2 Neural Dynamics

2.1 Introduction

The human brain consists of around 100 billion neurons being interconnected in numerous ways. Its activation patterns are among the most complex observed biological structures. A comparatively simple neural network such as the thoroughly investigated stomatogastric nervous system of crustacians contains less than 100 neurons. Even this rather small number of cells can produce a wide variety of collective rhythmic behaviour controlling the digestive system.

In this lecture we will investigate the dynamics of a single neuron using biophysical models. Among these we select a rather simple model which will be analysed using the qualitative theory of ordinary differential equations as well as numerical simulations. Our model neuron can show various different patterns of activation depending on its intrinsic parameters as well as on the stimulus intensities. These patterns can propagate in the form of waves along axons and dendrites. The spatial propagation of neural activity allows for the coupling and therefore communication of a neuron with many others.

2.2 Model for the electric excitability of a neuron

The cellular membrane is characterised by a low conductance. In case of an electric potential difference V between the two sides of the membrane, an electric field over the membrane will be established. The membrane then acts as a capacitor with the capacity (per area) C_m:

$$C_m = \frac{q}{V} \tag{1}$$

with q denoting the charge density on both sides of the membrane. Small ions such as K^+, Na^+, Ca^{2+}, and Cl^- which are present in the cytoplasm and the extracellular medium can mediate an electric current I_{Ion} as the result of their mobility. The ionic current results in a loss of charge

$$I_{Ion} = -\frac{dq}{dt}. \tag{2}$$

Combining this with (1) yields

$$C_m \frac{dV}{dt} + I_{Ion} = 0. \tag{3}$$

Alan Hodgkin, Andrew Huxley, und Bernard Katz showed that the ionic current can be considered as a sum of currents being carried by single ion species:

$$I_{Ion} = \sum_{\text{ion species } i} I_i. \tag{4}$$

In the squid giant axon – their subject of research – the participating ions are K^+, Na^+, and Cl^-. Together with John Eccles, they were awarded the nobel prize for medical research in 1963 for their results regarding the generation of the action potential. In the concluding work a detailed mathematical model for the explanation of their experimental results is formulated (Hodgkin & Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117 (1952) 500–544). In this model the following assumptions for the I_i's are made:

1. the ionic currents obey Ohm's law (with conductivities g_i);
2. the driving force is the difference between the membrane potential V and Nernstian equilibrium potential V_i for the corresponding ion species.

One obtains for the current mediated by a species i:

$$I_i = g_i(V - V_i). \tag{5}$$

The equilibrium potential can be calculated from the ion concentrations c_i on both sides of the membrane

$$V_i = \frac{RT}{F} \ln \frac{c_i(\text{outside})}{c_i(\text{inside})}. \tag{6}$$

Combining (3)–(5) yields the equation governing the membrane potential

$$C_m \frac{dV}{dt} + \sum_i g_i(V - V_i) = 0. \tag{7}$$

2.3 Ionic channels

Nowadays we know that ionic currents are mediated by specific ionic channels. The opening and closing of these channels is influenced by the membrane potential. Although not knowing the molecular aspects of ionic conductivity, Hodgkin, Huxley, and Katz managed to characterise in detail the voltage dependency of the conductances in the squid giant axon. In their experiments they kept the voltage V constant (voltage clamp) and used specific inhibitors for the single ionic currents (ionic channels). In this way the functions $I_i(V)$ could be measured. If the ion concentrations are known, the functions $g_i(V)$ can then be determined using equations (5) and (6). Further, they expressed the $g_i(V)$ as functions of so-called *gating variables* W_j:

$$g_i = \tilde{g}_i \sigma_i(W_1, \ldots, W_n); \tag{8}$$

with $\tilde{g}_i$ denoting the maximal conductivity of the channel and $\sigma_i(W_1, \ldots, W_n)$ being a function with values between 0 and 1.

In steady state, the gating variables assume a value $W_{j,\infty}(V)$ and the relaxation behaviour is governed by

$$\frac{dW_j}{dt} = \phi \frac{W_{j,\infty}(V) - W_j}{\tau_j(V)}. \tag{9}$$

The relaxation time τ_j is generally also a function of V. The factor ϕ is a function of the temperature (relaxation toward the steady state is faster for high temperatures). So far the Hodgkin-Huxley model from 1952 has been described in its generalised form. Hodgkin and Huxley derived the following formulation:

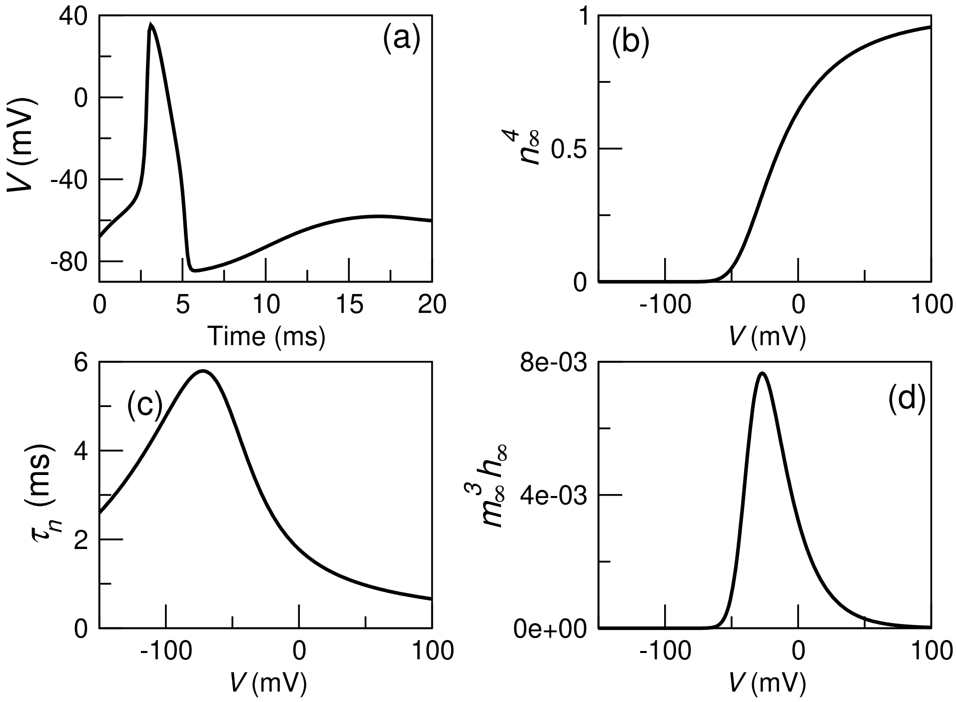

Figure 1: The Hodgkin-Huxley Model. (a) Typical action potential obtained with the Hodgkin-Huxley model. (b) Steady state value of the potassium channel open probability (σ_K). (c) Characteristic time of the potassium channel (similar form for the other two gating variables). (d) Steady state value of the natrium channel open probability (σ_{Na}). The function h_∞ decreases with depolarisation whereas m_∞ increases, the product of both function gives the shown bell shaped curve.

Ionic currents: $i =$ K^+-, Na^+-, and *leak*- (predominantly Cl^-) current.

Conductivities: $\sigma_{Na} = m^3 h$, $\sigma_K = n^4$, and $\sigma_{leak} =$ constant, with the gating variables m, h, and n. The functions $m_\infty(V)$, $n_\infty(V)$, increases with depolarisation whereas $h_\infty(V)$ decreases. All three functions together with $\tau_m(V)$, $\tau_h(V)$, and $\tau_n(V)$ were determined experimentally.

A typical action potential obtained with the mathematical model proposed by Hodgkin and Huxley is shown in Fig.1a. This reproduces the observed action potential – a splendid confirmation of their theory of neural activation.

2.4 A simple model for action potentials

The Hodgkin-Huxley model shows a wide variety of dynamical phenomena aside from action potentials. A general analysis of these phenomena is very complex since the model has four system variables. We will focus on a simpler model showing many similarities with the Hodgkin-Huxley model. An important method for reducing the complexity of models has been presented in the lecture on dynamic systems: the quasi-steady-state approximation. Here, fast gating variables (small τ's) will be set to $W \approx W_\infty(V)$. Morris

Parameter	Fig. 1,3,4	Fig. 5,6	Fig. 7
V_1	–1.2 mV	–	–
V_2	18 mV	–	–
V_3	2 mV	12 mV	12 mV
V_4	30 mV	17.4 mV	17.4 mV
V_K	–84 mV	–	–
V_L	–60 mV	–	–
V_{Ca}	120 mV	–	–
g_K	8 mS/cm^2	–	–
g_L	2 mS/cm^2	–	–
g_{Ca}	4.4 mS/cm^2	4.0 mS/cm^2	4.0 mS/cm^2
C_m	20 μF/cm^2	–	–
ϕ	0.04	0.0667	0.23
k	–	–	1/s
ε	–	–	200
K_z	–	–	1 μM

Table 1: Parameter values for the ML-model

and Lecar derived a model for electrically active muscle fiber cells in barnacles (Biophys. J. 35 (1981) 193–213). The model describes three ionic currents: a K^+, Ca^{2+}, and a leak-current (Ca^{2+} plays a similar role as Na^+ in the Hodgkin-Huxley model). The model has only two dyanamic variables: the membrane potential V and the gating variable w for the K^+-conductivity

$$C_m \frac{dV}{dt} = -g_{Ca} m_\infty(V)(V - V_{Ca}) - g_K w (V - V_K) - g_L (V - V_L) \tag{10}$$

$$\frac{dw}{dt} = \phi \frac{w_\infty(V) - w}{\tau(V)}, \tag{11}$$

where

$$m_\infty(V) = \frac{1}{2}(1 + \tanh\{(V - V_1)/V_2\}), \tag{12}$$

$$w_\infty(V) = \frac{1}{2}(1 + \tanh\{(V - V_3)/V_4\}), \tag{13}$$

and

$$\tau(V) = 1/\cosh\{(V - V_3)/(2V_4)\}. \tag{14}$$

The parameters used in model calculations and in the tutorial are listed in Tab. 1.

2.5 Excitation and action potential

The simplification proposed by Morris and Lecar proves to be very useful for the investigation of electrical excitation of membranes [1]. The presence of only two variables allows for studying the system in the phase plane spanned by the two variables V and w (Fig. 2). The two curves along which V and w do not change ($dV/dt = 0$ and $dw/dt = 0$) are called

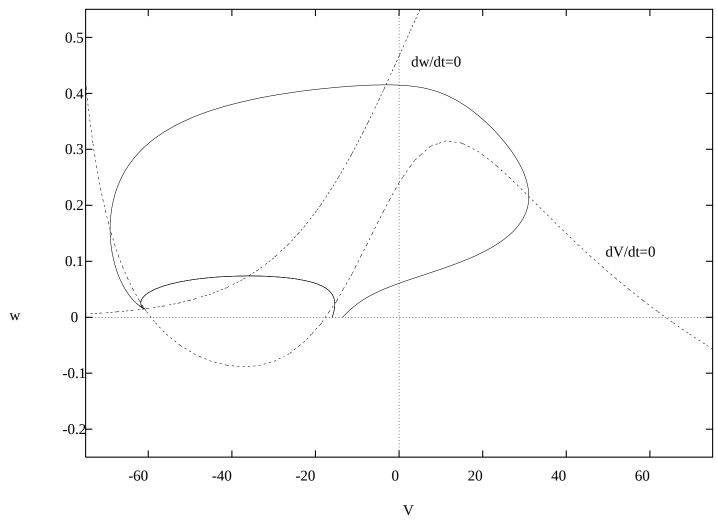

Figure 2: Phase plane of the ML-model without external input.

nullclines and are represented by dashed lines. At their (unique) intersection, both, V and w, remain constant – this is the steady state of the system. In steady state the membrane potential is approximately -60 mV and the potassium channels are only slightly opened.

The cell might be displaced from its rest state by an instantaneous depolarisation using a brief electric pulse. For small pulses the membrane potential relaxes directly to the rest state. For sufficiently large pulses, however, the cell responds by firing an action potential: the Ca^{2+}-channel is activated, its own conductivity increases due to the depolarisation and the increasing Ca^{2+}-current further depolarises the membrane (positive feedback). With a delay also the K^+-conductivity ($\sim w$) increases and the K^+-current eventually returns the membrane potential to its resting value.

The two solution paths ("trajectories") in Fig. 2 demonstrate that there is a narrow threshold for the generation of action potentials, almost an "all-or-nothing" behaviour. In fact, the threshold is graded. For decreasing ϕ the threshold gets narrower while increasing ϕ leads to a more gradual behaviour of the action potential and a sharp threshold ceases to exist. It has indeed been confirmed that at higher temperatures (increase in ϕ) the squid giant axon shows a gradual reaction behaviour.

[1] The Morris-Lecar model has being extensively analysed in J. Rinzel & G. B. Ermentrout, Analysis of neural excitability and oscillations, in: Methods in neural modeling: From ions to networks (eds. C. Koch & I. Segev), MIT Press 1998.

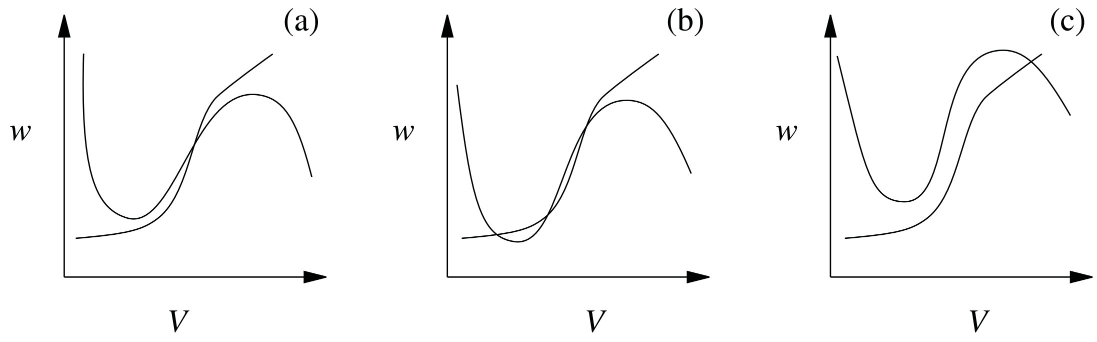

Figure 3: Possible configurations for the nullclines when $I_0 > 0$: (a) one steady state where the V-nullcline has positive slope, (b) three steady states, and (c) one steady state in the right part of the V-nullcline with negative slope.

2.6 Synaptic stimulus and periodic firing

Experimentally the depolarisation can be induced using electrodes. How is it generated *in vivo*? Mainly by electric currents induced by synapses which can be taken into account by an additional term in the current balance equation (10). A depolarising (hyperpolarising) current can be considered as a summation over excitatory and inhibitory synaptic currents. We denote the sum of such currents reaching the soma with $I(t)$. For the sake of simplicity we define – in contrast to the convention for ionic currents – a depolarising synaptic stimulus as positive ($I(t) > 0$). Therefore the current balance equation reads

$$C_m \frac{dV}{dt} = -g_{Ca} m_\infty(V)(V - V_{Ca}) - g_K w(V - V_K) - g_L(V - V_L) + I(t). \qquad (15)$$

A short depolarising pulse $I(t) > 0$ can trigger an action potential.

What happens if a depolarising synaptic current is applied for a longer time, e.g. a constant current $I(t) = I_0 > 0$? The phase plane is altered as follows. The equation for w (and therefore the w-nullcline) remains unchanged. The V-nullcline, however, is now given by

$$w(V) = \frac{-g_{Ca} m_\infty(V)(V - V_{Ca}) - g_L(V - V_L)}{g_K(V - V_K)} + \frac{I_0}{g_K(V - V_K)}, \qquad (16)$$

meaning it is shifted upwards by $I_0/(g_K(V - V_K))$ (note that this amount is a function of V). Three new constellations are possible (Fig. 3).

We can gather information about the system's dynamics by investigating the stability of the steady state (or states as in Fig. 3b). Denoting the steady state by $(\bar{V}, \bar{w})$, its local stability is revealed by the solutions of the quadratic equation (see lecture on dynamic systems)

$$\lambda^2 - (a + d)\lambda + (ad - bc) = 0, \qquad (17)$$

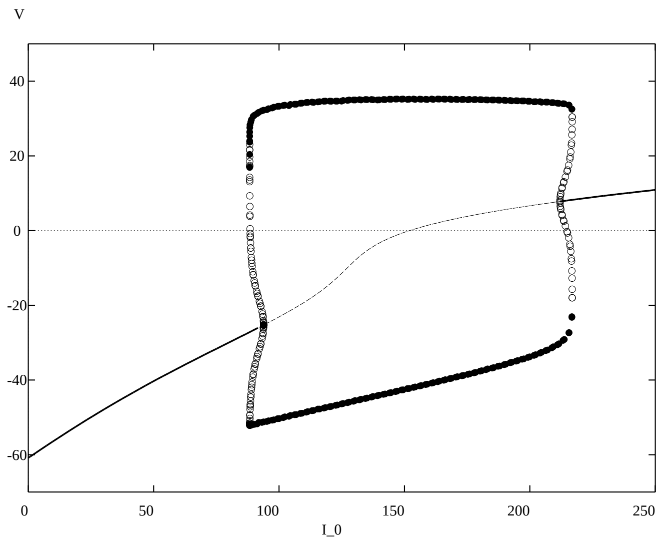

Figure 4: Bifurcation diagram of the Morris-Lecar model with two Hopf bifurcations by which periodic firing occurs. Stable and unstable stationary states are indicated by solid and dashed lines, respectively. Stable (unstable) limit cycles are indicated by black (white) circles.

where

$$a = -\left.\frac{\partial I_{Ion}(V,w)}{\partial V}\right|_{\bar{V},\bar{w}}, b = -\left.\frac{\partial I_{Ion}(V,w)}{\partial w}\right|_{\bar{V},\bar{w}}, c = \left.\frac{\phi}{\tau(\bar{V})}\frac{dw_\infty(V)}{dV}\right|_{\bar{V}}, d = -\frac{\phi}{\tau(\bar{V})} \quad (18)$$

are the coefficients of the Jacobian evaluated at the steady state $(\bar{V}, \bar{w})$. It is not possible to find a closed expression for the steady state $\bar{V}$. However, it is implicitely given by the relation

$$I_{Ion}(\bar{V}, w_\infty(\bar{V})) = I_0. \quad (19)$$

Let us first consider the cases in Figs. 2a and 2c. There exists one intersection of the nullclines, therefore Eq. (19) possesses one solution. This was also the case in the previous section where the steady state was stable: after perturbing the membrane potential the system returns to its steady state. However, it is possible that the steady state loses its stability and becomes unstable.

A steady state can become unstable but still remains the only steady state of the model. As we know from the lecture on dynamic systems, an occuring instability always involves the change of the sign of the real part of one or more eigenvalues of the characteristic equation (17). In our case, bifuration theory makes the following limitation: to avoid more steady states to occur, the instability means *a change of sign of a pair of complex conjugated eigenvalues*. This so-called Hopf bifuration takes place when

$$\frac{\partial I_{Ion}(V,w)}{\partial V} + \frac{\phi}{\tau(V)} = 0. \quad (20)$$

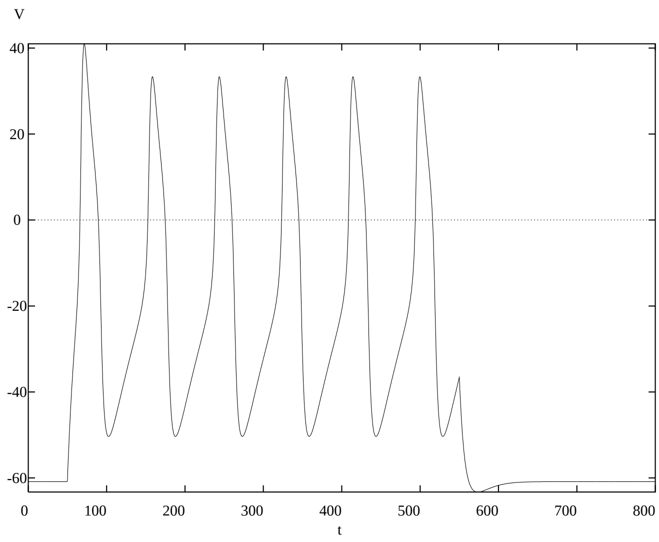

Figure 5: Stimulation of the ML-neuron with $I_0 = 150\ \mu\text{A/cm}^2$ between $t = 50$ ms and 550 ms.

A negative left hand side of the equation involves an unstable steady state $(\bar{V}, \bar{w})$. Therefore, an instability can only occur if: 1) the instantaneous I–V relation has negative slope at $\bar{V}$ (negative resistance)

$$\frac{\partial I_{Ion}(V, w)}{\partial V} < 0,$$

and 2) the relaxation time τ of the activating K^+-channels is sufficiently large such that

$$\frac{\phi}{\tau(V)} < \left|\frac{\partial I_{Ion}(V, w)}{\partial V}\right|.$$

The "negative resistance" in the Morris-Lecar model is the result of the positive feedback of the depolarising Ca^{2+}-current on its own conductivity. In the Hodgkin-Huxley model this corresponds to the positive feedback of the depolarising Na^+-current on the Na^+-conductivity.

Let us now investigate numerically what happens at such an instability. Figure 4 shows the behaviour of the model when varying the input I_0 between 0 and 250 $\mu\text{A/cm}^2$. Below $I_0 = 93.85\ \mu\text{A/cm}^2$ and above 212 $\mu\text{A/cm}^2$ the steady state is stable, in between it is unstable. At these points (Hopf bifurcations) a periodic solution, a *limit cycle* emerges. The limit cycle corresponds to an oscillation of the membrane potential – a constant excitatory synaptic current can make the neuron fire periodically (Fig. 5). The two Hopf bifurcations are called subcritical: the limit cycles arising from them are unstable (white circles in Fig. 4). This often leads to coexistence of a stable limit cycle and a stable steady state in the paremeter regions near the Hopf bifurcations.

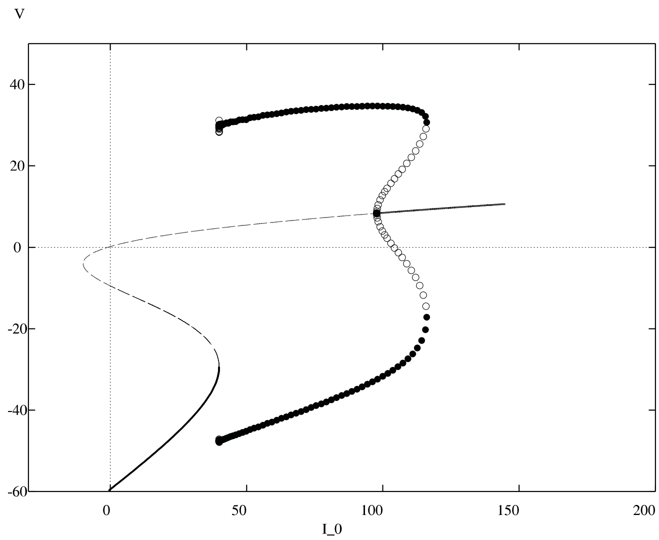

Figure 6: Bifurcation diagram of the ML-model with multistationarity, saddle-node-loop and Hopf bifurcation.

2.7 Slow oscillations and bursting

Action potentials and regular oscillations generated by a Hopf bifurcation are not the only dynamic patterns the model can produce. Here we discuss two different modes of behaviour which are also observed in neurons. These modes can be observed if the parameters of the model lie in a range in which the situation depicted in Fig. 3b can occur for some input I_0.

(i) Oscillations with very large period

Figure 6 shows a bifurcation diagram in which both, oscillations and three coexisting steady states (multistationarity), are present. At high values of I_0 there exists one unique steady state. Decreasing I_0, this steady state becomes unstable at about $I_0 = 100\ \mu\mathrm{A/cm}^2$, and oscillations emerge (via a subcritical Hopf bifurcation). On the other hand, following the fix point curve from low values of I_0, one reaches a "knee" at $I_0 \approx 40$ (a so-called saddle-node bifurcation). It is exactly at this value of I_0 where the branches (coming from the right) of the limit cycles (oscillations) vanish. These two incidences indicate a drastic change of the phase portraits, a global bifurcation. A result of this bifurcation is the occurrence of a limit cycle (coming from the left, i. e. increasing I_0) with infinitely slow period (Fig. 7). Of course, this involves periods which are orders of magnitude slower than the characteristic time τ of the K^+-channel. This example demonstrates the impossibility of extracting the temporal behaviour of ionic channels from experimentally observed firing rates of neurons.

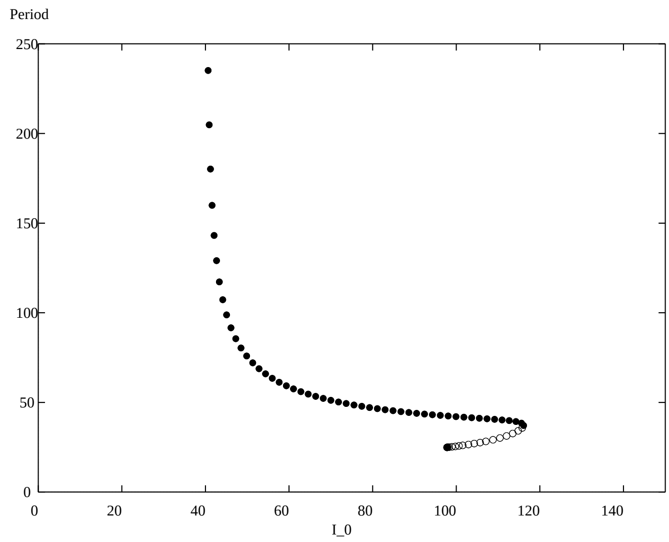

Figure 7: Period of the oscillations in the bifurcation diagram in Fig. 6.

(ii) Bursting

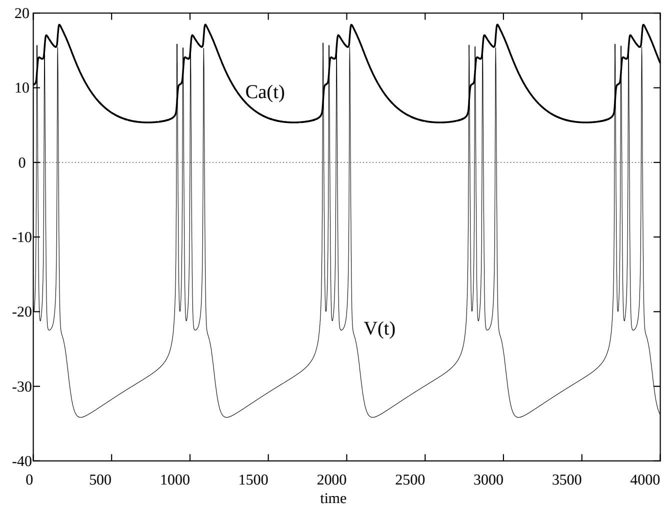

Figure 8: *Bursting*-oscillations with slow Ca^{2+}-dynamics

Other possibilities to generate slow oscillations are of course slowly opening or closing channels or other slow processes. In the following we consider an example for the interaction of a slow and a fast oscillation within a neuron. For instance, many cells possess a Ca^{2+}-activated K^+-channel

$$I_{K-Ca} = g_{K-Ca}\, z(V - V_K) \tag{21}$$

which we assume to be activated instantaneously by Ca^{2+}:

$$z = \frac{Ca}{K_z + Ca}. \tag{22}$$

We add this to the current balance equation (15). The Ca^{2+}-concentration in the cytoplasm of the cell is governed by the Ca^{2+}-influx via Ca^{2+}-channels (I_{Ca}) and the active transport of Ca^{2+} out of the cell by the Ca^{2+}-ATPase:

$$\frac{dCa}{dt} = \frac{1}{\kappa}\left(-\frac{I_{Ca}}{F} - k\,Ca\right), \tag{23}$$

where F is the Faraday constant and k the rate constant of the Ca^{2+}-ATPase. Ca^{2+} is strongly buffered inside the cell (mainly through binding by proteins); the parameter κ is the so-called buffer capacity which in neurons lies in the range between 100 and 1000. As a consequence, the calcium concentration varies slowly on the time scale of neural dynamics.

The dynamics of the model including I_{K-Ca} is depicted in Fig. 8. A typical firing pattern of certain neurons, especially in invertebrates, evolves: *bursting* – a cyclic expression of short action potentials. In the present case this works as follows. Under conditions with low Ca^{2+}-concentration the Ca^{2+}-activated K^+-channels are mostly closed and the membrane depolarises spontaneously – action potentials are fired. Since these are supported by an influx of Ca^{2+}, the Ca^{2+}-concentration increases successively until the resulting current I_{K-Ca} affects the state of the membrane to drop beneath the activation threshold. This in turn reduces I_{Ca} and Ca^{2+} is slowly being pumped out of the cell. As a consequence, the Ca^{2+}-dependent K^+-channels are closed and the cell begins firing anew.

2.8 References

Hodgkin, A. and Huxley, A. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117: 500–544.

Morris, C. E. and Lecar, H. (1981). Voltage oscillations in the barnacle giant muscle fiber. *Biophys. J.* 35: 193–213.

Rinzel, J. and Ermentrout, G. B. (1998). Analysis of neural excitability and oscillations. In: *Methods in neural modeling: From ions to networks*, eds. C. Koch and I. Segev, 2nd ed., pp. 251–291. MIT Press: Cambridge.

2.9 Tutorial

1. How do the Ca^{2+}- and K^+-channels respond to an increasing membrane potential V? This dependency is determined by equations (12) and (13). What can you say about the time dependency of this response – see Eq. (11).

2. A simple qualitative model for action potentials based on the Hodgkin-Huxley equations was derived by Fitzhugh. It reads

$$\frac{dV}{dt} = V(a-V)(V-1) - W \tag{24}$$

$$\frac{dW}{dt} = b\,(V-W)\,, \tag{25}$$

with $a < 1$. Sketch the nullclines $dV/dt = 0$ and $dW/dt = 0$ in the phase plane for $a = 0.25$. With this parameter value, can the model possibly describe an action potential and periodic firing? For the answer, calculate the steady state and investigate its stability.

3. Use `Mathematica` to numerically integrate the Morris-Lecar model for $I(t) = 0$ using the parameter values used for Fig. 2 (see Table 1). Determine the range of excitation values for which an action potential is generated by chosing different initial conditions for V. Plot the Ca^{2+}-current and K^+-current as a function of time during an action potential.

4. Numerically integrate the Morris-Lecar model for the same parameter values but different $I_0 > 0$ (excitatory synaptic stimuli). Use Fig. 4 as an orientation. Plot the oscillations as functions of time as well as in the phase plane.

5. (extra task – difficult!!) Can you find values for I_0, for which oscillations can be terminated by a cleverly chosen depolarising or hyperpolarising stimulus? Such a "black-hole"-behaviour has been experimentally observed, e. g. in the heart muscle. Try to realise this mode of behaviour in the model.