Exploring GABAergic and Dopaminergic Effects in a Minimal Model of a Medium Spiny Projecting Neuron

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Abstract

Exploring GABAergic and Dopaminergic effects in a minimal model of a medium spiny projecting neuron

This Master’s thesis examine a model displaying dopamine-induced bistability in striatal neurons. Striatum is an input structure in the basal ganglia, a collection of nuclei in the mid-brain, involved in a large part of cognitive and motor work. Many striatal neurons react in a reward-dependent manner, which make them likely to be participating in the reinforcement learning system. The reward system in the brain is heavily linked to the dopaminergic neuron originating in substantia nigra. They send projections to e.g. the striatum. The role of dopamine in the striatum can be seen clearly when production diminish as a result of Parkinson’s disease. Therefore it is of great importance to show how dopamine influence the neurons and interact with other transmitters e.g. GABA. This is the second part of my work, to include a GABAergic signal in the proposed model.
Sammanfattning

Undersökning av GABAerga och dopaminerga effekter i en förenklad modell av ett striatumneuron

Det här examensarbetet har som mål att undersöka en modell för dopamin-styrad bistabilitet hos neuroner i striatum. Striatum utgör insteget i de basala ganglierna, en samling kärnor i mellanhjärnan, som är involverade i en stor del av det sensoriska och motoriska arbetet. Många neuron i striatum reagerar på ett belöningsstyrt sätt, det gör att de troligen påverkar inlärning. Hjärrans belöningssystem är starkt länkat till de dopaminerga neuronerna i svarta kärnan. De har förgrenade kontakter i bland annat striatum. Dopaminets roll i striatum märks tydligt när dopaminproduktionen upphör i de svarta kärnorna som följd av Parkinsons sjukdom. Det är därför av stor vikt att kunna visa hur dopamin påverkar neuronerna och samspelet med andra transmittersubstanser, som t.ex GABA. Detta utgör en andra del av mitt arbete, att utöka den föreslagna modellen med en insignial styrd av GABA.
Förord

Ett stort tack till....

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Chapter 1

Introduction

The work in this master thesis include analysing a model displaying dopamine-induced bistability by Gruber et al [3]. Their goal was to formulate a biophysically grounded model of the membrane voltage showing the characteristic up/down state behaviour of medium spiny neuron. Dopamine receptors D1 have been reported to both enhance and suppress the responses of medium spiny neurons by introducing bistability. This could demonstrate how dopamine can modulate the reward dependence in neostriatal neurons.

1.1 Learning - some basic concepts

Through evolution the organisms best adapting to the environment survived. This could be done by primitive learning or an ability to reinforce appropriate behaviour.
The brain in higher species (including humans) has a powerful ability to learn new skills. Unlike instinctive behaviours, learning is defined as a change of behaviour.
When repeatedly being confronted with similar situations, organisms evolve better responses. Predictions about the outcomes of possible behaviour can also give advance information, a learning through repeated experience.
Pairing between an arbitrary stimulus and primary reward leads to an associative learning when being repeated. Associating sensory events, as stimuli or cognitive functions, as moving with rewards form new associative chain. This is a fundamental base in learning and planning.[2][11]

Reward - a very important signal

Many cognitive functions (e.g responding to outer stimuli) in the brain are dependent on motivation. Movement planning and activity related to visual stimuli is correlated with the expectancy of a reward, on doing the “right”
choice. Many task-related activities can be enhanced or suppressed depending on the anticipated reward for correct performance. Motivational values can be either rewarding or punishing. A rewarding signal can elicit an approach behaviour towards objects previously associated with e.g. food. The frequency and intensity of behaviour can be increased by rewards, thereby serving to maintain knowledge. Animal studies have showed that task supposed to be rewarded can elicit higher activity among neurons. Also the onset of a visual stimuli related to a reward can elicit activity. Despite their importance, rewards do not influence the brain in the same way as the primary sensory system through dedicated peripheral receptors. Instead the highly variable nature of rewards require high degree of adaption in neuronal systems processing them. Information regarding rewards are collected from different parts of the stimuli system by use of special neural mechanisms. A part of this is believed to take place in the basal ganglia, a group of nucleus in the mid-brain.[11]

1.2 Elements of the brain involved in learning

The reward functions in the brain is not maintained by a single system analogous to the sensory functions (e.g visual and auditory system). The effect of lesions, receptor blocking and drugs of abuse suggest that the basal ganglia dopamine system is involved in processing reward information and learning approach behaviour. Most dopaminergic neurons in the basal ganglia become activated after rewards and reward-predicting stimuli.
Figure 1.2: Almost all of cortex projects to striatum. The direct pathway project from striatum to globus pallidus interior and back to cortex through thalamus.[12]

Many cognitive function dependent on motivational behaviour are linked to the striatum, an input region of the basal ganglia.

**The Basal Ganglia**

The basal ganglia is a collection of nucleus in the mid-brain, see figure 1.1. It was early demonstrated that basal ganglia was important in motor processing. More recent ideas also suggest the involvement in sensory and cognitive functions. Many of the associated activities can be detected when basal ganglia malfunction, as in Parkinson and Huntington’s diseases.

**Main pathway in basal ganglia**

Almost all parts of cerebral cortex projects to striatum, the input stage of basal ganglia, via excitatory glutamatergic synapses. In striatum, the medium spiny neurons constitutes 90% of all neurons. The output from striatum (see figure 1.2) can be divided coming from two groups mediated by different dopamine receptors: **The direct pathway** via Globus Pallidus interior (GPi) and Thalamus gives positive feedback to cortex and is mediated by $D_1$ receptors in striatum.
The indirect pathway is mediated by D2 receptors in striatum and gives a negative feedback to cortex. In the indirect pathway the medium spiny neurons projects via Globus Pallidus exterior (GPe) to GPi.[8]

**Striatum - input state to the basal ganglia**

Striatum is the largest component of the basal ganglia. It is composed of two types of neurons, medium projecting neurons and the local interneurons. The medium spiny neurons outnumber the much larger interneurons and are GABAergic, using GABA (γ-aminobutyric acid) as neurotransmitter. Each neuron in striatum receives glutamatergic excitatory input from a large number of cortical neurons. How the action potential firing in spiny neurons are controlled decides the main function of the striatum. One theory was that medium spiny neurons controlled neighbouring neurons with the use of dense axons collateral. Instead most of the GABAergic synapses are formed with the inter-neurons, particularly the fast spiking inter-neurons (FSI). They provide strong feed-forward inhibition synapses on the medium spiny neurons, thereby controlling the action potential firing. FSI respond faster then the medium spiny neurons on cortical input and at lower intensity of stimulation. Duration of FSI spike is shorter then medium spiny neurons. [6][10]

### 1.3 Dopamine modulates the striatum

Dopamine modulates the electro-physiological properties in striatum. The dopaminergic neurons in Substantia Nigra pars compacta (SNc) are activated by unpredicted rewards and by sensory stimuli (e.g visual stimuli) that precede a reward signal. They do not respond to the expected reward itself. The occurrence of reward must be unpredicted to activate dopamine neurons. Depression at the time of omitted rewards could be mediated by inhibitory inputs from striatal neurons.[5][11]

### 1.4 Two-state behaviour

When recorded in vivo medium spiny neurons show a characteristic pattern of spontaneous activity, with long periods of silence and short episodes of firing. During learning of motor behaviour similar episodes are recorded during parts of training. The episodic bursts of firing is attributed to depolarising of the membrane due to excitatory input from cerebral cortex and thalamus. The fact that the shift between the states is short suggests the existence of two discrete membrane states. A silent down state, where the membrane potential is hyperpolarized down to around -85 mV. In the depolarised up
state the membrane potential is around -55 mV.
Transition to up state from down state can only be made after integration
of excitatory input from large number of cortical synapses. Only experiments
in vivo show the spontaneous transition to up state, whereas experiments
made in vitro a constant down state is measured. This demonstrate that the
transition between down and up states is driven by cortical input, which is
absent in vitro when all cortical projection is absent.[3][6][7][9][13]
Chapter 2

Method

The nervous system in the body is fundamental for communication and to handle information from the outside world. Cells in the nervous system communicate through electrical and chemical synapses formed on the membrane. The properties of the membrane rules the cell response to signalling from other neurons. To investigate the processing of information in the nervous system an understanding of signal transfer is required.

2.1 Theory background to the membrane potential model

Neuronal cells are characterised by their ability to perform intercellular signalling by generating action potentials. The membrane surrounding the neurons have a potential difference with a more negative inside. This potential difference leads to electrical currents flowing through the membrane in special ion channels. The ion channels are mediated by neurotransmitters released from neighbouring neurons by action potentials. The properties of the ion channels make the membrane function similar to a electrical circuits and the biological membrane can thus be described using electric terms.

Equivalent electric circuit

The electrical circuit in figure 2.1 represent the membrane properties of a neuron. This is an equivalent electrical circuit for the membrane. Membrane conductance in neurons are often highly voltage dependent and represents ion permeation through membrane ion channels. The potential is a non-linear function of the ionic currents. Currents can be classified into groups of diverse types. The time and voltage dependence on differential currents depend on the diverse function of ion channels. Different types of channels can be distinguished on the basis of e.g ion selectivity and
Figure 2.1: A equivalent electric circuit for typical membrane currents. $G$ represent the ionic conductance and are voltage dependent. Reversal potential, $E$ define the voltage level when ionic flow reverse direction. $C_m$ represent the membrane capacitance.[12]

electro-physiological properties. Most ion channels are only permeable to one type of ions.

**Rectified currents**

When the membrane conductance varies with voltage, the I-V relation becomes rectified. Membrane rectifications are defined as a nonlinear relation between the current and membrane potential. When outward (inward) currents flow more easily then inward (outward) the membrane currents are said to be outward (inward) rectified. The rectification is highly diverse among ion currents and rules the complex membrane behaviour.

**2.2 A membrane voltage model**

Using the equivalent electrical circuit to represent the membrane and Kirchhoff’s law a differential equation for the membrane voltage can be written. The equation represents the change of potential as a function of total current
flow through membrane.

\[-C_{m} \frac{dV_{m}}{dt} = (I_{K_{ir}} + I_{L-Ca}) + I_{K_{si}} + I_{L} + I_{s}\]  

(2.1)

Most currents can be modelled as the product of the conductance and the driving force. Driving force is the difference between the membrane voltage and the reversal potential. At the reversal potential the current change direction through the cell membrane. $C_{m}$ represent the membrane capacitance.

\[I_{i} = g_{i}(V_{m} - E_{i})\]  

(2.2)

Equation 2.2 model the ionic current as a function of the membrane voltage ($V_{m}$) for ionic type $i$, where $E_{i}$ is the reversal potential (for parameter values see appendix Appendix B).

The ionic conductance is often a voltage dependent function in excitable cells.

\[g_{i} = \frac{g_{i}(V_{m})}{1 + \exp \left( -\frac{V_{m} - V_{c}}{V_{e}} \right)}\]  

(2.3)

\[L_{i}(V_{m}) = \frac{1}{1 + \exp \left( -\frac{V_{m} - V_{c}}{V_{e}} \right)}\]  

(2.4)

The logistic function $L_{i}(V_{m})$ define the voltage dependence for the ionic conductances and the resulting ionic currents. Calcium currents are not adequately represented by the general equation for ionic current due to the low internal concentration. Instead the Goldman-Hodgkin-Katz (GHK) equation better represent the Ca$^{2+}$ current.

\[I_{L-Ca} = P_{L-Ca} \left( \frac{z^{2}V_{m}F^{2}}{RT} \right) \left( \frac{[Ca]_{i} - [Ca]_{o} \exp \left( -\frac{zV_{m}F}{RT} \right)}{1 + \exp \left( -\frac{zV_{m}F}{RT} \right)} \right)\]  

(2.5)

\[P_{L-Ca} = \overline{P}_{L-Ca} L_{L-Ca}(V_{m})\]  

(2.6)

Equation 2.6, where $P_{L-Ca}$ is the membrane permeability, represent the voltage dependence of Ca$^{2+}$ current.

### 2.3 XPPAUT — a program for differential equations

All the equation in the actual model is implemented och calculated by the use of the program XPPAUT. The program is written by Bard Ermentrout and Eusebius Doedel (AUTO part). It is a program for handling e.g differential equations, equilibrium and boundary problems. Those problems are
frequent in equations for membrane modelling. All equation and start values are written in an ASCII readable file and translated to machine usable code by the XPPAUT parser. XPPAUT can also evaluate bifurcation points of non-linear solutions to differential problems. The homepage for XPP contains a substantial manual to XPPAUT and program files for Linux and Windows.[14]
Chapter 3

The model by Gruber et al.

The model by Gruber et al. [3] is constructed based on experimental findings of the neuron membrane. The aim is to investigate and test the hypothesis that dopamine modulation of two ionic currents is sufficient to explain reward-dependent enhancement and suppression of the bistable medium spiny neurons. Gruber et al. investigate the D1 receptor-mediated responses to cortical input with a single-unit model. The outcome is compared with data recorded in animal experiments.

3.1 Model description

The membrane potential is regulated by a combination of several inward and outward currents. Dopamine is released in striatum by neurons projecting from SNC. The neurons in SNC is triggered by the detection of reward-conditioned stimuli (see further in section 1.1). Dopaminergic innervation is incorporated in the model by the neuromodulatory factor $\mu$.

Membrane currents

The model contains only currents important for the bistability omitting currents producing action potentials (e.g. Sodium). Raised dopamine levels enhance the Kir2 and L-type calcium currents.

Potassium currents

The conductances for the potassium currents $I_{Kir2}$ and $I_{Kst}$ are voltage dependent. These vary as a function of the membrane potential is reproduced in figure 3.1. Parameters for half-activation and the slope of the curve is based on experiments.

The two $K^+$ currents included in the model have been shown to account
Figure 3.1: The ionic currents in the model for potassium $I_{K_{ir2}}$ and $I_{K_{si}}$ have different voltage dependence and are therefore activated in down and up state respectively.

for the characteristic nonlinear voltage dependence of the outward current measured in spiny neurons. The outward current acts in opposition to inward synaptic currents to regulate membrane potential in the up/down state.

The down-state is only slightly more depolarised then the reversal potential for K, approximately $-89.99$ mV. In down-state the dominating current is the inward rectifying potassium $I_{K_{ir2}}$. As the membrane becomes more depolarised by cortical input, the $I_{K_{ir2}}$ current decrease and is eventually blocked. Dopamine enhance the $I_{K_{ir2}}$ current.

In up-state the outward rectifying potassium current $I_{K_{si}}$ dominates. This current is activated by depolarising and and inhibit further depolarisation. The reversal potential for all potassium currents and leak current is $-90$ mV.

**Calcium current**

Calcium currents are activated by depolarisation and is inward at normal membrane potentials, see figure 3.2. This current modulate the voltage range of the up state. The calcium currents have no real reversal current due to the low internal concentration. Dopamine enhance the L-type calcium current.
Figure 3.2: The ionic current for calcium $I_{L_{Ca}}$ is voltage dependent and is activated at depolarising.

**Leak and synaptic current**

The glutamatergic input to striatum from cortex is represented as the synaptic current $I_s$. Signals from many cortical neurons are summed in one, as in real where the medium spiny neuron integrate signals from a wide range of cortical neurons onto one single neuron. Glutamate activate AMPA/NMDA receptors that produces excitatory postsynaptic responses. This is represented by the net conductance $g_s$ in the model. A signal from cortex result in a higher value in $g_s$ (glutamate receptors open ionic channels mostly permeable to Na$^+$ and K$^+$) and thereby raising the input current $I_s$.

**3.2 Results**

**Implementation**

I implemented the model using the program XPPAUTO, see section 2.3 and Appendix C. All parameter values from the original model was used, see Appendix B.
Figure 3.3: Operational curves for low dopamine level, all equilibrium points are stable. The membrane potential $V$ responds to glutamatergic input conductance $g_s$.

Figure 3.4: Operational curves for high dopamine level, equilibrium points for $g_s$ are only stable in the outermost domains. Thinner line mark unstable membrane potential. The membrane potential $V$ responds to glutamatergic input conductance $g_s$. 

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Steady-state behaviour

Steady-state solutions to the differential equation 2.1 correspond to equilibrium values for the membrane potential $V_m$ and they are solutions to

$$\frac{dV_m}{dt} = 0$$

(3.1)

The membrane potential is controlled by the net ionic currents, therefore solutions to equation 3.1 most satisfy

$$\mu(I_{Kir2} + I_{L-Ca}) + I_{Ksi} + I_L = -I_s$$

(3.2)

Values of $V_m$ satisfying equation 3.2 are fixed points. Once the membrane potential reached a fixed point, the value will not change unless the system is perturbed.

Dopamine induced bifurcations at this points leads to bistability. Operational curves for the membrane potential is reproduced in figures 3.3 and 3.4

Equilibrium

The equilibrium values of $V_m$ depends on $\mu$ and $g_s$. Net ionic current is always outward when the membrane is depolarised from rest. The synaptic current $I_s$ is negative, thus inward. For high and low values of $g_s$ the membrane potential is a single-valued function for all $\mu$. Synaptic conductance $g_s$ is the reciprocal of membrane channel resistance, represent the glutamatergic connection formed with cortical axons on the dendrites.

Operational curves are used to explore the relation between the state variable $V_m$ and the neuromodulatory factor $\mu$ and the synaptic conductance $g_s$. They display the consequences of neuromodulation. Instability emerge for intermediate values of $g_s$ due to the enhancement of the Kir2 and L-type Ca ionic currents.
Figure 3.5: The intersection between operational curves for $\mu=1.0$ and $1.4$ mark the critical point corresponding to equation 3.2.

**Critical point**

The cancellation between the Kir2 and L-type Ca current results in the arises of the critical points, see figure 3.5, solutions to the equation

$$I_{Kir2} + I_{L-Ca} = 0 \quad (3.3)$$

Critical points depend on the parameters characterising Kir2 and L-type Ca currents, independent of $\mu$ and $g_s$.

All operational curves for various values on $\mu$ pass the critical point ($V_m = -55.1 \, mV$).
Figure 3.6: Transition from down state passing near the critical point (curve A) exhibit a noticeable slowdown.

**Slow-down effect on the membrane transition**

The critical point introduce a slowdown effect on the model. Near the critical point, due to the cancellation between the Kir2 and L-type Ca currents, equation 3.3, it follows from equation 2.1 that the membrane potential can be written

\[-C_m \frac{dV_m}{dt} = I_{Ksi} + I_L + I_s\]  \hspace{1cm} (3.4)

Transitions from down to upstate (or up to down state) passing nearby the critical point will have a noticeable longer transition time (curve A in figure 3.6.)
Figure 3.7: When the cortical input is weak (curves a) the onset of dopamine hyperpolarise the membrane further (b). For strong cortical signals (c) the effect is the opposite, dopamine depolarise the membrane (d).

**Dopamine influence**

The membrane response to cortical input in the absence of a reward follows the curve for low dopamine level, see figure 3.3. State transition occur for strong inputs and can result in the intermediate values. No hyperpolarized effect emerge. Whenever the trajectories in the $V_m - g_s$ plane pass near the critical point the slowing down is particularly noticeable as the modulated currents are cancelled and the time course of $V_m$ is slow. In the nearby area of the critical point the effect of GABAergic connections with FSI have high influence.

The dual effect of dopamine, acting both hyperpolarise and depolarising is demonstrated by keeping $g_s$ constant for different levels of dopamine (figure 3.7). When the cortical input is weak (curves a) the onset of dopamine hyperpolarise the membrane further (b). For strong cortical signals (c) the effect is the opposite, dopamine depolarise the membrane (d).

Low dopamine level, corresponding to neuromodulatory factor $\mu=1$, characterises the condition in unrewarded trials when no dopamine is released into striatum, see section (1.1).
Chapter 4

Modified model

4.1 Background

The model presented by Gruber et al. is not in accordance with the biophysically experiment it is grounded on. The membrane potential $V_m$ in medium spiny neurons mostly fluctuate between two stable states. Up state being depolarised to about -55 mV and downstate hyperpolarized to -85 mV. Operational curves of the presented model has a up state highly depolarised to -40 mV. This is above threshold for action potential although the medium spiny neurons are mostly silent. Gruber et al. present a simplified model, thereby excluding currents that may effect the outcome. Also the model depend on parameters obtained in different experiments. Because experiments often involves techniques that change the outcome many of the parameters have been adjusted. This has been the starting point for my modification of the model. [1][3]
Figure 4.1: The currents in the model proposed by Gruber et al.[3] with neuromodulatory factor $\mu=1.4$.

4.2 Changes made to the model

My goal has been to lower the up state to a more plausible level. This was achieved by changing the existing currents in the model, testing the hypothesis that their activating curves were different. In up-state the outward rectifying potassium current $I_{K,si}$ dominate and prevent the membrane from further depolarising, see figure 4.1. To lower the up-state, the half activating parameter for the Ksi current, $V_h^{K,si}$, was made more negative, thus making the current activating at more hyperpolarized potential. In order to keep the bifurcation at raising dopamine levels, activation of L-type calcium current was shifted the same amount as for Ksi current. The up-state was thereby lowered to around $-55$ mV, a more physical correct value. When the up state was lowered the outcome of the model changed. Bistability then emerged also at low dopamine levels. To address this I lowered the permeability of the L-type calcium channel $P_{L-Ca}$.

4.3 Results of the changes

The result of the changes made to the original model is shown in the operational curves in figures 4.2 and 4.3. The modified model exhibit the same dynamic responses to changes of $g_a$ as the original model by Gruber et al. For low levels of dopamine the equilibrium values of the membrane potential correspond to single-valued solutions. The fixed points are all stable against
Figure 4.2: Operational curve for low dopamine level ($\mu=1.0$) is a single valued function of $g_s$. Analysis from XPPAUT. Y axis represent membrane potential, x axis represent dopaminergic input conductance $g_s$.

Figure 4.3: Operational curves for high dopamine level ($\mu=1.4$) consists of 2 stable branches and an unstable branch for the intermediate values of $g_s$. Analysis from XPPAUT. Y axis represent membrane potential, x axis represent dopaminergic input conductance $g_s$. 

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perturbation, see figure 4.2.
At high dopamine level the steady solution consists of 2 stable branches and
an unstable branch for the intermediate values of $g_s$, see figure 4.3.

**Regions of bistability**

Using the program XPPAUT, see 2.3, the $\mu$-$g_s$ plane can be visualised. This
show the regions of bistability as a function of neuromodulatory factor $\mu$ and
the input conductance $g_s$.
In the original model the region of bistability is not continuous, for some
values of $\mu$ two unstable branches exist with a stable branch in-between. This
is shown in figure 4.4. The outcome of the modified model is a continuous
region of bistability, se figure 4.5.
Figure 4.4: The region for instability using the original model[3]. Several regions of instability is seen in the figure.

Figure 4.5: The region for instability in the modified model. For values of dopamine (DA) above 1.2 a region of unstable membrane potential emerge.
Figure 4.6: Operational curves for the changed model intersecting at the critical point.

**Critical point**

The intersection of operational curves for all values of $\mu$ is the critical point. The critical point is lowered for the modified model compared to the original, figure 4.6.
Chapter 5

Enhanced model - GABAergic modulation

5.1 The role of GABA for spiny projecting neurons

GABAergic synapses to medium spiny neurons are made both by interneurons and neighbouring projecting neurons. In a hyperpolarized down-state they contribute by a small outward current, causing the membrane to depolarise. This depolarising is far from causing a transition to upstate alone. In depolarised up-state GABA is believed to cause a small hyper-polarisation, delaying the onset of a action potential. This is not part of the modul due to the absence of currents for a action potential. Receptors activated by GABA open ion channels permeable to Cl⁻. GABA inputs can thus both delay and advance the onset of a action potential. This dual effect of GABAergic input is the response to the reverse potential at -60mV introduced.

5.2 Implementation of a GABAergic signal

The effect of GABAergic signal input is modelled using a Cl current. The current is added to the net ionic currents in differential equation for the membrane voltage. A Cl current can be modelled as the product of a linear driving force \( V_{m-E_{GABA}} \) and a conductance \( g_{GABA} \). The value for the conductance was determined to elicit a depolarisation from down-state around 1 mV. The reversal potential for GABA-mediated currents is usually between -60 and -50 mV.[10]
5.3 Using of the enhanced model

I tested the hypotheses that GABAergic input can facilitate the up transition and thereby making it faster. The facilitation occurs when excitatory inputs arrive after the GABAergic connection become silent, but the membrane is still depolarised from rest. [10]

Simulations

To simulate the effect of GABA-mediated current the input signal was raised in a stepwise way. The GABAergic input signal was momentarily raised during 100 ms, simulating a depolarisation around 1 mV. When \( g_{GABA} \) is raised from a zero level a small depolarisation is seen. Cortical input in the form of a higher \( g_s \) is introduced after 25 ms, leading to a prominent depolarise. Dopamine modulation starts when GABA input have ceased at 100 ms. The resulting diagram is presented in figure 5.1. The same simulation is done when the membrane is at rest near the critical point at -69 mV, figure 5.2.

Results of GABAergic signal input

Responses of GABA on the model was tested by a stepwise increase in input signal. The result was a faster transition to up-state with a previous GABAergic depolarisation as predicted. Time difference was dependent on the previous membrane voltage. Membrane voltages hyperpolarized to levels near the down-state elicited a larger time difference.
Figure 5.1: Dynamic responses of $V_m$ to step changes in input signal from a downstate at -82.4 mV (a). An increase in $g_s$ cause $V_m$ to depolarise to (b) or (c) depending on the level of dopamine. A small previous depolarisation provided by increase in $g_{GABA}$ (e) can facilitate the transition to upstate.

Figure 5.2: Dynamic responses of $V_m$ to step changes in input signal from near the critical point at -69 mV (a). An increase in $g_s$ cause $V_m$ to depolarise to (b) or (c) depending on the level of dopamine. A small previous depolarisation provided by increase in $g_{GABA}$ (e) can facilitate the transition to upstate.
Figure 5.3: The transition to up-state is facilitated by the previous depolarisation by GABA. Resting membrane voltage is -82.4 mV.

Figure 5.4: The transition to up-state is facilitated by the previous depolarisation by GABA when membrane is previously depolarised to a level near the critical point.
Chapter 6

Discussion

6.1 Implementation of the model

Dopamine can inhibit or enhance the glutamatergic excitatory stimuli from cerebral cortex projecting to striatum. The outcome of cortical signalling depends on the previous membrane potential:
In depolarised states the modulation of L-type Ca$^{2+}$ current enhance the evoked activity in medium spiny neurons.
In hyperpolarized states dopamine enhance the Kir2 current further and inhibit depolarising.
This is the starting point for the model, to explain this effect by the use of a minimum set of currents. The model depend heavily on the values for the included currents, hence a small shift in activation have a large impact on the outcome. The enhancement of L-type Ca$^{2+}$ current by dopamine leads to a higher frequency of spiking, not a higher up state.[4]

6.2 The modified model

By changing the values for the slope parameters of the Ks and L-type Ca current the model displays the characteristic behaviour of medium spiny neurons in up state. These parameters control the location of up state and therefore the activity of the medium spiny neurons.
The enhanced model displays the same characteristic behaviour as the original. This can be used to model other currents influencing to up/down transition of medium spiny neurons. A consequence of the modification was the different location of the critical point.

6.3 The GABAergic model

Adding a current representing GABAergic modulation further tested the modified model. The GABAergic input only depolarise the membrane mod-
estly, but influence on transition time can be dramatic. The modified model could replicate this behaviour. The critical point was shifted away from the reversal potential for Cl⁻.

6.4 Further work

Since the model only contains a small set of currents the adding of several others could modulate a more precise outcome. Many more currents are believed to modulate the control of medium spiny neurons. By including currents for spike generation (e.g., Sodium) a more accurate model for the up state could be derived.
References


# Appendix A

## Glossary

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>D&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>The most investigated receptor for dopamine, out of five known.</td>
</tr>
<tr>
<td>GABA</td>
<td>( \gamma )-aminobutyric acid, most common so-called neurotransmitter</td>
</tr>
<tr>
<td>in vitro</td>
<td>Biological phenomena occurring outside living organisms.</td>
</tr>
<tr>
<td>in vivo</td>
<td>Biological phenomena occurring within living organisms.</td>
</tr>
<tr>
<td>SNC</td>
<td>Substantia Nigra pars compacta, dopamine producing nucleus in the basal ganglia.</td>
</tr>
<tr>
<td>SNR</td>
<td>Substantia Nigra pars reticulata, output stage of the basal ganglia.</td>
</tr>
</tbody>
</table>
## Appendix B

### Parameters for the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Gruber et al.</th>
<th>modified model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m$</td>
<td>$\mu$F/cm$^2$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$E_K$</td>
<td>mV</td>
<td>-90</td>
<td>-90</td>
</tr>
<tr>
<td>$E_s$</td>
<td>mV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$g_L$</td>
<td>mS/cm$^2$</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>$V_{h,Kir2}^L$</td>
<td>mV</td>
<td>-111</td>
<td>-111</td>
</tr>
<tr>
<td>$V_{c,Kir2}^L$</td>
<td>mV</td>
<td>-11</td>
<td>-11</td>
</tr>
<tr>
<td>$g_{Kir2}$</td>
<td>mS/cm$^2$</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>$V_{h,Ksi}^L$</td>
<td>mV</td>
<td>-13.5</td>
<td>-35.5</td>
</tr>
<tr>
<td>$V_{c,Ksi}^L$</td>
<td>mV</td>
<td>11.8</td>
<td>14</td>
</tr>
<tr>
<td>$g_{Ksi}$</td>
<td>mS/cm$^2$</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>$V_{L-Ca}^L$</td>
<td>mV</td>
<td>-35</td>
<td>-57</td>
</tr>
<tr>
<td>$V_{C-L-Ca}$</td>
<td>mV</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td>$P_{L-Ca}$</td>
<td>nm/s</td>
<td>4.2</td>
<td>2.1</td>
</tr>
<tr>
<td>$[Ca]_o$</td>
<td>$\mu$mol/cm$^3$</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>$[Ca]_i$</td>
<td>pmol/cm$^3$</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Appendix C

XPPAUT code for implementation of the model

# A model for dopamine induced bifurcation
# Master thesis by Ebba Samuelsson
#
# Code based on article:
# Modulation of Striatal Single Units by Expected Reward:
# A Spiny Neuron Model Displaying
# Dopamine-Induced Bistability
#
# Author:
# Aaron J. Gruber; Sara A. Solla; D. James Surmeier;
# James C. Houk

# Parameters
param g_s=0.00881921507507382
param DA=1 GABA=0
param vh_Kir=-111 vc_Kir=-11 g_Kir_max=1.2
param vh_Ksi=-35.5 vc_Ksi=14 g_Ksi_max=0.45
param vh_LCa=-57 vc_LCa=6.1
param P_LCa=2.1
param Cai=10e-9 Cao=2e-3
param Cm=1
param Ek=-90 Es=0 Egaba=-60 g_l=.008
param Eleak=-90
param z=2
param F=96.480
param R=8.314 T_K=293

###### Stepfunctions #######
APPENDIX C: XPPAUT CODE FOR IMPLEMENTATION OF THE MODEL

```
param delta_glu=0.001 delta_da=0.1 delta_GABA=0.001
param n_glu=0 n_da=0 n_GABA=0
param t0_glu=50 t0_GABA=0 t0_da=75
param t_end_glu=800 t_end_GABA=200 t_end_da=600

# Stepfunction for input signal conductance
gs=g_s+(heav(t-t0_glu)-heav(t-t0_glu-t_end_glu))
   *delta_glu*n_glu

# Stepfunction for dopamine signal mu
my=DA+(heav(t-t0_da)-heav(t-t0_da-t_end_da))
   *delta_da*n_da

# Stepfunction for GABA signal conductance g_gaba
   g_gaba=GABA+(heav(t-t0_GABA)-heav(t-t0_GABA-t_end_GABA))
   *delta_GABA*n_GABA

# Variabel
xi=(z*v*F)/(R*T_K)

# Logic function L
L(v,vh_i,vc_i)=1/(1+exp(-(v-vh_i)/vc_i))

# Conductance function
gi(gi_max,v,vh_i,vc_i)=gi_max*L(v,vh_i,vc_i)

# Potassium currents
I_Kir=(v-Ek)*gi(g_Kir_max,v,vh_Kir,vc_Kir)
I_Ksi=(v-Ek)*gi(g_Ksi_max,v,vh_Ksi,vc_Ksi)

# Calcium current
I_LCa=P_LCa*L(v,vh_LCa,vc_LCa)*xi*z*F
   *(Cai-Ca0*exp(-xi))/(1-exp(-xi))

# More currents
I_Leak=g_l*(v-Eleak)
I_s=gs*(v-Es)
I_gaba=g_gaba*(v-Egaba)

# I_net, ionic currents
I_net=my*(I_Kir+I_LCa)+I_Ksi+I_Leak+I_gaba
I_tot=I_net+I_s
```
# Output
aux I_tot=I_tot
aux I_net=I_net
aux I_Kir=I_Kir*my
aux I_Ksi=I_Ksi
aux I_LCa=I_LCa*my
aux I_s=I_s
aux I_Leak=I_Leak
aux I_gaba=I_gaba
aux gs=gs
aux my=my
aux g_gaba=g_gaba
aux v=v

# To auto
© PARMAX=0.035 AUTOVAR=v AUTOXMIN=0 AUTOXMAX=0.02
© AUTOYMIN=-90 AUTOYMAX=-50

set Cruber {vh_Ksi=-13.5 vc_Ksi=11.8 vh_LCa=-35 P_LCa=4.2
T0=0 Total=400 yhi=-30 xhi=400 xlo=0}
© xnc=10 ync=10

init v=-85
dv/dt=-(I_tot)/Cm

done