surroundings. Let \( S(X_i, Y_i) \) be the entropy of the cell-surroundings, \( S(X_i) \) the internal entropy of the cell, and \( S(Y_i|X_i) \) the entropy of the information sensed by the cell. Then, the entropies are connected by the relation \( S(X_i, Y_i) = S(X_i) + S(Y_i|X_i) \). The optimization problem is finding \( P(X_i) \) that minimizes \( S(X_i, Y_i) \), while making sure that \( P(X_i) \) is normalized; in other words we impose

\[
\frac{\delta}{\delta P(X_i)} \{ S(X_i) + \beta \left[ \sum_p P(X_i) S(Y_i|X_i) - \bar{S}(Y_i|X_i) \right] - \lambda \left[ \sum P(X_i) - 1 \right] \} = 0,
\]

where \( \frac{\delta}{\delta P(X_i)} \) is the functional derivative, \( \bar{S}(Y_i|X_i) \) is the expected ensemble statistics [17], and \( \lambda \) and \( \beta \) are Lagrange multipliers. Taking into account the relations among entropies, equation (6) yields

\[
P(X_i) = \frac{e^{\beta S(Y_i|X_i)}}{Z} = \frac{1}{1 + e^{\beta \Delta S}},
\]

where \( Z \) is the normalization factor

\[
Z = \sum_{\alpha=0,1} e^{\beta S(Y_i|X_i=\alpha)} = e^{\beta S(Y_i|X_i=0)} + e^{\beta S(Y_i|X_i=1)}.
\]

Please note that the parameter \( \beta \) has a biological interpretation, since it quantifies the intensity with which a cell senses and complies to the microenvironment. To facilitate the evaluation of the entropy distribution of the microenvironment, we have used a Gaussian distribution, which approximates the binomial distribution (for \( N_T > 5 \)), i.e.

\[
P(N^X_i, p_1) \rightarrow N(N_T p_1, N_T(1-p_1)),
\]

for the microenvironment [18]. Now we can evaluate the equilibrium distribution \( P(X_i = 0) \) as

\[
P(X_i = 0) = \frac{e^{\beta S(Y_i = N^X_i|N_T = 0)}}{Z} = \frac{1}{1 + e^{\beta \Delta S}} = \frac{1}{1 + \left[ \frac{N^0_i (N_T - 1)}{N_T N^0_i - 1} \right]^{\frac{\beta}{2}}} = \frac{1}{1 + \left[ \frac{\rho_0 (p_i - \frac{1}{2})}{\rho_i (p_i - \frac{1}{2})} \right]^{\frac{\beta}{2}}},
\]

with the cell densities \( \rho_i^{0,1} := \frac{N^0_i}{N_T} \) (in the SI figure 12, we show the dependency of \( P(X_i = 0) \) on resting density \( \rho_0 \) and \( \beta \)). Accordingly, the probability of an \( i \)th cell’s phenotype \( P(X_i = 1) \) reads

\[
P(X_i = 1) = \frac{e^{\beta S(Y_i = N^X_i|N_T = 1)}}{Z} = 1 - \frac{1}{1 + e^{\beta \Delta S}} = 1 - \frac{1}{1 + \left[ \frac{N^0_i (N_T - 1)}{N_T N^0_i - 1} \right]^{\frac{\beta}{2}}} = 1 + \left[ \frac{\rho_0 (p_i - \frac{1}{2})}{\rho_i (p_i - \frac{1}{2})} \right]^{\frac{\beta}{2}}.
\]

Please note that, the difference between the microenvironmental entropy of the \( i \)th cell is

\[
\Delta S = S(Y_i = \{N^X_i \}|N_T = 1) - S(Y_i = \{N^X_i \}|N_T = 0) = \frac{1}{2} \ln \left[ \frac{N^0_i (N_T - 1)}{N^0_i (N_T - 1)} \right],
\]

where \( P \) (\( Y_i |X_i \)) can be interpreted as the probability that the cell perceives all other cells in its surroundings, and \( P(X_i) \) is the prior probability distribution of the cell’s phenotypes. The former probability distribution models the microenvironmental sensing conditioned by the intrinsic state \( X_i \). However, sensing other cells and evaluating \( P(Y_i|X_i) \) entails an energy cost. It is reasonable to assume that the cell will try to optimize its prior \( P(X_i) \) for the sake of energetic frugality.
Figure 1. Schematic diagram of (a) the microenvironment of a motile cell, where $\ell$ is the sensing radius. The sensed number of cells is proportional to the volume of the sensed microenvironment, i.e. $N \propto \ell^d$, where $d$ is the dimension. (b) Transitions in the ‘go or grow’ model [9]. The switching between motile ($X_i = 1$) and resting ($X_i = 0$) phenotype is shown, where the transition probabilities are defined as $W_{01}$ and $W_{10}$. The proliferation rate is defined by $r$.

In this section, we have defined a minimal LEUP-driven cell decision making model and derived the corresponding phenotypic steady states. Based on this, we subsequently develop a cell-based model to analyse the resulting multicellular spatiotemporal dynamics.

3. An IBM for LEUP-driven cell migration

We define a discrete stochastic, spatio-temporal IBM that incorporates the phenotypic switch dynamics according to LEUP. To this end, we model the movement of single cells with Langevin equations. Langevin equations are well-suited to model cell–cell interactions and cell migration [20, 21].

Our Langevin’s equation is defined on a domain $\mathcal{L} \subset \mathbb{R}^2$ with periodic boundary conditions. We define an interaction radius $\ell \in \mathbb{R}$ around the $i$th cell at position $x_i \in \mathcal{L}$. The expected interaction volume is $V \propto \ell^2$. The time evolution of our model is defined by the following rules:

(R1) Cells change their phenotype by sensing their microenvironment within the interaction radius $\ell$ according to LEUP.
(R2) Moving cells change their orientations randomly (random walk).
(R3) Once cells become migratory they move with a constant speed $\bar{v}$.

The above are translated to the following Langevin’s equations

$$\frac{d x_i}{d t} = \bar{v}_i(\theta_i),$$
$$\frac{d \theta_i}{d t} = \frac{1}{\bar{v}} \xi_i^\theta(t),$$
$$\frac{d p_i}{d t} = -\frac{1}{\tau} (p_i - p_i^{eq}),$$
$$v_i = \begin{cases} \bar{v}, & \text{if } X_i = 1, \\ 0, & \text{if } X_i = 0, \end{cases}$$

where $v_i = (\cos \theta_i, \sin \theta_i)^T$ is the direction of movement of cell $i$. For the temporal evolution of the probability $p_i$ of the motile state, we use the BGK (Bhatnagar–Gross–Krook) operator technique [22]. We assume that the probability $p_i$ evolves weakly out of its equilibrium probability $p_i^{eq}$, which is the LEUP steady state probability $P(X_i = 1)$ (see equation (11)). In turn, the parameter $\tau$ is the relaxation time toward
the corresponding probability distribution \( p^{eq}_i \). Here noise is assumed to have a zero-mean, white noise term, which has the statistical properties \( \langle \xi^\theta_i(t) \rangle = 0 \) and \( \langle \xi^\theta_i(t_1) \xi^\theta_j(t_2) \rangle = 2D_\theta \delta(t_1 - t_2) \delta_{ij} \), where \( t_1 \) and \( t_2 \) are two time points, \( D_\theta \in \mathbb{R}_+ \) is the angular diffusion coefficient, \( \delta(t) \) is the Dirac delta, and \( \delta_{ij} \) is the Kronecker delta. Parameter \( \bar{v} \) is the constant speed of every motile cell.

We simulate the Langevin model, on a two-dimensional domain, with a varying interaction radius \( \ell \), mean cell density and sensitivity \( \beta \). We assume an initial state that is approximately homogeneous in space and that each of the initial 1000 cells is in the resting/migratory state with equal probability. In figures 2(a) and (b), we showcase simulations that exhibit clustering and random spatial configurations, respectively. We consider a density regime which is compatible with typical situations during cancer invasion. In particular, the densities in figure 2 correspond to 1000 glioma cancer cells in a \( 2.5 \times 10^4 \) \( \mu m^2 \) domain, which agrees with the typical glioma cell density \( 4.5 \times 10^{-3} \) \( \mu m^{-2} \) [23].

To quantify cell clustering, we calculate the radial distribution function for different sensitivities and different interaction radii as shown in figures 3(a) and (b). The key observations from the simulation study are:

(a) There is a critical threshold for the parameter \( \beta > 0 \), where clustering of resting cells occurs (figure 3(a)). This is rather expected since a sufficient sensing of the microenvironment is required.
(b) For an intermediate interaction radius \( \ell \), we observe cell clusters as shown in figure 3(b). Very high \( \ell \) corresponds to a large number of sensed cells. This also leads to equal steady state probabilities, as the entropy difference in the microenvironment, associated with the single cell states becomes negligible. On the other hand, the lower bound of \( \ell \) is expected, since a sufficient sampling size of the cellular microenvironment is required to induce aggregation patterns.
(c) In figure 3(d), we show the phase diagram of the system, when parameter \( \beta \) and the average density are varied. In particular, we observe that there is a parametric regime where clustering behavior is emerging. Interestingly, high densities do not always imply patterning and require higher values of \( \beta \) to support cluster emergence (see figure 3(c)). Finally, as expected, low densities also reduce the area of the patterning regime for low \( \beta \).

Interestingly, existing radial distribution function data from patient-derived glioma tumors also show a ‘flat’ behavior, i.e. they do not exhibit any clustering [23]. In particular, the configuration in figure 2(b) corresponds to such a ‘flat’ radial distribution function, for \( \beta = 5 \), at densities relevant to real glioma tumors. However, there are some extra cell–cell interaction mechanisms acting in glioma cells, i.e. a repulsive force conferring a large volume exclusion effect. Studying effects of these additional mechanisms is the topic of current research.
Figure 3. Quantification of cell clustering. (a) Radial distribution function with standard deviation for different values of $\beta$, for a fixed interaction radius $\ell = 6$. The number of cells was fixed at 1000, corresponding to a mean cell density of 0.4. (b) Radial distribution function with standard deviation for varying interaction radius $\ell$ at fixed sensitivity $\beta = 100$. There is an optimal sensing radius for a given mean cell density, so that interaction radii that are too large or too low do not lead to aggregation, indicated by an almost flat radial distribution, see purple and blue lines. (c) Radial distribution function with standard deviation for different mean densities, at $\beta = 20$ and $\ell = 4$. When the mean density becomes too large, no clustering can be observed. The inlets in (a)–(c) show the corresponding fractions of motile (checkerboard bars) and resting (filled bars) cells. (d) Phase space diagram for cluster pattern formation. Here we define clustering by $\max_r g(r) > 1.09$ (see text for explanation). The interaction radius is fixed at $\ell = 4$. All data points in (a)–(d) correspond to the mean of 20 independent simulations at $t = 100$.

4. Mean-field approximation

In this section, we derive a continuous approximation of the aforementioned discrete model using a mean-field approach. The goal is to shed light on the pattern formation mechanisms, i.e. cell clustering, as observed in the microscopic simulations. The main idea of the mean-field approximation is to replace the description of many-particle interactions by a single particle description based on an average or effective interaction. Thereby, any multi-particle problem can be replaced by an effective description, that can be stated in the form of an ordinary (ODE) or partial differential equation (PDE). In order to proceed, we will first treat the switch dynamics and the migration process separately.

4.1. Mean-field description of the phenotypic switch dynamics

Let us consider cell $i$ at position $x_i$ with states $X_i = 0, 1$. The cell changes its state in dependence of the local microenvironment according to the LEUP with rates $W_{01}, W_{10}$ and the probabilities to be in either states are denoted by $p_{0,1}$. We assume that the system is always close to the steady state, so the master equation reads

$$\frac{dp_0}{dt} = W_{10}p_1 - W_{01}p_0 \approx 0,$$

and $p_{0,1}$ are given by equation (7). By rearranging the terms, we obtain for the switching rates

$$\frac{W_{10}}{W_{01}} = \frac{p_0}{p_1}.$$

For simplicity, we set $W_{01} = p_1$ where the transition probability toward motile phenotype is equal to the moving steady state probability $p_1$. This coincides with the ‘detailed balance condition’. The steady state
probabilities $p_{0,1}$ depend on the number of cells $N_{j}^{0,1}$ in the respective phenotypes in the microenvironment. Cell $i$ at position $x_i$ senses

$$N_{j}^{X}(x_1, \ldots, x_i, \ldots, x_N, t) := \sum_{j=1}^{N} \xi(x_j(t) - x_i(t), t) \delta_{x_j X}, \quad X = 0, 1. \tag{16}$$

Here, we sum over all cells $j$, and $\xi(x_j(t) - x_i(t), t)$ is a Boolean stochastic variable that serves as the sensing function of a cell at $x_i$. It depends on the distance between cells and time, and $\xi = 1$ indicates that the cell $j$ at $x_j$ is sensed by cell $i$ at position $x_i$. To match the IBM, we assume that

$$\xi(x_j(t) - x_i(t), t) = \Theta(\ell - |x_j(t) - x_i(t)|), \quad \ell > 0, \tag{17}$$

with the Heaviside step function $\Theta(x)$, so that all cells in a ball of radius $\ell$ around $x_i$ are sensed.

To proceed, we apply a mean-field approximation to calculate the expected switching rate $\langle W_{10}(N_0^0, N_1^1) \rangle \approx W_{01}(\langle N_0^0 \rangle, \langle N_1^1 \rangle)$. Note that we dropped the dependence on space and time for better readability. Let $\phi_i(x, x_i, t)$ denote the probability of finding cell $i$ in a small volume $dV$ around $x$ at time $t$ with the phenotype $X = 0, 1$. Formally we have

$$\phi_i(X, x, t) = \langle \delta(x - x_i(t)) \delta_{x_i X} \rangle, \tag{18}$$

where the average is the ensemble average, and the total densities of resting/migrating cells are

$$\Phi(x, t) := \sum_{i} \phi_i(0, x, t), \tag{19}$$

$$\Psi(x, t) := \sum_{i} \phi_i(1, x, t). \tag{20}$$

For the expected density of sensed cells in the microenvironment around $x$ we obtain

$$\rho_{0}(x, t) := \langle N_{j}^{0}(x, t) \rangle = \frac{1}{V} \int B_{\ell}(x) \Phi(y, t) \, dV, \tag{21}$$

$$\rho_{1}(x, t) := \langle N_{j}^{1}(x, t) \rangle = \frac{1}{V} \int B_{\ell}(x) \Psi(y, t) \, dV, \tag{22}$$

where $V \propto \ell^d$, and where we have already used equation (17). Consequently, we obtain the approximate switching rate

$$\bar{W}_{10} = p_0 \rho_0 - p_1 \rho_1, \tag{23}$$

and the switch dynamics is (dropping dependencies on space and time for simplicity)

$$\frac{\partial}{\partial t} \phi_i(0) = p_0 \phi_i(1) - p_1 \phi_i(0). \tag{24}$$

Summing over all cells, we obtain for the total density of resting cells

$$\frac{\partial}{\partial t} \Phi = p_0 \Psi - p_1 \Phi. \tag{25}$$

Note that this is a non-local, non-linear set of PDEs, which are difficult to treat analytically. However, we can further simplify our analysis by making another approximation, assuming that the sensing radius $\ell$ is much smaller than the total domain size. Then, we can replace the non-local sensing function $\xi(x_j(t) - x_i(t), t)$ by a local delta distribution

$$\xi(x_j(t) - x_i(t), t) \rightarrow \delta(x_j(t) - x_i(t)). \tag{26}$$

In this case, the expected number of sensed cells in the microenvironment around $x$ simply becomes the local density of the respective phenotype

$$\rho_{0}(x, t) := \langle N_{j}^{0}(x, t) \rangle = \frac{\Phi(x, t)}{\ell^d}, \tag{27}$$

$$\rho_{1}(x, t) := \langle N_{j}^{1}(x, t) \rangle = \frac{\Psi(x, t)}{\ell^d}. \tag{28}$$
Finally, the rate $W_{10}$ reduces to
\begin{equation}
W_{10} = p_0(\rho_0, \rho_1) = \frac{1}{1 + e^{\beta \Delta S}} = \frac{1}{1 + \left[\frac{\rho_0(\rho_1 - \rho_0)}{\rho_0^2}ight]^\tau},
\end{equation}
and the reversed transition probability $W_{01}$ is
\begin{equation}
W_{01} = p_1(\rho_0, \rho_1) = 1 - \frac{1}{1 + e^{\beta \Delta S}} = 1 - \frac{1}{1 + \left[\frac{\rho_0(\rho_1 - \rho_0)}{\rho_0^2}ight]^\tau},
\end{equation}
where the volume is defined as $V = \ell^d$.

4.2. Mean-field description of the cell migration process

In this section, we derive the macroscopic equation in two spatial dimensions for the motile cell population. As before we can write the corresponding stochastic Langevin’s equations as
\begin{align}
\frac{d}{dt} x_i &= \bar{v} \omega_i(t), \\
\frac{d}{dt} \theta_i &= \frac{1}{\bar{v}} \xi_i(t).
\end{align}
This process can be considered as a special kind of active Brownian motion. In this kind of Langevin’s equation, the stochastic force creates variations of orientation. According to [24] we can derive the corresponding Fokker–Planck equation for migrating cells using adiabatic elimination and averaging it over different noise realizations obtaining the following diffusion equation
\begin{equation}
\frac{\partial \rho_1(x, t)}{\partial t} = \frac{\bar{v}^4}{2D_1} \nabla^2 \rho_1(x, t).
\end{equation}
Here we define $D_1$ as diffusion coefficient which is $\frac{\bar{v}^4}{2V}$.

4.3. Coupling migration and switching dynamics

Combining our results in the previous sections, we can easily formulate a system of PDEs
\begin{align}
\partial_t \rho_0(x, t) &= \nu E(\rho_0, \rho_1), \\
\partial_t \rho_1(x, t) &= D_1 \nabla^2 \rho_1 - \nu E(\rho_0, \rho_1), \\
E(\rho_0, \rho_1) &= W_{10}(\rho_0, \rho_1)\rho_1 - W_{01}(\rho_0, \rho_1)\rho_0,
\end{align}
where $E(\rho_0, \rho_1)$ is the phenotypic exchange term and $\nu$ is the corresponding timescale ratio of the switching and diffusion processes, i.e. $\nu = \frac{\tau}{\tau_0}$. To ensure the numerical consistency of the above system, we assume that resting cells diffuse in a very slow manner i.e. $D_0 \ll D_1$, which results in the following reaction–diffusion system of equations
\begin{align}
\partial_t \rho_0(x, t) &= D_0 \nabla^2 \rho_0 + \nu E(\rho_0, \rho_1), \\
\partial_t \rho_1(x, t) &= D_1 \nabla^2 \rho_1 - \nu E(\rho_0, \rho_1).
\end{align}

5. Spatio-temporal dynamics of the LEUP-driven migration/proliferation plasticity

In this section, we study the mean-field approximation of the aforementioned stochastic plasticity dynamics for different regimes of the sensitivity $\beta$ and the interaction radius $\ell$. In particular, we initially study the system dynamics, when cells have a very large interaction radius ($\ell \gg 1$) and then a finite one. Finally, we study also the special case $\beta = 0$, i.e. cells decide independently of their microenvironment.

5.1. Large interaction radius case: existence of a critical sensitivity

Here, we focus on the very large interaction radius system ($\ell \gg 1 \implies V \gg 1$). Although, this parameter regime is not biologically relevant, it is very instructive since it allows us to derive analytical estimates for our systems dynamics. Here, we generalize the macroscopic system by adding proliferation dynamics.
(logistic growth). Our phenotypic switch dynamics are recapitulated by setting the proliferation rate to zero, i.e. $r = 0$. The full system reads

$$\frac{\partial \rho_0}{\partial t} = D_0 \nabla^2 \rho_0 + \nu E_0 (\rho_0, \rho_1) + r \rho_0 (1 - \rho_1 - \rho_0),$$

$$\frac{\partial \rho_1}{\partial t} = D_1 \nabla^2 \rho_1 - \nu E_0 (\rho_0, \rho_1).$$

(38)

In turn, we conduct a non-dimensionalization of equation (38) to identify the variables. Moreover, this helps us to gain knowledge about the relationships between the different model parameters. By assuming that the system size is fixed at $L$ the non-dimensional quantities read

$$x^* = \frac{x}{L} \implies \frac{\partial^2}{\partial x^2} = L^2 \frac{\partial^2}{\partial x^2},$$

$$t^* = \frac{D_0 t}{L^2} \implies \frac{\partial}{\partial t^*} = \frac{L^2}{D_0} \frac{\partial}{\partial t^*}.$$

$$\gamma = \frac{L^2 \nu}{D_0},$$

$$D = \frac{D_1}{D_0},$$

$$r' = \frac{r}{\nu}.\quad (39)$$

In the limit $V \gg 1$, equation (38) can also be written as

$$\frac{\partial \rho_0}{\partial t^*} = \nabla^2 \rho_0 + \gamma \left( (\rho_1 - \rho_0) \left( \frac{1}{2} - \tilde{\beta} \left( \frac{\rho_1 + \rho_0}{\rho_1 \rho_0} \right) \right) + r' \rho_0 (1 - \rho_1 - \rho_0) \right),$$

$$\frac{\partial \rho_1}{\partial t^*} = D \nabla^2 \rho_1 - \gamma \left( (\rho_1 - \rho_0) \left( \frac{1}{2} - \tilde{\beta} \left( \frac{\rho_1 + \rho_0}{\rho_1 \rho_0} \right) \right) \right).$$

(40)

To understand the behavior of the system at long times, we conduct a fixed point analysis. Initially we assume a well-stirred system, i.e. no spatial interactions. Then, equation (40) can be written as coupled non-linear ODEs which have three fixed points

$$\left( \rho_0^{b^*}, \rho_1^{b^*} \right) = \left( \frac{1}{2}, \frac{1}{2} \right),$$

$$\left( \rho_0^{b^*}, \rho_1^{b^*} \right) = \left( \frac{1}{2} \left( 1 + \sqrt{1 - 8 \beta} \right), \frac{1}{2} \left( 1 - \sqrt{1 - 8 \beta} \right) \right),$$

$$\left( \rho_0^{b^*}, \rho_1^{b^*} \right) = \left( \frac{1}{2} \left( 1 - \sqrt{1 - 8 \beta} \right), \frac{1}{2} \left( 1 + \sqrt{1 - 8 \beta} \right) \right).$$

(41)

The above imply a pitchfork bifurcation for the $\tilde{\beta} = \frac{D}{\nu}$ parameter, i.e. there exists a critical value $\tilde{\beta}_c$ that introduces the bistable state. From equation (41), we can easily deduce that the critical sensitivity value

$$1 - 8 \tilde{\beta}_c = 0 \iff \beta_c = V.\quad (42)$$

This is an acceptable approximation even for the finite interaction radius system (see next section). In the following, we analyze if the system is able to produce spatial patterns. Applying linear stability analysis for the spatially resolved system equation (40), we can deduce that no pattern formation is possible (for details check next section). Any perturbations to the homogeneous state always lead to a spatially homogeneous steady state. When $r = 0$ this result is consistent with our findings in discrete IBM simulations where very large interaction radii do not confer any clustering, as shown in figure 3(b).

5.2. The finite interaction radius case: emergence of a bistable switch between ‘fluid’ and ‘solid’ tissue phases and pattern formation

Now we turn to the full system for intermediate interaction radius also (assuming proliferation). This implies a finite interaction volume $V$ and for analytical feasibility we are interested in the Gaussian approximation of the switching probabilities and their corresponding mean-field terms. The full system of
Now, we can write the system of PDEs (i.e., equation (38)) in a generalized matrix form
\[
\frac{\partial \rho_0}{\partial t} = \nabla^2 \rho_0 + \gamma \left( \frac{\rho_1 - \rho_0}{\left( \frac{\rho_1}{\rho_0} - 1 \right)^{\frac{3}{2}}} + r' \rho_0 (1 - \rho_1 - \rho_0) \right),
\]
\[
\frac{\partial \rho_1}{\partial t} = D \nabla^2 \rho_1 - \gamma \left( \frac{\rho_1 - \rho_0}{\left( \frac{\rho_1}{\rho_0} - 1 \right)^{\frac{3}{2}}} \right). \tag{43}
\]

Since a closed expression of steady states is not analytically feasible, we obtain the bifurcation diagram numerically, see figure 4(a). We observe the existence of a supercritical pitchfork bifurcation and the existence of a critical $\beta_c$. For $\beta \geq \beta_c$, the systems depart from the balanced state ($\rho_0 = \rho_1 = \frac{1}{2}$) to the coexistence of a ‘fluid’ (most cells migrate) and a ‘solid’ (most cells are resting) phase. The switch is controlled by the perturbation of the ratio of migratory and resting cells. Interestingly, we can compare the analytic estimate of $\beta_c = V$, from the $V \gg 1$ case, with the one calculated for the finite $V$ system. Figure 4(b) shows that the infinite system approximation provides an upper bound for $\beta_c$, which is not too far from the real value of finite systems. The existence of a critical $\beta_c$ with respect to the two phases is evident in the IBM simulations as well. In particular if we quantify the ratio of stationary over motile cells, we observe a similar behavior of the critical sensitivity for increasing $V$, since it decreases (see figure 13 in SI). However, we cannot conduct a strict quantitative comparison since our bifurcation analysis does not involve any diffusion as opposed to the IBM simulation.

In turn, we apply linear stability analysis to identify parameter regimes that promote diffusion driven pattern formation or Turing instability. To analyze the Turing instability [25] we have to find the system’s steady state, (i.e. when diffusion is not present in the systems of equation (38)). It has been shown that $d = \frac{\beta_c}{\beta_0} \gg 1$ is a necessary condition for the emergence of a spatially heterogeneous solution, i.e. patterns. Now, we can write the system of PDEs (i.e. equation (38)) in a generalized matrix form
\[
\frac{\partial \rho}{\partial t} = D \nabla^2 \rho + \gamma R \rho, D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix},
\]
\[
R = \begin{pmatrix} \frac{\partial E_0 (\rho_0, \rho_1)}{\partial \rho_0} + r' (1 - \rho_1 - \rho_0) - r' \rho_0 & \frac{\partial E_0 (\rho_0, \rho_1)}{\partial \rho_1} - r' \rho_0 \\ \frac{\partial E_0 (\rho_0, \rho_1)}{\partial \rho_0} & \frac{\partial E_0 (\rho_0, \rho_1)}{\partial \rho_1} \end{pmatrix}, \tag{44}
\]
\[
= \begin{pmatrix} f_0 & 0 \\ f_1 & -f_r \end{pmatrix} (\rho_0, \rho_1)^T,
\]
where $\rho$ is defined as $(\rho_0, \rho_1)^T$ and $R$ is the Jacobian at $\rho^* = (\rho_0^*, \rho_1^*)$. Using the Turing conditions of instability [25], we found patterns when $N$ is finite in zero-flux boundary conditions. We have checked all
Figure 5. Spatio-temporal pattern formation in dependence of sensitivity $\beta/2$, proliferation rate $r'$ and inverse sensing volume $a = \frac{1}{V}$. (a)–(c) The critical diffusion coefficient $d_c = D_1/D_0$ decreases for increasing sensitivity or increasing proliferation rate. (d)–(f) The critical wave number $k_c$ of the observed pattern increases for an increasing sensitivity.

Interestingly, only when the density of resting cells is larger than that of the moving cells, patterns are formed under Turing instability conditions. In order to investigate the system’s potential to exhibit pattern formation, we check the range of validity of the Turing instability criteria (45). Diffusion-driven instability conditions are satisfied for a large portion of the parameter space. In turn for these parameters, we calculate the critical diffusion coefficient $d_c$. For values $d > d_c$ we are able to observe patterns. This condition is generally fulfilled as the resting cells are only moving passively due to external noise and cell–cell interactions like cell–cell adhesion, while the migratory cells also move actively. The existence of $d_c$ is associated with the existence of a critical wavenumber $k_c$ [25].

\[
d_c = -\frac{2(2f_vg_u - f_ag_v)}{2f_u^2} \pm \sqrt{\frac{(2(2f_vg_u - f_ag_v))^2 - 4f_v^2g_u^2}{2f_u^2}},
\]

\[
k_c = \gamma \left[ \frac{\text{Det}(A)}{d_c} \right]^{\frac{1}{2}}.
\]

In figure 5 we identify the parameter regime that allows us to observe patterns and corresponding $d_c$ and $k_c$.

By fixing the initial conditions to a cosine wave, we observe in one dimension the existence of regular spikes as shown in figure 6. Please note that the exact pattern is sensitive to the initial conditions. In turn, we simulate our system in 2D and for the same parameters and we observe patterning in the form of dots. Finally, we investigate if the type of patterns changes for variations in parameters $\beta$ and $r'$ (see figure 7). If $d > d_c$ then we need a large domain or size of the system to observe the patterns. In the 2D case, we have observed the discoidal patterns of resting phenotype which resemble the 1D case. So, the radius of the circles of the patterns is increased if we fix the domain size. Moreover, we observe that in both dimensions (i.e. 1D and 2D) the critical spatial frequency increases with decreasing $r'$ (figure 8). In comparison with the discrete IBM simulations, we have to state that the simulation clusters can be identified by the discoidal mean-field patterns. We find that:
Figure 6. Pattern formation in the mean-field model. Densities of proliferating (a) and migrating (b) cells at $t = 50,000$. Starting from an almost homogeneous initial state with a sinusoidal perturbation, the resting cells form a periodic pattern of high-density spikes, while the density of moving cells has minima at the positions of the high-density spikes of the resting cells.

Figure 7. Spatio-temporal pattern formation of the mean-field model. (a) Turing space and critical wave number. (b)–(c) Density of resting cells over time. (b) A single high-density spike forms in agreement with the prediction of a small critical wavelength for the given parameters [red dot TS1 in (a)]. (c) For a higher sensitivity and proliferation rate a periodic pattern with smaller wave length emerges, corresponding to the prediction of a larger critical wave number [red dot TS2 in (a)]. Here $\beta' = \frac{\beta}{\rho_0}$ and $a = \frac{\beta}{\rho_0}$.

Figure 8. Two-dimensional simulation of the mean-field approximation with finite interaction radius. (a) Initial state, (b) $t = 2700$, (c) $t = 10,200$ corresponding to a stable steady state. Parameters refer to point (TS1) in the Turing space, as displayed in figure 7.

(a) There exists a critical $\beta$ that allows for the emergence of patterns as in the IBM simulations.
(b) For very low and very high interaction radius $\ell$, we observe no patterns, which is consistent with our IBM results (see figure 3(b)).
5.3. Microenvironment independent phenotypic switching leads to uncontrolled growth dynamics

Finally we investigate the case $\beta = 0$ where cells do not sense their microenvironment and so we end up with the following system,

\[
\begin{align*}
\frac{\partial \rho_0}{\partial t^*} &= \nabla^2 \rho_0 + \gamma \left( \frac{(\rho_1 - \rho_0)}{2} + r' \rho_0 (1 - \rho_0 - \rho_0) \right), \\
\frac{\partial \rho_1}{\partial t^*} &= D \nabla^2 \rho_1 - \gamma (\rho_1 - \rho_0) / 2.
\end{align*}
\] (47)

We can do a fixed point analysis similar to equation (40). Assuming no spatial dynamics, we can find two fixed points i.e.

\[
\begin{align*}
(\rho_0^*, \rho_1^*) &= \left( \frac{1}{2}, \frac{1}{2} \right), \\
(\rho_0^{\infty}, \rho_1^{\infty}) &= (0, 0).
\end{align*}
\] (48)

For further details see figure 9 in S.I. We can clearly show that the fixed point (0,0) is unstable and \( \left( \frac{1}{2}, \frac{1}{2} \right) \) is a saddle point. We can also write the coupled PDE equations as a single PDE as well, if we consider \( \rho_0 = \rho_1 = \tilde{\rho} \). Then we obtain

\[
\frac{\partial \tilde{\rho}}{\partial t^*} = \frac{(1 + D)}{2} \nabla^2 \tilde{\rho} + \frac{r}{2} \tilde{\rho} \left(1 - 2 \tilde{\rho} \right).
\] (49)

Now we can clearly see that equation (49) is similar to the Fisher–Kolmogorov equation [25]. It is known that the Fisher–Kolmogorov equation does not exhibit any pattern formation instabilities. The latter observation is consistent with our discrete IBM simulations, where no clustering is observed.

6. Discussion

Recently, the Least microEnvironmental Uncertainty Principle (LEUP) has been proposed as an organization principle for cell decision-making in multicellular systems. In this paper, we apply this principle to shed light on the effects of phenotypic plasticity for tissue dynamics with a mathematical model. We focus on two types of plasticity: a go or rest, and a go or grow phenotypic dichotomy, which play key roles in important processes in biological development and pathological situations as cancer invasion. We assume that in any given spatial mesoscopic sample the presence of cell phenotypes follows a binomial distribution. Using this assumption, we are able to calculate the microenvironmental entropy and the LEUP-driven probability distribution of each phenotype. On the basis of this distribution, we defined an appropriate microscopic stochastic model for the spatio-temporal dynamics of both phenotypes, and in turn derived the corresponding mean-field description resulting in a system of coupled reaction–diffusion equations. The main results of our study are: (i) in the case of go or rest plasticity, there exists a supercritical pitchfork bifurcation that defines a switch between a ‘fluid’ and a ‘solid’ phase, and (ii) in the case of go or grow plasticity, for the ‘solid’ phase, we can derive conditions for the emergence of Turing patterns.

Interestingly, the existence of Turing patterns requires a critical LEUP sensitivity to the microenvironment and a minimum interaction range. Note that in this work we refer to a clustered, immobile configuration as ‘solid’ and the homogeneous mobile configuration as ‘fluid’. In physics, solid states are characterized by deep ‘valleys’ in their radial distribution function, separated by characteristic distances controlled by the underlying repulsive and adhesive forces. Here, the radial distribution function of our ‘solid’ state does not behave like physical analogs because we do not include cell–cell adhesion and volume exclusion in our cell dynamics. We expect that adding such interaction forces to our IBM would result in classical solid and fluid radial distribution functions, which is subject to future work.

Our model assumes binary transitions between two discrete phenotypes, which is an extreme simplification of biological reality. Certainly, one could include a continuous spectrum of motile/proliferative phenotypes that is expected to imply even richer spatio-temporal dynamics. Indeed, assuming a continuous state (velocity) space would potentially lead to further interesting bifurcations, such as the metastable EMT state as found in [26, 27], or complex spatiotemporal patterns as indicated in [28]. But the very abstracted case chosen here is still instructive to indicate how entropy-driven phenotypic decisions can lead to particular types of spatio-temporal pattern formation.

Interestingly, our LEUP-driven IBM is an extension of a Vicsek-type model [29], formulated in the context of self-propelled particles [30]. Our model exhibits a novel collective behavior when compared to published results of Vicsek-type models. In particular, to our knowledge it is the first time that such models produce Turing patterns, i.e. dynamic clusters of non-motile cells of specific characteristic wavelength.
Typically, in Viscek-type models we may observe moving clusters of swirling cells (e.g. the milling Viscek model) but never static ones.

At this point, let us focus on the biological assumptions and implications of our study. The molecular regulatory mechanisms involved in EMT or GoG remain largely unknown, where the latter can be viewed as an EMT with proliferation constrained to the epithelial/resting phase. Here, we assume that the phenotypic regulation of both mechanisms is based on the minimization of microenvironmental entropy in physiological tissues, which allows us to predict the multicellular spatiotemporal dynamics. This assumption is supported by the fact that healthy physiological processes, biological development or processes like wound healing, where EMT/MET or GoG are present, typically lead to an ordered (low entropy) tissue from a disordered initial condition. On the other hand, deregulation of EMT and GoG have been already identified as pivotal elements in invading cancers [9, 31], where genetic and phenotypic heterogeneity, characterized by high entropy, is a key characteristic. Assuming a LEUP-driven migration/proliferation phenotypic regulation allows us to understand how cells control multicellular dynamics in terms of growth and patterning.

**Implications on multicellular growth control:** The central finding of our study is associated with the bifurcation diagram of the LEUP sensitivity parameter $\beta$ in figure 4(a). As stated before, the parameter $\beta$ quantifies how prone cells are in sensing and responding to their microenvironmental stimuli. When $\beta = 0$ cells migrate and proliferate independent of their microenvironmental cues, which corresponds to one of the cancer hallmarks [32]. In this case, the systems grows uncontrollably, resembling a cancerous tissue [32]. The resulting Fisher–Kolmogorov macroscopic behavior has been prototypically used to model invading tumors [33]. Moreover, for low $\beta$ our theory predicts no spatial order in terms of clustering, implying ‘flat’ radial distribution functions (see figure 2(b)). This finding is confirmed by the spatial analysis of patient glioma biopsy samples in Jiao et al [23]. On the other hand, by adding a death process for any motility state in the GoG model, we can recapitulate the Allee effect (bistability between extinction and growth) as found in Böttger et al [34]. A cell population in the ‘fluid’ state will go extinct (motile cells do not proliferate but still have a probability to die) whereas systems in the ‘solid’ state will always grow until carrying capacity. Therefore, in the bistability regime cell sensing properties lead to multicellular growth control.

**Implications on multicellular pattern control:** Increased cell sensing $\beta$ represents the physiological tissue dynamics, since it allows the system to control its behavior. By tuning $\beta$ and the ratio of motile/resting cells, the system exhibits a bistable behavior between a ‘fluid’/mesenchymal-type and a ‘solid’/epithelial-type tissue phase. This kind of tissue level switch is of utmost importance in physiological processes such as wound healing or embryogenesis [35]. After a tissue injury, the healing is characterized by a ‘fluid’ diffusive expansion of fibroblast cells, that adopt a migratory phenotype via EMT [36]. After covering the wound, the ‘solid’ phase emerges as cells stop the migration program and proliferate to finalize tissue repair. In the absence of proliferation, the bistable switch from the ‘solid’ to the ‘fluid’ state could potentially explain the jamming phase transition observed in epithelial colonies, under EGF modulation and Rab5a knock-out [37]. Typically, the ‘solid’ multicellular phase is prone to the emergence of pattern formation, which frequently occurs in physiological epithelial tissues [36, 38]. When EMT is combined with a Notch-Delta cell–cell communication then epithelial/immotile cell clusters emerge [27], as observed in our IBM and mean-field simulations. Adding proliferation in the GoG model, the type and the size of such emerging patterns require a tight regulation of microenvironmental sensing $\beta$ and proliferation rate $r$, as indicated by figure 11(a), since the critical wavelength $k_c$ depends on the ratio $\frac{\beta}{r}$. Such Turing patterns are in agreement with previous GoG studies [39], where Turing patterns where emerging.

At this point, we would like to outline some ideas on the experimental validation of LEUP. An ideal experimental system would involve a cell population exhibiting either EMT/MET or migration/proliferation plasticity. As an example of EMT/MET plasticity, we can choose an epithelial cell colony. The main premise of LEUP is that cells equip Bayesian inference to decide over their phenotypes, expressed as a combination of a sensed microenvironmental distribution of external variables and a phenotypic prior (cell intrinsic variable). As internal variables we can choose the cell motility and proliferation rates. The former can be measured by particle image velocitometry and the latter by live imaging or Ki67 (or BrdU) staining. Also we could pharmacologically control cell proliferation. As extrinsic variables we can assume the local cell density and in particular the corresponding fluctuations. The second moment of the local cell density depends on the average local cell density (first moment) and can be manipulated by localized cell ablation or by mixing with non-cellular material, such as collagen, thus creating different spatial cell distributions. After splitting the experiments in training and test data, one needs to fit the LEUP parameters, i.e. the sensitivity to the microenvironment and the interaction radius, according to training data in order to predict the experimentally measured test data. A good basis for our approach are experiments by Puliafito [40], which
show that increasing density in a colony of epithelial kidney cells may induce transitions from the mesenchymal to the epithelial phenotype (MET). In the future, one could also investigate the inverse transition and control the changes in the local cell density distribution. Such an experimental setting would allow us to support the LEUP hypothesis.

The focus of this paper is the application of the LEUP idea to study collective effects of different types of phenotypic plasticity allowing reversible adaptations to changing environmental conditions. However, the LEUP idea can also be applied to analyze collective effects of irreversible cell fate determination playing a key role in cell differentiation and development. In particular, early embryonic tissue consists of a mix of proliferating pluripotent progenitor cells [41]. In this case the cellular microenvironment possesses a high phenotypic entropy since all possible phenotypes are still equiprobable. Subsequently, spatial mechanochemical perturbations produce appropriate microenvironmental changes leading to so-called stem cell niches that allow for cell differentiation [42]. Pluripotent cells sense a broad spectrum of microenvironmental cues aiming to find an appropriate differentiation niche. As pluripotent cells further specialize, they irreversibly fine-tune their sensing machinery to adapt to the corresponding microenvironment which further differentiates to a specific tissue (implying minimization of microenvironmental entropy). A particularly important cell fate specification mechanism is the Notch-Delta interaction [43], where neighboring cells use lateral inhibition to adapt distinct fates (high Delta low Notch and vice versa). The collective effect of this mechanism is the evolution of the system to low entropy organized patterns [44]. Currently, we try to understand cell fate determination and tissue development under the prism of LEUP. Our vision is that describing phenotypic plasticity and cell fate determination within the LEUP framework allows to develop a unified theory for both types of cell decision-making and their corresponding dynamics.

In conclusion, our study shows how individual LEUP-driven cell decisions affect the dynamics at the tissue level and how knowledge of collective cell decision-making can be used to control growth and pattern formation.

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