Diffusion Across Semi-permeable Barriers: Spectral Properties, Efficient Computation, and Applications

Nicolas Moutal1 · Denis Grebenkov1

Received: 29 June 2018 / Revised: 18 February 2019 / Accepted: 17 September 2019 / Published online: 26 September 2019
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Abstract
We present an efficient method to compute the eigenvalues and eigenmodes of the diffusion operator $\nabla (D \nabla)$ on one-dimensional heterogeneous structures with multiple semi-permeable barriers. This method allows us to calculate the diffusion propagator and related quantities such as diffusion MRI signal or first exit time distribution analytically for regular geometries and numerically for arbitrary ones. The effect of the barriers and the transition from infinite permeability (no barriers) to zero permeability (impermeable barriers) are investigated.

Keywords Diffusion · Semi-permeable barriers · Laplacian spectrum · Multilayer · Composite medium · Diffusion MRI · First-passage phenomena

1 Introduction
Diffusion is a very broad transport mechanism which may describe heat conduction in solids as well as molecular exchanges in biological systems, among many examples. One often characterizes diffusion processes by the “diffusion propagator” (or “heat kernel”) $G(x_0 \to x, t)$ which is the probability density of reaching position $x$ after a time $t$ starting from $x_0$. When diffusion takes place in a homogeneous medium without boundaries, the propagator is a Gaussian distribution centered on $x_0$ with variance $2Dt$, where $D$ is the diffusion coefficient in the medium. On the other hand diffusion in complex systems such as biological cells or composite materials may exhibit non-Gaussian behavior due to confinement, hindrance by semi-permeable barriers or heterogeneity of the diffusion coefficient.

Generally speaking, the diffusion propagator obeys the diffusion equation:

$$\frac{\partial G}{\partial t} = \nabla (D \nabla G), \quad G(x_0 \to x, t = 0) = \delta(x - x_0), \quad (1)$$

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10915-019-01055-5) contains supplementary material, which is available to authorized users.

Nicolas Moutal
nicolas.moutal@polytechnique.edu

1 Laboratoire de Physique de la Matiere Condensee, Ecole Polytechnique, CNRS, IP Paris, 91128 Palaiseau, France
where $\delta$ is the Dirac distribution, $\nabla = \frac{\partial}{\partial x}$ in the one-dimensional case, and the diffusion coefficient $D$ can in general be space and time dependent to capture heterogeneities of the medium [1,2]. Throughout this article, we refer to $\nabla(D\nabla)$ as the “diffusion operator”. Note that if the diffusion coefficient is uniform, then the diffusion operator is simply proportional to the Laplace operator $\nabla^2$. The complexity of the geometry is hidden in the boundary conditions imposed on $G$ at the outer boundaries and possible inner semi-permeable barriers. Analytical solutions of Eq. (1) mainly rely on spectral decomposition over the diffusion operator eigenmodes which are explicitly known only for few geometries: slab, disk, sphere (and some simple extensions) [3]. The study of more complicated structures requires numerical simulations such as stochastic Monte-Carlo simulations [4,5] or PDE solving with finite element or finite difference methods [6]. On top of being time-consuming these techniques give little theoretical insight into the dependence of the propagator on the physical parameters of the simulated medium. In this situation, one-dimensional models of heterogeneous systems partitioned by semi-permeable barriers can help to uncover this dependence and to understand the role of diffusive exchange across the barriers. Note that three-dimensional diffusion in a stack of parallel planes with lateral invariance is naturally reduced to one-dimensional models. As a consequence, these models have a wide variety of applications, for example multilayer electrodes [7–9], coating of electronic components and improving the performance of semi-conductors [10–12], geophysics and thermal analyses of buildings [13–17], industrial processes [18–20], waste disposal and gas permeation in soils [21–24], drug delivery [25–27] and modeling tumor growth [28]. They can also be applied as approximation schemes for finding the spectrum of Sturm-Liouville problems where the coefficients of the differential operator are replaced by piecewise constant (or polynomial) functions (the so-called “Pruess method”) [29–33]. Two applications of particular interest to us are diffusion magnetic resonance imaging (dMRI), a powerful experimental technique for probing diffusion inside complex media such as biological tissues (see Sect.4.2), and first-passage phenomena (Sect. 4.3).

Because of this diversity of applications, many authors have more or less independently tackled such models of one-dimensional diffusion in heterogeneous structures, with various computational techniques: spectral decompositions, Green functions, Laplace transforms and others (see [34,35] for a review of the subject). In this article we consider finite geometries, which are best treated by spectral decompositions (or “separation of variables”). To our knowledge, the most recent and complete work on this topic is the one by Hickson et al. [6,19,20]. However it was mainly devoted to the case of heterogeneous structures with distinct diffusivities and without barriers. Moreover the spectrum was computed numerically and only few analytical results were obtained. On the other hand, some very general mathematical results were obtained by Gaveau et al. for generic heterogeneous media without barriers [36]. Another technique was proposed in the recent work by Carr and Turner [37], in which the solution of Eq. (1) was decomposed on the Laplacian eigenmodes of each compartment separately, instead of the eigenmodes of the whole structure. This technique presents numerical advantages without providing analytical insights onto the spectrum of the diffusion operator.

In this article we present an efficient method to compute the eigenvalues and eigenfunctions of the diffusion operator in one-dimensional domains with multiple barriers. This method allows us to calculate the diffusion propagator and related quantities such as dMRI signal or first exit time distribution analytically for sufficiently regular geometries such as a finite periodic geometry or a micro-structure inside a larger scale structure, and numerically for arbitrary structures.
The article is organized as follows. Section 2 is entirely devoted to analytics. We start with standard computations using transition matrices (Sect. 2.1) and obtain the equation of the spectrum as a transcendental equation \( F(\lambda) = 0 \) (Eq. (22)). Three following subsections are more technical and may be omitted in a first reading. In particular, we express the normalization constant of the eigenmodes as a function of \( F \) (Eq. (24)), and we derive general consequences of the symmetry or the periodicity of the medium (Sects. 2.3 and 2.4, respectively). In Sect. 2.5, we study in more detail the function \( F \) and obtain simple estimates of its roots with respect to the geometrical parameters of the medium, in particular the permeability of the barriers. This part is crucial for the numerical implementation of the method. This section is concluded with some extensions of our model. Section 3 illustrates our general approach on the example of a (finite) periodic structure with multiple identical barriers and compartments. The numerical implementation of the method is presented in Sect. 4. This section is concluded with some extensions of our model. Section 5 concludes the paper and presents further perspectives and open problems.

The electronic Supplementary Material (SM) contains additional developments. Section SM. I is devoted to the application to dMRI. The dependence of the acquired signal on the geometrical parameters of the medium is thoroughly discussed. In Sect. SM. II, the effect of semi-permeable barriers on the diffusive motion is studied from another viewpoint, namely the first exit time distribution. Some technical results are moved to Sect. SM. III, which contains proofs of the existence of infinitely many eigenvalues, their non-degeneracy, their monotonic growth with respect to the barrier permeabilities, as well as a Courant nodal theorem for our particular model of diffusion with barriers.

### 2 Computation of the Eigenmodes of the Diffusion Operator

#### 2.1 General Case

In this section we study the eigenmodes of the “diffusion operator” \( \nabla (D \nabla) \) in a one-dimensional geometry (see Fig. 1). We reproduce the general computational scheme from Ref. [38] and propose improvements specific to the one-dimensional geometry. An interval \([0, L]\) is divided by barriers into \( m \) compartments (or “cells”) \( \Omega_i = (x_{i-1,i}, x_{i,i+1}) \), \( i = 1, \ldots, m \), where \( x_{1,2}, \ldots, x_{m-1,m} \) are the positions of \( m-1 \) inner barriers, and \( x_{0,1} = 0 \) and \( x_{m,m+1} = L \) correspond to the outer barriers. Each compartment is characterized by its

[Fig. 1 Illustration of the geometry. Arbitrarily spaced barriers split the interval \([0, L]\) into \( m \) compartments \( \Omega_i \) of length \( l_i \) and diffusion coefficient \( D_i \). The positions of the barriers are denoted by \( x_{i,i+1} \) and their permeabilities by \( \kappa_{i,i+1} \). One can also take into account relaxation or leakage at the two outer barriers by permeabilities \( K_- \), \( K_+ \).]
length \( l_i = x_{i,i+1} - x_{i-1,i} > 0 \) and diffusion coefficient \( D_i > 0 \) and each barrier by its permeability \( k_{i,i+1} \geq 0 \) or equivalently by its “resistance” to diffusive exchange: \( r_{i,i+1} = 1/k_{i,i+1} \).

Finally one can take into account some relaxation or leakage at the endpoints by non-negative permeabilities (or relaxaton coefficients) \( K_− \) and \( K_+ \).

The diffusion coefficient \( D \) is thus a piecewise constant function:

\[
D(x) = \sum_{i=1}^{m} D_i I_{\Omega_i}(x),
\]

where \( I_{\Omega_i} \) denotes the indicator function of \( \Omega_i \): \( I_{\Omega_i}(x) = 1 \) if \( x \in \Omega_i \) and 0 otherwise. This implies that the diffusion operator can be split into two terms:

\[
\nabla(D\nabla) = D\nabla^2 + (\nabla D)\nabla = D\nabla^2 + \left( \sum_{i=1}^{m-1} (D_{i+1} - D_i) \delta(x - x_{i,i+1}) \right) \nabla.
\]

The second term vanishes at the interior points so that the diffusion operator is reduced to \( D\nabla^2 \). The same is true for the general class of diffusion operators \( \nabla(D^\alpha \nabla(D^{1-\alpha} \cdot)) \), where \( 0 \leq \alpha \leq 1 \) is the Itô-Stratonovitch interpretation parameter (some authors use \( 1 - \alpha \) instead of \( \alpha \)) [39,40]. Here we consider heterogeneous diffusion coefficients with discontinuities at the barriers, hence these operators coincide inside the compartments but yield different boundary conditions at the barriers. Our choice \( \nabla(D\nabla) \) corresponds to the Hänggi–Klimontovich interpretation [41–45] with \( \alpha = 1 \), which is most often used in physical applications. The main reason is that it corresponds to the standard Fick law and that equilibrium solutions of the diffusion equation are constant, which is expected for, say, water diffusing in an isothermal medium. From a mathematical point of view, this choice ensures that the operator is self-adjoint, which allows us to use standard spectral methods.

The \( L^2 \)-normalized eigenmodes \( u \) of the diffusion operator are then determined by the equation

\[
Du'' + \lambda u = 0,
\]

with the boundary conditions

\[
D_i u'|_{\Omega_i} = D_{i+1} u'|_{\Omega_{i+1}} \text{ at the barrier at } x_{i,i+1}
\]

\[
D_i u'|_{\Omega_i} = k_{i,i+1}(u|_{\Omega_{i+1}} - u|_{\Omega_i}) \text{ at the barrier at } x_{i,i+1}
\]

\[
D_1 u'(0) = K_- u(0)
\]

\[
D_m u'(L) = -K_+ u(L),
\]

and the normalization condition

\[
\int_0^L u^2 = 1,
\]

where \( u|_{\Omega_i} \) is the restriction of \( u \) to the cell \( \Omega_i \) \((i = 1, \ldots, m)\) and prime denotes the derivative with respect to \( x \).

Equations (5) and (6) express the flux conservation across the barriers (no accumulation of diffusing particles) and the drop of particle density due to the non-zero resistance of the barriers, respectively. Note in particular that Eq. (5) ensures the continuity of \( D\nabla u = Du' \).

The infinitely thin barriers that we consider can approximate barriers of thickness \( h_{i,i+1} \) with the standard continuity conditions. When \( h_{i,i+1} \) is much smaller than other length scales, one can interpret \( k_{i,i+1} h_{i,i+1} \) as the diffusion coefficient inside the barrier, whereas \( (u|_{\Omega_{i+1}} - u|_{\Omega_i})/h_{i,i+1} \) approximates the derivative of \( u \) across the barrier of thickness \( h_{i,i+1} \).
If $\kappa_{i,i+1} = \infty$ there is no barrier and Eq. (6) becomes a continuity condition for $u$ at $x = x_{i,i+1}$. In the opposite limit $\kappa_{i,i+1} = 0$ the compartments $\Omega_i$ and $\Omega_{i+1}$ do not communicate with each other: the flux $Du'$ is zero at the barrier and the discontinuity $(u|_{\Omega_{i+1}} - u|_{\Omega_i})(x_{i,i+1})$ is arbitrary. One can then study the two parts $[0, x_{i,i+1}]$ and $[x_{i,i+1}, L]$ separately.

To avoid such trivial separations, we consider only non-zero permeabilities: $\kappa_{i,i+1} > 0$ throughout this article. Under this assumption we prove in Sect. SM. III that there are infinitely many eigenvalues $\lambda_n$, $n = 1, 2, \ldots$, and all $\lambda_n$ are simple. One can also easily prove that they are non-negative, and we sort them by ascending order: $0 \leq \lambda_1 < \lambda_2 < \ldots$. Moreover, thanks to the self-adjointness of the diffusion operator $\nabla (D \nabla)$ we know that the eigenmodes $u_n$, $n = 1, 2, \ldots$ form a complete orthonormal basis in the space $L^2(0, L)$ of square-integrable functions on $(0, L)$ [34,35].

For simplicity we further assume that $K_- < \infty$, which allows us to write

$$u = \beta v, \quad v(0) = 1,$$

(10)

with $\beta$ being a normalization constant that ensures Eq. (9). The case of Dirichlet boundary conditions ($K_- = \infty$) requires another convention which is detailed in Sect. SM. IV.5. We study the (non-normalized) eigenmode $v$ first and then we compute the normalization constant $\beta$.

Throughout this section we assume $\lambda \neq 0$. One can see that $\lambda = 0$ is only possible if the relaxation coefficients $K_\pm$ are equal to zero and in this case one gets a constant eigenmode $v = 1$ (and $\beta = 1/\sqrt{L}$).

Equation (4) has a general solution

$$v|_{\Omega_i}(x) = a_i^l \cos(\sqrt{\lambda/D_i}(x - x_{i-1,i})) + b_i^l \sin(\sqrt{\lambda/D_i}(x - x_{i-1,i})),$$

(11)

or equivalently

$$v|_{\Omega_i}(x) = a_i^r \cos(\sqrt{\lambda/D_i}(x - x_{i,i+1})) + b_i^r \sin(\sqrt{\lambda/D_i}(x - x_{i,i+1})),$$

(12)

where $a_i^l, b_i^l$ and $a_i^r, b_i^r$ are constants to be determined, related by

$$\begin{bmatrix} a_i^l \\ b_i^l \\ a_i^r \\ b_i^r \end{bmatrix} = \mathcal{R}_i \begin{bmatrix} a_i^l \\ b_i^l \\ a_i^r \\ b_i^r \end{bmatrix}, \quad \text{where} \quad \mathcal{R}_i = \begin{bmatrix} \cos(\sqrt{\lambda/D_i}l_i) & \sin(\sqrt{\lambda/D_i}l_i) \\ -\sin(\sqrt{\lambda/D_i}l_i) & \cos(\sqrt{\lambda/D_i}l_i) \end{bmatrix}.$$ 

(13)

Note that

$$v|_{\Omega_i}(x_{i,i+1}) = a_i^r, \quad D_i v|_{\Omega_i}(x_{i,i+1}) = \sqrt{\lambda D_i} b_i^r,$$

(14)

with similar formulas for $a_i^l, b_i^l$, so that one can write the boundary equations (5) and (6) as

$$\begin{bmatrix} a_{i+1}^l \\ b_{i+1}^l \\ a_{i+1}^r \\ b_{i+1}^r \end{bmatrix} = \mathcal{K}_{i,i+1} \begin{bmatrix} a_i^l \\ b_i^l \\ a_i^r \\ b_i^r \end{bmatrix}, \quad \text{with} \quad \mathcal{K}_{i,i+1} = \begin{bmatrix} 1 & r_{i,i+1} \sqrt{\lambda D_i} \\ 0 & \sqrt{D_i/D_{i+1}} \end{bmatrix}.$$ 

(15)

The equations at the barriers can thus be restated in a matrix form:

$$\begin{bmatrix} a_{i+1}^l \\ b_{i+1}^l \\ a_{i+1}^r \\ b_{i+1}^r \end{bmatrix} = \mathcal{M}_{i,i+1} \begin{bmatrix} a_i^l \\ b_i^l \\ a_i^r \\ b_i^r \end{bmatrix},$$

(16)

with the notation for the “transition matrix”:

$$\mathcal{M}_{i,i+1} = \mathcal{K}_{i,i+1}\mathcal{R}_i,$$

(17)
with \( R_i \) and \( K_i, K_{i+1} \) defined by Eqs. (13), (15). In the same way, one can rewrite the endpoint conditions (7), (8):

\[
\begin{bmatrix}
-K_- \sqrt{\lambda D_1} \\
\end{bmatrix}
\begin{bmatrix}
al_1^l \\
b_1^l \\
\end{bmatrix} = 0 \quad \text{and} \quad
\begin{bmatrix}
K_+ \sqrt{\lambda D_m} \\
\end{bmatrix}
\begin{bmatrix}
a_m^r \\
b_m^r \\
\end{bmatrix} = 0.
\]

We have the additional condition \( a_1^l = v(0) = 1 \), therefore

\[
\begin{bmatrix}
al_1^l \\
b_1^l \\
\end{bmatrix} = \begin{bmatrix}
1 \\
K_- \sqrt{\lambda D_1} \\
\end{bmatrix} \quad \text{and} \quad
\begin{bmatrix}
a_m^r \\
b_m^r \\
\end{bmatrix} = \epsilon \begin{bmatrix}
1 \\
-K_+ \sqrt{\lambda D_m} \\
\end{bmatrix},
\]

where \( \epsilon \) is an unknown proportionality coefficient.

Equation (16), which relates the coefficients of one cell to those of the next cell, is compatible with Eq. (18), which prescribes the first and last cell coefficients (up to a proportionality factor), only if \( \lambda \) is an actual eigenvalue of the diffusion operator \( \nabla (D \nabla) \). That is, by writing explicitly the condition that the product of all the transition matrices \( M_i, M_{i+1} \) should send the previously determined \((a_1^l, b_1^l)\) onto the \((a_m^r, b_m^r)\), we get the equation on the spectrum of the diffusion operator:

\[
T \begin{bmatrix}
1 \\
K_- \sqrt{\lambda D_1} \\
\end{bmatrix} = \epsilon \begin{bmatrix}
1 \\
-K_+ \sqrt{\lambda D_m} \\
\end{bmatrix},
\]

with

\[
T = R_m M_{m-1, m} \cdots M_{1, 2}.
\]

Note that this condition is equivalent to

\[
\begin{bmatrix}
K_+ \sqrt{\lambda D_m} \\
\end{bmatrix} T = \eta \begin{bmatrix}
-K_- \sqrt{\lambda D_1} \\
1 \\
\end{bmatrix},
\]

and to

\[
F(\lambda) := \begin{bmatrix}
K_+ \sqrt{\lambda D_m} \\
\end{bmatrix} T(\lambda) \begin{bmatrix}
1 \\
K_- \sqrt{\lambda D_1} \\
\end{bmatrix} = 0.
\]

The proportionality coefficients \( \epsilon \) and \( \eta \) are constrained by the relation: \( \epsilon \eta = \det T = \sqrt{D_1 / D_m} \).

### 2.2 Computation of the Norm

Now we compute the normalization constant \( \beta \). Since the eigenmode \( v \) is a piecewise combination of sine and cosine functions, the constant \( \beta \) can be obtained by a direct integration (see Ref. [38]). This approach is convenient for numerical computations. Here we present another approach which is more suitable for analytical derivations. The starting point of the method is the spectral decomposition of the diffusion propagator:

\[
G(t, x_0 \to x) = \sum_{n=1}^{\infty} u_n(x_0) u_n(x) e^{-\lambda_n t} = \sum_{n=1}^{\infty} \beta_n^2 v_n(x_0) v_n(x) e^{-\lambda_n t},
\]

where \( n = 1, 2, \ldots \) spans the infinitely many eigenmodes of the diffusion operator. We now compute this propagator in a different way by solving explicitly Eq. (1). Again, we use Eq. (3) to transform \( \nabla (D \nabla) \) into \( D \nabla^2 \) at the interior points. Let \( \tilde{G}(s, x_0 \to x) \) denote the Laplace transform of the propagator: \( \tilde{G}(s, x_0 \to x) = \int_0^{\infty} e^{-s t} G(t, x_0 \to x) \, dt \). Then \( \tilde{G} \) obeys the equation

\[
D(x) \tilde{G}''(s, x_0 \to x) = s \tilde{G}(s, x_0 \to x) - \delta(x - x_0),
\]
with the same boundary conditions (5)–(8) as for the propagator $G$ in time domain. As in the previous section, prime denotes derivative with respect to $x$. We use the method from Sect. 2.1 to solve the homogeneous equation with the inner boundary conditions (5), (6) imposed at the barriers: if $s \neq 0$ we can build two solutions $\phi(s, x)$ and $\psi(s, x)$ such that:

\[- \phi(s, x) \text{ is built from } \begin{bmatrix} a_s^1 \\ b_s^1 \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \end{bmatrix} : \text{at the left endpoint its derivative with respect to } x \text{ is zero and its value is one},\]

\[- \psi(s, x) \text{ is built from } \begin{bmatrix} a_s^1 \\ b_s^1 \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \end{bmatrix} : \text{at the left endpoint its derivative with respect to } x \text{ is } \sqrt{s/D_1} \text{ and its value is zero.}\]

It is then easy to obtain the complete solution because the Wronskian matrix $\mathcal{W} = \begin{bmatrix} \phi(s, x) & \psi(s, x) \\ \phi'(s, x) & \psi'(s, x) \end{bmatrix}$ is quite simple. Indeed over any layer $\Omega_i$ the determinant of $\mathcal{W}$ is constant and equal to $\sqrt{sD_1}/D_i$. This is obtained from the differential equation obeyed by $\phi(s, x)$ and $\psi(s, x)$ and the boundary conditions at each barrier. The standard method for solving the second order differential equations then yields

$$\tilde{G} = \mu \phi + \nu \psi,$$

with the equation on $\mu$, $\nu$:

$$D(x) \begin{bmatrix} \mu'(s, x) \\ \nu'(s, x) \end{bmatrix} = \mathcal{W}^{-1} \begin{bmatrix} 0 \\ -\delta(x - x_0) \end{bmatrix} = -\frac{D(x)}{\sqrt{D_1 s}} \delta(x - x_0) \begin{bmatrix} -\psi(s, x) \\ \phi(s, x) \end{bmatrix}.$$

After a straightforward integration, we obtain

$$\tilde{G}(x_0 \rightarrow x, s) = \left( A + \frac{1}{\sqrt{D_1 s}} \psi(s, x_0) H(x - x_0) \right) \phi(s, x) + \left( B - \frac{1}{\sqrt{D_1 s}} \phi(s, x_0) H(x - x_0) \right) \psi(s, x),$$

which is valid for any $x_0, x \in [0, L]$, and $s \neq 0$, where $H$ is the Heaviside function and the constants $A$ and $B$ remain to be determined. We consider general relaxing conditions at the endpoints:

$$\begin{cases} D_1 \frac{\partial \tilde{G}}{\partial x}(x = 0) = K_- \tilde{G}(x = 0) \\ D_m \frac{\partial \tilde{G}}{\partial x}(x = L) = -K_+ \tilde{G}(x = L) \end{cases},$$

from which

$$A = \frac{\phi(s, x_0)(D_m \psi'(s, L) + K_+ \psi(s, L)) - \psi(s, x_0)(D_m \phi'(s, L) + K_+ \phi(s, L))}{D_m K_- \psi'(s, L) + K_+ K_- \psi(s, L) + D_m \sqrt{D_1 s} \phi'(s, L) + K_+ \sqrt{D_1 s} \phi(s, L)},$$

$$B = \frac{K_- A}{\sqrt{D_1 s}}.$$

Now we simplify the above expressions. We anticipate that the non-normalized eigenmodes are $v_n(x) = v(\lambda_n, x)$, with

$$v(s, x) = \phi(s, x) + \frac{K_-}{\sqrt{D_1 s}} \psi(s, x),$$
and we use Eq. (14) to get

\[ A\phi(s, x) + B\psi(s, x) = \frac{v(s, x)\phi(s, x)}{K_-} - \frac{\sqrt{D_1}s}{K_-} v(s, x) v(s, x_0) \left[ \begin{array}{c} K_+ \sqrt{D_m}s \\ T(s) \end{array} \right] \frac{1}{F(s)}, \]

with \( T \) and \( F \) defined in Eqs. (20), (22), respectively, in which \( \lambda \) is replaced by \( s \). To obtain the propagator in time domain, one needs to perform an inverse Laplace transform. This is done by looking for the poles \( s = \lambda_n \) of \( \tilde{G} \) and the above formula shows that they are given by the zeros of \( F(s) \), as expected. We prove in Sect. SM. III.2 that these zeros are simple. At \( s = \lambda_n \), one can use Eqs. (19) and (21) to compute the residue of \( \tilde{G} \), which yields simply

\[ \text{Res}_{s=\lambda_n} (\tilde{G}) = \frac{-\eta_n}{\eta_n} \sqrt{D_1}s v(s, x) v(s, x_0) \frac{dF}{ds} \bigg|_{s=\lambda_n}. \]

By comparison with Eq. (23), this allows us to conclude:

\[ \beta_n^{-2} = -\frac{1}{\eta_n \sqrt{D_1\lambda_n}} \frac{dF}{d\lambda} (\lambda_n). \]  

(24)

In general, one obtains \( \eta_n \) by computing the matrix product in Eq. (21). A great simplification occurs in the case of symmetric geometries, which is the topic of the next section.

### 2.3 Symmetry Properties

For a geometry which is symmetric with respect to the middle of the interval \([0, L]\), some simplifications occur. In fact the symmetry of the geometry implies that the eigenmodes are either symmetric or anti-symmetric with respect to the middle of the interval, and as a consequence \( \epsilon = \eta = +1 \) or \( \epsilon = \eta = -1 \), respectively. These statements can be easily proved with the above matrix formalism. In fact, the symmetry of the geometry is equivalent to the two properties:

1. The endpoints vectors \( V_+ = \left[ -\frac{1}{K_+} \right] \) and \( V_- = \left[ \frac{1}{K_-} \right] \) have equal first components and opposite second components, which follows from the symmetry \( K_- = K_+, D_1 = D_m \). With the notation \( S = \left[ \begin{array}{cc} 1 & 0 \\ 0 & -1 \end{array} \right] \), this can be restated as \( V_\pm = SV_\mp \).

2. The inverse of the transition matrix \( T \) is obtained by replacing the off-diagonal terms by their opposite in its expression (note that this corresponds to the transformation \( \sqrt{\lambda} \rightarrow -\sqrt{\lambda} \)). In fact, this property is clearly true for the “elementary blocks” \( K \) and \( \mathcal{R} \) and thus it is also the case for \( \mathcal{R}_m K_{m-1,m} \mathcal{R}_{m-1} \ldots \mathcal{K}_{1,2} \mathcal{R}_1 \) because \( \mathcal{R}_i = \mathcal{R}_{m+1-i} \) and \( \mathcal{K}_{i,i+1} = \mathcal{K}_{m-i,m+1-i} \). In other words, \( T^{-1} = \mathcal{S}T \).

The consequence of these two properties is that Eq. (19) can be restated as: “\( V_- \) is an eigenvector of \( ST \)” and that this matrix is equal to its inverse:

\[ (ST)^{-1} = T^{-1}S^{-1} = ST. \]

This implies that the eigenvalues of this matrix, hence the proportionality coefficients \( \epsilon, \eta \) in Eqs. (19) and (21), are equal to \( \pm 1 \). We can also easily prove the symmetry or anti-symmetry of the eigenmodes. In fact, one has
\[
\begin{bmatrix}
\alpha_i' \\
\beta_i'
\end{bmatrix} = K_{i-1,*} R_{i-1} \ldots R_1 \mathcal{V}_-
\]
\[
\begin{bmatrix}
\alpha_{m+1-i}' \\
\beta_{m+1-i}'
\end{bmatrix} = K_{m+1-i,*} R_{m+1-i}^{-1} R_{m+2-k} \ldots R_m \mathcal{V}_+
\]

Hence
\[
\begin{bmatrix}
\alpha_{m+1-i}' \\
\beta_{m+1-i}'
\end{bmatrix} = SK_{i-1,*} S R_{i-1} \ldots S R_1 S \mathcal{V}_+ = \epsilon S \begin{bmatrix}
\alpha_i' \\
\beta_i'
\end{bmatrix}.
\]

Let \( x \in \Omega_i \), we write \( x = x_{i-1,*} + \xi \), with \( 0 < \xi < l_i \), which implies by symmetry that \( L - x = x_{m+1-i,*} + \xi \). According to Eqs. (11), (12), and (25), we have then
\[
v(x) = \begin{bmatrix}
\alpha_i' \\
\beta_i'
\end{bmatrix} \begin{bmatrix}
\cos(\xi \sqrt{\lambda_i / D_i}) \\
\sin(\xi \sqrt{\lambda_i / D_i})
\end{bmatrix} = \epsilon v(L - x),
\]

since \( D_i = D_{m+1-i} \). Therefore the eigenmode is symmetric if \( \epsilon = +1 \) and anti-symmetric if \( \epsilon = -1 \). Moreover from Eq. (24) we deduce that the derivative \( \frac{dF}{d\lambda}(\lambda_n) \) and \( \eta_n \) have opposite signs. Because the eigenvalues \( \lambda_n \) are the zeros of \( F \), the derivative alternates between positive and negative sign, and so do \( \eta_n \) and \( \epsilon_n \). In particular, in the case of a symmetric geometry, the modes \( u_n \) are alternately symmetric and anti-symmetric. One can show that the first mode \( u_1 \) is always symmetric (\( \epsilon_1 = \eta_1 = 1 \)), hence
\[
\epsilon_n = \eta_n = (-1)^{n-1}.
\]

### 2.4 Periodicity Properties

A finite periodic geometry is an \( M \)-times repetition of an elementary block composed of \( N \) compartments: \( (D_1; l_1), (D_2; l_2), \ldots, (D_N; l_N) \). The transition matrix of the block is
\[
\mathcal{M} = K_{\text{inter}} R_N K_{N-1,N} \ldots R_1,
\]

where \( K_{\text{inter}} \) is the matrix corresponding to the inter-block barriers. Then the complete transition matrix \( T \) is equal to
\[
T = K_{\text{inter}}^{-1} \mathcal{M}^M.
\]

Because of the periodicity,
\[
\det \mathcal{M} = \sqrt{\frac{D_N}{D_1}} \sqrt{\frac{D_{N-1}}{D_N}} \ldots \sqrt{\frac{D_1}{D_2}} = 1.
\]

This property makes the computation of \( \mathcal{M}^M \) easier, thanks to the formula
\[
\mathcal{M}^M = \frac{\sin M \psi}{\sin \psi} \mathcal{M} - \frac{\sin(M - 1) \psi}{\sin \psi} \mathcal{I}_2,
\]

where \( \mathcal{I}_2 \) is the \( 2 \times 2 \) identity matrix and \( \psi \) is implicitly defined by
\[
\cos \psi = \frac{1}{2} \text{Tr} \mathcal{M}.
\]
Fig. 2 Example of roots which may prove challenging to find numerically with standard methods. We consider five compartments and \( D_1 = \ldots = D_5 = 1 \), \( r_{1,2} = \ldots = r_{4,5} = 10 \) and the lengths \( l_i \) of the five compartments are: 1; 1.2; 1.5; 1.2; 1, with reflecting boundary conditions at the endpoints: \( K_\pm = 0 \). The root \( z = 6.30446 \) (b) corresponds to \( l_3 = 1.5 \), with \( n = 3, \zeta = 2 \), whereas the two roots \( z_{\pm} = 6.2991316 \pm 8.7 \cdot 10^{-6} \) (c) correspond to \( l_1 = l_5 = 1 \), with \( n = 2, \zeta = 1 \) (see explanations in the text). Notice the scale changes, horizontally and vertically, between (a), (b) and (c).

Formula (29) implies that the inter-block variation of the coefficients \( a, b \) has the form:

\[
a_{i_0+N(j-1)} = A \cos(j\psi) + B \sin(j\psi), \quad j = 1, \ldots, M,\]

with a similar formula for \( b \), where \( A \) and \( B \) are coefficients which depend on the choice of the origin \( i_0 \in \{1, \ldots, N-1\} \). Thus \( \psi \) governs the global behavior of the mode (when the number \( M \) of repeated blocks is sufficiently large).

### 2.5 Study of the Spectrum

The main numerical difficulty of the above method is to solve Eq. (22) on the spectrum, that is to find the zeros of \( F(\lambda) \). In fact, a standard method to find all the zeros of a function in a given interval is to compute the function on a fine array \((0, \epsilon, 2\epsilon, \ldots)\) and to look for the sign changes, that indicate the presence of at least one zero. By decreasing \( \epsilon \), one is assured at some point to find all the zeros of the function. However, in general one knows neither the number of zeros of the function in a given interval nor the minimal spacing between the zeros. In turn, missing some zeros would result in missed eigenmodes, and thus in inaccurate computation of the propagator and the related diffusion quantities. An example of \( F(\lambda) \) shown in Fig. 2 illustrates that some roots may be very close to each other. We provide here a rough analysis of Eq. (22) in order to study this phenomenon.

We discard the elementary case of a single interval \((m = 1)\) where the roots of \( F \) are explicitly known \([1,2]\). Let us assume for simplicity that all the diffusion coefficients \( D_i \) and the barrier resistances \( r_{i,i+1} \) are identical (denoted \( D \) and \( r \), respectively). Furthermore we
set the relaxation coefficients $K_\pm$ to zero. We change the variable $\lambda$ by $z = \sqrt[\lambda/D}$ and reveal an explicit dependence of $F$ on the geometry (omitting $D$ and $r$ for the sake of clarity):

$$F(\lambda) = F_m(z; l_1, \ldots, l_m).$$

### 2.5.1 Regime $r \to 0$

First we consider the regime of quasi-permeable barriers, that is $r \to 0$. One has

$$K = I_2 + r D z N, \quad N = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix},$$

from which we deduce the first-order expansion

$$F_m(z; l_1, \ldots, l_m) \approx -\sin(z L) + r D z \sum_{i=1}^m \sin(z(l_1 + \ldots + l_i)) \sin(z(l_{i+1} + \ldots + l_m)).$$

This formula implies that the roots are approximately equal to $z_0 = n \pi / L$, with an integer $n$. In fact, one can compute the first order correction to this formula, which yields

$$z \approx \frac{n \pi}{L} \left(1 - \frac{r D}{l} \left[ \frac{1}{m} \sum_{i=1}^m \sin^2 \left(\frac{n \pi (l_1 + \ldots + l_i)}{L} \right) \right] \right),$$

where $l = L/m$ is the arithmetic mean of the $l_i$. The factor inside the brackets is always less than 1, hence the (first order) relative perturbation of the roots is at most $r D / l$. Therefore in the regime of quasi-permeable inner barriers ($r D / l \ll 1$) the roots are easy to find numerically because we have a good estimate of their position and a good lower bound of the distance between them.

### 2.5.2 Regime $r \to \infty$

Now we turn to the opposite regime of almost impermeable barriers: $r \to \infty$. In this case one writes

$$K = r D z \left( N + \frac{1}{r D z} I_2 \right).$$

For $z$ large enough such that $r D z \gg 1$, this yields

$$F_m(z; l_1, \ldots, l_m) \approx (-r D z)^{m-1} \sin(z l_1) \cdots \sin(z l_m)
\times \left(1 - \frac{1}{r D z} \sum_{i=1}^{m-1} \sin(z(l_i + l_{i+1})) \sin(z l_{i+1}) + \ldots \right).$$

From this expression one gets the approximate roots $z_0 = n \pi / l_i$ with an integer $n$, as expected. The non-zero permeability of the barriers increases the values of the roots by coupling the compartments to their nearest neighbors. The higher-order terms of the expansion (33) involve coupling between next-nearest neighbors, etc. From the above formula we expect the increase to be of order $(r D z_0)^{-1}$. The case $n = 0$ (that is, $z_0 = 0$) is special and we treat it later. Note that the above expansion is valid around $z_0 = n \pi / l_i$ (with $n > 0$) if $r D z \gg 1$, that is $r D / l_i \gg 1$. 

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If we consider an isolated root $z_0 = n\pi/l_i$ (which means that all the other $n'/\pi/l_{i'}$ are located at a relative distance much greater that $(rDz_0)^{-1}$), then we get

$$z \approx \frac{n\pi}{l_i} + \frac{\zeta_i}{n\pi rD},$$

where $\zeta_i$ is the number of neighbors of the cell $i$ ($\zeta_i = 2$ if $1 < i < m$, otherwise $\zeta_i = 1$).

The case of non-isolated roots is more complicated but also more interesting. In fact all the numerical difficulties come from this case. From the equation

$$\mathcal{R}_i \begin{bmatrix} 1 \\ 0 \end{bmatrix} [0 1] \mathcal{R}_i - \begin{bmatrix} 1 \\ 0 \end{bmatrix} = -\sin(zl_i)\mathcal{R}_i,$$

we deduce the following general relation which is valid for any $i$ from 1 to $m - 1$:

$$F_m(z; l_1, \ldots, l_m) = \left[ F_i(z; l_1, \ldots, l_i) F_{m+1-i}(z; l_1, \ldots, l_m) - F_{i-1}(z; l_1, \ldots, l_i-1) F_{m-i}(z; l_{i+1}, \ldots, l_m) \right] F_i(z; l_i).$$

(35)

Now we assume that there exist $i_1 < i_2$ such that

$$z_0 = \frac{n_1\pi}{l_{i_1}} = \frac{n_2\pi}{l_{i_2}},$$

with $n_1, n_2$ integers. Note that $n_1/n_2 = l_{i_1}/l_{i_2}$. We look for an approximate root of the form $z = z_0(1 + \eta)$, with $\eta \sim (rDz_0)^{-1}$ (where $\sim$ means “is of the same order of magnitude as”).

First let us consider the case where two compartments $i_1$ and $i_2$ are not neighbors, that is $i_1 + 1 < i_2$. From Eq. (33) we infer

$$F_{i_1+1}(z; l_1, \ldots, l_{i_1+1}) \sim (rDz)^{i_1} \eta \sim (rDz)^{i_1-1},$$

$$F_{m-i_1}(z; l_{i_1+1}, \ldots, l_m) \sim (rDz)^{m-1-i_1} \eta \sim (rDz)^{m-2-i_1},$$

$$F_{i_1}(z; l_1, \ldots, l_{i_1}) \sim (rDz)^{i_1-1} \eta \sim (rDz)^{i_1-2},$$

$$F_{m-i_1}(z; l_{i_1+1}, \ldots, l_m) \sim (rDz)^{m-2-i_1} \eta \sim (rDz)^{m-3-i_1},$$

hence Eq. (35) becomes

$$F_m(z; l_1, \ldots, l_m) = \frac{F_{i_1}(z; l_1, \ldots, l_{i_1}) F_{m+1-i_1}(z; l_{i_1}, \ldots, l_m)}{F_i(z; l_i)} (1 + O((rDz)^{-2})) .$$

We deduce that the roots of $F_m(z; l_1, \ldots, l_m)$ are given by the roots of the functions $F_{i_1}(z; l_1, \ldots, l_{i_1})$ and $F_{m+1-i_1}(z; l_{i_1}, \ldots, l_m)$, which are not coupled to the first order in $(rDz)^{-1}$:

$$z \approx z_0 + \frac{\zeta_{i_1}}{n_1\pi rD}$$

and

$$z \approx z_0 + \frac{\zeta_{i_2}}{n_2\pi rD}.$$

(36)

Note that the same is true for any number of “coinciding” roots as long as they correspond to non-adjacent compartments. The roots are at a relative distance of order $(rDz_0)^{-1}$ if $n_1/\zeta_{i_1} \neq n_2/\zeta_{i_2}$. If $n_1/\zeta_{i_1} = n_2/\zeta_{i_2}$ one has to compute the next-order corrections which involve the length of the other compartments, as explained previously. One can show that the term of order $(rDz_0)^{l_1-l_2}$ is always non-zero; for symmetric geometries $(rDz_0)^{l_1-l_2}$ may be the first non-zero term of the expansion of the relative difference of the roots.
Now we consider the case $i_2 = i_1 + 1$. We use Eq. (33) to get

$$F_m(z; l_1, \ldots, l_m) \approx (-rDz)^{m-3} \left( \prod_{i \neq i_1, i_1+1} \sin(zl_i) \right) \times \left( n_1n_2X^2 - (\xi_{i_1}n_1 + \xi_{i_2}n_2)X + (\xi_{i_1}\xi_{i_2} - 1) \right),$$

where $X = rD\pi\eta$. Thus we obtain two roots:

$$z_{\pm} = z_0 + \frac{X_{\pm}}{rD\pi}, \quad \text{with} \quad X_{\pm} = \frac{\xi_{i_1}n_1 + \xi_{i_2}n_2 \pm \sqrt{(\xi_{i_1}n_1 - \xi_{i_2}n_2)^2 + 4n_1n_2}}{2n_1n_2}.$$

(37)

Note that $z_+ - z_- \geq \frac{2}{\pi\sqrt{n_1n_2rD}}$. One can perform the same computations for a larger number of adjacent cells with “coinciding” roots: at the end one has to solve a polynomial equation in the variable $X$. The roots are always distinct and separated by a relative distance of order $(rDz_0)^{-1}$. Section 3.1 is devoted to the exact computation of the roots for an array of identical cells, which is a good example of such a situation.

In all the above computations we assumed $z_0 = n\pi/l_i$ with positive $n$. However there are also $m$ roots located near zero. To find them we expand the sine and cosine functions in Eq. (33) and get to the first order in $zl$ a polynomial equation of degree $m$ in the variable $Z = rDl z^2$, where $l$ is the harmonic mean of the $l_i$. Hence we obtain $m$ roots of the form:

$$z_n = \sqrt{\frac{Z_n}{rDl}}, \quad n = 1, \ldots, m$$

(38)

with $Z_n$ spanning the solutions of the polynomial equation. Note that we assumed $rD/l_i \gg 1$ hence one has $zl \ll 1$, which legitimates a posteriori the polynomial expansion. Furthermore, the first coefficients of the polynomial expansion are readily available from Eq. (33) and we get from them that:

$$\sum_{n=1}^{m} Z_n \approx 2m.$$

(39)

This formula is valid in the regime $rD/l \gg 1$ and its simplicity comes from the particular choice of $l$ we made (harmonic mean of the $l_i$). If one assumes that the roots $Z_n$ are approximately equispaced at small $n$, then one obtains immediately that the first roots $Z_n$, and hence $\lambda_n$, follow a $1/m^2$ dependence on $m$.

From this analysis of the low permeability regime ($rD/l_i \gg 1$ for all $i$) we can draw several conclusions, partly illustrated in Fig. 2.

– the $m$ first roots ($zl \ll 1$) behave differently than the other ones. They typically spread over a distance $(rDl)^{-1/2}$.

The following points only apply to the other roots ($zl \gtrsim 1$).

– all the roots increase from the limits $z_0 = n\pi/l_i$ with the permeability of the inner barriers (a general mathematical proof of this statement is given in Sect. SM. III.3). The relative increase is of the first order in $(rDz_0)^{-1}$;

– very close roots associated to adjacent cells are coupled by the permeability of their barrier and separate from each other by a relative distance of order $(rDz_0)^{-1}$;

– very close roots associated to non-adjacent cells are not coupled to the first order in $(rDz)^{-1}$. The difficult case is when the two cells have the same length: then $n_1 = n_2$ and the relative distance between the two roots is in the best case of order $(z_0rD)^{-2}$. In fact,
it depends on the length of all other cells. For example, symmetric geometries typically lead to a relative distance between roots of order \((z_0 r D)^{-|i_2-i_1|}\).

All the previous computations are somewhat schematic because we made a particular choice of geometry (same diffusion coefficients, same permeability and no relaxation at the outer boundaries) from the beginning. However, the above conclusions are globally still valid in the general case, with appropriate modifications. For example if one considers perfectly relaxing condition at the endpoints \((K_\pm = \infty)\), then in the low-permeability limit the roots corresponding to the outer compartments are \(z_0 = (n + 1/2)\pi / l_i\) \((i = 1 \text{ or } m)\), whereas the roots corresponding to the other compartments are \(z_0 = n\pi / l_i\), \(1 < i < m\) (with an integer \(n\)). Thus one has to consider separately the case of the outer compartments depending on the conditions at the outer boundaries. We come back to the relaxing case in Sect. SM. II and Sect. SM. IV.5. Moreover, the case of heterogeneous diffusion coefficients is treated analytically in the simplest case of a bi-periodic structure in Sect. SM. V.

### 2.6 Extensions

The above analysis may be extended in many ways. First, one can consider more general boundary conditions. In particular, many experiments in heat conduction are done with one end of the system in contact with a heat source (acting as a constant heat flux or as a thermostat with a constant temperature). One should then replace our homogeneous outer boundary conditions (7), (8) by inhomogeneous boundary conditions. The only difference is in the steady-state solution \((\lambda = 0)\) which is easy to obtain, whereas the transient solution remains the same (see [19,34]). One is then often interested in the “critical time”, i.e. the typical time required to reach the steady-state solution. More precisely, one definition of the critical time is the time at which the average temperature over the sample is equal to some fraction \(\alpha < 1\) of the average steady-state temperature over the sample. Other definitions and a thorough comparison of these definitions are detailed in [46,47]. This time is essentially given by the study of the first non-zero eigenvalue of the diffusion operator, for which we are able to obtain estimates with respect to the geometrical parameters of the medium (such as Eq. (38), which yields \(\lambda \sim (rlm^2)^{-1}\), in the low-permeability regime). The situation is different when the boundaries are subject to modulated heating, which is the case in geophysics and building design [13–17], and in photothermal measurements [11,12]. One can still transform the problem into an homogeneous boundary problem but it requires adding a suitable source term to the diffusion equation [34]. In some cases the main mechanism of heat relaxation at the outer boundaries is not conduction–convection but radiation, with a non-linear \(T^4\) heat flux [48]. Finally, when considering diffusion of ions in multilayer chemical system such as electrodes, one writes chemical equilibrium condition at the interfaces: the ratio of concentrations on both sides of the interface is equal to the partition coefficient [7–9,49,50]. This is another type of inner boundary condition, which leads to different \(K\) matrices, quite similar to the case of heterogeneous diffusion coefficients and no barriers.

Another possible generalization is the inclusion of bulk reaction rates inside the compartments. That is, to change Eq. (1) to a reaction–diffusion equation:

\[
\frac{\partial G}{\partial t} = D\nabla^2 G + \mu G, \tag{40}
\]

where \(\mu\) may depend on space and \(G\) [46]. If \(\mu\) is constant, then one gets the solution of Eq. (40) by multiplying the solution of Eq. (1) by \(\exp(\mu t)\). The case of piecewise constant \(\mu\) (\(\mu = \mu_i\) on \(\Omega_i\)) is slightly more complicated but may be easily incorporated into our
computations. Such reaction–diffusion models may describe diffusion of molecules that can be trapped, killed, destroyed, or loose their activity [51–55] or, on the opposite, self-heating by temperature-induced oxidation [56] ($\mu > 0$). Other applications include ecology dynamics [57] and fabrication of multilayer foil materials [58,59].

Last, one can consider other equations than the diffusion equation (1), for example:

- inhomogeneous Laplace (Poisson) equation: $\nabla(D\nabla\Psi) = F$,
- inhomogeneous Helmholtz ($s > 0$) or modified Helmholtz ($s < 0$) equations: $(s + \nabla D\nabla)\Psi = F$, \(\nabla(D\nabla\Psi) = F, \Psi(x, t = 0) = U(x),\)
- inhomogeneous diffusion equation: $\frac{\partial \Psi}{\partial t} - \nabla(D\nabla\Psi) = F, \Psi(x, t = 0) = U(x)$, $\frac{\partial \Psi}{\partial t}(x, t = 0) = V(x)$,

where $F, U, V$ are given functions, and with the boundary conditions (5), (6), (7), and (8). Thanks to the knowledge of the eigenmodes basis of the diffusion operator $\nabla(D\nabla)$, the above equations may be solved by decomposing $u$ and $F$ over this basis [1,2].

The computational method that we presented is therefore relevant to many models and applications. In the Supplementary Material we discuss two particular examples: diffusion MRI (Sect. SM. I) and first exit time distribution (Sect. SM. II).

3 Example: Simple Periodic Geometry

In this section, we illustrate the application of our general method to the case of a (finite) periodic structure which is relevant for various applications. Throughout this section, we assume that all $l_i, D_i, \kappa_{i,i+1}$ are the same (denoted $l, D, \kappa$ in the following). We apply the results of Sect. 2 and obtain the eigenmodes and eigenvalues $u_n, \lambda_n$. Similar computations for more complicated structures are presented in Sect. SM. V (bi-periodic geometry) and Sect. SM. VI (two-scale geometry).

3.1 Eigenmodes

We assume reflecting boundary conditions at the endpoints ($K_{\pm} = 0$) and introduce the dimensionless parameters

$$\alpha = \sqrt{\lambda/Dl} \quad \text{and} \quad \tilde{r} = 1/\tilde{\kappa} = rD/l.$$  \hfill (41)

Then the transition matrix of the elementary block is simply

$$\mathcal{M} = \mathcal{K} = \begin{bmatrix} \cos \alpha - \tilde{r} \alpha \sin \alpha & \sin \alpha + \tilde{r} \alpha \cos \alpha \\ -\sin \alpha & \cos \alpha \end{bmatrix},$$ \hfill (42)

and Eq. (19) on the spectrum becomes

$$\mathcal{K}^{-1} \mathcal{M}^m \begin{bmatrix} \alpha \\ 0 \end{bmatrix} = \epsilon \begin{bmatrix} \alpha \\ 0 \end{bmatrix}.$$ \hfill (43)

Since the geometry is symmetric, we already know that $\epsilon = \pm 1$. Furthermore we use the results of Sect. 2.4 to compute $\mathcal{M}^m$: first we apply Eq. (30) to define $\psi$:

$$\cos \psi = \cos \alpha - \frac{\tilde{r}}{2} \alpha \sin \alpha,$$ \hfill (44)
then from Eq. (29), we get

$$M^m = \begin{pmatrix} (\cos \alpha - \tilde{r} \alpha \sin \alpha) \frac{\sin m\psi}{\sin \psi} - \sin \alpha \frac{\sin(m-1)\psi}{\sin \psi} & (\sin \alpha + \tilde{r} \alpha \cos \alpha) \frac{\sin m\psi}{\sin \psi} \\ -\sin \alpha \frac{\sin m\psi}{\sin \psi} & \cos \alpha \frac{\sin m\psi}{\sin \psi} - \frac{\sin(m-1)\psi}{\sin \psi} \end{pmatrix}. \quad (45)$$

Equation (43) can be further simplified by using the fact that $K = \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$. We thus have the simple condition

$$M^m \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \epsilon \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad (46)$$

which gives the equation on $\alpha$ (and thus on eigenvalues $\lambda$)

$$\sin \alpha \frac{\sin m\psi}{\sin \psi} = 0. \quad (47)$$

This corresponds to two cases:

- $\sin \alpha = 0$, that is $\alpha = j\pi$, with $j = 0, 1, 2, \ldots$. We denote these solutions by $\alpha_{j,0}$ if $j$ is even and $\alpha_{j,m}$ if $j$ is odd. The vector $\begin{bmatrix} 1 \\ 0 \end{bmatrix}$ is an eigenvector of the matrix $M$ with the eigenvalue $(-1)^j$, thus $\epsilon = (-1)^j$.
- $\frac{\sin m\psi}{\sin \psi} = 0$, which gives $m\psi = p\pi$, where $p \in \{1, \ldots, m-1\}$, and can be restated according to Eq. (44) as:

$$\cos \alpha - \frac{\tilde{r}}{2} \alpha \sin \alpha = \cos p\pi/m, \quad p \in \{1, \ldots, m-1\}. \quad (48)$$

For each value of $p$ this yields an infinite array of solutions that we will denote as $\alpha_{j,p}$, where the $j$ index means $j\pi \leq \alpha_{j,p} < (j+1)\pi$ ($j = 0, 1, \ldots$). We have $M^m = (-1)^p I_2$, therefore $\epsilon = (-1)^p$.

Figure 3 illustrates the solutions $\alpha_{j,p}$ in the case $m = 4$ and $\tilde{r} = 0.4$. One can see that the solutions are grouped in branches of $m$ values. Each branch begins at a multiple of $\pi$ and
Fig. 4 Plot of the diffusion operator eigenmodes for the array of $m = 4$ identical cells of length 1 with impermeable outer boundaries and $\tilde{r} = 0.4$. (left) $j = 0, p = 0, \ldots, m - 1$; (right) $j = 1, p = m, \ldots, 1$. Note the discontinuities at the barriers which increase when $\alpha_{j, p}$ increases.

ends below the next one. The branches of even $j$ begin with $\psi = 0$ ($p = 0$) and increase with increasing $p$, whereas the odd $j$ branches begin with $\psi = \pi$ ($p = m$) and increase with decreasing $p$. Note that we discard the branches with negative $j$ because $\alpha \geq 0$ according to Eq. (41).

Note that $\alpha$ (or $j$) dictates the intra-compartment variation of the mode, whereas $\psi$ (or $p$) is related to its inter-compartment variation (as we explained in Sect. 2.4). In fact, the index $j$ is equal to the number of extrema of the mode in the first compartment (not counting the one at $x = 0$). If one is interested in the inter-compartment variation only, for example by looking at the value of the mode at the beginning of each compartment, then $p$ represents the number of extrema of this variation over the whole interval. Moreover, the Courant nodal theorem (proved for our particular model in Sect. SM. III.4) states that each eigenmode changes sign $p + jm$ times. Figure 4 shows the first modes of an array of $m = 4$ identical cells with impermeable outer barriers. The first two branches are represented. We have additionally plotted dots at the beginning of each compartment to make the inter-compartment variation more visible.

One can compare the results of this section with Bloch waves in solid state physics. Indeed the branches of solutions $\alpha_{j, p}$ are similar to energy bands, where $j$ and $p$ are analogous to the band index $n$ and the wavenumber $k$, respectively. This is no surprise because we are dealing with a (finite) periodic geometry. Although the periodicity is not expressed through an energy potential but boundary conditions, the mathematical framework is the same. This explains the striking similarity between Fig. 3 and energy band diagrams (where only the $k \geq 0$ half would be represented).

3.2 Computation of the Norm

Because the geometry is symmetric and the relaxation coefficients $K_{\pm}$ are equal to zero, one can transform the formula (24) of the normalization constant into
\[ \beta_{j,p}^2 = \frac{l}{2} \left[ \begin{bmatrix} 0 & 1 \end{bmatrix} \frac{d}{d\alpha} \begin{bmatrix} 1 \\ 0 \end{bmatrix} \right]_{\alpha = \alpha_{j,p}} = \frac{l}{2} \left[ \begin{bmatrix} 0 & 1 \end{bmatrix} \frac{dM^m}{d\alpha} \begin{bmatrix} 1 \\ 0 \end{bmatrix} \right]_{\alpha = \alpha_{j,p}} = \frac{l}{2} \left| \frac{d}{d\alpha} \left( \sin \alpha \frac{\sin(m\psi)}{\sin \psi} \right) \right|_{\alpha = \alpha_{j,p}}. \]  

(49)

Now we use Eq. (47), which leads us to distinguish the two cases as above:

- \( \sin \alpha = 0 \): it corresponds to \( \alpha = j\pi \), with a positive integer \( j \) (recall that we discard \( \alpha = 0 \)). Then \( \cos \psi = (-1)^j \) and \( \frac{\sin m\psi}{\sin \psi} = m(-1)^{(m-1)} \). We conclude that the norm of the mode is:
  \[ \beta_{j,p}^2 = \frac{2}{ml}. \]  

(50)

- \( \frac{\sin m\psi}{\sin \psi} = 0 \): it corresponds to \( \alpha_{j,p} \) (\( \psi = p\pi/m \), \( p = 1, \ldots, m-1 \) and \( j = 0, 1, \ldots \)). In this case, the derivative in Eq. (49) is easily computed by the chain rule:

\[ \frac{d}{d\alpha} \left( \sin m\psi \right) = \frac{d}{d\alpha} \cos \psi \frac{d\psi}{d\alpha} \frac{d}{d\psi} \sin \psi \left( \frac{\sin m\psi}{\sin \psi} \right) = -\left( \sin \alpha \left( 1 + \frac{r}{2} \right) + \frac{r}{2} \alpha \cos \alpha \right) \frac{m \cos m\psi \sin \psi - \sin m\psi \cos \psi}{\sin^2 \psi}, \]

which by evaluation at \( \alpha_{j,p} \) yields:

\[ \beta_{j,p}^2 = \frac{2}{ml} \frac{\sin^2 \frac{p\pi}{m}}{\sin \alpha_{j,p} \left( \frac{1 + \frac{r}{2}}{2} + \frac{r}{2} \alpha_{j,p} \cos \alpha_{j,p} \right)}. \]  

(51)

4 Implementation and Applications

4.1 Numerical Implementation

From a numerical point of view, the computational steps are the following: (i) to compute the transition matrix \( M_{i,i+1} \) in Eq. (17) for each compartment; (ii) to apply Eq. (20) to get the complete transition matrix; (iii) to solve Eq. (22) to get the spectrum of the diffusion operator; each solution of Eq. (22) determines one eigenvalue whereas Eqs. (16) and (18) yield the coefficients \( a_i, b_i, k = 1, \ldots, m \) for each (non-normalized) mode; (iv) to compute the normalization constant; combined with Eq. (11) it allows one to compute the eigenmode at any point of the interval.

Steps (i) and (ii) are easy and fast since we are dealing with \( 2 \times 2 \) matrices. Step (iv) can be done either with Eq. (24), which involves a numerical derivative, or by a direct computation, using:

\[ \int_0^l \left( a \cos(kx) + b \sin(kx) \right)^2 \, dx = \frac{(a^2 + b^2)l}{2} + \frac{(a^2 - b^2)}{4k} \sin(2kl) + \frac{ab}{4k} \left( 1 - \cos(2kl) \right). \]  

(52)

The most complicated and time-consuming step is (iii). As we explained in Sect. 2.5, two or more solutions of Eq. (22) may be very close to each other in the case of low-permeability barriers (typically \( \kappa \ll D/l \)). The estimates we derived allow us to localize the roots that speeds up the computation. This is the crucial point and one of the major practical achievements of the paper. This numerical improvement allows us to detect very
close zeros (as those shown in Fig. 2) and to compute the eigenmodes of the diffusion operator in heterogeneous structures with hundreds of barriers. Moreover, Fig. 2 illustrates an interesting property of $F_m(z; l_1, \ldots, l_m)$ as a function of $z$: two local extrema are apparently always separated by a zero. Although we have no mathematical proof for this observation, it is very helpful because it allows us to detect pairs of close zeros by the change of sign of the derivative of the function, which may take place on a much larger scale than the change of sign of the function itself. One can also take advantage of the Courant nodal theorem (which is proven for our particular model in Sect. SM. III.4): the $n$-th eigenmode has $n$ nodal domains (connected components on which the eigenmode has a constant sign), or equivalently, the $n$-th eigenmode changes sign $n - 1$ times (possibly at the barriers). This can be used as an efficient test to check a posteriori that no eigenvalue is missed.

In practice, the standard floating-point precision limits the relative accuracy of a numerical computation to about $10^{-15}$. Let us assume that we are dealing with a geometry such that two eigenvalues $\lambda_1$ and $\lambda_2$ are much closer than this limit; for example they coincide up to $10^{-20}$. With the above tricks we are still able to detect those roots and even to compute accurately their position and spacing. However, the subsequent computations performed on $\lambda_1$ and $\lambda_2$ (for example, the computation of the eigenmodes or their norm) treat $\lambda_1$ and $\lambda_2$ as equal numbers. Even worse: the closeness of $\lambda_1$ and $\lambda_2$ is related to the very fast local variations of $F(\lambda)$ with $\lambda$, and as a consequence of the coefficients $(a_i^l, b_i^l)$ and of the norm of the eigenmode. Therefore it is very difficult to compute accurately these quantities for two eigenmodes corresponding to very close eigenvalues. The estimates derived in Sect. 2.5 can be used to detect a priori such situations in which the spectral decomposition can numerically fail.

If one is interested in the diffusion propagator (23) or related quantities, the infinite collection of eigenmodes has to be truncated. This is done by sorting the eigenvalues $\lambda_n$ in ascending order and then cutting off the ones such that $\lambda_n t \gg 1$, where $t$ is the smallest diffusion time for which the computation is needed. The precise choice of the truncation threshold is a compromise between precision and speed of computation. Practically, one can check the validity of the truncation by re-doing the computation with a higher threshold and then comparing the two results.

We have implemented the proposed method for an arbitrary configuration of barriers and diffusion coefficients as a Matlab code. The numerical results presented in the Supplementary Materials were obtained on a basic laptop computer by using this code. The code can be sent upon request.

### 4.2 Application to Diffusion MRI

Diffusion of spin-bearing particles (such as nuclei of hydrogen atoms in water molecules) may be surveyed by diffusion magnetic resonance imaging (dMRI), which is a powerful imaging technique with many biomedical applications [60–63]. From the knowledge of the diffusion propagator one can access the dMRI signal under the so-called Narrow-Pulse Approximation (NPA), thus motivating numerous theoretical and experimental works on diffusion in complex geometries. As explained previously, restricted diffusion in simple domains such as slab, cylinder, sphere, can be treated analytically [64–67]. In contrast, most works devoted to multi-layered systems with semi-permeable barriers are numerical. Tanner took advantage of the simple expression of the Laplace eigenmodes in a slab geometry to study a finite periodic repetition of semi-permeable barriers [68]. The same method was applied later by Kuchel and Durrant to unevenly spaced membranes [69]. These approaches were generalized
Fig. 5 Temporal profile $f(t)$ for Pulsed-Gradient-Spin-Echo (PGSE) experiments. The Narrow-Pulse Approximation (NPA) is the limit case $\delta \to 0$ while $\gamma g \delta$ remains constant by Grebenkov with a matrix formalism allowing efficient computation of the signal in general multi-layered planar, cylindrical or spherical structures, without the NPA restriction [38].

Powles and co-workers proposed in [70] an opposite approach based on the (one-dimensional) analytical solution of $G$ for one semi-permeable barrier extended to several barriers by multiple reflections. Other numerical techniques such as a finite differences method were reported [71]. The first analytical expression of the dMRI signal in a one-dimensional geometry with periodic permeable barriers was provided by Sukstanskii et al. [72]. Relying on the periodicity of the system they computed directly the signal in Laplace domain without having to derive the diffusion propagator. Unevenly spaced membranes were treated in [73,74] from the analytical solution for one membrane and under the assumption that the diffusing time is sufficiently short so that the layers are independent. Note that in contrast to almost all previously cited works the analysis performed in [74] does not confine to infinitely narrow pulses. Finally, Novikov et al. studied the effect of randomly placed semi-permeable barriers on the diffusive motion [75,76]. Using a renormalization group technique, they obtained structural universality classes characterized by the disorder introduced by the barriers, which in turn govern the long-time asymptotic behavior of the mean square displacement.

In the general case, the signal is obtained by solving the Bloch-Torrey equation for the local magnetization $m(x, t)$:

$$\frac{\partial m}{\partial t} = D \nabla^2 m + i \gamma g x f(t)m,$$

(53)

where $D$ is the diffusion coefficient, $\gamma$ the gyromagnetic ratio of the nuclei, $g$ the magnetic field gradient and $f(t)$ a customizable temporal profile [60–62]. In our one-dimensional geometry, the signal is then given by

$$S(t) = \frac{1}{L} \int_0^L m(x, t) \, dx.$$

(54)

The method developed in Sect. 2 for computing the diffusion operator eigenmodes allows us to calculate the signal analytically for infinitely narrow gradient pulses, or numerically for arbitrary pulse sequences (such as the one in Fig. 5). In particular, this method generalizes earlier approaches [68,71–73] and opens unprecedented opportunities for studying more sophisticated configurations of barriers such as microstructures inside larger scale structures.

The computations are detailed in Sect. SM. I. We explain how one can obtain the dMRI signal from the Fourier transform of the eigenmodes $u_n$ in the so-called narrow pulse regime, then we derive the expression of the signal for the periodic geometry presented in Sect. 3. We discuss the effect of the permeability of the barriers on the dMRI signal in the regimes of short and long diffusion time. In particular, we obtain a scaling law of the form $\tilde{\kappa} t / (\tilde{\kappa} + 1)$ involving $t$ and $\tilde{\kappa} = \kappa l / D$, which is valid in the long time regime ($t \gg l^2 / D$). Computations for more sophisticated geometries are presented in Sect. SM. IV (relaxation at the outer boundaries), SM. V (bi-periodic geometry), and SM. VI (two-scale geometry).
4.3 First Exit Time Distribution

Another application of the diffusion operator eigenmodes is the computation of the first exit time distribution. First exit times are a particular case of first passage phenomena, which find many applications in physics, chemistry, biology, or economy. In particular, one-dimensional models are relevant to a wide variety of phenomena in which an event is triggered when a fluctuating variable reaches a given threshold (examples include avalanches, neuron firing, or sell/buy orders) as well as diffusion controlled reactions such as fluorescence quenching or predation [77, 78]. In general planar domains, exit times were thoroughly investigated in the so-called “narrow-escape limit” [79] and few results are available for arbitrary escape areas [80, 81].

For this purpose, let us consider perfectly relaxing conditions at the outer boundaries of the interval [0, L]: \( K_\pm = \infty \). Then the quantity

\[
\int_0^L G(x \to x', \tau) \, dx'
\]

represents the probability of not reaching the outer boundaries for a particle starting at \( x \), up to the time \( \tau \). In other words, if one denotes by \( T_x \) the random variable equal to the first exit time of a particle starting at \( x \), then the tail distribution and the probability density of \( T_x \) are respectively given by:

\[
\mathbb{P}(T_x > \tau) = \int_0^L G(x \to x', \tau) \, dx' = \sum_{n=1}^\infty e^{-\lambda_n \tau} u_n(x) \left( \int_0^L u_n(x') \, dx' \right), \quad (55)
\]

\[
\rho_{T_x}(\tau) = \frac{\mathbb{P}(\tau < T_x < \tau + d\tau)}{d\tau} = \sum_{n=1}^\infty \lambda_n e^{-\lambda_n \tau} u_n(x) \left( \int_0^L u_n(x') \, dx' \right). \quad (56)
\]

The computations are detailed in Sect. SM. II. We rely on the computation of the eigenmodes for a periodic geometry with perfectly relaxing outer boundaries performed in Sect. SM. IV and obtain the first exit time distribution for this structure. We study the limit of a large number of barriers (where the size \( L \) of the large interval remains constant). Similarly to the computation of the dMRI signal, we obtain a scaling law of the form \( \tilde{\kappa} t / (\tilde{\kappa} + 1) \). Then we turn to irregular geometries where \( l_i \) and \( \kappa_{i,i+1} \) are randomly distributed and we observe the same scaling law, with a new definition for \( \tilde{\kappa} \) which depends on permeabilities and positions of the barriers. Numerical computations show a very good agreement even for a moderate number of barriers (\( m \approx 10 \)). Moreover, we analyze the regime of very low permeability, where the diffusive motion can be replaced by a discrete hopping model, and exhibit a perfect agreement with previously obtained results.

5 Conclusion

We presented an efficient method to compute the eigenmodes of the diffusion operator on a one-dimensional interval segmented by semi-permeable barriers, which in turn give access to the diffusion propagator. One can then compute several diffusion-related quantities such as the dMRI signal for any pulse sequence or the first exit time distribution.

Although the general matrix formalism is applicable to other multi-layered structures such as concentric cylindrical or spherical shells [38], the main analytical simplifications follow from the translation invariance of the Laplacian eigenmodes which is specific to
one-dimensional models. In particular we derived some estimates that help us to accurately compute the eigenvalues, even when they are extremely close to each other. This is the crucial numerical step that allowed us to deal with heterogeneous structures with hundreds of semi-permeable barriers. This efficient method opens unprecedented opportunities to investigate the impact of microstructure onto diffusive motion.

Acknowledgements We acknowledge the support under Grant No. ANR-13-JSV5-0006-01 of the French National Research Agency.

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