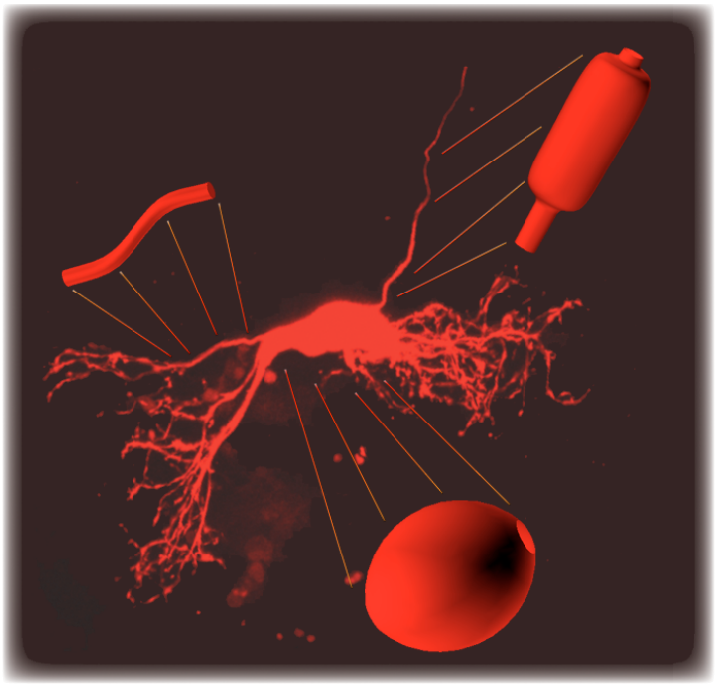
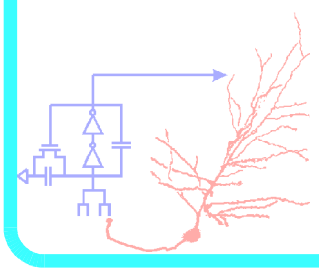
Modeling Coincidence Detection In Nucleus Laminaris

Jonathan Z. Simon





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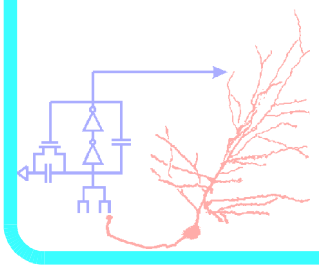
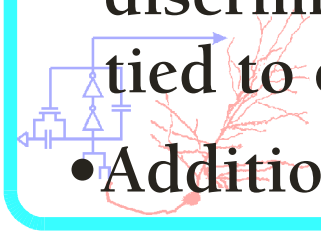
New Results



Introduction

- Sound localization by birds requires computation of interaural time differences (ITDs) in Nucleus Laminaris (NL)
- A robust coincidence detector neuron should fire when inputs from two *independent* neural sources coincide (or almost coincide), but not when two inputs from the *same* neural source (almost) coincide
- NL has a distinctive tonotopic gradient for dendritic length and other anatomical (and biophysical?) parameters. Presumably this is important.
- This biophysical model, using NEURON, examines how NL neurons detect and report ITDs, primarily based on physiology and anatomy of chick (with generalizations to other birds)
- Two versions: one with reasonable coincidence detection/ITD discrimination, and the other, still work in progress, with data tied to chick as closely as possible
- Additional emphasis: user-friendly model



Model Description

Stimulus Frequency (Hz)	1000
Stimulus Phase Ipsi (deg)	0
Stimulus Phase Contra (deg)	0
Stimulus Vector Strength ([0->1])	0.43
Probability Rate (ms^-1)	0.55
Generic Parameter 1	1
Generic Parameter 2	1
Action Pot. Threshold (mV)	-35
Period Histogram bins	16
Ignore spikes before (ms)	15
Cells per Array (arrays)	2

# [Ex Syn] (syn/dend)	30
Center [Ex Syn] ([0->1])	0.5
Distribution [Ex Syn] ([0->1])	1
tau [Ex Syn] (ms)	0.1
gmax [Ex Syn] (uS)	0.015
e [Ex Syn] (mV)	-10
Duration [Ex Syn] (ms)	1

Delay [In Syn] (ms)	0.1
Integration factor [In Syn]	3
tau [In Syn] (ms)	8
gmax [In Syn] (uS)	0.03
e [In Syn] (mV)	-60

# [Den] (dendrites)	2
Length [Den] (um)	68
Diameter [Den] (um)	4
Ax. Resist. [Den] (ohm cm)	200
gL [Den] (S/cm^2)	0.00028
gK LVA_m [Den] (S/cm^2)	0.003
gK HVA_m [Den] (S/cm^2)	0.12
# Compartments [Den]	10
lambda [Den] (um)	422.58

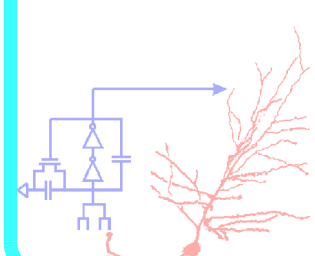
Length [Soma] (um)	15
Diameter [Soma] (um)	15
Ax. Resist. [Soma] (ohm cm)	200
gK LVA_m [Soma] (S/cm^2)	0.003
gK HVA_m [Soma] (S/cm^2)	0.03
gLeak [Soma] (S/cm^2)	0.00028
gNa_m [Soma] (S/cm^2)	0
gKHH_m [Soma] (S/cm^2)	0
# Compartments [Soma]	5

Clamp Voltage 1 (mV)	0
Clamp Duration 1 (ms)	0
Clamp Voltage 2 (mV)	0
Clamp Duration 2 (ms) (ms)	0
Clamp Voltage 3 (mV)	0
Clamp Duration 3 (ms)	0
Clamp Resistance (MOhm)	0.1

Length [Hillock] (um)	30
Diameter [Hillock] (um)	8
Ax. Resist. [Hillock]) (ohm cm)	200
gLeak [Hillock] (S/cm^2)	0.00028
gNa_m [Hillock] (S/cm^2)	0.32
gKHH_m [Hillock] (S/cm^2)	0
gK LVA_m [Hillock] (S/cm^2)	0.003
gK HVA_m [Hillock] (S/cm^2)	0.03
# Compartments [Hillock]	10
Length [Myelin] (um)	100
Diameter [Myelin] (um)	2
Ax. Resist. [Myelin] (ohm cm)	200
gLeak [Myelin] (S/cm^2)	3.5e-06
C [Myelin] (uF/cm^2)	0.0125
# Compartments [Myelin]	10
Length [Node] (um)	2
Diameter [Node] (um)	2
Ax. Resist. [Node] (ohm cm)	200
gLeak [Node] (S/cm^2)	0.00028
gNa_m [Node] (S/cm^2)	0.32
gKHH_m [Node] (S/cm^2)	0.08
# Compartments [Node]	1

Current amplitude (nA)	0
Current Delay (ms)	5
Current Duration (ms)	15

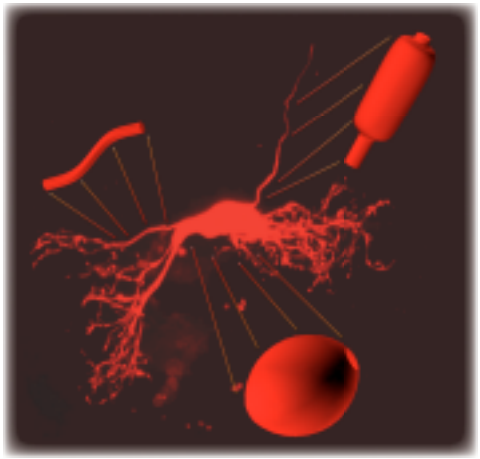
eNa (mV)	40
eK (mV)	-60
eLeak (mV)	-45
alpha0 HVA (ms^-1)	0.11
alphaVHalf HVA (mV)	-19
alphaK HVA (mV)	9.1
beta0 HVA (ms^-1)	0.103
betaVHalf HVA (mV)	-19
betaK HVA (mV)	20
alpha0 LVA (ms^-1)	0.2
alphaVHalf LVA (mV)	-50
alphaK LVA (mV)	10
beta0 LVA (ms^-1)	0.17
betaVHalf LVA (mV)	-50
betaK LVA (mV)	10
q10 HVA	2
T0 HVA (C)	23
q10 LVA	2
T0 LVA (C)	23
alphamVHalf Na (mV)	-30
betamVHalf Na (mV)	-55
alphahVHalf Na (mV)	-55
betahVHalf Na (mV)	-25
q10 Na	2.3
q10 KHH	2.3

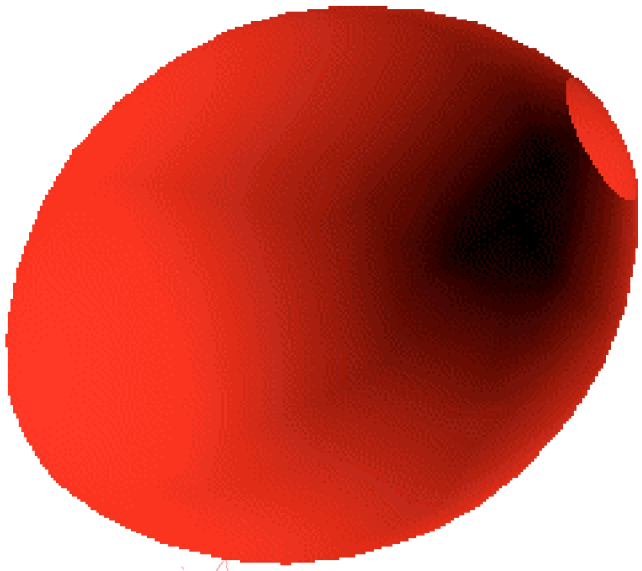


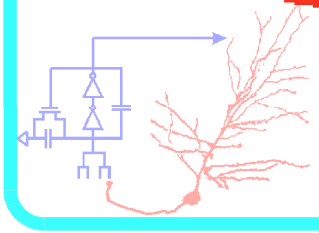
```
/* CDlab: a coincidence detector laboratory */
/* NEURON program modeling an avian brainstem auditory coincidence detector. */
/* by Jonathan Z. Simon */
/* originally based on his project from the Woods Hole MBL course */
/* "Methods in Computational Neuroscience". */
/* cdlab.hoc version 4.0dxx (requires special mod files, cvode ready) */
/* formerly known as multicoincidence.hoc */
strdef versionStr
versionStr = "CD Lab v. 4.0d10"

/* copyright 1999-2001 Jonathan Z. Simon and University of Maryland */

/* We simulate cells, each with soma, an axon and some
 * number of pairs of dendrites. The stimulation is from
 * synapses on the dendrites. Each synapse fires with
 * time-dependent Poisson statistics, with probability proportional
 * to a periodic stimulus. The stimuli from each ear are identical,
 * except (in general) the phase. */

// For neuron 4.3 & above, no redefinition of template, so no loading twice.
//firstrun = (name_declared("cdlabVersion") != 2)
//if (firstrun) { // prep for first time
 cdlabVersion = 4.0
 dll_loaded = 0  // Load dll if necessary (mac or pc)
 if (unix_mac_pc() == 2) {dll_loaded = nrn_load_dll("cdlabmac.dll")} // mac
 if (unix_mac_pc() == 3) {dll_loaded = nrn_load_dll("cdlabpc.dll")}  // pc
 {load_file("noload.hoc")} // Despite name, loads the standard run libraries.
 useGraphics = 1 // if 0, can be run on unix terminal remotely, without X
//} else { // reloading
// forall delete_section()
//}

/***************
 * Declarations *
 ***************/

objref qu
                // global constants & utilities
objref gpi
                // global parameter info
objref gp
                // global parameters
objref gr
                // global run variables & procedures
objref go
                // global output
objref cvode                                    // allows use of NetCons and
variable time_step
objref timeGraphList                            // protect graphs from garbage
collection
strdef stimProcName         // changeable stimulus function (e.g. bin/monaural)
poissClock = -1             // if stimulus needs a (Poisson process) clock.


strdef tmpStr // for temporarily holding a string
objref tmpObj // for temporarily holding an object
objref nil    // null object

// These procedures always executed: initally empty but user can override
proc userpreinit() {}
proc userpostinit() {}
proc userpostrun() {}
proc usercleanup() {}
```

~7500 lines/100 pages of NEURON code

Soma







Length/Diameter, e.g. 20 μm

Leak conductance, e.g. 0.0002 S/cm^2

K^{LVA} (Low Voltage Activated) conductance, e.g. 0.01 S/cm^2

K^{HVA} (High Voltage Activated) conductance, e.g. 0.05 S/cm^2

Na conductance, e.g. 0.05 S/cm^2

Axial resistivity, e.g. 2 ohm·cm
Number of compartments, e.g. 3

Dendrites

Number of dendrites, e.g. from 2 to 26

Length, e.g. from 10 to 700 □m

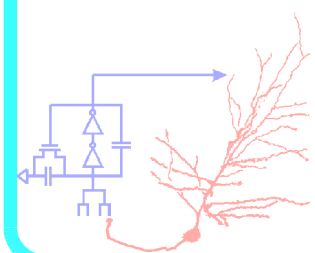
Diameter, e.g. 2 □m

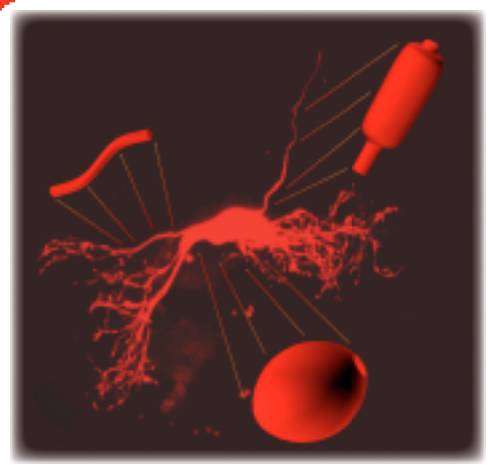
Leak conductance, e.g. 0.0002 S/cm^2

K^{LVA} conductance, e.g. 0.0015 S/cm^2

K^{HVA} conductance, e.g. 0.07 S/cm^2

Axial resistivity, e.g. 2 ohm·cm
Number of compartments, e.g. 9





Excitatory Synapses

Maximum synaptic conductance, e.g. 0.007 □S

□(of □ function), e.g. from 0.1 to 0.3 ms

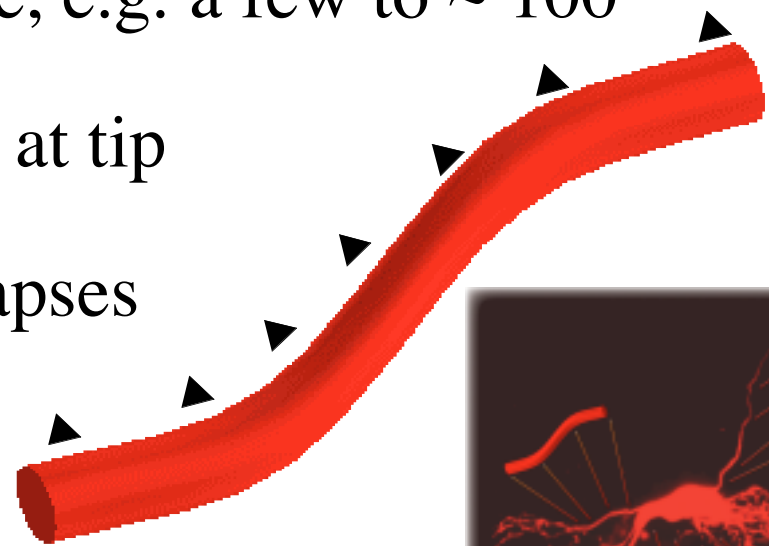
Synaptic reversal potential, e.g. 0 mV

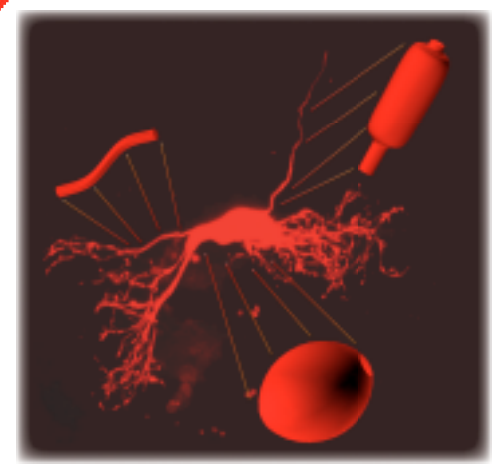
Number of synapses per dendrite, e.g. a few to ~ 100

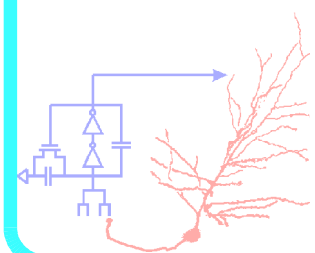
Distribution, e.g. uniform, or all at tip

Independence of individual synapses

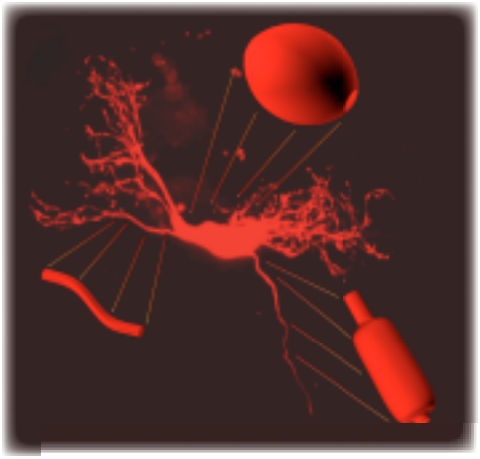
Minimum interval, e.g. 1 ms

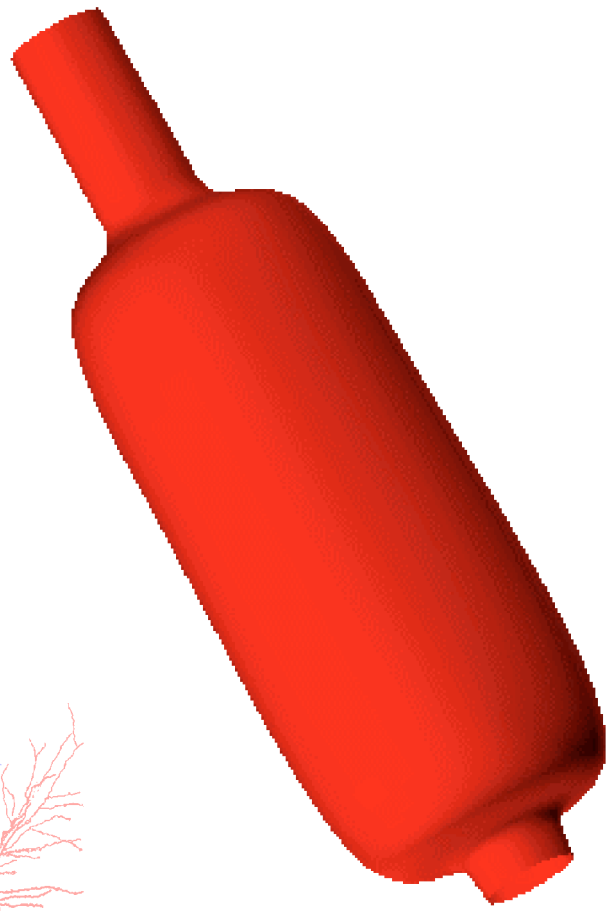


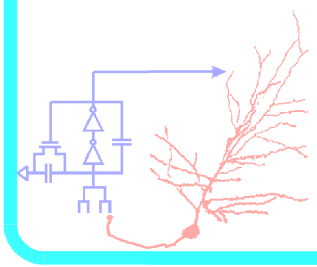




Axon







Hillock

Length, e.g. 30 μm
Diameter, e.g. 2 μm
Leak conductance, e.g. 0.0002 S/cm^2
K^{LVA} conductance, e.g. 0.0015 S/cm^2
K^{HVA} conductance, e.g. 0.07 S/cm^2
Na conductance, e.g. 0.05 S/cm2

Myelinated Segment

Length, e.g. from 60 μm
Diameter, e.g. 2 μm
Leak conductance, e.g. 0.000004 S/cm^2
Capacitance, e.g. 0.02 μF/cm^2

Axial resistivity, e.g. 2 ohm·cm
Number of compartments, etc.

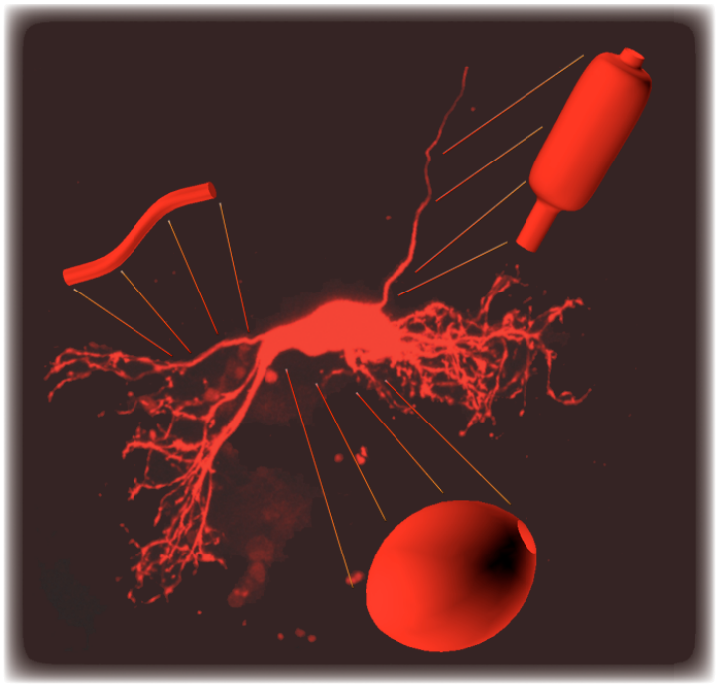
Neuron-wide Parameters

Reversal Potentials

E_{Na}, e.g. +40 mV

E_K, e.g. –80 mV

E_{Leak}, e.g. –50 mV



K^{LVA} activation

τ_0^{LVA}, e.g. 0.05 ms

$\tau_{V_{Half}}^{LVA}$, e.g. –50 mV

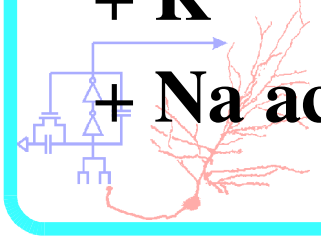
$\tau_{V_K}^{LVA}$, e.g. 10 mV

Q_{10}^{LVA}, e.g. 2τ/(10 °C)

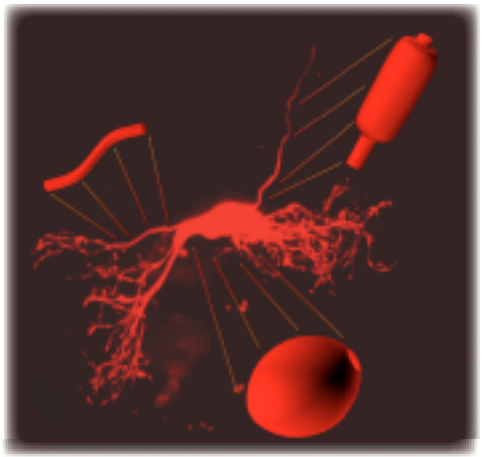
+ K^{LVA} deactivation

+ K^{HVA} activation & deactivation

+ Na activation, deactivation, inactivation & deinactivation



(Slow) Inhibition



Integrate & Fire

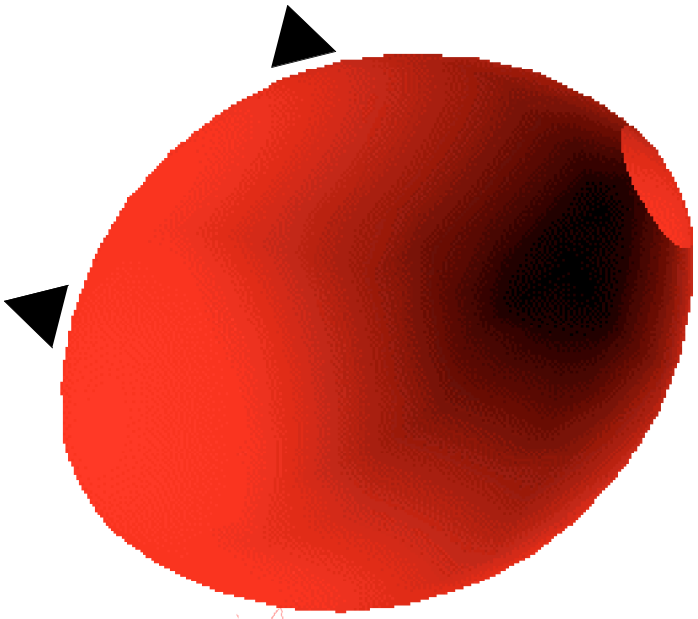
Maximum synaptic conductance,

e.g. 0.08 □S

□(of □ function), e.g. 8 ms

Synaptic reversal potential, e.g. -55 mV

Delay, Integration factor

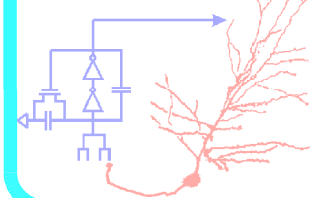


OR

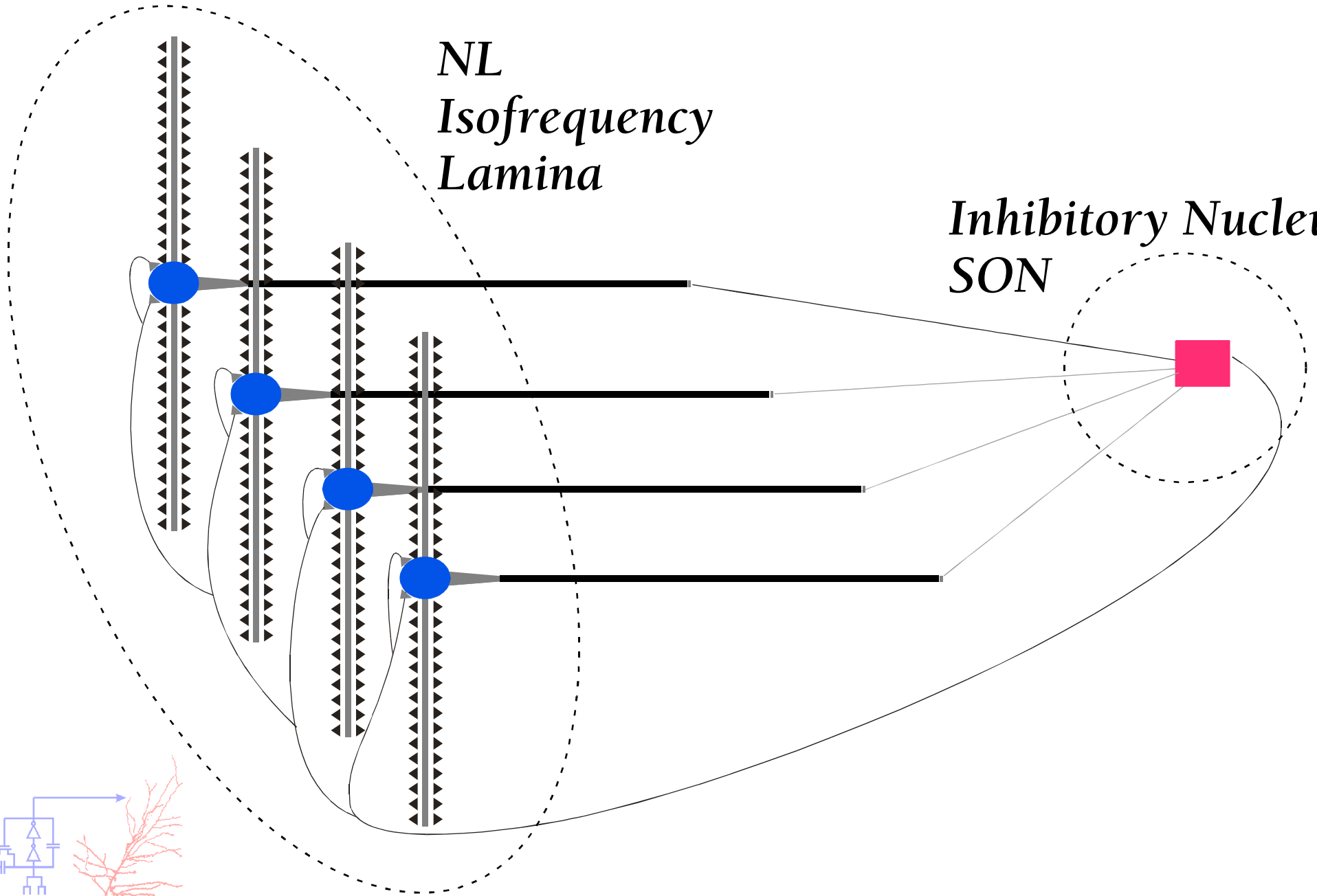
Model of Superior Olivary Nucleus (SON)

Hodgkin-Huxley-like model

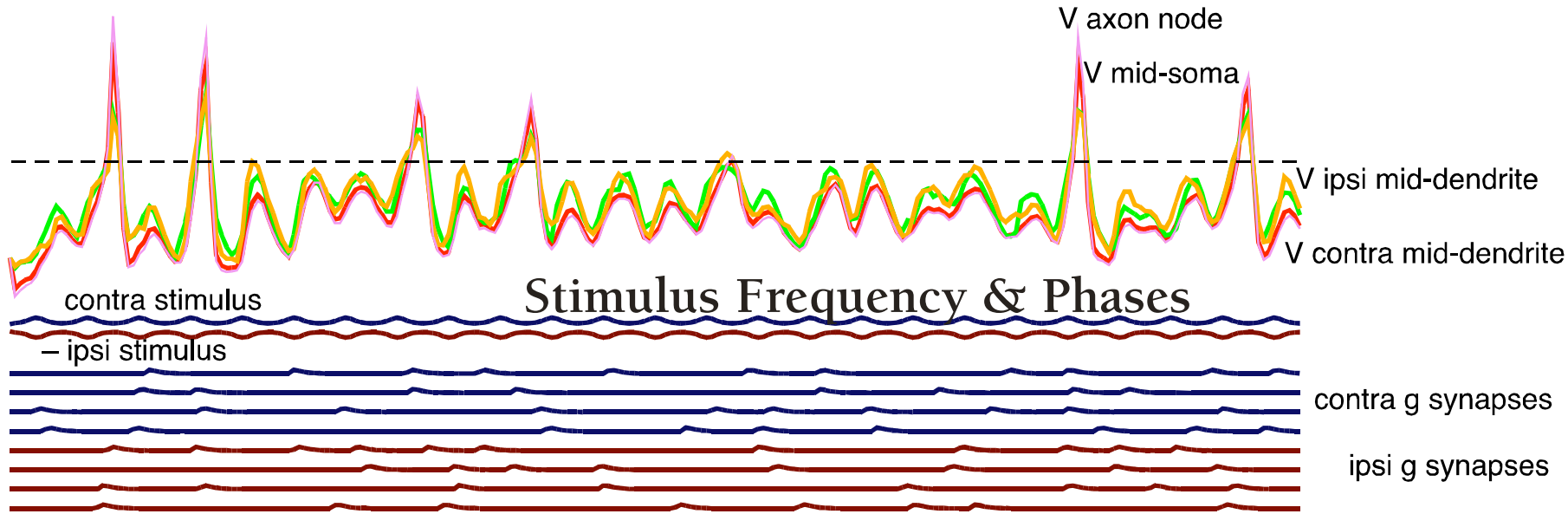
with NL & NA input



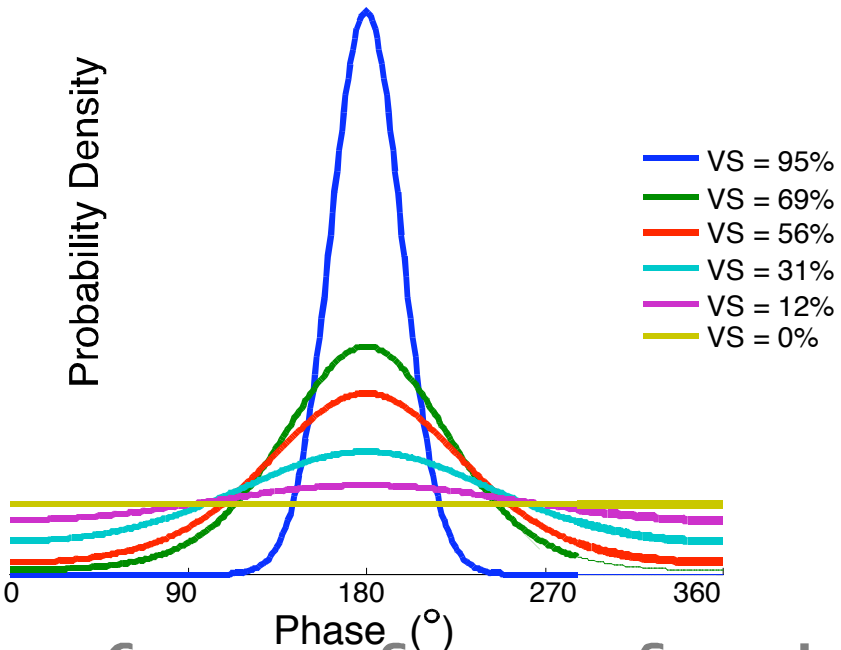
Geometry & Connectivity

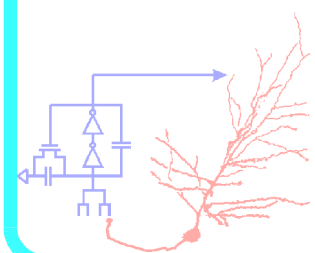


Stimulus & Conductance Input

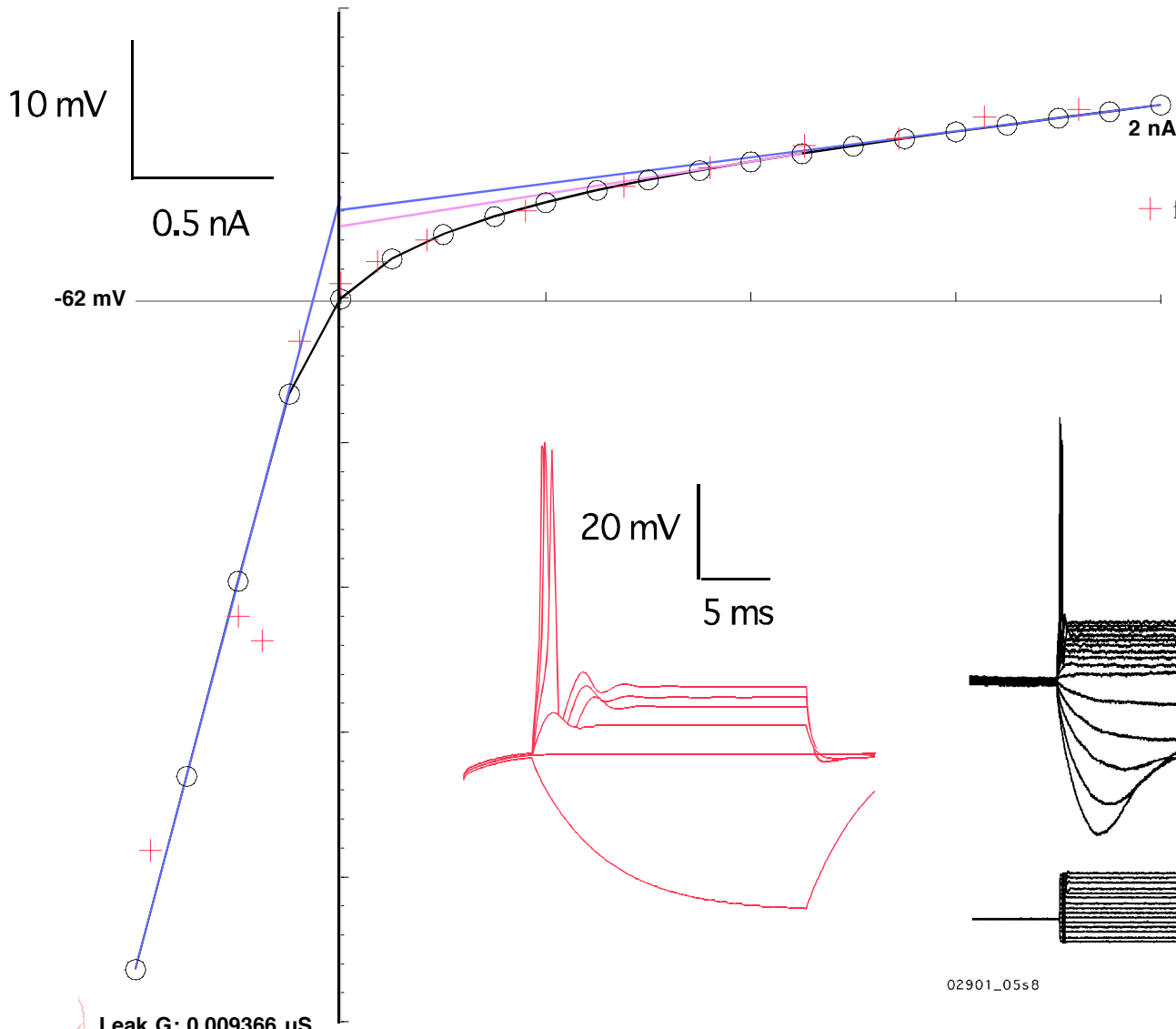


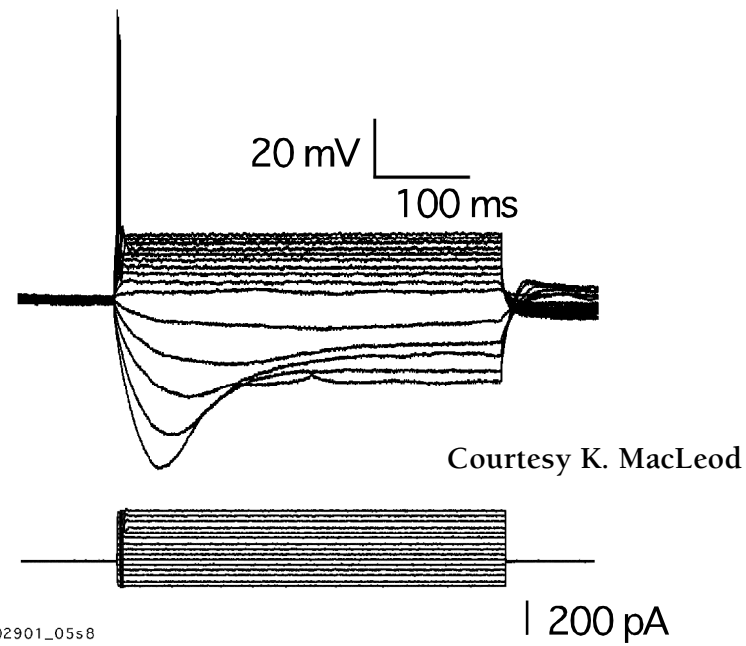
Stimulus probability distributions

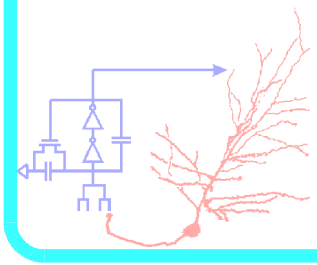




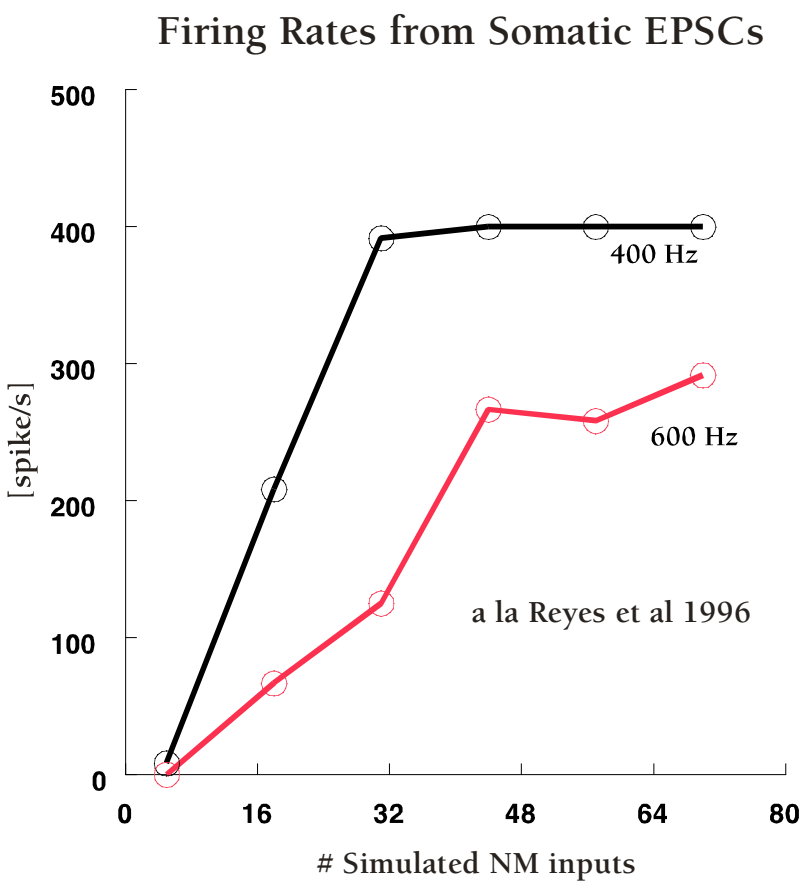
Estimating Model Parameters

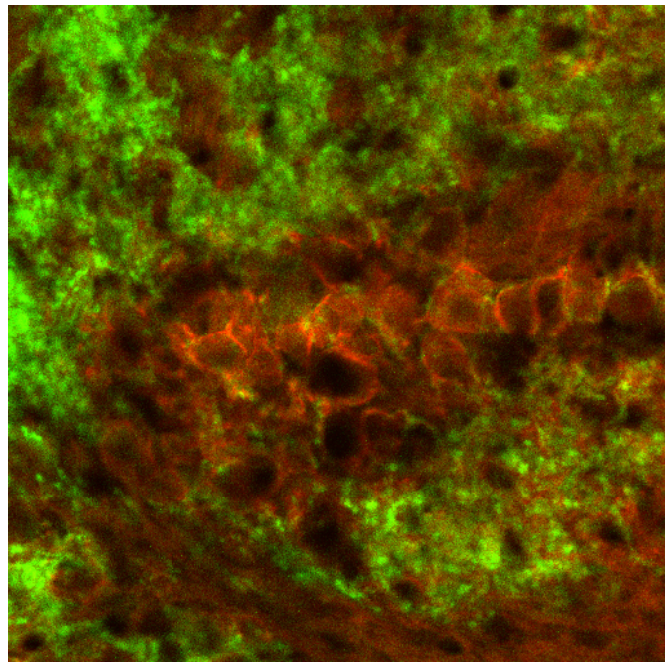






Estimating Model Parameters

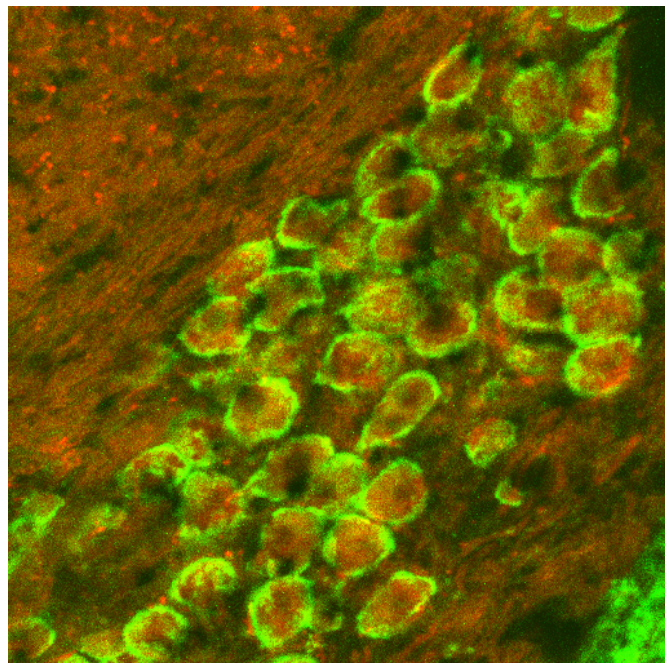




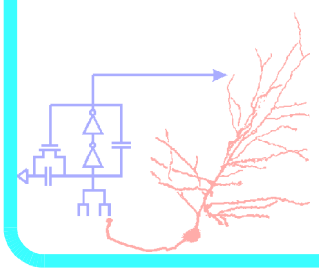
Kv3.1 immunoreactivity (red, CYC3) in low BF region of NL outlines cell bodies and proximal dendrites of NL neurons.

NM terminals in NL are delineated by staining with the synaptic vesicle marker (SV2, green FITC).

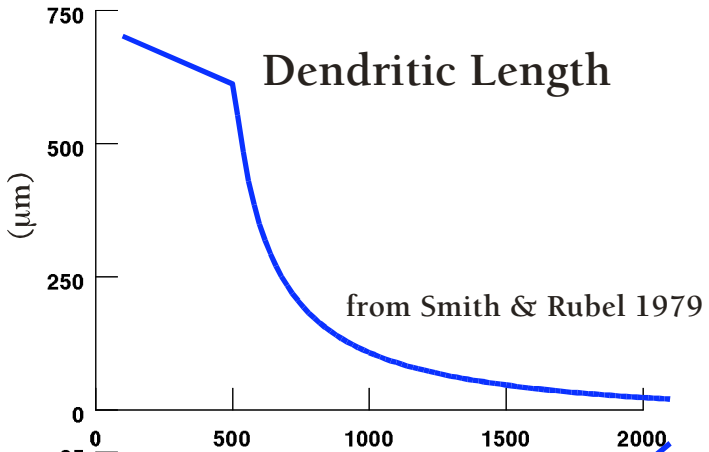
Parameshwaran et al 2001

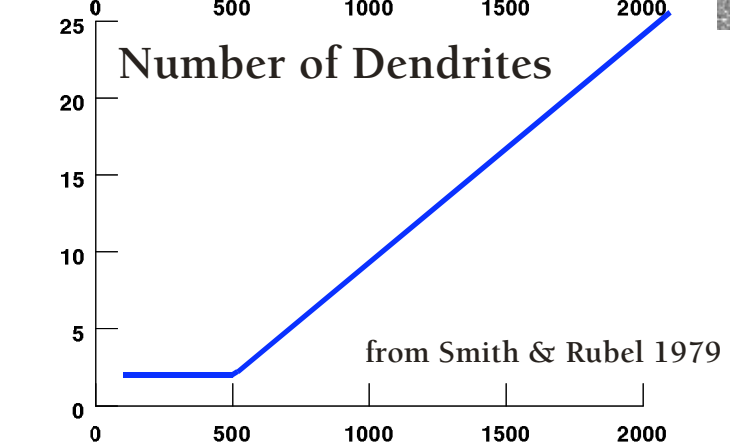


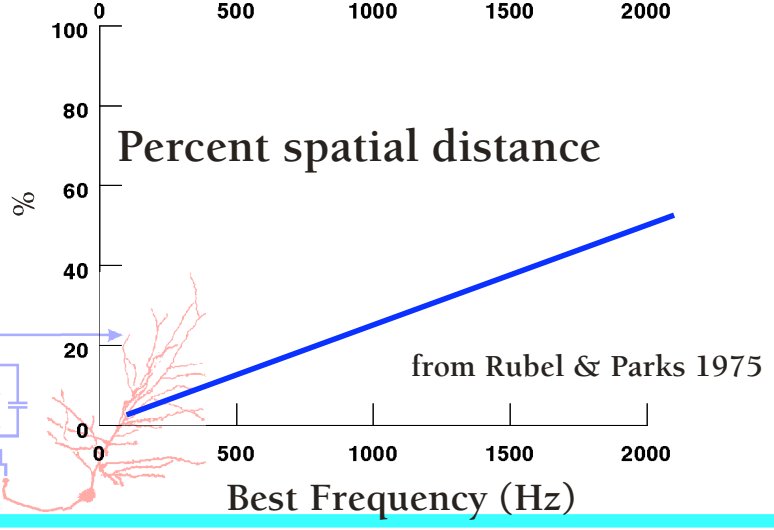
Synaptic vesicle protein (SV2) immunoreactivity in NM labels endbulb terminals in NM

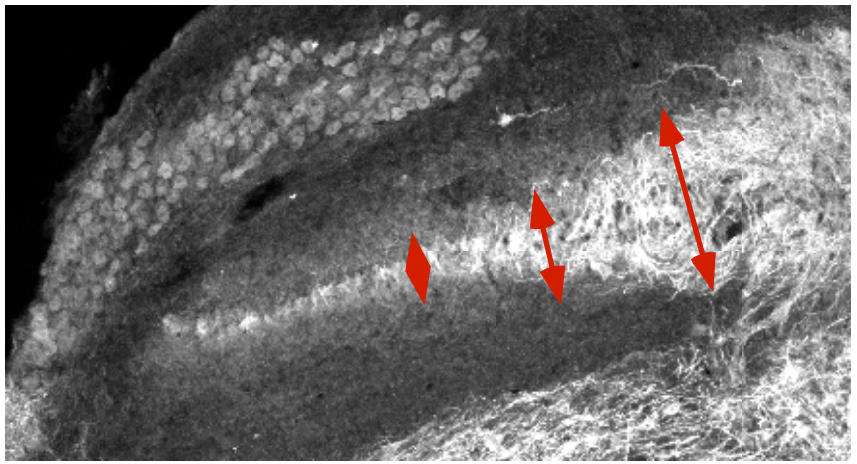


Tonotopic Gradients

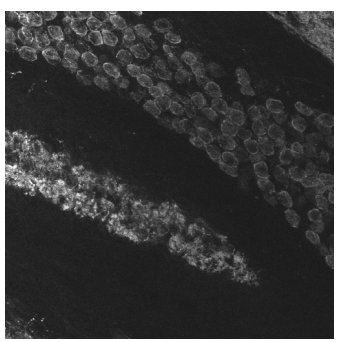




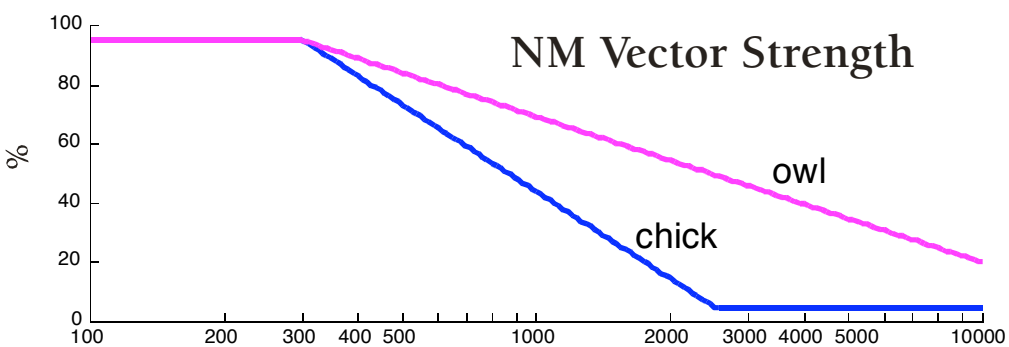




Transverse section labels both NM and NL and shows tonotopic increase in dendritic length with decreasing best frequency in NL [Microtubule associated protein (MAP2. FITC) immunoreactivity]



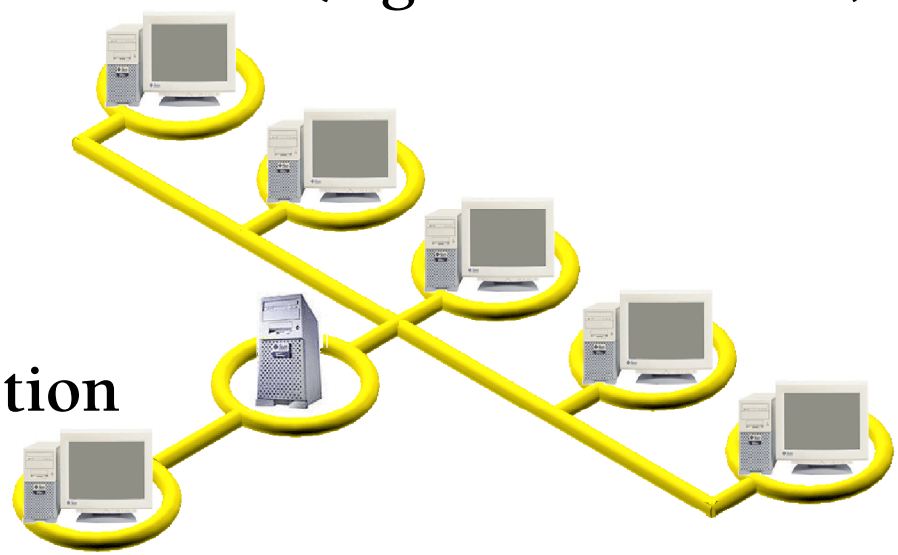
Oblique section approximately isofrequency slab—dendritic length approximately constant



from Köppl, 1997, Warchol & Dallos, 1990.

Searching Parameter Space

- Brute force approach when all else fails
- Distributed over > 30 Sun workstations via shared filesystem
- Asynchronously, fault tolerant, crash resistant
- Runtimes = few hours – few days
- Slightly less than linear scaling with nodes (e.g. 3.5x /5 nodes)

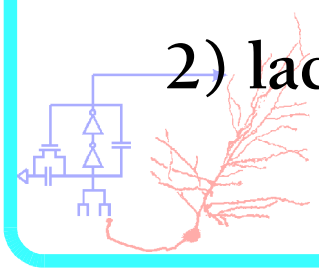


- Does ***not*** compensate for

  1) exponential dependence on number of parameters and resolution

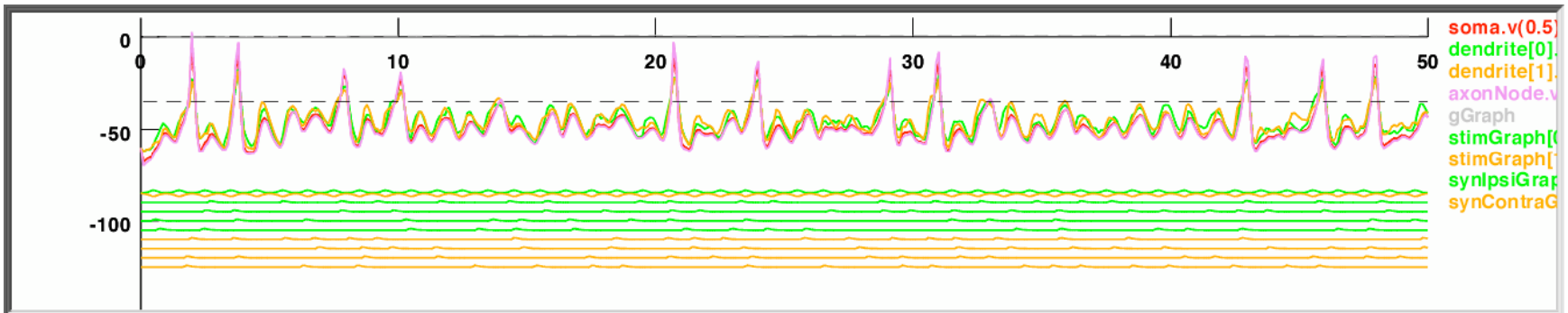
  OR

  2) lack of physiological common sense



Voltage, Conductance, Inputs

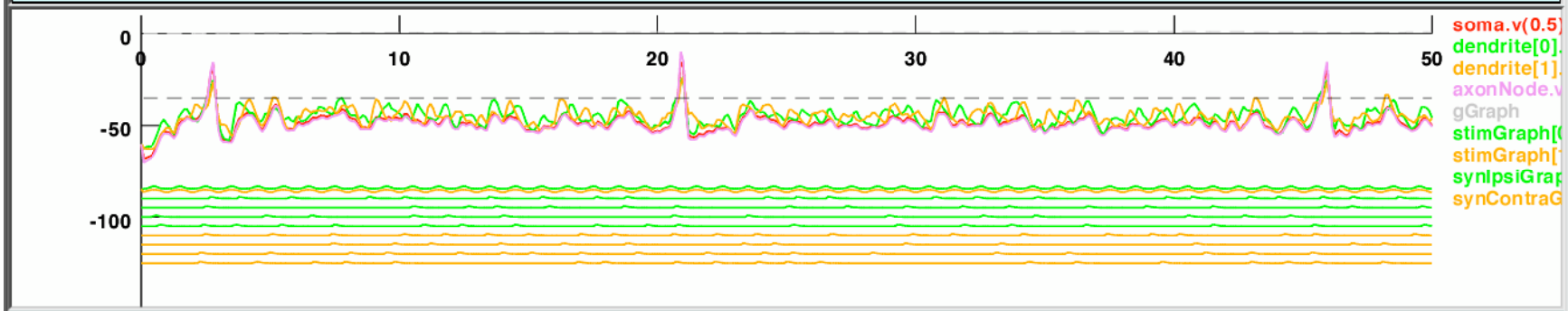
binaurally in-phase



Spikes (at axon tip)	8	Spike Rate (at axon tip)	228.57	Vector Strength (at axon tip)	0.83536	Vector Phase (at axon tip)	286.76

Time Plot | Space Plot | Spike & Dendrite PSTHs | Synapse PSTHs | Parameters

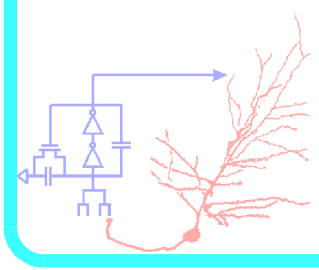
binaurally out-of-phase



Spikes (at axon tip)	2	Spike Rate (at axon tip)	57.143	Vector Strength (at axon tip)	0.96246	Vector Phase (at axon tip)	263.25

Time Plot | Space Plot | Spike & Dendrite PSTHs | Synapse PSTHs | Parameters

Spike Rate Ratio (at axon tip)	4

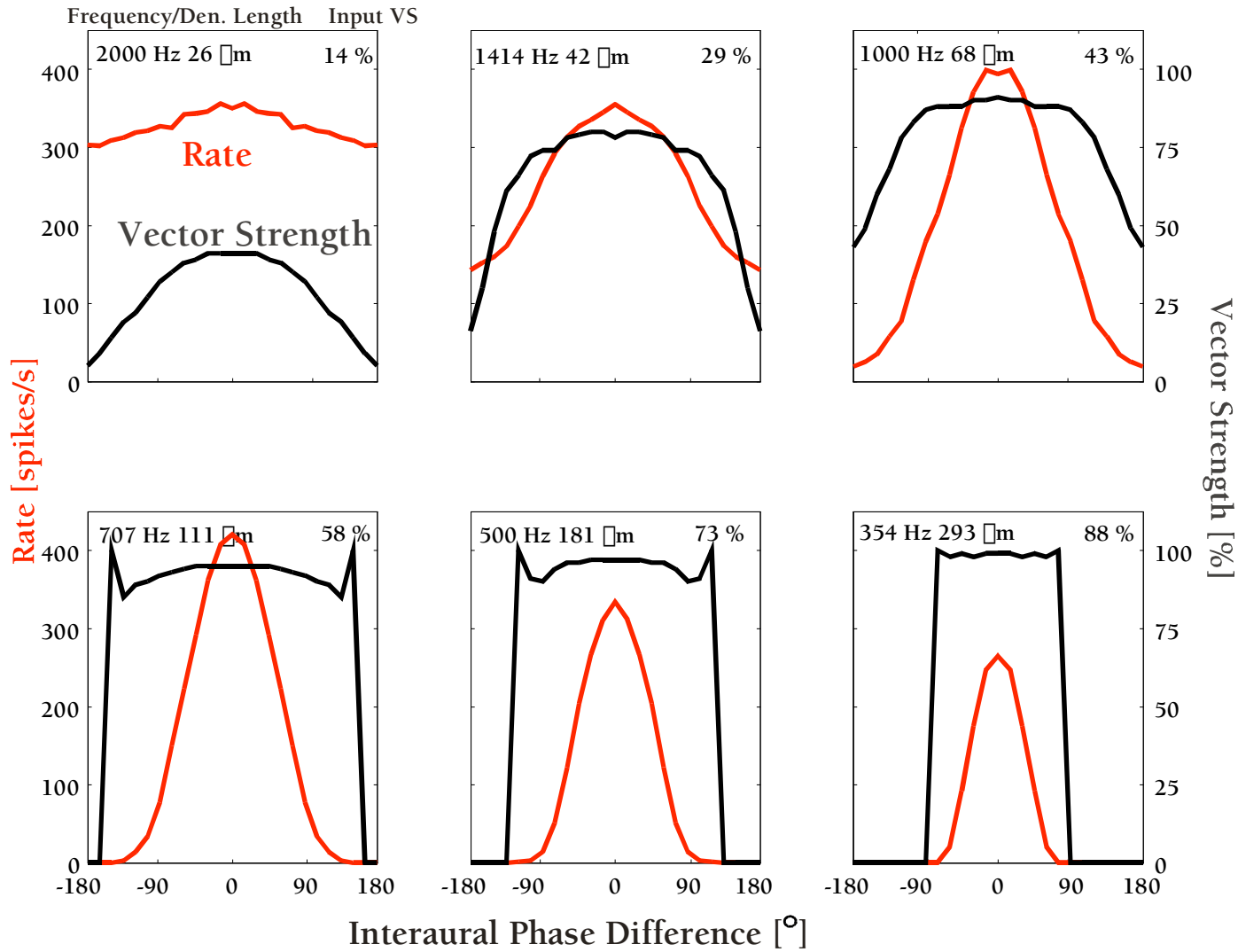


Same stimulus probability distributions,
e.g., f =1 kHz, VS = 50%

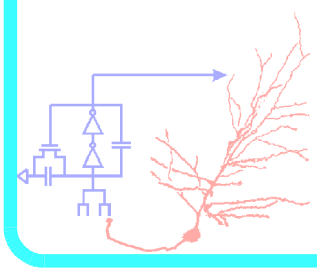
Phase Locking

Rate IPDs

Vector-strength IPDs

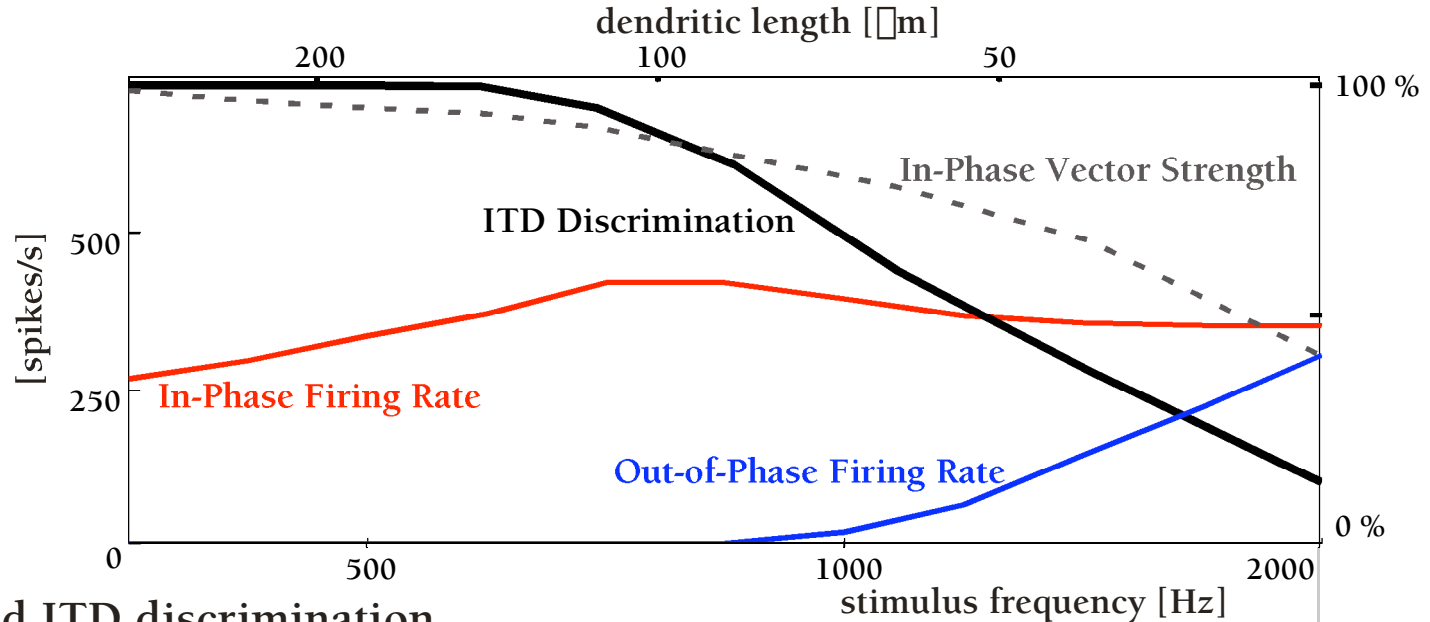


Note: Over-enhancement of output VS over input VS:
VS-coded IPD curves appear flat
Over-suppression of rates for nearly out-of-phase inputs:
rate-coded IPD curves appear too sharp



ITD Discrimination

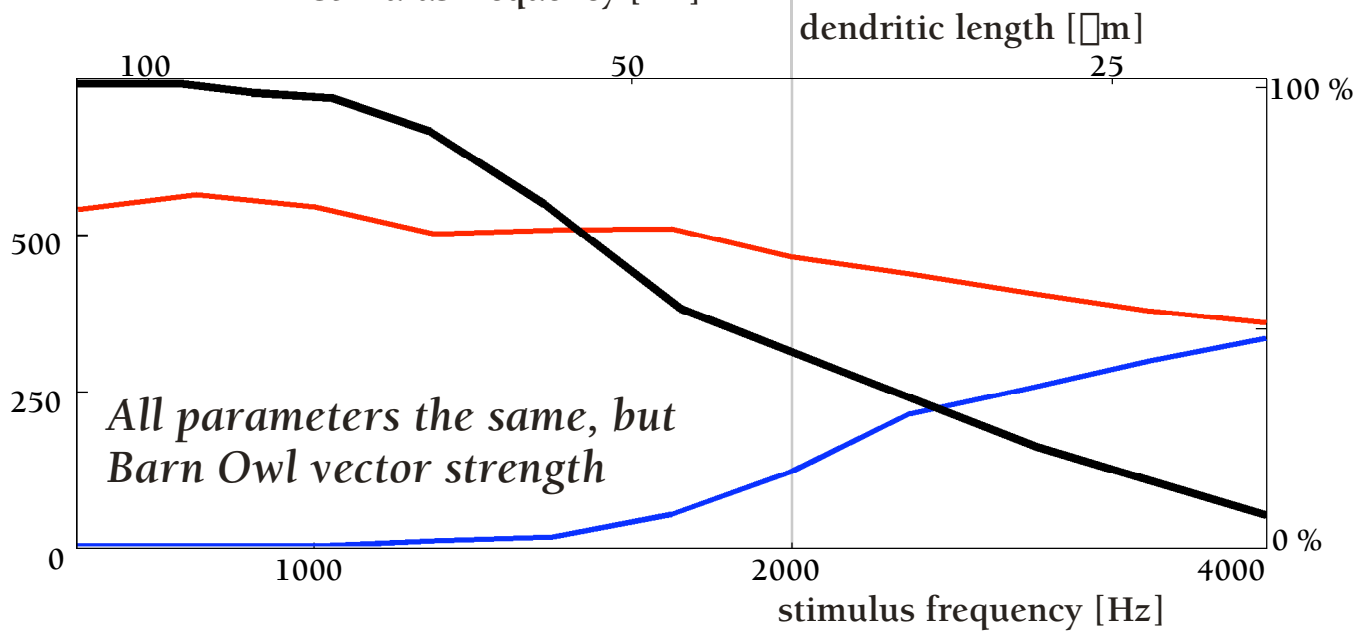
$$\text{Discrimination} = 1 - \frac{\text{out-of-phase rate}}{\text{in-phase rate}}$$

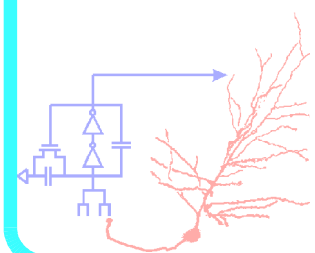


In-Phase Rate
Out-Phase Rate
} spikes/s

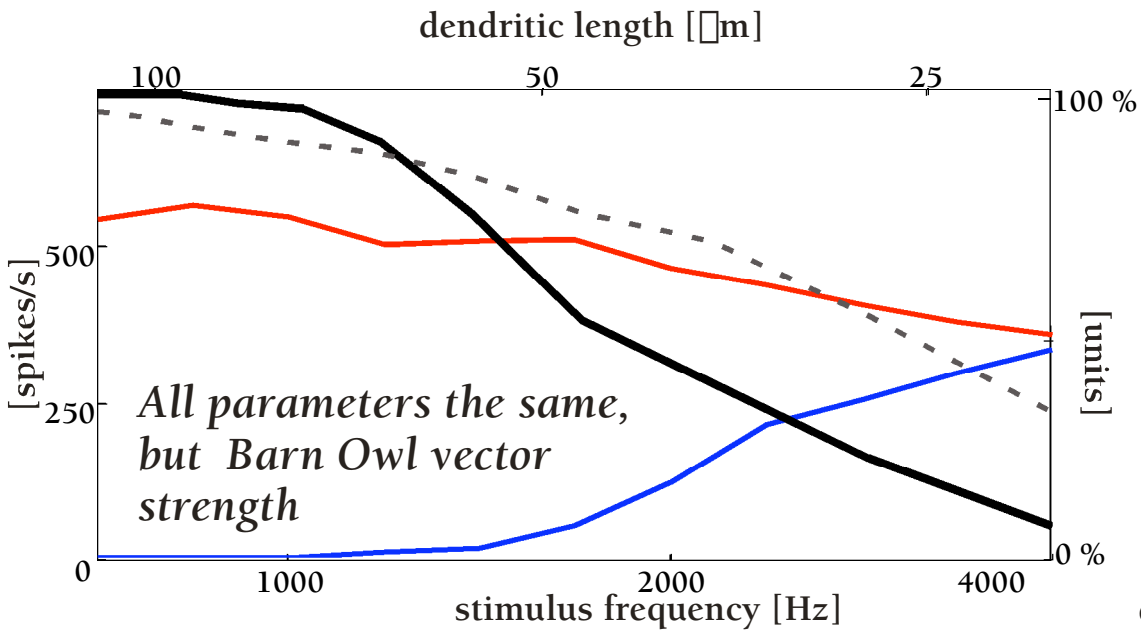
Discrimination
In-Phase VS
} %

Good ITD discrimination (high ratio) until ~2 kHz. Sharp phase tuning appears as ceiling effect on ITD Discrimination index



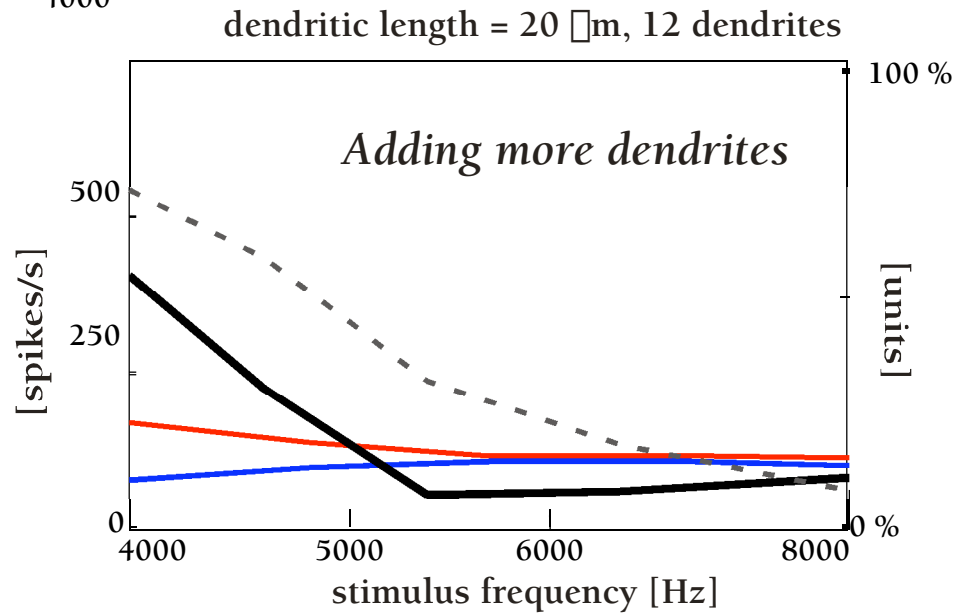


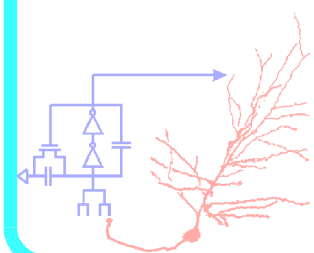
ITD Discrimination—Barn Owl



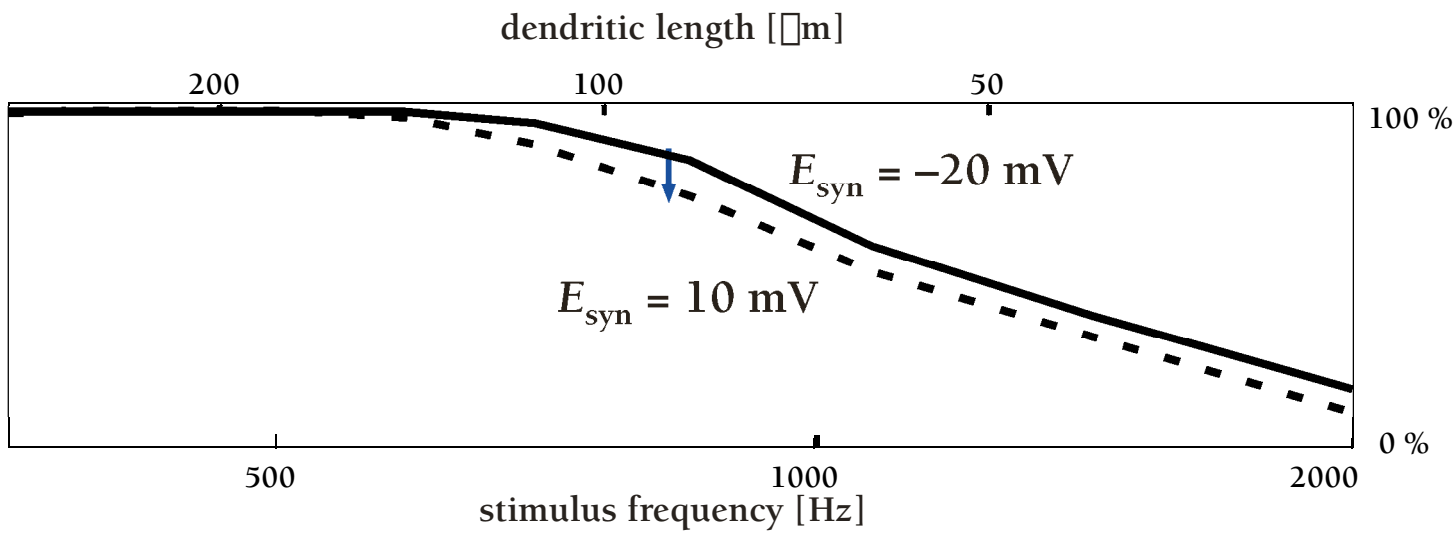
In-Phase Rate
Out-Phase Rate

Discrimination
In-Phase VS





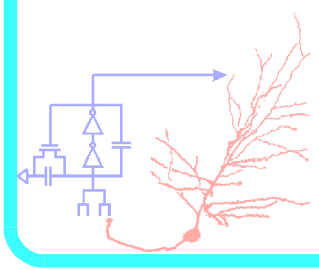
Synaptic Sub-Linearity



Synaptic reversal potential more depolarized ↗

reduces dendritic sub-linearity ↘

worsening discrimination ↘

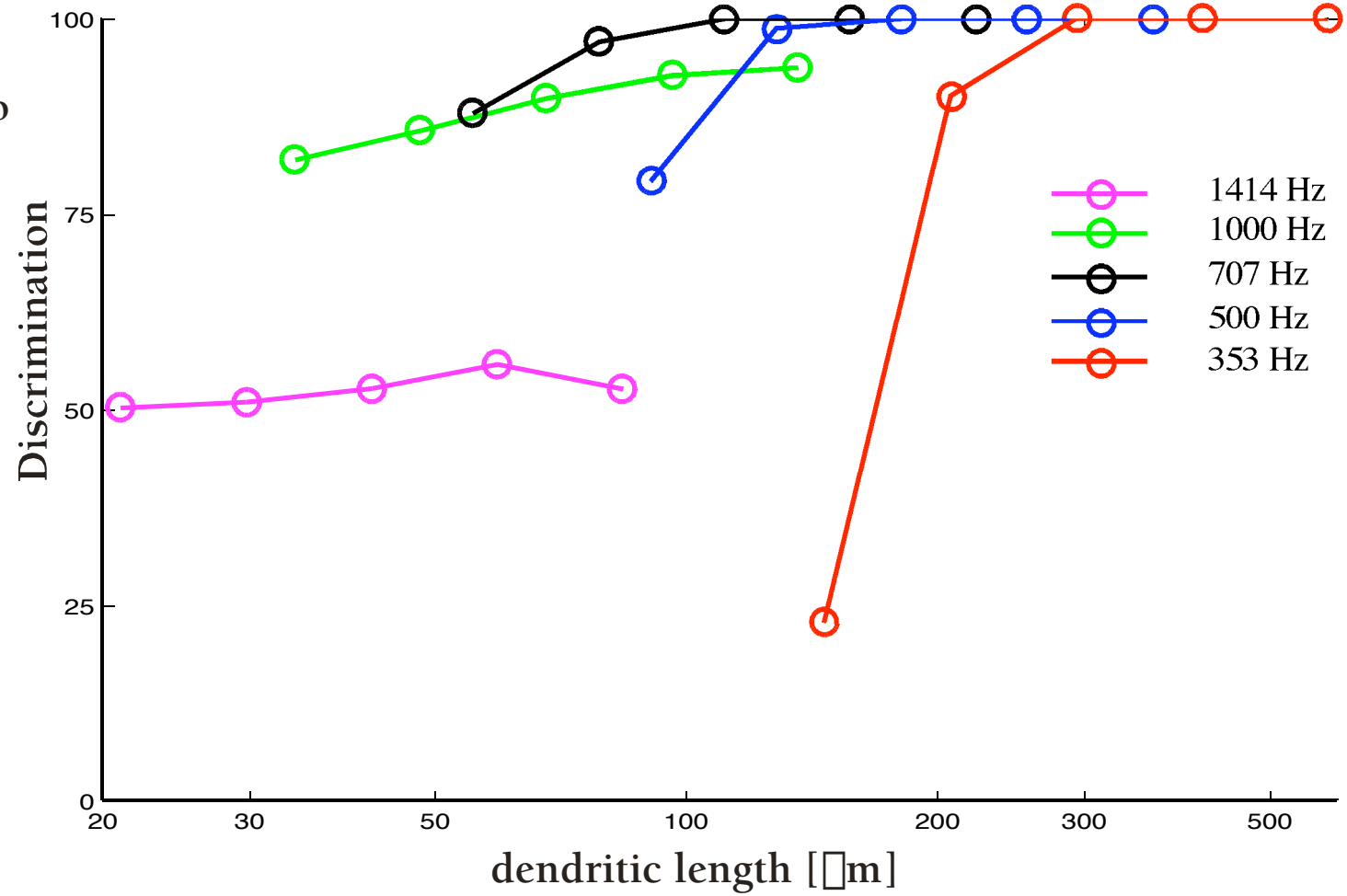


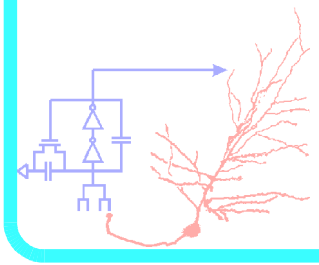
Dendritic Length Gradient Predicted

Intra-dendritic sublinearity leads to optimal dendritic length, as shown by Agmon-Snir et al. 1998

For every stimulus frequency there is a dendritic length, longer than which, performance no longer increases.

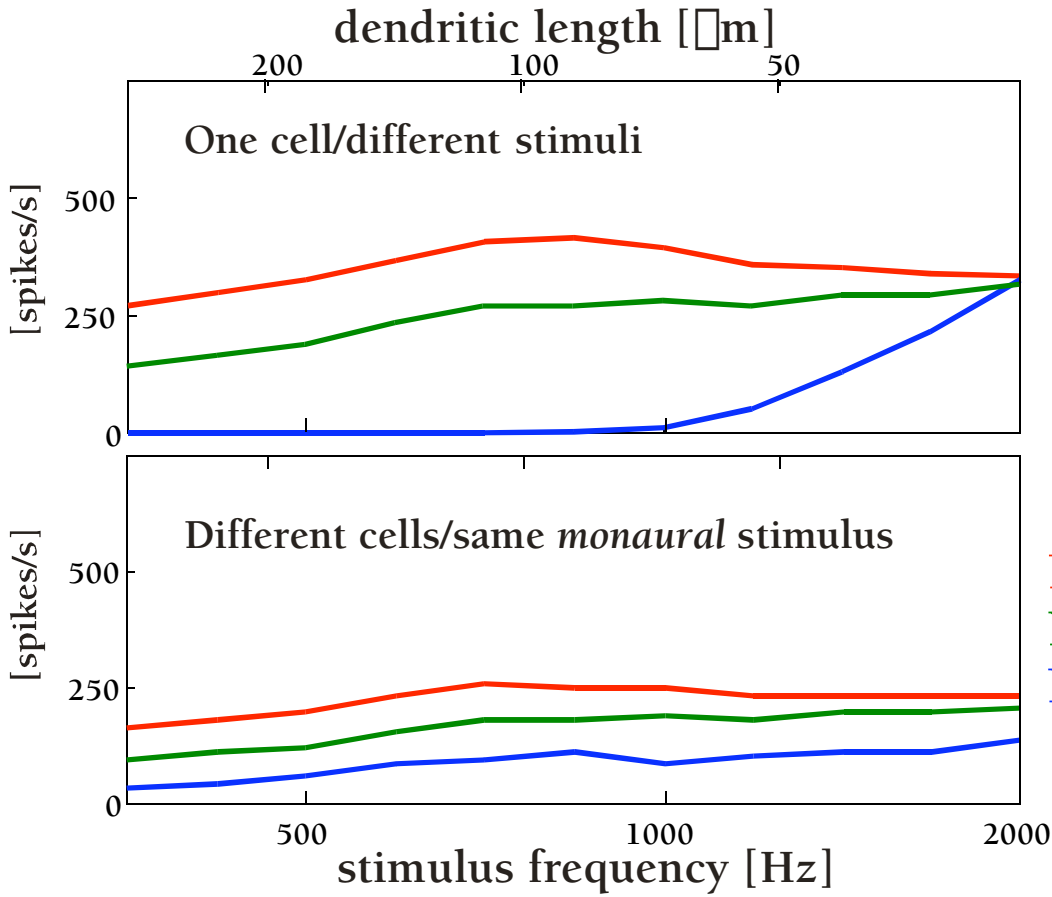
The effect is most pronounced at lower frequencies.





Subtraction Non-Linearity

Out-of-phase rate suppressed relative to monaural rate



In-Phase Rate
Monaural Rate
Out-Phase Rate

Potassium acts as current sink

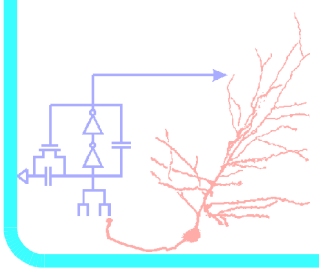
Dendrite removed
Normal Cell
High K Conductance

Cells fire well with *no* stimulus on the opposite side.

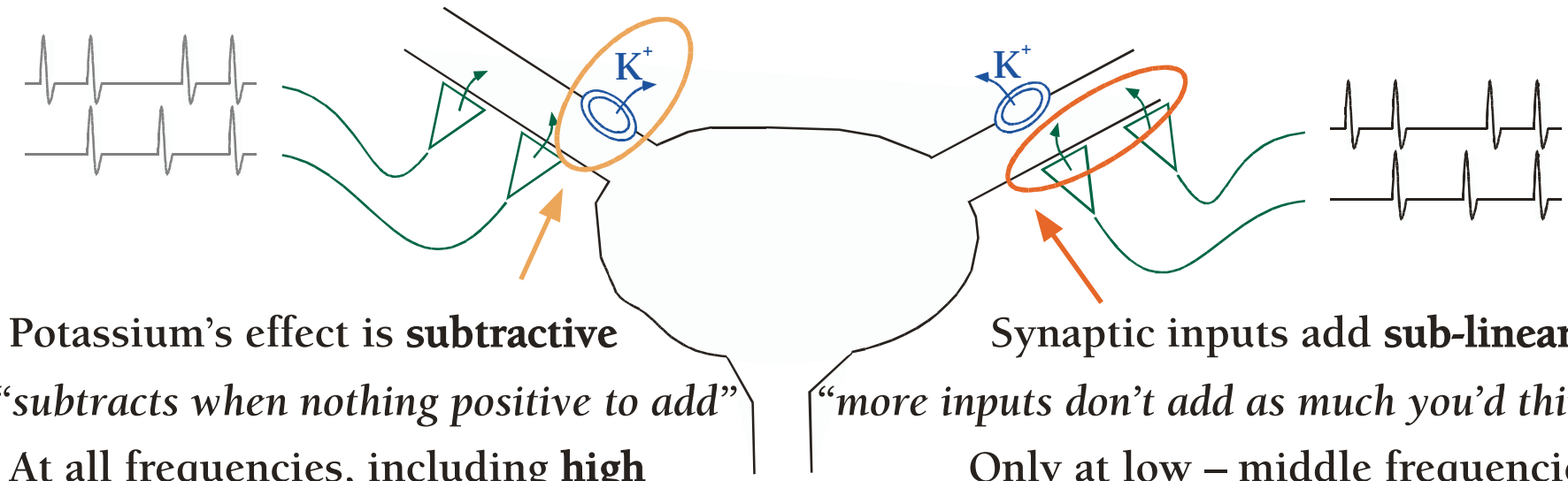
Not just a "coincidence" detector

Effect present at all frequencies

Meeting of in- and out- rates at ~ 2 kHz a consequence of poorly phase-locked inputs



Non-Linearities



Potassium's effect is **subtractive**

"subtracts when nothing positive to add"

At all frequencies, including **high**

Synaptic inputs add **sub-linearly**

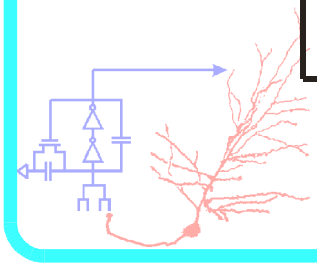
"more inputs don't add as much you'd think"

Only at low – middle frequencies

Found by Agmon-Snir et al. 1998

Both effects reduce false positives

Firing Rates	with non-linearities	without non-linearities
In-Phase		
Out-of-Phase		too many false positives

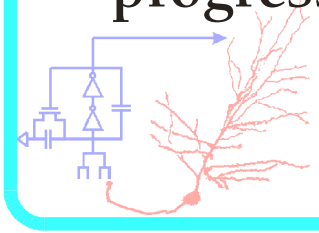


Results

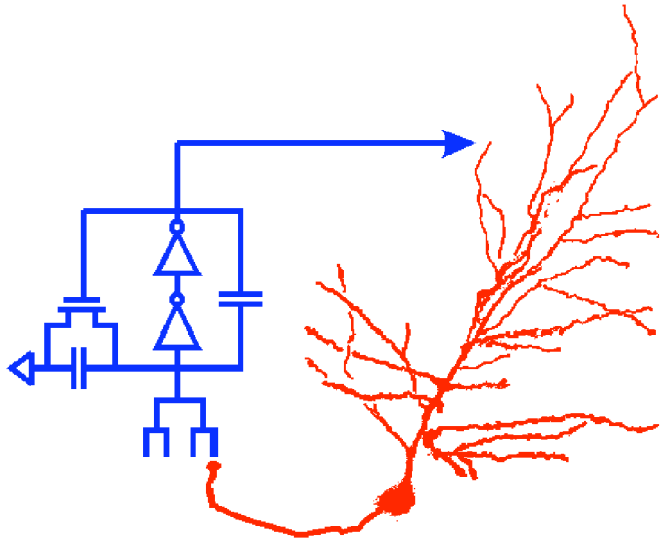
- Typical chick-like parameters allow ITD discrimination up to 2 kHz.
- Typical chick-like parameters but with barn-owl-like phase locking allow ITD discrimination up to 6 kHz.
- Two non-linearities aid ITD discrimination:

  1) intra-dendritic inputs sum sub-linearly.

  2) inter-dendritic interactions subtractively inhibit out-of-phase inputs.
- Response to monaural input does not require spontaneous activity from opposite side.
- Rate-coded ITD tuning curves convey more information than Vector-Strength-coded curves (despite/due to Vector Strength enhancement).
- Adjustments to tie parameters even more closely to the biology are in progress.



Computational Sensorimotor Systems Laboratory



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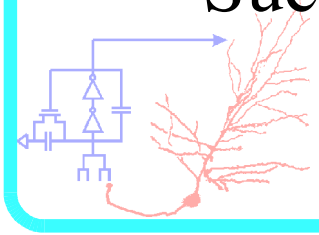

NIDCD/National Institutes of Health R03DC04382

Model Description

The model emulates an array of neurons, each with an adjustable number of dendrites, a soma, and an axon with an axon hillock, a myelinated segment, and a node of Ranvier. Each section has an adjustable number of equipotential compartments. All geometric, electrical, and channel parameters are adjustable, as are the number of synapses/dendrite, the synaptic locations, and the distribution of synaptic locations. Channel types include potassium (high [~Kv3.1] and low voltage activated [~Kv1.1, 1.2] and delayed rectifier), sodium, and passive. Values were obtained from physiological studies of Nucleus Magnocellularis (NM) and NL. Voltage dependent channels are specified by Hodgkin-Huxley-like parameters. Each neuron in the array feeds into a single inhibitory neuron, which feeds back onto all neurons in the array.

The stimulus is a pure tone of adjustable frequency, with each neuron in the array receiving a different interaural phase difference (or contralateral monaural stimulus with variable ipsilateral spontaneous activity). More complex stimuli can be easily introduced.

The synapses fire with conductance proportional to an alpha-function, with adjustable time constant, peak conductance, and reversal potential. The excitatory synapses fire as individual Poisson processes, with probability rate given by a exponentiated sinusoid, with adjustable amplitude and vector strength. The inhibitory neuron is a simple integrate-and-fire neuron.

The implementation uses the program NEURON and has a graphical user interface for controlling parameters and running the model. There is a real-time display of data and analysis including: membrane potential at multiple locations, the two stimuli, synaptic firings, spike counts, period histograms of synaptic firings and action potentials, and their vector strengths.