Summary

Nerve cells (neurons) play an important role in information processing in the brain. At locations where their extensions (axons and dendrites) approach each other, contact points (synapses) between neurons can be formed. Through these synaptic connections, neurons establish large neuronal networks. Within these networks, neurons transmit electrical signals (action potentials) to each other, and the exchange of electrical signals across synapses constitutes the basis of cognitive processes. The particular structure of the patterns of electrical activity (in time and space) characterizes what we do with our brain, such as thinking, learning, remembering, and talking. These cortical patterns of activity involve simultaneous activation (synchrony) of many neurons, which is a characteristic feature of activity in many brain areas. Since groups of neurons are not continuously active, the average electrical activity will vary in intensity, giving rise to oscillations.

The research described in this thesis focuses on the emergence of synchronous activity in neuronal networks, and on how oscillations arise from the basic properties of neurons and their interconnections. The electrical behaviour of nerve cells is determined by the properties of their membrane. By the exchange of ions, a potential (voltage) difference is created across the membrane. The momentary opening of ion channels in the membrane leads to an exchange of ions, resulting in a short electrical signal. Depending on the type of ion channel, the membrane potential may increase or decrease. Which type of ion channel is opened depends on the presynaptic neuron (the one that delivers the electrical signal to the synapse). An excitatory neuron will stimulate the activity of its target neuron (postsynaptic neuron), whereas an inhibitory neuron will inhibit the activity of its target cell.

The research was motivated by questions arising from experiments in laminar brain slices. In these experiments, the electrical activity was measured in thin slices of the prefrontal cortex (PFC) and hippocampus of the rat.

The study was divided into three parts. First, we focussed on the question of how oscillations in electrical activity in neuronal networks emerge as a result of interactions between populations of excitatory and inhibitory neurons, and in particular what the mechanism is that generates temporal fluctuations in oscillation amplitude. Second, we examined the influence of a specific ion channel on oscillatory network activity. Third, we analysed the behaviour that is generated when two networks of neurons, each consisting of an excitatory and inhibitory population and on their own oscillating at different frequencies, are synaptically connected. All the investigations were carried out using a computational approach. That is, neurons and networks were studied by means of computational models. The advantage of this approach is that the electrical behaviour of neurons and their networks can be analysed in great detail.

Chapter 2 shows how oscillations can arise in a network of excitatory and inhibitory neurons when stimulated by external action potentials and/or electric currents. The oscillations arise when excitatory neurons stimulate inhibitory neurons which in turn inhibit excitatory neurons, forcing them to cease their activity. After the membrane potentials are restored, excitatory neurons can be activated again and the process is repeated. The amplitude of the oscillations is determined by the degree of synchrony in the firing of the cells. We have shown how variations in synchrony lead to fluctuations in oscillation amplitude, and how the switching between periods of high and low synchrony (amplitude) depends on external stimuli such as action potentials and additional depolarizing currents. The dependence found in

the model is in good agreement with the dependence observed experimentally in in-vitro brain slices that were stimulated by the neuromodulator Carbachol (CCh).

In Chapter 3, we look at resonance phenomena in membrane potential fluctuations as a result of the activation of a specific ion channel called the h-channel. This channel is activated by membrane hyperpolarization and contributes its own current to the ion flux across the membrane. The presence of h-channels leads to fluctuations in membrane potential that are dependent on the stimulation frequency. When the fluctuations cross the firing threshold of the cell, an action potential is generated (firing). We show that activation of h-channels in excitatory cells decreases the duration of the hyperpolarization state, and causes a more depolarized resting state of the membrane. This raises the probability of firing during resting periods of the cell. It also interrupts the synchrony between the neurons, resulting in a loss of rhythm in the activity of the network. This means that h-channels not only affect the dynamics of the membrane potential, but also alter the synchronous activity in neuronal networks.

In Chapter 4, we study the effect of interconnections between two networks, each of which oscillates at a different base frequency. We limited ourselves to feed-forward connections, where one of the two networks (source network) sends action potentials to the other (target) network. The question was how the electrical behaviour of the target network was affected. To address this question, we systematically varied the nature and strength of the connections between the two networks, while quantifying the electrical behaviour of the target network. With strong inter-network connections, the source network can impose its rhythm onto the target network. This proved to be especially effective when the source network oscillated at a low frequency and the target network at a higher frequency. With weaker inter-network connections, we observed the emergence of multiple frequencies in the target network. This finding is important because of similar experimental observations. Prefrontal cortex of rats can alternate between two distinct oscillation frequencies, or can express a single frequency with alternating periods of high and low amplitude.

In summary, our research shows that a rich repertoire of oscillation patterns can arise from the elementary properties of neurons that are synaptically connected in networks. Our results give insight into and offer possible explanations for experimental observations of oscillatory electrical activity in the brain. We hope that our findings will contribute to research about the brain as an information processing organ.