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Stochastic diffusion processes on Cartesian meshes

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ABSTRACT

Diffusion of molecules is simulated stochastically by letting them jump between voxels in a Cartesian mesh. The jump coefficients are first derived using finite difference, finite element, and finite volume approximations of the Laplacian on the mesh. An alternative is to let the first exit time for a molecule in random walk in a voxel define the jump coefficient. Such coefficients have the advantage of always being non-negative. These four different ways of obtaining the diffusion propensities are compared theoretically and in numerical experiments. A finite difference and a finite volume approximation generate the most accurate coefficients.

1. Introduction

Small copy numbers of many molecular species in biological cells require stochastic models of the chemical reactions between the molecules and their diffusive motion. One example is gene expression where the number of molecules involved is small and only stochastic models can explain observations in experiments [1,2]. Continuum models for the concentrations of the chemical species based on partial differential equations (PDEs) capture neither the randomness in the chemical reactions nor the fact that the number of molecules is integer.

In a well stirred system, there is no space dependence of the distribution of the species. Gillespie [3] invented an algorithm to simulate such chemical systems, the Stochastic Simulation Algorithm (SSA). The efficiency of the algorithm is improved in [4]. It is extended in [5,6] to space-dependent systems where the diffusion of the molecules cannot be neglected.

The domain of interest is Ω with boundary $\partial\Omega$. It is partitioned by a Cartesian mesh into compartments or voxels $\mathcal{V}_i$ with volume $|\mathcal{V}_i|$ and a node $\mathbf{x}_i$ in the center in [5]. The molecules jump between the voxels (or between the nodes in the lattice) with a certain probability. The time until a molecule jumps from $\mathcal{V}_i$ to the adjacent $\mathcal{V}_j$ is assumed to be exponentially distributed with parameter λ_{ij}. With n_i neighbors, the total jump propensity out of $\mathcal{V}_i$ is

$$\lambda_i = \sum_{j=1}^{n_i} \lambda_{ij}. \tag{1}$$

The diffusion propensity is $\lambda_i m_i$ with m_i molecules in $\mathcal{V}_i$. Then the SSA for the diffusion in the molecular system is:

1. Initialize the number of molecules m_k, $k = 1, \ldots, K$, in the K voxels at $t = 0$.
2. Sample the exponentially distributed time Δt_k with rate $\lambda_k m_k$ to the first diffusion event in all K voxels and let $t_k = \Delta t_k$.
3. Determine the smallest t_k. Let t_i be the minimum of all t_k in voxel $\mathcal{V}_i$.

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4. For the jump from $\mathcal{V}_i$, sample a jump to $\mathcal{V}_j$ with probability $\theta_{ij} = \lambda_{ij}/\lambda_i$.
5. Update $t := t_i$ and molecule numbers $m_i := m_i - 1$ and $m_j := m_j + 1$.
6. Sample Δt_i and Δt_j with rates $\lambda_i m_i$ and $\lambda_j m_j$ and let $t_i = t + \Delta t_i$ and $t_j = t + \Delta t_j$ and go to 3.

In the algorithm, the number of molecules m_i in each voxel is updated if it has changed after an event and a new time t_i is determined for the next event in the same voxel. The SSA generates one realization of a continuous time, discrete space Markov process. We will compare different ways of determining non-negative jump coefficients λ_{ij} for a Cartesian mesh where all voxels have equal size assuming that the rates to jump from $\mathcal{V}_i$ to $\mathcal{V}_j$ and back again are equal, $\lambda_{ij} = \lambda_{ji}$.

Let $u_i(t)$ be the numerical approximation at $\mathbf{x}_i$ on the Cartesian mesh of the concentration $u(\mathbf{x}, t)$ satisfying the diffusion equation in the domain Ω

$$\frac{\partial u(\mathbf{x}, t)}{\partial t} = \Delta u(\mathbf{x}, t), \quad \mathbf{x} \in \Omega,\ t \geq 0, \tag{2}$$

with Neumann boundary condition $\mathbf{n} \cdot \nabla u = 0$ at the boundary $\partial\Omega$ with the outward normal $\mathbf{n}$. Choose the λ_{ij} coefficients such that they approximate the Laplacian in node i at $\mathbf{x}_i$

$$\begin{aligned}\Delta u(\mathbf{x}_i, t) &\approx \sum_{j=1}^{n_i} \lambda_{ji} u_j(t) - \sum_{j=1}^{n_i} \lambda_{ij} u_j(t) = \sum_{j=1}^{n_i} \lambda_{ij}(u_j(t) - u_i(t)) \\ &= \sum_{j=1}^{n_i} \lambda_{ji} u_j(t) - \lambda_i u_i(t).\end{aligned} \tag{3}$$

The node at $\mathbf{x}_i$ has n_i adjacent nodes at $\mathbf{x}_j$ used in the approximation. In the limit of a large total number of molecules $M = \sum_{k=1}^{K} m_k$, the time dependent expected values of the concentrations $\tilde{u}_i = m_i/(M|\mathcal{V}_i|)$ in the voxels in SSA with the jump coefficients in (3) converge to the deterministic concentrations u_i solving the discretized diffusion equation (2) using (3), see [7]. The distribution for the difference between $\tilde{u}_i$ and u_i is given in [8].

In an equidistant Cartesian mesh, the Laplacian is discretized with a finite difference method (FDM) in [5,6,9]. Unstructured triangular meshes in 2D and tetrahedral meshes in 3D are better suited to represent complicated geometries inside the cell effectively. The coefficients for these unstructured meshes are derived from a finite element method (FEM) for the Laplacian in [10,11] and with a finite volume method (FVM) in [12].

The jump propensities λ_{ij} have to be non-negative to be meaningful in the SSA. The standard 5-point (2D) and 7-point (3D) approximations of the Laplace operator in (2) with FDM on a Cartesian mesh yield positive λ_{ij} for the neighboring voxels but the FEM coefficients for an unstructured mesh may be negative for a poor mesh [11]. The numerical discretization of the diffusion equation (2) by a common FVM method may be inconsistent [13] and not converge to the analytical solution on a general unstructured mesh but the coefficients are non-negative.

If the jump coefficients are negative, the numerical solution of (2) will in general not be monotone and not satisfy the discrete maximum principle. For the discrete maximum principle to hold the coefficients must satisfy the following conditions, see [14]: (1) is valid for interior nodes; $\lambda_{ij} \geq 0$; and λ_i is greater than the sum of the off-diagonal elements for at least one boundary node. Thus, the two first conditions apply for both the diffusion coefficients in the SSA and the spatial discretization of the diffusion equation.

Many papers are devoted to the derivation of consistent FEM and FVM approximations fulfilling the discrete maximum principle for triangular and quadrilateral meshes in 2D and tetrahedral meshes in 3D, e.g. [15–19]. They are nonlinear and the coefficients in (3) depend on the solution u_i making them less suitable as jump propensities in the SSA or rely on meshes with geometrical properties that may be difficult to achieve with a mesh generator. In [20,21] it has been shown that it is impossible to construct a linear method, i.e. λ_{ij} is constant in (3), satisfying the discrete maximum principle for a linear elliptic equation on general quadrilateral meshes in 2D.

As an alternative, we solve the diffusion equation on a local domain and use the solution to calculate the mean first exit time (FET) from that domain for a molecule in Brownian motion. The molecule is released at $\mathbf{x}_i$ at $t = 0$ and after a random walk it leaves a subdomain defined by the convex hull of the adjacent nodes $\mathbf{x}_j$, $j = 1, \ldots, n_i$, for the first time at $t = \tau$. The expected value of τ from this subdomain is the inverse of the rate λ_i. The mesh is Cartesian in 2D with different mesh sizes h_x and h_y in the x and y directions, respectively. Jumps are allowed in the coordinate directions and along the diagonals, see Fig. 1. The probability to exit from $\mathcal{V}_i$ to $\mathcal{V}_j$ depends on the distance between the nodes $\mathbf{x}_i$ and $\mathbf{x}_j$, i.e. h_x and h_y. The FET coefficients are always non-negative. They are compared with the methods above for approximations of the Laplacian. The coefficients derived with FDM, FEM, and FVM also depend only on h_x and h_y in the mesh. The jump coefficients obtained by the FET and the systematic comparison with the coefficients from numerical discretizations are the main contributions of this paper. The analysis is extended to the fully unstructured case in [22].

The expected FET can be utilized in a different way to solve (2), see [23] and the references therein. Stochastic simulations determine the FET in polygonal domains with general boundary and initial conditions in a Monte Carlo method suitable for high dimensions. Here we are interested in using FET to find the probabilities of the motion of molecules on a discrete lattice.

In Section 2, we present the FDM, FEM, and FVM discretizations of the Laplacian and how to derive the jump coefficients from them. We compute expressions for the FET in Section 3 to derive new jump coefficients from the exit behavior of