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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 implied 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 Ca^{2+}-calmodulin-dependent 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

Basala ganglierna utgör tillsammans en viktig struktur som ligger centralt placerad i hjärnan. De får in signaler från motor-, associativa- samt limbiska areor och projicerar i sin tur främst till talamus och hjärnstammen. Basala ganglierna antas ha både motoriska och kognitiva funktioner. Genom att studera sjukdomar som påverkar detta system, som Parkinsons och Huntingtons sjukdom, kan vi få en insyn i dess funktioner. Även drogberoende verkar påverka basala ganglierna.

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) projektionsneuroner 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 synkroniserar deras effekt på MS-neuronerna. Basala ganglierna ligger hela tiden och inhiberar förberedda motorkommandon. När vi ska utföra en motorisk handling lyfts inhibitionen via disinhibition från MS-neuronerna.

Insignalen från cortex till striatum varierar i intensitet. Det är främst under *up-states*, perioder av hög aktivitet, som MS- och FS-neuronerna spikar. Jag har studerat FS-neuronernas förmåga att detektera upstates. Detta är viktigt eftersom FS-neuronerna kan påverka när MS-neuronerna spikar. Vidare vet man att tiden mellan starten på ett upstate och första spiken hos MS-neuronerna påverkar hur mycket kalcium som kommer in in cellen, vilket i sin tur påverkar plasticitet och inlärning av beteenden. Jag har studerat hur både upstate-detektion och synkronisering mellan par av FS-neuroner påverkas av att de kopplas ihop elektriskt med *gap junctions*. Här har kopplingarnas konduktans, antal och placering varierats. En slutsats var att både proximala och distala gap junctions synkroniserade spikandet, men att de proximala kopplingarna gav en mer precis synkronisering. FS-neuronernas förmåga att detektera upstates påverkades även av huruvida deras granne också fick upstate-insignal från cortex eller inte. Här var kontrasten störst för distala gap junctions, på grund av större shuntningseffekt i dendriterna.

Vi har också utfört stokastiska 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 mikrostrukturen i striatum. Syftet är att öka vår förståelse för informationsbehandlingen i striatum.

To my family and friends

Acknowledgements

I would like to begin by thanking my supervisors Dr. Jeanette Hellgren Kotaleski and Prof. Anders Lansner for giving me the opportunity to work in this interesting field. I would also like to thank the members of the basal ganglia seminar group at the Karolinska Institute (KI) for enlightening and insightful discussions.

Thanks to all the members of the CBN (former SANS) group at Royal Institute of Technology (KTH) for providing a stimulating working environment. Thanks to Erik Fransén and Örjan Ekeberg for their valuable critique and good sense of humour, and to Mikael Djurfeldt for first introducing me to the basal ganglia. Thanks also to Malin Sandström, Anna Svantesson, Mikael Huss, Christopher Johansson, Martin Rehn and Fredrik Edin for collaboration and help on various projects and courses, making it both fun and educational. Thanks also to Roland Orre and Anders Sandberg for inspiration and visionary discussions about unrelated scientific topics, and to Harriet Johansson for help with administrative matters. The friendly members of the neighbouring NA-group also deserve to be mentioned.

I would also like to thank my friends and family, although not directly involved in this project, they have provided both valuable support and the necessary distraction.

Contents

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 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 called down-states (Plenz and Kitai, 1998). **Paper II** concentrates on up-state 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^{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 Kotaleski, The significance of gap junction location in striatal fast spiking interneurons, *CNS Edinburgh* Submitted, 2006

Paper II. Johannes Hjorth, Jeanette Hellgren Kotaleski, 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 Hellgren Kotaleski, The impact of the distribution of isoforms on CaMKII activation *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

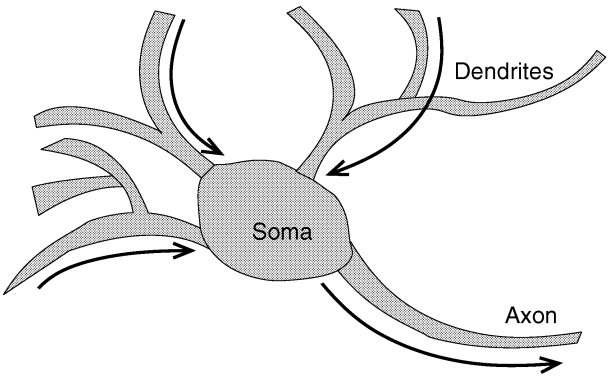

Figure 2.1. *Schematic drawing of a neuron. Here we can see the three main parts; the dendritic tree receiving input, the cell body (soma) and the axon that relay information onwards.*

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 transmittors, 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 transmittor 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 transmittors 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 transmittor 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 transmittor 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 notable 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 Na^{2+} 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, ones 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,

2002; Söhl *et al.*, 2005). 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 inactivate 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).

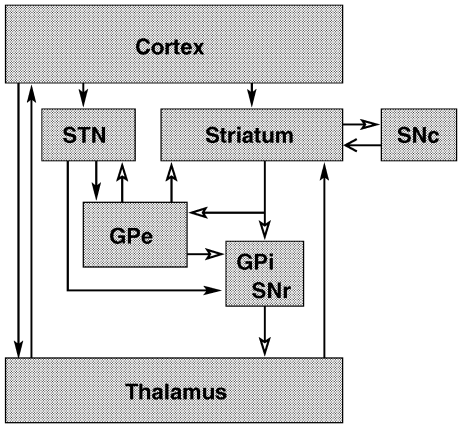

Figure 2.2. *Basal ganglia circuitry. The striatum and the sub-thalamic nucleus (STN) receive input from the cortex. Both striatum and the tonically active STN project to globus pallidus interna (GPi), substantia nigra reticulata (SNr) and globus pallidus externa (GPe). Further the striatum has a reciprocal 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 singulate 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, 2005).

The majority of the neurons in the striatum are GABAergic medium spiny (MS) projection neurons. These neurons receive corticostriatal 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 GPi. 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; Bargas *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 Plenz, 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; Koós 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 largly 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 unpredicted 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 (Moghal *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 Parkison 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 to 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 neurons. 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 $1\,\mu\mathrm{F/cm}^2$.

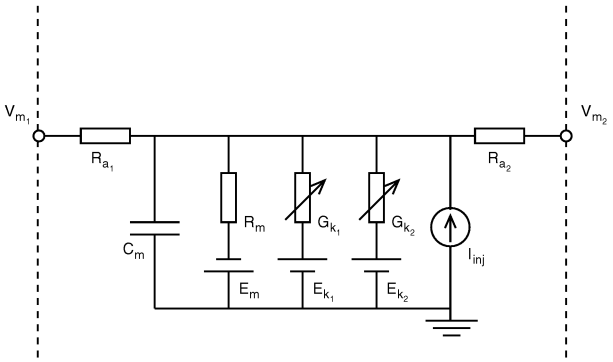

Figure 3.1. *Equivalence circuit for a generic neural compartment. The capacitor (C_m) represents the cell membrane. The leak currents are represented by a resistor (R_m coupled with a battery (E_m). Batteries with voltages corresponding to reversal potentials (E_k) coupled with a variable resistance (G_k) represent the different ion species. Resistive elements couple neighbouring compartments together and current injections can be easily modelled (I_{inj}).*

When using compartmental models the neuron is divided into a number of compartments that are each assumed to be iosopotential, 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,

$$C\frac{dV}{dt} = I_{comp} - I_{ion} - I_{syn} - I_{leak} - I_{inj} \tag{3.1}$$

where I_{comp} is the current entering the compartment from neighbouring compartments, I_{ion} the current through the ion channels, I_{syn} the current through the synaptic ion channels, I_{leak} the leak current through the membrane and I_{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,

$$I = g_{max}(V - V_{rev})X^nY^m \tag{3.2}$$

where g_{max} is the maximal conductance and V_{rev} is the reversal potential, e.g. E_k in Figure 3.1. The gates are opened and closed with rates α and β, and the

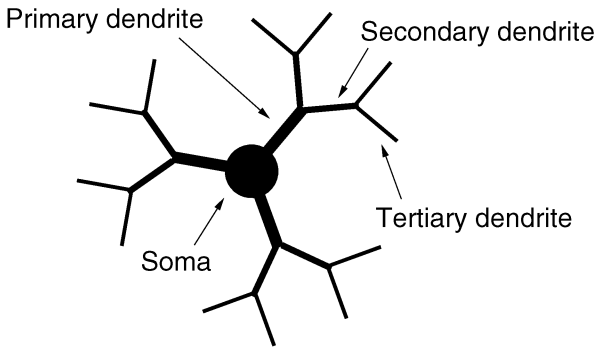

Figure 3.2. *Schematic drawing of a modelled FS neuron showing the soma, three primary dendrites, six secondary dendrites and twelve tertiary dendrites.*

state of the gate can thus be calculated from

$$\frac{dx}{dt} = \alpha(1 - x) - \beta x \tag{3.3}$$

where the values of α and β can vary as the membrane potential varies. If the voltage is held fixed the value of x will reach a steady state value,

$$x_{ss} = \frac{\alpha}{\alpha + \beta} \tag{3.4}$$

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 corticostriatial input as well as spike bursts in MS 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 corticostriatal 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 Kotaleski *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.*, 200). 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 Kotaleski *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,

$$I_{Na} = m^3 h \cdot \bar{g}_{Na}(V - 0.045) \tag{3.5}$$

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 (α) and closing rate (β) for the gating particle m are,

$$\alpha_m = \frac{10^6 \cdot (3.020 - 40 \cdot V)}{e^{(0.0755+V)/0.0135} - 1} \tag{3.6}$$

$$\beta_m = 1226.2 \cdot e^{-V/0.042248} \tag{3.7}$$

and the corresponding rates for h are

$$\alpha_h = 3.5 \cdot e^{-V/0.024186} \tag{3.8}$$

$$\beta_h = \frac{10^3 \cdot (0.8712 + 17 \cdot V)}{1 - e^{-(0.05125+V)/0.0052}} \tag{3.9}$$

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 Kotaleski *et al.* (2006) 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,

$$I_{Kv1.3} = n^4 \cdot \bar{g}_{Kv13}(V + 0.090) \tag{3.10}$$

where the opening and closing rates for n are,

$$\alpha_n = \frac{616 + 14000 \cdot V}{1 - e^{-(0.044+V)/0.0023}} \tag{3.11}$$

$$\beta_n = 4.3 \cdot e^{-(0.044+V)/0.034} \tag{3.12}$$

Transient Potassium Channel Kv3.1-Kv3.2

The transient potassium channel Kv3.1-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,

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

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

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

$$\beta_n = 25 \cdot e^{-V/0.022222} \tag{3.15}$$

Transient Potassium A-channel

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

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

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

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

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

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

$$\tau_h = 0.014 \tag{3.20}$$

This can then be used in

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \tag{3.21}$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \tag{3.22}$$

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-correlogran (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 JPSTH 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 JPSTH 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 JPSTH 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

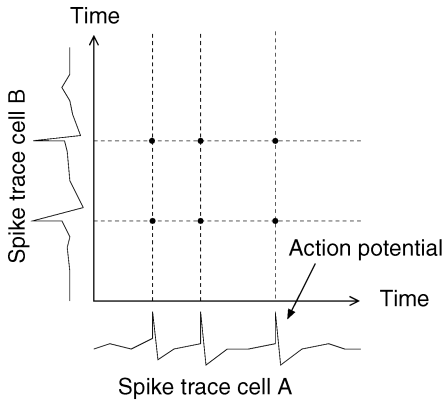

Figure 3.3. *Creation of a joint peristimulus time histogram (JPSTH). Traces from two simultaneously recorded neurons are binned against each other. If they have a tendency to synchronize a cluster of filled bins will appear on the diagonal.*

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,

$$S \rightleftharpoons P \tag{3.23}$$

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

$$v = -\frac{d[S]}{dt} = \frac{d[P]}{dt} \tag{3.24}$$

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

$$v = k_1[S] = k_{-1}[P] \tag{3.25}$$

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

$$K_{eq} = \frac{[P]}{[S]} = \frac{k_1}{k_{-1}} \tag{3.26}$$

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 (Michaels and Menten, 1913).

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightleftharpoons} E + P \tag{3.27}$$

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

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

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,

$$[ES] = \frac{k_1[E_0][S]}{k_{-1} + k_2 + k_1[S]} \tag{3.29}$$

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

$$v = \frac{k_1 k_2[E_0][S]}{k_{-1} + k_2 + k_1[S]} = \frac{k_2[E_0][S]}{\frac{k_{-1}+k_2}{k_1} + [S]} \tag{3.30}$$

which is recognised as

$$v = \frac{V_{max}[S]}{K_m + [S]} \tag{3.31}$$

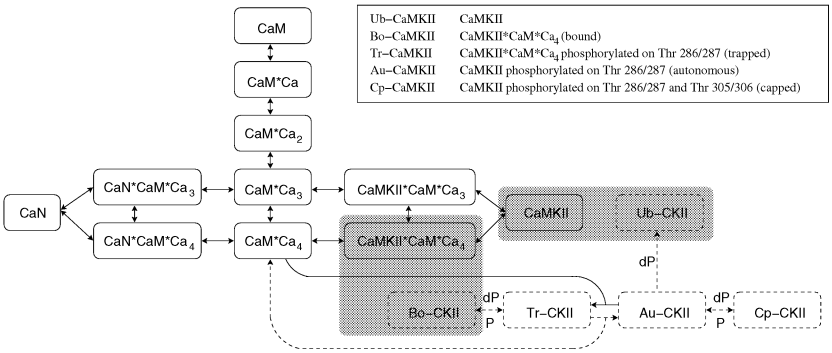

Figure 3.4. *Biochemical network of the CaMKII model. The stochastic parts are dashed, solid parts correspond to the deterministic parts. The grey boxes indicate where the two models are coupled.*

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

$$A \xrightarrow{k_f} B \tag{3.32}$$

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

$$p = e^{-k_f \cdot dt} \tag{3.33}$$

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 $CaMCa_4$'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.

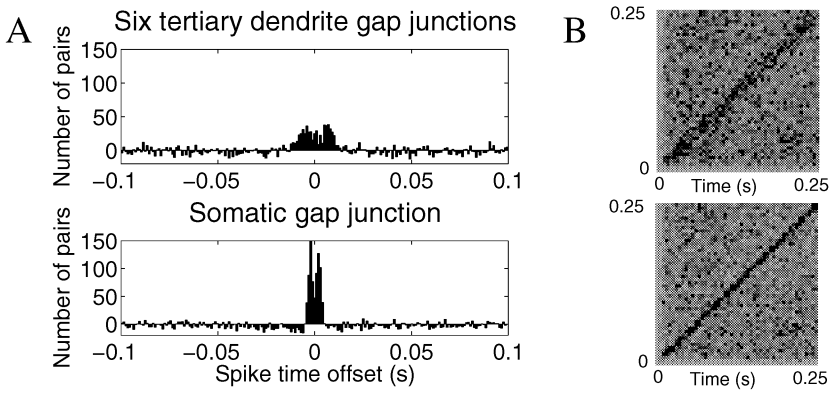

Figure 4.1. *Synchronisation effect of gap junctions. (A) Shuffle-corrected cross-correlogram. Both somatic and the tertiary dendritic gap junctions synchronise the two neurons, but the time window is narrower for somatic couplings. (B) Joint peristimulus histogram (JPSTH). The upper figure shows the raw JPSTH for the tertiary dendritic gap junctions and the lower for the somatic gap junctions (Palm* et 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 JPSTHs 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 corticostriatal 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).

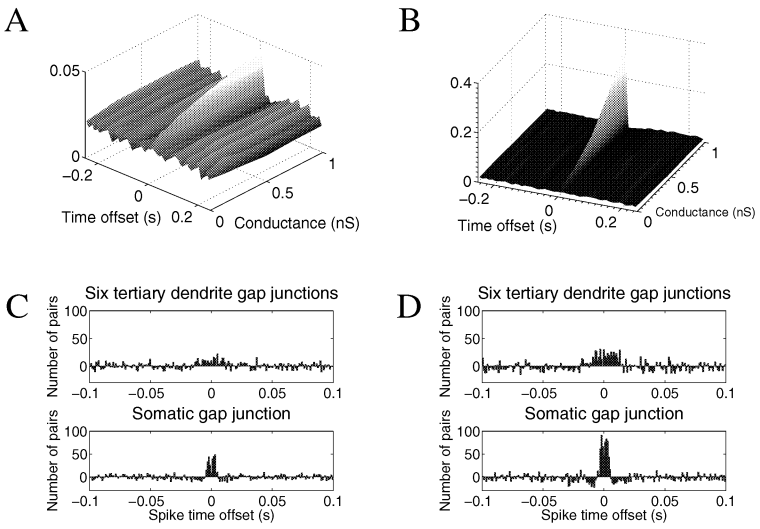

Figure 4.2. *Shuffle corrected cross correlogram (SCCC). Two FS neurons connected through distal gap junctions (A) or proximal gap junctions (B), normalised SCCC. SCCC for conductance 0.20 nS without dopamine (C) and with dopamine (D).*

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 10^5 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.

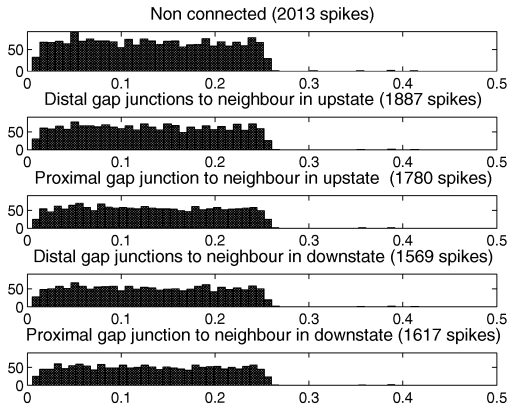

Figure 4.3. *Up-state detection. Histogram of spike times during the periods, the FS neuron spikes more if its neighbour receives up-state input also. The figure shows 250 ms up-state followed by 250 ms down-state.*

4.3. Biochemical Modelling

Reinforcement learning and plasticity are important for the function of the striatum. Bhalla (2003) and Kotaleski *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 (Kotaleski *et al.*, 2005), which is equally important since dopamine has a role in plasticity.

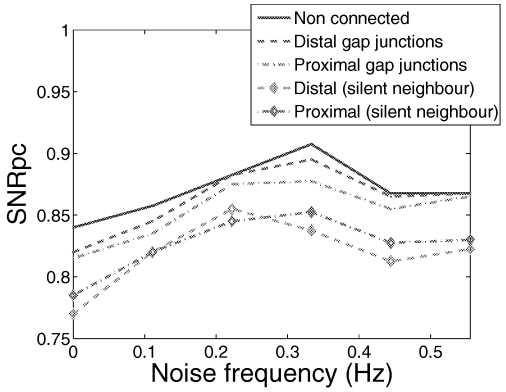

Figure 4.4. *Noise variations of the signal to noise ratio. Moderate amounts of noise increase the signal to noise ratio. Comparing the FS neurons whose neighbours also receive up-state input with those that have a silent FS neighbour receiving downstate input we see that increased noise can compensate 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; McNeill *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 (Kotaleski *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 easen 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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Part I.

Papers

Paper I

The significance of gap junction location in striatal fast spiking interneurons

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Abstract

Fast spiking interneurons (FS) in the striatum are hypothesised to control spike timing in the numerous medium spiny projection neurons (MS) by inhibiting or delaying firing in the MS neurons. The FS neurons are connected to each other through electrical gap junctions. This might synchronise the FS neurons, leading to increased influence on target neurons. Here we explore the possible difference between proximal and distal gap junction locations. Somatic and distal dendritic gap junctions with equal coupling coefficient, as defined for steady-state somatic inputs, showed significantly different coupling coefficient with transient inputs. However, the ability to synchronise spiking in pairwise coupled FS neurons, which received synaptic inputs as during striatal up-state periods, was as effective with distal gap junctions as with proximal ones. Proximal gap junctions, however, caused synchronisation within a more precise time window.

Key words: Striatum, fast spiking interneurons, gap junctions, synchronisation

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1 Introduction

The basal ganglia are involved in action selection and behavioural control [10]. The input stage is called the striatum and it receives input from both the motor and limbic systems. The principal neurons in the striatum are the medium spiny projection neurons (MS) which project to the basal ganglia output stages. The cortical input to the striatum is glutamatergic and varies in intensity, giving rise to up-states and down-states in the striatal neurons. Approximately 50 % of the inputs to the MS neurons are GABAergic [2]. Since the MS neuron collaterals are weak [12] it has been speculated that the inhibition is mediated by the fast spiking interneurons (FS). The FS neurons are not as numerous but they form inhibitory pericellular baskets with low failure rates on the MS neurons and are able to delay or altogether prevent the MS neuron from firing [3, 13, 15].

In addition to having chemical synapses, the FS neurons are connected to each other through electrical synapses, i.e. gap junctions. In one study FS neurons were found to be coupled to one third of the neighbours [6]. To measure the strength of a gap junction coupling one can use the coupling coefficient [9], which is defined as the ratio between the voltage change in the coupled neuron divided by the voltage change in the stimulated neuron. When injected with 50 ms current pulses the coupling coefficient has been found to vary between 3 % and 20 % [13]. The situation is quite different for transient activations. In fact, the coupling resulting from a short pulse, like an action potential, is much smaller [6]. Here we investigate through computational modelling how the coupling coefficient is affected by the duration of the input pulse and discuss how this can be used as an alternative way to determine if the gap junctions are proximal or distal. We also explore the role of gap junction location for the ability to synchronise spiking between FS neurons receiving synaptic input as during up-state periods.

2 Methods

Fast spiking interneurons were simulated using GENESIS [4] on a Debian GNU/Linux system. The cell model has been described in detail recently [11]. It has three primary dendrites that branch into six secondary dendrites which in turn branch into a total of twelve tertiary dendrites (see Figure 1A). The model has Na, K_{3132}, K_{13} and K_A conductances.

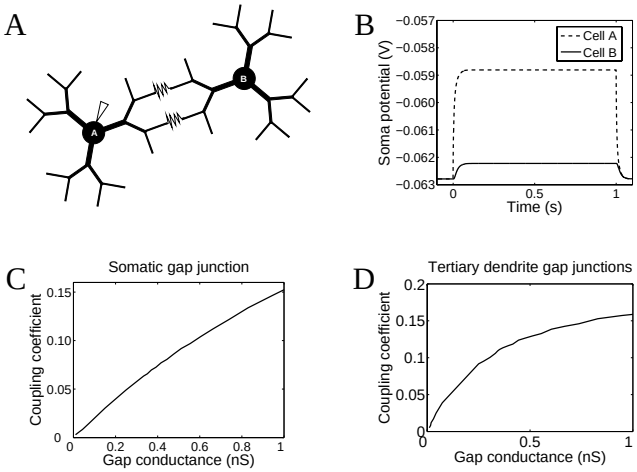

Fig. 1. Tuning of gap junction conductance. (A) shows two FS neurons connected through gap junctions on the tertiary dendrites. Here only two out of six gap junctions are shown. (B) To determine the coupling coefficient a current was injected into the soma of one neuron and the depolarisation was measured both in that neuron (Cell A) and in the coupled neuron (Cell B). (C) shows the coupling coefficient for different gap junction conductances when only one somatic gap junction was used. For 0.38 nS, which is within the physiological range, a coupling coefficient of 14 % was achieved. (D) shows the coupling coefficient when six tertiary dendritic gap junctions were used, yielding 14 % coupling at 0.67 nS. The coupling is lower when the six distal gap junctions are used, because they are more electrotonically distant from the current injection.

Synaptic conductances, distributions and activation frequency are adjusted to reproduce the amplitude, rise time and inter event interval distribution histograms as measured during spontaneous activity in co-cultures [11].

The FS neurons were pairwise connected through gap junctions (see Figure 1A). Studies indicate that gap junctions are usually located at the same electrotonic distance from the soma in both neurons [7]. Thus we investigated two configurations; in the first configuration the FS neurons are connected through one somatic gap junction; in the second configuration they are connected through gap junctions located on the tertiary dendrites.

To quantify spike synchronising properties in pairwise coupled FS neurons we used a shuffle-corrected cross-correlogram (SCCC). The construction of such an SCCC has been described in detail previously [5, 14]. The inter spike intervals between all combinations of spikes from the two FS neurons were binned and a histogram was created. To remove bias the spike train of one FS neuron was shifted relative to the other and a new histogram was generated. This was done for all possible shifts and the average shifted histogram was

subtracted from the original histogram, yielding the SCCC.

We also generated the normalised joint peristimulus time histogram (NJPSTH) [1, 14] for the data. An ordinary JPSTH is a 2D-diagram where each combination of spike time in cell A and cell B is indicated. Diagonal elements thus represent simultaneous spiking in both neurons. By calculating the surprise measure as defined previously [1, 14] the significance of the synchronisation can be estimated. A "surprise" value of 2.996 corresponds to $p = 0.05$. When studying a JPSTH, regions of elevated "surprise" are of interest. Part of the JPSTH calculations was done by matlab code generously provided by Jeff Keating.

3 Results and Discussion

The proximal and distal gap junction conductances were adjusted to have the same coupling coefficient under steady-state conditions by injecting 1 s current pulses into the soma of one of the modelled FS neuron (Figure 1B, cell A) and measuring the corresponding voltage change in the neighbouring FS neuron (Figure 1B, cell B). For somatic gap junctions a coupling coefficient around 14 % was achieved at 0.38 nS (Figure 1C), a gap junction strength within the physiological range of 0.13–0.58 nS [8]. To reproduce the same coupling coefficient using distal gap junctions with reasonable conductances we used six gap junctions. The gap junction conductance used for these tertiary dendritic gap junctions was 0.67 nS (Figure 1D) and we distributed them so that they did not share secondary dendrites. These gap junction conductances were then used in the simulation below unless otherwise stated.

To investigate how the coupling coefficient was affected by transient somatic inputs the input pulse duration in the simulation was varied between 1 ms and 100 ms in 1 ms increments. For shorter input pulses the two configurations differed. Brief pulses give larger coupling coefficients when proximal gap junctions are used (Fig 2A, solid line) compared to distal gap junctions (Fig 2A, dashed line). Short pulses are thus filtered more by distal gap junctions. In Figure 2B we also confirm that the coupling coefficient for an excitatory postsynaptic potential (EPSP) resulting from an activation of an AMPA synapse on one of the cells behaves in a similar manner. These relative differences in coupling coefficients for steady state versus transient inputs could be used to give a rough estimation of the location of gap junctions.

Gap junctions are able to synchronise neurons that are triggered to fire repeatedly by somatic current injection [9]. To compare the synchronising effects of

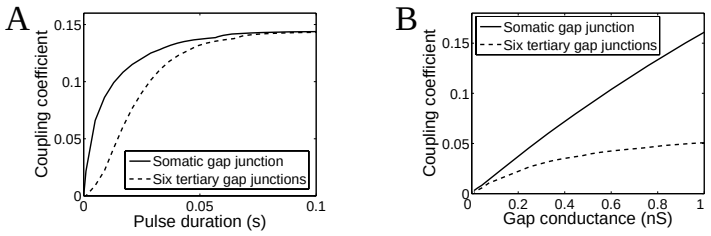

Fig. 2. Role of stimulus duration for the coupling coefficient. (A) The coupling coefficients for two different configurations of gap junctions were compared for different durations of injected current. Despite a similar coupling coefficient for steady state inputs, tertiary dendritic gap junctions (dashed) are significantly less effective for shorter pulses than somatic ones (solid). (B) shows the coupling coefficient for somatic (solid) and six tertiary dendritic gap junctions (dashed) when an AMPA EPSP was elicited in one neuron's soma.

the somatic and tertiary dendritic gap junction configurations we simulated periods of up-state and down-state synaptic input to the neurons. Three pairs of FS neurons were created. The pairs differed in how the cells were connected to each other. One pair was connected through somatic gap junctions, another pair was connected through six tertiary dendritic gap junctions and the third pair was left unconnected for reference. From the SCCC shown in Figure 3A we see that both the proximal and the distal gap junction configuration were able to synchronise the neurons, however the somatic configuration had a narrower peak in the SCCC. In the JPSTH the synchronisation can be seen as a diagonal (Figure 3B). The diagonal is visible both for the tertiary dendritic gap junctions configuration and the somatic gap junction configuration. We also calculated the normalised JPSTH and its surprise values and found the synchronisation to be significant, $p < 0.05$ [1, 14]. Figure 3C shows the significance level of the different spike intervals.

In summary, this study investigated whether fast spiking interneurons in the striatum connected through proximal as well as distal gap junctions can synchronise activity during up-state periods. The simulation results suggest that although the distal gap junctions have a significantly smaller coupling coefficient as measured by transient somatic input, both gap junction configurations synchronise the spikes between the coupled cells. However, with distal gap junctions the synchronising window is more dispersed.

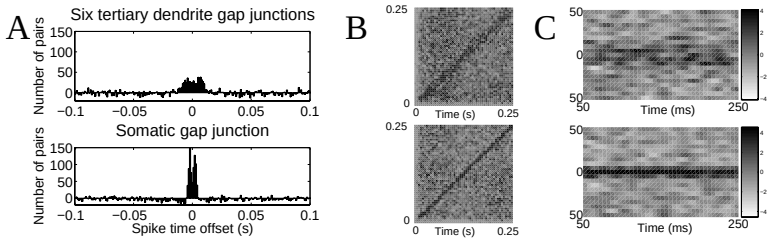

Fig. 3. Synchronisation effect of gap junctions. (A) Shuffle-corrected cross-correlogram. Both somatic and the tertiary dendritic gap junctions synchronise the two neurons, but the time window is narrower for somatic couplings. (B) Joint peristimulus histogram (JPSTH). The upper figure shows the raw JPSTH for the tertiary dendritic gap junctions and the lower for the somatic gap junctions [1, 14]. The diagonal representing synchronisation can be seen for both the tertiary dendrite and somatic gap junction cases. (C) Delayed coincidence matrix for the corresponding JPSTHs in B. The figures show the significance value of spike intervals -50 to 50 ms and from 50 ms to 250 ms of the up-state period. There is a significant synchronisation, the diagonal bins have $p < 0.05$.

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Paper II

Up-State signalling and Coincidence Detection in Striatal Fast Spiking Interneurons Coupled through Gap Junctions

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May 2006

Abstract

The main population of neurons in the input stage of the basal ganglia, the striatum, are the medium spiny (MS) projection neurons. In addition to the MS neurons there are several other small neuron populations, one of which is the fast spiking (FS) interneuron. Both MS and FS neurons receive glutamatergic input from cortex and thalamus as well as dopamine from substantia nigra. The FS neurons form pericellular baskets on the MS neurons, this allow them to exert powerful inhibition on the MS neurons activity. Furthermore, the FS neurons are connected to each other through gap junctions, forming electrical networks. Here we further explore the role of gap junctions for up-state signalling, coincidence detection and synchronisation. These factors could all contribute to the control of spike timing in MS neurons. We have found that an FS neuron that is connected with intermediate gap junction strength to another FS neuron have 7 % or 14 % more spikes for proximal and distal gap junctions, respectively. Furthermore, gap junctions allow coincidence detection of transient inputs arriving close in time to the electrically coupled neurons.

Introduction

The basal ganglia are a group of subcortical nuclei that are involved in cognitive and motor functions. The input stage of the basal ganglia is called the striatum and it receives glutamatergic input from large regions of the cortex (Bolam et al., 2000; Bar-Gad et al., 2003; Graybiel, 2005). The striatum also receives modulating dopaminergic input from substantia nigra compacta (SNRc) and the ventral tegmental area (VTA) and there exist projections from the striatum back to the dopamine producing neurons (Canales, 2005). The majority of the neurons in the striatum are medium spiny (MS) projection neurons that project to the globus pallidus and substantia nigra. The MS neurons also form collaterals onto other MS neurons in the striatum but these have been shown to be relatively weak (Jaeger et al., 1994).

There are other neurons in the striatum in addition to the MS neurons. Amongst these are the parvalbumin positive fast spiking (FS) interneurons. The FS neurons are able to fire in rapid succession in response to depolarising input. By forming pericellular baskets on the MS neurons the FS neurons can exert powerful inhibition with low failure rates which can delay or prevent an action potential in MS neurons (Bolam et al., 2000; Koós and Tepper, 1999; Tepper et al., 2004). Each FS neuron synapse onto 135–541 MS neurons, and each MS neuron is innervated by at least four (4–27) FS neurons (Koós and Tepper, 1999). The activity of the FS neuron can thus change MS neuron spike timing. There are variations in the synaptic strength between an FS neuron and its different target MS neurons, but generally the feedforward connections from cortex, via FS to MS neurons, are twice as strong and roughly 1 ms faster than the MS to MS neuron feedback loop (Gustafson et al., 2006). The cortical input to both MS and FS neurons varies in frequency between the relatively silent down-state and the more active up-state. It is during the up-state that the MS neurons in the striatum mainly fire and their activity reflects encoding of procedural memories (Barnes et al., 2005). Both during up-state and down-state approximately 50 % of the striatal input is GABAergic (Blackwell et al.,

2003).

In addition to chemical synapses, recent studies have detected electrical coupling between FS neuron in the striatum that is mediated through gap junctions. Networks of FS neurons are thus formed where each FS neuron may connect to one third of its neighbours (Koós and Tepper, 1999; Galarreta and Hestrin, 2001b). Gap junctions have been shown to synchronise neurons, both experimentally (Traub et al., 2001; Connors and Long, 2004) and in computational studies (Gibson et al., 2005), including in the striatum (Hjorth et al., 2006). Therefore, if several striatal FS neurons fire simultaneously during an up-state period, their effects on the MS neurons become more robust. Through computational modelling we investigate the effect gap junctions have on synchronisation, up-state signalling and coincidence detection during physiologically realistic input. We show that an FS neuron coupled to a neighbouring FS neuron has more spikes during up-state periods if the neighbouring neuron also receives up-state input. Furthermore, simulations suggest that coupled neurons, receiving simultaneous depolarising inputs, can both depolarise more than without gap junctions. Also gap junctions allow coincidence detection which in some cases leads to spike synchronisation.

Methods

Cell model

The fast spiking (FS) interneuron were modelled using GENESIS (Bower and Beeman, 1994) on a Debian GNU/Linux system. The model has been described before in detail (Hellgren Kotaleski et al., 2006). Briefly it consists of a soma compartment connected to three primary dendrites that branch into six secondary dendrites that in turn branch into a total of twelve tertiary dendrites. The model implements fast sodium channels, potassium channels (Kv1.3 and Kv3.1-Kv3.2) as well as a transient potassium channel (A-channel). The fast activation of Kv3.1-Kv3.2 is responsible for the FS neurons ability to spike rapidly (Erisir et al., 1999). All dendritic branches are passive except for proximally distributed K_A conductances.

Synaptic Input

AMPA synapses are evenly distributed over the neuron, but the GABA synapses are concentrated on the soma and proximally on the dendrites. The synapses are activated by Poisson trains to give postsynaptic inputs that have the right interspike interval, rise time and amplitude distributions and the simulated input can recreate the characteristic phases of up-states and down-states (Hellgren Kotaleski et al., 2006). Each synapse is activated during up-state periods with the frequency of 20/9 Hz and during down-state with 1/9 Hz. For the correlation we have used a generative measure as defined by Rudolph and Destexhe (2001) with $C = 0.5$. Correlation is generated by having fewer input trains than synapses, which results in some input trains being reused. If N is the number of synapses and N_0 is the number of independent input trains then

$$N_0 = N + \sqrt{C}(1 - N).$$

For each time step the input trains were reconnected to random synapses in such a way that the number of synapses per input train were constant. We changed the previous implementation by generating a mother process from which the spikes for the input train were randomly selected. The reason for this was that GENESIS did not allow reconnection of the spike trains during a simulation. The mother process had a frequency of $f_m = N_0 \cdot f$ where f is the desired frequency on the input trains. Each spike in the mother process was then selected for inclusion in an input train on average N/N_0 times yielding the desired correlation. In this implementation AMPA and GABA inputs were not activated simultaneously. This gave rise to slightly larger spike probability but is well within the experimentally obtained range for FS neurons (Blackwell et al., 2003; Hellgren Kotaleski et al., 2006).

Gap Junctions and Coupling Coefficient

A gap junction is modelled as a passive resistive element connecting two compartments of neighbouring neurons. The coupling coefficient is defined as the ratio between the somatic voltage change in the neighbouring neuron divided by the soma response in the directly stimulated neuron. Since it is not known where the gap junctions are located between striatal FS neurons we investigated proximal (soma–soma) as well as distal (tertiary dendrites–tertiary dendrites) gap junction configurations.

Detection of Spike Synchronisation

Synchronisation was tested by giving two neurons simulated up-state input. Here the up-states occurred simultaneously, but the input spikes to either neuron were uncorrelated between the neurons. From the resulting spike trains we generated shuffle corrected cross-correlograms (SCCC) (Brody, 1999). The inter-spike intervals between all combinations of spike pairs from the two FS neurons were binned and a histogram was then created. To remove any bias the spike train of the first FS neuron was shifted relative to the other and a new shifted histogram was generated. This new shifted histogram could then be used to remove the bias, since correlations are assumed to occur only on a short timescale, and these interactions are destroyed by the shifting, leaving only the bias in the shifted histogram. This process was repeated for all possible shifts and the average shifted histogram was then subtracted from the original histogram, yielding the SCCC. The procedure is described in detail in Brody (1999).

Results

Coupling Coefficient During Steady State versus Transient Inputs

Gap junctions can be formed at different distances from the soma (Tamás et al., 2000; Fukuda et al., 2006), however studies of fast spiking (FS) interneurons in the brain indicate that gap junctions are usually located at the same electrotonic distance from the soma in both coupled neurons (Galarreta and Hestrin,

2001a). As in an earlier study (Hjorth et al., 2006), we defined two reference cases in order to investigate whether the results are critically dependent on the location of gap junctions. In one case FS neurons were connected through somatic gap junctions and in the other case FS neurons were connected through gap junctions located on the tertiary dendrites. We calibrated the conductance so that the steady state coupling would be comparable between the two cases and within the physiological range of 3–20 % (Koós and Tepper, 1999). In order to fulfil this constraint for different gap junction locations we had to use more than one tertiary dendrite gap junction. We used a configuration of six tertiary dendrite gap junctions distributed so that they did not share secondary dendritic branches (Figure 1A). The gap junction conductance calibration was done by connecting two neurons through gap junctions and injecting current into the first neuron, while measuring the resulting voltage change in both this neuron and in the neighbouring neuron, when steady state had been reached (Figure 1B). This was repeated for the two different configurations of gap junction locations and for different conductances. The two curves intersect at 0.22 nS, which means that the gap junction conductance is equal for both proximal and distal configurations and within experimentally measured values of 0.13–0.58 nS (Galarreta and Hestrin, 2002) (Figure 1C). The resulting coupling coefficient was measured to be 0.088, also within the physiological range. In this study we used this as a reference value unless otherwise stated.

When cells are electrically coupled to other cells, the voltage changes may be shunted away through the gap junction conductances. We therefore investigated how the shunting ratio varied. This ratio we defined as the depolarisation caused by a somatic current injection in a neuron, when this neuron was coupled to a neighbouring neuron, divided by the depolarisation in the same neuron without any gap junction couplings (Figure 1D).

The coupling coefficient is in general dependent on the dynamics of the input (Galarreta and Hestrin, 2001b) which normally are transient. We investigated this quantitatively for both proximal and distal inputs. In Figure 2A we injected current pulses of different durations into the soma of the first neuron in order to observe the effect of the electrical coupling. Short pulses were filtered more, i.e. had a lower coupling coefficient, than long pulses both for proximal and distal gap junctions. The exact coupling differed for the two gap junction reference cases; the proximal connections had a higher coupling coefficient than the distal connections for pulses of intermediate length (Hjorth et al., 2006). For comparison, a more physiological transient input generated by an AMPA activation was also used as an input. When activating an AMPA EPSP on the soma the proximal gap junction was more efficient than the distal gap junctions, Figure 2B. In real cells much of the input comes from dendritic synapses. We therefore also injected currents to the end points of all dendrites and calculated the somatic coupling coefficient as shown in Figure 2C. Here we see that, in contrast to proximal inputs, the distal gap junctions are much more efficient in terms of coupling coefficient. This is because the electrotonic distance to both somas, as seen from the more peripheral injection site, are not that different. We did also elicit AMPA EPSPs at the endpoints of all tertiary dendritic compartments, as shown in Figure 2D. Here the distal gap junctions gave a coupling coefficient almost three times as large as if proximal gap junctions are used. The above results show that, depending on the input location, either proximal or distal gap junctions can be more efficient as measured by the coupling coefficient.

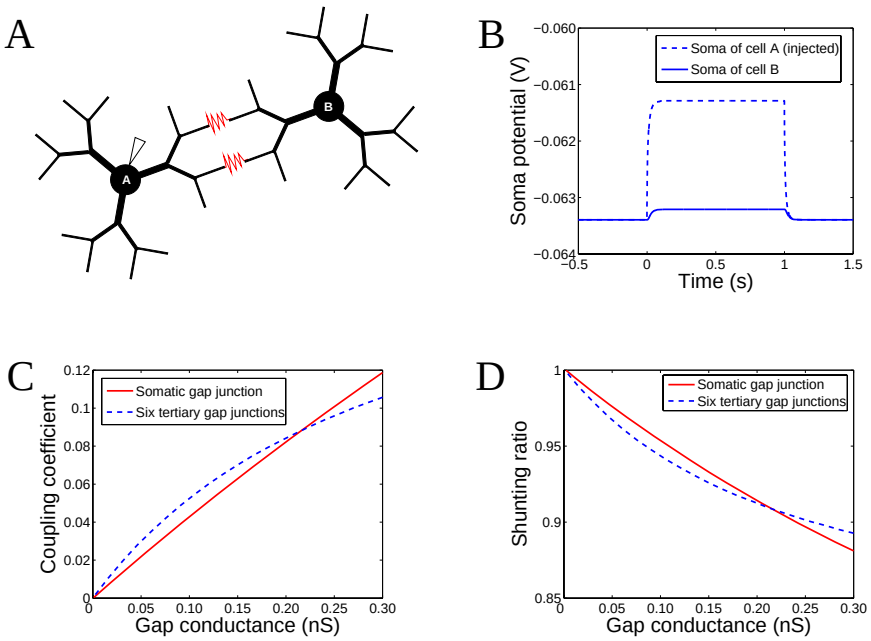

Figure 1: Calibrating the gap junction conductances. (A) shows two FS neurons connected through tertiary dendrite gap junctions, here only two out of six gap junctions are shown. (B) To determine the coupling coefficient a current was injected into the soma of one neuron and the depolarisation was measured both in that neuron (Cell A) and in the coupled neuron (Cell B). (C) shows the steady state coupling coefficient as a function of gap junction conductance, both for one somatic gap junction and six tertiary dendrite gap junctions. At 0.22 nS both the somatically coupled and the tertiary coupled FS neurons have a coupling coefficient of 0.088. (D) Shunting ratio of somatic potential defined as depolarisation in Cell A with gap junction coupling to another cell, divided by the depolarisation in Cell A when lacking gap junctions.

Critical Window

A depolarised cell electrically coupled to another less depolarised cell might loose charge, and the less depolarised cell will gain depolarisation. We investigated if there is some case where two FS neurons could both gain electrical charge and become more depolarised for a certain input, by being connected through gap junctions. We assumed that we had two FS neurons connected by distal gap junctions. Close to a gap junction at the first neuron we activated an AMPA EPSP, close to another gap junction in the second FS neuron we also activated an AMPA EPSP as shown in Figure 3A. These AMPA EPSPs can be activated simultaneously or with a time offset. If there were no gap junctions, each of the two neurons would just see one AMPA EPSP which would lead to a depolarisation in the soma (dashed line in Figure 3B). If we add the gap

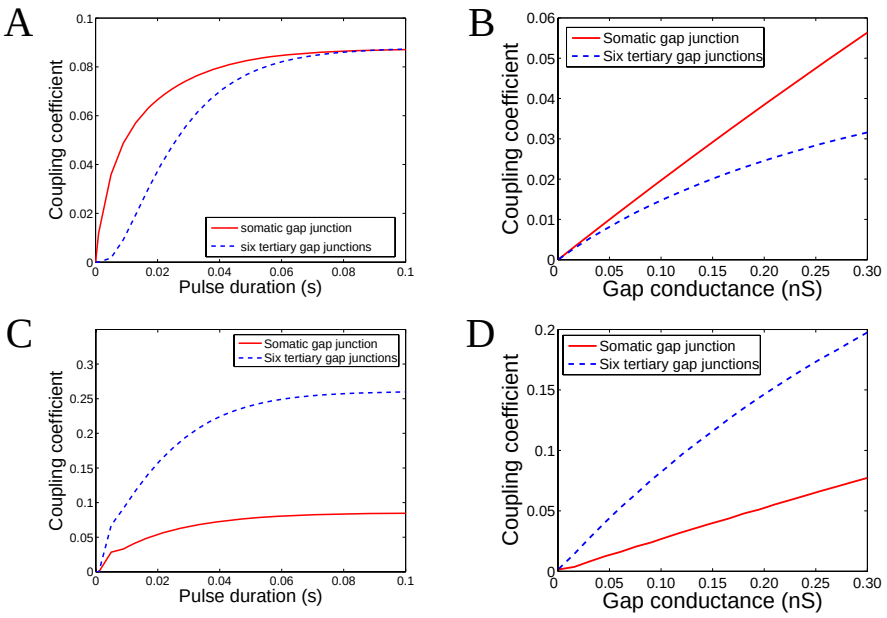

Figure 2: Role of stimulus duration for the coupling coefficient. (A) The coupling coefficients for two different configurations of gap junctions were compared for different durations of injected current into the soma. Despite a similar coupling coefficient for steady state inputs, tertiary dendrite gap junctions (dashed) are significantly less effective for shorter pulses than somatic (solid) ones. (B) shows the coupling coefficient for somatic (solid) and six tertiary dendrite gap junctions (dashed) when an AMPA EPSP was elicited in one neuron's soma. (C) Here the injected current was given to the endpoints of all tertiary dendrites. We see that the tertiary gap junctions are considerably more effective. (D) Coupling coefficient measured when the endpoints of the tertiary dendrites all received an AMPA EPSP.

junctions and activate an AMPA EPSP in one of the neurons then what we see is that some of the charge entering the dendrite will be shunted away to the neighbouring neuron's dendrite. This leads to a lower depolarisation in the first soma (Figure 3B, line at -61.6mV). But since the current that enters the first dendrite is proportional to the difference between the reversal potential and the dendrite's local potential more charge will enter the cell if taking into account also the charge that is lost to the neighbouring cell. Now if we also activate a second AMPA EPSP in the other cell, then we find that it too will be more efficient in transporting charges into the dendrite. Summing the charges entering into the neurons we see that both neurons have each received more than they would have without the gap junction. Thus if the two neurons are activated almost simultaneously, the maximal somatic depolarisation in each of the neurons reaches above the value they would have had without gap junctions and when receiving the same synaptic activation (Figure 3B, peak around time offset 0 s). The amplitude of the postsynaptic responses depends on when the other neuron receives an input. For assymetrical couplings, where a gap junction might be located proximally on one neuron and distally on the neighbour, there is still a critical window, but it is shifted in time either left or right in the figure. An example of a somatic voltage trace is shown in Figure 3C for three different cases (indicated as α, β and γ in B). Next we wanted to see if the presence of gap junctions could help elicit an action potential when an activation of an AMPA synapse was done simultaneously in both neurons. Figure 3D shows that when we are close enough to the threshold potential the presence of gap junctions can lead to a spike as a result, while in the case without gap junctions the spiking threshold was not reached.

Synchronisation is Affected by Gap Junction Location and Strength

It is generally believed that gap junctions synchronise neurons (Bennett and Zukin, 2004; Connors and Long, 2004) and this has also been shown for striatal FS neurons (Hjorth et al., 2006). To quantify further to what extent this occurs in the striatum during periods of up and down-states, the FS neurons were connected pairwise with gap junctions and given simulated 250 ms up and down-states of synaptic input. The synaptic inputs were correlated within each neuron as described in Methods, but not between the two neurons. We compared proximal and distal gap junctions capability to synchronise spikes for different gap junction conductances. This was done by calculating the shuffle corrected cross-correlogram from the resulting spike traces. Here we made use of the fact that in a simulation it is possible to repeat the same experiment exactly, so we used the same synaptic inputs for all gap junction conductances.

What we see for both proximal and distal gap junctions is that the synchronisation increases as we increase the gap junction conductance. The effect is more pronounced for proximal gap junctions (compare Fig. 4A and B). Figure 4C and D illustrate, using a SCCC, more visibly that the number of spikes occurring almost simultaneously in the coupled cells are dispersed if distal gap junctions are used. This general tendency is seen also when dopamine effects are simulated. Dopamine was simulated by reducing the GABA efficiency to 80 % and depolarising the neuron 2 mV as in previous simulations (Hellgren Kotaleski et al., 2006). This results in increased excitability of the neuron and

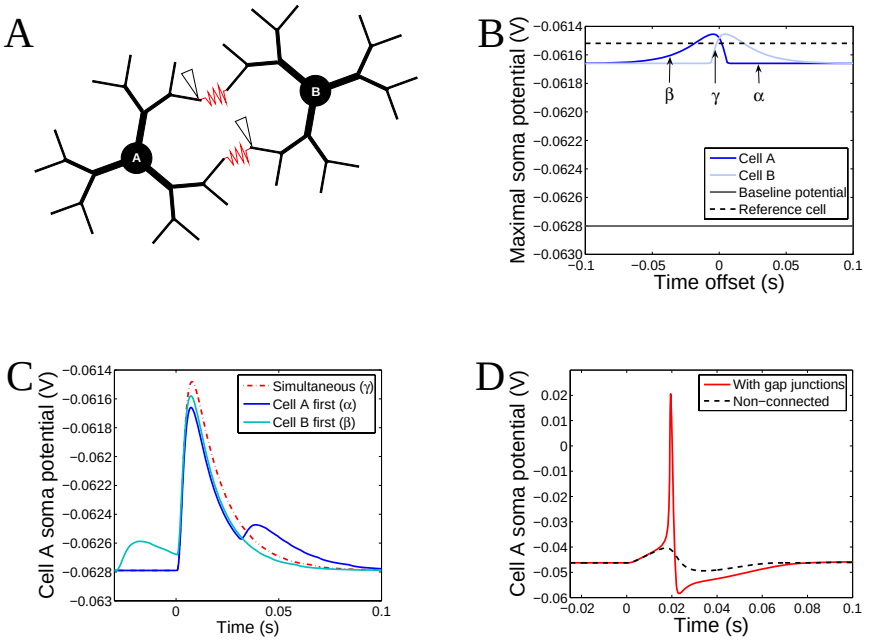

Figure 3: Critical window for increased depolarisation. (A) AMPA synapses were activated close to the tertiary dendrite gap junctions. (B) Comparison between two coupled neurons (cell A and cell B) and uncoupled reference neurons, all neurons receive one AMPA EPSP on a tertiary dendrite. The maximal depolarisation of the neuron can be up to 16 % larger if the other neuron receives an AMPA EPSP during a critical time window of a few milliseconds. (C) Voltage traces showing the effect of spike timing. The largest depolarisation occurs when the coupled neurons receive their inputs almost simultaneously. (D) When keeping the neurons close to the threshold a simultaneous AMPA input to both neurons will evoke a spike in the electrically coupled pair but not in the non-connected reference cells.

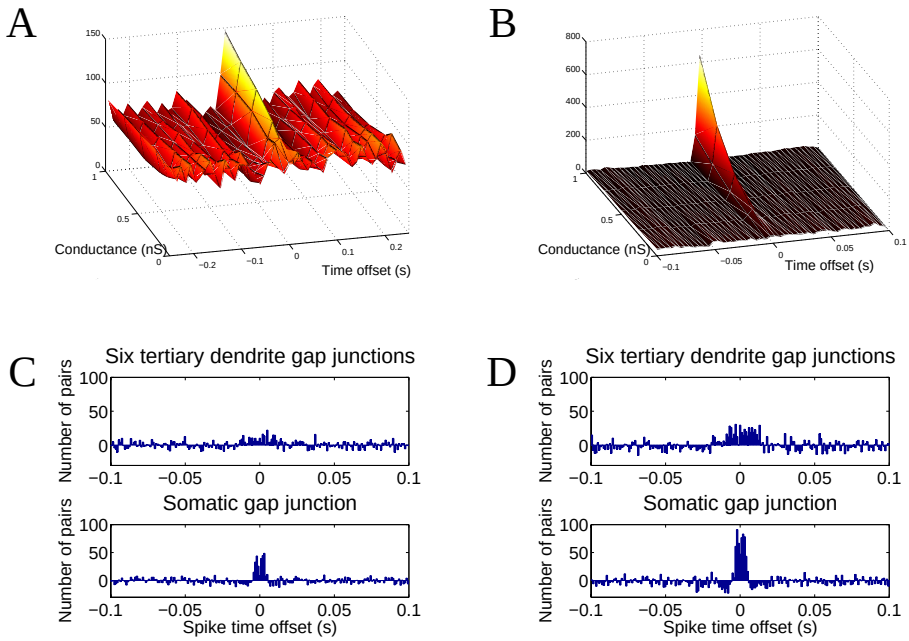

Figure 4: Shuffle corrected cross-correlograms (SCCC). Two FS neurons connected through six tertiary dendritic gap junctions (A), or somatic gap junctions (B) when the conductance is varied. SCCC for a gap junction conductance of 0.22 nS without dopamine (C) and with dopamine (D).

more spikes in the up-state.

The total number of spikes, however, decreases with increasing gap junction conductance as a result of shunting as further explained below.

Robustness and Up-state Detection

The shunting through gap junctions would transfer charge between the two neurons to even out the potential difference between them. We investigated to what extent this could be used to detect if both FS neurons received up-states simultaneously or not. An up-state is considered detected if the FS neuron fires a spike during its duration.

In Table 1 the number of spikes during periods of 250 ms up- and 250 ms down-states are shown. During up-state periods the neurons connected to a neighbour FS neuron, which also receives up-state inputs, spike significantly more, 7 % and 14 %, with proximal and distal gap junctions with the reference conductance of 0.22 nS, respectively. With simulated dopamine effects the neurons become less dependent on their neighbours for detecting up-states. The above results are robust to varying the background (i.e. down-state) noise, see also Hellgren Kotaleski et al. (2006).

Although there is an increased up-state detection when the neighbours are also in up-states, there are still slightly fewer spikes as compared to the uncon-

Configuration	Detected up-states/falsely detected down-states (± SEM)			
	Reference		Dopamine	
Six tertiary	0.708 ± 0.010	0.003 ± 0.001	0.873 ± 0.007	0.010 ± 0.002
Somatic	0.680 ± 0.010	0.002 ± 0.001	0.849 ± 0.008	0.008 ± 0.002
Six tertiary to silent	0.619 ± 0.011	0.003 ± 0.001	0.817 ± 0.009	0.009 ± 0.002
Somatic to silent	0.635 ± 0.011	0.003 ± 0.001	0.823 ± 0.009	0.008 ± 0.002

Table 1: Number of spikes for different gap junction configurations and using the reference gap junction of 0.22 nS conductance. Proximally connected neurons have 7 % more spikes if their neighbour is also receiving up-state input than if it is silent. Distally connected neurons have 14 % more spikes if their neighbour is in an up-state. When we add dopamine these numbers change to 3 % and 7 %, respectively.

nected reference cell pair, which had 0.733 ± 0.010 detected up-states without dopamine and 0.887 ± 0.007 with dopamine. By driving two coupled neurons with successively more and more correlated input between the cells, one can even reach a value slightly above the reference case. This implies that coincidence detection within the critical window has a small but measurable effect during physiological up-states, when the inputs to both neurons have highly correlated inputs.

Exploring the Mechanisms

From the above results it is shown that the spiking activity is altered in the presence of gap junctions. Two opposite phenomena are at play, action potentials arise or disappear as a result. Here we will illustrate examples of these cases and try to pinpoint the mechanisms. We have simulated three FS neuron pairs with cells labelled A and B. All neurons labelled A receive the same input and all neurons labelled B receive the same input. The first pair was left unconnected as reference, the second pair was connected through proximal gap junctions and the third pair was connected through distal gap junctions. The initial conditions for all pairs were identical. We ran the simulation for 250 ms and then reset it and repeated the run with new inputs to the pairs. The reason for the reset is that the the spike history affects the timing of subsequent spikes, this makes a direct comparison harder and could hide some of the more subtle mechanisms we are looking for. The spike traces were then analysed both by inspection and by automated matlab scripts to see which pair configuration that had spiked first.

The mechanisms are grouped into three categories: a) shunting, where spikes that exist in the reference traces disappear when the neurons are connected through gap junctions; b) subthreshold detection, where the coupled neurons have spikes that none of the unconnected reference neurons have; c) suprathreshold detection or synchronisation, when a spike in the first neuron induces a spike in the neighbouring neuron.

Shunting occurs because charge leaks through the gap junctions, e.g. a neuron depolarised closer to the threshold looses positive charge to a more hyperpolarised neighbour. This mechanism can reduce the number of spikes as shown in Figure 5A. This is because it evens out the depolarisation between

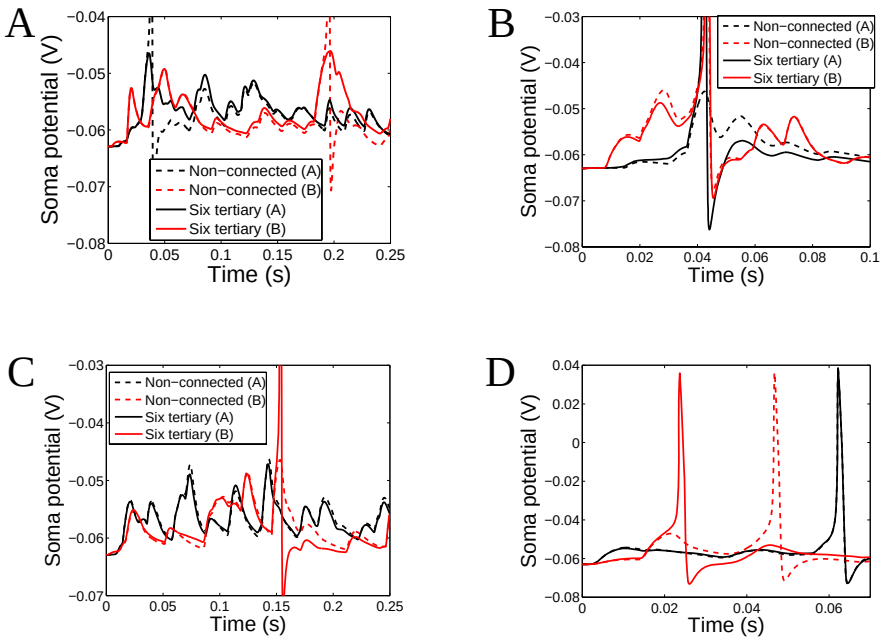

Figure 5: Gap junction effects. Non-connected and distally coupled neurons are compared. (A) Shunting: Number of spikes are reduced because charge leaks to the neighbouring neuron. (B) Suprathreshold detection: One spike in the reference trace becomes two spikes in the coupled neurons. (C) Subthreshold detection: No spike in the reference trace, the previous subthreshold excitation give rise to a spike in the coupled neurons if they are already close enough to the threshold. (D) Changes in spike timing.

the two neurons.

Additional simultaneous spikes can appear (i.e. synchronisation or suprathreshold detection occurs) in the coupled neurons, when for instance the depolarisation during, or just before, an action potential in one neuron helps the coupled neuron to also reach the threshold for a spike (Figure 5B).

It could also be the case that a spike appears in at least one of the neurons where there are no spike in any of the reference neurons (Figure 5C). This, which we call subthreshold detection, can occur because the spiking neuron had moments before gained charge from its neighbour through the gap junctions, moving it closer to the threshold than in the unconnected reference case.

All the above mechanisms also affect neuronal spike timing. For example when one of the neurons spikes the after-hyperpolarisation will reduce the likelihood of any subsequent action potentials directly following the first, see Figure 5D. Studying the traces in detail we see that the neurons take turns lending charge to each other. Depending on where the input arrives in the dendritic tree different amounts of charge will flow to the neighbour thus either increasing or decreasing the probability to reach spike threshold.

Discussion

Studies have shown that gap junctions can synchronise spiking activity in neurons (Bennett and Zukin, 2004; Connors and Long, 2004). We extend an earlier study (Hjorth et al., 2006) showing that both proximal and distal gap junctions between striatal FS neurons can cause spike synchronisation during up-state periods. This synchronisation occurs over a large range of gap junction conductances (see Fig 4), however, the synchronisation for distal gap junctions was less precise in time. In addition to causing more synchronous activity in coupled FS neurons, the presence of gap junctions affected the ability to detect up-state periods (compare Table 1). Significantly more up-state periods were detected, and more up-state spikes occurred if the neighbour neurons also received up-state synaptic inputs. This effect was more pronounced with distal gap junctions. The total number of spikes could even increase above the reference case with no gap junctions, if correlated inputs were given to the coupled FS cells. The addition of gap junctions can also help detect coincident subthreshold excitation in a pair or network of FS neurons. This can evoke spikes in one of the coupled neurons, while no spiking occurred in the reference case without gap junctions (see Fig. 5C). Thus, both increased spike synchronisation, subthreshold coincidence detection and the neighbour dependent ability to spike during up-state periods would increase the total GABAergic synaptic output from groups of FS neurons connected through gap junctions. In this context it is interesting that FS neurons can delay the spiking of medium spiny projection neurons (MS) (Koós and Tepper, 1999). This may be important since it has been shown that the delay to the first spike after up-state onset in MS neurons affects calcium levels (Kerr and Plenz, 2004), which in its turn might have important implications for synaptic plasticity and learning in this system.

Spike synchronisation and subthreshold coincidence detection in FS neurons could also enable stronger and simultaneous inhibition of a larger number of MS neurons, possibly allowing for a more widespread inhibition. This might be required for a "winner takes all" mechanism, which is hypothesised to exist in the striatum (Djurfeldt et al., 2001; Plenz, 2003). An interesting possibility, which is not currently known, would be that FS neurons that synapse onto functionally similar MS neuron also are connected through gap junctions. FS neurons are furthermore known to form GABAergic synapses with other FS neurons, in addition to MS neurons (Kita et al., 1990). The detailed organisation of GABA synapses and gap junctions between striatal FS cells is not known, but different possibilities of implementing lateral inhibition, not only between functional groups of MS neurons, but likewise between groups of FS neurons might be possible.

Spontaneous up- and down-state activity occurs in organotypic co-cultures in vivo (Plenz and Aertsen, 1996). In awake behaving animals studies of cross-correlograms have also shown bursting in the MS neuron. This taken together with the fact that MS neuron do not have an intrinsic bursting mechanism indicate that there are indeed elevated periods of activity (up-states) also in awake animals (Nicola et al., 2004). It is, however, not known to what extent neighbouring FS and MS neurons have synchronous up-states. Highly synchronised up-states might be an artefact of the anaesthetics commonly used. In this context it is interesting to see that the FS neurons detect up-states in neighbouring neurons and spike significantly more if the coupled cells also receives

up-state input. Using intermediate gap junction conductances, we show that if a neighbouring connected FS neuron also receives up-state input the neuron will spike 7 % more if they are connected through proximal gap junctions and 14 % more with distal gap junctions. Interestingly, it seems that in the presence of dopamine the neurons become less dependent on their neighbours. Although, it would be hard to link this observation to the functioning of the microcircuitry, it is interesting that dopamine affects gap junctions (O'Donnell and Grace, 1993; Onn and Grace, 1999). Also pharmacological blocking of the gap junctions between the FS neurons by intra-striatal infusion affects dopamine mediated behaviour in rats (Moore and Grace, 2002).

It is important to note that this study only deals with pairs of neurons connected through gap junctions, for larger networks the proportion of input through the gap junction is larger and some of the effects may be more pronounced (Andreu et al., 2001). In summary, however, the present study highlights questions regarding the functional organisation of the striatal microcircuitry. Interesting questions are: a) to what extent are up-states in neighbouring neurons simultaneous in vivo, and does this change during behavioural tasks; b) do gap junctions connect functionally similar FS neurons; c) do the GABAergic FS to FS synapses occur between FS neurons activated during different or similar functional tasks, and d) to what extent do neighbouring FS neurons receive correlated inputs from cortex.

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Paper III

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The impact of the distribution of isoforms on CaMKII activation

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Abstract

We have developed a computational model of the regulation of α- and β-CaMKII activity, in order to examine (i) the importance of neighbour subunit interactions and (ii) the effect the higher $CaMCa_4$ affinity of β-CaMKII has on the holoenzyme activity in different configurations with the same α:β ratio. The model consists of a deterministic biochemical network coupled to stochastic activation of CaMKII. The results suggest that CaMKII holoenzyme activity is non-linear and dependent on the holoenzyme configuration of isoforms. This is especially pronounced in situations with a high-dephosphorylation rate of CaMKII.
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Keywords: CaMKII; Plasticity; Computer modelling; Stochastic model

1. Introduction

Calcium/calmodulin-dependent kinase type II, CaMKII, has long been the focus of much interest since it is crucial for plasticity and learning [7]. It has four types of isoforms; α, β, γ and δ. In the brain, CaMKII holoenzymes are mainly composed of the α and β isoforms, which are typically present in the same holoenzyme [1,4,5]. α-CaMKII, but probably not β-CaMKII, may also form homomers [1].

The ratio α:β is different in different parts of the brain—it is for instance 3:1 in the rat forebrain but 1:4 in the rat cerebellum [9]. Reported values of α:β ratios range from 6:1 to 1:8 [5]. There has been some controversy over the structure of the CaMKII holoenzyme, but the most probable structure is a dodecamer composed of two hexameric rings [4].

One of the key features of CaMKII holoenzymes is the neighbour-dependent phosphorylation [7]. The requirement for initiation of phosphorylation is that two neighbouring subunits have bound CaM at the same time. Thus, different subunit affinities for CaM may influence the rate and probability of phosphorylation.

The α and β isoforms have different affinities for CaM and different rates of neighbour-dependent phosphorylation [4]. Both of these differences will affect the dependence of CaMKII activation on Ca^{2+} stimulus frequency, but earlier simulations indicate that the rate of phosphorylation will have the largest effect [4]. The average proportion of α to β within a holoenzyme has also been shown to be regulated by the cell spiking activity. Low firing levels increase the relative amount of the β isoform, while higher firing levels decrease it [11].

Taken together, these facts imply that overall enzyme properties depend on the isoform composition of CaMKII, and that changes in composition might have functional relevance. These possibilities have been discussed before [1] but not investigated by computational modelling.

2. Methods

We have developed a computational model of regulation of α and β CaMKII activity. The mathematical model is implemented in Matlab. Our modelling partly follows the example of Holmes [6], with a deterministic biochemical network coupled to stochastic activation of CaMKII (see Fig. 1). The model includes five different CaMKII activity states for each subunit. Concentrations and rates were the same as in [6], with the following exceptions:

- β-CaMKII was added;
- CaN and CaMKII binding to $CaMCa_X$, $X \leqslant 2$ was excluded;

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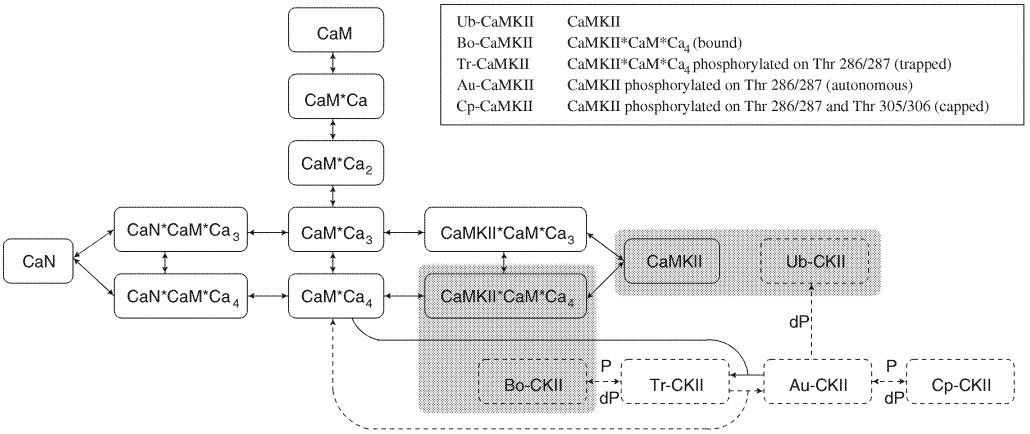

Fig. 1. Biochemical network of the model. Dashed boxes denote the stochastic parts of the model. Dashed arrows show stochastic transitions and solid arrows show deterministic reactions. Shadowed boxes show the correspondences that link the deterministic and stochastic model parts. When needed for the calculations, concentrations were converted to numbers of molecules and vice versa.

- only the volume corresponding to the PSD was simulated;
- the dephosphorylation rate was increased by a factor of 10;
- the Ca^{2+} concentration was modeled by a 4 Hz sine function with a maximum of 2 μM.

Many models of CaMKII activation have been published previously [2,3,6,8,10,12]. Few published models include all CaMKII activity states and, to the best of our knowledge, no published model includes both α and β isoforms.

We have used the CaMKII activation scheme from Holmes' model [6], which allows study of neighbour subunit interactions in a way suitable for the question at issue. Each CaMKII subunit can be of either α or β type and then, independently of isoform type, be in one of five different activity states. This means the "influencing neighbour" of a subunit can be one of ten choices, giving a total of 10^6 possible configurations for a hexameric ring. Thus, with a deterministic model, over one million equations would be needed in order to capture the same level of detail—for one hexameric ring—as with the stochastic model we use.

Our approach allows us to include both α- and β-CaMKII isoforms and, crucially, to study the neighbour subunit interactions in detail. Interactions between neighbours are assumed to be in one direction, and there is no interaction between the two hexamer rings. This means that the state of each subunit is only affected by the state of one other subunit. In this work, the influencing neighbour is taken to be the neighbour to the right of the subunit.

We have investigated the amount of activation resulting from two different configurations of CaMKII, both with an 3:1 ratio of α to β. Assuming the most likely configuration of two hexamer rings [4], we have tested a 'separated' and a 'mixed' case: $\alpha\alpha\alpha\alpha\alpha\alpha-\beta\beta\beta\alpha\alpha\alpha$ and $\alpha\alpha\alpha\alpha\alpha\alpha-\beta\alpha\beta\alpha\beta\alpha$.

3. Results and discussion

Our simulation results indicate that (i) the subunit activation state is strongly dependent on subunit type, and (ii) the probability of activation of a certain subunit is strongly dependent on the isoform type (i.e. $CaMCa_4$ affinity and/or phosphorylation rate) of its neighbour.

Due to the larger β affinity for $CaMCa_4$, almost all active β subunits are in the trapped form, see Figs. 2 and 3. β subunits in the bound state will quickly become phosphorylated (trapped), and autonomous β subunits will quickly rebind $CaMCa_4$. This means that most of the autonomous activity comes from the α subunits, especially those with β neighbours. One of the main reasons for the difference between the isoforms in activation is the rebinding of $CaMCa_4$ to autonomous α- and β-CaMKII subunits, the rate of which is assumed to be higher for β subunits due to their higher affinity for $CaMCa_4$. Based on [4], we have chosen a 3 times larger $CaMCa_4$ affinity for β than for α. This may be a conservative estimate; according to [1] the differences are larger.

In our simulations, we can see that β subunits with an α neighbour are much less activated than those with a β neighbour though the amount of bound subunits is largely equal (see Fig. 2). Similarly, α subunits with a β neighbour are substantially more activated than those with an α neighbour (see Fig. 2). This suggests that the role of neighbour interactions is crucial: due to the fact that trapping is a long-lived state, the activity of the trapped β subunits "forces up" the activity of their

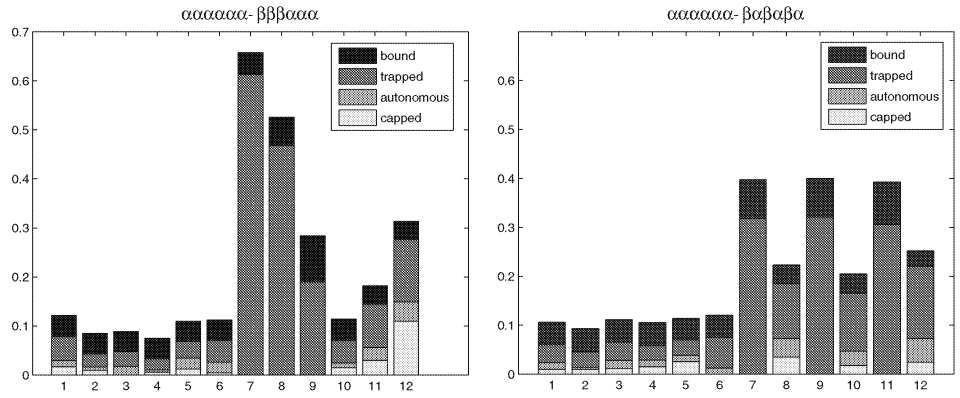

Fig. 2. To the right the $6\alpha-\beta\beta\beta\alpha\alpha\alpha$ configuration, and to the left the $6\alpha-\beta\alpha\beta\alpha\beta\alpha$ configuration. In grayscale of decreasing darkness: probability for a subunit in this position to be in the bound, trapped, autonomous and capped states at the end of the simulation. Note that the "influencing neighbour" is the one to the subunit's right-hand side (higher number), and that the hexameric structure means that subunits #1 and #7 are the neighbours of subunits #6 and #12, respectively. 100 CaMKII holoenzymes were simulated. Simulation time was 80 s, using 50 μM of CaM and a 4 Hz Ca^{2+} stimulus. The dephosphorylation rate was $0.03\,s^{-1}$. The $CaMCa_4$ affinity of β-CaMKII and the probability of β-CaMKII phosphorylation were both assumed to be 3 times that of α-CaMKII.

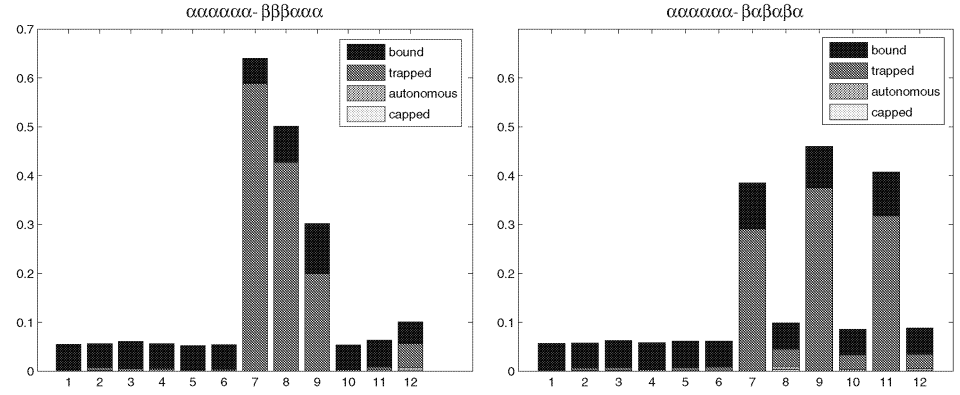

Fig. 3. The same situation as in the previous figure, but with a ten times larger dephosphorylation rate.

neighbours. If the neighbour is a β this leads to further trapping, if the neighbour is an α a larger relative part of its activity is often autonomous (and subsequentially capped).

The "neighbour forcing" effect becomes more pronounced when the dephosphorylation rate of CaMKII is higher (see Fig. 3, compare the relative difference between subunit #12 in this figure and in Fig. 2. #12 is an α that becomes much more active than other α:s due to its β neighbour—but the difference in activation level, compared to other α:s, is much larger with the high dephosphorylation rate than with the lower dephosphorylation rate). Also, β activity is much less sensitive to changes in the dephosphorylation rate than α activity (see Fig. 3). The apparent insensitivity of β-CaMKII compared to α-CaMKII is due to the fact that α-CaMKII more easily becomes autonomous, and subsequentially inactive when dephosphorylated. If trapped β-CaMKII is dephosphorylated it will return to the bound state from which it relatively quickly becomes trapped again.

Due to the relative insensitivity of β-CaMKII its activity will be much harder to regulate than the activity of α-CaMKII. A β-homomer would, in our conditions, probably show a rather uninteresting behaviour compared to α-homomers and heteromers—its subunits would generally be either trapped or inactive.

Doubling the concentration of CaM had no qualitative influence on these results (not shown).

We conclude that the seemingly modest differences between α and β CaMKII in $CaMCa_4$ affinity and

autophosphorylation rate can have large non-linear effects on holoenzyme activity. Changing the ratio of α:β or the rate of dephosphorylation will not only adjust the level of CaMKII activity, but also the distribution of activity states. Thus, the regulation of the α:β ratio in response to spiking may have more complex consequences than the simple gain control proposed in [11] and the shift of Ca^{2+} frequency sensitivity examined in [1].

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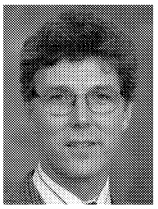

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