Models of Calcium-Induced Neurotransmitter Release

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Outline

• Description of the synapse
• Ca^{2+} Microdomains
• Neurotransmitter release
• Postsynaptic response to released transmitter
• A complete model for neural communication
The Synapse
Neural Communication

Drawing by Cajal of Purkinje cells (A) and granule cells (B) from the pigeon cerebelum.

The cells interact through synapses.
The Synapse

Illustration of a neuromuscular junction.

(Levitan and Kaczmarek 1991)
Neurotransmitter Release is Evoked by Ca\textsuperscript{2+}

Proteins in the vesicle membrane and the membrane of the presynaptic terminal (SNARE proteins) form a complex (the core complex) that primes the vesicle for release. Ca\textsuperscript{2+} binding to synaptotagmin leads to fusion of the two membranes and exocytosis of transmitter molecules.

Shepherd, 1994
Channels and Vesicles

• Early freeze-fracture studies of the squid giant synapse (Pumplin et al., 1981) showed presynaptic “particles” aggregated in 1 μm² circular patches with 38 nm separation between particles. These particles are the Ca²⁺ channels, with diameter of 9 nm.

• Transmitter-filled vesicles are 30-50 nm in diameter. Those in the readily releasable pool are docked at the membrane. This pool is supplied by the reserve pool.

• Vesicles and Ca²⁺ channels are clustered into active zones.
Vesicles are Close to Ca$^{2+}$ Channels

Electrophysiological Evidence

• Postsynaptic response occurs 200 μsec after an increase in presynaptic I$_{ca}$ (Llinas et al, 1976).
• Vesicle fusion and transmitter release (ACh) can occur within 200-400 μsec of the opening of a single Ca$^{2+}$ channel in a chick calyx-type synapse (Stanley, 1993).

Structural and Functional Evidence

• Exocytosis requires a high Ca$^{2+}$ concentration, with a threshold of 20-50 μM (Heidelberger et al, 1994).
• The SNARE proteins syntaxin and SNAP25 bind to presynaptic Ca$^{2+}$ channels (Sheng et al, 1996).
Calcium Microdomains
Transmitter Release is Evoked by Ca$^{2+}$ in Single or Overlapping Microdomains

Ca$^{2+}$ microdomains form at active zones within a squid giant synapse.

Llinas et al, 1992
An Early Mathematical Model of Ca\textsuperscript{2+} Microdomains

One of the earliest models of the presynaptic terminal that appreciated the importance of Ca\textsuperscript{2+} microdomains was by Simon and Llinas (1985).

Ca\textsuperscript{2+} diffusion equation was solved numerically using spherical coordinates in the vicinity of a single open Ca\textsuperscript{2+} channel. Simulations also performed on a 3-D Cartesian grid. In the latter case, Ca\textsuperscript{2+} channels were treated as equally-space point sources on one face of the numerical domain.

Mobile Ca\textsuperscript{2+} buffers were included in the simulations. Examples of endogenous buffers are calbindin and calmodulin. Examples of exogenous buffers are BAPTA, EGTA, and Fura-2.
Reaction-Diffusion Equations

\[ \frac{\partial C_a}{\partial t} = D_c \nabla^2 C_a + R + \frac{\sigma}{2F} \sum_j \delta(r_j) \]  
\text{Ca}^{2+} \text{ concentration}

\[ \frac{\partial B}{\partial t} = D_b \nabla^2 B + R \]  
buffer concentration

\[ R = -k^+ B C_a + k^- (B_{tot} - B) \]  
binding reaction

\( D_c \) and \( D_b \) are diffusion coefficients and \( \sigma \) is the flux through an open channel. \( F \) is Faraday’s constant. 
\( k^+ \) and \( k^- \) are buffer binding and unbinding rates. 
\( B_{tot} \) is total buffer concentration, \( B \) is free (unbound) concentration, and \( B_{tot} - B \) is the bound buffer concentration.
Main Results from Simon and Llinas (1985)

• Within 10’s of nm from an open channel, the Ca\(^{2+}\) reaches steady state within a \(\mu\)sec of channel opening.

⇒ Within a microdomain one need only solve the steady state reaction-diffusion equations.

• In the vicinity of an open channel, \([Ca^{2+}] \propto i_{Ca}\)

• Stationary buffers do not affect steady state \(Ca^{2+}\), only the time required to reach steady state.

• Mobile buffers affect both steady state \(Ca^{2+}\) and the time required to achieve steady state.
Neurotransmitter Release
Voltage-Dependent Ca$^{2+}$ Influx

Flux through an open channel is proportional to the driving force, $i_{Ca} \propto (V - V_{Ca})$.

Low V:

Few vesicles see high Ca$^{2+}$

High V:

Many vesicles see lower Ca$^{2+}$
Transmitter Release During Voltage Clamp

Presynaptic $V$ and $I_{Ca}$, and postsynaptic current in squid giant synapse.

Augustine et al. (1985)

Much of the transmitter release is induced by $Ca^{2+}$ tail currents.
Excess Buffer Approximation (EBA)

Two simplifications can be used to reduce the system of reaction-diffusion equations to a single equation.

**Excess buffer approximation** (Neher, 1986; Smith, 1996) assumes that mobile buffer is present in excess and cannot be saturated.

\[
\frac{\partial Ca}{\partial t} = D_c \nabla^2 Ca - k^+ B_{tot} (Ca - Ca_{bk}) + \sigma \delta(r)
\]

where \(Ca_{bk}\) is the “bulk calcium” concentration, far from the channel.
Steady State EBA

\[ Ca = \frac{\sigma}{4\pi D_c r} e^{-r/\lambda} + Ca_{bk} \]

Where \( \lambda \) is the characteristic length, which depends on the calcium diffusion coefficient, the buffer binding rate, and the free buffer far from the channel,

\[ \lambda = \sqrt{\frac{D_c}{k^+ B_{bk}}} \]
Rapid Buffer Approximation (RBA)

This approximation assumes that Ca\(^{2+}\) binding to buffer is fast compared to the Ca\(^{2+}\) diffusion rate (Wagner and Keizer, 1994). This leads to local equilibration: at every point in space the Ca\(^{2+}\) and buffer are equilibrated, \( B = \frac{KB_{tot}}{K + Ca} \) where \( K \) is the dissociation constant of the buffer.

The Ca\(^{2+}\) and buffer diffusion equations can be combined to a single diffusion equation for the weighted sum of free and bound Ca\(^{2+}\), \( w = D_c Ca + D_b CaB \),

\[
\frac{dw}{dt} = [D_c \beta + D_b (1 - \beta)] \nabla^2 w
\]

The diffusion coefficient of this combined equation depends on \( \beta \), which is a function of the total mobile buffer concentration and Ca.
Smith (1996) derived a steady state RBA, intended to describe the Ca$^{2+}$ concentration near an open Ca$^{2+}$ channel, where steady state is rapidly achieved.

\[
Ca = \frac{1}{2D_c} \left( -D_c K + \frac{\sigma}{4\pi r} + D_c Ca_{bk} - D_B B_{bk} + \sqrt{\Omega} \right)
\]

where

\[
\Omega = \left( D_c K + \frac{\sigma}{4\pi r} + D_c Ca_{bk} - D_B B_{bk} \right)^2 + 4D_c D_B B_{tot} K
\]
EBA vs. RBA

- EBA appropriate when the saturability of mobile buffer is negligible. For example, this is the case for millimolar concentrations of Calbindin-D_{28K} in the saccular hair cell.
- RBA appropriate when there is significant saturability of mobile buffer and when buffer kinetics are fast relative to Ca^{2+} diffusion. This is often the case near Ca^{2+} channels in synapses, and near IP_3 or ryanodine receptors in the ER/SR.
- Smith et al. (2001) did an asymptotic analysis of buffered Ca^{2+} diffusion near a point source, and determined mathematical conditions for when RBA or EBA are appropriate.

\[
\lim_{r \to 0} B \approx B_{bk} \quad \text{(EBA)} \quad \lim_{r \to 0} B \approx 0 \quad \text{(RBA)}
\]

buffer unperturbed \quad buffer saturates
Postsynaptic Response to Released Transmitter
Postsynaptic Response to Transmitter

Neurotransmitter released from the presynaptic terminal can bind to receptors in the postsynaptic cell (nerve or muscle). This results in opening of ion channels, producing a synaptic current.

\[
C_m \frac{dV_{\text{post}}}{dt} = -(I_{\text{ion}} + I_{\text{syn}})
\]

where \( I_{\text{syn}} = g_{\text{syn}}(t)(V - V_{\text{syn}}) \).

Two ways to model \( g_{\text{syn}}(t) \): (1) \( \alpha \)-function, or (2) kinetic model.
The \( \alpha \)-Function

First used by Rall (1967) to describe the postsynaptic response in a passive dendrite.

\[
g_{syn}(T) = \bar{g}_{syn} \alpha T e^{-\alpha T}
\]

\( \bar{g}_{syn} \) = maximum conductance

\( \alpha = \frac{\tau_m}{t_{peak}} \), \( T = \frac{t}{\tau_m} \) and \( \tau_m = R_m C_m \) is the membrane time constant
Kinetic Models

Two problems with the a function:
(1) Does not provide for the summation or saturation of postsynaptic currents that can occur with release of several vesicles.
(2) Does not describe receptors/channels with multiple states.

Excellent description of kinetic models by Destexhe et al. (1994).

Simple 2-state kinetic model: \[ C \xleftrightarrow{\beta} O \]

By law of mass action: \[ \frac{dO}{dt} = \alpha C - \beta O = \alpha(1 - O) - \beta O \]

Then \[ g_{syn}(t) = g_{syn}O. \]
More Complex Kinetic Models

Receptor with a desensitized state, e.g. AMPA-type glutamate receptor

NMDA-type glutamate receptor, blocked by Mg$^{2+}$
Complete Model
A Complete Model for Neural Communication

- Each release site sees a Ca\(^{2+}\) channel that is 10 nm away.
- Each release site has one low-affinity binding site (\(K_D = 170 \, \mu\text{M}\)).
- The steady state RBA is used for microdomain Ca\(^{2+}\) concentration, \(Ca_D\).
- Stochastic channel opening is replaced with a deterministic formulation. **Average domain Ca\(^{2+}\) is used in the release model:** \(<Ca_D> = Ca_D \text{Prob(channel open)}\).
- (Concentration released transmitter) \(\propto\) Prob(release).
- 2-state postsynaptic receptor, reversal potential of 0 mV.
- Postsynaptic membrane is passive.
Response to a Single Presynaptic Action Potential
Response to a 100 Hz Train of Action Potentials
References

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Mathematical Models of Synaptic Plasticity

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• Presynaptic enhancement
• Mathematical models of short-term enhancement
• Presynaptic depression
• A network simulation with presynaptic depression
• Learning and memory
How is Postsynaptic Response Measured?

Post synaptic Potential:

(1) Excitatory postsynaptic potential (EPSP) is measured in the soma, in response to input from the dendrites.
(2) End-plate potential (EPP) is measured in the muscle of a neuromuscular junction in response to synaptic input.

Post synaptic Current:

The postsynaptic cell is voltage clamped and the postsynaptic current measured in response to input from dendrites (EPSC) or in response to neuromuscular synaptic input (EPC).
How is Short-Term Synaptic Plasticity Measured?

• Paired-pulse experiments – two presynaptic impulses are induced. The ratio of the postsynaptic responses is the measure of plasticity:

\[ SP = \frac{P_2}{P_1} \]

• Impulse train experiments – N presynaptic impulses are induced at a frequency of \( f \) Hz. Plasticity per impulse is then:

\[ SP_n = \frac{P_n}{P_1} \]

SP > 1 ⇒ enhancement
SP < 1 ⇒ depression
Short-Term Presynaptic Enhancement
Paired-Pulse Facilitation

In this system, facilitation decreases with repeated testing. *Aplysia* sensory neuron synapse.

Jiang and Abrams (1998)
Augmentation

The slope of the EPSP rises during a 10-sec train of presynaptic impulses at 50 Hz. Slowly declines after cessation of the train. Squid giant synapse.

Swandulla et al (1991)
Forms of Presynaptic Potentiation

**Facilitation** – Decay time constant ($\tau$) 10s to 100s of milliseconds

**Augmentation** – $\tau \sim 5$-10 seconds

**Post-tetanic potentiation** -- $\tau = 30$ sec to a few minutes
Presynaptic Enhancement is Associated with Accumulation of Ca$^{2+}$

Accumulation of intracellular Ca$^{2+}$ during a 1 Hz train of presynaptic impulses. Also, slow increase of the postsynaptic response. Hippocampal mossy fiber synapse.

Regehr et al (1994)
Fogelson-Zucker Model

• First mathematical model of facilitation.
• Model consists of a PDE for 3-D Ca\(^{2+}\) diffusion in the presynaptic terminal.
• Facilitation due to slow increase of average Ca\(^{2+}\) concentration during a train of impulses.

In simulation of squid giant synapse, average Ca\(^{2+}\) concentration slowly rises during 20 Hz train of presynaptic impulses, and falls following the train.

Fogelson and Zucker (1985)
A Model Based on Residual Bound Ca$^{2+}$

Bertram, Sherman, and Stanley model (1996)

\[
U_j + Ca \underset{k^-}{\overset{k^+}{\leftrightarrow}} B_j
\]

\[j = 1, 2, 3, 4\]

\[R = B_1 B_2 B_3 B_4\]

The Ca$^{2+}$ unbinding rate ($k^-$) is large for site 4 and progressively smaller for other binding sites. As a result, some Ca$^{2+}$ remains bound when the second impulse occurs.
A Third Facilitation Model: Buffer Saturation

Klingauf and Neher (1997) modeled buffered Ca\(^{2+}\) diffusion in a neuroendocrine cell (chromaffin cell). Granules thought to be farther from Ca\(^{2+}\) channels (200-300 nm) than in synapses. At these distances, buffers can have a large effect on the Ca\(^{2+}\) time course.

Model simulations, Ca\(^{2+}\) at different distances from a channel.

No exogenous buffer

500 \(\mu\)M Fura-2
Synaptic Depression
Buffer Saturation Increases $\text{Ca}^{2+}$ Signal

During a train of impulses the buffer can become saturated. This is due to residual $\text{Ca}^{2+}$ binding between pulses. Matveev et al. (2004) did a numerical study of this form of facilitation that was first suggested by Klingauf and Neher (1997).
Many synapses exhibit depression rather than potentiation, particularly the smaller synapses in the central nervous system. This is thought to be due primarily to a depletion of vesicles in the Readily Releasable Pool (RRP).

Depression in a pyramidal neuron from the rat cortex.

Markram et al. (1998a)
Depression and Gain Control

Cortical neurons integrate input from about 10,000 synapses. The presynaptic afferents produces impulses with rates from about 1 Hz to 200 Hz. Why don’t the high-frequency inputs dominate the low-frequency inputs?

**Gain control**: synapses firing at high frequency are depressed, so response to each impulse is smaller.

Relative response amplitude, \( A(r) \), declines as \( 1/r \) for \( r \) greater than some limiting frequency.

Total synaptic conductance is \( rA(r) \).

Abbott et al. (1997)
A Role for Depression in Network Dynamics

Developing neural networks tend to be characterized by excitatory coupling:
Runaway Train

If synaptic connections are purely excitatory, then the network exhibits positive feedback. This should insure that the network spikes continually at a high rate, right?
If synaptic connections are purely excitatory, then the network exhibits positive feedback. This should insure that the network spikes continually at a high rate, right?

Wrong!
Population Bursts in Developing Spinal Cord

Spontaneous episodes of activity recorded from ventral roots of the chick embryo at embryonic day 7.5. From Tabak et al, 2000.
A Model Using Two Forms of Synaptic Depression

(Tabak et al, 2000)

\[
\frac{da}{dt} = \left[ a_\infty(a, d, s) - a \right] / \tau_a
\]

\[
\frac{dd}{dt} = \left[ d_\infty(a) - d \right] / \tau_d
\]

\[
\frac{ds}{dt} = \left[ s_\infty(a) - s \right] / \tau_s
\]

a=mean firing rate of the population

d=fraction of synapses without fast depression

s=fraction of synapses without slow depressed
Slow Depression as a Mechanism for Population Bursts

From Tabak et al, 2000
Dynamics Revealed Through Fast/Slow Analysis

From Tabak et al, 2000
Learning and Memory
Learning and Memory

Learning occurs through the strengthening or weakening of synaptic connections. This is described by Hebb’s rule (1949):

- Increase weight: Pre → Post
- Decrease weight: Pre ↔ Post
LTP and LTD: Correlates for Hebb’s Rule

LTP = Long-Term Potentiation. Postsynaptic strength increases when the postsynaptic neuron fires vigorously in response to presynaptic stimulation.

LTD = Long-Term Depression. Postsynaptic strength decreases when the postsynaptic neuron fires weakly in response to presynaptic stimulation.

The calcium level in the postsynaptic spine determines which occurs.

- Calcium low $\rightarrow$ LTD
- Calcium high $\rightarrow$ LTP
LTP/LTD Often Studied in Hippocampus

Wikipedia, Long-Term Potentiation
Simple Biophysical Model for LTP/LDP

\[ \frac{dW}{dt} = \eta(Ca) \left[ \Omega(Ca) - \lambda W \right] \]

- \( W \) = synaptic strength of synapse
- \( \lambda \) = decay constant (0 or 1)
- \( \Omega \) = sign and magnitude of plasticity
- \( \eta \) = learning rate

Scholarpedia,
Models of synaptic plasticity
References

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