New and Notable

Stochastic Resonance at the Molecular Level

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Stochastic resonance (SR) has received renewed interest since having been demonstrated in sensory biology a few years ago. It is the process, evident in a class of nonlinear systems subject to weak input signals, whereby the introduction of a random process, or "noise" as it is called, can enhance the information content at the output of the system. Introduced in 1981 by Angelo Vulpiani and others as a theory of the periodic recurrences of the Earth's ice ages (Nicolis, 1993), it was later applied to a wide variety of physical systems, eventually moving to biology (Moss and Wiesenfeld, 1995) and even medical science, as shown by the innovative experiments of Faye Chiou-Tan and her colleagues and by Robert Morse and Edward Evans. Until the present work of Sergey Bezrukov and Igor Vodyanoy, reported in this issue of the *Biophysical Journal*, SR was confined to systems at the macroscopic level: ring lasers, superconducting magnetometers, sensory neurons, and the like. Now, in a remarkable experiment, they have demonstrated SR at the molecular level, using alamethicin voltage-dependent ion channels reconstituted in a lipid bilayer membrane.

It is not surprising that SR has been demonstrated in a diversity of systems, in view of the simplicity of the mechanism. At first thought, to require dynamical systems with bi- or multistable energy potentials, it was later shown by Laszlo Kiss and his co-workers that the simplest version of SR was manifest in nondynamical systems consisting of only three ingredients: a threshold, a weak information-laden signal lying beneath the threshold, and noise. Certainly thresholds and noise are ubiquitous in nature, especially in neurons and in ion channels.

But that's not all! As Bezrukov and Vodyanoy also elucidate in the present paper, not even the threshold is necessary! This finding, in a single stroke, has greatly expanded the class of systems wherein SR might feasibly be sought. Again, the mechanism is quite simple. The system is presumed to generate a series of events occurring at random times, the instantaneous event rate being exponentially dependent on the noise plus the weak signal. Upon increase in the noise intensity with fixed signal amplitude, SR is observed as a maximum in the signal-to-noise ratio at the output. An optimal level of noise encodes the maximum amount of information about the weak signal. In a wide variety of processes, the source of the noise can be identified with thermal fluctuations. Such "*kT*-driven" systems, as Bezrukov and Vodyanoy refer to them, are commonly found in both physical and biological settings. Two examples, for which SR has been demonstrated, are the excitation of electrons across a barrier in a back-biased solid-state diode and, as Bezrukov and Vodyanoy describe in the present work, the random openings and closings of ion channels in a biological membrane. Indeed, the latter may explain the ubiquitous noisiness in the firing times observed for virtually all neurons in living systems, as well as their potential to exhibit (White et al., 1996) or even to make use of SR.

Can this demonstration of SR at the molecular and cellular levels help to explain the exquisite sensitivity of an-

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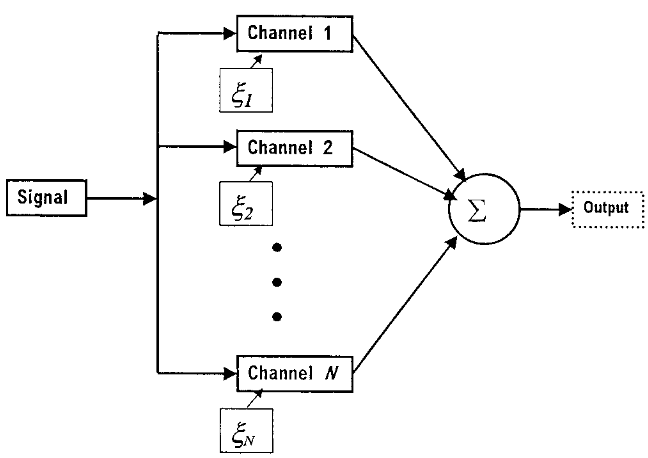

FIGURE 1 An array of N stochastic resonators, each with its own incoherent noise source ξ_i. Averaged in the output, the noise intensity from the individual elements is proportional to $\sqrt{N}$, and the common signal is enhanced by the factor N. Thus, considering only the individual channel noises, the output signal-to-noise ratio thus grows as $\sqrt{N}$ with increasing N.

imals to weak external stimuli? This, and a related question regarding the possible sensitivity of individual cells embedded within living material to external low frequency electric and magnetic fields, are controversial (Astumian et al., 1997; Bezrukov and Vodyanoy, 1997). Nevertheless, some animals, sharks and rays, for example, can detect extraordinarily tiny electric fields (*nano*volts per centimeter imposed on receptors spaced a few centimeters apart) (Kalmijn, 1982). For comparison, typical membrane potentials are several tens of *milli*volts. It is difficult to imagine how a modulation of a few parts in a million, even in a differential arrangement, could result in a detectable change in the spike rate of so noisy a detector as a single sensory neuron. One possibility is that individual neurons and/or ion channels do not act alone, but instead, improved sensitivity may be a property of arrays. Indeed, while the Bezrukov and Vodyanoy experiment and theory apply to an array of channels acting in parallel across the membrane, the signal and noise were applied from a single external source, and hence both were common to all channels. A further step will be to consider an array with each channel subject to its own noise source (see Fig. 1). Consistent with thermal fluctuations as the source, the noise in each channel is expected to be incoherent with all of the others. Jim Collins and his colleagues have explained how, in theory, these internal noises can average out across a population of elements, where each is a stochastic resonator (e.g., an ion channel or a sensory neuron), thus enhancing the coherent, and therefore additive, weak signal. Experimental tests of this suggestion remain to be carried out. They will be important for further understanding of noise-assisted information processes in sensory biology.

The experimental determination of the minimum detectable signal by a single cell or an array of cells or sensory neurons remains a fundamental question. The work of Bezrukov and Vodyanoy reported today, however, moves a considerable distance toward an answer and will certainly stimulate renewed explorations in that direction.

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