Characterizing neurons in networks with noisy input

Thursday 7 October 2010

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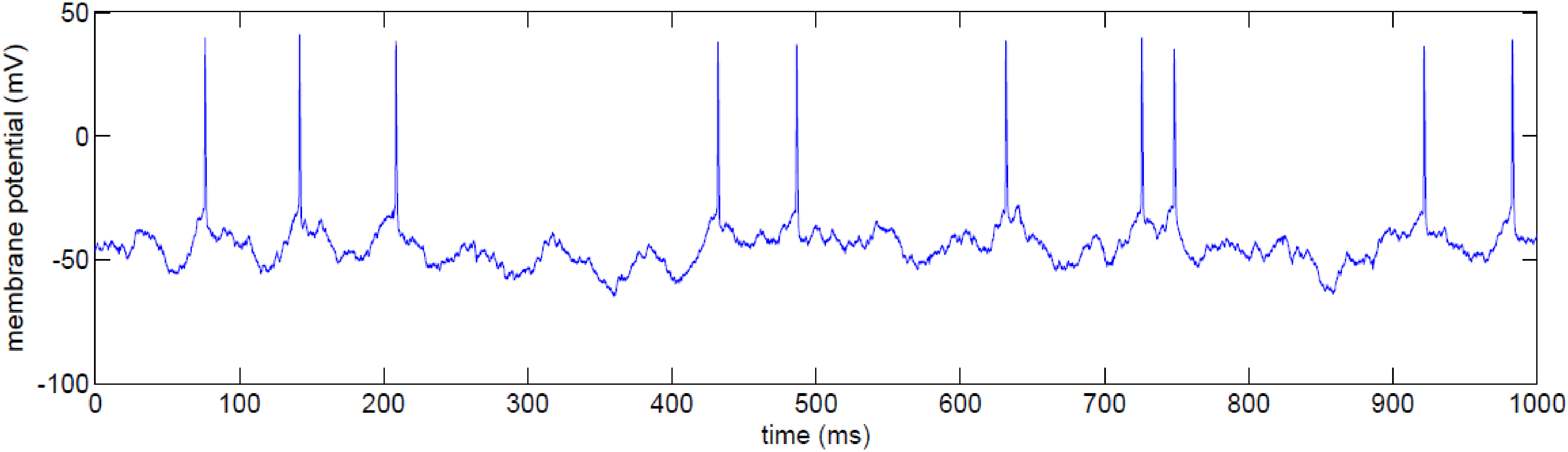
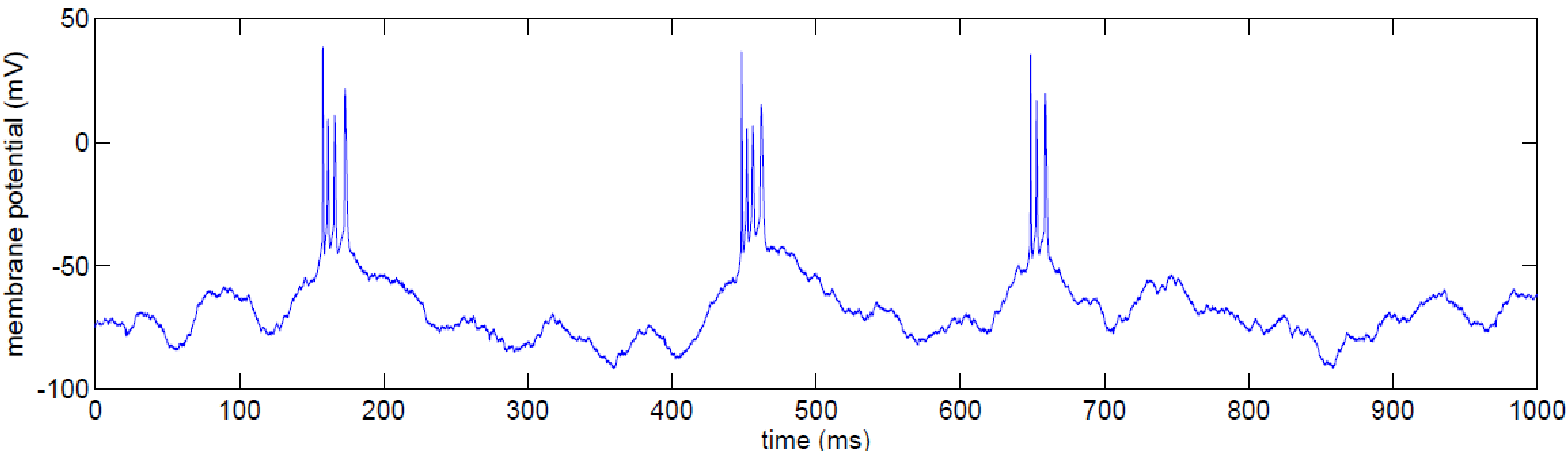
This is unfinished work

- Please interrupt me for any hints, suggestions, corrections, etc

Bursting



membrane potential (mV)
50
0
-50
-100
0
100
200
300
400
500
600
700
800
900
1000
time (ms)



membrane potential (mV)
50
0
-50
-100
0
100
200
300
400
500
600
700
800
900
1000
time (ms)

Bursting

Different theories

- Lisman: bursts are code, spikes are noise
- Sherman: bursts are ‘wake-up call’ (feature detection versus stimulus estimation)
- Reliability, STDP, resonance, parallel coding

Main goal

- What do spikes and bursts code for?
- How is this influenced by the surrounding network?

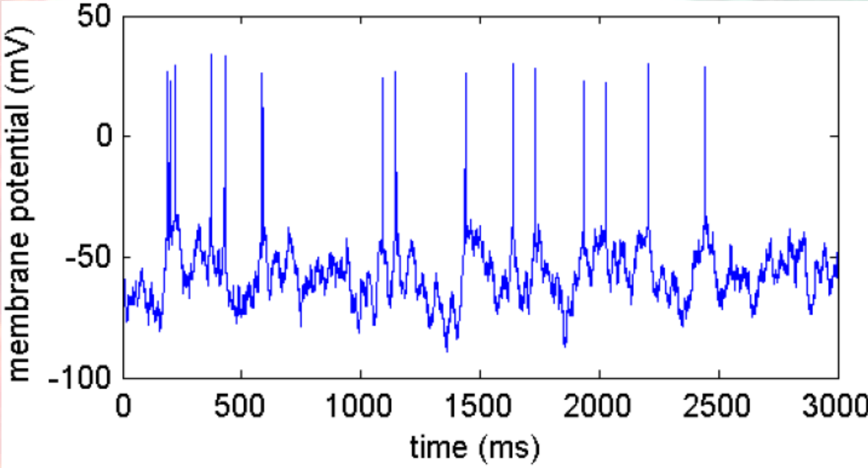
- Two model systems
  - Thalamus
  - CA3 Hippocampus

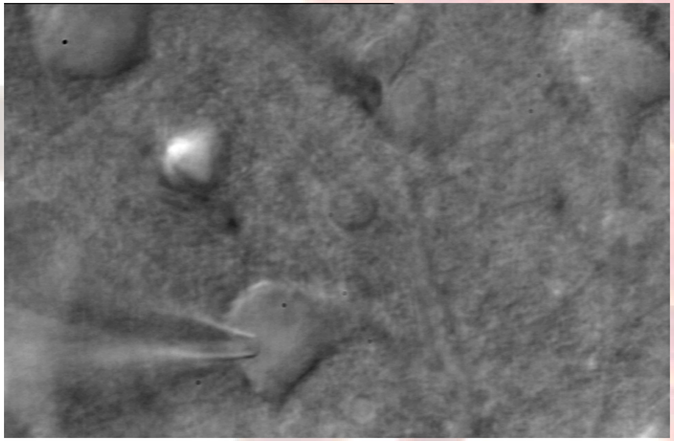
Outline

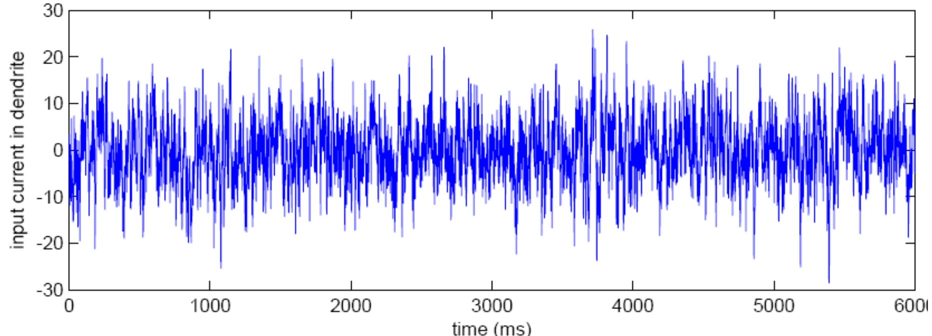
- Robustness and precision
- Regime changes in thalamo-cortical (tc-relay) relay cells
  - experiments
  - models

In-vitro Experiments (brain-slice)

- Inject frozen noise input
  - In experiment







Compare with computational models

- Inject frozen noise input
  - In experiment or model

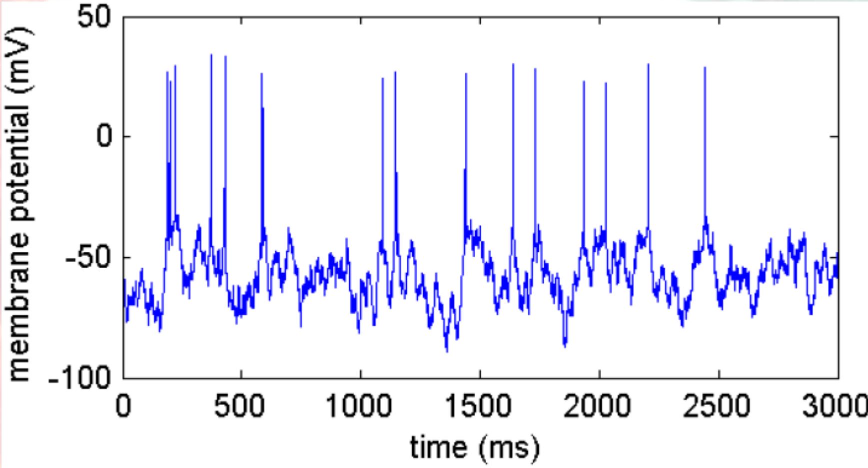
$$C\frac{dv}{dt} = -I_{Na} - I_K - I_L + I$$

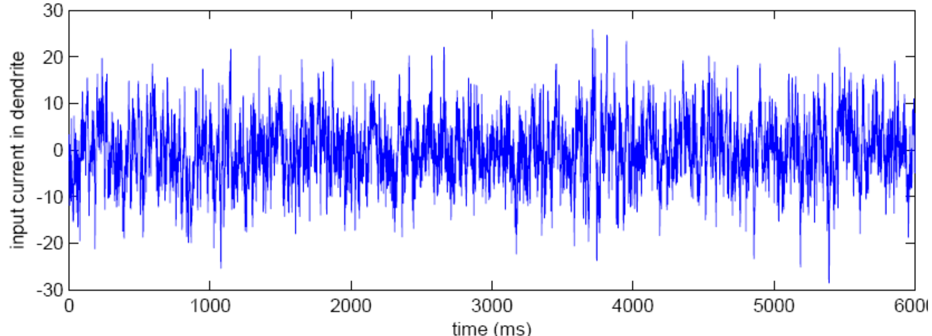
$$I_{Na} = g_{Na} m_\infty^3(v) h (v - v_{Na})$$

$$I_K = g_K n^4 (v - v_K)$$

$$I_L = g_L (v - v_L)$$

$$\frac{du}{dt} = \frac{u_\infty(v) - u}{\tau_u(v)}$$





Set-up

- Find current that keeps neuron at desired membrane potential
- Inject noise on top
- Noisy input current
  - σ = 75 or 100 pA
  - exponential filter, τ=10 ms

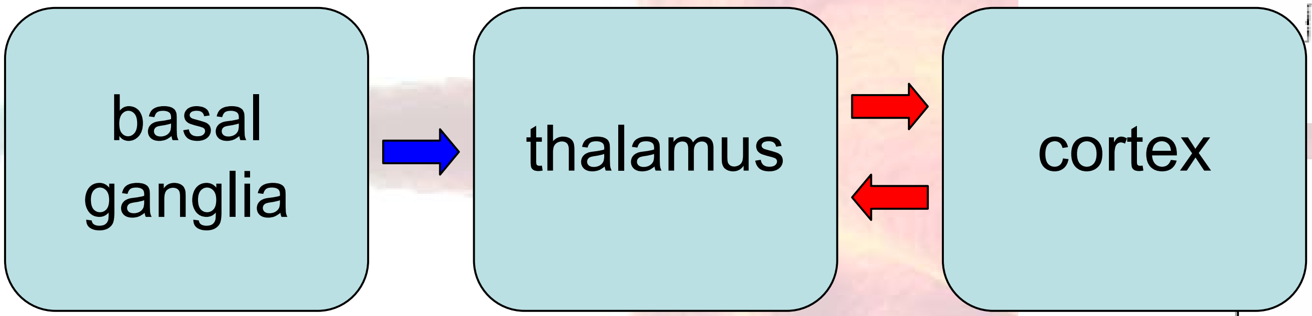
Main goal

- What do spikes and bursts code for?
- How is this influenced by the surrounding network?

- Two model systems
  - Thalamus
  - CA3 Hippocampus

Thalamocortical relay cells

- Two response modes:
  - single spike



- Change mean of input to mimic basal ganglia input

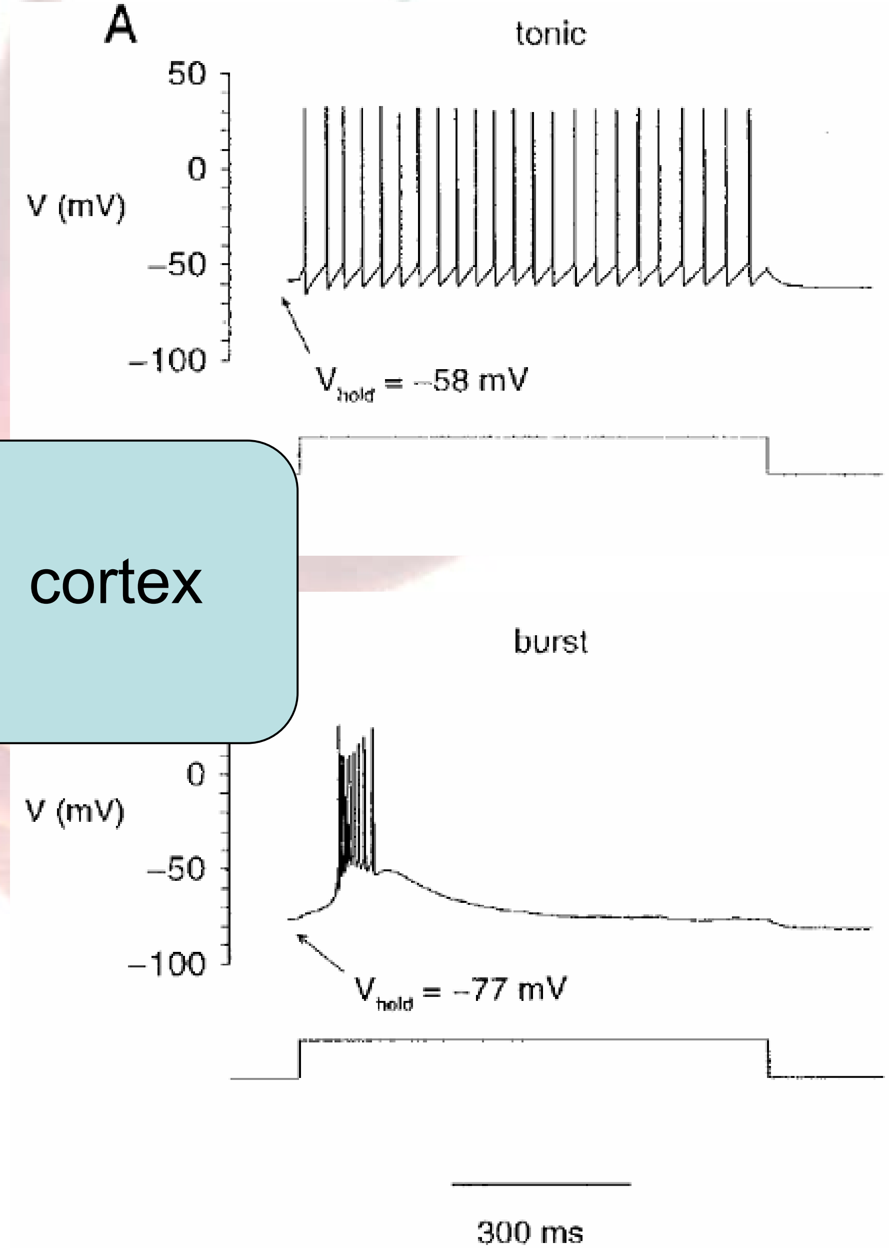


Image: Smith et al, J. Neurophys. 2000

Main goal

- What do spikes and bursts code for?
- How is this influenced by the surrounding network?

- Two model systems
  - Thalamus
  - CA3 Hippocampus

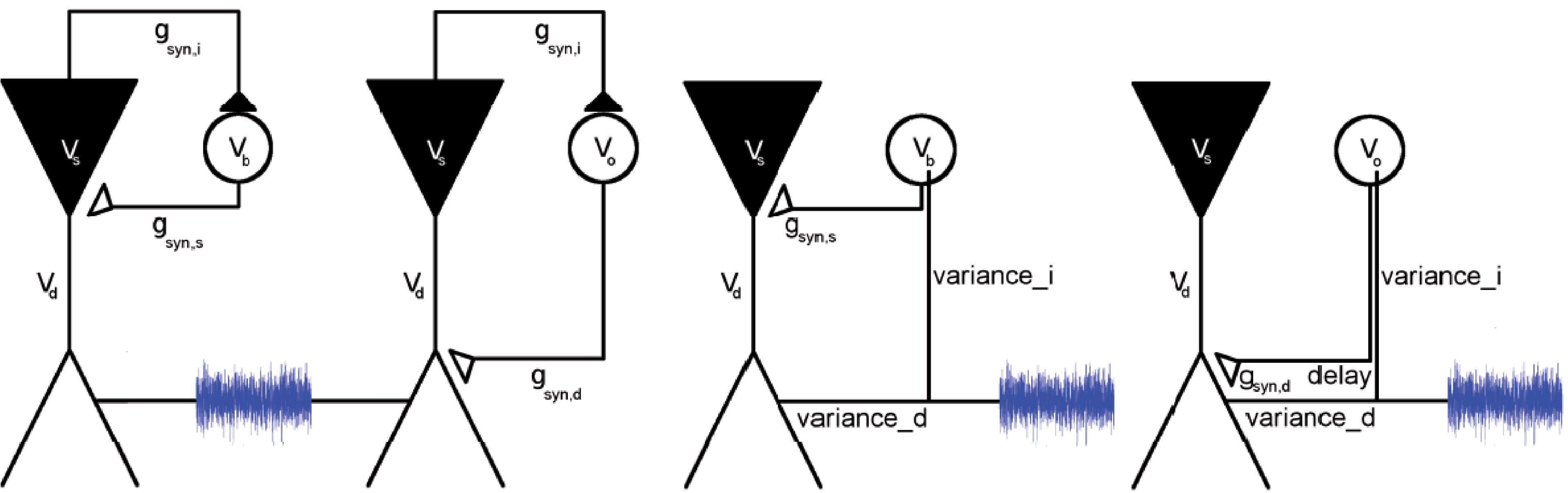
Inhibition in the hippocampus

- CA3 pyramidal neurons to burst as a result of ‘ping-pong’ effect between soma and dendrite
- When do these neurons respond with a single spike and when with a burst?
- How does inhibition influence this?

Hippocampus (CA3)

- Models:

Feedback inhibition   Feed-forward inhibition



- Experimental: first data from pyramidal and O-LM cells

- But first…

Do cells respond in a stereotypical manner?

- Do neurons respond stochastically or deterministically?
- If every neuron has its ‘own code’ → hard to generalize
- If all neurons exactly the same → how does a neuron adapt to environment?
- Ideally: every neuron type/class responds in a similar way

Do cells respond in a stereotypical manner?

- Inject frozen noise multiple times
- Bin spike trains, look for coincident spikes
- Coincidence factor
  - 1 if spike trains are the same
  - 0 if train 2 is random (Poisson)
  - negative for correlations<0
  - precision

(Kistler, Gerstner & van Hemmen 1997)
(Jolivet et al 2006)

$$\Gamma = \frac{N_{coinc} - \langle N_{coinc} \rangle}{\frac{1}{2}(N_1 + N_2)} \frac{1}{\mathbf{N}}$$

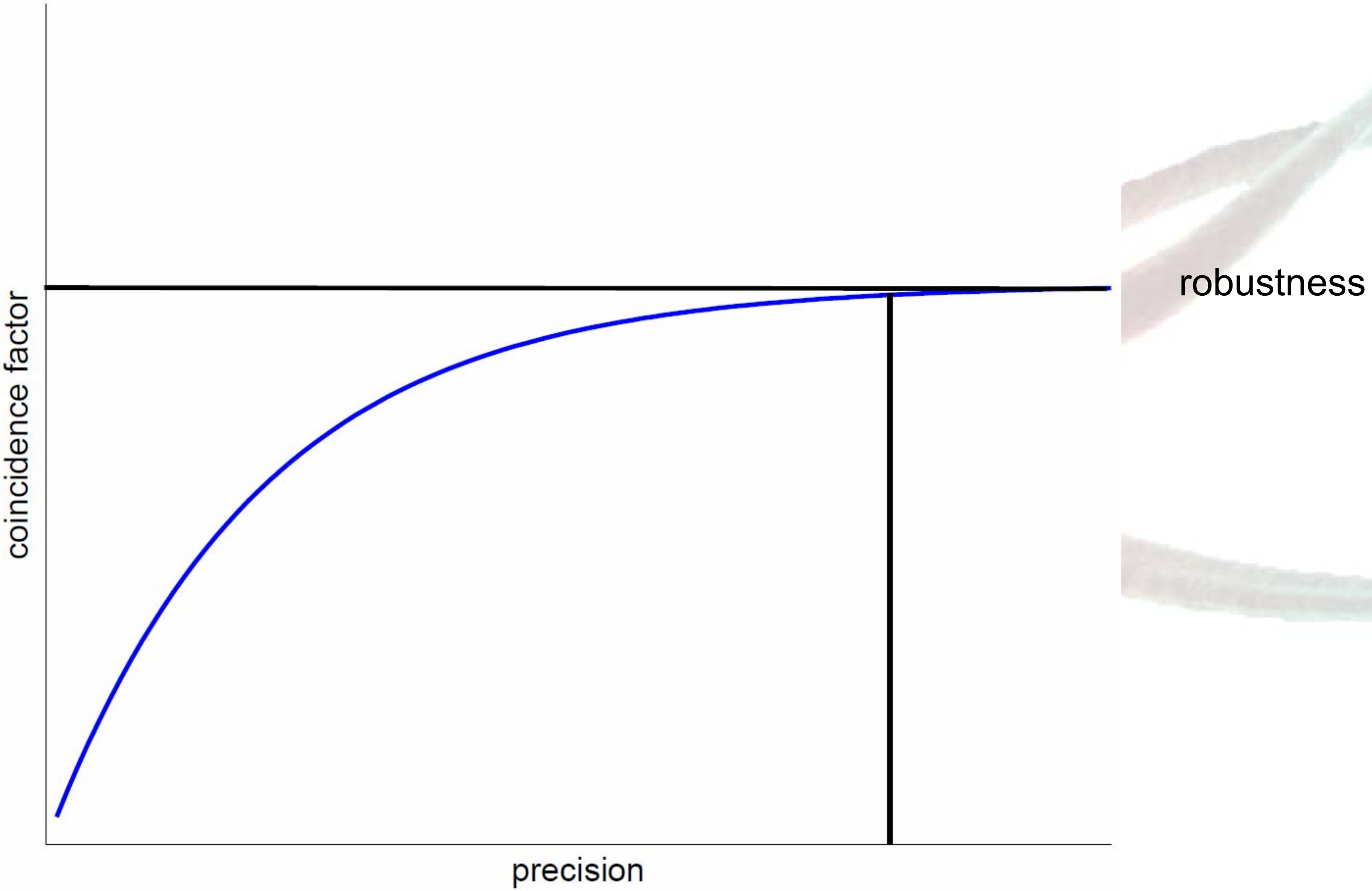
$\langle N_{coinc} \rangle = 2 * \nu_2 * \text{precision} * \mathrm{N}_1$

(expected # coincidences Poisson process)

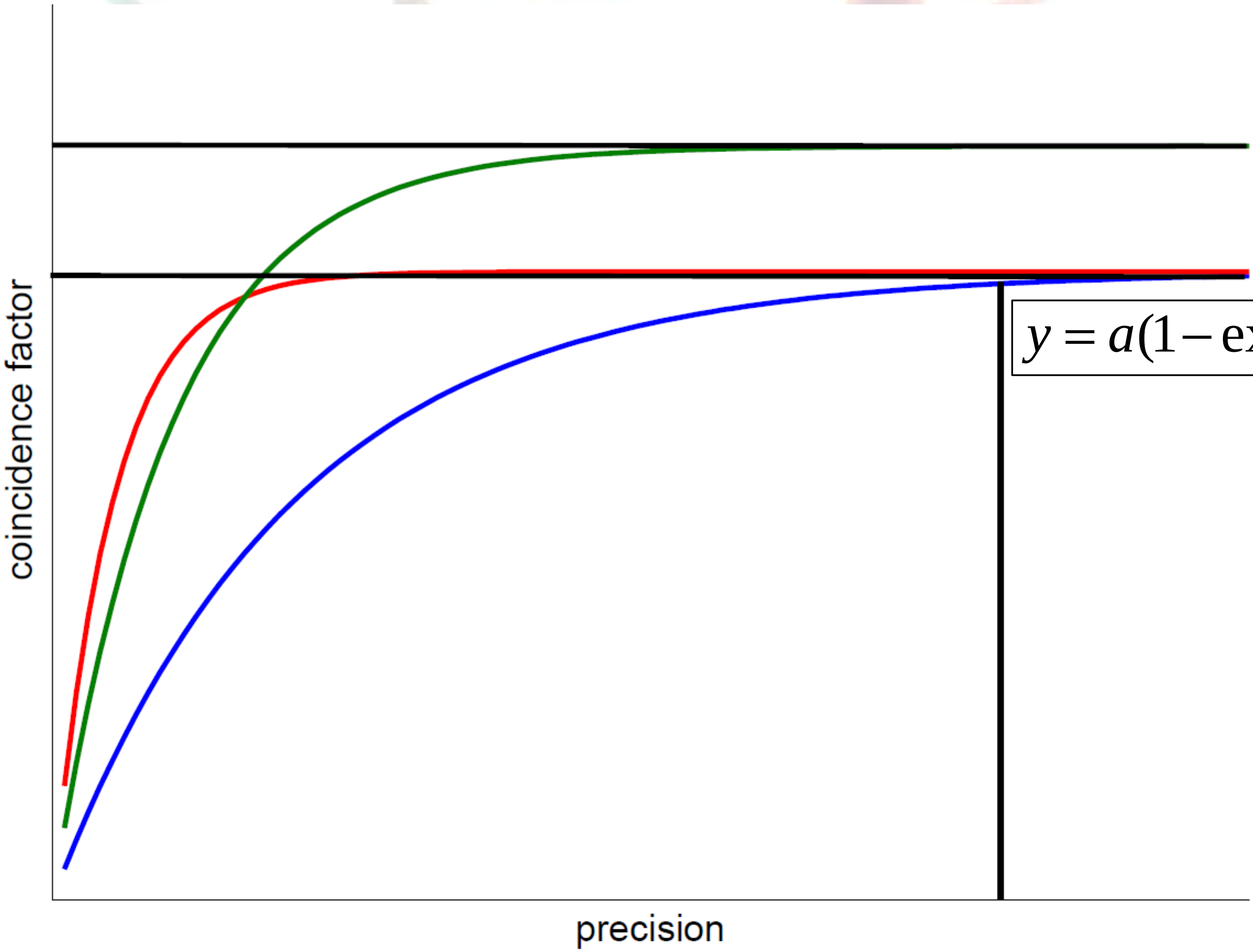
$N_{1,2} = \#$ of spikes in train 1,2

$\mathbf{N} = 1 - 2 * \nu_2 * \text{precision}$

Precision and robustness



Precision and robustness



Proposal

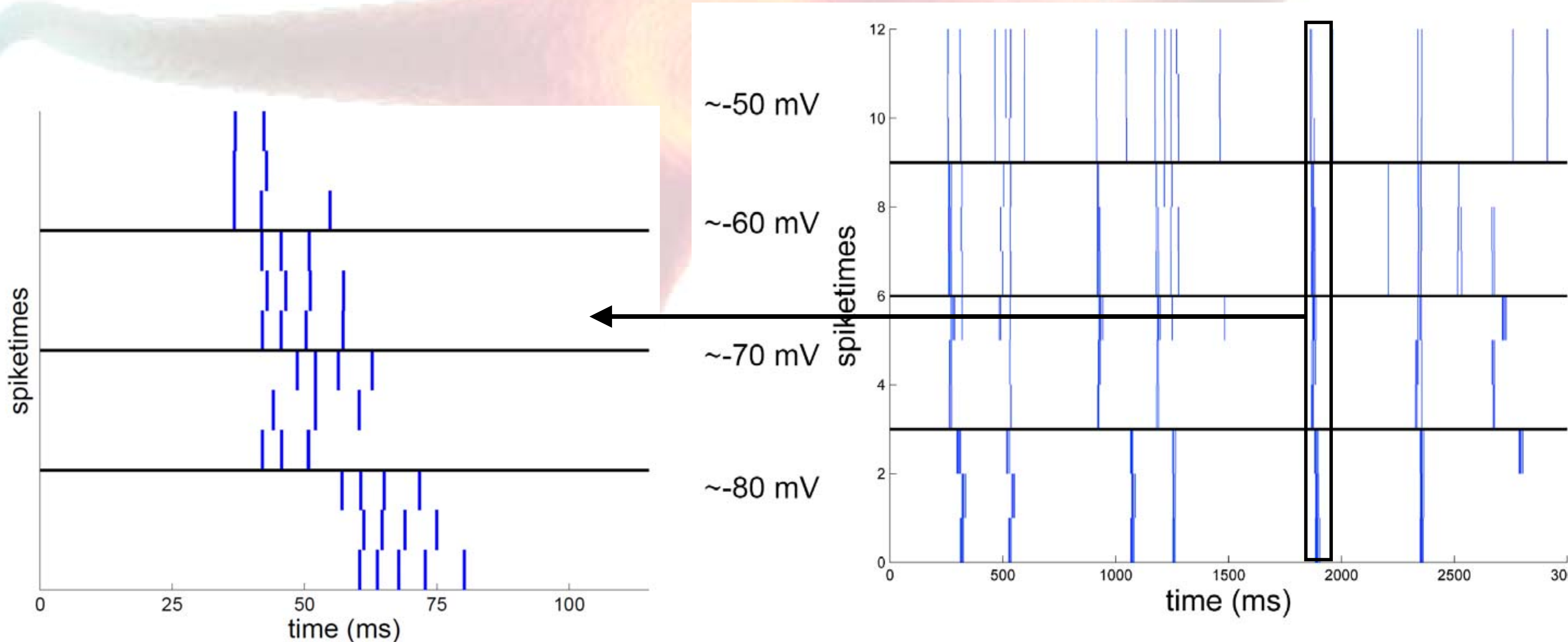
- fit to single exponent

$$y = a(1 - \exp(-b \cdot precision))$$

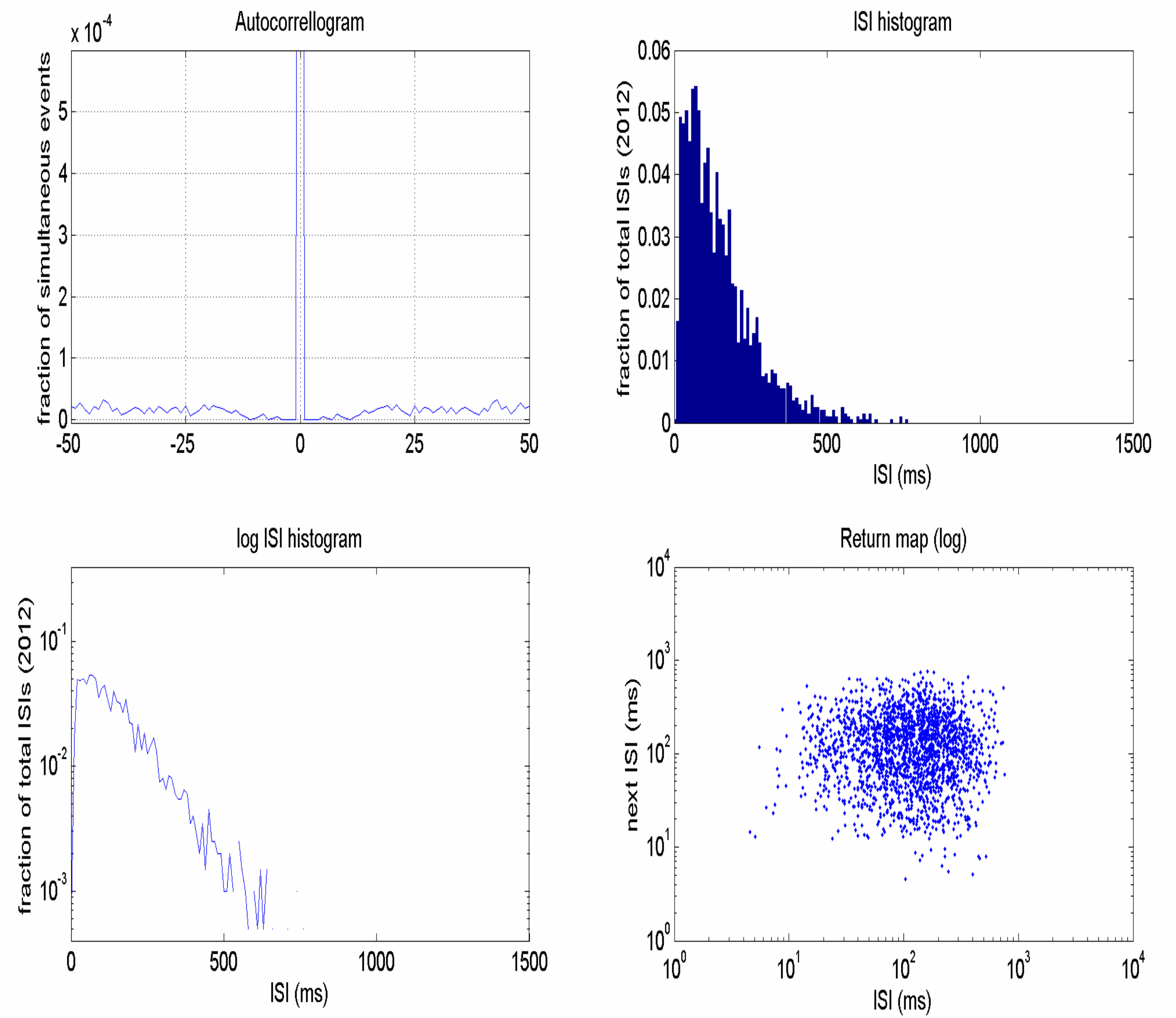
- a=robustness
- b=‘precision coefficient’

Tc relay cells

- Inject the same noise multiple times
- Increase mean: shift bursting-> spiking
- NB Burst is counted as single event

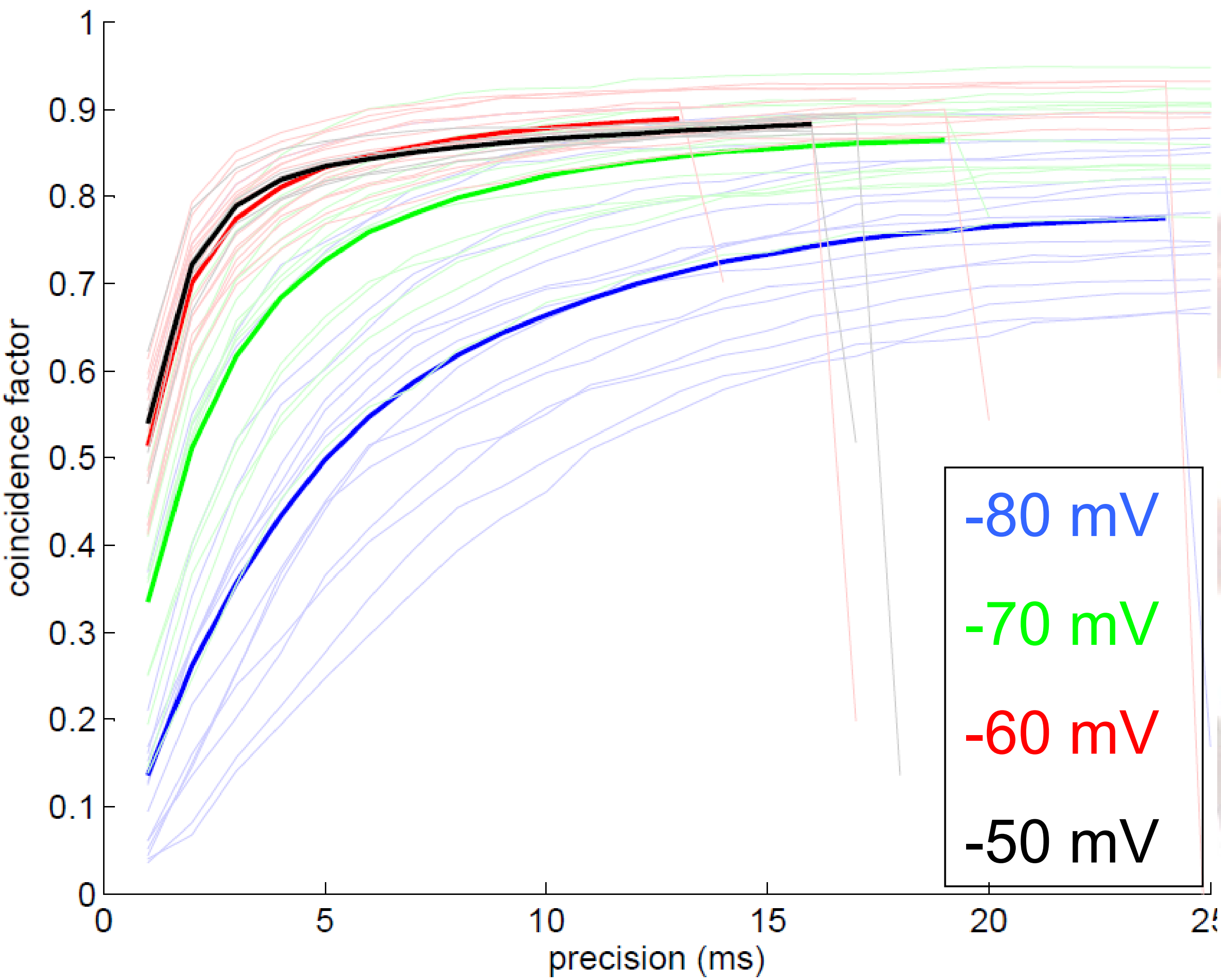


Burstiness


Autocorrellogram
x 10^-4
fraction of simultaneous events
0
1
2
3
4
5
-50
-25
0
25
50
ISI histogram
fraction of total ISIs (2012)
0.06
0.05
0.04
0.03
0.02
0.01
0
0
500
1000
1500
ISI (ms)
log ISI histogram
fraction of total ISIs (2012)
10^-1
10^-2
10^-3
0
500
1000
1500
ISI (ms)
Return map (log)
next ISI (ms)
10^4
10^3
10^2
10^1
10^0
10^0
10^1
10^2
10^3
10^4
ISI (ms)

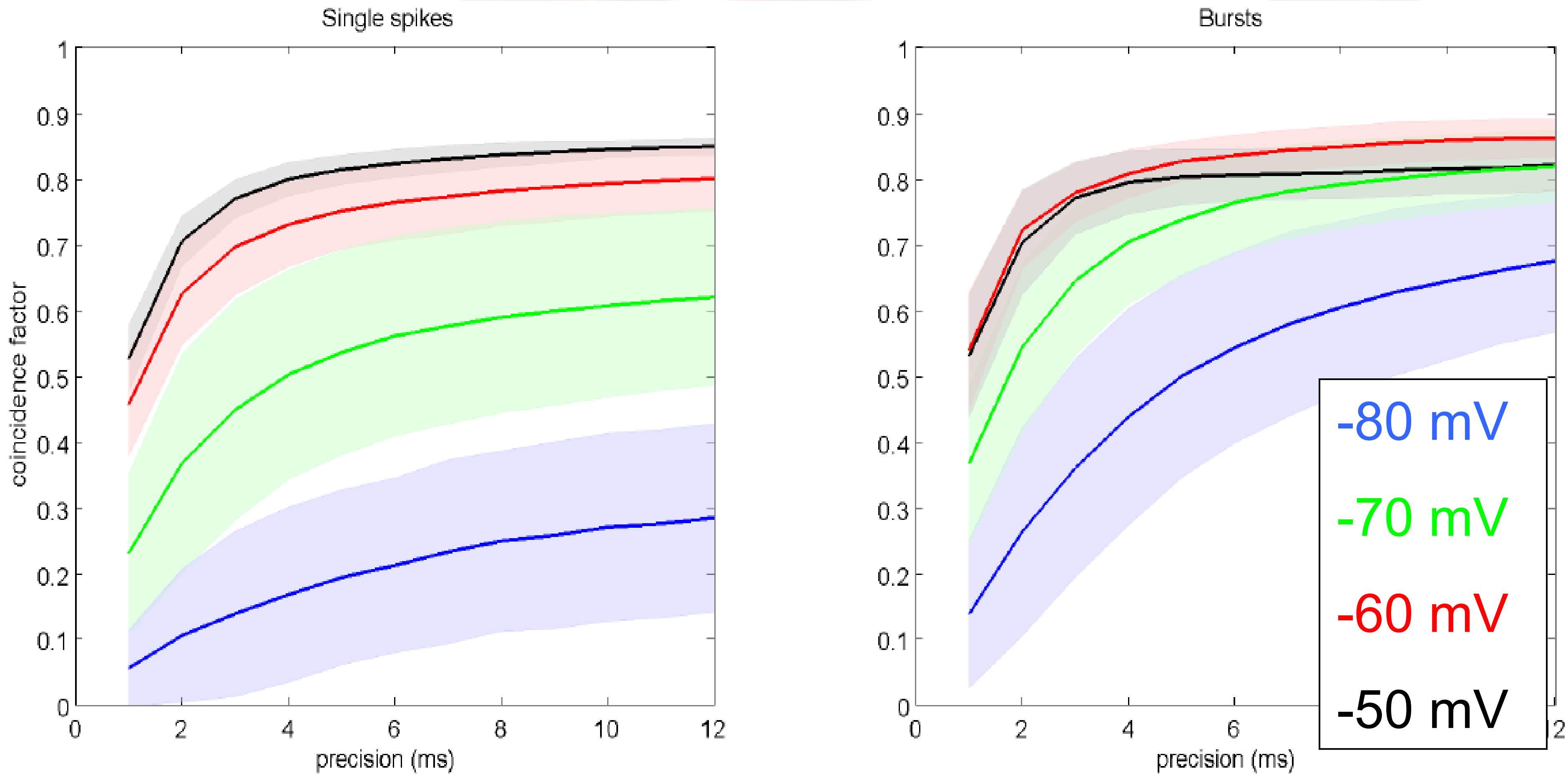
Coincidence factor: thalamus

- Compare same cell; vary mean input current

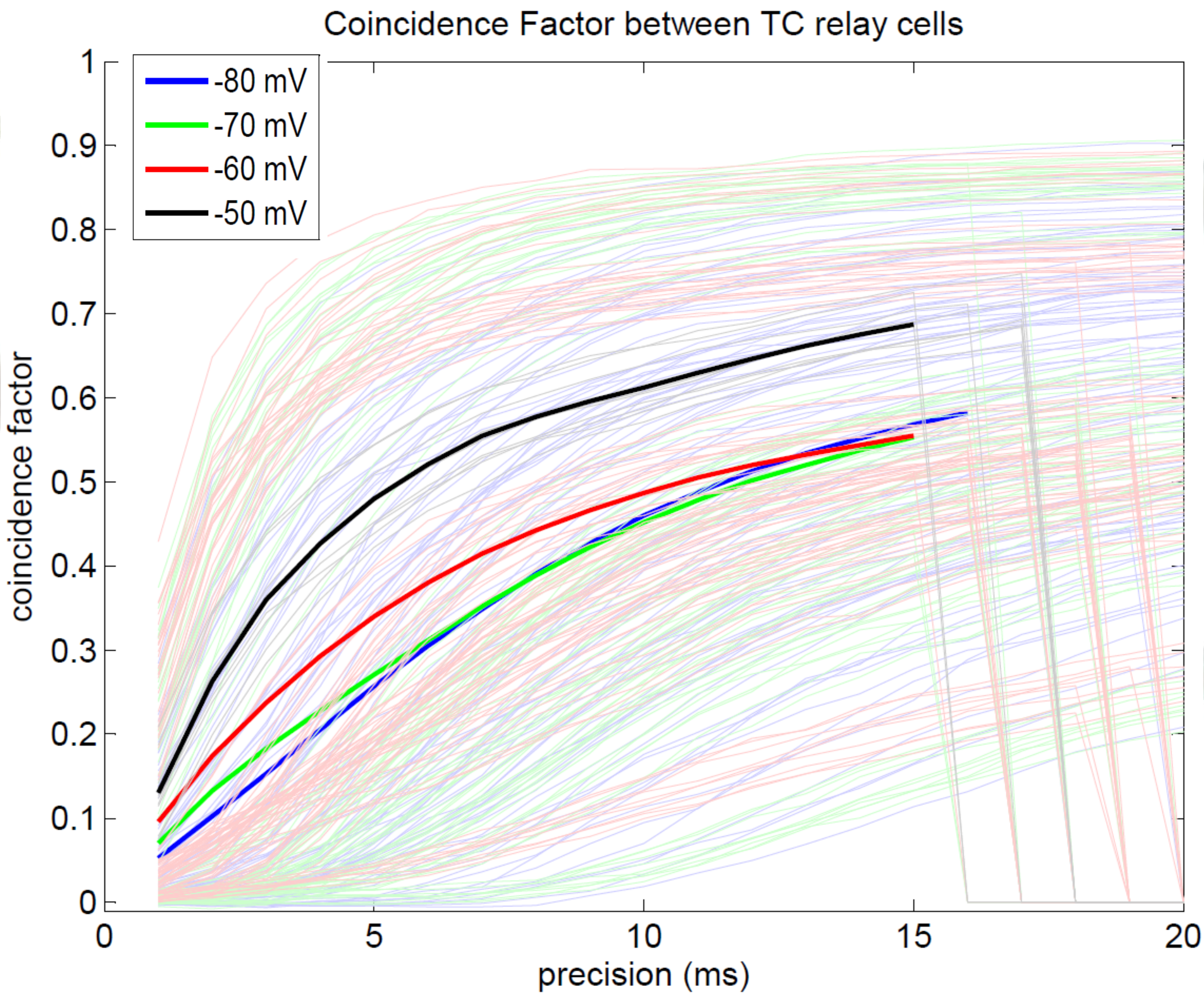


Increasing membrane potential: increasing robustness and precision

Are bursts less precise/robust than spikes?

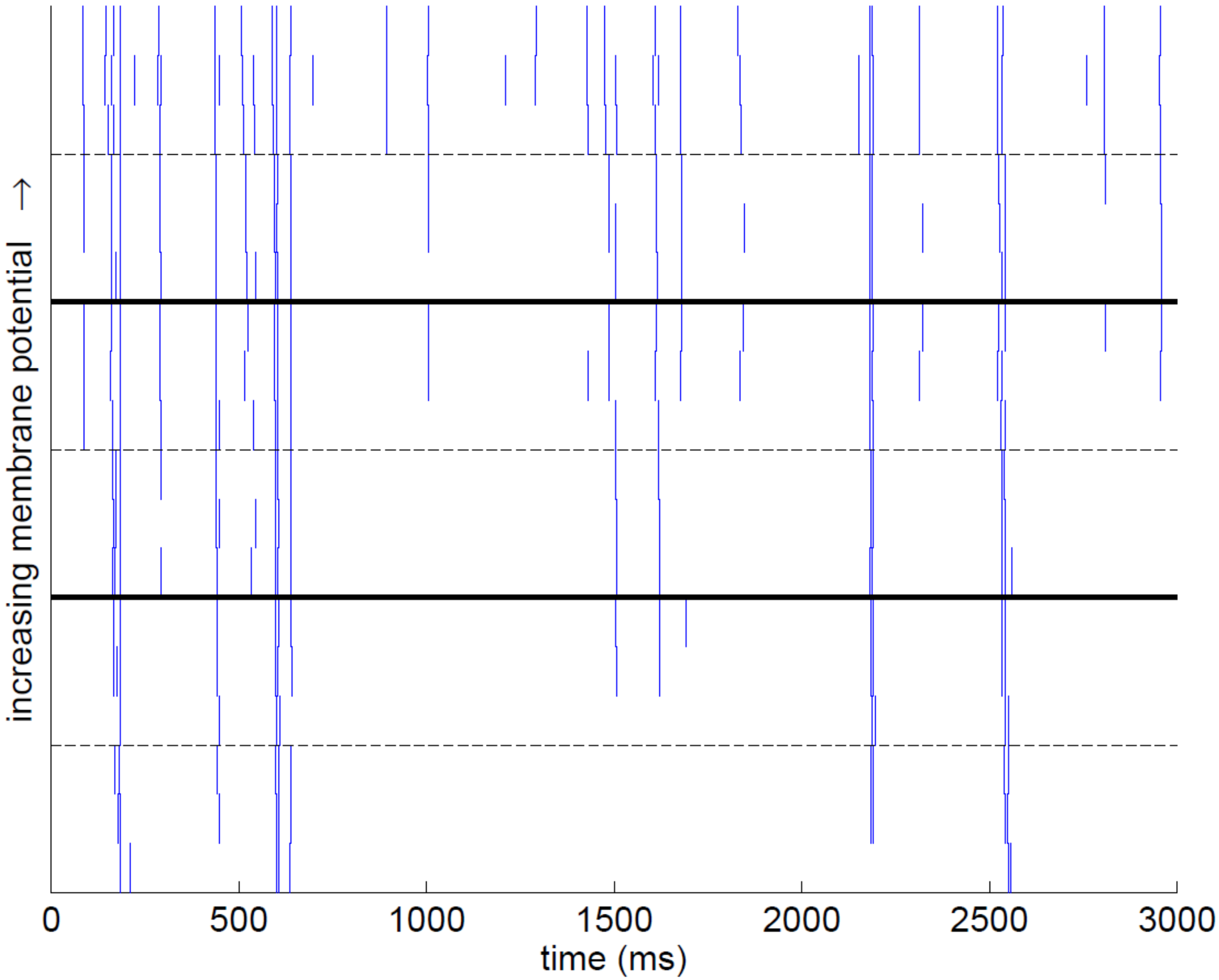


Coincidence factor: thalamus



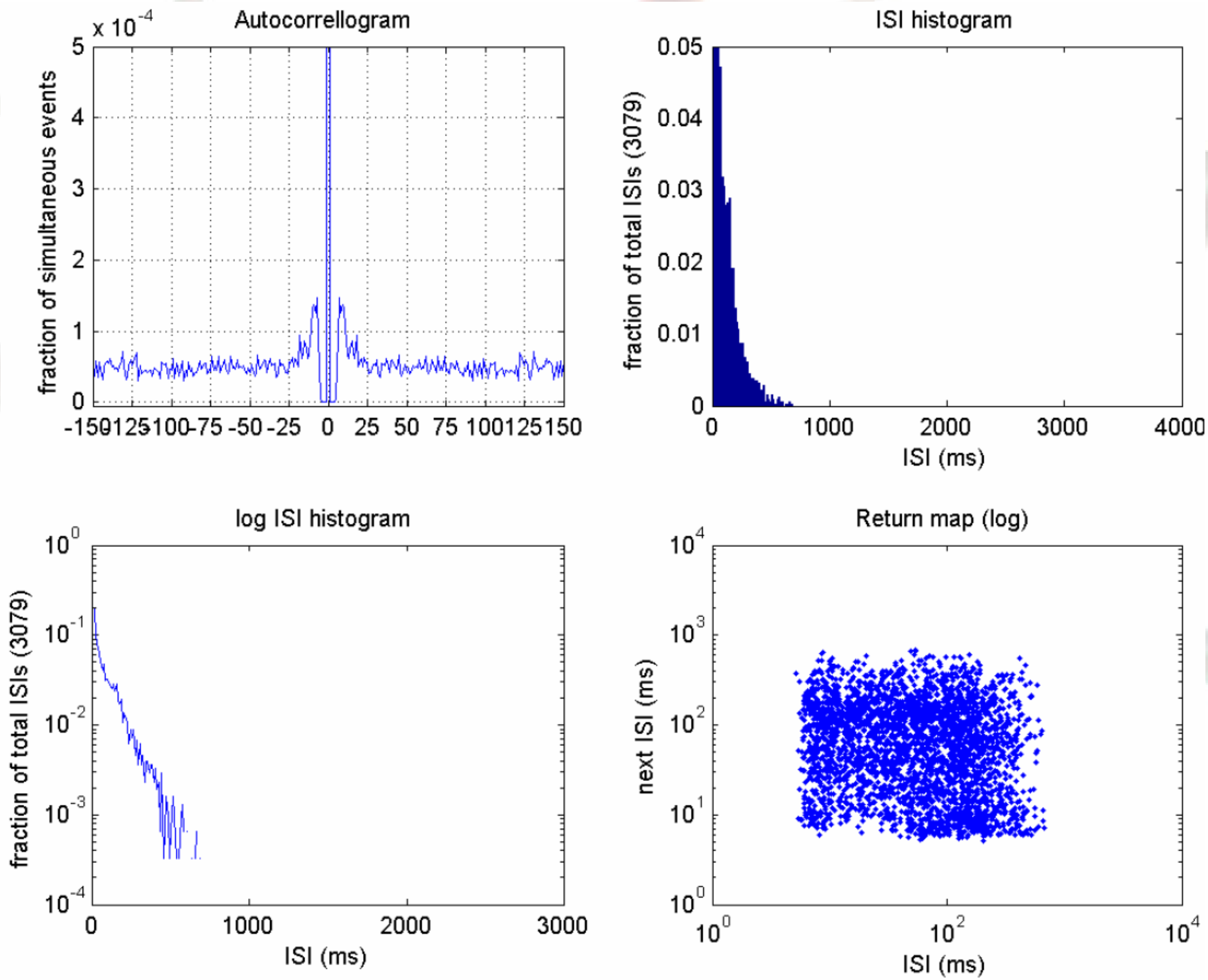
Hippocampal CA3 pyramidal cell

How robust is a cell?



- Inject the same noise multiple times
- Increase mean: # bursts constant, more single spikes
- NB Burst is counted as single event

Burstiness



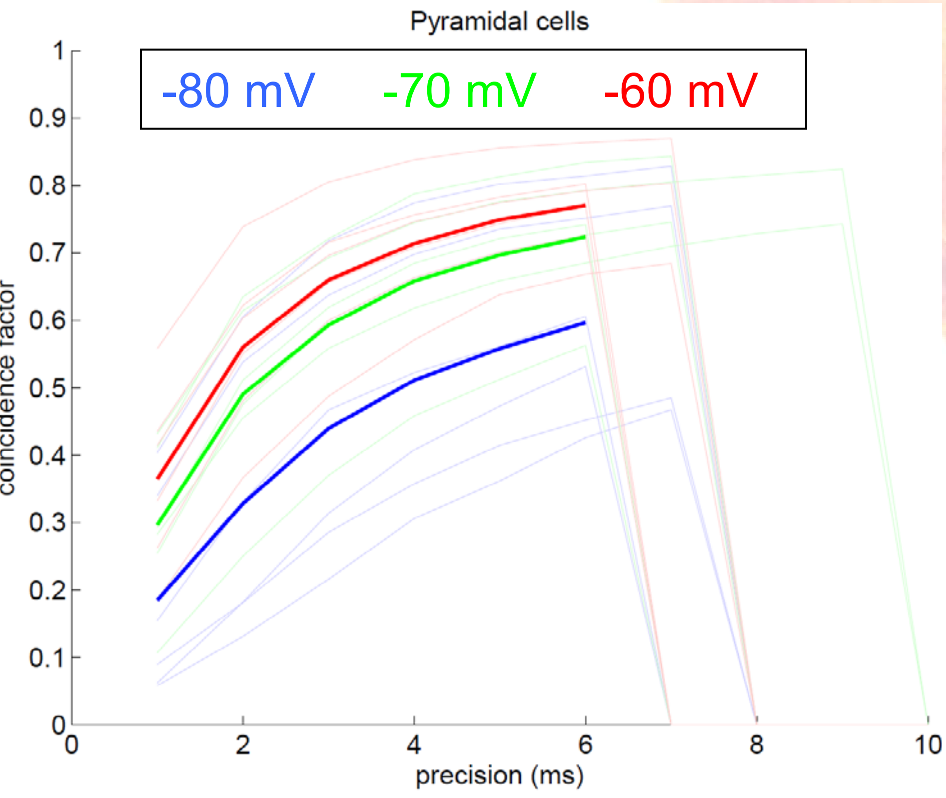
Autocorrellogram
x 10^-4
fraction of simultaneous events
5
4
3
2
1
0
-150 -125 -100 -75 -50 -25 0 25 50 75 100 125 150
ISI histogram
fraction of total ISIs (3079)
0.05
0.04
0.03
0.02
0.01
0
0 1000 2000 3000 4000
ISI (ms)
log ISI histogram
fraction of total ISIs (3079)
10^0
10^-1
10^-2
10^-3
10^-4
0 1000 2000 3000
ISI (ms)
Return map (log)
next ISI (ms)
10^4
10^3
10^2
10^1
10^0
10^0 10^2 10^4
ISI (ms)

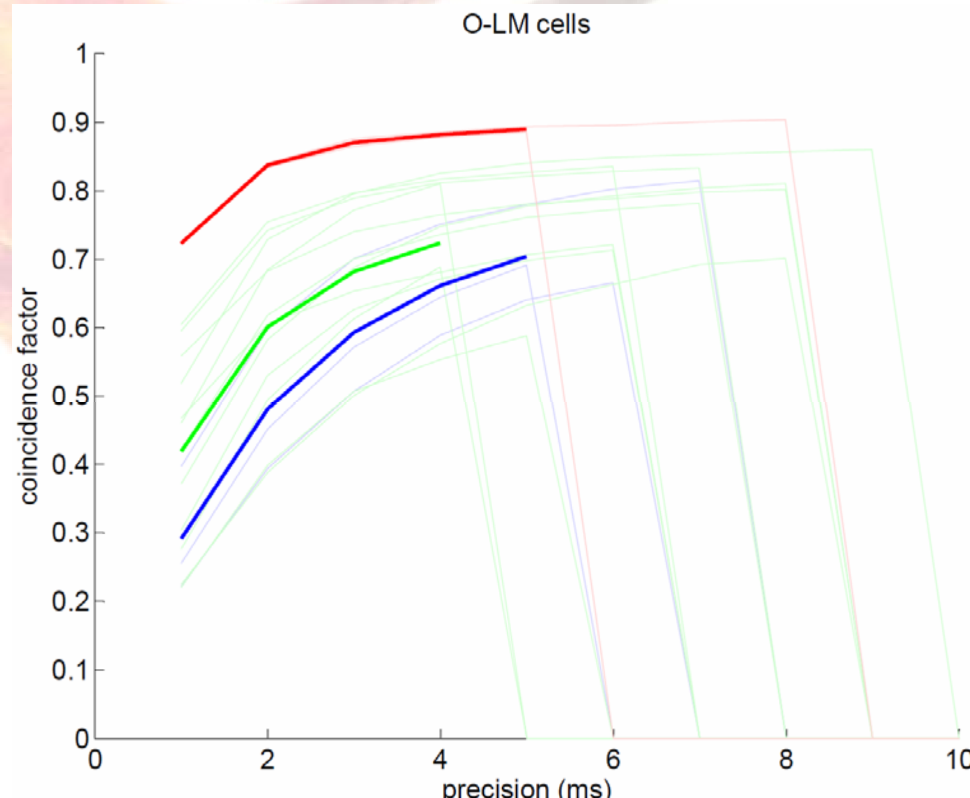
Coincidence factor: hippocampus

How robust is a single cell?

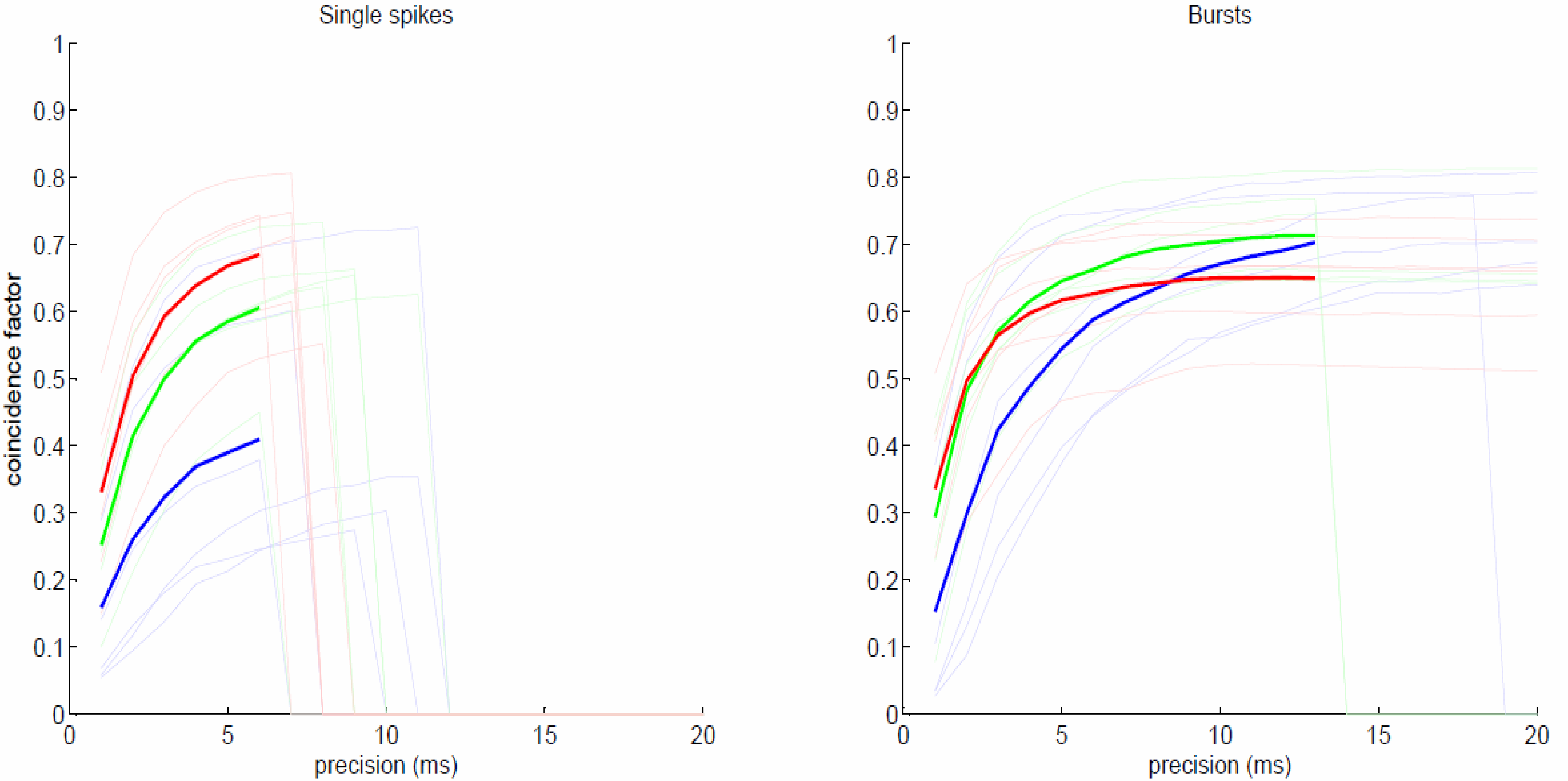
Pyramidal: increasing mean voltage → increasing robustness

O-LM (no bursting): increasing mean voltage → increasing robustness and precision?

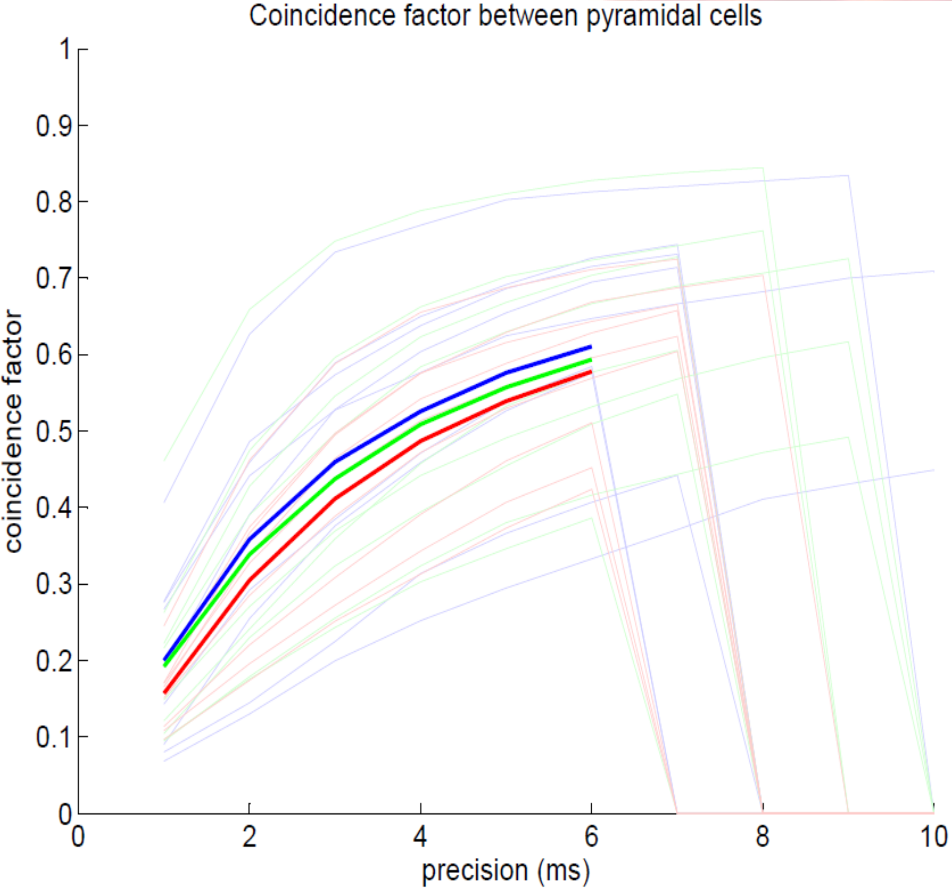


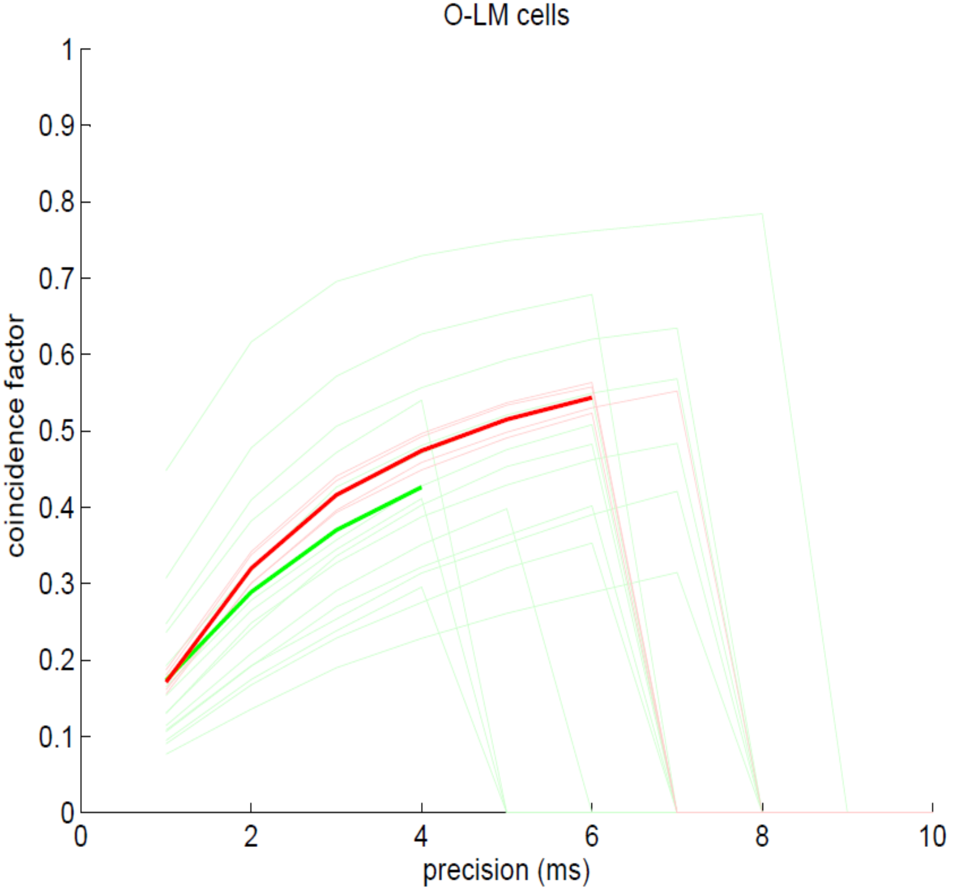


Spikes and bursts



Coincidence factor: hippocampus





Summary: stereotypical behaviour of cells

- Increasing the mean membrane potential makes the response of these neurons more robust
- In tc-relay cells it also makes the response more precise
- Bursts seem to be more robust than single spikes at low membrane potentials in both pyramidal and tc relay cells

Do cells respond in a stereotypical manner?

- So the answer is yes:
  - Cells seem to respond to specific features in the input
  - Different cells of the same type respond in a similar way

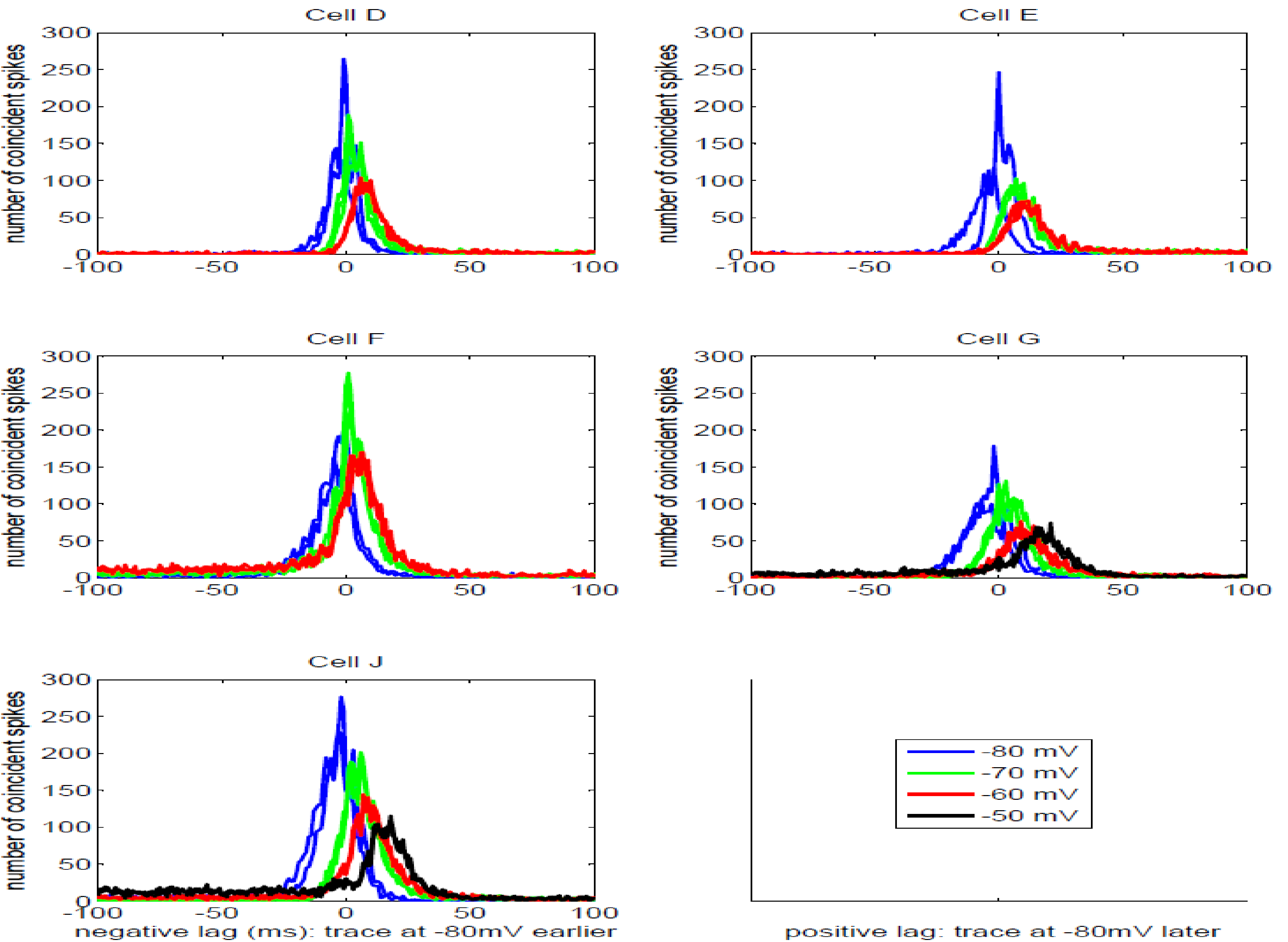
Main goal

- What do spikes and bursts code for?
- How is this influenced by the surrounding network?

- Two model systems
  - Thalamus

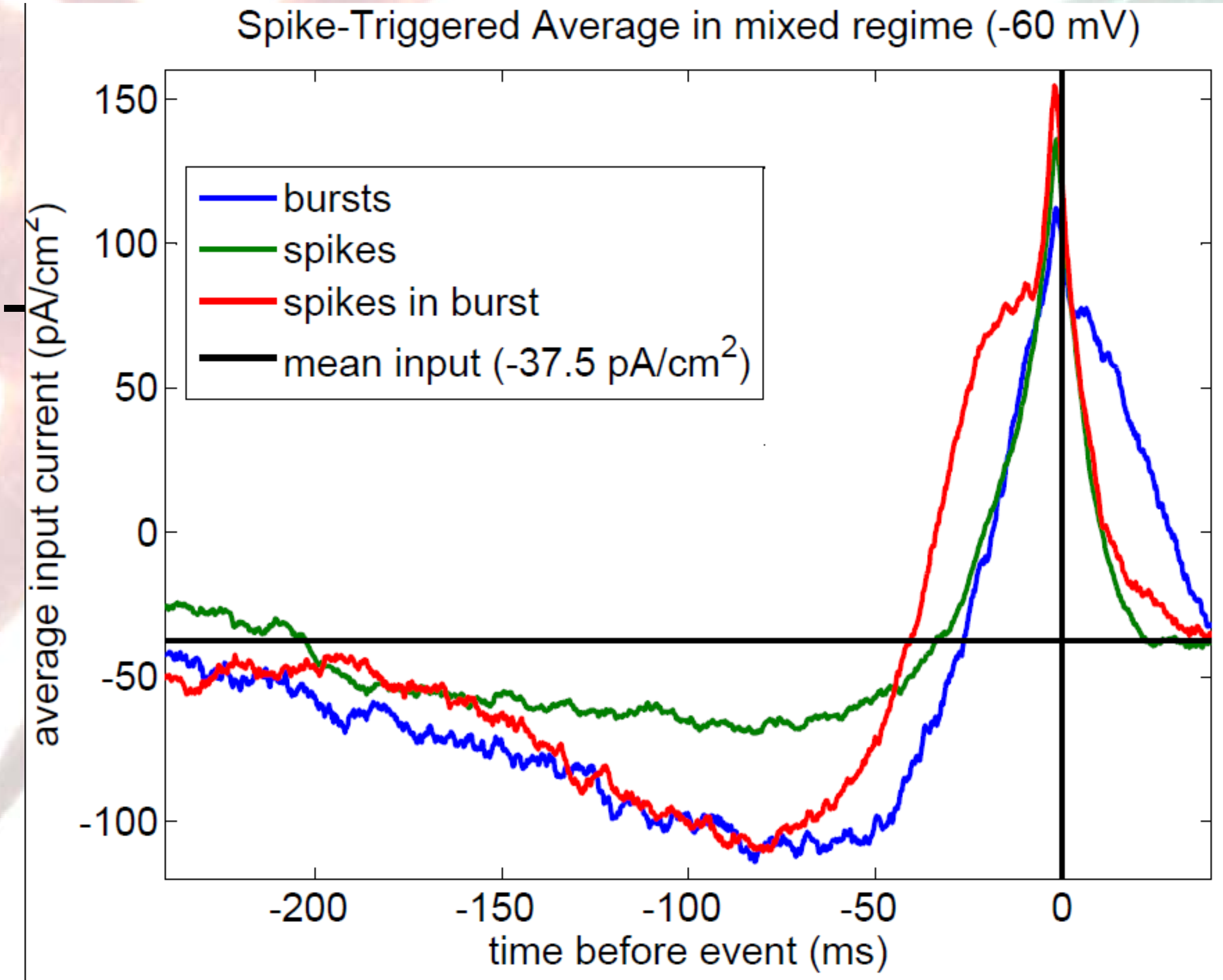
TC relay cells

- Cells seem to respond to specific features in the input
- Increasing the mean voltage results in
  - Shift bursting to spiking
  - More precise firing
  - Earlier firing


Cell D
Cell E
Cell F
Cell G
Cell J
number of coincident spikes
300
250
200
150
100
50
0
-100
-50
0
50
100
negative lag (ms): trace at -80mV earlier
positive lag: trace at -80mV later
-80 mV
-70 mV
-60 mV
-50 mV

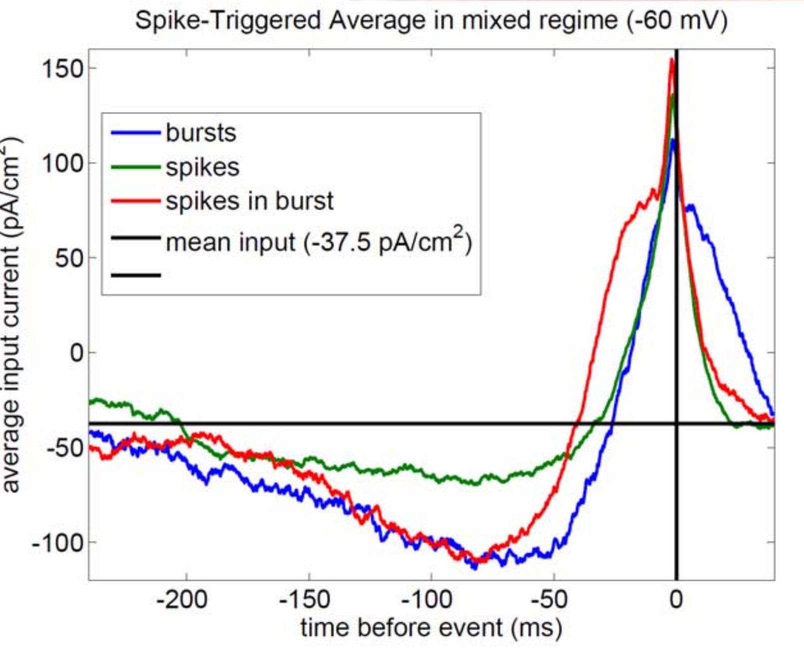
Do bursts and spikes code for different input features?

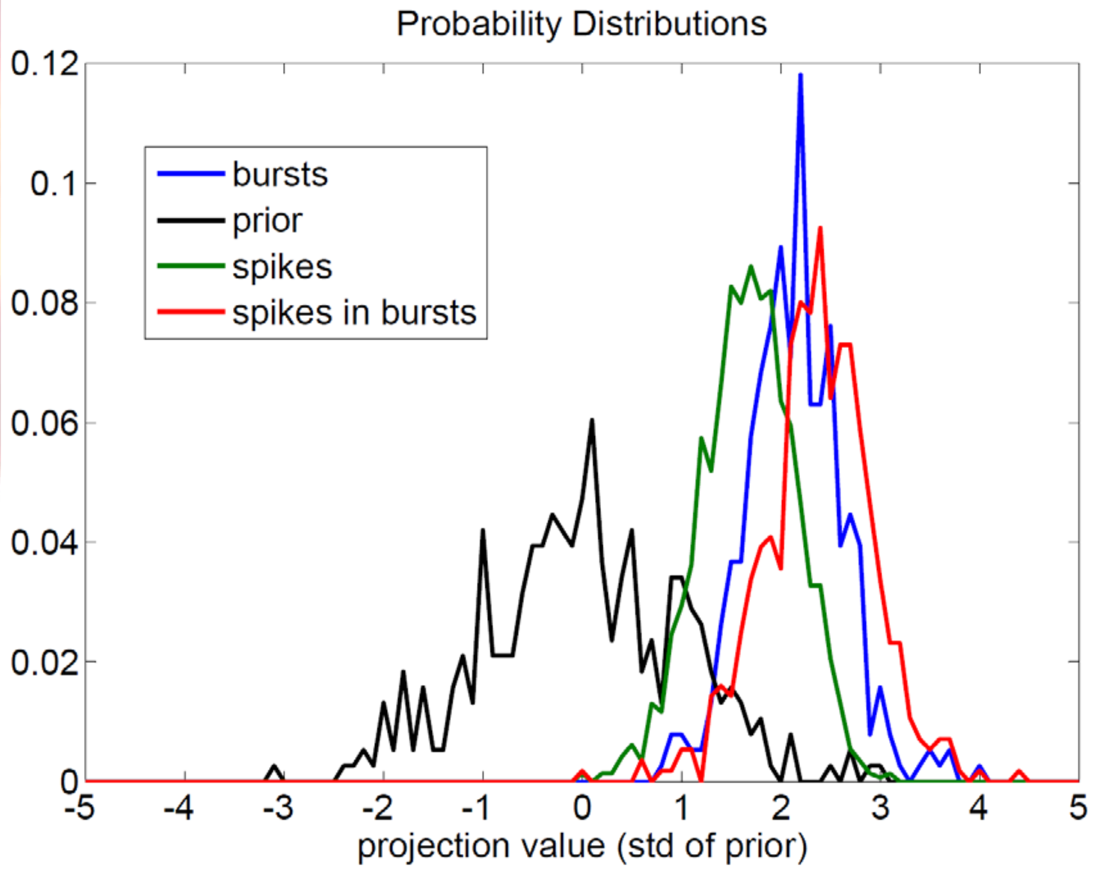
- Bursts need both more negative and longer positive input than spike: ‘wake-up call’
- Spikes in burst need input at two timescales



Results: Do bursts and spikes code for different input features?

- Threshold for bursts higher: ‘wake-up call’



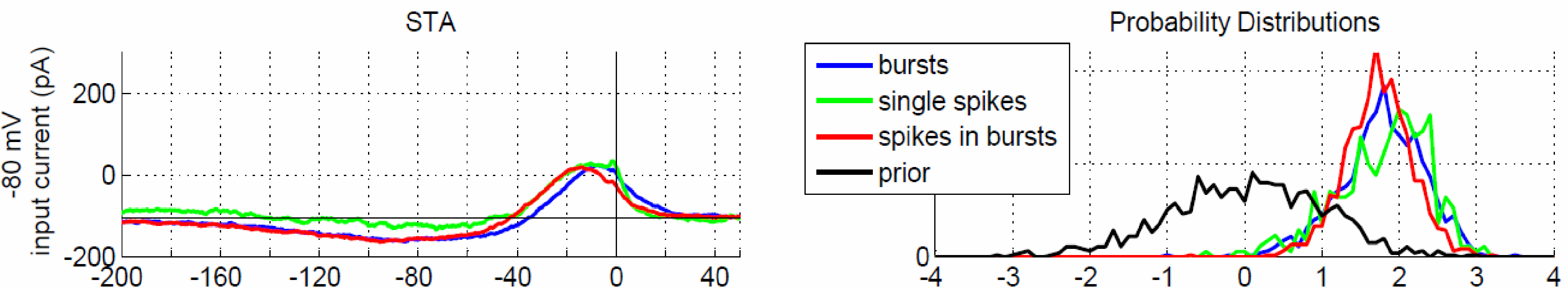


Conclusions

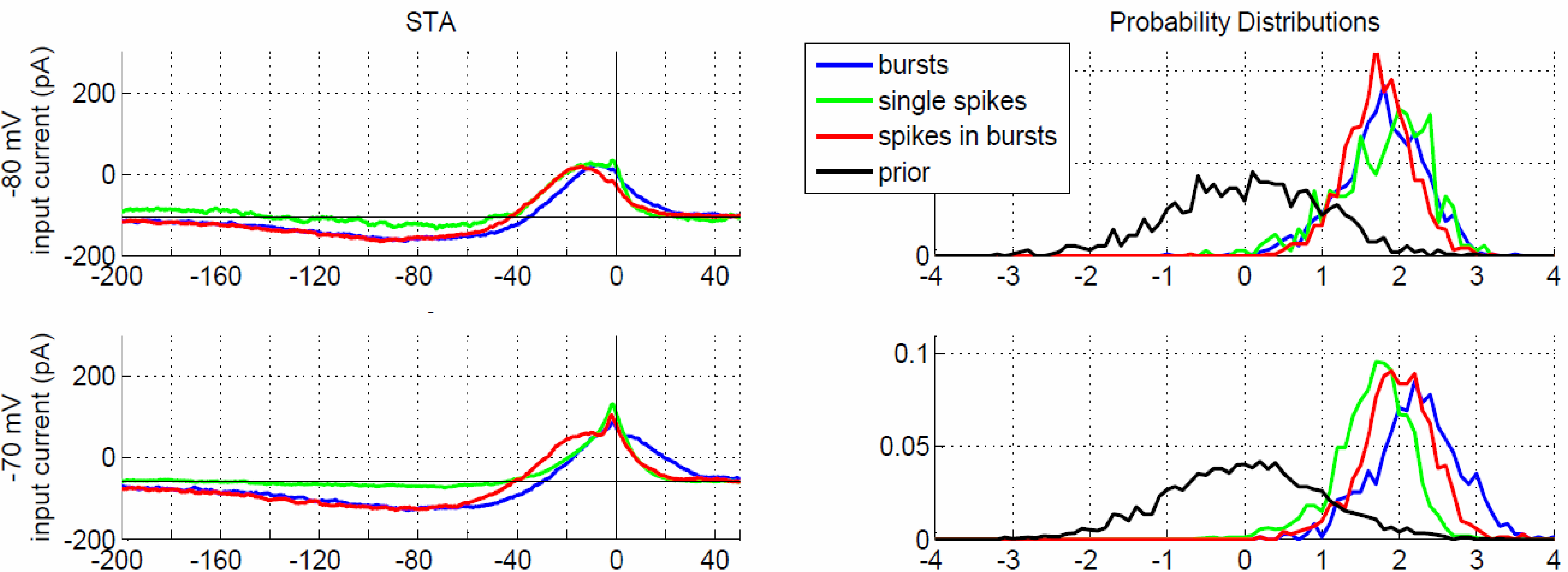
In a mixed regime, (spikes in) bursts code for more ‘extreme’ events, with a higher threshold: wake-up call?

Two separate timescales play a role: slow one for T-current, fast for spike generation

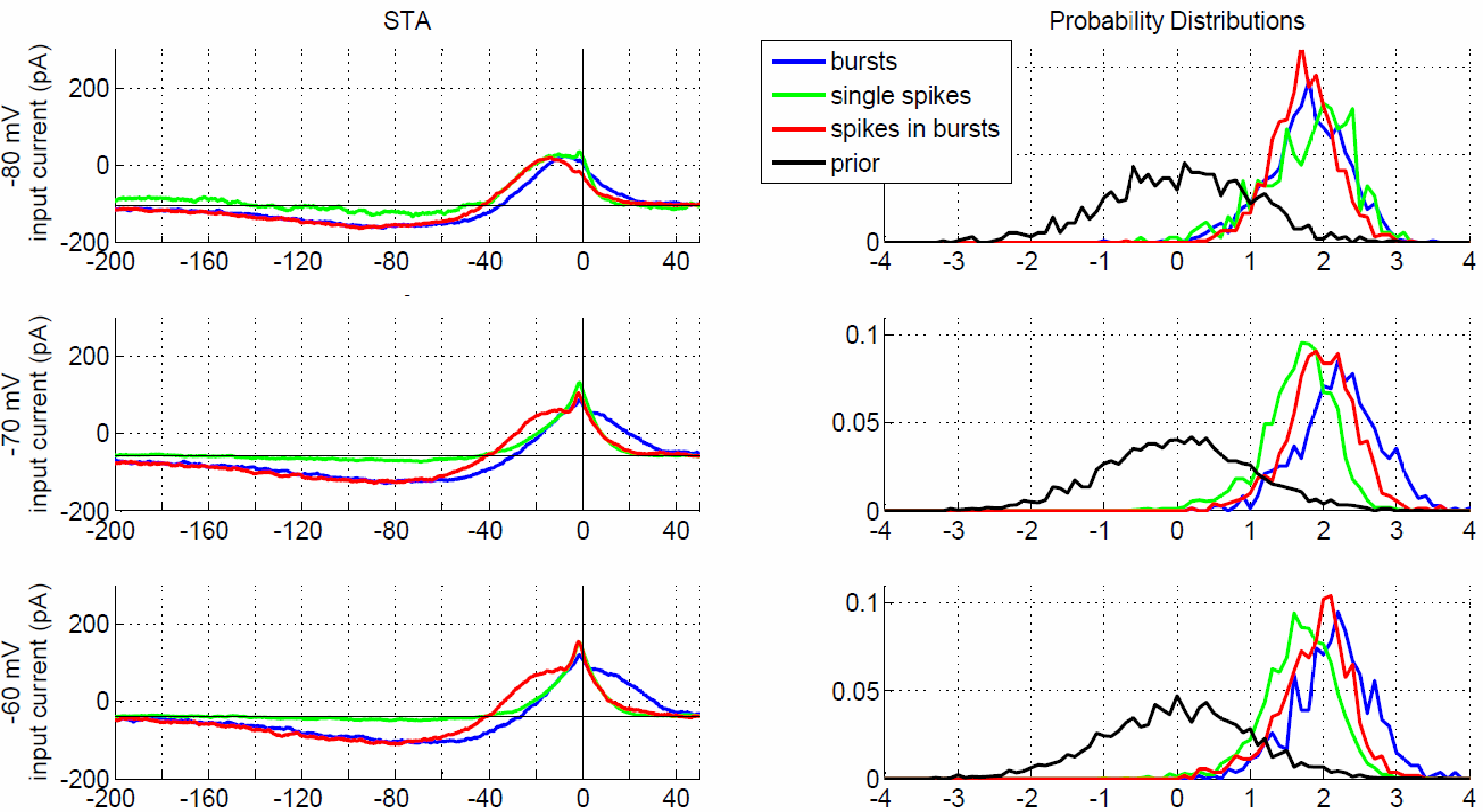
How does this change in the different regimes?



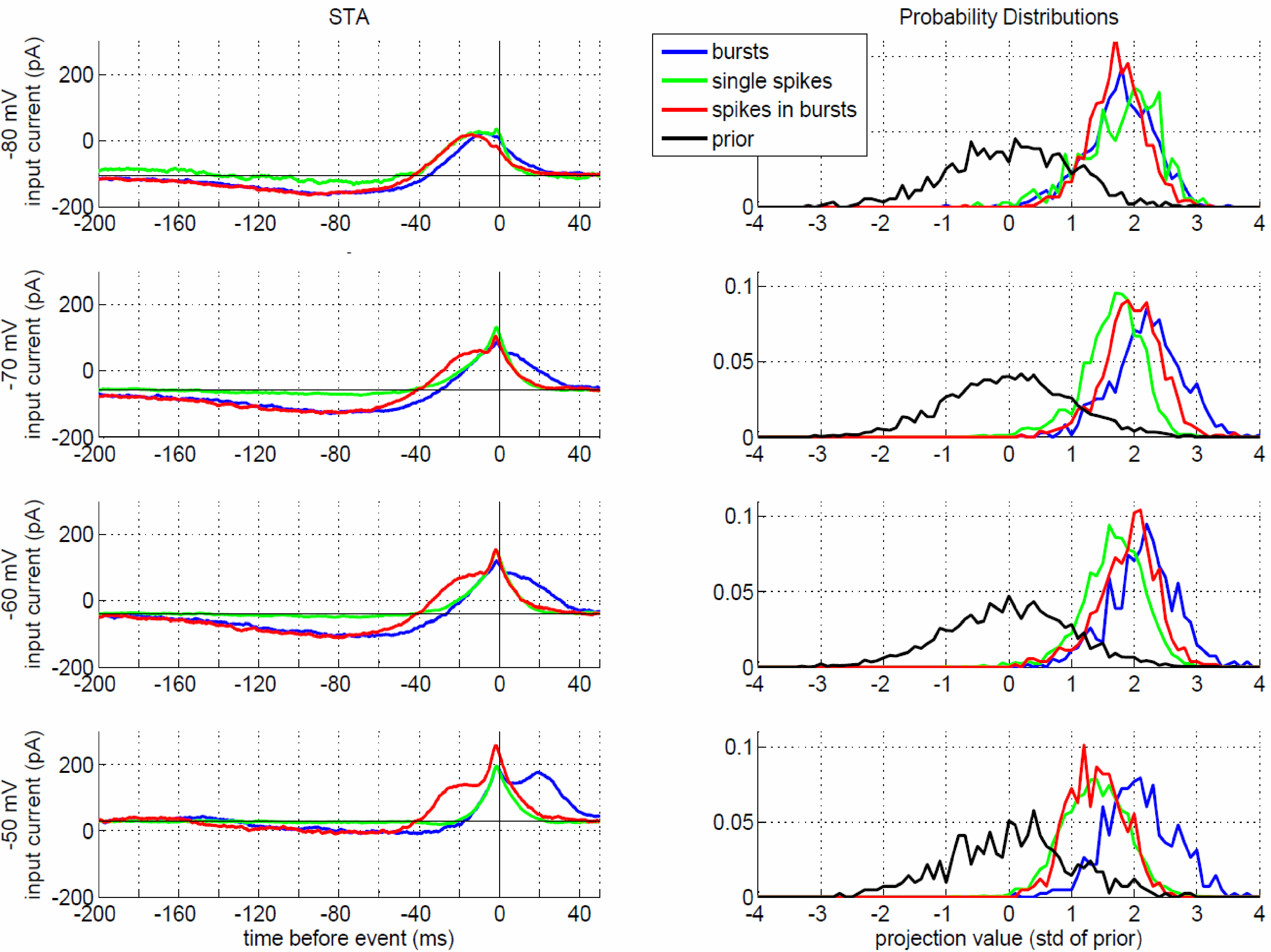
- At -80 mV:
  - – Bursting regime: not many spikes
  - – All events need ‘slow’ timescale
  - – Bursts need more hyperpolarization



- At -70 mV:
  - Mixed regime: spikes and bursts
  - Separation of timescales
  - Separation of thresholds



- At -60 mV:
  - Mixed regime: spikes and bursts
  - Spikes become faster, spikes in bursts higher threshold

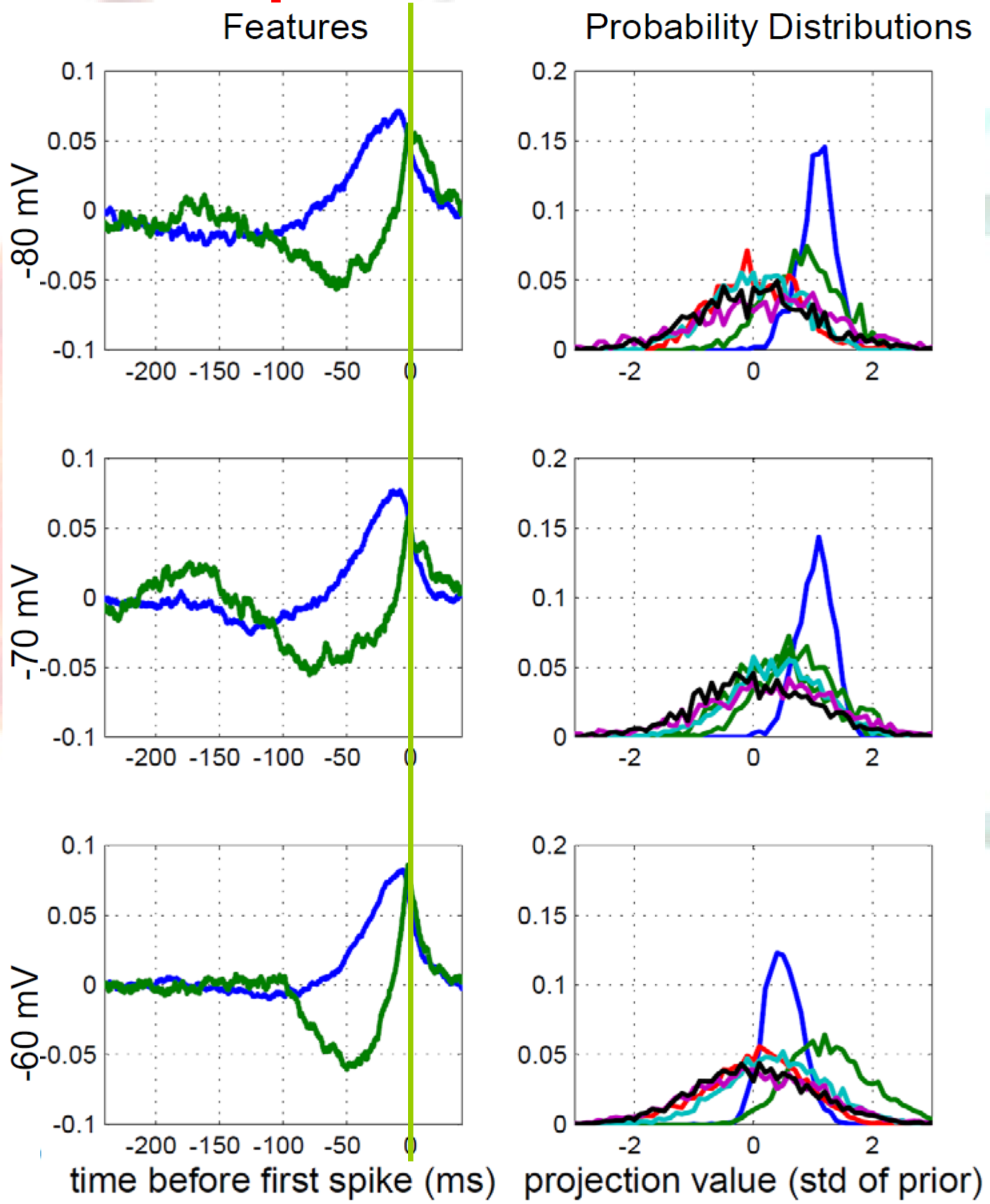


STA
Probability Distributions
bursts
single spikes
spikes in bursts
prior
-80 mV
-70 mV
-60 mV
-50 mV
input current (pA)
time before event (ms)
projection value (std of prior)

How does negative (basal ganglia) input influence spikes?

Negative input from the basal ganglia makes spikes less selective to the second fluctuating filter, but more to the first integrating filter

Increasing (negative) basal ganglia input



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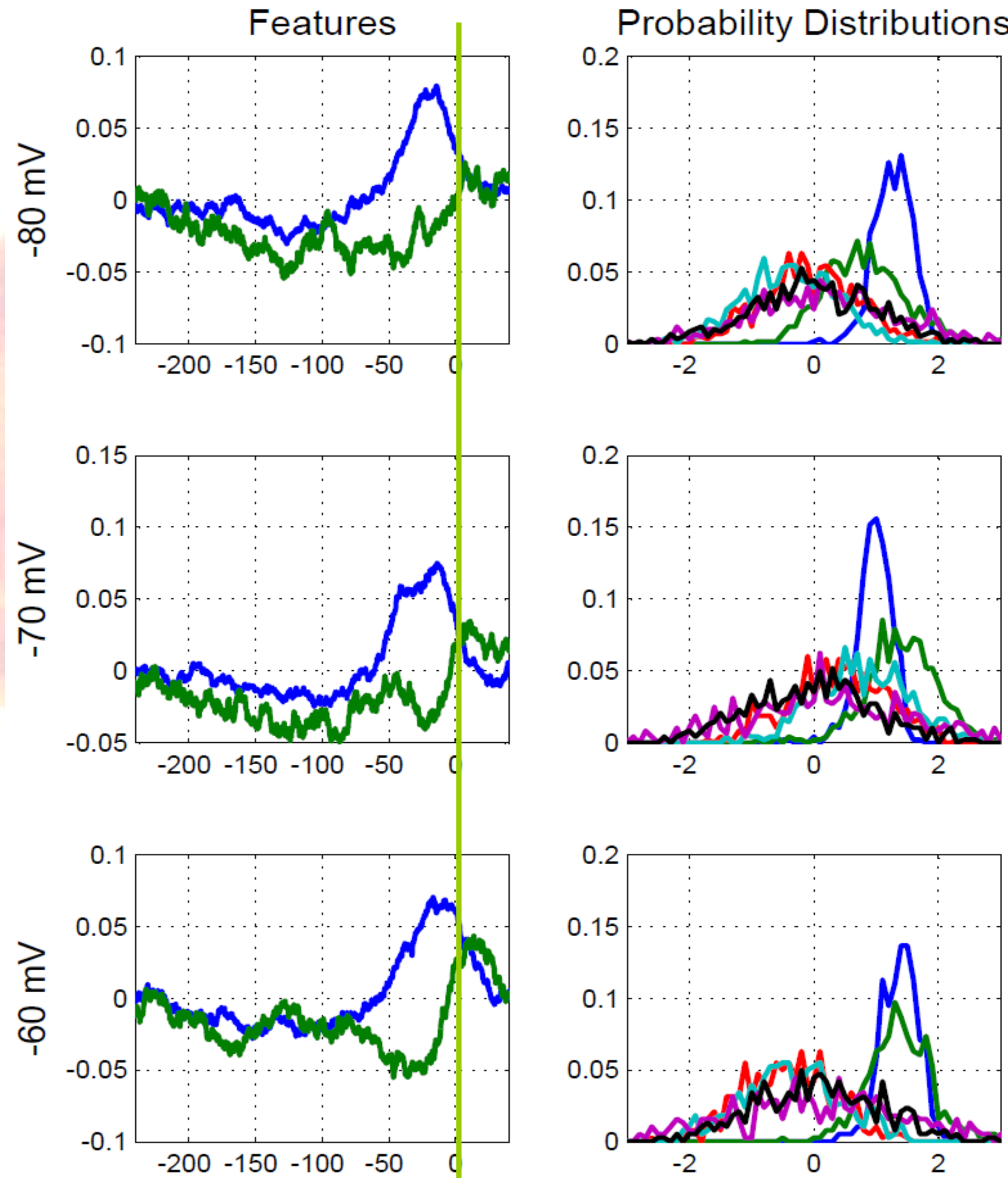
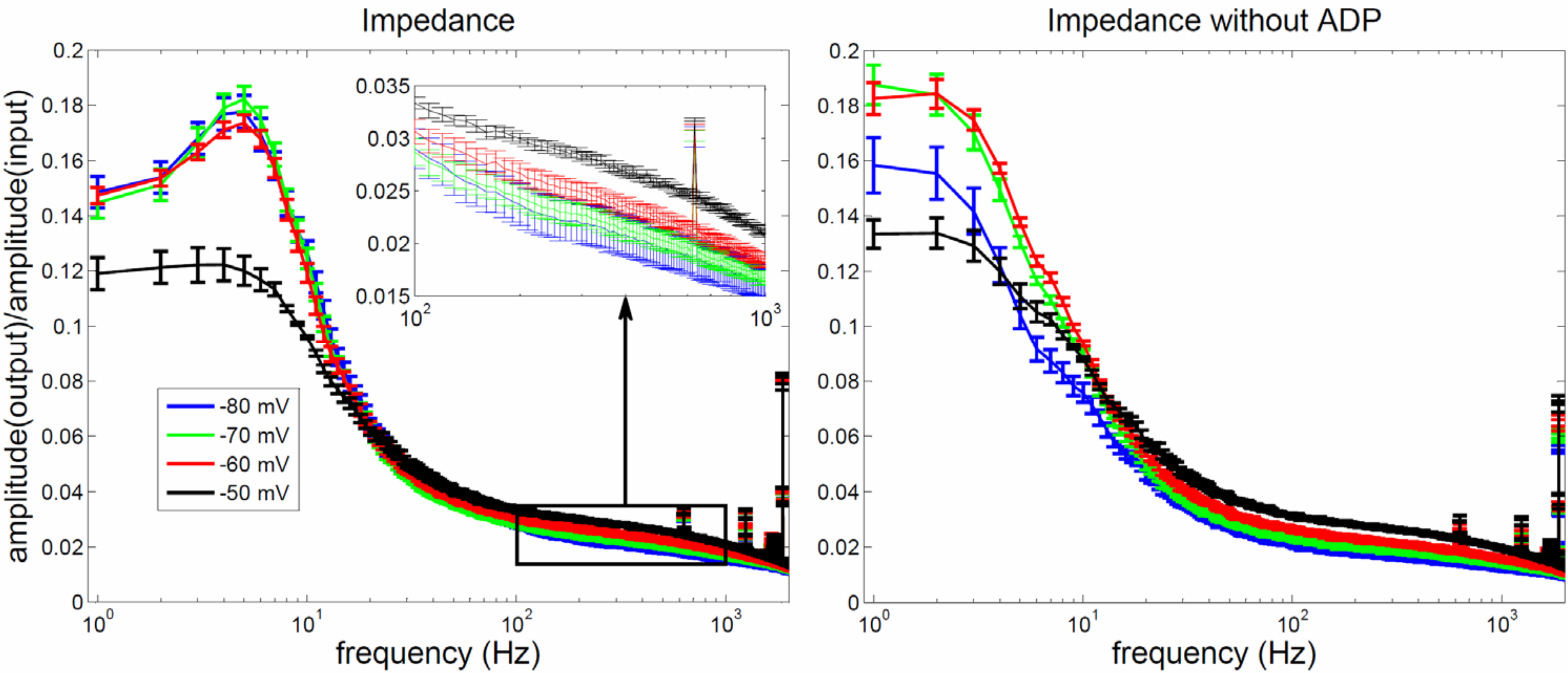


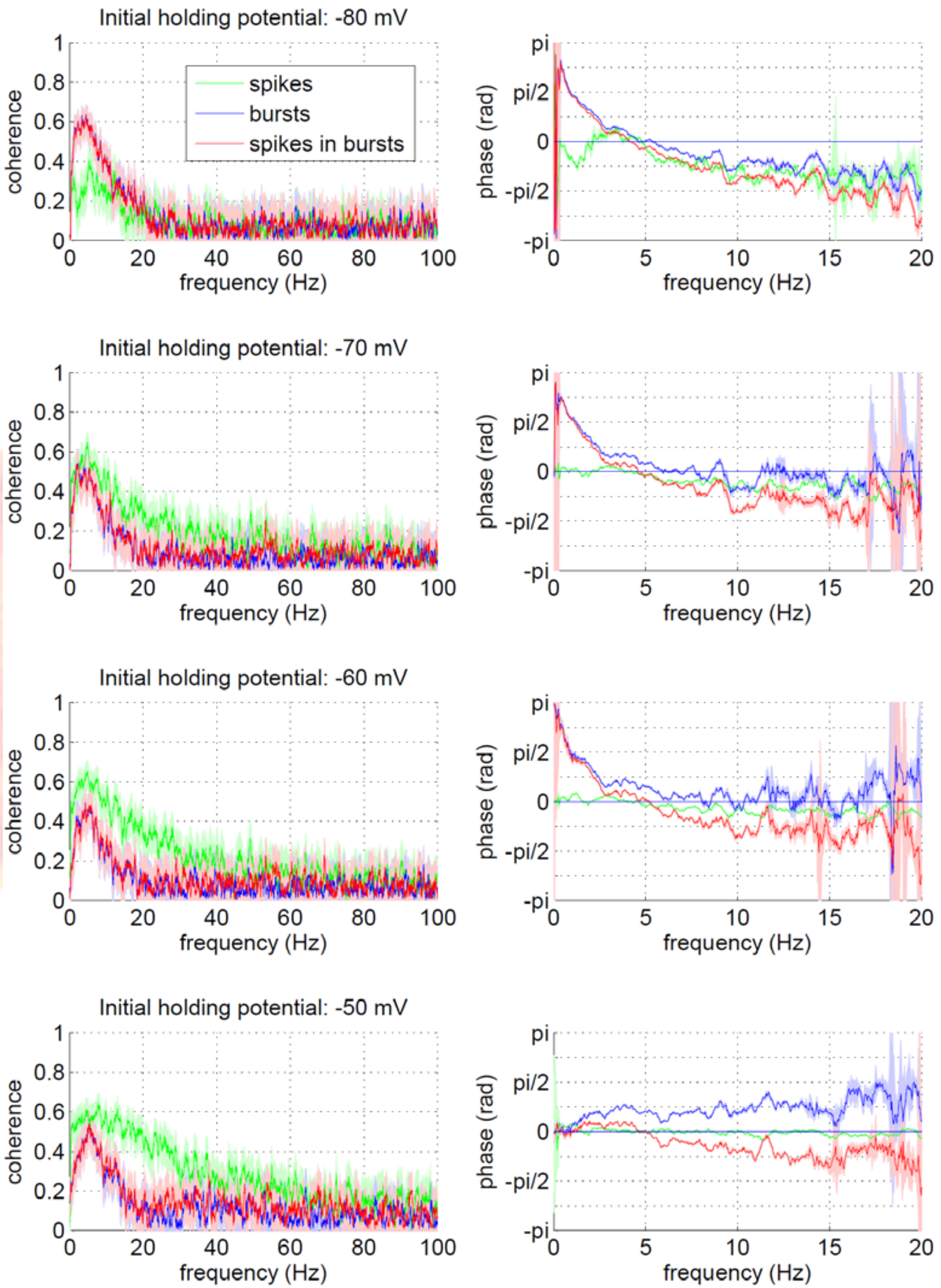
Impedance (subthreshold)



- Neuron is low-pass filter
- More high frequencies for stronger positive input
- Resonance for bursts

Coherence

- Bursts phase-lock to low frequencies, spikes are more broadband



Conclusions

- Negative (basal ganglia) input makes tc relay neurons
  - bursting
  - less precise&robust
  - later
  - less selective for fast fluctuations, more for slower integration
  - Phase-locking to low frequencies

- Positive input makes tc relay neurons
  - spiking
  - more precise&robust
  - earlier
  - more selective for fast fluctuations, less for slower integration
  - Broadband phase-locking

In a mixed regime, bursts code for more ‘extreme’ events: wake-up call?

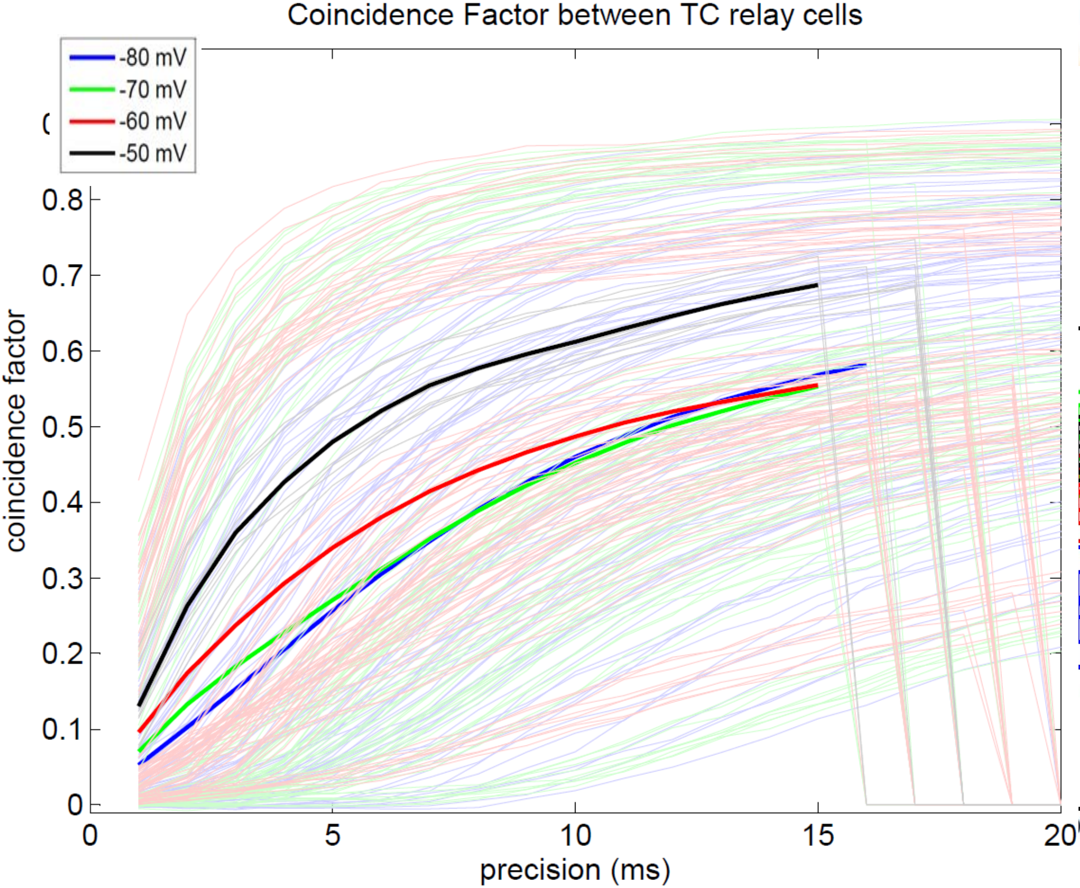
But…

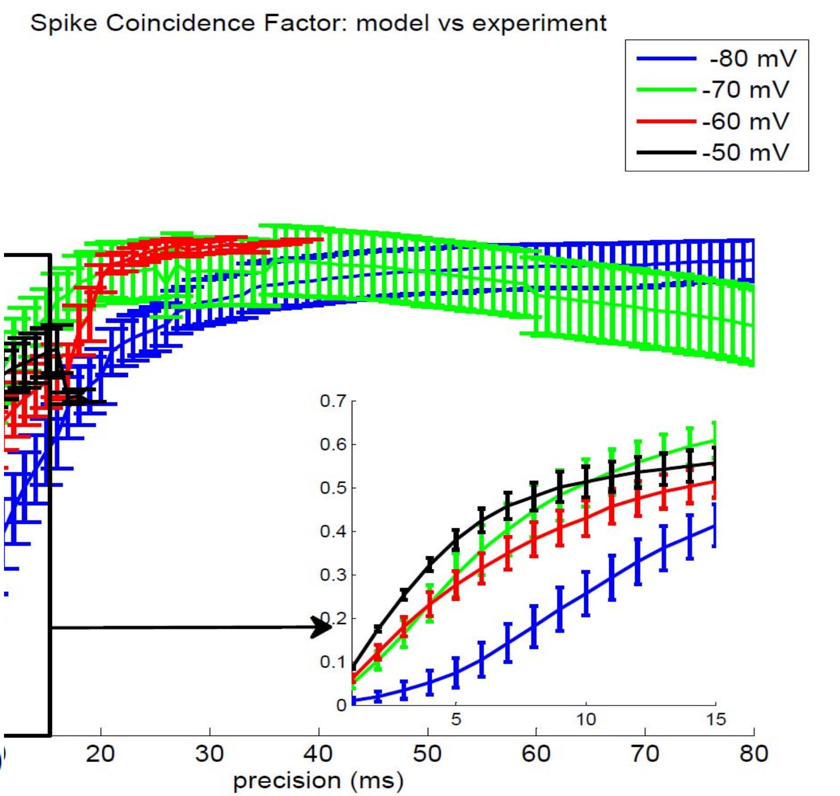
- Not really long enough traces
- Back to the encoding: What biophysical properties make this happen?

→ modelling

What is a good model?

- Transmits the same information, i.e. spikes at the same time





Model: Destexhe et al 1998

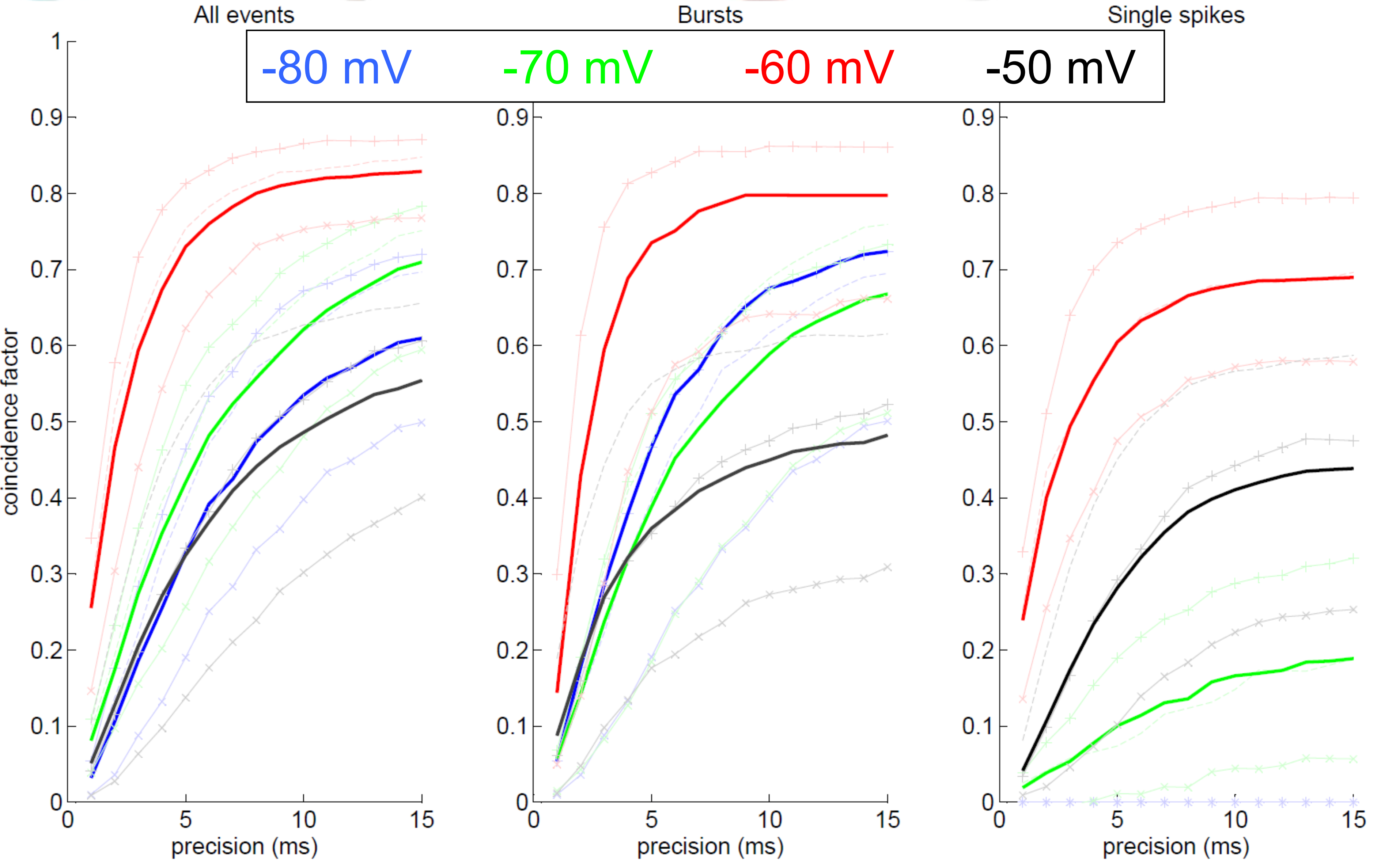
- 3 compartments
- Currents:
  - Sodium (only soma)
  - Potassium (only soma)
  - Leak
  - T-type (more dendrite)
  - h

  (Destexhe et al 1996)

- caveats
  - too many spikes in burst
  - too active in spiking regime
  - too deep undershoot after spike

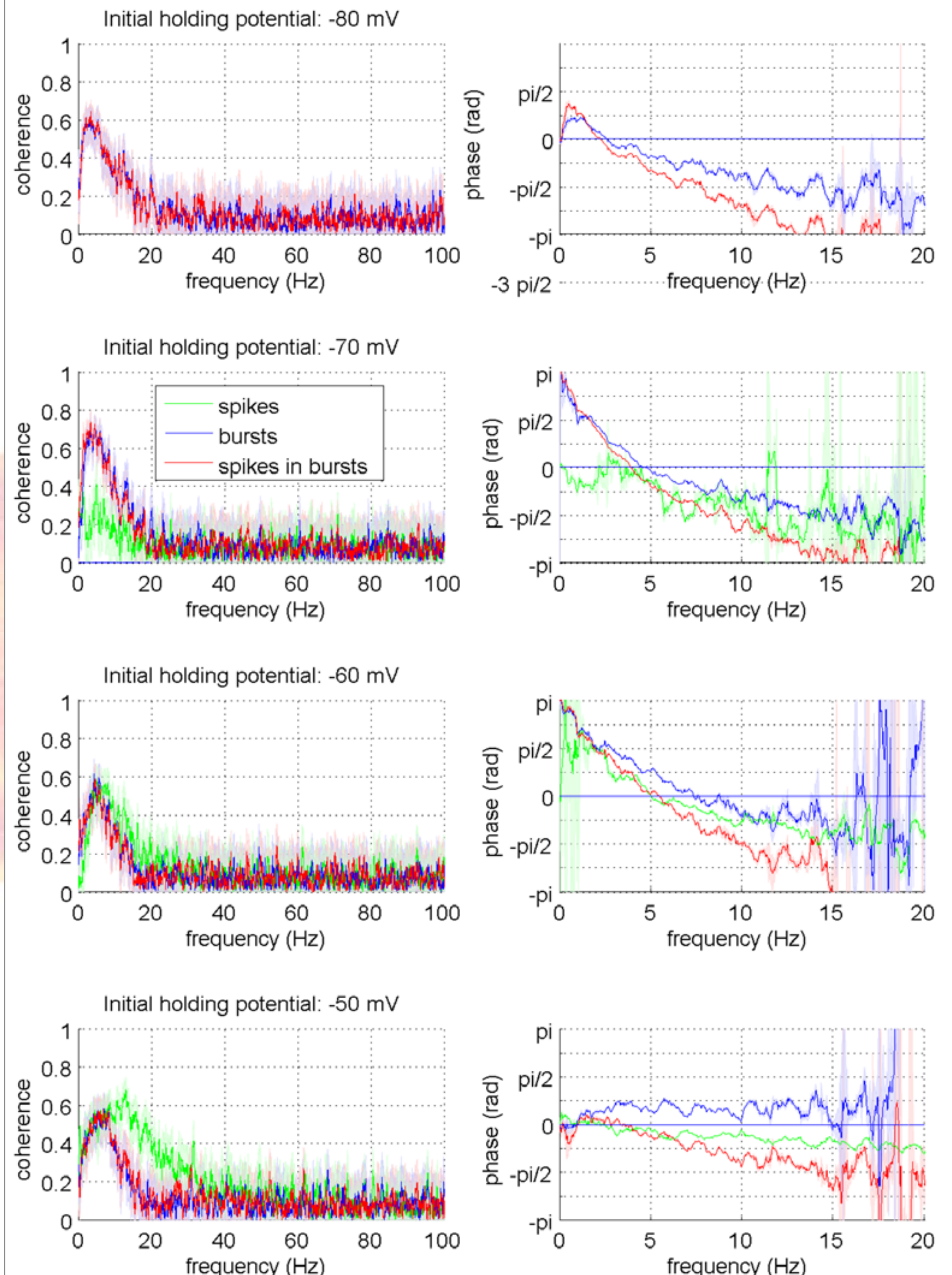
NB checked STA, correlations, intrinsic precision: all similar to experiments

Precision and robustness

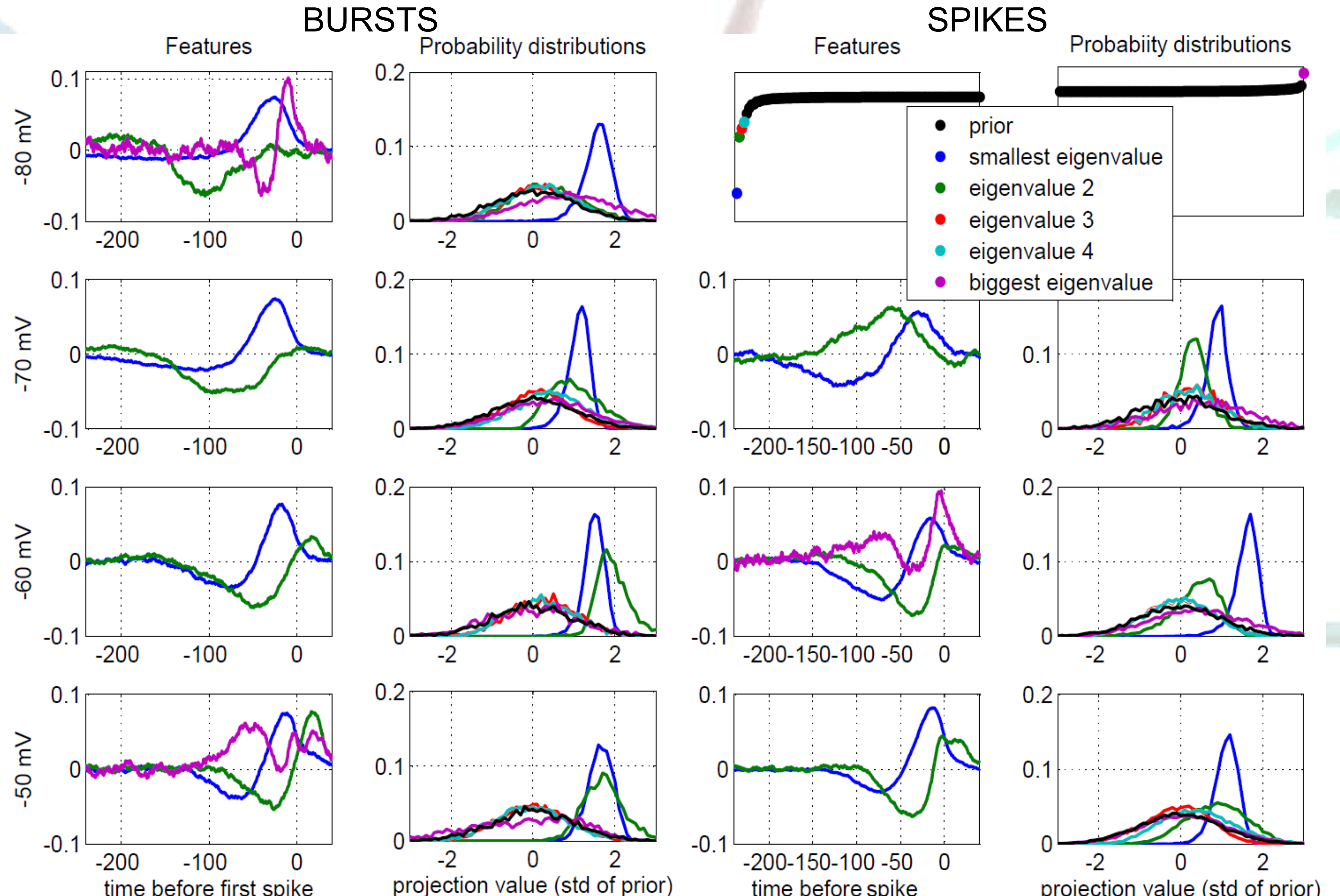


Coherence: model

- Bursts phase-lock to low frequencies, spikes are more broadband
- Low-frequency phase-locking independent of h-current



Spike Triggered Covariance



Conclusions: bursts and spikes in tcrelay cells

- At low membrane potentials bursts are more robust than single spikes; this can also be simulated in a model
- Bursts seem to respond to more ‘extreme’ events than single spikes
- Bursts phase-lock to low frequencies, whereas single spikes are more broadband

Conclusions: negative input in tcrelay cells

- Neuron moves from spiking to bursting regime
- Events are later in time
- Neuron becomes less precise and robust
- Filtering becomes more low-pass
- Neuron becomes less selective for fluctuations, more of an ‘integrator’

Thanks to

- Wytse J. Wadman
- Pascal J.P. Chameau

Inhibition in the hippocampus

- CA3 pyramidal neurons to burst as a result of ‘ping-pong’ effect between soma and dendrite
- When do these neurons respond with a single spike and when with a burst?
- How does inhibition influence this?

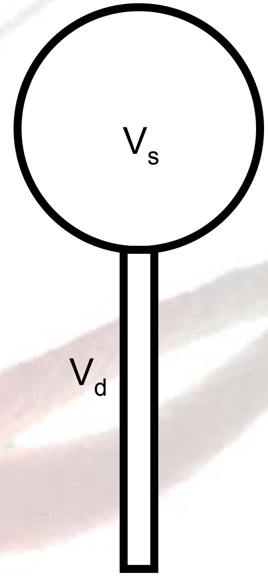
Hippocampus

Inhibitory circuitry

- feed-forward and feedback inhibition (Elfant, Pal, Emptage, & Capogna, 2008; Wierenga & Wadman, 2003)
- Fast and slow $GABA_A$ (Banks, Li, & Pearce, 1998; Pearce, 1993).
- Perisomatic vs dendritic projection (Miles, Toth, Gulyas, Hajos, & Freund, 1996; Pouille & Scanziani, 2004)

Methods: Pyramidal cell model Pinsky & Rinzel 1994

- Two compartments: soma and dendrite
- Single spikes initiated in soma
- Bursts as a result of dendritic action potential (DAP)

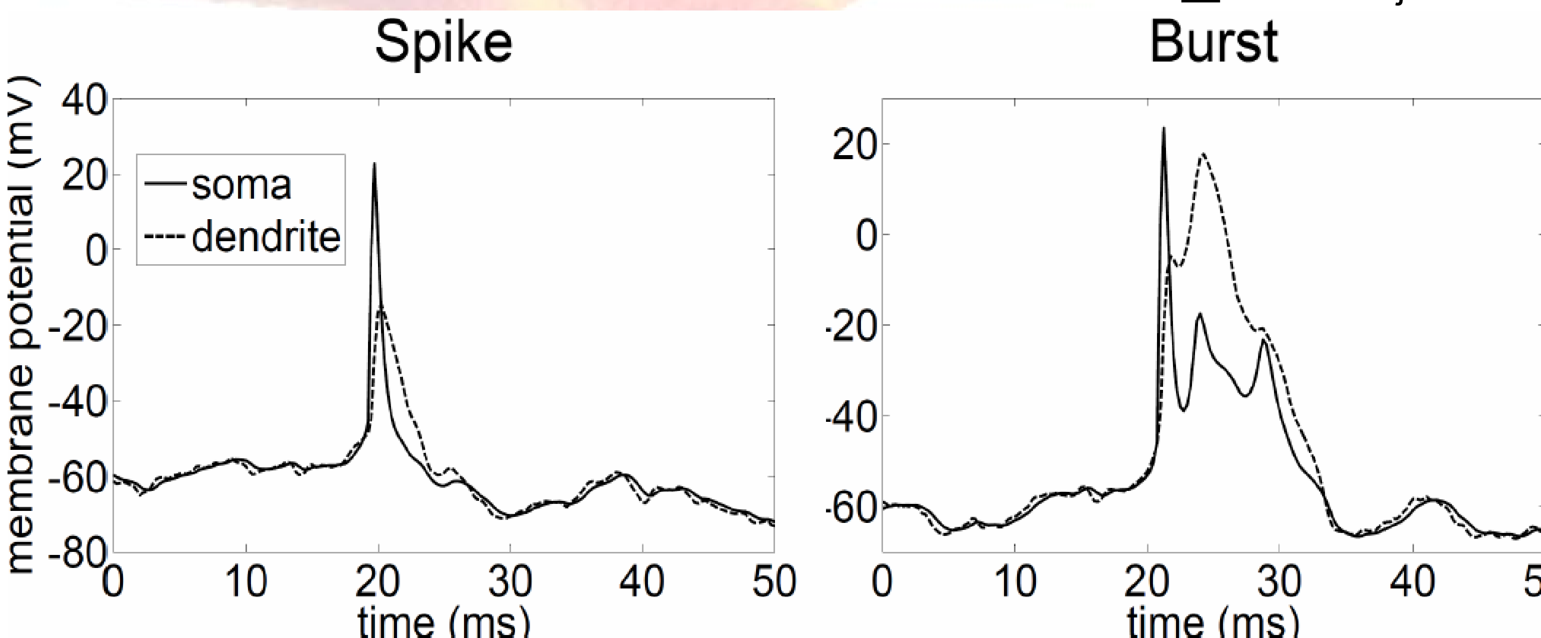


Soma:

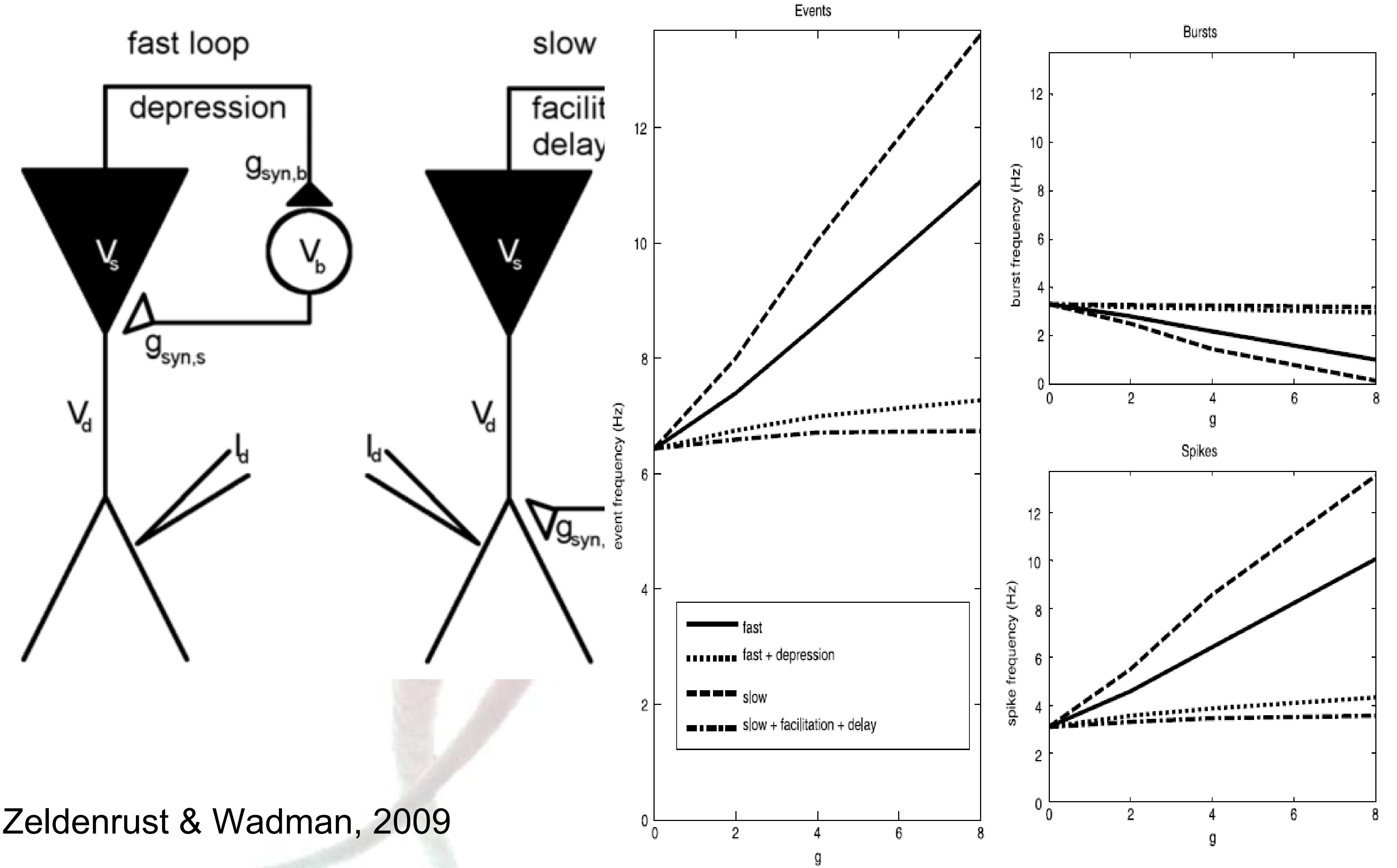
- I_{Na}
- $I_{K\text{-}DR}$

Dendrite:

- I_{Ca}
- $I_{K\text{-}C}$
- $I_{K\text{-}AHP}$
- Injected current

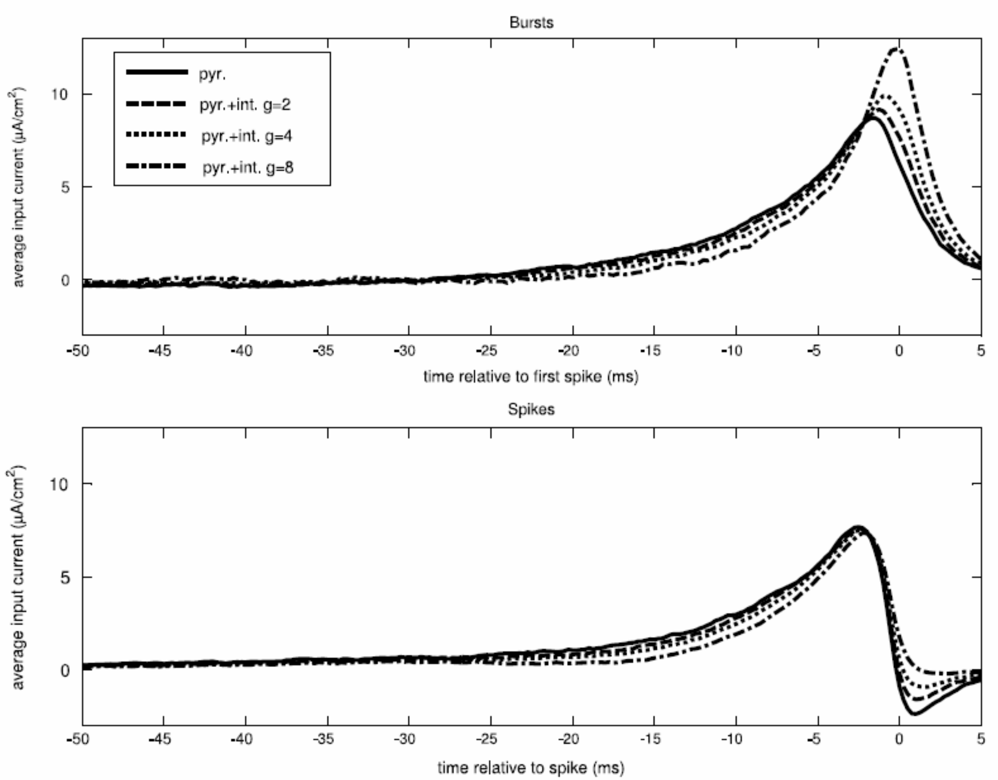


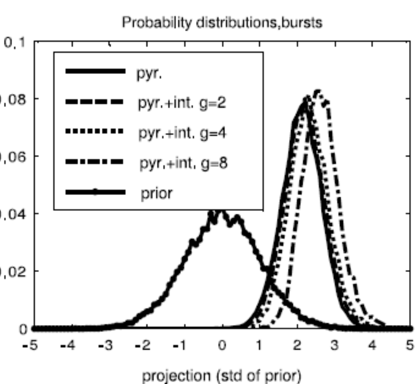
Feedback inhibition

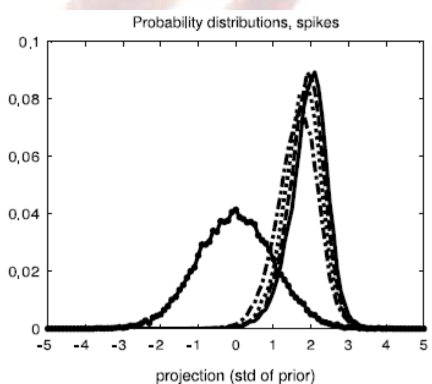


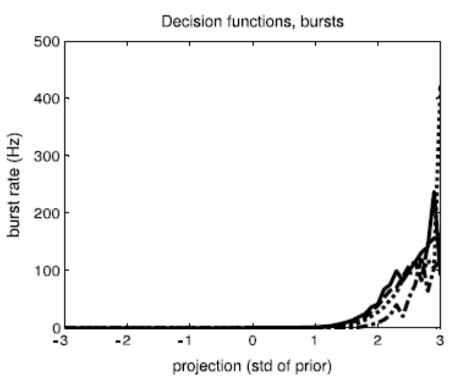
Zeldenrust & Wadman, 2009

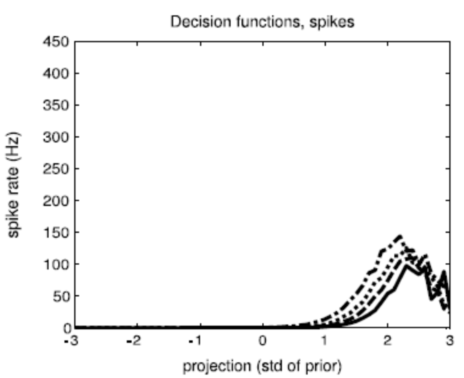
Feedback inhibition







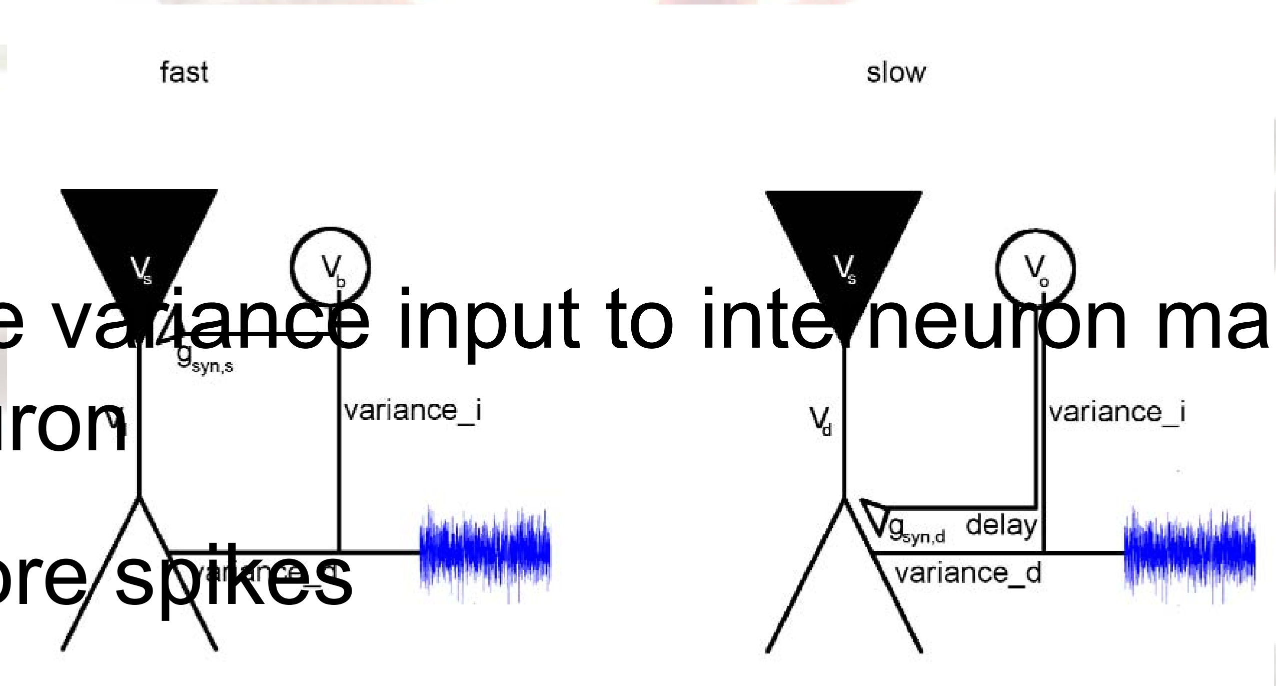




Feedback inhibition

- Increasing strength in the loop moves neuron from slow bursting to fast spiking regime
- Slow dendritic loop less effective than fast somatic loop due to delays
- Bursting mechanism and AHP current play crucial role
- Role of short-time plasticity (facilitation and depression) depend strongly on firing rate

Feed-forward inhibition

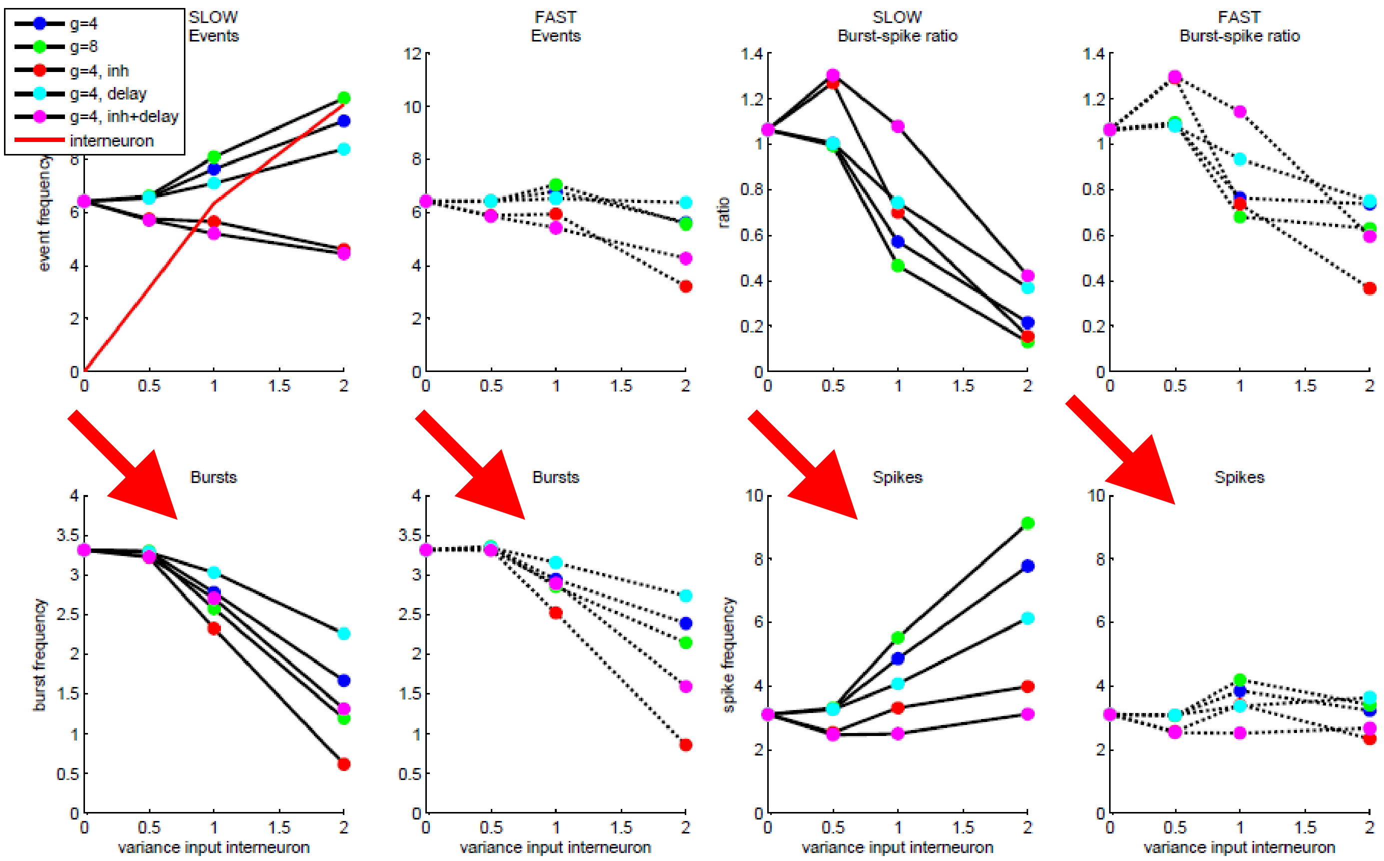


Increase variance input to interneuron makes interneuron

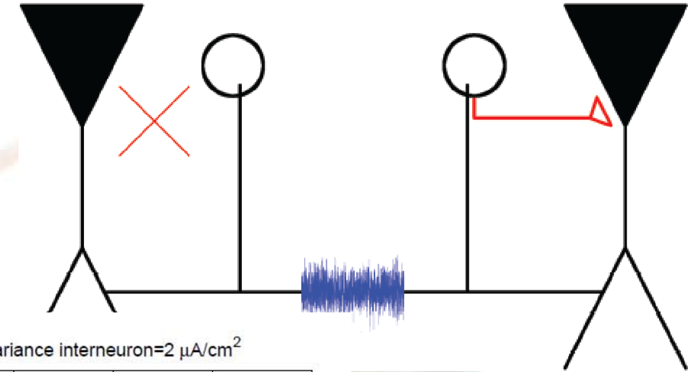
- fire more spikes
- fire spikes earlier in time
- NB interneuron spikes correlate more with pyramidal single spikes than bursts

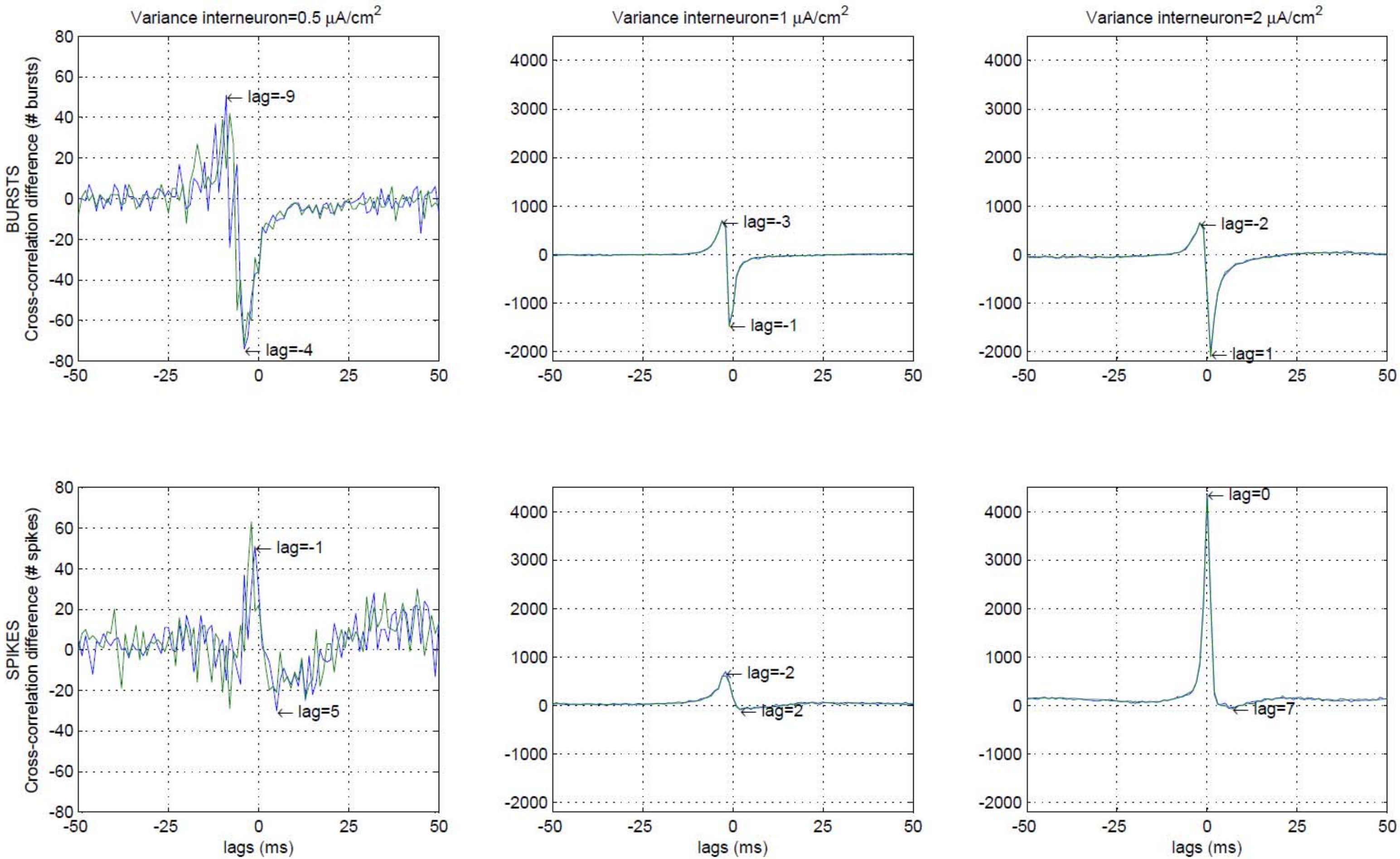
Feedforward inhibition

- Inhibition tends to suppress bursts
- Slow dendritic shunting inhibition can increase single spike rate

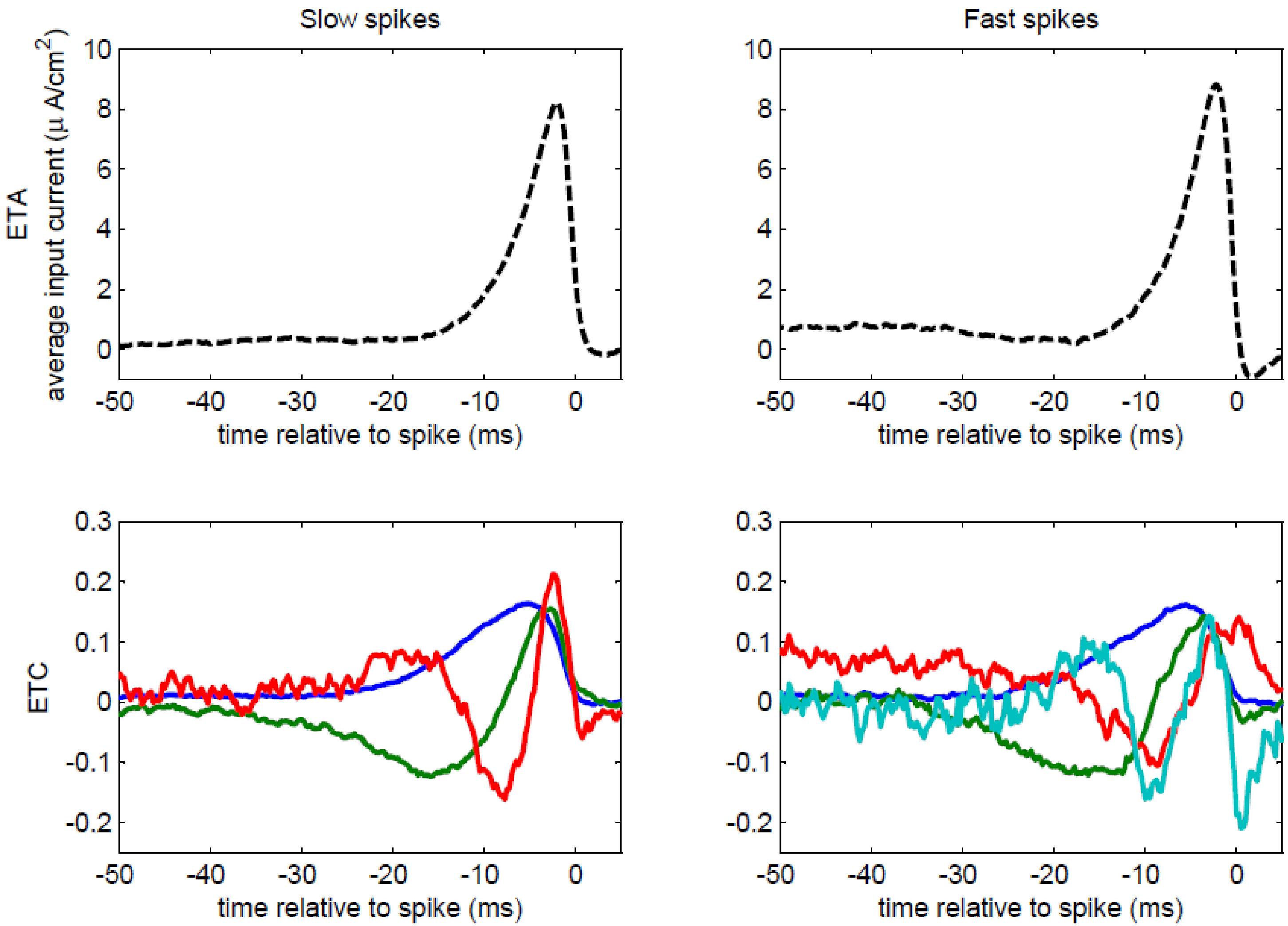


When are extra events created?



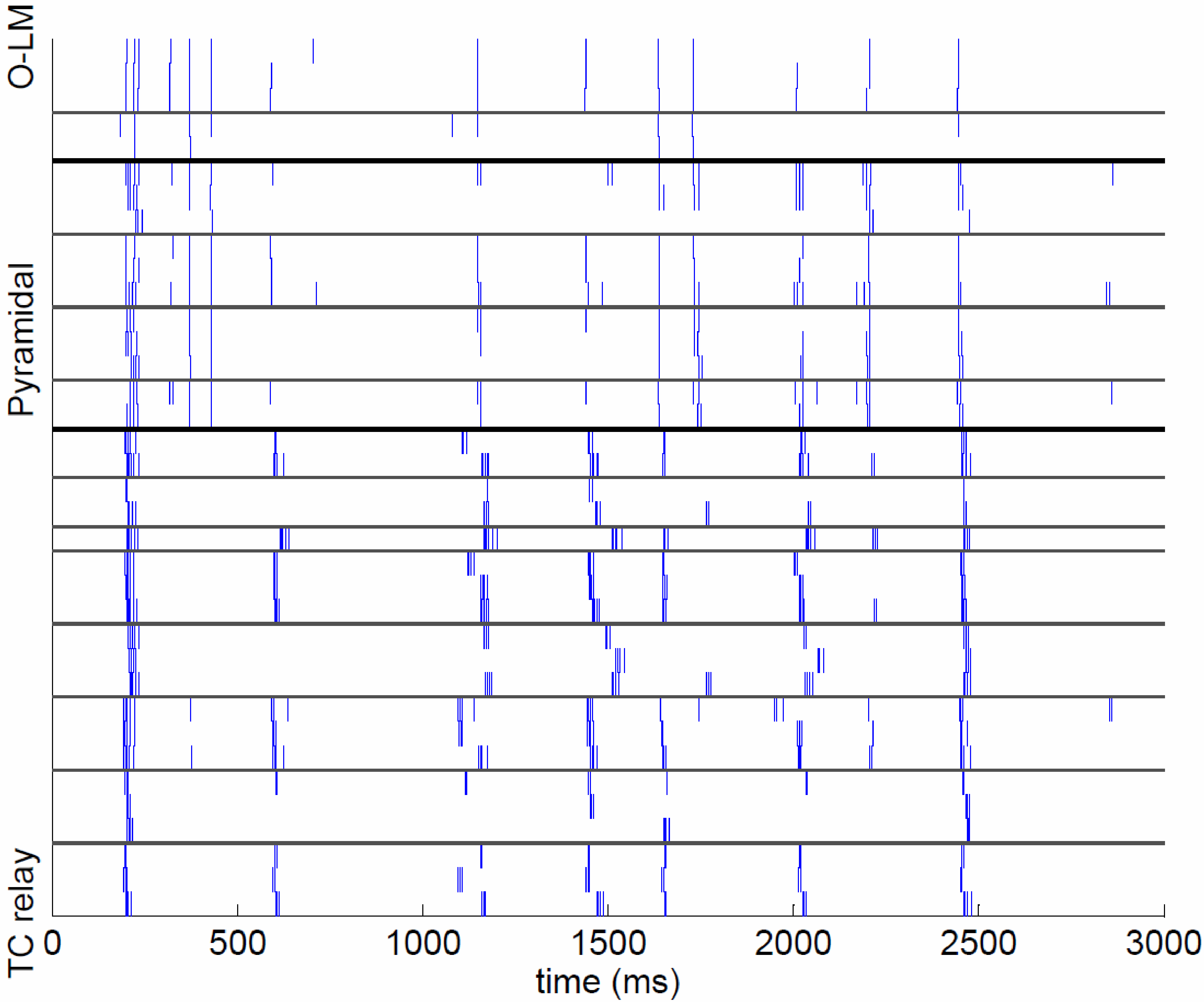


Filtering for single spikes with 2 types of inhibition



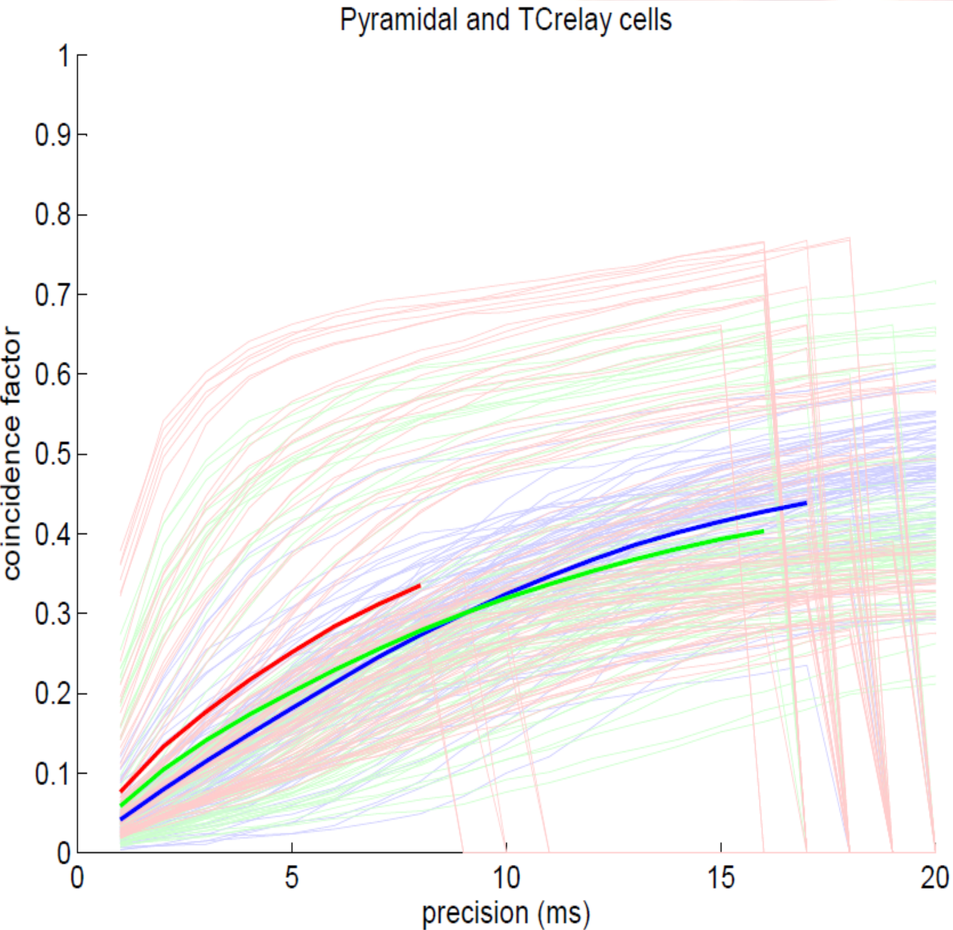
Conclusion: inhibition in CA3

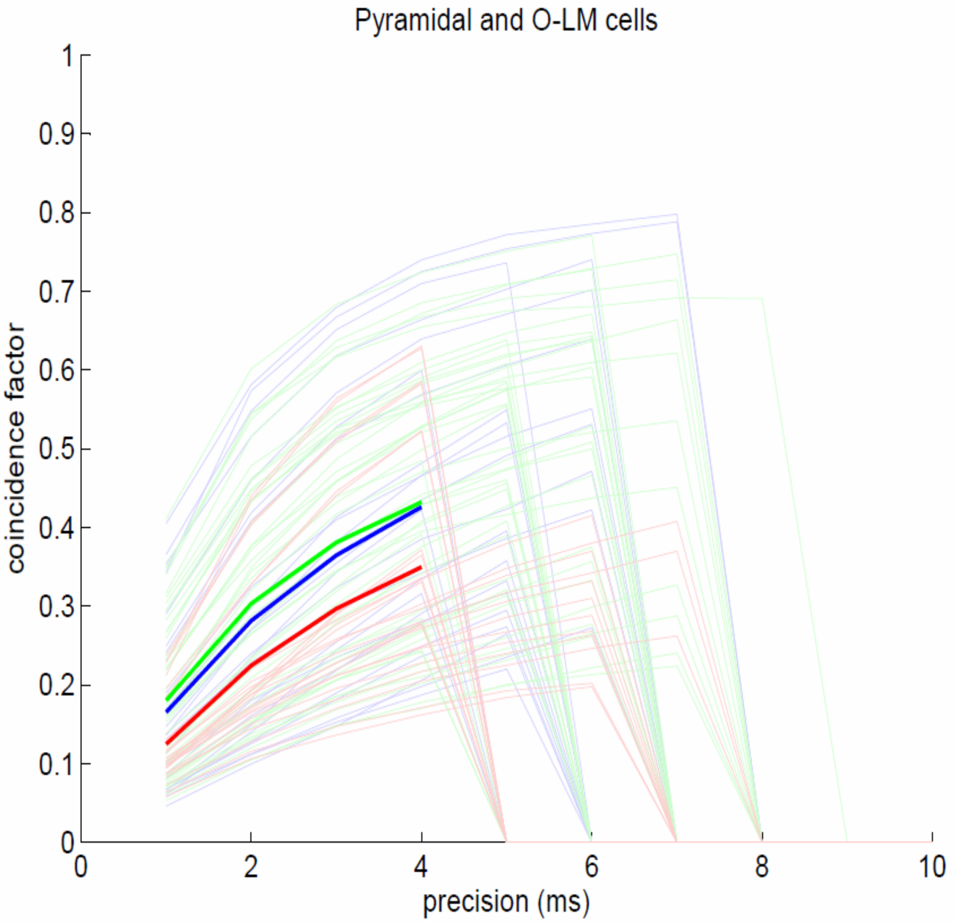
- Effects depend strongly on location, timing, short-term plasticity and type (feed-forward, feedback, shunting, inhibitory)
- Well-timed inhibition can shift the neuron from a slow bursting to a fast spiking regime
  – Cossart et al (2001), Wendling et al (2002): temporal lobe epilepsy: decreased inhibition in pyramidal cell dendrites, but increased inhibition around the soma.

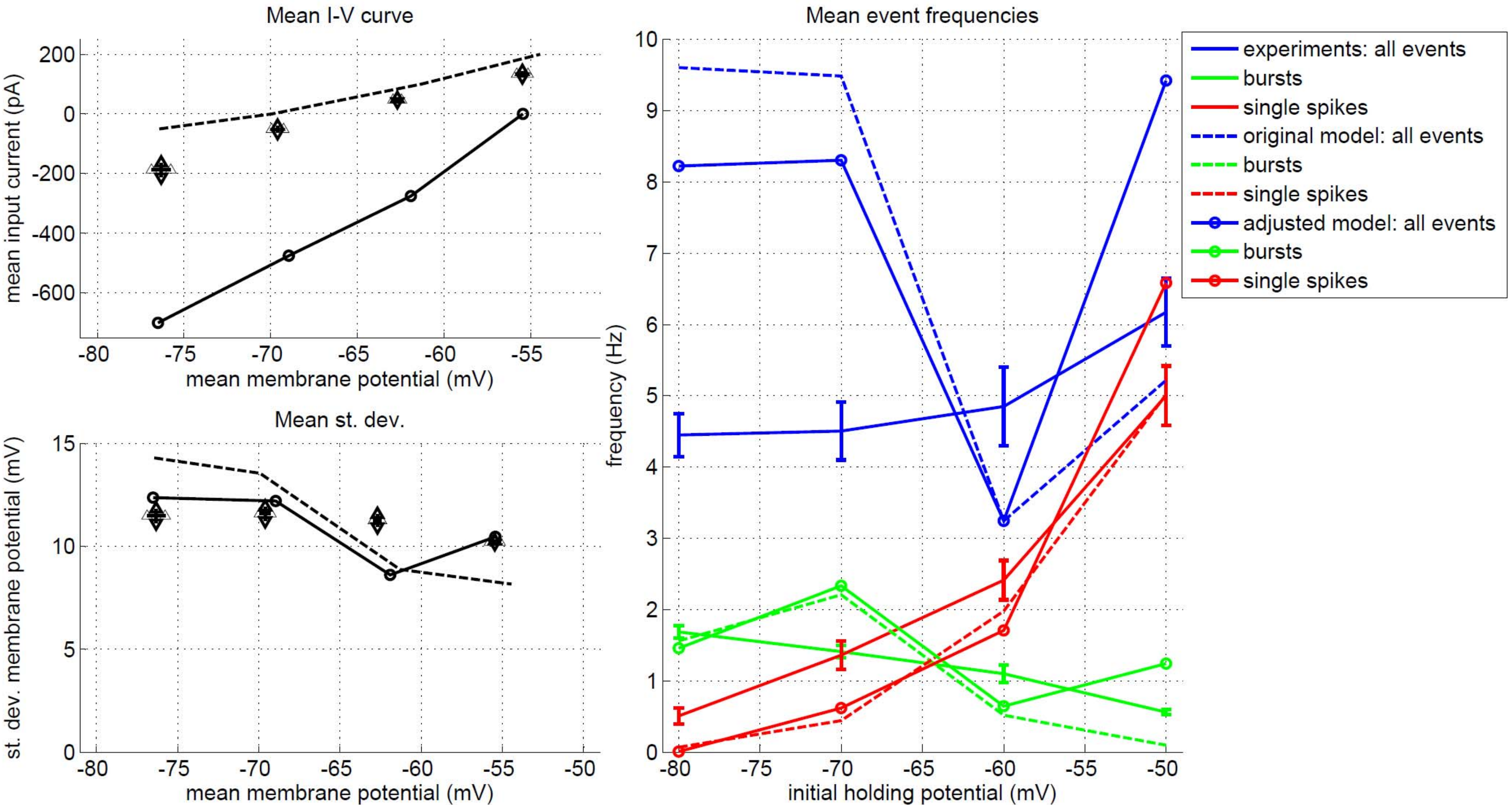


O-LM
Pyramidal
TC relay
0
500
1000
1500
2000
2500
3000
time (ms)

Coincidence factor: different cell types

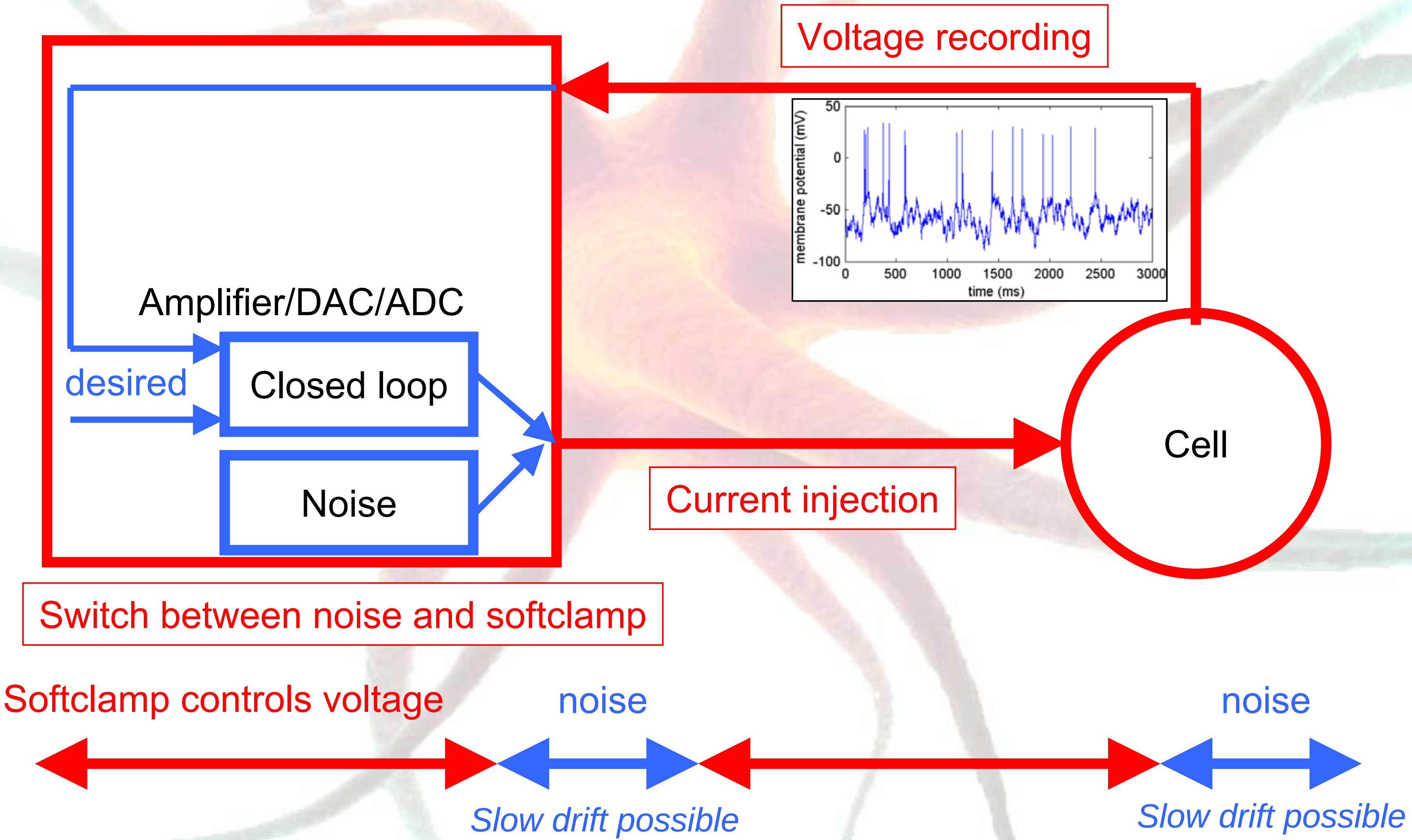




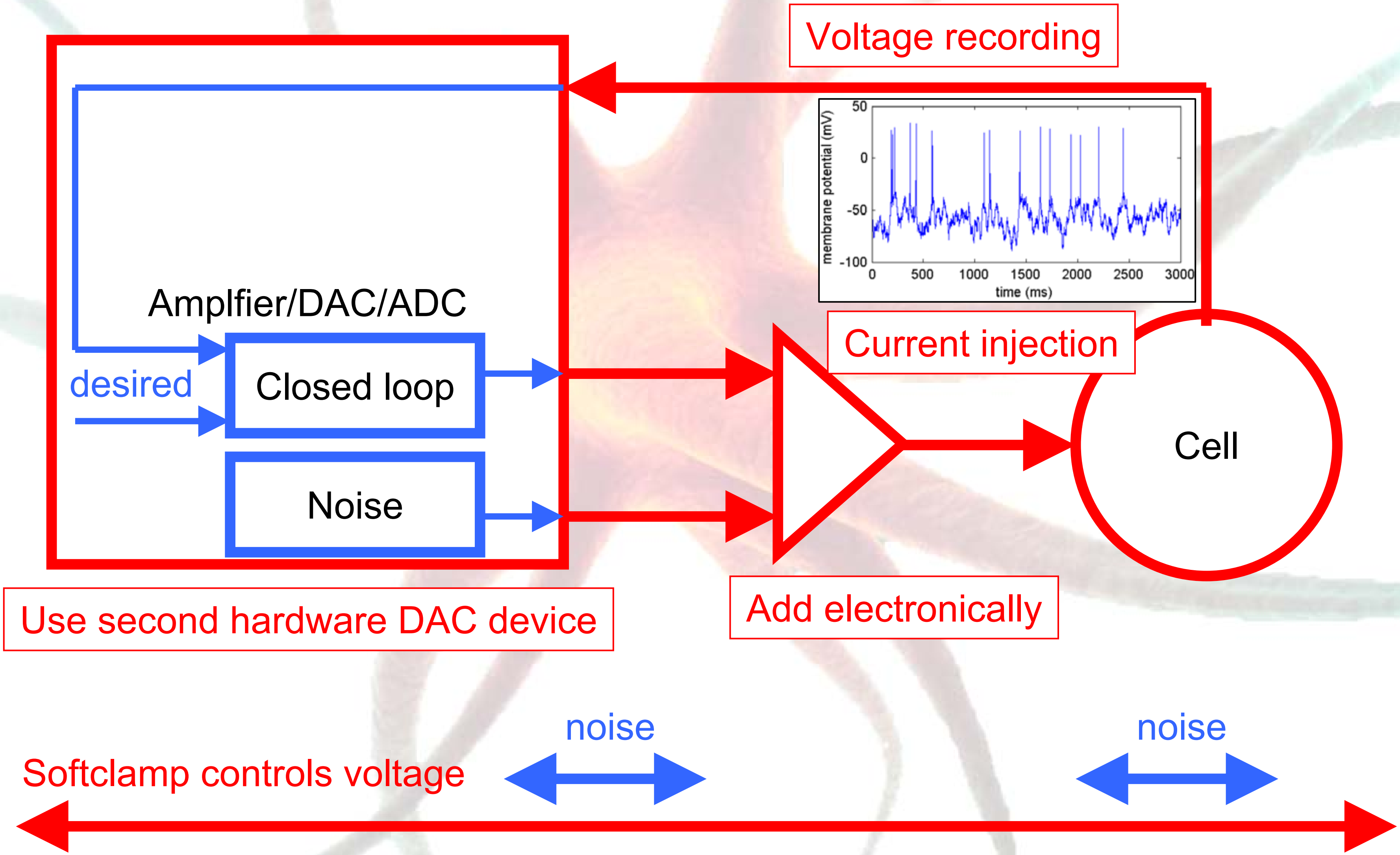


Mean I-V curve
mean input current (pA)
200
0
-200
-400
-600
-80
-75
-70
-65
-60
-55
mean membrane potential (mV)
Mean st. dev.
st. dev. membrane potential (mV)
15
10
5
0
-80
-75
-70
-65
-60
-55
-50
mean membrane potential (mV)
Mean event frequencies
frequency (Hz)
10
9
8
7
6
5
4
3
2
1
0
-80
-75
-70
-65
-60
-55
-50
initial holding potential (mV)
experiments: all events
bursts
single spikes
original model: all events
bursts
single spikes
adjusted model: all events
bursts
single spikes

Current experimental approach



Need to be improved to:



Carefully limit and determine spectral response of the softclamp