Controlling Nonchaotic Neuronal Noise Using Chaos Control Techniques

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Chaos control techniques have been used to control a wide variety of experimental systems, including physiological systems. Here chaos control, periodic pacing, and anticontrol were applied to a noise-driven, nonchaotic neuronal model, and results similar to those recently reported for apparently chaotic, in vitro neuronal networks were obtained. Similar results were produced when chaos control was applied to a simple stochastic system. These suggest that the neuronal networks may not have been chaotic and that chaos control techniques can be applied to a wider range of experimental systems (e.g., stochastic systems) than previously thought.

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Chaos control techniques have been applied to a wide variety of experimental systems, including magnetoelastic ribbons [1], electronic circuits [2], lasers [3], chemical reactions [4], arrhythmic cardiac tissue [5], and spontaneously bursting neuronal networks [6]. An underlying assumption in all of these studies is that the system being controlled is chaotic. However, the identification of chaos in experimental systems, particularly physiological systems, is a difficult and often misleading task [7]. Here we apply chaos control techniques and related methods to a noise-driven, nonchaotic neuronal model and compare the results to those reported by Schiff *et al.* [6] for apparently chaotic, in vitro neuronal networks.

Schiff *et al.* [6] studied the firing behavior of neuronal networks in hippocampal slices of rat brain. They generated noiselike (possibly chaotic) burst-firing activity in these networks by exposing the hippocampal slices to K^+-enriched artificial cerebrospinal fluid. As a simple analog to this system, we considered the firing behavior of a noise-driven neuron. Specifically, we implemented the FitzHugh-Nagumo (FHN) neuronal model [8] as given by the following equations:

$$\epsilon \dot{v} = v(v - a)(1 - v) - w + V_A + \xi(t),$$
$$\dot{w} = v - w - b, \tag{1}$$

where $v(t)$ is the voltage variable, $w(t)$ is the recovery variable, V_A is a tonic activation signal of 0.2 V, $\xi(t)$ is Gaussian white noise with zero mean and standard deviation $= 6.325 \times 10^{-4}$ V [9], $\epsilon = 0.005$, $a = 0.5$, and $b = 0.15$. The FHN equations were solved numerically [10] using an algorithm developed by Mannella and Palleschi [11] for stochastic differential equations. The interspike intervals (ISIs) were computed using the method described by Longtin [8]. In the absence of additive noise, the model fired regularly with a period of 0.761 s. Phase-plane analysis showed that the additive noise simply caused the firing period to fluctuate about its mean value. The periodic orbit was structurally preserved. There were no global bifurcations; thus, the additive noise did not induce chaos.

To evaluate the presence of chaos in the aforementioned neuronal networks, Schiff *et al.* [6] analyzed the first-return maps of the burst ISIs for different hippocampal-slice preparations. According to their criteria, a system could be considered chaotic if its ISI time series contained recurrent sequences that approached an unstable periodic flip-saddle fixed point (in the first-return map) along a stable direction (manifold) and departed from it in an exponential fashion along a locally linear unstable manifold. The ISI first-return maps for the in vitro neuronal networks of Schiff *et al.* [6] satisfied the above chaos criteria. However, we found that the ISI time series from our noise-driven, nonchaotic neuronal model also occasionally satisfied these criteria, as illustrated in Fig. 1. Figure 1(a) is an ISI first-return map showing eight sequential points (numbered 1–8). Points 2–8 define an apparent flip-saddle unstable manifold because the sequence alternates on either side of the line of identity (where $\mathrm{ISI}_n = \mathrm{ISI}_{n-1}$) while diverging exponentially away from it along a nearly straight line. The intersection of the line of identity with a straight line fit to the points of the apparent unstable manifold defines the location of the apparent unstable periodic fixed point. Point 1 is considered to lie on an apparent stable manifold because point 2 lies near the apparent unstable periodic fixed point. Figure 1(b) is an ISI first-return map showing recurrent sequences (from a single ISI time series) that approached and exponentially diverged from an apparent unstable periodic fixed point. Note that each sequence starts in a region near the apparent stable manifold. The second point for each sequence lies near the apparent unstable periodic fixed point. Each sequence then departs from the apparent unstable periodic fixed point in exponentially diverging jumps on alternating sides of the line of identity along the apparent unstable manifold. It should be noted that the plots in Fig. 1 are similar in structure to those in Fig. 2 in Ref. [6].

We use the term "apparent" to describe the candidate fixed points in our model's output because the aforementioned phase-plane analysis showed that for the parameter

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values used, the model does not have any unstable periodic fixed points. To confirm this finding, we generated ten 5000-ISI time series from the noise-driven model neuron. For each ISI time series, we then generated a set of ten randomly shuffled surrogate data sets. We found that the probability of finding candidate unstable periodic fixed points [12] in the original time series was not statistically significantly different from the probability of finding such points in the respective surrogate data sets (p values ranged from 0.37–0.90, with mean 0.61). These results, together with those in Fig. 1, demonstrate that apparent unstable periodic fixed points can arise simply by chance in our noise-driven, nonchaotic neuronal model, and therefore, the chaos criteria used by Schiff *et al.* [6] are not sufficient for the definitive identification of deterministic chaos.

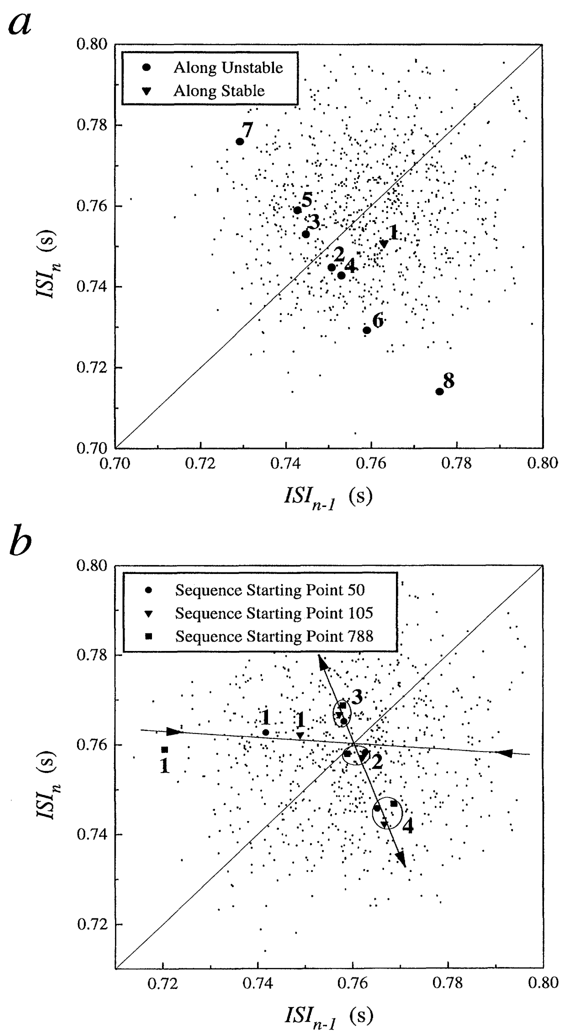

FIG. 1. Plots of interspike intervals ISI_n versus the previous interval ISI_{n-1} for the noise-driven, nonchaotic neuronal model [Eqs. (1)] without control. (a) First-return map showing eight sequential points (numbered 1–8), which approached and exponentially diverged from an apparent unstable periodic fixed point. (b) First-return map showing recurrent sequences (from a single ISI time series), which approached and exponentially diverged from an apparent unstable periodic fixed point. The starting point for each sequence, numbered 1 in each, began at spike numbers 50 (circles), 105 (triangles), and 788 (squares), out of a total series of 791 spikes. The apparent stable manifold is indicated by arrows pointing towards the apparent unstable periodic fixed point, and the apparent unstable manifold is indicated by arrows pointing away from the apparent unstable periodic fixed point.

The original chaos control technique developed by Ott, Grebogi, and Yorke (OGY) [13] is based on the fact that there are an infinite number of unstable periodic orbits embedded within a chaotic attractor. With this approach, a chaotic system is stabilized about one of these periodic orbits by making small time-dependent perturbations to an accessible system-wide parameter such that the system's trajectory is attracted towards the stable manifold of the desired unstable orbit. The OGY technique is useful in many situations because it requires no knowledge of the underlying system equations. Recently, the OGY technique was modified so that chaos control could be applied to systems where no system-wide parameters are readily available for manipulation. This modified method, which is called proportional perturbation feedback (PPF) control [5], involves the application of perturbations to the system variable to be controlled. With this approach, the goal is to apply perturbations so as to place the system's state point onto the stable manifold of a desired unstable periodic fixed point. With excitable systems (e.g., neurons), an electrical stimulus is used to shorten a predicted ISI (by inducing a premature spike at a calculated time) such that the system's state point is placed onto the stable manifold.

Schiff *et al.* [6] implemented PPF control in in vitro neuronal networks by delivering precisely timed electrical stimuli to their hippocampal-slice preparations. Similarly, we applied PPF control to our noise-driven, nonchaotic neuronal model. For the trial shown in Fig. 2, the apparent unstable periodic fixed point and set of apparent stable and unstable manifolds were determined during the first temporal region A, prior to control initiation [14]. PPF control was then activated for 200 points (region B in Fig. 2) [15]. We achieved a level of control success (Fig. 2), which was similar to that obtained by Schiff *et al.* [6] for in vitro neuronal networks (see Figs. 3 and 4 in Ref. [6]). For instance, in both our study and the study of Schiff *et al.* [6], the width of the ISI band (i.e., the amount of ISI fluctuation) was reduced considerably from the precontrol stage to the PPF control stage.

To compare PPF control with simple periodic pacing, we repeatedly stimulated the noise-driven, nonchaotic neuronal model at a constant pulse interval for 200 points (region C, Fig. 2), following 100 points without control (second region A). (The periodic-pacing pulse interval was equal to the value of the apparent unstable periodic fixed point used for PPF control.) Our periodic-pacing re-

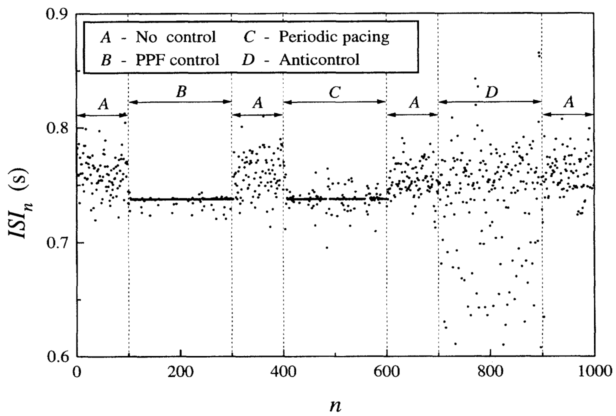

FIG. 2. Plot showing interspike intervals ISI_n for the noise-driven, nonchaotic neuronal model without control (temporal regions A), and with proportional perturbation feedback (PPF) control (region B), periodic pacing (region C), and anticontrol (region D).

sults (Fig. 2) were similar to those reported by Schiff *et al.* [6] for in vitro neuronal networks (see Fig. 3 in Ref. [6]). In both our study and the study of Schiff *et al.* [6], periodic pacing produced qualitatively different results from PPF control, e.g., periodic pacing frequently allowed ISIs that were considerably larger than the stimulation interval.

It has been suggested that the underlying existence of low-dimensional chaos in the nervous system may offer the opportunity to desynchronize the periodic behavior typical of epileptic seizures [16]. In line with this hypothesis, Schiff *et al.* [6] showed that a technique called anticontrol could be used to reduce the periodicity of their hippocampal-slice preparations. Anticontrol [6,17], which is essentially the inverse of chaos control, increases the aperiodicity of a system by placing its state point away from the unstable periodic fixed point. We applied anticontrol to our noise-driven, nonchaotic neuronal model for 200 points (region D, Fig. 2), following 100 points without control (third region A). The algorithm for anticontrol was the same as the algorithm for PPF control except that the system's state point was placed onto an unstable repellor line [18] instead of the apparent stable manifold. The anticontrol results shown in Fig. 2 were similar to those reported by Schiff *et al.* [6] for in vitro neuronal networks (see Fig. 4 in Ref. [6]); i.e., anticontrol reduced the ISI periodicity in the model neuron.

With PPF control, a system is controlled, in principle, by exploiting the features of one of its unstable periodic fixed points. It was surprising therefore that PPF control could effectively control our noise-driven, nonchaotic neuronal model, given that the model does not have any unstable periodic fixed points. Figure 3 clarifies this apparent contradiction. In Fig. 3(a), it can be seen that in repeated control attempts, the effectiveness of control varied as new apparent unstable periodic fixed points were defined,

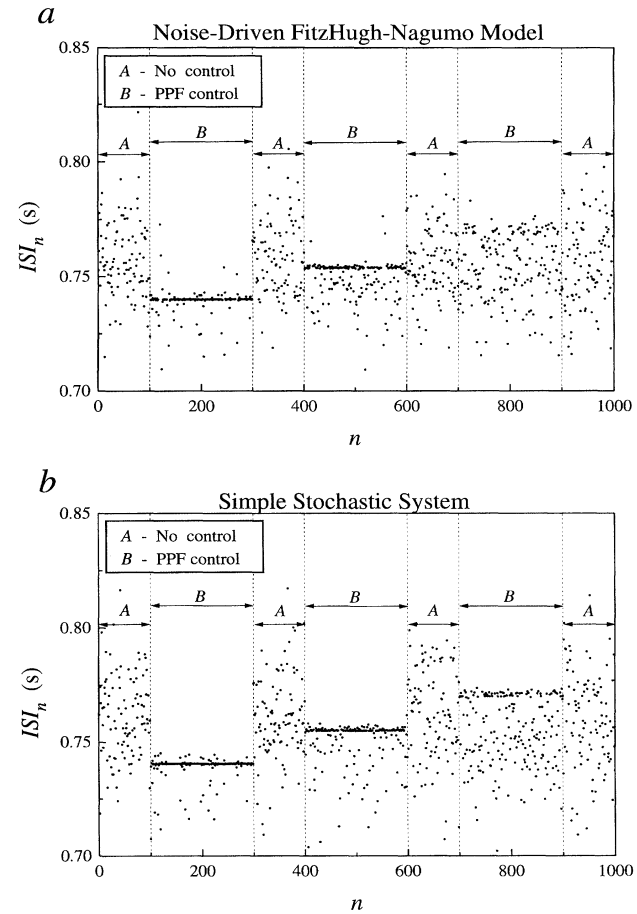

FIG. 3. (a) Plot showing interspike intervals ISI_n for the noise-driven, nonchaotic neuronal model without control (temporal regions A) and for three distinct periods of PPF control (regions B). For each PPF control region, a new apparent unstable periodic fixed point and set of apparent stable and unstable manifolds were determined during the preceding control-free region. (b) Plot showing three distinct periods of PPF control (regions B) of simulated interspike intervals ISI_n produced by the simple stochastic system [Eq. (2)].

i.e., larger fixed points were associated with decreased levels of control success [similar to the results shown in Fig. 5(b) in Ref. [6]]. The differences between the respective control regions can be attributed solely to the quantitative differences between the values of the selected fixed points; the response of the system to PPF control was not qualitatively different for the different control regions. Note that the spread (range) of ISIs below each fixed point was not significantly different from that of the uncontrolled regions. [Similar results can be seen in Fig. 5(b) in Ref. [6].] PPF control thus largely served to eliminate ISIs that were larger than the value of the selected fixed point. Similar results could have been obtained with demand pacing, which is a simple, well-known technique [19,20] that is not based on chaos theory and that does not require the determination of stable and unstable manifolds—with demand pacing, stimuli are used to prevent the ISIs of a system from exceeding some predetermined value.

In order to explore these points further, we considered the following simple stochastic system (which models the behavior of our noise-driven model neuron to the lowest order):

$$\mathrm{ISI}_n = \overline{\mathrm{ISI}} + \xi_n\,, \tag{2}$$

where ISI_n is a variable that we take to represent the current interspike interval, $\overline{\mathrm{ISI}}$ is a constant parameter that represents the mean value (0.761 s) of the interspike interval, and ξ_n is Gaussian white noise with zero mean and standard deviation $= 0.02$ s [9]. By design, this stochastic system does not have any unstable periodic fixed points, and it is incapable of displaying deterministic chaos. However, as with our noise-driven model neuron, this system does display (by chance) apparent unstable periodic fixed points. We applied PPF control to this simple system [21] and obtained results [Fig. 3(b)] that were similar to those described above for our noise-driven, nonchaotic neuronal model [Fig. 3(a)] and those reported by Schiff *et al.* [6] for in vitro neuronal networks [see Fig. 5(b) in Ref. [6]]. This work clearly demonstrates that PPF control can control a stochastic system, one that does not have any unstable periodic fixed points, with a level of success similar to that reported by Schiff *et al.* [6]. These findings thus provide an alternative explanation for some of the results reported by Schiff *et al.* [6], namely, that their hippocampal-slice preparations may have been stochastic in nature. This point is corroborated by a recent study [22], which showed that the majority of the ISI time series from similar hippocampal-slice preparations failed to demonstrate evidence of deterministic structure.

The recent success of chaos control in physiology has led to speculations that these techniques may be clinically useful [5,6,23]. The present findings do not discount that possibility; rather, our work suggests that chaos control techniques can be applied to a wider range of experimental systems (e.g., stochastic systems) than previously thought. Moreover, because PPF control can be applied to both chaotic and nonchaotic systems, the difficult problem of distinguishing between deterministic chaos and noise in physiological systems [7] appears to be a nonissue for this application. Clearly, however, the nature of the control success will depend critically upon the characteristics (e.g., the presence of unstable periodic fixed points) of the system to be controlled.

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