Equilibration in two chambers connected by a capillary of arbitrary shape

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The present work is devoted to the study of the unbiased diffusion of particles to escape from a micron-sized vesicle, through a channel of arbitrary geometry. The use of propagators allows us to describe the diffusion between the vesicle and the interstitial space. The computed relaxation time of the system only depends on its geometric parameters and the diffusion coefficient. It is noted that the whole problem can be reduced to the study of diffusion in the channel. Finally, we give a procedure to find the solution of the Fick-Jacobs’ equation for a channel with radial symmetry but with constant diffusion coefficient.

Keywords: Controlled release, micron-sized vesicle, unbiased diffusion; narrow channels; Fick-Jacobs’ equation.

En este trabajo se estudia el tiempo de liberación de un fármaco que se encuentra inicialmente dentro de una microcápsula de volumen determinado. El fármaco difunde desde el interior de la cápsula hacia el espacio intersticial pasando a través de un canal o poro de aberturas conocidas. Se emplea el método de los propagadores para describir la difusión en esta geometría, formada por tres volúmenes: la cavidad de la vesícula, el canal y el espacio intersticial. Posteriormente se calculan las funciones de relajación del sistema y se escriben en términos de los parámetros geométricos del problema y del coeficiente de difusión. Se observa que el problema puede trasladarse al estudio de la difusión a través de un canal. Finalmente, se establece un procedimiento algebraico para encontrar la solución de la ecuación de Fick-Jacobs para un canal con simetría radial pero de perfil arbitrario y con un coeficiente de difusión constante.

Descriptores: Liberación controlada; microcápsulas; difusión; canales estrechos; ecuación de Fick-Jacobs.

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1. Introduction

Diffusion arrangements in micro-heterogeneous systems, such as porous materials and membranes of various origins in the intracellular and intercellular space, among many other systems, are substantially different from predictions of the classic theory of diffusion in an unlimited homogeneous space [1]. In porous media, diffusion takes place under limitations caused by the geometry of the medium, which noticeably manifest themselves when movements of a diffusing particle involve overcoming high entropy barriers [2] between the nearest medium’s structural elements after extended wandering in them. Such structures are characteristic of many polymeric membranes [3], electrodes of fuel cells, and devices for controlled drug delivery to ill organs [4]. Entropy barriers make migration a multistage process.

By considering each stage as a particle transformation (or decay) event, can be calculated the probability of the occurrence of separate stages and their duration by methods of the theory of diffusion-controlled reactions. The idea of using the methods and results of the theory of diffusion-controlled reactions for describing the migration of particles was advanced in Ref. 5 and 6, where diffusion in a three-dimensional periodic lattice formed by connected cavities was studied. This approach was also used to study the escape of Brownian particles from cavities [7], transport of metabolites through membrane channels [8-10], and the kinetics of ligand binding by hidden reaction centers in cavities [11,12] and membrane channels [13,14].

Theoretically, the transport in systems of varying geometry has been widely studied in recent years, since these systems are ubiquitous in nature, and in technology [15-20]. Diffusion in two and three-dimensional, has been formulated as a one dimension problem in terms of the effective one-dimensional concentration of diffusing molecules. If one assumes that the distribution of the solute in any cross section of the tube is uniform as it is at equilibrium, directing the \( x \)-axis along the centerline of a tube, one can write an approximate one-dimensional effective diffusion equation as

\[
\frac{\partial}{\partial t} c(x, t) = \frac{\partial}{\partial x} \left[ D(x) A(x) \frac{\partial}{\partial x} c(x, t) \right] \quad (1)
\]

where \( D(x) \) is a position-dependent effective diffusion coefficient, \( A(x) \) is the cross-section area of the tube of radius \( r(x) \), and \( c(x, t) \) is the effective one-dimensional concentration of the diffusing particles at a given \( x \). Jacobs developed the first approach to this kind of equations in 1967 [21]. In his work, Jacobs derived the following expression, which is known as the Fick-Jacobs’ equation,

\[
\frac{\partial}{\partial t} c(x, t) = D \frac{\partial}{\partial x} \left[ A(x) \frac{\partial}{\partial x} c(x, t) \right] \quad (2)
\]

As Zwanzig pointed out [15], (1) can be considered as the Smoluchowski equation for diffusion in the entropy potential \( U(x) \) defined as

\[
U(x) = -k_B T \ln \frac{A(x)}{A_{\text{ref}}} \quad (3)
\]
where \( k_B \) is the Boltzmann constant, and \( T \) the absolute temperature. The entropic-like potential \( U(x) \) at \( x = x_{\text{ref}} \) is taken to be zero, \( U(x_{\text{ref}}) = 0 \). In the present paper we study the kinetics of a drug within a capsule delivered by a single pore channel with a well-defined morphology. To this end, equilibrium is treated as a three-state non-Markovian system, each system standing for the capsule, the channel and the reservoir. In our analysis we ignore the hydrodynamic interaction of the particle with the walls.

We shall focus on determine the average escape time of the drug from the capsule. The mean escape-time can be written as a function of the geometric parameters of the capsule, the channel, and the diffusion coefficients (in the channel, in the capsule’s cavity, and in its surroundings). To know the mean escape-time of a drug could be of critical importance since the drug must reach its specific receptors before it can react with interstitial substances in the medium or lose their healing properties.

2. Definition of the problem

The release of a drug from the interior of a microcapsule into the interstitial space is a first-passage problem. The first-passage time, namely, the probability that a diffusing particle or a random-walk first reaches a specified site (or set of sites) at a specified time, is known to underlie a wide range of stochastic processes of practical interest [1].

The substance of interest diffuses in a cell as shown in Fig. 1. The volume of the capsule is denoted by \( V_1 \), the volume of the channel is \( V_c \), and the interstitial volume is \( V_2 \). The diffusion coefficients are: \( D_1 \) in the cavity of the capsule, \( D_c \) within the channel and \( D_2 \) in the interstitial space. The channel of length \( L \) has cylindrical symmetry around the \( x \)-axis, their openings are \( r_1 \) in \( x = 0 \) and \( r_2 \) in \( x = L \), its radius is denoted by \( r(x) \) and its cross-sectional area is \( A(x) = \pi r(x)^2 \).

3. Methods

3.1. The propagator method and the relaxation functions

To find how the drug composed by point particles initially inside the microcapsule, diffuse through the channel into the interstitial space, we use a pair of propagator functions [24]. A propagator, denoted by \( G_{ij}(t) \), where \( i, j \) can take on the values 1, 2 (the volumes \( V_1 \) or \( V_2 \)) or \( c \) (the channel), is defined as the probability that a particle in volume \( i \) at time \( t \) will be found in volume \( j \) at time \( t > 0 \). For long periods of time the system reaches the equilibrium, where the particles are uniformly distributed through the entire volume \( (V_1 + V_2 + V_c) \). So, the equilibrium probabilities, \( P_{ij}^{eq} \), are found to be

\[
\lim_{t \to \infty} G_{ij}(t) = P_{ij}^{eq} = \frac{V_j}{V_1 + V_2 + V_c}, \quad j = 1, 2, c
\]

To describe the propagator functions of the system, we can use a couple of relaxation functions \( R_{ij}(t) \), which indicate how the particles in volume \( j \) reach the equilibrium if a fixed concentration of particles are initially placed in volume \( i \). The propagators can be related to the relaxation functions and equilibrium probabilities.

If all the particles are initially in volume 1, we have,

\[
G_{11}(t) = P_{11}^{eq} + (1 - P_{11}^{eq})R_{11}(t)
\]

\[
G_{21}(t) = P_{21}^{eq} [1 - R_{21}(t)]
\]

In order to calculate the \( R_{ij}(t) \) it will be necessary to introduce new functions that describe the probability fluxes escaping from the openings of the pore at time \( t \), under the condition that the particles go into the channel from volume \( i \) at \( t = 0 \), where \( i = 1, 2 \). These fluxes are produced by particles trajectories that escape from the channel for the first time at time \( t \). We denote fluxes due to translocating and returning particle trajectories by \( f_{tr,i}(t) \) and \( f_{r,i}(t) \), respectively. Accordingly, the integral of the fluxes are the translocation and return probabilities:

\[
P_{tr,i} = \int_{0}^{\infty} f_{tr,i}(t) dt, \quad P_{r,i} = \int_{0}^{\infty} f_{r,i}(t) dt
\]
which will be solved with the following initial conditions: $G_{11}(0) = 1$ and $G_{21}(0) = 0$. The constants $k_i = 4Dr_iV_i^{-1}$, $i = 1, 2$, are the rate constants which satisfy the propagator functions, $G_{ij}(t)$, given in (5), in a two-state kinetics [7].

Now, focusing on the right-hand side of (7), we see that the first term accounts for those realizations of particle’s trajectory that leave $V_1$ at time $t$. The second term accounts for those realizations that leave chamber 1 at time $\xi$, returning to $V_1$ at time $t$ without entering volume 2. The third term accounts for those realizations that go into the capillary from $V_2$ at time $\xi < t$, spend a time $t - \xi$ in the channel, and escape into $V_1$ at time $t$ (see Fig. 2). The terms on the right-hand side of (8) can be interpreted in a similar way.

Equations (7) and (8), with the initial conditions previously defined, can be solved in the Laplace space, where the Laplace transform of a generic function $h(t)$ is

$$\hat{h}(s) = \int_0^\infty e^{-st}h(t)dt$$

The Laplace transform of (7) and (8) changes our integro-differential equation problem into a pair of solvable linear equations,

$$s\hat{G}_{11}(s) - 1 = -k_1\hat{G}_{11}(s) + k_1\hat{f}_{r,1}(s)\hat{G}_{11}(s) + k_2\hat{f}_{r,2}(s)\hat{G}_{21}(s)$$  \hspace{1cm} (9)

$$s\hat{G}_{21}(s) = -k_2\hat{G}_{21}(s) + k_2\hat{f}_{r,2}(s)\hat{G}_{21}(s) + k_1\hat{f}_{r,1}(s)\hat{G}_{11}(s)$$  \hspace{1cm} (10)

Working through the system we found for $\hat{G}_{11}(s)$ and $\hat{G}_{12}(s)$

$$\hat{G}_{11}(s) = \frac{s + k_2[1 - \hat{f}_{r,2}(s)]}{\Pi(s)}$$ \hspace{1cm} (11)

$$\hat{G}_{21}(s) = \frac{k_1\hat{f}_{r,1}(s)}{\Pi(s)}$$ \hspace{1cm} (12)

where $\Pi(s)$ is given by

$$\Pi(s) = \{s + k_1[1 - \hat{f}_{r,1}(s)]\} \times \{s + k_2[1 - \hat{f}_{r,2}(s)]\} - k_1k_2\hat{f}_{r,1}(s)\hat{f}_{r,2}(s)$$

Then, using the equilibrium probabilities (7) and (8), we can write the Laplace transform of the $\hat{R}_{i1}(s)$, $i = 1, 2$, as functions of the Laplace transforms of the translating and returning fluxes from the pore; and these are given by

$$\hat{R}_{11}(s) = \frac{\hat{G}_{11}(s) - s^{-1}P_1^{eq}}{1 - P_1^{eq}}$$  \hspace{1cm} (13)

$$\hat{R}_{21}(s) = \frac{\hat{G}_{21}(s) - s^{-1}P_2^{eq}}{-P_2^{eq}}$$

**Figure 2.** Representation of the trajectories that are related to each term on the right-hand side of (7)
3.2. The fluxes from the channel: boundary conditions

According to (11) and (12), to find the $\hat{R}_{ij}(t)$ (13), it follows to obtain expressions for the Laplace transforms of the translating and returning fluxes from the channel, $f_{r,1}(t)$ and $f_{r,2}(t)$, respectively, specifically in the positions $x = 0$ and $x = L$ (the pore openings). For the sake of simplicity, we consider that the pore or channel walls are reflective and their openings as circular absorbing disks of radii $r_1$ at $x = 0$, and $r_2$ at $x = L$. So, we can use the following Robin type boundary conditions (or radiative boundary conditions):

$$D_e \hat{c}_r(x, s)|_{x=0} = \kappa_1 \hat{c}(0, s)$$
$$D_e \hat{c}_r(x, s)|_{x=L} = -\kappa_2 \hat{c}(L, s)$$

(14)

where $\kappa_i = 4D/\pi r_i$, $i = 1, 2$, is the efficiency of particles leaving from the $V_i$ to the correspondent channel opening [24]. The Laplace transform of (14) evaluated at positions $x = 0$ and $x = L$ is used to obtain the following relation between the translocating and returning fluxes from the channel,

$$\hat{f}_{r,1}(s) = \kappa_1 \hat{c}(0, s|0)$$
$$\hat{f}_{r,2}(s) = \kappa_2 \hat{c}(L, s|0)$$
$$\hat{f}_{r,2}(s) = \kappa_2 \hat{c}(L, s|L)$$

(15)

which are the boundary conditions we will use later on this work.

3.3. Diffusion through the channel: the assumptions

To calculate the propagators and relaxation functions of the system, we must obtain the translocating and returning fluxes through the channel with the boundary conditions described before. This is achieved by solving the diffusion equation within the channel, a task which has been currently a subject of deep study and still offers a challenge for modern mathematics. The calculation of fluxes from the pore is based on the reduction of a three dimensional channel, by an effective diffusion on one dimension. Zwanzig theoretically justified this mapping as follows [15]. Starting with the Smoluchowsky equation in three dimensions with a general potential, $U(r)$, where $r = (x, y, z)$:

$$\frac{\partial}{\partial t}C(r, t) = D\nabla e^{-\beta U(r)} \cdot \nabla e^{\beta U(r)} C(r, t)$$

(16)

where $\beta = k_B/T$, $k_B$ and $T$ retain their usual meaning. For small deviations from equilibrium, we integrate with respect to $y$ and $z$ along the $x$-axis,

$$\frac{\partial}{\partial t}c(x, t) = D \int \int \nabla e^{-\beta U(r)} \cdot \nabla e^{\beta U(r)} C(r, t) dydz$$

(17)

where the linear concentration $c(x, t)$ is defined by

$$c(x, t) = \int \int C(r, t) dydz$$

(18)

Then, introducing the free energy $F(x)$, we can write,

$$e^{-\beta F(x)} = \int \int e^{-\beta U(r)} dydz$$

(19)

Defining later the conditional probability as

$$\rho(x|y, z) = \frac{e^{-\beta U(r)}}{e^{-\beta F(x)}}$$

(20)

and under the local equilibrium hypothesis, we can also define,

$$C(r, t) \simeq c(x, t) \rho(x|y, z)$$

(21)

Thus substituting the two last expressions in (17) we obtain the Fick-Jacobs equation, where $F(x) = A(x)$ (the shape of the channel is like an entropic barrier, see [15,25,26]),

$$\frac{\partial}{\partial t}D_c \frac{\partial}{\partial x} \left[ A(x) \frac{\partial}{\partial x} c(x, t) \right]$$

(22)

The range of validity of the Fick-Jacobs equation has been recently established for narrow and short channels [25–28].

4. Results

In this work we want to obtain the mean escape-time of a drug from a capsule of arbitrary geometry using the relaxation functions, to this end, the proposed methodology is summarized as follow: A) In order to calculate the Laplace transform of the relaxation functions, the Laplace transforms of the propagators are required, see (13). B) Propagators are written in terms of the translocating and returning fluxes from the channel, see (11) and (12). C) To calculate these fluxes we use the reduction of the original three-dimensional problem to one dimension as given by (22) with boundary conditions given in (14). D) The main result of this paper is a procedure to find the solution of the Fick-Jacobs’ equation in a channel of arbitrary shape.

4.1. The general solution of the Fick-Jacobs’ equation

For the sake of simplicity we set $D_1 = D_2 = D$. The Laplace transform of (22) is used with the following initial condition,

$$c(x, 0) = \delta(x - x_0)$$

(23)

then, we have

$$s\hat{c}(x, s)\delta(x - x_0) = D_c \left( \hat{c}'(x, s) - \frac{A'(x)}{A(x)} \hat{c}(x, s) \right) + \frac{A'(x)^2}{A(x)^2} - \frac{A''(x)}{A(x)} \hat{c}(x, s)$$

(24)

where $A'(x) = \partial A(x)/\partial x$, $A''(x) = \partial^2 A(x)/\partial x^2$, and the same notation is used for $\hat{c}'(x, s)$ and $\hat{c}''(x, s)$. We use the substitution $\hat{c}(x, s) = v(x, s)\hat{u}(x)$, where

$$\hat{u}(x) = \exp \left[ \frac{1}{2} \int \frac{A'(x)}{A(x)} dx \right]$$

(25)
and from the \textit{canonical form} of (24), \(v(x,s)\) satisfies
\[
v''(x,s) + \left[ \frac{1}{4} \frac{A'(x)^2}{A(x)^2} - \frac{1}{2} \frac{A''(x)}{A(x)} - \frac{s}{D_e} \right] = 0 \tag{26}
\]

Thus taking the limit \(\Phi\) finding to Eq. (27) we obtain a system of two linear equations to algebraic manipulations it follows that

\[
\hat{c}(x,s) = \begin{cases} 
\sqrt{A(x)} [F_1(x, s) + \phi F_2(x, s)] \Phi & \text{for } 0 \leq x < x_0 \\
\sqrt{A(L-x)} [F_1(L-x, s) + \psi F_2(L-x, s)] \Psi & \text{for } x_0 < x \leq L
\end{cases}
\tag{27}
\]

where there are four constants to be determined: \(\Phi, \phi, \Psi\) and \(\psi\). To obtain \(\Phi\) and \(\psi\) the Laplace transform of the boundary conditions, (14), are used,

\[
D_e \hat{c}'(x,s) \bigg|_{x=0} = \kappa_1 \hat{c}(0,s) \\
D_e \hat{c}'(x,s) \bigg|_{x=L} = -\kappa_2 \hat{c}(L,s) \tag{28}
\]

and evaluating separately in the positions \(x_0 = 0\) and \(x_0 = L\) according with (28), we find that

\[
\phi = \frac{\kappa_1 - D \left[ \frac{F_1(x,s)}{F_2(x,s)} + \frac{A'(x)}{2A(x)} \right] \bigg|_{x=0}}{\kappa_1 - D \left[ \frac{F_1(x,s)}{F_2(x,s)} + \frac{A'(x)}{2A(x)} \right] \bigg|_{x=0}} \tag{29}
\]

\[
\psi = \frac{\kappa_2 - D \left[ \frac{F_1(L-x,s)}{F_2(L-x,s)} + \frac{A'(L-x)}{2A(L-x)} \right] \bigg|_{x=L}}{\kappa_2 - D \left[ \frac{F_1(L-x,s)}{F_2(L-x,s)} + \frac{A'(L-x)}{2A(L-x)} \right] \bigg|_{x=L}} \tag{30}
\]

The equations to find \(\Phi\) and \(\Psi\) are obtained using the continuity condition around \(x_0\) in (24). After several lines of algebraic manipulations it follows that

\[
\left[ \frac{A'(x)}{A(x)} \hat{c}(x,s) - \hat{c}'(x,s) \right] \bigg|_{x_0 + \epsilon} = \frac{1}{D} \bigg|_{x_0 - \epsilon} \tag{31}
\]

Thus taking the limit \(\epsilon \to 0\) and evaluating in \(x_0 = 0\) according to Eq. (27) we obtain a system of two linear equations to find \(\Phi\) and \(\Psi\),

\[
\Phi = \frac{\Gamma_1(x,s)}{DA(x,s)} \bigg|_{x=0}, \quad \Psi = \frac{\Gamma_2(x,s)}{DA(x,s)} \bigg|_{x=0} \tag{32}
\]

Depending on \(A(x)\), (26) will have or not analytical solution. Let us suppose it does; so we will say it is a special function \(F(x,s)\), so that, the general solution of (22) in the Laplace space has the form

\[
\Lambda(x,s) = \Gamma_1(x,s) \left[ \frac{A'(x)}{A(x)} \Gamma_2(x,s) - \Gamma_2'(x,s) \right] - \Gamma_2(x,s) \left[ \frac{A'(x)}{A(x)} \Gamma_1(x,s) - \Gamma_1'(x,s) \right]
\]

and

\[
\Gamma_1(x,s) = \sqrt{A(x)} [F_1(x, s) - \phi F_2(x, s)] \\
\Gamma_2(x,s) = \sqrt{A(L-x)} [F_1(L-x, s) - \psi F_2(L-x, s)]
\]

Once we have obtained the four constants, the general solution to Fick-Jacobs’ equation is well defined. The next step is a substitution in (13) to find the Laplace transform of the returning and translocating fluxes through the channel. Then, with these expressions, we can write the propagators and henceforth the relaxation functions of the system, following (11), (12) and (13), respectively. Note that these results depend only on geometrical parameters and the diffusion coefficient. The general solution to the Fick-Jacobs’ equation, (27), given by the expressions (29)-(32) is the main result of this paper.

4.2. Case studies: cylindrical and conical channels

There are previous works that study the diffusion through cylindrical, conical and periodic channels, see [24-30]. However, the study of diffusion in channels with different morphologies is a current topic.

The solution to the Fick-Jacobs’ equation for a cylindrical capillary, when \(A(x) = 1\) was reported in Ref. 24. This solution is recovered from equations (29)-(32). From equation (26), it is noted that \(F_1(x,s) = e^{-\sqrt{s}/Dx}\) and \(F_2(x,s) = e^{-\sqrt{s}/Dx}\) and the solution to the Fick-Jacobs’ equation is

\[
\hat{c}_{cyl}(x,s) = \begin{cases} 
\left[ e^{\sqrt{s}/Dx} - \phi_{cyl} e^{-\sqrt{s}/Dx} \right] \Phi_{cyl} & \text{for } 0 \leq x < x_0 \\
\left[ e^{\sqrt{s}/D(L-x)} - \psi_{cyl} e^{-\sqrt{s}/D(L-x)} \right] \Psi_{cyl} & \text{for } x_0 < x \leq L
\end{cases} \tag{33}
\]
where
\[ \phi_{cyl} = \psi_{cyl} = \frac{\kappa - \sqrt{sD}}{\kappa + \sqrt{sD}}, \quad \kappa_1 = \kappa_2 = \kappa \]
and
\[ \Phi_{cyl} = \frac{e^{\sqrt{s/D}L} - \phi_{cyl}e^{-\sqrt{s/D}L}}{2\sqrt{sD}(e^{\sqrt{s/D}L} - \phi_{cyl}^2e^{-\sqrt{s/D}L})} \]

and
\[ \Phi_{con} = \Phi_{cyl} - \frac{e^{\sqrt{s/D}L} - \phi_{con}e^{-\sqrt{s/D}L}}{2\sqrt{sD}(e^{\sqrt{s/D}L} - \phi_{con}^2e^{-\sqrt{s/D}L})} \]

\[ \psi_{con} = \frac{\sqrt{s/D}L}{\kappa_2 - \sqrt{sD} - \sqrt{s/D}} \]

in this case \( \kappa_i = 4D/\pi r_i, \ i = 1, 2 \), and the openings of the channel have radii \( r_1 = 1 \) and \( r_2 = 1 + \lambda L \). To obtain the constants \( \Phi_{con} \) and \( \psi_{con} \), the Eq. (32) is used. The solution for the conical channel recovers the case of the cylindrical channel when \( \lambda = 0 \).

The development of new solutions to the Fick-Jacobs’ equation depends largely on the complexity of the channels shape, \( A(x) \). In the next section we mention some problems about it and how to try to overcome them.

5. Discussion

The discussion of the results obtained up to this point in our work will focus on two main themes. The first one is about the use of an effective diffusion coefficient in the Fick-Jacobs’ equation, and the second one is about the possibility of obtaining analytical solutions of the problem.

The calculation of effective diffusion coefficients is a current topic. Several studies have shown that when a two- or three-dimensional diffusion problem is mapped onto a problem in one-dimension, an effective diffusion coefficient, \( D(x) \), is required [15,25-29], and the Fick-Jacobs’ equation must be modified as follows

\[ \frac{\partial}{\partial t} c(x,t) = \frac{\partial}{\partial x} \left[ D(x) A(x) \frac{\partial}{\partial x} c(x,t) \right] \] (35)

However, computing the effective diffusion coefficient (or its experimental determination) is still an issue of research [19,30-32]. Some studies have suggested functional representations of \( D(x) \) and others have tested its validity for channels with well-known morphologies. For example, Zwanzig [15] derived the following expression for the effective diffusion coefficient using small deviations from the local equilibrium,

\[ D_{zw}(x) = D \left[ 1 - \frac{1}{2} r'(x) \right] \approx \frac{D}{1 + \frac{1}{2} r'(x)^2} \] (36)

Similar results are obtained for a conical channel when \( A(x) = \pi (1 + \lambda x)^2 \), because again \( F_1(x,s) = e^{\sqrt{s/D}x} \) and \( F_2(x,s) = e^{-\sqrt{s/D}x} \), but the structure of the solution is, [25,29]

\[ \psi_{cyl} = \frac{1 - \psi_{cyl}}{2\sqrt{sD}(e^{\sqrt{s/D}L} - \psi_{cyl}^2e^{-\sqrt{s/D}L})} \]

Then Reguera and Rubí improved the estimation of Zwanzig using heuristic arguments [16],

\[ D_{RR}(x) = \frac{D}{\sqrt{1 + r'(x)^2}} \] (37)

In recent years Kalinay and Percus [30,31] obtained the expression suggested by Reguera and Rubí as a particular case after mapping the diffusion equation on a line and using perturbation theory. Bradley reached similar results in the two-dimensional case for asymmetric channels [19]. Nevertheless, these studies considered small deviations in the channels radius, \( r(x) \). Recently, Kalinay and Percus have analyzed the problem when the channel morphology changes abruptly [32].

In the mathematical development of this work we have considered for simplicity a constant diffusion coefficient, \( D \). However, if the change in the shape of the channel is not abrupt, i.e. when \( r(x) \) can be neglected, it is clear that the coefficients in (36) and (37) can be used in the solution given by (27).

In other hand, even using a constant diffusion coefficient, to write the solution to the Fick-Jacobs’ equation for any \( A(x) \) is a challenge of great difficulty. Take a look at the factor of the second term, \( \Xi(x,s) \), of (26)

\[ \Xi(x,s) = \frac{A'(x)^2}{4A(x)^2} - \frac{A''(x)}{2A(x)} - \frac{s}{D} \] (38)

According with (26), in the neighborhood of \( s = 0 \), see [24], actually \( v(x,s) = v(x) \) and hence \( \Xi(x,s) = \Xi(x) \). Then, (38) is an ordinary differential equation whose solution depends on the form of \( \Xi(x) \), in other words, the channel’s shape given by \( A(x) \) must satisfy (38) in order to obtain analytical solutions to the Fick-Jacobs’ equation. The identification of the cases with analytical solutions remains as an open problem. It is clear that the explicit expressions of \( A(x) \) that yield manageable solutions to the Fick-Jacobs’ equation are those corresponding to cylindrical, conical shaped or those channels whose radii \( r(x) \) is a \( C^1 \) type function.
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6. Conclusions

In this paper the methodology to study the diffusion of small particles inside a capsule with a pore of arbitrary shape has been established. The method used, based on the propagator functions, enable us to obtain analytical expressions for the Laplace space, for the relaxation time of the system. The fluxes through the channel and the relaxation functions were calculated and written in terms of the geometric parameters of the problem, \( V_1, V_2, L, r_1, r_2 \), and the diffusion coefficient, \( D \).

Once this information is accessible to the designer, he will be enabled to manipulate different characteristics \( (v: \text{gr}, \text{wall thickness, sizes of pore openings and channels shapes}) \) to control the time a drug takes to be released once the capsule has reached its destination. That is, the release time can be modulated by varying the geometric parameters of the capsule or the shape of the channel. And vice versa: if there are techniques that produce certain types of capsules with well-defined pores, analyzing and characterizing the microstructure of these channels we could estimate the mean escape-time of a drug released from the cavity of the microcapsule. This knowledge has important implications from a physiological point of view and also has interesting applications to biology (in the study of biological transport through protein channels) and engineering (in the study of transport through carbon nanotubes), among others.

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