When giving your final presentation
Form for you to fill out for other student talks

1= strongly agree 5= strongly disagree

1) Speaker’s name:
2) What is the main article/subject?
3) What is the main point/subject?
4) Why should you care?
5) What two things did you learn from this talk?
6) Was the talk well organized?
7) Was the student able to answer questions?
8) Quality of slides?
9) Overall grade(1 is best):
10) General Comments.
Modified Grading

No final (yeah!)

**Grading**

34%: Homework (≈10 total)
34%: Written Project & Oral Project– Same topic
-- 19% on written report: 10 pg report.
-- 15% on oral report: 8-12 min plus 4 min for questions.
20% on midterm exam
10% on classroom participation /class evaluation
In-class Quiz: 2%
Chemical Synapse

How one nerve talks to a nerve, an organ (muscle, pancreas...)

Neurons create action potential—electrical impulse
Flow of sodium (and later potassium).
This causes a signal at end of neuron (at axon).
To transfer info, must cause a chemical change across synapse.
How to do it:
Depolarization causes Glutamate to diffuse
Interacts with AMPAR
Repetitive firing leads to short-term and long-term learning and memory.

Vision: photons (next lecture) → nerve impulse. Initiate chemical signal using a metatropic

Glutamate: an amino acid

\[
\text{HO}\text{C} - \text{CH}_2 - \text{CO}_2\text{H} \quad \text{NH}_2
\]
AMPARs trafficking is important for learning and memory.

Why study AMPAR trafficking?
- Alters synaptic strength
- Molecular basis of learning and memory
- More AMPAR → memory; less AMPAR → forgetting

Open questions:
- How AMPAR trafficking into synapse?
- Diffusion behavior in synapse?
AMPAR and NMDAR: ion channels in synapse, lead to action potentials.

Short-term memory & long-term memory:
More AMPAR in synapse of hippocampus—stronger response, more STM.
Sleep (& other processes) leads to long-term memory.
Long-term Potentiation—best model for memories.
Neurons (Nerve cells) and Synapses

• Neuron:
  – Building blocks of nervous systems.
• Soma
  – Cell body
• Dendrites
  – Collect signals
• Axon
  – Sends signals
• Synapse
  – Dendrite-axon junctions

Neurons transmit signals via synapses.
The Synapse

- Synapse
  - Presynapse (Axon)
  - Postsynapse (dendrite)
  - Synaptic cleft (~30 nm)
- Active zone (PAZ)
  - Vesicle release
- Postsynaptic density (PSD)
  - Receptors
  - Scaffold proteins
- PSD size is 250 -500 nm

The PSD is small, comparable to the light diffraction limit. Super-resolution techniques are required for imaging the PSD.
A first view of the Synaptic cleft

- Synaptic vesicle
- Voltage-gated Ca$^{++}$ channel
- Neurotransmitter re-uptake pump
- Neurotransmitter receptors
- Post-synaptic density
- Axon terminal
- Synaptic cleft
  - Dendritic
What are the proteins which are sensitive to glutamate? **AMPAR and NMDAR**

**AMPA receptor** because it is particularly sensitive to \(\alpha\)-amino-3-hydroxy-5-\textit{m}ethyl-4-\textit{iso}xazole-propionic acid.

**NMDA receptor** because it is particularly sensitive to the glutamate agonist \(N\)-\textit{m}ethyl-\textit{D}-\textit{a}spariate.

AMPAR are directly responsive to Glutamate (letting in \(K^+\), \(Na^+\)).

NMDAR are responsive to glutamate (\& glycine) \& voltage-dependent blockage due to \(Mg^{2+}\).

NMDAR controls the amount of AMPAR.

AMPAR can be in the post-synaptic membrane and in recycling endosomes.

The more AMPAR in the post-synaptic membrane, the stronger is the result.
AMPA Receptors

• What is AMPAR?
  – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: an inhibitor of AMPAR.
  – Transmembrane ion channel
  – Glutamate gated
  – Mediate Fast synaptic transmission

• AMPAR trafficking
  – Alters the synaptic strength

We want to understand how AMPAR trafficking at the synapse.
NMDAR
believed to be structurally similar to AMPAR

The NMDA receptor forms a heterotetramer between two NR1 and two NR2 subunits.

Glutamate-binding, Glycine-binding
High-calcium permeability
Voltage-dependent magnesium block.

Activated NMDAR

![Diagram showing activated NMDAR with glutamate and glycine binding sites, calcium channel, and intracellular and extracellular spaces.](image)
How does nerve impulse traveling down the axon lead to vesicle fusion and glutamate release?

The action potential travels down the axon to the terminal. Arrival at the terminal causes membrane depolarization, which opens voltage-dependent $\text{Ca}^{2+}$ channels situated in the active zone where the neurotransmitter vesicles are docked. $\text{Ca}^{2+}$ binds to proteins, mainly synaptotagmin (a presynaptic protein—see next pg), which cause vesicle fusion mainly through an interaction of synaptotagmin with the SNARE proteins.
How does synaptic vesicle attach to membrane?
SNARE proteins on vesicle and membrane are Ca\(^{2+}\)-dependent

http://www.sumanasinc.com/webcontent/animations/content/receptors.html
See
http://icarus.med.utoronto.ca/neurons/index.swf
Long-term Potentiation (LTP), a phenomenon in which brief repetitive activity causes a long lasting (many weeks) enhancement in the strength of synaptic transmission, is generally accepted to be a key cellular substrate for learning and memory.

http://keck.ucsf.edu/neurograd/faculty/nicoll.html
Roger Nickoll’s, UCSF
In 1988, Dr. Nicoll was the first to show that LTP (long-term potentiation) is triggered by a rise in calcium concentration within the postsynaptic terminal. In subsequent papers, his lab demonstrated that calcium mediates LTP induction by activating CAMKII.
AMPAR and NMDAR
Increase in # of AMPAR via NMDAR, leads to learning & Memory

(a) Glutamate binding to AMPA and NMDA receptors

(b) Ca^2+ influx through NMDA receptors

(c) AMPA receptors activated

Molecules of glutamate bind to recognition sites of NMDA receptors as well as AMPA receptors. The ionotropic AMPA receptors admit sodium ions when activated, resulting in a moderate local depolarization...

...that dislodges the magnesium ions blocking the NMDA receptors. Large quantities of calcium ions may now enter the neuron through the NMDA receptors' calcium channels. The NMDA receptor is thus both ligand and voltage gated. The calcium influx affects the metabolic machinery of the cell...

...resulting in the addition of more AMPA receptors to the postsynaptic membrane. The synapse has thus been strengthened—it will respond more rapidly and more strongly to future releases of glutamate.

Memory, Learning!

http://www.biopsychology.com/6e/step/04/0402-1-L.jpg
Need more than one action potential for nerve to fire, LTP.
**Short-term Memory**: Info. Stored in temporary links in Hippocampus

**Long-term Memory**: links transferred to cerebral cortex, possibly during sleep.

Hippocampus: Essential for acquiring new long-term memory. Injury to hippocampus: cannot form any new lasting memories but can recall events from before their injury.
Memory & Learning

Example of Neural Plasticity (synaptic plasticity)

Long-term and Short-term Memories

LTM stored in Cerebral cortex

Adult brain viewed from the rear

Cerebrum (including cerebral cortex)

Thalamus

Midbrain

Hindbrain

Cerebellum

Cerebral cortex

Corpus callosum

Basal nuclei

Cerebellum

Cerebrum
Long-Term Potentiation (LTP)

In neuroscience, **long-term potentiation (LTP)** is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying synaptic plasticity, the ability of chemical synapses to change their strength. As memories are thought to be encoded by modification of synaptic strength, LTP is widely considered one of the major cellular mechanisms that underlies learning and memory.

LTP shares many features with long-term memory, making it an attractive candidate for a cellular mechanism of learning. For example, LTP and long-term memory are triggered rapidly, each depends upon the synthesis of new proteins, each has properties of associativity, and each can last for many months. LTP may account for many types of learning, from the relatively simple classical conditioning present in all animals, to the more complex, higher-level cognition observed in humans.
LTP & Relation to Memory

At a cellular level, LTP enhances synaptic transmission. It improves the ability of two neurons, one presynaptic and the other postsynaptic, to communicate with one another across a synapse. The precise molecular mechanisms for this enhancement of transmission have not been fully established, in part because LTP is governed by multiple mechanisms that vary by species and brain region. In the most well understood form of LTP, enhanced communication is predominantly carried out by improving the postsynaptic cell's sensitivity to signals received from the presynaptic cell. These signals, in the form of neurotransmitter molecules, are received by neurotransmitter receptors present on the surface of the postsynaptic cell. LTP improves the postsynaptic cell's sensitivity to neurotransmitter in large part by increasing the activity of existing receptors and by increasing the number of receptors on the postsynaptic cell surface.
Two classes of Receptors: Ionotrophic and Metabotrophic Receptors

• See Chpt 7. Ionotrophic. Opened or closed in response to the binding of a chemical messenger (i.e., a ligand), such as a neurotransmitter (response to: Glutamate, excitatory; GABA, glycine, inhibitory

• Metabotrophic Glutamine—e.g. in Vision (next)

• metabotrophic receptors do not form an ion channel pore; rather, they are indirectly linked with ion-channels on the plasma membrane of the cell through signal transduction mechanisms, often G proteins.

http://en.wikipedia.org/wiki/Ionotrophic
http://en.wikipedia.org/wiki/Metabotrophic_receptor
Recent (2009, Nature) results: **AMPA Receptors**

Rectangular geometry, maximize packing?

X-ray crystal structure of the (GluA2)$_4$ AMPAR, showing the two-fold crystal structure (left) and schematic (right). If the sub-units are labeled as shown by the solid dots (right) the expected distances will be 9 and 15 nm. (From Sobolevsky, 2009)
Class evaluation

1. What was the most interesting thing you learned in class today?

2. What are you confused about?

3. Related to today’s subject, what would you like to know more about?

4. Any helpful comments.

   Answer, and turn in at the end of class.
Synaptic transmission from a presynaptic neuron to a postsynaptic cell.

Note that with the exception of the final step, the entire process may run only a few tenths of a millisecond, in the fastest synapses.

1. The process begins with a wave of electrochemical excitation called an action potential traveling along the membrane of the presynaptic cell, until it reaches the synapse.
2. The electrical depolarization of the membrane at the synapse causes channels to open that are permeable to calcium ions.
3. Calcium ions flow through the presynaptic membrane, rapidly increasing the calcium concentration in the interior.
4. The high calcium concentration activates a set of calcium-sensitive proteins attached to vesicles that contain a neurotransmitter chemical.
5. These proteins change shape, causing the membranes of some "docked" vesicles to fuse with the membrane of the presynaptic cell, thereby opening the vesicles and dumping their neurotransmitter contents within 180 μsec into the synaptic cleft, the narrow space between the membranes of the pre- and postsynaptic cells.
6. The neurotransmitter diffuses within the cleft. Some of it escapes, but some of it binds to chemical receptor molecules located on the membrane of the postsynaptic cell. The membrane added by this fusion is later retrieved by endocytosis and recycled for the formation of fresh neurotransmitter-filled vesicles.
7. The binding of neurotransmitter causes the receptor molecule to be activated in some way. Several types of activation are possible. In any case, this is the key step by which the synaptic process affects the behavior of the postsynaptic cell.
8. Due to thermal shaking, neurotransmitter molecules eventually break loose from the receptors and drift away.
9. The neurotransmitter is either reabsorbed by the presynaptic cell, and then repackaged for future release, or else it is broken down metabolically.

http://en.wikipedia.org/wiki/Chemical_synapse