# NARROW ESCAPE TIME IN BIOLOGY

by

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# ABSTRACT

## NARROW ESCAPE TIME IN BIOLOGY

In biological systems, the main challenges in modeling transport processes can be summarized as being inside a heterogeneous medium, which is a fluctuating environment, and striving to reach to a chemically active receptor, which acts like an absorbing boundary while the other organelles of the interior of a living cell acting like active obstacles. These are very complex problems in general. The only viable approach known is to develop some stochastic models to take into account these aspects. A continuous random process, mostly Brownian motion, is commonly used to model the motion of chemicals in the intracellular transport. In certain cases, these chemicals display Brownian motion on the 2D surface of the cell. Therefore, the first passage time of such chemicals is the main determining mechanism for triggering critical biological processes.This requires studying a stochastic process on a two-dimensional surface which is topologically a sphere with small disks on them. These small disk like regions represent absorbing boundaries corresponding to the receptors. Some studies show that the calculated first passage times for such environments grow with the logarithm of the size of the disk like regions. In some cases, this time scale can be very long compared to the motion of the cell in its environment. For the dynamical model where the surface is fluctuating slowly as the particle executes Brownian motion on this surface, we can make use of a stochastic process with a variable background metric. Since the variations of the metric are slow we may use an adiabatic approximation. We analyze the variation of first passage times within this dynamical model.

# ÖZET

## MOLEKÜLÜN RESEPTÖRE İLK KEZ GELME ANININ HESAPLANMASI

Biyolojik sistemlerde hücre içi molekül geçişlerinin modellenmesindeki temel sorunların başında hücre içinin heterojen yapıda olmasıdır ki bu durum hücre içinin daha değişken bir yapıda olmasına neden olmaktadır. Diğer bir parametre ise molekül kimyasal olarak aktif bir reseptöre ulaşmaya çalışır ki bu durumda da reseptör molekülü emen bir yüzey olarak işlev görür. Bu süreç içerisinde hücre içindeki diğer organeller aktif bariyer olarak düşünülebilir. Bunlar oldukça karmaşık problemlerdir. Tüm bu parametreleri hesaba kattığımızda bunların çözümü için kullanacağımız en güvenilir yol stochastic modeller geliştirmektir. Sürekli random olarak gelişen süreçlerde, kimyasal moleküllerin hücre içi geçişlerinin modellenmesinde genel olarak Brownian hareketi kullanılır. Bazı özel durumlarda, kimyasal moleküller hücre yüzeyi üzerinde iki boyutlu Brownian hareketi yapmaktadır. Bu nedenle biyolojik süreçlerin takibinde moleküllerin ilk geçiş ya da varış anının hesaplanması temel mekanizmadır. Bu durum stochastic süreçlerin iki boyutlu yüzeyler üzerinde çalışılmasını gerektirmektedir. Bu iki boyutlu yüzeyler topolojik olarak üzerinde küçük diskler barındıran daire olarak düşünülebilir. Bu küçük disk yüzeyler emici yüzeyler yani reseptörler olarak işlev görür. Bazı çalışmalar göstermiştir ki hesaplanan ilk geçiş anı diske benzeyen alanların boyutlarının logaritmik değişimi ile büyümektedir. Bazı durumlarda hücrenin hareketi düşünüldüğünde zaman oldukça uzun olabiliyor. Dinamik modeller için ki burada yüzey yavaşça dalgalanmaktadır molekülümüz yüzey üzerinde Brownian hareketi yapmaktadır ve burada biz daha değişken bir metric kullanabiliriz. Metric değişimi oldukça yavaş olduğundan adiabatic yaklaşımı kullanarak biz bu çalışmamızda dinamik modellerde ilk geçiş anını hesapladık.

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# LIST OF SYMBOLS

| | |
|---|---|
| $b(x)$ | The boundary impedance |
| $C(N)$ | A set of numbers |
| $D$ | Diffusion coefficient |
| $G(z;\vec{x},\vec{y})$ | Generating function |
| $k$ | Killing rate |
| $N(x,\xi)$ | The Neuman function |
| $S(t)$ | The survival probability |
| $T(y)$ | The stochastic time |
| $U(x)$ | Potential equation |
| $u_0(x)$ | Eigenfunction |
| $X(t)$ | Position of the particle |
| $\gamma$ | The viscosity parameter |
| $\xi(t)$ | Gaussian noise |
| $\lambda_0^g$ | Eigenvalue |
| $\varrho(x)$ | Weight function |
| $\tau(x)$ | Narrow escape time |
| $\tau^a$ | The fist time that the targeted molecule reaches the absorbing boundary alive |
| $\tau^k$ | The first time that the targeted molecule is killed before it arrives the absorbing boundary |
| $\tau_D$ | The diffusion time scale |
| $\tau_G$ | The geometric evolution time scale |
| $\tau_{MFPT}$ | The mean first passage time scale |
| $\phi$ | The transition probability |
| $\chi(k)$ | The structure function of the lattice |
| $\Omega$ | Domain |

| | |
|---|---|
| $\partial\Omega_a$ | Absorbing part of the boundary |
| $\partial\Omega_r$ | Reflecting part of the boundary |

# LIST OF ACRONYMS/ABBREVIATIONS

| | |
|---|---|
| FP | Fokker Planck Equation |
| FPT | First Passage Time |
| MFPT | Mean First Passage Time |
| NEP | Narrow Escape Problem |
| NET | Narrow Escape Time |
| ODE | Ordinary Differential Equation |
| SPDF | Survival Probability Density Function |
| 1D | One Dimensional |

# 1. INTRODUCTION

The efficient delivery of proteins and other molecules to their correct location within a cell plays a fundamental role in normal cellular function and development [1]. Furthermore, the failure in intracellular transport leads to serious degenerative diseases. In particular, the breakdown of intracellular transport is especially acute for brain cells, neurons, which are the most complex and the largest cells in the body. In general, the regulation of protein trafficking within neurons is of essential importance to control the intensity of synaptic connections between neurons [3]. For instance, synapses can be strengthen or weaken over time and this ability of synapses in neuroscience is called as synaptic plasticity. The increase or decrease in the activities of synapses and the alteration of the distribution of neurotransmitter receptors are some of the factors which lead to the synaptic plasticity. On the other hand, it is thought that the permanent changes in synapses affects recording information. Hence the synaptic plasticity is central to understanding the mechanisms of learning and memory. As a result, degeneracy of this structure and dysfunction in protein trafficking are associated with serious illnesses such as memory loss including Alzheimer. [4]

Understanding intracellular transport has been still a challenging task of cellular biology and required contributions from the different fields of science such as biophysics, statistical physics and applied mathematics [5]. In our study we will provide the general perspective on stochastic models of intracellular transport. In particular, one of the major aims is to cover a wide range of models and analytical methods specifically over time.

To understand the synaptic dynamics we have studied the Brownian motion since the environment of a cell is highly viscous [3]. It is thought that a particle is in a restricted domain with a small window on the boundary. One of the major characteristics of diffusive transport inside the cell is that the Brownian particle on

reflecting bounded domain aims to escape from this domain through a small absorbing window.

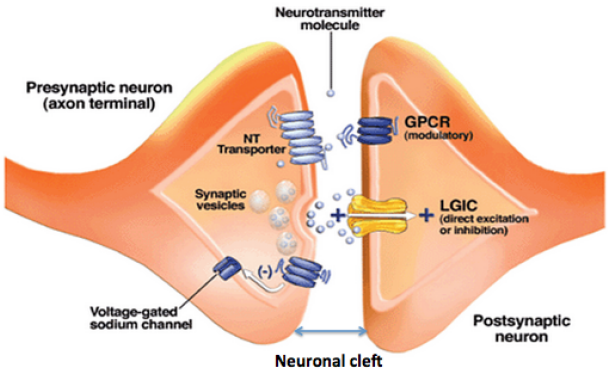


Figure 1.1. Schematic expression of a synapse between two neurons [2].

This case is known as the narrow escape problem, (NEP). The narrow escape problem in diffusion theory is the calculation of the mean first passage time. When we formulate the narrow escape time, (NET), in terms of boundary value problems for partial differential equations, their singular perturbation analysis gives the exact asymptotic expression. The diffusion coefficient, the ambient potential, dimensions, and the local and global geometrical properties of the domain, and its boundary are some of the fundamental elements of this analysis.The mathematical modeling of the neuronal synapse and the function of its different parts can be thought as the application of the narrow escape problem [6]. Specifically, a synapse between two neurons is represented schematically in the Figure 1.1. There are electrical and chemical signal conductions from the presynaptic to the postsynaptic neuron by releasing certain neurotransmitters. The neurotransmitters can diffuse across the neuronal cleft until they bind to receptors in the postsynaptic neuron, or be absorbed by the surrounding cells such as glia cells.

The geometrical shape of a spine is definitely important for the physiological function of the cell. Since diffusion is a major part on the regulation of several physiological phenomena in dendritic spines, the dramatic increase in calcium concentration will induce synaptic plasticity. Beside spine geometry, endogenous buffers and the rate of exchangers have also impact on this process. Here the determination of the ionic flux from the spine head through the neck to the dendrite is thought as actually the narrow escape problem. Obviously we can define most of functions at the cellular level as NEP.

# 2. NARROW ESCAPE TIME

The calculation of the mean first passage time is defined as the narrow escape problem in diffusion theory. The Brownian particle on reflecting bounded domain aims to escape from this domain through a small absorbing window. As the absorbing window shrinks to zero, the mean time to absorption diverges to infinity and thus the narrow escape turns out to be a singular perturbation problem.

The narrow escape problem corresponds to deriving the solution to the mixed Dirichlet-Neumann boundary value problem for the case of the Poisson equation with small Drichlet and large Neumann parts. The root of the narrow escape problem goes back to Helmholtz (1860) and Lord Rayleigh (1945) in the context of acoustic. The interest in the problem is renewed because the narrow escape time (NET) plays a crucial role to determine biological cell functions from its geometrical structure.The NET is essential in molecular and cellular biology since it represents the mean time that it takes for a molecule to hit a target-binding site shown in the Figure 2.1. It is expressed in many models such as in stochastic models of chemical reactions, in modeling the early steps of viral infection in cells, and in the regulation of diffusion between the mother and daughter cells during division. In the NET coarse-grains diffusion from the molecular to the cellular scale, current is observed on the time scale of the NET.

Another application field of the NET is the context of calcium dynamics in neuronal synapsis which is one of the fundamental cases that manifest the stimulation of several interacting species in a confined microdomain. The number of molecule in the reaction is assumed approximately of the order of tens to hundreds. By using fluorescent dynes we can track molecules in the reaction and diffusion process. Similarly in the simulation of synaptic transmission we can look at the process of the arrival of neurotransmitter molecules at receptors on the postsynaptic membrane.

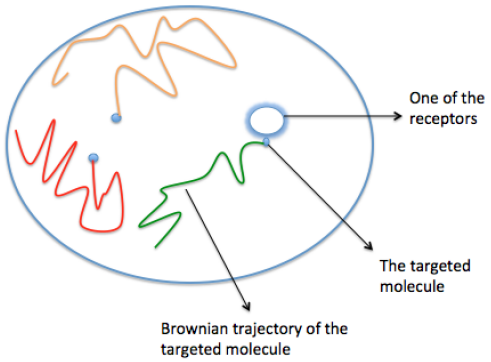


Figure 2.1. Brownian trajectory on the cell.

## 2.1. Formulation of the Narrow Escape Problem

Before we embark on the narrow escape problem, we review the basic aspects of probabilistic approach to simple processes.

### 2.1.1. Random Walks

We now look at the basic features of a probability distribution of a random walk, as well as the relation between random walks and diffusion, and hence we follow essentially the book [20]. In this sense, we use some derivations which also serve to introduce the mathematical tools such as Fourier and Laplace transforms, the generating function, and simple asymptotic analysis. The generating function is a mathematical expression, depending on a power series expansion, that simplifies a number of problems. Furthermore, it holds all information associated with the functions producing the generating function in an exceedingly compact form. Before studying same standard problems, let us understand the general strategy to solve these problems. Consider a set of numbers C(N), and assume that C(N) satisfies a complicated recurrence relation which is difficult to solve with a simple algebraic method. In the generating function approach, one has the following steps:

$$G(z) = \sum_{N=0}^{\infty} C_N z^N \tag{2.1}$$

Note that we may recover $C_N$ via Chauchy Theorem.

$$C_N = \frac{1}{2\pi i} \oint \frac{G(z)}{z^{N+1}} dz \tag{2.2}$$

Moreover, for large values of $N$ we may use an exponential form assuming that we can calculate $G(z)$.

$$C_N = \frac{1}{2\pi i} \oint e^{ln(G(z)) - (N+1)ln(z)} dz \tag{2.3}$$

In the limit $N \to \infty$, if we can find a saddle point, this gives us an asymptotic solution for $C_N$. To illustrate this approach, we will apply these ideas to the Random Walk. Let's suppose a particle jumps at discrete times between the nearest neighboring sites on a one-dimensional (1D) lattice with unit distance. At each step, the probability for taking a unit step to the right is $p$ and for the left site the probability is $q = (1 - p)$. Note that $P_N(r)$ indicates the probability that an N-step walk is at site $r$. The evolution of the probability is simply given by the equation;

$$P_N(x) = pP_{N-1}(x-1) + qP_{N-1}(x+1), \qquad r \in \mathbb{Z} \tag{2.4}$$

In our discussion, if $p = q = \frac{1}{2}$, then such a walk is called symmetric walk, whereas if $p < q$ or $p > q$, it is biased to the left or right.

Now we generalize the 1D Random Walk. To higher dimension consider $C(N;\vec{x},\vec{y})$ is the same as the number of N-step walks that begin from the point $\vec{x}$ and end up at the point $\vec{y}$. Then the generating function is the following equation in terms of $z$ ,$\vec{x}$ ,$\vec{y}$

$$G(z,\vec{x},\vec{y}) = \sum_{N=0}^{\infty} z^N C(N,\vec{x},\vec{y}) \tag{2.5}$$

By definition of the generating function, $C(N,\vec{x},\vec{y})$ is the coefficient of $z^N$ in this expansion as a function of $z$. The probability that an N-step walk starts out from the point $\vec{x}$ and ends at $\vec{y}$ is given by $C(N,\vec{x},\vec{y})$ divided by the total number of walks. For an N-step walk on the lattice, the number of walks that begin at site $\vec{x}$ and end up at site $\vec{y}$ is equal to the sum of the number of $(N-1)$ step walks starting at $\vec{x}$ and ending at sites that are the nearest neighbors to $\vec{y}$.

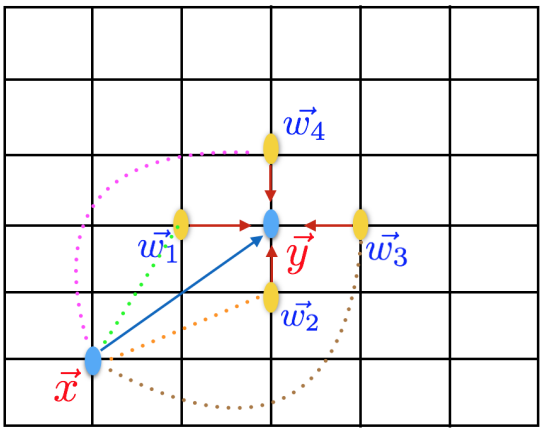


Figure 2.2. The recursion relation for random walks.

$$C(N;\vec{x},\vec{y}) = \sum_{i} C(N-1;\vec{x},\vec{w}_i) \tag{2.6}$$

where $w_i$ are the sites adjacent to $\vec{y}$. The relationship between $C(N;\vec{x},\vec{y})$ and the corresponding quantities is defined in the Equation 2.6. The Figure 2.2, based on the figure in the book [20], is a pictorial description of the process expressed in the Equation 2.6. This equation considers all positive, non-zero values of N. When N=0, our equation becomes $C(0;\vec{x},\vec{y}) = \delta_{\vec{x},\vec{y}}$, where $\delta$ is the discrete delta function. As the next step, we construct the generating function defined by the Equation 2.5

$$G(z;\vec{x},\vec{y}) = \sum_{N=1}^{\infty} z^N C(N;\vec{x},\vec{y})$$

Next we use the recursion relation by the generating function.

$$\begin{aligned} G(z;\vec{x},\vec{y}) &= \sum_{N=1}^{\infty} z^N \left( \sum_i C(N-1;\vec{x},\vec{w}_i) \right) \\ &= z \sum_i \sum_{N=0}^{\infty} z^N C(N;\vec{x},\vec{w}_i) \\ &= z \sum_i G(z;\vec{x},\vec{w}_i) \end{aligned} \tag{2.7}$$

If we add the term $z^0 C(0;\vec{x},\vec{y}) = \delta_{\vec{x},\vec{y}}$, when $N = 0$, we end up with

$$G(z;\vec{x},\vec{y}) = z \sum G(z;\vec{x},\vec{w}_i) + \delta_{\vec{x},\vec{y}} \tag{2.8}$$

Notice that the left hand side of the equation depends on the position vector $\vec{y}$, whereas the right hand side involves the locations, $\vec{w}_i$, adjacent to $\vec{y}$. In such a form, it is not easy to solve the equation by a simple algebraic method. This relation is mainly based on the translational symmetry of the lattice. By using the symmetry,

we can express both $C(N;\vec{x},\vec{y})$ and the generating function $G(z;\vec{x},\vec{y})$ in terms of the difference of the position vectors $\vec{x}$ and $\vec{y}$. This enables us to rewrite the generating function in the form of $G(z;\vec{x}-\vec{y})$. Then, we take a spatial Fourier expansion of $G(z;\vec{x},\vec{y})$, if

$$g(z;\vec{k}) = \sum_{\vec{x}} G(z;\vec{x}-\vec{y}) e^{i\vec{k}\cdot(\vec{x}-\vec{y})} \tag{2.9}$$

then, we multiply $G(z;\vec{x}-\vec{y})$ by $e^{i\vec{k}\cdot(\vec{x}-\vec{y})}$ and sum over $\vec{x}$,

$$\begin{aligned} g(z;\vec{k}) &= z\sum_{\vec{x},\vec{w}_i} e^{i\vec{k}\cdot(\vec{x}-\vec{y})} G(z;\vec{x}-\vec{w}_i) + 1 \\ &= z\sum_{\vec{x}-\vec{w}_i,\vec{w}_i} e^{i\vec{k}\cdot(\vec{x}-\vec{w}_i)} G(z;\vec{x}-\vec{w}_i) e^{i\vec{k}\cdot(\vec{w}_i-\vec{y})} + 1 \\ &= z g(z;\vec{k}) \sum_{\vec{w}_i} e^{i\vec{k}\cdot(\vec{w}_i-\vec{y})} + 1 \\ &= z g(z;\vec{k}) \chi(\vec{k}) + 1 \\ g(z;\vec{k}) &= \frac{1}{1-z\chi(\vec{k})} \end{aligned} \tag{2.10}$$

where $\chi(\vec{k})$ is called the structure function of the lattice. $\chi(\vec{k})$ depends on the lattice geometry. In 1-D case, we construct the probability distribution by using the inverse transform.

$$P(x,N) = \oint \frac{dz}{2\pi i z^{N+1}} \int_{-\pi}^{\pi} \frac{dk}{2\pi} e^{-ikz} g(z,k) \tag{2.11}$$

with the z-contour which is taken around the unit circle. When we expand $g(z,k)$ in a Taylor series with respect to $z$, the inverse of generating function yields

$$P(x,N) = \frac{1}{2\pi} \oint e^{-ikx} \chi(k)^N dk \tag{2.12}$$

where $\chi(k) = pe^{ik} + qe^{-ik}$. To evaluate the integral, we write $\chi(k)^N = (pe^{ik} + qe^{-ik})^N$ in terms of a binomial series. This gives

$$\begin{aligned} P(x,N) &= \frac{1}{2\pi} \oint e^{-ikx} \sum_{m=0}^{N} \binom{N}{m} p^m e^{ikm} q^{N-m} e^{-ik(N-m)} dk \\ &= \frac{N!}{\left(\frac{N+x}{2}\right)! \left(\frac{N-x}{2}\right)!} p^{\frac{N+x}{2}} q^{\frac{N-x}{2}} \end{aligned} \tag{2.13}$$

String's approximation for any large n;

$$\log(n!) \approx n \log(n) - n + \frac{1}{2} \log(2\pi n) \tag{2.14}$$

simplifies the expansion for large $N$ and this binomial approach in the long-time limit results in the solution

$$P(x,N) \to \frac{1}{\sqrt{2\pi N p q}} e^{-\frac{(x-Np)^2}{2Npq}} \tag{2.15}$$

In fact, the Gaussian distribution in the large time limit arises for any hopping process in which the mean and variance of the displacement $x$ in a single step are finite. This is known as the statement of the central-limit theorem. When $\langle x \rangle$ and $\langle x^2 \rangle$ are both finite, $\chi(k)$ has the-small-k series expansion.

$$\begin{aligned} \chi(k) &= 1 + ik\langle x \rangle - \frac{1}{2} k^2 \langle x^2 \rangle ..... \\ &\sim e^{ik\langle x \rangle - \frac{1}{2}\langle x^2 \rangle} , \qquad k \to 0 \end{aligned} \tag{2.16}$$

When we substitute this result for $\chi(k)$ into the Eq 2.12, the integral is dominated by the behavior in the region around $k = 0$. For large $N$, the resulting Gaussian integral gives the approximation

$$P(x, N) \to \frac{1}{\sqrt{2\pi N\langle x^2\rangle}} e^{-(x-\langle x\rangle)^2/2N\langle x^2\rangle} \tag{2.17}$$

The Equation 2.17 gives the probability distribution in 1-D discrete random walk. Now, let's take an appropriate continuum limit to derive a diffusion equation in continuous space and time. For the continuum analogy of the occupation probability of the random walk, first we should introduce infinitely small step lengths $\delta x$ and time interval $\delta t$ for space and time respectively. Then, we set

$$P_N = c(x, t)\delta x \quad with \quad x \mp 1 \mapsto x \mp \delta x \ , \quad t = N\delta t \tag{2.18}$$

For the next step, we substitute reconstructed $P_N(x)$ into the master equation 2.4, and it gives the following relation for the probability density $c(x, t)$;

$$\begin{aligned} c(x,t) &= pc(x-\delta x, t-\delta t) + qc(x+\delta x, t-\delta t) \\ &\simeq (p+q)\left[c(x,t) - \frac{\partial c}{\partial t}\delta t\right] - (p-q)\frac{\partial c}{\partial x}\delta x \\ &+ \frac{(p+q)}{2}\frac{\partial^2 c}{\partial^2 x}\delta x^2 \end{aligned} \tag{2.19}$$

where we expand $c$ to first order in $\delta t$ and to second order in $\delta x$. We use that $p + q = 1$. Dividing both sides by $\delta t$ and taking continuum limit $\delta x$, $\delta t \to 0$ gives finite quantities such as $V$ and $D$.

$$V = \lim_{\delta x, \delta t \to 0} (p-q)\frac{\delta x}{\delta t} \ , \qquad D = \lim_{\delta x, \delta t \to 0} \frac{\delta x^2}{2\delta t} \tag{2.20}$$

We obtain the fundamental convection-diffusion equation, in other words, the Fokker-Planck equation with constant drift.

$$\frac{\partial c(x,t)}{\partial t} = -V\frac{\partial c(x,t)}{\partial x} + D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{2.21}$$

For the symmetric random walk, the probability distribution satisfies the simple diffusion equation.

$$\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{2.22}$$

If we apply the continuum limit to the Gaussian distribution Equation 2.17 under the initial condition $c(x,0) = \delta(x)$, it yields the density.

$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-(x-Vt)^2/4Dt} \tag{2.23}$$

Although we will primarily consider continuum models of diffusion, there are several different approaches to develop theories of diffusion in complex media and related phenomena such as anomalous diffusion.

### 2.1.2. Langevin Equation

Langevin equation, which is introduced by Langevin in 1908 to describe the Brownian motion, is the simplest and the most widely known stochastic differential equation. It is a first order differential equation which contains an additive Gaussian white noise. To explain the importance of the Langevin differential equation, we review the paper [3] and we use basically the books [21], [24] and finally [25]. Let us consider the case of a moving microscopic particle subjected to an external

force having magnitude $F$ in a water solution such as cytoplasm. In such a case, the fluid molecules collide with the microscopic particles and these collisions will result in two distinct effects. First, collisions with fluid molecules will cause an obvious diffusive or Brownian motion of the particle. Second, these collisions will produce an influential frictional force that resists motion caused by the external force for microscopic particles. Since the water has low Reynolds number it will behave like an extremely viscous medium in the case of microscopic particles. So if we neglect inertial impacts, any particle quickly reaches terminal velocity. In this sense, the Langevin or stochastic differential equation can express the influence of all collisions on the motion of the particle.

$$\frac{dX}{dt} = \frac{F(X(t))}{\gamma} + \xi(t) \tag{2.24}$$

where $X(t)$ denotes the position of the particle at time $t$ in stochastic case, $\gamma$ is the viscosity parameter, and $\xi(t)$ represents a Gaussian noise term which is specified by the conditions,

$$\langle \xi(t) \rangle = 0, \quad \langle \xi(t)\xi(t') \rangle = 2D\delta(t - t') \tag{2.25}$$

In order to simplify the derivation, suppose that $F$ is a constant.The integration of the Equation 2.24 with the initial condition $X(0) = 0$ ends up with

$$X(t) = Vt + \int_0^t \xi(t')dt' \tag{2.26}$$

where $Vt = F/\gamma$ represents the terminal velocity. In the next step, we take the average relative to the noise term then this implies that

$$\begin{aligned} \langle\ X(t)\rangle\ &= \langle\ Vt\rangle + \int_0^t \langle\ \xi(t')\rangle\ dt', \qquad \langle\xi(t)\rangle = 0 \\ \langle\ X(t)\rangle\ &= Vt \end{aligned} \tag{2.27}$$

If we square the equation for $X(t)$ and take the average;

$$\begin{aligned} \big(X(t) - Vt\big)^2 &= \int_0^t \xi(t')\xi(t'')dt'dt'', \\ \langle\ \big(X(t) - Vt\big)^2\rangle\ &= \int_0^t \langle\xi(t')\xi(t'')\rangle\ dt'dt'', \qquad \langle\xi(t')\xi(t'')\rangle = 2D\delta(t' - t'') \\ \langle\ \big(X(t) - Vt\big)^2\rangle\ &= 2Dt \end{aligned} \tag{2.28}$$

where $D$ is a diffusion coefficient. Furthermore, the position of a Brownian particle, $X(t)$, proceeds the Gaussian process, and the probability density $p(x)$ derived from the Langevin equation obeys the Fokker-Planck equation. Under the initial condition $p(x = 0) = \delta(x)$, the result of the calculations displays the Gaussian distribution in a remarkable way .

For the stochastic systems, we can only explain the probability of finding the system in a given state. If the probability depends on the state of the system in the immediate past, but not its entire history, this process is defined to be a Markov process. For the mathematical definition of a Markov process, we should follow the definition of the hierarchy of the probability density functions for a given process which is described by

$$P(x_1, t_1; .....; x_m, t_m \mid x_{m+1}, t_{m+1}.....; x_n, t_n) \tag{2.29}$$

These joint probability density functions describe that the system is in state $x_1$ at time $t_1$ , state $x_2$ at time $t_2$,..and state $x_n$ at time $t_n$. Therefore, the most general stochastic cases can be thought as a set of conditional probabilities. The Markov process is defined to be

$$P(x_1, t_1; .....; x_m, t_m \mid x_{m+1}, t_{m+1}.....; x_n, t_n) = P(x_1, t_1; .....; x_m, t_m \mid x_{m+1}, t_{m+1}) \tag{2.30}$$

The right-hand side represents the conditional probability density functions and specifies that the system is in state $x_1$ at time $t_1$ ,....,$x_m$ at time $t_m$ given that it was in state $x_{m+1}$ at time $t_{m+1}$ irrespective of the previous location at previous times. As a consequence, $P(x, t \mid x', t')$ determines the hierarchy of the probability density functions and if an infinite distribution is given, we set the transition functions as:

$$P(x_2, t_2) = \int dx_1 P(x_2, t_2 \mid x_1, t_1) P(x_1, t_1) \tag{2.31}$$

This implies the following integral relation for the transition probabilities:

$$P(x_3, t_3 \mid x_1, t_1) = \int dx_2 P(x_3, t_3 \mid x_2, t_2) P(x_2, t_2 \mid x_1, t_1), \qquad t_1 < t_2 < t_3 \tag{2.32}$$

The probability differential function $P(x, t \mid x', t')$ defines the transition probability and the Equation 2.32 refers the Chapman-Kolmogorov equation which is a special case of the Fokker-Planck equation that is used to describe very interesting stochastic processes in which the system requires a continuous sample path. Let's rewrite the Chapman-Kolmogorov equation in a general form

$$P(x, t \mid x_0, t_0) = \int_{-\infty}^{\infty} P(x, t \mid x', t') P(x', t' \mid x_0, t_0) dx' \tag{2.33}$$

for any $t' \in [t_0, t]$. Consider an infinitesimal version of this equation and let's take $t \to t + \tau$, $t' \to t$ and $\phi(x, t; a, \tau) = p(x + a, t + \tau \mid x, t)$ and our equation becomes

$$p(x, t + \tau) = \int_{-\infty}^{\infty} \phi(x - a, t; a, \tau) p(x - a, t) da \tag{2.34}$$

since $\tau$ is very small, the left-hand side of the equation is following;

$$p(x, t + \tau) = p(x, t) + \tau \frac{\partial p(x, t)}{\partial t} \tag{2.35}$$

we perform a Taylor expansion with respect to $a$ and the right-hand side of the equation is given by

$$p(x - a, t) = p(x, t) - a \frac{\partial p(x, t)}{\partial x} + \frac{a^2}{2!} \frac{\partial^2 p(x, t)}{\partial x^2} + ..... \tag{2.36}$$

We can combine these series to reconstruct the Equation 2.34.

$$\begin{aligned} p(x, t) + \tau \frac{\partial p(x, t)}{\partial t} &= p(x, t) \int_{-\infty}^{\infty} \phi(x, t; a, \tau) da \\ &\quad - \frac{\partial p(x, t)}{\partial x} \int_{-\infty}^{\infty} a \phi(x, t; a, \tau) da \\ &\quad + \frac{\partial^2 p(x, t)}{\partial x^2} \int_{-\infty}^{\infty} \frac{a^2}{2} \phi(x, t; a, \tau) da ..... \end{aligned} \tag{2.37}$$

Let us define $\alpha_n(x, t)$ to simplify the equation

$$\alpha_n(x, t) = \int_{-\infty}^{\infty} \phi(x, t; a, \tau) a^n da \tag{2.38}$$

Finally we obtain the following equation

$$p(x,t+\tau) = \alpha_0(x,t)p(x,t) - \frac{\partial}{\partial x}[\alpha_1(x,t)p(x,t)] + \frac{1}{2}\frac{\partial^2}{\partial x^2}[\alpha_2(x,t)p(x,t)] + ... \quad (2.39)$$

We aim to find out the coefficient of $\alpha_n$ and so that we rewrite the Langevin Equation 2.24 in the infinitesimal form

$$X(t+\tau) = x + \frac{F(x)\tau}{\gamma} + \tau\xi(t) \quad (2.40)$$

given that $X(t) = x$ is the initial position. For the transition probability $\phi$ we can write

$$\begin{aligned} \phi(x,t;a,\tau) &= \langle \delta(x + a - X(t+\tau)) \rangle_\xi \\ &= \langle \delta(a - \frac{F(x)\tau}{\gamma} - \tau\xi(t)) \rangle_\xi \end{aligned} \quad (2.41)$$

If we discretize time in the unit of $\tau$, $\xi(t)$ becomes a Gaussian random variable and its mean gives zero and variance is $2D/\tau$. The corresponding probability density is the following equation

$$p(\xi) = \sqrt{\tau/4\pi D}e^{-\xi^2\tau/4D} \quad (2.42)$$

The averaging with respect to $\xi(t)$ gives the transition probability $\phi$.

$$\begin{aligned} \phi(x,t;a,\tau) &= \langle \delta(x + a - X(t+\tau)) \rangle_\xi \\ &= \int \delta(u - F(x)\tau/\gamma - \tau\xi(t))p(\xi)d\xi \\ &= \sqrt{\frac{1}{4\pi D\tau}}e^{-(a-F(x)\tau/\gamma)^2/4D\tau} \end{aligned} \quad (2.43)$$

For the coefficients we evaluate the expansion in the Equation 2.38 and the results are following

$$\alpha_0 = 1, \qquad \alpha_1 = F(x)\tau/\gamma, \qquad \alpha_2 = 2D\tau + \alpha_1^2, \tag{2.44}$$

and $\alpha_m = O(\tau^2)$ for $m > 2$. In the next step, we substitute these results into the Equation 2.39 and take the limit $\tau \to 0$ and eventually we end up with the Fokker-Planck (FP) equation

$$\frac{\partial p(x,t)}{\partial t} = -\frac{1}{\gamma}\frac{\partial [F(x)p(x,t)]}{\partial x} + D\frac{\partial^2 p(x,t)}{\partial x^2} \tag{2.45}$$

For higher dimensions it is straightforward to generalize the Equation 2.45 and it becomes

$$\frac{dX_i}{dt} = \frac{F_i(\mathbf{X})}{\gamma} + \xi_i, \qquad i = 1, ...., d \tag{2.46}$$

with $\langle \xi_i(t) \rangle = 0$ and $\langle \xi_i(t)\xi_j(t') \rangle = 2D\delta_{i,j}\delta(t-t')$. Finally the corresponding Fokker-Planck equation is given by

$$\frac{\partial p(\mathbf{x},t)}{\partial t} = -\frac{1}{\gamma}\boldsymbol{\nabla} \cdot [\mathbf{F}(\mathbf{x})p(\mathbf{x},t)] + D\boldsymbol{\nabla}^{\mathbf{2}} p(\mathbf{x},t) \tag{2.47}$$

We can write the Fokker-Planck equation as a continuum equation in one dimension.

$$\frac{\partial p(x,t)}{\partial t} + \frac{\partial J(x,t)}{\partial x} = 0 \tag{2.48}$$

where the probability current $J(x,t)$ is given by

$$J(x,t) = \frac{1}{\gamma}F(x,t)p(x,t) - D\frac{\partial p(x,t)}{\partial x} \tag{2.49}$$

Let us suppose that the system is described on the interval $[a,b]$. If the boundaries are reflecting, there is no net flow of probability across the boundaries. This implies that

$$\begin{aligned} J(a,t) &= 0 \\ J(b,t) &= 0 \end{aligned} \tag{2.50}$$

An equilibrium steady-state solution gives the conditions $J = 0$ and $\frac{\partial p(x,t)}{\partial t} = 0$. The substitution of the corresponding conditions into the Equation 2.49 yields the first-order ODE for the density $P(x,t)$

$$D\frac{\partial P(x,t)}{\partial x} - \frac{1}{\gamma}F(x,t)P(x,t) = 0 \tag{2.51}$$

This may be integrated to give

$$P(x) = Ne^{-U(x)/\gamma D} \tag{2.52}$$

where $U(x) = -\int_x F(y)dy$ is a potential energy function and $N$ is a normalization function. In order to look at the comparison of equilibrium distribution with Boltzmann-Gibbs distribution and the Einstein relation, firstly we should write the equation of motion in 1D.

$$m\frac{d^2x}{dt^2} = -\alpha\frac{dx}{dt} - \frac{dV}{dx} + \xi(t) \tag{2.53}$$

where the viscosity of the fluid gives the first term on the right-hand side and $\alpha$ is the friction constant. $V(x)$ is a potential and it represents the interaction of the particle with any external force. Finally, $\xi(t)$ is the random force as a result of collisions with

the liquid molecules and also is frequently called the noise term. The statistics of the fluctuation force $\xi(t)$ are

- $\langle\xi(t)\rangle = 0$, since it is not expected one direction to be favored over the other.
- $\langle\xi(t)\xi(t')\rangle = 2D\delta(t-t')$, we suppose that after a few molecular collisions, $\xi$ will not depend on the formal value. This implies that the force of $\xi$ becomes uncorrelated over times. This is slightly observable on the time scale, so that we take the correlation function as a delta function.
- $\xi$ shows Gaussian distribution.

Then, we may rewrite the Equation 2.53

$$\frac{dx}{dt} = v$$

$$m\frac{dv}{dt} = -\alpha v + \frac{dV}{dt} + \xi(t) \tag{2.54}$$

We assume that there is no external force and hence $\frac{dV}{dt} = 0$. The last expression may be written in the form of the Langevin equation.

$$\frac{dv}{dt} = -\gamma v + \boldsymbol{\xi(t)}, \qquad v(0) = v_0 \tag{2.55}$$

where $\gamma = \alpha/m$ and $\boldsymbol{\xi(t)} = \xi(t)/m$. We recall that

$$\langle \boldsymbol{\xi(t)} \rangle = 0 \quad and \quad \langle \boldsymbol{\xi(t)\xi(t')} \rangle = \frac{2D}{m^2}\delta(t - t') \tag{2.56}$$

Multiply the Langevin equation 2.55 by $e^{\gamma t}$

$$\frac{d}{dt}[v(t)e^{\gamma t}] = \boldsymbol{\xi(t)}e^{\gamma t}$$

$$v(t) = v_0 e^{-\gamma t} + e^{-\gamma t}\int_0^{t'} dt' \boldsymbol{\xi(t')}e^{\gamma t'} \tag{2.57}$$

By taking the average of the expression for $v(t)$

$$\langle v(t) \rangle = v_0 e^{-\gamma t} \tag{2.58}$$

If we take the square of the Equation 2.58 for $v(t)$ and take the average;

$$\langle v(t)^2 \rangle = v_0^2 e^{-2\gamma t} + \frac{D}{\alpha m}[1 - e^{-2\gamma t}] \tag{2.59}$$

which means that

$$\lim_{t\to\infty}\langle v^2(t)\rangle = \frac{D}{\alpha m} \tag{2.60}$$

as $t \to \infty$, the Brownian particle will be in thermal equilibrium. From the statistical mechanics, the mean kinetic energy of the Brownian particle in equilibrium is given by

$$\lim_{t\to\infty}\langle v^2(t)\rangle = v_{eq}^2 \qquad and \qquad \frac{1}{2}mv_{eq}^2 = \frac{1}{2}kT \tag{2.61}$$

where $T$ is temperature of the liquid, $k$ is Boltzmann constant. Eventually, this yields the following relation

$$\begin{aligned} \frac{1}{2}m\left(\frac{D}{\alpha m}\right) &= \frac{1}{2}kT \\ D &= \alpha kT \end{aligned} \tag{2.62}$$

which implies that the liquid molecules act as a heat bath for the system. The Equation 2.62 is one of the simple examples of a fluctuation-dissipation theorem and gives $D$ in terms of the friction constant, $\alpha$, and the temperature of liquid, $T$.

### 2.1.3. First Passage Time

One of the important ways to quantify the efficiency of diffusive transport is the calculation of the first passage time, FPT. By definition FPT is the time when a targeted particle arrives for a specific point at the first time. Understanding of the FPT for a small absorbing boundary is essential since the calculation of the mean first passage time gives us the narrow escape time, NET. In this section, we follow

basically the article [3] and we use the books [21], [24] as well as [25] to explain the main concept in this process. Consider a particle whose position satisfies 1-D Langevin Equation 2.24 and its motion is confined in the bounded domain $x \in [0, L]$. Suppose that the corresponding FP Equation 2.45 has mix boundary conditions of reflection at $x = 0$ and absorption at $x = L$, and thus

$$J(0,t) = 0\ , \qquad p(L,t) = 0 \tag{2.63}$$

Our basic goal is to find out the stochastic time $T(y)$ for the particle which starts at a point $y \in [0, L]$ at time t and leaves the right hand boundary. The first step is to introduce the survival probability $S(y,t)$ that the particle is still in the interval at time $t$:

$$S(y,t) = \int_0^L p(x,t \mid y,0)dx \tag{2.64}$$

It follows that

$$Prob[T(y) \leq t] = 1 - S(y,t) \tag{2.65}$$

and let us define $f(y,t)$ as the first passage time (FPT) density. This implies that

$$f(y,t) = -\frac{\partial S(y,t)}{\partial t} \tag{2.66}$$

The FPT density obeys the backward FP equation derived from the Chapman-Kolmogorov equation which is given by

$$P(x,t \mid x_0,t_0) = \int_{-\infty}^{\infty} P(x,t \mid x',t')P(x',t' \mid x_0,t_0)dx' \tag{2.67}$$

For the backward FP equation, we take the differential of both sides with respect to the intermediate time $t'$.

$$\begin{aligned}\frac{\partial P(x,t \mid x_0,t_0)}{\partial t'} &= \int dx' \frac{\partial}{\partial t'} p(x,t \mid x',t')p(x',t' \mid x_0,t_0) \\ &+ \int dx' p(x,t \mid x',t') \frac{\partial}{\partial t'} p(x',t' \mid x_0,t_0)\end{aligned} \tag{2.68}$$

Since $\frac{\partial P(x,t|x_0,t_0)}{\partial t'} = 0$, we can rewrite our equation

$$\int dx' \frac{\partial}{\partial t'} p(x,t \mid x',t')p(x',t' \mid x_0,t_0) + \int dx' p(x,t \mid x',t') \frac{\partial}{\partial t'} p(x',t' \mid x_0,t_0) = 0 \tag{2.69}$$

To derive the backward FP equation, we can introduce the Fokker-Planck operator $L_{FP}$

$$\frac{\partial P}{\partial t'} = -L_{FP}P \tag{2.70}$$

and $L_{FP}$ is defined by

$$L_{FP} = \frac{\partial}{\partial x'} \cdot A(x') - \frac{\partial}{\partial x'} \cdot D \cdot \frac{\partial}{\partial x'} \tag{2.71}$$

where $A(x') = \frac{F(x')}{\gamma}$, moreover we may take $D$ position dependent as well. Substituting the Fokker-Planck operator $L_{FP}$ into the Equation 2.69 gives the following relation

$$\int dx' \frac{\partial}{\partial t'} p(x,t \mid x',t') p(x',t' \mid x_0,t_0) - \int dx' p(x,t \mid x',t') L_{FP} p(x',t' \mid x_0,t_0) = 0$$
$$\int dx' \left[ \frac{\partial}{\partial t'} p(x,t \mid x',t') - L_{FP}^{\dagger} p(x,t \mid x',t') \right] p(x',t' \mid x_0,t_0) = 0 \quad (2.72)$$

Finally the derivative of the Chapman-Kolmogorov equation with respect to $t'$ generates

$$\frac{\partial}{\partial t'} p(x,t \mid x',t') - L_{FP}^{\dagger} p(x,t \mid x',t') = 0 \quad (2.73)$$

here the adjoint operator is defined to be

$$L_{FP}^{\dagger} = -A(x') \cdot \frac{\partial}{\partial x'} - \frac{\partial}{\partial x'} \cdot D \cdot \frac{\partial}{\partial x'} \quad (2.74)$$

If there is time translation invariance, we obtain the following relation

$$\frac{\partial}{\partial t'} p(x,t \mid x',t') = -\frac{\partial}{\partial t} p(x,t \mid x',t') \quad (2.75)$$

and the backward FP equation can be written

$$\frac{\partial}{\partial t} p(x,t \mid x',t') = A(x') \frac{\partial}{\partial x'} p(x,t \mid x',t') + D \frac{\partial^2}{\partial x'^2} p(x,t \mid x',t') \quad (2.76)$$

Let us take $x' \to y$ and $t' = 0$, the integration of Equation 2.75 with respect to $x$ shows that $S(y,t)$ and also $f(y,t)$ satisfy the backward FP equation.

$$\frac{\partial S(y,t)}{\partial t} = A(y)\frac{\partial S(y,t)}{\partial y} + D\frac{\partial^2 S(y,t)}{\partial y^2} \tag{2.77}$$

In particular, the mean first passage time MFPT, $\tau(y)$, is given by

$$\begin{aligned}\tau(y) = \langle T(y)\rangle &= \int t\frac{\partial}{\partial t}Prob[T(y) \leq 1] \\ &= \int_0^\infty f(y,t)tdt = -\int_0^\infty t\frac{\partial S(y,t)}{\partial t}dt \\ &= \int_0^\infty S(y,t)dt \end{aligned} \tag{2.78}$$

The mean first passage time is defined as the mean of the stochastic time $T(y)$. We know the probability of the particle to be captured at the boundary up to $t$ but we need to convert it to around $t$. Therefore we take the derivative of the probability density. For the final result we use the *integration by parts technique* because $S(t)$ is decaying fast. Then the integration of both sides of Equation 2.78 indicates that the MFPT satisfies the ODE.

$$\begin{aligned}\int_0^\infty \frac{\partial S(y,t)}{\partial t}dt &= A(y)\frac{\partial}{\partial y}\int_0^\infty S(y,t)dt + D\frac{\partial^2}{\partial y^2}\int_0^\infty S(y,t)dt \\ S(y,\infty) - S(y,0) &= A(y)\frac{\partial}{\partial y}\tau(y) + D\frac{\partial^2}{\partial y^2}\tau(y) \\ -1 &= A(y)\frac{\partial}{\partial y}\tau(y) + D\frac{\partial^2}{\partial y^2}\tau(y)\end{aligned} \tag{2.79}$$

with the reflecting and absorbing boundary conditions

$$\tau'(0) = 0\ , \qquad \tau(L) = 0 \tag{2.80}$$

We can solve directly Equation 2.79 by taking integration. The solution, after manipulation, can be introduced in terms of

$$\psi(y) = exp\left(\frac{1}{D}\int_0^y A(y')dy'\right) = exp\left(-\frac{U(y)}{k_BT}\right) \tag{2.81}$$

where $\frac{A(y)}{D} = \frac{F(y)}{D\gamma}$ and here $U(y)$ is a potential energy. Eventually Equation 2.79 becomes

$$\frac{d}{dy}\left[\psi(y)\tau'(y)\right] = -\frac{\psi(y)}{D} \tag{2.82}$$

so that

$$\psi(y)\tau'(y) = -\frac{\psi(y)}{D} \tag{2.83}$$

where the boundary condition $\tau'(0) = 0$. We integrate once more with respect to $y$ and use $\tau(L) = 0$ then the integration yields

$$\tau(y) = \int_y^L \frac{dy'}{\psi(y')}\int_0^{y'} \frac{\psi(y'')}{D}dy'' \tag{2.84}$$

In the case of pure diffusion $A(x) = 0$

$$\psi(y) = 1 \qquad and \qquad \tau(y) = \frac{L^2 - y^2}{2D} \tag{2.85}$$

for any finite $L - y$,

$$\tau(y) \to \infty \quad as \quad L \to \infty \tag{2.86}$$

and hence, although 1D diffusion is recurrent, the average time goes to infinite. This time, let's suppose that $L$ is finite and the particle starts at the left-hand side boundary. The related MFPT is generated by

$$\tau(y) = \frac{L^2}{2D} \tag{2.87}$$

It is also possible that we can look at the case where the targeted particle goes to a specific receptor and it can exit from one of the ends. In this case, we keep track the end which the particle exits and we may evaluate our calculations under the concept of splitting probability. Finally, we will again find out the mean exit time. Let's assume $G_0(x,t)$ denotes the probability that the particle goes through $x = 0$ after time $t$, having started at the point $x$. Thus this probability satisfies

$$G_0(x,t) = -\int_t^\infty J(0,t' \mid x,0)dt' \tag{2.88}$$

and $J(0,t \mid x,0)$ is defined by

$$J(0,t \mid x,0) = A(0)p(0,t \mid x,0) - D\left(\frac{\partial p(y,t \mid x,0)}{\partial y}\right)_{y=0} \tag{2.89}$$

The next step is to take the derivative of $G_0$ with respect to $t$ and use the backwards FP Eq 2.75. Thus we obtain the following relation.

$$\begin{aligned}\frac{\partial G_0(x,t)}{\partial t} &= J(0,t \mid x,0) = -\int_t^\infty \frac{\partial J(0,t' \mid x,0)}{\partial t'} dt' \\ &= A(x)\frac{\partial G_0(x,t)}{\partial x} + D\frac{\partial^2 G_0(x,t)}{\partial x^2}\end{aligned} \tag{2.90}$$

The hitting or splitting probability that the particle exits at $x = 0$ rather than $x = L$ is defined by $\Pi_0(x)$, and

$$\Pi_0(x) = G_0(x,0) \tag{2.91}$$

Furthermore, the probability that the particle exit through $x = 0$ after time t is given by

$$Prob(T_0 > t) = \frac{G_0(x,t)}{G_0(x,0)} \tag{2.92}$$

where $T_0$ is the corresponding conditional FPT. The mean exit time, given that exist is through $x = 0$ satisfies

$$\begin{aligned}\tau_0(x) &= -\int_0^\infty t\frac{\partial Prob(T_0(x) > t)}{\partial t} dt \\ &= \int_0^\infty \frac{G_0(x,t)}{G_0(x,0)} dt\end{aligned} \tag{2.93}$$

Simply the Equation 2.90 is integrated with respect to $t$ and it yields

$$A(x)\frac{\partial \Pi_0(x)\tau_0(x)}{\partial x} + D\frac{\partial^2 \Pi_0(x)\tau_0(x)}{\partial x^2} = -\Pi_0(x) \tag{2.94}$$

with boundary condition

$$\Pi_0(0)\tau_0(0) = \Pi_0(L)\tau_0(L) = 0 \tag{2.95}$$

Eventually, by letting $t \to 0$ in the Eq 2.90, we see that

$$J(0,0 \mid x,0) = 0 \qquad if \quad x \neq 0 \ , \tag{2.96}$$

and we get

$$A(x)\frac{\partial \Pi_0}{\partial x} + D\frac{\partial^2 \Pi_0(x)}{\partial x^2} = 0 \tag{2.97}$$

the boundary condition this time is

$$\Pi_0(0) = 1 \qquad and \qquad \Pi_0(L) = 0 \tag{2.98}$$

We can carry out the similar analysis for exit through the other end $x = L$ and it also satisfies this condition

$$\Pi_0(0) + \Pi_0(L) = 1 \tag{2.99}$$

Note that it is clear how to generalize the above analysis to higher dimensions. In particular, consider that a particle satisfies the Fokker Planck Equation 2.47 in a compact domain with boundary $\partial\Omega$. Let's consider that the particle is initially at the point $y \in \Omega$ and $T(y)$ is the first passage time to reach any point on the

boundary $\partial\Omega$. The probability that the particle, initially at y, is somewhere on the boundary $\partial\Omega$ after a time t is

$$S(\mathbf{y},t) = \int_{\Omega} p(\mathbf{x},t \mid \mathbf{y},0)dx \tag{2.100}$$

where the solution of FP Equation 2.47 with an absorbing boundary condition on $\partial\Omega$ is $p(\mathbf{x},t \mid \mathbf{y},0)$. Let $f(y,t)$ denote the FPT density;

$$f(\mathbf{y},t) = -\frac{\partial S(\mathbf{y},t)}{\partial t} \tag{2.101}$$

by using the Equation 2.47 and the divergence theorem, we express the function as

$$f(\mathbf{y},t) = -\int_{\partial\Omega} \big[ -\mathbf{A}(\mathbf{x})p(\mathbf{x},\mathrm{t} \mid \mathbf{y},\mathbf{0}) + D\nabla p(\mathbf{x},\mathrm{t} \mid \mathbf{y},\mathbf{0}\big].d\sigma \tag{2.102}$$

with $\mathbf{A} = \frac{\mathbf{F}}{\gamma}$. As a result of constructing the corresponding backwards FP equation, the MFPT obeys this relation;

$$\mathbf{A}(\mathbf{y}) \cdot \nabla\tau(\mathbf{y}) + D\nabla^2\tau(\mathbf{y}) = -1 \tag{2.103}$$

where $\tau(\mathbf{y}) = 0$ for $\mathbf{y} \in \partial\Omega$.

As in 1D case, we calculate the FPT density precisely. As an example we work out 1D, we can set the conditional probability density without boundary condition;

$$p(x,t \mid x_0,0) = p(x - x_0,t) \tag{2.104}$$

Similarly, we can write the FPT density of arriving for the first time at $x$ time $\tau$ starting from $x_0$

$$f(x, \tau \mid x_0, 0) = f(x - x_0, \tau) \tag{2.105}$$

The relation between densities $p$ and $f$ is given by

$$p(x - x_0, t) = \int_0^t p(x - x', t - \tau) f(x' - x_0, \tau) d\tau \tag{2.106}$$

After Laplace transform, the equation becomes

$$\widetilde{p}(x - x_0, s) = \widetilde{p}(x - x', s) \widetilde{f}(x' - x_0, s) \tag{2.107}$$

The Laplace transformation of the Gaussian distribution Equation 2.23 for $V = 0$ produces

$$\widetilde{p}(x, s) = \frac{1}{\sqrt{4\pi D s}} e^{-\sqrt{x^2 s/D}} \tag{2.108}$$

so that

$$\widetilde{f}(x - x_0, s) = e^{-\sqrt{(x - x_0) s/D}} \tag{2.109}$$

The inverse Laplace transform gives the Levy-Smirnov distribution which is a continuous probability distribution for a non-negative random variable.

$$f(x-x_0,t)=\frac{1}{t}\sqrt{\frac{(x-x_0)^2}{4\pi Dt}}e^{-(x-x_0)^2/4Dt} \tag{2.110}$$

Obviously this inverse-Gaussian decays asymptotically as $f(x,t)\sim t^{-3/2}$ for short times, as in the infinite system. Subsequently, the MFPT from $x_0$ to $x$ diverges with time. On the other hand,

$$\int_0^\infty f(x-x_0,t)dt=1 \tag{2.111}$$

and this implies that the diffusing particle will almost certainly hit any point $x$ during its motion.

After reviewing the basics topics in diffusion theory, we will start to formulate a more interesting version of this process, which is the narrow escape problem, NEP. Let us consider that we have a Brownian particle on a bounded domain with a large reflecting boundary and it intends to escape from this domain through a small absorbing window. Here our purpose is to find out the narrow escape time, NET. In a confined domain, the solution of the homogenous mixed Neumann-Dirichlet boundary value problem for the Poisson equation gives the formulation of the NET. If the Dirichlet part of the boundary goes to zero, the NET will diverge and, as it turns out, it renders a singular perturbation problem. In two dimension the singularity of the Neumann function is logarithmic while it gives algebraic solutions in higher dimension and thus the problem is unique in 2D. For the computation part, we calculate specifically the principal eigenvalue of the mixed Neumann-Dirichlet problem for the Laplace equation in the domain where the Dirichlet boundary is quite small.

### 2.1.4. The Mixed Boundary Value Problem

We first take a look at free Brownian motion in a bounded domain $D \subset \mathbb{R}^d$ (d=1,2,3). We recover mainly the studies [6], [7], [8], [9], [11], and [12], as well as the books [22], and [23] to explain the basic concept behind the narrow escape problem.

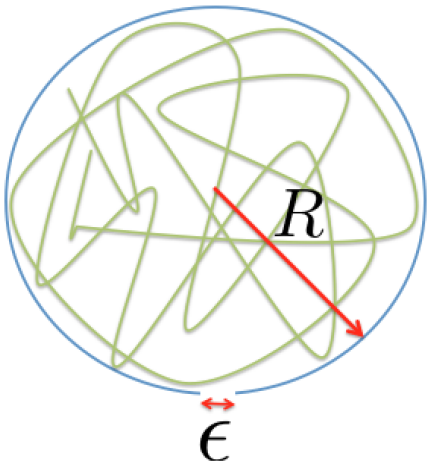


Figure 2.3. Brownian trajectory escaping through a small absorbing window in a domain otherwise it shows the reflecting boundary properties.

Let us suppose the boundary $\partial\Omega$ is sufficiently smooth. The Brownian trajectory $\boldsymbol{x}(t)$ is reflected at the boundary whereas it is absorbed on a small hole $\partial\Omega_a$. The reflecting part of the boundary is

$$\partial\Omega_r = \partial\Omega - \partial\Omega_a \tag{2.112}$$

The lifetime of a Brownian particle in the domain in the domain $\Omega$ starting at a point $\boldsymbol{x} \in \Omega$ at $t = 0$ is the first passage time (FPT) $\tau$ of the trajectory to its absorbing boundary $\partial\Omega_a$. The NET is given by

$$\tau(\mathbf{x}) = \int_0^\infty f(\mathbf{x}, t) t dt \tag{2.113}$$

The NET is finite under general conditions. As the diameter of the absorbing hole goes to zero, but that of the domain remains finite, the NET increases indefinitely. For a measure of smallness, we can choose the ratio between the surface area of the absorbing boundary and volume of the entire region;

$$\epsilon = \frac{\mid \partial\Omega_a \mid^{1/(d-1)}}{\mid \Omega \mid^{1/d}} \ll 1 \tag{2.114}$$

In our case, the NET $\tau(x)$ is the solution of the mixed boundary value problem;

$$\nabla^2 \tau(\boldsymbol{x}) = -\frac{1}{D} \quad for \quad \boldsymbol{x} \in \Omega, \tag{2.115}$$

$$\tau(\boldsymbol{x}) = 0 \quad for \quad \boldsymbol{x} \in \partial\Omega_a, \tag{2.116}$$

$$\frac{\partial \tau(\boldsymbol{x})}{\partial n(\boldsymbol{x})} = 0 \quad for \quad \boldsymbol{x} \in \partial\Omega_r, \tag{2.117}$$

where $D$ is the diffusion constant and $\mathbf{n}(\mathbf{x})$ is the unit outer normal vector. The integration of the Equation 2.115 over $\Omega$ and using the Equation 2.116 and the Equation 2.117 give the compatibility equation.

$$\begin{aligned}\int \nabla^2\tau(\mathbf{x})d^3\mathbf{x} &= \int \vec{\nabla}\cdot(\vec{\nabla}\tau)d\mathbf{x} = \oint_{\partial\Omega} \vec{\nabla}\tau\cdot\hat{n}da = -\frac{1}{D}\int d^3\mathbf{x} \\ &= \int_{\partial\Omega_a} \frac{\partial\Omega}{\partial n}\cdot dS_{\mathbf{x}} + \int_{\partial\Omega_r} \vec{\nabla}\tau\cdot\hat{n}dS_{\mathbf{x}} = -\frac{1}{D}\int d^3\mathbf{x} \\ &= \int_{\partial\Omega_a} \frac{\partial\tau}{\partial n}dS_{\mathbf{x}} = -\frac{\mid\Omega\mid}{D} \end{aligned} \tag{2.118}$$

We will look at an asymptotic approximation to $\tau(\mathbf{x})$ for small $\epsilon$, because the solution of $\tau(\mathbf{x})$ diverges to infinity as the hole goes to zero, $\epsilon \to 0$, except around the boundary layer near $\partial\Omega_a$, otherwise the compatibility equation is not satisfied in this limit.

2.1.4.1. Neumann's Function and a Helmholtz Integral Equation. Let us observe that the solution of $\tau(\mathbf{x})$ diverges to infinity for all $\mathbf{x} \in \Omega$ as $\epsilon \to 0$, we can write the leading order approximation to the boundary flux density, which is also given by

$$g(\mathbf{x}) = \frac{\partial\tau(\mathbf{x})}{\partial n} \qquad for \quad \mathbf{x} \in \partial\Omega_a \tag{2.119}$$

This provides the solution of Helmholtz integral equation. In order to calculate the NET $\tau(\mathbf{x})$, we use a solution of boundary value problem.

$$\nabla^2_{\mathbf{x}} N(\mathbf{x},\xi) = -\delta(\mathbf{x}-\xi) \qquad for \quad \mathbf{x},\ \xi \in \Omega \tag{2.120}$$

$$\frac{\partial N(\mathbf{x},\xi)}{\partial n(\mathbf{x})} = -\frac{1}{\mid\partial\Omega\mid} \qquad for \quad \mathbf{x} \in \partial\Omega,\ \ \xi \in \Omega \tag{2.121}$$

where $N(\mathbf{x},\xi)$ is the Neumann function. Green's identity and the boundary conditions give

$$\begin{aligned}\int N(\mathbf{x},\xi)\nabla^2\tau(\mathbf{x})d\mathbf{x} - \tau(\mathbf{x})\nabla^2 N(\mathbf{x},\xi)d\mathbf{x} = \\ &= \int \Big\{ \Big[\vec{\nabla}\cdot\Big(N(\mathbf{x},\xi)\vec{\nabla}\tau(\mathbf{x})\Big) - \vec{\nabla}N(\mathbf{x},\xi)\cdot\vec{\nabla}\tau(\mathbf{x})\Big] \\ &- \Big[\vec{\nabla}\cdot\Big(\tau(\mathbf{x})\vec{\nabla}N(\mathbf{x},\xi)\Big) - \vec{\nabla}\tau(\mathbf{x})\cdot\vec{\nabla}N(\mathbf{x},\xi)\Big]\Big\} d\mathbf{x} \\ &= \int \vec{\nabla}\cdot\Big[N(\mathbf{x},\xi)\vec{\nabla}\tau(\mathbf{x}) - \tau(\mathbf{x})\vec{\nabla}N(\mathbf{x},\xi)\Big]\, d\mathbf{x} \\ &= \oint_{\partial\Omega}\left[N(\mathbf{x},\xi)\frac{\partial\tau(\mathbf{x})}{\partial n} - \tau(\mathbf{x})\frac{\partial N(\mathbf{x},\xi)}{\partial n}\right] dS_{\mathbf{x}} \qquad (2.122)\end{aligned}$$

The boundary conditions in the Equation 2.115 and the Equation 2.120 imply that

$$\oint_{\partial\Omega}\Big[N(\mathbf{x},\xi)\vec{\nabla}\tau(\mathbf{x}) - \tau(\mathbf{x})\vec{\nabla}N(\mathbf{x},\xi)\Big]\, d\mathbf{S}_{\mathbf{x}} = \tau(\xi) - \frac{1}{D}\int_{\Omega} N(\mathbf{x},\xi)\mathbf{x} \qquad (2.123)$$

For the next step, we submit the boundary conditions into our calculation and finally we end up with

$$\tau(\xi) - \frac{1}{D}\int_{\Omega} N(\mathbf{x},\xi)d\mathbf{x} = \int_{\partial\Omega} N(\mathbf{x},\xi)\frac{\partial\tau(\mathbf{x})}{\partial n}dS_{\mathbf{x}} + \frac{1}{\mid\partial\Omega\mid}\int_{\partial\Omega}\tau(\mathbf{x})dS_{\mathbf{x}} \qquad (2.124)$$

The second integral on the right hand side of the Equation 2.124 is an additive constant.

$$C_{\xi} = \frac{1}{\mid\partial\Omega\mid}\int_{\partial\Omega}\tau(\mathbf{x})dS_{\mathbf{x}} \qquad (2.125)$$

Note that the integral in the Equation 2.125 gives the average of the NET on the boundary. Now let's rewrite the Equation 2.124

$$\tau(\xi) = \frac{1}{D}\int_{\Omega} N(\mathbf{x},\xi)d\mathbf{x} + \int_{\partial\Omega_a} N(\mathbf{x},\xi)\frac{\partial\tau(\mathbf{x})}{\partial n}dS_{\mathbf{x}} + C_{\xi} \tag{2.126}$$

The Equation 2.126 takes the form of the integral representation of $\tau(\xi)$. The boundary conditions in the Equation2.116 and the Equation 2.119 give

$$0 = \frac{1}{D}\int_{\Omega} N(\mathbf{x},\xi)d\mathbf{x} + \int_{\partial\Omega_a} N(\mathbf{x},\xi)g(\mathbf{x})dS_{\mathbf{x}} + C_{\xi} \quad for\ all\ \ \xi \in \partial\Omega_a \tag{2.127}$$

For the asymptotic approximation to the solution, the first integral in the Eq 2.127 is a regular function of $\xi$ on the boundary. Due to the symmetry of the Neumann function, the solution of boundary gives

$$\nabla_{\xi}\int_{\Omega} N(\mathbf{x},\xi)d\mathbf{x} = -1 \qquad for \quad \xi \in \Omega \tag{2.128}$$

$$\frac{\partial}{\partial n(\xi)}\int_{\Omega} N(\mathbf{x},\xi)d\mathbf{x} = -\frac{\mid \Omega \mid}{\mid \partial\Omega \mid} \qquad for \quad \xi \in \partial\Omega \tag{2.129}$$

Now it is clearly seen that the Equation 2.128 and the boundary conditions in the Equation 2.129 are independent of the hole $\partial\Omega_a$.

$$\int_{\partial\Omega_a} N(\mathbf{x},\xi)g(\mathbf{x})dS_{\mathbf{x}}$$

Therefore, the first integral of the Equation 2.127 is defined as a regular function of $\xi$. Consequently we can write the solution of the Helmholtz integral equation

$$Singular\left(\int_{\partial\Omega_a} N(\mathbf{x},\xi)g(\mathbf{x})dS_{\mathbf{x}}\right) = Singular\left(-C_\xi\right) \quad for\ \ \xi \in \partial\Omega_a \tag{2.130}$$

For all $\mathbf{x} \in \Omega$, if $\epsilon \to 0$, the NET ,$\tau(\mathbf{x})$,diverges to infinity, and likewise singular $C_\xi$ goes to infinity in this limit. For $\xi \in \partial\Omega_a$, this implies that the second integral in the Equation2.127 must go to infinite, since the first integral is independent of $\partial\Omega_a$. As a consequence of these relations, the result of the Equation2.130 gives the leading-order approximation to the solution of $g(\mathbf{x})$ in the Equation2.127.

2.1.4.2. The NET Problem in 2 Dimension. Let us take a Brownian trajectory $\mathbf{x}(\mathbf{t})$ in a bounded domain $\Omega$ on a 2D Riemann manifold $(\Sigma, g)$. For a domain $\Omega \subset \Sigma$ with a smooth boundary $\partial\Omega$, the Riemann surface area of $\Omega$ is shown by $\mid \Omega \mid_g$, and also the arch length of its boundary is computed with respect to the metric $g$. The boundary is divided into two parts; an absorbing part $\partial\Omega_a$ and reflecting part $\partial\Omega_r = \partial\Omega - \partial\Omega_a$. Assume that the absorbing part is small and

$$\epsilon = \frac{\mid \partial\Omega_a \mid}{\mid \partial\Omega_g \mid} \ll 1 \tag{2.131}$$

$\epsilon$ can only affect the absorbing and reflecting part on the boundary. The mean of the first passage time $\tau$ of the Brownian motion from $\Omega$ to $\partial\Omega_a$ is finite,

$$\tau(\mathbf{x}) = \int_0^\infty f(\mathbf{x},t)tdt \tag{2.132}$$

and the mixed Neumann-Dirichlet boundary value problem for the 2 dimension is written as

$$\nabla_g^2 \tau(\mathbf{x}) = -\frac{1}{D} \qquad for \qquad \mathbf{x} \in \Omega \tag{2.133}$$

$$\frac{\partial \tau(\mathbf{x})}{\partial n} = 0 \qquad for \qquad \mathbf{x} \in \partial\Omega_r \tag{2.134}$$

$$\tau(\mathbf{x}) = 0 \qquad for \qquad \mathbf{x} \in \partial\Omega_a \tag{2.135}$$

where the function of $\tau(\mathbf{x})$ satisfies the boundary conditions, $D$ is the diffusion coefficient and $\nabla_g$ is the Laplace-Beltrami operator on $\Sigma$. In differential geometry, we use the Laplacian to operate on functions defined on a surface in Euclidean spaces as models of on Riemann manifolds. The Laplace-Beltrami operator is applied to as the divergence of the covariant derivative. Like the Laplacian, the most basic definition of the Laplace-Beltrami operator is the divergence of the gradient on a function:

$$\nabla^2 f = \nabla \cdot \nabla f \tag{2.136}$$

Let us take the integral of the Equation2.136

$$\int_V \nabla \mathbf{f} \cdot \nabla \mathbf{f} dV = \int_V \left(\nabla^2 \mathbf{f}\right) \mathbf{f} dV \tag{2.137}$$

where $\nabla \mathbf{f}$ is defined in terms of the metric tensor as

$$\nabla \mathbf{f} = g^{ij} \partial_j \mathbf{f} \tag{2.138}$$

here $g$ is described by

$$\langle t_i, t_j \rangle = g_{ij} \tag{2.139}$$

where $t_i$ denotes the basis of the tangent space and let us define $g_{11}$, $g_{22}$, and $g_{12}$

$$\langle t_1, t_1 \rangle = g_{11} \tag{2.140}$$

$$\langle t_2, t_2 \rangle = g_{22} \tag{2.141}$$

$$\langle t_1, t_2 \rangle = g_{12} = cos(\theta) \tag{2.142}$$

thereby, $sin(\theta)$ is given by

$$sin(\theta) = \sqrt{g_{11} g_{22} - \left(g_{12}\right)^2} \tag{2.143}$$

actually this means

$$sin(\theta) = \sqrt{det \begin{pmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{pmatrix}} = \sqrt{det(g)} \tag{2.144}$$

Ultimately, we can write the volume element

$$dV = \sqrt{det(g)}d\xi^1 d\xi^2 \tag{2.145}$$

The pictorial representation of the metric transition is given in the subsequent figure.

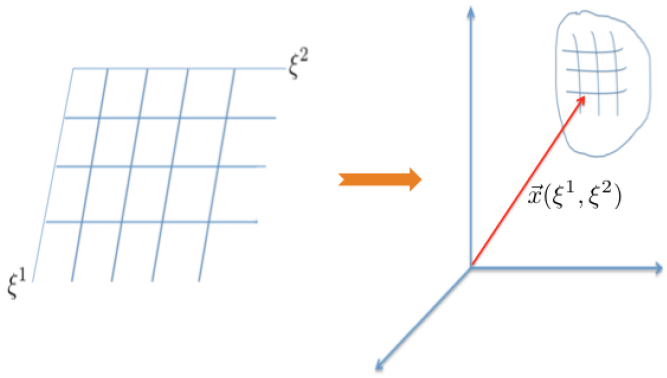


Figure 2.4. The metric transition.

In the next step, we substitute all newly defined variables into the Equation 2.137

$$\int \left(g^{ij}\partial_j \mathbf{f}\right) g_{ik} \left(g^{kl}\partial_l \mathbf{f}\right) \sqrt{det(g)}d\xi^1 d\xi^2 = \int \left(\nabla^2 \mathbf{f}\right)\mathbf{f} dV \tag{2.146}$$

and $\delta_i^l = g_{ik}g^{kl}$ therefore,

$$\begin{aligned}
\int \left(\nabla^2 \mathbf{f}\right)\mathbf{f} dV &= \int \left(g^{ij}\partial_j \mathbf{f}\right)\left(\delta_i^l \partial_l \mathbf{f}\right) \sqrt{det(g)}d\xi^1 d\xi^2 \\
&= \int g^{ij}\partial_j \mathbf{f}\partial_i \mathbf{f} \sqrt{det(g)}d\xi^1 d\xi^2 \\
&= \int -\frac{1}{\sqrt{det(g)}}\partial_j \left(\sqrt{det(g)}g^{ij}\partial_i \mathbf{f}\right)\mathbf{f}\sqrt{det(g)}d\xi^1 d\xi^2
\end{aligned} \tag{2.147}$$

As a result, we obtain the Laplace-Beltrami operator which is explicitly given by

$$\nabla_g f = \frac{1}{\sqrt{detg}} \sum_{i,j} \frac{\partial}{\partial \xi^i} \left( g^{ij} \sqrt{detg} \frac{\partial f}{\partial \xi^j} \right) \tag{2.148}$$

here the terms on the operator are given by

$$\boldsymbol{t_i} = \frac{\partial \mathbf{x}}{\partial \xi^i}, \qquad g_{ij} = \langle \mathbf{t_i}, \mathbf{t_j} \rangle, \qquad g^{ij} = g_{ij}^{-1} \tag{2.149}$$

If $\tau(\mathbf{x}) \to \infty$ as $\epsilon \to 0$, we expect that $\mathbf{x}$ is in the boundary layer near $\partial\Omega_a$. To find out the NET, we take the origin $\mathbf{0} \in \partial\Omega_a$ and the boundary curve $\partial\Omega$ is indicated by the arclength $s = \big(x(s), y(s)\big)$ as well as rescaling $s$ yields

$$\begin{aligned} \partial\Omega &= \left\{ \big(x(s), y(s)\big) : -\frac{1}{2} < s < \frac{1}{2} \right\} \\ \left( x(-\frac{1}{2}), y(-\frac{1}{2}) \right) &= \left( x(\frac{1}{2}), y(\frac{1}{2}) \right) \end{aligned} \tag{2.150}$$

We suppose that $x(s)$ and $y(s)$ are properly real analytic in the interval $2 \mid s \mid < 1$ and the absorbing part of the boundary $\partial\Omega_a$ is respectively the arc, which is given by

$$\partial\Omega_a = \left\{ \big(x(s), y(s)\big) :\mid s \mid < \epsilon \right\} \tag{2.151}$$

We can write the Neumann function as

$$N(\mathbf{x}, \xi) = -\frac{1}{2\pi} \log(d(\mathbf{x}, \xi)) + v_N(\mathbf{x}, \xi), \qquad for \qquad \mathbf{x} \in B_\delta(\xi) \tag{2.152}$$

here $B_\delta(\xi)$ is a geodesic ball with the radius $\delta$ centered at $\xi$ and $v_N(\mathbf{x},\xi)$ is a regular function. We choose a normal geodesic coordinate system $(x, y)$ at the origin and one of the coordinates should intersect with the tangent coordinate of $\partial\Omega_a$. For the simplicity, we take unit vectors $e_1$, $e_2$ which are orthogonal bases in the tangent plane at 0. In this sense we can write any vector field as

$$\mathbf{X} = x_1\mathbf{e_1} + x_2\mathbf{e_2} \tag{2.153}$$

and the corresponding metric tensor $g$ is given by

$$g_{ij} = \delta_{ij} + \epsilon^2 \sum_{kl} a_{ij}^{kl} x_k x_l + O(\epsilon^2) \tag{2.154}$$

Since $\epsilon$ is small, $\mid x_k \mid < 1$. Let's consider that $\mathbf{x}$ and $\mathbf{y}$ are centered at the origin of the geodesic ball with radius $\epsilon$ and

$$d(\mathbf{x},\mathbf{y}) = d_E(\mathbf{x},\mathbf{y}) + O(\epsilon^2) \tag{2.155}$$

where $d_E$ is the Euclidean metric. For the asymptotic expansion of the solution of the Equation 2.130 for small $\epsilon$, when $\mathbf{x}$ and $\xi$ are on the boundary, $v_N(\mathbf{x},\xi)$ turns out to be a singular function. Consequently the singular part gains an additive factor of 2, because of the "image charge". Substituting the new regular part,$\tilde{v}_N$ , into the Equation 2.104 gives $N$. Therefore, we can write the corresponding relation

$$\int_{|s'|<\epsilon} \left[\tilde{v}_N(\mathbf{x}(s');\xi(s)) - \frac{\log(d(\mathbf{x}(s');\xi(s)))}{\pi}\right] f(s')S(ds') = C_\epsilon \tag{2.156}$$

where the induced length on the boundary is denoted by $S(ds')$, and the further terms are explained in the following steps

$$\mathbf{x} = \big(x(s), y(s)\big), \qquad \xi = \big(\xi(s), \eta(s)\big), \qquad f(s') = g_0(\mathbf{x}(s')) \tag{2.157}$$

We expand the logarithmic function with respect to $\epsilon$

$$\log(d(\mathbf{x}(\mathbf{s}), \xi(\mathbf{s}'))) = \log\left(\sqrt{\big(x(s') - \xi(s)\big)^2 + \big(y(s') - \eta(s)\big)^2}\big(1 + O(\epsilon^2)\big)\right) \tag{2.158}$$

and the other functions are written in powers of $s$ and $s'$

$$S(ds)f(s) = \sum_{j=0}^{\infty} f_j s^j ds \tag{2.159}$$

$$\tilde{v}_N\big(\mathbf{x}(\mathbf{s}');\xi(\mathbf{s})\big)S(ds') = \sum_{j=0}^{\infty} v_j(s')s^j ds' \qquad for \qquad |\ s\ | < \epsilon \tag{2.160}$$

where $v_j(s')$ and $f_j$ are unknown coefficients. For the exact results, we substitute them into the Equation 2.156. Now we are looking for the expansion of the logarithmic term in the Equation 2.156. As $x(s')$, $y(s')$, $\xi(s)$ and $\eta(s)$ are analytic functions, we can write

$$\begin{aligned}\int_{-\epsilon}^{\epsilon}(s')^n \log(d\big(\mathbf{x}(\mathbf{s}),\xi(\mathbf{s}')\big))ds' &= \int_{-\epsilon}^{\epsilon}(s')^n \log\sqrt{\big(x(s')-\xi(s)\big)^2+\big(y(s')-\eta(s)\big)^2}\\ &\quad * \big(1+O(\epsilon^2)\big)ds'\\ &= \int_{-\epsilon}^{\epsilon}(s')^n \log\left\{\mid s'-s \mid \left(1+O\big((s'-s)^2\big)\right)\right\}\\ &\quad * \big(1+O(\epsilon^2)\big)ds' \qquad (2.161)\end{aligned}$$

We consider only the leading term in the Taylor expansion of logarithmic term and hence we end up with

$$\int_{-\epsilon}^{\epsilon}\log(s-s')^2 ds' = 4\epsilon\big(\log\epsilon-1\big)+2\sum_{j=1}^{\infty}\frac{1}{(2j-1)j}\frac{s^{2j}}{\epsilon^{2j-1}} \qquad (2.162)$$

For even $n \geq 0$, we obtain

$$\int_{-\epsilon}^{\epsilon}(s')^n \log(s-s')^2 ds' = 4\left(\frac{\epsilon^{n+1}}{n+1}\log\epsilon-\frac{\epsilon^{n+1}}{(n+1)^2}\right)-2\sum_{j=1}^{\infty}s^{2j}\frac{\epsilon^{n-2j+1}}{j(n-2j+1)} \qquad (2.163)$$

whereas odd $n$ values give

$$\int_{-\epsilon}^{\epsilon}(s')^n \log(s-s')^2 ds' = -4\sum_{j=1}^{\infty}\frac{s^{2j+1}}{2j+1}\frac{\epsilon^{n-2j}}{n-2j} \qquad (2.164)$$

Substitution of the expansions into the Equation 2.156 gives

$$0 = \int_{-\epsilon}^{\epsilon} \Bigg\{ -\frac{1}{\pi} \log \Bigg[ \mid s' - s \mid^2 \left( 1 + O\big((s'-s)^2\big) \right) \Big] \big(1 + O(\epsilon^2)\big) \Bigg] + \sum_{j=0}^{\infty} v_j(s') s^j \Bigg\} * \sum_{j=0}^{\infty} f_j s'^j ds' + C_\epsilon \tag{2.165}$$

In the expansion of $s$, the leading order is given by

$$\epsilon(\log \epsilon - 1) f_0 + \sum_p \left( \frac{\epsilon^{2p+1}}{2p+1} \log \epsilon - \frac{\epsilon^{2p+1}}{(2p+1)^2} \right) f_{2p} = \frac{\pi}{2} \int_{-\epsilon}^{\epsilon} v_0(s') ds' + C_\epsilon \tag{2.166}$$

To find out the leading term in the expansion of $C_\epsilon$ we define the relation as

$$\frac{1}{2} \int_{-\epsilon}^{\epsilon} f(s) S(ds) = \sum_p \frac{\epsilon^{2p+1}}{2p+1} f_{2p} \tag{2.167}$$

The compatibility condition in the Equation 2.118 yields

$$\int_{-\epsilon}^{\epsilon} f(s) S(ds) = -\frac{\mid \Omega_g \mid}{D} \tag{2.168}$$

and also using the fact that

$$\int_{-\epsilon}^{\epsilon} v_0(s') S(ds) = O(\epsilon) \tag{2.169}$$

Using the Equation 2.130 in this setting and performing an asymptotic solution, finally the leading order singularity $C_\epsilon$ is reduced to the following form

$$C_\epsilon = \frac{\mid \Omega_g \mid}{D\pi}\left[\log\frac{1}{\epsilon} + O(1)\right], \qquad for \quad \epsilon \ll 1 \tag{2.170}$$

We obtain ultimately the $NET$ from a point $\mathbf{x} \in \Omega$ outside of the boundary layer by solving the Helmholtz integral equation in the Equation 2.130

$$\tau(\mathbf{x}) = \frac{\mid \Omega_g \mid}{\pi D}\left[\log\frac{1}{\epsilon} + O(1)\right] = C_\epsilon, \qquad for \quad \epsilon \ll 1 \tag{2.171}$$

where $D$ is the diffusion coefficient. If there is no boundary other than the absorbing one, for example a compact closed surface such as a sphere, Neumann and Dirichlet become the same problem and we do not need to put the image correction. For the exact solution of sphere, Z. Schuss and his colleagues solved this problem and the result is given by

$$\tau(\mathbf{x}) = \frac{\mid \Omega_g \mid}{2\pi D}\left(\log\frac{1}{\delta} + O(1)\right) \tag{2.172}$$

here $\delta$ is the opening angle of the spherical cap and $\mid \Omega_g \mid = 4\pi R^2$ is the area of the 2 dimensional surface of the sphere [9].

# 3. ASYMPTOTIC EXPANSION AND NARROW ESCAPE TIME

## 3.1. Perturbation of Boundary Condition

In this part, we treat the boundary conditions under the case of a strong localized perturbation and mainly follow the articles [16], [17], [18] and [19]. This is going to be the basis of our approach in subsection *Exit Time for Time Dependent Metrics*. For possible future applications, we prefer to review the more general case here. For the general case, let us look at the unperturbed eigenvalue problem for the Schrödinger operator in a domain, $\Omega$, of $R^n$.

$$\left[-\nabla^2 + U(x)\right] u_0(x) = \lambda_0^g \varrho(x) u_0(x) \ , \quad x \in \Omega \tag{3.1}$$

$$\left[\partial_n + b(x)\right] u_0(x) = 0 \ , \quad x \in \partial\Omega \tag{3.2}$$

$$\int_\Omega u_0^2(x)\varrho(x)dx = 1 \tag{3.3}$$

where $U(x)$ is the potential, $\varrho(x)$ is the weight function and $b(x)$ is called the boundary impedance. We assume that the solution to the Equation 3.1, 3.2 and 3.3 gives a simple isolated eigenvalue, $\lambda_0^g$, and $u_0(x)$ is the corresponding eigenfunction.

Next, we have a sphere of radius $\epsilon$ centered at a point $x_0$ on $\partial\Omega$, but this time we will look for the solution to a strong perturbation of the boundary condition for the Equation 3.2. Let us rewrite the boundary conditions;

$$\nabla^2 u(x,\epsilon) + [\lambda(\epsilon)\varrho(x) - U(x)]\, u(x,\epsilon) = 0, \quad x \in \Omega, \tag{3.4}$$

$$\partial_n u(x,\epsilon) + bu(x,\epsilon) = 0, \quad x \in \partial\Omega, \tag{3.5}$$

$$\epsilon\partial_n u(x,\epsilon) + \kappa u(x,\epsilon) = 0, \quad x \in \partial\Omega_\epsilon, \tag{3.6}$$

$$\int_\Omega u^2(x,\epsilon)\varrho(x)dx = 1 \tag{3.7}$$

where $\kappa$ is a constant term, $\partial\Omega_\epsilon$ is the part of boundary within the sphere of radius $\epsilon$, and finally $\partial\Omega$ is the remaining part of the boundary of $\Omega$. We assume that the constant in the Equation 3.6 is altered to $\frac{\kappa}{\epsilon}$ within the sphere and hence we multiply the first equation in the left-hand side with $\epsilon$.

### 3.1.1. Deletion of A Small Subdomain (n=2)

Now we study the perturbed eigenvalue problem in 2 dimension. We construct the perturbed solutions by using the method of matched asymptotic expansions. For the inner expansion, large changes occur in the solution around the strong perturbation whereas the outer expansion leads to relatively small effects. We expect that these two expansions are matched on the boundary, and hence we can find out the unknown coefficients in the expansions. Since the perturbation in the inner region produces more considerable effects we magnify the extent, and thus we introduce the stretched variables to define the inner expansion of $u$

$$y = \frac{x - x_0}{\epsilon} \qquad \textit{and} \qquad v(y,\epsilon) = u(x_o + \epsilon y, \epsilon) \tag{3.8}$$

and we write the inner expansion of $u$ as

$$u(x_0+\epsilon y,\epsilon) = v(y,\epsilon) = \mu_0(\epsilon)v_0(y)+\mu_1(\epsilon)v_1(y)+\mu_2(\epsilon)v_2(y)+\mu_3(\epsilon)v_3(y)+..... \quad (3.9)$$

The outer expansion of $u$ is given by

$$u = u_0(x) + \nu_1(\epsilon)u_1(x) + \nu_2(\epsilon)u_2(x) + \nu_3(\epsilon)u_3(x) + ..... \qquad \mid x - x_0 \mid \gg O(\epsilon) \quad (3.10)$$

here $\nu_i(\epsilon)$ is the gauge functions which satisfy $\nu_i(\epsilon) \ll 1$ and $\nu_i(\epsilon) \gg \nu_{i+1}(\epsilon) \quad as \quad \epsilon \to 0$. In the same way, we expand the eigenvalue, $\lambda(\epsilon)$:

$$\lambda(\epsilon) = \lambda_0^g + \nu_1(\epsilon)\lambda_1 + \nu_2(\epsilon)\lambda_2 + \nu_3(\epsilon)\lambda_3 + .... \quad (3.11)$$

For the solution to the outer expansion, we submit the Equation 3.10 and the Equation 3.11 into the boundary condition in the Equation 3.4.

$$\begin{aligned}
\nabla^2 \left[u_0(x) + \nu_1(\epsilon)u_1(x) + ...\right] + \left[\lambda(\epsilon)\varrho(x) - U(x)\right]\left[u_0(x) + \nu_1(\epsilon)u_1(x) + ...\right] &= 0 \\
\nabla^2 u_0(x) + \left(\lambda_0^g\varrho - U(x)\right)u_0 + \nabla^2\left(\nu_1 u_1\right) + \nu_1\lambda_1\varrho u_0 + \lambda_0^g\varrho\mu_1 u_1 - U\nu_1 u_1.... &= 0 \\
\nabla^2 u_1 + \lambda_1\varrho u_0 + \lambda_0^g\varrho u_1 - U u_1 &= 0 \\
\nabla^2 u_1 - U u_1 + \lambda_0^g\varrho u_1 = -\lambda_1\varrho u_0, \qquad \mid x - x_0 \mid &\gg O(\epsilon)
\end{aligned} \quad (3.12)$$

For the outer correction $u_1$, the outer expansion on the boundary in the Equation 3.5 produces

$$\begin{aligned}
\left(\partial_n + b\right)\left[u_0 + \nu_1(\epsilon)u_1 + \nu_2(\epsilon)u_2 + \nu_3(\epsilon)u_3...\right] &= 0 \\
\left(\partial_n + b\right)u_0 + \left(\partial_n + b\right)u_1.... &= 0 \\
\left(\partial_n + b\right)u_1 = 0, \qquad x \in \partial\Omega &
\end{aligned} \quad (3.13)$$

If we submit the outer expansion in the final Equation 3.7, we end up with

$$\int \left[u_0 + \nu_1(\epsilon)u_1 + \nu_2(\epsilon)u_2 + ...\right] \varrho \left[u_0 + \nu_1(\epsilon)u_1 + \nu_2(\epsilon)u_2 + ...\right] dx = 1$$

$$\int u_0^2 \varrho dx + \int u_0 \varrho u_1 dx + ... = 1$$

$$\int u_0 u_1 \varrho dx = 0 \qquad (3.14)$$

After all calculations, let us summarize the final results in the outer region. Substituting the outer expansion in the Equation 3.10 and the eigenvalue expansion in the Equation 3.11 into the boundary conditions gives

$$\nabla^2 u_1 - U u_1 + \lambda_0^g \varrho u_1 = -\lambda_1 \varrho u_0, \qquad | \, x - x_0 \, | \gg O(\epsilon) \qquad (3.15)$$

$$(\partial_n + b)\, u_1 = 0, \qquad x \in \partial\Omega \qquad (3.16)$$

$$\int u_0 u_1 \varrho dx = 0 \qquad (3.17)$$

Now we define the perturbed eigenvalue problem by extracting a small subdomain $\Omega_\epsilon$ with radius $O(\epsilon)$ from $\Omega$. The subdomain $\Omega_\epsilon$ is located at a point $x_0$ in $\Omega$, and we use the boundary conditions in the Equation 3.4, 3.5, 3.6 and 3.7 on the resulting hole. In the inner region, we use the stretched variable $y = \frac{x - x_0}{\epsilon}$ and set $v(y, \epsilon)$ and then we end up with

$$\nabla_y^2 v - \epsilon^2 U(x_0 + \epsilon y) v = -\epsilon^2 \lambda \varrho(x_0 + \epsilon y) v, \qquad y \notin \Omega_1 \qquad (3.18)$$

$$\partial_n v + \kappa v = 0, \qquad y \in \partial\Omega_1 \qquad (3.19)$$

where $\nabla_y^2$ and $\partial_n$ are the derivatives with respect to $y$ and $\Omega_1$ defines the domain $\Omega_\epsilon$ in the $y$ variables. Substituting the Equation 3.9 into the Equation 3.18 yields

$$\left[\nabla_y^2 - \epsilon^2 U\right] \left[\mu_0(\epsilon)v_0 + \mu_1(\epsilon)v_1 + ...\right] = -\epsilon^2 \lambda \varrho \left[\mu_0(\epsilon)v_0 + \mu_1(\epsilon)v_1 + ...\right] \tag{3.20}$$

$$\nabla_y^2 \mu_0 v_0 - \epsilon^2 U \mu_0 v_0 ..... = -\epsilon^2 \lambda \varrho \mu_0 v_0 ..... \tag{3.21}$$

The leading term in the inner expansion gives

$$\nabla_y^2 v_0 = 0, \qquad y \notin \Omega_1 \tag{3.22}$$

Next we analyze the boundary condition in the Equation 3.19 for the inner region and we look for the leading term.

$$\begin{aligned} \left(\partial_n + \kappa\right) \left[\mu_0(\epsilon)v_0 + \mu_1(\epsilon)v_1 + \mu_2(\epsilon)v_2 + ...\right] &= 0 \\ \left(\partial_n + \kappa\right) v_0 = 0, \qquad & y \in \Omega_1 \end{aligned} \tag{3.23}$$

We assume that there is an overlap domain for these expansions. We can determine the unknown coefficients, since the inner and outer expansions must give the similar asymptotical results in this overlap domain. Hence, the matching condition in this domain is provided by

$$u_0(x) + \nu_1(\epsilon)u_1(x) + \nu_2(\epsilon)u_2(x)... \sim \mu_0(\epsilon)v_0(y) + \mu_1(\epsilon)\nu_1(y) + \mu_2(\epsilon)\nu_2... \tag{3.24}$$

Next, we consider the case of $\kappa > 0$ to find out the first correction to $\lambda_0$. In two dimensions, the fundamental solution of the Laplace equation of $v_0$, the Equation 3.22, is given asymptotically by

$$\hat{v}(y) = \log \mid y \mid - \log [d(\kappa)] + ....., \qquad as \qquad \mid y \mid \to \infty \tag{3.25}$$

In the case of $\kappa > 0$, the solution is unique and the constant $d(\kappa)$ based on simple hole geometries is found out. Let us consider a more specialized case, when $\kappa = \infty$, $d(\infty)$ is defined as the logarithmic capacitance of $\Omega_1$. We note that a circular domain has the smallest logarithmic capacitance. In the matching conditions, $u_0$ on the left part and $\mu(\epsilon)v_0(y)$ on the right are the leading terms in the Equation 3.24. They satisfy the matching condition if

$$\mu_0(\epsilon) = -\frac{1}{\log [\epsilon d(\kappa)]}$$

$$v_0(y) = u_0(x_0)\hat{v}(y) = u_0(x_0) [\log \mid y \mid - \log (d(\kappa))] \tag{3.26}$$

Next, we substitute these defined coefficients in the Equation 3.26 into the matching conditions and it gives

$$u_0(x) + \nu_1(\epsilon)u_1(x) + \nu_2(\epsilon)u_2(x) + .... \sim \left[-\frac{1}{\log (d(\kappa))}\right] u_0 [\log \mid y \mid - \log (d(\kappa))]$$

$$+ \mu_1(\epsilon)v_1(y) + \mu_2(\epsilon)v_2(y) + .... \tag{3.27}$$

Due to the fundamental solution of the Laplace equation of $v_0$, the matching order change and hence the first equation $u_0$ on the left matches with the second equation on the right. On the other hand, the second equation $\nu_1(\epsilon)u_1(x)$ on the left part should be matched with the first term on the right.

$$\nu_1 u_1 = \left[-\frac{1}{\log\left(d(\kappa)\right)}\right] u_0 \log \mid y \mid, \qquad y = \frac{x - x_0}{\epsilon}$$

$$\nu_1 u_1 = \left[-\frac{1}{\log\left(\epsilon d(\kappa)\right)}\right] u_0 \log \mid x - x_0 \mid$$

$$\nu_1 = \left[-\frac{1}{\log\left(\epsilon d(\kappa)\right)}\right] \qquad and \qquad u_1 \sim u_0 \log \mid x - x_0 \mid \qquad as \quad x \to x_0 \tag{3.28}$$

Using Green's theorem and the boundary conditions, we obtain the solvability condition for $u_1$

$$\begin{aligned} -\lambda_1 \int_{\Omega/\Omega_\sigma} u_0^2(x)\varrho(x)dx &= \int_{\partial\Omega_\sigma} \left(u_0 \partial_n \nu_1 - u_1 \partial_n u_0\right) dx \\ -\lambda_1 &= \int_{\partial\Omega_\sigma} \left[u_0 \partial_n \left(u_0 \log \mid x - x_0 \mid\right) - \left(u_0 \log \mid x - x_0 \mid\right) \partial_n u_0\right] dx \\ \lambda_1 &= 2\pi \left[u_0(x_0)\right]^2 \end{aligned} \tag{3.29}$$

where $\Omega_\sigma$ is a small sphere with radius $\sigma$ centered at $x_0$ and $\partial_n$ is the outward normal derivative. For the other terms in the expansion of the eigenvalue, in the outer region we take the gauge functions as

$$\nu_j(\epsilon) = \left(-\frac{1}{\log\left[\epsilon d(\kappa)\right]}\right)^j \qquad for \quad j = 1, 2, 3... \tag{3.30}$$

Then, we rewrite the outer and eigenvalue expansions with the new gauge functions in the conditions given in the Equation 3.4, 3.5, 3.6, 3.7, and eventually we obtain following relations for $u_j(x)$

$$\nabla^2 u_j - U(x)u_j + \lambda_0^g \varrho(x)u_j = -\lambda_j \varrho(x)u_0 - \sum_{i=1}^{j-1} \lambda_{j-i}\varrho(x)u_i, \quad |\, x - x_0 \,| \gg O(\epsilon), \tag{3.31}$$

$$[\partial_n + b]\, u_j = 0, \qquad x \in \Omega \tag{3.32}$$

$$\sum_{i=0}^{j} \int_\Omega u_i u_{j-i} \varrho(x) dx = 0 \tag{3.33}$$

For the inner region, we choose the gauge functions as

$$\mu_j(\epsilon) = \left[ -\frac{1}{\log\left[\epsilon d(\kappa)\right]} \right]^{j+1} \qquad for \quad j = 0, 1, 2, 3... \tag{3.34}$$

Likewise in the outer region, we rewrite the conditions in the Equation 3.4, 3.5, 3.6, 3.7 with the new variables and we end up with

$$\begin{aligned} \nabla_y^2 v_j &= 0, \qquad y \notin \Omega \\ \partial_n v_j + \kappa v_j &= 0, \qquad y \in \partial\Omega_1 \end{aligned} \tag{3.35}$$

Since $v_j$ grows logarithmically as $|\, y \,| \to \infty$, we take

$$v_j(y) = a_j u_0(x_0)\hat{v}(y) \tag{3.36}$$

where $a_j$ is a constant and $\hat{v}(y)$ is the fundamental solution of Laplace equation of $v(y)$. From the matching condition in the Equation 3.26, we find out $a_0 = 1$. Let us rewrite the inner expansion with the new coefficients

$$v(y,\epsilon) \sim a_0 u_0(x_0) + \sum_{i=1}^{\infty} \left[ -\frac{1}{\log\left[\epsilon d(\kappa)\right]} \right]^i u_0(x_0) \Big( a_{i-1} \log \mid x - x_0 \mid + a_i \Big) + .... \quad (3.37)$$

In the matching condition we find $u_1$ in the Equation 3.28 and similarly $u_j$ should have the following singular behavior as $x \to x_0$.

$$u_j(x) \sim a_{j-1} u_0(x_0) \log \mid x - x_0 \mid, \qquad for \quad j = 1, 2, 3... \quad (3.38)$$

Using Green's theorem and the boundary conditions in the Equation 3.31, 3.32, 3.33 give the solvability condition for $u_j$ and ultimately we obtain

$$\lambda_j = 2\pi a_{j-1} \left[u_0(x_0)\right]^2 - \sum_{i=1}^{j-1} \lambda_{j-1}(u_i, u_0), \qquad for \quad j = 1, 2, 3... \quad (3.39)$$

The following step is that we substitute the Equation 3.39 into the Equation 3.11 for the expansion of $\lambda(\epsilon)$

$$\lambda(\epsilon) = \lambda_0^g + \Big( -\frac{1}{\log\left[\epsilon d(\kappa)\right]} \Big) 2\pi \left[u_0(x_0)\right]^2 + \sum_{j=2}^{\infty} \Big( -\frac{1}{\log\left[\epsilon d(\kappa)\right]} \Big)^j \lambda_j + .... \quad (3.40)$$

After all calculations, we can summarize our results as follows. The outer expansion is given by

$$u(x,\epsilon) = u_0(x) + \sum_{j=1}^{\infty} \Big( -\frac{1}{\log\left[\epsilon d(\kappa)\right]} \Big)^j u_j(x) + ..., \qquad \mid x - x_0 \mid \gg \epsilon \quad (3.41)$$

Ultimately we find out the inner expansion in the following statement

$$u(x,\epsilon) = u_0(x_0)\hat{v}\left(\frac{x-x_0}{\epsilon}\right)\sum_{j=0}^{\infty}\left(-\frac{1}{\log\left[\epsilon d(\kappa)\right]}\right)^{j+1} a_j + ...., \qquad \mid x - x_0 \mid = O(\epsilon) \tag{3.42}$$

### 3.1.2. Exit Time Distribution

Let us suppose that a particle initially starting from $y$ at time zero performs a Brownian motion in 3D domain, $\Omega$. The domain $\Omega$ has reflecting wall $\partial\Omega$ which includes $N$ small holes. The radius of each hole is $\epsilon$ and its hole is centered at $x_0^i$. The probability density that the particle is at $x$ time $t$ is denoted by $p(x,y,t,\epsilon)$. We assume that a diffusion coefficient $\kappa > 0$, and then $p$ satisfies

$$\begin{aligned} p_t &= D\nabla_x^2 p, \qquad x \in \Omega \\ \partial_n p &= 0, \qquad x \in \partial\Omega_r \quad i = 1, ...N \\ p &= 0, \qquad x \in \partial\Omega_\epsilon \quad i = 1, ...N \\ p &= \delta(x-y), \qquad t = 0 \end{aligned} \tag{3.43}$$

The conditions in the Equation 3.43 give the solution

$$p(x,y,t,\epsilon) = \sum_{n=1}^{\infty} e^{-(\lambda_n(\epsilon)Dt)} u_n(x,\epsilon)u_n(y,\epsilon) \tag{3.44}$$

where $\lambda_n$ is the nth eigenvalue and $u_n$ displays the normalized eigenfunction.

$$\begin{aligned} \nabla_x^2 u_n(x,\epsilon) &= -\lambda_n(\epsilon)u_n(x,\epsilon), \qquad x \in \Omega \\ \int_\Omega u_n^2(x,\epsilon)dx &= 1 \end{aligned} \tag{3.45}$$

The probability $P(y,t,\epsilon)$ that the particle is in $\Omega$ at time $t$ is

$$\begin{aligned} P(y,t,\epsilon) &= \int_{\Omega} p(x,y,t,\epsilon)dx \\ &= \sum_{n=1}^{\infty} exp\left[-\lambda_n(\epsilon)Dt\right] u_n(y,\epsilon) \int_{\Omega} u_n(x,\epsilon)dx \end{aligned} \tag{3.46}$$

Let us assume that the initial position of $y$ is uniformly distributed over $\Omega$. Next, we divide the solution of the Equation 3.43 by the volume of $\Omega$, and after that, the integration of the result with respect to $y$ gives

$$p_0(x,t,\epsilon) = \frac{1}{V} \sum_{n=1}^{\infty} exp\left[-\lambda_n(\epsilon)Dt\right] u_n(x,\epsilon) \int_{\Omega} u_n(y,\epsilon)dy \tag{3.47}$$

here $V = \mid \Omega \mid$. Eventually, the probability $P_0(t,\epsilon)$ they the particle is in $\Omega$ at time $t$ under the uniform distribution is produced by

$$P_0(t,\epsilon) = \int_{\Omega} p_0(x,t,\epsilon)dx = \frac{1}{V} \sum_{n=1}^{\infty} exp\left[-\lambda_n(\epsilon)Dt\right] \left( \int_{\Omega} u_n(x,\epsilon)dx \right)^2 \tag{3.48}$$

For the case $\epsilon = 0$, we take that $\lambda_{n0}$ and $u_{no}$ are the nth eigenvalue and normalized eigenfunction respectively. We follow the examples for 2 and 3 dimensions given in Ward et al [16]. The next step is to determine the correction to $\lambda_{n0}$. Thereby, the inner expansion should be near each $x_0^i$, and the outer expansion should be constructed away from the perforations. Finally, we end up with

$$\lambda_n(\epsilon) = \lambda_{n0} + 2\pi\epsilon \sum_{i=1}^{N} C^i(\infty) \left[u_{n0}(x_0^i)\right]^2 + ... \tag{3.49}$$

$$u_n(x,\epsilon) = u_{n0}(x) + \epsilon u_{n1}(x) + ..... \qquad \mid x - x_0^i \mid \gg O(\epsilon) \qquad i = 1, ...N \tag{3.50}$$

where $C^i(\infty)$ is the capacitance of ith hole. The correction term $u_{n1}$ for the outer expansion satisfies

$$\nabla_x^2 n_{n1} + \lambda_{n0} u_{n1} = -\lambda_{n1} u_{n0}, \qquad x \in \Omega \tag{3.51}$$

$$\partial_\nu u_{n1} = 0, \qquad x \in \Omega \tag{3.52}$$

$$u_{n1} \sim -\frac{u_{n0}(x_0^i) C^i(\infty)}{\mid x - x_0^i \mid} \quad as \quad x \to x_0^i \qquad i = 1, ....N \tag{3.53}$$

The inner expansion of $u_n(x, \epsilon)$ near $x_0^i$ is given by

$$u_n = v_0^i \left( \frac{x - x_0^i}{\epsilon} \right) + ... \qquad \mid x - x_0^i \mid = O(\epsilon) \qquad i = 1, ...N \tag{3.54}$$

If we use local curvilinear coordinate systems near $x_0^i$, each term $v_0^i$ will satisfy the boundary conditions. Let us consider the case of the absence of the hole, the first eigenvalue is

$$\lambda_{10} = 0 \tag{3.55}$$

and the corresponding eigenfunction is

$$u_{10} = \frac{1}{\sqrt{V}} \tag{3.56}$$

Since the $u_{n0}$ is orthogonal, subsequently we get

$$\int_\Omega u_{n0}(x) dx = 0 \quad for \quad n \geq 2 \tag{3.57}$$

The Equation 3.57 and the Equation 3.49 yield

$$\int_{\Omega} u_n(x,\epsilon)dx = \sqrt{V}\delta_{n1} + \epsilon \int_{\Omega} u_{n1}(x)dx + O(\epsilon) \tag{3.58}$$

Let us rewrite the probability $P_0(t,\epsilon)$ that the particle is in $\Omega$ at time $t$ in terms of newly defined variables.

$$P_0(t,\epsilon) = exp\left[-\frac{2\pi\epsilon Dt}{V}\sum_{i=1}^{N} C^i(\infty)\right]\left(1 + 2\epsilon\frac{2}{\sqrt{V}}\int_{\Omega} u_{11}(x)dx + O(\epsilon)\right) \tag{3.59}$$

$$p_0(x,t,\epsilon) = \frac{1}{V}exp\left[-\frac{2\pi\epsilon Dt}{V}\sum_{i=1}^{N} C^i(\infty)\right](1 + O(\epsilon)) \tag{3.60}$$

For $t \gg O(-log(\epsilon))$, $p_0(x,t,\epsilon)$ in the Equation 3.59 is

$$p_0(x,t,\epsilon) = \frac{1}{V}exp\left[-\frac{2\pi\epsilon Dt}{V}\sum_{i=1}^{N} C^i(\infty)\right]\left(1 + \epsilon\sqrt{V}u_{11}(x) + \frac{\epsilon}{\sqrt{V}}\int_{\Omega} u_{11}(y)dy + O(\epsilon)\right) \tag{3.61}$$

Let us assume that each hole is circular and the radius is $\epsilon$, and then

$$C^i(\infty) = \frac{2}{\pi} \quad for \quad i = 1, ...N \tag{3.62}$$

Thereby the exponential terms in the Equation 3.60 and the Equation 3.61 are replaced by $exp\Big[-\frac{4\epsilon DtN}{V}\Big]$. Similarly we can do this analysis for the 2D case. Consider that each absorbing segment is $\partial\Omega_\epsilon$ and their length is $2\epsilon$. Then we use the eigenvalue in the Equation 3.49 with $d(\infty)=\frac{1}{2}$. Finally, we end up with

$$P_0(t,\epsilon)=exp\Big[-\frac{\pi NDt}{V}\nu(\epsilon)\Big]\Big(1+2\nu(\epsilon)\frac{1}{\sqrt{V}}\int_\Omega u_{11}(x)dx+O(\nu(\epsilon))\Big) \tag{3.63}$$

where $\nu(\epsilon)=\Big(-\frac{1}{\log(\frac{\epsilon}{2})}\Big)$, and $V$ is the area of $\Omega$. The outer solution turns out to be

$$u_n(x,\epsilon)=u_{10}+\nu(\epsilon)u_{11}+... \tag{3.64}$$

here $u_{11}$ satisfies the conditions in the Equation 3.51 and the Equation 3.53 with $n=1$. Eventually, we replace the Equation 3.53 with

$$u_{11}(x)\sim\frac{1}{\sqrt{V}}\log\mid x-x_0^i\mid \quad as \quad x\to x_0^i \quad i=1,...N \tag{3.65}$$

### 3.1.3. Exit Time for Time Dependent Metrics

Let us consider the two time scales: the diffusion time scale is here shown by $\tau_D$ and the geometric evolution scale is denoted by $\tau_G$. This is the typical time scale over which the geometry, i.e.. metric changes are not small. We know typically $\tau_D \ll \tau_G$. Hence as long as diffusion is concerned we may take $g_{ij}$ (coming from the embedding) as fixed. Yet in reality we know that $g_{ij}$ should be taken time dependent. The evolution of the metric is given by some equation determined by

geometric objects like extrinsic curvature etc. Yet we should take into account the fact that $\tau_{MFPT} \gg \tau_G$ for narrow escape problem, NEP. The standard equation is the diffusion equation,

$$-D\nabla_g^2 p = \frac{\partial p}{\partial t} \tag{3.66}$$

However this has a problem for a totally reflecting boundary. Total probability is not conserved if $g(t)$ is time dependent. We propose the subsequent form containing a correction term for probability conservation;

$$\left[\nabla_g^2 - \left(\frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g}\right)\right] p = \frac{\partial p}{\partial t} \tag{3.67}$$

We shall assume that $\frac{1}{\sqrt{g}}\frac{\partial}{\partial t}$ is a very small correction term in typical cases. Let us check the probability conservation,

$$\begin{aligned}
\frac{d}{dt}\int p\sqrt{g}d^2\xi &= \int \frac{\partial p}{\partial t}\sqrt{g}d^2\xi + \int p\frac{\partial}{\partial t}\sqrt{g}d^2\xi \\
&= \int \left[\nabla_g^2 - \frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g}\right] p\sqrt{g}d^2\xi + \int p\frac{\partial}{\partial t}\sqrt{g}d^2\xi \\
&= \int \left[\nabla_g^2 p\sqrt{g} - \frac{\partial}{\partial t}\sqrt{g}p\right] d^2\xi + \int p\frac{\partial}{\partial t}\sqrt{g}d^2\xi \\
&= \int \nabla_g^2 p\sqrt{g}d^2\xi
\end{aligned} \tag{3.68}$$

As a result, the Equation 3.67 evidently satisfies the probability conservation. If there is a reflecting boundary or no boundary

$$\begin{aligned}\frac{d}{dt}\int p\sqrt{g}d^2\xi &= \int \nabla_g^2 p\sqrt{g}d^2\xi \\ &= \int_{\partial\Omega} n_i g^{ij}\partial_j p ds = 0 \\ &\simeq \int_{\partial\Omega} \overrightarrow{\nabla} p \cdot \widehat{n} ds = 0\end{aligned} \tag{3.69}$$

Consider that $p(x,t \mid y)$ satisfies the forward Fokker-Planck equation

$$\frac{\partial p}{\partial t} + D\left[-\nabla_g^2 + \left(\frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g}\right)\right]p = 0 \tag{3.70}$$

For writing down an explicit solution, let us define the following eigenvalue equation,

$$\lambda_i^g \psi_i = \left[-\nabla_g^2 + \left(\frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g}\right)\right]\psi_i \tag{3.71}$$

Since the metric is a slowly changing function, we can take as an approximation for the transition probability $p(x,t \mid y,0)$ given in the subsequent form

$$p(x,t \mid y,0) \cong \sum_i e^{-\int_0^t \lambda_i(t')dt'} u_i(x \mid t) u_i(y \mid 0) \tag{3.72}$$

where we assume that the derivative of the wave-functions is negligible. If $t \to 0^+$, the summation becomes

$$\sum_i u_i(x \mid 0)u_i(y \mid 0) = \delta_g(x, y) \tag{3.73}$$

which is true due to completeness of the wave-functions at the same moment. As required we should check wether the transition probability satisfies the Chapman-Kolmogorov equation.

$$\int p(x,t \mid y,s)p(y,t \mid z,u)d_g y = \sum_{i,j} exp\big(-\int_s^t \lambda_i^g(t')dt'\big) \int u_i(x \mid t)u_i(y \mid s)\times$$

$$u_j(y \mid s)u_j(z \mid u)exp\big(-\int_u^s \lambda_j^g(t')dt'\big)d_g y$$

$$=\sum_{i,j} exp\big(-\int_s^t \lambda_i^g(t')dt'\big) - \int_u^s \lambda_j^g(t')dt' u_i(x \mid t)\delta_{ij}u_j(z \mid u)$$

$$=\sum_i exp\big(-\int_s^t \lambda_i^g(t')dt' + \int_u^s \lambda_i^g(t')dt'\big)u_i(x \mid t)u_i(z \mid u)$$

$$=p(x,t \mid z,u) \tag{3.74}$$

where we use the orthogonally of the wave-functions at any given instant. This relation shows that probability satisfies a proper evolving condition and hence it is important. According to the perturbation theory, we can write $\lambda$ and $u$ in the following form

$$\begin{aligned} u_i &= u_i^{(0)} + u_i^{(1)} \\ \lambda_i^g &= \lambda_i^{g(0)} + \lambda_i^{g(1)} \end{aligned} \tag{3.75}$$

and consequently our equation becomes

$$\left(\lambda_i^{g(0)} + \lambda_i^{(1)}\right)\left(u_i^{(0)} + u_i^{(1)}\right) = \left[-\nabla_g^2 + \left(\frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g}\right)\right]\left(u_i^{(0)} + u_i^{(1)}\right) \tag{3.76}$$

here $\lambda_i^{g(1)}$ is determined by

$$\lambda_i^{g(1)} = \langle u_i^{(0)} \mid \frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g} \mid u_i^{(0)}\rangle \tag{3.77}$$

and $u_i^{(1)}$ is given subsequently

$$u_i^{(1)} = \sum_{i\neq 0} \frac{\langle u_i^{(0)} \mid \frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g} \mid u_i^{(0)}\rangle}{\lambda_i^{g(0)} - \lambda_0^{g(0)}} \mid u_i^{(0)}\rangle \tag{3.78}$$

Now let us rewrite $p$ with the perturbed terms without adding the wave function corrections

$$p \cong \sum_i exp\Big[-\int_0^t \lambda_i^{g(0)}(t')dt' - \int_0^t \langle u_i^{(0)}(t') \mid \frac{1}{\sqrt{g}}\frac{\partial}{\partial t}\sqrt{g} \mid u_i^{(0)}(t')\rangle dt'\Big] u_i^{(0)}(x \mid t) u_i^{(0)}(y \mid 0) \tag{3.79}$$

The initial distribution is given by

$$p_{t=0}(y) = \frac{1}{\mid \Omega_{g(0)} \mid} \tag{3.80}$$

The average probability $\tilde{p}$ is thought to be

$$\begin{aligned}\tilde{p} &= \int p(x,t \mid y,0) p_{t=0}(y) d_g y \\ &= \sum_i exp\Big( - \int_0^t \lambda_i^{g(0)}(t')dt' - \int_0^t \langle u_i^{(0)}(t') \mid \frac{1}{\sqrt{g}} \frac{\partial}{\partial t} \sqrt{g} \mid u_i^{(0)}(t') \rangle dt' \Big) \times \\ & \quad u_i^{(0)}(x \mid t) \int u_i^{(0)}(y \mid 0) \frac{1}{\mid \Omega_{g(0)} \mid} d_g y \end{aligned} \tag{3.81}$$

We know that $u_0^{(0)}(x \mid t)$

$$u_0^{(0)}(x \mid t) = \frac{1}{\sqrt{\mid \Omega_{g(t)} \mid}} \tag{3.82}$$

and the integral of $u_0^{(0)}(y \mid 0)$ gives

$$\int u_0^{(0)}(y \mid 0) \frac{1}{\mid \Omega_{g(0)} \mid} d_g y = \frac{1}{\sqrt{\mid \Omega_{g(0)}}} \tag{3.83}$$

Consequently $\tilde{p}$ becomes

$$\begin{aligned}\tilde{p} \sim & exp\Big( - \int_0^t \lambda_0^{g(1)}(t')dt' - \int_0^t \int \sqrt{g} d^2\xi \frac{1}{\sqrt{\mid \Omega_{g(t')} \mid}} \Big[ \frac{1}{\sqrt{g}} \frac{\partial}{\partial t'} \sqrt{g} \Big] \frac{1}{\sqrt{\mid \Omega_g(t') \mid}} dt' \Big) \\ & \times \frac{1}{\sqrt{\mid \Omega_{g(t)} \mid}} \frac{1}{\sqrt{\mid \Omega_{g(0)} \mid}} \\ = & exp\Big( - \int_0^t \lambda_0^{g(1)}(t')dt' - \int_0^t \frac{1}{\mid \Omega_{g(t)} \mid} \frac{\partial}{\partial t'} \int_M \sqrt{g} d^2\xi dt' \Big) \frac{1}{\sqrt{\mid \Omega_{g(t)} \mid}} \frac{1}{\sqrt{\mid \Omega_{g(0)} \mid}} \end{aligned} \tag{3.84}$$

We know that

$$\int_M \sqrt{g} d^2\xi = \mid \Omega_{g(t)} \mid \tag{3.85}$$

Substituting the result into $\tilde{p}$ gives the corresponding relation

$$\begin{aligned} \tilde{p} =& exp\bigg( - \int_0^t \lambda_0^{g(1)}(t')dt' - \int_0^t \frac{\partial}{\partial t'} \ln \mid \Omega_g \mid dt' \bigg) \frac{1}{\sqrt{\mid \Omega_{g(t)} \mid}} \frac{1}{\sqrt{\mid \Omega_{g(0)} \mid}} \\ =& exp\bigg( - \int_0^t \lambda_0^{g(1)}(t')dt' - \ln \frac{\mid \Omega_{g(t)} \mid}{\mid \Omega_{g(0)} \mid} dt' \bigg) \frac{1}{\sqrt{\mid \Omega_{g(t)} \mid}} \frac{1}{\sqrt{\mid \Omega_{g(0)} \mid}} \end{aligned} \tag{3.86}$$

Eventually we find out $\tilde{p}$ in the following form

$$\tilde{p} = \frac{\sqrt{\mid \Omega_{g(0)} \mid}}{\mid \Omega_{g(t)} \mid^{3/2}} e^{-\int_0^t \lambda_0^{g(1)}(t')dt'} \tag{3.87}$$

Now we take the integral of $\tilde{p}$ over $d_g x$ and $dt$

$$\tau_{NET} = \int_0^\infty dt \int_{|\Omega|} \tilde{p} d_g x = \int_0^\infty dt e^{-\int_0^t \lambda_0^{g(1)}(t')dt'} \sqrt{\frac{\mid \Omega_{g(0)} \mid}{\mid \Omega_{g(t)} \mid}} \tag{3.88}$$

where we call $d_g x = \sqrt{det(g)} d\xi^1 \xi^2$. From the asymptotic analysis we know that

$$\lambda_0^g = \lambda_0^g(\epsilon = 0) + [-\log(\epsilon)]^{-1} 2\pi D \frac{1}{\mid \Omega_g \mid} + .... \tag{3.89}$$

where $\lambda_0^g(\epsilon = 0) = 0$ and thus the smallest eigenvalue for very small $\epsilon$ looks like

$$\lambda_0^{g(1)} \cong \frac{2\pi D}{\mid \Omega_g \mid} \frac{1}{\log\left(\frac{1}{\epsilon}\right)} + ... \tag{3.90}$$

Therefore we can write the following relation

$$\tau_{NET} = \int_0^\infty exp\Bigg(-2\pi D[\log(1/\epsilon)]^{-1} \int_0^t \frac{dt'}{\mid \Omega_g(t') \mid}\Bigg) \sqrt{\frac{\mid \Omega_{g(0)} \mid}{\mid \Omega_{g(t)} \mid}} \tag{3.91}$$

As a further approximation we give roughly the solution of the integral as an average. The idea behind this is the following. The 2 dimensional closed surface moves while preserving the volume inside. This can be thought as an oscillation around an average area. We propose the following model for the changes of area. Assume that the enclosed volume remains constant and as a result area fluctuates. To a first approximation we assume

$$\Omega_g(t') \cong \Omega_{g(0)} + \delta\Omega cos(\omega t) \tag{3.92}$$

where $\Omega_{g(0)}$ refers to an average area for the cell and $\delta\Omega$ represents the change of area. Moreover, $\omega = \frac{2\pi}{T}$ is relatively small and $\Omega_{g(0)}^2 > \delta\Omega_{g(t)}^2$ but not necessarily so small to be negligible. Eventually our result is that

$$\begin{aligned} \Omega_{g(0)} + \delta\Omega cos(\omega t) =& \Omega_{g(0)} + \delta\Omega\big(2cos^2(\frac{\omega t}{2}) - 1\big) \\ =& \Omega_{g(0)} - \delta\Omega + 2\delta\Omega cos^2(\frac{\omega t}{2}) \\ =& \big(\Omega_{g(0)} - \delta\Omega\big)\big[1 + \frac{2\delta\Omega}{\Omega_{g(0)} - \delta\Omega} cos^2(\frac{\omega t}{2})\big] \end{aligned} \tag{3.93}$$

As a result, our formula will be slightly modified

$$\tau_{NET} \cong \int_0^\infty \left[ exp\left( -2\pi D[\log(\frac{1}{\epsilon})]^{-1} \int_0^t \frac{dt'}{\mid \Omega_g(t') \mid} \right] dt \right) \sqrt{\frac{\mid \Omega_{g(0)} \mid}{\mid \Omega_{g(t)} \mid}}$$
$$\cong \int_0^\infty \left[ exp\left( -2\pi D[\log(\frac{1}{\epsilon})]^{-1} \int_0^t \frac{dt'}{\left(\Omega_{g(0)} - \delta\Omega\right)\left[1 + \frac{2\delta\Omega}{\Omega_{g(0)} - \delta\Omega} cos^2(\frac{\omega t}{2})\right]} \right] \right)$$
$$* \sqrt{\frac{\mid \Omega_{g(0)} \mid}{\mid \Omega_{g(t)} \mid}} dt \tag{3.94}$$

For the simplification, let us call $\left( -2\pi D[\log(\frac{1}{\epsilon})]^{-1} \right) = a$ in the Equation 3.94 and determine new terms as follows

$$\alpha = \left[ a \frac{2}{\omega \mid \Omega_{g(0)} \mid \sqrt{1 - \left(\frac{|\delta\Omega|}{|\Omega_{g(0)}|}\right)^2}} \right]$$

$$\beta = \frac{1 - \frac{|\delta\Omega|}{|\Omega_{g(0)}|}}{\sqrt{1 - \left(\frac{|\delta\Omega|}{|\Omega_{g(0)}|}\right)^2}} = \sqrt{\frac{1 - \frac{|\delta\Omega|}{|\Omega_{g(0)}|}}{1 + \frac{|\delta\Omega|}{|\Omega_{g(0)}|}}} \tag{3.95}$$

Since $\beta < 1$, $\frac{1-\beta^2}{\beta^2}$ gives the corresponding ratio

$$\frac{1 - \beta^2}{\beta^2} = \frac{2\delta\Omega}{\Omega_{g(0)} - \delta\Omega} = \frac{\frac{2\delta\Omega}{\Omega_{g(0)}}}{1 - \frac{\delta\Omega}{\Omega_{g(0)}}} \tag{3.96}$$

and we assume $\frac{1-\beta^2}{\beta^2} < 1$. Let us describe another term to simplify the calculations. To define $cos^2(\frac{\omega t}{2})$ we choose $tanu = \beta tan(\omega t)$, and the derivative of $tan(\omega t)$ with respect to time yields

$$d(tanu) = \frac{du}{cos^2 u} = \beta\omega \frac{dt}{2cos^2(\frac{\omega t}{2})} \tag{3.97}$$

Eventually we can write $cos^2(\frac{\omega t}{2})$ in the following form

$$cos^2(\frac{\omega t}{2}) = \frac{1}{\frac{1}{\beta^2}tan^2u + 1} \tag{3.98}$$

This allows us to express volume fluctuation also in terms of $tan(u)$. Substituting these terms into the Equation 3.93 gives

$$\begin{aligned}\Omega_{g(0)} + \delta\Omega cos(\omega t) =& \big(\Omega_{g(0)} - \delta\Omega\big)\left[1 + \frac{1-\beta^2}{\beta^2}cos^2(\frac{\omega t}{2})\right] \\ =& \big(\Omega_{g(0)} - \delta\Omega\big)\left[1 + \frac{1-\beta^2}{\beta^2}\frac{1}{\frac{1}{\beta^2}tan^2u + 1}\right]\end{aligned} \tag{3.99}$$

Let us write the ratio $\left(\frac{1}{\Omega_{g(0)}+\delta\Omega cos(\omega t)}\right)^{1/2}$

$$\begin{aligned}\left(\frac{1}{\Omega_{g(0)} + \delta\Omega cos(\omega t)}\right)^{1/2} =& \frac{1}{\big(\Omega_{g(0)} - \delta\Omega\big)^{1/2}}\frac{\left(\frac{1}{\beta^2}tan^2u + 1\right)^{1/2}}{\left[\frac{1}{\beta^2}tan^2u + 1 + \frac{1-\beta^2}{\beta^2}\right]^{1/2}} \\ =& \frac{1}{\big(\Omega_{g(0)} - \delta\Omega\big)^{1/2}}\frac{\left(\frac{1}{\beta^2}tan^2u + 1\right)^{1/2}}{\left[\frac{1}{\beta^2}tan^2u + 1 + \frac{1}{\beta^2} - 1\right]^{1/2}} \\ =& \frac{1}{\big(\Omega_{g(0)} - \delta\Omega\big)^{1/2}}\frac{\left(\frac{1}{\beta^2}tan^2u + 1\right)^{1/2}}{\left[\frac{1}{\beta^2}\frac{1}{cos^2u}\right]^{1/2}}\end{aligned} \tag{3.100}$$

Now we can write the subsequent expansion with respect to $\beta^2$

$$\frac{1}{\Big[\Omega_{g(0)}+\delta\Omega cos(\omega t)\Big]^{1/2}} = \frac{1}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[\frac{1}{\beta^2}tan^2u+\frac{1}{\beta^2}+1-\frac{1}{\beta^2}\Big]^{1/2}\beta cosu$$

$$= \frac{1}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[\frac{1}{cos^2u}+\beta^2-1\Big]^{1/2}cosu$$

$$= \frac{1}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[1+\big(\beta^2-1\big)cos^2u\Big]^{1/2} \tag{3.101}$$

In the next step, we replace $cos^2u$ with $(1-sin^2(u))$, and consequently it reduces the expression to the form

$$\frac{1}{\Big[\Omega_{g(0)}+\delta\Omega cos(\omega t)\Big]^{1/2}} = \frac{1}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[1+\big(\beta^2-1\big)\big(1-sin^2u\big)\Big]^{1/2}$$

$$= \frac{1}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[1+\big(1-\beta^2\big)sin^2u+\beta^2-1\Big]^{1/2}$$

$$= \frac{\beta}{\mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\Big[1+\big(\frac{1-\beta^2}{\beta^2}\big)sin^2u\Big]^{1/2} \tag{3.102}$$

Ultimately we can recast our result into

$$\tau_{NET} \cong \int_0^\infty e^{-\alpha u}\frac{2du \mid \Omega_{g(0)} \mid^{1/2}\beta}{\beta\omega \mid \Omega_{g(0)}-\delta\Omega \mid^{1/2}}\frac{\big[1+\frac{1-\beta^2}{\beta^2}sin^2u\big]^{1/2}}{\big[1+\frac{1-\beta^2}{\beta^2}sin^2u\big]}$$

$$\cong \int_0^\infty e^{-\alpha u}\frac{2du}{\omega \mid 1-\frac{\delta\Omega}{\Omega_{g(0)}} \mid^{1/2}}\frac{1}{\big[1+\frac{1-\beta^2}{\beta^2}sin^2u\big]^{1/2}} \tag{3.103}$$

Afterwards, we expand $\frac{1}{\left[1+\frac{1-\beta^2}{\beta^2}sin^2u\right]^{1/2}}$. For the simplicity, we call $x = \frac{1-\beta^2}{\beta^2}sin^2u$ and the expansion results in

$$\frac{1}{(1+x)^{1/2}} = \sum_{m=0}^{\infty} \frac{(-\frac{1}{2})....(-\frac{1}{2}-m)}{m!}x^m, \qquad and$$

$$\int_0^{\infty} sin^{2m}(u)e^{-\alpha u}du = \frac{2(2m)!}{\alpha\Big((\alpha^2+2^2)....(\alpha^2+(2m)^2)\Big)} \tag{3.104}$$

Since $\alpha = \frac{4\pi D[\log(1/\epsilon)]^{-1}}{\omega|\Omega_{g(0)}|\sqrt{1-\frac{|\delta\Omega|^2}{|\Omega_{g(0)}|^2}}}$, in the computation of $2^2+\alpha^2$, $4^2+\alpha^2$,...$(2m)^2+\alpha^2$ etc as $\epsilon \to 0^+$, $\alpha^2$'s are all negligible. Finally we substitute the expansion into the Equation 3.103, $\tau_{NET}$ becomes

$$\tau_{NET} \cong \sum_{m=0}^{\infty} \frac{(2m+1)!}{(m!)2^m}\left(\frac{1-\beta^2}{\beta^2}\right)^{2m}\frac{(2m)!}{2^{2m}(m!)^2}\frac{\mid \Omega_{g(0)} \mid \sqrt{1-\frac{|\delta\Omega|^2}{|\Omega_{g(0)}|^2}}}{a}$$

$$\cong \frac{\mid \Omega_{g(0)} \mid \log(\frac{1}{\epsilon})\sqrt{1-\frac{|\delta\Omega|^2}{|\Omega_{g(0)}|^2}}}{2\pi D}\sum_{m=0}^{\infty}\frac{(2m+1)!}{(m!)2^m}\left(\frac{1-\beta^2}{\beta^2}\right)^{2m}\frac{(2m)!}{2^{2m}(m!)^2} \tag{3.105}$$

Schuss looks at the problem for a frozen metric and typically the motion of the cell is not considered. Let us comment on the exact solution of the NET for a sphere as given in [9]

$$\tau = \frac{\mid \Omega_g \mid}{2\pi D}\left(\log\frac{1}{\delta} + O(1)\right)$$

where $\delta$ is defined to be the opening angle of the spherical cap and the area of the 2 dimensional sphere surface is represented by $\mid \Omega_g \mid = 4\pi R^2$. As we let $\delta\Omega \to 0$ we recover the result since $\beta \to 1$ in this limit. Yet in our solution, we assume that the motion of a cell can be thought of as an oscillation. Ultimately our result shows that the impact of oscillation around an average area has considerable effect on the NET, $\tau_{NET}$.

# 4. KILLING PROCESS AND NARROW ESCAPE TIME

## 4.1. Killing Process in General Approach

The success of a targeted Brownian molecule to arrive a specific point on the cell may be limited by a killing activity. To model the killing activity we will use the steady state killing rate $k$. In this section we basically follow Holcman's paper [13] to understand the general approach in the killing process. Let us consider the probability $P_N$, which is the arrival probability and $\tau_N$ is the mean time. Since receptors hold a relatively small fraction of the total area, we can asymptotically estimate $P_N$ and $\tau_N$ as a function of the diffusion constant $D$ and the killing rate $k$, which is in general a space dependent rate.

Let us take the probability $P_N(x)$ that the targeted particle arrives at a receptor and it is still alive in the domain $\Omega$. Subsequently the survival probability density function SPDF is given in the following form

$$p(x,t \mid y)dx = Pr\big\{X(t) \in x + dx, \tau^k > t, \tau^a > t \mid X(0) = y\big\} \tag{4.1}$$

here $\tau^a$ is described as the first time that the targeted molecule reaches the absorbing boundary $\partial\Omega_a$ alive and $\tau^k$ is reported as the first time that is killed. In the calculation part, it is known that the SPDF $p(x,t \mid y)$ satisfies the forward Fokker-Planck equation.

$$\frac{\partial p(x,t \mid y)}{\partial t} = D\nabla^2 p(x,t \mid y) - k(x)p(x,t \mid y), \qquad in \ \ \Omega \tag{4.2}$$

where the initial condition is given by

$$p(x, 0 \mid y) = \delta(x - y), \quad for \quad x, y \in \Omega \tag{4.3}$$

and the boundary conditions are the following

$$\begin{aligned} p(x, t \mid y) =& 0, \qquad on \quad \partial\Omega_a \\ \mathbf{J}(\mathbf{x}, \mathbf{y} \mid \mathbf{t}) \cdot \mathbf{n_x} =& 0, \qquad on \quad \partial\Omega_r \end{aligned} \tag{4.4}$$

here $\partial\Omega_a$ is defined as the absorbing part as well as $\partial\Omega_r$ is the reflecting part. Furthermore, $\mathbf{n_x}$ represents the normal derivative at a boundary point $x$, and finally the flux density vector $\mathbf{J}(\mathbf{x}, \mathbf{y} \mid \mathbf{t})$ is determined by

$$J^i(x, y \mid t) = -D\nabla p(x, t \mid y) \tag{4.5}$$

The expression of probability $P_N(y)$ that the targeted molecule started from the initial condition $y$ arrives at a receptor before being killed is given by

$$P_N(y) = Pr\{\tau^a < \tau^k \mid X(0) = y\} \tag{4.6}$$

Similarly we can define the probability of being killed before arriving at the absorbing part $Pr\{\tau^k < \tau^a \mid X(0) = y\}$. We can express these probabilities in terms of SPDF by integrating the Fokker-Planck equation in 4.2 over time and the domain $\Omega$. Consequently we end up with

$$1 = \int_0^\infty \oint_{\partial\Omega} \boldsymbol{J(x, y \mid t)} \cdot \boldsymbol{n(x)} dS_x dt + \int_0^\infty \int_\Omega k(x) p(x, t \mid y) dx dt \tag{4.7}$$

Let us express the probabilities separately

$$P_N(y) = Pr\{\tau^a < \tau^k \mid X(0) = y\} = \int_0^\infty \oint_{\partial\Omega} \boldsymbol{J(x, y \mid t)} \cdot \boldsymbol{n(x)} dS_x dt \tag{4.8}$$

and

$$\begin{aligned} Pr\{\tau^k < \tau^a \mid X(0) = y\} &= \int_0^\infty \int_\Omega k(x) p(x, t \mid y) dx dt \\ &= \int_\Omega k(x) \tilde{p}(x, y) dx \end{aligned} \tag{4.9}$$

where we define $\tilde{p}(x, y)$ as follow

$$\tilde{p}(x, y) = \int_0^\infty p(x, t \mid y) dt \tag{4.10}$$

and it is the solution of

$$D\nabla^2 \tilde{p} - k(x)\tilde{p} = -\delta(x - y), \qquad for \quad x, y \in \Omega \tag{4.11}$$

If $p_i$ is given as the initial distribution, we can define the averaging probability

$$\tilde{p}(x) = \int_\Omega \tilde{p}(x \mid y) p_i(y) dy \tag{4.12}$$

As the averaging probability satisfies the Fokker-Planck equation in 4.2, the solution is given by

$$D\nabla^2\tilde{p}(x) - k(x)\tilde{p}(x) = -p_i(x) \qquad for \quad x \in \Omega \tag{4.13}$$

Now let us define the time dependent averaged probability

$$\tilde{p}(x,t) = \int_\Omega \tilde{p}(x,t \mid y)p_i(y)dy \tag{4.14}$$

and the corresponding flux is

$$J^i(x,p_i \mid t) = -D\nabla^{(i)}\tilde{p}(x,t) \tag{4.15}$$

Eventually we describe the probability $P_N$ to arrive at a receptor as the reaching probability averaged over the initial position.

$$\begin{aligned} P_N =& \int_\Omega Pr\{\tau^a < \tau^k \mid X(0) = y\}p_i(y)dy \\ =& 1 - \int_\Omega k(x)\tilde{p}(x)dx \end{aligned} \tag{4.16}$$

To find out the mean time to reach a receptor $\tau_N$, we obtain a set of partial differential equations satisfied by the mean first passage time MFPT. We first derive an equation for the probability distribution function of the killing time and we have that

$$Pr\{\tau^k < t \mid \tau^a > \tau^k, p_i\} = \frac{Pr\{\tau^k < t, \tau^a > \tau^k \mid p_i\}}{Pr\{\tau^a > \tau^k \mid p_i\}} \tag{4.17}$$

Let us define these probabilities separately

$$\begin{aligned} Pr\{\tau^a > \tau^k \mid p_i\} &= \int_0^\infty \int_\Omega \int_\Omega k(x)p(x,s \mid y)p_i(y)dxdyds \\ &= \int_\Omega k(x)\tilde{p}(x)dx \end{aligned} \tag{4.18}$$

and

$$\begin{aligned} Pr\{\tau^k < t, \tau^a > \tau^k \mid p_i\} &= \int_0^t \int_\Omega \int_\Omega k(x)p(x,s \mid y)dxdyds \\ &= \int_0^t \int_\Omega k(x)\tilde{p}(x,s)dxds \end{aligned} \tag{4.19}$$

Eventually the expression in the Equation 4.17 becomes

$$Pr\{\tau^k < t \mid \tau^a > \tau^k, p_i\} = \frac{\int_0^t \int_\Omega k(x)\tilde{p}(x,s)dxds}{\int_\Omega k(x)\tilde{p}(x)dx} \tag{4.20}$$

After integrating by parts, the MFPT is obtained by

$$\begin{aligned} \tau_K =& E[\tau^k \mid \tau^k < \tau^a, p_i] \\ =& \int_0^\infty t\frac{d}{dt}Pr\{\tau^k < t \mid \tau^a > \tau^k, p_i\}dt \\ =& \frac{\int_0^t \int_t^\infty \int_\Omega k(x)\tilde{p}(x,s)dxdsdt}{\int_\Omega k(x)\tilde{p}(x)dx} \\ =& \frac{\int_0^\infty s \int_\Omega k(x)\tilde{p}(x,s)dxds}{\int_\Omega k(x)\tilde{p}(x)dx} \end{aligned} \tag{4.21}$$

For the analytical expression of the Equation 4.21, we derive the partial differential equation as follow

$$q(x) = \int_0^\infty s\tilde{p}(x,s)ds \tag{4.22}$$

The integral of the Fokker-Planck equation in 4.2 after multiplying by $t$ results in

$$\int_0^\infty t\frac{\partial p(x,t \mid y)}{\partial t}dt = D\nabla^2 q(x \mid y) - k(x)q(x \mid y), \quad for \quad x \in \Omega \tag{4.23}$$

Hence the function $q$ satisfies the boundary value problem

$$\begin{aligned} -\tilde{p}(x \mid y) =& D\nabla^2 q(x \mid y) - k(x)q(x \mid y), \quad for \quad x \in \Omega \\ q(x) =& 0, \quad for \quad x \in \partial\Omega_a \\ \mathbf{J}(\mathbf{x} \mid \mathbf{y}) \cdot \mathbf{n} =& - D\nabla^2 q(x) \cdot \mathbf{n} = 0, \quad for \quad x \in \partial\Omega_r \end{aligned} \tag{4.24}$$

Therefore the expression of the conditional MFPT to be killed is given in the subsequent relation

$$E[\tau^k \mid \tau^k < \tau^a, p_i] = \frac{\int_\Omega k(x)q(x)dx}{\int_\Omega k(x)\tilde{p}(x)dx} \tag{4.25}$$

Similarly for the survival trajectories we use the probability distribution function of the absorbing time $\tau^a$, and thus we find out the conditioned MFPT $\tau^a$

$$Pr\{\tau^a < t \mid \tau^a < \tau^k, p_i\} = \frac{\int_0^t J(s \mid p_i)ds}{1 - \int_0^\infty \int_\Omega k(x)\tilde{p}(x)dxds} \tag{4.26}$$

where the flux is given by

$$J(s \mid p_i) = \oint_{\partial\Omega} \mathbf{J}(\mathbf{x}, \mathbf{p_i} \mid \mathbf{t}) \cdot \mathbf{n}(\mathbf{x}) dS_x \tag{4.27}$$

Finally the mean time $\tau^a$ to absorption is the following expression

$$\begin{aligned}
\tau_N =& E[\tau^a \mid \tau^a < \tau^k, p_i] \\
=& \int_0^\infty \big(1 - Pr\{\tau^a < t \mid \tau^a < \tau^k, y\}\big) dt \\
=& \frac{\int_0^t sJ(s \mid p_i) ds}{1 - \int_\Omega k(x)\tilde{p}(x) dx} \\
=& \frac{\int_\Omega \tilde{p}(x) dx - \int_\Omega k(x) q(x) dx}{1 - \int_\Omega k(x)\tilde{p}(x) dx}
\end{aligned} \tag{4.28}$$

This is the general approach to understand the killing process under a zero drift. For the next step, Holcman looks at the problem for a small killing rate $k \ll 1$ [13]. Owing to the boundary conditions, Holcman uses the image source method to deal with the problem. Therefore the singularity of the Green's function changes and the ultimate result is multiplied by a factor 2. As a result, Holcman's result in 2 dimension turns out to be in the consequent form for a single absorber.

$$\tau_N \cong \frac{\frac{|\Omega_g|}{\pi D} \log(\frac{1}{\epsilon})}{1 + \frac{log(\frac{1}{\epsilon})}{\pi D} \int_\Omega k(x) d_g x} \tag{4.29}$$

## 4.2. An Alternative Derivation

Alternatively let us apply another technique to check wether we can come up with the same solution with Holcman's result. This time we propose the asymptotic expansion of the eigenvalue to obtain the MFPT. The asymptotic analysis formula is given in the following relation

$$\lambda(\epsilon) = \lambda_0^g + \left(\frac{1}{\log[\frac{1}{\epsilon}]}\right) 2\pi D\big[u_0(x_0)\big]^2 + ..... \tag{4.30}$$

The perturbation of the initial $\lambda_0$ and $u_0(x_0)$ are given by

$$\lambda_0^g = \lambda_0^{g(0)} + \lambda_0^{g(1)} \qquad and \qquad u_0 = u_0^{(0)} + u_0^{(1)} \tag{4.31}$$

Let us substitute the perturbed values into the Equation 4.30 and our formula becomes

$$\lambda(\epsilon) = \lambda_0^{g(0)} + \lambda_0^{g(1)} + \left(\frac{1}{\log[\frac{1}{\epsilon}]}\right) 2\pi D\big[u_0^{(0)} + u_0^{(1)}\big]^2 + ..... \tag{4.32}$$

where $u_0^{(0)} = \frac{1}{\sqrt{|\Omega_g|}}$ and $\lambda_0^{g(0)} = 0$. The perturbed form of $\lambda_0^{g(1)}$ and $u_0^{(1)}$ are described as

$$\lambda_0^{g(1)} = \langle u_0^{(0)} \mid k(x) \mid u_0^{(0)} \rangle = \int_\Omega k(x) \frac{dx}{\mid \Omega_g \mid} \tag{4.33}$$

We assume $\lambda_0^{g(1)} \ll 1$ and $u_0^{(1)}$ is indicated by

$$u_0^{(1)}(x) = \sum_{i \neq 0} \frac{\langle u_i^{(0)} \mid k \mid u_0^{(0)} \rangle}{\lambda_i^{(0)} - \lambda_0^{(0)}} u_i^{(0)}(x) \tag{4.34}$$

where $\langle u_i^{(0)} \mid k \mid u_0^{(0)} \rangle = \int_\Omega k(x) u_i^{(0)} d_g x \frac{1}{\sqrt{|\Omega_g|}}$ and $\lambda_0^{g(0)}$ is zero, we can rewrite $u_0^{(1)}$ in the following form,

$$u_0^{(1)} = \sum_{i \neq 0} \frac{1}{\lambda_i^{g(0)}} \frac{1}{\sqrt{\mid \Omega_g \mid}} \int_\Omega k(x) u_i^{(0)} d_g x \tag{4.35}$$

Now $\lambda(\epsilon)$ with the new perturbed variables is given by

$$\begin{aligned} \lambda(\epsilon) &= \lambda_0^{g(0)} + \lambda_0^{g(1)} + \left( \frac{1}{\log[\frac{1}{\epsilon}]} \right) 2\pi D \left[ u_0^{(0)} + u_0^{(1)} \right]^2 + ..... \\ &\cong 0 + \int_\Omega \frac{k(x) d_g x}{\mid \Omega_g \mid} + \frac{1}{\log[\frac{1}{\epsilon}]} 2\pi D \left[ u_0^{(0)2} + u_0^{(1)} u_0^{(0)} \right] + .... \end{aligned} \tag{4.36}$$

As $\frac{1}{\log[\frac{1}{\epsilon}]} \ll 1$ , the product of $\frac{1}{\log[\frac{1}{\epsilon}]}$ with $u_0^{(1)} u_0^{(0)}$ is negligible. Ultimately we can call the final result as $\lambda_0^{g(1)}(\epsilon)$

$$\lambda_0^{g(1)}(\epsilon) \cong \int_\Omega k(x) \frac{d_g x}{\mid \Omega_g \mid} + \frac{2\pi D}{\log[\frac{1}{\epsilon}]} \frac{1}{\mid \Omega_g \mid} \tag{4.37}$$

In Holcman's study [13], the mean time $\tau_N$ is given by

$$\tau_N = \frac{\left[ \int_\Omega d_g x \int_\Omega p_i(y) d_g y \int_0^\infty p(x, s \mid y) ds - \int_\Omega k(x) d_g x \int_0^\infty s ds \int_\Omega p_i(y) p(x, s \mid y) d_g y \right]}{1 - \int_\Omega k(x) d_g x \int_0^\infty s ds \int_\Omega p_i(y) p(x, s \mid y) d_g y} \tag{4.38}$$

Since the survival probability density function $p(x, s \mid y)$ satisfies the forward Fokker-Planck equation, we can write the solution in the following expression

$$p(x, y \mid s) = \sum_{i=0}^{\infty} e^{-\lambda_i^g(\epsilon) s} u_i(x) u_i(y) \tag{4.39}$$

To calculate the survival probability, let us take the integral with respect to time

$$\begin{aligned}\int_0^\infty p(x,s \mid y)ds &= \sum_{i=0}^{\infty}\int_0^\infty e^{-\lambda_i^g(\epsilon)s}u_i(x)u_i(y)ds \\ &= \sum_{i=0}^{\infty}\frac{1}{\lambda_i^g(\epsilon)}u_i(x)u_i(y) \end{aligned} \tag{4.40}$$

Since $\lambda_0^{g(0)} = 0$ and the correction $\lambda_0^{g(1)}$ is small, we have the dominant contribution still coming from the $\lambda_0^g(\epsilon)$ term,

$$\int_0^\infty p(x,s \mid y)ds \cong \frac{1}{\lambda_0^{g(1)}(\epsilon)}u_0(x)u_0(y) \tag{4.41}$$

Let us write the perturbed values of $u_0$

$$\begin{aligned}\int_0^\infty p(x,s \mid y)ds &\cong \frac{1}{\lambda_0^{g(1)}(\epsilon)}[u_0^{(0)}(x)+u_0^{(1)}(x)][u_0^{(0)}(y)+u_0^{(1)}(y)] \\ &\cong \frac{1}{\lambda_0^{g(1)}(\epsilon)}\left[\frac{1}{\mid \Omega_g \mid}+\frac{1}{\sqrt{\mid \Omega_g \mid}}[u_0^{(1)}(x)+u_0^{(1)}(y)]\right] \end{aligned} \tag{4.42}$$

In the following step, we will check all integrals in the Equation 4.38 one by one. For the first integral part, we solve the integral by using the perturbed values and it produces

$$\begin{aligned}\int_\Omega d_g x\int_\Omega p_i(y)d_g y\int_0^\infty p(x,s \mid y)ds =& \frac{1}{\lambda_0^{g(1)}(\epsilon)}\left[\int_{\Omega_g}\frac{d_g x}{\mid \Omega_g \mid}\right. \\ &+\sum_{i\neq 0}\frac{1}{\mid \Omega_g \mid}\int_\Omega d_g x\frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)}\rangle}{\lambda_i^{g(0)}} \\ &\left.*\left(u_i^{(0)}(x)\int_\Omega p_i(y)d_g y+\int_\Omega u_i^{(0)}(y)p_i(y)d_g y\right)\right] \end{aligned} \tag{4.43}$$

The summation part is of order $O(k)$ whereas the integral part is $O(1)$, and $O(1) \gg O(k)$, hence we can rewrite the relation

$$\int_\Omega d_g x \int_\Omega p_i(y) d_g y \int_0^\infty p(x, s \mid y) ds = \frac{1}{\lambda_0^{g(1)}(\epsilon)} \Bigg[ 1 + \sum_{i \neq 0} \Bigg( \frac{\int_{\Omega_g} u_i^{(0)}(x) d_g x}{\mid \Omega_g \mid} + \frac{\mid \Omega_g \mid}{\mid \Omega_g \mid} \int_\Omega u_i^{(0)}(y) p_i(y) d_g y \Bigg) \frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} \Bigg] \tag{4.44}$$

For the second integral part in the Equation 4.38, let us redo the calculations with the perturbed values

$$\begin{aligned} \int_\Omega k(x) d_g x \int_0^\infty sds \int_\Omega p_i(y) p(x, s \mid y) d_g y &= \int_\Omega k(x) \frac{1}{[\lambda_0^{g(1)}(\epsilon)]^2} \Bigg[ \frac{1}{\mid \Omega_g \mid} + \\ &\sum_{i \neq 0} \frac{1}{\mid \Omega_g \mid} \frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} \Bigg( u_i^{(0)}(x) + \int_\Omega u_i^{(0)}(y) p_i(y) d_g y \Bigg) \Bigg] \\ = \frac{1}{[\lambda_0^{g(1)}(\epsilon)]^2} \Bigg[ \int_\Omega \frac{k(x) d_g x}{\mid \Omega_g \mid} &+ \sum_{i \neq 0} \Bigg( \frac{\int_\Omega k(x) u_i^{(0)}(x) d_g x}{\mid \Omega \mid} \frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} + \\ \int_\Omega \frac{k(x) d_g x}{\mid \Omega_g \mid} \int_\Omega u_i^{(0)} p_i(y) d_g y &\frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} \Bigg) \Bigg] \end{aligned} \tag{4.45}$$

Finally, the last part in the Equation 4.38 induces the following relation

$$\begin{aligned} 1 - \int_\Omega k(x) d_g x \int_0^\infty sds \int_\Omega p_i(y) p(x, s \mid y) d_g y = 1 - \frac{1}{[\lambda_0^{g(1)}(\epsilon)]^2} \Bigg[ \int_\Omega \frac{k(x) d_g x}{\mid \Omega_g \mid} + \\ \sum_{i \neq 0} \Bigg( \frac{\int_\Omega k(x) u_i^{(0)}(x) d_g x}{\mid \Omega \mid} \frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} + \\ \int_\Omega \frac{k(x) d_g x}{\mid \Omega_g \mid} \int_\Omega u_i^{(0)} p_i(y) d_g y \frac{\langle u_0^{(0)} \mid k \mid u_i^{(0)} \rangle}{\lambda_i^{g(0)}} \Bigg) \Bigg] \end{aligned} \tag{4.46}$$

We make a very crude approximation and remove all terms of order $O(k)$, hence the first part yields

$$\int_\Omega d_g x \int_\Omega p_i(y) d_g y \int_0^\infty p(x, s \mid y) ds \cong \frac{1}{\lambda_0^{g(1)}(\epsilon)} \int_\Omega \frac{d_g x}{\mid \Omega_g \mid} \cong \frac{1}{\lambda_0^{g(1)}(\epsilon)} \tag{4.47}$$

The second integral part gives the corresponding relation

$$\int_\Omega k(x) d_g x \int_0^\infty s ds \int_\Omega p_i(y) p(x, s \mid y) d_g y = \int_\Omega \frac{k(x)}{\mid \Omega \mid} \frac{1}{[\lambda_0^{g(1)}]^2} d_g x \tag{4.48}$$

Eventually, the last part reduces to the integral

$$1 - \int_\Omega k(x) d_g x \int_0^\infty s ds \int_\Omega p_i(y) p(x, s \mid y) d_g y = 1 - \int_\Omega \frac{k(x)}{\mid \Omega \mid} \frac{1}{[\lambda_0^{g(1)}]^2} d_g x \tag{4.49}$$

Now, let us submit the results of our crude approximation into the Equation 4.38 [13]

$$\begin{aligned} \tau_N \cong & \frac{\frac{1}{\lambda_0^{g(1)}(\epsilon)} - \int_\Omega \frac{k(x)}{|\Omega|} \frac{1}{\lambda_0^{g(1)2}} d_g x}{1 - \int_\Omega \frac{k(x)}{|\Omega|} \frac{1}{\lambda_0^{g(1)2}} d_g x} \\ \cong & \frac{\frac{|\Omega_g|}{2\pi D} \log(\frac{1}{\epsilon})}{1 + \frac{\log(\frac{1}{\epsilon})}{2\pi D} \int_\Omega k(x) d_g x} \end{aligned} \tag{4.50}$$

Let us compare this outcome with Holcman's result. Holcman finds the mean time $\tau_N$ for 2 dimension in the following form

$$\tau_N \cong \frac{\frac{|\Omega_g|}{\pi D} \log(\frac{1}{\epsilon})}{1 + \frac{\log(\frac{1}{\epsilon})}{\pi D} \int_\Omega k(x) d_g x}$$

Holcman takes a regular boundary condition, thus he considers the image source. As a consequence, the singularity of the Green's function in his calculations is multiplied by a factor 2. Finally the difference between two results is due to the image charge.

# 5. CONCLUSION

In biological systems modeling of transport is a challenging process because there is a highly viscous and heterogeneous medium. Furthermore, medium has a fluctuating environment. The purpose of our targeted molecule is to arrive at a chemically active receptor, which acts like an absorbing boundary. Consider other organelles of the interior of a cell, they act like an obstacle and that means our targeted molecule can be killed before reach the receptor. In these complex processes, a simple and feasible approach known is to develop stochastic models. In the intracellular transport, Brownian motion is commonly used to model the motion of the molecules. In certain case, these molecules display Brownian motion on the 2D surface of the cell. Therefore the first passage time of such molecules is the fundamental mechanism for critical biological processes. Another argument is that our Brownian particle on reflected domain intends to escape from this domain through a small absorbing window. This case is defined as the narrow escape problem (NEP). The narrow escape problem in diffusion theory is defined as the calculation of the mean first passage time. Schuss uses Neumann-Drichlet Boundary Condition to calculate the mean first passage time. Another group Ward uses Perturbation of Boundary Condition in their calculations. They use matched asymptotic expansion. Here, for the inner expansion, large changes occur in the solution around the strong perturbation whereas the outer expansion leads to relatively small effects. We expect that these two expansions are matched on the boundary. In some cases, this time scale can be very long compared to the motion of the cell in its environment. For the dynamical model where the surface is fluctuating slowly as the particle displays Brownian motion on this surface, we can apply a stochastic process with a variable background metric. Since the modification of the metric is slowly, we can use an adiabatic approximation. We analyze the variation of first passage times within this dynamical model. We find out that oscillation of the surface in a cell has a significant effect on the NET. Additionally we investigate the killing process in biological systems. Holcman approaches this problem by using Green's function. In

our technique, we apply the asymptotic expansion of the eigenvalue. Specifically we use perturbation of the initial eigenvalue and eigenfunction. Both results are satisfied by each other but because of the singularity of the Green's function, Holcman's result is multiplied by a factor 2. This difference between two results comes from the image charge in Holcman's calculations.

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