Ramon y Cajal

Learning objectives for Lecture 7

• Be able to add a synapse in an equivalent circuit model

• To describe a simple model of synaptic transmission

• To be able to describe synaptic transmission as a convolution of a linear kernel with a spike train

• To understand synaptic saturation

• To understand the different functions of somatic and dendritic inhibition
Chemical synapse

- Structure of typical excitatory synapse

![Diagram of a chemical synapse]

- Pre-synaptic terminal
- Post-synaptic terminal (spine)
- Axon
- Dendrite
- Synaptic vesicle (30-40nm dia)

Approximate dimensions:
- 500 nm
- 0.5 μm
- ~20 nm
Chemical synapse

- Sequence of events in synaptic transmission

[Diagram of a chemical synapse showing AP, voltage-gated Ca- channels, and membrane potentials (+50mV and -60mV)]
Chemical synapse

• Sequence of events in synaptic transmission

'ligand' = 'neurotransmitter'

Last step: Neurotransmitter reuptake

![Diagram of chemical synapse with ion channels and neurotransmitter release]

- \( I_{syn} \)
- \( V_m \)
- \( G_{syn} \)
Anatomy of synapses/axons/dendrites

• Synapses are small – contact area~0.5μm

• High packing density ~10^9 synapses/mm^3
  – 1.1μm on a 3D lattice
  – 4.1km of axon (0.3μm dia)
  – 500m of dendrite

• A cell receives many synapses
  – 10000 synapses
  – on 4mm of dendrites (4 cm of axon)
  – 10^5 neurons/mm^3 in mouse cortex
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How does a synapse respond?

- Ionotropic receptors

Two electrode voltage-clamp experiment

Frog sartorius muscle fiber

Magleby and Stevens, 1972
How does a synapse respond?

- Ionotropic receptors

\[
I_{\text{syn}}(t) = G_{\text{syn}}(t) \left[ V - E_{\text{syn}} \right]
\]

\[
G_{\text{syn}}(t)
\]

I-V Curve

\[
I_{\text{max}}
\]

\[
V
\]

-100 50 mV

\[
E_M (\text{mV})
\]

\[
I_{\text{ep}} (\text{nA})
\]

0 100

\[
\text{Shock}
\]

\[
+38 \text{ mV}
\]

\[
+22 \text{ mV}
\]

\[
-40 \text{ mV}
\]

\[
-120 \text{ mV}
\]

0 2 4 6 8

Time after shock to nerve (ms)

Frog endplate

Annotated figure on lower right © Hille, Bertil. *Ion Channels of Excitable Membranes* (3rd Ed.). 2001, Sinauer / Oxford University Press. All rights reserved. This content is excluded from our Creative Commons license. For more information, see https://ocw.mit.edu/help/faq-fair-use/.
Equivalent circuit model of a synapse

- Current flow through a synapse results from changes in synaptic conductance

\[ I_{\text{syn}}(t) = G_{\text{syn}}(t)\left[V - E_{\text{syn}}\right] \]
Excitatory synapses

- Increased synaptic conductance causes the membrane potential to approach the reversal potential for that synapse.

\[ I_{syn}(t) = G_{syn}(t) \left[ V - E_{syn} \right] \]

\[ E_{syn} = 0 \text{ mV} \]

Now we can change the 'holding potential of the cell by injecting a little current (current clamp experiment)
Excitatory and inhibitory synapses

- Increased synaptic conductance causes the membrane potential to approach the reversal potential for that synapse.

\[ I_{syn}(t) = G_{syn}(t) \left[ V - E_{syn} \right] \]

Excitatory synapse if \( E_{syn} > V_{th} \)

\( E_{syn} = 0 \text{ mV} \)

Excitatory postsynaptic potential (EPSP)

Excitatory and inhibitory synapses

- Increased synaptic conductance causes the membrane potential to approach the reversal potential for that synapse.

\[ I_{syn}(t) = G_{syn}(t) \left[ V - E_{syn} \right] \]

- GABAergic synapse

- Inhibitory synapse if \( E_{syn} < V_{th} \)

\[ E_{syn} = -75 \text{ mV} \]

Inhibitory postsynaptic potential (IPSP)

Equivalent circuit model of a synapse

- Current flow through a synapse results from changes in synaptic conductance
  \[ I_{syn}(t) = G_{syn}(t) \left[ V_m(t) - E_{syn} \right] \]

- Ligand gated ion channels ‘flicker’ between open and closed states.

- We can write the synaptic conductance in terms of the probability \( P_R(t) \) that a receptor is ‘open’.
  \[ G_{syn}(t) = \hat{g}_R N_R P_R(t) \]
  \( \hat{g}_R \) = unitary ‘open’ conductance
  \( N_R \) = number of receptors
Kinetic model of synapse gating

- We can describe the open probability using a ‘kinetic’ model.

\[ \text{'closed'} \xrightleftharpoons[\beta]{\alpha} \text{'open'} \]

\[ 1 - P_R \quad P_R \]

\( \alpha, \beta \) are transition rate constants

Probability per unit time;

units are 1/s

- What controls the rate at which channels open?

Neurotransmitter!
Equivalent circuit model of a synapse

- Simplified version of Magleby-Stevens model

\[
\frac{d P_R}{dt} = \alpha [A]^n (1 - P_R) - \beta P_R
\]

\[
P_R(t) = P_{\text{max}} e^{-t/\tau_s}
\]

\[
G_{\text{syn}}(t) = \hat{g}_R N_R P_R(t)
\]
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Response of a synapse to a spike train input

- This simple model makes it very easy to describe the response of a synapse to a train of spikes!

\[ K(t) = G_{\text{max}} e^{-t/\tau_s} \]

\[ G(t) = \int_{-\infty}^{\infty} K(\tau) S(t - \tau) \, d\tau \]
Response of a synapse to a spike train input

- This simple model makes it very easy to describe the response of a synapse to a train of spikes!

- We just **convolve** the spike train with the linear response of the synaptic conductance

\[
G(t) = \int_{-\infty}^{\infty} K(\tau) S(t - \tau) \, d\tau
\]

Impulse response

\[
K(t) = G_{\text{max}} \, e^{-t/\tau_s}
\]
Response of a synapse to a spike train input

- We just **convolve** the spike train with the linear response of the synaptic conductance

\[ G(t) = \int_{-\infty}^{\infty} K(\tau) S(t - \tau) \, d\tau \]

- Easy to do in MATLAB®
  - use the `conv` function
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Synaptic saturation

• Let’s examine how the voltage in a dendrite changes as a function of the amount of excitatory conductance…
Synaptic saturation

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Synaptic saturation

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As synaptic input increases, the postsynaptic response saturates to a constant value.
Synaptic saturation

• Let’s examine how the voltage in a dendrite changes as a function of the amount of excitatory conductance…

Kirchhoff’s current law says:

\[ I_{\text{syn}} + I_L = 0 \]

\[ G_{\text{syn}} [V - E_{\text{syn}}] + G_L [V - E_L] = 0 \]

\[ G_{\text{syn}} V - G_{\text{syn}} E_{\text{syn}} + G_L V - G_L E_L = 0 \]

\[ V (G_{\text{syn}} + G_L) - (G_{\text{syn}} E_{\text{syn}} + G_L E_L) = 0 \]

\[ V = \frac{G_L E_L + G_{\text{syn}} E_{\text{syn}}}{G_L + G_{\text{syn}}} \]
Synaptic saturation

• Let’s examine how the voltage in a dendrite changes as a function of the amount of excitatory conductance...

\[ V = \frac{G_L E_L + G_{syn} E_{syn}}{G_L + G_{syn}} \]

For \( G_L >> G_{syn} \)

\[ V \approx E_L + \left( \frac{E_{syn}}{G_L} \right) G_{syn} \]

For \( G_{syn} >> G_L \)

\[ V \rightarrow E_{syn} \]
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Inhibitory inputs

• The effect of inhibitory input depends strongly on where the inhibitory synapse is.
Inhibitory inputs

• The effect of inhibitory input depends strongly on where the inhibitory synapse is
Crayfish as a model system

- Stereotypic behavior
- Identifiable neurons
- Identifiable circuits

Escape behavior in crayfish

- MG (medial giant) escape
- LG (lateral giant) escape
- Non-giant escape

Figure: Edwards et al. (Trends Neurosci, 1999)

LG is a ‘command neuron’

• LG neuron is **sufficient** for LG escape.
  – Electrical stimulation of LG neuron produces tail flip.

• LG neuron is **necessary** for LG escape.
  – Tail flip is not elicited if the LG neuron is hyperpolarized.

Figure removed due to copyright restrictions. See Fig. 1 in Wine, J.J. and D.C. Mistick. “Temporal Organization of Crayfish Escape Behavior: Delayed Recruitment of Peripheral Inhibition.” *J. Neurophysiology* 40 no. 4 (1977):905-925.

Wine & Mistick (1977)
Escape behaviors are strongly modulated by inhibition

- Escape response is suppressed while another escape response is in progress
  - Recurrent inhibition of LG neurons (and many other neurons) during escape behavior

- Escape response is suppressed when the animal is restrained

Hold off escape until timely moment?

Figure removed due to copyright restrictions. See Fig. 2 in Krasne, F.B. and J.J. Wine. “Extrinsic Modulation of Crayfish Escape Behaviour.” J. Experimental Biology 63 (1975): 433-450.

Krasne & Wine (1975)
Escape behaviors are strongly modulated by inhibition

- Escape response is suppressed while the animal is eating

- But not while the animal is searching for food

Krasne & Lee (1988)
Two types of modulation of LG escape reflex

- **Absolute inhibition**: The escape is inhibited no matter how strong the excitation is.

- **Relative inhibition**: The likelihood of escape is reduced, but it is still possible to override this kind of inhibition.
Location of inhibitory synapses

• Proximal inhibition:
  – Near the spike initiating zone
  – Arises from motor circuits that generate the MG escape
  – Called ‘recurrent inhibition’

• Distal inhibition:
  – Intermixed with excitatory afferents further out on the dendrite
  – Arises from sensory areas
  – Called ‘tonic inhibition’

Previous hypothesis:
Distal inhibition allows selective inhibition for particular dendritic branches
Measuring the effect of different types of inhibition

Sensory root stimulation

Current injection

MG stimulation

restraint, sucrose block

 Vu and Krasne, 1992
Equivalent circuit model

- $R_L$: longitudinal resistance
- $R_P$: proximal resistance
- $R_D$: distal resistance
- $E_e$: reversal potential for excitatory synapse (100 mV)
- $G_e$: excitatory conductance
- $G_i$: inhibitory conductance
Proximal versus Distal inhibition

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Proximal inhibition

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Distal inhibition

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More ‘realistic’ multi-compartment model

proximal inhibitory synapses

excitatory synapses, distal inhibitory synapses

Vu et al. (JNS, 1993)
Different functions for proximal and distal inhibition

- Two-compartment model shows that the effect of proximal and distal inhibition are different.
  - Proximal inhibition: absolute
  - Distal inhibition: relative

- Qualitatively similar effects were seen when more complicated models were used.
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9.40 Introduction to Neural Computation
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