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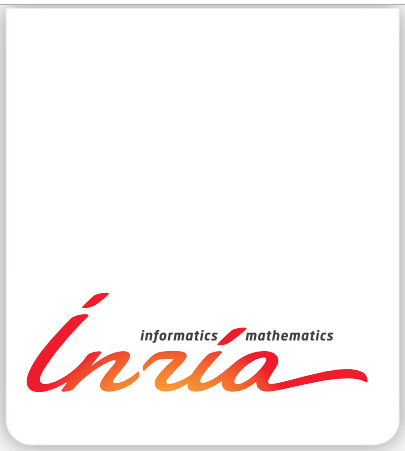


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Estimation of the mean residence time in cells surrounded by semi-permeable membranes by a Monte Carlo method

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Abstract: This report aims at validating a Monte Carlo algorithm to simulate the behavior of diffusive particles in a media with semi-permeable membranes seen as approximations of a thin layer problems. Following some homogenization approach for solving a diffusion Magnetic Resonance Imaging problem (dMRI), we estimate the mean residence time inside a cell living a in one-dimensional periodic media and compare the estimated value with the one computed by solving an eigenvalue problem. The numerical analysis shows a good agreement, unless the strength of the membrane is too strong.

Key-words: brain imaging, diffusion MRI, benchmark test, thin layer problem, estimation of the smallest positive eigenvalue, Monte Carlo methods, mean-residence time

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Estimation du temps moyen de résidence dans des cellules entourées de membranes semi-perméables par une méthode de Monte Carlo

Résumé : The rapport vise à valider un algorithme de Monte Carlo pour simuler le comportement d'une particule qui diffuse dans un milieu avec des barrières perméables vues comme des approximations de problèmes de couche mince. En suivant une approche d'homogénéisation pour résoudre un problème d'imagerie cérébrale en utilisant la technique dite de *diffusion MRI*, nous estimons le temps moyen passé par la particule dans une cellule dans un milieu périodique uni-dimensionel, et nous comparons la valeur trouvée avec celle calculée par résolution d'un problème de valeur propre. Les deux valeurs sont proches, sauf lorsque la force de la membrane est trop forte.

Mots-clés : imagerie cérébrale, technique diffusion MRI, test numérique de performance, problème de couche mince, estimation de la première valeur propre, méthode de Monte Carlo, temps de résidence moyen

This new version corrects a mistake in the previous one from April 2015 regarding the scaling used in the simulation.

1 Introduction

Interface conditions are ubiquitous in diffusion models, such as the Fick or the Darcy law. Such interfaces represents discontinuities of the diffusion coefficients, or the presence of semi-permeable or permeable membranes. While the Monte Carlo simulation of diffusion in media with permeable membranes have recently attracted a lot of interest (See the references in [16]), this is not the case for semi-permeable membranes for which fewer work exist despite its practical applications [1, 5, 6]. Motivated by a brain imaging problem, we propose a benchmark test which we apply to the simulation technique proposed in [12].

This reports focuses on a problem arising the diffusion Magnetic Resonance Imaging (dMRI), in which the mean square displacement of water submitted to a diffusive behavior is recorded through an image of contrast produced by the magnetization of water's proton subject to an external signal (See *e.g* [3, 9, 11]). The diffusive behavior of the water is not free as the water particles interact with membranes, tissues, fibers, ... The details of the macroscopic architecture of the fiber may be found by solving an inverse problem involving the resolution of the Bloch-Torrey equation for the magnetization. This equation involves a diffusion coefficient to be found and that depends on the media, as well as source term that depends on the magnetic signal.

Monte Carlo methods arise then naturally as a way to solve such a problem by simulating the displacement of a free particles in the media. Yet the dynamics of the particles should be precisely taken into account for a right estimation. In free space, the particles moves according to a Brownian motion, which means that their displacement follow a Gaussian distribution for small time steps. However, this is no longer true in presence of interfaces which should be properly taken into account. Here, we consider the problem of water reaching the membrane separating inter and extra-cellular compartment [5, 8]. Being a thin layer, the model for this membrane can be simplified as a *semi-permeable barrier*. In [12], we have proposed a way to simulate exactly the particle close to this interface with a given time step.

This report aims at testing and validating this Monte Carlo method by estimating the *mean-residence time* for a periodic one-dimensional media. This macroscopic quantity governs the rate of convergence toward the equilibrium. It is then of fundamental importance to understand the large-scale behavior of the water, and to simplify the Bloch-Torrey by homogenization techniques, giving rise to the Kärger equations [9], and ordinary equations of similar kind relying on change of scale techniques [2, 21, 22]. The dynamic of the particle being only locally influenced by the interface, there is no restriction to consider only the simplest possible model to perform validation.

In our case, the mean residence time is related to the smallest positive eigenvalue of the associated PDE, which could be estimated numerically by a root finding procedure. Also, the mean residence time is estimated on the tail of the probability of presence of the particles in the intra-cellular compartment.

2 The interface problems

Following the Fick law, the diffusion of water is modeled using a Laplace operator with diffusivity D. The space is divided by the intra-cellular compartment and the extra-cellular compartment, which are separated by membranes. The difficulties lies in the modeling and simulating the behavior of water particles at the interface. We present first a one-dimensional model for the water displacement and we study an approximation of this model.
The residence time characterizes the time spend by the water in the cell [8]. We will show that it is related to a smallest positive eigenvalue problem.

2.1 The residence time

Let us consider a model where the concentration is periodic over some interval $[0, L]$ and is given by

$$\begin{cases} \partial_t C(t,x) = \nabla(D(x)\nabla C(t,x)), \\ C(t,L) = C(t,0) \text{ (periodic boundary condition)}, \\ C(t,z) \text{ satisfies some interface condition at some given points } z \in \mathcal{I}, \\ C(0,x) \text{ is given.} \end{cases} \tag{1}$$

The diffusivity D may be heterogeneous. Let $\mathcal{L} = -\nabla(D(x)\nabla\cdot)$ (note the minus sign for convenience) be the corresponding operator with a domain $\mathrm{Dom}(\mathcal{L})$ such that the solution to (1) belongs to the domain. In our cases, there are two interface conditions that we consider. For a function f in the domain $\mathrm{Dom}(\mathcal{L})$ of $\mathcal{L}$ and a point $z \in \mathcal{I}$ at which there is an interface, either

$$D(z+) = D(z-),\ \nabla f(z+) = \nabla f(z-) \text{ and } \kappa(f(z+) - f(z-)) = D(z)\nabla f(z) \tag{$\star$}$$

for some $\kappa > 0$, or

$$f(z+) = f(z-) \text{ and } D(z+)\nabla f(z+) = D(z-)\nabla f(z-). \tag{$\star\star$}$$

It is easily checked that with these interfaces conditions, there exists a choice of $\mathrm{Dom}(\mathcal{L})$ such that $(\mathcal{L}, \mathrm{Dom}(\mathcal{L}))$ is a self-adjoint operator. Besides, it has a compact resolvent. Hence, there exists a family $\{\lambda_k\}_{k\geq 0}$ of eigenvalues with a family of not identically vanishing functions $\{\phi_k\}_{k\geq 0}$ solution to $\mathcal{L}\phi_k = -\lambda_k\phi_k$. Using the normalization $\int_0^L |\phi_k(x)|^2\,\mathrm{d}x = 1$, the set $\{\phi_k\}_{k\in\mathbb{N}}$ form an orthonormal basis of the space $\mathrm{L}^2_{\mathrm{per}}([0,L])$ of square-integrable periodic functions over $[0,L]$.
The concentration $C(t,x)$ solution to (1) may be expressed as

$$C(t,x) = \int_{[0,L]} p(t,x,y)C(0,y)\,\mathrm{d}y,$$

where for each y, $p(t,x,y)$ is solution to (1) with $p(t,x,y) = \delta_y(x)$. This function is the *fundamental solution*. It is well known that it may be expressed as

$$p(t,x,y) = \sum_{k=0}^{+\infty} e^{-\lambda_k t}\phi_k(x)\phi_k(y). \tag{2}$$

By convention, we assume that $0 \leq \lambda_0 \leq \lambda_1 \leq \lambda_2 \leq \cdots$.
The eigenvalue λ_0 is equal to 0, and $\phi_0 = 1/\sqrt{L}$.
Using the orthogonality of the eigenfunctions, we then deduce that

$$\int_{[0,L]} p(t,x,y)\,\mathrm{d}y = 1,\ \forall t > 0.$$

From the conservation of mass, if $C(0,x) \geq 0$, then $C(t,x) \geq 0$. One could see $p(t,x,y)$ as the density at time $t > 0$ of a large number of particles with total mass equal to 1 initially released at position x. Now, let us consider that the "periodic cell" $[0,L]$ is decomposed as the intra-cellular part Ω_i and the extra-cellular part Ω_e. At time 1, we inject some particles with a total mass equal to 1 at the point x. At time t, the mass of the particles in Ω_i and Ω_e are given by

$$u_i(t,x) = \int_{\Omega_i} p(t,x,y)\,\mathrm{d}y \text{ and } u_e(t,x) = \int_{\Omega_e} p(t,x,y)\,\mathrm{d}y.$$

We rewrite (2) as

$$p(t,x,y) = \frac{1}{L} + e^{-\lambda_1 t}\phi_1(x)\phi_1(y) + \mathrm{o}(e^{-\lambda_1 t}).$$

If $v_i = |\Omega_i|/L$ (resp. $v_e = |\Omega_e|/L$) the fraction of the volume of the interior (resp. exterior) part,

$$u_i(t,x) = v_i + e^{-\lambda_1 t}\phi_1(x)\int_{\Omega^i} \phi_1(y)\,\mathrm{d}y + \mathrm{o}(e^{-\lambda_1 t}), \tag{3}$$

$$u_e(t,x) = v_e + e^{-\lambda_1 t}\phi_1(x)\int_{\Omega^i} \phi_1(y)\,\mathrm{d}y + \mathrm{o}(e^{-\lambda_1 t}). \tag{4}$$

Note that we have

$$u_i(t,x) + u_e(t,x) = 1 \text{ and } v_i + v_e = 1.$$

This way,

$$\begin{aligned} u_i(t,x) - \frac{v_i}{v_e}u_e(t,x) &= 1 - \left(1 + \frac{v_i}{v_e}\right)u_e(t,x) \\ &= 1 - \left(1 + \frac{v_i}{v_e}\right)(v_e + e^{-\lambda_1 t}c(x) + \mathrm{o}(e^{-\lambda_1 t})) = -\left(1 + \frac{v_i}{v_e}\right)c(x)e^{-\lambda_1 t} + \mathrm{o}(e^{-\lambda_1 t}) \end{aligned} \tag{5}$$

with $c(x) = \phi_1(x)\int_{\Omega^e} \phi_1(y)\,\mathrm{d}y > 0$.
The *intra-cellular residence time* is given by (See [2, 10])

$$\frac{1}{\tau} = \lim_{t\to\infty} \frac{\dfrac{\partial u_e(t,x)}{\partial t}}{u_i(t,x) - \dfrac{v_i}{v_e}u_e(t,x)}. \tag{6}$$

Hence, for t large enough,

$$\frac{\partial u_e(t,x)}{\partial t} \approx -\lambda_1 e^{-\lambda_1 t} c(x).$$

It follows from (5) and (6) that

$$\frac{1}{\tau} \approx \frac{\lambda_1}{1+\frac{v_i}{v_e}} = v_e \lambda_1. \tag{7}$$

2.2 A semi-permeable membrane

The media is assumed to be one-dimensional and periodic. Hence, we consider an interval $[0,L]$ which is decomposed into an intra-cellular domain $[0,L_1]$ and an extra-cellular domain $[L_1,L]$ with $L_1 \in (0,L)$.
Our model implies a diffusivity coefficient D_0 which is equal in the intra- and the extra-cellular compartments, and a parameter κ relating the jump of the concentration to the flux at the interfaces.
The density of water is then model by the following equation with two interfaces at 0 (this point is identified to L due to the periodicity) and at L_1:

$$\begin{cases} \dfrac{\partial C(t,x)}{\partial t} = \nabla(D_0 \nabla C(t,x)), \ x \in [0,L], \\ \kappa(C(t,0+) - C(t,L-)) = D_0 \nabla C(t,0), \quad \text{(interface condition at } 0 = L), \\ D_0 \nabla C(t,0) = D_0 \nabla C(t,L), \quad \text{(continuity of the flux at the endpoints)}, \\ \kappa(C(t,L_1+) - C(t,L_1-)) = D_0 \nabla C(t,L_1), \quad \text{(interface condition at } L_1), \\ D_0 \nabla C(t,L_1+) = D_0 \nabla C(t,L_1-), \quad \text{(continuity of the flux at } L_1). \end{cases} \tag{8}$$

Here, an interface has been considered at 0 in order to simplify the computations.
We are interested in the eigenvalues of $(\mathcal{L}, \mathrm{Dom}(\mathcal{L}))$ with $\mathcal{L} = -\nabla(D_0 \nabla \cdot)$. For this, we have to find values of $\lambda > 0$ such that the following system has a solution which is not identically equal to zero:

$$\begin{cases} \nabla(D_0 \nabla C(t,x)) = -\lambda \phi(x), \ x \in [0,L], \\ \kappa(\phi(0+) - \phi(L-)) = D_0 \nabla \phi(0), \\ D_0 \nabla \phi(0) = D_0 \nabla \phi(L), \\ \kappa(\phi(L_1+) - \phi(L_1-)) = D_0 \nabla \phi(L_1), \\ D_0 \nabla \phi(L_1+) = D_0 \nabla \phi(L_1-). \end{cases}$$

It is easily seen that λ_0 is an eigenvalue with the normalized eigenfunction $1/\sqrt{L}$. Introducing

$$\mu = \sqrt{\frac{\lambda}{D_0}},$$

we seek ϕ with the form

$$\phi(x) = \begin{cases} \alpha \cos(\mu x) + \beta \sin(\mu x), & x \in [0,L_1], \\ \gamma \cos(\mu x) + \delta \sin(\mu x), & x \in [L_1,L]. \end{cases}$$

The interface condition at L yields:

$$\begin{bmatrix} \kappa & -D_0\mu \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = \begin{bmatrix} \kappa\cos(\mu L) & \kappa\sin(\mu L) \\ -\sin(\mu L) & \cos(\mu L) \end{bmatrix} \begin{bmatrix} \gamma \\ \delta \end{bmatrix},$$

which we may rewrite as

$$\begin{bmatrix} \cos(\mu L) & -\kappa^{-1}D_0\mu\cos(\mu L) - \sin(\mu L) \\ \sin(\mu L) & -\kappa^{-1}D_0\mu\sin(\mu L) + \cos(\mu L) \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = \begin{bmatrix} \gamma \\ \delta \end{bmatrix}. \tag{9}$$

The interface condition at L_1 yields

$$\begin{bmatrix} \kappa\cos(\mu L_1) + D_0\mu\sin(\mu L_1) & \kappa\sin(\mu L_1) - D_0\mu\cos(\mu L_1) \\ -\sin(\mu L_1) & \cos(\mu L_1) \end{bmatrix} \begin{bmatrix} \gamma \\ \delta \end{bmatrix} = \begin{bmatrix} \kappa\cos(\mu L_1) & \kappa\sin(\mu L_1) \\ -\sin(\mu L_1) & \cos(\mu L_1) \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix}. \tag{10}$$

Unless $\mu = 0$, the involved matrices are all invertible. Combining (9) and (10) when $\lambda \neq 0$, we then obtain that there exists a matrix $A(\lambda)$ such that

$$(A(\lambda) - \mathrm{Id}) \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = 0. \tag{11}$$

The function ϕ will be an eigenfunction if there exists a non-zero solution to (11) and then if $\det(A(\lambda) - \mathrm{Id}) = 0$. The problem is easily studied through a numerical procedure.

2.3 The thin layers approximation

The semi-permeable model, in which condition ($\star$) is used, is derived as an approximation of the thin layer model which involved two close permeable membranes modelled by ($\star\star$) ([24, Chap. 13]). Hence, we will also solve the smallest positive eigenvalue problem with this condition, to show that both models, for our range of parameters, show the same rate of convergence toward equilibrium.
Between the intra- and extra-cellular compartments, we consider a layer with a small width δ and a diffusivity D_1 such that $D_1/\delta = \kappa$. The concentration is assumed to be continuous over the domain as well as the flux.
Here, we consider that a intra-cellular compartment of length L_1 lies in the middle of $[0, L + \delta]$ and we then use the decomposition of Figure 1.

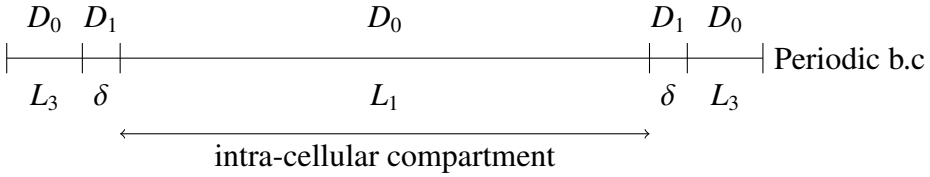


Figure 1: The domain using thin layers to model membranes.

Here, we assume that $\delta \ll L_1$ and $\delta \ll L_2$ and we set

$$L = L_2 + L_1 + 2\delta,\ L_3 = \frac{L_2}{2},$$
$$D(x) = \begin{cases} D_1 & \text{if } x \in [L_3, L_3+\delta] \cup [L_3+L_1+\delta, L_3+L_1+2\delta], \\ D_0 & \text{otherwise.} \end{cases}$$

The concentration $C(t,x)$ of the water is then equal to

$$\begin{cases} \dfrac{\partial C(t,x)}{\partial t} = \nabla(D(x)\nabla C(t,x)),\ x \in [0,L], \\ D_0 \nabla C(t,z) = D_1 \nabla C(t,z) \text{ for } z = L_3, L_3+\delta+L_1, \\ D_1 \nabla C(t,z) = D_0 \nabla C(t,z) \text{ for } z = L_3+\delta, L_3+2\delta+L_1, \\ C(t,z) = C(t,z) \text{ for } z = L_3, L_3+\delta, L_3+L_1+\delta, L_3+L_1+2\delta, \\ C(t,L) = C(t,0) \text{ (periodic boundary condition).} \end{cases} \tag{12}$$

Let us seek an eigenvalue λ with an eigenfunction ϕ in the form

$$\phi(x) = \alpha(x)\cos(\sqrt{\lambda/D(x)}x) + \beta(x)\cos(\sqrt{\lambda/D(x)}x),$$

where $\alpha(x)$ and $\beta(x)$ are constant on each interval on which $D(x)$ is constant.
The conditions at an interface at point z yield

$$B(z-)\begin{bmatrix}\alpha(z-)\\ \beta(z-)\end{bmatrix} = B(z+)\begin{bmatrix}\alpha(z+)\\ \beta(z+)\end{bmatrix}$$

with

$$B(x) = \begin{bmatrix} \cos(\sqrt{\lambda/D(x)}x) & \sin(\sqrt{\lambda/D(x)})x \\ -\sqrt{\lambda D(x)}\sin(\sqrt{\lambda/D(x)}x) & \sqrt{\lambda D(x)}\cos(\sqrt{\lambda/D(x)}x) \end{bmatrix}.$$

Let us note that

$$\det(B(x)) = \sqrt{\lambda D(x)},$$

so that $B(x)$ is invertible unless $\lambda = 0$.
With the domain described in Figure 1,

$$\begin{bmatrix}\alpha(x)\\ \beta(x)\end{bmatrix} = \begin{bmatrix}\alpha_i\\ \beta_i\end{bmatrix} \text{ with } i = \begin{cases} 1 & \text{if } x \in [0, L_3], \\ 2 & \text{if } x \in [L_3, L_3+\delta], \\ 3 & \text{if } x \in [L_3+\delta, L_3+\delta+L_1], \\ 4 & \text{if } x \in [L_3+\delta+L_1, L_3+2\delta+L_1], \\ 5 & \text{if } x \in [L_3+2\delta+L_1, L]. \end{cases}$$

Hence,

$$\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = B(L_3-)^{-1}B(L_3+)\begin{bmatrix}\alpha_2\\ \beta_2\end{bmatrix}$$

and then

$$\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = B(L_3-)^{-1}B(L_3+)B((L_3+\delta)-)^{-1}B((L_3+\delta)+) \times B((L_3+\delta+L_1)-)^{-1}B((L_3+\delta+L_1)+) B((L_3+2\delta+L_1)-)^{-1}B((L_3+2\delta+L_1)+)\begin{bmatrix}\alpha_5\\ \beta_5\end{bmatrix}.$$

On the other hand, the periodic boundary condition yields

$$\begin{bmatrix}1 & 0\\ 0 & \sqrt{\lambda/D_0}\end{bmatrix}\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = B(L)\begin{bmatrix}\alpha_5\\ \beta_5\end{bmatrix}$$

or equivalently

$$\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = \begin{bmatrix}\cos(\sqrt{\lambda/D_0}L) & \sin(\sqrt{\lambda/D_0}L)\\ -\sin(\sqrt{\lambda/D_0}L) & \cos(\sqrt{\lambda/D_0}L)\end{bmatrix}\begin{bmatrix}\alpha_5\\ \beta_5\end{bmatrix}$$

which could be written

$$\begin{bmatrix}\alpha_5\\ \beta_5\end{bmatrix} = \begin{bmatrix}\cos(\sqrt{\lambda/D_0}L) & -\sin(\sqrt{\lambda/D_0}L)\\ \sin(\sqrt{\lambda/D_0}L) & \cos(\sqrt{\lambda/D_0}L)\end{bmatrix}\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix}.$$

Combining this systems, we may write as previously that for a matrix $A'(\lambda)$, an eigenvalue exists when

$$(A'(\lambda) - \mathrm{Id})\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = 0 \tag{13}$$

has a non-zero solution. Hence, we are interested in solving $\det(A'(\lambda) - \mathrm{Id}) = 0$.

3 Monte Carlo estimation of the smallest positive eigenvalue

Thanks to (3), we have related the smallest positive eigenvalue to the exponential rate of convergence of $u_i(t,x)$ toward v_i.

3.1 Estimation of the smallest positive eigenvalue from the proportion of particles in the intracellular compartment

If $p(t,x,y)$ is the density transition function of a stochastic process X_t, then $u_i(t,x)$ is the probability that $X_t \in \Omega_i$ when $X_0 = x$. We select a starting point x and drop any reference to it.
Provided that one knows how to simulate the process X, it is then possible to simulate many independent realizations $X^{(1)},\dots,X^{(N)}$ of the path of X and counting for a given set of times $t_1,\dots,t_m$ the empirical proportions

$$v_N(t_j) = \frac{1}{N}\sum_{i=1}^{N}\mathbf{1}_{X_{t_j}^{(i)}\in\Omega_i}.$$

From the law of large numbers, it holds that

$$v_N(t_j) \approx_{N\to\infty} u_i(t_j, x_0).$$

Hence, $v_N(t)$ converges to v_i, at the exponential rate λ_1 as t converges to infinity.
With (3),

$$v_N(t_j) = v_i + ce^{-\lambda_1 t_j} + \epsilon_a(t_j) + \epsilon_{MC}(t_j, N), \tag{14}$$

where $\epsilon_a(t) = \mathrm{o}(e^{-\lambda_1 t})$ contains the higher order terms in the development of $u(t,x)$, and $\epsilon_{MC}(t,N)$ is the Monte Carlo error in the approximation of $u_i(t,x)$. For large N, the random variable $\epsilon_{MC}(t,N)$ is approximately Gaussian with

$$\operatorname{Var} \epsilon_{MC}(t,N) \approx \frac{u_i(t,x)(1-u_i(t,x))}{N}.$$

Hence, it is possible to estimate λ_1 from the $v_N(t_j)$, by noting that however

- For t small enough, $\epsilon_a(t_j)$ is not negligible in front of $ce^{-\lambda_1 t}$, so one should take t_j large enough.
- For t large, $ce^{-\lambda_1 t}$ is negligible in front of $\epsilon_{MC}(t_j, N)$, which means that the Monte Carlo error dominates the estimation.

Hence, the difficulty consists in finding two times T_- and T_+ such that the term $ce^{-\lambda_1 t}$ dominates $\epsilon_a(t)$ and $\epsilon_{MC}(t)$.
Hence, to estimate λ_1, (14) is rewritten after expanding the logarithm as

$$\log|v_N(t_j) - v_i| = \log|c| - \lambda_1 t_j + |c|^{-1} e^{\lambda_1 t}(\epsilon_a(t_j) + \epsilon_{MC}(t_j, N)),\ t_j \in [T_-, T_+]. \tag{15}$$

We stop our simulation algorithm at a time T_{MC} when $|v_N(T_{MC}) - v_i| \le 3\sqrt{v_i(1-v_i)/N}$. However, a time T_+ might be smaller that T_{MC}.
We explain our procedure in the next Section.

3.2 Statistical estimation of the smallest positive eigenvalue

Our estimator λ_{MC} of λ_1 is constructed by performing a least square procedure on (15). This means that we compute $(\alpha_{\mathrm{MC}}, \lambda_{\mathrm{MC}})$ as the values for which the residual sum of squares

$$\mathrm{RSS} = \sum_{j \text{ s.t. } t_j \in [T_-, T_+]} (\log|v_N(t_j) - v_i| - \alpha + \lambda t_j)^2$$

is minimal. This is equivalent to solve a linear regression problem by assuming that the terms $Z_j = |c|^{-1} e^{\lambda_1 t}(\epsilon_a(t_j) + \epsilon_{MC}(t_j, N))$ follow a Gaussian distribution each with the same variance σ and mean 0.
Solving a least square procedure is routine, but the choice of T_- and T_+ is crucial and should be done to balance the effect of the Monte Carlo error and the weight of the second positive eigenvalue which is unknown. Along with the choice of T_- and T_+ comes the number of times t_j used for the estimation. In previous works, we have set up procedures to select T_- and T_+.

In this report, we propose a new procedure which is based on the *Akaike Information Criterion* (AIC), a model selection criteria which balance the likelihood and the number of parameters (See *e.g.* [23, Example 13.6, p. 179].
If $\log|v_N(t_j) - v_i| \sim \mathcal{N}(\alpha + \lambda t_j, \sigma)$, then σ is estimated by $\sigma_{\mathrm{MC}} = \mathrm{RSS}(\lambda_{\mathrm{MC}}, \alpha_{\mathrm{MC}})/n$, and the maximized log-likelihood when n points are used is

$$\log \mathrm{Llh}(\alpha_{\mathrm{MC}}, \lambda_{\mathrm{MC}}, \sigma_{\mathrm{MC}}) = -\frac{n}{2}\log(2\pi\sigma^2_{\mathrm{MC}}) - \frac{n}{2}.$$

and is the AIC is

$$\mathrm{AIC} = n\log(2\pi\sigma^2_{\mathrm{MC}}) + n + 2p,$$

with $p = 2$, the number of parameters to estimate (here, α and λ). We use the customary simplified form

$$\mathrm{AIC} = n\log(\sigma^2_{\mathrm{MC}}) + 2p = n\log(\mathrm{RSS}(\lambda, \alpha)) - n\log n + 4.$$

We randomly sample values of T_- and T_+, which impact the number n of samples, and we choose the regression coefficients over the window $[T_-, T_+]$ which provides the lowest AIC coefficients.
In Figure 2, we represent the evolution of $v_N(t_j)$ with the time.
In particular, T_0 should be large enough so that the term in $\exp(-\lambda_1 t)$ dominates the effect of all the other eigenvalues.
On the other hand, T_1 should not be too large in order to keep a good accuracy because of the statistical fluctuations of v_N around v_i when the steady state is reached. Let us fix the ideas that t is large enough so that the distribution of X_t is uniform over the media. Then $\mathbf{1}_{\{X_t \in \Omega_i\}}$ is a Bernoulli random variable, with variance $v_i(1 - v_i)$. From the Central Limit Theorem, for a fixed t, $v_N(t)$ may be approximated by $v_i + Z_t$, where Z_t is a normal random variable with variance $v_i(1 - v_i)/N$. This means that the fluctuations of $v_N(t)$ around v_i have an order of magnitude of $\log(\sqrt{v_i(1 - v_i)/N})$, which is roughly equal to $-\log(N)/2$ for N large enough. Such fluctuations could be seen in Figure 2. On the other hand, we estimate the coefficient λ_1 in a function of type $v_i + ce^{-\lambda_1 t}$. It is then clear that an accurate estimation of λ_1 from the $v_N(t)$ could be performed only if $e^{-\lambda_1 t} \gg Z_t$ and then if $t \ll \log(N)/2\lambda_1$.

4 Numerical comparisons of the smallest eigenvalues

We now compare the eigenvalues of the two models. For this, we use a realistic range of parameters given in Table 1.

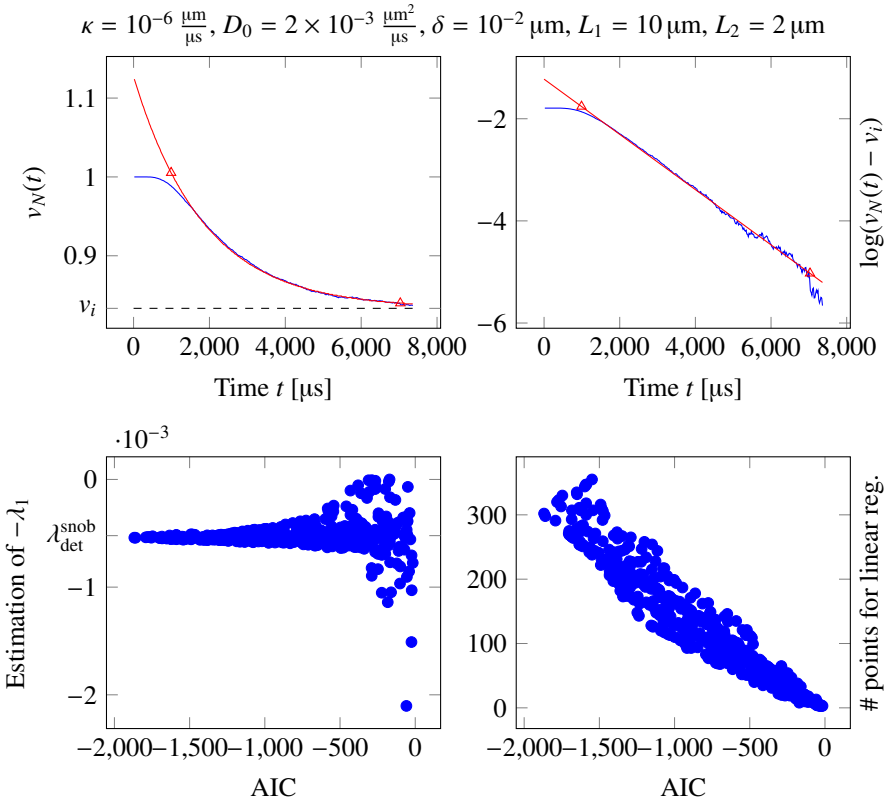


Figure 2: Evolution of the concentration in the intra-cellular domain and estimation of the smallest positive eigenvalue.

Value	From	To
$\kappa = \dfrac{D_1}{\delta}$	$10^{-6}\,\frac{\mu m}{\mu s}$	$10^{-4}\,\frac{\mu m}{\mu s}$
D_0	$2\times 10^{-3}\,\frac{\mu m^2}{\mu s}$	$3\times 10^{-3}\,\frac{\mu m^2}{\mu s}$
L_1	$5\,\mu m$	$20\,\mu m$
L_2	$\approx L_1/10$	
T	$20{,}000\,\mu s$	$50{,}000\,\mu s$

Table 1: A realistic range of parameters.

The matrices $A(\lambda)$ and $A'(\lambda)$ appearing in (11) and (13) are easily computed from the numerical point of view (See Figures 3 and 4). The peaks of the curves of $\log|\det(A(\lambda) - \mathrm{Id})|$ give hints about the values of λ at which $A(\lambda) - \mathrm{Id}$ is not invertible.
We see that for $\delta = 10^{-2}\,\mu m$ or $\delta = 10^{-3}\,\mu m$, the curves are close and give then similar eigenvalues. For $\delta = 10^{-1}\,\mu m$, some difference may exist.

Hence, for estimating the smallest positive eigenvalue λ_1, which is related to the residence time, using the model with thin layers given by (12) instead of the model (8) seems to be an acceptable choice when the parameters are in the range given by Table 1.

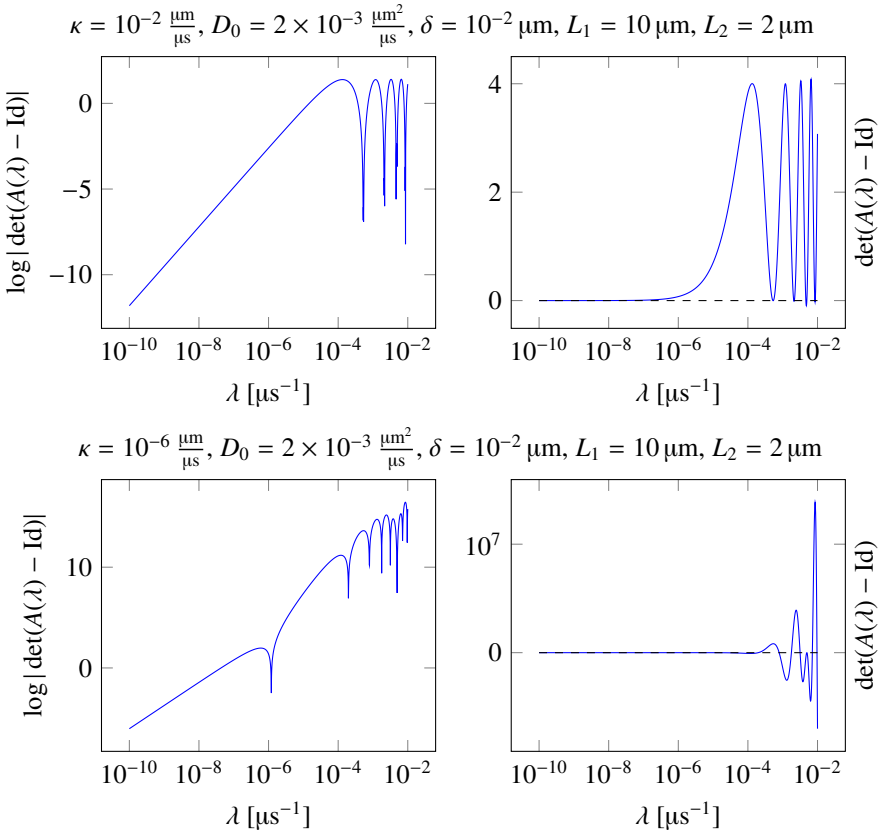


Figure 3: Evolution of $\det(A(\lambda) - \mathrm{Id})$ in logarithmic (left) and natural scale (right) for $L_{\text{extra}} = 2$ for the semi-permeable membrane.

We also note (See Figures 3 and 4) that the distance between the two smallest positive eigenvalues seems to increase when κ decreases.

5 Monte Carlo simulations

We now perform some tests on Monte Carlo simulations in order to estimate the smallest positive eigenvalue, which is related to the residence time through (7).
For this, we use 100,000 particles. We estimate the smallest positive eigenvalue λ_{MC} with the procedure described in Section 3.2, which we compare with λ_{det} which is obtained by a root-finding procedure as shown in Section 4.
The width of the layer is $\delta = 10^{-2}\,\mu m$. The time step of the scheme for moving the particles is $\delta t = 10^{-2}\,\mu s$.

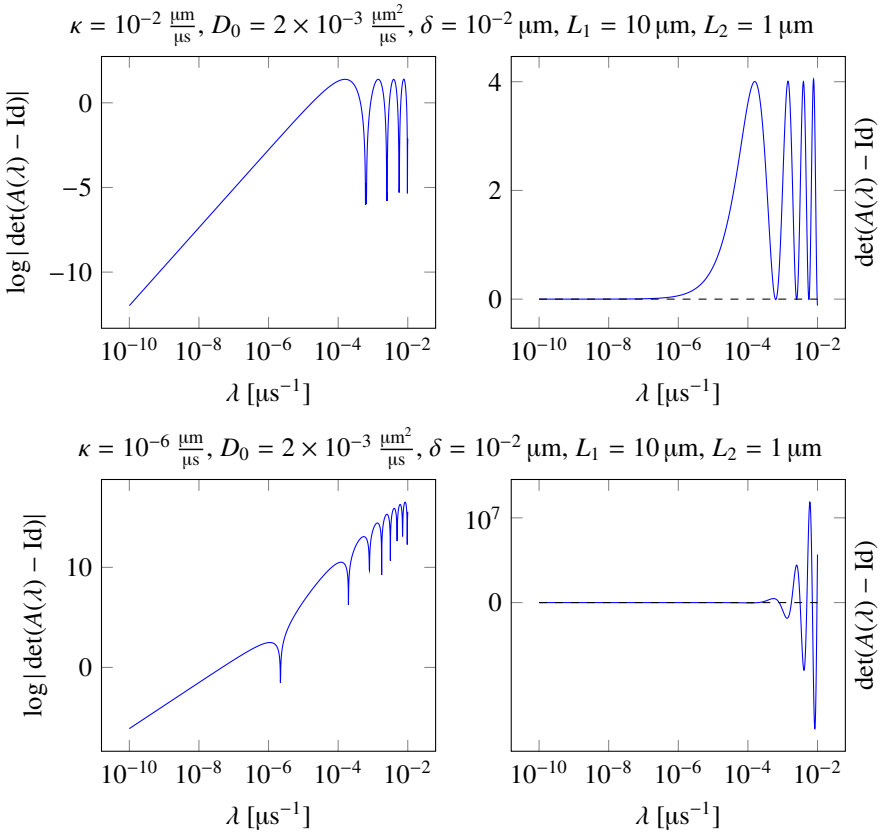


Figure 4: Evolution of $\det(A(\lambda) - \mathrm{Id})$ in logarithmic (left) and natural scale (right) for $L_{\text{extra}} = 1$ for the semi-permeable membrane.

The estimator tends to overestimate the value of the smallest positive eigenvalue when κ decreases, and then to underestimate the value of the residence time.
Using the method presented in [16], we could have simulated the process in the media with the thin layer. It led to similar numerical results. Yet the width of the layer implies to take a very small time step. This leads to a much more higher computational cost.

6 Change of scale and reduction to the snapping out Brownian motion

To estimate the rate of convergence toward the steady-state regime, we simulate the process X generated by $-\mathcal{L} = \nabla(D_0\nabla\cdot)$ with the semi-permeable interface condition prescribed by (8) at 0. The density transition function of X is solution to

$$\begin{cases} \partial_t p(t,x,y) = D_0 \partial^2_{xx} p(t,x,y) \text{ for } x \in [0,L] \setminus \{x_1, x_2\}, \\ \kappa(p(t,x_i+,y) - p(t,x_i-,y)) = D_0 \partial_x p(t,x_i,y),\ i = 1,2, \\ p(t,0,y) = p(t,L,y) \qquad \text{(periodic conditions)}, \end{cases}$$

κ	D_0	δ	L_1	L_2	λ_{MC}	$\lambda_{\mathrm{det}}^{\mathrm{snob}}$	$\lambda_{\mathrm{det}}^{\mathrm{thin}}$
$\frac{\mu m}{\mu s}$	$\frac{\mu m^2}{\mu s}$	μm				$\frac{1}{\mu s}$	
1×10^{-2}	2×10^{-3}	10^{-2}	10	2	5.57×10^{-4}	5.22×10^{-4}	5.22×10^{-4}
7.5×10^{-3}	"	"	"	"	5.34×10^{-4}	5.14×10^{-4}	5.14×10^{-4}
5×10^{-3}	"	"	"	"	5.22×10^{-4}	5.30×10^{-4}	5.28×10^{-4}
2.5×10^{-3}	"	"	"	"	5.41×10^{-4}	4.62×10^{-4}	4.72×10^{-4}
1×10^{-3}	"	"	"	"	4.55×10^{-4}	3.89×10^{-4}	3.89×10^{-4}
7.5×10^{-4}	"	"	"	"	4.28×10^{-4}	3.63×10^{-4}	3.64×10^{-4}
5×10^{-4}	"	"	"	"	3.58×10^{-4}	3.28×10^{-4}	3.27×10^{-4}
2.5×10^{-4}	"	"	"	"	2.54×10^{-4}	2.30×10^{-4}	2.29×10^{-4}
1×10^{-4}	"	"	"	"	1.38×10^{-4}	1.08×10^{-4}	1.08×10^{-4}
7.5×10^{-5}	"	"	"	"	1.18×10^{-4}	8.33×10^{-5}	8.31×10^{-5}
5×10^{-5}	"	"	"	"	8.52×10^{-5}	5.70×10^{-5}	5.69×10^{-5}
1×10^{-5}	"	"	"	"	4.29×10^{-5}	1.18×10^{-5}	1.19×10^{-5}
1×10^{-6}	"	"	"	"	3.11×10^{-5}	1.20×10^{-6}	1.20×10^{-6}
1×10^{-2}	2×10^{-3}	10^{-2}	10	1	5.53×10^{-4}	6.11×10^{-4}	6.12×10^{-4}
7.5×10^{-3}	"	"	"	"	5.33×10^{-4}	6.00×10^{-4}	6.00×10^{-4}
5×10^{-3}	"	"	"	"	5.19×10^{-4}	5.77×10^{-4}	5.77×10^{-4}
2.5×10^{-3}	"	"	"	"	5.44×10^{-4}	5.21×10^{-4}	5.21×10^{-4}
1×10^{-3}	"	"	"	"	4.57×10^{-4}	4.18×10^{-4}	4.18×10^{-4}
7.5×10^{-4}	"	"	"	"	4.29×10^{-4}	3.85×10^{-4}	3.85×10^{-4}
5×10^{-4}	"	"	"	"	3.60×10^{-4}	3.41×10^{-4}	3.40×10^{-4}
2.5×10^{-4}	"	"	"	"	2.53×10^{-4}	2.81×10^{-4}	2.81×10^{-4}
1×10^{-4}	"	"	"	"	1.38×10^{-4}	1.97×10^{-4}	1.97×10^{-4}
7.5×10^{-5}	"	"	"	"	1.17×10^{-4}	1.52×10^{-4}	1.52×10^{-4}
5×10^{-5}	"	"	"	"	8.55×10^{-5}	1.05×10^{-4}	1.04×10^{-4}
1×10^{-5}	"	"	"	"	4.29×10^{-5}	2.16×10^{-5}	2.17×10^{-5}
1×10^{-6}	"	"	"	"	3.11×10^{-5}	2.18×10^{-6}	2.19×10^{-6}

Table 2: Monte Carlo estimation of the smallest positive eigenvalue using the SNOB. The units are the same as the one of Table 1.

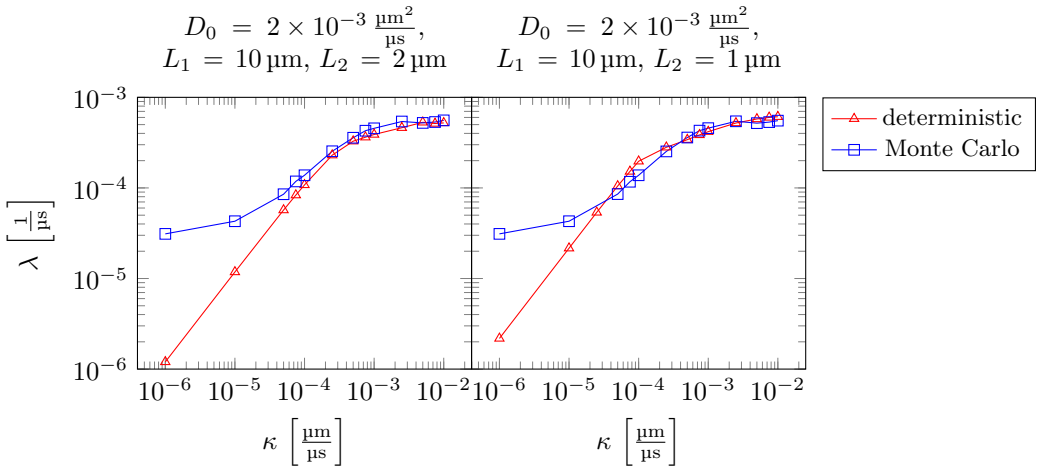


Figure 5: Deterministic and probabilistic estimation of the smallest positive eigenvalue for several values of κ.

for any y, where $\mathcal{I} = \{x_1, x_2\}$ are the positions of the semi-permeable membranes.
Actually, the simulation will be done by a change of scale technique. For a position variable z, set $z' = z\sqrt{2D_0}$. Set

$$q(t,x,y) = p\left(t, x\sqrt{2D_0}, y\sqrt{2D_0}\right)\sqrt{2D_0},$$

so that $\int_0^{\check{L}} q(t,x,y)\,dy = \int_0^L p(t,x,y)\,dy = 1$ with $\check{L} = L/\sqrt{2D_0}$. Then

$$\partial_t q(t,x,y) = \partial_t p\left(t, x\sqrt{2D_0}, y\sqrt{2D_0}\right)\sqrt{2D_0} \text{ with } \partial^2_{xx} q(t,x,y) = (2D_0)^{3/2}\partial^2_{xx} p(t, x\sqrt{2D_0}, y\sqrt{2D_0}).$$

From this,

$$\begin{cases} \partial_t q(t,x',y') = \dfrac{1}{2}\partial^2_{x'x'} q(t,x',y') \text{ for } x' \in [0,L'] \setminus \{x'_1, x'_2\}, \\ \frac{2\sqrt{2}\kappa}{\sqrt{D_0}}(q(t,x'_i+,y') - q(t,x'_i-,y')) = 2\partial_{x'} q(t,x'_i,y'),\ i = 1,2, \\ q(t,0,y') = q(t,L',y') \qquad \text{(periodic conditions).} \end{cases}$$

Finally, if $X_t = Y_t\sqrt{2D_0}$, then for $z \in [0,L]$,

$$\int_0^z p(t,x,y)\,dy = \mathbb{P}_x[X_t \le z] = \mathbb{P}_{x/\sqrt{2D_0}}\left[Y_t \le \frac{z}{\sqrt{2D_0}}\right].$$

It follows that q is the density transition function of the process Y.
Hence, given $X_t = x$ and a time step Δt, one may simulate $X_{t+\Delta t}$ by simulation $Y_{t+\Delta t}\sqrt{2D_0}$ with $Y_t = x/\sqrt{2D_0}$.

Locally around each interface and using a translation for placing the interface at 0, this process is a *snapping out Brownian motion (SNOB) of parameter* $\kappa' = 2\sqrt{2}\kappa/\sqrt{D_0}$ described in [12]. This is justified by the fact that the q has Gaussian bounds and then $q(t, x, y)$ decreases at exponential rate with $|y - x|$. It means that for a time step Δt small enough, we could neglect the probability that $\sup_{t\in[0,\Delta t} |Y_t - x| \geq 4\Delta t$ (See *e.g.* [16] for a discussion).

6.1 The problem of small values of κ

However, let us note that for $\kappa = 10^{-6}\,\mu\text{m/s}$ and $D_0 = 2 \times 10^{-3}\,\mu\text{m}^2/\mu\text{s}$, $\lambda \approx 1.6 \times 10^{-5}/\mu\text{m}$ while for $\kappa = 1 \times 10^{-4}\,\mu\text{m/s}$ and $D_0 = 2 \times 10^{-3}\,\mu\text{m}^2/\text{s}$, $\lambda \approx 1.5 \times 10^{-3}/\mu\text{s}$.
The corresponding parameter for the SNOB is $\kappa' = 8.9 \times 10^{-5}$ for $\kappa = 10^{-6}\,\mu\text{m/s}$, and $\kappa' = 8.9 \times 10^{-3}$ for $\kappa = 1 \times 10^{-4}\,\mu\text{m/s}$.
For a time step Δt between $1 \times 10^{-4}\,\mu\text{s}$ and $100\,\mu\text{s}$, the mean value of the local time L_t of the Brownian motion (hence of Y) ranges from 0.38 to 6.26. When it hits the interface at a time t between 0 and Δt, then the probability it changes its sign is $(1 - \exp(-\kappa' L_t))/2$. We then see that for our range of values of κ and D_0, we see that the probability to cross the interface is approximately equal to λL_t and is then very small. Again, without a variance reduction technique, our method is not able to catch effectively the value of the smallest positive eigenvalue.

7 Conclusion

In this report, we have studied the use of the snapping out Brownian motion [12] to simulate the stochastic process that simulate a diffusive particle in a medium with semi-permeable membranes.
In view of solving a dMRI problem, we have computed the mean residence time in a cell, a macroscopic parameter, using a Monte Carlo in order to compare it with its analytic value obtained both the thin layer problem, or its approximation, the semi-permeable membrane. The mean-residence time is related to the smallest positive eigenvalue of the diffusion problem.
The statistical estimation shows a good agreement with the theory, unless the strength of the membrane is too strong, in which case variance reduction techniques should probably be used.
Since the mean-residence time is estimated from the exponential rate at which the proportion of particles are in the cell tend toward equilibrium, we have refined the approaches proposed in [13, 14, 19] using the Akaike Information Criteria to select the best time interval on which estimating this rate to avoid statistical fluctuations in the steady state regime and the influence of the eigenvalue λ_2 in short time.
This report completes then a recent stream of researches concerning the Monte Carlo simulation of particles in media with interfaces or complex geometries, a subject with many domains of applications (See *e.g.* the references in [7, 16, 25]).

A Simulation of the snapping out Brownian motion

Steps of the snapping out Brownian Motion may be simulated in an exact manner, using the strong Markov property. For this, we use two ingredients: the simulation of the first passage time of the Brownian bridge, and a simple formula for the simulation of the joint law of the local time and the reflected Brownian motion.

We fix a time step Δ, and we simulate the successive positions $X_0, X_\Delta, X_{2\Delta}, ...$ of the SNOB. Thanks to the Markov property, the position $X_{(k+1)\Delta}$ at time $(k+1)\Delta$ depends only on the position of $X_{k\Delta} = x$ for some integer k.
In this section, we assume that $\sigma = 1$. Otherwise, we use the scaling property as seen in Section 6.
Actually, we only use the algorithm when the particle is "close" enough to the interface. Actually, the probability of crossing the interface decreases exponentially with the variance. We thus use a standard normal step $y \leftsquigarrow x + \mathcal{N}(0,\Delta)$

A.1 Simulation of the first passage time of the Brownian bridge

A Brownian bridge is a process with the distribution of the Brownian motion with $X_0 = x$ and $X_\Delta = y$ given.
If the signs of x and y differ, then the Brownian bridge has passed through 0. Otherwise, there is a probability $\exp(-2|xy|/\Delta)$ that it has crossed 0.
In both cases, the random time τ at which it crosses 0 is $\tau = \Delta\zeta/(1+\zeta)$ where ζ follows an inverse Gaussian distribution $\mathcal{IG}(\mu,\alpha)$ with density

$$r(x) = \frac{\alpha}{2\pi x^3}\exp\left(\frac{-\alpha(x-\mu)^2}{2\mu^2 x}\right) \text{ with } \begin{cases}\mu = \frac{-|x|}{|y|},\\ \lambda = \frac{x^2}{2\Delta}.\end{cases}$$

Random variate with inverse Gaussian distribution are easily simulated using the algorithm given in [4, p. 148] following a method proposed in [20].
However, to deal with the snapping out Brownian motion, the SNOB we simulate stops at 0+ or 0− if it hits 0 before the time Δ, depending on the sign of X_0.

A.2 Simulation of the local time and a reflected Brownian motion

For a Brownian motion $(B_t)_{t\geq 0}$ with symmetric local time $(L_t)_{t\geq 0}$ at 0, the following equality in distribution holds [17, 18]:

$$(L_\Delta, |B_\Delta|) \overset{\text{dist}}{=} (\ell, \ell - H) \text{ with } \begin{cases}\ell = \frac{1}{2}(H + \sqrt{H^2+V^2}),\\ H \sim \mathcal{N}(0,\Delta),\\ V \sim \exp(1/2\Delta).\end{cases}$$

A.3 Representation of the semi-group of the snapping out Brownian motion

For a Brownian motion $(B_t)_{t\geq 0}$ with its symmetric local time $(L_t)_{t\geq 0}$ at 0, the semi-group of the SNOB $(X_t)_{t\geq 0}$ has the following representation

$$\mathbb{E}_x[f(X_t)] = \mathbb{E}_x\left[\frac{1+e^{-\kappa L_t}}{2} f(\operatorname{sgn}(x)|B_t|)\right] + \mathbb{E}_x\left[\frac{1-e^{-\kappa L_t}}{2} f(-\operatorname{sgn}(x)|B_t|)\right],$$

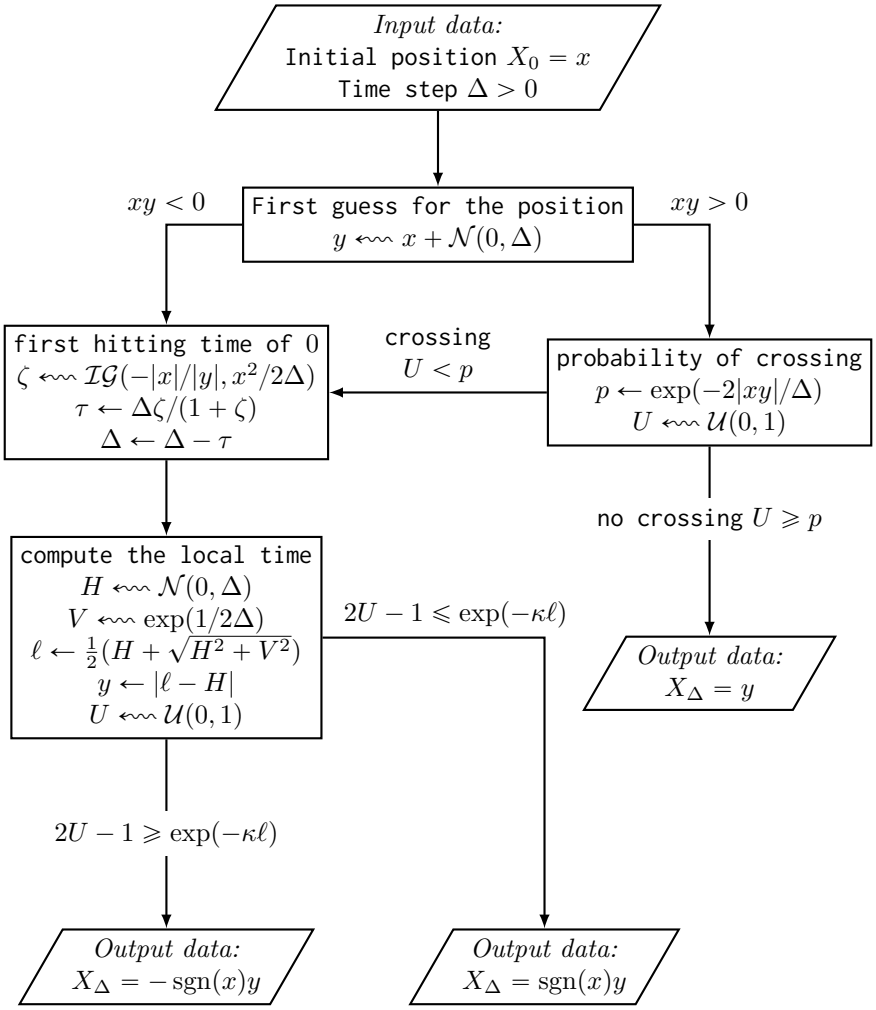
where f is any measurable and bounded function.
Hence, if $U \sim \mathcal{U}(0,1)$ is uniform random variable independent from $(B_t)_{t\geq 0}$, then

$$\mathbb{E}_x[f(X_t)] = \mathbb{E}_x\left[\mathbf{1}_{e^{-\kappa L_t}\geq 2U-1} f(\operatorname{sgn}(x)|B_t|)\right] + \mathbb{E}_x\left[\mathbf{1}_{e^{-\kappa L_t}\leq 2U-1} f(-\operatorname{sgn}(x)|B_t|)\right],$$

since $\mathbb{P}[e^{-\kappa L_t} \geq 2U-1] = (e^{-\kappa L_t}+1)/2$. Thus, X_t is simulated from $(L_t, |B_t|)$, when $x = 0+$ or $x = 0-$, as $X_t = \eta\,\mathrm{sgn}(x)|B_t|$ with $\eta = 1$ if $e^{-\kappa L_t} \geq 2U-1$ and $\eta = -1$ otherwise.
In the simulation algorithm, we let the SNOB start from $0+$ or $0-$, depending on the sign of x.

A.4 The simulation algorithm

The simulation algorithm of X_Δ when $X_0 = x$ and the time step Δ are known and which combines the previous considerations of Sections A.1-A.3 is given in Algorithm 1.



$\leftarrow$ means variable assignation, $\rightsquigarrow$ means random variate generation

Algorithm 1: Simulation of the SNOB

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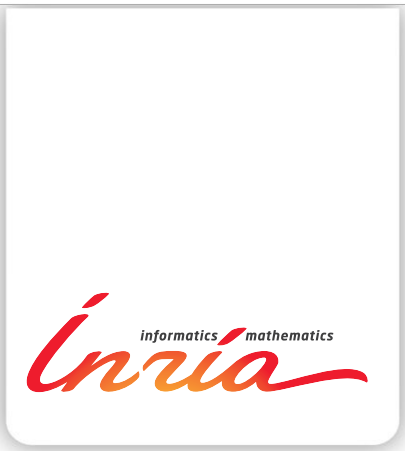
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