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A Monte Carlo estimation of the mean residence time in cells surrounded by thin layers

Antoine Lejay*

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Abstract

We present a new Monte Carlo method to estimate the mean-residence time of a diffusive particle in a domain surrounded by a thin layer of low diffusivity. Through a homogenization technique, the layer is identified with a membrane. The simulations use a stochastic process called the snapping out Brownian motion whose density matches the suitable transmission conditions at the membrane. We provide a benchmark test, which is a simplified form of a real-life problem coming from brain imaging techniques. We also refine the ways to estimate the exponential rate of the tail of the distribution function using Monte Carlo simulations.

Keywords: elastic Brownian motion, snapping out Brownian motion, thin layer problem, estimation of the mean-residence time, Monte Carlo methods, homogenization, first eigenvalue estimation.

1 Introduction

Understanding the dynamic of a diffusive process in a medium with interfaces is of great importance both for modelling and simulations. An interface could be a permeable or a semi-permeable barrier. It arises as a limit for a sharp change in the properties of the underlying material. In geophysics, sudden changes of the diffusivity of the media give rise to such effect, just to cite one among the many possible domains of applications (see *e.g.* references in [1, 10]).

We consider here a media with a “thin layer” of low diffusivity seen after a change of scale [15] as a semi-permeable barrier the particle has difficulty to pass through. The membrane surrounding living cells is an example of such layer. Brain imaging techniques such as *diffusion Magnetic Resonance Imaging* (dMRI) record the mean square displacement of particles of water [5]. Reconstructing the brain activity is done by estimating the diffusion coefficient through an inverse problem, solved through a direct problem. Understanding the diffusive behavior of particles in living tissue is then of essential for applying Monte Carlo methods [13].

In brain imaging, the *mean residence time* (MRT) in the cells is an important macroscopic parameter related to the rate of convergence toward equilibrium. It could serves as an input for simplified, homogenized models (see *e.g.* [2, 3, 12]). The MRT is also commonly used in pharmacokinetics and geophysics.

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We propose a way to estimate the MRT from Monte Carlo simulation. We should simulate paths of a stochastic process whose density solves the PDE giving the concentration of the species of interest. To avoid the large computational cost induced by the layer, which forces to use a small time step around it, we replace the process by a simpler one called the *snapping out Brownian motion* [8]. This is equivalent to replace the thin layer by a semi-permeable membrane. We then show how to estimate the MRT from the Monte Carlo simulation and we improve the estimation of a first eigenvalue problem by completing the work [9]. Finally, we provide a one-dimensional benchmark test which shows the effectiveness of our approach unless the strength of the membrane is too strong.

2 A Monte Carlo estimation of the mean residence time

The concentration $C(t, x)$ of the diffusive species (water, ...) follows an equation of type

$$\frac{\partial C}{\partial t}(t, x) = \nabla \cdot (D(x) \nabla C(t, x)), \quad t > 0, \quad x \in \mathbb{R}^d, \quad d = 1, 2, 3. \quad (1)$$

In our model, D is a constant scalar excepted in the layer of constant width ϵ enclosed by two surfaces Γ_- and Γ_+ , where it takes value $\mu\epsilon$. Under the above conditions, (1) is well posed and has a unique solution for any initial condition which is bounded and measurable.

2.1 The transmission condition

Since D is regular excepted on the interfaces Γ_- and Γ_+ , the problem (1) could be transform into a *transmission problem*. When $n_{\pm}(x)$ is the normal derivative at a point of Γ_{\pm} which is directed inward Ω , the concentration C is of class \mathcal{C}^1 on the left and right of Γ_{\pm} . Besides, it satisfies

$$[n_{\pm}(x) \cdot D(x) \nabla C(t, x)]_{\Gamma_{\pm}} = 0 \quad \text{and} \quad [C(t, x)]_{\Gamma_{\pm}} = 0, \quad (2)$$

where at a point $x \in \Gamma_{\pm}$,

$$[f(x)]_{\Gamma_{\pm}} = \lim_{\eta \rightarrow 0} f(x + \eta n_{\pm}(x)) - f(x - \eta n_{\pm}(x)).$$

The condition (2) is called the *transmission condition* (see [6, §III.13, p. 224]). It specifies here the continuity of the *flow* $n_{\pm} \cdot D(x) \nabla C(t, x)$ across the interface Γ_{\pm} as well as the continuity of the concentration.

2.2 The associated stochastic process

Let us consider the stochastic process X associated to the divergence form operator $\mathcal{L} = \nabla \cdot (D \nabla \cdot)$ (see *e.g.* [16]). This process is a strong Markov process with continuous paths. Unless the diffusion coefficient is regular enough, it is not in general the solution of a Stochastic Differential Equation (SDE).

The probability that the particle moves at the distance at least R during a time step Δt decreases exponentially fast with $R^2/\Delta t$ (this is a consequence of the Gaussian estimates on the density transition function of X [16]). In view of numerical simulation, we could substitute to $\{X_{t+s}\}_{s \geq 0}$ a process $\{Z_{t+s}\}_{s \geq 0}$ with the same distribution as X until they leave the ball U of radius R centered on X_t . For this, R should be assumed large enough with respect to Δt . In practice, $R = 4\sqrt{D_0 \Delta t}$ is sufficient (see *e.g.* the discussion in [10]). For away from the interfaces, Gaussian steps could be used. We then focus on the dynamic of the process only at the immediate vicinity of the layers.

Let ϕ be a one-to-one \mathcal{C}^2 diffeomorphism of \mathbb{R}^d . Then $Y_t = \phi(X_t)$ is also a strong Markov process with continuous paths. From standard computations, its infinitesimal generator \mathcal{A} is

$$\begin{aligned} \mathcal{A}f(x) = \mathcal{L}(f \circ \phi)(\phi^{-1}(x)) = D(\phi^{-1}(x)) \sum_{i,j,k=1,\dots,d} \frac{\partial^2 f}{\partial x_j \partial x_k}(x) \frac{\partial \phi_k}{\partial x_i}(x) \frac{\partial \phi_j}{\partial x_i}(x) \\ + D(\phi^{-1}(x)) \sum_{i,j=1,\dots,d} \frac{\partial f}{\partial x_j}(x) \frac{\partial^2 \phi_j}{\partial x_i^2}(x). \end{aligned} \quad (3)$$

for any function $f \in \text{Dom}(\mathcal{L})$, the domain of \mathcal{L} . Besides, $\text{Dom}(\mathcal{A}) = \phi(\text{Dom}(\mathcal{L}))$. We note in particular that $\mathcal{A}f(x) = \mathcal{L}f(\phi(x))$ when ϕ is a translation or a rotation.

We assume that the layer is surrounded by two interfaces Γ_- and Γ_+ at distance ϵ and is of class \mathcal{C}^2 . We use an argument similar to the one of [1] to reduce the problem to a “nearly 1-dimensional” one.

Proposition 1. *At the vicinity of any point \hat{x} in Γ_- , there exists a \mathcal{C}^2 diffeomorphism such that $\phi(\Gamma_-)$ and $\phi(\Gamma_+)$ are the hyperplanes orthogonal to $(1, 0, \dots, 0)$ passing through 0 and $(\epsilon, 0, \dots, 0)$.*

Proof. Up to composition with a rotation and a translation, we may assume that our reference point $\hat{x} = 0$ and $\Gamma_- = U \cap \{(\omega(x'), x') \mid x' \in \mathbb{R}^{d-1}\}$ for a smooth map $\omega : \mathbb{R}^{d-1} \rightarrow \mathbb{R}$ and a neighborhood U of 0. Let $d : \mathbb{R}^d \rightarrow \mathbb{R}_+$ be the distance between a point and Γ_- . At the vicinity of Γ_- , the distance is a well defined function with the same regularity as Γ_- [4]. In addition, there exists a unique point y in Γ_- such that $d(x) = |x - y|$. Let $n(x) = \nabla \omega(x')$ be the unit vector normal to Γ_- oriented toward the exterior of the cell at the point $x = (\omega(x'), x')$. Write $\psi(d, x') = x + dn(x)$ with $x = (\omega(x'), x')$ for $d \in \mathbb{R}$ and $x' \in \mathbb{R}^{d-1}$. Thus, ψ is locally a diffeomorphism and ψ^{-1} maps $\Gamma_- \cap V$ to $\{(0, x') \mid x' \in \mathbb{R}^{d-1}\} \cap U$ as well as $\Gamma_+ \cap V$ to $\{(\epsilon, x') \mid x' \in \mathbb{R}^{d-1}\} \cap U$ for two neighborhoods V and U of 0. \square

Using this, we focus on the component which is normal to the interface Γ_{\pm} .

Corollary 1. *Using the diffeomorphism ϕ given above at the vicinity of the layer, the process $Y_t = \phi(X_t)$ has for first component Y^1 a diffusion process whose infinitesimal generator is $\mathcal{P} = \partial_x(D(x, 0, \dots, 0)\nabla\partial_x)$ with domain $\text{Dom}(\mathcal{P})$ is the closure with respect to the graph norm of*

$$\{f \in \mathcal{C}(\mathbb{R}) \cap \mathcal{C}^2(\mathbb{R} \setminus \{0\}) \mid [D\partial_x f]_0 = [D\partial_x f]_{\epsilon} = 0\}.$$

2.3 The thin layer approximation

The particles have difficulties in traversing the thin layer which is then seen as a semi-permeable barrier. Our diffusion equation could be replaced by a simpler one where the layer enclosed between Γ_+ and Γ_- is reduced to a single interface Γ and the following condition on the interface

$$\mu(C(t, x+) - C(t, x-)) = D_0 n_+(x) \cdot \nabla C(t, x) \text{ and } [n_+(x)C(t, x)]_{\Gamma} = 0, \quad x \in \Gamma_{\pm},$$

where C is the solution to the PDE $\partial_t C(t, x) = D_0 \Delta C(t, x)$ away from Γ_{\pm} (see e.g. [15]).

In dimension 1, a similar analysis can be carried at the level of the stochastic process. Therefore, X may be replaced by a simpler process. Up to a change of scale presented below, this is an elastic Brownian motion with rebirth when killed, which we analyzed in [8]. The latter process is called the *snapping out Brownian motion* (SNOB) and depends on a parameter κ which characterizes the strength of the membrane. Its infinitesimal generator is $\mathcal{S} = \frac{1}{2}\Delta$. When the interface is at 0, the domain of \mathcal{S} contains functions satisfying the transmission conditions

$$\nabla u(0+) = \nabla u(0-) \text{ and } \kappa(u(0+) - u(0-)) = 2\nabla u(0)$$

and which are bounded and of class \mathcal{C}^2 elsewhere with a bounded second order derivative.

The state space of this process is the disjoint union $(-\infty, 0-] \cup [0+, \infty)$, meaning that 0 is “duplicated”. The process could only reborn at 0+ or 0-. It then lives in the corresponding half-line as an elastic Brownian motion, that is until its local time at 0_{\pm} goes above an independent exponential random variable of mean $1/\kappa$.

Corollary 2. *With ϕ and Y as above, for $\psi(x) = \int_0^x 1/\sqrt{D(y)} dy$, the process $Z = \psi(Y)$ is a SNOB of parameter $\kappa = 2^{3/2}\mu/\sqrt{D_0}$ when restricted to the vicinity of 0.*

When f is a bounded, continuous function and Z a SNOB of parameter κ ,

$$\mathbb{E}_x[f(Z_t)] = \mathbb{E}_x \left[\frac{1 + e^{-\kappa L_t^0(B)}}{2} f(|B_t|) \right] + \mathbb{E}_x \left[\frac{1 - e^{-\kappa L_t^0(B)}}{2} f(-|B_t|) \right] \text{ for } x \geq 0, \quad (4)$$

where B is a Brownian motion and $L_t^0(B)$ its symmetric local time at 0.

Using the representation (4) of the semi-group and some explicit formula for the simulation of the local time [11], a simulation algorithm could be given for the SNOB which is presented in [7, 8].

The tangential components behaves like a Brownian motion and are then easily simulated.

2.4 A Monte Carlo estimator of the mean residence time

The MRT is an important macroscopic quantity that could be used to construct two-scale models. Its simplifies the resolution of problems such as one arising in dMRI [2].

In a periodic medium, the operator \mathcal{L} with domain $\text{Dom}(\mathcal{L})$ is self-adjoint. In particular, it admits a spectral decomposition $0 \leq \lambda_0 < \lambda_1 < \dots$ with eigenfunctions ϕ_0, ϕ_1, \dots chosen orthonormal for the L^2 scalar product (regarding the sign of the eigenvalues, we use the convention $\mathcal{L}\phi_k = -\lambda_k\phi_k$). The first eigenvalue is $\lambda_0 = 0$ and its associated eigenfunction is $\phi_0(x) = 1/\sqrt{V_{\text{per}}}$, there V_{per} is the volume of the periodic cell.

Proposition 2 ([2, 7]). *The mean residence time $1/\tau$ in the cell is then given approximatively by*

$$\frac{1}{\tau} \approx \frac{V_{\text{intra}}}{V_{\text{per}}} \lambda_1, \quad (5)$$

where V_{extra} is the volume of exterior part of the cell.

Determining the first eigenvalue λ_1 is then crucial for estimating the MRT. We explain now its relationship with the process X .

The density transition function $p(t, x, y)$ with respect to the Lebesgue measure of the projection of the process X onto the cell admits the spectral expansion

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

Since $\phi_0(x)$ is constant and for a fixed point x ,

$$p(t) = \int_{\Omega_{\text{intra}}} p(t, x, y) dy = \frac{V_{\text{intra}}}{V_{\text{per}}} + C \phi_1(x) e^{-\lambda_1 t} + o(\exp(-\lambda_1 t)) \quad (6)$$

with $C = \int_{\Omega_{\text{intra}}} \phi_1(y) dy$.

On the other hand, $p(t) = \mathbb{P}_x[X_t \in \Omega_{\text{intra}}]$. By simulating a large number N of paths of the stochastic process X_t , we estimate $p(t)$ at some given times $\{t_k\}_{k=1,\dots,M}$ using the empirical estimators

$$p_N(t_k) = \frac{1}{N} \sum_{i=1}^N \mathbb{1}_{X_{t_k}^{(i)} \in \Omega_{\text{intra}}}, \quad (7)$$

where $X^{(1)}, \dots, X^{(N)}$ are N independent samples of the paths X .

As t increases, $p(t)$ converges to the ratio $V_{\text{intra}}/V_{\text{per}}$, and $-\lambda_1$ is actually the exponential rate of convergence toward equilibrium.

From the knowledge of $\{p_N(t_k)\}_{k=1,\dots,M}$, we estimate λ_1 through a linear regression on $\{\log(p_N(t_k) - L)\}_{k=1,\dots,M}$. However, the first and last times t_1 and t_M shall be carefully chosen. For this, we use the procedure presented in Section 3.

3 A procedure to estimate some exponential rate from Monte Carlo measurement

Let $p(t)$ be the probability of an event which decreases to 0 with the time t at some exponential rate λ . This is typical for first eigenvalues problems, such as (6) and the estimation of survival probability of a Brownian motion killed when it exits from a domain [9].

More precisely, we state that

$$p(t) = p_\infty + c \exp(-\lambda t) + r(t) \text{ with } r(t) = o_{t \rightarrow \infty}(\lambda t), \quad (8)$$

where $p_\infty \geq 0$ is known, yet $c > 0$, $\lambda > 0$ and r are unknown. In particular, we ignore how fast $r(t)\exp(\lambda t)$ decreases to 0.

Our aim is then to estimate λ and c .

At different times $0 < t_1 < \dots < t_M$, this quantity $p(t_i)$ is estimated by $p_N(t_i)$ from a Monte Carlo estimation with N independent samples. A Gaussian confidence interval allows one to assert that with a probability α ,

$$|p(t) - p_N(t)| \leq c_\alpha \frac{\sqrt{p(t)(1-p(t))}}{\sqrt{N}} \text{ for } N \text{ large enough,} \quad (9)$$

with *e.g.*, $c_\alpha = 2.57$ for $\alpha = 99\%$.

Without the Monte Carlo error and the remainder term r , the problem of estimation of λ is pretty simple, as $\log(p(t) - p_\infty) = \log c - \lambda t$. Thus, one has only to estimate the slope of $\log(p(t) - p_\infty)$, using for example a linear regression.

Our problem is then to filter out the times at which $r(t)$ (for small t) and the Monte Carlo error have small impact so that $\log(p_N(t) - p_\infty)$ is close to be linear.

The Monte Carlo error has an impact when $c_\alpha \sqrt{p(t)(1-p(t))}/\sqrt{N}$ has the same order as $p(t) - p_\infty = c \exp(-\lambda t)$. Hence, it is useless to consider $p_N(t)$ at times t such that

$$c_\alpha \frac{\sqrt{p_N(t)(1-p_N(t))}}{\sqrt{N}} \geq \beta(p_N(t) - p_\infty) \text{ with say } \beta = \frac{1}{10}.$$

This criterion fixes a limit for the maximum sampling time t_M to consider. After this time, the estimations are no more relevant as being ‘‘flooded’’ by the Monte Carlo error.

Getting rid of $r(t)$ is more cumbersome, as this function is generally unknown. Several criteria have been proposed in [9] to find the best time interval $[t_-, t_+]$ for estimating λ through a least squares procedure. Yet they partially rely on a graphical procedure.

When t_- and t_+ are fixed, c_{est} and λ_{est} are the values which minimize

$$\text{SQ}(t_-, t_+; c, \lambda) = \sum_{\substack{i=1, \dots, M \\ t_- \leq t_i \leq t_+}} (\log c - \lambda t_i - \log(p_N(t_i) - p_\infty))^2,$$

We then set the residual sum of squares

$$\text{RSS}(t_-, t_+) = \text{SQ}(t_-, t_+; c_{\text{est}}, \lambda_{\text{est}}) = \min_{c, \lambda} \text{SQ}(t_-, t_+; c, \lambda). \quad (10)$$

In the report [7], we have proposed a new methodology in which t_- and t_+ are determined automatically using the Akaike Information Criteria (AIC) (see *e.g.* [14, Example 13.6, p. 179]). This approach is suitable as the number of values $p_N(t_i)$ to use varies with t_- and t_+ .

Since there are two parameters (c and λ) to estimate, we use the customary simplified formula

$$\begin{aligned} \text{AIC}(t_-, t_+) &= n \log(\text{RSS}(t_-, t_+)) - n \log n + 4 \\ &\text{with } n = \#\{t_- \leq t_i \leq t_+; i = 1, \dots, M\}. \end{aligned}$$

We draw randomly some pairs (t_-, t_+) with $t_- < t_+$ and we select the one for which $\text{AIC}(t_-, t_+)$ is minimized.

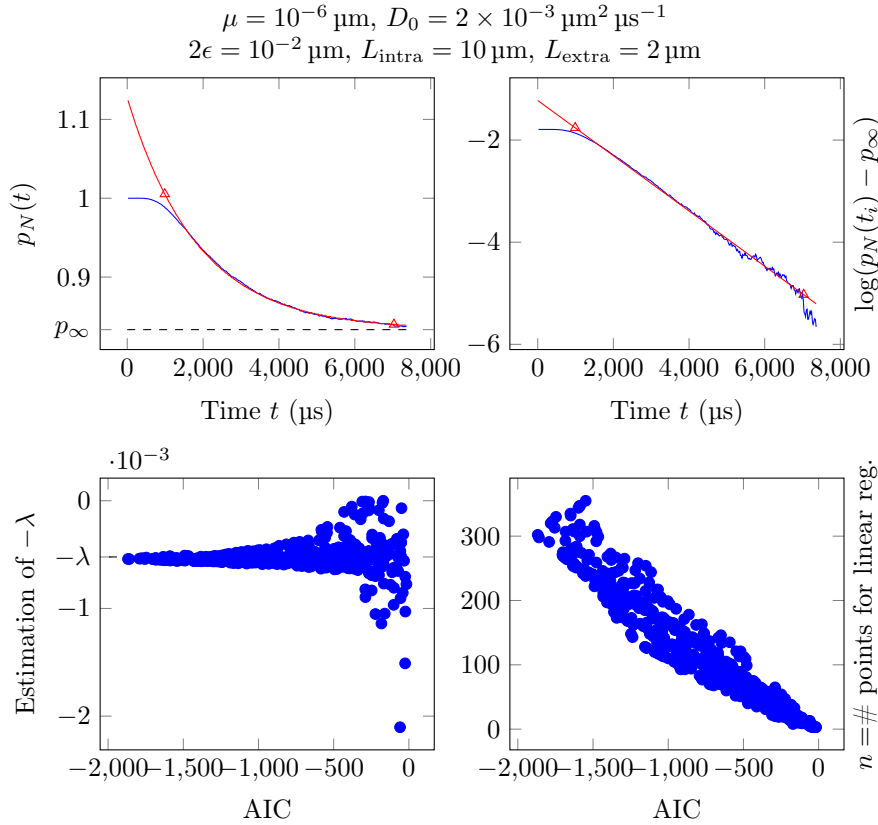


Figure 1: Estimation of λ using a least square procedure. The curve in red represents the estimated function $c \exp(-\lambda t)$ from the time interval $[t_-, t_+]$ delimited by the triangle. The two bottom figures show that the values which are close to the minimum of AIC provides pretty close estimated values of λ and use a lot of sample times. We have used $N = 100\,000$ paths and $t_{i+1} - t_i = 20 \mu\text{s}$.

This procedure, whose result is illustrated in Figure 1, appears to be effective and no longer relies on a graphical interpretation as in [9].

| Name | Quantity | From | To |
|--|-------------------------------|---|---|
| D_{intra} | cells' diffusivity | $2 \times 10^{-3} \mu\text{m}^2 \mu\text{s}^{-1}$ | $3 \times 10^{-3} \mu\text{m}^2 \mu\text{s}^{-1}$ |
| D_{extra} | diffusivity outside the cells | | $= D_{\text{intra}}$ |
| D_{memb} | membrane diffusivity | | |
| ϵ | membrane width | | $0.01 \mu\text{m}$ |
| $\mu = \frac{D_{\text{memb}}}{\epsilon}$ | membrane strength | $10^{-6} \mu\text{m} \mu\text{s}^{-1}$ | $10^{-4} \mu\text{m} \mu\text{s}^{-1}$ |
| L_{intra} | cell size | $5 \mu\text{m}$ | $20 \mu\text{m}$ |
| L_{extra} | outer cell size | | $\approx L_{\text{intra}}/10$ |
| L_{per} | media's period | | $L_{\text{intra}} + L_{\text{extra}}$ |
| T | max. observation time | $20\,000 \mu\text{s}$ | $50\,000 \mu\text{s}$ |

Table 1: A realistic range of parameters.

4 A computational benchmark test in dimension one

We test our simulation scheme on a simple situation and compare it to the numerical, deterministic estimation of an eigenvalue problem. For this, we place ourselves in a one-dimensional media, which allows explicit computations of the first positive eigenvalue $\lambda = \lambda_1$. We consider a cell surrounded by two thin membranes in a periodic media. The diffusivity D_{intra} in the cell is the same as the diffusivity D_{extra} outside the cell. In the thin membrane, of width ϵ , the diffusivity is $D_{\text{memb}} = \mu\epsilon$.

The infinitesimal generator of X is $\mathcal{A} = \nabla \cdot (D \nabla \cdot)$ with $D(x) = D_{\text{intra}}$ or $D(x) = D_{\text{memb}}$ according to the position of x inside or outside the membrane. For each membrane at position y , the thin layer approximation means that any solution to $\mathcal{A}u = f$ with f continuous satisfies

$$\mu(u(y+) - u(y-)) = D_{\text{intra}} \nabla(y\pm) \text{ and } [\nabla u]_y = 0.$$

We simulate the process $Y_t = X_t / \sqrt{2D_{\text{intra}}}$. Thus, this process Y has diffusivity 1 outside and inside the cell. At each membrane, Y acts like a SNOB with parameter $\kappa = 2^{3/2} \mu / \sqrt{D_{\text{intra}}}$. According to (5), the MRT is then approximated by $\tau \approx \lambda^{-1} L_{\text{per}} / L_{\text{intra}}$.

We use a realistic range of parameters described in Table 1. Performing N independent simulations to obtain with (7) empirical estimation $p_N(t_k)$ of $p(t_k)$ given by (6) at a given set of times $0 < t_1 < \dots < t_M \leq T$. We then use the procedure of Section 3.

Being the first non-zero eigenvalue of \mathcal{A} , λ could also be computed deterministically as an eigenvalue of a Sturm-Liouville problem. Numerically, it is easily checked that the eigenvalues with the thin layer approximation are close to the ones of the original problem [7]. The process is simulated only using the thin layer approximation, which leads to faster computations. Without the thin layer approximation, the simulations could be performed using the algorithms given in [10]. Yet the thinness of the layer forces to use a very small time step, burdening the computational cost.

Numerical results are given in Figure 2. Unless μ is too small, the Monte Carlo results are in good agreements with the deterministic approach. A small value of μ means that the strength of the membrane is high and particles have difficulties to pass through it. This problem is related to a rare events simulation problem. This shall be subject to future investigations.

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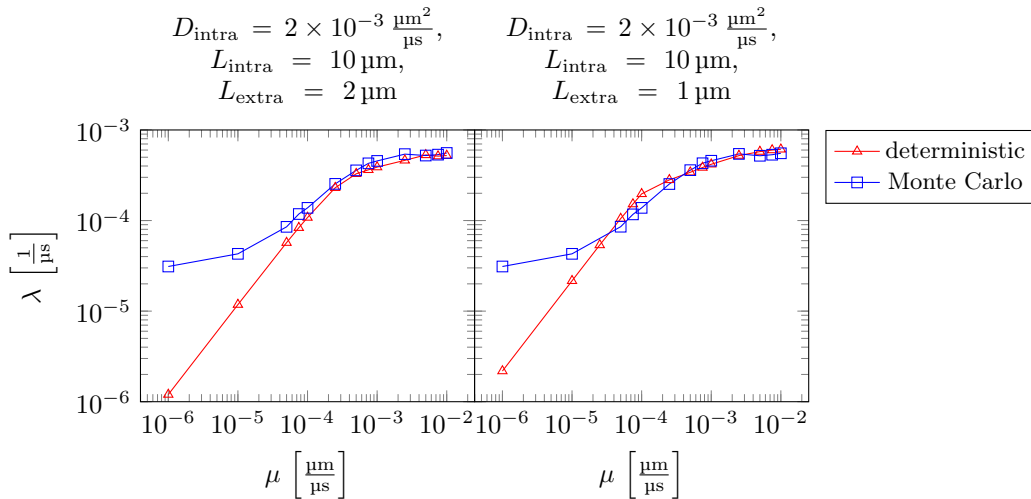


Figure 2: Estimation of λ by a deterministic method and a Monte Carlo one with $N = 100000$ particles.

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