ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 25

Friday March 7, 2014

Neural synapses:

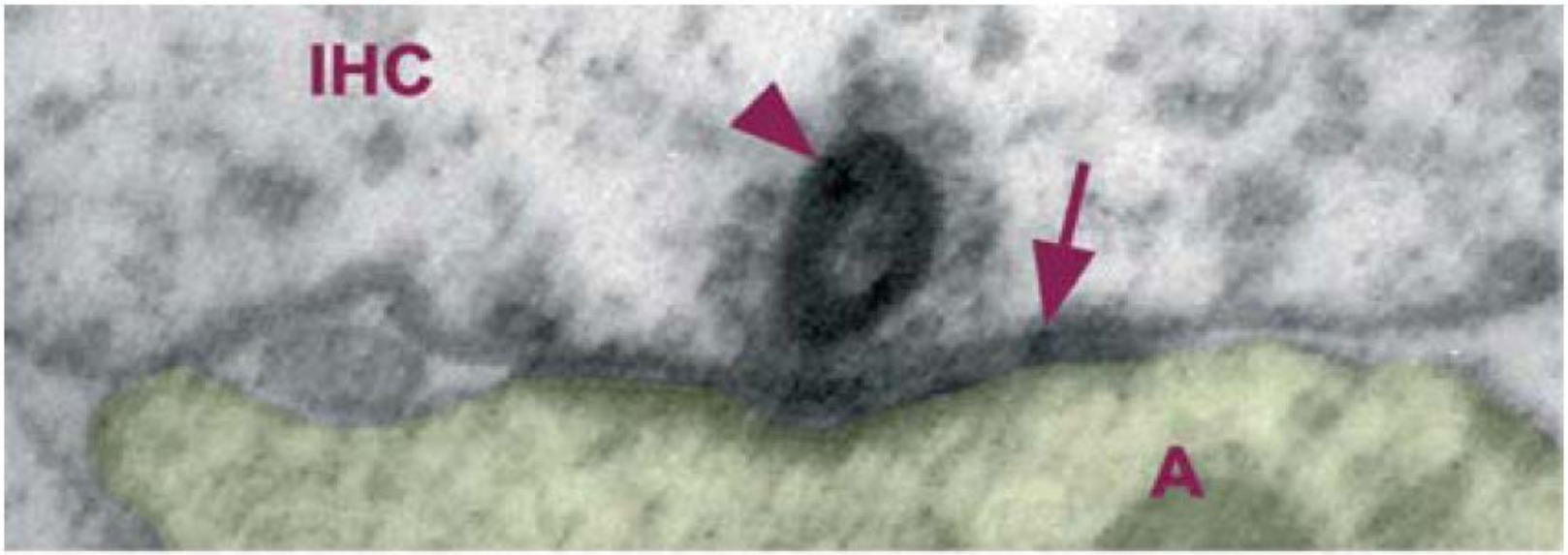
The specialized contact zones between neurons are called *synapses*.

In the nervous system, *chemical synapses* are much more common than *electrical synapses* (*gap junctions*).

Most chemical synapses are unidirectional — the *presynaptic* neuron releases *neurotransmitter* across the *synaptic cleft* to the *postsynaptic terminal*, which leads to activation of a neurotransmitter-gated ion channel.

Neural synapses (cont.):

In the electron micrograph below, a presynaptic body in the inner hair cell is seen to hold a cluster of neurotransmitter vesicles. A thickening of the cell membranes is observed between the pre- and post-synaptic terminals, and a very narrow synaptic cleft exists.



(from Francis et al., Brain Res. 2004)

Neural synapses (cont.):

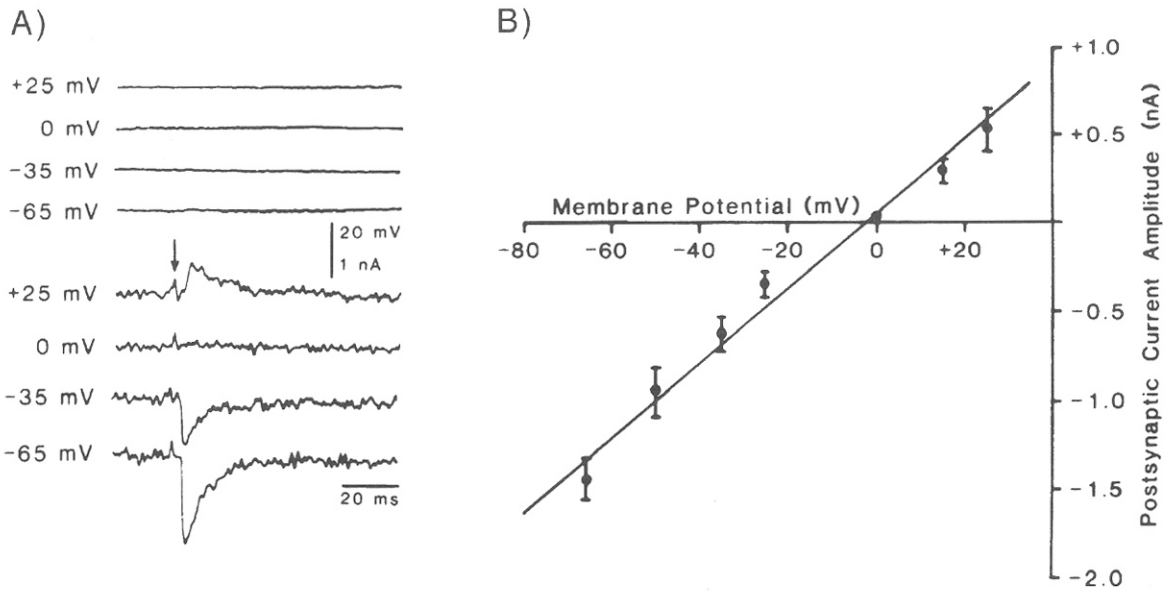


Fig. 1.6 A Fast Excitatory Synaptic Input Excitatory postsynaptic current (EPSC) caused by the simultaneous activation of synapses (arrow) made by the mossy fibers onto CA3 pyramidal cells in the rodent hippocampus (Brown and Johnston, 1983). This classical experiment showed how a central synapse can be successfully voltage clamped. **(A)** The voltage-clamp setup stabilizes—via electronic feedback control—the membrane potential at a fixed value. Here four experiments are shown, carried out at the holding potentials indicated at the left. The current that is drawn to keep the membrane potential constant, termed the clamp current, corresponds to the negative EPSC. It is maximal at negative potentials and reverses sign around zero. The synaptic current rises within 1 msec to its peak value, decaying to baseline over 20–30 msec. The experiments were carried out in the presence of pharmacological agents that blocked synaptic inhibition. **(B)** When the peak EPSC is plotted against the holding potential, an approximately linear relationship emerges; the regression line yields an x-axis intercept of -1.9 mV and a slope of 20.6 nS. Thus, once the synaptic reversal potential is accounted for, Ohm's law appears to be reasonably well obeyed. We conclude that synaptic input is caused by a transient increase in the conductance of the membrane to certain ions. Reprinted by permission from Brown and Johnston (1983).

(from Koch)

Neural synapses (cont.):

Equivalent electric circuit of a fast chemical synapse:

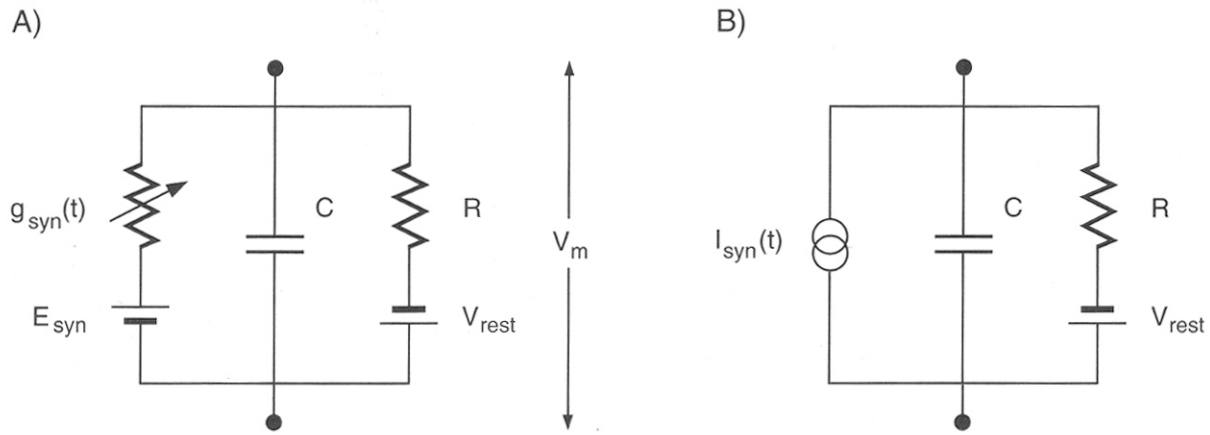


Fig. 1.7 Equivalent Electrical Circuit of a Fast Chemical Synapse **(A)** Electrical model of a fast voltage-independent chemical synapse. This circuit was put forth to explain events occurring at the neuromuscular junction by Katz (1969). Remarkably, all fast chemical synapses in the central nervous system, with the exception of the voltage-dependent NMDA receptor-synaptic complex, operate on the same principle. Activation of the synapse leads to the transient opening of ionic channels, selective to certain ions. This corresponds to a transient increase in the membrane conductance $g_{syn}(t)$ in series with the synaptic reversal potential E_{syn}, shown here in parallel with a passive membrane patch. **(B)** If the evoked potential change is small relative to the synaptic reversal potential, the synapse can be approximated by a current source of amplitude $g_{syn}(t)E_{syn}$. In general, however, this will not be the case and synaptic input must be treated as a conductance change, a fact that has important functional consequences.

(from Koch)

Neural synapses (cont.):

The *postsynaptic current* (PSC) has the same form as a voltage-gated ion channel:

$$I_{\mathrm{syn}} = g_{\mathrm{syn}}(t)\,[V_m(t) - E_{\mathrm{syn}}]\,, \qquad \text{(K1.18)}$$

but the conductance $g_{syn}(t)$ is controlled by the reception of neurotransmitter (rather than the transmembrane potential), which has a waveform that is often approximated by a so-called alpha function:

$$g_{\mathrm{syn}}(t) = \mathrm{const} \cdot t\, \mathrm{e}^{-t/t_{\mathrm{peak}}}. \qquad \text{(K1.21)}$$

Neural synapses (cont.):

The direction of the postsynaptic current depends on the value of E_{syn}:

- if $E_{syn} > V_{rest}$, then I_{syn} will be a negative (i.e., inward) current, which will *depolarize* the cell.
  Consequently, this current is referred to as an *excitatory postsynaptic current* (EPSC), and the resulting membrane depolarization is referred to as an *excitatory postsynaptic potential* (EPSP).

Neural synapses (cont.):

- if $E_{syn} < V_{rest}$, then I_{syn} will be a positive (i.e., outward) current, which will *hyperpolarize* the cell. Because hyperpolarization takes the membrane potential further away from the threshold potential, this is a form of *inhibition*. Consequently, this current is referred to as an *inhibitory postsynaptic current* (IPSC), and the resulting membrane hyperpolarization is referred to as an *inhibitory postsynaptic potential* (IPSP).

Neural synapses (cont.):

- if E_{syn} ¼ V_{rest}, then I_{syn} will be a negligible when the membrane is at rest. However, if current is injected into the membrane by a propagating EPSP or action potential or an applied current source, the increased conductance of $g_{syn}(t)$ will tend to "shunt" this injected current, such that the membrane is locked at V_{rest}. Because this prevents action potential generation, it is referred to as *shunting inhibition*.

Neural synapses (cont.):

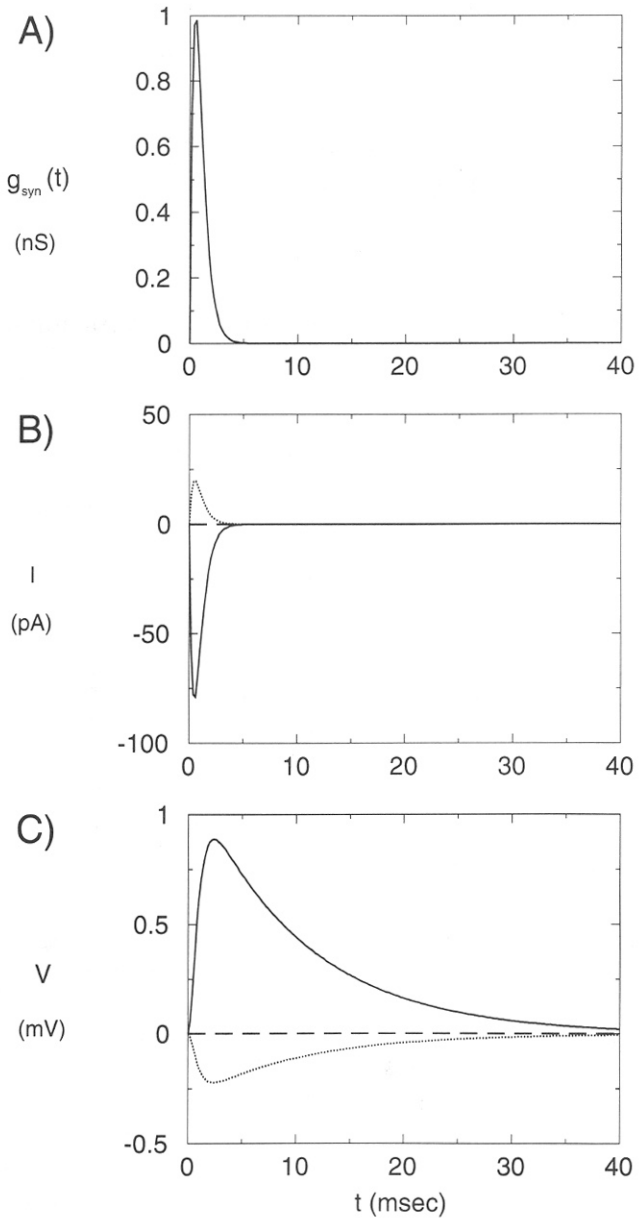
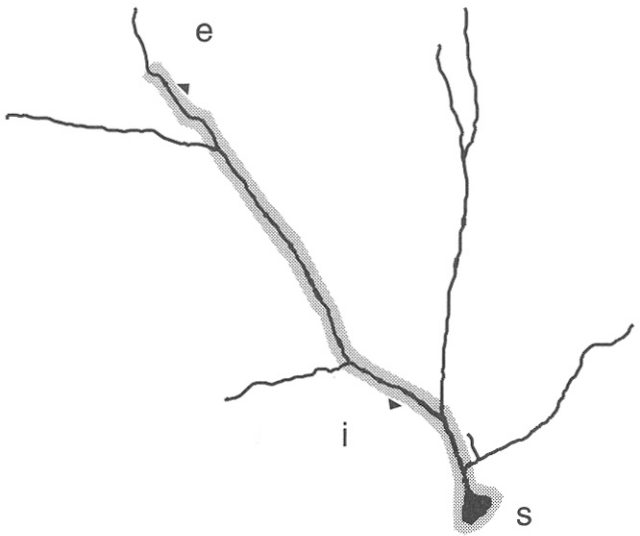


Fig. 1.8 Action of a Single Synapse Inserted into a Membrane Three different types of synaptic inputs and their differential effect on the membrane potential. **(A)** Time course of the synaptic-induced conductance increase, here with t_{peak}=0.5 msec and $g_{peak} = 1$ nS (Eq. 1.21). The synapse is inserted into a patch of membrane (Fig. 1.7A) with $R = 100$ MΩ, $C = 100$ pF, and $\tau = 10$ msec. **(B)** Postsynaptic current in response to the conductance increase if the synaptic reversal potential is positive ($E_{syn} = 80$ mV relative to rest; solid line), negative ($E_{syn} = -20$ mV; dotted line), and zero (so-called shunting inhibition; dashed line). By convention, an inward current that depolarizes the cell is plotted as a negative current. **(C)** Associated EPSP (solid line) and IPSP (lower dashed line), relative to V_{rest}, solved by numerical integration of Eq. 1.20. Notice that the time course of the postsynaptic potential is much longer than the time course of the corresponding postsynaptic current due to the low-pass nature of the membrane. Shunting inhibition by itself does not give rise to any change in potential (center dashed line).

(from Koch)

Neural synapses (cont.):

Shunting inhibition is most effective if placed on the path between an excitatory synapse and the soma.



(from Koch)

Fig. 5.2 Interaction among an Excitatory and an Inhibitory Synapse How does the interaction between an excitatory synapse (at location *e*) and an inhibitory synapse (at *i*) in a passive dendritic tree depend on their spatial positions? And what role do the synaptic architecture and the dendritic morphology play? In general, the potential at the soma *s* is not simply the sum of the individual IPSP and EPSP but can be much less. If the inhibition is of the *shunting* type, with a reversal potential close to the resting potential of the cell, inhibition by itself leads to no significant potential change while still being able to veto the EPSP, as long as the inhibitory synapse is either close to the excitatory one or "on the direct path" between excitation and the soma *s* (shaded area). The effectiveness of shunting inhibition drops substantially outside this zone.

Neural synapses (cont.):

TABLE 6.1 Some Fast Chemical Synapses

Postsynaptic cell	Response	E_{rev} (mV)[a]	Conductance increase	Receptor
Frog skeletal muscle[1,2]	epp	–5	Cations	nACh
Cat motoneuron[3]	epsp	0	Cations	Glutamate
Crayfish leg muscle[4]	epsp	+6	Cations	Glutamate
Crayfish leg muscle[5,6]	ipsp	–72	Anions	$GABA_A$
Aplysia ganglion cell[7]	ipsp	–60	Anions	ACh
Cat motoneuron[8,9]	ipsp	–78	Anions	Glycine
Hippocampal pyramidal cell[10,11]	ipsp	–70	Anions	$GABA_A$

References: [1]Fatt and Katz (1951); [2]Takeuchi and Takeuchi (1960); [3]Coombs et al. (1955b); [4]Dekin (1983); [5]Fatt and Katz (1953b); [6]Onodera and Takeuchi (1979); [7]D. J. Adams et al. (1982); [8]Coombs et al. (1955a); [9]Eccles (1964); [10]Eccles et al. (1977); [11]Nicoll (1988).

[a]E_{rev} is the reversal potential of the conductance increase.

(from Hille)

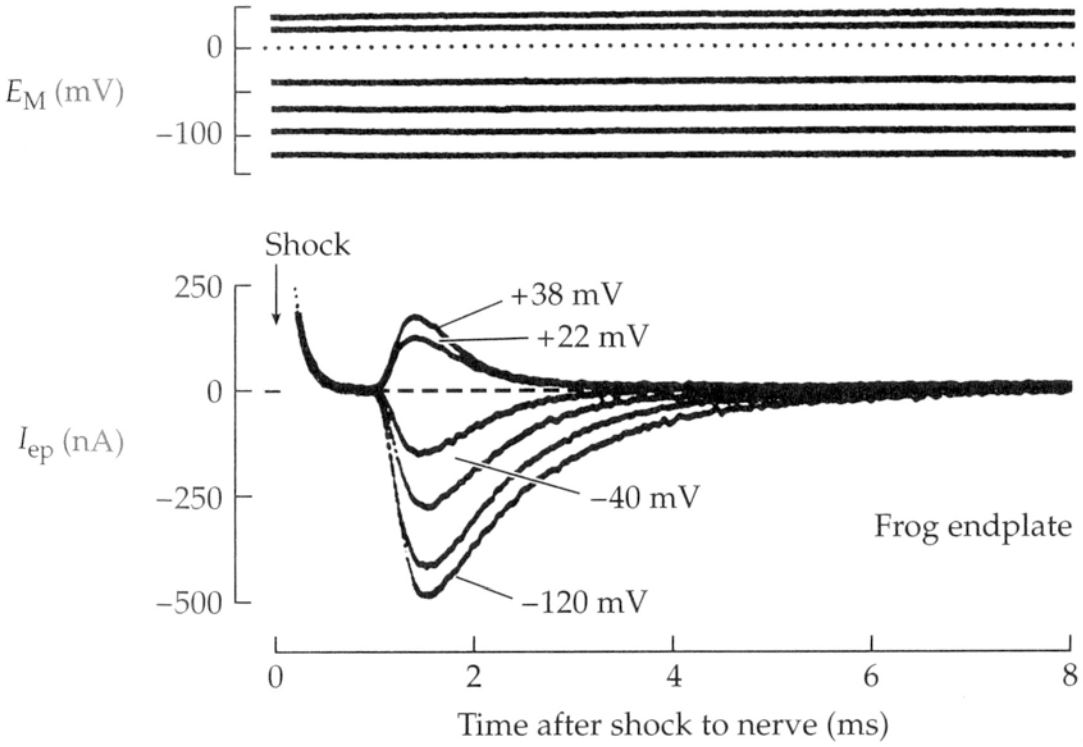
Neural synapses (cont.):

The maximum conductance g_{peak} is not fixed in many synapses. Rather, the efficiency of a synapse can be increased or decreased, depending on the pattern of synaptic input and/or whether an EPSP produced a spike in the post synaptic neuron.

An increase in synaptic efficiency is referred to as *long term potentiation* (LTP), while a decrease is known as *long term depression* (LTD).

These are forms of *neural plasticity*.

Receptor gating kinetics:



(from Hille)

6.5 Nerve-Evoked Endplate Currents The membrane potential of a frog sartorius muscle fiber is held at various levels by a two-microelectrode voltage clamp. The motor nerve is stimulated by an electric shock producing a brief artifact in the current record. About 1 ms later, the nerve action potential reaches the nerve terminal, releasing transmitter vesicles and opening postsynaptic nAChR channels transiently. The endplate current reverses sign near 0 mV and decays faster when the muscle is depolarized, and slower when hyperpolarized. T = 25°C. [From Magleby and Stevens 1972a.]

Receptor gating kinetics (cont.):

What causes the rate of exponential decay in the synaptic current of ligand-gated channels of fast chemical synapses?

A. The rate at which the neurotransmitter leaves the synaptic cleft?

B. The rate at which the channel naturally closes?

Receptor gating kinetics (cont.):

A. The rate at which the neurotransmitter leaves the synaptic cleft?

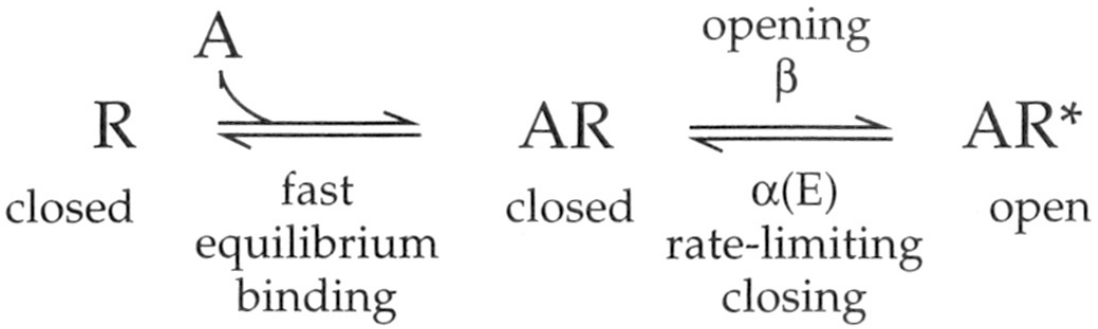
Apparently not!

1. The rate of decay shown in Fig. 6.5 of Hille is voltage dependent, which should not occur for a chemical diffusion process.
2. The rate of decay is temperature dependent, with a Q_{10} of 2.8, which is too high for a chemical diffusion process.

Receptor gating kinetics (cont.):

B. The rate at which the channel naturally closes?

If so, then the process might be modelled with the following kinetics:



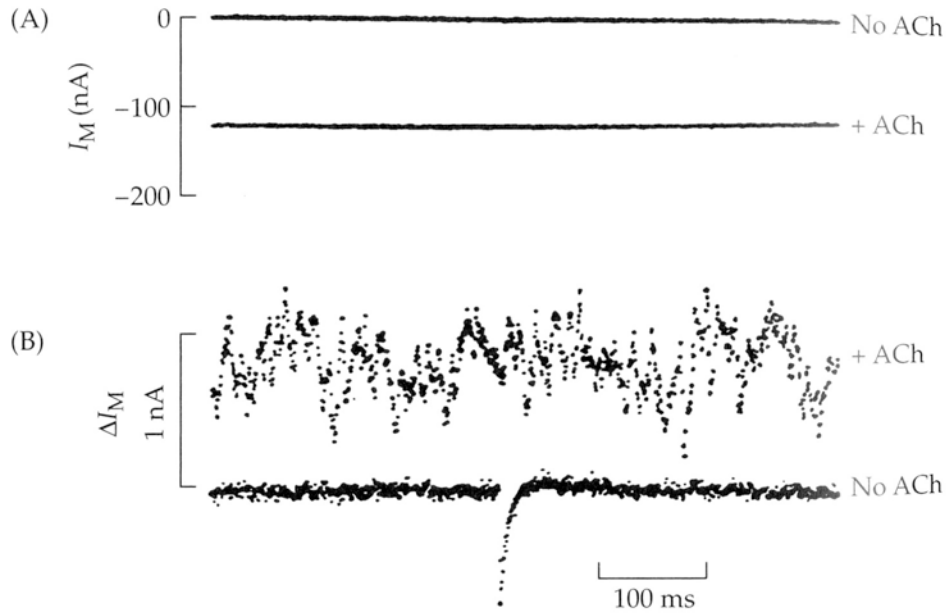
(H6.1)

Receptor gating kinetics (cont.):

From Eqn. (6.1) of Hille, it would be predicted that for a constant concentration of neurotransmitter in the synaptic cleft, such that the binding and unbinding of neurotransmitter is in equilibrium, then fluctuations should still be observed in the synaptic current with the same rate of decay.

This is indeed the case, as illustrated in the next two slides.

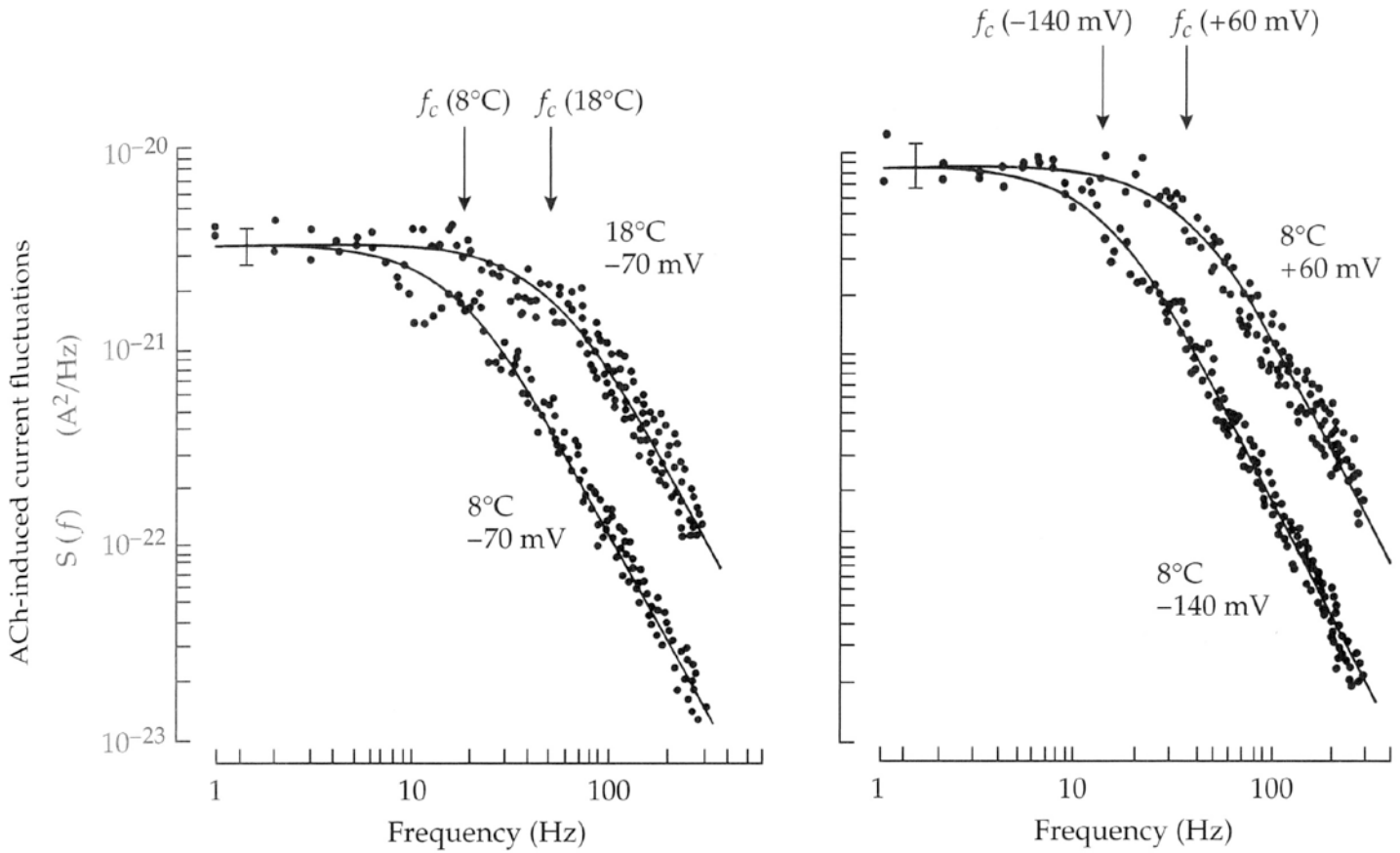
Receptor gating kinetics (cont.):



6.7 Endplate Current Fluctuations Currents measured from a frog sartorius muscle under voltage clamp. The currents are displayed (A) at low gain through a dc-coupled amplifier and (B) at much higher gain through an ac-coupled amplifier. In the resting endplate, the low-gain record shows a zero net current. The high-gain record shows low noise and a single inward current transient, which is a miniature endplate current from the spontaneous discharge of a single presynaptic transmitter vesicle. When a steady low concentration of ACh is applied iontophoretically to the endplate, the low-gain record shows a large steady inward endplate current. The high-gain record reveals fluctuations due to the superimposed stochastic opening of many channels. T = 8°C. [Adapted from Anderson and Stevens 1973.]

(from Hille)

Receptor gating kinetics (cont.):



6.8 Power Spectra of Current Fluctuations Power-density spectra of ACh-induced fluctuations recorded from frog muscle, as in Figure 6.7B. Current variance is plotted versus frequency on log-log axes. The lines are Lorentzian curves (Equation 6.2) and the arrows indicate the corner frequency of the Lorentzian. Depolarization and warming both increase the corner frequency. [From Anderson and Stevens 1973.]

(from Hille)

Receptor gating kinetics (cont.):

The power spectrum of an exponential decay has the form:

$$S(f) = \frac{S(0)}{1+(f/f_c)^2} = \frac{S(0)}{1+(2\pi f\tau)^2}, \quad \text{(H6.2)}$$

where $f_c = 1/(2\pi\tau)$ corresponds to the –3dB cutoff frequency.

The values of ¿ determined from this method match the values of ¿ obtained for synaptic input, supporting the proposed model.

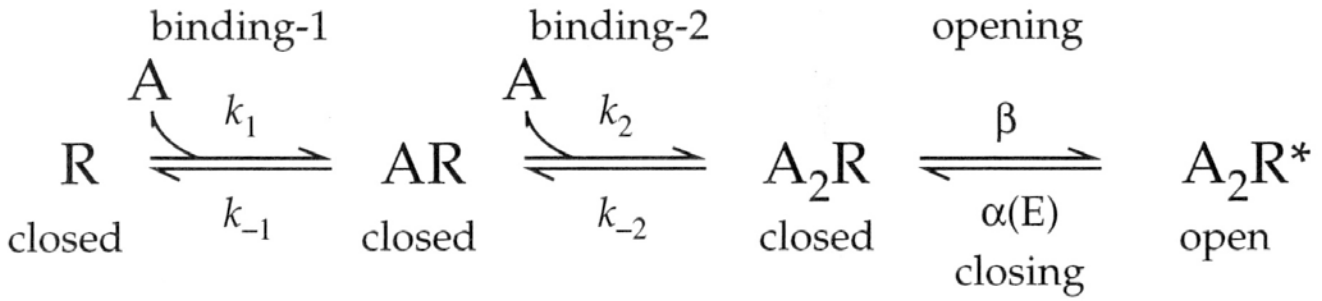
Receptor gating kinetics (cont.):

Further improvements on the model given by Eqn. (6.1) of Hille have consequently been developed.

1. The postsynaptic receptor may require binding of more than one neurotransmitter molecular, e.g., two ACh molecules per ACh receptor.
2. The neurotransmitter unbinding process is slow, such that gaps can appear in the conductance of single ACh receptor currents.

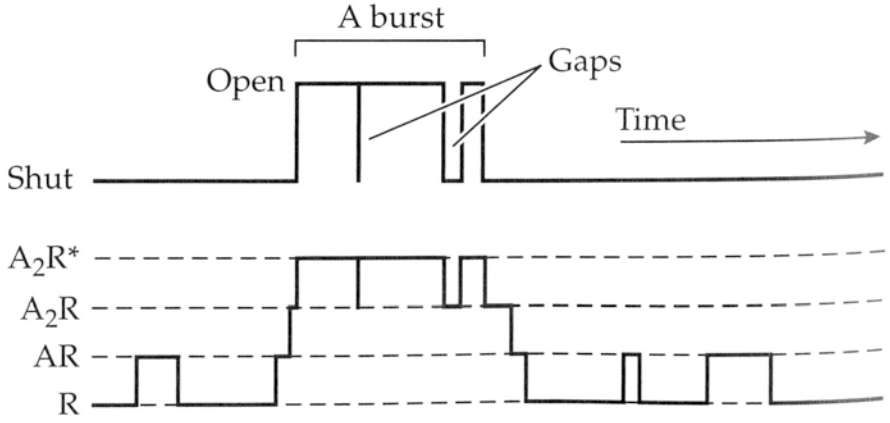
Receptor gating kinetics (cont.):

The refined kinetic model is:



(H6.3)

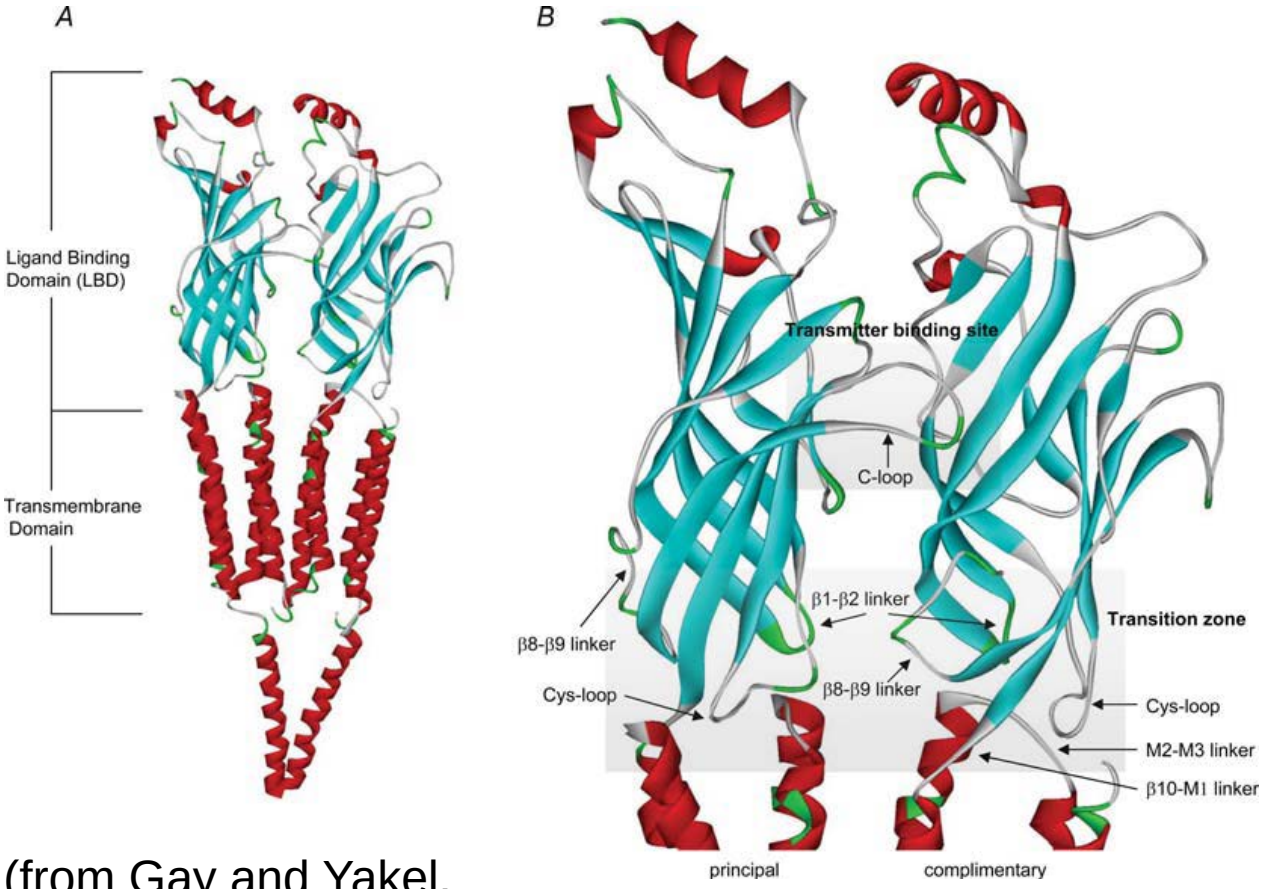
6.9 Microscopic States of nACh Receptors
Interpretation of the flickering conductance time course of an ACh receptor channel in terms of a four-state state diagram. In this hypothetical case, the empty (and closed) receptor R becomes singly occupied AR four times. On one occasion it becomes doubly occupied A_2R, which initiates an opening event with three elementary openings before one of the agonist molecules leaves again.



(from Hille)

Receptor gating kinetics (cont.):

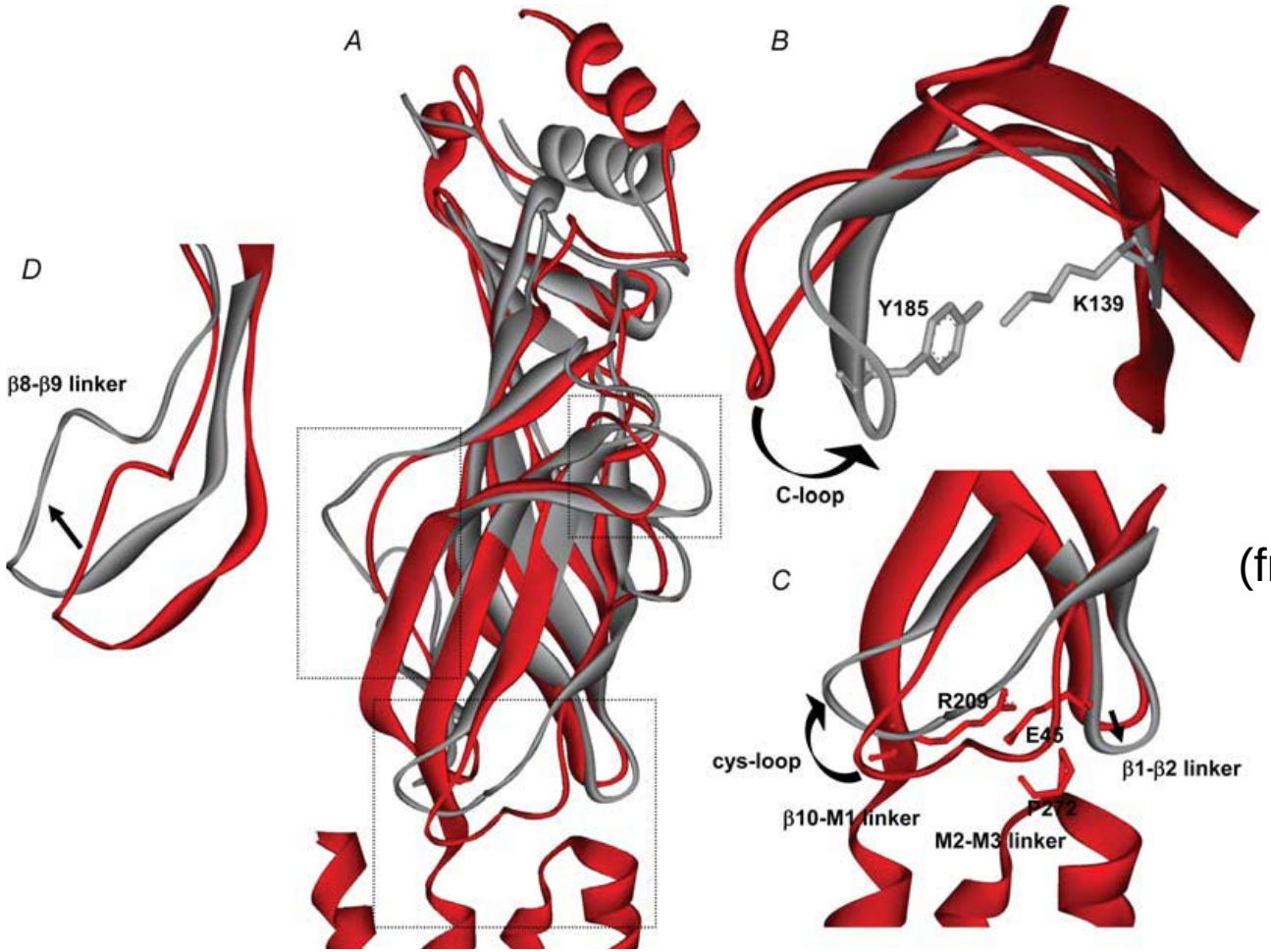
A structural model of gating of the ACh receptor has been proposed.



(from Gay and Yakel, *J. Physiol.* 2007)

Receptor gating kinetics (cont.):

Possible gating movements of the ACh receptor protein upon agonist binding:



(from Gay and Yakel, *J. Physiol.* 2007)