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Diplom-Mathematiker Hamid Reza Noori

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Mathematical Modelling of the Neurochemical Processes in Schizophrenia

Hamid Reza Noori

Gutachter: **Prof. Dr. Dr. h. c. mult. Willi Jäger**

Prof. Dr. Dr. hc. Hans Georg Bock

This thesis is dedicated to my parents.

Abstract

Schizophrenia is an endogenous psychosis with a 1% prevalence in world population. Several pharmacological studies suggest that alterations in the function of different neurotransmitter systems such as dopamine or glutamate are related to schizophrenic symptoms. This thesis represents mathematical models that are constructed to investigate the dynamical behaviour of the neurochemical systems in the human brain. These models formulate the anatomical properties and physiological processes of synapses, single brain compartments and large neurochemical pathways involved in the regulation of behaviour such as the basal ganglia and the limbic system. The interaction between the neurochemical systems and the electrophysiological activities are considered by modelling in different scales. In the synaptic scale, it has been shown that the transport of neurotransmitters in the synaptic cleft is merely governed by electrical forces than diffusion. The intra-synaptic concentration of neurotransmitters is modelled using partial differential equations and is coupled to the Hodgkin-Huxley equation (neurochemical modification) to model the effect of neurotransmitter-receptor binding in the generation of post-synaptic potentials. Considering the morphological and ultra-morphological studies of brain compartments, the averaged electrophysiological activity is modelled by integral equations respecting these internal structures. A system comprised by nonlinear delay differential equations is constructed to simulate the dynamical behaviour of neurochemical concentrations, coupled to the local electrophysiological activity of the compartments, on the brain pathways. By parameter sensitivity analysis, we have also investigated qualitatively the influence of certain anti-psychotic agents. Synchronized oscillations are experienced in electrophysiological systems. The neurotransmitter concentrations also demonstrate an oscillatory behaviour. The resulting oscillatory dynamics of these processes reveals a profound view on the relation between the dynamical behaviour of the neu-

rochemical systems and the occurrence of psychotic states. These facts led us to establish a hypothesis on this relation, called the oscillation hypothesis of psychosis. Because of the general formulation of the models, these are not only useful for schizophrenia, but also for the investigations of other neurological diseases.

Zusammenfassung

Die Krankheit Schizophrenie ist eine endogene Psychose mit einer Prävalenz von 1% in der Bevölkerung. Mehrere pharmakologische Studien setzen die schizophrenen Symptom-Erscheinungen mit den funktionalen Veränderungen der verschiedenen Neurotransmitter-Systeme wie zum Beispiel den dopaminergen und glutamatergen Systemen in Verbindung. Diese These repäsentiert mathematische Modelle, welche für die Untersuchung der neurochemischen Prozesse im Gehirn konstruiert sind. Diese Modelle formulieren die anatomischen Eigenschaften und die physiologischen Prozesse der Synapsen, der einzelnen Gehirn-Regione sowie der neurochemischen Bahnen, die wie die Basal Ganglien und das limbische System in der Steuerung des menschlichen Verhaltens involviert sind. Die Wechselwirkung der neurochemischen Systeme mit den elektrophysiologischen Aktivitäten wurde in allen Skalen berücksichtigt. Bei der Untersuchung der Synapsen wurde gezeigt, dass die Diffusionskräfte im Vergleich zu den elektrischen Kräften eine eher schwächere Rolle bei dem Transport der Neurotransmitter im synaptischen Spalt spielen. Die intra-synpatischen Neurotransmitter-Konzentrationen sind mit Hilfe partieller Differentialgleichungen modelliert und wurden zum Zweck der Simulation der Effekte der Neurotransmitter-Rezeptor-Bindung auf die Erzeugung der post-synaptischen Potentiale mit den Hodgkin-Huxley Gleichungen gekoppelt (neurochemische Modifizierung). Die gemittelte Aktivität der Gehirn-Regionen wurde mit Integralgleichungen modelliert, die die morphologischen und ultra-morphologi-schen Eigenschaften dieser Regionen beinhalten. Ein System bestehend aus nicht-linearen retardierten Differentialgleichungen wurde konstruiert, um das dynamische Verhalten der neurochemischen Konzentrationen gekoppelt mit den elektrophysiologischen Aktivitäten der Regionen auf Gehirn-Bahnen zu simulieren. Durch Parameter-Sensitivitätsanalysen wurde auch der Effekt der anti-psychotischen Pharmaka qualitativ untersucht. Die neurochemischen sowie die elektrophysi-

ologischen Systeme zeigen oszillatorische Verhaltensmuster. Diese oszillatorische Dynamik der Prozesse offenbart eine starke Verbindung zwischen der Erscheinung psychotischer Symptome und dem Verhalten der neurochemischen Prozesse, welche in der Gestalt einer Hypothese, die Oszillationshypothese der Psychosen, formuliert wird. Aufgrund der allgemeinen Formulierung der Modelle sind diese neben der Schizophrenie auch für die Untersuchung einiger anderer neurologischer Erkrankungen geeignet.

Contents

Chapter Premier

Introduction

Schizophrenia [1] is a psychiatric diagnosis that describes a family of mental diseases characterized by impairments in the perception or expression of reality, most commonly manifesting as auditory hallucinations, paranoid or bizarre delusions or disorganized speech and thinking in the context of significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood, with approximately 1% of the population affected.

Pharmacological studies on the treatment of psychoses especially schizophrenia suggest that the emergence of psychotic states is directly related to the abnormal dynamical behaviour of neurotransmitter systems in brain pathways such as basal ganglia. Hyperactive dopaminergic transmission and hypo-functionality of glutamate systems in basal ganglia's network are both substantial assertions on the role of anomalies of neurotransmitter systems in producing schizophrenic symptoms (Carlsson, 1988; Carlsson and Carlsson, 1990; Moghaddam and Adams, 1998; Moghaddam, 2003; Moghaddam and Krystal, 2003; Coyle, 2006).

The quantitative analysis of the dynamics of basal ganglia has been done in several studies but only restricted to the electrophysiological aspects (Bevan et al. 2002, Frank 2004, Rubin et al. 2002, 2004). The interactions of neurochemical within the electrophysiological systems suggest models including both. In the present work, mathematical models will be introduced that simulate the dynamical behaviour of the neurochemical systems corresponding to the related electrophysiological activities, in three scales: the synaptic level, the level of single compartment activities, and the multi-compartmental system-level.

This thesis is subdivided into five parts. The most important facts of any section in these parts are expressed as statement in special box-environments. The first part is a brief introduction to the physiological and psychiatric as-

[1] from the Greek roots schizein ("to split") and phre-n("mind")

pects of schizophrenia. Synaptic processes, important neurochemical brain pathways, anatomical and physiological properties of the brain compartments, basics on the disease schizophrenia and its neuropathological and pharmacological aspects are discussed. The reader becomes acquainted with the physiological and clinical background of schizophrenia which is the foundation of the mathematical models introduced in the second part of this work. The experienced readers can also skip this part and leap directly to the mathematical part. The reader is advised to consider the fifth part, the supplement, for more information on the neurobiological and psychiatric aspects of the schizophrenia.

The second part is subdivided into three chapters. The first chapter of this part abstracts the physiological and anatomical structure of the brain pathways as graphs. These graphs are then analyzed in terms of their topological and algebraic properties. The dimension of cycle-subspaces are calculated and a cycle-basis is given. From the algebraic point of view, the automorphism groups and spectrums are calculated and the dynamical generators of the graphs are characterized. These results are very useful for the construction of the mathematical models and also for the latter analysis of the dynamical patterns.

The second chapter of the computational part is the actual modelling part. In this chapter, the neurochemical systems of the human brain are mathematically formulated in three scales. In the microscpic scale, synaptic processes are analyzed and modelled. The dynamical behaviour of the presynaptic membrane is described in other works (Yusim et al. 1999) which has been reviewed and embedded into our model as a system of ordinary differential equations describing the release behaviour of neurotransmitters into synapses. The behaviour of neurotransmitter concentrations in the synaptic cleft has also been investigated.

It appears that the dynamics of the neurotransmitters in the synaptic cleft is merely governed by intra-synaptic electrical fields, generated by the potential difference of pre- and post-synaptic membranes and the charge of neurotransmitters, than the diffusion-forcing concentration gradients. This fact led to two models:

1. A system of coupled partial differential equations consists of a concentration transport equation and an equation describing the dynamics of the membrane electrical fields as a function of neurotransmitter concentration gradients. The spatial alteration of the neurotransmitter concentration influences the process of de/hyperpolarization of both synaptic membrane sides and thus the temporal change in the electrical field generated by the membrane potentials. This system qualita-

tively contains the release, and re-uptake processes and the action of transporter molecules on the neurotransmitters:

$$\frac{\partial E}{\partial t} \;=\; \beta\ \nabla\rho\ ,\ \beta z > 0$$

$$\frac{\partial \rho}{\partial t} + div(-\alpha\ \rho E) \;=\; f_{release}(\rho, t) - \gamma_{ex}\ .$$

2. A modified version of the Poisson-Nernst-Planck equations[2]:

$$\frac{\partial \rho}{\partial t} + div(-\mu k \frac{T}{q}(\frac{\partial \rho}{\partial x}) - \mu c z \rho(\frac{\partial \psi}{\partial x}) - z\alpha\rho E) = f(t, \nabla\rho, \psi)\ ,\ \text{in}\ (0,T]\times\Omega$$

$$\Delta\psi \;=\; z\rho\ ,\ \text{in}\ \Omega$$

$$\frac{\partial E}{\partial t} \;=\; \beta\ \nabla\rho\ ,\ \beta z > 0\ \text{in}\ \Omega$$

$$\rho = \rho_{\partial\Omega}\ ,\ \psi = \psi_{\partial\Omega},\ \text{on}\ (0,T]\times\partial\Omega\ ,$$

$$\rho(0,x) = \rho_0(x)\ ,\ \text{in}\ \Omega\ .$$

The first system has been simulated with Gascoigne (a finite element library developed in the work-group of Prof. Dr. R. Rannacher, University of Heidelberg). As expected a fore- and backward transport of neurotransmitters in the synaptic cleft is observed which will be discussed in the third part of this thesis in detail. The dynamical behaviour of the neurotransmitters in the synaptic cleft is not observable experimentally in a reasonable resolution. This makes these investigations more meaningful. Because of the complexity of the modified Nernst-Planck equations, these will be given and discussed compactly.

The scale-transition from the synaptic level to the multi-compartmental model becomes feasible by the models for single brain compartments. Considering the morphology and ultra-structural morphology of single brain compartments, integral equations has been developed to model the upscaled activity from the synapses to the networks comprised by different kind of neurons and different connectivity characteristics. The integral equations describe the integration of information along groups of interneurons with a given density distribution and internal synaptic connectivity:

[2]The parameters are taken to be: μ the mobility, z the valency, T the temperature in Kelvin, k the Boltzmann constant, c a parameter obtained by Einstein-relation; and α and β are proper multiplicative constants.

$$v_t(z) \;=\; \int_{\Omega_h} \rho(z,y) \cdot \frac{\sum_{i\in I} \chi_i(y)(\sum_{x\in\Omega_i} \psi(x,y)u_t(x))}{|I|\, g(\chi(y))} dy \;,\; \bigcup_i \Omega_i \;\subseteq \Omega_h \;,$$

where $\chi_i(y)$ describes the summation weight depending on the y-location of Ω_i. $\chi(y) = (\chi_i(y))$ is the i-vector of the summation weights. And $g : \mathbb{R}^{|I|} \to \mathbb{R}$ is the averaging parameter.

In this section the reader will be introduced to experimental methods to obtain the (for modelling) required morphological and ultra-structural parameters. Thereafter, the mathematical model will be constructed regarding to the measurable parameters.

The single compartment model allow the consideration of multi-compartment systems. Such abstract systems which denote the physiological pathways in the human brain are spatially extended. Because of the extreme mathematical complexity of systems including the spatial extension and dynamical behaviour of states, the duration of spatial propagation (τ_{ij}) and the duration of synthesis (τ_i^k) are replaced by experimentally obtained and physiologically reasonable time-lags. It follows that the dynamical behaviour of neurotransmitter concentrations along networks such as basal ganglia and the limbic system can be modelled by systems of nonlinear delay differential equations. These systems consist of equations describing the local neurotransmitter concentration in brain regions (compartments) depending to their projections and innervations, depending on their dynamical release, re-uptake and synthesis behaviour [3] and also the local electrophysiological activities:

$$\frac{ds_i^k(t)}{dt} = \sum_j (-f_{ij}^k(s_i^k, u_i)s_i^k(t) + g_{ji}^k(s_i^k, \gamma_i^k, u_j)s_j^k(t-\tau_{ij}) + \sigma_i^k(g_{ji}^k, \omega(u_i))s_i^k(t-\tau_i^k)).$$

Considering the electrophysiological activity in compartments calculated by the developed integral equations as an elicitor for the release, re-uptake and synthesis behaviour of neurotransmitters, the electrophysiological and neurochemical systems get coupled by this model. This coupling helps to connect the directly observable electrophysiological activities with pharmacological results on the behaviour of neurochemical systems. To achieve more in this direction, pharmacological parameters describing the effect of neurotransmitter-antagonization, synthesis inhibition and the blockade of transporter molecules are embedded into the model and simulated.

[3] s_i^k denotes the concentration of substance k n the region i. The functions f, g and σ describe the release, re-uptake and synthesis rates of the neurotransmitters.

Before the numerical simulation, some fundamental aspects of the models are analyzed. The influence of synthesis time-delays on the dynamical patterns is investigated in detail. It reveals that the synthesis-delays can produce considerable oscillatory effects on the system states depending on the frequency of the local neurotransmitter synthesis. The influence of the pharmacological parameters on the dynamical behaviour of the systems is also investigated due to sensitivity analysis. To obtain the trajectory sensitivity vector, it is necessary to specify the sensitivity equation for the drug-parameters. The complexity of this equation suggests that the solutions of this sensitivity equation are not allocable purely analytically. For this reason, the parameter sensitivity analysis for the time-varying synthesis-parameter is superseded by numerical simulations of the neurochemical trajectories as functions of perturbations in the parameter system by the method of internal numerical differentiation. It reveals that the system is structurally stable under drug-parameter perturbation chosen from certain ranges. By singular drug application, the neurochemical/electrophysiological orbits escapes their normal course temporarily and reverse back to their original course after a short time period of about 2 seconds.

The third part, the numerical simulations, is subdivided in the same order as the modelling part by the scales. The intra-synaptic concentration of neurotransmitter is modelled by a system of partial differential equations, which is simulated with Gascoigne. The results are represented in graphics and discussed in detail. The single compartment models are simulated for two special brain nuclei: the corpus striatum and the subthalamic nucleus. These nuclei represent two categories of brain regions: the corpus striatum consists of four families of interneurons; the subthalamic nucleus only of one. There are two methods used to simulate the single compartment models. First, network simulations regarding to the density distribution of interneurons and their synaptic connectivities reveal oscillatory patterns in electrophysiological activity of the corpus striatum. Second, the integral equation of the neural activity of the subthalamic nucleus is calculated and represented by a diagram. The oscillatory pattern also appears here. These oscillations are experimentally expectable as long field potential studies suggest. The next step is clearly the simulation of the multi-compartment model.

ARCHI, an explicit Runge-Kutta code for solving delay and neutral differential equations and parameter estimation problems, is used to simulate the designed model comprised by a nonlinear system of delay differential equations. The initial values for the neurotransmitter concentrations are estimated from micro-dialysis experiments on human. The time-delays are partly obtained from anatomical studies and are partly calculated based on anatomical observations. The physiological parameters are also obtained by

physiological and pharmacological observations on the behaviour of neurotransmitters and drugs. The simulations of this model reveal oscillations in the single compartment's electrophysiological activity as well as in the local neurotransmitter concentrations.

The physiological interpretation of these oscillatory patterns is a result of discussions with neuroscientists (Prof. Dr. A. Carlsson and others) and is given in part IV. Drug parameter tests in the simulations suggest that the antagonizing the effects of dopamine as a therapeutic strategy for paranoid schizophrenia shifts the level and phase of the neurochemical oscillations only temporarily. The system reverses back to its original state after a short time period. This behaviour is also clinically observable. The synthesis-inhibitors in contrast forces such changes for a longer time period. Thus, because the effect of anti-psychotic drugs leads to changes in the oscillatory patterns, it is a reasonable hypothesis that the mental states are related to certain oscillatory patterns. This fact led to the formulation of the main result of this thesis represented in part VI, called the oscillation hypothesis of psychosis. After the introduction of the oscillation hypothesis, some pharmacological and mathematical perspectives are introduced.

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Part I

Clinical Psychiatry

Chapter Two

Neurophysiology of Behaviour

Complex information require adapted and proper media to be processed. Sensory and motor nerve cells are capable to receive, integrate and relay the environmental signals. Cellular interactions in clustered or unclustered population networks (brain regions) and higher projections between these areas allow the nervous system to process problems of higher complexity and cognitive information. Thus, to study the information processing in the brain, we have to investigate the physiology of cellular processes as well as the structure and functionality of brain compartments as discrete nuclei and as functional groups.

In this chapter, the principal facts on the neurophysiology of the brain will be introduced. First, the synaptic processes will be discussed. Then, the information processing will be investigated on the basis of brain's macro-circuits. Following the structure of the macro-circuits, we will discuss the importance of the brain compartments from functional and neurochemical point of view for the modelling. The aim is to construct a general schematic network including the principal neural projections and innervations which are important for behaviour. The reader can use the supplement for more information on the neurochemical substances and the anatomy of the brain compartments.

2.1 Synaptic Processes

Synaptic transmission refers to the propagation of nerve impulses from one nerve cell to another. This occurs at a specialized cellular structure known as the synapse, a junction at which the axon of the pre-synaptic neuron terminates at some location upon the post-synaptic neuron. The end of a pre-synaptic axon, where it is juxtaposed to the post-synaptic neuron, is enlarged

and forms a structure known as the terminal button. An axon can make contact anywhere along the second neuron: on the dendrites (an axodendritic synapse), the cell body (an axosomatic synapse) or the axons (an axo-axonal synapse). At the pre-synaptic ending, an electrical impulse (action potential) will trigger the migration of vesicles containing neuroactive substances (neurotransmitters resp. neuromodulators), which are fixated with synapsin on the actin-filaments and micro-tubuli, toward the pre-synaptic membrane. These vesicles are equal in the concentration of neuroactive substances but not in volume. The incoming action potential induces a depolarization (or hyperpolarization) of the pre-synaptic membrane, thus the Ca^{2+}-channels will open. The Ca^{2+}-ions flow through the channels from the extracellular space, this leads to an increased concentration of -ions inside the cell. The increased concentration of Ca^{2+}-ions inside the cell trigger the vesicles to migrate to the pre-synaptic membrane. The vesicle membrane will fuse with the pre-synaptic membrane releasing the neurotransmitters into the synaptic cleft. The release of the neuroactive substances is controlled by a special machinery of autoreceptors and Ca^{2+}-influx. These molecules then diffuse across the synaptic cleft where they can bind with receptor sites on the post-synaptic ending through electrical dipole-dipole binding. When the transmitter binds to the receptor ion channels are opened either direct (ionotropic receptors) or indirectly (metabotropic receptors). If the ions depolarize the post-synaptic cell-membrane they produce an excitatory post-synaptic potential wave (EPSP). In general, glutamate and acetylcholine produce EPSPs in the central nervous system synapses. If the ions hyperpolarize the post-synaptic membrane they produce an inhibitory post-synaptic potential wave (IPSP). The major transmitters producing IPSPs are glycine and GABA (γ-amino-butyric acid). The generation of an action potential on the post-synaptic membrane depends from the localization of receptors and the superposition of the potential waves. If there are enough EPSPs (well distributed) the post-synaptic membrane will be depolarized to the threshold level and an action potential will be produced, then the signal will travel along the second neurone. Once the signal has been delivered the transmitter must be removed so that new signals may be received. In some cases the transmitter is metabolized by an enzyme in the synaptic cleft. In other cases the transmitters are attracted by pre-synaptic transport molecules, are recycled and absorbed by the pre-synaptic neurone. In still other cases these both processes are combined.

2.2 Information Processing and Behaviour

Complex information require high-grade integrated systems to be proceeded. Considering the properties of the brain compartments, complex behavioural or vegetative tasks require the interaction between different compartments. For any kind of information, such as motor, sensory, or emotional one or more macro-circuits which consist of a set of brain compartments, will interact and process the inputs. Here, the most important circuits for motor and emotional information processing will be discussed, and their interactions will be investigated.

2.2.1 The Basal Ganglia

The basal ganglia are a richly interconnected set of brain nuclei found in the prosencephalon and mesencephalon of mammals, birds and reptiles. The most widely accepted views of basal ganglias functions are based on observations of human afflicted with degenerative diseases that attack these structures. These observations have led most clinical investigators to view the basal ganglia as components of a system that is somehow involved in the generation of goal-directed voluntary movement but in complex and subtle aspects of that process. Current views based on experimental studies suggest a more general role for the basal ganglia in selection among candidate movements, goals, strategies, and interpretations of sensory information. The anatomical connections of the basal ganglia link it to elements of the sensory, motor, cognitive, and motivational apparatus of the brain.

The basal ganglia are large subcortical nuclear masses considered to be derivatives of the forebrain. These are connected components of parallel organized functional basal ganglia-thalamocortical circuits. The elements of each circuit include discrete, essentially non-overlapping parts of striatum, globus pallidus, substantia nigra, thalamus and cortex (figure 2.1). In each case, specific cortical areas send excitatory, glutamatergic projections to selected portions of the striatum (comprising caudate nucleus, ventral striatum and dorsal striatum), which is generally thought to represent the input stage of basal ganglia. By virtue of their high rates of spontaneous discharge, the basal ganglia output nuclei (the internal and ventral segments of globus pallidus GPi and GPe; substantia nigra pars reticulata SNr) exert a tonic, GABA-mediated, inhibitory effect on their target nuclei in the thalamus. Within each circuit, this inhibitory outflow appears to be differentially modulated by two opposing but parallel pathways that pass from the striatum to the basal ganglia output nuclei. Each circuit includes a direct pathway to the

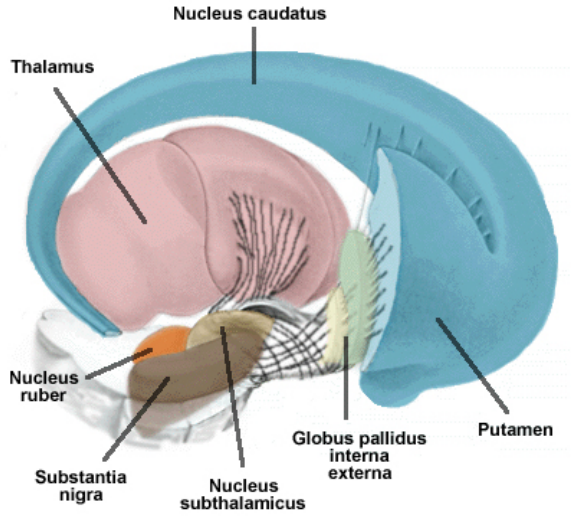

Figure 2.1: The basal ganglia (copyright: www.clinic-clinic.com)

output nuclei, which arise from inhibitory striatal efferent that contain both GABA and substance P. Activation of this pathway tends to disinhibit the thalamic stage of the circuit. The direct pathway should be able to mediate the excitatory glutamatergic input from the cortex to the thalamus via the striatum and the medial section of pallidum. This, also the existence of only two GABAergic neuron chains result in thalamic and behavioural stimulation. Each circuit also includes an indirect pathway, which passes first to the external segment of the globus pallidus (GPe) via striatal projection neurons that contain both GABA and enkephalin, then from GPe to the subthalamic nucleus via a purely GABAergic pathway and finally to the output nuclei via an excitatory, probably glutamatergic, projection from the subthalamic nucleus. The high spontaneous discharge rate of most GPe neurons exerts a tonic inhibitory influence on the subthalamic nucleus. Activation of the inhibitory GABA/Enkephalin projection from the striatum tends to suppress the activity of GPe neurons and thereby disinhibit the subthalamic nucleus, increasing the excitatory drive on the output nuclei and increasing the inhibition of their efferent targets within thalamus. The two striatal efferent systems of each circuit thus appear to have opposing effects upon the basal ganglia output nuclei and, accordingly, upon the thalamic targets of basal ganglia outflow (Alexander et al. 1986).

The corticostriatal projections appear to be essentially glutamatergic and

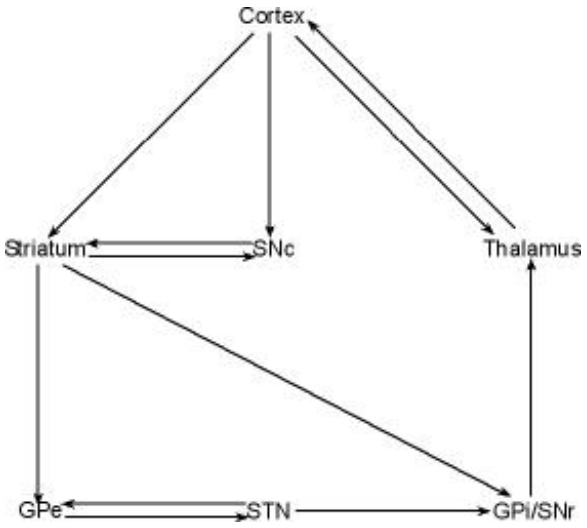

Figure 2.2: The projection network of the basal ganglia

have an excitatory influence on the striatum. The projections from the dorsal and ventral striatal complexes to the thalamus, apparently often with collaterals projecting on the mesencephalic reticular formation, appear to be largely inhibitory and possibly GABAergic. This leads some neurologists to consider the above circuit as a negative feedback loop. In this context the thalamus could be looked upon as a filter for sensory inputs. This filter is under the control of the cerebral cortex via corticostriato-thalamic loops. In this way the cortex is able to protect itself from an overload of sensory information arising via the sensory pathways to the thalamus, as well as from hyper-arousal via the afferent pathways to the reticular formation (Carlsson 1988). The clinical relevance of basal ganglia circuits depends directly from the balance between the different neurotransmitter concentrations. The exact balance in the dopamine, acetylcholine and GABA systems is prerequisite for normal motor function. The degeneration of pigmented neurons in substantia nigra leads to depleted dopamine values in striatum and result to morbus Parkinson. Also genetic anomalies in the acetylcholine- and GABAergic systems in striatum could lead to chorea Huntington. There are also psychophysiologic hypotheses based on the dysfunctionalities in the dopaminergic and glutamatergic systems which will be discussed now in more accuracy. In 1963, a specific stimulating action on dopamine (and noradrenalin) turnover of the major neuroleptics chlorpromazine and haloperidol was discovered and proposed to be due to blockade of dopamine (and noradrenalin) receptors. When these studies were extended to a large number

of antipsychotic agents, blockade of dopamine receptors, appeared to be the common denominator. This led to the notion that blockade of dopamine receptors is the most essential component in the action of the major antipsychotic agents. The fact that dopaminergic agonists are capable of faithfully mimicking certain schizophrenic disease states led to propose that dopamine may be involved in schizophrenia. This theory has played a prominent role in schizophrenia research for more than four decades. However, some important caveats must be considered. First, the hypothesis rests almost entirely on indirect pharmacological evidence. A disturbance in dopaminergic functions in the brains of schizophrenic patients remains to be demonstrated beyond doubt. Second, a fair proportion of schizophrenic patients respond poorly, or not at all, to treatment with anti-dopaminergic drugs. Third, dopaminergic agonists can only mimic the paranoid form of schizophrenia. Non-paranoid schizophrenia, and especially negative symptoms, can be mimicked more faithfully by glutamatergic NMDA-receptor antagonists. Arvid Carlsson, one of the leaders in this area, considered the circuits of basal ganglia to explain the pharmacological effects of antipsychotic drugs (dopamine antagonists) and their influence on neurophysiology. Carlsson and Carlsson (1990) have emphasized the inhibitory influence of the striatum on the thalamus and thus interpreted the basal ganglia-thalamocortical circuits as negative feedback loops. Their conclusion was based on the fact that the mesostriatal dopaminergic pathways are behaviourally stimulating and that most of neurophysiologists seem to agree that the dopaminergic input to the striatum has a mainly inhibitory action on striatal projection neurones.

2.2.2 The Limbic System

In 1878, the French neurologist Paul Broca called attention to the fact that, on the medial surface of the mammalian brain, right underneath the cortex, there exits an area containing several nuclei of grey matter (neurons) which he denominated limbic lobe (from the Latin word "limbus" that implies the idea of circle, ring, surrounding, etc.) since it forms a kind of border around the brain stem (in another part of this text we shall write more about these nuclei). The entirety of these structures, that, years later would receive the name of "limbic system", developed with the emergence of the inferior (primitive) mammals. This system commands certain behaviours that are necessary for the survival of all mammals. It gives rise and modulates specific functions that allow the animal to distinguish between the agreeable and the disagreeable. Here specific affective functions are developed, such as the one that induces the females to nurse and protect their toddlers, or the one which induces these animals to develop ludic behaviours (playful moods). Emotions

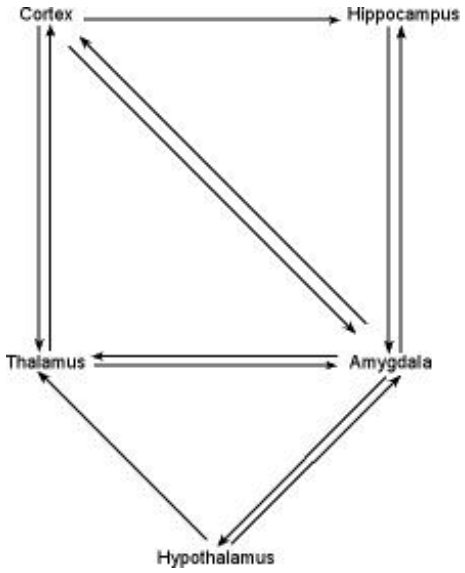

Figure 2.3: The projection network of the limbic system

and feelings, like wrath, fright, passion, love, hate, joy and sadness, are mammalian inventions, originated in the limbic system. This system is also responsible for some aspects of personal identity and for important functions related to memory.

The complex structure of the limbic system affords it to process high-complex information like the emotional behaviour (figure 2.3). Because of its connections to extra-limbic structures, the limbic system is also involved in processing of other information. This will be discussed in the next section.

2.2.3 Generalized Information Processing Pathway

Statement: The limbic system and basal ganglia solely are not sufficient to process the complex information in the brain. A complex pathway comprised by these systems and other brain nuclei is required to precede information of different kinds simultaneously and to complete complex behavioural tasks.

The physiological and anatomical properties of two major brain macro-circuits have been discussed in the last paragraphs. The neural projections and the interconnections were restricted to a single system, and the cross-projections between the systems have been neglected.

Considering the interconnectivity between single compartments of these macro-circuits suggest that high-complex information processing such as behavioural facial mimics (as a combination of motor and emotional information processing) requires a larger network which is comprised by at least basal ganglia and the limbic system. Such a network allows the brain to precede information of different kinds simultaneously and to complete complex behavioural tasks. Realistic mathematical models for the neurochemical processes behind mental disorders such as schizophrenia need networks including all major pathways.

We have constructed a schematic network comprised by basal ganglia, the limbic system (LBG network) and other important nuclei such as nucleus raphe with regard to their bilateral projections (2.5). Nucleus Raphe is the major brain region containing serotonin, which plays an important role in the generation of optical hallucinations (LSD-effects). The neurotransmitter systems are embedded on the network such that a classification of network-projections reveals (figure 2.4).

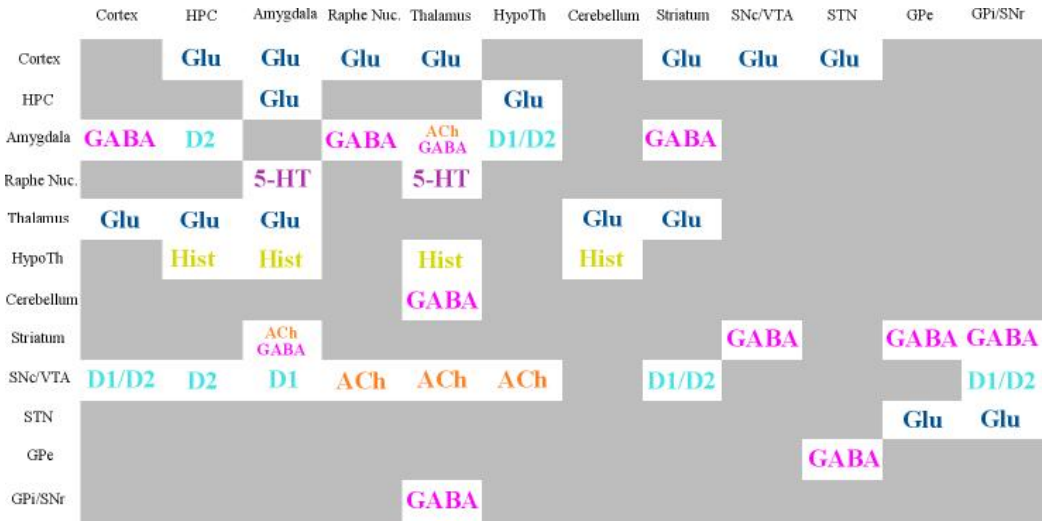

Figure 2.4: The neurotransmitter matrix of the LBG network

The LBG-network generalizes the common view of information processing and allows us to analyze the neurochemical and electrophysiological dynamics of the brain in more detail. In the computational part of this work, a mathematical model comprised by a system of nonlinear delay differential equations is constructed based on the geometry of the LBG-network to analyze quantitatively the dynamical influence of different neurotransmitter systems on behaviour, and especially on the mental states.

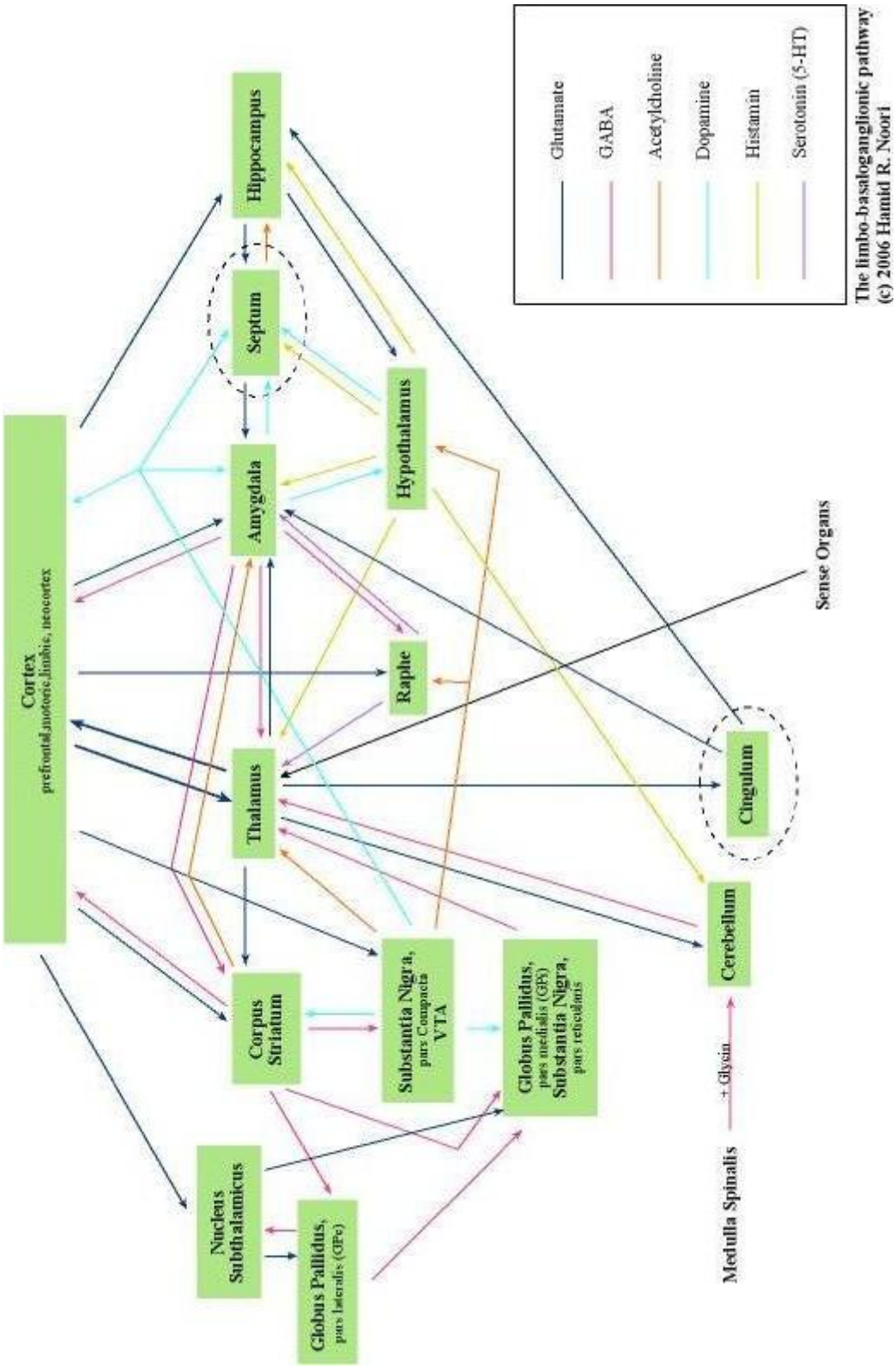

Figure 2.5: The LBG (limbic-basal ganglia) network

2.3 Brain Compartments

About 100 billions of nerve cell bodies including their fibers, glia cells and blood vessels build a complex structure called the brain or cerebrum. The brain compartments are classified either by their developmental history in telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon; or by their anatomical properties in cortex, basal ganglia, thalamus, hypothalamus, tectum, tegmentum, cerebellum, pons and medulla oblongata. Because of the important role of telencephalon in the integration and processing of complex inputs, especially cognitive, emotional and fine-regulative information, its anatomical structure in general will be discussed here. The telencephalon consists essentially of basal nuclei and the cortex cerebri.

Supported by our interest in large-scale information processing in the brain, we also discuss the morphology and physiology of the principal compartments of the generalized pathway. The knowledge of the structure and physiology of these compartments will be used in the mathematical modelling of information processing inside brain nuclei by integral operators.

In this work, we will use results on the morphology and the ultra-structural properties of the brain compartments based on immunohistochemical and Golgi-expermients. These results are represented in the supplement. The reader is advised to consider these results for better understanding of the mathematical models.

Chapter Three

Schizophrenia and Schizophrenia-like Disorders

Estimates of the incidence and prevalence of schizophrenia depend on the criteria for diagnosis and the population surveyed. The annual incidence is probably between 0.1 and 0.5 per 1000 population. The onset of schizophrenia characteristically occurs between the ages 15 to 45. While schizophrenia occurs equally in men and women, the mean age of onset is about five years earlier in men (Häfner et al. 1989). The lifetime risk of developing schizophrenia is probably between 7.0 and 9.0 per 1000 (Jablensky 1986). The point prevalence of schizophrenia in European countries is probably between 2.5 and 5.3 per 1000 (Jablensky 1986). Collaborative studies by the WHO have shown that the prevalence of schizophrenia, when assessed in comparable ways, is similar to different countries (Jablensky et al. 1992).

Of all the major psychiatric syndromes, schizophrenia is to difficult to define and describe. The main reason for this difficulty is that, over the past 100 years, many widely divergent concepts of schizophrenia have been held in different countries and by different psychiatrists. Radical differences of opinion persist to the present day. If these conflicting ideas are to be made intelligible, it is useful to start with a simple comparison between two basic concepts - acute schizophrenia and chronic schizophrenia.

Essentially, the predominant clinical features in acute schizophrenia are delusions, hallucinations, and interference with thinking. Features of this kind are often called 'positive' symptoms. Some patients recover from the acute illness whilst the others progress to chronic syndrome. In contrast, the main features of chronic schizophrenia are apathy, lack of drive, slowness, and social withdrawal. These features are often called 'negative' symptoms. Once the chronic syndrome is established, few patients recover completely.

Most of the disagreements about the diagnosis of schizophrenia are con-

cerned with the acute syndrome. The criteria for diagnosis are concerned with both the pattern of symptoms and the course of the disorder. There are disagreements about both, the range of symptoms that are required and the duration that these symptoms should have been present in order to make the diagnosis.

3.1 Etiology

Of the predisposing causes, genetic factors are most strongly supported by the evidence, but the fact that some patients with schizophrenia have no family history of the disorder suggest that environmental factors are likely to play a part as well. The nature of these environmental factors is uncertain. Perinatal neurological damage has been suggested, and so have interpersonal and social influences. A theory of the pathogenesis of schizophrenia based on the evidence of abnormalities in brain structure and morphology (the neurodevelopmental hypothesis) is outlined as follows. Schizophrenia is associated with a subtle, static structural brain lesion that involves a diffuse system of periventricular limbic and diencephalic nuclei and their connections to the dorsolateral prefrontal cortex (Weinberger 1986).

In the present work, the biochemical abnormalities and morphological changes in the schizophrenic brains are of much more interest. Thus, we will not further discuss the aetiology and begin with clinical features of this disease and its biochemical anomalies.

3.2 Clinical Features

3.2.1 The Acute Syndrome

In appearance and behaviour some patients with acute schizophrenia are entirely normal. Others seem changed and different, although not always in a way that would immediately point to psychosis. They may be preoccupied with their health, their appearance, religion, or other intensive interests. Social withdrawal may occur. Some patients smile or laugh without obvious reason. Some appear to be constantly perplexed. Some are restless and noisy, or show sudden and unexpected changes of behaviour. Others retire from company, spending a long time in their rooms, perhaps lying immobile on the bed apparently preoccupied in thought.

The speech often reflects an underlying though disorder. In early stages, there is vagueness in the patient's talk that makes it difficult to grasp his meaning. Some patients have problems with dealing with abstract ideas

(concrete thinking). Other patients become preoccupied with vague pseudo-scientific or mystical ideas.

When the disturbance is more severe, two characteristic kinds of abnormalities may occur. Disorders of the stream of thought include pressure of thought, poverty of thought, and thought blocking. Thought withdrawal is sometimes classified as a disorder of the stream of thought, but it is more usefully considered as a form of delusion.

Loosing of association denotes a lack of connection between ideas. This may be detected in illogical thinking or talking past the point. In the severest form of loosing structure and coherence of thinking is lost, so that utterances are jumbled (word salad). Some patients use ordinary words in unusual ways (metonymy), and a few new words (neologisms).

Abnormalities of mood are common and are of three main kinds. First, there may be sustained abnormalities of mood such as anxiety, depression, irritability, or euphoria. Second, there may be blunting of affect, sometimes known as flattening of affect. Third, there is incongruity of affect.

Auditory hallucinations are among the most frequent symptoms. They may take form of noises, music, single words, brief phrases, or whole conversations. They may be unobtrusive or so severe as to cause great distress. Some voices seem to give commands to the patient. Some patients hear their own thought apparently spoken out loud either as they think them (Gedankenlautwerden) or immediately afterwards. Some voices seem to discuss the patient in the third person. Other comment his actions.

Visual hallucinations are less frequent and usually occur with other kinds of hallucinations. Tactile, olfactory, gustatory, and somatic hallucinations are reported by some patients.

Delusions are characteristic. Primary delusions are infrequent and are difficult to identify with certainty. Delusions may originate against a background of so-called primary delusional mood (Wahnstimmung). Persecutory delusions are common, but are not specific to schizophrenia. Of great diagnostic value are delusions of reference and of control, which are less common.

In acute schizophrenia orientation is normal. Impairment of attention and concentration is common, and may result in memory impairment. Insight is usually impaired. Most patients do not accept that their experiences result from illness, but usually ascribe them to the malevolent actions of other people. This lack of insight is often accompanied by unwillingness to accept treatment.

Schizophrenic patients do not necessarily experience all these symptoms. The most common symptoms are the lack of insight, auditory hallucinations, and ideas of reference.

3.2.2 The Chronic Syndrome

The chronic syndrome is characterized by thought disorder and the negative symptoms of under-activity, lack of drive, social withdrawal, and emotional apathy. Roughly spoken, in contrast to positive symptoms of acute syndrome, the negative symptoms are related to a loss of cognitive and motor abilities.

The most striking feature of the syndrome is diminished volition, that is a lack of drive and initiative. A variety of motor disturbances occur but most are uncommon. Disorders of motor activity are often called catatonic. Stupor and excitement are the most striking catatonic symptoms. A patient in stupor is immobile, mute, and unresponsive, although fully conscious. Stupor may change (sometimes quickly) to a state of uncontrolled motor activity and excitement. Various disorders of movement occur in schizophrenia such as stereotypy, mannerism, and ambitendence.

Social behaviour may deteriorate. Self-care may be poor, and particularly in women, the style of dress and presentation may be careful but somewhat inappropriate. Some patient collect and hoard objects, so that their surroundings become cluttered and dirty. Other break social conventions by talking intimately to strangers or shouting obscenities in public.

Speech is often abnormal, showing evidence of thought disorder of the kinds found in acute syndrome. Affect is generally blunted; when emotion is shown, it is often incongruous. Hallucinations are common, in any of the forms occurring in the acute syndromes. Delusions are often systematized. In chronic schizophrenia, delusions may be held with little emotional response. Delusions may also be 'encapsulated' from the rest of patient's belief.

Because of the over-simplified character of these classifications two points need to be stressed. First, different features may predominate within a syndrome. Second, some patients have features of both syndromes.

Chapter Four

The Neuropathology and Psychopharmacology of Schizophrenia

4.1 Pathological Abnormalities of Schizophrenia

The existence of neuropathological abnormalities in schizophrenia suggests deformations in the network structure of schizophrenic brains, and abnormalities in the information processing sequence. Here, we review the recent MRI findings in schizophrenia based on the work of M. Shenton and co-workers (Shenton et al. 2001), beginning with ventricle findings to subcortical structures.

Lateral ventricular enlargement may indicate tissue loss in surrounding brain regions or it may indicate a failure in development (neurodevelopmental hypothesis). Over 75% of CT findings (Johnstone et al. 1976; Shelton et al. 1986) and about 80% of the MRI findings (Buckley 1998; Gur and Pearlson 1993; Henn and Braus 1999; Lawrie and Abukmeil 1998; McCarley et al. 1999; Nelson et al. 1998; Pearlson and Marsh 1993, 1999; Pfefferbaum et al. 1990; Pfefferbaum and Zipursky 1991; Rauch and Renshaw 1995; Raz and Raz 1990; Seidman 1983; Shelton and Weinberger 1986; Shenton 1996; Shenton et al. 1997, 2001; Weight and Bigler 1998; Yurgelun-Todd 1999) report enlarged lateral ventricles. Moreover, even studies not reporting lateral ventricle enlargement have reported enlargement in the temporal horn portion of the lateral ventricular system (Shenton et al. 1992). These findings are also consistent with several post-mortem findings which have reported both reduced volume in the amygdala-hippocampal complex and increased

temporal horn volume (Bogerts et al. 1985; Brown et al. 1986; Colter et al. 1987; Falkai and Bogerts 1986, 1988; Jakob and Beckmann 1989; Jeste and Lohr 1989; Kovelman and Scheibel 1984).

Over 73% of the MRI studies observed an increased volume of the third ventricle. The proximity of the third ventricle to the thalamus is likely important, then an increased liquid volume in third ventricle would lead to a reduction of thalamic volume, which is of enormous importance in information processing and thus to schizophrenia.

It has been suggested that schizophrenia is also related to abnormalities in the hippocampus (Bogerts 1997; Dwork 1997; Keltner 1996; Zaidel et al. 1997) and amygdala (Bogerts 1997; Breier et al. 1992; Shenton et al. 1992). The abnormalities of the hippocampus consist of volume changes, cell density changes, periventricular gliosis, senile degeneration, and normal neuronal size, shape, position, and/or orientation (Dwork 1997). A study compared the left and right pyramidal neurons in the hippocampus. Examination of post-mortem tissue of participant's brains using neurons digitized from the central parts of hippocampal subfields CA4, CA3, CA2, and CA1 found that schizophrenic group had considerably smaller neurons than the normal group in the left CA1, the left CA2, and the right CA3 fields.

Anatomical abnormalities in the left hippocampal region and the posterior side of the left temporal lobe are correlated with delusions, hallucinations, and bizarre behaviour (Bogerts 1997). Most MRI studies combine the amygdala and hippocampus into the amygdala-hippocampal complex because it is difficult to separate them on coronal slices. In agreement to the post-mortem studies, volume reduction in the amygdala-hippocampal complex and parahippocampal gyrus are present in chronic, and first episode schizophrenia patients (Becker et al. 1990; Bogerts et al. 1990, 1993; Breier et al. 1992; Chua and McKenna 1995; DeLisi et al. 1988, 1991; Hirayasu et al. 1998; Kawasaki et al. 1993; Lawrie et al. 1999; Shenton et al. 1992). About 67% of MRI studies that evaluated superior temporal gyrus (STG) grey and white matter volume combined report STG volume reductions in schizophrenia. MRI studies evaluating only the grey matter volume of STG reported unanimously volume reductions (Holinger et al. 1999; Marsh et al. 1997; Menon et al. 1995; Vita et al. 1995). Studies of electrical stimulations to more anterior portions of STG have resulted in complex auditory hallucinations and verbal memories (Penfield and Roberts 1959). These findings are similar to common symptoms of acute schizophrenia which include verbal memory deficits, disordered thinking, and auditory hallucinations. With respect to correlations with other brain regions, it is interesting to note that volume reduction in the hippocampus, amygdala, parahippocampal gyrus and STG is highly intercorrelated (Shenton et al. 1992), suggesting that re-

gions that are functionally interrelated also evince volume reductions. Wible and co-workers (1995) showed correlations between left prefrontal grey matter and left amygdala-hippocampal complex, left parahippocampal gyrus, and left STG. Moreover, Nestor et al. (1993) observed an association between poor performance on verbal memory, abstraction, and categorization, and volume reduction in both the parahippocampal gyrus and posterior STG. These cognitive deficits are consistent with the function of these brain regions and their role in associative links in memory, particularly verbal memory. Nestor et al. (1997) interpreted these findings as indicative of a dysfunctional semantic system in schizophrenia.

The prefrontal cortex is one of the mostly highly complex and evolved neocortical regions of the human brain, comprising close to 30% of neocortex in human, with both afferent and efferent connections to all other areas of cortex, as well as to limbic and basal ganglia structures (Fuster 1989; Goldman-Rakic et al. 1984; Pandya and Seltzer 1982). This brain region serves an important modulatory role in all aspects of human functioning. The MRI studies suggest that differences in the prefrontal cortex may be too small to detect, but which are nonetheless correlated with reductions in areas of the temporal lobe that are neuroanatomically and functionally related, as well as symptoms thought to be associated with frontal lobe functioning (Wible et al. 1995, 2001).

Despite of the recent evidences suggesting that cerebellum may play a critical role in higher cognitive functioning and may be implicated in the neuropathology of schizophrenia, there are no significant differences in its volume in schizophrenic and control patients.

Post-mortem studies of basal ganglia structures (Heckers et al. 1991) and 68% of MRI studies report increases in volume, but further studies suggest that the increased volume of basal ganglia structures may be a function of conventional neuroleptic medications whereas atypical neuroleptics do not exert the same effect. Recent studies (Shenton et al. 2001) reported smaller caudate in a group of neuroleptic nave subjects with related schizotypal personality disorder. However, Gur and co-workers (1998) evaluated basal ganglia structures in neuroleptically nave and previously treated patients and reported no differences in the volume of basal ganglia structures between the neuroleptically nave group and controls.

Summarising the findings, there are large evidences for volume differences in ventricle systems, temporal lobe structures (amygdala-hippocampal complex), and correlated abnormalities with prefrontal cortex. In general, there are no significant differences in the volume of thalamus, basal ganglia structures, and cerebellum, which could be also caused by the measurement difficulties, small ensemble of studies, and influence of antipsychotic agents

as a disturbing parameter.

4.2 The Dopamine Hypothesis

In 1963, a specific stimulating action on dopamine (and noradrenaline) turnover of the major neuroleptics chlorpromazine and haloperidol was discovered and proposed to be due to blockade of dopamine (and noradrenaline) receptors (Carlsson and Lindqvist 1963). When these studies were extended to a large number of antipsychotic agents, blockade of dopamine receptors, rather than adrenergic receptors, appeared to be the common denominator (Andn et al. 1970; Nybck et al. 1970). This led to the notion that blockade of dopamine receptors is the most essential component in the action of the major antipsychotic agents. There is overwhelming evidence that the major antipsychotic agents are capable of blocking dopamine receptors. Thus, they have been shown to antagonize the central action of dopamine and other dopaminergic agonists, actions such as stimulation of locomotor activity and stereotyped behaviour, and disruption of a discriminative task, inhibition of firing by dopaminergic neurons and of dopamine synthesis and turnover, hyperthermia and decrease in prolactin secretion. The fact that dopaminergic agonists are capable of faithfully mimicking certain schizophrenic disease states led Randrup and Munkvad (1965) to propose that dopamine may be involved in schizophrenia. All the above observations form the basis for the dopamine hypothesis of schizophrenia.

Beside the importance of this theory for schizophrenia research and its therapeutic value, some important caveats must be discussed. First, the hypothesis rest almost entirely on indirect pharmacological evidences. Our quantitative analysis of the basal ganglia's network, where the highest dopamine concentrations are located, with a view toward to schizophrenia is a possible investigation of this caveat. Second, dopaminergic agonists can only mimic the acute schizophrenia. The chronic schizophrenia is better mimicked by agents acting on the glutamatergic systems, especially located in prefrontal cortex. Our study reveals that for totally mimicking of schizophrenic symptoms a neurotransmitter-interaction model is required.

4.3 The Glutamate Hypothesis

The idea of a glutamatergic abnormality in schizophrenia was first proposed by Kim, Kornhauber, and colleagues in 1980 (Kim et al. 1980) based on their findings of low cerebrospinal fluid (CSF) glutamate levels in patients with

schizophrenia. This theory was not received well because, first, these findings could not be replicated in subsequent studies and, second, our limited knowledge of the glutamate system at the time suggested that disruptions in glutamate neurotransmission would result in overt toxicity and gross developmental abnormalities, something not seen in schizophrenia.

During the last two decades considerable interest has focused on the possible role of glutamate in schizophrenia (Bunney et al. 1995; Moghaddam and Adams 1998; Moghaddam 2003; Moghaddam and Krystal 2003). One reason for this is the discovery that phencyclidine (PCP), that can induce a psychotic condition mimicking schizophrenia, perhaps even more faithfully than amphetamines, is a powerful antagonist on NMDA receptor. This receptor is equipped with an ion channel regulating the penetration of calcium and other cations into the neuron. PCP binds to a specific site in this channel, thereby blocking the function of the receptor. Different NMDA antagonists such as MK-801, AP5, and CGS 19755, seem to be psychostimulants, at least in rodents, and are psychotogenic in humans (Lodge et al. 1989). thus a deficiency of glutamate function in schizophrenia must be considered.

4.4 The Oscillation Hypothesis

Hypothesis: The local neurotransmitter concentrations on the brain pathways oscillate. Sensitivity analysis of the drug-parameter suggest that the concentrations also oscillate in disease cases. It appears that the mental states are associated with characteristic neurochemical oscillations.

The foundations of this hypothesis are the neurochemical oscillations revealed by our mathematical investigation of the neurochemical dynamics on the networks involved in schizophrenia. The neurotransmitter concentrations oscillate in normal as well as in "diseased" cases. Parameter sensitivity analysis suggests that the quantitative behaviour of the brain's biochemical circuitries depend strongly on the interaction between the different neurotransmitter systems. It reveals also that to any mental state a characteristic oscillation is associated, and schizophrenic moods are possibly related to disturbances of these oscillations (Noori and Jäger 2007). This hypothesis will be discussed in more detail in the next chapters.

Part II

Computational Psychiatry

Chapter Five

Graph Theory and Applications

The human brain consists of a set of compartments which are interconnected through neural projections. Each compartment is a set of neurons which are in a characteristic synaptic way interconnected. The internal connectivity is described through the morphology of these compartments. The fact that these biological structures are discrete set of compartments (or neurons) and are connected through projection neurons (or axons) suggests that they could be considered as graphs. The translation of the neural morphology into graph structures is accompanied with strong simplifications in the biological nature of the neural processes but allows us to investigate the processes quantitatively by mathematical models.

The translation of biological data into abstract mathematical notation is the main objective of this chapter. The physical realization of graphs called networks, build the foundation of the construction of dynamical systems describing the biological processes behind the graph structures. To understand the construction of such dynamical systems, the theory of networks will be discussed. First, an introduction to the theory of graphs will be given which is very useful to work with the right notation. Second, an abstract formulation of the anatomical and physiological facts (known from the part I) will be introduced. After the mathematical formulation of the problem, the principal characteristics of the graphs will be investigated. This investigation includes the determination of the number of cycles of the graphs and the determination of generators of the dynamical patterns behind the graphs. The knowledge of the structural properties of the networks corresponds with the dynamical behaviour of the states of their vertices. This correspondence is not investigated in this thesis.

5.1 An Introduction to Graph Theory

A *graph* G is an ordered pair of disjoint sets (V, E) such that E is a subset of the set of unordered pairs of V. If elements of E are ordered pairs of V then G is called a *directed graph*. The set V is the set of vertices and E the set of edges [1]. The *order* of G is the number of vertices ($|G|$). The *size* of G, $e(G)$,is the number of edges with $0 \leq e(G) \leq \frac{n!}{2!(n-2)!}$.

$G' = (V', E')$ is a *subgraph* of $G = (V, E)$ if $V' \subseteq V$ and $E' \subseteq E$. If G' contains all edges of of G that join two vertices in V' then G' is said to be the subgraph *induced* or *spanned* by V' and is denoted by $G[V']$.

Two graphs $G = (V, E)$ and $G' = (V', E')$ are *isomorphic* if there exists a bijection $\phi : V \to V'$ such that $xy \in E$ iff $\phi(x)\phi(y) \in E'$. The set of vertices adjacent to a vertex $x \in G$ is denoted by $\Gamma(x)$. The *degree* of x is $d(x) = |\Gamma(x)|$. For directed graphs, we define *in-degree* and *out-degree* as the number of edges incident into and out of a vertex. The minimum degree of the vertices of a graph is denoted by $\delta(G)$; the maximum degree by $\Delta(G)$.

A *walk* W is an alternating sequence of vertices and edges. If a walk $W = x_0 x_1 \cdots x_l$ is such that $l \geq 3$, $x_0 = x_l$ and the vertices x_i, $0 < i < l$ are distinct from each other and x_0 then W is said to be a *cycle*.

A graph is *connected* if for any pair $\{x, y\}$ of distinct vertices there is a path from x to y.

Let $G = (V, E)$ be a finite connected graph. For $x_i \in V$, if $\Gamma(x_i) \neq 0$, then x_i is a linear function on a proper subset of V. Considering all $x_i \in V$ as linear functions on subsets f V, then a linear system appears [2].

A *generating set* of a graph G is a set consists of solutions of the linear systems.

A minimal generating system B is called a *basis* for graph G.

Remarks:

- A basis B for the graph G is not unique;
- If $B \cong B'$, then $G \cong G'$ isomorphic;
- If B is a basis for graph G, a finite connected and directed graph defining a dynamical system. Then the system G can be reduced to B

A similar way to define a basis for a graph is the following. The *vertex space* $C_0(G)$ of a graph G is the complex vector space of all functions from

[1] The edge between x and y is denoted by xy.

[2] see Noori 2007

V into $\mathbb{C}$. Similarly the *edge space* $C_1(G)$ is the complex vector space of all functions from E into $\mathbb{C}$. Let $V = \{v_1, \cdots, v_n\}$ and $E = \{e_1, \cdots, e_m\}$. The elements of $C_0(G)$ are usually written in the form $x = \sum_{i=1}^{n} x_i v_i$. This sum is the formal sum of the vertices but if we think of v_i as the function $V \to \mathbb{C}$ which is 0 everywhere except at the vertex v_i, where it is 1, then $v_1, \cdots, v_n$ is called a *basis* of $C_0(G)$.

There are several matrices naturally associated with a graph and its vector spaces. The *adjacency matrix* $A = A(G) = (a_{ij})$ of a graph G is the $n \times n$ matrix given by

$$a_{ij} = \begin{cases} 1 & v_i v_j \in E \\ 0 & \text{otherwise} \end{cases}$$

It is clear that A represents an endomorphism of $C_0(G)$.

The *spectrum* of a graph G is the set of numbers which are eigenvalues of $A(G)$, together with their multiplicities. If the distinct eigenvalues of $A(G)$ are λ_i, and their multiplicities are $m(\lambda_i)$, then we shall write

$$Spec(G) = \begin{pmatrix} \lambda_0 & \lambda_1 & \cdots & \lambda_s \\ m(\lambda_0) & m(\lambda_1) & \cdots & m(\lambda_s) \end{pmatrix} .$$

The *automorphism group of a graph* G is the group, $Aut(G)$ of permutations of the vertices preserving adjacency. Each $\pi \in Aut(G)$ induces an endomorphism of $C_0(G)$ which is described by a permutation matrix P. It commutes with the adjacency matrix A,

$$PA \;=\; AP \; .$$

There is also another useful matrix structure, the *incidence matrix*, which we will use to understand the algebraic properties of the cycle-subspaces of graphs. The *incidence matrix* $D(G)$ of a graph G, with respect to a given orientation of G, is the $n \times m$ matrix d_{ij} whose entries are

$$d_{ij} = \begin{cases} +1 & v_i \text{the positive end of } e_j \\ -1 & v_i \text{the negative end of } e_j \\ 0 & \text{otherwise} \end{cases}$$

These remarks indicate how the methods of representation theory may be used to characterize the graphs by their algebraic and analytic properties through their adjacency and incidence matrices and automorphism groups.

5.2 Graph-Theoretical Characterization of the System

In the first part, the LBG-network has been introduced. It consists of fourteen complex compartments [3] and is comprised mainly by tow subgraphs, namely the limbic system and the basal ganglia. First, these two subgraphs will be investigated separately, then their composition into the LBG-network will be discussed. The graph-theoretical study of these structures reveal topological properties of the systems which are interesting in their own right and are also important for the understanding of the dynamical behaviour behind the structures.

5.2.1 The Structure of the Limbic System G_1

Theorem: The limbic system as a graph is 2-dimensional (two minimal generators) and has an 8-dimensional cycle-subspace.

The limbic system is a graph structure which contains five compartments: the cortex (v_1), the hippocampus (v_2), the amygdala (v_3), the hypothalamus (v_4), and the thalamus (v_5) (figure 5.1). We first begin with the quantitative analysis of the algebraic properties of the limbic system through its adjacency matrix, and then we investigate its cycle-space by the kernel of its incidence matrix. Finally, possible minimal generating sets will be introduced.

The lowest (δ) and highest (Δ) in/out-degrees are: $\delta_{in}(G_1) = 1$, $\delta_{out}(G_1) = 1$, $\Delta_{in}(G_1) = 4$ and $\Delta_{out}(G_1) = 4$. The amygdala is the compartment with the highest in/out-degrees. For further investigations, it is necessary to construct the adjacency and the incidence matrix.

$$A(G_1) = \begin{pmatrix} 0 & 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 0 \end{pmatrix} .$$

The spectrum of G_1 is then given as

$$Spec(G_1) = \begin{pmatrix} 2.6 & -1.4 + 0.2i & -1.4 - 0.2i & 0.1 + 0.4i & 0.1 - 0.4i \\ 1 & 1 & 1 & 1 & 1 \end{pmatrix} .$$

[3] The physiological processes in each compartment will be modelled by multi-kernel integral operators respectively to its internal morphology.

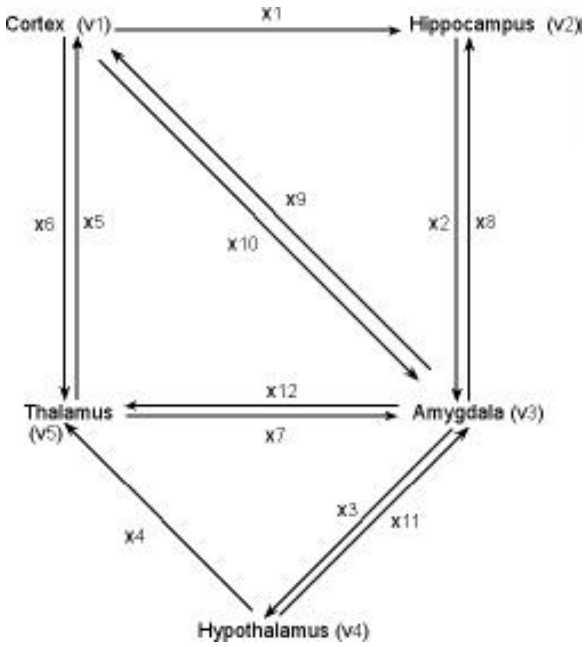

Figure 5.1: The directed graph of the limbic system

The existence of complex eigenvalues is caused by the non-symmetric structure of $A(G_1)$ (G_1 is a directed graph).

The automorphism group of the limbic system is an 8-dimensional subspace of the form:

$$Aut(G_1) = \{M \in GL(5,\mathbb{R}) | M = \begin{pmatrix} \lambda_1 & * & * & * & * \\ \lambda_2 & * & \lambda_3 & * & * \\ \lambda_4 & * & \lambda_5 & \lambda_3 & \lambda_6 \\ * & * & \lambda_7 & * & * \\ \lambda_8 & * & \lambda_7 & * & * \end{pmatrix}\} ,$$

where the $*$ represent linear combinations of the λ_i-components.

By incidence matrix $D(G)$, we can make some foundamental statements on the dimension of cycle-subspaces of a graph, and also the number of its components.

$$D(G_1) = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & -1 & 1 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 & 0 & -1 & 1 & 1 & -1 & -1 & 1 \\ 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & -1 \end{pmatrix} .$$

If c is the number of components of graph G, n the number of its vertices and m the number of its edges, then

$$rank(D(G)) \ = \ n \ - \ c \ , \ co-rank(D(G)) \ = \ m \ - \ n \ + \ c \ .$$

The incidence matrix of G_1 has rank 4. It means that G_1 consists of only one component. The co-rank of $D(G_1)$ is 8. Using our knowledge that the *cycle-subspace* of G is the kernel of the incidence matrix of G and the kernel of the incidence matrix is a vector space whose dimension is equal to the co-rank of G (Biggs 1993), then the cycle-subspace of the limbic system is an 8-dimensional vector space with the following basis (figure 5.2):

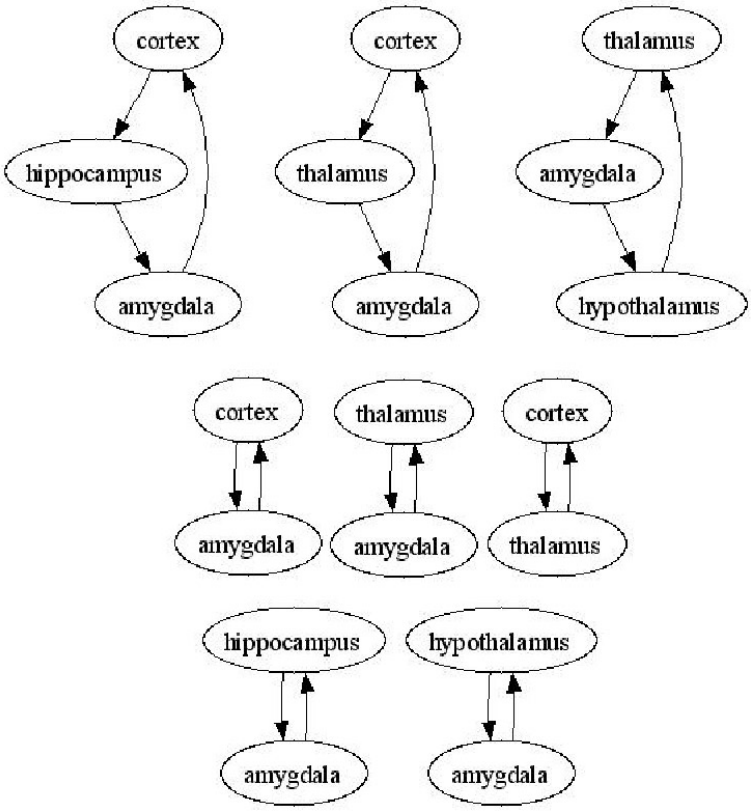

Figure 5.2: The cycle basis of the limbic system

There are two possible generating sets fulfilling the minimality property of bases:

$$\boxed{B_1 = \{\text{Cortex , Amygdala}\} \text{ and } B_2 = \{\text{Thalamus , Amygdala}\}.}$$

It means that the compartments of the limbic system are all structurally dependent on the basis set consists of the cortex (resp. the thalamus) and the amygdala.

5.2.2 The Structure of the Basal Ganglia G_2

Theorem: The basal ganglia as a graph is 3-dimensional (three minimal generators) and has a 6-dimensional cycle-subspace.

The basal ganglia is a graph structure which contains seven compartments: the cortex (w_1), the corpus striatum (w_2), the substantia nigra pars compacta (w_3), the globus pallidus externa (w_4), the nucleus subthalamicus (w_5), the globus pallidus interna (w_6) ,and the thalamus (w_7) (figure 5.3). We first begin with the quantitative analysis of the algebraic properties of the limbic system through its adjacency matrix, and then we investigate its cycle-space by the kernel of its incidence matrix. Finally, possible minimal generating sets will be introduced.

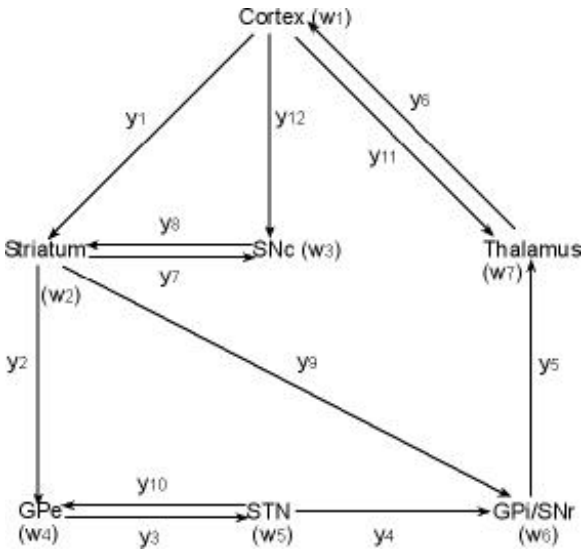

Figure 5.3: The directed graph of the basal ganglia

The in/out-degrees are: $\delta_{in}(G) = 1$, $\delta_{out}(G) = 1$, $\Delta_{in}(G) = 2$ and $\Delta_{out}(G) = 3$. For further investigations, it is necessary to construct the adjacency and the incidence matrix.

$$A(G_2) = \begin{pmatrix} 0 & 1 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

The spectrum of G_2 is given as

$$Spec(G_2) = \begin{pmatrix} 1.6 & 0.7+0.6i & 0.7-0.6i & 0 & -1.3 & -1 & -0.6 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{pmatrix}.$$

The existence of complex eigenvalues is again caused by the non-symmetric structure of A_2 (G_2 is a directed graph).

$$D(G_2) = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 1 & 1 \\ -1 & 1 & 0 & 0 & 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & -1 \\ 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & -1 & 0 \end{pmatrix}.$$

The incidence matrix of G_2 has rank 6. It means that G_2 consists of only one component. The co-rank of $D(G_2)$ is also 6. The cycle-subspace of the basal ganglia is an 6-dimensional vector space with the following basis (figure 5.4):

There are eight possible generating sets fulfilling the minimality property of bases:

$\boxed{B_1 = \{\text{Cortex, Striatum, Nucleus Subthalamicus}\};}$

$\boxed{B_2 = \{\text{Cortex, Substantia Nigra, Nucleus Subthalamicus}\};}$

$\boxed{B_3 = \{\text{Cortex, Striatum, Globus pallidus externa}\};}$

$\boxed{B_4 = \{\text{Cortex, Substantia Nigra, Globus pallidus externa}\};}$

$\boxed{B_5 = \{\text{Thalamus, Striatum, Nucleus Subthalamicus}\};}$

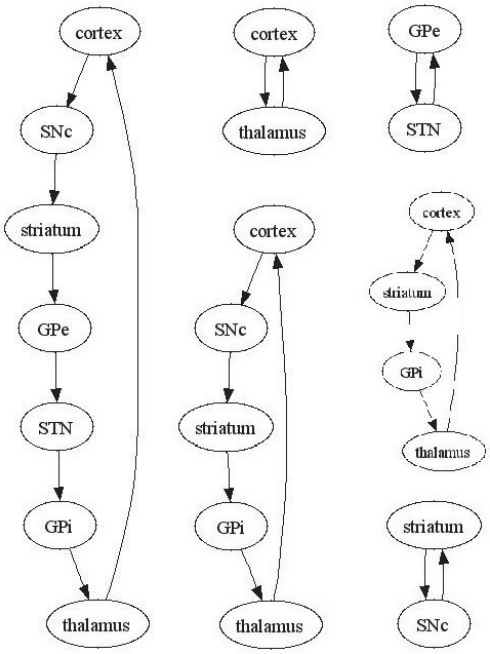

Figure 5.4: The cycle basis of the basal ganglia

$B_6 = \{\text{Thalamus, Substantia Nigra, Nucleus Subthalamicus}\};$

$B_7 = \{\text{Thalamus, Striatum, Globus pallidus externa}\};$

$B_8 = \{\text{Thalamus, Substantia Nigra, Globus pallidus externa}\};$

5.2.3 The Structure of the LBG-Network G_3

Theorem: The LBG-network is 6-dimensional and has a 36-dimensional cycle-subspace.

It reveals that the cortex (resp. the thalamus) are generators of both pathways. Considering figure 2.5, the generalized information processing pathway, we recognize that both compartments are bridges between the two pathways: the limbic system and the basal ganglia. Because of the inclusion of some extra compartments which are not compartments of the limbic system or

basal ganglia, the structure of the LBG-network is more complicated as the union of both pathways through cortical and thalamic bridges.

The complexity of the LBG-network reveals also in the structure of the adjacency matrix and the spectrum:

The spectrum of G_3 is given as

$$Spec(G_3) = \begin{pmatrix} 4.2 & -2.3 & 1.5 & 1.03i & -1.03i & 0.9 & 0.3 & -0.5 & -1 & 0 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 4 & 2 \end{pmatrix} ,$$

calculated from the following adjacency matrix $A(G_3)$

$$A(G_3) = \begin{pmatrix} 0 & 1 & 1 & 1 & 1 & 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} .$$

Analysis of the incidence matrix suggests that $rank(D(G_3)) = 13$, which leads to the fact that the LBG-network has also only one component and is fully connected. The co-rank of $D(G_3)$, which is also the dimension of the cycle-subspace of G_3 is

$$co - rank(D(G_3)) = 49 - 14 + 1 = 36 .$$

Thus, the cycles-subspace of G_3 is a 36-dimensional subspace. The inclusion of brain regions that are not compartments of the basal ganglia and the limbic system, such as nucleus raphe, and the strong interactions between both systems, is a possible reason for the increased dimension of the cycle-subspace. An interesting observation is also that the generating sets of the LBG-network fulfilling the minimality property for bases are unions of the bases of the limbic system, the basal ganglia and the hippocampus. The possible minimal generating sets for the LBG-network consist of:

The cortex (resp. the striatum), the substantia nigra, the nucleus subthalamicus, the thalamus, the amygdala, and the hippocampus.

Now, we are ready to introduce mathematical models of dynamical processes on the graph structures of the basal ganglia, the limbic system and also the LBG-network. We have classified these structures by their spectra, their cycle-subspaces and their generating sets.

Remark: The discovered algebraic and topological properties of these structures are useful to interpret the generation of dynamical patterns on these networks as functions of the activity of certain compartments (probably on networks with reduced structures). This correspondence is not investigated in this thesis but is of great interest for the future research.

Chapter Six

Electrophysiological and Neurochemical Modelling

In this chapter, the principal investigations on the modelling of neurochemical and electrophysiological processes on neural pathways will be introduced. First, classical models of the synaptic processes such as Hodgkin-Huxley equations and kinetic Markov models will be discussed. Then, the problem of neurotransmitter diffusion or active transport in synapses is discussed, mathematically analyzed and models will be introduced. Neurochemical modification of the Hodgkin-Huxley equations is the main result of our electrophysiological investigations on synaptic processes, which will also be used in higher scales. After the discussions on the synaptic processes, the physiological processes in a single compartment are modelled considering its ultra-structural and general morphology, by integral equations. Multi compartment models are the key to attach the neurophysiology with mental diseases. Therefore, the dynamical behaviour of neurotransmitter systems is analyzed in terms of their regional concentrations corresponding to the local electrophysiological acitivities.

6.1 Synaptic Modelling

The Hodgkin-Huxley equations (Hodgkin and Huxley 1952) describe the change in membrane potential or voltage V as a function of the sodium (I_{Na^+}), potassium (I_{K^+}), leakage (I_{leak}), and stimulating (I_{input}) currents across the membrane as well as membrane capacitance C. The most general form of the Hodgkin-Huxley equations is:

$$C\frac{dV}{dt} = -I_{Na^+} - I_{K^+} - I_{leak} + I_{input} \ .$$

Although the Hodgkin-Huxley equations consider the biochemical processes by including ionic currents, they disregard the action and influence of neurotransmitters in the generation of action potentials. There are several attempts to enhance this problem. Kinetic Markov models connect the ligand-gating processes and the post-synaptic electrophysiology in this sense. These models contain general information (such as neurotransmitter concentrations) on the way how neurotransmitters act on receptors at post-synaptic membranes but they do not include specific properties of the different neurotransmitter systems, which are necessary to investigate the quality of their influence.

Following a brief review of the Hodgkin-Huxley equations and the kinetic models, we shall study novel neurochemical modifications of these equations, which consider the influence of the concentration-values of specific neurotransmitters on the process of the generation of action potentials. To get a nearly complete overview on synaptic processes, we introduce a model for neurotransmitter transport (diffusion), which also describes the physiological processes at pre-synaptic membranes, such as the interaction between autoreceptors, Ca^{2+}-influx and neurotransmitter release.

6.1.1 Hodgkin-Huxley Equation

The scientific content of the Hodgkin-Huxley equations comes from two sources First is the observance of Ohm's law for the individual currents. The second is the hypothesis that the Na^+, K^+ and leakage currents are all independent and therefore sum in the general equation. As each current obeys Ohm's law, the current $I = g(V - E)$, where g is the electrical conductance (reciprocal of the resistance), V is the voltage across the membrane, and E is the equilibrium potential of the ion in question computed from the Nernst equation:

$$E \;=\; \frac{RT}{zF} ln(\frac{C_{out}}{C_{in}}) \;,$$

where z is the charge on the ion in question, and C_{out} and C_{in} are the respective concentrations of the ion outside and inside the cell. R and F are respectively the thermodynamics gas constant and the Faraday constant, and T is the temperature in degrees Kelvin.

The capacitance C arises from the fact that the lipid bilayer of the axon membrane forms a thin insulting sheet that serves to store electrical charge in the same way as an electrical capacitor (Hille 1992). Hodgkin and Huxley discovered empirically that the conductances were not constant but rather functions of the membrane potential V, and this voltage dependence is the

key to understanding action potentials. Therefore, they reformulated the above equation as:

$$C\frac{dV}{dt} = -g_{Na^+}m^3h(V-E_{Na^+}) - g_{K^+}n^4(V-E_{K^+}) - g_{leak}(V-E_{leak}) + I_{input}$$

$$\frac{dm}{dt} = \frac{1}{\tau_m(V)}(-m+M(V))$$
$$\frac{dh}{dt} = \frac{1}{\tau_h(V)}(-h+H(V))$$
$$\frac{dn}{dt} = \frac{1}{\tau_n(V)}(-n+N(V))$$

where

$$\tau_i = \frac{1}{\alpha_i+\beta_i}\ ,\ i \in \{m,h,n\}$$

and

$$\alpha_m = 0.1\ (V+25)\ e^{-(\frac{V+25}{10}-1)}\ ,\ \beta_m = 4\ e^{\frac{V}{18}}$$

$$\alpha_h = 0.07\ e^{\frac{V}{20}}\ ,\ \beta_h = e^{-(\frac{V+30}{10}+1)}$$

$$\alpha_n = 0.01\ (V+10)\ e^{-(\frac{V+10}{10}-1)}\ ,\ \beta_n = 0.125\ e^{\frac{V}{80}}\ .$$

In the first equation, E_{Na^+}, E_{K^+}, and E_{leak} are the equilibrium potentials at which each of the three currents is balanced by ionic concentration differnces across the membrane. Evidently, the Hodgkin-Huxley equations are a fourth order system of nonlinear differential equations. The additional variables m, h, and n represent the rates of Na^+ conductance channel activation, Na^+ channel inactivation, and K^+ channel activation respectively. Nonlinearity results from the fact that equilibrium values of these variables, $M(V)$, $H(V)$, and $N(V)$ are all functions of the membrane potential V, as are the time constants τ_m, τ_h, and τ_n. Simulation of these equations reveals dynamical patterns, which are very similar to the clamp-experimental observations (figure 6.1).

If $I_{input} = 0$, the rest state of the model is linearly stable but is *excitable*; that is, if the perturbation from the steady state is sufficiently large there is a large excursion of the variables before returning to the steady state.

If $I_{input} \neq 0$, there is a range of values where regular repetitive firing occurs; that is the mechanism displays limit cycle characteristic (Murray 1989). Both types of phenomena have been observed experimentally.

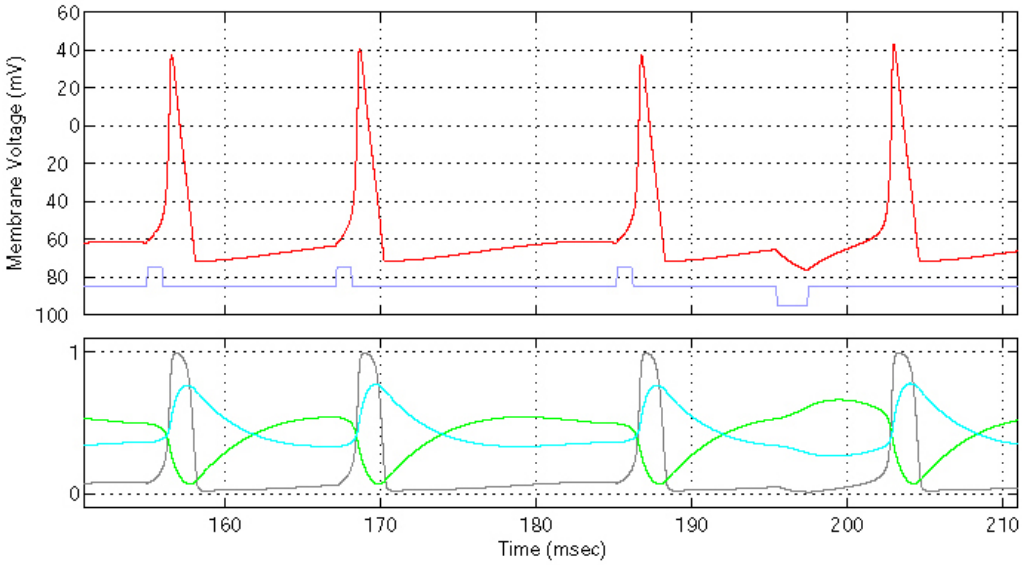

Figure 6.1: Graphical representation of the solutions of the Hodgkin-Huxley equations; (Grey:m; Green:h; Cyan:n)

6.1.2 Kinetic Markov Models

The behaviour of the synaptic currents can be captured using kinetic models that describe the transitions between conformational states of these ion channels. This class of models, of which the Hodgkin-Huxley model is an instance, are commonly known *Markov models*. First, we begin formally to describe state diagram for different types of gating, present the corresponding kinetic equations, and explain how to relate them. Second, the explicit models for the transmitter release and post-synaptic currents will be introduced (Destexhe et al. 1998). And finally some simulation results will be presented.

Generally, kinetic models are written as state diagrams

$$S_1 \rightleftharpoons S_2 \rightleftharpoons \cdots \rightleftharpoons S_n \ ,$$

where $S_1, \cdots, S_n$ represent the various states of the channel. The transition between any pair of states can be written as

$$S_i \underset{r_{ji}}{\overset{r_{ij}}{\rightleftharpoons}} S_j \quad ,$$

where r_{ij} and r_{ji} are the rate constants that govern the transition between

states S_i and S_j. The fraction of channel in state S_i, s_i, obeys the relation

$$\frac{ds_i}{dt} \;=\; \sum_{j=1}^{n} s_j r_{ji} \;-\; \sum_{j=1}^{n} s_i r_{ij} \;,$$

which is the conventional kinetic equation for the various states of the system.

In the case of voltage-dependent channels, the rate constants will depend on voltage:

$$S_i \underset{r_{ji}(V)}{\overset{r_{ij}(V)}{\rightleftharpoons}} S_j \quad .$$

The voltage dependence of the rate constants can be expressed as

$$r_{ij}(V) \;=\; e^{-\frac{U_{ij}(V)}{RT}} \;,$$

where $U_{ij}(V)$ is the free-energy barrier for the transition from state S_i to S_j, R is the gas constant and T is the absolute temperature. The exact form of $U_{ij}(V)$ involves both linear and nonlinear components arising from interactions between the channel protein and the membrane electrical field.

In the case of ligand-gated channels, the transition between unbound and bound states of the channel depends on the concentration of ligand:

$$L + S_i \underset{r_{ji}(V)}{\overset{r_{ij}(V)}{\rightleftharpoons}} S_j \quad .$$

Here, L is the ligand, S_i the unbound state, S_j the bound state, and r_{ij} and r_{ji} rate constants, as defined before.

These models have to be fitted by complex algorithms to the experimental data.

Following the excellent work of Parnas work-group (Yusim et al. 1999) on the mechanism of controlled neurotransmitter release, we introduce their hypothesis and related kinetic models on this subject. Their investigations lead to the foundation of the theory that

- Depolarization shifts the autoreceptor from a high affinity state (R_H) to a low affinity state (R_L), and repolarization induces the reverse transition;
- The autoreceptor R must be bound to the neurotransmitter ($\bullet$) before it can become associated with the exocytotic apparatus (Ex), and Ex will soon detach from the unbound autoreceptor;
- Association of a (bound) autoreceptor with Ex blocks it, making it unable to induce release.

This hypothesis is supported by the following experiments. Electrically evoked release of ACh was enhanced by antagonists (hyoscine, scopolamine or atropine) of muscarinic ACh receptors ($mAChRs$) in guinea pig ileum (Morita et al. 1982; Peteris and Ogren 1988), rat urinary bladder (DAgostino et al. 1986), rat or mouse phrenic nerve (reviewed by Wessler 1989) and using methoctramine in frog neuromuscular junction (Slutsky et al. 1999). The same effect was found in a glutamergic system, using APV as an antagonist of glutamergic synapses in crayfish (Parnas et al. 1994).

Since decreased transmitter binding decreases the amount of Ex associated with an autoreceptor, the experimental finding that decreased transmitter binding increases release is quite direct evidence that Ex is blocked when it associates with a bound autoreceptor.

Statement: Depolarization acts in two parallel ways; one is to open voltage-dependent Ca^{2+} channels, and another is to free the exocytotic apparatus from the blocking autoreceptor. This liberation of the exocytotic apparatus from the autoreceptor must occur if release is to proceed; free exocytotic machinery acts together with Ca^{2+} to induce release.

Having described the essence of how the control mechanism works, we turn now to a mathematical formulation of an integrated model for the control of release [1]. We begin with differential equations that describe the processes that determine the intracellular Ca^{2+} concentration Ca_{in}, together with equations that describe the joint actions of Cain and the free exocytotic machinery Ex in inducing release.

The assumptions which are employed concerning calcium are quite conventional: entry occurs via voltage-dependent calcium channels and calcium is removed by saturating processes. For evoked release, Ca_{in} is determined by adding to the resting level, Ca_r , the depolarization-dependent calcium entry diminished by the calcium removal process. The kinetics are thus given by (Lustig et al. 1990)

$$\frac{dCa_{in}}{dt} \;=\; Entry(t) \;-\; Removal(t)\;; Ca_{in}(0) \geq Ca_r\;,$$

where $Entry(t)$ and $Removal(t)$ are the entry and removal rates at time t, respectively. The phenomenological equations that describe the entry and removal rates are

[1] These paragraphs are based (in sense and text) on the paper Yusim et al. (1999) and have only to be considered as an introduction into the current research in the area of kinetic modelling of synapses

$$Entry(t) \;=\; \frac{E_{max} Ch_o(t) Ca_e}{K_e(\phi) C Ca_e} \;,$$

$$Removal(t) \;=\; \frac{R_{max}(Ca_{in}(t) \;-\; Ca_r)}{K_r C(Ca_{in}(t) \;-\; Ca_r)} \;.$$

Here, Ca_e denotes the extracellular Ca^{2+} concentration, E_{max} represents the maximal possible entry per open channel, $Ch_o(t)$ describes the concentration (per unit area) of open channels as a function of time. The half-saturation coefficient K_e is assumed to be an increasing function of depolarization ϕ. The maximum rate of removal R_{max} and the half-saturation parameter K_r for the removal rate are not voltage dependent. Channel kinetics is given by the kinetic scheme

$$Ch_o \underset{k_{op}^{\phi}}{\overset{k_c^{\phi}}{\rightleftharpoons}} Ch_c \;\;,$$

which leads to the following differential equations

$$\frac{dCh_o}{dt} \;=\; k_{op}^{\phi} Ch_c \;-\; k_c^{\phi} Ch_o \;,\; Ch_c \;+\; Ch_o \;=\; Ch_T \;,$$

where Ch_T denotes the total concentration of the channels and Ch_c and Ch_o, respectively, denote the concentrations of closed and open channels. The superscript ϕ denotes voltage dependence.

In the present model, the combined action of Ex and Ca_{in} yields a complex Q. Cooperative action of four Q molecules with a vesicle V activates V to V^* and leads to release L:

$$Ex \;+\; Ca_{in} \underset{c_{-1}}{\overset{c_1}{\rightleftharpoons}} Q \;\;,$$

$$4Q \;+\; V \underset{c_{-2}}{\overset{c_2}{\rightleftharpoons}} V^* \xrightarrow{c_3} L \longrightarrow recovery \;\;.$$

Following Lustig (1989), it has been assumed that when recovery occurs the four molecules participating in the release of a single vesicle will be returned to the pool of control molecules. Yusim et al. (1999) postulated that the molecules participating in release will return to Ex, i.e.,

$$L \;\overset{c_4}{\rightarrow}\; 4\; Ex \;.$$

We now present the kinetic differential equations for the autoreceptor, for Ex, and for the joint effect of Ex and Ca_{in} on release:

$$\frac{dR_H}{dt} = -(k_3 + b_2 Tr)R_H + k_{-3}R_L + b_{-2}R_H^\bullet \ ,$$

$$\frac{dR_L}{dt} = -(k_{-3} + b_3 Tr + b_4 Ex)R_L + k_3 R_H + b_{-3}R_L^\bullet + b_{-4}R_L \wedge Ex \ ,$$

$$\frac{dR_H^\bullet}{dt} = -(k_2 + b_{-2} + a_2 Ex)R_H^\bullet + k_{-2}R_L^\bullet + b_2 Tr R_H + a_{-2}R_H^\bullet \wedge Ex \ ,$$

$$\frac{dR_L^\bullet}{dt} = -(k_{-2} + b_{-3} + a_3 Ex)R_L^\bullet + k_2 R_H^\bullet + b_3 Tr R_L + a_{-3}R_L^\bullet \wedge Ex \ ,$$

$$\frac{dR_L \wedge Ex}{dt} = -(b_{-4} + a_4 Tr)R_L \wedge Ex + b_4 Ex R_L + a_{-4}R_L^\bullet \wedge Ex \ ,$$

$$\frac{R_H^\bullet \wedge Ex}{dt} = -(k_1 + a_{-2})R_H^\bullet \wedge Ex + k_{-1}R_L^\bullet \wedge Ex + a_2 R_H^\bullet Ex \ ,$$

$$\frac{R_L^\bullet \wedge Ex}{dt} = -(k_{-1}+a_{-3}+a_{-4})R_L^\bullet \wedge Ex + k_1 R_H^\bullet \wedge Ex + a_3 R_L^\bullet Ex + a_4 Tr R_L \wedge Ex \ ,$$

$$\frac{dEx}{dt} = -(a_2 R_H^\bullet + a_3 R_L^\bullet + b_4 R_L)Ex + a_{-2}R_H^\bullet \wedge Ex$$
$$+a_{-3}R_L^\bullet \wedge Ex + b_{-4}R_L \wedge Ex - c_1 Ex Ca_{in} + c_{-1}Q + 4c_4 L \ ,$$

$$\frac{dQ}{dt} = -c_{-1}Q - 4c_2 V Q^4 + c_1 Ex Ca_{in} + 4c_{-2}V^* \ ,$$

$$\frac{dV^*}{dt} = -(c_{-2} + c_3)V^* + c_2 V Q^4 \ ,$$

$$\frac{dL^*}{dt} = c_3 V^* - c_4 L \ .$$

The simulations of these equations reveal graphs which are qualitatively similar to the experiments (figure 6.2: Yusim et al., 1999).

In the case of post-synaptic currents, detailed models based on activation by a very brief increase in transmitter concentration must capture three principal aspects of receptor gating kinetics:

- Activation/binding: The time course of the rising phase of the synaptic current can be determined either by the rate of opening after neurotransmitter is bound to the receptor of, at low concentrations, by the amount of neurotransmitter present;

- Deactivation/unbinding: The time course of decay can be determined by either deactivation following transmitter removal or desensitization;

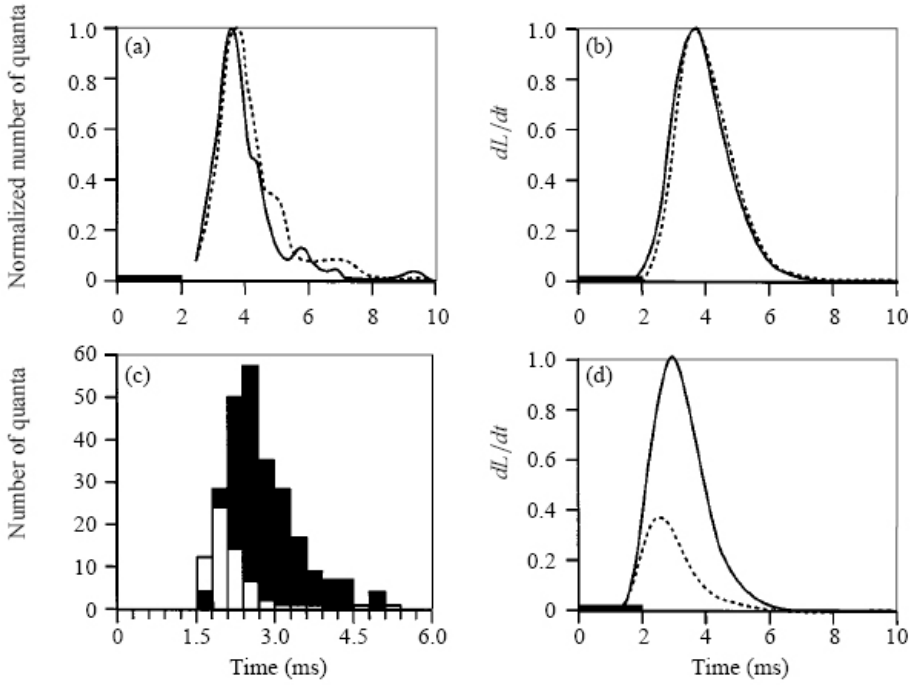

Figure 6.2: Dependence of the evoked release on membrane potential. (a) Experimental results concerning the dependence of the time course of release at two levels of depolarization (Parnas et al. 1989). Graphs are normalized, each to its peak amplitude. (b) Theoretical results corresponding to (a). High depolarization (solid line) is represented by $k_1 = k_2 = k_3 = 8$, low depolarization (dashed line) is represented by $k_1 = k_2 = k_3 = 2$. (c) Experimental results concerning the diminution of quantal content by post-pulse hyperpolarization (Arechiga et al. 1990). (d) Theoretical results corresponding to (c). Depolarization pulse: $k1 = k2 = k3 = 2m/s$. Hyperpolarizing pulse: $k_{-1} = k_{-2} = k_{-3} = 0.9m/s$. (copyright: Yussim et al. 1999)

- Desensitization: Synaptic receptor-gated channels can be closed by entering a desensitized state. It can prolong the decay time and shorten the rise time.

The Markov kinetic models for synaptic currents are constructed in the same way as for the release procedure of neurotransmitters, considering the mentioned receptor states. The kinetic models are capable to be fitted to the experiments very accurately, but the differences between the various neurotransmitter groups are neglected. These models also disregard the spatial extension of the synaptic cleft, and also possible transmitter transport processes in this area and diffusion in the extracellular space.

6.1.3 Diffusion or Active Synaptic Transport?

Statement: The electrical flux is 10^3 times stronger than the diffusion flux in the synaptic cleft.

The qualitative and quantitative description of the motion of neurotransmitters in the synaptic cleft (sc) reveals to be one of the most difficult problems in the modelling of synapses. Synapses usually are about a few nm wide and have diameters of about $20 - 25\mu m$. These dimensions make it nearly impossible to get experimental data on the intra-synaptic processes, such as the motion of neurotransmitters from the pre-synaptic to the post-synaptic membranes. There are several suggestions on the physiology of this procedure. For some researchers, it is obvious that the gradient of neurotransmitter concentration in the sc leads to a passive diffusion, which is best modelled by diffusion equations in heterogeneous media. The existence of only a few thousand molecules in a very small area in the process of motion makes this idea at least from the mathematical point of view useless. The existence of electrical fields in the synapses generated by the membrane potentials, the polarity of the neurotransmitters and also the dipole-dipole interaction of neurotransmitters with receptors suggest that the motion of neurotransmitters is probably caused by such temporal electrical fields.

To ensure that a special inclusion of the electrical fields is also physiologically treatable, we compared the order of magnitude of the diffusion flux $(-D\frac{\partial c}{\partial x})$ for 10^5 dopamine molecules with the electrical current density $(\sigma \cdot E)$ generated by the electrical potential difference between the pre- and post-synaptic membranes. The investigation suggested that the order of magnitude of the current density preponderates the diffusion flux' on a factor of 10^3.

$$J_{diff} << J_{EM} \ .$$

It justifies our ambitions to consider the motion of neurotransmitters in the intra-synaptic area as an active electrical transport and to model it with methods of electrodynamics and statistical mechanics. We would like to underline the fact that the above consideration does not preclude the possibility of extracellular diffusion which is in fact often observed and is physiologically relevant (Bach-y-Rita 2001; Vizi 2000).

The hypothesis of intra-synaptic active electrical transport could be also supported by the physiology of neurotransmitter-transporters like $hDAT$ and the functionality of autoreceptors. The function of both structures depends strongly on the membrane potentials (Sonders et al. 1997; Parnas et al.

2000). Ample electrophysiological evidence shows that activation of autoreceptors in dopaminergic cells in the substantia nigra and ventral tegmental area causes the cells to hyperpolarize through the G-protein-mediated opening of K^+ channels (Lacey 1993). Experiments by Sonders and colleagues (1997) suggest that in regions of dopaminergic neurons in which $hDAT$ and D_2 receptors are colocalized, hyperpolarization attributable to autoreceptor activation by DA will increase the DAT turnover rate and thus accelerate the clearance of extracellular DA. The stability of this process is guaranteed by the fact that the DA-activated K^+ conductance would act to offset the depolarizing action of the transport-associated current, and thereby cancel the small, positive feedback effect that DA uptake might contribute toward promoting Ca^{2+}-dependent vesicular DA release.

Statement: The neurotransmitters are transported merely by the intra-synaptic electrical field from the pre- to the post-synaptic membrane. The concentration gradient of neurotransmitters in the synaptic cleft changes the polarity of the intra-synaptic electrical field. Higher neurotransmitter concentration at the post-synaptic membrane leads to its de/hyperpolarization because of the higher probability of neurotransmitter-receptor bindings.

To mathematically model the motion of neurotransmitters in a changing electrical field which interacts with the local concentration of the neurotransmitters, we utilize well-known methods and formulations from electrodynamics and statistical mechanics. Let us remind the continuity equation and equation for electrical force in a field [2]:

$$\frac{\partial \rho}{\partial t} + div(\rho v) \;=\; 0 \;,$$

$$F \;=\; -q \cdot E \;.$$

The velocity of the neurotransmitters has the negative direction of the electrical fields and is directly proportional to their values.

$$F \;=\; -qE \;=\; \frac{m v_d}{\tau} \;,$$

v_d is the drift velocity and τ the time between collisions. Thus, the product of the electrical field and the concentration has been taken to describe the current density, similar to the Nernst-Planck-equations. The release of neurotransmitters in the sc ($f_{release}(\rho, t)$) and the nonsynaptic diffusion of

[2] ρ denotes the density of particles and v their velocity; q the electrical charge of a particle in a field with the strength E.

neurotransmitters (γ_{ex}) produce an inhomogeneity in the continuity equation. These considerations modify the continuity equation to the form:

$$\frac{\partial \rho}{\partial t} + div(-\alpha \rho E) \;=\; f_{release}(\rho, t) - \gamma_{ex} \;,\; \alpha = const. \;.$$

We also mentioned that the temporal change of electrical field depends on the alterations of the local concentration of neurotransmitters. This could be modelled by:

$$\frac{\partial E}{\partial t} \;=\; \beta \; \nabla \rho \;,\; \beta = const. \;,\; \beta z > 0$$

Resume: Experiments on the dependency of neurotransmitter dynamics from the membrane potentials, the comparison of order of magnitudes of diffusion and electrodynamical processes, and already existing ideas from physics, led us to derive the following model for the motion of neurotransmitters in the synaptic cleft:

$$\frac{\partial E}{\partial t} \;=\; \beta \; \nabla \rho \;,\; \beta z > 0$$

$$\frac{\partial \rho}{\partial t} + div(-\alpha \rho E) \;=\; f_{release}(\rho, t) - \gamma_{ex} \;.$$

The initial boundary problem is determined by Dirichlet boundary conditions for ρ and E, with a potential decline on the side-boundaries. Iterative methods provide solutions for the above system. The iterations are necessary because of the integro-differential structure of the equations.

The above model is also advantageous to connect the pre- and post-synaptic processes together and hence, the synaptic processes could be modelled as a unit. The electrophysiological and neurochemical processes on synaptic membranes will be modelled by a biochemical modification of the Hodgkin-Huxley equations and kinetic models in the next section; and the interconnection with the active transport through the changes in electrical field strength will be discussed.

Statement: Although the diffusion flux is 1000-times smaller than the electrical flux, it is not fully insignificant. This fact suggests to apply a modification of the Poisson-Nernst-Planck equations to model the transport in the synaptic cleft.

Similar to the concept of the ion transport through membranes, we use the Poisson-Nernst-Planck equations to model the transport of neurotransmitters

inside the synaptic cleft. There are two major electrical fields that influence the motion of neurotransmitters, the density electrical field $grad\psi$ obtained by the Poisson-equation, and the external membrane field E which depends on the concentration gradient of neurotransmitters in the cleft. The reason for this dependency is on the pre-synaptic membrane the existence of transporter molecules and on the post-synaptic membrane side, the generation of action potentials as a function of neurotransmitter concentration (the more neurotransmitters at the post-synaptic membrane the more receptors are activated). The sum of these potentials is the effective electrical potential in the synapses. Beside the electrical fields, the existing neurotransmitter concentration gradient between the pre- and post-synaptic membrane after the release of neurotransmitters generates also a flux directed to the post-synaptic side.

Let Ω be a bounded domain of the d-dimensional Euclidean space $\mathbb{R}^d$, $d \leq 3$, and $[0,T]$ a bounded time-interval. We Supposing that the boundary $\partial\Omega$ of Ω is the union of two disjoint parts $\partial\Omega_1$ and $\partial\Omega_2$, then the following initial boundary value problem describes the dynamics of neurotransmitter concentrations in the synaptic cleft:

$$\frac{\partial \rho}{\partial t} + div(-\mu k \frac{T}{q}(\frac{\partial \rho}{\partial x}) - \mu c z \rho(\frac{\partial \psi}{\partial x}) - z\alpha\rho E) = f(t, \nabla\rho, \psi) \ , \text{ in } (0,T] \times \Omega$$

$$\Delta\psi \ = \ z\rho \ , \text{ in } \Omega$$

$$\frac{\partial E}{\partial t} \ = \ \beta \ \nabla\rho \ , \ \beta z > 0 \text{ in } \Omega$$

$$\rho = \rho_{\partial\Omega} \ , \ \psi = \psi_{\partial\Omega}, \text{ on } (0,T] \times \partial\Omega \ ,$$

$$\rho(0,x) = \rho_0(x) \ , \text{ in } \Omega \ ,$$

where the parameters are taken to be: μ the mobility, z the valency, T the temperature in Kelvin, k the Boltzmann constant, c a parameter obtained by Einstein-relation and α a multiplicative constant.

We have to remark that E describes the electrical field of the synaptic membranes. It also depends on external influences such as incoming action potentials. Thus, its dynamical behaviour is investigated separately.

It is a very difficult problem to investigate the existence and uniqueness of the above equations with arbitrary fields E. By imposing the following hypotheses, there exists a unique solution of similar problems for known external fields E (Gajewski, 1985):

- $\rho_0 \in L_2^+ = \{g \in L_2 | g(x) \geq 0 in \Omega\}$.

- The mobilities have the form $\mu = m + M(|\nabla\psi|, x)$, $0 < m = const.$. The functions $x \to M(s,x)$ for $s \geq 0$ are measurable. Furthermore there are constants M_1 and M_2 such that for all $s, s_1 \geq 0$

$$|M(s,x)s| \leq M_1 \ , \ |M(s,x)s - M(s_1,x)s_1| \leq M_2|s - s_1| \ in \ \Omega \ .$$

- The boundary $\partial\Omega$ is the union of two $(d-1)$-dimensional parts $\partial\Omega_1$ and $\partial\Omega_2$. $\partial\Omega_1$ is closed in $\partial\Omega$.

- $0 \leq \sigma \in L_\infty(\partial\Omega)$, $mes(\partial\Omega_1 \cup supp\sigma) > 0$. $\partial\Omega_1$, $\partial\Omega_2$ and σ are such that the map $g \to \psi$ with: $-\Delta\psi = g$ in Ω; $B\psi = 0$ on $\partial\Omega$; $B\psi = \psi$ on $\partial\Omega_1$ and $B\psi = \frac{\partial\psi}{\partial\nu} + \sigma\psi$ on $\partial\Omega_2$; is an isomorphism of L_r onto W_r^2 $(d < r < 6)$.

- There exist functions $P \in W_r^2$ and $R \in W_r^1$ such that $BP = \psi_{\partial\Omega}$ and $R = \rho_{\partial\Omega}$ on $\partial\Omega_1$ and $R \geq c > 0$ in $\bar{\Omega}$.

6.1.4 Biochemical Modifications of the Hodgkin-Huxley Equations

Statement: In chemical synapses the neurotransmitter-receptor binding causes the depolarization of membranes. The higher the neurotransmitter concentration (up to a certain threshold) the oftener this binding and the higher the probability of the generation of post-synaptic potentials. The gating parameters of the Hodgkin-Huxley equations express this probability. By including the quadratic value of the neurotransmitter concentration in the equations for gating parameters and neurotransmitter-specific ion channels, the HH-equations become neurochemically modified.

In the last sections, we discussed the existing mathematical methods for the generation of action potentials, the neurotransmitter-receptor kinetics (especially interesting for pre-synaptic processes), and we have developed an active transport model for neurotransmitters in the synaptic cleft caused by electrical fields which are generated by membrane potentials. In this section we modify the Hodgkin-Huxley equations neurochemically, by making them dependent from the special properties of neurotransmitters.

In general, the Hodgkin-Huxley equations are based on Ohm' law and the fact that ionic diffusion through ion channels leads to de-/hyperpolarization of the membranes. Any neurotransmitter acts on proper receptors which interact with special ion channels. Let us consider for a moment the $GABA_A$-receptors as an example. The binding of $GABA$ on these receptors causes

confirmation changes of neighboring Cl^--channels. Other neurotransmitters interact in a similar way with various but specific ion channels.

It is obvious that the generation of action potentials at the post-synaptic membranes depends also from the concentration of neurotransmitters at the post-synaptic membrane. Then, if there are not enough neurotransmitters to bind on receptors, the membrane depolarization could not be achieved.

These observations are the foundation of the modified Hodgkin-Huxley equations. We will embed the concentration of neurotransmitters $c_k(x,t)$ [3] in the equation for the gating parameters p_k, then it expresses the probability of ligand-gating. The relation between different neurotransmitters and ion channels will also be used in terms of currents through special ion channels, denoted by index r, it means that the main equation does not only include the Na^+ and K^+ ion currents but also other related ion channels for certain neurotransmitters. We can formulate these modifications by the following model:

$$\begin{aligned} \frac{dp_k}{dt} &= \xi \cdot (c_k(x,t))^2(1-p_k) \; - \; \varsigma \cdot p_k \; , \\ I_k^r &= \bar{g}_k^r \cdot p_k \cdot (u_k - H_k^r) \; , \\ C_m \frac{du_i}{dt} &= - \sum_k (\sum_r I_k^r) \; + \; I_{leak} \; . \end{aligned}$$

These equations correspond directly with the active transport equations of the last section. The concentration of neurotransmitters $c_k(x,t)$ is the value of $\rho_k(x,t)$ in a volume dV or in the one-dimensional case in a line dx:

$$c_k(x,t) \; = \; \int \rho_k(x,t) dx \; .$$

The electrical potential u_k which can be calculated from the above equations is also related to the active transport equations, namely by E. The membrane potentials generate the electrical field with the strength E, also:

$$u_i(pre, post) \; \longleftrightarrow \; E \; .$$

These correspondences unify the models for different synaptic processes as one connected process. Kinetic models represent the release of neurotransmitters, caused by an arriving action potential and dependent from the membrane potential by the action of autoreceptors. The active transport model describe the temporal and spatial changes in intra-synaptic concentration of neurotransmitters in dependence to membrane potentials and the temporal

[3] Index k denotes the kind of neurotransmitters; The quadratic value of concentration is embedded to make the parameters more sensitive to its changes.

changes in membrane potentials coupled to the changes in neurotransmitter concentrations. The modifications of the Hodgkin-Huxley equations close the whole process by modelling the generation of post-synaptic action potentials as a function of neurotransmitter concentrations as dependent from the special properties of neurotransmitters.

6.2 Single Compartment Models

The brain does not integrate information in the synaptic scale but it has developed connected regions called Nucleus which process a high amount of synaptic information. To understand the physiology of this integration process, it is necessary to understand the neuronal architecture of the regions and classify them by their morphological and ultra-morphological properties. The morphology and ultra-structural morphology of the nuclei are often studied by neurohistochemical methods, such as Golgi-studies and immunohistochemical investigations. The immunohistochemical studies reveal the appearance of certain neurotransmitter systems in a structure; Golgi-studies, on the other hand, reveal information about the form of neurons expressing the obtained neurotransmitter systems and their interconnections. In general, the topology of the structure is then obtained. The knowledge about the appearance of different neurons and the synaptic interactions between different kinds of neurons inside a nucleus allow us to abstract its structure through networks.

The experiments on the topology of brain regions suggest that these structures could be subcategorized as heterogeneous media. There are various mathematical methods describing dynamical processes in heterogeneous media, such as asymptotic analysis, homogenization, and integral equations. Here, we decided to embed the network structure in two scales into an integral operator, which is supposed to describe the electrophysiological integration processes inside a nucleus. The idea is to use the mentioned experiments by modelling the synaptic interactions of different neurons in a small network structure, a neuron-complex set, which we call a *n-cell*. Assembling a convenient number of n-cells by considering the large scale interaction between the n-cells, we get a model how a nucleus integrates a number of incoming electrophysiological synaptic inputs, which are already modelled (figure 6.3).

We will begin with an introduction of the experimental methods, which are of interest for the analysis and modelling of single compartment integration processes. In the second part of this section, we construct a mathematical model for these processes, roughly explained in the above paragraphs. Collecting the models up to the present, we will then be ready to build up the

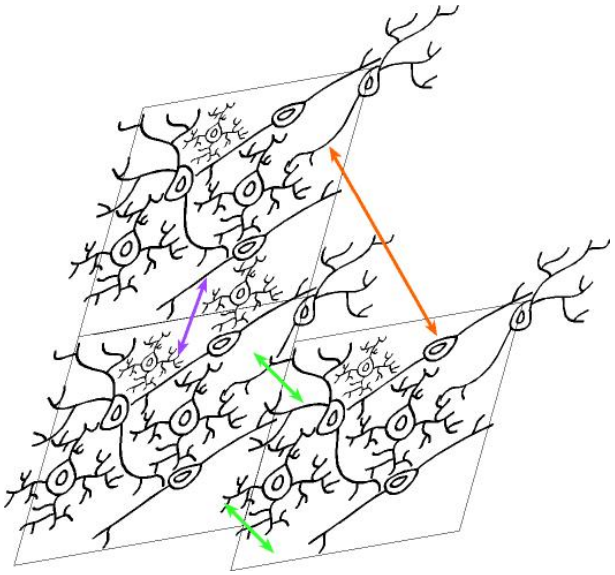

Figure 6.3: Composition of n-cells

desired multi-compartment model for information processing in the human brain.

6.2.1 Morphological Study of the Brain Compartments

Immunohistochemical Experiments:

The immunocytochemical method is widely used to display certain components of neurons. Those components allow statements about their molecular composition, especially of proteins and neurotransmitter origin. To make this statements specific, antibodies are required which are directed against structures or substances.

The structure can be directly or indirectly identified through the characteristics of the antibodies.

- Direct Method: The most simple way to proof the existence of an antigen is to use a specific antibody, which is coupled to a fluorescence artificial or to an enzyme. The binding between the fluorescence or enzyme coupled antibody and the antigen can be observed either through a fluorescence microscope or could be verified by light-microscopes after an enzymatic reaction. The low amount of non-specific impregnations and the fast implementation are the advantages of the direct over the

indirect methods. The disadvantages are the low sensibility and the high amount on primary antibodies which are required for the procedure.

- Indirect Method: An antigen-specific unconjugated antibody binds to the antigen (primary antibody). Fluorescence resp. enzyme conjugated secondary antibodies against the primary antibodies are used to visualize the bindings.

Golgi-Impregnations:

Golgi-impregnation is a great method to display neuronal branches and bifurcations, that was developed by the Italian pathologist Camillo Golgi in 1873 (Golgi 1873). The quality of the Golgi-impregnation is quit impressive. Neurons are displayed as black subjects on a light background. Although the neurons usually do not get impregnated completely, the neuronal branches, dendrites, collaterals, and even spines are represented clearly. Within this method, we are able to understand the topology of neurons, by terms like the shape of dendritic branches, maximal length of dendrites, and the coordination of spines. We will use this topological information to consider a brain compartment as a network with different kind of vertices, which are classified by their topological properties.

6.2.2 Modelling the Internal Information Processing by Integral Operators

Statement: The integration of the activity in a brain compartment depends on the density distribution and the interconnectivity of its interneurons as well as the topology of the compartment.

For one network cell, the model consist of an integral operator which includes discrete kernels in general. $\rho(z, y)$ describes the distribution of the z-neurons [4] in the 3-dimensional space $\Omega_z \ni y$. The range of this function is estimated by Golgi-studies on the morphology of brain compartments. As an example, we characterized the distribution of four different families of neurons in the corpus striatum qualitatively (figure 6.4).

The function $\psi(x, y)$ describes the synaptic connection-affinity of different neurons on a fixed network structure of a n-cell (fundamental domain). Its

[4] The z-neurons denote the family of neurotransmitters which are considered.

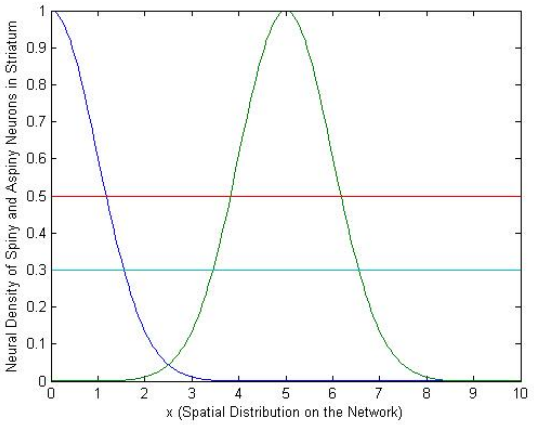

Figure 6.4: The spatial distribution of striatal neurons

possible values could be obtained by ultra-structural morphology experiments of brain compartments, which have also a sensibility to special z-neurons.

Within these functions our operator is:

$$v(t,z) \;=\; \int_{\Omega_z} \rho(z,y) \cdot (\sum_{x\in\Omega} \psi(x,y)u(t,x))dy \ .$$

Considering a family of fundamental domains - instead of only one local n-cell structure - then the above integral operator has to be generalized. Thereby, one has to consider the interconnections between different fundamental domains as well as the correct way of the potential superposition. These facts leads to the averaged multi-layer-network integral operator:

$$v(t,z) \;=\; \int_{\Omega_h} \rho(z,y) \cdot \frac{\sum_{i\in I} \chi_i(y)(\sum_{x\in\Omega_i} \psi(x,y)u(t,x))}{|I|\, g(\chi(y))}dy \ , \ \bigcup_i \Omega_i \ \subseteq \Omega_h \ .$$

$\chi_i(y)$ describes the summation weight depending on the y-location of Ω_i. $\chi(y) = (\chi_i(y))$ is the i-vector of the summation weights. And $g : \mathbb{R}^{|I|} \to \mathbb{R}$ is the averaging parameter.

It reveals that for $u(y)^i := \sum_{i\in I} \chi_i(y)(\sum_{x\in\Omega_i} \psi(x,y)u(t,x))$, the product

$$\rho(z,y) \cdot u(y)^i \;\equiv\; const. \ , \ \forall y \ .$$

Simulations showing the effect of this transition procedure are represented in the third part.

6.3 Multi Compartment Models

We have introduced mathematical models of synaptic processes, which have been transformed by integral equations into higher scales. The level of single compartments is our first approach to interpret the integration of synaptic signals as neural information. If we want to connect the behaviour with the physiology, it is necessary to design mathematical models, which realistically represent the interactions between different brain compartments. These models have to include the neurochemical as well as the electrophysiological processes. Considering both processes allows us to study and characterize the influence of drugs on the behaviour by perturbations in the dynamical patterns generated by our models and to validate our results with experiments which are often from the electrophysiological point of view, such as EEG and long field potentials (LFPs).

To embed the interactions between brain compartments into a mathematical model, we first require information on the topology of the brain. Therefore, we begin with a discussion of the topological properties of the brain such as distances between different brain regions and their spatial relations, then information need time to be transported from one compartment to other ones. We will introduce a well-known idea to translate spatial distances by temporal differences.

We will then represent the main part of this work, namely a neurochemical multi compartment model of the human brain. It only contains general anatomical and physiological assumptions. Parameters will be introduced which allow the inclusion of characteristics of neurological and psychiatric diseases as well as the influence of drugs. From mathematical point of view, it is a system of coupled nonlinear delay differential equations of local neurotransmitter concentrations and electrophysiological activities, which gets its input from our models for synapses and single compartments.

6.3.1 Spatial Propagation and Time-Delays

EEG studies suggest that the information processing of very simple motor activities takes about 100 ms. The reason for this duration is not only the integration of information in the compartments, it is also the time, which is required for the propagation of the signals along neural projections between the compartments. The simplified assumption that the propagation has a constant velocity along any neural projection and innervation in the whole brain allow us to substitute the spatial distances by applicable time intervals. In other words, we will substitute distances by time-delays. It means that the

rate of change of the neurochemical systems depends not only on their present state, but also on their past history. The general form of such dynamical systems is:

$$\frac{dx}{dt} = f(x(t), x(t-\tau_i), t) \ .$$

The neurochemical dynamical system which we attempt to construct will describe the changes of neurotransmitter concentrations in the brain regions coupled with the local electrophysiological activities. As we have seen before the macroscopic electrophysiological activity is a function of synaptic potentials which are interacting with synaptic neurotransmitter dynamics. Coupling these complex coherencies into a dynamical system enforces the equations to have nonlinear right hand sides. It is expected that such nonlinear delay-differential equations reveal oscillatory behaviour.

Our propose to design a mathematical model consist of a coupled system of nonlinear delay differential equations to describe the neurochemical processes adds up if and only if solutions exist and are stable. Therefore, we introduce a theorem (Driver 1962) on the existence and uniqueness of solutions of a delay-differential system. We have to remark that because of the nonlinearities of the equations and the number of delay parameters, analysis of the system reveals highly non-trivial problems which bust the scope of this thesis.

Theorem [Existence and Uniqueness]

Let the (right-hand side) functional $F(t, \psi(.))$ be (i) continuous in t, and (ii) locally Lipschitz with respect to ψ, and let ϕ be any member of $C([\alpha, t_0] \rightarrow D)$. Then there exists a unique solution, $y(t) = y(t; t_0, \phi)$ on $[\alpha, \beta)$ where $t_0 < \beta \leq \gamma$, and if $\beta < \gamma$ and β cannot be increased, then for any compact set $A \subset D$ there is a sequence of numbers $t_0 < t_1 < t_2 < \cdots \rightarrow \beta$ such that

$$y(t_k) \in D - A \ for \ k = l, 2, \cdots,$$

i.e. $y(t)$ comes arbitrarily close to the boundary of D or else $y(t)$ is unbounded.

6.3.2 The Dynamics of Neurotransmitter Concentrations

Statement: The neurotransmitter dynamics on the brain pathways depend on the connections of the compartments. Its value depends on the outgoing dynamical behaviour (release), the incoming dynamical behaviour (re-uptake), the regulatory mechanisms (synthesis) and the local electrical potential, which is a function of neurotransmitter concentrations. The spatial extension of the brain regions are expressed by time-delays.

Considering the network structure and neurotransmitter interactions in the LBG-network, and the knowledge on the criteria for the existence and stability of nonlinear delay differential equations, we are now able to construct an applicable mathematical model. Any equation of this model shall describe the time development of the concentration of a certain neurotransmitter system in a brain compartment, which we denote by s_i^k [5]. The following tables clarify our notation for compartments and substances.

Table 1: Notation for Brain Compartments			
Cortex	1	Globus Pallidus pars externa	7
Nucleus Subthalamicus	2	Substantia Nigra pars compacta	8
Striatum	3	Nucleus Raphe	9
Thalamus	4	Hypothalamus	10
Amygdala	5	Globus Pallidus pars interna	11
Hippocampus	6	Cerebellum	12

Table 2: Notation for Substances	
Glutamate	1
GABA	2
Acetylcholine	3
Dopamine	4
Histamine	5
Serotonin (5-HT)	6

These model equations comprise a large coupled system of time developments of extracellular neurotransmitter concentrations at different compartments, which depends on the neurotransmitter averaged release behaviour, averaged uptake procedure to the original compartment, and the synthesis of

[5] The low index denotes the region of consideration; The up index denotes the neurotransmitter system.

the neurotransmitters. The uptake process depends on the spatial distances and the duration of information integration in single compartments, thus it includes time-lags $\tau_{ij} = \tau_{ji}$, which shall be estimated by metric data of the brain. The synthesis machinery reacts not instantaneously on the release-uptake dynamics. Hence, it also includes time-lags τ_i^k which depend on the compartment and neurotransmitter properties.

Initial values for the neurotransmitter concentrations are estimated by extracellular neurotransmitter concentrations obtained from microdialysis experiments (Ungerstedt 1984; Globus et al. 1988; Wassle and Chun 1988; Sunol et al. 1988; Meyerson et al 1990; Ronne-Engstrom 1992; Kanthan 1995; Hutchinson et al. 2000; Hutchinson et al. 2002).

The release function $f_{release} = f_{ij}^k(s_i^k, u_i)$ from i to j is a function of arriving potentials at the compartment i and the amount of existing neurotransmitter concentration in the same compartment. It is a bounded, continuous and differentiable function which is the solution of systems differential equations (Parnas et al. 1989; Destexhe et al. 1994; Aharon et al. 1994; Destexhe et al. 1998; Yusim et al. 1999; Parnas et al. 2000; Sela et al. 2005). Its boundedness is because of the boundedness of neurotransmitter concentration values as well as the existence of autoreceptors which control the release procedure. The re-uptake process includes a bounded, continuous and differentiable function $g_{uptake} = g_{ji}^k(s_i^k, \gamma_i^k)$ which depends clearly on the value of released neurotransmitters, and also on the synaptic metabolization factor γ_i^k. The time-lags are in the ms scale. The synthesis process depends clearly on the value recycled neurotransmitters, and also on the frequency of the arriving action potentials $\omega(u_i)$. These facts suggest the general form of the equations:

$$\frac{ds_i^k(t)}{dt} = \sum_j (-f_{ij}^k(s_i^k, u_i)s_i^k(t) + g_{ji}^k(s_i^k, \gamma_i^k, u_j)s_j^k(t-\tau_{ij}) + \sigma_i^k(g_{ji}^k, \omega(u_i))s_i^k(t-\tau_i^k)).$$

The neurochemcial system consists of a large system of equations of the above form which are given explicitly in the following paragraphs. Instead of reducing this system to a smaller one at the beginning, the system is comprised as general as possible to avoid the possibility of neglecting important dynamical behaviour of any compartments.

The Cortex:

$$\frac{ds_1^1(t)}{dt} = -f_{\{12,13,14,15,16,18,19\}}^1(u_1(s_3^2, s_4^1, s_5^1, s_8^4))s_1^1 + g_{21}^1(u_2(s_1^1, s_7^2))s_2^1(t-\tau_{12}) +$$

$$g^1_{31}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^1_3(t-\tau_{13}) + g^1_{51}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^1_5(t-\tau_{15}) +$$
$$g^1_{61}(u_6(s^1_1, s^4_5, s^5_{10}))s^1_6(t-\tau_{16}) \; + \; g^1_{81}(u_8(s^1_1, s^2_3))s^1_8(t-\tau_{18}) \; +$$
$$g^1_{91}(u_9(s^1_1, s^2_5, s^3_8))s^1_9(t-\tau_{19}) \; +$$
$$f^1_{41}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^1_4(t) \; + \; \sigma^1_1(\sum g^1_{j1}, \omega(u_1))s^1_1(t-\tau^1_1) \; ;$$

$$\frac{ds^2_1(t)}{dt} \; = \; -g^2_{13}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^2_1(t-\tau_{13}) - g^2_{15}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^2_1(t-\tau_{15}) +$$
$$f^2_{21}(u_2(s^1_1, s^2_7))s^2_2(t) \; + \; f^2_{51}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^2_5(t) \; ;$$

$$\frac{ds^4_1(t)}{dt} \; = \; -g^4_{18}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^4_1(t-\tau_{18}) \; + \; f^4_{81}(u_8(s^1_1, s^2_3))s^4_8(t) \; ;$$

The Nucleus Subthalamicus:

$$\frac{ds^1_2(t)}{dt} \; = \; -f^1_{27,211}(u_2(s^1_1, 2^2_7))s^1_2(t) \; + \; f^1_{12}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \; +$$
$$g^1_{72}(u_7(s^1_2, s^2_3))s^2_7(t-\tau_{72}) \; +$$
$$g^1_{112}(u_{11}(s^1_2, s^2_3, s^4_8))s^1_{11}(t-\tau_{211}) \; + \; \sigma^1_2(\sum g^1_{j2}, \omega(u_2))s^1_2(t-\tau^1_2) \; ;$$

$$\frac{ds^2_2(t)}{dt} \; = \; f^2_{72}(u_7(s^1_2, s^2_3))s^2_7(t) \; - \; g^2_{27}(u_2(s^1_1, s^2_7))s^2_2(t-\tau_{72}) \; ;$$

The Corpus Striatum:

$$\frac{ds^1_3(t)}{dt} \; = \; -g^1_{31}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^1_3(t-\tau_{13}) \; + \; f^1_{13}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \; +$$
$$-g^1_{34}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^1_3(t-\tau_{34}) \; + \; f^1_{42}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^1_4(t) \; ;$$

$$\frac{ds^2_3(t)}{dt} \; = \; -f^2_{\{31,35,37,38,311\}}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^2_3(t) + g^2_{13}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^2_1(t-\tau_{13}) +$$
$$g^2_{73}(u_7(s^1_2, s^2_3))s^2_7(t-\tau_{27}) + g^2_{83}(u_8(s^1_1, s^2_3))s^2_8(t-\tau_{38}) + g^2_{113}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t-\tau_{113})$$

$$+ f^2_{53}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^2_5(t) \; + \; \sigma^2_3(\sum g^2_{j3}, \omega(u_3))s^2_3(t - \tau^2_3) \; ;$$

$$\frac{ds^3_3(t)}{dt} \; = \; -f^3_{35}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^3_3(t) + g^3_{53}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^3_5(t-\tau_{35}) +$$
$$\sigma^3_3(g^3_{53}, \omega(u_3))s^3_3(t - \tau^3_3) \; ;$$

$$\frac{ds^4_3(t)}{dt} \; = \; -g^4_{38}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^4_3(t - \tau_{38}) \; + \; f^4_{83}(u_8(s^1_1, s^2_3)s^4_8(t) \; ;$$

The Thalamus:

$$\frac{ds^1_4(t)}{dt} \; = \; -f^1_{\{41,43,45,412\}}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^1_4(t) \; +$$
$$g^1_{34}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^1_3(t - \tau_{34}) \; + \; g^1_{54}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^1_5(t - \tau_{54}) +$$
$$g^1_{124}(u_{12}(s^1_4, s^5_{10}))s^1_{12}(t - \tau_{412}) +$$
$$f^1_{14}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \; + \; \sigma^1_4(\sum g^1_{j4}, \omega(u_4))s^1_4(t - \tau^1_4) \; ;$$

$$\frac{ds^2_4(t)}{dt} \; = \; -g^2_{45}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t - \tau_{45}) \; -$$
$$g^2_{411}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t - \tau_{411}) \; -$$
$$g^2_{412}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t - \tau_{412}) +$$
$$f^2_{54}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^2_5(t) \; + \; f^2_{112}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t) +$$
$$f^2_{122}(u_{12}(s^1_4, s^5_{10}))s^2_{12}(t) \; ;$$

$$\frac{ds^3_4(t)}{dt} \; = \; -g^3_{48}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^3_4(t - \tau_{48}) \; +$$
$$f^3_{84}(u_8(s^1_1, s^2_3))s^3_8(t) \; ;$$

$$\frac{ds^5_4(t)}{dt} \; = \; -g^5_{410}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^5_4(t - \tau_{410}) \; +$$
$$f^5_{104}(u_{10}(s^2_5, s^1_6, s^3_8))s^5_{10}(t) \; ;$$

$$\frac{ds^6_4(t)}{dt} \; = \; -g^6_{49}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^6_4(t - \tau_{49}) \; +$$

$$f^6_{94}(u_9(s^1_1, s^2_5, s^3_8))s^6_9(t) \ ;$$

The Amygdala:

$$\frac{ds^1_5(t)}{dt} = -g^1_{51}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^1_5(t-\tau_{51}) - g^1_{54}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^1_5(t-\tau_{54}) + f^1_{15}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) + f^1_{41}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^1_4(t) \ ;$$

$$\frac{ds^2_5(t)}{dt} = -f^2_{\{51,54,59\}}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^2_5(t) + g^2_{15}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^2_1(t-\tau_{15}) + g^2_{41}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t-\tau_{14}) + g^2_{95}(u_9(s^1_1, s^2_5, s^3_8))s^2_9(t-\tau_{59}) + f^2_{35}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^2_3(t) + \sigma^2_5(\sum g^2_{j5}, \omega(u_5))s^2_5(t-\tau^2_5) \ ;$$

$$\frac{ds^3_5(t)}{dt} = f^3_{35}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^3_3(t) - g^3_{53}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^3_5(t-\tau_{35}) \ ;$$

$$\frac{ds^4_5(t)}{dt} = -f^4_{56}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^4_5(t) + g^4_{65}(u_6(s^1_1, s^4_5, s^5_{10}))s^4_6(t-\tau_{65}) - g^4_{58}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^4_5(t-\tau_{58}) + f^4_{85}(u_8(s^1_1, s^2_3)s^4_8(t) + g^2_{105}(u_{10}(s^2_5, s^1_6, s^3_8))s^4_{10}(t-\tau_{510}) + \sigma^4_5(g^4_{65}, \omega(u_5))s^4_5(t-\tau^4_5) \ ;$$

$$\frac{ds^5_5(t)}{dt} = -g^5_{510}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^5_5(t-\tau_{510}) + f^5_{105}(u_{10}(s^2_5, s^1_6, s^3_8))s^5_{10}(t) \ ;$$

$$\frac{ds^6_5(t)}{dt} = -g^6_{59}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^6_5(t-\tau_{59}) + f^6_{95}(u_9(s^1_1, s^2_5, s^3_8))s^6_9(t) \ ;$$

The Hippocampus:

$$\frac{ds^1_6(t)}{dt} = -f^1_{\{65,610\}}(u_6(s^1_1, s^4_5, s^5_{10}))s^1_6(t) - g^1_{61}(u_6(s^1_1, s^4_5, s^5_{10}))s^1_6(t-\tau_{16}) -$$

$$f^1_{16}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \ + \ \sigma^1_6(\sum g^1_{j6}, \omega(u_6))s^1_6(t - \tau^1_6) \ ;$$

$$\frac{ds^4_6(t)}{dt} \ = \ f^4_{56}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^4_5(t) - g^4_{65}(u_6(s^1_1, s^4_5, s^5_{10}))s^4_6(t-\tau_{65}) \ ;$$

$$\frac{ds^5_6(t)}{dt} \ = \ -g^5_{610}(u_6(s^1_1, s^4_5, s^5_{10}))s^5_6(t - \tau_{610}) \ + \ f^5_{106}(u_{10}(s^2_5, s^1_6, s^3_8))s^5_{10}(t) \ ;$$

The Globus Pallidus pars externa (GPe):

$$\frac{ds^1_7(t)}{dt} \ = \ -g^1_{72}(u_7(s^1_2, s^2_3))s^1_7(t - \tau_{27}) \ + \ f^1_{27}(u_2(s^1_1, s^2_7))s^1_2(t) \ ;$$

$$\frac{ds^2_7(t)}{dt} \ = \ -f^2_{\{72,711\}}(u_7(s^1_2, s^2_3))s^2_7(t) \ - \ g^2_{73}(u_7(s^1_2, s^2_3))s^2_7(t - \tau_{37}) \ +$$
$$f^2_{37}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^2_3(t) \ + \ g^2_{27}(u_2(s^1_1, s^2_7))s^2_2(t - \tau_{27}) \ +$$
$$g^2_{117}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t - \tau_{117}) \ + \ \sigma^2_7(\sum g^2_{j7}, \omega(u_7))s^2_7(t - \tau^2_7) \ ;$$

The Substantia Nigra pars compacta (SNc/VTA):

$$\frac{ds^1_8(t)}{dt} \ = \ -g^1_{81}(u_8(s^1_1, s^2_3))s^1_8(t - \tau_{18}) \ + \ f^1_{18}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \ ;$$

$$\frac{ds^2_8(t)}{dt} \ = \ -g^2_{83}(u_8(s^1_1, s^2_3))s^2_8(t - \tau_{38}) \ + \ f^2_{38}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^2_3(t) \ ;$$

$$\frac{ds^3_8(t)}{dt} \ = \ -f^3_{\{84,89,810\}}(u_8(s^1_1, s^2_3))s^3_8(t) + g^3_{48}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^3_4(t-\tau_{48}) +$$
$$g^3_{89}(u_9(s^1_1, s^2_5, s^3_8))s^3_9(t - \tau_{89}) \ + \ g^3_{108}(u_{10}(s^2_5, s^1_6, s^3_8))s^3_{10}(t - \tau_{810}) \ +$$
$$\sigma^3_8(\sum g^3_{j8}, \omega(u_8))s^3_8(t - \tau^3_8) \ ;$$

$$\frac{ds^4_8(t)}{dt} \ = \ -f^4_{\{81,83,85,811\}}(u_8(s^1_1, s^2_3))s^4_8(t) \ + \ g^3_{18}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^4_1(t - \tau_{18}) \ +$$

$$g^4_{38}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^4_3(t-\tau_{38}) \ + \ g^4_{58}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^4_5(t-\tau_{58}) \ +$$
$$g^4_{118}(u_{11}(s^1_2, s^2_3, s^4_8))s^4_{11}(t-\tau_{811}) \ + \ \sigma^4_8(\sum g^4_{j8}, \omega(u_8))s^4_8(t-\tau^4_8) \ ;$$

The Nucleus Raphe:

$$\frac{ds^1_9(t)}{dt} \ = \ -g^1_{91}(u_9(s^1_1, s^2_5, s^3_8))s^1_9(t-\tau_{18}) \ + \ f^1_{18}(u_1(s^2_3, s^1_4, s^1_5, s^4_8))s^1_1(t) \ ;$$

$$\frac{ds^2_9(t)}{dt} \ = \ -g^2_{95}(u_9(s^1_1, s^2_5, s^3_8))s^2_9(t-\tau_{59}) + f^2_{59}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^2_5(t) \ ;$$

$$\frac{ds^3_9(t)}{dt} \ = \ -g^3_{98}(u_9(s^1_1, s^2_5, s^3_8))s^3_9(t-\tau_{89}) \ + \ f^3_{89}(u_8(s^1_1, s^2_3))s^3_8(t) \ ;$$

$$\frac{ds^6_9(t)}{dt} \ = \ -f^6_{\{94,95\}}(u_9(s^1_1, s^2_5, s^3_8))s^6_9(t) + g^6_{49}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^6_4(t-\tau_{49}) +$$
$$g^6_{59}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^6_5(t-\tau_{59}) \ + \ \sigma^6_9(\sum g^6_{j9}, \omega(u_9))s^6_9(t-\tau^6_9) \ ;$$

The Hypothalamus:

$$\frac{ds^1_{10}(t)}{dt} \ = \ -g^1_{106}(u_{10}(s^2_5, s^1_6, s^3_8))s^1_{10}(t-\tau_{610}) \ + \ f^1_{610}(u_6(s^1_1, s^4_5, s^5_{10}))s^1_6(t) \ ;$$

$$\frac{ds^3_{10}(t)}{dt} \ = \ -g^3_{108}(u_{10}(s^2_5, s^1_6, s^3_8))s^3_{10}(t-\tau_{810}) \ + \ f^3_{89}(u_8(s^1_1, s^2_3))s^3_8(t) \ ;$$

$$\frac{ds^4_{10}(t)}{dt} \ = \ -g^2_{105}(u_{10}(s^2_5, s^1_6, s^3_8))s^4_{10}(t-\tau_{510}) + f^4_{510}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^4_5(t) \ ;$$

$$\frac{ds^5_{10}(t)}{dt} \ = \ -f^5_{\{104,105,106,1012\}}(u_{10}(s^2_5, s^1_6, s^3_8))s^5_{10}(t) + g^5_{610}(u_6(s^1_1, s^4_5, s^5_{10}))s^5_6(t-\tau_{610} +$$
$$g^5_{410}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^5_4(t-\tau_{410}) \ +$$

$$g^5_{510}(u_5(s^1_1, s^3_3, s^1_4, s^1_6, s^4_8, s^6_9, s^5_{10}))s^5_5(t-\tau_{510}) +$$
$$g^5_{1210}(u_{12}(s^1_4, s^5_{10}))s^5_{12}(t-\tau_{1012}) \ + \ \sigma^5_{10}(\sum g^5_{j10}, \omega(u_{10}))s^5_{10}(t-\tau^5_{10}) \ ;$$

The Globus Pallidus pars interna (GPi/SNr):

$$\frac{ds^1_{11}(t)}{dt} \ = \ -g^1_{112}(u_{11}(s^1_2, s^2_3, s^4_8))s^1_{11}(t-\tau_{112}) \ + \ f^1_{211}(u_2(s^1_1, s^2_7))s^1_2(t) \ ;$$

$$\frac{ds^2_{11}(t)}{dt} \ = \ -f^2_{114}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t) \ - \ g^2_{113}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t-\tau_{311}) +$$
$$f^2_{311}(u_3(s^1_1, s^1_4, s^2_5, s^4_8))s^2_3(t) \ + \ g^2_{411}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t-\tau_{411}) +$$
$$f^2_{711}(u_7(s^1_2, s^2_3))s^2_7(t) \ + \ g^2_{117}(u_{11}(s^1_2, s^2_3, s^4_8))s^2_{11}(t-\tau_{711}) +$$
$$\sigma^2_{11}(\sum g^2_{j11}, \omega(u_{11}))s^2_{11}(t-\tau^2_{11}) \ ;$$

$$\frac{ds^4_{11}(t)}{dt} \ = \ -g^4_{118}(u_{11}(s^1_2, s^2_3, s^4_8))s^4_{11}(t-\tau_{118}) \ + \ f^4_{811}(u_8(s^1_1, s^2_3))s^4_8(t) \ ;$$

The Cerebellum:

$$\frac{ds^1_{12}(t)}{dt} \ = \ -g^1_{124}(u_{12}(s^1_4, s^5_{10}))s^1_{12}(t-\tau_{124}) + f^1_{412}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^1_4(t) \ ;$$

$$\frac{ds^2_{12}(t)}{dt} \ = \ -f^2_{124}(u_{12}(s^1_4, s^5_{10}))s^2_{12}(t) + g^2_{412}(u_4(s^1_1, s^2_5, s^3_8, s^6_9, s^5_{10}, s^2_{11}, s^2_{12}))s^2_4(t-\tau_{412}) +$$
$$\sigma^2_{12}(g^2_{412}, \omega(u_{12}))s^2_{12}(t-\tau^2_{12}) \ ;$$

$$\frac{ds^5_{12}(t)}{dt} \ = \ -g^5_{1210}(u_{12}(s^1_4, s^5_{10}))s^5_{12}(t-\tau_{1210}) \ + \ f^1_{1012}(u_{10}(s^2_5, s^1_6, s^3_8))s^5_{10}(t) \ ;$$

6.3.3 System Parameters and the Influence of Drugs

Statement: The influence of anti-psychotic drugs can be modelled by time-dependent parameters. The antagonists inhibit the generation of post-synaptic potentials, thus the antagonist are modelled as parameters reducing the effect of neurotransmitter concentrations in the modified HH-equation. The synthesis-inhibitors can be introduced directly in the synthesis part of the equations of the multi-compartment model as reduce-parameters.

We have constructed a mathematical model which describes in a realistic way the physiological processes in the brain at three different level and interconnect these levels together. To make this model also useful for pharmacological and thus, clinical application, it is necessary to embed parameters into the system which represent the influence of drugs on the system. There are two major possibilities to introduce the action of drugs into our system.

First, parameters describing the action of agonists and antagonists at post-synaptic membranes shall be introduced at synaptic level. The parameter $\vartheta_i^k(t)$ operates on the intrasynaptic concentration of neurotransmitters which is responsible for de-/hyperpolariaztion of post-synaptic membranes through gating parameters.

$$\frac{dp_k}{dt} \;=\; \xi \cdot (\vartheta^k(t) \cdot c_k(x,t))^2(1-p_k) \;-\; \varsigma \cdot p_k \;.$$

If $\vartheta^k(t)$ tends to zero, a lower amount of neurotransmitters will be available to produce polarizing effects on the post-synaptic membranes. It means that for $0 \leq \vartheta^k(t) < 1$, $\vartheta^k(t)$ represents the action of an antagonist on the receptors. For $\vartheta^k(t) > 1$, the parameter describes the action of agonists in synapses. These kind of parameters are also capable to mimic the influence of blockers of transporter molecules, because of the strong interaction between the intrasynaptic neurotransmitter concentration and the activity of neurotransmitter transporter proteins.

Second, parameters representing the action of neurotransmitter synthesis-inhibitors shall be embedded into the system at macroscopic model, by operation on the synthesis functions of the multi-compartment model. These parameters denoted by $\delta_i^k(t)$ are scalar factors on σ_i^k which decrease (or increase) the magnitude of neurotransmitter synthesis.

$$\frac{ds_i^k(t)}{dt} \;=\; \sum_j (-f_{ij}^k(s_i^k,u_i)s_i^k(t) \;+\; g_{ji}^k(s_i^k,\gamma_i^k,u_j)s_j^k(t-\tau_{ij}) \;+$$

$$\delta_i^k(t) \cdot \sigma_i^k(g_{ji}^k, \omega(u_i)) s_i^k(t - \tau_i^k)).$$

The combination of these two parameters allow us to investigate the physiological influence of common anti-psychotic and also anti-epileptic drugs on the human brain as a set of compartments. It is quit simple to include release/re-uptake effecting parameters into the system in the same way as introduced above.

In the next chapter, we will analyze the influence of these parameters on the local and global properties of the system. It contains information on the stability behaviour of the system in dependency to the drug parameters and the parameter sensitivity analysis, a standard method to obtain the importance factor of a parameter in a dynamical system.

Chapter Seven

Analysis of the Dynamical Patterns

7.1 Delay Induced Dynamics

Statement: The synthesis-delays influence the dynamics of the neurotransmitter concentrations by oscillations depending on the frequency of the local synthesis rate.

There are two different categories of time-delays in our model. The first group τ_{ij} denotes the duration of signal propagation along neural projections from the brain compartment i to the brain compartment j. This group of delays clearly influences the electrophysiological processes as well as the neurochemical state of any compartment. Because of the large number of time-delays and equations, it is not possible to represent analytically lucid explanation on their dynamical influence on the system within this thesis. Thus, we concentrate on the second category of time-delays, namely the synthesis-delays τ_i^k. Our attempt is to analyze whether/how these delays influence the neurochemical dynamics for very small re-uptake functions ($g_{ji}^k \to 0$).

Thus, we consider a simplified version of the neurochemical equations. Assuming that the compartments are not interconnected to singulate a region, then any equation gets the form:

$$\frac{ds_i^k(t)}{dt} \;=\; -f_{ij}^k(s_i^k)s_i^k(t) \;+\; \sigma_i^k(s_i^k, \omega(u_i))s_i^k(t-\tau_i^k)\;.$$

The release and synthesis functions are obtained by systems of differential equations. To reduce the complexity of this investigation, we approximate these function with regard to their physical nature.

The facts that the neurotransmitter concentration and synthesis rate are inversely proportional and the direct (but controlled) relation between relation between the collective release behaviour and neurotransmitter concentrations suggest that the dynamical behaviour of the above equation could be approximated by equations of the following form:

$$\dot{x}(t) \;=\; -ax(t)^2 \;+\; b\omega(t)\frac{x(t-\tau)}{x(t)} \;,$$

where a, b are proportionality factors of the release and synthesis rates, and $\omega(t)$ is the frequency of regional depolarizations. Let us assume that $\omega(t) \neq 0$. It follows then clearly the existence of a τ-periodic solution in the second part of the above equation

$$x(t) \;=\; x(t-\tau) \;.$$

Depending on the values of a and b and also the behaviour of $\omega(t)$, this τ-periodic part changes the course of the neurochemical trajectories. The shape of these trajectories is in the case of $a > b$ and $\omega(t) = const.$, horizontally asymptotic decreasing with small damping oscillations after decreasing. If $\omega(t)$ is piecewise nonlinear increasing and b is large enough, then the oscillations dominate the behaviour of the solutions.

The above analysis suggests that the influence of synthesis-delays depends strongly on the regional depolarization-frequencies and is in general non-negligible. Following numerical simulations will also confirm this hypothesis.

7.2 Parameter Sensitivity Analysis

Statement: The influence of the anti-psychotic drug parameters on the dynamical behaviour of the system is negligible after a certain time-period. The system reverse back to its original state after a perturbation, in other words the system is structurally stable.
[1]

The mathematical problem to be solved in sensitivity theory is the calculation of the change in the system behaviour due to parameter variations. There are several ways to define quantities for the characterization of the parameter sensitivity of a system. We will first summarize these definitions (Frank 1978,Tomovic and Vukobratovic 1972), and then calculated the sensitivity functions of our system related to parameters $\vartheta_i^k(t)$ and $\delta_i^k(t)$.

[1] The concept of structural stability was first introduced by Andronov (Andronov 1966).

Let the behaviour of the dynamic system be characterized by a quantity $\psi = \psi(\alpha)$, called a system function, which among other dependencies, is a function of the parameter vector $\alpha = (\alpha_1 \cdots \alpha_n)^t$. Let the initial parameter vector be denoted by α_0 and the initial system function by ψ_0. Then

Definition

The *absolute sensitivity function* is defined as

$$S_j \ := \ \frac{\partial \psi(\alpha)}{\partial \alpha}|_{\alpha_0} \ = \ S_j(\alpha_0) \ .$$

Definition

The *parameter induced error* of the system function is

$$\Delta\psi \ := \ \sum_{j=1}^{n} S_j \ \Delta\alpha_j \ .$$

Definition

The *maximum error* of the system function is

$$|\Delta\psi| \ := \ \sum_{j=1}^{n} |S_j| \ |\Delta\alpha_j| \ .$$

Consider the general actual vector state equation of a continuous, possibly nonlinear system

$$\dot{x} \ = \ f(x, \alpha, t, u) \ ,$$

where α is a time-varying parameter according to $\alpha(t) = \alpha_0 + \epsilon\delta\alpha(t)$. The first variation $\delta\alpha$ is subject to the requirements of uniform boundedness and integrability. α_0 and ϵ are constant with respect to time; $\epsilon > 0$ is a small number.

It is assumed that the solution of the above state equation can be written as

$$x(t, \epsilon) \ = \ x_0(t) \ + \ \epsilon\delta x(t) \ ,$$

where $x_0(t)$ is the initial value of the state equation. The first variation δx allows for the characterization of the sensitivity of the system in a manner similar to the sensitivity function. This follows from the fact that the relation between the parameter-induced error and δx is given by

$$x - x_0 \ = \ \epsilon\delta x \ .$$

Using the initial values, the nonlinear system can be written as

$$\dot{x}_0 + \epsilon\delta\dot{x} \;=\; f(x_0 + \epsilon\delta\dot{x}, \alpha_0 + \epsilon\delta\alpha, t, u) \;.$$

Expanding the right-hand side of this equation into a Taylor series at the initial point (x_0, α_0), we obtain

$$\dot{x}_0 + \epsilon\delta\dot{x} \;=\; f(x_0, \alpha_0, t, u) + \epsilon\frac{\partial f(x,\alpha,t,u)}{\partial x}|_{\alpha_0}\delta x \;+$$

$$\epsilon\frac{\partial f(x,\alpha,t,u)}{\partial \alpha}|_{\alpha_0}\delta\alpha \;+\; R(\epsilon) \;.$$

Let us assume that for th term $R(\epsilon)$ containing all higher-order terms in ϵ the following limit exists:

$$lim_{\epsilon\to 0}[R(\epsilon)\frac{1}{\epsilon}] \;=\; 0 \;.$$

Introducing the initial values, one obtains

$$\epsilon\delta\dot{x} \;=\; \epsilon\frac{\partial f(x,\alpha,t,u)}{\partial x}|_{\alpha_0}\delta x \;+\epsilon\frac{\partial f(x,\alpha,t,u)}{\partial \alpha}|_{\alpha_0}\delta\alpha \;+\; R(\epsilon) \;.$$

If we now divide both sides by ϵ and then take the limit $\epsilon = 0$, we have

$$\delta\dot{x} \;=\; \frac{\partial f(x,\alpha,t,u)}{\partial x}|_{\alpha_0}\delta x \;+\frac{\partial f(x,\alpha,t,u)}{\partial \alpha}|_{\alpha_0}\delta\alpha \;.$$

The initial condition vector δx^0 of the above differential equation is zero since x^0 is not a function of α. The result can be written as

$$\delta\dot{x} \;=\; \frac{\partial f}{\partial x}|_{\alpha_0}\delta x \;+\frac{\partial f}{\partial \alpha}|_{\alpha_0}\delta\alpha \;,\; \delta x^0 \;=\; 0 \;.$$

This is the general *sensitivity equation* of a continuous, possibly nonlinear system with time-varying parameters.

In the following paragraphs, we will investigate our nonlinear systems, for sensitivity behaviour related to the time-varying parameters $\vartheta_i^k(t)$ and $\delta_i^k(t)$.

Statement: Most of the anti-psychotic drugs have temporally limited receptor-binding periods. The number of active anti-psychotic substances decreases in a certain time period after their indication.
The parameters $\vartheta(t)$ and $\delta_i^k(t)$ are descending, continuous, positive functions in time defined by exponential functions:

$$\delta_i^k : \mathbb{R} \;\to\; \mathbb{R}_+ \;,\; \delta_i^k(t) \;=\; e^{-\theta_i^k/t} + at + b \;,\; \delta_i^k(0) = 1 \;,$$

$$\vartheta_i^k : \mathbb{R} \;\to\; \mathbb{R}_+ \;,\; \vartheta_i^k(t) \;=\; e^{-\kappa_i^k/t} + ct + d \;,\; \vartheta_i^k(0) = 1 \;,$$

for some $\kappa_i^k, \varsigma_i^k > 0$ and constants a, b, c, d, which depend on the local neurotransmitter properties of the considered brain compartments.

Similar models on the decrement of drugs in the human body are introduced also in other works (Nocedal 2006).

We begin with the sensitivity analysis of the synaptic models related to the parameter $\vartheta_i^k(t)$. The (partial) antagonists as well as agonists of the neurotransmitters act in the synapses by influencing the ligand-binding procedure to alter the process of de-/hyperpolarization at the membranes. This action could be described by perturbations in the dynamics of the gating parameters of the modified Hodgkin-Huxley equations:

$$\frac{dp_k}{dt} \;=\; \xi \cdot (c_k(x,t))^2(1-p_k) \;-\; \varsigma \cdot p_k \;.$$

For the influence in a certain compartment i the equation becomes:

$$\frac{dp_k}{dt} \;=\; \xi \cdot \vartheta^k(t) \cdot (c_k(x,t))^2(1-p_k) \;-\; \varsigma \cdot p_k \;.$$

The sensitivity equation of the differential equation of gating parameters in dependency to an unknown intrasynaptic neurotransmitter concentration $c(x,t)$ is

$$\dot{\delta p_k} \;=\; (\xi c_k(x,t)^2 - \zeta)\delta p \;+\; 2\xi c_k(x,t)^2 \delta\vartheta^k \;.$$

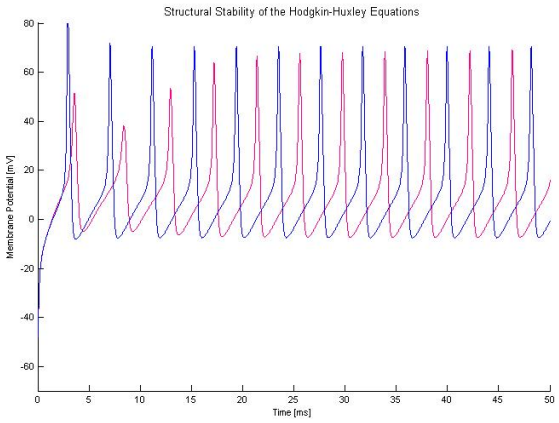

Figure 7.1: The trajectories of the membrane potentials with (red) and without (blue) drug indication. It appears that the system is structurally stable under parameter small perturbations ($\beta_i^k \in [0, 0.61)$). Minimal variations of this perturbation range lead to substantial dynamical alterations of the system.

It appears that the antagonists change the phase and amplitude of the oscillations for a certain time period, then the system reverses back to its initial oscillations (structural stability). It means that the influence of the

drug parameters after a certain time is negligible, which is physiologically acceptable.

The sensitivity behaviour of the synthesis-parameter $\delta_i^k(t)$ is more difficult. Reminding the general form of the DDEs in the model:

$$\frac{ds_i^k(t)}{dt} = \sum_j (-f_{ij}^k(s_i^k, u_i)s_i^k(t) + g_{ji}^k(s_i^k, \gamma_i^k, u_j)s_j^k(t-\tau_{ij}) + \sigma_i^k(g_{ji}^k, \omega(u_i))s_i^k(t-\tau_i^k)).$$

The influence of synthesis-inhibitors on this equation is modelled by multiplying the last part of the right-hand-side of the equation with $\delta_i^k(t) = e^{-\kappa_i^k/t}$.

Here, we use the method of internal numerical differentiation [IND] (Bock 1981) to obtain the sensitivity of the multi-compartment system (delay-differential equations) regarding to the parameters κ_i^k. "The main idea of IND is to differentiate the approximative solution of the initial value problem which is generated adaptively by an integration method of variable order and increment control." To investigate the variation problem of the parameter sensitivity function, we integrate the perturbed system with the same discretization-scheme as the normal system and the build their difference quotient. The simulation-results are represented in the following (Figures 7.2, 7.3).

The DDE-system of the multi-compartment model appears to be structurally stable under drug-perturbation parameters. However, these parameters are not negligible. They significantly change the dynamical behaviour of the system for a certain time period. In fact, this result is qualitatively compatible with the clinically observed drug-influence on the neurophysiological systems.

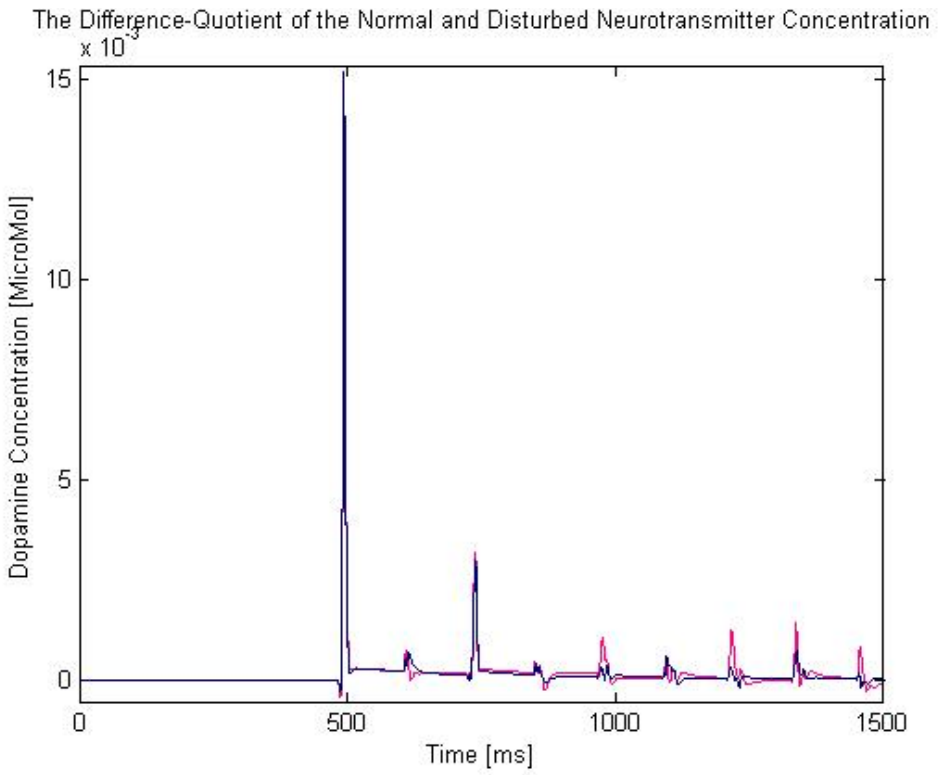

Figure 7.2: The difference of the normal and disturbed (blue: weak perturbation parameter $\kappa^1_{th} = 0.4$; red: strong perturbation $\kappa^1_{th} = 0.9$) dopamine-concentration trajectories of the substantia nigra. It appears that the dopaminergic system is stable under perturbations in the synthesis of glutamate in thalamus. The alteration in the dynamical behaviour of the system tends to zero for $t \to \infty$.

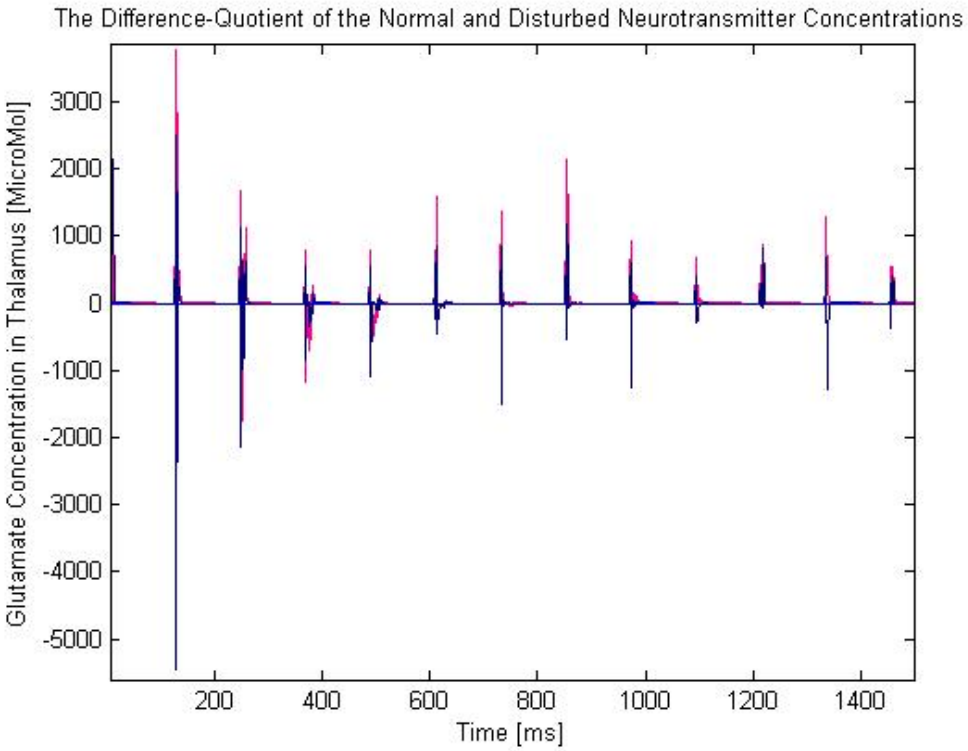

Figure 7.3: The difference of the normal and disturbed (blue: weak perturbation parameter $\kappa_{th}^1 = 0.4$; red: strong perturbation $\kappa_{th}^1 = 0.9$) glutamate-concentration trajectories of the thalamus. The glutamatergic system reveal strong sensitivity to synthesis-inhibitor parameters. Nevertheless, it is considerable that the system is structurally stable. The amplitudes of the oscillation of the difference function oscillate to zero for $t \to \infty$ (damped oscillation).

Part III

Numerical Simulations

Chapter Eight

Synaptic Processes

We have developed two mathematical models to simulate the dynamical behaviour of neurotransmitter concentrations in the synaptic cleft. Because of the experimental difficulties to observe this behaviour, such models reveal physiological and pharmacologically important information on this subject. In this chapter, we will use the finite element library Gascoigne by Prof. Dr. R. Becker and Prof. Dr. M. Braack (http://www.gascoigne.de/) to simulate the first model. The simulation toolkit Gascoigne is developed for incompressible, compressible, non-reacting and reacting flows in two and three dimensions. It combines error control, adaptive mesh refinement and a fast solution algorithm based on multigrid methods. The discretization of the underlying partial differential equations is done by stabilized finite elements on locally refined meshes.

The second model was a modified version of Poisson-Nernst-Planck equations with Dirichlet boundary conditions. For known external fields and some assumptions for the boundaries, we used the work of Gajewski (Gajewski, 1985) on the existence and uniqueness of the solution. We focus here only on the numerical simulation of the first model. This model is quit similar to the modified Poisson-Nernst-Planck equations and will be simulated using the method of vanishing viscosities. Because of the importance of the extrasynaptic neurotransmitter concentration for the validation of our model, as a result of the potential decline at side-boundaries, we will give a short discussion on the estimation of its value by our model at the end of this chapter.

8.1 Intrasynaptic Concentrations of Neurotransmitters

Resuming the main facts on our model, it is a coupled system of partial differential equations with Dirichlet boundary condition and given initial values. We use the method of vanishing viscosity to adapt the last equation for numerical methods used in Gascoigne:

$$\frac{\partial E}{\partial t} \;=\; \beta\, \nabla\rho \;,$$

$$\frac{\partial \rho}{\partial t} + div(-\alpha\rho \cdot E) - \epsilon\Delta\rho \;=\; f_{release}(\rho, t) - \gamma_{ex} \;,\; \epsilon \to 0 \;.$$

This allows us to use the simulation toolkit Gascoigne to simulate the model. We simplified the geometrical shape of the synaptic cleft to a rectangle with prolonged length. The release of neurotransmitters was given to be asymmetrically.

The simulations suggest that the intra-synaptic concentration of neurotransmitters is transported by the electrical field inside the synaptic cleft, from the pre- to the post-synaptic membrane. After arriving on the post-synaptic membrane, the polarity of the electrical field changes that forces the neurotransmitters to be back-transported (re-uptake) to the pre-synaptic membrane (figure 8.1). This behaviour is physiologically expected. It is also observable that an amount of the neurotransmitter concentration tends to the side-boundaries (diffusion to the extra-synaptic space), which will explain the observation a fractional amount of the released neurotransmitters in the extra-synaptic space.

This simulated concentration of neurotransmitters can directly be embedded into the modified Hodgkin-Huxley equations to produce a realistic effect of the neurotransmitters on the electrophysiological system. It is also very useful for the optimization of anti-psychotic drug-dosage.

Result: The mathematical model for intra-synaptic concentrations reveals an expected behaviour. The electrical field and the concentration gradient interact. There exists a fractional amount of neurotransmitters that diffuse out to extra-synaptic space.

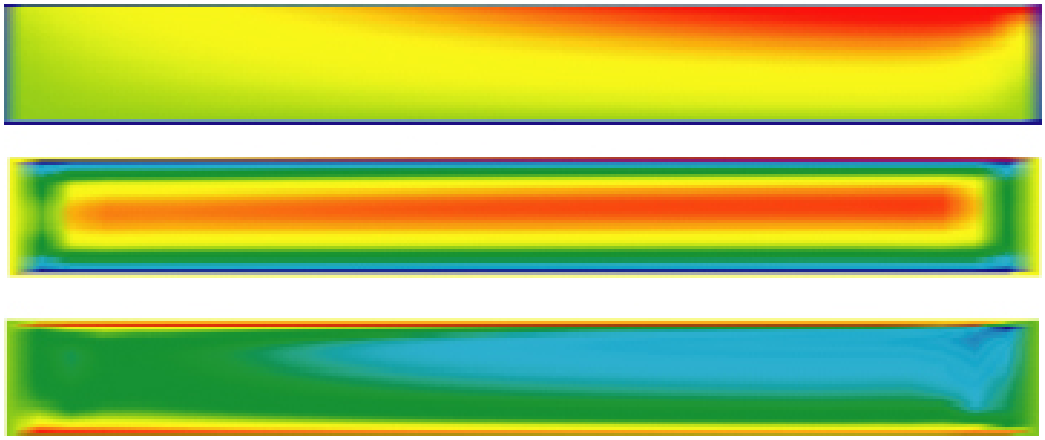

Figure 8.1: The intra-synaptic concentration of neurotransmitters in three time steps. 1) The neurotransmitters are released asymmetrically from the pre-synaptic membrane into the synaptic cleft. 2) The neurotransmitter concentration is transported by the existing electrical field inside the membrane to the post-synaptic membrane. 3) The neurotransmitter concentration gradient at the post-synaptic membrane side changes the polarity of the intra-synaptic electrical field followed by the activation of transporter molecules on the pre-synaptic membranes, which forces the re-uptake of neurotransmitters.

8.2 Estimations of Extrasynaptic Neurotransmitter Concentration Values

As we have seen, a certain amount of neurotransmitters diffuses to the extra-synaptic space during the synaptic processes. The extra-synaptic concentration of neurotransmitters is experimentally observable by micro-dialysis and voltammetry studies. By understanding the fractional level of extra-synaptic diffusion in relation to the released concentration, we can estimate an average realistic value for intra-synaptic neurotransmitter concentrations by parameter estimation methods. This knowledge is helpful for the quantitative analysis of the effectivity of the neurotransmitter synthesis-inhibitors which happens to be of therapeutic importance in schizophrenia.

Remark: For a realistic validation with observed extra-synaptic concentrations further modelling steps are required. The existence of several neighboring synapses, and the complex topology of the brain reveal some problems that are not discussed here.

Chapter Nine

Examples for the Single Compartment Model

The aim of this chapter is to numerically investigate the behaviour of a compartment by known dynamics of single neurons. We just represent our method through two examples: the corpus striatum and the subthalamic nucleus. First, we remind on the main morphological and ultrastructural properties of the compartments, namely the spatial distribution of the different neural populations, the neurochemical classification and the interconnection between the neurons. Second, the simulation results will be discussed and compared with the experiments. It reveals that both examples show oscillatory dynamics which was expected.

9.1 The Corpus Striatum

The neuronal populations of the striatum could be divided into four classes: Spiny projection neurons (about 96% of the whole neural population) are GABAergic neurons, which get external inputs from cortical areas and substantia nigra pars compacta. These neurons also get inputs from the dopaminergic, GABAergic and acetylcholinergic interneurons. Large aspiny neurons (cholinergic), GABAergic interneurons and dopaminergic neruons comprise the rest population of straital neurons. The cholinergic interneurons get external inputs from thalamus and substantia nigra pars compacta; and internal inputs from the GABAergic interneurons. They project to the dopaminergic and projection neurons. The action of the cholinergic interneurons antipodal to the action of the dopaminergic neurons. The cholinergic neurons inhibit the activity of the projection neurons of the direct pathway (mostly D_1 system) and disinhibit the activity of the indirect pathway neurons (D_2 system).

The interactions between the different neural populations is much precisely represented in the figure 9.1.

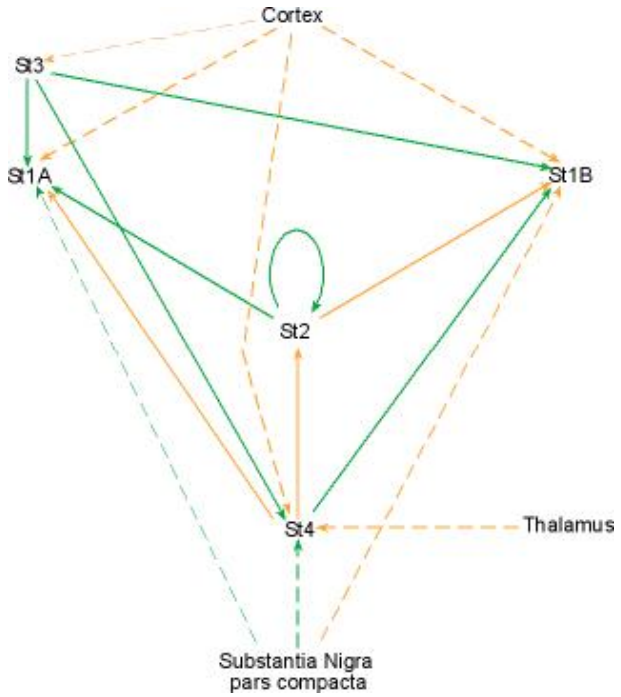

Figure 9.1: Schematic ultra-structural morphology of the primate's striatum, including the neurochemical synaptology. The green/orange arrows denote inhibitory/excitatory afferents. The dashed arrows are external efferents to the striatal neurons. Hereby, St_{1A} and St_{1B} denote the spiny projection neurons which project to GPe and GPi/SNr. St_2 denotes the dopaminergic interneurons, St_3 the GABAergic interneurons, and St_4 the acetylcholinergic neurons.

Considering the structure of figure 9.1 as the internal structure of the n-cells which we introduced in the last chapter and the specific distribution of neural population, we are able to simulate the propagation and summation of the electrophysiological activity in the striatum based on the activation of a single neuron. The special network structure of the n-cells suggests a specific activity transmission. It reveals that the activity transmission induced by a constantly activated neurons is approximately radial and oscillatory. The constant activity of a single neuron produces activation-waves on the striatal populations (figure 9.2).

Such neurons are simplified versions of the tonic activated cholinergic interneurons. Activations of neurons of other classes suggest similar activation waves along the striatal populations. We assume that these oscillations are correlated with the LFP studies of basal ganglia which also suggest oscillations in control patients (Boraud et al. 2005).

9.2 The Subthalamic Nucleus

Based on cellular and dendritic morphology neurons in the subthalamic nucleus appear to be of one main type, which nonetheless show a variance in the dimension of the cell soma and dendritic ramifications (Kita et al. 1993; Yelnik and Percheron 1979). In rats, the cell somata are ovoid or polygonal with a medium size ranging $11 - 18\mu m$ in diameter. Most subthalamic neurons extend $3 - 4$ primary dendrites which taper and branch into secondary and tertiary dendrites. Dendrites show infrequent spines, which, if present, are located on more distal parts of the dendrites. The dendrites spread in varying patterns within the nucleus. In general, dendrites appear to distribute roughly equally in an ovoid area in both the frontal and sagittal planes, thus showing a greater extension in the rostro-caudal dimension than in the dorsal and ventral dimension. Subthalamic neurons across species appear to be similar in morphologic type, although the planar distribution patterns of the dendrites vary from species to species. This presumably reflects different geometries of the different inputs in different species (Gerfen and Wilson 1996).

Neurons in the subthalamic nucleus appear to be of one neurochemical type in that most are immunoreactive for glutamate.

Using the integral operator introduced in the last chapter, it reveals that the electrophysiological activity of a large population of neurons in subthalamic nucleus is a phasic summation of the single activations and has bursting effects (figure 9.3).

Both examples show oscillatory activity of large neural populations comprising compartments by single/multiple activation of the neurons. It is to be expected that by taking a realistic number of neurons, the results of our model directly fit the experimental results.

Result: The electrophysiological activity of the single compartments is of oscillatory nature and depends on the morphological structure of the compartments.

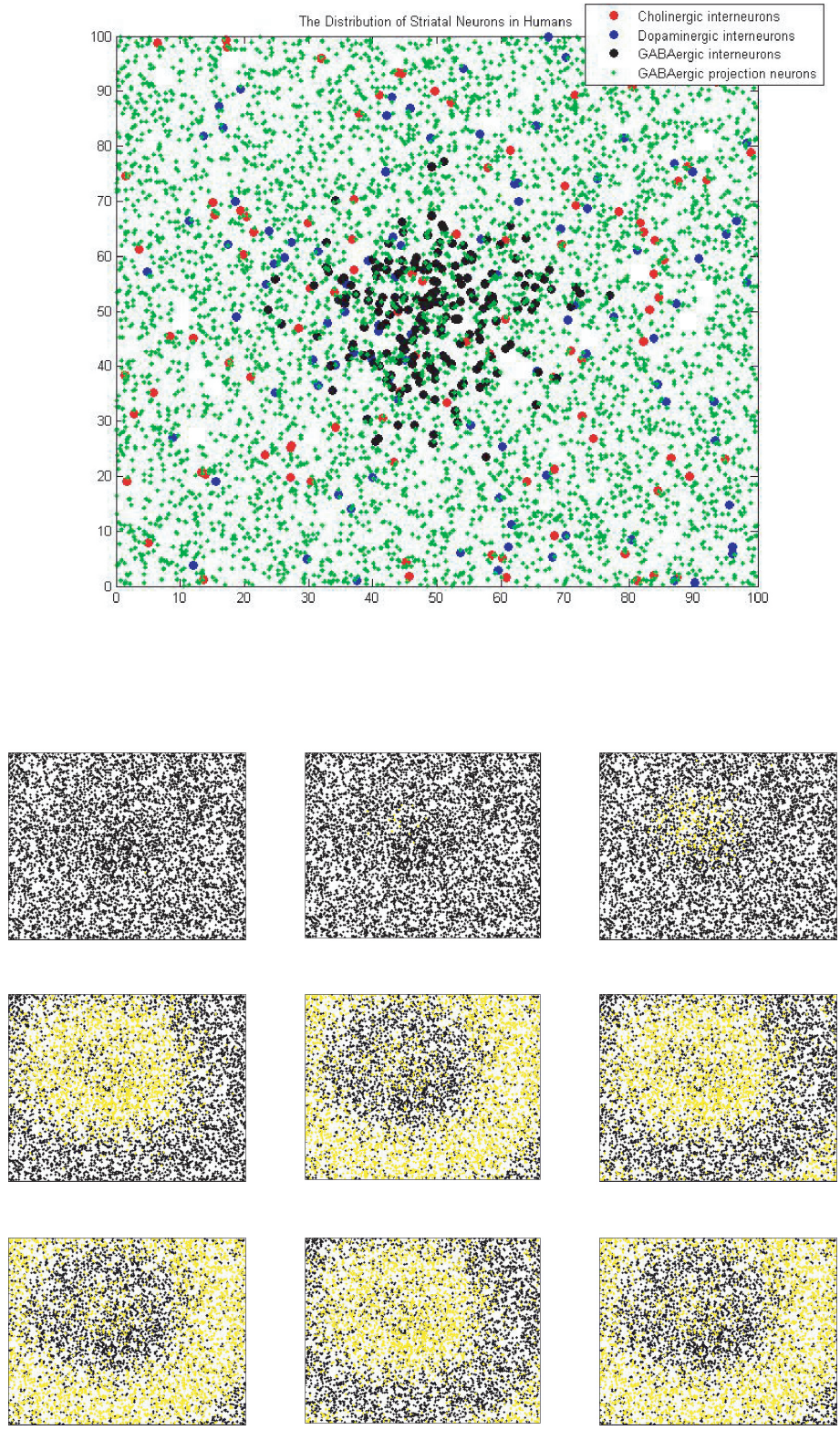

Figure 9.2: The oscillatory dynamics of the activity of striatal neurons by a single constant activation with a realistic spatial distribution of the neurons.

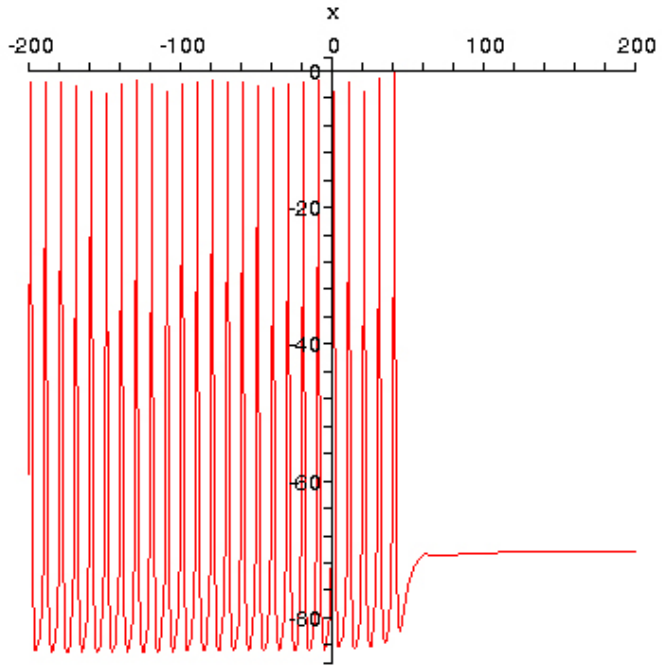

Figure 9.3: The internal electrophysiological activity of the subthalamic nucleus with respect to its morphology.

Chapter Ten

Simulations of the Multi-Compartment Systems

Following Baker and Paul (1993), we describe a Runge-Kutta method for delay differential equations of the form

$$u'(t) \;=\; F(t, u(t), u(t-\tau(t))) \;\; t \geq t_0 \;,$$

subject to the initial condition $u(t) = \psi(t)$ for $t_{min} \leq t \leq t_0$. The extension to equations with more than one delay is clear. The particular DDE method to be described can be associated with a choice of continuous Runge-Kutta triple $\{c, A, b(\theta)\}$. The method may be motivated as an adaptation of the basic Runge-Kutta method for $y'(t) = f(t, y(t))$, as follows:

The approximate solution $\tilde{u}(t)$ is sought on the interval $[t_0, T]$ through the computation of its values $\{\tilde{u}_n \equiv \tilde{u}(t_n)\}$ on the mesh $\Gamma := \{t_0, t_1, \cdots, t_N\}$ and either the internal stage-values $\{U_{ni}\}$ or the internal derivative approximations $\{U'_{ni}\}$ associated with points $\{t_{ni}\}$. Suppose that the solution has advanced to the point $t = t_n$ and, assuming that $\gamma(t_{ni}) \leq t_n$, that a continuous extension $\tilde{u}(t)$ to $u(t)$ is available for $t \in [t_0, t_n]$. Its form is supposed to be

$$\tilde{u}(t_k + \theta H_k) \;=\; \tilde{u}_k + H_k \sum_l b_l(\theta) U'_{kl} \;\; 0 \leq \theta \leq 1 \;\; (k = 0, 1, \cdots, n-1) \;.$$

Our numerical strategy for the DDE now reduces to invoking the numerical solution by a Runge-Kutta process of a related equation of the form $y'(t) = f(t, y(t))$, in which

$$f(t, y(t)) \;=\; F(t, y(t), \tilde{u}(t-\tau(t))) \;.$$

The formula motivating the method is given by $\tilde{u}_n \equiv \tilde{u}(t_n) \approx u(t_n)$ where $\tilde{u}_0 = u(t_0)$,

$$\begin{aligned} \tilde{u}_{n+1} &= \tilde{u}_n + H_n \sum_{i=1}^{\nu} b_i U'_{ni} \ , \\ U'_{ni} &= F(t_{ni}, U_{ni}, \tilde{u}(\gamma_{ni})) \ , \end{aligned}$$

with

$$U_{ni} = \tilde{u}_n + H_n \sum_{j=1}^{i-1} a_{ij} U'_{ni} \ , \ \gamma_{ni} = t_{ni} - \tau(t_{ni}) \ ,$$

where $\tilde{u}(\gamma_{ni}) = \psi(\gamma_{ni})$ if $\gamma_{ni} < t_0$, whilst

$$\tilde{u}(\gamma_{ni}) = \tilde{u}(t_j + \theta_{ni} H_j) = \tilde{u}_j + H_j \sum_k b_k(\theta_{ni}) U'_{jk}$$

in the case that $\gamma_{ni} = t_j + \theta_{ni} H_j$ for $0 \leq \theta_{ni} \leq 1$ and $j \in \{0, 1, \cdots, n\}$.

If we solve for the values $\{U'_{ni}\}$, we now have the equations

$$U'_{ni} = F(t_{ni}, \tilde{u}_n + H_n \sum_{j=1}^{i-1} a_{ij} U'_{nj}, \tilde{u}(\gamma_{ni})) \ ,$$

with the relevant expression for $\tilde{u}(\gamma_{ni})$ expressed as above. In the case that $\gamma_{ni} > t_n$, the argument in the value $\tilde{u}(\gamma_{ni})$ lies to the right of t_n, and outside of the current range of $\tilde{u}(\cdot)$. Thus, the explicit Runge-Kutta formulae become implicit equations for $\{U'_{ni}\}$. Maintaining an explicit method imposes the restriction that

$$\gamma_{ni} \leq t_n \qquad \forall i \ .$$

For the class of DDEs which we are interested in (without singularities and vanishing time-lags), a strategy to avoid the Runge-Kutta formulae becoming implicit is to reduce the stepsize H_n until the restriction on γ_{ni} is satisfied.

For the numerical investigation of our neurochemical model comprised by a system of nonlinear delay differential equations, we chose the solver ARCHI. ARCHI is an explicit Runge-Kutta code for solving delay and neutral differential equations and parameter estimation problems developed by the Manchester Centre for Computational Mathematics, which uses the described method to construct smooth solutions for systems of delay differential equations.

In the following section, we introduce the initial functions and delay parameters of our system. These values are taken by neurosurgical experiments such as microdialysis, intracellular studies on different brain compartments and estimations of the delay parameters based on the neuroanatomical facts. The last section includes all numerical results on the neurochemical dynamics obtained from our mathematical model.

10.1 Initial Functions and Delay Ranges

To simulate a system of delay differential equations, we first need to obtain the initial functions and the time-delays. For the current initial value problem, we assume that the initial functions correspond to the initial concentration values which were obtained experimentally by micro-dialysis experiments. The mentioned initial values for the neurotransmitter concentrations are estimated by extracellular neurotransmitter concentrations obtained from microdialysis experiments (Ungerstedt, 1984; Globus et al. 1988; Wassle and Chun, 1988; Sunol et al., 1988; Meyerson et al, 1990; Ronne-Engstrom, 1992; Kanthan, 1995; Hutchinson et al., 2000; Hutchinson et al., 2002).

The time-delays are mostly estimated by morphological studies on the neuronal characteristics of the brain compartments, their projections and innervations. The experimentally unknown values have been estimated by mathematical calculations based on the anatomical and morphological properties of the brain pathways. The connection delay parameters are represented in a table in this section.

10.2 Results

The neurochemical and electrophysiological systems have been simulated with and without considering time-lags. In both cases the trajectories of neurotransmitter concentrations and electrical potential differences reveal stable oscillatory pattern (figures 10.1,10.2,10.3,10.4,10.5,10.6). In the case of simulations of delay-differential equations, the initial function has been chosen to be constants the same as the initial values of the variables. These show the qualitative behaviour of the neurochemical and electrophysiological systems and the emergence oscillatory pattern.

Parameter sensibility tests (different orbital colors) suggest that the oscillatory behaviour of the orbits remains stable. Perturbations in the release parameters on the feedback loop of subthalamic nucleus (STN) and globus pallidus pars externa (GPe) show significant changes in the oscillation characteristics of basal ganglia, especially in the synchronization of the dopaminergic oscillations on the nigrostriatal feedback loop. The simulation results suggest that the interaction between different neurotransmitter systems is of great importance for the generation and characterization of the oscillatory patterns.

These oscillations are caused by the nonlinearities of the system and also the delays in signal processing and propagation. Oscillations of basal gan-

Connection	Parameter	Source
CTX-STN	$\tau = 2.5ms$	Fujimoto and Kita (1993)
CTX-St	$\tau = 10ms$	Gerfen and Wilson (1996)
CTX-Th	$\tau = 15ms$	Estimate based on the innervation distances
CTX-Amy	$\tau = 2ms$	Estimate based on the innervation distances
CTX-HC	$\tau = 1ms$	Estimate based on the innervation distances
CTX-SNc	$\tau = 12ms$	Estimate based on the innervation distances
CTX-Raphe	$\tau = 18ms$	Estimate based on the innervation distances
STN-GPe	$\tau = 2ms$	Kita and Kitai (1991)
STN-GPi	$\tau = 1.5ms$	Nakanishi et al. (1987)
St-Th	$\tau = 4ms$	Estimate based on the innervation distances
St-Amy	$\tau = 8ms$	Estimate based on the innervation distances
St-GPe	$\tau = 5ms$	Kita and Kitai (1991)
St-SNc	$\tau = 6ms$	Estimate based on the innervation distances
St-GPi	$\tau = 4ms$	Nakanishi et al. (1987)
Th-Amy	$\tau = 10ms$	Estimate based on the innervation distances
Th-SNc	$\tau = 3ms$	Estimate based on the innervation distances
Th-Raphe	$\tau = 5ms$	Estimate based on the innervation distances
Th-HT	$\tau = 1.5ms$	Estimate based on the innervation distances
Th-GPi	$\tau = 4ms$	Estimate based on the innervation distances
Th-Cb	$\tau = 20ms$	Estimate based on the innervation distances
Amy-HC	$\tau = 1ms$	Estimate based on the innervation distances
Amy-SNc	$\tau = 6ms$	Estimate based on the innervation distances
Amy-Raphe	$\tau = 12ms$	Estimate based on the innervation distances
Amy-HT	$\tau = 4ms$	Estimate based on the innervation distances
HC-HT	$\tau = 5ms$	Estimate based on the innervation distances
SNc-Raphe	$\tau = 3ms$	Estimate based on the innervation distances
SNc-HT	$\tau = 6ms$	Estimate based on the innervation distances
SNc-GPi	$\tau = 5ms$	Estimate based on the innervation distances
Cb-HT	$\tau = 18ms$	Estimate based on the innervation distances

Table 10.1: Connection delay parameters

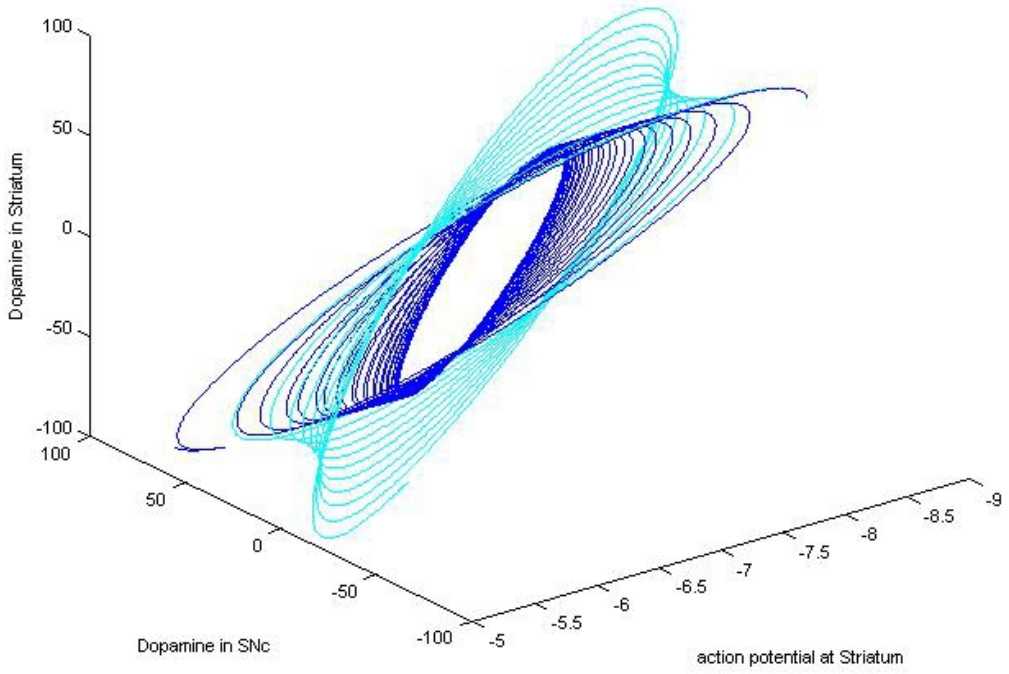

Figure 10.1: The nigrostriatal dopamine concentrations in relation to the electrophysiological activity of striatum; Different colors reveal perturbation in neurotransmitter release parameters.

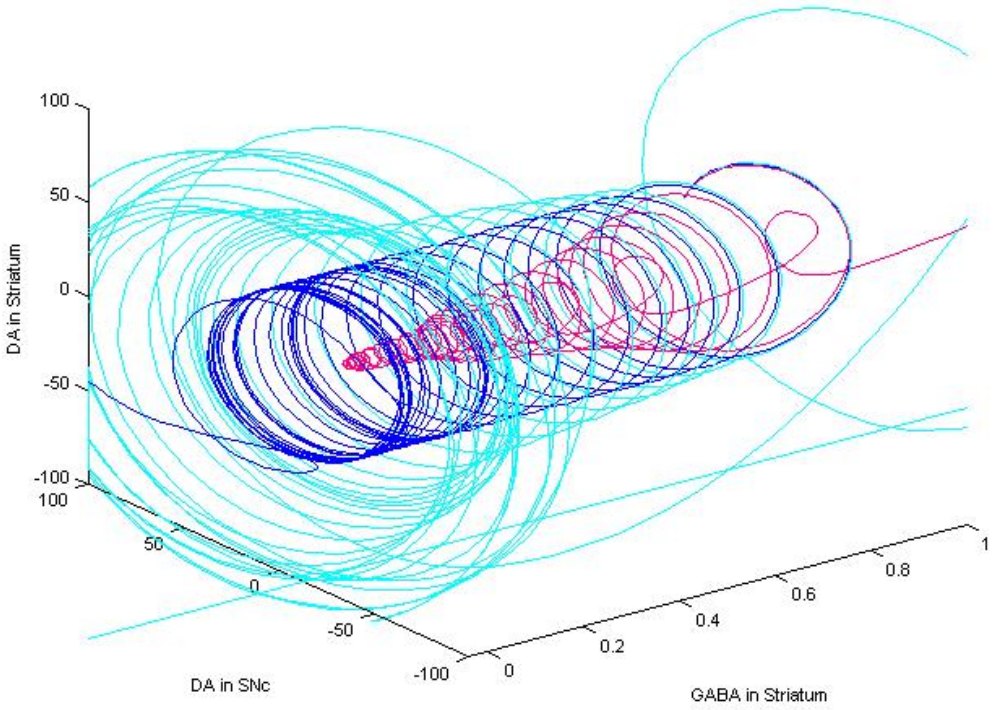

Figure 10.2: The nigrostriatal dopamine concentrations in relation to the GABA concentration in striatum; Different colors reveal perturbation in neurotransmitter release parameters; Three cases of dynamical pattern emerge: A) stable cylindrical trajectories [dark blue], B) Damping trajectories [pink], C) unstable trajectories [cyan]. The cases A and B show reversal behaviour after small parameter perturbations.

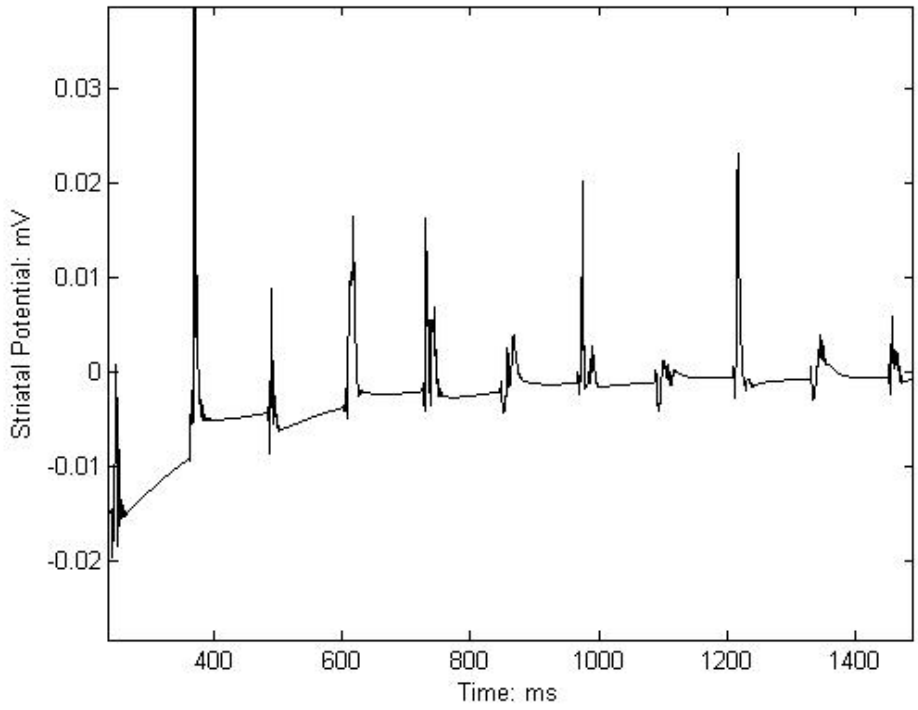

Figure 10.3: The electrophysiological activity of corpus striatum [Simulation with time-lags].

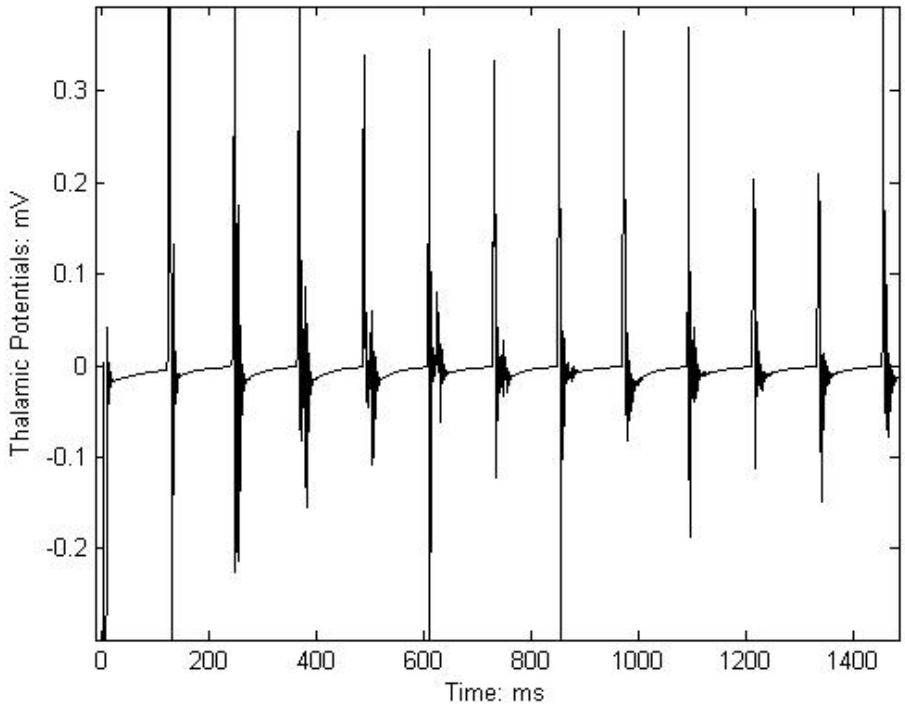

Figure 10.4: Synchronized electrophysiological oscillations in thalamus [Simulation with time-lags].

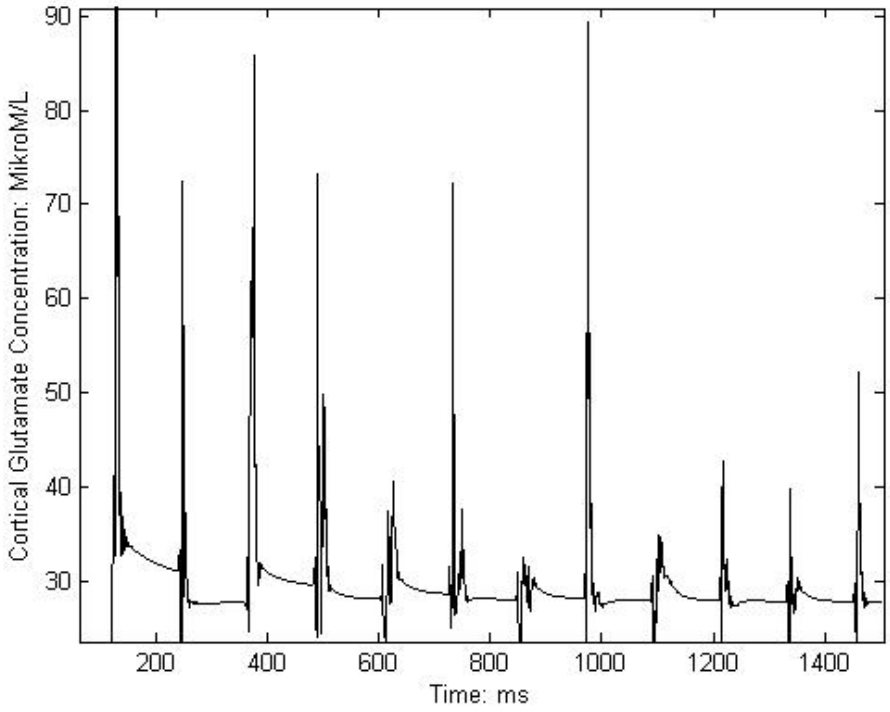

Figure 10.5: The oscillatory pattern of the cortical glutamate concentration [Simulation with time-lags].

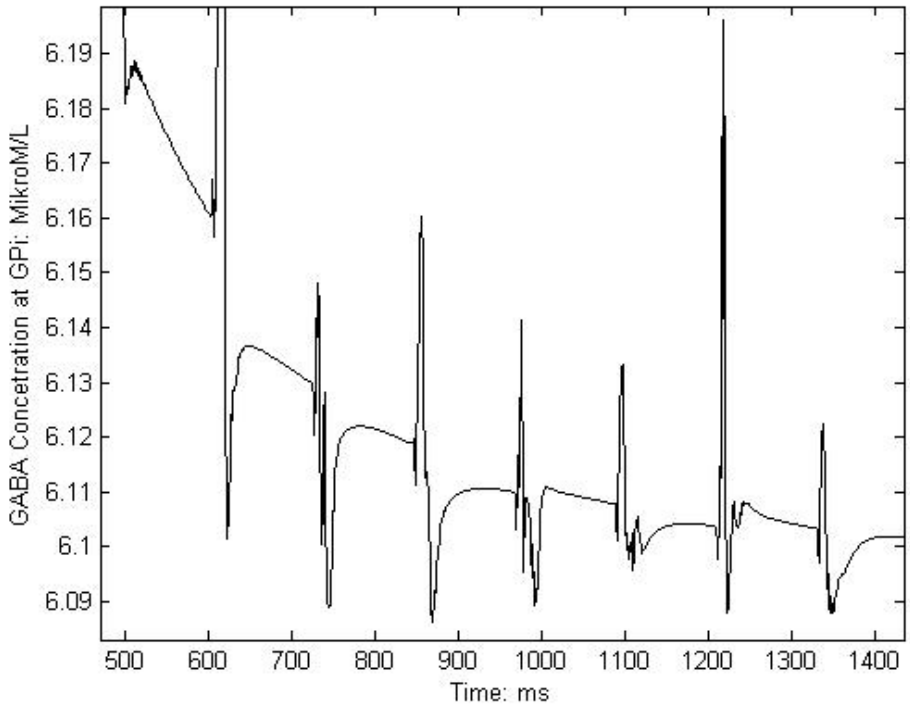

Figure 10.6: The GABA concentration in Globus pallidus pars externa [Simulation with time-lags].

glia's electrophysiological system are also observed in LFP (local field potentials) studies in control patients and also in animals (Cassim et al. 2002 Magill et al. 2004; Boraud et al., 2005).

The qualitative behaviour of the solutions of the system depends strongly on the dynamics of each neurotransmitter system. The interactions amongst the neurotransmitter systems are also studied experimentally (Konradi et al. 2002; Chesselet, 2002). Beside the strong neurochemical sensibility, the system is able to reverse to its original stable states after small dynamical disturbances. This fact suggest an interpretation in the sense of circular and temporal emergence of illness symptoms.

Thalamus as a part of the network is also able to control the interval of oscillation-phases, -frequencies and -amplitudes of its efferent. Changes in the oscillatory behaviour of basal ganglia, a clustered part of this network, influence the scale of control-limits of thalamic efferent. In this sense, one can talk about a thalamic filter (Carlsson et al. 1999) and consider basal ganglia as the calibrator of this filter.

The reaction of the system on neuroleptics-like parameters has been numerically investigated. By singular application of pure dopamine antagonists in striatal D_2-receptor, it reveals that a short-time change in the oscillation characteristic emerges (figure 13.5). This behaviour suggests that changes in the dynamical pattern of neurochemical systems in basal ganglia, especially in the nigrostriatal system, are related with mental states.

Resume: The neurochemical concentrations reveal oscillatory dynamics. This dynamical behaviour is correlated to the local electrophysiological activity of the compartments. The drug-parameters change the activity pattern, in terms of phase and level of the oscillation, for a short time-period that is also clinically observable in the same way.

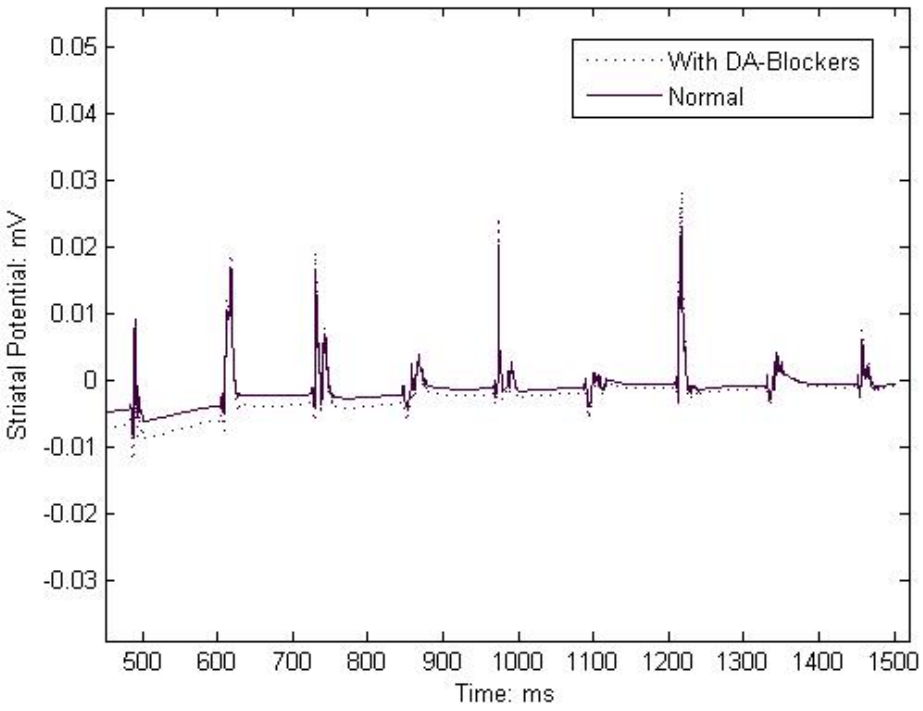

Figure 10.7: The short-time change in the oscillatory pattern of electrophysiological activity of striatum after a singular indication of dopamine D_2-antagnoists [Simulation with time-lags].

Part IV

Physiological Discussion

Chapter Eleven

Oscillatory Dynamics and the Physiology of Behaviour

This chapter is supposed to represent the connection between the results of our mathematical model and the observable physiological processes behind psychotic states. Based on the well-known anatomical facts and the consequences of the oscillatory dynamics of neurotransmitter concentrations, we recognized special pathways as to be fundamental for the generation of mental behaviour. These hypotheses are also supported by our investigations on the influence of drug-parameters on the system. The results of these investigations suggest also a correlation between the characteristics of the physiological oscillations and the neurochemical states of the system, which are in the own right directly correlated to mental states. These correlations led us to the idea of the "Oscillation Hypothesis of Schizophrenia" which will be introduced in detail.

11.1 Functional Anatomy of Schizophrenia

Several pharmacological and neurophysiological studies (Bhatia and Marsden 1994; Carlson 1980; Carlsson 1988; Carlsson 1995; Dean and Hussain 2001; Glenthoj and Hemingson 1999; Grunder et al. 2006; Heinz 2000; Hirvonen et al. 2006; Hollerman et al. 2000; Levy and Dubois 2006; Mehler-Wex et al. 2006; Middleton and Strick 2000; Ono et al. 2000; Saint-Ogr et al. 1995; Schmitt et al. 2005; Sedvall 1990; Stathis et al. 2007; Talvik et al. 2006; Wilson 2004) assign basal ganglia an important role in the physiology of schizophrenia. The high density of dopamine receptors in the striatum, the interactions between dopaminergic system with other neurotransmitter

systems, and the sensitive reaction of mental state as a consequence of alterations in dopaminergic activities are the foundations of the above correlation between basal ganglia' physiology and schizophrenia.

There are also strong evidences for the influence of the glutamatergic system and its interactions with dopaminergic system on the mental states (Carlsson and Carlsson 1990; Javitt 2007; Moghaddam and Krystal 2003; Larnelle et al. 2003; Stone et al. 2007; Wu et al. 2003). These hypotheses are not in contradiction to the correlation between the basal ganglia and schizophrenia. The cortical glutamatergic projections to the basal nuclei represent the majority of the external inputs into the basal ganglia structures which correlate the glutamatergic activities with these subcortical structure in support to the above correlation.

The clinical relevance of the basal ganglia circuits depends directly on the balance between different neurotransmitter systems. Beside basal ganglia, the influence of the limbic system is also of interest in the physiological investigation of the schizophrenia. The fact that other neurotransmitter system than dopaminergic and glutamatergic systems such as $5-HT$-system in nucleus Raphe led to the inclusion of a couple of new compartments into the area of investigation. Our graph-theoretical analysis suggests that the resulting network, the LBG-network, is represented by a set of compartments containing dopamine, glutamate and GABA. These compartments (cortex, substantia nigra pars compacta, subthalamic nucleus, thalamus, amygdala and hippocampus) suppose to generate the dynamical patterns of the mammalian brain and are independent. Numerical simulations also suggest that the reciprocal influence of the limbic and basal ganglia structures is not negligible. Thus, we suggest the LBG-network to be correlated more than any of its substructures (the basal ganglia and the limbic system) to the schizophrenia.

Concluding, the graph-theoretical analysis, the numerical simulations and the well-known physiological aspects of the schizophrenia suggest that

- The synaptic behaviour of the neurotransmitter in the sense of their inhibitory/excitatory effects on the synaptic membranes differs in general from their influence in the network-scale on regional activities[1].

- The neurochemical system of the human brain reveals oscillatory behaviour which depends on the physiological state of the system (i.e. the oscillations change their properties in the case of disease and lesions), but it remains also in the healthy brains.

[1]This is also correlated with the results Wu et al. 2000, on the inhibitory glutamate regulation of evoked DA-release in striatum.

- Small perturbations in the neurochemical dynamics instabilize the orbits which have the dynamical property to revert back to its initial stable moods or to jump to other stable moods. These properties are associated with the real act of information processing in the human brain. Roughly spoken, a man needs time to get on with a problem or the problem changes his mood irrecoverable but not irreversible. This also suggest an interpretation in the sense of circular and temporal emergence of illness symptoms.

- There are certain brain compartments which mainly produce the dynamical behaviour of the brain. These are: the cortex, the substantia nigra pars compacta, the subthalamic nucleus, the thalamus, the amygdala and the hippocampus. Thalamus as a generator, is a relay-filter for cortical afferents to protect the cerebral cortex from signal overload and to control the interval of oscillation-phases, -frequencies and -amplitudes of its efferents. Other generators determine the oscillation characteristics which are correlated to mental states.

- Because of the strong reciprocal influence of the limbic and the basal ganglia structures, it is assumable that the LBG-network correlates more intensive with schizophrenia than its substructures.

11.2 Oscillation Hypothesis of Schizophrenia

The foundation of the 'Oscillation Hypothesis' of psychosis is the oscillatory nature of neurotransmitter dynamics. We have analyzed numerically the influence of typical anti-psychotic drugs on the system. It appears that the exhibition of these family of D_2-antagonists changes the oscillation characteristics for a certain time interval but the states then reverse back to its original oscillation state. These parameter test have been done without considering any anomalies in the LBG-network. This situation happens to be phenomenologically similar to the real case of the action of typical anti-psychotic drugs on schizophrenic patients.

By singular application of pure dopamine antagonists in striatal D_2-receptor, it reveals that a short-time change in the phase of the oscillations emerges. The phasic changes are not restricted to the dopaminergic system but the glutamatergic system has been also altered in a similar way.

Changes in the oscillatory behaviour of the neurochemical system caused by anti-psychotic drugs, which influence the psycho-behaviour, reveal a phys-

iological relationship between mental states and the neurochemical oscillations. This suggests that mental disorders (e.g. schizophrenia) (-as well as neurological diseases (e.g. Chorea Huntington)), could be caused by anomalies in the phases of the neurochemical oscillations. It establishes a direct correspondence of oscillation-characteristics with mental states. In this case, the symptoms of mental disorders due to temporal changes of phases and amplitudes of basal ganglia's neurochemical oscillations. Considering the mental states as classes of quasi-stable states and the fact that changes of sensibility and precision of thalamic filtration induce state transitions, then the symptoms are evidenced with certain disturbances in neurotransmitter systems which force the whole system to jump from its initial state to other stable states or snatch its ability to revert back rapidly to the initial state.

Since, the psychotic symptoms are produced internally by the brain, so one can consider them as signals with abnormal oscillatory behaviour which are usually filtered by thalamus. These series of correlations between abnormal oscillatory behaviour and the temporal mental state, led to the "Oscillation Hypothesis of Schizophrenia":

Any mental state is associated to a characteristic neurochemical oscillation in the brain.

Chapter Twelve

Pharmacological and Mathematical Perspectives

The correlation between mental states and oscillation characteristics of neurochemical dynamics reveals new perspectives in the design of effective anti-psychotic drugs. Computational investigations of the combinatorial influence of drug-parameters on the dynamical behaviour of the system suggest new purchases for the pharmacological combination-therapy strategies in the treatment of schizophrenia. Here, we discuss the impact of this method by clinically interpreting the computational results on the dopamine's synthesis-inhibition. The qualitative effects of the synthesis-parameters on the dynamics of the neurochemical system led us to the idea that the combination of synthesis inhibitors and partial antagonists will produce the optimized effect on the mental appearance.

12.1 On the Role of Synthesis-Inhibitors

Beside the computed effects of typical anti-psychotic drugs on the neurochemical oscillations which led us to the formulation of the oscillation hypothesis of schizophrenia, we also numerically investigated the influence of neurotransmitter synthesis-rate parameters and their perturbations on the dynamics of our system. The dopamine synthesis has been studied in more detail. The results were very fascinating and valuable.

It appears that the dopamine synthesis-inhibitors are able to fundamentally change the oscillation characteristics of the whole neurochemical system, but especillay the dopaminergic system of the nigrostriatal complex. The synthesis-inhibitors decrease significantly the level of dopaminergic oscillations and alter their amplitudes. These effects are of long durance.

As a consequence of the oscillation hypothesis, there is a relationship between these alterations and mental states. This fact is also supported by recent pharmacological experiments (Huttunen et al. 2007; Fohey et al. 2007; Stone et al. 2007). Changes in the dopamine level for a long time interval and in the oscillation amplitudes suggest that dopamine synthesis-inhibitors should be considered as powerful and effective therapeutics in the treatment of schizophrenia.

The effects produced by perturbations in the synthesis behaviour of other neurotransmitter systems are also very interesting. The absence of experimental references on the possible relevance of the non-dopaminergic synthesis factors in the pharmacology of schizophrenia withdraws us the physiological interpretation on the computed results on the dynamical influence of these factors on the system.

12.2 Mathematical Perspectives

There are some mathematical problems revealed here which explode the framework of this thesis. Although, these problems are of great interest for further investigations. The following items list these crucial problems:

- The transition between different scale has to be further investigated.
- Understanding the correspondence between the structural and algebraic properties of a graph and the dynamical behaviour on it.
- Analysis of the existence, uniqueness and stability behaviour of the solutions for transcendent delay differential equations with multiple delays such as the multi-compartment model introduced in 6.3.
- Development and implementation of better (more accurate and effective) simulation tools and solvers than ARCHI by multi-step methods. (ARCHI is a Runge-Kutta based solver)
- Study the delay induced dynamics in more general situations as discussed here.

Part V

Supplement

Chapter Thirteen

Neurobiological Supplement

13.1 Neurotransmitters and Neuromodulators

The molecular spectrum of neuroactive substances ranges from ordinary intermediates of amino acid metabolism, like glutamate and GABA, to highly effective peptides, proteohormones and corticoids. Neurotransmitters are the most common class of chemical messengers in the nervous system. A neuroactive substance which fulfills the following criteria can be classified as Neurotransmitters (von Bohlen und Hallbach and Dermietzel 2006):

- It must be of neural origin and accumulate in the pre-synaptic terminals, from where it is released upon depolarization;
- The released neurotransmitters must induce post-synaptic effects upon its target cells, which are mediated by neurotransmitter-specific receptors;
- The substance must be metabolically inactivated or cleared from the synaptic cleft by re-uptake mechanisms;
- Experimental application of the substance to nervous tissue must produce effects comparable to those induced by naturally occurring neurotransmitter.

The neurotransmitters are synthesized in the cytosol of the pre-synaptic cells and are active transported into vesicles. There are three main categories of neurotransmitters in the central nervous system: acetylcholine, amino acids and decarboxilated amino acids (catecholamines, serotonin, histamine and GABA).

Acetylcholine [[2-(acetyloxy)ethyl]trimethylammonium]: Acetylcholine (ACh) was the first neurotransmitter discovered. It plays a significant role in synaptic transmission in the central and peripheral nervous system. Ach is a simple molecule synthesized from choline and acetyl-CoA through the action of choline acetyltransferase. Neurons that synthesize and release ACh are termed cholinergic neurons. ACh receptors are ligand-gated cation channels composed of four different polypeptide subunits arranged in the form [(a2)(b)(g)(d)]. Two main classes of ACh receptors have been identified on the basis of their responsiveness to the toadstool alkaloid, muscarine, and to nicotine, respectively: the muscarinic receptors and the nicotinic receptors (Dale-classification). Both receptor classes are abundant in the human brain. Nicotinic receptors are further divided into those found at neuromuscular junctions and those found at neuronal synapses. The activation of ACh receptors by the binding of ACh leads to an influx of Na^+ into the cell and an efflux of K^+, resulting in a depolarization of the post-synaptic neuron and the initiation of a new action potential [1].

Amino Acids [(2S)-2-aminopentanedioic acid]: Glutamate represents a principal part of the category of amino acids. It is an excitatory neurotransmitter and has both kinds of receptors, ligand-binding receptors [AMPA / kainate] and G-protein coupled receptors [NMDA]. Glutamate neurons are particularly prominent in the cerebral cortex. They project to a variety of subcortical structures: these include the hippocampus, the basolateral complex of the amygdala, the substantia nigra, the corpus striatum, the thalamus, the red nucleus (nucleus ruber) and the pons. Various intrinsic glutamatergic pathways have been described in the hippocampus and also glutamatergic projections from hippocampal formation to the hypothalamus, the nucleus accumbens and the lateral septum.

Decarboxilated Amino Acids:

- **Dopamine** [4-(2-aminoethyl)benzene-1,2-diol]: It was thought for a long time that dopamine was simply an intermediate product in the synthesis of norepinephrine. However, it has been shown that dopamine is a prominent neurotransmitter in the brain with several potential functions and a distinct distribution. Dopamine has been found to be enriched, for example, in the substantia nigra and in the striatum, whereas norepinephrine is absent from these brain regions. The differential distribution of dopamine is suggestive of a specific function for

[1] The cholinergic interneurons in corpus striatum which interact with the dopaminergic terminals from the substantia nigra are of great importance in this work.

this A)neurotransmitter in neuroregulative processes. With respect to the peripheral nervous system, dopamine has long considered to constitute the precursor of the other catecholamines. However, dopaminergic neurons were found (Bell 1989) to occur in peripheral nerves. Consequently, dopamine has also been regarded as a transmitter in peripheral nervous tissues.

Dopamine, like other neurotransmitters, is not capable of crossing the blood-brain barrier. However, the precursors of dopamine, phenylalanine and tyrosine are able to cross it. The biosynthesis of dopamine takes place within nerve terminals. Dopamine is synthesized by hydroxylation of tyrosine to DOPA and the decarboxylation of DOPA to dopamine.

Most dopaminergic receptors are located post-synaptically, but some are located pre-synaptically in the substantia nigra (pars compacta), the hypothalamus, the corpus striatum and the structures of the limbic system. Stimulation of the pre-synaptic dopaminergic receptors results in activation or inhibition of the release and synthesis of dopamine (autoreceptors). The autoreceptors are found at nerve terminals, as well as on the soma and on the dendrites of most dopaminergic neurons. Stimulation of autoreceptors located at the nerve terminals results in an inhibition of dopamine release and synthesis, whereas stimulation of somatodendritic autoreceptors decreases the firing rate of the dopaminergic neurons. In general, autoreceptors regulate the release and synthesis dynamics of dopamine.

The dopaminergic receptors are divided into the D1 and D2 groups. The D1 group consists of D1 and D5 receptors, which are positively linked to adenylate cyclase. The D2 group consists of D2, D3 and D4 receptors and each of these receptor types exists in different isoforms. The dopaminergic autoreceptors belong to the family of D2 receptors.

From a clinical point of view, dopamine attracted considerable interest since it became evident that this monoamine is involved in several major brain disorders, like Parkinsonism and Schizophrenia.

- **Serotonin** [5-Hydroxytryptamine]: The name serotonin is an acronym composed of serum and tonus because of its vasotonic properties. Serotonin is a monoamine, with similar functional features as D-lysergic acid diethylamide (LSD, a prominent hallucinogenic drug), mainly located in the nucleus raphe with diffuse innervations. A relatively high density of serotonergic projections occurs in the cerebral cortex, the hippocampus, the amygdala, the basal ganglia, the lateral geniculate nucleus, the

suprachiasmatic nucleus, the tectum opticum, the substantia gelatinosa and in the ventral horn of the spinal cord.

Neurons provide the only source for serotonin in the central nervous system. The precursor of serotonin is the essential amino acid tryptophan and the availability of tryptophan represents the rate-limiting factor in the synthesis of serotonin.

The largest group of serotonin receptors belongs to the superfamily of G protein-coupled receptors. To date, seven subtypes of 5-HT receptors have been distinguished ($5-HT_1$ to $5-HT_7$) on the basis of cloning data. A further subdivision of the seven subclasses has been achieved by classifying them on the basis of their structural and pharmacological properties.

- **Histamine** [4-(2-aminoethyl)-1,3-diazole]: The principal storage sites of histamine are basophilic leucocytes and mast cells, which release histamine as part of their reaction to allergens. Other sources include the epidermis, the intestinal mucosa and the central nervous system. Histaminergic neurons are predominantly located in the tuberal area of the posterior hypothalamus (tuberomammillary nucleus). From this nucleus, the histaminergic neurons project diffusely into several brain areas; and their axonal collaterals give rise to projections, for example to the forebrain, the cerebellum and the mesencephalon. A dense histaminergic innervation is also obvious in thalamic areas as well as in the nucleus accumbens. Histaminergic projections have been found also in the cerebral cortex and in the hippocampus. Three different receptor subtypes, termed H_1, H_2 and H_3, bind histamine specifically. The three receptor subtypes can be distinguished by their different binding patterns and different biological effects.

- **γ-Amino Butyric Acid (GABA)**: Several amino acids have distinct excitatory or inhibitory effects upon the nervous system. The amino acid derivative, γ-aminobutyrate, also called 4-aminobutyrate, (GABA) is a well-known inhibitor of pre-synaptic transmission in the central nervous system, and also in the retina. The formation of GABA occurs by the decarboxylation of glutamate catalyzed by glutamate decarboxylase (GAD). GAD is present in many nerve endings of the brain as well as in the β-cells of the pancreas. Neurons that secrete GABA are termed GABAergic. GABA exerts its effects by binding to two distinct receptors, $GABA_A$ and $GABA_B$. The $GABA_A$ receptors form a Cl^--channel. The binding of GABA to $GABA_A$ receptors increases the Cl^--conductance of pre-synaptic neurons. The anxiolytic

drugs of the benzodiazepine family exert their soothing effects by potentiating the responses of $GABA_A$ receptors to GABA binding. The $GABA_B$ receptors are coupled to an intracellular G-protein and act by increasing conductance of an associated K^+-channel. In several places, GABAergic cells occur at high densities. A prominent example is the corpus striatum, where nearly 96% of the cell somata are GABAergic. Additional brain areas, identified as exhibiting GABAergic cells in large amounts and densities are the globus pallidus, the substantia nigra (pars reticularis) and the cerebellum. GABAergic interneurons are most frequent in the thalamus, the hippocampus and in the cerebral cortex.

In contrast to neurotransmitters, neuromodulators can be divided into several subclasses. The largest subclass is composed of neuropeptides. Additional neuromodulators are provided by some neurobiologically active gaseous substances and some derivatives of fatty acid metabolism. The main differences between neurotransmitters and neuromodulators are in their size and duration of post-synaptic activity.

13.2 Ionic Channels and the Generation of Action Potentials

Neuronal signalling depends on rapid changes in the electrical potential difference across nerve cell membranes. During an action potential the membrane potential changes quickly, up to 500 V/s. These rapid changes in potential are made possible by ion channels, a class of integral proteins that traverse the cell membrane. These channels have three important properties: first, they conduct ions, second, they recognize and select among specific ions, and third, they open and close in response to specific electrical (Voltage-gated), mechanical (pressure or stretch) and chemical (transmitter-gated) signals. The idea of the existence of a narrow region in the channels acts like a molecular sieve led to an explanation of channel selectivity. At this selectivity filter, an ion sheds most of its waters of hydration and forms a weak chemical bond with charged or polar amino acid residues that line the walls of the channel. Since the shedding of waters of hydration is energetically unfavourable, an ion will permeate a channel only if the energy of interaction with the selectivity filter compensates for the loss of waters of hydration. Permeant ions remain bound to the selectivity filter for a short time, after which the electrochemical gradient propels the ion through the channel. This

idea was extended from the original pore theory first by Loren Mullins, and later by George Eisenman and Bertil Hille.

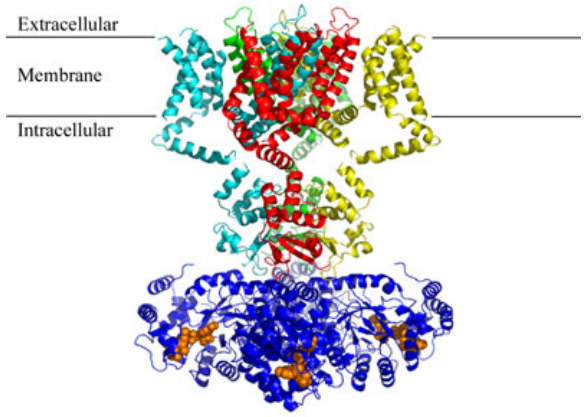

Figure 13.1: The crystal structure of the potassium-ion channel (copyright: www.nsls.bnl.gov)

The kinetics of ion flow through a channel is characterized by the size and voltage-dependence of the channels conductance. The conductance is determined by measuring the current that flows through the open channel in response to a given electrochemical driving force. The net electrochemical driving force is determined by two factors: the electrical potential difference and the concentration gradient of the permeant ions across the membrane. In some channels, the current flow through the open channel is a nonlinear function of driving force.

Each channel protein has two or more conformational states that are relatively stable. Each of these stable conformations represents a different functional state. For example, each allosteric channel has at least one open state and one close state, and may have more than one of each. The transition of a channel between closed and open states is called gating. Some ion channels are regulated by the non-covalent binding of chemical ligands. These ligands may be neurotransmitters or hormones in the extracellular environment that bind to the extracellular side of the channel, or they may be intracellular second messengers that are activated by transmitters. The second messenger may act inside of the channel either directly, by binding to the channel, or indirectly, by initiating protein phosphorylation that is mediated by enzymes, called protein kinases. This covalent modification of the channel is reversed by dephosphorylation, a reaction catalyzed by protein phosphatases. Covalent modification results in relatively long-lasting changes in the functional states of ion channels called modulatory changes. Because ion channels are

integral membrane proteins, some are subject to the influence of two other classes of allosteric regulators: the electric field across the membrane and the mechanical stretch of the membrane. Under the influence of allosteric regulators, ion channels can enter one of three functional states: closed and activatable; open; closed and non-activatable.

Another interesting subject of investigation is the physiology behind the changes in conformation of a channel after a given stimulus. For transmitter-gated channels, the change in free energy of the ligand bound to its site on the channel as compared to the ligand solution leads to channel opening. For voltage-gated channels, the opening and closing is associated with a movement of a charged region of the channel through the electric field of the membrane. Changes in the membrane voltage tend to move this charged region back and forth through the electric field, and thus drive the channel between closed and open states. For mechanically activated channels the energy associated with membrane stretch is thought to be transferred to the channel through the cytoskeleton.

Every neuron has a separation of electrical charge across of its cell membrane consisting of a thin cloud of positive and negative ions spread over the inner and outer surfaces of the membrane. A nerve cell at rest has an excess of positive charges on the outside of the membrane and an excess of negative charges on the inside. This separation of charge is maintained because the lipid bilayer acts as a barrier to the diffusion of ions. The charge separation gives rise to an electrical potential difference across the membrane. The potential difference, or voltage, is called the resting membrane potential. It is directly proportional to the charge separation across the membrane. In most neurons the resting membrane potential ranges from about 60 to 70 mV.

The term resting membrane potential applies to the potential across the membrane when the cell is at rest. The more general term membrane potential refers to the electrical potential difference across the membrane at any moment in time; at rest or during signalling. The charge separation across the membrane is disturbed whenever there is a net flux of ions into or out of the cell, thus altering the polarization of the membrane. A reduction of the charge separation is called depolarization; an increase in charge separation is called hyperpolarization. Passive depolarizing or hyperpolarizing responses of the membrane potential to current flow are called electrotonic potentials. Hyperpolarizing responses are purely passive. Small depolarisations are also passive. However, at a critical level of depolarization, called the threshold, the cell responds actively with an all-or-none action potential.

The distribution of ionic channels on the post-synaptic membrane is of great significance for the local generation of action potentials. In the case of transmitter-gated channels, the critical level of depolarization is achieved

by the superposition of excitatory and inhibitory potential waves on the membrane. The superposition of waves is depending on the localization of the initial point of generation of the potential waves and also on their relative distances.

Back to the physiology of the generation of voltage-dependent action potentials, Hodgkin and Katz proposed that the depolarization that initiates an action potential causes a transient change in the membrane that briefly switches its predominant permeability from K^+ to Na^+. These permeability changes occur because of the opening of voltage-sensitive channels in the membrane that allow Na^+ to move down its concentration gradient into the cell. These Na^+-channels are normally kept closed by a voltage-sensitive gating mechanism. Depolarization opens these Na^+-channels, allowing increased Na^+ influx into the cell, thereby producing the rising phase of the action potential. The falling phase of the action potential is caused by the subsequent closing of the Na^+-channels, which reduces Na^+ influx, and by the opening of voltage-gated K^+-channels, which allows increased K^+ efflux from the cell. According to the ionic hypothesis developed by Hodgkin and Huxley (Hodgkin and Huxley 1952), the action potential is produced by the movement of ions across the membrane through voltage-gated channels. This movement, which occurs only after the channels are opened, changes the distribution of charges on either side of the membrane. An influx of Na^+, and in some cases Ca^{2+}, reverses the resting charge distribution, after which K^+ efflux repolarizes the membrane by restoring the initial charge distribution. Most of the ion-channels are opened primarily when the membrane potential is near the action potential threshold, and thus have profound effects on the firing patterns generated by the neuron.

13.3 Anatomy of the Brain compartments

The Cerebral Cortex: The cerebral cortex is a folded sheet of cells that varies from 2 to 4 mm in thickness. The cortex that is visible on the external surface of the brain is called the neocortex because it is the part of cortex most recently acquired in evolution. The neocortex is by far the largest component of the human brain. The most striking morphological feature of the neocortex is that its neurons are arranged in several well-defined layers. The other parts of the cortex arose earlier in vertebrate evolution and are called the allocortex. The allocortex lies deep within the temporal lobe near the zone where olfactory input reaches the cerebral cortex.

The cell bodies of cortical neurons have a variety of shapes, but in general two main types can e distinguished in all areas of the cortex: pyramidal

cells and several types of non-pyramidal cells. Pyramidal cells are so called because they have a cell body shaped like a pyramid, with the apex gives rise to a dendrite that runs toward the outermost layer of the cortex, intersecting the overlying layers roughly at right angles. The base of the cell body, which may be $30\mu m$ across, gives rise to several dendrites that course laterally within the layer containing the cell body. The non-pyramidal cells usually have round, smaller cell bodies, often stellated in shape, seldom measuring more than $10\mu m$ in diameter. Their dendrites may arise from all aspects of the cell body. The axons of pyramidal and non-pyramidal cells also differ. Although the axon of a pyramidal cell may have several collateral branches that terminate near the cell body, the main trunk of the axon enters the white matter and terminates either in another area of the cortex or at a more distant site in the central nervous system. In contrast, the axon of a non-pyramidal cell branches perfusely in the region near the cell body and rarely extends beyond this region.

Because of these differences, pyramidal cells are projection neurons and non-pyramidal cells are responsible for local intern information processing. Individual layers of the cortex do not contain equal proportions of pyramidal and non-pyramidal cells, and the type of the cell that predominates in a layer provides an important clue about the function of that layer.

The neocortex is divided into six layers, numbered sequentially from the surface next to the pia matter to the white matter underlying the cortex. Layer I contains only a few neuron bodies. It is composed largely of axons that run laterally through the layer and glia cells. The axons that run through layer I synapse on the apical dendrites of cells lying in deeper layers and presumably interconnect local cortical areas. Layer II, which contains mostly small pyramidal neurons, and Layer III, which contains larger pyramidal cells, provide much of the output to the other cortical regions. Layer IV is rich in non-pyramidal cells and receives most the afferent input from the thalamus. Layer V has the largest pyramidal cells; these cells give rise to long axons that leave cortex and descend to the basal ganglia (corticostriatal projection neurons), the brain stem, and the spinal cord. Layer VI also contains pyramidal cells, many of which project back to the thalamus. Neurons of Layers IV and VI build the thalamocortical feedback loop.

The characteristic pattern of layering in different cortical areas was clearly shown by K. Brodmann (Brodmann 1907), who examined the organization of the cells and fibers in the cortex. He divided the human cerebral cortex into about 50 cytoarchitectural areas according to cell size, cell density, the number of layers in each region, and the density of myelinated axons. He assigned a number to each structural area, most of which have discrete functions (figure 13.2).

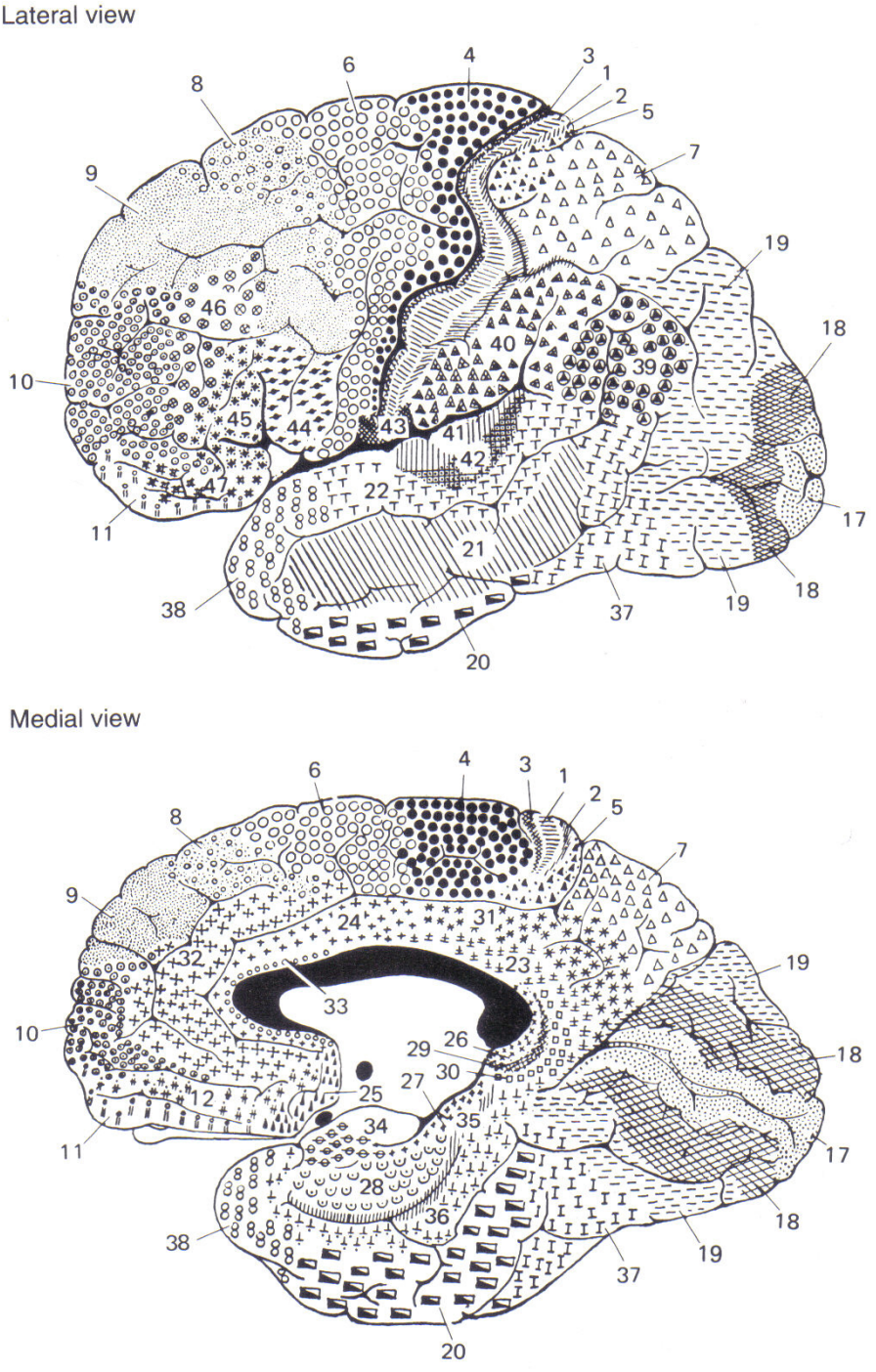

Figure 13.2: Cytoarchitectural classification of the human cerebral cortex by K. Brodmann. Brodmann's areas have consistently been found to correspond to distinctive functional fields, each of which has a characteristic pattern of connections. Area 4, the primary motor cortex, occupies most of the precentral gyrus. The primary somatic sensory cortex includes areas 1,2, and 3 in the postcentral gyrus. Area 17 is the primary visual cortex. Areas 41 and 42 comprise the primary auditory cortex. The prefrontal association cortex and the parietal-temporal-occipital association cortex are also composed of a number of distinct cytoarchitectonic areas. (copyright: Kandel et al. 2000)

For example, the primary visual cortex, the area that receives direct input from the lateral geniculate nucleus, corresponds to Brodmanns area 17. He also correctly identified the boundaries of the primary motor and somatosensory areas and suggested that there may be many separate functional zones within individual association areas. Recent research has shown that there are, in fact, more functional zones in the association cortex than even Brodmann recognized.

The Cerebellum: The cerebellum constitutes only 10% of the brain, yet it contains more than half of all the neurons. These neurons are arranged in a highly regular manner that results from repetition of the same basic circuit module. Despite its structural regularity the cerebellum is divided into several distinct regions, each of which makes connections with different areas of the brain. These features suggest that all areas of the cerebellum perform similar functions but that each area performs that function on a different set of inputs. The cerebellum is not necessary for perception or for the contraction of muscle. Even though the cerebellum contains both sensory and motor components, its complete removal does not impair either sensory perception or muscle strength. Rather, the cerebellum regulates movement and posture indirectly by adjusting the output of the major descending motor systems of the brain.

A striking feature of the cerebellar surface is the many parallel transverse convolutions that run from one side to the other. Two deep transverse fissures divide the cerebellum into three major lobes. The primary fissure, located on the upper surface, divides the cerebellum into anterior and posterior lobes. The posterolateral fissure on the underside of the cerebellum separates the large posterior lobe from the small flocculonodular lobe (figure 13.3).

The cerebellum is organized into three functional regions, each with distinct anatomical connections to the brain and spinal cord: the vestiobulocerebellum, the spinocerebellum, and the cerebrocerebellum. These three regions correspond roughly to anatomical subdivisions that have evolved successively in phylogeny. Each region receives its main inputs from a different source and sends its outputs to a different part of the brain.

There are three layers to the cerebellar cortex; from outer to inner layer, these are the molecular, the purkinje, and granular layers. The function of the cerebellar cortex is essentially to modulate information flowing through the deep nuclei. Mossy and climbing fibers carry sensorimotor information into the deep nuclei, which in turn pass it on to various premotor areas, thus regulating the gain and timing of motor actions. Mossy and climbing fibers also feed this information into the cerebellar cortex, which performs various computations, resulting in the regulation of Purkinje cell firing. Purkinje

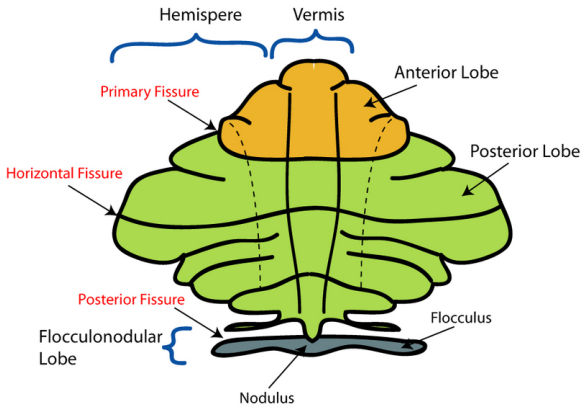

Figure 13.3: Regional organization of the cerebellum

neurons (GABAergic) feed back into the deep nuclei via a potent inhibitory synapse. This synapse regulates the extent to which mossy and climbing fibers activate the deep nuclei, and thus control the ultimate effect of the cerebellum on motor function. The synaptic strength of almost every synapse in the cerebellar cortex has been shown to undergo synaptic plasticity. This allows the circuitry of the cerebellar cortex to continuously adjust and fine-tune the output of the cerebellum, forming the basis of some types of motor learning and coordination.

The Hypothalamus: The hypothalamus is extensively interconnected with a ring of cortical structures that are part of the limbic system. The hypothalamus can be grossly divided in the lateral medial direction into lateral, medial, and periventricular regions. It can also be divided in the anterior-posterior direction into anterior, middle, and posterior regions. The lateral region has long fibers that project to the spinal cord and cortex, and also has extensive short-fiber, multisynaptic ascending and descending pathways. Most prominent of these fiber systems is the medial forebrain bundle, a major tract that runs through the lateral hypothalamus and continues rostrally to end in the telencephalon. Many aminergic neurons originating in the brain stem project to neocortical regions by way of fibers in the medial forebrain bundle and its rostral continuation in the cingulum bundle. The medial region of the hypothalamus is separated from the lateral region by the descending columns of the fornix. It contains most of the well-delineated nuclei of the hypothalamus, including (1) the preoptic nuclei and suprachiasmatic nuclei in the anterior region; (2) the dorsomedial, ventromedial, and paraventricular nuclei in the middle region; and (3) the posterior nucleus and

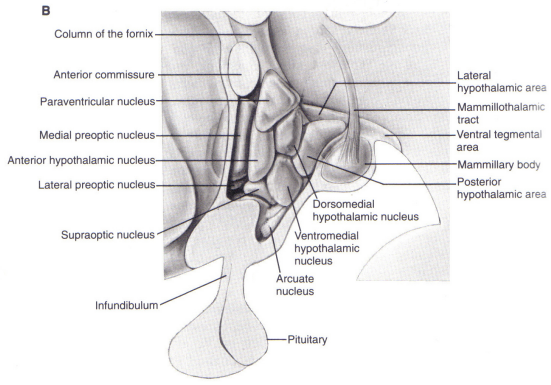

Figure 13.4: Medial view showing the positions of the main hypothalamic nuclei (copyright: Kandel et al. 2000)

mammilary bodies in the posterior region (figure 13.4).

The periventricular region consists of those parts of the hypothalamus immediately bordering the third ventricle. The basal portion of the medial region and the periventricular region contain many of the small (parvicellular) hypothalamic neurons that secrete the substances that control the release of anterior pituitary hormones.

Each nucleus of the hypothalamus typically subserves a variety of functions. This is most clearly seen in the paraventricular nucleus, a highly differentiated structure that contains anatomically discrete regions of neurons containing specific peptides and combinations of peptides.

Most fiber systems of the hypothalamus are bidirectional. Projections to and from areas caudal to the hypothalamus are carried in the medial forebrain bundle, the mammillotegmental tract, and the dorsal longitudinal fasciculus. Rostral structures are interconnected to the hypothalamus by means of the mammillothalamic tract, fornix, and stria terminalis. There are two exceptions to the rule that fibers are bidirectional in the hypothalamus. The hypothalamohypophyseal tract contains only descending axons of paraventricular and supraoptic neurons, which terminate primarily in the posterior pituitary. The hypothalamus also receives one-way afferent connections directly from the retina. There fibers terminate primarily in the suprachiasmatic nucleus, which is involved in generating light-dark cycles.

Histamine has been shown to be a transmitter in invertebrates, and binding sites for certain kinds of antihistaminic drugs have been localized to neurons in the vertebrate brain. This putative vertebrate transmitter substance

is concentrated in the hypothalamus. This knowledge allows us to embed histaminergic pathways into our simplified network of the limbic system.

The Corpus Amygdaloideum: The amygdala as a component of the limbic system coordinates the actions of the autonomic and endocrine systems and is involved in emotions. The amygdala is composed of many nuclei that are reciprocally connected to the hypothalamus, hippocampal formation, neocortex, and thalamus. It gives rise to two major efferent projections: the stria terminalis and the ventral amygdalofugal pathway. The stria terminalis innervates the bed nucleus of the stria terminalis, the nucleus accumbens, and the hypothalamus. The ventral amygdalofugal pathway provides input to the hypothalamus, dorsal medial nucleus of the thalamus, and rostral cingulate gyrus. The amygdala in turn receives an important afferent input from the olfactory bulb and also inputs from the other afferent systems.

Despite its extensive olfactory input, the amygdala is not essential for olfactory discrimination. Lesions and electrical stimulations of the amygdala produce a variety of effects on autonomic responses, emotional behaviours, and feeding. It has been also implicated in the process of learning, particularly those tasks that require coordination of information from different sensory modalities, or the association of a stimulus and an affective response. The output of amygdala, as well as afferent input that is triggered as a consequence of the activity of autonomic effectors, feeds back to cortical structures, such as the prefrontal cortex, and results in a conscious emotional experience.

Amygdala is of central importance from the pharmacological point of view, then the GABA receptors to which benzodiazepines bind are concentrated in the limbic system, specifically in the amygdala.

The Hippocampus: Like amygdala, hippocampus is also a part of the limbic system. The hippocampus is involved in memory storage. Its function in the process of memory storage is clarified by the fact that Alzheimer disease which is the most common form of dementia is often observed to be carried with a neural degeneration in hippocampus.

The hippocampus forms a principally uni-directional network with input from the entorhinal cortex (EC) that forms connections with the dentate gyrus (DG) and CA3 pyramidal neurons via the perforant path (PP [Lateral and Medial]). CA3 neurons also receive input from the DG via the mossy fibers (MF). They send axons to CA1 pyramidal cells via the Schaffer collateral pathway (SC), as well as CA1 cells in the contralateral hippocampus via the associational commissural pathway (AC). CA1 neurons also receive input directly from the perforant path and send axons to the subiculum (Sb). These neurons in turn send the main hippocampal output back to the EC,

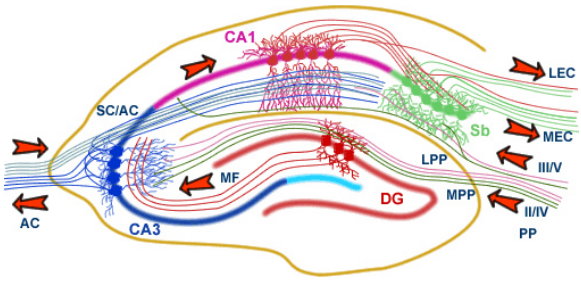

Figure 13.5: The network structure of the hippocampus (copyright: www.bris.ac.uk)

forming a loop (figure 13.5).

Thus, the hippocampus receives its major input from the entorhinal cortex by the way of the perforant path. The entorhinal cortex in turn receives its input from areas of the association cortex and thereby provides a link between neocortex and the limbic system. Fibers from the entorhinal cortex that reach the hippocampus by means of the perforant pathway pass through subiculum, an area of cortex that receives major output from the hippocampus and has extensive reciprocal connections with many areas of the brain, including several areas of the neocortex. The subiculum is the origin of those fibers in the fornix that innervate the hypothalamus. The fornix also contains axons of hippocampal pyramidal cells that innervate non-hypothalamic structures.

The Thalamus: The thalamus relays sensory input to the primary sensory areas of the cerebral cortex, as well as information about motor behaviour to the motor areas of the cortex. It prevents also an overflow of cortical afferents. A major result of this work is also the fact that thalamus also filters cortical afferent signals of abnormal characteristics which will be discussed later.

The thalamus is composed in part of distinct sensory nuclei that receive input about different sensory modalities, including somatic sensation, audition, and vision. The thalamus also mediates motor function by transmitting information from the cerebellum and basal ganglia to the motor regions of the frontal lobe the primary motor cortex and higher-order motor areas. In addition, the thalamus is involved in autonomic reactions and the maintenance of consciousness. Almost all the thalamic nuclei project to and receive input from the cerebral cortex. Thalamocortical connections are made through the internal capsule, a large fiber bundle that carries most of the axons running to and from the cerebral hemisphere. The internal capsule contains not only the rostral continuation of the somatic afferent pathway and the projection

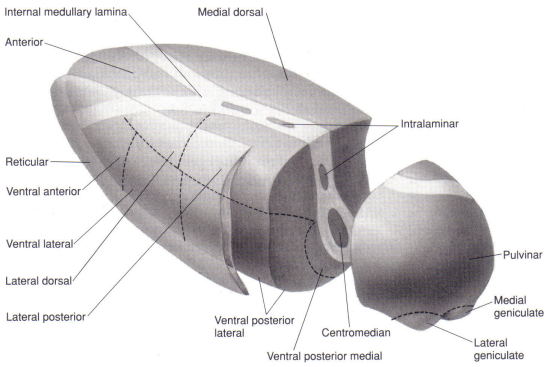

Figure 13.6: The major nuclei of the thalamus as seen on the left side of the brain (copyright: Kandel et al. 2000)

fibers from the various nuclei of the thalamus, but also the fibers descending from the cortex to the brain stem and spinal cord.

A Y-shaped sheet of fibers called the internal medullary lamina separates the thalamic nuclei into six groups: Lateral, Medial, Anterior, Intralaminar, Midline and Reticular (figure 13.6).

Each lateral nucleus receives restricted sensory or motor input and projects to and receives input from a specific region of sensory, motor, or association cortex, especially from and to the cingulate gyrus, a portion of the limbic system in the cerebral cortex and parietal lobe. The lateral nuclei are relay nuclei that are divided into two tiers, ventral and dorsal.

The medial nuclei are also relay nuclei. The largest component of the medial group is the medial dorsal nucleus.

The anterior nuclei participate in emotion by relaying information from the hypothalamus to the cingulate gyrus.

The intralaminar, reticular, and midline nuclei are diffuse-projection nuclei. The intralaminar nuclei lie within the internal medullary lamina; the largest of these cell groups is the centromedian nucleus. Cells in this nucleus have axons that terminate in several cortical areas in the frontal lobe and in two major components of the basal ganglia, the caudate nucleus and putamen. These projections make this nucleus of special interest for our investigations. Then, thalamus become a central vertex in the generalized network of the brain and therefore, one of the generators of the dynamical patterns of neurochemical substances.

The Corpus Striatum: The striatum is a subcortical part of telencephalon and a major input nucleus of the basal ganglia. The dorsal striatum

forms a continuous and large mass, topographically separated by the internal capsule into the caudate nucleus medially, the putamen laterally and the fundus below, linking the two preceding ventrally; but a single entity. It consists of four neuronal types:

- Spiny neurons relatively close from the pyramidal neurons of the cortex due to the presence of spines with spine apparatus (acanthodendritic neurons), and make up 96% of the striatum;
- Leptodendritic neurons (2%) with large, poorly bifurcated, arborisation looking like pallidonigral neurons;
- Spidery cholinergic interneurons (1%) morphologically entirely different from those observed in rodents (which must lead to very careful interspecific correlations).In primates they are the tonically Active Neurons (TANs). These briefly stop firing in concomitance to behaviourally salient situations and reward-related events;
- GABAergic interneurons, which are fast-spiking/low threshold spiking, and express dopamine receptors.

The striatum is spatially organized according to several levels. The dorsal striatum is a single entity closed and continuous with a toric topology. The observable anatomical subdivisions of the dorsal striatum (caudate nucleus and putamen) essentially induced by the internal capsule do not completely overlap with now accepted anatomic-functional subdivisions. The selective distribution of the axonal terminal arborisations of cortical sources differentiate the sensorimotor striatum, mainly putaminal but located in its dorsal part and in the lateroinferior part of the caudate. A great part of the remaining of the volume (essentially caudate) receiving from axonal endings from the frontal, parietal, temporal cortex forms the associative striatum. The separation between these two territories is rather clear-cut and observable using calbindin immunochemistry. A third entity, the most inferomedial, raises more problems as there is no general agreement about its border with the associative striatum.

The most important afferent in terms of quantity of axons is the corticostriatal connection. Many parts of the neocortex innervate the dorsal striatum. The cortical pyramidal neurons projecting to the striatum are located in the lamina V. They end mainly on the spines of the spiny neurons. They are (glutamatergic), exciting striatal neurons. Another well known afferent is the nigrostriatal connection arising from the neurons of the substantia nigra pars compacta. While cortical axons synapse mainly on spine heads of spiny

neurons, nigral axons synapse mainly on spine shafts. The thalamostriatal afferent essentially comes in primates from the central region is glutamatergic. The participation of truly intralaminar neurons is much more limited. The striatum receives afferents from other elements of the basal ganglia such as the subthalamic nucleus (glutamatergic) or the external globus pallidus (GABAergic).

The main efferent target of the striatum is the pallidonigral set. The basal ganglia core is made up of the striatum and its direct targets through the striato-pallidonigral bundle. The striato-pallidonigral bundle is a very dense bundle of a few myelinated axons giving the whitish aspect to the set. This comprises successively the external globus pallidus (GPe), the internal globus pallidus (GPi), the pars compacta of the substantia nigra (SNc) and the substantia nigra pars reticulata (SNr). This set is made up of the same genus of neurons. Its neurons are inhibited by GABAergic synapses from the dorsal striatum. Among these targets, one does not send axons outside the system (GPe, thus a regulator). Another sends axons to the superior colliculus. Two others are the bases of basal ganglia system output to the thalamus forming two separate channels: one through the internal segment of the globus pallidus to VO and from there to the cortical SMA and another through the substantia nigra to VA and from there to the frontal and the oculomotor cortex (figure 13.7).

Metabotropic dopamine receptors are present both on spiny neurons and on cortical axon terminals. Second messenger cascades triggered by activation of these dopamine receptors can modulate pre- and post-synaptic function, both in the short term and in the long term. The striatum is best known for its role in the planning and modulation of movement pathways but is also involved in a variety of other cognitive processes involving executive function. In humans the striatum is activated by stimuli associated with reward, but also by aversive, novel, unexpected or intense stimuli, and cues associated with such events.

The high concentration of dopamine receptors in striatum is a major reason for it involving in several neurological diseases such as Chorea Huntington, Morbus Parkinson, and also schizophrenia. Thus, the synaptic dynamic of its neurotransmitter systems, its upscaled dynamical behaviour as a nucleus, and its interactions in the brain macro-circuits will be quantitatively analyzed and interpreted through this work.

The Globus Pallidus: The globus pallidus (or pallidum) is derived from the diencephalon and lies medial to the putamen and lateral to the internal capsule. It is divided into internal and external segments. The internal segment (GPi) receives inputs from corpus striatum, substantia nigra

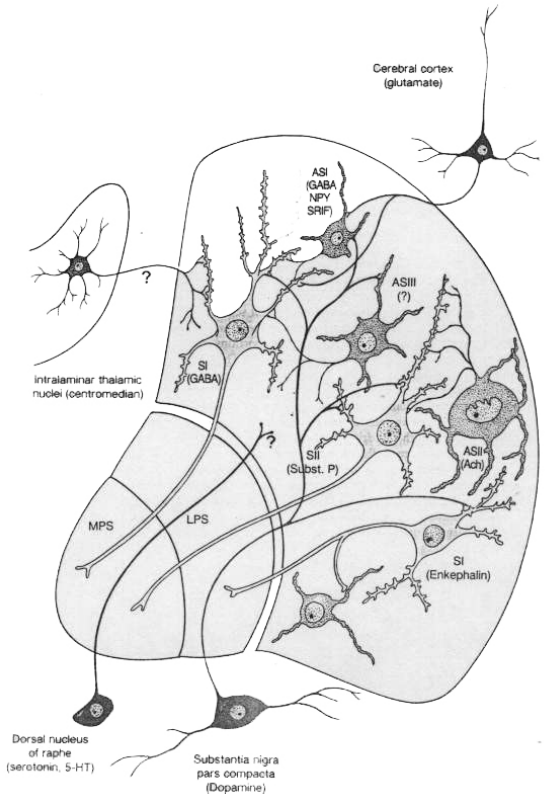

Figure 13.7: Striatal structure and connections with the medial and lateral globus pallidus (MPS, LPS)

pars compacta, and nucleus subthalamicus. The efferent of GPi reach thalamus and enclose the basal ganglias feedback loop. The external segment (GPe) builds a feedback loop with nucleus subthalamicus, which is of major importance in the information processing by basal ganglia.

The Nucleus Subthalamicus: The principal type of neuron found in the subthalamic nucleus has rather long dendrites devoid of spines. The dendritic arborisations are ellipsoid, replicating in smaller dimension the shape of the nucleus. The dimensions of these arborisations (1200, 600 and 300 m) are similar across many speciesincluding rat, cat, monkey and manwhich is unusual. However, the number of neurons increases across evolution as well as the external dimensions of the nucleus. Due to the bending of dendrites at the border, the subthalamic nucleus is a close nucleus, able to receive information only in its space. The principal neurons are glutamatergic, which give them a particular functional position in the basal ganglia system. In humans there are also a small number (about 7.5%) of GABAergic interneurons that

participate in the local circuitry.

The subthalamic nucleus receives its main input from the lateral pallidum (external segment of the globus pallidus) (84.2% of its axons), not so much through the ansa lenticularis as often said but by radiating fibers crossing the medial pallidum first and the internal capsule (see figure). This afference is GABAergic, inhibiting the neurons of the subthalamic nucleus. Excitatory, glutamatergic inputs come from the cerebral cortex (particularly the motor cortex), and from the pars parafascicularis of the central complex. The subthalamic nucleus also receives neuromodulatory inputs, notably dopaminergic axons from the substantia nigra pars compacta.

The axons of subthalamic nucleus neurons leave the nucleus dorsally. The efferent axons are glutamatergic (excitatory). Except for the connection to the striatum (17.3% in macaques), most of the subthalamic principal neurons are multi-targets and directed to the other elements of the core of the basal ganglia. Some send axons to the substantia nigra medially and to the medial and lateral nuclei of the pallidum laterally (3-target, 21.3%). Some are 2-target with the lateral pallidum and the substantia nigra (2.7%) or the lateral pallidum and the medial (48%). Less are single target for the lateral pallidum. In the pallidum, subthalamic terminals end in bands parallel to the pallidal border. When all axons reaching this target are added, the main afference of the subthalamic nucleus is, in 82.7% of the cases, clearly the medial pallidum (internal segment of the globus pallidus).

The first intracellular electrical recordings of subthalamic neurons were performed using sharp electrodes in a rat slice preparation (Nakanishi et al., 1987). In these recordings three key observations were made, all three of which have dominated subsequent reports of subthalamic firing properties. The first observation is that, in the absence of current injection or synaptic stimulation, the majority of cells were spontaneously firing. The second observation is that these cells are capable of transiently firing at very high frequencies. The third observation concerns non-linear behaviour, when cells are transiently depolarized after being hyperpolarized below 65mV. They are then able to engage voltage-gated calcium and sodium currents to fire bursts of action potentials.

Several recent studies have focused on the autonomous pace making ability of subthalamic neurons. These cells are often referred to as "fast-spiking pacemakers" since they can generate spontaneous action potentials at rates of 80 to 90Hz in primates.

Strong reciprocal connections link the subthalamic nucleus and the external segment of the globus pallidus. Both are fast-spiking pacemakers. Together, they are thought to constitute the "central pacemaker of the basal ganglia" with synchronous bursts.

The connection of the lateral pallidum with the subthalamic nucleus is also the one in the basal ganglia system where the reduction between emitter/receiving elements is likely the strongest. In terms of volume, in humans, the lateral pallidum measures 808 mm, the subthalamic nucleus only 158 mm. This translated in numbers of neurons represents a strong compression with loss of map precision.

The systemic position of this circuit is particular in the basal ganglia system that may be revealed by contrast versus outputs subsystems. There are two output paths starting from the striatum. The first has a first relay in the medial pallidum (GABAergic inhibitory) and the second in the nigra reticulata (GABA). These two output subsystems do not send regulatory messages to other elements of the basal ganglia system: striatum, lateral pallidum or subthalamic nucleus. The lateropallido-subthalamic subsystem is particular in that it does the reverse. It does not send axons to the thalamus and from there to the cortex. All efferent axons of the subsystem are indeed returning inside the basal ganglia system. This topologically makes it a regulator. Some axons from the lateral pallidum go to the striatum. The activity of the medial pallidum is influenced by afferences from the lateral pallidum and from the subthalamic nucleus. The subthalamic nucleus sends axons to another regulator: the pedunculo-pontine complex.

The Substantia Nigra: The substantia nigra lies in the midbrain and has two zones. The ventral pale zone, the pars reticulata (SNr), resembles the globus pallidus cytologically. A dorsal, darkly pigmented zone, the pars compacta (SNc), is composed of dopaminergic neurons whose cell bodies contain neuromelanin. The dark pigment, a polymer derived from dopamine, gives the substantia nigra its name, because in human this part of the brain appears black in cut sections. Because of the striking similarities in cytology, connectivity, and function of GPi and SNr, these two nuclei can be considered as a single structure arbitrarily divided by the internal capsule.

The substantia nigra receives afferents from cortex and corpus striatum and projects dopaminergic pathways to the limbic system, GPi/SNr, thalamus, and striatum. The nigrostriatal feedback loop is of great importance in the generation of psychotic salience and in the general information processing in basal ganglia.

Because of the very high dopamine concentration in substantia nigra and the richness of dopaminergic projections into different circuits like the limbic system and basal ganglia, substantia nigra is probably involved in a lot of neurological and psychological diseases, also in learning processes, and addiction.

The Raphe Nuclei: The raphe nuclei are traditionally considered to be the medial portion of the reticular formation, and they appear as a ridge of cells in the center and most medial portion of the brain stem. In order from caudal to rostral, the raphe nuclei are known as the nucleus raphe obscurus, the raphe magnus, the raphe pontis, the raphe pallidus, the nucleus centralis superior, nucleus raphe dorsalis, nuclei linearis intermedius and linearis rostralis. The raphe nuclei can be of particular interest to neurologists and psychologists since many of the neurons in the nuclei (but not the majority) are serotonergic. Serotonin seems to be the culprit in many of our modern psycho-pharmaceutical problems, such as anorexia, depression, and sleep disorders.

13.4 On the Antipsychotic Agents

Antipsychotic drugs have been used clinically for 50 years. Reserpine and chlorpromazine were the first drugs found to be useful in schizophrenia. Although chlorpromazine is still sometimes used for the treatment of psychoses, these forerunner drugs have been superseded by many newer drugs.

A number of chemical structures have been associated with antipsychotic properties. The drugs can be classified into the following groups:

- Phenothiazine derivatives: Three subfamilies of phenothiazines, based primarily on the side chain of the molecule, were once the most widely used of the antipsychotics. Aliphatic derivatives (e.g. Chlorpromazine) and piperidine derivatives (e.g. Thioridazine) are the least potent. Piperazine derivatives are more potent in the sense that they are effective in lower doses. The piperazine derivatives are also more selective in their pharmaceutical effects;

- Thioxanthene derivatives: This group of drugs is exemplified primarily by thiothixene. In general, these compounds are slightly less potent than their phenothiazine analogues;

- Butyrophenone derivatives: This group, of which haloperidol is the most widely used, has a very different structure from those of the preceding groups. Diphenylbutylpiperidines are closely related compounds. These agents tend to be more potent and to have fewer autonomic effects;

- Miscellaneous Structures: The newer drugs have a variety of structures and include pimozide, molindone, loxapine, clozapine, olanzapine, risperidone and ziprasidone.

The first phenothiazine antipsychotic drugs, with chlorpromazine as the prototype, proved to have a wide variety of central nervous system, autonomic, and endocrine effects. These actions were traced to blocking effects at a remarkable number of receptors. These include dopamine and a-adrenoceptor, muscarinic, H_1 histaminic, and serotonine $(5 - HT_2)$ receptors. After dopamine was recognized as a neurotransmitter, various experiments showed that its effects on electrical activity in central synapses and on production of cAMP by adenylyl cyclase could be blocked by most antipsychotic drugs. This evidence led to the conclusion in the early 1960s that these drugs should be considered dopamine antagonists. The antipsychotic action is now thought to be produced by their ability to block dopamine in the mesolimbic and mesofrontal systems. Recently, partial antagonists has been developed to reduce the motor side effects of the antipsychotic drugs of the first generation expressed above.

Chapter Fourteen

Psychiatric Supplement

14.1 Historical Evolution of the Concept of Schizophrenia

The existence of a schizophrenia-like syndrome can be found in literature dating back to antiquity. Historical accounts of mania and melancholia certainly are found in ancient Greek writings. Even earlier ancient writings of Mesopotamia contain evidence of psychiatric illness, with clear descriptions of schizophrenia-like syndromes that included paranoid delusions.

In the first century, AD, Celsus proposed a classification of mental disorders into three separate categories: delirium, melancholia, and a third that remained unnamed, but was subdivided into two forms with and without hallucinations. Galen, who lived from 122-199 AD, while not describing a separate schizophrenic-like illness, stated that fanatic imaginations could occur during melancholia. Nevertheless, it was not until the late 18th and early 19th century, that the modern descriptions of 'schizophrenia' began to emerge.

Morel introduced the term 'demence praecox' in the mid 19th century to refer to the condition of an adolescent patient, originally bright and active, who gradually became gloomy, silent and withdrawn. In 1863 Kahlbaum described a condition which he termed 'katatonia' as pathologically charged motor tension, while a distinct syndrome of auditory hallucinations and persecutory delusions, he termed 'basania typical'.

Kraepelin's contribution, then in 1898, only shortly after psychiatry itself became known as a separate entity, was the integration of these separate symptoms into a clinically distinct disorder. He defined the syndrome, 'dementia praecox', as a psychosis with an early age of onset and chronic deterioration in mental functioning, in contrast with the manic-depressive

psychoses, which were characterized by recurrent episodes of illness.

The term 'schizophrenia' (split-mind), was actually introduced by E. Bleuler, in 1908 to describe this syndrome as a 'splitting or incongruity' of mental functions. By splitting he meant a dissociation between thought and affect, leading to illogical thought connections, thus creating the typical schizophrenic though disorder. He suggested that the aetiology was physically and likely to be of multiple aetiologies. In his classic monograph, 'Dementia Praecox of the Group of Schizophrenias' (1911), he further expanded on Kraepelin's concepts and emphasized that there were two clusters of symptoms that appeared to characterize the disorders. He defined primary symptoms as those specifically characteristic of the disorder (disturbances of association, affectivity, ambivalence, and autism), while the secondary symptoms (e.g. hallucinations, delusions) may be found in other disorders as well. The relative importance of this grouping of symptoms to the diagnosis and aetiology of schizophrenia remains an issue today.

14.2 Schizophrenic Subtypes

The variety of the symptoms and course of schizophrenia has led to several attempts to define subgroups. Patients with hebephrenic schizophrenia often appear silly and childish in their behaviour. Affective symptoms and thought disorders are prominent. Delusions are common and not highly organized. Hallucinations are also common, and are not elaborate.

Catatonic schizophrenia is characterized by motor symptoms, by changes in activity varying between excitement and stupor. In paranoid schizophrenia the clinical picture is dominated by paranoid delusions. The patient may appear normal until the abnormal beliefs are uncovered.

Simple schizophrenia is characterized by the insidious development of odd behaviour, social withdrawal, and declining performance at work.

14.3 Schizophrenia-like Disorders

Whatever definition of schizophrenia is adopted, there will be cases that resemble schizophrenia in some respects and yet do not meet the criteria for diagnosis, either because of the duration or the absence of some common symptoms. Schizophrenia-like disorders can be divided into four groups:

- Delusional or paranoid disorder;
- Brief disorders (at least one of the acute phase positive symptoms / Short duration);

- Disorders accompanied by prominent affective symptoms (reversible);
- Disorders without all required symptoms for schizophrenia.

14.4 Social Factors Modifying the Clinical Features

The amount of social stimulation has a considerable effect on the clinical picture. Under-stimulation increases 'negative' symptoms such as poverty of speech, social withdrawal, apathy, and lack of drive. Over-stimulation precipitates 'positive' symptoms such as hallucinations, delusions, and restlessness. Modern treatment is designed to avoid under-stimulation, and as a result 'negative' features are less frequent than in the past.

The social background of the patient may effect the content of some symptoms. Age also seem to modify the clinical features of schizophrenia. In adolescents and young adults the clinical features often include thought disorder, mood disturbance, passivity phenomena, and thought insertion. With increasing age paranoid symptomatology is more common, with more organized delusions (Häfner et al. 1993).

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