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Abstract. We theoretically describe how weak signals may be efficiently transmitted throughout more than one frequency range in noisy excitable media by a sort of *stochastic multiresonance*. This helps us to reinterpret recent experiments in neuroscience and to suggest that many other systems in nature might be able to exhibit several resonances. In fact, the observed behavior happens in our model as a result of competition between (i) changes in the transmitted signals as if the units were varying their activation threshold, and (ii) adaptive noise realized in the model as rapid activity-dependent fluctuations of the connection intensities. These two conditions are indeed known to characterize heterogeneously networked systems of excitable units, e.g. sets of neurons and synapses in the brain. Our results may find application also in the design of detector devices.

Some systems occurring in nature are known to efficiently process weak signals in noisy environments. A novel mechanism that explains such an ability is known as *stochastic resonance* (SR). This is associated with the occurrence of a peak or bell-shaped dependence in the transfer of information through an excitable system as a noise source is conveniently tuned. More specifically, low or slow noise impedes the detection of a relatively weak signal, but as the noise rises, the system eventually gives a response that is correlated with the signal, which shows as a peak in information transfer. The signal is again obscured at higher noise levels. This has been reported to occur in different settings, including electronic circuits, ring lasers, crayfish mechanoreceptors, ion channels, sensory neurons, hippocampus, brain stem and cortical areas [1]–[4]. An intriguing issue raised is whether a given system may filter with gain in different noise regimes, which would have technological application. After the first

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proposal of stochastic *multiresonance* (SMR) [5], the existence of two or more resonant peaks has been predicted for single-mode lasers [6], surface phenomena [7], biological diversity [8] and intracellular calcium oscillations in hepatocytes [9, 10], and it has also been described in somewhat more abstract settings [11]–[16]. Although there is as yet no definite claim of experimental evidence of SMR, two recent sets of experimental data [17, 18] admit such an interpretation.

Here we demonstrate that a single resonant mechanism may indeed help in transmitting signals throughout different noise frequencies. More specifically, we use an explicit mathematical model—based on independent familiar empirical descriptions for both *neuron* units and their *synaptic* links—to reveal the existence of a double resonance in an experiment concerning the human tactile blink reflex [18]. Our model behavior is also consistent with recent reports on the transfer of information with different frequencies in the hippocampus [19]. On the other hand, the model here allows one to modify the separation between the two peaks by one order of magnitude or more, and it may admit generalization to show more than two resonances, which makes the 'device' very versatile.

Our main result suggests looking for SMR in nature as part of a needed effort to better understand how the details of excitable systems influence transmission. Previous studies of SR and SMR in nonlinear settings most often involved a source of controlled, additive noise getting rid of correlations. The case of an *intrinsic*, therefore uncontrolled, noise resulting from inherent activity in the medium is even more interesting and likely to occur in nature. In a cortical region, for instance, a given neuron may receive, in addition to the (weak) signal of interest, uncorrelated i.e. just noisy signals from other neurons at frequencies that vary in time during the normal operation of the system. Following previous efforts [20, 21], we consequently investigated the possibility of correlating SMR with the fact that both the main signal and the noise transmit through dynamic connections, e.g. synapses, whose weights change with time and therefore constantly modulate transmission. We found in this way that short-term activity-dependent 'fatigue plasticity'—such as synaptic *depression* and *facilitation* that is known to modify the neural response causing complex behavior [22]–[26]—may indeed produce SMR in a model of neural media in agreement with recent observations. The setting in this paper, which may be seen as an application of a general study within a biological context [21], is intended both to serve as a simple illustration of our point and to make contact with a specific experiment. However, it is sensible to anticipate that the main outcome here may hold rather generally in excitable systems, given that these seem to share all the relevant features in our model [27, 28].

Consider a networked system in which the units, say neurons, receive: (i) a weak signal from other *brain* areas and/or from the *senses* or whatever external terminals and, in addition to this, (ii) uncorrelated, noisy signals from other units. The latter signals will be portrayed by means of action potentials (AP)—from the many *presynaptic* neurons to the *postsynaptic* neuron—e.g., APs whose rates follow a Poisson distribution with mean f. Besides the stochasticity that this implies, we shall imagine the neurons to be connected by dynamic, activity-dependent links. To be specific, we shall adopt the model of *dynamic synapses* in [29]. That is, we shall capture the required stochastic nature of any synaptic link, say i, by assuming that it is composed of an arbitrary number, M_i, of functional contacts, each releasing its transmitter content with probability u when an AP signal from other units arrives. Furthermore, to implement excitability (and, more important here, a kind of threshold fickleness), the contact is assumed to become inactive afterwards for a time interval τ; this is a random variable with exponential distribution $p_t(\tau)$ of mean τ_{rec} at time t. Therefore, each activation event,

i.e. the arrival of an AP at i at time t_i, generates a (postsynaptic) signal, $I_i(t)$, which evolves according to

$$\frac{\mathrm{d}I_i(t)}{\mathrm{d}t} = -\frac{I_i(t)}{\tau_{\mathrm{in}}} + \sum_{\ell=1}^{M_i} J_{i,\ell}\, x_{i,\ell}\, \delta(t - t_i). \tag{1}$$

Here, $J_{i,\ell}$ is the modification in the signal produced by the AP in contact ℓ after the release event; and $x_{i,\ell}(t) = 1$ if the contact is activated, which occurs with probability $u[1 - p_t(\tau)]$, and 0 otherwise. The time constant τ_{in} is a measure of the transmission duration (of the order of milliseconds for a known type of fast postsynaptic receptors). For N units, the total postsynaptic signal is $I_N(t) = \sum_{i=1}^{N} I_i(t)$. We also assume, as in [29], that both the number and the strength of functional contacts that a presynaptic unit i establishes, namely, M_i and $J_{i,\ell}$ vary with i according to Gaussian distributions of mean and standard deviation (M, Δ_M) and (J, Δ_J), respectively. To compare with a specific experiment, we assume $M = 50 \pm 0.1$ contacts, $J = 0.3 \pm 0.1\,\mathrm{mV}$, $u = 0.5$, $\tau_{\mathrm{in}} = 1\,\mathrm{ms}$ and $\tau_{\mathrm{rec}} = 500\,\mathrm{ms}$.[3] Just for simplicity[4], we consider a weak, low-frequency sinusoidal signal $S(t) \equiv d_{\mathrm{s}}\cos(2\pi f_{\mathrm{s}} t)$ which is transmitted to the (postsynaptic) unit to monitor the corresponding response and the conditions in which resonance occurs. With this aim, we then compute the generated voltage, $V(t)$, assuming a generic dynamics of the form

$$\frac{\mathrm{d}V}{\mathrm{d}t} = F(V, I_N, S), \tag{2}$$

where the function F is to be determined.

Once the links are determined, specifying F means adopting a model for each unit. A familiar choice is the *integrate-and-fire* (IF) model in which F is linear with V [33]. This assumption of a fixed firing threshold is a poor description for most purposes (see also for instance [34]), however. Instead, one could assume a networked stochastic set of (postsynaptic) units—e.g. a convenient adaptation of the network model in [27, 28]—but for the sake of simplicity we shall restrict ourselves to the FitzHugh–Nagumo (FHN) model [35]. The excitability is then implemented assuming that the thresholds for neuron shoots constantly adapt to the input current, which is realistic for neuron media [36]. Summing up, the unit dynamics is

$$\frac{\mathrm{d}V(t)}{\epsilon\,\mathrm{d}t} = V(t)\,[V(t) - a]\,[1 - V(t)] - W(t) + \frac{\tilde{S}(t)}{\epsilon\tau_{\mathrm{m}}}, \tag{3}$$

where $\tilde{S}(t) = S(t) + \rho I_N(t)$ is the input, with ρ being a resistance that transforms the current I_N into a voltage. $W(t)$, which stands for a (slow recovery) variable accounting for the refractory time of the unit, satisfies

$$\frac{\mathrm{d}W(t)}{\mathrm{d}t} = bV(t) - cW(t). \tag{4}$$

For comparison with the experiment of interest, we shall take $a = 0.001$, $b = 3.5\,\mathrm{ms}^{-1}$, $c = 1\,\mathrm{ms}^{-1}$ and $\epsilon = 1000\,\mathrm{ms}^{-1}$, which causes the (dimensionless) voltage $V(t) = 1$ to correspond

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[3] In practice, M varies widely, namely, $M \in [5, 50]$ depending on the neuron type and functionality; see, for instance [30, 31]. Well within the reported physiological range are also our values for the link strength J [32] and for u and τ_{rec} [22].

[4] This choice does not affect our conclusions. In fact, the same behavior results in figure 1 when using Poissonian signals as in the experiment of interest [18].
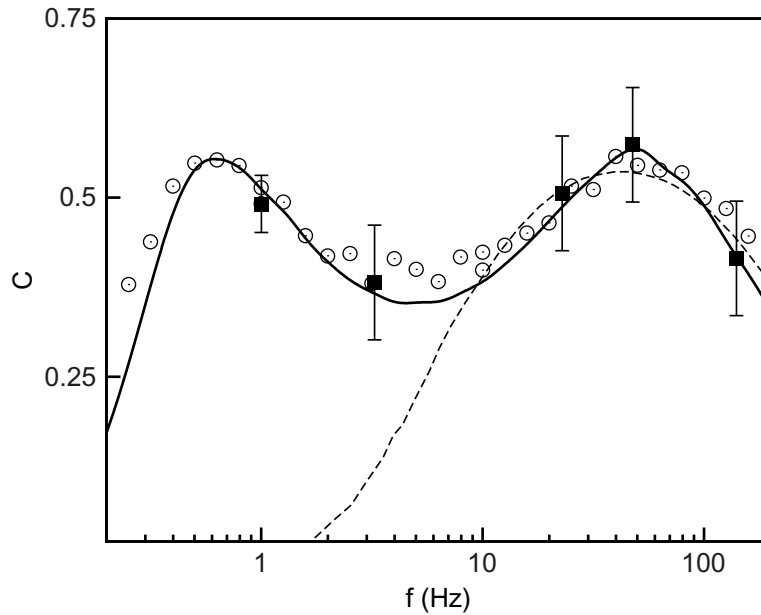
Figure 1. The function C (as defined in the text but scaled, arbitrary units so that it measures relative variations of the relevant correlation), according to the experimental data in [18] (full squares with their error bars) and our prediction (solid line). The empty symbols represent the response when the signal $S(t)$, instead of the sinusoidal (therefore time correlated) one producing the solid line, consists of a train of (uncorrelated) Poissonian pulses that, as the main signal, also endure the model synaptic dynamics; the only noticeable change is that the response is more noisy in this case due to extra randomness. The dashed line corresponds to the interpretation of these data given in [18]. (The parameter values used in these plots are well within the corresponding physiological range; for details see footnote 5 and the main text.)

to 100 mV and the time variable to be within the ms range. We further assume a membrane resistance $\rho = 0.1\,G\,\Omega\,$mV and a time constant $\tau_m = 10\,$ms both within the physiological range [37].

The degree of correlation between the input signal and the output $V(t)$ is defined as

$$C = \langle S(t)\nu(t) \rangle \equiv \frac{1}{T} \int_{t_0}^{t_0+T} S(t)\nu(t)\,\mathrm{d}t. \qquad (5)$$

Here, $\nu(t)$ is the instantaneous firing rate of the postsynaptic unit, that is, the average number of APs generated at time t as a consequence of input $\tilde{S}$. (In practice, the average is over a set of different postsynaptic AP trains generated under the same experimental conditions.) The function $C(f)$ that follows from this is shown as a solid line in figure 1.[5]

[5] Experimental data points in the figure have been transformed using (6) with $f_0 = 1\,$Hz, $\alpha = 1.8\,$Hz/dB, $A_0 = 73\,$dB and $\sigma_A = 9\,$dB. This choice does not affect essentially our findings, however. For example, using a different linear relationship at low and high f (as in [18]) produces data that are well within the indicated error bars. On the other hand, the Poissonian-distributed pulses used for the empty circles are of amplitude $\delta = 0.4$ and mean frequency $f_s = 3\,$Hz and we checked in a temporal window of $\Delta t = 10\,$ms after each pulse for a neuron response to it, in order to maintain the closest similarity possible with the experiment in [18].

As stated above, previous studies illustrated SR as a peak of C when one varies the level of a noise that is apropos injected in the system. In our excitable model system, however, it is the synaptic current $I_N(t)$—and not an external noise—that directly affects dynamics. Tuning the level of noise now means increasing the frequency f of the uncorrelated AP that are responsible for the generation of $I_N(t)$. The noise embedded in the AP trains does not directly affect the unit, and this has a strong consequence on the shape of C. That is, SMR is then a consequence of the interplay between short-term (*synaptic*) plasticity and threshold variability associated with dynamics (2).

To be more specific, let us write the total signal as $I_N = \bar{I}_N \pm \sigma_I$, where $\bar{I}_N > 0$. In the IF model (fixed threshold), $\bar{I}_N$ tends to reduce the voltage needed for the generation of an AP, so that the excitability of the neuron increases with $\bar{I}_N$. In the FHN model, however, the main effect of $\bar{I}_N$ is to move the stationary solution of system (3) and (4) (and the V nullcline) towards more positive values, so that both the resting voltage value and the voltage threshold become more positive. Then, for the range of $\bar{I}_N$ values of interest here, the neuron excitability depends more on the fluctuation σ_I than on $\bar{I}_N$. On the other hand, for dynamic synapses, $\sigma_I = \sigma_I(f)$ has a non-monotonic dependence on f—it first increases from 0, reaches a maximum, say f^*, and then decreases with increasing f to zero again. As a result, if the level of fluctuations at f^* is such that the unit is above threshold, there will be two frequency values for which—according to familiar arguments [1]— fluctuations may eventually overcome the potential barrier between silent and firing states, which results in two resonant peaks.

The model here allows one to understand, even semi-quantitatively, the recent data of Yasuda *et al* [18] showing how short-term synaptic depression causes SR in human tactile blink reflex. These authors monitored an input–output correlation function between tactile signal and blink reflexes associated with postsynaptic responses of neurons in the caudal pontine reticular nucleus (PnC) of the brainstem [38]. In addition to the (weak) tactile signal, these neurons received uncorrelated auditory inputs that are viewed as a noise background. Yasuda *et al* then concluded that, for realistic short-term depression parameters, the postsynaptic neuron acts as an error-free detector. That is, the value of the input–output correlation function is maintained at optimal high values for a wide range of background noisy rates.

A close inspection of the Yasuda *et al* data from the above perspective reveals some significant discrepancies in the fit in that study at low noise rates. That is, while experiments for low noise rates show a high input–output correlation level (see table 1 in [18]), the theory—based on the oversimplified, linear IF neuron model with fixed firing threshold—that they use to interpret and compare with their data does not predict SMR but predicts a very low level of correlation at low frequency which is not supported by data (consequently, the authors in [18] excluded their low-frequency data from their analysis). This is shown in figure 1. The disagreement may be justified by accepting that, at such low rate and due to the high neuron threshold in PnC area, the auditory noise is not enough to evoke a postsynaptic response correlated to the signal. So the high level of the correlation observed can only be understood by the effect of noise coming from other brain areas. Those authors did not study this additional noise source, however, so that the question of whether other brain areas play a role here remains unanswered. On the other hand, if such a noise is relevant, its effect should be a constant noise added to the auditory noise. Therefore, it should induce a constant increment in the noise level, which cannot explain two local maxima apparently observed in the experimental correlation data (figure 1) at noise levels around 1 and 50 Hz, respectively.
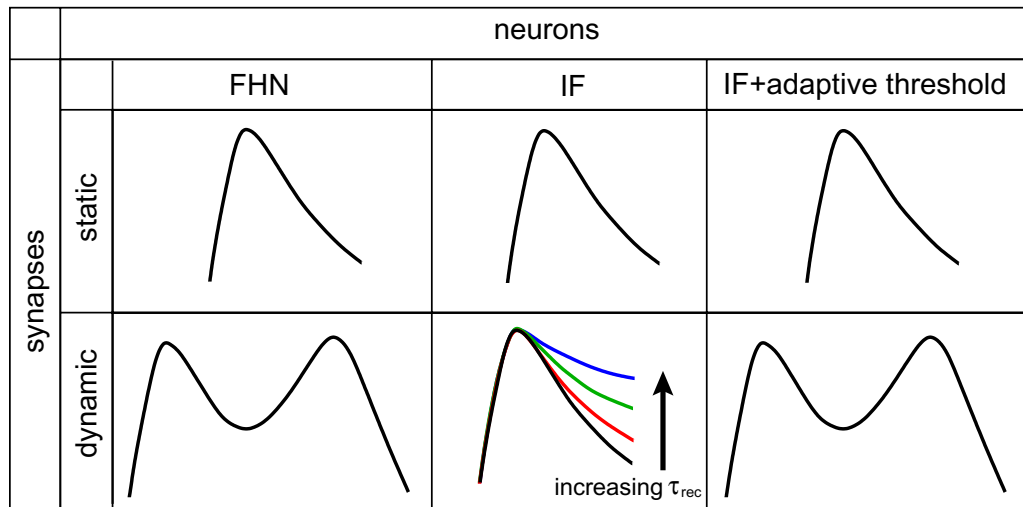
Figure 2. Schematic diagram showing how the form of the information transfer depends on assumptions concerning the neuron units and the synaptic links. That is, an IF model unit can produce only a single resonance, and the same is true for FHN units and for IF units with varying activation threshold as long as the connections are frozen. Nevertheless, these two model units can produce two resonance peaks if the connections are dynamic, e.g. if they show short-time fatigue plasticity that is known to occur in many networks in nature.

The drawing of data in the plot of figure 1, particularly those for small f undervalued in [18], requires a comment (see footnote 5). That is, one needs to use a specific relationship between the auditory noise and f. Let us assume [39] that the firing rate of neuron i in the PnC area induced by an auditory input A is $f_i = f_0 + \alpha A \Theta(A - A_i)$, where f_0 is the level of activity in the absence of any input, α is a constant, $\Theta(x)$ is the step function and A_i is the minimum input needed to induce non-spontaneous activity in neuron i. The known variability of the firing thresholds in most (e.g., PnC) neurons [38] suggests one to sample A_i from a Gaussian distribution with mean A_0 and variance σ_A^2. It then follows that the mean firing rate (in Hz) induced in the PnC area by an auditory input A (in dB) is

$$f = f_0 + \frac{\alpha A}{2}\left\{1 + \mathrm{erf}\left(\frac{A - A_0}{\sqrt{2}\sigma_A}\right)\right\}. \tag{6}$$

This, which generalizes the linear relationship used in [18] within a restricted range, transforms all levels of auditory noise (between 30 and 90 dB in the experiment of interest) into the frequency domain. For $A \gg A_0$, (6) reduces to a linear relation.

Summing up, our model system predicts two maxima, and not only one, in the transfer of information during the specific situation that we show in figure 1. This, to be interpreted as SMR phenomena, provides *a priori* a good description of the only sufficiently detailed observation we know, namely, it fits *all* the data in [18], and it is also in qualitative agreement with several predictions, as mentioned above, and with the global behavior reported in various experiments [17, 19]. The minimum that is exhibited between the two peaks is to be associated with noise-induced firings that are uncorrelated with the signal. The occurrence of an extra peak at low frequency, which is also suggested by experimental data in [40], is most interesting,

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e.g., as a way of efficiently detecting incoming signals along two well-defined noise levels. This seems to occur in nature and could also be implemented in man-made devices.

The number of peaks and the frequency range at which they are located can easily be controlled in the model by tuning the parameter values, particularly those concerning *synaptic dynamics*.

Finally, we remark on the model indication of two main ingredients of SMR. On the one hand, the system is expected to have activity-dependent excitability. This may require short-term variations of intensity links in a networked system, which is very common in practice [27]. On the other hand, the units in our model are able to adapt activation or firing thresholds to the level of mean input. It is sensible to expect such adaptive thresholds [21, 41], and they have been observed recently in actual cortical regions [42], for instance. A major conclusion therefore is that SMR should be observed rather generally in neural media and in other excitable systems. We summarize in figure 2 the conditions under which such an interesting phenomenon may occur. Incidentally, it is also worth mentioning that the present work adds to previous efforts to analyze the consequences in many branches of science of the interplay between the nonlinearities, signal and forces, and environmental noise [43].

Acknowledgments

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