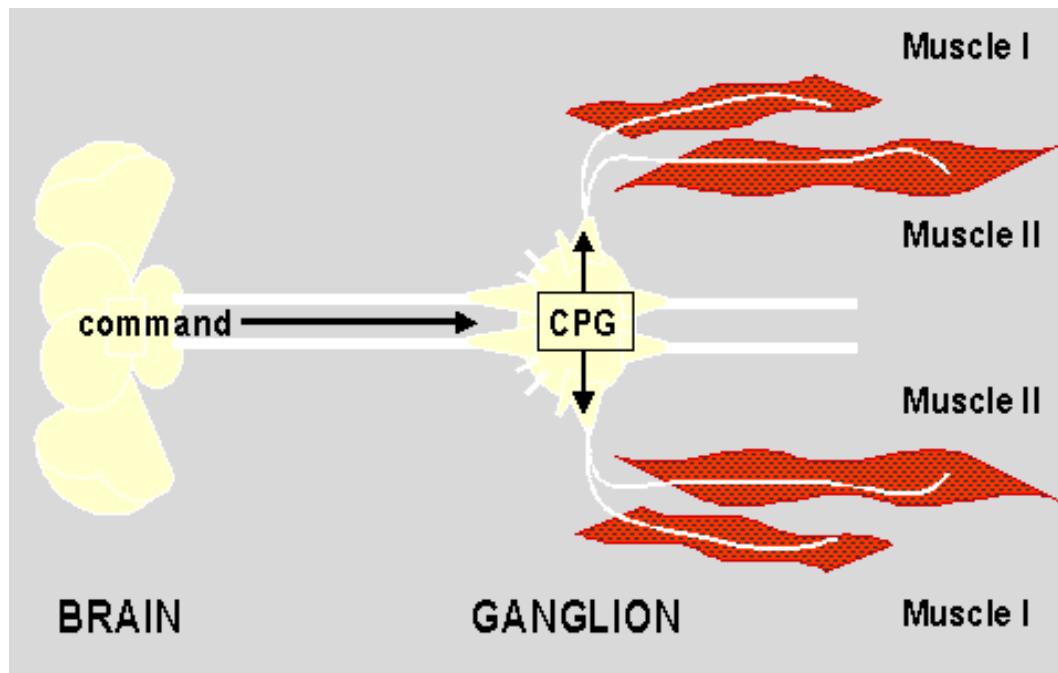


Central Pattern Generators

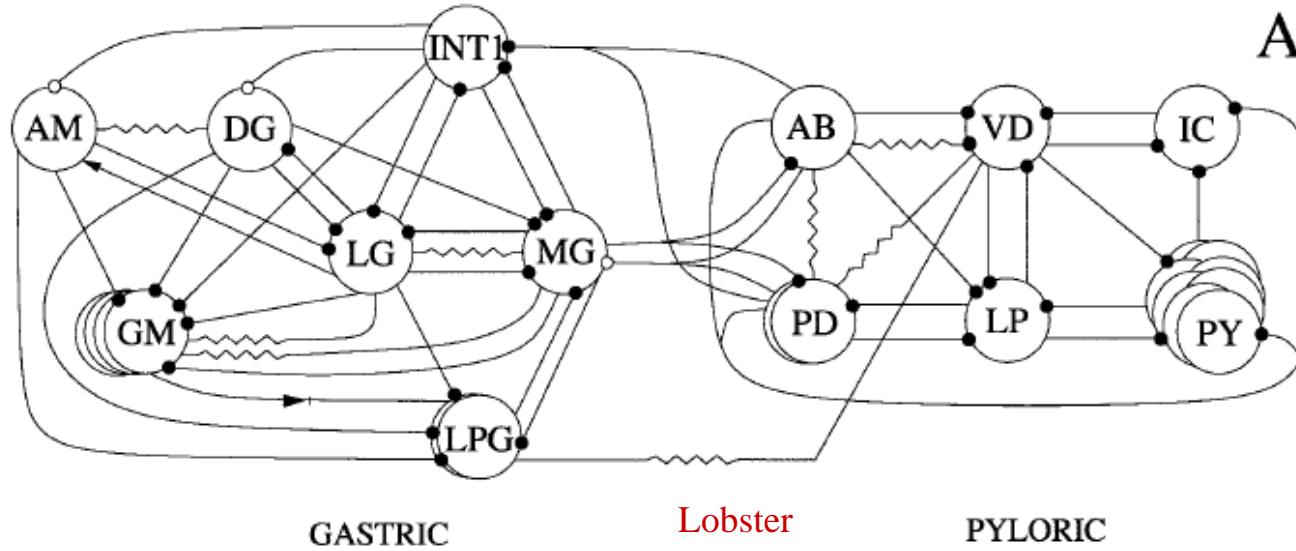
Escuela Politécnica Superior
Universidad Autónoma de Madrid, Spain

Central Pattern Generators (CPGs)

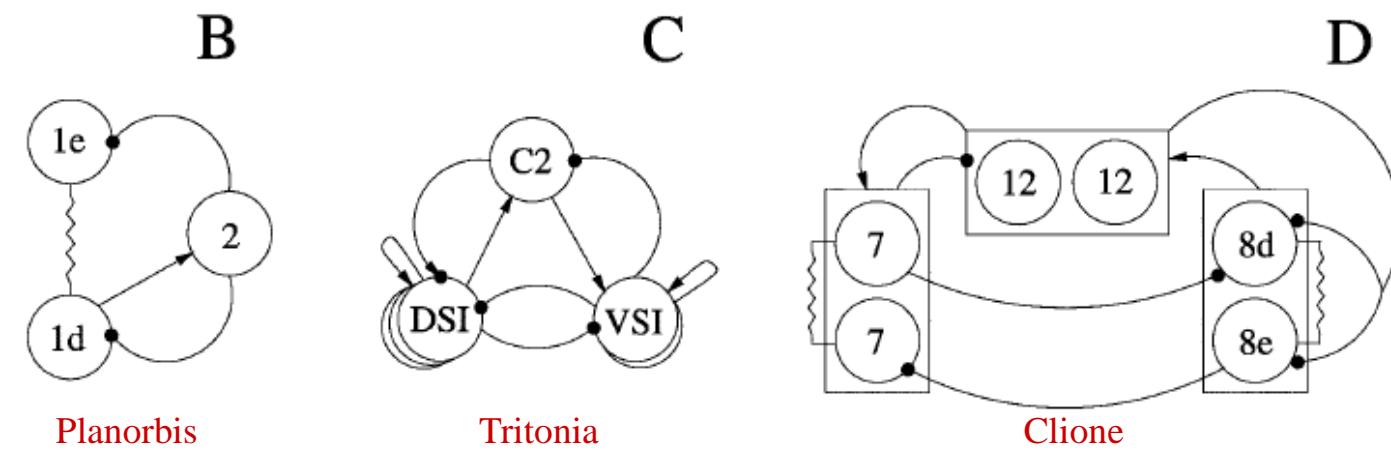
- A central pattern generator is a neural network that can endogenously produce rhythmic patterned outputs.
- These outputs are used to control a large variety of motor movements



CPGs have non-open topologies



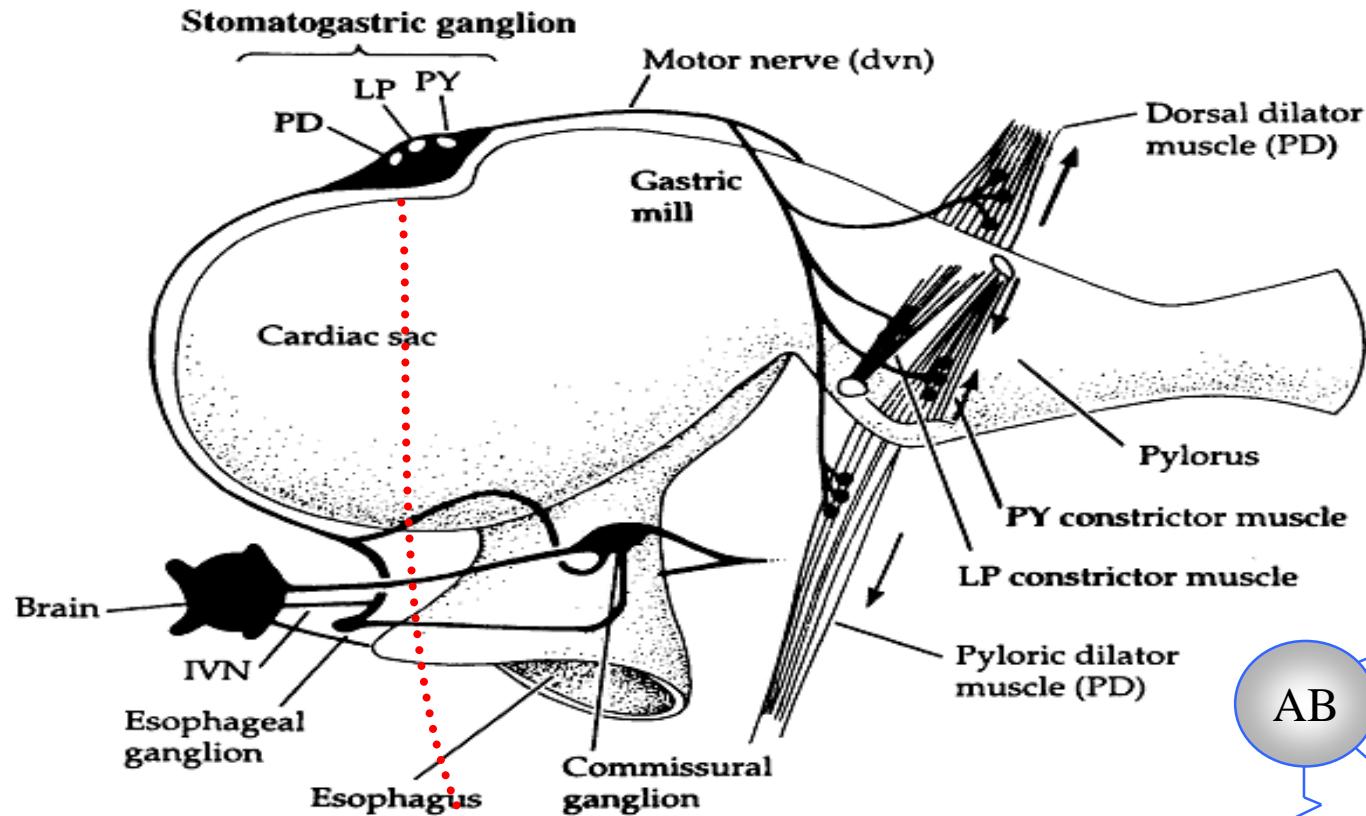
Non-open topology: every member of the circuit receives at least one connection from another member of the CPG



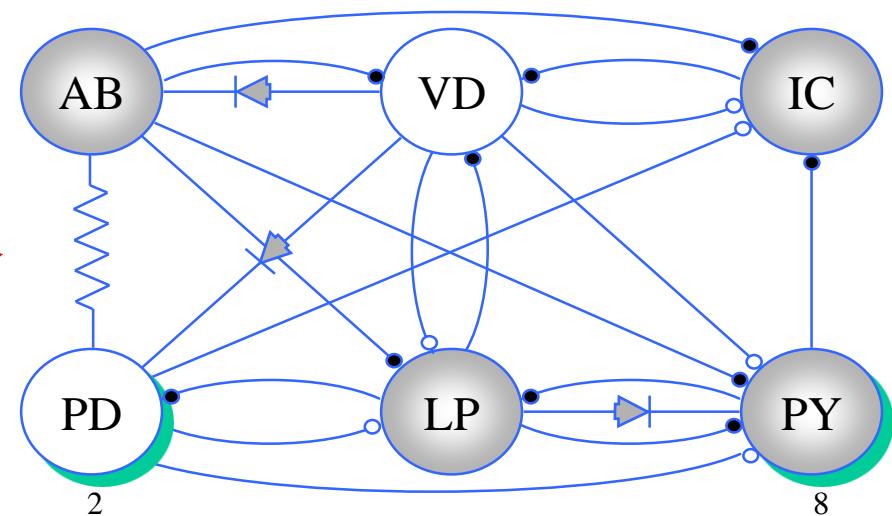
Open topology: at least one neuron does not receive synapses from any other circuit member.

Examples on non-open topologies

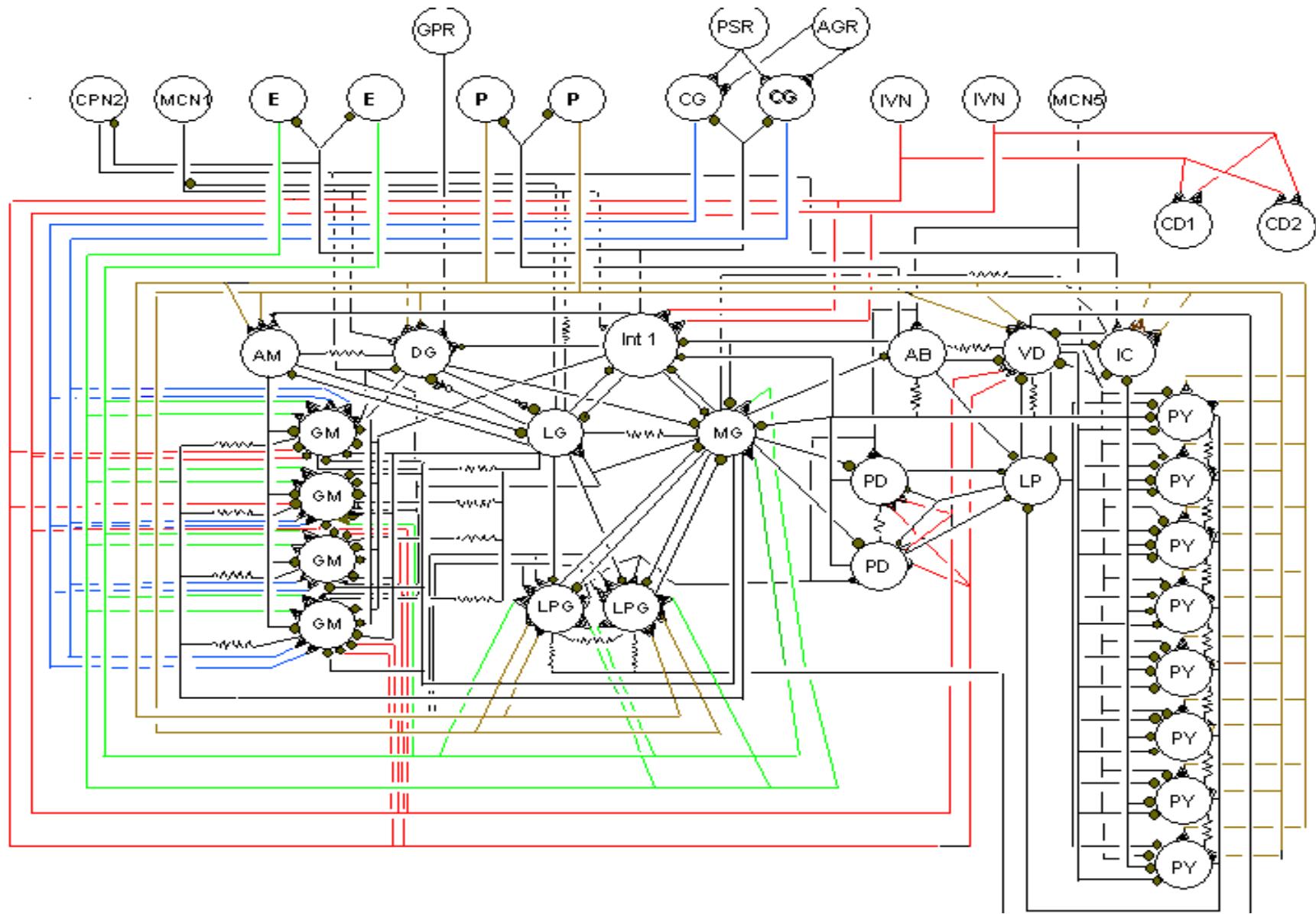
Gastric system of crustacean



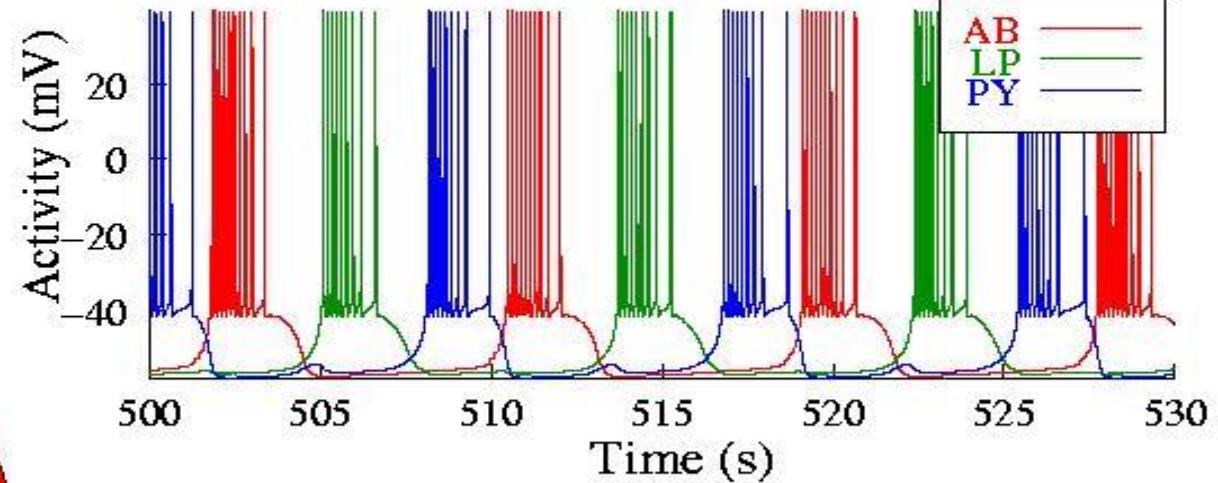
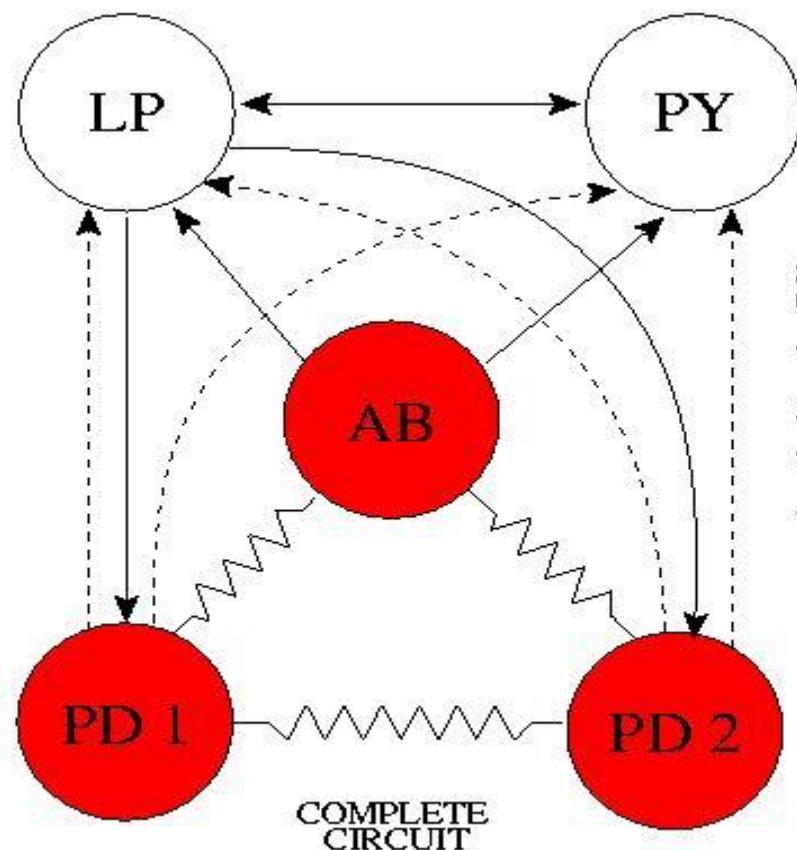
Pyloric CPG: 14 neurons



Gastric and Pyloric CPGs

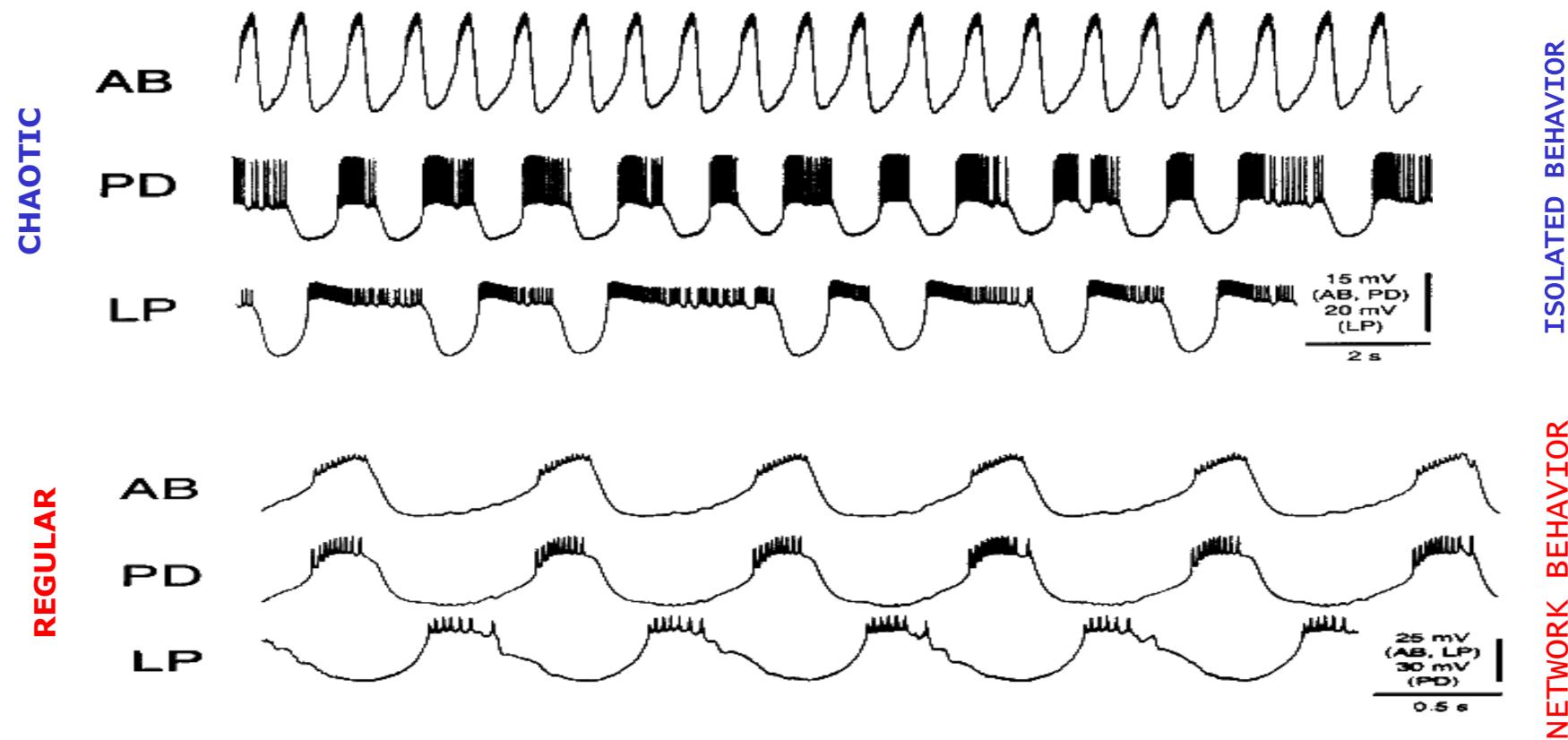


Pyloric Triphasic Rhythm



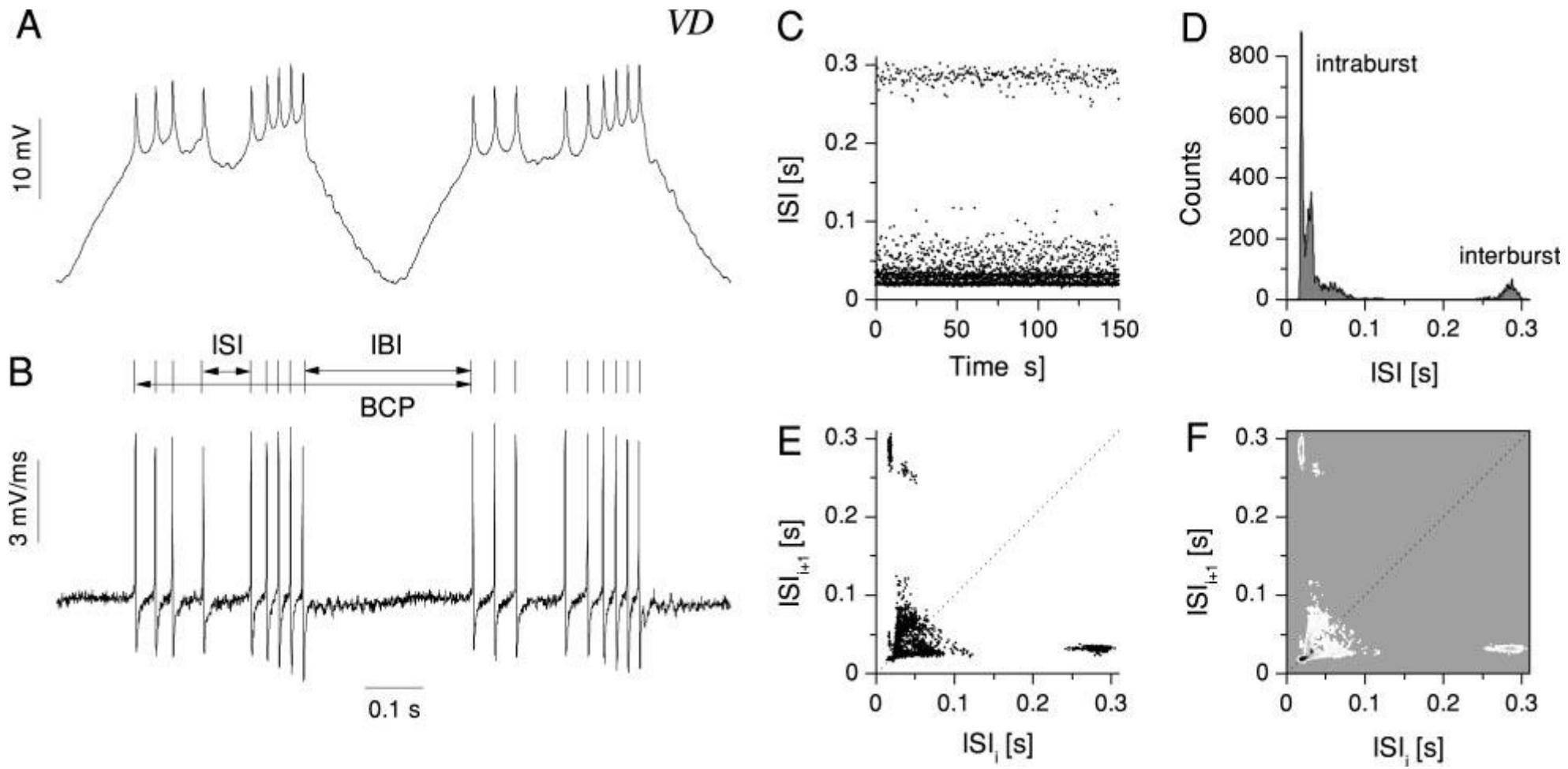
Pyloric CPG rhythm

- When isolated, most pyloric CPG neurons display a characteristic chaotic activity. The AB interneuron is always regular.



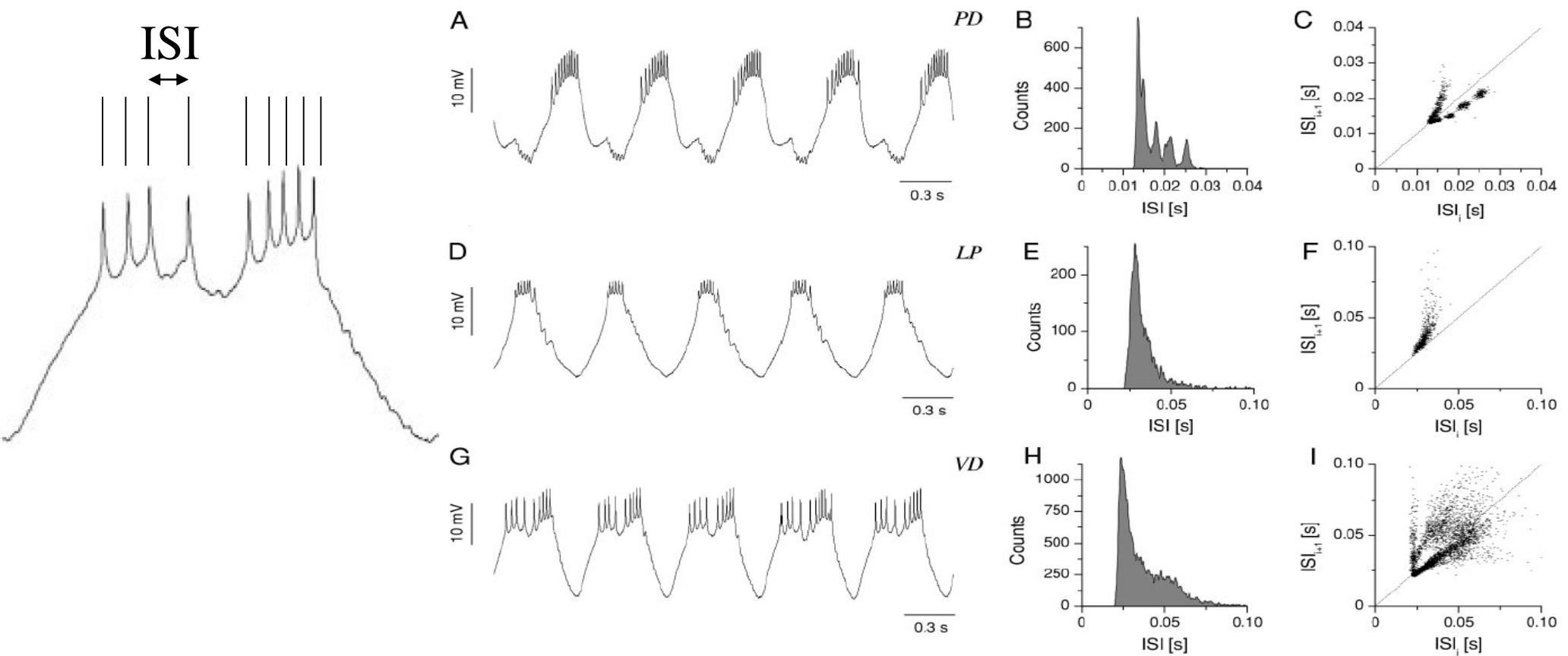
- When the neurons are connected, all of them display a regular behavior with a precise and robust rhythm.

Analysis of spiking bursting activity

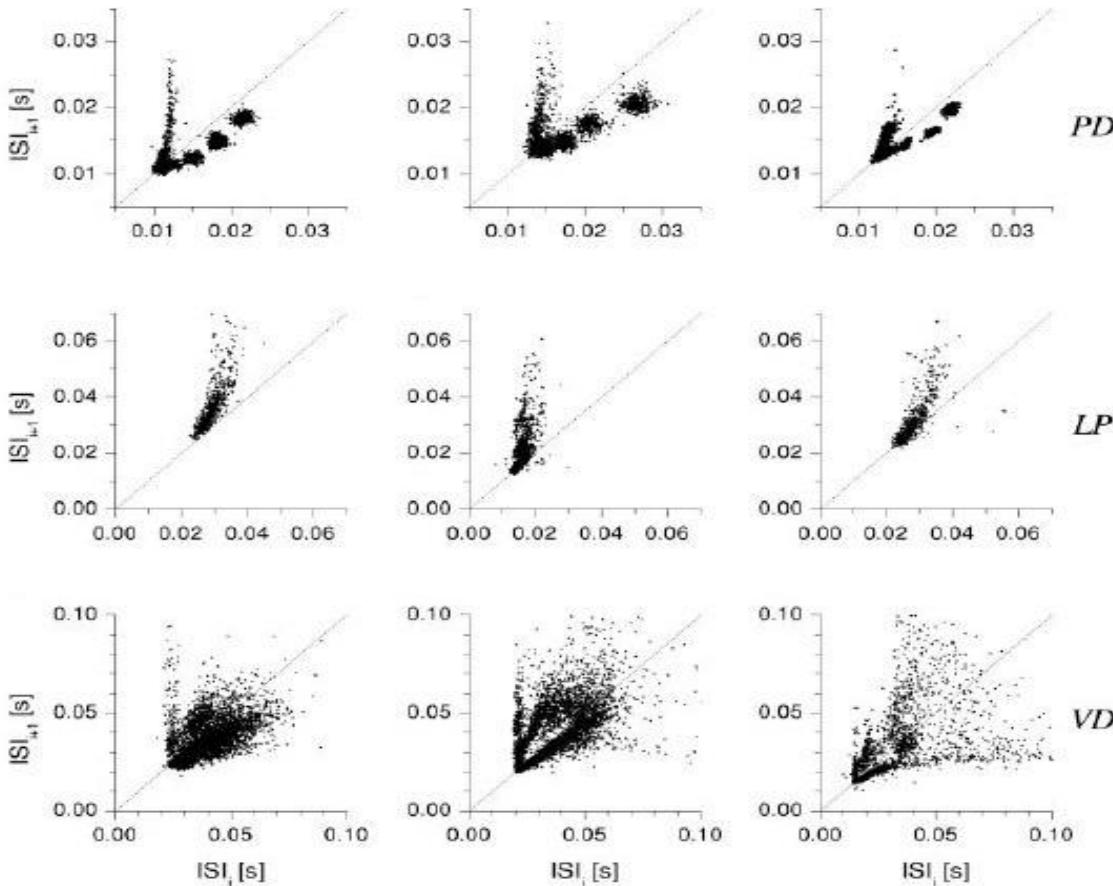


Szücs et al. 2003, *J. Neurophysiol.* 89: 1363

Neural Signatures in spiking-bursting activity

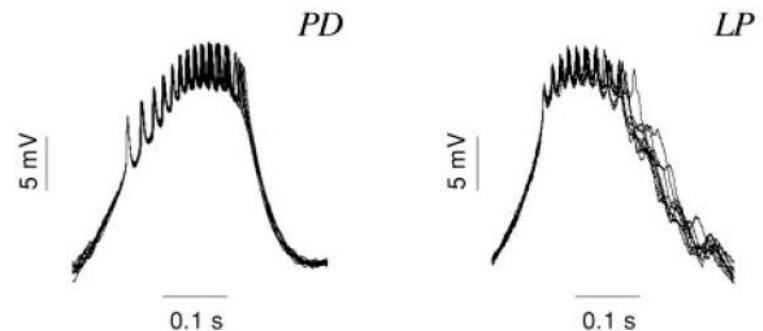


Neural Signatures



Signatures of PD, LP and VD pyloric neurons from 3 different animals

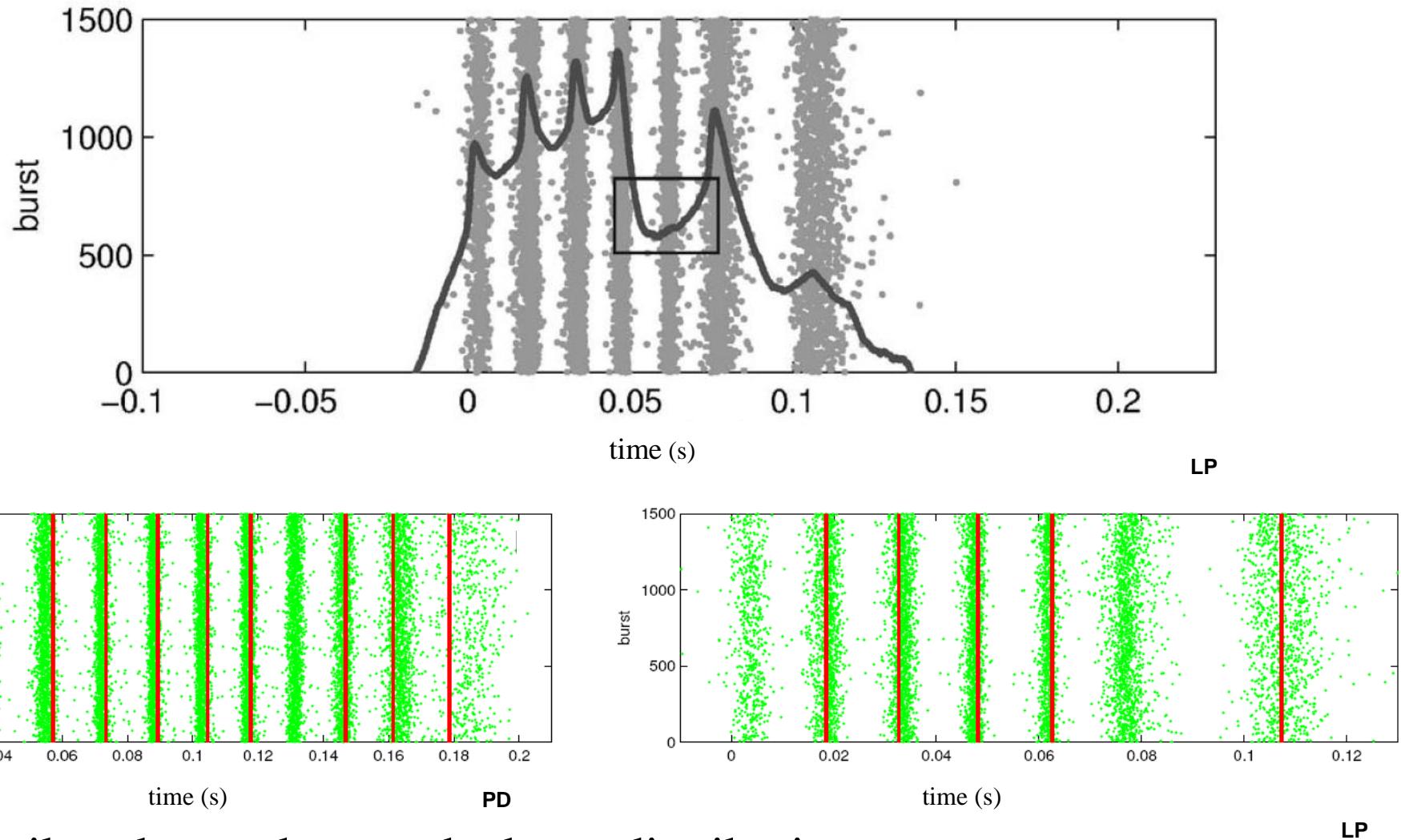
Szücs et al. 2003, *J. Neurophysiol.* 89: 1363



Ten traces of consecutive bursts

A neural signature is a reproducible, cell-specific, intraburst interspike interval distribution.

Neural signatures are robust



Missing spikes do not destroy the burst distribution

Open questions from the experimental recordings

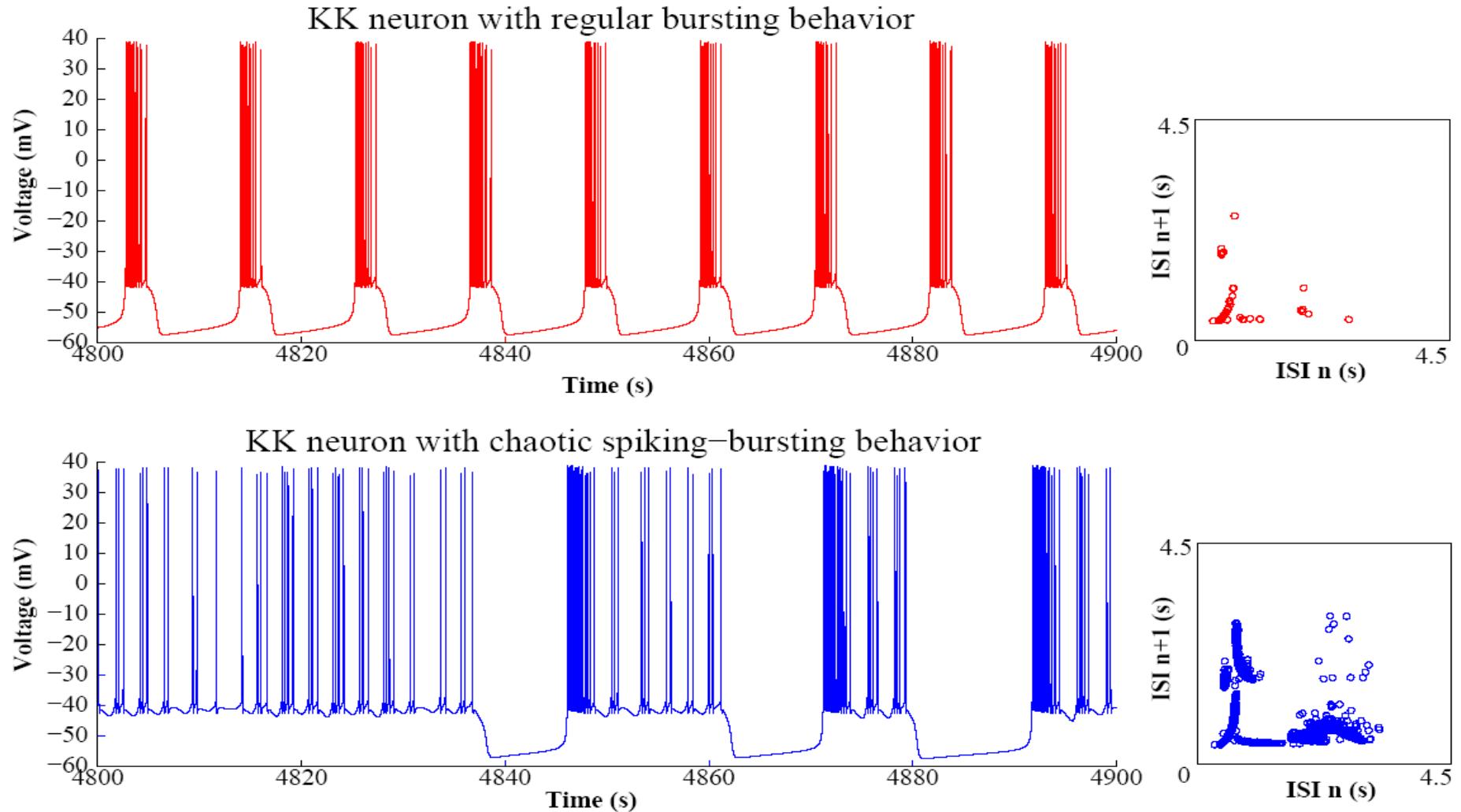
What is the origin of the signatures?

Individual internal dynamics, morphology, architecture of the network, external neuromodulation...

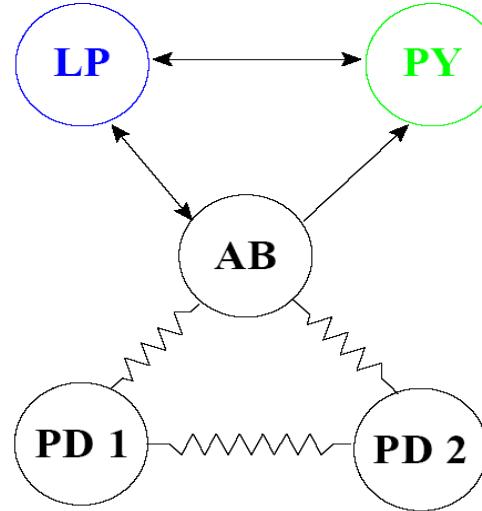
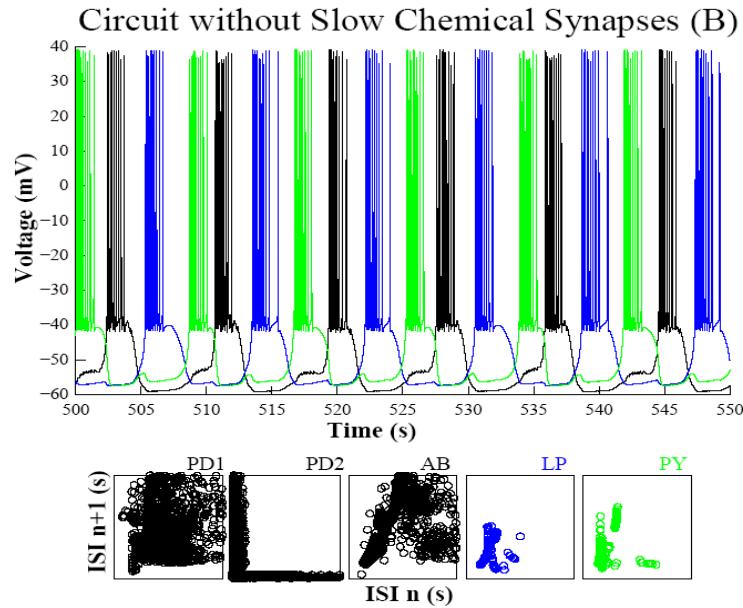
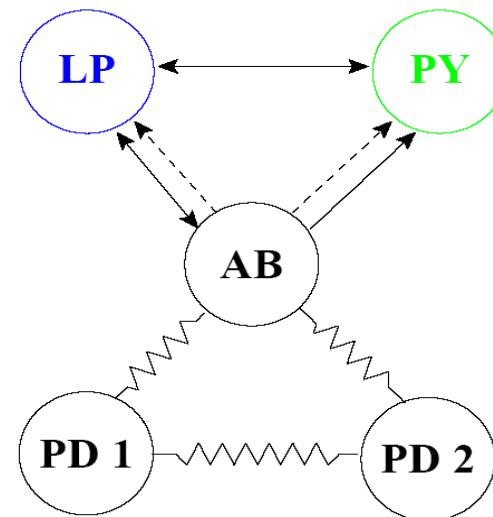
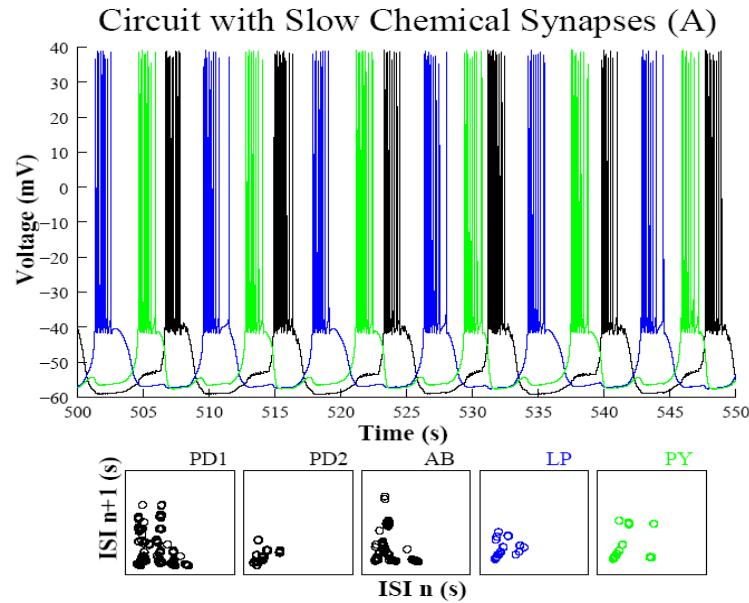
Do they have any functional meaning?

- Within the network
- For other CPGs
- For the muscles

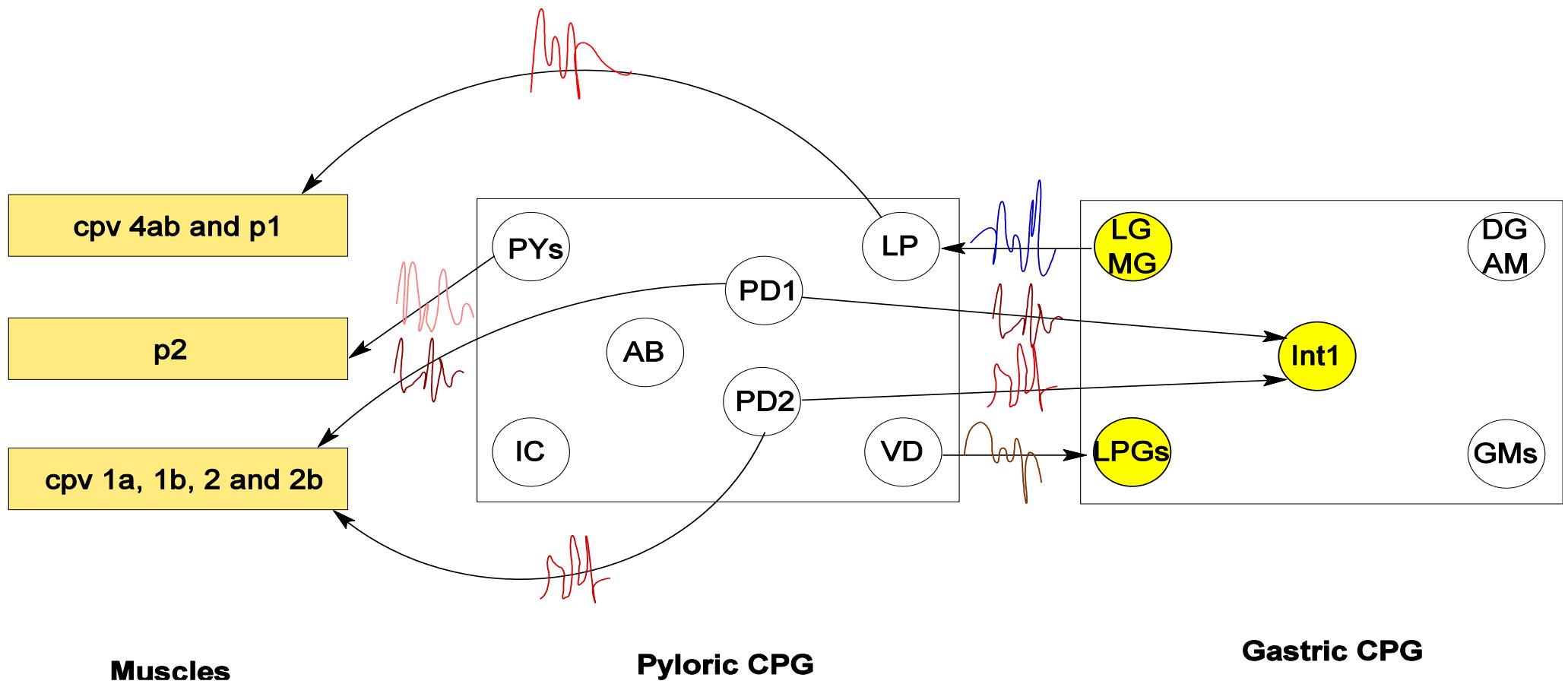
Individual dynamics and signatures



Neural signatures are shaped by the connections



Signature emitters and readers

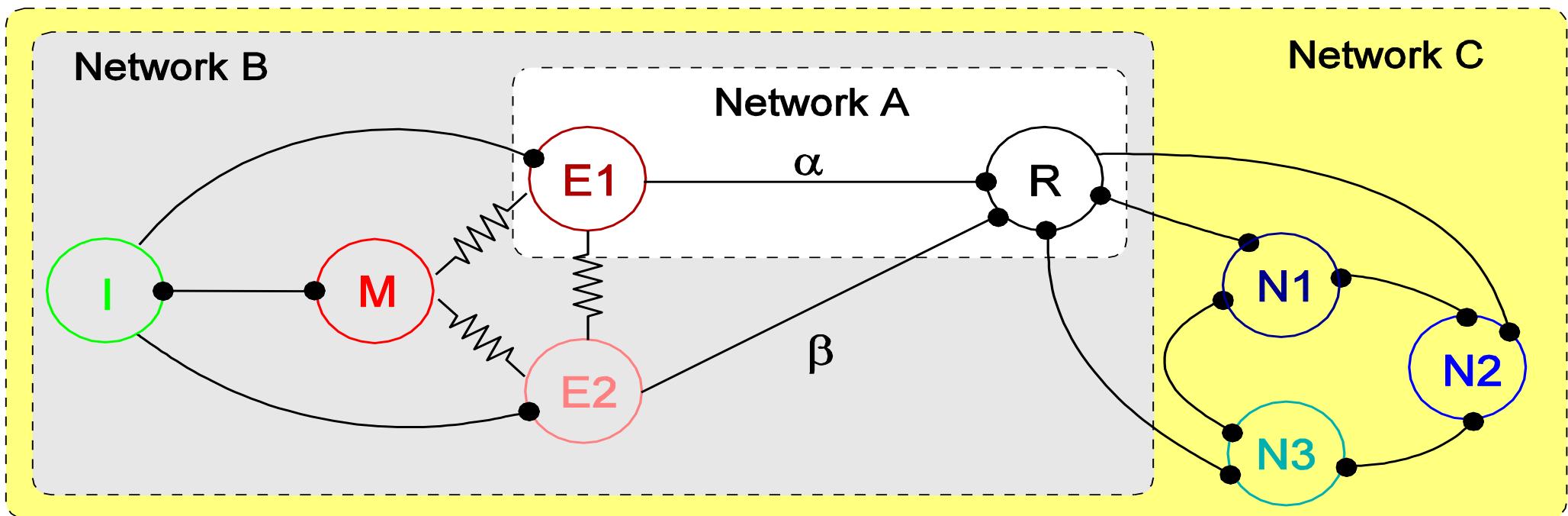


Modeling goals

It is difficult to address the role of neural signatures in *in vitro* experiments. Models are useful to:

- To test whether cell-specific spike distributions inside the bursts can be meaningful for a neural reader.
- To test the hypothesis of multiple coding in single signals.

Emitter and Reader model networks



Signature emitter system

Signature reader system

CPG models

Single neuron model:

To model the individual behavior of each neuron we use a conductance-based stomatogastric neuron model [Liu et al., 1998]

$$C \frac{dV}{dt} = -(I_{Na} + I_{CaT} + I_{CaS} + I_A + I_{KCa} + I_{Kd} + I_H + I_{leak})$$

Synapse models:

1. Fast inhibitory graded chemical synapses (black dots). This is the most common synapse in the pyloric CPG
2. Gap junctions (resistance symbols) to implement a pacemaker group in the emitter CPG

$$I_{fastX} = \sum_Y \frac{g_{fastYX} \cdot (V_X - E_{syn})}{1.0 + \exp(s_{fast} \cdot (V_{fast} - V_Y))}$$

$$I_{elecX} = \sum_Y g_{elecYX} \cdot (V_X - V_Y)$$

Signature measures

To characterize the intraburst spike activity we use two different representations:

1. Bar plots of the time interval to the first spike (I2FS)
2. Interspike interval bar plots

Neurons with the same (or very similar) signatures have the same (or very similar) representations.

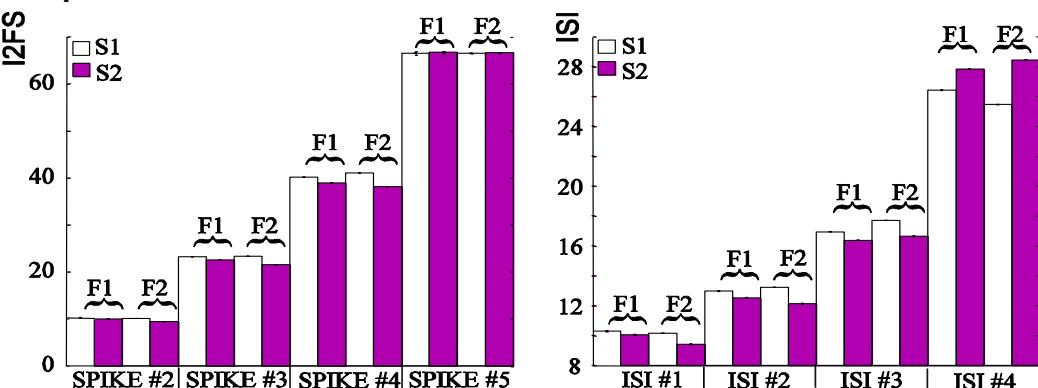
To quantitatively measure how similar two different signatures are, e.g., S1 and S2, let us call $ISI_{i,j}^{SX}$ to the i -th ISI in burst number j in signal SX. We can use as a measure of the distance between two signatures $d_{S1;S2}$ an L2 norm as follows:

$$d_{S1, S2} = \sqrt{\frac{1}{B1 \cdot B2} \sum_i^{B1} \sum_j^{B2} \sum_k^N (ISI_{k,i}^{S1} - ISI_{k,j}^{S2})^2}$$

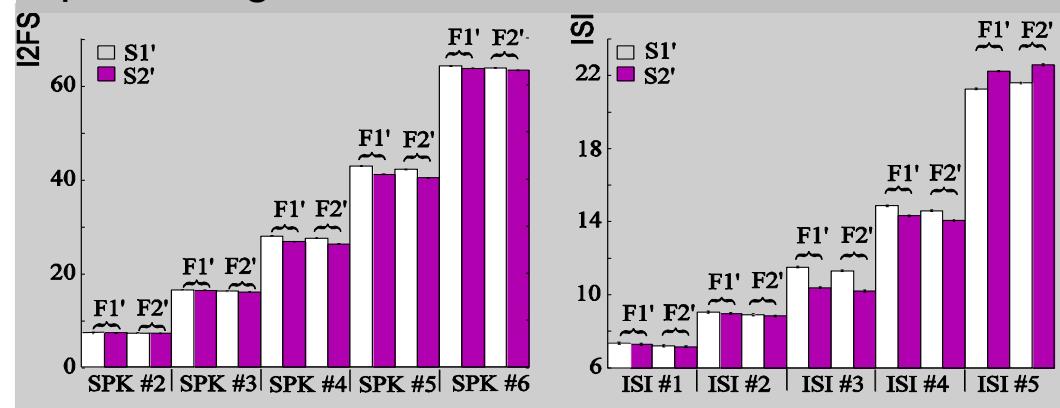
where $B1$ and $B2$ are the number of bursts in signal S1 and in signal S2, respectively; and N is the number of ISIs per burst.

Emitter signals

Network A: Signals are generated by the E1 cell. Signature depends on the E1 cell parameters



Network B and C: Signals are generated by E1 and E2 cells simultaneously. Each cell has a specific signature



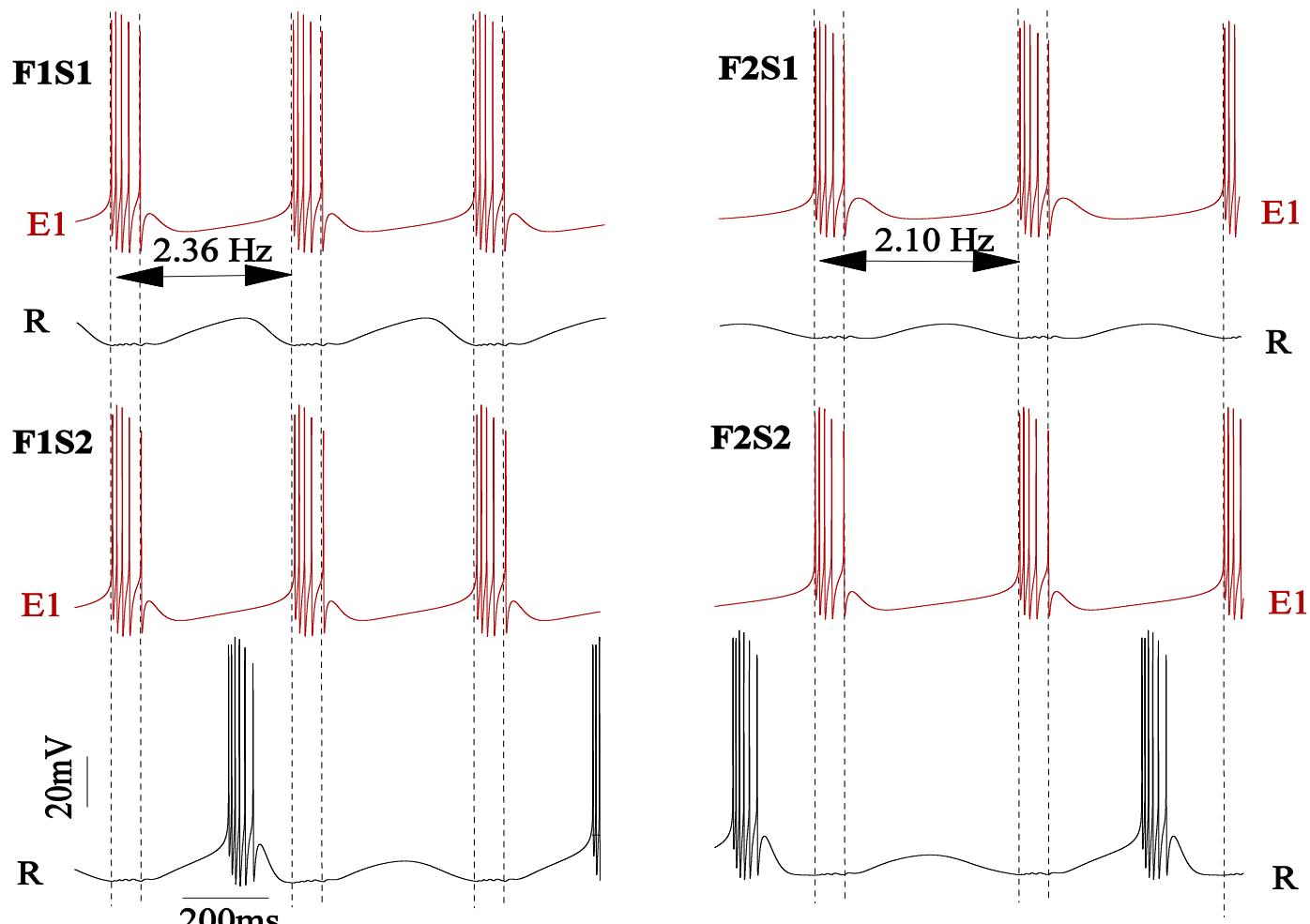
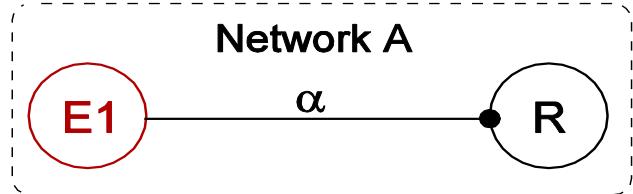
$d_{S1,S2}$	F1S1	F1S2	F2S1	F2S2
F1S1	0.02			
F1S2	2.20	0.01		
F2S1	1.28	2.83	0.01	
F2S2	2.38	1.01	3.45	0.01

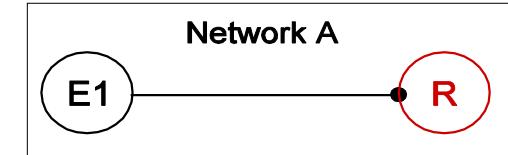
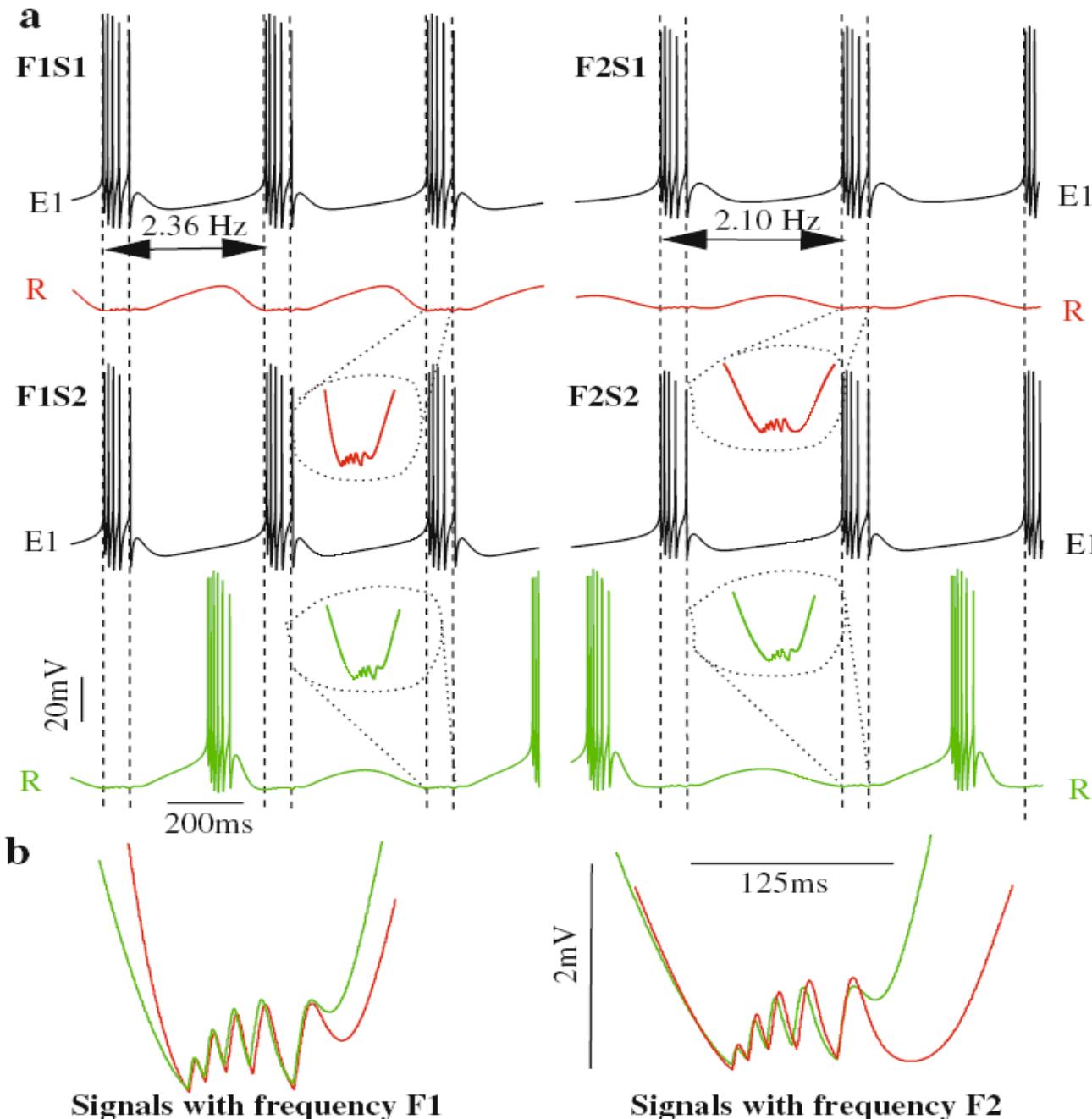
$d_{S1',S2'}$	F1'S1'	F1'S2'	F2'S1'	F2'S2'
F1'S1'	0.02			
F1'S2'	1.04	0.01		
F2'S1'	0.08	0.97	0.02	
F2'S2'	1.10	0.08	1.03	0.02

Distances between signals with the same signature and different slow wave frequency (**bold**) are always less than distances between signals with different signature (*italic*)

Signature recognition (network A)

In Network A, the isolated R neuron has always spiking-bursting activity. However, when the connection from E1 is established the behavior of R changes. When it reads the signature S1 (with F1S1 and F2S1), R displays subthreshold oscillations while if it receives S2 (with F1S2 and F2S2), it shows spiking-bursting activity.





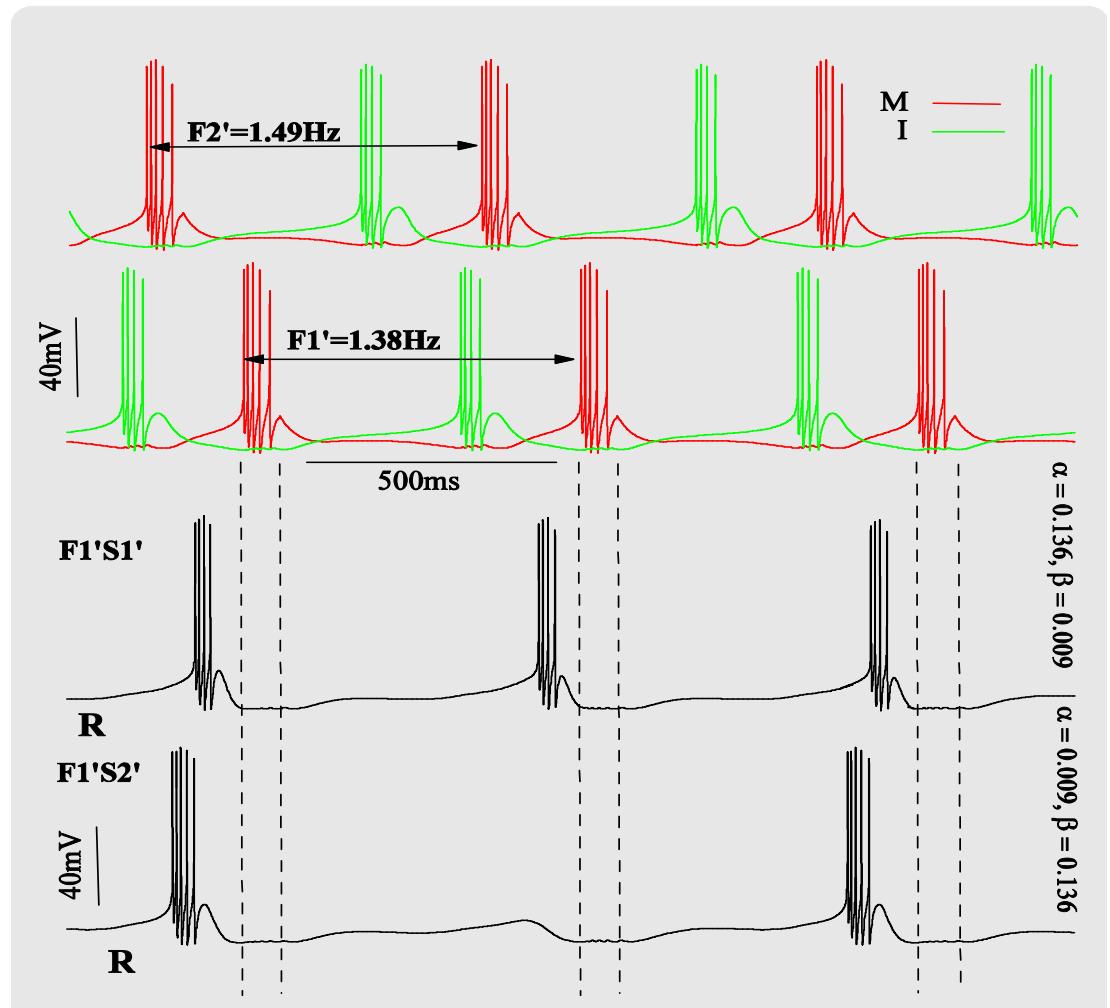
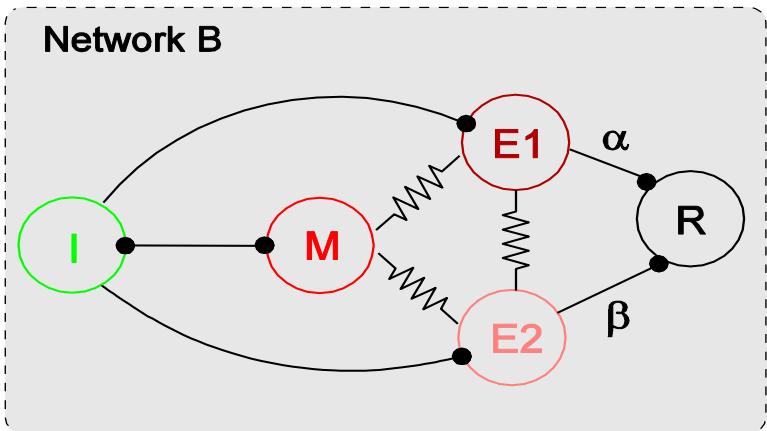
Note the earlier rise of the membrane potential for S2 (this rise also takes place from a more depolarized potential than for S1).

Because of this effect,
with signature S_1 neuron
 R cannot reach the firing
threshold.

With signature S2 neuron
 R goes beyond the
spiking threshold

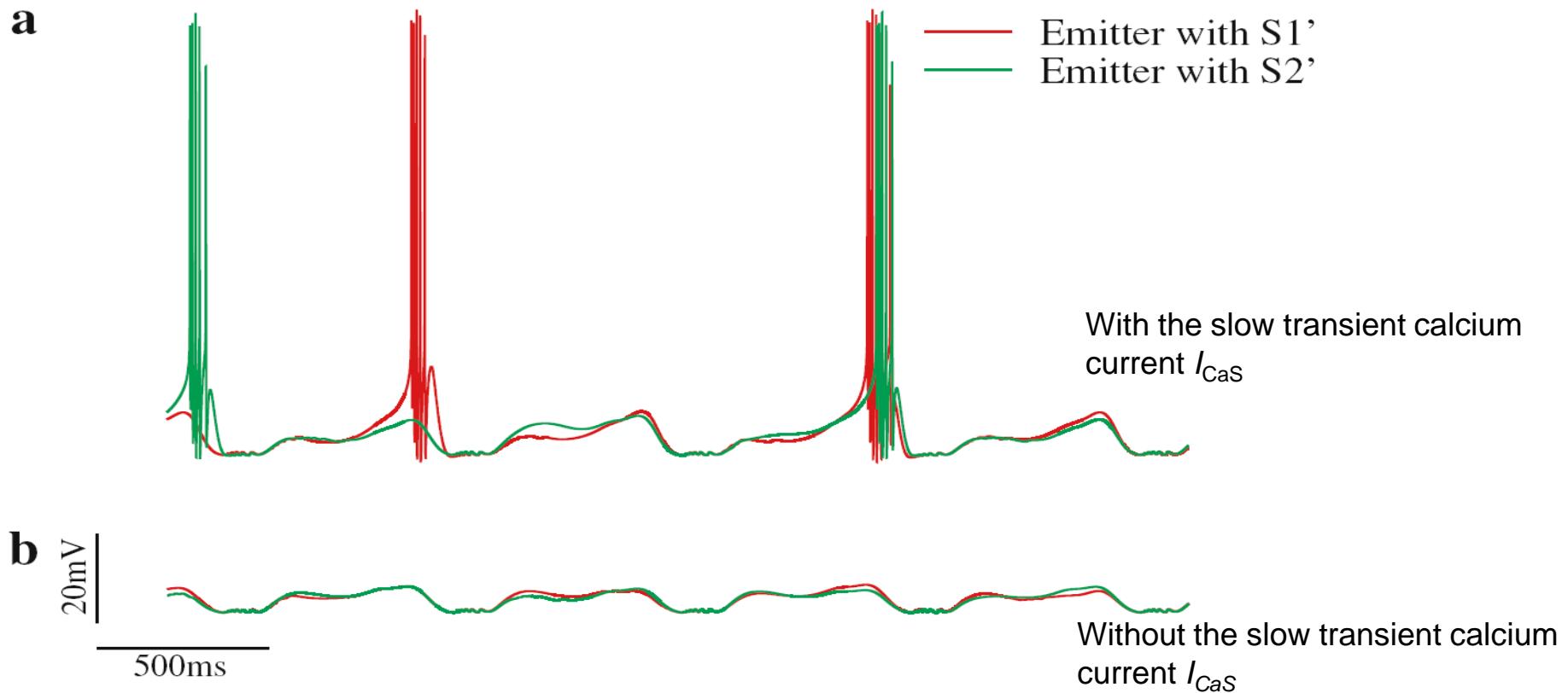
Signature recognition (B)

In network B, the R cells shows spiking-bursting behavior with different frequencies as a function of the signature received from the emitter CPG. In Network C this changes are propagated to the rest of the CPG and the rhythm generated by the circuit also depends on the signature.



Ionic basis for the signature recognition

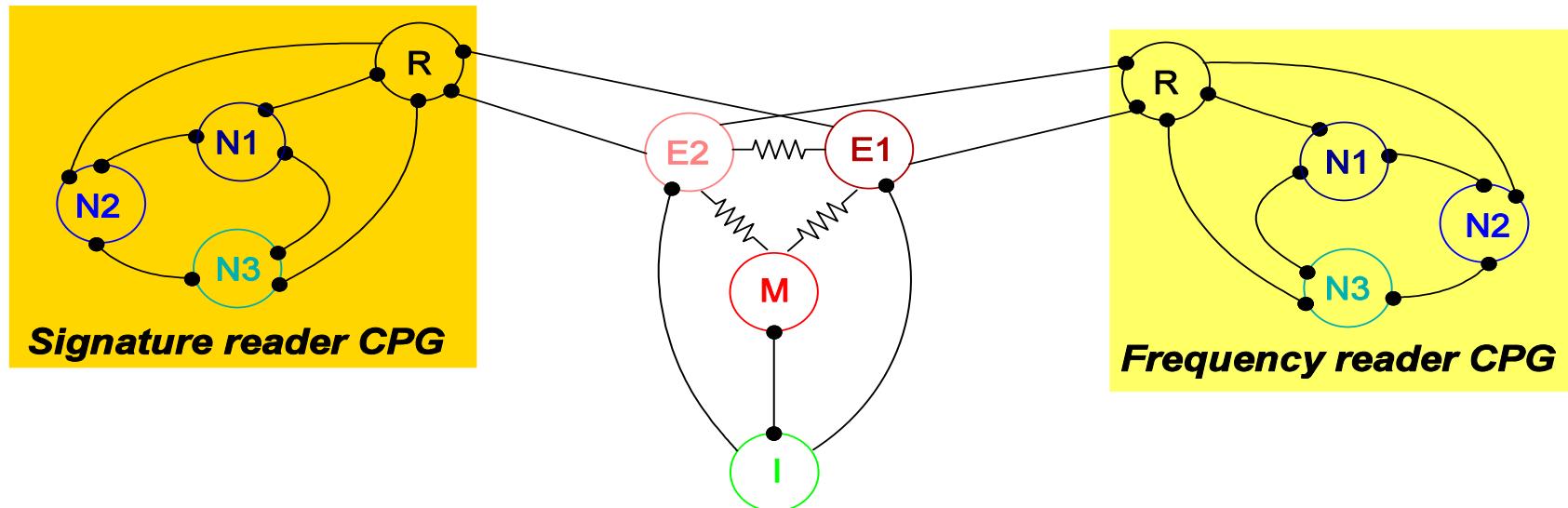
R response



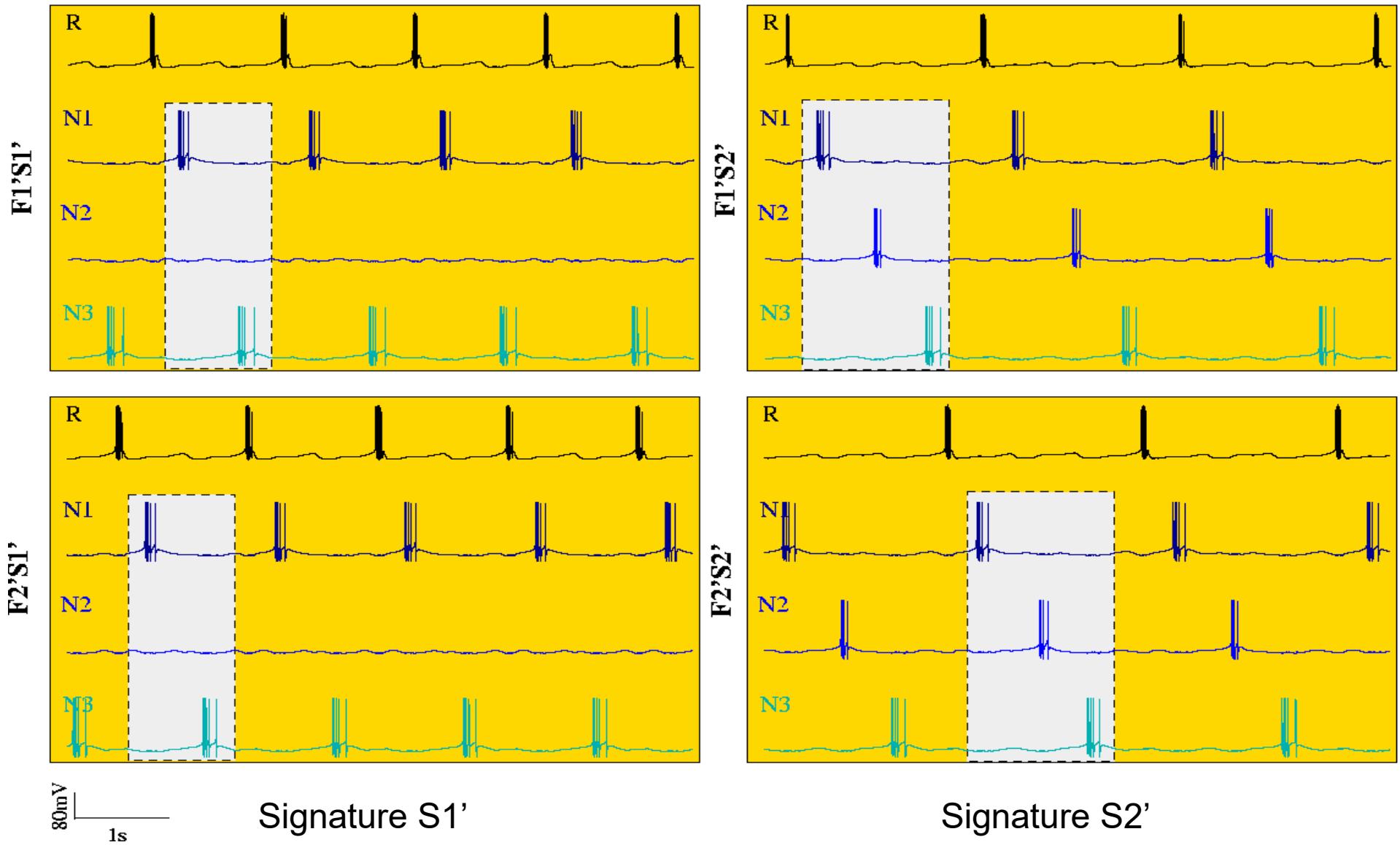
- (a) With I_{Cas} S1' evokes a higher slow wave frequency in R (upper red trace).
- (b) Without I_{Cas} the R neuron always displays subthreshold oscillations and there is no apparent distinction in the response to the two different signatures in the emitter.

Multicoding

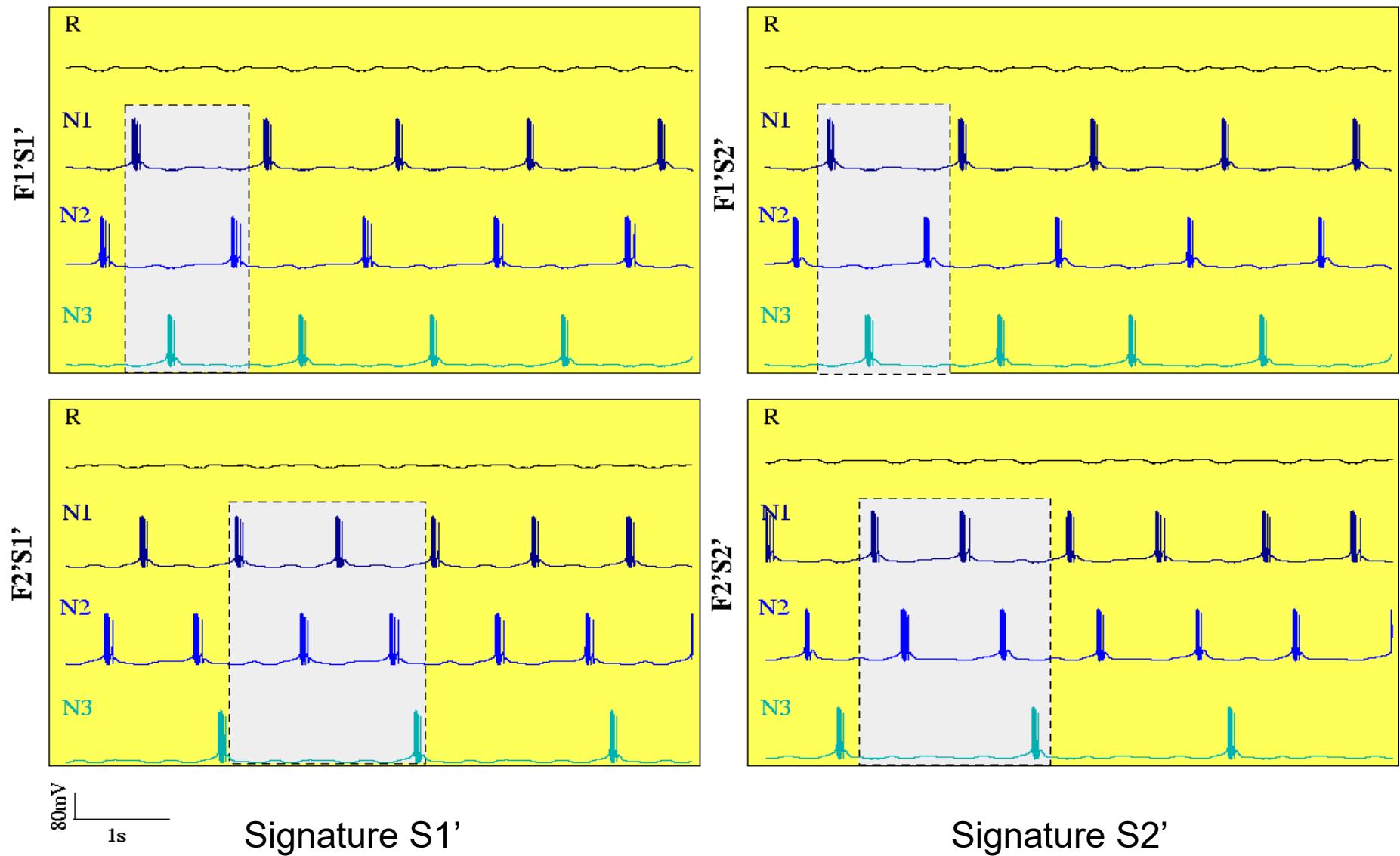
- If a reader system is able to recognize different signatures, then a multicode could be used to send distinct information within the same signal.
- To test this hypothesis we have built a model network where the signal from an emitter CPG is injected in two CPGs: a frequency reader CPG and a signature reader CPG. The emitter system is the same described previously. Inputs to both reader circuits are the same, but their response is different depending on the slow wave frequency or the signature.
- The frequency reader and the signature reader are identical, the only difference between them are the connectivity parameters.



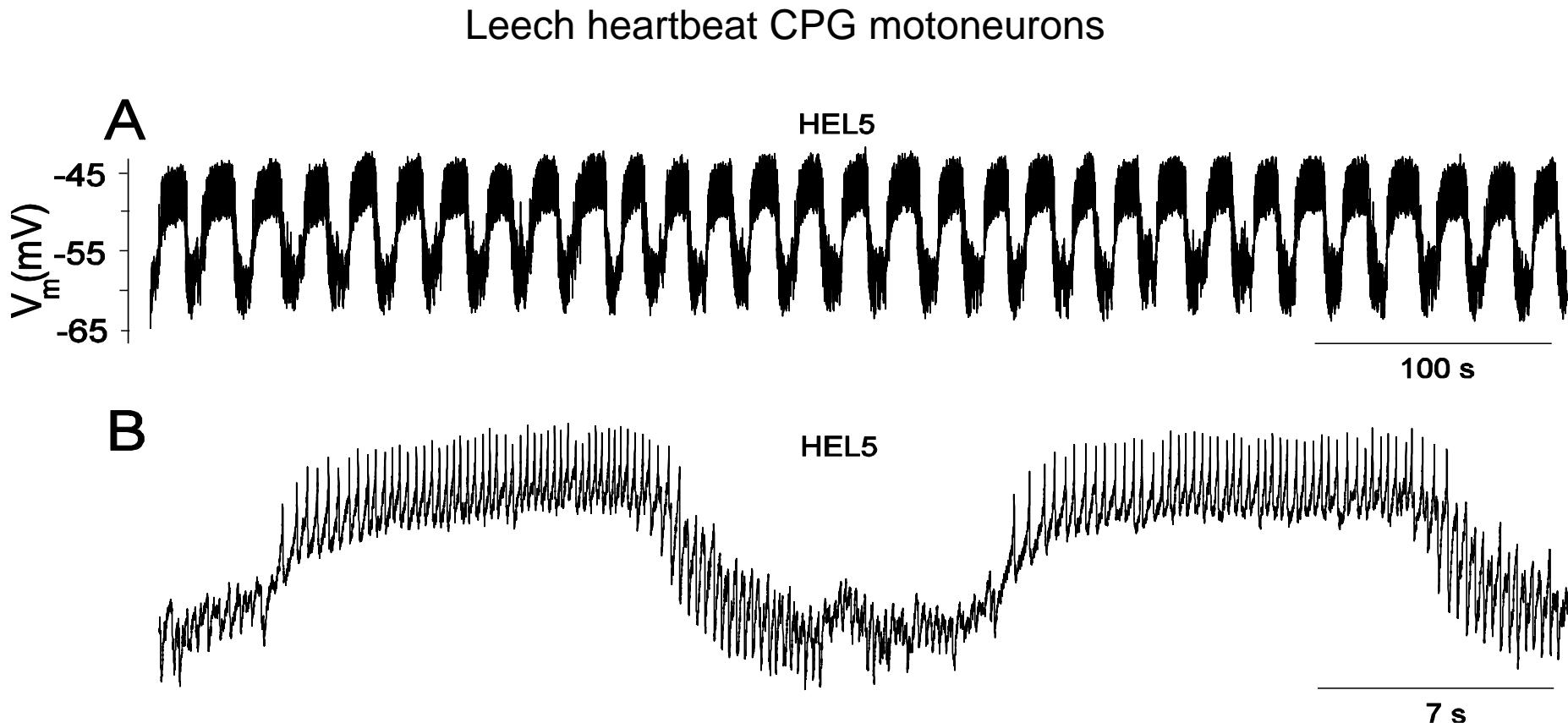
Multicoding: signature reader CPG



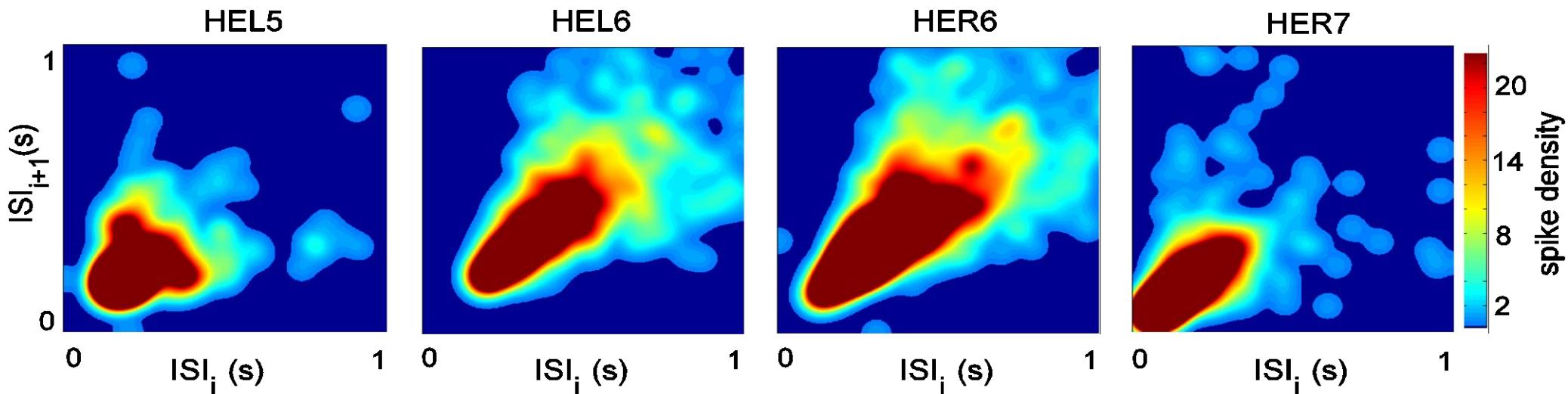
Multicoding: frequency reader CPG



Other CPGs also display neural signatures



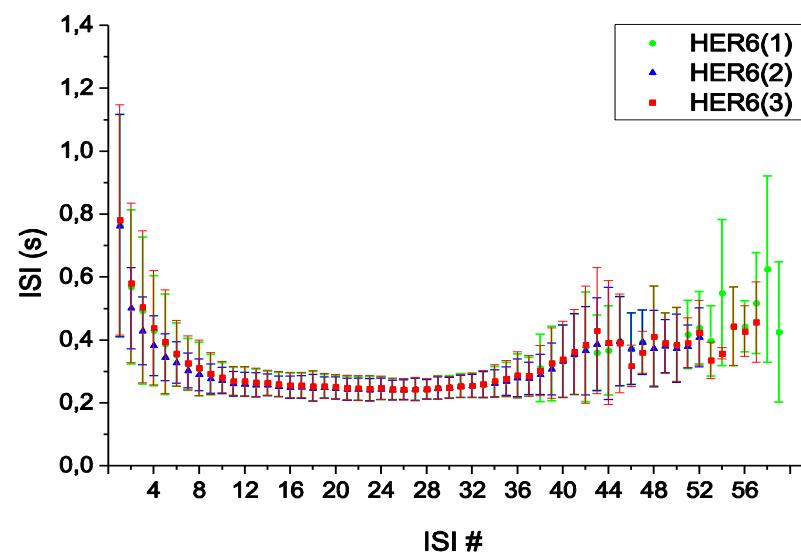
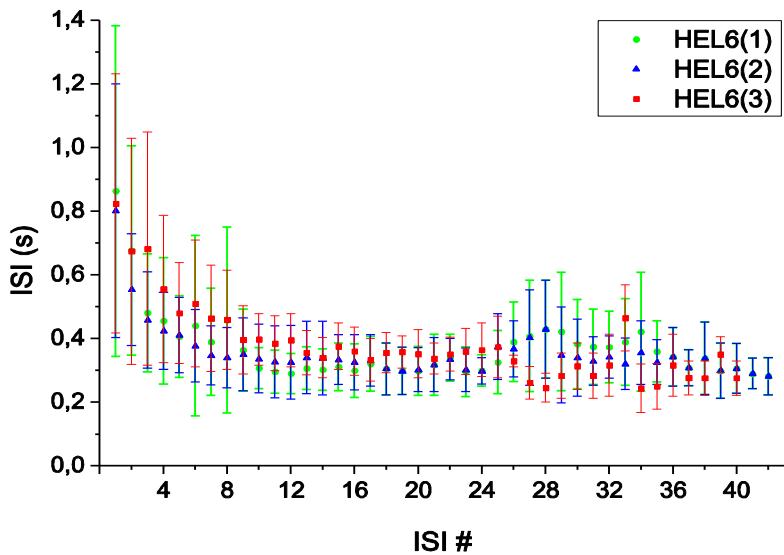
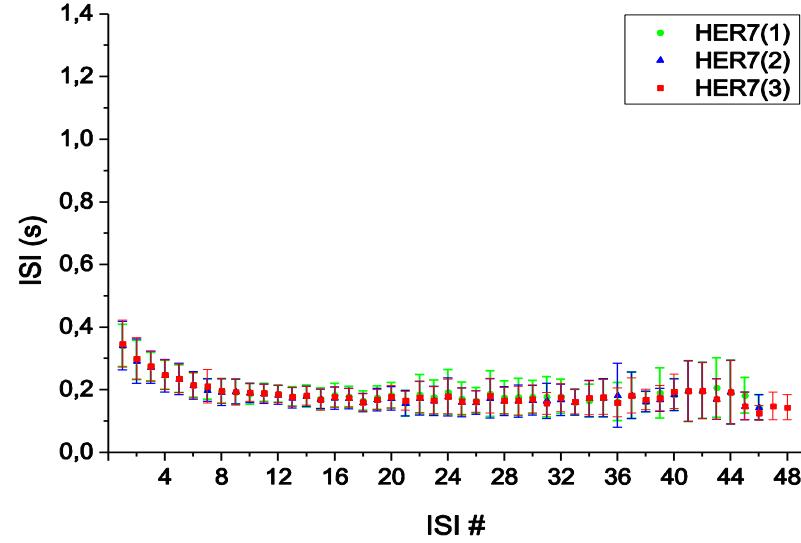
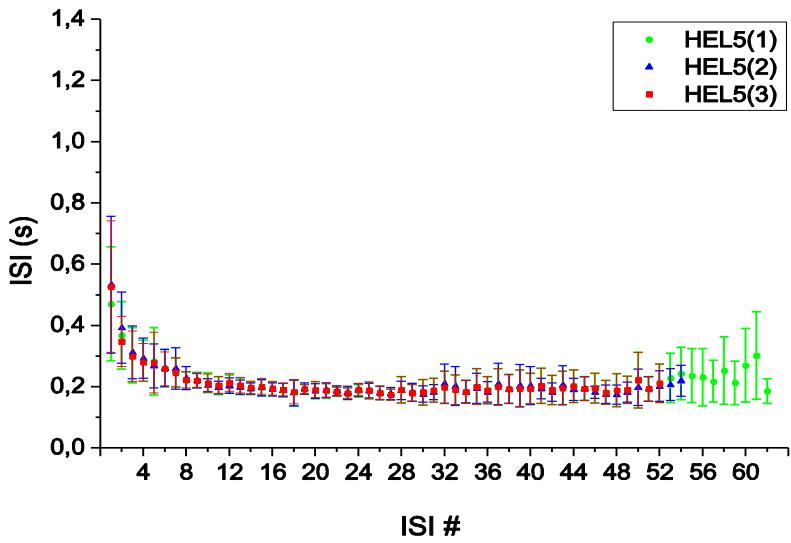
Leech heart CPG signatures



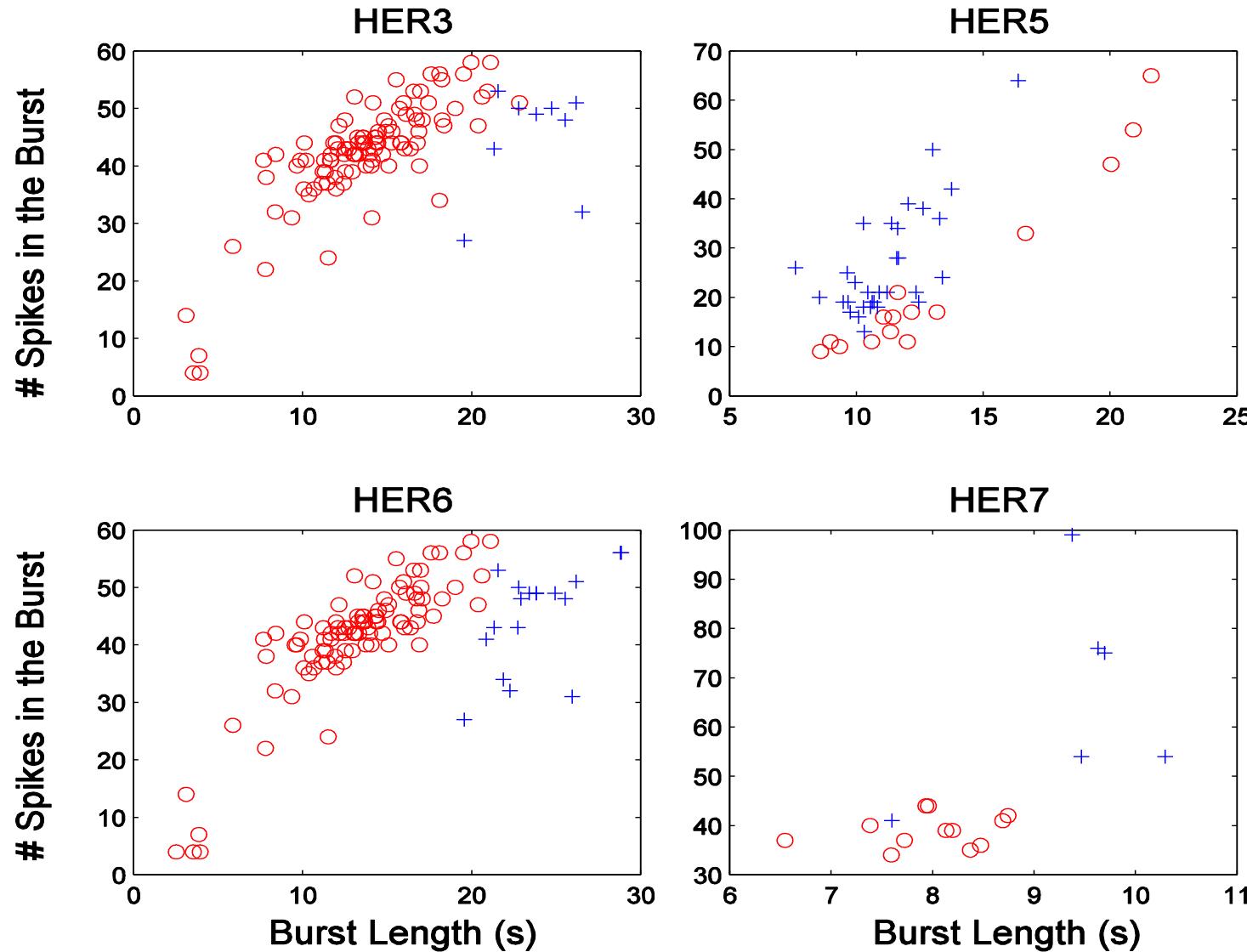
Signatures of heart motoneurons HEL5, HEL6, HER6 and HER7 represented with return maps (ISI_i vs ISI_{i+1}). In these panels the color scale represents the density of points. The value of the density plot at each point is obtained by the sum of bidimensional Gaussian kernels centered at ISI_i, ISI_{i+1} . This representation emphasizes the temporal relations between adjacent spikes.

Leach heart motoneurons

- The variability is reproduced from experiment to experiment

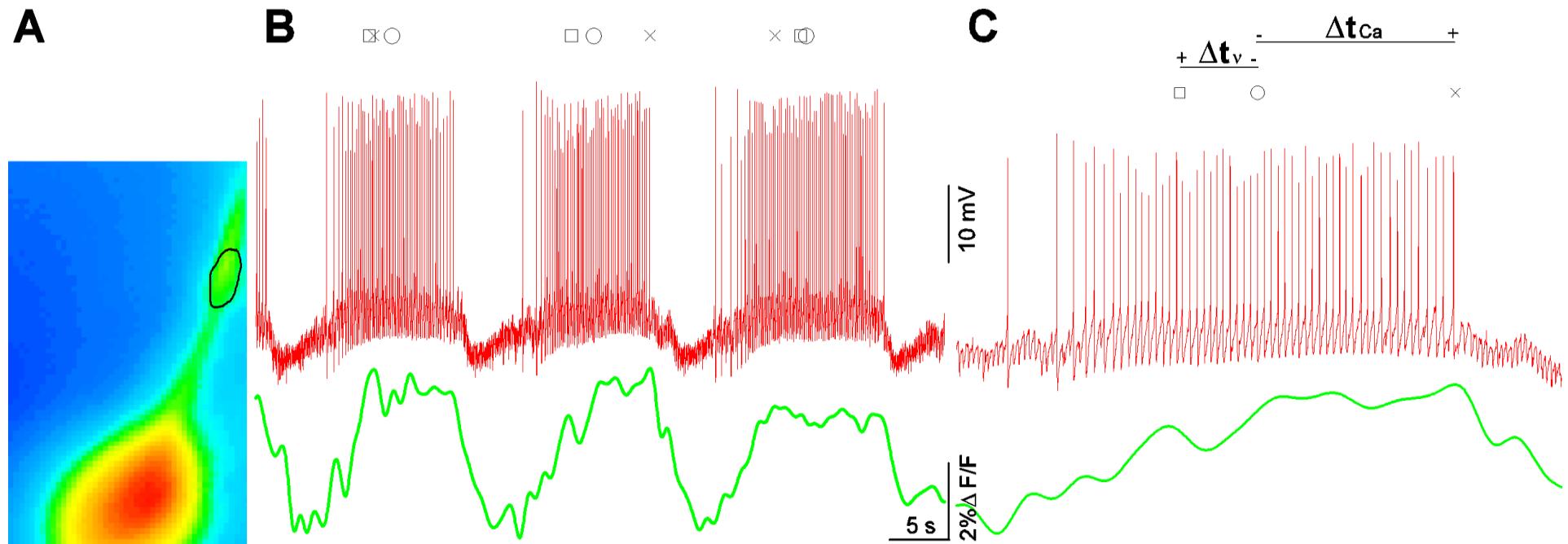


Burst classification (K-means) taking into account only the six first spikes



Imaging and intracellular recordings

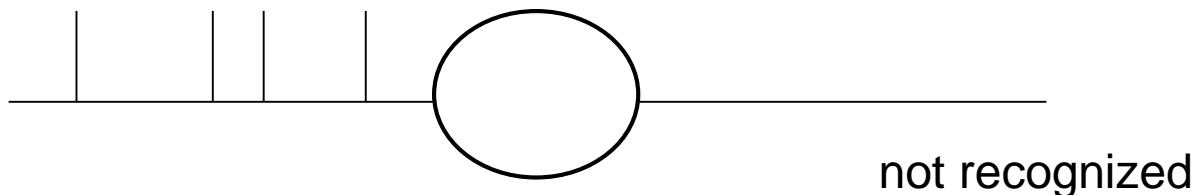
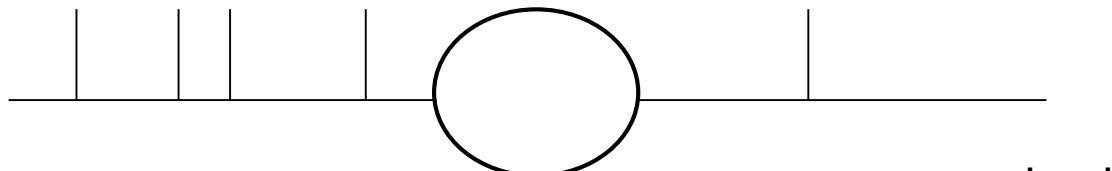
The role of the interaction between slow and fast dynamics in shaping the neural signatures can be studied with calcium imaging and intracellular recordings.



Conclusions

- Neural signatures are present in different neural circuits.
- They are shaped by the intrinsic cell dynamics and by the connectivity.
- Bursting activity can implement multiple codes.
- Spike timing distribution can identify the emitter and announce the length and number of spikes.
- Neural signatures can be a general mechanism to contextualize or discriminate information, and thus enhance the capacity of a neural network to perform a given task.

What is the minimum dynamical mechanism to read a signature?



Signatures can be used to implement preferred input/output relationships

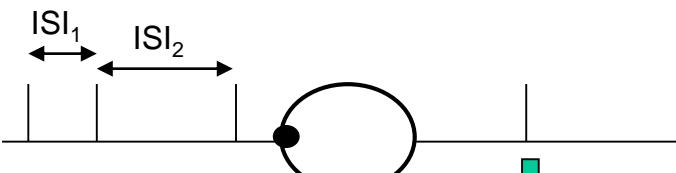
Neuron model to recognize triplets

- In model neurons with dynamics on multiple time scales the concept of frequency preference can be broaden to take into account preference towards temporally specific n -uples of presynaptic inputs.
- We have built a 3-dimensional conductance based model with a persistent Na current, a low-threshold K current and a hyperpolarization activated resonant h current.
- Real neurons display several amplifying and resonant variables acting on comparable time scales, hence it is reasonable to hypothesize that such an interaction might give rise to complex input-output relationships.
- We prove this hypothesis by injecting triplets of presynaptic spikes with different ISIs in a model neuron and observing whether a triplet elicits a spike or not.

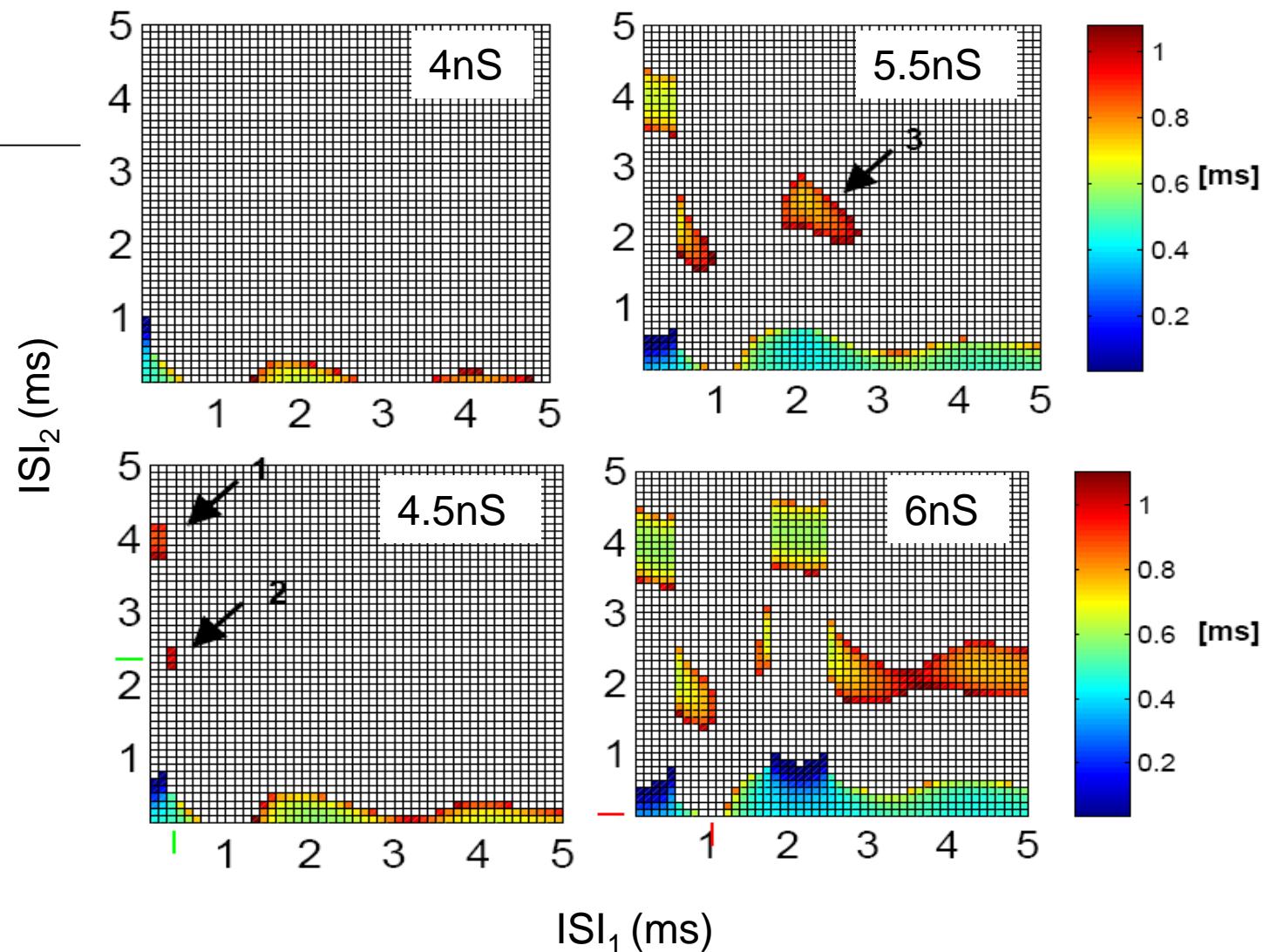
$$C \frac{dV}{dt} = -(g_L(V - E_L) + g_{Na}m_\infty(V)(V - E_{Na}) + g_Kn(V - E_K) + g_hm(V - E_h) + I_{Syn})$$

$$\frac{dn}{dt} = \frac{1}{1 + \exp(\frac{-45 - V}{5})} - n \quad m_\infty(V) = \frac{1}{1 + \exp(\frac{-30 - V}{7})} \quad 2 \frac{dm}{dt} = \frac{1}{1 + \exp(60 + V)} - m$$

Input/output preferences

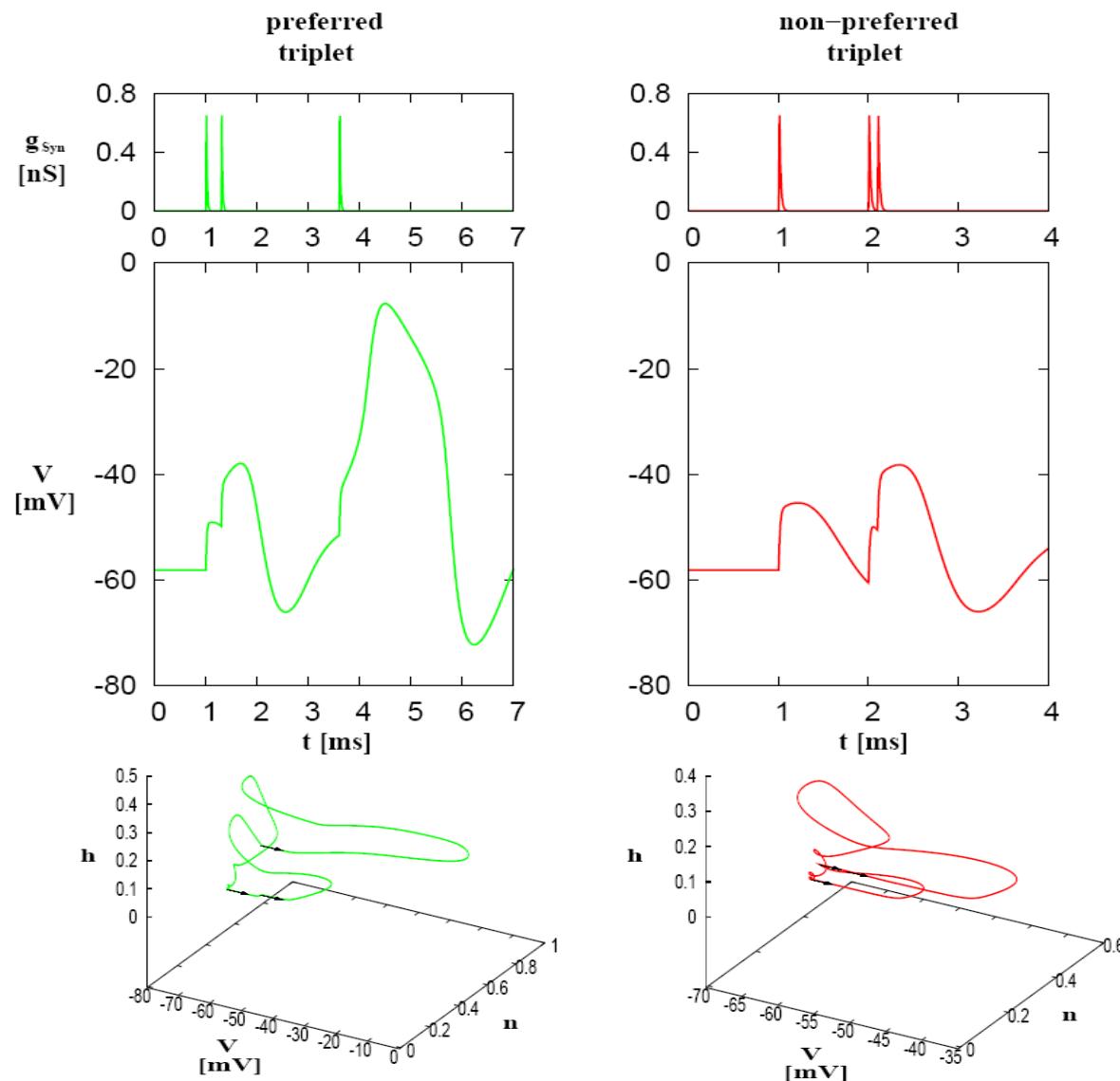


Grid has color only if the presynaptic triplet evokes a postsynaptic spike

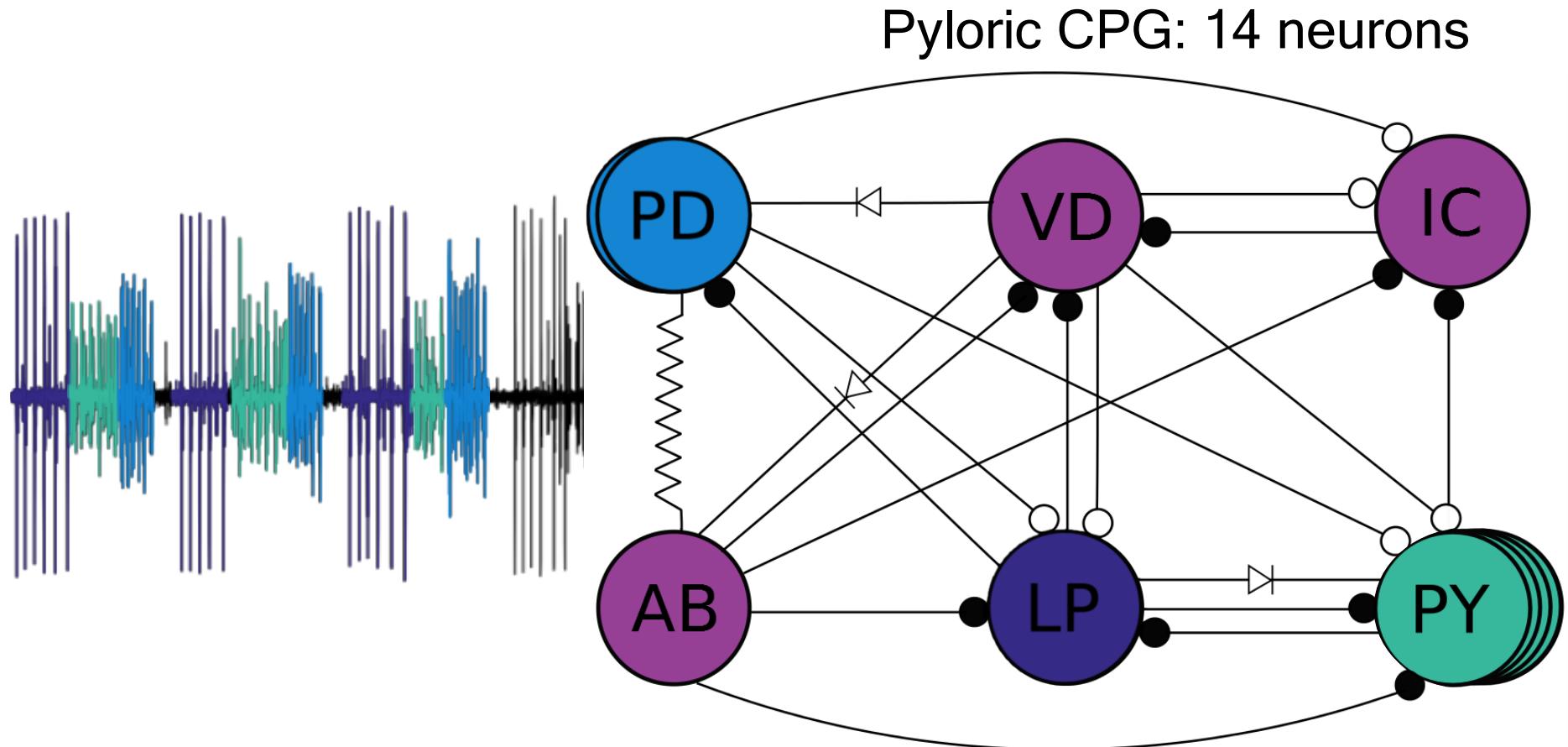


The color represents the latency of the postsynaptic spike with respect to the immediately preceding presynaptic spike.

Input/output preferences

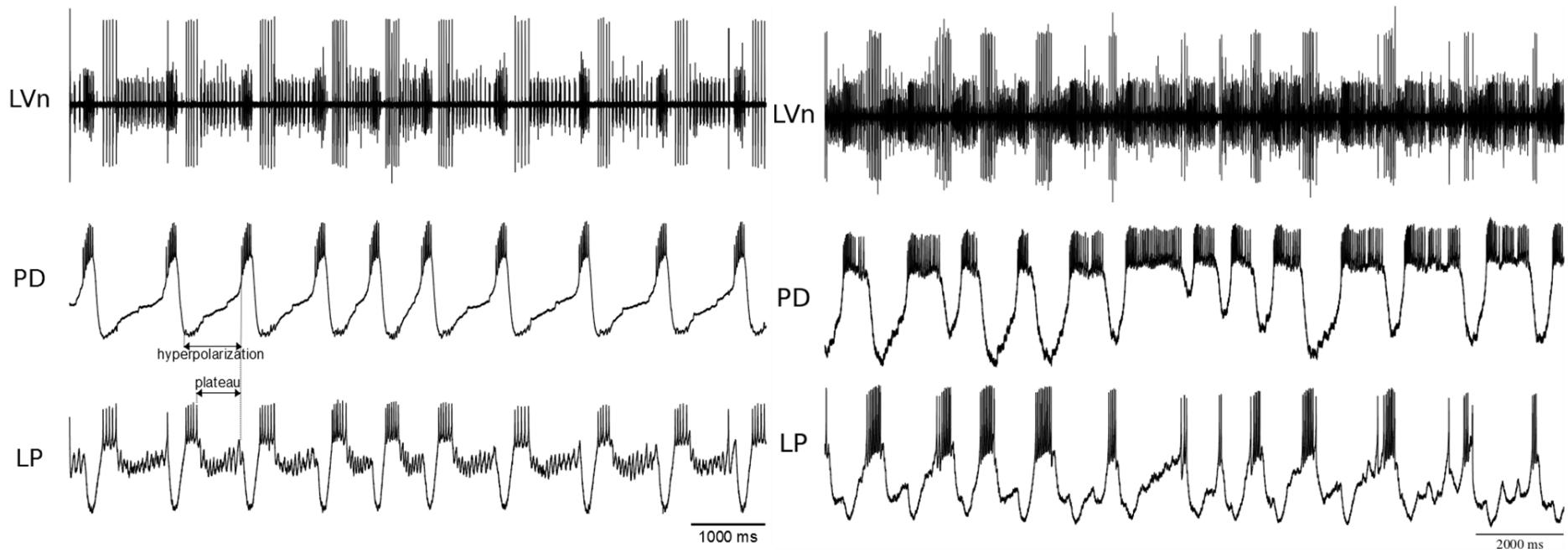


Pyloric CPG triphasic rhythm



Pyloric CPG irregular regimes

Regular Control	Irregular control (Intrinsic)	Ethanol
<ul style="list-style-type: none">Constant PD burst durationConstant LP burst durationConstant hyperpolarization	<ul style="list-style-type: none">Constant PD burst durationHigher variability in LP burst durationLP presents larger plateauIrregular hyperpolarization	<ul style="list-style-type: none">Flexible and very long PD burst durationRestricted LP spike burst durationIrregular hyperpolarization



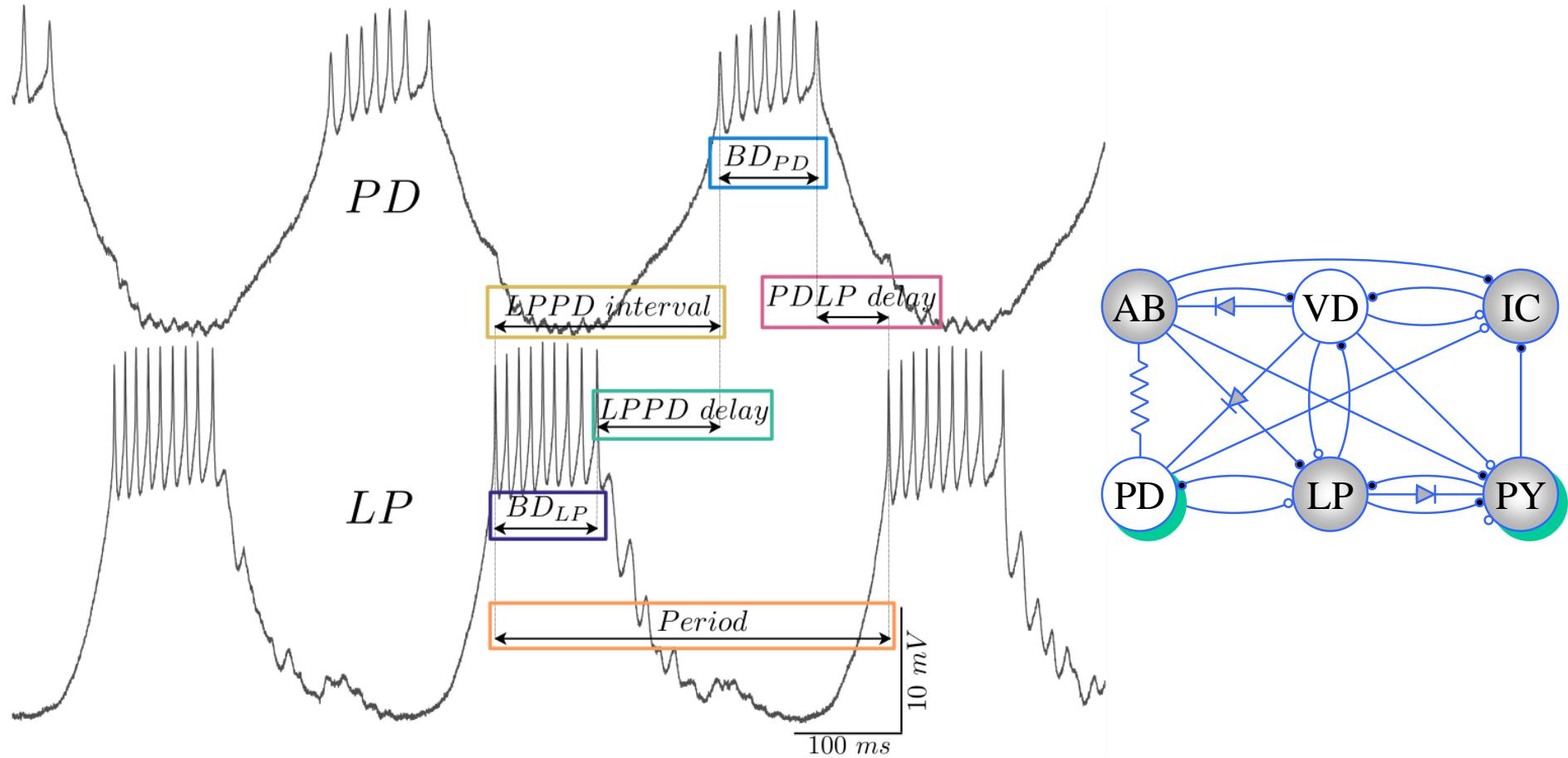
Intrinsic irregularity

Ethanol-induced irregularity

Why are CPG irregular regimes interesting?

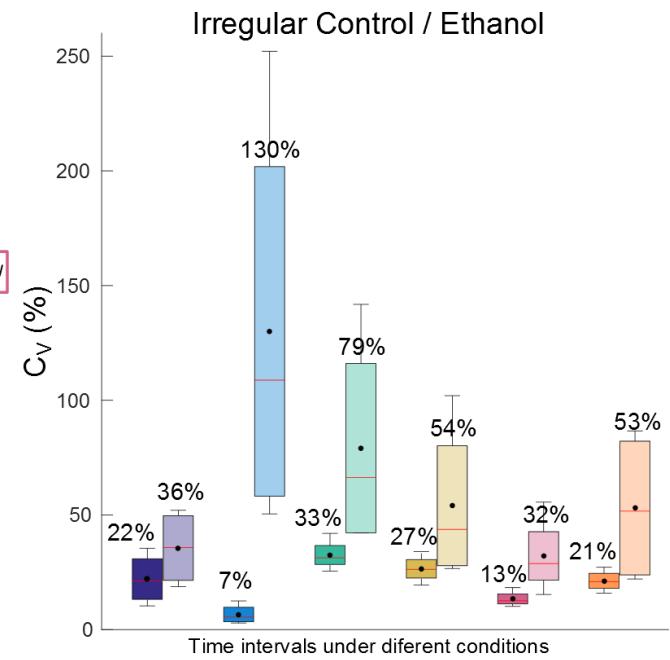
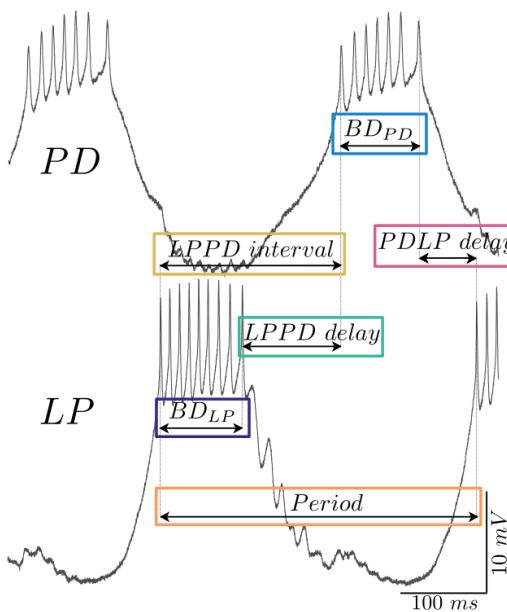
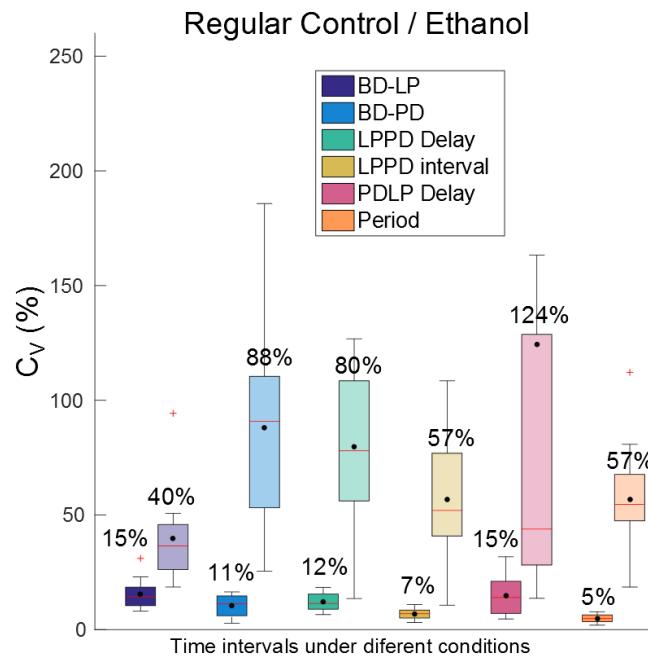
- Experimental and computational studies of CPGs typically examine their rhythmic output in steady states with regular spiking-bursting activity.
- Cycle by cycle analysis of irregular regimes can unveil important properties of the robust dynamics controlling rhythm coordination: i.e. dynamical invariants.
- Two sources of rhythm transients:
 - External outputs.
 - Intrinsic cell properties.
 - Topology of the circuit.
- Experimentally irregularity can be observed:
 - in control conditions, due to intrinsic properties of the circuit
 - under the effect of some chemicals

Sequence analysis & characterization

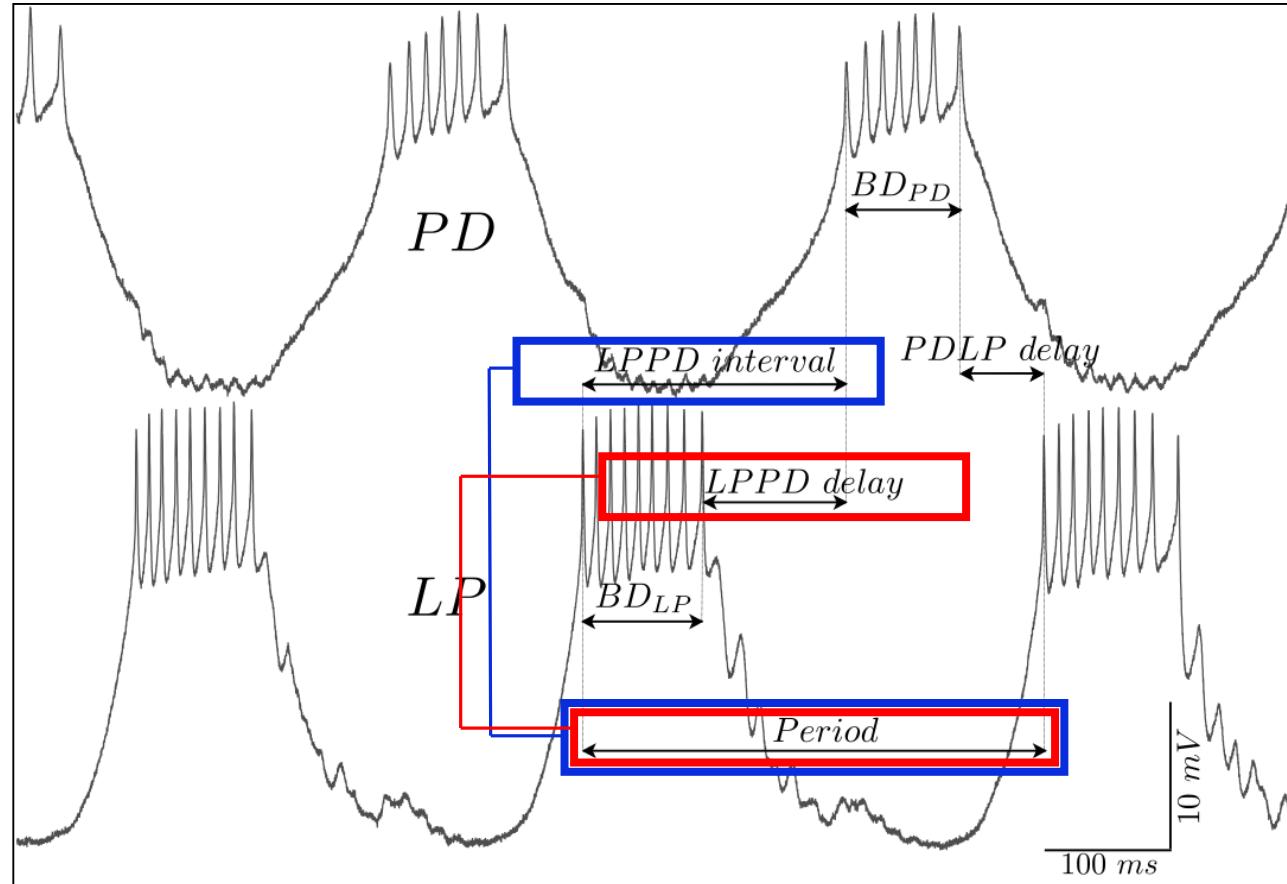


Variability analysis

$$C_v = \frac{\sigma}{\mu}$$

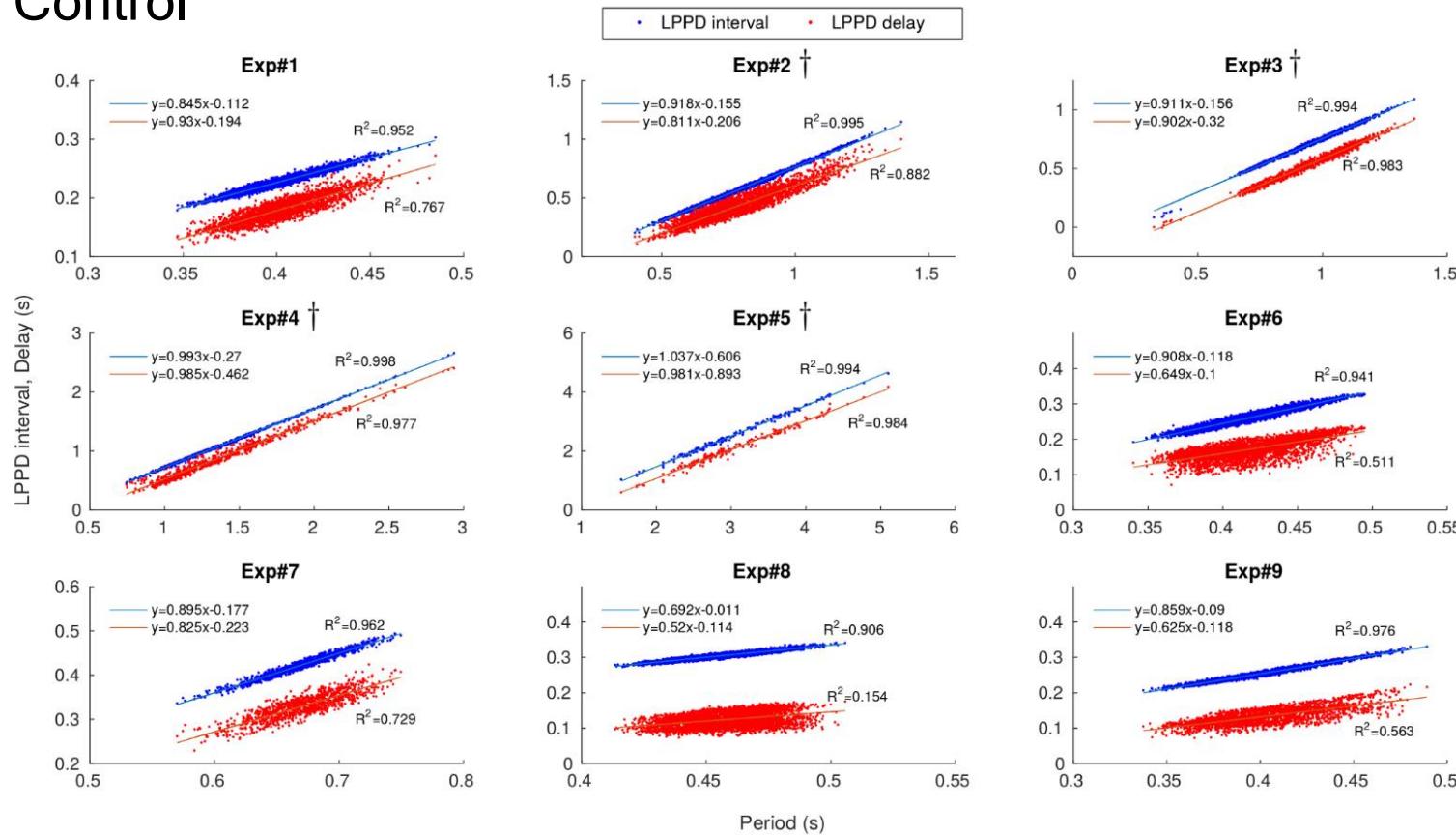


Pivotal intervals in the sequence



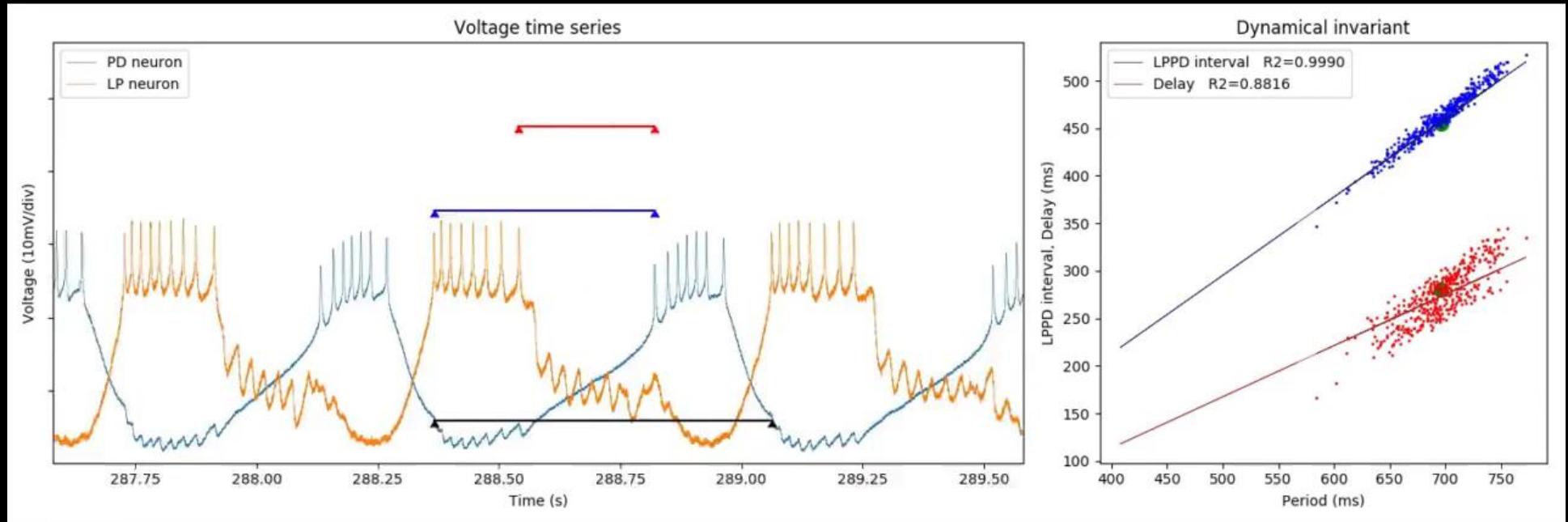
Dynamical invariants

- Control

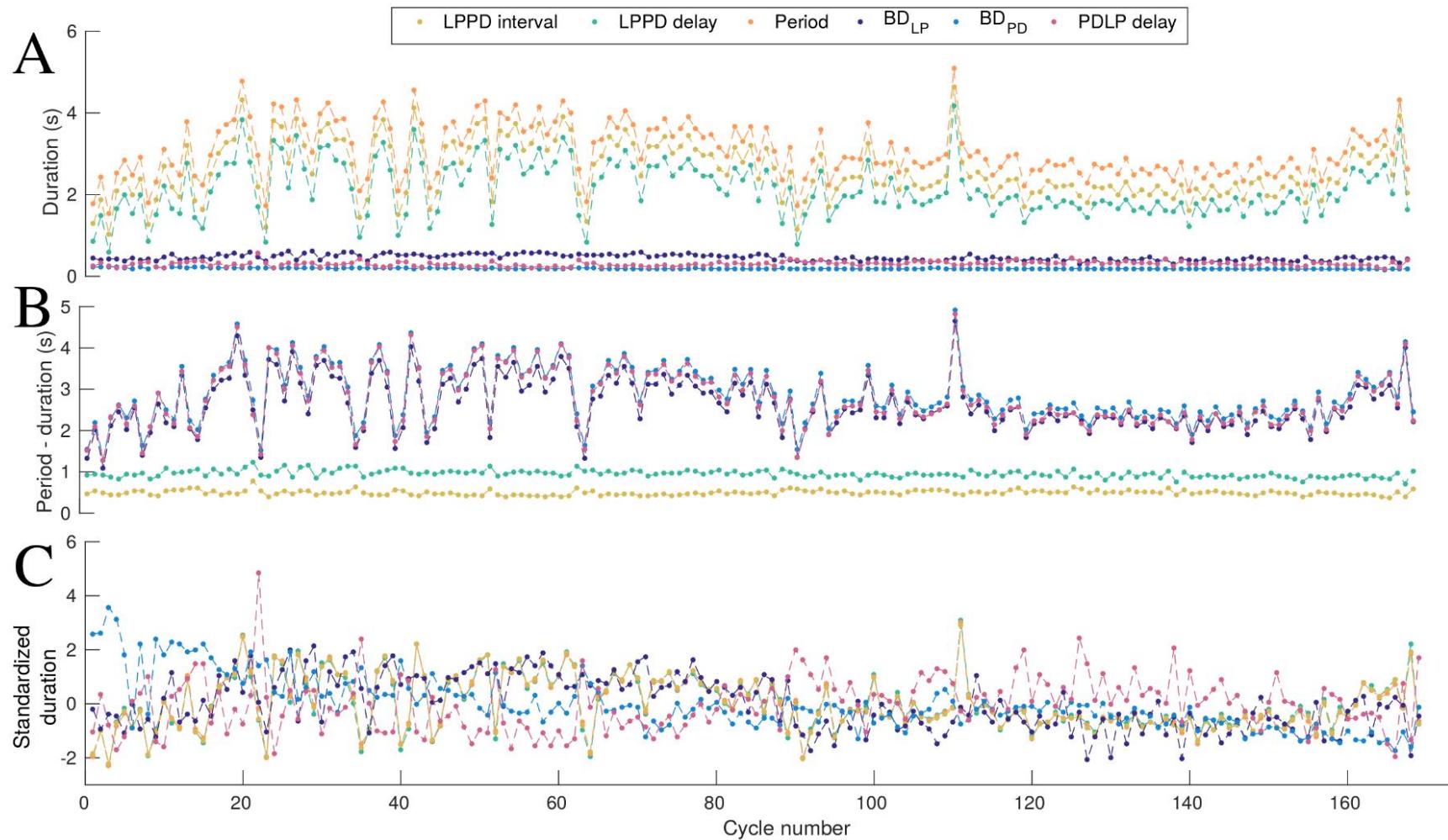


We found two dynamical invariants considering the measures analyzed: LPPD interval and Period and LPPD delay and Period.

Dynamical invariants



Cycle by cycle analysis

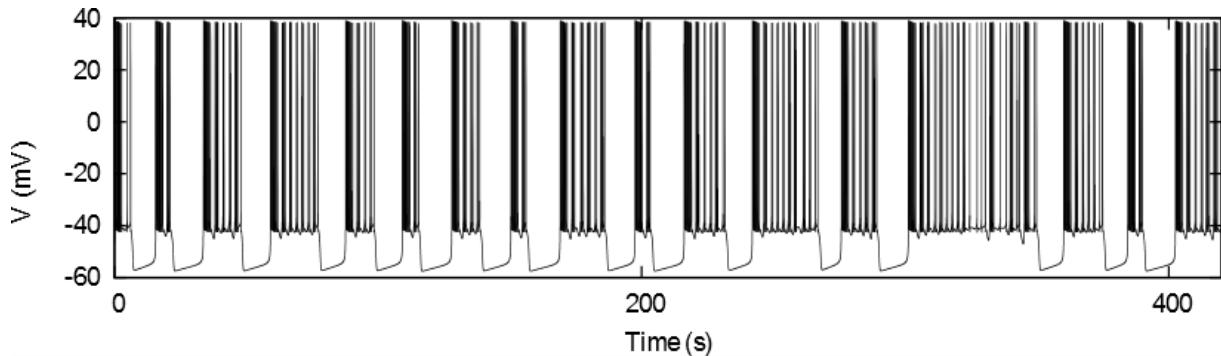
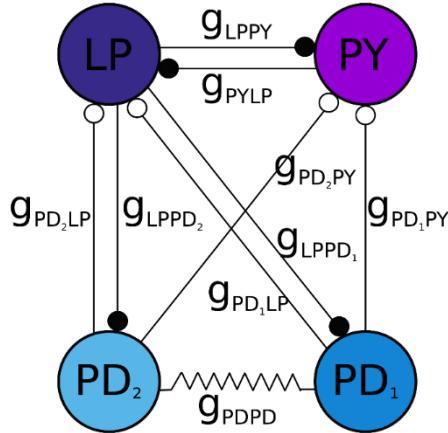


Elices, Levi, Arroyo, Rodriguez, and Varona, (2019). Robust dynamical invariants in sequential neural activity. *Scientific Reports* 9: 9048

CPG models

Can the results be reproduced in a model?

Conductance based model set in chaotic regime (Komendantov and Kononenko. 1996, *J. Theor. Biol.*)

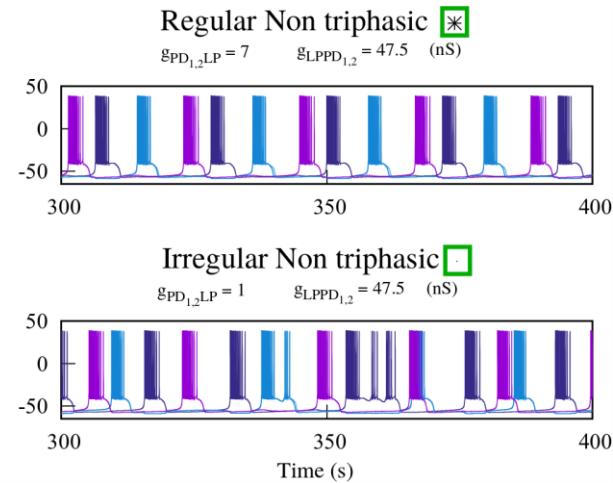
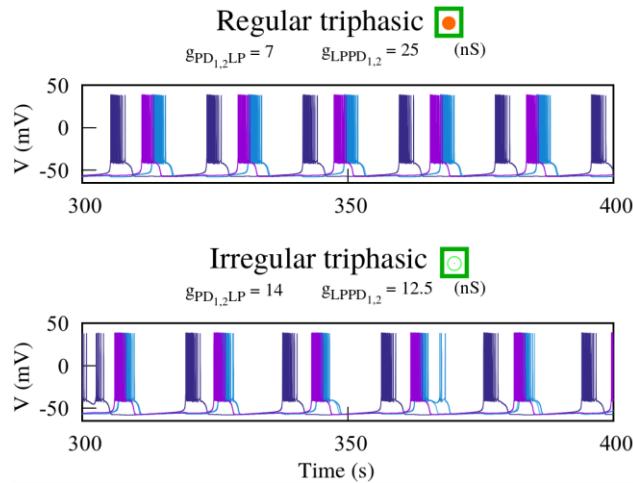


$$\bullet \longrightarrow I_{post}^f = \frac{g_{prepost}^f (V_{post} - E_{Syn})}{1.0 + \exp(s^f(V^f - V_{pre}))}$$

$$I_{post}^s = g_{prepost}^s m_{post}^s (V_{post} - E_{Syn})$$

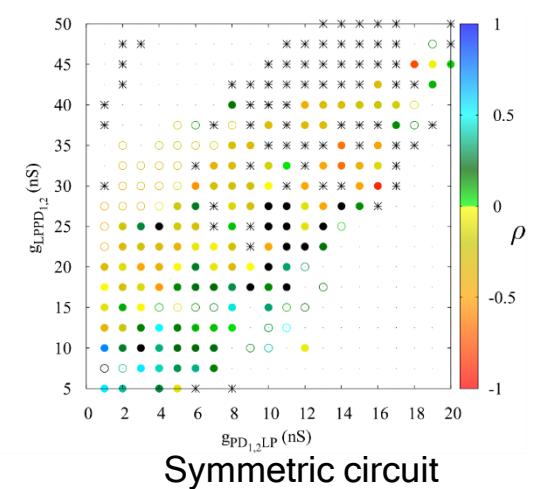
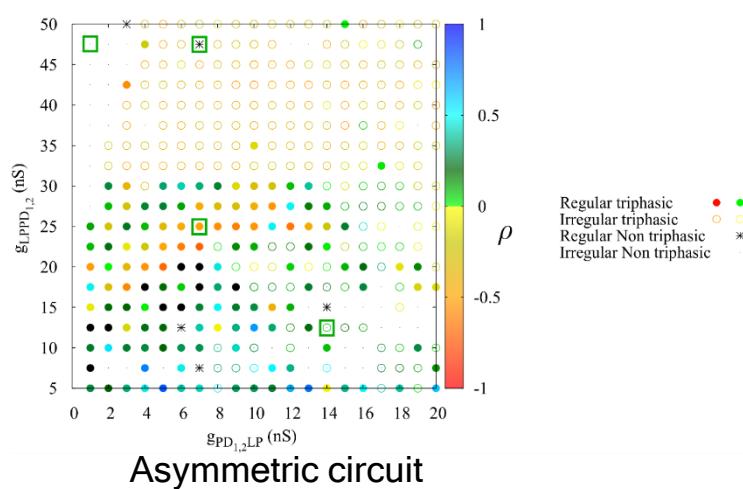
$$\textcircled{O} \longrightarrow \frac{dm_{post}^s}{dt} = \frac{k_1(1.0 - m_{post}^s)}{1.0 + \exp(s^s(V^s - V_{pre}))} - k_2 m_{post}^s$$

CPG models

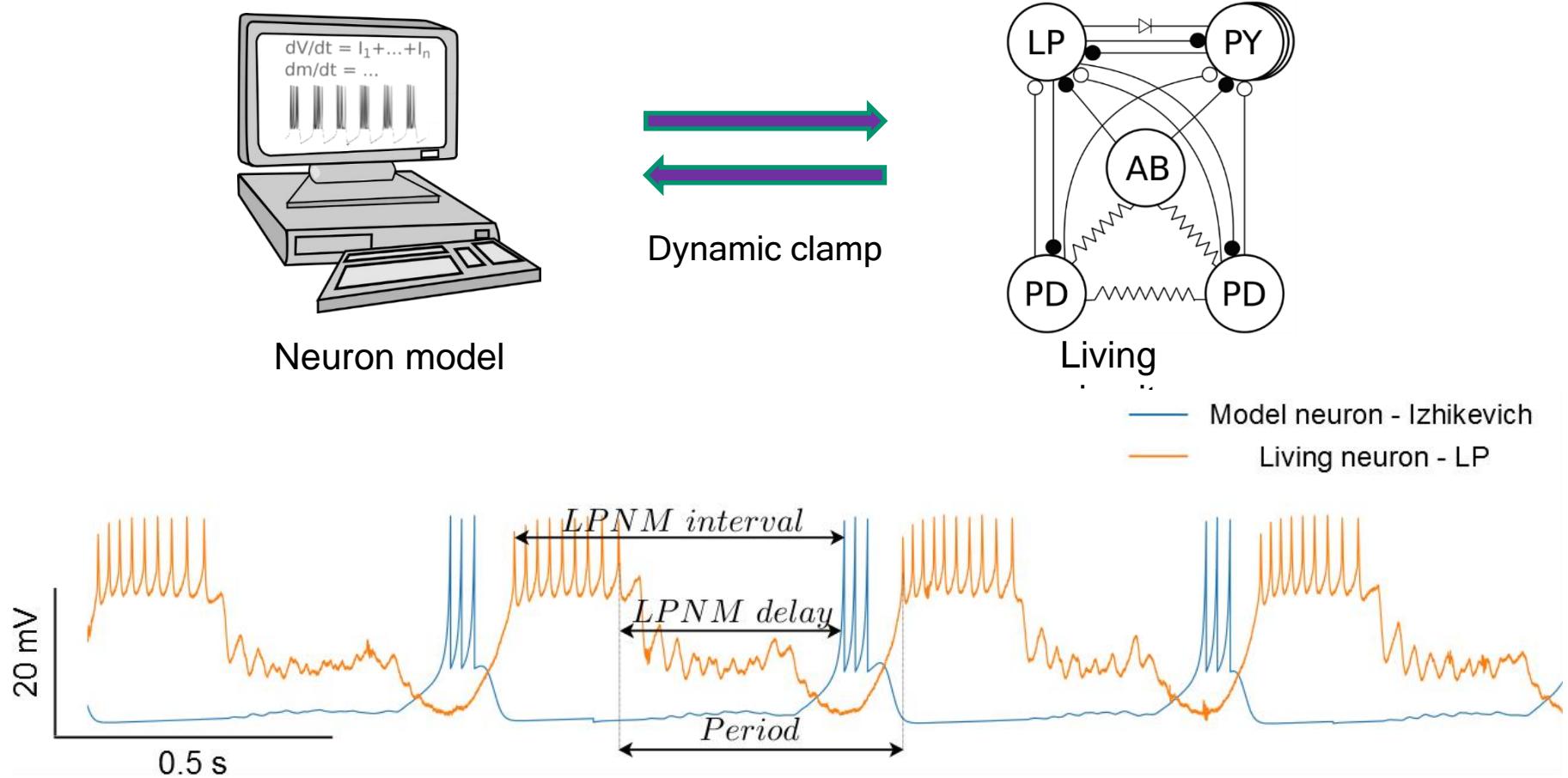


Asymmetric maximal conductances and synaptic time scales contribute to expand the **triphasic rhythm parameter space**.

Nontrivial dynamical invariants are not reproduced in the models.

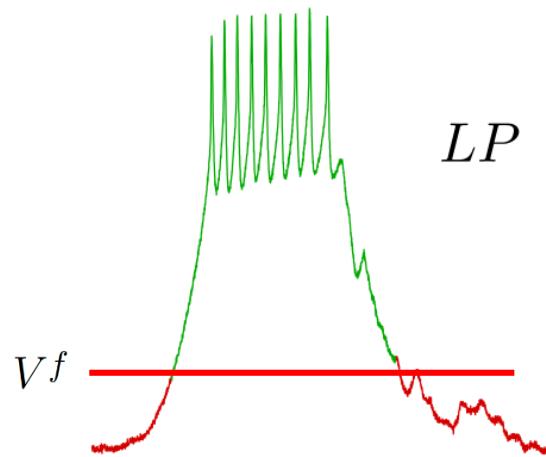


Hybrid circuits to address dynamical invariants



RTHybrid: www.github.com/GNB-UAM/RTHybrid

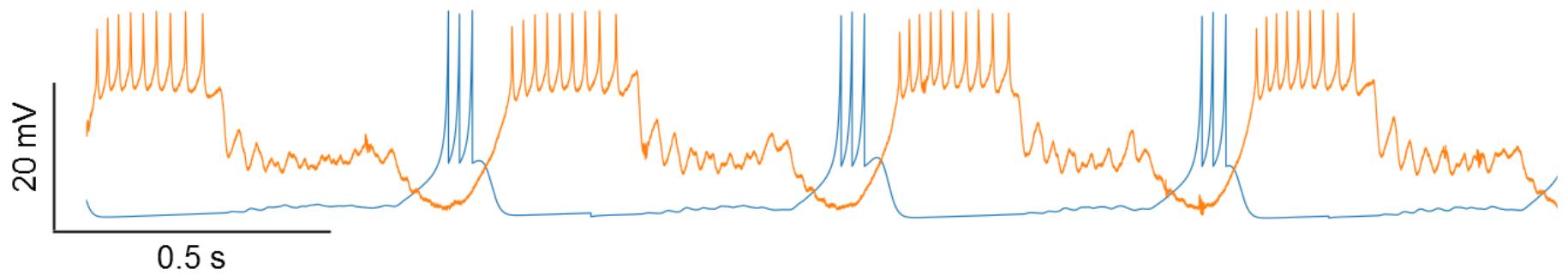
Hybrid connection



● → $I_{post}^f = \frac{g_{prepost}^f (V_{post} - E_{Syn})}{1.0 + \exp(s^f (V^f - V_{pre}))}$

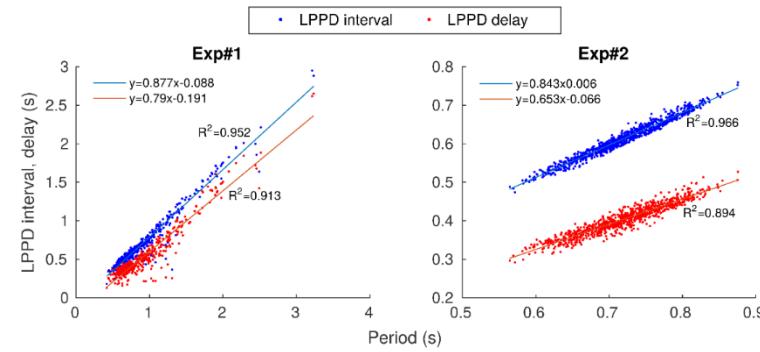
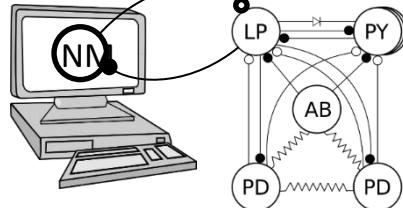
○ → $I_{post}^s = g_{prepost}^s m_{post}^s (V_{post} - E_{Syn})$

$$\frac{dm_{post}^s}{dt} = \frac{k_1(1.0 - m_{post}^s)}{1.0 + \exp(s^s(V^s - V_{pre}))} - k_2 m_{post}^s$$

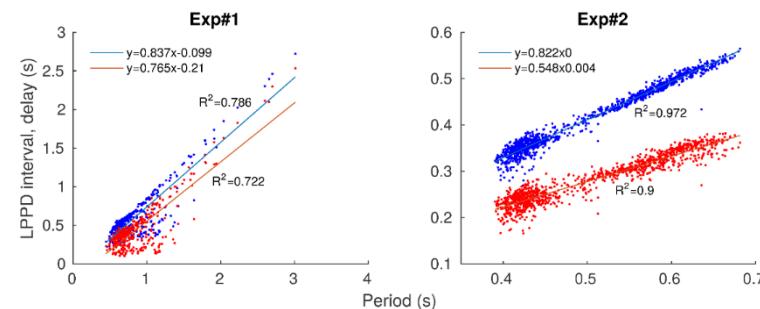
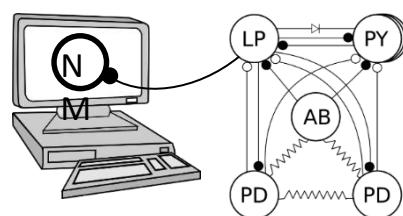


Hybrid circuit invariants

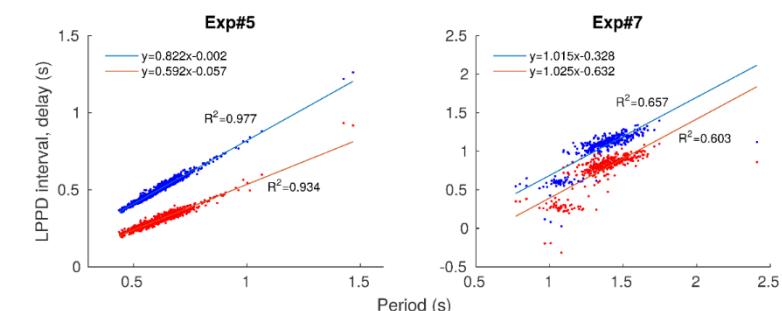
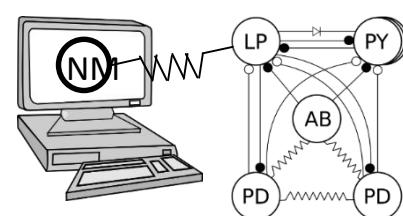
- Bidirectional chemical synapse



- Monodirectional fast chemical synapse from LP to neuron model



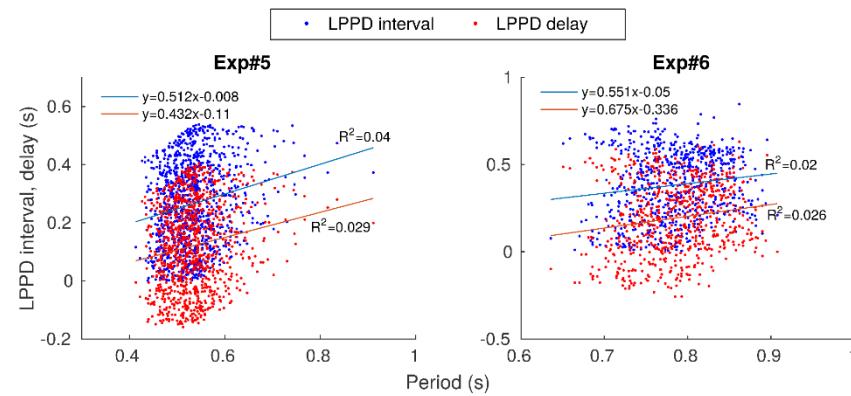
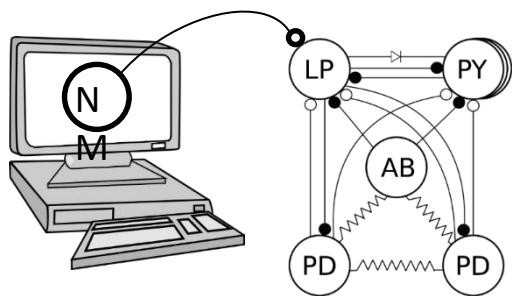
- Bidirectional negative electrical synapse



The dynamical invariants between **Period** and the analogous intervals **LPNM interval** and **LPNM delay** are propagated through bidirectional chemical and electrical synapsis and through a monodirectional chemical synapse from LP to the neuron model (NM). These invariants arise as a function of the connectivity parameters.

Hybrid circuit invariants

- Monodirectional slow chemical synapse from neuron model to LP



Monodirectional chemical synapses from the neuron model to the LP neuron **are not effective** to sustain the antiphase and therefore to propagate the invariants.