Diffusion limited escape rate of a complex molecule in muti-dimensional confinement

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The rate at which a Brownian particle confined in a closed space escapes from the space by passing through a narrow passage is called escape rate. The escape rate is relevant to many diffusion limited processes in polymer and colloidal systems, such as colloidal aggregation, polymerization reaction, and polymer translocation through a membrane, etc. Here we propose a variational principle to calculate the escape rate of complex molecules doing Brownian motion in multi-dimensional phase space. We propose a regional minimization method in which we divide the whole phase space into regions and conduct the minimization for each region, and combine the results to get the minimum in the entire space. As an example, we discuss (1) the escape rate of a point particle that escapes from a confinement passing through a long corridor, and (2) the escape rate of a rod-like particle which escapes through a small hole made in the wall of the confinement.

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I. INTRODUCTION

The rate at which a Brownian particle confined in a closed space leaves the space passing through a narrow passage is called the escape rate[1,2]. Calculation of the escape rate is a classical problem in stochastic process, and is related to many problems in colloid and polymer science, such as the aggregation of colloidal particles[3], polymerization reaction[4], and polymer translocation through a membrane[5]. In these problems, the rate is determined by the diffusion of particles or molecules, and can be calculated by solving diffusion equations under certain boundary conditions.

Many works have been done on the escape rate in this context. However, most works are for point like particles doing simple diffusion. On the other hand, not many works have been done for non-spherical particles or polymers, the Brownian motion of which involves rotational diffusion, and other internal random motions[6]. To calculate the escape rate, one needs to solve the diffusion equation in multi-dimensional phase space[7,8]. This makes the analysis difficult.

The difficulty may be understood by the example shown in Fig. 1 (a). Here a rod-like particle is placed in a large box that has a small hole of radius a. The particle can go out passing through the hole. The problem is to calculate the rate at which the particle goes out from the hole when it is doing random Brownian motion. For spherical particle, this problem can be solved easily, but for rod-like particle, the problem is difficult and has been solved only numerically[9].

In this paper, we propose a variational principle to calculate the escape rate of non-spherical particles or polymers. The problem is generally defined as a problem of calculating the escape rate of a representative point doing Brownian motion in a multidimensional phase space (or configurational space). From this view point, the diffusion limited rate of aggregation, reaction and/or translocation can be discussed in the same framework as that to be discussed in this paper.

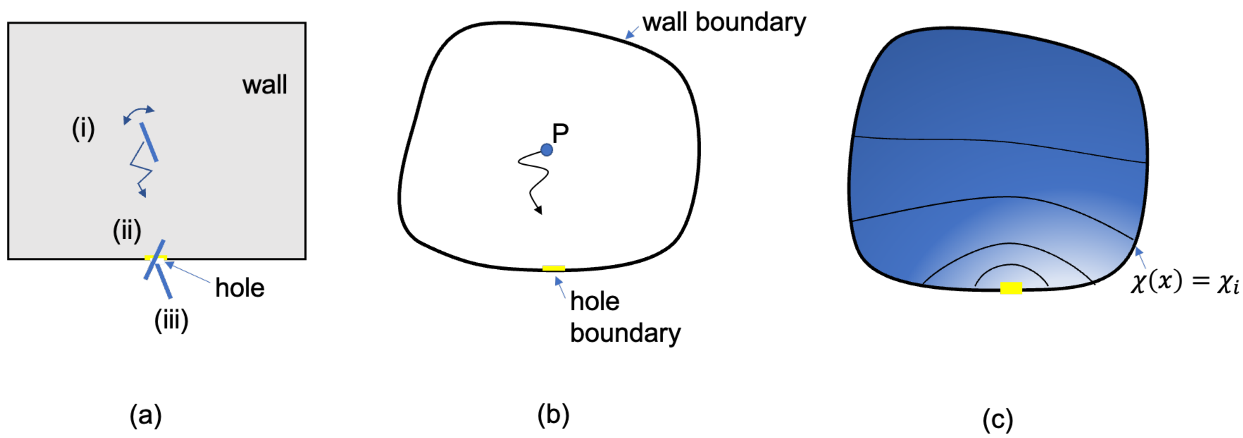


FIG. 1. (a) An escape rate problem of rod-like polymer. A Brownian rod is confined in a box and moves out through a small hole made at the wall. The problem is to calculate the rate at which the rod moves out from the box. (b) The phase space representation of the problem. The motion of the rod is represented by a Brownian motion of representative point confined in the phase space. The hole is represented by a hypersurface in the space. (c) Picture of the eigen function which gives the smallest eigenvalue.

II. MATHEMATICAL FORMULATION

A. Eigenvalue problem formulation for the escape rate

We consider a polymer molecule placed in a box of volume V. The box has a small hole through which the molecule can go out, and the problem is to calculate the rate at which the molecule goes out of the box by Brownian motion.

The state of the molecule is represented by a set of coordinates $x = (x_1, x_2, ...x_f)$ which specifies the configuration of the molecule. (The system is assumed to be over-damped and therefore x represents the position coordinate of the center of mass and other internal coordinates specifying the configuration of the molecule). The motion of the molecule is represented by a random motion of the point $(x_1, x_2, ...x_f)$ in the f dimensional space.

Let $\psi(x,t)dx$ be the probability of finding the molecule in a small region at x of volume $dx = dx_1 dx_2 ...dx_f$ in the phase space at time t. The distribution function satisfies the following Smoluchowskii equation[6]:

$$\frac{\partial \psi}{\partial t} = \sum_{i,j} \frac{\partial}{\partial x_i} \left[D_{ij}(x) \left(\frac{\partial \psi}{\partial x_j} + \beta \psi \frac{\partial U}{\partial x_j} \right) \right], \tag{1}$$

where $U(x)$ is the potential energy, $\beta = 1/k_B T$ is the inverse of the temperature, and $D_{ij}(x)$ is the diffusion coefficient. It has been shown that $D_{ij}(x)$ is symmetric and positive definite, i.e.,

$$D_{ij}(x) = D_{ji}(x), \tag{2}$$

$$\sum_{i,j} D_{ij}(x)\xi_i\xi_j \geq 0 \qquad \text{for any real number} \quad \xi_i. \tag{3}$$

We assume that the molecule is eliminated from the system once it goes out from the box. Therefore ψ satisfies the following boundary condition

$$\psi(x) = 0 \qquad \text{at the hole.} \tag{4}$$

Here (and in the following) the "hole" means the hypersurface defining the boundary of the in-box region and out-of-box region in the phase space. Similarly, the "wall" of the box is the rest part of the boundary in the phase space.

On the other hand, since the molecule is confined by the wall of the box, ψ satisfies the reflective boundary condition at the wall

$$\sum_i n_i(x) J_i(x) = 0 \qquad \text{at the wall,} \tag{5}$$

where n_i is the unit vector normal to the wall pointing outward and $J_i(x)$ is the flux given by

$$J_i(x) = -\sum_j D_{ij}(x) \left(\frac{\partial \psi}{\partial x_j} + \beta\psi \frac{\partial U}{\partial x_j} \right). \tag{6}$$

We assume that the system is initially at equilibrium in the box with the hole closed. Hence $\psi(x,t)$ satisfies the initial condition, $\psi(x,0) = \psi_{eq}(x)$, where

$$\psi_{eq}(x) = \frac{\exp[-\beta U(x)]}{\int dx \exp[-\beta U(x)]}. \tag{7}$$

$\psi(x,t)$ is obtained by solving eq. (1) under the boundary conditions (4), (5), and the initial condition (7).

If $\psi(x,t)$ is obtained, the probability that the particle remains in the system at time t is calculated by

$$P(t) = \int dx \psi(x;t). \tag{8}$$

$P(t)$ is generally written as a sum of exponentially decaying functions. The escape rate we are discussing here is the smallest decay rate, i.e., the decay rate which determines the long time behavior.

Solution of the above initial value problem is formally obtained by the eigen-function expansion method. Let $\psi_n(x)$ and ϵ_n be the eigen-functions and the eigenvalues for the operator on the right hand side of eq.(1) subject to the boundary conditions (4) and (5), i.e.,

$$\sum_{i,j} \frac{\partial}{\partial x_i}\left[D_{ij}\left(\frac{\partial \psi_n}{\partial x_j} + \beta\psi_n \frac{\partial U}{\partial x_j}\right)\right] = -\epsilon_n \psi_n. \tag{9}$$

Using the property of (2) and (3), it can be shown that the eigenvalues are non-negative. We order them as

$$0 \le \epsilon_1 \le \epsilon_2 \le \epsilon_3 \le \cdots . \tag{10}$$

The solution of eq.(1) is written as

$$\psi(x,t) = \sum_{n=1}^{\infty} a_n \psi_n(x) e^{-\epsilon_n t}, \tag{11}$$

where a_n are constants determined by the initial condition.

For the solution (11), $P(t)$ is written as

$$P(t) = \sum_{n=1}^{\infty} b_n e^{-\epsilon_n t}, \tag{12}$$

where b_n are another constants.

It has been shown that if the hole is much smaller than the box size, only the first term, the term having the smallest eigenvalue matters, i.e., a_1 and b_1 are nearly equal to 1 and the rest terms are negligible[7] . Therefore the decay rate of $P(t)$ is given by the the smallest eigenvalue ϵ_1 for the eigenvalue equation (9). It has been shown that ϵ_1 is proportional to $1/V$, and the coefficient

$$k = \lim_{V\to\infty} \epsilon_1 V \tag{13}$$

depends on the molecule and the hole, but does not depend on the box shape. We shall call k intrinsic escape rate. The k corresponds to the first order reaction rate in the problem of diffusion controlled chemical reaction[7].

In the following, we write the probability distribution function as $\psi(x,t) = \chi(x,t)\psi_{eq}(x)$, and use the function $\chi(x,t)$ for our discussion. Rewriting eq.(1) to an equation for $\chi(x,t)$ is straightforward. The eigen-function $\chi_n(x)$ satisfies the following eigenvalue equation

$$\sum_{i,j} \frac{\partial}{\partial x_i}\left[\psi_{eq} D_{ij}\left(\frac{\partial \chi_n}{\partial x_j}\right)\right] = -\epsilon \psi_{eq} \chi_n. \tag{14}$$

The boundary condition for $\chi_n(x)$ is

$$\chi_n(x) = 0 \qquad \text{at the hole,} \tag{15}$$

$$\sum_i n_i D_{ij} \frac{\partial \chi_n}{\partial x_j} = 0 \qquad \text{at the wall.} \tag{16}$$

The above eigenvalue problem can be cast into a variational principle. Consider the functional $\tilde{I}[\chi(x)]$ defined by

$$\tilde{I}[\chi(x)] = \frac{\int dx \psi_{eq}(x) \sum_{i,j} D_{ij}(x) \frac{\partial \chi(x)}{\partial x_i} \frac{\partial \chi(x)}{\partial x_j}}{\int dx \psi_{eq}(x) \chi(x)^2}. \tag{17}$$

Then, it can be shown that the smallest eigen value ϵ_1 is equal to the minimum of the functional $\tilde{I}[\chi(x)]$ (see details in Appendix I.). In other word, the following inequality holds for any function that satisfies the the boundary conditions (15) and (16),

$$\epsilon_1 \leq \tilde{I}[\chi(x)] \qquad \text{or} \qquad k \leq V\tilde{I}[\chi(x)]. \tag{18}$$

Equation (18) indicates that the best estimate for the escape rate is given by the minimum of the functional $\tilde{I}[\chi(x)]$.

B. Escape rate in the limit of $V \to \infty$

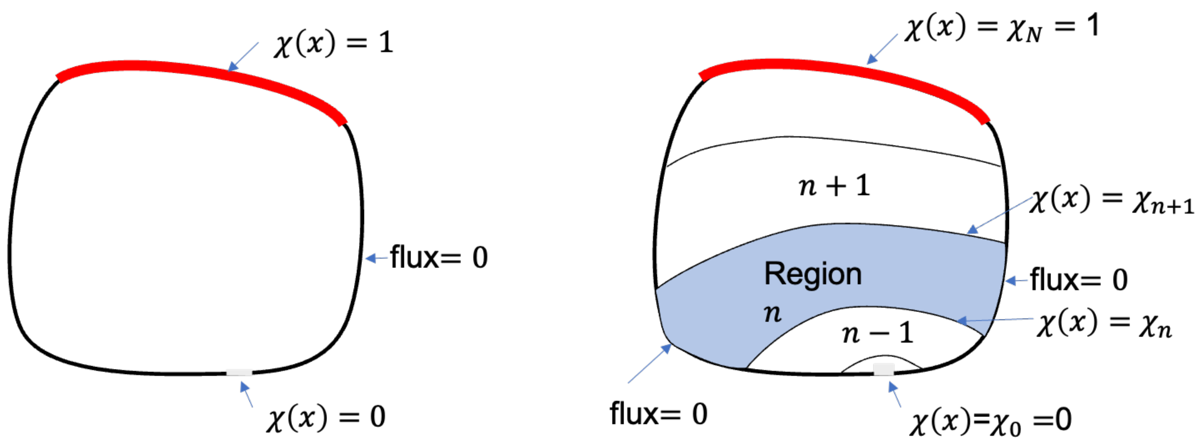
If the system size is much larger than the hole size, the above equations can be simplified. In this case, the distribution function $\psi(x,t)$ remains to be close to that of equilibrium $\psi_{eq}(x)$ in most part of the phase space, and $\psi(x,t)$ is different from $\psi_{eq}(x)$ only in the region near the hole (see Fig. 1 (c)). In other words, the function $\chi(x)$ which minimizes the functional $\tilde{I}[\chi(x)]$ is constant in most part of the system and becomes x dependent only in the region near the hole.

For such function, the denominator of eq. (17) is approximated as

$$\int dx \psi_{eq}(x) \chi(x)^2 \cong \int dx \psi_{eq}(x) \chi_\infty^2 = \chi_\infty^2, \tag{19}$$

where χ_∞ is the asymptotic value of $\chi(x)$ far from the hole. If we write $\chi(x)/\chi_\infty$ as a new function $\chi(x)$, then eq.(18) is written as

$$k \leq VI[\chi(x)], \tag{20}$$



(a) (b)

FIG. 2. (a) Boundary value problem to calculate the translocation rate. (b) The boundary condition we impose on $\chi(x)$ in the regional minimization method.

where

$$I[\chi(x)] = \int dx \psi_{eq}(x) \sum_{i,j} D_{ij}(x) \frac{\partial \chi}{\partial x_i} \frac{\partial \chi}{\partial x_j}, \tag{21}$$

and the function $\chi(x)$ satisfies the following conditions

$$\chi = 0 \qquad \text{at the hole,} \tag{22}$$

$$\sum_{i,j} n_i D_{ij} \frac{\partial \chi}{\partial x_j} = 0 \qquad \text{at the wall,} \tag{23}$$

$$\chi(x) \to 1 \qquad \text{far from the hole.} \tag{24}$$

Equation (21) leads to a variational method for a particle confined in a large space and escaping through a small hole. Notice that the extra condition eq.(24) is consistent with eq.(23) and that it does not affect the eigenvalues and the eigen functions. However, introducing such condition is convenient to see the relation of this variational principle with other type of variational principle.

C. Boundary value problem for the escape rate

The escape rate can be defined in other form. Since the eigen-function that gives the smallest eigenvalue is almost constant far from the hole, we may replace the boundary condition for the boundary located far from the hole. Consider the problem shown in

Fig. 2 (a), where the boundary condition at certain part of the wall, far from the hole, is replaced with the condition $\chi(x) = 1$. We shall call this part source boundary.

The boundary condition at the source boundary is an inhomogeneous condition, and cannot be used for the eigen value problem. However, we can use this boundary condition to determine the eigen function $\chi_1(x)$ that corresponds to the smallest eigenvalue. Since the smallest eigenvalue is written as $\epsilon_1 = k/V$, the equation to be satisfied by the eigen function $\chi_1(x)$ reduces to the following form in the limit of $V \to \infty$:

$$\sum_{i,j} \frac{\partial}{\partial x_i} \left(\psi_{eq} \sum_{i,j} D_{ij} \frac{\partial \chi}{\partial x_j} \right) = 0. \tag{25}$$

Equation (25) can be solved for $\chi(x)$ under the following boundary condition

$$\chi(x) = 0 \qquad \text{at the hole,} \tag{26}$$

$$\sum_{i,j} n_i D_{ij} \frac{\partial \chi}{\partial x_j} = 0 \qquad \text{at the wall,} \tag{27}$$

$$\chi(x) = 1 \qquad \text{at the source boundary.} \tag{28}$$

Let $\chi^*(x)$ be the solution of this equation. For such function, the functional $I[\chi^*(x)]$ is evaluated as

$$I[\chi^*(x)] = \int dx \sum_{i,j} \psi_{eq} D_{ij} \frac{\partial \chi^*}{\partial x_i} \frac{\partial \chi^*}{\partial x_j} \tag{29}$$

$$= \int_{hole} dS \chi^* \sum_{i,j} n_i D_{ij} \psi_{eq} \frac{\partial \chi^*}{\partial x_j} + \int_{source} dS \chi^* \sum_{i,j} n_i D_{ij} \psi_{eq} \frac{\partial \chi^*}{\partial x_j} \tag{30}$$

$$= \int_{source} dS \sum_{i,j} n_i D_{ij} \psi_{eq} \frac{\partial \chi^*}{\partial x_j} \tag{31}$$

$$= - \int_{hole} dS \sum_{i,j} n_i D_{ij} \psi_{eq} \frac{\partial \chi^*}{\partial x_j}, \tag{32}$$

where the second equation is derived by integration by part , the third equation is derived by eq.(26) and (28), and the last equation is derived by the condition of flux conservation.

Equation (31) clarifies the physical meaning of this formalism. Consider the steady state of a system in which particles are generated at the source boundary and eliminated at the hole boundary. In the steady state, $\chi(x)$ satisfies eq.(25). Equation (32) stands for the total outgoing flux at the hole, and it indicates that the flux is given by the escape rate (multiplied by the number density of particles which is $1/V$). In addition, the escape rate is inversely proportional to the mean first passage time (or the mean lifetime). This has been proven for general Markovian processes[11].

To summarize, the escape rate can be obtained by minimizing the functional $I[\chi(x)]$ for $\chi(x)$ that satisfies the boundary conditions (26)-(28). We have used a somewhat tortuous argument to arrive at this conclusion. The inequality (20) can be proven more straightforwardly for the function $\chi(x)$ which satisfies the boundary conditions (26)-(28).

D. Regional minimization method

The variational principle is useful for getting approximate solutions. Here we discuss a method which we will use in subsequent sections. The method is illustrated in Fig. 2 (b). Here we divide the phase space into sequential regions, region 0, region 1, region 2,..., region N, each of which consists of two boundaries with the neighboring regions, and wall boundary as it is shown in Fig. 2 (b). (The region 0 and the region N have the hole and the source boundary respectively.) We impose additional condition that $\chi(x)$ takes a constant value χ_n at the boundary between the region n and $n-1$. The advantage of this method is that the minimization can be done for each region independently of other regions. The functional $I[\chi(x)]$ is now written as

$$I[\chi(x)] = \sum_n I_n[\chi(x)] \tag{33}$$

with

$$I_n[\chi(x)] = \int_{Region\ n} dx \psi_{eq}(x) \sum_{i,j} D_{ij} \frac{\partial \chi}{\partial x_i} \frac{\partial \chi}{\partial x_j}, \tag{34}$$

where the integral is done only in the region n.

It is easy to confirm that the minimum value of $I_n[\chi(x)]$ depends on $\chi_n - \chi_{n-1}$ only and can be written as

$$\min(I_n) = K_n(\chi_n - \chi_{n-1})^2, \tag{35}$$

where K_n is the minimum of $I_n[\chi(x)]$ subject to the condition $\chi(x) = 1$ and $\chi(x) = 0$ at the two non-wall boundaries of region n.

From eqs.(33) and (35), the minimum of the functional $I[\chi(x)]$ is calculated as (see details in Appendix I)

$$\min(I[\chi(x)]) = \min_{\chi_1, \chi_2, \cdots \chi_{N-1}} \left(\sum_n K_n(\chi_n - \chi_{n-1})^2 \right) = \left(\sum_{n=1}^{N-1} \frac{1}{K_n} \right)^{-1}. \tag{36}$$

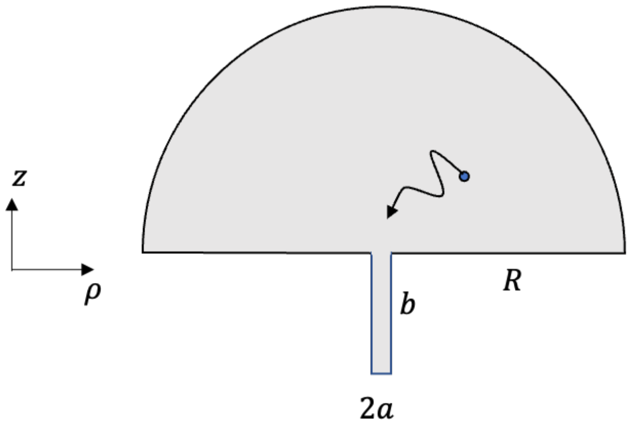


FIG. 3. The translocation rate of a particle through a hole which exists at the end of a cylindrical channels of radius a and length b. The particle is originally placed in the big chamber of radius R.

Hence the variational principle gives the following inequality for the intrinsic escape rate k:

$$k \le \frac{V}{\sum_{n=1}^{N-1} K_n^{-1}}. \tag{37}$$

We shall show the application of this method in the subsequent sections.

III. SIMPLE EXAMPLE: ESCAPE RATE OF A PARTICLE THROUGH A LONG CHANNEL

A. Escape by free diffusion

As an application of the above variational principle, we first consider the problem shown in Fig. 3. The particle is confined in a space made of large half sphere (of radius R) and a small cylinder (of radius a and length b) connected to the sphere at the center. The end of the cylinder is open, giving the hole in our problem.

Since the system has an axial symmetry, the particle position is represented by cylindrical coordinate (ρ, z), where the origin is taken as the center of the half sphere. The distance from the center is represented by $r = \sqrt{\rho^2 + z^2}$.

First we consider the case of $U(\rho, z) = 0$; there is no potential everywhere in the system. The diffusion equation (25) is then written as

$$D\nabla^2\chi = 0. \tag{38}$$

The boundary condition for $\chi(\rho, z)$ is

$$\chi(\rho, z) \rightarrow 1 \quad \text{for} \quad z > 0 \quad \text{and} \quad r \rightarrow \infty, \tag{39}$$

$$\chi(\rho, z) = 0 \quad \text{at} \quad z = -b, \tag{40}$$

$$\boldsymbol{n} \cdot \nabla\chi = 0. \quad \text{at the wall.} \tag{41}$$

We consider the problem by dividing the space into three regions,

Region 0: $\rho < a$ and $0 > z > -b$

Region 1: $r < a$ and $z > 0$

Region 2: $r > a$and $z > 0$

and assume that $\chi(\rho, z)$ is constant at the boundaries, equal to χ_1 and χ_2 at the boundary of region 0 and region 1, and that of region 1 and region 2 respectively.

The function which minimizes $I[\chi]$ for each region is the solution of eq. (38). In region 0, this is given by

$$\chi(\rho, z) = \chi_1 \left(1 + \frac{z}{b}\right). \tag{42}$$

In region 2, it is given by

$$\chi(\rho, z) = 1 - (1 - \chi_2)\frac{a}{r}. \tag{43}$$

The solution is not easy in region 1, but if we assume that $\chi_2 = \chi_1$, then the solution is easy, given by $\chi(\rho, z) = \chi_1$ in region 1. For such function, straightforward calculation gives

$$I = \frac{1}{V}\left[2\pi Da(1 - \chi_1)^2 + \frac{\pi a^2 D}{b}\chi_1^2\right], \tag{44}$$

where $V = (2\pi/3)R^3 + \pi a^2 b \approx (2\pi/3)R^3$ is the total volume of the system. Minimizing, eq. (44) with respect to χ_1, we finally obtain an upper bound for the intrinsic escape rate k:

$$k \leq V \min(I) = 2\pi Da\frac{a}{a + 2b}. \tag{45}$$

For the case of $b \gg a$, eq.(45) gives $k = \pi a^2/b$, which is exact. On the other hand, eq.(45) does not give the exact result for $b \rightarrow 0$. In the limit of $b \rightarrow 0$, the escape rate is given by the solution of the Laplace equation with the boundary condition $\chi(\rho, z) = 0$ on the disk placed at the bottom of the sphere. Such solution gives $k = 4aD$ for $b \rightarrow 0$. If we eliminate the region 1, and impose the condition $\chi(\rho, z) = \chi_1$ at $z = 0$, and use the exact solution for the Laplace equation of the disk boundary, we have

$$I = \frac{1}{V}\left[4Da(1 - \chi_1)^2 + \frac{\pi a^2 D}{b}\chi_1^2\right]. \tag{46}$$

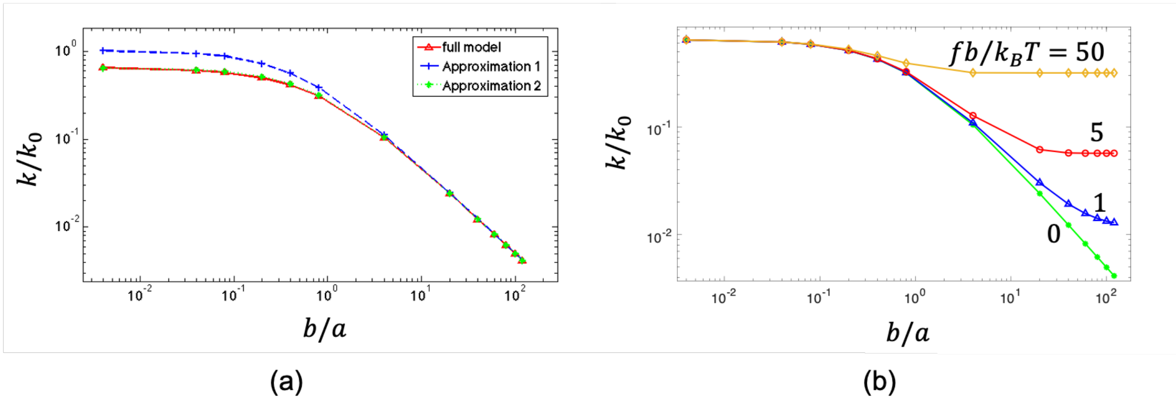


FIG. 4. (a) The translocation rate of a particle exiting at the end of a cylindrical well which has radius a and length b. The reference rate k_0 is defined by $4Da$ (b) Translocation rate for field driven particle: In the channel, the particles are driven by the potential $U(z) = fz$ for $-b < z < 0$.

Minimization of the right hand side gives the following intrinsic escape rate

$$k = 4aD\frac{a}{a + (4/\pi)b}. \tag{47}$$

This is exactly the formula (37) for the simple particle.

The escape rate of a Brownian particle has been studied extensively in literature (see Berezhkovskii *et al* (2009)[12] and the references therein). Equation (47) agrees with that given in[12] in the limit that the particle is confined in a volume V which is much larger than the volume of the passage $\pi a^2 b$.

Fig. 4 (a) compares the exact solution,which is obtained by the numerical solution of the original equation with eqs. (45) and (47). It is seen that eq.(47) gives quite accurate result for the escape rate.

B. Guided escape in the channel

So far, we have assumed $U(\rho, z) = 0$. We now discuss the effect of a potential field exerted on the particle in the cylinder. Suppose that the particle placed at z in the cylinder feels a potential field $U(z)$ for $-b \le z \le 0$. Then the function $\chi^*(z)$ which minimizes $I[\chi]$ for the cylinder region satisfies the following equation

$$\frac{\partial}{\partial z}\left(e^{-\beta U}\frac{\partial \chi^*}{\partial z}\right) = 0, \tag{48}$$

and the boundary conditions, $\chi^*(z) = 0$ at $z = -b$ and $\chi^*(z) = \chi_1$ at $z = 0$. The solution of this equation gives the following minimum for $I[\chi]$ for the cylinder region,

$$\min I_{cyinder} = \frac{\chi_1^2 D\pi a^2}{V \int_{-b}^{0} dz e^{\beta U(z)}}. \tag{49}$$

This gives the following intrinsic escape rate.

$$k = 4aD \left[1 + \frac{1}{4\pi a}\int_{-b}^{0} dz e^{\beta U(z)}\right]^{-1}. \tag{50}$$

If the particle in the cylinder feels a constant force f which guides the particle to the exit, the potential force is written as $U(z) = fz$. Fig. 4 (b) shows the intrinsic escape rate in such situation. In the presence of such guiding force, the escape rate naturally increases with f, and becomes independent of the force f and the length b of the channel. This is because the escape rate is now governed by the diffusion outside of the cylinder.

IV. ESCAPE RATE OF A ROD THROUGH A HOLE

A. Diffusion equation

We now consider the system shown in Fig. 1 (a); a rod-like polymer is confined in a space of volume V and escapes from the confinement through a hole of radius a. The length of the rod L is much larger than a. The diameter of the rod is assumed to be much smaller than a, and is ignored in the following analysis.

The state of the rod is characterized by two vectors, $\boldsymbol{r}$, the position vector of the rod center relative to the hole center, and $\boldsymbol{u}$, the unit vector parallel to the rod (see Fig. 5 (a)). Since the rod has no polarity, the state $(\boldsymbol{r}, \boldsymbol{u})$ and the state $(\boldsymbol{r}, -\boldsymbol{u})$ are equivalent. Therefore, the state of the rod is described by vector $\boldsymbol{r}$ which is in the volume V and the unit vector $\boldsymbol{u}$ which is on the surface of the half sphere of $|\boldsymbol{u}| = 1$ and $u_z \geq 0$.

The rod starts to enter the hole when the bottom end of the rod is in the hole.

$$r_z - \frac{L}{2}u_z = 0 \qquad \text{and} \qquad [r_x - \frac{L}{2}u_x]^2 + [r_y - \frac{L}{2}u_y]^2 \leq a^2. \tag{51}$$

On the other hand, the rod escapes from the hole when the top end comes to the hole, i.e.,

$$r_z + \frac{L}{2}u_z = 0 \qquad \text{and} \qquad [r_x + \frac{L}{2}u_x)]^2 + [r_y + \frac{L}{2}u_y]^2 \leq a^2, \tag{52}$$

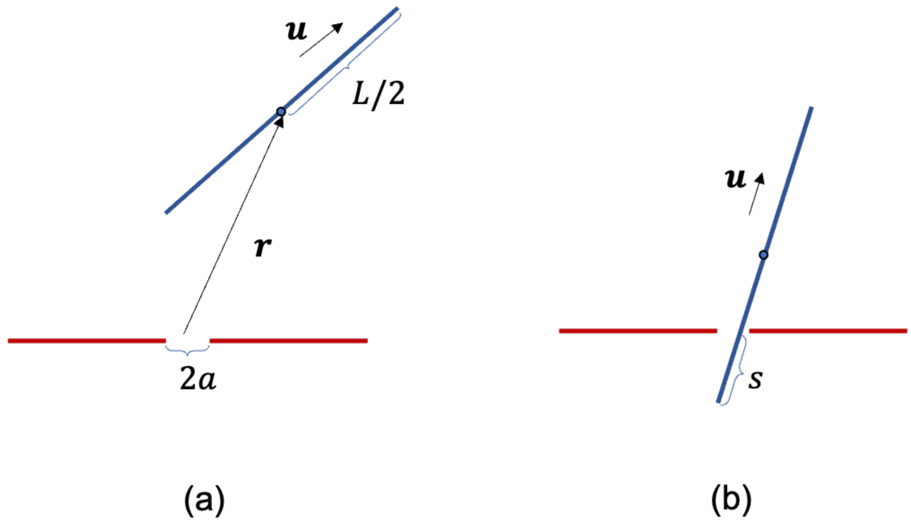


FIG. 5. (a) Rod-like polymer in the free state. (b) Rod-like polymer in the captured state.

Equation (52) defines the hole hyper surface in the phase space $(\boldsymbol{r}, \boldsymbol{u})$.

The Brownian motion of rod includes translational diffusion (stochastic motion of $\boldsymbol{r}$), and rotational diffusion (stochastic motion of $\boldsymbol{u}$), each characterized by the translational diffusion constant D_t and the rotational diffusion constant D_r. Strictly speaking, the translational diffusion constant is a tensorial quantity, and depends on the distance from the wall if the rod is located near the wall[6]. However, here, we assume that D_t and D_r are constants independent of $\boldsymbol{r}$ and $\boldsymbol{u}$.

Under such assumption, the diffusion equation for the probability distribution function $\psi(\boldsymbol{r}, \boldsymbol{u}, t)$ is written as

$$\frac{\partial \psi}{\partial t} = D_t \nabla \cdot \left[\nabla \psi + \beta \psi \nabla U \right] + D_r \mathcal{R} \cdot \left[\mathcal{R} \psi + \beta \psi \mathcal{R} U \right], \tag{53}$$

where ∇ and $\mathcal{R}$ are defined by

$$\nabla = \frac{\partial}{\partial \boldsymbol{r}}, \qquad \mathcal{R} = \boldsymbol{u} \times \frac{\partial}{\partial \boldsymbol{u}}, \tag{54}$$

and U is the potential energy representing the constraint imposed by the wall.

In the steady state, the distribution function is written as $\psi(\boldsymbol{r}, \boldsymbol{u}) = \psi_{eq}(\boldsymbol{r}, \boldsymbol{u}) \chi(\boldsymbol{r}, \boldsymbol{u})$, where $\chi(\boldsymbol{r}, \boldsymbol{u})$ satisfies

$$D_t \nabla \left[\psi_{eq} \cdot \nabla \chi \right] + D_r \mathcal{R} \left[\psi_{eq} \cdot \mathcal{R} \chi \right] = 0. \tag{55}$$

Equation (55) is obtained from the minimum condition of the following functional

$$I[\chi(\boldsymbol{r}, \boldsymbol{u}] = \int d\boldsymbol{r} d\boldsymbol{u} \psi_{eq} \left[D_t (\nabla \chi)^2 + D_r (\mathcal{R} \chi)^2 \right]. \tag{56}$$

The minimum value of this functional gives the escape rate.

To minimize the functional, we use the regional minimization method. We divide the phase space into two regions, the captured region and the free region. In the captured region, the rod is penetrating the hole and the motion is essentially a one-dimensional diffusion along itself (Fig. 5 (b)). In the free region, the rod is not constrained by the hole and its motion is essentially a free diffusion in 3D space (Fig. 5 (a)). The boundary between the two regions is given by eq. (51). In the following we will first calculate the minimum of the functional $I[\chi(\boldsymbol{r}, \boldsymbol{u}]$ for each region.

B. Captured region

In the captured region, the escape rate is governed by the one-dimensional diffusion of the rod along itself. To describe such motion, we introduce the coordinate s defined in Fig. 5 (b): s denotes the length between the rod end and the hole. We assume that the function $\chi(\boldsymbol{r}, \boldsymbol{u})$ in the steady state depends on s only. Then the functional to be minimized is written as

$$I[\chi(s)] = D_t \int_0^L ds \tilde{\psi}_{eq}(s) \left(\frac{\partial \chi}{\partial s} \right)^2, \tag{57}$$

where $\tilde{\psi}_{eq}(s)$ is the equilibrium distribution function for s. Notice $\tilde{\psi}_{eq}(s)$ is not constant, since thermal rotation of the rod tends to push s to the end, and $\tilde{\psi}_{eq}(s)$ takes minimum at $s = L/2$. In Appendix I, it is shown $\tilde{\psi}_{eq}(s)$ is given by

$$\tilde{\psi}_{eq}(s) \propto \left[1 + 12 \left(\frac{s}{L} - \frac{1}{2} \right)^2 \right], \tag{58}$$

The functional in eq.(57) is minimized by $\chi(s)$ which satisfies

$$\frac{\partial}{\partial s} \left(\tilde{\psi}_{eq}(s) \frac{\partial \chi(s)}{\partial s} \right) = 0. \tag{59}$$

Solving (59) under the boundary condition $\chi(0) = 0$ and $\chi(L) = 1$, we have

$$K_{captured} = \frac{1}{V} \frac{3\sqrt{3}a}{2L} a D_t. \tag{60}$$

If the rod is confined by a tube of radius a, its rotational motion is prohibited, and the equilibrium distribution becomes independent of s. In this case, $K_{captured}$ is given by $\pi D a^2/VL$ (see eq.(44)). $K_{captured}$ of eq. (60) is smaller than this by factor $3\sqrt{3}/2\pi = 0.82\cdots$. This is because the rotational motion of a rod captured by a hole creates an energy barrier for the rod to pass through the hole.

C. Free region

To calculate the escape rate K_{free} in the free region, we have to minimize the functional $I[\chi]$ defined by eq. (56) subject to the constraint that $\chi(\boldsymbol{r},\boldsymbol{u})$ becomes zero at the hyper surface defined by eq. (51). As a function satisfying this boundary condition, we choose the following;

$$\chi(\boldsymbol{r},\boldsymbol{u}) = \alpha_1 f(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a) + (1-\alpha_1) f(\boldsymbol{r}; \frac{L}{2} + a), \tag{61}$$

where the function $f(\boldsymbol{r};a)$ is defined by

$$f(\boldsymbol{r};a) = (1 - \frac{a}{|\boldsymbol{r}|})\Theta(|\boldsymbol{r}| - a). \tag{62}$$

and $\Theta(x)$ is the step function ($\Theta(x) = 0$ if $x < 0$, and $\Theta(x) = 1$ if $x > 0$).

The function $f(\boldsymbol{r};a)$ takes the value 0 if $|\boldsymbol{r}|$ is less than a, and gradually increases with $|\boldsymbol{r}|$ approaching to 1 as $|\boldsymbol{r}| \to \infty$. One can check that $\chi(\boldsymbol{r},\boldsymbol{u})$ defined by eq. (62) satisfies the conditions that it takes 0 at the hypersurface of eq. (51), and approaches to 1 far from the surface.

The equilibrium distribution function is given by

$$\psi_{eq}(\boldsymbol{r},\boldsymbol{u}) = \frac{1}{2\pi V}\Theta(r_z - \frac{L}{2}u_z). \tag{63}$$

The function $\Theta(r_z - \frac{L}{2}u_z)$ represents the condition that the rod cannot penetrate the wall.

If eq. (61) is used for eq. (56), $I[\chi]$ can be expressed as a quadratic function of α_1. All coefficients are calculated analytically as it is described in Appendix II. Once such quadratic function is obtained, the minimization is easy, and the minimum value of $I_{free}[\chi(x)]$ is obtained as (see Appendix II)

$$K_{free} = \frac{2\pi D_t a}{V}\frac{1 + \frac{L^2 D_r}{6D_t}}{1 + \frac{4aLD_r}{9D_t}}. \tag{64}$$

Equation (64) gives the rate at which either end of the rod touch upon the hole. We now discuss the physical implication of this equation.

If $D_r = 0$, i.e., if the rotational motion is frozen, the rod end does simple Brownian motion with diffusion constant D_t. Therefore K_{free} must be equal to that of free particle, i.e., $4aD_t/V$ (see eq. (47)). According to eq. (64), K_{free} approaches to $2\pi a D_t/V$ for $D_r \to 0$. The two results agree with each other apart from the numerical factor.

With the increase of the rotational diffusion constant, the rate K_{free} will increase, but should remain finite since the translational diffusion constant D_t is finite. Indeed eq. (64) indicates that K_{free} approaches to $(3\pi/4)D_tL/V$ for $D_r \to \infty$. Notice that the rate is not proportional to a, but is proportional to L. This is because in the limit of $D_r \to \infty$, the rod end hits on the hole as soon as the rod center comes within the distance $(L/2)$ from the hole.

Therefore eq (64) is giving correct asymptotic behavior of K_{free} in the two limits of $D_r \to 0$ and $D_r \to \infty$, and is expected to be a good approximation for the entire value of D_rL^2/D_t.

The above discussion is for the hypothetical situation that D_r and D_t can take any value. In reality, D_r and D_t are determined by hydrodynamic friction, and it is known that D_rL^2/D_t is of the order of 1. Since L/a is much larger than 1, eq. (64) is simplified as

$$K_{free} = \frac{\nu D_t a}{V}, \tag{65}$$

where ν is a constant given by by

$$\nu = 2\pi(1 + \frac{D_r L^2}{6D_t}). \tag{66}$$

D. Escape rate

Given the rate for each region, K_{free} and $K_{captured}$, the escape rate k for the whole system is calculated by eq. (37):

$$k = V\frac{K_{free}K_{captured}}{K_{free} + K_{captured}}, \tag{67}$$

For $L \gg a$, $K_{captured} \ll K_{free}$. Therefore the escape rate is given by

$$k = VK_{captured} = \frac{3\sqrt{3}a}{2L}aD_t. \tag{68}$$

Therefore, the escape rate is essentially determined by the process in which the rod passes through the hole.

Similar analysis may be conducted for flexible polymers, but becomes more complex. Flexible polymers have much larger degrees of freedom, and requires the analysis in high dimension. However, we can still divide the whole process into the free stage in the bulk and the captured stage constrained by the hole. From the above analysis, we expect that the overall process is governed by the captured stage, and the escape rate is estimated to be given by a^2D/LV. However, it is difficult to get precise form for the escape rate of flexible polymers, and one might use other methods which have been developed significantly in recent years[13].

V. SUMMARY

We have shown a variational principle to calculate the escape rate, or more generally the diffusion-limited rate, of polymers and colloids doing Brownian motion in multi-dimensional phase space. The variational principle is derived for the eigenvalue problem and for the boundary value problem. They give the same answer for the molecule escaping from a region of infinitely large volume thorough a narrow channel. We have demonstrated the usefulness of the regional minimization method, where we divide the whole process as a sequence of sub processes each representing the diffusion from one hyper-surface to another hyper-surface. The analysis of the sub process can be done separately, and the escape rate for the whole process can be calculated by combining such analyses. As an example, the escape rate of a rod like molecule escaping from a hole is calculated by this method.

APPENDIX I: DERIVATIONS OF SOME EQUATIONS

Derivation of eq.(17). We show that the smallest eigenvlaue of eq. (14) corresponds to the global minimimumof (17). Firstly, it is easy to see that minimizing the functional of (17) is equivalent to minimize the functional

$$I[\chi(x)] = \int dx \psi_{eq}(x) \sum_{i,j} D_{ij}(x) \frac{\partial \chi(x)}{\partial x_i} \frac{\partial \chi(x)}{\partial x_j}$$

subject to the condition $\int dx \psi_{eq}(x) \chi(x)^2 = 1$.

By introducing a Lagrangian multiplier ϵ, the minimizer of the above problem corresponds to the Euler-Lagrange equation of the augmented Lagrangian,

$$\mathcal{L}(\chi, \epsilon) = \int dx \psi_{eq}(x) \sum_{i,j} D_{ij}(x) \frac{\partial \chi(x)}{\partial x_i} \frac{\partial \chi(x)}{\partial x_j} - \epsilon \Big(\int dx \psi_{eq}(x) \chi(x)^2 - 1 \Big).$$

The Euler-Lagrange equation reads

$$\int dx\psi_{eq}(x)\sum_{i,j} D_{ij}(x)\frac{\partial\chi(x)}{\partial x_i}\frac{\partial\tilde{\chi}(x)}{\partial x_j} = \epsilon\int dx\psi_{eq}(x)\chi(x)\tilde{\chi}(x), \qquad \forall\tilde{\chi},$$
$$\int dx\psi_{eq}(x)\chi(x)^2 = 1. \tag{69}$$

By integration by part, this gives immediately the eigenvalue problem (14) with normalized eigen functions. Let χ^* be the eigenfunction corresponding to the smallest ϵ. Then the pair (χ^*, ϵ) solve the above equation. By setting χ and $\tilde{\chi}$ to be χ^* in equ. (69), we can see that ϵ is the minimal value of the functional $I[\chi]$.

Derivation of eq.(36). We compute the minimum of $f(\chi_1, \chi_2, ...\chi_{N-1}) = (\sum_n K_n(\chi_n - \chi_{n-1})^2)$ with respect to $\chi_2, \chi_3, ...\chi_{N-1}$. The condition $\partial f/\partial\chi_i = 0$ gives

$$K_i(\chi_i - \chi_{i-1}) = K_{i+1}(\chi_{i+1} - \chi_i), \qquad i = 2, \cdots, N-1$$

Hence $(\chi_i - \chi_{i-1}) = const/K_i$. The constant is determined by the condition $\chi_0 = 0$ and $\chi_N = 1$. This gives eq. (36).

Derivation of eq.(58). Consider a rod of length L, confined by a hole at a point separated from the end by s and $L - s$, and rotating with an angular velocity ω. The kinetic energy of the rod is written as

$$K(s) = \frac{1}{2}J(s)\omega^2 \tag{70}$$

where $J(s)$ is a moment of the inertia, which depends on s, and is given by

$$J(s) = J_0\left[1 + 12\left(\frac{s}{L} - \frac{1}{2}\right)^2\right], \tag{71}$$

where J_0 is the moment of inertia when $s = L/2$. The equilibrium probability $\psi_{eq}(s)$ for s is proportional to the integral of the Boltzmann factor $\exp(-K(s)/k_BT)$ with respect to the angular momentum $\boldsymbol{L} = J(s)\omega$, i.e.,

$$\psi_{eq}(s) \propto \int d\boldsymbol{L}\exp(-K(s)/k_BT) = \int d\boldsymbol{L}\exp(-\boldsymbol{L}^2/2J(s)k_BT). \tag{72}$$

Conducting the integration for $\boldsymbol{L}$ over the 2D plane normal to $\boldsymbol{u}$, we have eq.(58)

Derivation of eq. (60). Assume that the volume of the cavity V is much larger than $\pi a^2 L$. In the captured region, we have the relation $\int_0^L \tilde{\psi}_{eq}(s)ds \approx \frac{\pi a^2 L}{V}$. Using eq.(58), we derive

$$\tilde{\psi}_{eq} = \frac{\pi a^2}{2V}\left[1 + 12\left(\frac{s}{L} - \frac{1}{2}\right)^2\right].$$

By eq. (59) and using the boundary condition for $\chi(s)$, we have

$$\frac{\partial \chi(s)}{\partial s} = \frac{c_0}{\tilde{\psi}_{eq}(s)},$$

with

$$c_0 = \left[\int_0^L \frac{1}{\tilde{\psi}_{eq}(s)} ds\right]^{-1} \approx \frac{3\sqrt{3}a^2}{2VL}, \qquad \text{for} \quad L \gg a.$$

Using eq. (57), we get the minimum value of $I(\chi)$ as

$$K_{captured} = D_t \int_0^L ds \tilde{\psi}_{eq}(s) \left(\frac{\partial \chi}{\partial s}\right)^2 = D_t \int_0^L ds \frac{c_0^2}{\tilde{\psi}_{eq}(s)} = D_t c_0.$$

This leads to eq. (60).

APPENDIX II: CALCULATIONS FOR THE MOTION OF A ROD IN A CAVITY

Using eq.(61) for eq.(56), we have

$$\begin{aligned}
& I[\chi(\boldsymbol{r}, \boldsymbol{u})] \\
=& D_t \int d\boldsymbol{r} d\boldsymbol{u} \psi_{eq} \left[\alpha_1^2 \boldsymbol{f}'^2(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a) + \alpha_2^2 \boldsymbol{f}'^2(\boldsymbol{r}; \frac{L}{2} + a) + 2\alpha_1\alpha_2 \boldsymbol{f}'(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a) \cdot \boldsymbol{f}'(\boldsymbol{r}; \frac{L}{2} + a)\right] \\
& + D_r \int d\boldsymbol{r} d\boldsymbol{u} \psi_{eq} (\frac{\alpha_1 L}{2})^2 \boldsymbol{f}'(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a) \cdot (\boldsymbol{I} - \boldsymbol{u}\boldsymbol{u}) \boldsymbol{f}'(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a).
\end{aligned} \tag{73}$$

where

$$\mathbf{f}'(\mathbf{r}; a) = \frac{\partial f}{\partial \mathbf{r}} = \frac{a}{|\mathbf{r}|^2} \frac{\mathbf{r}}{|\mathbf{r}|} \Theta(|\mathbf{r}| - a), \tag{74}$$

We compute the integral term by term as follows.

The first term is

$$\begin{aligned}
& \int d\boldsymbol{r} d\boldsymbol{u} \psi_{eq} \boldsymbol{f}'^2(\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}; a) \\
=& \frac{1}{4\pi} \int d\boldsymbol{r} d\boldsymbol{u} \Theta(r_z - \frac{L|u_z|}{2}) \frac{a^2}{|\boldsymbol{r} - \boldsymbol{u}L/2|^4} \Theta(|\boldsymbol{r} - \frac{\boldsymbol{u}L}{2}| - a) \\
\approx& \frac{1}{4\pi} \int d\boldsymbol{R} d\boldsymbol{u} \Theta(R_z) \frac{a^2}{|\boldsymbol{R}|^4} \Theta(|\boldsymbol{R}| - a) = \int_a^\infty dR \frac{a^4}{|R|^4} 2\pi R^2 = 2\pi a.
\end{aligned}$$

In the following calculation, we will use the equation

$$\int d\boldsymbol{u} \Theta(r_z - \frac{L|u_z|}{2}) = \begin{cases} 8\pi \frac{r_z}{L}, & \text{if } r_z < L/2; \\ 4\pi & \text{if } r_z > L/2; \end{cases} \tag{75}$$

The second term is calculated as

$$
\begin{aligned}
&\int d\boldsymbol{r}d\boldsymbol{u}\psi_{eq}\boldsymbol{f}'^2(\boldsymbol{r};\frac{L}{2}+a)\\
=&\frac{1}{4\pi}\int d\boldsymbol{r}d\boldsymbol{u}\Theta(r_z-\frac{L|u_z|}{2})\frac{(L/2+a)^2}{|\boldsymbol{r}|^4}\Theta(|\boldsymbol{r}|-\frac{L}{2}-a)\\
=&\frac{1}{4\pi}\int d\boldsymbol{r}[\int d\boldsymbol{u}\Theta(r_z-\frac{L|u_z|}{2})]\frac{(L/2+a)^2}{|\boldsymbol{r}|^4}\Theta(|\boldsymbol{r}|-\frac{L}{2}-a)\\
=&\int_{\{|\boldsymbol{r}|>\frac{L}{2}+a,r_z>0\}}d\boldsymbol{r}\frac{(L/2+a)^2}{|\boldsymbol{r}|^4}-\int_{\{|\boldsymbol{r}|>\frac{L}{2}+a,0<r_z<\frac{L}{2}\}}d\boldsymbol{r}(1-\frac{2r_z}{L})\frac{(L/2+a)^2}{|\boldsymbol{r}|^4}\\
\approx&\pi L-\frac{\pi L}{4}=\frac{3}{4}\pi L.
\end{aligned}
$$

The third term is

$$
\begin{aligned}
&\int d\boldsymbol{r}\boldsymbol{f}'(\boldsymbol{r}-\frac{\boldsymbol{u}L}{2};a)\cdot\boldsymbol{f}'(\boldsymbol{r};\frac{L}{2}+a)\\
=&\frac{1}{4\pi}\int d\boldsymbol{r}d\boldsymbol{u}\Theta(r_z-\frac{L|u_z|}{2})\frac{a(a+\frac{L}{2})(\boldsymbol{r}-\frac{\boldsymbol{u}L}{2})\cdot\boldsymbol{r}}{|\boldsymbol{r}-\boldsymbol{u}L/2|^3|\boldsymbol{r}|^3}\Theta(|\boldsymbol{r}|-\frac{L}{2}-a)\Theta(|\boldsymbol{r}-\frac{\boldsymbol{u}L}{2}|-a)\\
=&\frac{a(a+L/2)}{4\pi}\int d\boldsymbol{r}\frac{1}{|\boldsymbol{r}|^2}\Theta(|\boldsymbol{r}|-\frac{L}{2}-a)\Theta(r_z)\left[\int d\boldsymbol{u}\frac{(\boldsymbol{r}-\boldsymbol{u}L/e)\cdot\boldsymbol{r}}{|\boldsymbol{r}-\boldsymbol{u}L/2|^3|\boldsymbol{r}|}\Theta(r_z-\frac{L|u_z|}{2})\right]\\
=&\frac{a(a+L/2)}{4\pi}\int d\boldsymbol{r}\frac{1}{|\boldsymbol{r}|^2}\Theta(|\boldsymbol{r}|-\frac{L}{2}-a)\Theta(r_z)\frac{4\pi}{|r|^2}\left[1-\frac{\sqrt{L^2/4-r_z^2}}{L/2}\Theta(\frac{L}{2}-r_z)\right]\\
=&a(a+\frac{L}{2})\left[\int_{\frac{L}{2}+a}^{\infty}dr\frac{1}{r^4}2\pi r^2-\int_0^{\frac{L}{2}}dr_z\frac{\sqrt{L^2/4-r_z^2}}{L/2}\int_{\sqrt{(a+\frac{L}{2})^2-r_z}}^{\infty}\frac{1}{(\hat{r}^2+r_z^2)^2}(2\pi\hat{r})d\hat{r}\right]\\
\approx&2\pi a(1-\frac{\sqrt{2}+\ln(1+\sqrt{2})}{4}).
\end{aligned}
$$

The fourth term is calculated as

$$
\begin{aligned}
&\int d\boldsymbol{r}d\boldsymbol{u}\psi_{eq}\boldsymbol{f}'(\boldsymbol{r}-\frac{\boldsymbol{u}L}{2};a)\cdot(\boldsymbol{I}-\boldsymbol{u}\boldsymbol{u})\cdot\boldsymbol{f}'(\boldsymbol{r}-\frac{\boldsymbol{u}L}{2};a)\\
=&\frac{1}{4\pi}\int d\boldsymbol{R}d\boldsymbol{u}\Theta(R_z)\boldsymbol{f}'(\boldsymbol{R};a)\cdot(\boldsymbol{I}-\boldsymbol{u}\boldsymbol{u})\cdot\boldsymbol{f}'(\boldsymbol{R};a)\\
=&\frac{1}{4\pi}\int d\boldsymbol{R}\Theta(R_z)\boldsymbol{f}'(\boldsymbol{R};a)\cdot\Big[\int(\boldsymbol{I}-\boldsymbol{u}\boldsymbol{u})d\boldsymbol{u}\Big]\boldsymbol{f}'(\boldsymbol{R};a)\\
=&\frac{2}{3}\int d\boldsymbol{R}\Theta(R_z)\frac{a^2}{|\boldsymbol{R}|^4}\Theta(|\boldsymbol{R}|-a)=\frac{4\pi a}{3}.
\end{aligned}
$$

By combining these terms, we have

$$
I[\chi(\boldsymbol{r},\boldsymbol{u}]=D_t\left[2\pi a\alpha_1^2+\frac{3}{4}\pi L\alpha_2^2+4\pi a(1-\frac{\sqrt{2}+\ln(1+\sqrt{2})}{4})\alpha_1\alpha_2\right]+\frac{\pi aL^2}{3}D_r\alpha_1^2.
$$

Using $\alpha_2 = 1 - \alpha_1$, we minimize this equation with respect to α_1, and get the following expression for the minimum value of $I[\chi]$

$$K_{free} = \min(I[\chi]) = \frac{2\pi D_t a}{V} \frac{(1 + \frac{D_r L^2}{6D_t})\frac{3L}{8a} \underline{-(1 - \frac{\sqrt{2}+\ln(1+\sqrt{2})}{4})^2}}{\frac{D_r L^2}{6D_t} + \frac{3L}{8a} \underline{+ \frac{(\sqrt{2}+\ln(1+\sqrt{2}))}{2} - 1}}.$$

Since we are considering the case of $L/a \gg 1$, the underlined part can be ignored, and we finally get eq. (64).

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