Chapter 5

Summary and concluding remarks

In the concluding Chapter, a summary of the major results obtained in the thesis is given. In Chapter 1, a general introduction to the topics studied in the thesis is given. The problems studied include: (i) reaction diffusion (RD) processes on different types of networks, (ii) the functional characteristics of a special motif which appears in the gene transcription regulatory network of pancreatic β-cells and (iii) transient pulse formation in the jasmonate (JA) signaling pathway. We have provided a brief description of the genesis of the problems as well as associated concepts and techniques.

In Chapter 2, we have studied the formation of Turing patterns on three different types of networks: regular, random and scale-free. The RD processes are described by a model which is a discretized version of the Gierer-Meinhardt (GM) model. The model dynamics lead to the formation of stationary Turing patterns in the steady state in certain parameter regions. We observed that the formation of Turing patterns is most favourable in the case of the regular network. To make a meaningful comparison, we kept the size and average degree of all the three networks the same. Some general features of Turing patterns were studied like the average activator concentration versus $d = d_h/d_a$, the ratio of the diffusion coefficients of the inhibitor and the activator, the number of nodes N_a at which the activator concentration a_i is greater than or equal to a threshold value versus d, the height of a_i versus d, and the distribution of activator concentrations amongst the network sites. In each case, the results for the random and scale-free networks show a marked difference from those in the case of the regular network. In our study the value of D_h, the diffusion coefficient of the inhibitor, has been kept constant to identify the systematic trends associated with the variation of D_a.

The range of D_h values for which Turing patterns form in the steady state is not sufficiently extended to study the variation with respect to D_h, keeping D_a fixed. Turing instability in activator-inhibitor systems is a paradigm example of self-organization in the non-equilibrium. RD systems, in general, exhibit a range of self-organized patterns such as stationary dissipative structures, traveling fronts and pulses, rotating spiral waves and chemical turbulences [1, 2, 3, 4, 5, 6]. The study reported in the thesis [7] is one of the first investigations of RD processes occurring on random/scale-free networks. Recently, Nakao et al.[13] have studied self-organization phenomena in an activator-inhibitor model, the so-called Mimura-Murray model, defined on random and scale-free networks. Some of the results obtained are in agreement with the results of our earlier study. In both the cases, a spontaneous differentiation of the network nodes into activator-rich and activator-poor groups takes place. When diffusional mobility, D_{act}, of the activator (D_{act} is the diffusion coefficient of the activator) is small, only a subset of the highly connected nodes undergoes differentiation. For a large D_{act}, activator-rich nodes have just a few links. The new study further illustrates a dramatic consequence of self-organization in the form of multiple coexisting stationary states and hysteresis effects. Random and scale-free networks are examples of small-world networks. Diffusional mixing on such networks is fast because of the small diameter of the networks. The few studies carried out so far [8, 9] motivate further investigations with the complex networks ranging from ecological systems [10] to neuronal networks [11].

In Chapter 3, we have studied the functional characteristics of a two-gene motif consisting of a double positive feedback loop and an autoregulatory negative feedback loop. The motif appears in the gene regulatory network controlling the functional activity of pancreatic β-cells. The model exhibits bistability and hysteresis in appropriate parameter regions. The two stable steady states correspond to low (OFF state) and high (ON state) protein levels respectively. Using a deterministic approach, we have shown that the region of bistability increases in extent when the copy number of one of the genes is reduced from two to one. The negative feedback loop has the effect of reducing the size of the bistable region. Loss of a gene copy, brought about by mutations, hampers the normal functioning of the β-cells giving rise to the genetic disorder, maturity-onset diabetes of the young (MODY). The diabetic phenotype makes its appearance when a sizable fraction of the β-cells is in the OFF state. Using stochastic simulation techniques, we have shown

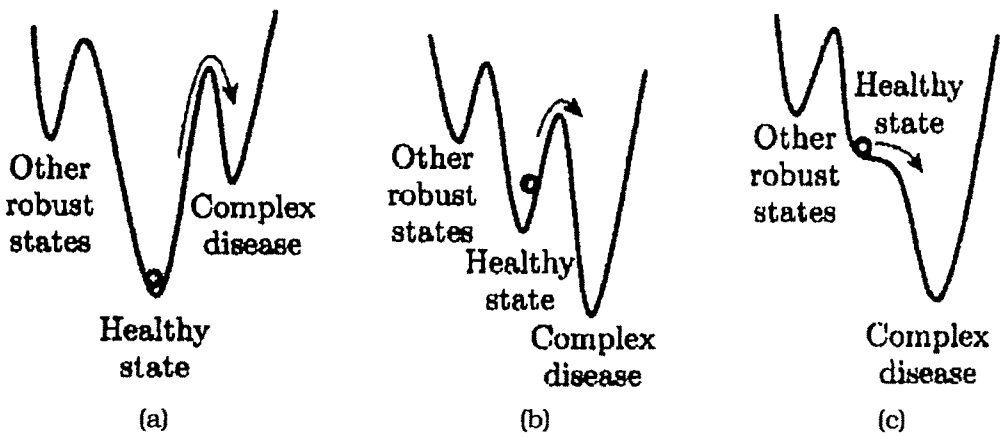

Figure 5.1: Functional landscape in gene expression (a) Under normal conditions, the healthy state is globally stable (b) disease state is more stable than healthy state. The latter state, however, may still have a long life time. (c) The healthy state is locally unstable making the disease incurable/untreatable [12].

that, on reduction of the gene copy number, there is a transition from the monostable ON to the ON state in the bistable region of the parameter space. Fluctuations in the protein levels, arising due to the stochastic nature of gene expression, can give rise to transitions between the ON and OFF states. We further demonstrated that as the strength of autorepression increases, the ON→OFF state transitions become less probable whereas the reverse transitions are more probable. The implications of the results in the context of the occurrence of MODY have been pointed out. The stochastic dynamical model of MODY developed in the thesis can be generalised to study the genesis and progression of diseases which involve multiple stable states of gene expression. Recently, Ao et al.[12] have developed such a scheme in the case of cancer. In their model, the multiple stable states constitute the minima of a gene-expression landscape. The states include healthy states as prevails in normal situations, states corresponding to rare stressful situations and the so-called 'disease' states. Figure 5.1 illustrates three typical situations in the dynamics of disease initiation and progression. Development of a similar landscape picture in the case of MODY would provide useful insight on the prevention and curability of the disease.

In Chapter 4, the dynamics of the JA signaling pathway has been investigated. The JA signaling pathway in plants is activated as defense response to a number of stresses like attacks by pests or pathogens and wounding

by animals. Some recent experiments provide significant new knowledge on the molecular detail and connectivity of the pathway. The pathway has two major components in the form of feedback loops, one negative and the other positive. We have constructed a minimal mathematical model, incorporating the feedback loops, to study the dynamics of the JA signaling pathway. The model exhibits transient gene expression activity in the form of JA pulses in agreement with experimental observations. The dependence of the pulse amplitude, duration and peak time on the key parameters of the model has been determined computationally. The deterministic and stochastic aspects of the pathway dynamics have been investigated using both the full mathematical model as well as a reduced version of it. We also compared the mechanism of pulse formation with the known mechanisms of pulse generation in some bacterial and viral systems. The formation of a transient pulse is an example of self-organization in the non-equilibrium. As commented in Chapter 4 of the thesis, there are alternative scenarios for transient pulse formation some of which have been explored extensively in bacterial and viral systems [14, 15, 16]. In the case of HIV-1 AIDS virus, the transient pulse originates in a feedback resistor mechanism. There is recent experimental evidence [17] that the HIV-1 gene expression occurs through randomly timed bursts of transcriptional activity. This in turn gives rise to transient pulses of the key regulatory protein Tat. Active viral replication requires the Tat level to be high. Thus, stochastic gene expression influences the choice of the AIDS virus to enter either active replication resulting in proliferation of the virus or latency. In the case of the JA signaling pathway, further experiments are needed to pinpoint the mechanism and origins of JA-pulse formation. In particular, the role of gene expression noise in the generation of JA pulse should be investigated in detail.

In summary, the problems studied in the thesis illustrate various types of self-organization in complex systems. The Turing pattern is an example of spatio-temporal self-organization. The distribution of specific gene expression levels is bimodal in the case of MODY. In the JA signaling pathway, JA pulses activate the appropriate response. In the latter two cases, self-organization is temporal in nature. In all the three cases, the underlying systems are complex and self-organization is a manifestation of the emergent behaviour of a number of interacting components.

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