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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.

Keywords

stochastic simulation; diffusion; unstructured mesh

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 The law of large numbers is no longer applicable and a deterministic equation for the concentration is inaccurate.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, 2, 3, 4, 5, 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.

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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 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, 19, 20, 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 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

$$1. \lambda_{ij} \geq 0, \quad 2. \sum_{j: j \neq i} \lambda_{ij} = \lambda_i, \quad (1)$$

where λ_i is the total jump rate out of $\mathcal{V}_i$. The corresponding approximation of u 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, 25, 26, 27, 28, 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, 36, 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, 40, 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 Sect. 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 Sect. 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 $\mathcal{V}_i$, $i = 1, \dots, N$, covering the whole domain $\Omega = \bigcup_{i=1}^N \mathcal{V}_i$ without overlap between them $\mathcal{V}_i \cap \mathcal{V}_j = \emptyset$. 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 of one molecule of Y from $\mathcal{V}_i$ to $\mathcal{V}_j$ is written as a chemical reaction with the linear propensity v_{ij}

We have a positive λ_{ij} only for cells that are connected by $\mathbf{e}_{ij}$.

The master equation for the PDF $p(\mathbf{y}, t)$ of the diffusion in (2) is

$$\frac{\partial p(\mathbf{y}, t)}{\partial t} = \sum_{i=1}^N \sum_{j=1}^N \lambda_{ij} (\mathbf{y} - \boldsymbol{\mu}_{ij}) p(\mathbf{y} - \boldsymbol{\mu}_{ij}, t) - \lambda_{ij}(\mathbf{y}) p(\mathbf{y}, t). \quad (3)$$

The transition vector $\boldsymbol{\mu}_{ij}$ is zero except for two components: $\mu_{ij,i} = -1$ and $\mu_{ij,j} = 1$. When there is a jump from $\mathcal{V}_i$ to $\mathcal{V}_j$ then the number of Y decreases by 1 in $\mathcal{V}_i$ ($\mu_{ij,i} = -1$) and the number of Y in $\mathcal{V}_j$ increases by 1 ($\mu_{ij,j} = 1$). All other copy numbers are constant. Molecules in $\mathcal{V}_i$ sharing a part of the boundary $\mathcal{V}_{ib}$ with Ω cannot jump across $\mathcal{V}_{ib}$.

There is a system of ordinary differential equations (ODEs) for the mean values $\bar{y}_i(t)$ [42, 43, 44]

$$\frac{d\bar{y}_i}{dt} = \sum_{k=1}^N \sum_{j=1}^N \mu_{kj,i} v_{kj}(\bar{\mathbf{y}}) = \sum_{j=1}^N \mu_{ji,i} \lambda_{ji} \bar{y}_j + \sum_{j=1}^N \mu_{ij,i} \lambda_{ij} \bar{y}_i = \sum_{j=1}^N \lambda_{ij} \bar{y}_j - \bar{y}_i \sum_{j=1}^N \lambda_{ij}, \quad i=1, \dots, N. \quad (4)$$

This equation is exact since the propensity v_{kj} is linear. The concentrations of the mean values $c_i = \bar{y}_i/V_i$ satisfy

$$\frac{dc_i}{dt} = \sum_{j=1}^N \frac{V_j}{V_i} \lambda_{ji} c_j - c_i \sum_{j=1}^N \lambda_{ij}, \quad i=1, \dots, N. \quad (5)$$

2.2. Discretization of the diffusion equation

At the macroscopic level, the diffusion equation governs the concentrations of the species $\varphi(\mathbf{x}, t)$

$$\frac{\partial \phi}{\partial t} = \gamma \Delta \phi, \mathbf{x} \in \Omega, \quad (6)$$

with the diffusion coefficient γ . The boundary condition at Ω with normal $\mathbf{n}$ is a Neumann condition $\mathbf{n} \cdot \nabla \phi = 0$. Discretize the space derivatives by a FEM as in [15] or a FVM on an unstructured mesh defined by the voxels $\mathcal{V}_i$ with a node or vertex $\mathbf{x}_i$ in the center. The

primary mesh consists of triangles in 2D and tetrahedra in 3D. The secondary or dual mesh is in 2D defined by the bisectors of the triangles as in Fig. 1(b). An edge $\mathbf{e}_{ij}$ will always cross the boundary between $\mathcal{V}_i$ and $\mathcal{V}_j$. The dual mesh is defined in a similar manner in 3D, see e.g. [45]. Let the concentration of the species be ϕ_i in $\mathcal{V}_i$. Then ϕ is the solution of the system of ODEs

$$\frac{d\phi_i}{dt} = \sum_{j=1}^N \gamma D_{ij} \phi_j = \sum_{j=1, j \neq i}^N \gamma D_{ij} \phi_j - \gamma D_{ii} \phi_i, \quad i=1, \dots, N, \quad (7)$$

where

$$\mathbf{D} = \mathbf{A}^{-1} \mathbf{S}, \quad D_{ii} = - \sum_{j \neq i} D_{ij}, \quad \mathbf{A} = \text{diag}(A_{ii}). \quad (8)$$

With a FDM on a Cartesian mesh, $\mathbf{A} = \mathbf{I}$ and $\mathbf{S}\phi$ approximates the Laplacian in the voxels. The coefficients on a Cartesian mesh are defined by FDM, FEM, and FVM and compared in [38].

Let the boundary $\mathcal{V}_i$ consist of several straight segments $\mathcal{V}_{ij}, j = 1, \dots, n_i$, of length $|\mathcal{V}_{ij}|$ with normal $\mathbf{n}_{ij}$ of unit length, see Fig. 1(a). A straightforward finite volume approximation of the Laplacian at $\mathbf{x}_i$ is then

$$\frac{1}{V_i} \int_{\mathcal{V}_i} \Delta \phi dv = \frac{1}{V_i} \int_{\partial \mathcal{V}_i} \mathbf{n} \cdot \nabla \phi ds \approx \frac{1}{V_i} \sum_{j=1}^{n_i} \mathbf{n}_{ij} \cdot \mathbf{e}_{ij} (\phi_j - \phi_i) \frac{|\partial \mathcal{V}_{ij}|}{\|\mathbf{e}_{ij}\|^2}. \quad (9)$$

In (8), A_{ii} is then equal to V_i and $\mathbf{S}\phi$ approximates the fluxes across $\mathcal{V}_i$. The element $S_{ij} = \mathbf{n}_{ij} \cdot \mathbf{e}_{ij} |\mathcal{V}_{ij}| / \|\mathbf{e}_{ij}\|^2$ in the stiffness matrix is always non-negative. In a Voronoi mesh, $\mathbf{e}_{ij}$ and $\mathbf{n}_{ij}$ are parallel and the approximation (9) is consistent with ϕ , [46, 47]. This is not necessarily the case on a general mesh. Much more complicated coefficients are then needed in 2D [26, 27] depending on the solution ϕ which are difficult to generalize to 3D. The FVM in [17] is cell centered while it is vertex centered in (9).

Linear Lagrangean test and basis functions $\psi_i(\mathbf{x})$ are used in [15] to derive jump coefficients with FEM for the diffusion in a general unstructured mesh defined by a triangle in 2D and by tetrahedra in 3D as in Fig. 1(b). The subdomain ω_i is the union of the triangles or tetrahedra with a corner at $\mathbf{x}_i$. The basis function ψ_i is linear in each triangle or tetrahedron and vanishes outside ω_i . The voxels $\mathcal{V}_i$ consist of the mesh cells in the dual mesh and $\mathcal{V}_i \subset \omega_i$. The matrix $\mathbf{A}$ is defined by lumping the mass matrix $\mathbf{M}$. The components of $\mathbf{A}$ and the stiffness matrix $\mathbf{S}$ are:

$$A_{ii} = V_i, \quad S_{ij} = - \int_{\omega_i} \nabla \psi_i \cdot \nabla \psi_j dv, \quad S_{ii} = - \sum_j S_{ij} \leq 0. \quad (10)$$

In 2D,

$$S_{ij} = \sin(\varphi + \theta) / (2 \sin(\varphi) \sin(\theta)) \quad (11)$$

where the angles φ and θ are opposing edge $\mathbf{e}_{ij}$ between $\mathbf{x}_i$ and $\mathbf{x}_j$ [29], see Fig. 1(b). If φ and θ are too large such that $\varphi + \theta > \pi$, then $S_{ij} < 0$ and there is no interpretation of S_{ij}/V_i as a conditional probability. A 2D mesh generator usually avoids such angles in the triangles [34] but the condition in 3D on the angles for $S_{ij} \geq 0$ in [29] is more difficult to satisfy in practice [48]. The FEM based on mass lumping is consistent with the Laplacian in the sense that the solution converges in the L_2 -norm as $\mathcal{O}(h^2)$ where h is a measure of the length of an edge [49, p. 240].

In 1D with the distances Δx_{i-1} and Δx_i between three consecutive nodes x_{i-1} , x_i , and x_{i+1} , the simplest finite difference approximation of u'' is

$$u'' \approx \frac{2}{\Delta x_{i-1}(\Delta x_{i-1} + \Delta x_i)} u_{i-1} - \frac{2}{\Delta x_{i-1} \Delta x_i} u_i + \frac{2}{\Delta x_i(\Delta x_{i-1} + \Delta x_i)} u_{i+1}. \quad (12)$$

The approximation is the same with hat functions as basis and test functions in FEM and in a FVM with a voxel boundary between $\mathcal{V}_{i-1}$ and $\mathcal{V}_i$ at $(x_{i-1} + x_i)/2$ as in [50].

For the concentrations of the mean values c_i in (5) to be equal to the macroscopic concentrations φ_i in (7) we let

$$\lambda_{ji} = \gamma \frac{V_i}{V_j} D_{ij} = \gamma \frac{V_i}{V_j} \frac{S_{ij}}{A_{ii}}. \quad (13)$$

In the case of the FVM in (9) and the FEM in (10) the jump coefficient in (1) is

$$\lambda_{ji} = \gamma \frac{S_{ij}}{V_j} = \gamma \frac{S_{ji}}{V_j}, \quad (14)$$

since $\mathbf{S}$ is symmetric.

It seems to be difficult to combine the following properties of a discretization on a general unstructured mesh:

1. Consistency for the Laplacian,
2. The discrete maximum principle,
3. A linear formula,

see e.g. [24, 25, 26, 27, 28, 29]. It is shown in [51] that it is impossible on a quadrilateral mesh in 2D to fulfill all conditions by a scheme. We therefore give up consistency in Section 3 and derive the jump coefficients from the expected first exit time for a molecule leaving a domain instead. This is another property of stochastic diffusion and is an important characteristic in biological models.

2.3. The Stochastic Simulation Algorithm

The dimension of the domain of the DME in (3) is the number of voxels N which may be large. Since the diffusion propensity is linear, the analytical solution can be expressed in convolutions of basic Poisson and multinomial distributions [52] but the solution would be very complicated to compute. Instead, trajectories of the system are generated by the Stochastic Simulation Algorithm (SSA) by Gillespie [9]. The original algorithm was developed for a well stirred system with only reactions. The time to the next reaction is sampled from the cumulative distribution function (CDF) of the exponential distribution. The algorithm is extended to spatially dependent problems with diffusion in the next subvolume method (NSM) [12]. The events in a diffusive system up to the final time T are simulated as follows.

1. Initialize the number of molecules y_k , $k = 1, \dots, N$, in the N voxels at $t = 0$.
2. Sample the exponentially distributed time t_k with rate $\lambda_k y_k$ to the first diffusion event in all N voxels.
3. Let $i = \operatorname{argmin}\{t_k, k = 1, \dots, N\}$. If $t_i \geq T$ then continue otherwise **stop**.
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 $t := t_i$, y_i and y_j . Sample t_i and t_j and recompute $t_i = t + t_i$ and $t_j = t + t_j$. Go to 3.

Reactions are included by also introducing reaction events in the voxels with rates depending on the copy numbers in the voxels, see e.g. [12]. The time to the next event is sampled as in step 3 above and the type of event is sampled as in step 4.

3. First exit times

We determine the jump coefficients in (1) by computing the first exit time locally from a subdomain ω of Ω or globally from the whole domain of interest. To model the speed of diffusion correctly is of importance in biological models, e.g. where it is critical to determine the time it takes for a molecule in the interior to reach the cell membrane. The notation is restricted to 2D problems for simplicity but it can easily be extended to 3D.

3.1. General relations for first exit times

A molecule moves by Brownian motion and a diffusion constant γ in the cell, represented by the domain Ω with boundary $\partial\Omega$. Let T , T_ω , and $\mathbf{X}$ be random variables. The first exit time for the molecule starting at $\mathbf{x}$ in Ω is $T(\mathbf{x})$. Let ω be a subdomain or protective domain in Ω , $\omega \subseteq \Omega$, with boundary $\partial\omega$, see Fig. 2(a). The first time for a molecule initially at $\mathbf{x}_0 \in \omega$ at $t = 0$ to reach $\partial\omega$ is $T_\omega(\mathbf{x}_0)$. If the molecule leaves ω at $\mathbf{X}(\mathbf{x}_0)$ then the total time to reach $\partial\Omega$ in two steps, first from $\mathbf{x}_0$ to $\mathbf{X}(\mathbf{x}_0)$ and then from $\mathbf{X}(\mathbf{x}_0)$ to $\partial\Omega$ (cf. Fig. 2a) is

$$T(\mathbf{x}_0) = T_\omega(\mathbf{x}_0) + T(\mathbf{X}(\mathbf{x}_0)). \quad (15)$$

Let $\mathbf{x}_0$ be the initial position in ω and the molecule is known to exit ω at time t . Then the probability that the molecule exits at point $\mathbf{x} \in \partial\omega$ conditioned on the starting position $\mathbf{x}_0$

and the exit time being t , is denoted by $p(\mathbf{x}|\mathbf{x}_0, t) = j(\mathbf{x}, \mathbf{x}_0, t)$. Let $\mathbf{x}(s)$, $s \in [0, S]$, be the coordinates of the boundary ω of Ω . Since $p(\mathbf{x}|\mathbf{x}_0, t)$ is a PDF, we have $\int_{\omega} j(\mathbf{x}(s), \mathbf{x}_0, t) ds = 1$, for every $\mathbf{x}_0$ and a given exit time t . The probability that a molecule starting at $\mathbf{x}_0$ exits ω at time t is $p_{\omega}(t|\mathbf{x}_0)$, the local exit time PDF. The global exit time PDF out of Ω is denoted by $p_{\Omega}(t|\mathbf{x}_0)$. The expected first exit time from Ω and from ω starting at $\mathbf{x}$ are denoted by $E(\mathbf{x}) = E[T(\mathbf{x})]$ and $e(\mathbf{x}) = E[T_{\omega}(\mathbf{x})]$, respectively, and the probability to exit ω at $\mathbf{x}$ and t is $p_1(\mathbf{x}(s), t|\mathbf{x}_0)$ where

$$p_1(\mathbf{x}(s), t|\mathbf{x}_0) = p(\mathbf{x}|\mathbf{x}_0, t) p_{\omega}(t|\mathbf{x}_0). \quad (16)$$

The PDF $p_2(\mathbf{x}(s)|\mathbf{x}_0)$ for the probability that the molecule leaves ω at $\mathbf{x}(s)$ given that it started at $\mathbf{x}_0$ is

$$p_2(\mathbf{x}(s)|\mathbf{x}_0) = \int_0^{\infty} p_1(\mathbf{x}(s), t|\mathbf{x}_0) dt. \quad (17)$$

The PDF for the remaining time τ when the molecule hits the boundary Ω after passing through ω is then

$$p_3(\tau|\mathbf{x}_0) = \int_{\partial\omega} p_{\Omega}(\tau|\mathbf{x}(s)) p_2(\mathbf{x}(s)|\mathbf{x}_0) ds, \quad (18)$$

with the expected value

$$E[T(\mathbf{X}(\mathbf{x}_0))] = \int_0^{\infty} \tau p_3(\tau|\mathbf{x}_0) d\tau. \quad (19)$$

Then by conditioning on the first step and (16), (17), (18), and (19), the relation between $E(\mathbf{x}_0)$ and $e(\mathbf{x}_0)$ is by (15)

$$E(\mathbf{x}_0) = e(\mathbf{x}_0) + E[T(\mathbf{X}(\mathbf{x}_0))] = e(\mathbf{x}_0) + \int_0^{\infty} \int_0^{\infty} \int_{\partial\omega} \tau p_{\Omega}(\tau|\mathbf{x}(s)) p(\mathbf{x}(s)|\mathbf{x}_0, t) p_{\omega}(t|\mathbf{x}_0) ds dt d\tau = e(\mathbf{x}_0) + \int_{\partial\omega} \int_0^{\infty} \tau p_{\Omega}(\tau|\mathbf{x}(s)) \int_0^{\infty} j(\mathbf{x}(s), \mathbf{x}_0, t) dt ds, \quad (20)$$

where

$$e(\mathbf{x}_0) = \int_0^{\infty} t p_{\omega}(t|\mathbf{x}_0) dt, \quad E^s[j(\mathbf{x}(s), \mathbf{x}_0, \cdot)] = \int_0^{\infty} j(\mathbf{x}(s), \mathbf{x}_0, t) p_{\omega}(t|\mathbf{x}_0) dt.$$

To work with discrete meshes we let the boundary ω be defined by the nodes $\mathbf{x}_i$, $i = 1, \dots, n_0$, adjacent to $\mathbf{x}_0$. The nodes can be determined by a triangular mesh in 2D where $\mathbf{x}_0$ and $\mathbf{x}_i$ are connected by an edge $\mathbf{e}_{0i}$. Then a polygonal boundary ω is obtained by letting ω consist of the edges $\mathbf{e}_{i,i+1}$ between the nodes $\mathbf{x}_i$ and $\mathbf{x}_{i+1}$, $i = 1, \dots, n_0 - 1$, and $\mathbf{e}_{n_0,1}$, see Fig. 2(b) with $n_0 = 6$. If $\omega = \Omega$, then $E(\mathbf{x}(s)) = 0$ in (20) and $E(\mathbf{x}_0) = e(\mathbf{x}_0)$.

An approximation of the integral over ω in the last expression of (20) is necessary.

Introduce s_i and $s_{i\pm 1/2}$ such that $\mathbf{x}(s_i) = \mathbf{x}_i$, $\mathbf{x}(s_{i-1/2}) = \frac{1}{2}(\mathbf{x}_{i-1} + \mathbf{x}_i)$, and

$\mathbf{x}(s_{i+1/2}) = \frac{1}{2}(\mathbf{x}_i + \mathbf{x}_{i+1})$. The expected value $E(\mathbf{x}(s))$ is approximated by $\tilde{E}(\mathbf{x}(s))$ on ω . Using an indicator function χ_i , $\tilde{E}(\mathbf{x}(s))$ is piecewise constant as follows

$$\tilde{E}(\mathbf{x}(s)) = \sum_{i=1}^{n_0} E(\mathbf{x}_i) \chi_i(s), \quad \chi_i(s) = \begin{cases} 1, & s \in [s_{i-1/2}, s_{i+1/2}], \\ 0, & \text{otherwise.} \end{cases} \quad (21)$$

Let the temporal mean value of j be denoted by

$$\bar{j}_0(\mathbf{x}(s)) = E^s[j(\mathbf{x}(s), \mathbf{x}_0, \cdot)]. \quad (22)$$

Then the integral over ω in (20) is

$$\begin{aligned} E[T(\mathbf{X}(\mathbf{x}_0))] &\approx \int_{\partial\omega} \tilde{E}(\mathbf{x}(s)) \bar{j}_0(\mathbf{x}(s)) ds \\ &= \int_{\partial\omega} \sum_{i=1}^{n_0} E(\mathbf{x}_i) \chi_i(s) \bar{j}_0(\mathbf{x}(s)) ds \\ &= \sum_{i=1}^{n_0} E(\mathbf{x}_i) \int_{s_{i-1/2}}^{s_{i+1/2}} \bar{j}_0(\mathbf{x}(s)) ds \\ &= \sum_{i=1}^{n_0} E(\mathbf{x}_i) \bar{j}_{0i}, \quad \bar{j}_{0i} \\ &= \int_{s_{i-1/2}}^{s_{i+1/2}} \bar{j}_0(\mathbf{x}(s)) ds. \end{aligned} \quad (23)$$

An interpretation of $\bar{j}_{0i}$ is that it is the probability to exit through the section $\omega_i = [x(s_{i-1/2}), x_i, x(s_{i+1/2})]$ of $\partial\omega = \bigcup_{j=1}^{n_0} \partial\omega_j$, see Fig. 2(b).

The error ε in the approximation with $\tilde{E}$ in (23) compared to the last integral in (20) is

$$\varepsilon = \int_{\partial\omega} (E(\mathbf{x}(s)) - \tilde{E}(\mathbf{x}(s))) \bar{j}_0(\mathbf{x}(s)) ds, \quad k=1, 2. \quad (24)$$

The error in (24) is of $\mathcal{O}(\Delta s)$ if Δs is the maximum length of an interval $[s_{i-1/2}, s_{i+1/2}]$. This is shown in the following way. Since $E(\mathbf{x}(s))$ and $j(\mathbf{x}(s), \mathbf{x}_0, t)$ are continuous on ω but in general have a jump in the derivative along s at the corners $\mathbf{x}(s_i) = \mathbf{x}_i$ of ω , the integral on the interval $S_i = [s_i, s_{i+1/2}]$ can be written

$$\int_{S_i} E(\mathbf{x}(s)) \bar{j}_0(\mathbf{x}(s)) ds = E(\mathbf{x}_i) \int_{S_i} \bar{j}_0(\mathbf{x}(s)) ds + E'_{i+} \int_{S_i} (s - s_i) \bar{j}_0(\mathbf{x}(s)) ds + \mathcal{O}(\Delta s^3). \quad (25)$$

The derivatives of $E(\mathbf{x}(s))$ to the left and right of s_i are denoted by E'_{i-} and E'_{i+} , respectively. A bound on the contribution to the error term in (23) on S_i is then to leading order

$$\left| E'_{i+} \int_{s_i} (s - s_i) \bar{j}_0(\mathbf{x}(s)) ds \right| \leq |E'_{i+}| \max_{s \in S_i} \bar{j}_0(\mathbf{x}(s)) \frac{(s_{i+1/2} - s_i)^2}{2}. \quad (26)$$

A similar bound is valid for the interval $[s_{i-1/2}, s_i]$. Since

$$|\varepsilon| \leq \max_{s \in [0, S]} \bar{j}_0(\mathbf{x}(s)) \sum_{i=1}^n \max\{|E'_{i-}|, |E'_{i+}|\} \Delta s^2 \leq C_1 \Delta s,$$

ε is bounded by $C_1 \Delta s$ where C_1 depends on $E(\mathbf{x})$, j , and the length of ω .

In a more accurate approximation in (23) and (21), $\tilde{E}(\mathbf{x}(s))$ varies linearly between the nodes. Then one can show that the error ε is bounded by $C_2 \Delta s^2$ for some C_2 .

With the discretization of the functions on ω , the approximation in (23) and the notation $E_i = E(\mathbf{x}_i)$ and $e_0 = e(\mathbf{x}_0)$, the numerical approximation of the relation between the expected values in (20) is

$$E_0 = e_0 + \sum_{i=1}^{n_0} \bar{j}_{0i} E_i. \quad (27)$$

Note that the conditional probability $\bar{j}_{0i}$ is scaled such that the sum is 1

$$\sum_{i=1}^{n_0} \bar{j}_{0i} = \int_{\partial\omega} \bar{j}_0(\mathbf{x}(s)) ds = \int_{\partial\omega} E^s[j(\mathbf{x}(s), \mathbf{x}_0, t)] ds = E^s[1] = 1. \quad (28)$$

As above, let $E(\mathbf{x})$ denote the time it takes for a molecule starting from $\mathbf{x}$ to reach the cell membrane. If the cell is a connected domain Ω , $E(\mathbf{x})$ satisfies the following PDE, [53, Ch. 9]:

$$\begin{aligned} \gamma \Delta E(\mathbf{x}) &= -1, & \mathbf{x} \in \Omega, \\ E(\mathbf{x}) &= 0, & \mathbf{x} \in \partial\Omega. \end{aligned} \quad (29)$$

In 1D, the solution is

$$E(x) = \frac{1}{2\gamma} x(1-x), \quad x \in \Omega = [0, 1]. \quad (30)$$

Rearrange the terms in (27) as

$$\sum_{i=1}^{n_0} \frac{\bar{j}_{0i}}{e_0} E_i - \frac{1}{e_0} E_0 = \sum_{i=1}^{n_0} \frac{\bar{j}_{0i}}{e_0} (E_i - E_0) = -1, \quad (31)$$

and interpret (31) as a discretization of (29) at $\mathbf{x}_0$ in Ω . As the jump propensity from the node x_0 , λ_0 is the inverse of the expected time e_0 and the coefficients to reach a neighboring node are

$$\lambda_{0i} = \bar{j}_{0i} / e_0 = \bar{j}_{0i} \lambda_0 \text{ and } \sum_{i=1}^{n_0} \lambda_{0i} = \lambda_0 \sum_{i=1}^{n_0} \bar{j}_{0i} = \lambda_0. \quad (32)$$

In (14), the same coefficients are derived, since using different approximation techniques to numerically solve (29) or the diffusion equation (6) on a mesh covering Ω means discretizing the Laplacian. Hence, the coefficients λ_{0i} can be used to approximate both, the equations for the distribution of molecules and their exit times. Moreover, they define a discretization of the relation in (20). The errors due to the numerical discretization and the statistical error are discussed and illustrated in Sect. 4.

On an equidistant Cartesian mesh in 2D with square subdomains ω in [38], the boundary ω is defined by $\mathbf{x}_i$, $i = 1, \dots, 8$, with the step length h between $\mathbf{x}_i$, see Fig. 3(a). The coordinates $s_{1/2}$ and $s_{3/2}$ defining ω_1 around the midpoint $\mathbf{x}_1 = (x_{11}, x_{12})$ in (23) are chosen to be

$$s_{3/2} = x_{12} + \beta h, \quad s_{1/2} = x_{12} - \beta h, \quad \beta \in [0, 1]. \quad (33)$$

The other intervals ω_3 , ω_5 , and ω_7 are defined similarly and ω_2 , ω_4 , ω_6 , and ω_8 are the complementary intervals associated with the corners $\mathbf{x}_2$, $\mathbf{x}_4$, $\mathbf{x}_6$, and $\mathbf{x}_8$. We have to choose $\beta = 0.56$ for the coefficients of the first exit time approach to equal those of a second order FDM approximation of the Laplacian including the corners, resulting in:

$$\bar{j}_{0i} = \int_{s_i - \frac{1}{2}}^{s_i + \frac{1}{2}} \bar{j}_{0i}(\mathbf{x}(s)) ds = 0.2053, \quad i = 1, 3, 5, 7 \quad (34)$$

for jumps along the Cartesian axes and $\bar{j}_{0i} = 1/4 - 0.2053 = 0.0447$ for $i = 2, 4, 6, 8$, the jumps to the corners.

3.2. Local first exit time

We now want to compute the local exit time to leave voxel $\mathcal{V}_0$ and jump to a neighbor $\mathcal{V}_i$. One approach is to consider jumps between the vertices $\mathbf{x}_0$ and $\mathbf{x}_i$. The molecule has left $\mathbf{x}_0$ when it reaches any of the neighboring vertices. This defines a protective domain ω_0 , including the neighboring nodes, which the molecule has to leave for a jump away from $\mathbf{x}_0$. Depending on where it leaves ω it will jump to vertex $\mathbf{x}_i$ or another adjacent vertex. Another view is to assume that the position of the molecule is uniformly distributed first in $\mathcal{V}_0$. Then the molecule crosses the boundary $\mathcal{V}_{0i}$ to $\mathcal{V}_i$ and becomes uniformly distributed there and prepared for a new jump. The protective domains ω_0 and ω_i around $\mathcal{V}_i$ overlap but $\mathcal{V}_0 \cap \mathcal{V}_i = \emptyset$. This is illustrated in Fig. 3(a). The molecule travels at least distance h before it is recorded at the next node. It is not sufficient to leave the smaller voxel $\mathcal{V}_0$, since the molecule has then only reached the boundary between two voxels and cannot yet be

considered as well mixed in its new voxel. On an equidistant mesh in 1D with mesh size h , $\mathcal{V}_0$ is $[x_0 - h/2, x_0 + h/2]$ and ω_0 is $[x_0 - h, x_0 + h] = [x_{-1}, x_1]$.

To calculate the local exit time to leave ω and j_{0i}^- we define $c(\mathbf{x}, \mathbf{x}_0, t)$ as the probability density to find a random walker located inside an infinitesimal area at $\mathbf{x}$ in ω at time t given that he started at $\mathbf{x}_0$ at $t = 0$ and has not yet left ω . The mean value of the first exit time e_0 and the jump probabilities j_{0i}^- in (27) can be computed directly from c in ω . The PDE satisfied by c in ω is [37]

$$\frac{\partial c(\mathbf{x}, \mathbf{x}_0, t)}{\partial t} = \gamma \Delta c(\mathbf{x}, \mathbf{x}_0, t), \quad \mathbf{x} \in \omega, \quad c(\mathbf{x}, \mathbf{x}_0, t) = 0, \quad \mathbf{x} \in \partial\omega, \quad c(\mathbf{x}, \mathbf{x}_0, 0) = \delta(\mathbf{x} - \mathbf{x}_0). \quad (35)$$

The solution is non-negative by the maximum principle and $\mathbf{n} \cdot \nabla c = 0$ at $\partial\omega$ with the normal $\mathbf{n}$ directed outward from ω .

When $c > 0$ in ω , then there is a probability that the molecule has survived in ω and not reached the boundary, [19]. The survival probability for a molecule initially at $\mathbf{x}_0$ is

$$S(t) = \int_{\omega} c(\mathbf{x}, \mathbf{x}_0, t) d\omega = P(T_{\omega}(\mathbf{x}_0) \geq t), \quad (36)$$

which is the probability for the walker to exit at a time greater than t . The CDF of T_{ω} is $1 - S(t)$. Hence, the PDF for a molecule to exit at time t is given by (35) and Gauss' formula

$$p_{\omega}(t|\mathbf{x}_0) = -\frac{\partial S(t)}{\partial t} = -\int_{\omega} \gamma \Delta c d\omega = -\gamma \int_{\partial\omega} \mathbf{n} \cdot \nabla c ds \geq 0. \quad (37)$$

Since $S(t)/t \rightarrow 0$ and $S(0) = 1$, the survival probability decays monotonically as t increases. Furthermore, the expected value e_0 of the exit time is obtained from p_{ω}

$$e_0 = \int_0^{\infty} t p_{\omega}(t|\mathbf{x}_0) dt = \int_0^{\infty} S(t) dt. \quad (38)$$

Analytical solutions of (35) on ω are known only in special cases. For a general ω , e_0 is obtained from an accurate numerical solution of (35), e.g. by a FEM solution on each ω in the mesh (see Sect. 4).

Interpreting $-\gamma \nabla c \cdot \mathbf{n}$ as the flux out of the volume ω , the conditional probability that the molecule leaves ω at $\mathbf{x}$ given that the time is t is by (37)

$$j(\mathbf{x}, \mathbf{x}_0, t) = \frac{-\gamma \mathbf{n} \cdot \nabla c(\mathbf{x}, \mathbf{x}_0, t)}{p_{\omega}(t|\mathbf{x}_0)} = \frac{\mathbf{n} \cdot \nabla c(\mathbf{x}, \mathbf{x}_0, t)}{\int_{\partial\omega} \mathbf{n} \cdot \nabla c(\mathbf{s}, \mathbf{x}_0, t) ds}, \quad (39)$$

and consequently, the probability for the molecule to exit along the edge ω_i is

$$j_i(\mathbf{x}_0, t) = \int_{\partial\omega_i} j(\mathbf{x}(s), \mathbf{x}_0, t) ds = \frac{\int_{\partial\omega_i} \mathbf{n} \cdot \nabla c(\mathbf{x}(s), \mathbf{x}_0, t) ds}{\int_{\partial\omega} \mathbf{n} \cdot \nabla c(\mathbf{x}(s), \mathbf{x}_0, t) ds}. \quad (40)$$

Solving (35) and computing e_0 in (38) and the expected relative coefficients j_{0i}^- as $E[j_i(\mathbf{x}_0, \cdot)]$ in (40) (and also in (23)) is an alternative to discretizing the Laplacian as in Sect. 2.2 to determine the parameters in (27) and the jump coefficients in (32).

A standard unstructured mesh generator to discretize space will generate nodes $\mathbf{x}_i$ which are connected by edges $\mathbf{e}_{ij}$. A straightforward ω consists of line segments in 2D and flat faces in 3D defined by the nodes adjacent to the center node in ω . Then ω is a polygon in 2D and a volume bounded by polygonal surfaces in 3D. In 1D, ω is two points x_{i-1} and x_{i+1} and

$$j_{i\pm 1}(x_0, t) = \frac{\pm c_x(x_{i\pm 1}, x_0, t)}{c_x(x_{i+1}, x_0, t) - c_x(x_{i-1}, x_0, t)}, \quad c_x = \frac{\partial c}{\partial x}. \quad (41)$$

If $\mathbf{x}_0 \in \Omega$, then its ω is constructed in 2D by adding new nodes outside Ω for simulation of reflecting boundary conditions for the molecules. For each node $\mathbf{x}_i$, $i = 1, \dots, n_{0\mathcal{J}}$, in the interior of Ω and connected to $\mathbf{x}_0$ by an edge, a node $\tilde{\mathbf{x}}_i$ is created by reflection in Ω such

that $\tilde{\mathbf{x}}_i - \mathbf{x}_i$ is orthogonal to the boundary at $\bar{\mathbf{x}}_i = \frac{1}{2}(\tilde{\mathbf{x}}_i + \mathbf{x}_i) \in \partial\Omega$, and $\|\mathbf{x}_i - \mathbf{x}_i\| = \|\tilde{\mathbf{x}}_i - \mathbf{x}_i\|$. Then ω is defined by $\mathbf{x}_i$, $\tilde{\mathbf{x}}_i$, $i = 1, \dots, n_{0\mathcal{J}}$, and the two nodes $\mathbf{x}_{b1}$, $\mathbf{x}_{b2}$, on $\partial\Omega$ adjacent to $\mathbf{x}_0$, see Fig. 3(b). The jump coefficients are computed as before, but the conditional probability j_{0i}^- for a jump to an exterior node $\tilde{\mathbf{x}}_i$ is added to j_{0i}^- of the corresponding interior node $\mathbf{x}_i$. Interpreting j_{0i}^- as the coefficients in a difference formula they approximate $\mathbf{n} \cdot \nabla \varphi = 0$, the reflecting boundary condition for the distribution of molecules.

In order to obtain a continuous-time Markov chain for the diffusion jump process, we approximate the distribution of the first exit time for a molecule leaving ω via ω_i by an exponential distribution with rate λ_{0i} . Then

$$p_{\omega_i}(t|\mathbf{x}_0) \approx \tilde{p}_{\omega_i}(t|\mathbf{x}_0) = \lambda_{0i} \exp(-\lambda_{0i}t). \quad (42)$$

The total rate to exit ω is then $\lambda_0 = \sum_i^{n_0} \lambda_{0i}$ and the exit time T_ω from ω is also exponentially distributed with

$$\tilde{p}_\omega(t|\mathbf{x}_0) = \lambda_0 \exp(-\lambda_0 t). \quad (43)$$

Hence, by (37) and (38) we arrive at

$$\tilde{S}(t) = \exp(-\lambda_0 t), \quad e_0 = 1/\lambda_0. \quad (44)$$

The rate λ_{0i} to leave at node i is related to e_0 and j_{0i}^- by $\lambda_{0i} = j_{0i}^-/e_0 = j_{0i}^- \lambda_0$, cf. (32). The approximation in (43) is inherent to all Markov processes simulating diffusion, since the

exponential distribution for the next event time is the only one fulfilling the Markov property. In Sect. 4 we examine the error in the limit of large molecule numbers. We generate random numbers for the next jump time from a distribution $p_{\omega}(t|\mathbf{x}_0)$ with the same expected value λ_0 as for the exact time distribution $p_{\omega}(t|\mathbf{x}_0)$ and hence do not introduce an additional error in the first moment by the approximation in (43). The total error depends only on the statistical and the spatial discretization errors. The typical behavior of $S(t)$ and $j_i(\mathbf{x}_0, t)$ is found for a 1D problem in Fig. 4(a). Here, $S(t)$ is well approximated by a $\tilde{S}(t)$ based on the approximation in (42).

Also $j_i(\mathbf{x}_0, t)$ can be approximated by a sum including an exponential, see Fig. 4(b). Suppose that

$$j_i(\mathbf{x}_0, t) = a_i + b_i \exp(-d_i t). \quad (45)$$

Then the conditional probability j_{0i} in (23) satisfies

$$\frac{\lambda_{0i}}{\lambda_0} = \bar{j}_{0i} = \int_0^\infty (a_i + b_i \exp(-d_i t)) \tilde{p}_{\omega}(t|\mathbf{x}_0) dt = a_i + b_i \frac{1}{1 + d_i/\lambda_0}, \quad (46)$$

with the approximations in (43) and (45).

The rate λ_0 can be computed in different ways from a numerical solution of (35). Discretize (35) in time and on a mesh covering ω using e.g. a FEM and solve for c . Integrate c as in (36) to obtain $S_k = S(t_k)$ at time points t_k , $k = 0, 1, \dots, K$, with $t_0 = 0$ and $t_k = t_{k-1} + \Delta t$ for t_K sufficiently large. Then λ_0 is determined using the trapezoidal rule in (38), the linear least squares method on the logarithm of (44), or nonlinear least squares directly on (44)

1. $\lambda_0^{-1} = \int_0^\infty S(t) dt \Rightarrow \lambda_0^{-1} = \frac{\Delta t}{2} S_0 + \sum_{k=1}^{K-1} \Delta t S_k + \frac{\Delta t}{2} S_K,$
2. $\lambda_0 t_k \approx -\log S_k \Rightarrow \lambda_0 = - \sum_{k=0}^K t_k \log S_k / \sum_{k=0}^K t_k^2,$
3. $g(\lambda) = \sum_{k=0}^K (\exp(-\lambda t_k) - S_k)^2 \Rightarrow \lambda_0 = \arg \min g(\lambda).$

The approximations of j_{0i} are obtained in the same manner. Compute $j_{0i}(t_k) = j_i(\mathbf{x}_0, t_k)$ using c with a quadrature formula in (40). Let $a_i = j_{0i}(t_k)$ and $b_i = j_{0i}(t_0) - a_i$. Then d_i is calculated by fitting $\exp(-d_i t_k)$ to $(j_{0i}(t_k) - a_i)/b_i$ using linear or nonlinear least squares as above.

The approximation in (44) is necessary for using the SSA, but the approximation in (45) is only for computational reasons. Representing $j_i(\mathbf{x}_0, t)$ by the invertible function in (45) allows us to use inverse transform sampling efficiently when sampling from the time dependent distribution for a direction to jump. The alternative would be to store $j_i(\mathbf{x}_0, t_k)$ in a lookup table for discrete t_k and perform a computationally more costly search in each sampling step. When using the time independent expected value j_{0i} instead we see in experiments that the approximation in (46) is close to the exact value

$\bar{j}_{0i} = \int_0^\infty j_i(\mathbf{x}_0, t) p_\omega(t|\mathbf{x}_0) dt$ and the dominant part of the error is due to the statistics and the discretization of Ω by a mesh.

With $\omega = [x_{i-1}, x_{i+1}] = [0, h(1 + \kappa)]$, $\kappa > 0$, and $x_i = h$ in 1D, the space step to the left is h and κh to the right of x_i . The solution to (35) with $x_0 = x_i$ is

$$c(x, t) = \sum_{n=1}^{\infty} \frac{2}{h(1+\kappa)} \sin\left(\frac{n\pi}{1+\kappa}\right) \sin\left(\frac{n\pi x}{h(1+\kappa)}\right) \exp\left(-\frac{n^2 \pi^2 \gamma t}{h^2(1+\kappa)^2}\right), \quad (47)$$

the survival probability in (36) is

$$S(t) = \sum_{j=1}^{\infty} \frac{4}{(2j-1)\pi} \sin\left(\frac{(2j-1)\pi}{1+\kappa}\right) \exp\left(-\frac{(2j-1)^2 \pi^2 \gamma t}{h^2(1+\kappa)^2}\right), \quad (48)$$

and the expected exit time from ω in (38) is

$$e_i = \frac{4h^2(1+\kappa)^2}{\pi^3 \gamma} \sum_{j=1}^{\infty} \frac{1}{(2j-1)^3} \sin\left(\frac{(2j-1)\pi}{1+\kappa}\right). \quad (49)$$

In the same manner the expected relative coefficients $j_{i,i\pm 1}$ are computed from (41). Then we have

$$e_i = \frac{1}{\lambda_i} = \frac{h^2 \kappa}{2\gamma}, \quad \bar{j}_{i,i-1} = \frac{\lambda_{i,i-1}}{\lambda_i} = \frac{\kappa}{1+\kappa}, \quad \bar{j}_{i,i+1} = \frac{\lambda_{i,i+1}}{\lambda_i} = \frac{1}{1+\kappa}. \quad (50)$$

With this choice of ω the coefficients are the same as those derived from the finite difference formula in (12), cf. [35, Ch. 16.5], [15, p. 1780]. By the Cauchy product, the equations (47)–(49) can be extended to hyperrectangles in higher dimensions.

3.3. Global first exit time

Another possibility to determine the diffusion jump rates is to use the triangular mesh in 2D or a tetrahedral mesh in 3D on Ω and first solve (29) with Dirichlet boundary conditions for E by the FEM on that mesh with linear Lagrangean basis functions $\psi_i(\mathbf{x})$ as in Sect. 2.2. The subvolume ω_i surrounding the node $\mathbf{x}_i$ as in Sect. 3.2 is where $\psi_i = 0$. At $\mathbf{x}_i$ the solution E_i satisfies the discretization (31). Compared to the analytical solution $E(\mathbf{x})$ of (29), the error in E_i is of $\mathcal{O}(\delta^2)$ where δ is the maximum length of an edge in the mesh. Let $a_{ij} = \gamma \mathcal{S}_{ij}/V_i$ be determined by the Laplacian in the interior of Ω and homogeneous Neumann conditions at Ω and use that $\int_{\Omega} \psi_i d\Omega = \int_{\omega_i} \psi_i d\Omega = V_i$, as in [15] and Sect. 2.2. Assume that $\mathbf{x}_i$ is connected by edges to n_i vertices $\mathbf{x}_j$, that $i \in \mathcal{I}$ if the node is in the interior of Ω and that $i \in \mathcal{B}$ if $\mathbf{x}_i \in \partial\Omega$. The set of all nodes is $\mathcal{N} = \{1, \dots, N\} = \mathcal{I} \cup \mathcal{B}$. If $\mathbf{x}_i$ is in the interior of Ω then we have

$$\sum_{j=1}^{n_i} \alpha_{ij} (E_j - E_i) = -1, \quad i \in \mathcal{I}. \quad (51)$$

If $i \in \mathcal{B}$ then there is no relation (51) for E_j but the coefficients α_{ij} are defined by the Neumann condition at Ω and

$$\sum_{j=1}^{n_i} \alpha_{ij} (E_j - E_i) = \sum_{j=1}^{n_i} \alpha_{ij} E_j = \eta_i, \quad i \in \mathcal{B}, \quad (52)$$

since $E_i = 0$ if $i \in \mathcal{B}$, see (29). If $\alpha_{ij} = 0$ and the discrete maximum principle is satisfied at Ω , then $E_j > 0$ and we have $\eta_i > 0$, for $i \in \mathcal{B}$.

Some of the α -coefficients may be negative if the mesh is of insufficient quality. In this case we choose λ_{ij} close to α_{ij} satisfying (51) in the interior, (52) on the boundary and $\lambda_{ij} = 0$. If the coefficients α_{ij} are non-negative we use them as the jump coefficients. This is accomplished by letting λ_{ij} solve the quadratic programming (QP) problem for each node $\mathbf{x}_i$, $i \in \mathcal{N}$,

$$\min_{\lambda_{ij}} \sum_{j=1}^{n_i} (\lambda_{ij} - \alpha_{ij})^2, \quad \sum_{j=1}^{n_i} \lambda_{ij} (E_j - E_i) = \eta_i, \quad \lambda_{ij} \geq 0, \quad j=1, \dots, n_i, \quad (53)$$

where $\eta_i = -1$ for $i \in \mathcal{I}$. The equality constraint is such that, locally at $\mathbf{x}_i$, the numerical approximation of (20) in (31) is satisfied. Using the vectors $\boldsymbol{\lambda}$, $\boldsymbol{\alpha}$, and $\boldsymbol{\beta}$ with $\beta_j = E_j - E_i$, the equivalent QP problem is

$$\min_{\boldsymbol{\lambda}} \boldsymbol{\lambda}^T \boldsymbol{\lambda} - 2\boldsymbol{\alpha}^T \boldsymbol{\lambda}, \quad \boldsymbol{\beta}^T \boldsymbol{\lambda} = \eta_i, \quad \boldsymbol{\lambda} \geq 0. \quad (54)$$

If $\mathbf{u} = 0$ for a general vector $\mathbf{u}$, then $u_i = 0$ for all components. If $\boldsymbol{\alpha} = 0$ then $\boldsymbol{\lambda} = \boldsymbol{\alpha}$ is the solution of (53) or (54) since both the minimum of the objective function is achieved and the constraints are satisfied. The coefficients λ_{ij} define a system of linear equations

$$\mathbf{A}\mathbf{E} = \boldsymbol{\eta}, \quad (55)$$

where $A_{ij} = \lambda_{ij}$. The solution $\mathbf{E}$ is an approximation to E in (29) and also solves (55) with $A_{ij} = \alpha_{ij}$ in (51). The approximation of the Laplacian with $A_{ij} = \lambda_{ij}$ in (55) is not consistent but it is chosen such that the exit times are well approximated.

An alternative to solve (54) is to choose the simpler QP problem

$$\min_{\boldsymbol{\mu}} \boldsymbol{\mu}^T \boldsymbol{\mu} - 2\boldsymbol{\alpha}^T \boldsymbol{\mu}, \quad \boldsymbol{\mu} \geq 0. \quad (56)$$

The optimal solution in (56) is

$$\mu_j = \max(\alpha_j, 0). \quad (57)$$

The solution is non-negative and is the choice in [15]. One small QP problem in (54) or (56) is solved for every node $\mathbf{x}_i$ to find the jump coefficients λ_{ij} there.

The λ -coefficients are determined in (54) by an orthogonal projection of α on the subspace defined by the equality and the non-negativity constraints. The equality constraint is added in the interior of Ω to ensure that taking λ as the coefficients in a discretization of the Laplacian yields a good approximation for the global exit time problem in (29) but regarded as such a discretization it is in general not consistent if some $\alpha_j < 0$.

The constraint set $\mathcal{F}_i = \{\lambda | \beta^T \lambda = \eta_i, \lambda \geq 0\}$ in (54) is convex and polyhedral and the objective function is bounded from below. Hence, if $\mathcal{F}_i \neq \emptyset$ then the QP problem has a unique solution.

In order to investigate if the feasible set $\mathcal{F}_i$ is empty or not consider two cases with $\eta_i < 0$ and $\eta_i > 0$. If $\eta_i < 0$ e.g. for $i \in \mathcal{I}$ and there is at least one $\beta_k = E_k - E_i < 0$, then there is one positive $\lambda_k = \eta_i / \beta_k$ and $\mathcal{F}_i$ is not empty. On the other hand, if $i \in \mathcal{I}$ and $\beta \geq 0$ then there is no feasible solution. This is possible in spite of $\alpha^T \beta = -1$ in (51) if at least one $\alpha_k < 0$. If $\beta \geq 0$ then E_i is a local minimum and the solution is not satisfying the discrete maximum principle. Let $i \in \mathcal{B}$ with $\eta_i > 0$. Then there is a $\lambda \geq 0$ and $\mathcal{F}_i \neq \emptyset$ if and only if at least one $\beta_k > 0$, i.e. $E_k > 0$ and the discrete maximum principle holds at least locally since $E_i = 0$. The case with $\eta_i < 0$ and $i \in \mathcal{B}$ is treated in the same way as for $i \in \mathcal{I}$ above. If $\mathcal{F}_i = \emptyset$ then the rate coefficients are chosen as in (56) without the equality constraint to ensure that a λ is always found.

By adding the inequality constraints on μ in (56) the difference between μ and α is the vector $\delta\mu$ with elements $\delta\mu_j = \mu_j - \alpha_j = |\min(0, \alpha_j)|$. When the equality constraint is added on λ in (54) a bound for the difference $\|\lambda - \mu\|$ is derived in the following proposition.

Proposition. Assume that $\mathcal{F}_i \neq \emptyset$. Let the solutions to (54) and (56) be λ and μ . Introduce the sets $\mathcal{J}_1 = \{j | \lambda_j = 0\}$, $\mathcal{J}_2 = \{j | \mu_j = 0\}$, and $\mathcal{J} = \mathcal{J}_1 \cup \mathcal{J}_2$ with k elements in $\mathcal{J}$. The n elements in β are ordered such that the k components in $\mathcal{J}$ appear first in β such that

$$\beta = \begin{pmatrix} \beta_k \\ \beta_{n-k} \end{pmatrix}, \beta_k \in \mathbb{R}^k, \beta_{n-k} \in \mathbb{R}^{n-k}.$$

Assume that $k < n$ and $\beta_{n-k} \geq 0$. Then the difference between λ solving the QP with the additional equality constraint and μ is

$$\|\lambda - \mu\| \leq \left(1 + \frac{\|\beta_k\|}{\|\beta_{n-k}\|}\right) \|\delta\|. \quad (58)$$

where

$$\delta_i = |\min(0, \alpha_i)|.$$

Proof. The solution $\boldsymbol{\mu} = \boldsymbol{\alpha} + \boldsymbol{\delta}$ also satisfies

$$\min_{\boldsymbol{\mu}} \boldsymbol{\mu}^T \boldsymbol{\mu} - 2\boldsymbol{\alpha}^T \boldsymbol{\mu}, \boldsymbol{\beta}^T \boldsymbol{\mu} = \boldsymbol{\beta}^T \boldsymbol{\alpha} + \boldsymbol{\beta}^T \boldsymbol{\delta} = \eta + \boldsymbol{\beta}^T \boldsymbol{\delta}, \boldsymbol{\mu} \geq 0. \quad (59)$$

We will compare the solutions to (54) and (59) using [54].

Introduce $\mathbf{D}_0 \in \mathbb{R}^{(k+1) \times n}$, $\mathbf{d}_0 \in \mathbb{R}^{k+1}$, and the identity matrix $\mathbf{I}_k \in \mathbb{R}^{k \times k}$ in

$$\mathbf{D}_0 = \begin{pmatrix} \mathbf{I}_k & 0 \\ \boldsymbol{\beta}_k^T & \boldsymbol{\beta}_{n-k}^T \end{pmatrix}, \mathbf{d}_0 = \begin{pmatrix} 0 \\ -\boldsymbol{\beta}^T \boldsymbol{\delta} \end{pmatrix}.$$

If $\boldsymbol{\beta}_{n-k} \neq 0$ then $\mathbf{D}_0$ has full row rank and its generalized inverse $\mathbf{D}_0^+$ and $\mathbf{D}_0^+ \mathbf{d}_0$ are defined by

$$\mathbf{D}_0^+ = \mathbf{D}_0^T (\mathbf{D}_0 \mathbf{D}_0^T)^{-1} = \begin{pmatrix} \mathbf{I}_k & 0 \\ -\xi \boldsymbol{\beta}_{n-k} \boldsymbol{\beta}_k^T & \xi \boldsymbol{\beta}_{n-k} \end{pmatrix}, \mathbf{D}_0^+ \mathbf{d}_0 = \begin{pmatrix} 0 \\ -\xi \boldsymbol{\beta}_{n-k} \boldsymbol{\beta}^T \boldsymbol{\delta} \end{pmatrix},$$

with $\xi = 1/\|\boldsymbol{\beta}_{n-k}\|^2$. Then using (3.4) and (3.11) in [54] we conclude that

$$\|\boldsymbol{\lambda} - \boldsymbol{\mu}\| \leq \|\mathbf{D}_0^+ \mathbf{d}_0\| = \xi |\boldsymbol{\beta}^T \boldsymbol{\delta}| \|\boldsymbol{\beta}_{n-k}\| = \frac{|\boldsymbol{\beta}^T \boldsymbol{\delta}|}{\|\boldsymbol{\beta}_{n-k}\|} \leq \left(1 + \frac{\|\boldsymbol{\beta}_k\|}{\|\boldsymbol{\beta}_{n-k}\|}\right) \|\boldsymbol{\delta}\|,$$

and the proposition is proved.

Remark 1. It follows from the proposition that when $k = 0$ then $\boldsymbol{\lambda} = \boldsymbol{\mu}$, i.e. the equality constraint has not changed the solution and $\boldsymbol{\alpha} = \boldsymbol{\lambda} = \boldsymbol{\mu}$. The most common case is that k is small, e.g. $k = 1$. Then $\|\boldsymbol{\beta}_k\|/\|\boldsymbol{\beta}_{n-k}\|$ is often small and the change in the solution is approximately $\|\boldsymbol{\delta}\|$.

Remark 2. How restrictive are the assumptions $k < n$ and $\boldsymbol{\beta}_{n-k} \neq 0$? All inequality constraints are satisfied as equalities when $k = n$: either $\lambda_i = 0$ or $\mu_i = 0$ or $\lambda_i = \mu_i = 0$ for every i . As we are minimizing the distance between $\boldsymbol{\alpha}$ and $\boldsymbol{\mu}$ or $\boldsymbol{\lambda}$, λ_i is 0 only when $\mu_i = 0$ except for special cases. Hence, for $k = n$ with $\mu_i = 0$ for every i implies that the original stiffness matrix contained a row $\boldsymbol{\alpha}$ with only non-positive entries on the off-diagonal. Since $S_{ii} = -\sum_{j \neq i} a_{ij} \geq 0$ in (10) this is possible only if $a_{ij} = 0$ for all j which is a singular discretization. Then consider $k = 1$ with $\boldsymbol{\beta}_{n-1} = 0$ and two cases $\lambda_1 = 0$ and $\mu_1 = 0$. When $\lambda_1 = 0$ then $\lambda_j > 0, j = 2, \dots, n$. Then $\boldsymbol{\beta}^T \boldsymbol{\lambda} = 0$ and $\boldsymbol{\lambda}$ is not feasible for interior nodes and $\mathcal{F}_i = \emptyset$. Suppose that $\mu_1 = 0$. Then $a_1 = 0$ and $\mu_j = a_j, j = 2, \dots, n$. Since $\boldsymbol{\beta}^T \boldsymbol{\alpha} = \beta_1 a_1 = -1$ in the

interior, we have that $\beta_1 > 0$ but $\beta_1 \lambda_1 = 0$ and λ is not feasible. Hence, $\beta_{n-1} = 0$ in the interior and the sufficient condition is satisfied when $k = 1$.

Suppose that $\phi + \theta = \pi + \nu$ with $\nu > 0$ in a triangular mesh as in Fig. 1(b) in Sect. 2.2. Then the FEM jump coefficient along the edge $\mathbf{e}_{ij}$ in (11) and (14) is given by

$$(\alpha_j = \gamma S_{ij} / V_j = -\gamma \sin(\nu) / (2V_j \sin(\varphi) \sin(\theta)) < 0,$$

which is small for small ν .

Since

$$\|\lambda - \alpha\| \leq \|\lambda - \mu\| + \|\mu - \alpha\| \leq 2 \left(1 + \frac{\|\beta_k\|}{\|\beta_{n-k}\|} \right) \|\delta\|,$$

the conclusion is that small negative α_i will introduce only small changes in λ compared to α . By adding the equality constraint in (54) the error changes by a factor $2(1 + \|\beta_k\|/\|\beta_{n-k}\|)$. So if $\|\beta_k\|/\|\beta_{n-k}\|$ is large then the best choice may be to solve (56) and take $\lambda = \mu$.

Suitable other linear equality constraints in (54) are likely to improve the quality of λ , too, but there may be no non-negative λ satisfying the extended constraints. As an example consider the consistency conditions for a FDM approximating the Laplacian in 2D. The Taylor expansion of E_j at $\mathbf{x}_j = \mathbf{x}_i + (h_{xj}, h_{yj})$, $j = 1, \dots, n_i$, is

$$E_j = E_i + h_{xj} E_x + h_{yj} E_y + 0.5 E_{xx} h_{xj}^2 + E_{xy} h_{xj} h_{yj} + 0.5 E_{yy} h_{yj}^2 + \mathcal{O}(h_j^3),$$

where E_x, E_y, E_{xx}, E_{xy} , and E_{yy} are the first and second derivatives of E about $\mathbf{x}_i$ and $h_j = \max(h_{xj}, h_{yj})$. Then the consistency conditions on λ_{ij} are

$$\sum_j^{n_i} \lambda_{ij} h_{xj} = 0, \quad \sum_j^{n_i} \lambda_{ij} h_{yj} = 0, \quad (60a)$$

$$\sum_j^{n_i} \lambda_{ij} h_{xj}^2 = 2, \quad \sum_j^{n_i} \lambda_{ij} h_{xj} h_{yj} = 0, \quad \sum_j^{n_i} \lambda_{ij} h_{yj}^2 = 2, \quad (60b)$$

by requiring that $\sum_j \lambda_{ij} (E_j - E_i) = -E + \mathcal{O}(h_j)$. If the number of adjacent nodes to $\mathbf{x}_i$ is three, then $n_i = 3$ in (60) and it is improbable that all five equalities can be satisfied even without imposing non-negativity on λ_{ij} . When $n_i = 4$ in a Cartesian mesh a non-negative solution exists due to the symmetry in the constraints. By adding only the first two constraints in (60), a convective part is avoided in the approximation of the Laplacian. Alternatively, these two constraints can be interpreted as the Laplacian applied to a field with $E(x, y) = x$ and

$E(x, y) = y$. At least one h_{xj} and one h_{yj} must have a different sign than the other ones for a solution $\lambda > 0$ to exist. The larger n_i is the more probable it is that (60) can be satisfied by non-negative λ_{ij} . A larger n_i can be obtained by including not only the adjacent nodes connected by one edge to the center but also nodes reached via paths consisting of two edges.

4. Numerical Experiments

For the numerical experiments in 1D, 2D, and 3D in this section we choose the edges $\mathbf{e}_{jj+1}$ between the nearest neighbors $\mathbf{x}_j$ and $\mathbf{x}_{j+1}$ of a vertex $\mathbf{x}_i$ to define ω in (20) when the local first exit times (LFET) are used to generate the jump coefficients as in Sect. 3.2, see Fig. 2(b) and 9. This is the simplest way of choosing ω on an unstructured mesh. In Sect. 3.3, the non-negative diffusion coefficients are derived from the global first exit time (GFET) in (54), which we will examine in other numerical experiments in 2D and 3D. For comparison, simulations with the modified FEM coefficients in (56) and the FVM coefficients in (9) are also made. Triangular and tetrahedral meshes in 2D and 3D are generated by COMSOL Multiphysics. The placement of nodes is manipulated manually in 2D to obtain meshes of poor quality. The solutions to (35) in LFET and PDEs for comparisons are obtained by the same software. All methods are tested in stochastic simulations. In a recent paper [55] we examine the PDEs for the mean values by backward analysis and compare the solutions computed by different approximations.

4.1. Local first exit times in 1D

In the following, we simulate diffusion in 1D by using the LFET from a vertex x_i . The subdomain ω , which the molecules have to leave to be recorded at the next vertex, is the interval between the neighboring vertices x_{i-1} and x_{i+1} . The interval $\Omega = [0, 1]$ is partitioned randomly into 20 subintervals with one vertex at 0.5. Then we release $M = 10^4$ molecules at $x_0 = 0.5$ at $t = 0$ with a diffusion constant $\gamma = 10^{-3}$. The distribution of the molecules at the final time $T = 20$ is found in Fig. 5(a) and a comparison is made with the solution of the mean field equation

$$\frac{\partial \phi(\mathbf{x}, \mathbf{x}_0, t)}{\partial t} = \gamma \Delta \phi(\mathbf{x}, \mathbf{x}_0, t), \mathbf{x} \in \Omega, \frac{\partial \phi(\mathbf{x}, \mathbf{x}_0, t)}{\partial n} = 0, \mathbf{x} \in \partial\Omega, \phi(\mathbf{x}, \mathbf{x}_0, 0) = \delta(\mathbf{x} - \mathbf{x}_0). \quad (61)$$

We observe that the LFET yields a good approximation of diffusion in 1D even on a very irregular mesh. This agrees with the results from Sect. 3.2, which show that the one-dimensional first exit times reproduce the coefficients of a finite difference approximation and in [36].

The error in the concentration $\tilde{\phi}$ from the stochastic simulation of the diffusion compared to the analytical solution ϕ of (61) and the numerical solution ϕ_h of (61) is known in general to behave as

$$\|\phi - \tilde{\phi}\| \leq \|\phi - \phi_h\| + \|\phi_h - \tilde{\phi}\| = \mathcal{O}(h^2) + \mathcal{O}(M^{-\frac{1}{2}}), \quad (62)$$

where h is the maximum mesh size and M is the number of molecules in the stochastic simulation. Then φ_h converges to the analytical solution as h^2 with a standard FEM discretization and the stochastic simulation converges to the numerical approximation as $M^{-\frac{1}{2}}$ for a given $h > 0$ [56]. Convergence for φ in h is confirmed numerically in 2D for Cartesian meshes in [38] and for unstructured meshes in [15].

The convergence of the simulated exit time from the center of the interval is compared in Fig. 5(b) to the $E(x)$ satisfying (29). We discretize $[0, 1]$ with 11 equidistant vertices and release the molecules at $x_0 = 0.5$ and measure the time when they hit the boundary. The average of M trajectories is compared to the theoretical expected exit time in (30)

$$E(x_0) = \frac{1}{2\gamma} x_0(1 - x_0) = 125. \quad (63)$$

The error in Fig. 5(b) decreases as $\sim M^{-\frac{1}{2}}$ as expected for a Monte Carlo method and for the concentration in (62). The approximation in (43) is needed in all stochastic jump processes to fulfil the Markov property. The additional error due to this approximation is small in the first moment.

The discretization error $\|\varphi - \varphi_h\|$ vanishes since the approximation in (12) solves the differential equation (29) exactly.

4.2. General triangular meshes in 2D

We now want to investigate the LFET and GFET on triangular meshes in 2D. The square $[-0.5, 0.5] \times [-0.5, 0.5]$ is triangulated in two meshes, one with approximately equal edge lengths and one with a perturbed area. As both meshes are of good quality in Figs. 6(a) and 6(b) and no negative entries occur in the off-diagonal elements of the diffusion matrix, the FEM and the GFET methods are identical.

The LFET jump coefficients λ_0 and j_{0i}^- are determined by the procedure in Sect. 3.2. The deterministic reference solution to (61) is computed on the same meshes. The simulations in Fig. 6 are performed for $M = 10^5$ molecules initialized at the center vertex with a diffusion constant $\gamma = 10^{-3}$ until the final time $T = 50$. Let M_i be the number of molecules in node i with the coordinates $\mathbf{x}_i$ and N the number of nodes. Then

$$\boldsymbol{\mu} = \left(\sum_{i=1}^N M_i \mathbf{x}_i \right) / M \quad (64)$$

is the center of mass with the variance

$$\sigma_j^2 = \left(\sum_{i=1}^N M_i x_{ij}^2 \right) / M - \mu_j^2, \quad j=1, 2, \quad (65)$$

where σ_j^2 and x_{ij} are the x or y -coordinates of σ^2 and $\mathbf{x}_i$. The center of mass and its sample variance are tabulated in Table 1 for the distributions simulated by the two methods on the two meshes shown in Fig. 6. We compare them to the deterministic reference solutions in Fig. 6(c) and (d). The analytical value of the expected μ is $(0, 0)$. The GFET results are closer to the expected μ and the reference σ^2 than the LFET values.

We observe that the molecules in the LFET simulation in Figs. 6(g), 6(h) and Fig. 8 accumulate in the smallest voxel. This phenomenon can be explained by considering a Cartesian grid. There are only a few neighboring nodes, which do not uniquely define the domain ω . This is in contrast to the 1D problem in the previous section where the two adjacent nodes uniquely define the interval ω . In Fig. 7, we show three different possibilities how to choose ω . Any symmetric choice of ω will have $j_{0i} = 1/4$. The LFET approach of defining ω by the closest vertices with an edge connecting to the center vertex corresponds to the ω given by the blue line. The expected first exit time $1/\lambda_0$ from a vertex is $E = h^2/4\gamma$ on a Cartesian grid with grid size h resulting in a discretization of the Laplacian of second order accuracy [38]. This is obtained by choosing ω to be the red circle [53, p. 125],[37]. This circle covers a larger area than the blue diamond and hence the mean exit time computed from our first ω is too short. Too few discretization points of ω lead to a bad approximation of the boundary leading to inaccurate local first exit time approximations. The splitting probabilities between the vertices on ω are the time averages of the fluxes over the edges, see (22) and (23). In Fig. 7(b), the temporal mean (22) is plotted showing the variation along a square ω with $s = 0$ being a corner. This variation is not resolved sufficiently well on the blue square in Fig. 7(a). There is no possibility to jump to the point with the highest probability. Moreover, the short first exit time shifts the temporal mean in favour of the shorter jumps, which have higher probabilities for short times, see Fig. 4(b). The resolution of the boundary is improved by letting ω consist of the eight vertices marked by the green line in Fig. 7(a). A better quality of the jump coefficients is confirmed in numerical experiments in [38].

In Fig. 9, we depict a part of the mesh used in the right column of Fig. 6, where ω is defined by the colored edges and has different edge lengths between the central vertex and its neighbors. The jump propensities provided by FEM are all positive. Table 2 shows how the LFET calculates a faster jump propensity λ_0 and how this changes the distribution of jumps between the adjacent vertices. If molecules prefer to jump along the short edges they will finally accumulate in the small voxels with the short edges in the interior. Choosing the circle as ω would solve this problem on a Cartesian grid but this approach is not generalizable to unstructured meshes.

There is no guarantee that ω is sufficiently well resolved for LFET on a general mesh. Therefore, we continue only with tests of the GFET approach.

4.3. Diffusion and reactions on unstructured meshes in 2D and 3D

We examine the difference between the FEM coefficients fulfilling (56), the GFET coefficients fulfilling (54), the FVM coefficients in (9), and the coefficients guaranteeing a non-convective discretization (NCD) fulfilling the QP problem with the constraints (60a).

Two meshes are generated of bad quality, see in Fig. 10. Molecules are released in the center node and the time when they reach the boundary is averaged over $M = 10^5$ molecules. In the 2D example in Table 3, we find that the mean exit time computed by a GFET simulation converges towards the theoretical value when refining the mesh, whereas the FEM, FVM, and NCD results do not seem to converge. The theoretical exit time is determined by truncation and summation of the analytical formulas for the 2D exit time on a square in (49).

We perform a similar experiment in 3D. The geometry consists of a sphere with radius 1. Discretizing with tetrahedra leads to about 17 per cent negative edges for both mesh sizes. The initial position of the molecules is the center and the average of the first exit time is recorded. The analytical value is given by [53, Ch. 7.4]. The GFET and FVM mean exit times are close to the theoretical value in Table 4 but the FEM and NCD results are less accurate.

We observe that the NCD results in a maximum preserving discretization without a convective contribution but with an error in the exit times comparable to the FEM. Adding the constraints (60a) is not sufficient to obtain an accurate exit time.

To investigate the effect of the diffusion speed in a reaction system, we simulate diffusion with the reaction in Table 5 on the mesh in Fig. 11 where we release $4.2 \cdot 10^5 A$ molecules at the boundary $x = 0$ and equally many B molecules at the boundary $x = 2$. The quality of the mesh is better on the right hand side in Fig. 11(a) with fewer negative elements in the discretization. The SSA in Sect. 2.3 is extended as in [9, 12] to handle also the chemical reactions. The reaction parameters are scaled by the size of the voxels.

The concentrations of A and B in the voxels are compared in Fig. 12 to a reference solution obtained on a high quality mesh.

The GFET algorithm handles the bad quality of the mesh in Fig. 11 well in Fig. 12(b) and the distribution of molecules is symmetric as in the reference solution. The difference between the results in Fig. 12(a) and Fig. 12(b) is most likely explained by the variation in the voxel size between the regular and irregular meshes. The negativity of the off-diagonal elements for the mesh in Fig. 11 is small in absolute value and the FEM approach gives a qualitatively similar result. Since both molecular species diffuse with the same constant they, on average, react in the center at $x = 1$. In simulations with 10 times as many molecules as in the Fig. 12 the GFET leads to an average reaction position of $x = 0.9999 \pm 0.0248$ and $x = 1.0005 \pm 0.0262$ with FEM. This further shows that both methods can handle the bad quality of the mesh fairly well.

4.4. A special triangular mesh in 2D

We consider the mesh covering the rhombus in Fig. 13(a) with a regularity such that the problem with negative coefficients is the same at all inner vertices. The angles opposing an edge along the long diagonal add up to more than π and the corresponding FEM coefficients are negative (11). There is now a possibility to control the effects of bad meshes by choosing a ϕ . Increasing ϕ from $\pi/2$ leads to an increasingly negative entry on the off-diagonal of the $\mathbf{D}$ matrix in (8) using the FEM according to (11) with $\theta = \phi$. The GFET coefficients are

computed with the optimization procedure in (54). For the upper right and lower left corners, the right hand side η_i of (54) is negative and $E_i = 0$. All $E_j = 0$ except for the vertex with $E_j > 0$ and $a_{ij} < 0$. Hence, the optimization problem cannot be solved for a $\lambda_{ij} > 0$ and λ is chosen as in (57). In experiments, we see that the optimization in (54) sets the negative element to zero and adjusts the jump rates along the remaining edges of each node such that the global exit time is preserved. In Fig. 14, we show the FEM discretization and the matrix resulting from the GFET algorithm. The off-diagonal bands of negative entries disappear in Fig. 14(b) and the symmetry for left-right and up-down jumps is lost in the GFET matrix.

A reference solution for the expected first exit time is computed by solving (29) numerically on a mesh with 3254 nodes and no negative edges, see Fig. 13(b). The first exit time is recorded for a molecule starting at different vertices along the long diagonal in the rhombus in Fig. 13(b) with $M = 10^4$ trajectories from each vertex. The average value approximates the expected first exit time. The first exit time is very well approximated by the GFET coefficients in (54) in Fig. 15. The FEM coefficients in (56) result in too fast diffusion and the diffusion with FVM is too slow in agreement with Table 3. A ϕ closer to $\pi/2$ in Fig. 13(a) results in smaller deviations for both FEM and FVM.

As in (62), the error between the analytical expected first exit time E in (29) and the calculated mean value E_s from a stochastic discrete simulation can be split up as

$$\|E - E_s\| \leq \|E - E_h\| + \|E_h - E_s\|, \quad (66)$$

where E_h is the numerical solution of (29). By using a linear FEM discretization the error $\|E - E_h\|$ behaves as h^2 , where $h = \max(h_x, h_y)$. In Fig. 16, E_s is determined by GFET and the error $\|E_h - E_s\|$ decays asymptotically as $M^{-\frac{1}{2}}$ as predicted in [56] for the solution of the diffusion equation for the concentrations (61).

The concentrations determined by a stochastic simulation with FEM, GFET, and FVM coefficients on the mesh with the structure in Fig. 13 with 21×21 nodes are compared to a computed reference solution of (61) on a fine mesh with 879 nodes in Fig. 17. Again we observe that with FEM the diffusion is too fast, the FVM diffusion is too slow, whereas the GFET gives a qualitatively better solution. On this severely skewed mesh we can observe the loss of consistency due to forcing the jump coefficients to be non-negative. This leads to solutions obtained by simulations that depend not only on mesh parameters such as mesh size and element shape but also on the non-negativity constraint.

4.5. Boundary Reactions

The importance of the right diffusion speed is examined by simulating the system in Table 6 representing a simple signaling pathway. The signal A is created in the center of the cell, represented by the rhombus Ω in Fig. 13, it diffuses in the cytosol to the boundary $\partial\Omega$ where it releases protein B , which then diffuses in the cytosol and is annihilated.

This reaction-diffusion system can be modelled deterministically by the PDEs for the concentrations a and b

$$\begin{aligned} \frac{\partial a}{\partial t} &= k_1 \delta(\mathbf{x}_0) + \gamma \Delta a, \text{ in } \Omega, & \gamma \mathbf{n} \cdot \nabla a &= -\mu a, \text{ on } \partial\Omega, \\ \frac{\partial b}{\partial t} &= -k_2 b + \gamma \Delta b, \text{ in } \Omega, & \gamma \mathbf{n} \cdot \nabla b &= \mu a, \text{ on } \partial\Omega, \end{aligned} \quad (67)$$

where the normal $\mathbf{n}$ at Ω is pointing out from Ω . The steady state equations for a and b are

$$k_1 \delta(\mathbf{x}_0) + \gamma \Delta a = 0, \quad -k_2 b + \gamma \Delta b = 0. \quad (68)$$

Integrate the equations in (68) over Ω to obtain

$$\int_{\Omega} k_1 \delta(\mathbf{x}_0) + \gamma \Delta a d\Omega = k_1 + \gamma \int_{\partial\Omega} \mathbf{n} \cdot \nabla a dS = 0, \quad \int_{\Omega} -k_2 b + \gamma \Delta b d\Omega = -k_2 \int_{\Omega} b d\Omega + \gamma \int_{\partial\Omega} \mathbf{n} \cdot \nabla b dS = 0. \quad (69)$$

By the boundary conditions and (69), the total amount of B at steady state is

$$b_{tot} = \int_{\Omega} b d\Omega = \frac{\gamma}{k_2} \int_{\partial\Omega} \mathbf{n} \cdot \nabla b dS = \frac{\mu}{k_2} \int_{\partial\Omega} a dS = -\frac{\gamma}{k_2} \int_{\partial\Omega} \mathbf{n} \cdot \nabla a dS = \frac{k_1}{k_2}. \quad (70)$$

To be able to solve the equation analytically for a , the equation is first restricted to 1D. The equation in $[-\ell, \ell]$ is

$$\frac{\partial a}{\partial t} = k_1 \delta(\mathbf{x}_0) + \gamma \frac{\partial^2 a}{\partial x^2}, \quad x = -\ell: \gamma \frac{\partial a}{\partial x} = \mu a; x = \ell: \gamma \frac{\partial a}{\partial x} = -\mu a, \quad (71)$$

with the stationary solution

$$a(x) = \begin{cases} \frac{k_1}{2\gamma} x + \frac{k_1}{2} \left(\frac{\ell}{\gamma} + \frac{1}{\mu} \right), & x < 0, \\ -\frac{k_1}{2\gamma} x + \frac{k_1}{2} \left(\frac{\ell}{\gamma} + \frac{1}{\mu} \right), & x \geq 0. \end{cases} \quad (72)$$

The total amount of A at steady state is

$$a_{tot} = \int_{\Omega} a d\Omega = \frac{k_1 \ell}{2} \left(\frac{1}{\mu} + \frac{\ell}{2\gamma} \right). \quad (73)$$

The stationary solution of a in a sphere of radius R in 3D with center at $r=0$ is

$$a(r) = \frac{k_1}{4\pi\gamma} \left(\frac{1}{r} - \frac{1}{R} \left(1 - \frac{\gamma}{\mu R} \right) \right), \quad (74)$$

and the total amount of A in the sphere is

$$a_{tot} = \frac{k_1 R}{3} \left(\frac{1}{\mu} + \frac{R}{2\gamma} \right). \quad (75)$$

The conclusion from (70) is that the total amount of B only depends on k_1 and k_2 and from (73) and (75) that the total amount of A depends on the diffusion constant. A high diffusion constant γ results in a lower concentration of A molecules and vice versa. In Fig. 18, we present the simulation of the system in Table 6 with the FEM, GFET, and FVM and the dotted reference solution on a mesh with 105 nodes and without negative coefficients. The results are averaged over 50 simulations and the GFET agrees very well with the reference solution. The FEM, with too fast diffusion corresponding to a larger γ , results in a lower concentration of A molecules, which agrees qualitatively with what is expected from the solution of the steady state equations (72) and (73) in 1D and (74) and (75) in 3D. The concentration of species B is not affected by the diffusion speed and is close to k_1/k_2 after the transient phase as in (70).

The expected first exit time in Fig. 15(a) depends on the diffusion as $E \sim 1/\gamma$ and the quotients between the maxima of E with FEM and GFET and FVM and GFET are about 0.55 and 2.2, respectively. It follows from (73) with a large μ that $a_{tot} \sim 1/\gamma$. In Fig. 18, the quotient between a_{tot} with FEM and GFET is about $40/70 \approx 0.57$ and between FVM and GFET $150/70 \approx 2.1$. An interpretation of the FEM coefficients is that they represent diffusion with a higher coefficient γ , about 1.8 times larger, in these two cases. Similarly, for the FVM coefficients the diffusion is too low by a factor 2. This also yields that the FEM reaches the steady state in B faster than the reference solution and FVM reaches it slower.

The same reaction system is simulated in 3D in a sphere with $R = 1$ discretized into 263 nodes leading to about 17 per cent negative edges. The molecules are released in the center with diffusion constant $\gamma = 0.17$. The mean field theory in (75) and (70) predicts that $a_{tot} \approx k_1/6\gamma \approx 50$ and $b_{tot} = k_1/k_2 = 50$. In Fig. 19, we observe that the GFET and FVM yield similar results close to the mean field solutions whereas the FEM simulates slightly faster diffusion approaching a lower level of species A . This is in agreement with the exit times in Table 4.

5. Conclusions

We have applied the theory of first exit times in stochastic diffusion to derive jump coefficients for stochastic simulation of diffusion in a spatial domain discretized by an unstructured mesh. The theory is applied locally (LFET) and globally (GFET). The methods are compared to diffusion simulated with the coefficients obtained from a finite element method (FEM) and a finite volume method (FVM). The objectives of the two different ways of defining the jump coefficients are different. The aim of the GFET coefficients is to achieve the right speed to the boundary and the aim of the unmodified FEM and FVM coefficients is to approximate the Laplacian.

The FEM coefficients approximate the Laplacian and are non-negative on a high quality mesh. However, sometimes in 2D and more often in 3D, mesh generators produce skewed meshes yielding negative jump coefficients with FEM. The FVM coefficients are always non-negative but the approximation is consistent with the Laplacian only on meshes of Voronoi type. The coefficients are non-negative with LFET and GFET but they do not approximate the Laplacian to second order accuracy anymore. It is probably impossible to

combine linearity (in the sense that the coefficients are independent of the solution), non-negative coefficients (ensuring that the discrete maximum principle is satisfied for the Laplace equation), and a consistent approximation of the Laplacian on a general unstructured triangular or tetrahedral mesh. Therefore, we abandon the consistency and replace it by conditions based on the first exit time, which is an important feature for some biological applications. Other conditions also satisfied by diffusion are discussed briefly.

In the numerical experiments, the coefficients derived by LFET are found to be sensitive to the geometry of the triangles in 2D with a lack of robustness often resulting in too fast diffusion. The definition of the local domain around a vertex is critical when the vertex is surrounded by only a few other vertices.

By using the first exit time from the whole domain of interest, GFET coefficients are computed by projecting the FEM coefficients on the subspace with non-negative solutions satisfying a first exit time constraint locally. If the original FEM coefficients are non-negative then the GFET and the FEM coefficients are identical. Then in a number of numerical experiments in 1D, 2D, and 3D including on a highly skewed mesh, the expected first exit times determined by simulations are compared to the computed solution of a PDE with good agreement. The GFET coefficients always deliver accurate solutions while FEM and FVM coefficients have difficulties for some meshes. Finally, the signal strength in a simple model for nucleus-membrane signalling in cells using the GFET coefficients agrees well with mean field theory and an accurate reference solution.

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Figure 1.

(a) Partitioning of Ω into voxels $\mathcal{V}_i$. (b) The primary and secondary mesh with triangles (green and black) and voxels (red) defined by a triangulation.

Figure 2.

(a) Exit times from a subdomain ω and Ω . (b) Discretization of the subdomain ω .

Figure 3.

(a) Cartesian mesh with the protective domain ω (blue) and the secondary voxel $\mathcal{V}_0$ (dashed line). (b) Boundary treatment.

Figure 4.

First exit time properties on the interval $[0, 1]$ with $\gamma = 1$ and $x_0 = \frac{1}{3}$. (a) $S(t)$, (b) $j_i(x_0, t)$ and their exponential approximations.

Figure 5.

(a) Diffusion with $\gamma = 10^{-3}$ simulated by local first exit times for $M = 10^4$ molecules released at $x_0 = 0.5$ until time $T = 20$ on the interval $[0, 1]$ partitioned into $n = 21$ nodes. The vertices are marked by dots. (b) The error in the simulated exit time depending on the number of trajectories M when $n = 11$.

Figure 6.

Diffusion of the concentrations on the two meshes depicted in the first row with $\gamma = 10^{-3}$ until $T = 50$. The second row shows the deterministic reference solution. The third and fourth rows show the concentrations computed with the GFET and the LFET methods, respectively.

Figure 7.

(a) Different ω on a Cartesian grid. (b) Expected value in time of the flux $j_0(\bar{x}(s))$ out of a square starting at the midpoint. The parametrization is such that $s = 0$ corresponds to a corner.

Figure 8.
The rescaled distribution in Fig. 6(h).

Figure 9.
Unsymmetric ω defined by the numbered vertices.

Figure 10.

- (a) Mesh of bad quality with 61 nodes. The red edges denote 14 negative jump coefficients.
(b) Refinement of the mesh in (a) with 227 nodes and 47 negative edges.

Figure 11.

(a) Irregular mesh. (b) Positions of vertices (blue) and vertices with negative coefficients α_{ij} (red).

Figure 12.

Concentrations of molecules with the reaction in Table 5 simulated until a time $T = 100$. The x coordinate of the node of the voxel is the abscissa. (a) Reference solution on a regular mesh. (b) GFET simulated on the mesh in Fig. 11.

Figure 13.

(a) Skewed mesh for $\phi = 3\pi/4$. (b) Reference solution for the first exit time $E(\mathbf{x})$ and the long diagonal (black).

Figure 14.

Jump coefficient matrices for the mesh in Fig. 13 with $\varphi = 3\pi/4$ and $n_x = n_y = 5$. (a) A FEM discretization of the Laplacian. (b) After optimization with the equality constraint (GFET).

Figure 15.

Expected first exit times along the diagonal scaled by 5 in Fig. 13 calculated by the average of 10^4 FEM, GFET and FVM simulations and a reference solution computed on a high

quality mesh with 3254 nodes. E is calculated on two rhombus meshes, where (a) $\phi = \frac{3}{4}\pi$. (b)

$\phi = \frac{\pi}{2} + 0.1$.

Figure 16.

The error $\|E_h - E_s\|$ at $x = (1, 0.5)$ for an increasing number of molecules M in the mean value E_s computed with GFET.

Figure 17.

Numerical simulation until time $T = 0.025$ with $\gamma = 1$ for $M = 10^5$ molecules initially at $\mathbf{x}_0 = (1, 0.5)$. (a) Reference solution on good quality mesh with 879 nodes. (b) Stochastic simulation with FEM coefficients solving (56). (c) Stochastic simulation with GFET coefficients solving (54). (d) Stochastic simulation with FVM coefficients in (9).

Figure 18.

Average of 50 simulations of the system in Table 6 simulated on the mesh in Fig. 13 with $n_x = n_y = 21$ until time $T = 15$. The dotted lines are the reference solutions calculated on an unstructured grid with 105 nodes leading to no negative edges. (a) FEM. (b) GFET. (c) FVM.

Figure 19.

Average of 100 simulations of the system in Table 6 with $\gamma = 0.17$. The molecules are released in the center of a sphere with radius 1. The discretization is made with (a) FEM. (b) GFET. (c) FVM.

Table 1

Center of mass, μ , and variance, σ^2 for the distributions calculated by GFET and LFET shown in Fig. 6.

	Mesh (a)		Mesh (b)	
	μ	σ^2	μ	σ^2
Reference	$\begin{pmatrix} -0.0001 \\ 0.0000 \end{pmatrix}$	$\begin{pmatrix} 0.0675 \\ 0.0675 \end{pmatrix}$	$\begin{pmatrix} -0.0018 \\ 0.0020 \end{pmatrix}$	$\begin{pmatrix} 0.0673 \\ 0.0674 \end{pmatrix}$
GFET	$\begin{pmatrix} 0.0000 \\ -0.0006 \end{pmatrix}$	$\begin{pmatrix} 0.0690 \\ 0.0695 \end{pmatrix}$	$\begin{pmatrix} 0.0006 \\ 0.0008 \end{pmatrix}$	$\begin{pmatrix} 0.0696 \\ 0.0692 \end{pmatrix}$
LFET	$\begin{pmatrix} -0.0037 \\ 0.0039 \end{pmatrix}$	$\begin{pmatrix} 0.0764 \\ 0.0754 \end{pmatrix}$	$\begin{pmatrix} 0.0039 \\ 0.0096 \end{pmatrix}$	$\begin{pmatrix} 0.0738 \\ 0.0742 \end{pmatrix}$

Table 2

Comparing the FEM and LFET on the unstructured ω in Fig. 9.

	FEM	LFET
λ	4.0655	5.5919
1	0.1379	0.1197
2	0.1777	0.1526
3	0.1584	0.1558
4	0.1947	0.2739
5	0.1588	0.1427
6	0.1725	0.1553

Table 3

Expected first exit times and the 95% confidence intervals computed for $M = 10^5$ molecules on the meshes in Fig. 10 and $\gamma = 10^{-3}$ with the GFET, FEM, FVM and NCD. The confidence interval is computed by $\pm 1.96\sigma/M$, where σ is the standard deviation.

Theoretical value	73.6714	
No. of nodes	61	227
FEM	71.7530 $\pm$ 0.3354	71.5927 $\pm$ 0.3182
GFET	72.0883 $\pm$ 0.3393	73.2327 $\pm$ 0.3288
FVM	77.0513 $\pm$ 0.3636	78.4446 $\pm$ 0.3533
NCD	71.3658 $\pm$ 0.3348	71.5083 $\pm$ 0.3206

Table 4

Expected first exit times and the 95% confidence intervals computed for $\gamma = 1$ with $M = 10^5$ molecules on two meshes discretizing the sphere in 3D with the GFET, FEM, FVM, and NCD. The confidence interval is computed by $\pm 1.96\sigma/\sqrt{M}$, where σ is the standard deviation.

Theoretical value	0.1667	
No. of nodes	109	1630
FEM	0.1570 ± 0.0007	0.1493 ± 0.0006
GFET	0.1731 ± 0.0008	0.1634 ± 0.0007
FVM	0.1735 ± 0.0008	0.1656 ± 0.0007
NCD	0.1563 ± 0.0007	0.1484 ± 0.0006

Table 5

The parameters are $k = 5$, $\gamma = 10^{-3}$.

$$A+B \stackrel{k}{\rightarrow} \emptyset \text{ in } \Omega$$

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Table 6

The parameters in the biochemical model are $k_1 = 50$, $k_2 = 1$, $\mu = 200$, $\gamma = 0.04$.

$$\emptyset \xrightarrow{k_1} A \text{ at } \mathbf{x}_0 = (1, 0.5)$$

$$A \xrightarrow{\mu} B \text{ on } \partial\Omega$$

$$B \xrightarrow{k_2} \emptyset \text{ in } \Omega$$