Figure 6.8: Electrical circuit model of the cell membrane.

Normally, cells are net negative inside the cell which results in a non-zero resting membrane potential. The membrane potential of most cells is kept relatively stable. Nerve cells, skeletal, and cardiac muscle cells, however, are specialized to use changes in membrane potential for fast communication, primarily with other cells of their type. Within a millisecond, their membrane potential changes from positive to negative and back. This feature is referred to as action potential.

6.3.4 Action potential

The action potential is a self-regenerating pulse-like wave of electro-chemical activity that allows some cell types to rapidly carry signals over long distances. A typical action potential is initiated by a sudden change in the transmembrane potential. As the membrane potential is depolarized, both sodium and potassium channels begin to open generating an inward sodium current balanced by an outward potassium current. For only small perturbations, the potassium current wins and the membrane potential returns to its resting state. For sufficiently large perturbations of approximately 20 mV, however, the sodium current wins producing a positive feed back. The cell produces an action potential, we say the cell fires. One very important feature of the action potential is that its amplitude is independent of the degree of stimulation. Larger stimuli do not generate larger action potentials. This characteristic property of action potentials is referred to as *all or none response*, either the fires or it does not.

The initiation and propagation of electrical signals by the controlled opening and closing of ion channels is one of the most important cellular functions. Its first quantitative model was proposed half a century ago and awarded the Nobel Prize in 1963 [18]. Although originally developed for neurons, this theory was soon modified and generalized to explain a wide variety of excitable cells. To gain a better understanding of these models, let's take a look at equation (6.3.2) which we can rephrase as follows.

$$\dot{\phi} = -\frac{1}{C_m} I_{\text{ion}} \qquad \text{with} \qquad I_{\text{ion}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{Cl}} + I_{\text{Ca}^{2+}}. \tag{6.3.3}$$

Here $\dot{\phi} = d\phi / dt$ is the change in the transmembrane potential, C_m is the transmembrane capacitance, and I_{ion} is the total ionic current. This current results from the flux of sodium I_{Na}, potassium I_{K}, chloride I_{Cl}, and calcium $I_{\text{Ca}^{2+}}$ ions across the cell membrane. If we measured the transmembrane potential of different cells types found in the heart and plotted it over time, it would look somewhat like the illustraton in figure 6.9. Apparently, different cell types seem to have different action potentials.
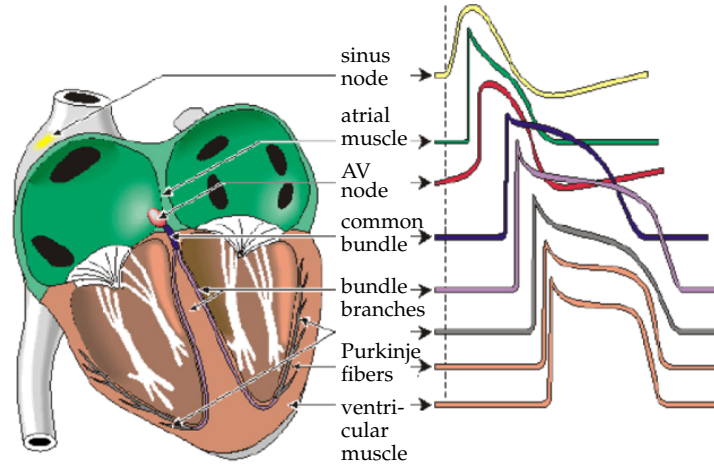
Figure 6.9: Electrophysiology of the heart: Characteristic action potentials and activation delay for various different cell types in the heart, adopted from [15].

So the key question in describing the curves in figure 6.9 with equation (6.3.3) is, what is the total ionic flux I_{ion} that drives the evolution of the transmembrane potential ϕ? Two categories of models have been proposed to describe different action potentials: (i) ionic models and (ii) phenomenological models. Both are, of course, models and just a simplification of the reality. While ionic models represent the flux of all ions, the opening and closing of all channels, and the gating of ion channels in a very accurate way [4, 25, 32], phenomenological models actually only try to reproduce the action potential curve in a sufficiently accurate, but less expensive way [12, 22].

The FitzHugh-Nagumo model

Probably the most prominent phenomenological model is the FitzHugh-Nagumo model [13, 31]. It is based on an extremely elegant two-parameter formulation that allows the rigorous analysis of the underlying action potentials with well-established mathematical tools. Most importantly, it allows for a graphic representation in the phase plane. Let's look how the FitzHugh-Nagumo model can be derived. We start with a linear second order equation to describe the oscillations ϕ.

$$\ddot{\phi} + k\,\dot{\phi} + \phi = 0 \tag{6.3.4}$$

In this equation, we replace the constant damping coefficient k with a quadratic term in terms of the potential $k = c\,[\,\phi^2 - 1\,]$ to obtain the following non-linear equation.

$$\ddot{\phi} + c\,[\,\phi^2 - 1\,]\,\dot{\phi} + \phi = 0 \tag{6.3.5}$$

With the help of Liénard's transformation

$$r = -\tfrac{1}{c}\,\dot{\phi} - \tfrac{1}{3}\,\phi^3 + \phi \qquad\qquad \dot{r} = -\tfrac{1}{c}\,\ddot{\phi} - [\,\phi^2 - 1\,]\dot{\phi} \tag{6.3.6}$$

this second order equation can be transformed into a system of two first order equations. Its first equation follows from equation $(6.3.6)_1$, its second equation follows from

equation (6.3.5) multiplied with $-\frac{1}{c}$ in combination with equation $(6.3.6)_2$.

$$\dot{\phi} = c\left[-\tfrac{1}{3}\phi^3 + \phi - r\right] \qquad\qquad \dot{r} = \tfrac{1}{c}\,\phi \qquad\qquad (6.3.7)$$

Its fast variable, the transmembrane potential ϕ, has a cubic non-linearity allowing for regenerative self-excitation through a fast positive feedback. The slow variable, the recovery variable r, has a linear dynamics providing slow negative feedback. Keep in mind that although r is something like a phenomenological representation of the influence of all ionic fluxes, it has no real physically measurable interpretation. Last, we add a possible external stimulus I to the first equation and two additional terms a and $b\,r$ to the second equation to obtain the classical FitzHugh-Nagumo model.

$$\dot{\phi} = c\left[-\tfrac{1}{3}\phi^3 + \phi - r + I\right] \qquad\qquad \dot{r} = \tfrac{1}{c}\left[\phi - b\,r - a\right] \qquad\qquad (6.3.8)$$

Nagumo et al. [31] contributed essentially to their understanding by building the corrensponding circuit to model the cell through a capacitor C for the membrane capacitance, a non-linear current-voltage device for the fast current and a resistor, an inductor and a battery in series for the recovery current, see figure 6.10, right.
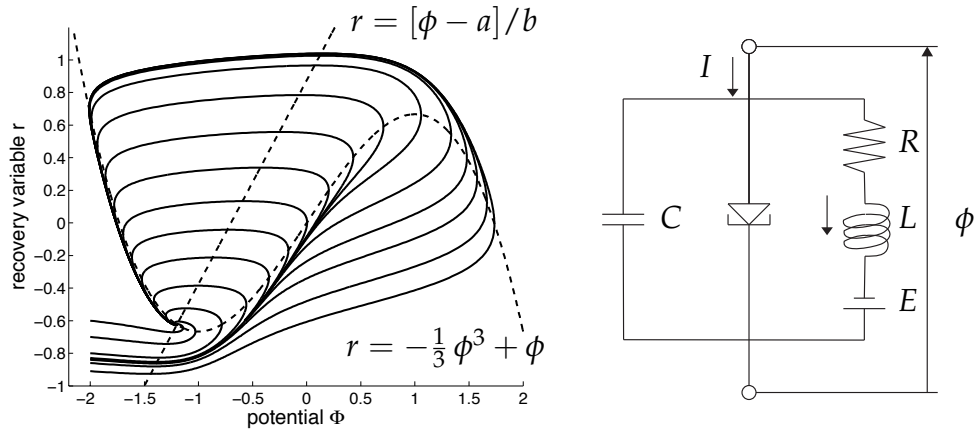

Figure 6.10: Phase portrait of classical FitzHugh-Nagumo model with a=0.7, b=0.8, c=3, left. Trajectories for distinct initial values of potential ϕ and recovery variable r converge to steady state. Dashed lines denote nullclines with $r = -\tfrac{1}{3}\phi^3 + \phi$ for $\dot{\phi} = 0$ and $r = [\phi - a]/b$ for $\dot{r} = 0$. Circuit diagram of corresponding tunnel-diode nerve model, right.

Being restricted to only two degrees of freedom, the FitzHugh-Nagumo model can be analyzed and interpreted in the two-dimensional phase space as illustrated in Figure 6.10, left. The dotted lines represent the two nullclines for $r = -\tfrac{1}{3}\phi^3 + \phi$ for $\dot{\phi} = 0$ and $r = [\phi - a]/b$ for $\dot{r} = 0$, respectively. The nullclines are assumed to have a single intersection point which represents the steady state of equilibrium at which both $\dot{\phi} = 0$ and $\dot{r} = 0$. For low external stimuli I, this equilibrium point is stable, as shown in figure 6.10. It is located to the left of the local minimum of the cubic nullcline, and all trajectories ultimately run into this stable equilibrium point. An increase of the external stimulus I shifts the cubic nullcline upwards. This causes the equilibrium point

to move to the right. For sufficiently large stimuli, the steady state is located on the unstable middle branch of the cubic nullcline, and the model exhibits periodic activity referred to as tonic spiking.

The four phases of excitation

Nerve cells, skeletal muscle cells, and cardiac muscle cells are said to be excitable: A sufficiently large perturbation from the steady state sends the state variables on a trajectory that initially runs away from equilibrium before returning to the steady state. This excitation is characterized through four phases as illustrated in figure 6.11.
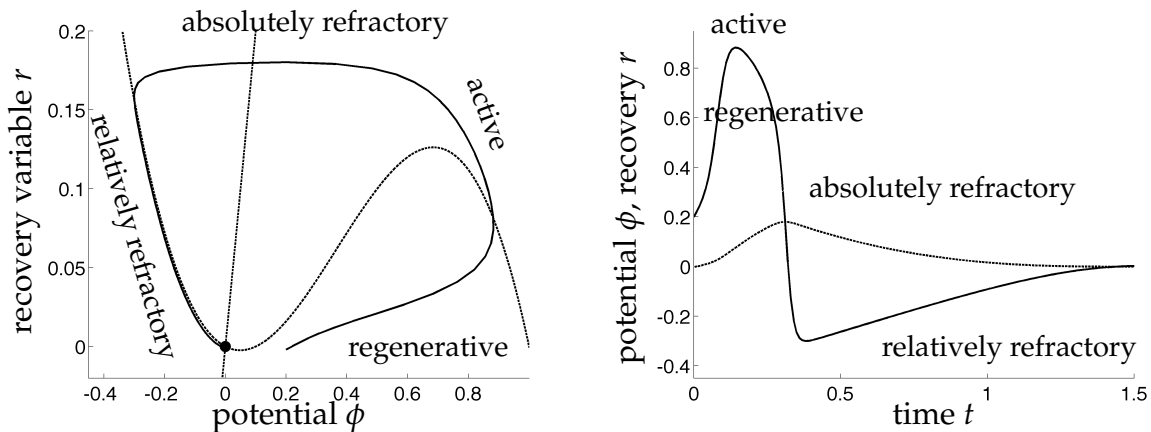

Figure 6.11: Four phases of the action potential: Regenerative phase, active phase, absolutely refractory phase, and relatively refractory phase. Simulations are based on the classical FitzHugh-Nagumo model Dashed lines in the phase portrait illustrate the nullclines, the dot at their intersection corresponds to the resting state, left. In the physiological state diagram, solid lines indicate the temporal evolution of the membrane potential ϕ and dashed lines correspond to the recovery variable r, right.

Regenerative phase Excitation begins with the rapid depolarization of the cell characterized through a fast upstroke of the membrane potential ϕ. The depolarization opens both sodium and potassium channels initiating an outward potassium current and an inward sodium current. For small enough stimuli, the outward potassium current overwhelms the inward sodium current and the cell returns to its resting state. For sufficiently large stimuli, however, a positive feedback is generated. More and more sodium channels open and the membrane potential is rapidly increased.

Active phase The active phase is characterized through a high and almost constant membrane potential ϕ which initiates a slow increase of the recovery variable r. Sodium permeability is maximized but decreases as more and more sodium channels tend to close again. Also, potassium channels now begin to open. This marks the end of the active phase.

Absolutely refractory phase During the absolutely refractory phase the membrane potential ϕ decreases smoothly whereas the recovery r is almost constant. Some cell types tend to hyperpolarize, i.e., they initially overshoot the resting state. Action po-

tentials cannot follow one another immedaitely since the ion channels need to return to their resting state. The absolutely refractory period characterizes the period during which the cell is recovering. During this period, it is unable to generate a new action potential.

Relatively refractory phase The relatively refractory phase is characterized through a decrease of the recovery variable r as the solution slowly returns to the resting state. During this phase, the ion channels gradually return to their initial state. A new action potential can be generated during this phase, however, the required stimulus might be significantly larger than in the resting state.

Stable non-oscillatory and unstable oscillatory cells

Action potentials occur when the cell membrane depolarizes and then repolarizes back to the steady state. There are two conceptually different action potentials in the heart: action potentials for pacemaker cells such as the sinoarial and the atrioventric-
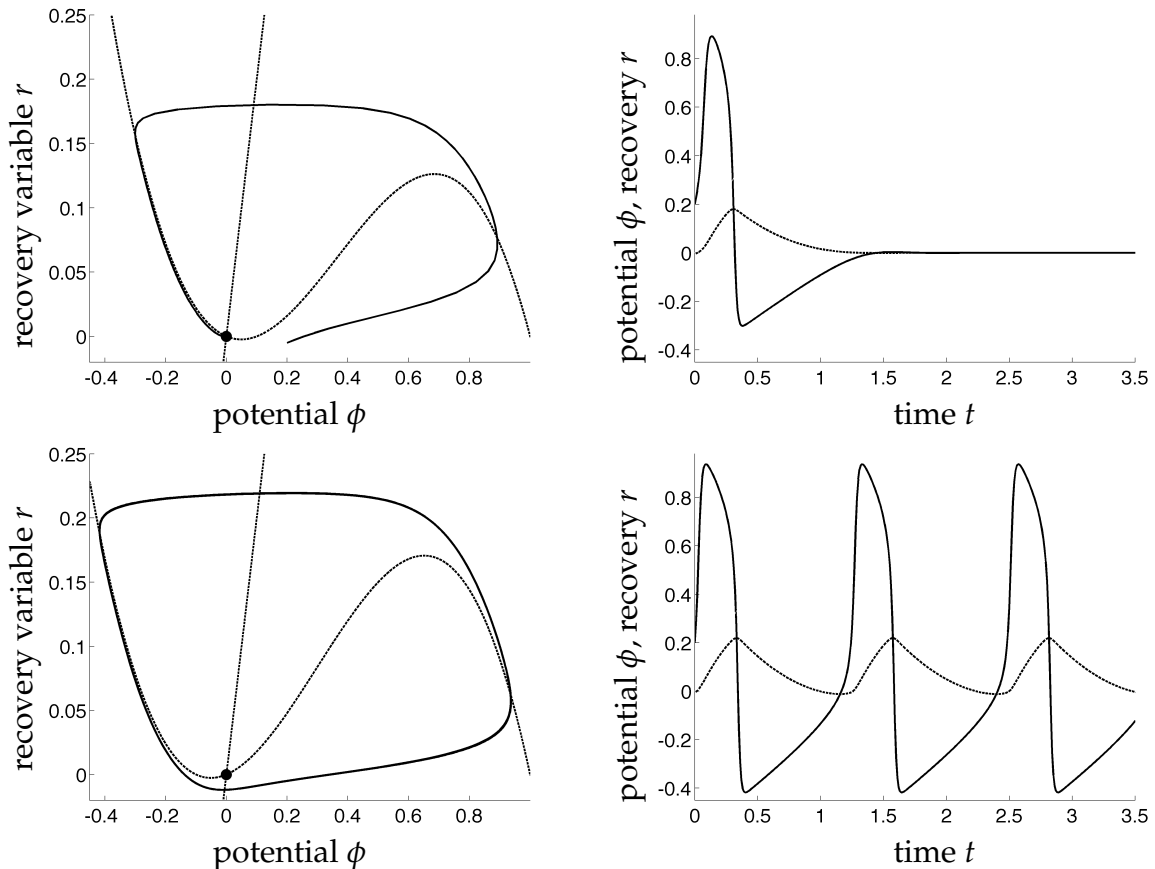

Figure 6.12: Phase portrait and physiological state diagram for stable non-oscillatory FitzHugh-Nagumo model with $\alpha = -0.1$, top, and for unstable oscillatory FitzHugh-Nagumoe model with $\alpha = +0.1$, bottom. For the non-oscillatory model, top row, the steady state, i.e., the intersection of nullclines, is situated to the left of the intersection in the stable regime. For the non-oscillatory model, bottom row, the steady state, i.e., the intersection of nullclines, is situated to the right of the intersection in the unstable regime.

ular node, and action potentials for non-pacemaker cells such as atrial or ventricular muscle cells. Pacemaker cells are capable of spontaneous action potential generation, whereas non-pacemaker cells have to be triggered by depolarizing currents from adjacent cells. To compare non-oscillatory and oscillatory cells, it is convenient to rewrite the FitzHugh-Nagumo system (6.3.10) in a slightly modified form.

$$\dot{\phi} = c\left[\phi\left[\phi + \alpha\right]\left[1 - \phi\right] - r\right] \qquad \dot{r} = \phi - b\,r - a \qquad (6.3.9)$$

Based on this reformulation, we can easily distinguish between stable non-oscillatory muscle cells for $\alpha < 0$ and unstable oscillatory pacemaker cells for $\alpha > 0$, see figure 6.12. For the documented example, $b = 0.5$ and $c = 100$. Figures 6.12, top, show a stable non-osciallory pacemaker cell for $\alpha = -0.1$. Right after the action potential, the membrane returns to its resting state. Figures 6.12, bottom, display a characteristic membrane potential for oscillatory cells for $\alpha = +0.1$. The fast and slow variable undergo an oscillation through the four phase cycle of the regenerative, the active, the absolutely refractory, and the relatively refractory phase. After this cycle, however, the membrane potential is above the critical threshold to initiate a new excitation cycle.

Traveling waves of excitation

To account for the nature of traveling waves in excitable media, a phenomenologic diffusion term $\text{div}(q)$ can be added to the first equation of the original FitzHugh-Nagumo equations. Based on the assumption that the spatial range of the signaling phenomenon ϕ is significantly larger than the influence domain of the recovery variable r, the second equation is considered to be strictly local.

$$\dot{\phi} = \text{div}(q) + c\left[-\tfrac{1}{3}\phi^3 + \phi - r + I\right] \qquad \dot{r} = -\tfrac{1}{c}\left[\phi - b\,r - a\right] \qquad (6.3.10)$$

The easiest assumption is that the flux is proportional to the gradient of the membrane potential $q = D\,\nabla\phi$, where D denotes the conductivity. Typical conductivities in cardiac tissue are 0.05 m/s for the sinoatrial and the atrialventricular node, 1 m/s for atrial pathways, the bundle of his and ventricular muscle, and 4 m/s for Purkinje fibers [15]. Table 6.2 illustrates characteristic values for action potentials of different cell types.

animal	cell type	resting potential [mV]	potential increase [mV]	potential duration [ms]	conduc- tivity [m/s]
squid (loligo)	giant axon	-60	120	0.75	35
earthworm (lumbricus)	median giant fiber	-70	100	1.00	30
cockroach (periplaneta)	giant fiber	-70	80–104	0.40	10
frog (rana)	sciatic nerve axon	-60–-80	110–130	1.00	7-30

Table 6.2: Typical value of resting potential, action potential increase, action potential duration, and conduction speed for action potentials of different cell types.