Physical model of protein cluster positioning in growing bacteria

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Abstract
Chemotaxic receptors in bacteria form clusters at cell poles and also laterally, and this clustering plays an important role in signal transduction. These clusters were found to be periodically arranged on the surface of the bacterium Escherichia coli, independent of any known positioning mechanism. In this work we extend a model based on diffusion and aggregation to more realistic geometries and present a means based on “bursty” protein production to distinguish spontaneous positioning from an independently existing positioning mechanism. We also consider the case of isotropic cellular growth and characterize the degree of order arising spontaneously. Our model could also be relevant for other examples of periodically positioned protein clusters in bacteria.

INTRODUCTION
Bacterial cells lack organelles and compartments, nevertheless many proteins display precise intracellular spatio-temporal organization that is important for their functioning. Over the past few years, advances in imaging techniques such as fluorescence microscopy have led to an increased appreciation of the scope and character of protein organization in cells [1]-[7]. Protein organization plays an important role in a number of cellular functions that include signal transduction [8] and maintenance of characteristic cell shapes [9]. One of the central questions in bacterial cell biology is to understand the physical mechanisms underlying protein organization [5]. A particularly striking example of subcellular protein organization was revealed by membrane-associated chemotaxis receptors in Escherichia coli [10–13]. It had been known that these receptors form large clusters at the polar caps of these rod-shaped bacteria, and that clustering of receptors [14]-[18] plays a crucial role in the signal integration and receptor cooperativity required for chemotaxis [8], i.e., directed movement in chemical gradients. While investigating how receptors target the cell pole, Thiem et al. [10, 11] discovered clusters of chemotaxis receptors that are approximately periodically positioned along the cell wall, independent of any known positioning mechanism such as the Min system. It has been proposed that periodic cluster spacing ensures that each daughter cell receives at least one cluster following cell division or fragmentation of a filamentous cell. Other examples of periodically positioned protein clusters have emerged as well [19, 20]; for example, protein aggregates associated with cellular aging in bacteria exhibit a regular distribution along the cell’s long axis in filamentous E. coli. The question that had been posed in Hui et al. [21] was whether such periodic organization could emerge spontaneously or whether it requires the existence of a positioning system.
In order to address this question, we adopt and extend the model by Hui et al. [21] and represent the membrane as a hexagonal lattice, with particles (protomers, representing receptor clustering units) allowed to hop between lattice sites. We include nearest-neighbor particle-particle interactions favoring clustering. We study two cases: (a) longitudinal cellular growth (as in E. coli), implemented by insertion of columns of lattice sites, and (b) two-dimensional growth, implemented by addition of both rows and columns of lattice sites. While Hui et al. [21] demonstrated, in the context of their minimal model, that protein clustering and periodic positioning of clusters can emerge spontaneously in growing cells, in order to uncover the essential physics, their work contained some simplified assumptions. For example, for computational efficiency, the circumference of the cell was treated as much shorter than the length, making the system effectively one-dimensional, and leaving open the question about the generalizability of the mechanism to two-dimensional geometries. Our purpose in this paper is to investigate the robustness of this mechanism for more realistic two-dimensional geometries, to investigate in greater detail the underlying biophysics, and, finally, to identify possible experimental means of distinguishing between spontaneously generated periodicity and an independently existing positioning mechanism as had been originally suggested in Thiem et al. [11]. We demonstrate that period positioning can emerge spontaneously even for more realistic two-dimensional geometries and that the distribution of inter-cluster spacing resembles that generated by a noisy positioning mechanism. In order to distinguish between an independently existing positioning mechanism and spontaneous positioning, we suggest controlling how proteins are produced (and hence inserted into the membrane). We demonstrate how our proposed mechanism generates very different distributions of inter-cluster distances depending on whether proteins are produced continuously or in bursts. Moreover, we study the distribution of cluster sizes and dependence of cluster growth on size, since these can be measured experimentally [11, 13] and compare the results from our simulations with expressions based on simplified analytical calculations. As was discussed in [22], cluster size distributions also have biological significance in the context of polar localization of chemotaxis receptors. Finally, we study how uniform expansion of the cell (corresponding to spherical growth) would affect such spontaneous cluster positioning.

**LATTICE MODEL OF RECEPTOR CLUSTERING**

We approximate the cell membrane as a lattice as in [21]; however, unlike [21] we choose here a triangular lattice to be better compatible with realistic receptor packing in clusters and thus avoid any lattice artifacts, see Fig. 1. We will study two cases: where the lattice expands in one direction and where it expands in both directions, corresponding to longitudinal growth and spherical growth respectively. Expansion in one dimension was accomplished by inserting columns randomly anywhere in the lattice, while expansion in both the dimensions was done by randomly adding both rows and columns. The instantaneous expansion rate was assumed to be proportional to the corresponding cellular dimension in order to implement an exponential rate of growth with the length growing as $L_0 e^{\gamma t}$ in the case of one-dimensional growth and as $L_x e^{\gamma x}$ and $L_y e^{\gamma y}$ in the case of two-dimensional growth. Proteins were randomly deposited on the lattice at a rate of $k_n$ per available unoccupied site of the lattice.
The proteins interact through a nearest-neighbor attractive interaction of energy $J$. The total energy of the system in units of the thermal energy, $k_B T$, is given by

$$E = -J \sum_{i,j} \sigma_i \sigma_j + \alpha J N,$$

where $i,j$ in the equation above correspond to nearest-neighbor lattice sites, and the lattice variable $\sigma_i$ equals 1 if the $i$-th site is occupied and 0 otherwise. The second term in the equation is the conformational energy cost, given by $\alpha J$, for each particle with any neighbors (where $N$ is the number of such particles with one or more neighbors), which accounts for the loss of internal entropy when a particle associates with a cluster or a second particle. This term serves to introduce a nucleation barrier towards cluster formation. The system is simulated using a Metropolis Monte Carlo algorithm. At each step a particle is randomly chosen and moved to an empty nearest-neighbor lattice site. If the energy of the system is lower after the move, the move is accepted. Otherwise a random number is chosen between 0 and 1 and only if this number is smaller than $e^{-\Delta E}$ is the move accepted, where $\Delta E$ represents the change in energy. Only individual particles are allowed to move and not clusters, consistent with experiments suggesting that membrane-associated receptor clusters are relatively immobile [11].

For our simulations, unless stated otherwise, we set the following values for the model parameters: $k_+ = 10^{-8}$, $\alpha = 0.6$, $J = 4$, and $\gamma = 10^{-6}$, where the Monte Carlo time step defines the unit of time. These parameters correspond to to an average density of particles $\rho \approx 0.01$ on the lattice. To check this, note that in a time $dt$ the lattice expands by a length $\gamma L_x dt$ in the $x$ direction. The total number of particles in this expanded portion at uniform density $\rho$ would be $\gamma \rho L_x L_y dt$ which should equal the total number of particles added to the lattice $k_+ L_x L_y dt$, leading to $\rho = k_+ / \gamma \approx 0.01$.

### CLUSTER POSITIONING FOR CONTINUOUS DEPOSITION VERSUS DEPOSITION IN BURSTS

We briefly review the mechanism proposed in [21] for the spontaneous generation of periodically positioned protein clusters in growing cells. In the model, existing clusters act as sinks for proteins newly inserted in the membrane, locally reducing the density of particles and thus preventing nucleation of new clusters. As cells grow, existing clusters move further apart, ultimately allowing new clusters to nucleate at a characteristic spatial separation set by insertion, diffusion, interaction strength, and growth rates. Thus if we start the simulations with one cluster at each end of a quasi-1D simulation domain, once the lattice (representing the cell surface) has expanded sufficiently a new cluster will typically form around mid-cell where the density of free particles is highest. As the cell continues to grow, new clusters will appear typically around a quarter and three-quarters of the cell length (roughly mid-point between already existing clusters). In this manner, new clusters appear around certain characteristic positions. The proposed mechanism is based on a reaction-diffusion system, thus sharing aspects of pattern formation arising from a Turing instability [23]. However the proposed mechanism and Turing instability are also quite distinct.
particularly in the sense that in the model proposed here the system is close to equilibrium due to the small value of the cellular growth rate (it is cellular growth that drives the system away from equilibrium in this case) in contrast to the Turing case, which concerns pattern formation in systems far from equilibrium [23].

The simulations presented in [21] assume, for computational simplicity, a relatively small width of 50 lattice spacings, making the system essentially one-dimensional. This is inaccurate in the sense that for *E. coli* the length and circumference are comparable. Thus our first task is to check that the results can be generalized to more accurate two-dimensional geometries. For this purpose, we start with an initial lattice of length $L_x = 300$ and $L_y = 500$, measured in units of lattice spacing, and allow the lattice to expand in the $x$ direction. The overall density of particles on the lattice is taken to be $\rho = 0.01$.

The expansion of the lattice is implemented by random insertion of empty columns at a rate $\gamma = 10^{-6}$ with equal probability anywhere in the lattice, and in order to maintain a constant density, particles are randomly deposited onto the lattice at a rate $k+$ per available (i.e., unoccupied) site. As depicted in Figs. 2 and 3(a), even for these much larger lattice widths, we find that approximately periodically spaced clusters appear spontaneously during lattice growth. In Fig. 4(a), we plot the distribution of inter-cluster distances projected along the $x$-axis (the direction of growth), demonstrating a clear peak. We focus on the projected distance in order to quantify the degree to which clusters are arranged periodically in the direction of growth.

What is interesting about the distribution depicted in Fig. 4 is that it resembles the expected distribution that would have been generated by an independently existing noisy positioning mechanism as had been proposed by Thiem *et al.* [11] to explain their data. To see this, consider the case where clusters, on average, are approximately periodically spaced, each with a Gaussian distribution about its periodic position, as might be expected for a noisy positioning mechanism. Thus we approximate the probability of finding the $i$th cluster at position $x$ as $P(x, i) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp[-(x - d\times i)^2/2\sigma^2]$, where $\sigma$ is a constant representing the width of the distribution and $d$ is the average distance between neighboring clusters. Hence if we have $n$ clusters, the probability of finding cluster 1 at position $x_1$, cluster 2 at position $x_2$, etc., goes as $P(x_1, 1) \cdots P(x_n, n)$. Hence the probability that the distance between any two clusters is $\Delta x$ goes as

$$\int \int dx_1 \ldots dx_n \sum_{i,j} \delta(x_i - x_j - \Delta x)[P(x_1, 1) \cdots P(x_n, n)], \quad (2)$$

where $\delta$ represents the Dirac delta function. This can be written as

$$\sum_{i,j} \int dx_1 \ldots dx_n \delta(x_i - x_j - \Delta x)P(x_i, i)P(x_j, j) = \sum_{i,j} \int dx_1 P(x_i, i)P(x_i + \Delta x, j). \quad (3)$$

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The exponential in the integrand above is \( \exp\left\{-\frac{[(x_i - d \cdot i)^2 + (x_i + \Delta x - d \cdot j)^2]}{2\sigma^2}\right\} \), which can be rewritten as
\[
\exp\left\{-\left[2 - (x_i - (\Delta x - d(i + j)/2))^2 + (\Delta x + d(i - j))^2/2\right]2\sigma^2\right\}.
\] (4)

By substituting in Eq. 3, and integrating over \( x_i \), we find that the \( \Delta x \) dependence goes as \( \exp\left\{-(\Delta x - d(i - j))^2/4\sigma^2\right\} \). Hence the probability for the distance between clusters to be equal to \( \Delta x \) is proportional to
\[
\sum_{ij} \exp\left\{-(\Delta x + d(i - j))^2/4\sigma^2\right\}.
\] (5)

For \( d = L/N \), where \( L \) corresponds to length of the system and \( N \) is a positive integer, \( i \) and \( j \) can go from 1 to \( N - 1 \). Moreover, for positive \( \Delta x \), in this double sum we assume \( j > i \). In Fig. 4, we display the corresponding curve for \( N = 8 \) and \( \sigma^2 = 0.01 \), measured in units of 3000 lattice spacings, and find an approximate fit to simulation data.

Is there a way to experimentally distinguish between an independently existing positioning mechanism and spontaneous positioning? One suggestion is to control how proteins are produced (and hence inserted into the membrane), so that they are produced in bursts rather than continuously. For an independently existing positioning mechanism this should not affect cluster spacing. The question then is how bursty production would affect spontaneous cluster positioning. In order to address this, we simulated particle deposition in bursts, which we implemented as follows: The cell was allowed to grow with no deposition until the length of the cell became twice its initial length, at which instant particles were uniformly deposited in the cell to reach particle density \( \rho = 0.01 \). As we can see by comparing snapshots in Figs. 3(a) and 3(b), with quantification in Fig. 4(a) and (b), the distribution of clusters sizes and spacings are markedly different even for the same average receptor density, thus offering a way to experimentally distinguish between the two scenarios. While we can still fit the simulation data by assuming periodic placement of clusters with a Gaussian distribution about the mean, as can be seen from Fig. 4(b), the values of the mean inter-cluster distance and the variance in the distribution are now completely different from the non-bursty case.

**RATE OF CLUSTER SIZE CHANGE**

Having studied the distribution of inter-cluster spacings, we next consider the dependence of the rate of growth of a cluster on its size. On average because larger clusters have longer perimeters, the average flux of particles into larger clusters should also be greater. Hence we expect larger clusters to have higher growth rates, as seen in Fig. 5. To get an understanding of the form of the dependence of cluster growth rate of cluster size, we assume each cluster is surrounded by other clusters and competes with them to capture newly deposited particles. For simplicity, we assume circular symmetry around the center of the focal cluster. The diffusion equation in a circularly symmetric system has the usual form...
\[ \frac{\partial C}{\partial t} = D \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C}{\partial r} \right) + k_+ , \quad (6) \]

where \( C(r, t) \) represents the particle concentration and \( k_+ \) is the rate of addition of particles per unit area in the zone surrounding the cluster. At steady state, this becomes

\[ 0 = D \frac{1}{r} \frac{d}{dr} \left( r \frac{dC}{dr} \right) + k_+ , \quad (7) \]

implying

\[ D \frac{rdC}{dr} = c_1 - k_+ r^2 / 2, \quad (8) \]

where \( c_1 \) is a constant. Therefore

\[ D \frac{dC}{dr} = \frac{c_1}{r} - k_+ r / 2, \quad (9) \]

which has the solution

\[ DC(r) = -k_+ r^2 / 4 + c_1 \log r + c_2, \quad (10) \]

where \( c_2 \) is a constant.

In order to determine the constants of integration, for a cluster of radius \( a \), we impose the fully absorbing boundary condition \( C(a) = 0 \). Also, letting \( R_0 \) represents a typical radial distance from the cluster center to the neighboring clusters, we apply an approximate boundary condition \( C(R_0) = C_0 \), where \( C_0 \) is assumed to be a constant independent of cluster size. Hence we obtain the equations

\[ c_1 \log a + c_2 - k_+ a^2 / 4 = 0 \quad (11) \]

and

\[ c_1 \log R_0 + c_2 - k_+ R_0^2 / 4 = DC_0. \quad (12) \]

Thus we find
\[ c_1 = \frac{k_+ (R_0^2 - a^2) + 4DC_0}{4 \log(R_0/a)} \]  \hspace{1cm} (13)

For sufficiently high value of \( J \), so that we can ignore flux of particles out of the cluster, the rate at which a cluster grows equals the flux of particles into the cluster and is given by

\[ \frac{dM}{dt} = 2 \pi a D \frac{dC}{dr} \Bigg|_{r=a} = 2 \pi D (c_1 - k_+ a^2 / 2). \]  \hspace{1cm} (14)

We assume dense packing of particles in the cluster, so that there is one particle per lattice site, and we denote the corresponding density of particles by the constant \( \rho_0 \). The number of particles in the cluster \( M \) then goes as \( M \approx \pi \rho_0 a^2 \). Substituting \( a = M / \pi \rho_0 \), we obtain the following expression for the rate of cluster growth:

\[ \frac{dM}{dt} = \left( \frac{k_+ (\tilde{M}_0 - M) + DC_0}{\rho_0 \ln(M_0/M)} \right) - k_+ M / \rho_0, \]  \hspace{1cm} (15)

where \( \tilde{M}_0 \equiv \pi \rho_0 R_0^2 \) represents the number of particles corresponding to a cluster of radius \( R_0 \), and \( \tilde{C}_0 = 4 \pi \rho_0 C_0 \). We fit this form to our simulation results in Fig. 5.

**VARIATIONS IN CLUSTER SIZE**

We next consider cluster-size distributions generated by our simulations. We consider two different values of average density, \( \rho = 0.01 \) and \( \rho = 0.001 \). We plot the cluster-size distributions in the case of one-dimensional expansion. Unless otherwise stated, the cell is expanded from an initial length of \( L_x = 30 \) to a final length of \( L_x = 3000 \). We assume a high interaction energy of \( J = 7 \) so that cluster-associated particles are unlikely to disassociate, that is, clusters are very sticky. The rate of expansion is taken to be \( \gamma = 10^{-6} \) and the coefficient for conformational energy cost is taken to be \( \alpha = 0.5 \).

Fig. 6, insets, show snapshots from the end of two typical simulations, and cluster-size distributions are plotted in Fig. 6. The most visible difference between the two snapshots is the presence of large clusters at \( \rho = 0.01 \) that are absent at \( \rho = 0.001 \). The cluster-size distribution at \( \rho = 0.01 \) clearly exhibits an exponential decay in the frequencies as a function of cluster-size, as seen in Fig. 6. This exponential decay can be understood by a simple calculation (we follow here a similar calculation in [13]). In order to evaluate \( M \) as a function of time \( t \), ignoring the linear in \( M \) term in comparison to the leading order, we approximate Eq. 15 as

\[ \frac{dM}{dt} \approx \frac{\alpha'}{\beta - \ln M}. \]  \hspace{1cm} (16)

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where $\alpha'$ and $\beta = \ln[\pi \rho_0 R_0^2]$ are constants. Integrating $dM/dt$ we obtain

$$\alpha'(t - t_0) = [(\beta + 1)(M - M_0) - M \ln M + M_0 \ln M_0], \quad (17)$$

where we have assumed that the cluster nucleated at time $t = t_0$ with initial cluster-size $M_0$.

Since the cell expands according to the equation $L_x = L_0 e^{\gamma t}$, and in steady state we expect the number of clusters per unit length to remain unchanged, the number of clusters should also grow exponentially $N_{\text{clusters}}(t) \propto \exp(\gamma t)$. It follows that the number of new clusters produced in an interval of time $dt$ also grows exponentially $dN_{\text{clusters}} \propto dt \exp(\gamma t)$. At a particular time $t_0$, the probability that a given cluster was nucleated at a previous time $t'$ also satisfies $P(t_0, t') \propto e^{-\gamma(t_0 - t')}$. The distribution of cluster sizes, measured by the number of proteins in a cluster, is given by

$$P(M) = \frac{dt'}{dM} P(t', t'(M)). \quad (18)$$

We can thus readily check that this yields a probability distribution of the form:

$$P(M) \approx c_1 e^{-c_2 M + c_3 M \ln M}, \quad (19)$$

where $c_1$, $c_2 = \gamma(\beta + 1)/\alpha$, and $c_3 = \gamma/\alpha$ are constants. Since $c_2 >> c_3$, we can neglect the $c_3$ term except at very high values of $M$, which then indicates an exponential decay of the distribution with cluster size (Eq. 19 is not applicable for arbitrarily large values of $M$, since our approximations break down). We also see this decay in Fig. 6, and a similar exponential decay in cluster size distribution is seen experimentally [13, 22].

**CLUSTER DISTRIBUTION FOR ISOTROPIC CELL GROWTH**

In order to investigate the effect of uniform growth on pattern formation, we next consider uniform expansion of the lattice (in contrast to longitudinal expansion as we studied above) corresponding to spherical cell growth, This could be relevant both for more spherical bacteria as well as, e.g., *mreB* mutants [4] of rod-shaped bacteria such as *E. coli*. We ran our simulations so that the cell grows at the same rate $\gamma = 10^{-6}$ in both directions. The initial lengths are taken to be $L_x = 3$ and $L_y = 3$ and the final lengths $L_x = 3000$ and $L_y = 3000$. The average density of particles is taken as $\rho = 0.01$, and the coefficient for conformational energy cost for particles in clusters is $\alpha = 0.5$. For interaction energies we consider two cases: (i) where the strength of nearest-neighbor interactions is $J = 4$ (thermalized case), and (ii) where $J$ is sufficiently high (effectively infinite) that the clusters are sticky and particles are not allowed to leave a cluster. The snapshots at the end of the simulation are depicted in Fig. 7, insets, and the cluster-size distribution is plotted in Fig. 7.
While we notice in the snapshots a much larger number of clusters for two-dimensional expansion compared to expansion in one dimension, the density of clusters is not appreciably different. We also notice that the geometry of the clusters is more compact and circular in the thermalized case and the clusters are more irregularly shaped in the sticky case (we find a similar result for 1D expansion). However, the most stark contrast between the thermalized and the sticky cases correspond to the size and density of clusters; relatively fewer but larger clusters are a hallmark of the thermalized case while a larger number of smaller clusters is a hallmark of the sticky case. The origin of this difference can be traced to the relative ease of starting new clusters in the sticky case due to a far smaller critical nucleation size (two particles that stick to each other start a new cluster in the sticky case).

In the case of one-dimensional expansion of the lattice we focused on distance along the direction of expansion. To characterize inter-cluster spacing in two dimensions, we first obtain the centroids of the clusters and then, in order to identify neighboring clusters, we construct Voronoi polygons surrounding each of these points, where a Voronoi polygon for a given centroid contains the set of all points that are closer this centroid than to any of the other centroids (see Fig. 8(a), also compare with Fig. 8(b) corresponding to randomly placed clusters). Two centroids whose Voronoi polygons share at least one edge are considered as nearest neighbors. Using this information we plot the distribution of the nearest-neighbor distances in Fig. 9 compared to the distribution for randomly placed clusters. As shown, the distance distribution for randomly placed clusters peaks at a smaller value of inter-cluster distance and is broader compared to the distribution of self-organized clusters, consistent with a greater degree of positional order in the arrangement of clusters in the latter case.

**DISCUSSION AND CONCLUSIONS**

The physical principles underlying protein organization in bacterial cells is one of the central questions in bacterial cellular biology. In this work we have investigated a physical mechanism for spontaneously generating periodic cluster organization along the inner membrane of a growing bacterial cell. This paper generalizes earlier work by [21], simulating the deposition, diffusion, and clustering of proteins on the cell membrane through a Metropolis Monte Carlo algorithm of an expanding lattice. We demonstrate the applicability of the basic model to more realistic two-dimensional geometries, and show how protein deposition on the membrane in discrete bursts produces a strikingly different distribution of cluster positions. We find that the cluster-size distribution displays an exponential decay. Finally, we considered the case of uniform cell growth, and find that clusters still demonstrate a degree of order in terms of their two-dimensional arrangement.

Our results suggest that the dependence of inter-cluster distance distribution on the burstiness of protein deposition can be used to discriminate between spontaneous cluster positioning versus an independently existing positioning mechanism [11], since in the latter case we expect the distribution to be independent of burstiness, up to a threshold set by saturation of the positioning sites. Biologically, burstiness can be tuned or varied by controlling genetic promoter architecture, where slow binding/unbinding kinetics of transcription factor to the promoter can lead to more bursty gene expression. In [24], the authors constructed a set of promoters in *E. coli*, and demonstrated that promoter strength,
transcription-factor binding strength, and transcription-factor copy numbers can be systematically varied, and these, in turn, affect the burstiness of gene expression. Alternatively, bursting could be controlled directly with a time course of induced gene expression. For chemical inducers, this can be accomplished in a microfluidics setting via regulated flow [25], but recent developments also allow arbitrary time courses of induction in bulk cultures using optogenetics [26]. Regarding duration of the expression bursts, our expectation is that for a detectable effect this duration should be shorter than the timescale to nucleate new clusters. For the experiments reported in Thiem et al. [11], it is reasonable to assume that the nucleation time-scale is comparable to the lifespan of the bacterial cells between successive divisions, since otherwise we would have expected far more (or no) periodically placed clusters in the cell. Thus, bursts of the duration of a few minutes, say around 1-5 minutes, with comparable or larger intervals between the bursts, should have a detectable effect.

In this paper we have concentrated on cluster size distributions and cluster localization/positioning in the context of lateral chemotaxis receptor clusters, this might also be important in the context of synthetic biology. For example, [22] demonstrated how, based on insight from structural and clustering properties of chemotaxis receptors, one could engineer artificial protein complexes with similar clustering properties and localization profiles as chemoreceptors. Future theoretical/computational studies could extend our current model to include curvature sensitivity of chemoreceptors by incorporating an intrinsic curvature for the clusters [27]. This would then provide an unified framework for lateral and polar localization/positioning of chemoreceptors and possibly other synthetically engineered protein clusters [22].

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FIG. 1.
Schematic of the lattice model. Particles hop at random between neighboring lattice points on a triangular lattice representing the membrane and can join or leave an existing cluster. Columns of lattice sites are inserted to mimic cell growth, and particles are inserted at random at unoccupied lattice sites to mimic protein insertion in the membrane.
FIG. 2.
Snapshots of the model cell membrane undergoing one dimensional expansion, with lattice width $L_y = 500$ lattice units and length changing from $L_x = 600$ lattice units in the top snapshot to $L_x = 3000$ lattice units for the one at the bottom. Around 1% of the lattice sites are occupied on average, and interaction energy is set at $J = 4$. 

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FIG. 3.
Snapshots at a lattice length of 3000 units and width of 500 units of the lattice membrane undergoing one dimensional expansion. (a) Particles were deposited randomly throughout the duration of the expansion and over the length of the cell. (b) Particles were deposited in a burst at every doubling of the cell length.
**FIG. 4.**
Distribution of inter-cluster distance (projected along the direction of expansion) for (a) uniform, and (b) bursty deposition. Distance is measured in units of 3000 lattice units and the data is obtained from 87 independent simulations equivalent to the examples shown in Figs. 3(a) and (b). For (a) uniform deposition, the data is fit to the curve generated by the equation $y = \frac{1}{420} \sum_{i=1,6} \exp(- (x + 0.125(i-7))^2 / 0.04)$. For (b) bursty deposition, the data is fit to the curve $y = \frac{1}{53000} \sum_{i=1,60} \exp(- (x + 0.075(i-13))^2 / 1)$. 
FIG. 5.
Rate of change of cluster size, plotted as a function of cluster size $M$. The cell is grown in one direction from $L_x = 30$ to $L_x = 3000$, while $L_y$ is held fixed at 500. We take the average density $\rho = 0.013$, interaction energy $J = 7$, and $\gamma = 10^{-6}$. The simulations are run beginning with clusters of size 750 at each end of the simulation domain. Data was binned by cluster size in bins of size 5. We fit the data to a curve of the form

$$k + (M_0 - M) + DC_0 \rho\ln(M_0/M) - kM\rho_0$$

where $DC_0 = 0.45$ and $M_0 = 3000$. 

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FIG. 6.
Cluster-size distribution for two values of lattice occupancy depicted on a semi-log plot. (a) For average lattice occupancy $\rho = 0.001$, hardly any large clusters are observed. (b) For $\rho = 0.01$, the cluster-size distribution exhibits exponential decay. The insets correspond to snapshots from the end of two typical simulations at $\rho = 0.001$ and $\rho = 0.01$. 
FIG. 7.
Cluster-size distributions in the case of two dimensional expansion of the cell for (a) the thermalized case, with $J = 4$, and (b) when particles are not allowed to leave clusters. The insets depict corresponding snapshots from the simulations when the lattice has expanded to $L_x = 3000$ and $L_y = 3000$. 
FIG. 8.
Voronoi cells of the centroids of the clusters (a) obtained from simulations of isotropic lattice growth, and (b) for random distribution of cluster centroids. The length and width of the lattice are both 3000 lattice units.
FIG. 9.
Distribution of distance between clusters, in the case of isotropic expansion in two dimensions, compared with random placement of 70 clusters. The distribution for the random arrangement of the clusters is broader and peaked at lower cluster size, implying an order in the arrangement of the clusters for isotropic expansion.