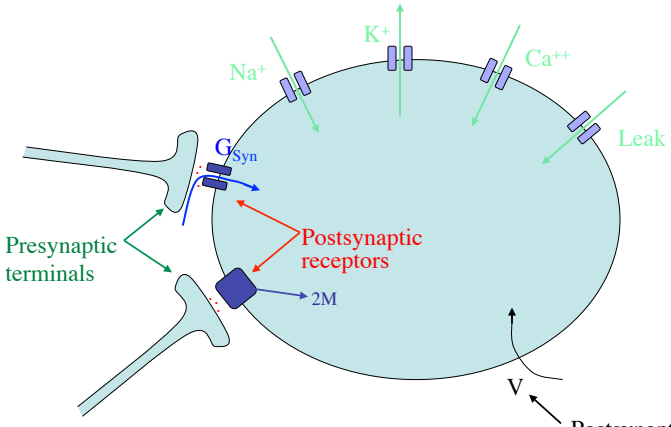
Synaptic Transmission: Ionic and Metabotropic

D. Purves et al. *Neuroscience* (Sinauer Assoc.) Chapters 5, 6, 7.

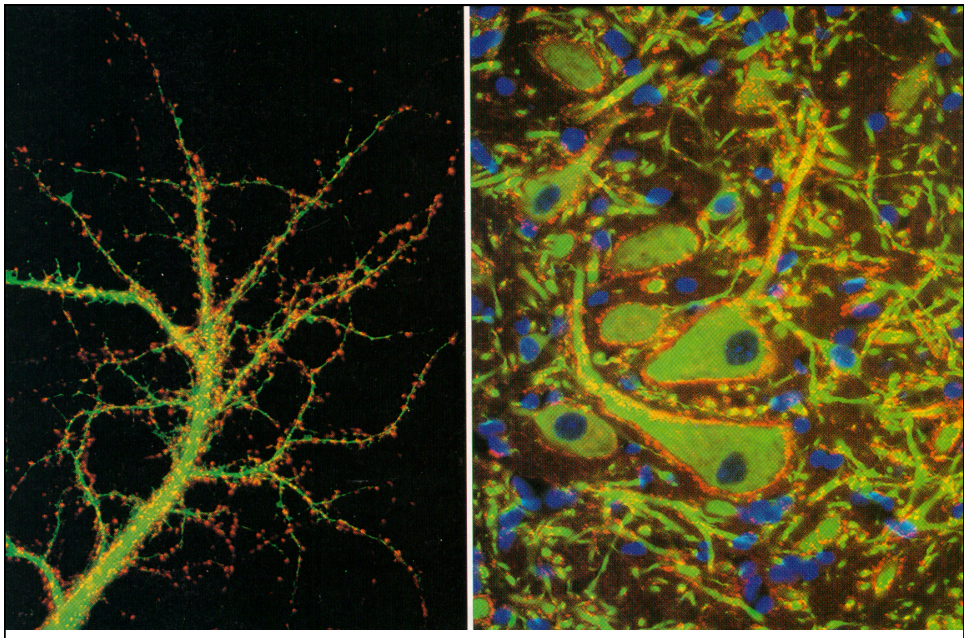
C. Koch. *Biophysics of Computation* (Oxford) Chapter 4.

J.G. Nicholls et al. *From Neuron to Brain* (Sinauer Press). Chapters 9-14, especially 9-11.

The inputs to neurons are synapses. Mostly these are chemical synapses, shown below, at which neurotransmitter is released from the presynaptic terminal, binding to a postsynaptic receptor. The result is some effect on the postsynaptic cell, ultimately changing its membrane potential or other properties.



Postsynaptic receptors can be **ionotropic**, directly gating an ion channel G_{syn} or **metabotropic**, producing an indirect effect through production of a second messenger *2M*.



Special stains for synapses (red) show their high density on dendrites and somas on CNS neurons.

The sequence of steps in synaptic transmission:

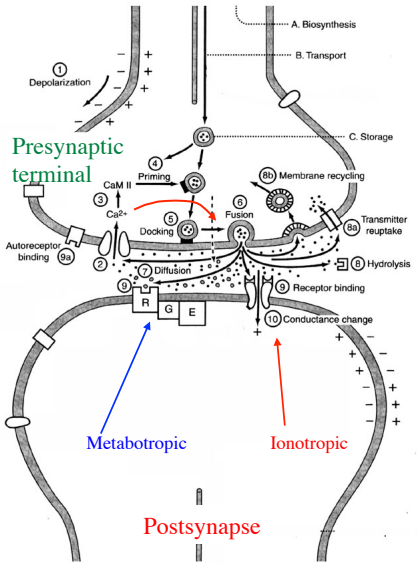
1. Depolarization of the presynapse
2. Calcium entry through V-gated calcium channels

3-5. Transfer of synaptic vesicles to the membrane.

6. Fusion of the vesicle with the membrane, releasing neurotransmitter.
7. Diffusion of the neurotransmitter across the synaptic cleft
9. Binding of transmitter to the postsynaptic receptor.
10. Changes in the postsynaptic cell

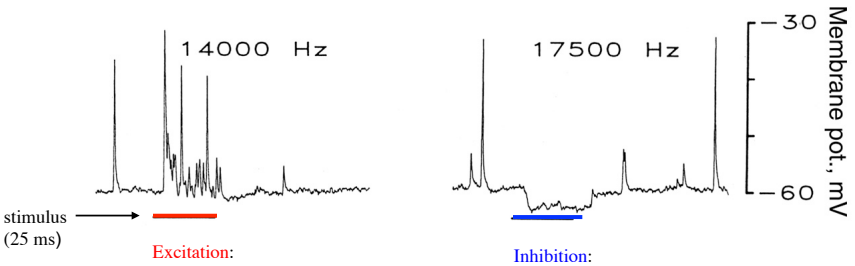
11. To terminate the synaptic action, the transmitter is metabolized (8) or removed from the cleft by reuptake (8a, 8b) in the neuron itself or in adjacent glia.

Some synaptic vesicles are synthesized in the cell body (A) and transported to the terminal (B), where they are filled with transmitter, primed (4) and docked (5) in preparation for release. Others are synthesized in the terminal; after release (6) the vesicle membrane is recycled by uptake (8b) and refilled with transmitter.



Modified from Shepherd, 2004.

Excitation and *inhibition* correspond to depolarization and hyperpolarization of the postsynaptic membrane

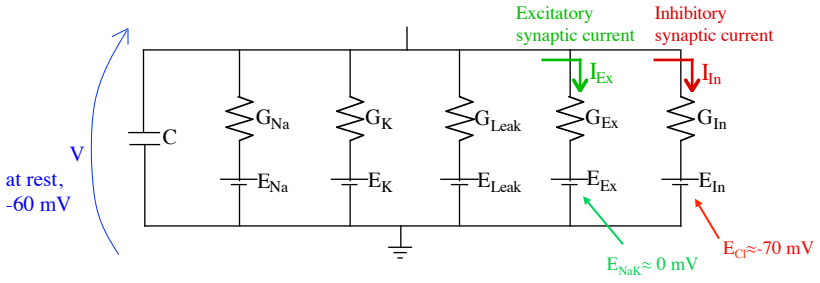


Excitation:
depolarization
EPSPs (excitatory post-synaptic potentials)
Increased spike rate

Inhibition:
hyperpolarization
IPSPs (inhibitory post-synaptic potentials)
Decreased spike rate

Smith and Rhode, 1987

To model postsynaptic ionotropic effects, excitatory and inhibitory synaptic conductances are added to the membrane model.



$$I_{Cap} = -[I_{Na} + I_K + I_{Leak} + I_{Ex} + I_{In}]$$

$$C\frac{dV}{dt} = -[G_{Na}(V - E_{Na}) + G_K(V - E_K) + G_{Leak}(V - E_{Leak}) + G_{Ex}(V - E_{Ex}) + G_{In}(V - E_{In})]$$

The battery-resistor model is very accurate for the ion channels of most ionotropic neurotransmitter receptors. When open, these channels show no rectification.

As with ion channels, the effect, excitatory or inhibitory, of a particular synaptic channel is determined by the ions that pass through the channel. For ionotropic channels in the brain, the following transmitters and ion channels are seen:

Transmitter	Receptor	Ions	Effect
Glutamate	AMPA, kainate	Na, K, (some Ca)	Excitatory (E_{exc}=0 mV)
	NMDA	Na, K, Ca	Excitatory
GABA	A	Cl	Inhibitory (E_{inh}=-70 mV)
Glycine		Cl	Inhibitory
Acetylcholine	Nicotinic	Na, K, Ca	Excitatory
Serotonin (5-HT)	5-HT_3	Na, K	Excitatory
ATP	Purine P1	Na, K	Excitatory

The main synaptic systems in the brain

Synaptic conductances G_{Ex} and G_{In} can be simulated by kinetic models like the one below.

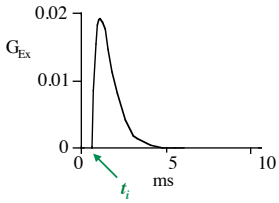
$$T + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} TR \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} TR^* \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} D$$

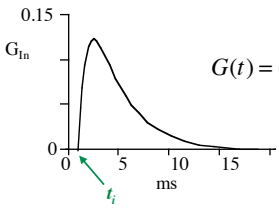
$$G = (const)\, TR^*$$ ← the channel conductance

T is the transmitter, R is the receptor, TR is the bound receptor, TR^* is the receptor in the open-channel state, and D is a desensitized state from which the channel exits slowly. This is a simplification; usually more than one T must bind and there are additional TR and D states.

Activation of the receptor is modeled by letting T be a short pulse and beginning the simulation with all the receptor in the R state.

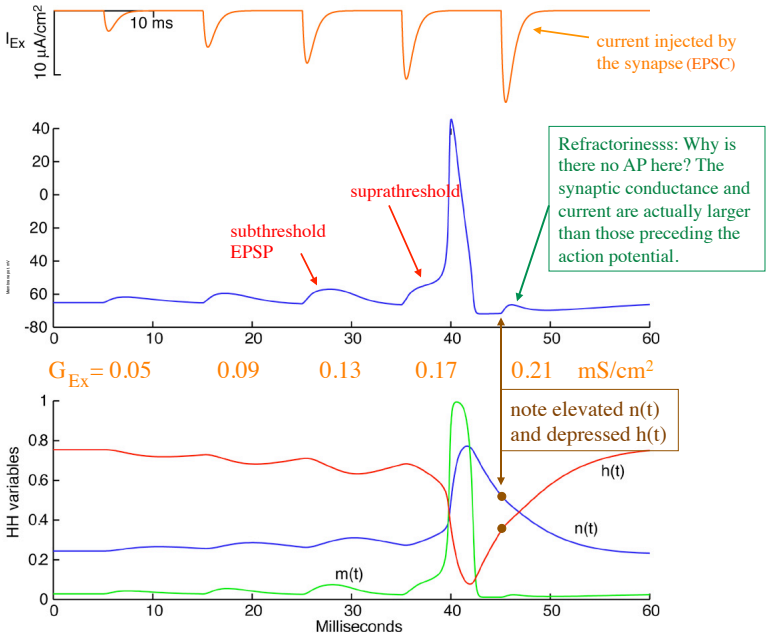
The solutions for $TR^*(t)$ or $G(t)$ are similar to the functions below. In fact, these are approximations, called α functions, with duration parameter τ.





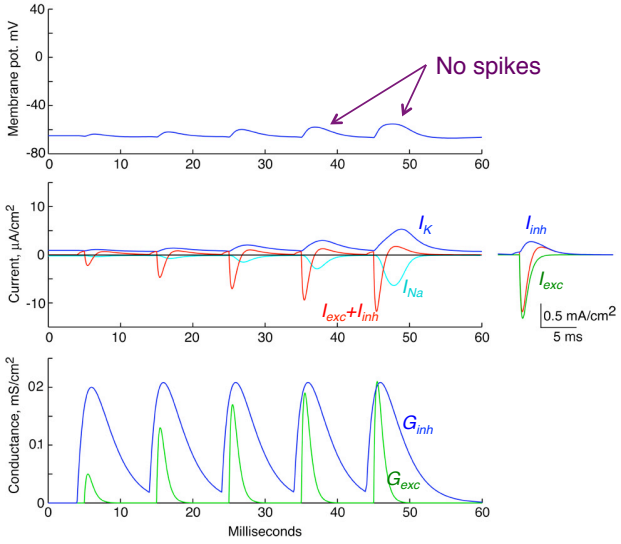
$$G(t) = (const)(t - t_i)\, e^{-(t-t_i)/\tau}$$

The HH model with synaptic inputs shows *threshold* and *refractoriness*, similar to the phenomena in real neurons.

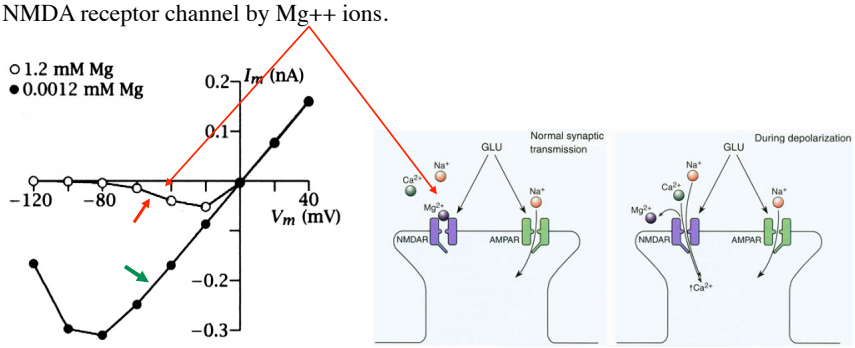


Adding inhibitory conductances blocks the excitatory effect by two mechanisms:

1. Injecting an outward current that hyperpolarizes the cell.
2. Increasing membrane conductance, which reduces the effect of the excitatory synapse (shunting).

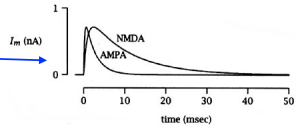


Glutamate receptors require further comment. NMDA-type glutamate receptors are conditionally activated, depending on the presence of glutamate AND depolarization of the postsynaptic terminal. The depolarization is necessary to relieve a block of the NMDA receptor channel by Mg++ ions.



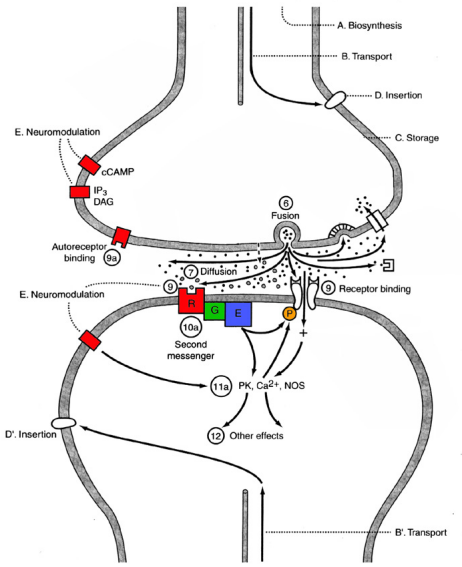
NMDA channels show two additional differences from other types of glutamate channels (AMPA or kainate):

1. NMDA currents last longer
2. NMDA channels admit Ca^{++}, which other types may or may not do. These Ca^{++} signals will be important later.



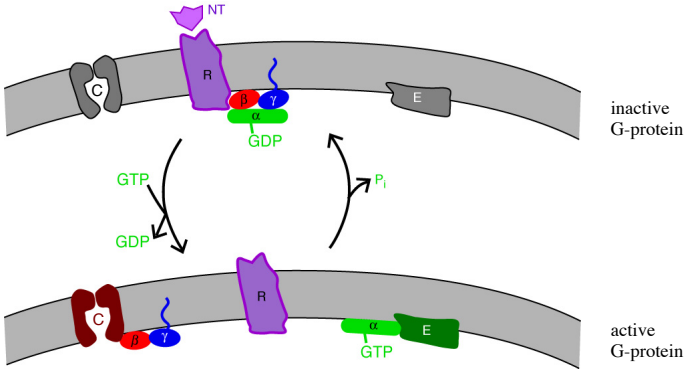
Malenka and Siegelbaum 2001 Johnstone and Wu, 1995

Metabotropic receptors are ones that do not couple directly to an ion channel; rather they couple to effector proteins that indirectly cause some change in the cell, often through phosphorylation of a protein. While this may result in opening or closing of ion channels, the connection is indirect and often can be quite indirect. Virtually all aspects of neuron physiology can be affected by neuromodulation.

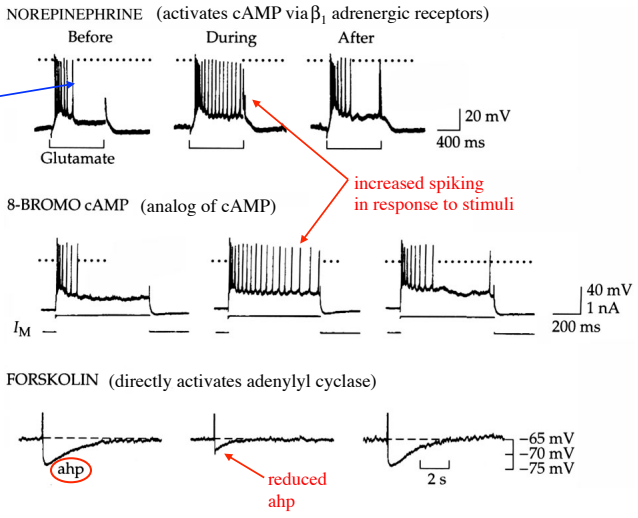


Modified from Shepherd, 2004

The best understood metabotropic effects occur through activation of G-proteins. The general scheme of G-protein activation is shown below. When the receptor (*R*) binds a transmitter (*NT*), the G-protein complex exchanges its GDP moiety for a GTP and cleaves into an α-subunit-GTP part and a β−γ subunit part. These diffuse in the membrane and both can activate other proteins, either enzymes (*E*) or ion channels (*C*). The G-protein is inactivated when the α-subunit cleaves its GTP to GDP + P_i and the subunits recombine.



Examples of changes in the response properties of neurons in the hippocampus due to cAMP modulation. The effect occurs by reducing the conductance of SK type K(Ca) channels. These channels are gated by Ca^{++} and produce the afterhyperpolarization (ahp) that follows one or more action potentials, as in the third trace below.



Why does the SK channel decrease spike rate during the stimulus as here?

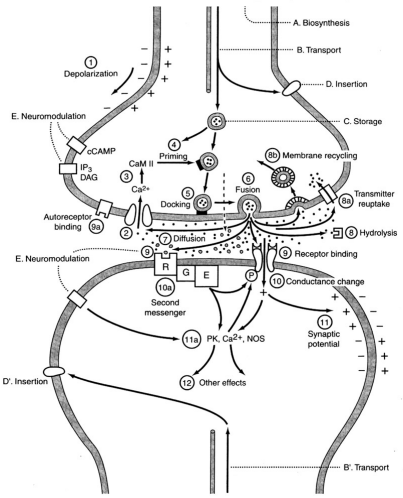
Note the example shown here works differently than the GIRK channel of the previous slide. Here the G protein activates the enzyme adenylyl cyclase that produces cAMP which activates a kinase to phosphorylate the channel and reduce its conductance.

Hillle, 2001

What is the strength of a synapse? This question will be central to the lectures on plasticity and network theory later in the course.

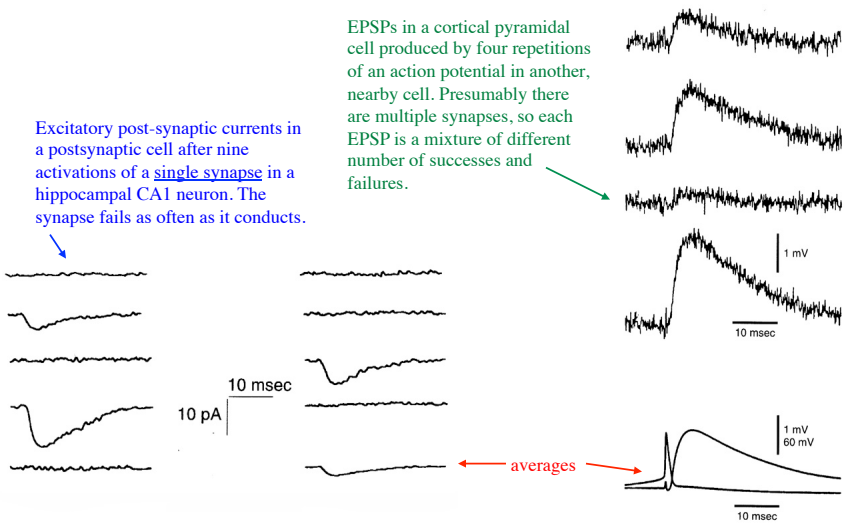
Synaptic strength is determined by a number of factors:

1. The size of the neurotransmitter release can be varied by presynaptic inhibition, often through metabotropic mechanisms (e.g. decreasing Ca currents in the presynaptic terminal).
2. Synaptic facilitation, due to accumulation of Ca^{++} in the presynaptic terminal, can increase transmitter release.
3. Synaptic depression, due to depletion of synaptic vesicles, can decrease release.
4. Synaptic depression due to desensitization of receptors (similar to inactivation, see slide 11).
5. Number of receptors. The postsynaptic effect of NT release depends on the number of receptors in the postsynaptic membrane, especially AMPA receptors. Important for long-term plasticity.
6. Postsynaptic electrical processing. Changes in potassium currents through modulation of K^+ channels can change the EPSP or IPSP produced by the synapse.



Shepherd, 2004

Synaptic strength is variable, due to randomness in the release of neurotransmitter. Two examples are shown below.



Wang and Stevens, unpub. and Mason et al. 1991, reproduced in Koch, 1999.

Summary of neurotransmitters and synaptic actions:

Synaptic actions in the brain can be roughly grouped into three categories, based on the nature of the postsynaptic pathway evoked:

1. Direct ionotropic mechanisms. The receptor is coupled directly to the ion channel. The effects are immediate (latency <1 ms) and relatively short-lasting (<10 ms). The most common transmitters are glutamate (excitatory), GABA (inhibitory), and glycine (inhibitory). Most signal processing in the brain involves ionotropic mechanisms.

2. Short-pathway metabotropic mechanisms. The receptor is coupled to a second messenger, such as a G-protein, which has a direct effect on an effector, such as opening an ion channel or releasing vesicles at a synapse.

3. Long-pathway metabotropic mechanisms (discussed later). The receptor is coupled to a second messenger cascade which leads to multiple effects or to a complex and long-lasting change in the cell's properties. For example, long-term plasticity (LTP) at synapses occurs with calcium acting as a messenger that initiates a cascade ultimately resulting in the placement of new ionotropic glutamate receptors in the post-synaptic membrane, increasing the strength of the synapse.