

## Time-Interval Sequences in Bistable Systems and the Noise-Induced Transmission of Information by Sensory Neurons

André Longtin

*Complex Systems Group and Center for Nonlinear Studies, Theoretical Division B213,  
Los Alamos National Laboratories, Los Alamos, New Mexico 87545*

Adi Bulsara

*Naval Ocean Systems Center, San Diego, California 92152*

Frank Moss

*Department of Physics, University of Missouri at St. Louis, St. Louis, Missouri 63121  
(Received 11 March 1991)*

We discuss the two time-interval sequences which play a crucial role in studies of escape times in bistable systems driven by periodic functions embedded in noise. We demonstrate that the probability density of escape times for one of the sequences exhibits all the substantive features of experimental interspike interval histograms recorded from real, periodically forced sensory neurons. Our analysis relies on linking this interval sequence to the firing-reset mechanism of real neurons, and illustrates the importance of the noise, *without which the substantive features cannot exist*, for the transmission of sensory information.

PACS numbers: 87.22.Jb, 02.50.+s, 42.66.Ew

It has been well known for decades that a major component of sensory information is transmitted to the brain using a code based on the time intervals between firings of neurons, that is, action potentials or spikes [1,2]. Moreover, statistical analyses of experimentally obtained spike trains have concluded that the time intervals contain a significant random component [3]. Exactly how the sensory information is encoded and how this process is affected by noise—whether the noise simply obscures it by introducing random interval errors, or whether it plays a deeper role—is, however, presently not clear. A useful and widely used ensemble average of neural firing data is the interspike interval histogram (ISIH) in which the time intervals between successive spikes are assembled into a histogram. In this paper, we are interested in the properties of these ISIH's when the stimulus to a particular sensory modality is a periodic function of time. We reproduce in Fig. 1 two such histograms, obtained 23 years apart: the first from older experiments on single auditory nerve fibers of monkeys [4], shown in Fig. 1(a), and the second from recent experiments on single neurons in the primary visual cortex of a cat [5], shown in Fig. 1(b). The histograms from these elegant experiments depict striking sequences of decaying peaks. The similarity is remarkable, even though the cat data were obtained from a neuron located within the visual cortex, in contrast to the monkey data, which were obtained from a nerve fiber much closer to the transducer (the ear), suggesting that these detailed patterns may play an essential role in neural information transfer. Two features of these data are notable: First, the modes are located at integer multiples of the stimulus period, and second, the mode amplitudes decay rapidly, approximately exponentially, as shown by the inset in Fig. 1(a).

We take a reductionist's view of these data; that is, our object here will *not* be to create a better or more detailed neuron model, but rather to discover the *simplest* possible physical mechanism which can capture the dominant features of the aforementioned ISIH's. Similar approaches have recently been used to address other questions in biology, for example, that of oscillator synchronization [6]. We take our initial clues from Landahl, McCulloch, and Pitts [7], who first modeled neurons with stochastically driven two-state processes. Since we are concerned with periodically stimulated neurons, we consider the properties of a general bistable system driven by a sinusoidal function with added noise. For simplicity, we consider only the limit of large damping:

$$\dot{x} = -\frac{dU(x)}{dx} + \xi(t) + m \sin(\omega t), \quad (1)$$

where  $U(x)$  is a double-well potential, and  $\xi(t)$  is a noise which we take to be white and Gaussian with zero mean. Under the influence of the noise alone, the system switches between its two wells, say,  $A$  and  $B$ , at random times. For  $m > 0$ , the switching times become, to some degree, correlated with the periodic function. This results from the fact that the transition probabilities become periodically modulated: a general process which has been studied under the name *stochastic resonance* [8]. We are interested here only in the time intervals of the transitions between wells, not in the detailed motion within the wells. Under these conditions, the dynamics of Eq. (1) can be replaced with a "two-state" dynamics, realizable, for example, by a Schmitt trigger [9]. For symmetric double wells, restricted to the two-state dynamics, the only parameters which govern the response are the height of the potential barrier separating the wells and the locations of

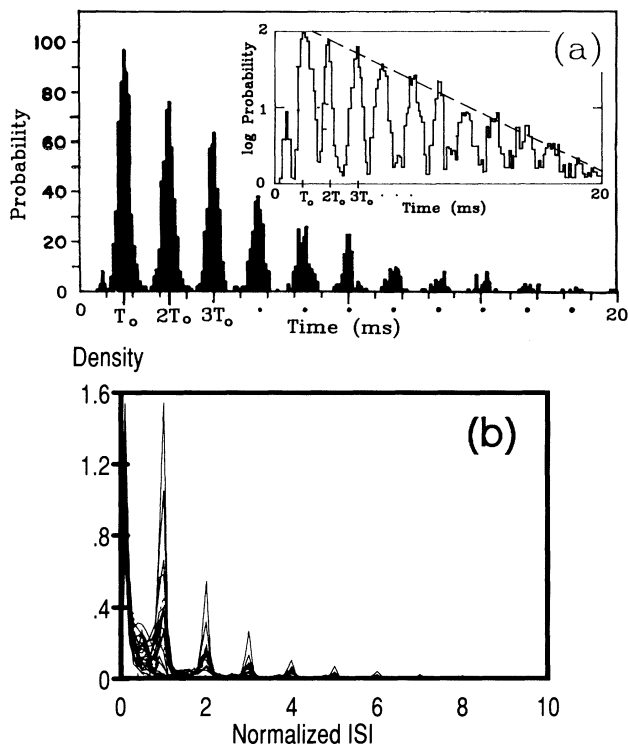


FIG. 1. (a) An experimental ISIH obtained from a single auditory nerve fiber of a squirrel monkey with a sinusoidal 80-dB sound-pressure-level stimulus of period  $T_0 = 1.66$  ms applied at the ear. Note the modes at integer multiples of  $T_0$ . Inset: The same data replotted on a semilogarithmic scale. Reproduced with permission from Ref. [4]. (b) A series of 26 overlaid ISIH plots measured on the primary visual cortex of a cat for 26 different stimulus periods. The time scale of each ISIH was normalized by its stimulus period showing the modes located at all integer multiples of  $T_0$  for the set of all periods. Reproduced with permission from Ref. [5].

the stable states. The response of such a two-state system is shown in Fig. 2.

Only two sequences of consecutive time-interval measurements can be obtained, as shown by the upper and lower sets of labels,  $T_i$ , in Fig. 2. The ISIH's assembled from the two sequences are different. The top sequence measures the escape time from well  $B$ , a process for which a recent approximate theory has been developed [10]. This process, which we shall call the *ABBA* process, results in an ISIH with modes located at *odd-integer multiples* of  $T_0/2$ , where  $T_0$  is the period of the sine function [11]. By contrast, the sequence defined by the bottom set of labels, which we call the *ABAB* sequence, and for which the theory of Ref. [10] has not yet been adapted, results in an ISIH with modes located at *all integer multiples* of  $T_0$ . An example of ISIH, measured on our Schmitt trigger for the *ABAB* sequence, is shown in Fig. 3(a). The similarities between this ISIH and those shown in Fig. 1 are clear. Assuming only that

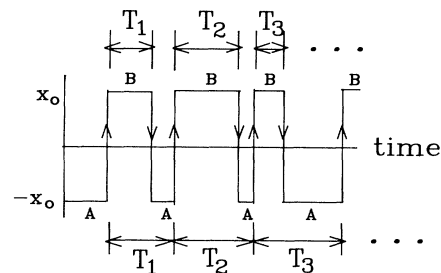


FIG. 2. An example output from a two-state device driven by noise plus a weak sinusoidal function. The two stable states at  $\pm x_0$  are labeled  $A$  and  $B$ . The upper set of time labels indicates the *ABBA* sequence. The lower set indicates the *ABAB* sequence. These are the only two possible consecutive time-interval sequences available to a two-state system from which to construct ISIH's.

actual neurons do behave in some respects as two-state systems, a supposition for which much evidence has been accumulated [3], one must conclude that an *ABAB*-type process underlies the physiological ISIH's. For the same conditions, we also measured the ISIH for the *ABBA* sequence, as depicted in the inset of Fig. 3(a). Clearly this sequence results in a *phase-shifted* set of peaks located at the odd-integer multiples of  $T_0/2$ . That only the *ABAB* sequence is observed in experiments on actual neurons is significant. It tells us that an additional event—a reset mechanism—*must* exist between every pair of spikes. We identify these *BA* events with the well-known repolarization of the neuron membrane which occurs some time after the depolarizing upstroke of an action potential [3] and which may or may not be automatic even in the absence of noise [12]. For example, it is known from numerical studies of Hodgkin-Huxley-type equations that bistability in the firing dynamics is possible [13], due in part to the N-shaped current-voltage characteristic, qualitatively the same as  $dU/dx$  in Eq. (1), of excitable cells.

In addition, the experimental ISIH's of Fig. 1 show modal decay rates which are, to the precision of the reported data, and except for the first few peaks, indistinguishable from exponential functions [14], i.e.,  $A_{\max} \propto \exp(-\lambda T)$ . This suggests that the spike rates, and possibly also the reset mechanisms, are governed by rate processes. Figure 3(b) shows the *ABAB* sequence data plotted on a semilogarithmic scale with the dashed line indicating the exponential decay law. In our simulations, the decay constant  $\lambda$  depends strongly on both stimulus,  $m$ , and noise,  $\langle \xi^2 \rangle$ , intensities, and over certain ranges these quantities seem to play interchangeable roles; that is, we found that  $\lambda \propto \exp(\beta m)$  with fixed  $\langle \xi^2 \rangle$ , and  $\lambda \propto \exp(\gamma \langle \xi^2 \rangle)$  with fixed  $m$  ( $\beta, \gamma$  positive constants). In the biological experiments, the noise intensity cannot be externally controlled; however, the results of the auditory nerve experiments cited in Ref. [4] indicate a similar dependence on stimulus intensity.

Many experiments [15–18] have yielded ISIH's with

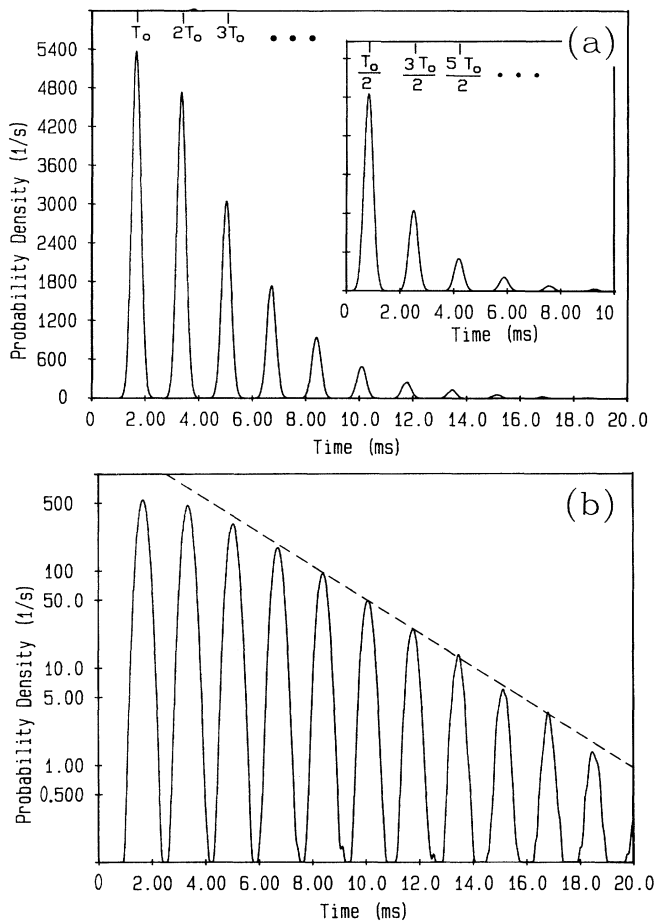


FIG. 3. (a) An ISIH measured on the Schmitt trigger for the *ABAB* sequence with the same  $T_0$  ( $=1.66$  ms) as in Fig. 1(a). Note that the modes lie at *all integer* multiples of  $T_0$  as indicated by the labels along the upper horizontal axis. Inset: An ISIH measured for the *ABBA* sequence but with otherwise identical conditions. Note the mode locations at *odd-integer* multiples of  $T_0/2$ . (b) The same data as in (a) (*ABAB* sequence) plotted on a semilogarithmic scale.

some similarity to those of Refs. [4] and [5]. The present results demonstrate that the dominant features of the multimodal ISIH's measured on periodically stimulated neurons of the auditory and visual systems can be understood, in the simplest view, as arising from a periodically modulated two-state system with added noise.

Our model is similar in spirit to an early stochastic model proposed by Gerstein and Mandelbrot [19] (GM), who viewed the firing events as triggered by threshold crossings of the membrane potential undergoing a biased random walk, driven by excitatory and inhibitory postsynaptic potentials. Later, Geisler and Goldberg [20] proposed an exponential function activated by a Gaussian, colored (i.e., finite bandwidth) noise crossing a single threshold. An early review of such models was provided by Fienberg [21]. A more recent review is given by

Tuckwell [3]. The emphasis of all these models has been on the spontaneous, i.e., unstimulated, behavior which results in unimodal ISIH's. GM did, however, briefly investigate their model numerically with a periodically modulated drift and were thus able to generate a multimodal ISIH [22]. None of these, however, have attempted to explain the role of the two sequences in determining the locations of the modes of the ISIH's or their approximately exponential decay.

In contrast, we have demonstrated that these two essential features can be reproduced by an elementary two-state device, a Schmitt trigger, stimulated by a periodic function with additive Gaussian noise. We can accurately reproduce data such as that of Ref. [4], *by adjusting only one parameter*: either the noise or the stimulus intensity, given that the other lies within some range not very different from the height of the potential barrier. Moreover, the sequence and exponential decay behaviors are robust to radical changes in the bistable potential. For example, we have observed that upon substituting a soft potential [ $\lim_{x \rightarrow \infty} U(x) \propto x$ ] for the infinitely hard Schmitt-trigger potential, the resulting ISIH's differ only in some details, such as the width of the peaks, the shape of the minima, and the number of short-interval events due to multiple-barrier crossings near the metastable state. The latter produce a peak near the origin similar to those seen in Fig. 1(b), and in Rose *et al.* [4] at lower frequencies, and can thus be linked to spontaneous firings. Scatter plots of one time interval versus the following one were found to exhibit much the same structure as reported in Ref. [5] except for small asymmetries not reproducible by our model. It remains to be seen whether our model can account for other statistics such as the pulse number distributions analyzed in Ref. [18].

Finally, we remark that the distinctive mode sequences, observed both in the experiments and in our simulations, *cannot exist in the absence of noise*. Supposing, as seems reasonable, that the brain interprets the mode sequence and decay across arrays of neurons in order to obtain information on the frequency and intensity of the stimulus, one comes to the inescapable conclusion that the noise plays an essential role in this process. This work complements the recent and growing body of literature wherein various aspects of noise in neuronal processes have been addressed [3,23-25].

We are grateful to M. C. Teich, who originally called our attention to the data of Rose *et al.* [4], thus triggering this investigation, and to G. L. Gerstein, M. V. Gremillion, and J. D. Farmer for crucial and stimulating discussions. We are grateful to G. H. Weiss for an illuminating discussion on periodically modulated random walks. We thank J. F. Brugge and R. M. Siegel for permission to reproduce their data. One of us (A.L.) wishes to thank the Natural Sciences and Engineering Research Council (Canada) and the Los Alamos National Laboratory for financial support. This work was supported by

Office of Naval Research Grants No. N00014-90-J-1327 and No. N00014-90-AF-001, by the Department of Energy, and by National Institute of Mental Health Grant No. 1-R01-MH47184-01.

- [1] J. C. Eccles, *The Understanding of the Brain* (McGraw-Hill, New York, 1973).
- [2] S. W. Kuffler, R. Fitzhugh, and H. B. Barlow, *J. Gen. Physiol.* **40**, 683 (1957); G. L. Gerstein and N. Y-S. Kiang, *Biophys. J.* **1**, 15 (1960); N. Y-S. Kiang, T. Watanabe, E. C. Thomas, and L. F. Clark, MIT Research Monograph No. 35 (Technology Press, Cambridge, MA, 1965).
- [3] H. C. Tuckwell, *Stochastic Processes in the Neurosciences* (SIAM, Philadelphia, 1989); A. V. Holden, *Models of the Stochastic Activity of Neurons*, Lecture Notes in Biomathematics Vol. 12 (Springer, Berlin, 1976); G. Sampath and S. K. Srinivasan, *Stochastic Models for Spike Trains of Single Neurons*, Lecture Notes in Biomathematics Vol. 16 (Springer, Berlin, 1977).
- [4] J. E. Rose, J. F. Brugge, D. J. Anderson, and J. E. Hind, *J. Neurophysiol.* **30**, 769 (1967).
- [5] R. M. Siegel, *Physica* (Amsterdam) **42D**, 385 (1990).
- [6] B. C. Matthews and S. H. Strogatz, *Phys. Rev. Lett.* **65**, 1701 (1990).
- [7] H. Landahl, W. S. McCulloch, and W. Pitts, *Bull. Math. Biophys.* **5**, 115 (1943).
- [8] For a recent review, see F. Moss, in "Rate Processes in Dissipative Systems: 50 Years after Kramers," edited by P. Hänggi and J. Troe (Berichte der Bunsen-Gesellschaft für Physikalische Chemie, to be published).
- [9] This is a device with two thresholds,  $V_A$  and  $V_B > V_A$ , which obeys the following state-point logic:  $A \rightarrow B$  if the state is not already  $B$  whenever the input crosses  $V_B$  from below and the converse. See, for example, B. K. Jones, *Electronics for Experimentation and Research* (Prentice Hall, Engelwood Cliffs, NJ, 1986), p. 83.
- [10] T. Zhou, F. Moss, and P. Jung, *Phys. Rev. A* **42**, 3161 (1990).
- [11] The reason for this sequence is clear: Suppose the state is  $A$ , and time is marked by an  $A \rightarrow B$  transition when the probability for this event is maximum, for example, at  $\omega t = \pi/2$ . The most probable time for the  $B \rightarrow A$  reset event will occur at  $\omega t = 3\pi/2$ . If, by chance, this transition does not occur, then the state point remains in  $B$  with large probability until the next most probable time for the  $B \rightarrow A$  transition at  $\omega t = 7\pi/2$ , or  $3T_0/2$  after the time mark.
- [12] In our model, the  $BA$  events can be either completely stochastic and symmetric, with the probabilities  $P_{AB}(t) = P_{BA}(t + \pi)$ , or deterministic, wherein every  $AB$  (firing) event is followed by a  $BA$  event after some absolute refractory period, or some combination of these cases. In our simulations, deterministic  $BA$  events result in a large increase in the decay rate of the peaks (unpublished results).
- [13] J. Rinzel and E. B. Ermentrout, in *Method in Neuronal Modelling*, edited by C. Koch and I. Segev (MIT Press, Cambridge, MA, 1989).
- [14] This nonrenewal component is the consequence of the statistics of the  $ABAB$  events. While the probability  $P(n)$  of firing after  $n$  cycles can be shown, using a simple statistical argument, to decay exponentially for the  $ABBA$  events, it behaves for the  $ABAB$  events as  $P(n) = n\epsilon^2(1 - \epsilon)^{n-1}$ , where  $\epsilon$  is the firing probability during one cycle. This leads to  $\ln P(n) = an + b + \ln(n)$  ( $a, b$  constant,  $a < 0$ ), which is linear only for large  $n$ . This stimulates well biological memory effects arising when stimulus and refractory periods are comparable, and is further evidence that the neurons in the experiments of Refs. [4] and [5] behave as noise-driven bistable systems.
- [15] J. E. Rose, J. F. Brugge, D. J. Anderson, and J. E. Hind, *J. Neurophysiol.* **32**, 402 (1969).
- [16] D. J. Anderson, J. E. Rose, J. E. Hind, and J. F. Brugge, *J. Acoust. Soc. Am.* **49**, 1131 (1971).
- [17] D. H. Johnson, *J. Acoust. Soc. Am.* **68**, 1115 (1980).
- [18] M. C. Teich and S. M. Khanna, *J. Acoust. Soc. Am.* **77**, 1110 (1985).
- [19] G. L. Gerstein and B. Mandelbrot, *Biophys. J.* **4**, 41 (1964).
- [20] C. D. Geisler and J. M. Goldberg, *Biophys. J.* **6**, 53 (1966).
- [21] S. E. Fienberg, *Biometrics* **30**, 399 (1974).
- [22] In the absence of periodic drift, GM calculated the mean first passage time to cross a threshold, but, lacking a theory for the periodic case, were limited to numerical studies. A recent theory has been given by J. E. Fletcher, S. Havlin, and G. H. Weiss, *J. Stat. Phys.* **51**, 215 (1988).
- [23] J. G. Milton, A. Longtin, A. Beuter, M. C. Mackey, and L. Glass, *J. Theor. Biol.* **138**, 129 (1989); A. Longtin, J. G. Milton, J. E. Bos, and M. C. Mackey, *Phys. Rev. A* **41**, 6992 (1990); J. G. Milton, U. an der Heiden, A. Longtin, and M. C. Mackey, *Biomed. Biochim. Acta* 697 (1990).
- [24] W. Bialek, in *1989 Lectures in Complex Systems*, Santa Fe Institute Studies in the Sciences of Complexity Vol. II, edited by E. Jen (Addison-Wesley, New York, 1990).
- [25] E. R. Lewis, *Hear. Res.* **25**, 83 (1987).