Protein Drift-Diffusion Dynamics and Phase Separation in Curved Cell Membranes and Dendritic Spines: Hybrid Discrete-Continuum Methods

Patrick D. Tran, Thomas A. Blanpied, and Paul J. Atzberger

1 Physics, College of Creative Studies, University of California, Santa Barbara (UCSB)
2 Department of Physiology, University of Maryland
3 Department of Mathematics and Mechanical Engineering, University of California, Santa Barbara (UCSB)

We develop methods for investigating protein drift-diffusion dynamics in heterogeneous cell membranes and the roles played by geometry, diffusion, chemical kinetics, and phase separation. Our hybrid stochastic numerical methods combine discrete particle descriptions with continuum-level models for tracking the individual protein drift-diffusion dynamics when coupled to continuum fields. We show how our approaches can be used to investigate phenomena motivated by protein kinetics within dendritic spines. The spine geometry is hypothesized to play an important biological role regulating synaptic strength, protein kinetics, and self-assembly of clusters. We perform simulation studies for model spine geometries varying the neck size to investigate how phase-separation and protein organization is influenced by different shapes. We also show how our methods can be used to study the roles of geometry in reaction-diffusion systems including Turing instabilities. Our methods provide general approaches for investigating protein kinetics and drift-diffusion dynamics within curved membrane structures.

I. INTRODUCTION

In cellular biology, the morphological shapes of cell membranes play important roles in protein transport and kinetics. Cell membranes often take on shapes having characteristic geometries or topologies associated with biological function [1–7]. Membranes arising in cell biology consist of heterogeneous mixtures of lipids, proteins, and other small molecules [1]. The individual and collective dynamics of membrane associated molecules carry out diverse functions in cellular processes ranging from signaling to motility [1, 8–12]. Membranes are effectively two dimensional fluid-elastic structures resulting in processes that can be significantly different than their counter-parts occurring in bulk three dimensional fluids [13–16]. Investigating such cellular processes using computational simulation requires the ability to capture these effects and the geometric and topological contributions of curved membrane structures to protein drift-diffusion dynamics and kinetics.

We introduce computational methods based on a hybrid approach coupling discrete and continuum descriptions. For low concentration species, we track individual proteins as discrete particles. For other species, we track contributions using continuum fields. We circumvent many of the challenges of differential geometry and directly approximating surface PDEs by developing discrete localized models that capture geometric effects. In this way, behaviors of our model emerge on larger length-scales in a manner capturing the relevant underlying physical phenomena, while avoiding some of the more common challenges associated with direct application of PDE discretizations and differential geometry. We also provide stochastic local models to account for discrete effects and other fluctuations.

Many computational methods have been introduced for studying membranes. Methods modeling at the level of continuum fields and partial differential equation (PDE) descriptions include continuum concentration and phase fields in vesicles in [17], protein aggregation in [18], and phase separation in [19]. Methods modeling at the level of particles include Monte-Carlo (MC) Methods and Kinetic MC (KMC) in [20–26], Molecular Dynamics (MD) studies in [27–29], and Coarse-Grained (CG) Models in [30, 31]. Some work has been done on hybrid discrete-continuum approaches for membranes in [32–38], and taking into account geometric effects in [35, 39], and through point-cloud representations in [26, 40–43].

Our methods complement these approaches, and provide ways for handling the contributions of geometry for investigating curved heterogeneous membrane structures. Our methods include tracking individual particles for the protein drift-diffusion dynamics with bi-directional coupling with evolving continuum fields. Continuum fields can include the concentrations of more numerous molecular species or the order parameter for the local environment in phase separation.

Our methods are motivated by processes in curved cell membranes, such as neuronal dendritic spines, which are critical structures in the brain mediating the input of synaptic communications between neurons. Dendritic spines are small ~ 500nm structures that are attached along the larger shaft of the dendrites of neurons [44, 45]. Dendritic spines have unique morphologies that physiologically change in molecular composition, size, and shape to modulate the synaptic strength between neurons as part of long-term learning and memory [45–48].

* patrickduytran@gmail.com
† atzberg@gmail.com
The important connection between membrane geometry and synaptic strength is an active area of current theoretical and experimental research [49–61]. Recent advances in microscopy and single-particle tracking techniques are providing data sets giving hints on the underlying processes regulating protein transport and kinetics within spines [46, 62–68].

A hypothesis which we explore with our methods is that proteins locally can nucleate phase separation and that the associated evolution of the phase domains and coupling with protein dynamics can influence both diffusive transport and kinetics. We develop spatial-temporal models using our discrete-continuum approach to investigate the roles of geometry in the protein dynamics and spatially evolving heterogeneities.

We discuss details of our approach for modeling protein drift-diffusion dynamics in Section II. For curved membranes, we develop discretizations based on Markov-Chains and an estimator for the jump rates capturing similar transport properties as the Laplace-Beltrami operator in Section II B. We develop methods motivated by detailed-balance considerations in Section II C and investigate approximation errors in Section II D. We show how first passage times and other statistics can be computed efficiently using our methods, and in some cases that this can be done without the need to perform Monte-Carlo sampling in Section II E. We perform simulations using our methods of discrete and continuum systems in III. We develop continuum field methods for reaction-diffusion processes regulating protein transport and kinetics within curved membranes. We discuss a few results related to the drift-diffusion dynamics of particles useful in developing our methods. We then approximate the particle dynamics using Monte-Carlo sampling (top-right).

![Markov-Chain Discretization of Particle Drift-Diffusion on Curved Surfaces.](image)

**FIG. 1.** Markov-Chain Discretization of Particle Drift-Diffusion on Curved Surfaces. The surface is discretized using a triangulation with random walks between centroids \(x_i\) and \(x_j\) having jump rates \(M_{ij}\) determined by the local geometry (top-left) which can be expressed as a Markov-Chain (bottom). The Markov-Chain discretization yields a backward equation for \(\Omega\) allowing readily for computation of first-passage times \(\tau\) (FPTs) for reaching the boundary \(\partial \Omega\) and other statistics without the need in some cases for Monte-Carlo sampling (top-right).

## II. HYBRID DISCRETE PARTICLE-CONTINUUM APPROACH FOR CURVED SURFACES

We develop models using a hybrid discrete particle and continuum field approach for investigating protein transport and kinetics within curved membrane structures. The methods allow for taking into account the geometry, discrete effects, and coupling with local phase, or other evolving fields, within curved membrane structures.

### A. Particle Drift-Diffusion Dynamics

We discuss a few results related to the drift-diffusion dynamics of particles useful in developing our methods. We then approximate the particle dynamics using a Markov-Chain process [69] with jump rates based on estimating the local geometry.

The drift-diffusion dynamics of a particle immersed within a viscous fluid in flat euclidean space is given by the Langevin equation [70, 71]

\[
m d\mathbf{V}_t = -\gamma \mathbf{V}_t dt - \nabla U(\mathbf{X}_t) dt + \sqrt{2k_B T \gamma} d\mathbf{W}_t,
\]

where \(d\mathbf{X}_t = \mathbf{V}_t dt\). This is to be interpreted as an Itô process [70, 72]. The \(\gamma\) is the drag, \(U(x)\) is a potential energy, \(k_B\) is Boltzmann’s constant, and \(T\) is the temperature [71]. The \(d\mathbf{W}_t\) are increments of the Wiener process [70, 72]. The diffusion coefficient is given by \(D = k_B T / \gamma\). When \(m/\gamma \ll \ell^2/D\), where \(\ell\) is the radius of the particle, the inertial contributions are negligible. In this regime, the Langevin equation can be reduced to the over-damped Smoluchowsky equation

\[
d\mathbf{X}_t = -\frac{1}{\gamma} \nabla U(\mathbf{X}_t) dt + \sqrt{2D} d\mathbf{W}_t.
\]

This can be expressed in terms of probability densities \(\rho(x, t)\) for when \(\mathbf{X}_t = x\). This satisfies the Fokker-Planck (FP) equation

\[
\frac{\partial \rho}{\partial t} = -\nabla \cdot \mathbf{J}, \quad \mathbf{J} = \left( -\frac{1}{\gamma} \nabla U \right) \rho - D \nabla \rho.
\]

When \(U = 0\), this has the well-known Green’s Function for Euclidean space

\[
K(x', x; t) = \frac{1}{(4\pi Dt)^{d/2}} \exp \left( -\frac{(x' - x)^2}{4Dt} \right).
\]
From the FP equation, the $K(x', x; t)$ has the interpretation of the probability of a particle starting with $X_0 = x$ and diffusing to location $X_t = x'$ over the time duration $t$. We will use a related approach to determine our Markov-Chain jump rates. The FP equation has a steady-state $\rho^*$ with detailed balance if

$$J[\rho^*] = -\gamma^{-1} \nabla U \rho^* - D \nabla \rho^* = 0.$$  \hspace{1cm} (5)

For a smooth $U(x)$ with a sufficient growth rate as $|x| \to \infty$, the FP equation has steady-state with detailed balance for the distribution

$$\rho^*(x) = \frac{1}{Z} \exp \left( -\frac{U(x)}{kT} \right).$$  \hspace{1cm} (6)

This is the Gibbs-Boltzmann distribution, and $Z$ is the partition function normalizing this to be a probability density [71].

B. Markov-Chain Discretization for Particle Drift-Diffusion Dynamics on Curved Surfaces

We model the drift-diffusion dynamics of individual particles on curved surfaces using discrete Markov-Chains with the jump rates based on the local geometry. The surface is discretized into a triangulated mesh and each particle is tracked by the triangle which it occupies. We use that the surface metric is induced by the surrounding embedding space [73, 74]. We use for the local jump rates

$$M_{ij} = C_i \exp \left( -\frac{|x_i - x_j|^2}{\epsilon^2} \right).$$  \hspace{1cm} (7)

To approximate the diffusion over the time-scale $\Delta t$ on the surface $\mathcal{M}$, we use $\epsilon = \sqrt{4D\Delta t}$. The $x_i \in \mathcal{M}$ are the centers of the surface triangulation. The $C_i$ denotes the normalization constant when summing over index $j$ ensuring that $M$ is a right stochastic matrix [69].

The kernel $M_{ij}$ has been shown in the limit of refining the surface sampling to approximate diffusion under the surface Laplace-Beltrami operator $D\Delta_M$ [75, 76]. This has been shown to have the accuracy

$$\lim_{N \to \infty} \sum_{j=1}^{N} (M_{ij} - I_{ij})u_j = \frac{\epsilon^2}{4} D\Delta_M u(x_i) + O \left( \frac{1}{N^{1/2}}, \epsilon^4 \right).$$  \hspace{1cm} (8)

The $O$ holds with $\epsilon \to 0$. The $N$ is the number of points sampling $\mathcal{M}$ subject to a uniformity condition [41, 75, 76]. The $u_j = u(x_j)$ samples a smooth test function $u$. Intuitively, this follows since the stochastic matrix $M$ converges to the operator as $\exp(\epsilon^2 \Delta_M/4) = \exp(D\Delta\Delta_M) \approx \exp(D\Delta\Delta) + \exp(D\Delta t\Delta_M) \approx I + D\Delta t\Delta_M \approx I + D\Delta t\Delta \approx I + M$, where $\Delta = \nabla^2$ is the standard Laplacian. The last two terms are motivated by the Taylor expansions of the exponential and the geometric terms as $\epsilon \to 0$.

Since the the surface properties will only be approximated when there are a sufficient number of sample points in the support of the kernel, for a given $N$ there is a trade-off in the choice of $\epsilon$. If $\epsilon$ is too large the approximation will not be of local surface properties. If $\epsilon$ is too small only the center point will contribute significantly to the kernel. We investigate further this trade-off in $\epsilon$ and the resulting approximation accuracy in Section IID.

C. Detailed Balance and Area Corrections

To incorporate the contributions of the drift arising from $U$ in equation (1), we consider the Gibbs-Boltzmann distribution expressed as $\rho(x) = Z^{-1} \exp (-\beta U(x))$, with $\beta = (k_B T)^{-1}$ the inverse thermal energy. We seek discretizations preserving statistical structure, such as detailed-balance as in [77, 78]. For our curved surfaces, we seek discretizations for methods that have at steady-state the surface Gibbs-Boltzmann distribution with detailed balance [71]. We can express the evolution of the discrete probability in terms of net fluxes as

$$p_i^{(n+1)} = p_i^{(n)} + \sum_{j \neq i} J_{ij}^{(n)}, \quad J_{ij}^{(n)} = p_j^{(n)} M_{ji} - p_i^{(n)} M_{ij}.$$  \hspace{1cm} (9)

At steady-state $p_k^{(n+1)} = p_k^{(n)} = p_k^*$ we design our transition rates so that the we have a discrete surface Gibbs-Boltzmann distribution with approximate detailed balance. The discrete detailed-balance $J_{ij} = 0$ gives the
conditions
\[ p_i^* = \exp(-\beta U_i) A_i / Z, \quad \frac{M_{ij}}{M_{ji}} = \frac{p_j^*}{p_i^*} = \exp(-\beta U_j) A_i / \exp(-\beta U_i) A_j, \]
where \( U_k = U(x_k) \) and \( Z = \sum_i \exp(-\beta U_i) A_i. \)

Motivated by these conditions, we discretize using the transition rates
\[ M_{ij} = C_i \exp \left( -\frac{|x_i - x_j|^2}{\varepsilon^2} \right) \times \exp \left( \frac{U(x_i) - U(x_j)}{2k_B T} \right), \]
\[ \times \exp \left( \frac{1}{2} \ln \frac{A_j}{A_i} \right), \]
(11)
where \( C_i \) normalizes the \( M_{ij} \) to be a probability when summing over the index \( j \). The conditions hold up to the normalization ratio \( C_i/C_j \rightarrow 1 \) as the discretization is refined with \( N \rightarrow \infty, \epsilon \rightarrow 0. \)

D. Approximation Errors

We investigate the accuracy of the surface discretizations and the trade-offs in the choice of \( \epsilon \) between sufficient sampling and maintaining locality. We perform our studies for the surface of the unit sphere \( S^2 \), which has the Laplace-Beltrami operator \( \Delta_M \) with eigenfunctions corresponding to the spherical harmonics \( [74, 79, 80] \). In the comparisons, our numerical operator \( M \) is obtained from equation (11) and the scalings indicated in (8) to yield the approximation \( L = (M - I) \simeq (\epsilon^2/4)\Delta_M \). In practice for efficient calculations, the \( M_{ij} \) is constructed by truncating the kernel only to use neighbors \( x_j \) within the distance \( r_0 \) with \( |x_i - x_j| < r_0. \) We consider the errors for a test function \( v \) given by
\[ e_{LB}[v] = \left( \frac{4}{\epsilon^2} (M - I) - \Delta_{S^2} \right) v. \]
(12)

In Figure 2, we show the relative error \( ||e_{LB}[v]||_1/A \) averaged over the surface when \( v \) is the spherical harmonic corresponding to \( v = v(x, y, z) = z \) restricted to the surface. We consider how the error varies for \( N = 10,000 \) for different choices of \( \epsilon \in [0.25, 2.0] \) and \( r_0 \in [0.5, 2.0] \). Letting \( \delta x = \min_{ij} |x_i - x_j| \), we find that when \( \epsilon \ll \delta x \) there are insufficient number of points in the support of the kernel to estimate the surface geometry and the error becomes large. We find when \( \epsilon \gg \delta x \) is large there are many points within the support of the kernel, but the area of support is not localized enough to provide a good estimate of the operator. We also show both the case with and without the area correction terms. We find for our relatively uniform triangulations these give comparable overall errors here. We find that for our discretizations of the sphere with \( N = 10,000 \) points and \( r_0 \geq 1.5 \), the optimal choice is \( \epsilon \simeq 1 \), see Figure 2.

E. Role of Geometry in First-Passage Times and Other Statistics

We perform analysis to develop some results showing how our methods can be used for investigating the role of geometry of the first-passage times and other statistics associated with the drift-diffusion dynamics of particles on curved surfaces. Our Markov-Chain discretizations allow in some cases for computing efficiently statistics without the need to resort to Monte-Carlo sampling, provided the state space is not too large. We consider statistics of the form
\[ u_i^{(n)} = E \left[ f(X^{(N)}) + \sum_{k=n}^{N-1} g(X^{(k)}, t) \bigg| X^{(n)} = x_i \right]. \]
(13)
Let \( \mathbf{u}^{(k)} \) be the column vector with components \( [\mathbf{u}^{(k)}]_i = u_i^{(k)}. \) The \( f, g : M \rightarrow \mathbb{R} \) are any two smooth functions on the surface \( M \). Let \( [f]_i = f(x_i) \) and \( [g^{(k)}]_i = g(x_i, t) \) be column vectors. We also consider statistics of the form
\[ u_i^{(\tau)} = E \left[ f(X^{(\tau)}) + \sum_{k=0}^{\tau_0 - 1} g(X^{(k)}) \bigg| X^{(0)} = x_i \right]. \]
(14)
For the domain \( \Omega \), the \( \tau_0 = \inf\{k \geq 0 \mid X^{(k)} \not\in \Omega\} \) is the stopping time index for the process to reach the

![First Passage Times for Spine Shapes](image)

FIG. 3. First-Passage Times for Spine Shapes. First passage times are computed when a protein starts at the top of the bulb-like head region and reaches the boundary. To investigate the role of the neck region versus other aspects of the shapes, three cases are considered for the boundary location, (i) at the base of the spine, (ii) in the middle of the neck, and (iii) within the spherical head region just above the neck. The results show that the neck region plays the dominant role in the geometry. As the neck narrows, the diffusion of the protein to leave the head region and enter the tubular domain has a first-passage time that significantly increases from the geometry.
TABLE I. Parameters for Gray-Scott Reaction-Diffusion System in Figure 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\epsilon_u$</td>
<td>diffusion scale for $u$</td>
<td>$1.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$\epsilon_v$</td>
<td>diffusion scale for $v$</td>
<td>$5.0 \times 10^{-3}$</td>
</tr>
<tr>
<td>$r_0$</td>
<td>diffusion cut-off radius</td>
<td>1.0</td>
</tr>
<tr>
<td>$a$</td>
<td>$u + 2v \rightarrow 3v$ reaction rate</td>
<td>$4.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$b$</td>
<td>$v \rightarrow p$ reaction rate</td>
<td>$6.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$T_{sim}$</td>
<td>total time duration</td>
<td>$5.0 \times 10^{3}$</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>time-step</td>
<td>$1.0 \times 10^{-1}$</td>
</tr>
<tr>
<td>$n_{rk}$</td>
<td>Runge-Kutta steps</td>
<td>100</td>
</tr>
</tbody>
</table>

Proof. (see Appendix A)

Theorem 2. The statistics $w^{(k)}(\Omega)$ in equation 14 satisfies

\[ (\hat{M} - \hat{I})w = -g \]
\[ \partial w = f. \]

The $\partial w$ extracts entries for all indices with $x_i \in \partial \Omega$. The $\hat{M}, \hat{I}$ refers to the matrix only with the rows with indices in the interior of $\Omega$.

Proof. (see Appendix A)

In the case that $f = 0, g = 1$, this becomes the First-Passage Time (FPT) statistic $w_i = E[\tau_{\Omega} | X(0) = x_i]$. These results allow for the statistics of equations 13 and 14 to be computed efficiently without the need for Monte-Carlo sampling provided the state space is not too large.

Motivated by observations that the neck geometry appears to be a strong factor in compartmentalization in dendritic spines [67, 81], we compute the first passage times of protein diffusions for different spine shapes in Figure 3. First passage times are computed for when a protein starts at the top of the head region with the bulb-like shape and reaches the boundary. To investigate the role played by the neck region compared to the influence of the other aspects of the geometry, three cases are considered for the boundary location. These are boundaries located (i) at the base of the spine, (ii) in the middle of the neck, and (iii) within the spherical head just above the neck. These results indicate that compared to the other geometric features, the width of the neck region plays the dominant role in the first passage times. As the neck narrows, the first-passage time for the protein diffusion significantly increases from these changes in the geometry, see Figure 3.

FIG. 5. Evolution of Turing Instabilities for Gray-Scott Reactions. Shown is the evolution of the reaction-diffusion pattern formation process on the dendritic spine shape having the narrowest neck, label A. The pattern progresses first by forming within the bulb-like head region, and then spreads through the neck to form patterning on the tubular part of the domain. The time-steps are shown for $n = 0, 400, 800, 1200, 1600, 2000$.

III. SIMULATIONS

A. Turing Instabilities on Curved Surfaces

We show how our discretization approach can be used to develop methods for performing simulations of general reaction-diffusion processes on curved surfaces of different shapes. We consider reaction-diffusions, such as the pattern formation process based on Turing’s instability mechanism [82], where the geometry and topology of the domain can impact the patterns that are obtained [83, 84]. Consider the system with two molecular species with concentrations $u, v$

\[ \frac{\partial u}{\partial t} = D_u \Delta_M u + f(u, v), \quad \frac{\partial v}{\partial t} = D_v \Delta_M v + g(u, v). \]

FIG. 4. Role of Topology and Geometry on Pattern Formulation. The Gray-Scott reaction-diffusion shows different patterns depending on the shape of the surface. Shown are the cases of (i) square, (ii) cylinder, (iii) sphere, and (iv) torus. The surfaces have area one and when there are edges we use reflecting boundary conditions. For the shapes (i)-(ii) spotted patterns emerge having roughly a hexagonal pattern. For spherical topology (iii) a regular hexagonal pattern without defects is no longer possible, and instead striped patterns mix with spots. For the case of a torus (iv), which can sustain a hexagonal pattern in principle, the heterogeneity of the curvature appears to drive the formation of localized stripe-like patterns. These results indicate that both the geometry and topology can significantly impact pattern formation.
TABLE II. Parameters for Gray-Scott Reaction-Diffusion System in Figures 5 and 6.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\epsilon_u$</td>
<td>diffusion scale for $u$</td>
<td>$1.0 \times 10^{-1}$</td>
</tr>
<tr>
<td>$\epsilon_v$</td>
<td>diffusion scale for $v$</td>
<td>$5.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$r_0$</td>
<td>diffusion cut-off radius</td>
<td>1.0</td>
</tr>
<tr>
<td>$a$</td>
<td>$u + 2v \rightarrow 3v$ reaction rate</td>
<td>$4.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$b$</td>
<td>$v \rightarrow p$ reaction rate</td>
<td>$6.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>$T_{sim}$</td>
<td>total time duration</td>
<td>2.0</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>time-step</td>
<td>$1.0 \times 10^{-3}$</td>
</tr>
<tr>
<td>$n_{rk}$</td>
<td>Runge-Kutta steps</td>
<td>1</td>
</tr>
</tbody>
</table>

The diffusivities $D_u$ and $D_v$ will in general be different. Through the non-linear reaction terms, the difference in diffusivity can cause the homogeneously mixed concentrations to become unstable resulting in pattern generation [82, 83].

We consider Gray-Scott reactions [85], which can exhibit different patterns depending on the initial conditions and interactions with noise and other perturbations [83, 86]. For the Gray-Scott reactions [85], the terms are $f(u,v) = -uv^2 + a(1-u)$ and $g(u,v) = uv^2 - (a+b)v$. The rate parameters $a$, $b$ are for the chemical reactions $u + 2v \rightarrow 3v$ and $v \rightarrow p$.

We start with a homogeneous steady-state solution for the system $(u,v) = (1,0)$, and add small perturbations based on uniform random noise $\pm 10\%$ of the steady-state at each location $x_i$ within a region $\Gamma \subseteq \Omega$. Throughout our simulations, we choose $a = 0.04$, $b = 0.06$, guided by the parameters of the phase diagram of [87]. We investigate how the Gray-Scott patterns are influenced by different geometries and topologies.

We model the reaction-diffusion system in our simulations by splitting the time-step integration into a diffusion step and reaction step. For the diffusion time-step $\Delta t$ we use our Markov-Chain discretization to update the concentration fields. For the reactions, we use the smaller time-steps $\delta t = \Delta t/n_{rk}$ which are integrated with the fourth-order Runge-Kutta method RK4 [88, 89]. We alternate between these steps in our simulations.

Using our Markov-Chain discretizations, we develop numerical methods for the spatial-temporal evolution of the concentration fields. By equation (7), we obtain a stochastic matrix $M$. We model the concentrations by $u(x,t) = (n_u/A)p_u(x,t)$, $v(x,t) = (n_v/A)p_v(x,t)$, where $A$ is the surface area. The $p = [p_u, p_v]$, with $[p^n]_i = p(x_i, t_n)$, are obtained from the probability evolution for the Markov-Chain given by $p^n = p^{n+1}M$. In this way, we obtain a model that approximates the evolution of the continuous concentration fields.

Our approaches for the diffusion also can be used for discrete particle simulations with individual random walkers. This would have the same distribution as our continuum model when taking appropriate limits. Our methods allow for either (i) to perform stochastic simulations of random walks tracking individual particles to account for discrete spatial-temporal fluctuations from finite number effects, or (ii) to perform deterministic simulations tracking the probability distribution of the walkers. For the reaction-diffusion studies we use approach (ii). For later studies involving phase separation, we use approach (i).

We consider the Gray-Scott reaction-diffusion process on the following geometries (i) flat sheet with boundaries, (ii) finite cylinder with boundaries, (iii) surface of a sphere, (iv) surface of a torus, see Figure 4. The surfaces have one area and when there are boundary edges we use reflecting boundary conditions. For the shapes (i)-(ii) spotted patterns emerge having roughly a hexagonal pattern. For the spherical topology (iii) a regular hexagonal pattern without defects is no longer possible, and instead striped patterns mix with spots. For the case of a torus (iv), which can sustain a hexagonal pattern in principle, the heterogeneity of the curvature appears to drive the formation of localized stripe-like patterns. The results obtained with our methods indicate that both the geometry (curvature and scale effects) and the topology can impact significantly the pattern formation process.

We also consider more complicated shapes for the Gray-Scott reactions given by our mechanistic dendritic spine geometries with different neck sizes, see Figures 5, 6. These shapes consist of a bulb-like head region (representing the spine) which is connected by a neck structure to a tube-like region (representing the dendrite). We vary the shapes by changing the thickness of the neck-like structure joining the two regions. The evolution of the pattern formation process for the geometry with the narrowest and widest neck shapes are shown in Figure 5. For the narrowest necks, the confinement in the head region appears to result in stripe-like patterns that also
extend through the neck. In the larger tube-like region, the spotted patterns form inter-mixed with the stripe pattern, see Figure 6. These results indicate how local regions can exhibit different patterning depending on the local geometry.

B. Dendritic Spines and Protein Kinetics

We develop a mechanistic model for dendritic spines to investigate the dependence of protein transport and kinetics on geometry and heterogeneities arising from phase separation. Our investigations are motivated from experiments on SynGAP and PSD-95 proteins, where phase separation may play a role in driving receptor organization [90]. Phase separation can arise from nucleation or modulating local concentrations in the cell membrane, which is a heterogeneous mixture of lipids, proteins, and other small molecules [1, 91, 92].

In our mechanistic model, we investigate how the spine geometry and phase separation can influence reaction kinetics. We start with a two species system. The A and B molecular species are tracked at the individual particle level. In the absence of phase separation, this would diffuse freely over the membrane surface. As a starting point, we study the basic chemical kinetics $A + B \rightarrow C$. The discrete particles react with probability $p$ when coming within a reaction distance $r < r_0$. This is motivated by Smoluchowsky reaction kinetics [93–96].

To model such effects at a coarse-level, we track a continuum phase field $\phi = \phi(x, t)$ which can couple to the local diffusive motions of the discrete protein particles. We consider in our initial model the case of a local order parameter associated with phase separation based on Ginzburg-Landau (GL) theory [97, 98]. Other phase-separation phenomena and approaches also could be considered in principle within our framework, such as the second-order Allen-Cahn [99] or the conservative fourth-order Cahn-Hilliard [100], with additional work on the numerical methods for the operators on curved surfaces and coupling with the Markov-Chain discretization [101]. For notational convenience, we will denote $q \approx \phi(x)$, so $q : \mathcal{M} \rightarrow \mathbb{R}$ for the phase variable map for the curved surface $\mathcal{M}$. This gives at lattice site $i$, $q_i \approx \phi(x_i)$. The GL functional is $V_0[q] = \int_{\mathcal{M}} (\nabla \phi(x))^2 + V_2[\phi(x)] dx$. The first term accounts for a line tension between phases and the second term drives the phase to $\pm 1$ with local energy density $V_2[\phi] = K(1 - \phi^2)^2$. To capture similar effects as $V_0[q]$, we use the simplified discrete model

$$V_0[q] = \frac{1}{n^2} \sum_i \sum_{j \neq i} V_1[q_i, q_j] + \frac{1}{n} \sum_i V_2[q_i], \quad (20)$$

with

$$V_1[q_i, q_j] = \alpha_1 W_1(q_i - q_j)^2, \quad V_2[q] = \alpha_2 (1 - q^2)^2. \quad (21)$$

FIG. 7. Chemical Kinetics and Phase Separation. We consider chemical kinetics where molecular species $A, B$ diffuse freely and react to form $C$ by $A + B \rightarrow C$. The molecular species $C$ can nucleate phase $q = -1$. The drift-diffusion of $C$ is coupled to the local phase by equation 22. This results in a bi-directional confinement force from the phase field $q$ acting on $C$ to keep within regions with $q = -1$. This also results in an equal-and-opposite force acting on the phase field from equation 22 driving nucleation and phase separation.

FIG. 8. Dendritic Spine Model: Role of Geometry in Phase Separation. The dendritic spine model consists of a head region connected by a neck region to a tubular domain. The active proteins $A, B$ in the model all originate at the top of the head region. The phase separation occurring in the two cases is shown for (i) a narrow neck constricting the protein diffusion and spread of the phase separation (top), (ii) a wide neck through which the proteins can readily diffuse and the phase can separate (bottom). The phase $q = 1$ is red and $q = -1$ is blue, shown are time-steps 50, 300, and 2000. At around time-step $\sim 300$ (middle), the the protein diffusion and phase separation comes into contact with the neck region. In the narrow case, the neck region acts effectively like an entropic barrier for the diffusion arising from the geometry.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>GL phase interfacial tension</td>
<td>$1.0 \times 10^5$</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>GL phase polarity</td>
<td>$1.0 \times 10^4$</td>
</tr>
<tr>
<td>$\alpha_3$</td>
<td>GL protein-phase coupling</td>
<td>1.0</td>
</tr>
<tr>
<td>$a$</td>
<td>protein phase radius</td>
<td>0.1</td>
</tr>
<tr>
<td>$N$</td>
<td>$A, B$ initial protein count</td>
<td>1000</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>diffusion scale for proteins</td>
<td>0.1</td>
</tr>
<tr>
<td>$r_0$</td>
<td>diffusion cut-off radius</td>
<td>0.5</td>
</tr>
<tr>
<td>$p$</td>
<td>$A + B \rightarrow C$ reaction probability</td>
<td>0.01</td>
</tr>
<tr>
<td>$T_{\text{sim}}$</td>
<td>total time duration</td>
<td>200.0</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>time-step</td>
<td>0.1</td>
</tr>
<tr>
<td>$n_{\text{rk}}$</td>
<td>Runge-Kutta steps</td>
<td>100</td>
</tr>
</tbody>
</table>

TABLE III. Parameters for Dendritic Spine Phase Separation.
The first term models the interfacial tension, where the coefficient \( W_{ij} = W(r_{ij}) \) decays in \( r_{ij} = |x_i - x_j| \). The second term models the order parameter which locally is at a minimum for \( q = \pm 1 \). The \( \alpha_1, \alpha_2 > 0 \) control the strength of the interfacial tension and the phase variable ordering. We use for the decay coefficient \( W_{ij} = \exp(-r_{ij}^2/\epsilon^2) \) which is truncated for large \( r_{ij} \gg \epsilon \).

To couple protein motions \( \mathbf{X}(t) \) and their ability to induce local phase ordering in \( q \), we use the free energy term

\[
V_3^{(i)}[q, X] = \alpha_3(q_i - (-1)^k)\eta_a(x_i - X). \tag{22}
\]

The \( \alpha_3 > 0 \) controls the strength of this coupling. The \( \eta_a \) gives a kernel function with support localized around the protein location \( X = X(t) \). This term drives the phase field toward \( q = -1 \) in a region around the protein location \( X(t) \). We use \( \eta_a(r) = \exp(-r^2/a^2) \) and

\[
V_3[q, X] = \frac{1}{n} \sum_i V_3^{(i)}[q, X]. \tag{23}
\]

The free energy for full system \((q, X)\) with protein configuration \( X \) and phase-field \( q \) is

\[
V[q, X] = V_0[q] + \sum_k V_3[q, X^k]. \tag{24}
\]

The discrete protein positions \([X]_k = X^k\) are updated using the Markov-Chain discretization in equation (11) for the drift-diffusion dynamics. The energy for the protein configuration is given by \( U(\mathbf{X}) = V[q, \mathbf{X}] \). The time evolution of the phase field is given by

\[
\frac{dq_i}{dt} = -\nabla_q V[q, X]. \tag{25}
\]

This is discretized and integrated over sub-time-steps \( \delta t = \Delta t/n_{rk} \) using Runge-Kutta RK4 \([88, 89]\). Modeling the discrete system using the common free energy \( V \) ensures the bi-directional coupling gives equal-and-opposite forces between the phase-field \( q \) and the proteins \( X \).

We perform simulations to investigate how the dendritic spine geometry impacts the protein reaction kinetics and phase-separation, see Figure 7 and Table I. The proteins couple to the phase separation by having the ability to drive nucleation of local patches with \( q = -1 \) near the protein location \( X(t) \). The geometries were chosen with the neck region taking on shapes varying from narrow to wide, see Figure 4. The protein species \( A, B \) are modeled as originating in the top head region of the spine. This could arise for instance if these species correspond to tracking proteins only after they have become activated in this region. The proteins can then diffuse, and may induce local phase-separation through the coupling \( V_3 \). The proteins can also interact to form a complex which is tracked by molecular species \( C \).

We show how the phase separation proceeds over time as the size of the neck region varies in Figure 8. As the neck region narrows, the protein diffusion and the phase separation are restricted to be localized in the head region. As the neck becomes wide, the protein diffusion and phase separation can readily proceed to spread more rapidly into the tubular region, see Figures 8, 9. Further effects arise from the coupling of the proteins with the local phase.

FIG. 9. Dendritic Spine Model: Average Phase. The proteins \( C \) can nucleate phase with \( q = -1 \). Shown are how the geometry impacts phase evolution for five different sizes for the neck region with labels A-F ordered from narrowest to widest as in Figure 6. The phase separation is found to slow down considerably for the narrowest neck (label A) relative to the widest neck (label F). The differences emerge around time-step \( \sim 300 \), when the bulb-like head region is saturated. We see over the 2000 time-steps the widest neck results in almost the entire domain including the tubular region converting to phase \( q = -1 \). For the narrowest neck shape, we see at time-step 2000 the phase separation is primarily isolated to the head head region and surrounding area, while the rest of the domain remains primarily \( q = 1 \).

FIG. 10. Dendritic Spine Model: Proteins \( C \) in the Head Region. Shown are the number of proteins \( C \) within the bulb-like head region over time. We see the reactions producing \( C \) proceed almost independent of the geometry up to time-step \( \sim 300 \). Afterwards, the shapes with the narrowest necks results in far more \( C \) proteins being produced and retained within the head region. This shows how phase-separation can serve to enhance retaining proteins near the top of the spine.
The protein dynamics are impacted by both the geometry and the local phase. In our simulation studies, the coupling coefficients are taken to be $\alpha_A = \alpha_B = 0$ and $\alpha_C = 1.0$. For this case $C$ can nucleate phase separation nearby since it prefers the phase field have $q = -1$. This also results for $C$ experiencing a trapping force within regions with $q = -1$, from the free energy in equation (22). This restricts the movements of $C$. The evolution of the creation of $C$ is shown in Figure 10. The number of $C$ formed and retained in the head region is significantly impacted by the neck geometry and phase separation. When the neck is narrow, the confinement of $A, B$ and the phase separation to the head region, both enhances the creation of $C$ by more frequent $A-B$ encounters and in $C$’s retention to the head region from the phase trapping forces. As the neck becomes wide, the $A, B$ can diffuse more freely and when the phase does nucleate it can more rapidly spread throughout the whole domain. This results in a much smaller number of $C$ being created and retained in the head region.

Our basic mechanistic model shows that the morphology and phase separation can interact to serve together to enhance retaining proteins near the top of the dendritic spine. These results are expected to carry over to more complicated chemical kinetic systems. The further interactions between diffusion, kinetics, phase separation, and the geometry can regulate in different ways the spatial arrangements and the local effective rates of reactions in curved cell membranes.

IV. CONCLUSIONS

We have developed computational simulation methods for tracking at the discrete protein level drift-diffusion dynamics incorporating the role of geometry, chemical kinetics, and coupling to continuous phase fields. The introduced methods can be used broadly for investigating protein transport and kinetics within curved cell membranes. The methods allow for taking into account the geometry, discrete effects, and coupling with local phase, or other evolving fields, within curved membrane structures.

V. ACKNOWLEDGEMENTS

The authors P.J.A. and P.T. would like to acknowledge support for this research from the grants NSF Grant DMS-1616353 and DOE Grant ASCR PHILMS DESC0019246. The author T.A.B. would like to acknowledge support from grant NIH R37MH080046. P.T. would like to acknowledge a Goldwater Fellowship and College of Creative Studies Summer Undergraduate Fellowship. P.J.A. would like to acknowledge a hardware grant from Nvidia. Authors also would like to acknowledge UCSB Center for Scientific Computing NSF MRSEC (DMR1720256) and UCSB MRL NSF CNS-1725797.

Appendix A: Results on Statistics of Markov-Chains and Backward Equations

We discretize the particle drift-diffusion dynamics on the surface using a Markov-Chain with jump rates $M_{ij}$. The First Passage Time (FPT) and other statistics can be computed efficiently from the Markov-Chain without the need for Monte-Carlo sampling when the discrete state space is not too large. We show how results similar to the Backward-Kolmogorov PDEs [72] can be obtained for our discrete Markov-Chains.

Theorem 1. Let $u$ be a column vector with components in $i$ associated with the statistics

$$u_i^{(n)} = E \left[ f(X^{(N)}) + \sum_{i=n}^{N-1} g(X^{(t)}, t) \mid X^{(n)} = x_i \right].$$

(A1)

The statistics $u^{(k)}$ satisfy

$$u^{(n-1)} = Mu^{(n)} + g^{(n-1)}$$

(A2)

$$u^{(N)} = f.$$  

(A3)

The $M$ is the right-stochastic matrix of the Markov-Chain. For a given choice of functions $f,g$, we collect the values $[f]_i = f(x_i)$ and $[g^{(\ell)}]_i = g(x_i, \ell)$ as column vectors $f,g^{(\ell)}$.

Proof. For the initial condition $X^{(n)} = x_i$, let the matrix $p^{(m)}$ have the components $P_{ij}^{(m)} = P_{ij}^{(m)}$. For $m \geq n$, the $p_j^{(m)}$ is the solution of $p^{(m+1)} = p^{(m)}M$, starting with $p_i^{(n)} = [p]_{ij} = \delta_{ij}$. The $\delta_{ij}$ is the Kronecker $\delta$-function. For $m = n$, we have $P_{ij}^{(n)} = \delta_{ij}$. This gives

$$u_i^{(n)} = E \left[ f(X^{(N)}) + \sum_{i=n}^{N-1} g(X^{(t)}, t) \mid X^{(n)} = x_i \right]$$

$$= \sum_j p_{ij}^{(N)} f(x_j) + \sum_{i=n}^{N-1} \sum_j p_{ij}^{(t)} g(x_j, t)$$

$$= \sum_j \sum_{i=n}^{N-1} \sum_k p_{ik}^{(n)} (M^{N-n})_{kj} f(x_j)$$

$$+ \sum_{i=n}^{N-1} \sum_j \sum_k p_{ik}^{(n)} (M^{t-n})_{kj} g(x_j, t)$$

$$= \sum_j (M^{N-n})_{ij} f(x_j) + \sum_{i=n}^{N-1} \sum_j (M^{t-n})_{ij} g(x_j, t)$$

$$= [M^{N-n} f + \sum_{i=n}^{N-1} M^{t-n} g^{(t)}]_{i} = [Mu^{(n+1)} + g^{(n)}]_{i},$$

(A4)

At time $t = N$, only the term with $f$ contributes and we obtain $u_i^{(N)} = [f]_i$. □

Theorem 2. Let $w$ be a column vector with components $w_i$ associated with the first-passage-time statistics

$$w_i = E \left[ f(X^{(\tau)}) + \sum_{t=0}^{\tau-1} g(X^{(t)}) \mid X^{(0)} = x_i \right],$$

(A5)

where $\tau_\Omega = \inf\{k \geq 0 \mid X^{(k)} \notin \Omega\}$. The $w$ satisfies the linear equation

$$\left(\hat{M} - \hat{I}\right)w = -g$$

(A6)

$$\partial \hat{w} = f.$$  

(A7)

The $\partial \hat{w}$ extracts entries for all indices with $x_i \in \partial \Omega$. The $M$ refers to the rows with indices in the interior of $\Omega$.

Proof. Since the equation is linear, we will first consider the case with $f = 0, g \neq 0$ and then the case with $f \neq 0, g = 0$. The general solution is then the sum of these two cases. For the case with $f = 0, g \neq 0$ we have

$$w_i = E \left[ \sum_{t=0}^{\tau-1} g(X^{(t)}) \mid X^{(0)} = x_i \right]$$

$$= \sum_{n=0}^{\infty} E \left[ \sum_{t=0}^{n-1} g(X^{(t)}) \mid X^{(0)} = x_i, \tau = n \right] \text{Pr}\{\tau = n\}$$

$$= \sum_{n=0}^{\infty} g(x_i) \text{Pr}\{\tau = n\} + \sum_{n=0}^{\infty} \sum_{x_j \in \Omega} \text{Pr}\{X^{(1)} = x_j \mid X^{(0)} = x_i\} \text{Pr}\{\tau = n\}$$

$$\times E \left[ \sum_{t=1}^{n-1} g(X^{(t)}) \mid X^{(0)} = x_i, X^{(1)} = x_j, \tau = n \right]$$

$$= g(x_i) + \sum_{x_j \in \Omega} M_{ij} \sum_{n=0}^{\infty} \text{Pr}\{\tau = n\}$$

$$\times E \left[ \sum_{t=1}^{n-1} g(X^{(t)}) \mid X^{(0)} = x_i, X^{(1)} = x_j, \tau = n \right]$$

$$= g(x_i) + \sum_{x_j \in \Omega} M_{ij} w_j.$$  

(A8)

In matrix form,

$$\dot{w} = g + \hat{M} w,$$

(A9)

where $\dot{w}, \hat{M}$ refers to the entries in the rows with indices of points in the interior of the domain $\Omega$. This can be expressed as

$$\left(\hat{M} - \hat{I}\right)w = -g.$$  

(A10)

The $\hat{I}$ is the linear map that extracts entries within the interior of the domain $\Omega$. 
We next consider the case with \( f \neq 0 \) and \( g = 0 \). Similarly, this follows from

\[
W_i = \mathbb{E} \left[ f(X^{(\tau)}) \Bigg| X(0) = x_i \right] \\
= \sum_{n=0}^{\infty} \mathbb{E} \left[ f(X^{(n)}) \Bigg| X(0) = x_i, \tau = n \right] \Pr\{\tau = n\} \\
= \sum_{n=0}^{\infty} \sum_{x_j \in \Omega} \Pr\{X^{(1)} = x_j \big| X(0) = x_i\} \Pr\{\tau = n\} \\
\times \mathbb{E} \left[ f(X^{(n)}) \Bigg| X(0) = x_i, X^{(1)} = x_j, \tau = n \right] \\
= \sum_{x_j \in \Omega} M_{ij} \sum_{n=0}^{\infty} \Pr\{\tau = n\} \\
\times \mathbb{E} \left[ f(X^{(n)}) \Bigg| X^{(1)} = x_j, \tau = n \right] \\
= \sum_{x_j \in \Omega} M_{ij} w_j, \\
\text{(A11)}
\]

For \( x_i \in \partial \Omega \) we have \( W_i = \mathbb{E} \left[ f(X^{(\tau)}) \bigg| X(0) = x_i \right] = f(x_i) \), since \( \tau = 0 \) in this case. In matrix form this gives

\[
(\hat{M} - \hat{I})w = 0. \tag{A12}
\]

The \( \partial w \) extracts the entries with indices \( i \) corresponding to the boundary \( \partial \Omega \). Putting both cases together we have that \( w \) satisfies for general \( f, g \) the linear system

\[
(\hat{M} - \hat{I})w = -g \\
\partial w = f. \tag{A13}
\]

These results provide approaches for computing efficiently the statistics \( u \) and \( w \) without the need in some cases for Monte-Carlo sampling when the state space is not too large. These results provide an analogue of the Backward-Kolmogorov PDEs in the setting of our Markov-Chain discretizations of particle drift-diffusion dynamics on curved surfaces.