Biophysical Model Of Coincidence Detection In Nucleus Laminaris Neurons

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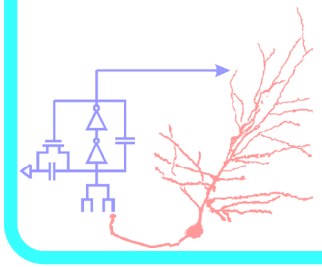

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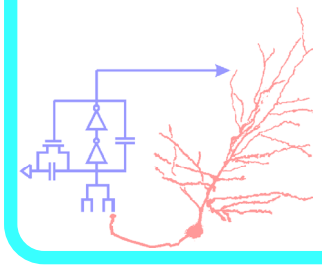
Computational Sensorimotor Systems Laboratory

Introduction

- Sound localization requires the computation of interaural time differences (ITDs) for frequencies below a few kHz. This is performed by binaural cells in the avian Nucleus Laminaris (NL), and its mammalian homologue, the Medial Superior Olive (MSO).
- An "ITD discriminator" 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.
- A biophysical model is constructed, using the program NEURON, to examine how NL neurons detect and report ITDs, their mechanisms and their limitations. It is based primarily on physiology and anatomy of the chicken.
- Two versions are presented here: one with reasonable coincidence detection/ITD discrimination, and the other, still work in progress, with data tied to chick as closely as possible.



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 dendritic 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.

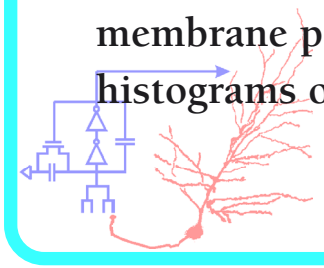
Model Description

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.



NEURON Panels

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

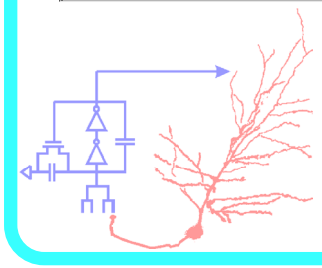
Length [Soma] (um)	15
Diameter [Soma] (um)	15
Ax. Resist. [Soma] (ohm cm)	200
gK LVA_m [Soma] (S/cm^2)	0.003
gK HVA_m [Soma] (S/cm^2)	0.03
gLeak [Soma] (S/cm^2)	0.00028
gNa_m [Soma] (S/cm^2)	0
gKHH_m [Soma] (S/cm^2)	0
# Compartments [Soma]	5

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 gu
objref gpi          // global constants & utilities
objref gp           // global parameter info
objref gr           // global parameters
objref go           // global run variables & procedures
objref cvode        // global output
                                        // 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
```

~7500 lines/100 pages of NEURON code

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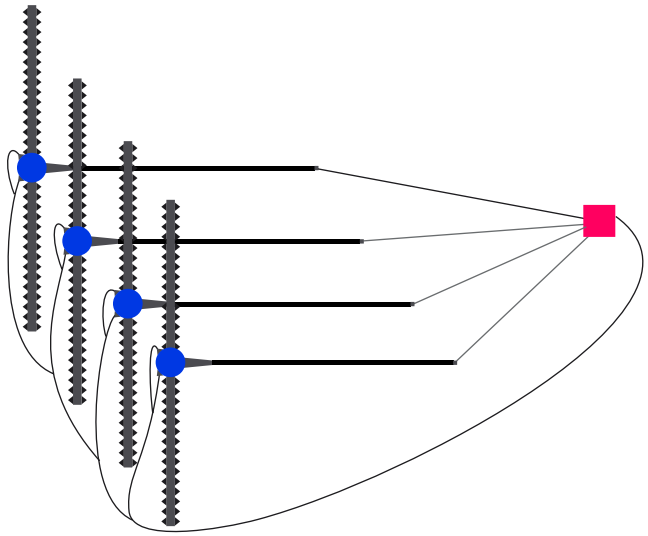
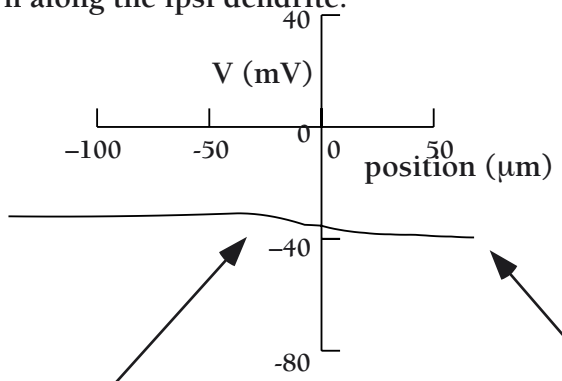
Geometry & Connectivity

A typical model cell has 2 - 24 dendrites, each 20 - 700 mm long and 2 - 4 mm in diameter, a spherical soma of diameter 15 mm, and an axon. Each dendrite has 1 - 50 excitatory synapses. The axon has an axon hillock, a segment with myelination, and a node of Ranvier. The output feeds into an integrate-and-fire inhibitory cell which feeds back to all cells in the array. Every cell in the array receives the same stimulus except for varying interaural phase differences

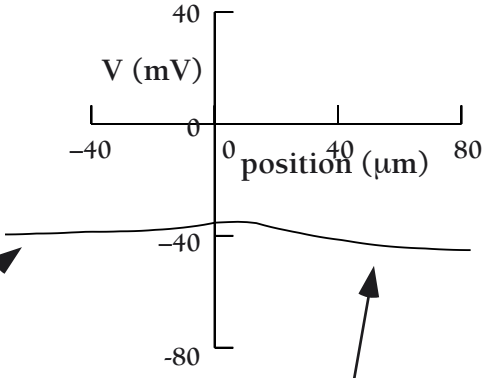


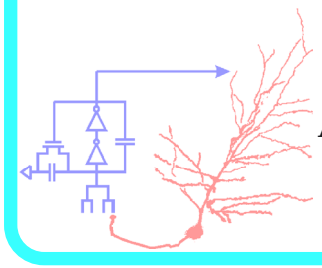
Spatial intracellular potential plots

Position down the axon, through the soma, and down along the ipsi dendrite.



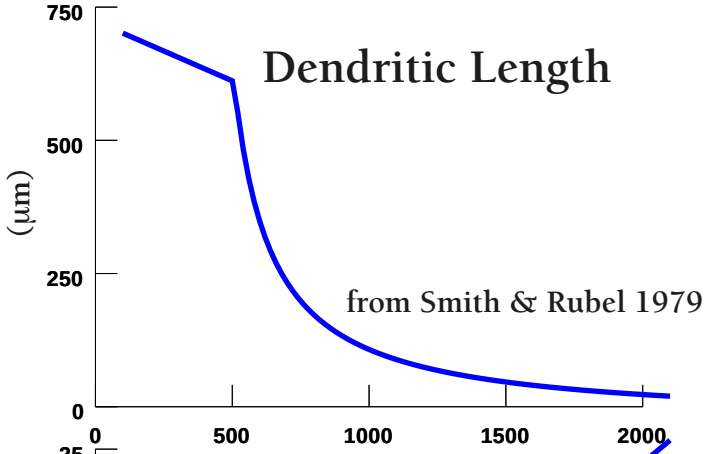
The potential up the ipsi dendrite, through the soma, and down along the contra dendrite.

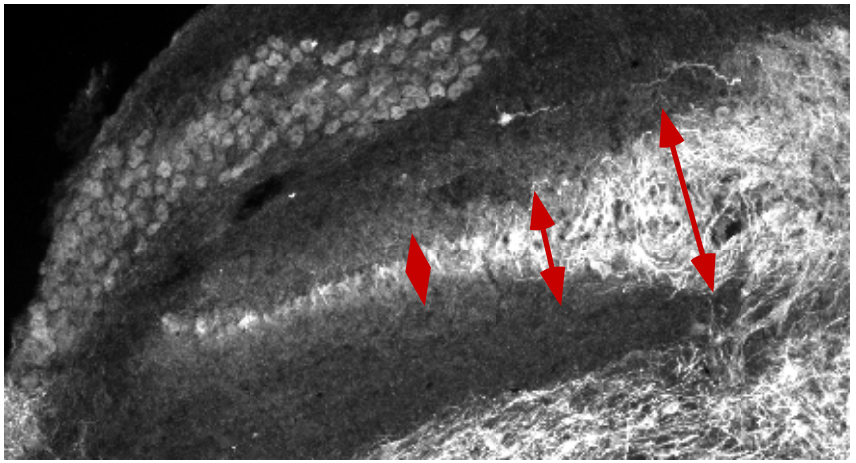




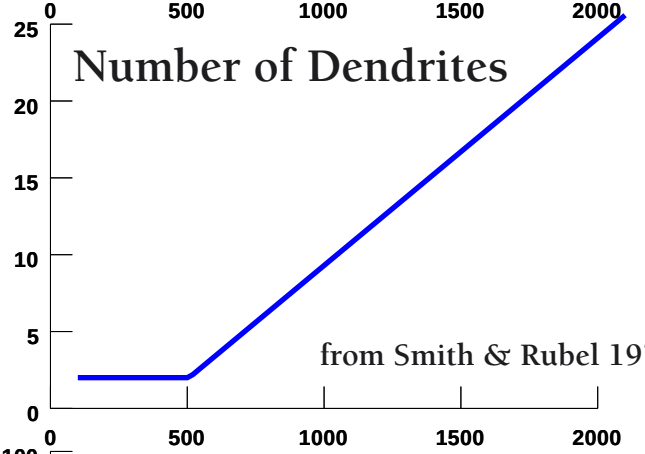
Axon hillock initiating spike due to ipsilateral current surge, despite contralateral current drain

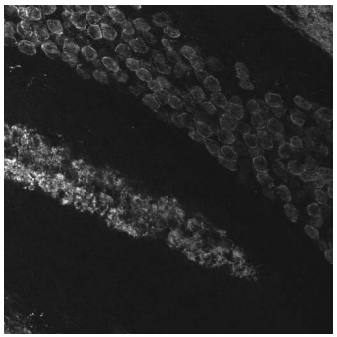
Tonotopic Gradients



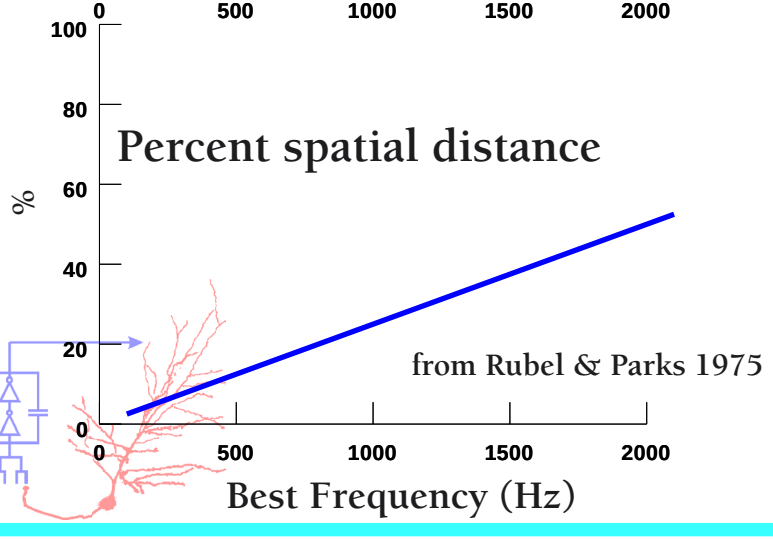


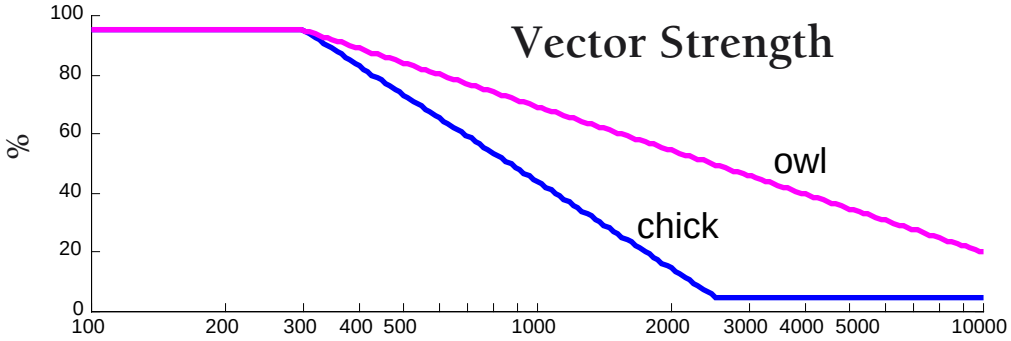
Transverse section through chicken brainstem labels both NM and NL, and shows the tonotopic decrease in dendritic length with increasing best frequency in NL [Microtubule associated protein (MAP2. FITC) immunoreactivity]





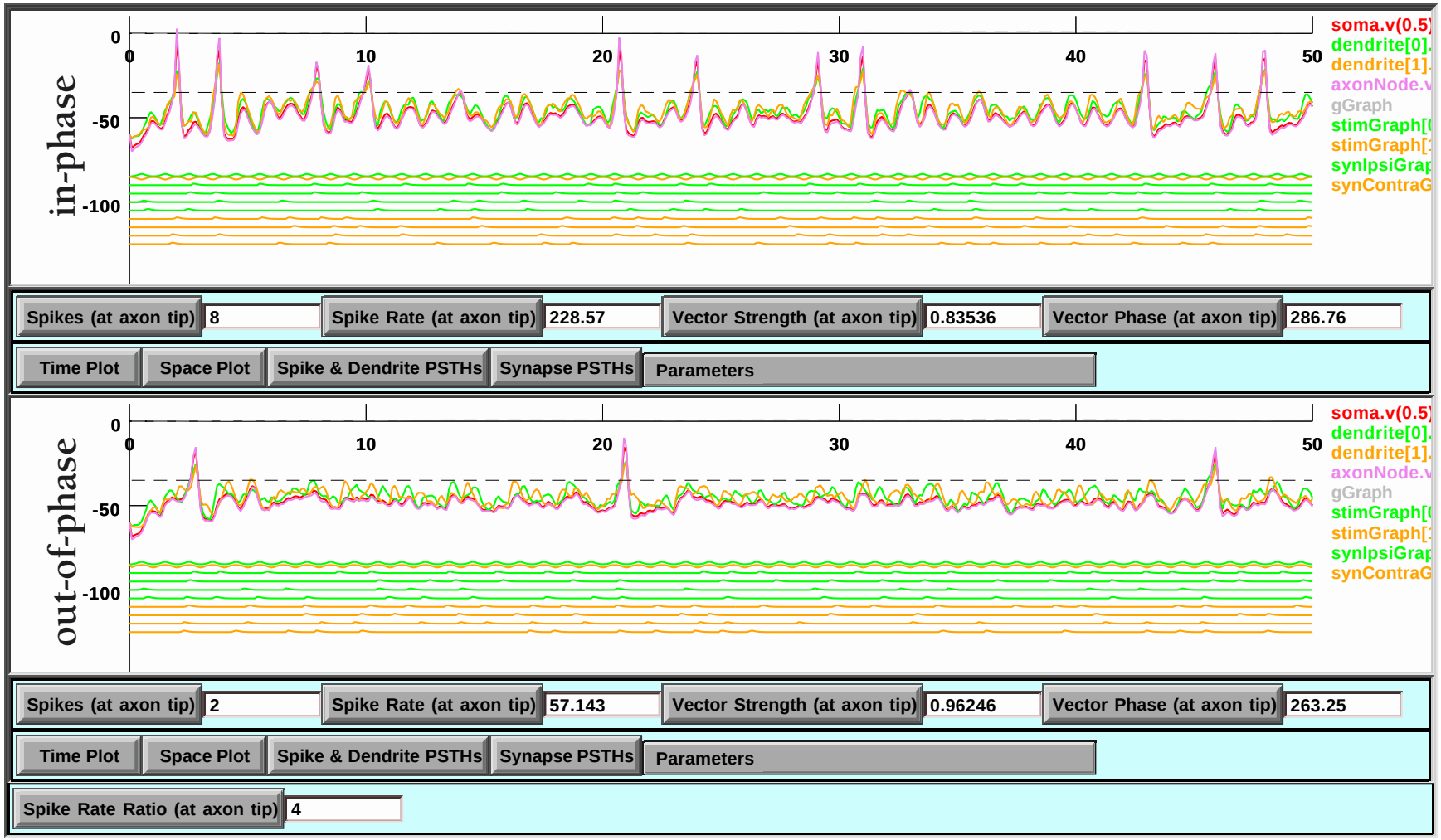
Oblique section through chicken brainstem displays an approximately isofrequency slab in chick NL. Note that the dendritic length is approximately constant.

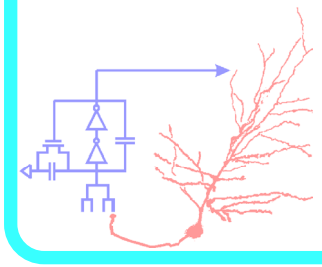




from Köppl, 1997, Warchol & Dallos, 1990.

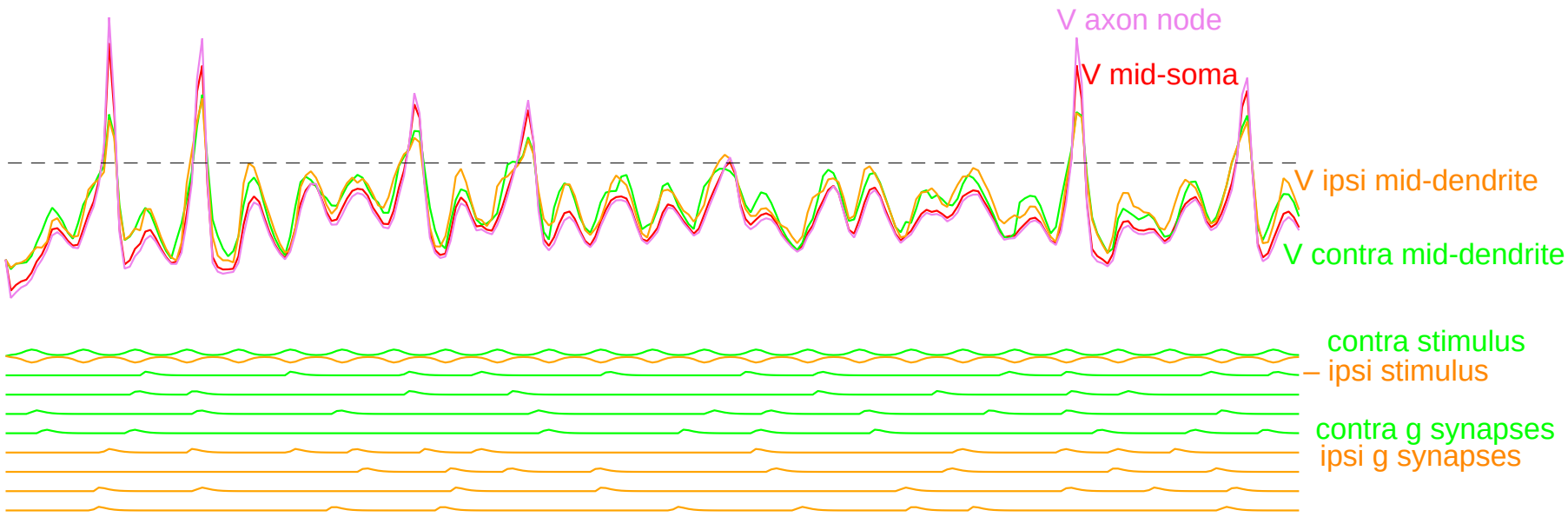
Voltage, Conductance, Inputs





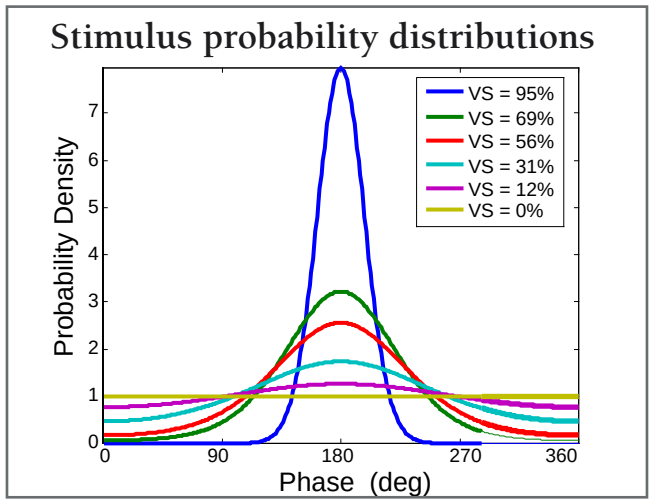
A pair of cells receives the same stimulus probability distributions (here, f =1 kHz). The top receives its inputs binaurally in-phase, and the bottom out-of-phase.

Voltage, Conductance, Inputs

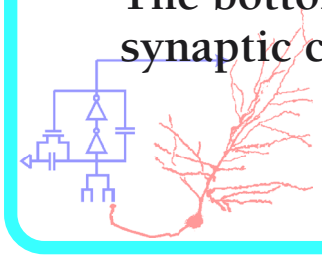


Red tracks the intracellular potential in mid-soma, magenta at the axon tip.

Directly beneath are the pair of presynaptic stimulus probability distributions. See figure to right for other examples of stimulus probability distributions.



The bottom 8 curves of each graph show realized synaptic currents (note spread from Poisson process).

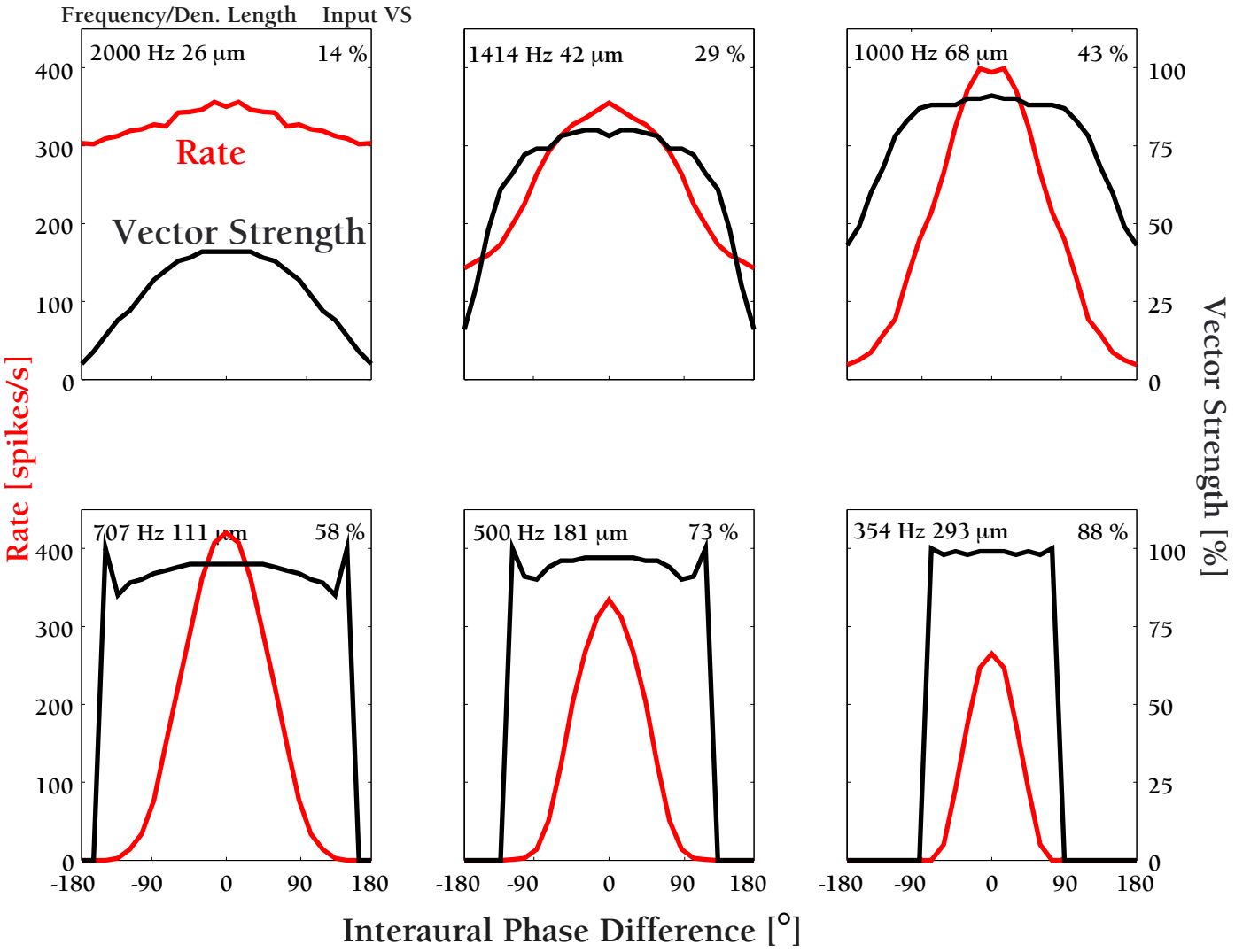


Phase Locking

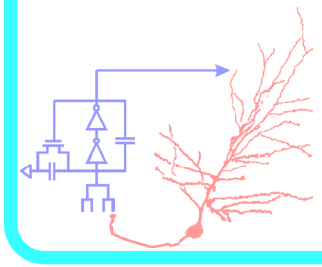
The responses to a 360° range of phase difference give ITD tuning curves (Interaural Phase Difference + frequency gives ITD)

Rate coding and vector-strength coding give two separate ITD tuning curves.

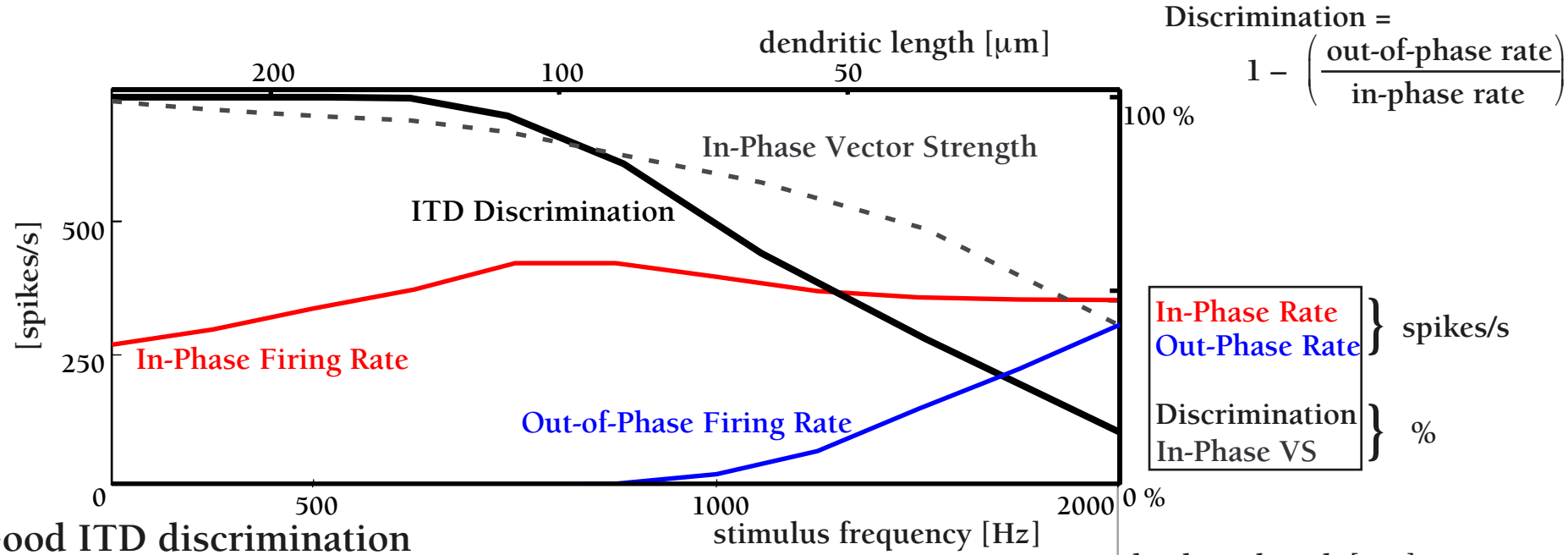
The "rate" ITD curves are more sharply tuned than the "vector-strength" ITD curves (note that the vector strength is not reliable when the firing rate is low).



These results show 1) an over-enhancement of output VS over the input VS, making the VS-coded ITD tuning curves appear extra flat, and 2) an over-suppression of rates for nearly out-of-phase inputs, which makes the rate-coded ITD tuning curves look extra sharp (compared to experiment)

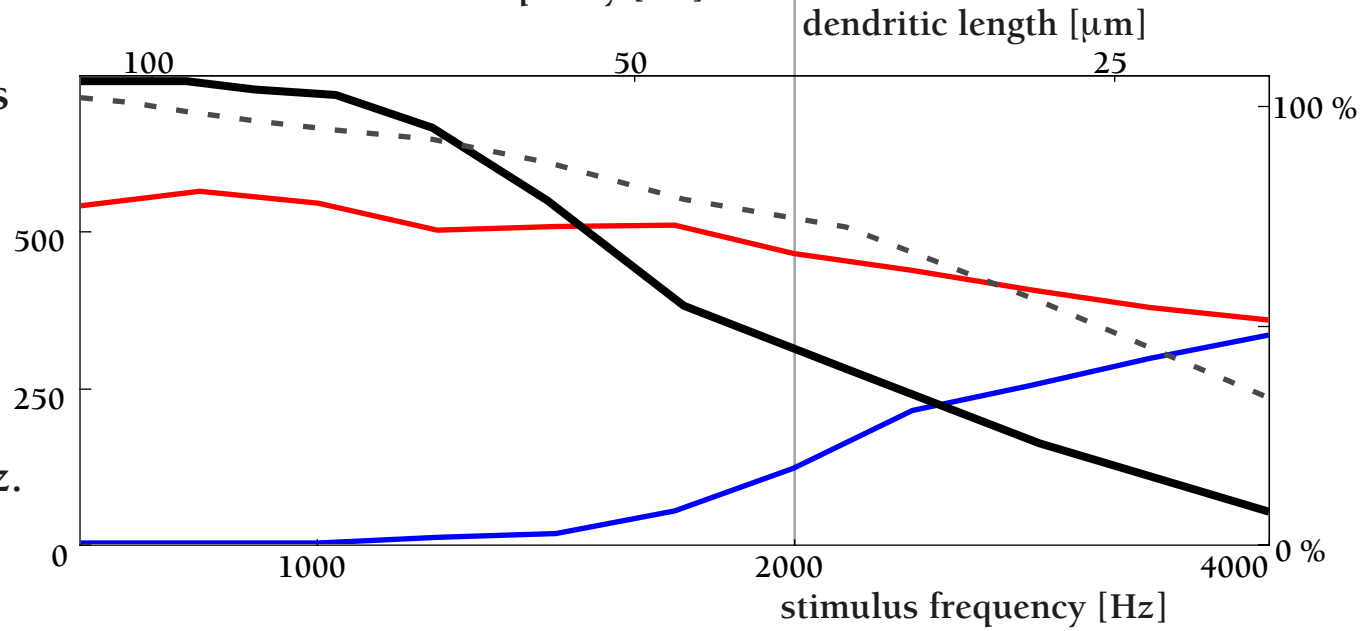


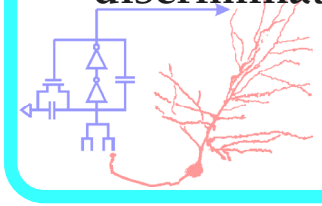
ITD Discrimination



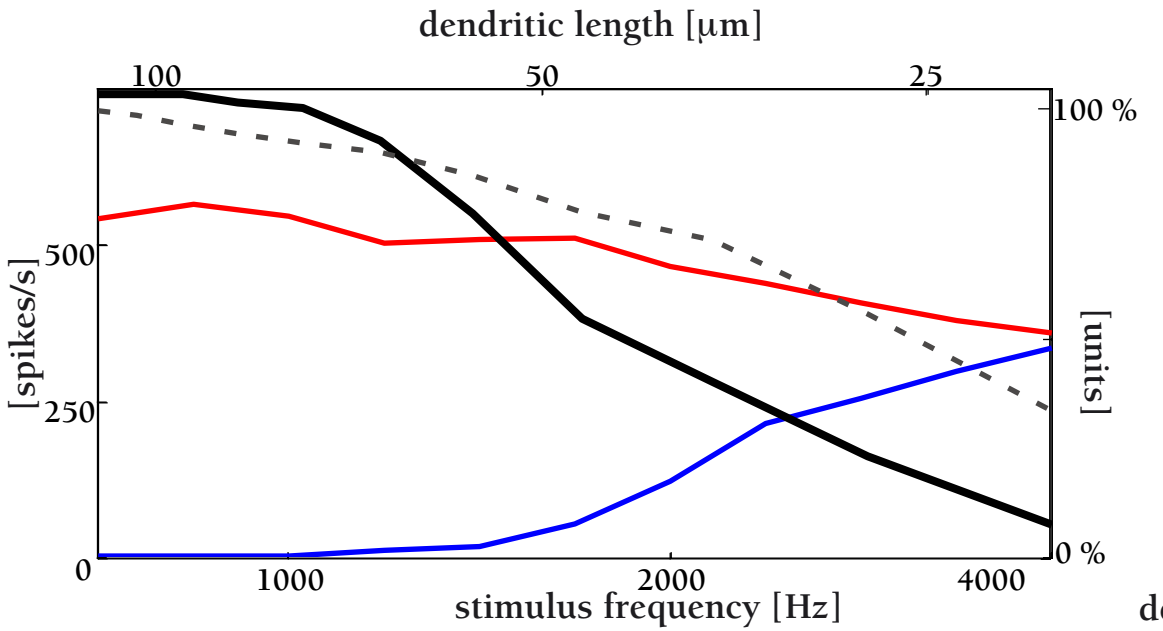
Good ITD discrimination (high ratio) until ~2 kHz. Sharp phase tuning appears as ceiling effect on ITD Discrimination index

At right, keeping all parameters the same, but using Barn Owl vector strength gives good ITD discrimination until ~4 kHz.





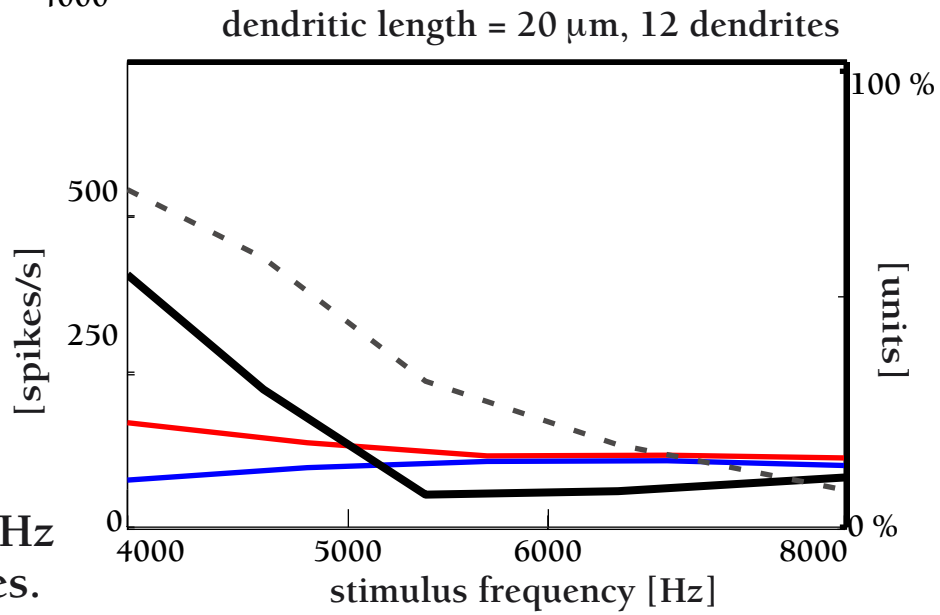
ITD Discrimination—Barn Owl



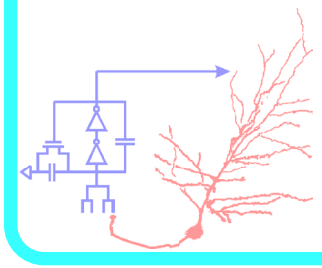
In-Phase Rate
Out-Phase Rate

Discrimination
In-Phase VS

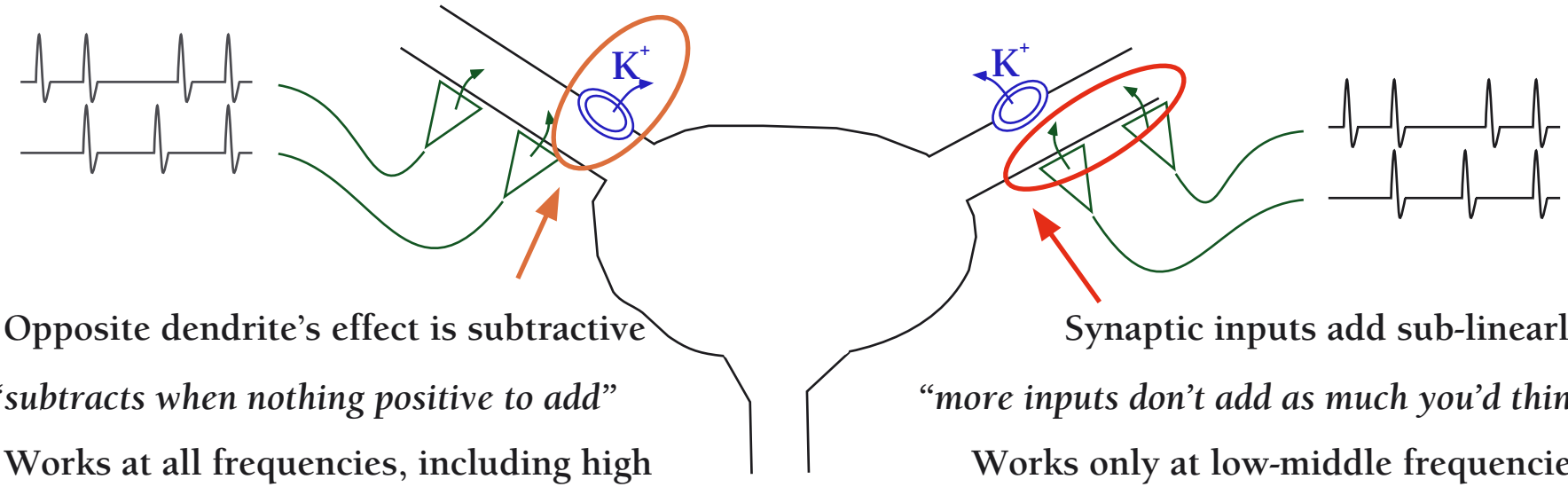
The top plot shows ITD discrimination using chick-like parameters, but merely increasing the vector-strength to that of the barn owl.



The right plot shows ITD discrimination going up to ~6 kHz by simply adding more dendrites.



Non-Linearities



Opposite dendrite's effect is subtractive

"subtracts when nothing positive to add"

Works at all frequencies, including high

New result

Synaptic inputs add sub-linearly

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

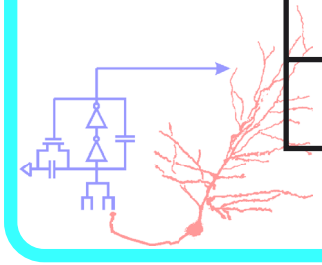
Works only at low-middle frequencies

Found by Agmon-Snir et al. 1998

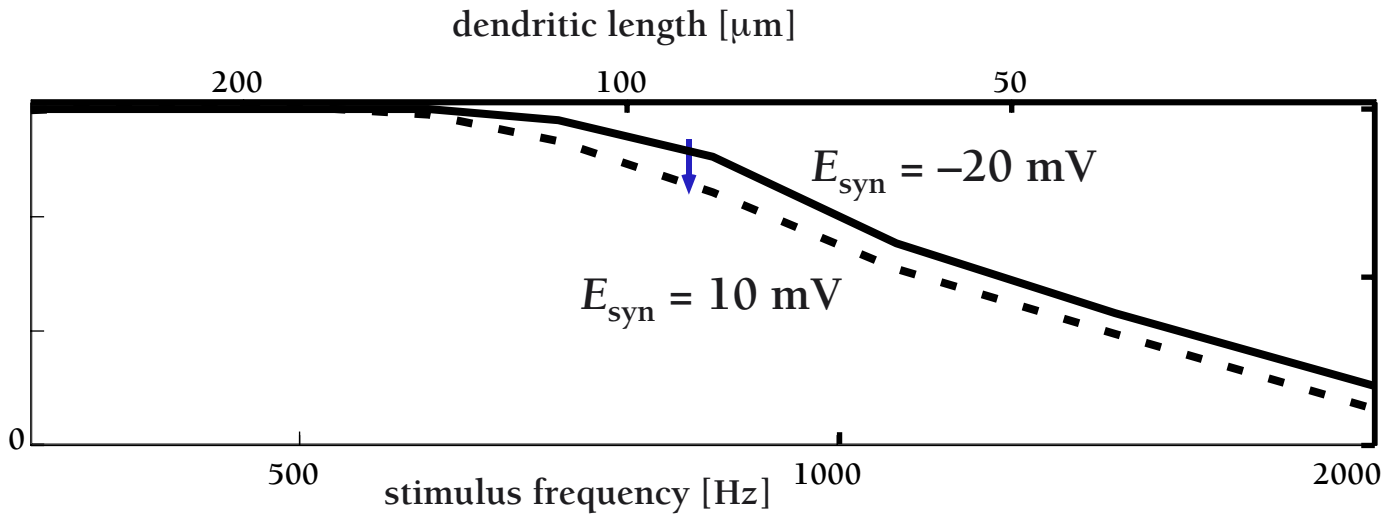
Both effects prevent many inputs from right side wrongly causing cell to fire without inputs from the left side.

Reduction in "false positives"

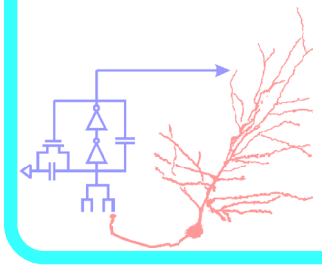
Firing Rates	with non-linearities	without non-linearities
In-Phase		
Out-of-Phase		too many false positives



Sub-Linearity Results



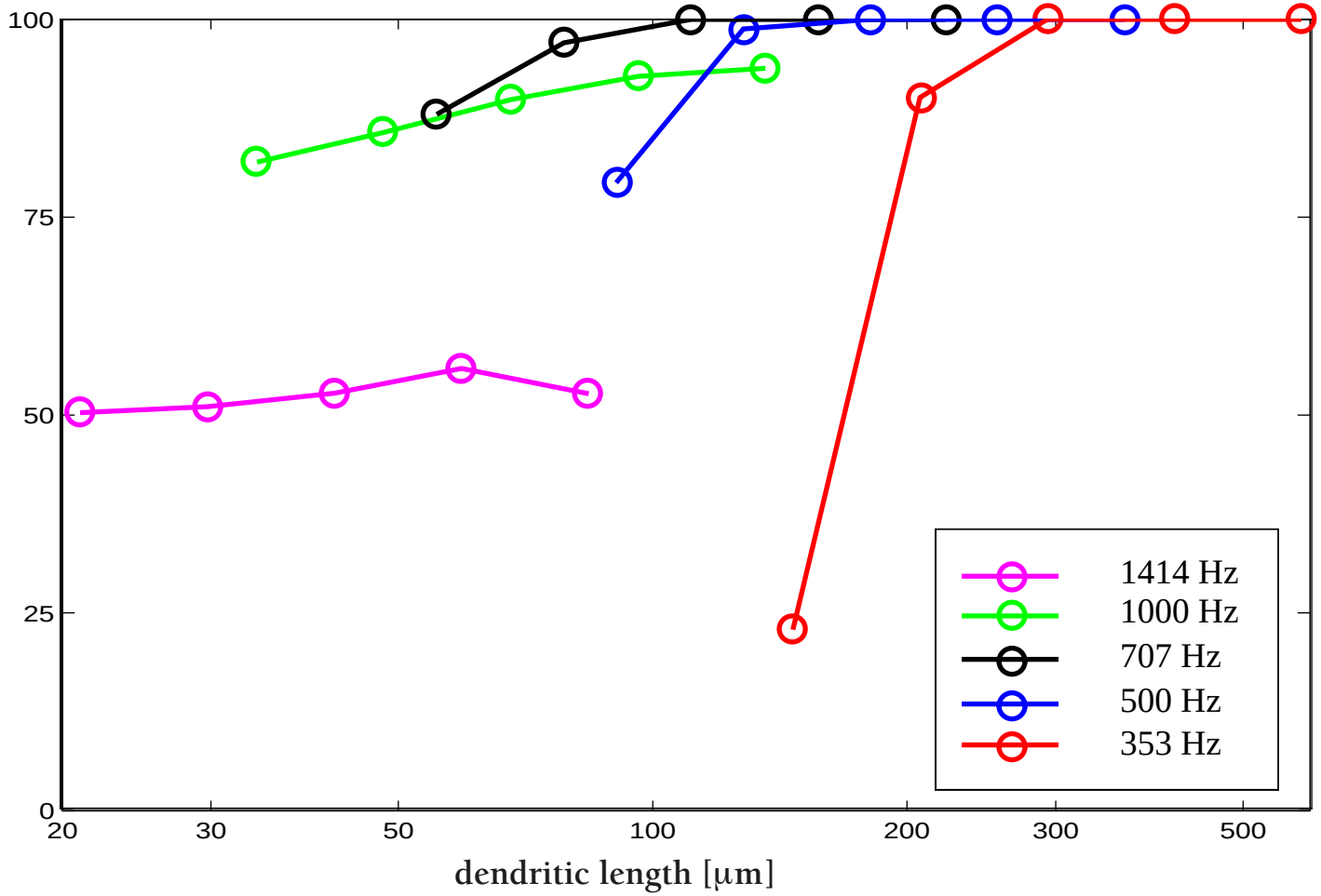
- Shifting the synaptic reversal potential upwards reduces the sub-linearity, worsening the ratio of in-phase/out-of-phase firing rates.

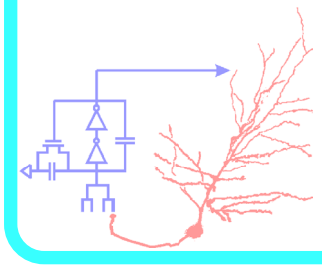


Dendritic Length

The Intra-dendritic sublinearity leads to an 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.

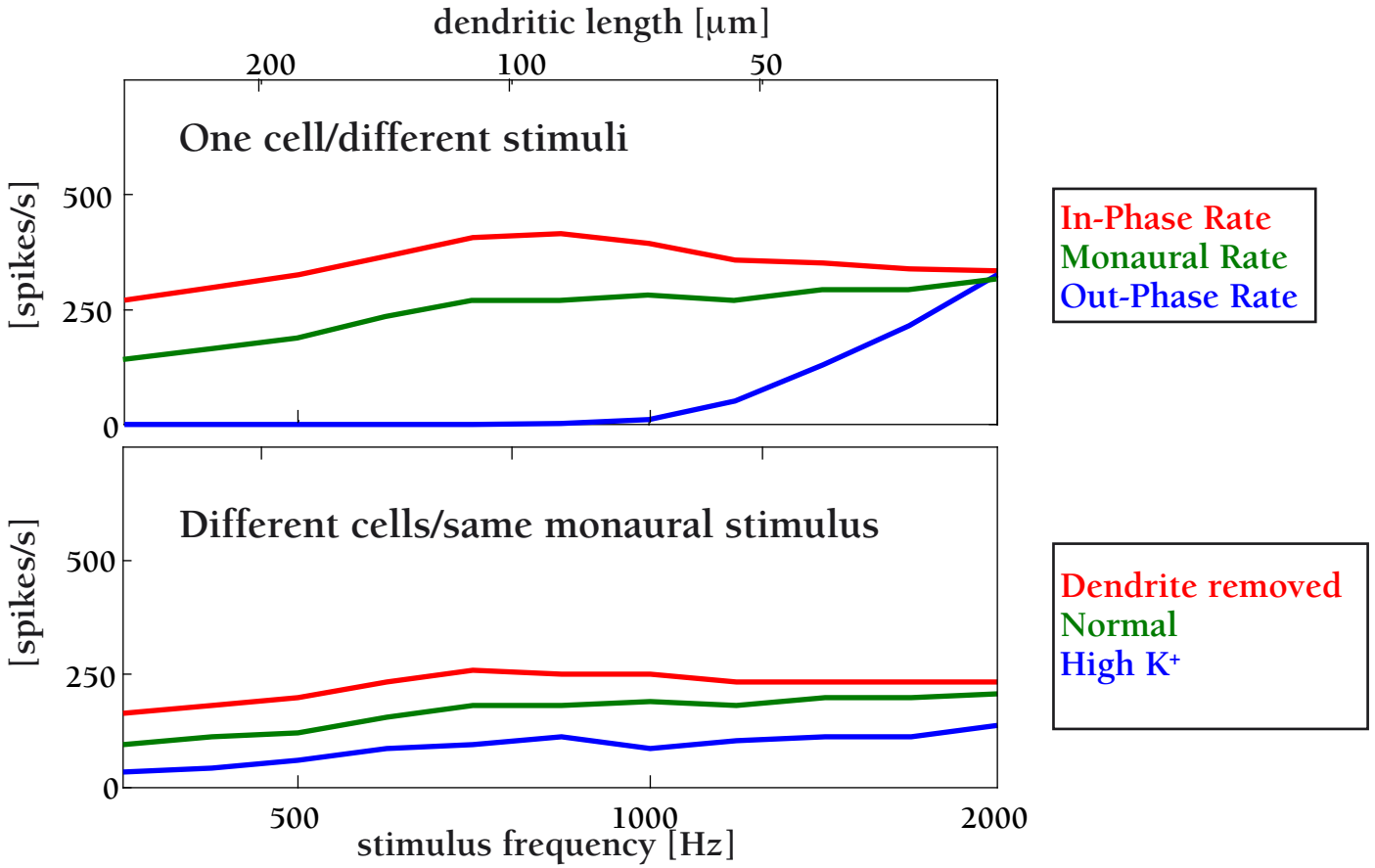




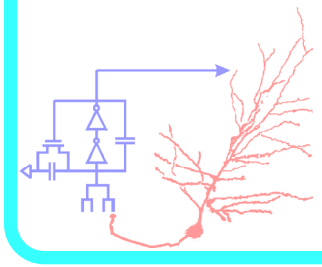
Subtraction Non-Linearity

The out-of-phase rate is suppressed relative to the monaural rate.

The opposite dendrite acts as a current sink.

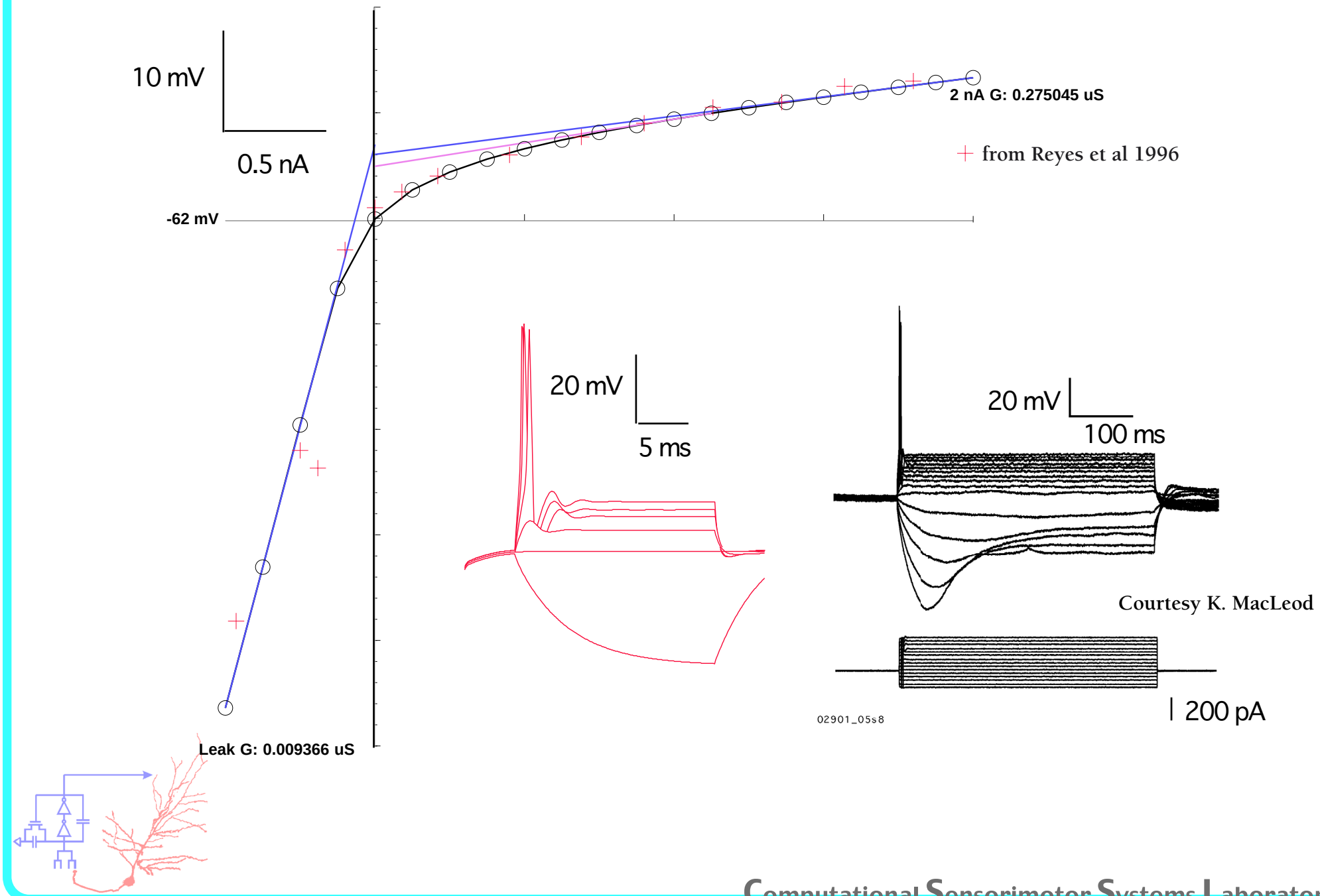


Note that the cells fire well with *no* stimulus on the opposite side. The cell is not just a coincidence detector, it is an ITD discriminator: it does not need spontaneous activity on the opposite side in order to fire.

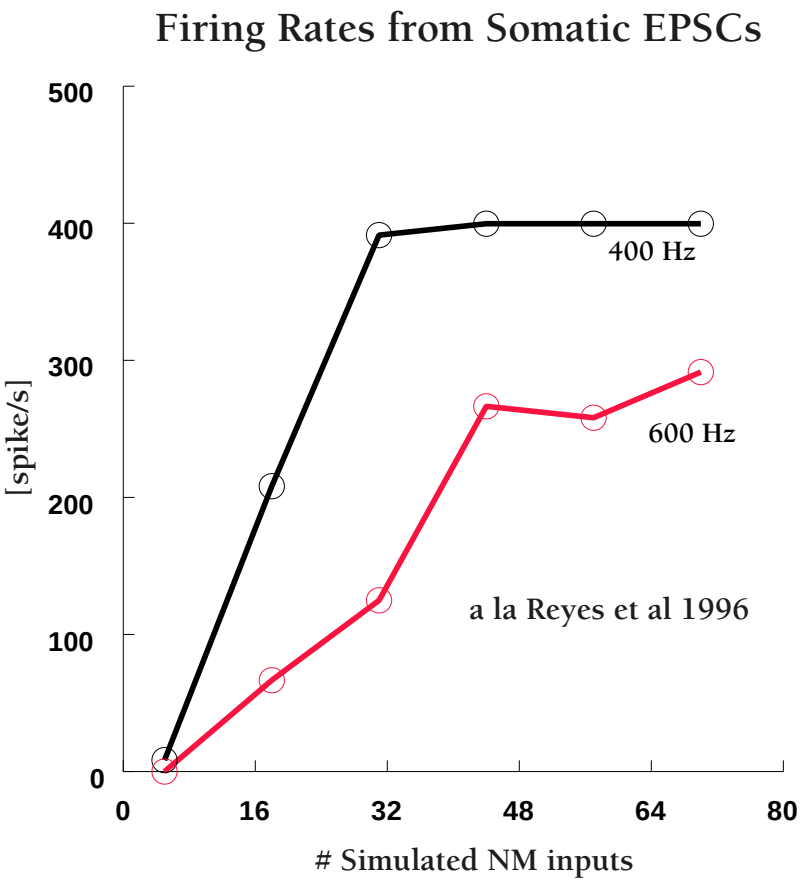


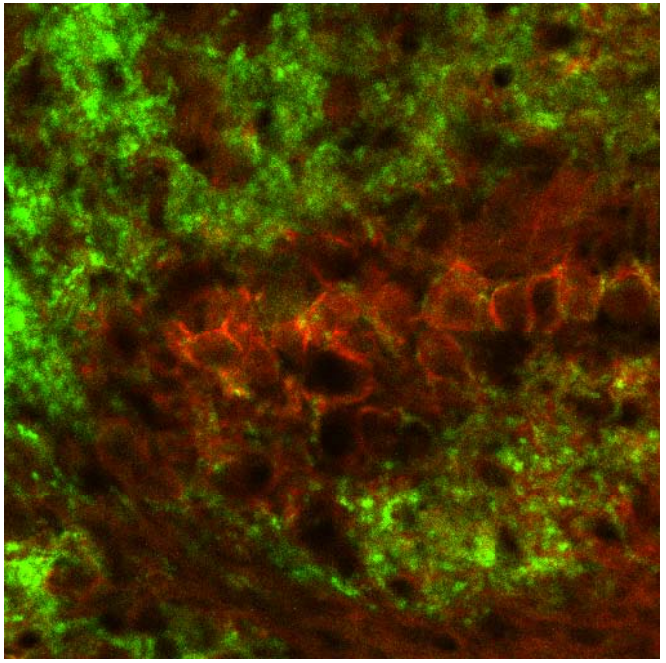
The effect is present at all frequencies.
(The meeting of in- and out- rates at ~ 2 kHz is a consequence of poorly phase-locked inputs.)

Estimating Model Parameters

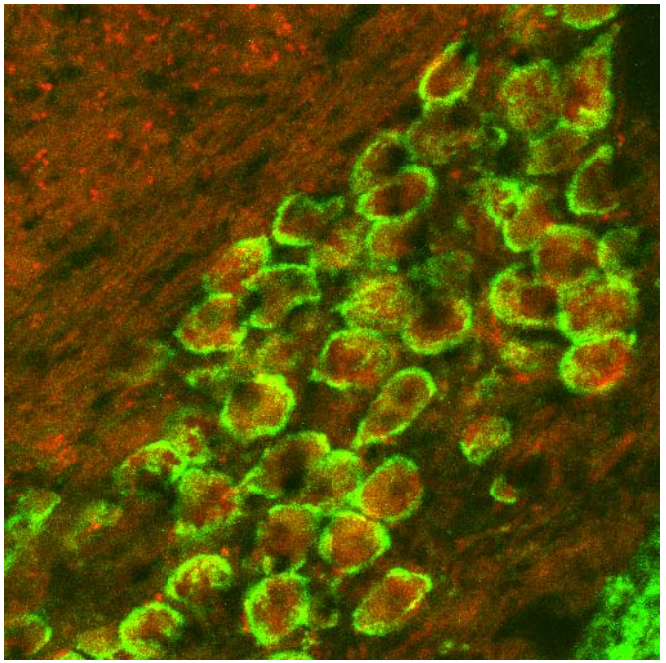


Estimating Model Parameters



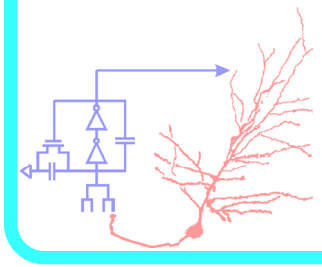


Kv3.1 immunoreactivity (red, CYC3) in the low BF region of NL in the chicken outlines the cell bodies and proximal dendrites of NL neurons. NM terminals in NL are delineated by staining with the synaptic vesicle marker (SV2, green FITC).



Parameshwaran et al 2001

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



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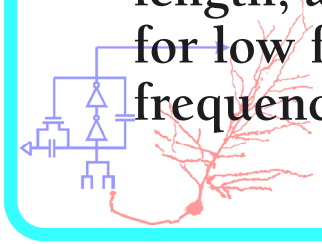
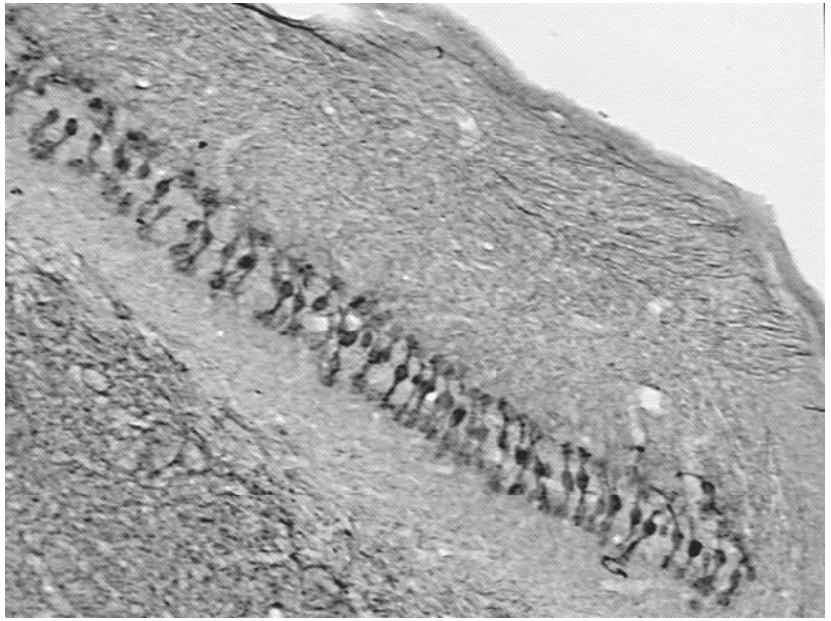
Abstract

A biophysically detailed model of avian brainstem Nucleus Laminaris (NL) neurons investigates the ability of a single neuron to detect when inputs from ipsilateral and contralateral Nucleus Magnocellularis (NM) are coincident. Coincidence detection, in concert with organized input delays, is sufficient to encode the interaural time differences necessary to localize sound sources. The model (written in NEURON) simulates an array of neurons, each with a soma, an axon, and an adjustable number of dendrites (each with multiple compartments), and with synapses of adjustable number, strength, and spatial distribution. Channels include K (high and low voltage activated, and delayed rectifier), Na (axon only), and leak. Neural inhibitory feedback is included. For in vivo emulations the stimulus is a binaural pure tone with adjustable frequency and interaural phase difference (or monaural stimulus with spontaneous activity). The phase-locking of NM inputs can be free or a function of stimulus frequency. Results from the model (both new and confirmations of old) include: active potassium channels increase coincidence detection at high frequencies; rate-coded output is more robust than vector-strength-coded output at distinguishing coincidences from partial coincidences; phase locking of output spikes is sharper than the phase locking of the synaptic inputs; there is an optimal dendritic number and length per stimulus frequency, dendritic length, and number of synapses; there is an optimal distribution of synapses for low frequencies; the most efficient dendritic length decreases with best frequency. Supported by: NIH R03DC04382 (JZS) & NIH DCD 00436 (CEC)



Emu
Nucleus Laminaris



Wednesday, Nov. 14, AM

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The Substrate For ITD Detection In
The Emu (Dromaius Novaehollandiae)

D. Soares*; K. MacLeod; C. E. Carr; J. Simon