A Multiscale Model of Cell Motion in a Chemotactic Field

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Abstract. The Cellular Potts Model (CPM) has been used at a cellular scale for simulating various biological phenomena such as differential adhesion, fruiting body formation of the slime mold Dictyostelium discoideum, angiogenesis, cancer invasion, chondrogenesis in embryonic vertebrate limbs, and many others. Continuous models in the form of partial differential, integral or integro-differential equations are used for studying biological problems at large scale. It is crucial for developing multi-scale biological models to establish a connection between discrete stochastic models, including CPM, and continuous models. To demonstrate multiscale approach we derive in this paper continuous limit of a two dimensional CPM with the chemotactic interactions in the form of a Fokker-Planck equation describing evolution of the cell probability density function. This equation is then reduced to the classical macroscopic Keller-Segel model. Theoretical results are verified numerically by comparing Monte Carlo simulations for the CPM with numerics for the Keller-Segel model.

Keywords. Cellular Potts Model, Multiscale Model, Chemotaxis, Discrete Stochastic System, Monte-Carlo Simulation, Continuous Limit.

1. Introduction

Models of biological problems fall into two categories: continuous models that use families of differential or integro-differential equations to describe "fields" of interaction, and discrete models in which space, time or state may be discrete. Models may be deterministic or stochastic. Equations in the continuous models

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often describe fields of cell concentration or force and long-range interactions including chemotaxis. Discrete models describe individual (microscopic) behaviors. They are often applied to microscale events where a small number of elements can have a large (and stochastic) impact on a system. For example, while many periodic growth patterns can be modeled using continuous methods, such patterns which depend sensitively on substrate concentration are best modeled with discrete methods including Cellular Potts Model (CPM) first introduced in [1, 2, 3].

CPM is a cell-level, energy-minimization-based, lattice model which uses an effective energy \( H \) coupled to external fields, e.g., the local concentrations of diffusing chemicals, to describe cell-cell interactions, cell adhesion, motion, differentiation, division and apoptosis. The effective energy mixes true energies, like cell-cell adhesion, and terms that mimic energies, e.g., the response of a cell to a chemotactic gradient. Given an effective energy one can calculate the resulting cell motion, with individual lattice sites evolving according to the classical Metropolis algorithm with Boltzmann statistics, as the gradient of the effective energy. Since the cells’ environment is extremely viscous, cells move to minimize their total effective energy, given the form of the energy, constraints and boundary conditions.

A CPM consists of a list of biological cells, a list of generalized cells, a set of chemical diffusants and a description of their biological and physical behaviors and interactions embodied in the effective energy, with auxiliary equations to describe absorption and secretion of diffusants and extracellular materials, state changes within the cell, mitosis and cell death, and the behavior of extracellular diffusants.

Multiscale, experimentally motivated simulations have successfully used the CPM to reproduce, amongst others, morphological phenomena in the cellular slime mould Dictyostelium discoideum [4, 5], vascular development [6] and behavior of eukariotic cells [7]. In [8, 9] a three-dimensional multiscale approach based on combining discrete and continuum models of biological mechanisms, has been used for simulating the proximo-distal increase in the number of skeletal elements in the developing avian limb.

The CPM discretizes space into a 3D lattice. Each lattice point contains an integer index that identifies the cell, ECM element or other object to which it belongs. Separate lattices contain concentrations of diffusants, which evolve under partial differential equations (PDEs), while sets of state maps and ordinary differential equations (ODEs). The effective energy mixes true energies, like cell-cell adhesion, and terms that mimic energies, e.g., the response of a cell to a chemotactic gradient. The configuration evolves through attempts to copy an index from a site into a neighboring site with a different index. This index copy changes the effective energy and the change is accepted with a probability that depends on the change of energy due to the copy according to an acceptance function. A typical CPM effective energy might contain terms for adhesion, a cell volume constraint and chemotactic term

\[
E = E_{\text{Adhesion}} + E_{\text{Volume}} + E_{\text{Chemical}}.
\] (1.1)
Thus the pattern evolves (and cells move) to minimize the total effective energy. This algorithm implements Metropolis dynamics with Monte-Carlo Boltzmann acceptance.

There is a vast literature on studying continuous limits of point-wise discrete microscopic models. In particular, classical Keller-Segel model [11] has been derived from a model with point-wise representation for cells undergoing random walk [12, 13, 14, 15]. However, much less work has been done on deriving macroscopic limits of microscopic models which treat cells as extended objects. One of the first attempts at combining microscopic and macroscopic levels of description of cellular dynamics has been described in [18] where the diffusion coefficient for a collection of noninteracting randomly moving cells has been derived from a one dimensional CPM. Recently a microscopic limit of subcellular elements model [19] was derived in the form of an advection-diffusion partial differential equation for cellular density.

In the present paper we establish a connection between a two-dimensional CPM of a cell moving on a substrate and reacting to a chemical field, and a Fokker-Planck equation for the cell probability density function. This equation is then reduced to the classical macroscopic Keller-Segel equation. In particular, we derive all coefficients of the Keller-Segel model from parameters of the CPM. We also compare Monte Carlo simulations for the CPM with numerics for the Keller-Segel model to support our theoretical results.

Unified multiscale approach, described in this paper and based on combining microscopic and macroscopic models, can be applied to studying biological phenomena of streaming in *Dictyostelium discoideum*. In starved populations of *Dictyostelium* amoebae, cells produce and detect a communication chemical (cAMP). The movement of *Dictyostelium* cells changes from a random walk to a directed walk up the cAMP gradient resulting in formation of streams of cells towards the aggregation center (see Fig. 1a) and subsequent formation of multi-cellular fruiting body. Figure 1b shows cells' movement from left to right in response to waves of cAMP travelling through the aggregation stream from right to left. The cAMP gradient on the up-down direction is very small and could be ignored. Figure 1c schematically demonstrates the main features of the cell movement. Unlike differential adhesion, chemotactic cell motion is highly organized over a length scale significantly larger than the size of a single cell. (For details about modeling *Dictyostelium discoideum* fruiting body formation see e.g. [20, 21]).

The structure of this paper is as follows. We describe first a CPM for chemotactic cell movement in one spatial dimension. Models of this type arise e.g. in streaming of cells as described above. We investigate the continuum limit of this model and recover the well-known Keller-Segel equations in the limit of the lattice grid size going to zero. We extensively tested our results numerically. These results have appeared in a previous paper [22].

In the second part of the paper we extend our approach to a two dimensional CPM with simplified spin flip rules for studying cell motion in a plane. We derive the continuum limit of this model and test our results numerically.
2. One dimensional model

We consider a quasi-one-dimensional CPM, which means that cells are assumed to move along $x$ direction only and have fixed thickness $l_y$ in $y$ direction (see Fig. 1). Let $\varepsilon \Delta x$ denote the size of lattice site, where $0 < \varepsilon \ll 1$, $\varepsilon$ is the small dimensionless constant and $\Delta x$ is dimensional constant of the order of one. Each lattice site is described by its index $i = 0, 1, \ldots$, so that the center of each lattice site is located at $x = i \varepsilon \Delta x$ with the lattice site left border at $x_l = (i - \frac{1}{2}) \varepsilon \Delta x$ and the lattice site right border at $x_r = (i + \frac{1}{2}) \varepsilon \Delta x$ (see Figure 2.)
In what follows, we will consider a dynamics of single cell so that spin $\sigma$ can take two values: 0 if cell is absent at given site and 1 if cell occupies given site. However, our results remain valid for an ensemble of $n$ cells which are well separated from each other, so that probability that two cells would try to occupy the same volume is negligible. This allows to neglect cell-cell contact interaction. We assume that cell can interact only with the substrate and the chemical field $c(x)$. Chemical field is assumed to depends only on $x$ but not on $y$. Cells can also produce a chemical which then diffuses. In Section 6 we discuss production of chemicals by cells.

For a given configuration $\sigma$ of spins, let $N = N(\sigma)$ denote the number of lattice sites that the cell occupies. The length of the cell is equal to $L = N\varepsilon\Delta x$. We denote the position of the center of mass of the cell by $x$ and denote position of the left and right ends of the cell by $x_l$ and $x_r$ respectively. Then $L = x_r - x_l$ (see Figure 2).

We assume that the chemical field $c(x)$ is a slow function of time so its typical time scale is much bigger than the time step of a Monte Carlo algorithm. Then the Hamiltonian is then given by the formula:

$$E = J_{cm} \cdot (2L + 2\ell_y) + \lambda (L - L_T)^2 + \mu c(x)L.$$  \hfill (2.1)

The first term is a surface energy term which corresponds to the cell-substrate interaction energy, where $J_{cm}$ is an interaction energy between the cell and the medium per unit length. The second term is a length-constraint term which penalizes deviations of the cell length $L$ from the target cell length $L_T$. Here $\lambda$ is a positive constant. Choice of $\lambda$ and $\beta$ is determined by the typical scale of fluctuations of cellular membraim. The third term in (2.1) is the coupling chemical energy. This term will favor cell motion down or up the chemical gradient for $\mu > 0$ and $\mu < 0$ respectively. We assume that the concentration $c(x)$ is a slow function of $x$ on a scale of the typical cell’s length $L$:

$$x_c/L \gg 1,$$  \hfill (2.2)
where \( x_c \) is a typical scale for variation of \( c(x) \) in \( x \). This is consistent with the generally accepted view that cells are typically too small to detect chemical gradients without moving. Note that chemical energy can defined as \( \mu \int_{x_l}^{x_r} c(x)dx \). But in the limit (2.2) it is equivalent to the form used in the Hamiltonian (2.1).

3. Discrete evolution equation for probability density of a cell in CPM

In this section we develop analytical model for the evolution of the stochastic dynamics of a cell in CPM.

Let \( P(x, L, t) \) be the probability density for the cell with the center of mass at \( x \) of length \( L \) at time \( t \). Spins \( \sigma(i) \) are defined on the lattice \( \mathcal{L} \) so that length of the cell \( L \), which is the difference between positions of right and left ends of cell: \( L = x_r - x_l \), can take values \( n\varepsilon \Delta x, n = 1, 2, \ldots \). Position of the center of mass \( x = (x_r + x_l)/2 \) can take values \( n\varepsilon \Delta x/2, n = 1, 2, \ldots \). That is, the CPM grid is twice the size of the grid of center of mass. In particular, if \( 2\varepsilon \Delta x/2 \) is an even number (i.e. \( x \) coincides with one of the lattice sites) then ratio \( L/\varepsilon \Delta x \) is also an even number. Alternatively, if \( 2\varepsilon \Delta x/2 \) is an odd number (i.e. \( x \) coincides with a boundary between two neighboring lattice sites) then the ratio \( L/\varepsilon \Delta x \) is an odd number.

\( P(x, L, T) \) is normalized in such a way as to make it a probability density function for a continuous limiting equation. It means that probability for a cell to have the center of mass at \( x \) and the length \( L \) at time \( t \) is given by \( (\varepsilon \Delta x)^2 P(x, L, T) \), where \( \varepsilon \Delta x/2 \) is spacing between nodes \( 2\varepsilon \Delta x \) the spacing in \( L \) for a fixed \( x \).

The time interval between two Monte Carlo steps is \( \varepsilon^2 \Delta t \), where \( \Delta t \) is a fixed constant of dimension of time. This implies diffusive time-space scaling,

\[
\frac{\varepsilon^2 \Delta t}{(\varepsilon \Delta x)^2} = \frac{\Delta t}{(\Delta x)^2}
\]

which is independent of the scaling parameter \( \varepsilon \). We now switch from measuring time in Monte Carlo steps \( n = 0, 1, \ldots \), to a continuous time variable \( t = n \varepsilon^2 \Delta t \).

Suppose at time \( t \) the cell is at a state \( (x, L) \) meaning that it has length \( L \) and its center of mass is at \( x \). Stochastic discrete system at time \( t + \varepsilon^2 \Delta t \) can switch to one of the following four possible states:

(a) \( (x + \varepsilon \Delta x/2, L + \varepsilon \Delta x) \) by adding the lattice site \( x_r + \varepsilon \Delta x \) to the right end of cell;
(b) \( (x + \varepsilon \Delta x/2, L - \varepsilon \Delta x) \) by taking away the site \( x_l \) from the left end of the cell;
(c) \( (x - \varepsilon \Delta x/2, L + \varepsilon \Delta x) \) by adding the lattice site \( x_l + \varepsilon \Delta x \) to the left end of cell;
(d) \( (x - \varepsilon \Delta x/2, L - \varepsilon \Delta x) \) by taking away the site \( x_r \) from the right end of the cell.
Therefore, the most general master equation has the form
\[
P(x, L, t + \varepsilon^2 \Delta t) = \left[ 1 - T_l(x - \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x; x, L, t) \right.
\]
\[-T_r(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x; x, L, t) - T_l(x + \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x; x, L, t)
\]
\[-T_r(x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x; x, L, t) \right] P(x, L, t)
\]
\[+ T_l(x, L; x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x, t) P(x + \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x, t)
\]
\[+ T_r(x, L; x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x, t) P(x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x, t)
\]
\[+ T_l(x, L; x - \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x, t) P(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x, t)
\]
\[+ T_r(x, L; x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x, t) P(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x, t),
\]
(3.1)
where \(T_l(x, L; x', L')\) and \(T_r(x, L; x', L')\) correspond to transitional probabilities for a cell of length \(L'\) and center of mass at \(x'\) to change into a cell of length \(L\) and center of mass at \(x\). Subscripts "l" and "r" corresponds to transition due to addition/removal of a pixel from the left/right side of a cell respectively. These transition probabilities are given by
\[
T_l(x, L; x', L') = T_r(x, L; x', L') = \frac{1}{4} \Phi \left( E(x, L) - E(x', L') \right),
\]
(3.2)
where \(E(x, L)\) is the Hamiltonian (2.1) and \(\Phi(\Delta E)\) is given by Eq. (2.3). Factor 1/4 in (3.2) accounts transitions to 4 possible states (a)-(d). For computational purposes it is convenient to rewrite (2.3) in an equivalent form
\[
\Phi(\Delta E) = 1 - \left[ 1 - \exp \left( -\beta \Delta E \right) \right] \Theta(\Delta E).
\]
(3.3)
Here \(\Theta(x) = 1\) for \(x \geq 0\) and \(\Theta(x) = 0\) for \(x < 0\) is a Heaviside step function.

4. Continuous evolution equation for probability density of CPM

In follows we assume \(\varepsilon\) to be small so that a change of a cell size and position is small at each Monte-Carlo step. Now we substitute Taylor’s series expansion in \(\varepsilon\) in Eq. (9.1). One has to take special care of \(\Theta(\Delta E)\) terms in the expansion because the Heaviside step function is not analytic. To avoid this difficulty we do not expand the function itself but only its argument instead. There is an important simplification which comes from the fact that \(\Theta(\Delta E) + \Theta(-\Delta E) = 1\) so that in Eq. (9.1) we obtain that \(T_{l, r}(x, L; x', L', t) + T_{l, r}(x', L'; x, L, t) = (1/4) \exp \left( -\beta |E(x, L) - E(x', L')| \right)\). This yields mutual cancellation of nonanalytical terms up to order \(O(\varepsilon^2)\). Then, equating coefficients in Taylor’s expansion in Eq. (3.1) up
to $O(\varepsilon^2)$ results in the Fokker-Planck equation
\[
\partial_t P(x, L, t) = D(\partial_x^2 + 4\partial_L^2)P + 8D\beta\lambda\partial_L(\bar{L}P) + D\beta\mu\partial_x[c'(x)P],
\]
\[
\bar{L} = \frac{1}{\lambda}\left[J_{cm} + \lambda(L - L_T) + \frac{1}{2}\mu c(x)\right], \quad D = \frac{(\Delta x)^2}{8\Delta t}. \quad (4.1)
\]

Assume that terms $D4\partial_L^2P + 8D\beta\lambda\partial_L(\bar{L}P)$ dominate other terms in the right hand side of Eq. (4.1) under certain conditions to be described in the end of this section. It means that at the leading order one can neglect terms with "x" derivatives. Under that assumption, the probability density $P(x, L, t)$ approaches the Boltzmann distribution of cell’s length exponentially in time at the rate of $8D\beta\lambda$:
\[
P(x, L, t) = P_{Boltz}(x, L)p(x, t), \quad (4.2)
\]
where $p(x, t)$ is a probability density function of finding cell’s center of mass at $x$. $P_{Boltz}(x, L)$ is a Boltzmann distribution of cell’s length given by
\[
P_{Boltz}(x, L) = \frac{1}{Z}\exp(-\beta\Delta E_{length}), \quad (4.3)
\]
\[
\Delta E_{length} = E(L) - E_{min} = \lambda\bar{L}^2, \quad (4.4)
\]
where $E_{min}$ is a minimum of energy $E(L)$ as a function of $L$ for a given $x$,
\[
E_{min} = E(L_{min}), \quad L_{min} = L_T - \frac{J_{cm}}{\lambda} - \frac{\mu c(x)}{2\lambda}, \quad (4.5)
\]
and $Z$ is a partition function
\[
Z(x) = 2\varepsilon\Delta x \times \sum_{L=(1+\alpha)\varepsilon\Delta x, (3+\alpha)\varepsilon\Delta x, (5+\alpha)\varepsilon\Delta x,...} \exp(-\beta\Delta E_{length}), \quad \alpha = 1 \text{ for } \frac{x}{\varepsilon\Delta x} = n, \quad \alpha = 0 \text{ for } \frac{x}{\varepsilon\Delta x} = n + 1/2, \quad n \in \mathbb{N}. \quad (4.6)
\]
Here we use the fact that due to discrete nature of our model, the position of the center of mass, $x$, could be located at one of the lattice sites $x = m\varepsilon\Delta x$ ($m$ being an integer number) if length of a cell $L$ is an even number of units $\varepsilon\Delta x$ or $x$ could be located at a boundary between two neighboring lattice sites in case of $L$ being equal to an odd number of units of $\varepsilon\Delta x$. Factor $(\varepsilon\Delta x)^2$ in the definition of a partition function (4.6) is chosen in such a way as to yield $\int P(x, L, t)dLdx = 1$ one in continuous limit. We can also normalize $\int P(x, L, t)dLdx = N$ to a total number of cells in the system $N$.

In continuous limit, $\varepsilon \to 0$, summation in Eq. (4.6) is transformed into integral
\[
Z \approx \int_{-\infty}^{+\infty} \exp(-\beta\Delta E_{length})dL = \frac{\sqrt{\pi}}{\sqrt{\beta\lambda}} \quad x \to 0. \quad (4.7)
\]
Here we extend limits of integration from $(0, +\infty)$ to $(-\infty, +\infty)$. Of course physically length of a cell $L$ is always positive. A typical fluctuation of a cell size $\delta L = L - L_{min}$ about $L_{min}$ is determined by the Boltzmann distribution (4.2) as
\( \beta \lambda \delta L^2 \sim 1 \). In what follows we make a biologically motivated assumption about fluctuations of a cell size being much smaller than \( L \): \( |\delta L| \ll L_{\text{min}} \) which results in the condition

\[
\beta L_{\text{min}}^2 \lambda \gg 1. \tag{4.8}
\]

This justifies use of integration limits \((-\infty, +\infty)\) in Eq. (4.7) instead of \((0, +\infty)\) because under this condition \( \exp(-\beta \Delta E_{\text{length}}) \) peaks around \( L_{\text{min}} \) and replacement of integration limits results in an exponentially small correction.

Now we can specify conditions for applicability of the Boltzmann distribution approximation (4.2). Because of \( \beta \lambda \delta L^2 \sim 1 \), one can neglect first term with \( x \) derivative in right hand side of Eq. (4.1), \( |\partial_2^2 x P| \ll |4 \partial_2^2 L P| \), provided that

\[
\beta x_0^2 \lambda \gg 1. \tag{4.9}
\]

Here \( x_0 \) is a typical scale of \( P \) with respect of \( x \). We assume that \( L_{\text{min}} \ll x_0 \), i.e. that the typical length of a cell is much smaller than \( x_0 \). Then condition (4.9) follows from (4.8). The second condition for applicability of Boltzmann distribution approximations is an assumption of the last term with \( x \) derivative in Eq. (4.1) being small, \( |\beta \lambda \nu \partial_x [c'(x) P]| \ll |4 \partial_2^2 L P| \). This results in

\[
|L_{\text{min}} \mu c_0|(1 + \frac{x_c}{x_0}) \ll \lambda x_0^2, \tag{4.10}
\]

where \( c_0 \) is a typical amplitude of \( c(x) \) and \( x_c \) is a typical scale of variation of \( c(x) \) with respect to \( x \). Lastly, recall that we derived continuous Eq. (4.1) from master equation (9.1) under the condition of step in \( x \) being small

\[
\varepsilon \ll 1. \tag{4.11}
\]

Notice that \( \beta \) in the expression for a diffusion coefficient \( D \) in Eq. (4.1) does not have a meaning of an inverse temperature. It determines instead a rate of convergence \( 8D\beta \lambda \) of \( P(x, L, t) \) to the Boltzmann distribution (4.2).

We have solved both master equation (3.1) and its continuous limit (4.1) numerically with initial conditions \( P(x, L, 0) \) different from the Boltzmann distribution (3.1). Simulation described in Section 7 demonstrate that for each \( x \) solution \( P(x, L, t) \) indeed converges with respect to time to the Boltzmann distribution at an exponential rate of \( \sim 8D\beta \lambda \).

5. Fokker Planck equation for probability density \( p(x) \)

We now turn to calculating probability density \( p(x) \) of a center of cell’s mass being at \( x \). It is given by the sum over all possible lengths of a cell

\[
p(x, t) = 2\varepsilon \Delta x \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x, \ldots} P(x, L, t) \simeq \int_{-\infty}^{+\infty} P(x, L, t) dL,
\]

\[
\varepsilon \to 0, \quad \alpha = 1 \text{ for } \frac{x}{\varepsilon \Delta x} = n, \quad \alpha = 0 \text{ for } \frac{x}{\varepsilon \Delta x} = n + 1/2, \quad n \in \mathbb{N}, \tag{5.1}
\]

which reduces to Eq. (4.2) in the Boltzmann distribution approximation limit.
To derive closed equation for \( p(x) \) we substitute ansatz (4.2) into (4.1) and integrate both right hand and left hand sides of Eq. (4.1) with respect to \( L \) to obtain

\[
\partial_t p = D \partial_x^2 p - \partial_x [\xi(x)p \partial_x c(x)],
\]

\[
\xi(x) = \frac{D}{\lambda} \beta \mu\left[J_{cm} - \lambda L T + \frac{1}{2} \mu c(x)\right], \quad D = \frac{(\Delta x)^2}{8\Delta t}.
\] (5.2)

The conditions of applicability of Eq. (5.2) are given by Eqs. (4.8), (4.9), (4.10) and (4.11).

6. Reduction to Keller-Segel model

In this section we add time dependence to the chemical field \( c \) (concentration of chemoattractant) by including a diffusion equation with the source determined by the secretion of chemical by a cell

\[
\partial_t c = D_c \partial_x^2 c - \gamma c + a p,
\] (6.1)

where \( D_c \) is a diffusion coefficient of the chemical field, \( \gamma \) is a decay rate of the chemical field and \( a \) is a production rate of the chemical field.

The system of equations (5.2) and (6.1) is applicable if can be used under assumption that typical time scale \( \tau_c \) of diffusion of \( c(x, t) \), given by \( \tau_c = \frac{\Delta x^2}{D_c} \), is large in comparison with relaxation time \( \tau_r = \frac{1}{8D\beta\lambda} \) of \( P(x, L, t) \) to the Boltzmann distribution (4.2). Namely, this condition has the form

\[
\frac{\tau_c}{\tau_r} = 8D\beta\lambda \tau_c \gg 1,
\] (6.2)

where \( x_c \) is a typical spatial width of the distribution of \( c(x, t) \).

Eqs. (5.2) and (6.1) form a closed set of equations which is equivalent to the classical Keller-Segel model [24] of chemotaxis. If parameters satisfy condition

\[
|J_{cm} - \lambda L T| \gg \frac{1}{2} |\mu c(x)|,
\] (6.3)

than Eq. (5.2) reduces to the following commonly used form of the Keller-Segel model

\[
\partial_t p = D \partial_x^2 p - \xi_0 \partial_x [p \partial_x c],
\]

\[
\xi_0 = D\lambda \beta \mu J_{cm} - \lambda L T, \quad D = \frac{(\Delta x)^2}{8\Delta t}.
\] (6.4)

Probability density \( p(x, t) \) is a microscopic density in the Keller-Segel model. Notice that both in the Keller-Segel model and CPM model considered in this section, there is no direct interaction between cells except through production and reaction to a chemoattractant. In other words, cells are treated in a way similar to a dilute gas with long range nonlocal interactions due to reaction to a chemical field.
7. Numerical results and comparison between discrete and continuous models

In this section we describe numerical tests on comparison between Monte Carlo simulations of CPM and simulations of both discrete and continuous models for the probability densities $P(x, L, t)$ and $p(x, t)$.

7.1. Monte Carlo simulations

The computation of the frequency distribution of the cell center of mass and length for the CPM has been carried out as follows:

1. We ran a large number $N$ of CPM simulations with one cell with the same initial conditions.
2. We fixed a time interval $\delta t = \varepsilon^2 \triangle t$, i.e. a fixed number of Monte Carlo steps. For each simulation we recorded the locations of the center of mass and lengths of the cell at the times $t = \delta t, 2\delta t, 3\delta t, \ldots$.

The frequency distribution $P_{\text{cpm}}(x, L, t) = M(x, L, t) / (N(\varepsilon \Delta x)^2)$ is an approximation of the probability density function $P(x, L, t)$ for the center of mass of a cell of length $L$ being at $x$ at time $t$. Therefore, we compare $P_{\text{cpm}}(x, L, t)$ with $P(x, L, t)$ which is a solution of the either the master equation (3.1) or the Fokker-Planck equation (4.1). To approximate the probability density of center of mass $p(x, t)$ we sum up over all values of $L$ on the grid in a way used in Eq. (5.1)

$$p_{\text{cpm}}(x, t) = 2\varepsilon \Delta x \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x, \ldots} P_{\text{cpm}}(x, L, t),$$

$$\alpha = 1 \quad \text{for} \quad \frac{x}{\varepsilon \Delta x} = n, \quad \alpha = 0 \quad \text{for} \quad \frac{x}{\varepsilon \Delta x} = n + 1/2, \quad n \in \mathbb{N}. \quad (7.1)$$

In what follows we compare $p_{\text{cpm}}(x, t)$ for $\varepsilon \ll 1$ with the $p(x, t)$, a solution of the continuous Eq. (5.2), corresponding to the following choice of parameters

$$\lambda = 4, L_T = 5, J_{cm} = 2, \beta = 15, \mu = 0.1, \Delta x = 1, \Delta t = 1. \quad (7.2)$$

The size of the CPM lattice is chosen to be $L_{\text{cpm}} = 100$; and the model is typically run from $t_0 = 0$ to $t_{\text{end}} = 200$. The number of the CPM lattice sites and the number of Monte Carlo steps are chosen to be $L_{\text{cpm}} / \varepsilon \Delta x$ and $t_{\text{end}} / \varepsilon^2 \Delta t$ respectively. We use a range of values of $\varepsilon$ between 0.2 and 0.001.

The initial conditions for each CPM run are chosen as follows. A random pixel in the interval $[40, 60]$ is selected as a center of mass of a cell, and then the length $L$ for the cell is chosen with probability $Z_l^{-1} \exp(-\beta E(L))$. Here the normalization constant $Z_l$ is chosen to have the total probability 1. In most simulation we use the following distribution for the chemical field $c(x)$

$$c(x) = \frac{(x - 70)^2}{400}. \quad (7.3)$$
7.2. Monte Carlo simulations versus numerical solutions of the discrete master equation and Fokker-Planck equations

We first compare Monte Carlo simulations with the numerics for the master equation (3.1) and the Fokker-Planck equation (4.1). Simulations of the Fokker-Planck equation (4.1) have been performed by using finite-differences scheme. Figure 3 shows probability densities for all three types of simulations. Difference between the master equation (3.1) and the Fokker-Planck equation (4.1) simulations is negligibly small for $\varepsilon = 0.01$ (Fig. 3a) but can be clearly seen for $\varepsilon = 0.1$ (Fig. 3b). We conclude that for $N \to \infty$ Monte Carlo simulations converge to the solution of the master equation (3.1) for any $\varepsilon$. The rate of convergence is about $N^{-1/2}$.

For small $\varepsilon \to 0$ solution of the Fokker-Planck equation (4.1) also converges to the solution of the master equation.

7.3. Convergence of the probability density $P(x, L, t)$ to the Boltzmann distribution

To demonstrate quick convergence of $P(x, L, t)$ to the Boltzmann distribution (4.2) (indicated in Section 4) we solved numerically both the master equation (3.1) and its continuous limit (4.1) with initial conditions $P(x, L, 0)$ being different from the Boltzmann distribution (3.1). Linear-log plot in the Figure 4 indicates that convergence is indeed exponential in time with high convergence rate $\tau^{-1}$ ($\tau^{-1} = 98.55$ for parameters of Fig. 4). Because of $x$-dependent chemical field convergence rate is also $x$-dependent and closed analytical expression for convergence rate $\tau$ is difficult to obtain from Eq. (4.1) for general form of $c(x)$. However even simple estimate $\tau^{-1} = 8D\beta\lambda$ of convergence rate gives 60 for parameters of Figure 4 which is qualitatively close to 98.55 which was obtained from the linear fit presented in Figure 4.

Also, we observed that an increase in temperature in Monte Carlo simulations so that condition (4.8) was not held any more, resulted in a significant departure from the Boltzmann distribution (4.2) which confirms theoretical results of Section 4.

7.4. $P(x, L, t)$ vs. $p(x, t)$ simulations

Ansatz (4.2) can be used for a fast simulation of solutions of the discrete master equation. Summing up over all values of $L$ in the master Eq. (3.1) taking into account (4.2) results in a discrete equation for the probability density $p(x, t)$

$$p(x, t + \varepsilon^2 \Delta t) = \left[ 1 - T(x + \frac{\varepsilon}{2} \Delta x; x, t) - T(x - \frac{\varepsilon}{2} \Delta x; x, t) \right] p(x, t)$$

$$+ T(x; x - \frac{\varepsilon}{2} \Delta x, t) p(x - \frac{\varepsilon}{2} \Delta x, t) + T(x; x + \frac{\varepsilon}{2} \Delta x, t) p(x + \frac{\varepsilon}{2} \Delta x, t),$$

(7.4)

where $T(x; x', t)$ is a transition probability of a change of position of a center mass from $x'$ to $x$ at time $t$. Expressions for $T(x; x', t)$ are described in the Appendix. They are calculated only once at the beginning of a simulation which makes numerics for discrete Eq. (7.4) very efficient.
We have run simulations for the discrete equation (7.4) and continuous Eq. (5.2) and compared them with the solutions of discrete (3.1) and continuous (4.1) equations, respectively. We found, taking into account Eq. (4.2), that indeed the
differences between these solutions are very small for the typical values of parameters.

We conclude that the Monte Carlo simulations of CPM are equivalent in the limit of large $N$ to the the simulations of the discrete Eq. (7.4) for any $\varepsilon$.

7.5. Comparison of a continuous Eq. (5.2) with CPM

Below we denote as $p_{cpm}$ both Monte Carlo simulations and numerical solutions of Eq. (7.4) and as $p_{cont}(x, t)$ solutions of (5.2).

Figure 5 shows a series of simulations of the CPM (solid line) and numerical solutions of the continuous Eq. (5.2) (dotted line) for different values of $\varepsilon$. This Figure demonstrates that $\varepsilon$ decreases solution of the continuous Eq. (5.2) converges to CPM.

We have also run a series of tests for different forms of the chemical field $c(x)$ and demonstrated that solutions of the CPM and continuous Eq. (5.2) were close for small values of $\varepsilon$. Figure 6 shows a typical result of numerical simulations for a “double well” chemical concentration $c(x) = \cos(4\pi x/100)$. We conclude that numerical simulations show excellent agreement between CPM and continuous Eq. (5.2) provided that parameters satisfy conditions (4.8), (4.9), (4.10),(4.11) and $\varepsilon \to 0$, which correspond to a continuous limit of CPM.
Figure 5. Plots of $p_{cpm}$ (dotted line) and $p_{cont}(x, t)$ (solid line) as functions of $x$ for a series of decreasing values of $\varepsilon$ at time $t = 200$. All other parameters are the same as in Figure 3.

Figure 6. Typical results of CPM simulations. In this simulation, $t = 400$, number of Monte Carlo simulations is $N = 2 \times 10^5$, $c(x) = \cos(4\pi x/100)$, $\varepsilon = 0.01$. The same notation for solid, dashed and dotted curves as in Figure 3 is used here. The difference between position of solid curve and a dashed curve is again negligibly small.

8. Two dimensional CPM

In this section we assume that a cell has a rectangular shape and it moves or changes its shape by adding or removing a row or column of pixels (Fig. 7).
In Equation (1.1), $E_{\text{Adhesion}}$ phenomenologically describes the net adhesion or repulsion between cell membranes and ECM. It is the product of the binding energy per unit area, $J_{cm}$, and the area of contact between the cell and ECM. $J_{cm}$ depends on the specific properties of the interface between the interacting cell and ECM:

$$E_{\text{Adhesion}} = 2J_{cm}(L_x + L_y)$$  \hspace{1cm} (8.1)

In the typical CPM model, a cell has a prescribed target volume. We used target lengths $(L_x, L_y)$ of $x$ and $y$ directions to describe the size of the rectangular cell. $E_{\text{Volume}}$ exacts an energy penalty for deviations of the actual volume from the target volume and of the actual shape from the target shape:

$$E_{\text{Volume}} = \lambda_x (L_x - L_{T_x})^2 + \lambda_y (L_y - L_{T_y})^2,$$  \hspace{1cm} (8.2)

where $\lambda_x$ and $\lambda_y$ are constants, $L_{T_x}$ and $L_{T_y}$ are target cell lengths on $x$ and $y$ directions. $L_x$ and $L_y$ are real cell lengths on $x$ and $y$ directions. Another, alternative volume constraint term is $E_{\text{Volume}} = \lambda(L_x L_y - A_T)$, where $A_T$ is a constant target area. We will however use the term (8.2) exclusively here.

Cells can move up or down gradients of both diffusible chemical signals (i.e. chemotaxis) and insoluble ECM molecules (i.e. haptotaxis). The energy terms for...
both chemotaxis and haptotaxis are local. The simplest form for chemotactic or haptotactic effective energy is:

$$E_{\text{Chemical}} = \mu c(r)L_x L_y, \mathbf{r} = (x, y),$$  \hspace{1cm} (8.3)$$

where $C(r)$ is the local concentration of a particular species of signaling molecule in extracellular space and $\mu$ is the effective chemical potential.

Consider cell with rectangular shape so it has the length $L_x$ in $x$–direction and $L_y$ in $y$–direction. Generalization of the Hamiltonian to 2D gives

$$E(\mathbf{r}, \mathbf{L}) = 2J_{\text{chem}}(L_x + L_y) + \lambda_x (L_x - L_{T_x})^2$$
$$+ \lambda_y (L_y - L_{T_y})^2 + \mu c(r)L_x L_y,$$

$$\mathbf{r} = (x, y), \quad \mathbf{L} = (L_x, L_y).$$  \hspace{1cm} (8.4)$$

Here $L_{T_x}$ and $L_{T_y}$ are target lengths of cell in $x$ and $y$ directions, respectively.

9. Full 2D model for $P(\mathbf{r}, \mathbf{L}, t)$ function

Let $P(\mathbf{r}, \mathbf{L}, t)$ be a probability density for the rectangular cell with the center mass at $\mathbf{r} = (x, y)$ to have the size $(L_x, L_y)$ at time $t$. We use vectors $\mathbf{e}_{1,2}$ for jumps in $x$ and $y$ directions: $\mathbf{e}_1 = \triangle r(1, 0)$, $\mathbf{e}_2 = \triangle r(0, 1)$ and define vectors $\mathbf{L} = (L_x, L_y)$, $\mathbf{r} = (x, y)$. Lengths of these vectors can be made different by the factor $L_x/L_y$ to reflect the fact that change of cell size at each step can depend on length of cell in $x$ or $y$ direction, respectively. So that average change of cell’s size could be made proportional to either $1/L_x$ (in $x$ direction) or $1/L_y$ (in $y$ direction). From computational point of view however it would be easier not to change lengths of vectors $\mathbf{e}_{1,2}$ (to keep computation grid fixed) but multiply transition probabilities by additional $L_x$ and $L_y$ dependent factors. We however for now do not consider either of these two possible modifications.
The most general model which model Monte-Carlo simulations is the following master Eq.:

\[
P(r, L, t + \varepsilon^2 \Delta t) = \sum_{j=1}^{2} \left\{ \left[ 1/2 - T_{l}(r - \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}; r, L, t) - T_{r}(r + \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}; r, L, t) \right. \right.
\]
\[
- T_{l}(r - \varepsilon \frac{e_{j}}{2}, L - \varepsilon \triangle x; r, L, t) - T_{r}(r + \varepsilon \frac{e_{j}}{2}, L - \varepsilon \triangle x; r, L, t) \]
\[
+ T_{l}(r, L; r + \varepsilon \frac{e_{j}}{2}, L - \varepsilon e_{j}, t) P(r + \varepsilon \frac{e_{j}}{2}, L - \varepsilon e_{j}, t) \]
\[
+ T_{r}(r, L; r - \varepsilon \frac{e_{j}}{2}, L - \varepsilon e_{j}, t) P(r - \varepsilon \frac{e_{j}}{2}, L - \varepsilon e_{j}, t) \]
\[
+ T_{l}(r, L; r - \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}, t) P(r - \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}, t) \]
\[
+ T_{r}(r, L; r + \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}, t) P(r + \varepsilon \frac{e_{j}}{2}, L + \varepsilon e_{j}, t) \}
\]

(9.1)

where \(T_{l}(r, L; r', L')\) and \(T_{r}(r, L; r', L')\) correspond to to transition probability for jumps from cell with length \(L'\) and center of mass at \(x'\) to the cell with length \(L\) and center of mass at \(x\). Subscript "l" corresponds to transition due to addition/removal of element from the left side of cell (addition corresponds to \(|L| > |L'|\) and removal corresponds to \(|L| < |L'|\)) while subscript "r" corresponds to addition/removal of element from the right side of cell. According to Monte-Carlo algorithm these transition probabilities are given by

\[
T_{l}(x, L; r', L') = T_{r}(r, L; r', L') = \frac{1}{8} \Phi \left( E(r, L) - E(r', L') \right).
\]

(9.2)

Factor 1/8 here is due to the fact that we have 8 possibilities: increase or decrease \(L_{x}\) (4 possibilities) and increase or decrease \(L_{y}\) (4 possibilities).

Taylor series expansion of the master Eq. (9.1) in small \(\varepsilon\) gives full continuous model for probability density, \(P(r, L, t)\), for the cell with the center mass at \(r\) to have the length \(L\) at time \(t\):

\[
\partial_{t} P(r, L, t) = D_{2}(\partial_{x}^{2} + 4 \partial_{L_{x}}^{2}) P
\]
\[
+ 8 D_{2} \beta_{x} \partial_{L_{x}} \left( \tilde{L}_{x} P \right) + 8 D_{2} \beta_{y} \partial_{L_{y}} \left( \tilde{L}_{y} P \right) + D_{2} \beta_{x} L_{y} \mu \partial_{x} \left[ P \partial_{x} c \right],
\]
\[
\tilde{L}_{x} = \frac{1}{\lambda_{x}} \left[ J_{cm} + \lambda_{x}(L_{x} - L_{T_{x}}) + \frac{1}{2} L_{x} \mu c(r) \right],
\]
\[
\tilde{L}_{y} = \frac{1}{\lambda_{y}} \left[ J_{cm} + \lambda_{y}(L_{y} - L_{T_{y}}) + \frac{1}{2} L_{y} \mu c(r) \right], \quad D_{2} = \frac{(\Delta r)^{2}}{16 \Delta t},
\]
\[
\partial_{x}^{2} = \partial_{x}^{2} + \partial_{L_{x}}^{2}, \quad \partial_{L_{x}}^{2} = \partial_{L_{x}}^{2} + \partial_{L_{x}}^{2}.
\]

(9.3)

Note the difference in definition of the diffusion coefficient \(D_{2}\) here compare with the definition of the diffusion coefficient \(D\) in 1D, see equation (5.2).
10. Reduced model in 2D

Now assume that

\[ P(\mathbf{r}, \mathbf{L}, t) = P_{\text{Boltz}}(\mathbf{r}, \mathbf{L}) p(\mathbf{r}, t), \]  

(10.1)

where \( P_{\text{Boltz}}(\mathbf{r}, \mathbf{L}) \) is the Boltzmann distribution given by

\[ P_{\text{Boltz}}(\mathbf{r}, \mathbf{L}) = \frac{1}{Z(\mathbf{r})} \exp(-\beta \triangle E_{\text{length}}), \]  

(10.2)

and

\[ \triangle E_{\text{length}} = E(\mathbf{r}, \mathbf{L}) - E_{\text{min}} = \lambda_x \tilde{L}_x^2 + \lambda_y \tilde{L}_y^2 + \tilde{L}_x \tilde{L}_y \mu c(\mathbf{r}), \]

\( \tilde{\mathbf{L}} = \mathbf{L} - \mathbf{L}^{(\text{min})}, \)

(10.3)

\( E_{\text{min}} \) is the minimal value of the Hamiltonian as a function of \( \mathbf{L} \) for given \( \mathbf{r} \) which is achieved for \( \mathbf{L} = \mathbf{L}^{(\text{min})} \).

\[ E_{\text{min}} = E(\mathbf{r}, \mathbf{L}^{(\text{min})}), \]

\[ L_x^{(\text{min})} = 2 \frac{-2 \lambda_y (J_{cm} - \lambda_x L_{T_x}) + (J_{cm} - \lambda_y L_{T_y}) \mu c(\mathbf{r})}{4 \lambda_x \lambda_y - \mu^2 c(\mathbf{r})^2}, \]

\[ L_y^{(\text{min})} = 2 \frac{-2 \lambda_x (J_{cm} - \lambda_y L_{T_y}) + (J_{cm} - \lambda_x L_{T_x}) \mu c(\mathbf{r})}{4 \lambda_x \lambda_y - \mu^2 c(\mathbf{r})^2}, \]

(10.4)

and \( Z(\mathbf{r}) \) is the partition function:

\[ Z(\mathbf{r}) = (2 \varepsilon \triangle r)^2 \sum_{\mathbf{L}} \exp(-\beta \triangle E_{\text{length}}) \approx \int_{-\infty}^{+\infty} \exp(-\beta \triangle E_{\text{length}}) dL_x dL_y \]

\[ \approx \frac{2\pi}{\beta \sqrt{4 \lambda_x \lambda_y - \mu^2 c(\mathbf{r})^2}}, \]

\( \triangle r \to 0 \)

(10.5)

If we substitute ansatz (10.1) into Eq. (9.3) and integrate both left-hand-side (lhs) and right-hand-side (rhs) over \( L_x \) and \( L_y \) we arrive at reduced continuous model for probability density \( p(\mathbf{r}, t) \) for the location of the cell’s center of mass:

\[ \partial_t p = D_2 \partial^2_r p + \partial_r \cdot [\xi p], \]

\[ \xi(\mathbf{r}) = D_2 \mu \left\{ \frac{\eta_1 \eta_2}{[4 \lambda_x \lambda_y - \mu^2 c(\mathbf{r})^2]^2} - \frac{\mu c(\mathbf{r})}{4 \lambda_x \lambda_y - \mu^2 c(\mathbf{r})^2} \right\} \partial_r c(\mathbf{r}), \]

\[ \eta_1 = [-2 (J_{cm} - \lambda_y L_{T_y}) \lambda_x + (J_{cm} - \lambda_x L_{T_x}) \mu c(\mathbf{r})], \]

\[ \eta_2 = [-2 (J_{cm} - \lambda_x L_{T_x}) \lambda_y + (J_{cm} - \lambda_y L_{T_y}) \mu c(\mathbf{r})], \]

\[ D_2 = \frac{(\triangle r)^2}{16 \Delta t}. \]

(10.6)
The conditions of applicability of Eq. (10.6) are similar to conditions (4.8), (4.9), (4.10) and (4.11) for applicability of Eq. (10.6) with straightforward generalization to 2D case.

11. Reduction to Keller-Segel model in 2D

Similar to Section 6, we can add time dependence to the chemical field $c$ in 2D as

$$\partial_t c = D_c \nabla^2 c - \gamma c + a p,$$

(11.1)

where $D_c$ is a diffusion coefficient of the chemical field, $\gamma$ is a decay rate of the chemical field and $a$ is a production rate of the chemical field. The applicability conditions are the same as in Section 6.

Eqs. (10.6) and (11.1) form a closed set of equations which is equivalent to the classical Keller-Segel model [24] of chemotaxis in 2D. However, we can make additional biologically relevant assumption that

$$4 \lambda_x \lambda_y \gg \mu^2 c(r)^2,$$

(11.2)

which means that change of typical cell size due to chemotaxis, $(\delta L_x^{(\text{chemo})}, \delta L_y^{(\text{chemo})})$ is small, $|\delta L_x^{(\text{chemo})}| \ll L_x^{(\text{min})}$. In such a case $L_x^{(\text{min})}$ will not depend on $(x, y)$ and Eq. (10.6) further reduces to

$$\partial_t p = D_c \nabla^2 p - \chi_0 \nabla \cdot [p \nabla c(r)],$$

$$\chi_0 = -D_c \beta \nabla (\frac{\mu}{\lambda_x} L_T x),$$

$$D_2 = \frac{(\Delta t)^2}{16 \Delta t},$$

$$L_x^{(\text{min})} = L_T x - \frac{J_{cm}}{\lambda_x},$$

$$L_y^{(\text{min})} = L_T y - \frac{J_{cm}}{\lambda_y}.$$  

(11.3)

This is the most common form of the Keller-Segel model. So we showed in that Section that 2D Potts model with chemotactic interaction is equivalent in macroscopic limit to 2D Keller-Segel model for cellular density.

12. Comparison of numerical simulations of 2D

In this section, we describe numerical tests comparing Monte Carlo simulations of the CPM and simulations of both discrete and continuous models for the probability density functions $P(r, L, t)$ and $p(r, t)$, as given by Eqs. (9.1), and (10.6).
12.1. Monte Carlo simulations

The computation of the frequency distribution of the cell center of mass and length for the CPM has been carried out as follows:

1. We run a large number \( N \) of one cell CPM simulations with the same initial conditions.
2. We fix a time interval \( \delta t = \varepsilon^2 \Delta t \), i.e., we fix the time interval between successive Monte Carlo steps. In each Monte Carlo step, we randomly choose \( x \) or \( y \) direction to make a flip attempt on cell boundaries and calculate the corresponding acceptance probability from the energy change. If the flip attempt is accepted, then changes corresponding location of center of mass and lengths of the cell.
3. For each simulation we record the center of mass position and lengths of the cell \((L_x \text{ on } x \text{ direction and } L_y \text{ on } y \text{ direction}) \) at required time points.
4. After the \( N \) runs, the recorded data give a frequency distribution \( M(r, L, t) \) for the location of the center of mass of the cell and length of the cell.

The frequency distribution \( M(r, L, t) \) determines the approximation \( P_{cpm}(r, L, t) = \frac{M(r, L, t)}{(N (\varepsilon \Delta r)^2)} \) of the probability density function \( P_{cpm}(r, L, t) \) for the center of mass of a cell of length \( L \) being at \( r \) at time \( t \). Therefore, we compare \( P_{cpm}(r, L, t) \) with \( P(r, L, t) \) which is a solution of either the master equation (9.1) or the equation (10.6). To approximate the probability density function of center of mass \( p(r, t) \) we sum up over all values of \( L \) on the grid:

\[
p_{cpm}(r, t) = \left(2\varepsilon \Delta r\right)^2 \sum_{Q1} \sum_{Q2} P_{cpm}(r, L, t),
\]

\[
Q1 : L_x = (1 + \alpha)\varepsilon \Delta r, (3 + \alpha)\varepsilon \Delta r, (5 + \alpha)\varepsilon \Delta r, \ldots
\]

\[
Q2 : L_y = (1 + \beta)\varepsilon \Delta r, (3 + \beta)\varepsilon \Delta r, (5 + \beta)\varepsilon \Delta r, \ldots
\]

\[
\alpha = 1 \text{ for } x = n, \quad \alpha = 0 \text{ for } x = n + 1/2, \quad n \in \mathbb{N}
\]

\[
\beta = 1 \text{ for } y = n, \quad \beta = 0 \text{ for } y = n + 1/2, \quad n \in \mathbb{N}. \quad (12.1)
\]

In what follows, we compare \( p_{cpm}(r, t) \) for \( \varepsilon \ll 1 \) with \( p(r, t) \), a solution of the continuous Eq. (10.6), corresponding to the following choice of parameters \( \lambda_x = \lambda_y = 4, L_x^0 = 7, L_y^0 = 1, J_{cm} = 2, \beta = 15, \mu = 0.1, \Delta r = 1, \Delta t = 1 \).

The size of the CPM lattice is chosen to be \( L_x^c = L_y^c = 100 \); and the model is typically run from \( t_0 = 0 \) to \( t_{end} = 200 \). The number of the CPM lattice sites and the number of Monte Carlo steps are chosen to be \( \frac{L_x^c \cdot L_y^c}{(\varepsilon \Delta r)^2} \) and \( \frac{t_{end}}{\varepsilon^2 \Delta t} \) respectively. We use a range of values of \( \varepsilon \) between 0.2 and 0.01.

The initial conditions for each CPM run are chosen as follows. A random pixel in the interval \([40, 60], [40, 60] \) is selected as a center of mass of a cell, and then the length \( L \) for the cell is chosen with probability \( Z^{-1}_l \exp(-\beta E(L)) \). Here the normalization constant \( Z_l \) is chosen to have the total probability 1. In most simulations, we use the following distribution for the chemical field \( c(x, y) \):
\[ c(x, y) = \frac{(x - 70)^2 + (y - 60)^2}{400}. \] (12.2)

### 12.2. \( P(r, L, t) \) vs. \( p(r, t) \) simulations

The Eq. (10.1) can be used for fast simulations of solutions of the discrete master equation. Summing up over all values of \( L \) in the master Eq. (9.1) and taking into account (10.1) result in a discrete equation for the probability density function \( p(r, t) \)

\[
p(r, t + \varepsilon^2 \Delta t) = p(r, t) + \sum_{\Delta r} \left[ T(r, r + \Delta r, t)p(r + \Delta r, t) - T(r + \Delta r, r, t)p(r, t) \right],
\] (12.3)

where \( T(r, r', t) \) is a transition probability of a change of position of a center mass from \( r' \) to \( r \) at time \( t \). Expressions for \( T(r, r', t) \) are described in the previous paper [22]. They are calculated only once at the beginning of a simulation which makes the numerics for discrete Eq. (12.3) very efficient.

#### 12.3. Monte Carlo simulations versus numerical solutions of the discrete master equation

Numerical solution of the equation (9.1) requires huge computer memory to accommodate four dimensional array of \( P(x, y, L_x, L_y) \) for small \( \varepsilon \) ranged from 0.2 – 0.01 and in this case numerical calculation for (9.1) is impossible. We used the equation (12.3) to compare with the Monte Carlo simulations. We calculated solutions of the equation (12.3) with large \( \varepsilon \) values (i.e. 0.1). Figure 8 shows the result. We conclude that the Monte Carlo simulation of the CPM are equivalent in the limit of large \( N \) to the the simulations of the discrete Eq. (12.3) for any \( \varepsilon \). In this section, we cannot compare the result of the equation (9.1) with Monte Carlo simulations directly. However, based on our previous 1D results [22], we can conclude that the equation (9.1) converges with the equation (12.3) for any \( \varepsilon \). Therefore we also conclude that for \( N \to \infty \), the Monte Carlo simulations converge to the solution of the master equation (9.1) for any \( \varepsilon \). The rate of convergence is about \( N^{-1/2} \).

#### 12.4. Comparison of the continuous model with the CPM

Below we denote \( p_{cont}(x, y, t) \) as the solutions of the Eq. (10.6). Simulations of the continuous equation (10.6) have been performed by using a finite-differences scheme. The size of the mesh used in the finite-difference method is 200 \( \times \) 200 and the time step is 0.00002. We also tried smaller time steps to ensure the convergence of the result. Results are presented in Fig. 9.

The difference between the Monte Carlo simulation and the continuous model (10.6) is negligibly small for \( \varepsilon = 0.01 \) but can be clearly seen for \( \varepsilon = 0.1 \) in Fig. 9. For \( \varepsilon = 0.1 \), master equation (12.3) still converges to the Monte Carlo simulation (Figure 8). For small \( \varepsilon \to 0 \), the solution of the continuous equation (10.6) still
converges to the solution of the master equation because the master equation also converges to the Monte Carlo simulations when the $\varepsilon$ is small.

13. Conclusions

We combine microscopic and macroscopic levels of description of two dimensional cellular dynamics [23]. The microscopic level is represented by a two dimensional
Figure 9. Probability densities for Monte Carlo simulations $p_{cpm}(x, y, t)$ and $p(x, y, t)$ for the continuous Eq. (10.6) (a) Two dimensional probability density distributions for Monte Carlo simulation and the continuous model (the Eq. (10.6)), $\varepsilon = 0.1, 0.01$ $t = t_{end}$.  (b) Cross sections of probability densities of Monte Carlo simulations ($p_{cpm}(x_0, y, t)$ $\varepsilon = 0.1, 0.01$, The continuous model ($p_{con}(x_0, y, t)$) and the Master Eq. (12.3) ($p(x_0, y, t)$). $x_0 = 55.25$. For $\varepsilon = 0.01$, the difference between the Monte Carlo simulation and the continuous model is very small. However, for $\varepsilon = 0.1$, the difference between the Monte Carlo simulation and the continuous model is clear. The $c(x, y)$ is given by Eq. (12.2).

CPM with chemotaxis and without cell-cell adhesion term. We study a continuous macroscopic limit of our CPM as the size of Monte-Carlo step is made small under the assumption that changes in the cell’s position and length are also small. In this limit, we derive the Fokker-Planck equation for the probability density function...
$p(r, t)$ of cells and then further reduce it to the well-known macroscopic continuous Keller-Segel model for the chemotactic aggregation of cells.

We use numerical simulations to test hierarchy of models and assumptions which we used to derive continuous equation. In particular, we compare Monte Carlo simulations with simulations of both the discrete master equation and the Fokker-Planck equation. We find that, as expected from our theoretical analysis, all models agree for small $\varepsilon$. Also Monte Carlo simulations agree with the solutions of the discrete master equation for arbitrary $\varepsilon$. And finally, we find that numerical simulations show excellent agreement between Monte Carlo simulations of CPM and the continuous macroscopic model.

References


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