CAMP 2019

NEURON: Synaptic Plasticity

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What are we going to learn in terms of using NEURON?

Modeling passive neurons and building multicompartmental models

Modeling ion channels

Multicompartmental model of real 3D neuronal reconstructions

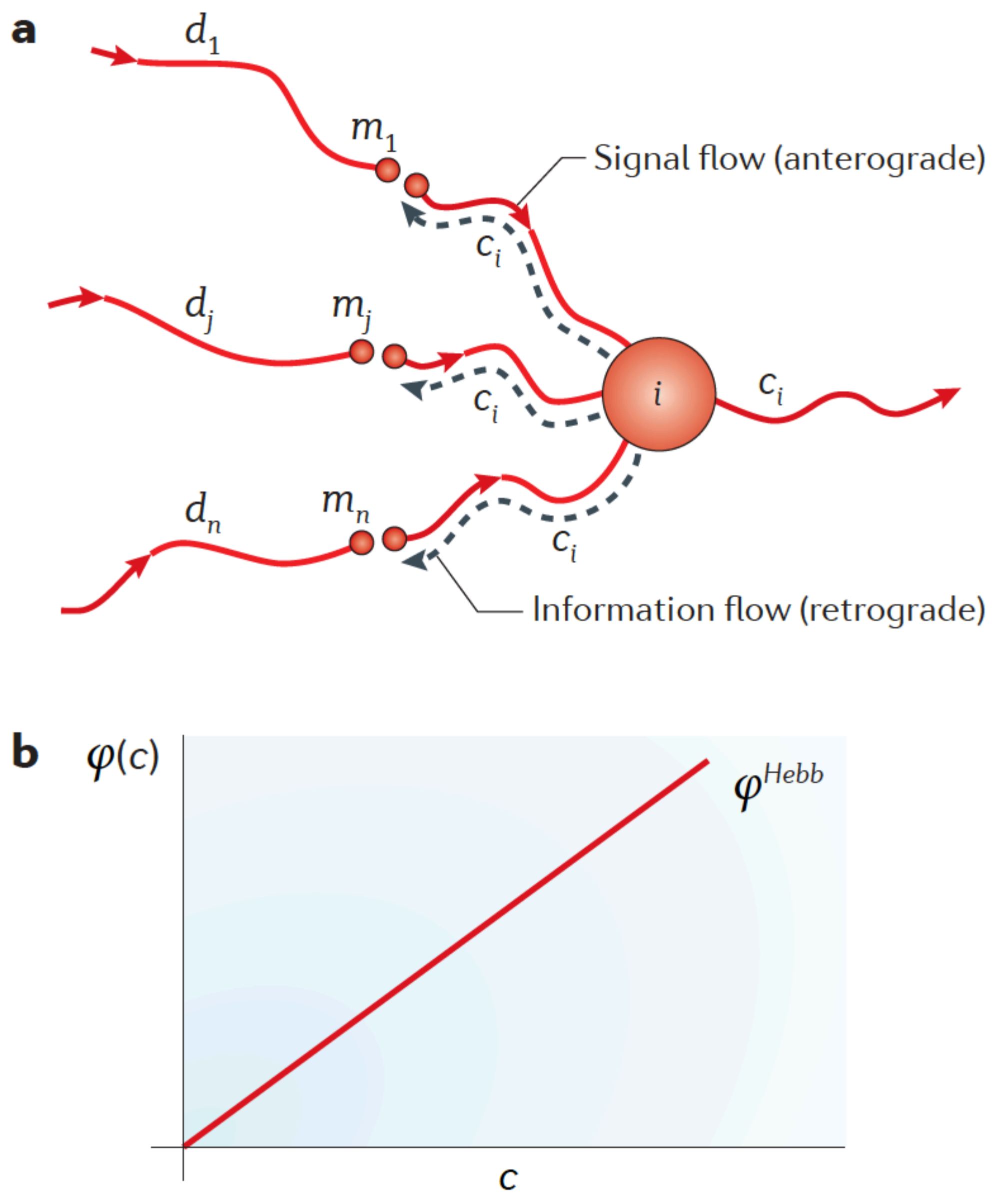
Modeling calcium handling

Modeling synapses

Use these components to build a model of synaptic plasticity

Hebb's postulate

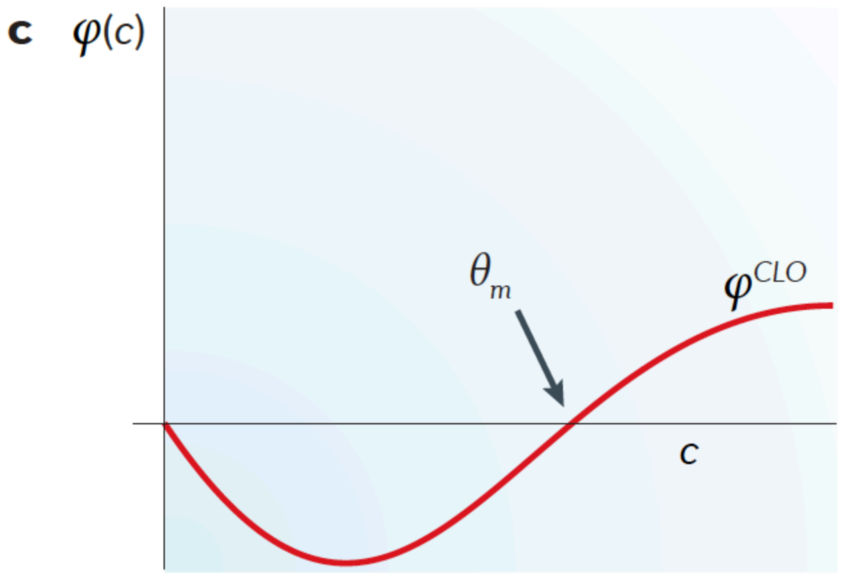
"When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells, such that A's efficiency, as one of the cells firing B, increases."

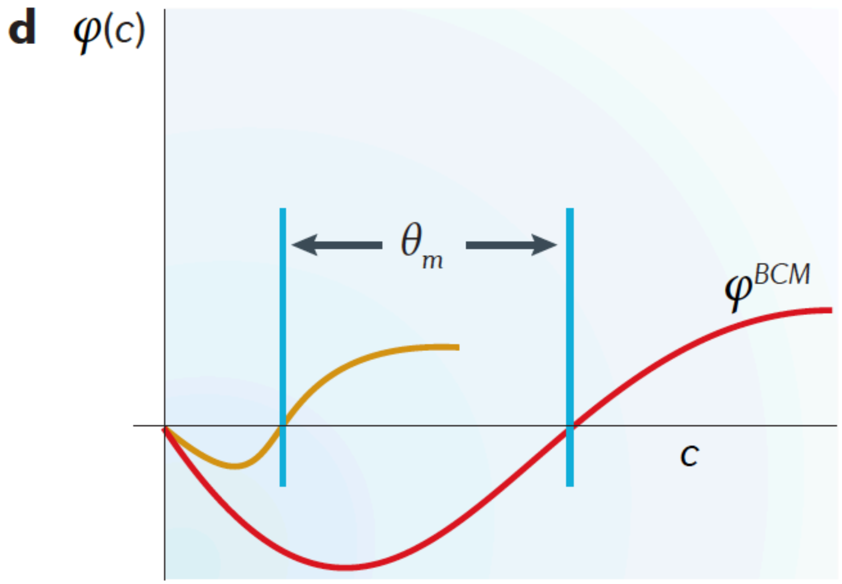


Stability?

Cooper and Bear, Nature Reviews, 2012

BCM theory and Metaplasticity





Cooper, Liberman & Oja, Biol. Cybern., 1979

Bienenstock, Cooper & Munro, J Neuroscience, 1982

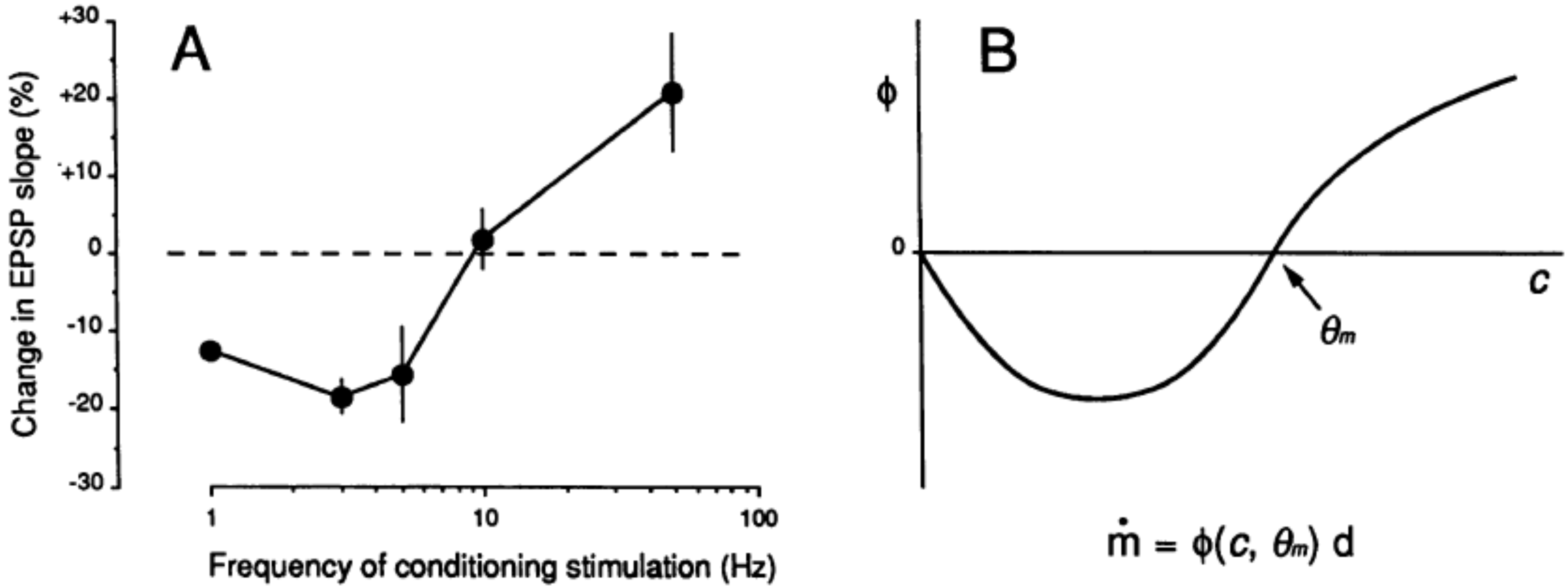
Experimental verification of the BCM theory

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 4363–4367, May 1992
Neurobiology

Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade

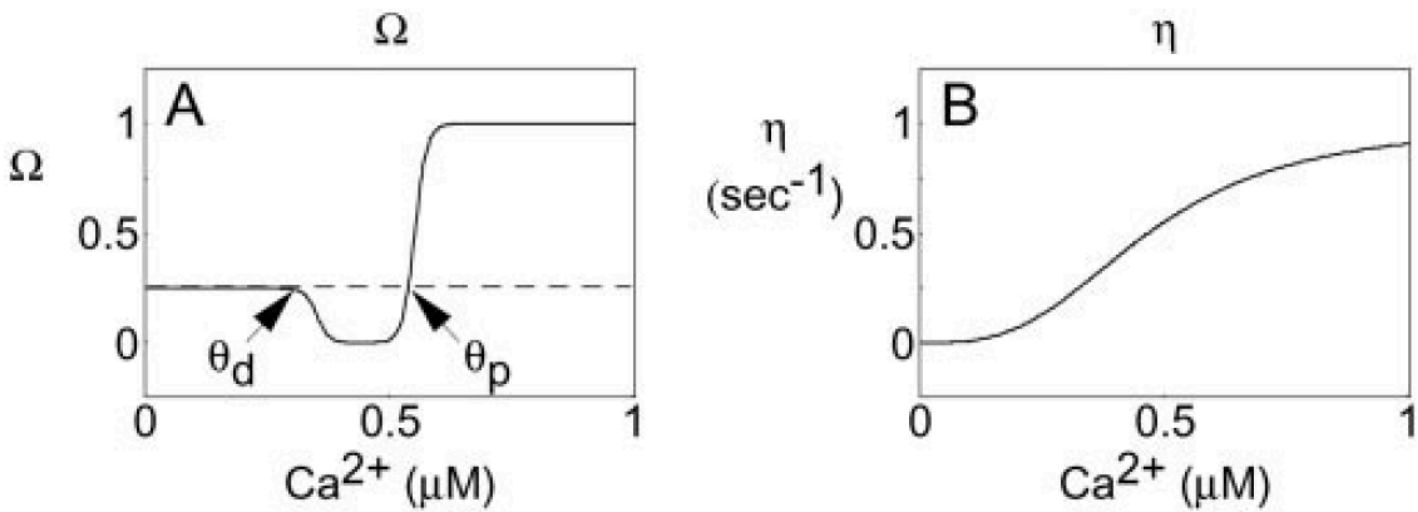
(long-term potentiation/hippocampal slice/synaptic plasticity/learning/memory)

SERENA M. DUDEK AND MARK F. BEAR*



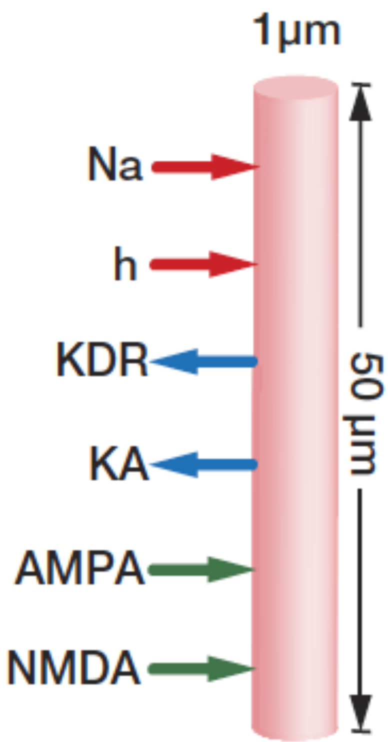
A unified model of NMDA receptor-dependent bidirectional synaptic plasticity

Harel Z. Shouval*†, Mark F. Bear*‡§, and Leon N Cooper*‡¶



$$\dot{W}_j = \eta([Ca]_j)(\Omega([Ca]_j) - W_j).$$

BCM model for synaptic plasticity



Synaptic receptors

Calcium dynamics

Synaptic weight update rule

Stimulation protocol

Weight profiles

Modified from Narayanan and Johnston, J Neurophysiology, 2010

Recap!
Conductance-based models

AMPAR

$$I(t,V) = \bar{g}\; s(t)\; (V - V_{syn})$$

NMDAR

$$I(t,V) = \bar{g}\; B(V)\; s(t)\; (V - V_{syn})$$

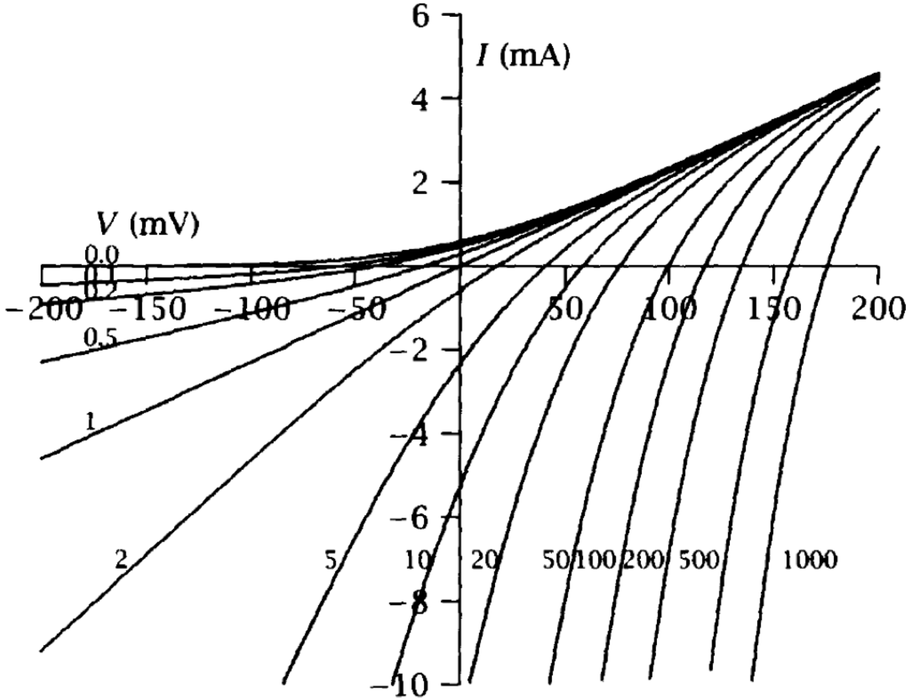
$$\boxed{B_{NMDAR}(V) = \left(1 + \frac{\exp(-aV)[Mg^{2+}]_{out}}{b}\right)^{-1}}$$

Voltage and magnesium-dependent conductance

s(t) : Time-varying signal dependent on presynaptic timings

Recap!
GHK current equation

$$I = \frac{Pz^2F^2}{RT} V \left(\frac{[C]_{in} - [C]_{out} \exp\left(-\frac{zVF}{RT} \right)}{1 - \exp\left(-\frac{zVF}{RT} \right)} \right)$$



Replicates highly rectified membrane currents!

GHK current equation for modeling synaptic currents

$$I_{AMPA}(v,t) = I^{Na}_{AMPA}(v,t) + I^{K}_{AMPA}(v,t)$$

where

$$I^{Na}_{AMPA}(v,t) = \bar{P}_{AMPAR}\, wP_{Na}s(t)\,\frac{vF^2}{RT}\left(\frac{[Na]_i - [Na]_o \exp\left(-\frac{vF}{RT}\right)}{1-\exp\left(-\frac{vF}{RT}\right)}\right)$$

$$I^{K}_{AMPA}(v,t) = \bar{P}_{AMPAR}\, wP_{K}s(t)\,\frac{vF^2}{RT}\left(\frac{[K]_i - [K]_o \exp\left(-\frac{vF}{RT}\right)}{1-\exp\left(-\frac{vF}{RT}\right)}\right)$$

How to model the gating variable?

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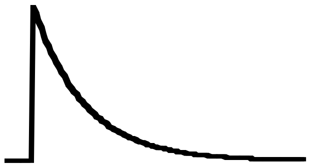
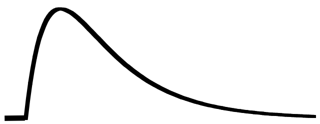


Ignore the rise and model only the decay as a single or double exponential starting at the point of the event (action potential)

$$E(t) = A\exp\left(-(t - t_0)/\tau\right)$$

Model the rise and decay using an alpha function

$$\alpha(t) = \frac{A(t - t_0)}{\tau}\exp\left(1 - \frac{t - t_0}{\tau}\right)$$



Model the rise and decay using difference of two exponentials

$$\mathrm{DoE}(t) = A\left(\exp\left(-(t - t_0)/\tau_d\right) - \exp\left(-(t - t_0)/\tau_r\right)\right)$$

Example: ghknmda.mod

```
BREAKPOINT {
        SOLVE state METHOD cnexp
        P=B-A
        mgb = mgblock(v)

        ina = P*mgb*ghk(v, nai, nao,1)*Area
        ica = P*10.6*mgb*ghk(v, cai, cao,2)*Area
        ik = P*mgb*ghk(v, ki, ko,1)*Area
        inmda = ica + ik + ina
}

DERIVATIVE state {
        A' = -A/taur
        B' = -B/taud
}
```

Demo 1: NMDA mod file

How to model calcium dynamics?

Only the Ca^{2+} concentration in a thin shell beneath the membrane is modeled. The **influx** of Ca^{2+} into such a thin shell is:

$$\frac{d[Ca]_i}{dt} = -\frac{k\,I_{Ca}}{2Fd}$$

F= 96489 C/mol, Faraday constant
d: depth of the thin shell
k : constant

The **efflux** of Ca^{2+} through pumps, buffers, etc.:

$$\frac{d[Ca]_i}{dt} = \frac{[Ca]_i^{\infty} - [Ca]_i}{\tau_{Ca}}$$

Together, calcium ion kinetics is controlled by

$$\boxed{\frac{d[Ca]_i}{dt} = -\frac{k\,I_{Ca}}{2Fd} + \frac{[Ca]_i^{\infty} - [Ca]_i}{\tau_{Ca}}}$$

Dextexhe et al., Biophys. J., 1993

GHK current equation for modeling synaptic currents

$$I_{AMPA}(v,t) = I_{AMPA}^{Na}(v,t) + I_{AMPA}^{K}(v,t)$$

where

$$I_{AMPA}^{Na}(v,t) = \bar{P}_{AMPAR}\, w P_{Na} s(t)\, \frac{vF^2}{RT} \left(\frac{[Na]_i - [Na]_o \exp\left(-\frac{vF}{RT}\right)}{1 - \exp\left(-\frac{vF}{RT}\right)} \right)$$

$$I_{AMPA}^{K}(v,t) = \bar{P}_{AMPAR}\, w P_{K} s(t)\, \frac{vF^2}{RT} \left(\frac{[K]_i - [K]_o \exp\left(-\frac{vF}{RT}\right)}{1 - \exp\left(-\frac{vF}{RT}\right)} \right)$$

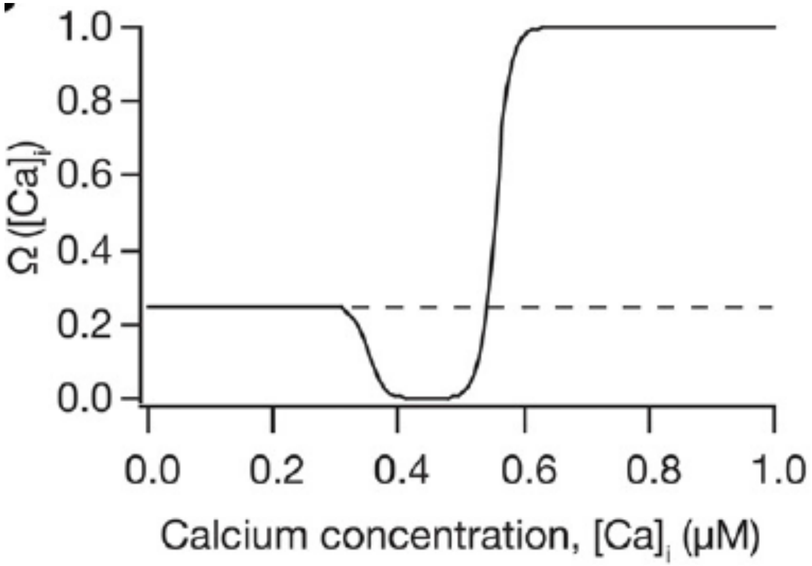
How to model the weight?

Synaptic weight update rule

$$\frac{dw}{dt} = \eta([Ca]_i)(\Omega([Ca]_i - w))$$

$$\eta([Ca]_i) = \frac{1}{\tau([Ca]_i)}$$

$$\tau([Ca]_i) = P_1 + \frac{P_2}{P_3[Ca]_i^{P_4}}$$



Example: Wghkampa.mod

```
BREAKPOINT {
        SOLVE state METHOD cnexp
        P=B-A

        ina = P*w*ghk(v, nai, nao,1)*Area
        ik = P*w*ghk(v, ki, ko,1)*Area
        iampa = ik + ina
}

DERIVATIVE state {
        lr=eta(cai)
        w' = lr*(Omega(cai)-w)
        A' = -A/taur
        B' = -B/taud
}
```

Demo 2: AMPA mod file

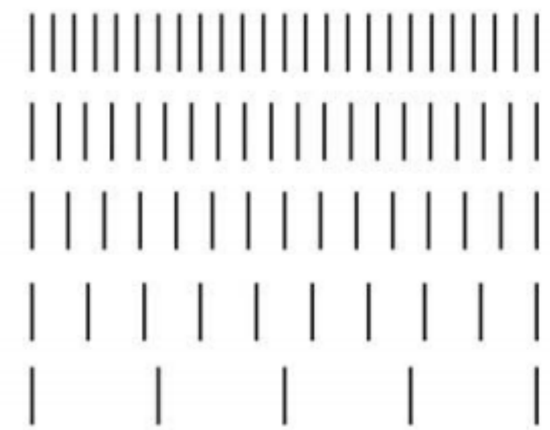
Recap!
How to use in HOC?

```
objref ampa, nmda, ncl

ncl=new List()

ampa=new Wghkampa(0.5)
dend ncl.append(new NetCon(s, ampa, 0, 0, 0))
ampa.taur                    = 2
ampa.taud                    = 10
ampa.Pmax                    = P
ampa.winit                   = w

nmda=new ghknmda(0.5)
dend ncl.append(new NetCon(s, nmda, 0, 0, 0))
nmda.taur                    = 5
nmda.taud                    = 50
nmda.Pmax                    = P*NAR
```

Demo 3: BCM_part1.hoc

Stimulation Protocol

900 spikes of frequencies between 1- 25Hz using a uniform spike generator

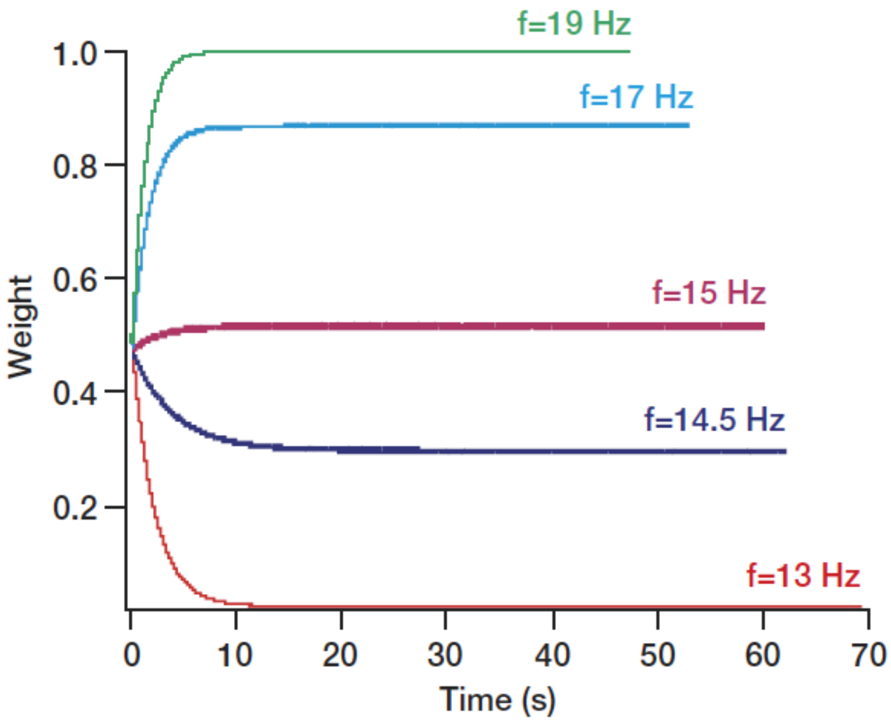


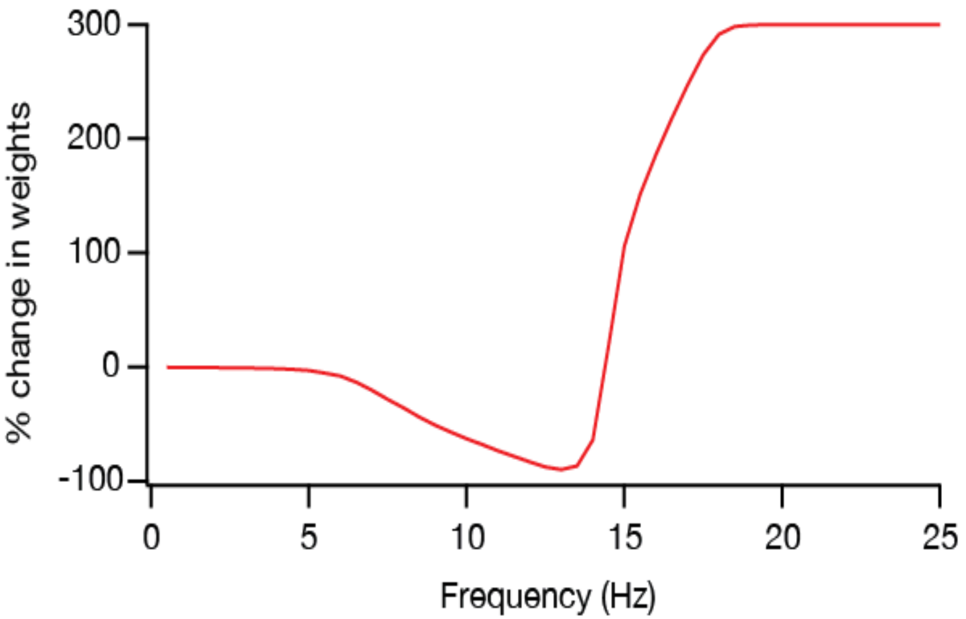
How to do implement this in hoc?

```
objref s
s = new NetStim(0.5)
s.interval=intrvl    // ms (mean) time between spikes
s.number=nmbr        // (average) number of spikes
s.start=tsyn         // ms (mean) start time of first spike
s.noise=0            // range 0 to 1. Fractional randomness
```

Demo 4: BCM_part2.hoc

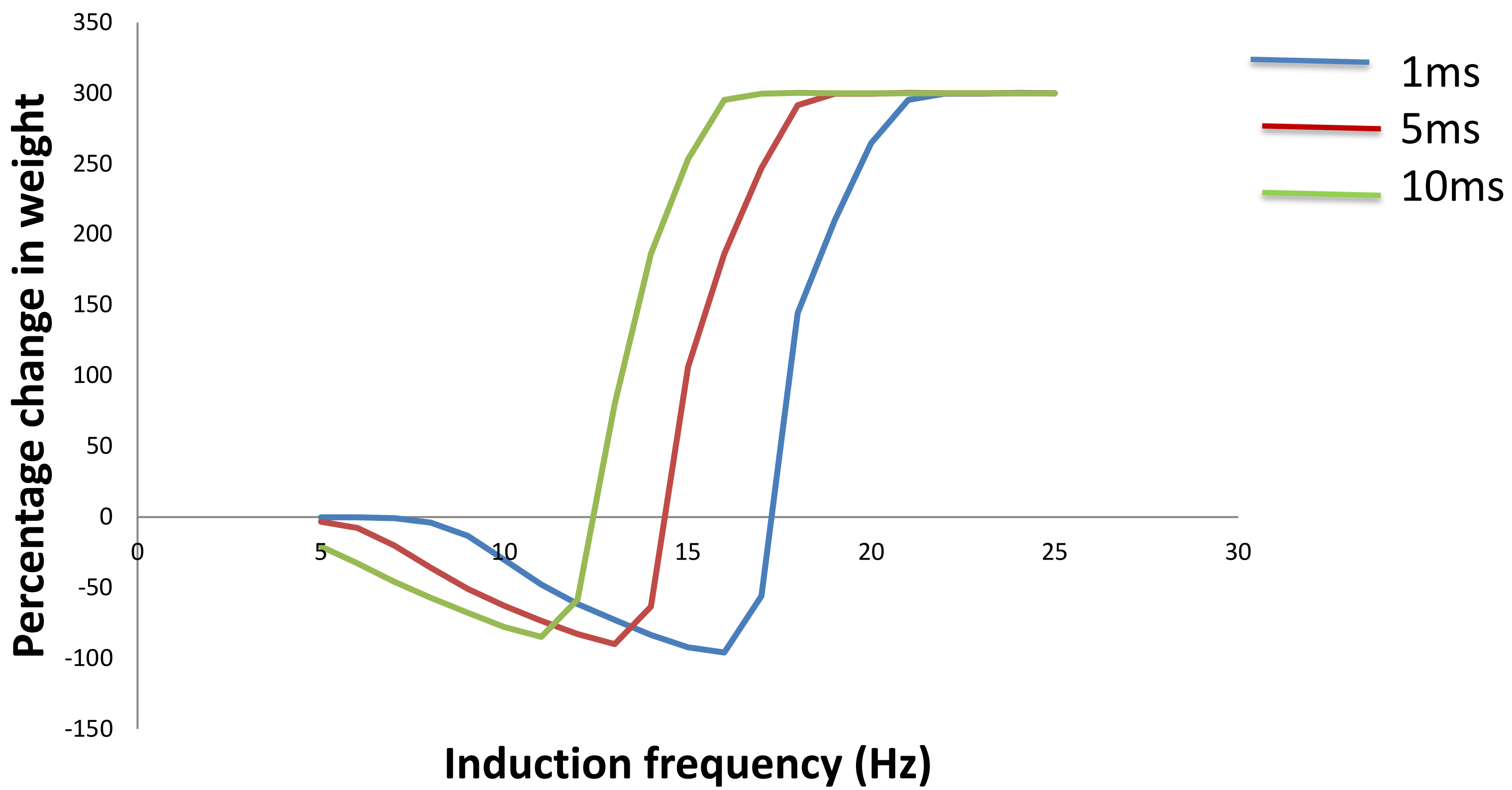
Evolution of synaptic weights and the BCM curve





Narayanan and Johnston,
J Neurophysiology, 2010

Metaplasticity



Slower NMDAR kinetics shifts the curve towards left

What did we learn?

Built a single compartment model with different synaptic receptors, ion channels and calcium handling mechanisms

Introduced a synaptic weight update rule that is dependent on the intracellular calcium concentration

Observed the evolution of synaptic weights at different frequencies and replicated the BCM profile

Both synaptic and intrinsic factors affect the functional form of synaptic plasticity