Chapter 4
Discussion and Conclusion

In chapter 2, ligand-gated ion channel, we discuss as folllow. The developed model, Matsson (1996, 2001), Grzegorczyk, Jacobsson, Jardemark and Matsson (1998), and also Matsson, Sa-yakanit and Boribarn (2003) are applied to derive whole cell currents in ligand-gated ion channel systems at nonstationary boundary conditions. Contrary to the Hill, Langmuir and Ising type models, this lyotropic model yields an EC_{50} expressed in terms of the reactant concentrations. Interestingly, in the lyotropic model there is no direct link between order of cooperativity and the Hill coefficient. Despite inclusion of the long range, cooperative interaction to all orders in the derived total current has a slope $n_H = 1$.

In order to demonstrate that the previously derived, Matsson (2001) provides a possible solution to these problems, and also admits reasonable estimates of parameters such as the EC_{50} value. We use data recorded from Jardemark, Nystrom, Rydenhag, Hamberger and Jacobson (1995) that whole cell currents mediated by an AMPA receptor system expressed on *Xenopus* oocytes injected with total RNA from the human epileptic temporal lobe. The experimental data obtained by exposure to various kainate concentrations were in that case fitted by the logistic equation, essentially the Hill equation with K replaced by the assessed EC_{50}^n, and with an average Hill coefficient of $n_H = 0.93 \pm 0.04$ exhibiting little or no short range cooperativity in the sense of Hill. The assessed value $EC_{50} = 125 \pm 11\ \mu M$ $(N = 5)$ is in the range reported previously for oocytes injected with total RNA from rat brain. However, this EC_{50} value is about 10 times larger than that of the Hill equation with a separately assessed affinity of

$K = 9\ \mu M$ and, as stated by Barlow and Blake (1989), the logistic equation lacks an explanation from the molecular interaction level.

The present model derived from the non-stationary molecular interaction,and provides a solution to these problems and does not enforce a half-maximal response directly related to the affinity. Rather, it yields the microscopic relation, which admits realistic values for all involved parameters.

Apart from solving the problems with a scaling parameter related to the equilibrium constant, and obtaining the nonlinear form which relates the long range cooperativity to the Hill coefficient $n_H = 1$, the derived lyotropic, nonstationary response provides a molecular physics explanation to the actual physiological parameters. Since the $K = 9\ \mu M$ is small compared to the saturating kainate concentration of $\rho_0 = 3.00\ \mu M$, the assessed EC_{50} value should agree almost exactly with the derived EC_{50}, because r_K and ρ_K in could then be safely replaced by the corresponding start concentrations. With a stationarised spare receptor density at $r = 0.03\ r_0$, a Hill factor $n_H = 1$, and an assumed efficacy factor $E = 0.785$, which yields an $EC_{50} = 115 \pm 7\ \mu M$, in Fig. (2.2), the current derived from the model fits recorded data excellently.

We concluded that in ligand-receptor systems with $n_H = 1$, the proposed nonstationary, lyotropic response theory satisfies observed experimental data significantly better than the stationary type models. It also provides an understanding of the nonequilibrium dynamics and some biological functions of chemically open cells. Needless to say, the present study does not provide the ultimate answers. The functional dependence of the current on receptor synthesis, membrane geometry, and cooperativity effects with $n_H \neq 1$ are some of the questions that have not yet been considered. However, to a leading order ap-

proximation the model proposed complies with prevailing physical conditions of living cells.

Celentano and Wong (1994) demonstrated the model obtained is self-dual as Onsager (1944) in a lyotropic sense. They implied that it is consistent with a lyotropic type duality transformation that relates the dynamics at low reactant concentrations to that at high reactant concentrations. In this sense the suggested lyotropic model provides a self-consistent description of concentration dependent dynamics and biological functions of living cells, for instance works of Grzegorczyk, Jacobsson, Jardemark and Matsson(1998) in firing in neurons, Matsson (2001) in DNA replication and cell cycle progression.

Questions such as those of scaling, slope of response, long and short range cooperativity, functional dependence of EC_{50} on the reactant concentrations, spare receptors, relative potency of various humoral factors and drugs, and pharmacological thresholds, are of general interest in science and pharmaceutical industry. Further studies in these physical directions are indeed required. For instance, to study the combined effects of long and short range cooperativity in a model like this, but with $n_H \neq 1$, would require a nonstationary, lyotropic generalization of the one-dimensional Ising type model.

It is hoped that the model applied in this work could contribute to a better understanding of the function of neurons, DNA replication, cell cycle progression, division of cells and also applied to neural networks how a brain can think and remember by using two-dimensional Ising model.

In chapter 3, ligand-binding, Sa-yakanit and Boribarn (2001) modified the Feynman path integral method applied to the rate reaction coupled to a complex environment, the model consisting of the reaction coefficient coupled to

the microscopic heat bath with an infinite set of oscillators. This heat bath is assumed to behave as in Eq. (3.16) and consists of two adjustable parameters s and ω_c.

This empirical spectral function suggests that there exists a single dominant frequency occuring at $\omega \simeq s\ \omega_c$. This can be seen by maximizing the spectral function Eq. (3.16). However with this single oscillator there are still two parameters in the model: κ representing the amplitude of fluctuation and ω representing the frequency of the oscillator. How these two parameters allow a discussion of a wide range of physical quantities is shown.

Wang and Wolynes(1993) introduced the bottleneck problem corresponding to add quadratic potential with α representing the amplitude of the bottleneck. Because the bottleneck models are quadratic all path integrals can be performed exactly. The generating function associated with the effective action is obtained and used to calculate the survival path given in Eq. (3.24), the survival probability in Eq. (3.31), with the effective rate and the correlation function given in Eqs. (3.32) and (3.33), respectively.

This shows that for $\alpha = 0$ the equilibrium path is obtained. When $\alpha > \kappa/m$ the survival path is unstable and starts to oscillate instead of decaying exponentially. For $\alpha < \kappa/m$ all survival paths are stable and decay exponentially. The effective rate is also derived from the pre-factor of the propagator limit of large β. Finally it is shown that for the survival probability can be obtained from the pre-factor. In order to compare the results with those of Wang and Wolynes, several limiting cases were considered. Sa-yakanit and Boribarn (2001) showed that for the special case of $\Omega = \Psi$ exactly the same equilibrium result as Wang and Wolynes was obtained.

Finally, these method developed can be generalized to include the full spectral function with a complete and complex environment as well as a more complicated coefficient reactions such as Gaussian or exponential.