PERGAMON

Chaos, Solitons and Fractals 11 (2000) 1819–1822

CHAOS
SOLITONS & FRACTALS

www.elsevier.nl/locate/chaos

Introduction

Stochastic resonance in biological systems

The aim of the conference was an updated overview and a critical discussion of the role and the meaning of stochastic resonance (SR) in biological systems. Accordingly, the groups involved in SR and biology were invited. Most of the participants belonged to the SR community, but several were biophysicists who work on biological systems using mathematical and physical approaches. These two components made the conference more interesting and the discussion richer and livelier.

The main issues considered in the conference concerned the detection and encoding of signals in neural cells and the use of neural models to approach this problem. Transmission and amplification in living organisms occurs by enzymatic cascades or by taking advantage of the energy stored in the electrochemical gradient through the cell membrane. The latter case occurs at the molecular level (ion channel transduction) and at the macroscopic level when action potentials fire. SR can occur in either case, and ion channels and action potential models were the topics most considered in the conference.

SR is a simple phenomenon, initially studied in bistable systems under the action of internal noise, that causes transitions, and of a external periodic perturbation, that synchronizes them. SR is not limited, however, to bistable systems. Each time a noisy below-threshold signal crosses threshold, SR is obvious: too little noise results in few crossings, and too much noise results in loss of the signal. More generally SR occurs when the probability of stochastic events is affected by the signal (e.g. ion channel switching or, in some conditions, action potential firing are events whose probability depends on the stimulus). The first paper connecting SR with neural spiking was published in 1993 [1]; it was based on the reconsideration of interspike interval histograms in auditory fibers, known since 1967 [2]. The similarity of the multimodal experimental histograms with those produced in bistable systems was the key to interpret the generation of spikes in auditory fibers as due to a stochastic process (or equivalent to it).

There was a strong focus on the auditory system in this conference. The mechano-electrical transduction in the cochlea is a case of high sensitivity and does not involve enzymatic amplification; moreover, auditory fibers require stochastic encoding because they are unable to fire at high frequency. Therefore auditory fibers are a candidate in which SR can play a physiological role, for instance, by matching the threshold for firing with the actual value of noise. Encoding signals in spike trains involves several sources of noise: (1) ion channels in the hair bundle open mechanically by the relative movement of long, medium, and short hairs; (2) Brownian motion of the hair bundle contributes to the openings of ion channels; (3) the stochastic release of the transmitter is voltage-controlled. The latter depends not only on ion channels in the hairs but also on the ion channels in the cell body.

A simulation of these processes indicates that the threshold for hearing is just at the value that maximizes transmission with the noise due to three processes listed above [3]. Results of experiments in which a noisy signal affects the movements of the hair bundle, simulating their Brownian motion, were reported [4]. They showed an increase in the signal transmitted to the generator potential increasing the noise in the movement imposed to the hair bundle. However this occurs 1 or 2 orders of magnitude above the threshold for hearing. An interesting observation for stochastic phase locking in this system comes from cochlear implants. Cochlear implants directly stimulate nerve fibers completely destroying or ignoring tonotopic organization. The nervous system is plastic, and, if information arrives this restores perception. Particular tricks in cochlear implants tend to introduce a difference in the firing pattern among various fibers (e.g., restoring stochastic phase locking), improving hearing in persons using such implants [5,6].

Many talks dealt with neural models with different levels of complexity. These ranged for Hodgkin–Huxley equations and FitzHugh–Nagumo models to operational models of integrate-and-fire systems

PII: S 0 9 6 0 - 0 7 7 9 (9 9) 0 0 1 1 7 - 4

[7–10]. Although these models have less flexibility than real neurons, there are cases in which such "toy-models" are stimulating. One example is the solution of the first-passage time for leaky integrator [11]. This equation coincides with the Langevin equation of a free Brownian particle in an oscillating field in presence of an absorbing barrier. Particular emphasis in the conference as well as in recent papers has been put on the search for a measure of the influence of the stimulus on the output [12–14]. This measure has to be equivalent to the signal-to-noise ratio (SNR) in simpler cases, but the concept is valid for more general stimuli than periodic perturbations.

An alternate approach is the attempt to use information theory on spike trains [15]. An interesting observation is the dependence of the probability of errors, even in a simple voltage-to-frequency converter, on the value of the input signal [16]. This poses obstacles towards straightforward application of information theory to neural encoding.

An effect reported both in experimental work and neural models in the below-threshold regime is the dependence of tuning curves for receptors on noise level. Increasing the noise results in an opening of the tuning curves (decreasing selectivity). This was found in experimental data (in mechanoreceptors as well as in thermo- and electro-sensory receptors) [17], and in stimulations of neural models [10] and of auditory transduction [3].

A session of the conference concerned arrays of interacting stochastic elements [18,19] searching for the best organization (in terms of strength of interaction and noise, which appear to play more or less an equivalent role). The idea was not to improve the SNR above usual expectations but rather to find parameters that allow synchronization of the array to obtain a reasonable spatial image. Specific effects due to the memory in arrays of neuron-like units were also considered.

Another theme in the conference was centered on SR and statistics. The connection between stochastic switching of ion channels and spectral properties of the transmitted signal was evaluated and the dependence of the transmission on rate constants was discussed. Improvement of transmission occurs by increasing the spontaneous rate of the stochastic events or strengthening the link between rate constants and external forcing, because this improves the statistics by increasing the number of events. The initial work [20] on this assumed an exponential dependence of the rate constants on the voltage, analogous to a barrier separating two states. During the conference it became clear that any nonlinear dependence could produce an SR effect. This result can be interpreted as follows: SR is not physical, but rather a statistical effect. If SR is merely an improvement of statistics, this rules out interpretation such as "the energy flow from the internal noise to the output signal cause SR", as often used in the literature.

This brings into focus another issue that concerns SNR. Initially, the existence of a maximum in the output SNR induced the expectation that SR was a tool to override linear devices in separating signal and noise. The expectation was false for basic reasons, as confirmed analytically [15,21,22]. Nevertheless, the idea that SR is a tool for detecting small signals persisted; however, one needs to define "small" in this context. If small indicates a "below-threshold signal" for a given stochastic detector, SR can indeed detect small signals. If, on the other hand, small means "smaller than the noise present in the signal", SR cannot make detection possible [23].

Thus SR does not account for the high sensitivity of living systems to very weak stimuli, in agreement with the discussion in Ref. [24]. This result is actually more general, because nonlinear systems cannot override linear systems to detect small signals hidden in a large noise. In technical terms, we may say that Linear Response Theory (LTR) applies. An analytical approach has given in each case (bistable systems, threshold comparators, modulation of rate constants) expressions for SNR at the output [15,21,22]. These show that noisy transmission deteriorates the output signal compared to the input. LTR and the expressions for Poisson-modulated random events show, however, that the noise introduced can be relatively low for certain parameters [20].

SNR gain can be achieved in a different context [25], namely small noise and large signal; however signal-to-noise gain in the nonlinear response limit has nothing to do with the detection of signals contaminated by a large noise.

Several biological systems show remarkable sensitivity to electrical fields, which are weak compared to their thermal noise. Major topics of the conference were the interaction of ion channel kinetics and calcium oscillations in stochastic cellular systems [26] and the reaction of sharks to electric fields [27–29] (1–2 nV/cm), which represented an interesting platform to discuss both SNR evaluation and undue expectations towards SR [30]. The overview of experimental results on physics and physiology of electro-reception given by Ad. Kalmijn during the conference was extremely stimulating, giving a connection between the sensitivity in electro-reception and the way sensory epithelium works: the specificity of sensory epithelium includes how ion channels depend on membrane potential (excitability). A method to measure the dependence of rate constants on membrane potential during a continuously time-varying stimulation is described in Ref. [31].

The common source of both the signal and the noise in nerve cells is well understood [32] and this topic often recurred during the discussions at the conference. Excitability emerges from the superposition of random events (conformational changes of ion channels) that are coupled through voltage. This is analogous to the way thermodynamic laws arise from the underlying thermal motion molecules. The properties of ion channels are, however, very specific and the nonlinear behavior of channels is the basis for membrane excitability. The superposition of random events produces potential fluctuations, which might be large enough to develop into action potentials. Considering this mechanism enables us to predict the density of channels and the dimensions of cells (capacitance) in which excitability can take place. This means that "threshold" and "noise" are inevitably connected and that there is no deterministic threshold below which excitability does not exist. A common process that encodes the input stimulus through small underlying events, as it is for example the case in chemical synapses, introduces a link between noise and signal (for instance in the generator potential). This substantially reduces the freedom in simulations aiming to reproduce the behavior of neurons or neural tissue.

The perspective emerging from many talks was to study SR, and to understand other stochastic phenomena, one must know how specific information is encoded in natural systems. This is usually unknown, making it difficult to analyze fluctuations and tempting to exaggerate the power of SR to extract information. The conference highlighted such concerns with possible outcome that future work on SR in biological systems will benefit.

References

[1] Longtin A, Bulsara A, Pierson D, Moss F. Bistability and the dynamics of periodically forced neurons. Biol Cybernet 1993;70:569–78.

[2] Rose JE, Brugge JF, Anderson DJ, Hind JE. Phase-locked response to low frequency tones in single auditory nerve fibers of the squirrel monkey. J Neurophys 1967;30:769–93.

[3] Gebeshuber IC. The influence of stochastic behavior on the human threshold of hearing. Chaos, Solitons & Fractals 2000;11:1855–68.

[4] Jaramillo F, Wiesenfeld K. Physiological noise level enhances mechano electrical transduction in hair cells. Chaos, Solitons & Fractals 2000;11:1869–74.

[5] Morse RP, Meyer GF. The practical use of noise to improve speech coding by analogue cochlear implants. Chaos, Solitons & Fractals 2000;11:1885–94.

[6] Rattay F. Basics of hearing theory and noise in cochlear implants. Chaos, Solitons & Fractals 2000;11:1875–84.

[7] Barbi M, Chillemi S, Di Garbo A. The leaky integrate-and-the-fire with noise: a useful tool to investigate SR. Chaos, Solitons & Fractals 2000;11:1849–53.

[8] Fronzoni L, Krueppel T, Lueken W, Nieri L, Ricci N. A statistical study of the dynamics of the membrane voltage in protozoa *Euplotes vannus*. Chaos, Solitons & Fractals 2000;11:1917–22.

[9] Huber MT, Krieg JC, Dewald M, Voigt K, Braun HA. Stochastic encoding in sensory neurons: impulse patterns of mammalian cold receptors. Chaos, Solitons & Fractals 2000;11:1895–1903.

[10] Longtin A. Effect of noise on the tuning properties of excitable systems. Chaos, Solitons & Fractals 2000;11:1835–48.

[11] Bulsara AR, Lowen SB, Rees CD. Cooperative behavior in the periodically modulated Wiener process: noise-induced complexity in a model neuron. Phys Rev E 1994;49:4989–5000.

[12] Henegham C, Chow CC, Collins JJ, Imhoff TT, Lowen SB, Teich MC. Information measures quantifying aperiodic stochastic resonance. Phys Rev E 1996;54:R2228–31.

[13] Noest AJ. Tuning stochastic resonance. Nature 1995;378:341–2.

[14] Collins JJ, Chow CC, Imhof TT. Tuning stochastic resonance (reply). Nature 1995;378:341–2.

[15] Dee Weese M, Bialek W. Information flow in sensory neurons. Nuovo Cimento D 1995;17:733–41.

[16] Contribution to the conference by Chialvo DR.

[17] Ivey C, Apkarian AV, Chialvo DR. Noise-induced tuning curve changes in mechanoreceptors. J Neurophysiol 1998;79:1879–90.

[18] Rozenfeld R, Schimansky-Geier L. Array enhanced stochastic resonance in finite systems. Chaos, Solitons & Fractals 2000;11:1937–44.

[19] Contributions to the conference by Ditto WL, Inchiosa ME, Chialvo DR, Bulsara AR, Apkarian AV.

[20] Bezrukov SM, Vodyanoy I. Stochastic resonance in non-dynamical systems without response thresholds. Nature 1996;385:319–21.
[21] Kiss LB. Possible breakthrough: significant improvement of signal to noise ratio by stochastic resonance. In Proceedings of Third Conference on Nonlinear Dynamics. New York: AIP, 1995. pp. 1–15.
[22] Loerincz K, Gingl Z, Kiss LB. A stochastic resonator is able to greatly improve signal-to-noise ratio. Phys Lett A 1996;224:63–7.
[23] Petracchi D. What is the role of stochastic resonance? Chaos, Solitons & Fractals 2000;11:1827–34.
[24] Dykman MI, McClintock PVE. What can stochastic resonance do? Nature 1997;344.
[25] Gingl Z, Vajtai R, Kiss LB. Signal-to-noise ratio gain by stochastic resonators in bistable systems. Chaos, Solitons & Fractals 2000;11:1929–32.
[26] Sandblom J, Galvanovski J. Electromagnetic field absorption in stochastic cellular systems: enhanced signal detection in ion channels and calcium oscillators. Chaos, Solitons & Fractals 2000;11:1905–11.
[27] Kalmijn AJ. The detectionof electric fields from inanimate and animate sources other than electric organs. Handbook of sensory physiology 1974;3:147–200.
[28] Kalmijn AJ. Electric and magnetic field detection in elasmobranch fishes. Science 1982;218:816–8.
[29] Kalmijin AJ. Electric and near-field acoustic detection, a comparative study. Acta Physiol Scand 1997;161 Suppl 638:25–38.
[30] Petracchi D, Cercignani G. A comment on the senitivity of fish to low electric fields. Biophys J 1998;75:1.
[31] Menconi CM, Pellgrini M, Petracchi D. Evaluation of rate constants of single ion channel transitions under periodic forcing. Chaos, Solitons & Fractals 2000;11:1913–15.
[32] DeFelice LJ. Linear analysis in non-linear systems: signal-to-noise ratios in noisy neurons. Chaos, Solitons & Fractals 2000;11:1823–26.

Donatella Petracchi
Istituto di Biofisica, Via S. Lorenzo 36,
56127 Pisa, Italy

Ilse C. Gebeshuber
Physics Department, University of California,
Santa Barabara, CA 93106, USA

Louis J. DeFelice
Department of Pharmacology,
Centre for Molecular Neuroscience,
Nashville TN 37232-6600, USA

Arun V. Holden
School of Biomedical Sciences
and Centre for Nonlinear Studies,
University of Leeds,
Leeds LS2 9JT, UK