TRANSPORT DRIVEN BY A RANDOM TELEGRAPH FORCE IN AN ASYMMETRIC MEMBRANE CHANNEL

By

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For my family and friends ...

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Abstract

Channel proteins that selectively conduct molecules across the cell membrane often exhibit an asymmetric structure. By means of a stochastic model the channel asymmetry in the presence of non equilibrium fluctuations can influence the transport through such channels by a ratchet like mechanism. In general, the ratchet effect refers to the generation of directed motion of Brownian particles in a spatially asymmetric (ratchet) potential in the presence of non equilibrium fluctuations and externally applied time periodic force with mean zero. Using this structure, Schulten and Kosztin [1] have numerically studied the behavior of steady state flux by considering various cases of an external tilting force. Being interested in seeking analytical results, we model the potential of the channel by a ratchet like potential and obtain analytical expressions for the steady state flux of glycerol through the channel due to a concentration gradient, constant force, periodically switching force and non equilibrium fluctuations of the cell membrane. In addition we compare our results with the numerical results obtained in [1].

Chapter 1

Introduction

Aquaporins (AQPs) are membrane water channels present in all life forms and more than 100 of them have been characterized. Aquaporin-1 was first identified as an integral membrane protein in red blood cells and renal proximal tubules, where it functions as water-selective membrane pore. Eleven human AQPs have been identified and their impaired function may lead to pathological situations, such as nephrogenic diabetes insipidus and congenital cataract of the eye [2]. All members of the AQPs super family acts as a passive transporters of water. Aquaglyceroporins, a subfamily of AQPs, have the ability to conduct small, linear polyols stereoselectively in addition to water molecules. The most studied Aquaglyceroporin is the Escherichia coli glycerol uptake facilitator (GlpF) is a channel used by organisms to absorb glycerol molecules from the environment for use in metabolism when there is little glycerol available.

AQPs transport water efficiently, but they are impermeable to charged species. Glycerol diffuses into the cell through GlpF and is phosphorylated by the glycerol kinase (GlpK), which prevents back-diffusion. All of these channels (GlpF and AQPs) are strictly selective for non-ionic compounds, thus preventing the dissipation of the membrane potential. Such selectivity is of crucial importance to the proper function of the cell membrane, as the flow of water in the response to osmotic stress must not disturb the electrochemical

properties of the membrane. Blockage of protons is essential in maintaining the transmembrane proton gradient in the cell. However, this property is somewhat unexpected given the presence of a chain of water molecules in the pore.

Transport inside GlpF is done by a ratchet like mechanism[1]. In a wide sense, a ratchet is a system in spatially periodic but asymmetric potential driven by a zero mean force, deterministic or/and stochastic ones. Feynman [4], used the rachet and pawl to illustrate the meaning of the second law of thermodynamics and its implication. According to him if everything is at the same temperature then heat can not be converted to work by means of cyclic process. In other words it means that usefull work cannot be obtained from equilibrium (thermal) fluctuations. Magnasco [6], reformulated this problem in terms of a system of over damped Brownian particles in a periodic asymmetric (ratchet like) potential and pointed out that the ratchet can extract energy (for free) out of the time correlated pieces of a colored (non white) thermal bath and all that is needed to generate motion and force in the Brownian domain is loss of symmetry and substantially time correlations. Another ratchet like mechanism has been investigated, in which a spatially periodic potential is switched on and off periodically [8]. During the time interval in which the potential is switched off, particles diffuse freely and symmetrically. During the following on period particles move towards minima of the potential and because the potential is asymmetrical it pulls more particles in one direction than the other. The result of this off-on switching is macroscopic drift of particles in single direction.

Theoretical activity has been inspired by possible applications and explanation for some class of active processes in biochemical systems[2]. The effects of free energy driven oscillations and fluctuations on kinetics of chemical reactions including enzyme catalysis and the problem of extracting energy from the field of fluctuations were considered. Molecular motors were proposed to be modeled by ratchet type systems. Translocation of proteins

into or across cellular membrane requires driving forces that can be Brownian (thermal) and directed motion is induced not by a temperature gradient but by chemical reactions. As it is seen from above processes in spatially periodic and asymmetric systems influenced by random perturbations (thermal noise, non equilibrium fluctuations) are of great interest in almost all natural sciences starting from physics up to molecular biology.

Transport in asymmetric channel membrane is numerically studied by Schuten and Kosztin in [1]. They modeled the Escherichia coli glycerol uptake facilitator (GlpF) having a potential mean force (PMF) with a prominent potential well at the external (periplasm) side and a constriction potential barrier towards the internal (cytoplasmic) side of the channel. Numerically they computed the steady state flux of the glycerol molecules inside GlpF due to a concentration gradient, a constant force, a periodically switching force and a random telegraph force (RTF).

In seeking the analytical results, Alemayehu Dinkayehu [5] studied part of this work by modeling the PMF of the GlpF by a ratchet like potential. He found analytical expression for the steady state flux due to the concentration gradient only, constant force and periodically switching force. Based on the simple model of Alemayehu our aim is to extend his work to the case of a random telegraph force (RTF).

The rest of this thesis is organized as follows. In chapter two, we briefly present Alemayehu's work and we find the analytical expression for the steady state flux due to the concentration gradient only, constant force and periodically switching force. In chapter three, we give analytical expression for the steady state flux due to a random telegraph force (RTF) which is our new contribution for this system. The last chapter is devoted to summary and concluding remarks.

Chapter 2

Transport of glycerol inside GlpF

We take the glycerol uptake facilitator channel (GlpF) with a potential mean force (PMF) inside it as modeled by Schulten and Kosztin in [3] for numerical simulation. But we model the PMF by a simple ratchet like potential following Alemayehu's work. Glycerol molecules are considered as Brownian particles moving in a medium of high friction inside the channel and we find the analytical expression for the steady state flux due to

.concentration gradient

.external constant force and

.external periodically switching force

To do this, first we have to look at the transport of the glycerol molecule inside the channel.

2.1 Glycerol molecule inside GlpF

The Escherichia coli glycerol uptake facilitator (GlpF) is an aquaglycerol channel protein, which transports both water and glycerol molecules, but excludes charged solutes. In particular, molecular dynamics (MD) studies established that water and glycerol diffusion through GlpF is singlefile. The corresponding potential of mean force (PMF) [2] that guides transport of glycerol through the channel is highly asymmetric reflecting the atomic structure of GlpF as shown in Fig. (2.1a) with prominent potential well at the external

(periplasmic) side and a constriction region with several pronounced potential barriers towards the internal (cytoplasmic) side of the channel.

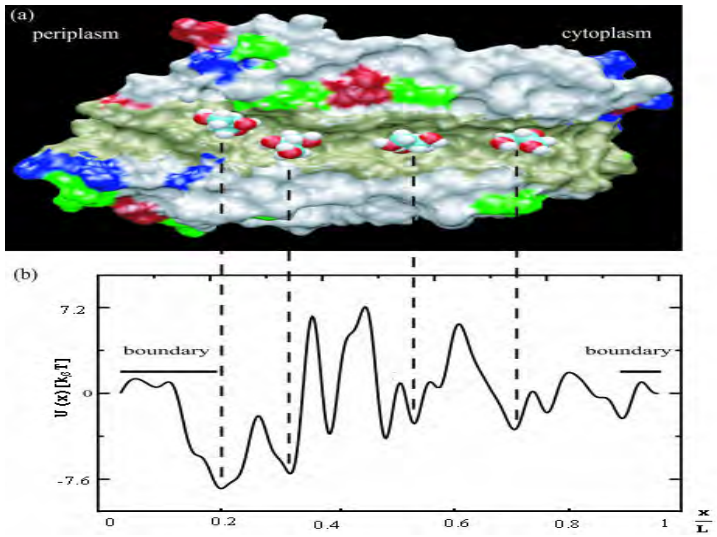

Figure 2.1: (a) Plot of section through the glycerol conduction pathway in GlpF and (b) the corresponding asymmetric PMF (solid curve)[4].

Glycerol transport through GlpF can be modeled in terms of over damped Brownian motion along the axis of the channel as a result of the concentration gradient established at the ends of the channel. The interaction of a diffusing glycerol molecule with protein, lipid, solvent and other glycerol molecules is taken into account through the PMF, $U(x)$. The motion of the glycerol molecule inside GlpF in the presence of an external force $F(t)$ in the strong friction limit is described by the Langevin equation

$$\gamma\dot{x} = f(x) + \xi(t) + F(t), \tag{2.1.1}$$

where γ is the friction coefficient, $f(x)$= - $U'(x)$ is the deterministic force derived from the potential mean force (PMF) and $\xi(t)$ is the Langevin force due to the equilibrium thermal fluctuations. $\xi(t)$ is a Gaussian white noise with $<\xi(t)>$=0 and $<\xi(t)\xi(0)>$=$2D\gamma^2\delta(t)$, where $\delta(t)$ is the Dirac-delta function and D is the effective diffusion coefficient of the glycerol molecule inside GlpF. According to the fluctuation-dissipation theorem, D and

γ are related through the Einstein relation $D = k_BT/\gamma$. We assume that $F(t)$ is a time dependent force, but homogeneous. It describes either an externally applied force or some intrinsic non equilibrium fluctuations of the system. This is due to the single file nature of the glycerol transport through GlpF *i.e.* a force applied at either end of the channel will be transmitted along the file without significant loss in intensity (incompressibility of the single file).

At this point, we introduce dimensionless units that will be employed throughout this thesis, unless otherwise stated. All other units can be expressed in terms of the following three: length of GlpF ℓ=L≈4.8 nm, diffusion time τ=τ_D=L^2/D≈10^{-7} s, and thermal energy ε=k_BT≈4.28 $\times 10^{-21}$ J, here k_B is the Boltzmann constant, T=310 K is the physiological temperature and D≈2.2×10^{-10} m^2/s is the effective diffusion coefficient of glycerol molecule inside GlpF. Thus the force is $F = \gamma D/L$=k_BT/L≈0.9 pN. In new units (dimensionless), the Fokker-Planck equation (FPE) corresponding to Eq. (2.1.1) is

$$\partial_t P(x,t) = -\partial_x J(x,t), \tag{2.1.2}$$

where

$$J(x,t) = -\partial_x P(x,t) + [f(x) + F(t)]P(x,t). \tag{2.1.3}$$

In the above equations $P(x,t)$ is the unnormalized probability density of the glycerol molecule (this is due to the fact that there exists a concentration gradient at the ends of the channel) and $J(x,t)$ is the local instantaneous flux of glycerol through the channel. The probability density $P(x)$ is related to the local concentration $C(x)$ by $P(x)$=$S(x)$ $C(x)$, where $S(x)$ is the area of the channel cross section and from the crystal structure, one finds that the opening area at both ends of GlpF is $S_0 \equiv S(0) \approx S(1) \approx 100 \mathring{A}^2$[3]. GlpF can be regarded as a nano pore, which connects two reservoirs of glycerol molecules located at $x = 0$ (periplasm) and at $x = 1$ (cytoplasm) with glycerol concentration $P_0 = P(0)$ and $P_1 = P(1)$ respectively and initially $P_0 > P_1$.

We study the conduction of glycerol molecule through GplF analytically, by taking a simple model potential (ratchet like potential) instead of PMF (see Fig. (2.1b)above), as shown in Fig. (2.2) below with the respective expressions for $U(x)$ be

$$U(x) = \begin{cases} \frac{Q_1 x}{L_1} \quad , & when \quad 0 \leq x \leq L_1 \\ \frac{(Q_2 - Q_1)x}{L_2 - L_1} + 2Q_1 - Q_2, & when \quad L_1 \leq x \leq L_2 \\ \frac{-Q_2 x}{L_3 - L_2} + \frac{5}{3}Q_2 \quad , & when \quad L_2 \leq x \leq L_3 \end{cases} \tag{2.1.4}$$

where Q_1=-7.6, Q_2=7.2, L_1=0.2, L_2=0.4, L_3=1.0 (all are dimensionless quantities)

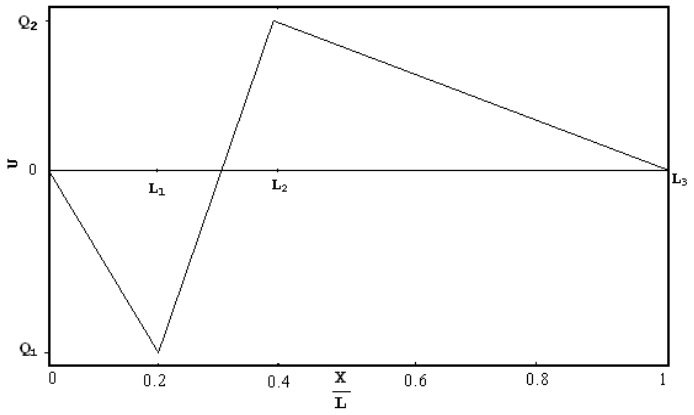

Figure 2.2: Plot of the model potential versus position .

Hence, the model potential is determined by the parameters L_1, L_2, L_3, Q_1 and Q_2 with a barrier height at L_2=0.4 and a minima at L_1=0.2.

2.2 Transport driven by concentration gradient

In this section, we consider our model with constant concentration values(P_0 and P_1) at the two ends of the channel. The existence of concentration gradient produces a constant flux, J_0 at steady state with in the channel. The corresponding FPE for this case from Eq. (2.1.2) is

$$\partial_t P(x,t) = -\partial_x J_0(x,t), \tag{2.2.1}$$

where

$$J_0(x,t) = -\partial_x P(x,t) + f(x)P(x,t) \tag{2.2.2}$$

In steady state the flux is constant throughout the channel, hence from Eq. (2.2.2) we obtain

$$\frac{dP_s(x)}{dx} + U'(x)P_s(x) = -J_0 \tag{2.2.3}$$

where $P_s(x)$ is the steady state probability density. Eq. (2.2.3) is a linear ordinary differential equation of first order, thus to solve it let us suppose its solution to be

$$P_s(x) = R(x)V(x) \tag{2.2.4}$$

where $R(x)$ and $V(x)$ are arbitrary functions of x to be determined. Substituting Eq. (2.2.4) into Eq. (2.2.3) we obtain

$$R(x)\frac{dV(x)}{dx} + V(x)[\frac{dR(x)}{dx} + U'(x)R(x)] = -J_0. \tag{2.2.5}$$

Since R(x)and V(x) are arbitrary functions of x, thus we may choose R(x), such that

$$\frac{dR(x)}{dx} + U'(x)R(x) = 0 \tag{2.2.6}$$

and the solution of this equation is

$$R(x) = C_1\ e^{-U(x)} \tag{2.2.7}$$

where C_1 is constant of integration. Substituting Eqs. (2.2.6) and (2.2.7) into Eq. (2.2.5) and rearranging the resulting equation we obtain

$$dV(x) = -\frac{J_0}{C_1}\ e^{U(x)}dx \tag{2.2.8}$$

and the solution of this equation is

$$V(x) = C_2 - \frac{J_0}{C_1}\int_0^x e^{U(x')}dx' \tag{2.2.9}$$

where C_2 is constant of integration. Substituting Eqs. (2.2.7) and (2.2.9) into Eq. (2.2.4) we obtain

$$P_s(x) = C\ e^{-U(x)} - J_0\ e^{-U(x)}\int_0^x e^{U(x')}dx' \tag{2.2.10}$$

where the constant $C = C_1C_2$ is obtained by imposing boundary condition. We know that at $x = 0$, $P_s(0)$=P_0 and substituting this condition into Eq. (2.2.10) we obtain

$$P_0 = C\ e^{-U_0} \tag{2.2.11}$$

where $U_0 = U(0)$. Thus the value of C is

$$C = P_0\ e^{U_0} \tag{2.2.12}$$

Substituting Eq. (2.2.12) into Eq. (2.2.10) we obtain

$$P_s(x) = P_0\ e^{U_0}\ e^{-U(x)} - J_0\ e^{-U(x)} \int_0^x e^{U(x')}dx'. \tag{2.2.13}$$

Similarly at $x = 1$,$P_s(1)$=P_1, using this condition into Eq. (2.2.13) and rearranging the resulting equation we obtain

$$J_0 = \ e^{U_0}\left[\int_0^1 e^{U(x)}dx\right]^{-1} P_0 - \ e^{U_1}\left[\int_0^1 e^{U(x)}dx\right]^{-1} P_1 \tag{2.2.14}$$

where U_1=$U(1)$.

But we know that $U(x)$ vanishes at the end points of the channel *i.e.* at $x = 0$ and $x = 1$ we have U_0=$U(0)$=0 and U_1=$U(1)$=0 respectively. Thus substituting these two values into Eq. (2.2.14) we obtain

$$J_0(P_0, P_1) = \left[\int_0^1 e^{U(x)}dx\right]^{-1} (P_0 - P_1) \tag{2.2.15}$$

This is the net flux of the glycerol inside the channel due to the concentration gradient established at the periplasmic (P_0) and cytoplasmic (P_1) side of the channel. Since $U(x)$ in our model potential is made up of three piecewise linear potentials, so that the integration of the potential across the channel can be carried out in a straightforward way:

$\int_0^1 e^{U(x)}dx = \int_0^{L_1} e^{U_1(x)}dx + \int_{L_1}^{L_2} e^{U_2(x)}dx + \int_{L_2}^{L_3} e^{U_3(x)}dx$

where $L_1 = 0.2$, $L_2 = 0.4$ and $L_3 = 1.0$. Hence

$\int_0^1 e^{U(x)}dx = \frac{1}{38}(e^{7.6} - 1) + \frac{1}{74}(e^{7.2} - e^{-7.6}) + \frac{1}{12}(e^{-7.2} - 1)$.

But we know that the value of $e^{-7.6} \ll e^{7.6}$ and $e^{-7.2} \ll e^{7.2}$ due to this the value of the above integral is

$\int_0^1 e^{U(x)}dx \cong 70.574869115$

2.3 Transport driven by potential gradient

In this section let us consider that a constant force $F(t)$=F_0 is externally applied to the channel in the presence of concentration gradient. Then the corresponding FPE is

$$\partial_t P(x,t) = -\partial_x J(x,t), \tag{2.3.1}$$

where

$$J(x,t) = -\partial_x P(x,t) + (f(x) + F_0)P(x,t). \tag{2.3.2}$$

We know that in steady state the flux is constant throughout the channel. Hence from Eq. (2.3.2) we obtain

$$\frac{dP_s(x)}{dx} + (U'(x) - F_0)P_s(x) = -J. \tag{2.3.3}$$

This is a linear ordinary differential equation of first order which is similar to Eq. (2.2.3) except the additional term F_0 and then its solution from Eq. (2.2.10) will be

$$P_s(x) = C'\ e^{-(U(x)-xF_0)} - J\ e^{-(U(x)-xF_0)} \int_0^x e^{U_{eff}(x')}dx' \tag{2.3.4}$$

where $U_{eff}(x)$=$U(x)$-xF_0 is the effective potential of the system and C' is constant of integration to be obtained by imposing boundary condition. If we apply all the steps used for in section 2.3 into this section we obtain

$$J(F_0, P_0, P_1) = \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_0 - \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_1\ e^{-F_0}. \tag{2.3.5}$$

This is the net flux of the glycerol molecule inside the channel due to a potential gradient (*i.e.* in the presence of an external constant load F_0) in addition to concentration gradient. In this case the net flux through the channel depends both on the concentration gradient and the load.

Let $J_+ = J(F_0, P_0, 0)$ be the inward flux of the glycerol molecule inside the channel due to an external load (the inward flux is calculated in the absence of cytoplasmic concentration). To calculate it let us substitute at $x = 0$, P_0 and at $x = 1$, $P_1 = 0$ into Eq.

(2.3.5) and we obtain

$$J_+ = \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_0 \tag{2.3.6}$$

This is the inward flux of the glycerol molecule inside the channel without the cytoplasmic concentration.

Similarly let $J_- = -J(F_0, 0, P_0)$ be the outward flux of the glycerol molecule inside the channel which is obtained by inverting the channel and in the absence of periplasmic concentration. Substituting at $x = 0$, $P_1 = P_0$ and at $x = 1$, $P_0 = 0$ and also F_0 by $-F_0$ into Eq.(2.3.5) we obtain

$$J_- = \left[\int_0^1 e^{\bar{U}_{eff}(x)}dx\right]^{-1} P_0\ e^{F_0}. \tag{2.3.7}$$

This is the outward flux of the glycerol molecule inside the channel due to an external force. Note that $\bar{U}_{eff}(x) = U(x) + xF_0$.

Why is the vestibule on the periplasm side and not on the cytoplasmic side? To address this question, we consider a channel with an inverted potential that means we invert the channel and the attractive well is facing the cytoplasmic side. Based on this the fluxes of the normal and reversed orientation corresponds to the inward and outward fluxes respectively. To see the difference between the inward and outward fluxes let us take the same concentration gradient P_0 and then we plot the outward flux, J_- and the inward flux, J_+ versus this concentration gradient as shown in Fig. (2.3)

This figure shows that when the value of the concentration gradient is very small the rate of the outward flux is the same as the inward flux while when the concentration gradient is large then the flux in the reversed channel is bigger than the flux in the normally oriented channel. For low enough concentration gradient interaction between the glycerol molecules can be neglected. If we define the direction of the net flux to be from periplasm to cytoplasm, then the net flux is given by subtracting an outward flux proportional

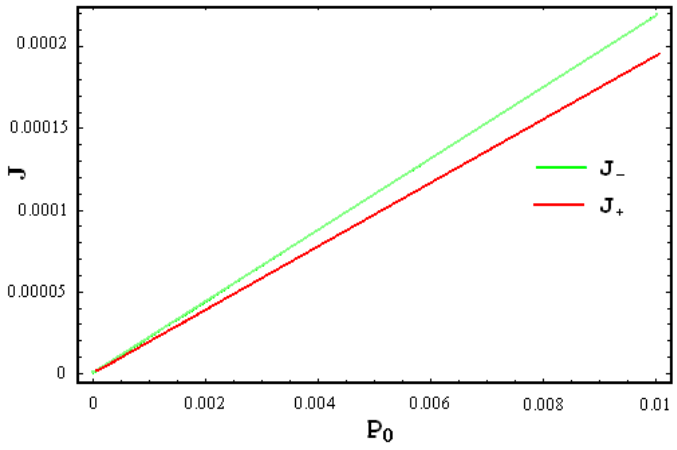

Figure 2.3: Plot of the outward flux, J_{-}=$J(F_0, 0, P_0)$ green and inward flux, J_{+}=$J(F_0, P_0, 0)$ red versus the outer concentration, P_0 for $F(t)$=F_0=2.

to the cytoplasmic concentration from an inward flux proportional to the periplasmic concentration. Accordingly, the net flux is proportional to the concentration difference, (C_{outer} - C_{inner}) (local concentration difference). Because the flux depends only on the concentration difference across the channel, then reversing the channel will not change the flux. Therefore, there seems to be no reason to prefer one direction over the other. At higher concentrations, however, interactions become important, and conduction is no longer linear. Since glycerol molecule held in the vestibule prevent others from being conducted, then the optimal direction can be estimated by putting the vestibule where it will be most rarely occupied: as close to the cytoplasm as possible. As a result, the reversed GlpF has an increased conduction rate due to reduced clogging in the vestibule and this is one explanation for channel orientation.

Thus, using Eq. (2.3.6) and Eq. (2.3.7) ratio of the outward flux J_{-} to inward flux J_{+} is given by

$$\frac{J_{-}}{J_{+}} = \frac{\left[\int_0^1 e^{U_{eff}(x)} dx\right] e^{F_0}}{\left[\int_0^1 e^{\bar{U}_{eff}(x)} dx\right]}. \tag{2.3.8}$$

We plot this ratio versus the force as shown in Fig.(2.4)

According to this figure, the ratio is increased monotonically as the constant load in-

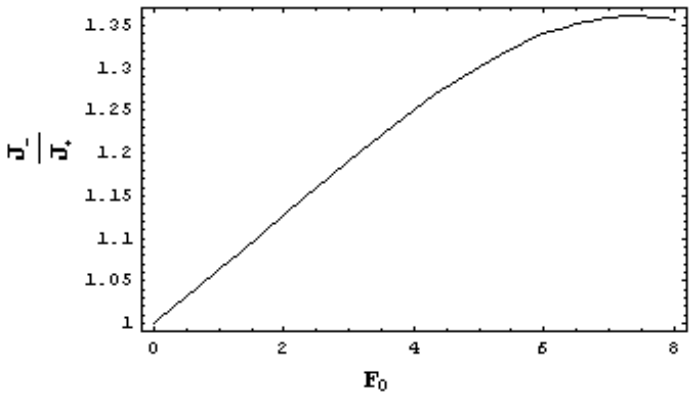

Figure 2.4: Plot of the ratio of the outward flux, J_- to the inward flux, J_+ versus a constant load, F_0 .

creased and this shows that the outward flux is larger than the inward flux for the same concentration and force level. When we compare our result with the numerical result obtained by Schulten and Kosztin [1] as shown in Fig. (2.5a), we found that the value of

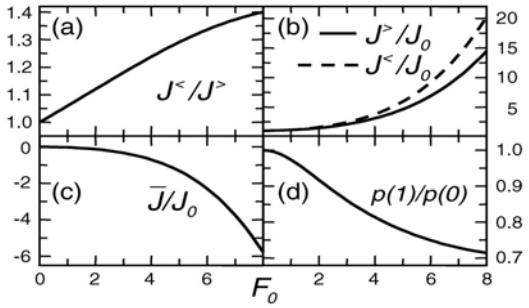

Figure 2.5: (a) Plot of the ratio of the outward flux, J_- to the inward flux, J_+ versus a constant load, F_0, (b)Plot of the ratio of the outward flux, J_- to the inward flux in the absence of the load, $J_0(o, P_0)$ (broken line) and the ratio of the inward flux, J_+ to the inward flux in the absence of the load, $J_0(o, P_0)$ (solid line), (c) the ratio of the average flux, $\bar{J}$, with equal concentration to the inward flux in the absence of the load, $J_0(o, P_0)$, (d) the ratio of the inner concentration, P_1 to the outer concentration, P_1 versus load, F_0 ((b)-(d) transport due to periodically switching force)[3].

the ratio $\frac{J_-}{J_+}$ in our case is less than the numerical result. This difference exists due to that in our model $U(x)$ is a simple ratchet like potential due to this we consider the channel has three different regions. While in the numerical consideration $U(x)$ is highly asymmetric with respect to the channel length and channel is a single region. But the value of the ratio $\frac{J_-}{J_+}$ in both cases are monotonically increases with increasing force and in both cases the outward flux is larger than the inward flux.

2.4 Transport driven by an external periodic driving force

Next, we consider an external force $F(t)$ that switches periodically between $\pm F_0$, where F_0 is constant ($i.e$ $F(t)$ is a square-wave force). Although the time average of $F(t)$ is zero, this force induces a finite flux of the glycerol molecule inside GlpF and the only difference from the transport due to constant force is that the force periodically switches between the + state and − state with a constant value F_0(then the force takes $+F_0$ in one time and $-F_0$ in another time). The FPE is similar to that of the FPE due to a constant force. Therefore, the steady state flux (net) is given by Eq. (2.3.5) $i.e$.

$$J(F_0, P_0, P_1) = \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_0 - \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_1\ e^{-F_0}. \tag{2.4.1}$$

The ratio of the inward flux J_+ to the inward flux in the absence of an external load with no cytoplasmic concentration $J_0(P_0, 0)$ is given by

$$\frac{J_+}{J_0(P_0,0)} = \frac{\int_0^1 e^{U(x)}dx}{\int_0^1 e^{U_{eff}(x)}dx}. \tag{2.4.2}$$

The ratio of the outward flux J_- to the inward flux in the absence of an external load with no cytoplasmic concentration $J_0(P_0, 0)$ is given by

$$\frac{J_-}{J_0(P_0,0)} = \frac{e^{F_0}\int_0^1 e^{U(x)}dx}{\int_0^1 e^{\bar{U}_{eff}(x)}dx}. \tag{2.4.3}$$

Note: we know that $U(x)$ has different values in each region so that the integrals in the above equations can be expressed as

$$\int_0^1 e^{U_{eff}(x)}dx = \int_0^{L_1} e^{(U_1(x)-xF_0)}dx + \int_{L_1}^{L_2} e^{(U_2(x)-xF_0)}dx + \int_{L_2}^{L_3} e^{(U_3(x)-xF_0)}dx \qquad (2.4.4)$$

where $L_1 = 0.2$, $L_2 = 0.4$ and $L_3 = 1.0$. Similar procedure applies for $\int_0^1 e^{\bar{U}_{eff}(x)}dx$. Then we plot the above two equation versus the force as shown in Fig. (2.6)

According to this figure the values of both ratios $\frac{J_+}{J_0(P_0,0)}$ and $\frac{J_-}{J_0(P_0,0)}$ are greater than one

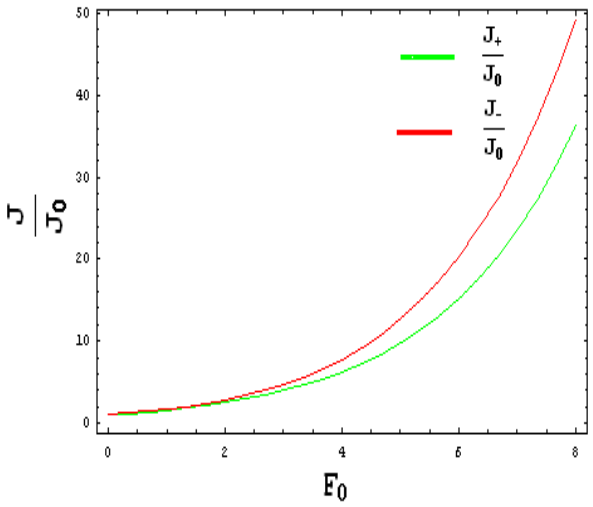

Figure 2.6: Plot of the ratio of the inward flux and the outward flux to the inward flux in the absence of the load green and red respectively versus the load.

and increases monotonically with the force. But if we compare these two figures one can see that the value of $\frac{J_-}{J_0(P_0,0)}$ is greater than the value of $\frac{J_+}{J_0(P_0,0)}$) which implies that the outward flux is larger than the inward flux for the same force level and concentration gradient. If we compare this plot with numerical plot obtained in [1] as shown in Fig. (2.5b), we obtained that the values of both ratios $\frac{J_-}{J_0(P_0,0)}$ and $\frac{J_+}{J_0(P_0,0)}$ in our case are greater than the numerical values. This is due to the fact that in our model $U(x)$ is linear with respect to the channel length and $U'(x)$ is constant but different values in the three regions while

in the numerical case these are not true. In these two plots we can see that in both cases

.both ratios $\frac{J_+}{J_0(P_0,0)}$ and $\frac{J_-}{J_0(P_0,0)}$ increases with increasing the force,

.the values of both ratios are greater than one which implies that the inward flux and outward flux are greater than the flux in the absence of the force and

.the ratio $\frac{J_+}{J_0(P_0,0)}$ is less than $\frac{J_-}{J_0(P_0,0)}$, this shows that the outward flux is lager than inward flux for the same force level and concentration gradient.

Assuming that one neglects the transient in the instantaneous flux after switching $F(t)$, then the mean flux $\bar{J}$ through the channel can be expressed as

$$\bar{J} = \bar{J}(F_0, P_0, P_1) = \frac{J(F_0, P_0, P_1) + J(-F_0, P_0, P_1)}{2}. \tag{2.4.5}$$

For $P_1 = P_0$ in Eq. (2.4.1) we obtain

$$J(F_0, P_0, P_0) = \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_0 - \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} P_0\ e^{-F_0}, \tag{2.4.6}$$

and

$$J(-F_0, P_0, P_0) = \left[\int_0^1 e^{\bar{U}_{eff}(x)}dx\right]^{-1} P_0 - \left[\int_0^1 e^{\bar{U}_{eff}(x)}dx\right]^{-1} P_0\ e^{F_0}. \tag{2.4.7}$$

Substituting Eqs. (2.4.6) and (2.4.7) into Eq. (2.4.5) and rearranging the resulting equation becomes

$$\bar{J} = \frac{[I_1 - I_2]P_0}{2} \tag{2.4.8}$$

where $I_1 = \left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} + \left[\int_0^1 e^{\bar{U}_{eff}(x)}dx\right]^{-1}$ and

$I_2 = e^{-F_0}\left[\int_0^1 e^{U_{eff}(x)}dx\right]^{-1} + e^{F_0}\left[\int_0^1 e^{\bar{U}_{eff}(x)}dx\right]^{-1}$

Thus the ratio of the the mean flux due to periodically switching external load, $\bar{J}$ to the inward flux in the absence of external load without cytoplasmic concentration, $J_0(P_0, 0)$ is given by

$$\frac{\bar{J}}{J_0(P_0,0)} = \frac{[(1-e^{-F_0})\int_0^1 e^{\bar{U}_{eff}(x)}dx + (1-e^{F_0})\int_0^1 e^{U_{eff}(x)}dx]\int_0^1 e^{U(x)}dx}{2\int_0^1 e^{U_{eff}(x)}dx\int_0^1 e^{\bar{U}_{eff}(x)}dx} \tag{2.4.9}$$

If we plot the above(Eq. (2.3.9)) ratio versus the load we obtain what is shown below in Fig. (2.7)

According to this figure, the ratio of the mean flux, $\bar{J}$ due to periodically switching

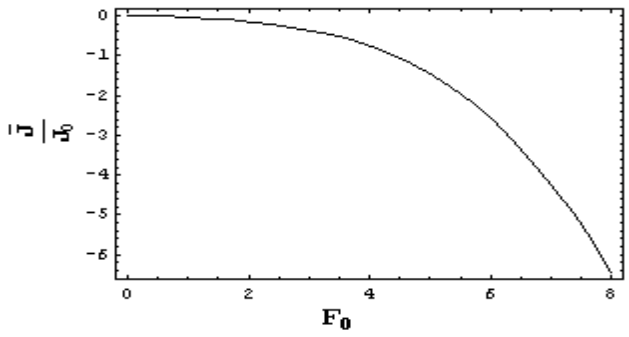

Figure 2.7: Plot of the ratio of the the mean flux, $\bar{J}$ to flux in the absence of the external load, J_o versus a load, F_0.

external load to the inward flux, $J_0(P_0, 0)$ in the absence of external load decreases monotonically as the load increased and this shows that the outward flux is greater than the inward flux for the same concentration and force level and also both the outward and inward fluxes are larger than the flux without the external force. Let us compare our result with the numerical result obtained in [1] as shown in Fig. (4.5c). In this case the magnitude of our result is smaller than the numerical result. This is due to that the value of both the inward flux and outward flux in our case are grater than the numerical one. In these two figures one can see that both in our and numerical cases the value of the ratio $\frac{\bar{J}}{J_0(P_0,0)}$ decreases monotonically as the force increases.

Further more, the ratio of the inner concentration, P_1 to the outer concentration, P_0 when the net flux through the channel vanishes is obtained by setting $\bar{J}(F_0, P_0, P_1) = 0$ into Eq. (2.4.1)

$$0 = J(F_0, P_0, P_1) + J(-F_0, P_0, P_1) \tag{2.4.10}$$

Substituting Eqs. (2.4.6) and (2.4.7) into Eq. (2.4.10) for $P_0 \neq P_1$ and rearranging the resulting equation we obtain

$$\frac{P_1}{P_0} = \frac{\int_0^1 e^{\bar{U}_{eff}(x)} dx + \int_0^1 e^{U_{eff}(x)} dx}{e^{-F_0} \int_0^1 e^{\bar{U}_{eff}(x)} dx + \ e^{F_0} \int_0^1 e^{U_{eff}(x)} dx} \tag{2.4.11}$$

To compare our result with the numerical result we plot the above ratio versus the force as shown in Fig. (2.8).

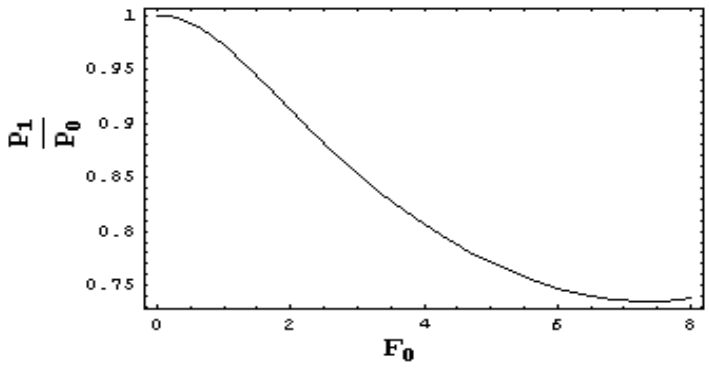

Figure 2.8: Plot of the ratio of the inner concentration, P_0 to the outer concentration, P_1 versus the load, F_0.

According to this figure, the ratio, $\frac{P_1}{P_0}$ decreases as the load, F_0 increases. If we compare this figure with the numerical obtained in [1] as shown in Fig.(4.5d) we find that in both cases the ratio $\frac{P_1}{P_0}$ decreases when the force increased and the value of $\frac{P_1}{P_0}$ is less than one which is expected and consistent(in both cases) with the fact that under the same force level and concentration gradient the inward flux is smaller than the outward flux. While the value of the ratio $\frac{P_1}{P_0}$ in our case is greater than the numerical value, since the flux(both inward and outward) in our case larger than in the numerical case.

In next chapter, I will present the case of random telegraph force which is our new contribution to this work.

Chapter 3

Transport driven by non equilibrium fluctuation

Again in this chapter we take the glycerol uptake facilitator channel (GlpF) with a potential mean force (PMF) inside it as modeled by Schulten and Kosztin [1], for numerical simulation. In our case we modeled the PMF by a simple ratchet like potential (as shown in Fig. (2.2)) and consider a non equilibrium fluctuation of the cell membrane to find the analytical expressions for the steady state flux of the glycerol molecule inside the channel.

Finally, we consider the effect of non equilibrium fluctuation of the cell membrane on the glycerol transport through GlpF. Let us model such fluctuations by a random telegraph force (RTF) *i.e* RTF is a homogeneous dichotomous force $F(t)$, which randomly switches between two states $\pm F_O$ [6] (where F_O is a constant), with switching time that obey a Poisson distribution. The RTF holds such that $< F(t) >= 0$ and $< F(t)F(0) >= F_0^2 e^{\frac{-2t}{T_0}}$, where T_0 is the mean switching time.

The differential equation satisfying the probability density of finding the glycerol molecule inside the channel is associated with the Fokker-Plank equation for the continuous variable x and the master equation describing the discrete states $(+)$state and $(-)$state. Thus

the associated FPE is a result of two coupled equations given by

$$\partial_t P_+(x,t) = \partial_x^2 P_+(x,t) - \partial_x[(f(x)+F_0)P_+(x,t)] - \frac{P_+(x,t)}{T_0} + \frac{P_-(x,t)}{T_0}, \tag{3.0.1}$$

and

$$\partial_t P_-(x,t) = \partial_x^2 P_-(x,t) - \partial_x[(f(x)-F_0)P_-(x,t)] + \frac{P_+(x,t)}{T_0} - \frac{P_-(x,t)}{T_0}. \tag{3.0.2}$$

where $P_\pm(x,t)$ is the conditional probability density that the RTF is in the $\pm F_0$ state respectively.

In steady state the above coupled equations reduced to

$$\frac{d^2P_+(x)}{dx^2} + \frac{d}{dx}[(U'(x)-F_0)P_+(x)] - \frac{1}{T_0}(P_+(x)-P_-(x)) = 0 \tag{3.0.3}$$

$$\frac{d^2P_-(x)}{dx^2} + \frac{d}{dx}[(U'(x)+F_0)P_-(x)] + \frac{1}{T_0}(P_+(x)-P_-(x)) = 0 \tag{3.0.4}$$

We know that in steady state the net flux through the channel is constant and this flux from Eq. (3.0.3) and Eq. (3.0.4) is given by

$$J = -P'(x) - U'(x)P(x) + F_0\Delta P(x) \tag{3.0.5}$$

where $P(x)$=$P_+(x)$ + $P_-(x)$ is the total probability density and $\Delta P(x)$=$P_+(x)$ - $P_-(x)$ But we know that in our case $U(x)$ has three different values and $U'(x)$ is constant in each of the three regions. Due to this reason we can rewrite Eq. (3.0.3) and Eq. (3.0.4) respectively as

$$\frac{d^2P_+(x)}{dx^2} + (U'(x)-F_0)\frac{dP_+(x)}{dx} - \frac{1}{T_0}(P_+(x)-P_-(x)) = 0 \tag{3.0.6}$$

$$\frac{d^2P_-(x)}{dx^2} + (U'(x)+F_0)\frac{dP_-(x)}{dx} + \frac{1}{T_0}(P_+(x)-P_-(x)) = 0 \tag{3.0.7}$$

From Eq. (3.0.6) we can solve for $P_-(x)$ in terms of $P_+(x)$ as

$$P_-(x) = -T_0\frac{d^2P_+(x)}{dx^2} - T_0(U'(x)-F_0)\frac{dP_+(x)}{dx} + P_+(x) \tag{3.0.8}$$

Substituting Eq. (3.0.8) into Eq. (3.0.7) we obtain

$$\frac{d^4P_+(x)}{dx^4} + 2U'(x)\frac{d^3P_+(x)}{dx^3} - (\frac{2}{T_0} + F_0^2 - U'(x)^2)\frac{d^2P_+(x)}{dx^2} - \frac{2U'(x)}{T_0}\frac{dP_+(x)}{dx} = 0 \quad (3.0.9)$$

If we integrate this equation over the variable x we obtain

$$\frac{d^3P_+(x)}{dx^3} + 2U'(x)\frac{d^2P_+(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - U'(x)^2)\frac{dP_+(x)}{dx} - \frac{2U'(x)}{T_0}P_+(x) = k \quad (3.0.10)$$

where k is a constant.

Similarly, we can solve for $P_+(x)$ from Eq. (3.0.7) in terms of $P_-(x)$ and substituting the resulting equation into Eq. (3.0.6) we obtain

$$\frac{d^3P_-(x)}{dx^3} + 2U'(x)\frac{d^2P_-(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - U'(x)^2)\frac{dP_-(x)}{dx} - \frac{2U'(x)}{T_0}P_-(x) = k \quad (3.0.11)$$

To solve these two differential equations we take the three regions separately, since $U'(x)$ has constant but different values in each of the respective region.

Region one

In this region, according to Eq. (2.1.4) the potential is $U_1(x) = -38x$, thus $U_1'(x) = -38$, then substituting all these values into Eq. (3.0.10) and Eq. (3.0.11) we obtain

$$\frac{d^3P_+^1(x)}{dx^3} - 76\frac{d^2P_+^1(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - 1444)\frac{dP_+^1(x)}{dx} + \frac{76}{T_0}P_+^1(x) = k_1 \quad (3.0.12)$$

$$\frac{d^3P_-^1(x)}{dx^3} - 76\frac{d^2P_-^1(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - 1444)\frac{dP_-^1(x)}{dx} + \frac{76}{T_0}P_-^1(x) = k_1 \quad (3.0.13)$$

where $P_\pm^1$ is the steady state probability density of the RTF in the $\pm F_0$ respectively in region one .

Eqs. (3.0.12) and (3.0.13) are linear third order differential equation of non homogeneous with constant coefficients. Generally the solutions of these equations are given by the sum of the complementary function $P_{\pm com}^1(x)$ which satisfies the homogeneous differential equation and the particular function $P_{\pm par}^1(x)$ is the solution of the nonhomogeneous differential equations and these functions respectively are

$$P_+^1(x) = P_{+com}^1(x) + P_{+par}^1(x) \quad (3.0.14)$$

$$P^1_-(x) = P^1_{-com}(x) + P^1_{-par}(x) \tag{3.0.15}$$

First let us take the homogeneous differential equations from Eq. (3.0.12) and Eq. (3.0.13) as

$$\frac{d^3P^1_+(x)}{dx^3} - 76\frac{d^2P^1_+(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - 1444)\frac{dP^1_+(x)}{dx} + \frac{76}{T_0}P^1_+(x) = 0 \tag{3.0.16}$$

$$\frac{d^3P^1_-(x)}{dx^3} - 76\frac{d^2P^1_-(x)}{dx^2} - (\frac{2}{T_0} + F_0^2 - 1444)\frac{dP^1_-(x)}{dx} + \frac{76}{T_0}P^1_-(x) = 0 \tag{3.0.17}$$

In standard form the solutions for these two homogeneous differential equations are respectively given by

$$P^1_{+com}(x) = C_1^+ e^{\lambda_1 x} \tag{3.0.18}$$

$$P^1_{-com}(x) = C_1^- e^{\lambda_1 x} \tag{3.0.19}$$

where $C_1^{\pm}$ are unknown constant coefficients to be determined by imposing the necessary boundary conditions and λ_1 is unknown eigen value which is similar for the two differential equations, since Eq. (3.0.16) and Eq. (3.0.17) have the same constant coefficients in which the eigne values are determined by them.

Note:since Eq. (3.0.16) and Eq. (3.0.17) are third order differential equations, then the constants $C_1^{\pm}$ and λ_1 can be more than one and Eq. (3.0.18) and Eq. (3.0.19) are a result of a superposition of such equations.

Substituting Eq. (3.0.18) into Eq. (3.0.16) or Eq. (3.0.19) into Eq. (3.0.17) we obtain

$$\lambda_1^3 - 76\lambda_1^2 - (\frac{2}{T_0} + F_0^2 - 1444)\lambda_1 + \frac{76}{T_0} = 0 \tag{3.0.20}$$

This is a cubic equation (a polynomial of degree three), which has three possible real roots which are given by

$$\lambda_{11} = (-\frac{b_1}{2} + i\sqrt{D_1})^{\frac{1}{3}} + (-\frac{b_1}{2} - i\sqrt{D_1})^{\frac{1}{3}} + \frac{76}{3} \tag{3.0.21}$$

$$\lambda_{12} = -\frac{l_1}{2} + \frac{\sqrt{3}}{2}[(i\frac{b_1}{2} + \sqrt{D_1})^{\frac{1}{3}} + (-i\frac{b_1}{2} + \sqrt{D_1})^{\frac{1}{3}}] + \frac{76}{3} \tag{3.0.22}$$

$$\lambda_{13} = -\frac{l_1}{2} - \frac{\sqrt{3}}{2}[(i\frac{b_1}{2} + \sqrt{D_1})^{\frac{1}{3}} + (-i\frac{b_1}{2} + \sqrt{D_1})^{\frac{1}{3}}] + \frac{76}{3} \tag{3.0.23}$$

where l_1=$(-\frac{b_1}{2}+i\sqrt{D_1})^{\frac{1}{3}}+(-\frac{b_1}{2}-i\sqrt{D_1})^{\frac{1}{3}}$

b_1=$\frac{109744}{27}+\frac{76}{3T_0}-\frac{76F_0^2}{3}$

D_1=$\frac{2085136F_0^2}{27}-\frac{2888F_0^4}{27}+\frac{F_0^6}{27}+\frac{8}{3T_0^3}+\frac{1444}{27T_0^2}+\frac{4F_0^2}{9T_0}+\frac{14440F_0^2}{27T_0}+\frac{2F_0^4}{9T_0}$

i=$\sqrt{-1}$

In terms of these three roots Eq. (3.0.18) and Eq. (3.0.19) can be rewritten as

$$P^1_{+com}(x)=C^+_{11}e^{\lambda_{11}x}+C^+_{12}e^{\lambda_{12}x}+C^+_{13}e^{\lambda_{13}x} \tag{3.0.24}$$

$$P^1_{-com}(x)=C^-_{11}e^{\lambda_{11}x}+C^-_{12}e^{\lambda_{12}x}+C^-_{13}e^{\lambda_{13}x} \tag{3.0.25}$$

Similarly, let us suppose that the solutions of the non homogeneous differential equations (the particular functions) be

$$P^1_{+par}(x)=A \tag{3.0.26}$$

$$P^1_{-par}(x)=B \tag{3.0.27}$$

where A and B are constants which are determined by substituting Eqs. (3.0.26) and (3.0.27) into Eq. (3.0.12) and Eq. (3.0.13) respectively and we obtain

$$A=\frac{T_0k_1}{76} \tag{3.0.28}$$

$$B=\frac{T_0k_1}{76} \tag{3.0.29}$$

Substituting Eq. (3.0.28) and Eq. (3.0.29) into Eq. (3.0.26) and Eq. (3.0.27) respectively we obtain

$$P^1_{+par}(x)=\frac{T_0k_1}{76} \tag{3.0.30}$$

$$P^1_{-par}(x)=\frac{T_0k_1}{76} \tag{3.0.31}$$

Substituting Eqs. (3.0.24), (3.0.30) and Eqs. (3.0.25), (3.0.31) into Eq. (3.0.14) and Eq. (3.0.15) respectively we obtain

$$P^1_{+}(x)=C^+_{11}e^{\lambda_{11}x}+C^+_{12}e^{\lambda_{12}x}+C^+_{13}e^{\lambda_{13}x}+\frac{T_0k_1}{76} \tag{3.0.32}$$

$$P^1_{-}(x)=C^-_{11}e^{\lambda_{11}x}+C^-_{12}e^{\lambda_{12}x}+C^-_{13}e^{\lambda_{13}x}+\frac{T_0k_1}{76} \tag{3.0.33}$$

Using these two equations, the total probability density, $P_1(x)$ and the difference in the probability density, $\Delta P_1(x)$ are respectively given by

$$P_1(x) = (C_{11}^+ + C_{11}^-)e^{\lambda_{11}x} + (C_{12}^+ + C_{12}^-)e^{\lambda_{12}x} + (C_{13}^+ + C_{13}^-)e^{\lambda_{13}x} + \frac{T_0 k_1}{38} \tag{3.0.34}$$

$$\Delta P_1(x) = P_1(x) = (C_{11}^+ - C_{11}^-)e^{\lambda_{11}x} + (C_{12}^+ - C_{12}^-)e^{\lambda_{12}x} + (C_{13}^+ - C_{13}^-)e^{\lambda_{13}x} \tag{3.0.35}$$

To find the relationship between $C_{i,j}^+$ and $C_{i,j}^-$ (where $i, j = 1, 2, 3$), let us calculate the constant flux in region one

$$J = -P_1'(x) - U_1'(x)P_1(x) + F_0\Delta P_1(x) \tag{3.0.36}$$

Substituting Eqs. (3.0.34) and (3.0.35) and the value of $U_1'((x)$ into Eq. (3.0.36) we obtain

$$J = \gamma_1 e^{\lambda_{11}x} + \gamma_2 e^{\lambda_{12}x} + \gamma_3 e^{\lambda_{13}x} + T_0 k_1 \tag{3.0.37}$$

where γ_1=$[(-\lambda_{11} + 38 + F_0)C_{11}^+ + (-\lambda_{11} + 38 - F_0)C_{11}^-]$

γ_2=$[(-\lambda_{12} + 38 + F_0)C_{12}^+ + (-\lambda_{12} + 38 - F_0)C_{12}^-]$

γ_3=$[(-\lambda_{13} + 38 + F_0)C_{13}^+ + (-\lambda_{13} + 38 - F_0)C_{13}^-]$

In the above equation one can see that on the right-hand side the only constant term is $T_0 k_1$ and all the other three terms are dependent on the variable x, then equating the left and right side we obtain

$$J = T_0 k_1 \tag{3.0.38}$$

while

$$\gamma_1 e^{\lambda_{11}x} + \gamma_2 e^{\lambda_{12}x} + \gamma_3 e^{\lambda_{13}x} = 0 \tag{3.0.39}$$

Since, on the left side of Eq.(3.0.37) there is no term dependent on x.

But we know that λ_{11}, λ_{12} and λ_{13} are different, then Eq. (3.0.39) holds true if and only if each of the coefficients of the exponentials vanish independently *i.e.*

$$(-\lambda_{11} + 38 + F_0)C_{11}^+ + (-\lambda_{11} + 38 - F_0)C_{11}^- = 0 \tag{3.0.40}$$

$$(-\lambda_{12} + 38 + F_0)C_{12}^+ + (-\lambda_{12} + 38 - F_0)C_{12}^- = 0 \tag{3.0.41}$$

$$(-\lambda_{13}+38+F_0)C_{13}^{+}+(-\lambda_{13}+38-F_0)C_{13}^{-}=0 \tag{3.0.42}$$

Hence

$$k_1=\frac{J}{T_0} \tag{3.0.43}$$

$$C_{11}^{-}=\frac{\lambda_{11}-38-F_0}{-\lambda_{11}+38-F_0}C_{11}^{+} \tag{3.0.44}$$

$$C_{12}^{-}=\frac{\lambda_{12}-38-F_0}{-\lambda_{12}+38-F_0}C_{12}^{+} \tag{3.0.45}$$

$$C_{13}^{-}=\frac{\lambda_{13}-38-F_0}{-\lambda_{13}+38-F_0}C_{13}^{+} \tag{3.0.46}$$

Substituting Eqs. (3.0.43), (3.0.44), (3.0.45) and (3.0.46) into Eq.(3.0.34) and Eq. (3.0.35) we obtain

$$P_1(x)=\frac{2F_0C_{11}^{+}}{\lambda_{11}-38+F_0}e^{\lambda_{11}x}+\frac{2F_0C_{12}^{+}}{\lambda_{12}-38+F_0}e^{\lambda_{12}x}+\frac{2F_0C_{13}^{+}}{\lambda_{13}-38+F_0}e^{\lambda_{13}x}+\frac{J}{38} \tag{3.0.47}$$

$$\Delta P_1(x)=\frac{2(38-\lambda_{11})C_{11}^{+}}{\lambda_{11}-38+F_0}e^{\lambda_{11}x}+\frac{2(38-\lambda_{12})C_{12}^{+}}{\lambda_{12}-38+F_0}e^{\lambda_{12}x}+\frac{2(38-\lambda_{13})C_{13}^{+}}{\lambda_{13}-38+F_0}e^{\lambda_{13}x} \tag{3.0.48}$$

Region two

We know that, region two is in the interval $L_1 \leq x \leq L_2$ with the corresponding potential $U_2(x)=74x-22.4$, thus $U_2'(x)=74$ then substituting this value into Eqs. (3.0.10) and (3.0.11) we obtain

$$\frac{d^3P_{+}^{2}(x)}{dx^3}+148\frac{d^2P_{+}^{2}(x)}{dx^2}-(\frac{2}{T_0}+F_0^2-5476)\frac{dP_{+}^{2}(x)}{dx}-\frac{148}{T_0}P_{+}^{2}(x)=k_2 \tag{3.0.49}$$

$$\frac{d^3P_{-}^{2}(x)}{dx^3}+148\frac{d^2P_{-}^{2}(x)}{dx^2}-(\frac{2}{T_0}+F_0^2-5476)\frac{dP_{-}^{2}(x)}{dx}-\frac{148}{T_0}P_{-}^{2}(x)=k_2 \tag{3.0.50}$$

where $P_{\pm}^{2}(x)$ is the steady state probability density of the RTF in the $\pm F_0$ respectively in region two.

Eq. (3.0.49) and Eq. (3.0.50) are similar form as that of Eq. (3.0.12) and Eq. (3.0.13) respectively in region one respectively except with different constant coefficients. Thus if we apply all the steps used for region one into region two we obtain

$$P_2(x)=\frac{2F_0C_{21}^{+}}{\lambda_{21}+74+F_0}e^{\lambda_{21}x}+\frac{2F_0C_{22}^{+}}{\lambda_{22}+74+F_0}e^{\lambda_{22}x}+\frac{2F_0C_{23}^{+}}{\lambda_{23}+74+F_0}e^{\lambda_{23}x}-\frac{J}{74} \tag{3.0.51}$$

$$\Delta P_2(x) = \frac{2(74+\lambda_{21})C_{21}^{+}}{\lambda_{21}+74+F_0}e^{\lambda_{21}x} + \frac{2(74+\lambda_{22})C_{22}^{+}}{\lambda_{22}+74+F_0}e^{\lambda_{22}x} + \frac{2(74+\lambda_{23})C_{23}^{+}}{\lambda_{23}+74+F_0}e^{\lambda_{23}x} \quad (3.0.52)$$

where $\lambda_{21}=(-\frac{b_2}{2}+i\sqrt{D_2})^{\frac{1}{3}}+(-\frac{b_2}{2}-i\sqrt{D_2})^{\frac{1}{3}}-\frac{148}{3}$

$\lambda_{22}=-\frac{l_2}{2}+\frac{\sqrt{3}}{2}[(i\frac{b_2}{2}+\sqrt{D_2})^{\frac{1}{3}}+(-i\frac{b_2}{2}+\sqrt{D_2})^{\frac{1}{3}}]-\frac{148}{3}$

$\lambda_{23}=-\frac{l_2}{2}-\frac{\sqrt{3}}{2}[(i\frac{b_2}{2}+\sqrt{D_2})^{\frac{1}{3}}+(-i\frac{b_2}{2}+\sqrt{D_2})^{\frac{1}{3}}]-\frac{148}{3}$

$l_2=(-\frac{b_2}{2}+i\sqrt{D_2})^{\frac{1}{3}}+(-\frac{b_2}{2}-i\sqrt{D_2})^{\frac{1}{3}}$

$b_2=-\frac{810448}{27}-\frac{148}{3T_0}+\frac{148F_0^2}{3}$

$D_2=\frac{29269806873872}{19682}+\frac{5704946084F_0^2}{2187}+\frac{310763F_0^4}{243}+\frac{F_0^6}{4}+\frac{2}{T_0^3}+\frac{1308764}{243T_0^2}+\frac{3F_0^2}{T_0^2}+\frac{10690214344}{2184T_0}+\frac{1374476F_0^2}{343T_0}+\frac{3F_0^4}{2T_0}$

$i=\sqrt{-1}$

Region three

Finally, in the third region the potential is given by $U_3(x) = -12x+12$, then $U_3'(x) = -12$, then substituting this value into Eq.(3.0.10) and Eq.(3.0.11) we obtain

$$\frac{d^3P_+^3(x)}{dx^3} - 24\frac{d^2P_+^3(x)}{dx^2} - (\frac{2}{T_0}+F_0^2-144)\frac{dP_+^2(x)}{dx} + \frac{24}{T_0}P_+^3(x) = k_3 \quad (3.0.53)$$

$$\frac{d^3P_-^3(x)}{dx^3} - 24\frac{d^2P_-^3(x)}{dx^2} - (\frac{2}{T_0}+F_0^2-144)\frac{dP_-^3(x)}{dx} + \frac{24}{T_0}P_-^3(x) = k_3 \quad (3.0.54)$$

where $P_\pm^3(x)$ is the steady state probability density of the RTF in the $\pm F_0$ state in region three respectively.

Again Eq. (3.0.53) and Eq. (3.0.54) are the same expression with those equations in region one except with different constant coefficients, Then following the same step as to region one into region three we obtain

$$P_3(x) = \frac{2F_0C_{31}^{+}}{\lambda_{31}-12+F_0}e^{\lambda_{31}x} + \frac{2F_0C_{32}^{+}}{\lambda_{32}-12+F_0}e^{\lambda_{32}x} + \frac{2F_0C_{33}^{+}}{\lambda_{33}-12+F_0}e^{\lambda_{33}x} + \frac{J}{12} \quad (3.0.55)$$

$$\Delta P_3(x) = \frac{2(12-\lambda_{31})C_{31}^{+}}{\lambda_{31}-12+F_0}e^{\lambda_{31}x} + \frac{2(12-\lambda_{32})C_{32}^{+}}{\lambda_{32}-12+F_0}e^{\lambda_{32}x} + \frac{2(12-\lambda_{33})C_{33}^{+}}{\lambda_{33}-12+F_0}e^{\lambda_{33}x} \quad (3.0.56)$$

where $\lambda_{31}=(-\frac{b_3}{2}+i\sqrt{D_3})^{\frac{1}{3}}+(-\frac{b_3}{2}-i\sqrt{D_3})^{\frac{1}{3}}+8$

$\lambda_{32}=-\frac{l_3}{2}+\frac{\sqrt{3}}{2}[(i\frac{b_3}{2}+\sqrt{D_3})^{\frac{1}{3}}+(-i\frac{b_3}{2}+\sqrt{D_3})^{\frac{1}{3}}]+8$

$\lambda_{33}=-\frac{l_3}{2}-\frac{\sqrt{3}}{2}[(i\frac{b_3}{2}+\sqrt{D_3})^{\frac{1}{3}}+(-i\frac{b_3}{2}+\sqrt{D_3})^{\frac{1}{3}}]+8$

l_3=$(-\frac{b_3}{2}+i\sqrt{D_3})^{\frac{1}{3}}+(-\frac{b_3}{2}-i\sqrt{D_3})^{\frac{1}{3}}$

b_3=$\frac{3456}{27}+\frac{24}{3T_0}-\frac{24F_0^2}{3}$

D_3=$768F_0^2-\frac{32F_0^4}{3}+\frac{F_0^6}{27}+\frac{8}{27T_0^3}+\frac{16}{3T_0^2}+\frac{4F_0^2}{9T_0^2}+\frac{160F_0^2}{3T_0}+\frac{2F_0^4}{9T_0}$

i=$\sqrt{-1}$

3.1 Boundary conditions

Next, we tried to impose the boundary conditions to calculate the analytical expression for the net constant flux through the channel.

1. At $x = 0$, we know that there is a left reservoir of glycerol molecule with a glycerol concentration $P(0) = P_0$. But according to our model potential region one is in contact with this reservoir, so that $P_1(0) = P_0$. Substituting $x = 0$ into Eq. (3.0.47) we obtain

$$\frac{C_{13}^{+}}{\lambda_{13}-38+F_0}=\frac{P_0}{2F_0}-\frac{C_{11}^{+}}{\lambda_{11}-38+F_0}-\frac{C_{12}^{+}}{\lambda_{12}-38+F_0}-\frac{J}{76F_0} \tag{3.1.1}$$

2. At $x = 1$ similarly we have a reservoir of glycerol molecule having a glycerol concentration $P(1) = P_1$, then using our model potential region three is in contact with right reservoir, hence we can have $P_3(1) = P_1$. Substituting $x = 1$ into Eq. (3.0.55) we obtain

$$\frac{C_{33}^{+}}{\lambda_{33}-12+F_0}=\frac{P_1e^{-\lambda_{33}}}{2F_0}-\frac{C_{31}^{+}e^{(\lambda_{31}-\lambda_{33})}}{\lambda_{31}-12+F_0}-\frac{C_{32}^{+}e^{(\lambda_{32}-\lambda_{33})}}{\lambda_{32}-12+F_0}-\frac{Je^{-\lambda_{33}}}{24F_0} \tag{3.1.2}$$

If we see our model potential there are two points of discontinuity throughout the whole channel since $U'(x)$ has three different values in the three regions and these points are $x = 0.2$ and $x = 0.4$. Even if there is a discontinuity point inside the channel, the net flux through the channel is constant and single valued at each point (*i.e.* $J = -P'(x) - U'(x)P(x) + F_0\Delta P(x)$=constant) and single valued. Based on this reason let us treat each of the three terms ($P'(x)$, $U'(x)P(x)$ and $\Delta P(x)$) at the point of discontinuity

independently. That means, the diffusion of the glycerol molecule inside the channel is in a single medium which implies that diffusion is continuous (*i.e.* $P'(x)$ is continuous). The continuity of the diffusion implies that the drift of the particles inside the same channel is continuous ($U'(x)P(x)$), this is due to the fact that the force resulted from the diffusion is balanced by the force due to the drift. The last term $\Delta P(x)$ is continuous due to the continuity of the net flux, the diffusion term and the drift term.

3. At $x = 0.2$

$$P'(0.2^-) = P'(0.2^+) \tag{3.1.3}$$

where 0.2^- is the limit from the left of $x = 0.2$ and 0.2^+ is the limit from the right of $x = 0.2$. Since, region one and two are to the left and right of $x = 0.2$ respectively. Substituting Eqs. (3.0.47) and (3.0.51) into Eq. (3.1.3) we obtain

$$\lambda_{23}\alpha_{23} = \lambda_{11}\alpha_{11} + \lambda_{12}\alpha_{12} + \lambda_{13}\alpha_{13} - \lambda_{21}\alpha_{21} - \lambda_{22}\alpha_{22} \tag{3.1.4}$$

where α_{11}=$\frac{C_{11}^{+}e^{0.2\lambda_{11}}}{\lambda_{11}-38+F_0}$, α_{12}=$\frac{C_{12}^{+}e^{0.2\lambda_{12}}}{\lambda_{12}-38+F_0}$, α_{13}=$\frac{C_{13}^{+}e^{0.2\lambda_{13}}}{\lambda_{13}-38+F_0}$, α_{21}=$\frac{C_{21}^{+}e^{0.2\lambda_{21}}}{\lambda_{21}+74+F_0}$
α_{22}=$\frac{C_{22}^{+}e^{0.2\lambda_{22}}}{\lambda_{22}+74+F_0}$ and α_{23}=$\frac{C_{23}^{+}e^{0.2\lambda_{23}}}{\lambda_{23}+74+F_0}$

4. At $x = 0.2$

$$U'(0.2^-)P(0.2^-) = U'(0.2^+)P(0.2^+) \tag{3.1.5}$$

Similarly using Eqs. (3.0.47) and (3.0.51) and the value of $U'(0.2)$ (in region one and two) into Eq. (3.1.5) we obtain

$$37\alpha_{23} = -19\alpha_{11} - 19\alpha_{12} - 19\alpha_{13} - 37\alpha_{21} - 37\alpha_{22} \tag{3.1.6}$$

where α_{11}, α_{12}, α_{13}, α_{21}, α_{22} and α_{23} are given above.

5. At x=0.2

$$\Delta P(0.2^-) = \Delta P(0.2^+) \tag{3.1.7}$$

Again substituting Eqs. (3.0.48) and (3.0.52) into Eq. (3.1.7) we obtain

$$\delta_{23} = (38-\lambda_{11})\alpha_{11} + (38-\lambda_{12})\alpha_{12} + (38-\lambda_{13})\alpha_{13} - (74+\lambda_{21})\alpha_{21} - (74+\lambda_{22})\alpha_{22} \tag{3.1.8}$$

where $\delta_{23}=\frac{C_{23}^{+}(\lambda_{23}+74)e^{0.2\lambda_{23}}}{\lambda_{23}+74+F_0}$ and α_{11}, α_{12}, α_{13}, α_{21} and α_{22} are given above.

6. At x= 0.4

$$P'(0.4^{-}) = P'(0.4^{+}) \tag{3.1.9}$$

where $0.4^{\pm}$ is the limit from the right and left of $x = 0.4$ respectively.

Using our model potential region two and three are located at the left and right respectively at the point $x = 0.4$. Substituting Eqs.(3.0.51) and (3.0.55) into Eq.(3.1.9) we obtain

$$\lambda_{32}\beta_{32} = \lambda_{21}\beta_{21} + \lambda_{22}\beta_{22} + \lambda_{23}\beta_{23} - \lambda_{31}\beta_{31} - \lambda_{33}\beta_{33} \tag{3.1.10}$$

where $\beta_{21}=\frac{C_{21}^{+}e^{0.4\lambda_{21}}}{\lambda_{21}+74+F_0}$, $\beta_{22}=\frac{C_{22}^{+}e^{0.4\lambda_{22}}}{\lambda_{22}+74+F_0}$, $\beta_{23}=\frac{C_{23}^{+}e^{0.4\lambda_{23}}}{\lambda_{23}+74+F_0}$, $\beta_{31}=\frac{C_{31}^{+}e^{0.4\lambda_{31}}}{\lambda_{31}-12+F_0}$, $\beta_{32}=\frac{C_{32}^{+}e^{0.4\lambda_{32}}}{\lambda_{32}-12+F_0}$ and $\beta_{33}=\frac{C_{33}^{+}e^{0.4\lambda_{33}}}{\lambda_{33}-12+F_0}$

7. At x= 0.4

$$U'(0.4^{-})P(0.4^{-}) = U'(0.4^{+})P(0.4^{+}) \tag{3.1.11}$$

Substituting Eqs. (3.0.51) and (3.0.55) and the value of $U'(0.4)$ (in region two and three) into Eq. (3.1.11) we obtain

$$6\beta_{32} = -37\beta_{21} - 37\beta_{22} - 37\beta_{23} - 6\beta_{31} - 6\beta_{33} \tag{3.1.12}$$

where β_{21}, β_{22}, β_{23}, β_{31}, β_{32} and β_{33} are given above.

8. At x= 0.4

$$\Delta P(0.4^{-}) = \Delta P(0.4^{+}) \tag{3.1.13}$$

In a similar fashion, substituting Eqs.(3.0.52) and (3.0.56) into Eq.(3.1.13) we obtain

$$\alpha_{32} = (\lambda_{21}+74)\beta_{21}+(\lambda_{22}+74)\beta_{22}+(\lambda_{23}+74)\beta_{23}-(12-\lambda_{31})\beta_{31}-(12-\lambda_{33})\beta_{33} \tag{3.1.14}$$

where $\alpha_{32}=\frac{(12-\lambda_{32})C_{32}^{+}e^{0.4\lambda_{32}}}{\lambda_{32}-12+F_0}$ and β_{21}, β_{22}, β_{23}, β_{31} and β_{33} are given above.

Thus, we have eight different equations, hence by combining these equations in a few steps the net constant flux of the glycerol molecule inside the channel is given by

$$J = \frac{(m_5 - m_6)(m_9 + m_{10})P_0 - 2(m_3 + m_4)(m_{11} + m_{12})P_1}{2(m_3 + m_4)(m_7 + m_8) + (m_2 - m_1)(m_9 + m_{10})} \tag{3.1.15}$$

where m_1, m_2, . . . and m_{12} are all constants which are give in the appendix.

In the above equation it is possible to obtain the expressions of the inward flux(J_{in}), outward flux(J_{out}), the concentration ratio($\frac{P_1}{P_0}$) and the net flux($J_{P_0=P_1}$) by setting the cytoplasmic concentration $P_1 = 0$, outer concentration $P_0 = 0$, the net flux J=0 and equal concentration gradient(P_1=P_0) respectively. All these expressions are respectively given by

$$J_{in} = \frac{(m_5 - m_6)(m_9 + m_{10})P_0}{2(m_3 + m_4)(m_7 + m_8) + (m_2 - m_1)(m_9 + m_{10})} \tag{3.1.16}$$

$$J_{out} = \frac{2(m_3 + m_4)(m_{11} + m_{12})P_0}{2(m_3 + m_4)(m_7 + m_8) + (m_2 - m_1)(m_9 + m_{10})} \tag{3.1.17}$$

$$\frac{P_1}{P_0} = \frac{(m_5 - m_6)(m_9 + m_{10})}{2(m_3 + m_4)(m_{11} + m_{12})} \tag{3.1.18}$$

$$J_{P_0=P_1} = \frac{[2(m_3 + m_4)(m_{11} + m_{12}) - (m_5 - m_6)(m_9 + m_{10})]P_0}{2(m_3 + m_4)(m_7 + m_8) + (m_2 - m_1)(m_9 + m_{10})} \tag{3.1.19}$$

Based on all these expressions we compare our results with the numerical results. To do this, from the numerical consideration we fix the value of the mean switching time be ($10^1, 10^2$ and 10^3). For each value of T_0 we vary the value of the random telegraph force F_0 between 0 and 8 (all are dimensionless). Then we find five different discrete values for each of T_0 for the ratio of the inward flux, outward and net flux(with equal concentration gradient) to the inward flux in the absence of the RTF. For example we take T_0=10^3 and then we plot the flux versus the load as shown in Fig. (3.1).

According to this figure the inward flux is smaller than both the outward flux and net flux(with equal concentration) for the same force level and concentration gradient. In the absence of a concentration gradient the flux is outward since the value of the net flux(with equal concentration) is greater than the inward flux. If we compare these results with the numerical results obtained by Skulten and Kosztin in [1] as shown in Fig. (3.2) we found in magnitude our results are smaller than the numerical results and as the force increases all the fluxes are decreased while in the numerical results both fluxes are increased when

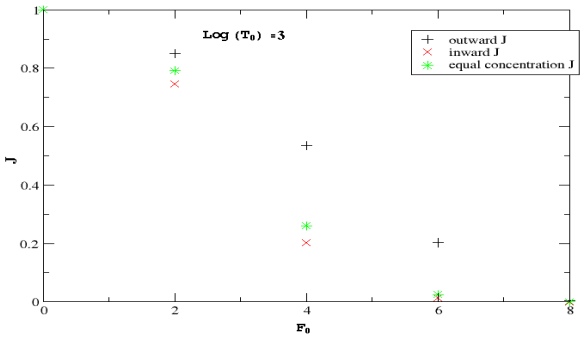

Figure 3.1: Plot of the outward flux (+), net flux with equal concentration (*) and inward flux (x) versus the load, F_0.

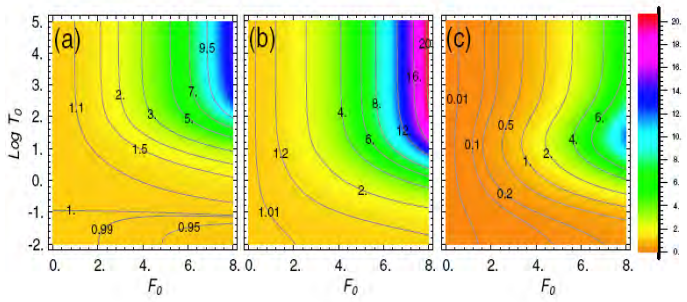

Figure 3.2: (color online)Contour density plots of the numerically evaluated relative (a)inward $\frac{J(F_0,T_0,P_0,0)}{J_0}$, (b) outward $\frac{-J(F_0,T_0,0,P_0)}{J_0}$, and (c)equal concentration $\frac{-J(F_0,T_0,P_0,P_0)}{J_0}$ glycerol flux in GlpF as a function of the amplitude F_0 and mean switching time T_0 of the RTF;$J_0 \equiv J(0, T_0, P_0, 0)$[3].

the force increased.

Finally, we plot the concentration ratio $\frac{P_0}{P_1}$(which is the inverse of the ratio$\frac{P_1}{P_0}$) versus the force as shown in Fig. (3.3)

From this figure one can see that the value the ratio $\frac{P_0}{P_1}$ is greater than one(or the inverse ratio $\frac{P_1}{P_0}$ is less than one). When we compare this result to the numerical result as shown in Fig. (3.4) we found the value of the ratio $\frac{P_1}{P_0}$ in our case is less than in the numerical case. But in both cases the value of the ratio $\frac{P_1}{P_0}$ is less than one and decreases as the

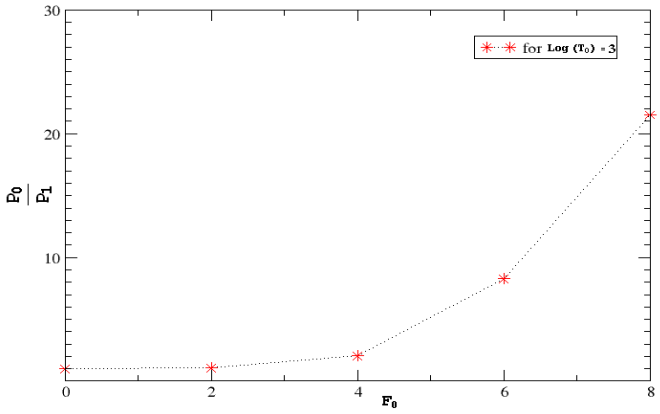

Figure 3.3: Plot of the concentration ratio $\frac{P_0}{P_1}$ versus the load, F_0.

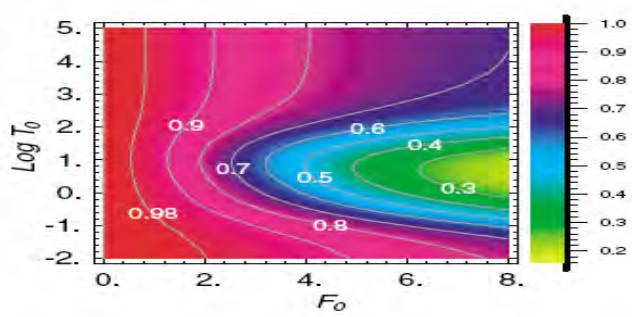

Figure 3.4: (contourline)Contour density plot of the concentration ratio $\frac{P_1}{P_0}$ at which current reversal (J=0)takes place in GlpF subjected to RTF versus the load, F_0[3].

value of the force increases which is consistent and expected to the fact that for the same force level and concentration gradient the out ward flux is larger than the inward flux.

Chapter 4

Summary and conclusion

We presented a model potential which is a simple ratchet like potential for the PMF inside the channel. We study the conduction of the glycerol molecule through the channel and we found the analytical expression for the steady state flux in the presence of a concentration gradient, constant force(or potential gradient), periodically switching force and a random telegraph force. In the absence of an external force the net flux is dependent only on the concentration gradient established at the ends of the channel but not on the asymmetry of the model potential and it vanishes if there is no concentration gradient. This implies that inorder to obtain a non zero net flux of the glycerol molecule through the channel even in the absence of a concentration gradient one needs to drive the system out of equilibrium by applying either an external force(constant and periodically switching) or a random telegraph force.

In the presence of periodically switching force the flux is dependent both on the force and the concentration gradient. In this case we found that both the net, outward and inward fluxes are greater than the flux due to a concentration gradient only. All these results are in good agreement with the numerical results obtained by Skulten and Kosztin in [1] even if there exists a magnitude difference between our results and the numerical results. These results imply that our model potential has important effect on the glycerol molecule transport through the channel which protects the cell against excess concentration of the

glycerol molecule. Finally, we subject the system to a nonequilibrium fluctuation of the cell membrane. We model such fluctuation by a random telegraph force(RTF). In this case we found both the outward and net fluxes are larger than the inward flux. The value of the concentration ratio $\frac{P_1}{P_0}$ is less than one which is expected and consistent to our results that in the presence of RTF the inward flux is smaller than the outward flux. In the presence of RTF our results are consistent to the numerical results in such away that in both cases both the outward and net fluxes are grater than the inward flux for the same force level and concentration gradient. And also the concentration ratio $\frac{P_1}{P_0}$ is less than one.

In conclusion, in our analytical calculation we have demonstrated that non equilibrium force fluctuations acting on the glycerol molecule in GlpF can have an important effect on the glycerol uptake by the cell. On one hand, fluctuations enhance the concentration gradient driven glycerol uptake, which may be vital for the cell under poor nutrient conditions. On the other hand, when glycerol is abundant, fluctuations provide an effective protection mechanism to the cell by stopping glycerol uptake well before the cytoplasmic concentration reaches the periplasmic one.

Appendix

In chapter three we found the analytical expression of the net constant flux interms of the constants m_1, m_2, ... and m_{12}. These constants are given by other constants a_1, a_2, ... and a_{14} and b_1, b_2, ... and b_{26} which are dependent on the roots λ_{11}, λ_{12}, ... and λ_{33}. All these constants are

a_1=$((19\lambda_{23}+37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+37\lambda_{12})e^{0.2\lambda_{12}})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_2=$((2812-37\lambda_{12}+19\lambda_{23})e^{0.2\lambda_{12}}-(2812-37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})((37\lambda_{11}+19\lambda_{23})e^{0.2\lambda_{11}}-(37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})$

a_3=$(\lambda_{11}\lambda_{23}+74\lambda_{11}-38\lambda_{23}-2812)e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+74\lambda_{13}-38\lambda_{23}-2812)e^{0.2\lambda_{13}}$

a_4=$((19\lambda_{23}-\lambda_{12}\lambda_{23}-37\lambda_{12})e^{0.2\lambda_{12}}-(19\lambda_{23}-\lambda_{13}\lambda_{23}-37\lambda_{13})e^{0.2\lambda_{13}})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_5=$(\lambda_{11}-38)e^{0.2\lambda_{11}}-(\lambda_{13}-38)e^{0.2\lambda_{13}}$

a_6=$(\lambda_{11}\lambda_{23}+74\lambda_{11}-38\lambda_{23}-2812)e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+74\lambda_{13}-38\lambda_{23}-2812)e^{0.2\lambda_{13}}$

a_7=$(2812-37\lambda_{13}+19\lambda_{23})((37\lambda_{11}+19\lambda_{23})e^{0.2\lambda_{11}}-(37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})+(19\lambda_{23}+37\lambda_{13})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_8=$(2812-37\lambda_{13}+19\lambda_{23})((\lambda_{11}\lambda_{23}+37\lambda_{11}-19\lambda_{23})e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+37\lambda_{13}-19\lambda_{23})e^{0.2\lambda_{13}})-(19\lambda_{23}-\lambda_{13}\lambda_{23}-37\lambda_{13})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_9=$(2812-19\lambda_{13}+19\lambda_{23})((2\lambda_{11}\lambda_{23}+74\lambda_{11}-38\lambda_{23})e^{0.2\lambda_{11}}-(2\lambda_{13}\lambda_{23}+74\lambda_{13}-38\lambda_{23})e^{0.2\lambda_{13}})+(\lambda_{13}\lambda_{23}-19\lambda_{23}+37\lambda_{13})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_{10}=$(2128-19\lambda_{13}+19\lambda_{23})((37\lambda_{11}+19\lambda_{23})e^{0.2\lambda_{11}}-(37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})+(38\lambda_{23}+$

$37\lambda_{13})((19\lambda_{23}+2812-37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+2812-37\lambda_{11})e^{0.2\lambda_{11}})$

a_{11}=$((19\lambda_{23}-\lambda_{12}\lambda_{23}-37\lambda_{12})e^{0.2\lambda_{12}}-(19\lambda_{23}-\lambda_{13}\lambda_{23}-37\lambda_{13})e^{0.2\lambda_{13}})((37\lambda_{11}+19\lambda_{23})e^{0.2\lambda_{11}}-(37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})$

a_{12}=$((19\lambda_{23}+37\lambda_{13})e^{0.2\lambda_{13}}-(19\lambda_{23}+37\lambda_{12})e^{0.2\lambda_{12}})((\lambda_{11}\lambda_{23}+37\lambda_{11}-19\lambda_{23})e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+37\lambda_{13}-19\lambda_{23})e^{0.2\lambda_{13}})$

a_{13}=$((2812-37\lambda_{12}+19\lambda_{23})e^{0.2\lambda_{12}}-(2812-37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})((\lambda_{11}\lambda_{23}+37\lambda_{11}-19\lambda_{23})e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+37\lambda_{13}-19\lambda_{23})e^{0.2\lambda_{13}})$

a_{14}=$(19\lambda_{23}+37\lambda_{13})((\lambda_{11}\lambda_{23}+37\lambda_{11}-19\lambda_{23})e^{0.2\lambda_{11}}-(\lambda_{13}\lambda_{23}+37\lambda_{13}-19\lambda_{23})e^{0.2\lambda_{13}})-(\lambda_{13}\lambda_{23}-19\lambda_{23}+37\lambda_{13})((37\lambda_{11}+19\lambda_{23})e^{0.2\lambda_{11}}-(37\lambda_{13}+19\lambda_{23})e^{0.2\lambda_{13}})$

b_1=$((6\lambda_{22}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{22}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_2=$((37\lambda_{32}+6\lambda_{22})e^{0.4\lambda_{32}}-(37\lambda_{33}+6\lambda_{22})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_3=$((37\lambda_{32}+6\lambda_{23})e^{0.4\lambda_{32}}-(37\lambda_{33}+6\lambda_{23})e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_4=$((2\lambda_{23}\lambda_{32}+74\lambda_{32}-12\lambda_{23})e^{0.4\lambda_{32}}-(2\lambda_{23}\lambda_{33}+74\lambda_{33}-12\lambda_{23})e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_5=$((2\lambda_{22}\lambda_{32}+74\lambda_{32}-12\lambda_{22})e^{0.4\lambda_{32}}-(2\lambda_{22}\lambda_{32}+74\lambda_{33}-12\lambda_{22})e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_6=$((37\lambda_{32}+6\lambda_{21})e^{0.4\lambda_{32}}-(37\lambda_{33}+6\lambda_{21})e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_7=$((37\lambda_{32}+6\lambda_{23})e^{0.4\lambda_{32}}-(37\lambda_{33}+6\lambda_{23})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_8=$((6\lambda_{23}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{23}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_9=$((2\lambda_{21}\lambda_{32}+74\lambda_{32}-12\lambda_{21})e^{0.4\lambda_{32}}-(2\lambda_{21}\lambda_{33}+74\lambda_{33}-12\lambda_{21})e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{10}=$((6\lambda_{21}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{21}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+$
$(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{11}=$((37\lambda_{32}+6\lambda_{21})e^{0.4\lambda_{32}}-(37\lambda_{33}+6\lambda_{21})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-$
$(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{12}=$((12-2\lambda_{32}+\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(12-\lambda_{33}+\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}+$
$(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{13}=$((\lambda_{32}-2\lambda_{33})e^{0.4\lambda_{32}}+\lambda_{33}e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-(24-\lambda_{32}-$
$\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{14}=$(\lambda_{33}-\lambda_{32})((\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+1.4\lambda_{32}-0.6\lambda_{33}}+(\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+2\lambda_{32})}-(\lambda_{33}-\lambda_{32})e^{\lambda_{31}+0.8\lambda_{32}-0.6\lambda_{33}})$

b_{15}=$((\lambda_{32}-2\lambda_{33})e^{0.4\lambda_{32}}+\lambda_{33}e^{\lambda_{32}-0.6\lambda_{33}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-$
$(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{16}=$(12-\lambda_{32})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}+(12-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}-(12-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(12-$
$\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}$

b_{17}=$(\lambda_{31}-\lambda_{33})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}-(2\lambda_{32}-2\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}+(2\lambda_{32}-2\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}+$
$(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}$

b_{18}=$((6\lambda_{22}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{22}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda 32)}-$
$(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{19}=$((\lambda_{22}\lambda_{32}+37\lambda_{32}-6\lambda_{22})e^{0.4\lambda_{32}}-(\lambda_{22}\lambda_{32}+37\lambda_{32}-6\lambda_{22})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-$
$(24-\lambda_{32}\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{20}=$((\lambda_{23}\lambda_{32}+37\lambda_{32}-6\lambda_{23})e^{0.4\lambda_{32}}-(\lambda_{23}\lambda_{32}+37\lambda_{32}-6\lambda_{23})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-$
$(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{21}=$((6\lambda_{23}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{23}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-$
$(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{22}=$((6\lambda_{21}+888-37\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(6\lambda_{21}+888-37\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-$
$(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{23}=$((\lambda_{21}\lambda_{32}+37\lambda_{32}-6\lambda_{21})e^{0.4\lambda_{32}}-(\lambda_{21}\lambda_{32}+37\lambda_{32}-6\lambda_{21})e^{\lambda_{32}-0.6\lambda_{33}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-$
$(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{24}=$((12-2\lambda_{32}+\lambda_{33})e^{\lambda_{32}-0.6\lambda_{33}}-(12-\lambda_{33}+\lambda_{32})e^{0.4\lambda_{32}})((\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}})$

b_{25}=$((6\lambda_{33}-\lambda_{32})e^{0.4\lambda_{32}})((24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}-(24-\lambda_{32}-\lambda_{31})e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}})$

b_{26}=$(24-\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}+(2\lambda_{32}-24)e^{0.4(\lambda_{31}+\lambda_{32})}-(24-2\lambda_{33})e^{\lambda_{31}+\lambda_{32}-1.2\lambda_{33}}+(24-\lambda_{33}-\lambda_{31})e^{0.4\lambda_{31}+\lambda_{32}-0.6\lambda_{33}}-(\lambda_{33}-\lambda_{31})e^{1.4\lambda_{31}-0.6\lambda_{33}}-(\lambda_{32}-\lambda_{33})e^{\lambda_{31}+0.4\lambda_{32}-0.6\lambda_{33}}$

m_1=$(2a_{10}(2a_4-a_2)-2a_9(a_1-a_2))(4\lambda_{23}a_5(a_4-a_{13})+4a_6(a_{11}-a_{12}))e^{0.2(\lambda_{13}+\lambda_{22})}$

m_2=$(8a_8(a_{11}-a_{12})+4a_{14}(a_4-a_{13})((a_4-74a_2a_5)-2a_6(a_1-a_2))e^{0.2(\lambda_{13}+\lambda_{22})}$

m_3=$(2a_3(a_1-a_2)-(a_4-74a_2a_5))(4\lambda_{23}a_5(a_4-a_{13})+4a_6(a_{11}-a_{12}))$

m_4=$(8\lambda_{23}a_3(a_{11}-a_{12})+4a_5(a_4-a_{13}))((a_4-74a_2a_5)-2a_6(a_1-a_2))$

m_5=$(4a_8(a_{11}-a_{12})+4a_{14}(a_4-a_{13}))((a_4-74a_2a_5)-2a_6(a_1-a_2))e^{0.2(\lambda_{13}+\lambda_{22})}$

m_6=$(a_7(2a_4-a_2)-2a_8(a_1-a_2))(4\lambda_{23}a_5(a_4-a_{13})+4a_6(a_{11}-a_{12}))e^{0.2(\lambda_{13}+\lambda_{22})}$

m_7=$37(b_{16}(2b_{20}-b_{21})-b_{26}(b_7-b_8))(12(b_9-b_6)-(b_{10}-b_{11}))(b_7-b_8)(\lambda_{22}-\lambda_{23})(\lambda_{32}-\lambda_{33})e^{0.4\lambda_{32}-0.6\lambda_{33}}$

m_8=$37(2b_{17}(b_7-b_8)-24b_{16}(b_3-b_4))((b_{10}-b_{11})(b_{20}-b_{21})-(b_{22}-b_{23})(b_7-b_8))(\lambda_{22}-\lambda_{23})(\lambda_{32}-\lambda_{33})e^{0.4\lambda_{32}-0.6\lambda_{33}}$

m_9=$48((b_1-b_2)(b_3-b_4)-(b_5-b_6)(b_7-b_8))((b_{10}-b_{11})(b_{20}-b_{21})-(b_{22}-b_{23})(b_7-b_8))$

m_{10}=$4((b_1-b_2)(b_{20}-b_{21})-(b_{18}-b_{19})(b_7-b_8))(12(b_9-b_6)-(b_{10}-b_{11}))(b_7-b_8)$

m_{11}=$37(3(b_{12}+b_{13})(b_{20}-b_{21})-(6b_{24}+b_{24})(b_7-b_8))(12(b_9-b_6)-(b_{10}-b_{11}))(b_7-b_8)(\lambda_{22}-\lambda_{23})e^{-0.6\lambda_{33}}$

m_{12}=$37(36(2b_{12}+b_{13})(b_3-b_4)+12(2b_{14}-b_{15})(b_7-b_8))((b_{10}-b_{11})(b_{20}-b_{21})-(b_{22}-b_{23})(b_7-b_8))(\lambda_{22}-\lambda_{23})e^{-0.6\lambda_{33}}$

Bibliography

[1] I.Kosztin and K.Schulten, Phys.Rev.Lett **93**, 238102(2004).

[2] D. Lu, P.Grayson and K.Schulten, Biophysical journal, vol. **85**,2977-2987(2003).

[3] M.Kustur and J.Luczka, Phys. Rev. Lett. Vol. **27**,663-675(1996)

[4] R.P.Feynman, R.B Leighton, M.Sands, The Feynman Lectures on Physics, Addison-Vesley, Reading 1966 vol. I, Chapter 46.

[5] D.Alemayehu, Msc thesis in Addis Ababa University (unpublished) 2005.

[6] Magnasco, Phys. Rev. Lett. **71**, 1477(1998).

[7] C.W.Gardiner, Stochastic methods: A Handbook for the Natural and Social Sciences 4^{th} Ed.(Springer Verlag, Berlin Heirdelberg)2009.

[8] A.Ajdari, J.Prost, C.R.Acad. Sci. Paris **315**, 1635(1992)

Declaration

This thesis is my original work, has not been presented for a degree in any other University and that all the sources of material used for the thesis have been dully acknowledged.

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