3.4 Biological Neuron Models

Learning objectives:

In this chapter I would like to introduce you to neuron models that allow to model the bio-chemical processes that take place in the nerve cells to generate an action potential. For this I present the Hodgkin and Huxley neuron model to you. As a further goal of this chapter, I would like to show how you can get from this rather complex model to more manageable models, which still allow conclusions to be drawn about the parameters for describing the ion dynamics. In the end I present an implementation within an electronic circuit to build a bridge to neuromorphic engineering.

In this chapter I would like to answer the following questions:

- What is the Hodgkin and Huxley neuron model?
- What are the gating variables and what do they describing?
- What is the FitzHugh-Nagumo neuron model?
- How works the phase plane analysis and what is a relaxation oscillator?
- How to solve the van der Pol oscillator?

3.4 Biological Neuron Models

- In the last chapter we showed that the following set of differential equations is sufficient to mathematically simulate the dynamics and behaviour of neurons.
  - In general terms we came to the general nonlinear integrate-and-fire model:

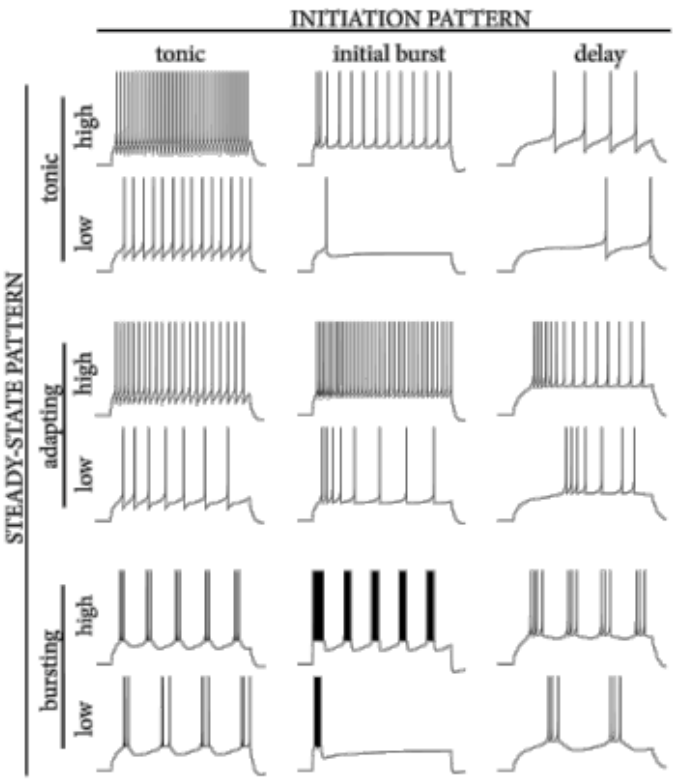
$$\tau \frac{\mathrm{d}u}{\mathrm{d}t} = f(u) + G(u)\, I$$

  - We were able to show that by choosing a suitable non-linearity for *f(u)* and by using a second differential equation, the complete behaviour of a neuron can be simulated (see figure):

$$\tau_m \frac{\mathrm{d}u}{\mathrm{d}t} = f(u) - R \sum_k w_k + R\, I(t)$$

$$\tau_k \frac{\mathrm{d}w_k}{\mathrm{d}t} = a_k \left(u - u_{\mathrm{rest}}\right) - w_k + b_k \tau_k \sum_{t^{(f)}} \delta\left(t - t^{(f)}\right)$$

  - However, this model does not allow any conclusions to be drawn about the bio-chemical processes that take place in the cell.

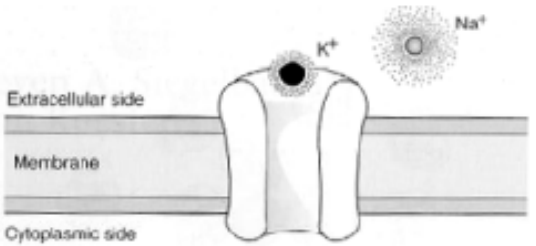


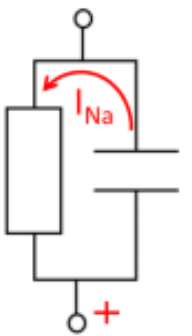
We therefore want to look at an expansion of the methodology for emulating the biochemical processes in this chapter

3.4 Biological Neuron Models

- Already in 1952, Hodgkin and Huxley examined the development of action potentials on the giant axon of a squid and, in addition to their measurements, designed a physical model, the so-called Hodgkin and Huxley neuron model.
  - In 1962 the two scientists received the Nobel Prize for their work.
  - The model originally describes three types of ion channels, but can be expanded to include more.

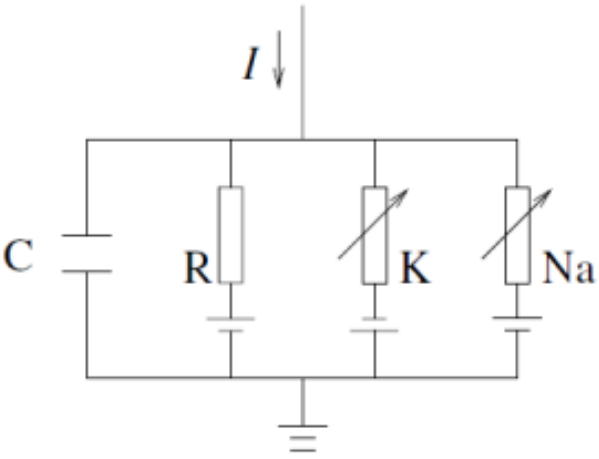
- Before we look at the model in detail, we should recall something about the generation of an action potential from chapter 2:
  - the origin of action potentials lies in the special property of the voltage dependency of ion channels: in response to a membrane polarization, sodium channels can open.
  - If a threshold value is reached during the depolarization of the membrane potential, ion channels open for Na^+ ions.
  - The more positive the membrane potential becomes, the more ion channels open.
  - When the membrane potential reaches about +50 mV, the ion channels close again and the cell interior is positively charged to the cell exterior.
  - This has an effect on K^+-ions, which are transported out of the cell, making the cell interior negative again.
  - This is easy to understand our small RC circuit: assuming the capacitor is charged, when the potential at the negative pole increases, the capacitor is discharged via the resistor.





3.4 Biological Neuron Models

- The Hodgkin and Huxley neuron model can be represented within a simple circuit model as shown in the figure:
  - According to the slide before capacitor acts as the cell membrane and separates the interior of the cell from the extracellular liquid.
  - If an input current I(t) is injected into the cell, the current either charges the capacitor or flow through the ion channels denote as an variable resistance R_K and R_{Na} in the model
  - Further the model accounts for a leakage channel/resistance R.
  - The battery (defined resting potential) accounts the fact that of active ion transport through the cell membrane, the ion concentration inside the cell is different from that in the extracellular liquid.
  - As the different ion channels have different resting potentials, one battery is uesd for each channel.



- In analogy to the LIF neuron, the circuit can easily be transferred into a mathematical equation:

$$I(t) = I_{\text{cap}}(t) + \sum_k I_k(t)$$

$C = Q/u$ and $I_{\text{cap}} = C\,\mathrm{d}u/\mathrm{d}t$.

$$C\frac{\mathrm{d}u}{\mathrm{d}t} = -\sum_k I_k(t) + I(t)$$

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- So far that's nothing great new. It is a bit like the one in the previous chapter. And yes the procedure is similar. Next you need the voltage dependence of the ion channels:
  - the sumof the ionic currents which pass through the cell membrane $\sum_k I_k$ must be rewritten by their voltage dependency.
  - This is exactly what Hodgkin and Huxley did and they found: $$\sum_k I_k = g_{\mathrm{Na}}\, m^3 h\, (u - E_{\mathrm{Na}}) + g_{\mathrm{K}}\, n^4\, (u - E_{\mathrm{K}}) + g_{\mathrm{L}}\, (u - E_{\mathrm{L}})$$

- This equation is somewhat complicated and requires closer examination.
  - But before we do so let's define the different variables:
  - The leakage channel is described by a voltage-independent conductance $g_L = \frac{1}{R}$.
  - Since u is the total voltage across the cell membrane and E_L the voltage of the battery (reverse potentials):
$$\Rightarrow I_L = g_L(u - E_L)$$
  - The conductance of the channels is voltage and time dependent. Thus, if all channels are open, they transmit currents with a maximum conductance g_K and g_{Na}.
  - Parameters for the Hodgkin-Huxley equations fitted on pyramidal neurons of the cortex are shown in the table.

x	E_x [mV]	g_x [mS / cm^2]
Na	55	40
K	-77	35
L	-65	0.3

3.4 Biological Neuron Models

- The important thing about the Hodgkin and Huxley model is that it contains information about the effective resistance of the individual ion channels as function of time and voltage. For this, they introduces the gating variables m, n, and h; with which the channel flows can be written as follows:

$$\Rightarrow I_{Na} = g_{Na} m^3 h (u - E_{Na}) \quad \text{and} \quad I_K = g_K n^4 (u - E_K)$$

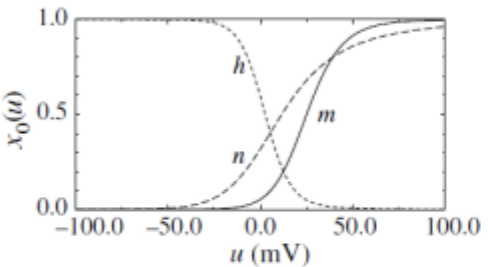
- Thus, the gating variables gives the probability that a channel is open at a given moment in time. The following functionalities are assigned to the variables in more detail:
  - The combined action of m and h controls the Na channels and the K channels are controlled by n.
  - m describes the activation (opening) of the Na channel and h its inactivation (blocking).
  - n describes the activation of the K channel.
- The three gating variables evolve according to differential equations of the form:

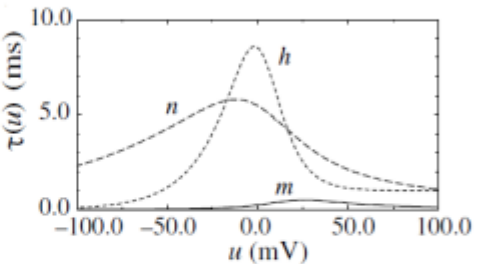
$$\dot{x} = \frac{dx}{dt} = -\frac{1}{\tau_x(u)}\left(x - x_0(u)\right) \qquad \text{for } x = m, h, or\ n$$

  - Here τ_x is the characteristic time constant of the respective ion channel, while x_0 is an asymptotic value that takes into account a maximum saturation value.

3.4 Biological Neuron Models

- We now have a system of differential equations that we can solve and we want to do this in the following. Since the solution is not really difficult but the equations are a bit long we want to proceed step by step.
  - Let's take a look at what the equation says: for a fixed value of u, the variable x approaches the value $x_0(u)$ with the time constant $\tau_x(u)$.
  - The voltage dependency of the two variables $x_0(u)$ and $\tau_x(u)$ is shown in the graphs on the right.
  - These were extracted from measurements of pyramidal neurons in the cortex and are therefore numerically determined functions.





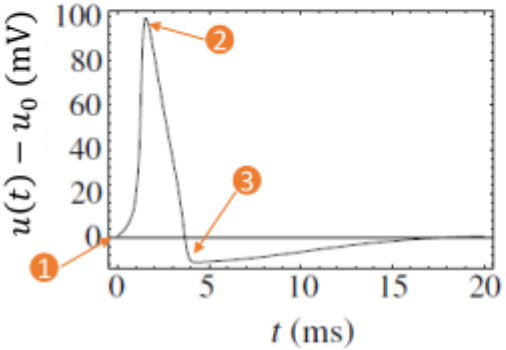
  - Let us now consider the example with the following boundary conditions: $u_0 = -65\ mV$ for $t < t_0$ and then switches to u. This can be used to calculate the equation for x and we get for the gating variables:

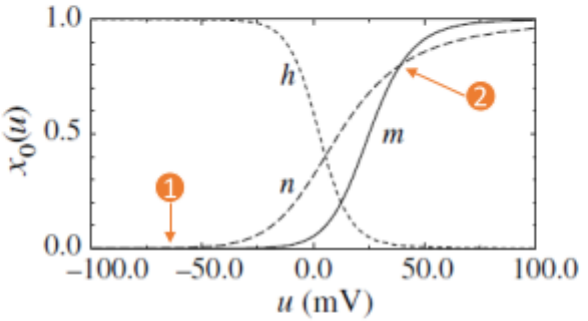
$$x(t) = x_0(u_1) + \left(x_0(u_0) - x_0(u_1)\right) \exp \frac{-(t - t_0)}{\tau_x(u_1)}$$

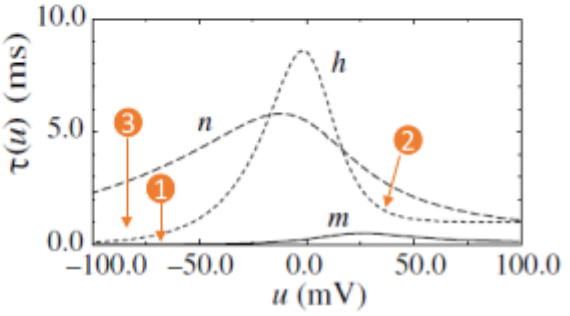
  - Thus with the use of the functions for x_0 and $\tau_x(u_1)$ we can calculate the sodium I_{Na} and potassium current I_K.

3.4 Biological Neuron Models

- Now, we have the necessary formulas together which enables us to understand the biophysics underlying the generation of an action potential:







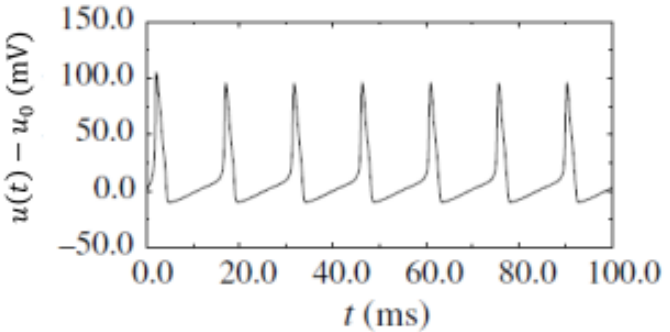
- The variables *n* and *m* increase and *h* decreases with increasing voltage *u* ($u_0 = -65\ mV$ which is labelled as 1).
- This leads to an opening of the ion channels and an action potential is initiated (**label 1**).
- At high values of *u*, the sodium conductance is slowly switched off by the factor *h:* τ_h is getting relatively small which leads to extreme short time constants in the exponential $\propto \exp\frac{-t}{\tau_h}$ and thus high impact of h (**label 2**).
- Since τ_h is always greater than τ_m, *h* reacts more slowly to a change in voltage than *m* the potassium (K^+) current sets in on a slow time scale: action potential followed by a negative overshoot (**label 3**).

3.4 Biological Neuron Models

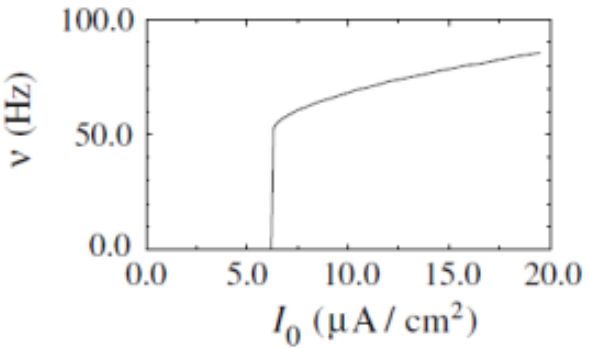
- In addition to generating the action potential, other important properties of neuronal excitation can also be demonstrated within the Hodgkin-Huxley model. A really important aspect is information coding:

$$C\frac{\mathrm{d}u}{\mathrm{d}t} = -\sum_k I_k(t) + I(t)$$

- If we consider a constant input current $I(t) = I_0$ for $t > 0$, we observe a constant spike pattern in the model for $I_0 \geq 2.7\ \mu m/cm^2$ (see figure on the right)



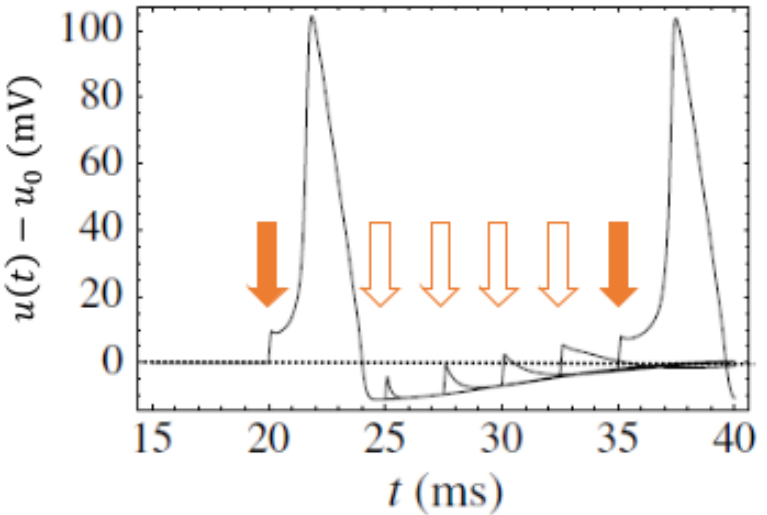
- This leads to the frequency-current representation shown in the figure below: firing rate $\nu = 1/T$ and T is the inter-spike interval.



- Now this should already be familiar to one or the other. If you do not know this, please look again in chapter 2 and find that this corresponds to the mean firing rate coding.

3.4 Biological Neuron Models

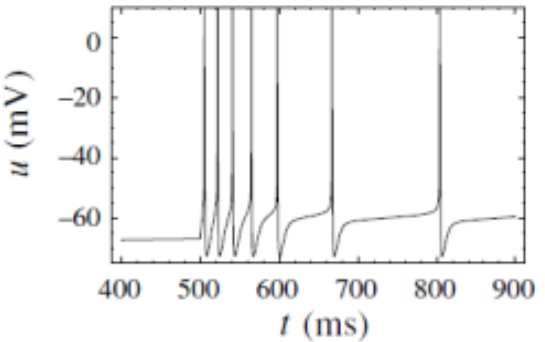
- Another important property of action potentials is the refractory period, which prevents two signals from becoming indistinguishable from each another.
  - ➢ This can or better say must be observed in the Hodgkin-Huxley model. If this were not possible, the model would not be complete ....
  - ➢ For this we consider the spike pattern in the figure:
    - for t = 20 ms a current pulse trigger an action potential (see first filled arrow).
    - further current pulses at t = 25, 27.5, 30, 32.5 ms are not sufficient to trigger an action potential (see not filled arrows)
    - However at t = 35 ms the same current pulse is able to trigger a second action potential (see second filled arrow)



- The reason for that is not so difficult to get: Since the voltage after an action potential lies far below the zero line, the strength of the current pulse is not sufficient to initiate an action potential. For this, the leakage term R_L is especially important, which leads to a reduction of the potential after the current induction.

3.4 Biological Neuron Models

- From the consideration of the important aspects that can be observed within a spike patterns of a neuron, we still lack another to be complete here. This is adaptation, i.e. the gradual decrease in spike intensity with constant excitation (see upper figure).

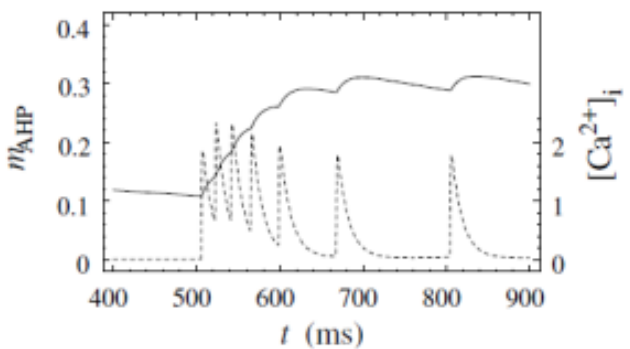


  - Here, in particular, the after hyperpolarization (AHP) is the principal feedback mechanism which control the frequency and patterning of neuronal firing.
  - Such a mechanism can be traced back to a calcium activated potassium current. Which can be taken into account in the model using another ion channel:

$$\sum_k I_K = g_L(u - E_L) + g_{Na} m^3 h (u - E_{Na}) + g_K n^4 (u - E_K) + I_{AHP}$$

with the ion current

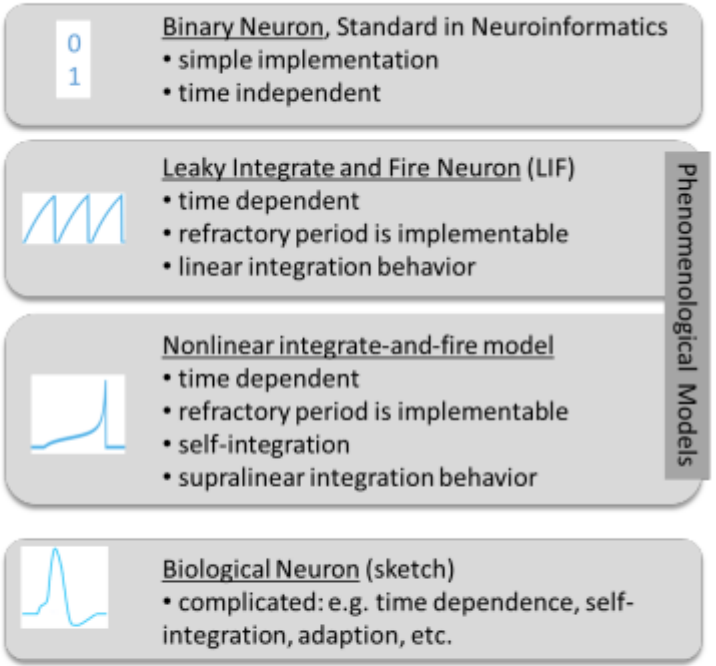
$$\begin{cases} I_{AHP} = g_{AHP}([Ca^{2+}]) m_{AHP} \cdot (u - E_K) \\ \dfrac{dm_{AHP}}{dt} = \alpha m_{AHP} - \beta(1 - m_{AHP}) \end{cases}$$



  - I_{AHP} depends on the calcium concentration within the synaptic gap, which, as shown in the figure (dashed line), initially makes a strong contribution, but decrease over time course of the spike train.
  - The initially sharp increase in the gating variable m_{AHP}, saturates over time as well. Thus, the contribution I_{AHP} to $\sum_k I_K$ is less over the time course.

3.4 Biological Neuron Models

- Thus with the Hodgkin-Huxley model we have a model with which we can describe the dynamics of the individual ion channels and thus gain insight into the functionality of the bio-chemistry of cells.
- As already mentioned, such a model helps to understand the bio-chemical processes in the cells. However, it is very cumbersome and far too complex to describe networks in which there are a large number of neurons.
- Therefore, there is a desire to make the model more handy: so to go back to a phenomenological model.
- Now the question arises, is that even possible? The answer is yes, and I would like to show this in the following.
- I would essentially like to show that complex biological models can be converted into phenomenological models and how these can then be built up in simple hardware circuits.
- let's go back to the beginning...



3.4 Biological Neuron Models

- We start with the Hodgkin-Huxley model in its full beauty:

$$C\frac{\mathrm{d}u}{\mathrm{d}t} = -\sum_k I_k(t) + I(t) \qquad \sum_k I_k = g_{\mathrm{Na}}\, m^3 h\,(u - E_{\mathrm{Na}}) + g_{\mathrm{K}}\, n^4\,(u - E_{\mathrm{K}}) + g_{\mathrm{L}}\,(u - E_{\mathrm{L}})$$

  - As a first step we like to reduce the variable in so-called concentrated parameters. Therefore we replace *n* and *h* by a single effective variable w:

$(b-h) = an$ and a,b are constants $\Rightarrow w = (b-h) = an,\ h = (b-w),\ \mathrm{n} = \frac{\mathrm{w}}{\mathrm{a}}$ and $m(t) \to m_0\,[u(t)]$

$$C\frac{\mathrm{d}u}{\mathrm{d}t} = \underbrace{-g_{\mathrm{Na}}[m_0(u)]^3\,(b-w)\,(u - E_{\mathrm{Na}}) - g_{\mathrm{K}}\left(\frac{w}{a}\right)^4 (u - E_{\mathrm{K}}) - g_L\,(u - E_L)}_{F(u,w)} + I$$

$$R = g_L^{-1},\ \tau = RC \qquad \boxed{\frac{\mathrm{d}u}{\mathrm{d}t} = \frac{1}{\tau}\left[F(u,w) + RI\right] \qquad \frac{\mathrm{d}w}{\mathrm{d}t} = \frac{1}{\tau_w} G(u,w)}$$

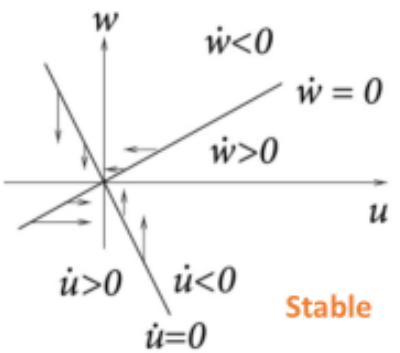
- This gives us the familiar form of the general LIF neuron model again. Only in the difference that we now have 2 variables *w* and *u*. The time dynamics of *w* can be summarized by a second differential equation and thus obtained in the model with concentrated parameters.

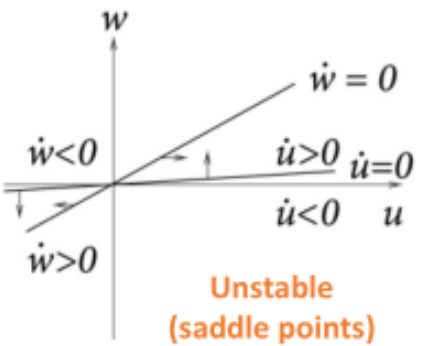
3.4 Biological Neuron Models

- In order to understand this rather general form for describing a neuron a little better and to see what generality is behind this representation, we consider the example of the FitzHugh-Nagumo neuron model:
  - FitzHugh and Nagumo claimed that for a discussion of action potential generation, the four equations of Hodgkin and Huxley can be replaced by two equations.
  - They obtained sharp pulse-like oscillations reminiscent of trains of action potentials by defining the two functions:

$$F(u,w) = u - \frac{1}{3}u^3 - w \quad \text{and} \quad G(u,w) = b_0 + b_1 u - w$$

  - A relatively elegant form of analysis of such two-dimensional neuron models can be made using a phase plane analysis, which is explained graphically in the pictures below:
  - The illustration shows 2 phases portraits around a fixed point:
    - The u-nullcline is the set of points were $\dot{u} = 0$
    - The w-nullcline is the set of points were $\dot{w} = 0$
    - the fixed points of the system, defined by $\dot{u} = \dot{w} = 0$
    - The arrows in the phase portrait are vertical on the u-nullcline and arrows are horizontal on the w-nullcline





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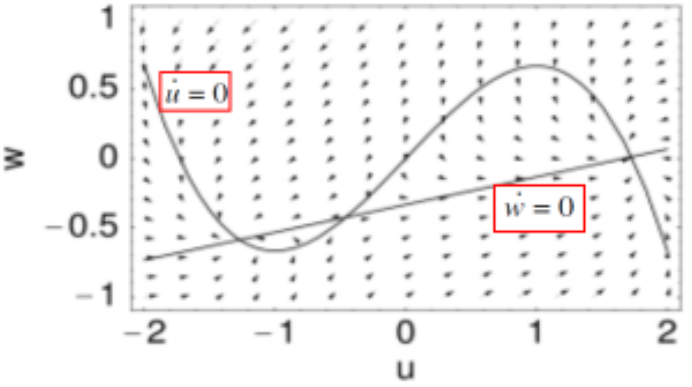
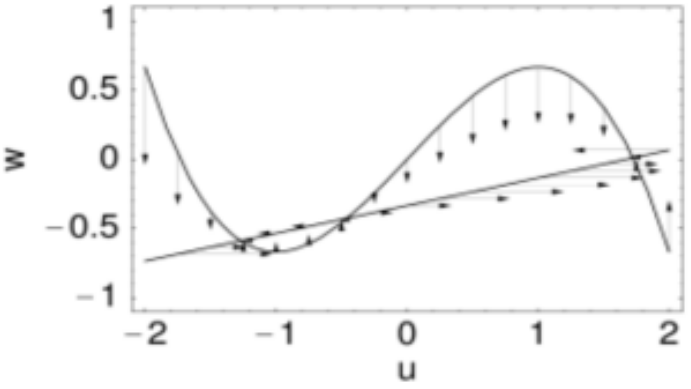
- Let's apply this procedure to the FitzHugh-Nagumo neuron model, i.e. we sign the phases portraits :
  - The u-nullcline (curved line) and the w-nullcline (straight line) intersect at the three fixed points.
  - The direction of the arrows indicates the flow.
  - Arrows on the u-nullcline point vertically upward or downward, while on the w-nullcline arrows are horizontal.
  - In the neighbourhood of the fixed points arrows have a short length indicating slow movement.
  - At the fixed point, the direction of the arrows change.





- next we want to look at what happens to the membrane voltage under external excitation, i.e. with the induction of a current value.

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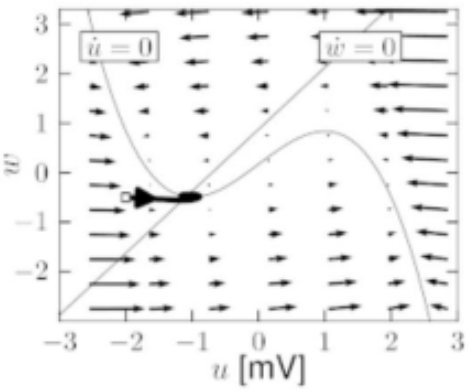
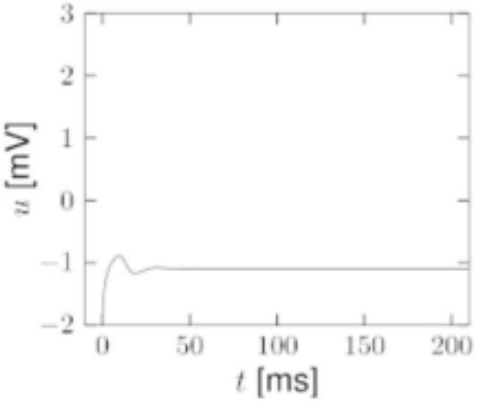
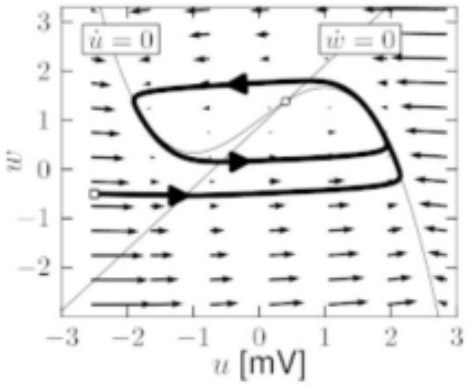
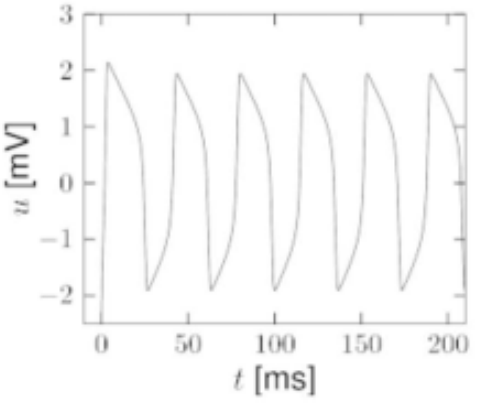
- But, first let's see what happens to the mebrane voltage *u* for zero input:
  - In the figures on the right we see that the phase portrait shows a fixed point without external stimulation.
  - This means that there is no oscillation, so spiking of the neuron is not possible.





- Now, let's give a positive input:
  - In the figures on the right we see that the fixed point is replaced by a so-called limit cycle (see bold line)
  - This enables constant oscillation, as can be seen in the right of the two diagrams.





3.4 Biological Neuron Models

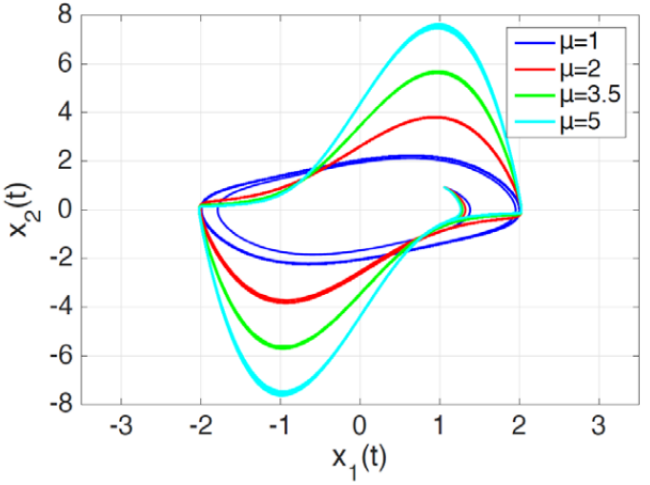
- Now we are so good at it and can further increase the level of abstraction of neuron models…
  - In the last example we saw that neurons can be described within an oscillator model. A very general oscillator model was set up by the Dutch physicist Balthasar van der Pol in 1927, who set up the following universal equation, which describes a large number of oscillators:

$$\ddot{x} - \mu(1 - x^2)\dot{x} + x = 0$$

  - The equation describes an oscillatory system with non-linear damping and self-excitation.
  - For small amplitudes the damping is negative (the amplitude is increased);
  - From a certain threshold value of the amplitude, the damping becomes positive, the system stabilizes and goes into a limit cycle.
  - The Liénard transformation converts the 2nd order differential equation into a 1st order one:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} x_2 \\ \mu(1 - {x_1}^2)x_2 - \omega^2 x_1 \end{bmatrix}$$

  - The phase portrait of the van der pol oscillator is shown in the figure.



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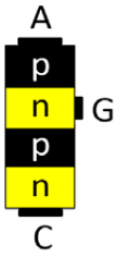
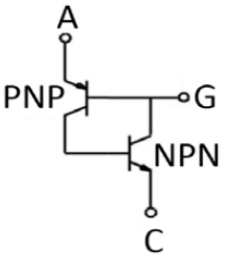
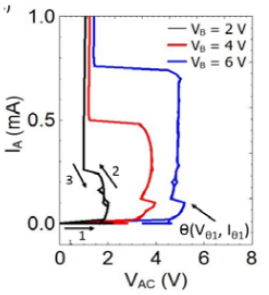
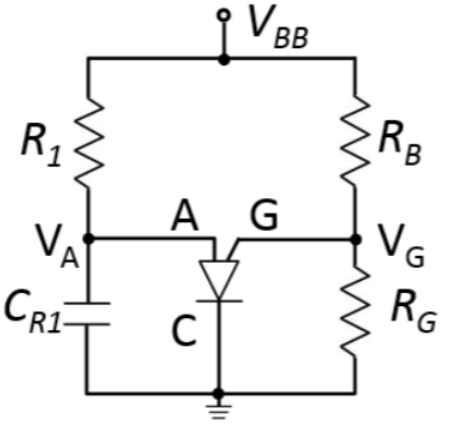
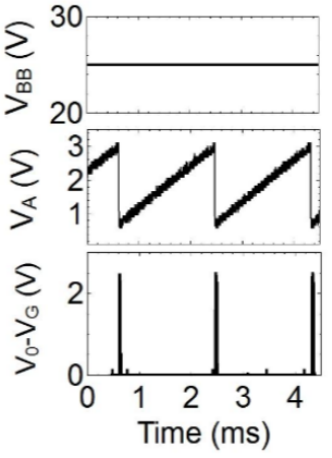
- Finally, I would like to show you that such a van der Pol oscillator can be easily implemented as an electronic circuit. Hence, we are back at neuromorphic circuits…
  - Therefore, we can a programmable unijunction transistor (PUT), which owns a negative differential resistance (see the I-V curve) and consist of a *pnpn* structure, as shown on the figure on the right side, and is a four-layered thyristor.
  - The self-sustained oscillator circuit (see figure below) consists of a resistor-capacitor integrator circuit at the anode (A) of the PUT.
  - A voltage divider consisting of two linear resistors (R_B, R_G) comprises the gate side (G) of the PUT.
  - A constant voltage V_{BB} applied to the oscillator circuit results in a charging of the capacitor.
  - If the capacitor voltage $V_C = V_A$ reaches the threshold V_θ of the PUT, it switches from off to on which leads to a sudden capacitor discharge: oscillation at the anode A can observed (see figure)











3.4 Biological Neuron Models

- I would like to end the chapter of the biologically inspired neuron models with a very brief summary.
  - ➢ We could see that with the rather complex Hodgkin and Huxley neuron model consisting of 4 equations, can be described well the bio-chemical processes of the ion channels.
  - ➢ The complexity of this model could be significantly reduced by the model of FitzHugh and Nagumo and still contains essential components of the Hodgkin and Huxley neuron model, although it only has 2 equations and not 4 equations.
  - ➢ Finally we have a neuromorphic circuit for which we have previously expanded the model FitzHugh and Nagumo to a relaxation oscillator described by the van der Pol equation.
- In the following chapter, we would like to continue here and ask ourselves the question of how can neurons be implemented as effectively as possible in hardware?
  - This especially requires good technology and the best we have at the moment is silicon technology ....but let's see this in the next chapter