Multiscale dynamics of biological cells with chemotactic interactions: from a discrete stochastic model to a continuous description

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The Cellular Potts Model (CPM) has been used 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. In this paper, we derive continuous limit of discrete one dimensional CPM with the chemotactic interactions between cells in the form of a Fokker-Planck equation for the evolution of the cell probability density function. This equation is then reduced to the classical macroscopic Keller-Segel model. In particular, all coefficients of the Keller-Segel model are obtained from parameters of the CPM. Theoretical results are verified numerically by comparing Monte Carlo simulations for the CPM with numerics for the Keller-Segel model.

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I. INTRODUCTION

Biological cell dynamics has been studied at two main scales of description. The macroscopic level provides one with a coarse-grained treatment of biological cells through their macroscopically averaged quantities such as local density of cells [1, 2, 3, 4]. The macroscopic scale is large in comparison with the typical size of a cell. Macroscopic models are usually continuous and utilize families of differential or integro-differential equations to describe “fields” of interaction. A much more detailed approach is needed at the second, microscopic level which takes into account stochastic fluctuations of the shape of each individual cell.

Discrete models describe individual (microscopic) behaviors of cells. 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, patterns which depend sensitively on interaction between cells and substrate are best modeled with discrete methods. Simplest discrete models describe cells as point-wise objects. Some bacteria are self-propelled and do not change considerably their shape during motion (e.g. E. Coli [2, 5] and M. xanthus [6, 7] bacteria). They can be successfully represented as point-wise objects undergoing reorientation while moving [2, 8, 9]. In contrast, some other bacteria (e.g. Dictyostelium discoideum [10]) experience essential random fluctuations of their shapes and need to be treated as extended objects of variable shapes.

One of the microscopic models dealing with differential adhesion and shape fluctuations is a Cellular Potts Model (CPM) which is an extension of the well known Potts Model from statistical mechanics [11, 12]. In this model each biological cell is represented by a cluster of pixels (spins). The CPM has been used to simulate various biological phenomena such as cell sorting [11, 12], fruiting body formation of the slime mold Dictyostelium discoideum [13, 14], angiogenesis [15], cancer invasion [16], chondrogenesis in embryonic vertebrate limbs [17, 18], and many others. (Different applications of the CPM have been reviewed in [19].) Recently a new alternative model was suggested [20] which represents a cell as collection of subcellular elements which interact with each other through phenomenological intra- and intercellular potentials.

In addition to short range cell-cell adhesion and interactions between cells and their surrounding extracellular matrix (haptotaxis), cell interact over long range through signal transmission and reception mediated by a diffusing chemical field (chemotaxis). Continuous macroscopic Keller-Segel model of the evolution of the density of cells with chemotactic interactions have been extensively studied over the years. In particular, it has been successfully applied to the description of Escherichia coli bacteria aggregation due to chemotaxis in [2]. The drawback of continuous models is that they have a lower resolution than discrete models. However, their advantage is the availability of a large set of analytical and numerical tools for analyzing solutions of the corresponding nonlinear partial differential

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equations (PDEs). By contrast, the analytical study of discrete models is often impossibly complicated, and their computational implementation is often much less efficient in comparison with numerical methods available for PDEs. It is thus important, for numerical, analytical, as well as conceptual reasons to establish connections between various discrete and continuous models of the same biological problem.

There is a vast literature on studying continuous limits of point-wise discrete microscopic models. In particular, classical Keller-Segel model has been derived from a model with point-wise representation for cells undergoing random walk \[8\ 21, 22\]. 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 \[23\] 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 \[24\] was derived in the form of continuous advection-diffusion equation for cellular density. In the present paper, we establish a connection between a one-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 such biological phenomena as streaming in \textit{Dictyostelium discoideum}. In starved populations of \textit{Dictyostelium} amoebae, cells produce and detect a communication chemical (cAMP). The movement of \textit{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. 1h) 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 1i schematically demonstrates the main features of the cell movement. Unlike differential adhesion [11, 12], chemotactic cell motion is highly organized over a length scale significantly larger than the size of a single cell. (For details about modeling \textit{Dictyostelium discoideum} fruiting body formation see e.g. \[13\ 14, 24, 25\].)

The paper is organized as follows. In Section II we describe a one dimensional CPM with chemotaxis. In Section III we derive from the Monte Carlo dynamics of the CPM the discrete master equation for the probability density function \(P(x, L, t)\): that is, the probability that at time \(t\), there is a cell whose length is \(L\) and whose center of mass is located at \(x\). In Section IV we use the discrete master equation to derive a partial differential equation for \(P(x, L, t)\) in a continuous limit which assumes that cell changes its position and length at each Monte Carlo step by a small amount. We show that the dependence of \(P(x, L, t)\) on \(L\) is very close to the Boltzmann distribution. This is used in Section V for the derivation of a Fokker-Planck equation for the probability density function \(p(x, t)\) of a cell’s center of mass being at \(x\) which is the main result of the paper. In Section VI it is shown that addition of the time dependence of chemical field reduces the Fokker-Planck equation to the Keller-Segel equations. Section VII deals with numerical verification of the theoretical results of the previous sections and compares the Monte Carlo simulations for our CPM and Keller-Segel models.

## II. THE CELLULAR POTT'S MODEL

The Cellular Potts Model (CPM), an extension of the Potts Model from statistical mechanics, is a flexible and powerful way to model cellular patterns. Its core mechanism is the competition between the minimization of various energy terms in some generalized functional of the cellular configuration, e.g., surface minimization, cell-cell contact and chemotactic interactions, and global geometric constraints. It simulates stochastic fluctuations of cell shapes as simple thermal fluctuations.

The CPM is defined on a rectangular lattice \(\mathcal{L}\), which is of the form \([0, m_x]\) (for 1 dimension), \([0, m_x] \times [0, m_y]\) (for 2 dimensions) or \([0, m_x] \times [0, m_y] \times [0, m_z]\) (for 3 dimensions). (Here \([0, m]\) = \([0, 1, \ldots, m]\).) The elements of \(\mathcal{L}\) are called the lattice sites (intervals in 1D, pixels in 2D, voxels in 3D). A lattice site is denoted by an index \(i \in \mathcal{L}\).

Each lattice site has an assigned “spin” \(\sigma(i)\) which can have values \(s = 0, 1, \ldots, Q\), where \(s = 0\) corresponds to absence of any cell at the given site and the value \(1 \leq s \leq Q\) means that the given site is occupied by the \(s\)th cell, where \(Q\) is the total number of cell in the system. Assume that we fix the values of \(\sigma(i)\) at each lattice site, then we refer to that set of values as a configuration. The best way to visualize a configuration is to regard the different spins as different colors. Each lattice site \(i\) has a color \(\sigma(i)\). The cells are the collections of lattice sites that have the same spin (color), so that each lattice site can be occupied by a single cell only. White color correspond to absence of any cell at given site: \(\sigma(i) = 0\). In the model considered here we assume that cells cannot divide so that sites with the same color are always connected.

We assume periodic boundary conditions so that pixels at zero position in \(x, y\), or \(z\) are identical to sites with
FIG. 1: (a) Streaming of *Dictyostelium discoideum* towards the aggregation center. Cells move chemotactically towards the aggregation center leading to formation of cell streams and finally mounds. (Reproduced from [26] with permission). (b) Example of a quasi-one-dimensional motion of *Dictyostelium discoideum* inside a stream (this picture is on much smaller scale compared with (a)). Cells are moving parallel to each other in the direction of chemical gradient (from left to right). Chemical gradient also causes polarization of cells so that they become elongated in the direction of a gradient. (Reproduced from [10] with permission.) (c) Schematic picture of cell motion in a gradient of chemical field (e.g. chemo-attractant cAMP). The concentration of the chemical field is shown schematically above the main figure.

\[ i_x = m_x + 1, \ i_y = m_y + 1 \text{ and } i_z = m_z + 1, \text{ respectively.} \]

The temporal dynamics of the system is defined by certain probabilistic transition rules between the configurations, giving rise to a Markov chain of configurations, i.e. a sequence of configurations \( \sigma^0, \sigma^1, \sigma^2, \ldots \). To describe the transition rules, we associate to each configuration \( \sigma \) an energy \( E(\sigma) \), also referred to as the Hamiltonian. The state changes from one configuration to the next are governed by an energy minimization principle with effective temperature \( T \). This is implemented by means of the Metropolis algorithm for Monte-Carlo Boltzmann dynamics. The algorithm works as follows:

Given a configuration \( \sigma^n \), we randomly select a lattice site \( i \in \mathcal{L} \) such that not all of its nearest lattice neighbors have the same spin. We then randomly choose a lattice neighbor \( i' \) of \( i \) with \( \sigma^n(i') \neq \sigma^n(i) \). Let \( \sigma' \) be the configuration we obtain by “flipping” the spin of \( i \), i.e. we have \( \sigma'(j) = \sigma^n(j) \) for all \( j \neq i \), and \( \sigma'(i) = \sigma^n(i') \). The new configuration \( \sigma^{n+1} \) is then either \( \sigma^n \) or the configuration \( \sigma' \). The probability \( \Phi(\Delta E) \) that \( \sigma' \) is accepted as the next configuration \( \sigma^{n+1} \) depends on the energy difference \( \Delta E = E(\sigma') - E(\sigma^n) \). The formula is

\[
\Phi(\Delta E) = \begin{cases} 
1, & \text{if } \Delta E \leq 0 \\
\exp(-\beta \Delta E), & \text{if } \Delta E > 0 
\end{cases}
\]

Here \( \beta = 1/T \) is a positive constant.

In this paper, 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 the \( y \)-direction (see Fig. 2). 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 a 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 the dynamics of a single cell so that the spin $\sigma$ can take two values: 0 if cell is absent at a given site and 1 if cell occupies a given site. However, our results remain valid for an ensemble of $n$ cells which are well separated from each other, so that the probability that two cells would try to occupy the same volume is negligible. This allows us to neglect cell-cell contact interactions. We assume that cells can interact only with the substrate (haptotaxis) and the chemical field $c(x)$ (chemotaxis). The chemical field is assumed to depend only on $x$ but not on $y$. Cells can also produce a chemical which then diffuses. In Section VI we discuss production of chemicals by cells.

A natural biological realization of this quasi-one-dimensional model is the motion of biological cells in streams \cite{25}. E.g. the amoebae Dictyostelium discoideum under starving condition typically forms streams \cite{24}. The biological cells inside each stream are moving towards the aggregation center (see Fig. 1b), which results in complicated 2D patterns \cite{27}. If we zoom to a small scale, we will see that the motion of cells inside each stream is quasi-one-dimensional with cells moving parallel to each other in $x$-direction (Fig. 1b). The chemical gradient of the other direction ($y$ direction) could be neglected and during cells movement there is no cell-cell interactions, such as cell collisions or cell signaling. Fig. 1a: schematically shows such a parallel motion of the cells from left to right under the action of the gradient of a chemical field (chemo-attractant).

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 $x_c$ and denote the 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 given by the formula:

$$E = J_{cm} \cdot (2L + 2\ell_y) + \lambda (L - L_T)^2 + \mu c(x) L.$$  \hspace{1cm} (2)

The first term is a surface energy term which corresponds to the cell-substrate interaction energy (haptotaxis), 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. The choice of $\lambda$ and $\beta$ is determined by the typical scale of fluctuations of the cellular shape. The third term in (2) 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 $L$:

$$x_c/L \gg 1,$$  \hspace{1cm} (3)

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. (See e.g. \cite{27}; however recent experimental evidence may put this view in question \cite{28}.)

Note that the chemical energy could also be defined as $\mu \int_{X_c} c(x)dx$. But in the limit (3), this is equivalent to the form used in the Hamiltonian (2).

III. DISCRETE EVOLUTION EQUATION FOR PROBABILITY DENSITY FUNCTION

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

Let $P(x, L, t)$ be a 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 the 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 $n\varepsilon\Delta x$, $n = 1, 2, \ldots$. The 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 $2\frac{x}{\varepsilon\Delta x}$ is an even number (i.e. $x$ coincides with one of the lattice sites) then the ratio $\frac{x}{\varepsilon\Delta x}$ is also an even number. Alternatively, if $2\frac{x}{\varepsilon\Delta x}$ is an odd number (i.e. $x$ coincides with a boundary between two neighboring lattice sites) then the ratio $\frac{x}{\varepsilon\Delta x}$ is an odd number.

For convenience, we choose a normalization for $P(x, L, t)$ such that the probability for a cell to have its center of mass at $x$ and length $L$ at time $t$ is given by $(\varepsilon\Delta x)^2 P(x, L, t)$. The factor $(\varepsilon\Delta x)^2$ results from the product of $\varepsilon\Delta x$ (the spacing between lattice sites) and $2\varepsilon\Delta x$ (the spacing in $L$ for a fixed $x$). With this normalization, $P(x, L, t)$ becomes a true probability density in the continuous limit $\varepsilon \to 0$.

We choose the time interval between two Monte Carlo steps to be $\varepsilon^2\Delta t$, 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 $x$. The 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 for evolution of the probability density $P(x, L, t)$ has the form

$$P(x, L, t + \varepsilon^2\Delta t) = \left[1 - T_l(x - \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x; x, L, t) - T_r(x + \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x; x, L, t) - T_l(x + \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x; x, L, t) - T_r(x - \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x; x, L, t)\right]P(x, L, t)$$

$$+ T_l(x, L; x + \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x; x, L, t)P(x + \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x, t)$$

$$+ T_r(x, L; x - \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x; x, L, t)P(x - \frac{\varepsilon}{2}\Delta x, L - \varepsilon\Delta x, t)$$

$$+ T_l(x, L; x - \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x; x, L, t)P(x - \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x, t)$$

$$+ T_r(x, L; x + \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x; x, L, t)P(x + \frac{\varepsilon}{2}\Delta x, L + \varepsilon\Delta x, t),$$

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

$$T_l(x, L; x', L') = T_r(x, L; x', L') = \frac{1}{4}\Phi\left(E(x, L) - E(x', L')\right),$$

where $E(x, L)$ is the Hamiltonian [2] and $\Phi(\Delta E)$ is given by Eq. [11]. Factor 1/4 in [5] accounts transitions to 4 possible states (a)-(d). For computational purposes it is convenient to rewrite [11] in an equivalent form

$$\Phi(\Delta E) = 1 - \left\{1 - \exp\left[-\beta\Delta E\right]\right\}\Theta(\Delta E).$$

Here $\Theta(x)$ is a Heaviside step function: $\Theta(x) = 1$ for $x > 0$ and $\Theta(x) = 0$ for $x < 0$. 
IV. CONTINUOUS EVOLUTION EQUATION FOR PROBABILITY DENSITY FUNCTION OF CPM

Below we assume \( \varepsilon \) to be small, \( \varepsilon \ll 1 \), so that the change of the cell size and position is small at each Monte-Carlo step. Now we carry out a Taylor series expansion in \( \varepsilon \) of the terms in Eq. (4). One has to take special care of \( \Theta(\triangle E) \) terms in the expansion because the Heavyside 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 \( \Theta(\triangle E) + \Theta(-\triangle E) = 1 \) so that in Eq. (4) we obtain that \( T_{\eta,\tau}(x, L; x', L', t) + T_{\eta,\tau}(x', L'; x, L, t) = (1/4) \exp\left(-\beta|E(x, L) - E(x', L')|\right) \). This yields mutual cancellation of nonanalytical terms up to order \( O(\varepsilon^2) \). Then, equating coefficients in the Taylor expansion in Eq. (4) in order \( O(\varepsilon^2) \) results in the Fokker-Planck equation

\[
\partial_t P(x, L, t) = D(\partial_x^2 + 4\partial_L^2)P + 8D\beta\lambda\partial_L(\hat{L}P) + D\beta L\mu\partial_x [c'(x)P],
\]

\[
\hat{L} = \frac{1}{\lambda}\left[J_{cm} + \lambda(L - L_T) + \frac{1}{2}\mu\varepsilon(x)\right], \quad D = \frac{\triangle x^2}{8\triangle t}.
\]

(7)

Now, under certain conditions to be described in the end of this section, the terms \( D4\partial_L^2P + 8D\beta\lambda\partial_L(\hat{L}P) \) dominate the other terms on the right hand side of Eq. (7). This means that at the leading order, one can neglect terms with \( x \)-derivatives. Under this assumption, the probability density function \( P(x, L, t) \) approaches a Boltzmann distribution for cell length exponentially in time at the rate of \( 8D\beta\lambda \):

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

(8)

where \( p(x, t) \) is a probability density function of finding cell’s center of mass at \( x \). \( P_{\text{Boltz}}(x, L) \) is the Boltzmann distribution for the cell length given by

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

\[
\Delta E_{\text{length}} = E(L) - E_{\text{min}} = \lambda L^2,
\]

(9)

(10)

where \( E_{\text{min}} \) is a minimum of energy \( E(L) \) as a function of \( L \) for a given \( x \),

\[
E_{\text{min}} = E(L_{\text{min}}), \quad L_{\text{min}} = L_T - \frac{J_{cm}}{\lambda} - \frac{\mu\varepsilon(x)}{2\lambda},
\]

(11)

and \( Z \) is a partition function

\[
Z(x) = 2\varepsilon\Delta x \times \sum_{L = (1+\alpha)\varepsilon\Delta x, (3+\alpha)\varepsilon\Delta x, (5+\alpha)\varepsilon\Delta x, \ldots} \exp(-\beta\Delta E_{\text{length}}),
\]

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

(12)

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 the length of the cell \( L \) is an even number of units \( \varepsilon\Delta x \) or \( x \) could be located at the boundary between two neighboring lattice sites in case of \( L \) being equal to an odd number of units of \( \varepsilon\Delta x \). The factor \( (\varepsilon\Delta x)^2 \) in the definition of the partition function \( (12) \) is chosen in such a way as to yield \( \int P(x, L, t)dLdx = 1 \) in the continuous limit. We can also normalize \( \int P(x, L, t)dLdx = N \) to the total number of cells in the system \( N \).

In the continuous limit, \( \varepsilon \rightarrow 0 \), the sum in Eq. \( (12) \) is transformed into the integral

\[
Z \simeq \int_{-\infty}^{+\infty} \exp(-\beta\Delta E_{\text{length}})dL = \frac{\sqrt{\pi}}{\sqrt{\beta\lambda}}, \quad x \rightarrow 0.
\]

(13)

Here we have extended the limits of integration from \((0, +\infty)\) to \((-\infty, +\infty)\). Of course physically, the length of the cell \( L \) is always positive. A typical fluctuation of the cell size \( \delta L = L - L_{\text{min}} \) about \( L_{\text{min}} \) is determined by the Boltzmann distribution \( (12) \) as \( \beta\lambda\delta L^2 \sim 1 \). In what follows we make a biologically motivated assumption about fluctuations of the cell size being much smaller than \( L \): \( |\delta L| \ll L_{\text{min}} \) which results in the condition

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

(14)

This justifies the use of the integration limits \((-\infty, +\infty)\) in Eq. \( (13) \) 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.
Let us now specify the conditions for the applicability of the Boltzmann distribution approximation \(\eqref{eq:boltzmann} \). For this, consider Eq. \(\eqref{eq:boltzmann} \). We have \(\beta \lambda L^2 \sim 1\). We now assume in addition the relation

\[
\beta x_0^2 \lambda \gg 1, \tag{15}
\]

where \(x_0\) is a typical scale of \(P\) with respect of \(x\). Note that under the assumption that \(L_{\text{min}} \ll x_0\), i.e. that the typical length of a cell is much smaller than \(x_0\), the condition \(\eqref{eq:condition1} \) follows from \(\eqref{eq:condition2} \). It follows from \(\eqref{eq:condition5} \) that \(|\partial_x^2 P| \ll |4\partial_x^2 P|\), and consequently, we may neglect the first term with \(x\)-derivative, \(\partial_x P\), on the right hand side of Eq. \(\eqref{eq:boltzmann} \).

The second condition for the applicability of the Boltzmann distribution approximation \(\eqref{eq:boltzmann} \) is the assumption that the last term with \(x\)-derivative in Eq. \(\eqref{eq:boltzmann} \) is small, \(|\beta L \mu \partial_x [c'(x)P] \ll |4\partial_x^2 P|\). This is true if

\[
|L_{\text{min}} \mu c_0| \left(1 + \frac{x_c}{x_0}\right) \ll \lambda x_0^2, \tag{16}
\]

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 derive the continuous Eq. \(\eqref{eq:master} \) from the master equation \(\eqref{eq:master} \) under the condition of the step in \(x\) being small

\[
\varepsilon \ll 1. \tag{17}
\]

Notice that diffusion coefficient \(D\) in Eq. \(\eqref{eq:boltzmann} \) does not depend on \(\beta\). Instead \(\beta\) determines a rate of convergence \(\tau_r^{-1} = 8D \beta \lambda\) of \(P(x, L, t)\) to the Boltzmann distribution \(\eqref{eq:boltzmann} \).

We have solved both the master equation \(\eqref{eq:master} \) and its continuous limit \(\eqref{eq:boltzmann} \) numerically with initial conditions \(P(x, L, 0)\) different from the Boltzmann distribution \(\eqref{eq:boltzmann} \). Simulations described in Section VII demonstrate that for each \(x\), the solution \(P(x, L, t)\) indeed converges in time to the Boltzmann distribution at an exponential rate of \(\sim 8D \beta \lambda\).

V. FOKKER-PLANCK EQUATION FOR PROBABILITY DENSITY FUNCTION \(p(x, t)\)

We now turn to calculating the probability density function \(p(x, t)\) of a center of cell’s mass being at \(x\). It is given by the sum over all possible lengths of a cell

\[
p(x, t) = 2 \varepsilon \Delta x \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x,...} P(x, L, t) \approx \int_{-\infty}^{+\infty} P(x, L, t) dL, \quad \varepsilon \to 0,
\]

\[
\alpha = 1 \text{ for } \frac{x}{\varepsilon \Delta x} = n, \quad \alpha = 0 \text{ for } \frac{x}{\varepsilon \Delta x} = n + 1/2, \quad n \in \mathbb{N}, \tag{18}
\]

which reduces to Eq. \(\eqref{eq:boltzmann} \) in the Boltzmann distribution approximation limit.

To derive closed equation for \(p(x, t)\) we substitute ansatz \(\eqref{eq:boltzmann} \) into \(\eqref{eq:boltzmann} \) and integrate both right hand and left hand sides of Eq. \(\eqref{eq:boltzmann} \) with respect to \(L\) to obtain

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

\[
\chi(x) = \frac{D}{\lambda} \beta \mu \left[J_{cm} - \lambda L_T + \frac{1}{2} \mu c(x)\right], \quad D = \frac{(\Delta x)^2}{8\Delta t}. \tag{19}
\]

This continuous equation is the main result of this paper. The conditions for the applicability of Eq. \(\eqref{eq:boltzmann} \) are given by Eqs. \(\eqref{eq:condition1} \), \(\eqref{eq:condition2} \), \(\eqref{eq:condition5} \) and \(\eqref{eq:condition6} \).

VI. REDUCTION TO KELLER-SEGEL MODEL

In this section we add time dependence to the chemical field \(c\) (concentration of chemoattractant or chemorepellant) by including a diffusion equation with the source term \(ap\) which determines the secretion of chemical by a cell

\[
\partial_t c = D_c \partial_x^2 c - \gamma c + a p, \tag{20}
\]

where \(D_c\) is a diffusion coefficient of the chemical field, \(\gamma\) is the decay rate of the chemical field and \(a\) is a production rate of the chemical field.
The system of equations (19) and (20) is applicable under the assumption that the typical time scale \( \tau_c \) of diffusion of \( c(x, t) \), given by \( \tau_c = \frac{\triangle x^2}{D_c} \), is large in comparison with convergence time \( \tau_r = 1/(8D\beta\lambda) \) of \( P(x, L, t) \) to the Boltzmann distribution \( \mathbb{B} \), where \( x_c \) is a typical spacial width of the distribution of \( c(x, t) \). Namely, this condition has the form

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

(21)

Eqs. (19) and (20) form a closed set of equations which is equivalent to the classical Keller-Segel model \([1]\) of chemotaxis. If the parameters satisfy condition

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

(22)

than Eq. (19) reduces to the following commonly used form of the Keller-Segel model \([2, 3]\):

\[
\partial_t p = D \partial_x^2 p - \chi_0 \partial_x [p \partial_x c], \\
\chi_0 = D\lambda \beta \mu (J_{cm} - \lambda L_T), \\
D = \frac{(\triangle x)^2}{8\triangle t}.
\]

(23)

The probability density function \( p(x, t) \) corresponds to the microscopic density in the Keller-Segel model. Notice that both in the Keller-Segel model and CPM considered in this paper, 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.

VII. COMPARISON OF NUMERICAL SIMULATIONS

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 \( P(x, L, t) \) and \( p(x, t) \), as given by Eqs. (4), (7) and (19).

A. 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 CPM simulations with one cell with the same initial conditions.
2. We fix a time interval \( \delta t = \epsilon^2 \triangle t \) i.e. we fix the time interval between successive Monte Carlo steps. For each simulation we record the locations of the center of mass and and lengths of the cell at the times \( t = \delta t, 2\delta t, 3\delta t, \ldots \)
3. After the \( N \) runs, the recorded data give a frequency distribution \( M(x, L, t) \) for the location of the center of mass of the cell and length of the cell.

The frequency distribution \( M(x, L, t) \) determines the approximation \( P_{cpm}(x, L, t) = M(x, L, t)/(N(\epsilon \triangle x)^2) \) 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 \( P_{cpm}(x, L, t) \) with \( P(x, L, t) \) which is a solution of either the master equation (4) or the Fokker-Planck equation (7). To approximate the probability density function of center of mass \( p(x, t) \) we sum up over all values of \( L \) on the grid in a way used in Eq. (18)

\[
p_{cpm}(x, t) = 2\epsilon \triangle x \sum_{L=(1+\alpha)\epsilon \triangle x, (3+\alpha)\epsilon \triangle x, (5+\alpha)\epsilon \triangle x, \ldots} P_{cpm}(x, L, t),
\]

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

(24)

In what follows, we compare \( p_{cpm}(x, t) \) for \( \epsilon \ll 1 \) with \( p(x, t) \), a solution of the continuous Eq. (19), corresponding to the following choice of parameters

\[
\lambda = 4, L_T = 5, J_{cm} = 2, \beta = 15, \mu = 0.1, \triangle x = 1, \triangle t = 1.
\]

(25)
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 \( \frac{L_{\text{cpm}}}{\epsilon^2 \Delta t} \) and \( \frac{L_{\text{end}}}{\epsilon^2 \Delta t} \) respectively. We use a range of values of \( \epsilon \) 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 \( Z_1^{-1} \exp (E(L) - E(L_T)) \). Here the normalization constant \( Z_1 \) is chosen to have the total probability 1. In most simulations, we use the following distribution for the chemical field \( c(x) \):

\[
c(x) = \frac{(x - 70)^2}{400}.
\]  

(26)

B. Monte Carlo simulations versus numerical solutions of the discrete master equation and the Fokker-Planck equations

We first compare Monte Carlo simulations with the numerics for the master equation (27) and its continuous limit (19) with initial conditions being different from the Boltzmann distribution (8). Namely, we choose initial value \( \beta \) distribution with different temperature \( T \). Also, we observe that if we increase temperature \( \epsilon \) of the master equation (4) for any \( \epsilon \), it results in a significant departure from the Boltzmann distribution (8) which confirms the theoretical results of Section IV.

C. Convergence of the probability density function \( P(x, L, t) \) to the Boltzmann distribution

To demonstrate quick convergence of \( P(x, L, t) \) to the Boltzmann distribution (8) (as discussed in Section IV), we solve numerically both the master equation (27) and its continuous limit (19) with initial conditions \( P(x, L, 0) \) being different from the Boltzmann distribution (8). Namely, we choose initial value \( P(x, L, 0) \) to be the Boltzmann distribution with different temperature \( \beta_{\text{ini}} = 1.5 \) so that Figure 4 shows convergence of initial state with temperature \( 1/\beta_{\text{ini}} \) to the quasi-equilibrium state with temperature \( 1/\beta = 1/15 \) used in the Monte Carlo algorithm. Linear-log plot in the Figure 4 indicates that convergence is indeed exponential in time with high convergence rate \( \tau_c^{-1} \) (\( \tau_c^{-1} = 98.55 \) for parameters of Fig. 4). By high convergence rate we mean that the typical convergence time \( \tau_c \) is small compare with e.g. the diffusion time \( x_0^2/D \) in \( x \) (see Eq. (17)). Because of the \( x \)-dependence of the chemical field, the convergence rate \( \tau_c \) is also \( x \)-dependent and a closed analytic expression for it is difficult to obtain from Eq. (17) for general \( c(x) \). However even a simple estimate \( \tau_c^{-1} = 8D\beta \) of the rate of convergence gives 60 for parameters of Figure 4 which is qualitatively close to numerical value 98.55. Here 98.55 is obtained from the linear fit presented in Figure 4.

Also, we observe that if we increase temperature \( T \) in Monte Carlo simulations, so that condition (14) is not true any more, then it results in a significant departure from the Boltzmann distribution (8) which confirms the theoretical results of Section IV.

D. \( P(x, L, t) \) vs. \( p(x, t) \) simulations

The ansatz (8) can be used for fast simulations of solutions of the discrete master equation. Summing up over all values of \( L \) in the master Eq. (4) and taking into account (8) result in a discrete equation for the probability density function \( p(x, t) \)

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

(27)

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 the numerics for discrete Eq. (27) very efficient.

We run simulations for the discrete equation (27) and the continuous Eq. (19) and compared them with the solutions of the discrete (4) and continuous (17) equations, respectively. We find, taking into account Eq. (8), that indeed the differences between these solutions are very small for the typical values of parameters.
FIG. 3: Probability densities for Monte Carlo simulations $p_{cpm}(x, t)$ (dotted line), $p(x, t)$ for the Master Eq. (4) (solid line) and the Fokker-Planck equation (7) (dashed line) versus $x$ for $t = t_{end}$. (a) $\varepsilon = 0.01$; (b) $\varepsilon = 0.1$. The difference between position of solid curve and a dashed curve is negligibly small in (a). Number of Monte Carlo simulations is $N = 2 \times 10^5$. We used $c(x)$ as given by (26).

We conclude that the Monte Carlo simulations of CPM are equivalent in the limit of large $N$ to the simulations of the discrete Eq. (27) for any $\varepsilon$.

E. Comparison of the continuous model with the CPM

Below we denote as $p_{cpm}$ both Monte Carlo simulations and numerical solutions of Eq. (27) and as $p_{cont}(x, t)$ solutions of (19).
FIG. 4: Exponential convergence of the Full Width Half Maximum (FWHM) of $P(x, L, t)$ in $L$ as a function of time for $x = 50$. The vertical axis corresponds to the normalized difference $[W(t) - W_\beta]/W_\beta$, where $W(t)$ is the FWHM at time $t$ and $W_\beta$ is the FWHM for the Boltzmann distribution $[8]$. Solid squares correspond to the numerical solution of both Eqs. (4) and (7). The solid line is the best linear fit which gives exponential convergence $e^{-98.55t}$. The same parameters as in Figure 3 are used here with $\varepsilon = 0.01$.

Figure 5 shows a series of simulations of the CPM (dotted line) and numerical solutions of the continuous Eq. (19) (solid line) for different values of $\varepsilon$. This Figure demonstrates that in the limit $\varepsilon \to 0$, the solution of the continuous Eq. (19) appears to converge to the cell probability density function of the CPM.

Figure 6 shows the normalized difference between solutions of (19) and the CPM. The normalized difference approaches 0 as $\varepsilon$ decreases. We also run a series of tests for different forms of the chemical field $c(x)$ and demonstrate that solutions of the CPM and continuous Eq. (19) are close for small values of $\varepsilon$. Figure 7 shows a typical result of numerical simulations for a “double well” chemical concentration $c(x) = \cos(4\pi x/100)$. We conclude that the numerical simulations show excellent agreement between the CPM and the continuous Eq. (19), provided that the Potts parameters satisfy conditions (14), (15), (16), (17) and $\varepsilon \to 0$, which correspond to the continuous limit of the CPM.

VIII. CONCLUSIONS

In this paper we combine microscopic and macroscopic levels of description of one dimensional cellular dynamics. The microscopic level is represented by a one dimensional 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 (19) for the probability density function $p(x, t)$ of cells and then further reduce it to the well-known macroscopic continuous Keller-Segel model (20) and (23) for the chemotactic aggregation of cells. All coefficients of the Keller-Segel model are derived from parameters of the CPM.

We use numerical simulations to test hierarchy of models and assumptions which we used to derive continuous equation (19). In particular, we compare Monte Carlo simulations with simulations of both the discrete master equation (4) and the Fokker-Planck equation (7) for $P(x, L, t)$. 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 (4) for arbitrary $\varepsilon$. We verify numerically that the probability density function $P(x, L, t)$ quickly converges to the Boltzmann distribution $[8]$. And finally, we find that numerical simulations show excellent agreement between Monte Carlo simulations of CPM and the continuous macroscopic model (19).

We are currently working on extending our results to a 2D case for modeling chondrogenic patterning in the presence of chemotaxis and fibronactin production [29].
FIG. 5: Plots of $p_{\text{cpm}}$ (dotted line) and $p_{\text{cont}}(x,t)$ (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.

FIG. 6: Normalized difference between solution of CPM and continuous Eq. 19 for the same parameters as in Figure 3 as a function of $\varepsilon$. Normalized difference is given by $1 - \int p_{\text{cpm}}(x,t) p_{\text{cont}}(x,t) dx / \int p_{\text{cont}}(x,t)^2 dx$ for $t = t_{\text{end}}$.

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FIG. 7: Typical results of CPM simulations. The same parameters as in Figure 3 are used except that \( c(x) = \cos(4\pi x/100) \), \( \varepsilon = 0.01 \). 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.

X. APPENDIX

The explicit expressions for the transitional probabilities \( T(x; x', t) \) used in Eq. 27 can be obtained by summing over all lengths (or, in other words, over even multiples of \( \varepsilon \Delta x \) (if \( 2x/(\varepsilon \Delta x) \) is an even number), and over odd multiples of \( \varepsilon \Delta x \) (if \( 2x/(\varepsilon \Delta x) \) is an odd number). A change in the position of the center of mass from \( x \) to \( x \pm \frac{\varepsilon}{2} \Delta x \)
can be made by adding/removing lattice sites from the left/right end of a cell which results in
\[
T(x; x - \frac{\varepsilon}{2} \Delta x, t) = \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x,...} \frac{1}{4Z(x-\frac{\varepsilon}{2} \Delta x)} \bigg\{ \exp \left[ -\beta \Delta E_{\text{length}}(x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) \right] \Phi \left( E(x, L) - E(x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) \right) \\
+ \exp \left[ -\beta \Delta E_{\text{length}}(x - \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) \right] \Phi \left( E(x, L) - E(x - \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) \right) \bigg\}\]
\[
T(x; x + \frac{\varepsilon}{2} \Delta x, t) = \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x,...} \frac{1}{4Z(x+\frac{\varepsilon}{2} \Delta x)} \bigg\{ \exp \left[ -\beta \Delta E_{\text{length}}(x + \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) \right] \Phi \left( E(x, L) - E(x + \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) \right) \\
+ \exp \left[ -\beta \Delta E_{\text{length}}(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) \right] \Phi \left( E(x, L) - E(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) \right) \bigg\}\]
\[
T(x + \frac{\varepsilon}{2} \Delta x; x, t) = \frac{1}{4Z(x)} \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x,...} \bigg\{ \exp \left[ -\beta \Delta E_{\text{length}}(x, L) \right] \Phi \left( E(x + \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) - E(x, L) \right) \\
+ \exp \left[ -\beta \Delta E_{\text{length}}(x, L) \right] \Phi \left( E(x + \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) - E(x, L) \right) \bigg\}\]
\[
T(x - \frac{\varepsilon}{2} \Delta x; x, t) = \frac{1}{4Z(x)} \sum_{L=(1+\alpha)\varepsilon \Delta x, (3+\alpha)\varepsilon \Delta x, (5+\alpha)\varepsilon \Delta x,...} \bigg\{ \exp \left[ -\beta \Delta E_{\text{length}}(x, L) \right] \Phi \left( E(x - \frac{\varepsilon}{2} \Delta x, L - \varepsilon \Delta x) - E(x, L) \right) \\
+ \exp \left[ -\beta \Delta E_{\text{length}}(x, L) \right] \Phi \left( E(x - \frac{\varepsilon}{2} \Delta x, L + \varepsilon \Delta x) - E(x, L) \right) \bigg\}\]
\[
\alpha = 1 \text{ for } \frac{x}{\varepsilon \Delta x} = n, \quad \alpha = 0 \text{ for } \frac{x}{\varepsilon \Delta x} = n + 1/2, \quad n \in \mathbb{N}. \tag{28}
\]

Here the partition function $Z(x)$ is given by (12). $Z(x)$ is $x$-dependent in the discrete case considered in this Appendix. This $x$-dependence is eliminated after going from a discrete summation in (12) to an integral (as in Eq. 13). We evaluate the transitional probabilities $T(x; x \pm \frac{\varepsilon}{2} \Delta x, t)$ and $T(x \pm \frac{\varepsilon}{2} \Delta x, t)$ numerically using (28) for each value of $x$ once at the beginning of each simulation and then calculate the discrete evolution of Eq. (27).

Notice that in the limit of small $\varepsilon \to 0$, the continuous equation (19) can be derived directly from (12), 27 and 28. However, this derivation is more tedious compared with the two-step derivation in Sections IV and V where continuous equation (7) is first derived and then integrated (7) over $L$ which results in Eq. (19).

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