Synapse models and their programming

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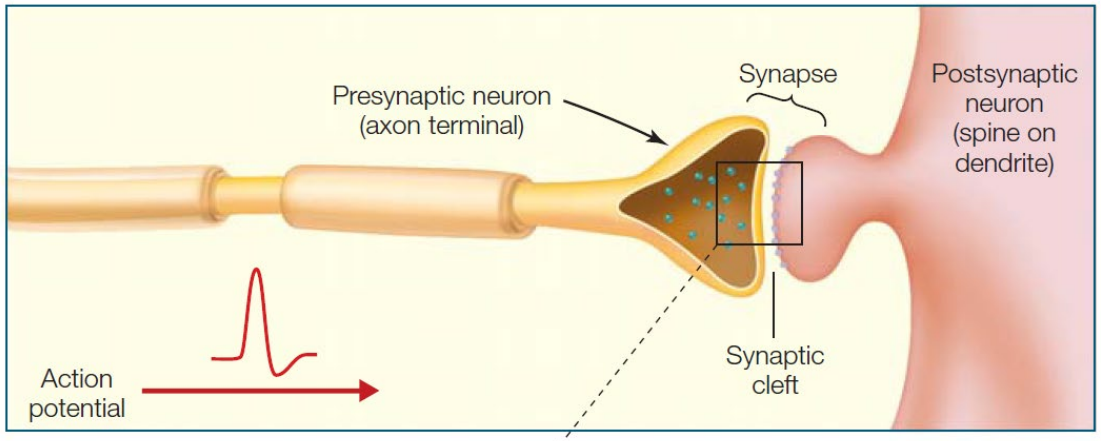
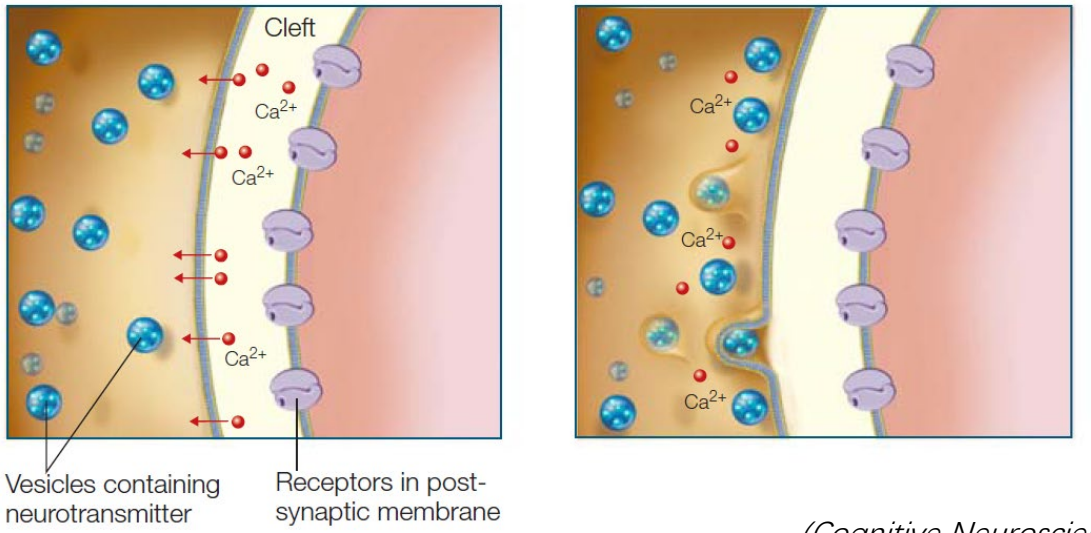
Neurotransmitter & Synapse



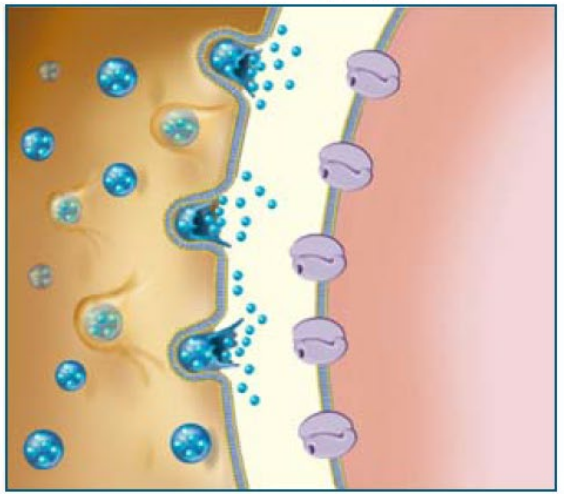
When the action potential invades the axon terminals, it causes voltage-gated Ca^{2+} channels to open (1), which triggers vesicles to bind to the presynaptic membrane (2). Neurotransmitter is released into the synaptic cleft by exocytosis and diffuses across the cleft (3). Binding of the neurotransmitter to receptor molecules in the postsynaptic membrane completes the process of transmission (4).

① Action potential depolarizes the terminal membrane, which causes Ca^{2+} to flow into the cell

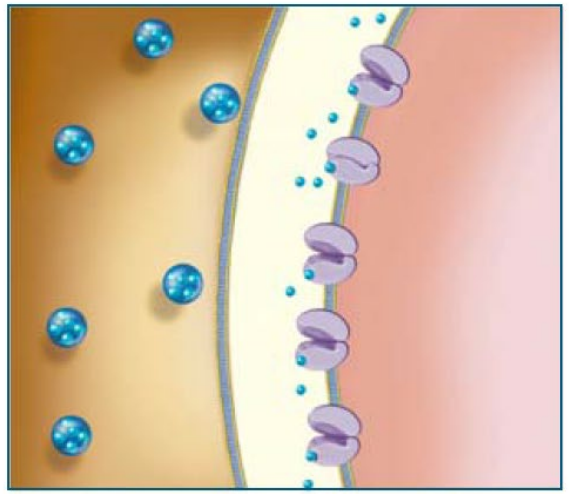
② Ca^{2+} causes vesicles to bind with cell membrane



③ Release of neurotransmitter by exocytosis into the synaptic cleft



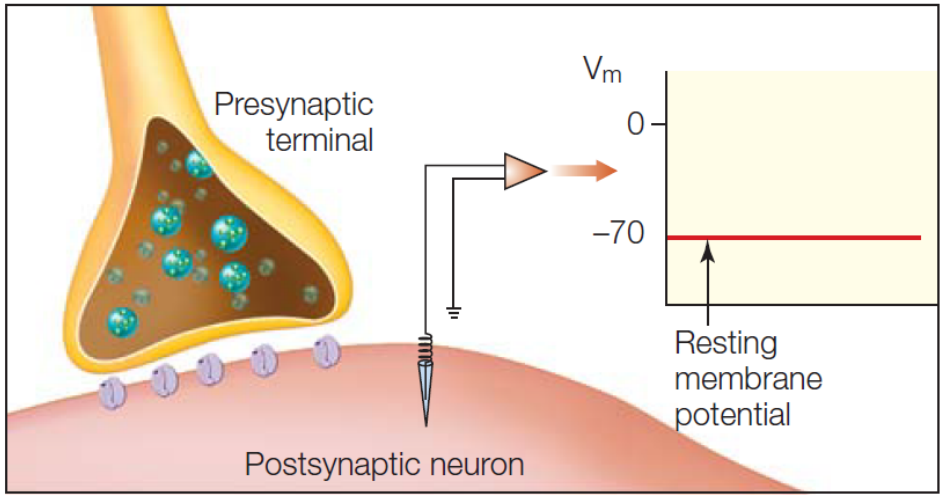
④ Transmitter binds with receptor



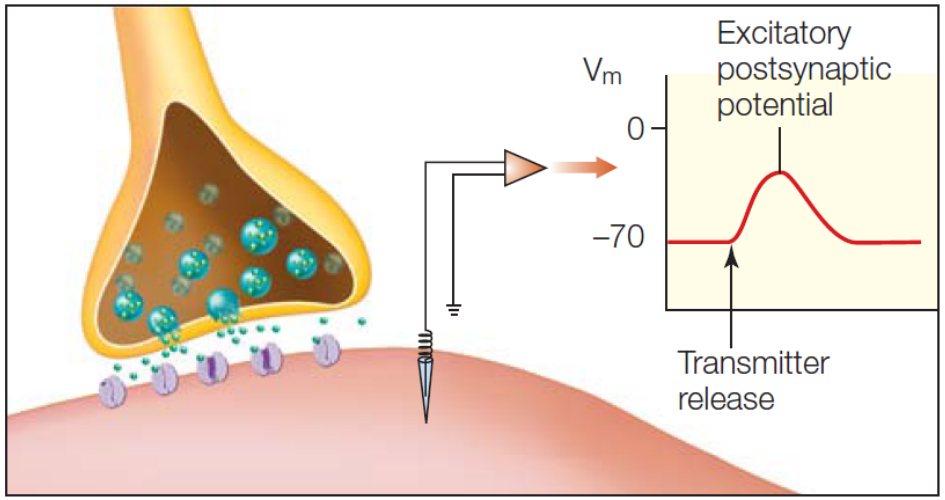
(Cognitive Neuroscience, 4th edition, 2013)

Neurotransmitter & Synapse

Before transmitter release



After transmitter release



Neurotransmitter leading to postsynaptic potential.

The binding of neurotransmitter to the postsynaptic membrane receptors changes the membrane potential (V_m). These postsynaptic potentials can be either excitatory (depolarizing the membrane), as shown here, or inhibitory (hyperpolarizing the membrane).

(Cognitive Neuroscience, 4th edition, 2013)

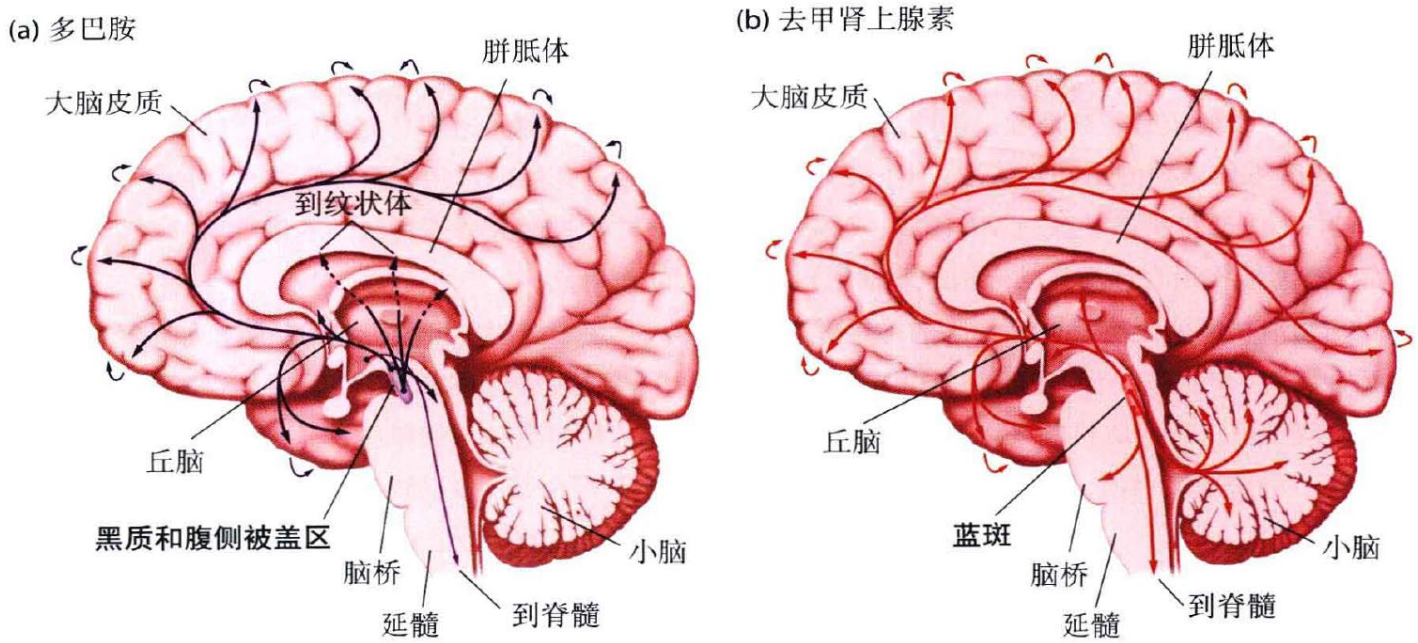
Neurotransmitters

兴奋性神经递质:

- 乙酰胆碱 (ACh)
- 儿茶酚胺 (catecholamines)
- 谷氨酸 (glutamate)
- 组胺 (histamine)
- 5-羟色胺 (serotonin)
- 某些神经肽类 (some of neuropeptides)

抑制性神经递质:

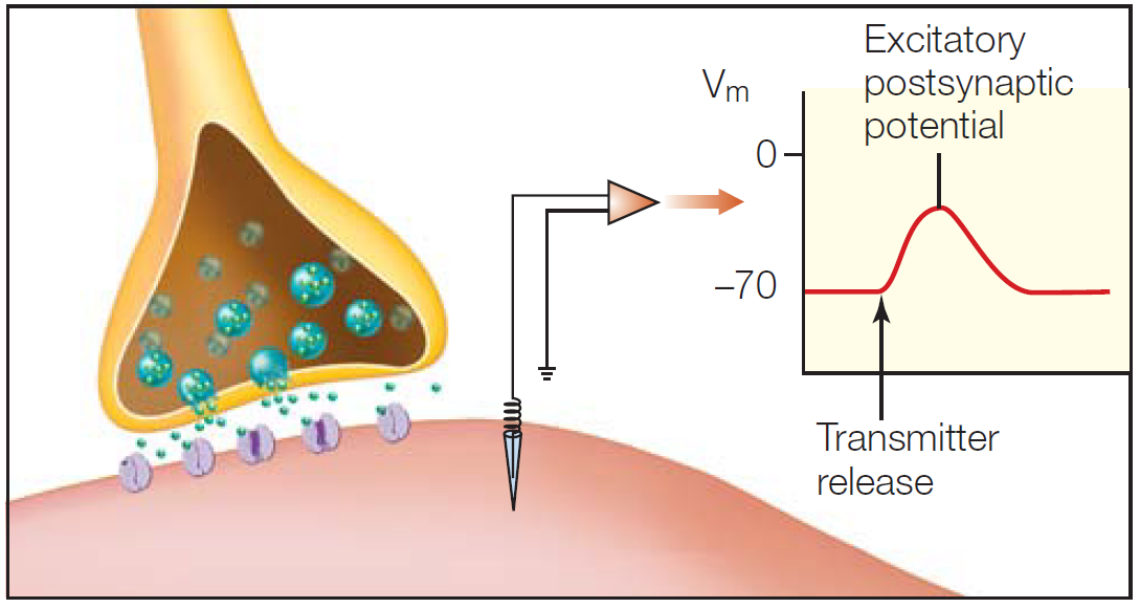
- GABA
- 甘氨酸 (glycine)
- 某些神经肽类 (some of peptides)



(Cognitive Neuroscience, 4th edition, 2013)

The postsynaptic response

The aim of a synapse model is to describe accurately the postsynaptic response generated by the arrival of an action potential at a presynaptic terminal.



1. The fundamental quantity to be modelled is the time course of the postsynaptic receptor conductance

2. The models:
   - Simple phenomenological waveforms
   - More complex kinetic schemes that are analogous to the models of membrane-bound ion channels

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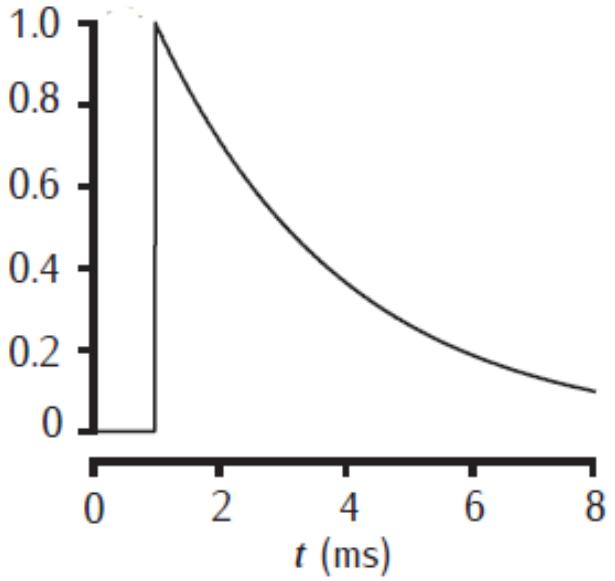
Phenomenological synapse models

Exponential Model



$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} e^{-(t-t0)/\tau}$$

- τ is the time constant
- t_0 is the time of the pre-synaptic spike
- $\bar{g}_{syn}$ is the maximal conductance

↓ corresponding differential equation

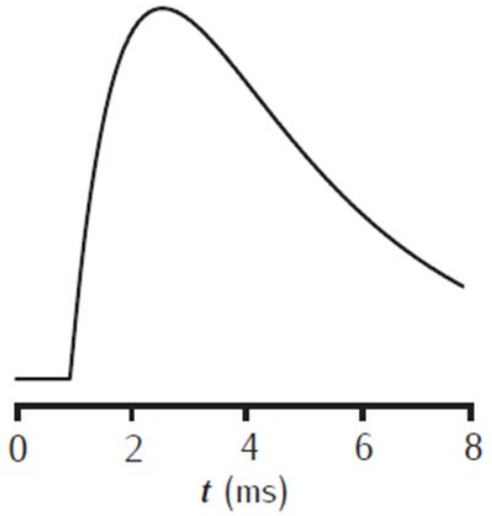
$$\tau \frac{dg_{\text{syn}}(t)}{dt} = -g_{\text{syn}}(t) + \bar{g}_{\text{syn}} \delta(t_0 - t)$$

Assumption:

- The release of neurotransmitter, its diffusion across the cleft, the receptor binding, and channel opening all happen very quickly, so that the channels instantaneously jump from the closed to the open state.

- Can fit with experimental data.
- A good approximation for $GABA_A$ and AMPA, because the rising phase is much shorter than their decay phase.

Dual Exponential Model



$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left(\exp\left(-\frac{t - t_0}{\tau_1} \right) - \exp\left(-\frac{t - t_0}{\tau_2} \right) \right)$$

- τ_1 is the decay synaptic time constant
- τ_2 is the rise synaptic time constant
- t_0 is the time of the pre-synaptic spike
- $\bar{g}_{syn}$ is the maximal conductance

↓ corresponding differential equation

$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} g$$

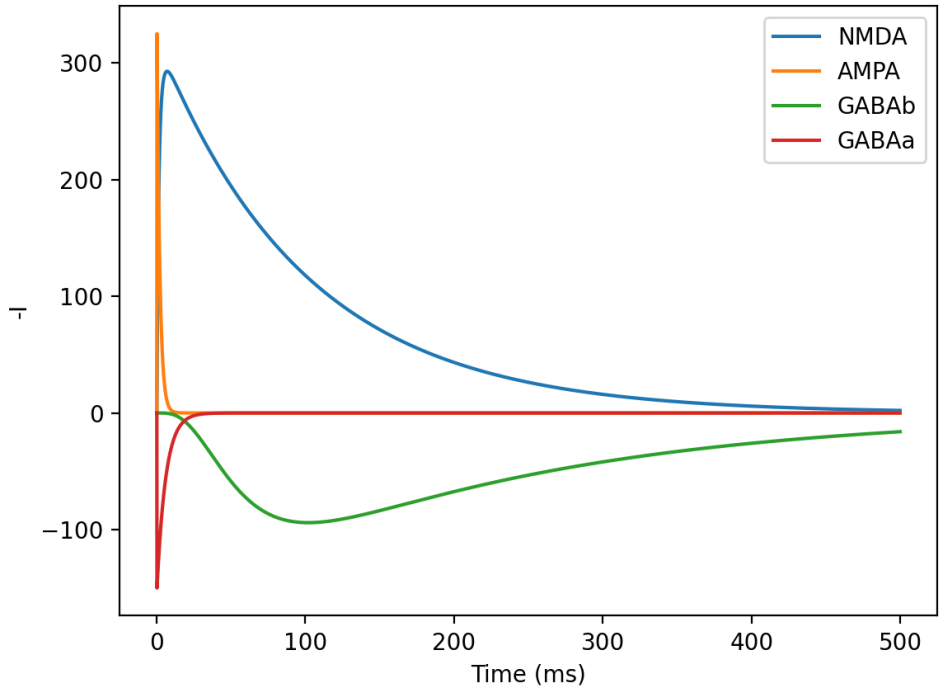
$$\frac{dg}{dt} = -\frac{g}{\tau_{\text{decay}}} + h$$

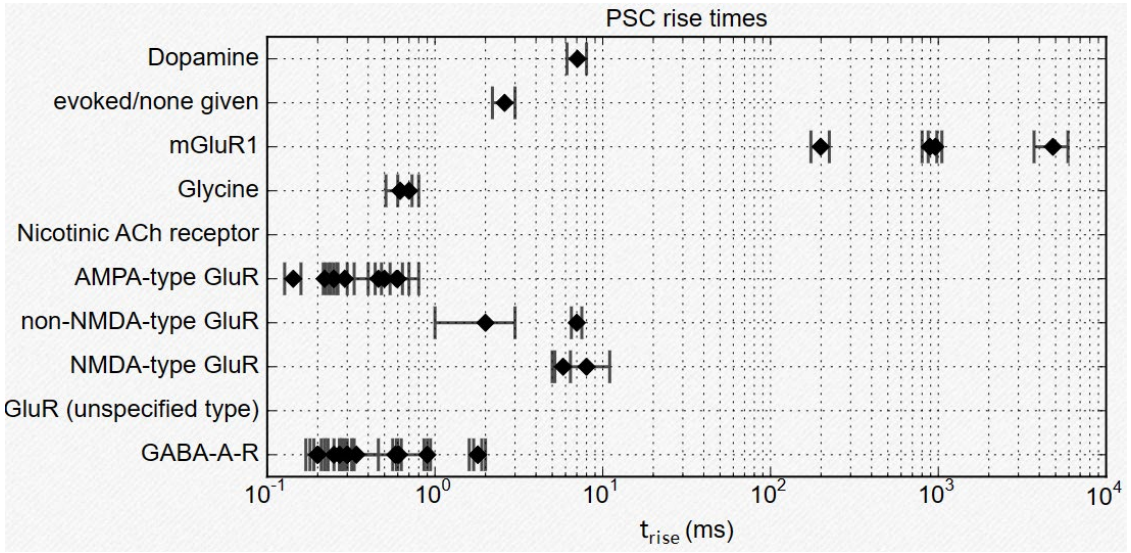
$$\frac{dh}{dt} = -\frac{h}{\tau_{\text{rise}}} + \delta(t_0 - t),$$

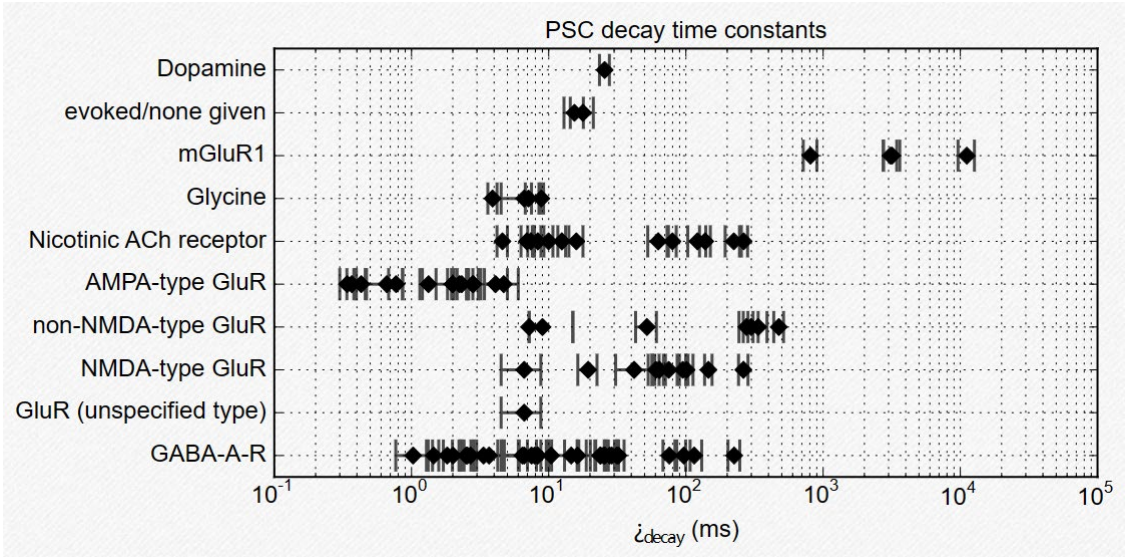
- For most synapses, the rising phase of synaptic conductance has a finite duration, which can have strong effects on network dynamics (van Vreeswijk et al., 1994).
- Dual exponential synapse provides a general way to describe the synaptic conductance with different rising and decay time constants.

- The time course of most synaptic conductance can be well described by this sum of two exponentials.

Synaptic time constants







http://compneuro.uwaterloo.ca/research/constants-constraints/neurotransmitter-time-constants-pscs.html

Synaptic time constants

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AMPA synapse

- t_{decay} = 0.18 ms in the auditory system of the chick nucleus magnocellularis (Trussell, 1999).
- t_{rise}= 0.25 ms and τ_{decay}=0.77 ms in dentate gyrus basket cells (Geiger et al., 1997).
- t_{rise}= 0.2 ms and τ_{decay}=1.7 ms in in neocortical layer 5 pyramidal neurons (Hausser and Roth, 1997b).
- Reversal potential is nearly 0 mV.

NMDA synapse

- The decay time constants (at near-physiological temperature):
  - ✓ 19 ms in dentate gyrus basket cells (Geiger et al., 1997),
  - ✓ 26 ms in neocortical layer 2/3 pyramidal neurons (Feldmeyer et al., 2002),
  - ✓ 89 ms in CA1 pyramidal cells (Diamond, 2001).
- The rise time constants are about 2 ms (Feldmeyer et al., 2002).
- Reversal potential is nearly 0 mV.

Synaptic time constants

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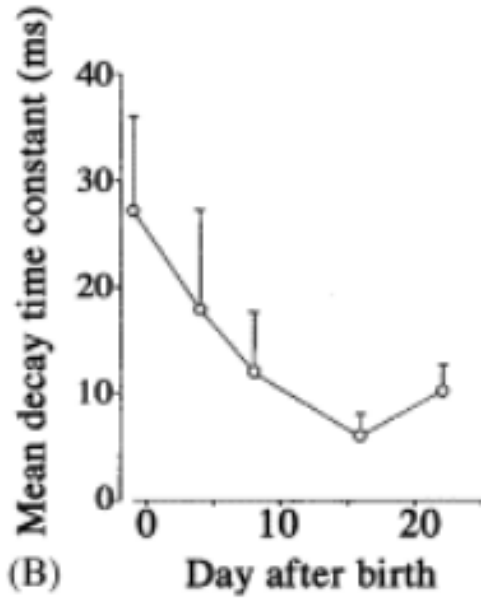
$GABA_A$ synapse

- GABAergic synapses from dentate gyrus basket cells onto other basket cells are faster: t_{rise} = 0.3 ms and t_{decay} = 2.5 ms (Bartos et al., 2001) than synapses from basket cells to granule cells: t_{rise} = 0.26 ms and t_{decay} = 6.5 ms (Kraushaar and Jonas, 2000).
- Reversal potential is nearly -80 mV.

$GABA_B$ synapse

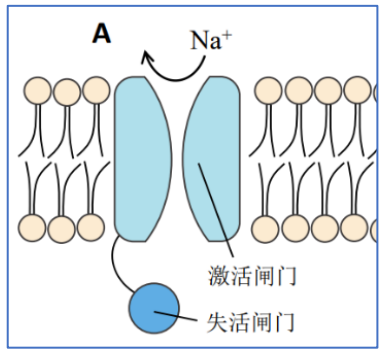
- Common models use models with a rise time of about 25-50 ms, a fast decay time in the range of 100-300ms and a slow decay time of 500-1000 ms.
- Reversal potential is nearly -90 mV.

General property of synaptic time constants



- The time constants of synaptic conductance vary widely among synapse types.
- The synaptic kinetics tends to accelerate during development *(T. Takahashi, Neuroscience Research, 2005)*.
- The synaptic kinetics becomes substantially faster with increasing temperature.

Current- and Conductance-based Response



Conductance-based Response

Most synaptic ion channels, such as AMPA and GABA, display an approximately linear current-voltage relationship when they open.

$$I_{syn} = g_{syn}(t)\,[V(t) - E_{syn}]$$

Ohmic conductance — Driving force

- E_{syn} is the reversal potential
- $V(t)$ is the post-synaptic current

For example:

- The synapse is located on a thin dendrite, because the local membrane potential V changes considerably when the synapse is activated.

Current-based Response

In some case, we can also approximate the synapses as sources of current and not a conductance.

$$I_{syn} = g_{syn}(t)\,[V_{rest} - E_{syn}]$$

$$I_{syn} = g_{syn}(t)\,J$$

- J is a constant

For example:

- The excitatory synapse on a large compartment, because the depolarization of the membrane is small.

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Programming of phenomenological synapse models

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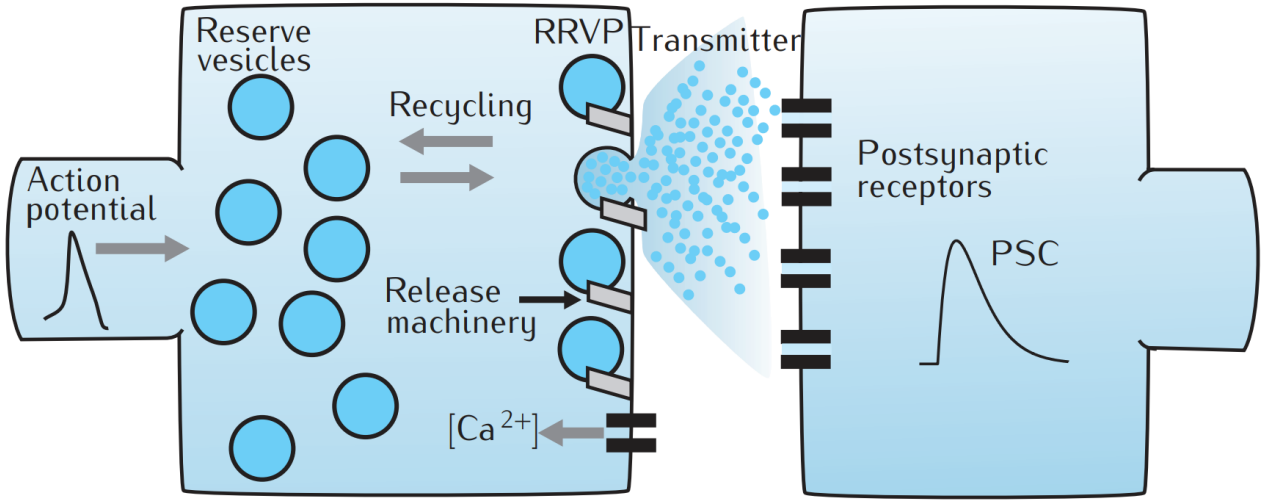
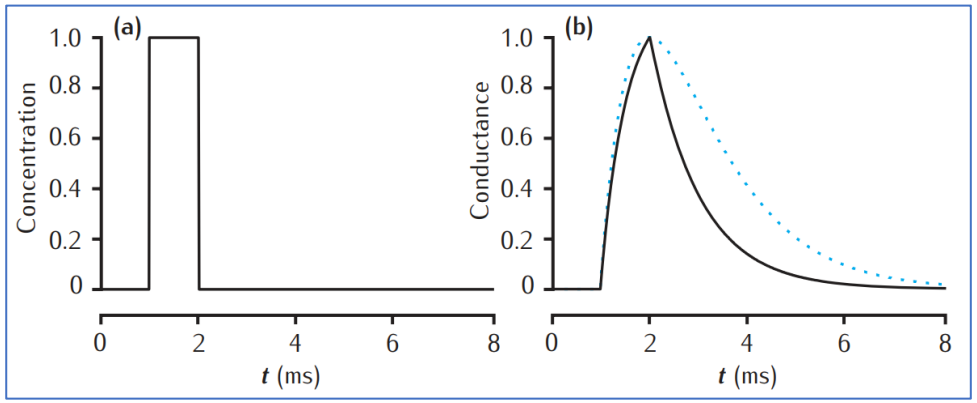
04

Biophysical synapse models

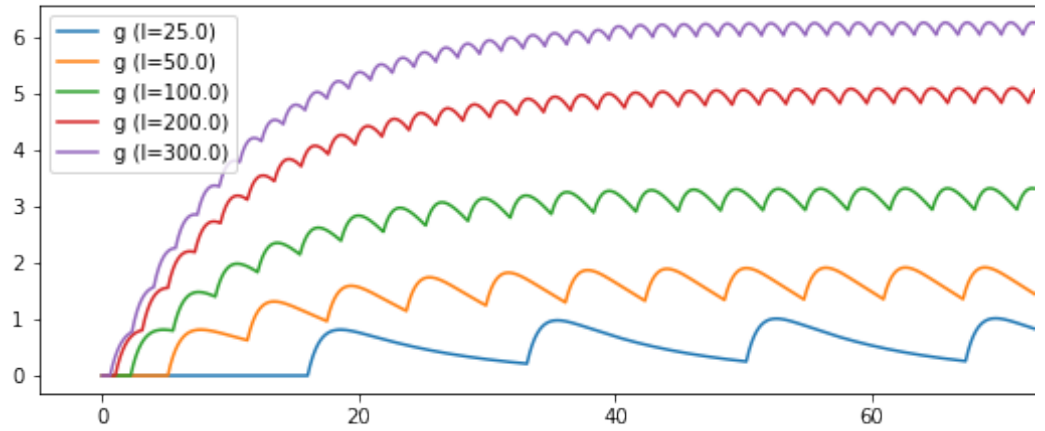
Limitations of phenomenological models



1. Saturation of postsynaptic receptors by previously released transmitter.
2. Certain receptor types also exhibit desensitization that prevents them (re)opening for a period after transmitter-binding, like sodium channels underlying action potential.

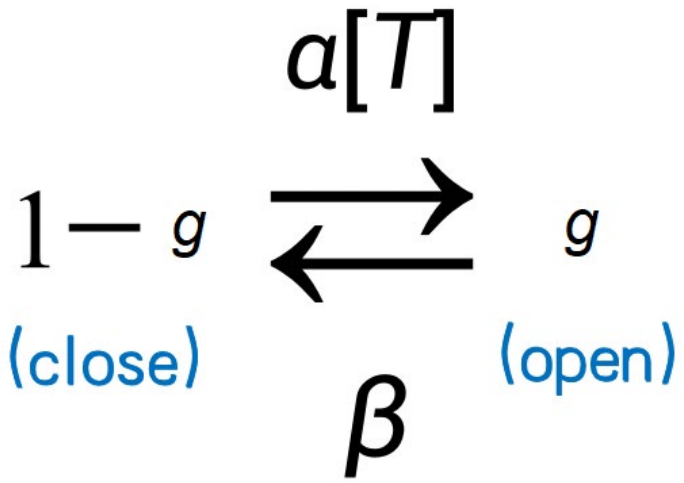


The realistic synaptic response



The modeling of phenomenological models

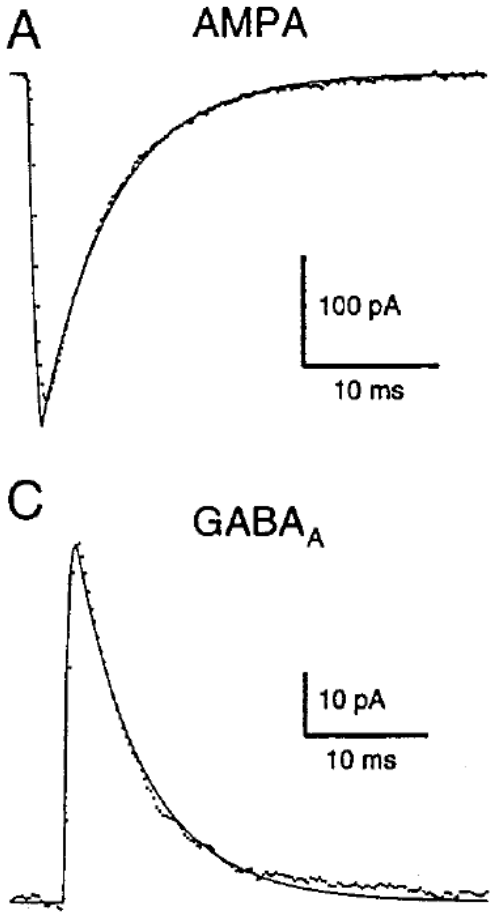
Kinetic/Markov models



- The simplest kinetic model is a two-state scheme in which receptors can be either closed, C, or open, O, and the transition between states depends on transmitter concentration, $[T]$, in the synaptic cleft:
- α and β are voltage-independent forward and backward rate constants.
- C and O can range from 0 to 1, and describe the fraction of receptors in the closed and open states, respectively.
- The synaptic conductance is:

$$g_{syn}(t) = \bar{g}_{max} g(t)$$

AMPA/GABA$_A$ synapse model



$$1-s \underset{\beta}{\overset{\alpha[T]}{\rightleftharpoons}} s$$

(close) (open)

$$\frac{ds}{dt} = \alpha[T](1-s) - \beta s$$

$$I = \bar{g}s(V-E)$$

- $\alpha[T]$ denotes the transition probability from state $(1-s)$ to state (s)
- β represents the transition probability of the other direction
- E is a reverse potential, which can determine whether the direction of I is inhibition or excitation.

- $E = 0\ mV$ => Excitatory synapse [AMPA]

- $E = -80\ mV$ => Inhibitory synapse [GABA$_A$]

Comparison

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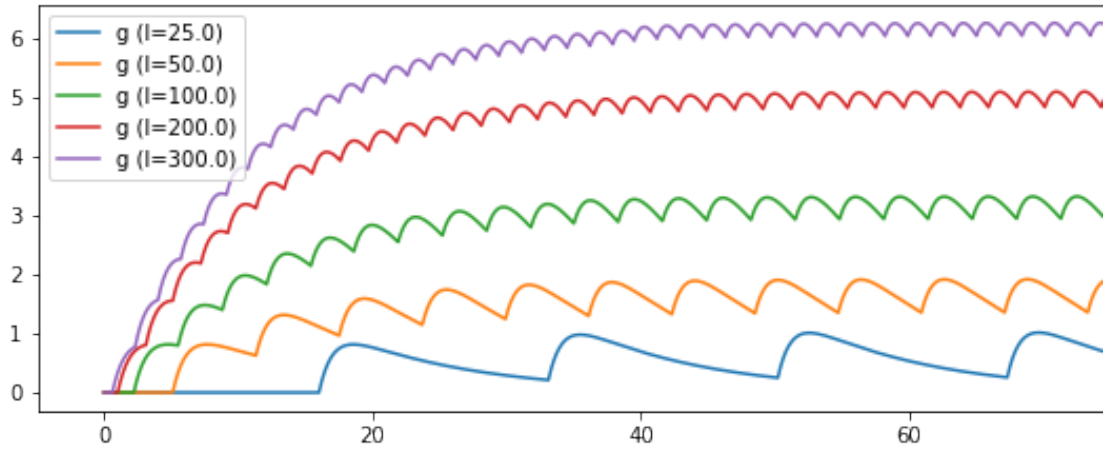
Dual Exponential Model

$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} g$$

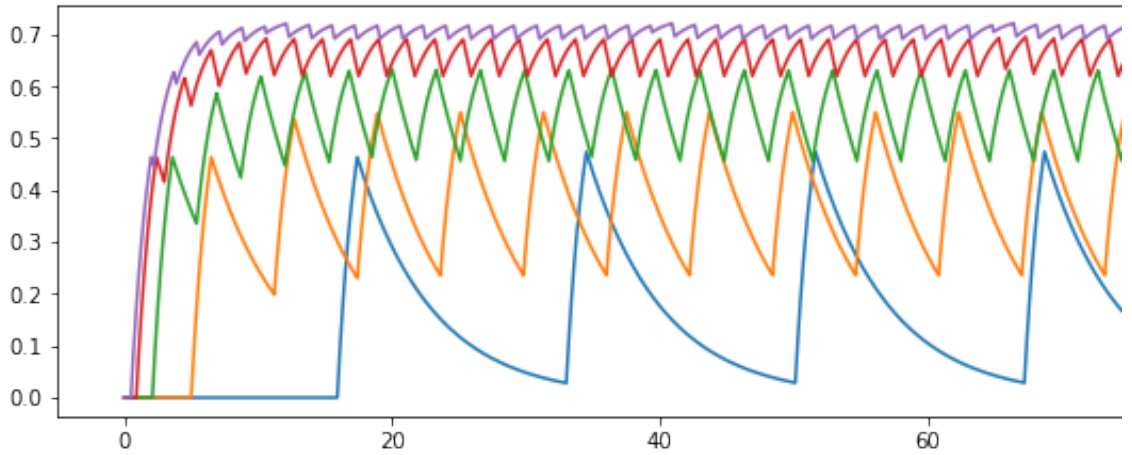
$$\frac{dg}{dt} = -\frac{g}{\tau_{\text{decay}}} + h$$

$$\frac{dh}{dt} = -\frac{h}{\tau_{\text{rise}}} + \delta(t_0 - t)$$

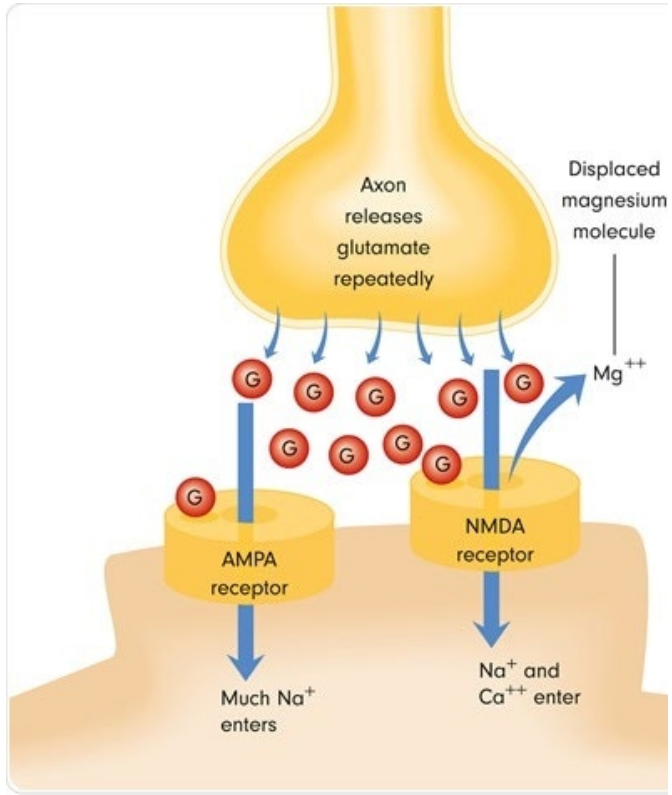


AMPA kinetic Model

$$\frac{ds}{dt} = \alpha[T](1 - s) - \beta s$$



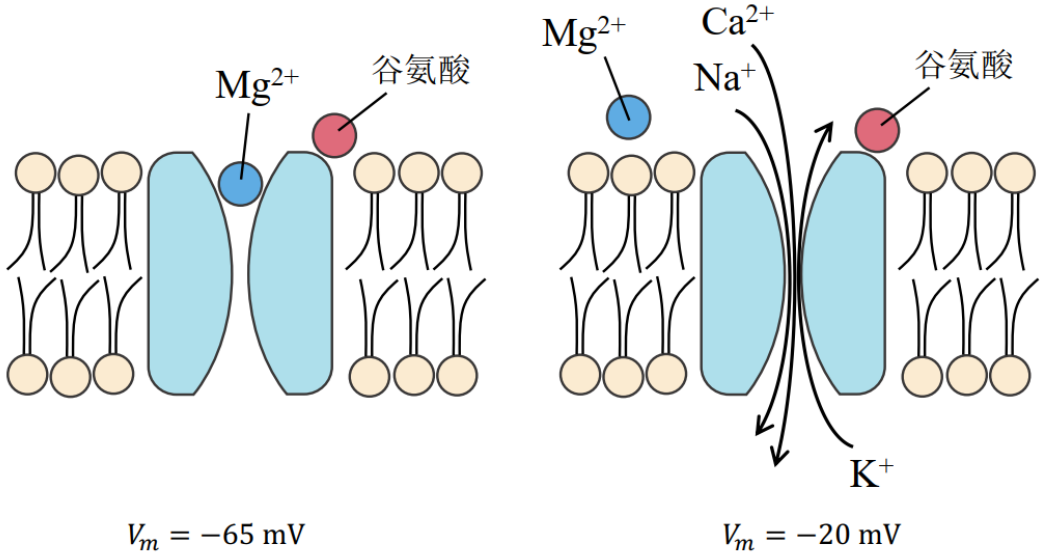
NMDA synapse model



$$\frac{ds}{dt} = \alpha[T](1 - s) - \beta s$$

$$I = \bar{g}sB(V)(V - E)$$

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



(a) V = −65mV 时 NMDA 的结构示意图　(b) V = −20mV 时 NMDA 的结构示意图

图 4.11: NMDA 受体结构示意图

- The magnesium block of the NMDA receptor channel is an extremely fast process compared to the other kinetics of the receptor (Jahr and Stevens 1990a, 1990b). The block can therefore be accurately modeled as an instantaneous function of voltage(Jahr and Stevens 1990b).

- where $[Mg^{2+}]_o$ is the external magnesium concentration (1 to 2mM in physiological conditions)

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05

Programming of biophysical synapse models

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06
Homework

- Implement exponential synapse model
- Implement dual Exponential synapse model
- Implement AMPA synapse model
- Implement GABA synapse model