Eur. Phys. J. B **24**, 409–413 (2001)
DOI:

THE EUROPEAN PHYSICAL JOURNAL B
EDP Sciences

Probabilistic properties of neuron spiking time-series obtained in vivo

A. Bershadskii[1,a], E. Dremencov[2], D. Fukayama[3], and G. Yadid[2]

[1] ICAR, PO Box 31155, Jerusalem 91000, Israel
and
Mason Laboratory, Yale University, New Haven, CT 06520-8284, USA
[2] Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan 52900, Israel
[3] Department of Physics, Chuo University, Tokyo 112-8551, Japan

Received 13 May 2001 and Received in final form 20 September 2001

Abstract. Probabilistic properties of spiking time-series obtained *in vivo* from singular neurons belonging to Red Nucleus of brain are analyzed for two groups of rats: genetically defined rat model of depression (Flinders Sensitive Rat Line – FSL) and a control (healthy) group. The FSL group shows a distribution of interspike intervals with a much longer tail than that found for normal rats. The former distribution (for the FSL group) indicates a power-law with exponent $\alpha = -1 \pm 0.1$. A simple thermodynamic (noise) model is elaborated to explain obtained results.

PACS. 87.19.La Neuroscience – 87.18.Sn Neural networks – 87.17.-d Cellular structure and processes – 87.10.+e General theory and mathematical aspects

1 Introduction

In recent years nonlinear properties of neuron firing are studied very intensively, especially in relation to noise effects (see, for instance, Refs. [1–10] and references therein). These investigations (both theoretical and experimental) were devoted mainly to enhancement of weak subthreshold signals by addition of noise due to the cooperative effect of noise on signal because of the nonlinear properties of the neuron. There are two main ways for experimental studies in this area: a) investigation of current-voltage characteristic curve, and b) extracting the information from time-series generated by neuron firing. In the present paper we are concentrated on the last method.

All types of information, which is received by sensory system, are encoded by nerve cells into sequences of pulses of similar shape (spikes) before they are transmitted to the brain. Brain neurons use such sequences as main instrument for intercells connection. The information is reflected in the time intervals between successive firings (interspike intervals of the action potential train or ISIs). There need be no loss of information in principle when converting from dynamical amplitude information to spike trains [11] and the irregular spike sequences is the foundation of neural information processing. Although understanding of the origin of interspike intervals irregularity has important implications for elucidating the temporal components of the neuronal code and for treatment of such mental disorders as depression and schizophrenia, the problem is still very far from its solution (see, for instance, Ref. [9] and references therein).

In experiments performed *in vitro*, cortical slices, for instance, showed regular firing patterns when stimulated by a constant current indicating that the irregular firing of neurons in the intact brain is due to strong temporal fluctuations of synaptic inputs. Therefore, electrophysiological experiments *in vivo* should be performed for achieving the above-mentioned purpose.

We study so-called Red Nucleus. The Red Nucleus is a prominent structure within the rostral midbrain. Very little is known about the functions of the Red Nucleus in humans. Inputs to the Red Nucleus arise from *motor* areas of the brain and in particular the deep cerebellar nuclei (*via* superior cerebellar peduncle; crossed projection) and the motor cortex (corticorubral; ipsilateral projection). Therefore, the Red Nucleus is supposed to be relatively "simple" from neural point of view [12]. The most important efferent projection of the Red Nucleus is to the contralateral spinal cord, *i.e.* the rubrospinal projection. The rubrospinal tract is thought to be involved in the control of both the flexor and extensor muscles, but even this is debated. The rubrospinal projection is also, of course, influenced by the motor information coming out of the cerebellum, as well as from motor cortex.

Our electrophysiological experiment *in vivo* was performed with two groups of rates. One group was

[a] e-mail: ark2@eudoramail.com

genetically defined rat model of depression (Flinders Sensitive Rat Line – FSL) and another was a control group. All rats were anaesthetized and mounted in a stereotaxic frame. Technical details of the electrophysiological measurements will be published elsewhere. Procedures involving animals and their care were conducted in conformity with the international laws and policies. All efforts were made to minimize animal suffering and to reduce the number of animal used.

It is known that humans with deep depression have intrinsic locomotor's problems. Therefore, investigation of Red Nucleus for genetically defined rat model of depression can be useful for understanding the mental disorder origin.

2 Data

Figure 1 – top, shows an example of 1000 subsequent interspike intervals obtained for a FSL's neuron (τ is length of interspike interval, in seconds) and Figure 1 – bottom, shows analogous set obtained for a neuron of a rat belonging to control group. We are investigating "slow" firing neurons, taking into account that we will compare (in our further investigations) these results with analogous observations for dopaminergic neurons from ventral tegmental area (VTA) of brain, which is believed to be responsible for "pleasure" reaction. The last neurons are known to be "slow"-firing ones.

Figure 2 shows probability density functions, $P(\tau)$, calculated for four neurons belonging to two FSL rats. Figure 3 shows probability density functions calculated for four neurons belonging to two rats from control (healthy) group. We choose log-log scales in these figures. One can see that the distribution falls off much faster for the normal rats than for the FSL ones. This is the main result of our measurements.

To understand reasons for the differences between the probability density functions produced by FSL and by healthy neurons we need in comparison with the data obtained by other authors and in some speculations.

The lognormal distribution is commonly used to fit spike train data for healthy neurons (see, for instance, Ref. [13] where data were obtained from cat cerebral cortex and other preparations, and Ref. [14] where data were obtained from retinal ganglion cells), though without theoretical explanation. Therefore, first of all we try to approximate the data represented in Figure 3 (for healthy neurons) by the lognormal distribution (solid curves in Fig. 3). Though it seems like a decent fit to a piece of a lognormal curve, it should be noted, that all the data are on one side of what would be the peak in the curve (well to the right of it except for one or two points). Therefore we cannot claim with definition that the data confirm the lognormal distribution for the healthy neurons. In any case, these data do not contradict to the data obtained by the other authors, which claim lognormal distribution as the most appropriate one in this case [13,14] (see also below). It should be also noted that data shown in Figures 3c and d could be also fitted by a more simple power-law

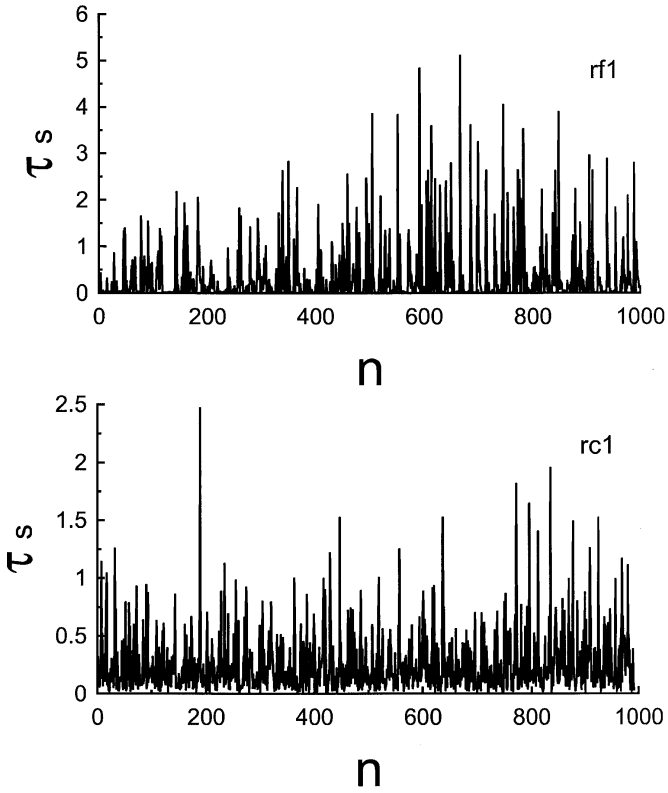

Fig. 1. Examples of 1000 subsequent interspike intervals obtained for a FSL's neuron (top) and for a neuron belonging to a rat from control group (bottom). τ is length of interspike interval, in seconds.

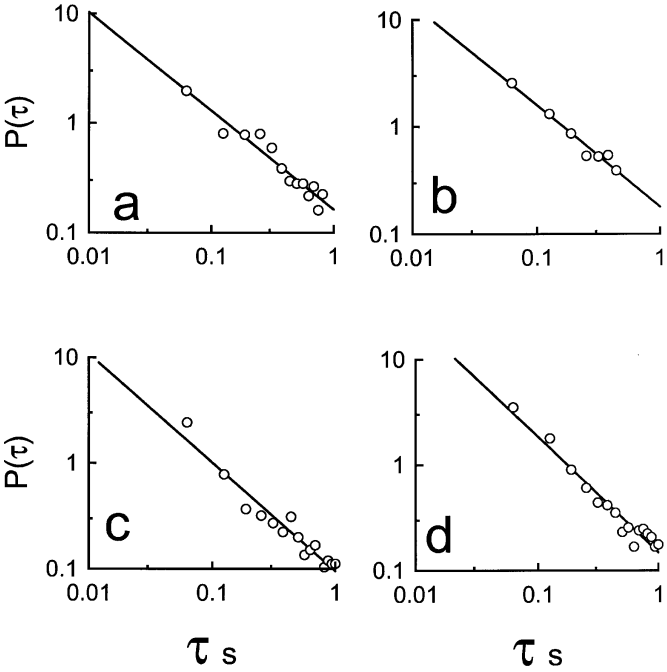

Fig. 2. Logarithm of probability density functions, $P(\tau)$, calculated for four neurons belonging to two FSL rats against logarithm of τ. Straight lines (best fit) are drawn to indicate power-law distribution (with exponent equal to -1 ± 0.1).

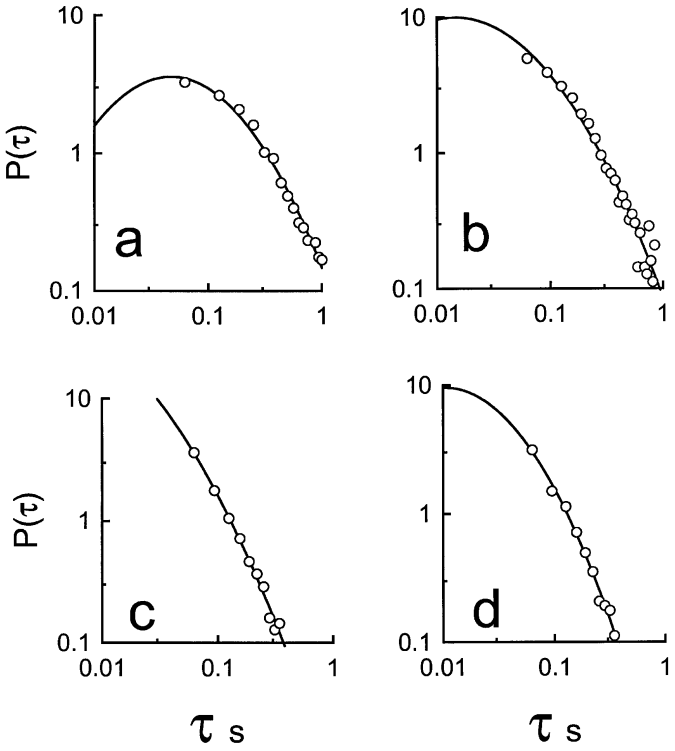

Fig. 3. Logarithm of probability density functions, $P(\tau)$, calculated for four neurons belonging to two rats from control group against logarithm of τ. Solid curves (best fit) are drawn to indicate lognormal distribution.

with an exponent close to -2. For a more quantitative comparison of these two types of approximation we made a regression analysis. Standard parameters of this analysis are following: $R^{[2]} = 0.67$, $R = -0.82$ and $SE = 0.67$ for power-law approximation in Figure 3c, while lognormal approximation gives $R^{[2]} = 0.91$, $R = 0.96$ and $SE = 0.36$ (close results are obtained for the data represented in Fig. 3d). Though the regression parameters for the lognormal approximation are considerably better than those obtained for power-law approximation, the power-law regression parameters are also not so bad.

For the FSL neurons this situation seems to be more clear. We use log-log scales in Figure 2, therefore the straight lines (best fit) drawn in this figure indicate power-law distribution

$$P(\tau) \sim \tau^{\alpha}. \tag{1}$$

Exponent α extracted from these graphs is equal to -1 ± 0.1. Since reference [15] the power-law distributions considered as indication of a self-organized critical process – SOC (for ideal SOC distribution of inter-burst intervals is exponential [16,17]).

3 Model

In models similar to that suggested reference [15] a thermal excitation process leading to crossover of a threshold (and, consequently, to jumps from one metastable state to another) plays a crucial role. Arrhenius relationship between typical crossing time, τ, and height of the threshold, E: [18]

$$\tau \simeq \tau_0 \, \mathrm{e}^{E/kT} \tag{2}$$

is used in the models (where T is some temperature-like parameter and k is the Boltzmann constant). If the threshold overcoming occurs in a nonlinear multistable system due to a noise, then we have a particular form of this relationship (Kramers relationship) with $T = D/k$, where D is noise strength [18]. Relationship (2) (in Arrhenius or in Kramers formulation) is independent on other SOC properties and can be considered for much more wide class of phenomena and, in particular, for neurons firing.

Let us recall some basic electrochemical properties of neuron [19–22]. Nerve cells are surrounded by a membrane that allows some ions to pass through while it blocks the passage of other ions. When a neuron is not sending a signal it is said to be "at rest". At rest there are relatively more sodium ions onside the neuron and more potassium ions inside that neuron. The resting membrane electrochemical potential (the voltage difference across the neural membrane) of a neuron is about -70 mV. If some event (a stimulus) causes the resting potential to move toward 0 mV and the depolarization reaches about -55 mV (a "normal" threshold) a neuron will fire an action potential. The action potential is an explosive release of charge between neuron and its surroundings that is created by a depolarizing current. If the neuron does not reach this critical threshold level, then no action potential will fire. Also, when the threshold level is reached, an action potential of a *fixed* size will always fire (for any given neuron the size of the action potential is always the same). The mechanism of depolarization can be described as following. A stimulus first results in the opening of sodium channels in the neuron membrane (membrane's channels are transmembrane proteins that open in response to changes in membrane potential allowing a particular ionic species to cross the membrane). Since there are a lot more (positive) sodium ions on the outside, and the inside of the neuron is negative relative to the outside, sodium ions rush into the neuron. Therefore the neuron becomes more positive and becomes depolarized. It takes longer to potassium channels to open. When they do open potassium rushes out of the cell, reversing the depolarization (action potential peaks at around 55 mV = Nerst equilibrium potential for Na^+). Also about this time, sodium channels start to close. This causes the membrane potential to go back toward the rest value -70 mV (a repolarization). It takes about 1.5 ms for a neuron to return to its resting potential. Even after the membrane is repolarised, some Na^+ channels remain inactivated, such that a second activation potential requires a higher stimulus than the previous threshold voltage. Depending on different types of voltage-dependent ion channels, different types of action potentials are generated in different cells types and the qualitative estimates of the potentials and time periods can be varied. Moreover, there is *a distribution* of threshold values over different

channels in the same membrane due to fluctuations in the local environment. If the threshold value is passed gating occurs and the channel opens with high probability. Probabilistic nature of neuronal threshold was experimentally proved rather long time ago (see, for instance, Ref. [24], where this phenomenon was related to the channel noise and Refs. [25–27] for recent achivments). In particular, it is shown in a recent paper reference [23] that a normal-like (Gaussian) distribution of the threshold values gives a fairly good fit of an available data on the current-voltage curve for ions channels (Boltzmann distribution is also discussed in this context).

Now we can return to the idea related to Arrhenius (Kramers) relationship (2). Membrane potential may overcome its threshold value due to a deterministic stimulus or due to stochastic oscillations, *e.g.* noise (though, modulated by a weak external stimulus). In the last case the overcoming of threshold have a probabilistic nature and typical crossing time can be established using Arrhenius (Kramers) equation (2). There are two main sources of electrical noise in neurons: noise from synaptic processes (see, for instance, Refs. [28–30]) and references therein) and channel noise (see for a recent review [25]). Neurons effectively utilize noise for detection of weak signals [1–10]. This situation may be most relevant to anaesthetized brain. If the thresholds are distributed according to some probability distribution $P_{\rm th}(E)$, then using (2) one obtains distribution of τ in a spiking train

$$P(\tau) = P_{\rm th}(E)\frac{{\rm d}E}{{\rm d}\tau} \sim \frac{P_{\rm th}(\log\tau)}{\tau}\,. \qquad (3)$$

The above mentioned *normal*-like distribution of the thresholds $P_{\rm th}$ after substitution into (3) results in *lognormal*-like distribution of interspike intervals τ

$$P(\tau) \sim \tau^{-1}\exp-\left[\frac{(\log\tau/\tau_{\rm c})^2}{2\sigma^2}\right] \qquad (4)$$

where $\tau_{\rm c}$ and σ are some constants. This result is consistent both with our data for control group (Fig. 3) and with results of measurements presented in references [13,14].

We have already mentioned that Gaussian (normal) distribution of the thresholds was considered in reference [23] as an alternative to Boltzmann distribution. Using (3) it is easy to show that Boltzmann distribution of the thresholds leads to a power law distribution of interspike intervals $P(\tau) \sim \tau^{\alpha}$ with $\alpha \sim -2$ (*cf.* Fig. 3c and d). We will discuss a possible competition between Boltzmann and Gaussian distributions of the thresholds in more details elsewhere in relation to neurons belonging to another area of brain (VTA, or "pleasure" zone) where this competition has principal character.

Now we can find distribution of the thresholds, which may result in the observed (Fig. 2) power-law distribution of interspike intervals τ. One can see that substitution of an *uniform*-like distribution of thresholds: $P_{\rm th}(E) \simeq$ const. into (3), results in the observed in our experiment with FSL rats probability distribution of interspike intervals

$$P(\tau) \sim \tau^{-1}. \qquad (5)$$

4 Discussion

Normal-like distribution of thresholds extracted from the data for the healthy neurons in references [13,14] (which is consistent with our data for control group) can be a broad one. However, one can speak about fluctuations in a vicinity of a certain threshold (normal fluctuations) in this case. For the uniform-like distribution of thresholds extracted from the data for FSL rats one cannot find a certain especial value of threshold, that should results in a loss of intelligence of corresponding neurons at their communication with other ones. This intelligence, then, could be partially restored only for sufficiently long trains of spikes, for which an average value of threshold may appear.

Given the central role that electrical excitability plays in neurons system function, it is not surprising that mutations of voltage-gated ion channels in ion membrane alter neuronal function. For example: a) Generalized epilepsy with febrile seizures is associated in some cases with a mutation of β_1 subunit of the Na^+ channel. This mutation may promote epilepsy by slowing the inactivation process in neuronal Na^+ channels (see above), leaving the brain hyper-excitable.

b) Some forms of episodic ataxia, a condition of triggered events of imbalance and uncoordinated movements, has been tied to a number of mutations of $K_\nu 1.1$ channel, which gives rise to an inactivating K^+ conductance and increases the threshold of activation.

In the present paper we discuss a possible mutation of *probabilistic* properties of the thresholds in Red Nucleus neurons of FSL rats, which may be partially responsible for their ill behavior. This discussion is based on calculations of probability distributions of the *in vivo* obtained spiking time-series and some general thermodynamic ideas. It should be noted, however, that the power-law fit with exponent -1 for the FSL rats is based only on just a bit more than one decade, so one has to be careful about the thermodynamic interpretation of the data. Another significant point which should be taken into account in further investigations is role of synaptic input, *i.e.* signal instead of noise. Our very simple model ignores these signals. It is interesting that interaction between noise and the informative signals may play crucial role in the neurons' communications due to stochastic resonance mechanism (see, for instance [31,32] and references therein). We hope to investigate this problem using our data in the future. What we can say definitely comparing Figures 1 and 2, that the distribution falls off much faster for the normal rats than for the FSL ones, and this observation can be used to distinguish between healthy and "depressive" neurons.

The authors are grateful to K.R. Sreenivasan and to the Referee for comments and suggestions. One of the authors (A.B.) is grateful to the Yale University (New Haven, USA) for hospitality.

References

1. C. Ivey, A.V. Apkarian, D.R. Chialvo, J. Neuroscience **79**, 1879 (1998).
2. D.R. Chiavlo, A. Longtin, J. Muautller-Gerking, Phys. Rev. E **55**, 1798 (1997).
3. R. Fakir, Phys. Rev. E **58**, 5175 (1998).
4. M. Di Mascio, G. Di Giovanni, V. Di Matteo, E. Esposito, Neuroscience **92**, 237 (1999).
5. J. Fing, B. Tirozzi, Phys. Rev. E **61**, 4207 (2000).
6. J.A. White, J.T. Rubinstein, A.R. Kay, Trends Neurosci. **23**, 131 (2000).
7. N. Hohn, A.N. Burkitt, Phys. Rev. E **63**, 031902 (2001).
8. H.E. Plesser, Th. Geisel, Phys. Rev. E **63**, 031916 (2001).
9. C. van Vreeswijk, H. Sompolinsky, Science **274**, 1724 (2001).
10. A. Silchenko, C-K. Hu, Phys. Rev. E **63**, 041105 (2001).
11. T. Sauer, Chaos **5**, 127 (1995).
12. M.B. Carpeuter, J. Sutin, *Human neuroanatomy* (Williams and Wilkins Co., Baltimore, 1983).
13. H. Tuckwell, *Introduction to theoretical neurobiology*, Vols. 1 and 2 (Cambridge University Press, New York, 1980).
14. M.W. Levine, Biol. Cybern. **65**, 459 (1991).
15. P. Bak, K. Sneppen, Phys. Rev. Lett. **71**, 4083 (1993).
16. P. Bak, C. Tang, K. Wiesenfeld, Phys. Rev. Lett. **59**, 381 (1987).
17. H.J. Jensen, *Sel-Organized Criticality: Emergent complex behavior in physical and biological systems* (Cambridge University Press, Cambridge, UK, 1998).
18. P. Hanggi, P. Talkner, M. Borkovec, Rev. Mod. Phys. **52**, 251 (1990).
19. D.J. Aidley, P.R. Stafield, *Ion Channels: Molecules in Action* (Cambridge University Press, Cambridge, UK, 1996).
20. F.M. Ashcroft, *Ion Channels and Disease* (Academic Press, San Diego, USA, 2000).
21. D. Johnson, S.M.-S. Wu, *Foundations of Cellular Neurophysiology* (MIT Press, Cambridge, MA, USA, 1995).
22. T.F. Weiss, *Cellular Biophysics* (MIT Press, Cambridge, MA, USA, 1996).
23. M.E. Green, J. Theor. Biol. **193**, 475 (1998).
24. F.J. Sigworth, J. Physiol. **307**, 97 (1980).
25. J.A. White *et al.*, J. Neurophysiol. **80**, 262 (1998).
26. R. Azour, C.M. Gray, Proc. Natl. Acad. Sci. USA **97**, 8110 (2000).
27. R.K. Powers, M.D. Binder, J. Physiol. **528**, 131 (2000).
28. W.H. Calvin, C.F. Stevens, J. Neurophysiol. **31**, 210 (1998).
29. L.G. Nowak *et al.*, Cereb. Cortex **7**, 487 (1997).
30. C.F. Stevens, A.M. Zador, Nat. Neurosci. **1**, 210 (1998).
31. J.K. Douglass, L. Wilkens, E. Pantazelou, F. Moss, Nature (London) **365**, 337 (1993).
32. J.J. Collins, T.T. Imhoff, P. Grigg, J. Neurophysiol. **76**, 642 (1996).