Neuroscience applications:

isochrons and isostables

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Isochrons and phase reduction of neurons

Koopman operator and isochrons

Isostables of excitable systems
Outline

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

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

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

(reduced) Hodgkin-Huxley neuron model

**membrane potential**

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

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

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

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

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

$$\dot{x} = F(x) + e_1 u(t)$$

with the infinitesimal phase response (iPRC) $Z(\theta) = \frac{\partial \theta}{\partial x} \cdot e_1$
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
The Koopman eigenfunctions are tightly connected to the phase reduction of the systems.

Level sets of $\phi_\lambda \equiv$ isochrons

Level sets of $\phi_\lambda \equiv$ isostables

Phase reduction of limit cycles and quasi-periodic tori

Phase reduction of fixed points (excitable systems)
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Isostables of excitable systems
The isochrons are the level sets of a Koopman eigenfunction.

Limit cycle frequency \( \omega \)

Period \( T = \frac{2\pi}{\omega} \)

Koopman eigenvalue \( i\omega \in \sigma(U) \)

Koopman eigenfunction \( \phi_{i\omega} \)

Level sets of the Koopman eigenfunction define a periodic partition:

\[
\angle \phi_{i\omega} = \frac{T\theta + \omega t}{\theta}
\]

\[
\Sigma_{\theta} = \{ x \in \mathbb{R}^n | \angle \phi_{i\omega} (x) = \theta \} \]
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 \( \phi_{i\omega} \) \( \Rightarrow \) \( f_{i\omega}^*(x) \equiv \phi_{i\omega}(x) \) if \( f_{i\omega}^*(x) \neq 0 \)

\[ \angle f_{i\omega}^*(x) = \theta \iff x \in \mathcal{I}_\theta \]

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
   \( \Rightarrow \) 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**

\[ \frac{\dot{V}}{\dot{n}} \quad \frac{\dot{n}}{\dot{h}} = \begin{align*}
V &= n - aV^3 + bVr - h + I \\
n &= c - dV^2 - n \\
h &= r(\sigma(V - V_0) - h)
\end{align*} \]
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

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

Prolonged system

\[
\begin{align*}
\dot{x} &= F(x) \\
\dot{\delta x} &= \partial F(x)\delta x
\end{align*}
\]

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

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

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

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

\[
Z(\theta) = \frac{\partial f^*_i(x)e_1}{i f^*_i(x)}
\]
Fo quasi-periodic tori, the Koopman eigenfunctions lead to the notion of «generalized» isochrons

We define $m$ families of generalized isochrons as the level sets

$$\mathcal{I}_{\theta_j} = \{ x \in \mathbb{R}^n | \angle \phi_{\omega_j}(x) = \theta_j \}$$

$j = 1, \ldots, m$

$m$-dimensional quasiperiodic torus (with frequencies $\omega_j$)

Koopman eigenvalues $i\omega_j \in \sigma(U)$

Koopman eigenfunctions $\phi_{i\omega_j}$

A generalized isochron converges to the same invariant curve $\gamma_{\theta_j}$

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

**Example:** 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 $x^*$

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

\[ \lambda_j \in \sigma \left( \frac{\partial F}{\partial x} \bigg|_{x^*} \right) \implies \text{Koopman eigenfunctions } \phi_{\lambda_j} \]

\[ \lambda_j \in \sigma(U) \]

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. 

\[ \mathcal{I}_\tau = \{ x \in \mathbb{R}^n \mid |\phi_{\lambda_1}(x)| = e^{R\{\lambda_1}\tau} \} \]

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

\[ \varphi^t(x) \to x^* + v_1^\pm e^{\lambda_1(t+\tau)} \quad \text{as } t \to \infty \]

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.

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

**Complex eigenvalue** \( \lambda_1 = \sigma + i\omega \)

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

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

as \( t \to \infty \)

**Isostables**
\[ |\phi_{\lambda_1}(x)| = r \quad \dot{r} = \sigma r \]

**Isochrons**
\[ \angle \phi_{\lambda_1}(x) = \theta \quad \dot{\theta} = \omega \]
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 \( \phi_\lambda \) \( \Rightarrow f^*_\lambda(x) \triangleq \phi_\lambda(x) \) 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 $\Rightarrow$ generalized isochrons
  to equilibria (excitable systems) $\Rightarrow$ isostables

Application to neuroscience (among others)

Perspectives:

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

  Application to control theory (e.g. optimal control)
Phase reduction and isochrons


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