Synchronisation predictions via extended phase response curves

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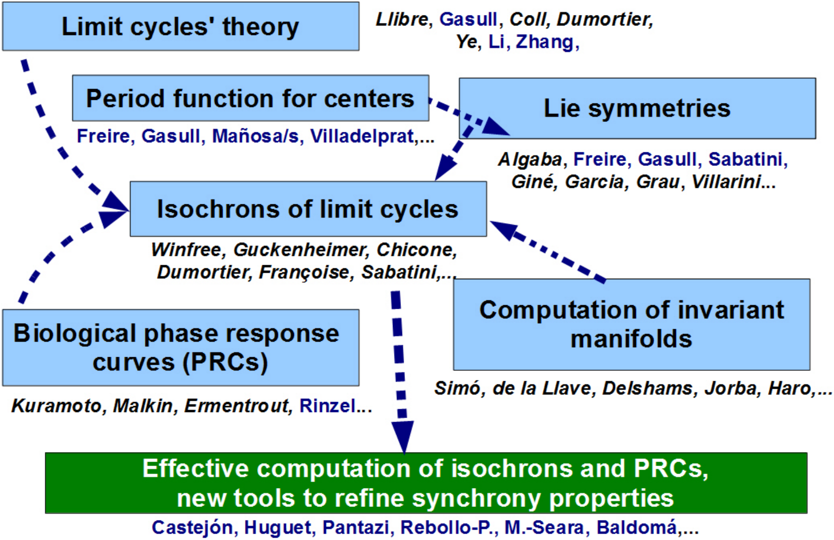
“Drinking” sources



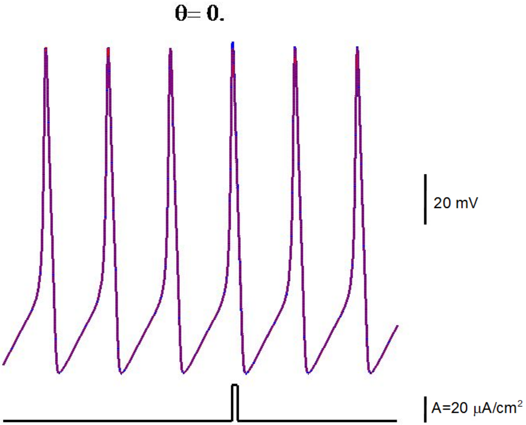
Outline

1. PRCs: a quick review of “classical” theory
2. Extensions of PRCs. . .
3. Poincaré phase maps extended

Experiments $\longrightarrow$ Modelling $\Rightarrow$ Predictions

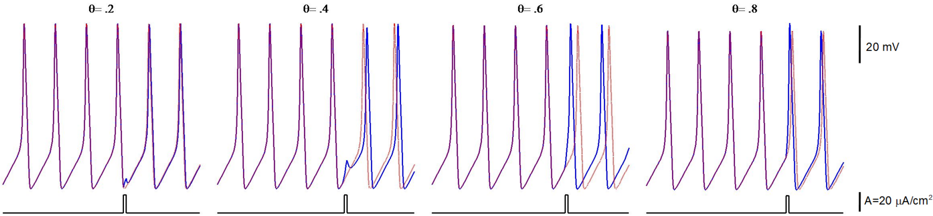
Phase variation: brief pulse stimulus of amplitude A at some phase $\theta \in [0,1)$

"Heuristic" computation of the **phase advancement**:

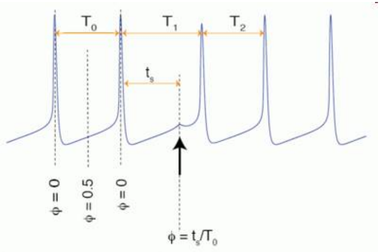


Phase variation: brief pulse stimulus of amplitude A at phase θ

“Heuristic” computation of the **phase advancement**:



Phase variation: amplitude A stimulus at phase $\theta \in [0, 1)$

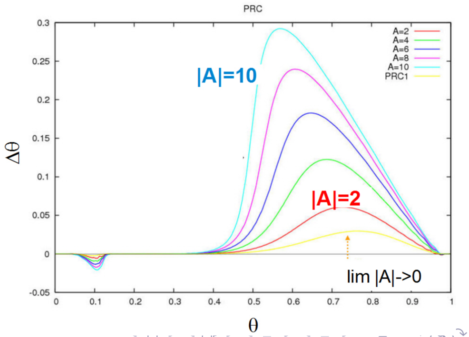


The **phase advancement/delay** due to an external input at time t_s is given by

$$\Delta\theta = (T_0 - T_1(\theta, A))/T_0,$$

$$\theta = (t_s - t_{last})/T_0 \in [0, 1).$$

Phase response curves: PRC(θ, A)



We assume to have an **attracting limit cycle** of the system

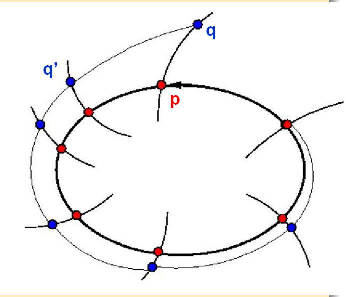
$$\Gamma := \{\widetilde{\gamma}(t), t \in [0, T_0)\} = \{\gamma(\theta), \theta \in [0, 1)\}.$$

Definition

We say that a point $q \in \Omega \subset \mathbb{R}^d$, Ω open domain containing the limit cycle Γ, is in **asymptotic phase** with a point $p \in \Gamma$ if

$$\lim_{t\to\infty} |\Phi_t(q) - \Phi_t(p)| = 0,$$

where $\Phi_t(x)$ is the trajectory of X such that $\Phi_0(x) = x$.
The set of points having the same asymptotic phase is called **isochron**.



Generalization of the phase in a neighbourhood of the limit cycle

This defines a unique scalar function in a neighbourhood Ω of Γ where:

$$\begin{array}{rll} \vartheta: & \Omega \subset \mathbb{R}^d & \to \mathbb{T} = [0,1) \\ & x & \mapsto \vartheta(x) \end{array}$$

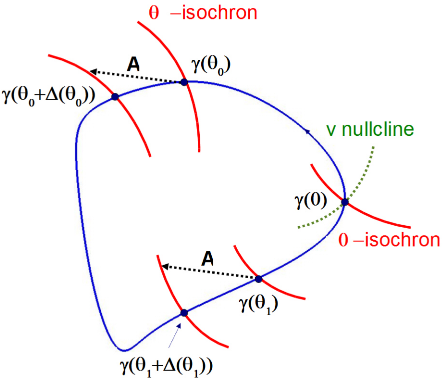
such that

$$\lim_{t\to\infty} |\Phi_t(x) - \gamma(\vartheta(x) + t/T)| = 0.$$

The value $\vartheta(x)$ is the **asymptotic phase** of x. The **isochrons** are the **level sets** of the function $\vartheta(x)$, and $\vartheta(\gamma(\theta)) = \theta$.

A brief pulse stimulus in the entire space: geometry and time

For a given stimulus **A**:



$\Delta(\theta; \mathbf{A}) = \vartheta(\gamma(\theta) + \mathbf{A}) - \theta$: phase variation depends on the **geometry of isochrons** and it needs some **time to relax back** before next stimulus.

Some results on isochrons

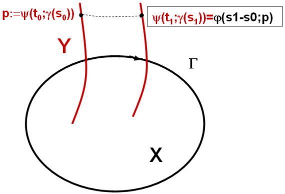
- [Winfree, 1974] When is a limit cycle isochronous?
- [Guckenheimer, 1975]: (From Coddington-Levinson 1955, Hirsch and Pugh, 1970) If γ is a stable (hyperbolic) limit cycle, then γ is isochronous; moreover, the isochrons are the leaves of the stable manifold, that is $W^s_{\gamma(\theta)}$, for $\theta \in \mathbb{T}$ and

$$W^s_\gamma = \bigcup_{\theta \in [0,1)} W^s_{\gamma(\theta)}.$$

- [Chicone-Liu, 2004] [Dumortier, 2006] (X being a planar vector field) γ is isochronous $\Leftrightarrow$ γ is hyperbolic or $\{\pi(p) = p, \pi'(p) = \cdots = \pi^{(k)}(p) = 0, \cdots = \pi^{(k+1)}(p) \neq 0\}$ and $\{\tau(p) = T, \tau'(p) = \cdots = \tau^{(n)}(p) = 0\}$, with $n \geq k \geq 2$.
- [Sabatini, 2004] (X being a planar vector field) γ is isochronous $\Leftrightarrow$ $\exists$ a vector field Y and a scalar μ such that $[Y, X] = \mu Y$. It does not require hyperbolicity.

Isochrons from Lie symmetry point of view

- Geometrical interpretation for flows of Lie symmetries: $[Y, X] = \mu Y \Rightarrow X$ brings orbits of Y to orbits of Y.



- Recall Lie bracket

$$[Y, X] = DX\, Y - DY\, X = \partial_Y X - \partial_X Y$$

- [Freire-Gasull-Guillamon, 2007] Let X being a planar vector field having a Lie symmetry. The characteristic exponent of γ is given by

$$\lambda = \int_0^1 \mu(\gamma(\theta))\, d\theta.$$

then,

$$\int_0^1 \mu(\gamma(\theta))\, d\theta = \int_0^1 \mathrm{div}(X(\gamma(\theta)))\, d\theta$$

Phase variation under a **weak** brief pulse: infinitesimal PRC

Consider a small perturbation of the system:

$$\dot{x} = X(x) + \vec{\epsilon}\, p(t), \qquad \vec{\epsilon} = (\epsilon, 0 \ldots, 0).$$

Theorem (Malkin, Kuramoto)

For weak perturbations, $|\epsilon| \ll 1$, the phase function satisfies

$$\dot{\theta} = \frac{1}{T_0} + \frac{1}{T_0} \epsilon \nabla\theta(\gamma(t)) \cdot p(t) + o(\epsilon).$$

- We will deal with **brief "delta" stimuli**, $p(t) = \delta(t - t_s)$, but it also works for $p(t)$ stochastic, synaptic couplings,...

One defines the **infinitesimal PRC** as: $iPRC(\theta)(x)) = \nabla\theta(x).p(t)$

The adjoint method

[see Malkin 1949-1956, Ermentrout and Kopell 1991, Hoppensteadt and Izhikevich 1997, Ermentrout 2002, Izhikevich 2007,...]

The iPRC can be obtained by solving a variational equation.

The function $\nabla\theta$ along the limit cycle (the PRC) is given by the T-periodic solution of the **adjoint equation**

$$\frac{dQ}{dt} = -DX^T(\gamma(t))Q, \tag{1}$$

where ϕ_t is the flow of the vector field X, with the condition

$$Q(\gamma(t)) \cdot X(\gamma(t)) = \frac{1}{T}$$

See also [Schultheiss-Prinz-Butera, *Phase Response Curves in Neuroscience; Theory, Experiment, and Analysis*, Springer 2012].

iPRC and synchronization under weak coupling I

iPRC have been successfully applied to systems of n weakly-coupled oscillators:

$$\dot{x}_i = f_i(x_i) + \epsilon \sum_{j=1}^{n} g_{ij}(x_i, x_j),$$

Phase reductions:

$$\dot{\theta}_i = 1 + \epsilon \nabla\theta_i(\gamma_i(t)) \cdot \sum_{j=1}^{n} g_{ij}(x_i(\theta_i), x_j(\theta_j)) + o(\epsilon).$$

Defining $\varphi_i = \theta_i - t$,

$$\dot{\varphi}_i = \epsilon \nabla\theta_i(\gamma_i(t)) \cdot \sum_{j=1}^{n} g_{ij}(x_i(t+\varphi_i), x_j(t+\varphi_j)) + o(\epsilon).$$

iPRC and synchronization under weak coupling II

Averaging last equation, one obtains:

$$\dot{\varphi}_i = \epsilon\omega_i + \epsilon \cdot \sum_{j \neq i}^{n} H_{i,j}(\varphi_j - \varphi_i) + o(\epsilon),$$

where

$$H_{ij}(\varphi_j - \varphi_i) = \frac{1}{T}\int_0^T \nabla\theta_i(\gamma_i(t)) g_{ij}(x_i(t), x_j(t + \varphi_j - \varphi_i)).$$

Beyond the phase reduction

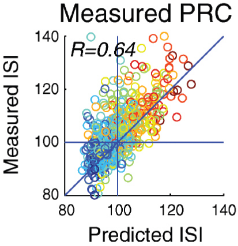
In realistic situations, we cannot determine whether we are *on a limit cycle*.

- Regular spiking, but it is not perfect, specially because of noise.
- Perturbations may send the dynamics away from the asymptotic state; then, the rate of convergence to the attractor plays an important role as well as the stimulation frequency ω_s. Other phenomena like bursting-like stimuli,...

Beyond the phase reduction: QUESTION 1

Assuming an underlying periodic attractor,

How is the phase variation out of it (that is, in transient states)? Can we rely on the phase reduction (PRC)?



[Netoff et al., 2005]

$\longrightarrow$ **Extension of PRCs to a neighbourhood of a limit cycle.**

Beyond the phase reduction: QUESTION 2

How far is the experimentally recorded phase variation from the theoretically predicted one?

$\longrightarrow$ **Comparison of 1D and 2D phase maps with the exact phase (academic examples).**

Beyond the phase reduction: QUESTION 3

Experimentally, one is able to compute the phase variation thanks to references with some specific membrane potential values (e.g. $v(t) = V_{max}$), but this might not be a good reference for the exact period.

How could we make the most of experimental data to refine the phase variation computation?

$\longrightarrow$ **New proposals using iterative recordings and the notion of isochrons.**

Beyond the phase reduction: QUESTION 4

How can we extend the PRCs to other attracting sets?

$\longrightarrow$ **Bistability case, tori, non-smooth,...**

QUESTION 1: Extensions of PRCs: the "**P**hase **R**esponse **Surfaces**"

How is the phase variation out of it (that is, in transient states)? Can we rely on the phase reduction (PRC)?

$\longrightarrow$ **Extension of PRCs to a neighbourhood of a limit cycle.**
[G-Huguet, SIADS 2009]

Application of the parameterization method

The parameterization method ([Cabré, Fontich, de la Llave, JDE 2005]) for **hyperbolic periodic orbits** of planar vector fields

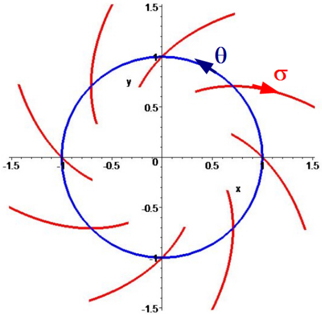
- We fix $\mathcal{X}$ and look for a map K such that

$$\left(\frac{1}{T}\partial_\theta + \frac{\lambda\sigma}{T}\partial_\sigma\right) K(\theta,\sigma) = X(K(\theta,\sigma)), \tag{2}$$

  where λ is the **characteristic exponent** of γ.

- $\mathcal{X}$: motion generated by X expressed in (θ,σ):

$$\begin{aligned} \dot\theta &= 1/T, \\ \dot\sigma &= \lambda\sigma/T. \end{aligned}$$



Computing the isochrons and PRSs (or 2D-PRCs) I

K, and λ allow us to compute **isochrons** and **Phase Resetting Surfaces** (PRS). We skip here numerical details, which are the core of [G-Huguet, SIADS 2009]. See also [Osinga-Moehlis, SIADS 2010] for another approach.

- Computing the **isochron**. The orbit of the points given by $K(\theta_0, \sigma)$, for any $\sigma \in U$ approaches **exponentially fast** the orbit of the point $K(\theta_0, 0) = \gamma(\theta_0)$.
- Parameterization of the **isochron** of the point $\gamma(\theta_0)$:

$$\begin{array}{rcl} K(\theta_0, \cdot) : U \subset \mathbb{R} & \longrightarrow & \mathbb{R}^2 \\ \sigma & \longmapsto & K(\theta_0, \sigma) \end{array}$$

Computing the isochrons and PRSs (or 2D-PRCs) II

- Computing the **PRS**. Natural extension: for any $p = K(\theta, \sigma)$ in a neighbourhood of the limit cycle γ, compute:

$$\nabla\vartheta(p) = \left(\frac{\partial\vartheta}{\partial x}(p), \frac{\partial\vartheta}{\partial y}(p)\right).$$

- $\nabla\vartheta(p)$ has the **same direction** as $Y^{\perp}(p)$, where

$$Y(p) = Y(K(\theta, \sigma)) := \partial_\sigma K(\theta, \sigma).$$

- We add some **normalization**. For a trajectory $\phi_t(p)$, $p \in \Omega$ we have

$$\frac{d\vartheta}{dt}(\phi_t(p)) = 1/T,$$

therefore

$$\frac{d\vartheta}{dt}(\phi_t(p)) = \nabla\vartheta(\phi_t(p)) \cdot \frac{d}{dt}\phi_t(p) = \nabla\vartheta(\phi_t(p)) \cdot X(\phi_t(p)) = 1/T,$$

Computing the isochrons and PRSs (or 2D-PRCs) III

- The PRS for any $p \in \Omega$ is given by

$$\nabla \vartheta(p) = \frac{Y^{\perp}(p)}{T < Y^{\perp}(p), X(p) >}$$

The adjoint method extended

The function $\nabla\vartheta$ along the orbits of the vector field X,

$$\nabla\vartheta(\phi_t(p)) = \frac{Y^\perp(\phi_t(p))}{T < Y^\perp(\phi_t(p)), X(\phi_t(p)) >}$$

satisfies the **adjoint equation**

$$\frac{dQ}{dt} = -DX^T(\phi_t(p))Q,$$

where ϕ_t is the flow of the vector field X, with the initial condition

$$Q(0) = \frac{Y^\perp(p)}{T < Y^\perp(p), X(p) >}.$$

PRC: $p \in \gamma$, then $\phi_t(p) = \gamma(t/T)$ with $\gamma(0) = p$

Computing the normal direction resetting surface, PRS_σ

- Similarly as we did for the $\nabla\vartheta$, given the function K we can compute

$$\nabla\sigma(p) = \frac{Z^\perp(p)}{\frac{T}{\lambda\sigma} < Z^\perp(p), X(p) >} = \frac{Z^\perp(p)}{< Z^\perp(p), Y(p) >},$$

where

$$Z(p) = Z(K(\theta,\sigma)) = \partial_\theta K(\theta,\sigma).$$

- **Remark**: We use the notation PRS_θ to denote the Phase Resetting Surface and PRS_σ to denote the Normal Resetting Surface.

$$\mathbf{PRS}_\sigma = \nabla\sigma(\mathbf{p}) \cdot \mathbf{A}$$

is the **first-order normal direction variation** after applying stimulus A on $p \in \Omega$.

Summarizing...

- "Classical version": PRC on $\gamma \cong \mathbb{S}^1$.
- "Extended version": PRS_θ and PRS_σ on $\Omega \cong \mathbb{S}^1 \times (\sigma_{low}, \sigma_{up})$, with $0 \in (\sigma_{low}, \sigma_{up})$.

Examples of isochrons and extended PRCs

A "minimal" example

Consider the system in polar coordinates,

$$\begin{cases} \dot{r} &= \alpha\, r(1-r^2), \\ \dot{\phi} &= 1+\alpha\, a\, r^2, \end{cases}$$

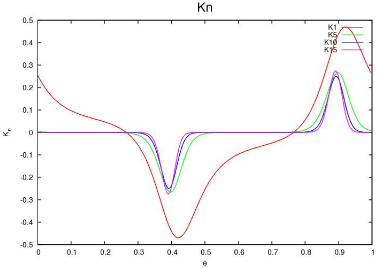
having a limit cycle γ of period $T_0 = 2\pi/(1+\alpha\, a)$, parameterized by $\theta \in [0,1)$ as $\gamma(\theta) = (\cos(2\pi\theta), \sin(2\pi\theta))$. Then,

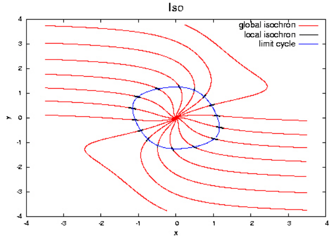
$$K(\theta,\sigma) = \left(\sqrt{\frac{1}{1-2\alpha\sigma}}\cos(\Omega), \sqrt{\frac{1}{1-2\alpha\sigma}}\sin(\Omega) \right),$$

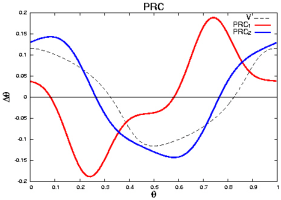
having defined $\Omega := 2\pi\theta + \frac{1}{2} a \ln(1-2\alpha\sigma)$.
Finally, we have

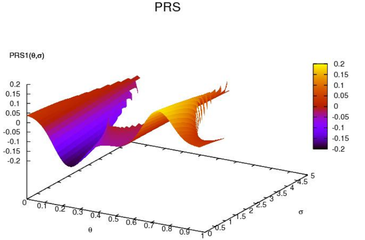
$$\begin{aligned} PRS_\theta(K(\theta,\sigma)) &= -\tfrac{\sqrt{1-2\alpha\sigma}}{2\pi}(\sin(\Omega) - a\cos(\Omega)) \\ PRS_\sigma(K(\theta,\sigma)) &= \tfrac{(1-2\alpha\sigma)^{3/2}}{\alpha}\cos(\Omega). \end{aligned}$$

The van der Pol oscillator $\begin{cases} \dot{x} &= x - x^3 - y, \\ \dot{y} &= x, \end{cases}$









The van der Pol oscillator

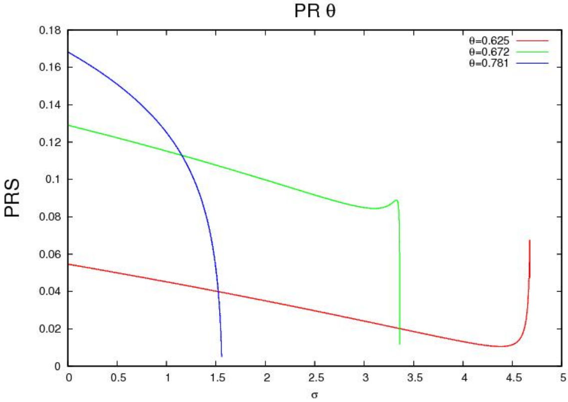


Figure: The Van der Pol oscillator. Notice the diversity of phase advancements that can be obtained in the same isochron (three isochrons are shown: $\theta = 0.625, 0.672, 0.781$).

2D Hodgkin-Huxley-like systems

The model considered is an $I_K + I_{Na}$-model

$$\begin{aligned}\dot{V} &= -\frac{1}{C_m}(g_{Na} m_\infty(V)(V - V_{Na}) + g_K n(V - V_K) + g_L(V - V_L) - I_{app})\\ \dot{n} &= n_\infty(V) - n\end{aligned}$$

where

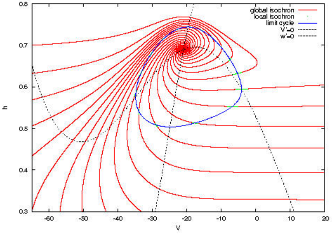
$$\begin{aligned}m_\infty(V) &= \frac{1}{1 + e^{-(V - V_{max,n})/k_m}}\\ n_\infty(V) &= \frac{1}{1 + e^{-(V - V_{max,m})/k_n}}\end{aligned}$$

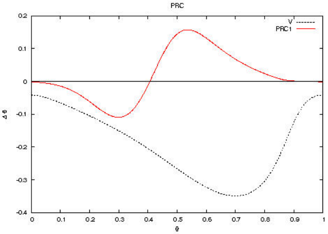
and the parameters are

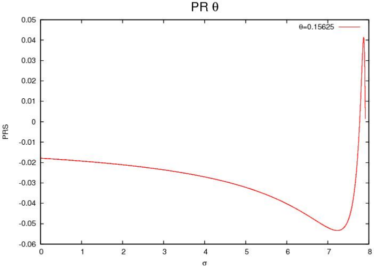
$$C_m = 1., g_{Na} = 20., V_{Na} = 60., g_K = 10., V_K = -90., g_L = 8., v_L = -80.$$

$$V_{max,m} = -20., k_m = 15., V_{max,n} = -25., k_n = 5.$$

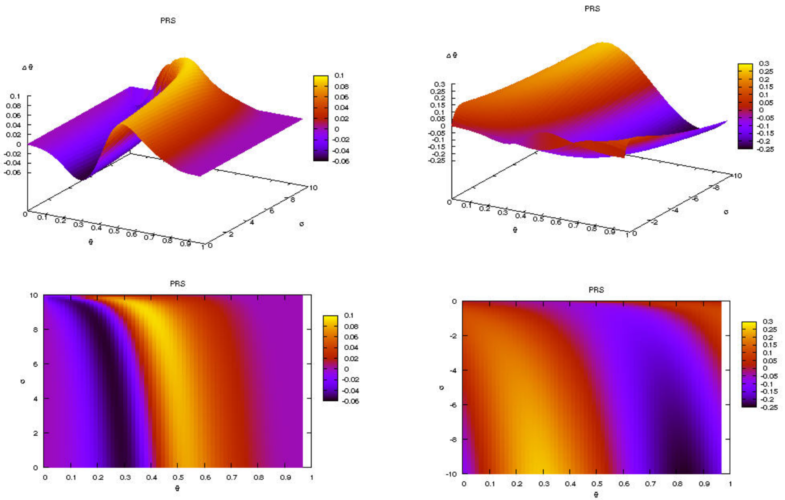
HH close to a Hopf bif. (Type II PRCs): 1D-PRCs



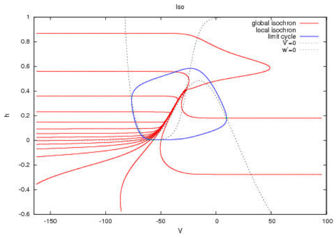


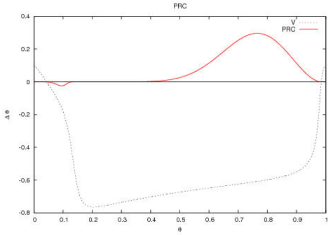


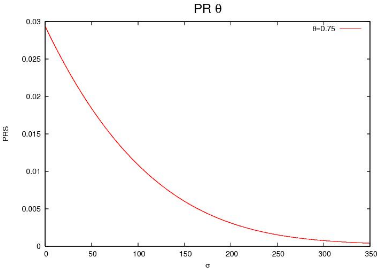
HH close to a Hopf bif. (Type II PRCs): 2D-PRCs



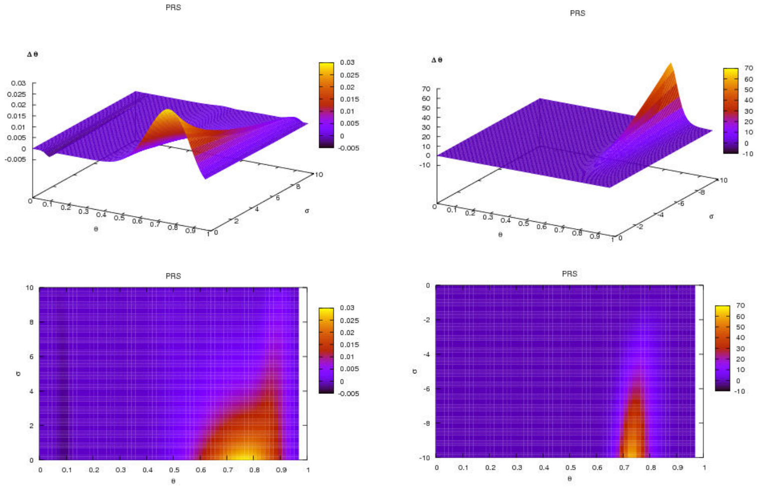
HH close to a SNIC bif. (Type I PRCs): 1D-PRCs







HH close to a SNIC bif. (Type I PRCs): 2D-PRCs



QUESTION 2: Poincaré phase maps extended

How far is the experimentally recorded phase variation from the theoretically predicted one?

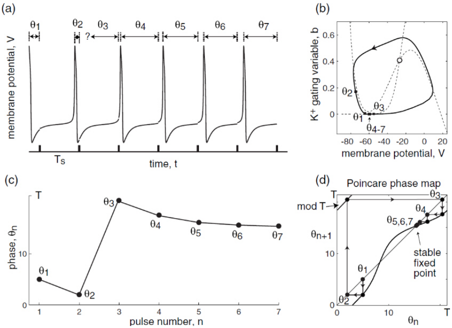
$\longrightarrow$ **Comparison of 1D and 2D phase maps with the exact phase (academic examples).**

Experimentally, one is able to compute the phase variation thanks to references with some specific membrane potential values (e.g. $v(t) = V_{max}$), but this might not be a good reference for the exact period.

Poincaré phase map

We stimulate an orbit of period T_0 and characteristic exponent λ with pulses of period $T_s << T_0$ in a neighbourhood of a limit cycle γ.
The new phase just before the j-th stimulus can be obtained recurrently through the **Poincaré phase map**:

$$\text{PRC} \quad \theta_j = \theta_{j-1} + PRC(\theta_{j-1}) + T_s/T_0 \mod(1),$$



with $PRC(\theta) = \nabla\theta \cdot A$.

The relevance of PRSs vs PRCs

With our extension, we can consider both:

1D-PRCs $\theta_j = \theta_{j-1} + PRC(\theta_{j-1}) + T_s/T_0,$

PRS, 2D-PRCs
$$\begin{cases} \theta_j &= \theta_{j-1} + PRS_\theta(\theta_{j-1}, \sigma_{j-1}) + T_s/T_0, \\ \sigma_j &= (\sigma_{j-1} + PRS_\sigma(\theta_{j-1}, \sigma_{j-1})) \exp(\lambda T_s/T_0), \end{cases}$$

This allows to **compare** Poincaré maps for **1D-PRCs** with those for **2D-PRCs**. Preliminary examples have shown notable differences: phase locking at different phase, phase loocking vs periodic orbits in phase,. . .

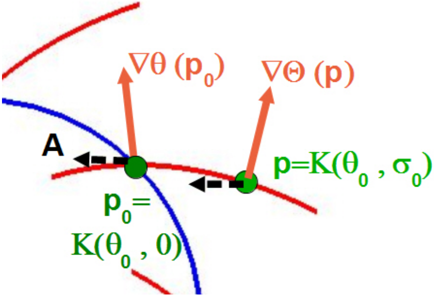
Theoretically expected errors

$$||\nabla\vartheta(p)\cdot\,\mathbf{A}-\nabla\theta(p_0)\cdot\,\mathbf{A}||=|\sigma|\,||K_2(\theta_0)\cdot J\,\mathbf{A}||+o(\sigma),$$

where $J=\begin{pmatrix}0&-1\\1&0\end{pmatrix}$ and $K(\theta,\sigma)=\sum_{j\geq 0}K_j(\theta)\,\sigma^j.$

So, we proof a quite intuitive statement: the **curvature of the isochrons** directly affects the errors in using the PRC, which are magnified according to the relative position of the curvature vector with respect to the stimulus direction.

In neuron models, the first component of the curvature of the isochrons.



A “minimal” example

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having a limit cycle γ of period $T_0 = 2\pi/(1 + \alpha\, a)$, parameterized by $\theta \in [0, 1)$ as $\gamma(\theta) = (\cos(2\pi\theta), \sin(2\pi\theta))$. Then,

$$K(\theta, \sigma) = \left(\sqrt{\frac{1}{1 - 2\alpha\sigma}} \cos(\Omega), \sqrt{\frac{1}{1 - 2\alpha\sigma}} \sin(\Omega) \right),$$

having defined $\Omega := 2\pi\theta + \frac{1}{2} a \ln(1 - 2\alpha\sigma)$.
Finally, we have

$$\begin{aligned} PRS_\theta(K(\theta, \sigma)) &= -\tfrac{\sqrt{1-2\alpha\sigma}}{2\pi}(\sin(\Omega) - a\cos(\Omega)) \\ PRS_\sigma(K(\theta, \sigma)) &= \tfrac{(1-2\alpha\sigma)^{3/2}}{\alpha}\cos(\Omega). \end{aligned}$$

Varying the stimulus frequency, ω_s

Parameter values for the initial simulation: $x_{ini} = 0$, $y_{ini} = 1.5$, $|\mathbf{A}| = \mathbf{0.05}$, $\alpha = 0.1$ (weak hyperbolicity), $a = 10$.

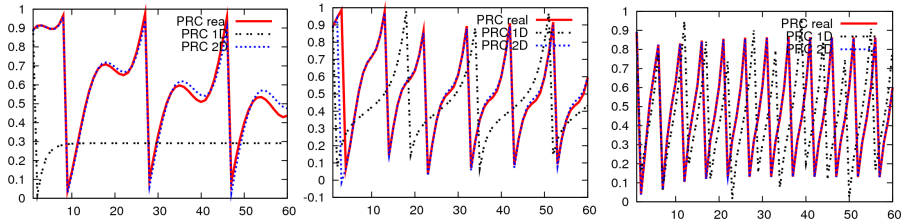


Figure: $\omega_s/\omega_0 \in \{20, 10, 5\}$. We observe that, as we increase the stimulus frequency, the validity of the iPRC is lost, whereas the extended iPRC still gives good predictions.

Varying the stimulus amplitude, $|A|$

Parameter values for the initial simulation: $x_{ini} = 0$, $y_{ini} = 1.5$, $\omega_s/\omega_0 = \mathbf{20}$, $\alpha = 0.1$ (weak hyperbolicity), $a = 10$.

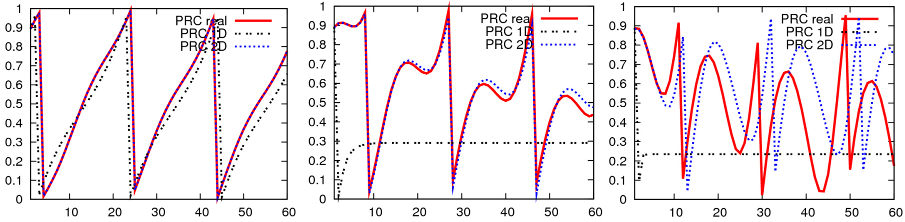


Figure: $|A| \in \{0.01, 0.05, 0.1\}$. We observe that as we increase the stimulus, the validity of the iPRC is lost, whereas the extended iPRC still gives good predictions.

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01005310$

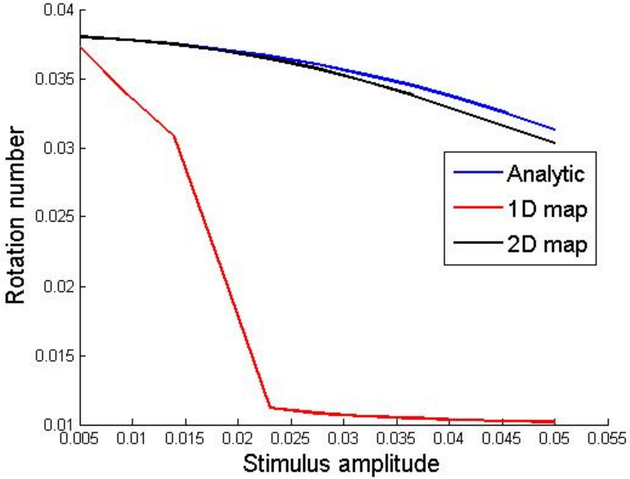


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01099560$

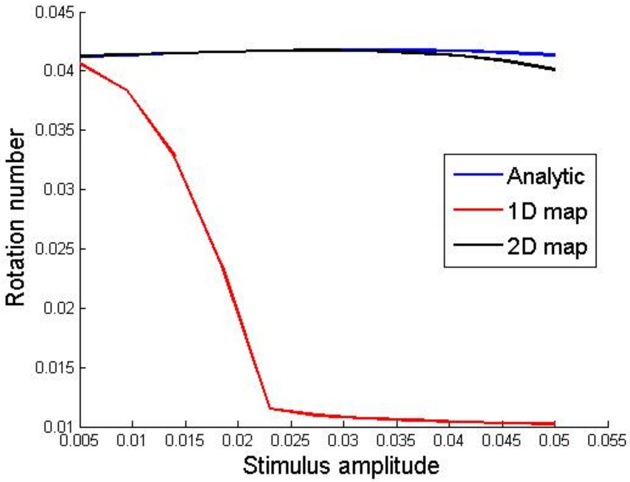


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01193810$

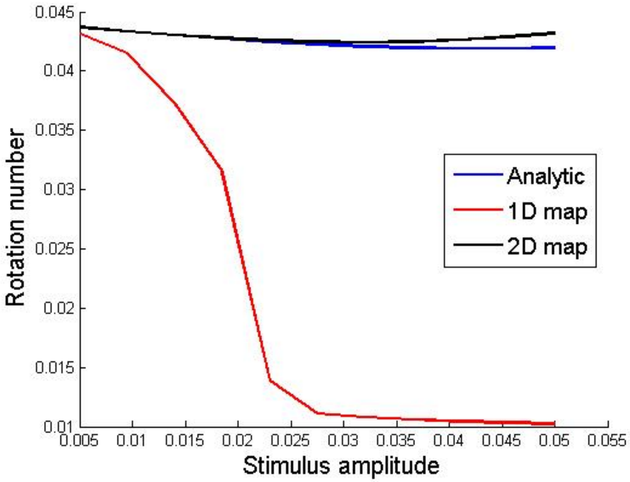


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01288050$

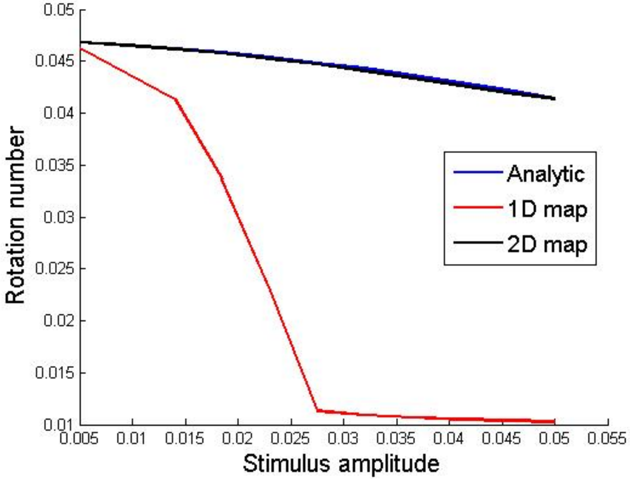


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01382300$

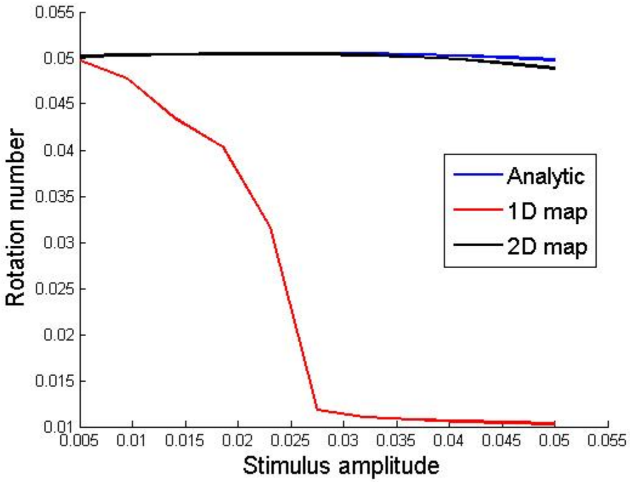


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01476550$

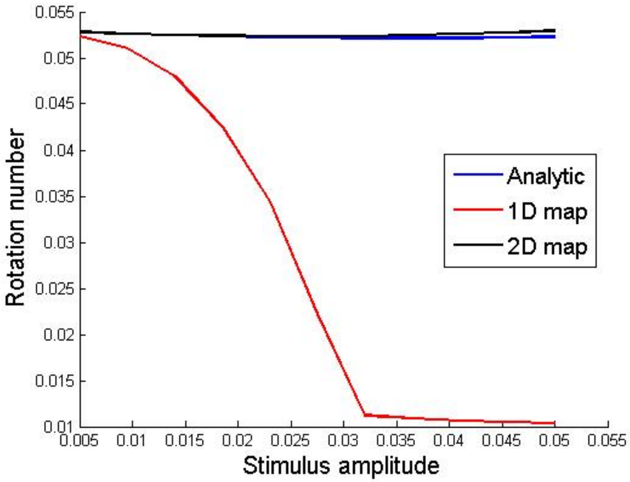


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.01570800$

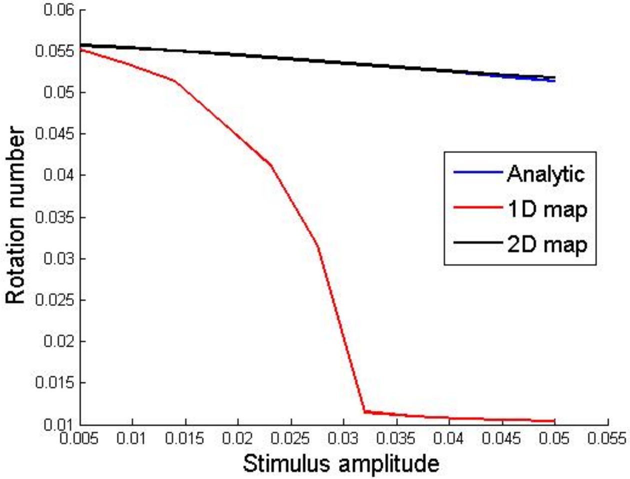


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.06283190$

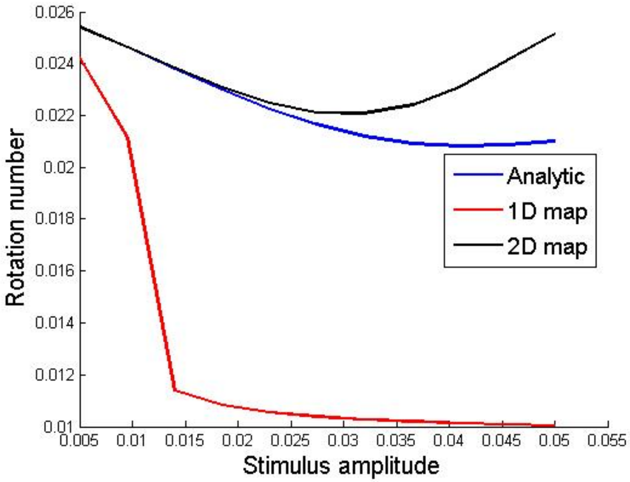


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.07225660$

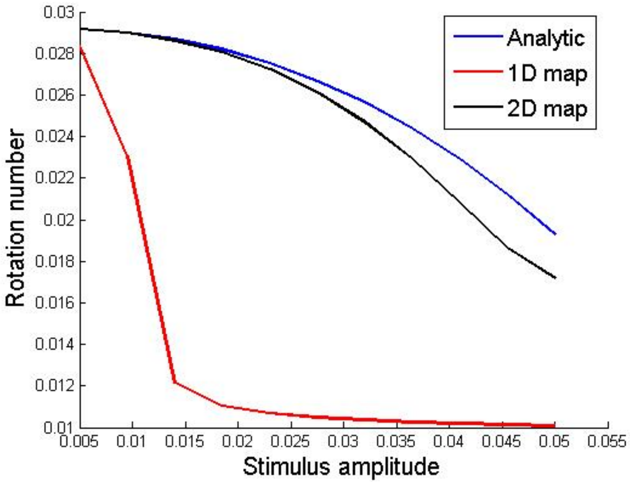


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.08168140$

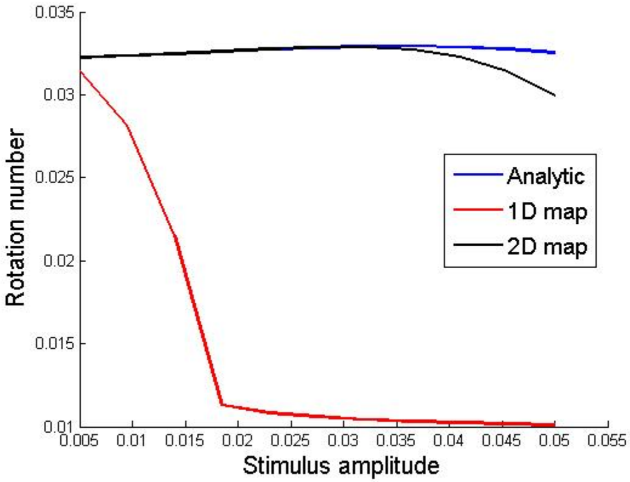


Figure:

Varying the stimulus amplitude, $|A|$, for $T_s = 0.09110620$

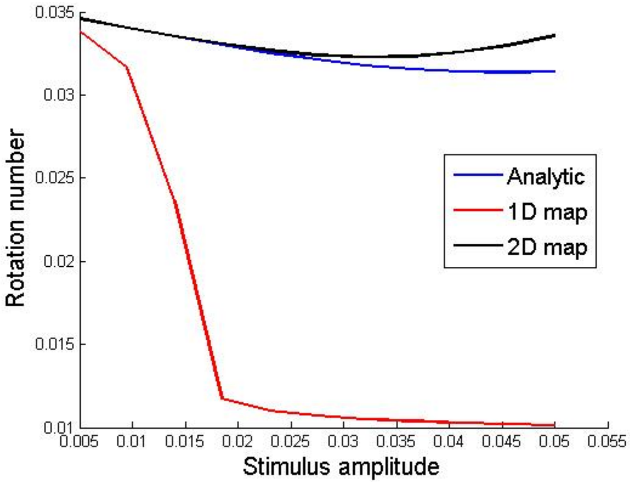
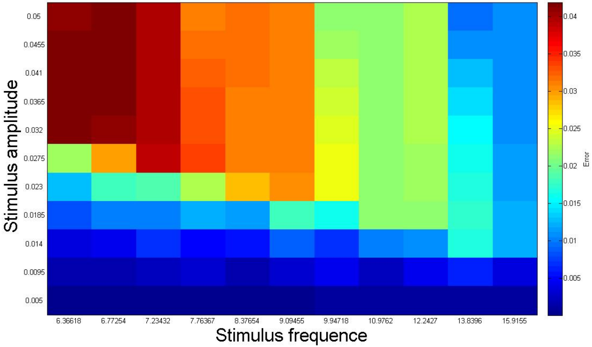


Figure:

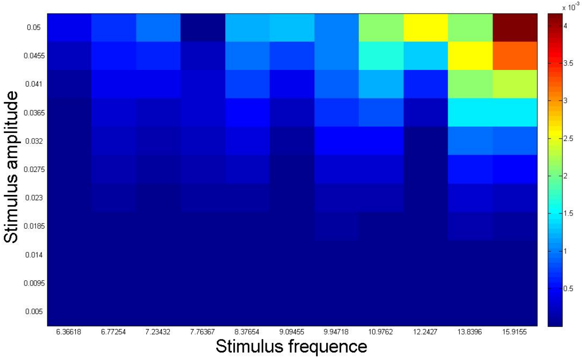
Rotation numbers

Comparison between rotation numbers of **1D-PRCs** and **analytic extended PRCs** vs. the "exact" ones: relative error of the 1D approach, e_1.



Rotation numbers

Comparison between rotation numbers of **1D-PRCs** and **analytic extended PRCs** vs. the "exact" ones: relative error of the 1D approach, e_2.



Rotation numbers

Comparison between rotation numbers of **1D-PRCs** and **2D-PRCs** vs. the "exact" ones: e_2/e_1.