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ABSTRACT

Natural systems are complex in nature due to random interaction of its constituent elements or components or objects and with environment. The biological systems are open and are kept far away from the thermodynamic equilibrium and their processes are rhythmic, non linear and non equilibrium. Stochastic modelling of biological systems has become a very important research field in computational biology in recent years. Experimental and theoretical studies have shown the importance of stochastic processes in genetic regulatory networks and cellular processes. Cellular networks and genetic circuits often involve small numbers of key proteins such as transcriptional factors and signalling proteins. It is not appropriate to use deterministic models such as ordinary differential equations to describe the dynamics of the systems with small molecular numbers.

In Chapter 2 we have given the details of all the numerical techniques used in the analysis of our work. We have developed our own code in java language to study the models for application purposes.

In Chapter 3 we investigated numerically the approximate estimation of thermodynamic limit which is the limiting value of mesoscopic to macroscopic transition. Since the number of oscillators (nuclei) in a single neurospora cytoplasm is small and finite, we employ specific coupling mechanisms namely diffusive and mean field couplings to study how multi-oscillator stochastic synchronization is achieved in this organism as a function of system size and coupling constant. We predict the destructive effect of noise in stochastic inter-oscillator synchronization at small system size i.e. mesoscopic system, however at larger system size i.e. macroscopic system this destructive effect is minimized and degree of synchronization is faster. We also claim that as the number of coupling molecular species increases, information processing among the coupled oscillators is much more quicker and so synchrony is faster at all macroscopic and mesoscopic systems. We find that a global mean--field coupling effects the most rapid approach to global synchrony, and that when the number of ``information carrying" molecular species increases, the rate of synchrony increases.

In Chapter 4 we study the temporal and the synchronous behaviours in p53-Mdm2 regulatory network due to the interaction of its complex network components with the nitric oxide molecule. In single cell process, increase in nitric oxide concentration gives rise the transition to various p53 temporal behaviours, namely fixed point oscillation, damped oscillation and sustain oscillation indicating stability, weakly activated and strongly activated states. The noise in stochastic system is found to help to reach these states much faster as compared to deterministic case which is evident from permutation entropy dynamics. In coupled system with nitric oxide as diffusively coupling molecule, we found nitric oxide as strong coupling molecule within a certain range of coupling strength ε beyond which it become weak synchronizing agent. We study these effects by using correlation like synchronization indicator γ obtained from permutation entropies of the coupled system, and found five important regimes in (ε-γ) phase diagram, indicating desynchronized, transition, strongly synchronized, moderately synchronized and weakly synchronized regimes respectively. We claim that there is the competition between the toxicity and the synchronizing role of nitric oxide that lead the cell in different stressed conditions.

Again we also study how the temporal behaviour of p53 and Mdm2 are affected by stress inducing bioactive molecules NO (Nitric Oxide) in the p53-Mdm2-NO regulatory network arranging in realistic three dimensional way. In the single cell study, we have found three distinct types of temporal behaviour of p53, namely, fixed point oscillation (or oscillation death), damped oscillation and sustain oscillation. We also study the group of such identical systems arranged in a three dimensional array with nearest neighbour diffusive coupling and found that the systems at near and far distances interact almost instantaneously which is identified by order parameter γ calculated via permutation entropy. The correlation among the coupled systems increases as the value of coupling constant (ε) is increased (γ increases) and become constant after certain value of ε. The permutation entropies H(ε) for p53 and

Mdm2 as a function of ε are found to be different due to direct and indirect interaction of NO with the respective proteins.

In Chapter 5 we examine the synchrony in the dynamics of localized $[Ca^{2+}]^i$ oscillations among a group of cells exhibiting such complex Ca^{2+} oscillations, connected in the form of long chain, via diffusing coupling where cytosolic Ca^{2+} and inositol 1,4,5-triphosphate (IP3) are coupling molecules. Based on our numerical results, we could able to identify three regimes, namely desynchronized, transition and synchronized regimes in the (T-k_e)(Time period-coupling constant) and (A-k_e)(Amplitude-coupling constant) spaces which is supported by phase plots ($\Delta\Phi$ verses time) and recurrence plots respectively. We further show the increase of synchronization among the cells as the number of coupling molecules increases in the (T-k_e) and (A-k_e) spaces.
Again we also study the integration of calcium and $p53-Mdm2$ oscillators model using deterministic as well as stochastic approaches to investigate the impact of calcium wave on single cell dynamics and on inter-oscillators interaction. The high dose of calcium in the system activates nitric oxide synthase synthesizing nitric oxide which then downregulates Mdm2 and influences drastically p53-Mdm2 network regulation, lifting the system from normal to stressed state. The increase in calcium level switches the system to different states as identified by different behaviours of p53 temporal dynamics i.e. oscillation death to sustain oscillation state via a mixed state of damped and oscillation death states. Further increase of calcium dose in the system switches the system from sustained to oscillation death state again, while an excess of calcium shifts the cell to apoptotic state. Another important property of calcium ion is its ability to behave as synchronizing agent among the interacting systems. The time evolution of p53 dynamics of two diffusively coupled systems at stress condition via Ca^{2+} shows synchronization between the two systems. The noise contained in the system interestingly helps the system to maintain its stabilized state (normal condition). However, noise has tendency to destruct the synchronization effect which means that it tries to restrict the system from external signals to maintain its normal condition. However, at stress condition, synchronization rate is found to be faster.

In Chapter 6 we examine the possibilities of various coupling mechanisms among a group of identical stochastic oscillators via Chemical Langevin formalism where each oscillator is modeled by stochastic model of testosterone releasing pathway. Our results show that the rate of synchrony among the coupled oscillators depends on various parameters namely fluctuating factor, coupling constants ε, and interestingly on system size. The results show that synchronization is achieved much faster in classical deterministic system rather than stochastic system. Then we do large scale simulation of such coupled pathways using stochastic simulation algorithm and the detection of synchrony is measured by various order parameters such as synchronization manifolds, phase plots etc and found that the proper synchrony of the oscillators is maintained in different coupling mechanisms and support our theoretical claims. We also found that the coupling constant follows power law behaviour with the systems size (V) by $\varepsilon \sim AV^{-\gamma}$, where $\gamma=1$ and A is a constant. We also examine the phase transition like behaviour in all coupling mechanisms that we have considered for simulation. The behaviour of the system is also investigated at thermodynamic limit; where $V\rightarrow\infty$, molecular population, $N\rightarrow\infty$ but $N/V\rightarrow$ finite, to see the role of noise in information processing and found the destructive role in the rate of synchronization.

In Chapter 7 we have investigated the five numerical techniques viz. deterministic, CLE, τ leap, SSA and DSSA. We have compared the first four techniques using Neurospora as a model. We first found that when these four techniques are applied in the single oscillator noise impact are in the order Deterministic $<$ CLE $<\tau$ leap $<$ SSA. Again system size is also inversely proportional to the noise. Again when we investigated the network of such nine oscillators we have found that the rate of synchronization are in the order of Deterministic $>$ CLE $>\tau$ leap $>$ SSA. This may be because noise impact on the oscillators are in the order Deterministic $<$ CLE $<\tau$ leap $<$ SSA. Thus noise plays a destructive role in achieving synchronization in the Neurospora model. We also investigate the time taken in simulating all these methods, we have found that Deterministic $<$ CLE $<\tau$ leap $<$ SSA. In terms of computational cost, it is in the order Deterministic $<$ CLE $<\tau$ leap $<$ SSA. All these methods have their own advantages and disadvantages, but where to use them depends upon the type of system we consider.