Neuroscience applications:

isochrons and isostables

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Outline

Isochrons and phase reduction of neurons

Koopman operator and isochrons

Isostables of excitable systems

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Isochrons and phase reduction of neurons

Koopman operator and isochrons

Isostables of excitable systems

Effect of a stimuli on the phase of a neuron

(reduced) Hodgkin-Huxley neuron model

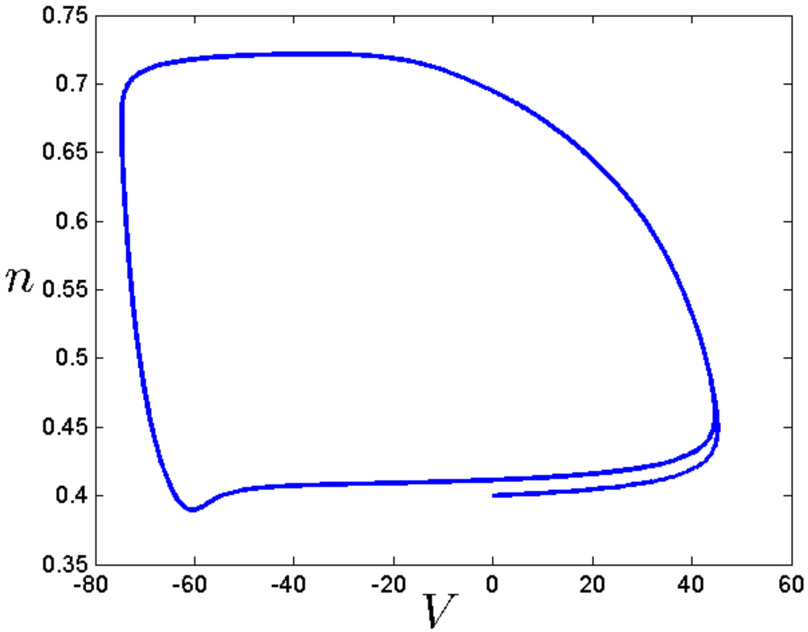
membrane potential

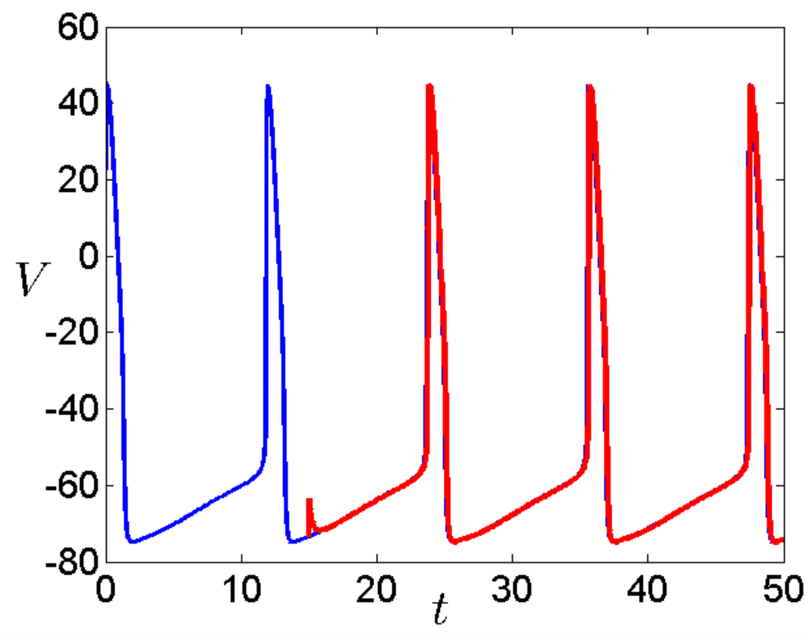
$$\dot{V} = \frac{1}{C}[I_{app} - \bar{g}_{Na}[m_\infty(V)]^3(0.8-n)(V-V_{Na}) - \bar{g}_K n^4(V-V_K) - g_L(V-V_L) + u(t)]$$

gating variable for the conductance channel

$$\dot{n} = \alpha(V)(1-n) - \beta(B)n$$

$$u(t) = 10\,\delta(t-15)$$





Effect of a stimuli on the phase of a neuron

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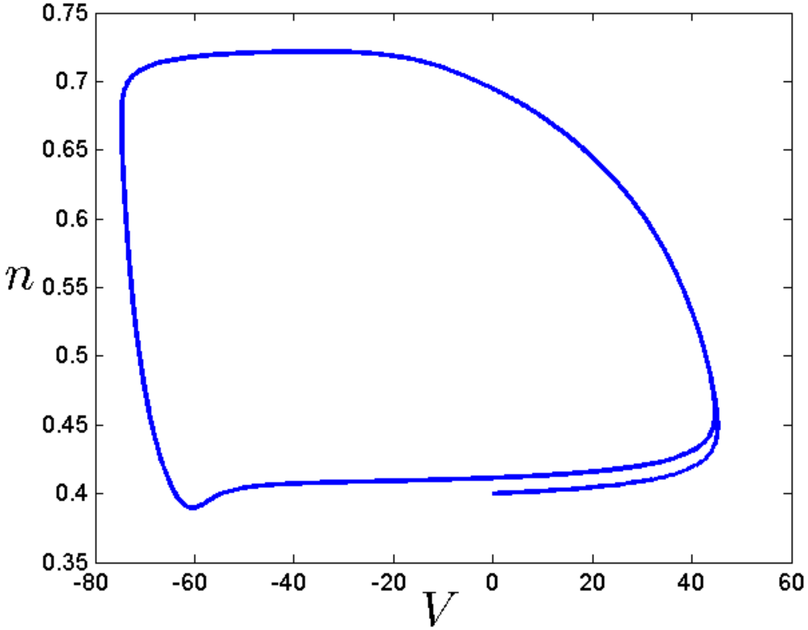
membrane potential

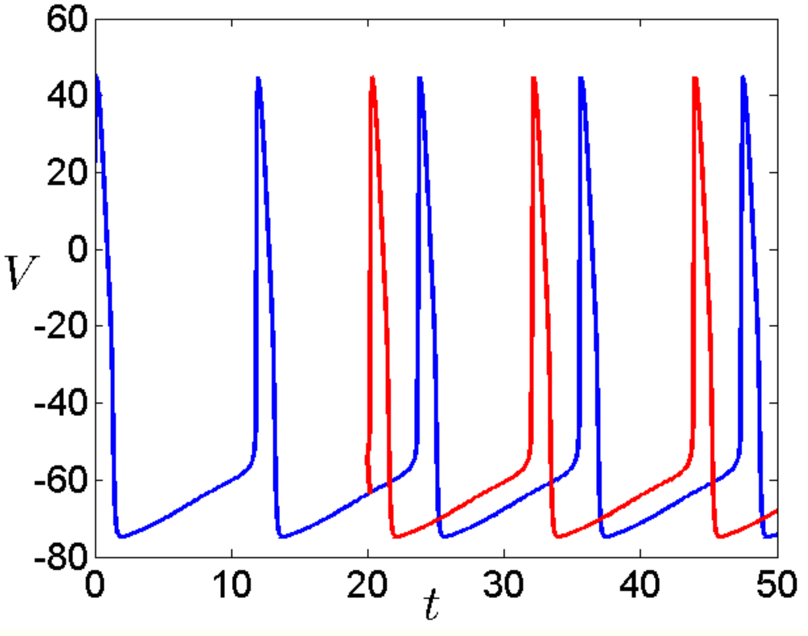
$$\dot{V} = \frac{1}{C}[I_{app} - \bar{g}_{Na}[m_\infty(V)]^3(0.8-n)(V-V_{Na}) - \bar{g}_K n^4 (V-V_K) - g_L(V-V_L) + u(t)]$$

gating variable for the conductance channel

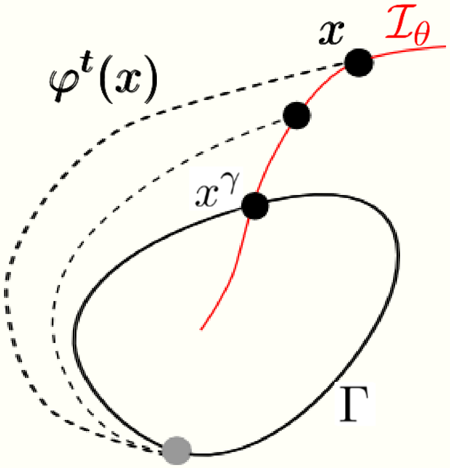
$$\dot{n} = \alpha(V)(1-n) - \beta(B)n$$

$$u(t) = 10\,\delta(t-20)$$

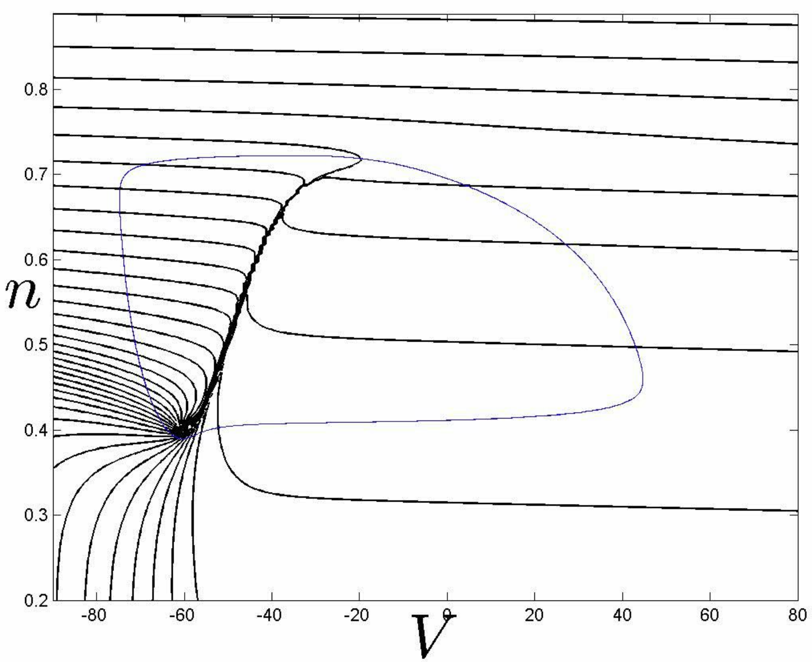




The isochrons are sets of initial conditions that share the same asymptotic behavior



$$\mathcal{I}_\theta = \{x \in \mathbb{R}^n | \lim_{t\to\infty} \|\varphi^t(x) - \varphi^t(x^\gamma)\| = 0\}$$



[Malkin, 1949]

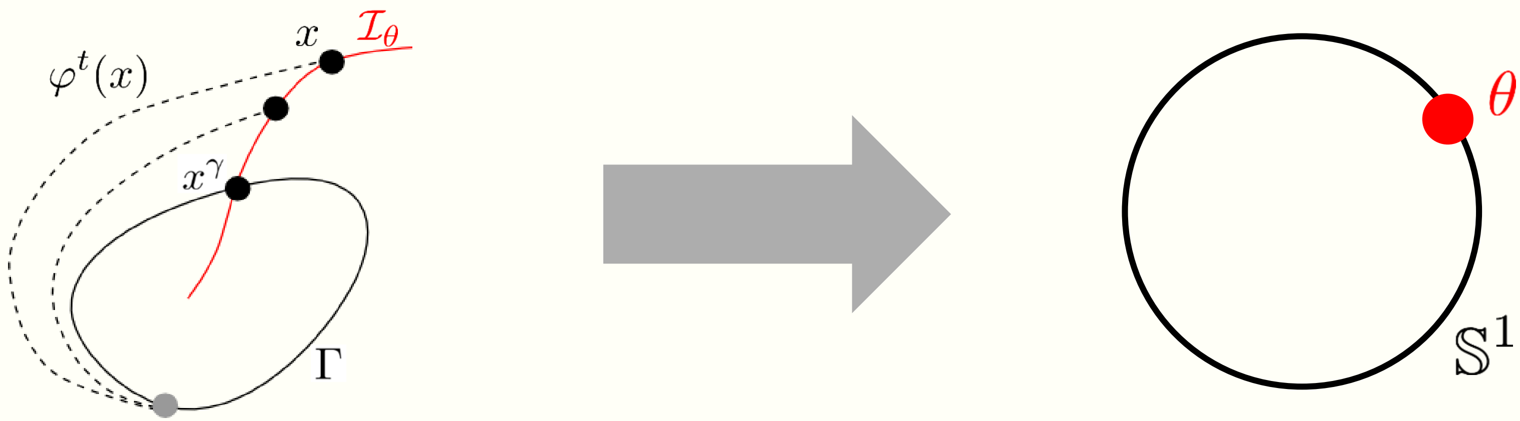
[Winfree, Journal Math Biol., 1974]

The isochrons yield a powerful phase reduction of high-dimensional limit-cycle oscillators

Powerful reduction from $\mathbb{R}^N$ to $\mathbb{S}^1$

$$\dot{x} = F(x)$$

$$\dot{\theta} = \omega$$



For weak input or coupling $u(t)$:

$$\dot{x} = F(x) + e_1 u(t) \quad \Rightarrow \quad \dot{\theta} = \omega + Z(\theta)u(t)$$

with the infinitesimal phase response (iPRC) $Z(\theta) = \dfrac{\partial \theta}{\partial x} \cdot e_1$

It is desirable but difficult to compute the global isochrons

Computation of the isochrons in the entire basin of attraction of the limit cycle

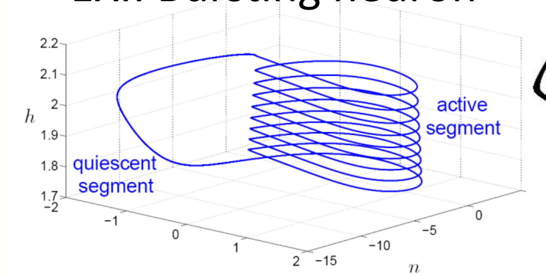
Why?
- global knowledge of the asymptotic behavior
- necessary for large inputs / strong couplings

How?
- standard backward integration *[e.g. Izhikevich, 2007]*
- solution of invariance equation + backward integration *[Guillamon & Huguet, 2009; Huguet & de la Llave, 2013]*
- continuation-based method *[Osinga & Moehlis, 2010]*

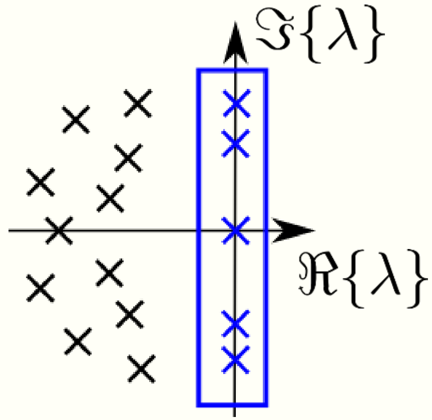
But the computation of the isochrons is difficult for

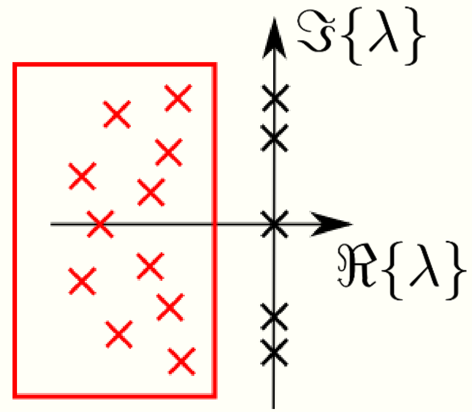
- high-dimensional systems
- slow-fast dynamics

EX.: Bursting neuron

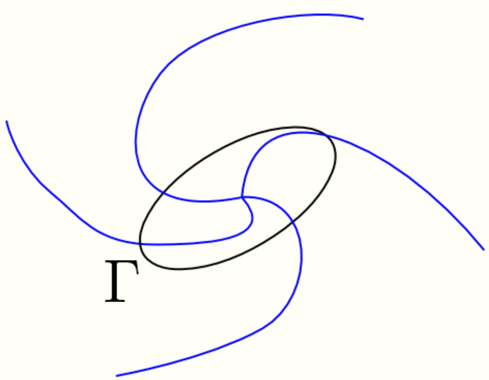


The Koopman eigenfunctions are tightly connected to the phase reduction of the systems

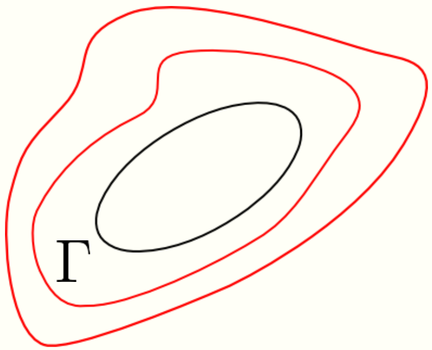




Level sets of ϕ_λ
≡ isochrons



Level sets of ϕ_λ
≡ isostables



phase reduction of limit cycles
and quasi-periodic tori

phase reduction of fixed points
(excitable systems)

Outline

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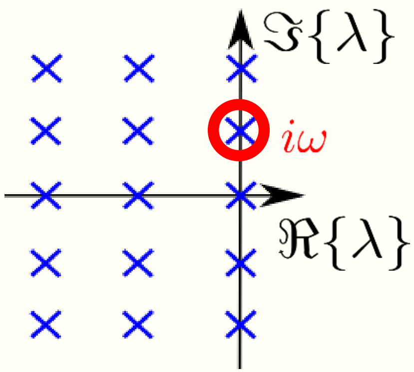
Isostables of excitable systems

The isochrons are the level sets of a Koopman eigenfunction

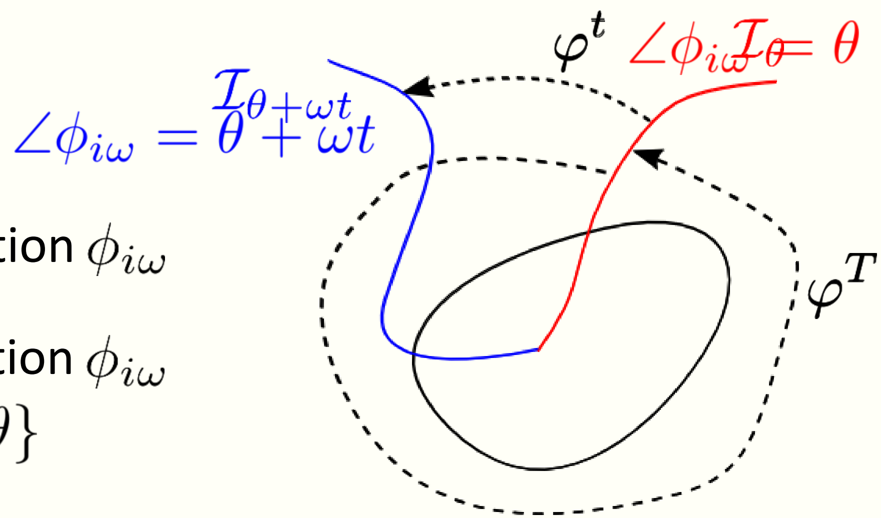
limit cycle frequency ω → Koopman eigenvalue $i\omega \in \sigma(U)$

period $T = 2\pi/\omega$ → Koopman eigenfunction $\phi_{i\omega}$



$$U^t \phi_{i\omega}(x) = \phi_{i\omega} \circ \varphi^t(x) = e^{i\omega t}\phi_{i\omega}(x)$$

$$\Rightarrow \quad \angle\phi_{i\omega} \circ \varphi^t(x) = \angle\phi_{i\omega}(x) + \omega t$$



The level sets of the Koopman eigenfunction $\phi_{i\omega}$ are the isochrons:

The level sets of the Koopman eigenfunction $\phi_{i\omega}$ define a periodic partition

$$\mathcal{I}_\theta = \{x \in \mathbb{R}^n | \angle\phi_{\omega_\Gamma}(x) = \theta\}$$

We obtain a novel efficient method for computing the isochrons

The Fourier average

$$f^*_{i\omega}(x) = \lim_{T\to\infty} \frac{1}{T} \int_0^T f \circ \varphi^t(x)\, e^{-i\omega t}\, dt$$

is a projection of f on $\phi_{i\omega}$ ➔ $f^*_{i\omega}(x) \equiv \phi_{i\omega}(x)$ if $f^*_{i\omega}(x) \neq 0$

$$\boxed{\angle f^*_{i\omega}(x) = \theta \;\Leftrightarrow\; x \in \mathcal{I}_\theta}$$

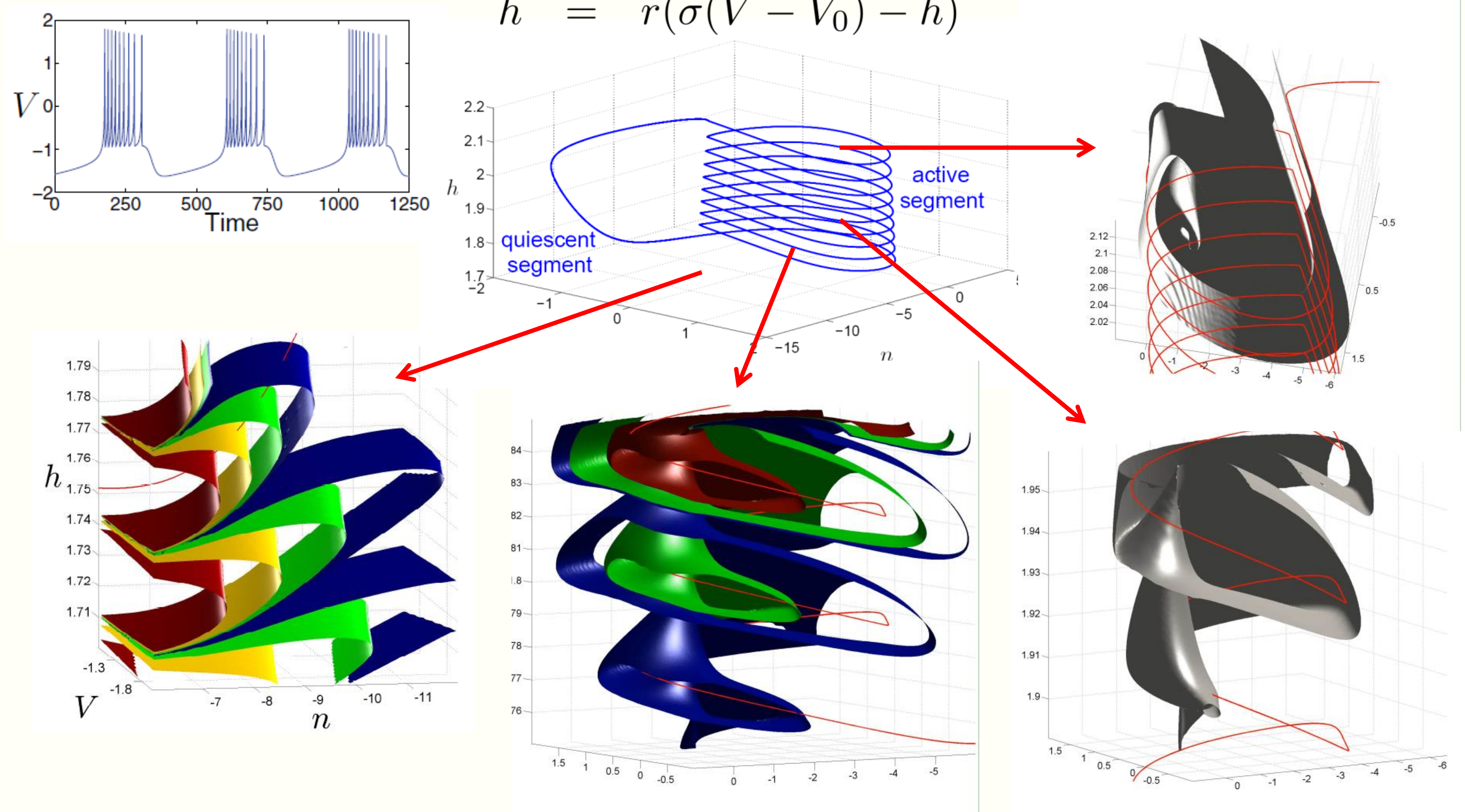
Algorithm: 1. Compute the Fourier averages on a (uniform/adaptive) grid
2. Compute the level sets of these values

This is a forward integration method
➔ well-suited to high-dimensional spaces and slow-fast dynamics

The Fourier average method is capable of computing the complex isochrons of bursting neurons

Hindmarsh-Rose model

$$\begin{aligned}\dot{V} &= n - aV^3 + bVr - h + I\\ \dot{n} &= c - dV^2 - n\\ \dot{h} &= r(\sigma(V - V_0) - h)\end{aligned}$$

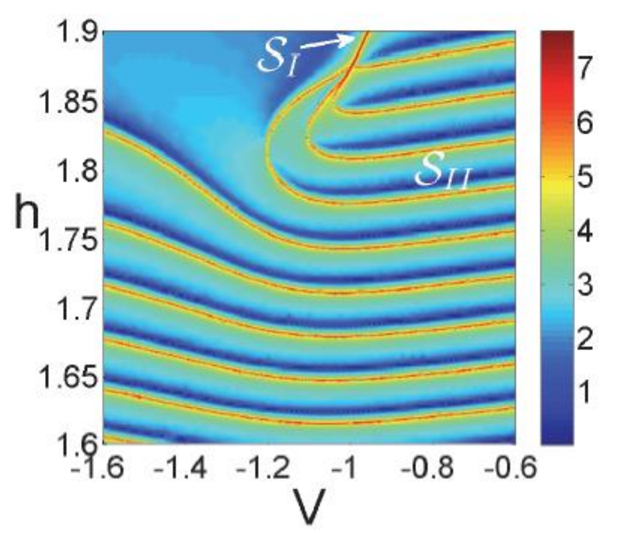


New phenomena were observed

Parabolic bursting neuron

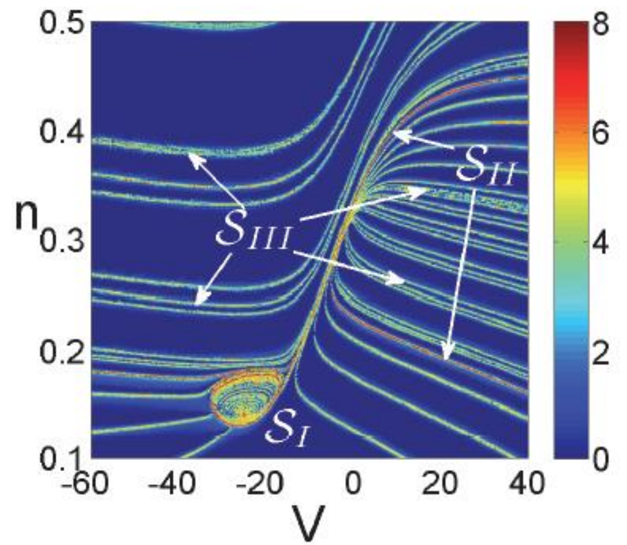
Existence of region of high phase variation (almost phaseless set)

➔ explain addition/deletion of spikes under the effect of small perturbations



Elliptic bursting neuron

The isochrons are fractal



[Mauroy et al, SIAM J. on Appl. Dyn. Syst., 2014]

The infinitesimal phase response curve is computed with Fourier averages of the prolonged system

Prolonged system

$$\dot{x} = F(x)$$
$$\dot{\delta x} = \partial F(x)\delta x$$

$$(x, \delta x) \mapsto (\varphi^t(x), \partial\varphi^t(x)\delta x)$$

Infinitesimal phase response curve $Z(\theta) = \frac{\partial\theta}{\partial x} \cdot e_1 = \partial\angle\phi_{i\omega}(x)e_1$

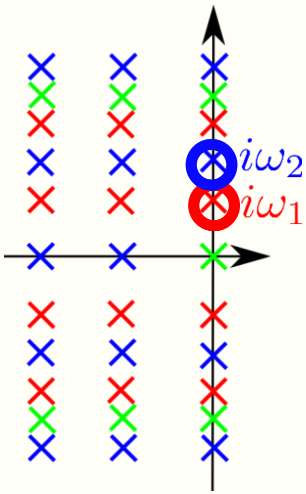
Fourier average of $\partial f(x)\delta x$ along the trajectories of the prolonged system

$$\partial f^*_{i\omega}(x)\delta x = \lim_{T\to\infty} \frac{1}{T}\int_0^T \partial f(\varphi^t(x))[\partial\varphi^t(x)\delta x]\, e^{-i\omega t}\, dt$$

We have $\partial\phi_{i\omega}(x)\delta x \equiv \partial f^*(x)\delta x$ and

$$\boxed{Z(\theta) = \frac{\partial f^*_{i\omega}(x)e_1}{i f^*_{i\omega}(x)}}$$

Fo quasi-periodic tori, the Koopman eigenfunctions lead to the notion of « generalized » isochrons



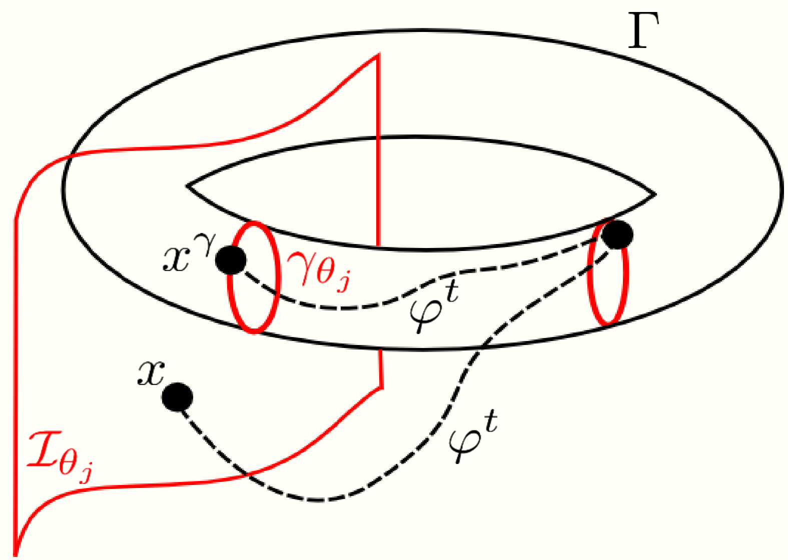
m-dimensional quasiperiodic torus (with frequencies ω_j) ⇒ Koopman eigenvalues $i\omega_j \in \sigma(U)$

Koopman eigenfunctions $\phi_{i\omega_j}$

We define m families of generalized isochrons as the level sets

$$\mathcal{I}_{\theta_j} = \{x \in \mathbb{R}^n | \angle\phi_{\omega_j}(x) = \theta_j\} \qquad j = 1, \ldots, m$$

A generalized isochron converges to the same invariant curve γ_{θ_j}



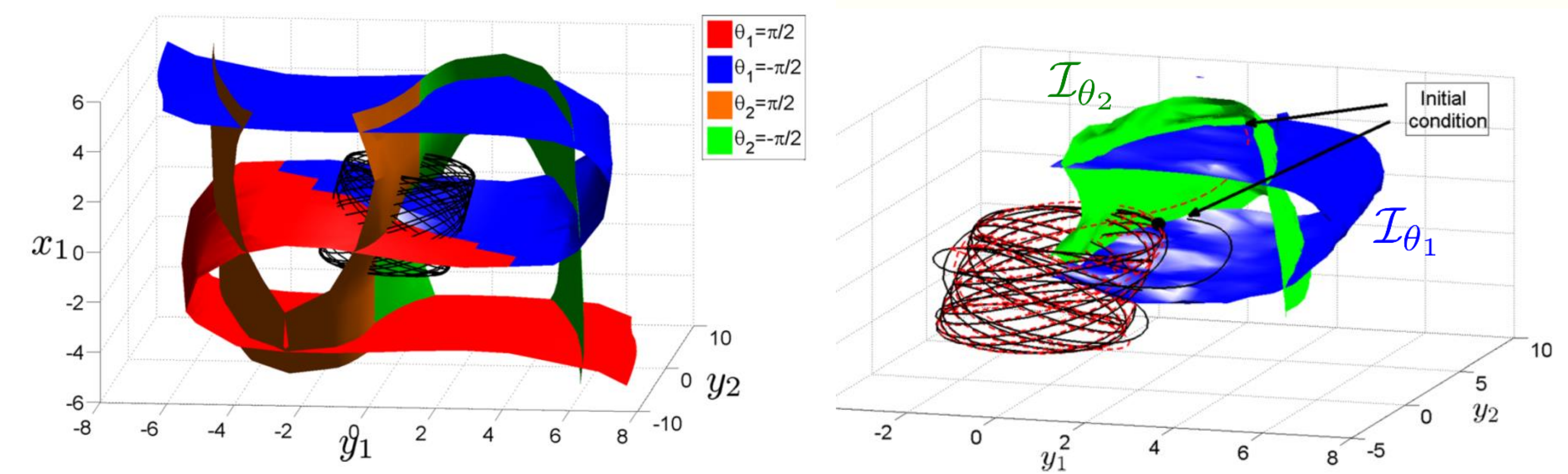
$$\mathcal{I}_{\theta_j} = \{x \in \mathbb{R}^n | \exists x^\gamma \in \gamma_{\theta_j} \text{ s.t. } \lim_{t\to\infty} \|\varphi^t(x) - \varphi^t(x^\gamma)\| = 0\}$$

The framework can be used to study synchronization in networks of « quasi-oscillators »

The intersection $\mathcal{I}_{\theta_1} \cap \cdots \cap \mathcal{I}_{\theta_m}$ is assigned with the phases $(\theta_1, \ldots, \theta_m)$

It is a fiber of the torus : every point of $\mathcal{I}_{\theta_1} \cap \cdots \cap \mathcal{I}_{\theta_m}$ converges to the same trajectory on the torus

<u>Example:</u> two coupled Van der Pol oscillators



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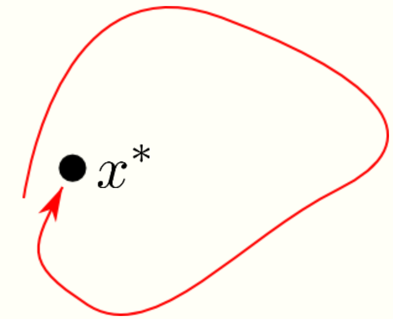
Isostables of excitable systems

Can we extend the notion of isochrons to stable fixed points?

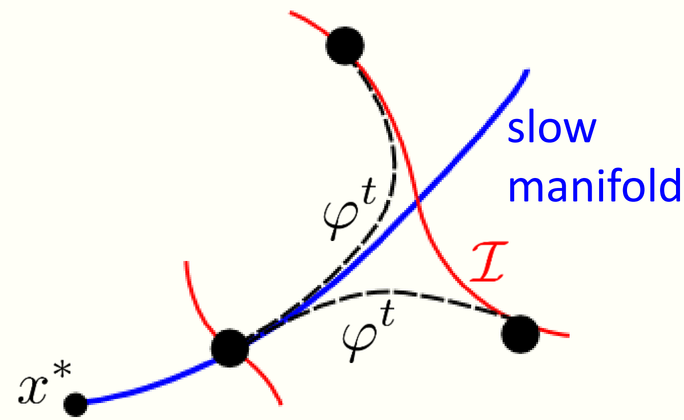
Excitable system (neuron, cardiac cell): stable equilibrium x^*



Phase reduction ⟺ sets of points that converge synchronously toward the equilibrium ?

Previous framework

☹ requires the existence of a slow manifold (slow-fast dynamics)
☹ no rigorous definition
☹ relies on backward integration



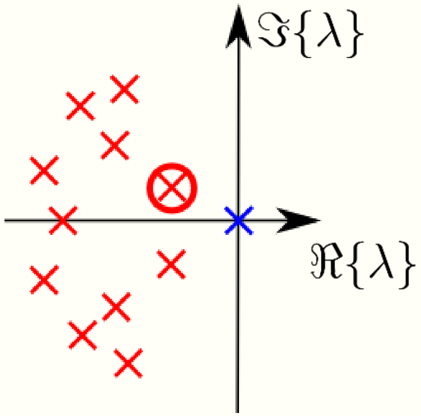
[Rabinovitch, 1999]

The Koopman operator provides a rigorous way to extend the notion of isochrons

$$\lambda_j \in \sigma\left(\left.\frac{\partial F}{\partial x}\right|_{x^*}\right) \quad \Rightarrow$$

Koopman eigenfunctions ϕ_{λ_j}

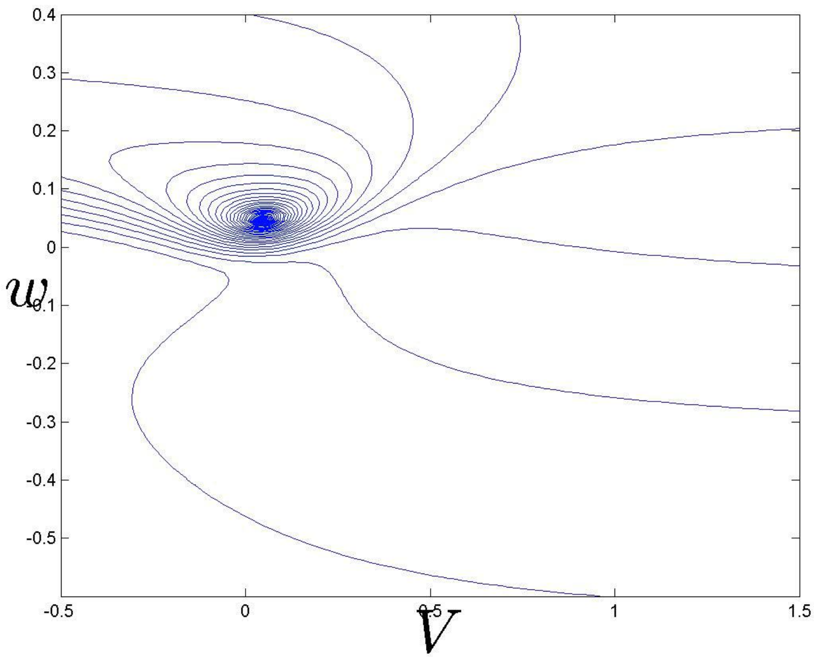
$$\lambda_j \in \sigma(U)$$



➔ we define the « isostables » as the level sets of $|\phi_{\lambda_1}(x)|$

Example:

FitzHugh-Nagumo model (excitable neuron)



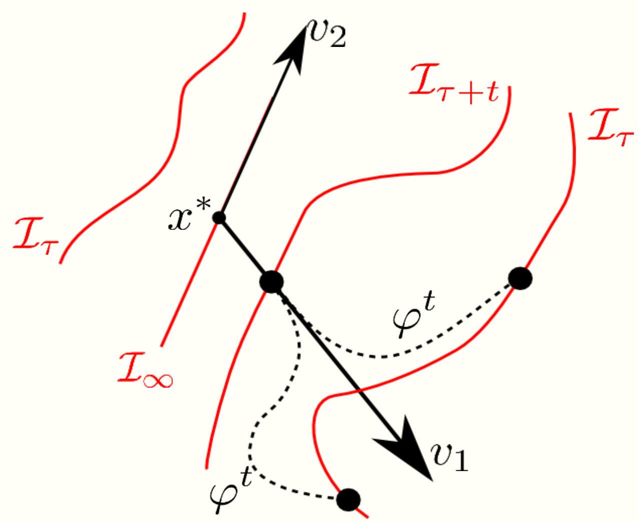
[Mauroy et al, Physica D, 2013]

The isostables are the sets of points that converge synchronously toward the fixed point

$$\mathcal{I}_\tau = \{x \in \mathbb{R}^n \,|\, |\phi_{\lambda_1}(x)| = e^{\Re\{\lambda_1\}\tau}\}$$

Real eigenvalue λ_1 $\quad x \in \mathcal{I}_\tau$ i.e. $|\phi_{\lambda_1}(x)| = e^{\tau\lambda_1}$

$\Rightarrow$ $\varphi^t(x) \to x^* + v_1^{\pm} e^{\lambda_1(t+\tau)}$ as $t \to \infty$



The isostables are the fibers of an invariant manifold (tangent to v_1 at x^*)

The isostables are the sets of points that converge synchronously toward the fixed point

$$\mathcal{I}_\tau = \{x \in \mathbb{R}^n \,|\, |\phi_{\lambda_1}(x)| = e^{\Re\{\lambda_1\}\tau}\}$$

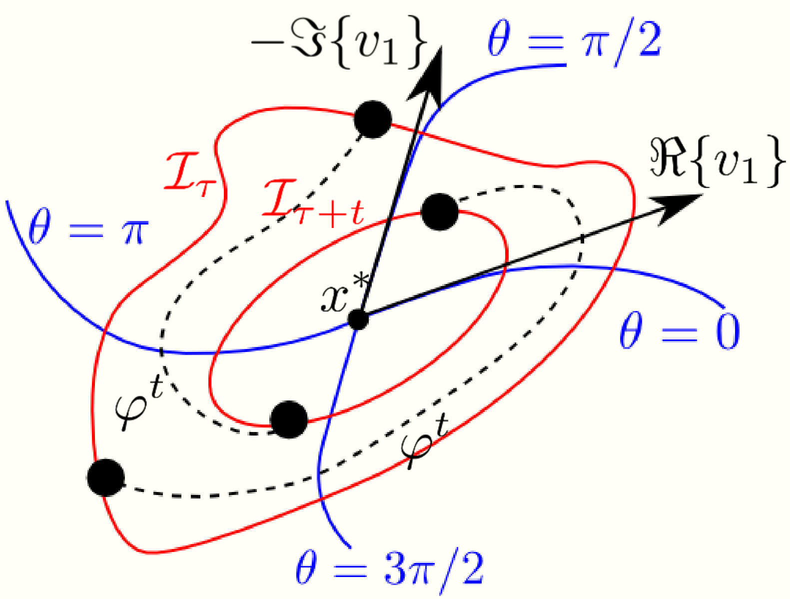
Complex eigenvalue $\lambda_1 = \sigma + i\omega$

$x \in \mathcal{I}_\tau$ i.e. $|\phi_{\lambda_1}(x)| = e^{\tau\sigma}$ $\quad \angle\phi_{\lambda_1}(x) = \theta$

$$\varphi^t(x) \to x^* + 2(\Re\{v_1\}\cos(\omega t + \theta) - \Im\{v_1\}\sin(\omega t + \theta))e^{\sigma(t+\tau)}$$

as $t \to \infty$

isostables	$\vert\phi_{\lambda_1}(x)\vert = r$	$\dot{r} = \sigma r$
isochrons	$\angle\phi_{\lambda_1}(x) = \theta$	$\dot{\theta} = \omega$



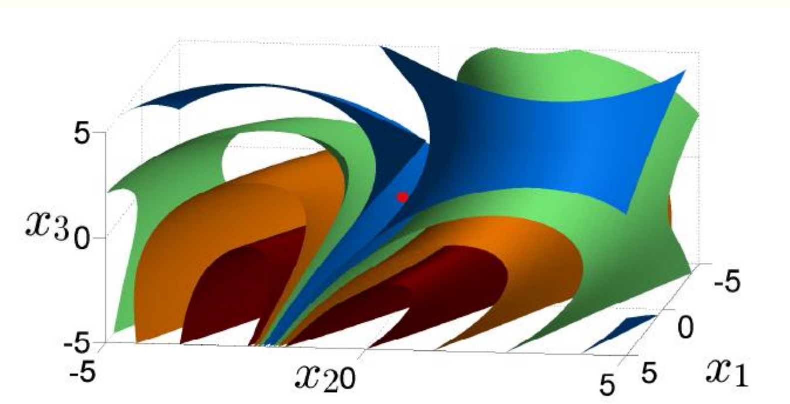
The isostables are computed with Laplace averages and used in several applications

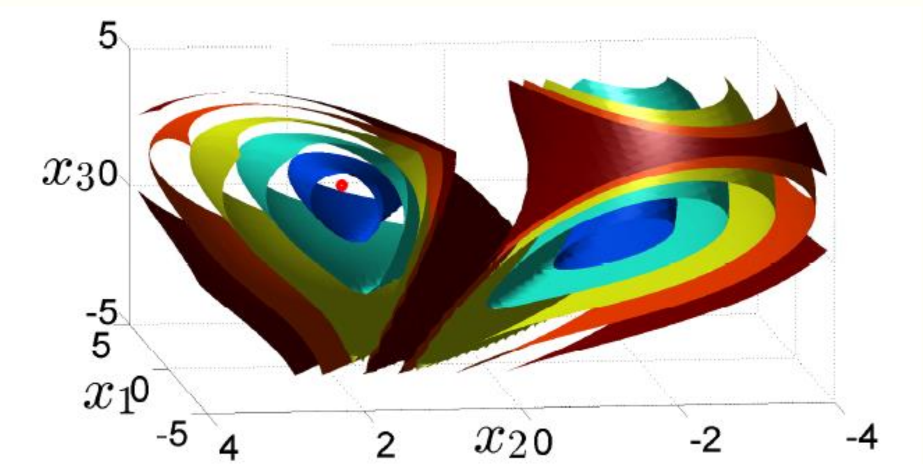
The Laplace average

$$f_\lambda^*(x) = \lim_{T\to\infty} \frac{1}{T}\int_0^T f\circ\varphi^t(x)\, e^{-\lambda t}\, dt$$

is a projection of f on ϕ_λ ➔ $f_\lambda^*(x) \triangleq \phi_\lambda(x)$ if $f_\lambda^*(x) \neq 0$

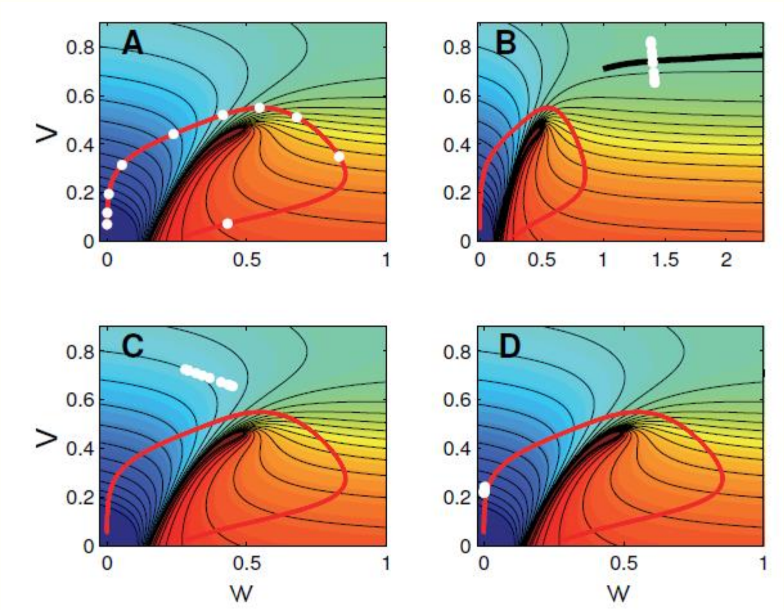
$$|f_\lambda^*(x)| = e^{\lambda\tau} \;\Leftrightarrow\; x \in \mathcal{I}_\tau$$



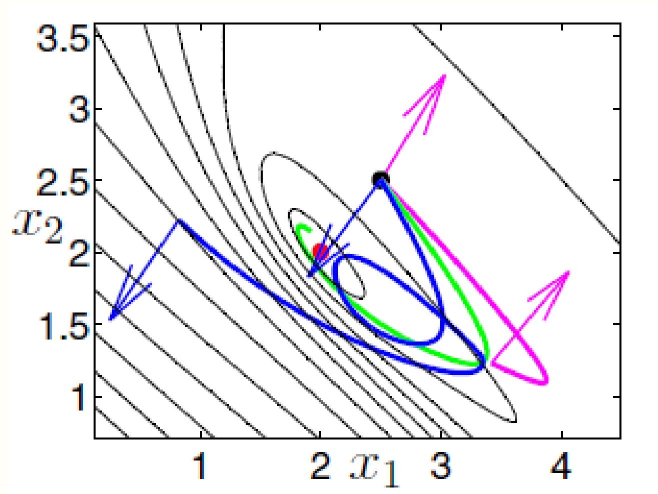


Several applications of the isostables

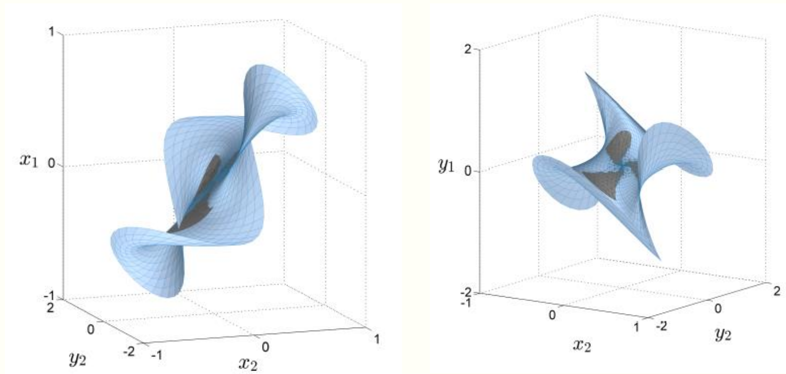
design of cardiac defibrillation techniques
[Wilson and Moehlis, SIAM review, 2015]



optimal escape - convergence
[Mauroy, CDC 2014]



nonlinear normal modes in vibration theory
[Cirillo et al., ASME 2015]



The spectral properties of the Koopman operator are related to phase reduction

The isochrons of limit cycle are the level sets of a Koopman eigenfunction

Phase reduction is generalized

to quasi-periodic tori ➔ generalized isochrons

to equilibria (excitable systems) ➔ isostables

Application to neuroscience (among others)

Perspectives:

Toward more general phase reductions (e.g. phase-amplitude)

Application to control theory (e.g. optimal control)

Bibliography

Phase reduction and isochrons

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Koopman operator and isochrons

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Koopman operator and isostables

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