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Abstract

A surprising experimental observation is that neuronal discharge times to simplistic stimuli such as a pacemaker current pulse train can be highly unpredictable and irreproducible from trial to trial, while those to complex realistic signals, say, resembling sample paths of a Gaussian process are reliable and reproducible. Using recently developed random dynamical system theory, we analyze the source of this stimulus-dependent difference in reliability. Our main conclusion is to derive an experimentally accessible measure that establishes how the interplay between intrinsic neuronal properties and stimulus characteristics determine whether a specific neuron type reliably encodes a certain class of stimuli.

Neurons encode stimuli into trains of stereotyped action potentials. An essential issue is whether a given stimulus is always encoded into the same sequence of discharge times evoked by repeated presentation of the same input. Experiments show that this is not the case. Some trial to trial variability exists in discharge times evoked by repeated presentation of a given input. As pointed out by Movshon (2000), determining the source and extent of this variability is essential for understanding the neuronal code, that is the relation between the stimulus and the spike train it evokes.

Since the early studies of Erlanger and his collaborators, random fluctuations of the excitability threshold of neurons have been known to hinder neuronal reliability (e.g. Blair and Erlanger, 1935/36). The unpredictable gating kinetics of individual ionic channels are one of the sources of this noise (White et al. 2000). In assemblies of interacting neurons, the discharge time variability due to channel noise is further augmented by the stochastic nature of synaptic transmission (e.g. Zador, 1998). These pieces of evidence combine with the reports of reliable spike generation (reproducible discharge times to the order of a few milliseconds) in diverse single neuron preparations, such from aplysia ganglions (Bryant and Segundo, 1976) and rat neocortex (Mainen and Sejnowski, 1995), to suggest that noise is the main limiting factor in the reliability of neurons. Models of neuronal membranes implementing the stochastic channel kinetics confirm this, as they show that the lower the channel noise level becomes, and the more reliable the discharge times tend to be (Schneidmann et al., 1998).

Based upon the above arguments, one may hastily conclude that, would it be not for noise, neuronal firing would be reliable. In other words, an ideal noise free neuron, would produce identical discharge times at multiple presentations of a given signal. This simplistic view of spike generation is clearly refuted by experiments. Indeed, neuronal firing can be unreliable, and apparently random and remain so even when noise levels reach extremely low levels. A highly illustrative example of this situation is provided by three centimeter space clamped patches of squid giant axons undergoing pacemaker pulsatile current injection (Kaplan et al, 1996). In this preparation, current is directly injected to the axon, so that synaptic noise is avoided. Furthermore, due to the space clamped preparation, voltage fluctuations due to channel noise reach undetectable levels. In other words, this preparation is one of the closest to a noise-free system one could hope for. Yet, for selected pulse amplitudes and interpulse periods, the discharge times of the axon are unpredictable (Kaplan et al, 1996), and irreproducible from trial to trial. Clearly, noise cannot be the main source of unreliability in this preparation. In this case, unreliability results from the nonlinear nature of spike generation, and is attributed to chaotic dynamics. Consequently, it would neither decrease nor vanish with the improvement of experimental conditions, such as an increase in the length of the patch to further reduce the impact of channel noise. In the same way that the claims about the role of noise on neuronal reliability were supported by mathematical and computational membrane models, the occurrence of chaos in neuronal membranes has also been explored with the help of a variety of membrane models (e.g. Aihara et al., 1984).

In summary, there are two distinct classes of experimental observations. The first ones tend to indicate that spike generation is reliable, limited only by noise, and the others reveal that, even when noise is almost completely eliminated,

tions. The starting point of our analysis is that there are two major differences in the two classes of experiments. The first is that the two classes of experiments are done with different neurons. Yet, it is well known that intrinsic neuronal properties strongly affect their response characteristics. So that whether a neuron's reliability is only limited by noise or not, may be entirely determined by its intrinsic properties. The other factor that differs between the two classes of experiments is in the signals used. In the former, neurons are stimulated by broad band Gaussian currents mimicking those some neurons receive in vivo, while in the latter, the stimulation is the simplistic periodic pulse train. Therefore, it may well be that neurons encode more or less reliably different classes of stimuli. Combining these observations, the problem addressed in our work is to determine the classes of neurons that encode reliably a given class of stimuli. The presentation will review our work over the past years leading to the answer to the above problem, and finishes with the latest results.

The first step in our program consisted in the analysis of the response of neurons to realistic noise-like stimuli such as those used in the experiments, one example being a sample path of a Gaussian process. Indeed, while there has been a vast theoretical literature using the methods of dynamical system theory to describe the behavior of periodically forced neurons (see Glass, 2000; and references in Stiber et al. 1997 and Yoshino et al, 1999), scant attention had been devoted to the case where the stimuli is as fluctuating as the realization of Gaussian processes. The main reason for this is that the mathematical tools, that is random dynamical system theory, to handle such systems have been developed only recently (Arnold, 1998). Indeed, the rapid and possibly fluctuations of such perturbations cannot be handled with the standard geometrical methods of dynamical system theory, and need other approaches. However, this is not merely a mathematical issue, because the same characteristics of the fluctuations mean that the dynamics of the perturbed system, no matter how small the perturbation intensity (such as the variance of the Gaussian distribution) becomes can be drastically different from those of the unperturbed system. This implies that randomly perturbed systems can have novel dynamics in comparison with smoothly perturbed systems. We were to remark that this feature could lie at the heart of the differences in the reliability of discharges evoked by periodic and realistic noise-like signals. This indicated the relevance of RDS methods to the analysis of neuronal reliability, and the gain that could result from their application to this field. However, it should be noted that the RDS theory is still currently under progress, and the tools available in applications have not yet reached the same level of accessibility and broad spectrum as those of the geometric of dynamical systems. In terms of our analysis, this meant that rather than having at our disposal a general result to apply, we needed to construct this result from the systematic study of examples. To this end, we proceeded with the systematic analysis of the reliability of discharge times in neuronal models of increasing complexity.

The first model was the standard leaky integrate and fire (LIF) system. The dynamics of the periodically forced LIF are well understood as they can be captured by iterates of orientation preserving circle maps (Pakdaman, 2001). These maps are easily obtained as the relation between input phases at successive discharge times. Thanks to them, it is possible to show that the LIF reproduces some of the complex responses of periodically neuronal membranes such as phase locked and quasiperiodic firings. However, when the input is aperiodic, such as the noise-like currents in the experiments, there are no input phases, and it is not possible to introduce the map in the same way as for periodic inputs. This difficulty not withstanding, we were able to introduce a different family of maps that captured the dynamics of aperiodically forced LIFs (Pakdaman et al. 2001). The geometric property of the orientation preserving circle map determines the dynamics of the periodically forced system. In the same way the key property of the family of maps associated with the aperiodically forced LIF indicates that for widely fluctuating signals such as the sample path of Gaussian processes, the LIF will be reliable. In this way, the results obtained from the analysis of the LIF confirmed that the RDS theory could provide the method that would clarify the source of differences in the reliability between the two classes of experiments mentioned above. Some of the differences in reliability observed in the experiments were also present in the LIF, and could be accounted for thanks to the differences in the associated maps.

The LIF can be considered as an overly simplistic description of neuronal membranes. The next stage consisted in expanding the results to a wider class of systems. These are the phase models, such as the active rotator (Pakdaman, 2002). Remarkably, we showed that families of maps similar to the ones obtained for the LIF could also be constructed for phase models. This indicated that the results obtained for the LIF could be carried over to these other models. In other words, such models reliably encode noise-like signals, even though they do not necessarily do so for periodic perturbations.

At this stage, the analysis took on two parallel directions. On the one hand, we examined the validity of the results for various fluctuating signals such as gamma and Poisson renewal processes (Yamanobe and Pakdaman, 2002), or combined periodic and aperiodic forcings (Pakdaman and Mestivier, 2001). On the other hand, we extended the analysis to more complex models, namely the FitzHugh-Nagumo (Kosmidis and Pakdaman, 2003), the Hodgkin-Huxley (Pakdaman and Tanabe, 2001), the Adelman-FitzHugh (Pakdaman and Mestivier, submitted) equations, as well as a number of bursting neuronal models (in preparation). Two conclusions were derived from these series of studies. The first conclusion was that, in general, these models produce reliable firing in response to aperiodic noise-

unreliable discharges such as chaotic ones under periodic forcing. The second conclusion was that this rule admitted exceptions, in the sense that, in models such as the FitzHugh-Nagumo equations, noise-like forcing did not always lead to reliable firing. In fact it could also lead to unpredictable firing due to the onset of stochastic chaos (Kosmidis and Pakdaman, in press). Surprisingly, the standard HH model did not produce similar results. This observation indicated that, besides differences in stimulus characteristics, differences in intrinsic neuronal properties could also play a prominent role in determining neuronal reliability. In other words, a stimulus could be encoded in a reliable manner by one neuron, but produce unreliable firing in another due to differences in their intrinsic properties.

The final stage of the analysis using RDS theory consisted in synthesizing the analyses of the different models into a coherent theory that would encompass neuronal membranes and, most importantly, be applicable to experiments. The analysis using RDS theory had yielded that the Lyapunov exponent associated with the dynamics of the system was the proper indicator of neuronal reliability. In general, Lyapunov exponents are used as measures of chaos. Positive exponents are signatures of sensitive dependence on initial conditions, a hall mark of chaos. In our analysis, we used Lyapunov exponents for a different purpose. For systems undergoing highly fluctuating stimuli, negative Lyapunov exponents indicate convergence (Arnold, 1998). When applied to neurons, this result means that negative Lyapunov exponents are indicators of reliable firing. Combining this, with the large number of neuronal models that we had examined, we proposed a closed form for the Lyapunov exponent of a neuronal oscillator forced by a weak aperiodic broad band signal. All terms within this expression can be, in principle, directly derived from experiments, with no reference to any mathematical model. The central contribution of this expression is to reveal quantitatively the relation between the spectral content of the signal and the intrinsic neuronal properties that ensure reliable firing. This fulfilled the original goal of the study.

Finally, throughout the analysis using RDS theory, we had neglected the role of noise. In the last stage of the study, we took this factor into account and examined how it affected neuronal reliability. The preconceived idea about noise is that it should hinder reliability by increasing discharge time variability. Our study revealed that it is not necessarily so. In other words, there are cases, where in fact, the presence of some noise can enhance discharge time reliability (Tanabe and Pakdaman, 2001c). While there have been many studies concerned with linearization by noise and stochastic resonance in neurons (Segundo et al. 1994), we have shown that the mechanisms underlying noise enhanced neuronal reliability is a noise induced transition observable at the level of the voltage dynamics and is therefore differ from the mechanisms of, say, linearization by noise (Tanabe et al., 1999; Tanabe and Pakdaman, 2001a, 2001b, Takahata et al. 2002). A consequence of this is that enhanced reliability does not occur at the same noise range as, say, linearization by noise (Tanabe and Pakdaman, 2001c).

In conclusion, the presentation will review our systematic investigation of neuronal reliability that started by trying to reconcile two apparently opposing classes of experiments on neuronal reliability. A number of novel results concerning various neuronal models, such as, for instance the construction of return maps for the aperiodically forced LIF, have been described in the process. These lead finally to the characterization of the interplay between neuronal properties and signal characteristics that explain why some stimuli evoke reliable firing in certain neurons and others not. Finally, our study also revealed a novel noise effect, namely noise enhanced neuronal reliability and clarified the mechanisms underlying it.

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