Chapter 3
Ligand-Binding

This chapter will be reviewed and improved in Sa-yakanit and Boribarn (2001). This problem, ligand-binding, concentrate to the ligand binding in heme case. It can be called bottleneck problem because of its shape of pocket of heme. We discuss in protein, surface membrane and continue in the fluctuating bottleneck problem, ligand-binding in heme.

3.1 Protein

As pointed out by Frauenfelder (1988), proteins can be considered as the machines of life constructed from 20 different building blocks, the amino acids. The order of 100 amino acids are covalently linked to form a long linear chain. The arrangement of the amino acids in this chain, the primary structure, determines the final tertiary structure and the function of a particular protein. In a solvent, the linear chain will fold into the space-filling tertiary structure, the working protein. The final protein looks like a miniature crystal, consisting of the order of 1,000 atoms and with linear dimensions of the order of a few nanometers.

Proteins are flexible and can behave like machine rather than like pieces of rock or rigid structures. The forces along the protein backbone, the polypeptide chain, are strong (covalent) and cannot be broken by thermal fluctuations. The forces that hold the tertiary structure together are weak, mainly hydrogen bonds and van der Waals forces. These weak bonds are continuously broken and

reformed. This motion is essential for many functions. It looks like fluctuating environment.

Austin, Beeson, Eisenstein, Frauenfelder and Gunsalus (1975), to study the states and motions of a protein, have investigested a simple process, the binding of a small molecule(ligand) such as dioxygen or caborn monoxide to myoglobin (Mb). Myoglobin is a protein of molecular weight 17.9 kD, with dimensions $2.5 \times 4.4 \times 4.4\ nm^3$, that reversibly stores dioxygen in muscles. The protein matrix cross-section is a planar organic molecule, heme, which contains an iron atom at its center. Storage of O_2 or CO occurs through covalent binding of the small molecule at the iron atom.

3.2 Ligand Binding

A molecule bound by a protein is called a ligand, and the site on the protein to which it binds is called the binding site. Proteins are not rigid and may undergo conformational changes when a ligand binds, a process called induced fit. In a multisubunit protein, the binding of a ligand to one subunit may affect ligand binding to other subunits. Ligand binding can also be regulated.

Oxygen-binding proteins such as myoglobin and hemoglobin represent useful models with which to illustrate these principles. These proteins contain a prosthetic group called heme, to which the oxygen binds. Heme consists of a single atom of ferrous iron coordinated within a porphyrin.

3.3 Binding of Ligand to Myoglobin

Austin, Beeson, Eisenstein, Frauenfelder, Gunsalus and Marshall(1974) and also Austin, Beeson, Eisenstein, Frauenfelder and Gunsalus(1975) observed the bind-

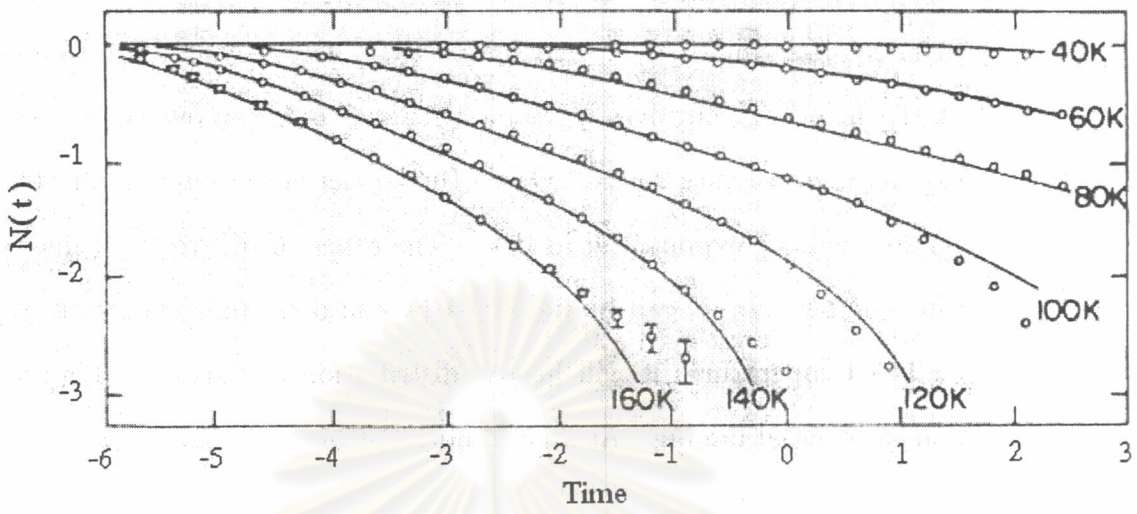

Figure 3.1: Time dependence of the binding of CO to Mb between 40 and 160 K. The solvent is glycerol-water (3:1). At each temperture, the two paremeters t_0 and n are determined. $N(t)$ is a fraction of Mb molecules that have not rebonded a CO molecule at the time t after photodissociation

ing of CO to Mb at the temperatures below about 200 K yielded a result that was at first very surprising. Below 200 K, the CO molecule remains in the heme pocket after photodissociation and rebinds from there. Then Frauenfelder and Wolynes (1985) studied the mechanism of the formation of the Fe-CO bond. The signal of process is time-dependent. It is not exponential in time however it can be approximated by power law

$$N(t) = \left(1 + \frac{t}{t_0}\right)^{-n} \tag{3.1}$$

where $N(t)$ is a fraction of Mb molecules that have not rebonded a CO molecule at the time t after photodissociation, t_0 and n are parameters depending on temperature.

Considering processes between 60 and 160 K approximated $n = 2.8 \times$

$10^{-3}T/K$ describing by Eq. (3.1) have been called endless. Nonexponential behavior like this is observed in many different systems. The covalent binding at the heme iron involves a potential barrier must be overcome. The simplest explanation becomes 2 cases. One if the barrier is the same in all Mb molecules, binding will be exponential in time. The other, if different Mb molecules have different barriers, it can be described by the nonexponential time dependence. At low temperatures it will have a distribution of barrier heights and show a nonexponential binding. At high temperatures more than 300 K, the transitions among Mb and CO occur.

These are a transport process over a barrier treated as chemical kinetics. One can look at the association and dissociation of the ligand in 4 ways.

(i) The single-particle(static) model. This model assumes that the protein forms an effective static potential in which the ligand moves. The general behavior in such a potential is easy to describe but a treatment is difficult and has not been achieved. The ligand will perform a complicated random walk in the potential.

(ii) The binding in reality. A ligand molecule in the solvent around Mb executes a Brownian motion in the solvent, moves into the protein matrix, migrates through the matrix to the heme pocket and finally binds covalently to the heme iron.

(iii) Protein motions. This is caused by the formation or breaking of the covalent bond at the iron. The total binding energy of a protein defined as the difference in Gibbs energy between the folded and unfolded state is of the order of 1eV and very small. A ligand moves through the protein matrix. It will affect the protein strongly and the covalent binding also involving an energy of

the order of 1 eV. It causes a major perturbation of the protein structure called proteinquake. Thus, one can neglect the motion of the ligand and consider only the protein motions.

(iv) Unified model. This model considers the motion of the protein and the ligand together. However, mechanism of the dynamics of the protein and the interaction of the ligand with the protein does not enough to clear.

In this chapter we will consider the single particle model with one oscillator environment by using nonlocal time path integral.

3.4 Complex Environment

The transport process of complex systems such as liquids, glasses and biomolecules over a barrier has been the subject of many studies. For molecules in a complex environment, the overall barrier-crossing reaction rate can be treated as classical phenomenological chemical kinetics. Numerous treatments of a molecule reaction dynamic using the reaction diffusion equation approach have been reported. However this approach is not applicable to reactions in a highly viscous environment. For example, Frauenfelder and Wolynes (1985) show that, in the case of carbon monoxide, recombination of myoglobin needs a higher-barrier relax equation of a highly non-exponential property.

Using Path Integral techniques, the survival paths for reaction dynamics in fluctuating environments has been investigated extensively by Wang and Wolynes (1993, 1994). They began by considering a simple model of the rate process in Gaussian fluctuating environments. This approach assumes that the fluctuations relax or a relaxation function exponentially according to the stretched exponential law see more details in Lindsey and Patterson (1980), Dixon and

Nagel (1988) and Nienhaus, Mourant and Frauenfelder (1992). These are given by

$$\langle r(\tau)\ r(\sigma)\rangle = \theta \exp\left[-(\lambda \mid \tau - \sigma|)^{\Gamma}\right] \tag{3.2}$$

where θ is the amplitude of equal time correlation, λ is the frequency or relaxation rate and Γ denotes the stretched parameters.

The $\Gamma = 1$ case corresponds to exponentially relaxing fluctuations, while $\Gamma < 1$ corresponds to the more general fluctuating environment, with stretched exponential relaxation encountered in glasses and biomolecules. To obtain an analytic result, Wang and Wolynes (1994) assume that the reaction terms are linear and quadratic where is another parameter such as α denoting the strength of the reaction oscillators. These linear and quadratic reaction terms, together with stretched exponential fluctuation in an analytical survival path with an effective rate as a constant, are obtained. In order to treat a more general effective rate coefficient, Wang and Wolynes (1996) have generalized the calculation of the reaction in a complex environment by using the instanton method to calculate the rate coefficient.

In these chapter we uses a path integral method for handling the reaction rate within a complex environment. However instead of assuming that the fluctuation decays as a stretched exponenl as discussed by Wang and Wolynes (1993), we consider the rate constant with the reaction coordinate coupled to the heat bath or an infinite set of oscillators. This microscopic Hamiltonian model describing a dissipative system became popular after Caldeira and Leggett (1983a, 1983b) and applied to the tunneling problem.This model was also discussed by Poulter and Sa-yakanit (1992). In this approch, we also assumed that the rate coefficient has a Gaussian dependence on its environment coordinates. We adopt

the Caldeira and Leggett model, and after eliminating the oscillators, an effective action was obtained. We consider only a single dominant oscillator.The justification of this assumption will be discussed. Within this limit, the effective action constraint of non-local action can be solved exactly.

3.5 Wang and Wolynes Model: Botttleneck Problem

Wang and Wolynes (1993, 1994) had developed a mathematical formulae for reactions in fluctuating environment. We can review their method as the survival probability associated with a reaction whose environment is described by a generalized Langevin or Fokker-Plank equation being presented as a functional integral over paths. Each exponential weight accords to the time integral of an appropriated Lagrangian along that path. They illustrated this by starting with the path probabilities in the absence of reaction and write:

$$P\left(r_f, r_i; \beta\right) = \int D\left[\, r\left(\tau\right)\right] \, \exp\left[-\int_0^\beta \, L\left(r, \dot{r}, \tau\right) \, d\tau\right] \tag{3.3}$$

Note that in this dissertation we have used the imaginary time and set $\hbar$ equals to 1. Moreover, it is necessary to consider cases where there is correlation between fluctuations of the coordinates r's at different times. Memory effects need to be taken into account. They extended the formulation for a general Gaussian memory noise form, the path probability Q can be written

$$Q\left(\left\{r\left(\tau\right)\right\}, \, r_f, r_i; \beta\right) = \, \exp\left[-\frac{1}{2}\int_0^\beta \int_0^\beta \, r\left(\tau\right) \, A\left(\tau, \sigma\right) \, r\left(\sigma\right) \, d\tau \, d\sigma\right] \tag{3.4}$$

which is the probability of observing a particular path $r\left(\tau\right)$ with the boundary values $r\left(0\right) = r_i$ and $r\left(\beta\right) = r_f$, where $A\left(\tau, \xi\right)$ is defined as

$$\int d\xi \; A\left(\tau, \xi\right) \; A^{-1}\left(\xi, \sigma\right) = \delta\left(\tau, \sigma\right) \tag{3.5}$$

$$A^{-1}(\tau,\sigma) = \langle\, r(\tau)\ r(\sigma)\rangle \tag{3.6}$$

That A^{-1} is defined as correlation function between environmental coordinates at different times (or memory effect) labeled by τ and σ which the brackets refer to an average over noise. From fluctuation-dissipation theorem it can be used the response of a system to an external disturbance (or relaxation function such as Eq. (3.2) a stretched exponential) equals to the correlation function that describes the spontaneous thermal fluctuations of an environmental variable $r(\tau)$.

The physical meaning is that survival probability equals the contribution from all the possible paths connecting the two points and weighted by the decay rate along each path. It can not be solved exactly thus the approximation has to be used. In their approaches, they choose a class of paths that gives the dominant contribution. They seek paths such that the path probability is a local maximum (or extremum) and maximize the exponent of the path probability with respect to by using the basic rule for variational differentiation. The boundary conditions, serve as constraints and therefore is equal to the use of the Lagrange multiplier.

In general, the correlation function can have many forms of time dependence. In complex systems such as proteins, glasses or complex structured fluids, non-exponential decay of the correlation function, which can be fitted to a stretched exponential law as Eq. (3.2), are often encountered, taking the path probability given in Eq. (3.3) to be valid when there is no reaction. The reaction, by recognizing that the survival probability decays along any given trajectory by the first-order kinetic equation, can also be taken into account. For simplicity, the back-reaction can be ignored:

$$\frac{dP}{d\tau} = -\ K(r)\ P \tag{3.7}$$

where, $K(r)$ is a decay rate (or the rate coefficient, also affinity constant) which depends on a control parameter (or the radius of the bottleneck) r . The rate can be used and estimated by the instantaneous transition state theory following Zwanzig (1992). The equilibrium flux through the bottleneck and is proportional to the geometrical area of the bottleneck r^2 with α constant ($K(r) \sim \alpha\, r^2$). Using Eqs. (3.3) and (3.4), they obtained a path integral expression for the calculation of the survival probability averaged over Gaussian noise as

$$\langle P(r_f, r_i; \beta) \rangle = \frac{\int D[\, r(\tau)] \exp\left[- \int_0^\beta K(r)\ d\tau - \frac{1}{2} \int_0^\beta \int_0^\beta\ r(\tau)\ A(\tau,\sigma)\ r(\sigma)\ d\tau\ d\sigma \right]}{\int D[\, r(\tau)] \exp\left[-\frac{1}{2} \int_0^\beta \int_0^\beta\ r(\tau)\ A(\tau,\sigma)\ r(\sigma)\ d\tau\ d\sigma \right]} \tag{3.8}$$

When the surviving population seeks out path $r(\tau)$, it is because the path probability is such a local maximum. When the variation of the exponential of the path probability with respect to $r(\tau)$ is undertaken, a nonlinear integral equation is obtained

$$\frac{dK}{dr} = - \int_0^\beta\ r(\sigma)\ A(\tau,\sigma)\ d\sigma \tag{3.9}$$

It can be written in the inverse form as

$$r(\tau) = - \int_0^\beta\ \frac{dK(r)}{dr}\ A^{-1}(\tau - \sigma)\ d\sigma \tag{3.10}$$

where, τ and σ are within the range of 0 and β. That is the variation equation for the general Gaussian fluctuating environment. The survival probability can easily be calculated by substituting the dominant path solution into the exponential of the path integral formulation. The rate coefficient is weakly dependent on the environment variable, the dominant survival path following the ordinary relaxation to equilibrium as in the Onsager and Machulp (1953) regression hypothesis. When the rate coefficient strongly depends on the environmental variable, the

dominant survival path exhibits behavior very distinct from ordinary relaxation, including reflection off rapid variations in the rate constant, as well as refraction, giving paths very different from equilibrium relaxation.

3.6 Caldeira and Leggett Model

In this model the reaction coordinate is coupled to the environment as a set of an infinite number of oscillators discussed by Caldeira and Leggett (1983b) and Poulter and Sa-yakanit (1992). Therefore, the Lagrangian model is

$$L\left(r,\dot{r},x_i,\dot{x}_i;t\right)=\frac{m}{2}\,\dot{r}^2\left(t\right)-K\;\left(r\left(t\right)\right)+\frac{1}{2}\sum_i M_i\;\left[\dot{x}_i^2\left(t\right)-\frac{\kappa_i}{M_i}\;\left(\,r\left(t\right)-x_i\left(t\right)\right)^2\right] \tag{3.11}$$

where r is the reaction coordinate with mass m moving in a potential $K\left(r\right)$ and x_i, M_i , κ_i are the coordinates, fictitious mass and coupling constant of the environment oscillators, respectively. This Eq. (3.11) change t time to $-i\tau$ imaginary time for using in statistic problem. By eliminating the environmental degrees of freedom, an effective euclidean action is obtained:

$$S=\int_0^\beta d\tau\;\left[\frac{m}{2}\,\dot{r}^2\left(\tau\right)+K\left(r\right)\right]-\frac{1}{2}\int_0^\beta\int_0^\beta d\tau\;d\sigma\;g\left(\tau-\sigma\right)\;\;\left|\,r\left(\tau\right)-r\left(\sigma\right)\right|^2 \tag{3.12}$$

Here $g.(\tau-\sigma)$ is the Green function as

$$g\left(\tau-\sigma\right)=\frac{1}{2\pi}\int_0^\infty d\omega\;J\left(\omega\right)\;\frac{\cosh\left[\omega\;\left(\;\left|\,\tau-\sigma\right|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]} \tag{3.13}$$

and, $J\left(\omega\right)$ denotes the spectral function

$$J\left(\omega\right)=\frac{\pi}{2}\;\sum_i\;\kappa_i\;\omega_i\;\delta\left(\omega-\omega_i\right) \tag{3.14}$$

with

$$\omega_i=\sqrt{\frac{\kappa_i}{M_i}} \tag{3.15}$$

This spectral function represents the heat bath of the system. In general, this spectral function is very complicated. Physically, this spectral function must be terminated by a certain cut-off frequency such as the Debye cut-off in the lattice dynamic problem and the electron-plasmon interaction employed in the electron gas problem. In the dissipation system, Leggett, Chakravarty, Dorsey, Fisher, Garg, and Zwerger (1987), there is a well known empirical expression

$$J(\omega) = \eta\, \omega^{s}\, \mathrm{e}^{-\omega/\omega_c} \tag{3.16}$$

where, η is the friction constant, s is the power of the ω , and ω_c is the oscillator cut-off frequency. Further, it is shown that if $s = 1$ this expression can lead to ohmic friction which is the dissipative transport equation. The case $0 < s < 1$ and $s > 1$ are known as sub-ohmic and super-ohmic, respectively. It is also assumed that there exists a single oscillator that dominates the spectral function and is identified as ω and κ which M equal to the fictitious mass. The above reaction coordinate cannot be solved exactly and therefore we need to simplify the problem.

3.7 Path Integral method: One Oscillator Model

In this model we further simply the problem and instead of using the simplied expression we consider Eq.(3.14) only one frequency $\kappa_i = \kappa$ i.e..

$$J(\omega) = \frac{\pi}{2}\, \kappa\, \omega_i\, \delta(\omega - \omega_i) \tag{3.17}$$

The physical meaning of this approximation is equivalent to a particle coupled to a fictitiuos mass as discussed in Sa-yakanit (1974) and was extended

to more general form by of Castrigiano and Kokiantonis (1983) as

$$S_0(\kappa,\omega) = \int_0^\beta d\tau \left[\frac{m}{2}\dot{r}^2(\tau) + K(r)\right] - \frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\, d\sigma \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]} |r(\tau)-r(\sigma)|^2 \tag{3.18}$$

Now consider Eq.(3.11),(3.13) and (3.17) when the rate K of the system is constant. Then the action is reduced to

$$S_0(\kappa,\omega) = \int_0^\beta d\tau \frac{m}{2}\dot{r}^2(\tau) - \frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\, d\sigma \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]} |r(\tau)-r(\sigma)|^2 \tag{3.19}$$

where κ and ω are two parameters. This action is similar to the polaron trial action by Sa-yakanit (1979). It can be written as the form

$$S_0(\kappa,\omega) = \int_0^\beta d\tau \frac{m}{2}\left\{\dot{r}^2(\tau) - \frac{\kappa}{m}r^2(\tau)\right\} + \frac{\kappa\,\omega}{4}\int_0^\beta\int_0^\beta d\tau\, d\sigma \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]} r(\tau)\, r(\sigma) \tag{3.20}$$

Since the action is quadratic, it can be calculated exactly. This model has been used by many authors such as Wang and Wolynes (1993,1994) for calculation in myoglobin or the transport through a bottleneck. When consider with rate in bottleneck problem

$$K(r) = \frac{m}{2}\alpha\, r^2 \tag{3.21}$$

substitute to Eq. (3.18). We obtainand

$$S(\alpha,\ \kappa,\ \omega;\ f(\tau)) = \int_0^\beta d\tau \left\{\frac{m}{2}\left[\dot{r}^2(\tau) - \left\{\alpha - \frac{\kappa}{m}\right\} r^2(\tau)\right] + f(\tau)\ r(\tau)\right\} - \frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\, d\sigma \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]} |r(\tau)-\ r(\sigma)|^2 \tag{3.22}$$

and will consider in next section.

3.8 Methods of Caculation

In order to calculate the survival path and correlation function, a generating function by introducing the driving force $f(\tau)$ must be constructed. Then the general action adapting from Castrigiano and Kokiantonis (1983) is:

$$S(\alpha,\ \kappa,\ \omega;\ f(\tau)) = \int_0^\beta d\tau \left\{ \frac{m}{2}\left[\dot{r}^2(\tau) - \left\{\alpha - \frac{\kappa}{m}\right\} r^2(\tau)\right] + f(\tau)\ r(\tau)\right\} \quad (3.23)$$
$$-\frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\ \tau-\sigma| - \beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ |\ r(\tau) - r(\sigma)|^2$$

or in the form

$$S(\alpha,\ \kappa,\ \omega;\ f(\tau)) = \int_0^\beta d\tau \left\{ \frac{m}{2}\left[\ \dot{r}^2(\tau) - \alpha\, r^2(\tau)\right] + f(\tau)\ r(\tau)\ \right\} \quad (3.24)$$
$$+\frac{\kappa\,\omega}{4}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\ \tau-\sigma| - \beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ r(\tau)\ r(\sigma)$$

The result in classical action and classical path are

$$S_{CL}(\alpha,\ \kappa,\ \omega;\ f(\tau)) = \frac{m}{2\omega}\ddot{\Delta}(0)\ (r_f - r_i)^2 + \frac{m\,\omega}{8\,\Delta(0)}\ (r_f + r_i)^2$$
$$+\int_0^\beta d\tau\ f(\tau)\ \left[\frac{\dot{\Delta}(\tau)}{\omega}(r_f - r_i) + \frac{\Delta(\tau)}{2\,\Delta(0)}\ (r_f + r_i)\right]$$
$$+\frac{1}{2m\omega}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ f(\tau)\ f(\sigma)\ \left[\frac{\Delta(\tau)\ \Delta(\sigma)}{\Delta(0)} - \Delta(|\tau-\sigma|)\right] \quad (3.25)$$

and

$$r(\tau) = \frac{\dot{\Delta}(\tau)}{\omega}(r_f - r_i) + \frac{\Delta(\tau)}{2\,\Delta(0)}\ (r_f + r_i)$$
$$+\frac{1}{m\omega}\int_0^\beta d\sigma\ f(\sigma)\ \left[\frac{\Delta(\sigma)\ \Delta(\tau)}{\Delta(0)} - \Delta(|\tau-\sigma|)\right] \quad (3.26)$$

where

$$\Delta(\tau) = \frac{\omega}{2}\ \left(\frac{\Omega^2-\omega^2}{\Omega^2-\Psi^2}\right)\ \frac{\cosh\left[\Omega\ (\tau-\beta/2)\right]}{\Omega\ \sinh\left[\Omega\beta/2\right]} + \frac{\omega}{2}\ \left(\frac{\Psi^2-\omega^2}{\Psi^2-\Omega^2}\right)\ \frac{\cosh\left[\Psi\ (\tau-\beta/2)\right]}{\Psi\ \sinh\left[\Psi\beta/2\right]} \quad (3.27)$$

with

$$\Omega^2 = \frac{1}{2}\left(\omega^2 - \alpha\right) + \frac{1}{2}\sqrt{\left(\omega^2 - \alpha\right)^2 - 4\omega^2\left(\frac{\kappa}{m} - \alpha\right)} \tag{3.28}$$

and,

$$\Psi^2 = \frac{1}{2}\left(\omega^2 - \alpha\right) - \frac{1}{2}\sqrt{\left(\omega^2 - \alpha\right)^2 - 4\omega^2\left(\frac{\kappa}{m} - \alpha\right)} \tag{3.29}$$

From the classical action Eq.(3.25), we can find the end point relation by differentiating S_{CL} with respected to r_f equal to 0, so

$$r_f = \left[\frac{m\omega}{4\,\Delta\left(0\right)} - \frac{m}{\omega}\,\ddot{\Delta}\left(0\right)\right] / \left[\frac{m\omega}{4\,\Delta\left(0\right)} + \frac{m}{\omega}\,\ddot{\Delta}\left(0\right)\right]\; r_i \tag{3.30}$$

We put it into the classical path to reduce coordinate to one point. Furthermore, the prefactor is given by

$$\Phi\left(\beta\right) = \left(\frac{m\omega}{8\pi\,\Delta\left(0\right)}\right)^{1/2} \frac{\sinh\left[\omega\beta/2\right]}{\sinh\left[\Omega\beta/2\right]\;\sinh\left[\Psi\beta/2\right]} \tag{3.31}$$

and the propagator becomes,

$$P\left(r_f, r_i;\;\beta\right) = \Phi\left(\beta\right)\;\exp\left[-S_{CL}\left(\alpha,\;\kappa,\;\omega\right)\right] \tag{3.32}$$

To obtain the survival probability $P\left(\beta\right)$ by tracing as

$$\begin{aligned} P\left(\beta\right) &= \mathrm{Tr}\left[P\left(r_f, r_i; \beta\right)\right] \\ &= \frac{1}{2}\frac{\sinh\left[\omega\beta/2\right]}{\sinh\left[\Omega\beta/2\right]\;\sinh\left[\Psi\beta/2\right]} \end{aligned} \tag{3.33}$$

It will give us the same physical meaning as the rate coefficient for approximated large time $\beta \to \infty$. That is the survival probability can be related with rate exponential depending on time. Since $P \sim \exp[-K_{eff}\;\beta]$, we can trace the propagator for eliminating space coordinates. So the effective rate can be obtained as

$$K_{eff} = -\frac{1}{\beta}\,\ln\left[\;\mathrm{Tr}\left\{\;P\left(r_f, r_i; \beta\right)\right\}\right] \tag{3.34}$$

From Eq. (3.25), the classical action, let $f(\tau) = 0$, then we consider the second term. It presents the non-translation invariant and will be respondsible to the decay of the equilibrium survival path. However, we know that the generating function allow us to carry out the calculations for physical quantities including the correlation function. From the generating function Eq. (3.25), we differentiate twice with respecting $f(\tau)$. We obtain the correlation function that

$$\langle r(\tau)\ r(\sigma)\rangle - \langle r(\tau)\rangle\ \langle r(\sigma)\rangle = \frac{1}{2\,m\,\omega}\left(\Delta(|\tau-\sigma|) - \frac{\Delta(\tau)\ \Delta(\sigma)}{\Delta(0)}\right) \quad (3.35)$$

When we adjust the parameters, we have found many thoughts and ideas in this mathematical technique. We can generate several cases by changing range of parameters as following

3.9 Limiting Cases

This section discusses the survival path using the results $\kappa/m \geq \alpha$ and showing by further constraint the parameters. Three limiting cases are considered.

3.9.1 $K(r)$ is a constant and symmetry in nonlocal time

From Eq. (3.23), we can be adjusted $\alpha = \kappa/m$ and $f(\tau) = 0$. We obtain

$$\begin{aligned} S_0(\kappa,\omega) &= \int_0^\beta d\tau\ \frac{m}{2}\,\dot{r}^2(\tau) \\ &\quad -\frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ |r(\tau)-r(\sigma)|^2 \end{aligned} \quad (3.36)$$

or in the form

$$\begin{aligned} S_0(\kappa,\omega) &= \int_0^\beta d\tau\ \frac{m}{2}\left\{\dot{r}^2(\tau)\ -\frac{\kappa}{m}\,r^2(\tau)\right\} \\ &\quad +\frac{\kappa\,\omega}{4}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ r(\tau)\ r(\sigma) \end{aligned} \quad (3.37)$$

These case corresponds

$$\Omega = \sqrt{\omega^2 - \frac{\kappa}{m}} \tag{3.38}$$

and

$$\Psi = 0 \tag{3.39}$$

when $\Delta(\tau)$ becomes to infinity. The classical action is obtained

$$S_{CL} = \frac{m}{2}\left[-\frac{\kappa}{2\,m\,\Omega}\coth\left[\Omega\beta/2\right] + \frac{\omega^2}{\Omega^2\beta}\right](r_f - r_i)^2 \tag{3.40}$$

and the classical path can be obtained

$$r(\tau) = \frac{\omega^2}{\Omega^2}\left(-\frac{1}{2} + \frac{\tau}{\beta} - \frac{\kappa}{m\,\omega^2}\frac{\sinh\left[\Omega\left(\tau - \beta/2\right)\right]}{2\sinh\left[\Omega\beta/2\right]}\right)(r_f - r_i) + \frac{1}{2}(r_f + r_i) \tag{3.41}$$

So from Eq. (3.30), the end points relate as

$$r_f = r_i \tag{3.42}$$

Then the survival probability becomes

$$P(r_f, r_i;\ \beta) = \left(\frac{m}{2\pi\beta}\right)^{1/2}\left(\frac{\Omega\sinh\left[\omega\beta/2\right]}{\omega\sinh\left[\Omega\beta/2\right]}\right)\exp\left[-S_{CL}\right] \tag{3.43}$$

Trace it, so

$$P(\beta) = \left(\frac{m}{2\pi\beta}\right)^{1/2}\left(\frac{\Omega\sinh\left[\omega\beta/2\right]}{\omega\sinh\left[\Omega\beta/2\right]}\right) \tag{3.44}$$

Using Eq. (3.34) to find the effective rate, for large thermal time $\beta \to \infty$, the effective rate is obtained

$$\begin{aligned} K_{eff} &= \frac{1}{2}(\Omega - \omega) \\ &= \frac{\omega}{2}\left[\sqrt{1 - \frac{\kappa}{m\,\omega^2}} - 1\right] \end{aligned} \tag{3.45}$$

The correlation function differenced from Castrigiano and Kokiantonis (1983) in the case $\tau > \sigma$ is obtained

$$\langle r(\tau)\ r(\sigma)\rangle - \langle r(\tau)\ \rangle\ \langle\ r(\sigma)\rangle = \frac{\kappa}{m^2\,\Omega^3\sinh\left[\Omega\beta/2\right]}\sinh\left[\Omega\,\sigma/2\right]\ \sinh\left[\Omega\left(2\tau - \sigma - \beta\right)/2\right]$$

$$+\frac{1}{2}\frac{\omega^2}{m\,\Omega^2}\left(\frac{\tau\,\sigma}{\beta}-\frac{\sigma^2}{2\beta}-\frac{\sigma}{2}\right) \tag{3.46}$$

For large thermal time $\beta \to \infty$, the correlation function for case $\tau > \sigma$ is

$$\langle r(\tau)\ r(\sigma)\rangle - \langle r(\tau)\ \rangle\ \langle\ r(\sigma)\rangle = -\frac{\omega^2}{4\ m\Omega^2}\sigma \tag{3.47}$$

This correlation function approaches to a constant.

3.9.2 $K(r)$ is a constant in equilibrium path and broken symmetry in nonlocal time

From Eq. (3.23), this case take $f(\tau) = 0$ and $\alpha = 0$. That is

$$\begin{aligned} S(0,\ \kappa,\ \omega;0) \ &= \ \int_0^\beta d\tau\ \left\{\frac{m}{2}\left[\dot{r}^2(\tau)+\frac{\kappa}{m}\,r^2(\tau)\right]+f(\tau)\ r(\tau)\right\} \\ &-\frac{\kappa\,\omega}{8}\int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\ \tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ |\ r(\tau)-\ r(\sigma)|^2 \end{aligned} \tag{3.48}$$

or

$$S(0,\ \kappa,\ \omega;\ 0) = \int_0^\beta d\tau\ \frac{m}{2}\,\dot{r}^2(\tau)+\frac{\kappa\,\omega}{4}\ \int_0^\beta\int_0^\beta d\tau\ d\sigma\ \frac{\cosh\left[\omega\left(|\ \tau-\sigma|-\beta/2\right)\right]}{\sinh\left[\omega\beta/2\right]}\ r(\tau)\ r(\sigma) \tag{3.49}$$

It is noted that the translation symmetry of the system is broken by $(\kappa/m)\ r^2$.

This case corresponds

$$\Omega^2 = \ \frac{1}{2}\ \omega^2\ (1+\delta) \tag{3.50}$$

and

$$\Psi^2 = \frac{1}{2}\ \omega^2\ (1-\delta) \tag{3.51}$$

where

$$\delta = \sqrt{1-4\frac{\kappa}{m\omega^2}} \tag{3.52}$$

so that

$$\Delta(\tau) = \frac{\omega}{2}\frac{1}{2}\left[\left(1-\frac{1}{\delta}\right)\frac{\cosh\left[\Omega\left(\tau-\beta/2\right)\right]}{\Omega\,\sinh\left[\Omega\beta/2\right]}+\left(1+\frac{1}{\delta}\right)\frac{\cosh\left[\Psi\left(\tau-\beta/2\right)\right]}{\Psi\,\sinh\left[\Psi\beta/2\right]}\right] \tag{3.53}$$

and we can find $\dot{\Delta}(\tau)$ and $\ddot{\Delta}(\tau)$ by differentiating with time. The equilibrium classical path and classical action can be obtained

$$S_{CL}(0,\ \kappa,\ \omega;0) = \frac{m}{2\omega}\ \ddot{\Delta}(0)\ \ (r_f - r_i)^2 + \frac{m\,\omega}{8\ \Delta(0)}\ \ (r_f + r_i)^2 \tag{3.54}$$

and

$$r(\tau) = \frac{\dot{\Delta}(\tau)}{\omega}(r_f - r_i) + \frac{\Delta(\tau)}{2\ \Delta(0)}\ \ (r_f + r_i) \tag{3.55}$$

The end point relation can be found from Eq.(3.30). The survival probability becomes

$$P(r_f, r_i;\ \beta) = \Phi(\beta)\ \exp\left[-S_{CL}(0,\ \kappa,\ \omega;0)\right] \tag{3.56}$$

Considering the survival probability that can consider without coordinates only β by tracing

$$P(\beta) = \frac{1}{2}\ \frac{\sinh\left[\omega\beta/2\right]}{\sinh\left[\Omega\beta/2\right]\ \sinh\left[\Psi\beta/2\right]} \tag{3.57}$$

and put in Eq. (3.34) to find the effective rate. For large thermal time $\beta \to \infty$, the effective rate is obtained

$$\begin{aligned} K_{eff} &= -\frac{1}{2}(\omega - \Omega - \Psi) \\ &\simeq \frac{\omega}{2}\left[\sqrt{2}\sqrt{1 - \frac{4\kappa}{m\omega^2}} - 1\right] \end{aligned} \tag{3.58}$$

The correlation function, in this case, is similar form as defining in Eq. (3.35).

3.9.3 Case $\Omega = \Psi$

This allow for a reduce two parameters to a single one, $\Omega = \Psi$, with the condition

$$\left(\omega^2 - \alpha\right)^2 - 4\omega^2\ \left(\kappa/m - \alpha\right) = 0 \tag{3.59}$$

implying that $\kappa/m > \alpha$. From Eq. (3.23), also set $f(\tau) = 0$ and then Ω is simpliflied to

$$\begin{aligned} \Omega &= \sqrt{\frac{1}{2}\left(\omega^2 - \alpha\right)} \\ &= \sqrt{\omega\sqrt{\kappa/m} - \alpha} \end{aligned} \tag{3.60}$$

so that

$$\Delta(\tau) = \frac{\omega}{2}\frac{\cosh\left[\Omega\left(\tau - \beta/2\right)\right]}{\Omega\sinh\left[\Omega\beta/2\right]} \tag{3.61}$$

The classical action and classical path can be obtained

$$S_{CL}(\alpha,\ \kappa) = \frac{m\,\Omega}{4}\left[\coth\left[\Omega\beta/2\right](r_f - r_i)^2 + \tanh\left[\Omega\beta/2\right]\ (r_f + r_i)^2\right] \tag{3.62}$$

and

$$r(\tau) = \frac{1}{\sinh\left[\Omega\beta\right]}\left[r_f\sinh\left[\Omega\tau\right] + r_i\sinh\left[\Omega\left(\beta - \tau\right)\right]\right] \tag{3.63}$$

The end point relation can also be obtained

$$r_f = \frac{1}{\cosh\left[\Omega\beta\right]}\,r_i \tag{3.64}$$

it can be written the classical path in term of r_i as

$$r(\tau) = r_i\frac{\cosh\left[\Omega\left(\beta - \tau\right)\right]}{\cosh\left[\Omega\beta\right]} \tag{3.65}$$

Then the survival probability becomes

$$P(r_f, r_i;\ \beta) = \left(\frac{m\Omega}{2\pi}\right)^{1/2}\left(\frac{1}{\sinh\left[\Omega\beta\right]}\right)^{1/2}\frac{\sinh\left[\omega\beta/2\right]}{\sinh\left[\Omega\beta/2\right]}\exp\left[-S_{CL}(\alpha,\ \kappa)\right] \tag{3.66}$$

and traces

$$P(\beta) = \frac{1}{2}\frac{\sinh\left[\omega\beta/2\right]}{\sinh^2\left[\Omega\beta/2\right]} \tag{3.67}$$

To find the effective rate using Eq. (3.34) and then, for large thermal time $\beta \to \infty$, the effective rate is obtained

$$\begin{aligned} K_{eff} &\simeq \Omega - \frac{\omega}{2} \\ &= \frac{\omega}{2}\left[\sqrt{2}\sqrt{1-\frac{\alpha}{\omega^2}}-1\right] \end{aligned} \tag{3.68}$$

The correlation function is

$$\langle r(\tau)\ r(\sigma)\rangle - \langle r(\tau)\ \rangle\ \langle\ r(\sigma)\rangle = \frac{1}{2\ m\ \Omega}\ \frac{1}{\sinh[\Omega\beta]}\ \sinh[\Omega(\beta-\tau)]\ \sinh[\Omega\sigma] \tag{3.69}$$

For large thermal time $\beta \to \infty$, the correlation function is

$$\langle r(\tau)\ r(\sigma)\rangle - \langle r(\tau)\ \rangle\ \langle\ r(\sigma)\rangle = \frac{1}{4\ m\ \Omega}\ \exp[-\Omega(\tau-\sigma)] \tag{3.70}$$

3.10 Survival Paths

In this section, the survival path is discussed. The survival classical path, see in Fig. (3.2) can be considered, obtained from Eq. (3.26) by setting $f(\tau) = 0$ and substitute the end point relation from Eq. (3.30) to reduce in one coordinate and set the one coordinate to 1 (r_i or $r_f = 1$). We obtain

$$r(\tau) = r_i\ \left\{\frac{\dot{\Delta}(\tau)}{\omega}\left(\frac{\frac{m\omega}{4\,\Delta(0)}-\frac{m}{\omega}\ddot{\Delta}(0)}{\frac{m\omega}{4\,\Delta(0)}+\frac{m}{\omega}\ddot{\Delta}(0)}-1\right)+\frac{\Delta(\tau)}{2\,\Delta(0)}\ \left(\frac{\frac{m\omega}{4\,\Delta(0)}-\frac{m}{\omega}\ddot{\Delta}(0)}{\frac{m\omega}{4\,\Delta(0)}+\frac{m}{\omega}\ddot{\Delta}(0)}+1\right)\right\} \tag{3.71}$$

to plot graph . The result are given for $\alpha = 0$, the equilibrium path and for $\alpha < \kappa/m$, all paths decay exponentially see in Fig. (3.2). However, for $\alpha > \kappa/m$, it is the unstable path not converse to the limit because it oscillates.

The survival probability can be obtain from Eq. (3.33), by setting $\alpha = 0.5$, and the result is present in Fig. (3.3).

The rate coefficient can be also obtained from Eq. (3.34) see in Fig. (3.4).

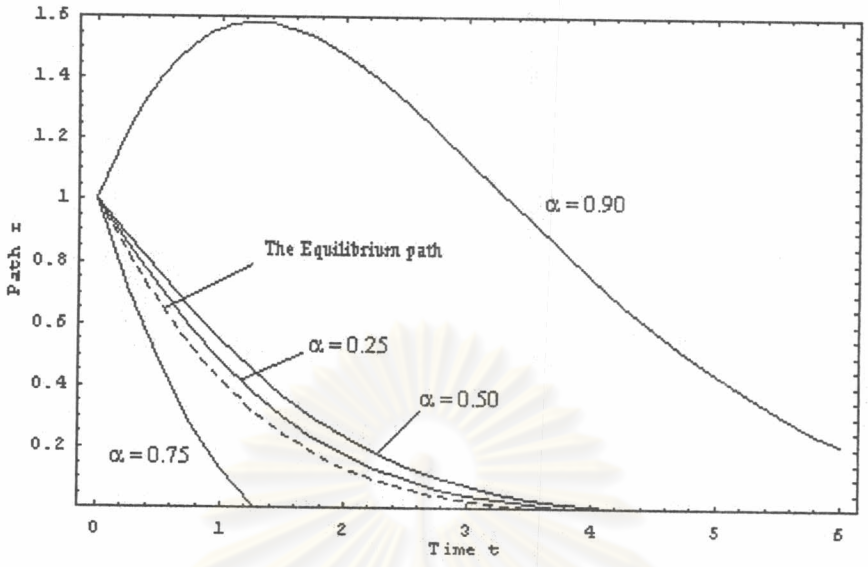

Figure 3.2: This show the equilibrium path (dashed line) which set $\alpha = 0$ and the decay path(all solid line) which set $\alpha < \kappa/m$ for any α, with $m = \kappa = \omega = 1$.

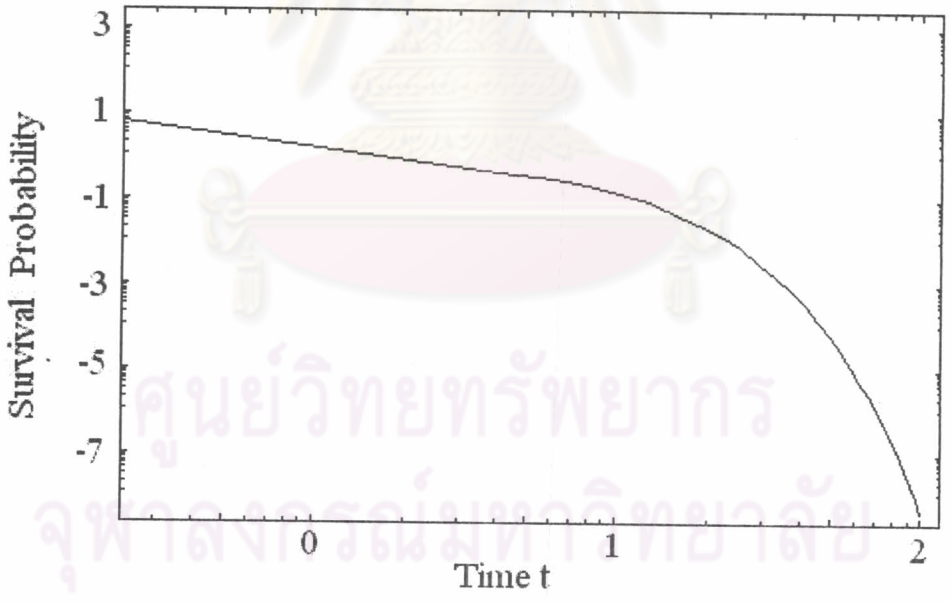

Figure 3.3: Log-log plot of the survival probability setting $m = \omega = \kappa = 1$ and $\alpha = 0.5$

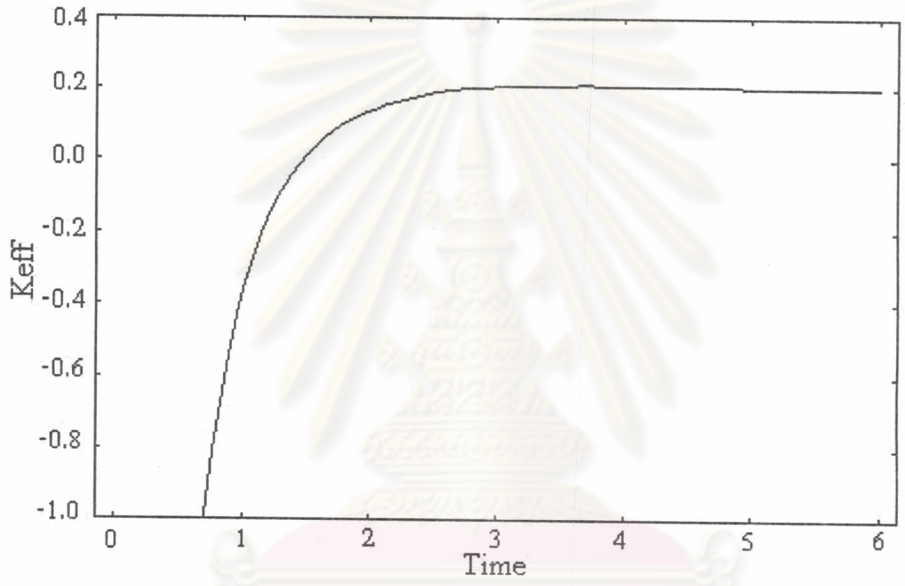

Figure 3.4: The effective rate coefficient setting $m = \omega = \kappa = 1$ and $\alpha = 0.5$