Chapter 6

Conclusions

6.1 Summary of Research

The objective of this thesis is to put some insight into the cause of dopamine depletion in Parkinson disease. It is well known fact that dopamine depletion in SNc (substantia nigra pars compacta) is the main reason for Parkinson disease but the reason is not known that why the dopamine generating neurons die. I have tried to achieve the objective by means of identifying the oscillating and bursting circuits in Parkinson disease and analyzing the discharge patterns of healthy primate and Parkinson disease condition in those circuits. The analysis is being performed by checking the sensitivity of the discharge patterns in STN-GPe network for various intrinsic parameters and comparison is being made by calculating the correlation coefficient between healthy and Parkinson disease discharge patterns. Analysis is also being performed on the basis of frequency trend and rate of discharge patterns and certain important findings have been reported. Simulations were performed using MATLAB 7.14 on i7 Intel processor and 4GB RAM machine. Modelled differential equations have been solved using ODE45 in MATLAB. Work has been listed
in 5 chapters.

Chapter 2 contains the literature survey for all problems stated in the objectives. The studies based on the specific objectives are presented in three subsequent chapters, from Chapter 3 to Chapter 5 and finally this chapter concludes the presented work and future scope. Each chapter is organized in a similar structure. Each of the Chapters 3 to 5 is divided into four sections, where the first section contains introduction of the problem, the second section contains the details of mathematical formulation, the third section presents results and discussion and the last section contains the summary of the results of the problem.

First problem was to formulate a conductance based model of basal ganglia in Parkinson disease which can reproduce the sequences (discharge patterns) generated experimentally in Parkinson disease patients. A conductance based model has been formulated for Basal ganglia initially and has been modified to replicate sequences in STN-GPe network in Basal ganglia. The model parameters has been modified by modulating their values and added some more ionic currents to replicate the discharge patterns in Parkinson disease. The purpose was to develop computationally efficient, single compartment, conductance based models of subthalamic nucleus cells to reproduce their primary electrical properties and using such models in anatomically consistent network topologies of the basal ganglia to reproduce in vivo macroscopic average behaviors, as extra-cellularly recorded in experiments on primates.

Second problem deals with the investigation of the parameters that alter the dynamics in Parkinson disease. Sensitivity within subthalamic nucleus model due to applied current, pre-synaptic membrane potential, feedback synaptic potential and calcium currents has been analyzed and results reveal the sensitivity of model towards calcium current. Results focus on the importance of observing the calcium current closely in order to identify
the cause to this disease. Problem three demonstrated that subthalamic nucleus model and synaptic input from GPe in hyper-direct pathway alone can account for the Parkinson disease symptoms. The abnormal calcium influx may be aggravated by subthalamic nucleus through a mechanism involving NMDA glutamate receptors. But for the entire process of excitations and inhibition due to glutamate and GABA receptors is limited by the timing of depolarization of the model. The model neuron reaches to a threshold value for a limited time period and hence firing in a specific region occurs. In this limited time period if the calcium influx is increased then the model displays the properties of Non-PD primate. Along with this, calcium receptors are influenced by the sodium and potassium activated receptors. Their role needs to be exploited in detail during the simulation of model for duration more than 500ms.

The results of problems showed that STN-GPe network is highly sensitive to calcium, potassium and sodium currents. Two time series i.e. Non-PD and Parkinson disease are somewhat overlapping initially but gradually with time the lag is increased between two. By changing one parameter and keeping others fixed, correlation patterns are also improving to some extent between Non-PD and Parkinson disease Patterns. The limitation of this study is that the firing behavior is studied for one parameter at a time. It does not account if I change two or more parameters simultaneously. Hence it needs to be observed how the correlation patterns varies with variation in all the reported parameters. Problem three also focus is on the synaptic conductance along with calcium and other ionic parameters in STN-GPe model that account for the symptoms of Parkinson disease. To improve the correlation coefficient among the discharge patterns generated in healthy primate and discharge patterns generated in Parkinson condition calcium as well as synaptic conductance also play an important role. Correlation coefficient has been relatively improved by modulating the synaptic conductance.
6.2 Suggestions for Future Research

The analysis and results of the thesis can be further improved by using some optimization technique and bifurcation analysis of the model is proposed to check the stability of the model.