Abstract

With an increased popularity for systems-based approaches in biology, a wide spectrum of techniques has been applied to the simulation and analysis of biochemical systems which involves uncertainty and stochasticity. It is particularly concerned with modelling and analysis of metabolic pathways, regulatory and signal transduction networks for understanding intra-cellular pathway behaviour. Typically, parameter estimation in ordinary differential equations (ODEs) models is used for this purpose when there is large number of molecules involved in the reaction system. However this approach is correct when the system is large enough to be deterministic in nature. But there are uncertainty involved in the system and the processes are stochastic in nature due to smaller population molecules participating in the pathway reactions.

In this thesis the common theme is the study of uncertainties in the chemical kinetics of biochemical reaction systems associated with various intra-cellular pathways and channels. The study is at the meso-scale of the system, i.e., we study systems that do not have too few molecules disallowing any higher scale system level approximation nor too many where a non-stochastic (mesoscale) system approximation will be valid.

In our first study we estimate the parameters in the mitogen activated protein kinase (MAPK) signal transduction pathway involved in the departure from the normal Epithelial Growth Factor (EGF) dose-dependency in prostate cancer cells. A model-based pathway analysis is performed. The pathway is mathematically modelled with 28 rate equations yielding those many ordinary differential equations (ODE) with kinetic rate constants that have been reported to take random values in the existing literature. This has led to us treating the ODE model of the pathways kinetics as a random differential
equations (RDE) system in which the parameters are random variables. The most likely set of values of the kinetic rate constants obtained from fitting the RDE model into the experimental data is then used in a direct transcription based dynamic optimization method for computing the changes needed in these kinetic rate constant values for the restoration of the normal EGF dose response. It identifies the parameters, i.e., the kinetic rate constants in the RDE model, that are the most sensitive to the change in the EGF dose response behaviour in the PC3 prostate cancer cells.

Biochemical pathways involving chemical kinetics equations in terms of low concentrations of the model variables can be represented as chemical Langevin equations (CLE) as there is stochasticity involved in the processes. Most CLE systems come with the implicit constraint that the concentration state cannot be negative at any time over the sample path. Due to the inherent stiffness (especially in diffusion coefficient) of the CLE system, it has been difficult for numerical schemes to meet this positivity constraint during numerical simulations. Most available methods resort to heuristics by dropping selective noise terms from the original CLE inconsistent with the mesoscale physics involved in forming the CLE. Other methods take very small time steps thus making the simulation inefficient. In our second study we preserve positivity by using a physically consistent numerical scheme which is a modified form of fully stochastic α method for stiff stochastic differential equation.

Ion channels are fundamental molecules in the nervous system that catalyse the flux of ions across the cell membrane. Single ion channel flux activity is comparable to the catalytic activity of single enzyme molecules. Saturating concentrations of substrate induce dynamic disorder in the kinetic rate processes of single enzyme molecules and consequently, develop correlative memory of the previous history of activities. Conversely, binding of substrate ion is known to alter the catalytic turnover of single ion channels. Here, we investigated the possible existence of dynamic disorder and molecular memory in single human TREK1 channel due to binding of substrate/agonist using the excised inside-out patch-clamp technique. Our results suggest that single hTREK1 channel behaves as a typical Michaelis-Menten enzyme molecule with a single high-affinity binding
site for substrate $K^+$ ion but with uncertainty in reaction rates.