

Playing with neurons: isolated and coupled

R. Barrio¹

¹Computational Dynamics group (CODY), Dept. Applied Mathematics
University of Zaragoza, SPAIN

rbarrio@unizar.es, <http://cody.unizar.es>

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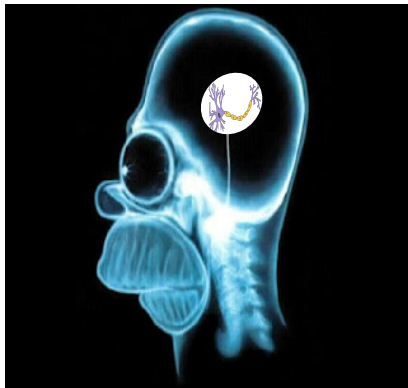
Motivation

Brain dynamics



Motivation

Brain dynamics: simplified model



Outline

- ▶ Study the parametric phase space of Neuron models
 - ▶ Chaotic structures and topological changes and Singular Perturbation limit
 - ▶ Central Pattern generators: coupled models
-

- 1 Study the parametric phase space of Neuron models
- 2 Template analysis and dependence on ε
- 3 Central Pattern generators: coupled models

Study the parametric phase space of Neuron models

Parametric phase space and main bifurcations

Hogkin and Huxley



Sir Andrew Fielding Huxley
(1917 - current)

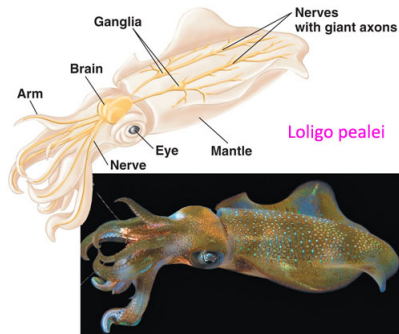


Sir Alan Lloyd Hodgkin
(1914 - 1998)

- Huxley and Hodgkin received the 1963 Nobel Prize in Physiology or Medicine for their work on action potentials together with John Carew Eccles who was cited for his work on synapses.
- Their work was one of the earliest applications of the then novel **voltage clamp** method to the **giant axon** of the Atlantic squid.

The Squid Giant Axon

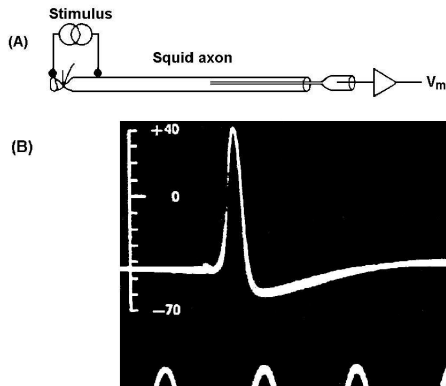
- The giant axon of the Atlantic Squid is part of its water propulsion system and optimized for speed. Since the axon is unmyelinated it requires a large diameter (up to 1 mm) to increase the conduction speed (up to 25 ms^{-1}).
- Fortuitously, the squid axon is also a very simple system with basically only two types of voltage dependent conductances.



squid giant axon

Due to its large size, the squid giant axon allowed Hodgkin and Huxley to insert the electrodes of the voltage clamp apparatus into the lumen of the axon. This ability combined with the system's simplicity was crucial for the success of their study of action potentials.

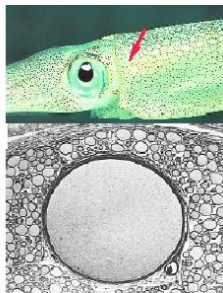
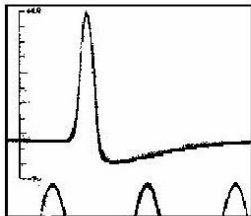
Measurement of Membrane Potential During Action Potential



- In the years 1939 and 1940 both Cole and Hodgkin successfully measured the action potential at the squid giant axon.
- The measurements revealed that the membrane potential not only goes toward zero (as proposed by Bernstein's theory) but actually significantly overshoots and reverses sign.

Mathematical neuron models

The Hodgkin-Huxley model is a mathematical model that describes how action potentials in neurons are initiated and propagated (1963 Nobel Prize in Medicine).



Other mathematical models:

FitzHugh-Nagumo model, Morris-Lecar model, **Hindmarsh-Rose model (1984)**, ...

The Hindmarsh and Rose model

The Hindmarsh and Rose model (1984)

A phenomenological system of ODEs for modeling bursting and spiking oscillatory activities in isolated neurons:

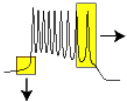
$$\begin{aligned}\dot{x} &= y - ax^3 + bx^2 - z + I \\ \dot{y} &= c - dx^2 - y \\ \dot{z} &= \varepsilon(s(x - x_0) - z)\end{aligned}\tag{1}$$

- x is treated as the membrane potential, while y and z describe some fast and slow gating variables for ionic currents.
- Slow “activation” of z is due to the small parameter $0 < \varepsilon \ll 1$.
- A key parameter is the external applied current I .

Fast-slow decomposition

Bursting classification (Rinzel-Izhikevich)

bifurcations of limit cycles



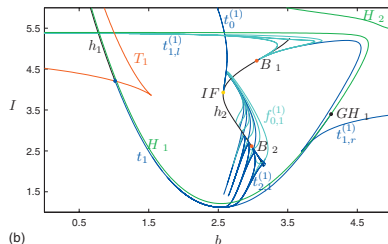
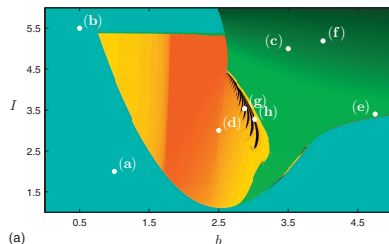
	saddle-node on invariant circle	saddle homoclinic orbit	supercritical Andronov- Hopf	fold limit cycle
saddle-node (fold)	fold/ circle	fold/ homoclinic	fold/ Hopf	fold/ fold cycle
saddle-node on invariant circle	circle/ circle	circle/ homoclinic	circle/ Hopf	circle/ fold cycle
supercritical Andronov- Hopf	Hopf/ circle	Hopf/ homoclinic	Hopf/ Hopf	Hopf/ fold cycle
subcritical Andronov- Hopf	subHopf/ circle	subHopf/ homoclinic	subHopf/ Hopf	subHopf/ fold cycle

Square-wave bursting (fold/**hom** bursting)

The Hindmarsh and Rose model

General bifurcation analysis: references

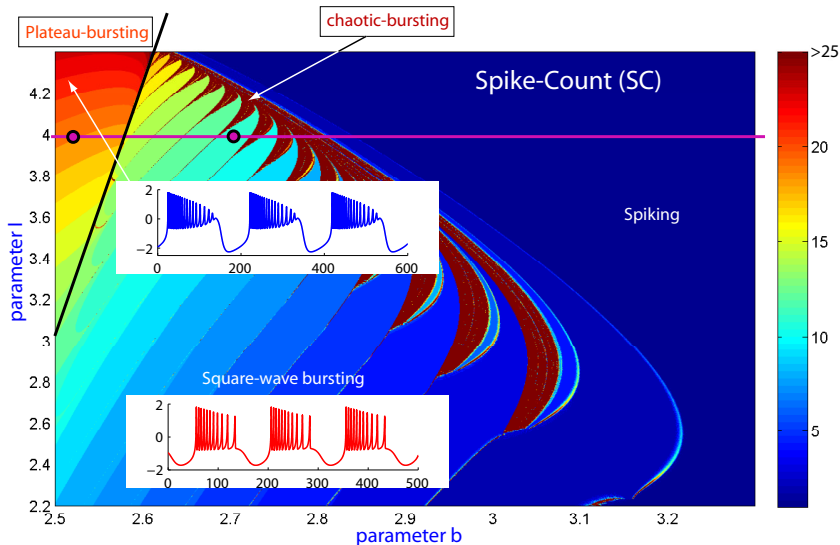
- M. Storace, D. Linaro, E. de Lange, Chaos 18 (2008).



- A. Shilnikov, M. Kolomiets, Int. J. Bifur. Chaos (2008).
- R. B., A. Shilnikov, Journal of Mathematical Neuroscience (2011).
- D. Linaro, A. Champneys, M. Desroches, M. Storace, SIADS (2012)
- R. B., M.A. Martinez, S. Serrano and A. Shilnikov, *Micro and Macro-Chaotic structures in the Hindmarsh-Rose neuron model*, Chaos, 2014.

The Hindmarsh and Rose model

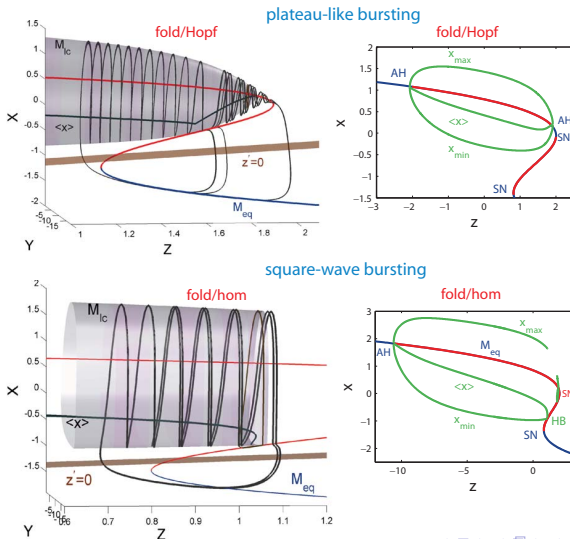
General brute-force analysis vs. particular ones: spike-count



The Hindmarsh and Rose model

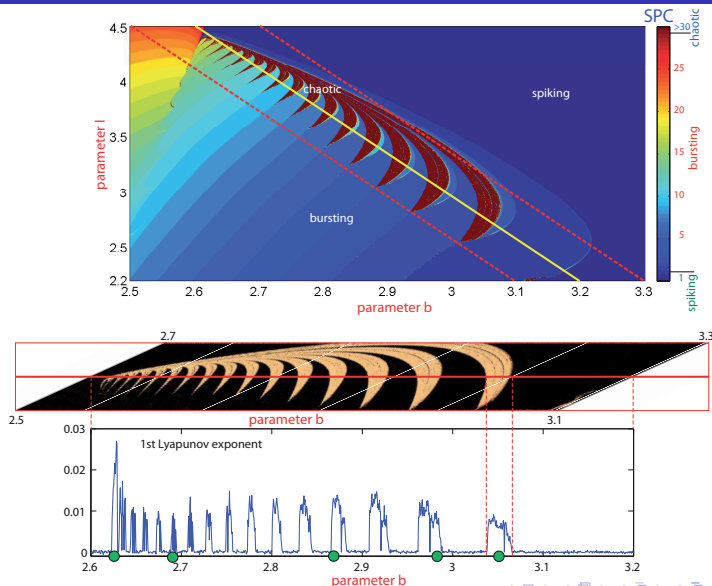
General brute-force analysis vs. particular ones: spike-count

So ... we can distinguish one kind of bursting from another one

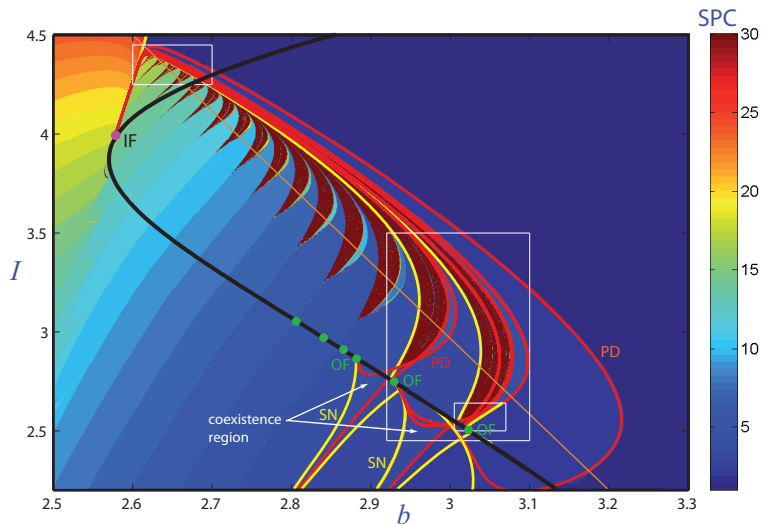


But ... why and where is the chaotic behavior?

Fast-slow system ... lets begin with $\varepsilon = 0.01$

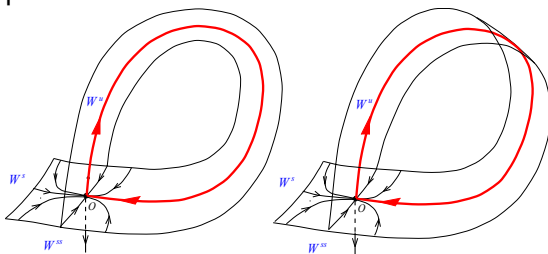


The Hindmarsh and Rose model: bifurcation analysis

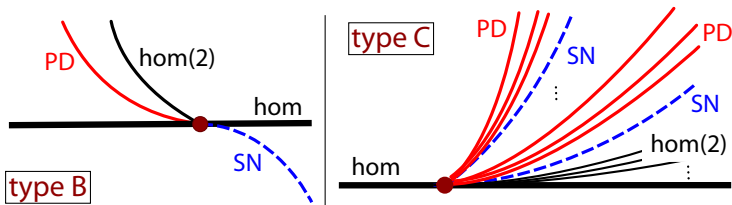


Codimension-two homoclinic bifurcation points

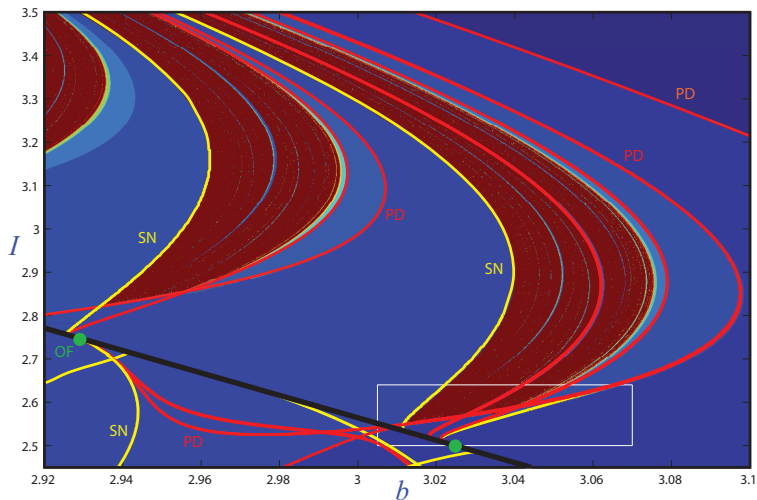
- Inclination flip



- Inclination flip + orbit flip homoclinic bifurcations

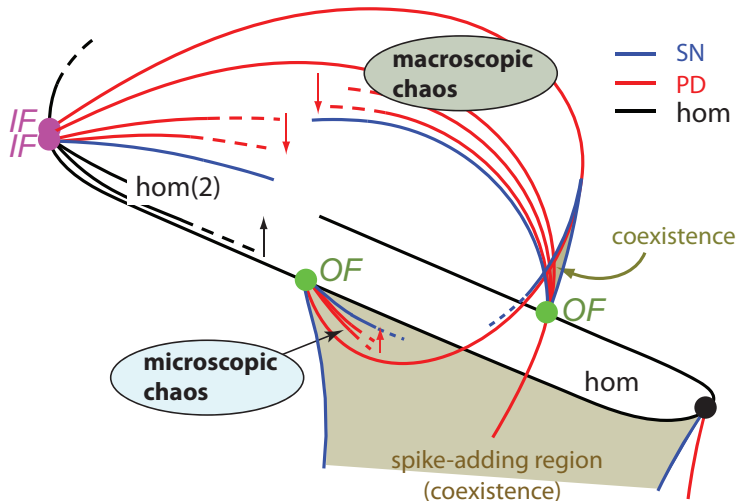


The Hindmarsh and Rose model



Hindmarsh and Rose: bifurcation sketch

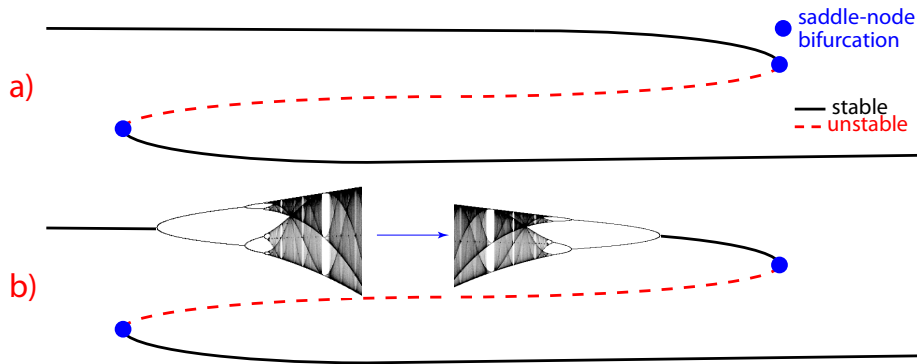
"a la Llinaro *et.al.*"¹⁹⁹⁶ + creation of chaotic structures



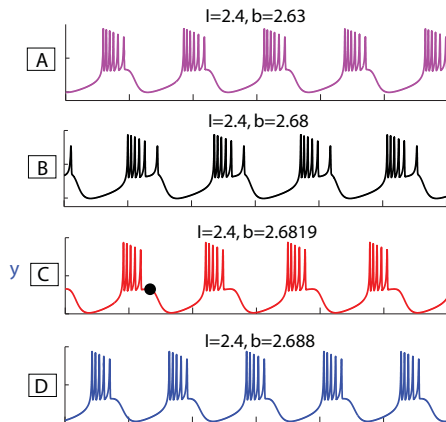
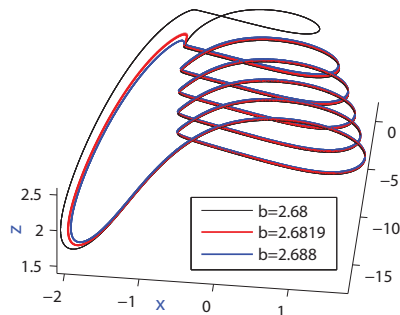
* D. Llinaro, A. Champneys, M. Desroches, M. Storace, SIAM J. Appl. Dyn. Syst., (2012)
R. Barrio, M. Martinez, S. Serrano, A. Shilnikov, *Chaos*, (2014).

Hysteresis: bistability in the spike-adding region

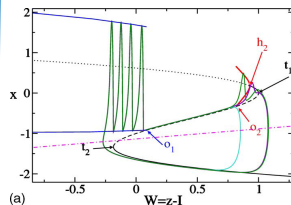
- Two bursting stable periodic orbits
- A “microscopic” chaotic bursting attractor and a stable periodic orbit



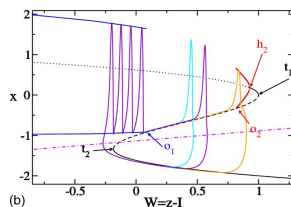
Classical spike adding process



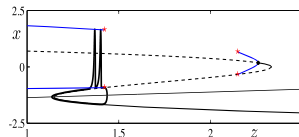
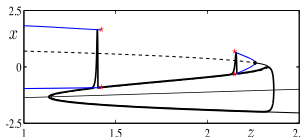
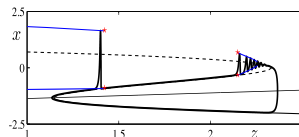
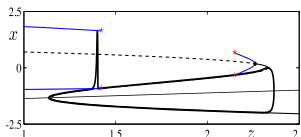
Classical spike adding process: canards[†]



(a)

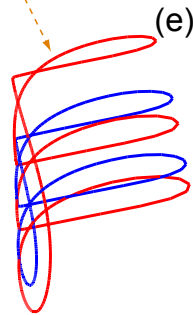
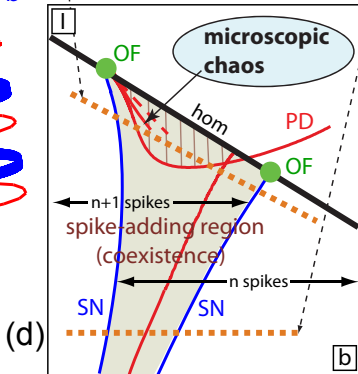
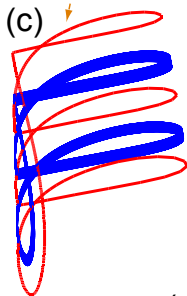
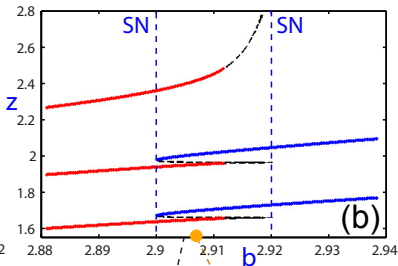
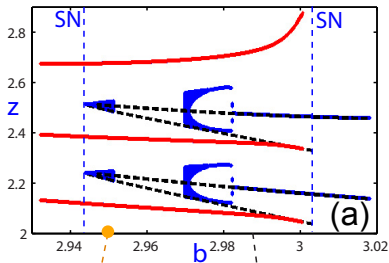


(b)

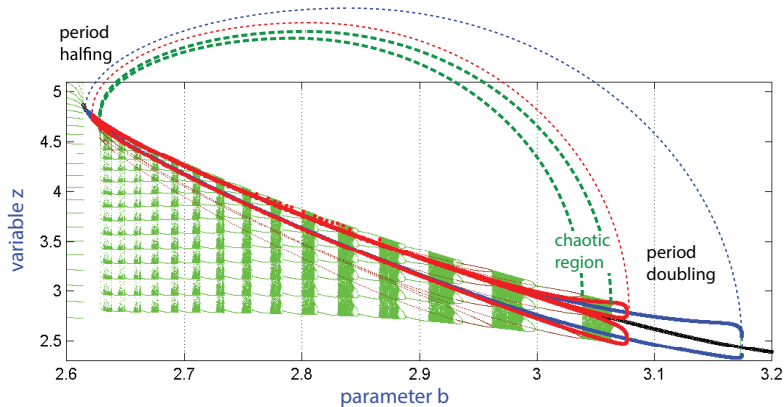


[†]M Desroches, TJ Kaper, M Krupa, *Mixed-mode bursting oscillations: Dynamics created by a slow passage through spike-adding canard explosion in a square-wave burster*, Chaos 23 (4), 046106, 2013.

G Innocenti, A Morelli, R Genesio, A Torcini, *Dynamical phases of the Hindmarsh-Rose neuronal model: studies of the transition from bursting to spiking chaos*, Chaos 17 (4), 043128, 2007.



The macro-chaotic structure



Template analysis of chaotic attractors and saddles

Topological templates

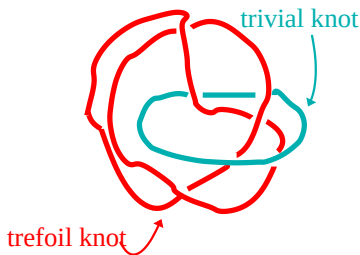
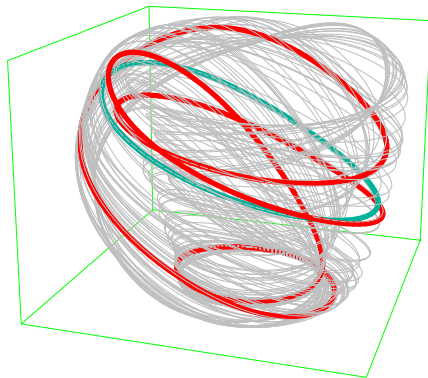
Given a three-dimensional (3D) hyperbolic chaotic flow Φ_t , Birman and Williams define the following equivalence relation which identifies points of the invariant set Λ having the same asymptotic future:

$$\forall x, y \in \Lambda, \quad x \sim y \Leftrightarrow \lim_{t \rightarrow \infty} \|\Phi_t(x) - \Phi_t(y)\| = 0$$

The Birman-Williams theorem states:

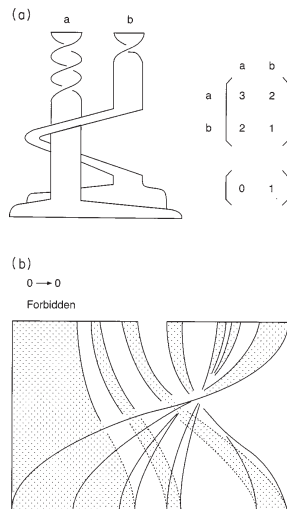
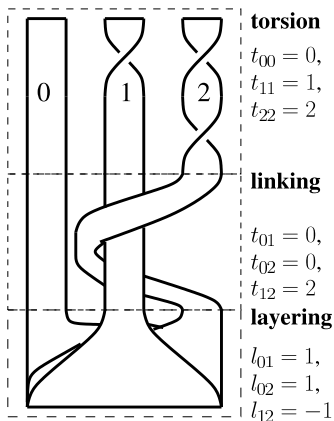
- 1 In the set of equivalence classes, the hyperbolic flow Φ_t induces a semi-flow $\bar{\Phi}_t$ on a branched manifold $\mathcal{K}$. The pair $(\bar{\Phi}_t, \mathcal{K})$ is called a *template*, or knot-holder
- 2 Unstable periodic orbits of Φ_t in Λ are in one-to-one correspondence with unstable periodic orbits of $(\bar{\Phi}_t, \mathcal{K})$. Moreover, every link of unstable periodic orbits of (Φ_t, Λ) is isotopic to the corresponding link of $(\bar{\Phi}_t, \mathcal{K})$.

Topological templates



Left: two periodic orbits of periods 1 and 4 embedded in a strange attractor; Right: a link of two knots that is equivalent to the pair of periodic orbits up to continuous deformations without crossings.

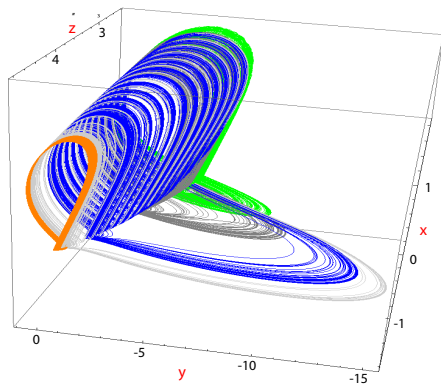
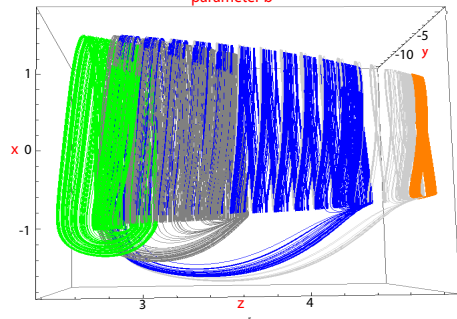
Topological templates: subtemplates



The Hindmarsh and Rose model: chaotic attractors

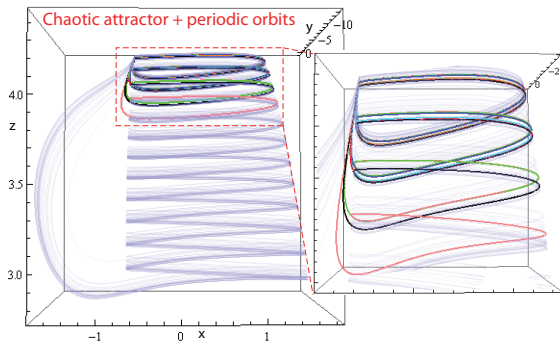
■ $b=3.05$ ■ $b=2.87$ ■ $b=2.69$ ■ $b=2.635$ ■ $b=2.625$

← parameter b

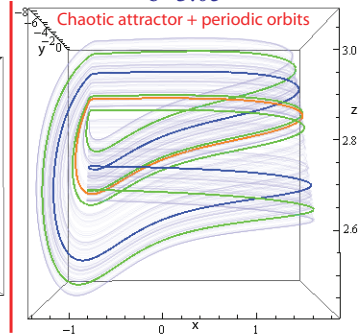


The Hindmarsh and Rose model: periodic orbits (towards a template analysis)

$b=2.69$

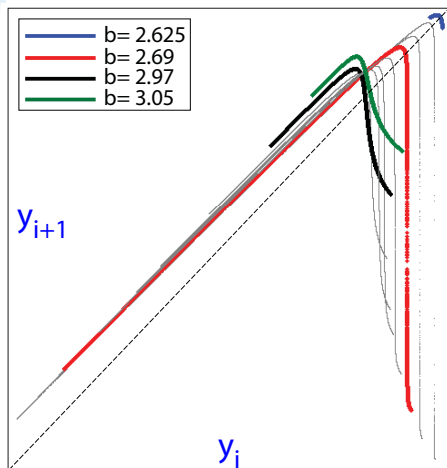


$b=3.05$



- Stability Transformation (Schemelcher and Diakonov) +
+ Optimized Newton method

The Hindmarsh and Rose model: first return map (towards a template analysis[‡])

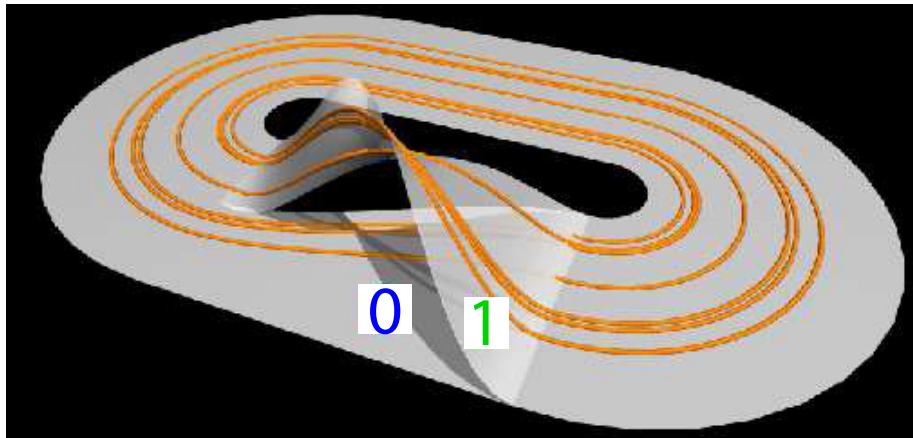


- Unimodal maps $\longrightarrow$ Two-branches topological templates.
- Three symbols are not necessary, although useful in some interpretations (X.J. Wang, *Physica D*, 62 (1995))
- Quite complex linking matrices
- Complete topological model (B., Lefranc, Martinez, Serrano 2015)

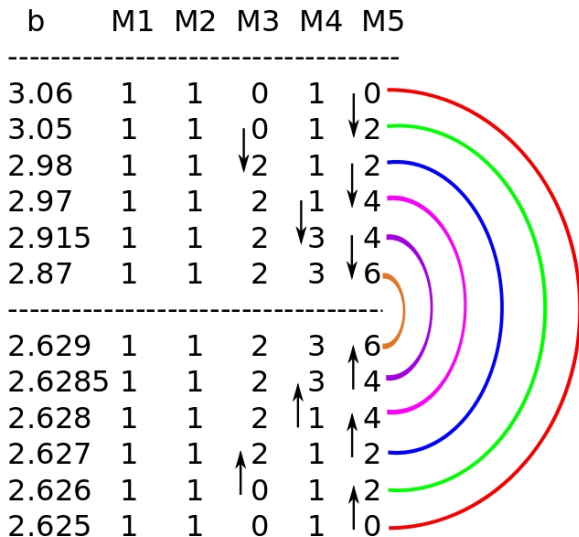
[‡]Barrio, R., Lefranc, M., Martinez, M.A., Serrano, S., *EPL* (2015).

Topological templates: Hindmarsh and Rose model

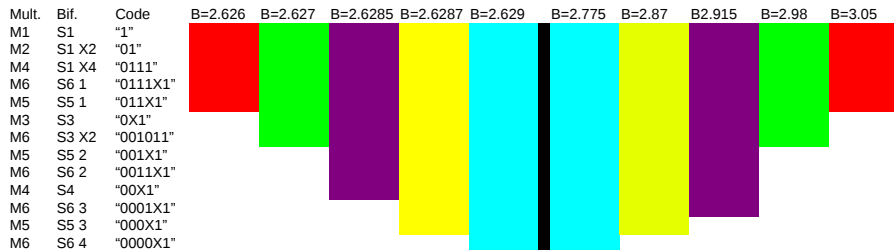
Hundreds of UPO's $\longrightarrow$ Global template: **Smale's template**



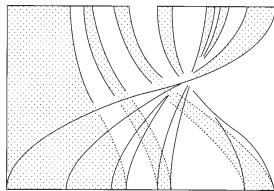
Topological templates: Hindmarsh and Rose model



Topological templates: Hindmarsh and Rose model

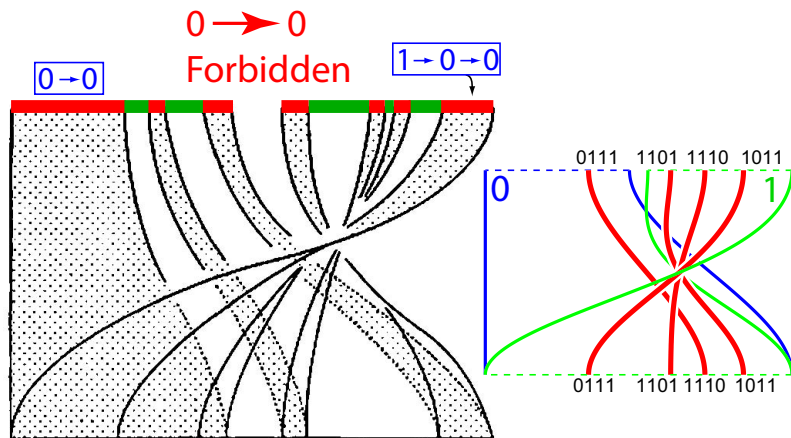


The topological template for the HR model is the Smale's horseshoe template but with **forbidden "lanes"**.



The templates follows the "onion" structure.

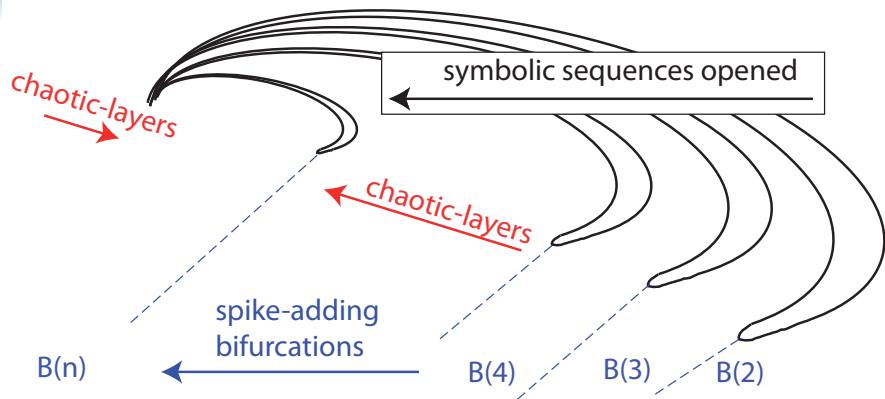
Topological templates: successive Cantor structures



✚ Theoretical framework[§] for the “onion-bulb” chaotic structures

[§]Barrio, R., Lefranc, M., Martinez, M.A., Serrano, S., *EPL* (2015).

Scheme of the macroscopic chaotic structures ($\forall \epsilon$)



Singular Perturbed limit

Let's consider an autonomous system written in the form (*slow-fast system* on *fast-time* formulation)

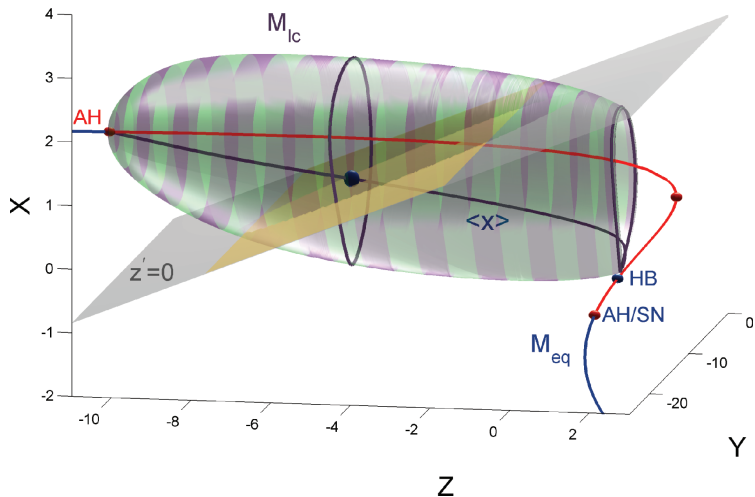
$$\begin{aligned}\dot{\mathbf{x}} &= f(\mathbf{x}, z; \varepsilon) = f_0(\mathbf{x}, z) + \varepsilon^2 \dots, & \mathbf{x} \in D \subset \mathbb{R}^2, \\ z &= \varepsilon \dot{g}(\mathbf{x}, z; \varepsilon) = \varepsilon \dot{g}_0(\mathbf{x}, z) + \varepsilon^2 \dots, & z \in G \subset \mathbb{R},\end{aligned}$$

where ε is a small parameter.

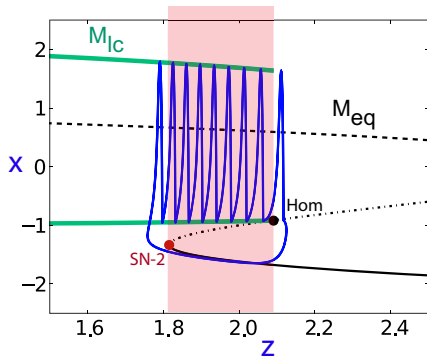
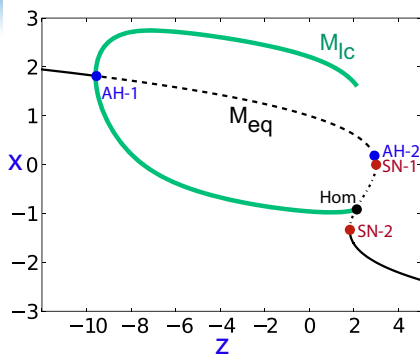
A phase point in the phase space of the HR model at $\varepsilon = 0$ converges to an attractor of its fast subsystem.

The attractor is either a stable equilibrium or a stable limit cycle. By varying z , we obtain a smooth attracting invariant manifold, which can be a space curve like M_{eq} in the phase space, or a two-dimensional cylinder M_{lc} spanned by the limit cycles of the fast subsystem ($\dot{\mathbf{x}} = f(\mathbf{x}, z; \varepsilon)$).

Fast-slow decomposition

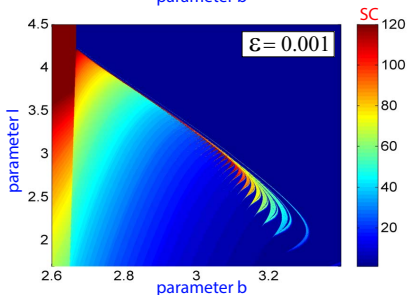
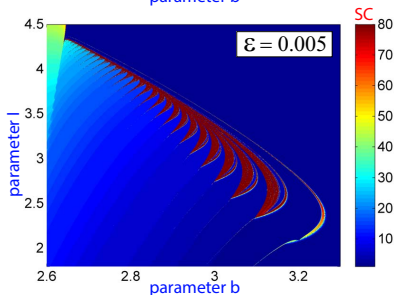
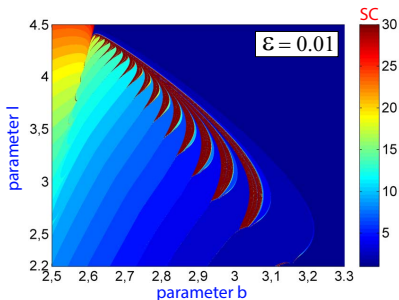
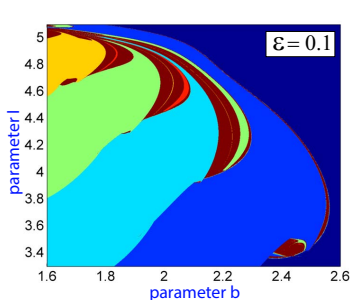


Fast-slow decomposition

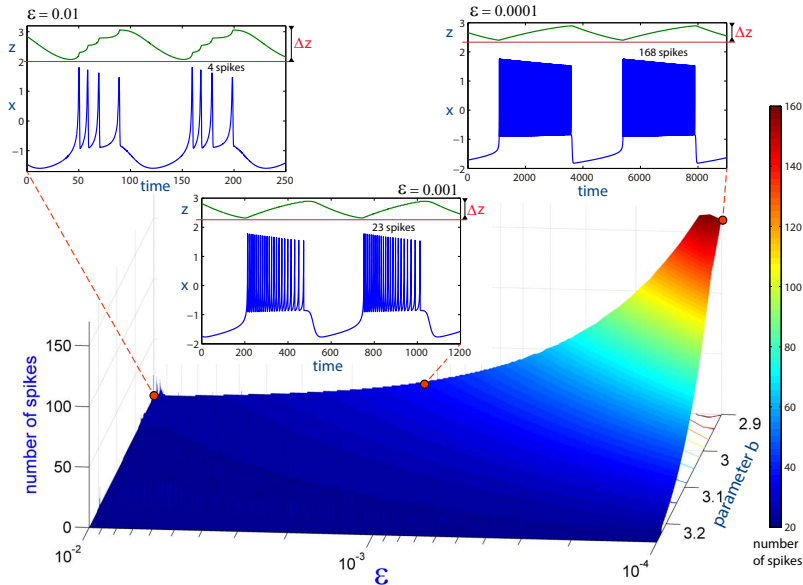


Spikes are located ($\mathcal{O}(\varepsilon)$) in the z interval $[SN_2, Hom]$, that is, it is determined by the time it needs to drift from the stable branch of M_{eq} to the homoclinic edge on M_{lc}

Dependence on ε

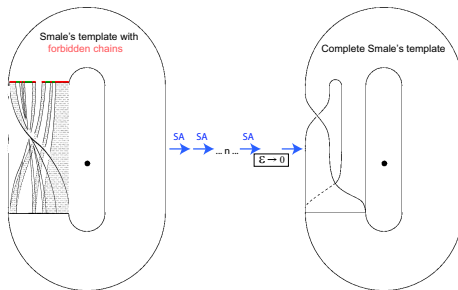


Dependence on ε



Dependence on ε

- The size of the n -spike-adding windows decreases when n grows and decreases with ε
- As from the Fenichel's theory the evolution of the z variable restricted to the spiking invariant manifold converges to the limiting case for $\varepsilon \searrow 0$ (the stable limit cycle) and therefore $(z_{\max} - z_{\min}) \searrow 0$.
- Therefore, the chaotic attractor will have a **more complex organization and more UPO's foliated** to it but it will be more compact, without spreading a lot in the phase space.



Realistic model: the leech heart interneuron model

The leech heart interneuron model (Shilnikov, Calabrese, Cymbalyuk (2005))

A phenomenological system of ODEs for modeling bursting and spiking oscillatory activities of a leech heart interneuron (derived through the Hodgkin-Huxley formalism):

$$C \frac{dV}{dt} = -I_{Na} - I_{K2} + I_L - I_{app} - I_{syn},$$

$$I_L = \bar{g}_L (V - E_L), I_{K2} = \bar{g}_{K2} m_{K2}^2 (V - E_K),$$

$$I_{Na} = \bar{g}_{Na} m_{Na}^3 h_{Na} (V - E_{Na}), m_{Na} = m_{Na}^\infty(V),$$

$$\tau_{Na} \frac{dh_{Na}}{dt} = h_{Na}^\infty(V) - h_{Na},$$

$$\tau_{K2} \frac{dm_{K2}}{dt} = m_{K2}^\infty(V) - m_{K2},$$

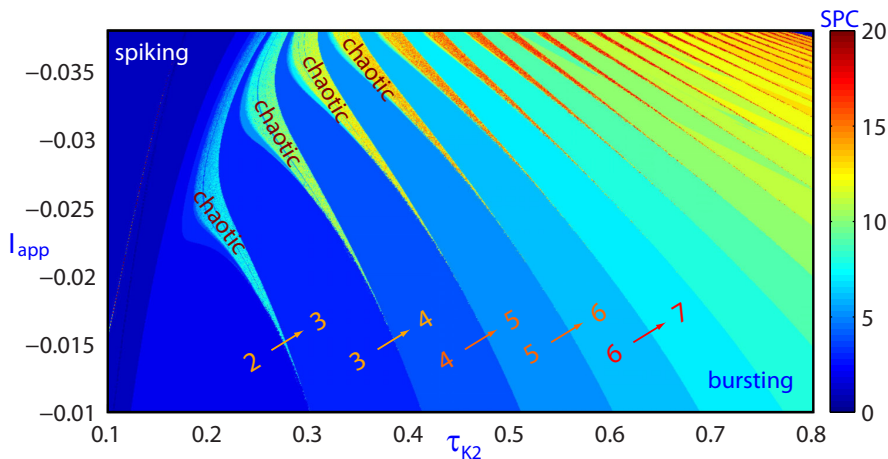
$$h_{Na}^\infty(V) = [1 + \exp(500(0.0333 - V))]^{-1},$$

$$m_{Na}^\infty(V) = [1 + \exp(-150(0.0305 - V))]^{-1}, \quad (2)$$

$$m_{K2}^\infty(V) = [1 + \exp(-83(0.018 - V + V_{K2}^{shift}))]^{-1}.$$

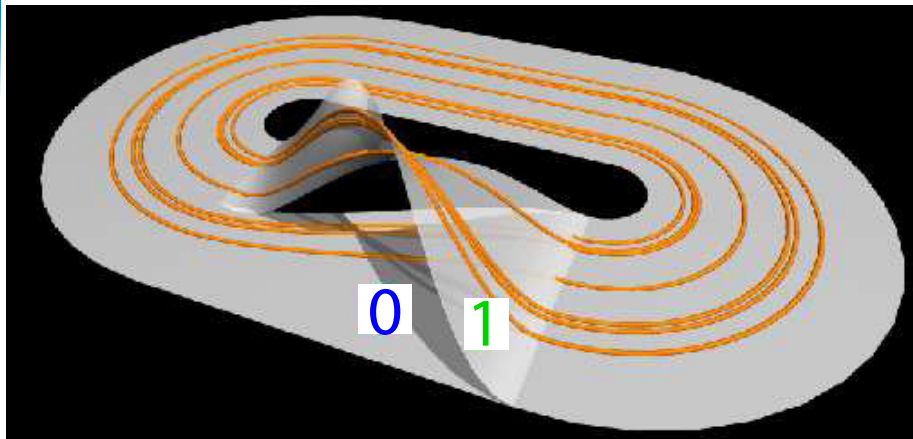
- I_{app} is the external applied current.
- V_{K2}^{shift} is the deviation from experimentally average voltage value.

The leech heart interneuron model



- Onion-like structures.
- Spike-adding bifurcations $\longrightarrow$ UPOs foliated in the attractor $\longrightarrow$??

Topological templates: Leech neuron model

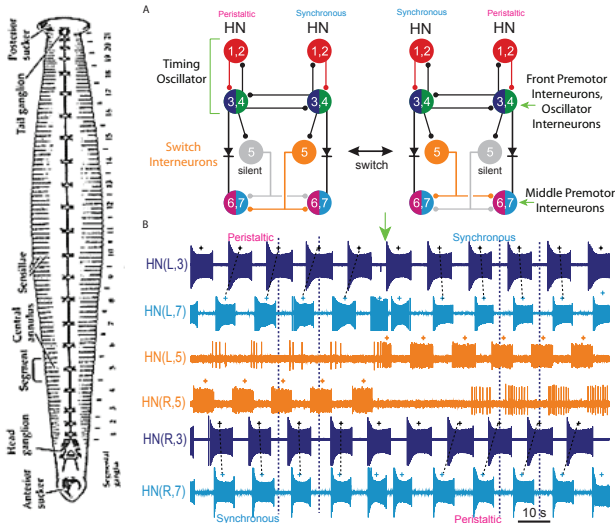


The same topological template^a
as the Hindmarsh-Rose simplified model !!

^aBarrio, R., Lefranc, M., Serrano, S., *preprint* (2016).

Central Pattern generators: coupled model of leech heart interneurons

The leech heart interneuron model**



** Weaver, A.L., Roffman, R.C., Norris, B.J., Calabrese, R.L. A role for compromise: synaptic inhibition and electrical coupling interact to control phasing in the leech heartbeat CPG. *Frontiers in behavioral neuroscience*. 2010.

Simple models: networks of oscillators

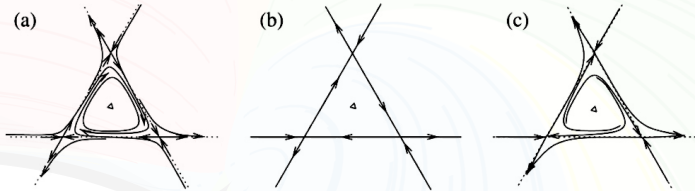
P. Ashwin, O. Burylko, Y. Maistrenko

A model for globally coupled phase oscillators

$$\dot{\theta}_i = \omega_i + \frac{K}{3} \sum_{j=1}^3 g(\theta_i - \theta_j)$$

with $g(x) = -\sin(x - \alpha) + r \sin(2x)$.

$\mathbb{Z}_3$ -heteroclinic bifurcation



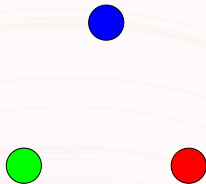
Synaptic connections

Consider a network of neurons:

$$\begin{cases} C V' = -I_{\text{Na}} - I_{\text{K2}} - I_{\text{L}} - I_{\text{app}} \\ \tau_{\text{Na}} h'_{\text{Na}} = h_{\text{Na}}^{\infty}(V) - h_{\text{Na}} \\ \tau_{\text{K2}} m'_{\text{K2}} = m_{\text{K2}}^{\infty}(V; V_{\text{K2}}^{\text{shift}}) - m_{\text{K2}} \end{cases}$$

$$\begin{cases} V' = \dots \\ h'_{\text{Na}} = \dots \\ m'_{\text{K2}} = \dots \end{cases}$$

$$\begin{cases} V' = \dots \\ h'_{\text{Na}} = \dots \\ m'_{\text{K2}} = \dots \end{cases}$$



Synaptic connections

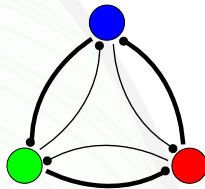
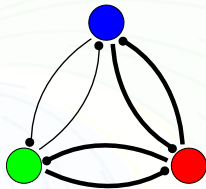
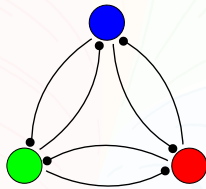
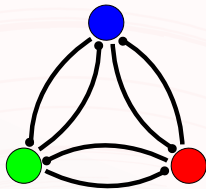
Consider a network of neurons:

$$\begin{cases} C V' = -I_{\text{Na}} - I_{\text{K2}} - I_{\text{L}} - I_{\text{app}} - I_{\text{syn}} \\ \tau_{\text{Na}} h'_{\text{Na}} = h_{\text{Na}}^{\infty}(V) - h_{\text{Na}} \\ \tau_{\text{K2}} m'_{\text{K2}} = m_{\text{K2}}^{\infty}(V; V_{\text{K2}}^{\text{shift}}) - m_{\text{K2}} \end{cases}$$

$$\begin{cases} V' = \dots \\ h'_{\text{Na}} = \dots \\ m'_{\text{K2}} = \dots \end{cases}$$

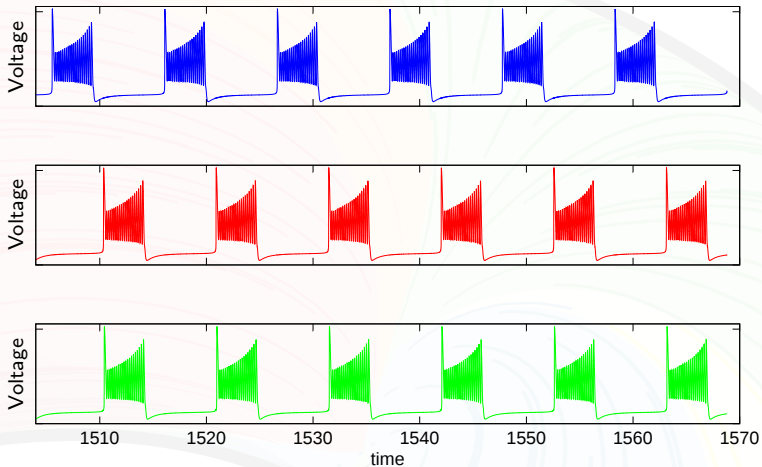
$$\begin{cases} V' = \dots \\ h'_{\text{Na}} = \dots \\ m'_{\text{K2}} = \dots \end{cases}$$

where $I_{\text{syn}} = \text{function}(V, V, V)$.

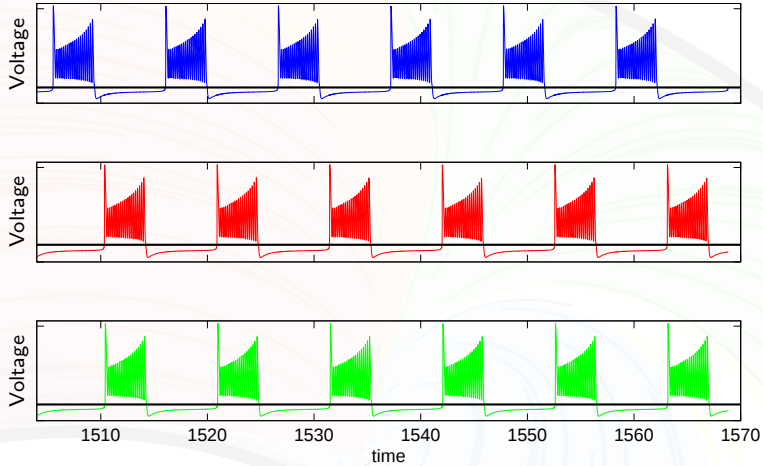


Convergence patterns

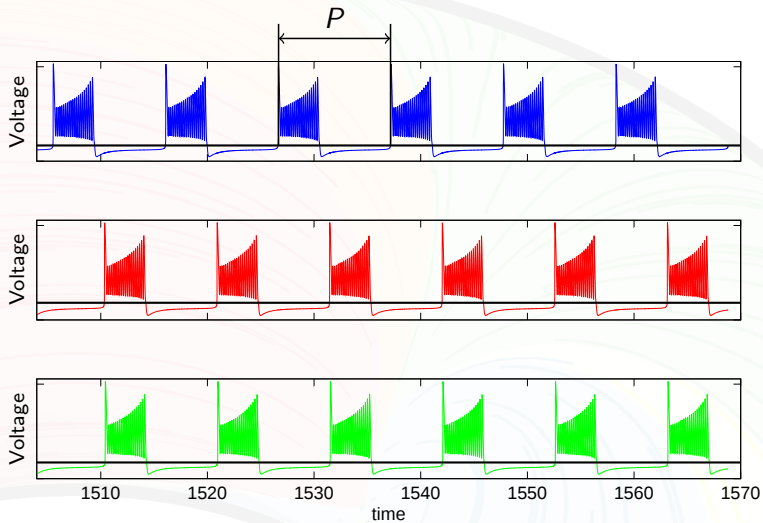
(Shilnikov et al., 2014)



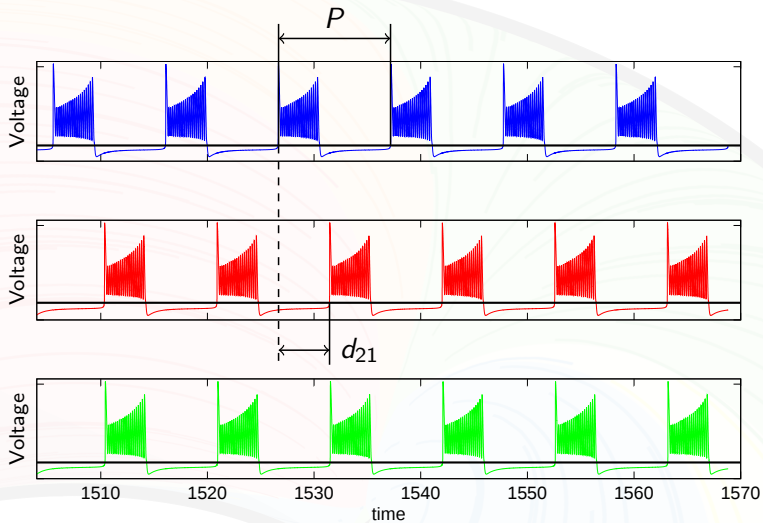
Convergence patterns



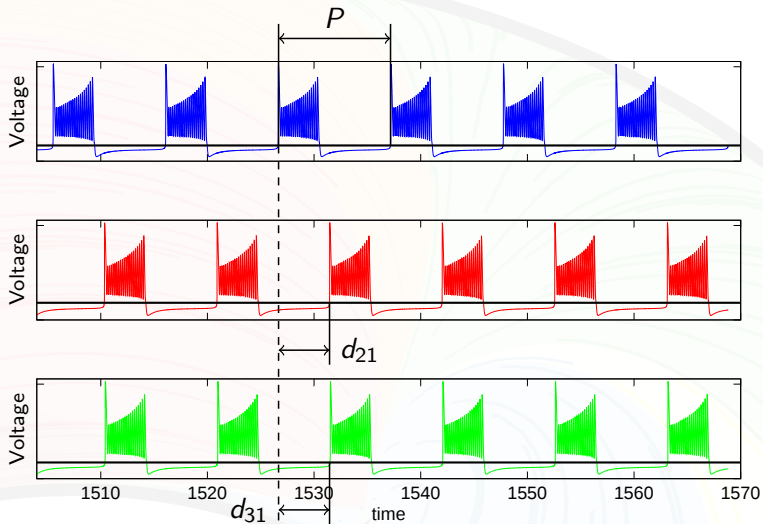
Convergence patterns



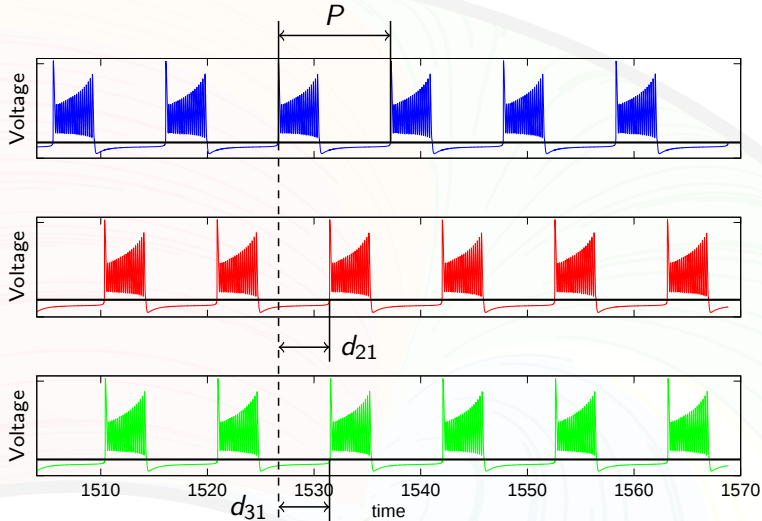
Convergence patterns



Convergence patterns

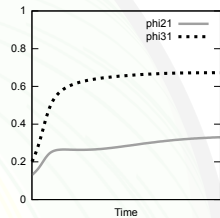
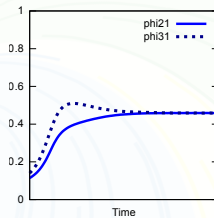
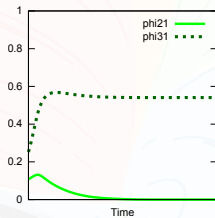
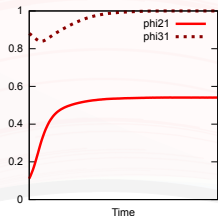
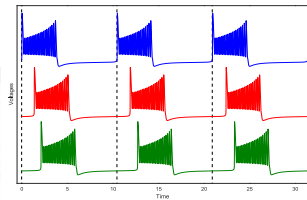
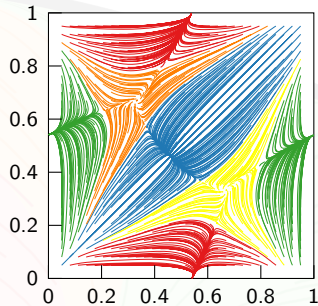
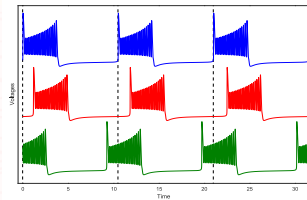


Convergence patterns

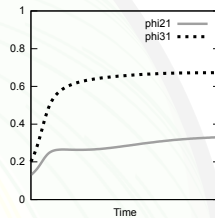
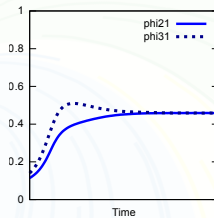
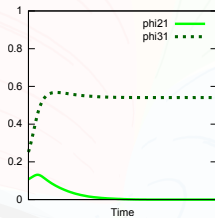
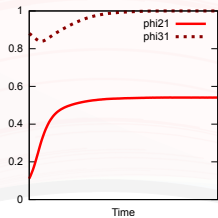
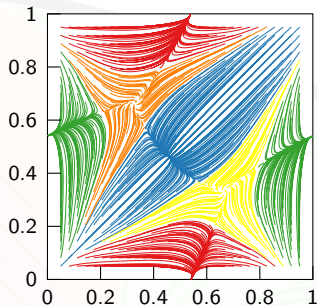


$$\varphi_{k1} = \frac{d_{k1}}{P}$$

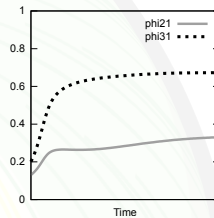
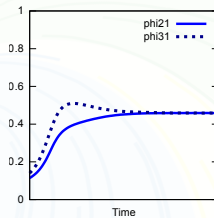
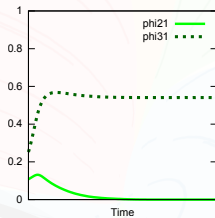
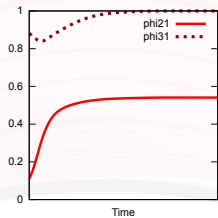
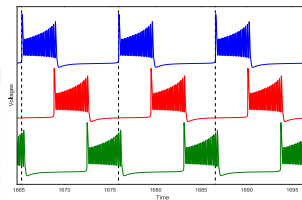
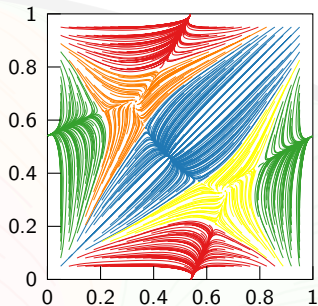
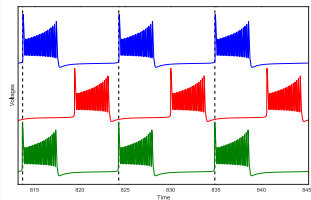
Convergence patterns



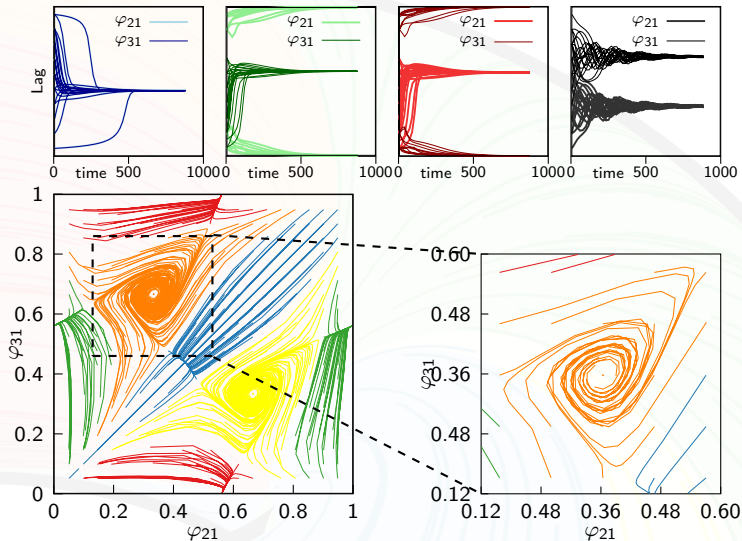
Convergence patterns



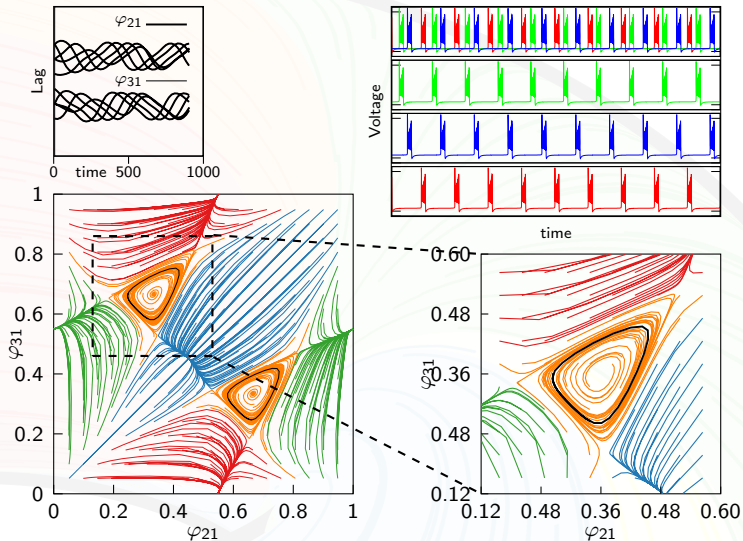
Convergence patterns



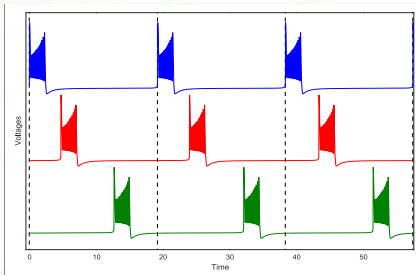
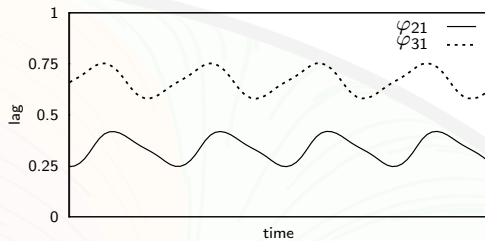
Network at $V_{K2}^{\text{shift}} = -0.0187$



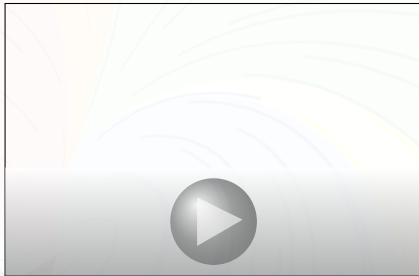
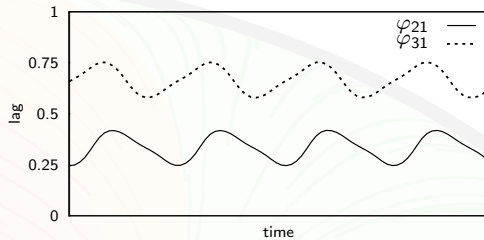
Network at $V_{K2}^{\text{shift}} = -0.01876$



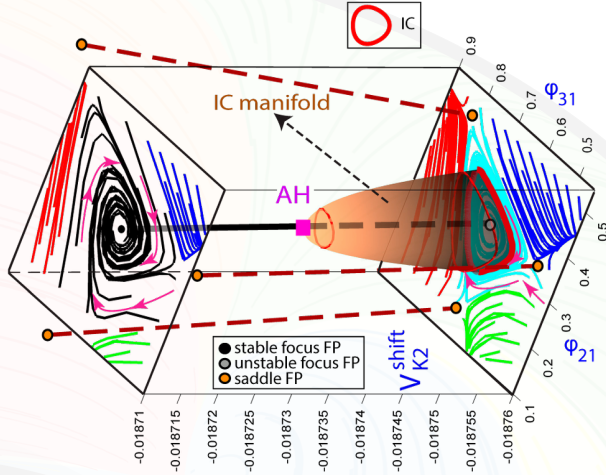
The jiggling state



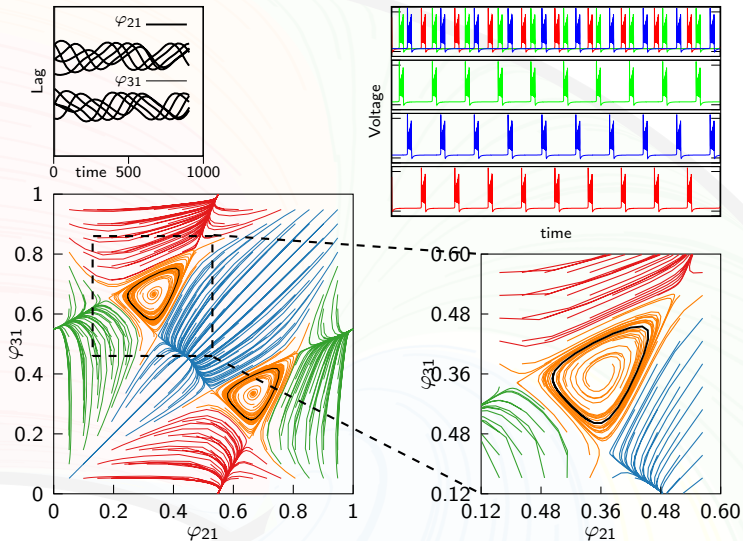
The jiggling state



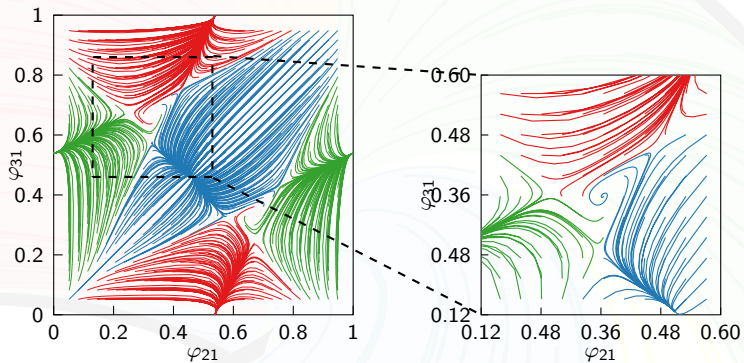
Andronov-Hopf bifurcation



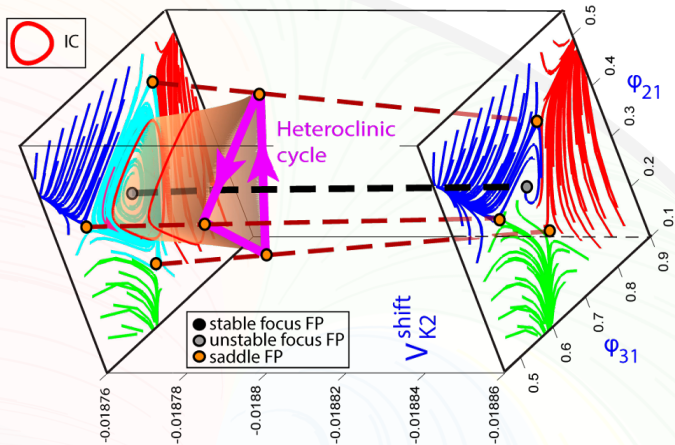
Network at $V_{K2}^{\text{shift}} = -0.01876$



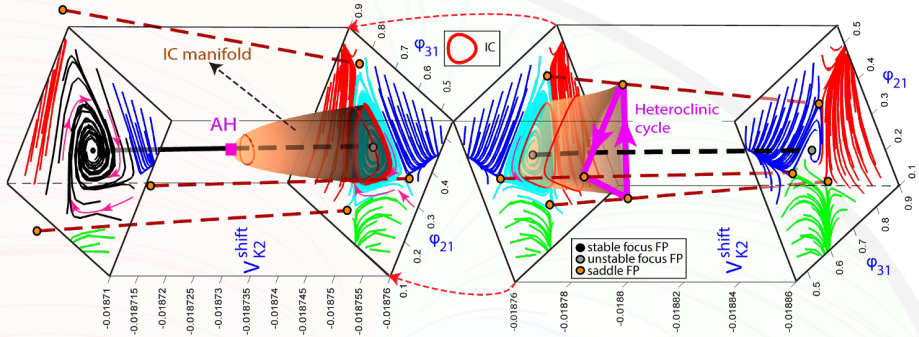
Network at $V_{K2}^{\text{shift}} = -0.01886$



$\mathbb{Z}_3$ -Heteroclinic bifurcation at $V_{K2}^{\text{shift}} = -0.0187875$



Andronov-Hopf and $\mathbb{Z}_3$ -Heteroclinic bifurcations



Not Using AUTO-like techniques. Parametric continuation in discrete phase space.

Outline

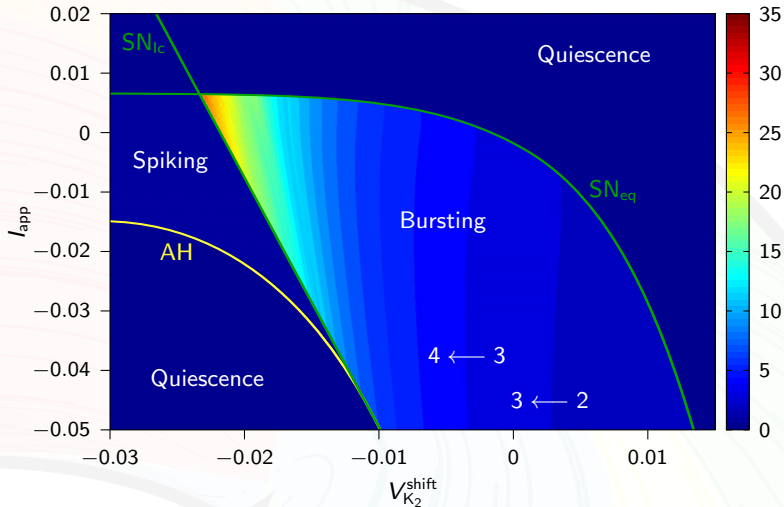
Single neuron analysis

A network of neurons. Bifurcations

Control the network

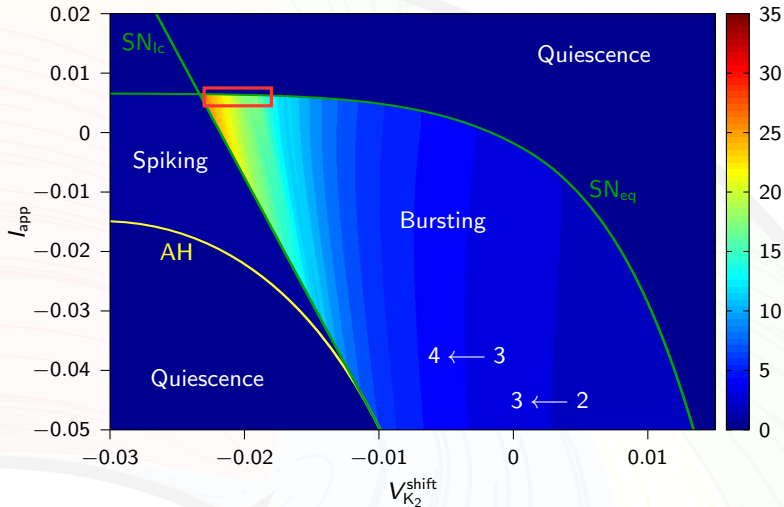
Control strategy: Inhibitory/Excitatory pulses

One neuron



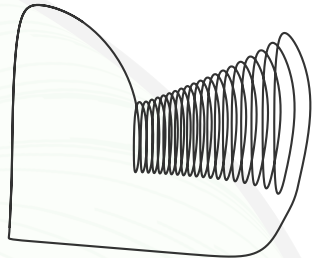
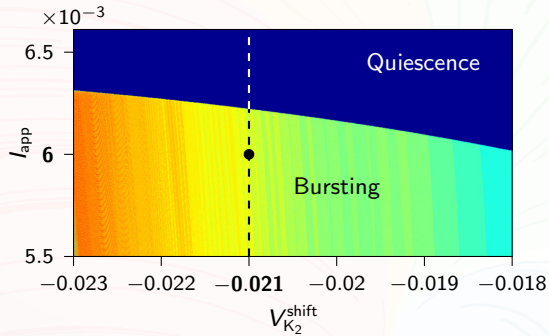
Control strategy: Inhibitory/Excitatory pulses

One neuron



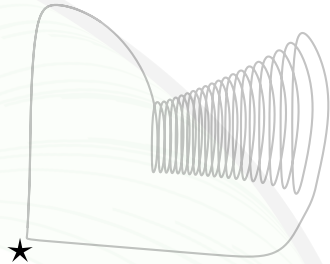
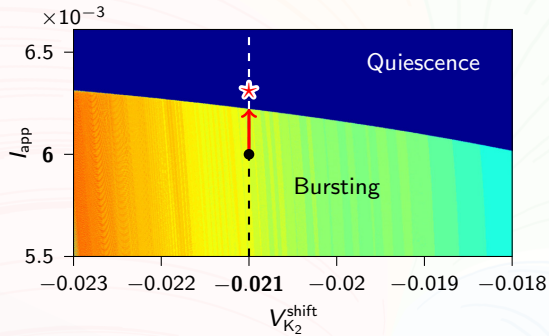
Control strategy: Inhibitory/Excitatory pulses

One neuron



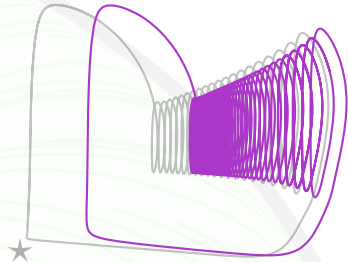
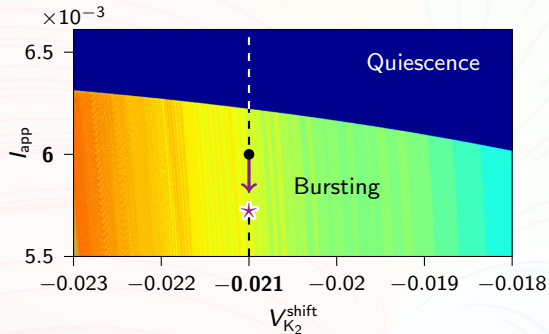
Control strategy: Inhibitory/Excitatory pulses

One neuron



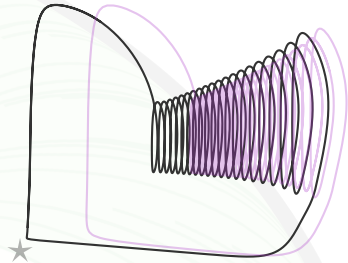
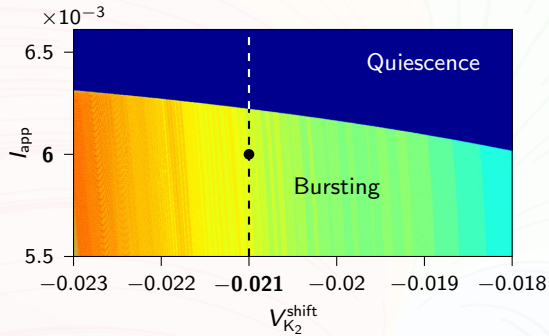
Control strategy: Inhibitory/Excitatory pulses

One neuron



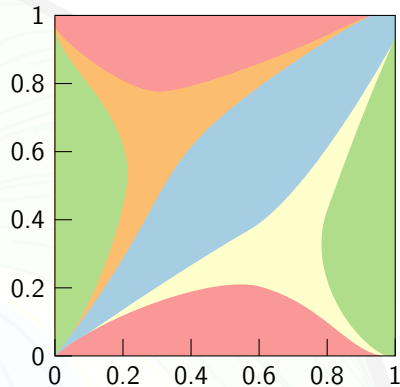
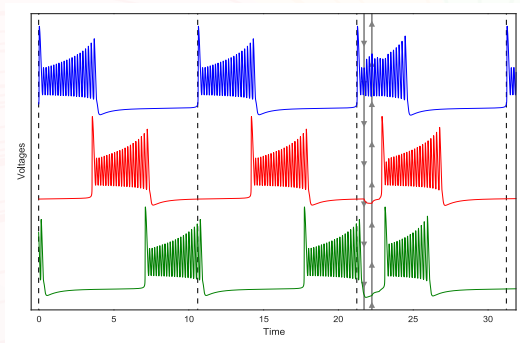
Control strategy: Inhibitory/Excitatory pulses

One neuron



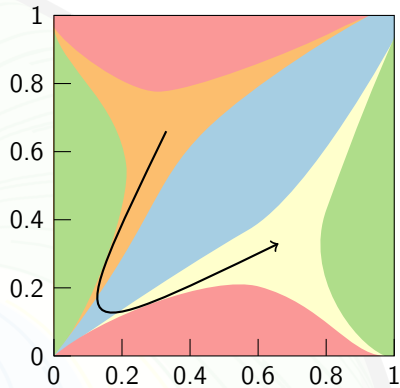
Control strategy: Inhibitory/Excitatory pulses

The network

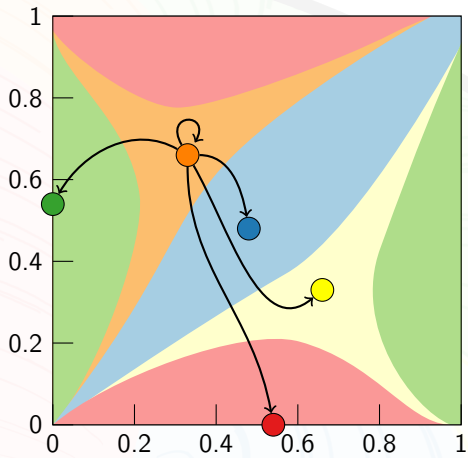


Control strategy: Inhibitory/Excitatory pulses

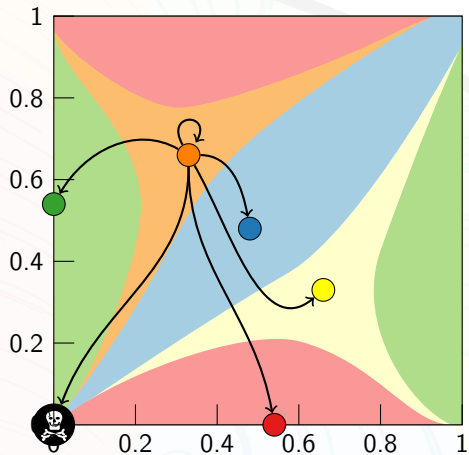
The network



Possible new states

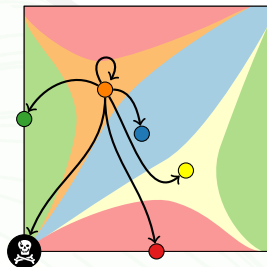
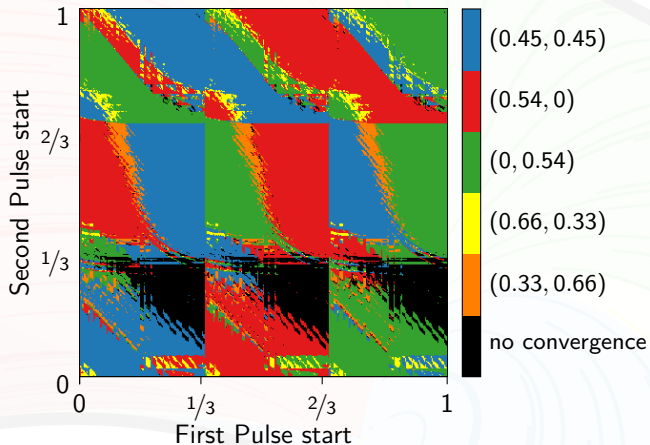


Possible new states



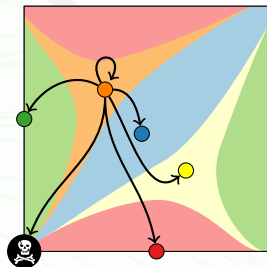
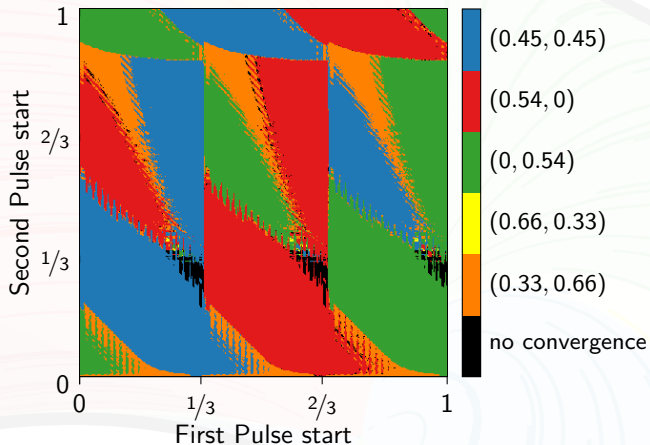
Long pulses

0.09 length of Period



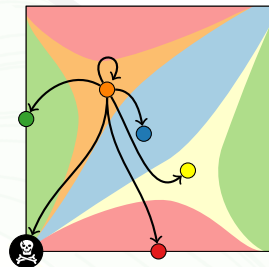
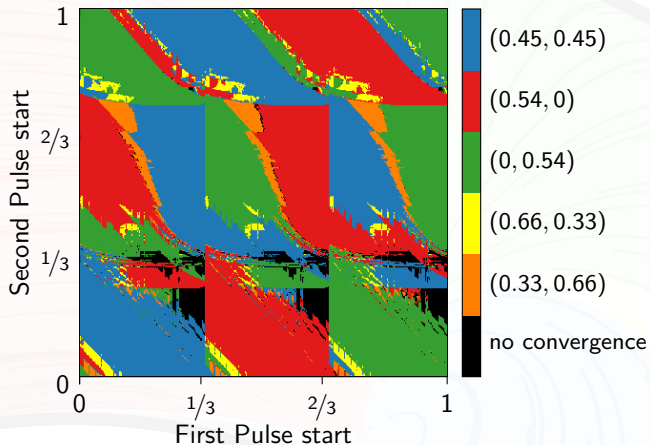
Short pulses

0.01 length of Period



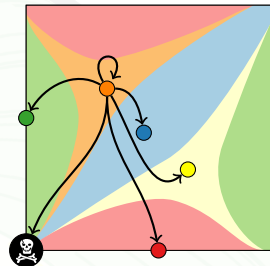
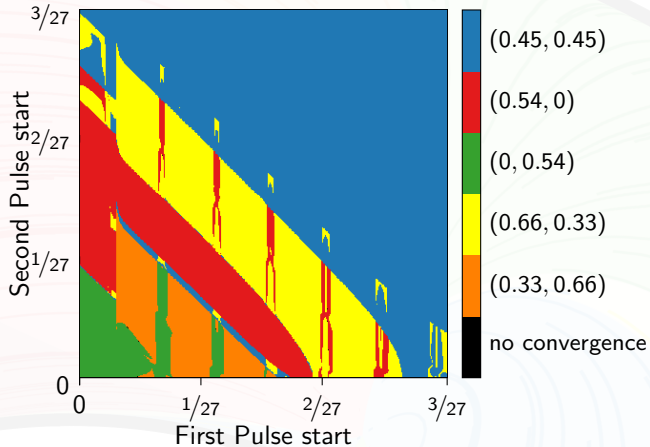
Medium length pulses

0.05 length of Period



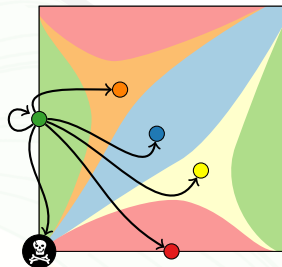
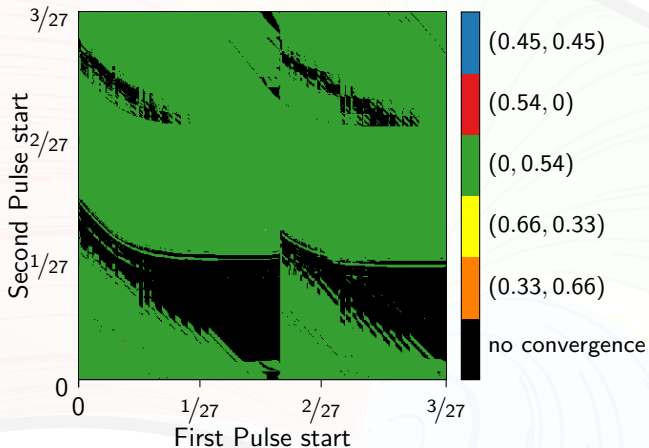
Medium length pulses: Zoom!!

0.05 length of Period



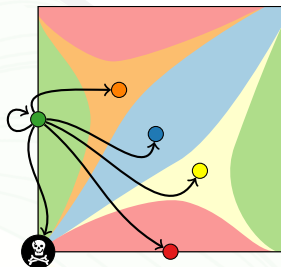
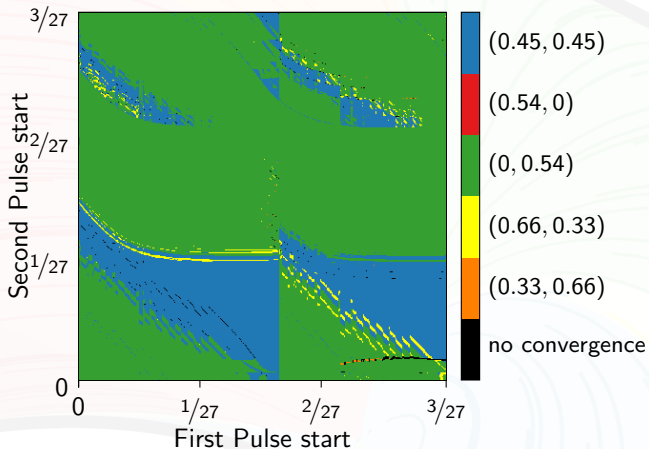
Start from other state

0.09 length of Period



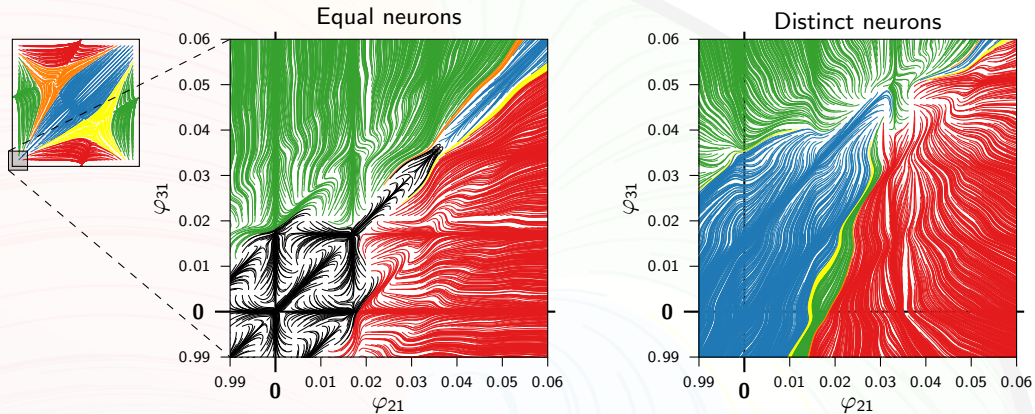
Start from other state

0.09 length of Period. Modify V_{K2}^{shift} around 1‰



Start from other state

0.09 length of Period. Modify V_{K2}^{shift} around 1‰



References



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That's all Folks!