Chapter 1

General Introduction
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1.1 Preface

Parkinson’s disease (PD) is a neurodegenerative movement disorder. As of 2005, approximately 4.1 to 4.6 million PD patients have been reported and it is projected that this number would reach 8.7-9.3 million by 2030, worldwide (Dorsey et al. 2007). Disease onset usually occurs around the age of 50, although PD is now being reported in people at much younger ages. Cardinal motor symptoms of PD include tremor, rigidity, akinesia and slowness of movement; while combination of symptoms exhibited and severity of each symptom varies from patient to patient. PD results from the loss of dopaminergic neurons in a small nucleus in the brain, the substantia nigra pars compacta (SNc). The SNc is part of a group of nuclei known as the Basal Ganglia (BG) which among others contribute to motor control. First symptoms of PD are observed when approximately 75-80 % of dopaminergic neurons are lost in the SNc. Loss of dopaminergic neurons in the SNc leads to an imbalance of activity patterns in brain regions involved with motor control.

Specific causes underlying degeneration of dopaminergic neurons remain unknown and a treatment which can stop the progression or reverse the effects of PD has not yet been found. Treatments available for PD are symptomatic. In the early stages of PD, different types of medication are used in order to increase dopamine levels and subsequently suppress the motor symptoms. These include dopamine replacement therapy (i.e. Levodopa), dopamine agonists, monoamine oxidase (MAO) - inhibitors or Catechol-O-methyl transferase (COMT) - inhibitors. Efficacy of medication decreases as time progresses since degeneration of dopaminergic neurons continues and in some patients severe side effects are observed (Obeso et al. 2000). Therefore, in the later stages of PD, surgical techniques such as lesioning or Deep Brain Stimulation (DBS) of specific brain regions are used (Benabid et al. 1991). Surgical techniques give rise to suppression of PD motor symptoms and in some cases enable the dosage of the medication used to be reduced (Rodriguez-Oroz et al. 2004; Wichmann and DeLong 2006).

Decreased efficacy of medication and side-effects associated with irreversible lesioning emphasized the need for alternative surgical treatment techniques. DBS is a brain pacemaker which involves delivery of high frequency pulses
to regions involved in motor control. DBS is a reversible surgical technique contrary to lesioning. Stimulation parameters used during DBS have been derived experimentally and are accepted as benchmark worldwide (stimulus frequency 120-180 Hz, stimulus amplitude 1-5 V, pulse width 60-200 µs) (Benabid et al. 1991). Despite the success of this surgical treatment technique in alleviating PD motor symptoms and wide-spread application worldwide, the mechanism behind the efficacy of DBS remains unknown (Dostrovsky and Lozano 2002; Hammond et al. 2007; Wichmann and DeLong 2006).
1.2 Basal Ganglia, Parkinson’s Disease and Deep Brain Stimulation

In the late 1980’s, a model for BG function was proposed based on experimental data obtained from MPTP treated primates (Alexander and Crutcher 1990; Alexander et al. 1986). This model has revolutionized the field, making it possible to identify surgical targets for movement disorders such as PD.

1.2.1 The Classical Model of the Basal Ganglia

The BG form complex parallel circuits, integrating various cortical inputs, and project onto the thalamus, which in turn projects back to the cortex, giving rise to the basal ganglia-thalamocortical loop (Fig. 1) (Alexander and Crutcher 1990; Alexander et al. 1986). The cortex projects to the striatum in a somatotopically organized fashion. The corticostriatal projection has an excitatory effect on the GABAergic striatal neurons. The striatal neurons in turn project onto the globus pallidus via two distinct pathways: direct and indirect pathways. The striatal neurons in the direct pathway project to the globus pallidus internum (GPi), and have an inhibitory effect on the GPi neurons. The striatal neurons in the indirect
pathway project to the globus pallidus externum (GPe), which inhibit the subthalamic neurons. The subthalamic neurons project onto the GPi neurons via an excitatory pathway. Therefore, the striatal neurons in the indirect pathway have an overall excitatory effect on the down-stream GPi neurons.

In the classical model, the output of the BG is determined by the opposing effects of the direct and indirect pathways on the GPi neurons, which in turn have an inhibitory effect on the thalamocortical neurons and the brain stem (Alexander and Crutcher 1990; Alexander et al. 1986). Experiments have shown that during movement, activity in the GPi is suppressed; giving rise to the hypothesis that facilitation of the direct pathway gives rise to facilitation of movement while facilitation of the indirect pathway gives rise to suppression of movement (Alexander and Crutcher 1990; Alexander et al. 1986; Chevalier and Deniau 1990).

Loss of dopaminergic neurons in the SNc during PD is believed to result in reduced inhibition of the striatal neurons in the indirect pathway and reduced excitation of the striatal neurons in the direct pathway, according to the classical model (Fig. 1B). Together, this results in an imbalance of activity in the direct and indirect pathways and leads to excessive inhibition of the GPe neurons and reduced inhibition of the GPi neurons (Fig. 1B). Therefore, during PD, the subthalamic and GPi neurons exhibit elevated activity levels; leading to excessive inhibition of the thalamocortical neurons and the brain stem (Alexander and Crutcher 1990; Alexander et al. 1986).

Surgical targets used in the treatment of PD have been chosen based on the classical model. Applying lesions to the subthalamic nucleus (STN) or the GPi leads to a reduction in the activity levels of these hyper-active nuclei, resulting in marked improvement in the PD motor symptoms (Benazzouz et al. 2000; Boraud et al. 1996). Later on, it was discovered that applying DBS to the STN or the GPi gives rise to similar clinical outcomes as lesioning these regions (Dostrovsky and Lozano 2002; Wichmann and DeLong 2006).

1.2.2 The revised model of the Basal Ganglia

There are several issues which are not addressed by the above mentioned classical model of the BG (Obeso et al. 2000). Recent immunostaining studies point out that striatal
neurons in the direct and indirect pathways are not as segregated as it is proposed by the classical model (Aizman et al. 2000; Yung et al. 1996). Moreover, it has been observed that connection levels between the striatal neurons increase significantly following dopamine depletion (Onn and Grace 1999). Dopamine has been shown to have a modulatory effect on the excitability of the striatal neurons rather than having a direct excitatory or inhibitory effect (Chase and Oh 2000; Kotter 1994). In the classical model, the effect of dopamine is limited to the striatum while there is growing evidence indicating that the effect of dopamine on the basal ganglia-thalamocortical loop is much more extensive, affecting more nuclei than originally anticipated (Joel and Weiner 2000; Smith and Kieval 2000).

In the classical model, hyperactivity of the subthalamic neurons during PD is explained via the increased inhibition of the GPe neurons. There is growing experimental evidence indicating that hyper-activity of the subthalamic neurons could arise from the interaction of many other mechanisms. The subthalamic neurons receive excitatory input from the cortex via the hyper-direct pathway and it has been noted that in 6-OHDA lesioned rats, activity levels in the STN increase prior to depletion of the striatal dopamine and that hyper-activity of the subthalamic neurons is not necessarily accompanied by a reduction in the GPe activity levels (Bezard et al. 1999; Hartmannvonmonakow et al. 1978; Nambu et al. 1996; Nambu et al. 2002; Obeso et al. 2000; Vila et al. 2000). Additionally, loss of dopaminergic neurons in the SNc could have a direct effect on the subthalamic neurons and it has been shown that dopamine modulates firing patterns of the subthalamic neurons (Brown et al. 2001; Levy et al. 2002).

1.2.3 Paradox of Deep Brain Stimulation

Remarkably, both lesioning and DBS of a specific brain region leads to alleviation of PD motor symptoms (Dostrovsky and Lozano 2002; Wichmann and DeLong 2006). The similarity in clinical outcomes obtained from lesioning or high frequency stimulation have perplexed researchers regarding the mechanism behind the efficacy of DBS. Based on the classical model, one would expect that high frequency stimulation of the hyper-active nuclei such as the STN or the GPi would reduce the activity patterns at the stimulated nucleus in order to result in alleviation of PD motor symptoms (Dostrovsky
Experimental studies have supported this hypothesis indicating that activity levels at the stimulated nucleus do indeed decrease (Benazzouz et al. 2000; Boraud et al. 1996). But it was not too long before these experimental results were challenged by contradicting evidence indicating that despite a decrease in the activity levels in the STN due to stimulation, activity of the down-stream GPi neurons increased (Hashimoto et al. 2003) and changes in firing rate exhibited dependency on DBS frequency (Dorval et al. 2008). Experiments by Hashimoto et al. (2003) were the first experiments showing down-stream effects of DBS; suggesting that clinical efficacy of DBS might not be due to reversible lesioning of the stimulated nucleus. The clinical study of Holsheimer et al. (2000) and the computational studies of McIntyre et al. (2004a and 2004b) provided a plausible explanation accommodating these two seemingly paradoxical experimental observations: somatic block at the stimulated nucleus and down-stream activation during DBS (Hahn et al. 2008; Holsheimer et al. 2000; Johnson and McIntyre 2008; McIntyre et al. 2004a; McIntyre et al. 2004b; McIntyre et al. 2004c; Miocinovic et al. 2006). These studies have shown that DBS inactivates cell bodies and activates passing fibers; hence transmitting the DBS induced high frequency activity patterns to down-stream nuclei (Hahn et al. 2008; Johnson and McIntyre 2008; McIntyre et al. 2004b; McIntyre et al. 2004c; Miocinovic et al. 2006).

Researchers were faced with a movement disorder strongly correlated with increased activity levels of the GPi and a surgical treatment technique alleviating the PD motor symptoms by further increasing the GPi activity levels (Hashimoto et al. 2003; Obeso et al. 2000). This has given rise to a departure from the firing-rate based models for PD and opened the door to activity pattern based depictions (Obeso et al. 2000).

### 1.2.4 Oscillations and the Basal Ganglia

The BG neurons possess the essential cellular dynamics for exhibiting oscillatory activity patterns (Bevan et al. 2002; Boraud et al. 2005). At a neuronal level, oscillatory activity patterns are generated as a result of the interaction between slow and fast membrane currents and the modulatory effect slow currents have on the faster membrane dynamics (Izhikevich 2000). Oscillations have been recorded from
different BG nuclei, both at a single cell level and at a neuronal population level. Furthermore, the theoretical model put forward by Terman et al. (2002) has demonstrated that a network of subthalamic and GPe neurons can exhibit both irregular firing patterns and synchronized oscillations depending on the level of inhibition the GPe neurons receive from the striatum via the indirect pathway (Terman et al. 2002).

Local field potential (LFP) recordings made in the putamen and caudate of macaque monkeys performing visuo-motor tasks have shown episodic oscillatory activity patterns in the beta frequency band (13-30 Hz) (Courtemanche et al. 2003). It has also been observed that beta band oscillations recorded from different locations inside the putamen and caudate are synchronized and that the level of synchrony and content of the beta band oscillations vary depending on the task being performed (Courtemanche et al. 2003). Use of DBS for the treatment of PD has enabled researchers to record LFPs from nuclei such as the STN or the GPi, while patients are performing voluntary motor tasks (Kuhn et al. 2004). A decrease in the beta band activity has been observed in the LFPs recorded from the STN prior to execution of externally paced voluntary movement (Kuhn et al. 2004). In the same study, it has also been reported that beta band activity is modulated differently depending on whether movement will be facilitated or suppressed (Kuhn et al. 2004). Additionally, level of synchrony in the beta band is reported to be context and task dependent (Kuhn et al. 2004).

On the other hand, during PD, the BG exhibit continuous synchronized oscillatory activity patterns, predominantly in the beta frequency band (Boraud et al. 2005; Brown 2003; Brown et al. 2001; Cassidy et al. 2002; Chen et al. 2007; Hammond et al. 2007; Kuhn et al. 2008; Kuhn et al. 2006; Kuhn et al. 2005; Kuhn et al. 2009; Kuhn et al. 2004; Trottenberg et al. 2006). It has been demonstrated that oscillatory activity patterns observed in the BG are strongly correlated with PD motor symptoms (Chen et al. 2007). It has also been reported that dopamine replacement therapy (i.e. Levodopa) leads to suppression of continuous synchronized oscillatory activity patterns in the beta band and enhancement of gamma band activity patterns (Kuhn et al. 2006). This observation has lead to the hypothesis that during PD, pathological synchronization which occurs in the basal
ganglia-thalamocortical loop is disrupted and suppressed by the treatment techniques used for the alleviation of PD motor symptoms such as Levodopa, lesioning and DBS (Brown 2003; Kuhn et al. 2008; Kuhn et al. 2006).

1.2.5 Paradox of Deep Brain Stimulation re-visited

DBS which owes its clinical success to the classical model of the BG (Alexander and Crutcher 1990; Alexander et al. 1986) has enabled acquisition of neuronal data from sub-cortical structures which have been used to revise the classical model. LFPs and single unit recordings have shown that firing patterns together with firing rate play a crucial role in normal functioning and in pathophysiology of the BG nuclei. While episodic activity patterns in the beta band contribute to normal functioning of the BG nuclei, continuous synchronized activity patterns in the same frequency band disrupt this function during PD. It is now hypothesized that DBS regularizes BG activity patterns and disrupts generation of continuous synchronized oscillations, alleviating PD motor symptoms. Experimental recordings obtained from the GPe, GPi and ventral part of the thalamus during STN-DBS have shown regularization in activity patterns providing corroborative evidence for the afore mentioned hypothesis (Dorval et al. 2008; Hashimoto et al. 2003).

1.2.6 Deep Brain Stimulation Parameters

An inverse relationship between DBS frequency and intensity, required to suppress PD motor symptoms, has been reported: i.e. as DBS frequency is reduced, stimulus intensity should be increased in order to sustain clinical efficacy (Benabid et al. 1991). Experimental work of Dorval et al. (2008) have highlighted that high frequency stimulation results in regularization of overtly synchronized BG activity patterns while low frequency stimulation is not as effective as high frequency stimulation for the same stimulus intensity.

With the realization that PD is associated with increased activity patterns in specific frequency bands and is not only dependent on changes in firing rate, research has been focused on whether frequencies less than the currently used stimulation frequencies could be used in the treatment of PD. Recent studies conducted by Neagu et al. (2009) and Tsang et al. (2009) indicate that stimulating at frequencies in the lower
gamma frequency band can lead to suppression of synchronized activity patterns in the beta band, similar to high frequency stimulation (Neagu et al. 2009; Tsang et al. 2009). Specific frequencies to be used during DBS have been derived in a patient specific manner in these studies (Neagu et al. 2009; Tsang et al. 2009).
1.3 Thesis Outline

There exists several competing hypothesis regarding the mechanism of DBS and why specifically high frequency stimulation is needed for suppression of PD motor symptoms. Theoretical and experimental studies at a neuronal and population level continue to shed light on the mechanism of DBS. In this thesis, we employ computational models in order to test certain hypothesis put forward in the field regarding the mechanism of DBS and efficacy of high frequency stimulation. Moreover, we make use of cellular recordings in order to test the validity of specific observations made using computational models. We incorporate population level recordings obtained from PD patients into a theoretical population level model in order to infer possible neuronal mechanisms giving rise to the recordings. Last but not least, we analyze experimental recordings obtained from PD patients and assess which signal properties are selective to certain brain regions of interest.

1.3.1 Utilizing theoretical models for investigating mechanism of Deep Brain Stimulation

A computational model put forward by Rubin and Terman (2004) investigated synchronous oscillatory activity patterns in the BG and the effect of high frequency stimulation (Rubin and Terman 2004; Terman et al. 2002). It has been highlighted in these studies that the subthalamic and GPe neurons exhibit oscillatory activity patterns depending on the level of inhibition the GPe neurons receive from the striatum. They have also suggested that during PD, relay fidelity of the thalamocortical relay neurons which receive phasic inhibitory input from the GPi is impaired and high frequency stimulation restores functionality of the thalamocortical relay neurons by replacing the phasic inhibition these neurons receive with constant inhibition (Rubin and Terman 2004).

In the second chapter of this thesis, we built upon the theoretical model of Rubin and Terman (2004) and investigated using a computational model how DBS parameters modulate the BG network and the down-stream thalamocortical relay neurons. We observed that during PD, the thalamocortical relay neurons are predominantly driven by oscillatory activity patterns from the BG and DBS suppresses relay of pathological BG oscillations and restores
the excitatory inputs that the thalamocortical relay neurons receive as the principal drivers of the thalamocortical output. We observed an inverse relationship between DBS frequency and amplitude, needed to suppress relay of pathological BG oscillations to the cortex. The inverse relationship is dependent on the BG network dynamics and the cellular properties of the thalamocortical relay neurons. High frequency stimulation is more effective in regularizing and de-synchronizing the BG activity patterns and in modulating membrane dynamics of the thalamocortical relay neurons.

In chapter 3, we investigated membrane properties of a thalamocortical relay neuron using numerical bifurcation analysis and observed that the thalamocortical relay neuron exhibits bistability (i.e. non-spiking or sub-threshold oscillations and rebound spiking locked to the bursting frequency of the pre-synaptic GABAergic GPi neurons). The thalamocortical relay neuron model is also used to investigate possible mechanisms underlying the existence of a clinically effective stimulation window, i.e. low stimulation amplitude and high frequency. To this end, we studied the effect of DBS parameters on thalamocortical relay of excitatory cortical inputs and pathological BG oscillations. We observed that low amplitude high frequency stimulation suppressed relay of pathological BG oscillations. However, excessively high amplitude high frequency stimulation blocked relay of excitatory cortical inputs. Together, this gave rise to a parameter window, where relay of low frequency oscillatory BG input is suppressed and relay of excitatory cortical input is preserved.

1.3.2 Parameters used during Deep Brain Stimulation

As an extension to the theoretical models, in chapter 4, we investigated whether theoretical observations regarding DBS parameter dependency of thalamocortical function can be reproduced experimentally. To this end, we conducted patch clamp experiments using an in-vitro slice preparation. Together with the validation that our theoretical model can be reproduced experimentally, we also observed that high frequency stimulation suppresses relay of oscillations by the thalamocortical relay neurons at specific phases of the inhibitory oscillatory input. Building on this observation, we applied phase locked pulses at different phases of the inhibitory oscillation and observed that when the pulse is
applied at the right phase of the oscillation, relay of oscillations by the thalamocortical relay neuron is suppressed comparable to high frequency stimulation.

1.3.3 Deep Brain Stimulation and target localization

In chapter 5, we investigated use of various signal processing techniques and developed an automatic STN detection algorithm based on a large number of surgical microelectrode recordings (MER). First, we determined which signal features extracted from the MERs reliably distinguish the STN from the surrounding structures and how selective these measures were. The algorithm developed, used combinations of measures to take into account variability among patients. To ensure that the algorithm could be extended to be used during surgery, it was tested on data which was not preprocessed and cleaned, and additionally, all methods used in the algorithm were chosen such that translation to a real-life system could be attainable.

1.3.4 Merging neuronal recordings with theoretical models

Basing theoretical models on experimental recordings and observations is crucial for the reliability of the theoretical models developed. Single unit recordings have been incorporated into theoretical models which were then used for investigating mechanisms of DBS (Guo et al. 2008). In addition to single unit recordings, population level recordings can also be obtained such as electroencephalograms (EEG) from cortical regions and LFPs from sub-cortical regions. Dynamic Causal Modeling is a theoretical framework which can be used to infer underlying network dynamics from these population level recordings through optimization of neural mass model parameters given a set of recordings and a network topology. In chapter 6, we investigated use of dynamic causal modeling to study modulatory effects of dopamine on connectivity strengths within the basal ganglia-thalamocortical loop. To this end, EEG recordings obtained during STN-DBS were used both when the patients were off Levodopa and when the patients were on Levodopa. Variants of the model which differed with respect to connections that were allowed to exhibit dopamine dependent changes were compared using Bayesian Model Comparison. This
comparison was used to establish which connectivity changes within the basal ganglia-thalamocortical loop best explain the differences in the recordings arising from administration of Levodopa.
Experimental measurements: from micro to macro

Cellular recordings

Patch clamp: Patch clamp technique allows the study of single/multiple ion channel(s) or whole cell. There are different types of patch-clamp experiments such as on-cell patch, and whole-cell patch. Depending on the type of patch-clamp experiment performed different membrane properties can be studied. Patch clamp experiments have been extensively utilized in defining membrane properties of different types of neurons and in building up detailed theoretical models, capturing various ion channel properties. Intracellular MERs allows one to record the potential difference between the intra-cellular space and a reference electrode. Intracellular MERs were used extensively by Hodgkin and Huxley who later on introduced voltage-clamp technique which is used to keep voltage across the membrane constant.

Population level recordings

Local Field Potential (LFP): LFP is a type of extracellular MER. LFP captures the slow dynamics and reflects synchronized activity patterns of a network of neurons. Synchronized activity patterns captured by LFPs reflect both synchronized sub-threshold oscillations and synchronized spike patterns. During PD for instance, LFPs obtained from different BG nuclei have components in the theta and beta frequency bands reflecting the synchronized oscillatory activity patterns exhibited by underlying neuronal units.

Electroencephalography (EEG): EEG recordings similar to LFPs, reflects synchronized activity patterns of underlying neurons. EEGs are generally obtained using electrodes placed on the scalp of the subject.

Hybrid recordings

Microelectrode recording (MER): MER is generally used during surgical procedures or during in-vivo/in-vitro experiments to record single/multiple unit activity patterns. Extracellular MERs record electrical activity of neuron(s) in the vicinity of the recording electrode. Types of signals that can be captured by extracellular MERs are usually fast electrical events such as action potentials. Extracellular MERs also capture the activity of the surrounding neurons thus enabling the study of both unit and population activity patterns.
Computational models: from micro to macro

Cellular models

Hodgkin and Huxley made use of intra-cellular recordings and voltage-clamp technique to study the ionic mechanisms underlying an action potential. Based on these cellular recordings, they developed sets of equations capturing the basic ionic mechanisms resulting in an action potential. Majority of single cell models used today are based on the formalism put forward by Hodgkin and Huxley, first published in 1952. Cellular morphology can be incorporated into a multi-compartment model where each compartment is described by a group of interacting ion channels. Conversely, dependency on the cellular morphology and dimensions can be removed and the neuron can be represented as a point process.

Population models

Large scale neural populations can be represented via neural mass models where dynamics of individual neurons making up the population are lumped together into series of coupled equations. Neural mass models can be used to study spontaneous or event related oscillations at a population level. These models can also be used to investigate physiological mechanisms underlying LFPs where population dynamics are represented as an overall increase or decrease in the firing rate of the population.
References


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