Estimation of the residence time in cells by a Monte Carlo methods

Antoine Lejay Jing-Rebecca Li

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Abstract

In this note, we study a Monte Carlo estimator of the residence time in the intra-cellular compartment.

1 Interface problems

The diffusion of water is modeled using a Laplace operator with diffusivity D_0. 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 a first 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. We will show that it is related to the first eigenvalues of some operator.

1.1 The residence time

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

$$\begin{cases} \partial C(t,x) = \nabla(D(x)\nabla C(t,x)), \\ C(t,L) = C(t,0) \text{ (periodic boundary condition)}, \\ C(t,z) \text{ satisfies some interface condition at some given point } z, \\ C(0,x) \text{ is given} \end{cases} \tag{1}$$

Let $L = \nabla(D(x)\nabla\cdot)$ be the corresponding operator with a domain $\mathrm{Dom}(L)$ 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 $\mathrm{Dom}(L)$ of L and a point z at which there is an interface,

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

and

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

It is easily checked that with these interfaces conditions, there exists a choice of $\mathrm{Dom}(L)$ such that $(L, \mathrm{Dom}(L))$ is a self-adjoint operator. Besides, it has a compact resolvent. Hence, there exists a family $\lambda_k > 0$ of eigenvalues for which there exist some functions φ_k not identically vanishing such that $L\varphi_k = -\lambda_k\varphi_k$. Using for φ_k a normalization such that $\int_0^L |\varphi_k(x)|^2\,\mathrm{d}x = 1$, the set $\{\varphi_k\}_{k\in\mathbb{N}}$ form an orthonormal basis of the space $\mathrm{L}^2_{\mathrm{per}}([0, L])$.
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 *fundemantal solution*. It is well known that it may be expressed as

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

By convention, we assume that $0 \leqslant \lambda_0 \leqslant \lambda_1 \leqslant \lambda_2 \leqslant \cdots$.
Remark that $\lambda_0 = 0$ and the corresponding eigenvalues are the constant functions. Using the orthogonality of the eigenvalues, we then obtain that

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

Besides, it may be shown that if $C(0, x) \geqslant 0$, then $C(t, x) \geqslant 0$. This means that a conservation principle for the mass apply. 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

$$p(t, x, y) = \frac{1}{L} + e^{-\lambda_1 t}\varphi_1(x)\varphi_1(y) + \mathrm{o}(e^{-\lambda_1 t}),$$

where φ_1 is the eigenfunction associated to λ_1, with $\int_{[0,L]} \varphi_1(x)^2 \, \mathrm{d}x = 1$.
If $v_i = |\Omega_i|/L$ (resp. $v_e = |\Omega_e|/L$) the fraction of the volume of the interior (resp. exterior) part,

$$u_i(t,x) = v_i + e^{-\lambda_1 t}\varphi_1(x) \int_{\Omega^i} \varphi_1(y) \, \mathrm{d}y + \mathrm{o}(e^{-\lambda_1 t}),$$
$$u_e(t,x) = v_e + e^{-\lambda_1 t}\varphi_1(x) \int_{\Omega^i} \varphi_1(y) \, \mathrm{d}y + \mathrm{o}(e^{-\lambda_1 t}).$$

Note that we have

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

This way,

$$\begin{aligned} u_i(t,x) - \frac{v_i}{v_e} u_e(t,x) &= 1 - \left(1 + \frac{v_i}{v_e}\right) u_e(t,x) \\ = 1 - \left(1 + \frac{v_i}{v_e}\right) (v_e + e^{-\lambda_1 t} c(x) + \mathrm{o}(e^{-\lambda_1 t})) &= - \left(1 + \frac{v_i}{v_e}\right) c(x) e^{-\lambda_1 t} + \mathrm{o}(e^{-\lambda_1 t}) \end{aligned} \tag{3}$$

with $c(x) = \varphi_1(x) \int_{\Omega^e} \varphi_1(y) \, \mathrm{d}y > 0$.
The *intra-cellular residence time* is given by (See [1])

$$\frac{1}{\tau} = \lim_{t \to \infty} \frac{\dfrac{\partial u_e(t,x)}{\partial t}}{u_i(t,x) - \dfrac{v_i}{v_e} u_e(t,x)}. \tag{4}$$

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 (3) and (4) that

$$\frac{1}{\tau} \approx \frac{\lambda_1}{1 + \dfrac{v_i}{v_e}} = v_e \lambda_1. \tag{5}$$

1.2 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 $[L_1, L_2]$ with $L_1 + L_2 = L$.

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:

$$\begin{cases} \dfrac{\partial C(t,x)}{\partial t} = \nabla(D_0 \nabla C(t,x)), \ x \in [0,L], \\ \kappa(C(t,0+) - C(t,L-)) = D_0 \nabla C(t,0), \\ D_0 \nabla C(t,0) = D_0 \nabla C(t,L), \ \text{(continuity of the flux)} \\ \kappa(C(t,L_1+) - C(t,L_1-)) = D_0 \nabla C(t,L_1), \\ D_0 \nabla C(t,L_1+) = D_0 \nabla C(t,L_1-), \ \text{(continuity of the flux)} \end{cases} \tag{6}$$

Here, we have chosen to write the interface at 0 in order to simplify the computations.
We are interested in the eigenvalues of the related operator. 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:

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

Let us already note that $\lambda = 0$ is an eigenvalue. The corresponding eigenfunctions are constants on $[0, L]$. Introducing

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

we seek φ with the form

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

The interface condition at L yields:

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

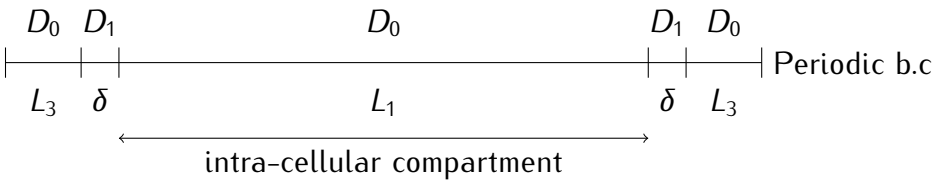


Figure 1: The domain using thin layers to model membranes.

which we may rewrite as

$$\begin{bmatrix} \cos(\mu L) & -\kappa^{-1} D_0 \mu \cos(\mu L) - \sin(\mu L) \\ \sin(\mu L) & -\kappa^{-1} D_0 \mu \sin(\mu L) + \cos(\mu L) \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = \begin{bmatrix} \gamma \\ \delta \end{bmatrix}. \tag{7}$$

The interface condition at L_1 yields

$$\begin{bmatrix} \kappa \cos(\mu L_1) + D_0 \mu \sin(\mu L_1) & \kappa \sin(\mu L_1) - D_0 \mu \cos(\mu L_1) \\ -\sin(\mu L_1) & \cos(\mu L_1) \end{bmatrix} \begin{bmatrix} \gamma \\ \delta \end{bmatrix} = \begin{bmatrix} \kappa \cos(\mu L_1) & \kappa \sin(\mu L_1) \\ -\sin(\mu L_1) & \cos(\mu L_1) \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix}. \tag{8}$$

Unless $\mu = 0$, the involved matrices are all invertible. Combining (7) and (8) when $\lambda \neq 0$, we then obtain that there exists a matrix $A(\lambda)$ such that

$$(A(\lambda) - \mathrm{Id}) \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = 0. \tag{9}$$

The function φ will be an eigenfunction if there exists a non-zero solution to (9) and then if $\det(A(\lambda) - \mathrm{Id}) = 0$. The problem is easily studied through a numerical procedure.

1.3 Using thin layers to model membranes

In order to set up a numerical Monte Carlo method to compute the residence time in the cells, we study now another model with interfaces conditions. 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 lies in the middle of $[0, L]$ and we then use the decomposition of Figure 1.

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

$$\begin{cases} \dfrac{\partial C(t,x)}{\partial t} = \nabla(D(x)\nabla C(t,x)),\ x \in [0,L], \\ D_0 \nabla C(t,z) = D_1 \nabla C(t,z) \text{ for } z = L_3, L_3+\delta+L_1, \\ D_1 \nabla C(t,z) = D_0 \nabla C(t,z) \text{ for } z = L_3+\delta, L_3+2\delta+L_1, \\ C(t,z) = C(t,z) \text{ for } z = L_3, L_3+\delta, L_3+L_1+\delta, L_3+L_1+2\delta, \\ C(t,L) = C(t,0) \text{ (periodic boundary condition).} \end{cases} \tag{10}$$

Let us seek an eigenvalue λ in the form

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

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, let us set

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

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

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

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

$$(A'(\lambda) - \mathrm{Id})\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} = 0 \tag{11}$$

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

2 Statistical estimation of the smallest non-negative eigenvalue

While there is no known probabilistic representation of the solution to (6), the stochastic process whose density $p(t, x, y)$ is solution to (10) may be simulated exactly. Several algorithms have been proposed to do so. Here, we used the one presented in [2] with a constant time step δt. For this, we use the thin layer approximation of our model. In Section 3, we discuss the viability of

this approach and show that for a layer width δ small enough, the smallest eigenvalues are for the two types of interfaces (semi-permeable or thin layer). Hence, when the starting point of the particle x_0 is known, we let the particle evolving in the media until a large time T. For N realizations $X^{(1)}, \ldots, X^{(N)}$ of the process X, we then define

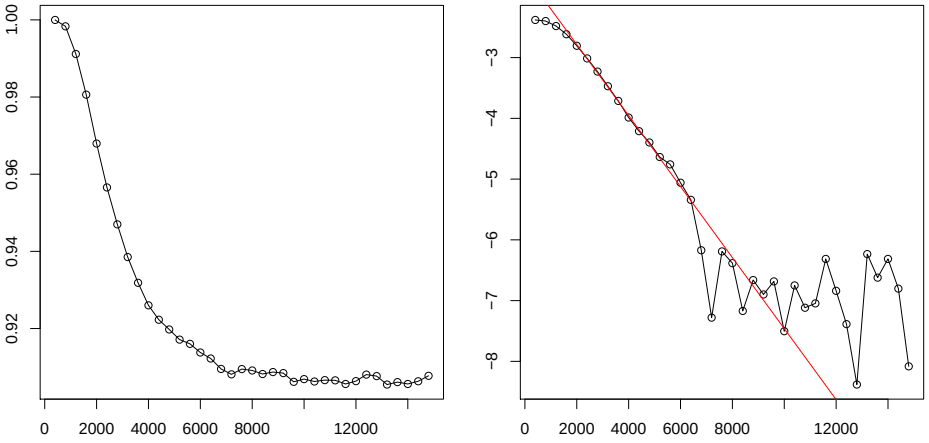
$$v_N(t) = \frac{1}{N} \sum_{i=1}^{N} \mathbf{1}_{\{X_t^{(i)} \in \Omega_i\}}.$$

From the law of large numbers, it holds that

$$v_N(t) \approx_{N \to \infty} u^i(t, x_0).$$

Hence, $v_N(t)$ converges to v_i, at some exponential rate λ as t converges to infinity.
In order to estimate λ and then τ by (5), we then estimate through a linear regression the slope of $(t_i, \log(|v_N(t_i) - v_i|))$ for a large family of times $\{t_i\}_{i=1,\ldots,M}$ in a window $[T_0, T_1]$.
The choice of $[T_0, T_1]$ is done "by hand". In particular, T_0 should be large enough so that the term in $\exp(-\lambda t)$ 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 in a function of type $v_i + ce^{-\lambda t}$. It is then clear that an accurate estimation of λ from the $v_N(t)$ could be performed only if $e^{-\lambda t} \gg Z_t$ and then if $t \ll \log(N)/2\lambda$.
The difficulty with this procedure is that it can only by done *a posteriori*, since the eigenvalues of the opeartors are not known. On the other hand, it is easy to graphically assess a time interval $[T_0, T_1]$ by plotting $u_i := \log(|v_N(t_i) - v_i|)$ against t_i for $i = 1, \ldots, M$.
The drawback of this procedure is that it cannot be fully automated. However, a simple estimation of the time interval $[T_0, T_1]$ can be performed by plotting ε_i against t_i, where ε_i is defined as

$$\varepsilon_i := \left(u_i - \pi(t_i; t_{(i-w):(i-1)}, u_{(i-w):(i-1)})\right)^2,$$



(a) $v_N(t)$ (b) $\log(v_N(t) - v_i)$

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

where $\pi(t; x_{j:k}, y_{j:k}) = \alpha + \beta t$ where α (resp. β) is the intercept value (resp. slope) given by linear least-squares performed on the vector $y_{j:k}$ against the vector $x_{j:k}$, and w is an integer, say $w = 5$. Here, we have used a Matlab like notation to consider only the components ranging from j to k of the vectors x and y. The value of ε_i simply compare the value of u_i with the predicted value of u_i given by a "moving" regression estimator (over a small window of size w) on $\{t_{(i-w):(i-1)}, w_{(i-w):(i-1)}\}$. We then keep the times $\{t_i\}$ for which ε_i is small.

3 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.

Value	From	To
$\kappa = \dfrac{D_1}{\delta}$	10^{-6} µm/µs	10^{-4} µm/µs
D_0	2×10^{-3} µm^2/µs	3×10^{-3} µm^2/µs
L_1	5 µm	20 µm
L_2	$\approx L_1/10$	
T	20,000 µs	50,000 µs

Table 1: A realistic range of parameters.

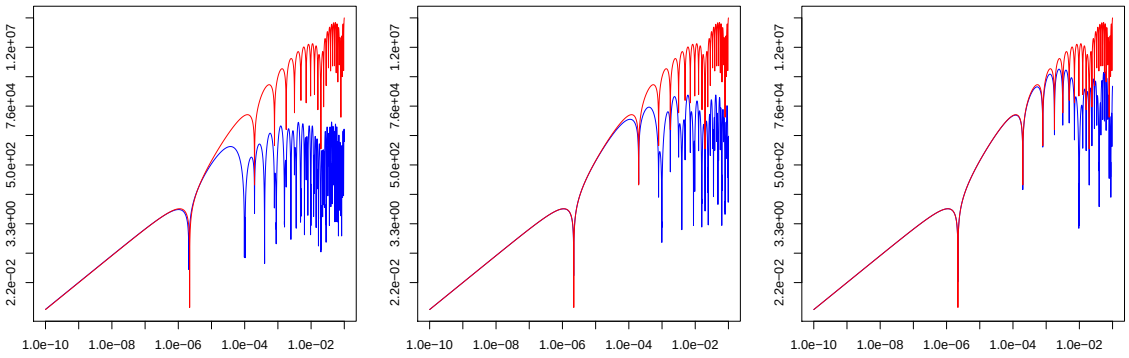
κ	D_0	δ	L_1	L_2	λ_{MC}	λ_{det}	T_0	T_1
10^{-3}	2×10^{-3}	10^{-2}	10	2	4.45×10^{-4}	3.89×10^{-4}	2,000	10,000
10^{-4}	2×10^{-3}	10^{-2}	10	2	1.52×10^{-4}	1.08×10^{-4}	5,000	20,000
10^{-5}	2×10^{-3}	10^{-2}	10	2	4.65×10^{-5}	1.18×10^{-5}	5,000	27,000
10^{-6}	2×10^{-3}	10^{-2}	10	2	4.20×10^{-5}	1.20×10^{-6}	10,000	40,000
10^{-3}	2×10^{-3}	10^{-2}	10	1	6.22×10^{-4}	4.18×10^{-4}	2,000	7,000
10^{-4}	2×10^{-3}	10^{-2}	10	1	2.66×10^{-4}	1.97×10^{-4}	2,000	13,000
10^{-5}	2×10^{-3}	10^{-2}	10	1	8.65×10^{-5}	2.16×10^{-5}	2,000	13,000
10^{-6}	2×10^{-3}	10^{-2}	10	1	7.93×10^{-5}	2.18×10^{-6}	2,000	15,000

Table 2: Monte Carlo estimation of the first non-zero eigenvalue. The units are the same as the one of Table 1.

The matrices $A(\lambda)$ and $A'(\lambda)$ appearing in (9) and (11) are easily computed from the numerical point of view. In Figures 3 and 4, we plot $\log_{10} |\det(A(\lambda) - \text{Id})|$ and $\log_{10} |\det(A'(\lambda) - \text{Id})|$. The peaks of the curves give the values of λ at which $A(\lambda) - \text{Id}$ and $A'(\lambda) - \text{Id}$ are not invertible.
We see that for $\delta = 10^{-2}$ or $\delta = 10^{-3}$, the curves are close and gives then similar eigenvalues. For $\delta = 10^{-3}$, some difference may exist.
Hence, for estimating the first eigenvalue, which is related to the residence time, using the model with thin layers given by (10) instead of the model (6) seems to be an acceptable choice when the parameters are in the range given by Table 1.
In Figure 5, we also plot the value of the first non-zero eigenvalue against κ in a log-log plot.
We also note (See Figures 3 and 4) that the distance between the two smallest non-zero eigenvalues seems to increase when κ decrease.

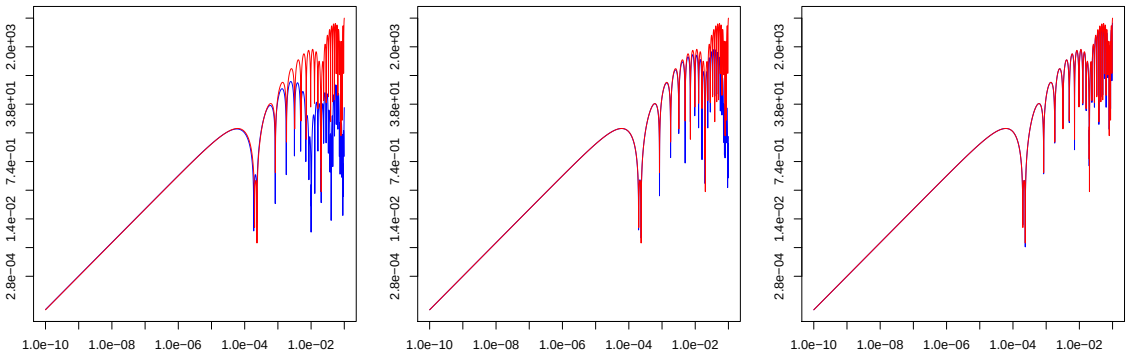
4 Monte Carlo simulations

We now perform some tests on Monte Carlo simulations in order to estimate the first non-zero eigenvalues, which is related to the residence time.
For this, we use 100,000 particles. We estimate the first eigenvalue λ_{MC} with the procedure described in Section 2, which we compare with λ_{det} which is obtained by a root-finding procedure as shown in Section 3.
The width of the layer is $\delta = 10^{-2}$. The time step of the scheme for moving the particles is $\delta t = 10^{-2}$.
The estimator tends to overestimate the value of the smallest non-zero eigenvalue when κ decreases, and then to underestimate the value of the residence time.



(a) $\delta = 10^{-1}$ (b) $\delta = 10^{-2}$ (c) $\delta = 10^{-3}$

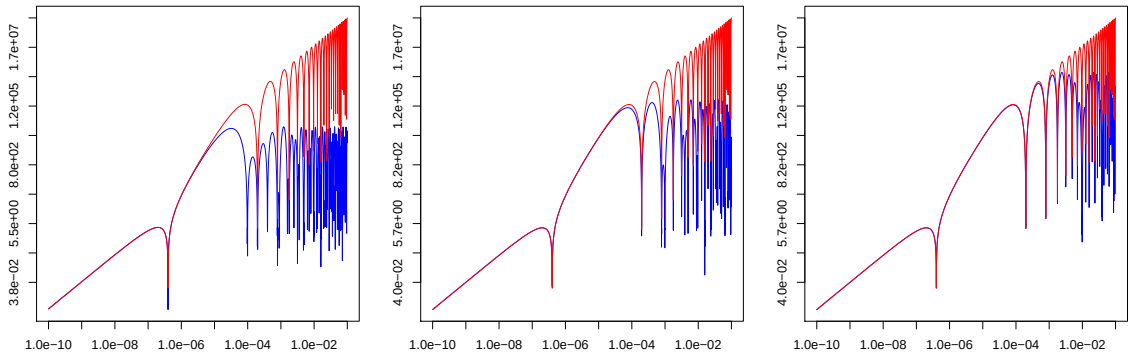
$D_0 = 2 \times 10^{-3}$, $\kappa = 10^{-6}$, $L_1 = 10$, $L_2 = 1$



(d) $\delta = 10^{-1}$ (e) $\delta = 10^{-2}$ (f) $\delta = 10^{-3}$

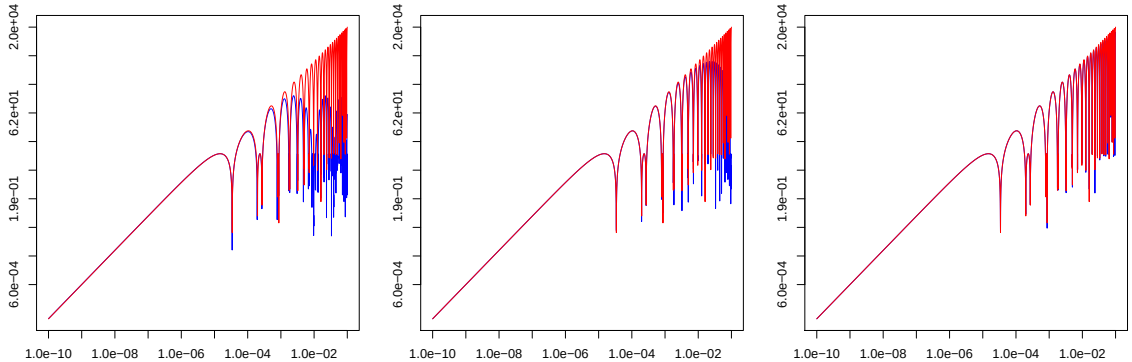
$D_0 = 2 \times 10^{-3}$, $\kappa = 10^{-4}$, $L_0 = 10$, $L_2 = 1$

Figure 3: Simulation of $\log_{10} |\det(A(\lambda) - \mathrm{Id})|$ (blue) and $\log_{10} |\det(A'(\lambda) - \mathrm{Id})|$ (red) as a function of λ.



(a) $\delta = 10^{-1}$ (b) $\delta = 10^{-2}$ (c) $\delta = 10^{-3}$

$D_0 = 2 \times 10^{-3}$, $\kappa = 10^{-6}$, $L_0 = 10$, $L_2 = 10$



(d) $\delta = 10^{-1}$ (e) $\delta = 10^{-2}$ (f) $\delta = 10^{-3}$

$D_0 = 2 \times 10^{-3}$, $\kappa = 10^{-4}$, $L_0 = 10$, $L_2 = 10$

Figure 4: Simulation of $\log_{10} |\det(A(\lambda) - \mathrm{Id})|$ (blue) and $\log_{10} |\det(A'(\lambda) - \mathrm{Id})|$ (red) as a function of λ.

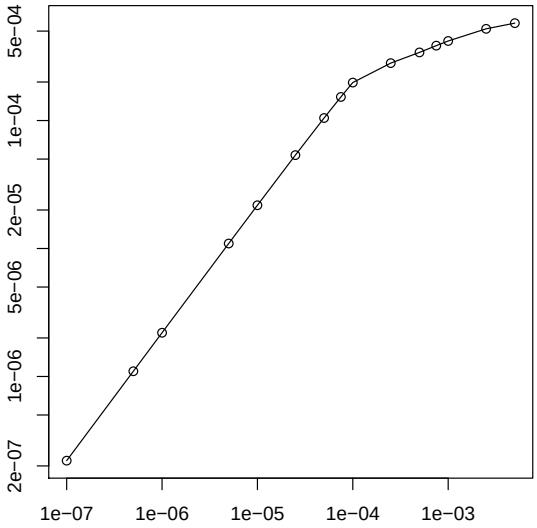


Figure 5: Log-log plot of the smallest non-zero eigenvalue λ against κ for $D_0 = 2 \times 10^{-3}$ µm^2/µs, $L_2 = 1$ and $L_1 = 10$. For $\kappa \leqslant 1 \times 10^{-4}$ µm/µs, the relation seems to be $\lambda = C\kappa$ for a constant $C \approx 1.8$, and then $\tau_i = v_e C/\kappa$.

References

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