Phase resetting as a two-point boundary value problem

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Summary. Phase resetting is used in experiments with the aim to classify and characterise different neurons by their responses to perturbations away from a periodic bursting pattern. The same approach can also be applied numerically to a mathematical model. Resetting is closely related to the concept of isochrons of a periodic orbit, which are the submanifolds in its basin of attraction of all points that converge to this periodic orbit with a specific phase. Until recently, such numerical phase resets were performed in an ad-hoc fashion, and the development of suitable computational techniques was only started in the last decade or so. We present an approach based on the continuation of solutions to a two-point boundary value problem that directly evaluates the phase associated with the isochron that the perturbed point is located on. We illustrate this method with the FitzHugh–Nagumo model and investigate how the resetting behaviour is affected by phase sensitivity in the system.

In certain physiological experiments, a perturbation is applied to an oscillator, and one is interested in how the dynamics relaxes back to its regular rhythm [3, 12]. The resulting phase-shift is known as a phase reset, and recorded in terms of a *phase response curve* (PRC) or *amplitude response curve* (ARC); these are obtained by varying the phase at which the reset is applied, or by varying the amplitude of the reset when applied at a fixed given phase, respectively. Phase resets give insight into the underlying dynamics of biological oscillator, such as circadian clocks, yeast cells, and the cell cycle [12].

Mathematically, the oscillator is an attracting periodic orbit. Points on the periodic orbit have a relative phase, and any point in the basin of attraction can similarly be assigned an asymptotic (or latent) phase, defined as the phase with which the point converges to the periodic orbit [11]. The set of all points with the same asymptotic phase forms a manifold, called an isochron, and the family of isochrons foliates the basin of attraction [5]. Theoretically, a PRC or ARC can be computed by determining the phases of the isochrons that are associated with the reset points. In practice, this idea has proved to be rather challenging. Traditionally, ad-hoc model simulation has been applied [2, 4, 11]. Recently, more accurate techniques have been developed for the computation of isochrons, which are amenable for isochrons of systems that exhibit strong or even extreme phase sensitivity in possibly large regions of phase space; see [8] and references therein. Consequently, there are now also much better algorithms for the computation of PRCs, ARCs, and other resetting curves [6, 9].

Our method [10] computes one-dimensional isochrons of planar systems by pseudo-arclength continuation of solutions to a suitable boundary value problem (BVP). It has the advantage that it can generate very accurate approximations of isochrons globally, over a very large part of phase space. We adapt this method here so that we can generate PRCs or ARCs also with a BVP approach; we use the package AUTO [1] throughout to obtain solution families of the respective BVPs. The BVP that defines a phase reset consists of four orbit segments that are related via boundary conditions. Each orbit segment is a solution to the vector field given in the form

$$\tfrac{d}{ds}\mathbf{u} = T\,\mathbf{f}(\mathbf{u}),$$

where $\mathbf{f} : \mathbb{R}^2 \to \mathbb{R}^2$ defines the original vector field and time is rescaled to time s measured in units T of total integration time of the respective orbit segment. Hence, T is treated as a parameter.

The first two orbit segments define the periodic orbit $\Gamma := \{\mathbf{u}(s) \in \mathbb{R}^2 \mid 0 \le s \le 1\}$, with period T_Γ, and its associated vector bundle $\mathbf{v} := \{\mathbf{v}(s) \in \mathbb{R}^2 \mid 0 \le s \le 1\}$ of the stable Floquet multiplier of Γ; each vector $\mathbf{v}(s)$ is tangent to the isochron associated with the point $\gamma_\vartheta \in \Gamma$ such that $\gamma_\vartheta = \mathbf{u}(s)$. For both orbit segments, the parameter T is set to the period T_Γ of Γ. Instead of imposing a phase condition—which would be necessary if one wants to continue Γ in a parameter—we allow the head point $\mathbf{u}(0) = \mathbf{u}(1)$ on Γ to vary; in other words, $\mathbf{u}(0)$ is not necessarily equal to the point $\gamma_0 \in \Gamma$ with phase 0. We keep track of the phase that corresponds to a shifted head point $\mathbf{u}(0)$ by way of a third orbit segment $\mathbf{w} := \{\mathbf{w}(s) \in \mathbb{R}^2 \mid 0 \le s \le 1\}$ that starts at $\mathbf{w}(0) = \mathbf{u}(0)$ and ends at $\mathbf{w}(1) = \gamma_0$. For numerical reasons, the end condition for $\mathbf{w}$ is relaxed so that $\mathbf{w}(1)$ is allowed to differ from γ_0 in the direction of its (linearised) isochron. The total integration time for $\mathbf{w}$ is measured in fractions of T_Γ, that is, we set $T = \nu\, T_\Gamma$ for this orbit segment. The fourth and final orbit segment defines the orbit segment $\mathbf{p} := \{\mathbf{p}(s) \in \mathbb{R}^2 \mid 0 \le s \le 1\}$ of a reset point $\mathbf{p}(0)$ converging back to Γ. Its total integration time is an integer multiple of T_Γ and its end point is $\mathbf{p}(1) = \mathbf{u}(0) + \eta\,\mathbf{v}(0)$, for some small parameter $0 < \eta \ll 1$; here, $\mathbf{v}(0)$ has length 1.

The PRC is then found by continuation in ν as the variation in phase $\varphi = 1 - \nu$, while $\mathbf{p}(0)$ traces the path of a shifted periodic orbit; the ARC is defined similarly by setting $\mathbf{p}(0) = \gamma_\vartheta + A\,\mathbf{d}$ and varying the reset amplitude A, where $\mathbf{d}$ is a reset direction.

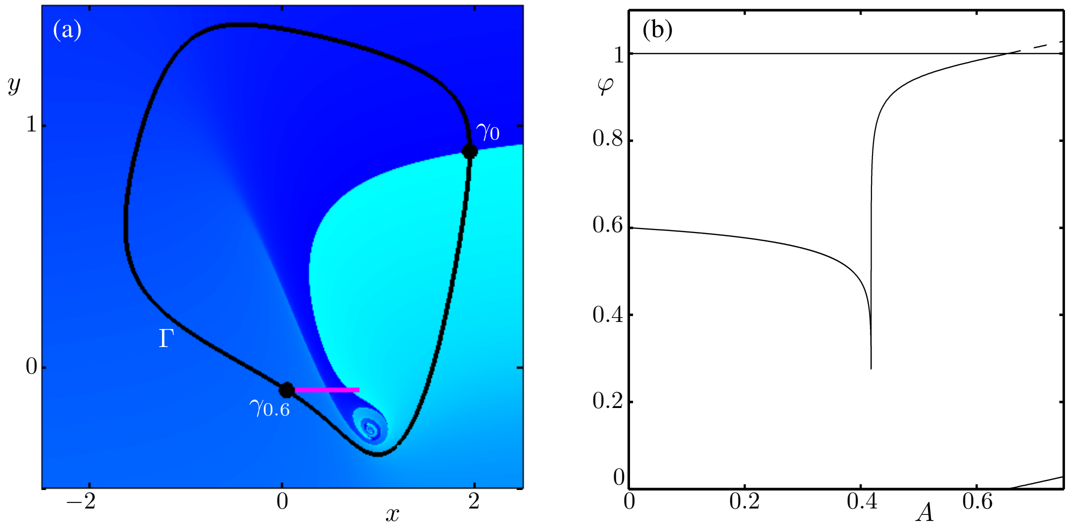

Figure 1: Phase-resetting for the FitzHugh–Nagumo system (1) where a reset is applied in the direction $\mathbf{d} = (1, 0)^t$ from the point $\gamma_{0.6} \in \Gamma$ with varying amplitude $A \in [0, 0.75]$. Panel (a) shows Γ with its isochrons plotted on a colour gradient from cyan at phase 0 to dark blue at phase 1; the purple curve indicates the A-dependent reset. Panel (b) shows the resulting phase $\varphi = 1 - \nu$ versus A.

As an example, we consider the two-dimensional FitzHugh–Nagumo system, which is the iconic polynomial model for which Winfree found that it exhibits extreme phase sensitivity due to its slow-fast nature [12]. The model is given as

$$\left\{ \begin{array}{rcl} \dot{x} & = & c\,\left(y + x - \frac{1}{3}\,x^3 + z\right), \\ \dot{y} & = & -\frac{1}{c}\,(x + a - b\,y), \end{array} \right. \tag{1}$$

where we fix $z = -0.4$, $a = 0.7$, and $b = 0.8$ as in [12], but set $c = 2.5$. For these parameter values, there exists an attracting periodic orbit Γ with period $T_\Gamma \approx 10.71$. We define the point with zero phase as the point $\gamma_0 \in \Gamma$ that has a maximum with respect to the x-coordinate; this point is $\gamma_0 \approx (1.94,\ 0.89)$.

Figure 1(a) shows Γ together with its isochrons; the isochron associated with γ_0 is coloured cyan and the other isochrons are similarly coloured on a colour gradient from cyan to dark blue. We apply a reset to the point $\gamma_{0.6}$ that lies on Γ at time $0.6\,T_\Gamma$ further along from γ_0. The reset is in the horizontal direction $\mathbf{d} = (1, 0)^t$, and we vary its amplitude A in the interval $[0, 75]$; see the purple line in Figure 1. Hence, $\gamma_{0.6}$ is reset to the point $\gamma_{0.6} + A\,\mathbf{d}$ and we compute the ARC as the corresponding A-dependent asymptotic phase $\varphi = 1 - \nu$ of the reset point $\gamma_{0.6} + A\,\mathbf{d}$.

Figure 1(b) shows the computed ARC as φ against A. Note that the A-parametrised line of reset points passes through a region with extreme phase sensitivity [7]. Consequently, the ARC becomes near vertical in this region, which lies approximately at $A = 0.42$. Our numerical continuation set-up has no trouble traversing such a phase-sensitive region and the ARC can be obtained reliably and efficiently even if it has a near-vertical derivative; note also the discontinuity at $A \approx 0.67$, where φ jumps from 1 to 0.

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