SPATIALLY ADAPTIVE STOCHASTIC NUMERICAL METHODS
FOR INTRINSIC FLUCTUATIONS IN REACTION-DIFFUSION
SYSTEMS

PAUL J. ATZBERGER *

Abstract. An approach is introduced for accounting for fluctuations in continuum concentration fields of reaction-diffusion systems when considered on small spatial-temporal scales. Stochastic numerical methods are developed which approximate the corresponding stochastic partial differential equations (SPDEs) on adaptive multilevel meshes subject to Neumann and Dirichlet boundary conditions and on domains having general geometries allowing for curved boundaries. As a demonstration of the stochastic numerical methods the role of concentration fluctuations is investigated in a model of biological cell direction sensing through concentration gradients. As a further demonstration of the methods a mechanism by which intrinsic fluctuations can induce spatial patterns is investigated for a variant of the Gray-Scott chemical reactions. The introduced approach for SPDE discretization on multilevel meshes is expected to be widely applicable in the study of spatially extended stochastic systems using adaptive stochastic numerical methods.

Key words. Adaptive Methods, Stochastic Numerical Methods, Stochastic Partial Differential Equations, Reaction-Diffusion, Multilevel Meshes, Multiscale Methods, MAC Discretization, Statistical Physics, Fluctuation-Dissipation, Pattern Formation, Gray-Scott Reaction, Gradient Sensing.

1. Introduction. In many physical systems arising in chemistry, biology, and material science a particularly important feature is the spatial distribution of molecular species which undergo diffusive migrations while participating in chemical reactions [54; 67–71; 90; 93]. The behavior of such physical systems can often be modeled at the mean-field level by a continuum field description governed by deterministic partial differential equations for the local concentration of molecules. However, at small length scales approaching the size of individual molecules non-negligible fluctuations are manifested as a consequence of microscopic positional and momenta degrees of freedom of the individual molecules, which are averaged or neglected in such continuum field descriptions. We shall consider the specific case in which fluctuations arise in reaction-diffusion systems primarily from the finite number of molecules which are undergoing the diffusive migrations, which we shall refer to as intrinsic density fluctuations. To study such fluctuations in reaction-diffusion systems we shall formulate stochastic partial differential equations and corresponding stochastic numerical methods.

A number of issues arise when numerically approximating stochastic partial differential equations. In general, solutions do not have comparable regularity to the corresponding deterministic equations, instead they may only exist in a generalized sense as a probability measure on a space of non-differentiable functions or linear functionals (distributions) [62; 65; 66; 72]. This presents a challenge since traditional numerical approaches often rely on the smoothness of the solutions. Finite element and spectral methods have been developed for stochastic partial differential equations and exhibit slower rates of convergence relative to the deterministic case [79; 81]. For finite difference methods the lack of regularity presents additional challenges since methods are often based on Taylor expansions and approximating point-wise values of the solution on a mesh, which may no longer yield a meaningful representation of such stochastic fields.

*University of California, Department of Mathematics, Santa Barbara, CA 93106; e-mail: atzberg@math.ucsb.edu; phone: 805-893-3239; Work supported by NSF Grant DMS-0635535.
In studying stochastic reaction-diffusion systems a common approach to cope with these issues is to formulate numerical methods on uniform periodic meshes. This allows for numerical solutions to be represented in terms of Fourier modes and allows for the use of the discrete Fast Fourier Transform [82]. However, for many reaction-diffusion problems interesting behavior is exhibited only in a sub-region of the spatial domain. Also, for many problems the natural domains are non-periodic having non-rectangular geometries with Neumann or Dirichlet boundary conditions [47; 69; 70].

To numerically approximate stochastic reaction-diffusion systems we shall take a finite difference approach on such domains which numerically approximates the action of the linear functionals which yield the physical observables of the system. Our approach uses a spatial averaging of the stochastic differential equations over disjoint volumes defined by the mesh. Finite difference schemes are developed to yield an approximation to the spatially averaged stochastic field values. An important feature of the numerical methods is that the stochastic driving field is discretized in a manner which produces a controlled approximation to the spatially averaged fluctuations of the continuum system.

In order for solutions to be resolved at select levels of resolution on subregions of the domain, stochastic numerical methods are developed for adaptive multilevel meshes. A challenge when using such meshes is to approximate appropriately the stochastic driving terms at the coarse-refined interfaces where the level of resolution of the mesh undergoes a change. Using naive finite difference approaches to discretize the stochastic driving term results in large errors at such interfaces with the introduction of long-range correlations into the fluctuations of the system. To control the errors of the discretization at such interfaces we shall use an approach which is an analogue of the fluctuation-dissipation principle of statistical mechanics applied in the context of the discrete stochastic dynamical system associated with the numerical discretization. The discretization is chosen such that the equilibrium fluctuations of the discrete system approximates the spatially averaged fluctuations of the continuum system. For problems with non-rectangular geometries stochastic numerical methods are developed which are accurate at curved boundaries. Similar issues arise for the stochastic driving term in the vicinity of the curved boundaries and an approach based on the fluctuation-dissipation principle is used to derive an appropriate discretization.

To demonstrate how the stochastic numerical methods can be used in practice two applications are considered. The first application concerns how biological cells sense concentration gradients in the environment. Such sensing plays a fundamental role in cell biology signaling motile cells to move toward nutrients or away from toxins [1]. As a basic illustration of how the stochastic numerical methods may be used to model the concentration fields in such systems, we investigate the case of a single cell in an environment exhibiting only a shallow concentration gradient obscured by concentration fluctuations. We present results investigating the role of stochastic effects in one proposed mechanism for cell gradient sensing [47]. The stochastic numerical methods are applied for a non-rectangular domain corresponding to the exterior of the biological cell and are used to represent the fluctuations in the concentration field of the environment.

As a further demonstration of the stochastic numerical methods a variant of the Gray-Scott chemical reactions in a spatially extended system is considered [77; 78; 83; 84; 97]. The corresponding deterministic reaction-diffusion system is found to only exhibit over time a stationary stable localized pattern. When taking into account intrinsic concentration fluctuations of the chemical species, it is found that stochastic
effects give rise to a rich collection of patterns emerging over time in which spotted regions migrate, combine, and replicate. The stochastic numerical methods are used to adaptively track with a high level of refinement the dynamically evolving subregion on which the chemical reactions are most active and where the patterns emerge.

The proposed numerical methods allow for reaction-diffusion systems with intrinsic concentration fluctuations to be studied on general geometric domains having curved boundaries. The methods allow for domains subject to Neumann or Dirichlet boundary conditions. The stochastic numerical methods on multilevel meshes potentially allow for significant gains in computational efficiency through adaptive resolution of phenomena occurring in spatially extended stochastic systems.

2. Reaction-Diffusion Systems with Intrinsic Concentration Fluctuations. To account for intrinsic fluctuations in the concentration of chemical species in reaction-diffusion systems we shall consider stochastic partial differential equations of the form

\[ \frac{\partial c(x,t)}{\partial t} = \nabla_x \cdot D \nabla_x c(x,t) + F[c] + n(x,t) \]  

\[ \langle n(x,t) n^T(x',t) \rangle = \Lambda(x,x') \delta(t-t') \]  

\[ \Lambda_{ij}(x,x') = -2\bar{c}_i \delta_{ij} \nabla_x \cdot D^{(i)} \nabla_x \delta(x-x') \]  

where \( c \) denotes the composite vector of concentrations of the chemical species, \( n \) is a stochastic field having spatial covariance structure \( \Lambda \) accounting for fluctuations in the concentration field, and \( \bar{c} = \langle c \rangle \) is a composite vector having components \( \bar{c}_i \) corresponding to the mean concentration of the \( i^{th} \) chemical species. We shall assume throughout that the chemical species diffuse independently, which corresponds to a composite diffusion tensor \( D \) which is block diagonal with symmetric and positive semidefinite blocks of size \( d \times d \), where \( d \) is the number of spatial dimensions. The block matrix \( D^{(i)} \) corresponds to the diffusion of the \( i^{th} \) chemical species. The term \( F \) denotes a functional accounting for the chemical reactions and can be deterministic or stochastic. The system 2.1 – 2.3 accounts for stochastic effects in the physical regime where fluctuations are small relative to the mean concentration and dominated by the density fluctuations of the system that arise from diffusion of the molecular species [6; 7; 9–11].

We now briefly discuss the motivation for the spatial covariance structure of the stochastic field \( n \). This is illustrated most readily in the case of a concentration field of a single non-reacting species with isotropic diffusion \( D = DI \). At equilibrium the fluctuations of the concentration field are uncorrelated with variance equal to the local mean concentration \( \bar{c} \)

\[ \langle (c(x) - \bar{c})(c(x') - \bar{c}) \rangle = \bar{c} \delta(x-x') \]  

Let \( A = D \Delta_x \) and

\[ C = \bar{c} \delta(x-x') \]  

Since the governing equations are linear the covariance of the equilibrium fluctuations \( C \) and the covariance of the stochastic field \( \Lambda \) are related by the following fluctuation-dissipation relation

\[ \Lambda = -AC - C^*A^* \]
where $A^* , C^*$ denote the adjoint operators [4; 9]. In the case of the concentration field of a single non-reacting species, $AC = (AC)^*$ is self-adjoint giving

$$\Lambda(x, x') = -2AC = -2D\bar{c}\Delta\delta(x - x').$$

(2.7)

The expression 2.3 follows by a similar calculation in the more general case of $A = \nabla \cdot D\nabla$ and $C_{ij} = \langle (c_i(x) - \bar{c}_i)(c_j(x') - \bar{c}_j) \rangle = \bar{c}_i\delta_{ij}\delta(x - x')$, [4; 7; 9; 10].


In order to discretize equation 2.1 in space, we divide the spatial domain $\Omega$ into a partition of cells $\{\Omega_m\}$ where $\Omega = \bigcup_{m=1}^{M} \Omega_m$ and the field values are averaged over the volume of each cell

$$c_m(t) = \frac{1}{|\Omega_m|} \int_{\Omega_m} c(x, t) dx.$$ (3.1)

We shall approximate the dynamics of $c_m(t)$ by an Ito Stochastic Differential Equation [10; 15] of the form

$$dc_t = Lc_t dt + dg_t.$$ (3.2)

where $c_t$ denotes the composite vector of concentrations over all the sets $\Omega_m$ at time $t$ and $L$ is a discrete approximation of the term $\nabla \cdot D\nabla$.

Motivated by equation 2.2 of the continuum system, we shall assume that $g_t$ is a mean zero Gaussian stochastic process which is $\delta$-correlated in time and which can be represented in terms of increments of Brownian motion as

$$dg_t = QdB_t.$$ (3.3)

In the notation, $dB_t$ are increments of a vector valued Brownian motion with $n$ independent components and $Q$ is an $m \times n$ matrix. Under these assumptions, the stochastic field $g_t$ is determined by its covariance

$$\langle dg_t dg_t^T \rangle = \langle QdB_t dB_t^T Q^T \rangle = QI\delta(t - t') dt dt' Q^T = \Gamma(t - t') dt dt'$$ (3.4)

where we let $\Gamma = QQ^T$. We have used the formal identity of Ito Calculus that $\langle dB_t dB_t^T \rangle = \delta(t - t') dt dt'$, which in our notation corresponds to Ito's Isometry [15].

In discretizing the equations, we must approximate the stochastic components of the system corresponding to equations 2.2 and 2.3. For the equilibrium of the discretized system we shall impose that $c_m$ have fluctuations consistent with averaging the continuum system over the partition. From equation 3.1 this requires

$$\langle (c_m - \bar{c}_m) (c_n - \bar{c}_n)^T \rangle = \frac{C}{|\Omega_m|} \delta_{m,n}$$ (3.5)

where $\bar{C}_{ij} = \bar{c}_i\delta_{ij}$. For the stochastic field of the discrete system we shall derive a covariance structure which is consistent with the equilibrium fluctuations given in equation 3.5. Let $C_t = \langle (c_t - \bar{c})(c_t - \bar{c})^T \rangle$ denote the covariance of the fluctuations of the field at time $t$ and $\Gamma = QQ^T$ denote the covariance structure of the stochastic field $g_t$. From Ito’s Lemma [15] we have

$$dC_t = (LC_t + C_t L^T + \Gamma) dt.$$ (3.6)
At statistical steady-state this has \( dC_t = 0 \). This shows that in order for equation 3.2 to have the equilibrium fluctuations given by equation 3.5, the stochastic field must have covariance

\[
\Gamma = -(LC + CL^T).
\]

In the case that \( LC \) is symmetric this can be reduced to

\[
\Gamma = -2LC.
\]

This gives for any choice of partition \( \Omega_m \) and discretization \( L \) the corresponding covariance structure for the stochastic field \( g_t \) to be used in equation 3.2. In the case of diffusion of a single non-reacting species, this choice of \( \Gamma \) formally approaches \( \Lambda \), giving \( \Gamma \to \Lambda \) as the partition is refined \( |\Omega_m| \to 0 \) and when making the formal associations \( L \to \Delta_x \) and \( \delta_{m,n}/|\Omega_m| \to \delta(x-x') \).

In order for this discretization to be useful in practice it is important that efficient numerical methods can be developed for the stochastic differential equation 3.2. A central issue in developing practical numerical methods is to generate efficiently the stochastic field \( g_t \) with the covariance structure given in equation 3.7. This will depend on the spatial partition used to discretize the system and on how the term \( \nabla \cdot D \nabla \) is approximated.

For discretizations corresponding to uniform meshes with periodic boundary conditions the Fast Discrete Fourier Transform can be used [5]. In this case the term \( \nabla \cdot D \nabla \) can be approximated spectrally and \( \Gamma \) diagonalized in Fourier space allowing for the stochastic fields to be generated efficiently [13]. However, these methods are no longer applicable for more general problems on non-periodic domains with Dirichlet or Neumann boundary conditions or for meshes that arise in adaptive numerical methods, which are no longer uniformly discretized in space. In this paper we shall address the challenge of developing efficient numerical methods for non-periodic non-uniform meshes having Neumann or Dirichlet boundary conditions.

### 3.1. Discrete Approximation of the Operator \( \nabla \cdot D \nabla \)

Since the chemical species are assumed to diffuse independently, the diffusion tensor \( D \) has diagonal blocks of size \( d \times d \), where \( d \) is the spatial dimension of the system. This allows for a decomposition into uncoupled operators \( \nabla_x \cdot D^{(k)} \nabla_x \) for each chemical species, where \( D^{(k)} \) is the block of the \( k^{th} \) chemical species. The block \( D^{(k)} \) is symmetric and can be diagonalized by \( D^{(k)} = P^T D^{(k)} P \) for some unitary \( P \). A linear change of variable \( x = Rx \) has \( \nabla_{x} \to R \nabla_{\bar{x}} \) and \( \nabla_{x'} = \nabla_{\bar{x}} \cdot R^T \). This gives

\[
\nabla_{\bar{x}} \cdot D^{(k)} \nabla_{\bar{x}} = \nabla_{\bar{x}} \cdot R^T D^{(k)} R \nabla_{\bar{x}}.
\]

In the case that \( D^{(k)} \) is positive definite, we have by letting \( R = P (\tilde{D}^{(k)})^{-1/2} \) that

\[
\nabla_{\bar{x}} \cdot D^{(k)} \nabla_{\bar{x}} = \Delta_{\bar{x}}.
\]

In the case that \( D^{(k)} \) is only semidefinite we set the entries to be zero which are undefined from division by zero in \( (\tilde{D}^{(k)})^{-1/2} \). With this definition of \( (\tilde{D}^{(k)})^{-1/2} \) we again have equation 3.10.

This shows that for any positive semidefinite \( D^{(k)} \) the operator \( \nabla_{\bar{x}} \cdot D^{(k)} \nabla_{\bar{x}} \) can always be obtained from the Laplacian by an appropriate change of variable. Since these operators are decoupled, we introduce for the concentration field of each chemical species a separate coordinate system \( \chi^{(k)} = R^{(k)} x \) and let \( c_k = c_k(\chi^{(k)}, t) \). Throughout, we take as the approximation for the operator \( \nabla \cdot D \nabla \) the discretization which is obtained by making the appropriate change of variable and approximating the Laplacian.
3.2. Discrete Approximation of the Laplacian on Uniform and Multilevel Meshes in 2D. Throughout, we shall consider the particular case of a spatial partition consisting of square cells which differ with their neighbors in the lengths of their sides by at most a factor of two. For convenience in describing the discretizations we shall define values both at the cell centers and at the faces of each cell, which we collectively refer to as the mesh, see Figure 3.1. To obtain a discrete operator approximating the Laplacian we define for the mesh a discrete gradient operator and a discrete divergence operator [19; 20; 23].

The discrete gradient operator computes from cell centered values an approximation to the gradient at each face center in the component corresponding to the direction of the face relative to the cell center. Given that neighboring cells can vary in size there are two cases for such meshes. In the case that a cell is the same size as its neighbor the discrete gradient component is defined on the shared face by

\[(Gc)^{(i)}_{m+h_i} = \text{sign}(h_i) \frac{c_{m+q_i} - c_m}{\Delta x_m} \]  

(3.11)

In the notation, the cell centered values are indexed by \( m = (m_1, m_2) \) and the face centered values correspond to indices of the form \( m' = (m_1 + d_1, m_2 + d_2) \), where \( d_k \in \{0, \pm \frac{1}{2}\} \) with the constraint that only one index of \( k \) may have \( d_k \neq 0 \). For example, the mesh cell centered at index \( m \) has face centered value in the direction of the negative x-axis given by \( m' = (m_1 - \frac{1}{2}, m_2) \). The superscript notation \( (i) \) refers to the vector component of the gradient, the face is specified by \( h_i = \pm \frac{1}{2}e_i \), with \( e_i \) the standard basis vector which has component \( i \) equal to one and all other components zero, and \( q_i = 2h_i \). The notation \( \Delta x_m \) refers to the side length of the cell with index \( m \).

In the case that a neighbor is of a different size, as shown in Figure 3.1, the gradient at the shared faces is defined by

\[(Gc)^{(1)}_{B} = \frac{c_A^{(1)} - \frac{1}{2} \left( c_B^{(1)} + c_C^{(1)} \right)}{\frac{1}{4} \Delta x_A} \]  

(3.12)
(3.13) 
\[(Ge)^{(1)}_C = \frac{c_A^{(1)}}{4 \Delta x_A} - \frac{1}{2} \left( \left( c_C^{(1)} + c_B^{(1)} \right) \right) \frac{1}{\Delta x_A} \]

(3.14) 
\[(Ge)^{(1)}_A = \frac{1}{2} \left( (Ge)_B^{(1)} + (Ge)_C^{(1)} \right) \]

Here we have given the expressions only for the special case depicted in Figure 3.1. The other cases are defined similarly, see [19; 20; 23].

A discrete divergence operator is now defined which computes from face centered values an approximation of the divergence at the cell center. For all cells the discrete divergence operator is defined by

(3.15) 
\[(Db)^{(i)}_m = \sum_{i=1}^{2} \frac{b^{(i)}_{m+h_i} - b^{(i)}_{m-h_i}}{\Delta x_m} \]

where \( b \) is the composite vector of face centered vector values of the mesh. At an interface between cells of different sizes we shall always assume that the face centered value of the coarse cell is the average of the face centered values of the two neighboring cells.

A discrete Laplacian for any such spatial partition can then be obtained from

(3.16) 
\[ L = DG. \]

This operator maps cell centered values to cell centered values. This discrete Laplacian can be shown to be locally second order accurate for cells having neighbors of the same size and first order accurate for cells having neighbors of a different size [19; 20; 23]. We shall refer to this as the "MAC Discretization" of the Laplacian.

3.3. Discrete Approximation of the Laplacian at Curved Boundaries in 2D. We now discuss the case where the domain has a non-rectangular geometry with curved boundaries. To approximate the Laplacian at such boundaries we shall introduce cells into the mesh which are cut by the boundary. The Laplacian is discretized in these regions using a finite volume method. Our approach follows closely the methods referred to as Embedded Boundary Methods, Cartesian Grid Methods, Cut-Cell Methods, see [35–41].

Dividing the spatial domain into a partitioning of regions \( \{ \Omega_m \} \) we have from the Divergence Theorem [85] on each partition element

\[ \int_{\Omega_m} \Delta c d\mathbf{x} = \int_{\partial \Omega_m} \nabla c \cdot \mathbf{n} dA. \]

By approximating the expressions for the integrals on the left and right sides we obtain a finite volume discretization of the form

\[ [Lc]^m = \frac{1}{|\Omega_m|} \sum_{j \in N_m} J^{(n)}_{m,j} |\partial \Omega_m| \]

where \( |\Omega_m| \) is the area of the partition element, \( N_m \) is an indexing set corresponding to the common edges shared with this partition element, \( |\partial \Omega_m| \) is the length of the \( j \)th edge of the partition element, and \( J^{(n)}_{m,j} \) approximates the normal component of the concentration flux corresponding to \( \nabla c \cdot \mathbf{n} \). Throughout, we shall use as our discrete degrees of freedom in the scheme the concentration field defined on the cell
centers of the regular mesh and flux components defined on the center of each edge, see Figure 3.2. For the fluxes we shall use \( J_{m,j}^{(n)} = \nabla \tilde{u}(x_{m,j}) \cdot n_{m,j} \) where for each edge the \( \tilde{u}(x) \) denotes the linear product interpolation of the concentration field at \( x \) using the four nearest neighbors and \( x_{m,j} \) denotes the location of the center of the \( j^{th} \) edge for mesh cell \( m \).

To obtain such a partition, space is initially discretized by regular mesh cells which are then intersected with the domain to determine sub-regions in each cell which are either inside or outside the domain. It is assumed that the boundary geometry is smooth, at least twice differentiable, so that at sufficient resolution the boundary can be approximated well by piecewise-linear segments intersecting exactly two edges of any cut mesh cell. Under these assumptions, only relatively few cases arise in the geometry of the cut cells and the areas of the sub-regions and lengths of the edges can be readily computed. It can be shown that this scheme yields a first order accurate approximation to the Laplacian at such curved boundaries [35; 36; 40; 41]. Away from the boundary the scheme corresponds to the standard second order accurate central difference approximation of the Laplacian.

In practice when using such schemes for time dependent problems an important issue arises from the small elements which introduce stringent stability constraints on the permissible time steps, as expressed in the Courant-Friedrichs-Lewy Condition of the scheme [37; 38; 86]. This can be most directly seen by noting that the stable time step size is bounded by the minimum area of the partition elements to algebraic order. This presents a difficulty in practice since small elements can in principle arise in any mesh since the boundary is arbitrary and the domain could intersect only small regions of a cut cell, for example, such as only very near to one of the cell corners. To reduce this source of instability in the scheme, we introduce a merging procedure into the discretization routines which fuse cut cell regions with a neighboring cell when such regions are smaller than some threshold percentage of the regular mesh cell size. For instance in Figure 3.2, if the split cell on the lower right were deemed too small it would be fused with the largest neighboring mesh cell, which in this case.
is the cell above it. The degree of freedom associated with the center of the regular cell containing the small split cell is then eliminated and all dependencies on this value in the scheme are replaced by a quadratic interpolation from the neighboring concentration values in the direction of the merged neighboring cell. All fluxes into to the small cut cell region are directed into the merged cell. This merging procedure can be shown to increase the stability of the scheme while retaining at least first order accuracy [35–41].

In order to obtain sufficient resolution at curved boundaries another issue encountered in practice concerns the relatively fine mesh which may be required while such a resolution may not be required globally. To achieve greater computational efficiency we shall use the approach in conjunction with multilevel meshing to adapt the level of spatial resolution in regions near the curved boundaries. We shall discuss how these methods can be used in the context of a specific application in Section 6.2.

4. Methods to Generate Increments of the Stochastic Field \( g(t) \). We shall now discuss approaches to discretize the stochastic driving field \( g(t) \) consistent with equations 3.2 – 3.8. Discretizations will be derived for a variety of different meshes. For uniform rectangular meshes discretizations for \( g \) will be derived in the case that Neumann or Dirichlet boundary conditions are imposed. For multi-level meshes discretizations for \( g \) will be derived for the coarse-refined interfaces of the mesh. In the case of non-rectangular meshes discretizations will be derived for \( g \) in the regions near the curved boundaries. In order for these discretizations to be useful in practice it is important that stochastic realizations of \( g \) can be computed efficiently. In each case, we shall discuss specific approaches by which to generate efficiently the increments of the stochastic field \( g(t) \).

4.1. Uniform Meshes with Dirichlet or Neumann Boundary Conditions on Rectangular Domains. In the case of a uniform mesh the Laplacian given by equation 3.16 corresponds to a central finite difference approximation of the Laplacian and yields the standard five point stencil. In this case \( C = \sigma^2 I \) with \( \sigma^2 = \bar{c}/|A| \) where \( |A| = \Delta x^2 \) is the volume of a cell of the uniform mesh. The covariance structure for the stochastic field becomes

\[
(4.1) \Gamma = -2LC
\]

since the product \( LC \) is symmetric. For uniform meshes the gradient is the negative transpose of the divergence operator \( G = -D^T \). This allows for the covariance to be expressed as

\[
(4.2) \Gamma = 2\sigma^2 DD^T = (\sqrt{2}\sigma D)(\sqrt{2}\sigma D)^T.
\]

This shows that increments of the stochastic field \( g \) can be generated using equation 3.3 with \( Q = \sqrt{2}\sigma D \) and increments of independent Brownian motions centered at the cell faces of the mesh.

Physically this approach corresponds to introducing "random fluxes" for the stochastic transport of conserved quantities between mesh cells, similar approaches have been discussed in the context of fluctuating hydrodynamics [7; 9]. The key point here is that the random fluxes arise naturally for the discretization of the physical system by the requirement that the equilibrium concentration fluctuations satisfy equation 3.7. We shall discuss in Section ?? the consequences of taking a less rigorous but more intuitive physical approach to obtain a discretization of the stochastic field \( g \). Such approaches can lead to numerical methods with significant errors which
are manifested in correlations being introduced into the equilibrium concentration fluctuations of the system.

We now discuss how various boundary conditions can be handled. The case of Dirichlet boundary conditions can be handled by introducing a set of "ghost cells" which comprise the boundary of the mesh. Since equation 3.2 is linear we can consider the case of homogeneous zero Dirichlet boundary conditions without loss of generality. A modified discrete divergence operator \( \tilde{D} \) consistent with the homogeneous Dirichlet boundary conditions can be obtained by setting in the matrix representation \( D \) all entries to zero in rows corresponding to the "ghost cells". A modified gradient operator \( \tilde{G} \) consistent with the boundary conditions can be obtained by setting in \( G \) all entries to zero in columns corresponding to the "ghost cells". The extended covariance matrix \( \tilde{C} \) then has zero entries for the "ghost" values since these remain fixed in time and do not fluctuate. A Laplacian consistent with the boundary conditions is then given by \( \tilde{L} = \tilde{D} \tilde{G} \). Since \( \tilde{G} = -\tilde{D}^T \) the covariance can be factored similarly to equation 4.2. This allows for increments of the stochastic field \( g \) to be generated with the factor \( \tilde{Q} = \sqrt{2\sigma \tilde{D}} \) using independent increments of Brownian motion for each face centered value in equation 3.3.

The Neumann boundary conditions are imposed by setting the gradient components at the face centered values of the mesh for cells on the boundary. Since equation 3.2 is linear we can consider the case of homogeneous zero Neumann boundary conditions without loss of generality. In this case a modified discrete divergence operator \( \hat{D} \) can be obtained by setting in the matrix representation \( D \) all entries to zero in columns corresponding to the boundary faces. A modified gradient operator \( \hat{G} \) is obtained from the matrix representation \( G \) by setting all entries to zero in rows corresponding to the boundary faces. The covariance matrix \( C \) is unaffected by the boundary conditions in this case. A modified Laplacian consistent with the boundary conditions is obtained by \( \hat{L} = \hat{D} \hat{G} \). Since the modified operators have the relationship \( \hat{G} = -\hat{D}^T \) the covariance can be factored similarly to equation 4.2. This allows for increments of the stochastic field \( g \) to be generated with \( \hat{Q} = \sqrt{2\sigma \hat{D}} \) using independent increments of Brownian motion for each face centered value in equation 3.3.

A mixture of Dirichlet and Neumann boundary conditions can also be handled by this approach. In this case the required factor \( Q \) is obtained by applying the above modifications individually to the matrix representations of the divergence operator \( D \) and gradient operator \( G \) on the extended mesh for each row or column corresponding to a cell centered or face centered value fixed by the boundary condition. Since the relationship \( \hat{G} = -\hat{D}^T \) is preserved by these modifications the factor can be obtained in a manner similar to equation 4.2.

An important feature of the matrix factors \( Q \) obtained by the methods above is that they are always sparse, with the number of non-zero entries proportional to the number of mesh cells. As a consequence the cost of generating increments of the stochastic field \( g \) has a computational complexity which scales only linearly \( O(N) \) in the number of mesh points \( N \). This is in contrast to other methods, such as the Cholesky algorithm for correlated variates [87]. The Cholesky algorithm requires two distinct computations. The first a computation scaling as the cube of the number of mesh points \( O(N^3) \) in order to determine the factor \( Q \). The second a computation to generate the increments of the stochastic field \( g \) scales quadratically in the number of mesh points \( O(N^2) \) since the Cholesky factor \( Q \) is typically not sparse [61; 82; 87].

4.2. Multilevel Meshes in 2D. We now discuss the case of multilevel meshes which contain mesh cells of varying levels of refinement. In this case the discrete
gradient operator is no longer proportional to the transpose of the divergence operator, \( G \neq -D^T \) as a consequence of the coarse-refined interfaces of the mesh. This prevents directly obtaining a factorization as in equation 4.2.

We shall instead consider a more general approach to factor \( \Gamma \). Let the stochastic field be expressed as a sum of two random variables \( g = g_1 + g_2 \), then the covariance can be expressed as

\[
\Gamma = \Gamma_1 + \Gamma_2 + \Gamma_{(1,2)} + \Gamma_{(2,1)}
\]

(4.3)

where \( \Gamma_k = \langle g_k g_k^T \rangle \), \( \Gamma_{(k,j)} = \langle g_k g_j^T \rangle \), \( k, j \in \{1, 2\} \), \( k \neq j \). Let \( g_1 = Q_1 n_1 \) and \( g_2 = Q_2 n_2 \) with \( n_1 \) and \( n_2 \) each being vectors having in each component an independent standard Gaussian with mean zero and variance one. We then have \( \Gamma_1 = Q_1 Q_1^T \), \( \Gamma_2 = Q_2 Q_2^T \), and \( \Gamma_{(1,2)} = \Gamma_{(2,1)} = 0 \) which gives

\[
\Gamma = \Gamma_1 + \Gamma_2.
\]

(4.4)

This shows that a decomposition of \( \Gamma \) into the sum of any two positive semidefinite matrices corresponds to expressing \( g \) as the sum of two independent Gaussian random variables with the corresponding covariances \( \Gamma_1 \) and \( \Gamma_2 \).

To use this decomposition to obtain a method to generate \( g \) requires finding factors \( Q_1 \) and \( Q_2 \) which satisfy equation 4.4 where \( \Gamma \) is determined from equation 3.7. For this purpose, we shall associated a composite vector \( n_1 \) of independent standard Gaussian random variables with the face centered values of the mesh and \( n_2 \) with cell centered values of the mesh.

To obtain \( \Gamma_1 \) we consider the modified divergence operator \( D' \) with all entries in columns corresponding to faces of coarse-refined interfaces set to zero. We similarly modify the gradient operator \( G' \) to have all entries in rows corresponding to faces of the coarse-refined interfaces set to zero. This corresponds to setting Neumann boundary conditions at the boundaries of cells at each coarse-refined interface, which form the border regions between different levels of refinement of the mesh. Since the modified divergence operator and gradient operator satisfy \( G' = -D'^T \) we can factor \( \Gamma_1 \) associated with the modified operators as in equation 4.2 to obtain a sparse factor \( Q_1 \). This can be used to generate \( g_1 = Q_1 n_1 \).

Now by equation 4.4 we must take \( \Gamma_2 = \Gamma - \Gamma_1 \). However, for the decomposition to be valid we must have that \( \Gamma_2 \) is positive semidefinite. Furthermore, for the decomposition to give an efficient method in practice for generating variates, the factor \( Q_2 \) should be as sparse as possible. An important feature of \( \Gamma_2 \) is that it consists of uncoupled blocks corresponding to small clusters of cells along the coarse-refined interface. This in part, motivated our choice of \( \Gamma_1 \). This reduces the problem to considering each individual block matrix corresponding to a cluster. Another feature is that the block matrices are all of a similar form. For brevity in the exposition we shall only discuss in detail the specific case of the cluster depicted in Figure 3.1. The other cases for the clusters follow similarly.

In the case depicted in Figure 3.1 the cluster associated with the coarse cell labeled by \( \mathcal{A} \) has the covariance block matrix given by

\[
M_A = \frac{8C_{AA}}{3\Delta x^4} \begin{bmatrix}
1 & -2 & -2 \\
-2 & 4 & 4 \\
-2 & 4 & 4
\end{bmatrix}
\]

(4.5)

where the row and column ordering is \( \mathcal{A}, \mathcal{B}, \mathcal{C} \) and \( C_{AA} \) denotes the corresponding matrix entry of \( \mathcal{A} \) in the covariance in equation 3.5. The eigenvectors and eigenvalues...
of the matrix are

\[(4.6) \quad v_1 = \frac{1}{\sqrt{5}} \begin{bmatrix} 2 \\ 1 \\ 0 \end{bmatrix}, \quad v_2 = \frac{1}{3\sqrt{5}} \begin{bmatrix} 2 \\ -4 \\ 5 \end{bmatrix}, \quad v_3 = \frac{1}{3} \begin{bmatrix} 1 \\ -2 \\ -2 \end{bmatrix}\]

with eigenvalues \(\lambda_1 = 0, \lambda_2 = 0, \lambda_3 = 9\) respectively. An especially important feature of these block matrices \(M\) is that they are positive semidefinite which shows that the decomposition chosen above for the covariance matrix is indeed valid and yields a method to generate the field by \(g = g_1 + g_2\). For this purpose random variates are used at cell centered values of each cluster to generate a variate with the required covariance structure \(M\)

\[(4.7) \quad r_A = \eta_1 \sqrt{\lambda_1} v_1 + \eta_2 \sqrt{\lambda_2} v_2 + \eta_3 \sqrt{\lambda_3} v_3\]

where \(\eta_k\) are independent standard Gaussian random variables of mean zero and variance one. Of course this can be simplified since \(\lambda_1 = \lambda_2 = 0\). The other cluster cases can be handled in a similar manner. To obtain \(g_2\) the appropriate components are set by independently generating \(r_A\) for each of the clusters. If we associate \(\eta_1, \eta_2, \eta_3\) with the \(n_2\) cell centered values of the mesh corresponding to \(A, B, C\) then equation 4.7 defines a sparse factor \(Q_2\) with the number of non-zero entries proportional to the number of mesh cells bordering coarse-refined interfaces. The above procedure is then equivalent to generating \(g_2 = Q_2 n_2\).

We now have a method to generate increments of the stochastic random field \(g\) on multilevel meshes with covariance satisfying equations 3.7. An important feature of this method is that the factors \(Q_1\) and \(Q_2\) can be constructed with linear computational complexity in the number of mesh cells \(O(N)\). Also, since the factors are each sparse the increments of the stochastic random field \(g\) can be generated with only a linear computational complexity in the number of mesh cells \(O(N)\). Dirichlet and Neumann boundary conditions on multilevel meshes on rectangular domains can also be handled by this method by modifying the discrete gradient and divergence operators in the same manner as described for the uniform mesh case in Section 4.1.

4.3. Meshes with Curved Boundaries in 2D. We now discuss an approach to generate the required increments of \(g\) satisfying equation 3.8 for meshes on domains with curved boundaries. Let \(G\) denote the operator which computes at the center of each edge the approximate normal component of the gradient of the concentration field used in \(J^{(n)}\). Let \(D\) denote the operator which yields the mesh centered values by acting on the flux values at the edge centers. The Laplacian can then be expressed as \(L = DG\). It can be shown that \(LC\) is symmetric so that the required covariance for \(g\) is given by \(\Gamma = -2LC\). Since in general \(D \neq -G^T\) directly factoring the covariance matrix is challenging. Instead, we shall again make use of the decomposition discussed in Section 4.2, in which \(\Gamma = \Gamma_1 + \Gamma_2\), where \(g = g_1 + g_2\) for independent \(g_1\) and \(g_2\) with \(\Gamma_1\) and \(\Gamma_2\) the respective covariances.

We shall find it useful to classify mesh cells into two distinct sets, a boundary set \(B\) and an interior set \(I\). The boundary set \(B\) consists of all mesh cells which are cut by the domain boundary along with all immediate neighboring cells. The interior set \(I\) consists of all of the remaining cells of the mesh. For the mesh cells in \(I\), let \(G'\) be the operator obtained from the matrix representation of the gradient operator \(G\) by setting all rows to zero which correspond to edges which are shared with mesh cells in \(B\). Also, set \(D'\) to be the operator obtained from the matrix representation of the
divergence operator $D$ by setting all the columns to zero which correspond to these same edges. To define $G'$ and $D'$ on the entire mesh all rows and columns are taken to be zero which correspond to cells not in $I$.

Now to obtain operators corresponding to the set $B$ of mesh cells, we define $G'' = G - G'$ and $D'' = D - D'$. By the definition of the operators, $D'G'' = D''G' = 0$, so that $L = L' + L''$ where $L' = D'G'$ and $L'' = D''G''$. We can further set $C = C' + C''$, where $C'$, $C''$ are obtained by setting all entries outside the corresponding sets of mesh cells to zero. With these definitions we obtain the decomposition $\Gamma = \Gamma_1 + \Gamma_2$ with $\Gamma_1 = -2L'C'$ and $\Gamma_2 = -2L''C''$. With this decomposition, the increments of $g_1$ can be readily generated since $\Gamma_1$ corresponds to the case of a mesh with Neumann conditions on a domain with a stair-case boundary, which falls into the previously discussed cases in Sections 4.1 and 4.2.

We now discuss a method to generate increments of the field $g_2$. Obtaining a factorization of $\Gamma_2$ is made challenging by the following issues: $D'' \neq -G''T$, the matrix entries are irregular with dependencies on the local geometry of the boundary, and the covariance matrix is only positive semi-definite. The Cholesky factorization algorithm is often used to generate correlated variates, however, for matrices which are only semi-definite it can not be used directly [82; 87]. To cope with these difficulties we shall generate the variates by using a decomposition of the matrix $\Gamma_2$ into its eigenvalues and eigenvectors. The increments of $g_2$ can then be generated using

$$g_2 = \sum_{k=1}^{M} \eta_k \sqrt{\lambda_k} v_k$$

where the $k^{th}$ eigenvalue and orthonormal eigenvector are denoted respectively by $\lambda_k$ and $v_k$, and the $\eta_k$ denote independent Gaussian random variables with mean zero and variance one.

It is important to mention that while computing the eigenvalue decomposition has computational complexity $O(M^3)$ in the worse case [61], the number of mesh cells $M$ corresponds only to the collection $B$ of cells needed to capture the one dimensional geometry of the boundary and can be performed independently for each separate unconnected curved boundary region. For problems where the boundaries do not change in time this decomposition of $\Gamma_2$ need only be computed once. To generate realizations of the stochastic field $g_2$ each time step incurs a computational cost of $O(M^2)$ since the eigenvectors will have in general have a full set of non-zero components.

The presented decomposition of $\Gamma$ allows for the stochastic driving field $g$ to be generated for domains having curved boundaries. While additional costs are introduced by the curved boundaries the numerical methods still utilize the previously developed explicit factorization expressions for the interior part of the mesh away from the boundaries. We discuss how this approach can be used in practice in the context of a specific application in Section 6.2.


As a validation of the stochastic numerical methods we show formally that the methods converge in the case when the system is near steady-state and the fluctuations are small relative to the mean concentration. As discussed in Section 1, an important issue is that the solutions of equation 2.1 are not well-defined in terms of classical functions with point-wise values, but are instead represented by distributions [62; 64; 66]. To simplify the discussion and to avoid delving into too many technical issues, we shall formally demonstrate a form of weak convergence of the
stochastic numerical methods semi-discretized in space.

The form of weak convergence we shall consider corresponds to convergence of the moments of linear functionals of the form

$$a(x, t) = A[c] = \int_\Omega \int_0^t \alpha(x, y, s)c(y, s)dsdy$$

when numerically approximated by

$$\tilde{a}(x, t) = \tilde{A}[\tilde{c}] = \sum_m \int_0^t \alpha(x, \tilde{y}_m, s)\tilde{c}_m(s)ds\Delta x^d$$

where $\alpha(x, y, s)$ is a bounded compactly supported smoothly varying function in space and time. We shall consider the following form of weak convergence

$$\|M_{A_1, A_2, \ldots, A_n}^{(n)} - M_{A_1, A_2, \ldots, A_n}^{(n)}\|_\infty \rightarrow 0$$

as $\Delta x \rightarrow 0$. The $n^{th}$ moment is defined by

$$M_{A_1, A_2, \ldots, A_n}^{(n)}(x_1, t_1, x_2, t_2, \ldots, x_n, t_n) = (a_1(x_1, t_1)a_2(x_2, t_2) \cdots a_n(x_n, t_n)).$$

This convergence is required for each moment $n \geq 1$ and choice of functionals $A_1, A_2, \ldots, A_n$ of the form of equation 5.1 approximated by equation 5.2. In the notation $\|f(x_1, t_1, x_2, t_2, \ldots, x_n, t_n)\|_\infty = \sup_{x_1, t_1, x_2, t_2, \ldots, x_n, t_n} |f|$. This is one of many different types of convergence which can be defined for stochastic processes, see [13].

As an intuitive motivation for this form of weak convergence, the functionals $A$ can be thought of as being analogues of physical observations as would be obtained from experimental measurements of an underlying fluctuating concentration field. In experiments any measured quantity is almost always averaged in space and time. Such averaging is represented in the functional by integrating the concentration field against the function $\alpha$. Weak convergence then corresponds to the situation where the statistics of any measurement of the underlying concentration field can be reproduced in simulations up to a specified precision by using a sufficiently refined discretization mesh.

A number of simplifications can be made by utilizing linearity of the functional $A$ and properties of $c$. From linearity and the smoothness of $\alpha$ we have that $a(x, t)$ is a Gaussian random field with well-defined point-wise values. This has the important consequence that statistics of the random field are completely determined by the first two moments. This requires only $n \leq 2$ need be considered in equation 5.3.

For the system close to statistical steady-state and for sufficiently small fluctuations relative to the mean concentration it is sufficient to consider the linearization of equations 2.1. This corresponds in equation 2.1 to a functional of the form $F[c] = Fc + f_0$ where $F$ denotes a linear functional and $f_0$ a constant field independent of $c$. In this regime, averaging equation 2.1 and equation 3.2 give for the first moment a deterministic reaction-diffusion equation. For the first moments the convergence follows straightforwardly from the deterministic convergence theory developed for MAC discretizations (cite). We shall focus on demonstrating convergence of the second moments, which arise from the fluctuations.

When working with the second moments it is helpful to consider the covariance function $R(x_1, t_1, x_2, t_2) = M_{A_1, A_2}^{(2)} - M_{A_1}^{(1)}M_{A_2}^{(1)}$, which can be expressed more explicitly as

$$R(x_1, t_1, x_2, t_2) = \int_\Omega \int_0^t \int_0^t \alpha(x, y_1, s_1)c(y_1, s_1)s_1ds_1dy_1 \alpha(x, y_2, s_2)c(y_2, s_2)s_2ds_2dy_2,$$
\[ R(x_1, t_1, x_2, t_2) = \int dy_1 dy_2 \int ds_1 ds_2 \alpha_1(x_1, y_1, s_1)q(y_1, s_1, y_2, s_2)\alpha_2(x_2, y_2, s_2) \]

\[ q(y_1, s_1, y_2, s_2) = \langle (c(y_1, s_1) - \bar{c})(c(y_2, s_2) - \bar{c}) \rangle \]

where \( \alpha_1 \) and \( \alpha_2 \) correspond to the linear functionals \( A_1 \) and \( A_2 \) represented in the form of equation 5.1. The integrals in \( y_1, y_2 \) and \( s_1, s_2 \) are taken over the bounded domain \( \{ (y_1, y_2, s_1, s_2) \in \Omega \times \Omega \times [0, t] \times [0, t] \} \). Similarly for the semi-discretized system we have the covariance function \( R(x_1, t_1, x_2, t_2) = M^{(2)}_{\tilde{A}_1, \tilde{A}_2} - M^{(1)}_{\tilde{A}_1, \tilde{A}_2} \), which can be expressed explicitly as

\[ R(x_1, t_1, x_2, t_2) = \sum_{m_1} \sum_{m_2} \int ds_1 ds_2 \alpha_1(x_1, y_{m_1}, s_1) \cdot \]

\[ \tilde{q}(y_{m_1}, s_1, y_{m_2}, s_2)\alpha_2(x_2, y_{m_2}, s_2)\Delta x^d_{m_1} \Delta x^d_{m_2} \]

\[ \tilde{q}(y_{m_1}, s_1, y_{m_2}, s_2) = \langle (c_{m_1}(s_1) - \bar{c})(c_{m_2}(s_2) - \bar{c}) \rangle . \]

Since \( c \) is a solution of equation 2.1 we have formally that \( c(y, s) = e^{(s-r)\mathcal{L}}c(y, r) \) when \( s > r \), where \( \mathcal{L} \) denotes the Laplacian a negative semidefinite linear differential operator and \( e^{t\mathcal{L}} \) denotes the solution operator over the time interval \([0, t]\) from the semi-group associated with equation 2.1, see [64; 72]. By the choice of stochastic driving field \( n \) in equation 2.2 we have \( \langle (c(y_1, s_1) - \bar{c})(c(y_2, s_2) - \bar{c}) \rangle = e^{(s_1-s_2)\mathcal{L}}C \), where \( s_1 \geq s_2 \) and

\[ C(y_1, y_2) = \bar{c}\delta(y_1 - y_2). \]

Substituting this into equation 5.5 yields

\[ R(x_1, t_1, x_2, t_2) = \int dy_1 dy_2 \int ds_1 ds_2 \alpha_1(x_1, y_1, s_1)e^{(s_1-s_2)\mathcal{L}}C\alpha_2(x_2, y_1, s_2) \]

\[ + \int dy_1 dy_2 \int ds_1 ds_2 \alpha_2(x_2, y_2, s_2)e^{(s_2-s_1)\mathcal{L}}C\alpha_1(x_1, y_1, s_1) . \]

By a similar argument for the semi-discretized equation 3.2 we have \( c(s) = e^{(s-r)\mathcal{L}}c(r) \) when \( s > r \), where \( L \) denotes the MAC-Laplacian represented by a negative semidefinite matrix and \( e^{tL} \) denotes the matrix exponential, see [80]. By the choice of stochastic driving field \( g_t \) in equation 3.7 we have \( \langle (c(s_1) - \bar{c})(c(s_2) - \bar{c}) \rangle = e^{(s_1-s_2)L}C \), where \( s_1 \geq s_2 \) and

\[ \frac{C^t_{m_1, m_2}}{\Delta x^d_{m_1}} = \delta_{m_1, m_2}/\Delta x^d_{m_1} \]

where \( \delta_{m_1, m_2} \) is the Kronecker delta function. In the notation \( [\cdot]_{m_1, m_2} \) denotes the \((m_1, m_2)\) matrix entry. Substituting this into equation 5.6 yields

\[ R(x_1, t_1, x_2, t_2) = \sum_{m_1, m_2} \int ds_1 ds_2 \alpha_1(x_1, y_{m_1}, s_1) \cdot \]

\[ \cdot [e^{(s_2-s_1)L}C]_{m_1, m_2} \alpha_2(x_2, y_{m_2}, s_2)\Delta x^d_{m_1} \Delta x^d_{m_2} \]

\[ + \sum_{m_1, m_2} \int ds_1 ds_2 \alpha_2(x_2, y_{m_1}, s_2) \cdot \]

\[ \cdot [e^{(s_2-s_1)L}C]_{m_1, m_2} \alpha_1(x_1, y_{m_2}, s_1)\Delta x^d_{m_1} \Delta x^d_{m_2} . \]
To show convergence it is useful to let
\begin{equation}
\beta_1(y, t) = \int e^{(t-s_2)L} C(y, y_2) \alpha_2(x_2, y_2) dy_2
\end{equation}
\begin{equation}
\tilde{\beta}_1(y_m, t) = \sum_{m_2} [e^{(t-s_2)L} C]_{m, m_2} \alpha_2(x_2, y_{m_2}, s_2) \Delta x^{d}_{m_2}
\end{equation}
with similar definitions for \( \beta_2, \tilde{\beta}_2 \). From the definitions of the operators \( e^{(t-s_2)L} \) and \( e^{(t-s_1)L} \) we have that \( \beta_1 \) and \( \tilde{\beta}_1 \) solve the following differential equations with specified initial values
\begin{equation}
\begin{cases}
\frac{\partial \beta_1}{\partial t} = L \beta_1, & \text{for } t > s_2 \\
\beta_1(y, s_2) = \int C(y, y_2) \alpha_2(x_2, y_2, s_2) dy_2, & \text{for } t = s_2
\end{cases}
\end{equation}
and
\begin{equation}
\begin{cases}
\frac{d\tilde{\beta}_1}{dt} = L \tilde{\beta}_1, & \text{for } t > s_2 \\
\tilde{\beta}_1(y_m, s_2) = \sum_{m_2} [C]_{m, m_2} \alpha_2(x_2, y_{m_2}, s_2) \Delta x^{d}_{m_2}, & \text{for } t = s_2
\end{cases}
\end{equation}
The \( \beta_2 \) and \( \tilde{\beta}_2 \) solve similar differential equations. Using the specific form of \( C \) and \( C \) given in equations 5.7 and equation 5.8 we have that \( \beta_1(y, s_2) = \alpha_2(x_2, y, s_2) \) and \( \tilde{\beta}_1(y_m, s_2) = \alpha_2(x_2, y_{m_2}, s_2) \). From the deterministic convergence theory developed for the MAC-Laplacian for such differential equations (cite), we have
\begin{equation}
\| \tilde{\beta} - \beta \|_{\infty} \to 0
\end{equation}
as \( \Delta x \to 0 \). We remark that while our analysis is only formal, such uniform convergence results are subject to technical conditions such as smooth initial conditions, a bounded domain \( \Omega \), time-independent boundary conditions, and a bounded steady-state solution, which we shall assume throughout [63].

The difference of the covariance functions of the discretized system and continuum system can be bounded using the triangle inequality by
\begin{equation}
\| \tilde{\mathbf{R}} - \mathbf{R} \|_{\infty} \leq I_1 + I_2 + I_3 + I_4.
\end{equation}
where
\begin{equation}
I_1 = \left\| \sum_m \int_{s_1 > s_2} ds_1 ds_2 \alpha_1(x_1, y_m, s_1) \left( \tilde{\beta}_1(x_1, y_m, s_1) - \beta_1(x_1, y_m, s_1) \right) \Delta x^{d} \right\|_{\infty}
\end{equation}
\begin{equation}
I_2 = \left\| \sum_m \int_{s_2 > s_1} ds_1 ds_2 \alpha_2(x_2, y_m, s_2) \left( \tilde{\beta}_2(x_2, y_m, s_2) - \beta_2(x_2, y_m, s_2) \right) \Delta x^{d} \right\|_{\infty}
\end{equation}
\begin{equation}
I_3 = \sum_m \int_{s_2 > s_1} ds_1 ds_2 \alpha_2(x_2, y_m, s_2) \tilde{\beta}_1(x_1, y_m, s_1) \Delta x^{d}
- \int dy \int_{s_2 > s_1} ds_1 ds_2 \alpha_2(x_2, y, s_2) \tilde{\beta}_1(x_1, y, s_1) \right\|_{\infty}
\end{equation}
\begin{equation}
I_4 = \sum_m \int_{s_1 > s_2} ds_1 ds_2 \alpha_1(x_1, y_m, s_1) \tilde{\beta}_2(x_2, y_m, s_2) \Delta x^{d}
- \int dy \int_{s_1 > s_2} ds_1 ds_2 \alpha_1(x_1, y, s_1) \tilde{\beta}_2(x_2, y, s_2) \right\|_{\infty}
\end{equation}
Using properties of the infinity norm \( \| \cdot \|_\infty \) the integral and sum can be bounded by

\[
I_1 \leq \left\| \sum_m \int_{s_2 > s_1} ds_1 ds_2 |\alpha_1(x_1, y_m, s_1)| \Delta x^d \right\|_\infty \| \tilde{\beta}_1 - \beta_1 \|_\infty.
\]

(5.16)

An important property of the estimate is that the first term remains bounded as \( \Delta x \to 0 \). This follows since \( \alpha_1 \) is compactly supported and the domains in space and time are bounded. Using this fact and equation 5.13 we have \( I_1 \to 0 \) as \( \Delta x \to 0 \). By a similar argument \( I_2 \to 0 \). For \( I_3 \) we have from equation 5.15 that the first term is the Riemann sum approximation of the second term. Since \( \alpha_1 \) is compactly supported and the domains in space and time are bounded this implies \( I_3 \to 0 \). By a similar argument \( I_4 \to 0 \).

These estimates formally show that

\[
\| \tilde{R} - R \|_\infty \to 0.
\]

(5.17)

This along with convergence of the first moments implies

\[
\| M^{(2)}_{A_1, A_2} - M^{(2)}_{\tilde{A}_1, \tilde{A}_2} \|_\infty \to 0.
\]

(5.18)

Since the random fields are Gaussian and completely determined by the first two moments this analysis formally establishes that the stochastic numerical methods weakly converge. An important feature of the form of weak convergence considered is that the stochastic methods produce statistics convergent not only for individual observables represented by \( A \). The stochastic methods are also convergent for any cross-correlation statistics for observables represented by \( A_1 \) and \( A_2 \) which reference the same underlying concentration field.

To obtain convergent stochastic numerical methods the analysis indicates that it is not only required that the discretization of the differential operator \( L \) be consistent, but that the discretized system have equilibrium fluctuations with a covariance structure consistent with \( C \) of the continuum system. An important issue in practice is that the equilibrium covariance structure is not discretized directly but rather arises from the fluctuations induced by the discretized stochastic driving field \( g_t \), as in equation 3.2. To control the discretization errors introduced in the fluctuations of the discretized system as the mesh is refined we utilized a variant of the Fluctuation-Dissipation Principle of statistical mechanics, see Section 3. This was used to ensure that the stochastic numerical methods exhibit equilibrium fluctuations with the specified covariance \( C \), which was chosen to be consistent with \( C \) of the continuum system. This approach is especially important at coarse-refined interfaces of adaptive meshes and cut mesh-cells near the domain boundaries to ensure consistent discretizations for the stochastic driving field \( g_t \).

5.1. Equilibrium Fluctuations at Coarse-Refined Interfaces. We now discuss how the choice of covariance structure for the stochastic field \( g \) influences the equilibrium fluctuations of the system. For dynamics given by equation 3.2, the general relationship in equation 3.8 shows how the covariance of the equilibrium fluctuations \( C \) are related to the covariance of the stochastic driving field \( \Gamma \). In the case when \( LC \) is symmetric and \( L \) is invertible, the equilibrium covariance \( C \) can be expressed directly in terms of \( \Gamma \)

\[
C = -\frac{1}{2} L^{-1} \Gamma.
\]

(5.19)
This expression shows that while discretization errors in approximating the covariance of the stochastic driving term may be localized the errors can have a non-local influence on the covariance of the equilibrium fluctuations of the system.

To illustrate how the choice of covariance influences the equilibrium fluctuations we shall compare three choices for the driving stochastic field $g$. The first is a variant of 'white noise' where $I_{m,n} = (I_m | A_m) \delta_{m,n}$. The second is an "intuitive physically motivated" random flux for the multilevel mesh which at coarse-refined interfaces uses for coarse-cells the average of the random fluxes of the neighboring refined mesh cells. The third is the choice derived from equation 3.5–3.7.

We shall make the comparisons on a periodic mesh. In this case an important technicality arises in that the operator $L$ is in general not invertible, since the constant concentration field is in the null space of $L$, in particular, $Lq = 0$ with $q_m = 1$ for all $m$. This means that the covariance $C$ is only defined by equation 3.7 up to an arbitrary rank one matrix of the form $\lambda q q^T$. To obtain an invertible operator $L$ we shall restrict ourselves to a subspace which corresponds to concentration fields which sum to a given fixed value $q^T c = c_0$, which determines $\lambda$.

The equilibrium fluctuations at the coarse-refined interface associated with each choice of the stochastic driving field are shown in Figures 5.1 and 5.2. We find that using a 'white noise' stochastic driving field introduces long-range correlations into the equilibrium fluctuations. Using the phenomenological discretization of averaged 'random fluxes' at the coarse-refined interface also results in long-range correlations in the equilibrium fluctuations of the system. The choice using the covariance derived
6. Applications. We now discuss how the stochastic numerical methods can be used in practice. We shall first discuss some important issues in modeling the chemical reaction terms of the stochastic reaction-diffusion system, which arise from the stochastic partial differential equation 2.1 only admitting generalized solutions. We then demonstrate how the methods can be used in the context of two specific applications. The first concerns how biological cells sense concentration gradients in the environment. The stochastic numerical methods are used to investigate the role of concentration fluctuations in a proposed mechanism for cell gradient sensing. The second application concerns the Gray-Scott chemical reactions in a spatially extended system. The stochastic numerical methods are used to investigate the role of concentration fluctuations in patterns exhibited in the system.

6.1. Modeling the Chemical Reactions. Since the stochastic partial differential equations 2.1–2.3 do not admit classical solutions the point-wise values of the stochastic concentration field, which are often used in modeling chemical reactions, may not be meaningful. To cope with this issue many studies of stochastic reaction-diffusion systems tacitly regularize the stochastic differential equations by discretizing the system on a regular lattice. As a consequence, many of the results reported in the literature have a direct dependence on the numerical scheme and discretization.

Fig. 5.2. The top row shows the covariance of the equilibrium fluctuations of the system for each choice of the stochastic driving field at a cell at the coarse-refined interface on the coarse side (see + symbol). In the second row, the covariance with this cell is plotted as a function of \( y \) at cross sections of the mesh near the interface.
parameters, such as the discrete lattice spacing [8; 73; 74; 76–78]. In many of the numerical schemes the magnitude of the concentration field fluctuations, which play an important dynamic role through the non-linear chemical reaction terms, even diverge in magnitude as the numerical mesh is refined [77; 78]. However, as a consequence of the finite number of molecules undergoing the diffusive migrations and chemical reactions one would expect on physical grounds that observations of the continuum concentration field representation of the system would exhibit fluctuations having contributions to the chemical reactions of only a finite size.

As with almost any field description arising in continuum mechanics, the continuum field description and governing equations are not expected to yield physically meaningful results beyond some small characteristic length scale of the system. For instance as a rather extreme example, one would not expect a continuum field description to accurately capture features of the physical system on length scales smaller than the distance of the mean free path of the molecular collisions. Similar issues arise for other descriptions such as the reaction-diffusion master’s equations in which spatial discretization parameters must be carefully tuned not to be too large or too small relative to the distance molecules migrate between chemical reactions (reaction mean-free path) in order to obtain physically reasonable results [8; 73; 74; 76; 96]. We shall avoid such fine tuning of the numerical methods by explicitly introducing an additional physical parameter in the parameterization of our models for use in an explicit regularization of the stochastic concentration field in order to appropriately account for the role of fluctuations in the chemical reactions of the system.

Many regularization procedures can be considered for the stochastic fields. Ideally, such a procedure would be motivated from studies of molecular dynamics simulations, particle based simulations, or quantum field theoretic models [73; 75; 88; 89; 91; 92; 96; 98–100]. Here we shall take a more phenomenological approach and use for the chemical reactions regularizations of the general form

\[ F[c](x, t) = \int \alpha(x, y, \eta(y, t)) dy \]

\[ \eta(y, t) = \int \beta(y, z)c(z, t) dz \]

\[ \int \beta(y, z) dy = 1. \]

In these expressions, \( \alpha \) accounts for the rate at which molecules of each chemical species are introduced or removed at location \( x \) by the reactions. The \( \beta \) term models the fraction of molecules at location \( z \) which migrate to participate in chemical reactions associated with location \( y \). These terms have the role of effectively smoothing the concentration field over some length scale \( \ell \). The expression can be conceptually motivated by thinking about the individual molecules for a given configuration represented by the continuum field when projecting the microscopic degrees of freedom of the diffusive migrations and reactions to obtain the rate of change of the continuum concentration field. We remark that such a conceptual approach could also be used in principle to derive additional terms from a microscopic model to account for stochastic contributions arising from the chemical reactions of the system, if these are of significant magnitude [99]. We now discuss how this general form relates to a commonly used model for the chemical reactions in reaction-diffusion master’s equations.

One approach used in modeling the chemistry of reaction-diffusion systems is based on extending the theory developed for homogeneous macroscopic chemical re-
actors to spatially extended systems by assuming that the system can be treated locally as homogeneous and well-mixed. In formulating continuum reaction-diffusion equations the chemical kinetics are modeled by $a(c)$ using the same functional form as for the chemistry in the homogeneous case but instead using the local concentration value. In stochastic models, such as the reaction-diffusion master’s equations, a length scale appears in the discretization of space into control volumes of size $\ell$. In the discretization it is tacitly assume that $\ell$ is larger than the distance of the mean free path of the molecular collisions but small enough that molecular species can be approximated locally as well-mixed and homogeneous [73, 76, 96]. From these considerations the reactions are approximated as occurring nearly independently in volumes of size $V = \ell^d$, where $d$ is the spatial dimension of the system.

In the case of a single molecular species, let $s$ denoting the local number of molecules in the control volume $V$. The reactions are then parameterized by a microscopic kinetic rate $\tilde{a}(s)$ for the number of molecules introduced or removed from the volume per unit time [73, 94, 95]. This rate is related to the macroscopic kinetic rate $a(c)$ used in continuum reaction-diffusion equations by

$$a(c) = \frac{\tilde{a}(s)}{V}$$

which uses that the macroscopic rate is given in terms of the concentration of molecules introduced or removed per unit time per unit volume. In the current setting, the term $s$ is given in terms of the continuum field description of the system by

$$s(x, t) = \int_{V(x)} c(y, t) dy.$$  

This gives for the chemical reactions a functional of the form

$$F[c](x, t) = \tilde{a}(s(x, t))/V.$$  

This corresponds to taking $\eta = s/V$, $\alpha(x, y, \eta) = (\tilde{a}(\eta V)/V)\delta(y - x)$, $\beta(y, z) = \chi_{V(y)}(z)/V$ where $V(y)$ is the control volume centered about $y$ and $\chi_V$ is the characteristic function over $V$. There are many possible choices for $V(x)$ and $\chi_V$, such as choosing a set $V(x)$ which is a disk or square centered at $x$ and a function $\chi_V$ which decays smoothly to zero over the set $V$. A similar expression can be obtained for the case of multiple species $c(x, t)$ and spatially varying rates $a(x, c)$. We remark that the functional yields fluctuations in concentration which contribute to the chemical reactions which are finite and are explicitly controlled by our choice of $\alpha, \beta$, as opposed to being controlled through features of the numerical discretization. Many other forms for the functionals can of course be introduced to model the contributions of the chemical reactions.

A key point to be emphasized is that when using stochastic partial differential equations to account for fluctuations in reaction-diffusion systems the particular functional used for the chemical reactions should be regarded as part of the modeling and parameterization of the system at a coarse-grained level. Ideally when modeling at the continuum level such functionals should be obtained from microscopic models of the physical system. We shall discuss some additional choices for the chemical reaction terms in the context of specific applications in Sections 6.2 and 6.3.

6.2. Gradient Sensing in Cell Biology (Concentration Fluctuations in Non-Rectangular Geometries). In cell biology the spatial distribution of chemical species plays a fundamental role in many cellular processes. For example, the
bacterium *Escherichia coli* detects gradients in the concentration of important nutrients in the environment which bias the direction a cell moves toward regions which are more nutrient rich. Individual *Dictyostelium discoideum* bacterium cells respond to spatial and temporal features of concentration fields of signaling molecules, such as cAMP generated by other cells, to coordinate collective movements which result in the formation of complex multicellular structures, such as fruiting bodies and spores [55; 56]. In the developmental biology of multicellular organisms concentration fields of many signaling molecules are used to determine cell differentiation within tissues [1; 93; 106; 107]. The means by which cells detect local concentrations and gradients of external chemical species and determine a response is a fundamental process in cell biology.

Features of the external concentration field are typically detected by cells through binding of the external molecules to receptor proteins which reside in the outer cell membrane. Receptor proteins upon binding undergo conformational changes which trigger local chemical reactions which produce products which diffuse along the cell membrane or into the cytoplasm [1; 106; 107]. While many proteins and metabolites involved in these processes are known, there are many questions concerning the particular interactions and mechanisms by which concentration field signals generate a cellular response. This is a rather active area of experimental and theoretical research [47; 101; 103–105; 107; 109; 110].

Here we formulate a basic model and investigate the role played by intrinsic fluctuations of the concentration field in the detection of concentration gradients. It is illustrative to characterize the concentration fluctuations on the length and time scales of individual cells. A typical cellular environment can have signaling chemical species, which are present in concentrations which can range from as small as picomolar (pM) to as large as molar (M), see [1; 49; 108; 109].

As an illustration consider an intermediate concentration of 1mM, and the length scale of a 100nm cubic box. One millimolar corresponds to \( mM = 10^{-3}N_A/litre = 6.022 \times 10^{23} \text{molecules/m}^3 \) with \( N_A \) Avogadro’s number. On the length scale of 100nm there is on average only \( 6.022 \times 10^2 \text{molecules per box} \). For a rough estimate of the time scale of the fluctuations we note that typical signaling molecules, such as cAMP, have diffusion coefficients on the order of \( 10^8 \text{nm}^2/s \), see [43]. For a box with edge length \( \ell = 100\text{nm} \) the amount of time required for a particle to diffuse out of the box is of the order \( \tau_D = \ell^2/D = 10^{-4}s \). This provides a rough estimate of the time scale on which fluctuations are expected to be correlated. Given that cells are observed to change course in chemotaxis in very shallow concentration gradients on the time scale of seconds or faster, fluctuations in concentration may play an important role [50]. Here we show how equations 2.1 – 2.3 and the proposed numerical methods can be used to investigate the role of fluctuations in concentration of the signaling chemical species.

To model how a cell initially processes a signal detected by membrane receptors we shall consider a system of three basic chemical species which originate and diffuse within the cellular membrane. The chemical species are (i) an activator molecular species denoted by A, (ii) an inhibitor molecular species denoted by I, and (iii) a reporter molecular species denoted by Q. The reporter species Q is meant to account for how the receptor binding events result in an internal chemical signal which feeds into further cellular reactions which give products within the cell membrane and cytoplasm, such as signals for cell motility (local actin polymerization), cell polarization, or calcium release from local buffers / internal stores [1; 47; 107; 109].
We shall consider each of the molecular species as being in one of two possible forms: active or inactive, which are denoted by $P^*$ and $P$, respectively. Transitions between inactive and active can occur, for example through phosphorylation or methylation of the individual proteins. We shall generically refer to this as the production of the active species or deactivation of the active species. In the model, we posit that the cell processes the external signal to form the reporter products $Q$ by two competing processes. The first involves increases in the concentration of species $A$ which increases the local production of the active reporter species $Q^* \rightarrow Q$. The second involves increases in the concentration of species $I$ which increases the local deactivation of the reporter species $Q \rightarrow Q^*$. The external concentration field influences these processes through the receptor binding events which locally produce active species of $A$ and $I$. More precisely, the model for the chemical species inside the biological cell is given by the following system of reaction-diffusion equations:

$$\frac{\partial E}{\partial t} = D_E \Delta E - \kappa_{de} E + \kappa_{re} S$$

Fig. 6.1. Gradient Sensing Schematic: (Top Left) Environmental concentration gradient interacting with a single cell. (Top Right) A schematic of the cellular gradient sensing mechanism. Molecules of the external concentration field bind to receptor proteins embedded in the cell membrane. Receptor binding events cause conformational changes of receptor proteins which activate chemical reactions which release product molecules which diffuse in the cell membrane and cytoplasm. (Bottom Left) The adaptive numerical mesh on which the stochastic concentration equation 6.7 is solved for a cell having the geometry of a disk. The gradient is not imposed but rather arises from sources and sinks at either end of the rectangular domain (Dirichlet Boundary Conditions). The obtained gradient profile is the solution of the concentration equations on the domain exterior to the disk shaped cell, on which no-flux boundary conditions are imposed (Neumann Boundary Conditions). (Right Bottom) Closer view of the adaptive mesh which includes cut-cells in the vicinity of the curved boundary of the biological cell which is adapted to obtain an accurate numerical solution.
Fig. 6.2. Gradient Sensing Simulation Results: The gradient sensing cell model was simulated with parameters chosen in a physical regime corresponding to typical rates of chemical reactions and diffusion reported in the cell biology literature, see Table 6.2. The mean concentration is plotted with estimated error bars corresponding to three standard deviations. For ease of comparison the concentration levels are scaled by the maximum mean concentration value for each chemical species. (Top Left) Shows the receptor activation level for a shallow external concentration gradient with fluctuations large relative to the gradient. The maximum mean concentration was 1.5mM. (Top Right) The concentration profile of the reporter chemical species which diffuses in the cell membrane. The maximum mean concentration was 9.3mM. (Bottom Left) The concentration profile of the inhibitor. The maximum mean concentration was 1.5mM. (Bottom Right) The concentration profile of the activator chemical species. The maximum mean concentration was 1.5mM.

\[ \frac{\partial I}{\partial t} = D_I \Delta I - \kappa_{dI} I + \kappa_{rI} S \]  
(6.5)

\[ \frac{\partial Q}{\partial t} = D_Q \Delta Q + \kappa_{qE} E (Q - Q) - \kappa_{qI} IQ, \]  
(6.6)

where \( Q_T = Q^* + Q \). We shall consider for the geometry of the cell a disk of radius \( R \) in two dimensional space. In this case, the cell membrane corresponds to the circle of radius \( R \). The equations 6.4 - 6.6 should be considered to reside on this circular membrane with periodic boundary conditions.

The external concentration field \( C(x,t) \) is obtained as the solution of

\[ \frac{\partial C}{\partial t} = D_C \Delta C + \eta \]  
(6.7)

\[ \langle \eta(x,t) \eta(x',t') \rangle = -2D_C \Delta \delta(x - x') \delta(t - t') \]  
(6.8)

where \( \eta \) satisfies the conditions in equation 2.1. The external concentration field \( c \) is obtained by solving equation 6.7 on a domain which has sources-sinks at the left and right edges which impose a fixed concentration (Dirichlet Boundary Conditions) and
Table 6.1  
Cell Gradient Sensing Model: Description of the Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>Radius of the disk shaped cell.</td>
</tr>
<tr>
<td>$D_S$</td>
<td>Diffusion coefficient of external signaling chemical species.</td>
</tr>
<tr>
<td>$a$</td>
<td>Receptor sensor associated length scale.</td>
</tr>
<tr>
<td>$D_E$</td>
<td>Diffusion coefficient of excitatory chemical species.</td>
</tr>
<tr>
<td>$\kappa_{re}$</td>
<td>Rate of receptor initiated activation of excitatory chemical species.</td>
</tr>
<tr>
<td>$\kappa_{de}$</td>
<td>Rate of degradation/deactivation of excitatory chemical species.</td>
</tr>
<tr>
<td>$D_I$</td>
<td>Diffusion coefficient of inhibitory chemical species.</td>
</tr>
<tr>
<td>$\kappa_{ri}$</td>
<td>Rate of receptor initiated activation of inhibitory chemical species.</td>
</tr>
<tr>
<td>$\kappa_{di}$</td>
<td>Rate of degradation/deactivation of inhibitory chemical species.</td>
</tr>
<tr>
<td>$Q_T$</td>
<td>Total concentration of reporter chemical species.</td>
</tr>
<tr>
<td>$D_Q$</td>
<td>Diffusion coefficient of reporter chemical species.</td>
</tr>
<tr>
<td>$\kappa_{qc}$</td>
<td>Rate of production of active reporter aided by the excitatory chemical species.</td>
</tr>
<tr>
<td>$\kappa_{qi}$</td>
<td>Rate of degradation/deactivation of active reporter aided by the inhibitory chemical species.</td>
</tr>
</tbody>
</table>

in a region exterior to the biological cell, which is treated as being impermeable to the external chemical species (no-flux Neumann Boundary Conditions), see Figure 6.1.

As we shall discuss the external concentration gradient is no longer strictly linear when taking into account the geometry and no-flux boundary of the biological cell. This potentially overlooked feature could have important implications in interpreting biological experiments. We remark that the mesh is adaptive in space and includes cut-cells near the curved surface of the biological cell, see Figure 6.1. More complex geometries in two and three dimensions can also be considered with a fairly straightforward extension of the methodology proposed here.

The external concentration field influences the production rates of internal chemical species by the receptor binding events, which in the model produce activator and inhibitor at the local rates $\kappa_{re}S$ and $\kappa_{ri}S$. The receptor binding events are modeled at a coarse-grained level by considering the local number of molecules which are in the vicinity of a receptor cluster. In our model we take $S_i(x,t) = \alpha n_i \delta(x-x_i)$ for each cluster, where $n_i$ denotes the number of molecules in the vicinity of cluster $i$ at location $x_i$. This corresponds to molecules diffusing near the receptor cluster binding at the rate $\alpha$.

To obtain $n_i$, a local integration of the concentration field is performed by convoluting with a kernel $\Lambda(x,x_i)$ centered at the $i^{th}$ receptor cluster at location $x_i$. Using a radial symmetric kernel we have

$$n_i = \int \Lambda(|x-x_i|)c(x,t)dx.$$  

We remark that in the case that $\Lambda(r) = 1$ for $r < a$ and zero otherwise, the $n_i$ would correspond to the number of molecules within distance $r_s$ of the receptor cluster. In practice, we will use a smooth kernel which decays rapidly for $r > a$ to help reduce artifacts which arise from shifts of $x_i$ relative to the discretization mesh.

We now discuss how the model can be used to investigate the effect of fluctuations on the cellular processing of an external concentration gradient. We consider the case when the fluctuations are large relative to the gradient around the cell perimeter. To
parameterize the model to be in an appropriate physical regime, we use kinetic rates and diffusion coefficients taken from the cell biology literature. Our specific choice of parameters can be found in Table 6.2.

Signaling molecules have diffusion coefficients on the order of $10^8 \text{nm}^2 \text{s}^{-1}$. For example, the signaling molecule cAMP is reported to have a diffusion coefficient of $2.7 \pm 0.2 \times 10^8 \text{nm}^2 \text{s}^{-1}$, see [43]. The diffusion coefficients of molecules diffusing in the cell can range from $10^5 \text{nm}^2 \text{s}^{-1}$ to $10^7 \text{nm}^2 \text{s}^{-1}$, see [44; 45]. In cell gradient sensing it is observed that cells are able to respond to changes in the external concentration field on the order of seconds [47; 55]. The rates of the biochemical chemical reactions are taken to occur in the model with first order rates ranging from $1 \text{s}^{-1}$ to $10^4 \text{s}^{-1}$ and second order rates $10^{-1} \text{mM}^{-1} \text{s}^{-1}$ to $1 \text{mM}^{-1} \text{s}^{-1}$.

Simulations of the cell gradient sensing mechanism were carried out by numerically integrating in time the discretized reaction-diffusion system using the Euler-Maruyuma Method [13]. In the discretizations used near the curved boundaries of the disk shaped cell in order to reduce stiffness in the discretized equations cut-mesh-cells were fused to form larger composite cells when smaller than 10% of the corresponding full mesh-cell size, as discussed in Section 3.3. For the receptor binding events and internal production of reaction products the kernel $\Lambda$ which is integrated over the mesh was taken to be a gaussian with standard deviation $a = 100 \text{nm}$. A time step of $2.5 \times 10^{-5} \text{s}$ was used and the model was simulated for $1.6 \times 10^6$ time steps corresponding to a physical time scale of 40s.

In Figure 6.2 the results of the simulation for the concentration fluctuations of the signaling and intracellular chemical species are reported. It is found that even when the concentration fluctuations are large to the gradient the proposed sending mechanism is capable of producing a reporter concentration profile which robustly indicates the external mean concentration gradient provided observations occur over a sufficient duration of time.
6.3. Gray-Scott Reaction-Diffusion (Fluctuation Induced Patterns). We now consider a variant of the Gray-Scott reaction-diffusion system given by

\begin{align}
\frac{\partial u}{\partial t} &= D_1 \Delta u + f[u, v] + \eta_1 \\
\frac{\partial v}{\partial t} &= D_2 \Delta v + g[u, v] + \eta_2
\end{align}

where \( \eta_1, \eta_2 \) account for the concentration fluctuations and are Gaussian random fields with mean zero and covariance

\begin{align}
\langle \eta_1(x, t) \eta_1(x', t') \rangle &= -2\bar{u} D_1 \Delta_x \delta(x - x') \delta(t - t') \\
\langle \eta_2(x, t) \eta_2(x', t') \rangle &= -2\bar{v} D_2 \Delta_x \delta(x - x') \delta(t - t') \\
\langle \eta_1(x, t) \eta_2(x', t') \rangle &= 0.
\end{align}

The \( D_1, D_2 \) are the diffusion coefficients of the chemical species. This corresponds to the physical regime in which concentration fluctuations are small relative to the mean concentration and are dominated by density fluctuations not depending directly on the chemical reactions. The chemical reactions of the molecular species are accounted for by the functionals \( f, g \) of the general cubic form:

\begin{align}
f[u, v](x, t) &= \alpha_0 n_u n_v^2 + \alpha_5 n_u^2 + \alpha_4 n_v^2 + \alpha_3 n_u n_v + \alpha_2 n_u + \alpha_1 n_v + \alpha_0 \\
g[u, v](x, t) &= \beta_0 n_u n_v^2 + \beta_5 n_u^2 + \beta_4 n_v^2 + \beta_3 n_u n_v + \beta_2 n_u + \beta_1 n_v + \beta_0
\end{align}

with

\begin{align}
n_u(x, t) &= \int \Lambda(y - x) u(y, t) dy \\
n_v(x, t) &= \int \Lambda(y - x) v(y, t) dy
\end{align}

where the kernel is taken to be \( \Lambda(z) = (1/\sqrt{2\pi\sigma^2}) \exp(-|z|^2/2\sigma^2) \). This has the effect of explicitly regularizing the concentration field over the length scale \( \sigma \).

To obtain a discrete approximation to the integrals in equations 6.16 – 6.17 on the multilevel mesh we shall use \( \bar{n}_m = \sum_n \Lambda_{m,n} n_m \Delta y_m \) with \( \Lambda_{m,n} = \frac{1}{\Delta x_m} \Lambda(x_m - x_n) \Delta x_n^d \) where \( Z_m \) normalizes the kernel to sum to one in the index \( n \) and is given by \( Z_m = \sum_n \Lambda(x_m - x_n) \Delta x_n^d \). We remark that as \( \Delta x \to 0 \) it follows that \( Z_m \to 1 \) and we have \( \bar{n}_m \to n_m \) giving a well-defined limit as the mesh is refined.

We now discuss the reaction-diffusion system for a particular choice of parameter values, see Table 6.3. For this choice, the phase portrait of the basic non-spatial two dimensional dynamical system corresponding to the chemical reactions \( f, g \) is given in Figure 6.3. In the system corresponding to the local dynamics there is only one stable steady-state at \( (n_u = 1.1, n_v = 1.0) \). However, an interesting feature of the phase space is that there is a region in which the two nullclines pass in close proximity (the system is close to undergoing a bifurcation [111]). An interesting behavior of the system is that even relatively small perturbations of the dynamical system in this region can cause the system state to cross the nullclines. Such back and forth switching could in principle effectively stabilizing states in this region of the phase plane. In the reaction-diffusion system, perturbations are introduced, from this perspective, to the local dynamical system through the internal concentration fluctuations and the spatial extent of the system in which diffusion and the regularization couples laterally.
the local dynamical states of the system. To investigate the behavior of the spatially extended system subject to fluctuations we shall use equations 2.2.3 approximated by the proposed adaptive stochastic numerical methods on a multilevel mesh.

In the simulations an initial perturbation is introduced into the system in which a small square region centered at the origin of edge length 17.6 is set to \((u = 1.07, v = 1.03)\), everywhere else is set to \((u = 1.1, v = 1.0)\). Since similar such states could arise spontaneously from fluctuations in the system, introduction of this initial perturbation avoids having to simulate the potentially long waiting time for a rare “nucleating event” which breaks the translational symmetry of the homogeneous state. In order to make sure this initial perturbation alone is not responsible for the observed results, simulations were performed in the absence of fluctuations, and it was found that a simple symmetric pattern of only four spots is obtained and appears stable for
Fig. 6.5. Gray-Scott Reaction-Diffusion System with Internal Concentration Fluctuations

long times, see Figure 6.4. To investigate the role of stochastic effects, the system with the same initial condition was simulated subject to intrinsic fluctuations, see Table 6.3. Unlike the deterministic case, a rich pattern of spot-like patterns emerges where the spots continually migrate and replicate, see Figure 6.5. Movies of the full evolution process of the emerging pattern can be found on-line [102]. We find that the fluctuations may play a non-negligible role in pattern formation processes and may introduce additional structures not observed in the corresponding deterministic system.
Table 6.3
Gray-Scott: Values of the Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha_0, \alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6]$</td>
<td>$[1.100605, -2.2, -1.10055, 2.2, 1.1, 0.0, -1.0] \times 10^6.$</td>
</tr>
<tr>
<td>$[\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6]$</td>
<td>$[-0.998845, 1.998845, 1.0, -2.0, -1.0, 0.0, 1.0] \times 10^6.$</td>
</tr>
<tr>
<td>$D_u$</td>
<td>$5.5 \times 10^3.$</td>
</tr>
<tr>
<td>$D_v$</td>
<td>$5.0 \times 10^3.$</td>
</tr>
<tr>
<td>$L$</td>
<td>$5.632 \times 10^2.$</td>
</tr>
<tr>
<td>$\bar{u}$</td>
<td>$1.1.$</td>
</tr>
<tr>
<td>$\bar{v}$</td>
<td>$1.0.$</td>
</tr>
</tbody>
</table>
7. Conclusions. In the context of reaction-diffusion systems we have shown how to approximate a class of stochastic partial differential equations using adaptive finite difference methods traditionally applied to deterministic equations. A key feature of the approach was to discretize the stochastic driving terms in a manner respecting fundamental statistical features of the equations. Our approach uses results for the stochastic differential equations which relate the covariance of the stochastic driving terms to the covariance of the equilibrium fluctuations to ensure that the Gaussian stochastic driving terms are discretized in a manner that at statistical steady-state exhibit fluctuations which agree with the averaged fluctuations of the continuum system. The stochastic numerical methods allow for reaction-diffusion systems with intrinsic fluctuations dominated by density fluctuations to be simulated on multilevel meshes and on domains which may have geometries with curved boundaries. The numerical methods potentially allow for significant gains in computational efficiency through adaptive resolution of phenomena occurring in spatially extended stochastic systems.

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