Simplicity in a complex world: Subthreshold membrane-potential resonances shape spike-train statistics

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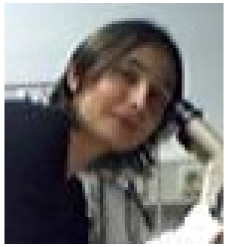
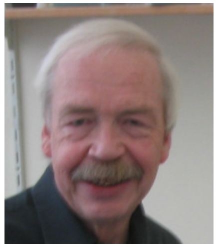
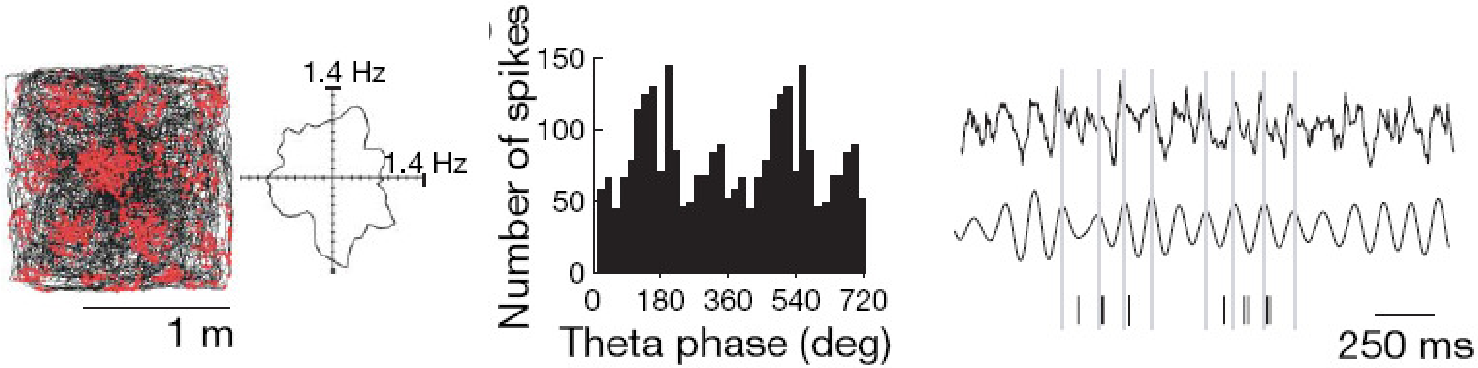




Tatiana Engel, Irina Erchova, Uwe Heinemann, Gunter Kreck, Lutz Schimansky-Geier, Susanne Schreiber

Erchova et al. J Phys 2004, Engel et al. J Neurophys 2008

Grid cells – rat entorhinal cortex (EC)



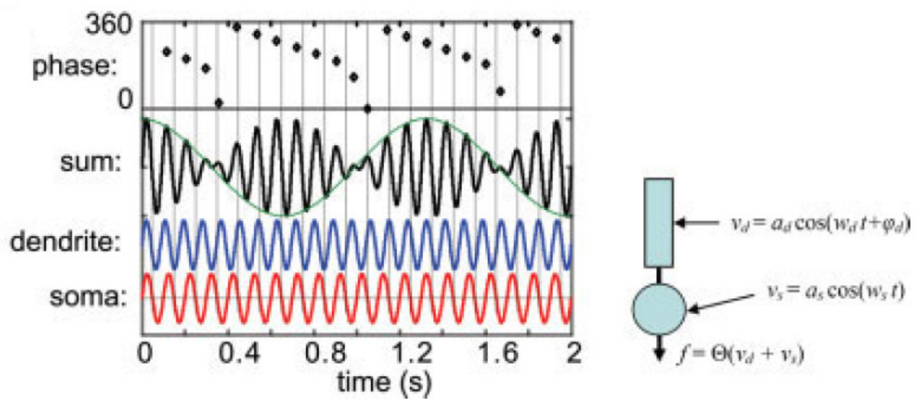
Hafting et al., 2008

Formation of grid fields:

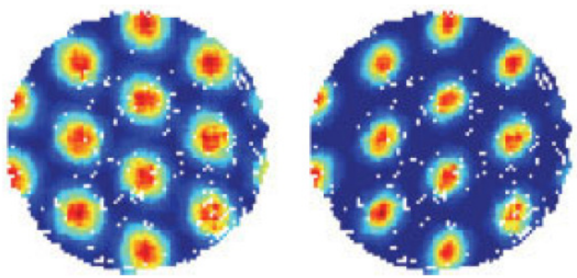
Mechanisms?
Single-cell vs. network?

→ What do we know about the intrinsic dynamics of EC cells?

In particular: about layer-II stellate cells?

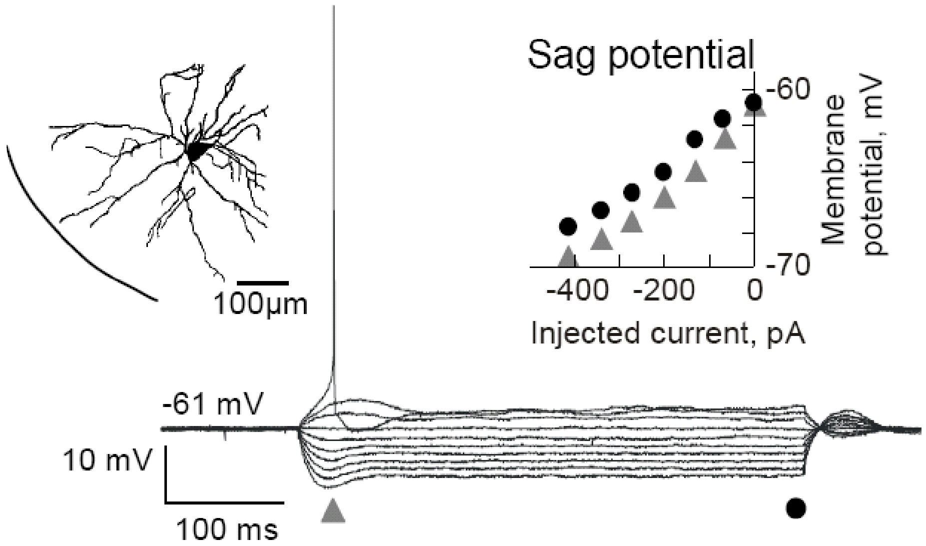


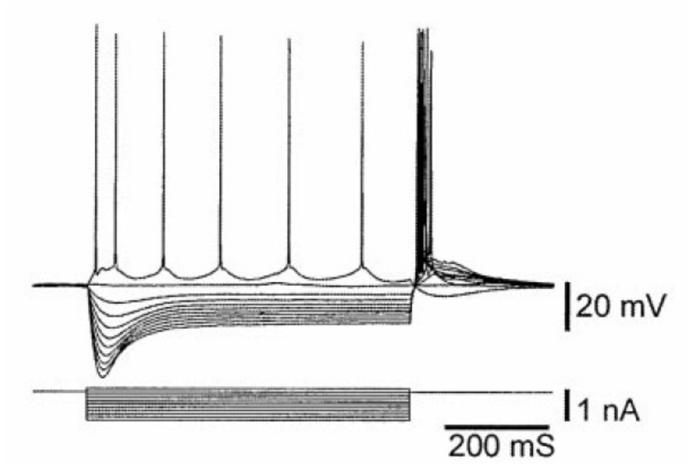
Burgess et al., 2007



Subthreshold dynamics: EC layer II stellate cells

Response to step-current inputs



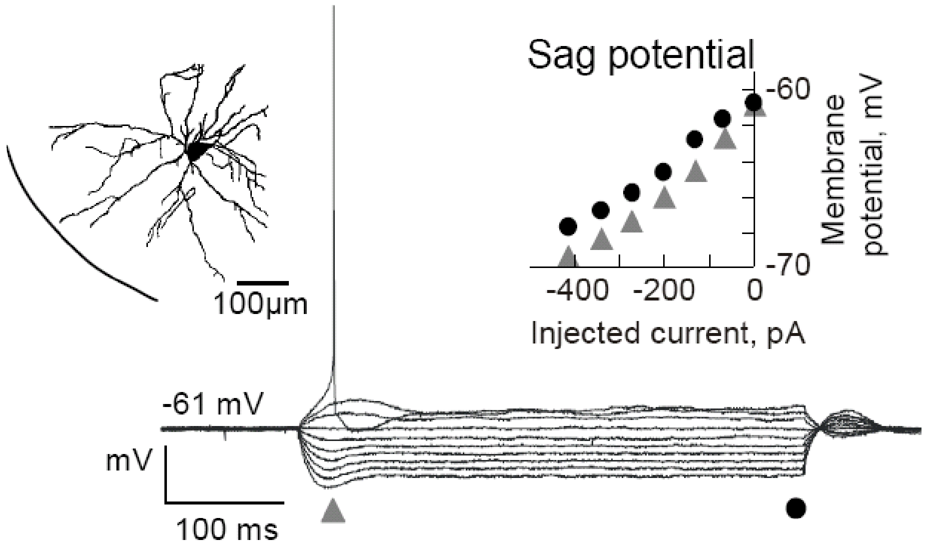


- Overshooting transients (on & off)

Dickson et al. 2000:
Same phenomena

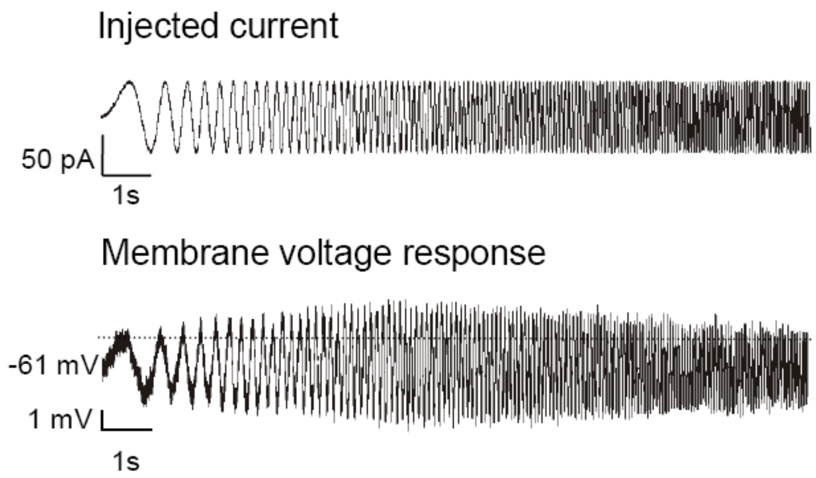
Subthreshold dynamics: EC layer II stellate cells

Response to step-current inputs

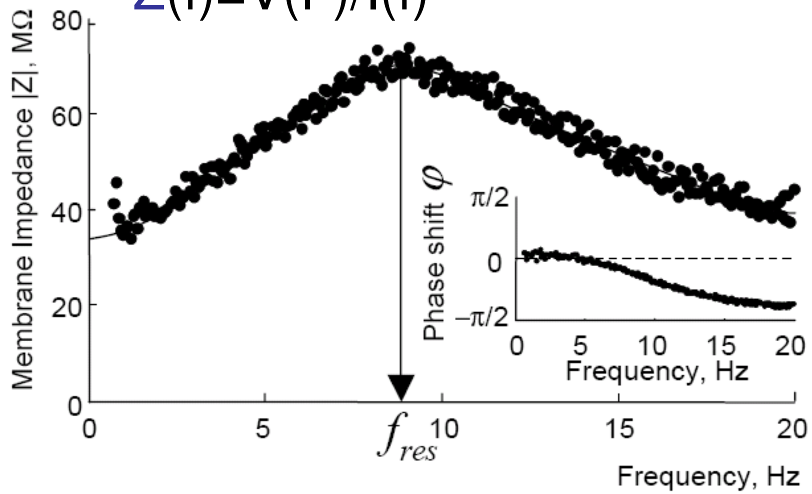


- Overshooting transients (on & off)
- Membrane-potential resonance
  [up to 2.1 fold response compared to DC inputs]

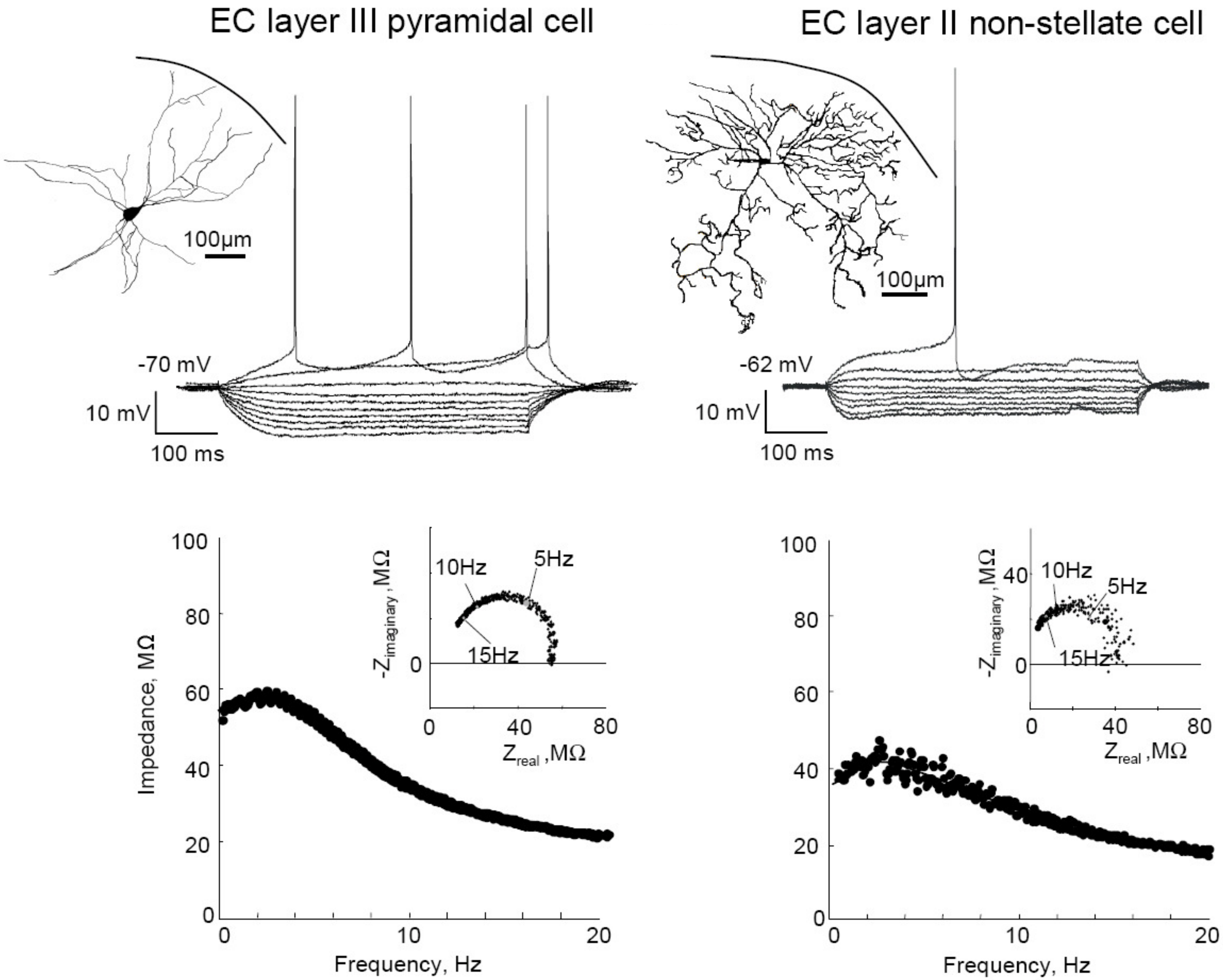
Response to ZAP currents (Impedance Amplitude Profile)



Z(f)=V(F)/I(f)

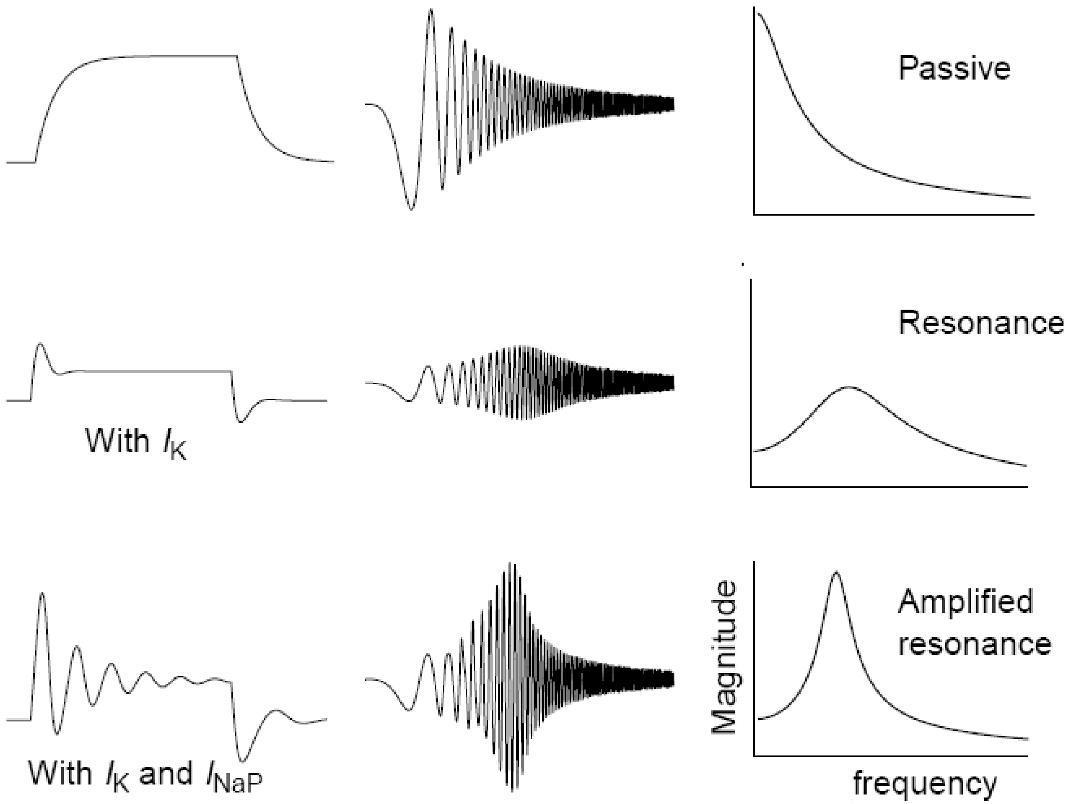


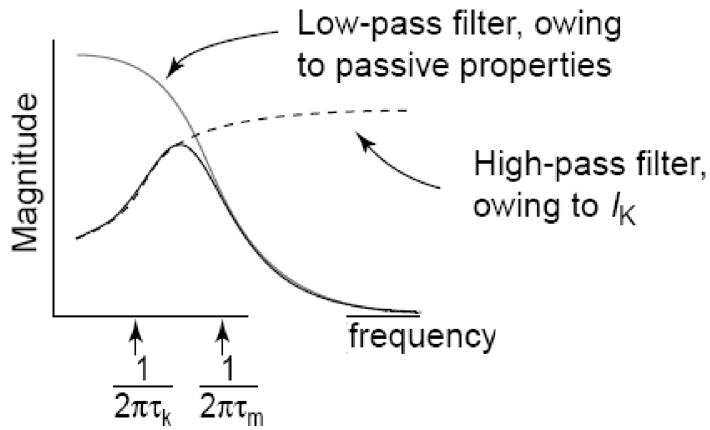
Subthreshold dynamics: other EC cells



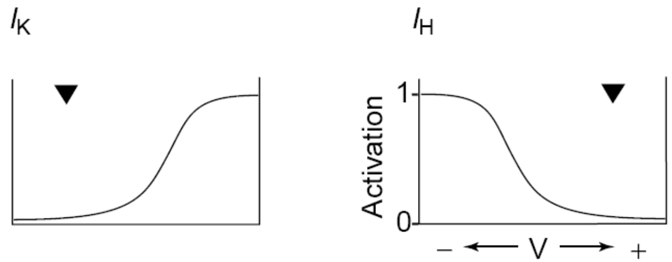
No or only weak membrane-potential resonance & sag potentials

Subthreshold resonance: biophysical mechanisms





Hutcheon & Yarom TINS 2002



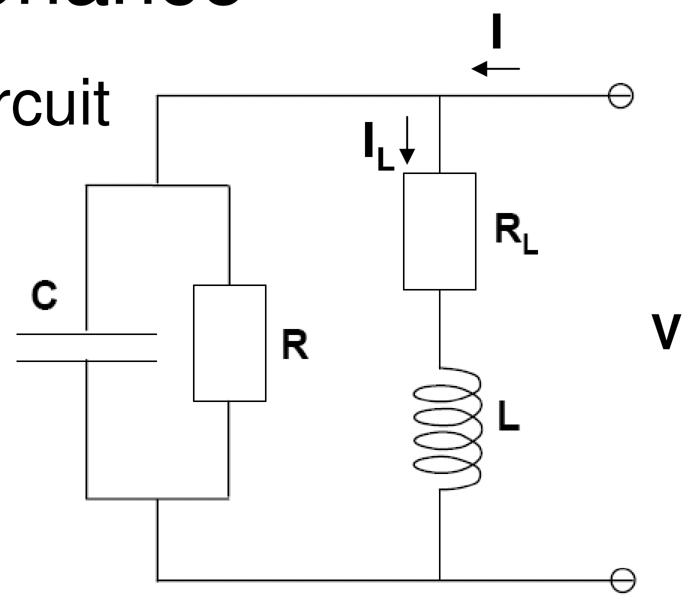
Key ingredient:

Some slowly activating current that opposes voltage changes, e.g., I_K or I_H

Modelling subthreshold resonance

Phenomenological approach: RLC circuit
(Mauro et al. 1970, Koch 1984)

Alternative interpretation:
2D-reduction of HH-Type model
(Koch 1999, Richardson et al. 2003)



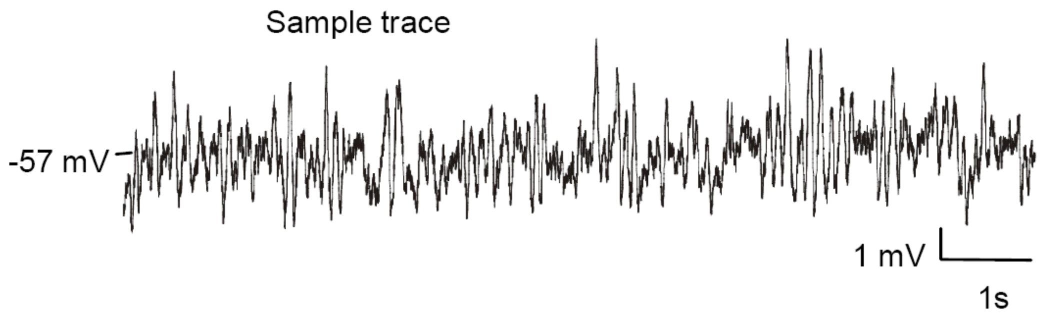
$C\, dV/dt = -VR^{-1} + (I - I_L)$

$L\, dI_L/dt = -R_L I_L + V$

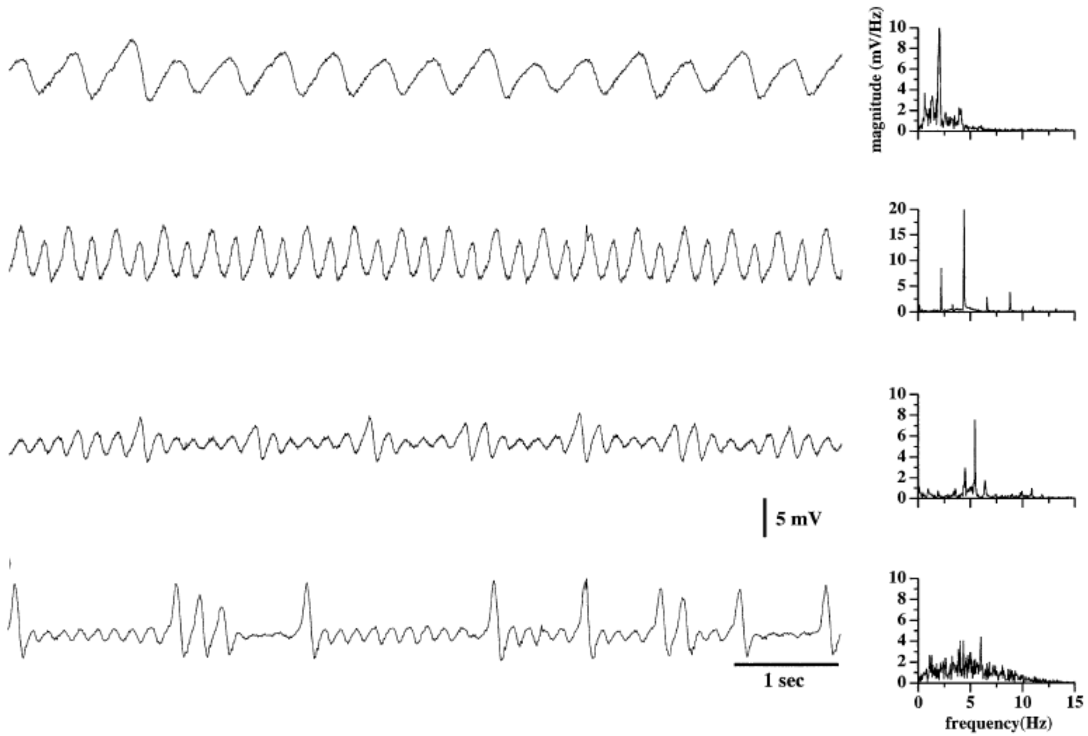
Slowly activating current opposing V changes [e.g., I_K, I_H]

C, R, R_L, L: state dependent ($\bar{V}$)

Membrane potential oscillations (MPOs)



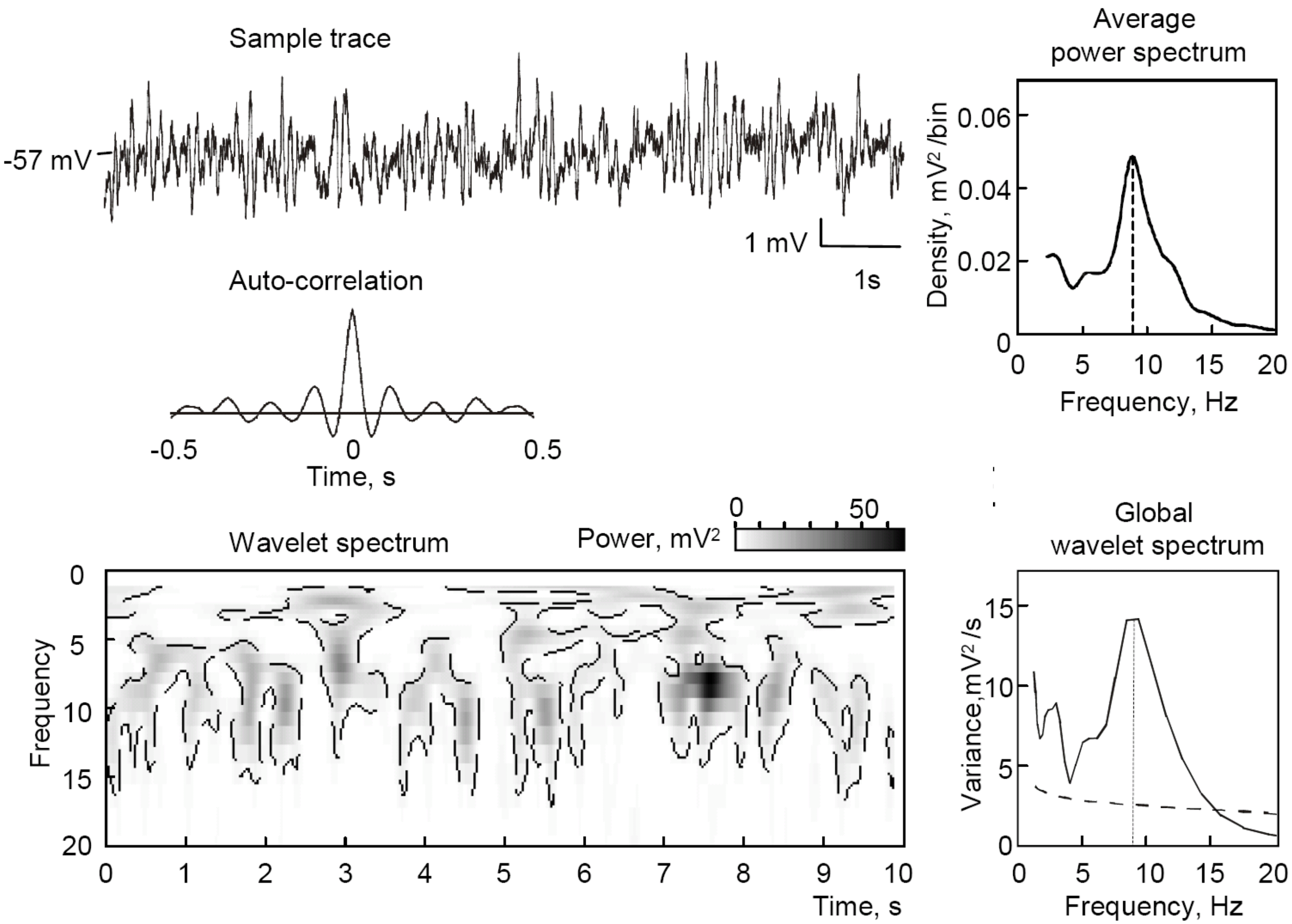
Channel-noise driven (White et al. 1998) ≠ deterministic limit cycles!



Inferior olive:
Gap-junction coupling

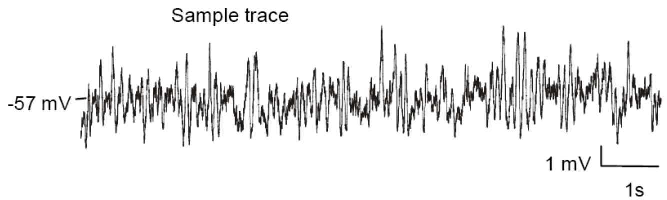
Lampl & Yarom 1997

Membrane potential oscillations (MPOs)

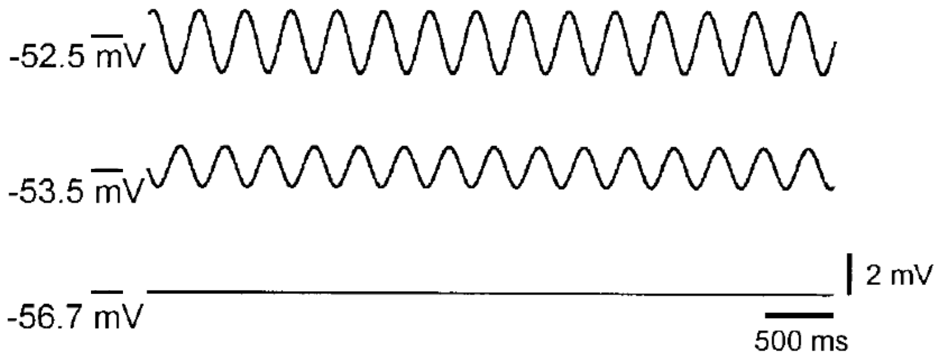


Channel-noise driven oscillations ≠ deterministic limit cycles!

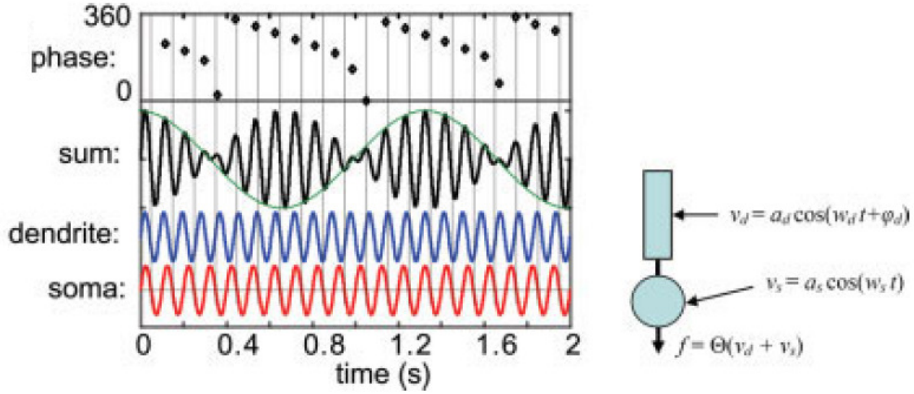
Stochastic MPOs → Models?



Deterministic descriptions:

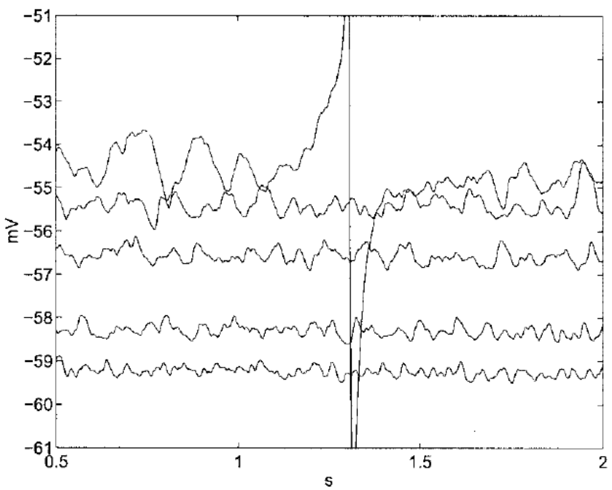


Dickson et al., 2000



Burgess et al., 2007

Stochastic descriptions:



Fransén et al. 2004:

the occurrence and stability of MPOs did not require the presence of noise (data not shown), but its presence increased the parameter interval within which oscillations were stable (see Discussion).

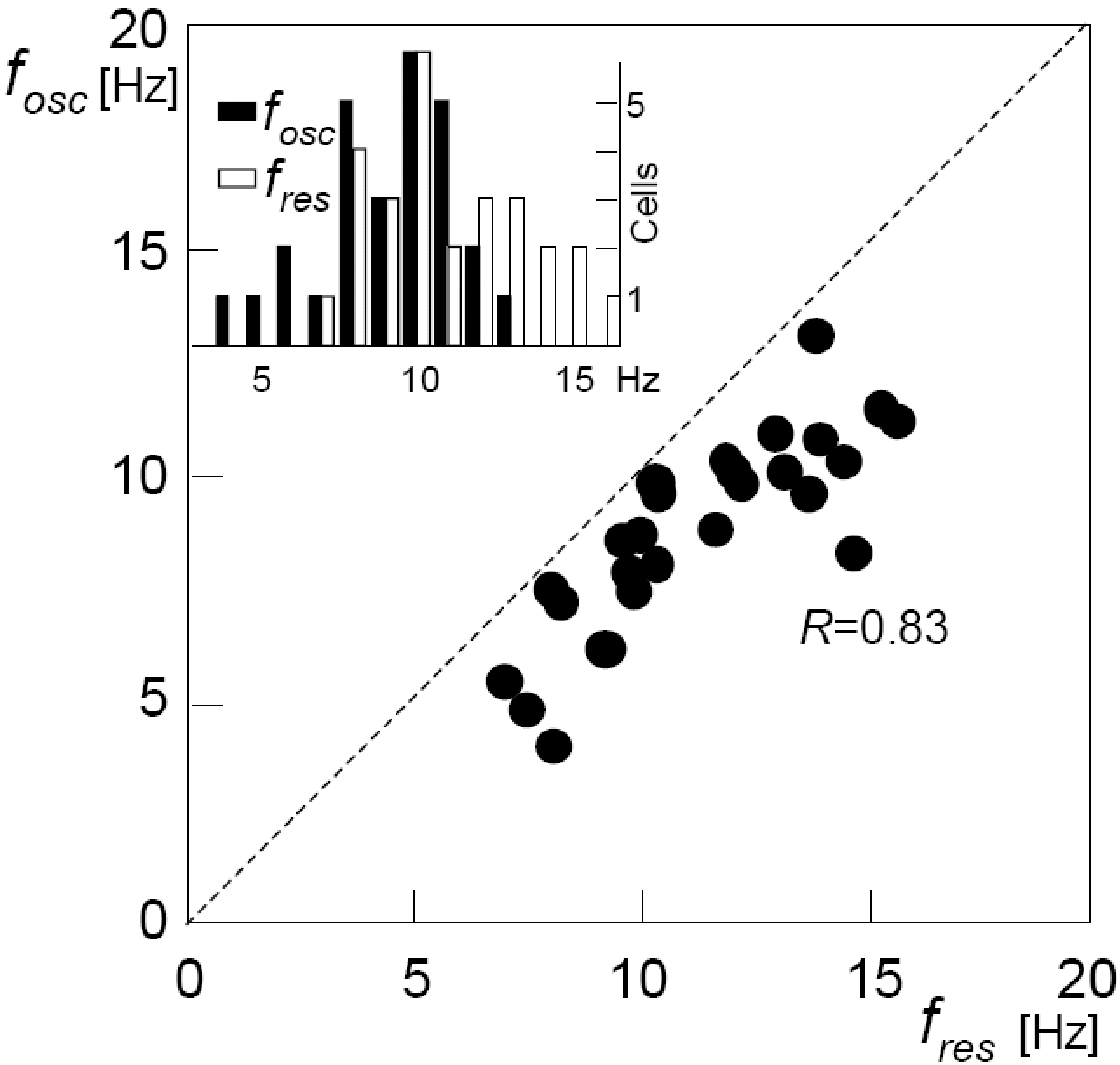
MPOs versus subthreshold resonance

Resonance & MPO frequencies: θ range

Resonance frequency is larger than MPO frequency

Harmonic oscillator model predicts opposite effect.

→ Nonlinearities ??
(Leung & Wu, 1998)



Modelling subthreshold dynamics

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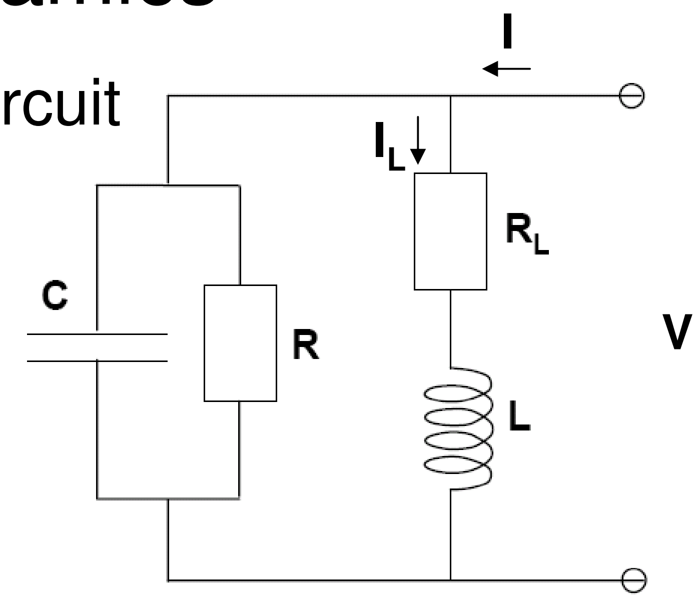
C, R, R_L, L: state dependent ($\bar{V}$)



C dV/dt = $-VR^{-1}+(I-I_L)$

L dI_L/dt = $-R_L I_L + V$

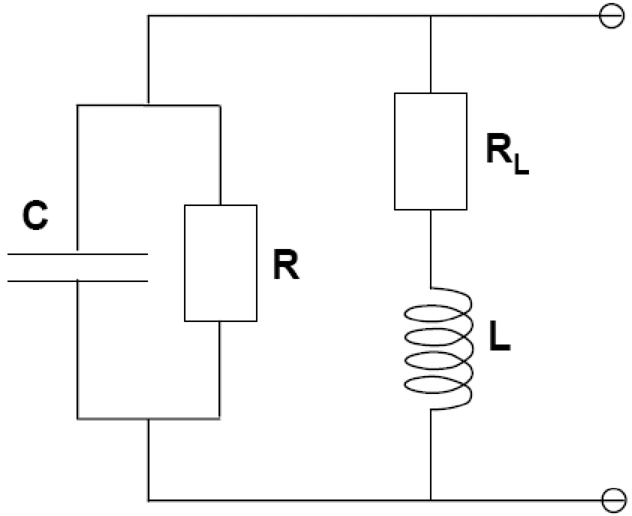
$I = I_{external} + I_{channel\ noise}$

Two operating regimes:

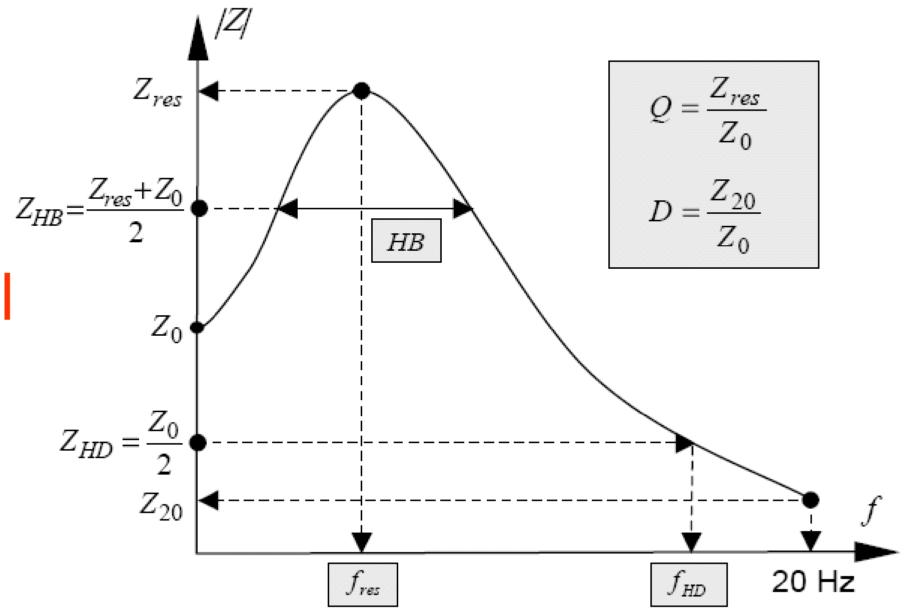
- resonance experiments: trial average $\rightarrow$ $\langle I_{channel\ noise} \rangle = 0$
- MPO experiments (spontaneous activity) $\rightarrow$ $I_{external} = 0$

Mathematical model → quantitative calculations / predictions

Modelling subthreshold dynamics I



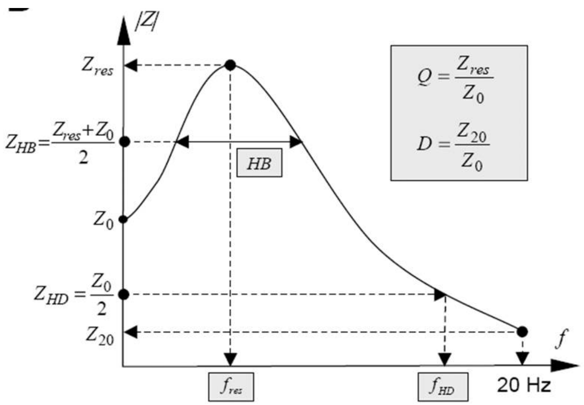
C, R, R_L, L: state dependent (V)

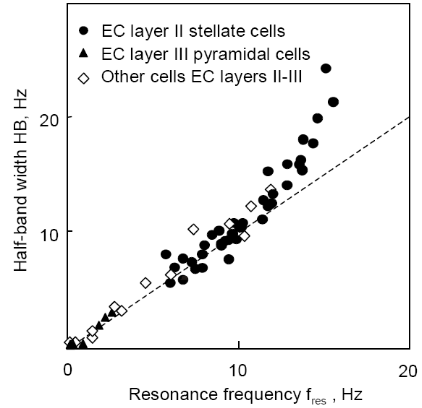


Directly related to:

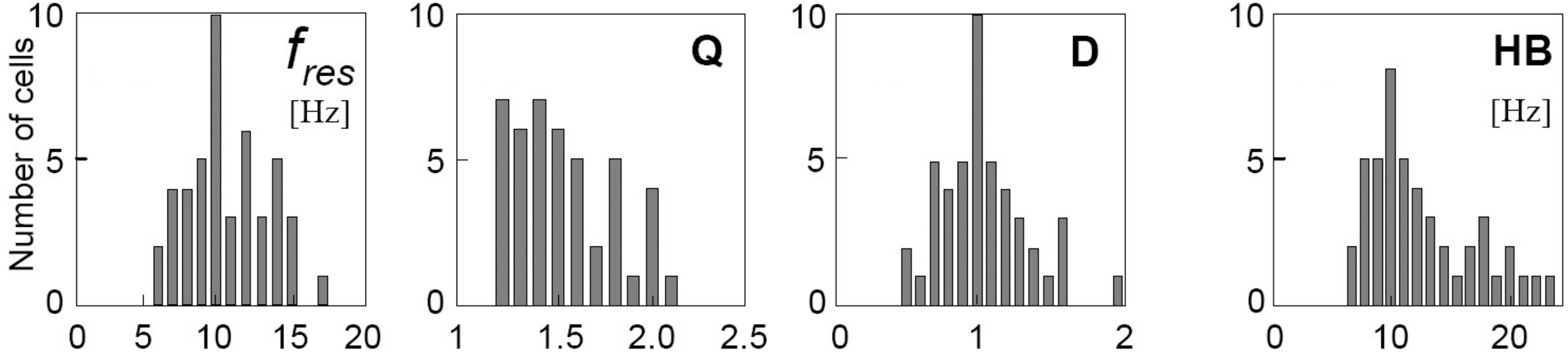
Phenomenological parameters that can be estimated for each cell from resonance experiments.

Population data

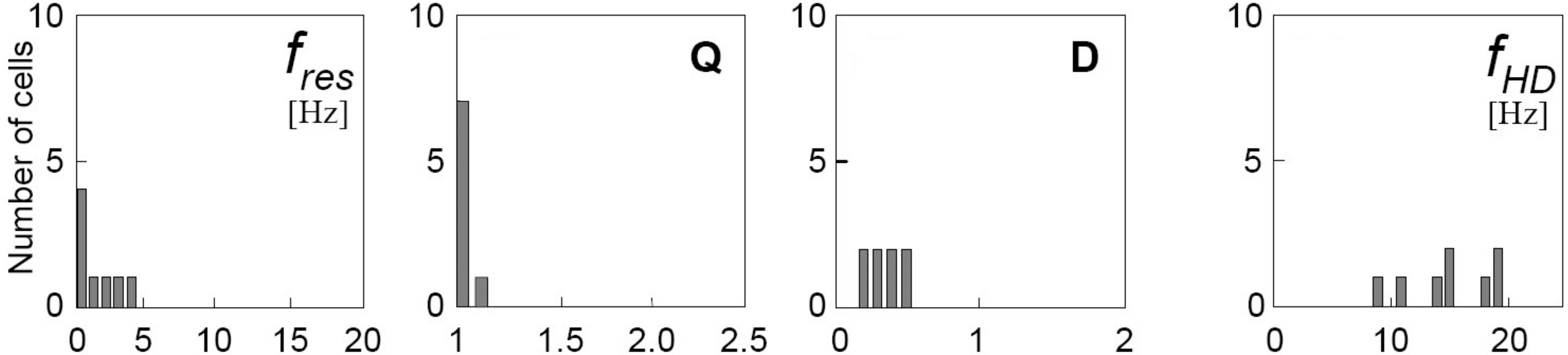




EC layer II stellate cells



EC layer III pyramidal cells

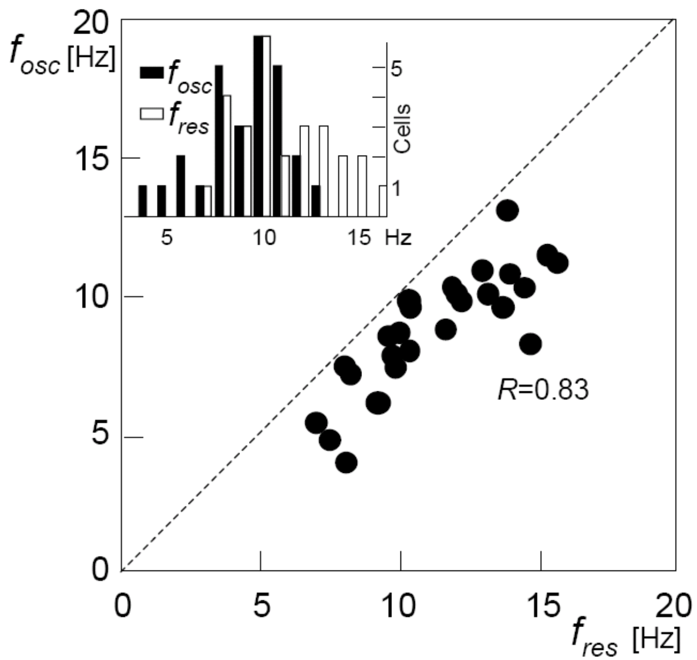


Large cell-to-cell variability → population averaging risky!

MPOs versus subthreshold resonance

Resonance frequency is larger than oscillation frequency.

Harmonic oscillator model predicts opposite effect.



Solution – 1st attempt:

RLC Model is *not* equivalent to a harmonic oscillator.
I and dI/dt enter the d^2V/dt^2 dynamics:

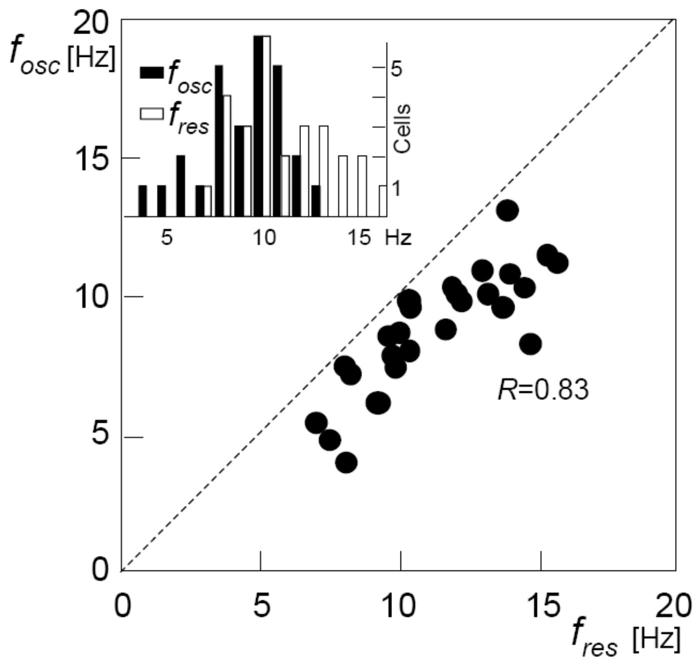
$C\, d^2V/dt^2 + \gamma\, dV/dt + \delta\, V = R_L\, I / L + dI/dt$ with $\gamma = 1/R + R_L\, C/L$ and $\delta = 1/L\,(1+R_L/R)$; results in $f_{res} > f_{osc}$

This solution does, however, not take stochasticity in account!

MPOs versus subthreshold resonance

Resonance frequency is larger than oscillation frequency.

Harmonic oscillator model predicts opposite effect.



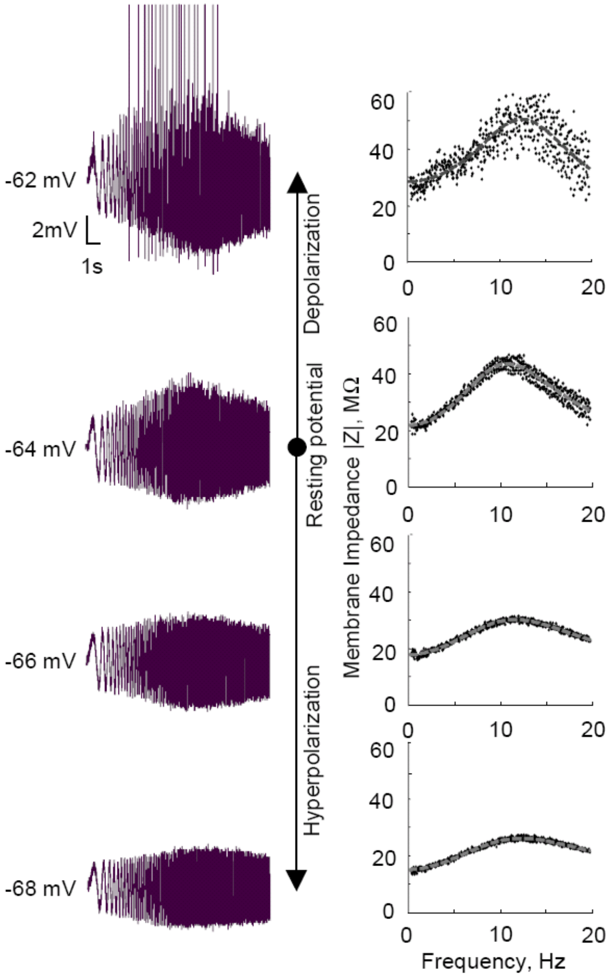
Solution:

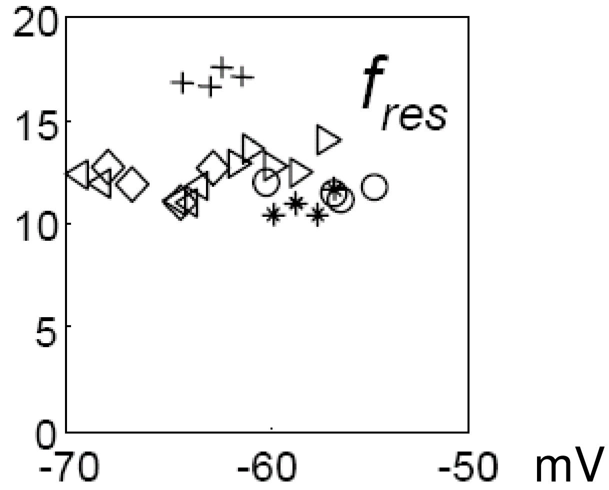
By definition: Z(f)=V(f) / I(f)

$$\rightarrow \quad |V|^2(f) = |I_{\text{channel noise}}|^2(f) * |Z|^2(f)$$

If $|I_{\text{channel noise}}|^2(f)$ decreases with f $\rightarrow$ $f_{osc} < f_{res}$

Voltage dependence of resonance properties





Resonance frequency:

- largely independent of holding potential
- varies from cell to cell

→ Any relevance for the *supra*threshold regime?

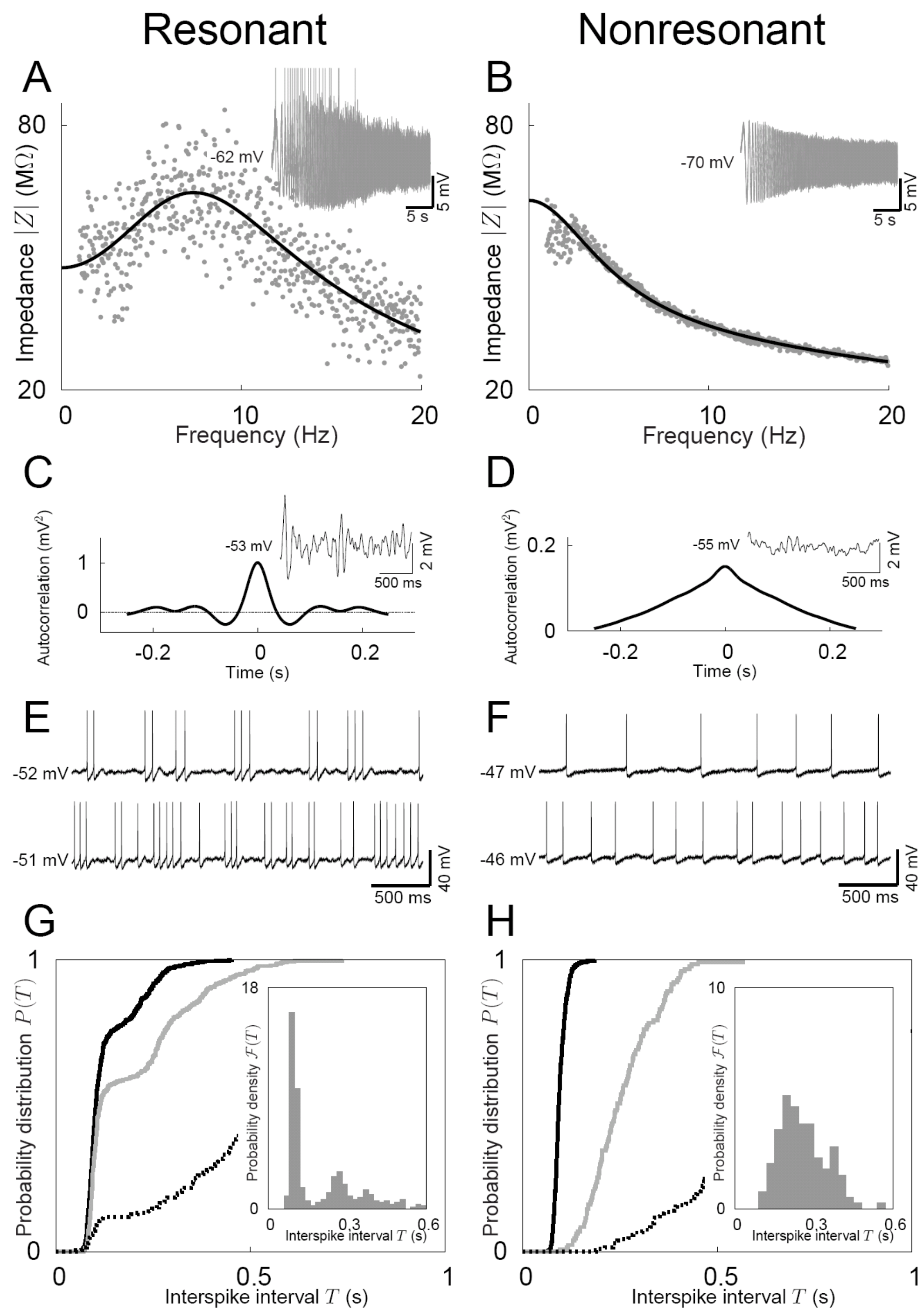
Spike trains I

What is the relation between

- MPOs
- Subthreshold Resonance
- and ISIs ?

Stellate Cells:

Intracluster ISIs do *not* depend on firing rate.

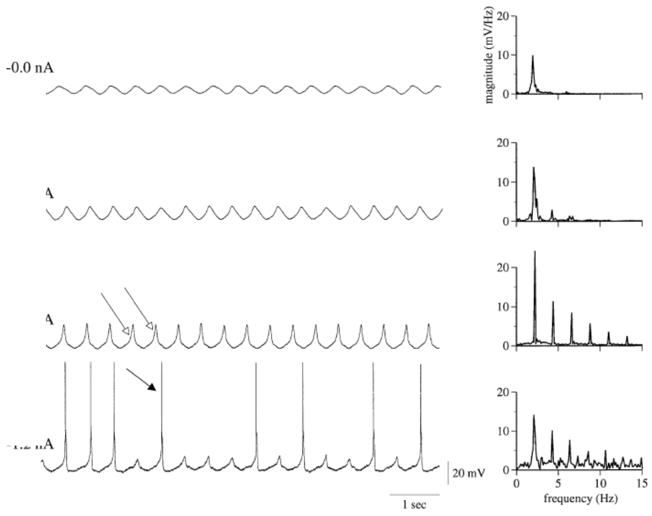


Intermezzo: inferior olive

APs ride on MPOs

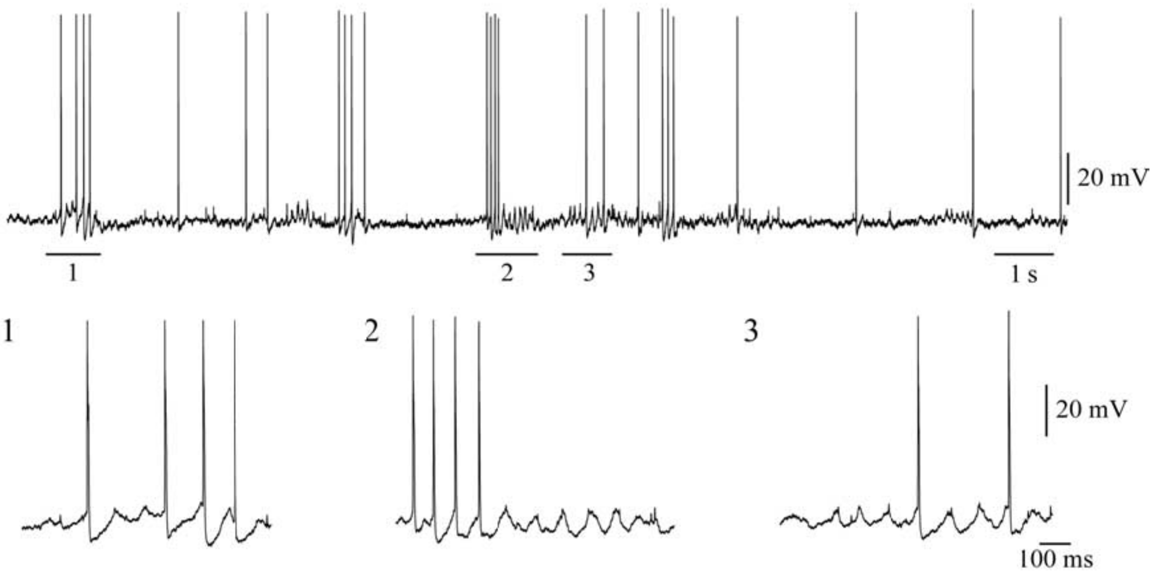
in vitro

and *in vivo*



Lampl & Yarom 1997

MPO frequency independent of holding potential

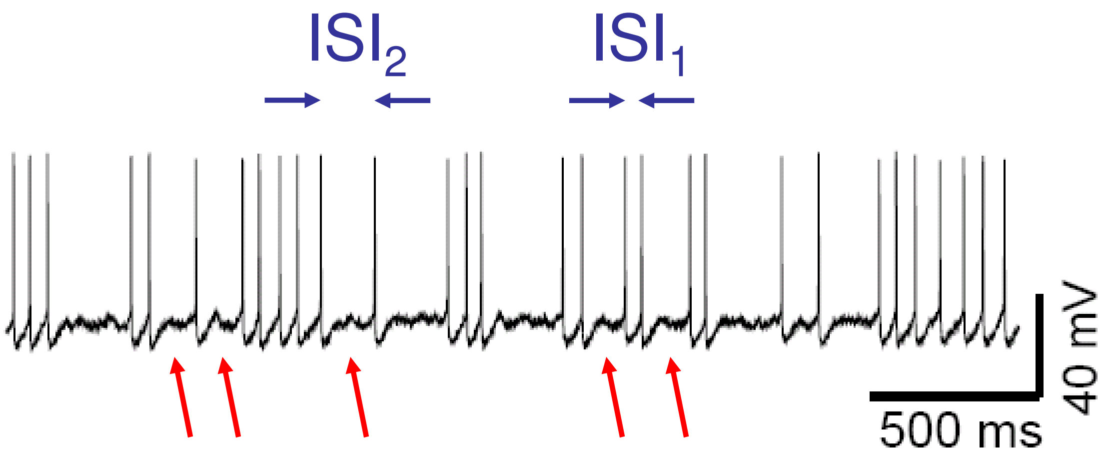


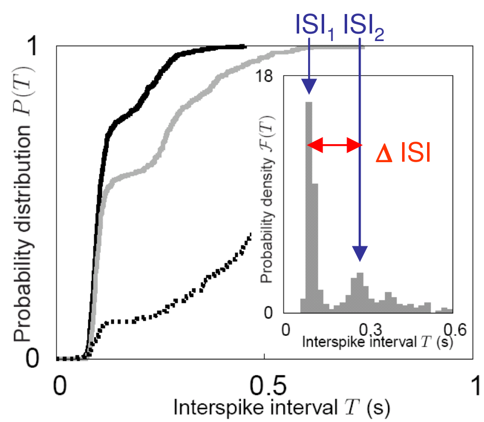
Chorev et al. 2007

ISIs vary slightly in time

Inferior olive: MPOs shaped by network interactions

Spike trains II

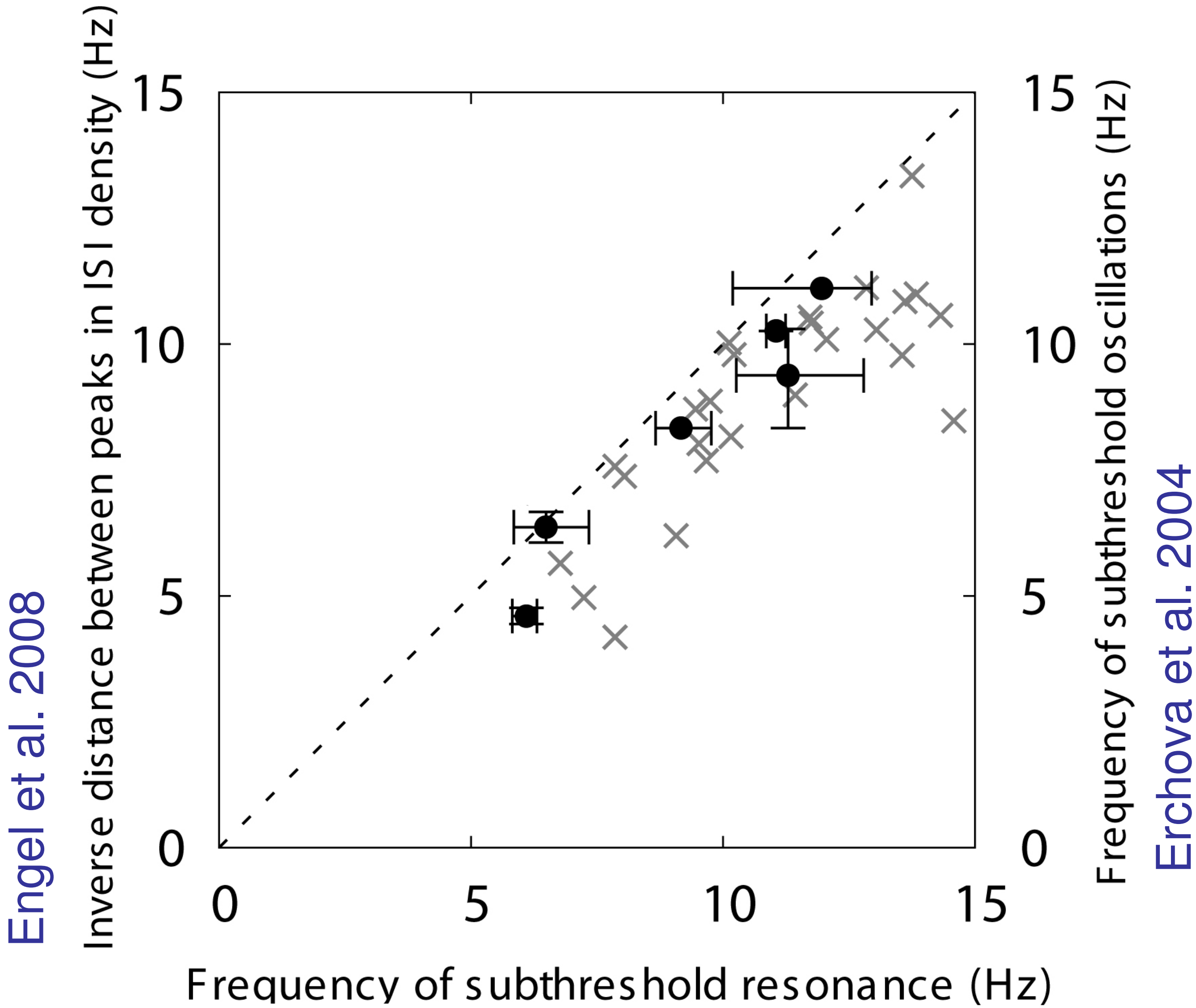




"skipped" spikes

$\rightarrow$ size of Δ ISI = $ISI_2 - ISI_1$??

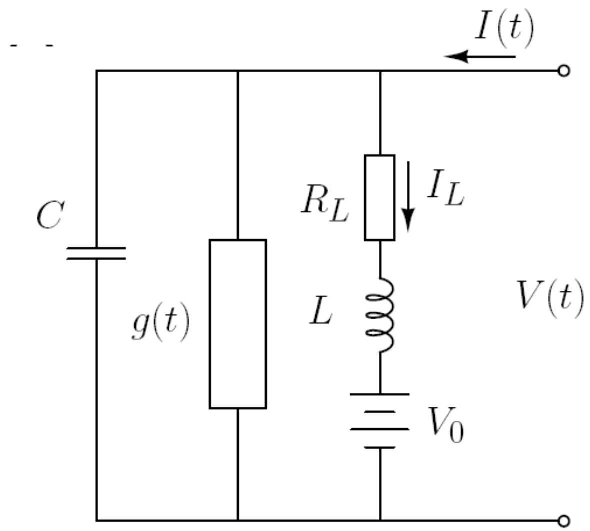
Spike trains III



Result: Δ ISI matches period of one subthreshold oscillation!

Modelling sub- & suprathreshold dynamics

Subthreshold regime



Stochastic conductance:

$$\dot{g}(t) = -\frac{1}{\tau}\left(g(t) - \frac{1}{R}\right) + \sqrt{2Q}\xi(t);$$

$$\langle g(t) \rangle = 1/R.$$

Parameters:

$$\delta = \frac{1}{L}\left(1 + \frac{R_L}{R}\right); \qquad \gamma = \frac{1}{R} + \frac{R_L C}{L};$$

$$R_0 = \frac{R_L}{1 + R_L/R}; \qquad V_r = \frac{V_0}{1 + R_L/R}.$$

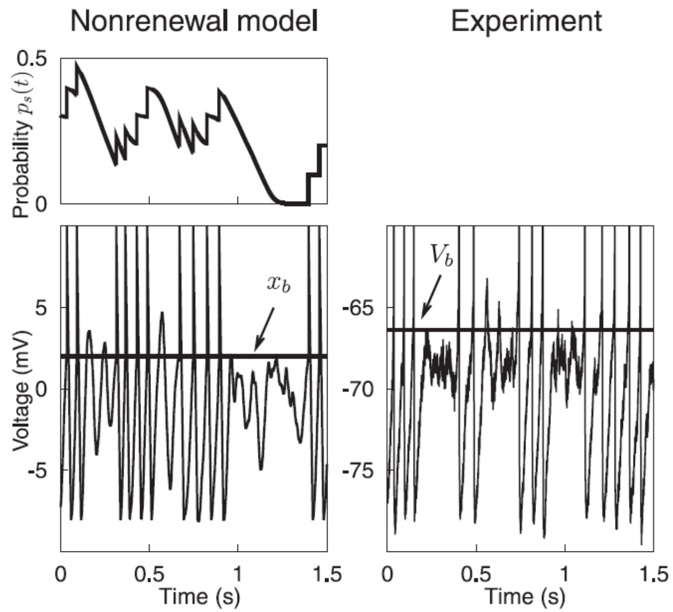
Superthreshold regime

a) Renewal model:

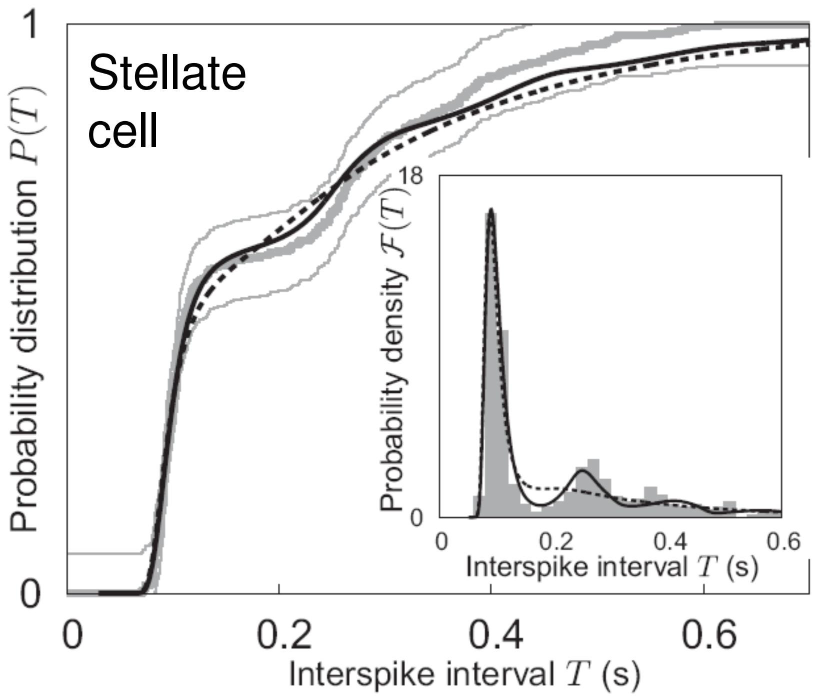
- Firing threshold V_t
- Voltage reset V_r
- Refractory period τ_r (with dV/dt=0)

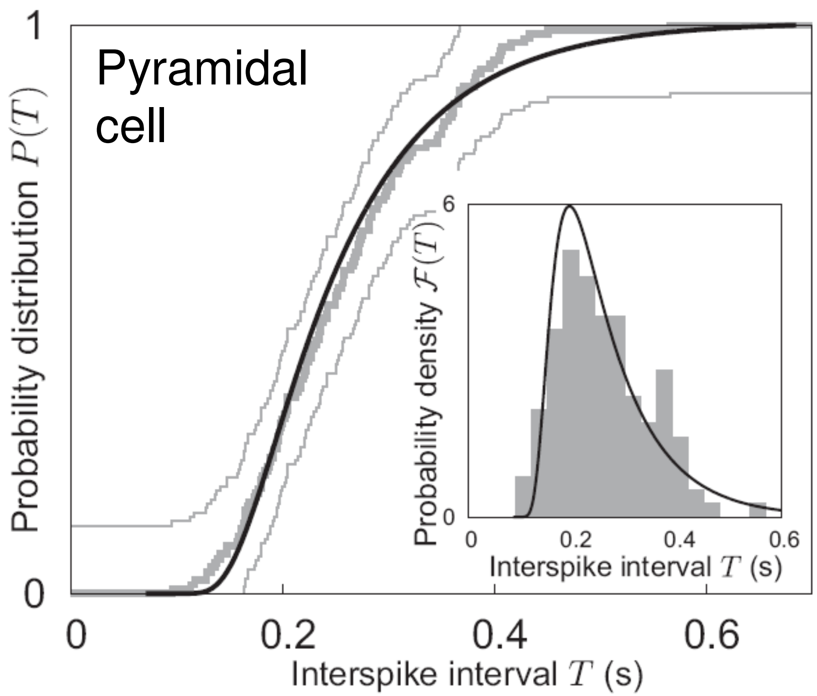
b) Non-renewal model:

Stochastic spike generation



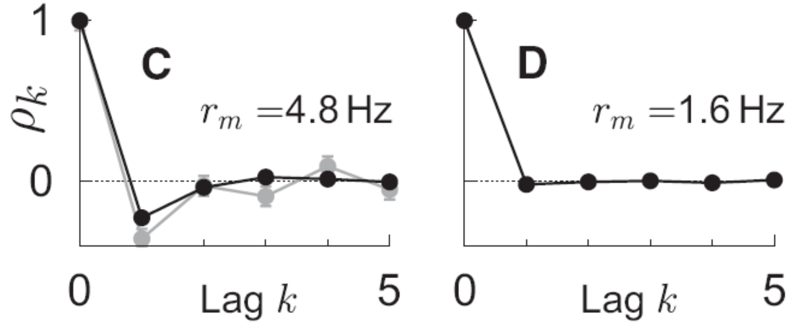
Modelling sub- & suprathreshold dynamics II





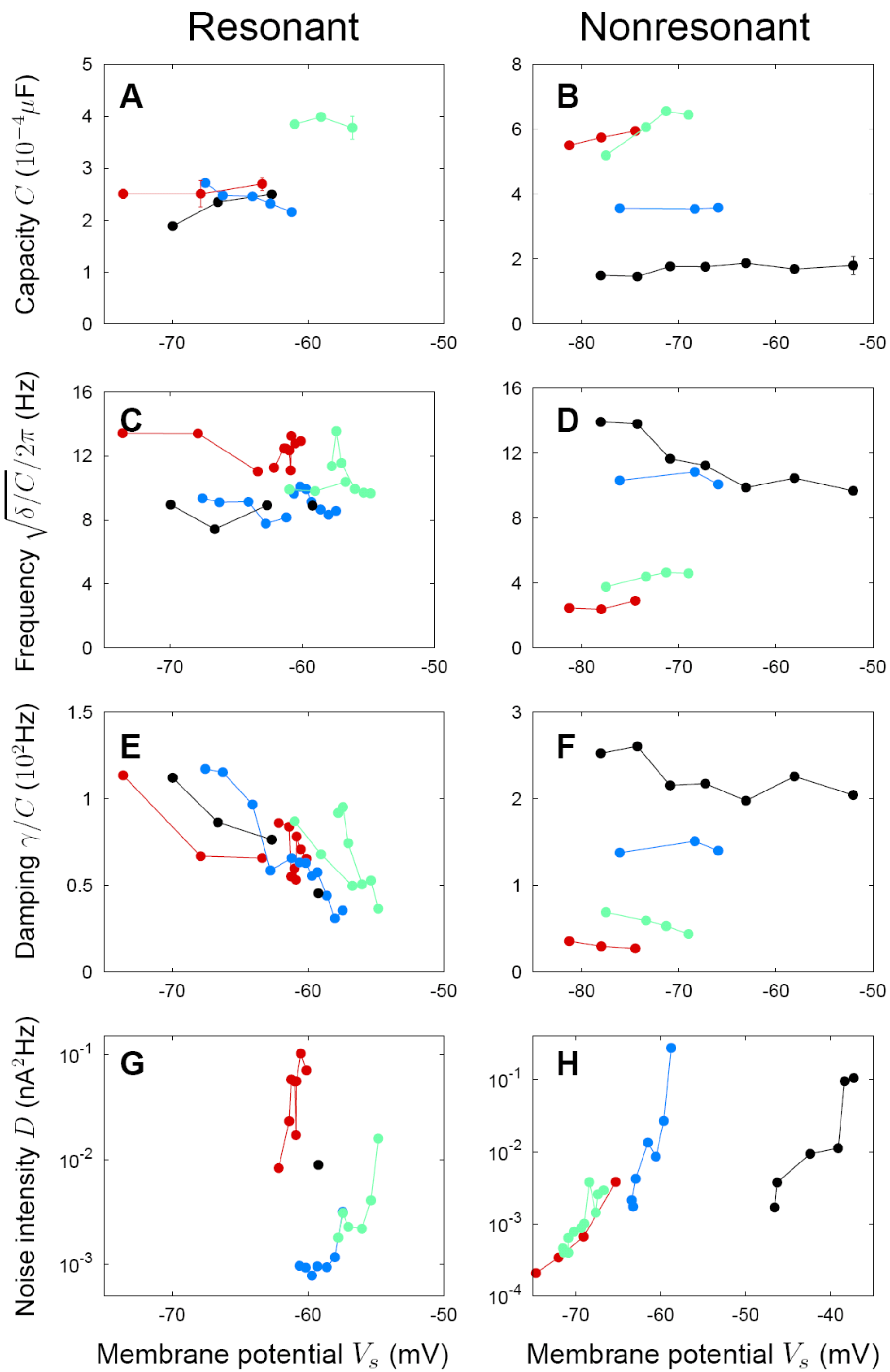
Good fit with
renewal model

further improvements
with non-renewal dynamics

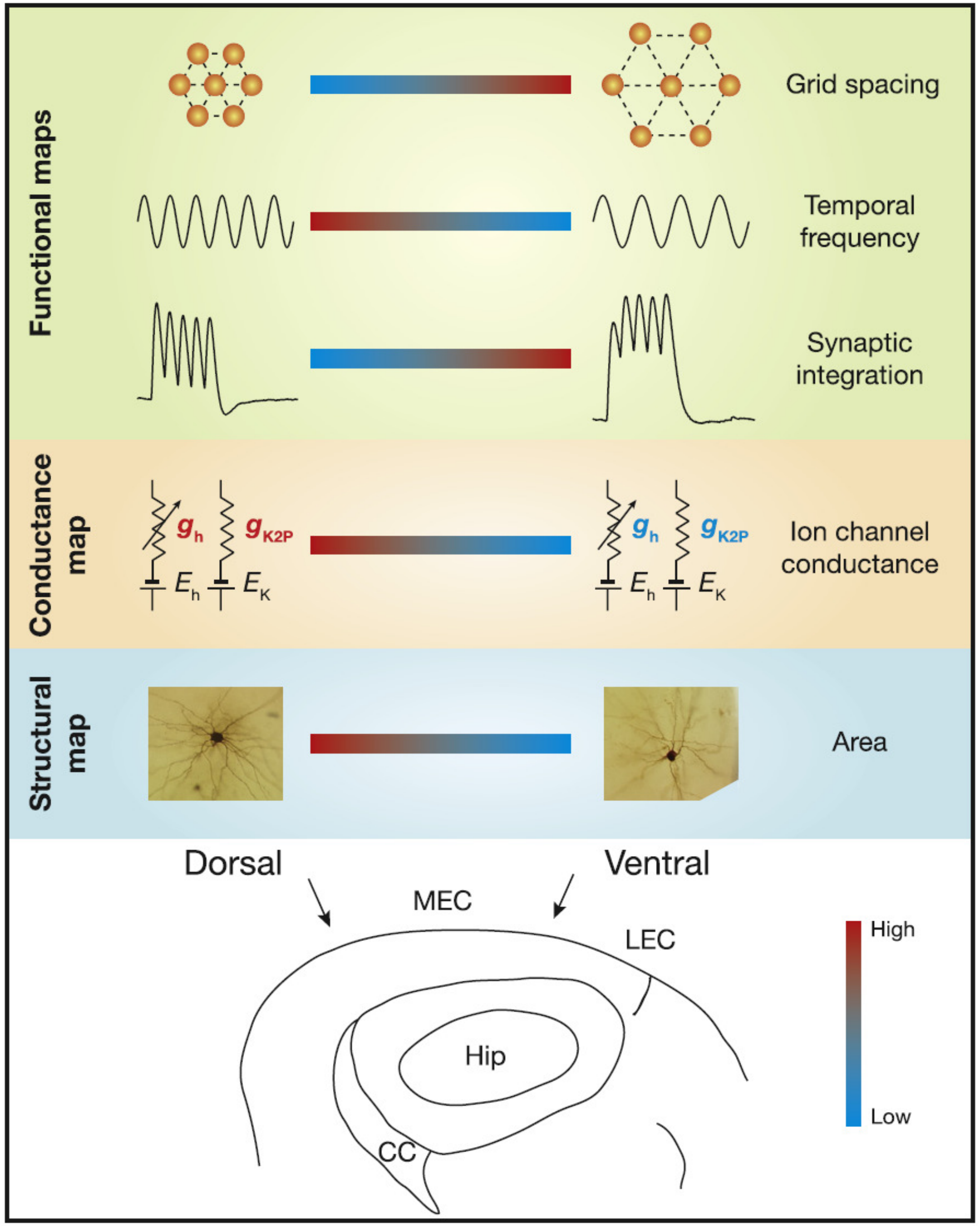


Stellate cell – serial ISI correlations

Voltage (in)dependence of parameter values



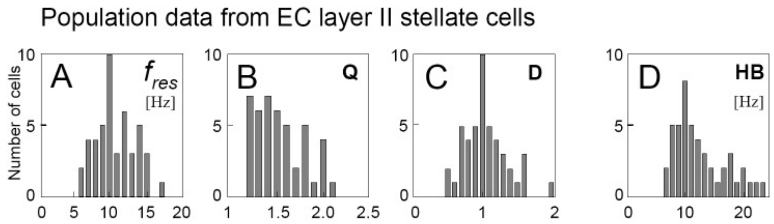
Outlook: Spatial gradients - physiology & anatomy



Moser et al. 2008

Giocomo et al. 2007

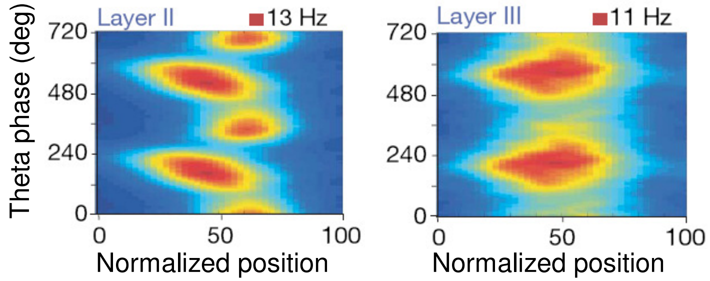
Garden et al. 2008



Narayanan & Johnston 2008

Conclusions & open questions:

- Dynamics of EC II stellate cells and EC III pyramidal cells differs strongly (sub- & suprathreshold); also *in vivo*: →



Hafting et al., 2008

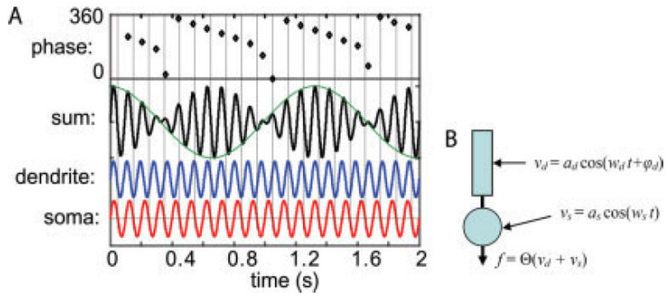
- subthreshold properties clearly visible even far above firing threshold
- simple mathematical framework sub- & superthreshold dynamics

Stellate cells:

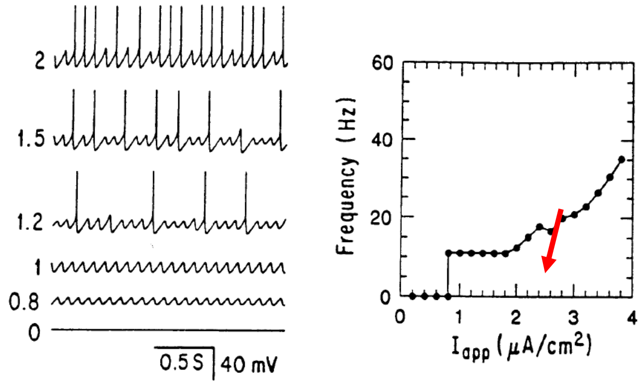
- resonance frequency largely independent of holding potential
- large range of intrinsic frequencies (6…16 Hz), spatial gradients
- short & long intra-cluster ISIs largely independent of firing rate

→ cell-intrinsic frequency memory

→ relevance under in vivo conditions???
[e.g. min ISIs ~ 5ms → input statistics?]



Voltage dependence of resonance properties: (further results)



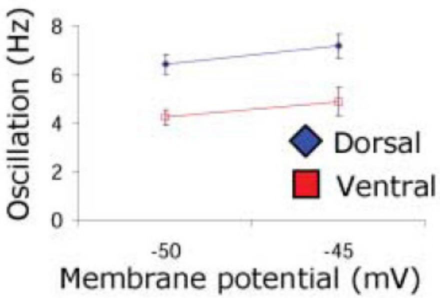
Wang 1993

Computational model: HH + I_{NaP} + I_H

Alonso & Klink 1993

- V-independent MPO frequency (see their Fig. 5F)
- MPO amplitude has inverted U-shape (their Fig. 4C) ??
- Frequency of interspike MPOs depends on firing state ??

Giocomo et al. 2007

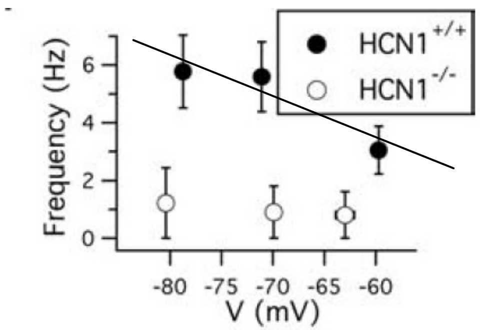


MPO frequency increases ←

decreases →

slightly with voltage

Nolan et al. 2007



A good working hypothesis: V-*independent* MPO frequency