Multi-Compartmental Modeling of Astrocytes

Gordon Erlebacher

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Research Group

- Evan Cresswell (Ms)
- Joel Tabak, (Univ. Exeter, UK)
- Nathan Crock (Ph.D.)
- James Schummers (Max Planck, FL)
- Monica Hildago (Max Planck, FL / Mexico)
- Gordon Erlebacher

Roadmap

- Motivation
- Biology (Neurons, Synapses, Astrocytes)
- Single point astrocyte model
- Multi-compartmental astrocyte model
- Results
- Future extensions

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James Schummers, PhD

Research Group Leader
Cellular Organization of Cortical Circuit Function

One Max Planck Way
Jupiter, FL 33458
(561) 972-9110

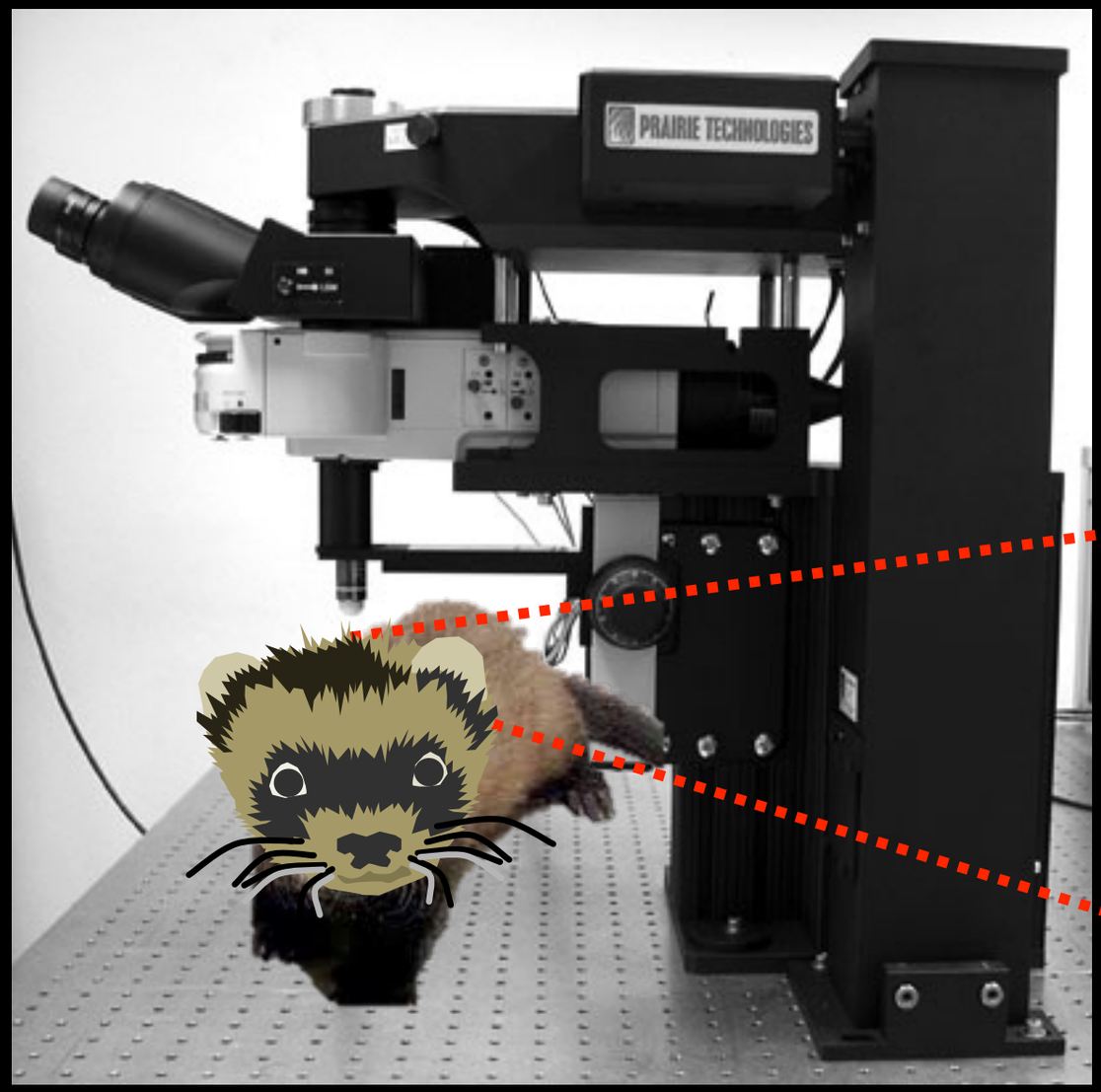
james.schummers@maxplanckflorida.org

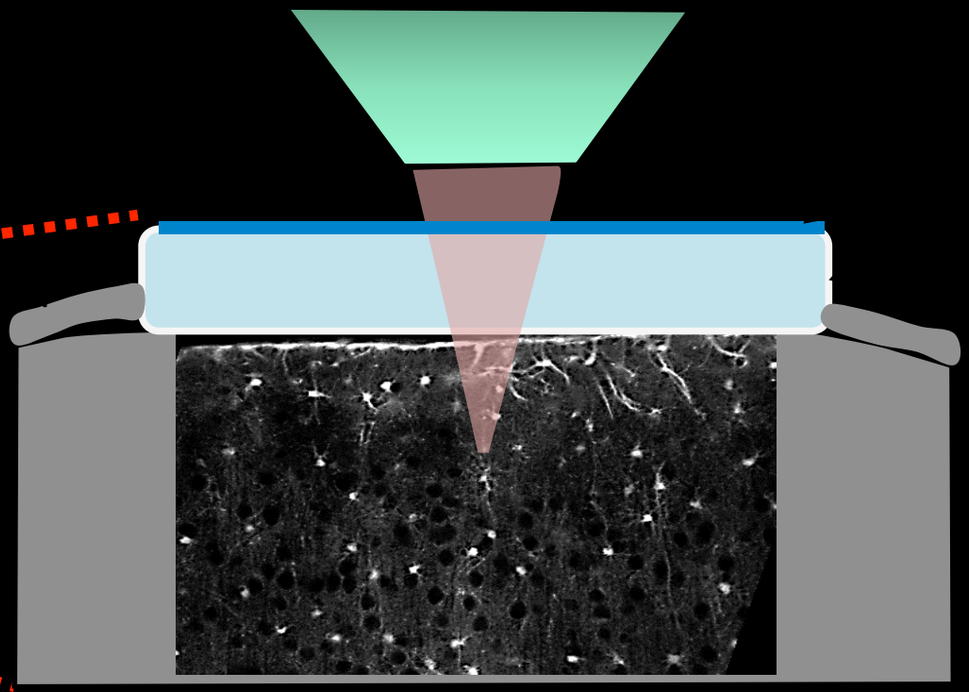
Researcher Bio

Dr. James Schummers was named an independent Research Group Leader at the Max Planck Florida Institute for Neuroscience in June 2010 and heads the Cellular Organization of Cortical Circuit Function research group. Dr. Schummers received his bachelor's degree in Neuroscience from Oberlin College in Oberlin, OH, where he studied the effects of the neurotransmitter neuropeptide-Y on long-term potentiation (LTP) in the hippocampus. He then moved to Denver CO, where he studied the effects of alcohol on LTP in the Department of Pharmacology at the University of Colorado Health Science Center. He received a PhD in Systems Neuroscience at the Massachusetts Institute of Technology with the support of a Howard Hughes Pre-Doctoral Fellowship. His thesis work combined intracellular and extracellular single neuron recordings with optical imaging approaches to study the integration of synaptic inputs in the context of visual processing. His postdoctoral work, also at MIT, focused on single-cell resolution imaging to study the response properties of different classes of cells, including both neurons and astrocytes, in the visual cortex.

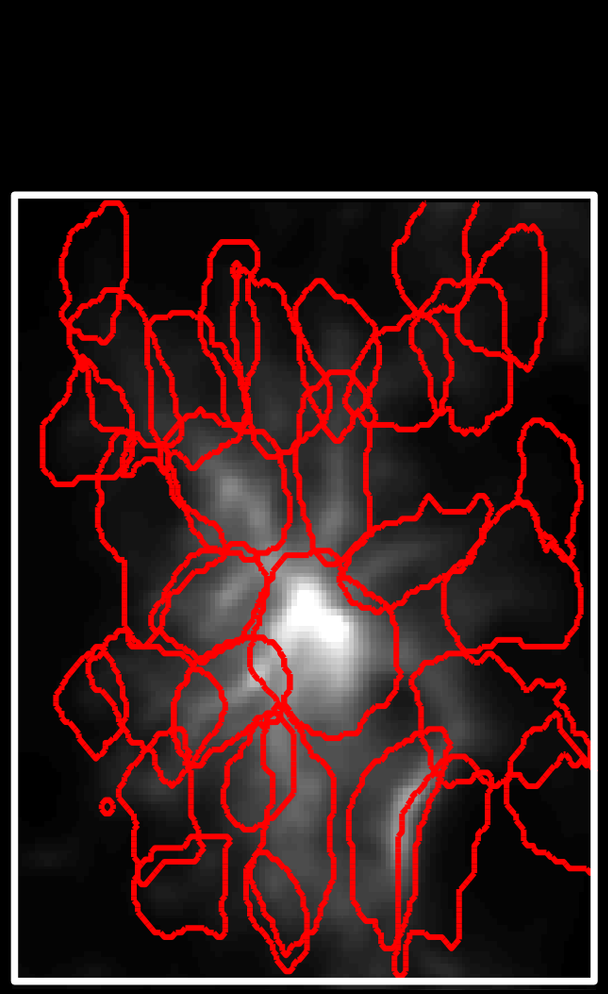
In vivo 2-photon imaging in ferret visual cortex

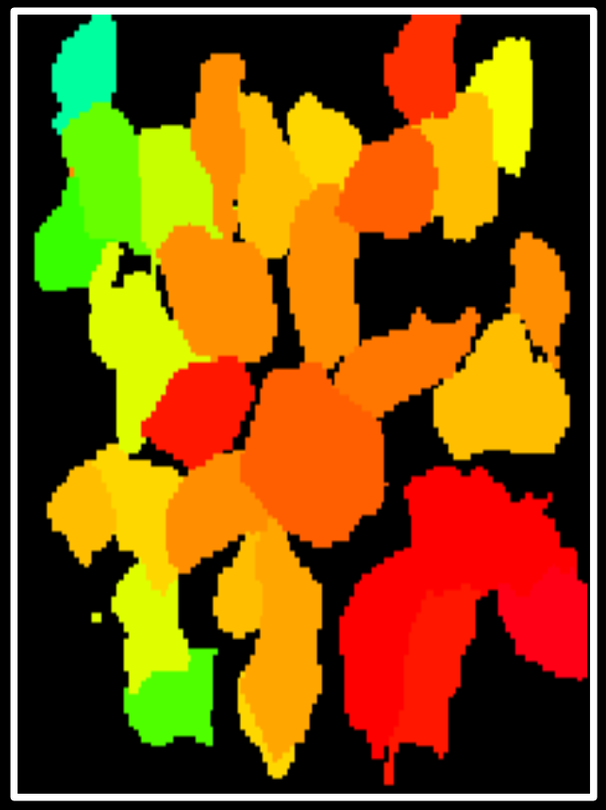
- in vivo two photon imaging
- Lightly anesthetized (isoflurane)
- Adult ferrets

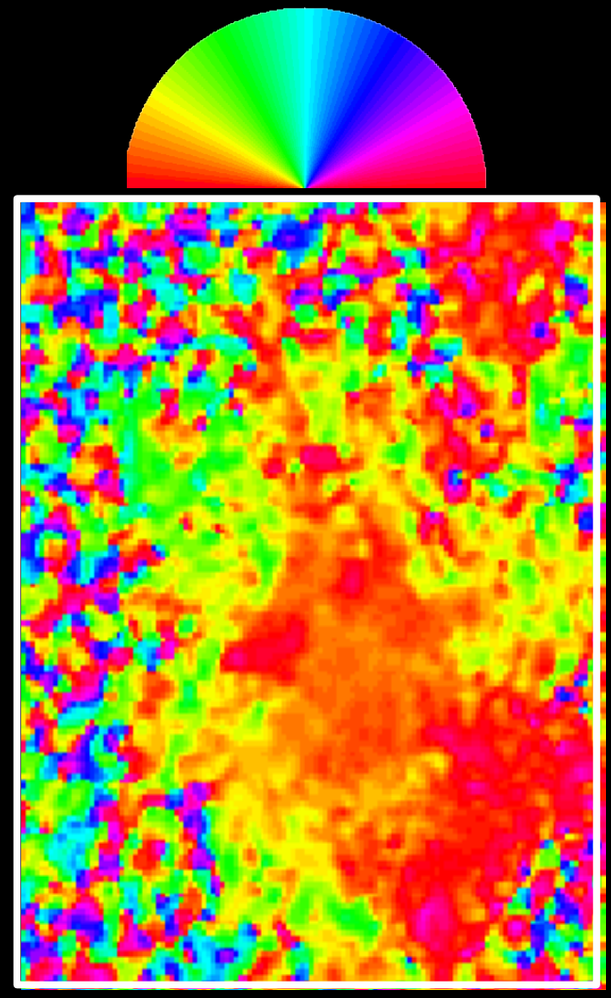




Orientation tuning in subcellular domains



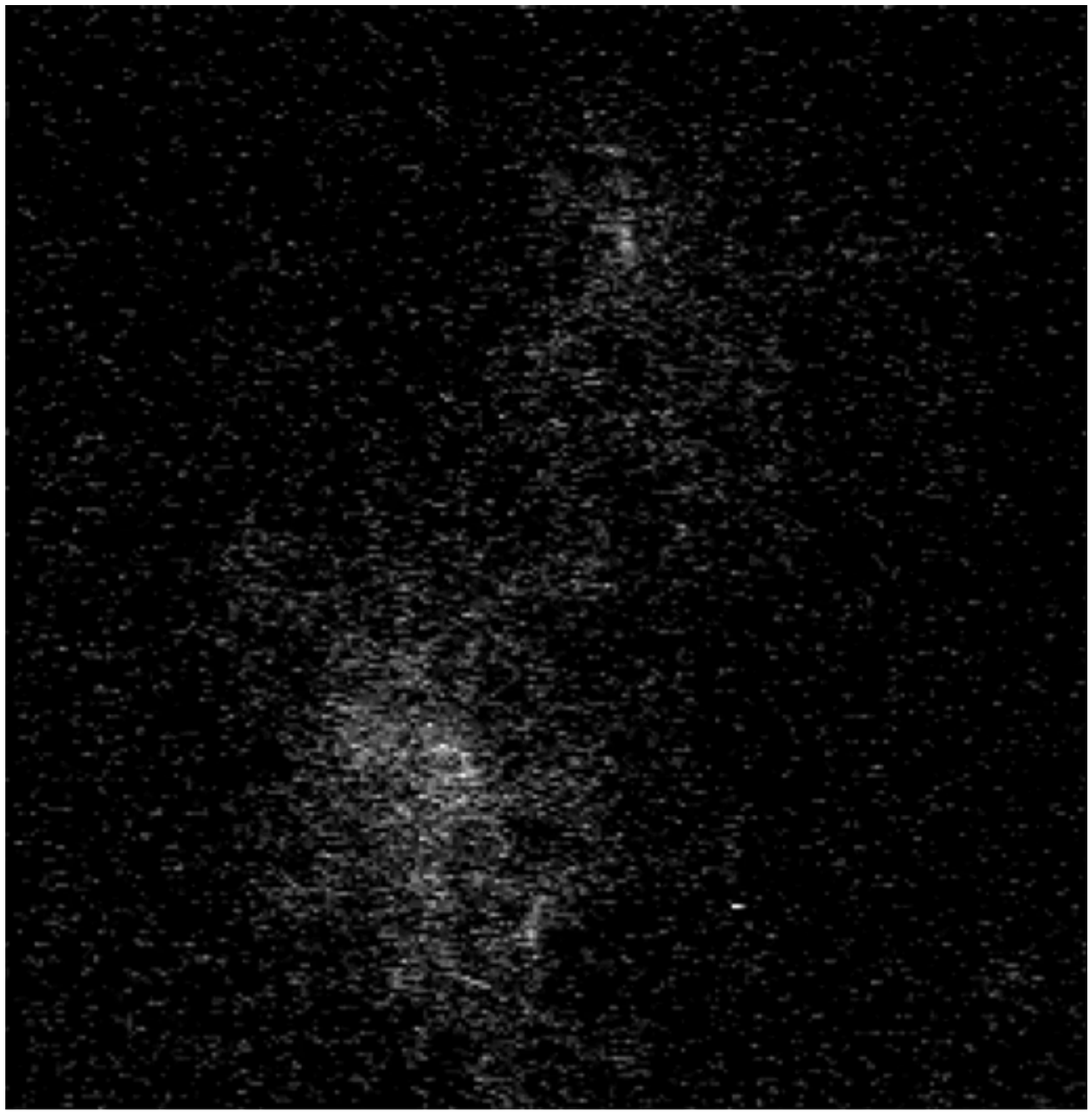


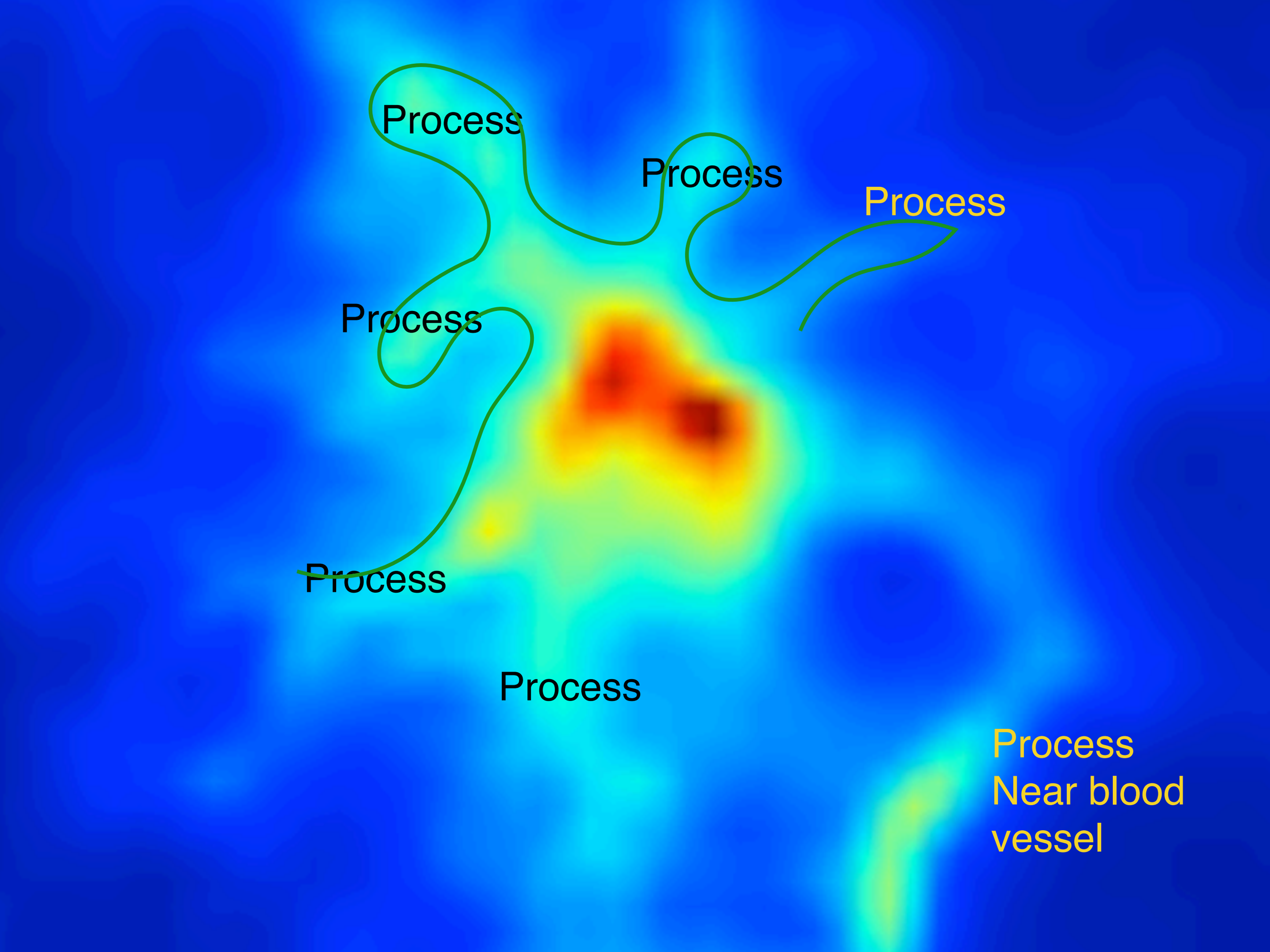


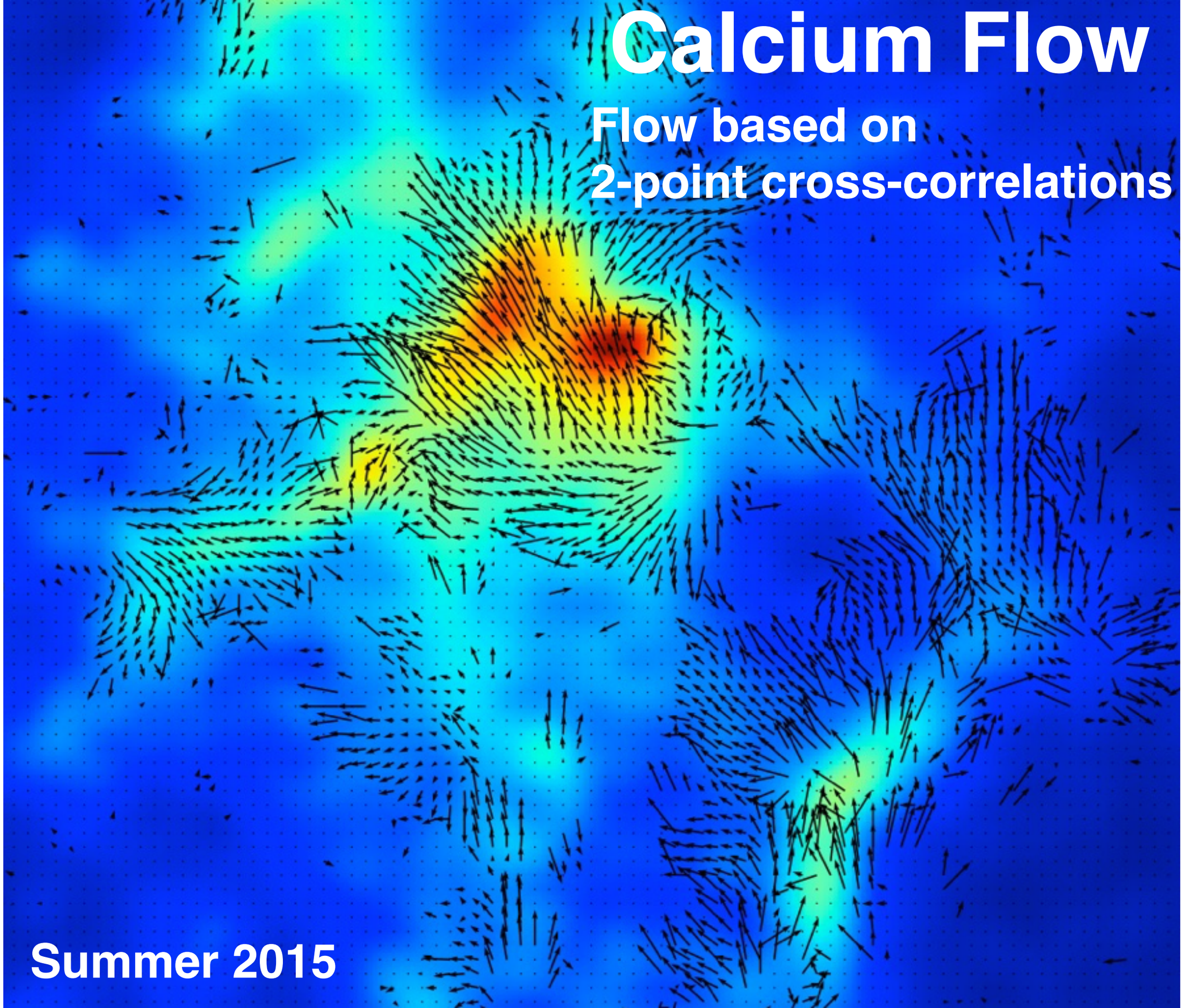
Each sub-domain has similar orientation tuning, with quantitative differences

Does this suggest that they are responding to distinct neural activity?

4Hz Animation: Raw Data, 256x256




Process
Process
Process
Process
Process
Process
Process
Near blood
vessel

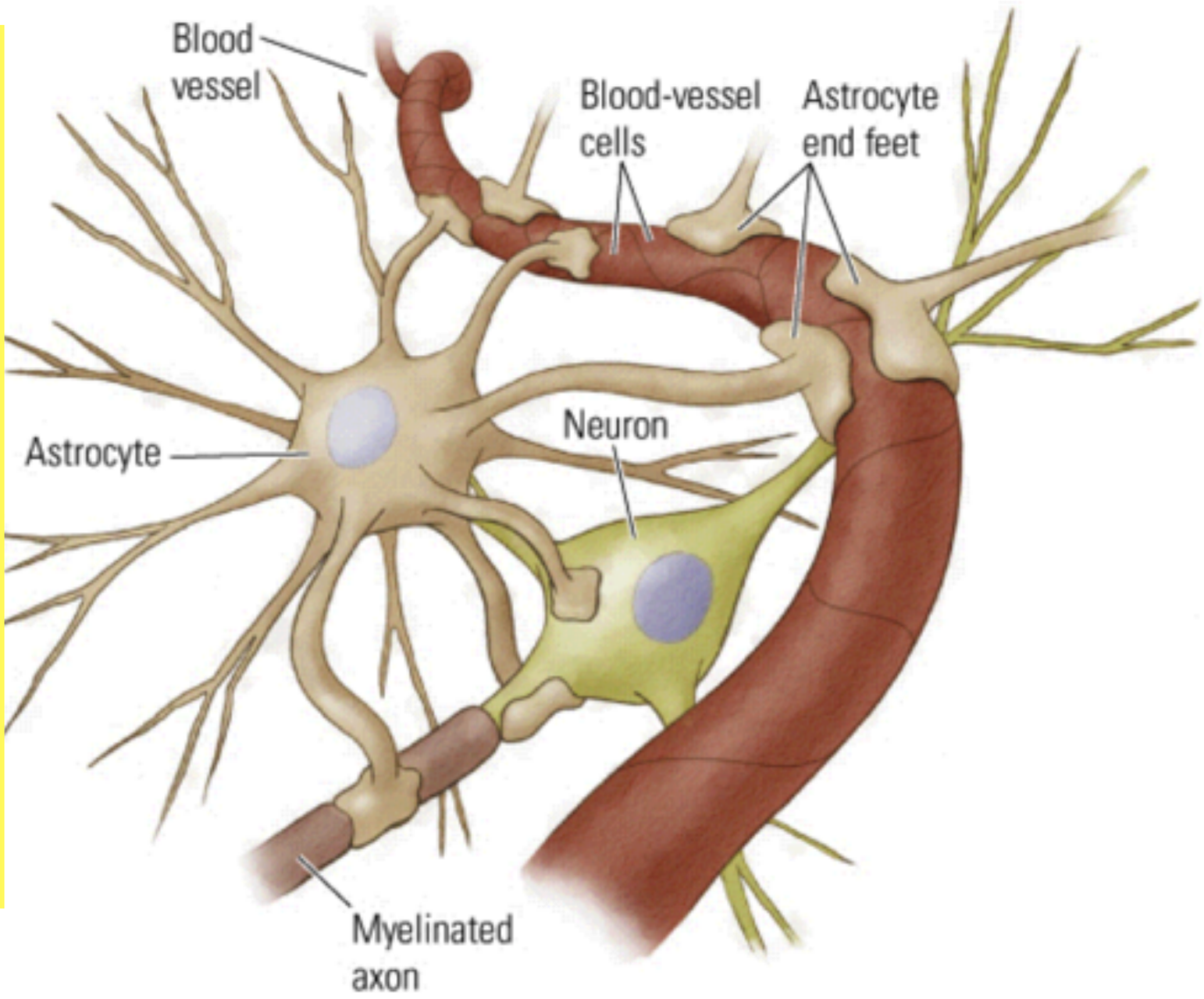

Calcium Flow
Flow based on
2-point cross-correlations
Summer 2015

Some Biology

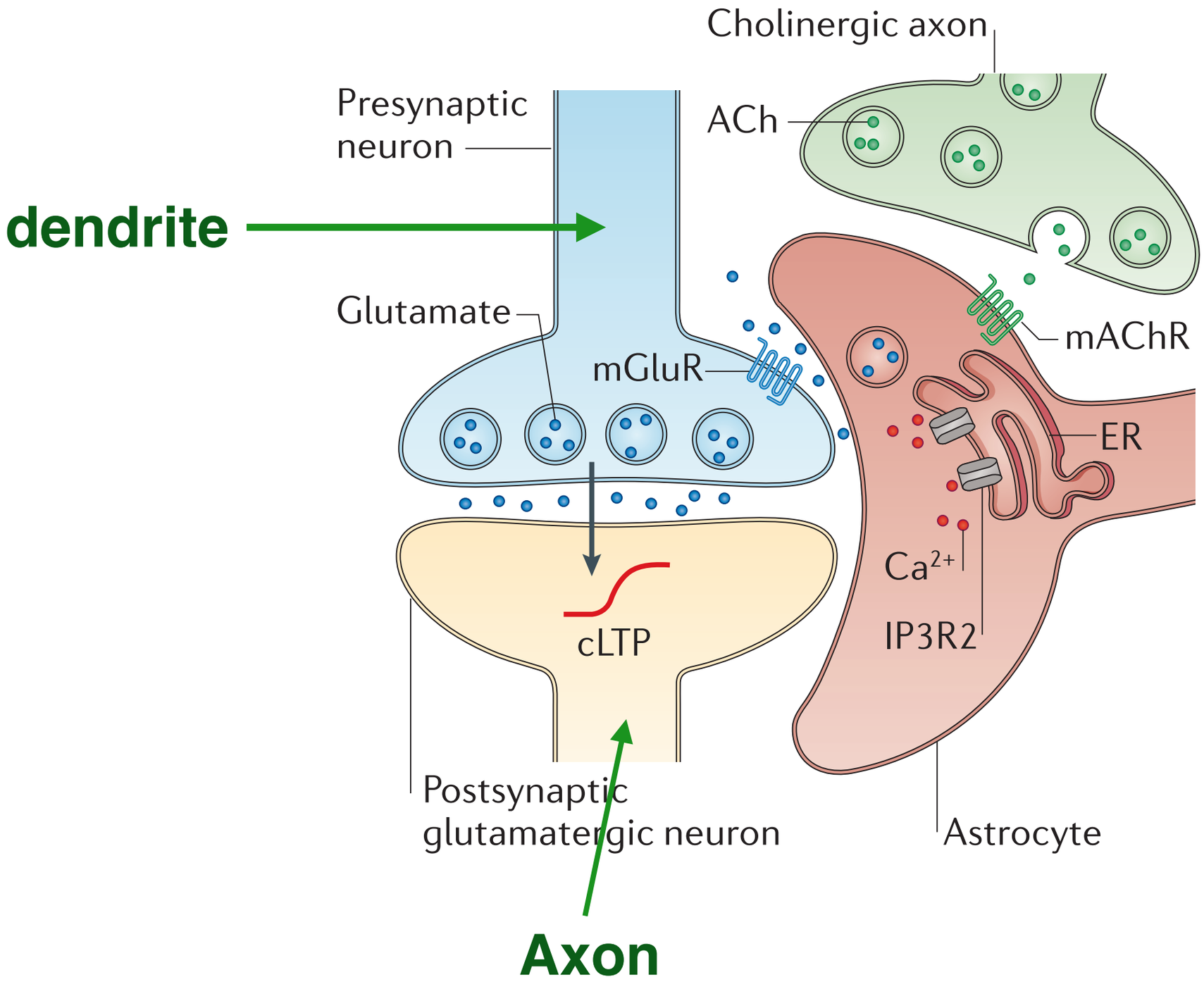
- Neurons
- Synapses
- Astrocytes
  - receptors, channels, ER
  - glutamate (neuro-transmitter)
  - IP3

Astrocytes

- Astrocytes have many functions
  - provide nutrients to neurons
  - regulate calcium flow
  - play a role in various medical disorders (e.g. epilepsy)
  - modulate synaptic strength of neurons



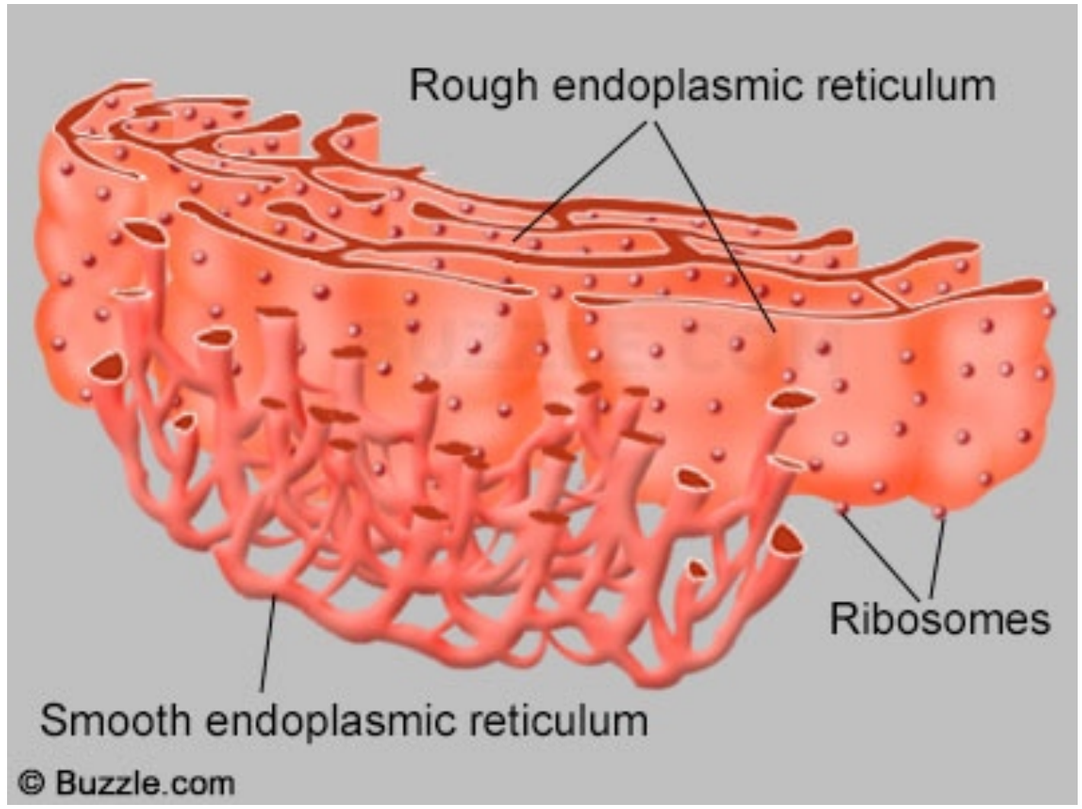
Tripartite Configuration



Astrocyte Ca2+ signalling- an unexpected complexity_2014_volterra_opinion.pdf

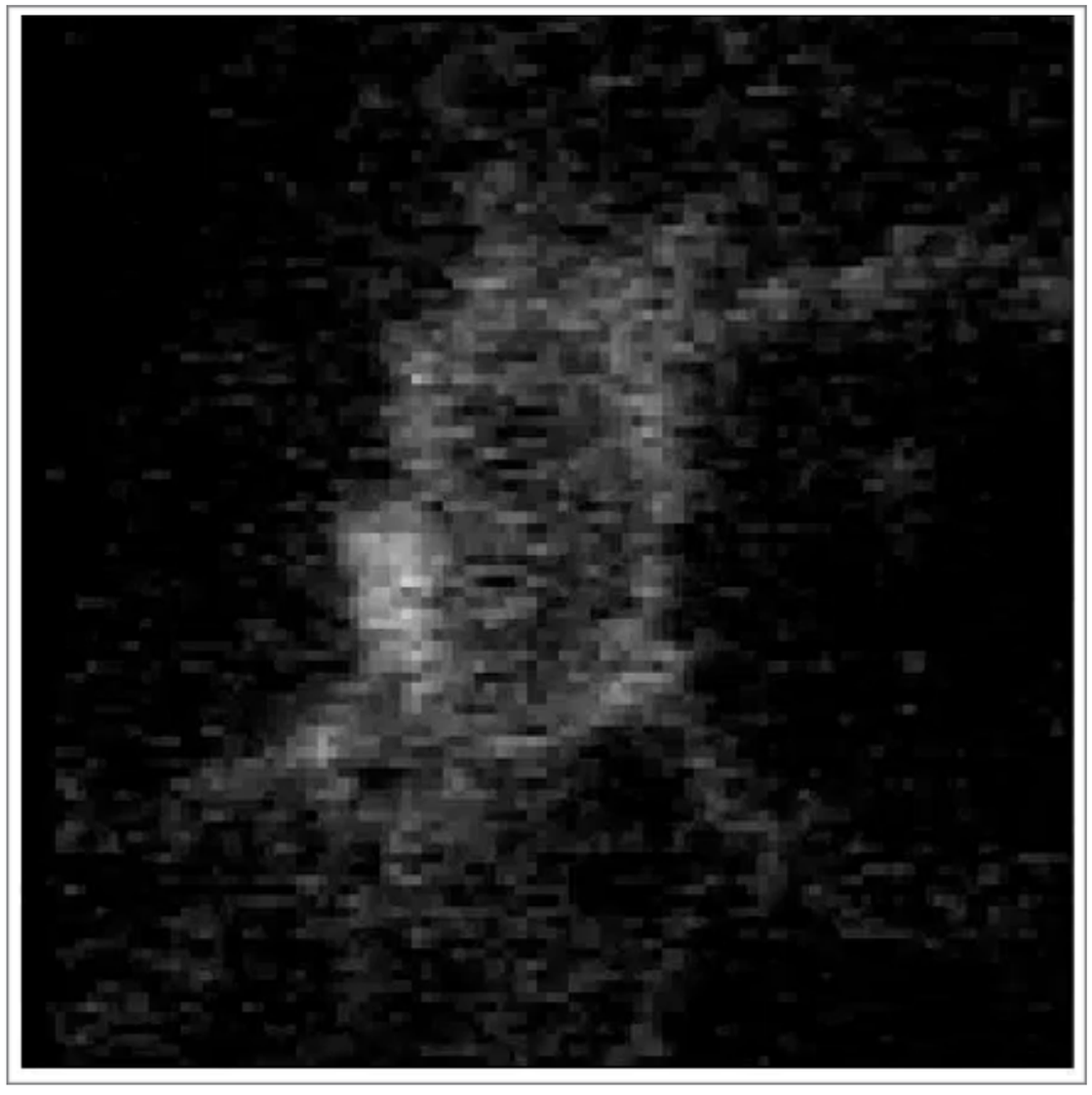
Endoplasmic Reticulum (in most cells)

An organelle is a watertight cellular compartment that acts as a store of calcium (among other things), which helps regulate calcium in the cytosol



Increased Temporal Resolution, 28Hz

Astrocyte: 256x256
28Hz recording, raw data



Notice “spikes” in soma and processes

Origin of these “spikes” is non-electrical.

Time scales or orders of magnitude longer than spikes in neuron traces.

Some Questions

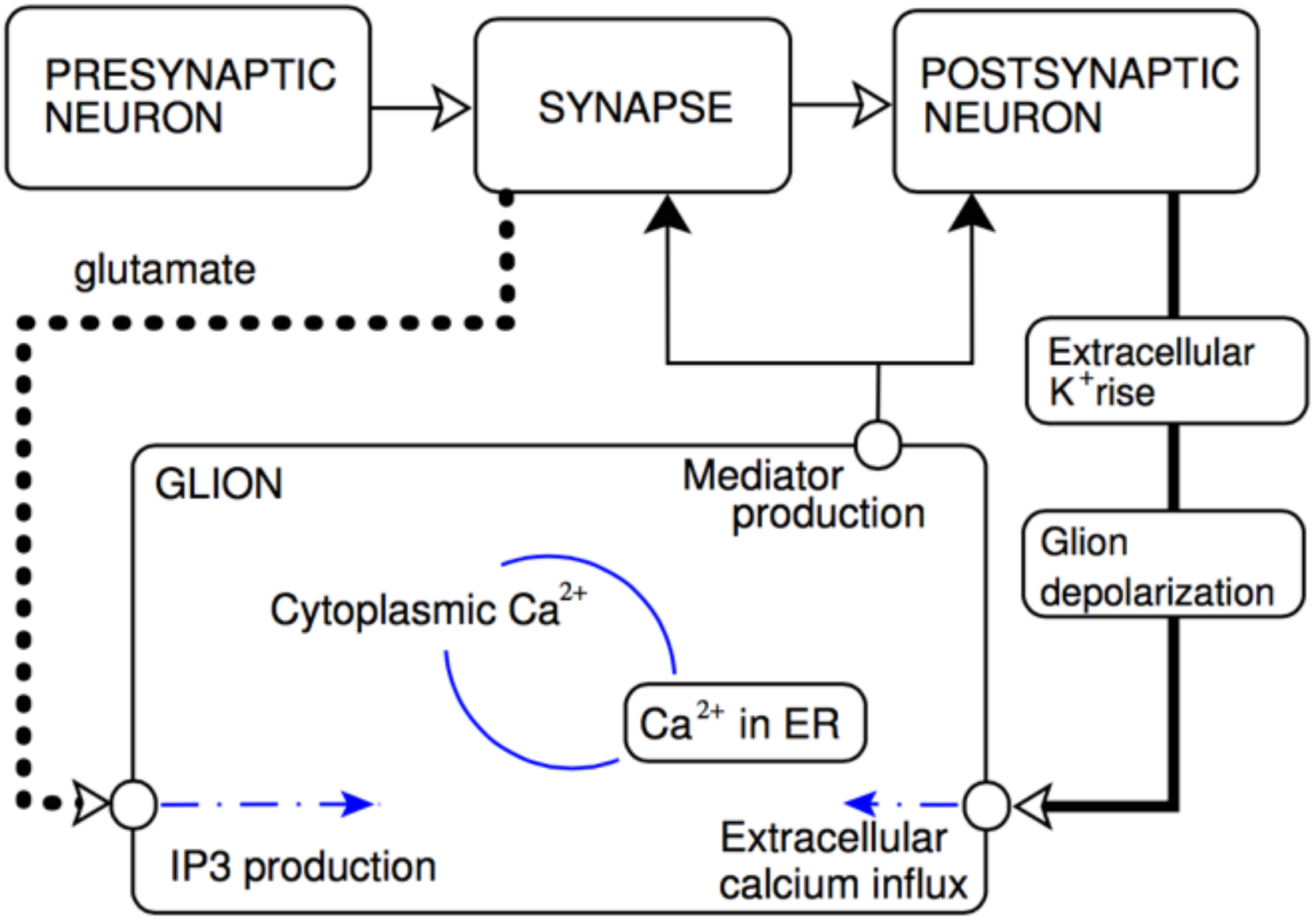
- Does the soma integrate inputs from all processes and "spike" when the summed input reaches a threshold?
  - does the soma exhibit less activity than processes?
  - what is the origin and characteristics of the "spikes"?
  - are all processes equivalent in influencing soma activity?
  - must processes spike to influence soma activity?
- Do all processes influence each other's activities or are they independently controlled by synaptic inputs?
- Do larger events have a larger spatial influence than smaller events?

Postnov Model (2007)

- Phenomenological
- Objective is to understand general characteristics, not quantitatively
  - What kind of spiking can occur in the astrocyte, under what conditions
  - Not modeling detailed biology

Biosystems. 2007 May-Jun;89(1-3):84-91. Epub 2006 Nov 12.
Functional modeling of neural-glial interaction.
Postno, Ryazanova, Sosnovtseva.

Postnov (2007)



Pre-synaptic neuron

$$\varepsilon_1 \frac{dv_1}{dt} = v_1 - \frac{v_1^3}{3} - w_1$$
$$\frac{dw_1}{dt} = v_1 + I_1 - I_{app},$$

Post-synaptic neuron

$$\varepsilon_2 \frac{dv_2}{dt} = v_2 - \frac{v_2^3}{3} - w_2$$
$$\frac{dw_2}{dt} = w_2 + I_2 - I_{syn} - I_{glion},$$

Synapse Activation

$$\tau_s \frac{dz}{dt} = (1 + tanh(s_s(v_1 - h_s)))(1 - z) - \frac{z}{d_s},$$
$$I_{syn} = (k_s - \delta G_m)(z - z_0).$$

$$I_{glion} = \gamma G_m.$$

Strength of various interactions

$$\alpha, \beta, \gamma$$

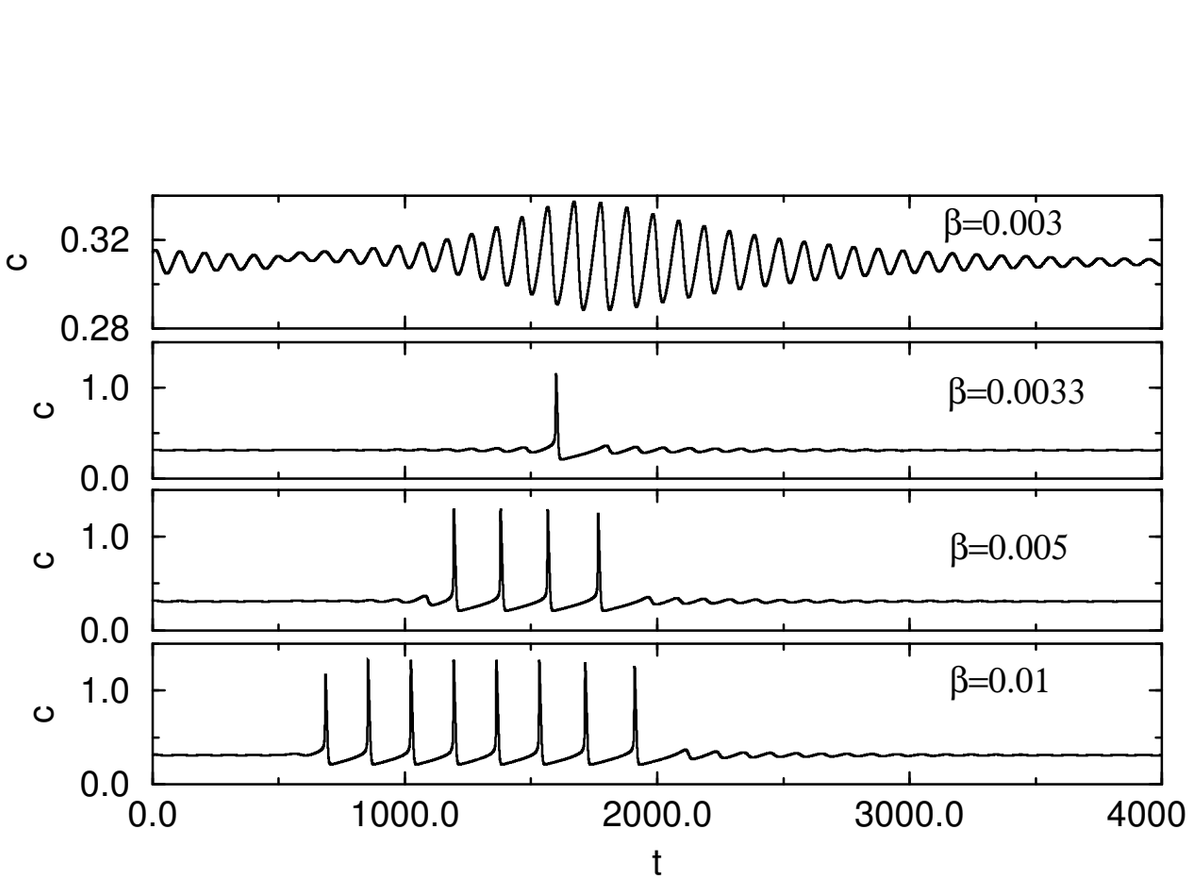
Calcium Cytosol <—> ER

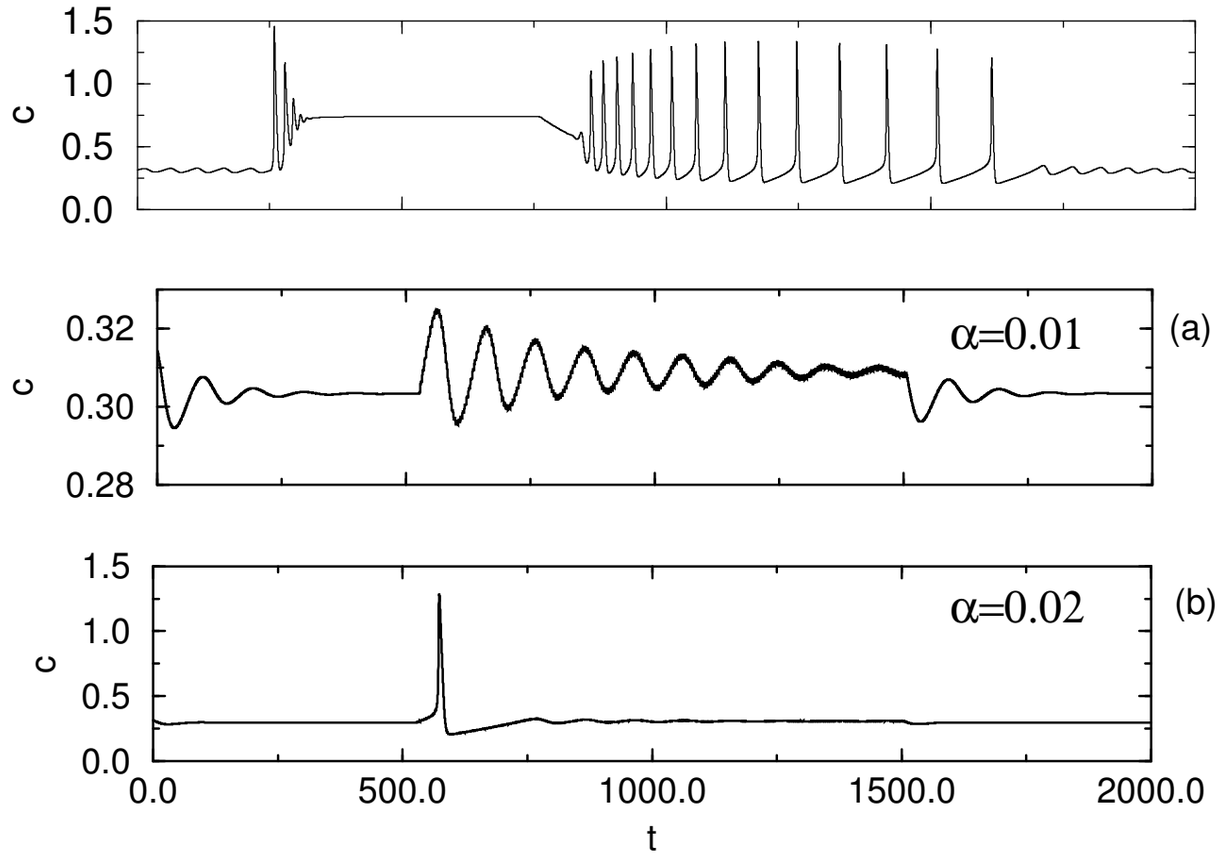
$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + (r + \alpha w_2 + \beta S_m),$$
$$\varepsilon_c \tau_c \frac{dc_e}{dt} = f(c, c_e).$$

Sm: IP3, Gm: glion mediator

$$\tau_{S_m} \frac{dS_m}{dt} = (1 + tanh(s_{S_m}(z - h_{S_m}))) \times$$
$$\times (1 - S_m) - \frac{S_m}{d_{S_m}},$$
$$\varepsilon_c \tau_{G_m} \frac{dG_m}{dt} = (1 + tanh(s_{G_m}(c - h_{G_m}))) \times$$
$$\times (1 - G_m) - \frac{G_m}{d_{G_m}},$$

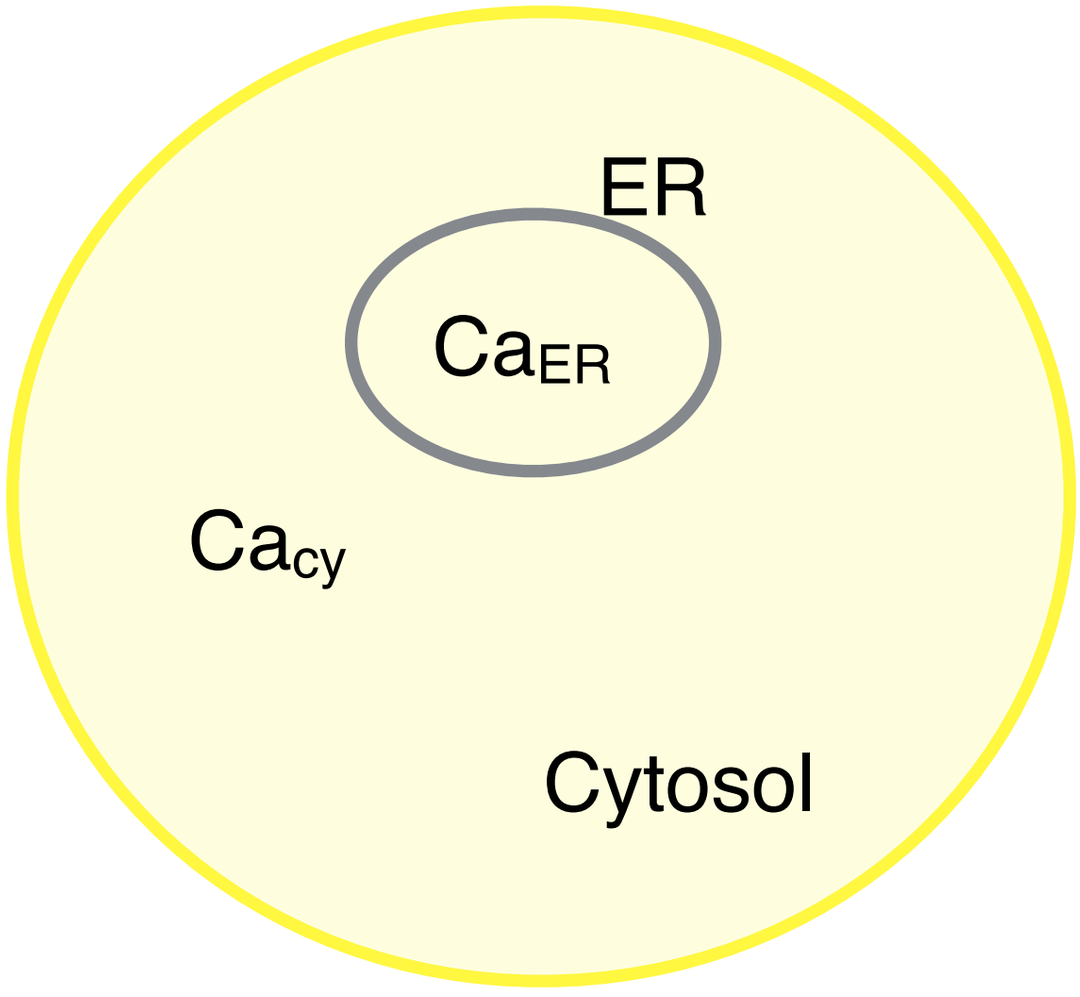
Some Results for Calcium
Postnov (2007)





Just shows the diversity of calcium spiking inside the Soma
Spiking is defined as width over spike-interval very very small

Single Point Astrocyte



Variables

Ca: calcium in cytosol

Ca_{ER}: calcium in ER

Parameters

Secondary messager: IP3

Neurotransmitter: Glutamate

Compartmental model

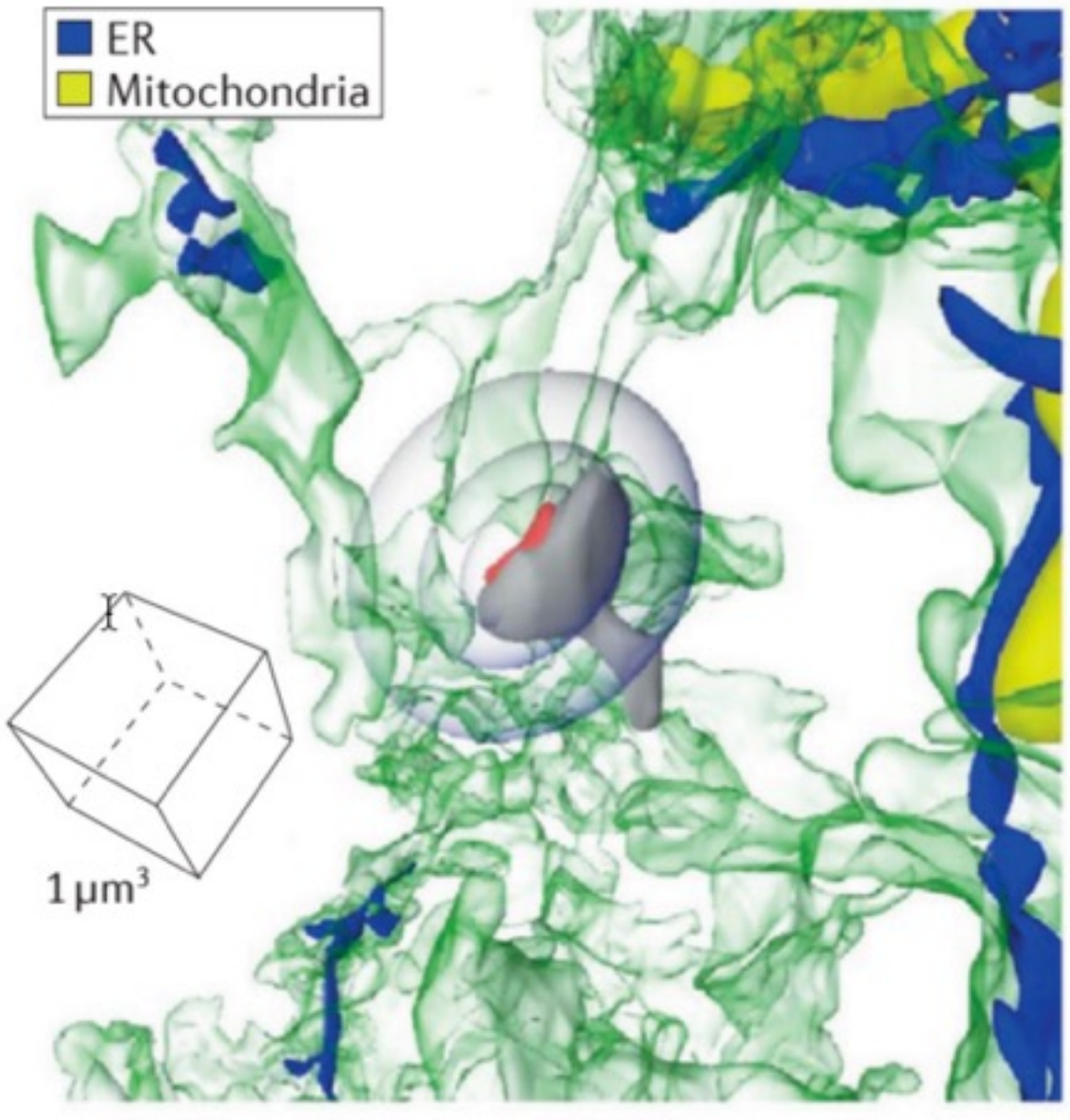
- Treat separately
  - each process
  - the soma

r: effect of neurons on astrocyte

d_c: Diffusion coef. in Cytosol

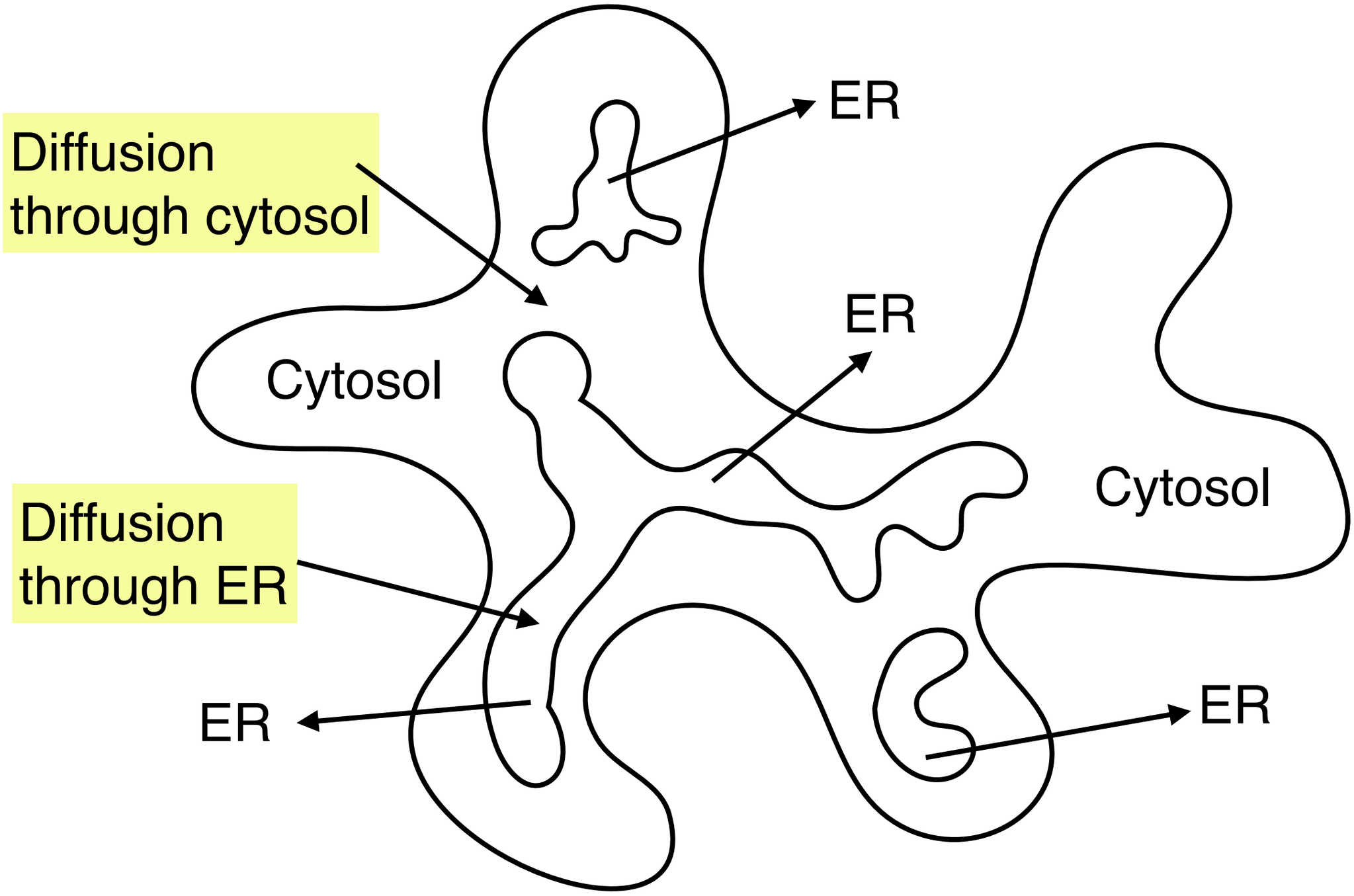
d_{er}: Diffusion coef. in ER

Endoplasmic Reticulum
of an Astrocyte

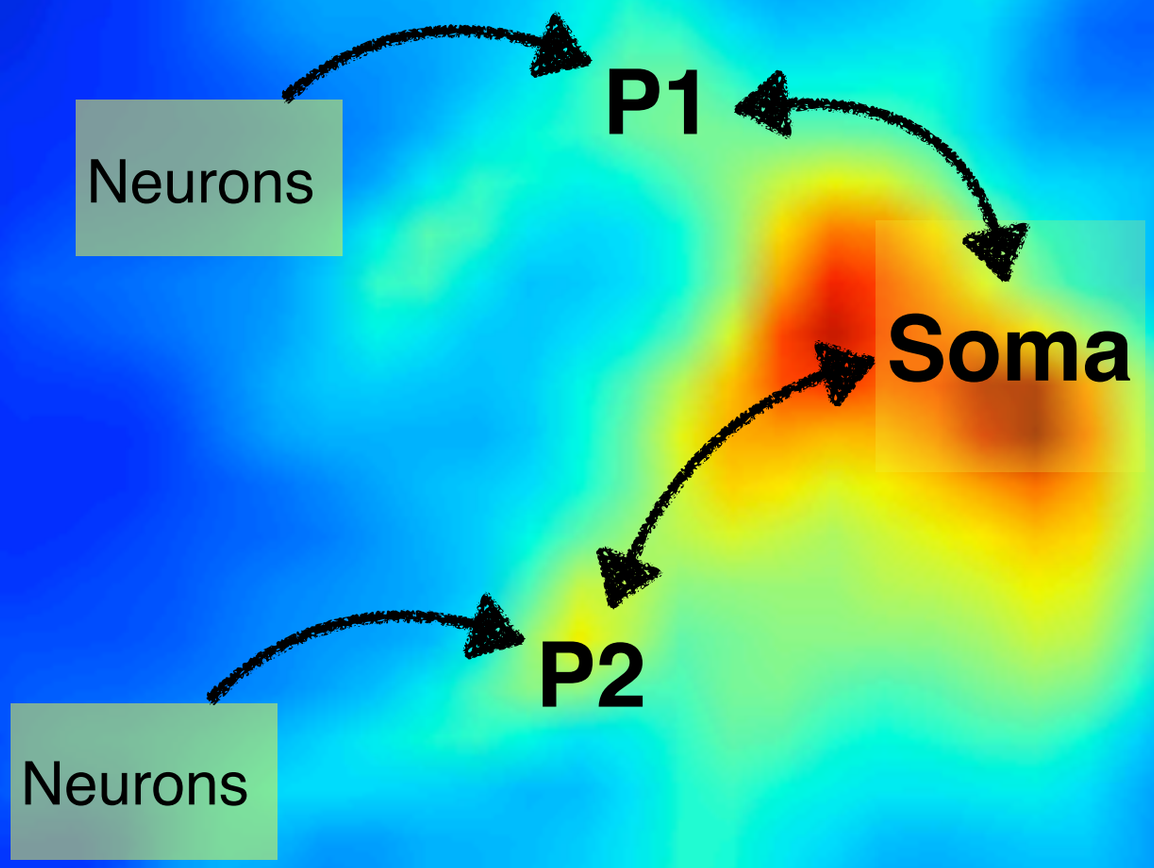


Singly connected entity?
Multiply connected?

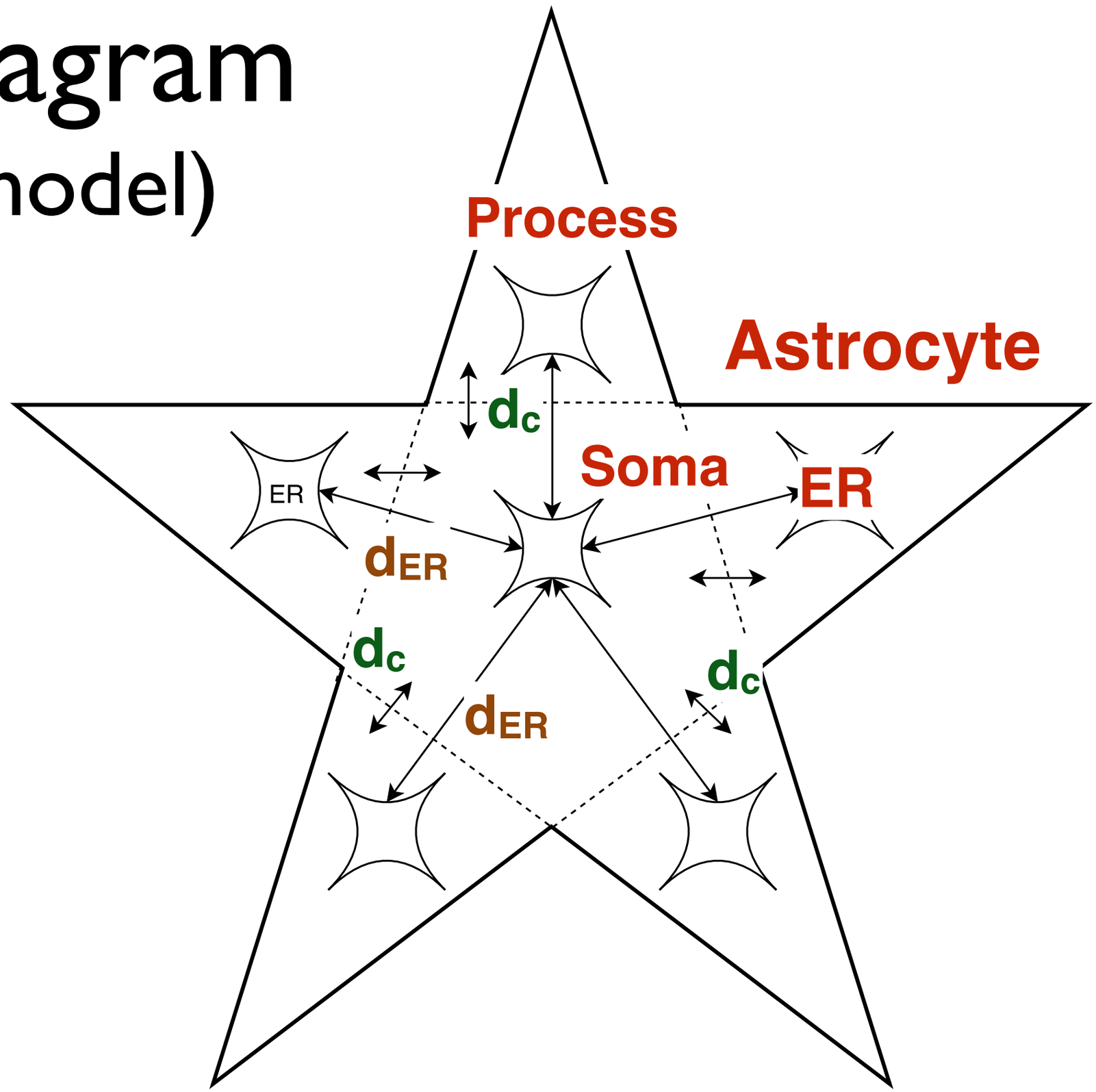
How Are The ER's Connected?



Idea Behind Our Model



Model Diagram
(N point model)



N processes

Source: Evan Cresswell

Our Model Based On Postnov (neurons modeled through $r_{Amp}(t)$)

$$\tau_p \frac{dCa_{p_i}}{dt} = r_L + r_{Amp} + r + \alpha w_{post_i} + \beta Sm_i - c_4 * f(Ca_{P_i}, Ca_{er_i}) + d_c(Ca_s - Ca_{p_i}) - Ca_{p_i}$$

$$\epsilon_c \tau_c \frac{dCa_{er_i}}{dt} = f(Ca_{p_i}, Ca_{er_i}) + d_{er}(Ca_{er_s} - Ca_{er_i})$$

Diffusion

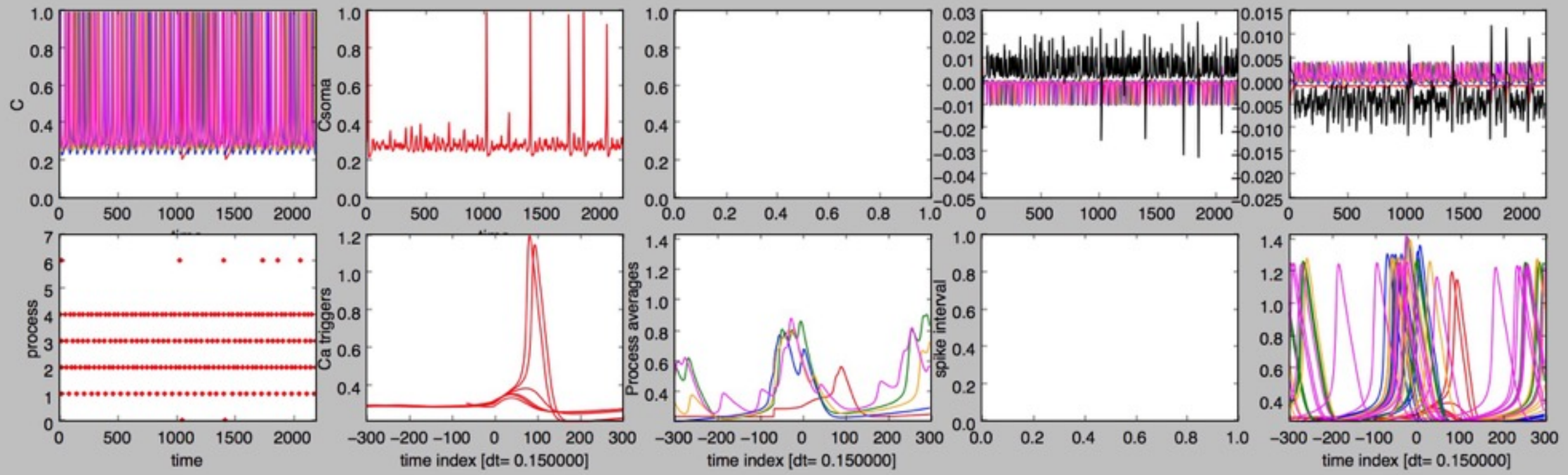
$$\tau_c \frac{dCa_s}{dt} = -Ca_s - c_4 * f(Ca_s, Ca_e) + (r + \sum_{i=1}^{n} d_c(Ca_{p_i} - Ca_s)$$

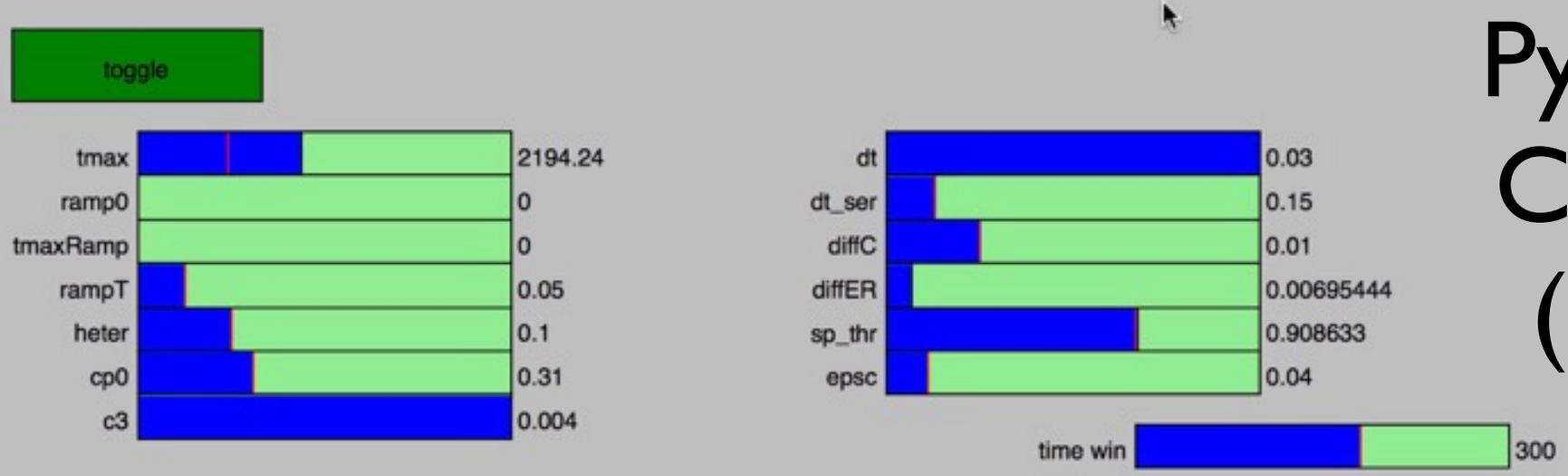
$$\epsilon_c \tau_c \frac{dCa_{er_s}}{dt} = f(Ca_s, Ca_{er_s}) + \sum_{i=1}^{n} d_{er}(Ca_{er_i} - Ca_{er_s})$$

Diffusion

Diffusion

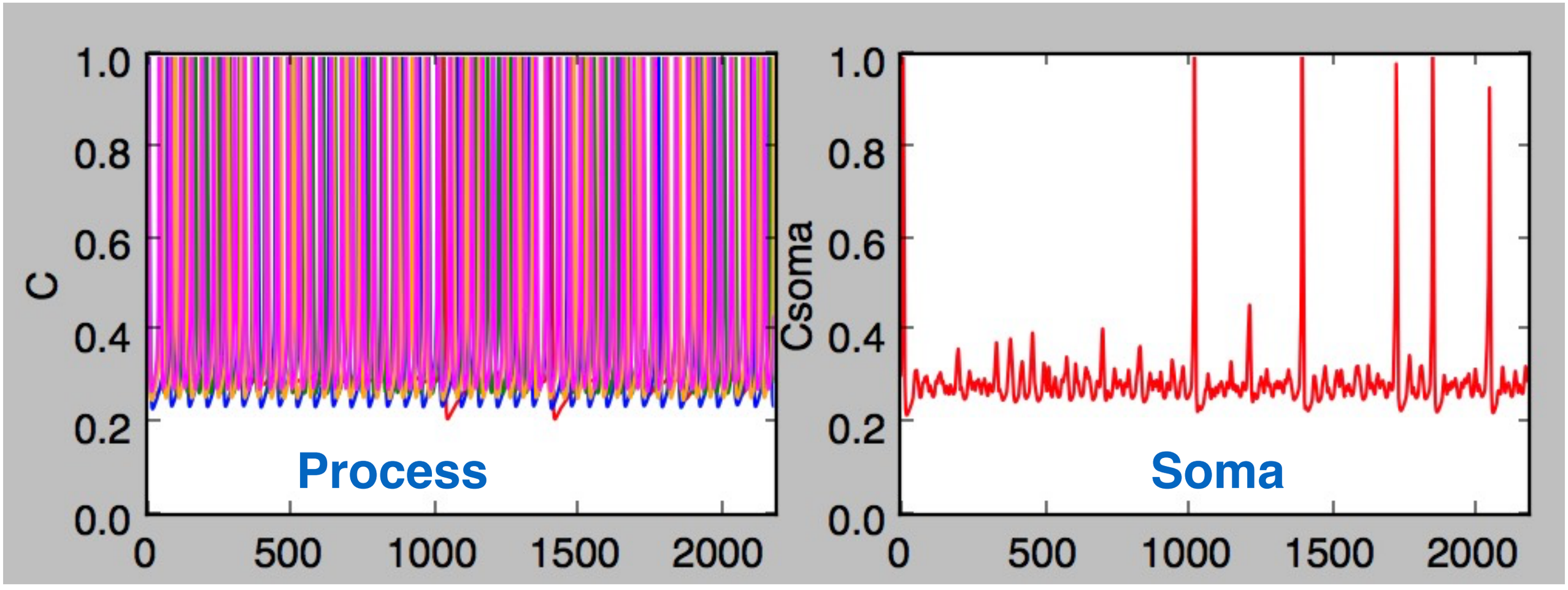
$$f(c, c_e) = c_1 \frac{c^2}{1 + c^2} - \left(\frac{c_e^2}{1 + c_e^2}\right)\left(\frac{c^4}{c_2^4 + c^4}\right) - c_3 c_e$$





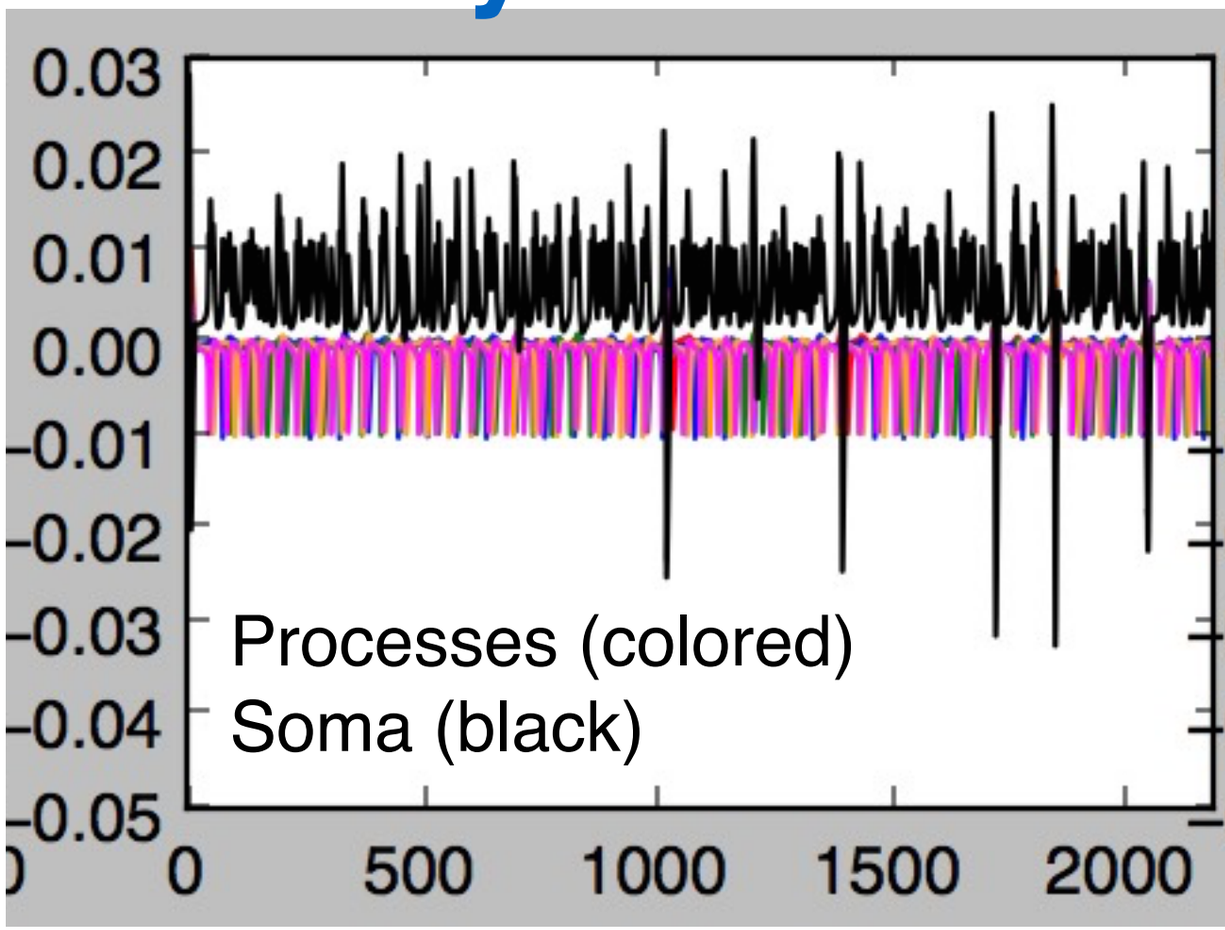
Python (GUI) + C++ Simulation (5 processes)

Calcium In The Process And The Soma

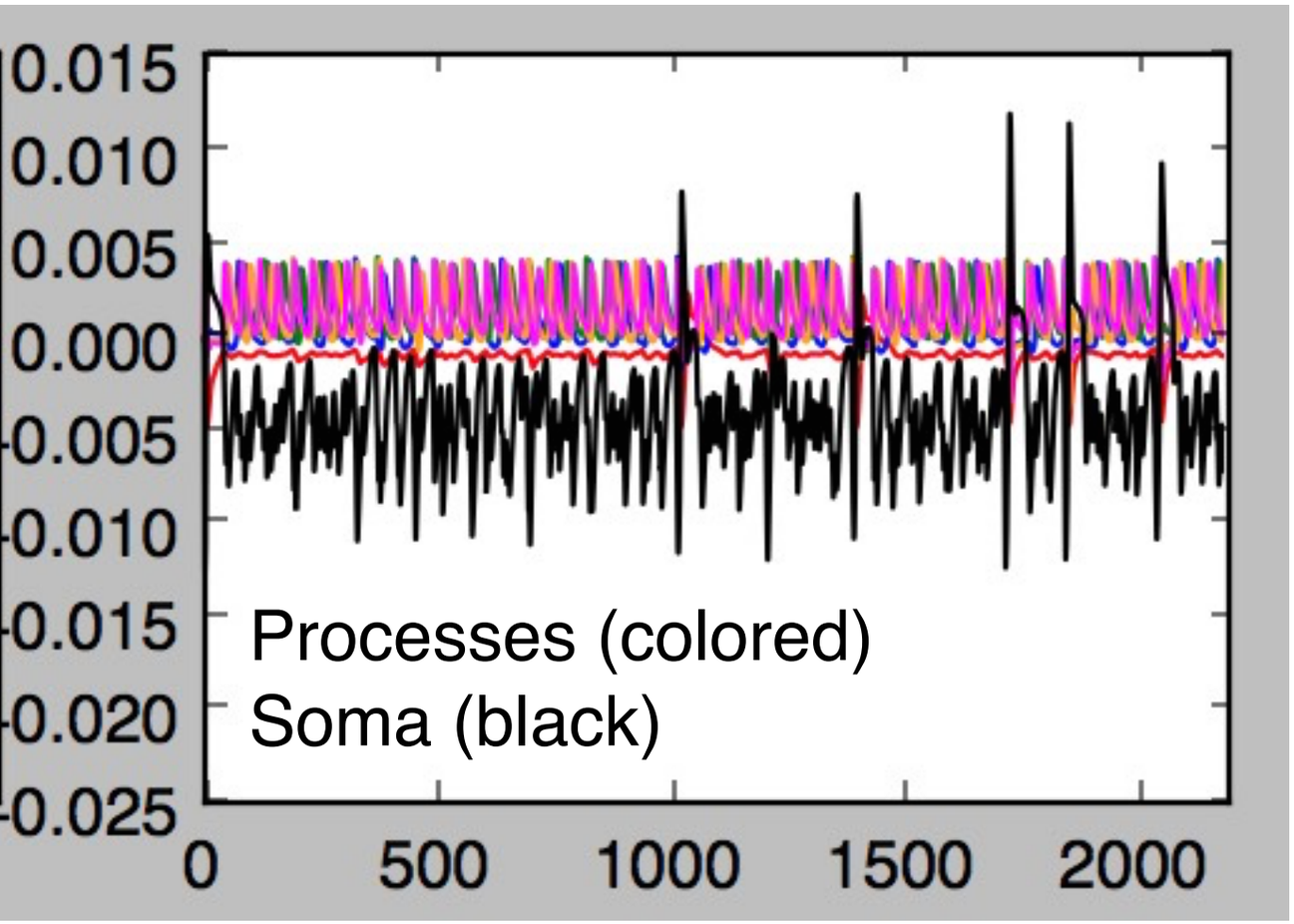


Diffusion terms

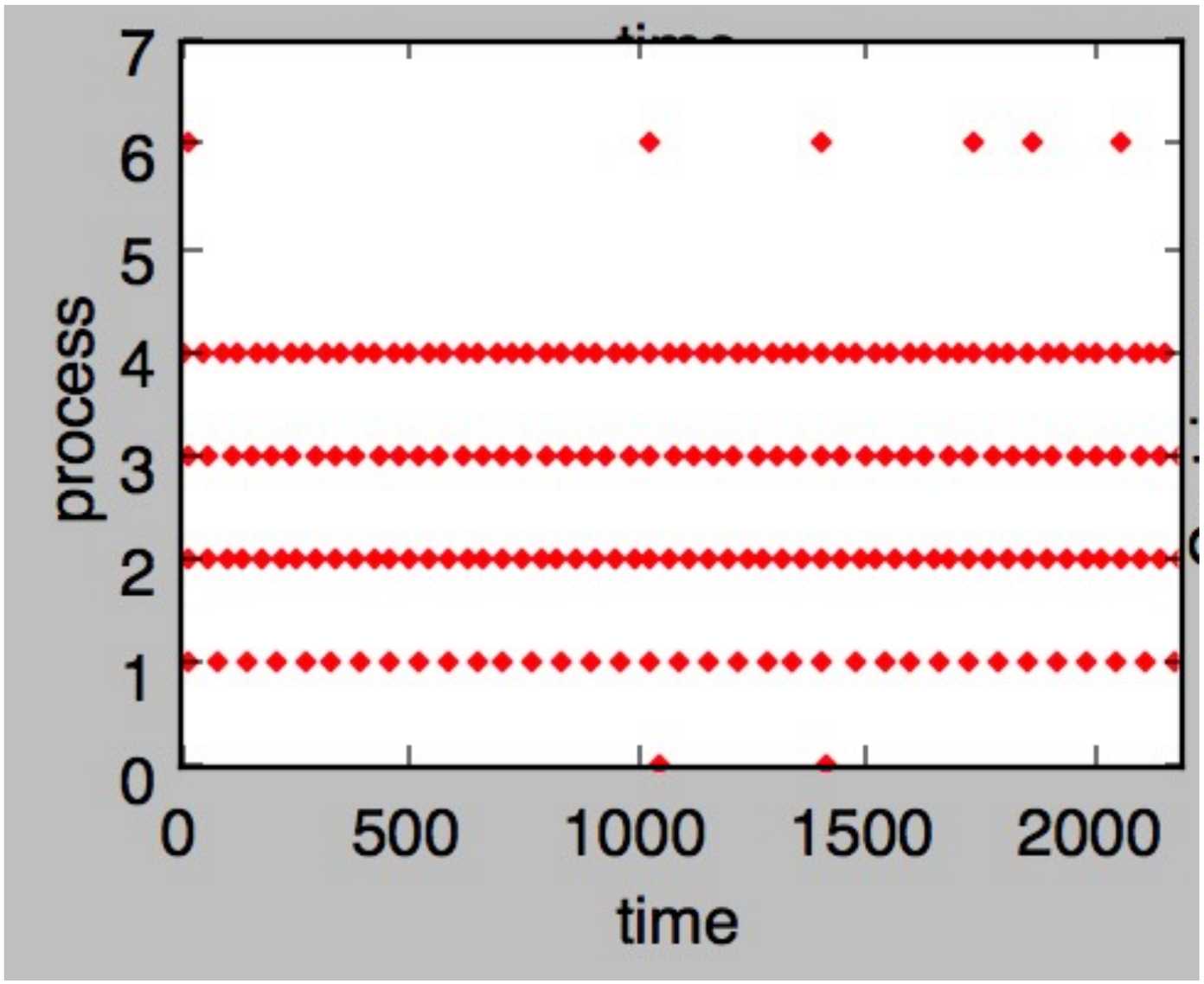
Cytosol



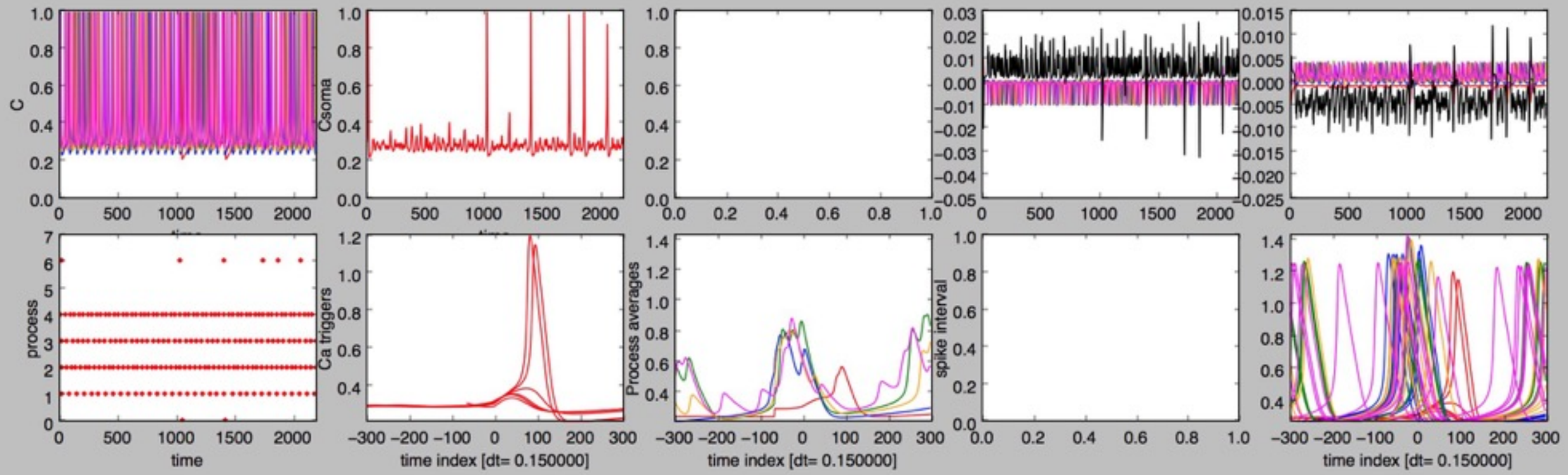
ER



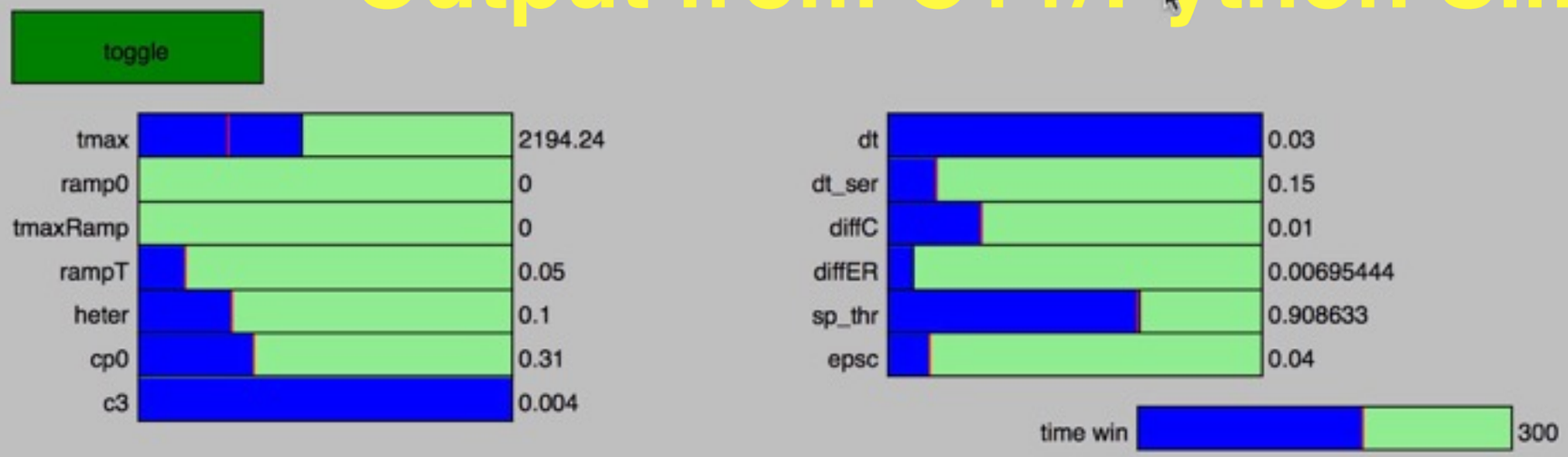
Raster Plot



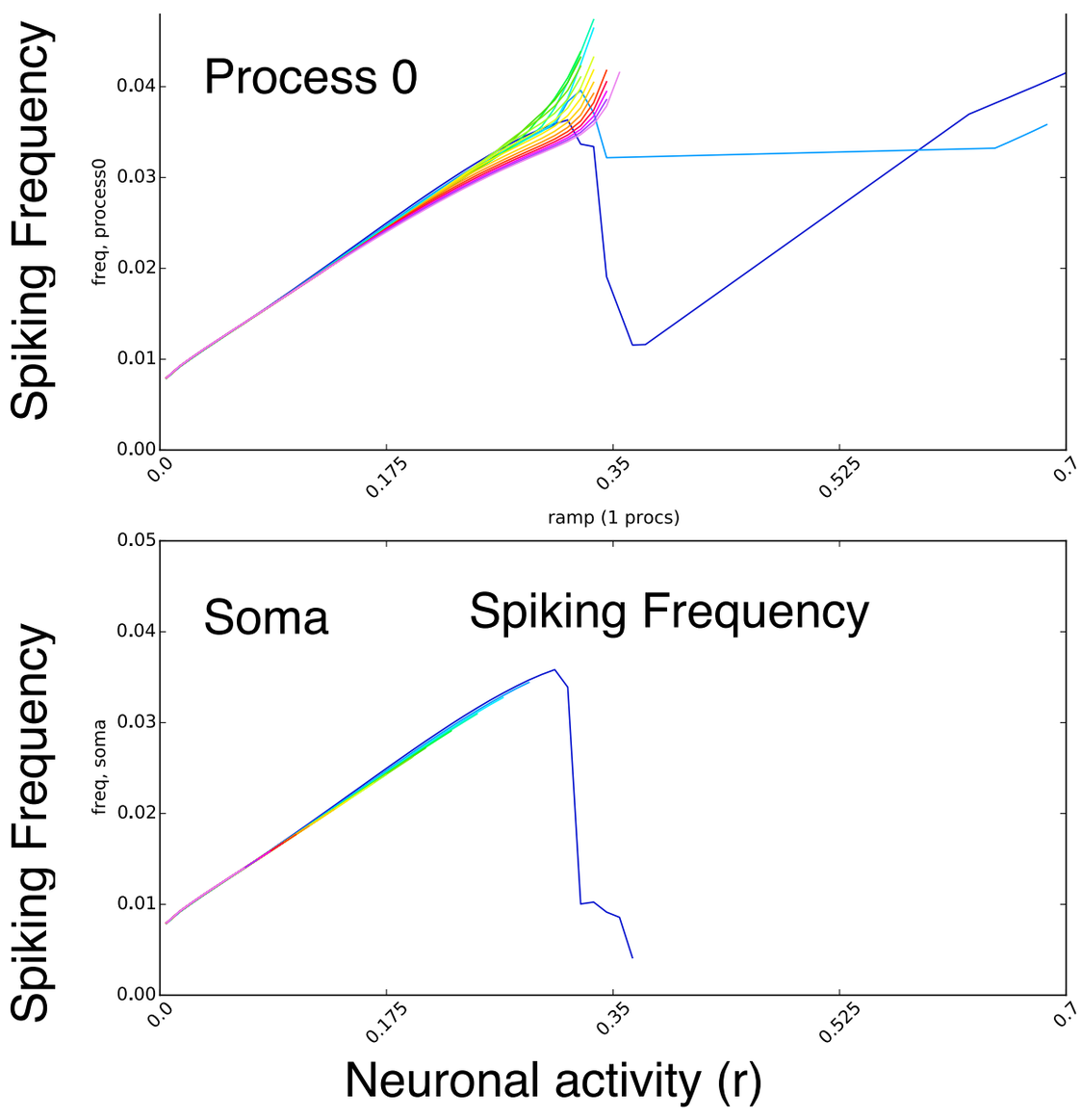
Record each spike when the signal is above the threshold

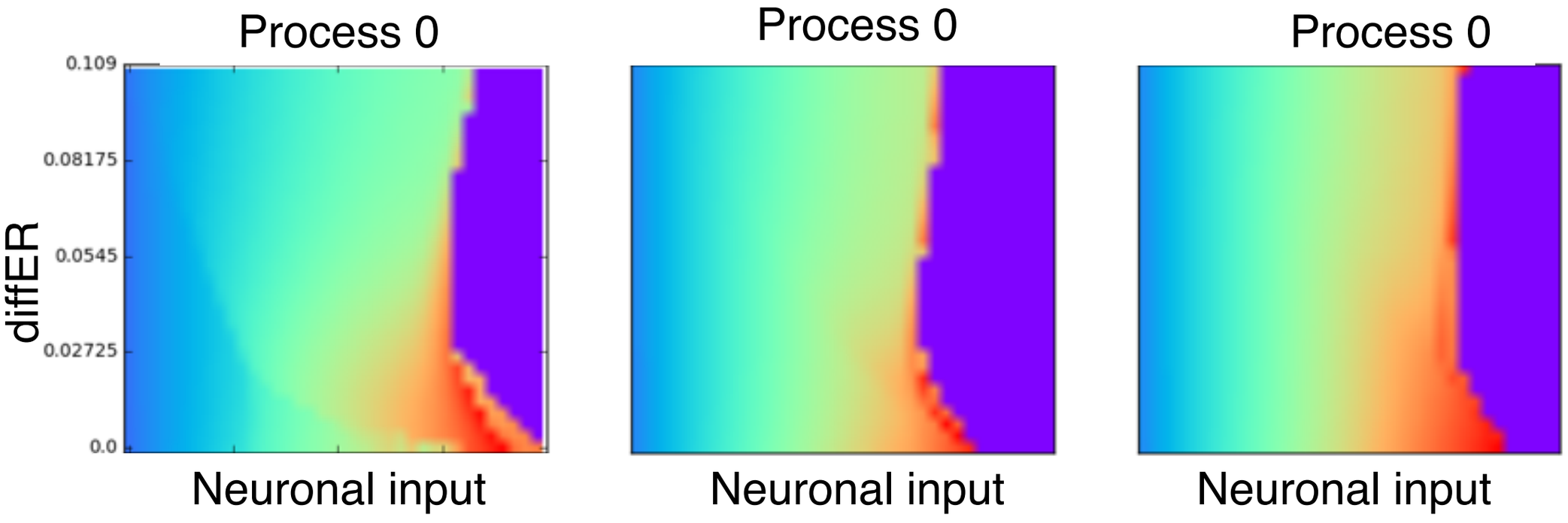


Output from C++/Python Simulation Code

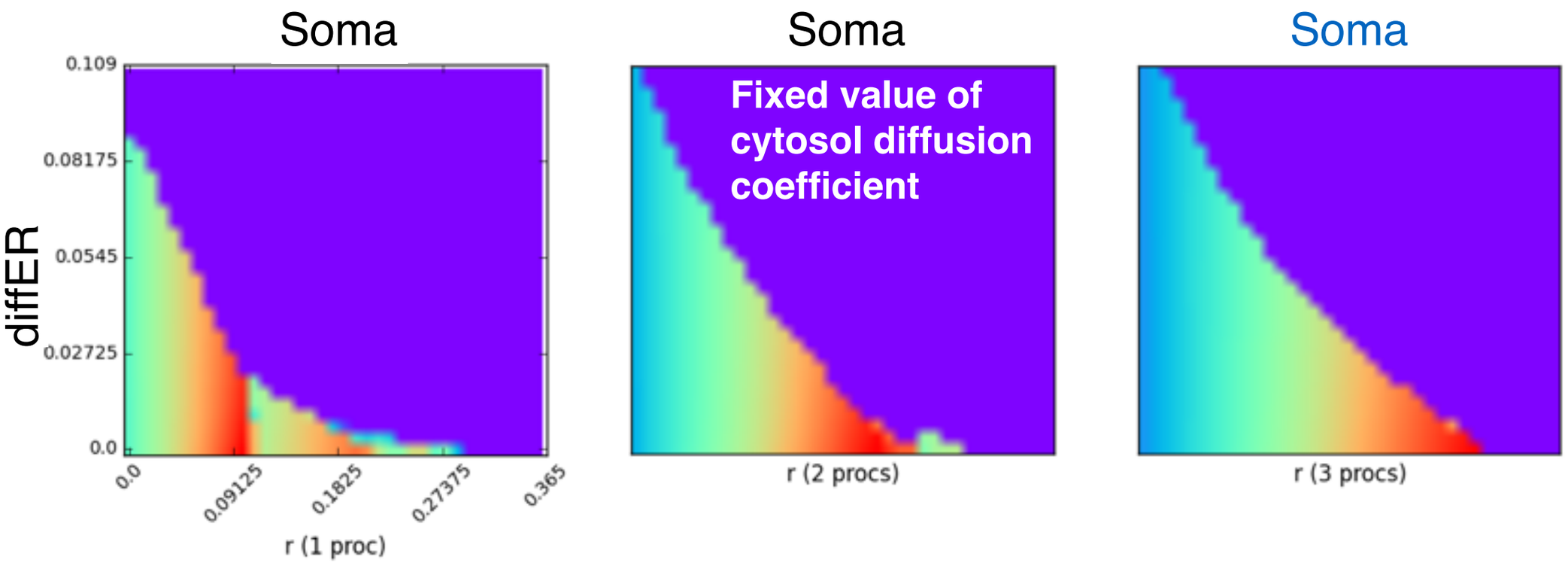


Spiking Frequency as a function of neural activity for different values of d_{er} (Diff ER)

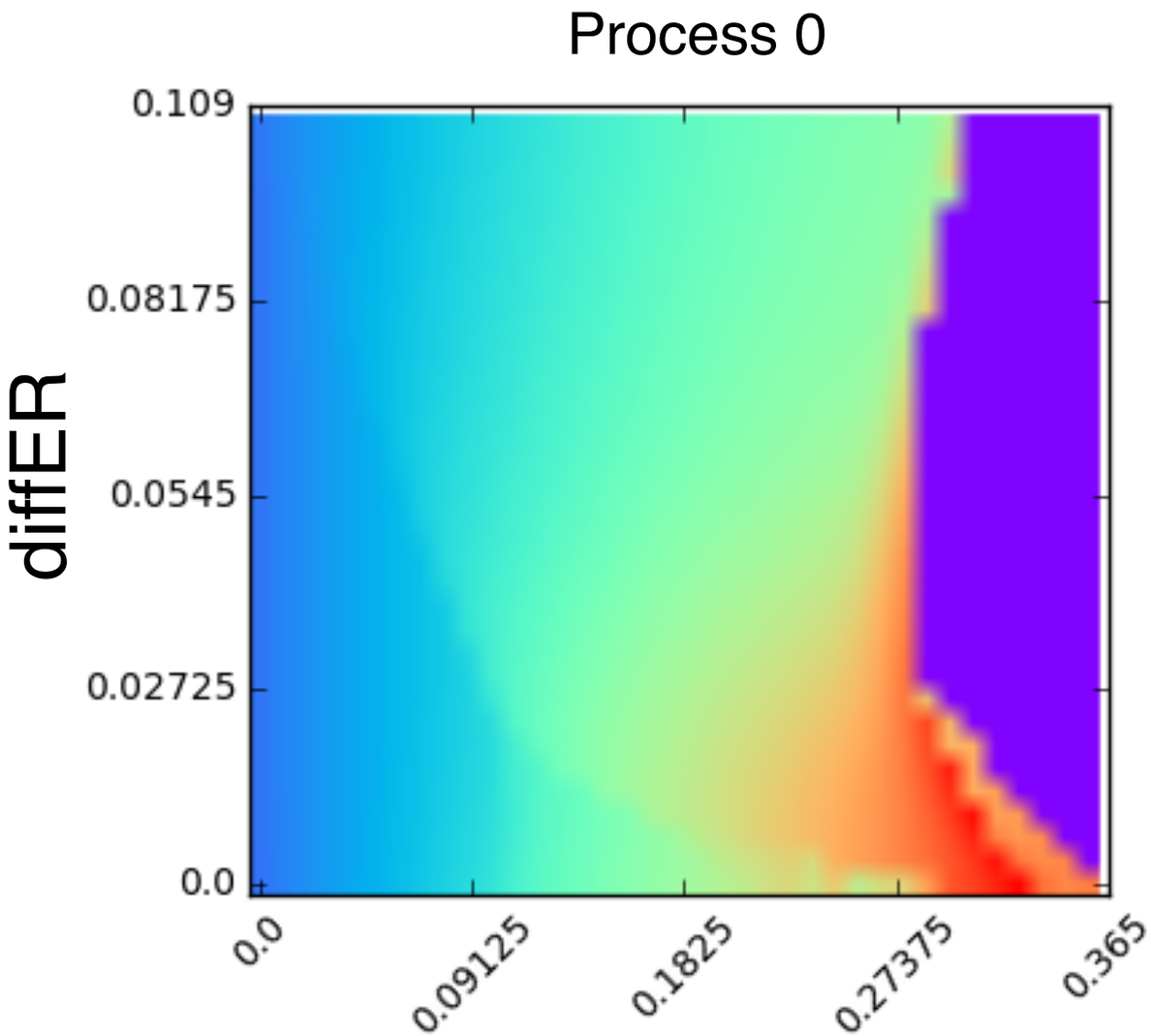


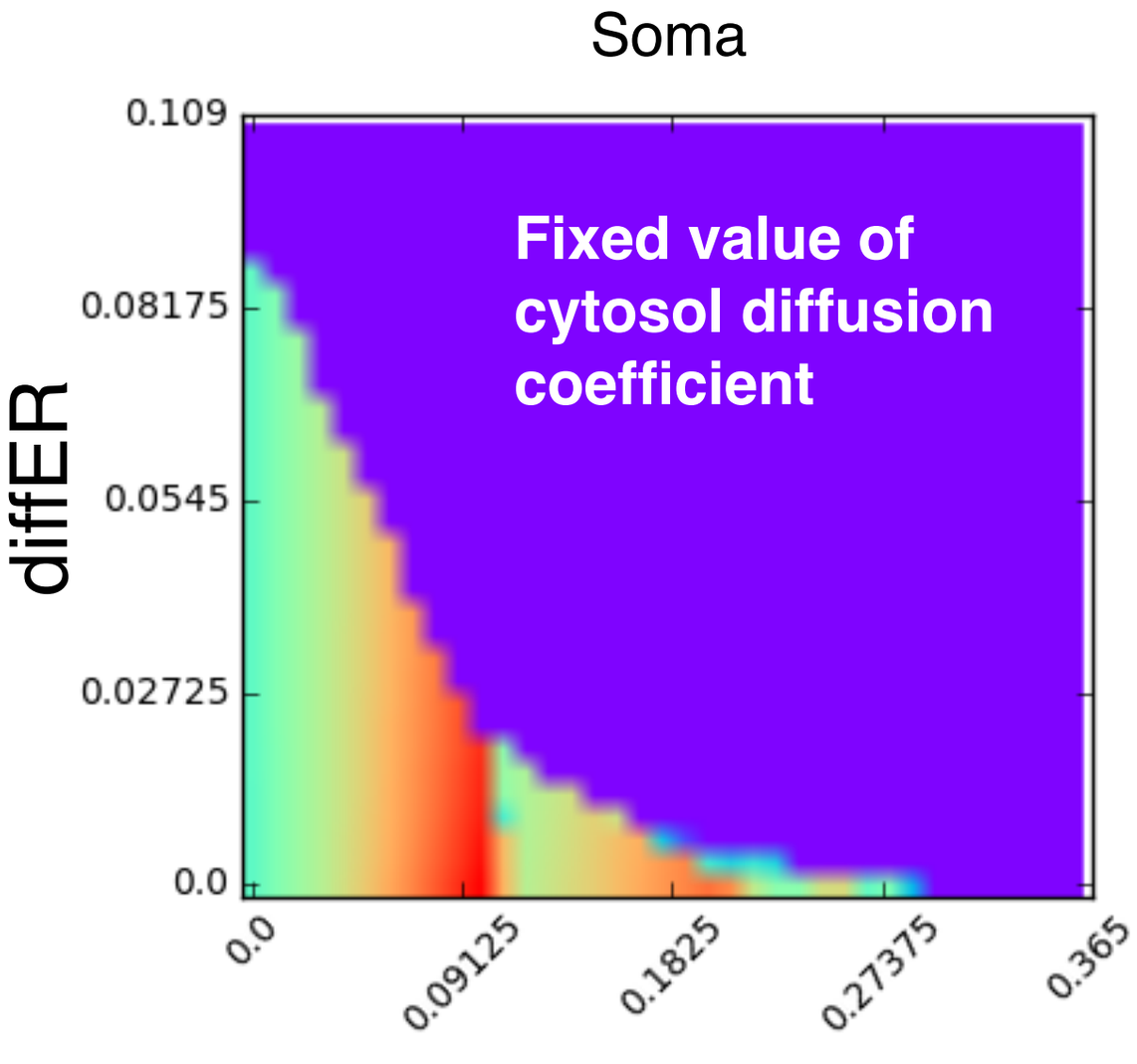


1 process **2 processes** **3 processes**

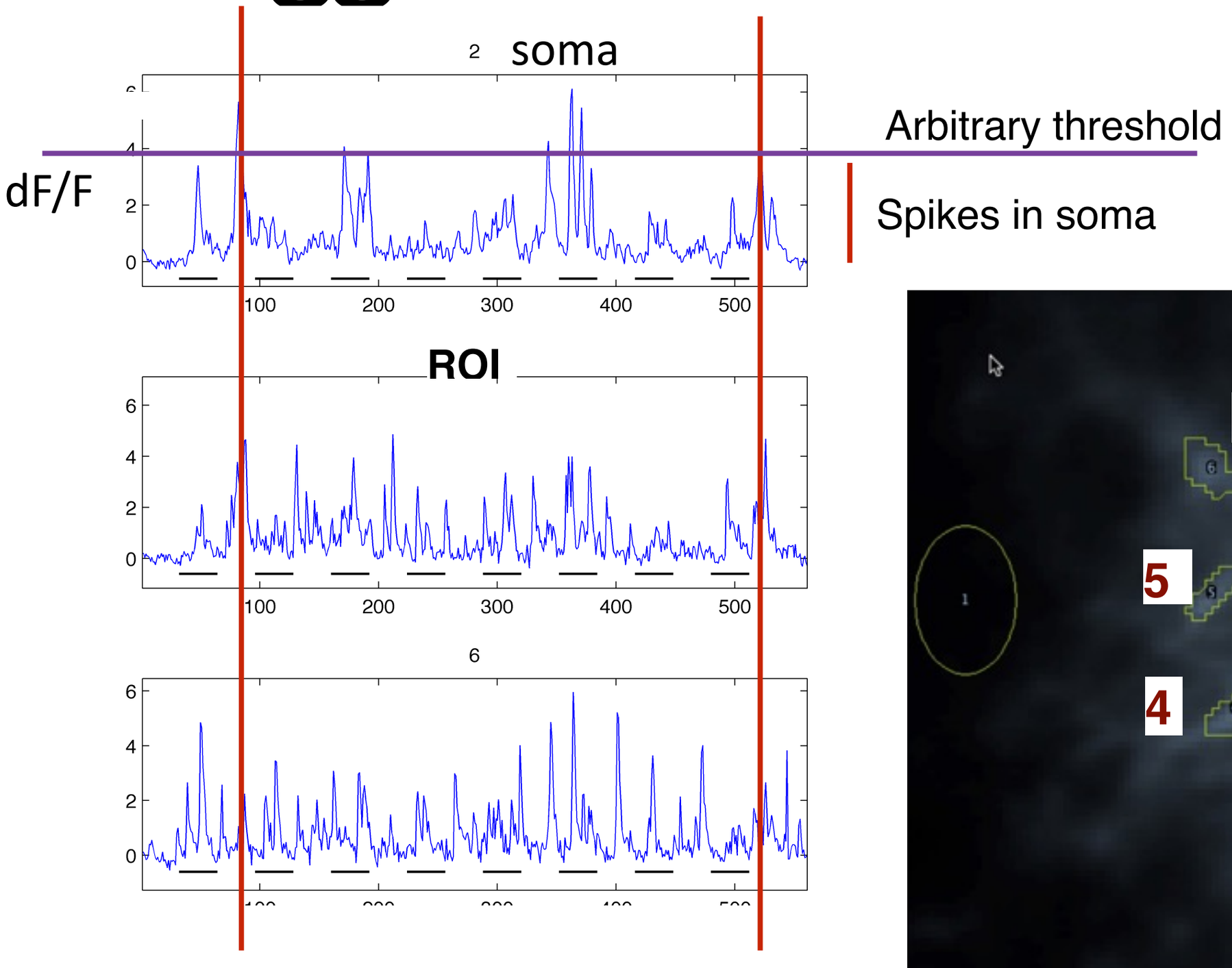


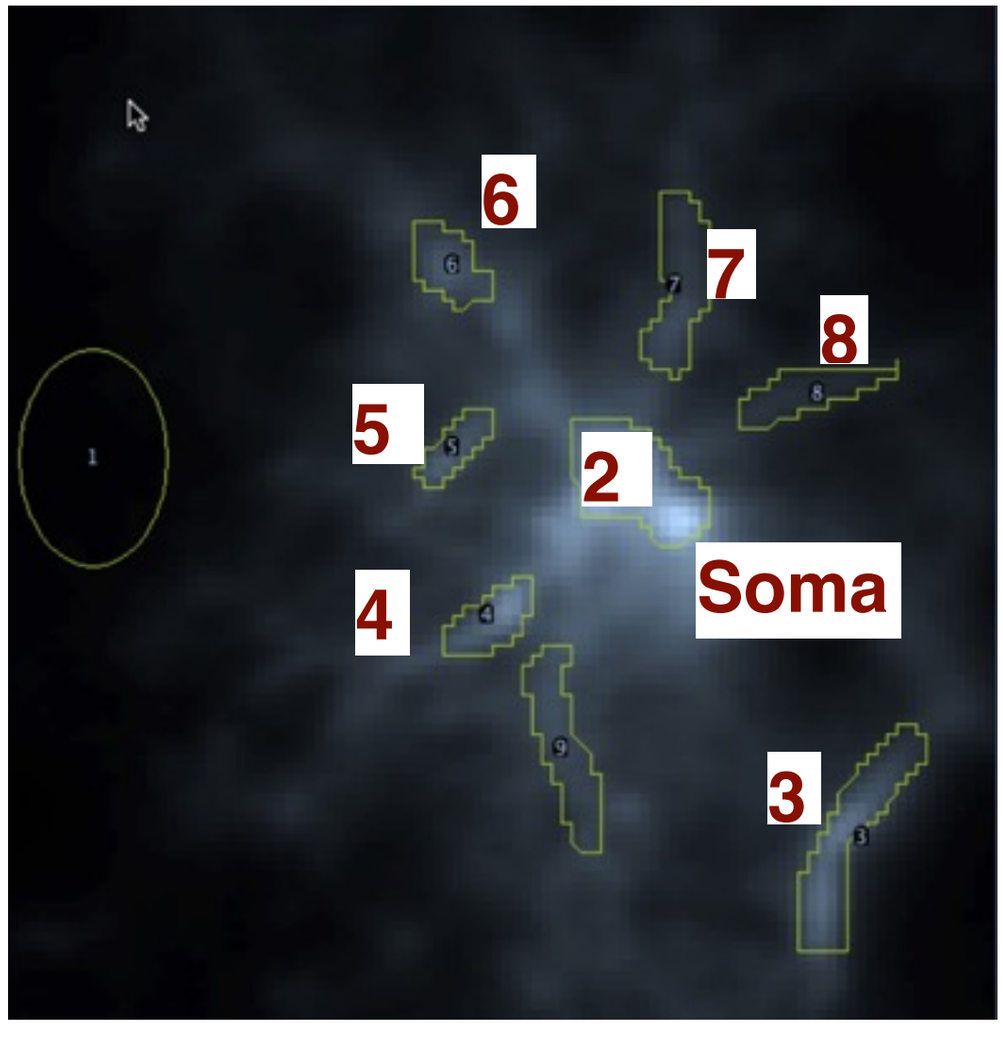
One process + Soma





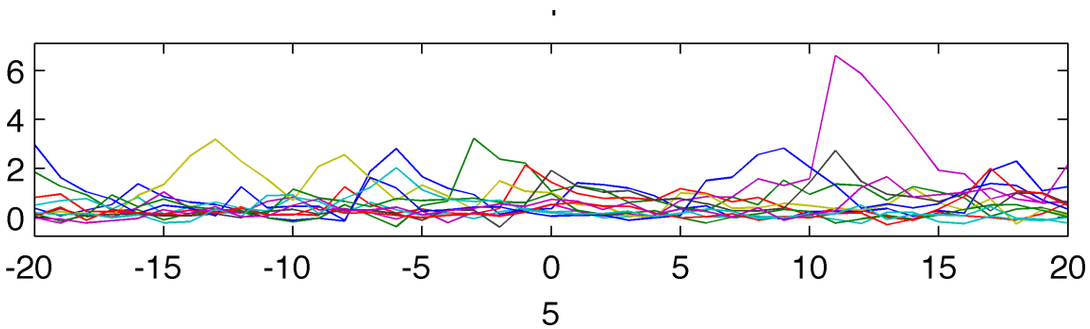
Trigger-Based Averaging

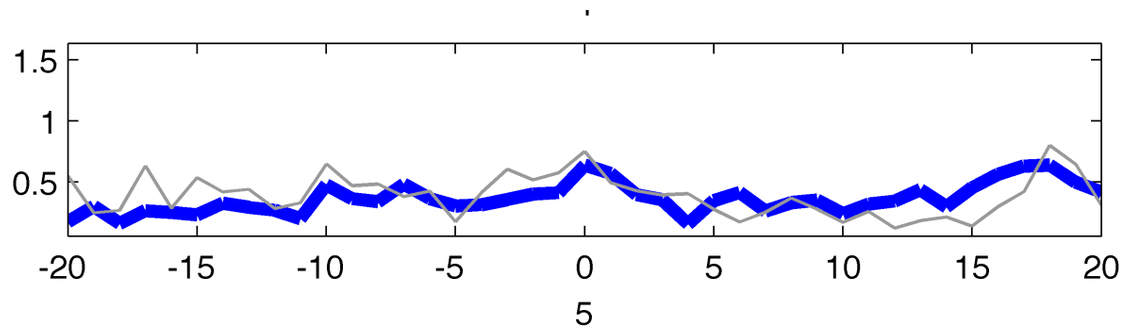


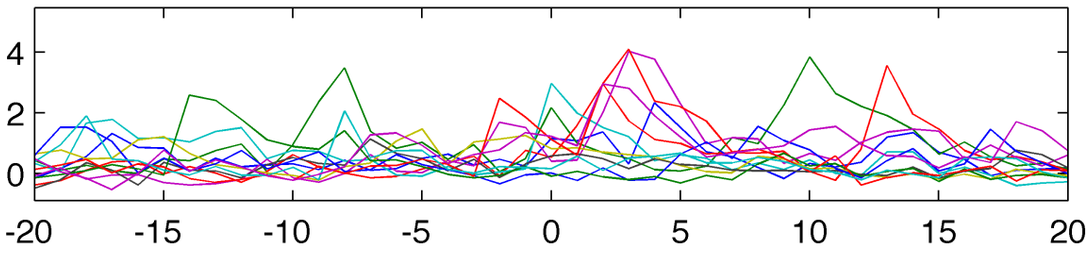


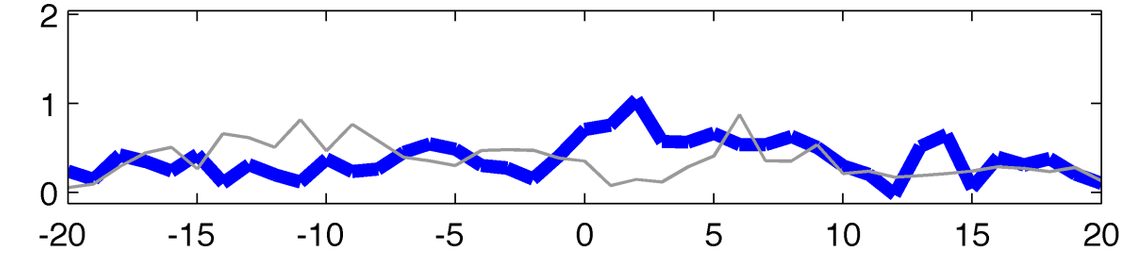
Trigger-Based Averages

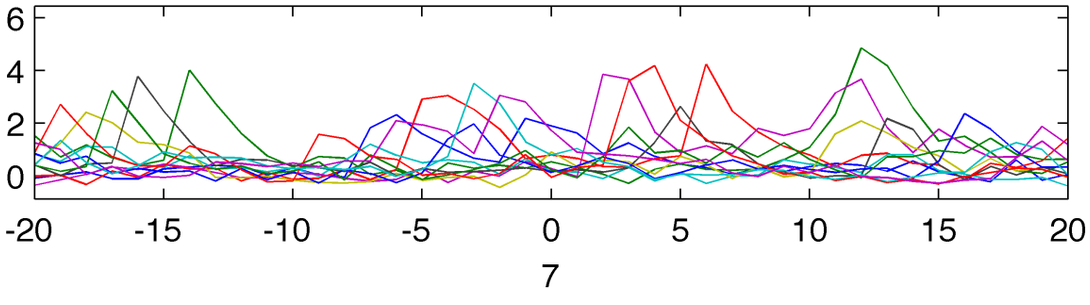
Threshold Amplitude: 1.25 - 1.5

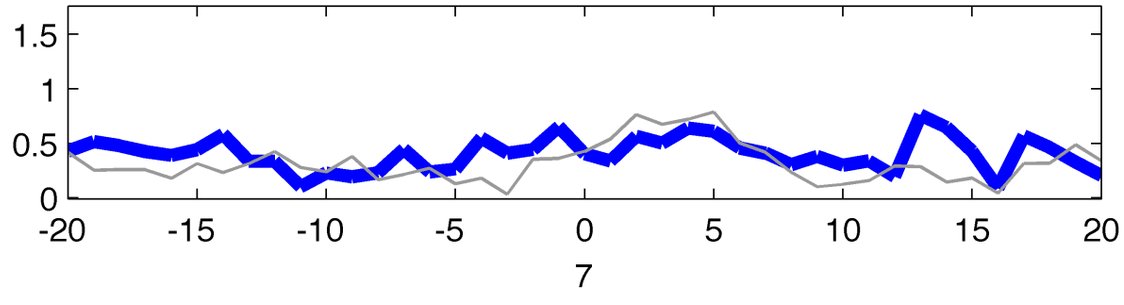






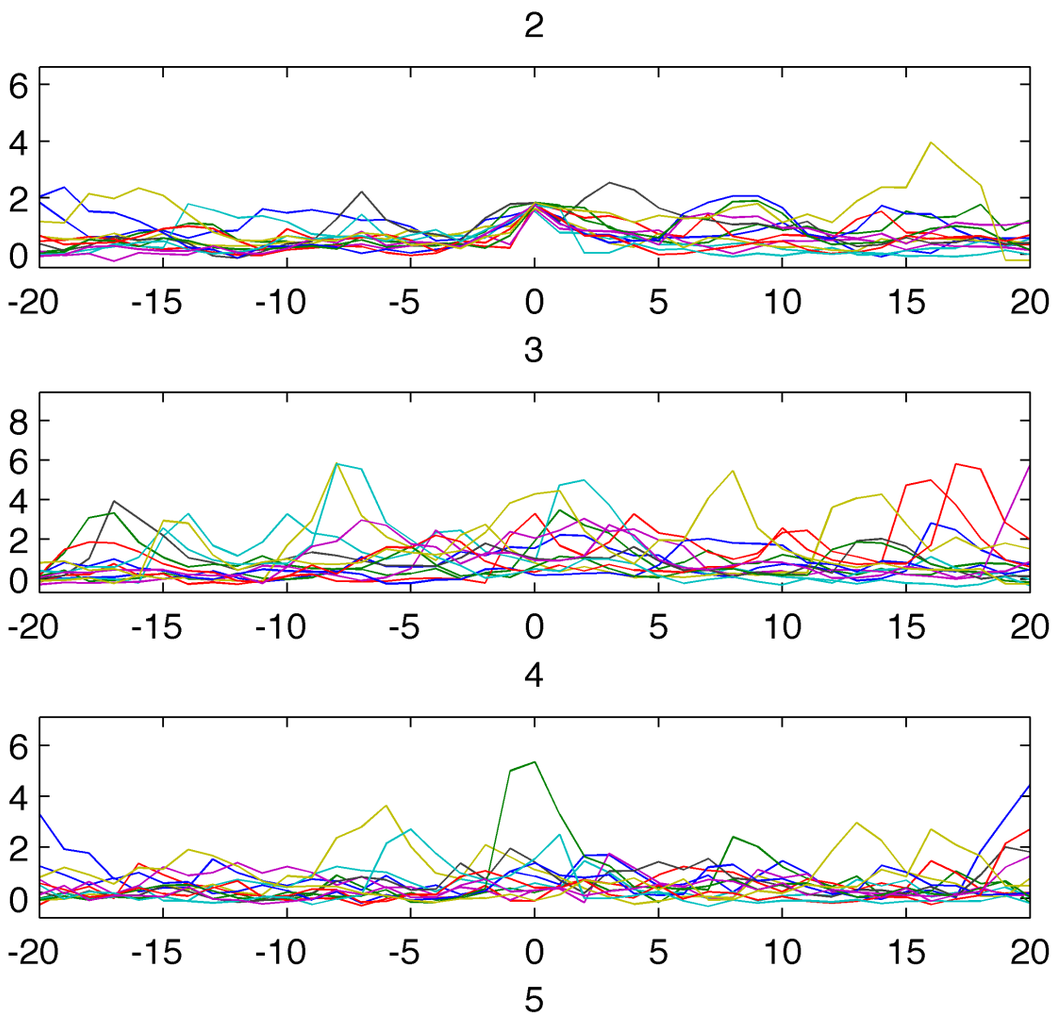


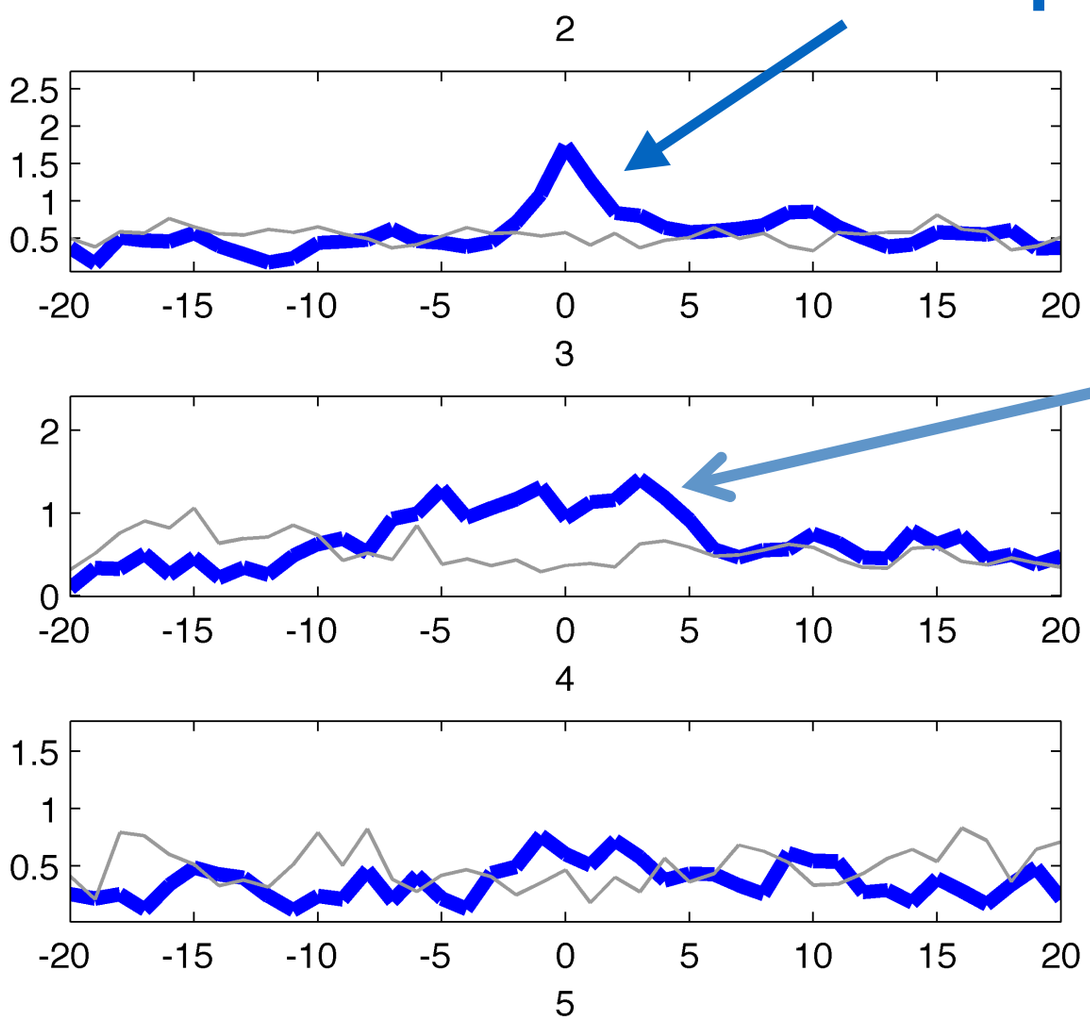




Trigger-Based Averages

Threshold Amplitude: 1.5 - 2.0



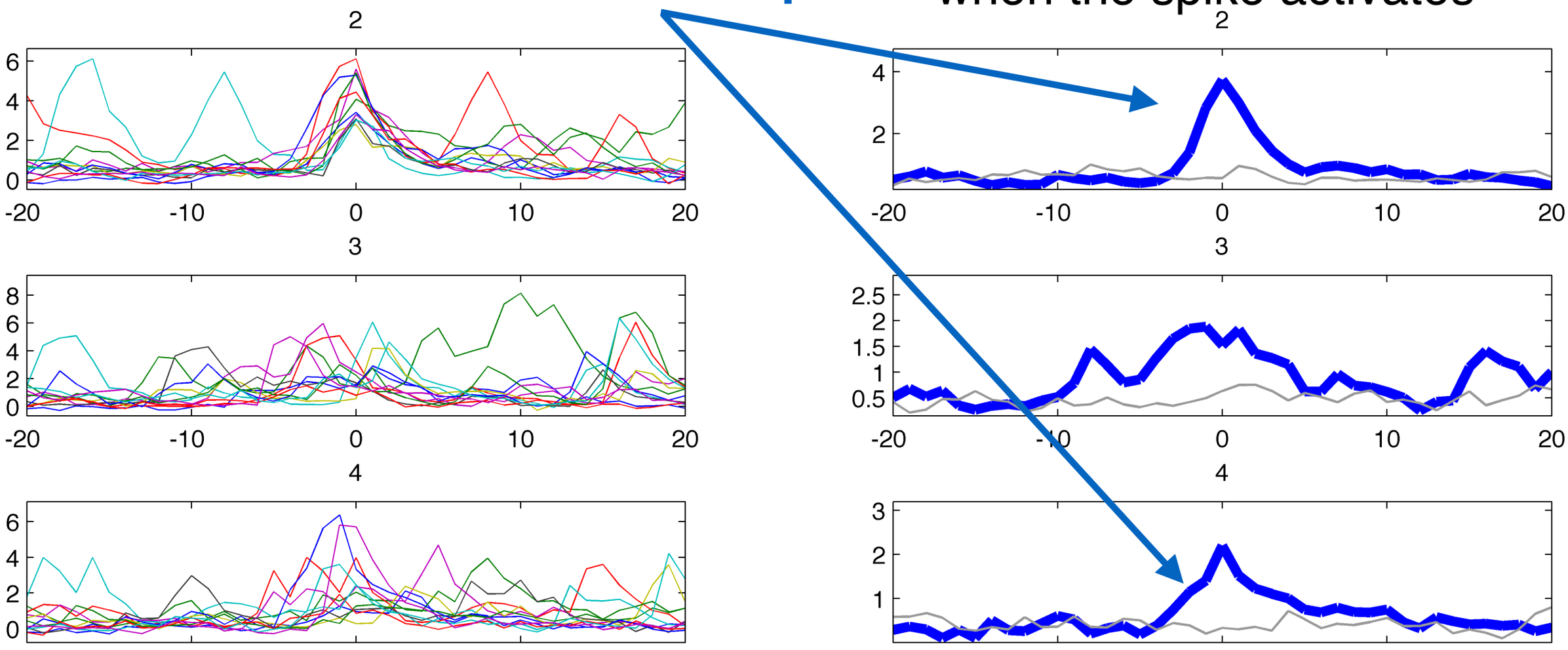


Trigger-Based Averages

Threshold Amplitude: 2.5-6.0

STA bump

Non-random process activity when the spike activates



Some Remarks

- All processes exhibit “spikes”
- Spikes are not all-or-none (amplitude varies)
- Activity seems mixed: spikes + “subthreshold” events
- Soma is less active than other processes – soma has fewer spikes, consistent with the need to receive enough inputs from processes to reach threshold
- Processes are more active than the soma – consistent with them being “closer” than soma to synaptic inputs

Questions To Ask With The Model

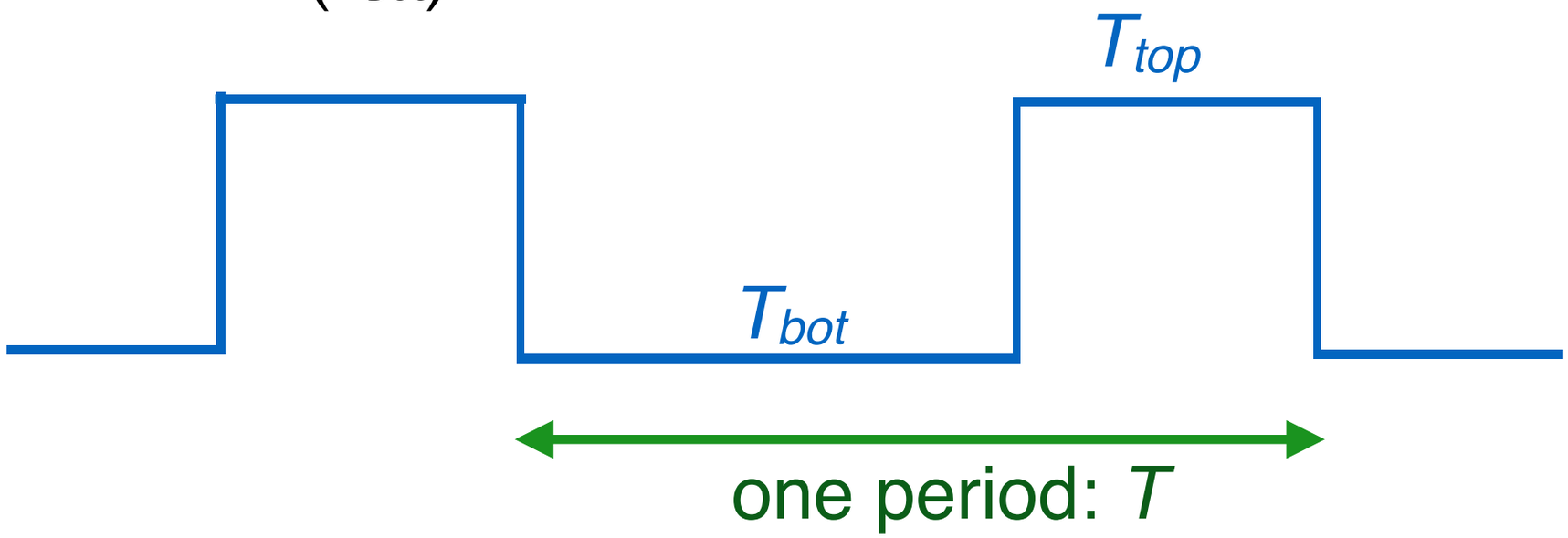
- Can we reproduce these results: processes are more active than soma; STAs of different ROIs are different, with bumps **preceding or following soma spikes**; activity is composed of events of various sizes; larger events are more likely to propagate further
- Do more active processes have STA bumps before soma spikes while less active processes have STA bumps following soma spikes?
- More generally (ambitiously) can we generate/explain the various shapes of the STAs observed experimentally

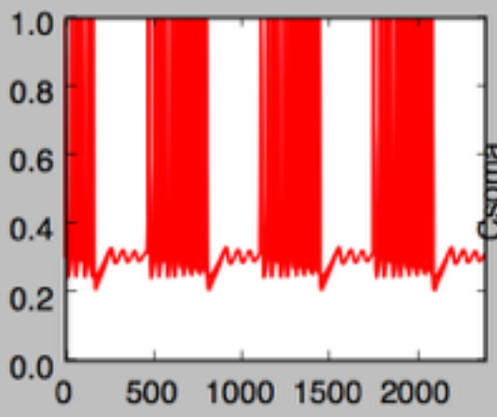
Random Square Pulse

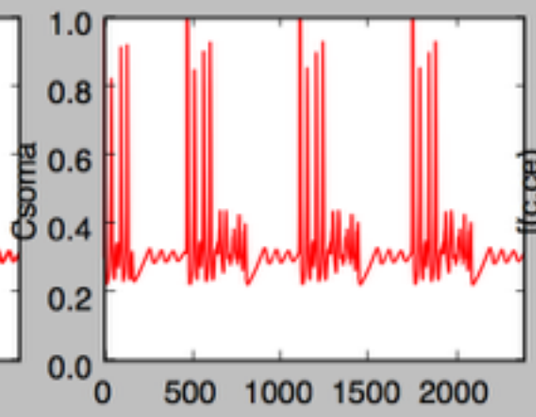
- To introduce randomness for "r" (neuronal activity), we turn "neurons" on and off to mimic experimental conditions
- We chose a square pulse
- We present a simple algorithm to generate square pulses [0 to 1 to 0] with control of frequency, and the time spent at 0 and 1.

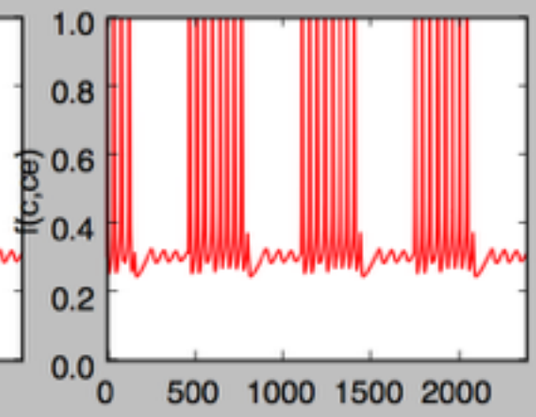
Create a Square Pulse

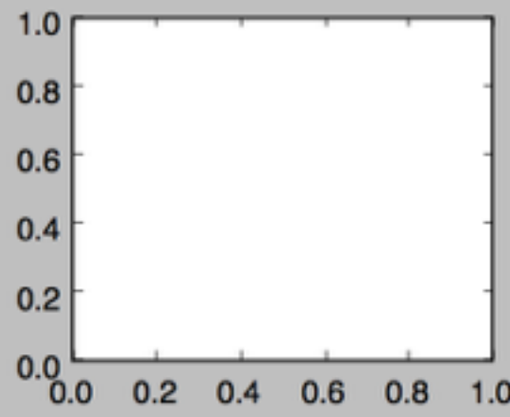
- Control the period T, and the length of the top (T_{top}) and bottom (T_{bot})

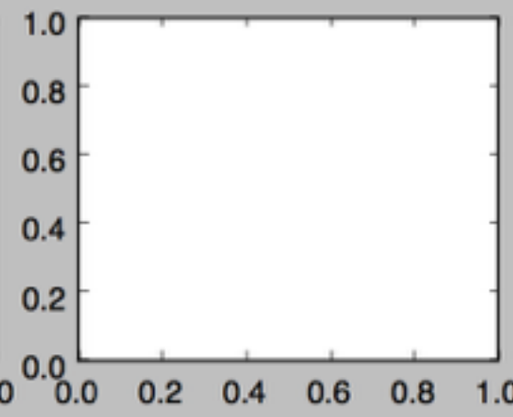


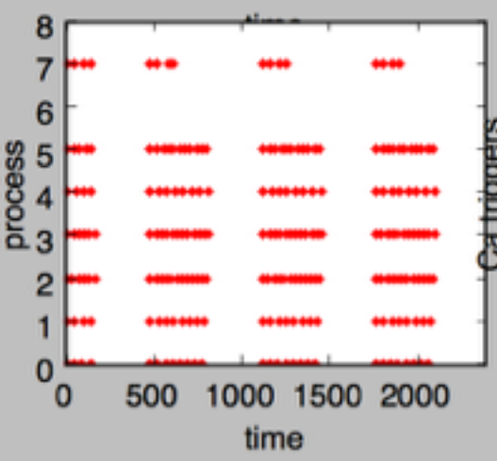

1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000

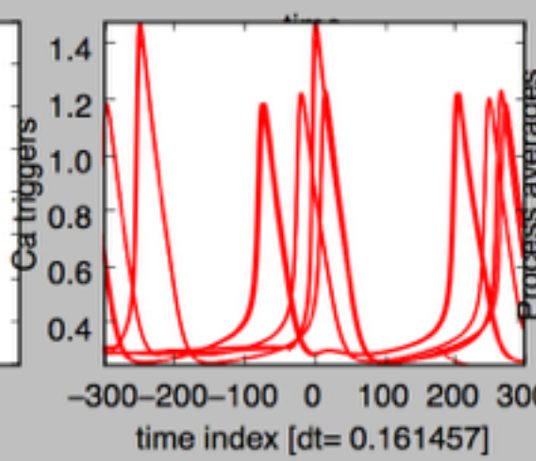

Csoma
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000

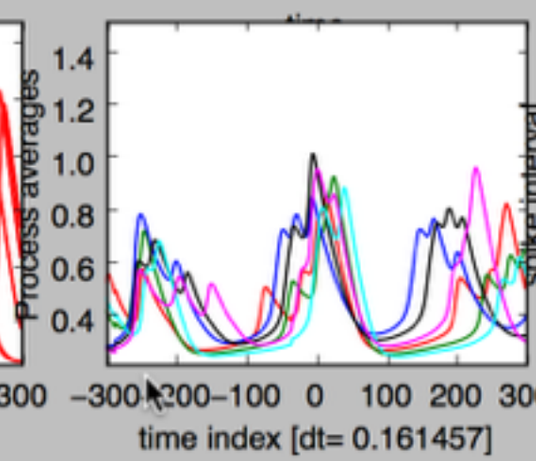

f(c;ce)
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000

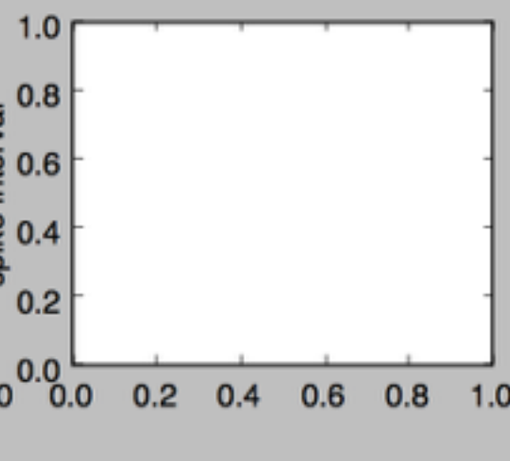

1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0

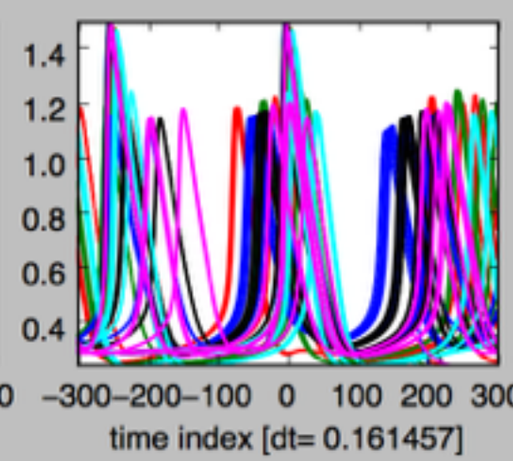

1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0


process
8
7
6
5
4
3
2
1
0
0
500
1000
1500
2000
time

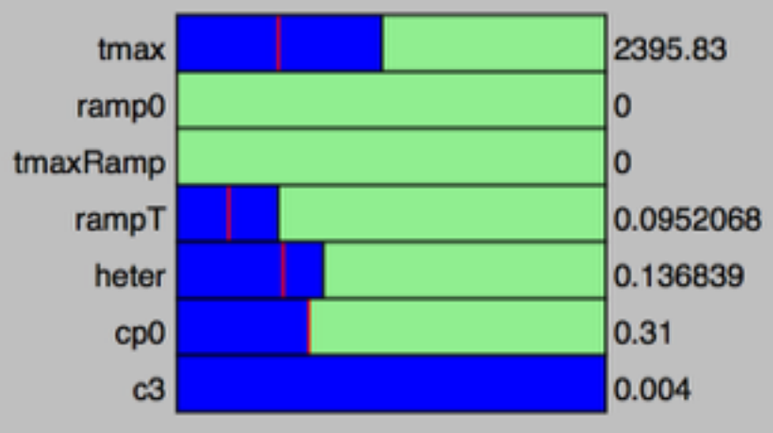

Ca triggers
1.4
1.2
1.0
0.8
0.6
0.4
–300
–200
–100
0
100
200
300
time index [dt= 0.161457]

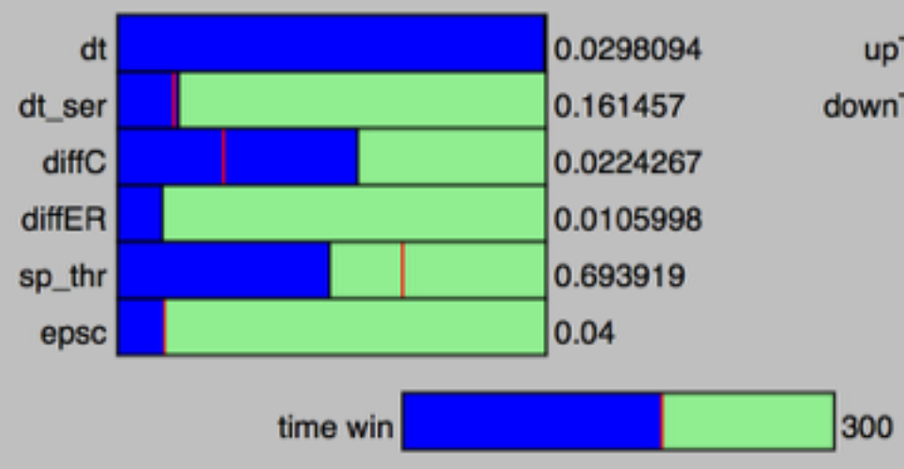

Process averages
1.4
1.2
1.0
0.8
0.6
0.4
–300
–200
–100
0
100
200
300
time index [dt= 0.161457]


spike interval
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0


1.4
1.2
1.0
0.8
0.6
0.4
–300
–200
–100
0
100
200
300
time index [dt= 0.161457]

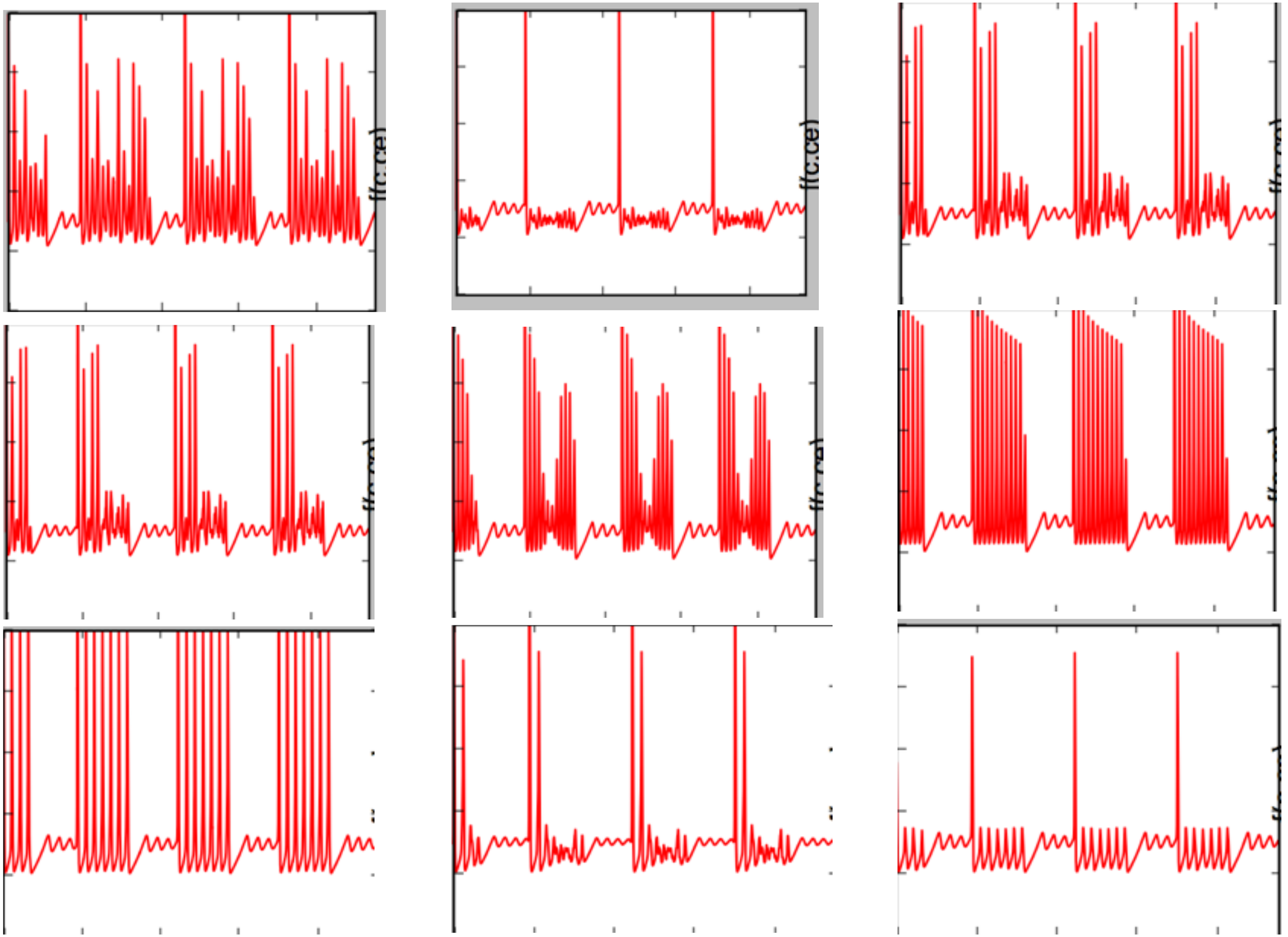

toggle


tmax
2395.83
ramp0
0
tmaxRamp
0
rampT
0.0952068
heter
0.136839
cp0
0.31
c3
0.004


dt
0.0298094
dt_ser
0.161457
diffC
0.0224267
diffER
0.0105998
sp_thr
0.693919
epsc
0.04
time win
300


upTime
335.338
downTime
306.743

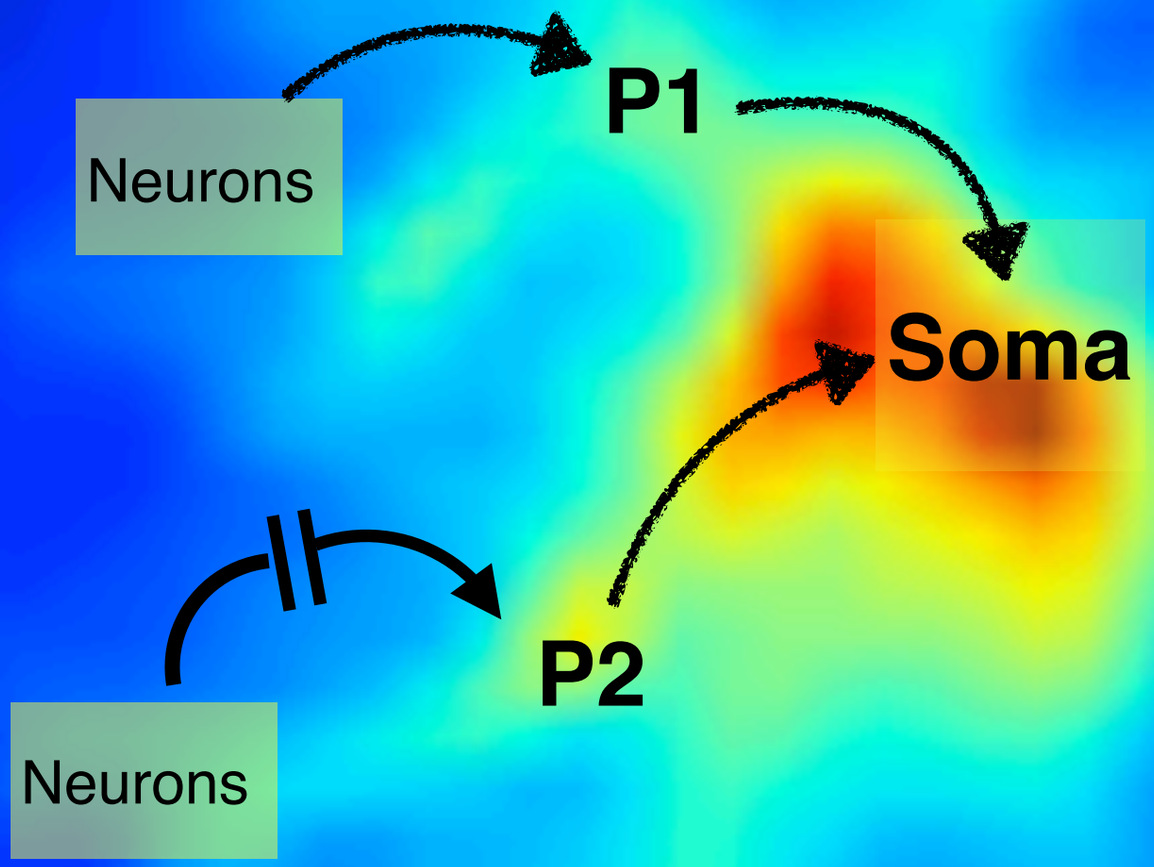
Soma activity



Effect of one process on another

- When a process spikes, what is its origin?
  - the soma?
  - neuronal input?
- We turn off process 0 to investigate

Effect Of One Process On Another

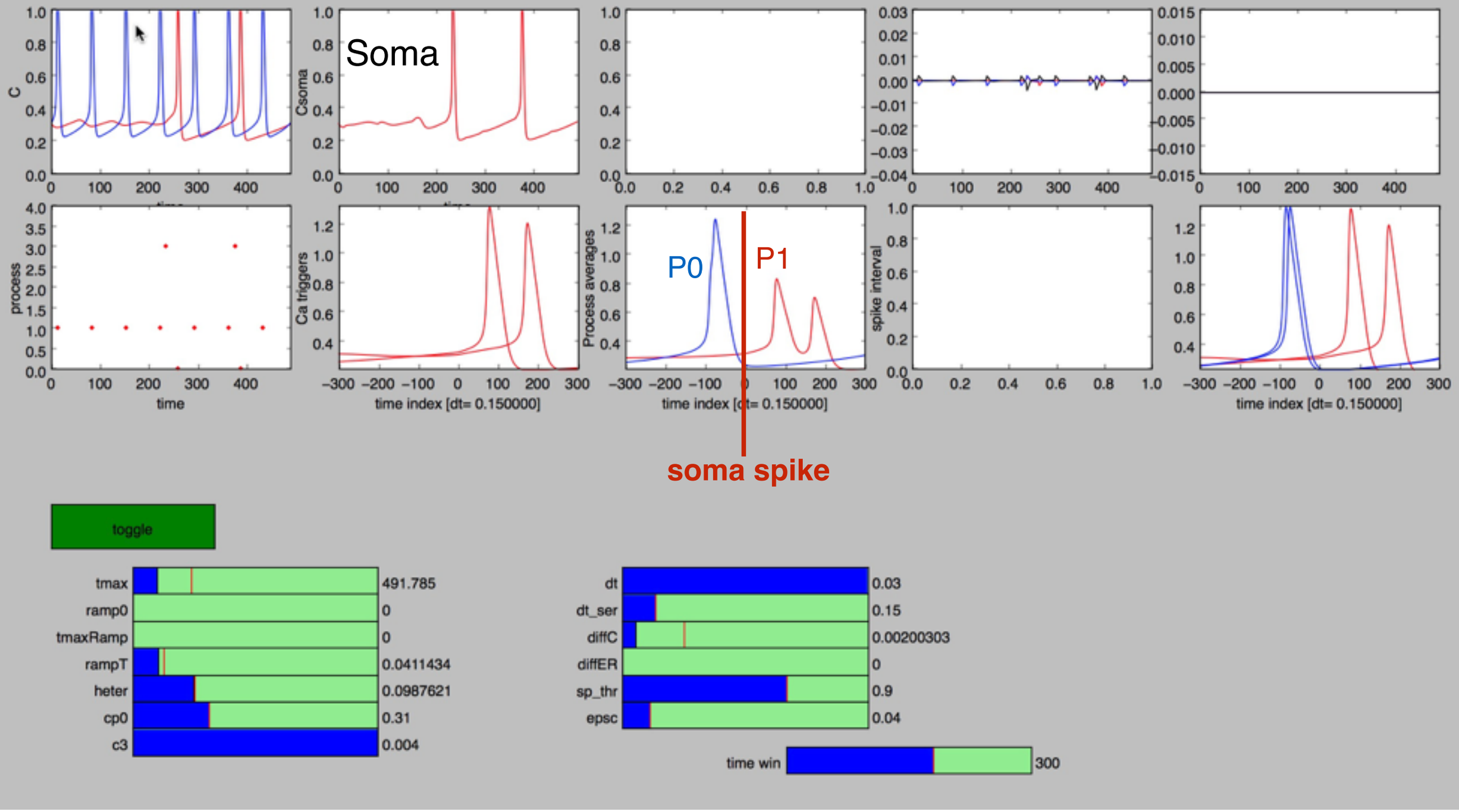


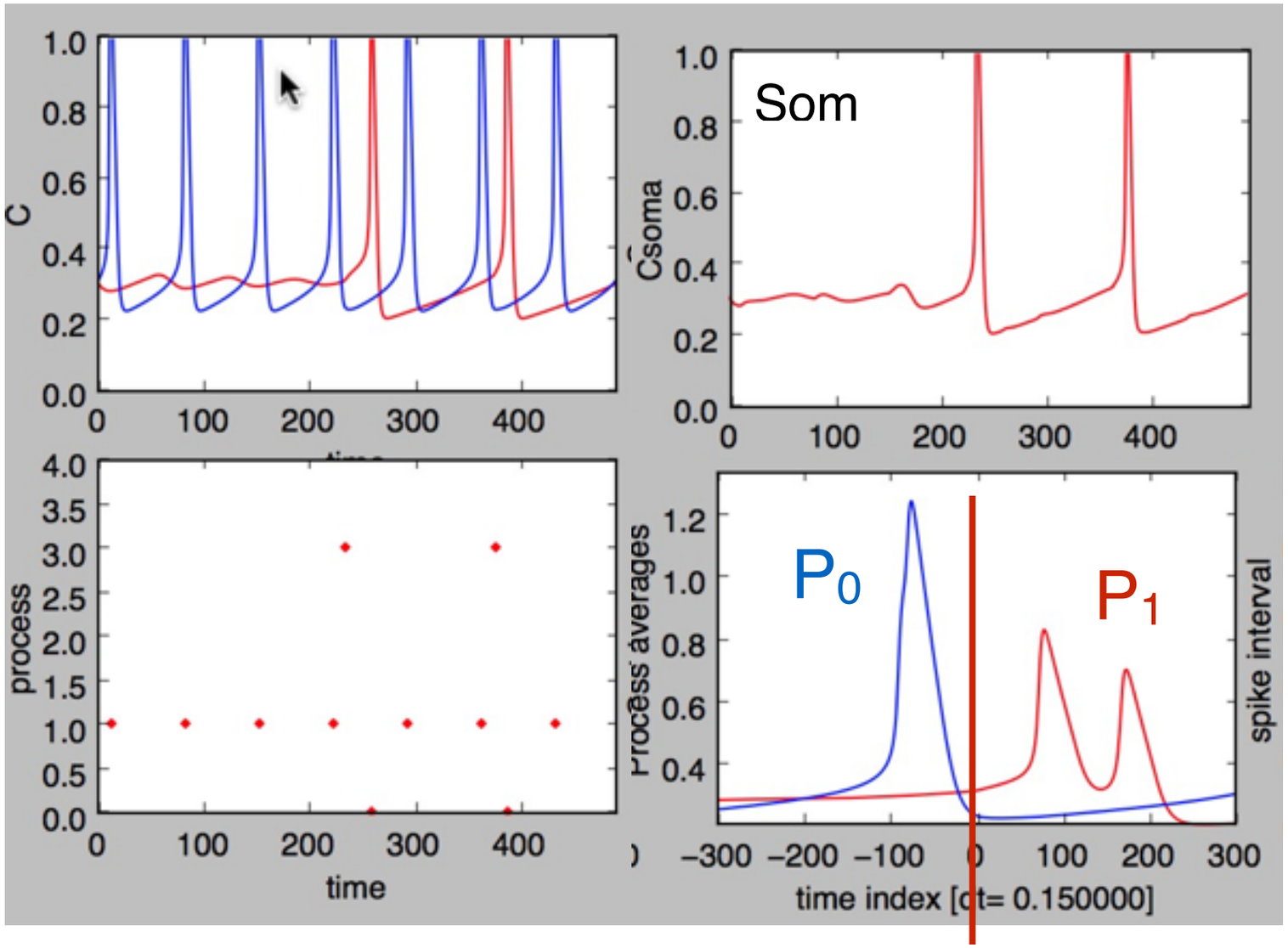
Effect of one process on another

$$\frac{dCa_{p_0}}{dt} = r_L + c_4 f() + \text{Diffusion}_0 - Ca_{p_0}$$

$$\frac{dCa_{p_i}}{dt} = r_L + r_{Amp} - c_4 f() + \text{Diffusion}_i - Ca_{p_i}$$

$$\ldots\ldots$$


Soma
P0
P1
soma spike
C
Csoma
process
Ca triggers
Process averages
spike interval
time
time index [dt= 0.150000]
toggle
tmax 491.785
ramp0 0
tmaxRamp 0
rampT 0.0411434
heter 0.0987621
cp0 0.31
c3 0.004
dt 0.03
dt_ser 0.15
diffC 0.00200303
diffER 0
sp_thr 0.9
epsc 0.04
time win 300



What happens in the real astrocyte?

What are the
mechanisms responsible
for spiking?

How are they modeled?

Can the model be predictive?

Future Work

- Summarize our results
- Catalog and characterize spiking patterns as a function of randomness
  - at this stage, multiple runs with randomness produce rather different results
  - consider more complex models that take channel and IP3 production into account
  - take neuronal input into account

Future work

Neurons

P1

Neurons

P1

Neurons

P1

Soma

Neurons

P2

Neurons

P2

Neurons

P2

Neurons are in the vicinity of the processes

Fully Spatial Model

- Once we develop intuition with the models above, we can develop a fully spatial model
  - ODEs become PDEs with standard diffusion terms:

$$D\nabla^2 Ca$$

Thank you!

Questions?