Diffusion in a soft confining environment: Dynamic effects of thermal fluctuations

Benoit Palmieri and Samuel A. Safran
Department of Materials and Interfaces, Weizmann Institute of Science, Rehovot 76100, Israel
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A dynamical model of a soft, thermally fluctuating two-dimensional tube is used to study the effect of thermal fluctuations of a confining environment on diffusive transport. The tube fluctuations in both space and time are driven by Brownian motion and suppressed by surface tension and the rigidity of the surrounding environment. The dynamical fluctuations modify the concentration profile boundary condition at the tube surface. They decrease the diffusive transport rate through the tube for two important cases: uniform tube fluctuations (wave vector, $q = 0$ mode) for finite tube lengths and fluctuations of any wave vector for infinitely long tubes.

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I. INTRODUCTION

Diffusion in channeled structures plays a central role in many chemical and biological processes. Crystalline channeled structures called zeolites are widely used in chromatography and as catalysts [1–3], ion channels regulate the flow of ions through cellular membranes [4,5], nuclear pore complexes allow the transport of biological molecules in and out of the cell nucleus [4,6], and recently, synthetic nanopores have been used to detect micro-RNA molecules [7,8]. Hence, considerable effort has been devoted to the development of theoretical models in order to improve the general understanding of the diffusion mechanisms in porous materials (for example, see Refs. [5,9–16]).

In a recent microscopic study of diffusion in zeolites by Palmieri and Ronis [10–12], the energy exchange between the vibrating crystal lattice and the diffusing component was included with a high level of accuracy. For the case of diffusion in a system with large energy barriers, the lattice vibrations were shown to significantly reduce the diffusion rate through the channel by two different mechanisms. First, the vibrations reduced the probabilities for the guest to cross energy barriers by increasing the activated state free energy. Second, they also decreased the correlation time of the of guest microscopic dynamics.

While microscopic models provide a very detailed description of the system, they come with a high computational cost, especially for complex biological systems; they also tend to be fairly specific. To gain conceptual insight into the generic features of the phenomenon we study diffusion in channeled structures from a phenomenological "coarse-grained" point of view. The first macroscopic theory for the diffusion in a tube of varying cross section is given by the Fick-Jacobs equation [17], and later extended by Zwanzig [18] and Reguera and Rubì [19]. These procedures map the three-dimensional diffusion process to a one-dimensional process along the longitudinal axis of the tube. Because the force exerted by the tube only acts at the boundaries, the effect of varying cross section of the tube is purely entropic. These early studies opened the door to many others. The same mapping procedure was done in Ref. [20], but with the hard walls of the tube replaced by soft walls. Burada and co-workers [21,22] proposed control mechanisms for external force induced transport inside irregular channeled structures with entropic barriers. Also related is the directed transport that can arise from the motion of the tube if that motion is biased towards asymmetric tube conformation. This phenomena was observed experimentally [23] and predicted theoretically [24]. Numerical simulations of an overdamped Brownian particle in an oscillating asymmetric tube also led to directed transport [25].

These recent studies considered the diffusion inside static tubes, simplified two-state tube model (one state is the flat tube, the other the deformed tube) with specific transfer rates or a tube whose boundaries oscillate with a given frequency. None of them includes the effects of unavoidable dynamical thermal fluctuations. Hence, the point of this paper is to quantify the effects of such fluctuations on the diffusion inside a soft tube. By soft tube, we mean that although amplitude of the tube fluctuations is constrained by elastic properties of the system, as is the case for polymeric and membrane systems, these fluctuations can be large. Our starting point is the standard diffusion equation,

$$\frac{\partial C(\mathbf{x},t)}{\partial t} = D\nabla^2 C(\mathbf{x},t), \tag{1.1}$$

where $C(\mathbf{x},t)$ is the concentration profile and D is the diffusion coefficient. The role of the thermal fluctuation here is very different from the one studied by Palmieri and Ronis. The transport process does not involve any barrier crossing events. In principle, the thermal fluctuations can also decrease the value of D in Eq. (1.1), but this effect should not be significant if the tube is sufficiently large. On the other hand, the transport is affected by fluctuation induced motion of the diffusing particles inside the tube as follows. For a uniform and static tube separating two bulk phases, the steady-state concentration profile inside the tube should be linear along the tube and uniform in the other directions. Local equilibrium is maintained perpendicular to the tube axis. The fluctuations of the tube will modify the transport process by constantly breaking that local equilibrium and by "pushing" diffusing particles along the tube axis. To quantify these effects, we use the relation between the steady-state flux J and the concentration at both ends of the tube to define an effective diffusion coefficient,

$$D_{\text{eff}} = -\frac{JL}{[C(x=L,t) - C(x=0,t)]}. \tag{1.2}$$

For a static and uniform tube at steady state, $C(x=L,t) - C(x=0,t) = -JL/D$ and $D_{\text{eff}} = D$. In this paper, we report how D_{eff} changes when dynamical thermal fluctuations of the tube are incorporated. Note that the long term objective of this research is to understand and characterize transport processes in confining and soft environment where large thermal fluctuations are observed. For example, this is the case of many biological systems and synthetic DNA brushes that were recently used to design biological chips [26].

The paper is organized as follows. Section II describes the system that we model. The boundary conditions for the concentration profile are specified and the thermal fluctuations of the tube are expressed as functions of the surface tension of the tube and elastic constants of the surroundings. In Sec. III, we show how the concentration profile can be obtained from a perturbative expansion in the displacements of the tube boundaries, which are assumed to be small. Section IV presents the results for the effective diffusion constant $D_{\rm eff}$ that is smaller than D for two illustrative cases: uniform fluctuations of finite tubes and undulations of long tubes. Finally, Sec. V summarizes our main results and concludes by identifying future avenues and extension of this work as well as its implications for directed transport.

II. DESCRIPTION OF THE SYSTEM

For mathematical simplicity, we consider diffusion in a two-dimensional (2D) soft tube whose boundaries undergo thermal fluctuations. The tube lies along the x axis, its boundaries are symmetric with respect to a reflection about $x = 0$ and are defined by $y = \pm h(x;t) = \pm[h_0 + \delta h(x;t)]$ at any particular times (see Fig. 1); here, $\delta h(x;t)$ is the time and space dependent fluctuation of the tube surface position, which in the absence of fluctuations is located at $y = h_0$. The tube length is equal to L and constant flux J in the tube (at $x = 0$) and out of the tube (at $x = L$) is imposed,

$$-D\left(\frac{\partial C(x,y;t)}{\partial x}\right)_{x=0} = -D\left(\frac{\partial C(x,y,t)}{\partial x}\right)_{x=L} = J. \quad (2.1)$$

It is more common to impose constant concentration at both ends of the tube (which corresponds to a tube separating two reservoirs of different concentrations). Remember that the effect of the tube fluctuations on diffusive transport is quantified by $D_{\rm eff}$ defined in Eq. (1.2). Our procedure solves for the concentration profile by fixing J at both ends of the tube. The resulting concentration difference is used to calculate $D_{\rm eff}$. Equivalently, we could have solved for the fluxes by fixing the concentration at both ends. Our boundary condition was chosen because it simplifies the mathematical analysis.

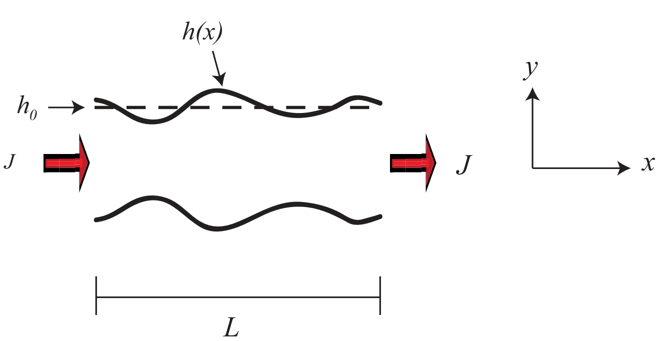

FIG. 1. (Color online) Schematic of 2D diffusion in a fluctuating tube. The tube has length L and lies along the x axis. Its boundaries are given by $y = \pm h(x;t) = \pm[h_0 + \delta h(x;t)]$ where h_0 is the average tube radius. Constant flux J boundary conditions are imposed at both ends of the tube [Eq. (2.1)]. Tube fluctuations modify the no flux condition at the tube boundaries according to Eq. (2.2).

The other boundary condition for the concentration at the tube surface takes the tube motion into account. At that boundary, there are two contributions to the flux normal to the tube. The first one is written as $-\hat{n}(x,t)\cdot D\nabla C(x,y;t)$ where $\hat{n}(x,t)$ is the outward normal of the tube at position x and time t. This contribution comes from the diffusive flux close to the tube boundary. The second one is written as $\hat{n}(x,t)\cdot \mathbf{v}_h C(x,y;t)$ where $\mathbf{v}_h = [0,\partial\delta h(x;t)/\partial t]$ is the velocity of the tube at position x and time t (the tube has no velocity in the x direction). This contribution is the dynamic one. It comes from the fact that the boundary "pushes" or "drags" the neighboring diffusing particles. For the diffusing particles to remain in the tube at all times, these two contribution to the net flux must be equal. Hence we obtain

$$\left[C(x,y;t)\frac{\partial\delta h(x;t)}{\partial t} \mp D\frac{\partial C(x,y;t)}{\partial x}\frac{\partial\delta h(x;t)}{\partial x} + D\frac{\partial C(x,y;t)}{\partial y}\right]_{y=\pm[h_0+\delta h(x;t)]} = 0. \quad (2.2)$$

At this point, it is important to point out that, writing Eqs. (1.1) and (2.2), we ignored any coupling with the hydrodynamic modes of the solvent. In reality, tube motion induced flows will contribute to the transport convectively. This effect goes beyond the scope of the current analysis and will be considered in the future.

The problem is fully specified once we characterize the tube fluctuations, $\delta h(x;t)$. The main assumption of this work is that the *tube fluctuations are unaffected by the diffusion process*. In other words, the tube fluctuations affect the diffusion, but the diffusion does not affect the tube. This assumption can be relaxed in future studies. For now, it allows us to construct a simple model for the tube free energy. First, each fluctuation mode (with wave vector q) gives rise to an energy cost due to (the 2D) line tension γ [27] of the tube boundary,

$$F_\gamma = \frac{\gamma}{2}\sum_{q=-\infty}^{\infty}\left(\frac{2\pi q}{L}\right)^2 \delta h(q;t)\delta h(-q;t), \quad (2.3)$$

where

$$\delta h(x;t) = \frac{1}{L^{1/2}}\sum_{q=-\infty}^{\infty}\delta h(q;t)e^{i2\pi qx/L} \quad (2.4a)$$

and

$$\delta h(q;t) = \frac{1}{L^{1/2}}\int_0^L dx\ \delta h(x;t)e^{-i2\pi qx/L} \quad (2.4b)$$

relate the local fluctuation of the tube boundary $\delta h(x;t)$ to its Fourier representation $\delta h(q;t)$. We will also work with the time Fourier transform of $h(x;t)$ defined as

$$\delta h(x;t) = \frac{1}{(2\pi)^{1/2}}\int_{-\infty}^{\infty} d\omega\ \delta h(x;\omega)e^{i\omega t}, \quad (2.5a)$$

and

$$\delta h(x;\omega) = \frac{1}{(2\pi)^{1/2}}\int_{-\infty}^{\infty} dt\ \delta h(x;t)e^{-i\omega t}. \quad (2.5b)$$

As seen from Eq. (2.3), line tension alone leads to unstable $q = 0$ mode, which can fluctuate with no energy cost. This is a consequence of the model that does not contain solvent and hence does not conserve the volume inside the tube. While this may be applicable for some narrow zeolitic channels, in larger pores such as ion channels or nuclear pores, the solvent incompressibility and/or hydrodynamic modes can further modify the fluctuation spectrum. Here, we propose a simple model in which the elasticity of the surroundings constrains the magnitude of the $q = 0$ fluctuations; this may be relevant to diffusion in the systems that we just mentioned.

Consider a tube embedded in a 2D elastic medium that is tethered at distance H away from the tube. 2D linear elasticity [28] can then be used to derive the following free-energy associated with tube fluctuations:

$$F_E = \sum_{q=-\infty}^{\infty} G_q \delta h(q;t)\delta h(-q;t), \tag{2.6}$$

where G_q is a function that depends on the compressional κ and shear μ moduli as well as the thickness of the surrounding elastic medium H. Here, the only relevant limit of $G(q)$ are small and large values of q,

$$G_q = \begin{cases} \frac{\kappa+\mu}{2H} & q \to 0 \\ \left|\frac{2\pi q}{L}\right| \mu \frac{\kappa+\mu}{\kappa+2\mu} & q \to \infty \end{cases}.$$

Hence, the medium deformations stabilize the small q fluctuations.

Assuming that the large q fluctuations are dominated by the restoring forces due to line tension of the tube (proportional to q^2), we use the following interpolation formula for the tube free-energy:

$$F_{\text{tube}} = \frac{1}{2} \sum_{q=-\infty}^{\infty} \Gamma_q \delta h(q;t)\delta h(-q;t), \tag{2.7}$$

where

$$\Gamma_q = \gamma_0 + \gamma \left(\frac{2\pi q}{L}\right)^2, \tag{2.8}$$

and where $\gamma_0 = (\kappa + \mu)/H$. We have neglected the linear term in q that appears in Eq. (2.7) at large q. In that range, the surface tension contributes a term $\propto q^2$ to the free energy which dominates the linear elastic term. Note that the details of the mechanism that leads to γ_0 is not important for the purpose of the present work. It is only important to understand that, for most realistic systems, the $q = 0$ modes should be stable. Here, we proposed a specific origin for γ_0 based on linear elasticity, but other mechanisms could also stabilize that mode.

The time dependence of the tube fluctuations are obtained from the Langevin equation,

$$\frac{\partial \delta h(q;t)}{\partial t} = -\xi \Gamma_q \, \delta h(q,t) + \zeta^\dagger(q;t), \tag{2.9}$$

where ξ is a phenomenological parameter that determines the fluctuations time scale [29]. The second fluctuation-dissipation theorem relates the white noise associated with the fluctuations and the damping,

$$\langle \zeta^\dagger(q;t)\zeta^\dagger(q';t')\rangle = 2\xi k_B T \delta_{q,-q'}\delta(t-t'). \tag{2.10}$$

In the last expression, we introduced the Dirac δ function $\delta(t)$, the Kronecker δ function $\delta_{q,-q'}$, the Boltzmann constant k_B, and the temperature T. From Eq. (2.9), it is straightforward to show that the tube fluctuations are fully determined by the fact that $\langle \delta h(x;t)\rangle = 0$, and by

$$\langle \delta h(q;t)\delta h(q';t')\rangle = \frac{k_B T}{\Gamma_q} e^{-\xi\Gamma_q|t-t'|}\delta_{q,-q'} \tag{2.11}$$

or

$$\langle \delta h(q;\omega)\delta h(q';\omega')\rangle = \frac{2\xi k_B T}{\xi^2\Gamma_q^2 + \omega^2}\delta_{q,-q'}\delta(\omega-\omega'). \tag{2.12}$$

The next section describes the procedure to obtain an effective diffusion coefficient by imposing the boundary conditions given by Eqs. (2.1) and (2.2) on the diffusion equation, Eq. (1.1), with tube fluctuations defined by Eq. (2.11) or (2.12).

III. PERTURBATION THEORY

We consider small amplitude fluctuations and find the first nonzero corrections to the concentration profile. In other words, we write $h(x;t) = h_0 + \epsilon\delta h(x;t)$ and derive a perturbation expansion for the particle concentration $C(x,y;t)$ in terms of ϵ,

$$C(x,y;t) = C_0(x) + \epsilon C_1(x,y;t) + \epsilon^2 C_2(x,y;t) + O(\epsilon^3). \tag{3.1}$$

ϵ is an expansion parameter that keeps track of the various orders of the fluctuation amplitude $\delta h(x;t)$. We will later set it to 1. Even for small fluctuations, we must include terms up to second order in ϵ because the first order corrections vanish when averaged over the fluctuations.

For the case of a straight 2D tube with no undulations, the unperturbed solution $C_0(x)$ is the usual linear concentration profile,

$$C_0(x) = -\frac{J}{D}(x - L), \tag{3.2}$$

and is independent of y and t. The first and second order corrections to C both satisfy the diffusion equation, Eq. (1.1), and the following boundary condition at $x = 0$ and L:

$$-D\left(\frac{\partial C_{1(2)}(x,y;t)}{\partial x}\right)_{x=0} = -D\left(\frac{\partial C_{1(2)}(x,y,t)}{\partial x}\right)_{x=L} = 0. \tag{3.3}$$

The constant flux boundary condition at both ends of the tube, Eq. (2.1), is satisfied by C_0 alone. To impose the boundary condition at the surface of the tube, we rewrite Eq. (2.2) to order ϵ and ϵ^2 to get

$$D\left(\frac{\partial C_1(x,y;t)}{\partial y}\right)_{y=h_0} = -C_0(x)\frac{\partial \delta h(x;t)}{\partial t} + D\frac{\partial C_0(x)}{\partial x}\frac{\partial \delta h(x;t)}{\partial x}, \tag{3.4}$$

which is the boundary condition for C_1, and

$$D\left(\frac{\partial C_2(x,y;t)}{\partial y}\right)_{y=h_0} = -\left[D\left(\frac{\partial^2 C_1(x,y;t)}{\partial y^2}\right)\delta h(x;t) - D\left(\frac{\partial C_1(x,y;t)}{\partial x}\right) \times \frac{\partial \delta h(x;t)}{\partial x} + C_1(x,y;t)\frac{\partial \delta h(x;t)}{\partial t}\right]_{y=h_0}, \tag{3.5}$$

which is the boundary condition for C_2. Clearly, one must first solve for C_1 and then for C_2.

Tube fluctuations destroy the uniformity of the unperturbed concentration profile along y. Hence, we define the following concentration profile which is averaged within the tube along the y-axis and ensemble averaged (or time averaged for ergodic systems) over the tube fluctuations,

$$\mathsf{C}(x;t) \equiv \left\langle \frac{1}{h_0 + \epsilon\delta h(x;t)} \int_0^{h_0+\epsilon\delta h(x;t)} dy\, C(x,y;t)\right\rangle, \tag{3.6}$$

where $\langle\cdots\rangle$ denotes the thermal average. $\mathsf{C}(x;t)$ is the quantity that we will use in Eq. (1.2) to define the effective diffusion coefficient. For small fluctuations, we expand the last expression order by order in ϵ and use the fact that $\langle\delta h(x;t)\rangle = 0$ to obtain

$$\mathsf{C}(x;t) = C_0(x) + \epsilon^2 \mathsf{C}_2(x;t) + O(\epsilon^4), \tag{3.7}$$

where

$$\mathsf{C}_2(x;t) = \frac{1}{h_0}\int_0^{h_0} dy\, \langle C_2(x,y;t)\rangle - \frac{1}{h_0^2}\int_0^{h_0} dy\, \langle C_1(x,y;t)\delta h(x;t)\rangle + \frac{1}{h_0}\langle C_1(x,y=h_0;t)\delta h(x;t)\rangle. \tag{3.8}$$

From this definition and Eq. (1.2), the effective diffusion coefficient is written as

$$D_{\text{eff}} = \frac{D}{1 - \frac{D}{JL}\Delta\mathsf{C}_2}, \tag{3.9}$$

where

$$\Delta\mathsf{C}_2 = \mathsf{C}_2(x=L;t) - \mathsf{C}_2(x=0;t). \tag{3.10}$$

The definition of D_{eff} is meaningful only if C_2 does not depend on time, which is indeed the case since we average over the tube fluctuations.

IV. RESULTS

Details of the perturbation theory to obtain $\Delta\mathsf{C}_2$ are given in Appendix A. Here, we summarize the main results. One important point is that the first and second order corrections to the concentration profile are written as follows after a Fourier transform in time:

$$C_{1,2}(x,y;\omega) = \sum_{l=1}^{\infty} f_l^{(1,2)}(\omega)\cos(\pi l x/L)\cosh[\lambda_l(\omega)y], \tag{4.1}$$

where

$$\lambda_l(\omega) = \sqrt{\frac{i\omega}{D} + \left(\frac{\pi l}{L}\right)^2}. \tag{4.2}$$

This form of $C_{1,2}(x,y;\omega)$ guarantees that the boundary condition at the tube ends, Eq. (3.3), as well as the diffusion equation (1.1), are obeyed. Only the coefficients $f_l^{(1,2)}$ need to be determined. This is done from the conditions at the tube boundaries, Eqs. (3.4) and (3.5).

The full expression for $\Delta\mathsf{C}_2$ is given by the sum of the two terms in Eqs. (A19) and (A29). The result is an infinite, multiple sum expression that is quite involved but that holds for all values of the system's parameters as long as $\delta h(x,t)$ is small. Next, we explore various limits where simpler expressions for $\Delta\mathsf{C}_2$ and D_{eff} can be obtained.

A. Uniform fluctuations

This is the simplest scenario. The fluctuations are independent of x. In other words, the tube walls remain flat on both sides, but the distance between them fluctuates as a function of time. In this case, $\Delta\mathsf{C}_2$ is given by Eq. (A19) but only the $q=0$ term is kept in the sum over all q. The result is

$$\Delta\mathsf{C}_2 = -\frac{8J\xi k_BT}{D^2h_0^2\pi^2}\sum_{l=1,\text{odd}}^{\infty}\frac{1}{\left(\frac{\xi\gamma_0}{D} + \left(\frac{\pi l}{L}\right)^2\right)l^2} = -\frac{Jk_BT}{Dh_0^2\gamma_0}\left(1 - \sqrt{\frac{4D}{\xi\gamma_0L^2}}\tanh\sqrt{\frac{\xi\gamma_0L^2}{4D}}\right). \tag{4.3}$$

This expression gives more insight when written in terms of parameters that reflect the physics. We can define $\tau = (t_{D,0}/t_{f,0})^{1/2}$ where $t_{D,0} = L^2/(4D)$ is the characteristic time scale for the diffusing particle to cross the entire tube length and $t_{f,0} = 1/(\xi\gamma_0)$ is the characteristic uniform fluctuation time scale. The effective diffusion coefficient is then obtained:

$$D_{\text{eff}} = \frac{D}{1 + \frac{k_BT}{\gamma_0h_0^2L}(1 - \tau^{-1}\tanh\tau)}. \tag{4.4}$$

This form leads to a simple interpretation. When the diffusion time is much longer than the characteristic fluctuation time scale, $t_{D,0} \gg t_{f,0}$ ($\tau\to\infty$), many fluctuation events modulate the transport process and the effect on D_{eff} is maximized. On the other hand, when $t_{D,0} \ll t_{f,0}$ ($\tau \to 0$), the fluctuations are slow compared to the diffusion process, so that the particle traverses the tube before the fluctuations can be "felt" so that there is almost no effect and $D_{\text{eff}} = D$. In summary,

$$D_{\text{eff}} = \begin{cases} \frac{D}{1+k_BT/\gamma_0h_0^2L} & \text{when} \quad \tau\to\infty, \\ D & \text{when} \quad \tau\to 0. \end{cases}$$

Note that $(1-\tau^{-1}\tanh\tau)$ monotonically increases from 0 to 1 as τ is varied from 0 to ∞. This means that *uniform fluctuations always decrease the effective diffusion coefficient*. For fluctuations evolving with any significant rate, the system "wastes" a lot of time in trying to equilibrate along the y axis while never reaching such a local equilibrium state. Hence, the effective diffusion along x—i.e., the tube axis—is reduced. The maximum reduction is determined by $\langle\delta h(t)^2\rangle/h_0^2 = k_BT/\gamma_0h_0^2L$. The reduction is larger at higher temperature and for softer tubes (smaller γ_0). The last equation also predicts

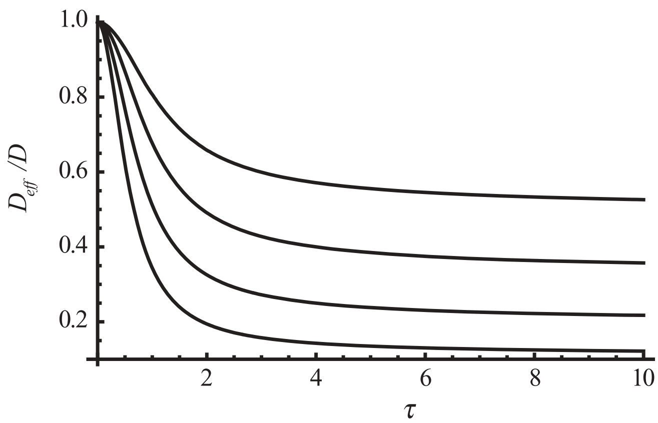

FIG. 2. Uniform tube fluctuations, $\delta h(q,t) = \delta_{0,q} L^{1/2} \delta h(t)$. The effective diffusion coefficient is monotonically decreasing with increasing $\tau = (t_{D,0}/t_{f,0})^{1/2}$ [see Eq. (4.4)]. From the top to the bottom curve, $k_B T/\gamma_0 h_0^2 L = 1$, 2, 4, and 8.

that the correction will be small for very long tube, i.e., when $k_B T/\gamma_0 h_0^2 L \ll 1$. When the tube is long, the energetic cost associated with the uniform displacement of the boundaries is large. Hence, the fluctuations are small and so is the correction to D. The results of the uniform tube fluctuations case are summarized in Fig. 2.

B. Long tube: Spatially dependent dynamical fluctuations

The infinite multiple sum expression for $\Delta\mathsf{C}_2$ given by Eqs. (A19) and (A29) simplifies considerably for a very long tube. In that limit, $\Delta\mathsf{C}$ can be written as

$$\begin{aligned} \Delta\mathsf{C}_{L\to\infty} &= -\frac{JL}{D} + \Delta\mathsf{C}_{2,L\to\infty} \\ &= -\frac{JL}{D}\left\{1 + \frac{\xi k_B T}{2\pi D}\int_{-\infty}^{\infty} dq \frac{1}{\Lambda(q)^2 h_0^2} \right. \\ &\quad + \frac{\xi k_B T}{2\pi}\int_{-\infty}^{\infty} dq\, q^2 \frac{\coth[\Lambda(q)h_0]}{\Lambda(q)h_0}\frac{1}{\xi\Gamma(q)} \\ &\quad - \frac{\xi k_B T}{4\pi D}\int_{-\infty}^{\infty} dq\, q^2 \frac{\coth[\Lambda(q)h_0]}{\Lambda(q)^3 h_0} \\ &\quad \left. \times \left(1 + \frac{\Lambda(q)h_0}{\cosh(\Lambda(q)h_0)}\right)\right\}, \end{aligned} \tag{4.5}$$

where $\Lambda(q)$ and $\Gamma(q)$ are defined in Eqs. (B4) and (B5). The derivation of this expression is found in Appendix B. Note that $\Delta\mathsf{C}_{L\to\infty}$ is still given in terms of one infinite sum here approximated as an integral. The $L\to\infty$ limit has eliminated one infinite sum out of the two in the original expression.

Before simplifying this result further, we can already derive some general insight from the form of $\Delta\mathsf{C}_{L\to\infty}$. Clearly, the second term inside the curly brackets on the right-hand side of the last equation is always positive and hence decreases $D_{\rm eff}$. The sign of the third and fourth terms is less obvious but can nevertheless also be shown to be always positive. If we combine them and write the common factor of the integrand as follows,

$$F(X,Q) = h_0^2\left[\frac{2X^2}{X^2 - Q^2} - \left(1 + \frac{X}{\cosh X}\right)\right], \tag{4.6}$$

with $X = \Lambda(q)h_0$ and $Q = qh_0$, it is easy to show that $F(X,Q) > 0$ for $\xi\Gamma(q)h_0^2/D = X^2 - Q^2 > 0$. Because this condition is satisfied for all values of the system parameters [see Eq. (B5) for $\Gamma(q)$], we see that the last term inside the curly brackets in Eq. (4.5) is also always positive. Note that the proof treated X and Q independently, which they are not. But $F(X,Q) > 0$ for all X and Q implies that F will also be positive for the special case where X is a function of Q. Hence, we have shown that, for large L and any other system's parameter, $-\Delta\mathsf{C}_{L\to\infty}$ is always increased by the tube fluctuations. According to Eq. (1.2), this means that *thermal fluctuations always decrease the effective diffusion coefficient for long tubes*.

The $q = 0$ contribution of the integral in Eq. (4.5) does not quite reproduce the behavior predicted by Eq. (4.3). Rather, the large τ limit of Eq. (4.4) is obtained. This occurs because, in the limit of large L, the ratio $t_{D,0}/t_{f,0} \to \infty$. In other words, for a very long and uniform tube, even if the tube fluctuates slowly, the diffusing species spend enough time in the tube to feel the effect of the fluctuations.

The integral that appears in the last term of Eq. (4.5) cannot be performed analytically. Moreover, one can show that it diverges logarithmically (the integrand goes like q^{-1} at large q). On the other hand, the Fourier expansion contains an upper cutoff that determines the largest wave number of the system, proportional to the inverse of the smallest characteristic distance in the microscopic structure of the tube—usually a molecular size. We denote this cutoff by $\mathcal{Q}$. We can obtain an analytical expression for the integral if we assume that $\xi\gamma_0 h_0^2/D > 1$. In this case, $\Lambda(q)h_0 > 1$, $\coth[\Lambda(q)h_0] \approx 1$ and $1/\cosh[\Lambda(q)h_0]$ is exponentially small. Using these approximations, the integral is performed to give

$$\begin{aligned} \Delta\mathsf{C}_{L\to\infty} &= -\frac{JL}{D}\left\{1 + \frac{k_B T}{16\pi\gamma_0\left(D^3 t_{D,\mathcal{Q}}^2 t_{D,h_0}\right)^{1/2}}\left[2\frac{\left(\frac{t_{f,\mathcal{Q}}}{t_{f,0}} + 2\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)}{\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}\right)^{3/2}}\ln\left\{\left[\frac{t_{f,0}}{4t_{D,\mathcal{Q}}}\right]^{1/2}\left[\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}\right)^{1/2} + \left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}+4\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)^{1/2}\right]\right\}\right.\right. \\ &\quad \left.\left. - 2\frac{t_{f,\mathcal{Q}}}{t_{f,0}}\tanh^{-1}\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}+4\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)^{-1/2} + \frac{2\pi\left(\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)^{1/2}\left(\frac{t_{D,\mathcal{Q}}}{t_{D,h_0}}\right)^{1/2}}{\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}\right)^{1/2}} + \frac{4\left(\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)}{\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}\right)\left(1+4\frac{t_{D,\mathcal{Q}}}{t_{f,\mathcal{Q}}}+4\frac{t_{D,\mathcal{Q}}}{t_{f,0}}\right)^{1/2}}\right]\right\} \end{aligned} \tag{4.7}$$

and

$$D_{\rm eff} = -\frac{JL}{\Delta\mathsf{C}_{L\to\infty}},$$

where $t_{f,0}$ is the characteristic time for the uniform fluctuations ($q=0$) defined in the previous section, $t_{D,\mathcal{Q}} = 1/(4D\mathcal{Q}^2)$ is the characteristic diffusion time scale to sample the largest wave-number undulation, $t_{D,h_0} = h_0^2/(4D)$ is the characteristic diffusion time scale to sample the tube cross section, and $t_{f,\mathcal{Q}} = 1/(\xi\gamma\mathcal{Q}^2)$ is the characteristic time for the maximum wave-number fluctuations. For large $\mathcal{Q}$, $t_{f,0}/t_{f,\mathcal{Q}}$, $t_{f,0}/t_{D,\mathcal{Q}}$, and $t_{D,h_0}/t_{D,\mathcal{Q}}$ are all large. Hence the dominant contribution to Eq. (4.7) comes from a term that contains the logarithm and its argument grows linearly with $\mathcal{Q}$ at large $\mathcal{Q}$. Equation (4.7) was tested against the full numerical integration of Eq. (4.5) and excellent agreement was obtained for all cases. Note that we have tried to approximate Eq. (4.5) by dropping all terms in Eq. (4.7) expect the one that contains the logarithm and that dominates at large $\mathcal{Q}$. This approximation was not always in good agreement with the full numerical integration of Eq. (4.5), especially when the ratio $t_{f,\mathcal{Q}}/t_{D,\mathcal{Q}}$ was large. Hence, we decided to work with the complete expression that appears in Eq. (4.7).

The decrease of the effective diffusion arises from several contributions. First, it comes from the time the system spends trying to follow the fast motion of the tube at large $\mathcal{Q}$. This contribution is represented by the second term on the right-hand side of Eq. (4.5). Second, it comes from the time it takes for the diffusing particles to sample undulations at the surface of the tube. This contribution is the third term on the right-hand side of Eq. (4.5). Note that this terms survives if the fluctuations are static ($\xi \to 0$). Finally, the fluctuating undulations are also able to "push" the diffusing particles along the direction of the tube axis. This contribution is represented by the fourth term on the right-hand side of Eq. (4.5). This effect contributes to an increase in D_{eff}, but it never dominates over the other contributions that tend to decrease the effective diffusion coefficient.

The overall competition of all terms leads to the closed form expression given by Eq. (4.7). It is then simple to show that the reduction of D_{eff} gets larger with increasing temperature T and decreasing average tube radius h_0 (or t_{D,h_0}), elastic restoring force of the elastic medium γ_0, diffusion coefficient D, and characteristic uniform fluctuation time scale $t_{f,0}$ (or $1/\xi$) for fixed $t_{f,\mathcal{Q}}$ and $t_{D,\mathcal{Q}}$. The two other independent variables, the tube surface tension γ and the wave-number cutoff $\mathcal{Q}$, are both absorbed in the definition of the two time scales $t_{f,\mathcal{Q}}$ and $t_{D,\mathcal{Q}}$, respectively. Note that the tube diffusion time scale $t_{D,0}$ defined in the previous section does not appear in the last expression. This happens because it tends to 0 as $L \to \infty$.

It might be interesting to know if the effective diffusion coefficient can be optimized by varying the system parameters. Clearly, this cannot arise from the prefactor $\chi = k_BT/16\pi\gamma_0(D^3t_{D,h_0})^{1/2}$ since this term is monotonic with respect to any of the variables. Figure 3 answers this question by looking at $\chi(D/D_{\text{eff}}-1)$. A maximum of that function is equivalent to a maximum reduction of D_{eff}. No maxima are observed. For fixed $t_{D,\mathcal{Q}}$, the reduction of D_{eff} decreases monotonically with $t_{f,\mathcal{Q}}$. Maximum reduction occurs for large $t_{f,\mathcal{Q}}$ (small surface tension). In this regime, the nonzero wave-number fluctuations are slow compared to typical diffusion time scales to sample undulations. Hence, this shows that the maximum reduction of D_{eff} occurs when the nonzero wave-number fluctuations are slow, contrary to the uniform fluctuations which decrease D_{eff} significantly when they are rapid. For smaller values of $t_{f,\mathcal{Q}}$, the undulations fluctuate more rapidly and hence push the diffusing particles along the tube axis, thereby contributing to an increase in D_{eff}, which nevertheless always remains smaller than D.

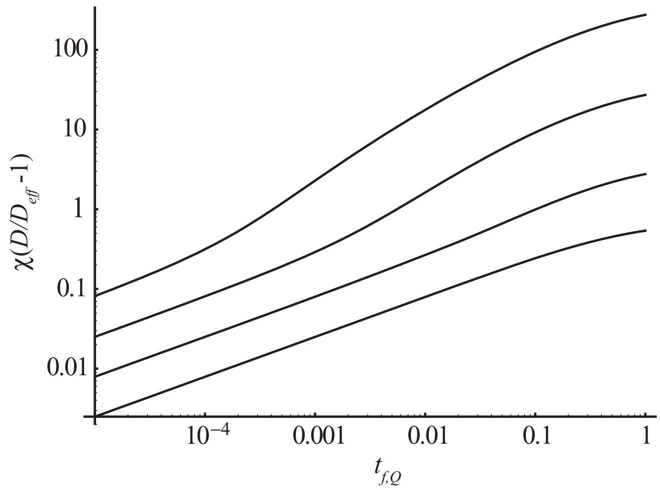

FIG. 3. The effects of $t_{f,\mathcal{Q}}$ and $t_{D,\mathcal{Q}}$ on D_{eff} is shown by plotting $\chi(D/D_{\text{eff}}-1)$ with $\chi = k_BT/16\pi\gamma_0(D^3t_{D,h_0})^{1/2}$ against $t_{f,\mathcal{Q}}$. From the top to the bottom curve, $t_{D,\mathcal{Q}} = 0.0001, 0.001, 0.01, 0.1$. When this function is large, D_{eff} is small.

V. DISCUSSION

In this paper, we considered the diffusion inside a two-dimensional tube that undergoes thermal fluctuations as a model for diffusive transport in a "soft" confining environment. Note that we considered thermal fluctuations because their statistical properties are well known, but the same method could be applied to systems whose fluctuations might be driven by nonequilibrium processes. Such soft environments are commonly encountered in many biological systems and can give rise to large amplitude fluctuations. In the model, the fluctuations are fully specified by the line tension of the tube and the rigidity of the surrounding environment. The effects of the tube undulations on the concentration profile of the diffusing particles are taken into account by the boundary condition at the tube surface. From the relationship between the concentration difference at both ends and the flow in and out of the tube, an effective diffusion coefficient was obtained [see Eqs. (4.4) and (4.7)]. In the two cases considered (uniform fluctuations and long tube with space and time dependent fluctuations), the thermal fluctuations always *decrease* the effective diffusion.

This result extends the microscopic observations made by Palmieri and Ronis [10–12] in their studies of transport processes in zeolites. There, it was shown that the diffusion inside channeled structure was well described by the Smoluchowski equation [30],

$$\frac{\partial C(x;t)}{\partial t} = \frac{\partial}{\partial x}\left(D_0 e^{-\beta W(x)}\frac{\partial}{\partial x}e^{\beta W(x)}C(x;t)\right), \qquad (5.1)$$

where the thermally fluctuating crystal lattice was shown to decrease the transport rate by both decreasing D_0 and increasing the potential energy barriers in the free energy $W(x)$. Hence, the thermal vibrations were shown to decrease the transport rate through zeolitic channels by two different mechanisms. They decrease the probability of barrier crossing events and help to decorrelate the diffusing guest motion as it moves inside the channel. In this work, we considered the diffusion inside a larger tube where many diffusing guests are coarse grained and represented by a concentration field. The interior of the tube is energetically flat [$W(x)$ is a constant] and the tube boundaries do not have any long range interaction with the diffusing species. The only boundary condition at the tube surface forces the particles to remain in the tube as it fluctuates. For this system, the observations made by Palmieri and Ronis probably mean that the tube fluctuations will have a small effect on D itself. In other words, diffusing guest dynamics decorrelation time will be dominated by the interactions with the solvent. Remember that we have assumed that the diffusing component does not perturb the tube.

However, we have shown that on top of this effect, the effective diffusion through a tube of macroscopic length is further decreased by other mechanisms. For spatially uniform thermal fluctuations, only one mechanism plays a role. The local equilibrium along the direction perpendicular to the tube axis is broken by the fluctuations. The system constantly tries to re-establish that local equilibrium and the net flow along the tube is reduced. For nonuniform fluctuations, three different mechanisms result in a decreased D_{eff}. The fact that local equilibrium is broken along the direction perpendicular to the tube still contributes to decrease D_{eff}, but this effect becomes less and less important as the fluctuation wave number increases. At large wave numbers, two other effects dominate. First, the system "wastes" time sampling the undulations created by the fluctuations. Note that this effect survives even if the fluctuations are quasistatic. Second, the nonuniform fluctuations can "push" the diffusive particles along the tube axis and enhance the transport. As shown in Eq. (4.7) and Fig. 3, the former mechanism always dominates and the effective diffusion is always reduced by thermal fluctuations. On the other hand, Fig. 3 shows that for fast nonuniform fluctuations, both mechanisms contribute significantly such that D_{eff} is reduced but much less. Our analysis predicts that the reduction of the effective diffusion coefficient will be largest at large temperature (T) and small tube radius (h_0), tube surface tension (γ) and elastic properties (γ_0), diffusion coefficient (D) and fluctuation time scale (ξ).

The first method for treating diffusion in a *static* tube of varying cross section is the well-known Fick-Jacobs equation [17,19] for the cross sectional integral of the local concentration, $\mathcal{C}(x;t)$,

$$\frac{\partial \mathcal{C}(x;t)}{\partial t} = D\frac{\partial}{\partial x}\left(h(x)\frac{\partial}{\partial x}\frac{\mathcal{C}(x;t)}{h(x)}\right). \tag{5.2}$$

In Appendix C, we demonstrate how our set of governing equations reduce to the Fick-Jacob (FJ) equation for slowly varying tube radius [$dh(x)/dx \ll 1$] and for infinitely slow fluctuations $\xi \to 0$. On the other hand, our work differs fundamentally from the FJ equation and its numerous extensions. The FJ approach deals with smooth spatial variation of $h(x)$ so that the assumption of local equilibrium in y is reasonable, but the amplitude of $h(x)$ is unrestricted. Our method does not assume local equilibrium perpendicular to the tube axis nor slowly varying cross section. This allows us to study dynamically fluctuating boundaries. On the other hand, we restrict ourselves to small amplitude fluctuations of $h(x)$. In the case of uniform fluctuations, these dynamical effects are solely responsible for the reduction of D_{eff} [in Eq. (4.4), $D_{\text{eff}} \to D$ as $\xi \to 0$]. For the nonuniform fluctuations of a long tube, these dynamical effects increase D_{eff}. Both our work and prediction based on the Fick-Jacobs equation show that static and nonuniform fluctuations always decrease D_{eff}. We have shown that dynamic, but spatially nonuniform fluctuations moderate the reduction of D_{eff}.

One of our main assumptions, used to simplify the problem and probably applicable to the case of dilute systems, is that the tube thermal fluctuations are unaffected by the diffusion process. This approximation will certainly break down when the tube size is reduced such that the particles interact with the tube boundaries in an increasingly frequent manner and/or deform the tube shape due to their larger sizes. It order to study the effects on thermal diffusion on single-file diffusion system [22], this approximation should be relaxed. This issue can be addressed in the future and will allow for a meaningful comparison with experiments. We also ignored coupling of the tube fluctuations with the solvent hydrodynamic modes which will have the effect of adding convection to the transport process in any real system. This contribution to the net transport will also be studied in the future. Another assumption that we have used is that the 2D tube maintains its symmetry with respect to a reflection about the tube axis as it fluctuates. In other words, the tube surface positions are given by $y = \pm h(x;t)$. We choose this for mathematical simplicity, but it would be trivial to repeat the analysis with uncorrelated fluctuations of the two boundaries. Since the two surfaces will have the same statistical properties, we do not expect that relaxing this approximation will modify our conclusions.

One of the most important implications of this work is perhaps on driven transport processes. Thermal fluctuations of the confining environment are unavoidable. The current work as well as the earlier work of Palmieri and Ronis suggest that they always decrease diffusive transport. This opens the door to the following question: Does this decrease in diffusive motion increase or reduce the efficiency of directional transport produced by molecular motors [31]? This question is biologically relevant and will be the topic of another publication.

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APPENDIX A: COMPLETE EXPRESSION FOR $\Delta \mathsf{C}_2$

We first write C_2 in terms of x and ω by Fourier transforming Eq. (3.8) in time and using Eq. (4.1) for $C_1(x,y;\omega)$ and $C_2(x,y;\omega)$,

$$\mathsf{C}_2(x;\omega) = \sum_{l=1}^{\infty} \cos\left(\frac{\pi l x}{L}\right)\left[\frac{\sinh[\lambda_l(\omega)h_0]}{\lambda_l(\omega)h_0}\langle f_l^{(2)}(\omega)\rangle + \frac{1}{(2\pi)^{1/2}h_0}\int d\omega_1 \left\{\cosh[\lambda_l(\omega_1)h_0] - \frac{\sinh[\lambda_l(\omega_1)h_0]}{\lambda_l(\omega_1)h_0}\right\}\langle f_l^{(1)}(\omega_1)\delta h(x;\omega-\omega_1)\rangle\right]. \tag{A1}$$

$f_l^{(2)}(\omega)$ can be expressed in terms of $f_l^{(1)}(\omega)$ by multiplying both sides of Eq. (3.5) by $\cos(\frac{\pi l x}{L})$ and integrating with respect to x from 0 to L,

$$D f_l^{(2)}(\omega)\lambda_l(\omega)\sinh[\lambda_l(\omega)h_0] = -\frac{1}{(2\pi)^{1/2}}\int d\omega_1 \sum_{k=1}^{\infty} f_k^{(1)}(\omega_1)\cosh[\lambda_l(\omega_1)h_0]\left[i\omega\frac{2}{L}\int_0^L dx_1\ \cos\left(\frac{\pi l x_1}{L}\right)\cos\left(\frac{\pi k x_1}{L}\right)\delta h(x_1;\omega-\omega_1) + D\left(\frac{\pi l}{L}\right)\left(\frac{\pi k}{L}\right)\frac{2}{L}\int_0^L dx_1\ \sin\left(\frac{\pi l x_1}{L}\right)\sin\left(\frac{\pi k x_1}{L}\right)\delta h(x_1;\omega-\omega_1)\right]. \tag{A2}$$

We then insert this equation in Eq. (A1); we use the definition of $\lambda_l(\omega)$ [Eq. (4.2)] and the fact that

$$\sum_{l=1}^{\infty}\cos\left(\frac{\pi l x}{L}\right)\cos\left(\frac{\pi l x_1}{L}\right) = \frac{L}{2}\delta(x-x_1) \tag{A3}$$

to obtain

$$\mathsf{C}_2(x;\omega) = \mathsf{C}_2^{(a)}(x;\omega) + \mathsf{C}_2^{(b)}(x;\omega), \tag{A4}$$

where

$$\mathsf{C}_2^{(a)}(x;\omega) = -\sum_{l=1}^{\infty}\frac{\cos\left(\frac{\pi l x}{L}\right)}{(2\pi)^{1/2}h_0}\int d\omega_1 \frac{\sinh[\lambda_l(\omega_1)h_0]}{\lambda_l(\omega_1)h_0}\langle f_l^{(1)}(\omega_1)\delta h(x;\omega-\omega_1)\rangle \tag{A5}$$

and

$$\mathsf{C}_2^{(b)}(x;\omega) = \sum_{l=1}^{\infty}\frac{\cos\left(\frac{\pi l x}{L}\right)}{(2\pi)^{1/2}\lambda_l(\omega)^2 h_0}\int d\omega_1 \sum_{k=1}^{\infty}\cosh[\lambda_k(\omega_1)h_0][G_{l,k}(\omega,\omega_1) - H_{l,k}(\omega,\omega_1)], \tag{A6}$$

and where

$$G_{l,k}(\omega,\omega_1) = \left(\frac{\pi l}{L}\right)^2 \frac{2}{L}\int_0^L dx_1\ \cos\left(\frac{\pi l x_1}{L}\right)\cos\left(\frac{\pi k x_1}{L}\right)\langle f_k^{(1)}(\omega_1)\delta h(x_1;\omega-\omega_1)\rangle, \tag{A7}$$

$$H_{l,k}(\omega,\omega_1) = \left(\frac{\pi l}{L}\right)\left(\frac{\pi k}{L}\right)\frac{2}{L}\int_0^L dx_1\ \sin\left(\frac{\pi l x_1}{L}\right)\sin\left(\frac{\pi k x_1}{L}\right)\langle f_k^{(1)}(\omega_1)\delta h(x_1;\omega-\omega_1)\rangle. \tag{A8}$$

If the fluctuations are uniform along the tube length, $\delta h(x;\omega)$ does not depend on x. In this case, one can show from the last two equations that $G_{l,k} = H_{l,k}$ and that $\mathsf{C}_2^{(b)}(x;\omega) = 0$. Hence, for uniform fluctuations, $\mathsf{C}_2(x;\omega) = \mathsf{C}_2^{(a)}(x;\omega)$.

We first derive an expression for $\mathsf{C}_2^{(a)}(x;\omega)$. We rewrite $f_l^{(1)}(\omega)$ by Fourier transforming Eq. (3.4) in time and again by multiplying both sides by $\cos(\frac{\pi l x}{L})$ and integrating with respect to x from 0 to L. This gives

$$D f_l^{(1)}(\omega)\lambda_l(\omega)\sinh[\lambda_l(\omega)h_0] = \frac{J}{L^{1/2}}\sum_{q=-\infty}^{\infty}\delta h(q,\omega)\left[\frac{i\omega}{D}G_{l,q}^{(1)} - \frac{i2\pi q}{L}H_{l,q}^{(1)}\right], \tag{A9}$$

where

$$G_{l,q}^{(1)} = \frac{2}{L}\int_0^L dx\ \cos\left(\frac{\pi l x}{L}\right)(x-L)e^{i2\pi q x/L}, \tag{A10}$$

and

$$H_{l,q}^{(1)} = \frac{2}{L}\int_0^L dx\ \cos\left(\frac{\pi l x}{L}\right)e^{i2\pi q x/L}. \tag{A11}$$

This is used together with Eq. (2.12) for the fluctuation correlations to give

$$\mathsf{C}_2^{(a)}(x;\omega) = -\frac{2J\xi k_B T\delta(\omega)}{(2\pi)^{1/2}Dh_0^2 L}\sum_{l=1}^{\infty}\cos\left(\frac{\pi l x}{L}\right)e^{-i2\pi q x/L}\left[\frac{iG_{l,q}^{(1)}}{D}I_1 - \frac{i2\pi q H_{l,q}^{(1)}}{L}I_2\right], \tag{A12}$$

where

$$I_1 = \int d\omega_1 \frac{\omega_1}{\lambda_l(\omega_1)^2\left(\xi^2\Gamma_q^2+\omega_1^2\right)} = \frac{-i\pi}{\Lambda_{l,q}^2} \tag{A13}$$

and

$$I_2 = \int d\omega_1 \frac{1}{\lambda_l(\omega_1)^2\left(\xi^2\Gamma_q^2+\omega_1^2\right)} = \frac{\pi}{\xi\Gamma_q\Lambda_{l,q}^2}, \tag{A14}$$

where

$$\Lambda_{l,q}^2 = \left[\frac{\xi\Gamma_q}{D} + \left(\frac{\pi l}{L}\right)^2\right]. \tag{A15}$$

These last two integrals are evaluated easily through contour integrations. The quantity we need is $\Delta\mathsf{C}_2$, so we will look at $\Delta\mathsf{C}_2^{(a)}(\omega) = \mathsf{C}_2^{(a)}(x=L;\omega) - \mathsf{C}_2^{(a)}(x=0;\omega)$,

$$\Delta\mathsf{C}_2^{(a)}(\omega) = \frac{(2\pi)^{1/2}2J\xi k_B T\delta(\omega)}{Dh_0^2 L}\sum_{l=1,\text{odd}}^{\infty}\sum_{q=-\infty}^{\infty}\frac{1}{\Lambda_{l,q}^2}\left(\frac{G_{l,q}^{(1)}}{D} - \frac{i2\pi q}{L}\frac{H_{l,q}^{(1)}}{\xi\Gamma_q}\right). \tag{A16}$$

Note that the sum over l is now over the odd values only. The last expression can be simplified by realizing that all factors multiplying $G_{l,q}^{(1)}$ are strictly even in q while all factors multiplying $H_{l,q}^{(1)}$ are strictly odd. Hence, the only parts of $G_{l,q}^{(1)}$ and $H_{l,q}^{(1)}$ that will survive the q sum are respectively the ones that are even in q and odd in q. These are readily obtained from the above integral expressions for $G_{l,q}^{(1)}$ and $H_{l,q}^{(1)}$. The results are

$$G_{l,q}^{(1)}(\text{even in } q, l \text{ odd}) = -\frac{4L(4q^2+l^2)}{\pi^2(l^2-4q^2)^2}, \tag{A17}$$

and

$$H_{l,q}^{(1)}(\text{odd in } q, l \text{ odd}) = -\frac{i8q}{\pi(l^2-4q^2)}. \tag{A18}$$

Using these simplifications and inverting the Fourier transform in time, the complete expression for $\Delta\mathsf{C}_2^{(a)}(t)$ becomes

$$\Delta\mathsf{C}_2^{(a)}(t) = -\frac{8J\xi k_B T}{D^2\pi^2}\sum_{l=1,\text{odd}}^{\infty}\sum_{q=-\infty}^{\infty}\frac{(l^2+4q^2)}{(\Lambda_{l,q}h_0)^2(l^2-4q^2)^2}\left[1+\frac{D}{\xi\Gamma_q}\left(\frac{2\pi q}{L}\right)^2\frac{l^2-4q^2}{l^2+4q^2}\right]. \tag{A19}$$

Obtaining a similar expression for $\mathsf{C}_2^{(b)}(x;\omega)$ is more involved but can nevertheless be done. We plug Eqs. (A9) and (2.12) for the fluctuations into Eq. (A6) to obtain

$$\mathsf{C}_2^{(b)}(x;\omega) = \frac{i2J\xi k_B T\delta(\omega)}{(2\pi)^{1/2}Dh_0 L}\sum_{l=1}^{\infty}\sum_{k=1}^{\infty}\sum_{q=-\infty}^{\infty}\frac{\cos\left(\frac{\pi l x}{L}\right)}{\lambda_l(\omega)^2}\left\{\left[\left(\frac{\pi l}{L}\right)^2 G_{l,k,q}^{(2)} - \left(\frac{\pi l}{L}\right)\left(\frac{\pi k}{L}\right)H_{l,k,q}^{(2)}\right]\left[\frac{G_{k,q}^{(1)}}{D}I_3 - \frac{2\pi q}{L}H_{k,q}^{(1)}I_4\right]\right\}, \tag{A20}$$

where

$$G_{l,k,q}^{(2)} = \frac{2}{L}\int_0^L dx\ \cos\left(\frac{\pi l x}{L}\right)\cos\left(\frac{\pi k x}{L}\right)e^{-i2\pi q x/L}, \tag{A21}$$

$$H_{l,k,q}^{(2)} = \frac{2}{L}\int_0^L dx\ \sin\left(\frac{\pi l x}{L}\right)\sin\left(\frac{\pi k x}{L}\right)e^{-i2\pi q x/L}, \tag{A22}$$

and

$$I_3 = \int d\omega_1\ \frac{\omega_1\coth\left[\lambda_k(\omega_1)h_0\right]}{\lambda_k(\omega_1)\left(\xi^2\Gamma_q^2+\omega_1^2\right)} = \frac{-i\pi\coth\left(\Lambda_{k,q}h_0\right)}{\Lambda_{k,q}}, \tag{A23}$$

$$I_4 = \int d\omega_1\ \frac{\coth\left[\lambda_k(\omega_1)h_0\right]}{\lambda_k(\omega_1)\left(\xi^2\Gamma_q^2+\omega_1^2\right)} = \frac{\pi\coth\left(\Lambda_{k,q}h_0\right)}{\xi\Gamma_q\Lambda_{k,q}}. \tag{A24}$$

Again, these last two integrals are evaluated through contour integrations. At this stage, we can write $\Delta\mathsf{C}_2^{(b)}(t)$ as

$$\Delta\mathsf{C}_2^{(b)}(t) = -\frac{2J\xi k_B T}{D h_0 L}\sum_{l=1,\text{odd}}^{\infty}\sum_{k=1}^{\infty}\sum_{q=-\infty}^{\infty}\frac{1}{\left(\frac{\pi l}{L}\right)^2}\left[\left(\frac{\pi l}{L}\right)^2 G_{l,k,q}^{(2)} - \left(\frac{\pi l}{L}\right)\left(\frac{\pi k}{L}\right)H_{l,k,q}^{(2)}\right]\frac{\coth(\Lambda_{k,q}h_0)}{\Lambda_{k,q}}\left[\frac{G_{k,q}^{(1)}}{D} - \frac{i2\pi q}{L}\frac{H_{k,q}^{(1)}}{\xi\Gamma_q}\right]. \tag{A25}$$

Using the integral representation of $G_{l,k,q}^{(2)}$ and $H_{l,k,q}^{(2)}$, the sum over l in the last expression can be performed. The two integrals are then evaluated to give

$$\sum_{l=1,\text{odd}}^{\infty}\left(G_{l,k,q}^{(2)} - \frac{k}{l}H_{l,k,q}^{(2)}\right) = -\delta_{k,\text{odd}}\frac{4q^2}{k^2-4q^2} + i\delta_{k,2q}\frac{\pi q}{2}. \tag{A26}$$

When this is used together with the q symmetries of $G_{k,q}^{(1)}$ and $h_{k,q}^{(1)}$, Eqs. (A17) and (A18), and

$$G_{2q,q}^{(1)}(\text{odd in } q) = (1-\delta_{q,0})\frac{-iL}{4\pi q} - \delta_{q,0}L, \tag{A27}$$

$$H_{2q,q}^{(1)}(\text{even in } q) = 1, \tag{A28}$$

we finally obtained an infinite sum expression for $\Delta\mathsf{C}_2^{(b)}(t)$,

$$\Delta\mathsf{C}_2^{(b)}(t) = -\frac{J\xi k_B T}{D^2\pi^2}\sum_{q=-\infty}^{\infty}\left[\frac{\pi^2\coth(\Lambda_{2q,q}h_0)}{4(\Lambda_{2q,q}h_0)}\left\{1-\delta_{q,0}+\left(\frac{2\pi q}{L}\right)^2\frac{4D}{\xi\Gamma_q}\right\}\right.$$
$$\left. + \sum_{k=1,\text{odd}}^{\infty}\frac{32q^2(k^2+4q^2)\coth(\Lambda_{k,q}h_0)}{(k^2-4q^2)^3(\Lambda_{k,q}h_0)}\left\{1+\frac{2D}{\xi\Gamma_q}\left(\frac{2\pi q}{L}\right)^2\frac{(k^2-4q^2)}{(k^2+4q^2)}\right\}\right]. \tag{A29}$$

APPENDIX B: $\Delta\mathsf{C}_2$ AT LARGE L

Inserting the definition of $\Lambda_{l,q}$ in Eq. (A15), the sum over l appearing in $\mathsf{C}_2^{(a)}$ [Eq. (A19)] can be performed analytically. The answer is

$$\mathsf{C}_2^{(a)} = -\frac{J\xi k_B T}{D h_0^2}\sum_{q=-\infty}^{\infty}\frac{1}{\xi\Gamma_q[1+4\varepsilon(q)^2q^2]}\left[1-\left(\frac{1+16\varepsilon(q)^4q^4}{1+4\varepsilon(q)^2q^2}\right)\frac{2\varepsilon(q)\tanh\left(\frac{\pi}{2\varepsilon(q)}\right)}{\pi}\right], \tag{B1}$$

where

$$\varepsilon(q)^2 = \frac{D\pi^2}{\xi\Gamma_q L^2}. \tag{B2}$$

From the definition of Γ_q in Eq. (2.8), it is easy to show that this parameter is small when $L\to\infty$, but that the product $[\varepsilon(q)q]$ remains finite for large q. Because $\varepsilon\tanh(\pi/2\varepsilon)\to 0$ when $\varepsilon\to 0$, the large L limit of $\Delta\mathsf{C}_2^{(a)}$ can be recast as

$$\Delta\mathsf{C}_{2,L\to\infty}^{(a)} = -\frac{J\xi k_B T}{D^2h_0^2}\sum_{q=-\infty}^{\infty}\frac{1}{\frac{\xi\Gamma_q}{D}+\left(\frac{2\pi q}{L}\right)^2} = -\frac{J\xi k_B T L}{2\pi D^2 h_0^2}\int_{-\infty}^{\infty}dq\,\frac{1}{\Lambda(q)^2}, \tag{B3}$$

where

$$\Lambda(q)^2 = \frac{\xi\Gamma(q)}{D} + q^2 \tag{B4}$$

and

$$\Gamma(q) = \gamma_0 + \gamma q^2, \tag{B5}$$

and where the last line is obtained converting the sum to an integral.

For $\Delta\mathsf{C}_2^{(b)}$, we will have to use the following identity:

$$\frac{\coth(\Lambda_{k,q}h_0)}{\Lambda_{k,q}h_0} = \frac{1}{h_0^2}\sum_{n=-\infty}^{\infty}\frac{1}{\frac{\xi\Gamma_q}{D}+\left(\frac{\pi k}{L}\right)^2+\left(\frac{\pi n}{h_0}\right)^2}. \tag{B6}$$

This identity is plugged into the second term on the right-hand side of Eq. (A29) and the sum over k is performed to give

$$-\frac{J\xi k_BT}{D^2\pi^2}\sum_{q=-\infty}^{\infty}\sum_{k=1,\mathrm{odd}}^{\infty}\frac{32q^2(k^2+4q^2)\coth(\Lambda_{k,q}h_0)}{(k^2-4q^2)^3(\Lambda_{k,q}h_0)}\left\{1+\frac{2D}{\xi\Gamma_q}\left(\frac{2\pi q}{L}\right)^2\frac{(k^2-4q^2)}{(k^2+4q^2)}\right\}$$
$$=\frac{J\xi k_BT}{4D^2h_0^2}\sum_{q=-\infty}^{\infty}\left[\sum_{n=-\infty}^{\infty}\left(\frac{1}{\frac{\xi\Gamma_q}{D}+\left(\frac{\pi n}{h_0}\right)^2}\left[\frac{1+20\varepsilon(q,n)^2q^2}{[1+4\varepsilon(q,n)^2q^2]^2}-\frac{1}{1+4\varepsilon(q,n)^2q^2}\frac{2D}{\xi\Gamma_q}\left(\frac{2\pi q}{L}\right)^2\right]+O[\varepsilon(q,n)]\right)\right], \quad \text{(B7)}$$

where

$$\varepsilon(q,n)^2=\frac{\pi^2}{\left[\frac{\xi\Gamma_q}{D}+\left(\frac{\pi^2n^2}{h_0^2}\right)^2\right]L^2}. \quad \text{(B8)}$$

Again, this last parameter is small for large L and it is even smaller for large value of q and n. Hence, terms of order $\varepsilon(q,n)$ are dropped, the sum over n in the last expression can be performed analytically, and $\Delta\mathsf{C}_2^{(b)}$ can be rewritten as

$$\Delta\mathsf{C}_{2,L\to\infty}^{(b)}=-\frac{J\xi k_BT}{2D^2}\sum_{q=-\infty}^{\infty}\left(\frac{2\pi q}{L}\right)^2\frac{\coth(\Lambda_{2q,q}h_0)}{(\Lambda_{2q,q}h_0)^3}\left[\frac{2D(\Lambda_{2q,q}h_0)^2}{\xi\Gamma_q}-h_0^2\left(1+\frac{\Lambda_{2q,q}h_0}{\cosh(\Lambda_{2q,q}h_0)}\right)\right]$$
$$=-\frac{J\xi k_BTL}{4\pi D^2}\int_{-\infty}^{\infty}dq\,q^2\frac{\coth[\Lambda(q)h_0]}{[\Lambda(q)h_0]^3}\left[\frac{2D\,[\Lambda(q)h_0]^2}{\xi(\gamma_0+\gamma q^2)}-h_0^2\left(1+\frac{\Lambda(q)h_0}{\cosh[\Lambda(q)h_0]}\right)\right]. \quad \text{(B9)}$$

The second line is obtained converting the sum to an integral.

APPENDIX C: COMPARISON WITH THE FICK-JACOBS EQUATION

Defining the cross-section integral of the local concentration as

$$\mathcal{C}(x;t)=\int_{-h(x)}^{h(x)}dy\,C(x,y;t), \quad \text{(C1)}$$

and using the boundary condition at the tube boundary with $\partial h(x;t)/\partial t=0$, we obtain

$$\frac{\partial\mathcal{C}(x;t)}{\partial t}=D\left[\frac{\partial^2\mathcal{C}(x;t)}{\partial x^2}-\left(\frac{\partial C[x,h(x);t]}{\partial x}+\frac{\partial C[x,-h(x);t]}{\partial x}\right)\frac{dh(x)}{dx}-\{C[x,h(x);t]+C[x,-h(x);t]\}\frac{d^2h(x)}{dx^2}\right.$$
$$\left.-\left(\frac{\partial C[x,h(x);t]}{\partial x}+\frac{\partial C[x,-h(x);t]}{\partial x}\right)\left(\frac{dh(x)}{dx}\right)^3\right]. \quad \text{(C2)}$$

Invoking the local equilibrium approximation,

$$C(x,y;t)\approx\frac{\mathcal{C}(x;t)}{2h(x)}, \quad \text{(C3)}$$

this last expression simplifies to

$$\frac{\partial\mathcal{C}(x;t)}{\partial t}=D\frac{\partial^2\mathcal{C}(x;t)}{\partial x^2}-D\frac{\partial}{\partial x}\left(\frac{dh(x)}{dx}\frac{\mathcal{C}(x;t)}{h(x)}\right)-\left(\frac{dh(x)}{dx}\right)^3\frac{\partial}{\partial x}\frac{\mathcal{C}(x;t)}{h(x)}. \quad \text{(C4)}$$

If the last term on the right-hand side of this equation is dropped, one recovers the standard Fick-Jacobs equation written in the text. This shows that the FJ equation is valid for slowly varying $h(x)$ and that the first corrections should be of order $[dh(x)/dx]^2$, something that has been first demonstrated in Ref. [18].

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