Information Processing in the Striatum

A Computational Study

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Abstract

The basal ganglia form an important structure centrally placed in the brain. They receive input from motor, associative and limbic areas, and produce output mainly to the thalamus and the brain stem. The basal ganglia have been implicated in cognitive and motor functions. One way to understand the basal ganglia is to take a look at the diseases that affect them. Both Parkinson’s disease and Huntington’s disease with their motor problems are results of malfunctioning basal ganglia. There are also indications that these diseases affect cognitive functions. Drug addiction is another example that involves this structure, which is also important for motivation and selection of behaviour.

In this licentiate thesis I am laying the groundwork for a detailed model of the striatum, which is the input stage of the basal ganglia. The striatum receives glutamatergic input from the cortex and thalamus, as well as dopaminergic input from substantia nigra. The majority of the neurons in the striatum are medium spiny (MS) projection neurons that project mainly to globus pallidus but also to other neurons in the striatum and to both dopamine producing and GABAergic neurons in substantia nigra. In addition to the MS neurons there are fast spiking (FS) interneurons that are in a position to regulate the firing of the MS neurons. These FS neurons are few, but connected into large networks through electrical synapses that could synchronise their effect. By forming strong inhibitory synapses on the MS neurons the FS neurons have a powerful influence on the striatal output. The inhibitory output of the basal ganglia on the thalamus is believed to keep prepared motor commands on hold, but once one of them is disinhibited, then the selected motor command is executed. This disinhibition is initiated in the striatum by the MS neurons.

Both MS and FS neurons are active during so called up-states, which are periods of elevated cortical input to striatum. Here I have studied the FS neurons and their ability to detect such up-states. This is important because FS neurons can delay spikes in MS neurons and the time between up-state onset and the first spike in the MS neurons is correlated with the amount of calcium entering the MS neuron, which in turn might have implications for plasticity and learning of new behaviours. The effect of different combinations of electrical couplings between two FS neurons has been tested, where the location, number and strength of these gap junctions have been varied. I studied both the ability of the FS neurons to fire action potentials during the up-state, and the synchronisation between neighbouring FS neurons due to electrical coupling. I found that both proximal and distal gap junctions synchronised the firing, but the distal gap junctions did not have the same temporal precision. The ability of the FS neurons to detect an up-state was affected by whether the neighbouring FS neuron also received up-state input or not. This effect was more pronounced for distal gap junctions than proximal ones, due to a stronger shunting effect of distal gap junctions when the dendrites were synaptically activated.

We have also performed initial stochastic simulations of the Ca²⁺-calmodulin-independent protein kinase II (CaMKII). The purpose here is to build the knowledge as well as the tools necessary for biochemical simulations of intracellular
processes that are important for plasticity in the MS neurons. The simulated biochemical pathways will then be integrated into an existing model of a full MS neuron. Another venue to explore is to build striatal network models consisting of MS and FS neurons and using experimental data of the striatal microcircuitry. With these different approaches we will improve our understanding of striatal information processing.

**Keywords:** striatum, fast spiking interneuron, gap junctions, synchronisation, up-state detection, CaMKII, mathematical modelling

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Sammanfattning


I denna licentiatavhandling lägger jag grunden för en detaljerad modell av striatum, som är första steget i signalbehandlingen i basala ganglierna. Striatum får glutamatergiska insignaler från cortex och talamus, samt dopamin från substantia nigra. De flesta neuroner i striatum är medium spiny (MS) projektiionsneuroner och projicerar främst till globus pallidus, men även till andra neuroner i striatum och till både dopaminproducerande och inhibitoriska neuroner i substantia nigra. Det finns även fast spiking (FS) interneuroner i striatum, vilka trots att de är relativt få, kan påverka MS-neuronernas spikande. FS-neuronerna är elektriskt kopplade till varandra via gap junctions, vilka synkronisera deras effekt på MS-neuronerna. Basala ganglierna ligger hela tiden och inhibitor förberedda motorkommandon. När vi ska utföra en motorisk handling lyfts inhibitionen via disinhibition från MS-neuronerna.


Vi har också utfört stökastiska simuleringar av Ca$^{2+}$-calmodulin-beroende protein kinas II (CaMKII). Detta var en förstudie till vidare biokemiska simuleringar av intracellulära processer som är viktiga för plasticitet i MS-neuronerna. Tanken är att dessa biokemiska simuleringar ska integreras i en existerande modell för FS-neuronen. Vi planerar även att bygga nätverk med FS- och MS-neuroner baserade på data om mikrostruktur i striatum. Syftet är att öka vår förståelse för informationsbehandlingen i striatum.
To my family and friends
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Chapter 1

INTRODUCTION

When I started my PhD studies at the Royal Institute of Technology (KTH) I began by attending a basic neuroscience course at the Karolinska Institute (KI). It was a fascinating course where we learned about how the brain and the nervous system worked. One episode in particular stood out from the ordinary lectures and laborations. As part of the course we were shown real human brains taken from deceased people and stored in formalin. The teaching assistant took a brain out of the plastic jar in which it was stored and showed it to us pointing out the different cortical landmarks. I remember standing there and looking at the brain she was holding and reflecting on the fact that my own brain, not all that different from that one, was trying to make sense of what it saw. How could a structure like that form a thought. The brain and the processes associated with it have puzzled humans for a long time. It is intimately tied with who we are and how we perceive ourselves. *Je pense, donc je suis* or, I think therefore I am, as René Descartes so eloquently put it.

It is a challenging task to try to understand how the brain works, a long journey paved with interesting puzzles and great discoveries. Each day we rely on our brains to make countless choices, some of the choices are life-altering, while others may be more mundane: what to make for dinner; how best to approach a possible mate; or whether to turn left or right at the next intersection. One interesting type of choices is action-selection (Barto, 1994). For example, if we are a monkey in an experiment hoping for some fruit juice, do we move our arm left or right in response to the picture shown on the screen ahead of us (Hollerman and Schultz, 1998; Cromwell and Schultz, 2003)? What processes in the brain enable us to perform action-selection?

As with so many other things, we only realise how important something is to us when we are about to lose it. Through the study of various neurological diseases and other, sometimes highly localised, damage to the brain, researchers and physicians have been able to understand what functions the damaged parts must have filled. From studies of Parkinson patients, where a loss of dopamine
producing neurons result not only in motor problems like rigidity, tremor and freezing, but also in non-motor problems like depression, passivity and dementia (Fahn, 2003; Parkinson, 1817), we learn that there is an important interaction between the cerebral cortex and a centrally placed structure called the basal ganglia, and that the signalling substance dopamine plays an important role in this (Schultz, 2006).

How can a complex system like the brain learn to perform certain tasks? In their book Sutton and Barto (1998) discuss different ways to make a machine learn new behaviours. An action that leads to a high reward would be selected over an action that leads to a low reward. This type of matching of behaviour and reward is relatively simple. However, what happens if the action does not directly result in a reward? Let us say a sequence of actions is required, like navigating a maze, before a reward can be collected at the end. How do we then assign values to the individual actions required? One solution could be to have two entities; a critic that tries to predict the reward associated with the current actions available and an actor that based on the predicted reward chooses an action. Both the actor and critic are improved afterwards based on the difference between their prediction and the actual reward. Over time the internal representation of the future reward will get better as the system learns. This system is also able to cope with changes in the environment.

What is so fascinating is that there are structures in the brain that are believed to implement this actor-critic type of learning (Houk et al., 1995; Djurfeldt et al., 2001; Bar-Gad et al., 2003). In particular we are interested in the function of the striatum, which is the input stage of the basal ganglia, an important structure for behavioural selection and motor learning that receives input from large areas of the cortex. The striatum is not homogenous, it can be divided into acetylcholinesterase-poor striosomes surrounded by the more enriched matrix (Graybiel and Ragsdale, 1978; Graybiel et al., 1981). The structure is further described in section 2.2.1. In the striatum the striosomes are believed to take the role of the critic and the surrounding matrix is thought to be the actor, also the dopamine signal they received have similarities with the temporal difference error in the actor-critic learning (Houk et al., 1995; Schultz et al., 1997; Dayan and Balleine, 2002; Reynolds and Wickens, 2002; Schultz, 2006).

1.1. Scope of the Thesis

We wish to understand the striatum’s structure on different levels. The work done in this thesis has been mainly on the fast spiking (FS) interneurons, which only make up a small part of the neuronal population in the striatum. However, the FS neurons are connected to each other through gap junctions, forming electrical networks that could probably synchronise their effect (Koós and Tepper, 1999; Galarreta and Hestrin, 2001; Traub et al., 2001; Connors and Long, 2004). This enables them to have a strong influence on the spiking of the medium spiny (MS) projection neurons (Bolam et al., 2000; Koós and Tepper, 1999; Tepper et al., 2004). The MS neurons are the main population of neurons in the striatum, and they are the only neuron type projecting to the
output stages of the basal ganglia. In Paper I I focus on the effect of different
gap junction localisations on synchronisation. Cortical input varies in intensity,
periods of higher activity are termed up-states, and periods of lower activity are
detection, or more precisely, the effect gap junctions have on the FS neurons
ability to fire an action potential in response to an up-state. In this paper I also
study different gap junction mechanisms at play during up-state detection. In
Paper III we perform some initial stochastic simulations of Ca\textsuperscript{2+}-calmodulin-
dependent kinase II (CaMKII). The goal here is to later implement this and other
biochemical networks into existing MS neuron models (Wolf et al., 2005). My
contribution here was mainly to help with a parallel implementation of the code
as part of a course project Malin Sandström and I worked on together.

1.2. List of Papers

Paper I. Johannes Hjorth, Alex H. Elias, Jeanette Hellgren Kotalaski, The sig-
nificance of gap junction location in striatal fast spiking interneurons, CNS
Edinburgh Submitted, 2006

Paper II. Johannes Hjorth, Jeanette Hellgren Kotalaski, Up-state signalling
and Coincidence Detection in Striatal Fast Spiking Interneurons Coupled
through Gap Junctions, Manuscript, 2006

Paper III. Malin Sandström, Johannes Hjorth, Anders Lansner, Jeanette Hell-
gren Kotalaski, The impact of the distribution of isoforms on CaMKII acti-
vation Neurocomputing, 69(10-11) 1010-1013, 2006
Chapter 2

BIological Background

Before we can dig into the modelling details we should first get a basic understanding of the system we are studying. How does a neuron work, how do they connect to their neighbours and what is the function of the local microcircuitry. We need to understand the system from a neuronal level all the way up to the network level. This chapter introduces the biological basis for the thesis. The first section deals with the basic functions of a neuron, focusing on the mechanisms required for information processing. It describes how signals are chemically transmitted between neurons, how the received signals are processed, and what mechanisms are needed to send the signal onwards to new neurons. The second section gives an overview of the structure of the striatum, touching upon the different parts and how they are connected. For a more detailed description, see one of the many good reviews available (Wickens et al., 2003; Bar-Gad et al., 2003; Hikosaka et al., 2006). The third section introduces three of the neuron types that can be found in the striatum; medium spiny (MS) projection neuron, fast spiking (FS) interneuron and tonically active (TA) interneuron. The fourth section talks about learning and plasticity in the striatum, introducing the role of dopamine. The fifth and last section talks about diseases that plague striatum and the basal ganglia, motivating us to better understand this important structure in the brain.

2.1. Basic Function of a Neuron

The human brain has 100 billion ($10^{11}$) neurons which is roughly equal to the number of stars in our galaxy. Connecting these neurons we have on the order of 100 trillion ($10^{14}$) synapses allowing them to share information and make decisions. Let us for a moment zoom in on one of these neurons. This particular neuron is for instance located in the striatum, which is the input stage of the basal ganglia. In Figure 2.1 we can see the three parts that a neuron consists
of a dendritic tree that receives inputs from other neurons, a cell body, or soma, where the input converges and an axon that connects to other neurons sharing the information (Kandel et al., 2000). Surrounding this neuron there is a cell membrane that prevents ions from flowing freely. There are different concentrations of ions on the inside and outside, leading to a potential difference across the membrane. The inside is more negatively charged than the outside. When ion channels in the membrane open, ions are allowed to try to reach their respective equilibrium potential. The neuron can become more depolarised, that is the potential difference goes towards zero, or a hyperpolarisation can occur, where the potential difference becomes even larger.

The neurons are connected to each other through both chemical and electrical synapses. Our neuron receives information from other neurons through synapses located on its soma or in the dendritic tree. Chemical signalling substances, called transmitters, are released from axon terminals and travel across the small gap, the synaptic cleft, between the axon of the first neuron and the dendrite of the second neuron. When the transmitter substances reach a receptor on the target side a reaction starts which results in ion channels opening, either depolarising or hyperpolarising a neuron from the resting potential. The chemical signal has become an electrical signal that is typically transmitted through the dendrites to the soma, where it is summed together with other electrical signals. If the depolarisation is large enough sodium channels will begin to open in a self-regenerating process resulting in an action potential, this creates a strong electrical signal that travels actively along the axon. The depolarisation resulting from the action potential opens channels at the axon terminal that allow calcium to flow into the neuron, calcium triggers the merging of synaptic vesicles with the cell membrane, releasing their content of transmitters into the synaptic cleft that are then transferred to the next neuron and the process begins anew.
2.1.1. Ligand Gated Channels

In order to receive the chemical signal that is transmitted by transmitter substances across the synaptic cleft the receiving neuron has to be able to detect the signal and transform it into an electrical signal. This can be done by ligand gated channels, a channel type which is one of many different types of channels in the neuron. A ligand gated channel is a channel that is activated by binding to a ligand, like for instance a transmitter substance such as glutamate, binding to the AMPA receptor. This binding of glutamate results in the channel opening, allowing sodium ions to flow into the neuron depolarising it. Below are a few examples of the different ligand gated channels that exist in the input stage of the basal ganglia, the striatum.

AMPA Receptors

AMPA is short for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. It is a specific agonist for the AMPA receptor. The AMPA receptor is a glutamate receptor that is permeable to cations as sodium and potassium (Hille, 2001). Some types of AMPA receptors are also permeable to calcium. The AMPA synapse has excitatory effects on the neuron and depolarises it bringing it closer to firing threshold.

NMDA Receptors

NMDA (N-methyl-D-aspartic acid) is an agonist for the NMDA receptor (Hille, 2001). The NMDA receptor is permeable to sodium and potassium but also to calcium. This is very important since the intracellular concentration of calcium is very low. The opening of NMDA channels results in a rotatable concentration change for calcium, which then activates other processes. At resting potential the NMDA channel is blocked by a magnesium ion. This block is however removed at more depolarised transmembrane potentials which means that glutamate alone can not activate this channel unless the neuron is already slightly depolarised by other inputs. This property is considered important for memory and learning. The NMDA channel is slower to activate and inactivate than the AMPA channel, which results in a more drawn out effect.

GABA Receptors

Gamma-aminobutyric acid, or GABA, is an inhibitory neurotransmitter that by binding to the GABA receptor opens a channel which allows negatively charged chloride ions to enter and positively charged potassium ions to exit, resulting in a hyperpolarisation of the neuron (Hille, 2001).

Dopamine

The dopamine receptors are metabotropic and act by second messenger pathways. There are two main types of dopamine receptors, the D1 and D2, that
have different effect and localisation. In striatum dopamine is believed to signal how unexpected a reward was (Schultz et al., 1997).

2.1.2. Voltage Gated Ion Channels

The voltage gated ion channels have a small charge in their protein structure that makes them sensitive to the transmembrane potential. A depolarisation of the neuron can either open or close the channel, changing the flow of ions across the membrane. This is important as it allows the neuron to respond in a nonlinear way, an example of this is the action potential. Here we give examples of two voltage gated channels, the sodium and potassium channels.

Sodium Channels

The voltage gated sodium channels are important for the eliciting of action potentials in the neuron, without it the neuron is unable to spike. The sodium channel is made up of four subunits that all must be open simultaneously to allow $\text{Na}^{+}$ to pass through (Hille, 2001). The more depolarised the neuron is the higher probability that the channel opens, but once it has opened it begins to inactivate. If more channels open than close then a self-sustained process will start. Open channels let sodium pass through, depolarising the neuron further, which in turn opens more channels, resulting in an action potential. After the sodium channels have opened, they become inactivated, a process that needs to be reversed by a hyperpolarisation, before they can open again. The action potential, once elicited, is actively propagated along the axon as neighbouring sodium channels sense the depolarisation and also open. The sodium channels are usually located on the soma and at the so-called nodes of Ranvier on the axons. There also exist neurons that have sodium channels on the dendrites.

Potassium Channels

The potassium channels are the most common ion channels, they come in many flavours and can be either voltage gated, ligand gated, calcium gated, etc. or purely passive leak channels (Hille, 2001). Potassium channels are responsible for the equilibrium potential in the neuron and they also activate during an action potential to hyperpolarise the neuron. The Kv3.1-Kv3.2 channel is important for the FS neurons ability to spike rapidly, which is discussed further in section 2.3.2.

2.1.3. Gap Junctions

The most common type of connections between neurons are the chemical synapses that can be either excitatory or inhibitory. In addition to the chemical synapses there are also electrical synapses, referred to as gap junctions. Gap junctions are reciprocal connections that allow ions and small molecules up to 1000 daltons to pass between the neurons. Nutrients, metabolites, second messengers, cations and anions can all diffuse through the central pore (Evans and Martin,
2. Biological Background

Gap junctions are simpler than chemical synapses and respond faster. The amount of coupling appears to be regulated by dopamine in the basal ganglia, probably through the addition or removal of gap junctions between the neurons. Experiments have been performed where Lucifer yellow, a dye used to stain cells, was injected into neurons to see how the dye would spread to neighbouring neurons through gap junctions. Activation of the D1-receptor decreases dye-coupling, and activation of the D2-receptor increases dye-coupling (O’Donnell and Grace, 1993). D1-receptors are usually associated with the direct pathway and D2 with the indirect pathway in the basal ganglia (see below). Several of the early studies did not detect dye coupling between fast spiking interneurons where more recent studies are able to detect electrical coupling. Bennett and Zukin (2004) offer some explanations to why this is the case, the geometry and dilution of tracers gave a measure below threshold for the early studies. In vivo recordings have shown that pharmacological manipulations of the dopamine system can result in a 4-fold increase in the number of couplings between e.g. MS neurons (Onn and Grace, 1999). Low cytoplasmic pH and high cytoplasmic Ca$^{2+}$ concentration block gap junctions. There is also to some extent transjunctional voltage gating (Bennett and Zukin, 2004). Early in development electrical coupling is present in many types of neurons, but gradually subsides as the animal matures (Peinado et al., 1993; Bennett and Zukin, 2004). In parvalbumin positive interneurons the gap junctions are also present in adult animals (Galarreta and Hestrin, 2002).

2.2. Basal Ganglia Nuclei

The basal ganglia consist of several nuclei as seen in Figure 2.2. Below we will briefly describe each of these with the focus on striatum which is the input stage of the basal ganglia, receiving inputs from large areas of the cortex. The basal ganglia are able to activate different behaviours through its connections to the thalamus and the brain stem.

In the classical view there are two main pathways through the basal ganglia: the direct and indirect pathway. The direct pathway goes from the striatum to the globus pallidus interna (GPI), whereas the indirect pathway goes through globus pallidus externa (GPe) to sub-thalamic nucleus (STN) and then to GPI. The direct pathway activates basal ganglia target areas, such as thalamus and the brainstem, by a process called disinhibition (that is removal of inhibition), while the indirect pathway acts inhibitory on the same areas. Dopamine can activate the direct pathway through the D1-receptor while decreasing the activity in the indirect pathway through the D2-receptor. Dopamine depletion leads to low activity in the direct pathway and too high activity in the indirect pathway. This is a simple model to explain the effects of Parkinson (DeLong, 1990). The MS neurons of the striatum that are part of the direct pathway are believed to activate motor commands and those that project to the indirect pathway inactive or prevent motor commands from starting (Bar-Gad et al., 2003). Newer studies however have shown that the division between the two pathways might be less distinct (Graybiel, 2005; Lévesque et al., 2005).
2.2. Basal Ganglia Nuclei

![Diagram of Basal Ganglia Circuitry](image)

**Figure 2.2.** Basal ganglia circuitry. The striatum and the sub-thalamic nucleus (STN) receive input from the cortex. Both striatum and the tonically active STN project to globus pallidus interna (GPI), substantia nigra reticulata (SNr) and globus pallidus externa (GPe). Further, the striatum has a reciprocal connection with the dopamine producing neurons in substantia nigra compacta. Thalamus, which acts as a relay station, receives input from cortex, GPI, SNr and projects back to both cortex and striatum. Filled arrows are glutamate, white arrows are GABA and open arrows are dopamine synaptic projections (Bar-Gad et al., 2003).

In addition to the projections to motor and premotor areas there are also extensive projections in an organised manner back to multiple areas of the prefrontal cortex indicating that the basal ganglia influence cognitive processes (Middleton and Strick, 2002). These prefrontal areas in turn project back to the input regions of the basal ganglia forming what appears to be closed loops. There seem to be separate loops for motor and cognitive functions (Bar-Gad et al., 2003).

### 2.2.1. Striatum

The striatum can be subdivided into two parts. One part is the dorsal striatum, which handles sensorimotor systems. In humans, this part consists of caudate and putamen. The other part is the ventral striatum which is part of the limbic system and consists of the nucleus accumbens. On a finer scale the striatum has an interesting structure with regions called striosomes surrounded by matrix (Graybiel and Ragsdale, 1978; Bar-Gad et al., 2003). The basal ganglia are thought to implement actor-critic reinforcement based learning (Sutton and Barto, 1998). The matrix is active during execution of behaviour and the striosomes are mainly active during learning of new behaviours indicating that the matrix is the actor and the striosomes are the critic (Houk et al., 1995; Djurfeldt et al., 2001). Furthermore the matrix receives input mostly from motor and somatosensory areas and posterior cingulate cortex while the striosomes receive
input mainly from prelimbic, infralimbic, orbital, and anterior cortices. Both anterior cingulate and orbitofrontal cortices are involved in motivation, learning and decision making (Canales, 2003).

The majority of the neurons in the striatum are GABAergic medium spiny (MS) projection neurons. These neurons receive corticostratal input and project to globus pallidus, they also form collaterals to neighbouring MS neurons however these collaterals have been shown to be weak (Jaeger et al., 1994). In addition to MS neurons there are fast spiking (FS) interneurons that form gap junction connected networks and inhibit the MS neurons, as further described below.

2.2.2. Sub-Thalamic Nucleus

The sub-thalamic nucleus (STN) receives glutamatergic input from the frontal cortex and cortical somato-motor areas (Bar-Gad et al., 2003). It is smaller than the striatum and populated mainly by tonically active projection neurons that form excitatory connections to globus pallidus and substantia nigra reticulata (SNr).

2.2.3. Globus Pallidus Externa

The globus pallidus externa (GPe) is part of the indirect pathway and receives input from the striatum and projects to the sub-thalamic nucleus (STN) (Bar-Gad et al., 2003). There are projections back from the STN to GPe and from GPe there are projections back to the parvalbumin positive fast spiking (FS) interneurons in striatum (Bevan et al., 1998). GPe also projects directly to SNr and to GPe. The majority of the neurons in GPe are GABAergic.

2.2.4. Globus Pallidus Interna

Globus pallidus interna (GPi) receives GABAergic input from GPe and glutamatergic input from STN (Bar-Gad et al., 2003). It is considered the output stage of the basal ganglia and projects both to the thalamus and the brain stem (Parent et al., 2001).

2.2.5. Substantia Nigra Reticulata

The substantia nigra reticulata (SNr) is an extension of Gpi which also receives input from the striatum, however it appears to be closer linked to substantia nigra pars compata (SNC) with more extensive dopamine connections (Bar-Gad et al., 2003).

2.2.6. Substantia Nigra Pars Compacta

Substantia nigra pars compacta (SNC) and other dopamine structures receive input from the striatum, STN and the limbic systems (Bar-Gad et al., 2003). Dopaminergic neurons in SNC fire tonically at low frequencies (4-10 Hz) (Schultz
et al., 1998), with increased or decreased activity for unexpected reward or absence thereof. The dopaminergic projections terminate onto the spines and the dendritic shafts of the MS neurons in the striatum.

2.3. Neurons in Striatum

There are several types of neurons in the striatum (Kawaguchi et al., 1995). Here we will focus on two of them: the medium spiny (MS) projection neuron and the fast spiking (FS) interneuron. The MS neurons are the most numerous and are the ones that project out of the striatum. The FS neurons are fewer, but are able to affect the MS neurons’ firing and thus affect the output of the striatum.

2.3.1. Medium Spiny Projection Neuron

The numerous medium spiny projection neuron (MS neuron) appears to be bistable and intense synaptic input can drive the neuron from the more hyperpolarised down-state to the up-state where the neuron may fire. Different studies investigate the MS response to the cortical and dopaminergic inputs (Wolf et al.; Gruber et al., 2003; Wolf et al., 2005; Kasanetz et al., 2002).

D1-dopamine receptors increase inward rectifying potassium and L-type Ca$^{2+}$ currents. The inward rectifying potassium current is activated at hyperpolarised potentials and acts to counter any depolarisations and stabilises the down-state (Niesenbaum and Wilson, 1995). A slowly inactivating potassium current delays the time to the first spike for the MS neuron upon depolarisation. The L-type Ca$^{2+}$-current is activated at subthreshold potentials and is also modulated by the D1-dopamine receptor and increases the excitability at depolarised potentials (Cooper and White, 2000; Bargbas et al., 1994). Thus dopamine has both excitatory and inhibitory effects, increasing the contrast (Nicola et al., 2004) by depolarising during up-states and hyperpolarising during down-states.

The MS neurons form collaterals to neighbour MS neurons, but these collaterals have been shown to be relatively weak (Jaeger et al., 1994). In addition, the MS neurons receive strong inhibitory input from another neuronal population, the fast spiking (FS) interneurons. It is the MS neurons that project out of striatum and their spike timing is important. It has been shown that the amount of calcium entering a MS neuron is dependent on how much time passes between onset of an up-state and the first spike (Kerr and Fein, 2004). Calcium levels are important for plasticity, so this might have functional consequences.

Dopamine activation of D1-receptor decreases gap junction coupling while D2-receptor activation appears to increase gap junction coupling (O’Donnell and Grace, 1993).

2.3.2. Fast Spiking Interneuron

The fast spiking (FS) interneurons only make up a small fraction of the neurons in the striatum, but they are connected to each other through gap junctions, into networks (Koós and Tepper, 1999; Galarreta and Hestrin, 2001). The FS
neurons form pericellular baskets on the MS neurons, allowing the FS neurons to exert powerful inhibition with low failure rates. They are thus in a position to affect the spike timing of the more numerous MS neuron, either delaying or altogether preventing firing (Bolam et al., 2000; Tepper et al., 2004; Köös and Tepper, 1999). The FS neurons also form GABAergic synapses on the somata and dendrites of other FS neurons (Chang and Kita, 1992), however it is unknown if they synapse on FS neurons that they also share gap junctions with. The FS neurons are unevenly distributed but are both present in the matrix and striosomes of the striatum and their dendrites cross the boundaries between the different regions (Kita et al., 1990).

The FS neurons are, as the name implies, able to fire in rapid bursts. It is the fast activation of the Kv3.1-Kv3.2 channel, named after the proteins that distinguishes this channel from other potassium channels, and allows for the FS neurons ability to fire at high frequencies. A common technique to investigate the effect of a channel is to use blockers that prevent the channel from working. TEA is a blocker that in small quantities blocks the Kv3.1-Kv3.2 channel but not other potassium channels. The Kv3.1-Kv3.2 channel is able to open and close rapidly (Erisir et al., 1999) and FS neurons without a functional Kv3.1-Kv3.2 channel were not able to sustain rapid firing. When the Kv3.1-Kv3.2 had been knocked out the remaining channels were unable to hyperpolarise the FS neuron fast enough, in order to remove the sodium inactivation, so that a new action potential could be elicited.

2.3.3. Tonically Active Interneuron

Tonically active (TA) interneurons fire largely due to intrinsic membrane properties and require only a modest amount of input to alter their firing patterns (Bar-Gad et al., 2003). TA neurons produce acetylcholine [ACh] which together with dopamine play an important role in striatum (Cragg, 2006). There are results indicating that it is D2-receptors on TA neurons that are also important for mediating a form of synaptic plasticity, called long term depression (LTD), in MS neurons, by first reducing ACh release (Wang et al., 2006).

2.4. Learning in the Striatum

The basal ganglia are important both for learning and action selection. Dopamine mediates reinforcement learning through synaptic plasticity and modulation of ionic channels of striatal neurons.

2.4.1. Dopamine – Temporal Difference Signal

In order to be able to distinguish between a good and a not so good outcome the body needs some kind of reward signal. Elevated levels of dopamine appear after an unexpected positive outcome while an unexpected negative outcome or the absence of a positive expected outcome results in depressed levels of dopamine. For expected positive or negative outcomes we get a tonic dopamine activation
of intermediate levels (Schultz et al., 1997). The dopamine signalling is time dependent, meaning that if an expected reward does not occur when it was expected but earlier or later it will result in changed dopamine levels (Hollerman and Schultz, 1998), this explains why trained animals in experiments continue to receive varying dopamine signals. D1-receptors also increase the activation of NMDA (Reynolds and Wickens, 2002; Gruber et al., 2003), which might be important for reward dependent learning as explained below.

2.4.2. Synaptic Plasticity – Three Factor Rule

Synaptic plasticity is the ability to change the efficacy of synaptic connections. For instance Hebbian learning uses the fact that neurons that fire together wire together, i.e., the strength of synaptic connections are either increased or decreased depending on when the neurons spike in relation to each other (Bi and Poo, 2001).

Three factors are important for plasticity; a phasic increase in dopamine release, presynaptic activity and postsynaptic depolarisation (Reynolds and Wickens, 2002). This can be summarised as follows. When cortical input elevates the neurons activity in conjunction with increased dopamine input we get long term potentiation (LTP). This results in a strengthening of the corticostriatal synapses. However if the dopamine input would decrease instead, then we would get LTP and weakened synapses (Hikosaka et al., 2006).

2.4.3. Actor-Critic Reinforcement Learning – Abstract Models

Before we begin diving into the biological jungle let us for a moment step back and study another concept, reinforcement learning. Assume we have some machine that we wish should be autonomous, able to perform tasks without outside interaction. This machine could be a Martian rover exploring the surface for signs of life or it could be a human maneuvering a bike through a forest.

Ideally we would want a machine that is able to learn and improve its behaviour by trial and error. It would then be able to adapt to unpredictable changes in the environment. We can classify the learning into two regimes, supervised and unsupervised. In the supervised learning the machine is shown a scenario and then afterwards told what is the correct response. However, in the unsupervised learning there is no one to provide the correct answer. Instead, at the end of the trial a reward is either given or not. This feedback could be in the form of money from winning a poker game or the pain from driving head first into a thorn bush. Based on this reward the machine has to optimise its behaviour. One solution is then to use a predictor for the reward. This predictor values immediate rewards more and later rewards are discounted the more distant they are.

Sutton and Barto (1998) describes a mechanism for unsupervised learning, called the actor-critic reinforcement learning. This system is based upon two entities within the machine. One actor that decides what action to take and a critic that grades the outcome using a prediction of the future reward. There will then be an error between the predicted reward and the actual reward, the
temporal difference (TD) error. The TD error is then used to update the actor’s and the critic’s behaviour accordingly. Remarkably this TD error is similar to the nigrostriatal dopamine signal. It has suggested that the striosomes together with the dopamine producing neurons, implement the critic. The striatal neurons receiving dopamine input but projecting to SNr and GPi, act as the actor, influencing motor outputs (Houk et al., 1995; Schultz et al., 1997; Hikosaka et al., 2006).

2.5. Some Disorders Involving Striatum

2.5.1. Addiction

In normal reinforcement learning, once the behaviour is properly predicted the dopamine signal will go down. However, in drug abuse the high levels of dopamine may remain, leading to pathological changes. Studies have shown that the initiation of addiction requires dopamine, however once the subject is addicted dopamine release is not critical for cravings, instead changes in the projections from cortex cause them (Kalivas and Volkow, 2005). These long lasting changes in the brain make it hard for addicts to stop and can also cause relapse after years of abstaining.

2.5.2. Parkinson

Parkinson’s disease affects roughly 3% of the population over the age of 65 (Moghel et al., 1995). It is characterised by a progressive decrease in motor function and is a result of imbalance between the direct and indirect pathways in the basal ganglia, leading to a rigid stance and problems initiating movement (Lang and Lozano, 1998a,b). Parkinson patients show a degeneration of dopamine producing nigrostriatal neurons, resulting in reduced dopamine mediated control of striatum (Picconi et al., 2005). Dopamine denervation causes the loss of both LTP (Long-term Potentiation) and LTD (Long-term Depression), which are required for plasticity. This denervation also leads to the reduction in dendrites (McNeill et al., 1988) and the number of spines on the MS neurons, and the remaining spines have abnormal size and shape (Day et al., 2006). This should lead to a reduction in firing, however the opposite appears to be the case, probably because of compensatory effects. In Parkinson patients oscillations appear between globus pallidus and the reciprocally connected sub-thalamic nucleus. Deep-brain stimulations silencing this abnormal patterns can lessen the motor symptoms shown (Gross et al., 2005).

Also interesting to note is that in Parkinson patients the ability to group a sequence of actions into a chunk disappears, forcing them to pay attention to all parts of the movement (Graybiel, 2004).
2.5.3. Huntington

Where Parkinson’s disease is a result of low activity in the direct pathway and too high in the indirect, Huntington’s disease is the opposite. Here instead patients have a problem to control their movements, leading to unvoluntary movement (Albin et al., 1989; Picconi et al., 2006). One early sign in Huntington’s disease is MS neuron cell death, although this disease is not understood fully (Handley et al., 2006).
Chapter 3

Methodological Approach

In this chapter we will first briefly discuss why we use computer models as a tool in neuroscience. Then in subsequent sections we will go through different models that can be fruitful to use, starting with compartmental neuron models. Here we describe the fast spiking (FS) interneuron model used in Paper I and Paper II. The Shuffle Corrected Cross-Correlogram (SCCC) and Joint Peristimulus Time Histogram (JPSTH), used to quantify spike synchronisation, are also discussed. The last section deals with Paper III and biochemical modelling, both stochastic and deterministic.

3.1. The Role of Modelling in Understanding the Brain

Biological systems such as a neuron are inherently complex, there are numerous variables to take into account and their interactions are often nonlinear. It is not enough to look at the isolated compartments to elucidate how things work, to get the big picture we need to look at the system as a whole. Here modelling plays a crucial role, allowing us to put together the pieces and see how they interact.

A model serves many purposes. It is a tool with which we can verify that the components we have identified and parameterised actually work together. If they do not work there must be something missing. Not all quantities can be readily measured, a model can help us find the range of a parameter, or rule out certain options or parameter ranges as unrealistic or impossible.

What characterises a good model? It should model the phenomena and be able to give accurate predictions. This could help reduce the number of experiments needed to be done on live animals, but it is important to understand that there will still be a need to do experiments to verify that the model’s predictions are valid. However, a good model should point at the experiments that need to be done.
A model should not be too complex. With a larger number of parameters we have a higher degree of freedom, meaning that the model can be made to fit a wider range of parameters and we could get all kinds of behaviours out of our model. If a certain behaviour is desired, a change of a few parameters could conjure it up. Instead it would be more interesting if there are strict limits on the parameter range, that the model will not allow values outside. Then it is far easier to make predictions. Fewer degrees of freedom also mean a simpler model, easier to tune and probably faster to simulate.

Our goal is to create a model representing the striatum, we are not there yet, however we have some of the building blocks required. Here it is important to make sure that the parts do work before connecting them together if we should have any hope to get the finished network to work. We need to identify what components are needed and what their characteristics are.

The models can be formulated on different levels. We have detailed biochemical models that describe interactions between molecules, processes that are important for instance synaptic plasticity involved in learning. There are cell models based on Hodgkin and Huxley formalism that describe the electrical properties. These cell models can be connected into a network of neurons to simulate interactions on a larger scale. In order to understand the full system we need them all.

### 3.2. Compartmental Modelling

When modelling a three dimensional neuron we have to deal with both the space and time dimensions. These equations would be quite complex. By dividing the neuron into compartments that are assumed to be isopotential we reduce the equations and have only to deal with time as a variable.

### 3.3. Modelling Channels with Hodgkin & Huxley Formalism

The Hodgkin-Huxley model (Hodgkin and Huxley, 1952) is a set of nonlinear ordinary differential equations that model the voltage dependent ion channels underlying the electrical characteristics of neurons. They were originally used to describe the squid giant axon, but has since found applications in numerous neuronal models. The cell is described by an equivalence scheme that has been inspired by electrical circuit theory as shown in Figure 3.1. Here the different components of a neuron are modelled by electrical components. The cell membrane, with its ion channels, has different permeability for different ions. This, in combination with active ion pumps, leads to a concentration difference between the inside and outside of the membrane for the ions. Since the ions have positive or negative charge this concentration gradient leads to a voltage potential across the membrane. The membrane itself is not normally permeable to ions, leading to the buildup of positive and negative ions on opposing sides of the membrane wall, in other words, the membrane acts as a capacitor with a typical capacitance of 1 \( \mu F/cm^2 \).
When using compartmental models the neuron is divided into a number of compartments that are each assumed to be isopotential, meaning that the voltage is the same inside the entire compartment. If the compartments are small enough this is a reasonable assumption. The potential in the compartment is determined by,

\[ C \frac{dV}{dt} = I_{\text{comp}} - I_{\text{ion}} - I_{\text{syn}} - I_{\text{leak}} - I_{\text{inj}} \]  

(3.1)

where \( I_{\text{comp}} \) is the current entering the compartment from neighbouring compartments, \( I_{\text{ion}} \) the current through the ion channels, \( I_{\text{syn}} \) the current through the synaptic ion channels, \( I_{\text{leak}} \) the leak current through the membrane and \( I_{\text{inj}} \) the injected current if there is an electrode.

Hodgkin & Huxley assumed that the ion channels had a number of gates that all had to be open in order to let ions through. These gates could open or close in a voltage dependent manner. For a channel with two types of gates \( X \) and \( Y \) with \( n \) and \( m \) instances respectively, the current entering through the channel can be described by,

\[ I = g_{\text{max}}(V - V_{\text{rev}})X^nY^m \]  

(3.2)

where \( g_{\text{max}} \) is the maximal conductance and \( V_{\text{rev}} \) is the reversal potential, e.g. \( E_k \) in Figure 3.1. The gates are opened and closed with rates \( \alpha \) and \( \beta \), and the
3.4. Modelling the Fast Spiking Interneuron

![Diagram of a neuron with dendrites](image)

**Figure 3.2.** Schematic drawing of a modelled FS neuron showing the soma, three primary dendrites, six secondary dendrites and twelve tertiary dendrites.

The state of the gate can thus be calculated from

\[
\frac{dx}{dt} = \alpha(1 - x) - \beta x
\]  

(3.3)

where the values of \( \alpha \) and \( \beta \) can vary as the membrane potential varies. If the voltage is held fixed the value of \( x \) will reach a steady state value,

\[
x_{ss} = \frac{\alpha}{\alpha + \beta}
\]

(3.4)

For channels that have more than one gating particle, all of the particles need to be in the open state for current to pass through.

3.4. Modelling the Fast Spiking Interneuron

The fast spiking (FS) interneuron model was implemented in GENESIS (Bower and Beeman, 1994) on a GNU/Linux system and originally published in Hellgren Kotaleski et al. (2006). It has been tuned to replicate FS cell behaviour in vivo.

3.4.1. Morphology

The neuron consists of a somatic compartment connected to series of cylindrical compartments of subsequently finer diameter forming the dendrites. There are three primary dendrites extending from the soma, each of these branches into two secondary dendrites that in turn branch into a total of twelve tertiary dendrites as shown in Figure 3.2.

3.4.2. Synaptic Input

The striatum receives extensive input from large regions of cortex. In anaesthetised animals the cortical input is very synchronised (Stern et al., 1998)
with aperiodic up-states appearing simultaneously in neighbouring neurons. In awake and behaving animals correlations have been found in the corticostriatal input as well as spike bursts in M5 neurons. These neurons do not have an intrinsic burst mechanism, indicating that there are indeed periods of higher cortical activity, however it is unknown whether these up-states are correlated or not (Nicola et al., 2004). It is interesting to note that the synchronisation detected in EEGs appears to increase when anaesthetised animals are further sedated (Contreras and Steriade, 1997).

In our model we have used periodic up-states with a frequency of 2 Hz and a duty cycle of 0.5 which corresponds to 250 ms up-state followed by 250 ms down-state. The up-state is caused by elevated corticostral synaptic input. The input frequency per synapse for up-states was 20/9 Hz and for down-states 1/9 Hz.

In order to quantify the correlation within the generated input we used the correlation measure from Rudolph and Destexhe (2001) that is based on the generation process of the input. In order to create N synaptic inputs with a given correlation C Rudolph and Destexhe (2001) generate \( N_0 = N + \sqrt{C(1 - N)} \) uncorrelated input trains and randomly distribute them over the N input trains. The uncorrelated trains were then reconnected in each timestep, so that it would not be the same synapses that were correlated all the time.

We used the same basic idea but modified the generation process. In order to create N synaptic inputs with frequency f and correlation C we generated a Poisson process with frequency \( f \cdot N_0 \). We then had two alternative generation mechanism, either we distributed each spike to \( N/N_0 \) synapses, or for each synapse and spike we allowed the spike to be sent to the given synapse with a probability \( p = 1/N_0 \). Both generation mechanisms give the same amount of spikes to each process but the variation differs. In our work we are focusing mainly on the former generation mechanism, in order to be able to compare results with Hellgren Kotalesski et al. (2006), but future developments will probably also investigate the latter.

### 3.4.3. Dopamine Input

The D2-receptor acts presynaptically reducing the amount of GABA that is released and the D5-receptor, which belongs to the D1 family, acts postsynaptically depolarising the neuron (Bracci et al., 2002; Centonze et al., 2003; Nicola et al., 2000). The dopamine’s effect was simulated by depolarising the neuron 2 mV and reducing the GABA-synapses efficiency to 80%.

### 3.4.4. AMPA and GABA Channel

The AMPA-channels are distributed throughout the entire dendritic tree. The GABA-channel distribution differs from the AMPA-channel distribution in that they are concentrated proximally, there are no GABA-channels on the tertiary dendrites. This was needed in order to get the right input characteristics (Hellgren Kotalesski et al., 2006).
3.4.5. Voltage Gated Ion Channels

Voltage gated ion channels are modelled using the Hodgkin and Huxley formalism. They open or close in response to a depolarisation. Below we will touch upon some of the channels that are important for the FS neuron.

Fast Sodium Channel

The fast sodium channel enables action potential. Hodgkin and Huxley (1952) proposed that the channel could be modelled as having four gating particles that each had to be in the opened state for current to flow through. Three of these gating particles are closed in hyperpolarised states and open in response to a depolarisation, but the fourth is open at hyperpolarised states, and slowly begins to close as the membrane is depolarised. It is this last particle that leads to the inactivation of the sodium channel. The current through the channel can be calculated by,

\[ I_{Na} = m^3h \cdot g_{Na}(V - 0.045) \]  \hspace{1cm} (3.5)

where \( m \) and \( h \) are the two types of gating particles. In the FS model the opening and closing rates are voltage dependent. The opening rate \( (\alpha) \) and closing rate \( (\beta) \) for the gating particle \( m \) are,

\[ \alpha_m = \frac{10^6 \cdot (3.020 - 40 \cdot V)}{e^{0.0755 + V}/0.035 - 1} \]  \hspace{1cm} (3.6)

\[ \beta_m = 1226.2 \cdot e^{-V/0.042248} \]  \hspace{1cm} (3.7)

and the corresponding rates for \( h \) are

\[ \alpha_h = 3.5 \cdot e^{-V/0.024186} \]  \hspace{1cm} (3.8)

\[ \beta_h = \frac{10^3 \cdot (0.8712 + 17 \cdot V)}{1 - e^{-(0.05125 + V)/0.052}} \]  \hspace{1cm} (3.9)

Here \( V \) is the membrane potential. Using the above equations together with equation 3.3 we can compute \( m \) and \( h \) used in equation 3.5 to calculate the current through the channel.

Potassium Channel Kv1.3

Hellgren Koteleski et al. (2005) found that the model required the potassium channel Kv 1.3 together with the Kv3.1-Kv3.2 channel to reproduce the experimentally observed spike latency and high firing rate. The current through this channel can be calculated by,

\[ I_{Kv1.3} = n^4 \cdot g_{Kv1.3}(V + 0.090) \]  \hspace{1cm} (3.10)

where the opening and closing rates for \( n \) are,

\[ \alpha_n = \frac{616 + 14000 \cdot V}{1 - e^{-(0.044 + V)/0.0623}} \]  \hspace{1cm} (3.11)

\[ \beta_n = 4.3 \cdot e^{-0.044 + V}/0.034 \]  \hspace{1cm} (3.12)
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Transient Potassium Channel $K_{V3.1-Kv3.2}$

The transient potassium channel ($K_{V3.1-Kv3.2}$) is a fast channel that is required for the FS neurons ability to fire rapidly (Erisir et al., 1999). The current through this channel is,

$$I_{K_{V3.1-Kv3.2}} = n^2 \cdot \bar{g}_{K_{V3.1-Kv3.2}} (V + 0.090)$$  \hspace{1cm} (3.13)

where the opening and closing rates for $n$ are given by,

$$\alpha_n = \frac{95000 - 10^6 \cdot V}{e^{(0.095-V)/0.0118} - 1}$$  \hspace{1cm} (3.14)

$$\beta_n = 25 \cdot e^{-V/0.02222}$$  \hspace{1cm} (3.15)

Transient Potassium A-channel

The model also includes a transient potassium A-channel. The current through it can be calculated by,

$$I_{KA} = m^4 h \bar{g}_{KA} (V + 0.090)$$  \hspace{1cm} (3.16)

Given enough time the fraction $m$ (and $h$) of open particles will have stabilised at a steady state value $m_\infty$ (and $h_\infty$). This value together with a decay constant $\tau_m$ (and $\tau_h$) can be used to describe the time evolution of $m$ (and $h$). These values can be calculated from,

$$m_\infty = \frac{1}{1 + e^{-(V+0.045)/0.013}}$$  \hspace{1cm} (3.17)

$$\tau_m = 0.001 \cdot (1 + e^{-(V+0.070)/0.013})$$  \hspace{1cm} (3.18)

$$h_\infty = \frac{1}{1 + e^{(V+0.077)/0.008}}$$  \hspace{1cm} (3.19)

$$\tau_h = 0.014$$  \hspace{1cm} (3.20)

This can then be used in

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}$$  \hspace{1cm} (3.21)

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}$$  \hspace{1cm} (3.22)

to get the values for $m$ and $h$.

3.4.6. Gap junctions

Gap junctions are modelled as a resistive element connecting two compartments of neighbouring neurons together. The conductance has been kept within the physiological range of 0.13–0.58 nS (Galarreta and Hestrin, 2002).
3.5. Analysis of Spiking Activity in FS neurons

3.5.1. Shuffle Corrected Cross-Correlogram

The Shuffle Corrected Cross-correlogram (SCCC) is used to find correlations in firing patterns between two neurons. An ordinary cross correlogram is generated by taking the spike traces from two neurons and then calculating all combinations of inter spike intervals between spikes from different neurons and then binning them. This histogram is the cross correlogram. For a signal that repeats itself it is possible to remove some of the bias in the signal. If we assume that the synchronisation properties are only active on a small timescale then we can get an estimate of the bias. By shifting the first spike trace one period forward in time we will destroy all the short time correlations but leave the bias. By binning once again all the inter spike intervals between all the combinations of spike pairs in different neurons we get a correction. To get a better correction we can shift the spike traces two periods and repeat the calculation, if we do this several times, shifting different number of periods and then averaging the results, we get the final correction, which is subtracted from the original cross correlogram to generate our shuffle corrected cross correlogram. For a more complete description see Brody (1999) and Palm et al. (1988).

3.5.2. Joint Peristimulus Time Histogram

The SCCC is unable to tell us if there are variations in the synchronisation during the up-state period since it bins all the data together. To get information about the temporal development and to get a measure of the significance values of the synchronisation we analyse the data with JPSHT also. The so-called surprise value has been described before (Palm et al., 1988; Aertsen et al., 1989). This surprise value estimates if the outcome differs significantly from the null hypothesis. In our simulations the null hypothesis is that the two neurons are uncorrelated. The surprise value is equal to the negative logarithm of the probability to find this outcome or a more deviant one under the null hypothesis. A “surprise” value of 2.996 corresponds to a significance value of 5%.

A JPSHT is useful when there is a periodic signal and the synchronisation between two neurons varies with time within the duration of each period. It consists of a two dimensional matrix where the coordinates of each bin correspond to a time in the first and in the second neuron. To generate a JPSHT each period is binned individually, if the same period has a spike both in the first and in the second neuron, the bin in the 2D matrix corresponding to these two times is marked. This is repeated for all combinations of spikes during the same period, in other words two spikes in the first neuron and three spikes in the second neuron will result in six bins in the matrix being marked as shown in Figure 3.3. Based on the probability to fire at a specific time for either neurons their joint probability to fire in the uncorrelated case can be calculated by simply multiplying the two. Using this as the null hypothesis we can calculate how unexpected the outcome was. If there is correlation it will appear as
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**Figure 3.3.** Creation of a joint peristimulus time histogram (JPSTH). Traces from two simultaneously recorded neurons are binned against each other. If they have a tendency to synchronize a cluster of filled bins will appear on the diagonal.

a denser region of marked bins on the diagonal, any variations in density along the diagonal indicate the variations in synchronisation during the time of the period.

3.6. Modelling of Biochemical Pathways

Cellular signalling circuits have grown in complexity through evolution to the point where they have become hard to overview without the help of additional tools. Through computer models developed, based on biological experiments, we can begin to understand better what is going on in these systems (Bhalla, 2004a). There are different assumptions that we have to make when doing modelling, for instance there is the question of how many pathways to include in the model. There have to be enough pathways to capture the behaviour of the system studied, but each adds to the complexity. Another factor we have to take into account is the scale of the system. On the larger scale we can use mass-action kinetics, where the outcome is deterministic. However on the smaller scale, where there might be only a few molecules taking part in the reaction we have to use stochastic algorithms that are inherently noisy.

Reactions that take place in the spines on the dendrites of the MS neurons are typical candidates for stochastic simulations, since the spines have a very small volume and diffusion through the neck of the spine is limited. In Paper III we model CamKII as a first step to understand better how to perform stochastic simulations. Also a one compartmental model with glutamate and D1-receptors have been implemented by (Kotaleski et al., 2005). The goal for us is to integrate these simulated biochemical pathways, that are important for synaptic plasticity, into the MS neuron model.
3.6.1. Deterministic Modelling

Modelling can take place on different scales. When we deal with large number of molecules the processes are deterministic as small fluctuations are averaged out, however we do not always have this luxury. For small volumes and few molecules the processes become stochastic and we need to change our modelling accordingly.

For large number of molecules we deal with concentrations, the concentration of a substance $X$ is denoted by $[X]$. A reaction where a substrate or reactant $S$ is transformed into a product $P$ through a biomolecular reaction or with the help of an enzyme $E$ is written as,

$$S = P$$  \hspace{1cm} (3.23)

and since each molecule of $S$ that undergoes this reaction turns into a $P$ we must have that,

$$v = -\frac{d[S]}{dt} = \frac{d[P]}{dt}$$  \hspace{1cm} (3.24)

which, using the forward $k_1$ and backward $k_{-1}$ reaction rates, can be written as,

$$v = k_1[S] = k_{-1}[P]$$  \hspace{1cm} (3.25)

and from this we can find the equilibrium constant $K_{eq}$

$$K_{eq} = \frac{[P]}{[S]} = \frac{k_1}{k_{-1}}$$  \hspace{1cm} (3.26)

for the reaction. This is valid for reactions allowed to reach steady state. For reactions where the substrates bind to a complex before finally forming the product we often use Michaelis-Menten kinetics (Michaelis and Menten, 1913).

$$E + S \stackrel{k_1}{\underset{k_{-1}}{\rightleftharpoons}} ES \stackrel{k_2}{\underset{k_3}{\rightleftharpoons}} E + P$$  \hspace{1cm} (3.27)

where $k_1$, $k_{-1}$ and $k_2$ are the reaction rates. The rate of change for the intermediate complex can be written as,

$$\frac{d[ES]}{dt} = k_1([E_0] - [ES]) \cdot [S] - k_{-1}[ES] - k_2[ES]$$  \hspace{1cm} (3.28)

where $[E_0] - [ES]$ represents the amount of available free enzyme. At steady state we have $d[ES]/dt = 0$. If we solve for $[ES]$ we get,

$$[ES] = \frac{k_1[E_0][S]}{k_{-1} + k_2 + k_1[S]}$$  \hspace{1cm} (3.29)

which, using the fact that $v = d[P]/dt = k_2[ES]$, can be written on the form

$$v = \frac{k_1k_2[E_0][S]}{k_{-1} + k_2 + k_1[S]} = \frac{k_2[E_0][S]}{k_{-1} + k_2 + k_1[S]}$$  \hspace{1cm} (3.30)

which is recognised as

$$v = \frac{V_{max}[S]}{K_m + [S]}$$  \hspace{1cm} (3.31)
3. Methodological Approach

![Diagram of CaMKII model](image)

**Figure 3.4.** Biochemical network of the CaMKII model. The stochastic parts are dashed, solid parts correspond to the deterministic parts. The grey boxes indicate where the two models are coupled.

### 3.6.2. Stochastic Modelling

Let us assume that we have a deterministic model that tells us that at a given time, 5% of the molecules are bound. If we have only ten molecules in our simulation, does that mean that we have half a molecule bound? Surely this can not be the case. To avoid this problem we turn to stochastic models, where each molecule is modelled individually instead of all molecules being modelled as a group (Bhalla, 2004b,c). At each timestep we calculate the transition probability for each molecule and draw a random number to see what the outcome for that particular molecule is. If we assume that the reaction is

\[ A \xrightarrow{k_f} B \]  

where \( k_f \) is the forward rate, then the probability that there has not been a transition in time \( dt \) is

\[ p = e^{-k_f \cdot dt} \]  

For large number of molecules this will be quite computer intensive, which is why there is still a place for deterministic models. However, for the cases with few interacting molecules, this approach works. Since the model is stochastic it means that if we run the simulation twice we will not get the same outcome. To verify our results, we thus often have to run the same simulation several times. These variations in results are the strength and weakness of stochastic modelling. The relative size of the variation in a Poisson process is inversely proportional to the square of the number of molecules. For a sufficiently large number of molecules these variations go to zero and we have the deterministic case.
3.6.3. Hybrid models

Sometimes it can be fruitful to combine stochastic and deterministic models (Vasudeva and Bhalla, 2004). Paper III, which is based on a model by Holmes (2000), is an example of such a case, see Figure 3.4. Here the calcium binding to calmodulin is deterministically modelled, while the CaM Ca₄’s interactions with CaMKII is modelled stochastically. The reason why the second half is stochastically modelled is because the activation of CaMKII subunits is dependent on their neighbouring subunit’s state. If we were to take all of these combinations into account we would have to evaluate many different possibilities in each timestep. Our approach is instead to do a stochastic simulation, where one of these possibilities is explicitly chosen in each timestep. The entire stochastic simulation is repeated to get a sample of the system’s behaviour. In the region where the two models meet we have to convert concentrations to discrete molecules and back (grey boxes in Figure 3.4).
Chapter 4

RESULTS AND DISCUSSION

With the background from the previous sections we can begin to summarise the results from this thesis. Below we discuss synchronisation and up-state detection in electrically coupled FS neurons. We also touch upon how noise can improve a weak signal. The last section of this chapter deals with biochemical modelling of CaMKII.

4.1. FS Neuron Spike Synchronisation

Between 4 and 27 FS neurons innervate each MS neuron (Koós and Tepper, 1999). If the FS neurons synchronise their activity, their inhibitory effect on the MS neuron should be even stronger and more robust. From previous experiments and modelling studies it is known that gap junctions can synchronise spiking between neighbouring neurons (Traub et al., 2001; Connors and Long, 2004; Gibson et al., 2005). Here we investigated the effect of gap junction localisation since it is currently not known where these gap junctions are located. To analyse the data we used both joint peristimulus time histogram (JPSTH) and shuffle corrected cross-correlogram (SCCC). The FS effect on MS spike timing is important since it affects calcium levels in the MS neurons (Kerr and Plenz, 2004), which have implications for plasticity. Also, it is the MS neurons that project to basal ganglia output stages, as mentioned above.

In Paper I we study the synchronisation of electrically coupled FS neurons that receive cortical input with physiological characteristics. The effect of the gap junction localisation is investigated. We compare two cases: proximal and distal gap junctions. Here the gap junction conductance for both cases has been calibrated so that they give the same coupling coefficient for a steady state injection into the soma. The coupling coefficient is defined as the voltage change in the neighbouring neuron’s soma divided by the voltage change in the stimulated neuron’s soma.
4.1. FS Neuron Spike Synchronisation

**Figure 4.1.** Synchronisation effect of gap junctions. (A) Shuffle-corrected cross-correlogram. Both somatic and the tertiary dendritic gap junctions synchronise the two neurons, but the time window is narrower for somatic couplings. (B) Joint peristimulus histogram (JPSIH). The upper figure shows the raw JPSIH for the tertiary dendritic gap junctions and the lower for the somatic gap junctions (Palm e. al., 1988; Aertsen et al., 1989). The diagonal representing synchronisation can be seen for both the tertiary dendrite and somatic gap junction cases.

From the SCCC in Figure 4.1A we can see that the peak for the proximal gap junctions is much higher and narrower, while the distal gap junction’s peak is more spread out in time. The gap junctions in this figure had been calibrated to have 14.1% somatic steady state coupling. Figure 4.2A and 4.2B both show a normalised SCCC for distal and proximal gap junctions respectively, these show how the synchronisation varies with conductance. We see that with increased conductance the synchronisation becomes more pronounced. Figure 4.2C shows the SCCC for proximal and distal gap junctions with conductance 0.20 nS corresponding to a somatic steady state coupling of 8.8%. Figure 4.2D shows the same configuration as the previous figure, but this time with dopamine added. We see that dopamine increases the activity in the FS neurons as compared to the reference case. The added spikes also make it easier to distinguish the difference in synchronisation between proximal and distal gap junctions.

The JPSIHs in Figure 4.1B show a clear diagonal, indicating synchronisation, both for the proximal and distal case, where the proximal is more precise, whereas the distal is more smeared out in time for gap junctions of comparable strength. It is hard to know exactly how important the spike timing is for this system, there are however reports of spike timing dependent plasticity (STDP) at the corticostratal synapses (Fino et al., 2005). Here the timing could be critical. As an example, the difference between long term potentiation (LTP) and long term depression (LTD) has been found to be a few milliseconds for STDP in the hippocampus (Bi and Poo, 1998).
4.2. Up-State Detection and the Robustness to Noise

As mentioned in Chapter 2 the input from the cortex has periods of elevated activity, up-states, follow by periods of lower activity, down-states. It is important that the neurons in the striatum can distinguish between the two, in particular we are interested in detecting the up-states. If a neuron fires during an up-state it is considered detected. At the same time we do not wish the neurons to fire when there is no up-state. Gap junction localisation can alter the total number of spikes fired as shown in Figure 4.3 and it also matters whether the neighbour receives up-state input simultaneously or not. In all cases where the individual input spikes were uncorrelated between the FS neurons we found that the total number of spikes were lower with gap junctions than without. However, if the two FS neurons were given correlated inputs we got a small increase in the number of spikes. The mechanisms behind this was discussed in Paper II.

In Figure 4.3 we can see that it takes a short while after up-state onset before the FS neuron begins to fire. Likewise there are some spikes following directly after the up-state ended. It is also clear that distal gap junctions of comparable strength to proximal gap junctions have more spikes when their neighbour is in up-state, and fewer spikes when their neighbour is in downstate. The shunting between the neurons is higher for distal gap junctions, resulting in a higher contrast between both neurons in up-state and only one of the neurons in up-state. This is perhaps not that surprising since normal neurons receive most of their inputs through the dendrites.
In order to quantify the up-state detection we now introduce a concept called signal to noise ratio percent correct (SNRpC). An up-state is considered correctly detected if it causes at least one spike in the neuron and a downstate is correctly rejected if there are no spikes during it. SNRpC is defined as the sum of the correctly detected up-states and correctly rejected down-states divided by the total number of up-states and down-states. SNRpC values below one means that not every up-state is correctly detected or the neurons spikes during some of the down-states. A value of zero means that we got everything wrong, and the cell spiked during down-states only.

Using such a measure, one can now quantify how up-state detection is affected by noise. The neuron fires an action potential in an all or none fashion if a threshold is passed, i.e. when more sodium channels open than close. The exact location of the threshold can vary a bit depending on whether the input makes the neuron slowly approach the threshold or not. This is because sodium channels inactivate after a while. If the threshold is approached rapidly the inactivation has not had time to set in and the point where more channels open than close will be reached faster. A system receiving input too weak to reach threshold could benefit from the addition of noise, which could bring the neuron’s potential above threshold more often. This only works for moderate amounts of noise as adding too much noise will drown the original signal in the extra noise.

To investigate how the up-state detection was affected by noise we varied the amount of noise that was added to the neuron during simulation and calculated the SNRpC. Figure 4.4 shows the five cases that were compared, each pair of neurons had the same input as the other pairs, however the input to the two neurons in each pair were independent. The simulation was run for 50 seconds, corresponding to 100 up/down-state periods. The first pair was left unconnected as reference, the second pair was connected through distal gap junctions and the third pair was connected through somatic gap junctions. The fourth and fifth pair were not connected to each other but to a neighbour that did not receive up-state input, where the fourth had distal gap junctions and the fifth had proximal gap junctions. For all cases we see that the SNRpC ratio increases with moderate levels of noise. This is termed stochastic resonance in some literature (Gammaitoni et al., 1998). Stochastic resonance was first used to describe the arrival of ice ages with a periodicity of $10^7$ years. Only the variations in the eccentricity of the planetary orbits due to neighbouring planets were on that timescale, but the effect was small. However, with the help of annual variations in solar influx (noise) the observed phenomenon could be modelled. The noise helped the weak signal carry through, giving us a wonderful sheet of ice and snow covering large parts of Europe, from time to time.

In our case there is a threshold effect, where we have an in signal that excites the neuron close to the threshold, and variations lead to the occasional spike. By adding noise to the $FS$ neuron we increase the frequency of both the upstate and downstate input. During the upstate the noise is able to increase the number of action potentials fired, however during downstate, the added noise is not enough to make the neuron fire.
4. Results and Discussion

![Figure 4.3](image)

**Figure 4.3.** Up-state detection. Histogram of spike times during the periods, the FS neuron spikes more if its neighbour receives up-state input also. The figure shows 250 ms up-state followed by 250 ms down-state.

4.3. Biochemical Modelling

Reinforcement learning and plasticity are important for the function of the striatum. Bhalla (2003) and Kotałeski et al. (2002) have shown that biochemical networks can perform temporal computations on the subcellular level. In order to understand better the information processing we have to be able to model the processes that are required for both long and short term plasticity. Plasticity often takes place in the spines, small compartments with a limited amount of molecules. **Paper III** is an initial study of stochastic simulations which are required when we can no longer assume that large quantities of substrates take place in the reaction. We have implemented a CaMKII model by Holmes (2000). CaMKII is important for Ca$^{2+}$-dependent plasticity and pathological high levels of phosphorylated α-CaMKII has been observed in Parkinson’s disease (Picconi et al., 2004). The subunits activity is dependent on their neighbouring subunit on one side, this interaction is one directional. Subunits of type α and β have different affinity for calmodulin (CaM) and different rates for neighbouring-dependent phosphorylation. The novelty in this study is to include both types of subunits and study how they interact. The different subunit types interact in a non-linear fashion where the order of the subunits types is significant for the activity.

A future step for the biochemical modelling is to combine the one compartment model with glutamate and D1-receptors with the MS neuron (Kotałeski et al., 2005), which is equally important since dopamine has a role in plasticity.
Figure 4.4. Noise variations of the signal to noise ratio. Moderate amounts of noise increase the signal to noise ratio. Comparing the FS neurons whose neighbours also receive up-state input with those that have a silent FS neighbour receiving downstate input we see that increased noise can compensate for a silent neighbour.
Chapter 5

Future Work

The long-term goal of this project is to understand better the mechanisms behind reinforcement learning and action selection in the basal ganglia. Here we wish to understand the process both on a neuronal, microcircuitry and network level as well as on the subcellular level. The former requires information on how the striatal neurons are connected on the microcircuitry level, and using models we can test how the processing of the corticostriatal input is affected. Future goals are to increase the insight of the information processing going on in the second messenger pathways and how this might be changed by neuromodulator interactions.

We already have a detailed model of the FS neuron and currently a MS model (Wolf et al., 2005) is being converted from Neuron to GENESIS. The current MS model lacks explicit spines and one plan is to add them on the dendrites to e.g. investigate the role of corticostriatal vs thalamic inputs. Using detailed models with spines and active dendrites also allows us to investigate the possible consequences of altering those properties. For example, dopamine denervation, which is seen in Parkinson’s disease, results in a rapid and profound loss of spines and glutamatergic synapses on striatopallidal MS neurons, but not on striatonigral MS neurons (Day et al., 2006; McNell et al., 1988). Simulations of reduced dendritic trees show a reduction in firing (Kötter and Wickens, 1998), however recent studies reviewed in Day et al. (2006) instead show an increase in excitability, probably because of compensatory mechanisms or changes in potassium currents. It would be interesting to investigate further the effects of Parkinson’s disease on both the individual MS neuron, and networks of connected MS and FS neurons.

Models of striatal FS and MS neurons including mechanisms for synaptic plasticity could also allow us to investigate further the systems capabilities for performing actor-critic reinforcement learning (Sutton and Barto, 1998). Houk et al. (1995) suggested such a mechanism in the striatum where the striosomes represent the critic and the matrix the actor. There are also other considerations
for studying networks instead of only pairs of neurons. Electrical coupling may have a stronger influence in networks that are highly connected, than can be shown in pairwise neuron simulations (Andreu et al., 2001).

Another interesting venue of research is to extend an already developed one compartment biochemical model (Kotalski et al., 2005), that currently implements the D1-receptor and glutamate activated second messenger pathways, with the D2-receptor and acetylcholine (ACh) dependent interactions. The dopamine and ACh signals interact with one another (Wang et al., 2006) and a quantitative model with both could be interesting to study further.

Through modelling of the striatum we will be able to increase our understanding of how the basal ganglia system work, and how different diseases affect them. This will enable researchers to design better treatments for diseases in this system. One hope is that one day they will be able not only to ease the burden for addicts and patients of Parkinson’s and Huntington’s disease, but to cure or even prevent the diseases. In order to do that, we first need to understand how these systems, and striatum in particular, work. Our research is hopefully a small piece in this puzzle.
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