Chapter 2

Review of Literature

This chapter is dedicated to the literature survey on the basis of various problems addressed by the scientist and researchers in the past. The survey was done in the area of one type of brain disorder, known as Parkinson disease. The objective of this survey was to focus on the symptoms of the disease, how this disease is caused, what are various factors that influence the disease and how computational modeling technique is beneficial in the diagnostic process. On the basis of above discussed factors this review has been divided in the following sections:

1. Literature survey for Parkinson disease and its symptoms.
2. Literature survey for computational model in Parkinson disease.
3. Literature survey for subthalamic nucleus (STN), globus pallidus (GP).
4. Literature survey for different pathways in basal ganglia and their importance.
5. Literature survey for the role of dopamine in Parkinson disease symptoms.
6. Literature survey for the importance of calcium current in Parkinson disease and
7. Literature survey for information processing and bifurcation analysis.
2.1 Literature survey for Parkinson disease and its symptoms

There are many types of brain disorders, which are caused due to the malfunction of neurons. Neurotransmitters responsible for certain functionality of brain stop working and due to this many disease are caused. One of the disease that is caused due to this is Parkinson disease. It is also one type of movement disorder explained by Beurrier et al. [5]. Pavlides et al. [10] has suggested that Parkinson disease (PD) is a progressive neurodegenerative disorder that affects 6 million (approx.) people worldwide. Many researchers have worked on the symptoms of Parkinson disease. There are many cells in our brain and simultaneously involved in the activation and in activation of brain. Various currents are also responsible like $K^+$, $T$, $L$ and $R$ type currents which fall into the category of different calcium current. These currents are involved in the frequent oscillations of membrane of cells. These frequent bursting in the cell membrane is one of the Parkinson characteristic in rat and primates. One of the nucleus of basal ganglia switch its activity from single spike to burst firing [5]. Hammond et al. [11] have shown in their work that there is excessive synchrony between beta level frequencies in Basal ganglia. Due to this the motor functions are affected in Parkinson disease. There are other important activities of human body that also depends upon the proper function of brain. Action selection is one of them. These excessive synchrony also affect action selection, due to which bradykinesia is caused. This function is noticed by a recent model of basal ganglia. Failure of action selection leads to bradykinesia. There is also a requirement of study that the cause to bradykinesia is excessive synchrony or something else. Study could be done to depict the disrupted motor function by giving direct stimulation to basal ganglia at beta band frequencies. Results were reported for bradykinesia for 10Hz and 20HZ stimulation, but
Rissanen et al. [12] have presented a study on the method, acceleration measurements and dynamic surface Image result for electromyography (EMG) for discriminating between Parkinson diseased patients and healthy primates. 76 percent Parkinson patients were differentiated from 90 percent of healthy controls in their earlier study. These studies were performed using acceleration methods and static EMG. In their current study the rate of differentiation was same for extension but the rate was different for flexion. Those clusters who were incorrectly measured were identified and characterized by the EMG and by oscillation or bursting. These findings were somewhat similar to earlier findings. In earlier findings there was loss of acceleration and also there was Higher level of bursting in the older age people as compared to younger ones. Age plays a very important role if we talk about the effect on EMG and different acceleration patterns. They have discriminated between Parkinson patients and healthy primate. They also evaluated methods which are effective in the treatment [12]. Brewer et al. [13] have suggested that if we could quantify the motor functions in Parkinson disease then it would definitely going to add value for the better medication and treatment of patient. They also suggested the application of various techniques like brain imaging, and high precision sensors in the assessment of Parkinson disease. It would enable the investigators to quantify the changes in motor functions in Parkinson disease. It will be extremely valuable for potential neuro-protective interventions and clinical trials. It will add value to different tests available for the symptoms of PD like UPDRS. This will help UPDRS to finely quantify the motor signs. Yunfeng Wu and Krishnan [14] have presented a study on the importance and effects of neurological disorders. They suggested that neurological disorders are more dangerous than aging. These affect the patients in more pronounced way then the aging. Though aging also played an important role in their study where they demonstrated that
gait variability would be increased in Parkinson disease in terms of statistical measures but neurological disorders have adverse effect more than aging.

There are many techniques to measure the performance of Parkinson disease patients. One of these technique is hybrid estimation technique. This technique was first applied by Oishi et al. [15]. They have used this technique to measure the performance of Parkinson disease patients. They have used the task of switched pursuit tracking. In this task they have used Kalman filter, LTI models(stochastic) and MMAE method for measuring the characteristics of Parkinson disease patient and their switching behavior. This method was very effective as the person in healthy primate has detected the changes consistently but persons with Parkinson disease were slower. They have suggested that this method is also effective in quantifying the motor performance in Parkinson disease along with neurological evidences. I know that basal ganglia are the interconnected collection of nuclei in brain which is responsible for motor function and movement generation. Haidar et al. [16] also linked the oscillation of basal ganglia in beta band with the symptoms of Parkinson disease. They have also provided various conditions under which these oscillations occurs. They specifically considered the role of pedunculopontine nucleus (PPN). They have studied and analyzed dynamics of firing rate for the existence of equilibrium. They have done the frequency analysis by using delayed MIMO and simulated the results. Xia and Mao [17] have also mentioned in their study that Parkinson disease is a neurological disorder which progresses with age and this study was supported by different motor symptoms like tremor, bradykinesia and rigidity. These symptoms worsen with time. They mentioned the cause to this disease is the loss of dopamine. Due to adverse effect of this disease, they have called it heterogeneous disease. Their are many supporting studies for the symptoms of Parkinson over time. Out of these symptoms, cardinal motor symptoms progresses with different rates. The rate are higher with patients having rigid-
ity and bradykinesia than having tremor. They focused on the review of recent studies which investigate the progression of disease and on the effect of drugs in the development of disease. They suggested that the treatment methods in which the medicine containing dopamine is used, control the worsening of the symptoms. But none of the drug can slow down or stop the disease progression if given at early stage [17]. Whereas Rigas et al. [18] has suggested that the most common disorder of motor is tremor. Its detection plays a very important role in the treatment of Parkinson disease. But the current diagnostic system involves clinical assessment, which can not capture the tremor features. Dovzhenok and Rubchinsky [1] explained that it is very difficult to identify the origin of tremor like activity in Parkinson disease. Its origin is still unknown. They have explained it by considering the basal ganglia circuit of thalamus and cortex by considering them as tremor generating circuits. They have done this by considering a conductance based model to represent basal ganglia circuit. They show it by the occurrence of tremor like burst firing activity by changing the strength of dopamine dependent connections. These tremor like activity are suppressed by increasing the strength of dopamine. Hence this basal ganglia circuit is said to be the tremor generating circuit as the generation of tremor is strengthened by loop strength and suppressed by disconnection of the loop. Therapies to suppress tremors like activities might have effects on other basal ganglia areas like different cortical and sub cortical areas. Blesa and Przedborski [19] have studied animal models and proposed that these models are closest to human. Hence there are various animal models of Parkinson disease that have been build to understand the test potential therapeutics and pathogenesis and of Parkinson disease.

Cebrin et al. [20] suggested that substantia nigra is the main region for the motor symptoms in Parkinson disease. These motor symptoms are due to the degeneration of dopamine neuron in substantia nigra. There are many neuroinflammatory processes in
substantia nigra that are exacerbated in Parkinson disease which include increased expression of substances which are pro-inflammatory, glial-mediated reactions, and lympho-cytic infiltration. Schirinzi et al. [21] suggested Parkinson disease as second most common neurodegenerative disorder after Alzheimer. They have also stressed upon the role of dopamine. As the disease progresses, clusters of dopaminergic neurons die. Due to which the neurotransmitter producing dopamine are reduced. This chemical dopamine is responsible for the proper coordination of muscle movements. The symptoms of Parkinson disease can not be known at early stages. When the diagnostic is done, 50 percent of dopaminergic neuron are already dead. They further suggested the symptoms of Parkinson disease as shaking in arms, legs, face and jaw; stiffness and rigidity in the trunks and limbs; slowness in activities and movements; lack of coordination in speech and body balance etc. These symptoms worsen with time in this disease. Hench early diagnostic of Parkinson disease is utmost important in order to manage the symptoms of disease and for the treatment suggested by Prashanth et al.[22]. This is also important to diagnose at early stage as 60 percent of dopaminergic neurons die when it is been diagnosed. No laboratory test exists for the diagnosis of the disease. Hence it is very important to identify the methods and techniques that facilitate the diagnostic system for the better treatment. Hence the diagnosis of Parkinson disease at early stage is very important for the better treatment. It is important because the symptoms of disease are visible when more than 60 percent dopaminergic neurons are lost. To diagnose the disease there is no laboratory test and it causes the wrong diagnostic or mis-diagnostic of disease at early stage. It leads to the ill treatment of the disease.
2.2 Literature survey for computational modeling in Parkinson disease

It has been suggested by the scientist that basal ganglia is the main region responsible for Parkinson symptoms and their many symptoms on the basis of which we can identify the occurrence of the disease. Now the question is how we can make the diagnostic system more effective so that we can diagnose the disease at early stage. Hence many scientist suggested the advantages to computational modeling to for better demonstration. Tsirogiannis et al. [23] has linked the neuro-physiological data with biophysical model that can reveal features of basal Ganglia. And these features can be revealed at a very high level of description. They also focused upon the role of synaptic parameters for a model to function like Parkinson behavior. They suggested that strength of synaptic parameter is important in Parkinson disease. Recent work of Schiff [24] has extended the model of Rubin and Terman [25]. They have taken into account different pathways of basal ganglia like direct and indirect pathways from striatum to different pathways of basal ganglia. Incorporation of more relevant biological structure of basal ganglia might give grater possibility to copy dynamics in Parkinson disease in basal ganglia. But this will give rise to more complex model hence accuracy of data will become an issue. They suggested that Parkinson will be the first movement disorder in which model based control will show some promising results. There are many areas in which work is to be done to improve the results. Cloutier and Wellstead [26] also suggested the importance of computational and mathematical modeling in order to investigate the features of Parkinson disease at early stage. They told that the research onto the symptoms of Parkinson disease is complex and very time consuming. Parkinson disease a complex state or condition that takes decades to develop in human brain.
Nambu et al. [27] has also presented that basal ganglia is the target region of Parkinson disease and the Malfunctions of this can cause dystonia and Parkinson disease. They also suggested that there are various models that can explain the pathophysiology of such disorders: (a) firing rate model: there is activity imbalance between different pathways like the direct and indirect pathways. Due to this the mean firing rate of output nuclei of basal ganglia has been changed and it causes hyperkinetic or hypokinetic movement disorders, (b) firing pattern model: These model are based upon the oscillatory patterns of basal ganglia in Parkinson disease and their information processing mechanism, (c) dynamic activity model: These model are based upon the activity changes in direct, indirect and hyper-direct pathways due to abnormal neuronal modulations. This disrupt the movement related balance and lead to motor symptom. Restrepo-Agudelo and Roldn-Vasco also [28] explained the importance of computational simulations for neuro-surgical training and for better understanding. They described the procedure to reconstruct the signal of basal ganglia in time domain for Parkinson disease patient. They propose a very simple technique of simulation. Hence, computational modeling and simulation is best suited for the better diagnostic and in identifying the better mechanism for treatment.

2.3 Literature survey for the importance of subthalamic nucleus and globus pallidus in basal ganglia

There are five main nuclei in basal ganglia, but subthalamic nucleus and globus pallidus play some important role in identifying the cause to Parkinson disease. Gillies and Willshaw [29] in their work has given a model to predict the role of subthalamic nucleus in basal ganglia. Subthalamic nucleus generate widely spread firing pulse of activities. Due to the abnormal condition in Parkinson disease, subthalamic nucleus and globus pallidus
produces low frequency oscillatory burst activity pattern when striatal inhibition is increased. This model also predict the interaction within subthalamic nucleus and their effect on the subthalamic axon. Kano et al. [30] also suggested the importance of role of subthalamic nucleus in Parkinson disease. They demonstrated it with the help of generating the increased multiple cell spike density (MSD) when an electrode is entered within subthalamic nucleus. Santaniello et al. [31] also have depicted the behavior of subthalamic nucleus in Parkinson disease patients. They have presented the behavior by analyzing two Parkinson patients by inserting the microelectrode during deep brain stimulation and by using the mathematical modeling. Their analysis demonstrated that the neural spikes generated near subthalamic nucleus band are according the beta distribution in Parkinson disease.

The work of Santaniello et al. [31] also deal with modeling of subthalamic nucleus and globus pallidus cell to mimic the behavior of Parkinson disease as described in the literature. To describe the behavior of most suitable and relevant ionic channel they have used the basic Hodgkin Huxley model. The result produced are on the basis of membrane potential of the cell, which is single compartment and conductance based. Steigerwald et al. [32] also presented the study describing the study of characteristics of patients suffering from Parkinson disease. They has focused upon the activity patterns generated in subthalamic nucleus. They first time used the control data of subthalamic nucleus of humans not suffering from Parkinson disease, this helped to verify the data of patients suffering from disease using the concept of basal ganglia dysfunction. Bergman et al. [33] confirmed the abnormal activity of neuronal firing of subthalamic nucleus in Parkinson disease as compared to the activity of subthalamic nucleus in normal state. They mentioned the overall increase in the rate of discharge and changes in the dynamics and neuronal patterns in Parkinson disease.
Kang and Lowery [7] put forward their simulation results of STN-GPe network. They have formulated a computational model which incorporated the hyper-direct pathway of basal ganglia network and investigated the neuronal oscillations in Parkinson disease. Result of their work followed the experimental results in Parkinson disease for beta band. Their results illustrated the possibility of experimentally detected oscillations in beta band and cortical origin. Along with the computational modeling of beta band oscillation, it is also very important to know the role and effect of synaptic input on neuronal discharge pattern. Wiecki and Frank [34] have discussed the role of synaptic input on output spiking patterns of a neuron. To understand the influence and effect of synaptic input can be the central problem in neural physiology. Spike threshold is dynamic in nature and becomes an essential of of such understanding of subthalamic neuron. Excitatory post synaptic potential (ESPS) and Inhibitory post synaptic potential (IPSP) has opposite effect on the membrane potential. They also have their effect on threshold both positive and negative as explained by Baufreton et al. [35]. Sodium channels play an important role in dynamic threshold. Along with this the voltage, cable property and geometry of spike initiation zone and sodium inactivation is also very important. All these factors are also very important along with other cellular properties. In order to fully tuned to specific cell function, the dynamics of threshold have to be in agreement with input and output relationship. Sarma et al. [36] have analyzed the characteristics of subthalamic neuron by applying point process model. They have performed recording of subthalamic neuron after inserting the electrode in Parkinson disease patient and healthy primate (non-human). They have done so to understand the importance of spiking history and movement on neural response. They used point process GLM representation for the development of model fitting likelihood approach and inference. This representation of point process model made feasible to identify the characteristics of subthalamic neuron in Parkinson disease. It in-
cluded bursting (10-30 Hz) and prior to movement, less directional tuning. The difference between the characteristics of subthalamic nucleus in Parkinson disease and subthalamic nucleus in healthy primate has earlier been defined using traditional methods. But such traditional techniques could lead to some incorrect results and the spiking behavior contains temporal dependencies. Hence point process method is a useful paradigm in quantitatively characterizing spiking activity of subthalamic neuron in Parkinson disease. Kubota and Rubin [37], Bergman et al. [33], Brown et al. [38], Gatev et al. [39], Levy et al. [40] and Magnin et al. [41] have stated that the subthalamic neuron mostly in normal condition present irregular spiking activity and an increased oscillation and bursting activity with overall higher firing rate in Parkinson condition. They have further extended the study by incorporating the rat slice data and they continuously monitored the additional currents in rat brain slice. The extended model resulted in robust bursting under the application of consistent hyper polarize current when the associated parameters are fit to experimental results. The resulting bursting activity of the model respond to the application of apamin as shown in the experimental results. They have also shown the importance of $Ca^{2+}$ influx in NDMA channels.

In order to predict the neural spiking activity of subthalamic nucleus, Michmizos et al. [42] have considered five nuclei and selected and processed the data from those nuclei. They have discussed the role of cascade model for predicting and characterizing subthalamic nucleus neural spiking activity. They acquired the spike timing and rhythmic activity from those five nuclei to model the neuron. They used all the recordings to check the accuracy of the model by calculating the inter-spike interval, spike timing and rhythms of the spike. They have shown that the resulting spikes fall into the 95 percent of the recorded spike confidence interval. Their model has provided quite accurate predictions for multiple recording of multiple neurons and they suggested that their model is simple yet biological
possible model for Parkinson disease patients. Pavlides et al. [43] have stressed upon
the role of subthalamic nucleus in deep brain stimulation. The disability caused due to
Parkinson disease has been significantly improved due to this. The improved outcome is
the result of multidisciplinary team building, patient selection and assessment on the basis
of refined protocols, improved targeting methods and good surgical technique. They also
suggested that there is an increased beta oscillations in Parkinson disease within basal
ganglia and it has been associated with difficulty in the initiation of movement. These
Beta oscillations has been caused by the network of subthalamic nucleus and globus spal-
lidus external. Cortex plays the major role in causing beta oscillation. There are other
model also that describe the methods of Beta oscillation generation in Parkinson condi-
tion. Stimulation therapy is improved if we are able to target the subthalamic nucleus
precisely [43]. Arnulfo et al. [44] has also suggested the importance of subthalamic nu-
cleus in Parkinson disease. By applying the deep brain stimulation to subthalamic nucleus
improves the condition of Parkinson patient and reduces motor disability.

2.4 Literature survey for different pathways in basal
ganglia and their importance

Basal ganglia has mainly five nuclei and they are connected with each other. Cortex send
signals to all the nuclei and receives processed signals from Thalamus. The connection
between different nuclei forms different paths and these paths are known as basal gan-
glian pathways. Every pathway has its importance in signal transmission and information
generation. It has been suggested by Terman et al. [45] that indirect pathway plays a
very important role in analyzing the role of inhibitory signals and firing patterns gener-
ated. Tremor like activities are also generated in the Indirect pathway. Tremor generation
can lead to synchronization of activities between STN-GPe network and switch of normal activities to oscillatory activity. They suggested that all the neurons group targeted to perform some particular task and they fall under same category. They group together according to their signaling class. One group of such class is known as neo-cortex. It is very difficult to identify each and every connections between a group of nuclei like neo-cortex. But the overall functionality can be defined on the basis of overall experience or feedback or plasticity. On the basis of their measurement or methods such as EEGs, they define the connections or wiring patterns [45].

The study of Modolo et al. [46] focuses on the pathways of subthalamic nucleus and globus pallidus external during deep brain stimulation. It is also true that there are other nuclei in the motor loop like globus pallidus internal, or motor cortex or thalamus, and their interaction with those nuclei also impact the behavior of STN-GPe loop. However, this is quite relevant to study their role for understanding the generation of rhythmic oscillations in the motor loop. This subthalmo-pallidal loop can also be extended by including the cortical cell population and closing the loop for exploring the behavior of these populations. Ma et al. [47] has also suggested in his study that disrupted connections between different region of brain might lead to neurological disorders. Parkinson disease is one of them. It is of great interest to develop the computational model of such areas to infer the relevant information from different pathways. These models can be used to infer brain functional information by using imaging data such as FMRI (functional magnetic resonance imaging). Saxena et al. [48] have performed an experiment and they have used point process model to investigate the physiological connectivity between globus pallidus external and internal. They have shown the impact of deep brain stimulation performed on globus pallidus external to spiking activities of globus pallidus internal. Their study using point process model is consistent with statistical analysis.
Neural network models play a very important role in replicating and filling the gap between the behavior and the neuronal signals as told by Wiecki and Frank [34]. They had this idea that they might see the bigger picture after integrating data from different domains into one complete model. For the best output of this model they only had one condition that was to stay close to the empirical data. Neural models always had an advantage over normal box and arrow models. They can be used to explore more complex dynamics and they are mathematical in nature. This approach is better suited to explore Basal ganglia dynamics and advantageous in brain disorder modeling. To analyze and quantify the signals generated between subthalamic nucleus and globus pallidus external of Parkinsonian rats, Cruz et al. [49] have used time series analysis. Due to Chronic dopamine depletion, firing rates have been changed and there was strong beta band oscillations in STN-GPe network. There was also an increase in STN-GPe bidirectional interactions. This has been measured by generating mutual information. It might not only contribute to excessive synchrony between STN-GPe network but it also facilitate information flow between STN-GPe network and entire basal ganglia region. Shah and Alexandre [50] have also presented their extended model to more realistically formulate neural computations with more realistic structure of network and more realistic learning protocol. The model has been modified drastically but it did not affect the action of the network. This model will surely go to help the neuro-scientists for the better understanding of basal ganglion circuits and for information processing. But it needs to be accessed better with regard to biological data. It will also be advantageous to criticize this model for the improvement of the system. Role of dopamine need to be accessed for its influence on the system.

Santaniello et al. [51] have developed a model using post synaptic neurons to adjust the stimulation amplitude for reducing the neuronal oscillatory activity of brain. They had
this objective in mind to develop a control system of close loop. They have used the input taken from electrical signal feedback which was recorded by implanted for stimulation in the brain. They have simulated around 100 neurons in ventral intermediate nucleus. They have used the local field potential as the control variable for controlling DBS amplitude. To validate the proposed approach they have used thalamic neuron population, that exhibit the neuronal firing pattern which is there in ventral intermediate nucleus. Their model has generated the spike trains that matched the spikes train recorded from ventral intermediate nucleus in both tremor and tremor free subjects. For the sake of simplicity they have also used point process approach. Shah and Alexandre [50] has extended their model for more realistic results for more realistic network of neurons. Their model is best suitable for neuro-scientists for better understanding of information representation. Kang and Lowery [52] suggested that there is critical role of synchronized oscillatory patterns generated in basal ganglia network in Parkinson disease. There are evidence that suggest the importance of such oscillation in pathophysiology of Parkinson disease. They have used a new closed loop network model to explore the interaction and generation of network oscillations. They have also studied the suppression of those oscillations during deep brain stimulation (DBS). They mentioned that due to the depletion of dopamine, the interaction between neuronal oscillations between subthalamic nucleus and cortex has increased. it lead to synchronized oscillatory activity. By applying deep brain stimulation, a decrease in beta band frequencies and tremor was observed. Their research played an important role in identifying the new insights of unwanted oscillatory activities [52]. Johnson et al. [53] discussed that it is very difficult to identify a particular cell in the brain which can be treated by neuromodulation therapies for any kind of disorder. These therapies show great promise in the area where traditional methods fail to control the disease. Vyas et al. [54] also made clear in their work that degeneration of dopamine is the major
feature of Parkinson disease. This degeneration takes place in SNc (substantia nigra pars compacta). But the pathogenesis of Parkinson Disease is still unclear. They stressed upon the fact that the research has grown in the area of molecular pathways and on the molecular basis of parkinson disease but the answers to these question remains unanswered: 1. why dopamine degeneration takes place, 2. why degeneration takes place in SNc and 3. what is the cause of dopamine degeneration. Hence it becomes important to understand the mechanisms whereby pathology becomes widespread and the vulnerability of the dopaminergic neurons and the are some of the primary objectives of research in Parkinson disease. To study the pathogenesis of Parkinson disease, animal models are the best tools.

2.5 Literature survey for the role of dopamine in Parkinson disease symptoms

Dopamine degeneration in substantia nigra pars compacta SNc in basal ganglia is known to be the main cause of Parkinson symptoms. Santens et al. [6] has suggested that due to the deficiency of dopamine electrophysiological changes are caused in basal ganglia, which further lead to biochemical alterations that result in altered gene transcription. Krishnan et al. [55] proposed a model which describes that basal ganglia is involved in both learning and performance. It is shown in the pattern of dependence in terms of time that conform to behavioral data. The model is able to learn naturally, a double saccade task without invoking assumptions like 'inhibition of return' using the RL machinery of basal ganglia. It also confirms the data obtained in dopamine depleted condition in monkeys. They discussed that the striatum nucleus has D1 and D2 types of neurons and they depends upon dopamine in opposite way. Activity inside D1 neurons is increased
and that of D2 neurons is decreased with increase in dopamine levels. The work of Cruz et al. [49] is related with beta frequency oscillation in STN-GPe network. They have done non linear time series analysis. This was done to quantify the relationship and interaction between STN-GPe of Parkinsonian rats. They have shown that the decrease in dopamine changes the firing rates and lead towards beta oscillations. This also leads to increase in mutual interaction between subthalamic nucleus and globus pallidus external. The increased synchrony and reciprocal coupling leads to excessive beta oscillation synchrony in Parkinson information generation. The effect of this synchrony and coupling, travel through the entire basal ganglia.

Shah and Alexandre [50] have proposed an extended model by reducing the dimensionality and by using more realistic neural computations and more realistic structure of network. After dimension reduction, it still is of good quality. But it does not answer the influence of dopaminergic influence on the system. Krishnan et al. [55] have modeled the functions performed by basal ganglia. They have focused upon the function of saccadic eye movement. Their model represent main nuclei, striatum, subthalamic nucleus, globus pallidus, SNr and SNC etc. They have used reinforcement learning framework and shown the error of temporal difference with dopamine depletion. The main role in this is of striatum. There are different pathways, out of which indirect pathways play the role of explorer. They have used few parameter to evaluate the task of basal ganglia like direction selectivity, successive saccade task and conjunction searches. They have observed distraction in feature search and with distractions there in increase in number of linear searches. They discussed that there is increase in saccade reaction time and lack of search efficiency which supports the Parkinson symptoms. They have also suggested that there is no significant change in the firing rate of STN-GPe network but the correlation among these two is increased. Cruz et al. [49] also analyzed the effect of dopamine depletion on the information flow
between subthalamic nucleus and globus pallidus. They have compared the neuronal activity within Parkinson rats and non Parkinson rats. In Parkinson rats, they observed abnormal increased synchrony and beta oscillations, and abnormal oscillatory synchrony is acknowledged as the pathophysiological symptom of Parkinson disease. But it is still a topic to debate that what is the cause of increase in oscillatory activity. Galea et al. [56] show that there is dopamine sensitive deficit in the people suffering from Parkinson disease. There is large prediction error in the patients suffering with Parkinson disease. It has been concluded by performing an experiment for computing a probabilistic reaction time for healthy and Parkinson disease patients. They also discussed that Parkinson patients have low dopamine levels and they are weak in sensory information processing. Galea et al. [56] have also suggested that person with dopamine deficiency are also weak in selecting the probability of future actions which are selected on the basis of previous knowledge.

Davidson et al. [57] have also confirmed that the dopamine depletion is the characteristic of Parkinson disease. Decrease in dopamine modulate the oscillatory activity of beta band in basal ganglia. The decrease in dopamine level increases with time and it is said to be proportional with the beta band activity. The decrease in dopamine also increase the functional coupling within basal ganglia network. It is of great concern that the motor symptoms are only visible when there is more than 50 percent loss in the dopaminergic neurons. It is also been suggested by Schapira [58] that degeneration of dopamine is the main feature of Parkinson symptom. It is diagnosed by the consequence of degeneration of dopamine in SNC and suggested the importance in the development of treatments that can prevent or delay the progression of neuro-degenerative process that affects both non-dopaminergic and dopaminergic neurons. Dragicevic et al. [59] suggested that mid-brain neurons which releases dopamine are essential for various brain functions. These functions
are emotion, cognition, working memory and voluntary movement. These dopaminergic neurons display variety of cellular properties and projections and are affected in different ways in various disease like hyperactivity disorder, schizophrenia and Parkinson disease. Sulzer et al. [60] have discussed the role of dopaminergic neuron in temporal accumulation of extra-cellular dopamine neurons when there is successive action potentials. They have review that how axonal dopamine release is regularized by neuronal activity. They also reviewed how this release is regulated by auto-receptors and hetero-receptors. They said that bursting inside a cell can generate discrete dopamine transients and tonic activity may translated into a tonic extra-cellular dopamine level.

2.6 Literature survey for the importance of calcium current in Parkinson disease

There are various ionic current and chemicals in our brain which flow through different nucleus and are used for information transfer between different cells. Different researchers have discussed the important of those ionic currents. Our focus is on calcium current in Parkinson disease whereas every current has its importance. Song et al. [61] have demonstrated the role of $K^+$ conductance. They said the slow kinetics of $K^+$ conductance produces a short term cellular memory. This memory has no correlation with synaptic input. They suggested that subthalamic nucleus play an important role in the selection of motor function and they also suggested the $Ca^{2+}$ current in important in the regulation of subthalamic Neuron. Results reveals that subthalamic neurons display low voltage activated $Ca^{2+}$ channels and also display several high-voltageactivated sub-types. They have stressed upon the possibility of low-voltageactivated channels in the distribution to the dendritic processes. It has been proposed by Cornelisse et al. [62] that activation of
KCa− channel can be caused by Ca2+ channel. This activation is proportional to the phase shift relative to intracellular concentration of Ca2+. It has low threshold value in presence of NaC channel as shown in the feature characteristic in the Xenopus of Ca2+ oscillation.

Gillies [63] found out that there are three primary channels that play important role in distinguished behavior. These channels are: 1. low voltage activated calcium channel, high voltage activated calcium channel and a small current calcium activated potassium channel. They have constructed a computational model using electrophysiological and morphological data and a restricted set of channel specifications of the rat subthalamic nucleus. This model exhibited a wide range of electrophysiological characteristic of rat subthalamic neurons. Kaufman et al. [64] have shown that Ca2+/Na+ valence selectivity and conduction of a simple calcium channel forms a regular structure of conduction bands. It is separated by non-conduction bands. They suggested the importance of Ca2+ channels in conduction and connectivity between ions.

Cal et al. [65] have discussed the role of calcium current in information transmission. They said that it works as messenger. It is an almost universal second messenger. It regulates all important activities of eukaryotic cells. It is of great importance to various neurons, which have developed intricate pathways to couple biochemical machinery to the Ca2+ signal. Especially, Ca2+ contribute in the synaptic activity and transmission of the depolarizing signal. Gillis et al. [66] have discussed characteristics of Ca2+ in handling neurons of the SNc. Rivero-Ros et al. [67] also discussed the importance of Ca2+ in Parkinson disease. They stressed that recent studies provide strong evidence that changed Ca2+ homeostasis might underlie disease patho-mechanism and could be an inherent feature of all vulnerable neurons. They have summarized that how abnormal Ca2+ their selective vulnerability, may compromise neuronal health in the context of
environmental, aging and genetic stress. A better understanding about calcium and its various effect would definitely provide insight into the progression of Parkinson disease.

2.7 Literature survey for information processing in basal ganglia network and bistability of the model

There are abnormal activities in the basal ganglia due to Paarkinson disease and negative reinforcement learning as suggested by Bar-Gad and Bergman [68]. Shilnikov et al. [69] have proposed a mechanism that explains bi-stability in the system. Bi-stability is where either mode can be attained by an appropriate choice of initial conditions, bursting mode or tonic spiking mode. Many scientist suggests that the useful information is conveyed by the timings of the events discussed by Sunghan Kim and McNames, 2006 [70]. They have made the frequency tracker used to estimates the ITF displayed by the neural recordings of the events. To detect spikes at the early stage is of common practice. Tremors are the fluctuations in the mean firing rates. Wang et al. [71] have explained the process of bifurcation. Bifurcation occurs when the leakage conductance is lower than a special value. A simple and unified state feedback method is used to control the Hopf bifurcation of Hodgkin Huxley model. This method could be of great help to design, a new closed-loop stimulation systems for various neurological disorders. Brody and Korngreen [72] have discussed the importance of rat globus pallidus. Repetitive stimulation evokes complex modulations of globus pallidus activity. Computational studies have suggested one of the underlying mechanisms as short-term synaptic plasticity (STP). To explore the possible effect of STP during low and high frequency stimulation (HFS), the current study used simplified single compartment modeling on the activity of globus pallidus neurons. To do this they have constructed a Globus pallidus neuron model which is connected to a small
network of neurons. These connecting neurons are: subthalamic nucleus (STN), striatum (Str) and GP collateral. These findings suggests that there exists slower short term dynamics in globus pallidus. Computational model can be further helpful in understanding the repetitive stimulation of GP.

Pavlides et al. [43] have identified that the mutually connected network of excitatory and inhibitory neurons generate oscillations. Changes in the cortical and striatal input changes this oscillations. Yadav et al. [73] have discussed the existence of extensors myopathies, segmental or generalized dystonia, anterior horn cell disorders, and muscle disorders in Parkinson disease. They suggested that deep brain stimulation have been a success in severe cases of Parkinson disease. Magrinelli et al. [74] have also suggested bradykinesia, rest tremor, and rigidity as cardinal motor features of Parkinson disease. These symptoms appear in the early stages of the disease and these symptoms largely depend on degeneration of dopamine. Advanced and intermediate stages of Parkinson disease are characterized by dyskinesia and motor fluctuations. Motor and non-motor symptoms are secondary symptoms to the loss of dopaminergic neurons. Motor problems, including balance, posture, and gait disturbances are result of non dopaminergic dysfunction. Such information becomes the basis for the neurosurgical, pharmacological and rehabilitative approaches to Parkinson disease. Michel et al. [75] have also suggested that Parkinson disease is a multi-factorial neuro-degenerative disorder, which is largely unknown. Primary clinical feature of the disease is progressive impairment of voluntary motor control. Loss of midbrain substantia nigra dopamine (DA) neurons causes the disease. They have presented a synthetic overview of cell autonomous mechanisms. This mechanism is likely to participate in dopaminergic neuron death in both inherited forms and sporadic and of the disease. Particularly they have described that aggregation and protein misfolding, endoplasmic reticulum (ER) stress and loss of calcium homeostasis produce cellular dis-
turbance to vulnerable DA neurons. In Parkinson disease they mutually cooperate to promote neuronal loss.

Muralidharan et al. [76] have discussed that how the Parkinson symptoms are developed, still remains poorly understood. It is not completely understood, how neurophysiological changes in the basal ganglia thalamo-cortical circuit are associated with the development of Parkinsonian motor signs. There is a change in mean discharge rate and Muralidharan et al. [76] have emphasized changes in increased oscillatory activity within the beta range. Perez-Lloret and Barrantes [77] also explained the degeneration of dopaminergic neurons as the most frequent motor symptoms of Parkinson Disease. They have reviewed the characteristics of cholinergic deficits in Parkinson disease. Root of several motor and cognitive functions remains at the synaptic dysfunction, gait dysfunction, psychosis, cognitive deterioration, autonomic dysfunction, sleep abnormalities and altered olfactory function.

For treating Parkinson disease motor symptoms and of inhibitors of the enzyme, several results suggested the clinical usefulness of antimuscarinic drugs acetylcholinesterase for the treatment of dementia. These pedunculopontine nucleus deep-brain stimulation and inhibitors and might also be effective in preventing falls. Finally, in Parkinson disease animal models, for treating levodopa-induced dyskinesias and cognitive impairment and as neuroprotective agents, several drugs acting on nicotinic receptors have proved efficacious. But the results in human patients are still not promising.