Single Neuron Dynamics —
Models Linking Theory and Experiment

Jan Benda
Spiking Neurons
Neurons are basic elements of information processing in animals. They receive continuously input from other neurons via synapses or are directly stimulated by physical stimuli, if they are receptor neurons. The input is collected on the dendritic tree, were it is low-pass filtered or even actively processed through dendritic nonlinearities. At the soma the resulting ionic current is transformed into a sequence of “spikes”, fast and nearly uniform deflections of the membrane potential. These spikes or “action potentials” travel down the axon and serve as input for other neurons (see Fig. 2.1).

The transformation of some ionic current into spikes is a central step in neural information processing. In the first section of this chapter a short introduction to conductance-based models is given, which describe the detailed biophysical mechanisms of this transformation process. After discussing the different time scales in a neuron in the second section, the scheme for reducing the number of variables in conductance-based models of Kepler et al. (1992) is briefly sketched (section 2.3). Finally in section 2.4 properties of two basic classes of spiking neurons are discussed. The concepts introduced here will become important in the following chapter, where simple models of the generation of spikes are presented, and in chapter 4, which covers spike-frequency adaptation.
2.1 CONDUCTANCE-BASED MODELS

Like any other cell a neuron has a double-lipid layer as a membrane, which separates the cytoplasm from the extracellular space (Madigan et al., 1997). In this membrane specialized proteins are embedded. Ion pumps build up concentration gradients of different types of ions over the membrane. The concentration of potassium ions inside the cell is higher than outside, while for sodium, calcium and chloride ions it is the other way around. Some of the membrane proteins form pores, which allow ions to flow through the membrane. Such ion channels can be highly selective for different ion types. The efflux of positively charged potassium ions through potassium channels down the concentration gradient builds up an electric field over the membrane. The membrane potential $V$, at which the electrical field is strong enough to prevent potassium ions to further flow outside the cell, is the reversal potential $E_K \approx -80\, \text{mV}$ of potassium. The influx of sodium ions depolarizes the membrane toward the reversal potential of sodium $E_{Na} \approx +50\, \text{mV}$. The resting potential of about $-60\, \text{mV}$ is more close to the potassium reversal-potential. The values of these potentials are only clues; they differ from cell to cell. Some of the ion channels are voltage gated, i.e. their probability to be open depends on the membrane potential $V$ (see Fig. 2.2). Such channels are necessary for the generation of spikes. Other channels open or close depending on the concentration of intracellular calcium or transmitter molecules in synapses, for example (see the textbooks Hille, 1992; Johnston & Wu, 1997; Koch, 1999, for more details).

Figure 2.1: SIGNAL FLOW IN A NEURON. A neuron receives various inputs on its dendritic tree (sketched as arrows), where they are processed and summarized. The resulting ionic current $I(t)$ flows into the soma. There, the current is transformed into a sequence of spikes $\{t_i\}$ traveling down the axon. Synapses transmit these spikes to other neurons.
Figure 2.2: ION CURRENTS THROUGH CHANNELS IN THE CELL MEMBRANE. A schematic drawing of a patch of a neuron’s membrane is shown. The double-lipid layer separates charge and therefore acts like a capacitor $C$. Different types of ion channels are embedded into the membrane, which are highly selective to ionic currents. In a good approximation the currents through these channels can be modeled by a conductance $g$ and a battery $E$, which is the reversal potential of the current, reflecting the electrochemical gradient over the membrane. There is a leakage current with constant conductance $g_L$ and reversal potential $E_L$. Some of the channels are voltage gated, i.e. their conductance depends on the membrane potential $V$. Such channels are responsible for the generation of spikes. The sodium current (captured by $g_{Na}$ and $E_{Na}$) initiating a spike is activated by depolarization. A spike in turn inactivates the sodium current and activates a potassium current ($g_K$ and $E_K$), forcing the membrane potential back to rest. An additional current $I$ can be injected by a microelectrode.

2.1.1 Ion currents

Ions flowing through the channels represent an electric current over the cell membrane. The total current density $i_k$ through a whole population of ion channels of a specific type $k$ is described by the Goldmann-Hodgkin-Katz (GHK) current-equation (Johnston & Wu, 1997)

$$i_k(V) = P_k z_k^2 F \frac{V C_{k_{in}} - C_{k_{out}} e^{-z_k V/\xi}}{\xi} \frac{1 - e^{-z_k V/\xi}}{1 - e^{-z_k V/\xi}}$$  \hspace{1cm} (2.1)

where $P_k$ is the permeability of the membrane due to the considered channels, which may depend on membrane voltage. The charge of the ion is denoted by $z_k$. With the Faraday constant $F = 96485 \text{C/mol}$, the ideal gas-constant $R = 8.3144 \text{J K}^{-1} \text{mol}^{-1}$ and the temperature $T$ the factor $\xi$ is defined as $\xi = RT/F$. Since the concentrations $C_{k_{in}}$ and $C_{k_{out}}$ of the ions inside and outside the cell differ in general, the current-voltage relation described by the GHK-equation (2.1) is nonlinear. However, in physiologically relevant voltage ranges (about $-100$ to $40 \text{mV}$) it can be approximated by a linear relation (Johnston & Wu, 1997)

$$i_k = g_k (V - E_k)$$  \hspace{1cm} (2.2)

where $g_k$ is the total conductance of the channels per membrane area and $E_k$ is the reversal potential, reflecting the electrochemical gradient over the membrane (see Fig. 2.3).
2.1 CONDUCTANCE-BASED MODELS

Figure 2.3: The current-voltage relation for sodium and potassium ions. Drawn are two graphs of the GHK current-equation (2.1). The concentrations \([\text{Na}]_{\text{in}} = 0.015 \text{ M}, [\text{Na}]_{\text{out}} = 0.109 \text{ M}, [\text{K}]_{\text{in}} = 0.124 \text{ M} \text{ and } [\text{K}]_{\text{out}} = 0.005 \text{ M}\) are chosen to provide realistic reversal potentials: \(E_{\text{Na}} = +50 \text{ mV} \text{ and } E_{\text{K}} = -80 \text{ mV}\). The thin lines are possible linearizations (2.2).

2.1.2 Membrane equation

Due to Kirchhoff’s law all the currents over the membrane have to be summed up resulting in the membrane or current-balance equation\(^1\):

\[
CV = \sum_{k=1}^{M} g_k (E_k - V) + I. \tag{2.3}
\]

The term on the left hand side is the current charging the membrane with capacitance \(C\). \(\dot{V}\) denotes the time derivative \(dV/dt\) of the membrane potential \(V\). The input current \(I\) either is injected by a microelectrode or is the current from the dendritic tree. The membrane equation (2.3) is the basic equation of conductance-based neuron models. These models differ in the number \(M\) of ionic currents considered and in the way, how the conductances are modeled.

The membrane equation as given in (2.3) is a model of a point neuron, i.e. the spatial properties of the neuron are completely neglected. For some neurons, especially for receptor neurons, this is a good approximation. Multi-compartmental models are needed to take the spatial structure of a neuron into account. These models combine many single-compartment equations (2.3) by means of the cable equation (Segev, 1992; Segev & Burke, 1998; Schutter & Smolen, 1998). In this thesis, however, the spatial structure of neurons is neglected and the membrane equation (2.3) is the starting point for the following analysis.

2.1.3 Gating variables

Hodgkin and Huxley were the first who measured the properties of ionic currents in the giant axon of the squid and summarized their results in a conductance-based model

\(^1\)Usually the parameter values of conductance-based models are given per membrane area, therefore the unit of the input current \(I\) is \(\mu\text{A/cm}^2\).
Figure 2.4: A spike simulated by the Hodgkin-Huxley model. A spike is triggered by a current pulse of $20 \mu A/cm^2$ and 0.5 ms duration, applied at $t = 20$ ms. The spike is the short deflection of the membrane potential $V$. Right after the spike there is an after-hyperpolarization where the membrane potential is below the resting potential. B The time courses of the gating variables corresponding to the spike shown in A. The increase of the membrane potential caused by the current pulse is sufficient to activate the sodium current by its $m$ gating-variable. The sodium current raises the membrane potential, a spike is generated. At high potentials the potassium current is activated via its gating variable $n$ and the sodium current is inactivated by $h$. The spike is terminated. The increased potassium current after a spike is responsible for the after-hyperpolarization.

(Hodgkin & Huxley, 1952, see appendix A–1 for a definition of the model). They also introduced the concept of gating variables to model voltage gated channels. Each current may have an activation-variable $m$ and an inactivation-variable $h$. The conductance $g$ of the current is given by a maximum conductance $\tilde{g}$ times integer powers $p$ and $q$ of the gating variables $m$ and $h$:

$$g = \tilde{g}m^p h^q$$  \hspace{1cm} (2.4)

(for clarity the indices $k$ at each variable are omitted). The dynamics of the gating variables are described by first order differential equations

$$\tau_m(V) \frac{d}{dt} m = m_\infty(V) - m$$  \hspace{1cm} (2.5)

$$\tau_h(V) \frac{d}{dt} h = h_\infty(V) - h.$$  \hspace{1cm} (2.6)
The time constants, $\tau_m$ and $\tau_h$, as well as the steady-state variables, $m_\infty$ and $h_\infty$, depend on the membrane potential $V$.

Ionic currents which are not voltage-gated are combined to the so called "leakage current"

$$I_L = \bar{g}_L(E_L - V).$$

Its conductance $g_L$ is constant and the corresponding reversal potential is typically near the neuron’s resting potential.

With this formalism Hodgkin and Huxley were able to reproduce the local spiking behavior of the axonal membrane in the squid (Hodgkin & Huxley, 1952; Guttman & Barnhill, 1970). See also Fig. 2.4 for an example.

The procedure of measuring the properties of each current, i.e. $\bar{g}$, $E$, $\tau_m$, $m_\infty$, $\tau_h$ and $h_\infty$, requires voltage-clamp experiments and the use of drugs to selectively block the different types of channels. It is a high experimental effort to get all the necessary parameters to define a conductance-based model for a specific neuron. It would, therefore, be very helpful for studying the functional role of specific neurons to have a model with parameters, that can directly and more easily be measured.

In this and the following two chapters various conductance-based models are used to visualize and analyze properties of spiking neurons. Their specifications are put together in appendix A.

### 2.2 Time scales of neural dynamics

As a first step towards a simplified model of a spiking neuron, the dynamics of the activation and inactivation variables can be grouped with respect to their time constants as in Fig. 2.5.

The sodium current has a very fast activation variable $m$, which is responsible for the initiation of a spike, whose time constant $\tau_m$ is below one millisecond. Then there are several variables, called recovery variables, which terminate the spike. These are the sodium inactivation $h$, the activation of the potassium current (the so called “delayed rectifier”) $n$ (Hodgkin & Huxley, 1952) and the activation of the calcium current $s$ (Jaffe et al., 1994). These variables have time constants below ten milliseconds. The variables of the $A$-current, a different type of potassium current, are acting within this range, too (Connor & Stevens, 1971; Connor et al., 1977; Numann et al., 1987).

These two types of fast gating variables are necessary for the generation of spikes. If a neuron with only such variables is stimulated with a constant input, it fires regularly with a constant firing frequency (Hodgkin & Huxley, 1952; Connor & Stevens, 1971; Morris & Lecar, 1981). To investigate the dynamics of the generation of spikes it is thus sufficient to study neurons that only exhibit those fast gating variables. In section 2.4 basic properties of such neurons are summarized, which are important for the models proposed in chapter 3. Slower variables are necessary to induce phenomena like spike-frequency adaptation or bursting. This is discussed in chapter 4.

### 2.3 Reduction of the number of dynamical variables

Replacing gating variables with similar time constants by a single variable reduces the large number of variables of a conductance-based model. Such a reduced model can
be analyzed more easily and helps to uncover the basic principles of a spiking neuron. Various studies proposed low-dimensional models as an approximation of a full conductance-based model. While the Fitzhugh-Nagumo model (Fitzhugh, 1961) only conceptually reproduced the Hodgkin-Huxley model, the similar model of Hindmarsh & Rose (1982) matched experimental data quite well. More recent studies started from detailed conductance-based models. They treated the sodium activation-variable $m$ as instantaneous and combined empirically the two recovery variables $h$ and $n$ (Morris & Lecar, 1981; Awiszus, 1992; Abbott & Kepler, 1990).

After a more intuitive approach (Abbott & Kepler, 1990), Kepler et al. (1992) presented an optimal strategy for combining variables in conductance-based models. This approach is briefly sketched in the following paragraphs. The concept of the equivalent potential and the resulting low-dimensional systems are used in this and the following chapter.

### 2.3.1 Equivalent potential

As a first step on the way to a reduction of the number of variables the gating variables $x$ are transformed to their equivalent potential $V_x$. It is defined by the inverse steady-state variable $x^{-1}_\infty(V)$ of the gating variable $x$

$$V_x = x^{-1}_\infty(x)$$

(2.8)
2.3 REDUCTION OF THE NUMBER OF DYNAMICAL VARIABLES

Figure 2.6: EQUIVALENT POTENTIALS. A Definition of the equivalent potential of a gating variable $x$ via its steady-state variable $x_\infty(V)$. B Time courses of the equivalent potentials of all four variables of the Traub-Miles model evoked by a random stimulus. $V_0$ denotes the membrane potential of the original model. C, D & E Comparison of the equivalent potentials from B. C The membrane potential $V_0$ is most of the time nearly identical to activation-variable $m$ of the sodium activation. They differ only during spikes (loop). Thus, both variables can be combined to a representative membrane potential $V$. D The gating variables $h$ and $n$ can be combined to a single recovery variable $U$. E The membrane potential and the equivalent potential of the potassium gating variable $V_n$ are not similar at all.
and makes the gating variables comparable to the membrane potential $V$. The definition of the equivalent potentials is illustrated in Fig. 2.6 A. Time courses of the equivalent potentials for all four variables of the Traub-Miles model evoked by a random stimulus are superimposed in panel B and compared to each other in panels C, D & E. See appendix A–2 for a definition of the Traub-Miles model.

### 2.3.2 Grouping

The next step is to detect variables with similar time courses. In the example shown in Fig. 2.6 B the four variables fall into two distinct groups. The sodium activation-variable $m$ has a very small time constant, thus most of the time its equivalent potential is identical to the membrane potential. Only during spikes they differ (loop in panel C). The other group consist of the two recovery variables $h$ (sodium inactivation-variable) and $n$ (potassium activation-variable). They have similar time constants and the time courses of their equivalent potentials are similar, too (panel D). All four variables cannot be combined into a single variable, since, for example, the equivalent potential $V_n$ of the potassium activation-variable $n$ is not correlated with the membrane potential (panel E).

The clustering of variables into groups is based on sharing both a common time scale and a common sign of influence on the ionic current, i.e. $\text{sign}(\partial \tilde{F}/\partial V_i) = \text{sign}(\partial \tilde{F}/\partial V_j)$ in (2.11) below (Kepler et al., 1992). For this reason the two variables $a$ and $b$ of the A-current of the Connor model cannot be combined, since they have opposite effects on the membrane current.

### 2.3.3 Reduction

The final step is to linearly combine variables with similar dynamics. The fast sodium activation-variable $m$ can be combined with the membrane potential $V_0$ to a representative membrane potential $V$

$$V := \alpha_0 V_0 + \alpha_m V_m.$$  \hspace{1cm} (2.9)

The coefficients $\alpha_0$ and $\alpha_m$ are constrained to sum to one. Slow variables like $h$ and $n$ can be combined to a single recovery variable $U$

$$U := \alpha_h V_h + \alpha_n V_n + \ldots.$$ \hspace{1cm} (2.10)

Even slower variables may be combined to additional representative potentials in the same way as it is shown here for the $U$ variable.

After expanding the time derivatives of $V$ and $U$ to first order in the corrections $\delta_i = V_i - V$ ($i = 0, m$) and $\delta_j = V_j - U$ ($j = h, n$), the coefficients $\alpha_i$ and $\alpha_j$ can be chosen so that the first order corrections $\delta_i$ and $\delta_j$ vanish and the expansion is valid to second order. The resulting reduced set of differential equations is

$$\begin{align*}
\frac{C}{\alpha_0} \frac{dV}{dt} &= \sum_{k=1}^{M} g_k m_{\alpha_k} (V_{m_k}) h_{\alpha_k} (V_{h_k}) (E_k - V) + I := \bar{F}(V,V_i) + I \approx F(V,U) + I \\
\dot{U} &= \sum_{j=1}^{N} \alpha_j \frac{x_{\alpha_j} (V) - x_{\alpha_j} (U)}{\tau_{\alpha_j} (V) \cdot d x_{\alpha_j} (U) / dU}.
\end{align*}$$  \hspace{1cm} (2.11)

The first equation is the membrane equation (2.3) summing up all $M$ ionic currents $I_k$. Their gating variables $m_k$ and $h_k$ are replaced by their steady-state variables $m_{\alpha_k}$ and $h_{\alpha_k}$.
2.3 REDUCTION OF THE NUMBER OF DYNAMICAL VARIABLES

Figure 2.7: THE REDUCED HODGKIN-HUXLEY MODEL. A phase portrait of the Hodgkin-Huxley model reduced by the scheme of Kepler et al. (1992) as described in the text is shown. Similar to the Traub-Miles model in Fig. 2.6 the sodium activation-variable $m$ is combined with the membrane potential to a representative membrane potential $V$ on the abscissa. To each value of $V$ corresponds a value of the gating variable $m$. The two remaining gating variables $h$ of the sodium current and $n$ of the potassium current are combined to a recovery variable $U$. Each value of $U$ is associated with corresponding values of these two gating variables. The dashed lines are the $V$ and $U$ nullclines for an input current $I = 0$. They intersect at $V = -65 \text{ mV}$ resulting in a stable fixed point (filled circle) — the resting potential. The $U$ nullcline is always given by the line $V = U$. The input current $I$ changes only the $V$ nullcline. For sufficiently high input currents stable limit cycles emerge — the neuron fires periodically. Four such limit cycles for different input currents as indicated in $\mu \text{A/cm}^2$ are shown. Note that the amplitude of a spike depends on the input current.

depending on the corresponding equivalent potentials $V_{m_k}$ and $V_{h_k}$. These equivalent potentials $V_i$ are replaced by the appropriate representative potentials $V$ or $U$. The coefficient $\alpha_0$ in the first equation of (2.11) is given by

$$\alpha_0 = \frac{C}{\tau_m[V]} + \frac{\partial F}{\partial V} - \sqrt{\left(\frac{C}{\tau_m[V]} - \frac{\partial F}{\partial V}\right)^2 - 4 \frac{C}{\tau_m[V]} \frac{\partial F}{\partial [m_{\infty}]} \frac{\partial [m_{\infty}]}{\partial V}} \right) \right).$$  (2.12)

The second equation in (2.11) sums over $N$ the gating variables $x_j$, which are combined within the representative potential $U$. The coefficients

$$\alpha_j = \frac{\partial F}{\partial V_j} \sum_{i=1}^N \frac{\partial F}{\partial V_i}$$  (2.13)

weigh the influence of the corresponding equivalent potential $V_j$ on the membrane equation.
2. SPIKING NEURONS

Class I:

\( I = -1 \)

\( I = 0 \)

\( I = 0.3 \)

\( I = 0.7 \)

\( I = 2 \)

\( I = 10 \)

\( t = 100 \text{ ms} \)

Class II:

\( I = -5 \)

\( I = 0 \)

\( I = 5 \)

\( I = 7 \)

\( I = 10 \)

\( I = 20 \)

\( t = 100 \text{ ms} \)

**Figure 2.8: Repetitive spiking in Class-I and Class-II model neurons.** Traces of the membrane potential computed from A the Traub-Miles model and B the Hodgkin-Huxley model for different constant input currents (bottom bar) as indicated (units are \( \mu \text{A/cm}^2 \)). The interspike interval \( ISI \) is defined as the time between two succeeding spikes. The latency \( \Delta t \) is the time from the onset of the stimulus to the first spike. Note that only a single spike is evoked by a current of \( I = 5 \mu \text{A/cm}^2 \) of the Hodgkin-Huxley model.
2.4 CLASS-I VERSUS CLASS-II NEURONS

Figure 2.9: $f$-$I$-CURVES OF CLASS-I AND CLASS-II MODEL NEURONS. Plotting the firing frequency $f$ as the reciprocal of the ISI against the strength of the constant input current $I$ results in the $f$-$I$-curve. A In class-I neurons, like the Traub-Miles model shown here, the $f$-$I$-curve is continuous. B $f$-$I$-curves of class-II neurons, like the Hodgkin-Huxley model, exhibit a discontinuous jump to a non-zero firing frequency at the threshold current $I_{th}$ (vertical line).

In Fig. 2.7 a phase portrait of the Hodgkin-Huxley equations reduced to two variables is shown. On the abscissa the membrane potential is drawn, which also represents the state of the $m$-gating variable. Both the $h$ and the $n$-gating variables are combined to the recovery variable $U$ on the ordinate. The dynamics of this reduced Hodgkin-Huxley model approximates the one of the full four-dimensional model very well (Kepler et al., 1992).

Combining all gating variables with similar dynamics reduces the number of variables, but does not reduce the number of parameters needed for the definition of the dynamics (2.11) of the remaining representative potentials. However, neglecting all processes with time constants greater than ten milliseconds, a simple two dimensional set of differential equations remains, which describes the essentials of generating spikes.

2.4 Class-I versus class-II neurons

Some years before Hodgkin and Huxley published their extraordinary work in 1952, it was already known that there are basically two types of excitable neurons, which were called class-I and class-II neurons (Hodgkin, 1948). They differ in some basic properties in their response to constant currents. Phase space analysis revealed two different bifurcation types for these two classes of excitable neurons (Rinzel & Ermentrout, 1998). From a functional point of view this is a very important finding.

In the following the differences of the two types of neurons as they were described by Hodgkin (1948), Hansel et al. (1995) and Ermentrout (1996) are demonstrated. Note that these differences mainly concern the transition from rest to repetitive spiking. Then the two different types of bifurcations for these two types of neurons are discussed. To illustrate the differences the Traub-Miles model as an example for a class-I neuron and the Hodgkin-Huxley model as an example for a class-II neuron are used. Both models are defined in appendix A.
2. SPIKING NEURONS

2.4.1 Firing frequency

Injecting constant currents of different intensities into a neuron results in voltage traces as shown in Fig. 2.8 for a class-I (panel A) and a class-II neuron (panel B). Both neurons have in common that they start to spike for strong enough input currents. They spike periodically with a period $T$, which is referred to as the interspike interval ($ISI$). The reciprocal $ISI$ is the firing frequency $f$ of the neuron. For small or negative currents the membrane potential stays at a fixed value. The minimum current necessary to evoke periodic spiking is the threshold current $I_{th}$.

The main difference between the two classes is the type of transition from the non-spiking state to repetitive spiking. Class-I neurons are able to spike with arbitrary low frequencies, while periodic spiking in class-II neurons sets in with a non-zero frequency.

This behavior can be summarized in firing-frequency-versus-input-intensity-curves ($f$-$I$-curves, $f(I)$), where the firing frequency $f = 1/T$ is plotted against the intensity of the injected current $I$ (see Fig. 2.9). The $f$-$I$-curve of the class-I neuron is monotonically increasing and reaches very high values. The $f$-$I$-curve of the class-II neuron has a discontinuous jump and is relatively insensitive to the current strength compared to the class-I neuron.

2.4.2 Latencies

Another difference pointed out by Hodgkin (1948) is the latency of the first spike after onset of an input current (see Fig. 2.10). In class-I neurons the latency can be very long (Koch et al., 1995) and is of the order of the corresponding interspike interval. Latency in class-II neurons is much shorter compared to the interspike intervals and is nearly independent of the input strength (see for example figure 1 in Fricker & Miles, 2000). While $f$-$I$-curves describe the steady-state behavior of a neuron for stimuli above threshold, latencies give additional information about the transition from rest to repetitive firing.
2.4 CLASS-I VERSUS CLASS-II NEURONS

Figure 2.11: Phase shift of a periodically spiking neuron. Given a constant input current $I$ the neuron is spiking periodically with some period $T_0$. At time $s$ relative to a spike a short and small perturbation is delivered. The succeeding spikes (solid line) are shifted relative to the unperturbed response (dashed line) by some time $\Delta t$ (time of the perturbed spike minus time of the unperturbed spike), but still have a period of $T_0$. Perturbing at different phases $\varphi = s/T_0$ results in different phase shifts $\Delta \varphi = \Delta t/T_0$. The phase shift $\Delta \varphi$ is positive, if the perturbation advances the following spike as illustrated, and negative, if the following spike is delayed.

Figure 2.12: Phase-resetting curves. At $\varphi = 0$ and $\varphi = 1$ are the maxima of the spikes. Phase-resetting curves for three perturbation intensities $\Delta I = 5, 10$, and $15 \mu A/cm^2$, each of 0.25 ms duration, are shown. A The Traub-Miles model as an example for a class-I neuron has mono-phasic phase-resetting curves. All positive perturbations advance the following spike. Only during the spikes in a small range of phases the neuron is insensitive to inputs. The input current was $I = 4 \mu A/cm^2$, and resulted in a firing period of 7.29 ms. B The Hodgkin-Huxley model representing a class-II neuron has a biphasic phase-resetting curve. Up to almost a phase of $\varphi = 0.4$ perturbations do not have any effect. In a following short range $\Delta \varphi$ is negative, thus the period is increased. If the perturbation is strong enough, the oscillation can be even stopped. Only during the last third of the period the following spike will be advanced. The input current was $I = 10 \mu A/cm^2$, and resulted in a period of 14.63 ms.
Figure 2.13: SADDLE-NODE BIFURCATION. **A** Below bifurcation there exist three fixed points. A stable node (black circle), a saddle (lower white circle) and an unstable spiral (upper white circle). Small perturbations of the rest state decay back to the stable fixed point, while a strong perturbation beyond the saddle causes a large excursion of the solution before returning to the equilibrium — a spike. Such a trajectory is called a periodic pseudo-orbit. **B** Right at the bifurcation the stable node collapses with the saddle, resulting in an unstable fixed point associated with a homoclinic orbit with zero frequency. **C** Above bifurcation the node and the saddle vanish and a stable limit cycle remains — the neuron fires periodically.

Figure 2.14: SADDLE-NODE BIFURCATION IN A CLASS-I NEURON (TRAUB-MILES). **A** Below the firing threshold the $V$ nullcline (dashed line) intersects three times the $U$ nullcline (circles, two are visible, the third is outside the panel to the right). The leftmost intersection is a stable fixed point (filled circle); the vectors of the flow-field are all pointing toward it. The middle intersection is a saddle point (open circle). Trajectories starting from below first approach the saddle and then turn either toward the stable fixed point directly (dotted line) or leave the panel to the right, circle round (which is a spike) and approach the fixed point from the left (solid line). A separatrix separates the spiking trajectories from the silent ones. **B** For super-threshold currents the two fixed points vanish. There is no longer a stable fixed point in the system. Instead the spiking trajectory is now a stable limit cycle (solid line): the neuron is firing periodically.
2.4 CLASS-I VERSUS CLASS-II NEURONS

Figure 2.15: SUPERCritical Hopf bifurcation. A First there is only a single stable fixed point. B With increasing bifurcation parameter a stable limit cycle emerges in coexistence with the stable fixed point. The basins of attraction are separated by an unstable limit cycle as indicated by the dashed line. C This separatrix shrinks toward the fixed point until at the Hopf bifurcation this fixed point loses stability and the stable limit cycle remains.

Figure 2.16: Hopf bifurcation in a class-II neuron (Hodgkin-Huxley). A The $\dot{V}$ and $U$ nullclines (dashed lines) intersect at one point only. For sub-threshold currents the fixed point is stable (filled circle). Small perturbations produce damped oscillations back to the fixed point (dotted line). Larger perturbations may induce a single (or several) spike (solid line) before the fixed point is reached again. In contrast to the saddle-node bifurcation there exists no separatrix associated with a saddle (Izhikevich, 2000). B With increasing strength of the input current, the trajectory of the spike becomes a stable limit cycle, which coexists with the still stable fixed point. The basin of attraction of the fixed point (loop around fixed point) decreases until the fixed point looses stability and a stable limit cycle remains.
2. SPIKING NEURONS

2.4.3 Phase-resetting curve

Besides the f-I-curves, which provide information about the period of the oscillation for a constant current I, the so-called “phase-resetting curve” characterizes the influence of perturbations on this oscillation. As illustrated in Fig. 2.11, without any perturbation the neuron fires with period $T_0$. A perturbation delivered at a given time $s$ after a spike may advance or delay the occurrence of the following spikes by $\Delta t$ relative to the unperturbed spikes. The perturbed interspike interval is then $T = T_0 - \Delta t$. The phase-resetting curve $\Delta \varphi(\varphi)$ is the phase shift $\Delta \varphi = \Delta t / T_0$ as a function of the phase $\varphi = s / T_0$ of the perturbation.

Ermentrout (1996) has proved, that the phase-resetting curve of a system at a saddle-node bifurcation like a class-I neuron is always positive, indicating that any positive perturbation advances the spikes (see Fig. 2.12). From simulation studies of class-II neurons it is known that they have biphasic phase-resetting curves (Hansel et al., 1995). In the middle part of the interspike interval, perturbations delay the following spike, while later perturbations advance it (see Fig. 2.12).

2.4.4 Bifurcation

The reason for these two completely different qualitative behaviors of neurons is the type of bifurcation. As shown by Rinzel & Ermentrout (1998) class-I neurons have a saddle-node bifurcation, while class-II neurons undergo a subcritical Hopf bifurcation (see also Izhikevich, 2000).

The generic form of a saddle-node bifurcation is demonstrated in Fig. 2.13 and in Fig. 2.14. For subthreshold input currents a stable node representing the resting potential lies directly on a periodic pseudo-orbit, which is the trajectory of a spike. At threshold the node loses stability and the pseudo-orbit becomes a stable limit cycle. The period is infinitely long, since the limit cycle passes the intersection of the two nullclines, where the derivatives equal zero. With increasing input current the nullclines no longer intersect, leading to increasing derivatives at the location of the former node. Therefore the
Figure 2.18: LIMIT CYCLES FOR DIFFERENT INPUT CURRENTS $I$. A The Traub-Miles model (class-I) and B the Hodgkin-Huxley model (class-II). Increasing the input current shifts only the minimum of the $\dot{V}$ nullcline upwards. Therefore differences between the limit cycles are mostly restricted to this region. The inner cycles correspond to high current levels.

2.4.5 Spike threshold

Due to the separatrix associated with the saddle, class-I neurons have a precisely defined threshold for the initiation of a spike. Crossing this separatrix generates a spike with full amplitude. Since the flow-field is uniquely defined by the input current $I$, the separatrix also depends on $I$. Furthermore the separatrix does not have to be a simple voltage threshold. In general it can be a more complicated function in the neuron’s phase space. Note, that crossing this threshold is not identical with immediately emitting a spike. It may take a while until the trajectory has passed the saddle point and eventually produces the spike (Gutkin & Ermentrout, 1998).

Class-II neurons do not have a well defined threshold. Instead they have a whole threshold set. They can generate spikes with arbitrary amplitudes, depending on where in the threshold set they start (Cole et al., 1970). However, this threshold set is usually very small so that in practice (adding just some noise) class-II neurons show a quasi-threshold behavior (Izhikevich, 2000).
2. SPIKING NEURONS

![Figure 2.19: AMPLITUDES OF SPIKES. A In the Traub-Miles model (class I) spike amplitudes are approximately constant, while B in the Hodgkin-Huxley model (class II) they vary strongly. Shown are the voltage traces to different Gaussian white noise stimuli with a cut-off frequency of 50 Hz.](image)

2.4.6 Spike amplitudes

For different super-threshold currents the limit cycles of a class-I and a class-II neuron differ mainly in the part of the spike upstroke (Fig. 2.18). While in the class-I example the limit cycles change only before the onset of the spike, the limit cycles of the class-II neuron differ also in the spike upstroke. This leads to spikes with different amplitudes as demonstrated in Fig. 2.19. There is no proof for this phenomenon, but it can be understood qualitatively. The flow-field of the former saddle of a class-I neuron still attracts the trajectories (arrow in Fig. 2.18 A), thus the various orbits converge after passing the saddle. In contrast the flow-field of a class-II neuron is dominated completely by the limit cycles, which are not influenced by the fixed point, resulting in trajectories more parallel to each other.

2.4.7 Real neurons

To my knowledge there are only a few neurons identified to be class-II neurons, as for example cortical interneurons (Alonso & Klink, 1993; Gloveli et al., 1997; Koch, 1999). The Hodgkin-Huxley equations, which are the most prominent example of a class-II neuron, describe properties of a patch of axonal membrane and not the spike initiating zone, which from a computational point of view is much more relevant. In contrast, the majority of neurons have a class-I $f$-$I$-curve. For example neocortical pyramidal and sparsely spiny stellate neurons (McCormick et al., 1985), CA1 interneurons (Lacaille & Williams, 1990), and layer III cells of the medial enthorhinal cortex (Gloveli et al., 1997). Thus, it is in general much more realistic to use a class-I neuron model instead of the Hodgkin-Huxley equations for simulation studies.

It has to be noted that due to noise the discontinuity in the class-II $f$-$I$-curves in real neurons may be smeared out (Schneidman et al., 1998; Koch, 1999). It is therefore harder to distinguish class-I from class-II neurons based only on their $f$-$I$-curves. However, other properties like latencies, phase-resetting curves or spike clustering still allows separating these two types of neurons.
Table 2.1: Properties of class-I and class-II neurons.

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>firing frequency</td>
<td>arbitrary low</td>
<td>frequency band</td>
</tr>
<tr>
<td>latency</td>
<td>arbitrary long</td>
<td>short</td>
</tr>
<tr>
<td>phase shift</td>
<td>advance</td>
<td>delay &amp; advance</td>
</tr>
<tr>
<td>bifurcation</td>
<td>saddle node</td>
<td>Hopf</td>
</tr>
<tr>
<td>noise</td>
<td>jitter</td>
<td>clustering</td>
</tr>
<tr>
<td>threshold</td>
<td>separatrix</td>
<td>threshold set</td>
</tr>
<tr>
<td>spike amplitudes</td>
<td>fixed</td>
<td>variable</td>
</tr>
<tr>
<td>conductance-based models</td>
<td>Traub et al. (1991)</td>
<td>Hodgkin &amp; Huxley (1952)</td>
</tr>
<tr>
<td></td>
<td>Connor et al. (1977)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bower (1989)</td>
<td></td>
</tr>
<tr>
<td>real neurons</td>
<td>Pyramidal cells</td>
<td>cortical interneurons</td>
</tr>
</tbody>
</table>

A summary of the differences of class-I and class-II neurons as discussed in the text. The conductance-based models as well as the real neurons listed here are only a few examples. For references to the examples of real neurons see section 2.4.7.

2.5 Summary

- Conductance-based models provide a detailed biophysical description of the dynamics of ionic currents in neurons.
- The time scales of different gating variables can be grouped.
- With the scheme for reducing the number of variables of Kepler et al. (1992) conductance-based models can be simplified.
- Two classes of neurons can be distinguished on the basis of $f$-$I$-curves, latencies, and phase-resetting curves as summarized in tab. 2.1.
- Class-I neurons start spiking through a saddle-node bifurcation, while class-II neurons have a subcritical Hopf bifurcation.