Adaptive estimation and control method for unstable periodic dynamics in spike trains

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(Received 10 May 1999; revised manuscript received 28 January 2000)

Dynamical control of excitable biological systems is often complicated by the difficult and unreliable task of precontrol identification of unstable periodic orbits (UPO's). Here we show that, for both chaotic and nonchaotic systems, UPO's can be located, and their dynamics characterized, *during* control. Tracking of system nonstationarities emerges naturally from this approach. Such a method is potentially valuable for the control of spike trains of excitable biological systems, for which precontrol UPO identification is often impractical, and nonstationarities (natural or stimulation induced) are common.

PACS number(s): 05.45.Gg, 07.05.Dz, 87.10.+e, 87.17.Nn

Chaos control techniques have been applied to a number of excitable biological systems [1–5] comprised of spontaneously firing cells. Such control typically attempts to replace an unwanted irregular or higher-order firing pattern with a lower-order periodic rhythm. One particular control technique, proportional perturbation feedback (PPF) control [1], uses isolated electrical stimuli to cause the cells to fire at a specified time, thus directly altering the variable of interest, the interexcitation interval [in contrast to Ott-Grebogi-Yorke (OGY) type control [6], which indirectly alters the variable of interest by perturbing a system parameter]. In the idealized situation presented in Refs. [1] and [2] the PPF stimuli achieve control by placing the state of the biological system onto the stable manifold of a desired unstable periodic orbit (UPO).

The successful application of PPF control requires an estimate of the location of the uncontrolled system's UPO and corresponding manifolds. UPOs and their eigenvalues [7] are typically characterized from measurements of the system in free-running mode, without external stimulation [1,2]. PPF-type [8] stimuli are then used to alter the interexcitation interval in an attempt to place the system state point onto the estimated stable manifold, and therefore stabilize the UPO.

Proper estimation of the UPO and its characteristics is of fundamental importance to PPF-type control for several reasons. First, optimal control (which we consider to be stabilization of the desired UPO with a minimal number of stimuli) is achieved when the system state is placed onto the stable manifold. Without placement directly onto a stable manifold, control can be achieved via alternative dynamical mechanisms [9–13] that require more frequent stimulation. Second, knowledge of unstable orbits can provide a skeleton upon which to build a model of the overall system. Third, the UPO may change over time; by continuously tracking the properties of the orbit, one can adaptively change the control parameters in order to maintain the controlled stability of the orbit. Changes in the UPO may stem from autonomous drifts in the properties of the biological system, or may be a response to the control stimuli (a tissue's dynamical or electrochemical properties may be modified by stimulation [14,15]). With these reasons in mind, this paper is concerned with ways to use PPF-type control in order to identify, control, and track such UPO's and their manifolds.

The detection of a UPO using data collected in the uncontrolled, free-running system [1,2] can be problematic. As mentioned above, one problem with such an approach is that excitable biological systems are typically nonstationary. Thus a precontrol UPO estimate may become invalid before or during the control stage. Another problem is that in the free-running system, the system's state may spend little time in the vicinity of the orbit. As an extreme case, a system with a stable attracting periodic orbit may well have other UPO's, but the free-running system will visit only the stable orbit. Even with a lengthy free-running data collection stage, there is no guarantee that there will be sufficient data from within the UPO neighborhood; a paucity of such data from within the UPO neighborhood renders the reliability of the estimated UPO characteristics dubious. Statistical tests have been proposed to validate UPO existence [16–18], but the most compelling evidence comes when control of a putative orbit is successfully achieved. With this in mind, an alternative to precontrol UPO identification is to locate and characterize a UPO while attempting control. Although adaptive OGY-type control techniques have been developed [19–23], PPF control is nonlinear near the fixed point (in contrast to OGY control), and therefore requires new adaptive approaches.

To this end, Kaplan [13] recently showed that a stimulus-pattern bifurcation that occurs at the location of a UPO can be detected (as described below) and therefore used as a means of locating UPO's during control. Such control allows the experimentalist to circumvent the major hurdle of precontrol UPO identification: the limited time that the state point spends in the UPO neighborhood. However, although the system's state stays near the UPO during such control, estimation of UPO characteristics is complicated by the fact that the natural UPO dynamics are masked by the control stimuli. So the experimentalist faces a choice of studying the free-running system with infrequent UPO data, or studying the controlled system with plentiful data but with obscured or altered dynamics. As we show in this paper, the latter alternative can be made feasible by circumventing the mask-

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ing in either of two ways: (1) estimating the natural UPO dynamics *between* intermittently applied stimuli, or (2) jiggling the control parameters.

We will examine systems whose natural, uncontrolled dynamics can be approximated by an autoregressive system $x_{n+1}=f(x_n,x_{n-1})$. For control of excitable biological systems, x_n is taken to be the time interval between the nth system firing and the previous firing. While the state point (x_n,x_{n-1}) is in the neighborhood of a UPO, the system dynamics can be approximated linearly as $x_{n+1}=ax_n+bx_{n-1}+c$, or, rewriting the constants a, b, and c in terms of the parameters of the UPO,

$$x_{n+1}=(\lambda_s+\lambda_u)x_n-\lambda_s\lambda_u x_{n-1}+x_\star(1+\lambda_s\lambda_u-\lambda_s-\lambda_u), \tag{1}$$

where λ_s and λ_u are the eigenvalues of the linearized system, and $x_\star$ is the location of the UPO sampled once per cycle. The notation is intended to suggest that there is one stable eigenvalue and one unstable eigenvalue, as required for a saddle-type fixed point. However, the equation is applicable even when both eigenvalues are unstable.

The application of PPF-type control changes the dynamics near the UPO to a nonlinear form:

$$x_{n+1}=\min\begin{cases}(\lambda_s+\lambda_u)x_n-\lambda_s\lambda_u x_{n-1} & \\ +x_\star(1+\lambda_s\lambda_u-\lambda_s-\lambda_u), & \text{natural dynamics}\\ \widehat{\lambda}_s(x_n-\widehat{x}_\star)+\widehat{x}_\star, & \text{control stimulus,}\end{cases} \tag{2}$$

where $\widehat{x}_\star$ and $\widehat{\lambda}_s$ are estimates of the UPO position $x_\star$ and stable manifold slope λ_s, respectively. Kaplan [13] showed that for a flip saddle, when $\widehat{x}_\star\approx x_\star$ and $|\widehat{\lambda}_s|<1$, the controlled system modeled by Eq. 2 will be characterized by a control stimulus applied either every interval (when $\widehat{x}_\star<x_\star$; due to the flip saddle, no naturally terminated intervals less than $\widehat{x}_\star$ can occur) or every second interval with the intermediate intervals being terminated naturally (when $\widehat{x}_\star>x_\star$; due to the flip saddle, there will be a naturally terminated interval less than $\widehat{x}_\star$ following each control stimulus). As shown in Ref. [13], $x_\star$ can be located by systematically scanning over a range of $\widehat{x}_\star$ for the stimulus-pattern bifurcation [24].

In the system of Eq. (2), it is not possible to estimate λ_s and λ_u because the natural dynamics are obscured by the control stimuli. For the flip saddle case where $\widehat{x}_\star<x_\star$ (when control stimuli are applied every interval), the controlled dynamics are simply

$$x_{n+1}=\widehat{\lambda}_s(x_n-\widehat{x}_\star)+\widehat{x}_\star. \tag{3}$$

The natural λ_s and λ_u do not enter into these dynamics, and therefore cannot be estimated from them. For the flip saddle case where $\widehat{x}_\star>x_\star$ (when control stimuli are applied every second interval), the controlled dynamics for intervals that end naturally without a control stimulus are

$$x_{n+1}=[\widehat{\lambda}_s(\lambda_s+\lambda_u)-\lambda_s\lambda_u]x_{n-1}+[1+\lambda_s\lambda_u-\widehat{\lambda}_s(\lambda_s+\lambda_u)]\widehat{x}_\star \tag{4}$$

[by substituting the bottom equation of Eq. (2) for x_n in the top equation]. Note that from measurements of x_{n+1} and x_{n-1}, only the lumped constant parameter $\lambda_s\lambda_u-\widehat{\lambda}_s(\lambda_s+\lambda_u)$ in Eq. (4) can be estimated—not λ_s and λ_u individually.

Christini and Collins [12] proposed a simplified modification of PPF control, which they termed stable manifold placement (SMP) control. They showed that effective control can be accomplished by turning off the control stimuli and allowing the system to free run according to the natural dynamics until the state point (x_n,x_{n-1}) wanders out of the UPO neighborhood. Only when the difference between (x_n,x_{n-1}) and the UPO $(x_\star,x_\star)$ reaches a threshold is control reactivated to return the state point to the UPO neighborhood via the stable manifold. In Ref. [12], the primary motivation for such intermittent perturbations was to minimize control interventions in order to limit stimulation-induced modification of the dynamical or electrochemical properties of the excitable tissue [14,15]. In the present context, intermittent stimulation provides another important benefit: allowing observation and characterization of the natural UPO dynamics between control perturbations.

When the control stimuli are turned off when using the SMP strategy, the system dynamics near the fixed point are given by Eq. (1). The parameters λ_s, λ_u, and $x_\star$ can then be estimated by linear regression of x_{n+1} on x_n and x_{n-1}. We define a ''natural triplet'' to be a sequence (x_{n+1},x_n,x_{n-1}) in which interval $n+1$ is terminated naturally, but intervals n and $n-1$ could be terminated naturally or by control stimuli. Only natural triplets can be used in the regression. In order to track UPO drift, estimates of λ_s, λ_u, and $x_\star$ are made from the last N natural triplets (x_{n+1},x_n,x_{n-1}). (In this paper, we take $N=10$.) After each such estimation, the control parameters $\widehat{\lambda}_s$ and $\widehat{x}_\star$ in Eq. (2) are reset to the new estimated values.

Care must be taken when performing the linear regression. If only one eigenvector is required to characterize the data fit to Eq. (1), then the parameter estimations will not accurately represent the natural two-manifold UPO dynamics. This situation occurs when one of the manifolds has little or no influence on the state dynamics for several consecutive natural triplets. For example, when control is turned off when using the SMP strategy, the state point will tend to retreat from the UPO along the unstable manifold. Thus the natural dynamics will be $x_{n+1}=\lambda_u(x_n-x_\star)+x_\star$, which does not reflect λ_s. If the N points used in the estimation consist mainly of such points, the parameter estimations will not accurately represent the natural two-manifold UPO dynamics. Such a situation can be detected by using singular value decomposition (SVD) [25] to carry out the linear regression: if the ratio of the regression's largest and smallest singular values is exceedingly large, the estimate is dubious. Thus SVD is particularly useful because, in addition to its ability to handle matrices that are either singular or very nearly singular, it provides validity information with each

estimate. If SVD indicates that an estimate is unreliable, $\hat{x}_\star$ and $\hat{\lambda}_s$ from the last valid estimation of Eq. (1) should be used for setting the control parameters in Eq. 2.

We illustrate the SMP characterization and tracking technique using the chaotic Hénon map,

$$x_{n+1}=A+Bx_{n-1}-x_n^2, \tag{5}$$

where $A=1.4$, $B=0.3$, and x_n represents the nth interexcitation interval. With these parameter values, the system is chaotic and has a flip saddle period-1 UPO at $x_\star=0.8839$, with $\lambda_u=-1.9237$ and $\lambda_s=0.1559$. The chaotic Hénon map was chosen because its uncontrolled dynamics have no stable periodic orbit and because its unstable flip saddle UPO is of the same type as that reported experimentally in studies of excitable media spike trains [16–18]. Because only the dynamics local to the UPO are exploited in the adaptive control method presented here, it is unimportant that the Hénon map's dynamics away from the UPO are not representative of those of excitable media.

Figure 1 shows a trial demonstrating adaptive estimation and control of the period-1 UPO. Following 100 points without control, control was activated setting $\hat{\lambda}_s=0$ and scanning for $x_\star$ by systematically increasing $\hat{x}_\star$. For $\hat{x}_\star<x_\star$ the resulting controlled dynamics show a fixed point at $\hat{x}_\star$, with a control stimulus being applied at every interval. At $\hat{x}_\star=x_\star$, a period-doubling bifurcation occurred [$n=174$; Fig. 1(b), inset], thus marking the location of the flip saddle UPO. Following detection of the bifurcation, control continued with $\hat{x}_\star$ set to 0.9073, the midpoint of the last prebifurcation pacing interval and the first post-bifurcation pacing interval. After N natural triplets had occurred [see the inset in Fig. 1(b)], the first SVD estimation of λ_s, λ_u, and $x_\star$ was performed [26]. After $n=190$, control followed the SMP protocol, with control stimuli used only when $|x_\star-x_n|>\delta$. (δ was set to 0.001 for all trials in this study.) SMP successfully stabilized the UPO with control stimuli being provided approximately every 20th interval as seen in Fig. 1(c). Figure 1(d) shows that the control-stage SVD estimates $\hat{\lambda}_s$ and $\hat{\lambda}_u$ (re-estimated via SVD following every natural interval using the most recent N natural triplets) were close to their true values.

After $n=500$, to simulate a noisy system, a Gaussian white noise iterate (standard deviation 0.0001) was added to each noncontrolled Hénon map iterate. In the noisy system, control required more frequent SMP perturbations because the additive noise caused the system state point to wander more quickly away from $x_\star$. Due to the additive noise, $\hat{\lambda}_s$ and $\hat{\lambda}_u$ fluctuated, but remained scattered around the true values [Fig. 1(d)].

We also used this adaptive approach to estimate and control the period-2 UPO of the chaotic Hénon map of Eq. (5). The control technique was modified so that perturbations and estimations occurred at alternate intervals instead of every interval. Effective control, including robustness to additive noise, was achieved.

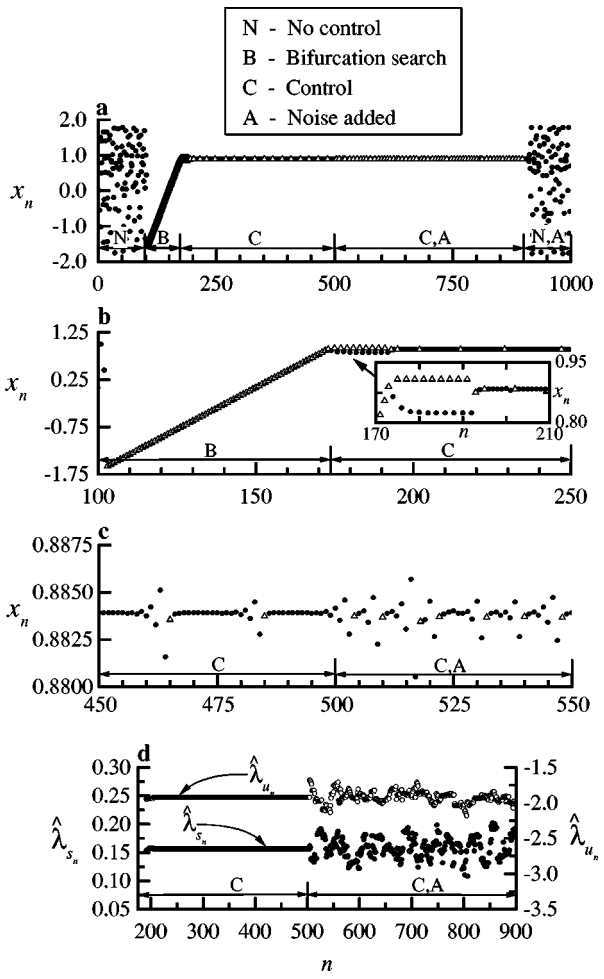

FIG. 1. A trial controlling the chaotic Hénon map of Eq. (5). (a), (b), and (c) show the intervals x_n vs interval number n for various stages of the control trial. Natural intervals are shown as filled circles, while control-induced intervals are shown as open triangles. (d) shows the SVD estimates (re-estimated following every noncontrol interval) $\hat{\lambda}_s$ and $\hat{\lambda}_u$ during the control stage.

This technique can also be used to locate and stabilize UPO's in nonchaotic systems. Figure 2 shows a trial controlling the Hénon map of Eq. (5) with $A=1.0$ and $B=0.3$. With these parameter values, the system settles into a stable period-4 rhythm. However, there is an underlying unstable flip saddle UPO at $x_\star=0.7095$, with $\lambda_u=-1.6058$ and $\lambda_s=0.1868$. This UPO cannot be detected from free-running data, but, as the figure demonstrates, the bifurcation search, SVD parameter estimation, and SMP control were able to locate and stabilize the UPO. As in Fig. 1, control remained effective when a Gaussian white noise iterate (at $n=500$; standard deviation 0.0001) was added to each noncontrolled Hénon map iterate. For this trial, the bifurcation search, individual control perturbations, and manifold estimations were all qualitatively similar to those shown for the chaotic Hénon map in Figs. 1(b), 1(c), and 1(d), respectively. Given the prevalence of pathologic nonchaotic rhythms in excitable biological systems [3–5], this trial demonstrates an important capability of this control technique.

It is of particular interest to be able to track drifting UPO's in nonstationary systems. To illustrate how this can be done, we use the Hénon map with a randomly drifting parameter,

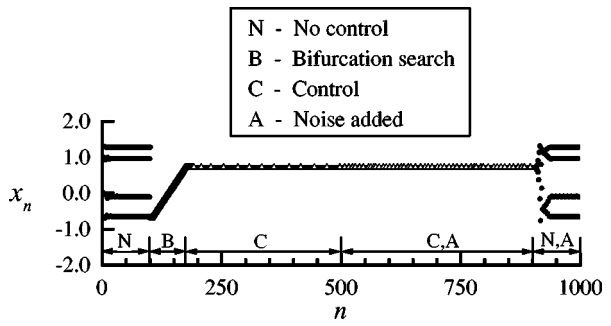

FIG. 2. A trial controlling the period-4 Hénon map of Eq. (5) with $A=1.0$ and $B=0.3$. The intervals x_n vs interval number n are shown for various stages of the control trial. Natural intervals are shown as filled circles, while control-induced intervals are shown as open triangles. At $n=500$, a Gaussian white noise iterate (standard deviation 0.0001) was added to each noncontrolled Hénon map iterate.

$$x_{n+1}=(A+\eta_n)+Bx_{n-1}-x_n^2, \tag{6}$$

where η_n is an iterate of a correlated noise process [27], given by $\eta_n=0.999\eta_{n-1}+4.5\times10^{-7}\zeta_n$, where ζ_n is Gaussian white noise with unity standard deviation. Figure 3(a) shows x_n versus n for a control trial of this nonstationary system. Figures 3(b), 3(c), and 3(d) show the analytically determined $x_{\star_n}$, λ_{s_n}, and λ_{u_n}, respectively, and their SVD estimates $\hat{x}_{\star_n}$,$\widehat{\lambda}_{s_n}$, and $\widehat{\lambda}_{u_n}$, respectively. The two distinct branches of $\widehat{\lambda}_{u_n}$ in Fig. 3(d) result from the repetitive pattern of SMP control and estimation that can be seen in the insets of Figs. 3(a) and 3(d). This figure demonstrates that the repeated SVD estimation was able to effectively track the parameters of the drifting system.

A second method for estimating λ_s and λ_u is applicable when the natural unstable dynamics are sufficiently strong that SMP control cannot be practically applied. It is not necessary for the control parameters $\widehat{\lambda}_s$ and $\widehat{x}_\star$ to match the natural parameters λ_s and $x_\star$ in order to accomplish successful control [13]—slight parameter misestimations lead to deviations from period-1 orbits, but not control failure. In the case of a flip saddle, for example, by setting the control parameter $\widehat{x}_\star$ slightly larger than the true fixed point location $x_\star$, the controlled system will have a period-2 orbit, where control stimuli are provided every second interval. By jiggling the control parameters in a small range around their nominal values, one eliminates the linear degeneracy of Eq. (3) and enables λ_s and λ_u to be separately estimated from the natural triplets (x_{n+1},x_n,x_{n-1}).

The techniques presented in this study dispense with precontrol data analysis and enable control of nonstationary UPO's in chaotic and nonchaotic systems. Thus they are more appropriate than previous PPF-type techniques for control of excitable biological systems. This fact, coupled with experimental evidence that model-independent control techniques can modify or eliminate pathological excitation patterns [1,3–5], implies that they may have clinical utility. As

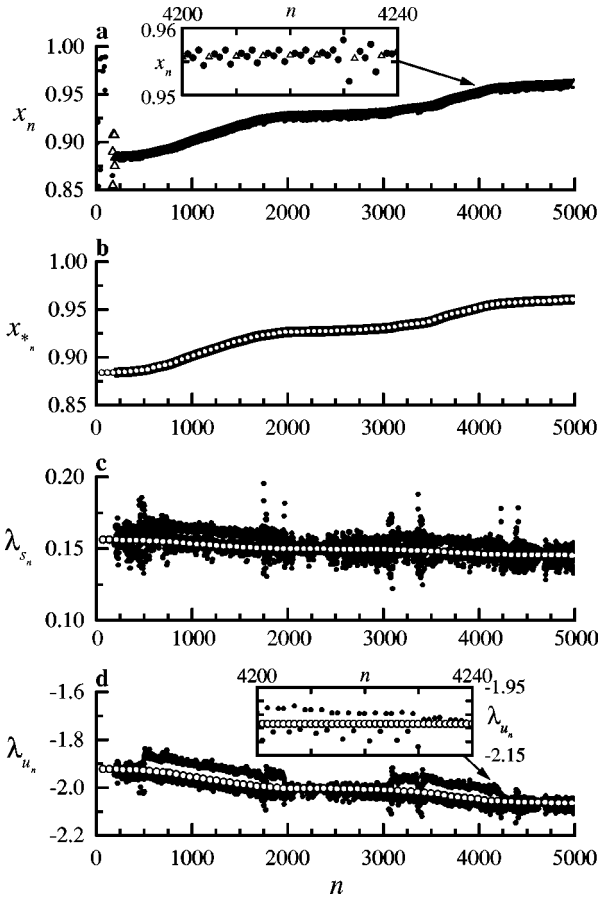

FIG. 3. A trial controlling the modified Hénon map of Eq. (6). (a) and the inset in (a) show the intervals x_n vs interval number n for the entire trial. Natural intervals are shown as filled circles, while control-induced intervals are shown as open triangles. (b), (c), (d), and the inset in (d) show the analytically determined (open circles) $x_{\star_n}$, λ_{s_n}, and λ_{u_n}, respectively, and their SVD estimates (closed circles behind the open circles) $\hat{x}_{\star_n}$, $\widehat{\lambda}_{s_n}$, and $\widehat{\lambda}_{u_n}$, respectively.

one possibility, we note that in some clinical applications of tachycardia pacing, one uses rapid pacing in order to capture the tissue's rhythm, and then gradually slows pacing to return the heart to an acceptably slow rhythm. The techniques described here may be useful in maintaining capture of the rhythm while the pacing rate is slowed.

While this study demonstrates the feasibility of controlling *models* of excitable biological spike trains, important questions regarding the physiological feasibility of control of *real* excitable biological systems remain unanswered. One question is whether SMP control stimuli, which are large perturbations to the electrochemical properties of the system, actually modify the underlying UPO dynamics [12,14,15]. Further investigation is needed to address this and other issues to determine whether such control is physiologically feasible and clinically useful.

This work was supported by grants from the American Heart Association (Grant Nos. 0030028N) and the National Institutes of Health (Grant Nos. R01 HL56139) (D.J.C.), and sabbatical support from Macalester College (D.T.K.).

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