Stochastic Resonance in Biology

How Noise Can Enhance Detection of Weak Signals and Help Improve Biological Information Processing

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Noise is usually thought of as the enemy of order rather than as a constructive influence. In nonlinear systems that possess some sort of threshold, random noise plays a beneficial role in enhancing the detection of weak information-carrying signals. This phenomenon, termed stochastic resonance, does find useful applications in physical, biological, and biomedical contexts. Certain biological systems may even use this effect for optimizing function and behavior.

Introduction

In everyday life, noise is generically viewed as being of harmful influence in detecting and transferring information. Stochastic resonance (SR)[1, 2] refers to a situation where the mere addition of random noise to the dynamics improves a system's sensitivity to discriminate weak information-carrying signals. Thus, this phenomenon constitutes yet another example where random perturbations play a useful role in enhancing detection and aiding the transmission efficiency of weak information in nonlinear systems. Because of its generic nature, this phenomenon boasts applications extending from classical and quantum physics to chemistry, engineering, and, in recent years, also in biology and medicine.[1–6]

The term stochastic resonance was originally coined in 1981 by Italian and Belgian physicists to explain a long-standing paradox in climatology: What causes the almost periodic recurrence of the primary cycle of ice ages every 100 000 years or so? There exists a periodically recurring wobble in the Earth's orbit about the sun every 100 000 years, which is related to the timing of glaciation. Yet, this perturbation is far too weak to cause a deterministic freeze because this very weak signal is embedded in much stronger noise arising from annual and even daily swings in the amount of heat received, retained, and reflected back from the Sun. These researchers proposed that the strong fluctuations are able to amplify the embedded weak periodic signal when they act together in a synergetic manner.

The Mechanism of SR

The basic mechanism for SR is depicted with Figure 1. Imagine a ball sitting in one of the two wells—let us say, a marble in an egg carton. A gentle force (periodic or aperiodic) rocks the whole system back and forth. This perturbation may be looked upon as an information-carrying signal acting on the nonlinear system.
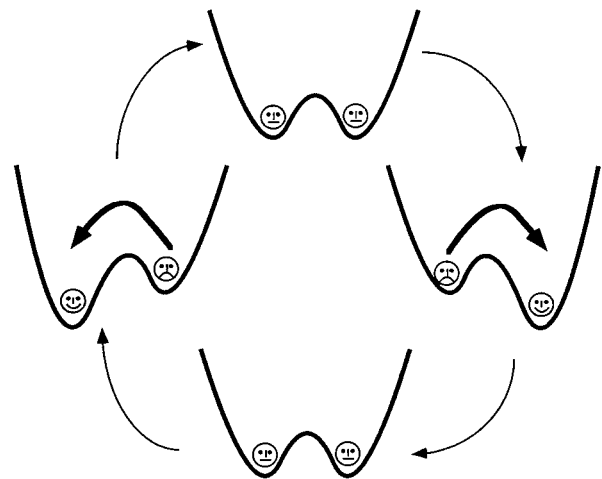

Figure 1. Mechanism of stochastic resonance: A symmetric bistable potential is periodically rocked by a weak signal. The presence of an optimal dose of noise (so that the average stochastic escape time approximately equals half the period of the signal) will statistically induce synchronized hopping events between the two locally stable states.

Under the influence of this weak force, the ball simply rolls around in the bottom of the well. If the ball's movement is detected only when it jumps into the neighboring well, this weak signal will go unnoticed. Adding noise to the system—by tilting randomly the egg carton up and down—will, *a priori*, only mask the weak perturbation further. In fact, under some suitable conditions just the opposite is true. The weak signal together with the noise will allow the ball to occasionally exit into the

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neighboring well. Now the theory of SR[1] says that these exit events do not occur completely at random but become correlated with the weak signal. To put it more technically, an increasing noise level yields—correlated with the signal—an increase of the chance (namely enhancement of the Arrhenius factor for the escape rate) for excursions over the barrier into the neighboring well. Thus, the dynamics of the jump events reveals a good deal of information about the time dependence of the information-carrying input signal. On the other hand, the sensitivity of the output response decreases inversely with increasing noise level; too much noise will deteriorate the coherence for the signal assisted, noise-induced exits. Thus, there does exist an optimal dose of noise up to which the addition of noise improves signal transduction. This scheme shows that the effect is rooted in three minimal ingredients: a) a source of background noise, b) a generically weak coherent input, and c) a characteristic sensory barrier or threshold that the system typically has to overcome in order to perform its useful task. These thresholdlike barrier-crossing events expose an element of nonlinear system dynamics by which random noise can benefit faint signals by boosting them in a correlated manner over a threshold. The noise-enhanced output response is, therefore, fairly regular with only small fluctuations. From this perspective we find that *SR is a cooperative phenomenon in which a weak, coherent input signal entrains ambient noise.*[4]

Characterizing SR

The typical characteristic of SR consists in its anomalous amplification of input signals by noise, Figure 2. The response itself serves thus as a natural measure of SR. In particular, for a periodic input signal the spectral power amplification[1, 5a, b] measures the ratio between the integrated spectral power of the output stored at the deltalike spike of the driven power spectrum at the driving frequency and the total power of the input signal. This amplification measure undergoes a resonance-like behavior: It increases with increasing noise intensity (SR regime) until it reaches an optimal maximum and then falls off; hence the term SR, Figure 2c. The spectral amplification quantifier also yields a measure of synchronization[1] between the input signal and the noise-activated output dynamics. Note that the effect of SR is *not* a resonance phenomenon for the rate for escape dynamics; the latter generally increases monotonically with both increasing noise and perturbation intensities. Another common approach to characterize SR is the signal-to-noise ratio (SNR).[5c] This quantity is formed from the ratio obtained from the output spectral power at the driving frequency and the background power spectrum multiplied by the experimental bin width of the driven stochastic dynamics at the driving frequency. Unlike the spectral amplification, however, this quantifier does, in leading order of the signal strength, not depend on the driving period; consequently, it cannot be related to a synchronization measure. Another quantifier is the residence-time probability distribution. This quantity is the familiar measure used by biologists, who prefer to call it the interspike interval histogram. The measure is composed of a set of separated peaks that vary in width and separation upon
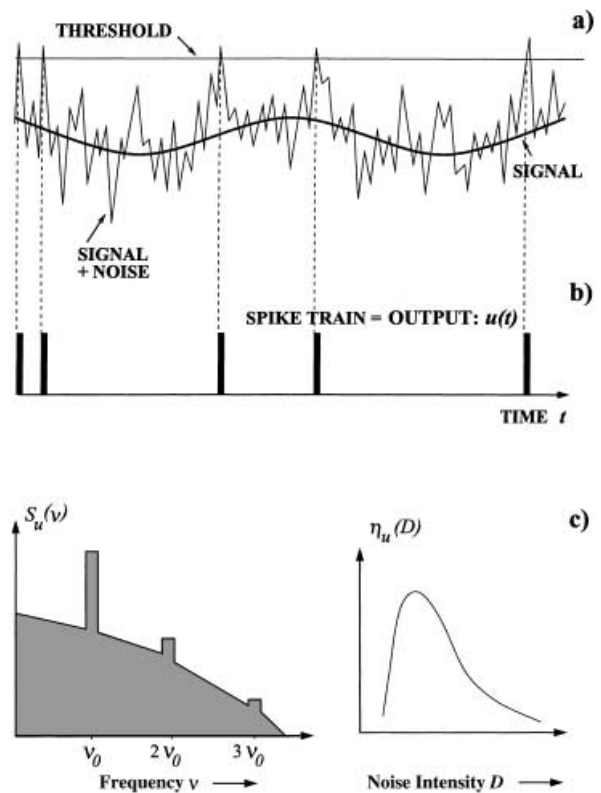

Figure 2. Threshold stochastic resonance: a) Neuronal-like dynamics detect those events that rise above some threshold value (the thin top line). A weak, periodic subthreshold signal (thick line) can therefore be detected only if its dynamics are assisted by noise (noisy trace). A crossing event occurs most likely when the weak signal assumes its peak value. b) Upward-directed crossing events trigger a firing of spike-train dynamics, u(t). c) The power spectrum $S_u(\nu)$ of the output dynamics are depicted on the left-hand side; superimposed on a typical broadband background the spectrum features sharp peaks at multiples of the driving frequency ν_0. The spectral power amplification, right-hand side, exhibits the typical SR signature of a bell-shaped resonance versus increasing noise intensity D. The peak value is assumed at an optimal dose of noise for which the periodically modulated threshold crossing rate approximately synchronizes the signal with the firing events.

increasing the noise intensity. This peaked histogram behavior taken alone, however, is no signature of SR;[1, 3] it is rather the integrated area under the corresponding lower order peaks that exhibits individual maxima with increasing noise intensity. Apart from certain situations (see below), the coherent input of biological information-carrying signals is generically not strictly periodic but rather is of a broad-band type. Put differently, a realistic biological input signal more closely resembles a realization from a stochastic process. In this latter case, measures of complexity that are based on entropy-related concepts, such as the rate of mutual information, the rate of Kullback entropy, or the rate of information gain, or diverse cross-correlation measures, are more suitable quantifiers for SR.[6, 7]

Stochastic Resonance in Biological Information Processing

Since its discovery in early 1981, the phenomenon of SR has been demonstrated repeatedly.[1–6] Moreover, SR has found diverse

applications in chemistry, physics, and technological sciences including its exploitation in developing novel sensory detection devices. The age of SR in biology started with benchmark publications in the early 1990s[8] wherein SR was discovered in sensory neurons that have been subjected to external noise. Such sensory neurons are ideally suited to exhibit SR as they are intrinsically noisy and do operate as threshold systems (compare Figure 2a). In these neuronal systems, a propagating action potential upon reaching the threshold triggers a firing (voltage) spike, followed by a quiescent time interval during which no firing events occur. These pioneering works have brought SR to the attention of a much wider community. The early findings inspired several novel electrophysiological SR studies. In a series of experiments, Frank Moss's group reported SR results on the hydrodynamically sensitive mechanoreceptor hair cells located in the tailfans of crayfish.[9] These cells respond best to stimuli between 8 and 25 Hz. The hair cells were stimulated by weak periodic water perturbations at frequencies from 5 to 100 Hz. This periodic stimulus alone was far too weak to induce firing events on its own. Environmental noise was then added externally as the random source. This combined set up simulated the almost periodic water vibrations generated by the tail of a swimming predator fish on the background of random water turbulence. The SNR extracted from the power spectrum of the stochastic spiking dynamics, see Figure 2b, clearly revealed that SR indeed could occur: The SNR *increased* with increasing, externally applied noise intensity, reached the typical SR maximum, and subsequently decreased, see Figure 3. Likewise, the analysis of the peak areas of the interspike histogram versus the noise intensity confirmed this very SR behavior. In another set of experiments on the cercal system of crickets by Levin and Miller,[10] SR has been established as well. This latter mechanosensory system can recognize weak, low frequency disturbances best between 80 and 150 Hz. This allows a cricket to sense from a long range an approaching predator wasp that intends to deposit eggs within the cricket's body. Interestingly enough, the typical frequency of the periodic wing beats lies just within this frequency range. Apart from applying weak periodic air flows to which broad-band noise was added, these authors also subjected the cells to weak broad-band input signals, thus demonstrating experimentally aperiodic SR.[1, 6, 7, 10] In this latter case, the rate of mutual information versus increasing noise intensity exhibited the very SR-like, bell-shaped behavior. For strong signals, they established that adding noise yields a decreasing rate of mutual information, meaning that too much noise degrades signal encoding. Moreover, they could show that adding noise to a weak stimulus improves the timing precision in neuronal activity and that the cells are able to adapt their intrinsic threshold values to the overall input signal power.[10b]

Despite all these positive SR findings, prominent questions regarding SR in sensory biology remain open. What is the role of internal noise of the sensory system? Moreover, does the biological system intrinsically use noise-enhanced signal detection, through SR, to optimize its function? Early experiments on ion channels and in hair cells of crayfish by controlling
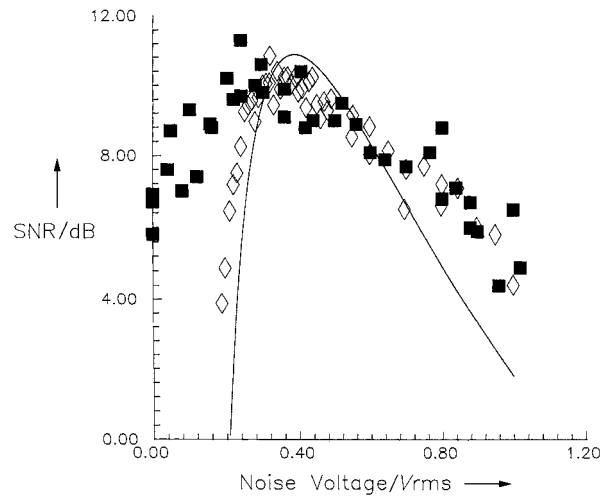

Figure 3. Signal-to-noise ratio (SNR) in crayfish mechanoreceptors (■) for a sinusoidal stimulus at a frequency of 55.2 Hz compared to simulations of a Fitzhugh – Nagumo model (◇) and a threshold-SR theory (——).[9] The abscissa represents the intensity of the noise: hydrodynamic noise in the case of the mechanoreceptors, electrical noise in the case of the neuron models. The crayfish data do not exhibit the typical decrease for weak noise because of residual internal noise of the neuron. Figure provided by Frank Moss.

internal noise through a variation of the surrounding temperature were not conclusive. A promising initial piece of evidence that SR occurs with internal noise has been shown in ref. [9c], where the internal noise may be varied by altering the light intensity that falls on the photoreceptive area in the hair cell. The role of noise for functional behavior was recently confirmed with experiments on the feeding behavior of paddlefish (*Polyodon spathula*, Figure 4) by Moss and collaborators.[11] Paddlefish use passive receptors to detect electric signals emitted from their prey zooplankton. In the experiment, the authors constructed a swim mill so that plankton were swept towards a swimming paddlefish. Plate electrodes were installed in the front and back of the paddlefish upon which randomly electric noise was applied. The measurement consisted in finding the spatial distribution of strike locations where the paddlefish caught the plankton. This distribution naturally broadened when the fish was able to locate more distant prey. Upon varying the electrical noise level, these authors found that the distribution began to widen, reached a maximal width at an optimal noise dose, and subsequently started to narrow again with still increasing noise. Moreover, at this optimal noise intensity, the capture rate for food raised in some cases by about 50%. The

Figure 4. A paddlefish uses stochastic resonance to locate zooplankton.

natural source for the noise is speculated to be provided in nature by the plankton themselves: The plankton form swarms that emit random electrical signals which provide the background noise that, in turn, increases the sensitivity of the paddlefish electroreceptors to detect individual plankton.

Biological SR on the Subcellular Level: SR in Ion Channels

Ever since the discovery of SR, the Holy Grail of biological SR-related research has been the validation of the premise that nature has adopted, during evolution, the use of intrinsic ambient noise for the optimization of sensory transduction on its most fundamental level: the ion channels. Presumably, SR has its origin in the stochastic properties of ion channel clusters that are located inside a receptor cell membrane. For an artificial system of ion channels composed of a parallel array of the peptide alamethicin, Bezrukov and Vodyanoy[12] found evidence that SR does in fact occur. This, in turn, provokes the challenge whether SR in biology is rooted as a collective effect in finite assemblies of natural ion channels or whether SR can occur already within a single ion channel. As mentioned briefly above, SR has not been seen in a potassium ion channel upon varying the temperature.[13] In recent work, however, it was demonstrated theoretically[14] that SR in a single Shaker potassium channel can indeed occur if the parameters for operation are located within a regime where the channel is dwelled predominantly in the closed state. This result is not only of interest in its own right but also impacts on prominent applications that involve manipulations on the nanoscale, such as the design of a single-molecular biosensor.

Where does SR originate from and what is its relevance in biological systems? Membrane patches that are able to exhibit an excitable dynamics must contain ion channels of at least two different kinds—such as potassium and sodium channels. The mean field model (and similar) of Hodgkin and Huxley for voltage-gated ion channels, when subjected to *external* noise, clearly exhibits the signature of SR in its firing dynamics.[1, 6] More challenging, however, is the question of whether this biological system, if amended by a leakage current due to chloride ions and *internal* noise that originates from the random fluctuations of stochastic opening and closing of individual channels, is capable of exhibiting SR. The intrinsic fluctuations within a given assembly of ion channels scale inversely with its system size. Indeed, the SNR of the spiking dynamics have recently been demonstrated to exhibit SR, which is solely due to internal noise.[15a, b] The SNR increases with increasing system size until it assumes a peak value at an optimal area of the ion channel assembly, Figure 5a. Notice that this SR behavior mimics SR for the amplification in Figure 2c but now with the noise intensity being read from right to left. Above the optimal area, the SNR decreases with increasing size. Only the addition of external noise will again restore the SR behavior in this regime, Figure 5b.
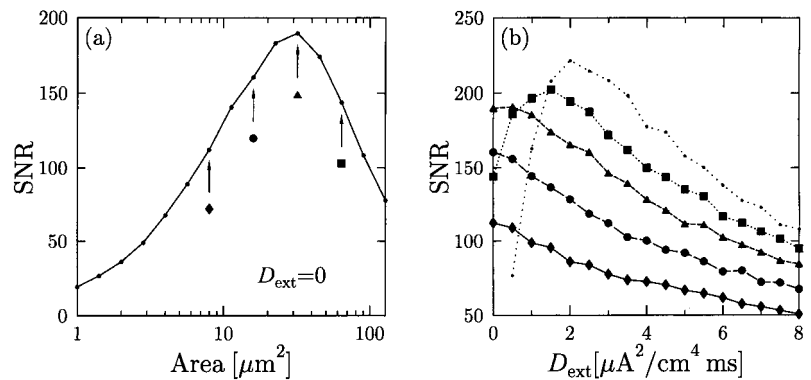

Figure 5. a) SNR data for a stochastic Hodgkin–Huxley modeling of an assembly of sodium and potassium ion channels and additional leakage channels for an external sinusoidal stimulus of amplitude $1.0\,\mu A\,cm^{-2}$ and angular frequency of $0.3\,ms^{-1}$.[15a] One observes intrinsic SR for a weak stimulus versus solely internal noise. The internal noise intensity decreases with increasing area of the membrane patch. b) If additional, external noise, $D_{ext} \neq 0$, is applied for the system sizes marked by the arrows in (a), one finds the SNR behavior for the corresponding membrane size versus D_{ext}. Notice that adding noise to small assemblies below optimal size only deteriorates the transduction behavior further; in clear contrast, however, for above-optimal sizes the addition of noise yields the conventional SR behavior. For comparison, the situation for infinite size (namely, the mean field limit) with zero internal noise is depicted by the dotted line.

Put differently, there exists an optimal size for which ambient internal noise is beneficial for the functionality of ion channel patches. For the suboptimal small sizes of ion channel assemblies, the addition of (external) noise—which simulates even smaller patch areas—will thus only degrade the transduction behavior. Moreover, there exists an internal noise-induced coherence phenomenon for which the spiking activity assumes, for an optimal patch size, a "most rhythmic" activity in the absence of any external input signal that stems solely from spontaneous internal ion channel noise.[15a, b] These findings yield support to the conjecture that SR, in fact, is biologically significant. Likewise, the observed SR in biological systems is most likely rooted in a collective property of globally coupled ion channel assemblies.

Biomedical Benefits from Stochastic Resonance

A most appealing feature of SR is the fact that it holds promise for the good of humanity for which numerous physiological functions are marked by threshold behaviors. For example, several disorders of the nervous system are caused by increased sensory thresholds, which lead to a reduced firing rate in the corresponding neurons. In this context, SR has been observed in mammalian neuronal networks,[16] from isolated rat skin,[16a] and also from live mammalian brain tissue.[16b] These results offered hope that SR will find its way into applications that are beneficial in providing some means for the possible cure of, for example, a disordered person's balance, a patient's locomotion, and other physiological functions. A spectacular result comes from James Collins's group.[17] They have used electrical or mechanical noise to enhance the ability of humans to detect subthreshold mechanical cutaneous stimuli. The main finding was that subthreshold stimuli could be detected when an optimal dose of noise of either type was applied to the patient. This SR-like

phenomenon has been used to improve a patient's tactile sensation when the mechanical stimulus is near or below threshold. In this context, the design of special interfaces, such as socks and gloves controlled with electrical noise, can be of use in situations that require an increased tactile sensation. Typical examples involve applications in telerobotics, microsurgery, and the like. Similar techniques can also be applied to individuals with elevated cutaneous sensory thresholds after having suffered a stroke or other cerebrovascular accidents.[17] The human visual perception system offers another example for SR.[8c, 18] Typical characteristics of SR have been rendered from the power spectrum of a periodic series of switching dynamics between two visual bistable percepts, as obtained from nonsimulated experiments with students. The subjects were exposed to the perceptual bistability inherent in ambiguous figures: In this case, the two possible percepts of a Necker cube (Figure 6) were chosen. An applied weak periodic perturbation, consisting of moving a point with a 10 s cycle along a rectilinear trajectory on the ambiguous picture, was displayed on a monitor placed in front from the observer's eyes. The experimental recordings
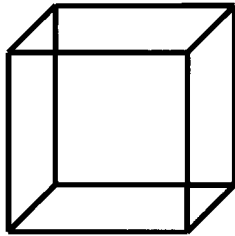

Figure 6. *The Necker cube, an example of a system visually interpretable in two ways.*

revealed SR features, which agreed qualitatively with the computer simulations of a corresponding, periodically perturbed neural-network model.[18a]

A recent fascinating application involves SR in the human blood pressure regulatory system, the "baroreflex" system.[19] This is a negative feedback system where an increase (decrease) in blood pressure is automatically compensated by a decrease (increase) in heart rate and vascular resistance. The system has two types of receptors, arterial and the venous, which, in turn, monitor the arterial and the venous blood pressure, respectively. The afferent inputs from these receptors are independently transmitted to the brain stem; from there, the integrated outputs to the peripheral organs such as the heart and the vascular system are sent via a common efferent pathway. The authors periodically stimulated the venous receptors of a test person who had been fixed on a sinusoidally oscillating, motor-driven tilt table with a period of 38.5 seconds. This subthreshold signal was far too weak to stimulate the baroreflex control system. Next, noise was added to the arterial pressure receptors located in the neck region by compressing and depressing a pneumatic neck chamber. The main finding was that a certain dose of noise optimized the heart rate response. This experiment differs from those earlier functional SR experiments by Moss and collaborators. In these new experiments, the signals from the arterial and venous receptors are directed on different paths into

the brain stem. The weak signal and the noise inputs were added there to yield an output response that was guided on a common pathway into the heart muscle. The functional SR thus acts on the higher level of the brain stem, indicating that the brain apparently uses noise in optimizing its response.

Summary and Outlook

In this survey we have summarized the main advances of the phenomenon of stochastic resonance for biological systems. The pursuit of SR into this domain, other than physics and chemistry, is very exciting and promising. Indeed, this change of focus from physical sciences towards life sciences carries a great potential and causes us to rethink and refine some of our usual concepts and issues. The lesson to be learned from all of these recent successes of SR research in the life sciences is that tuning the noise strength in nonlinear systems possessing some sort of thresholdlike barrier can provide a useful task rather than being a hindrance. It would indeed seem strange to me that nature would not have taken advantage of the benefits of ambient noise for nonlinear transmission and/or amplification of feeble information rather than ignoring it. Notably, there also exist several other mechanisms, being distinct from SR, where noise provides a constructive role such as, for example, in fluctuation-driven directed transport in Brownian and molecular motors.[20] Nevertheless, the case of noise-aided transmission of biological information should not be looked upon as a *unique* method which can perform the amplification and optimization of neuronal information transmission. Deterministic concepts rooted within nonlinear dynamics, such as amplification via bifurcation schemes,[21a] self-organization,[21b] and the phenomenon of synchronization induced by cross-coupling nonlinear elements,[1, 6] are also quite effective in detecting and amplifying weak biological information. Consequently, several challenges for SR in biology, and the purpose of noise in the life sciences as such, still need to be addressed. Some examples that come to mind are the question of finding the most appropriate quantifier that measures noise-enhanced biological action, and the constructive role of noise in adaption, refraction and memory (that is, non-Markovian dynamics) in biological sensory detection, to name only a few. Yet, what is most needed in the future, are further crucial experiments aimed at identifying and testing in more precise detail the hypothesis that noise actually *is* essential for the performance and the function of biological systems.

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