

EFFECTIVE MOTION OF A VIRUS TRAFFICKING INSIDE A BIOLOGICAL CELL*

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Abstract. Virus trafficking is fundamental for infection success, and plasmid cytosolic trafficking is a key step of gene delivery. Based on the main physical properties of the cellular transport machinery such as microtubules and motor proteins, our goal here is to derive a mathematical model to study cytoplasmic trafficking. Because experimental results reveal that both active and passive movements are necessary for a virus to reach the cell nucleus, by taking into account the complex interactions of the virus with the microtubules, we derive here an estimate of the mean time a virus reaches the nucleus. In particular, we present a mathematical procedure in which the complex viral movement, oscillating between pure diffusion and a deterministic movement along microtubules, can be approximated by a steady state stochastic equation with a constant effective drift. An explicit expression for the drift amplitude is given as a function of the real drift, the density of microtubules, and other physical parameters. The present approach can be used to model viral trafficking inside the cytoplasm, which is a fundamental step of viral infection, leading to viral replication and, in some cases, to cell damage.

Key words. virus trafficking, cytoplasmic transport, mean first passage time, exit points distribution, stochastic processes, wedge geometry

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1. Introduction. Because cytosolic transport has been identified as a critical barrier for synthetic gene delivery [1], the delivery of plasmids or viral DNAs from the cell membrane to the nuclear pores has attracted the attention of many biologists. The cell cytosol contains many types of organelles, actin filaments, microtubules, etc., so that to reach the nucleus, a viral DNA has to travel through a crowded and risky environment. We are interested here in studying the efficiency of the delivery process and we present a mathematical model of virus trafficking inside the cell cytoplasm. We model the viral movement as a Brownian motion. However, the density of actin filaments and microtubules inside the cell can hinder diffusion, as demonstrated experimentally [2]. In a crowded environment, we will model the virus as a material point. This reduction is simplistic for several reasons: an actin filament network can trap a diffusing object that is beyond a certain size, and, as observed experimentally, a DNA fragment cannot find its way across the actin filaments [2]. Active directional transport along microtubules or actin filaments seems then the only way to deliver a plasmid to the nucleus. The active transport of the virus generally involves motor proteins, such as kinesin (to travel in the direction of the cell membrane) or dynein (to travel toward the nucleus). Once a virus is attached to a dynein protein, its movement can be modeled as a deterministic drift toward the nucleus.

Recently, a macroscopic model has been developed to describe the dynamics of

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adenovirus concentration inside the cell cytoplasm [3]. This approach offers very interesting results about the effect of microtubules, but neglects the complexity of the geometry and cannot be used to describe the movement of a single virus, which might be enough to cause cellular infection. Modeling virus trafficking requires the use of a stochastic description. We model here the motion of a virus as that of a material point, so the probability of it being trapped by actin filaments or microtubules is neglected. In the present approximation, the viral movement has two main components: a Brownian one, which accounts for its free movement, and a drift directed toward the centrosome or MTOC (microtubules organization center), an organelle located near the nucleus. The magnitude of the drift along microtubules depends on many parameters such as the binding and unbinding rates and the velocity of the motor proteins [4].

In the present approach, we present a method to approximate a time-dependent dynamics of virus trafficking by an effective stochastic equation with a radial steady state drift. The main difficulties we have to overcome arise from the time-dependent nature of the trajectories which consists of intermittent epochs of drifts and free diffusion. We propose to derive an explicit expression for the steady state drift amplitude. In this approximation, the effective drift will gather the mean properties of the cytoplasmic organization such as the density of microtubules and its off binding rate.

Our method for finding the effective drift can be described as follows. First, we approximate the cell geometry as a two-dimensional disk and use a pure Brownian description to approximate the virus diffusion step. This geometrical approximation is valid for any two-dimensional cell such as the *in vitro* flat skin fibroblast culture cells [3]: indeed, due to their adhesion to the substrate, the thickness of these cells can be neglected in first approximation. Second, when the distribution of the initial viral position is uniform on the cell surface, we will estimate, during the diffusing period, the hitting position on a microtubule. By solving a partial differential equation, inside a sliced shape domain, delimited by two neighboring microtubules, we will provide an estimate of the mean time to the most likely hitting point. Finally, the amplitude of the radial steady state drift will be obtained by an iterative method which assumes that, after a virus has moved a certain distance along a microtubule, it is released at a point uniformly distributed on the final radial distance from the nucleus, ready for a new random walk. This scenario repeats until the virus reaches the nucleus surface. Finally, we will compute the mean time, the mean number of steps before a virus reaches the nucleus, and the amplitude of the effective drift by using the following criteria: The mean first passage time (MFPT) to the nucleus of the iterative approximation is equal to the MFPT obtained by directly solving an Ornstein–Uhlenbeck stochastic equation. The explicit computation of the effective drift is a key result in the estimation of the probability and the mean time a single virus or DNA molecule takes to reach a small nuclear pore [5].

2. Modeling stochastic viral movement inside a biological cell. We approximate the cell as a two-dimensional geometrical domain Ω , which is here a disk of radius R , and the nucleus located inside is a concentric disk of much smaller radius $\delta \ll R$. We model the motion of an unattached DNA fragment as a material point so that the probability of it being trapped by actin filaments or microtubules is neglected. The motion of a (DNA) molecule of mass m is described by the overdamped limit of the Langevin equation (Smoluchowski's limit) [6] for the position $\mathbf{X}(t)$ of the molecule at time t . When the particle is not bound to a microtubule filament, its movement is described as pure Brownian with a diffusion constant D . When the particle hits

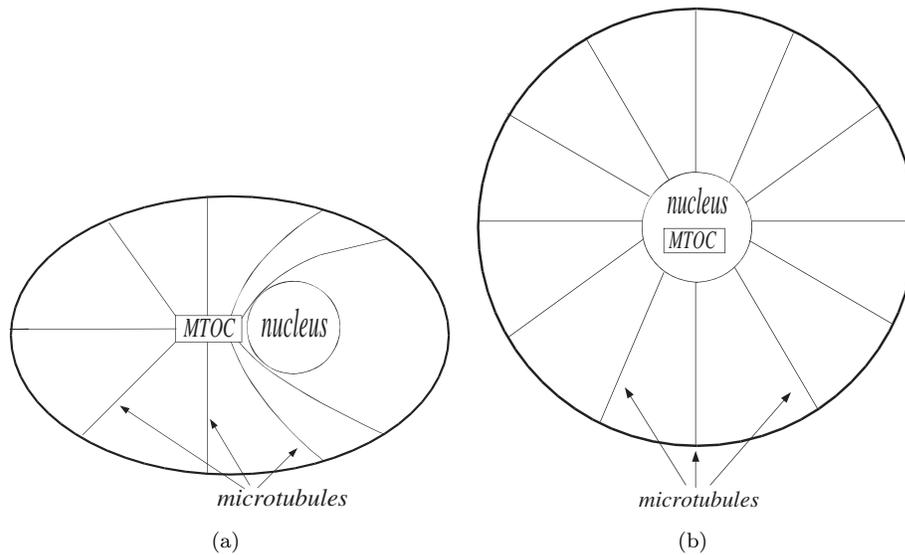


FIG. 2.1. *Cell geometry. (a) Cell's microtubules network. All microtubules starting from the cell membrane converge to the MTOC, located near the nucleus. (b) Simplified cell's microtubules network organization. The MTOC coincides with the nucleus.*

a filament, it binds for a certain random time and moves along with a deterministic drift. We take into account only the movement toward the nucleus, which coincides here with the MTOC, an organelle in which all microtubules converge (see Figure 2.1). For $\delta < |\mathbf{X}(t)| < R$, we describe the overall movement by the stochastic rule

$$(2.1) \quad \dot{\mathbf{X}} = \begin{cases} \sqrt{2D}\dot{\mathbf{w}} & \text{for } \mathbf{X}(t) \text{ free,} \\ V \frac{\mathbf{r}}{|\mathbf{r}|} & \text{for } \mathbf{X}(t) \text{ bound,} \end{cases}$$

where V is a constant velocity, $\dot{\mathbf{w}}$ a δ -correlated standard white noise, and \mathbf{r} the \mathbf{X} radial coordinate, the origin of which is the center of the cell. We assume that all filaments starting from the cell surface end on the nuclear surface. The binding time corresponds to a chemical reaction event; we assume that it is exponentially distributed, and for simplicity we approximate it by a constant t_m .

Once a virus enters the cell membrane, it moves according to the rule (2.1) until it hits a nuclear pore. Although nuclear pores occupy a small portion of the nuclear surface, we consider only the virus movement until it hits the nuclear surface $D(\delta)$. In this article, our goal is to replace (2.1) by a steady state stochastic equation

$$(2.2) \quad \dot{\mathbf{X}} = \mathbf{b}(\mathbf{X}) + \sqrt{2D}\dot{\mathbf{w}},$$

where the drift \mathbf{b} is radially symmetric. In a first approximation, we consider a constant radial drift $\mathbf{b}(\mathbf{X}) = -B \frac{\mathbf{r}}{|\mathbf{r}|}$ and compute hereafter the value of the constant amplitude B such that the MFPTs of the processes (2.2) and (2.1) to the nucleus are equal.

2.1. Modeling viral dynamics in the cytoplasm. Inside the cytosol, microtubules are distributed on the cell surface and converge radially to the MTOC. In the present analysis, we do not take into account the effect of organelle crowding due

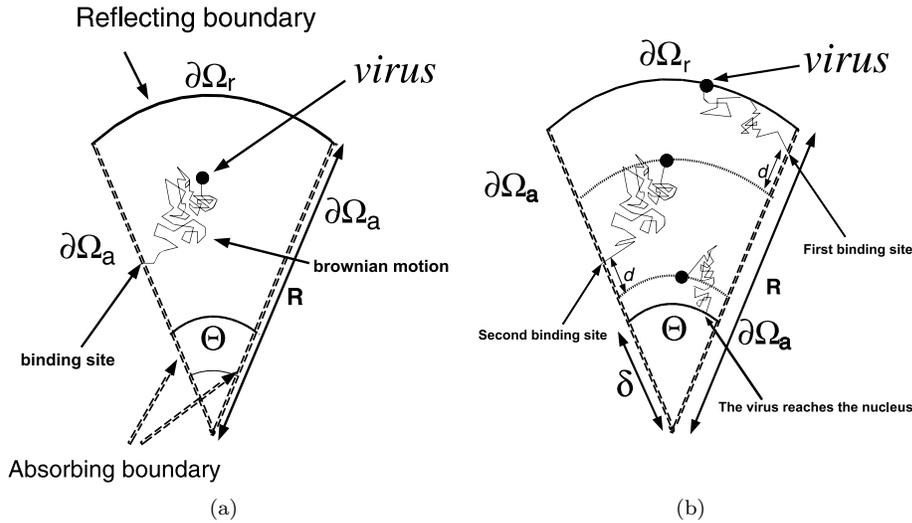


FIG. 2.2. *Virus trafficking inside a cell.* (a) Representation of the cell portion between two microtubules. (b) Transport along microtubules: Two fundamental steps are represented. A fundamental step is made of the two intermediate steps which are first the diffusion inside the domain and then the directed motion along the microtubule.

to the endoplasmic reticulum, the Golgi apparatus, etc. However, it is always possible to include them indirectly by using an apparent diffusion constant. We consider the fundamental domain $\tilde{\Omega}$ defined as the two-dimensional slice of angle Θ between two neighboring microtubules. We consider here that microtubules are uniformly distributed, and thus $\Theta = \frac{2\pi}{N}$, where N is the total number of microtubules.

Although a virus can drift along microtubules in both directions by using dynein (resp., kinesin) motor proteins for the inward (resp., outward) movement, we only take into account the drift toward the nucleus [7]. It is still unclear what is the precise mechanism used by a virus to select a direction of motion. Attached to a dynein molecule, the virus transport consists of several steps of few nanometers: the length of each step depends on the load of the transported cargo and adenosine tryphosphate (ATP) concentration [8]. We neglect here the complexity of this process, assuming that ATP molecules are abundant, uniformly distributed over the cell, and not a limiting factor. We thus assume the bound particle moves toward the nucleus with the mean constant velocity V . When the particle is released from the microtubule, inside the domain, the process can start afresh and the particle diffuses freely. Because the Smoluchowski limit of the Langevin equation does not account for the change in velocity, we release the particle at a certain distance away from the microtubule, but at a fixed distance from the nucleus (at an angle chosen uniformly distributed); see Figure 2.2.

Because microtubules are taken uniformly distributed, we can always release the virus inside the slice $\tilde{\Omega}$, between two neighboring microtubules. Thus the movement of the virus will be studied in $\tilde{\Omega}$: inside the cytosol, the viral movement is purely Brownian until it hits a microtubule, which is now the lateral boundary of $\tilde{\Omega}$ (see Figure 2.2). We assume that once a virus hits a microtubule, with probability one, the dynamics switches from diffusion to a deterministic motion with a constant drift. A virus spends on a microtubule a time that we consider to be exponentially distributed,

since this time is the sum of escape time from deep potential wells. We approximate the total time on a microtubule by the mean time t_m . Thus a virus moves at a distance $d_m = Vt_m$ along a microtubule, which depends only on the characteristic of the virus–microtubule interactions. To summarize, the virus trajectory is a succession of diffusion steps mixed with some periods of attaching and detaching to microtubules. This scenario repeats until the virus hits the nuclear surface (Figure 2.2).

2.2. Computing the MFPT to reach the nucleus. We define the *mean time to infection* as the MFPT a virus reaches the surface of the disk $D(\delta)$ inside the domain $\tilde{\Omega}$ (see Figure 2.2).

To estimate the mean time to infection, we note that we can decompose the overall motion as a repeated fundamental step. This step consists of the free diffusion of the particle inside the domain followed by the motion along the microtubule. The total time of infection τ_i is then the sum of times the particle spends in each step. Although the time on a microtubule is deterministically equal to t_m , the diffusing time is not easy to compute and depends on the initial condition. Ultimately τ_i depends on the number of times the fundamental step repeats before the particle reaches the nucleus.

Let us now describe each step. The first step starts when the virus enters the cell at the periphery $r = R = R_0$ (at a random angle $\theta \in [0; \Theta]$) and ends when the virus hits either the lateral boundary or the nucleus. We now consider the first passage time $u(R_0)$ to the absorbing boundary and denote by $r(R_0)$ the hitting position. To account for the deterministic drift, during a deterministic time t_m we move the virus from a distance d_m along the microtubule. In that case, the initial random position for the next step is given by $r = R_1 = r(R_0) - d_m$ and the total time in step 1 is $u(R_0) + t_m$.

We iterate the process as follows and consider in each step k the distance $R_k = r(R_{k-1}) - d_m$ from which the particle starts and the time $u(R_k) + t_m$ it spends inside the step. If we denote by n_s the random number of steps necessary to reach the nucleus $r = \delta$, the time to infection τ_i is given by

$$(2.3) \quad \tau_i = \sum_{k=0}^{n_s-1} u(R_k) + n_s t_m + t_r,$$

where t_r is a residual time, which is the time to reach the nucleus before a full step is completed.

We are interested in estimating the MFPT τ of τ_i , given by

$$(2.4) \quad \tau = E(\tau_i) = E\left(\sum_{k=0}^{n_s-1} u(R_k)\right) + \langle n_s \rangle t_m + \langle t_r \rangle,$$

where $\langle n_s \rangle$ is the mean number of steps and $\langle t_r \rangle$ is the mean residual time. If we introduce the probability distribution $p_m = \Pr\{n_s = m\}$, which states that the number of steps is exactly equal to m , we can write

$$(2.5) \quad \tau = E(\tau_i) = \sum_{m=1}^{\infty} E\left(\sum_{k=0}^{n_s-1} u(R_k) | n_s = m\right) p_m + \langle n_s \rangle t_m + \langle t_r \rangle.$$

To estimate the MFPT τ , we shall approximate the previous sum by using the MFPT $\bar{u}(R_k)$ in each step k . To estimate $\bar{u}(R_k)$, we will solve (in the next paragraph) the Dynkin's equation with the following boundary conditions: Inside $\tilde{\Omega}$, the particle is

reflected at the periphery $r = R$ and absorbed at the nucleus $\partial\tilde{\Omega}_a$ and at $\theta = 0$ and $\theta = \Theta$. We will also estimate the mean distance \bar{d}_k covered during step k . For that purpose we will estimate the mean exit position $r_m(R_k)$, conditioned on the initial position $r = R_k$. Indeed, we will thus get $\bar{d}_k = R_k - r_m(R_k) - d_m$. The estimates of the mean distances covered for each fundamental step will ultimately lead to an approximation of the mean number of steps $n = \langle n_s \rangle$: n will be computed such that $R_n \geq \delta$ and $R_{n+1} < \delta$ (where $R_n = r_m(R_{n-1}) - d_m$ is defined recursively). Finally, we will obtain the following approximation for the infection time:

$$(2.6) \quad \tau \approx \sum_{k=0}^{n-1} \bar{u}(R_k) + nt_m + \langle t_r \rangle.$$

The mean residual time $\langle t_r \rangle$ can be equal either to $\bar{u}(R_n) + \alpha t_m$, where $0 \leq \alpha < 1$ if the virus binds to a microtubule in the last step and travels a distance αd_m on the microtubule, or to the MFPT to the nuclear boundary if $r_m(R_n) < \delta$.

3. MFPT and exit point distribution. In a first approximation, under the assumptions of a sufficiently small radius $\delta \ll R$ and an angle $\Theta \ll 1$ for the computation of the MFPT and the distribution of exit points, we neglect the nuclear area. We define the full pie wedge Ω^R domain of angle Θ . Inside Ω^R , we use the boundary conditions described above. Consequently, the MFPT to a microtubule $u = u(r, \theta)$ of a virus starting initially at position (r, θ) is a solution of the Dynkin's equations [6]

$$(3.1) \quad \begin{aligned} D\Delta u(\mathbf{x}) &= -1 \text{ for } \mathbf{x} \in \Omega^R, \\ u(\mathbf{x}) &= 0 \text{ for } \mathbf{x} \in \partial\Omega_a^R, \\ \frac{\partial u}{\partial \mathbf{n}} &= 0 \text{ for } \mathbf{x} \in \partial\Omega_r^R, \end{aligned}$$

where $\partial\Omega_a^R = \{\theta = 0\} \cup \{\theta = \Theta\}$ and $\Omega_r^R = \{r = R\}$.

3.1. The general solution for the MFPT. In this paragraph only we reparametrize the domain by $-\Theta/2 \leq \theta \leq \Theta/2$. By writing (3.1) in polar coordinates and using the separation of variables, the general solution of equation

$$(3.2) \quad \left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r} \frac{\partial u}{\partial r} + \frac{1}{r^2} \frac{\partial^2 u}{\partial \theta^2} \right) (r, \theta) = -1 \text{ for } (r, \theta) \in \Omega^R,$$

$$(3.3) \quad u(r, \theta) = 0 \text{ for } (r, \theta) \in \partial\Omega_a^R,$$

is given by [9],

$$(3.4) \quad u(r, \theta) = \frac{r^2}{4D} \left(\frac{\cos(2\theta)}{\cos(\Theta)} - 1 \right) + \sum_{n=0}^{\infty} A_n r^{\lambda_n} \cos(\lambda_n \theta) \text{ for } \frac{-\Theta}{2} \leq \theta \leq \frac{\Theta}{2},$$

where the edge boundary is here located at position $\theta = \pm\Theta/2$. The sum in the right-hand side is the general solution of the homogeneous problem $\Delta u = 0$ in Ω^R . The boundary conditions on the sides of the wedge impose that

$$(3.5) \quad \lambda_n = (2n + 1) \frac{\pi}{\Theta},$$

while the reflecting condition for $r = R$ reads

$$(3.6) \quad \frac{\partial u}{\partial r}(R, \theta) = 0 \text{ for all } \theta \in \left[-\frac{\Theta}{2}, \frac{\Theta}{2} \right].$$

Using the uniqueness of Fourier decomposition and the boundary condition (3.6), we obtain that

$$(3.7) \quad A_n = \frac{(-1)^{n+1} 8R^{2-\lambda_n}}{D\Theta\lambda_n^2 (\lambda_n^2 - 4)}.$$

By averaging formula (3.4) over an initial uniform distribution, the MFPT to one of the absorbing edges of the wedge is given by

$$(3.8) \quad \bar{u}(r) = \frac{1}{\Theta} \int_{\theta=0}^{\theta=\Theta} u(r, \theta) d\theta = \frac{r^2}{4D} \left(\frac{\tan(\Theta)}{\Theta} - 1 \right) - \sum_{n=0}^{\infty} \frac{16R^{2-\lambda_n} r^{\lambda_n}}{D\Theta^2\lambda_n^3 (\lambda_n^2 - 4)},$$

where $\lambda_n = (2n + 1) \frac{\pi}{\Theta}$. For Θ small, (3.8) can be approximated by

$$(3.9) \quad \bar{u}(r) = \frac{r^2}{4D} \left(\frac{\tan(\Theta)}{\Theta} - 1 \right) - \frac{16\Theta R^2 (r/R)^{\pi/\Theta}}{D\pi^3 ((\pi/\Theta)^2 - 4)}.$$

3.2. Exit points distribution. To estimate the position at which a virus will attach preferentially to the microtubule, we determine the distribution of exit points, when the viral particle initially started at a certain radial distance from the nucleus. We recall that the probability density function (pdf) $p(\mathbf{r}, t | \mathbf{r}_0)$ for finding a diffusing particle in a volume element $d\mathbf{r}$ at time t inside the wedge $\tilde{\Omega}$, conditioned on the initial position $\mathbf{r} = \mathbf{r}_0$, is a solution of the diffusion equation

$$\begin{aligned} \frac{\partial p(\mathbf{r}, t | \mathbf{r}_0)}{\partial t} &= D\Delta p(\mathbf{r}, t | \mathbf{r}_0) \text{ for } \mathbf{r} \in \Omega^R, \\ p(\mathbf{r}, t | \mathbf{r}_0) &= 0 \text{ for } \mathbf{r} \in \partial\Omega_a^R, \\ \frac{\partial p(\mathbf{r}, t | \mathbf{r}_0)}{\partial n} &= 0 \text{ for } \mathbf{r} \in \partial\Omega_r^R, \end{aligned}$$

where the initial condition is $p(\mathbf{r}, 0 | \mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0)$. The distribution of exit points $\epsilon(\mathbf{y})$ is given by

$$(3.10) \quad \epsilon(\mathbf{y}) = \int_0^\infty j(\mathbf{y}, t) dt,$$

where the flux j is defined by

$$j(\mathbf{y}, t) = -D \frac{\partial p(\mathbf{r}, t)}{\partial \mathbf{n}} \Big|_{\mathbf{r} = \mathbf{y}}.$$

If we denote $C(\mathbf{r}_0, \mathbf{r}) = \int_0^\infty p(\mathbf{r}, t | \mathbf{r}_0) dt$, then C is a solution of

$$(3.11) \quad -D\Delta C(\mathbf{r}_0, \mathbf{r}) = \delta(\mathbf{r} - \mathbf{r}_0),$$

and we have

$$(3.12) \quad \epsilon(\mathbf{y}) = -D \frac{\partial C}{\partial n}(\mathbf{r}_0, \mathbf{y}) \text{ for } \mathbf{y} \in \Omega_a^R.$$

Consequently, to obtain the pdf of exit points ϵ , we use the Green function in the wedge domain Ω^R . By using a conformal transformation, we hereafter solve a simplified case

of an open wedge (i.e., without a reflecting boundary at $r = R$). This computation could be compared with the general one that will be derived in the next section.

To compute the exit points distribution, we consider the solution of (3.11), obtained by the image method and a conformal transformation from the open wedge to the upper complex half-plane. The Green function, solution of (3.11) in the upper complex half-plane, is given by

$$(3.13) \quad C(z) = \frac{1}{2\pi D} \ln \frac{z - z_0}{z - z_0^*},$$

where z_0^* is the complex conjugate of z_0 . Using the conformal transformation $\omega = f(z) = z^{\frac{\pi}{\Theta}}$ [10] that maps the interior of the wedge of opening angle Θ to the upper half-plane, the Green function in the wedge is given by

$$(3.14) \quad C(z) = \frac{1}{2\pi D} \ln \left(\frac{z^{\frac{\pi}{\Theta}} - z_0^{\frac{\pi}{\Theta}}}{z^{\frac{\pi}{\Theta}} - (z_0^*)^{\frac{\pi}{\Theta}}} \right).$$

The flux to the line θ is given by

$$\begin{aligned} \epsilon_\theta(r) &= -\frac{D}{r} \frac{\partial C}{\partial \theta}(re^{i\theta}) = \frac{1}{2\pi r} \frac{i\nu (re^{i\theta})^\nu \cdot (k_0 - k_0^*)}{((re^{i\theta})^\nu - k_0)((re^{i\theta})^\nu - k_0^*)} \\ &= \frac{1}{2\pi r} \frac{-2\nu (re^{i\theta})^\nu r_0^\nu \sin(\nu\theta_0)}{(re^{i\theta})^{2\nu} + r_0^{2\nu} - 2(re^{i\theta})^\nu r_0^\nu \cos(\nu\theta_0)}, \end{aligned}$$

where $\nu = \frac{\pi}{\Theta}$, $k_0 = z_0^\nu = (r_0 e^{i\theta_0})^\nu$. Finally, the exit point distribution for $\theta = \Theta$ is given by

$$(3.15) \quad \epsilon_\Theta(r) = \frac{r_0}{\Theta} \frac{(rr_0)^{(\nu-1)} \sin(\nu\theta_0)}{r^{2\nu} + r_0^{2\nu} + 2(rr_0)^\nu \cos(\nu\theta_0)},$$

while for $\theta = 0$ it is given by

$$(3.16) \quad \epsilon_0(r) = \frac{r_0}{\Theta} \frac{(rr_0)^{(\nu-1)} \sin(\nu\theta_0)}{r^{2\nu} + r_0^{2\nu} - 2(rr_0)^\nu \cos(\nu\theta_0)}.$$

A MATLAB check guarantees that

$$(3.17) \quad \int_0^\infty \{\epsilon_\Theta(r) + \epsilon_0(r)\} dr = 1.$$

This simple computation is instructive and shall be compared to the full one given in section 3.3.

3.3. Exit pdf in a pie wedge. To compute the exit points distribution in a pie wedge with a reflecting boundary at $r = R$, we search for an explicit solution of the diffusion equation in polar coordinates inside the pie wedge. We first consider the general diffusion equation

$$(3.18) \quad \begin{aligned} \frac{\partial p}{\partial t}(\mathbf{x}, t|\mathbf{y}) &= D \left(\frac{\partial^2 p}{\partial r^2} + \frac{1}{r} \frac{\partial p}{\partial r} + \frac{1}{r^2} \frac{\partial^2 p}{\partial \theta^2} \right) (\mathbf{x}, t|\mathbf{y}), \\ p(\mathbf{x}, 0|\mathbf{y}) &= \delta(\mathbf{x} - \mathbf{y}), \end{aligned}$$

where the boundary conditions are given in (3.1). We may often use the change of variable for all $n \in \mathbf{N}^*$:

$$k = \frac{n\pi}{\Theta}.$$

The initial condition is given by

$$p(\mathbf{x}, 0|\mathbf{y}) = p(r, \theta, 0|r_0, \theta_0) = \frac{2}{\Theta r_0} \delta(r - r_0) \sum_k \sin(k\theta) \sin(k\theta_0)$$

for $\theta < \theta_0$ (if $\theta > \theta_0$, θ_0 must be replaced by $\Theta - \theta_0$). To compute the solution of (3.18), we consider the Laplace transform \hat{p} of the probability p ,

$$\begin{aligned} s\hat{p}(r, \theta, s|r_0, \theta_0) - \frac{2}{\Theta r_0} \delta(r - r_0) \sum_k \sin(k\theta) \sin(k\theta_0) \\ = D \left(\frac{\partial^2 \hat{p}}{\partial r^2} + \frac{1}{r} \frac{\partial \hat{p}}{\partial r} + \frac{1}{r^2} \frac{\partial^2 \hat{p}}{\partial \theta^2} \right) (r, \theta, s|r_0, \theta_0). \end{aligned}$$

Using the separation of variables, we have

$$\hat{p}(r, \theta, s|r_0, \theta_0) = \sum_k R_k(r, s) \sin(k\theta) \sin(k\theta_0).$$

Using the change of variable, $x(s) = r\sqrt{\frac{s}{D}}$ and $x_0(s) = r_0\sqrt{\frac{s}{D}}$, we get for all k that

$$\begin{aligned} (3.19) \quad R_k''(x(s), s) + \frac{1}{x(s)} R_k'(x(s), s) - \left(1 + \frac{k^2}{x(s)^2} \right) R_k(x(s), s) \\ = -\frac{2}{\Theta D x_0(s)} \delta(x(s) - x_0(s)). \end{aligned}$$

$R_k(x(s), s)$ is a superposition of modified Bessel functions of order k : $I_k(x(s))$ and $K_k(x(s))$. Thus, for $x(s) \neq x_0(s)$ we obtain that

$$R_k(x(s), s) = A_k I_k(x(s)) + B_k K_k(x(s)),$$

where A_k and B_k are real constants. Since K_k diverges as $x(s) \rightarrow 0$, the interior solution for $(x(s) < x_0(s))$ depends only on I_k . We denote by D_k the exterior solution for $(x(s) > x_0(s))$. We use the general notation $x \wedge y = \min(x, y)$ and $x \vee y = \max(x, y)$; thus

$$R_k(x(s), s) = A_k I_k(x(s) \wedge x_0(s)) D_k(x(s) \vee x_0(s)).$$

To determine $D_k = a_k I_k + b_k K_k$, we use the reflecting condition at $x(s) = x_+(s) = R\sqrt{\frac{s}{D}}$ and we get that

$$A_k I_k(x_0(s)) \cdot \left(a_k I_k'(x_+(s)) + b_k K_k'(x_+(s)) \right) = 0.$$

We choose

$$a_k = -K_k'(x_+(s)) \text{ and } b_k = I_k'(x_+(s)).$$

Thus

$$R_k(x(s), s) = A_k I_k(x(s) \wedge x_0(s)) \left(I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k \right) (x(s) \vee x_0(s)).$$

The constants A_k are determined by integrating (3.19) over an infinitesimal interval that includes r_0 . Using the continuity of R_k , we get

$$(R_k)'_{x(s) > x_0(s)} |_{x(s)=x_0(s)} - (R_k)'_{x(s) < x_0(s)} |_{x(s)=x_0(s)} = -\frac{2}{\Theta D x_0(s)},$$

that is,

$$A_k \left(I_k \left(I'_k(x_+(s)) K'_k - K'_k(x_+(s)) I'_k \right) - I'_k \left(I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k \right) \right) (x_0(s)) = -\frac{2}{\Theta D x_0(s)}.$$

After some simplifications, we get

$$A_k I'_k(x_+(s)) \left(I_k K'_k - I'_k K_k \right) (x_0(s)) = -\frac{2}{\Theta D x_0(s)}.$$

Using the recurrent relation between modified Bessel functions (see [11] or [12, p. 489]),

$$I'_k(x_0(s)) = \left(I_{k-1} - \frac{k}{x_0(s)} I_k \right) (x_0(s)) \text{ and } K'_k(x_0(s)) = \left(-K_{k-1} - \frac{k}{x_0(s)} K_k \right) (x_0(s)),$$

we get

$$A_k I'_k(x_+(s)) \left(I_k \left(-K_{k-1} - \frac{k}{x_0(s)} K_k \right) - \left(I_{k-1} - \frac{k}{x_0(s)} I_k \right) K_k \right) (x_0(s)) = -\frac{2}{\Theta D x_0(s)},$$

that is

$$A_k I'_k(x_+(s)) (I_k K_{k-1} + I_{k-1} K_k) (x_0(s)) = \frac{2}{\Theta D x_0(s)}.$$

Finally, using this relation and the following Wronskian relation [12, p. 489]:

$$(I_k K_{k-1} + I_{k-1} K_k) (x_0(s)) = \frac{1}{x_0(s)},$$

we obtain that

$$A_k = \frac{2}{\Theta D I'_k(x_+(s))}.$$

Thus

$$R_k(x(s), s) = \frac{2}{\Theta D I'_k(x_+(s))} I_k(x(s) \wedge x_0(s)) \left(I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k \right) (x(s) \vee x_0(s)).$$

We can now express the solution \hat{p} for $\theta < \theta_0$ by

$$\hat{p}(r, \theta, s) = \frac{2}{\Theta D} \sum_k \frac{I_k(x(s) \wedge x_0(s)) \left(I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k \right) (x(s) \vee x_0(s))}{I'_k(x_+(s))} \sin(k\theta) \sin(k\theta_0).$$

The exit point distribution $\epsilon^0(r)$ is given by

$$(3.20) \quad \epsilon^0(r) = - \left(\frac{D}{r} \frac{\partial}{\partial \theta} \left(\int_0^\infty p(r, \theta, t) dt \right) \right) (\theta = 0).$$

To obtain an analytical expression for expression (3.20), we use the Laplace relation

$$\mathcal{L} \left(\int_0^t f(u) du \right) = \frac{F(z)}{z},$$

where $F = \mathcal{L}(f)$ is the Laplace transform of the function f . We have

$$\begin{aligned} \int_0^t p(r, \theta, u) du &= \mathcal{L}^{-1} \left(\frac{\hat{p}(r, \theta, s)}{s} \right) \\ &= \mathcal{L}^{-1} \left(\frac{2}{\Theta D} \sum_k \sin(k\theta) \sin(k\theta_0) \frac{I_k(x(s) \wedge x_0(s)) (I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k)(x(s) \vee x_0(s))}{s I'_k(x_+(s))} \right). \end{aligned}$$

The computation of the integral

$$(3.21) \quad \begin{aligned} I(r, \theta, t) &= \frac{1}{\Theta \pi D i} \sum_k \sin(k\theta) \sin(k\theta_0) \int_{-i\infty}^{+i\infty} \frac{I_k(x(s) \wedge x_0(s)) (I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k)(x(s) \vee x_0(s))}{s I'_k(x_+(s))} e^{st} ds \end{aligned}$$

uses the residue theorem, and the details are given in the appendix. We have

$$I(r, \theta, t) = \int_0^t p(r, \theta, u) du = \frac{2}{\Theta D} (S_1(r, \theta, t) + S_2(r, \theta, t)),$$

where

$$\begin{aligned} S_1(r, \theta, t) &= \sum_k \sin(k\theta) \sin(k\theta_0) \frac{r^k (r_0^{2k} + R^{2k})}{2k R^{2k} r_0^k}, \\ S_2(r, \theta, t) &= -2 \sum_k \sin(k\theta) \sin(k\theta_0) \sum_{j=1}^\infty e^{-D \alpha_{j,k}^2 t} \frac{J_k(r \alpha_{j,k}) J_k(r_0 \alpha_{j,k})}{(R^2 \alpha_{j,k}^2 - k^2) J_k^2(R \alpha_{j,k})}, \end{aligned}$$

and J_k are the k -order Bessel functions and $\alpha_{j,k}$ are the roots of the equation:

$$J'_k(R\alpha) = 0.$$

Consequently, for $r < r_0$, using (3.20), we get the following exit distribution (for $\Theta = 0$):

$$\epsilon^0(r) = \frac{2}{\Theta} \frac{\partial}{r \partial \theta} \left(\lim_{t \rightarrow \infty} (S_1(r, \theta, t) + S_2(r, \theta, t)) \right)_{\theta=0}.$$

Because

$$\lim_{t \rightarrow \infty} S_1(r, \theta, t) = S_1(r, \theta) \text{ and } \lim_{t \rightarrow \infty} S_2(r, \theta, t) = 0,$$

we finally obtain that

$$(3.22) \quad \epsilon^0(r) = \frac{1}{\Theta} \sum_k \sin(k\theta_0) \frac{r^{k-1} (r_0^{2k} + R^{2k})}{R^{2k} r_0^k},$$

and, for $r > r_0$, a similar computation leads to

$$(3.23) \quad \epsilon^0(r) = \frac{1}{\Theta} \sum_k \sin(k\theta_0) \frac{r_0^k (r^{2k} + R^{2k})}{R^{2k} r^{k+1}}.$$

These expressions can be further simplified. Indeed, we rewrite them as follows (for $r < r_0$):

$$\epsilon^0(r) = \frac{1}{\Theta r} \sum_k \sin(k\theta_0) \left(\frac{r}{r_0}\right)^k \left(1 + \left(\frac{r_0}{R}\right)^{2k}\right).$$

Thus,

$$\epsilon^0(r) = \frac{1}{\Theta r} \Im m \left(\sum_{n \geq 1} e^{in\nu\theta_0} \left(\frac{r}{r_0}\right)^{n\nu} \left(1 + \left(\frac{r_0}{R}\right)^{2n\nu}\right) \right),$$

where $\Im m$ denotes the imaginary part of the expression. We obtain two geometrical series that can be summed. We get

$$\epsilon^0(r) = \frac{1}{\Theta r} \Im m \left(\frac{e^{i\nu\theta_0} \left(\frac{r}{r_0}\right)^\nu}{1 - e^{i\nu\theta_0} \left(\frac{r}{r_0}\right)^\nu} + \frac{e^{i\nu\theta_0} \left(\frac{r}{r_0}\right)^\nu \left(\frac{r_0}{R}\right)^{2\nu}}{1 - e^{i\nu\theta_0} \left(\frac{r}{r_0}\right)^\nu \left(\frac{r_0}{R}\right)^{2\nu}} \right),$$

that is,

$$\epsilon^0(r) = \frac{1}{\Theta r} \Im m \left(e^{i\nu\theta_0} \left(\frac{\left(\frac{r}{r_0}\right)^\nu}{1 - e^{i\nu\theta_0} \left(\frac{r}{r_0}\right)^\nu} + \frac{\left(\frac{rr_0}{R^2}\right)^\nu}{1 - e^{i\nu\theta_0} \left(\frac{rr_0}{R^2}\right)^\nu} \right) \right).$$

After some rearrangements, we obtain the following exit point distribution on $\theta = 0$, conditioned on the initial position (r_0, θ_0) :

$$(3.24) \quad \begin{aligned} \epsilon^0(r) &= \epsilon^0(r|r_0, \theta_0) \\ &= \frac{1}{\Theta r} \left(\frac{(rr_0)^\nu \sin(\nu\theta_0)}{r^{2\nu} + r_0^{2\nu} - 2(rr_0)^\nu \cos(\nu\theta_0)} + \frac{(rr_0R^2)^\nu \sin(\nu\theta_0)}{(rr_0)^{2\nu} + R^{4\nu} - 2(rr_0R^2)^\nu \cos(\nu\theta_0)} \right), \end{aligned}$$

for $0 \leq r \leq R$. Similarly, for $\theta = \Theta$, we obtain

$$(3.25) \quad \begin{aligned} \epsilon^\Theta(r) &= \epsilon^\Theta(r|r_0, \theta_0) \\ &= \frac{1}{\Theta r} \left(\frac{(rr_0)^\nu \sin(\nu\theta_0)}{r^{2\nu} + r_0^{2\nu} + 2(rr_0)^\nu \cos(\nu\theta_0)} + \frac{(rr_0R^2)^\nu \sin(\nu\theta_0)}{(rr_0)^{2\nu} + R^{4\nu} + 2(rr_0R^2)^\nu \cos(\nu\theta_0)} \right). \end{aligned}$$

We notice that by letting R tend to ∞ , we recover the expressions computed in the open wedge case ((3.15) and (3.16)).

Exit radius distribution

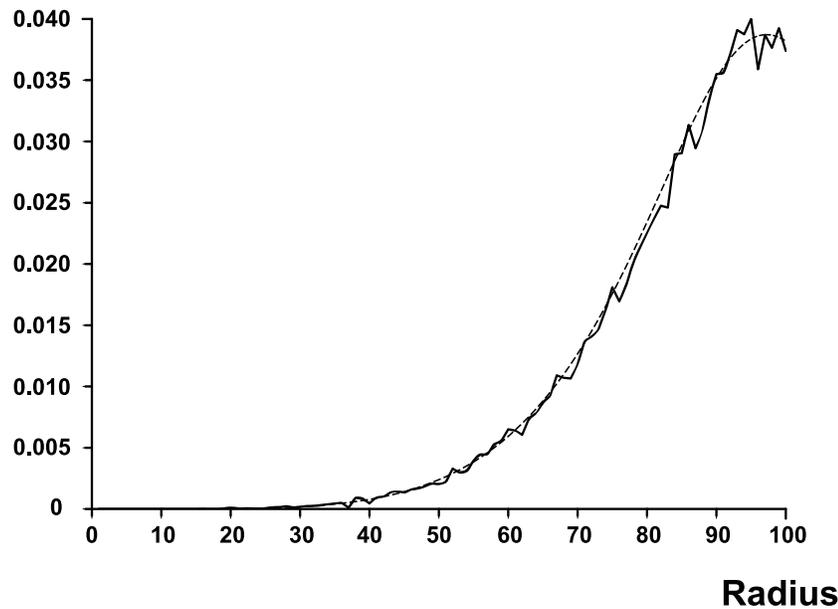


FIG. 3.1. Mean exit points distribution. The theoretical distribution (dashed line) is tested against the empirical one (solid line) obtained by running a simulation of 20,000 Brownian particles, starting on the wedge bisectrix ($\theta_0 = \frac{\Theta}{2}$ at $r_0 = R = 100$ for $\Theta = \frac{\pi}{6}$). Because the starting point is located on the bisectrix, $\epsilon^0(x) = \epsilon^\Theta(x)$, and thus the analytical curve is given by $\epsilon(r) = \epsilon^0(r) + \epsilon^\Theta(r) = \frac{2}{\Theta r} \left(\frac{(rr_0)^\nu}{r^{2\nu} + r_0^{2\nu}} + \frac{(rr_0 R^2)^\nu}{(rr_0)^{2\nu} + R^{4\nu}} \right)$. In that case, the maximum of the function $\epsilon(r)$ is achieved at $r = r_0 e^{\frac{1}{2\nu} \ln\left(\frac{\nu-1}{\nu+1}\right)}$.

3.4. The mean exit radius. To determine the mean exit distribution radius $\bar{\epsilon}(r|r_0)$ for a viral particle starting initially at position r_0, θ_0 , where θ_0 is uniformly distributed between 0 and Θ , we consider $\epsilon(r|r_0, \theta_0) = \epsilon^0(r|r_0, \theta_0) + \epsilon^\Theta(r|r_0, \theta_0)$ and estimate the integral

$$(3.26) \quad \bar{\epsilon}(r|r_0) = \frac{1}{\Theta} \int_{\Theta=0}^{\Theta} \epsilon(r|r_0, \theta_0) d\theta_0.$$

Integrating expressions (3.24) and (3.25), we get

$$\bar{\epsilon}(r|r_0) = \frac{2}{\Theta \pi r} \left(\ln \left(\frac{r^\nu + r_0^\nu}{|r^\nu - r_0^\nu|} \right) + \ln \left(\frac{R^{2\nu} + (rr_0)^\nu}{R^{2\nu} - (rr_0)^\nu} \right) \right).$$

We define the mean exit point as $r_m(r_0) = \mathbf{E}(r|r_0)$ conditioned on the initial radius r_0 . Thus,

$$(3.27) \quad r_m(r_0) = \mathbf{E}(r|r_0) = \int_0^R r \bar{\epsilon}(r|r_0) dr.$$

Using the expansion $\ln(1+x) = \sum_{n \geq 1} (-1)^{n+1} \frac{x^n}{n}$ for $x < 1$, we obtain by a direct integration that

$$(3.28) \quad r_m(r_0) = \frac{8}{\pi^2} \left(r_0 \left(\sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \left(\frac{1}{1 - \frac{1}{(2n+1)^2 \left(\frac{\pi}{\Theta}\right)^2}} \right) \right) - R \left(\sum_{n=0}^{\infty} \frac{\left(\frac{r_0}{R}\right)^{(2n+1)\frac{\pi}{\Theta}} \frac{\pi}{\Theta}}{(2n+1) \left(\left((2n+1) \frac{\pi}{\Theta} \right)^2 - 1 \right)} \right) \right).$$

Using the expansion in the first part,

$$(3.29) \quad \frac{1}{1 - \frac{1}{(2n+1)^2 \left(\frac{\pi}{\Theta}\right)^2}} = \sum_{p=0}^{\infty} \left(\frac{\Theta}{(2n+1)\pi} \right)^{2p},$$

and the approximation $\Theta \ll 1$, by using the value of the Riemann ζ -function, $\zeta(2) = \frac{\pi^2}{6}$ and $\zeta(4) = \frac{\pi^4}{90}$, we obtain that

$$(3.30) \quad r_m(r_0) \approx r_0 \left(1 + \frac{\Theta^2}{12} \right) - \frac{8R}{\pi^2} \left(\frac{r_0}{R} \right)^{\pi/\Theta} \frac{\pi/\Theta}{(\pi/\Theta)^2 - 1}.$$

For Θ small, the second term in the right-hand side of (3.30) is exponentially small.

4. Approximation of a virus motion by an effective Markovian stochastic equation. We replace the successive steps of viral dynamics with an effective stochastic equation containing a constant steady state drift.

4.1. Methodology. Virus motion described in subsection 2.2 consists of a succession of drift and diffusing periods. We start with the stochastic equation

$$(4.1) \quad \dot{\mathbf{X}} = -B \frac{\mathbf{r}}{|\mathbf{r}|} + \sqrt{2D} \dot{\mathbf{w}},$$

where \mathbf{r} is the radial component of \mathbf{X} and B is the amplitude of the drift. The MFPT of the process (4.1) to the nucleus, which is located at $r = \delta$, when the initial position is located on the cell surface $r = R$, is solution of

$$\begin{aligned} D \left(\frac{d^2 t}{dr^2} + \frac{1}{r} \frac{dt}{dr} \right) (r, \theta) - B \frac{dt}{dr} (r, \theta) &= -1 \text{ for } (r, \theta) \in \Omega, \\ t(r, \theta) &= 0 \text{ for } r = \delta, \\ \frac{dt}{dr} (r, \theta) &= 0 \text{ for } r = R. \end{aligned}$$

A similar equation can be written in the domain $\tilde{\Omega}$ with reflective boundary conditions of the wedge. Both processes in the full domain or in $\tilde{\Omega}$ lead to the same MFPT. The solution $t(B, r)$ is given by

$$(4.2) \quad t(B, r) = C - \int_r^R \left(\int_v^R \frac{ue^{-\alpha(u-v)}}{Dv} du \right) dv,$$

where $\alpha = \frac{B}{D}$ and

$$(4.3) \quad t(B, R) = C = \int_\delta^R \left(\int_v^R \frac{ue^{-\alpha(u-v)}}{Dv} du \right) dv.$$

For a fixed radius R , the derivative of the function $t(B, R)$ with respect to B is strictly negative, which shows that $B \rightarrow t(B, R)$ is strictly decreasing. To determine the value of the amplitude B , we match the mean time $t(B, R)$ with the MFPT to reach the nucleus within the iterative procedure, as described in subsection 2.2: at time zero, the virus starts at position $r = R = R_0$ and reaches the edge boundary in mean time $\bar{u}(R_0)$ and at mean position $r_m(R_0)$. The viral particle is then transported toward the nucleus over a distance d_m during time t_m . Either the particle reaches the nucleus before time t_m and then the algorithm is terminated, or in a second step it starts at position $R_1 = r_m(R_0) - d_m$. The process iterates until the particle reaches the nucleus. We consider the mean number of fundamental steps (diffusion step and directed motion along a microtubule step) that the virus needs to reach the nucleus to be equal to $n \geq 0$. Thus the mean time to reach the nucleus computed by (4.2) has to be equal to the mean time $\tau = \sum_{k=0}^{n-1} \bar{u}(R_k) + nt_m + \langle t_r \rangle$ of the iterative trajectory. In a first approximation, we neglect the mean residual time $\langle t_r \rangle$ and we thus get the equality

$$(4.4) \quad t(B, R) = \tau = \sum_{k=0}^{n-1} \bar{u}(R_k) + nt_m,$$

$$(4.5) \quad R_{k+1} = r_m(R_k) - d_m,$$

$$(4.6) \quad R_0 = R.$$

For a fixed radius R , equation (4.4) has a unique solution B , which can be found in practice by any standard numerical method.

Remark. The MFPT of a particle in which the trajectory consists of alternating drift (traveling along microtubules) and diffusion periods can be either higher or lower than the MFPT of a pure Brownian particle. Indeed, when $B < 0$, the drift effect is less efficient than pure diffusion. For example, for $\Theta = \frac{\pi}{6}$, $R = 100\mu m$, and $\delta = \frac{R}{4} = 25\mu m$, a large diffusion constant $D = 10\mu m^2 s^{-1}$ with the dynamical parameters $t_m = 1s$ and $d_m = 1\mu m$ leads to a negative mean drift

$$(4.7) \quad B \approx -0.14\mu m s^{-1}.$$

On the other hand, for a small diffusion constant $D = 1\mu m^2 s^{-1}$, an efficient microtubule transport obtained for $t_m = 1s$ and $d_m = 5\mu m$ leads to a mean positive drift

$$(4.8) \quad B \approx 0.13\mu m s^{-1}.$$

4.2. Explicit expression of the drift in the limit of $\Theta \ll 1$. When the number of microtubules is large enough, the condition $\Theta \ll 1$ is satisfied. Moreover, because a virus entering a cell surface has a deterministic motion, we can assume that the initial position satisfies $R_0 < R$ so that we can neglect any boundary effects and use the open wedge approximation, which consists of using formula (3.30) without the boundary layer term. Actually, this approximation is not that restrictive because after the first iteration process (movement along the microtubule followed by the particle release), the boundary layer term is negligible compared to the other term.

To obtain an explicit expression for the amplitude B , we consider the successive approximations

$$(4.9) \quad r_m(R_0) \approx R_0 \left(1 + \frac{\Theta^2}{12} \right)$$

and

$$\begin{aligned}
 R_0 &= R_0; \\
 R_1 &\simeq R_0 \left(1 + \frac{\Theta^2}{12} \right) - d_m; \\
 R_2 &\simeq R_0 \left(1 + \frac{\Theta^2}{12} \right)^2 - d_m \left(1 + \left(1 + \frac{\Theta^2}{12} \right) \right); \\
 &\vdots \\
 R_i &\simeq R_0 \left(1 + \frac{\Theta^2}{12} \right)^i - d_m \left(\sum_{k=0}^{i-1} \left(1 + \frac{\Theta^2}{12} \right)^k \right);
 \end{aligned}$$

that is,

$$(4.10) \quad R_i \simeq \left(R_0 - \frac{12d_m}{\Theta^2} \right) \left(1 + \frac{\Theta^2}{12} \right)^i + \frac{12d_m}{\Theta^2}.$$

Thus the particle reaches the nucleus after n iteration steps which approximatively satisfies $R_n = \delta$,

$$(4.11) \quad n \simeq \frac{\ln \left(\frac{1 - \frac{\delta\Theta^2}{12d_m}}{1 - \frac{R_0\Theta^2}{12d_m}} \right)}{\ln \left(1 + \frac{\Theta^2}{12} \right)} \approx \frac{R_0 - \delta}{d_m} + o(1).$$

If T_n denotes the mean time a viral particle takes to reach the nucleus, then using formula (3.9), we obtain

$$(4.12) \quad T_n \simeq n.t_m + \frac{\left(\frac{\tan(\Theta)}{\Theta} - 1 \right)}{4D} \sum_{i=0}^{n-1} R_i^2,$$

that is,

$$\begin{aligned}
 t &\simeq n.t_m + \frac{\left(\frac{\tan(\Theta)}{\Theta} - 1 \right)}{4D} \\
 &\quad \times \sum_{i=0}^{n-1} \left(\left(\frac{12d_m}{\Theta^2} \right)^2 + 2 \left(\frac{12d_m}{\Theta^2} \right) \left(R_0 - \frac{12d_m}{\Theta^2} \right) \left(1 + \frac{\Theta^2}{12} \right)^i \right. \\
 &\quad \left. + \left(R_0 - \frac{12d_m}{\Theta^2} \right)^2 \left(1 + \frac{\Theta^2}{12} \right)^{2i} \right), \\
 T_n &\simeq nt_m + \frac{\left(\frac{\tan(\Theta)}{\Theta} - 1 \right)}{4D} \\
 &\quad \times \left(n \left(\frac{12d_m}{\Theta^2} \right)^2 - \left(\frac{24d_m}{\Theta^2} \right) \left(R_0 - \frac{12d_m}{\Theta^2} \right) \frac{1 - \left(1 + \frac{\Theta^2}{12} \right)^n}{\frac{\Theta^2}{12}} \right. \\
 &\quad \left. + \left(R_0 - \frac{12d_m}{\Theta^2} \right)^2 \frac{1 - \left(1 + \frac{\Theta^2}{12} \right)^{2n}}{1 - \left(1 + \frac{\Theta^2}{12} \right)^2} \right).
 \end{aligned}$$

For $\Theta \ll 1$, a Taylor expansion gives that

$$T_n \simeq \left(\frac{R_0 - \delta}{d_m} \right) t_m + \frac{t_m (R_0 - \delta)}{24d_m} \left(1 + \frac{R_0 + \delta}{d_m} \right) \Theta^2 \\ + \frac{(R_0 - \delta)}{72D} \left(d_m + 3(R_0 + \delta) + \frac{2(R_0^2 + R_0\delta + \delta^2)}{d_m} \right) \Theta^4 + o(\Theta^4).$$

In small diffusion limit $D \ll 1$, $\Theta \ll 1$, the velocity is $B \simeq \frac{R_0 - \delta}{T_n}$, and consequently we obtain for $R_0 \approx R$ a second order approximation,

$$(4.13) \quad B \approx \frac{\frac{d_m}{t_m}}{1 + \left(1 + \frac{R + \delta}{d_m} \right) \frac{\Theta^2}{24} + O(\Theta^4)},$$

where d_m , t_m are the mean distance and the mean time a virus stays on the microtubule, R (resp., δ) is the radius of the cell (resp., nucleus) and $\Theta = \frac{2\pi}{N}$, where N is the total number of microtubules.

4.3. Justification of the MFPT criteria. To justify the use of the MFPT criteria to estimate the steady state drift, we run numerical simulations of 1,000 viruses inside a two-dimensional domain Ω ($\delta < r < R$) with intermittent dynamics, alternating between epochs of free diffusion and directed motion along microtubules, and compare the steady state distribution with the one obtained by solving the Fokker-Planck equation for viruses whose trajectories are described by the effective stochastic equation (2.2) with our computed constant drift

$$(4.14) \quad \mathbf{b}(\mathbf{X}) = - \frac{\frac{d_m}{t_m}}{1 + \left(1 + \frac{R + \delta}{d_m} \right) \frac{\Theta^2}{24}} \frac{\mathbf{r}}{|\mathbf{r}|} = -B \frac{\mathbf{r}}{|\mathbf{r}|}.$$

We imposed reflecting boundary conditions at the nuclear and the external membrane. The theoretical normalized steady state distribution ρ satisfies

$$D\Delta\rho - \nabla \cdot [\mathbf{b}\rho] = 0 \text{ in } \Omega, \\ \frac{d\rho}{dr}(R) = \frac{d\rho}{dr}(\delta) = 0,$$

and the solution ρ is given by

$$(4.15) \quad \rho(r) = \frac{e^{-\frac{Br}{D}}}{\int_{\delta}^R e^{-\frac{Br}{D}} 2\pi r dr} = \frac{e^{-\frac{Br}{D}}}{2\pi \frac{D}{B} (\delta e^{-\frac{B\delta}{D}} - R e^{-\frac{BR}{D}} + \frac{D}{B} (e^{-\frac{B\delta}{D}} - e^{-\frac{BR}{D}}))}.$$

The result of both distributions is presented in Figure 4.1, where we can observe that both curves match very nicely. This result shows that the criteria we have used is at least enough to recover the distribution. For the simulations, we consider that the directed run of the virus along a microtubule (loaded by dynein) lasts $t_m = 1s$ and covers a mean distance $d_m = 0.7\mu m$ [13]. The diffusion constant is $D = 1.3\mu m^2 s^{-1}$, as observed for the adeno-associated virus [14]. The two curves in Figure 4.1 fit very nicely except at the neighborhood of the nuclear membrane, where the simulation of the empirical distribution is plagued with a possible boundary layer. Another source of discrepancy comes from the difference of behavior of viruses far from and close to the nucleus: viruses far from the nucleus do not bind as often as those located in its neighborhood. Consequently, a constant effective drift cannot account for the radial geometry near the nucleus. A theory for radius-dependent effective drift has been derived in [15].

Steady State Distributions

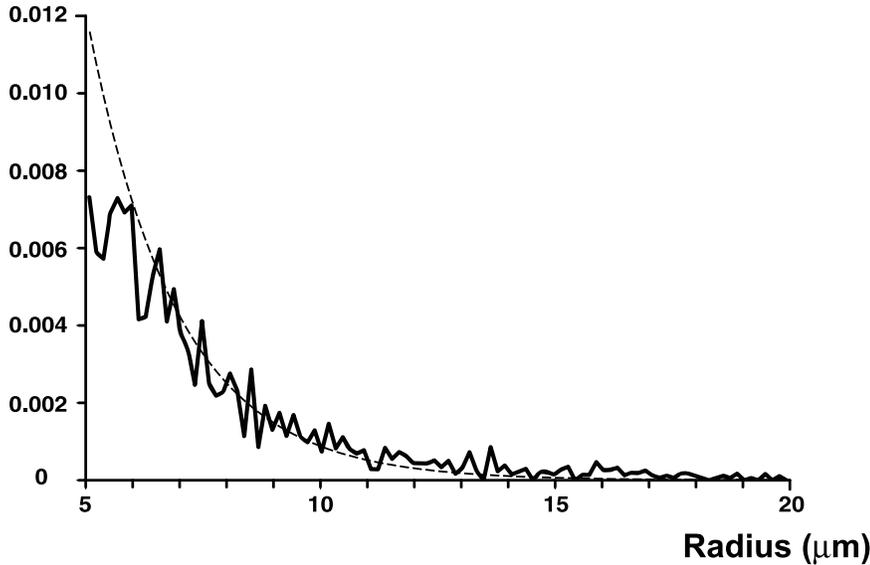


FIG. 4.1. *Steady state distributions. We show the empirical steady state distribution for 1,000 viral trajectories with an intermittent dynamic (solid line). The theoretical distribution of viruses whose trajectories are described by the stochastic equation (2.2) is shown by the dashed line. Geometrical parameters are $R = 20\mu\text{m}$, $\delta = 5\mu\text{m}$, and $\Theta = \frac{\pi}{24}$.*

5. Conclusion. For the limit of a cell containing an excess of microtubules, we have presented here a model to describe the motion of biological particles such as viruses, vesicles, and many others moving inside the cell cytoplasm by a complex combination of Brownian motion and deterministic drift. Our procedure consists mainly of approximating an alternative switching mode between diffusion and deterministic drift epochs by a steady state stochastic equation; it also consists of estimating the amplitude of the effective drift and is based on the criteria that the MFPTs to the nucleus computed in both cases are equal. In that case, this amplitude accounts for the directed transport along microtubules, the cell geometry, and the binding constants. The model has, however, several limitations. First, we do not take into account directly the backward movement of the virus along the microtubules [16, 17], which can affect the mean time and the amplitude of the drift. Second, the present computations are given only for two-dimensional cell geometry. It can still be applied to many in vitro culture cells; however, it is not clear how to generalize our approach to a three-dimensional cell geometry. For example, to study the trafficking inside cylindrical axons or dendrites of neuronal cells, a different approach should include these geometrical features. However, despite these real difficulties, the present model may be used to analyze plasmid transport in a host cell, at the molecular level, which is one of the fundamental limitations of gene delivery [18, 19, 20, 21].

Appendix. In this appendix, we provide an explicit computation of integral (3.21) using the method of the residues. This method was previously used in a similar context in [12, p. 386]. We denote by $(p_j^k)_{j \geq 0}$ the poles of the function

$$\Phi : s \rightarrow \frac{I_k(x(s) \wedge x_0(s)) \left(I'_k(x_+(s)) K_k - K'_k(x_+(s)) I_k \right) (x(s) \vee x_0(s))}{s I'_k(x_+(s))} e^{st},$$

where $(x(s) = r\sqrt{\frac{s}{D}}, x_0(s) = r_0\sqrt{\frac{s}{D}}, \text{ and } x_+(s) = R\sqrt{\frac{s}{D}})$. The associated residues are $(r_j^k)_{j \geq 0}$. We now compute the residues explicitly.

To identify the poles, we recall the relation between the k -order Bessel function J_k (that is true for z such that $-\pi < \arg(z) < \frac{\pi}{2}$) and the modified Bessel functions I_k [11, p. 375]:

$$(5.1) \quad I_k(z) = e^{-\frac{1}{2}k\pi i} J_k\left(ze^{\frac{1}{2}\pi i}\right).$$

All roots $\alpha_{j,k}$ of the equations

$$J'_k(R\alpha) = 0$$

are real, simple, and strictly positive [11, p. 370] because k is real and

$$k \leq \alpha_{1,k} < \alpha_{2,k} \dots$$

Thus,

$$I'_k(-iR\alpha_{j,k}) = 0.$$

Finally, the poles of Φ are simple, given by $p_0^k = 0$ and that for all $j \geq 1, p_j^k = -D\alpha_{j,k}^2$. Consequently the associated residues are given for each k for all $j \geq 0$ by

$$(5.2) \quad r_j^k = \lim_{s \rightarrow p_j^k} (s - p_j^k) \Phi(s).$$

Then using the residues, integral (3.21) is given by

$$I(r, \theta, t) = \frac{1}{\Theta\pi D i} \sum_k \sin(k\theta) \sin(k\theta_0) (2\pi i) \sum_{j \geq 0} r_j^k = \frac{2}{\Theta D} \sum_k \sin(k\theta) \sin(k\theta_0) \sum_{j \geq 0} r_j^k.$$

We now compute the residues r_j^k . The residue r_0^k is associated with the pole $p_0^k = 0$ and given by

$$r_0^k = \lim_{s \rightarrow 0} s\Phi(s).$$

Using the following identities on the modified Bessel functions [12, p. 489],

$$I'_k(z) = I_{k+1}(z) + \frac{k}{z} I_k(z) \text{ and } K'_k(z) = -K_{k-1}(z) - \frac{k}{z} K_k(z),$$

and substituting the derivatives I'_k and K'_k in the expression of Φ , we get

$$\begin{aligned} r_0^k &= \lim_{s \rightarrow 0} \frac{I_k(x(s) \wedge x_0(s))}{\left(I_{k+1} + \frac{k}{x_+(s)} I_k\right)(x_+(s))} \\ &\quad \times \left(\left(\left(I_{k+1} + \frac{k}{x_+(s)} I_k \right) (x_+(s)) K_k \right) \right. \\ &\quad \left. + \left(\left(K_{k-1} + \frac{k}{x_+(s)} K_k \right) (x_+(s)) I_k \right) \right) (x(s) \vee x_0(s)). \end{aligned}$$

Taking into account only the dominant terms, we get

$$r_0^k = \lim_{s \rightarrow 0} \frac{I_k(x(s) \wedge x_0(s)) (I_k(x_+(s)) K_k + K_k(x_+(s)) I_k)(x(s) \vee x_0(s))}{I_k(x_+(s))}.$$

To further compute this limit, we use the Taylor expansions of I_k and K_k [11, p. 375] expressed in terms of the Γ function:

$$I_k(z) \approx \frac{\left(\frac{1}{2}z\right)^k}{\Gamma(k+1)} \text{ and } K_k(z) \approx \frac{1}{2}\Gamma(k) \left(\frac{1}{2}z\right)^{-k}.$$

For $r < r_0$, we get

$$r_0^k = \lim_{s \rightarrow 0} \frac{\frac{\left(\frac{1}{2}(x(s))\right)^k}{\Gamma(k+1)} \left(\frac{\left(\frac{1}{2}(x_+(s))\right)^k}{\Gamma(k+1)} \frac{1}{2}\Gamma(k) \left(\frac{1}{2}(x_0(s))\right)^{-k} + \frac{1}{2}\Gamma(k) \left(\frac{1}{2}(x_+(s))\right)^{-k} \frac{\left(\frac{1}{2}(x_0(s))\right)^k}{\Gamma(k+1)} \right)}{\frac{\left(\frac{1}{2}(x_+(s))\right)^k}{\Gamma(k+1)}}.$$

Finally, using the relation $\Gamma(k+1) = k\Gamma(k)$ and the expressions of $x(s)$, $x_0(s)$, and $x_+(s)$, we get

$$r_0^k = \frac{r^k (r_0^{2k} + R^{2k})}{2kR^{2k}r_0^k}.$$

The computation of the other residues $(r_j^k)_{j \geq 1}$ is slightly different,

$$r_j^k = \lim_{s \rightarrow p_j^k} (s - p_j^k) \Phi(s),$$

where $p_j^k = -D\alpha_{j,k}^2$. Using the Wronskian relation [12, p. 489],

$$I_k(z) K_k'(z) - K_k(z) I_k'(z) = -\frac{1}{z},$$

we now substitute

$$K_k'(z) = \frac{-\frac{1}{z} + K_k(z) I_k'(z)}{I_k(z)}.$$

In the expression of Φ , we get

$$r_j^k = \lim_{s \rightarrow p_j^k} \frac{(s - p_j^k) e^{st} I_k(x(s)) \left(I_k'(x_+(s)) K_k - \left(\frac{-\frac{1}{x_+(s)} + K_k I_k'}{I_k} \right) (x_+(s)) I_k \right) (x_0(s))}{s I_k'(x_+(s))}.$$

Because

$$\lim_{s \rightarrow p_j^k} I_k'(x_+(s)) = I_k'(x_+(p_j^k)) = 0,$$

we obtain the expression for the residues:

$$r_j^k = \frac{e^{p_j^k t} I_k(x(p_j^k)) I_k(x_0(p_j^k))}{p_j^k I_k(x_+(p_j^k)) x_+(p_j^k)} \lim_{s \rightarrow p_j^k} \frac{(s - p_j^k)}{I_k'(x_+(s))}.$$

Finally, since

$$\lim_{s \rightarrow p_j^k} \frac{(s - p_j^k)}{I_k'(x_+(s))} = \frac{2\sqrt{Dp_j^k}}{R} \lim_{s \rightarrow p_j^k} \frac{x_+(s) - x_+(p_j^k)}{I_k'(x_+(s)) - I_k'(x_+(p_j^k))} = \frac{2\sqrt{Dp_j^k}}{RI_k''(x_+(p_j^k))},$$

we obtain

$$r_j^k = \frac{e^{p_j^k t} I_k(x(p_j^k)) I_k(x_0(p_j^k))}{p_j^k I_k(x_+(p_j^k)) x_+(p_j^k)} \frac{2\sqrt{Dp_j^k}}{RI_k''(x_+(p_j^k))}.$$

To simplify this expression, we use that I_k satisfies the differential equation [11, p. 374]

$$I_k''(z) + \frac{1}{z} I_k'(z) - \left(1 + \frac{k^2}{z^2}\right) I_k(z) = 0.$$

Thus for $z = x_+(p_j^k)$,

$$I_k''(x_+(p_j^k)) = \frac{p_j^k R^2 + Dk^2}{p_j^k R^2} I_k(x_+(p_j^k)).$$

We get

$$r_j^k = \frac{2De^{p_j^k t}}{R^2 p_j^k + Dk^2} \frac{I_k(x(p_j^k)) I_k(x_0(p_j^k))}{I_k^2(x_+(p_j^k))},$$

and finally, using (5.1), we get

$$r_j^k = \frac{2e^{-D\alpha_{j,k}^2 t}}{-R^2\alpha_{j,k}^2 + k^2} \frac{J_k(r\alpha_{j,k}) J_k(r_0\alpha_{j,k})}{J_k^2(R\alpha_{j,k})}.$$

Integral (3.21) is given by

$$(5.3) \quad I(r, \theta, t) = \frac{2}{\Theta D} \sum_k \sin(k\theta) \sin(k\theta_0) \sum_{j \geq 0} r_j^k = \frac{2}{\Theta D} (S_1(r, \theta, t) + S_2(r, \theta, t)),$$

where

$$S_1(r, \theta, t) = \sum_k \sin(k\theta) \sin(k\theta_0) \frac{r^k (r_0^{2k} + R^{2k})}{2kR^{2k}r_0^k},$$

$$S_2(r, \theta, t) = -2 \sum_k \sin(k\theta) \sin(k\theta_0) \sum_{j=1}^{\infty} e^{-D\alpha_{j,k}^2 t} \frac{J_k(r\alpha_{j,k}) J_k(r_0\alpha_{j,k})}{(R^2\alpha_{j,k}^2 - k^2) J_k^2(R\alpha_{j,k})}.$$

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