Action Potentials and Synaptic Transmission
Physics 171/271

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In this section, we consider two important aspects concerning the communication between nerve cells. Nerve cells signalling is mediated by brief transient depolarization of the membrane voltage, so-called action potentials. We will see how a bistability between the resting state and a depolarized state underlies action potential generation. Second, we will explore how neurons communicate with each other via chemical synapses, points of close proximity between two connected neurons where the electrical signal is transformed into a chemical signal and eventually transformed back into an electrical signal. This lecture is mostly concerned with the basic phenomenology. Details of action potential generation (Hodgkin-Huxley model) will be further discussed in following lectures.

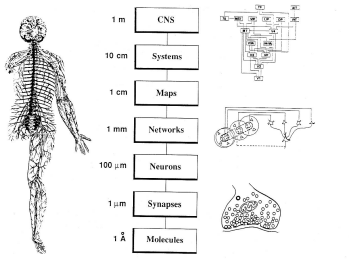

Figure 1: Spatial roadmap by orders of magnitude. This lecture is concerned with signaling between neurons by synapses (Churchland and Sejnowski, 1992).

1 Action Potential Generation: Rising Phase

Action potentials, short transient depolarizations of the membrane voltage, are the currency of neural signaling. Mathematical subtleties aside, an action potential is an all-or-none type of signal (digital signal). Here, we will look at a simple model of a neuron which shows the dynamic mechanism of the generation of such an all-or-none signal. Note that this is not yet the full description of the action potential since it leaves out the restoring force which takes the membrane

voltage back to its resting state; this will be discussed in a later lecture. Here, we start with a simple passive cell membrane consisting of a capacitance C and a leak conductance g_L in parallel.

$$C\frac{dV}{dt} = -g_L(V - E_L), \tag{1}$$

We now add a current which provides positive feedback to mediate the steep slope of the rising phase of the action potential:

$$C\frac{dV}{dt} = -g_L(V - E_L) - gp(V - E_p) \tag{2}$$

$$\tau(V)\frac{dp}{dt} = p_\infty(V) - p. \tag{3}$$

If we assume that $\tau(V)$ is very small, we can reduce the above system to the following one-dimensional system:

$$C\frac{dV}{dt} = I - g_L(V - E_L) - gp_\infty(V - E_p) \tag{4}$$

$$\tag{5}$$

For example, we chose a persisten sodium current with the following activation function:

$$p_\infty = \frac{1}{1 + \exp(V_{1/2} - V)/k} \tag{6}$$

Time-scale and activation thresholds of different ionic currents are shown in Figure **??**.

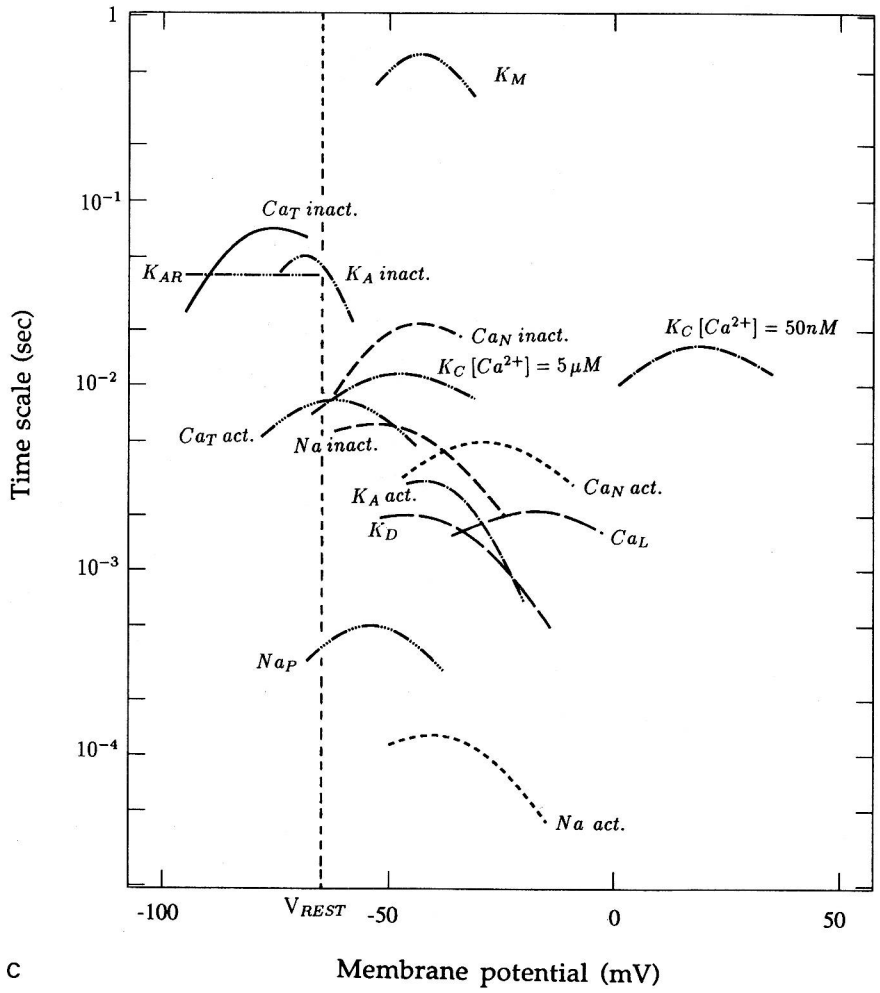

Figure 2: Time-scales and activation thresholds for different ionic currents (Churchland and Sejnowski, 1992).

We now analyze this system in the following steps:

1. Numerical Solution (Figure 3). Most of the differential equations which we encounter in this class will not have an analytical solution. We therefore have to resort to numerical solvers (e.g. using the Euler method) to find the time-courses of the state variables.

2. Plot $F(V) = \frac{dV}{dt}$ (Figure 4). From this plot, we can find the equilibria and determine if they are stable or unstable.

3. Determine how number and nature of equilibria change when we change a parameter in the

system (Figure 5). The most straightforward choice of parameter here is the amount of current I which we inject (Figure 6).

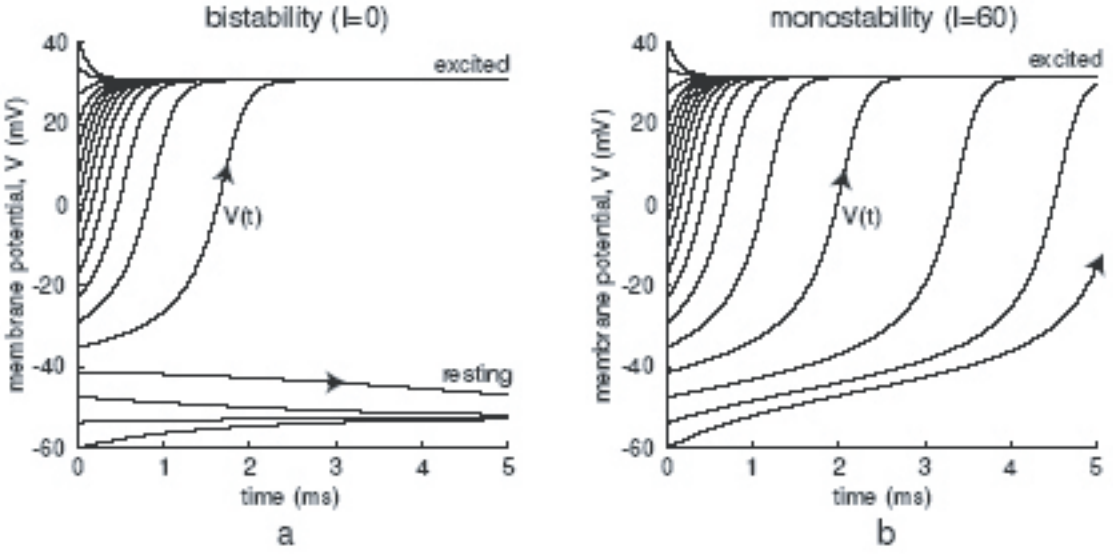

Figure 3: Membrane voltage time-course for $I = 0$ and $I = 60$ (Izhikevich, 2005).

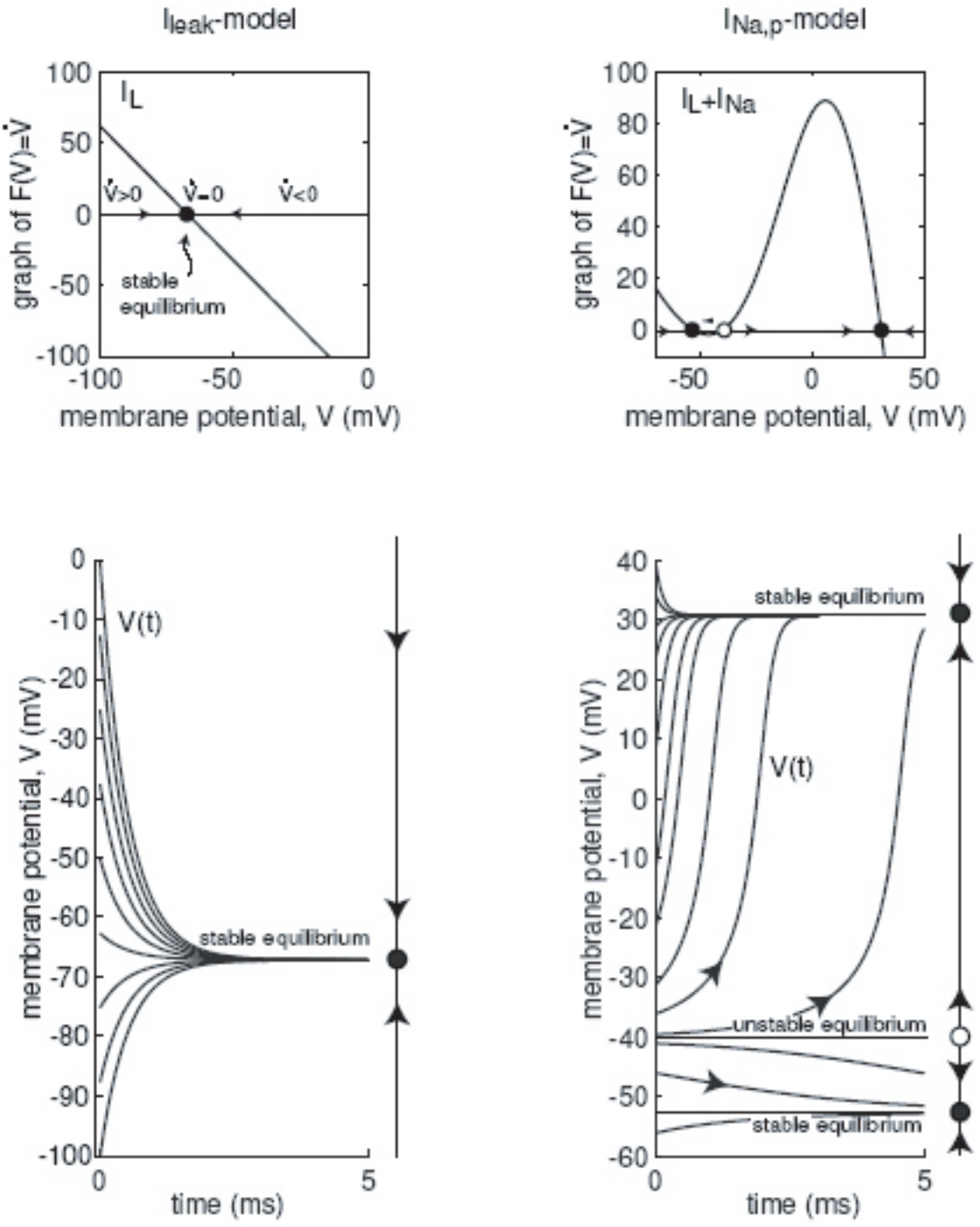

Figure 4: Equilibria (Izhikevich, 2005)

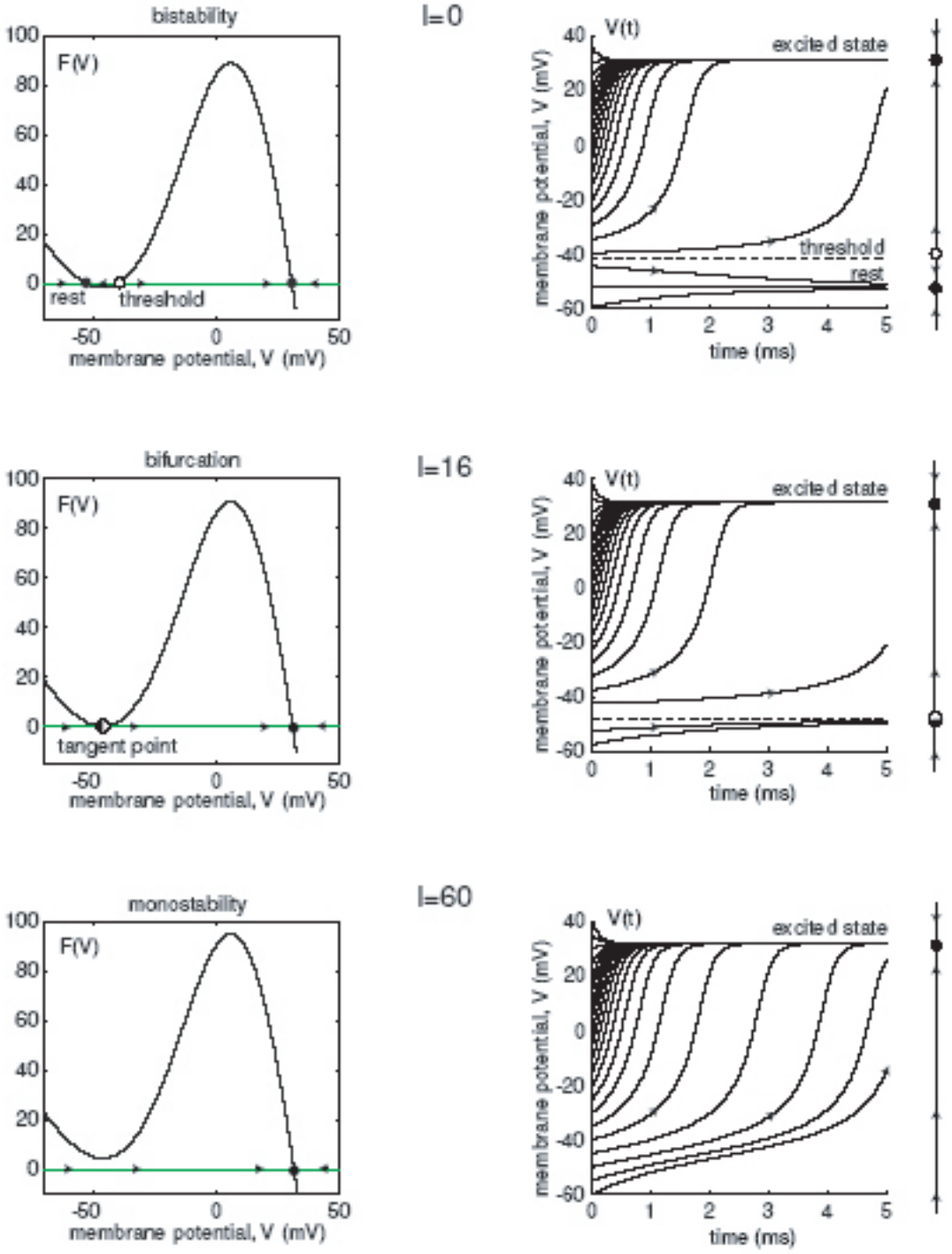

Figure 5: Change in equilibria for different values of I (Izhikevich, 2005).

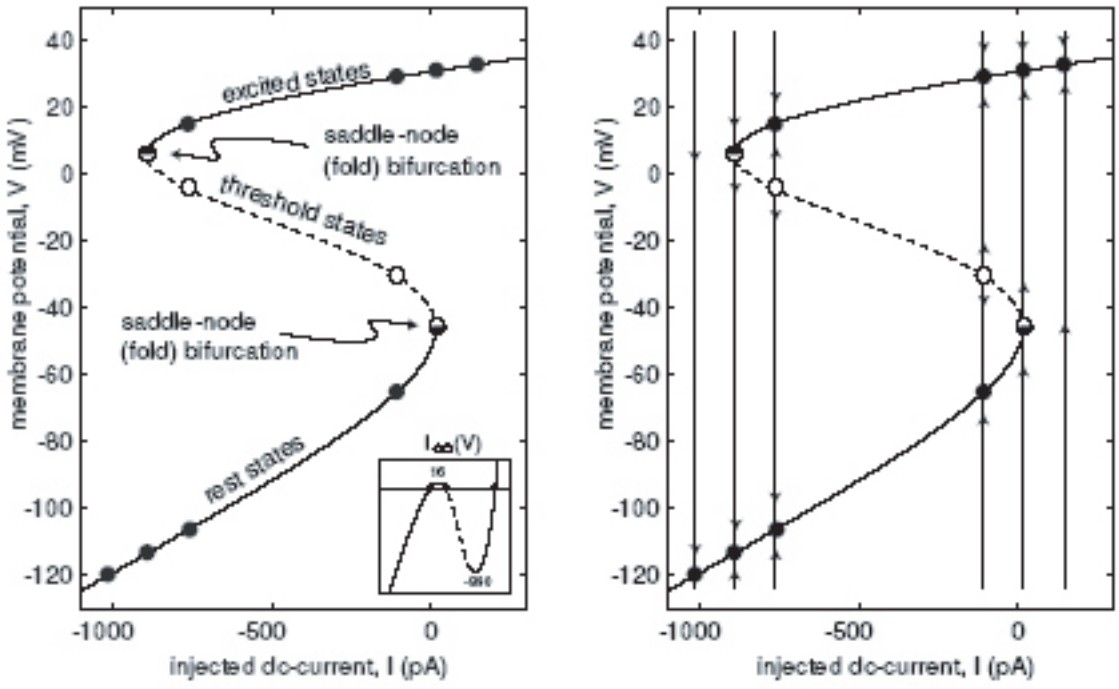

Figure 6: Bifurcation analysis with parameter. I (Izhikevich, 2005).

2 Chemical synaptic transmission

A chemical synapse connects two neurons with each other. Importantly, it is a unidirectional communication link[1] between two neurons. Therefore, we call the neuron which takes the role of the sender *presynaptic* neuron, whereas the receiver is called *postsynaptic neuron*.
The information transfer at a chemical synapse occurs by actuall physical transfer of siginalling molecules. *Neurotransmitter* released by the presynaptic neuron at the so-called *axonal terminal* diffuses across the so-called *synaptic cleft* to bind to receptors on the *dendrite* of the postsynaptic cell [2] Synpatic transmission can be separated into the following steps (Figure **??**):

1. Presynaptic action potential invades presynaptic terminal.

2. Resulting depolarization opens high-threshold calcium ion channels which permit calcium ions to enter the presynaptic terminal.

[1]Under some circumstances, communication goes the other way at a chemical synapse. This is called *retrograde signalling*. We will not discuss this any further here.

[2]There is whole variety of possible postsynaptic targets, including the actual cell body (*soma*) or axon. At this point, this destinction is not relevant.

3. Elevated calcium triggers the *exocytosis* (fusion with the membrane) of vesicles filled with neurotransmitter molecules.

4. Neutrotransmitter molecules cross the synaptic cleft (diffusion).

5. Neutransmitter bind to matching postsynaptic rececptors. The resulting actions can be manifold. Here, we distinguish between *ionotropic* and *metabotropic* chemical synaptic transmission (Figure 8).

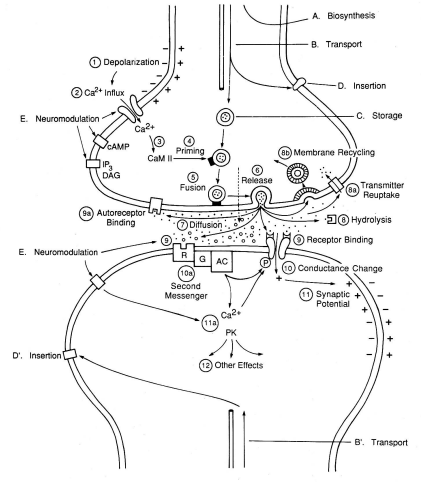

Figure 7: Pres- and postsynaptic signalling (Churchland and Sejnowski, 1992).

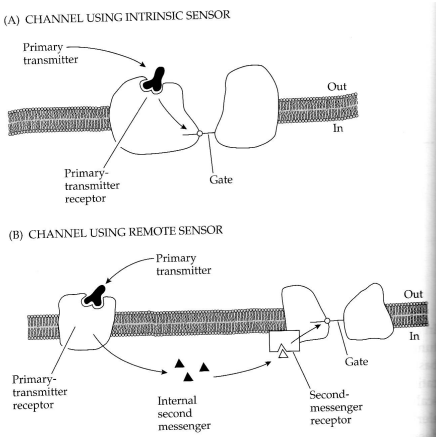

Figure 8: Ionotropic and metabotropic synaptic receptors (Hille, 2001).

Ionotropic synaptic transmission occurs via ionic influx through the receptors which bound the neurotransmitter. Specifically, the receptors undergo a conformational change triggerd by neurotransmitter binding such that the receptor forms a pore permeable to one or several ion types. In mathematical terms, this corresponds to a transient increase in the membrane conductance (since it is easier for ions to cross the cell membrane due to the open pores formed by the receptors). Ionotropic synaptic transmission is very fast and can be classified into *excitatory* and *inhibitory*. Excitatory synaptic conductances enable a depolarizing inward current when the receptos are activated, effectively bringing the neuron closer to its firing threshold. On the contrary, inhibitory synaptic conductances mediate an outward current which hyperpolarizes the cell, effectively inhibting firing since the neuron it moves the neuron farther awa from the firing threshold. Although different neurotransmitter types are usually associated with either of the two modes of action, it is important to understand that only the driving force term in the current equation determines the actual direction/sign of the synaptic current:

$$I_{\text{syn}} = G(V - E_{\text{rev}}). \tag{7}$$

Let's consider the most common neurotransmitters and the reversal potential of the current they mediate (Figures 9 and 10). Remember that the reversal potential is defined by the ionic concentration gradient across the membrane, the temperature, and the valence of the ion of consideration. The Nernst equation which we had derived in the previous lecture allows us to calculate the reversal potentials.

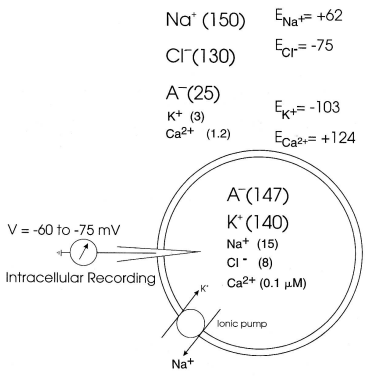

Figure 9: Intra- and extracellular ion concentrations. Resulting reversal potentials.

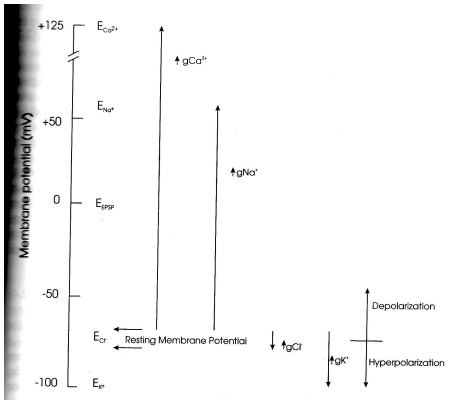

Figure 10:

Metabotropic synaptic transmission occurs on a slower time-scle. Binding of the neurotransmitter to the postsyanptic recpetors activates a signaling cascade within the postsynaptic cell which eventually targets one or several ion channel types. Usual targets include potassium channels. Since the reversal potential of potassium is below the resting potential, the resulting synaptic currents are of hyperolarizing / inhibiting nature.

2.1 Functional Properties of synapses

In the case where the time-course of the synaptic conductance is much faster than the membrane time-constant τ, the decay of a postynaptic potential is governed by the membrane time constant. For ionotropic receptors, we can safely assume that the change in conductance is instantaneous, effectively allow us to model a synapse with a conductance G in series with a battery for the reversal potential and a switch. The according electrical circuit diagram (Figure 11) for the case of two independent synapses with conductance G_1 and G_2 with the same reversal potential E_S is:

$$C\frac{dV}{dt} = -G_R(V - E_R) - G_1(V - E_S) - G_2(V - E_S) \quad (8)$$

$$= -V(G_R + G_1 + G_2) + E_R G_R + (G_1 + G_2)E_S. \quad (9)$$

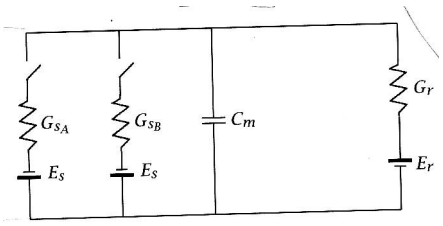

Figure 11: Equivalent electrical circuit diagram describing a passive cell membrane with two synapses.

We recognize the simple form of a first order differential equation with an inhomogenous term of the form:

$$\tau \frac{dx}{dt} = -x + A \tag{10}$$

In our case, we find:

$$\tau = \frac{C}{G_R + G_1 + G_2}. \tag{11}$$

In the case where the receptor channel is closed (corresponding to the switch being open), we find that

$$\tau = \frac{C}{G_R}. \tag{12}$$

We have therefore shown, that in case of instantaneous opening and closing of the channel the rising phase of the resulting postsynaptic potential is much fast than the decaying phase. By setting $dV/dt = 0$ to determine the steady-state solution (corresponding to the maximal depolarization), we find

$$V = \frac{E_R G_R + E_S(G_1 + G_2)}{G_R + G_1 + G_2}. \tag{13}$$

We therefore observe that the summation of the two inputs is nonlinear.

The more general form to describe n synaptic input is

$$C\frac{dV}{dt} \quad = \sum_{i=0}^{n} g_{syn,i}(t)(E_{syn,i} - V_m) + \frac{V_{rest} - V_m}{R}. \tag{14}$$

We now derive the solution to this more general equation describing the membrane voltage time course in presence of a time-dependent synaptic conductance. The general form the differential equation is

$$\tau \frac{dV}{dt} \quad = \quad -V + I(t) \tag{15}$$

where we now consider $I(t)$ to be the synaptic current. This equation can be solved be using the ansatz:

$$V(t) = Ae^{\frac{-t}{\tau}} + H(t)e^{\frac{-t}{\tau}} \tag{16}$$

We find $H(t)$ by plugging the ansatz into the differential equation. We then find:

$$H(t) = \frac{1}{\tau} \int_0^t e^{-\frac{t'}{\tau}} I(t')dt' \tag{17}$$

We can now rewrite the solution as

$$V(t) = Ae^{\frac{-t}{\tau}} + \frac{1}{\tau}\int_0^t e^{-\frac{-(t-t')}{\tau}} I(t')dt' \tag{18}$$

where we choose A to satisfy the initial conditions. This is the convultion integral. Basically, the membrane voltage is the filtered sum of the currents having occured in the past. Note that this corresponds to low-pass fiiltering of the input current received by the cell.