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Simulation of stochastic diffusion via first exit times

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ABSTRACT

In molecular biology it is of interest to simulate diffusion stochastically. In the mesoscopic model we partition a biological cell into unstructured subvolumes. In each subvolume the number of molecules is recorded at each time step and molecules can jump between neighboring subvolumes to model diffusion. The jump rates can be computed by discretizing the diffusion equation on that unstructured mesh. If the mesh is of poor quality, due to a complicated cell geometry, standard discretization methods can generate negative jump coefficients, which no longer allows the interpretation as the probability to jump between the subvolumes. We propose a method based on the mean first exit time of a molecule from a subvolume, which guarantees positive jump coefficients. Two approaches to exit times, a global and a local one, are presented and tested in simulations on meshes of different quality in two and three dimensions.

1. Introduction

In biochemical networks in cells, molecules diffuse in space and may react with other molecules when they are in the vicinity of each other. This process is often modeled by the reaction–diffusion equations, a system of deterministic partial differential equations (PDEs). This *macroscopic* model describes the evolution of the concentration of the molecules in time and space and is a good approximation for the behavior in the cell in the limit of large molecule numbers. However, many molecular species of interest in a biological cell, such as the DNA and transcription factors in gene regulation, are present only in very small copy numbers. The law of large numbers is no longer applicable and a deterministic equation for the concentration is inaccurate. We need to simulate the system in a stochastic manner as observed in experiments [1–6] or is justified theoretically [7,8]. Diffusion is then modeled as a random walk through space for the molecules and they react with each other with a certain probability when they meet.

One can distinguish at least two levels of modeling for such a random process. The first one is a discrete space, continuous time Markov process for the copy number of the molecules of the chemical species, called the *mesoscopic* model. Here the geometric domain is partitioned into compartments or voxels $\mathcal{V}$ in which the molecules are well mixed. The state of the system is the number of molecules of each species in each voxel. Molecules can then jump between adjacent voxels in diffusion or react with molecules within the same voxel. In a well stirred system, there is no space dependence and a trajectory of the system is generated by the Stochastic Simulation Algorithm (SSA) [9] or more efficient versions of it [10,11]. The algorithm was extended to problems with spatial variation on Cartesian meshes in [12] implemented in [13] and with curved boundaries in [14] and for unstructured meshes in [15] with software [16,17]. The second possibility is a continuous

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space, continuous time Markov process at the more detailed *microscopic* level. Here each individual molecule is tracked and moves by Brownian motion. The molecules react with a certain probability if they are close to each other. Methods and software for this approach are found in [18–21].

In this paper we focus on the description of diffusion at the mesoscopic level. The purpose is to derive the jump coefficients between adjacent voxels for unstructured meshes for simulation of stochastic diffusion by the SSA. Each voxel has a node and the nodes in the mesh are connected by a graph. The time between the jump events is assumed to be exponentially distributed and the jump coefficients are the rates for the jumps from one voxel to the neighboring voxels. These coefficients are determined in [15] by a finite element method (FEM) for the Laplacian Δ and in [17] by a finite volume method (FVM). It follows from [22] that when the number of molecules in the system increases, the concentration of the species will converge to the solution of the diffusion equation discretized in space by FEM or FVM. The jump coefficients depend on the geometry of the mesh and have to be non-negative. For a mesh of poor quality, some of the rates generated by FEM may be negative. The rates generated by a standard FVM are always non-negative but the coefficients do not always define a consistent discretization of the Laplacian.

The jump rates λ_{ij} from $\mathcal{V}_i$ to a neighboring $\mathcal{V}_j$ satisfy two conditions

$$1.\quad \lambda_{ij} \geq 0, \qquad 2.\quad \sum_{j,\, j\neq i} \lambda_{ij} = \lambda_i, \tag{1}$$

where λ_i is the total jump rate out of $\mathcal{V}_i$. The corresponding approximation of Δu in $\mathcal{V}_i$ on a mesh is then defined by the weights λ_{ij} for the solution values u_j in the neighboring voxels $\mathcal{V}_j$ and $-\lambda_i$ for the value u_i in $\mathcal{V}_i$. The analytical solutions to the Laplace equation or the diffusion equation satisfy a maximum principle. A discrete numerical solution preserving this property satisfies a discrete maximum principle. The same conditions on the coefficients in a discretization of the Laplacian as for the jump rates in (1) are sufficient for the solution to fulfill the discrete maximum principle [23] and the scheme to be monotone. The construction of such maximum preserving and consistent FEM and FVM for unstructured meshes in 2D and 3D is the subject of a number of papers e.g. [24–29]. In order for the solution to satisfy the discrete maximum principle for Lagrangian FEM there are either geometrical restrictions on the mesh, such as non-obtuse angles, or the coefficients depend on the solution. Also for mixed FEM with Raviart–Thomas elements, the discrete maximum principle is not always satisfied [30]. In [31], non-negativity constraints are added in an optimization problem for a mixed FEM formulation to assure non-negative solutions of the diffusion equation. Defining a linear scheme for a general unstructured mesh fulfilling (1) with constant coefficients seems to be difficult. Also, to generate a mesh with the angle constraint fulfilled is difficult [32,33] even in 2D although some progress has been made [34].

We determine λ_{ij} using a different principle. We give up consistency with the Laplacian and replace it by another relation satisfied by diffusive molecules in order to guarantee that (1) is satisfied. If the consistent FEM discretization leads to negative λ_{ij} they are often small in absolute value on realistic meshes. The perturbation by using non-negative λ_{ij} instead is small and our new discretization is close to the original, consistent discretization. The first exit time of a molecule from a domain ω is the time when a molecule initially inside reaches the boundary $\partial\omega$ of the domain and is absorbed there [35–37]. Non-negative jump coefficients are derived from the probability distribution of that time. The principle is applied locally for the molecules to leave a node and globally for them to leave the computational domain Ω. In [38], we compare this approach with FEM, FVM, and the finite difference method (FDM) for Cartesian meshes. The first exit time has previously been used in computational methods in [19,21,39–41] to sample a particle's exit time from its protective domain in particle based microscopic simulations.

In the next section, we explain in more detail the mesoscopic simulation algorithm intended for stochastic diffusion on lattices and the problems that are encountered on unstructured meshes. The coefficients are given by discretizations of the Laplacian. Then we present the theory of first exit times in Section 3 and how it can be used to calculate jump propensities. The numerical experiments with diffusive problems in two and three dimensions (2D and 3D) including chemical reactions are reported in Section 4. Finally, some conclusions are drawn.

Vectors and matrices are written in boldface. A vector $\mathbf{u}$ has the components u_i and the elements of a matrix $\mathbf{A}$ are A_{ij}. Vectors and matrices are measured in the Euclidean vector norm $\|\mathbf{u}\|$ and its subordinate spectral matrix norm $\|\mathbf{A}\|$.

2. Mesoscopic model for diffusion

In this section we derive the mesoscopic model for diffusion from a master equation, its mean value equations, and the discretization of the diffusion equation. The spatial domain Ω with boundary $\partial\Omega$ is partitioned into voxels $\mathcal{V}_i$, $i = 1, \ldots, N$, covering the whole domain $\Omega = \bigcup_{i=1}^{N} \mathcal{V}_i$ without overlap between them $\mathcal{V}_i \bigcap \mathcal{V}_j = \emptyset$. Each voxel has a node $\mathbf{x}_i$ inside the boundary $\partial\mathcal{V}_i$ with edges $\mathbf{e}_{ij}$ in a graph connecting $\mathbf{x}_i$ with the node $\mathbf{x}_j$ in the adjacent $\mathcal{V}_j$, see Fig. 1(a). The length, area, or volume of $\mathcal{V}_i$ in 1D, 2D, or 3D, is V_i. The copy number of chemical species Y in $\mathcal{V}_i$ is denoted by y_i. A molecule can jump from $\mathcal{V}_i$ to a $\mathcal{V}_j$ sharing a common part of the boundary $\partial\mathcal{V}_{ij}$ and an edge $\mathbf{e}_{ij}$.

2.1. The master equation

The probability density function (PDF) for a system with only diffusion satisfies a diffusion master equation (DME). The DME is a special case of the chemical master equation with linear reaction propensities [42, Ch. 8], [43, Ch. XIV]. The jump