An Engineering Model of Lower Thalamo-Cortico-Basal Ganglionic Circuit Function

By

Eugene J. Lim

Submitted to the Department of Electrical Engineering and Computer Science in Partial Fulfillment of the Requirements for the Master of Engineering in Electrical Engineering and Computer Science at the Massachusetts Institute of Technology

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Abstract

An engineering model of lower thalamo-cortico-basal ganglionic circuit functionality was extended and tested. This model attempts to explain the circuitry of the basal ganglia, examine its functional properties, and integrate these properties into an understanding of the diseases of the basal ganglia, such as Parkinson's disease and Huntington's disease. Using this model, simulations of various movements were developed, specifically those of the following: 1) one-step, cruise movements, 2) asynchronous, cruise movements, and 3) sequential cruise movements. Results of these movements include simulated movements of both normal patients and patients with movement disorders.

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Chapter 1: Introduction

The basal ganglia are a collection of subcortical nuclei that play an important role in motor control. These nuclei include the caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. Their primary input comes from the cerebral cortex, and their primary output goes back to the cortex through the thalamus. The importance of the basal ganglia in the control of movement was observed in clinical studies of patients with a specific set of movement disorders, which have become known as Parkinson's disease and Huntington's disease. These movement disorders often do not result in a focal disability, such as movement of one's arm. Rather, they appear to produce difficulties in the general control and initiation of movement.

While early theories viewed the basal ganglia as having merely a modulatory effect on motor control, more recent research has implicated the basal ganglia as having prominent roles in the contextual analysis of the environment and the use of this information for the formation and execution of motor programs and other aspects of intelligent behavior (Houk 1995). Some of these hypothesized roles include: sensory-motor associative learning, reinforcement learning, procedural learning, temporal order learning, choosing between competing actions, initiation of voluntary movement, working memory, and volition.

Despite the abundance of research on the anatomy, physiology, and pathology of the basal ganglia over the past few decades, there is little consensus as to the exact role the basal ganglia plays in behavior and motor control (Graybiel, 1995). While numerous models of basal ganglionic function have been proposed, relatively few are computational in nature. As a result, there are few simulations of such function that exist for the testing

of their hypothesis and comparing their results to neurological and physiological data. With that being said, the general goal of this thesis is to extend the understanding of the circuitry of the basal ganglia, examine some of its functional properties in health, and dysfunctional properties in disease.

Chapter 2: Background and Problem Statement

2.1 Anatomy of Basal Ganglia

To gain a better understanding of basal ganglionic function, it is necessary to first review the basic anatomy and circuitry of the basal ganglia. The basal ganglia receive input from many areas of the cerebral cortex and then project their output back to the frontal areas of the cortex through various parallel pathways (Alexander and Crutcher, 1990). Most of the cortical input is received by the striatum, which consists of the caudate and the putamen. The caudate circuit is thought to control the assembly of overall motor plans, while the putamen circuit is thought to scale the intensity of execution of motor plans in the context of task requirements (Brooks, 1986). The striatum projects primarily to the globus pallidus and substantia nigra. The globus pallidus is divided into two functionally different segments: the internal (GPi) and external (GPe) segments. The substantia nigra is also divided into two parts: the pars compacta (SNpc) and reticulate (SNpr). The GPi and the SNpr send the main signals out of the basal ganglia. These areas project to the thalamus, which are reciprocally connected with the frontal areas of the cortex.

This collection of projections from the cortex to the basal ganglia and then back to the cortex via the thalamus are called the cortico-basal ganglionic loop. This loop is illustrated in Figure 1. As stated earlier, the striatum receives a diverse output from nearly all of the neocortex. The striatum preserves the topography of the glutaminergic, excitatory afferents from the cortex (Berns and Sejnowski, 1995). The striatal projection neurons, which are GABAergic and inhibitory, project to the globus pallidus. In addition,

they also project reciprocally to the substantia nigra, the brain's primary source of dopamine. The GPe projects via GABAergic inhibitory neurons to the subthalamic

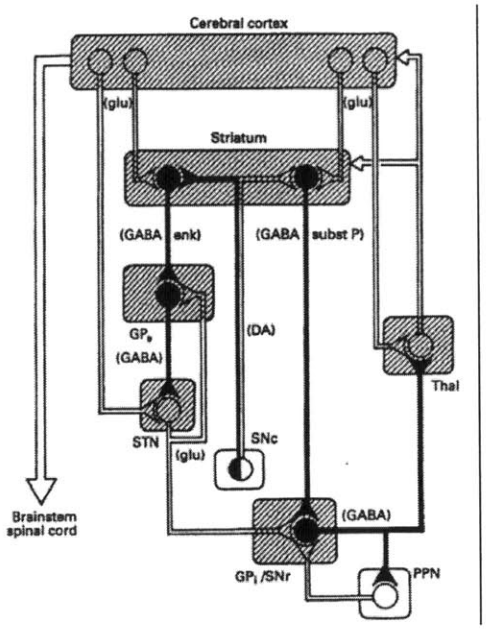

Figure 1: Overview of the main circuits and neurotransmitters involved in the thalamo-cortico-basal ganglionic loop. Excitatory connections are shown as open projections, while inhibitory projections are shown as filled. (Adapted from Alexander and Crutcher, 1990 – formal permission pending)

nucleus (STN). The STN also receives an excitatory cortical input. The STN projects via diffuse excitatory neurons to the GPi. Thus, the GPi receives an inhibitory projection from the striatum and an excitatory projection from the STN. The projection from the striatum to the GPi is called the direct pathway, while the projection from the striatum to the GPe, then to the STN, and then to the GPi is called the indirect pathway. It is believed that the direct pathway in the basal ganglionic circuit facilitates cortically initiated movements while the indirect pathway in this circuit inhibits such movements. The result of the direct and indirect pathway is smooth, coordinated movement.

2.2 Diseases of the Basal Ganglia

As mentioned earlier, diseases of the basal ganglia rarely involve a focal disability, such as the inability to move a limb. Rather, they result the loss of movement features, such as the initiation and control of movement. Such features can be classified into two opposing classes – hyperkinesias and hypokinesias. Hyperkinesias consist of excess or spontaneous involuntary movements while hypokinesias consist of a lack of or resistance to voluntary movement. From this perspective, there are two prototypical diseases of the basal ganglia – Parkinson's disease and Huntington's chorea. Parkinson's disease was first discovered in 1817 by James Parkinson, and Huntington's disease was discovered in 1872 by George Huntington (Cote and Crutcher, 1991).

Parkinson's disease is a hypokinetic disorder that is marked by akinesia/bradykinesia, rigidity, and tremor at rest. Akinesia refers to lack of voluntary movements, while bradykinesia refers to slowness of movement. Rigidity can be thought of as an involuntary resistance to passive manipulation or inability to change from a current position or state. Tremors are substantially oscillatory movements that result during voluntary movement or can occur at rest (Rothwell, 1994). Huntington's disease, at least in its early stages is chiefly a hyperkinetic disorder that is characterized by chorea, ballism, and atheosis. Chorea is the main symptom of Huntington's disease, and it involves excessive and erratic involuntary movements. Hemiballism, another movement disorder, involves rapid flailing or jerking movements.

These diseases appear to represent the two opposing extremes on the continuum of voluntary movement disorders caused by basal ganglionic lesions. From these features it was considered possible that these movement disorders result from imbalances in

specific neurotransmitters that contribute differently to the direct and indirect pathway in the basal ganglia. However, the detailed neurochemistry circuitry of the basal ganglia necessary to substantiate this theory was unknown until the mid-20th Century. It was not until the late 1950s that Oleh Hornykiewicz discovered by post-mortem examinations of Parkinson's patients that dopamine levels in their brains were drastically low and that there was significant loss of nerve cells in the substantia nigra. Parkinson's disease therefore became the first example of brain disease that was associated with a specific neurotransmitter (Cote and Crutcher, 1991). Huntington's disease was later found to result from the degeneration of cholinergic and GABAergic neurons in the striatum, in particular those that project to the GPi and SNpr. Note that both diseases involve the death of specific cells in the basal ganglia, which result in the reduction of specific neurotransmitters.

Figure 2 illustrates several models of how imbalances in specific neurotransmitters can lead to various movement disorders in the basal ganglia (Albin et al., 1989). Figure 2a shows the circuitry of the basal ganglia in a normal person. In Figure 2b, we see that lesions in the STN lead to a decrease in the excitatory glutaminergic input to the GPi and SNpr. The decrease of inhibitory output from these neurons result in disinhibition of the thalamus. This increase in thalamic activity can lead to over-excitation of the frontal areas of the cortex, which may result in the excessive or spontaneous movements found in those with hemiballism. In Huntington's disease (Figure 2c), we see that degeneration of neurons in the striatum result in a decrease of inhibition of the GPe and SNpr. This leads to an increase of GPe activation, which

produces greater inhibition of the STN. This, in turn, results in disinhibition of the thalamus, though less severe than in hemiballismus.

In general, these movement disorders appear to be due to an imbalance in the contributions of the direct and indirect pathways to the output nuclei of the basal ganglia. Parkinson's disease is caused by over-activation of the indirect pathway and under-activation of the direct pathway, while hemiballism and Huntington's disease are caused

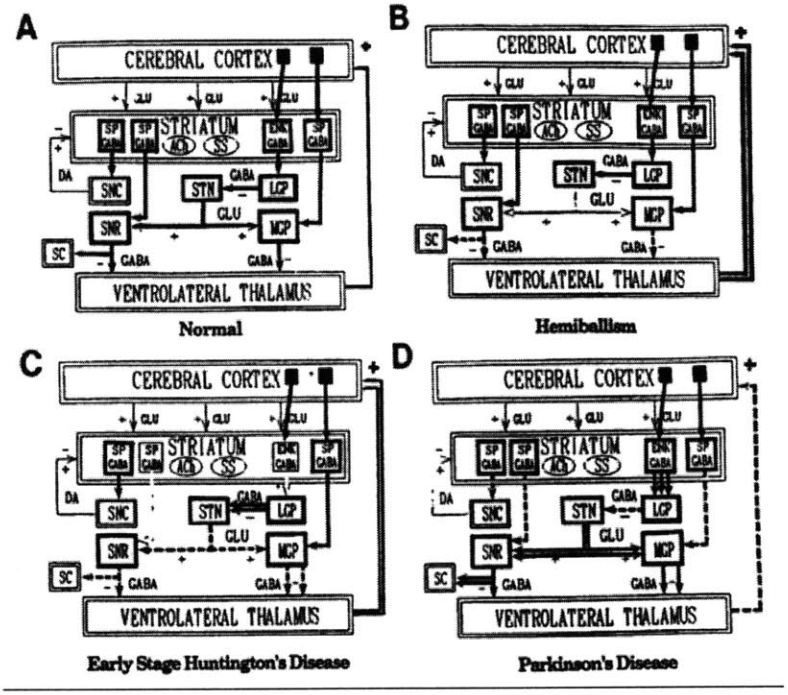

Figure 2: Ovals represent interneurons and boxes represent projections neurons. Doubling arrows represent a functional increase in a projection's activity, while interruption of arrows represents a functional decrease in activity without loss of anatomical integrity. The barely visible lines represent a degeneration of neurons and projections. (Adapted from Albin et al., 1989 – formal permission pending)

by over-activation of the direct pathway and under-activation of the indirect pathway. The direct pathway is a positive feedback loop through two inhibitory connections which cancel (disinhibition), so over-activation of the direct pathway will produce over-activation of the frontal cortical areas. Furthermore, under-activation of the direct pathway will produce under-activation of the frontal cortical areas. The indirect pathway

acts as a negative feedback loop, thus counteracting the direct pathway. Over-activation of the indirect pathway results in under-activation of the cortex while under-activation of the indirect pathway results in over-activation of the cortex.

Given these observations, one would expect that such disorders could be alleviated by partially inducing the causes of the opposite disorders. For example, some of the symptoms found in Parkinson's disease could be relieved by lesioning the STN (Albin et. al., 1989). This would reduce the activity of the GPi, thus negating the effects of having an under-active direct pathway and an over-active indirect pathway. Moreover, some of the symptoms found in Huntington's disease could be relieved by lesioning the GPe. This would counteract the effect of having over-excitation of the GPe (Albin et al., 1989).

2.3 Current Issues Regarding Basal Ganglia Function

2.3.1 General Direction of Basal Ganglia Modeling

It has been found that the basal ganglia processes cortical inputs and sends outputs to the thalamus and back up to the cortex (Alexander et al., 1996). Their involvement in the completion of the motor loop initially made the basal ganglia a focus of research. Questions about the basal ganglia's involvement in overall motor control arose: Are they responsible for directing movement? Are they involved in the planning or learning of a movement or sequence of movements? Do they affect the timing of a movement? What are the diseases of the basal ganglia, and how to they interfere with normal function? Why is the basal ganglia needed within the motor loop at all? These

questions and many others were a precursor to the first step of modeling simple arm movements and the basal ganglia's role in these movements.

2.3.2 Simple and Compound Movements

From a general perspective, all movements can be classified into two major categories – simple movements and compound movements. Simple movements are single, point-to-point movements whereas compound movements can involve multiple joints and/or multiple movements. In addition, compound movements can be synchronous or asynchronous. In considering multi-joint movements that are not synchronous, one would expect that there is an element of programming or switching taking place. For example, if a motor program involved moving one's arm and hand to grasp an object that is some distance away, what mechanism allows such controlled movement to take place? How are the basal ganglia involved in such movements?

Before answering these questions, it is necessary to explain why the basal ganglia are important in both simple and compound movements. In the case of simple movements, it has been found that the basal ganglia act as a switcher of frontal cortical neural circuits (Berns and Sejnowski, 1998). Furthermore, the approximate 10-Hz oscillation found in slow finger movements is consistent with the existence of an underlying high-speed switching mechanism (Vallbo and Wessberg, 1993). Finally, temporal accumulation of microelectrode stimulation effects in the sensorimotor cortex to produce movement and posture (Graziano et al., 2002), and the existence of reverberatory cortico-thalamic circuits (Beiser and Houk, 1998) are consistent with the notion of temporal integration of motor signals at the cortex. As a result, Massaquoi and Mao

(unpublished) hypothesized that the reverberatory activity can be represented by a neuronal integrator and that cruise movements are generated through rapid switching between the cortico-basal ganglionic-thalamocortical channels. In particular, the basal ganglia may act as a controllable movement rate-limiter that allows for the production of cruise movements. This proposed mechanism will be explained further in Chapter 3.

Compound movements are a superposition of simple movements with varying amplitude and timing. In such movements, one movement may occur followed by another movement, either asynchronously or sequentially. Whatever the case may be, there must be something that triggers a series of movements to be carried out in a systematic manner. This is where the basal ganglia come in, because Massaquoi and Mao propose that they act as a context-dependent switching mechanism, where the previous movement's context is a signal for the next successive movement. Therefore, successive movements can be executed within the context of the previous or ongoing movement.

2.4 Problem Statement

2.4.1 Specific Questions Addressed

Specific questions to be answered by this thesis include the following: What is the role of the basal ganglia in the overall motor control schema for simple movements? Can the proposed model be extended to explain more complex movements, and if so, how is this done? Can the proposed model produce symptoms of various movement disorders based on the commonly believed location of lesions in the basal ganglia?

2.4.2 Hypothetical Answers

A set of hypotheses were developed in addressing the specific questions above: The basal ganglia may act as a context-dependent switching device. This is true, not only for simple cruise movements, but for more complex movements as well, such as asynchronous cruise movements and sequential cruise movements. In addition, there may be neurons within the basal ganglia that act as "braking" neurons while other neurons are both task- and sequence-specific neurons. With these ideas in place, it is expected that, given the location of basal ganglionic damage for certain movement disorders, the proposed model will be able to exhibit symptoms of these diseases.

Chapter 3: Methodology

3.1 Overview

In an effort to explain the circuitry of the basal ganglia in the context of normal and abnormal movement, a basic engineering model of basal ganglionic circuitry and function was developed by Massaquoi and Mao (2002). The goal of this thesis was to extend this model to explain basal ganglionic function and dysfunction in three types of movements: 1) cruise movements, 2) asynchronous, cruise movements, and 3) sequential cruise movements. Studies were found in the literature describing the physiology of these movements in detail. Of particular interest were studies that included electrophysiological recordings of neurons in the basal ganglia. These studies were used to provide insight into developing valid extensions to the model developed by Massaquoi and Mao.

3.2 The Massaquoi-Mao Logical Switching Model of Basal Ganglionic Function

3.2.1 Basic Long-Loop Servo Control Model of Movement Control

3.2.1.1 Musculoskeletal Plant Model

Also included in Figure 3 is the plant, which represents the musculo-skeletal system. The musculoskeletal plant model is equivalent to a second-order lever-spring-dashpot system (or equivalently, a mass-spring-dashpot system) that describes a simplified single-joint system of the human body. The transfer function of the plant model can be re-written in the following form:

$$\frac{K_m}{\alpha s^2 + \beta_m s + K_m}$$

where α is the moment of inertia of the lever (or the mass, if considering a mass-spring-dashpot system), K_m is the spring constant, and β_m is the dashpot constant.

3.2.1.2 Trans Cerebrocorticol Servo Control

The important features of the Massaquoi-Mao model are the following: 1) a parietal region that computes a position error signal. This is expressed as $E(t) = \Theta_{target}(t)-\Theta_{movement}(t)$, shown in the top box of Figure 3. Berns and Sejnowski (1998) have hypothesized that the basal ganglia will receive inputs that represent the error or difference between the target movement and the actual movement. Based on these and other inputs, the basal ganglia will coordinate actions to decrease and eventually eliminate this error. 2) small- and large-capacity thalamo-cortical integrators. From stimulation of the sensorimotor area of monkeys, Graziano et al. (2002) found that in producing movement and posture, there was temporal accumulation of microelectrode stimulation effects in the sensorimotor cortex. This is consistent with temporal integration of motor signals at the cortex. Thus, it would seem reasonable to consider that an integrator could be found along the path that translates error into goal-directed movement, because an integrator is capable of producing a non-zero output given zero input. In other words, an integrator allows for output accumulation and maintenance for varying inputs.

In the case where the actual movement matches the target movement, there would be no error signal sent to the integrator. In the face of zero input, rather than its output diminishing, the integrator output would maintain its accumulated value. This is essential for performing a sequence of movements where, for example, the left arm is raised followed by the right arm so that both arms are raised at the end of this "motor program." Once the left arm has been fully raised, indicating that this particular part of the motor program is finished,

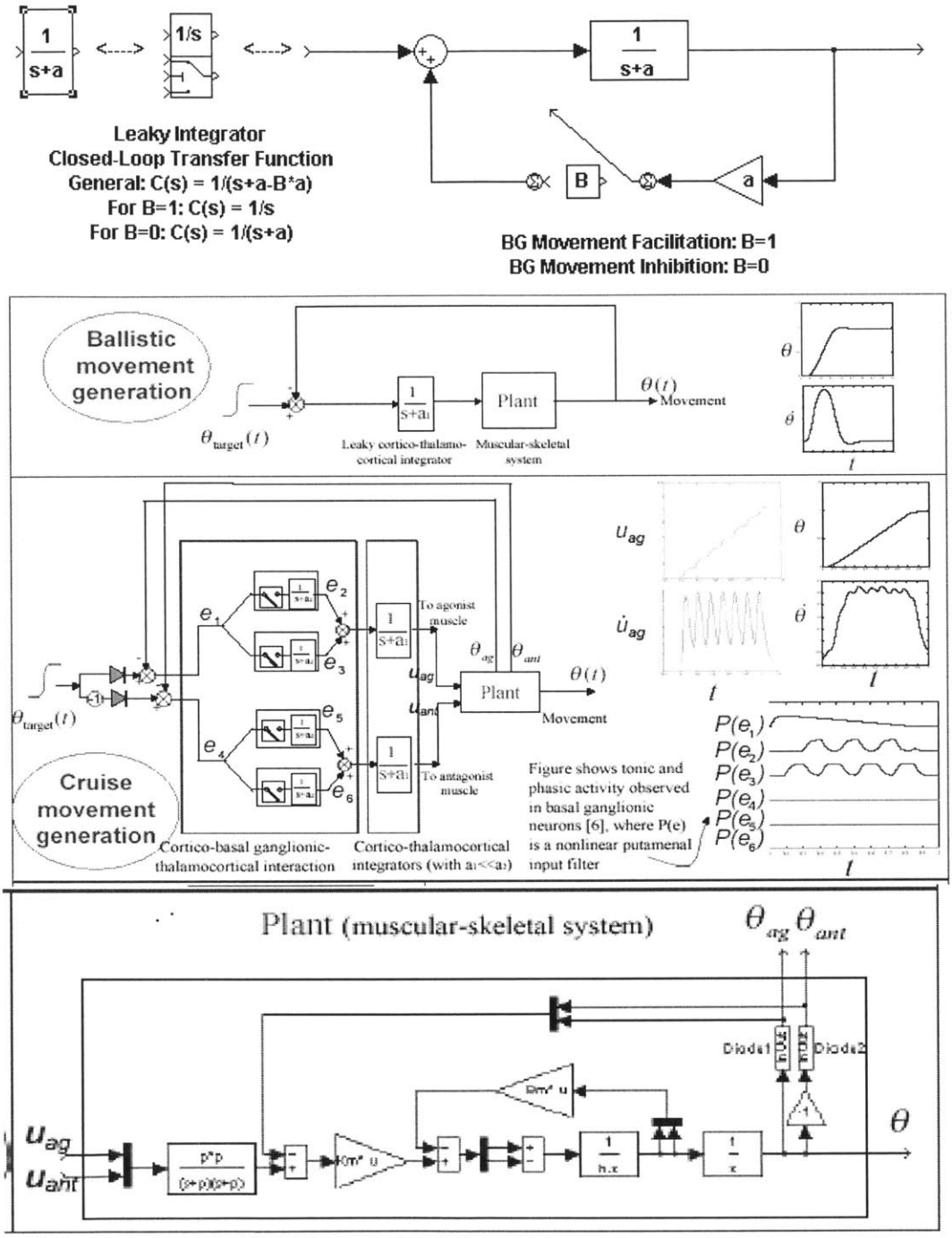

Figure 3: Proposed role of basal ganglia in the generation of cruise movements (Adapted from Mao, Lim, and Massaquoi, 2002). Figure 3a shows the detailed cortico-basal ganglionic thalamo-cortical interaction within a leaky integrator. Figure 3b shows the process, movement position, and movement velocity for ballistic movement generation. Figure 3c shows the process, movement position, movement velocity, and integrator activity for cruise movement generation. Figure 3d shows a representation of the musculo-skeletal system in the form of a plant.

there would be zero error input sent to the integrator responsible for raising the left arm. If there was no integrator along this path, then as the right arm is raised, the left arm would fall, because there would be no component that could maintain the current position of the left arm given zero error input. The output of the integrator could then correspond to $\Theta_{movement}(t)$ that, when compared to $\Theta_{target}(t)$, generates an error signal that is sent through the thalamo-cortico basal ganglionic loop. However, issues with the servo control mechanism include the realization that the loop normally has delays associated with it, and there are stability and compensation issues as well. Because these issues are not directly relevant to the process of switching, they are ignored in this thesis.

3.2.2 Logical Control Model of Basal Ganglia – Binary Vector Context Switching

Massaquoi and Mao, as well as others outside the Sensorimotor Control Group, have suggested that the basal ganglia may act as a context-dependent switching device. In their model, Massaquoi and Mao propose that there are groups of individual neuronal modules within the cerebral cortex that, depending on their levels of neuronal activity, represent a behavioral context. Thus, a specific context represented by n cerebral modules can viewed as an n-dimensional binary vector, where a "1" component value indicates that a particular neuronal module is on while a "0" component value indicates that a particular neuronal module is off. Given such a behavioral context as input, the role of the basal ganglia produces an output that serves to facilitate and/or inhibit a total of m executive circuits. In other words, basal ganglionic activity can generally be described as mapping an n-dimensional binary vector of context modules into an m-dimensional binary vector of executive modules. From a lower basal ganglionic perspective, the cerebral context modules can be seen as providing a status and/or progress report of what actions have been taken

along with information about one's environment and so forth. The cerebral executive modules can be seen as those generating the specific motor commands to be carried out. Therefore, the switching of basal ganglionic modules in the production of cruise movements (to be described in Section 3.2.3) can be likened to a binary motor program where the basal ganglia acts as a universal logic machine, taking in behavioral contexts and producing motor commands.

DeLong and Strick (1974) define ramp movements as movements having a relative constancy in speed, whereas ballistic movements are movements having a more bell-shaped velocity profile. For the purpose of simple point-to-point movements, Massaquoi and Mao (unpublished) have proposed that the interaction between the cortex, basal ganglia, and thalamus can be modeled as shown in Figure 3.

Shown in the top part of Figure 3 is a leaky cortico-basal ganglionic-thalamo-cortical integrator, where the behavior of the integrator depends on the activity of the basal ganglia. The closed-loop transfer function C(s) of this localized loop is the following: $C(s) = 1/(s+a-B*a)$, where B is the binary value indicating activity of the basal ganglia. Specifically, if the basal ganglia attempts to inhibit the activity of the integrator, then B=0, and the integrator behaves like a leaky integrator $C(s) = 1/(s+a)$ so that the output of the integrator will decay to zero over a period of time. If the basal ganglia facilitates activity of the integrator, then B=1, and the integrator behaves like an ideal integrator $C(s) = 1/s$ such that the output of the integrator can accumulate and be maintained over a period of time. These integrators are implemented as shown in the rest of Figure 3.

3.2.3 Description of Proposed Switching Model Function

3.2.3.1 Normal Cruise Movements

It is likely that when making a movement such as simple reaching, a person's cerebral cortex has a signal that represents the position of the target. This signal will initially differ from the actual movement signal. In the model, this difference, or error, will generate activity in the small- and large-capacity integrators along the appropriate (agonist or antagonist) pathway, which will generate actual movement.

In the model developed by Massaquoi and Mao, thalamo-cortical modules representing cortical neurons in particular are connected to the thalamus, which issues motor commands that result in movement. These neurons are modeled by leaky integrators that can drain or saturate depending on the status of the positive feedback loop through the thalamus. Small capacity neurons, neurons found possibly in the supplementary motor area (SMA), require only a small input before saturating. These neurons are proposed to switch on and off in an alternating fashion so that a nearly constant output can be sent to the large-capacity neuron, which is thereby capable of generating cruise movements. The process by which this flip-flopping or toggling (i.e. alternating leaking and saturating) takes place is proposed to be controlled by: 3) the basal ganglia via its output to the thalamus.

If a non-zero error, still exists, the integrators will remain active until the difference falls to zero. Note that small-capacity integrators will saturate quickly in response to a non-zero input, so during the time period over which there is a difference between the target movement signal and the actual movement signal, thus sending a constant output to the large-capacity integrators. This is the case, because if the opening and closing of the small-capacity integrators is switched in an alternating fashion, then the large-capacity integrator will receive pulses of roughly the same magnitude from

these small-capacity integrators. The output of these integrators will be roughly constant as well, thus producing the nearly perfect (but not perfect) ramp-like actual hand position profiles and plateau-shaped velocity profiles that define cruise movements.

Up to this point, the need for toggling per se has not been explained. In the model, once the small-capacity integrators saturate, the rate of change of the large-capacity integrator's output is fixed. This mechanism resembles that of a rate-limiter, causing ramp or cruise movements. However, this mechanism is non-linear. In particular, when a larger movement is desired, the output flow rate will remain constant. The maximum speed of this rate-limiter remains unchanged despite possible changes in movement amplitude. However, natural movements in humans tend to have velocities that scale with movement distance i.e. the control behaves much more linearly. Therefore, the toggling mechanism was designed to provide rate control so that the velocity profile is more constant i.e. plateau-like, and so that the height of this plateau scales up and down with attempted movement amplitude. In other words, this toggling mechanism can recover more linear behavior with respect to movement amplitude while retaining some non-linear behavior to produce more constant speed.

For the cruise movement generation process found in Figure 3, there are cerebral neuronal modules toggling for control in separate agonist and antagonist channels. Note that cortico-basal ganglionic-thalamocortical interaction and cortico-thalamo-cortical integrators are found along both channels. This is necessary in order for generation of extension and flexion movements i.e. movements involving agonist muscle groups and antagonist muscle groups. For example, a movement involving extension would involve

activity from the agonist channel while flexion movements would generate activity from the antagonist channel.

The logical progression of a motor program for the proposed model is shown in Figure 4. We propose that the behavioral context input, or set of monitored behavioral states, can be considered to consist of information regarding the position error and the activity of the small- and large- integrators, each of which can be viewed as being zero or nonzero (specifically a value of "1"). The status of the environment and internal integrators can be viewed as a total context vector. Given this 3-dimensional vector of cerebral context modules, the basal ganglia will map out a 2-dimensional vector motor command, consisting of cortical execution modules (small- and large-capacity thalamo-cortical integrators) either on ("1") or off ("0").

Monitored Behavioral States (BG Input)			**Executive Motor Commands (BG Output)**	
Error	**Small Integrator #1**	**Small Integrator #2**	**Small Integrator #1**	**Small Integrator #2**
1	0	0	0	1
1	0	1	1	0
Basal ganglia switch between these states until the movement has been completed i.e. the error is zero. Once this occurs, the movement sequence is completed, and the basal ganglia maps out commands to prevent further movement from taking place:				
0	0	1	0	0
0	1	0	0	0
0	0	0	0	0

Figure 4: Logical Progression of a Motor Program for the Model in Simple Cruise Movements. Given the monitored behavioral states as input, the basal ganglia will map out the appropriate executive motor commands to complete the movement.

3.2.3.2 Parkinson's Disease

Understanding the circuitry of the basal ganglia and examining its functional properties potentially allows for better understanding of diseases found in the basal ganglia. Of particular interest is Parkinson's disease, a condition that results in bradykinesia (slowness

of movement), rigidity, and rest tremor. It is believed that these signs occur as a result of dopamine loss, which serves to weaken the relative strength of the direct pathway in the basal ganglia while strengthening the indirect pathway. However, the detailed mechanism is unclear. Since the direct pathway facilitates movement while the indirect pathway inhibits movement, the net result is increased inhibition by the basal ganglia, which produces slower, more restrained movement. Cruise movements affected by Parkinson's disease were simulated by decreasing the relative strength of the direct pathway while increasing the relative strength of the indirect pathway.

3.2.3.3 Dystonia

Dystonia is another movement disorder associated with the basal ganglia. On their website, the National Institute of Neurological Disorders and Stroke (NINDS) classifies dystonia as a neurological disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, and sometimes painful, movements or postures. Dystonia can affect virtually any part of the body including the arms and legs, trunk, neck, eyelids, face, or vocal cords. Dystonia has occurred as a result of lesions in the putamen (Burton et al., 1984). Since the precise location and extent of these lesions are uncertain, to model a possible sccenario of dystonia, the relative strength of both the direct and the indirect pathways in the putamen was decreased.

3.2.3.4 Huntington's Chorea

Huntington's chorea is a degenerative brain disorder that slowly diminishes one's ability to walk, think, talk, and reason. An individual with Huntington's chorea will experience sudden, involuntary, and unsustained movement. It is believed that the disease is

caused by a lesion in the caudate and/or putamen, specifically along the indirect pathway (Pavese et al, 2003). Thus, in the model, the relative strength of the indirect pathway in the putamen was decreased to determine if the simulated system would demonstrate these symptoms.

3.2.3.5 Hemiballism

Another movement disorder of interest is hemiballism. Ballism is a disorder that causes involuntary movement where one, for example, violently flings or jerks a limb (i.e. an arm or a leg) in an uncoordinated manner. Ballism is caused by a lesion in the STN (Lehericy, 2001). Usually, only one side of the body is affected, and thus the condition is referred to as hemiballism. In the model, the relative strength of the STN was decreased to determine if the simulated test subject exhibited hemiballism.

3.3 Extensions to the Model

Extensions to the model were made in order for the model to predict and simulate asynchronous cruise movements and sequential cruise movements. Such extensions include the following: 1) braking neurons, discussed in Section 3.3.1, and 2) phase- and sequence-specific neurons, discussed in Section 3.3.2.

3.3.1 Normal Asynchronous Control of Two Joints

3.3.1.1 Proposed Cortical Control Modules

One objective of this thesis was to verify that the model could provide a mechanism for asynchronous cruise movements at two joints. In a paper written by Romo and Schultz (1996), neuronal activity in the GPi of Rhesus monkeys performing self-initiated (internally

cued) movements was recorded. In particular, once an audio signal was given to the monkeys indicating that the trial had begun, the monkeys were to, at their own volition, reach into an open box and grab a small food reward. Based on the measurements taken during the experiments, the activity of the GPi neurons could be classified into three major groups as shown in Figure 4. The first group of neurons (including the ones in A and B) showed significant activity during the movement preparation phase then became relatively inactive just before the movement onset phase.

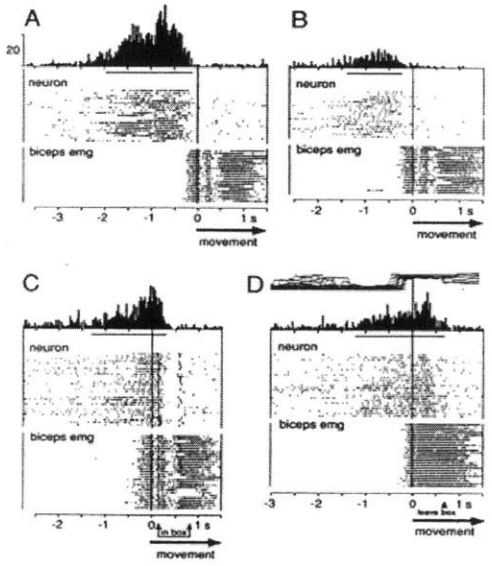

Figure 4: Activity in four putamen neurons preceding self-initiated arm movements. ***A, B*** *Activity terminated before movement onset.* ***C*** *Activity terminated just after entering the box.* ***D*** *Activity terminating after the task has been completed. (Adapted from Romo and Schultz, 1992 – formal permission pending).*

These two phases are separated by the vertical line at time=0 seconds considered to be "movement onset," where the region to the left of the line is the movement preparation phase while the region to the right is the movement phase. Another group of neurons (C) became active during the movement preparation phase and for most of the movement phase. However, neuronal activity stopped just as the arm reached the threshold of the box where

the food reward was found. The third group of neurons (D) became active during all of the movement preparation and movement phases.

Before attempting to explain the behavior of these three groups of GPi neurons, it is worth considering the components of such a reaching movement. For example, suppose that a test subject is asked to reach a short distance into a box and grab a ball. Based on observation and personal experience, one would expect the test subject to first move his hand towards the box, and once the hand is sufficiently close to the ball, open up his hand to grasp it. Typically, there is movement overlap between the arm and the hand during a small time period where the arm slows to a standstill while the hand begins to open up. Assuming that this movement process is present in some individuals, consider the following: if there were no movement of the hand during the early part of the movement phase, it is conceivable that there may be some mechanism that inhibits movement of the hand until a sufficient cue (nearing the ball) is received, which then releases this inhibiting mechanism. In particular, suppose that there are a group of neurons that act as braking mechanisms for the arm or the hand. If these neurons were active, movement of the arm or hand would be inhibited, but if these neurons were inactive, movement would then be allowed to take place. Given the model of the basal ganglia being considered here, it seems that the basal ganglia could play a role in switching such neurons on and off. To be more accurate, it may be fair to say that the second objective is to verify that the model can simulate asynchronous movements at two joints.

Fitting these assumptions into our model, our group hypothesized that there are neurons in the arm and in the hand that act as braking mechanisms. This expanded model is shown in Figure 5. The basal ganglia will receive inputs from the cerebral cortex and the integrators in both the agonist and antagonist muscle groups – inputs that are also received

by the basal ganglia for simple cruise movements. Note that for the sake of simplicity, the integrators for one muscle group at one joint are shown rather than integrators for both muscle groups at arm and hand joints. However, in addition to these inputs, the basal ganglia will receive inputs from the braking neurons as well as cue signals that come from the environment. Such cue signals might be a bell chime corresponding to the audio

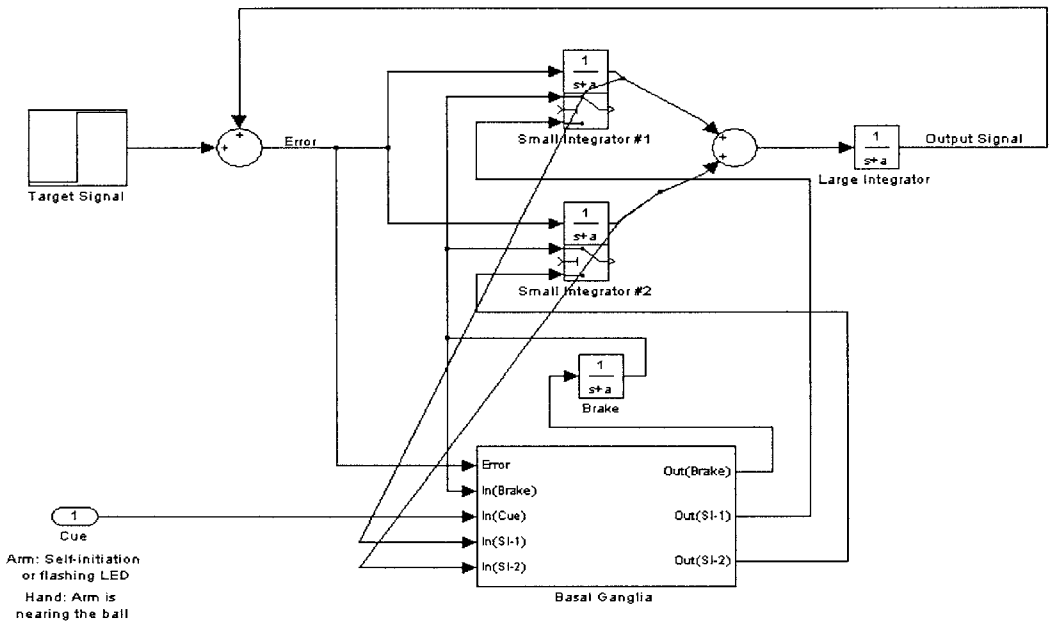

Figure 5: Block Diagram of Basal Ganglia for Asynchronous Cruise Movements

signal given to monkeys, and the visual image of having arrived at the box. Given these inputs, the basal ganglia will map out a set of motor commands to be generated so that the appropriate movements take place. The basal ganglia will send output to the thalamus which, in turn, sends the commands out to the cerebral cortex, the various integrators, and to the braking neurons.

3.3.1.2 Logical Program and Hypothesized Action

Figure 6 shows a logical program for asynchronous movements and how the basal ganglia play a role in such movements. We hypothesize that when a subject begins thinking

Monitored Behavioral States (BG Input)									Executive Motor Commands (BG Output)					
Error Signal	Arm Cue	Arm Brake	Arm SI-1	Arm SI-2	Hand Cue	Hand Brake	Hand SI-1	Hand SI-2	Arm Brake	Arm SI-1	Arm SI-2	Hand Brake	Hand SI-1	Hand SI-2
Before the start of the experiment:														
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
During the movement preparation phase - no movement occurs despite activity of integrators due to active brakes:														
1	0	1	0	0	0	1	0	0	1	0	1	1	0	1
1	0	1	0	1	0	1	0	1	1	1	0	1	1	0
1	0	1	1	0	0	1	1	0	1	0	1	1	0	1
Basal ganglia switch between these states until the arrival of an arm movement cue. At movement onset, upon arrival of flashing LED or self-initiated "GO" signal, the arm brake released, thus allowing movement of the arm to occur:														
1	1	1	1	0	0	1	1	0	0	0	1	1	0	1
1	1	0	0	1	0	1	0	1	0	1	0	1	1	0
1	1	0	1	0	0	1	1	0	0	0	1	1	0	1
Basal ganglia switch between these states until the arrival of a hand movement cue. When the arm reaches the box i.e. is close enough to the target, it is a cue that releases the hand brake, thus allowing movement of the hand to also occur:														
1	1	0	1	0	1	1	1	0	0	0	1	0	0	1
1	1	0	0	1	1	0	0	1	0	1	0	0	1	0
1	1	0	1	0	1	0	1	0	0	0	1	0	0	1
Basal ganglia switch between these states until the movement has been completed i.e. the error is zero. This will cause the braking neurons to become active, thus suppressing further movement.														
0	1	0	1	0	1	0	1	0	1	0	0	1	0	0
0	1	1	0	0	1	1	0	0	1	0	0	1	0	0

Figure 6: Logical Motor Program for Generation of Asynchronous, Cruise Movements. Given the monitored behavioral states as input, the basal ganglia will map out the appropriate executive motor commands to complete the desired movement.

about and preparing for movement, both the arm and hand braking neurons become active. For the monkeys, this occurred when they began to prepare for the desired movement. Although the small-capacity integrators may be active during this preparatory phase, the active braking neurons prevent activity of the large-capacity integrator thus inhibiting movement. Only when a specific cue arrives will these braking neurons become inactive, which will then allow for activity of the large-capacity integrator in generating movement. For the arm, this would occur when the subject is either given a specific cue signal or when internally-generated (self-initiated). For the hand, this would occur when the subject detected that he was sufficiently within reach of grabbing an object in the box. Once the error between the target movement and actual movement is zero, the braking neurons will become active again, preventing further movement.

We can now speculate as to what the three groups of neurons represent in the Romo and Schultz paper. The first group of neurons could represent braking neurons for the arm, because these neurons became active during the movement preparatory phase but then became inactive just before movement of the arm occurred. We will refer to these neurons as Group I (or Arm-brake) neurons. The second group of neurons could represent braking neurons for the hand, because these neurons remained active until a visual or proprioceptive cue arrived, specifically when the hand was in the box, as shown in Figure 4C. Only then did these neurons turn off. Thus, it is conceivable that movement in the hand occurred after these braking neurons became inactive. In other words, once the monkey saw that his hand was inside the box, it could be a cue that he was close enough to the food reward where he could then open up his hand and grasp it. We will refer to these neurons as Group II (or Hand-brake) neurons. The third group of neurons could represent the small-capacity neurons that are active (but toggle on and off) for the duration of the movement preparatory and movement phases. We will refer to these neurons as Group III neurons. The fluctuation in activity of these neurons is consistent with the possibility of toggling taking place. However, from the data in Romo and Schultz's study, it is not clear that intermittent toggling is visible. Their data is summed over many trials and may mask toggling if recording points are not always in the same place. Individual trials tend to show more intermittent bursting of activity.

Asynchronous, cruise movements were simulated for normal physiological conditions, Huntington's chorea, and hemiballism. These three scenarios were studied during the period of time over which this thesis was completed. Other scenarios have yet to be examined.

3.3.2 Normal Sequential Control of Single Joint

3.3.2.1 Proposed Cortical Control Modules

Another objective of this thesis was to determine if the model could provide a mechanism for the normal and abnormal control of sequential, cruise movements. An example of such a movement would be movement of the hand from one target, then to another target, then to a third target in a step-by-step manner. While many combinations of movements are possible in performing sequential movements, we will limit such variability to the simplified case where the arm moves towards three distinct targets, one after another in a particular order. Thus, such a task would be considered a three-phase movement.

In a paper written by Mushiake and Strick (1995), two monkeys were seated in a primate chair with their heads fixed. The animals were trained to perform sequential movements for both visually guided conditions and remembered conditions. For both conditions, the monkey faced a panel with five touch pads, numbered 1 to 5 (from left to right). The monkey began a trial by placing his right hand on a hold key in front of him for a "Hold" period of 1.5-2.5s. This hold key was situated in front of the touch pad designated by the number "3" such that the distance required to move the hand left to the "1" touch pad was the same as that required to move the hand right to the "5" touch pad. In the remembered task, LEDs over three touch pads were illuminated in a sequence as an instruction to the monkey. The LEDs remained lit until the end of the trial. After an instruction period of 1.5-2.5s, an auditory "Go" signal told the monkey to release the hold key and press the three touch pads as indicated by the sequence of illuminated LEDs. In this case, the specific sequence of movements that the monkey executed was internally cued. In the tracking task, an LED over a single touch pad was illuminated after a Hold period of 2.5-3.5s. The auditory "Go" signal was turned on at the same time, and the monkey was

required to release the hold key and press the illuminated touch pad as quickly as possible. As soon as the monkey touched made contact with this touch pad, a second LED was illuminated over another touch pad. The monkey was then required to touch this pad as well. When the monkey made contact with the second touch pad, a third LED was illuminated over a third touch pad, and the monkey was required to touch the third touch pad. In this case, the specific sequence of movements that the monkey performed was externally cued. Mushiake and Strick (1995) limited the tasks to eight different sequences of movements. Four of the sequences began with a movement to touch pad number 2 (sequences 2-1-3, 2-3-1, 2-3-5, 2-4-5), and another four began with a movement to touch pad number 4 (sequences 4-5-3, 4-3-5, 4-3-1, 4-2-1).

The activity of neurons in the globus pallidus was examined while monkeys performed sequential pointing movements under either visually guided conditions or remembered conditions. In the study, they found that nearly half of the neurons in the globus pallidus displayed changes in activity during a single phase of the remembered task (Mushiake and Strick, 1995). Such phase-specific neurons varied in activity depending on the particular sequence of movements performed. Some neurons displayed changes in activity for all possible movement sequences while others displayed a change in activity during only one specific sequence. An example of a neuron that was both phase- and sequence-specific is shown in Figure 6 (Mushiake and Strick, 1995).

For the purpose of explaining some of the neuronal activity from the Mushiake and Strick study in the context of our basal ganglionic model, we propose the following, as shown in Figure 7. The basal ganglia will receive inputs from the cerebral cortex and the integrators in both the agonist and antagonist muscle groups – inputs that are also received by the basal ganglia for simple cruise movements. Note that for the sake of simplicity, the

integrators for one muscle group are shown rather than integrators for both muscle groups. In addition to these inputs, the basal ganglia will receive information from the environment in the form of LED illumination over a particular touch pad and visual/tactile confirmation that the hand has completed a certain movement.

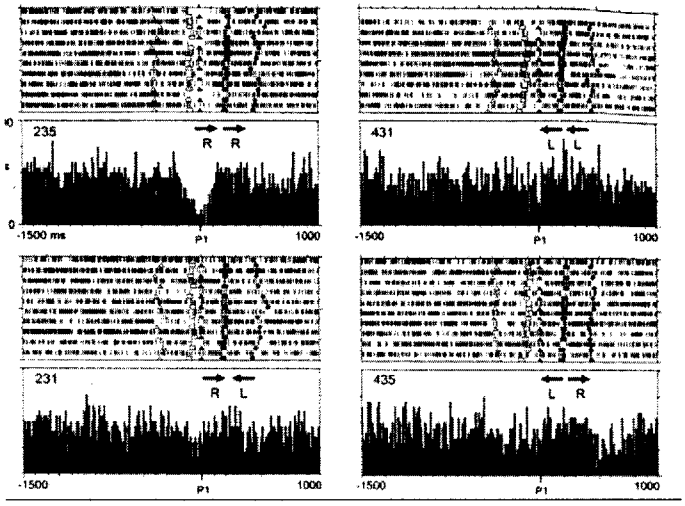

Figure 6: Pallidal neuron that is both sequence and phase-specific. Note how the neuron shows a significant decrease in activity only during the first phase of sequence 235 and not for any other phases or sequences. (Adapted from Mushiake and Strick, 1995 – formal permission pending)

In their model, Massaquoi and Mao propose that the basal ganglia are involved in sequential cruise movements, because they act as a context-dependent switching mechanism, where the previous movement's context is a signal for the next successive movement. As a result, successive movements can be executed within the context of the previous or ongoing movement. In Figure 7, we see that the basal ganglia will receive a behavioral context consisting of information regarding which part of the movement sequence is being carried out (first movement, second movement, or third movement), if the movement has been completed (error), and activity of the integrators. Based on these inputs, the basal ganglia will map out a vector of executive motor commands to the

integrators and to neurons responsible for continuing a movement (if a certain movement is not finished) or to commence another movement (if the movement is finished)

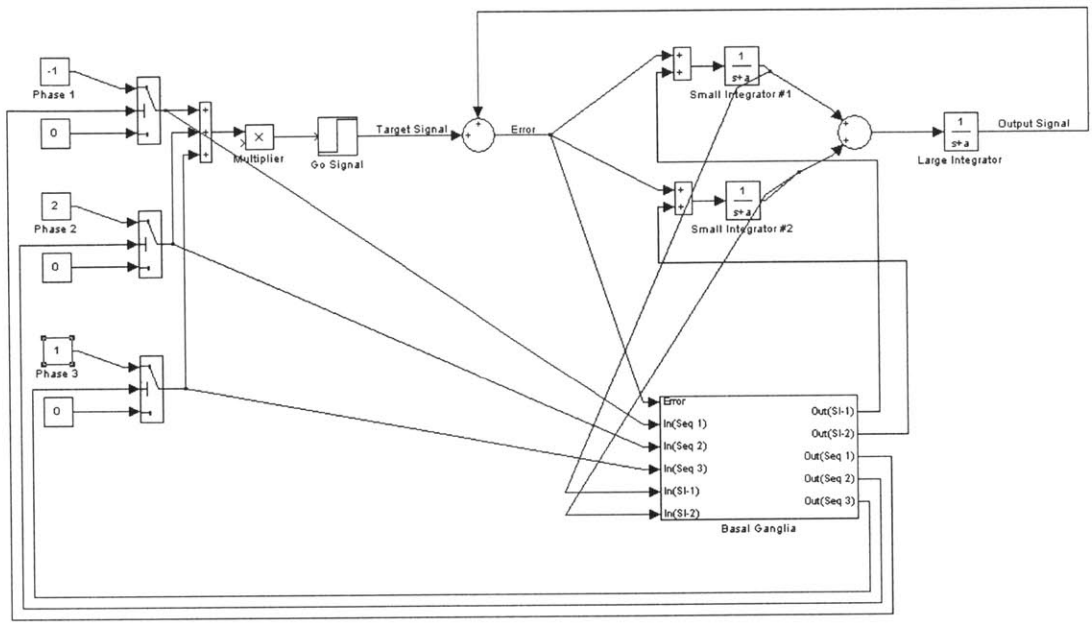

Figure 7: Block Diagram of Basal Ganglia for Sequential Cruise Movements

3.3.2.2 Logical Program and Hypothesized Action

Figure 8 shows a logical program for sequential movements and how the basal ganglia play a role in such movements. Note that in the table, if the first movement was taking place, then the "Seq 1" input (binary) value would be set to 1, and the "Seq 2" and "Seq 3" input values would be set to 0. Once the first movement of the sequence has been completed i.e. the error during that phase becomes 0, the basal ganglia will map out the motor commands to commence the second phase of the movement sequence. In this case, the values of "Seq 1" and "Seq 2" are set to 1, and the value of "Seq 3" is set to 0, and the same process continues until all three phases of the movement sequence has been completed.

One of the movement sequences used in Mushiake and Strick's study is the sequence 2-4-5. Since the monkey's hand is resting on the hold key directly in front of touch pad 3, the first movement of the sequence would require one step to the left, the second movement

Monitored Behavioral States (BG Input)						**Executive Motor Commands (BG Output)**				
Phase 1	**Phase 2**	**Phase 3**	**Error**	**SI-1**	**SI-2**	**Phase 1**	**Phase 2**	**Phase 3**	**SI-1**	**SI-2**
Before the start of the experiment:										
0	0	0	0	0	0	0	0	0	0	0
Once the "Go" signal has been sent, the monkey will press the first touch pad according to the instructed movement sequence :										
1	0	0	1	0	0	1	0	0	0	1
1	0	0	1	0	1	1	0	0	1	0
1	0	0	1	1	0	1	0	0	0	1
Basal ganglia switch between these states until the movement has been completed i.e. the error is zero. Once this occurs, the basal ganglia maps out commands to execute the second phase of the movement sequence:										
1	0	0	0	0	1	1	0	0	0	0
1	0	0	0	0	0	1	1	0	0	0
Once the command for the second movement has been sent, the basal ganglia will generate the necessary movements to press the second touch pad according to the instructed movement sequence:										
1	1	0	1	0	0	1	1	0	0	1
1	1	0	1	0	1	1	1	0	1	0
1	1	0	1	1	0	1	1	0	0	1
Basal ganglia switch between these states until the movement has been completed i.e. the error is zero. Once this occurs, the basal ganglia maps out commands to execute the third phase of the movement sequence:										
1	1	0	0	0	1	1	1	0	0	0
1	1	0	0	0	0	1	1	1	0	0
Once the command for the third movement has been sent, the basal ganglia will generate the necessary movements to press the third touch pad according to the instructed movement sequence:										
1	1	1	1	0	0	1	1	0	0	1
1	1	1	1	0	1	1	1	0	1	0
1	1	1	1	1	0	1	1	0	0	1
Basal ganglia switch between these states until the movement has been completed i.e. the error is zero. Once this occurs, the movement sequence is completed, and the basal ganglia maps out commands to prevent further movement from taking place:										
1	1	1	0	0	1	1	1	1	0	0
1	1	1	0	0	0	1	1	1	0	0

Figure 8: Logical Motor Program for Generation of Sequential, Cruise Movements. Given the monitored behavioral states as input, the basal ganglia will map out the appropriate executive motor commands to complete the desired movement.

of the sequence would require two steps to the right, and the third movement of the sequence would require one step to the right. If we consider movement to the left as negative movement and movement to the right as positive movement, then the sequence 2-4-5 would involve one negative step followed by two positive steps and another positive step. The Massaquoi-Mao model was used to demonstrate the role of the basal ganglia in this particular sequential movement and is shown in Chapter 4. Note that one neuron (Phase 1)

is on for all phases, one (Phase 2) is off for one phase, and one (Phase 3) is on for one phase. The first neuron could be representative of neurons found in Mushiake and Strick's study that are active for the duration of a particular movement sequence while the other two groups of neurons could be representative of neurons that are phase- and sequence-specific. However, there is not enough data to fully confirm the above ideas, but they are at least consistent so far. In addition, Phase 2 and Phase 3 neurons are not yet clearly sequence-specific.

Chapter 4: Results and Analysis

4.1 Model Function in Simple Cruise Movements and Disease States

4.1.1 Normal Condition

Figure 9 shows the output of the model for a one-step, single-joint flexion movement in a normal subject. Figure 9a shows how the small-capacity integrators behave in response to a difference, or error, between the target movement and the actual movement of the arm. The top three lines represent activity of the extensor muscle, while the bottom three lines represent activity of the flexor muscle. Within these three-line groupings, the top line represents the error between the target movement and the actual movement while the bottom two lines represent the activity of the small-capacity integrators throughout the experiment. Note that these integrators will normally be active during the time period over which there is a nonzero error in the muscle group. When the actual position matches the target movement i.e. when the arm reaches its desired target location, the small-capacity integrators will shut off, and movement will cease. Also found in Figure 9 are the position and velocity profiles of the movement, as shown in Figures 9b and 9c. For a normal subject, the position profile shows a relatively smooth cruise movement during the reaching process. Furthermore, the velocity profile of such movement resembles the shape of a plateau. These profile results are relatively consistent with those found in animal studies and human studies involving cruise (or ramp) movements (DeLong, 1974).

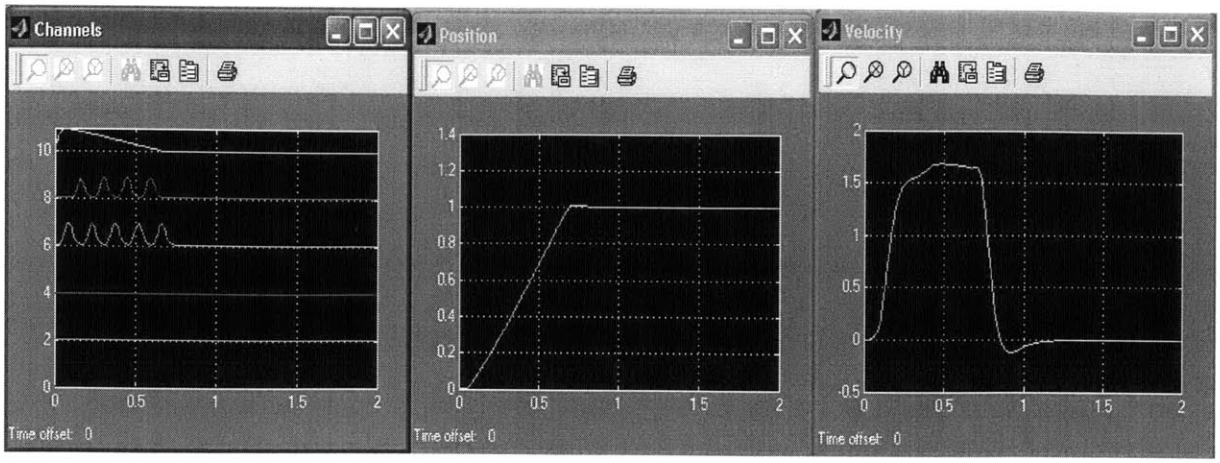

Figure 9: System Output for Cruise Movement in a Normal Subject: Figure 9a (left) shows output of putamenal neurons that registers status of error and small-capacity integrators due to error between goal-directed movement and actual movement. Figure 9b (center) shows the position profile of subject during movement. Figure 9c (right) shows the velocity profile of subject during movement.

4.1.2 Parkinson's Disease

Figure 10 shows simulation of the proposed activity of the basal ganglionic system for movement in a Parkinson's disease test subject. In figure 10a, the amplitudes of the small-capacity integrator outputs are smaller, indicating that the signals to these integrators are weaker or inhibited. The subject takes a longer time to reach the target, and when the arm reaches the target, a sustaining rest tremor occurs in the subject's arm. The frequency of tremor is approximately 4 Hz, and the observed tremor frequency of Parkinson's patients is between 3 and 6 Hz (Brooks, 1986). In Figures 10b and 10c, the position and velocity profiles reflect the slower process of movement followed by rest tremor upon completion of the movement. The small-capacity integrators in the flexor and extensor muscles are not both active simultaneously during any part of the simulation. Thus, rigidity, another symptom of Parkinson's disease, is not observed. It has been noted clinically (during tremor ablation neurosurgery) that some neurons in the putamen

show bursts at the rest tremor frequency. To our knowledge, the double frequency irregularity in velocity during motion has not yet been identified experimentally.

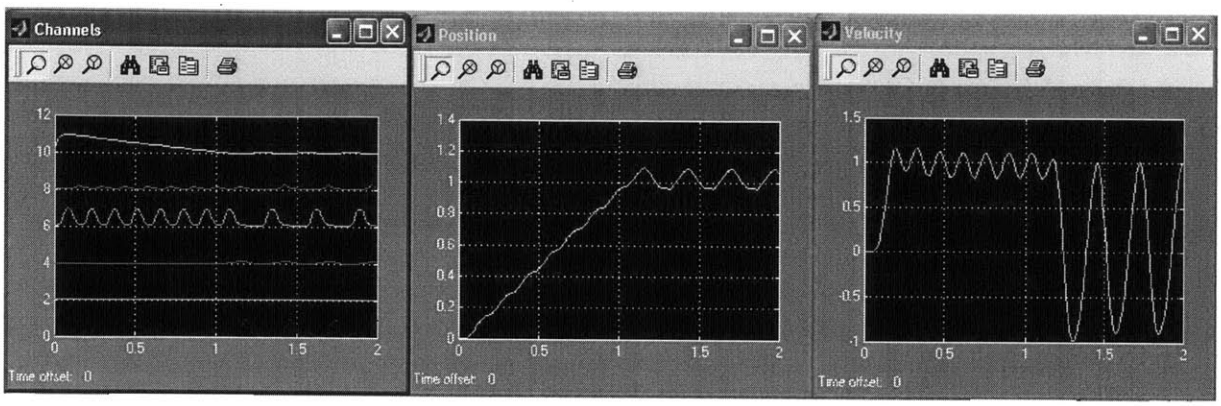

Figure 10: System Output for Cruise Movement in a Subject with Parkinson's Disease: Figure 10a (left) shows output of putamenal neurons that registers status of error and small-capacity integrators due to error between goal-directed movement and actual movement. Figure 10b (center) shows the position profile of subject during movement. Figure 10c (right) shows the velocity profile of subject during movement.

4.1.3 Dystonia

Figure 11 shows the simulation of the proposed activity of the basal ganglionic system for movement affected by dystonia. In figure 11a, the lesion (proposed to be along both the direct and indirect pathways of the putamen) causes both small-capacity integrators in the extensor muscle to switch on and remain on. In addition, the small-capacity neurons in the flexor muscle do not switch on in response to the arm overshooting its target. This aggregate behavior results in movement of the arm to the extent that it eventually cannot move further due to extreme movement restrictions governed by the musculoskeletal system. Such a movement would be an example of getting "stuck" in an abnormal, painful posture. In Figures 11b and 11c, the position and velocity profiles reflect the continuous and faster movement of the arm in one direction

that could lead to the aforementioned posture. However, there is no electrophysiological data to directly compare the results to. Therefore, we cannot corroborate the prediction of basal ganglionic neuronal behavior.

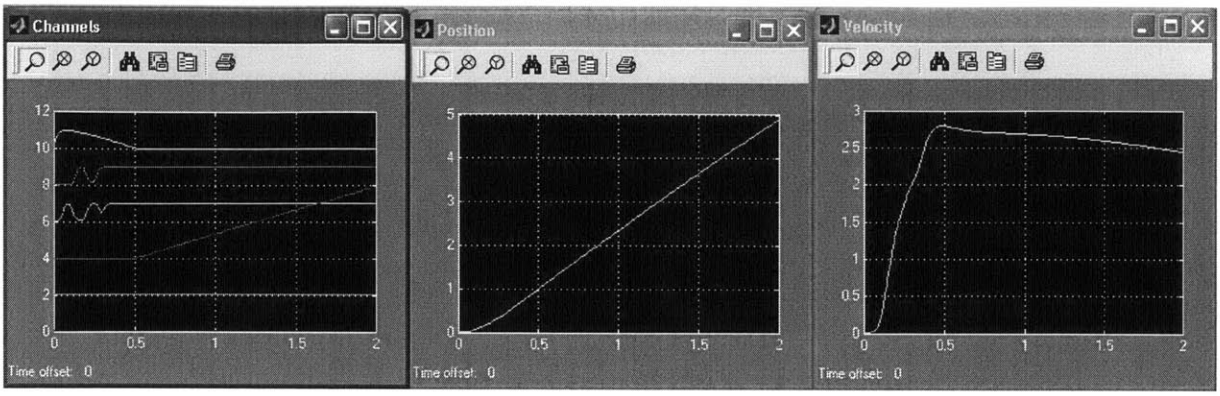

Figure 11: System Output for Cruise Movement in a Subject with Dystonia: Figure 11a (left) shows output of putamenal neurons that registers status of error and small-capacity integrators due to error between goal-directed movement and actual movement. Figure 11b (center) shows the position profile of subject during movement. Figure 11c (right) shows the velocity profile of subject during movement.

4.1.4 Huntington's Chorea

Figure 12 shows a simulation of the proposed activity of the basal ganglionic system for movement in a subject with Huntington's chorea. In figure 12a, the lesion (proposed to be along the indirect pathway of the striatum) causes both small-capacity integrators responsible for extension to suddenly switch on after a time when they had been alternating in activity. This may be due to the fact that since the indirect pathway is weakened, the inhibition mechanism is weakened, meaning that it becomes more difficult to shut off a neuron once it is on. As a result, it would become increasingly difficult to inhibit motor command signals to the point where some motor command signals may not shut off.

Upon further inspection, the arm does overshoot its target very slightly, and this sudden movement is not sustained. As shown in the position and velocity profiles in Figures 12b and 12c, the movement does stop. Note how the velocity of the movement changes when the unexpected movement occurs. The results are reasonable, because if a patient experienced sudden, involuntary, but unsustained movement, one would expect that the subject might overshoot its target by a small amount. This is reflected in these findings. Involuntary changes in movement speed are plausible components of chorea. However, we did not produce the dramatic movement amplitude irregularity that can be seen. Given the true anatomy of the Huntington's disease lesion, a possible explanation for not capturing chorea completely may be due to the failure to specifically model the operation of the caudate nucleus which is thought to possibly operate at higher levels of motor programming than represented in the current model. Further analysis and understanding of how the model parameters correspond to certain locations within the basal ganglia would be needed.

4.1.5 Hemiballism

Figure 13 shows a simulation of the proposed activity of the basal ganglionic system for movement in a subject with hemiballism. In figure 13a, the lesion (proposed to be in the STN) causes both small-capacity integrators responsible for extension to initially switch on and remain on until after the target location is reached.

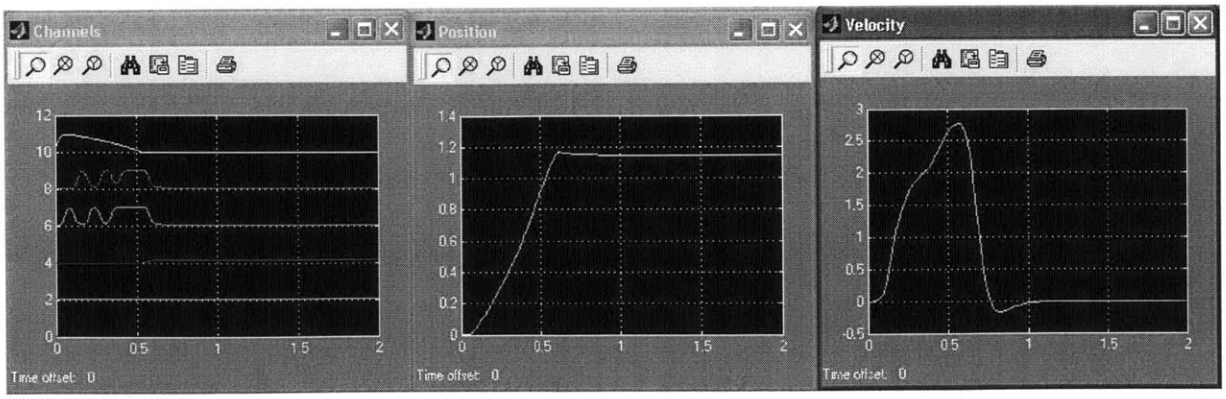

Figure 12: System Output for Cruise Movement in a Subject with Huntington's Chorea: Figure 12a (left) shows output of putamenal neurons that registers status of error and small-capacity integrators due to error between goal-directed movement and actual movement. Figure 12b (center) shows the position profile of subject during movement. Figure 12c (right) shows the velocity profile of subject during movement.

From the position and velocity profiles in Figures 13b and 13c, the rate of movement is significantly greater than normal. These results roughly capture the features of hemiballism, but at the present time, there is no independent experimental evidence that the internal signals have this observed behavior.

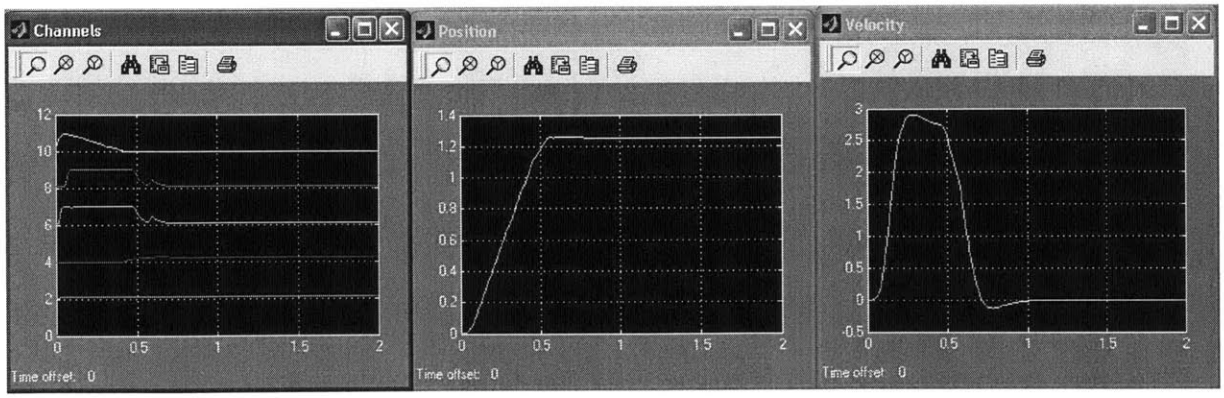

Figure 13: System Output for Cruise Movement in a Subject with Hemiballismus: Figure 13a (left) shows output of putamenal neurons that registers status of error and small-capacity integrators due to error between goal-directed movement and actual movement. Figure 13b (center) shows the position profile of subject during movement. Figure 13c (right) shows the velocity profile of subject during movement.

4.1.6 Overall Assessment of Model Function for Simple Cruise Movements

The proposed model was able to capture many of the characteristics of simple cruise movements in normal subjects, including a roughly ramp-like position profile and a plateau-shaped (with some initial overshoot) velocity profile. The model was able to capture most of the symptoms of Parkinson's disease, including a 3-6 Hz rest tremor and bradykinesia, but rigidity was not observed. This may be due to a limitation of the model where neurons involved in extension are active only when there is extension error, and neurons involved in flexion are only active when there is flexion error. For co-contraction to occur, there would need to be extension error and flexion error occurring simultaneously, which is not possible in the model. For the case of dystonia, the model was able to exhibit extreme movements and postures, but the lack of electrophysiological data for comparison prevents us from providing an internal state representation of the symptoms observed. The model was able to produce some sudden, involuntary movements typical of Huntington's chorea subjects, but the resulting overshoot was marginal. For the case of hemiballismus, the model was able to generate exaggerated limb movements, but again, the overshoot was not significant. In general, the model appears to capture many of the characteristics of simple cruise movement in normal subjects and in subjects with various movement disorders, but not all signs are captured, and the lack of electrophysiological data for dystonia, chorea, and hemiballismus makes these results cannot corroborate the prediction of basal ganglionic neuronal behavior.

4.2 Model Function in Asynchronous Two-Joint Cruise Movements

4.2.1 Normal Condition

In the previous section, we discussed the three different groups of neurons found in the Romo and Schultz study and then attempted to explain their behavior within the context of our basal ganglionic switching model. Figure 14 shows the simulated output of the model for asynchronous cruise movement. The figures on the left-hand side, Figures 14a and 14b, represent the behavior of arm neurons, while the figures on the right hand side, Figures 14c and 14d, represent the behavior of hand neurons. Figures 14a and 14c depicts how the small-capacity integrators behave in response to a difference, or error, between the target extension movement and the actual extension movement. Figures 14b and 14d depict this same error progression, but for flexion rather than extension. In each of these four plots, the top line represents the error as defined above. The second line represents the cue signal that arrives some time after the start of the experiment. The third line represents the activity of the small-capacity brake neuron, and the bottom two lines represent the activity of the small-capacity integrators.

The time course of the simulation can be broken down into five phases. The first phase is the pre-cue phase, which is the period of time from the start of the simulation to the arrival of the movement cue signal. During this phase, no movement will occur since the cue for movement has not yet been received. The second phase is the "movement before box" phase, which is the period of time over which the arm moves from its starting location and reaches the box. When the movement cue has arrived, the arm brake neuron will shut off, thus allowing movement of the arm to occur during this second phase. The third phase is the "movement overlap" phase, which is the short period of time where movement of the arm and movement of the hand overlap. Specifically, the arm comes to a halt after passing

the box, and the hand begins to open in order to grasp the food reward. When the hand reaches the box, it is a signal that the arm-hand combination is near its desired target. As a result, the hand brake neurons will shut off, which allows movement of the hand to commence during this third phase. The fourth phase is the "grasping" phase, where only the hand will now move in order to fully grasp the food reward. The small-capacity integrators in the arm will be turned off, and the arm brake neurons will be on, thus inhibiting further arm movement. The hand will continue to move until the desired target has been reached i.e. the food reward is fully grasped by the hand. The fifth and final phase is the "movement completion" phase, which occurs when all movement has been completed. During this time period, the small-capacity integrators in both the arm and hand neurons shut off, and the arm brake and hand brake neurons are turned back on, thus suppressing further movement.

The simulation outputs from the model relate to the three groups of neurons from Romo and Schultz' experiments in the following manner: the arm brake neurons turn on right after the subject begins preparing for the task but turn off just before any movement occurs. These neurons are indicative of Group A neurons. The hand brake neurons also turn on immediately after the subject begins preparing for the task. However, these neurons turn off when the arm has reached the box. This specific event becomes the cue to the hand neurons to release the brake and allow movement of the hand in order to grasp the object in the box. These neurons are indicative of Group B neurons. The small-capacity integrators are active for the duration of the experiment, independent of the cue signal or brake neurons but dependent upon the error between the target movement and the actual movement in the muscle.

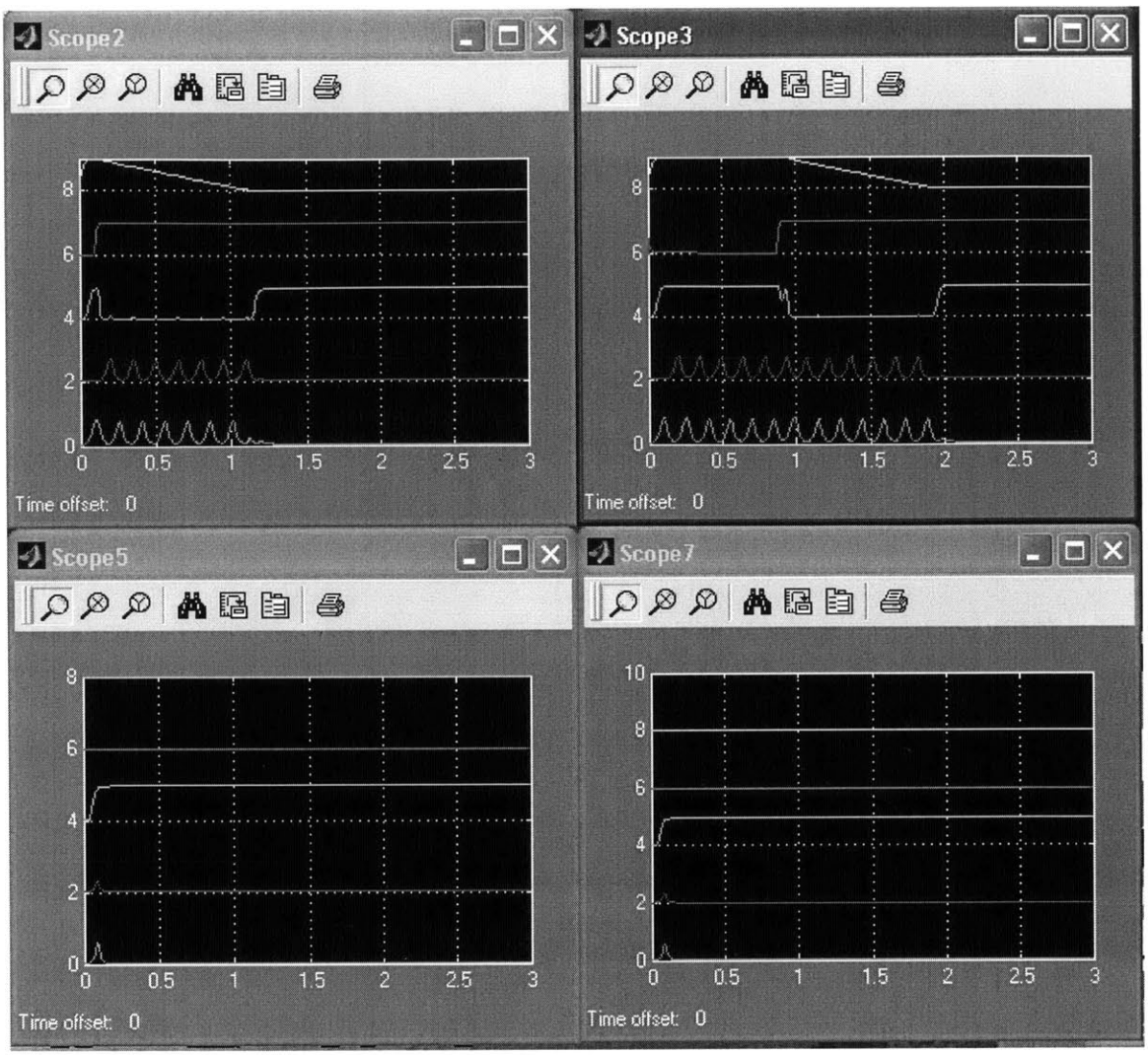

Figure 14: System Output for Asynchronous, Cruise (Pure Extension) Movement in a Normal Subject. Figure 14a (top left) shows the output for neurons responsible for arm extension. Figure 14b (top right) shows the output for the neurons responsible for hand extension. Figure 14c (bottom left) shows the output for neurons responsible for arm flexion. Figure 14d (bottom right) shows the output for neurons responsible for hand flexion.

These neurons are indicative of group C neurons. The position and velocity profiles of the arm and hand muscles in a normal subject are shown in Figure 15. The outputs of the model produce a ramp-like position profile and a plateau-like velocity profile, both of which are expected in such cruise movements performed by a normal subject.

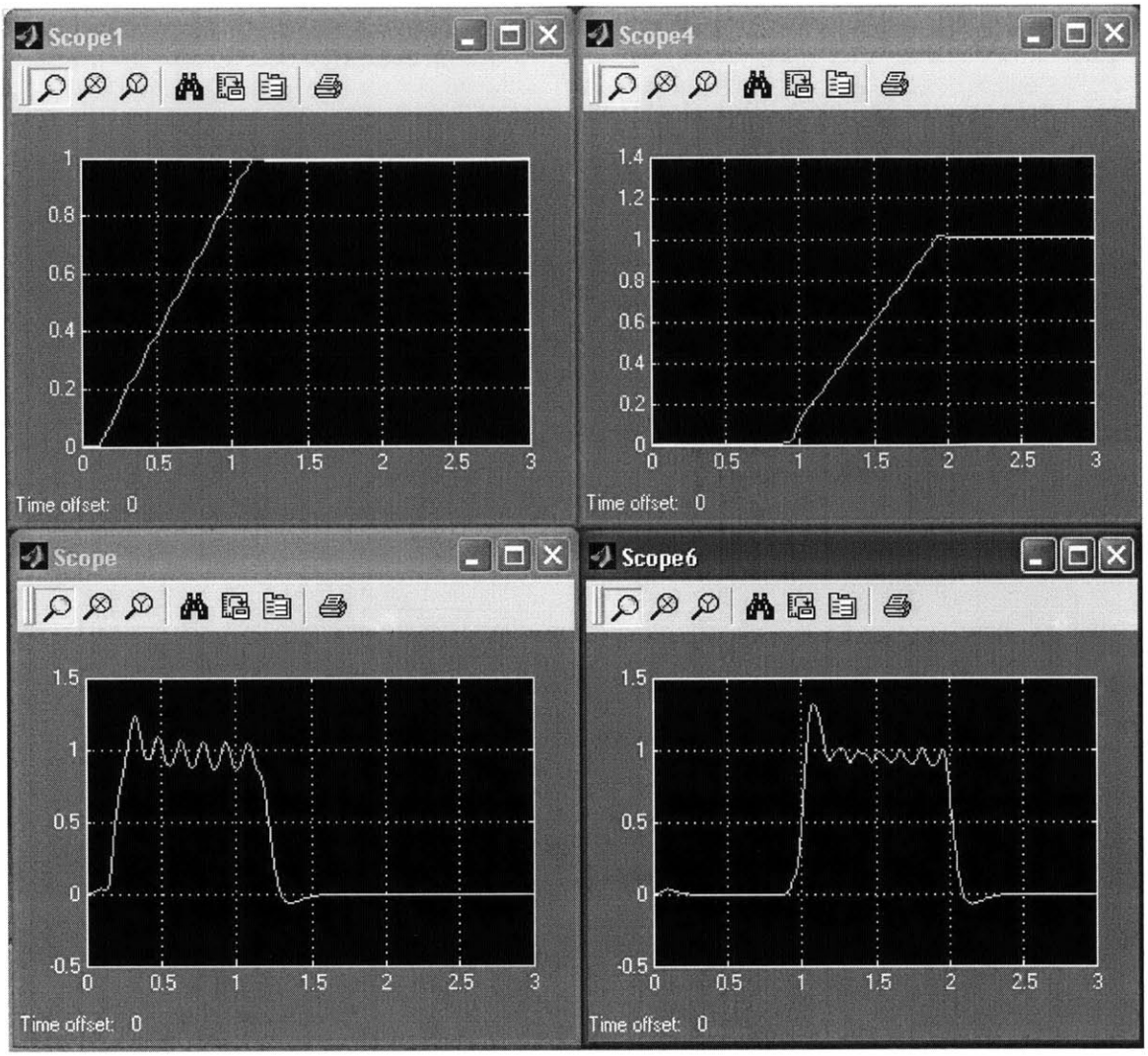

Figure 15: Position and velocity profiles for Asynchronous, Cruise Movement in a Normal Subject. Figure 15a (top left) shows the position profile relating to arm extension. Figure 15b (top right) shows the position profile relating to hand extension. Figure 15c (bottom left) shows the velocity profile relating to arm flexion. Figure 15d (bottom right) shows the velocity profile relating to hand flexion.

4.2.2 Huntington's Chorea

Figure 16 shows the simulation output for a test subject with Huntington's chorea. In Figure 16a and 16c, both small-capacity integrators in the extensor muscle suddenly switch on after a time when they had been alternating in activity. This occurs in both the arm and the hand. Figure 17 shows the position and velocity profile of a subject with Huntington's chorea. The velocity of the ramp movement increases when both small-

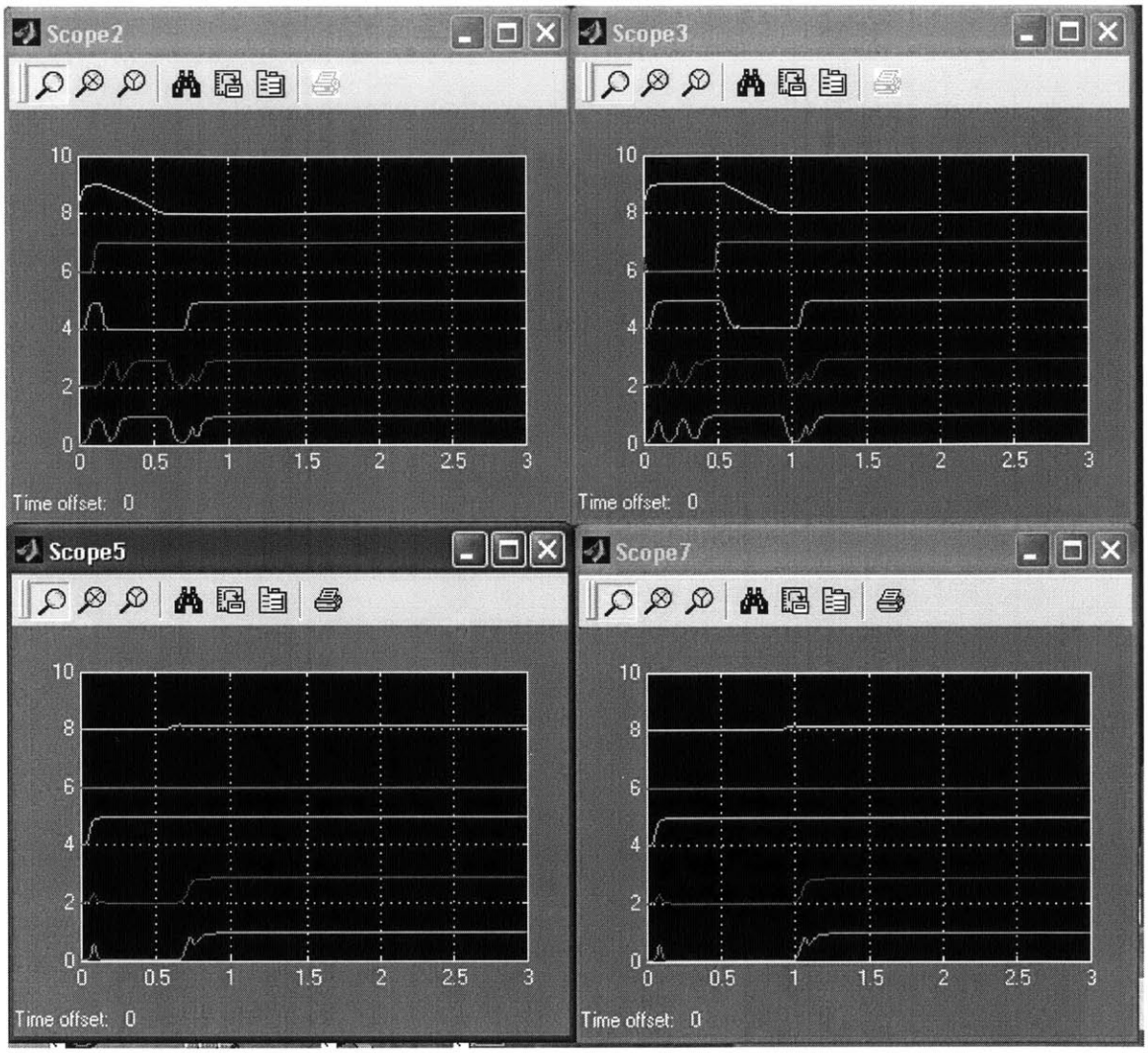

Figure 16: System Output for Asynchronous, Cruise Movement in a subject with Huntington's chorea. Figure 16a (top left) shows the output for neurons related to arm extension. Figure 16b (top right) shows output for neurons related to hand extension. Figure 16c (bottom left) shows output for neurons related to arm flexion. Figure 16d (bottom right) shows output for neurons related to hand flexion.

capacity integrators suddenly switch on. Furthermore, the arm overshoots its target position, but this unexpected movement is not sustained. These results are consistent for a test subject experiencing sudden, involuntary, but unsustained movements. While some inconsistencies exist in the velocity profile, abnormal movements of any significant size are not observed.

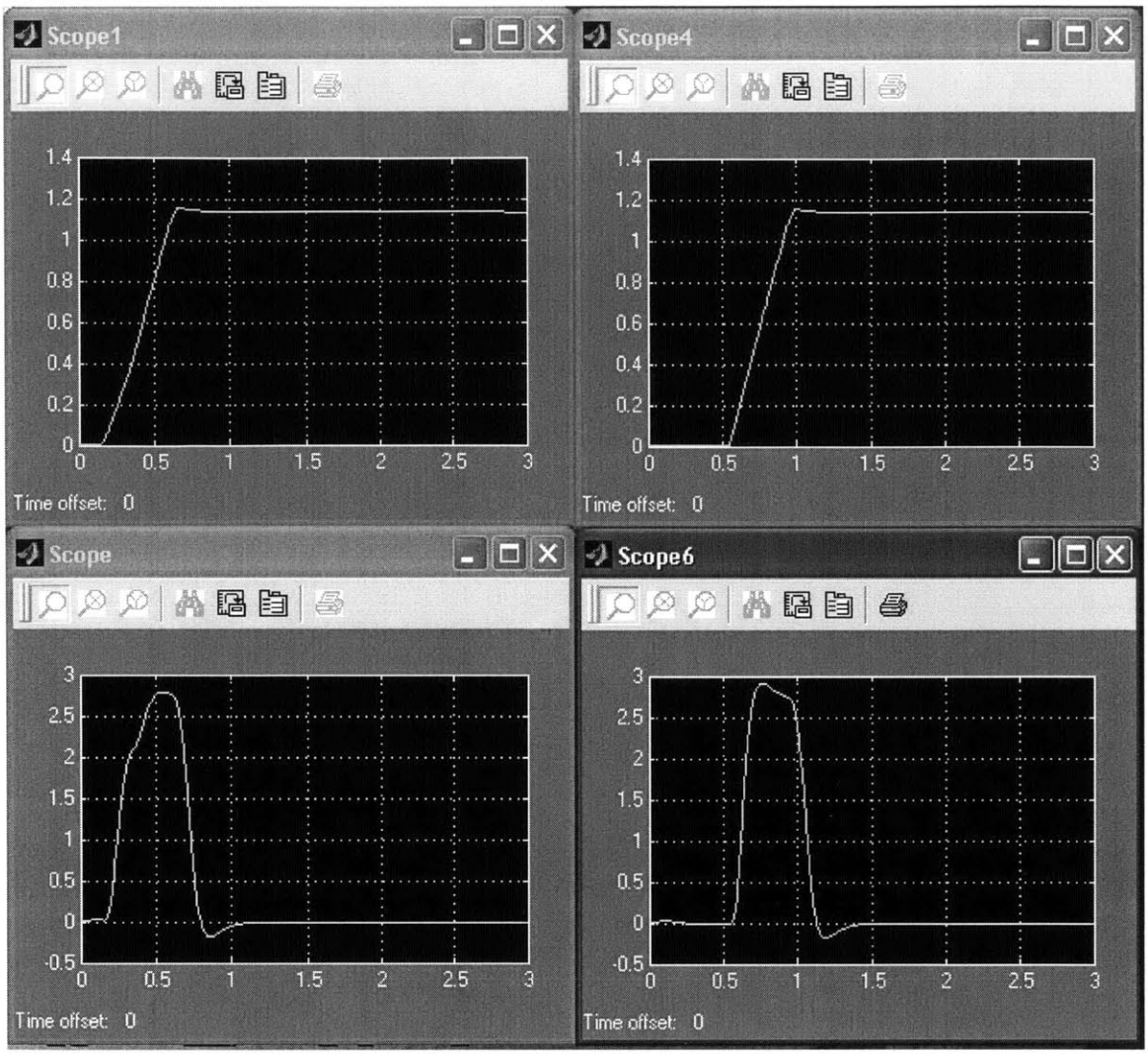

Figure 17: Position and velocity profiles for Asynchronous, Cruise Movement in a subject with Huntington's chorea. Figure 17a (top left) shows the position profile relating to arm extension. Figure 17b (top right) shows the position profile relating to hand extension. Figure 17c (bottom left) shows the velocity profile relating to arm flexion. Figure 17d (bottom right) shows the velocity profile relating to hand flexion.

4.2.3 Hemiballism

Figure 18 shows the simulation output for a test subject with hemiballism. In Figures 18a and 18b, both small-capacity integrators in the extensor muscle turn on and remain on for the duration of the experiment. This occurs in both the arm and the hand. Figure 19 shows the position and velocity profile of subject with hemiballism. The velocity of the ramp movement is much higher then the velocity of the same movement

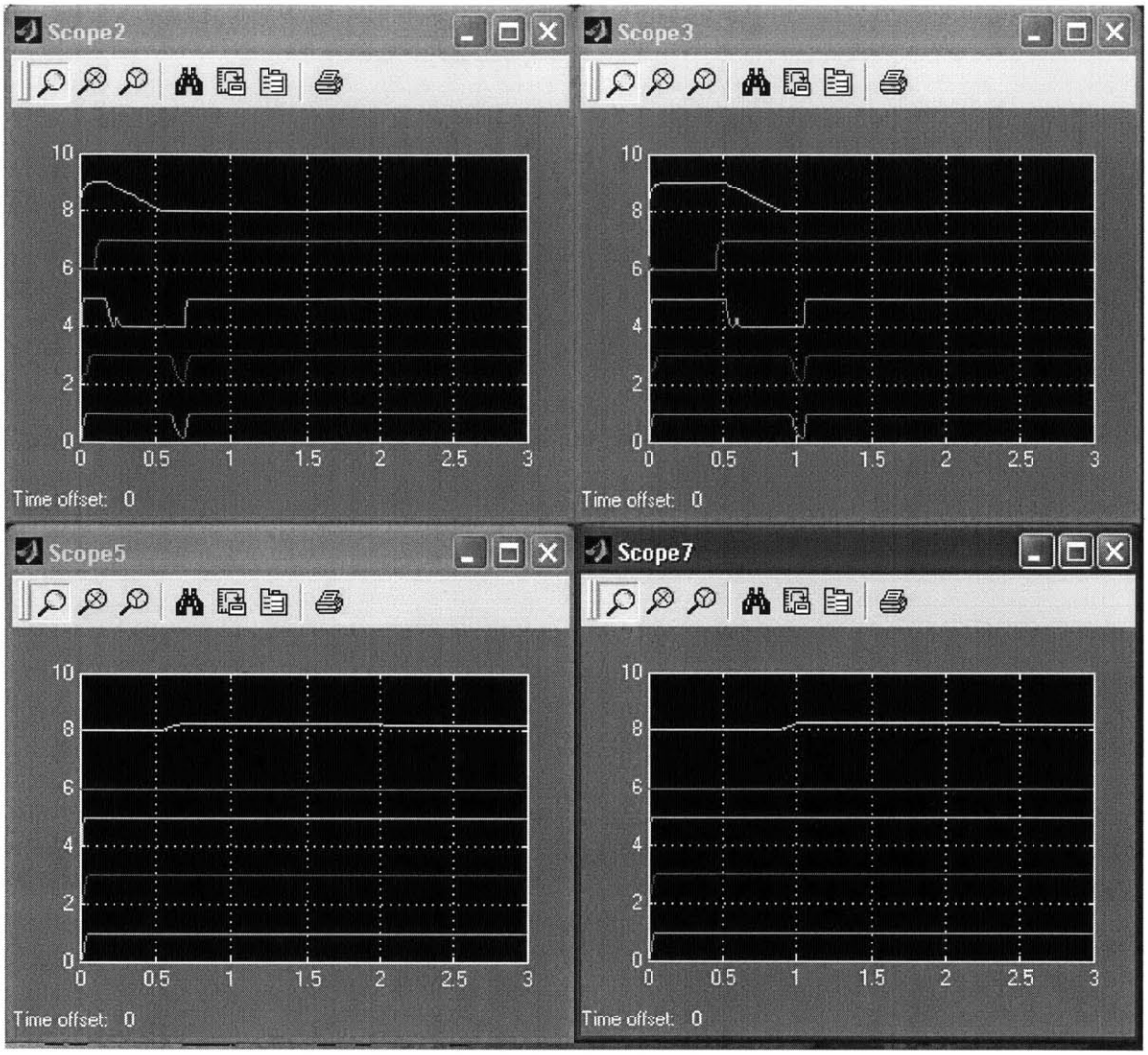

Figure 18: System Output for Asynchronous, Cruise Movement in a subject with hemiballism. Figure 18a (top left) shows output for neurons related to arm extension. Figure 18b (top right) shows output for neurons related to hand extension. Figure 18c (bottom left) shows output for neurons related to arm flexion. Figure 18d (bottom right) shows output for neurons relating to hand flexion.

in a normal subject. In addition, the arm overshoots its target position. These results seem consistent for a test subject experiencing exaggerated or jerking movements. However, there is no independent experimental data to support the hypothesis that the internal signals have this form.

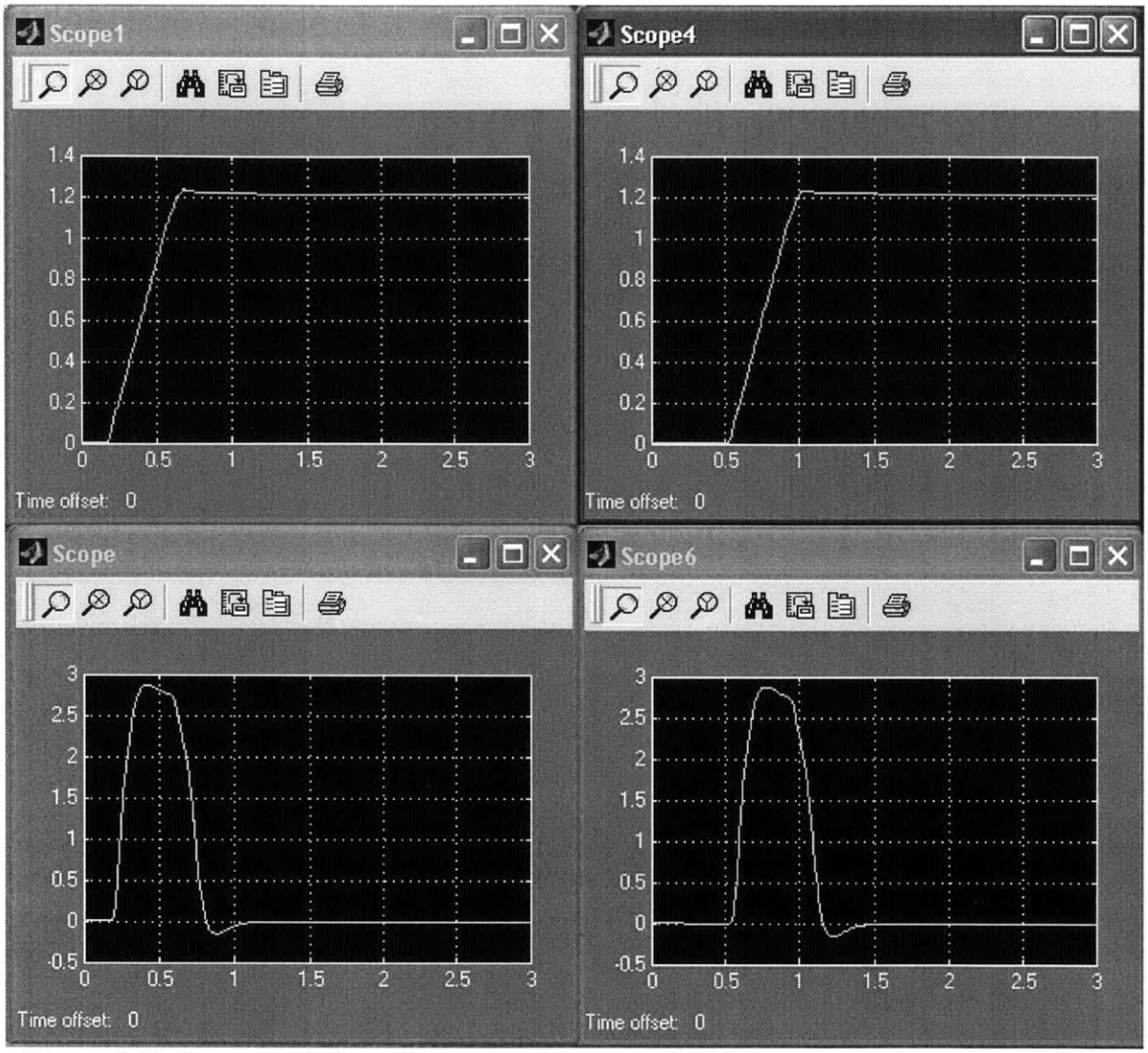

Figure 19: Position and velocity profile for Asynchronous, Cruise Movement in a subject with hemiballism. Figure 19a (top left) shows the position profile relating to arm extension. Figure 19b (top right) shows the position profile relating to hand extension. Figure 19c (bottom left) shows the velocity profile relating to arm flexion. Figure 19d (bottom right) shows the velocity profile relating to hand flexion.

4.2.4 Overall Assessment of Model Function in Asynchronous Cruise Movements

The proposed model provides relatively accurate asynchronous cruise movements for normal subjects if it can indeed be argued that the simplified grasping movement described in Section 3.3.1 can be broken down into the five movement phases as explained in Section 4.2.1. In addition, joint rotation and the possible involvement of other joints in such movements were not accounted for in this simplified experiment. In the case of both

Huntington's chorea and hemiballismus, there is no experimental data that support the hypothesis that the internal signals have the form demonstrated by the model. In addition, for the sake of simplicity, it was assumed that the neurons found in the arm and the hand were nearly identical. This explains why the activity of neurons in both the arm and the hand are very similar. This assumption may not be fully valid, and the model may require some modification as a result.

4.3 Model Function in Sequential, Single-Joint Cruise Movements

4.3.1 Normal Condition

As stated in Chapter 3, the movement sequence 2-4-5 was used in the Mushiake and Strick study to examine activity of neurons in the globus pallidus. From the resting position of the monkey's hand before the experiment, the sequence 2-4-5 would require one negative step, two positive steps, and one positive step. To best display the involvement of the basal ganglia in sequential movements, when the simulation began, the test subject was required to make one negative step of magnitude 0.5, two positive steps of magnitude 0.5, and one positive step of magnitude 0.5. This movement sequence is similar to the 2-4-5 sequence used in the Mushiake and Strick study.

Figure 20 shows activity of the small-capacity integrators due to a difference, or error, between the target movement and the actual movement. The top line represents error associated with extension movement, and the second and third lines represent the activity of the integrators associated with extension movement. The fourth line represents error associated with flexion movement, and the fifth and sixth lines represent the activity of the integrators associated with flexion movement. Based on the 2-4-5 sequence given, we see that a negative error of magnitude 0.5 is observed, and flexion movement (which we will consider as movement to the left for the sake of simplicity) of magnitude 0.5 occurs. Once this first phase of the sequence is completed, we see that a positive error of magnitude 1.0 is observed i.e. twice the magnitude of the first error, and extension movement (which we will consider as movement to the right for the sake of simplicity) of magnitude 1.0 occurs. Once this second phase of the sequence is completed, we see that a positive error of magnitude 0.5 is observed, and extension movement of magnitude 0.5 occurs. Once this third phase of the sequence is completed, then the movement sequence is finished, and no further movement

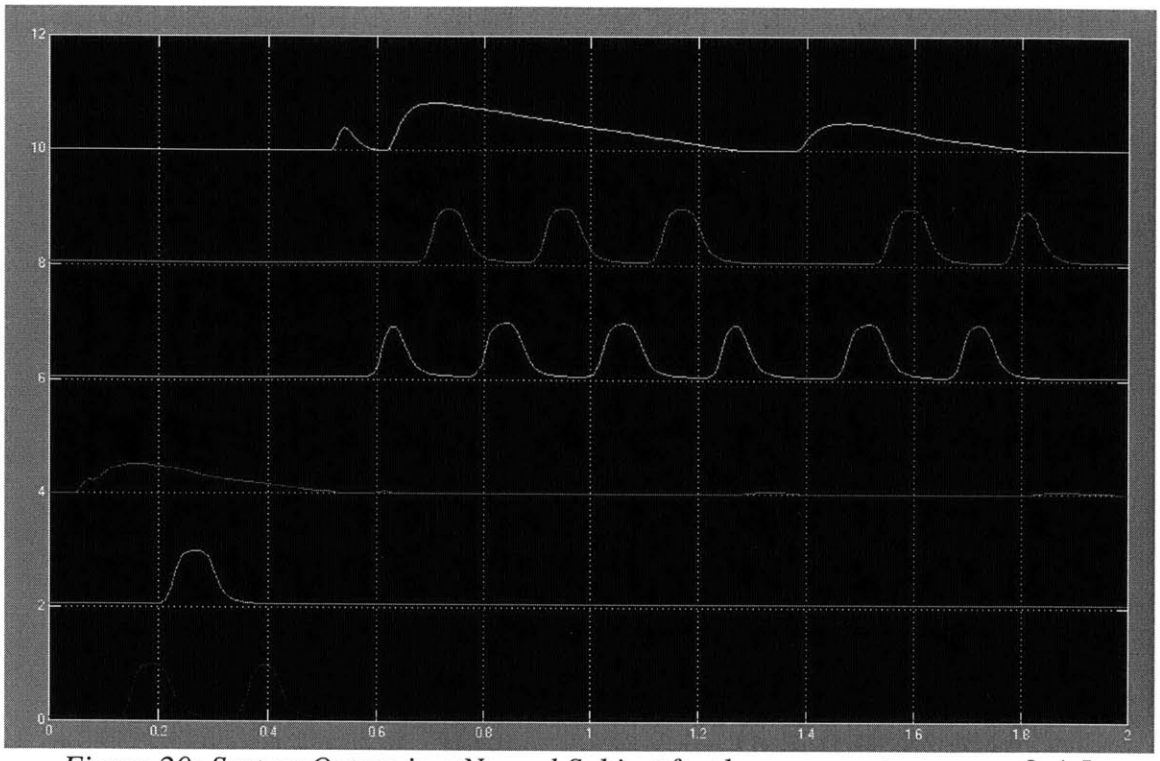

Figure 20: System Output in a Normal Subject for the movement sequence 2-4-5. Displays output of small-capacity integrators due to error between goal-directed movement and actual movement.

take place. Figure 21 shows the position and velocity profile of this movement sequence. A roughly ramp-like position profile is observed while, despite some initial overshoot, a plateau-like velocity profile is observed as well.

4.3.2 Huntington's Chorea

The neuronal outputs for a simulated test subject with Huntington's chorea revealed interesting results, as shown in Figures 22 and 23. From the integrator outputs, it appears as if the negative step is repeated, and in the position profile, we see that the subject does not move his hand the full step of -0.5 but rather stops short at -0.35 before moving in the positive direction. However, the subject does not move his hand the full step of 1.0 but

instead falls short at 0.05 before moving back in the negative direction, which is unexpected and not programmed.

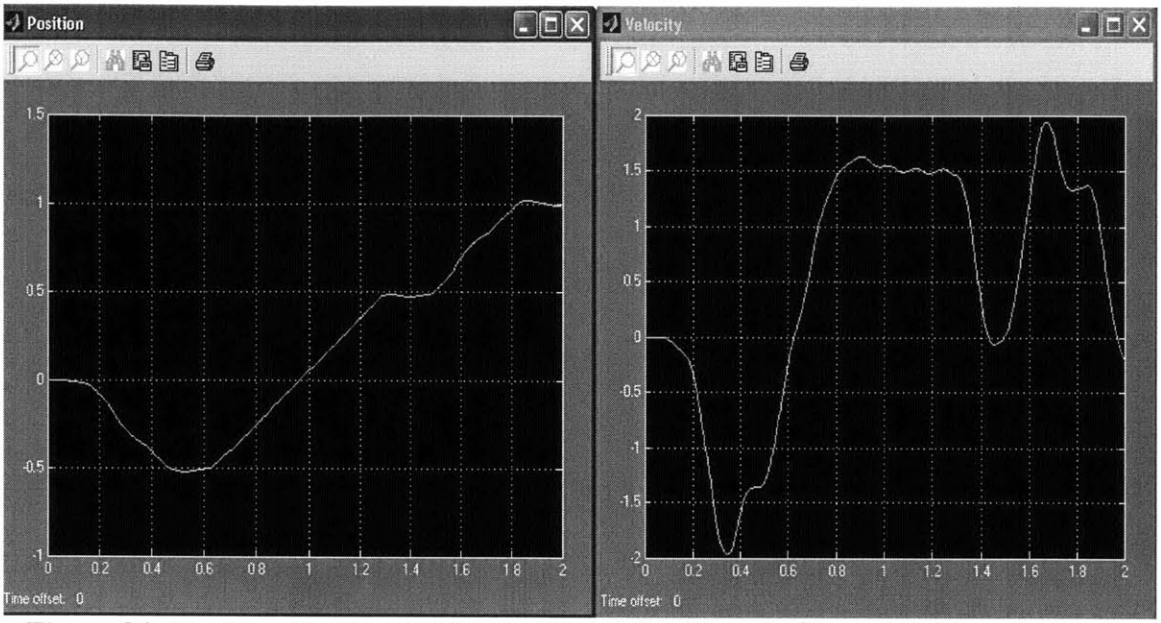

Figure 21: Position (Left) and Velocity (Right) Profiles of a Normal Subject during the movement sequence 2-4-5.

While no flailing movements were observed, unexpected movements did occur over the course of the movement sequence. This could be attributed to the weakening of the indirect pathway of the putamen due to a lesion in that area. As a result, it become increasingly difficult to shut off active neurons and maintain inhibition of suppressed neurons. This may account for the sudden and unexpected changes in negative and positive movement during the movement sequence.

Note that at the time of the writing of this thesis, insightful results were found only for normal conditions and for Huntington's chorea. Other movement disorders are being looked into, and results for these scenarios will be shown in future publications.

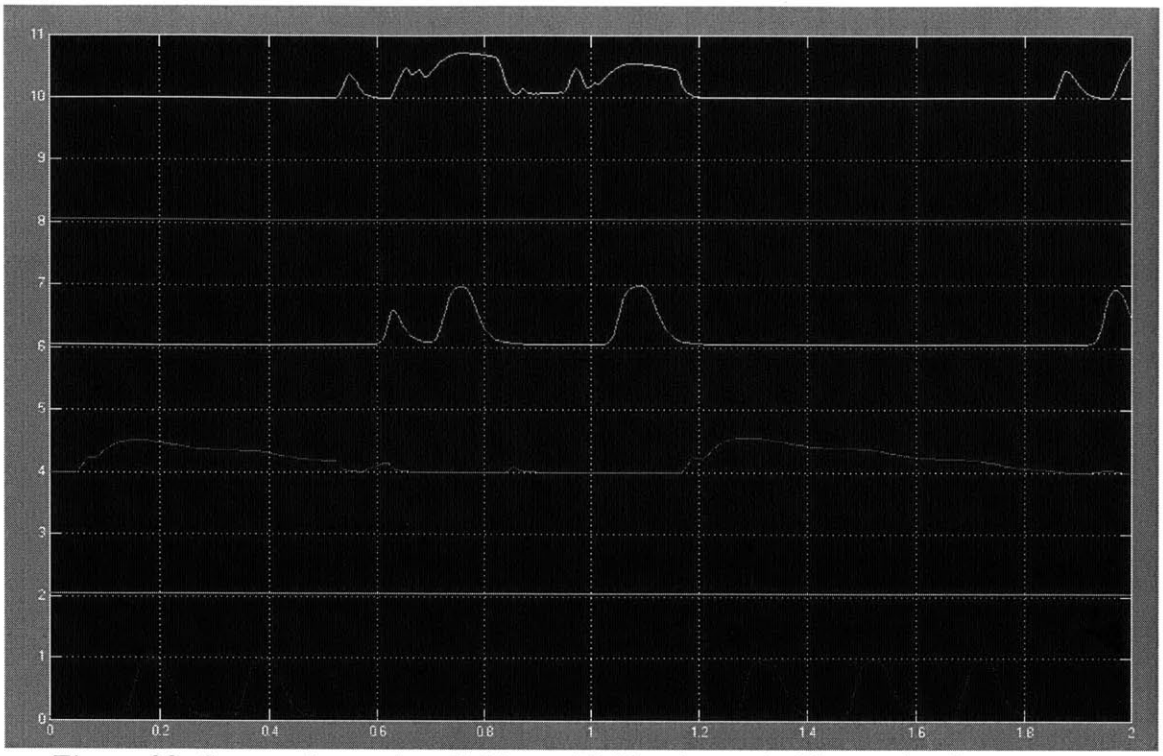

Figure 22: System Output in a Subject with Huntington's Chorea for the movement sequence 2-4-5. Displays output of small-capacity integrators due to error between goal-directed movement and actual movement.

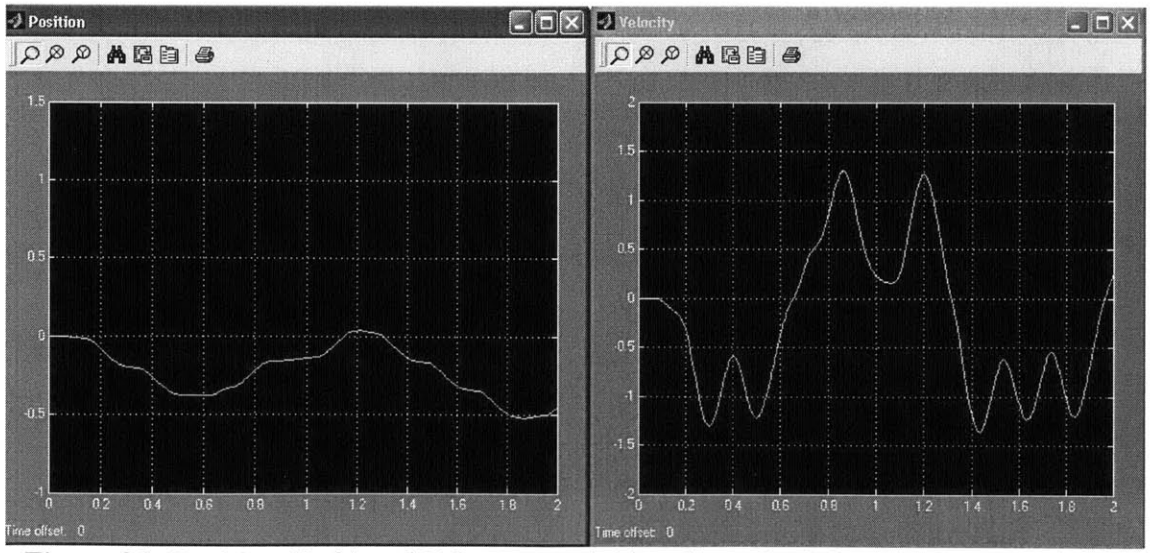

Figure 21: Position (Left) and Velocity (Right) Profiles of a Subject with Huntington's chorea during the movement sequence 2-4-5.

4.3.3 Overall Assessment of Model Function in Sequential Cruise Movements

The model was able to produce relatively smooth sequential cruise movements for the normal condition. It also provided insight into the effects of basal ganglionic damage in people with Huntington's chorea. However, there is no experimental data that support the hypothesis that the internal signals have the form demonstrated by the model. During this experiment, we observed neurons that became active during a single phase of movement for a movement sequence, specifically 2-4-5. While these neurons exhibited some properties of phase specificity, the current model is limited, because a neuron that is active during the second phase of movement sequence 2-4-5 will also become active during the same phase of movement sequence 2-4-3 due to the current logical programming of the model. As the monkey was able to memorize the instructed sequence before the trial during the remembered task, the model will need to be constructed so that knowledge of a particular sequence is known before movement occurs in order to model and simulate truly phase- and sequence-specific neurons. Furthermore, in developing the model, only the phase- and sequence-specific neurons were modeled for the sake of simplicity. Regardless of the success of this model, the model will need to be extended to take into account other types of neurons as well.

Chapter 5: Conclusion and Future Work

This extension of the model proposed by Massaquoi and Mao was successful in many respects. First of all, it was able to provide a fairly realistic reproduction of both kinematic and electrophysiological aspects simple cruise movements in the normal condition and the Parkinson's disease condition. The model appears to explain some parts of dystonia, Huntington's chorea, and hemiballismus, though electrophysiological data for these conditions are needed to verify the results produced by the model.

The asynchronous movements produced by the model seem plausible if it can be argued that a reaching and grasping movement can be broken down into the five phases mentioned in Section 3.3.1, particularly the notion that there is indeed a time period over which arm movement and hand movement overlap. The concept of including separate "braking" neurons for the arm and the hand may be feasible, but further research is needed to verify the existence of such neurons. The movement disorder simulations offered limited insight beyond what happened in simple point-to-point movements. This suggests that more structure is needed in the model, particularly inclusion of the caudate or else internally generated switching cues based on predicted motion rather than actual motion. Moreover, the neuronal architecture of the arm and the hand may differ to the point where the neurons in the arm and the hand may have to be modeled differently according to what is found in electrophysiological data.

In regards to sequential movements, the model was able to produce the sequence of movements used in animal experiments and provided insightful results for some scenarios. However, other movement disorders will have to be looked into, and the model will need to be extended to simulate genuinely phase- and sequence-specific neurons along with the other neurons found in the literature.

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