

Mean first passage times for bond formation for a Brownian particle in linear shear flow above a wall

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Motivated by cell adhesion in hydrodynamic flow, here the authors study bond formation between a spherical Brownian particle in linear shear flow carrying receptors for ligands covering the boundary wall. They derive the appropriate Langevin equation which includes multiplicative noise due to position-dependent mobility functions resulting from the Stokes equation. They present a numerical scheme which allows to simulate it with high accuracy for all model parameters, including shear rate and three parameters describing receptor geometry (distance, size, and height of the receptor patches). In the case of homogeneous coating, the mean first passage time problem can be solved exactly. In the case of position-resolved receptor-ligand binding, they identify different scaling regimes and discuss their biological relevance. © 2007 American Institute of Physics.

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I. INTRODUCTION

One of the hallmarks of biological systems is their tremendous specificity in binding reactions between receptors and ligands. On the molecular level, a prominent example is the antigen-antibody recognition, which allows our immune system to react to pathogens in a highly specific way. Although traditionally much attention has been devoted to the biochemical aspects of receptor-ligand binding, physical concepts are equally important in this context. In particular, a physical transport process is required to bring receptor and ligand to sufficient proximity for binding. A helpful concept is the notion that transport has to lead to the formation of an *encounter complex*, which then can react to form the final receptor-ligand complex.¹⁻⁴ In the language of stochastic dynamics, the formation of the encounter complex is a first passage problem which can be treated with appropriate tools from statistical physics. In many situations, the transport process is simple diffusion. However, more complex situations also exist, like the setup in affinity chips, where ligands are transported by hydrodynamic flow into a reaction chamber loaded with receptors.⁵

In cell adhesion, the physical transport processes required for specific bond formation tend to be even more complex, because here receptors and ligands are attached to surfaces and their movement is determined by the dynamics of the objects they are attached to. One important example in this context are white blood cells, which circulate the body with the blood flow and whose receptor-mediated binding to ligand-coated walls is usually studied experimentally in flow chambers.⁶⁻⁹ In order to fight pathogens in the surrounding tissue, white blood cells have to extravasate from the blood vessels. Initial binding is provided by transmembrane receptors from the selectin family binding to carbohydrate ligands on the vessel walls. Here, the probability to form an encoun-

ter complex is determined by the translational and rotational movements of the cell as determined by hydrodynamic, thermal, and other external forces. Similar situations also arise in microbiology, when bacteria adhere to the intestinal wall,¹⁰ in malaria infection, when infected red blood cells adhere to the vessel walls,¹¹⁻¹³ in the initial stages of pregnancy, when the developing embryo adheres to the uterus,¹⁴ and in biotechnology, e.g., when sorting cells on microfluidic chips.¹⁵

In this paper, we address this situation theoretically by combining methods from hydrodynamics and stochastic dynamics. In Fig. 1 we show the situation which is theoretically analyzed in the following. A spherical particle with radius R moves with hydrodynamic flow in the positive x direction at a height z above a wall. The simplest possible flow pattern is linear shear flow with shear rate $\dot{\gamma}$. For the usual dimensions in flow chamber experiments with white blood cells, this is the relevant flow profile. In the absence of external forces, there is no reason for the particle to drift towards the wall and the formation of an encounter complex has to rely com-

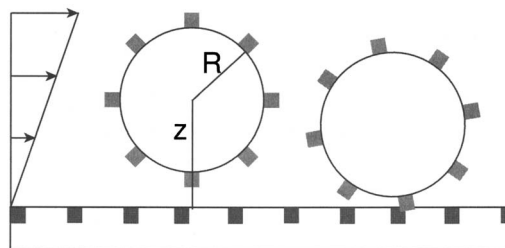


FIG. 1. Cartoon of a spherical particle with radius R moving in linear shear flow above a wall. The height z of the sphere center above the substrate obeys $z > R$. Bond formation between particle and wall is identified with spatial proximity between the receptor patches on the particle and the ligand patches on the wall being smaller than some prescribed encounter radius, that is, overlap of the gray areas.

pletely on thermal diffusion. In many situations of interest, however, there are forces pushing the particle towards the wall, e.g., gravitational or electric forces. In physiological blood flow, cell density is high and the driving force for encounter is provided mainly by hydrodynamic or contact interactions with other cells. For the sake of computational simplicity and for conceptual clarity, here we consider the simplest case of a force driving the particle onto the wall, namely, a constant gravitational force directed in negative z direction. Therefore, we introduce a mass density difference $\Delta\rho$ between the particle and the surrounding fluid. Again this is the relevant situation in flow chamber experiments, which are usually done with a diluted solution of cells, thus ruling out a dominant role for cell-cell interactions. Receptors are modeled as patches on the particle surface, while ligands are modeled as patches on the boundary wall. The formation of an encounter complex is then identified with the first approach of any pair of receptor and ligand patches which is smaller than a prescribed capture radius r_0 . The underlying stochastic process is rather complex due to position-dependent mobilities resulting from the hydrodynamic equations.

In order to solve the corresponding mean first passage time problem, here we use computer simulations of the appropriate Langevin equation. A short report of some of our results has been given before.¹⁶ We start in Sec. II by introducing the relevant concepts from hydrodynamics at small Reynolds numbers, in particular, the friction and mobility matrices resulting from the Stokes equation for a rigid particle in linear shear flow above a wall. In Sec. III we combine these results with concepts from stochastic dynamics in order to arrive at a Langevin equation describing particle motion subject to hydrodynamic, gravitational, and thermal forces. Due to the position-dependent mobility functions, we deal with multiplicative noise, that is, special care is needed to derive and interpret the noise terms. In Sec. IV our numerical scheme is applied to a sphere falling in shear flow. The comparison of the measured stationary height distribution function with the exact solution provides a favorable test for our numerical treatment. In Sec. V we show that for the case of homogeneous coverage of sphere and wall, the mean first passage time to contact can be solved exactly, again in excellent agreement with our numerical procedure. In Sec. VI we explain why the choice for the initial height is not essential. In the next two sections, we present and explain our simulation results, first for movement restricted to two dimensions in Sec. VII and then for the full three-dimensional case in Sec. VIII. We finally conclude in Sec. IX by discussing the biological and biotechnological relevance of our results.

II. FRICTION AND MOBILITY MATRICES

Due to their small sizes, the hydrodynamics of cells is in the low Reynolds number regime. Using a typical cell size $L=10\ \mu\text{m}$ and a typical velocity $v=\text{mm/s}$ (that is, the flow velocity at a distance L to a wall with linear shear flow of rate $\dot{\gamma}=100\ \text{Hz}$), the Reynolds number is $\text{Re}=\rho vL/\eta=10^{-2}$,

where $\rho=\text{g/cm}^3$ and $\eta=10^{-3}\ \text{Pa s}$ are density and viscosity of water, respectively. Therefore, we essentially deal with the Stokes equation for incompressible fluids,

$$\eta\Delta\mathbf{u}(\mathbf{r}) - \nabla P(\mathbf{r}) = -\mathcal{F}(\mathbf{r}), \quad \nabla \cdot \mathbf{u}(\mathbf{r}) = 0, \quad (1)$$

where $\mathbf{u}(\mathbf{r})$ is the fluid velocity field, $P(\mathbf{r})$ is the pressure field, and $\mathcal{F}(\mathbf{r})$ is the force density on the fluid by the particle. Here, we use the induced force picture, i.e., the fluid equations of motion [Eq. (1)] are extended to the interior of the particle and the particle is replaced by an appropriate force density $\mathcal{F}(\mathbf{r})$ acting on the fluid.¹⁷ The unperturbed flow field has to satisfy the homogeneous version of Eq. (1) as well as no-slip boundary conditions at the wall. In this paper, we use the simplest possible example, namely, linear shear flow, $\mathbf{u}^\infty = \dot{\gamma}z\mathbf{e}_x$.

The effective flow field in the region occupied by the rigid sphere reads

$$\mathbf{u}(\mathbf{r}) = (\mathbf{U} + \boldsymbol{\Omega} \times (\mathbf{r} - \mathbf{R}))\Theta(R - \|\mathbf{r} - \mathbf{R}\|), \quad (2)$$

where \mathbf{U} and $\boldsymbol{\Omega}$ are the translational and rotational velocities of the sphere, respectively. \mathbf{R} is the position of its center, R the sphere radius, and Θ the theta step function. The particle exerts on the fluid forces and torques which follow from the force density as

$$\mathbf{F}^H = \int \mathcal{F}(\mathbf{r})d\mathbf{r}, \quad \mathbf{T}^H = \int (\mathbf{r} - \mathbf{R}) \times \mathcal{F}(\mathbf{r})d\mathbf{r}. \quad (3)$$

Because we consider a rigid object, higher moments of the force density are not required in our context. For the unperturbed flow at the midpoint of the sphere, we make the following definitions:

$$\begin{aligned} \mathbf{U}^\infty &= \mathbf{u}^\infty(\mathbf{R}), \quad \boldsymbol{\Omega}^\infty = \left. \frac{1}{2} \nabla \times \mathbf{u}^\infty(\mathbf{r}) \right|_{\mathbf{r}=\mathbf{R}}, \\ \mathbf{E}_{ij}^\infty &= \left. \frac{1}{2} (\partial_i u_j^\infty(\mathbf{r}) + \partial_j u_i^\infty(\mathbf{r})) \right|_{\mathbf{r}=\mathbf{R}}, \end{aligned} \quad (4)$$

where the vector $\boldsymbol{\Omega}^\infty$ is called *vorticity* and the tensor \mathbf{E}^∞ the *rate of strain tensor*. Because we restrict ourselves to linear shear flow, all higher moments of the unperturbed flow vanish.

Due to the linearity of the Stokes equation, a linear relationship exists between the force density $\mathcal{F}(\mathbf{r})$ and the driving flow, which is the difference between real and unperturbed flows.¹⁸ Specified for the first moments of the force density, it leads to the relation

$$\begin{pmatrix} \mathbf{F}^H \\ \mathbf{T}^H \end{pmatrix} = -\mathbf{R}_u \begin{pmatrix} \mathbf{U}^\infty - \mathbf{U} \\ \boldsymbol{\Omega}^\infty - \boldsymbol{\Omega} \end{pmatrix} - \mathbf{F}^S, \quad (5)$$

where the *shear force* $\mathbf{F}^S = \mathbf{R}_E : \mathbf{E}^\infty$ with $\mathbf{A} : \mathbf{B} = \text{tr } \mathbf{A}\mathbf{B}^T$. It results from the perturbation of the flow by the presence of the wall and vanishes for free flow. The two matrices \mathbf{R}_u and \mathbf{R}_E are conveniently written as

$$\mathbf{R}_u := \begin{pmatrix} \zeta^{tt} & \zeta^{tr} \\ \zeta^{rt} & \zeta^{rr} \end{pmatrix}, \quad \mathbf{R}_E := \begin{pmatrix} \zeta^{td} \\ \zeta^{rd} \end{pmatrix}, \quad (6)$$

where the ζ are the symmetric *friction matrices* and the superscripts t , r , and d stand for *translational*, *rotational*, and

dipolar, respectively. In order to obtain the translational and rotational velocities of the sphere as a function of the hydrodynamic forces and torques, we have to invert Eq. (5),

$$\begin{pmatrix} \mathbf{U} \\ \boldsymbol{\Omega} \end{pmatrix} = \begin{pmatrix} \mathbf{U}^\infty \\ \boldsymbol{\Omega}^\infty \end{pmatrix} + \mathbf{M} \left[\begin{pmatrix} \mathbf{F}^H \\ \mathbf{T}^H \end{pmatrix} + \mathbf{F}^S \right]. \quad (7)$$

The symmetric matrix $\mathbf{M} = \mathbf{R}_u^{-1}$ is called *mobility matrix*. It is convenient to define the mobility tensors through

$$\mathbf{M} = \mathbf{R}_u^{-1} = \begin{pmatrix} \mu^{tt} & \mu^{tr} \\ \mu^{rt} & \mu^{rr} \end{pmatrix}, \quad \mathbf{R}_u^{-1} \mathbf{R}_E = \begin{pmatrix} \mu^{td} \\ \mu^{rd} \end{pmatrix}. \quad (8)$$

In order to calculate the friction and mobility tensors for the special case of a sphere in linear shear flow above a wall, we follow the procedure from Ref. 19. The friction tensors ζ introduced in Eq. (6) and the mobility tensors μ introduced in Eq. (8) are expressed in terms of scalar functions together with irreducible tensors formed from the Kronecker symbol δ_{ij} , the Levi-Civita symbol ϵ_{ijk} , and the normal vector $\mathbf{k} = \mathbf{e}_z$. The scalar friction and mobility functions are not known analytically, but can be obtained to high accuracy by the following numerical scheme. One introduces the variable $t = R/z$, where R is the radius of the sphere and z is its height above the wall. Thus, t can take values from the interval $[0, 1]$. In the limit $t \rightarrow 0$, that is, far away from the wall, one can expand the friction functions in powers of t . In the limit $t \rightarrow 1$, that is, close to the wall, analytical results can be obtained with lubrication theory. In order to cover the whole interval, the two limit solutions are matched using a Padé summation scheme.¹⁹ More details of this implementation are given in Appendix A. In contrast to the tabulated finite element results from Ref. 20, this implementation gives correct results for any possible configuration.

III. LANGEVIN EQUATION

The motion of a particle subject to thermal, hydrodynamic, and direct external forces like gravity is called *Stokesian dynamics*.²¹ In this section we derive the corresponding stochastic differential equation (*Langevin equation*). The Langevin equation will allow us to base our statistical treatment on the repeated simulation of individual trajectories. Because we are interested in the overdamped (Stokes) limit, we can neglect inertia in Newton's second law,

$$-\mathbf{F}^H + \mathbf{F}^D + \mathbf{F}^B = 0, \quad (9)$$

where $-\mathbf{F}^H$, \mathbf{F}^D , and \mathbf{F}^B are hydrodynamic, direct, and thermal forces acting on the sphere. An analogous balance exists for the torques. For the following, forces and torques as described above are united in one symbol. For example, from now on the symbol \mathbf{F} denotes (\mathbf{F}, \mathbf{T}) , a six-dimensional vector comprising force \mathbf{F} and torque \mathbf{T} , and \mathbf{U} denotes the six-dimensional particle translational/rotational velocity vector.

In the absence of Brownian forces, $\mathbf{F}^B = 0$ and $\mathbf{F}^D = \mathbf{F}^H$. Inserting this into Eq. (7) then gives

$$\mathbf{U} = \mathbf{U}^\infty + \mathbf{M}(\mathbf{F}^D + \mathbf{F}^S), \quad (10)$$

and the particle trajectory can be found with a simple Euler algorithm as $\mathbf{X}(t + \Delta t) = \mathbf{X}(t) + \mathbf{U}\Delta t + \mathcal{O}(\Delta t^2)$.

In the presence of Brownian motion, the situation is more complex, because thermal noise leads to terms of the order of $\Delta t^{1/2}$ and special care has to be taken to include all terms up to the order of Δt . Due to the fluctuation-dissipation theorem, for our problem Gaussian white noise reads

$$\langle \mathbf{g}_t \rangle = 0, \quad \langle \mathbf{g}_t \mathbf{g}_{t'} \rangle = 2k_B T \mathbf{M} \delta(t - t'). \quad (11)$$

Here, the subscript t corresponds to the fact that the thermal force \mathbf{g} is a random process. The left part of Eq. (11) states that the forces that the fluid exerts on the particles are equally distributed in all directions so there is no net drift due to thermal fluctuations. The right part of Eq. (11) states that forces at different times are not correlated, which is a good approximation because the diffusive forces act on a much faster time scale than the hydrodynamic forces. Because the mobility matrix \mathbf{M} is position dependent, we deal with so-called *multiplicative noise*. Since the δ correlation in Eq. (11) can be considered to be the limit of a process with an intrinsic time scale for thermal relaxation, which is much faster than the time scale of hydrodynamic movement, the Stratonovich interpretation of the stochastic process is appropriate.²² This means that for each time step, the mobility functions have to be evaluated at $\mathbf{X}(t + (1/2)\Delta t)$ [rather than at $\mathbf{X}(t)$ as in the Itô interpretation]. The Stratonovich interpretation also implies that the rules for integration and coordinate transformation are the same as for the Riemann integral in nonstochastic calculus.

The presence of the thermal noise [Eq. (11)] converts the position function $\mathbf{X}(t)$ into a random process \mathbf{X}_t . Multiplicative noise can result in additional drift terms. We therefore write the Langevin equation as

$$\partial_t \mathbf{X}_t = \mathbf{U}^\infty + \mathbf{M}(\mathbf{F}^D + \mathbf{F}^S) + k_B T \mathbf{Y} + \mathbf{g}_t^S, \quad (12)$$

where in comparison with the deterministic equation [Eq. (10)] we have added both the Gaussian white noise \mathbf{g}_t^S (to be interpreted in the Stratonovich sense) and some drift term \mathbf{Y} . The drift term \mathbf{Y} can be derived by requiring Eq. (12) to be equivalent to the appropriate Smoluchowski equation. The details of these calculations are given in Appendix B. The result is

$$\mathbf{Y} = \mathbf{B} \nabla \mathbf{B}^T, \quad \mathbf{M} = \mathbf{B} \mathbf{B}^T, \quad Y_i = \mathbf{B}_{ik} (\partial_l \mathbf{B}_{lk}), \quad (13)$$

$$M_{ij} = \mathbf{B}_{ik} \mathbf{B}_{jk}.$$

For additive noise, that is, for position-independent mobility functions, the additional drift term would vanish. In the case of position-dependent mobility matrices, the noise term \mathbf{g}_t^S alone would lead to a drift of the particle towards regions of lower mobility (that is, towards the wall, where mobility vanishes due to the no-slip boundary condition). This drift, however, is exactly compensated by the additional term \mathbf{Y} .³⁹

For the following, it is useful to nondimensionalize Eq. (12). For length, the natural scale is sphere radius R . For time, we use $6\pi\eta R^3/k_B T$, which is the time needed to diffuse the distance R . For force, we use $6\pi\eta R^2 \dot{\gamma}$, the Stokes force at velocity $R\dot{\gamma}$, that is, in linear shear flow a distance R away from the wall. The scalar friction and mobility functions ap-

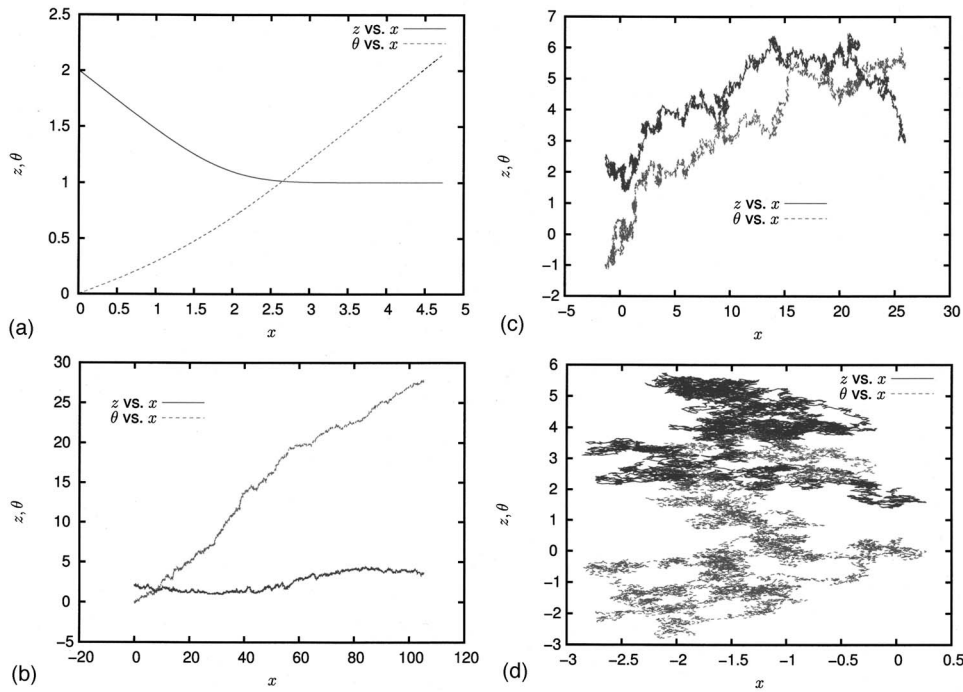


FIG. 2. Falling sphere in shear flow. For different values of the shear rate (represented by the Péclet number Pe) and the driving force (represented by f or $Pe_z = fPe$), the z coordinate and the orientation angle θ are plotted vs the x coordinate. (a) $Pe = \infty$, $f = 2.2$. (b) $Pe = 10$, $f = 0.11$, $Pe_z = 1.1$. (c) $Pe = 1$, $f = 0.11$, $Pe_z = 0.11$. (d) $Pe = 0$, $Pe_z = 0.11$.

peering in M , R_E , and R_u also become dimensionless as explained in Appendix A. The Langevin equation [Eq. (12)] now reads

$$\partial_t \mathbf{X}_t = Pe(\mathbf{U}^\infty + M(f\mathbf{F}^D + \mathbf{F}^S)) + \mathbf{B} \nabla \mathbf{B}^T + \mathbf{g}_t^S, \quad (14)$$

where the *Péclet number* $Pe = 6\pi\eta R^3 \dot{\gamma} / k_B T$ measures the relative importance of deterministic to Brownian motion. In the limit $Pe \rightarrow 0$ the particle only exhibits diffusive motion and in the limit $Pe \rightarrow \infty$ it is no longer subjected to diffusion. The second dimensionless parameter $f = \|\mathbf{F}^D\| / 6\pi\eta R^2 \dot{\gamma}$ measures the relative importance of direct forces/torques versus the shear force/torque. Measuring the time in units of the diffusive time scale is appropriate for Péclet numbers of the order of 10 or less. For simulations with larger Péclet numbers it is more suitable to scale time with the inverse shear rate $\dot{\gamma}^{-1}$. This has the effect of dividing Eq. (14) by Pe .

In order to solve Eq. (14) numerically, it has to be discretized with respect to time. The appropriate Euler algorithm can be derived by first rewriting Eq. (14) in the Itô version, which adds another drift term to the equation. As explained in Appendix C, the two drift terms together lead to the result

$$\partial_t \mathbf{X} = Pe(\mathbf{U}^\infty + M(f\mathbf{F}^D + \mathbf{F}^S)) + \nabla M + \mathbf{g}_t^I. \quad (15)$$

Its discretized version is simply

$$\Delta \mathbf{X} = [Pe(\mathbf{U}^\infty + M(f\mathbf{F}^D + \mathbf{F}^S))|_t + \nabla M|_t] \Delta t + \mathbf{g}(\Delta t) + \mathcal{O}(\Delta t^2). \quad (16)$$

This final result has been derived before in a different way by Brady and Bossis.²¹ For vanishing shear flow, it also agrees with the classical result by Ermak and McCammon.²³ In Appendix C, we describe the algorithms used to implement Eq. (16), in particular, the algorithm to generate the thermal forces $\mathbf{g}(\Delta t)$.

IV. SPHERE FALLING IN SHEAR FLOW

As explained in the Introduction, we consider a sphere whose density is slightly larger than that of the fluid. Due to this density difference $\Delta\rho$ a constant drift towards the wall exists. As we will see later, this drift ensures that on average the sphere will bind to the wall in finite time. The two independent parameters defined in Eq. (14) for this model system are Pe and $f = (2R\Delta\rho g) / (9\eta\dot{\gamma})$, with the earth's acceleration constant $g = 9.81 \text{ m/s}^2$. For later considerations, it is convenient to introduce also the parameter $Pe_z = fPe$, which we call the *Péclet number in z direction*. Pe and Pe_z represent the strengths of the hydrodynamic and gravitational forces in respect to the thermal force, respectively. Out of the three parameters Pe , f , and Pe_z , only two are independent, because $f = Pe_z / Pe$.

We first consider the path of a sphere falling in shear flow after it has been dropped at some initial height. Figure 2 illustrates the effect of the Péclet number by showing some representative simulation trajectories. For $Pe = \infty$ the motion of the sphere is purely deterministic and only governed by the parameter f . In the diffusive limit $Pe = 0$, the sphere makes a pure random walk (except for the drift in the z direction due to the gravitational force).

As the mobility matrix does only depend on the height of the sphere above the wall (see Appendix A), the motion in the z direction is independent of the position in the (x, y) plane and the orientation of the sphere. Therefore, it can be treated separately. The probability density $\Psi(z, t)$ for the sphere to be at height z at time t is the solution to a one-dimensional Smoluchowski equation

$$\partial_t \Psi(z, t) = -\partial_z J_z, \quad J_z = -M_{zz}(\partial_z \Psi + Pe_z \Psi). \quad (17)$$

This equation cannot be solved analytically as the mobility function M_{zz} is not known in closed form. In Fig. 3 we show numerical solutions obtained by simulating the equivalent

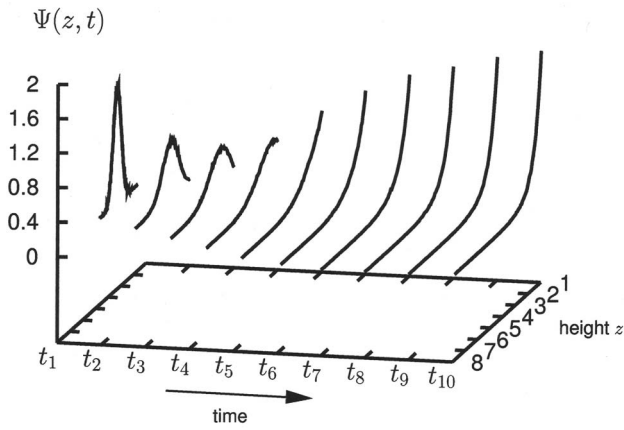


FIG. 3. Probability distribution function $\Psi(z, t)$ numerically obtained from $N=10^5$ sample paths for ten consecutive points in time. The initial distribution was $\Psi(z, t_0) = \delta(z-3)$ at $t=t_0$, $Pe_z=2$.

Langevin equation. One clearly sees that first the δ function at $t=0$ is broadened due to diffusion and then develops into a stationary solution which has its maximum at the wall. This stationary solution has a simple analytical form which follows from Eq. (17) by integrating $J_z=0$,

$$\Psi_s(z) = Pe_z e^{-Pe_z(z-1)}. \quad (18)$$

Thus, the stationary solution is simply the barometric formula, as it should be for thermodynamic reasons. We also find that the first two moments (mean and variance) are the same,

$$\langle z-1 \rangle = \sqrt{\langle z^2 \rangle - \langle z \rangle^2} = \frac{1}{Pe_z}. \quad (19)$$

In the limit of vanishing gravitational force ($Pe_z \rightarrow 0$), the probability distribution becomes flat and the probability of finding the sphere does not peak at the wall anymore.

V. FIRST CONTACT WITH HOMOGENEOUS COVERAGE

If the sphere and the wall are homogeneously covered with receptors and ligands, respectively, an encounter complex is established whenever the sphere comes sufficiently close to the wall. The mean time which elapses after the sphere is set free at some initial position until an encounter complex is established is then identical with the mean first passage time (MFPT) for a sphere dropped at initial height z_0 to reach the height z_1 . Note again that the motion in the z direction is independent of the values of the other coordinates. For a particle diffusing in an interval $[z_1, b]$, with z_1 being an absorbing boundary and b a reflective boundary, the MFPT T to reach z_1 when started at $z \in [z_1, b]$ is the solution to the following ordinary differential equation²²

$$A(z)\partial_z T(z|z_1) + D(z)\partial_z^2 T(z|z_1) = -1, \quad T(z_1|z_1) = 0, \quad (20)$$

$$\partial_z T(z|z_1)|_{z=b} = 0.$$

In our case, $b=\infty$. The drift term is $A(z) = -Pe_z \hat{\alpha}''(1/z) + \partial_z \hat{\alpha}''(1/z)$ and the diffusive term $D(z) = M_{zz} = \hat{\alpha}''(1/z)$, where $\hat{\alpha}''(1/z)$ is a scalar mobility function as explained in

Appendix A. The general solution to Eq. (20) is²²

$$T(z_0|z_1) = \int_{z_1}^{z_0} dz \frac{1}{\Phi(z)} \left(\int_z^\infty dy \frac{\Phi(y)}{D(y)} \right), \quad (21)$$

$$\Phi(z) = \exp \left(\int^z dx \frac{A(x)}{D(x)} \right).$$

This can be reduced up to an integral over $\hat{\alpha}''(1/z)$,

$$T(z_0|z_1) = \frac{1}{Pe_z} \int_{z_1}^{z_0} dz \frac{1}{\hat{\alpha}''(1/z)}. \quad (22)$$

Thus the dependence of $T(z_0|z_1)$ on Pe_z , the only parameter in this problem, is obtained exactly. It is important to note that the compact form for the MFPT in Eq. (22) is a result of the constant vertical force. For a more general vertical potential force $F_\perp = -\partial_z V(z)$ with a potential V , Eq. (21) can be reduced to

$$T(z_0|z_1) = \int_{z_1}^{z_0} \frac{dz}{\hat{\alpha}''(1/z)} \int_z^\infty dy e^{V(z)-V(y)}. \quad (23)$$

This equation shows that the potential must satisfy the condition $\lim_{y \rightarrow \infty} (V(z) - V(y)) \rightarrow -\infty$ for the MFPT to be finite. This holds true, e.g., for the gravitational force studied here or for the interaction of a charged object with an oppositely charged wall, but not, e.g., for a Lennard-Jones potential.

The integral [Eq. (22)] over the scalar mobility function $\hat{\alpha}''$ can easily be calculated numerically as $\hat{\alpha}''$ behaves well in the full range of z . In fact, $\hat{\alpha}''(t)$ can be approximated by its leading term from the lubrication analysis, i.e., $\hat{\alpha}''(t) \approx 1-t$. We then find

$$T(z_0|z_1) \approx \frac{1}{Pe_z} \left[z_0 - z_1 + \ln \left(\frac{z_0 - 1}{z_1 - 1} \right) \right]. \quad (24)$$

A numerical analysis shows that the approximation [Eq. (24)] deviates only by a few percent from the exact solution [Eq. (22)]. Thus, $T(z_0|z_1)$ is logarithmically divergent if the absorbing point is close to the wall, $z_1 \rightarrow 1$, and linearly divergent if the starting point is at infinite height, $z_0 \rightarrow \infty$.

For a sphere homogeneously covered with receptors each having a capture radius r_0 , the mean time for forming an encounter complex is $T(z_0|1+r_0)$. This time will serve as a useful limiting result in some of the considerations presented in the next sections. The exactly known result [Eq. (22)] provides also a good test for the algorithm we implemented. In Fig. 4(a) the MFPT obtained from simulation experiments and from the quadrature of Eq. (22) are compared. The two results agree very well (see Appendix D for a discussion of the statistical and systematic errors of the simulation results). In Fig. 4(b) we show the numerically obtained distribution of first passage times. One clearly sees that the larger the Pe_z , the stronger they peak around the mean.

We conclude the case of homogeneous coverage by noting that in order to obtain dimensionalized results, one has to multiply the MFPT by the diffusive time scale $6\pi\eta R^3/k_B T$. This result does not depend on shear rate $\dot{\gamma}$ because vertical and horizontal motions are decoupled and rotational motion is not relevant here. However, it depends on viscosity η ,

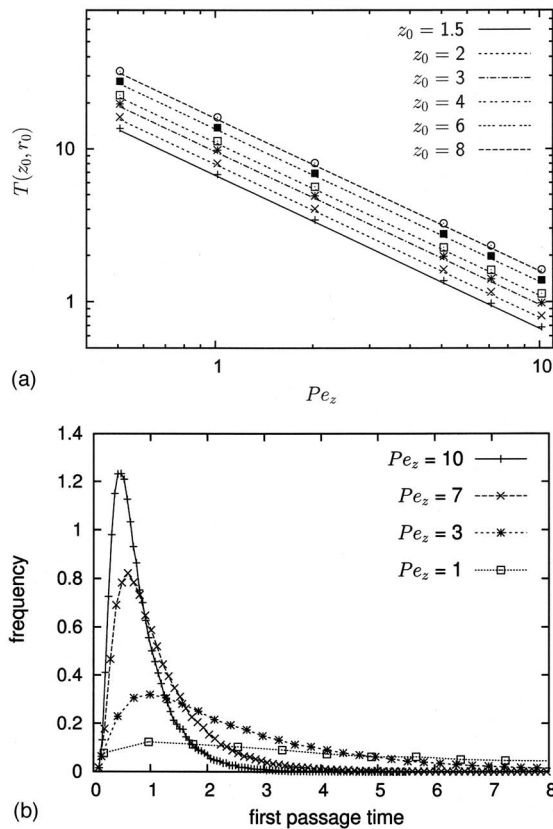


FIG. 4. Results of first passage time simulations with encounter radius $r_0 = 10^{-3}$. (a) Mean first passage time T as a function of Pe_z for different starting heights. Dots are the results from simulations with $N=10^4$ runs and time step $\Delta t=10^{-5}$. Lines are the results from the quadrature of Eq. (22). (b) Distribution of first passage times for different values of Pe_z (numerical parameters $N=10^5$, $\Delta t=10^{-5}$).

which sets the time scale for vertical motion. If one switched off thermal fluctuations, the falling time would be exactly the same as the MFPT from Eq. (22), but this is a special result for constant force and not true in general. If one removed the wall, the translational symmetry in the z direction would not be broken and the MFPT would be $T=(z_0-z_1)/Pe_z$, that is, the logarithmic term in Eq. (24) would be missing.

VI. EFFECT OF INITIAL HEIGHT

We now turn to the spatially resolved receptor coverage, that is, we consider a sphere which is covered by N_r equidistantly spaced receptor patches. For the moment being, the wall is still considered to be homogeneously covered with ligands. The MFPT $T(\theta, \mathbf{x}|C)$ now will depend on the initial position $\mathbf{x}=(x, y, z_0)$ and the initial orientation θ as well as on the absorbing boundary C in diffusion space. The latter is given by the special receptor and ligand geometry. In an experimental setup with linear shear flow it is possible to measure only particles which have been initially at a certain height. This is due to the fact that their average velocity as obtained from the solution of the Stokes equation [Eq. (7)] depends on their height in a unique way.⁸ However, it is almost impossible to prepare a certain initial orientation θ or (x, y) position relative to the ligands. Therefore, the quantity of interest to us will be a MFPT which is averaged over all

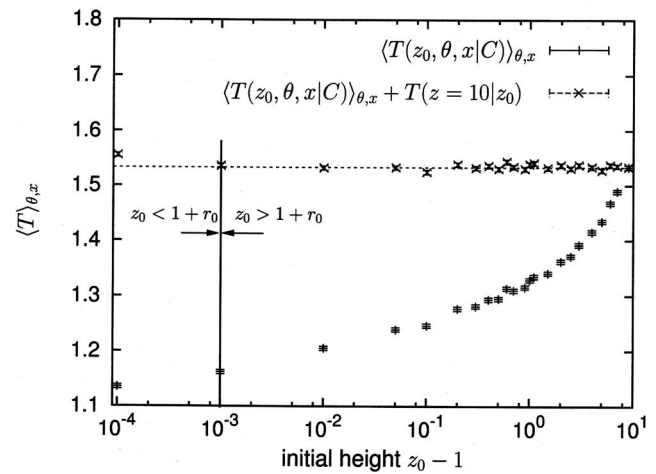


FIG. 5. Mean first passage time dependence on the initial height z_0 in two dimensions. The sphere is covered with $N_r=10$ receptor patches and the ligand density is $\rho_l=0.01$. We plot $\langle T(z_0, \theta, x|C) \rangle_{\theta, x}$ (+) and $\langle T(z_0, \theta, x|C) \rangle_{\theta, x} + T(z=10|z_0)$ (x) as a function of z_0 , where $T(z=10|z_0)$ is obtained from Eq. (22). For $z_0 > 1 + r_0$ the latter curve is constant at the value $\langle T(z=10, \theta, x|C) \rangle_{\theta, x}$ as predicted by the addition theorem [Eq. (26)] (numerical parameters: $N=10^5$, $\Delta t=10^{-5}$).

possible initial orientations θ and all initial positions (x, y) , which will be denoted as $\langle T(\theta, \mathbf{x}|C) \rangle_{\theta, (x, y)}$. The dependence of $\langle T(\theta, \mathbf{x}|C) \rangle_{\theta, (x, y)}$ on the initial height for $z_0 > 1 + r_0$ can be derived exactly. For homogeneous ligand coverage the quantity of interest is

$$\langle T(\theta, z_0|C) \rangle_{\theta} = \frac{1}{V_{\theta}} \int_{\theta} d^3 \theta T(\theta, z_0|C),$$

where C is the absorbing hypersurface in (θ, z) space and V_{θ} a normalization constant. Absorption is only possible if $z < 1 + r_0$, thus if we look at some intermediate height $z_0 > z_m > 1 + r_0$, then

$$T(\theta, z_0|C) = T(\theta, z_0|z_m) + \int d^3 \theta_m p(\theta_m|\theta) T(\theta_m, z_m|C), \quad (25)$$

where $p(\theta_m|\theta)$ is the conditional probability to pass the height z_m with the orientation θ_m when starting with the initial orientation θ at z_0 . $T(\theta, z_0|z_m)$ is independent of the initial orientation and can be calculated by means of Eq. (22). Now averaging Eq. (25) over the initial orientation gives

$$\begin{aligned} \langle T(\theta, z_0|C) \rangle_{\theta} &= T(z_0|z_m) + \frac{1}{V_{\theta}} \int d^3 \theta_m \left[\int d^3 \theta p(\theta_m|\theta) \right] T(\theta_m, z_m|C) \\ &= T(z_0|z_m) + \frac{1}{V_{\theta}} \int d^3 \theta_m T(\theta_m, z_m|C) \\ &= T(z_0|z_m) + \langle T(\theta_m, z_m|C) \rangle_{\theta_m}. \end{aligned} \quad (26)$$

Thus, if the orientation-averaged MFPT is known for some initial height $z_0 > 1 + r_0$, then the MFPT for any other initial height $z'_0 > 1 + r_0$ can be calculated by means of Eqs. (26) and (22). In Fig. 5, this result is verified by simulations for the two-dimensional case, that is, the sphere can only move in

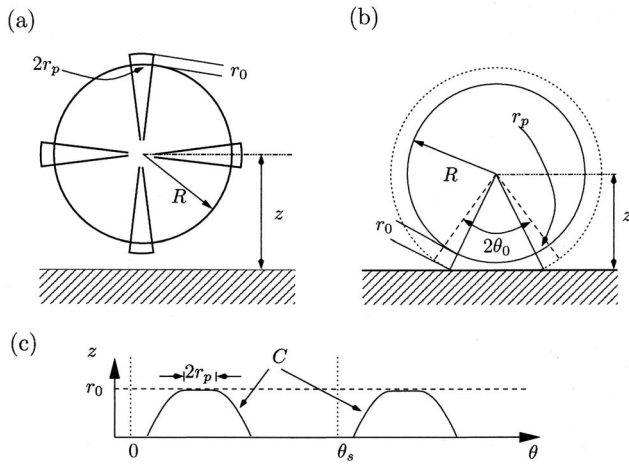


FIG. 6. (a) Example of a sphere restricted to move in two dimensions and covered with $N_r=4$ receptor patches, which are regularly distributed over the circumference. (b) Illustration of the range of θ in which encounter occurs. This range is given by $2\theta_0$ with $\theta_0(z)=\arccos(z/(1+r_0))+r_p$. (c) The absorbing boundary C in the (z, θ) plane is periodic with respect to θ with period $\theta_s=2\pi/N_r$. For large numbers of receptor patches θ_s the different patches start to overlap. Then encounter is possible for all values of θ .

the x - z plane and rotate only around the y axis (see Fig. 1). Due to the decomposition Eq. (26), the initial height is not essential. In the following, we will therefore always use the value $z_0=2$, that is, the sphere has to fall by one radius until it hits the substrate for the first time.

VII. MOVEMENT IN TWO DIMENSIONS

We now study the effect of shear rate for heterogeneous receptor distribution if the sphere is restricted to move only in two dimensions. Then, the receptor patches can be equidistantly distributed over the circumference, as illustrated in Fig. 6. Each receptor patch has a capture height of r_0 and a

width of $2r_p$. The two-dimensional (2D) receptor density is then $\rho_r=N_r r_p/\pi$. Orientation is now represented by a single angle θ . The absorbing boundary C is illustrated in Fig. 6. For each receptor patch, binding can occur over a range of $2\theta_0$, which consists of two parts. The inner part is valid already for $r_p=0$ and reflects the overlap due to a finite r_0 . The outer part is results from a finite r_p . Together this leads to $\theta_0(z)=\arccos(z/(1+r_0))+r_p$. The receptor patches establish a periodicity with period $\theta_s=2\pi/N_r$. As the number of receptor patches grows, this period decreases and one finally achieves overlap. Then, encounter becomes possible for all values of θ , that is, we are back to the case of homogeneous receptor coverage. In our case of nonhomogeneous coverage, the MFPT depends on Pe , Pe_z , N_r , r_0 , r_p , and z_0 . For the following simulations $r_p=r_0=10^{-3}$, $Pe_z=50$, and $z_0=2$ are chosen unless other values are explicitly mentioned.

Figure 7(a) shows the MFPT as a function of the Péclet number Pe . Note that in the log-log plot, an apparent plateau appears at small value of Pe , although in a linear plot there would be monotonous decay. Three regimes can be distinguished. For $Pe \approx 0$ (*diffusive limit*) the transport by the imposed shear flow is negligible and only diffusive transport is present. For very large values of Pe , $\langle T \rangle_\theta$ plateaus at the value given by Eq. (22) independent of N_r . In this limit the time for rotation to any certain orientation is negligible compared to the mean time to fall down close to the wall, therefore, the result for rotational symmetry is recovered. Between these two limits the MFPT decreases monotonically with increasing Pe . Figure 7(b) shows the data from Fig. 7(a) plotted as a function of the receptor density $\rho_r \propto N_r$. The larger the Pe the less pronounced is the dependence of $\langle T \rangle_\theta$ on N_r . For $Pe \approx 0$, however, $\langle T \rangle_\theta$ strongly depends on N_r . The latter relation is better illustrated in Fig. 7(c). There, at $Pe \approx 0$, $\langle T \rangle_\theta$ is shown for a wide range of N_r . The simulations were done for fixed patch size r_p but for four different values

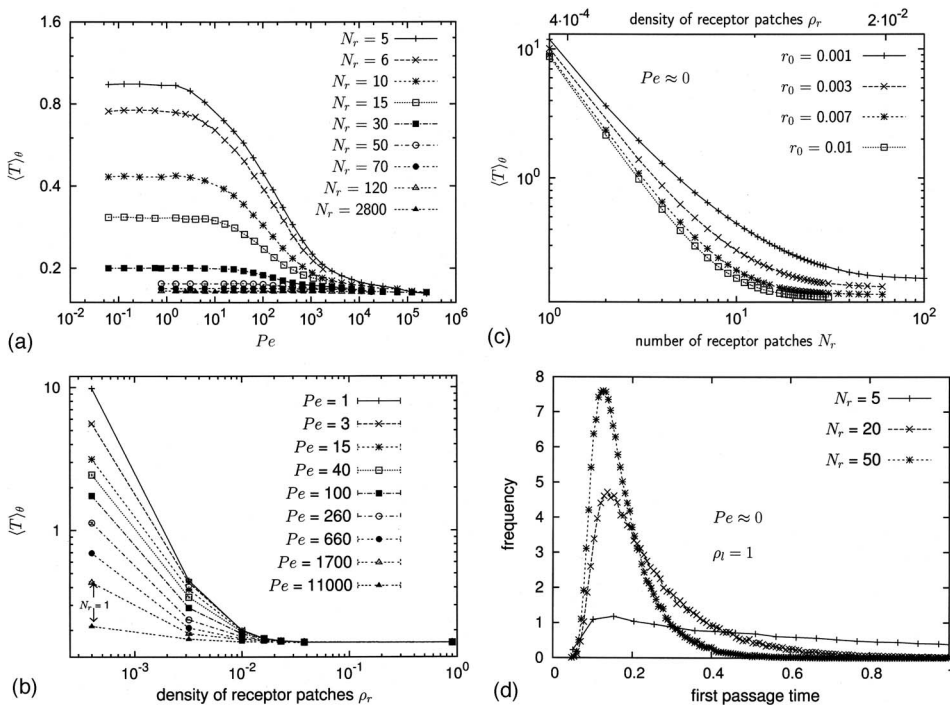


FIG. 7. The mean first passage time averaged over the initial orientation (log-log plots). (a) Plotted as a function of Pe ; different symbols refer to different numbers of receptor patches. (b) The mean first passage time is plotted as a function of the receptor density $\rho_r \propto N_r$ for different values of Pe . (c) $\langle T \rangle_\theta$ as a function of N_r in the diffusive regime ($Pe \approx 0$) for different values of the capture range r_0 , but fixed value of cluster size $r_p=0.001$. (d) The distribution of θ -averaged first passage time is shown for $N_r=5, 20, 50$ receptor patches (numerical parameters for each data point: $N=10^5$, $\Delta t=10^{-5}$).

of the capture radius r_0 (see Fig. 6). For $\rho_r \rightarrow 1$, $\langle T \rangle_\theta$ reaches the value given by Eq. (22). As described by Eq. (22), the smaller $\langle T \rangle_\theta$ is, the larger r_0 is. An increase in the number of receptor patches N_r leads to a strong decrease for the MFPT, however, no special scaling behavior can be observed. It is remarkable that the limiting value for the case of homogeneous receptor coverage is already reached for $\rho_r \approx 10^{-2}$. The larger the capture radius r_0 , the more pronounced this effect is. This can be understood by observing that the effective patch size as given by the angle $\theta_0 \geq r_p$ (see Fig. 6) is monotonically increasing with increasing r_0 .

We next try to qualitatively understand the effect of shear rate for the simulation results shown in Fig. 7(a). In general, it is very hard to separate the effects of diffusion and convection. The time for binding at $Pe \approx 0$ is determined purely by diffusion effects and will be denoted by T_D . As shear flow increases, the rotation of the sphere is increasingly dominated by convection. We now derive a convection time T_F which competes with the diffusion time T_D at large Péclet number. For very large Péclet number, we expect the MFPT to be the sum of the homogeneous result from Eq. (24) plus this additional time T_F . An important question then is at which Pe the convection time T_F become smaller than the diffusion time T_D .

On order to estimate T_F , we note that the main effect of increased shear rate is the faster rotation in the direction of flow. Once a receptor has rotated by an angle $\theta_s = 2\pi/N_r$, such that it opposes a ligand on the substrate, there is some probability p that the sphere is at the correct height that an encounter can occur. If no encounter occurs with the complementary probability $1-p$, the sphere has to rotate about another angle θ_s until the next receptor points downwards. Supposing that the time, $2t_0$, to rotate about the angle θ_s is large enough that there is no correlation between the height of the sphere before and after the rotation, then, an encounter occurs again with probability p (therefore this analysis also does not hold at very large Pe). Thus, the mean time T_F for encounter is

$$T_F = pt_0 + (1-p)(p3t_0 + (1-p)(p5t_0 + (1-p)(\dots)))$$

$$= pt_0 \sum_{i=0}^{\infty} (2i+1)(1-p)^i = t_0 \frac{2-p}{p} \approx \frac{2t_0}{p}, \quad (27)$$

where the series has been summed up by means of the geometric formula. In the last term we assumed that the probability p for the proper height is small due to a small capture distance r_0 . It follows from the stationary probability distribution $\Psi_s(z)$ given by Eq. (18),

$$p = \int_1^{1+r_0} dz \Psi_s(z) = 1 - e^{-Pe_z r_0} \approx Pe_z r_0. \quad (28)$$

The time t_0 to rotate about half of the angle θ_s is approximately $t_0 = \theta_s/Pe$. Therefore, we get

$$T_F \approx \frac{4\pi}{N_r Pe Pe_z r_0}. \quad (29)$$

In this analysis, the convection time T_F scales inversely with the number of receptor patches N_r and the Péclet number Pe .

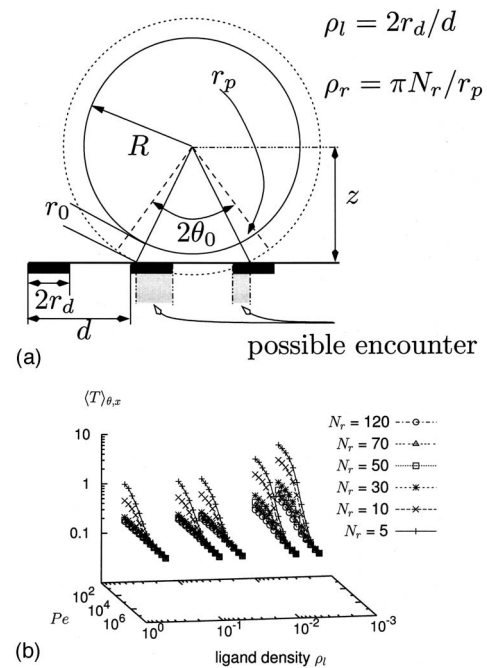


FIG. 8. (a) Illustration of the situation with a density of receptor patches ρ_r as well as a density of ligands ρ_l . The first passage time is now determined by an overlap of a receptor patch with a ligand patch. (b) $\langle T \rangle_{\theta,x}$ as function of the Péclet number Pe and the ligand density ρ_l for different values of N_r (numerical parameters: $\Delta t = 5 \times 10^{-6}$, $N = 10^4$).

As Pe increase, T_F gets smaller than T_D and then dominates the overall outcome. Comparing Eq. (29) to the simulation data for $Pe \approx 0$ shows that this crossover occurs in the range of $Pe \approx 10^1 - 10^2$ and that the corresponding value of Pe increases with increasing receptor number N_r , exactly as observed in the simulation data over the full range of Pe . However, the exact scaling of these data is not $\sim 1/N_r$ for large Pe as predicted by Eq. (29). In practice, the decay is somehow slower due to correlations between the height of the sphere at two successive instances of a receptor pointing downwards, which we have neglected in our analysis.

We briefly comment on the effect of the downward driving force, that is, Pe_z . Above, we have found that in two cases, homogeneous coverage from Eq. (22) and convection-dominated rotation from Eq. (29), the MFPT scales inversely with Pe_z . This scaling behavior is indeed found in the simulations, except that for very large values of Pe_z , the MFPT approximates a constant value (data not shown). The reason is that the larger the Pe_z , the smaller the mean time to fall below the height $z = 1 + r_0$. As indicated by Eq. (18), then the sphere stays below this height until an encounter occurs. This implies that in this limit, the MFPT depends only on rotational motion and the falling motion is irrelevant.

We now introduce spatially resolved ligands into the 2D model. Figure 8(a) shows the model definition: the ligand patches are considered to have the same radius $r_d = r_p$ as the receptor patches and they are located at a distance d from each other. This results in a one-dimensional ligand density given by $\rho_l = 2r_d/d$. The mean first passage time will now also depend on the initial x position, $T = T(z_0, \theta, x|C)$, where C is the hypersurface in (z, θ, x) space, where a receptor patch touches a ligand patch. But similarly as in the above

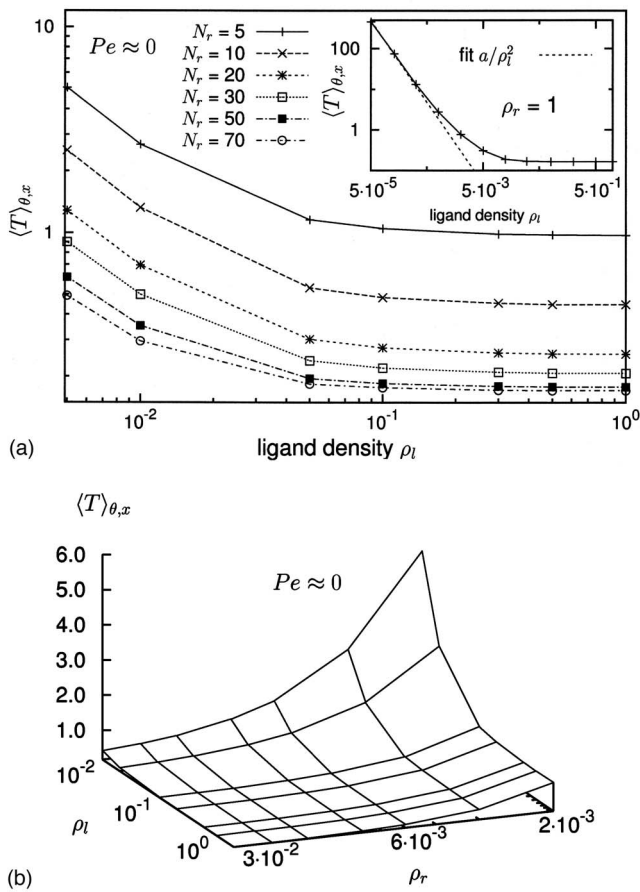


FIG. 9. (a) $\langle T \rangle_{\theta,x}$ is shown in the diffusive limit at $Pe \approx 0$ as a function of the ligand density ρ_l . Inset (plot for $\rho_r \approx 1$): The mean first passage time scales as $\langle T \rangle_{\theta,x} \propto 1/\rho_l^2$ (numerical parameters: $\Delta t = 10^{-5}$, $N = 10^5$). (b) Dependence of $\langle T \rangle_{\theta,x}$ in the diffusive limit at $Pe \approx 0$ on ρ_r, ρ_l , where ρ_r has been varied by changing N_r at fixed r_p (numerical parameters: $\Delta t = 10^{-5}$, $N = 10^5$).

section in regard to the initial orientation, the dependence on the initial x position is of minor interest and, therefore, we will discuss the MFPT averaged over the initial position and orientation, denoted by $\langle T \rangle_{\theta,x}$.

Figure 8(b) shows that by varying the Péclet number we can identify the same three regimes for all ligand densities as before. For $Pe \rightarrow 0$ in the limit of pure diffusive transport, $\langle T \rangle_{\theta,x}$ approaches a finite value, depending on ρ_r and ρ_l . With increasing Pe , $\langle T \rangle_{\theta,x}$ decreases monotonically and finally for $Pe \rightarrow \infty$ reaches the value of the MFPT in the limit of homogeneous receptor and ligand coverage. In contrast to above, however, in this limit the shear flow not only restores rotational invariance of the sphere but, in addition, also translational invariance of the substrate.

Figure 9(a) provides more details for $\langle T \rangle_{\theta,x}$ as a function of ρ_l in the diffusive limit ($Pe \approx 0$). We find that in the range of $0.1 < \rho_l < 1$ the MFPT is almost not affected by ligand concentration: as long as the ligand patches are sufficiently close to each other, a receptor patch touching the wall will most probably find a ligand before diffusing away again. The situation changes completely with small ligand density. For $\rho_l \ll 1$ the averaged mean first passage time $\langle T \rangle_{\theta,x}$ scales with the ligand density ρ_l as $\langle T \rangle_{\theta,x} \propto 1/\rho_l^2 \propto d^2$. This can be understood by calculating the position-averaged MFPT $\langle T \rangle_x$ for a

particle diffusing in an interval $[0, d]$ with diffusion constant D , which gives $\langle T \rangle_x = d^2/12D$. This suggests that the quadratic scaling with d results from the diffusive motion between adjacent ligand patches. Figure 9(b) summarizes our results for the dependence of the 2D MFPT $\langle T \rangle_{\theta,x}$ on ligand density ρ_l and receptor density ρ_r in the diffusive limit. Clearly there exists a large plateau around the value for the case of homogeneous coverage $\rho_r = \rho_l = 1$. This implies that if ligand and receptor patches are not too strongly diluted, the mean encounter time is still close to the optimal value given by Eq. (22). On the other hand, if the number of receptor and/or ligand patches is highly reduced the mean encounter time is strongly increased.

VIII. MOVEMENT IN THREE DIMENSIONS

We finally turn to the full three-dimensional (3D) situation, that is, the sphere may diffuse about all three axes, as described by Eqs. (16) and (C4). Receptors are located in spherical patches which are randomly distributed over the sphere. Each receptor patch has a radius r_p and a height (capture length) r_0 . That is the appropriate generalization of the situation shown in Fig. 6 for the 2D case. Thus, for N_r receptor patches the receptor density is $\rho_r = 2\pi N_r(1 - \cos(r_p))/4\pi \approx N_r r_p^2/4$ (for $r_p \ll 1$). In contrast to the preceding sections where the receptor patches could be regularly distributed over the circumference, this is no longer possible on the surface of a sphere. Therefore, we distribute the patches randomly over the sphere with equal probability for each position, with a hard disk overlap algorithm making sure that no two patches overlap.²⁴ One has to bear in mind that then for small N_r two different distributions may have slightly different binding properties. This effect becomes weaker for larger N_r ; therefore in the following we will only use $N_r \geq 10$. The quantity we measure in our simulations is now $\langle T \rangle_{\theta}$ in the case of homogeneous ligand coverage and $\langle T \rangle_{\theta,(x,y)}$ in the case that the ligands are located in spherical patches on a 2D lattice. Thus, we average the MFPT over the initial orientations and positions as explained above.

In order to explore the dependence of $\langle T \rangle_{\theta}$ on N_r and Pe we first simulated the receptor-ligand encounter in the case of homogeneous ligand coverage $\rho_l = 1$. In order to average over the initial positions we started each run with a randomly chosen initial orientation. After 100 runs we generated a new distribution, thus averaging out also the effect of different receptor distributions. In order to achieve reasonable statistics, we typically used 100 000 runs. Our results are shown in Fig. 10(a). Again we find three different regimes as a function of the Péclet number Pe . This proves that qualitatively the basic results of the 2D treatment remain valid in 3D. However, in detail there are important differences. In contrast to the 2D results presented above, $\langle T \rangle_{\theta}$ in the limit $Pe \rightarrow \infty$ is no longer given by Eq. (22) if N_r is small. That is due to the fact that for $Pe \rightarrow \infty$ the receptor patches effectively behave as ringlike structures. The rotation of such a ring about the x or y axis is not affected by Pe and thus still depends on diffusion. For large N_r , the rings cover the whole sphere and for $Pe \rightarrow \infty$, $\langle T \rangle_{\theta}$ is again given by Eq. (22).

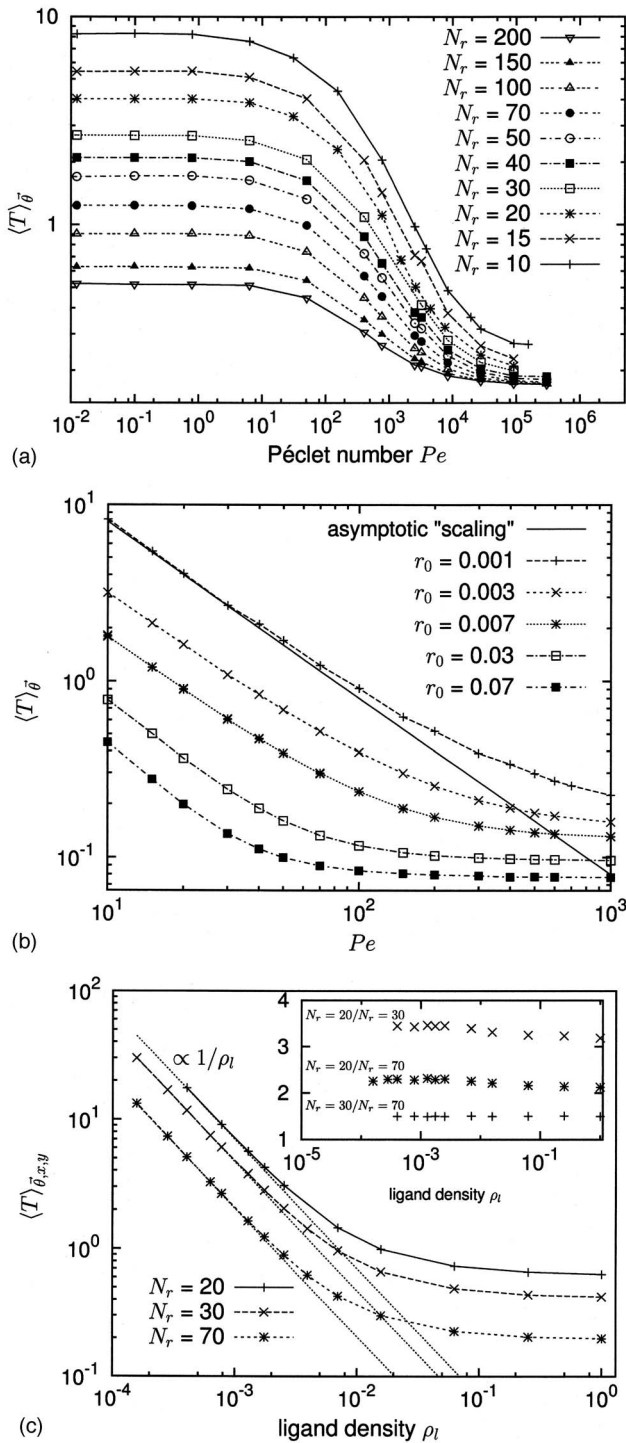


FIG. 10. (a) The mean time for a receptor to first reach a wall homogeneously covered with ligands $\langle T \rangle_\theta$ was calculated as a function of the Péclet number Pe . (b) The dependence of the MFPT on the number of receptor patches N_r for different values of the capture radius r_0 . Lines show the scaling with $1/N_r$. (c) Dependence of $\langle T \rangle_{\theta,x,y}$ on the 2D ligand density ρ_l in the diffusive limit $Pe \approx 0$. For $\rho_l \ll 1$ the mean first passage time is proportional to $1/\rho_l$ (dotted lines). In the inset are plotted the mutual ratios of the averaged mean first passage times for $N_r = 20, 30, 70$, showing that the dependence on the ligand density is nearly independent on the number of receptor patches N_r [numerical parameters: $N = 10^5$, $\Delta t = 5 \times 10^{-5}$, $r_p = 10^{-3}$, $r_0 = 10^{-3}$ for (a); $r_0 = r_d = 10^{-2}$ for (c)].

In Fig. 10(b) we plot the $Pe \rightarrow 0$ limit of $\langle T \rangle_\theta$ as a function of the number of receptor patches N_r , for different values of the capture radius r_0 . The fitted straight line for r_0

$= 10^{-3}$ shows that $\langle T \rangle_\theta$ approximately behaves like $\langle T \rangle_\theta \propto 1/N_r$. Neglecting effects of curvature, the average distance between two receptor patches is $d \propto (4\pi/N_r)^{1/2}$ and the mean time to diffuse that distance is $t_d \propto d^2 \propto 1/N_r$. This provides a simple explanation for the observed scaling behavior. For high N_r , the MFPT reaches a plateau value, given by Eq. (22). This plateau value depends on r_0 and is smaller if r_0 is larger. Also the crossover from the asymptotic behavior at small N_r to the plateau at large N_r is shifted with increasing capture radius r_0 towards smaller N_r .

In Fig. 10(c) we show the effect of a finite ligand density ρ_l at $Pe \approx 0$. For the simulations we distributed the ligands in circular patches of radius $r_d = 0.01$ on a quadratic lattice with lattice constant d , thus resulting in a ligand density $\rho_l = \pi r_d^2/d^2$. In our implementation, the intersection between the receptor patch and the wall is approximated by an appropriate circle, because it is easy to check if this circle overlaps with the ligand patch. The fits given in Fig. 10(c) show that for small ρ_l , the MFPT scales as $\langle T \rangle_{\theta,(x,y)} \propto 1/\rho_l \propto d^2$. Because the curves for different N_r appear to be rather similar, in the inset we plot the ratio of different pairs of these curves. As this results in approximately constant plateaus, we conclude that the scaling with ligand density is hardly affected by N_r . As in 2D, the inverse scaling with ligand density can be understood in simple terms by noting that the MFPT to diffusional capture scales like d^2 . At a coverage around 0.01, saturation occurs as it did for receptor coverage.

We finally discuss the influence of the receptor geometry described by the parameters r_0 and r_p . Because Pe changes the MFPT in a monotonous way, it is sufficient to study the diffusive limit $Pe \approx 0$. Figures 11(a) and 11(b) show $\langle T \rangle_\theta$ as a function of r_p for $r_0 = 0.001$ and $r_0 = 0.01$, respectively. In order to obtain smooth curves, in this case only one receptor distribution was used for all runs. We find that the curves can be fitted well to the function

$$\langle T(r_p) \rangle_\theta = \frac{a}{b + r_p} + T(z_0 = 2|z_1 = 1 + r_0), \quad (30)$$

where the second term is the homogeneous result from Eq. (22). This means that even for vanishing receptor size $r_p \rightarrow 0$, the MFPT remains finite. This makes sense because above we have shown that the effective patch size is determined both by r_p and r_0 . In detail, Fig. 6 showed that capture occurs over the solid angle $2\theta_0$ with $\theta_0(z) = \arccos(z/(1 + r_0)) + r_p$. For small r_0 and r_p , this allows us to define an effective patch size,

$$\begin{aligned} r_p^{\text{eff}} &= \arccos(\langle z \rangle / (1 + r_0)) + r_p \\ &\approx \arccos\left(1 - \frac{1}{2}r_0\right) + r_p \\ &\approx \sqrt{r_0} + r_p, \end{aligned} \quad (31)$$

where we have used $\langle z \rangle = 1 + r_0/2$. Suppose now that the sphere diffuses over the time t_d until a receptor patch points downwards, then it may encounter a ligand with a probability p that is given by the normalized area of one effective receptor patch,

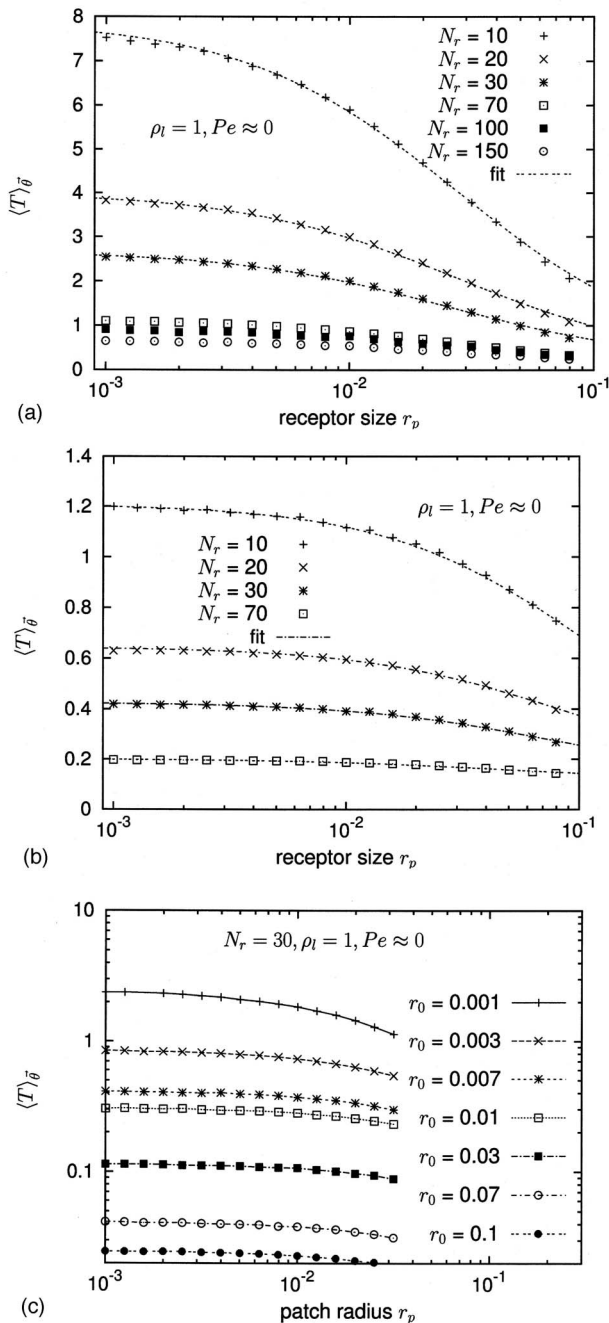


FIG. 11. [(a) and (b)] Dependence of $\langle T \rangle_\theta$ on the receptor patch radius r_p ($Pe \approx 0$). The dotted lines are fits of $a/(b+r_p)$ to the simulation results. (a) $r_0 = 0.001$ and (b) $r_0 = 0.01$ [numerical parameters: $N = (1-3) \times 10^5$, $\Delta t = 5 \times 10^{-5}$]. (c) For $N_r = 30$ the dependence on r_p is shown for different values of the capture radius r_0 . For better comparison the r_0 -dependent part of the MFPT as given by Eq. (22) was subtracted.

$$p = \frac{1}{2}(1 - \cos(r_p^{\text{eff}})) \approx \frac{1}{4}(\sqrt{r_0} + r_p)^2 \approx \frac{1}{2}\sqrt{r_0}\left(\frac{1}{2}\sqrt{r_0} + r_p\right). \quad (32)$$

If no encounter occurs, the sphere has to diffuse again a time t_d until the next encounter can occur. This leads to the mean encounter time $T = t_d/p$. Putting everything together gives Eq. (30) with $a = 2t_d/(\sqrt{r_0})$ and $b = \frac{1}{2}\sqrt{r_0}$. If checked against our simulation results, we indeed find that the fit parameter b is an increasing function of r_0 but varies only slightly with

N_r . The fit parameter a scales approximately as $\sim 1/N_r$ and varies with r_0 , also consistent with the above analysis. In Fig. 11(c) $\langle T \rangle_\theta$ is plotted as a function of r_p for several values of r_0 and $N_r = 30$. One clearly sees that increasing r_p has a much smaller impact on $\langle T \rangle_\theta$ than a comparable increase in r_0 , which is qualitatively well described by the preceding analysis.

In Figs. 11(a) and 11(b) the receptor density is varied over almost four orders of magnitude by changing r_p , but the largest measured decrease for $\langle T \rangle_\theta$ is only by a factor 4. In contrast, an increase of the receptor density by one order of magnitude due to tenfold more receptor patches leads to a decrease of $\langle T \rangle_\theta$ by almost also one order of magnitude. However, this is only true as long as N_r is not too large, as for large N_r , $\langle T \rangle_\theta$ saturates at the limiting value of homogeneous receptor coverage [see Fig. 10(b)]. The crossover from the $1/N_r$ behavior to the saturation should take place when the average distance between two receptor patches $d' \sim (4\pi/N_r)^{1/2}$ becomes comparable to the size of one receptor patch. This corresponds to $r_p^{\text{eff}} \sim (4\pi/N_r)^{1/2}$ or $N_r \sim 4\pi/(\sqrt{r_0} + r_p)$. This estimate predicts that the crossover takes place between several tens to several hundreds of receptor patches, depending on r_0 , in agreement with the data shown in Fig. 10(b).

IX. SUMMARY AND DISCUSSION

In this paper we have calculated the MFPTs for the initial encounter between spatially resolved receptors on a Brownian particle in linear shear flow and spatially resolved ligands on the boundary wall. Our main results were obtained by repeated simulations of the discretized Langevin equation [Eq. (16)]. Each data point shown corresponds to at least 100 000 simulation runs. It is important to note that these simulations are very time consuming because we resolve objects of the size of $10^{-3}R$, that is, for micrometer-sized particles we resolve the nanometer scale.

In general, we found that the MFPT was always monotonically decreased when the Péclet number was increased. That means that a particle which is covered with receptors in a way that it binds well to ligands already in the diffusive limit is even better suited to initiate binding at finite shear rate. In our simulations we modeled the receptor geometry using three parameters: the number of receptor patches N_r , the radius of the receptor patches r_p , and the capture radius r_0 . The efficiency of binding is mainly increased by N_r , but only up to a saturation value of the order of 100. An increase of r_p leads only to a weak enhancement of binding efficiency. The influence of r_0 to the MFPT is threefold: (i) it reduces the mean falling time, (ii) it increases the effective patch size, and (iii) according to the stationary probability distribution for the z direction, it becomes more probable for the sphere to be within the encounter zone when r_0 is increasing. An additional but more indirect effect of receptor protrusions is that the further the cell is away from the wall, the faster it can rotate (even in the diffusive limit) due to the larger mobility. As shown by Eq. (26), rotations play a role only within binding range, i.e., for $z < 1 + r_0$. Therefore, a large r_0 lets the cell also benefit from faster rotations. Summarizing our find-

ings in regard to receptor geometry we conclude that the most efficient design for particle capture under flow is to cover the particle with hundreds of receptor patches (N_r above threshold), each with a rather small area (small r_p), but formed as a protrusion (large r_0).

Indeed, this strategy seems to be used by white blood cells, which have evolved intriguing mechanisms both on the molecular and cellular scales in order to adhere effectively to the endothelium under the conditions of hydrodynamic flow. The typical size of white blood cells is $R \approx 5 \mu\text{m}$ and they are covered with a few hundreds of protrusions (*microvilli*) with the receptors (most notably L-selectin) localized to the microvilli tips.²⁵ In general, the microvilli of white blood cells are much more complex than the parameter r_0 in our model: they are rather long (typical length 350 nm, that is, $R/15$) and have their own physical properties (e.g., very flexible in the transverse direction and viscous in the longitudinal direction).²⁶ Nevertheless, it is striking that elevation of the receptors above the main cell surface seems to be a major design principle for white blood cells. In fact, the same strategy appears to be used also by malaria-infected red blood cells, which are known to develop a dense coverage with elevated receptor patches (*knobs*) on the cell surface.^{11–13} A typical value for the cell radius is $3.5 \mu\text{m}$.²⁷ The knobs have a typical height of 20 nm, a radius of about 90 nm, and a distance of 200 nm (for red blood cells infected by single parasites).¹² This dense and elevated coverage suggests that like the white blood cells, the malaria-infected red blood cells also function in the regime of homogeneous coverage.

In order to discuss the motion of white blood cells in more detail, it is instructive to consider the parameters for a typical flow chamber experiment. In aqueous solution and at room temperature, $\rho = \text{g}/\text{cm}^3$, $\eta = 10^{-3} \text{ Pa s}$, and $T = 293 \text{ K}$. Then, the dimensionless parameters determining cell motion become

$$\text{Pe} = 4.67R^3 \dot{\gamma}, \quad f = 2.17 \frac{R\Delta\rho}{\dot{\gamma}}, \quad \text{Pe}_z = 10.16R^4 \Delta\rho, \quad (33)$$

$$\Delta t = \frac{\text{Pe}}{\dot{\gamma}} = 4.67R^3 \text{ s},$$

where R is given in micrometers, $\Delta\rho$ in units of g/cm^3 , and the shear rate $\dot{\gamma}$ in units of s^{-1} ; Δt is the diffusive time scale. For leukocytes in flow chambers we typically have $R=5$, $\dot{\gamma} = 100$, and $\Delta\rho=0.05$, thus, for the two Péclet numbers we get $\text{Pe} = 6 \times 10^4$ and $\text{Pe}_z = 317$, respectively. Then, $f = \text{Pe}_z/\text{Pe} = 0.005$, that is, the effect of hydrodynamic deterministic motion will be very strong. The experimental time scale is given by the time for transversing the field of view, which is about 3 s at a shear rate of 100 Hz and length of $670 \mu\text{m}$. The diffusive time scale Δt for leukocytes is about 600 s (10 min), which reflects their large size and shows that diffusive motion is by far not sufficient to initiate binding. Binding becomes more favorable in the presence of convection. For a start height of one radius above the wall ($z_0=2$), our calculations give a MFPT of about 5 s, that is, much less than the diffusive time. However, this is still much larger than the experimental time scale. This proves that only those

cells have a chance to bind that flow very close to the wall, exactly as observed experimentally. *In vivo*, white blood cells therefore depend also on other mechanisms driving them onto the substrate, including contact and hydrodynamic interactions with other cells. These effects have been studied in detail before. For example, Sun *et al.* have shown that adhesion of leukocytes close the vessel wall in postcapillary venules is enhanced by red blood cells passing them.²⁸ King and Hammer have shown, using an algorithm capable of simulating several cells, that already adherent leukocytes can recruit other leukocytes via hydrodynamic interactions.²⁹ The results presented here, when specified to leukocytes, show that indeed these mechanisms are crucial for effective leukocyte capture under flow.

Our results also suggest that leukocytes are sufficiently large that thermal fluctuations are not dominant. This changes when studying smaller particles, e.g., receptor-covered spheres with $R \approx 1 \mu\text{m}$, whose binding also has been investigated with flow chambers.^{30,31} Equation (33) shows that the Péclet numbers scale strongly with particle radius R ; therefore, these beads are subject to much stronger thermal fluctuations than leukocytes. In Ref. 31 it has been verified that indeed in equilibrium such particles obey the barometric distribution from Eq. (18). In Ref. 30 it was found that the adhesion probability p_{ad} is proportional to the ligand density, $p_{\text{ad}} \sim \rho_l$. With $p_{\text{ad}} \sim 1/T$ it follows that $T \sim 1/\rho_l$ as found by our simulations in the limit of low ligand densities.

Throughout this paper we have considered the generic case of a constant downward acting force due to a density difference between the sphere and the surrounding fluid. In future work it might be interesting to examine also other forces which can easily be done in the framework presented here. As the addition formula [Eq. (26)] for falling and rotational MFPT was not derived under the assumption of a specific force, it is also true for nonconstant forces. For general potential forces the falling time [Eq. (22)] has then to be replaced by Eq. (23). Also the rotational MFPT is influenced by a vertical force via the stationary height distribution. Neglecting gravitational force and considering only short-ranged forces such as van der Waals or electrostatic forces would result in infinite MFPTs for the setup of the half space. This problem, however, can be solved by using an additional wall acting as an upper boundary.³²

In this paper we assumed a rigid Brownian particle. For cells, elastic deformations might be relevant. For free flow, a simple scaling estimate shows that the critical value for the shear rate leading to substantial deviations from the spherical shape is $(Eh)/(\eta R)$,³³ where $E=100 \text{ Pa}$ and $h=100 \text{ nm}$ are the Young modulus and thickness of the cellular envelope, respectively. The fact that the Young modulus E appears here indicates that cells tend to passively deform less than vesicles, whose elasticity is characterized rather by the bending rigidity.^{34,35} The scaling estimate leads to a critical shear rate of 10^3 Hz , which is above the value of a few 10^2 Hz (corresponding to $\text{Pe} \approx 10^5$ for white blood cells) which often provides an upper limit in flow chamber experiments. Simi-

lar but more complicated scaling arguments can be made for lubrication forces which arise when the cell approaches the wall.³⁶

To fully understand the rate of association between a receptor-covered particle in shear flow and a ligand-covered wall, our analysis should be completed by the implementation of an adhesion scenario, which in general should also include molecular determinants such as residence times and receptor flexibility. If one assumes that a bond between two encountering molecules is formed with a certain rate, then, the MFPT for encounter as reported here should be a good approximation for the mean adhesion time in the limit of zero shear rate, because in this limit the duration of each encounter should be sufficiently long for the formation of an adhesion contact. Then, the proper knowledge of the MFPT could also be used to design a cell sorting experiment. Suppose one has a mixture of different cells each bearing some receptors and the wall is covered with one kind of ligand. Then, the cells are flowed into the chamber and the flow is stopped. Certainly, only cells that bear receptors which fit to the ligands can attach to the wall. If the flow is then turned on again, the attached cells will be separated from the other cells. If the no-flow period is much shorter than the MFPT, only a few cells can attach. If the no-flow period is much longer than the MFPT, attached cells might already start to spread and are therefore difficult to remove. Only if the no-flow period is of the order of MFPT one gets an appreciable number of weakly attached cells. In this sense our theoretical analysis might be essential for appropriate biotechnological applications.

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APPENDIX A: IMPLEMENTATION OF FRICTION AND MOBILITY MATRICES

For the numerical implementation of the friction and mobility tensors for a sphere in linear shear flow above a wall, we use the results from Refs. 19 and 37. This implementation procedure has been described and tested in detail in Ref. 19. In this appendix, we briefly summarize it for the sake of completeness.

Writing the friction tensors in terms of irreducible tensors formed from δ_{ij} , ϵ_{ijk} , \mathbf{k} defines the scalar friction functions. In the case that the normal vector to the wall is $\mathbf{k}=\mathbf{e}_z$, these tensors read

$$\zeta^{tt} = \begin{pmatrix} \psi^{tt} & 0 & 0 \\ 0 & \psi^{tt} & 0 \\ 0 & 0 & \phi^{tt} \end{pmatrix}, \quad \zeta^{tr} = \psi^{tr} \begin{pmatrix} 0 & 1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} = \zeta^{rtT},$$

$$\zeta^{rr} = \begin{pmatrix} \psi^{rr} & 0 & 0 \\ 0 & \psi^{rr} & 0 \\ 0 & 0 & \phi^{rr} \end{pmatrix},$$

$$\zeta_{\alpha}^{td} = \begin{pmatrix} -\frac{1}{3}\delta_{\alpha 3}\phi^{td} & 0 & \frac{1}{2}\delta_{\alpha 1}\psi^{td} \\ 0 & -\frac{1}{3}\delta_{\alpha 3}\phi^{td} & \frac{1}{2}\delta_{\alpha 2}\psi^{td} \\ \frac{1}{2}\delta_{\alpha 1}\psi^{td} & \frac{1}{2}\delta_{\alpha 2}\psi^{td} & \frac{2}{3}\delta_{\alpha 3}\phi^{td} \end{pmatrix},$$

$$\zeta_{\alpha}^{rd} = \frac{1}{2}\psi^{rd} \begin{pmatrix} 0 & 0 & \epsilon_{3\alpha 1} \\ 0 & 0 & \epsilon_{3\alpha 2} \\ \epsilon_{3\alpha 1} & \epsilon_{3\alpha 2} & 0 \end{pmatrix},$$

$$\zeta_{\alpha}^{dt} = \begin{pmatrix} \frac{1}{2}\delta_{\alpha 3}\psi^{dt} & 0 & -\frac{1}{3}\delta_{\alpha 1}\phi^{dt} \\ 0 & \frac{1}{2}\delta_{\alpha 3}\psi^{dt} & -\frac{1}{3}\delta_{\alpha 2}\phi^{dt} \\ \frac{1}{2}\delta_{\alpha 1}\psi^{dt} & \frac{1}{2}\delta_{\alpha 2}\psi^{dt} & -\frac{2}{3}\delta_{\alpha 3}\phi^{dt} \end{pmatrix},$$

$$\zeta_{\alpha}^{dr} = \frac{1}{2}\psi^{dr} \begin{pmatrix} 0 & \delta_{\alpha 3} & 0 \\ -\delta_{\alpha 3} & 0 & 0 \\ -\delta_{\alpha 2} & \delta_{\alpha 1} & 0 \end{pmatrix}.$$

This defines the scalar friction functions ϕ^{tt} , ψ^{tt} , ψ^{tr} , ϕ^{rr} , ψ^{rr} , ϕ^{td} , ψ^{td} , ψ^{dr} . The scalar friction functions ϕ depend only on the inverse distance of the sphere from the wall, that is, the dimensionless variable $t=R/z$, which takes values from the interval $[0, 1]$. The friction functions can be expanded in powers of t . The numerically obtained first 20 coefficients of such a series expansion of the dimensionless scalar friction functions,

$$\hat{\phi}^{tt} = \phi^{tt}/6\pi\eta R, \quad \hat{\psi}^{tt} = \psi^{tt}/6\pi\eta R, \quad \hat{\phi}^{rr} = \phi^{rr}/8\pi\eta R^3,$$

$$\hat{\psi}^{rr} = \psi^{rr}/8\pi\eta R^3, \quad \hat{\psi}^{tr} = \psi^{tr}/8\pi\eta R^2 = -\hat{\psi}^{rt},$$

are tabulated in Ref. 37. For the other three dimensionless scalar friction functions,

$$\hat{\phi}^{td} = \phi^{td}/6\pi\eta R^2 = \hat{\phi}^{dt}, \quad \hat{\psi}^{td} = \psi^{td}/6\pi\eta R^2 = \hat{\psi}^{dt},$$

$$\hat{\psi}^{dr} = \psi^{dr}/8\pi\eta R^3 = -\hat{\psi}^{rd},$$

the first 32 coefficients of a series expansion in powers of t are tabulated in Ref. 19. For small values of t the series expansion converges quite well and only a few coefficients are needed to obtain accurate results. However, for $t \rightarrow 1$, i.e., close to the wall, the friction functions are better described in a lubrication expansion, which reads

$$\hat{\phi} \approx C_1 \frac{t}{1-t} + C_2 \ln(1-t) + C_3 + C_4 \frac{1-t}{t} \ln(1-t) + \mathcal{O}(1-t).$$

The coefficients C_1, C_2, C_3, C_4 for the eight friction functions defined above can be found in Ref. 19. In order to match the two limit cases, the asymptotic expansion of the $t \rightarrow 1$ limit is subtracted from the friction functions

$$\hat{\phi}(t) = \sum_{n=0}^{\infty} f_n t^n,$$

leading to a new series expansion,

$$\begin{aligned} \hat{\phi}(t) &= C_1 \frac{t}{1-t} - C_2 \ln(1-t) - C_4 \frac{1-t}{t} \ln(1-t) \\ &= f_0 + C_4 + \sum_{n=1}^{\infty} \left(f_n - C_1 + \frac{C_2}{n} - \frac{C_4}{n(n+1)} \right) t^n \\ &=: \sum_{n=0}^{\infty} g_n t^n. \end{aligned}$$

This series is truncated at $n_{\max}=N$ and the coefficients g_n are calculated from the coefficients f_n, C_i . Next the coefficients g_n ($n=0, \dots, N$) are not used to calculate the Taylor sum, but rather to calculate the Padé approximant to this function. The Padé approximant is given as

$$\mathcal{P}_N(t) = \frac{a_0 + a_1 t + a_2 t^2 + \dots + a_N t^N}{1 + b_1 t + b_2 t^2 + \dots + b_N t^N},$$

where the coefficients a_i, b_j are the solution to

$$\sum_{n=1}^N b_n g_{N-n+k} = -g_{N+k}, \quad \sum_{n=1}^k b_n g_{k-n} = a_k, \quad k = 1, \dots, N.$$

Finally, the numerically implemented friction functions become

$$\hat{\phi}(t) = C_1 \frac{t}{1-t} + C_2 \ln(1-t) + C_4 \frac{1-t}{t} \ln(1-t) + \mathcal{P}_N(t). \quad (\text{A1})$$

For the calculation of the coefficients a_i, b_j of the Padé approximant we use the algorithm provided in Ref. 38.

Having implemented the scalar friction functions, the implementation of the mobility tensors proceeds by substituting $\zeta \leftrightarrow \mu$, $\phi \leftrightarrow \alpha$, $\psi \leftrightarrow \beta$ in the above decomposition of the friction tensors. This defines the scalar mobility functions $\alpha^{tt}, \beta^{tt}, \alpha^{rr}, \beta^{rr}, \beta^{tr}, \alpha^{dt}, \beta^{dt}, \beta^{dr}$. Using Eq. (8) the dimensionless scalar mobility functions can be calculated from the scalar friction functions,

$$\hat{\alpha}^{tt} = 1/\hat{\phi}^{tt}, \quad \hat{\beta}^{tt} = \frac{\hat{\psi}^{tr}}{\hat{\psi}^{tr}\hat{\psi}^{rr} - (4/3)(\hat{\psi}^{tr})^2},$$

$$\hat{\alpha}^{rr} = 1/\hat{\phi}^{rr}, \quad \hat{\beta}^{rr} = \frac{\hat{\psi}^{tr}}{\hat{\psi}^{tr}\hat{\psi}^{rr} - (4/3)(\hat{\psi}^{tr})^2},$$

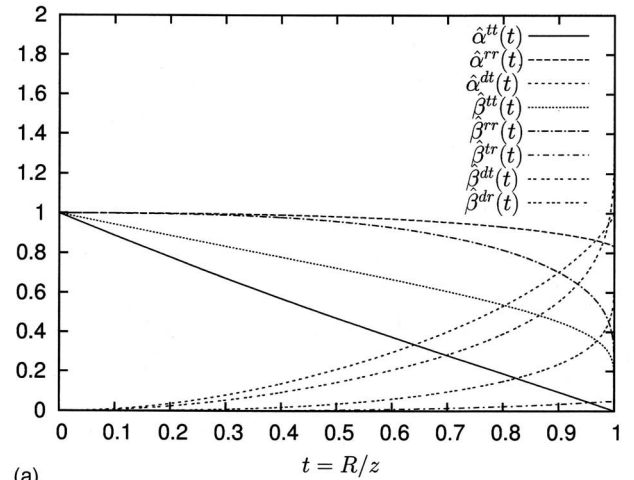
$$\hat{\beta}^{tr} = -\frac{4}{3} \frac{\hat{\psi}^{tr}}{\hat{\psi}^{tr}\hat{\psi}^{rr} - (4/3)(\hat{\psi}^{tr})^2},$$

$$\hat{\alpha}^{dt} = -\hat{\phi}^{dt}\hat{\alpha}^{tt}, \quad \hat{\beta}^{dt} = -\hat{\psi}^{dt}\hat{\beta}^{tt} - \hat{\psi}^{dr}\hat{\beta}^{tr},$$

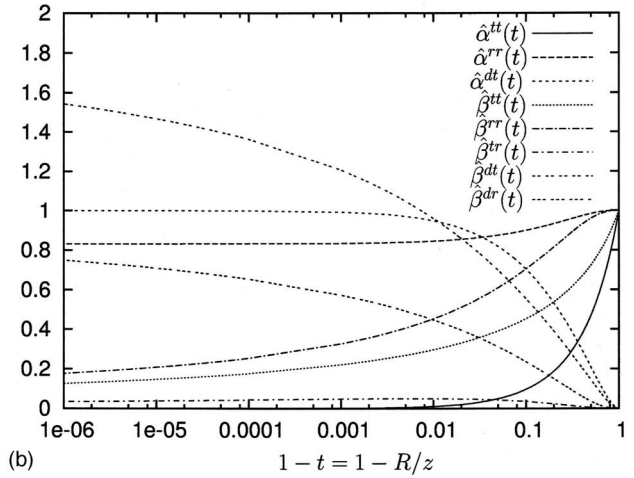
$$\hat{\beta}^{dr} = -\frac{3}{4}\hat{\psi}^{dt}\hat{\beta}^{tr} - \hat{\psi}^{dr}\hat{\beta}^{rr}.$$

In Fig. 12 we use our implementation to plot the eight dimensionless mobility functions.

The limit of an unbounded flow corresponds to $t \rightarrow 0$ and results in



(a)



(b)

FIG. 12. Dimensionless scalar mobility functions. On the left the functions are plotted vs the dimensionless parameter t . On the right the functions are plotted vs $1-t$, thus better illustrating the asymptotic behavior for $t \rightarrow 1$.

$$\zeta^{tt} = 6\pi\eta RI, \quad \zeta^{rr} = 8\pi\eta R^3 I, \quad \zeta^{tr} = \zeta^{rt} = \zeta^{rd} = \zeta^{td} = 0, \quad (\text{A2})$$

where I is the unity matrix. Thus Eq. (5) reduces to

$$\mathbf{F}^H = 6\pi\eta R(\mathbf{U} - \mathbf{U}^\infty), \quad \mathbf{T}^H = 8\pi\eta R^3(\boldsymbol{\Omega} - \boldsymbol{\Omega}^\infty), \quad (\text{A3})$$

which are the well-known Stokes laws for the friction force and torque exerted on a sphere moving in a fluid with relative velocity $\mathbf{U} - \mathbf{U}^\infty$. For the linear shear flow considered here, $\mathbf{U}^\infty = \dot{\gamma} z \mathbf{e}_x$ and $\boldsymbol{\Omega}^\infty = \dot{\gamma} \mathbf{e}_y / 2$.

APPENDIX B: RELATION TO THE SMOLUCHOWSKI EQUATION

The probability distribution $\Psi(\mathbf{X}, t)$ of a Brownian particle subject to external force/torque \mathbf{F} satisfies a continuity equation $\partial_t \Psi + \nabla \cdot \mathbf{J} = 0$. The probability flux \mathbf{J} contains a diffusive and a convective part,²²

$$J_i = -D_{ij} \partial_j \Psi + M_{ij} F_j \Psi, \quad (\text{B1})$$

where D and M are diffusion and mobility matrices, respectively, and \mathbf{F} is external force. In equilibrium, the flux has to vanish and the probability distribution has to become the Boltzmann distribution. This leads to the Einstein relation

$D = k_B T M$, which is a special case of the fluctuation-dissipation theorem. Using Eq. (B1) and the Einstein relation in the continuity equation leads to the Smoluchowski equation³⁹

$$\partial_t \Psi = \partial_i (M_{ij} (k_B T \partial_j \Psi - F_j \Psi)). \quad (\text{B2})$$

We will now derive the equivalent Langevin equation. In the case of constant mobility (*additive noise*), e.g., $M_{ij} = \delta_{ij}$, the appropriate Langevin equation is given by

$$\partial_t \mathbf{X}_t = \mathbf{M} \mathbf{F} + \mathbf{g}_t^S, \quad (\text{B3})$$

where \mathbf{g}_t^S is a Gaussian white noise term and the Stratonovich interpretation is used as explained in the main text. However, if \mathbf{M} depends on \mathbf{X} (*multiplicative noise*), an additional drift term occurs in the Langevin equation

$$\partial_t \mathbf{X}_t = \mathbf{M} \mathbf{F} + k_B T \mathbf{Y} + \mathbf{g}_t^S. \quad (\text{B4})$$

The following derivation of the drift term \mathbf{Y} proceeds in two steps.³⁹ First we perform a coordinate transformation which makes the noise additive. In the case of additive noise the Langevin equation [Eq. (B3)] and the Fokker-Planck equation [Eq. (B2)] are equivalent. Then starting from the Fokker-Planck equation in the new coordinates, we perform the transformation back to the old coordinates. Requiring the transformed Fokker-Planck equation to be of the same form as in Eq. (B2) determines the drift term \mathbf{Y} .

As we use the Stratonovich interpretation for the noise process the usual rules for differentiation and integration apply and we can perform the following coordinate transformation:

$$\mathbf{X}' = \int^{\mathbf{X}(t)} \mathbf{S}(\mathbf{X}'') d\mathbf{X}'', \quad (\text{B5})$$

with some regular matrix \mathbf{S} . The Langevin equation for the transformed coordinates then reads

$$\partial_t \mathbf{X}'_t = \mathbf{S} \partial_t \mathbf{X}_t = \mathbf{S} \mathbf{M} \mathbf{F} + k_B T \mathbf{S} \mathbf{Y} + \mathbf{S} \mathbf{g}_t^S. \quad (\text{B6})$$

From the requirement that $M'_{ij} = \delta_{ij}$, that is,

$$\langle \mathbf{S} \mathbf{g}_t \mathbf{S} \mathbf{g}_t \rangle = 2k_B T \mathbf{E}, \quad E_{ij} := \delta_{ij}, \quad (\text{B7})$$

we can fix \mathbf{S} to be the inverse of a matrix \mathbf{B} with

$$\mathbf{S} = \mathbf{B}^{-1}, \quad \mathbf{M} = \mathbf{B} \mathbf{B}^T \Leftrightarrow M_{ij} = B_{ik} B_{jk}. \quad (\text{B8})$$

As \mathbf{M} is a symmetric positive definite matrix, it is always possible to find a matrix \mathbf{B} with $\mathbf{M} = \mathbf{B} \mathbf{B}^T$. Defining

$$\mathbf{F}' := \mathbf{B}^T \mathbf{F} + k_B T \mathbf{S} \mathbf{Y}, \quad \tilde{\mathbf{g}}_t^S := \mathbf{S} \mathbf{g}_t^S = \mathbf{B}^{-1} \mathbf{g}_t^S, \quad (\text{B9})$$

the new Langevin equation for the primed coordinates and with additive noise reads

$$\partial_t \mathbf{X}'_t = \mathbf{M}' \mathbf{F}' + \tilde{\mathbf{g}}_t^S. \quad (\text{B10})$$

The corresponding probability distribution $\Psi'(\mathbf{X}', t)$ is the solution of the Smoluchowski equation

$$\partial_t \Psi'(\mathbf{X}', t) = \partial'_k \delta_{ki} (k_B T \partial'_i \Psi' - F'_i \Psi'). \quad (\text{B11})$$

Next we transform Eq. (B11) back to the unprimed coordinates. The preservation of probability requires that

$$\Psi'(\mathbf{X}', t) = J \Psi(\mathbf{X}, t), \quad (\text{B12})$$

where J is the Jacobian of the coordinate transformation,⁴⁰

$$J := \det \left(\frac{\partial X'_i}{\partial X_j} \right) = \det(\mathbf{B}), \quad \frac{\partial X'_i}{\partial X_j} = B_{ij}. \quad (\text{B13})$$

Inserting Eq. (B12) into Eq. (B11) gives

$$\begin{aligned} \partial_t \Psi' &= J \partial_t \Psi = \partial'_k (k_B T \partial'_k \Psi' - F'_k \Psi') \\ &= k_B T \partial'_k \partial'_k J \Psi - \partial'_k F'_k J \Psi. \end{aligned} \quad (\text{B14})$$

Dividing by J we obtain for the first term on the right hand side of Eq. (B14)

$$\begin{aligned} J^{-1} \partial'_k \partial'_k J \Psi &= J^{-1} (\partial'_k \partial'_k J) \Psi + 2J^{-1} (\partial'_k J) \partial'_k \Psi + \partial'_k \partial'_k \Psi \\ &= \partial_j (B_{jk} B_{lk} \partial_l \Psi + B_{jk} (\partial_l B_{lk}) \Psi). \end{aligned}$$

Here we made use of the identities

$$J^{-1} \nabla' J = \nabla B^T, \quad J^{-1} \partial'_i J = \partial_j B_{ji}, \quad \nabla' = B^T \nabla,$$

$$\begin{aligned} J^{-1} \partial'_i \partial'_j J &= J^{-1} \partial'_i (J J^{-1}) \partial'_j J \\ &= J^{-1} (\partial'_i J) J^{-1} \partial'_j J + \partial'_i (J^{-1} \partial'_j J) \\ &= (\partial_k B_{ki}) \partial_l B_{lj} + B_{li} \partial_l \partial_k B_{kj}. \end{aligned} \quad (\text{B15})$$

Again using the identity [Eq. (B15)] the second term of the right hand side of Eq. (B14) can be evaluated to be

$$J^{-1} \partial'_k F'_k J \Psi = J^{-1} (\partial'_k J) F'_k \Psi + \partial'_k F'_k \Psi = \partial_j (B_{jk} F'_k \Psi).$$

Adding both terms and inserting the definitions [Eqs. (B8) and (B9)], we have

$$\begin{aligned} \partial_t \Psi &= \partial_j (k_B T M_{jl} \partial_l \Psi + k_B T B_{jk} (\partial_l B_{lk}) \Psi - M_{jl} F_l \\ &\quad - k_B T Y_j \Psi). \end{aligned}$$

Comparing this with the required result [Eq. (B2)], we can read off \mathbf{Y} ,

$$\mathbf{Y} = \mathbf{B} \nabla B^T, \quad Y_i = B_{ik} (\partial_l B_{lk}).$$

Finally, shifting $\partial_t \mathbf{X}_t \rightarrow \partial_t \mathbf{X}_t - \mathbf{U}^\infty$, we obtain the Langevin equation as given by Eq. (12) combined with Eq. (13).

APPENDIX C: EULER ALGORITHM FOR A SPHERE ABOVE A WALL

In order to solve Eq. (14) numerically we use an Euler algorithm. As the physical situation requires to use the Stratonovich interpretation of the noise term \mathbf{g}_t^S , the displacement $\Delta \mathbf{X}$ of a particle from time t to time $t + \Delta t$ depends on the position of the particle at time $t + (1/2)\Delta t$, which is not known at time t . As usual, this problem is solved by rewriting the Langevin equation in the Itô version. Then the noise term can be evaluated at time t and as a compensation an additional drift term $\partial_l (B_{ik}) B_{lk}$ is added to Eq. (14).²² Because $B_{kl}^T \partial_l (B_{ik}) + B_{ik} \partial_l (B_{kl}^T) = \partial_l (B_{ik} B_{kl}^T) = \partial_l M_{il}$, we arrive at Eq. (15). In this equation, the random displacements $\mathbf{g}(\Delta t)$ must satisfy

$$\langle \mathbf{g}(\Delta t) \rangle = 0, \quad \langle \mathbf{g}(\Delta t) \mathbf{g}(\Delta t) \rangle = 2M\Delta t. \quad (\text{C1})$$

Following Ref. 23, $\mathbf{g}_i(\Delta t)$ is calculated from a weighted sum of normal deviate random numbers $\bar{x}_i \rightarrow \{x_i\}$ satisfying $\langle x_i \rangle = 0$, $\langle x_i x_j \rangle = 2\delta_{ij}\Delta t$. This sum is given by

$$\mathbf{g}_i(\Delta t) = \sum_{j=1}^i B_{ij} \bar{x}_j,$$

where the weighting factors are the elements of the matrix \mathbf{B} defined in Eq. (B8). They can recursively be calculated according to

$$B_{ii} = \left(M_{ii} - \sum_{k=1}^{i-1} B_{ik}^2 \right)^{1/2},$$

$$B_{ij} = \left(M_{ij} - \sum_{k=1}^{j-1} B_{ik} B_{jk} \right) / B_{jj}, \quad i > j,$$

$$B_{ij} = 0, \quad i < j.$$

In the case of a sphere above a wall we obtain the following dimensionless weighting factors (see Ref. 41):

$$\hat{B}_{11} = \sqrt{\hat{\beta}^{tt}}, \quad \hat{B}_{22} = \sqrt{\hat{\beta}^{tt}}, \quad \hat{B}_{33} = \sqrt{\hat{\alpha}^{tt}},$$

$$\hat{B}_{42} = -\hat{B}_{51} = -\frac{3}{4} \frac{\hat{\beta}^{tr}}{\sqrt{\hat{\beta}^{tt}}}, \quad (\text{C2})$$

$$\hat{B}_{44} = \hat{B}_{55} = \frac{3}{4} \frac{1}{\sqrt{\hat{\beta}^{tt}}} \left(\frac{4}{3} \hat{\beta}^{tr} \hat{\beta}^{rr} - (\hat{\beta}^{tr})^2 \right)^{1/2} \equiv \sqrt{\frac{3}{4\hat{\gamma}^{rr}}},$$

$$\hat{B}_{66} = \frac{1}{2} \sqrt{3\hat{\alpha}^{rr}}. \quad (\text{C3})$$

As pointed out in Ref. 42, using the Euler method, instead of normal deviate random variables, any uncorrelated random variable $\bar{x}_i \rightarrow \{x_i, i=1, \dots, 6\}$ can be chosen, as long as they fulfill the required relation for the first moments $\langle x_i \rangle = 0$, $\langle x_i x_j \rangle = 2\delta_{ij}\Delta t$. Thus, it is much faster to generate the random numbers according to $\bar{x}_i = \sqrt{12\Delta t}(\xi_i - 0.5)$, with $\xi_i, i=1, \dots, 6$ being uncorrelated random variables uniformly distributed in $[0,1]$. For the calculation of the random numbers we use the pseudo-random-number generator RAN3 from Ref. 38

Calculating the new configuration after each time step using Eq. (16) is straightforward for the spatial degrees of freedom. For the update of the orientation of the sphere we use a coordinate system spanned by three orthonormal basis vectors $\{\mathbf{n}_i | i=1, 2, 3; (\mathbf{n}_i)_j = \delta_{ij}\}$. The origin of this coordinate system shall be identical with the center of mass of the sphere and the relative orientations of this system and of the sphere are kept fixed. Given then an orientation update form [Eq. (16)] $\boldsymbol{\theta} := (\Delta \mathbf{X}_4, \Delta \mathbf{X}_5, \Delta \mathbf{X}_6)$, we decompose each of the basis vectors \mathbf{n}_i into a component parallel to $\boldsymbol{\theta}$ denoted by \mathbf{n}_{\parallel} and a component perpendicular to $\boldsymbol{\theta}$ denoted by \mathbf{n}_{\perp} (the index i is dropped for the sake of simplicity). These components are given by

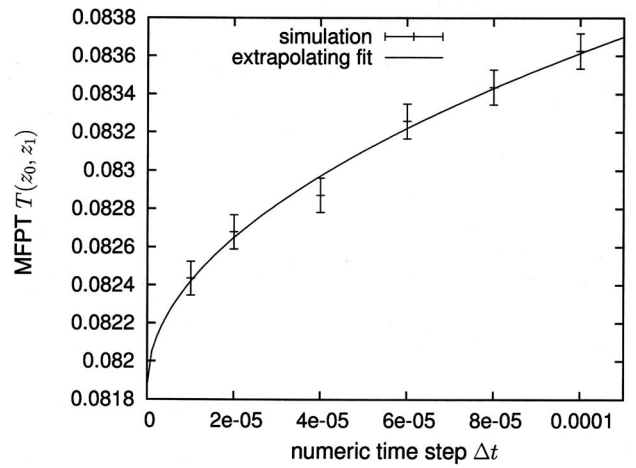


FIG. 13. The mean first passage times for $Pe_c=100$, $z_1=1.001$, $z_0=2$ as a function of the numerical time step. The points are the results from simulation experiments (error bars denote their statistical error) with $N=10^5$ iterations. The full line is a fit to $a+b\sqrt{\Delta t}$ using the GNU PLOT implementation of the nonlinear least-squares (NLLS) Marquardt-Levenberg algorithm. Extrapolating the fit to $\Delta t \rightarrow 0$ reduced the systematic error due to the finite time step.

$$\mathbf{n}_{\parallel} = \hat{\boldsymbol{\theta}}(\hat{\boldsymbol{\theta}} \cdot \mathbf{n}), \quad \hat{\boldsymbol{\theta}} := \boldsymbol{\theta} / \|\boldsymbol{\theta}\|,$$

$$\mathbf{n}_{\perp} = \mathbf{n} - \hat{\boldsymbol{\theta}}(\hat{\boldsymbol{\theta}} \cdot \mathbf{n}).$$

Then the orientation update affects only \mathbf{n}_{\perp} and the updated \mathbf{n}' is given by (with $\theta := \|\boldsymbol{\theta}\|$)

$$\mathbf{n}'_i = \hat{\boldsymbol{\theta}}(\hat{\boldsymbol{\theta}} \cdot \mathbf{n}_i)(1 - \cos \theta) + \mathbf{n}_i \cos \theta + \hat{\boldsymbol{\theta}} \times \mathbf{n}_i \sin \theta, \quad i = 1, 2, 3. \quad (\text{C4})$$

APPENDIX D: REDUCING THE SYSTEMATIC ERROR IN MEAN FIRST PASSAGE TIME ALGORITHM

Applying the Euler algorithm [Eq. (16)] to a mean first passage time problem gives rise to two sorts of errors. First there exists the statistical error, which is proportional to $1/\sqrt{N}$, where N is the number of iterations the algorithm is applied. The extent of the statistical error of the measured mean value can be calculated during the simulation. For the measurements performed in Secs. VII and VIII, typically $N = 10^4 - 10^5$ iterations were chosen resulting in statistical errors in the range of $< 1\%$. Error bars in these sections refer to the statistical error.

The systematic error for the mean first passage time calculated by the use of an Euler algorithm scales with $\sqrt{\Delta t}$, although the error of the particle position is only of the order of Δt .⁴² Thus to decrease the systematic error by a factor of 10 one must increase the numerical cost by a factor of 100. One way to obtain accurate results at moderate numerical cost is to measure the mean first passage time for various intermediate numerical time steps. Fitting these results to $a + b\sqrt{\Delta t}$ allows the extrapolation to $\Delta t \rightarrow 0$. Figure 13 shows an example where this procedure was applied to the case of homogeneous coverage as considered in Sec. V. The resulting mean first passage time then deviates by 0.2% from the

value obtained from the quadrature of Eq. (22). This is the same accuracy as we have for the implemented mobility functions themselves (see Appendix A).

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