Inhibition-based theta resonance in a hippocampal network

Horacio G. Rotstein
Department of Mathematical Sciences
New Jersey Institute of Technology
Department of Biological Sciences and CMBN
Rutgers University / NJIT

OSB Meting - Building and sharing models of the cortex
OSB symposium: Oscillations and resonance in CNS network loops
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Collaborators

- Eran Stark (NYU)
- Gyorgy Buzski (NYU)
- Lisa Roux (NYU)
- Shigeyoshi Fujisawa (Riken)

E. *Stark*, *R. Eichler, L. Roux, HGR & G. Buzsaki (Neuron, 2013)*

Oscillations in Neuronal Systems

Oscillations in Neural Systems at the Single Cell and Network levels

Goal: Understand the principles that underlie the generation of rhythmic activity in the nervous system over a wide spectrum of interacting levels of organization (subcellular, cellular, network)

- Mechanisms
  - Biophysical: ionic and synaptic currents, network topology
  - Dynamic: nonlinearities, time scales, time scale separation
- Functional role (cognitive, motor)
- How networks process information
- Computational properties of these networks

OSCILLATION IN NEURAL SYSTEMS

Frequency preference:

- **Intrinsic oscillations (natural frequency):** response to constant inputs
  - Single neurons
  - Networks
- **Resonance (resonant frequency):** response to oscillatory inputs
  - **Subthreshold** (membrane potential) **resonance**: amplitude, phase
  - **Spiking** (suprathreshold) **resonance**: firing rate, phase, coherence
  - **Synaptic resonance** (synaptic depression and facilitation)
  - **Network resonance:** firing rate (?), coherence (?), synchronization (?)

SUB-THRESHOLD RESONANCE

- Electric mechanisms

  - Low-pass filter
  - High-pass filter

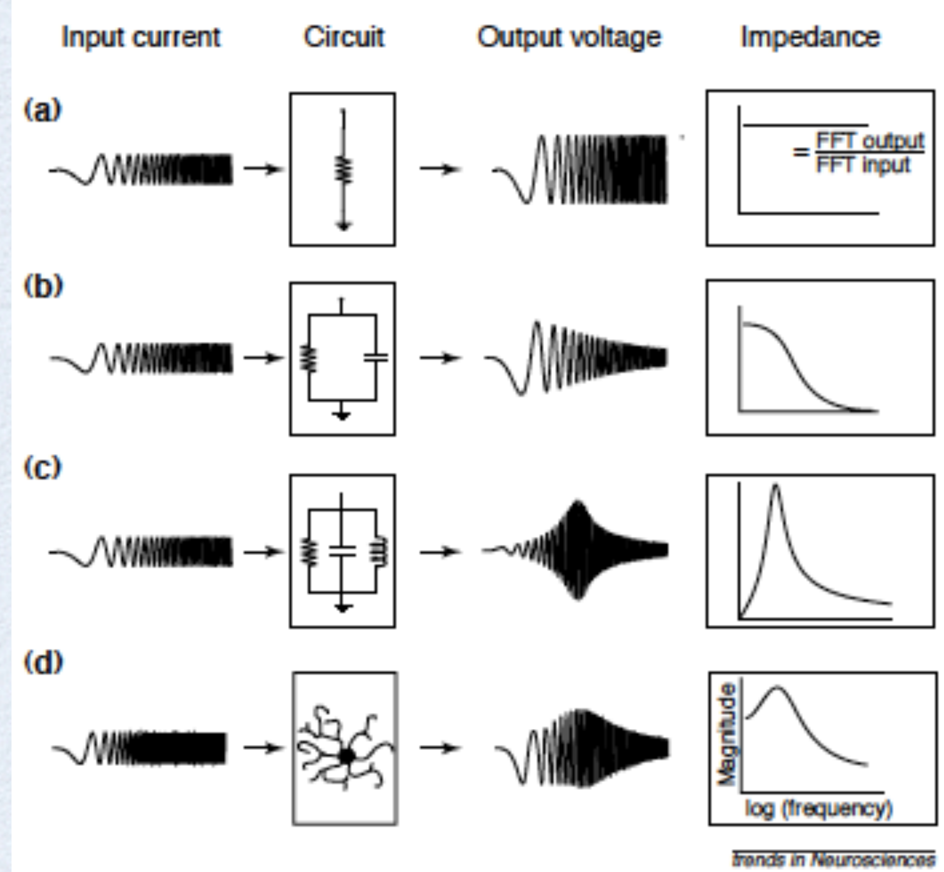
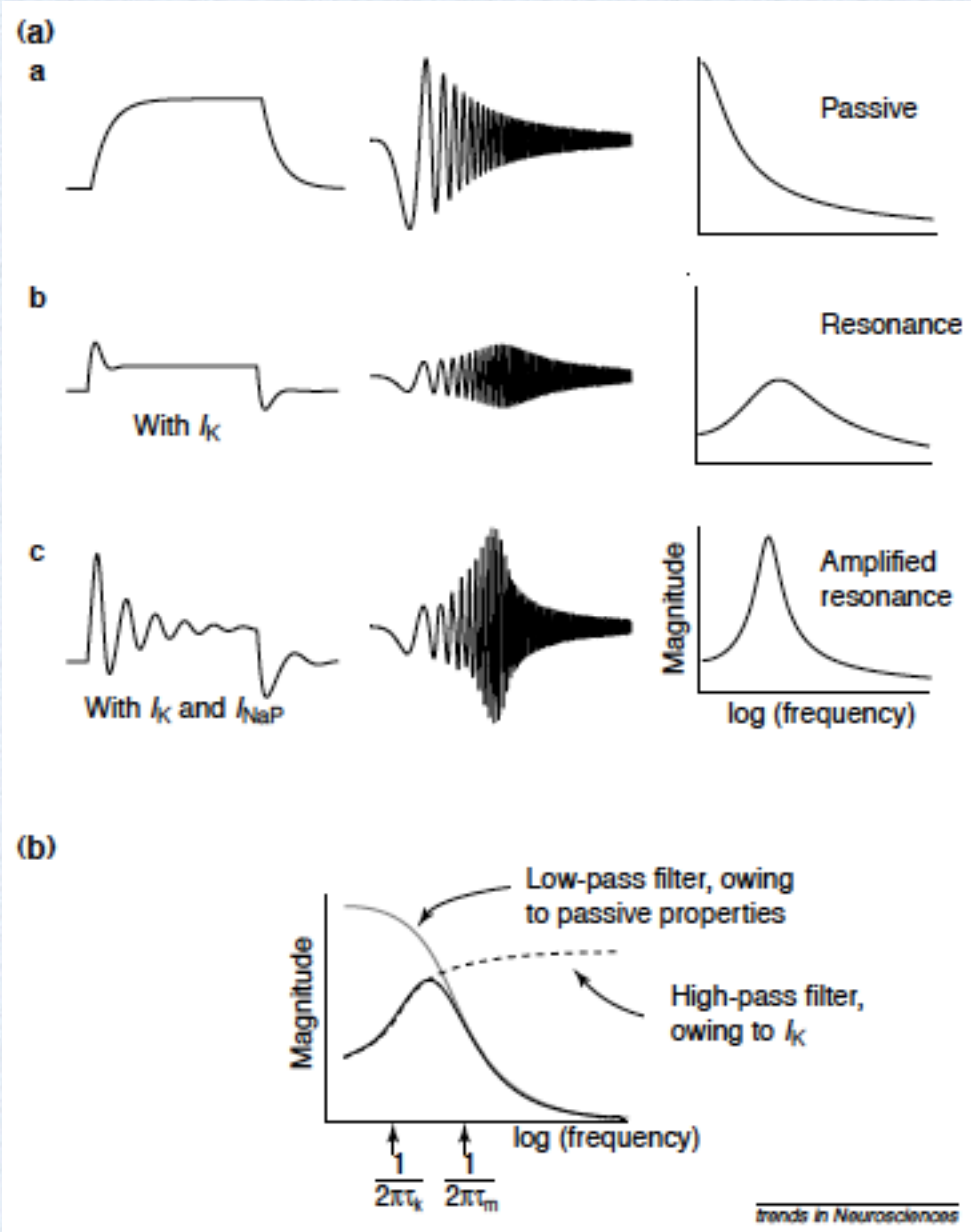


Fig. I. Frequency-dependent properties of electronic circuits and neurons: detection and analysis. The relationship between the current input (first column) and the voltage output (third column) of electrical circuits or neurons (second column) enables the calculation of the impedance as a function of frequency (fourth column). The use of a ZAP input function concentrates the analysis within a specific range of frequencies.

Hutcheon & Yarom (2002)

Sub-threshold resonance

- Ionic mechanisms
  - Passive current (low-pass filter): I_L
  - Resonant currents (high-pass filter): I_h, I_{Ks}
  - Amplifying currents: I_{Nap}, $I_{Ca,L}$
  - $I_{Ca,T}$
-
  - Resonant gating variables
  - Amplifying gating variables



Hutcheon & Yarom (2002)

SUBTHRESHOLD RESONANCE

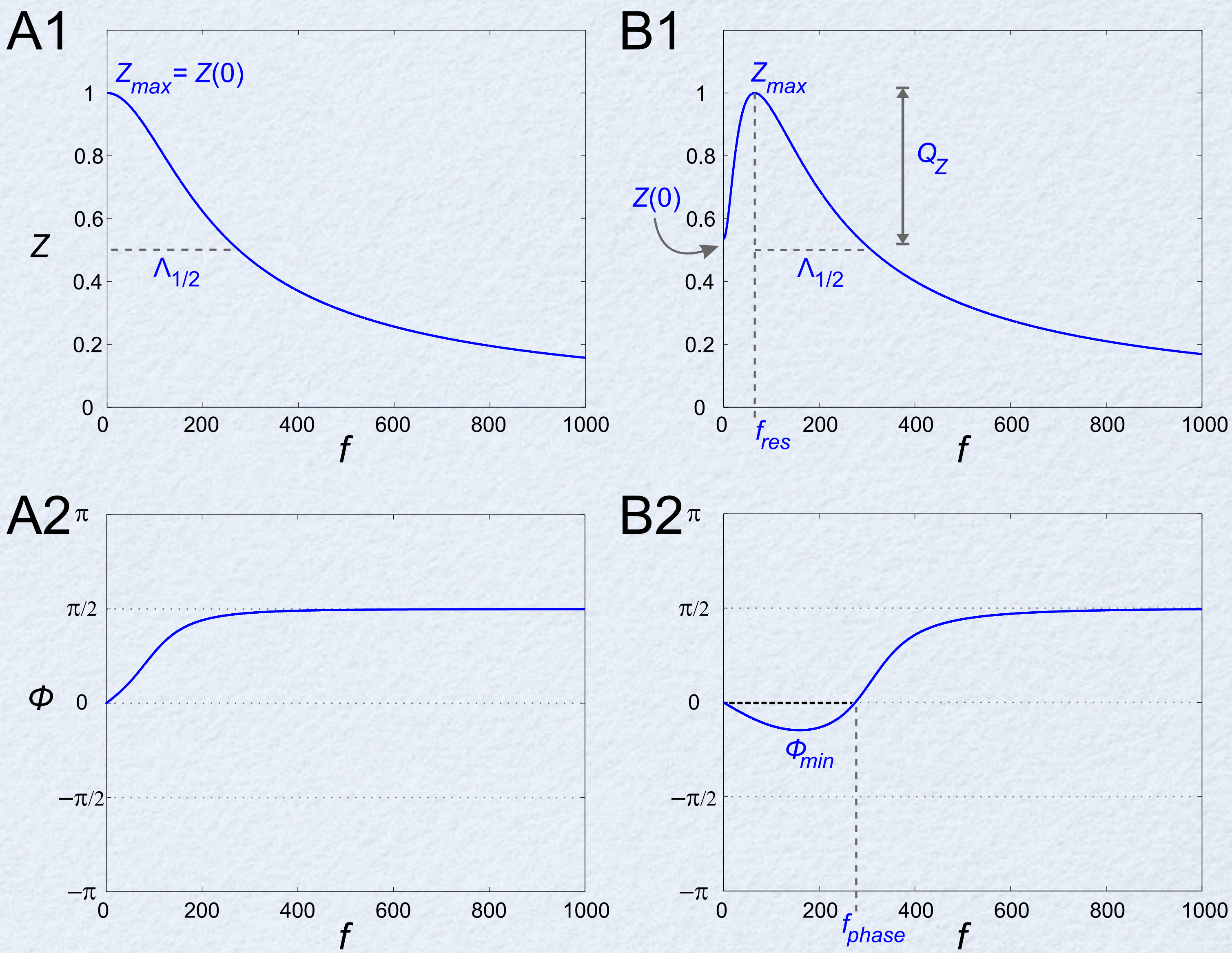
Voltage response to sinusoidal inputs

$$V_{out}(t;f) = A_{out}(f)\,\sin\left(\omega t + \phi(f)\right)$$

$$Z(f) = \frac{A_{out}(f)}{A_{in}}$$

Impedance

Phase



Impedance-like function

$$Z(f) = \frac{V_{max}(f) - V_{min}(f)}{2\,A_{in}}$$

Sub-threshold resonance

☑ Subthreshold (amplitude) resonance may occur in the absence of intrinsic subthreshold oscillations

☑ Subthreshold (amplitude) resonance may occur in the absence of phase-resonance

☑ Even in two-dimensional linear systems

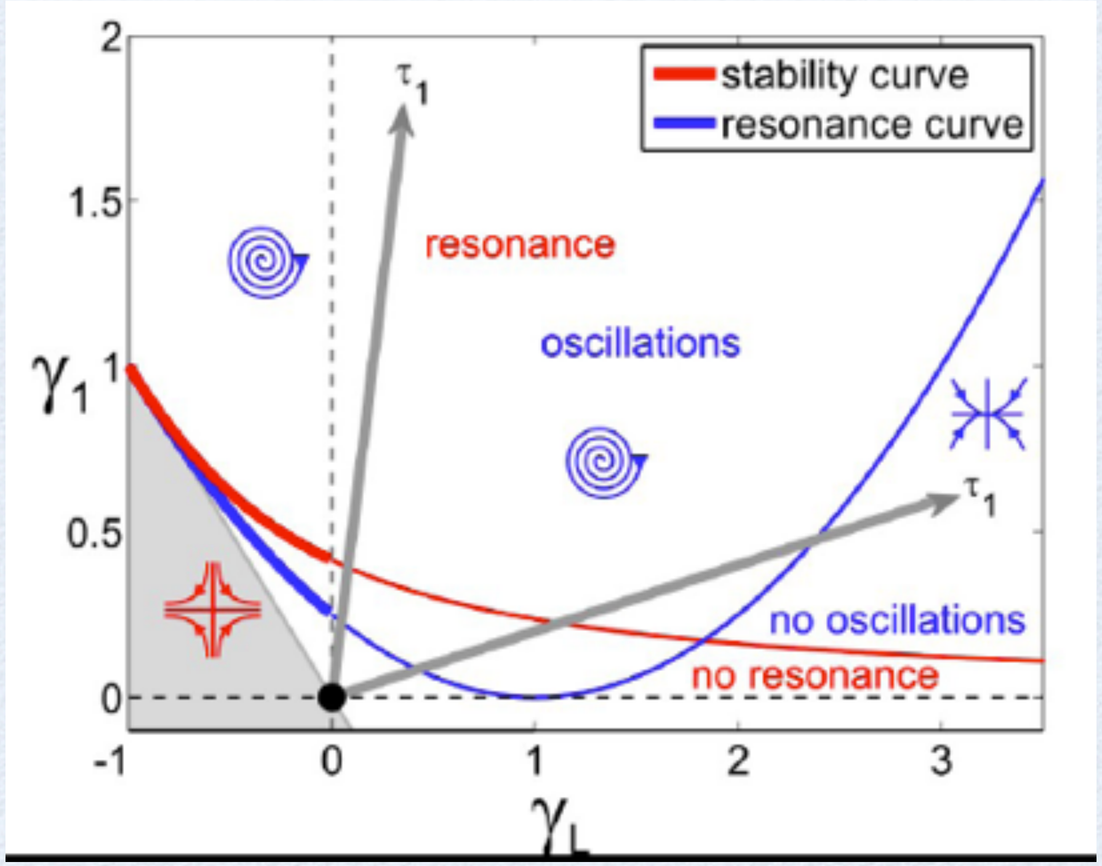
$$C\frac{dv}{dt} = -g_L v - g_1 w_1 + I_{in}(t),$$

$$\bar{\tau}_1 \frac{dw_1}{dt} = v - w_1$$

$$\hat{t} = \frac{t}{\bar{\tau}_1} \qquad \gamma_L = \frac{g_L \bar{\tau}_1}{C} \qquad \gamma_1 = \frac{g_1 \bar{\tau}_1}{C}$$

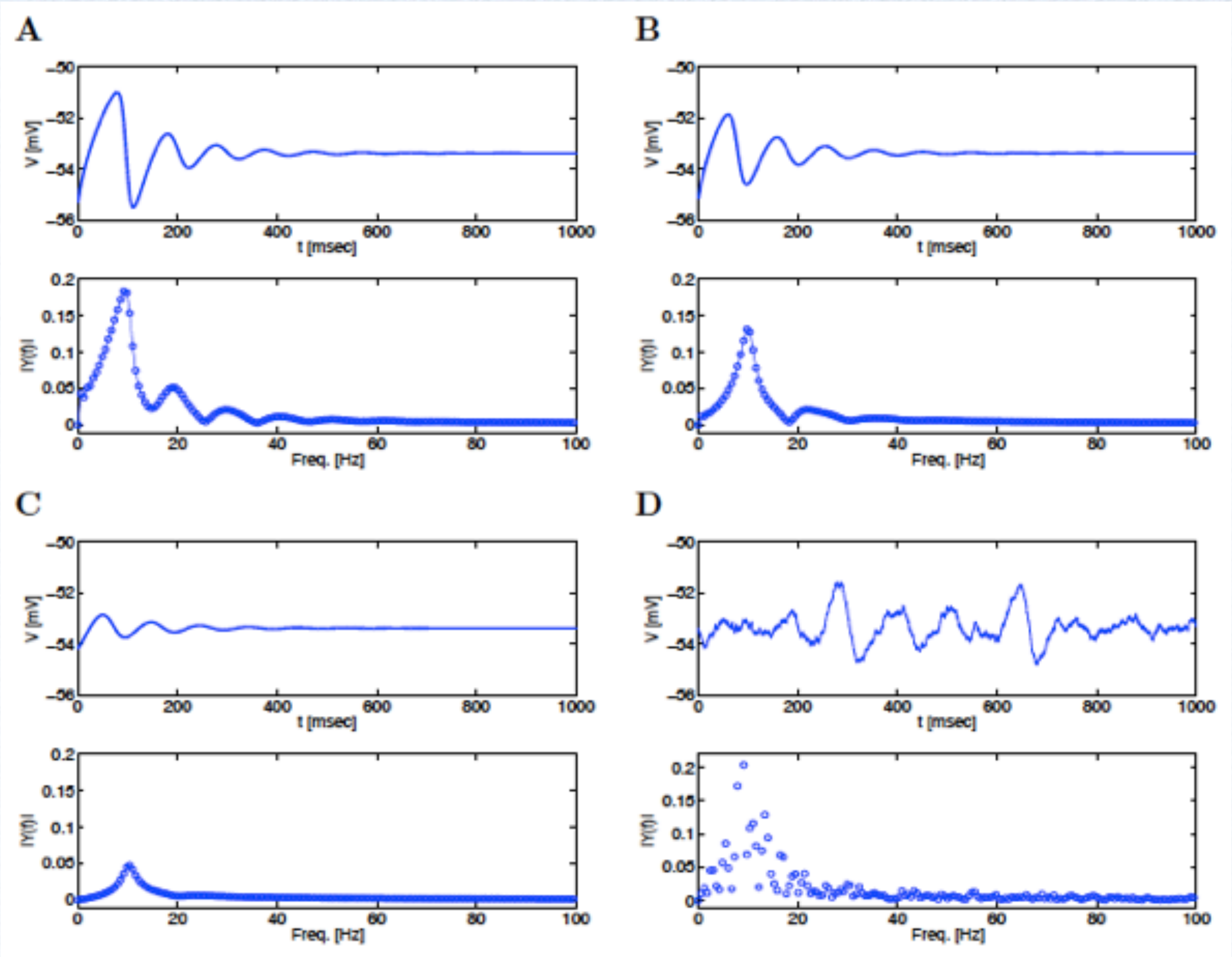
$$\frac{dv}{d\hat{t}} = -\gamma_L v - \gamma_1 w_1 + \hat{I}_{in}(\hat{t})$$

$$\frac{dw_1}{d\hat{t}} = v - w_1$$



Intrinsic Dynamics

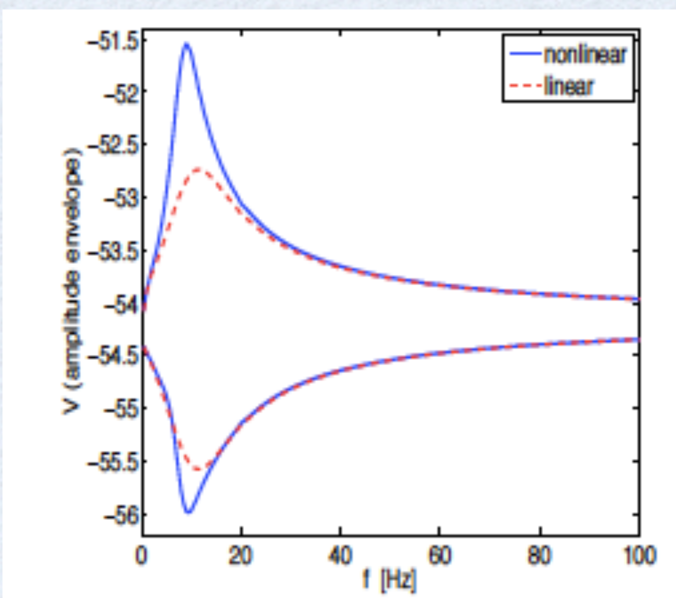
☑ Intrinsic subthreshold (membrane potential) oscillations (medial entorhinal cortex layer II stellate cell model) - I_h + I_{Nap} model



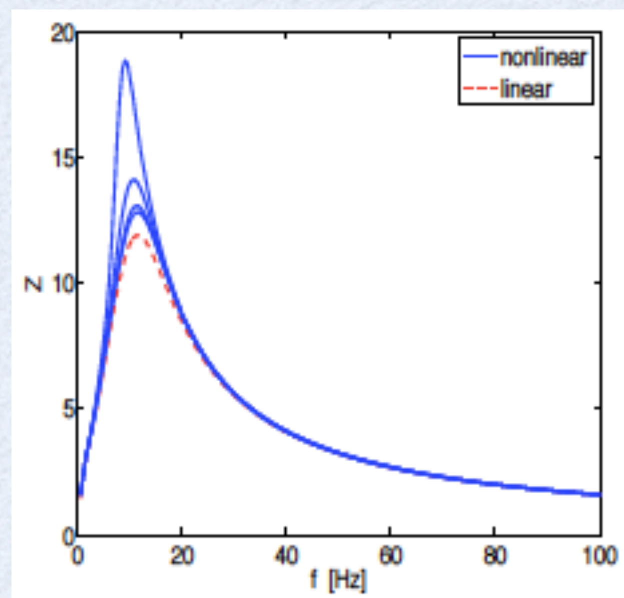
Sub-threshold Resonance

- Nonlinear & Linearized Voltage Response for the I_{Nap}-I_h model (quadratic-like)

  - Nonlinear effects
    - The impedance peak increases with increasing values of A_{in} (nonlinear amplification)
    - The resonant frequency decreases with increasing values of A_{in}



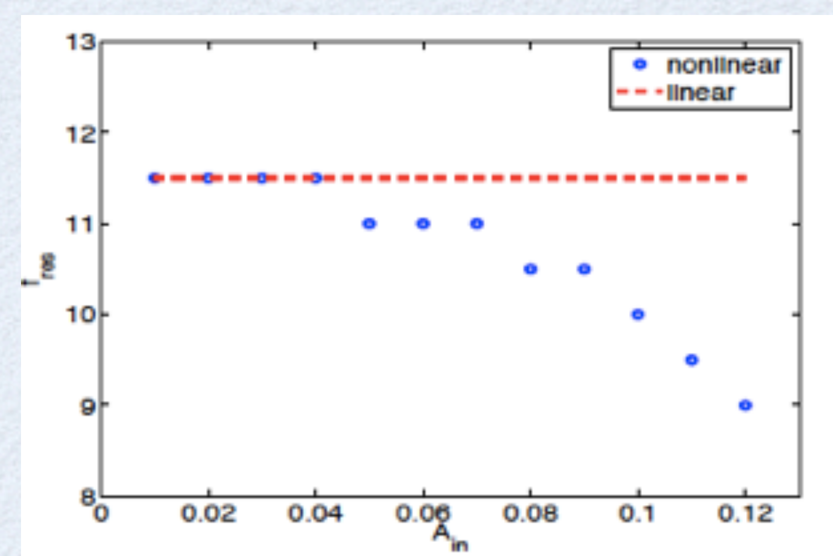
Voltage response -
Amplitude envelope



Impedance

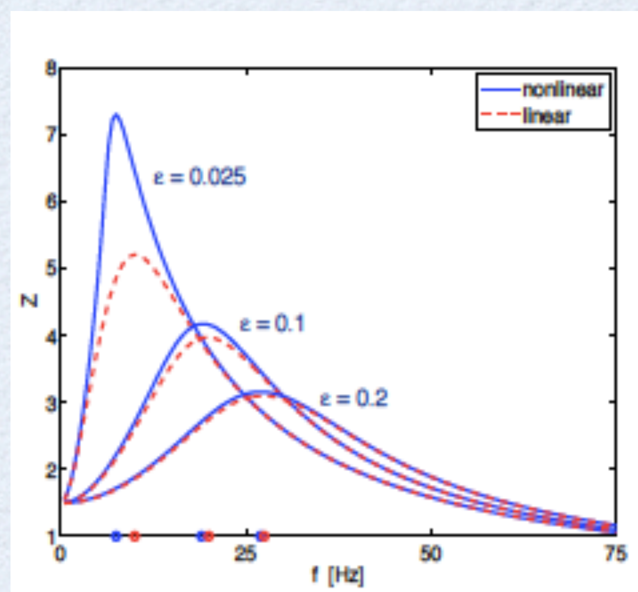
Nonlinear response

Linear prediction



Sub-Threshold Resonance

- Nonlinear & Linearized Voltage Response for the I_{Nap}-I_h model
  - An increase in the time scale separation (ε) increases the amplification of the voltage response and decreases resonant frequency
  - As the time scale separation decreases the nonlinear model behaves ``more linearly"



Nonlinear response
Linear prediction

E

Subthreshold Resonance

- ☑ **Frequency preference in two-dimensional neural models: a linear analysis of the interaction between resonant and amplifying currents** (2013). HGR and F. Nadim. *J Comp Neurosci.* (Biophysical mechanisms: I_h, I_M, I_{Nap})

- ☑ **Frequency preference response to oscillatory inputs in two-dimensional neural models: a geometric approach to subthreshold amplitude and phase resonance** (2014). HGR. *J Math Neurosci.* (Dynamic mechanisms)

- ☑ **Subthreshold resonance in models of quadratic type: nonlinear effects generated by the interplay of resonant and amplifying currents** (2014). HGR. Almost done (hopefully)

- ☑ **Inhibition-induced theta resonance in cortical circuits** (2013). E. Stark, R. Eichler, L. Roux, S. Fujisawa, HGR, G. Buzsaki. *Neuron*.

Theta Rhythm

Theta (4 - 8 Hz) oscillations

☑ Provide a basis for temporal coding of spatial information in the hippocampus (O'Keefe & Recce, Hippocampus, 1993)

☑ Generated by a consortium of mechanisms, including a septal pacemaker, circuit interactions, and intrinsic properties of single neurons (Buzsaki, Neuron, 2002; HGR. et al., J Neurophysiol, 2005)

☑ A theta dipole is produced by somatic IPSPs in pyramidal neurons (PYR) following theta-frequency burst discharge of basket cells (INT) (Cobb et al, Nature, 1995; Ylinen et al., Hippocampus, 1995)

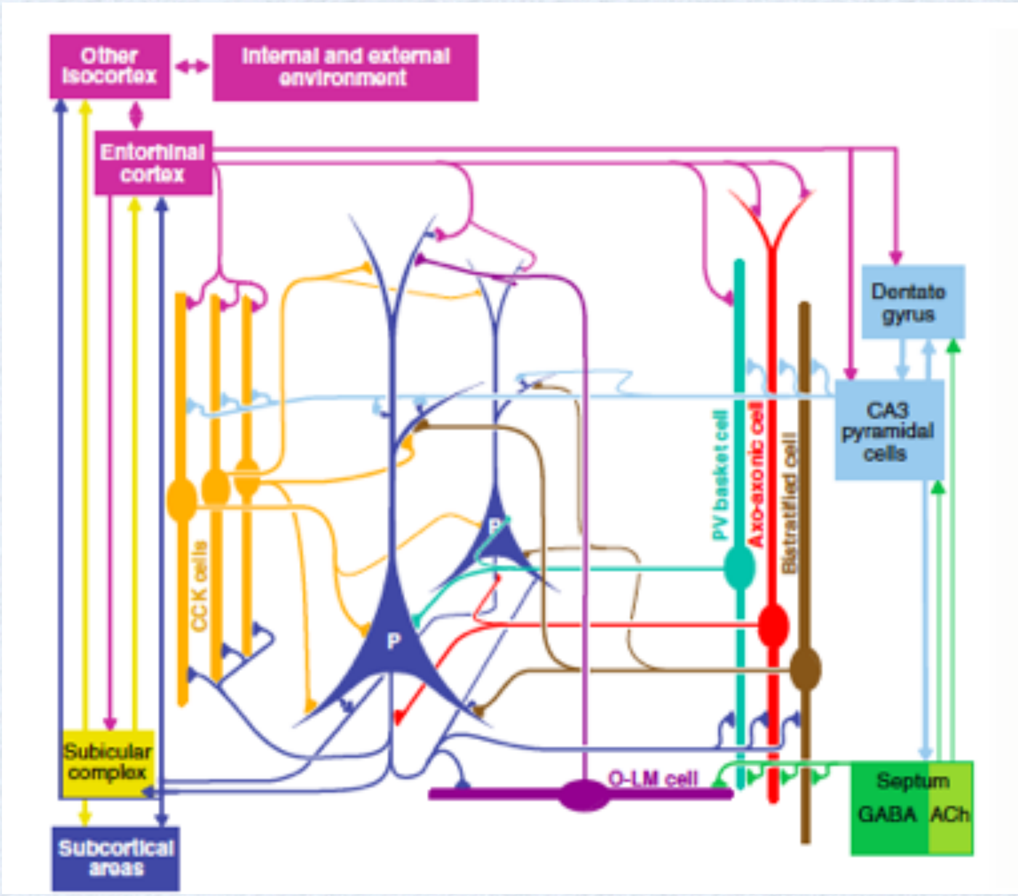
☑ Intracellular current injection yields theta-band limited subthreshold oscillations (Hu et al., J Physiol, 2002; Leung et al., J Neurophysiol, 1998; Gastrein et al., J Physiol, 2011)

☑ Whether and how these properties are translated to the suprathreshold (spiking) regime in behaving animals is not known.

THETA RESONANCE

Experimental results: **E. *Stark***, *R. Eichler, L. Roux, HGR & G. Buzsaki (Neuron, 2013)*

- ☑ Optogenetics (in freely moving rodents)
- ☑ Pyramidal cells (PYR)
- ☑ Parvalbumin-immunoreactive interneurons (INT)
- ☑ Oriens Lacunosum-moleculare (OLM)

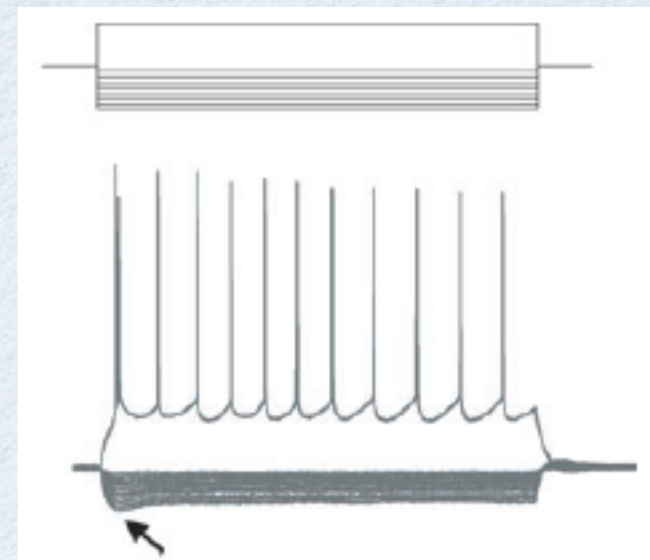


Klausberger et al. (Science, 2008)

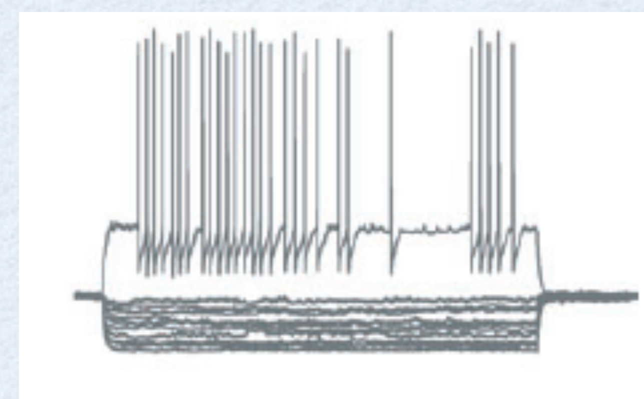
Response to constant DC current

- PYR and OLM: sag (h-current)
- INT: no sag

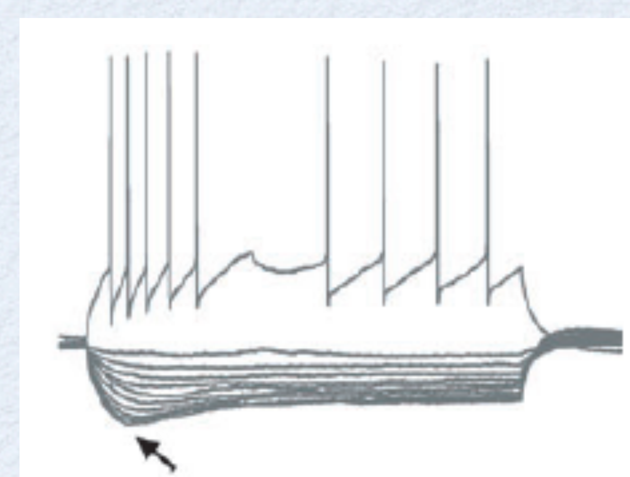
PYR

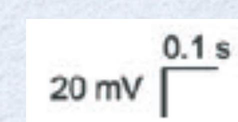


INT



OLM



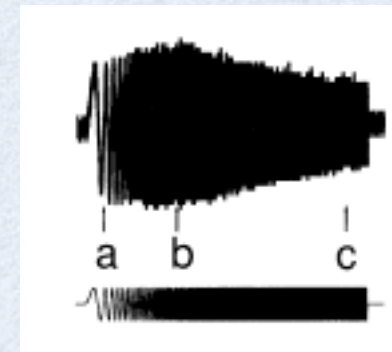


Zemankovics et al. (J Physiol, 2010)

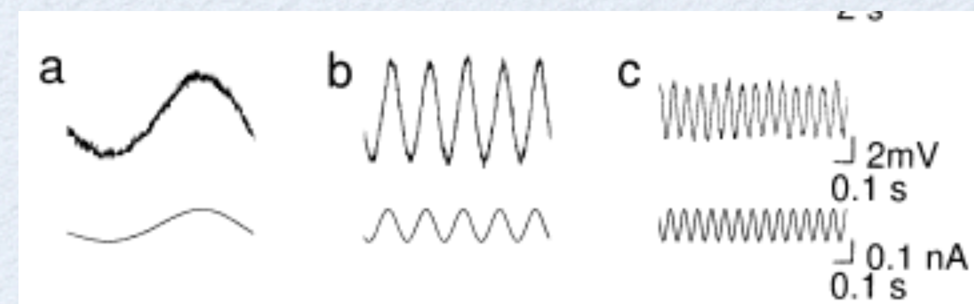
Theta Resonance

- ☑ **PYR *in vitro:*** subthreshold resonance (theta)
- ☑ **INT *in vitro:*** no subthreshold resonance

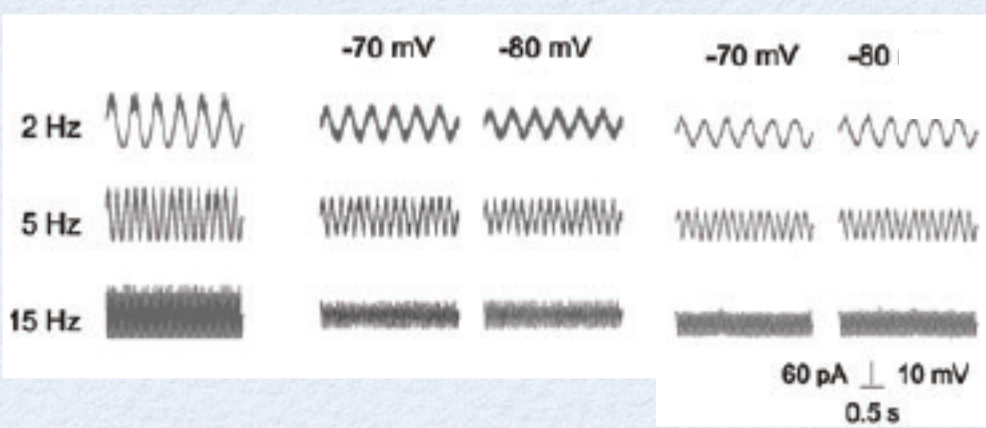
PYR



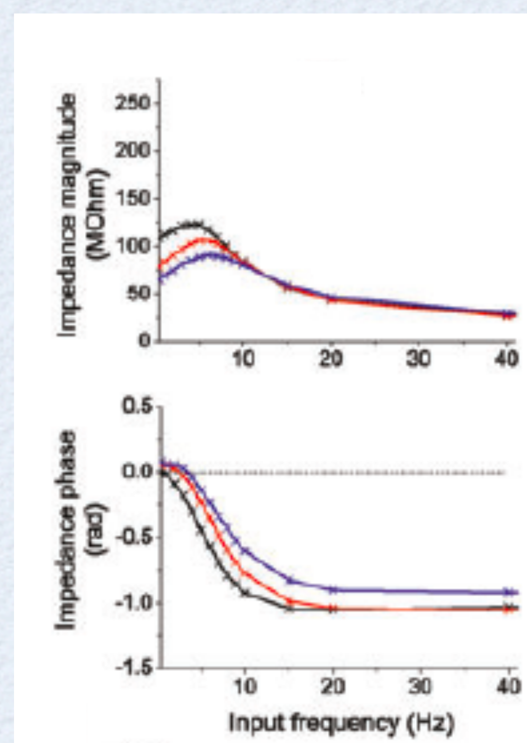
Hu et al. (J Physiol, 2002)

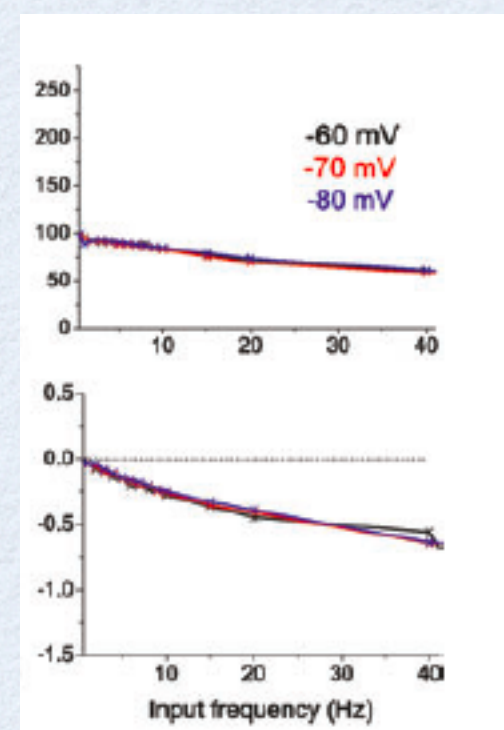


current wave | PYR | INT



PYR | INT



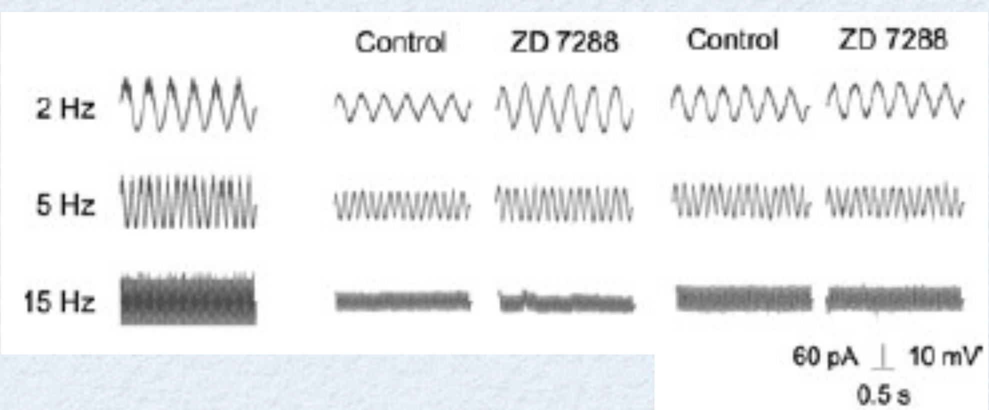


Zemankovics et al. (J Physiol, 2010)

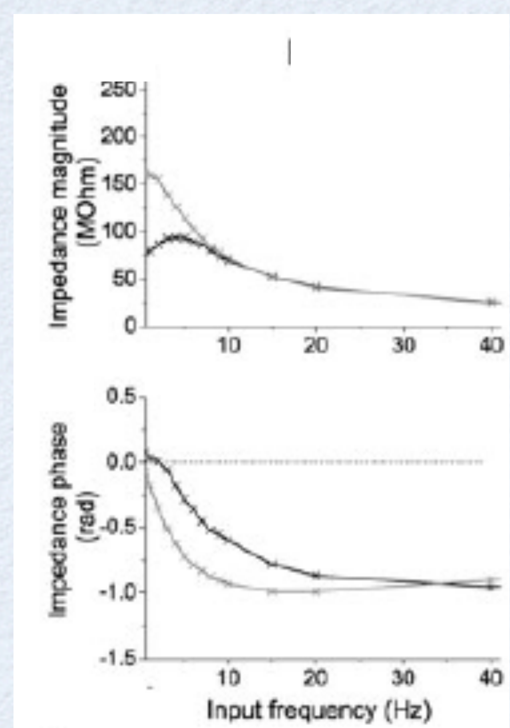
Theta Resonance

- **PYR** ***in vitro:*** subthreshold resonance (theta)   h-current dependent
- **INT** ***in vitro:*** no subthreshold resonance

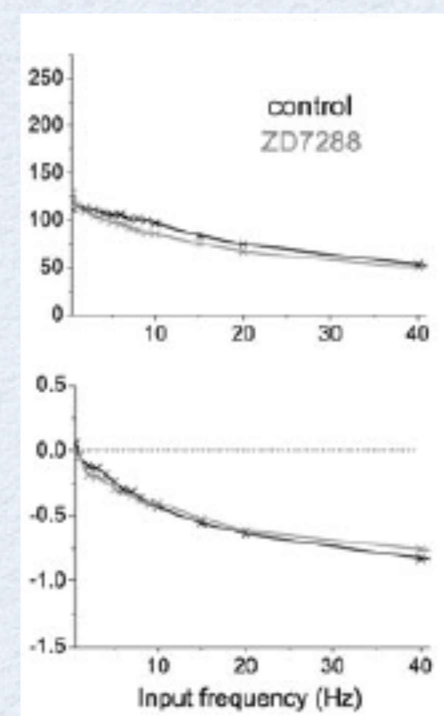
current wave   PYR   INT



PYR



INT



Zemankovics et al. (J Physiol, 2010)

Theta Resonance

Questions:

- **Does subthreshold resonance in PYR translate to the spiking regime in single cells and networks? (*in vivo*)**

- **(If yes) What are the mechanisms**

Experimental approach (in vivo)

- **Optogenetic** stimulation of PYR and INT (separately) using wide-band oscillatory signals (time varying chip pattern)

- **Dependence of spiking activity on input frequency:** spectral coherence between the input and output signals

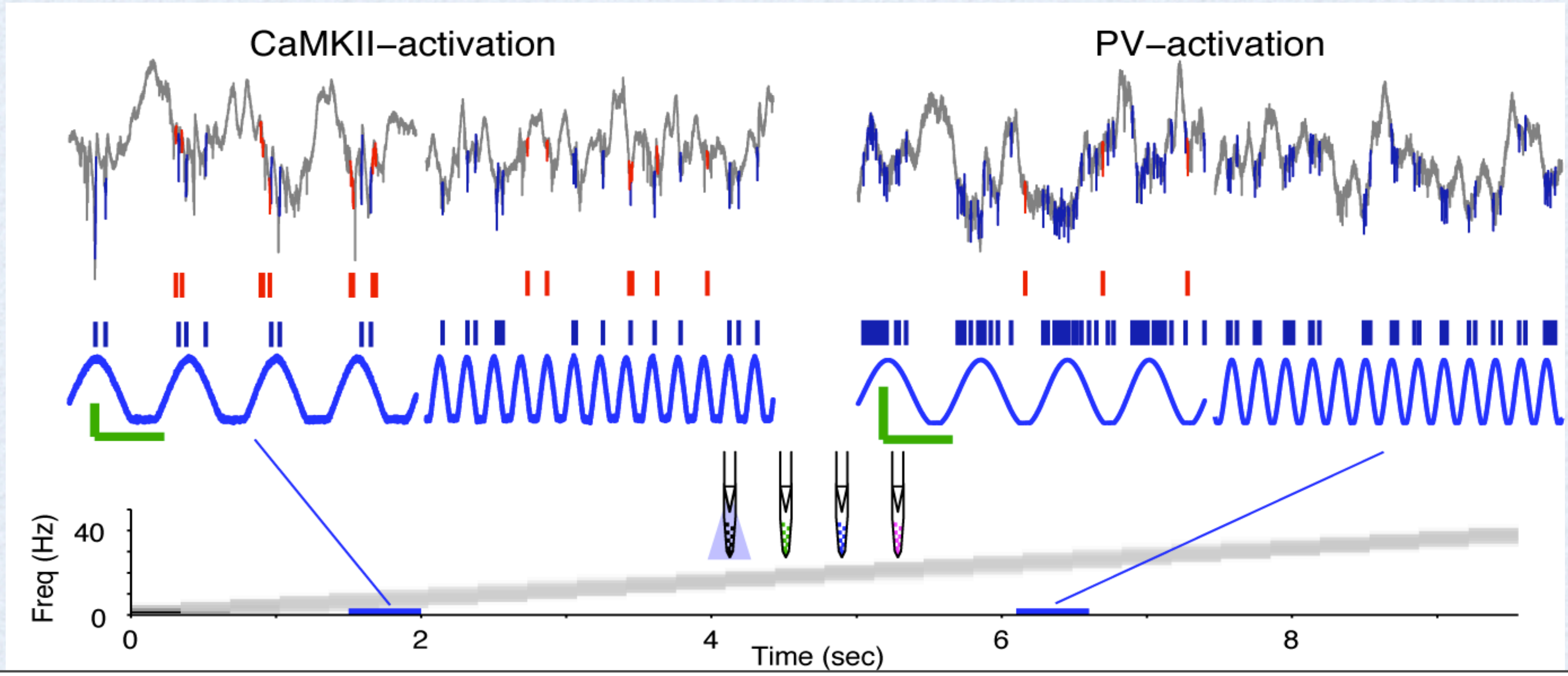
- **Resonance:** Preferred frequency response in the spectral coherence

Theta Resonance

- **Selective stimulation of PYR (CaMKII, left):** induced spiking at various frequencies with similar probabilities in single PYR and INT

  - **PYR:** Wide-band spiking
  - **INT:** Wide-band spiking

- **Selective stimulation of INT (PV, right):** induced
  - **INT:** Wide-band spiking
  - **PYR:** Theta band-limited spiking



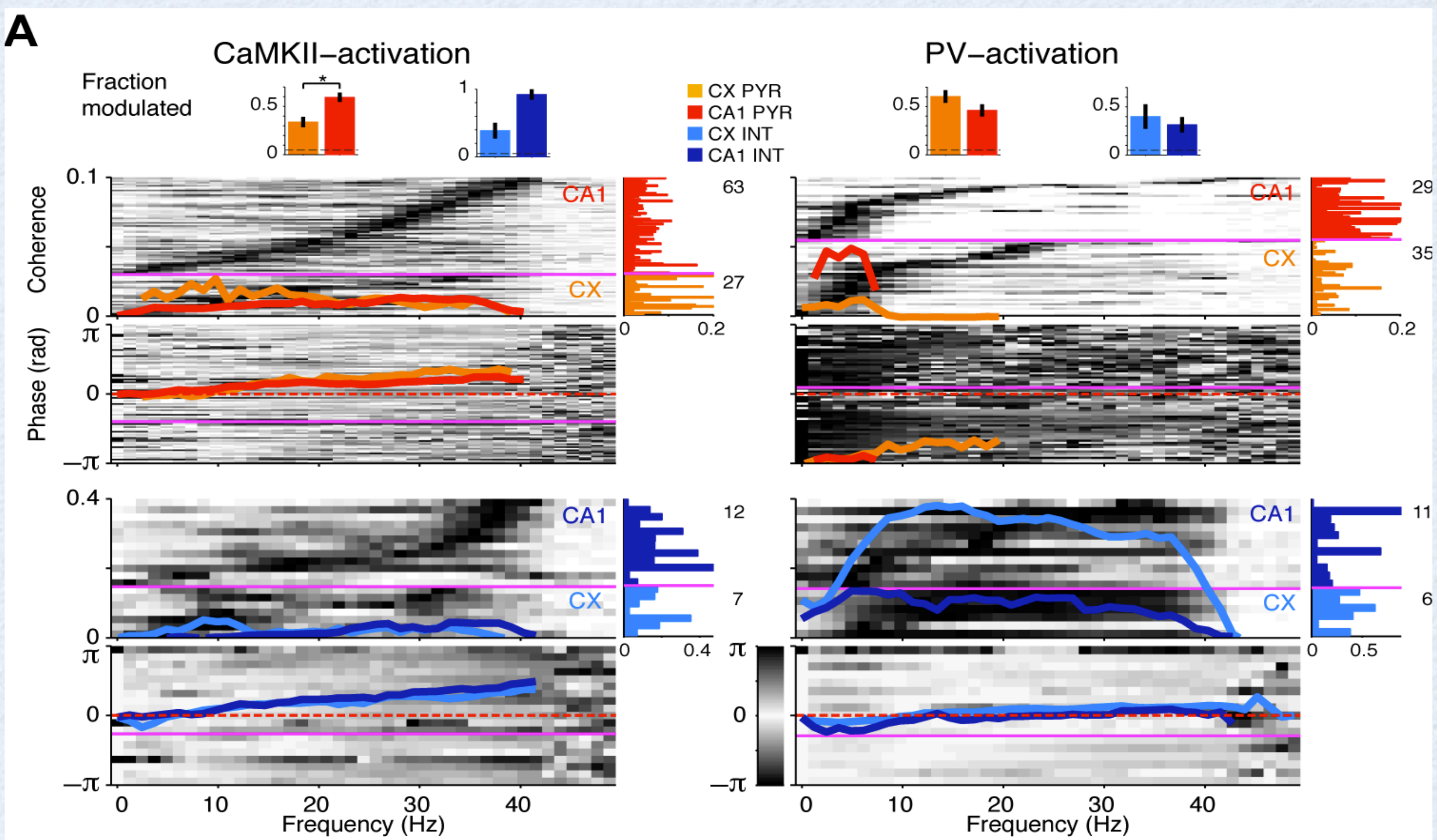
Red ticks: PYR spikes
Blue ticks: INT spikes

Eran Stark

Theta Resonance

- Selective stimulation of PYR (CaMKII, left):
  - PYR: Wide-band spiking
  - INT: Wide-band spiking

- Selective stimulation of INT (PV, right):
- INT: Wide-band spiking
  - PYR: Theta band-limited spiking



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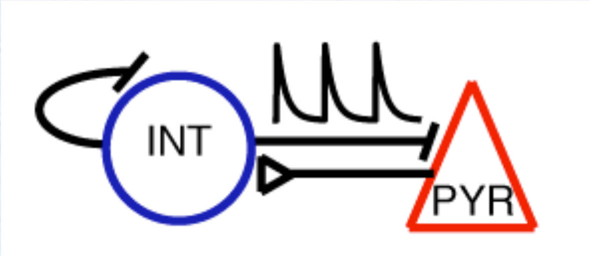
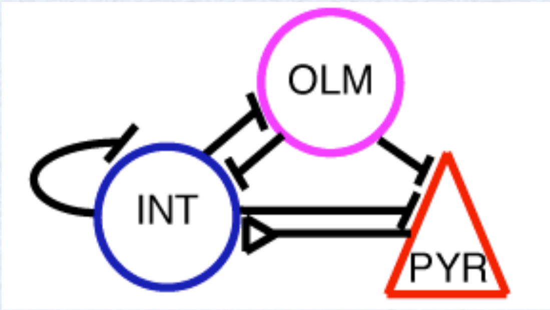
Model

Minimal network model:

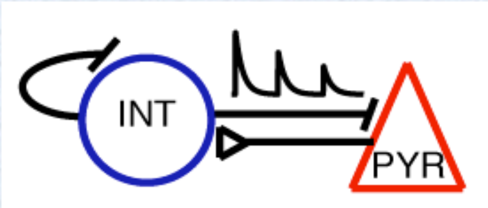
- ☑ PYR + INT





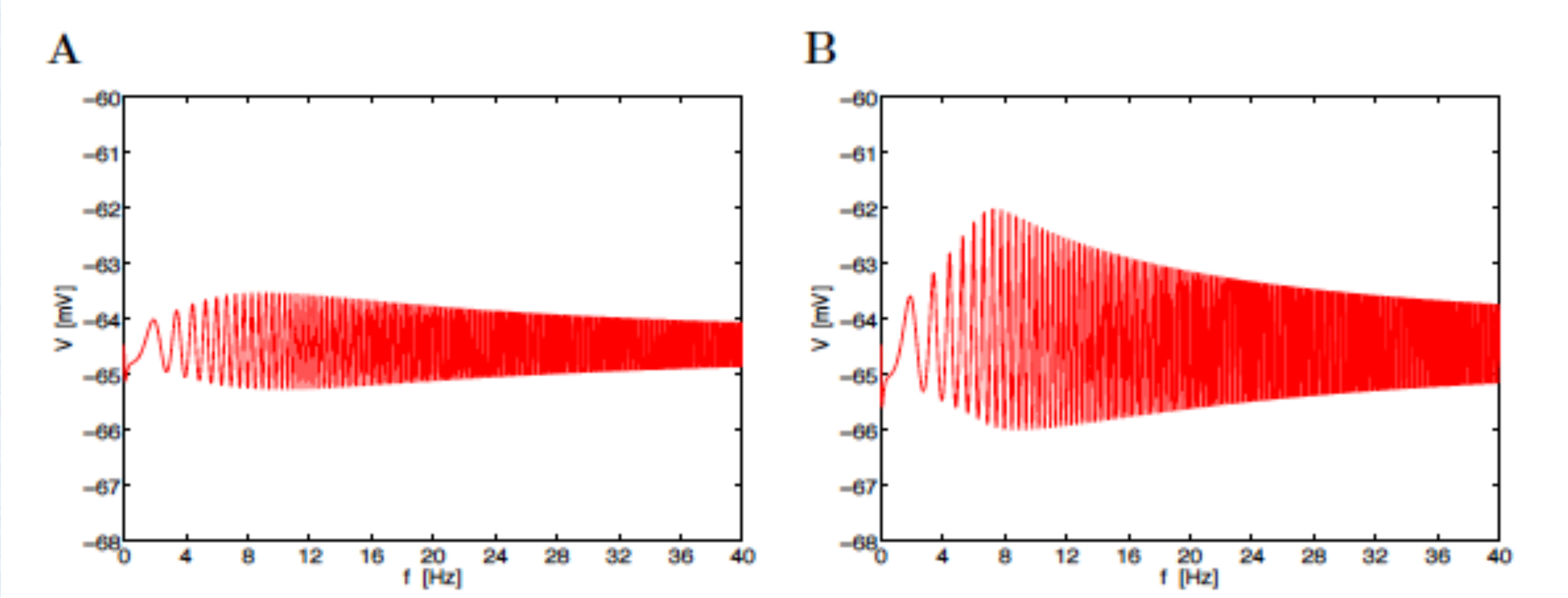
- ☑ PYR + INT + OLM

- ☑ PYR + INT + synaptic depression (I -> E)



Mechanism

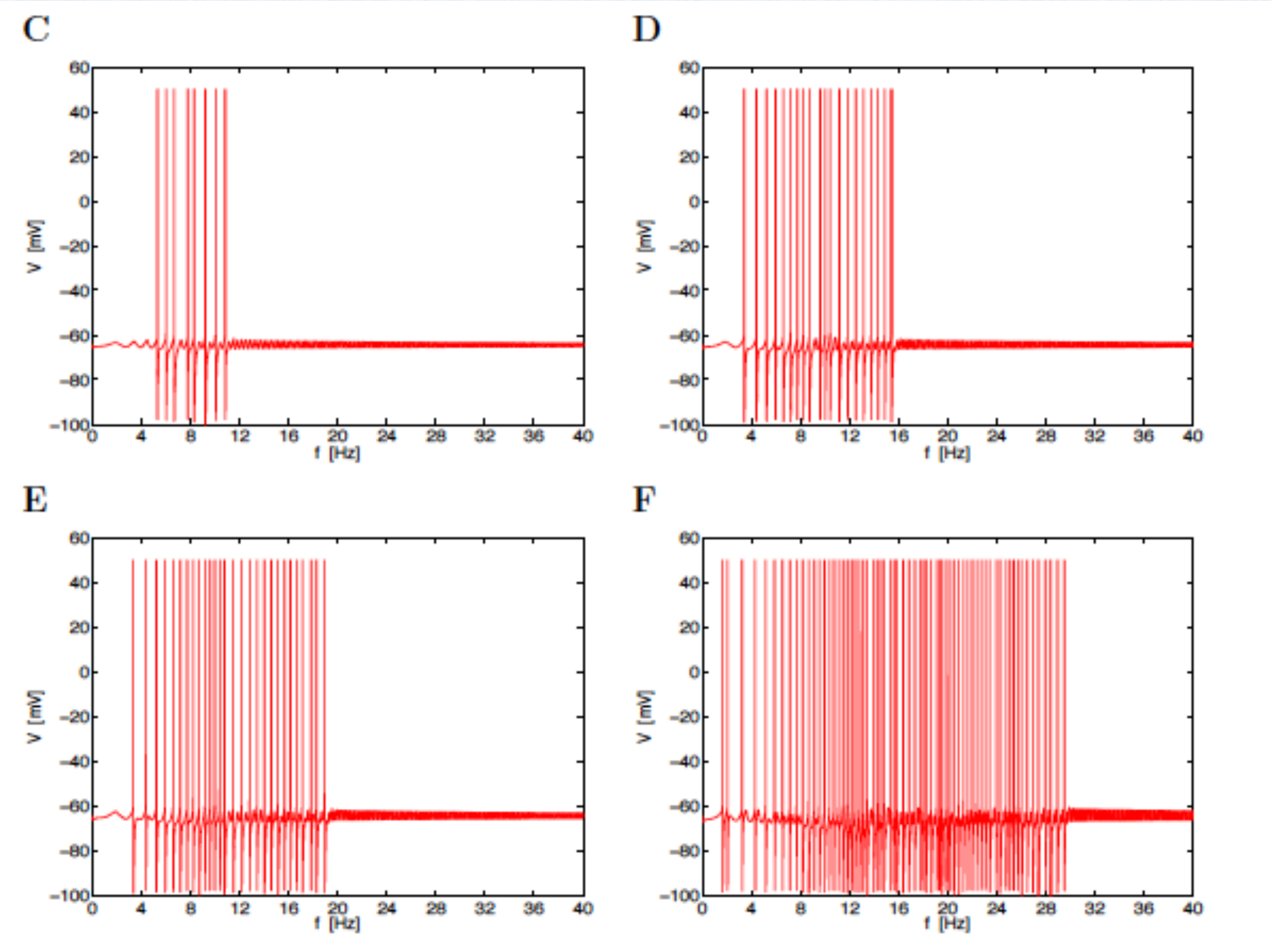
- PYR model: subthreshold resonance (h-current)



Zap input amplitude increases from A to B

MECHANISM

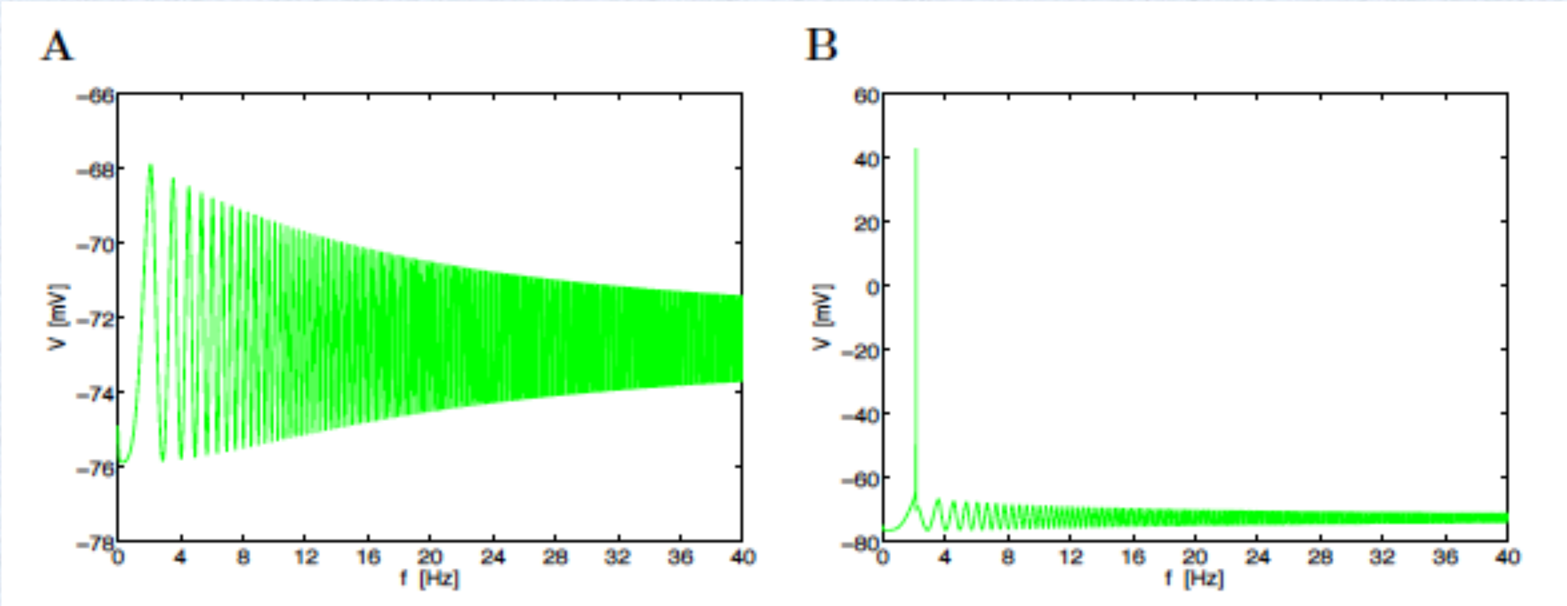
- PYR model: subthreshold resonance is not translated into spiking resonance



Zap input amplitude increases from C to F

Mechanism

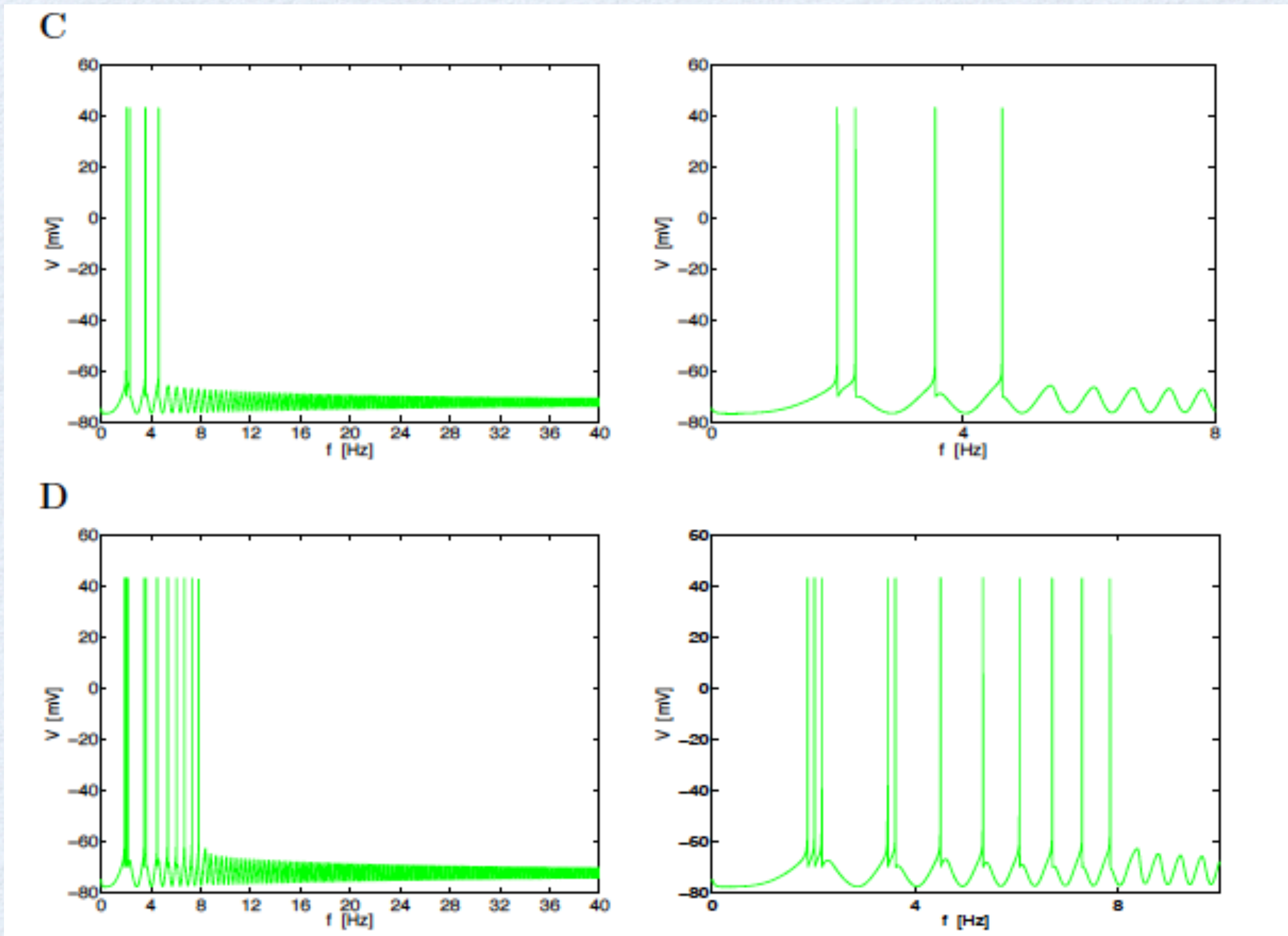
- INT model: no subthreshold resonance



Zap input amplitude increases from A to B

MECHANISM

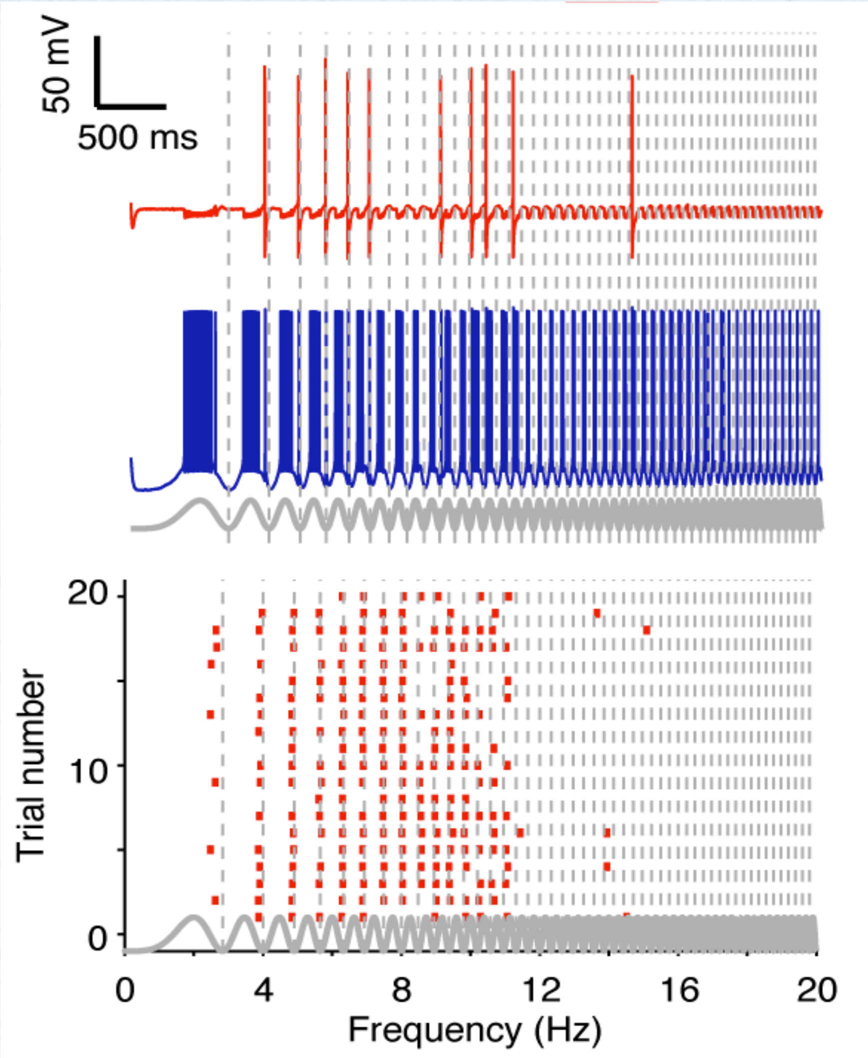
- INT model: no spiking resonance

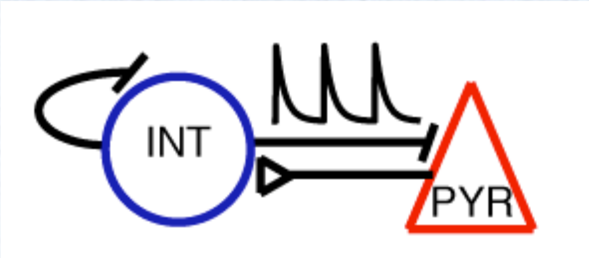


Zap input amplitude increases from C to F

Model

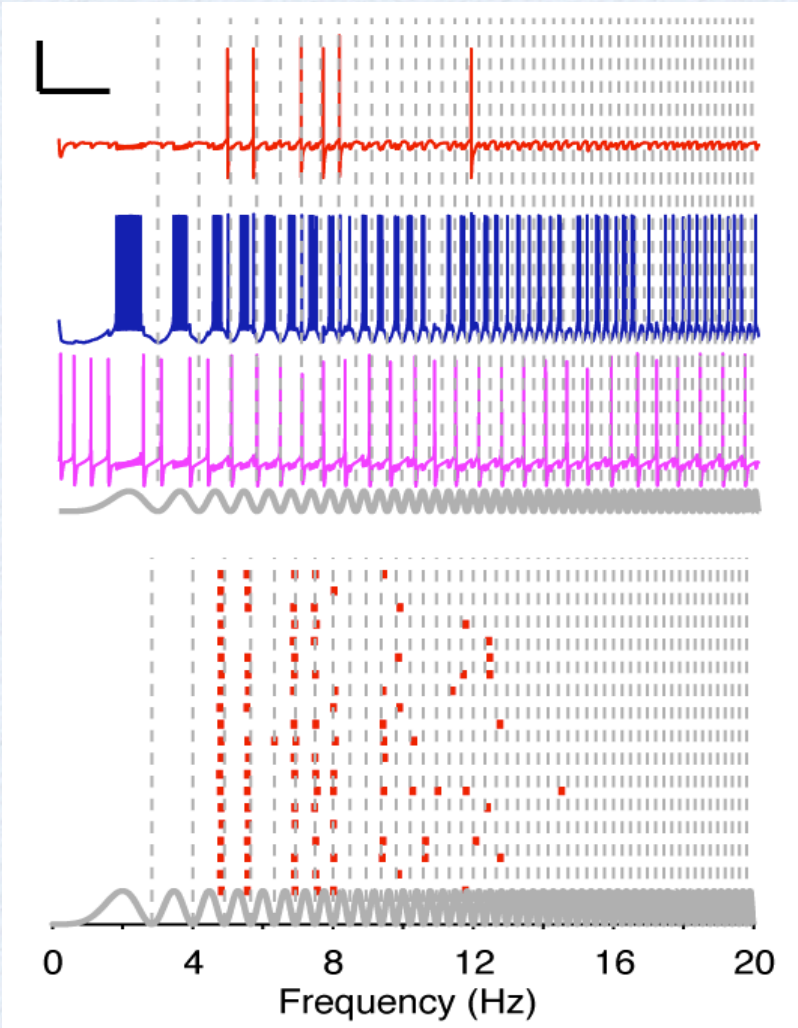
- PYR + INT model does not produce a robust theta frequency band in PYR

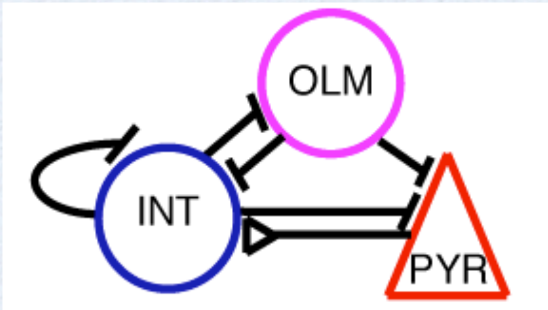




Model

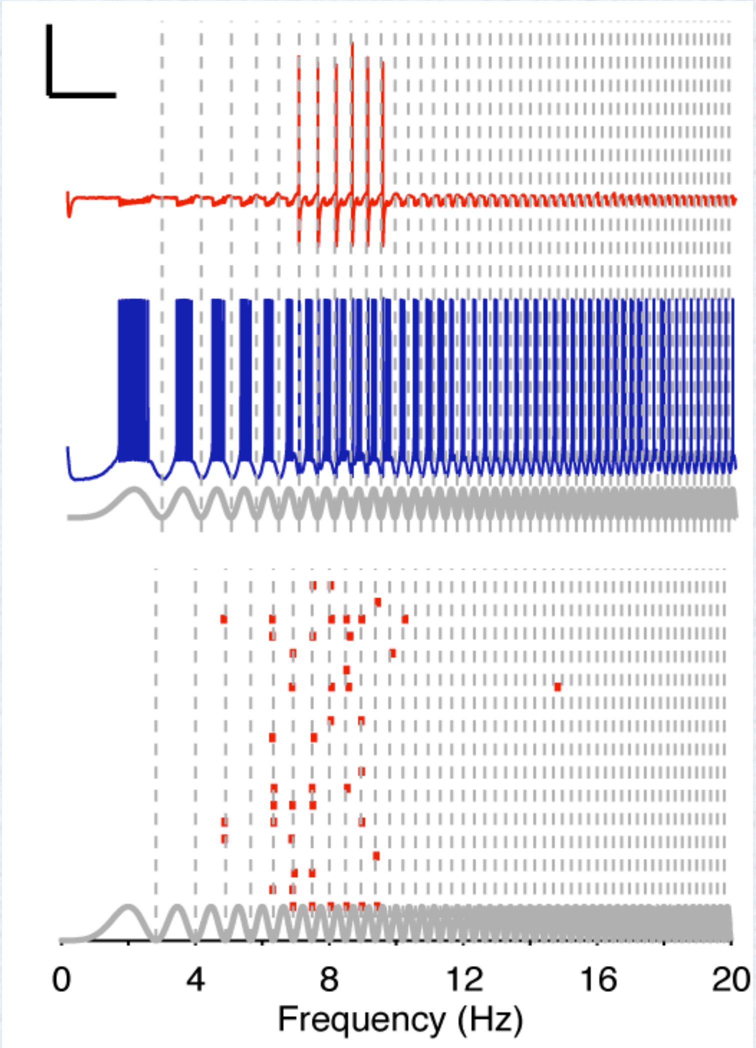
☑ **PYR + INT + OLM model produces a robust theta frequency band in PYR**

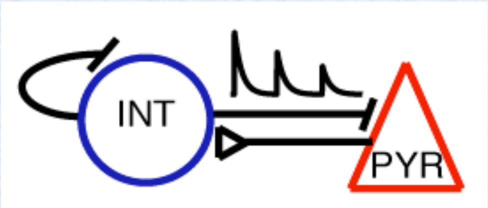




Model

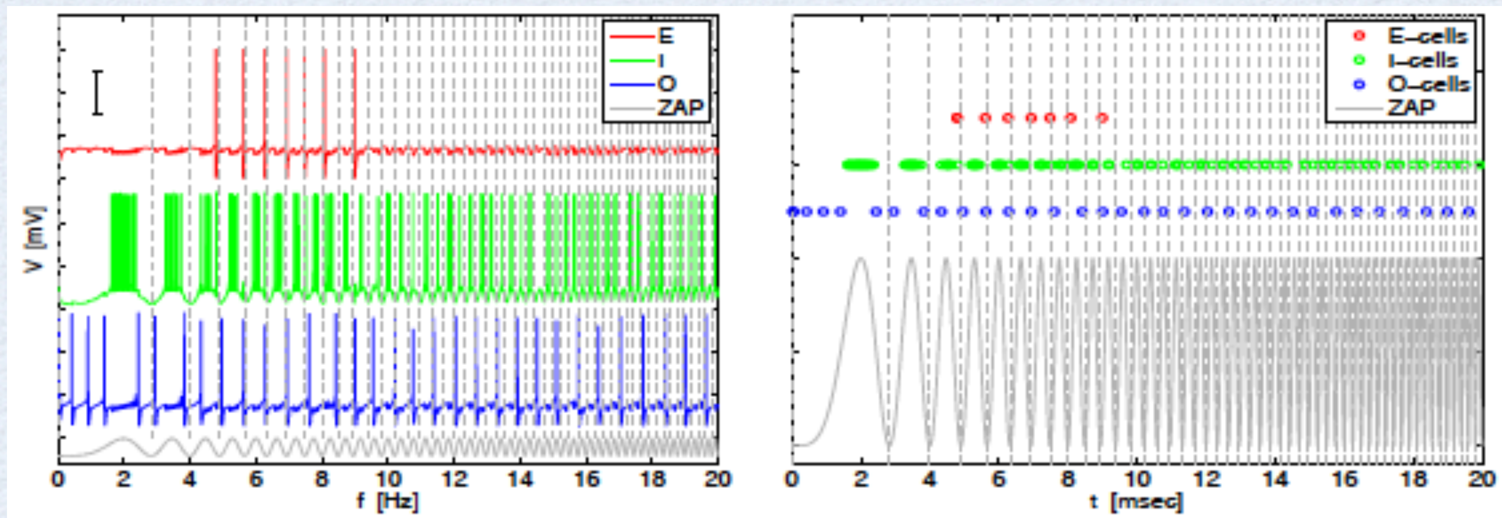
☑ **PYR + INT + synaptic depression (I->E) model produces a robust theta frequency band in PYR**



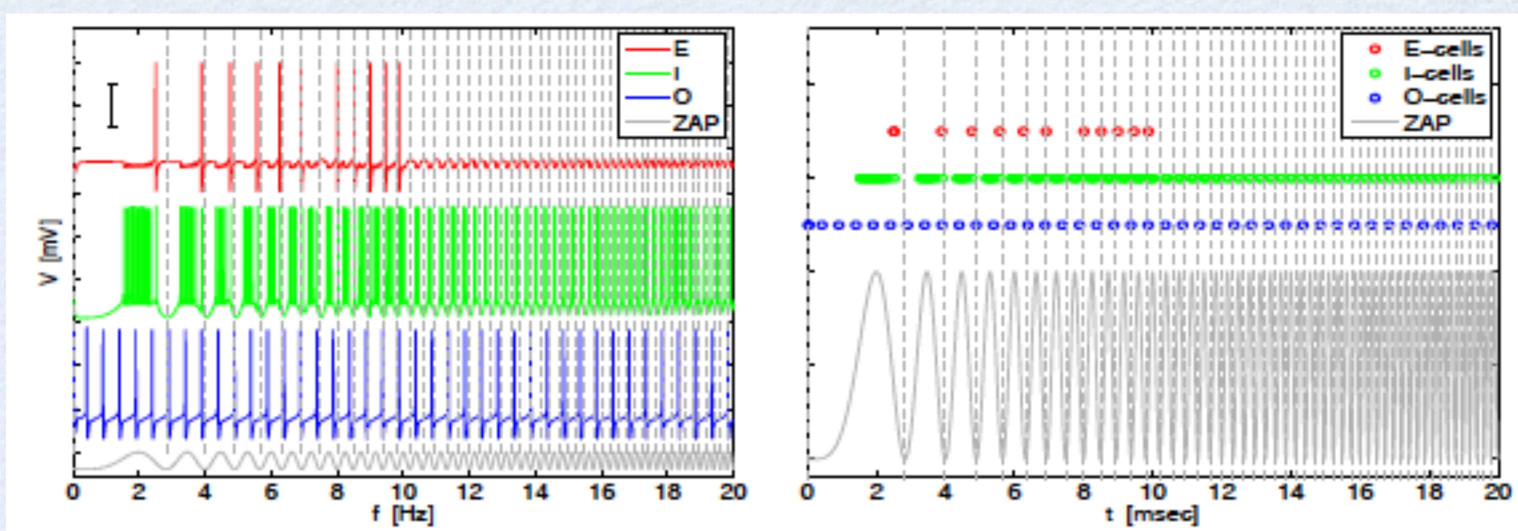


Model

- ☑ **PYR + INT + OLM model:** band-pass filter created by a timing mechanism



- ☑ **PYR + INT:** low-pass filter (absence of OLM)



SUMMARY

- ☑ Minimal network models capture the experimental *in vivo* results

- ☑ Subthreshold resonant properties of PYR model are not enough to generate robust PYR spiking resonance

- ☑ Rebound spiking (not clear whether it is the same or a different mechanism as resonance although both involve the h-current)

- ☑ Two possible timing mechanism to "erase" low frequency spiking

    - ☑ OLM

    - ☑ Synaptic depression (I ->E)

- ☑ Several open questions!!!

WHAT WE DID NOT DO

- Realistic models
- Only two timing mechanisms, but they could be other (?)
- Network resonance could be created by synaptic delays (?)
- How is subthreshold resonance related to rebound spiking
- How do the "participating individual resonances" interact to create "global resonances"
- Etc.
- Etc.
- Etc.

Acknowledgements

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- Yinbo Chen (NJIT / Rutgers)