Synapses

Models of the synapse

The contacts of the axon to target neurons are either located on the dendritic tree or directly on the soma, and are known as synapses. Most synapses are chemical contacts, that is, the arrival of an action potential at the synapse induces the secretion of a neurotransmitter that in turn leads to a change in the potential of the membrane of the target neuron. Depending on the type of synapse, an incoming pulse either causes an increase in electrical potential (excitatory synapse) or a decrease (inhibitory synapse).

Left: Schematic diagram showing release of neurotransmitter as vesicle membrane fuses with end bulb membrane. Right: Electron micrograph showing how synaptic vesicles fuse with cell membrane as neurotransmitter is discharged.

At a synapse presynaptic firing results in the release of neurotransmitters that causes a change in the membrane conductance of the postsynaptic neuron. This postsynaptic current may be written mathematically as

\[ I_s = g_s s (V_s - V) \]

where \( V \) is the voltage of the postsynaptic neuron, \( V_s \) is the membrane reversal potential and \( g_s \) is a constant. The term \( V_s - V \) is often called a shunt as it acts to push the voltage toward the synaptic reversal potential \( V_s \). The variable \( s \) corresponds to the probability that a synaptic receptor channel is in an open conducting state. This probability depends on the presence and concentration of neurotransmitter released by the presynaptic neuron. The sign of \( V_s \) relative to the resting potential (assumed to be zero) determines whether the synapse is excitatory (\( V_s > 0 \)) or inhibitory (\( V_s < 0 \)).

One major question is how best to determine \( s(t) \) from the presynaptic activity. The release of transmitter is quite complex. However, a good fit to the total amount of transmitter release by a single action potential is given by the expression:

\[ [T](V_{pre}) = \frac{T_{max}}{1 + e^{-(V_{pre} - V_p)/K_p}} \]

where \( T_{max} \) is the maximal concentration of transmitter in the synaptic cleft and \( K_p, V_p \) determine the stiffness and threshold for the release. A good value for these constants is \( V_p = 2 \text{ mV} \) and \( K_p = 5 \text{ mV} \). Typically, we will assume that 1 mM of transmitter is the maximum concentration released.
Post synaptic behavior

Given that a certain amount of transmitter is released from the synaptic terminal, we want to now model the current that appears in the postsynaptic site. To do this we need to model $s(t)$, the fraction of open channels open due to the transmitter $T$. The typical way to model these is via a series of reactions or so called Markov models (like we have already discussed for Na and K channels) in which the probability of channels opening and closing is described by a series of rate constants. This kind of detail is well beyond what one wants for simple modeling, thus, instead, we will describe a couple of simple models for the 4 primary types of postsynaptic response induced by the two principle neurotransmitters.

Glutamate. The neurotransmitter glutamate activates two different kinds of receptors: AMPA/kainate which are very fast and NMDA which is implicated in memory and long-term potentiation of synapses. Both of these receptors lead to excitation of the membrane.

AMPA/Kainate. A simple (exponential) model that can fit the fast excitatory AMPA receptor is:

$$s(t) = e^{-t/\tau}.$$ Thus the synapse responds instantaneously to the arrival of an action potentials and then decays with a time constant $\tau$. A better fit is obtained with the choice of a difference of exponentials:

$$s(t) = e^{-t/\tau_2} - e^{-t/\tau_1}.$$ Here $\tau_1$ is the rise time of the synapse and $\tau_2$ is the decay time of the synapse. If the two time-scales are close $\tau_1 = \tau = \tau_2$ the function is often called an ‘alpha’ function:

$$s(t) = t e^{-t/\tau}.$$ The AMPA synapses can be very fast. For example in some auditory nuclei, they have submillisecond rise and decay times. In typical cortical cells, the rise time is 0.4 to 0.8 ms. As a final note, AMPA receptors onto inhibitory interneurons are about twice as fast in rise and fall times.

NMDA. An important receptor found in cortical pyramidal neurons is the NMDA receptor. They are quite slow with rise times of about 20 ms and decay times of 25 to 120 ms. A fairly good simple model for the NMDA current is

$$I_{\text{NMDA}} = g_{\text{NMDA}} B(V)s(V_{\text{NMDA}} - V),$$

Post synaptic potentials (PSPs) arising from synaptic and dendritic processing have similar (difference of exponential) shapes.
where \( s(t) \) is a difference of exponentials. There is an important difference between NMDA and AMPA. The conductance depends in a complex fashion on the postsynaptic potential via the term \( B(V) \). This voltage dependent conductance depends on the level of external magnesium ions. Here is a physiological correlate of the Hebb rule that both pre- and postsynaptic cells must be coincidently active. The voltage dependence is mediated by magnesium ions which normally block the NMDA receptors. Thus, the postsynaptic cell must be sufficiently depolarized to knock out the magnesium ions. This can be modelled using

\[
B(V) = \frac{1}{1 + e^{-0.062V[Mg^{2+}]/3.57}}.
\]

**GABA.** \( \gamma \)-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter in the cortex. There are two main receptors for GABA, GABA\(_A\) and GABA\(_B\).

GABA\(_A\) is responsible for fast inhibition and require only brief stimuli to produce a response. The same simplified type of kinetic model used for AMPA synapses can be used for GABA\(_A\).

GABA\(_B\) is a much more complex receptor. It involves so-called second messengers. For the other three receptors, the receptor and the ion channel are part of the same protein complex. GABA\(_B\) responses occur when the GABA binds to another compound (the G-protein) which in turn binds to a potassium channel and opens it up. It takes 4 of the activated G-proteins to open the channel. For this reason, we must use a second order kinetic scheme (not shown) to properly model the GABA\(_B\) dynamics.

**More complex synapses**

There are many other types of synapses that can have more complex behavior. For example in the bullfrog sympathetic ganglion, synaptic cotransmission occurs in which a cocktail of several neurotransmitters is released which then bind to several different receptor types. With such complex synapses, it is possible to get an initial brief depolarization followed by hyperpolarization and then by a long lasting low amplitude depolarization. Many cortical neurons have AMPA synapses which depress. That is, when given repeated stimuli, the synapse produces less and less transmitter. We can readily model this by adding a desensitized state to the standard two-state model for the synapse. Instead of the open state going directly back to the closed state, we allow there to be an intermediate state (desensitised) which then returns to the closed state:

\[
C \xrightarrow{a} O, \quad O \xrightarrow{b_1} X, \quad X \xrightarrow{b_2} C.
\]

**Gap junctions**

A gap junction is a junction between cells that allows different molecules and ions to pass freely between cells. They are composed of two connexons (or hemichannels) which connect across the intercellular space.

A gap junction between two membranes with voltages \( V_{pre} \) and \( V_{post} \) carries a current

\[
g_{gap}(V_{pre} - V_{post}).
\]

Without the need for receptors to recognize chemical messengers, signaling at electrical synapses is more rapid than that which occurs across chemical synapses. The synaptic delay for a chemical
synapse is typically about 2 ms, while the synaptic delay for an electrical synapse may be about 0.2 ms. However, the difference in speed between chemical and electrical synapses is not as important in mammals as it is in cold-blooded animals. The relative speed of electrical synapses also allows for many neurons to fire synchronously. Because of the speed of transmission, electrical synapses are found in escape mechanisms and other processes that require quick responses. Electrical synapses are abundant in the retina and cerebral cortex of vertebrates. However, to use this tutorial properly (on your own) assumes that you are now familiar with the basic manipulations of the panels and graphs in NIA2.

**Worksheet: NIA2 - Synapses**

1. Run NIA2 and choose the The Neuromuscular Junction link.

2. Work through The Neuromuscular Junction being careful to read all the text and click on the hyperlink explanation for AlphaSynapse.

3. Go to the section Experiments and Observations, work through all aspects of the tutorial and remember to follow all the new hyperlinks. Record a brief commentary to each question on a separate sheet of paper – include your name in capitals at the top of the paper. **These will be collected at the end of the session by the lecturer.**

Continue with the tutorials Postsynaptic Inhibition and Interactions of Synaptic Potentials.

**My First NEURON**

Here we will follow a NEURON demo written by Arthur Houweling available at http://senselab.med.yale.edu/modeldb/ShowModel.asp?model=3808&file=\MyFirstNEURON\ There are many other models listed in the ModelDB at Yale: http://senselab.med.yale.edu/modeldb/

All of these can be run using the “Auto-launch” facility.

Record a brief commentary on each 'experiment' on a separate sheet of paper – include your name in capitals at the top of the paper. **These will be collected at the end of the session by the lecturer.**

1. Resting Potential [1-2]
• Run
• Reduce the sodium leak permeability to zero
• Change the external potassium concentration to 135 mM
• Reduce the potassium leak permeability to zero
• Set the potassium leak permeability to $3.45 \times 10^{-5}$ cm/s

2. Membrane Properties [3-4]
   • Run
   • Change the amplitude of the current clamp to 2 nA

3. Impulse Generation [5-6]
   • Run
   • Change the external concentrations of all ions to 0.1 mM, one at a time
   • Set $[Na^+]_o$ to 0.1 mM and base current to 2.25 nA (4 nA)
   • Set $[K^+]_o$ to 0.1 mM and base current to 0.8 nA
   • Play with the intracellular potassium concentration
   • Reduce $[K^+]_i$ to 0.1 mM
   • Keep above change and set base current to -3 nA

   • Run
   • Play with the internal and external concentrations of sodium and potassium, one at a time
   • Run a voltage clamp series
   • Reduce the maximum conductance of the fast sodium channel to zero and run the series again
   • Reduce the maximum conductance of the fast potassium channel to zero and run the series again

   • Run

   • Run
   • Reduce the maximum conductance $g_{K_{iA}}$ to zero
   • Choose voltage clamp in the Experiments menu and run a voltage clamp series
   • Change the external potassium concentration to 25 mM and run a voltage clamp series again

7. The L-Current and C-Current [12]
   • Run
   • Reduce the external calcium concentration to 0.01 mM
8. The AHP-Current [13]
   - Run
   - Reduce the maximum conductance $g_{k_{iAHP}}$ to zero
   - Reduce the external calcium concentration to 0.1 mM

9. The T-Current [14]
   - Run
   - Change the base current to 0.18 nA and the initial voltage to -60 mV
   - Reduce the maximum conductance of the fast sodium channel to zero
   - Reduce the external calcium concentration to 0.1 mM

10. The M-Current [15]
    - Run
    - Reduce the maximum conductance $g_{k_{iM}}$ to zero
    - Reduce the external calcium concentration to 0.1 mM
    - Choose voltage clamp in the Experiments menu and run
    - Play with the extracellular potassium concentration

11. Excitatory Postsynaptic Potentials [16]
    - Run
    - Set the IPSP conductances to zero
    - Keep above change and set the base current to 1.78 nA and the initial voltage to 20 mV

12. NMDA current [16]
    - Run
    - Set the base current to -0.52 nA and the initial voltage to -90 mV
    - Set the base current to 0.525 nA and the initial voltage to -30 mV
    - Set the base current to -0.52 nA and the initial voltage to -90 mV and $[Mg^{2+}]_o$ to 0.01 mM
    - Set the base current to 0.525 nA and the initial voltage to -30 mV and $[Mg^{2+}]_o$ to 0.01 mM
    - Select NMDA voltage clamp from the Experiments menu and run a voltage clamp series
    - Repeat the voltage clamp series but now with $[Mg^{2+}]_o = 0.001$ mM
    - Perform similar experiments with the AMPA receptor (switch AMPA and NMDA conductance values)

13. Inhibitory Postsynaptic Potentials [17]
    - Run
    - Set the base current to -0.38 nA and the initial voltage to -85 mV
    - Keep above change and set the external chloride concentration to 7 mM
• Set the base current to -0.5 nA and the external potassium concentration to 25 mM
• Select IPSP+EPSP from the Experiments menu and run (keep this selection below)
• Set the EPSP conductances to zero and the GABAA conductance to 0.2 nS
• Change the EPSP conductances back to 0.15 nS