Stochastic Resonance in Muscle Receptors

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Fallon, James B., Richard W. Carr, and David L. Morgan. Stochastic resonance in muscle receptors. *J Neurophysiol* 91: 2429–2436, 2004. First published January 21, 2004; 10.1152/jn.00928.2003. Noise is generally considered to have deleterious effects on the sensitivity of a signal detection system. There are, however, several mechanisms whereby the addition of noise to the input of a system can in fact improve sensitivity. One such mechanism is stochastic resonance. Although first proposed in 1981, conclusive experimental evidence for "fully tuneable stochastic resonance" in biological systems has not previously been reported. Evidence of fully tuneable stochastic resonance in the response of afferents from Golgi tendon organs and the primary and secondary endings of muscle spindles to imposed muscle length changes is presented.

INTRODUCTION

Stochastic resonance (SR) was first proposed in 1981 as a possible explanation for the apparent periodicity of Earth's ice ages (Benzi et al. 1981, 1982), and has since been proposed to occur in a variety of systems from a wide range of disciplines (for a comprehensive review, see Gammaitoni et al. 1998). In its most general form, the theory describes the phenomenon whereby a nonlinear system can detect an otherwise undetectable stimulus with the addition of a random stimulus, i.e., noise, to the input.

Benzi et al. (1981) initially coined the phrase "stochastic resonance" to describe the process whereby "a dynamical system subject to both periodic forcing and random perturbation may show a resonance which is absent when either the forcing or the perturbation is absent." The "beneficial" effects of additional input noise have since been interpreted as SR in a variety of ways, including "aperiodic stochastic resonance" (Collins et al. 1995) and "suprathreshold stochastic resonance."

Of the many definitions of SR, we have chosen to focus on the type of SR described by Gammaitoni et al. (1995). This type of SR is distinguished by the requirement that the maximum enhancement of the output signal-to-noise ratio (SNR) occurs when the noise induced rate, in their case the switching rate of a bistable system, matches the frequency of the subthreshold periodic stimulus (Gammaitoni 1995). Gammaitoni et al. (1995) defined this as a true resonance because there is a matching of time scales (or frequencies). That these results obtained in a bistable potential model represent a "bona fide" resonance has been questioned (e.g., see Choi et al. 1998).

In a system displaying the type of SR described by Gammaitoni et al. (1995), it should be possible to observe an improvement in output SNR either by tuning the frequency of the subthreshold periodic stimulus, while holding the ampli-
tude of noise constant, or alternatively, by tuning the amplitude of the noise added to the system, while holding the frequency of the subthreshold periodic stimulus constant (see Fig. 1). Consequently, we will subsequently refer to this type of SR as "fully tuneable stochastic resonance." Two key features of fully tuneable SR can be used to help distinguish it from other types of SR. First, the amplitude of the additional noise that results in the maximal output SNR must be dependent on the frequency of the subthreshold periodic stimulus. Specifically, subthreshold periodic stimuli of higher frequencies will require more additional noise to maximize the output SNR. Second, the amplitude of the additional noise that results in the maximal output SNR must be suprathreshold. This is in contrast to other types of SR, such as threshold SR, where the optimal amplitude of the noise is close to the threshold amplitude, and is independent of the frequency of the subthreshold periodic stimulus.

The first experimental evidence of SR was reported in 1983 for the Schmitt trigger, a simple two-state electronic system (Fauve and Heslot 1983). Ten years later, Douglass et al. (1993) reported the first evidence for SR in a biological system, the mechanoreceptor of the crayfish *Procambarus clarkii*. SR has since been reported in a range of biological systems from isolated cell membranes (Bezrukov and Vodyanoy 1995) to the feeding patterns of the paddle fish *Polyodon spathula* (Greenwood et al. 2000). The reports of SR in biological systems have included many varieties of SR, perhaps most notably "aperiodic stochastic resonance" in the cercal system of the cricket (Levin and Miller 1996), the slowly adapting cutaneous mechanoreceptors of the rat (Collins et al. 1996a) and tactile sensation in man (Collins et al. 1996b).

In biological systems, fully tuneable stochastic resonance has been demonstrated by showing a dependence of the optimal noise level on the frequency of the subthreshold periodic input in crayfish multimodal interneurons (Pei et al. 1996b), a visual perception task based on Haken's images (Chialvo and Apkarian 1993) and human mechanoreceptors (Ivey et al. 1998). We demonstrate conclusive evidence for fully tuneable stochastic resonance in an in vivo preparation of afferents from Golgi tendon organs and muscle spindle primary and secondary endings in the soleus muscle of the cat. Preliminary results have previously appeared in abstract form (Fallon et al. 1999).

METHODS

Experimental preparation

Experiments were performed on muscle receptors in the soleus muscle of the anesthetized cat (*Felis domesticus*) and had approval
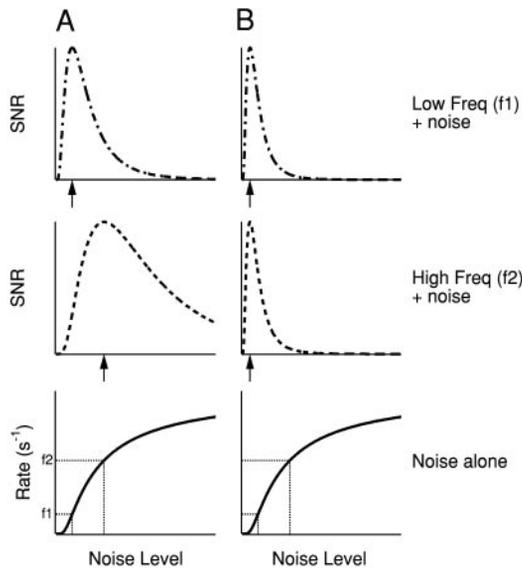

FIG. 1. *Top*: idealized output signal-to-noise ratio (SNR) resulting from the combination of a fixed-amplitude low-frequency, subthreshold, periodic input (f1) and varying amplitudes of noise to a system exhibiting either fully tuneable stochastic resonance (*A*) or threshold stochastic resonance (*B*). Both systems show an optimum output SNR with the addition of noise (vertical arrows). *Middle*: frequency of the periodic signal is increased (f2). Optimum amplitude of noise for threshold stochastic resonance does not change and remains dependent on the system's threshold. However, for the system displaying fully tuneable stochastic resonance, optimum amplitude of noise is increased from D_{PRE1} to D_{PRE2}, as predicted by the response of the system to noise alone (*bottom*).

from the local Standing Committee for Ethics in Animal Experimentation. Sixteen cats were used, with weights ranging from 3.5 to 7.0 kg. Anesthesia was induced with an intraperitoneal injection of pentobarbital sodium (40 mg/kg; Nembutal, Rhone Merieux Australia, Australia) and maintained with additional bolus doses administered via a cannula in the cephalic vein (12 mg/ml to effect). Anesthetic depth was monitored by checking for the presence of eye blink and withdrawal reflexes, assessing the level of muscle tone, as well as monitoring end tidal CO_2 levels (Normocap CD-102, Datex) via a tracheal cannula. The animal's body temperature was maintained in the range $38 \pm 1°C$ using a thermal blanket regulated by feedback.

The left soleus muscle and its tendon were dissected free. The tendon and its attached fragment of calcaneum were attached via an in-series strain gauge to an electro-magnetic position controller with feedback. The total compliance of the system was 5 μm/N. The mechanical response of the system was tested with both sinusoidal and noise command signals and was confirmed to be linear from DC to 200 Hz (with higher frequencies filtered out) over the range of lengths used in this study. Muscle lengths were referred to the maximum in situ physiological length (L_{MAX}). The left hindlimb was extensively denervated, including the hip, but sparing the nerve to soleus. A laminectomy was performed exposing the lumbo-sacral spinal cord from L_6 to S_2. Dorsal and ventral spinal roots were cut where they entered the cord and the peripheral portions of the dorsal roots were dissected into small filaments to obtain functionally single muscle receptor afferent axons. Pools, fashioned from skin flaps of the hindlimb and back, were filled with mineral paraffin oil and warmed with radiant heat.

Experimental protocol

Afferent axons in filaments of dorsal root were identified by the velocity of conduction of an action potential initiated by stimulation of the muscle nerve. Afferents were identified as innervating Golgi tendon organs by their "in series" response to a whole muscle twitch, while afferents exhibiting an "in parallel" response were classified as muscle spindles.

Muscle length was adjusted to a length immediately below that required to produce a maintained discharge. For Golgi tendon organs, this length was often just short of L_{MAX}, while for muscle spindle primary and secondary endings it was typically in the range $L_{MAX} -$ 10 mm to $L_{MAX} - 16$ mm. All measurements involving muscle spindles were performed after "hold test" conditioning (Proske et al. 1993) to ensure there was no slack present in the intrafusal fibers.

Evidence for stochastic resonance in muscle receptors was sought using random muscle length changes (noise) and subthreshold sinusoidal muscle length changes both individually and in combination. The noise signal consisted of a computer-generated random signal that had zero-mean and a uniform probability distribution between an upper and lower limit (typically ± 1 mm), resulting in a broadband (DC to 300 Hz) noise signal. A noise signal with a uniform probability distribution, rather than the more common Gaussian distribution, was used to limit the range of length changes possible. This was necessary to ensure that all length changes could be accurately reproduced by the electro-magnetic position controller. To aid comparison with previous reports, in which noise signals with Gaussian distributed amplitude were used, the amplitude of the noise signal was defined as the SD of the recorded length signal.

The response of muscle receptors to several frequencies of subthreshold sinusoidal length changes and various amplitudes of noise were measured. Sinusoidal frequencies were chosen to lie approximately within the linear region of the noise-alone response. This was expected to generate the greatest separation of the optimal noise amplitudes for each sinusoidal test frequency and resulted in the use of sinusoidal test frequencies between 1 and 30 Hz. These frequencies lie within the lower range of frequencies to which Golgi tendon organs (0–200 Hz), muscle spindle primary endings (0–500 Hz), and muscle spindle secondary endings (0–100 Hz) will respond (Brown et al. 1967). The amplitude of each sinusoidal test signal was adjusted to be "near" but below threshold.

Data collection and analysis

Action potentials were amplified using custom-built amplifiers before being digitally recorded using a commercial data acquisition card (PCI-MIO-16E-4, National Instruments, Austin, TX) in a G3 Macintosh computer (Macintosh, Cupertino, CA). All recording and analysis was done using custom software written within Igor Pro (Wavemetrics, Lake Oswego, OR).

The responses of muscle receptors to noise-alone length stimuli were quantified by calculating the average discharge rate during the period of stimulation. This corresponds to the noise induced frequency of our system and represents one of the time scales that must be matched for fully tuneable stochastic resonance to occur. The average noise-alone–induced firing rates were fitted by a curve based on Kramers' theorem and given by

$$\text{Rate} = \alpha e^{-\beta/D^2}$$

where D is the noise amplitude and α and β are arbitrary constants. From the noise-alone response, it is possible to predict the amplitude of noise, D_{PRE}, that should maximize the output SNR. D_{PRE} is the amplitude of noise that, when applied alone, produces an average response rate equal to the frequency of the subthreshold sinusoidal stimulus, one of the key features of fully tuneable stochastic resonance. This is illustrated by the dotted lines in the Fig. 1 (*bottom panel*). A noise-alone input of D_{PRE1} results in an average transition rate of f_1 and will optimize the response for a subthreshold periodic stimulus with a frequency of f_1 Hz. A larger noise-alone input, D_{PRE2}, results in a higher average transition rate, f_2, and a subthreshold periodic stimulus with a frequency of f_2 Hz would be required to optimize the response.

Due to the difficulties of using existing SNR measures (see DISCUSSION), a novel SNR measure was used to quantify the response of muscle receptors to combined subthreshold sinusoidal and suprathreshold noise stimuli. The responses of a Golgi tendon organ to a subthreshold sinusoidal length stimulus, a suprathreshold noise-alone length stimulus and a combination of the two stimuli are shown in Fig. 2. The afferent does not respond to subthreshold sinusoidal stimuli, resulting in a zero cycle histogram. The afferent response to suprathreshold noise-alone length changes is a series of action potentials at random times, illustrated in the cycle histogram as an almost even distribution across all phases of the stimulus. The addition of a subthreshold sinusoidal length stimulus to the suprathreshold noise signal results in a modulation of the cycle histogram. The Golgi tendon organ preferentially fires during a particular phase of the sinusoidal stimulus. The amount of signal present in the output can be quantified as the amount of modulation of the cycle histogram, SNR_{CYCLE}.

SNR_{CYCLE} was calculated by fitting a sinusoid to the cycle histogram of the response to the combined noise and subthreshold periodic stimuli as shown in Fig. 2. The amplitude of the fitted sinusoid is related to the amount of periodic signal present in the output, while the estimated error (SD) in the amplitude of the fitted sinusoid, calculated from the residuals, is related to the amount of noise in the output. Therefore SNR_{CYCLE} is defined as the amplitude of the fitted sinusoid divided by the estimated error in the amplitude of the fitted sinusoid. For the response shown in Fig. 2C, the amplitude of the fitted sinusoid is 0.018 ± 0.003 Pr/Bin, resulting in an SNR_{CYCLE} of 6.0. SNR_{CYCLE} is small, typically near unity, when a noise-alone signal is used (Fig. 2B) and increases with increasing amplitudes of sinusoidal length changes, as expected. Theoretically, SNR_{CYCLE} should equal unity for a noise-alone signal as the estimated error in the amplitude of the fitted sinusoid would equal the amplitude of the fitted sinusoid. Therefore SNR_{CYCLE} is defined as one for subthreshold signals when there is no afferent response (Fig. 2A).

SNR_{CYCLE} was determined for the response of muscle receptors to combined subthreshold sinusoidal and suprathreshold noise stimuli for a number of sinusoidal frequencies and noise amplitudes. The amplitude of noise that produced the maximum SNR_{CYCLE}, D_{OPT}, was calculated by fitting a log-Normal curve of the form

$$SNR = 1 + \alpha e - \left(\frac{\ln(D/D_{OPT})}{\beta} \right)^2$$

where D is the noise amplitude, D_{OPT} is the amplitude of noise that results in a maximal SNR_{CYCLE} value, and α and β are arbitrary constants. Evidence for stochastic resonance in muscle receptors was assessed by correlating D_{OPT} and D_{PRE}, respectively, the measured and predicted optimal noise amplitudes at different frequencies of subthreshold sinusoidal length change.

RESULTS

The response of a single Golgi tendon organ Ib afferent to both combined and individual subthreshold periodic and suprathreshold noise length stimuli is shown in Fig. 2. By definition, the receptor did not respond to the subthreshold periodic stimulus alone and therefore yielded a SNR_{CYCLE} of 1 (see METHODS). The suprathreshold noise-alone length stimulus produced a cycle histogram in which action potentials were almost evenly distributed across all phases of the stimulus, giving a SNR_{CYCLE} of 0.86. The combination of subthreshold sinusoidal and suprathreshold noise length stimuli resulted in a cycle histogram with a significant modulation of the action potential distribution across stimulus phase, giving a SNR_{CYCLE} of 6.0. Although not shown, the responses of muscle spindle primary and secondary endings to this stimulus protocol were similar to that shown for the Golgi tendon organ.

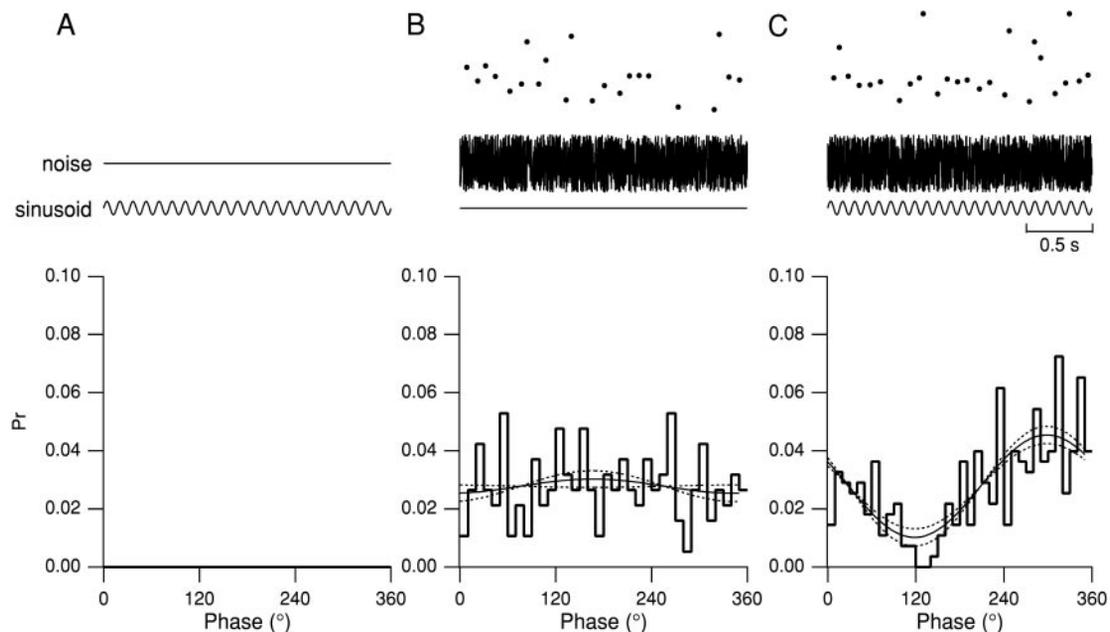Data obtained from a single Golgi tendon organ afferent

FIG. 2. Response of a single Golgi tendon organ Ib afferent to a subthreshold sinusoidal length stimulus (*A*), a suprathreshold noise-alone length stimulus (*B*), and a combination of the subthreshold sinusoidal and suprathreshold noise length stimuli (*C*). In each panel, the *top trace* is the instantaneous impulse/discharge rate of the receptor and the *bottom traces* are signals used to generate the imposed change in muscle length about a test length of $L_{MAX} - 1.5$ mm. *Bottom*: 20-s cycle histograms that have been fitted with a sinusoid (solid line). Amplitude of the fitted sinusoid along with an estimate of the error in the fit (dotted lines) is used to determine SNR_{CYCLE}. Stimulus parameters and resulting values of SNR_{CYCLE} for the 3 stimuli are (*A*) a 60-μm sinusoid at 11 Hz, yielding a SNR_{CYCLE} of 1; (*B*) a noise-alone stimulus of 150 μm, yielding a SNR_{CYCLE} of 0.86; and (*C*) a combination of a 60-μm sinusoid at 11 Hz and noise of 150 μm (i.e., a combination of the stimulus parameters in *A* and *B*), yielding a SNR_{CYCLE} of 6.0.
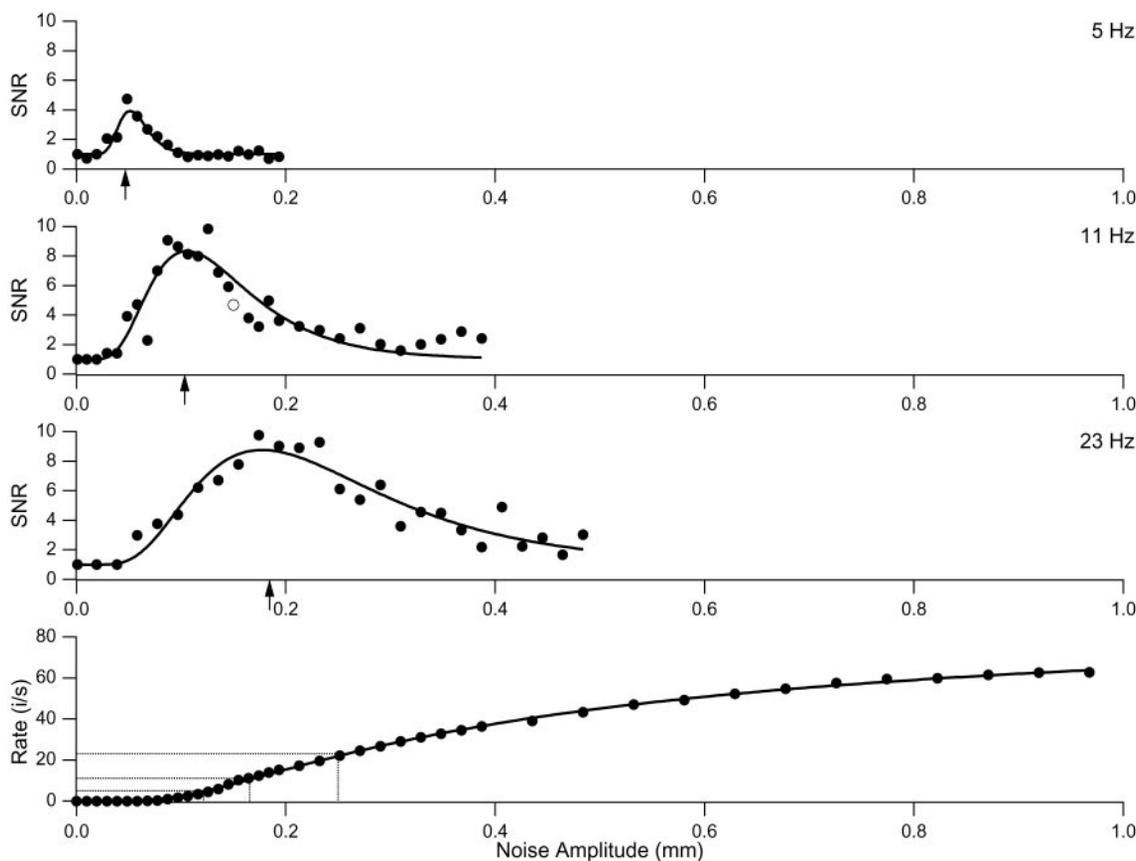
FIG. 3.   Response of a single Golgi tendon organ to stretches of a passive muscle shows many of the characteristic features of stochastic resonance. Each point is calculated from 20 s of response measured about a test length of $L_{MAX} - 1.5$ mm. Fitted curves in *top panels* are log-Normal curves used to estimate D_{OPT}, indicated by the arrows, while the fitted curve in the *bottom panel* is based on Kramers' rate and is used to determine D_{PRE} (see METHODS). Dotted lines in the *bottom panel* indicate predicted optimal noise value, D_{PRE}, for each test frequency—5, 11, and 23 Hz—and the open symbol represents the data illustrated in Fig. 2*C*. Amplitude of the subthreshold sinusoidal inputs was 60 μm for all 3 test frequencies.

exhibiting many features characteristic of fully tuneable stochastic resonance is shown in Fig. 3. The average discharge rate during the 20 s of imposed noise-alone movements about a test length of $L_{MAX} - 1.5$ mm is shown in the *bottom panel*. The noise-alone threshold was ~100 μm, above which the average discharge rate increased with increasing noise amplitude toward a plateau of ~65 i/s. The noise-alone response was well fitted by a curve based on Kramers' rate, allowing for accurate predictions of D_{PRE}. For the three test frequencies illustrated, 5, 11, and 23 Hz, the predicted optimal noise amplitudes were 121, 165, and 250 μm, respectively (dotted lines in Fig. 3, *bottom panel*). The combination of suprathreshold noise and subthreshold, periodic sinusoidal length changes produced SNR_{CYCLE} data that was well fitted by a log-Normal curve for each test frequency (Fig. 3, *top 3 panels*). The resulting noise amplitudes that maximized SNR_{CYCLE} were 46.9 ± 0.3, 103 ± 1, and 184 ± 1 (SE) μm for the 5-, 11-, and 23-Hz subthreshold sinusoidal length stimuli. The increase of D_{OPT}, with increasing frequency of subthreshold periodic stimulus, is a key feature of fully tuneable stochastic resonance that has not been shown in most previous studies. An increase in D_{OPT} resulting from an increase in frequency of the subthreshold periodic stimulus was also observed for the individual responses of muscle spindle primary (Fig. 4) and secondary ending afferents (Fig. 5).

The other key feature of fully tuneable stochastic resonance,

i.e., the matching of D_{PRE} and D_{OPT}, can be seen in the pooled data from the Golgi tendon organs (Fig. 6*A*) and the muscle spindle primary and secondary ending afferents (Fig. 6*B*). Individual data points indicate the measured optimal noise amplitude plotted against the corresponding optimal noise amplitude predicted from the noise-alone response of the receptor. There is a correlation between D_{OPT} and D_{PRE} for the Golgi tendon organ (Pearson product = 0.997) and the pooled (i.e., primary and secondary) muscle spindle ending afferents (Pearson product = 0.699).

DISCUSSION

We have chosen to focus on the relatively restricted/narrow interpretation of SR presented by Gammaitoni et al. (1995), whereby a resonance-like increase in the output SNR of a system is expected when there is a matching of the time scale (or frequency) of a subthreshold periodic input and the noise-induced response of the system. We have coined a new term for this type of SR, namely "fully tuneable stochastic resonance," in an effort to emphasize the matching of time scales (or frequencies) required to increase the output SNR that should be able to be achieved by either adjusting the frequency of the subthreshold periodic input, while holding the amplitude of additional suprathreshold noise constant or adjusting the
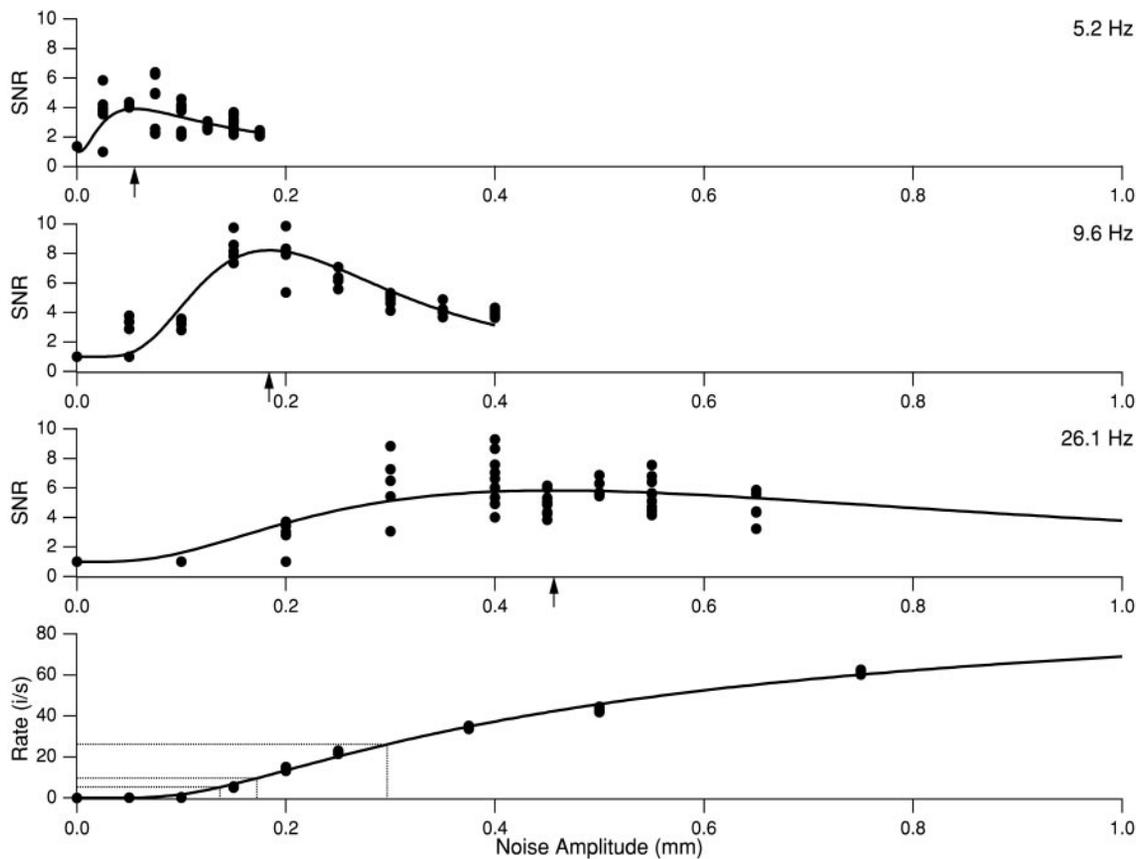
FIG. 4.   Response of a single muscle spindle primary ending to stretches of a passive muscle shows many of the characteristic features of stochastic resonance. Each point is calculated from 20 s of response measured about a test length of $L_{MAX} - 14.5$ mm. Fitted curves in *top panels* are log-Normal curves used to estimate D_{OPT}, indicated by the arrows, while the fitted curve in the *bottom panel* is based on Kramers' rate and is used to determine D_{PRE} (see METHODS). Dotted lines in the *bottom panel* indicate the predicted optimal noise value, D_{PRE}, for each test frequency—5.2, 9.6, and 26.1 Hz. Amplitude of the subthreshold sinusoidal inputs was 100 μm for all 3 test frequencies.

amplitude of the additional suprathreshold noise, while holding the frequency of the subthreshold periodic input constant.

Gammaitoni et al. (1995) claimed that the increase in output SNR they observed in their bistable potential was a "bona fide" resonance. The "bona fide" resonance was observed by using the area under the first peak of a residence time distribution (similar to an interspike-interval histogram). It should be noted that Choi et al. (1998) have criticized the work of Gammaitoni et al. (1995), particularly with respect to the use of a relatively large amplitude of the periodic signal compared with that of the noise. Using fully analytical results, Choi et al. (1998) have posited that, at least for small signal amplitudes, SR is not a "bona fide" resonance. Stocks (1995) also reported analytical evidence for a maximum SNR with changing frequency, again only with relatively large signal amplitudes, and attributed the increase in output SNR to a nonlinear effect. A detailed discussion of the controversy surrounding some of the propositions put forth in the Gammaitoni et al. (1995) paper is beyond the scope of this paper. However, their proposition that a matching of time scales (or frequencies) resulting in an increase in output SNR, is taken as sufficient justification for us to define fully tuneable stochastic resonance as an increase in a system's output SNR that can be optimized by tuning the frequency of a periodic subthreshold stimulus or the amplitude of the noise stimulus. It should also be noted that the subthreshold sinusoidal signal amplitudes used in the experiments de-

scribed here are smaller than the measured and predicted optimal noise levels and therefore the criticisms of Choi et al. (1998) of the Gammaitoni et al. (1995) paper do not apply to our results.

Many different types of neuronal models have been used in investigations of SR, ranging from simple integrate-and-fire (Barbi et al. 2000) and two-state models (Lindner and Schimansky-Geier 2000) to the multi-parameter Fitzhugh-Nagumo (Chialvo and Apkarian 1993) and Hodgkin-Huxley models (Kanamaru et al. 1998; Lee and Kim 1999; Pei et al. 1996a). Although we have cited Gammaitoni et al. (1995) as the basis for our definition of fully tuneable stochastic resonance, we wish to emphasize that this does not mean that we consider sensory receptors as a bistable system. We believe the concept of fully tuneable stochastic resonance, whereby an increase in the output SNR of a system results from the matching of the time scale (or frequency) of the subthreshold periodic input and the noise-induced response of the system, is broadly applicable and not confined to bistable systems.

An important point highlighted by the many studies of SR in neuronal models is that the assessment of stochastic resonance is dependent on the choice of analysis used (compare the reports from Kanamaru et al. 1998; Lee and Kim 1999; Pei et al. 1996a). It has been reported that some indices, such as those based on power spectrum, cannot be used to observe fully tuneable stochastic resonance (Fox 1989), while others, such as
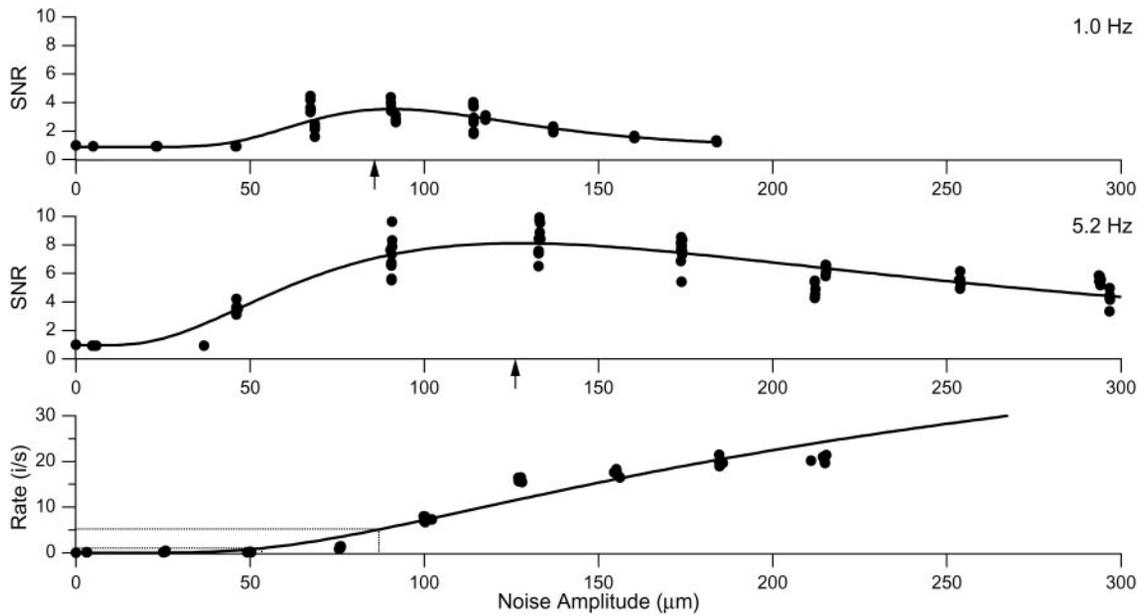
FIG. 5. Response of a single muscle spindle secondary ending to stretches of a passive muscle shows many of the characteristic features of stochastic resonance. Each point is calculated from 20 s of response measured about a test length of $L_{MAX} - 15.0$ mm. Fitted curves in *top panels* are log-Normal curves used to estimate D_{OPT}, indicated by the arrows, while the fitted curve in the *bottom panel* is based on Kramers' rate and is used to determine D_{PRE} (see METHODS). Dotted lines in the *bottom panel* indicate predicted optimal noise value, D_{PRE}, for each test frequency—1.0 and 5.2 Hz. Amplitude of the subthreshold sinusoidal inputs was 83 μm for all 3 test frequencies.

those based on the inter-spike interval histogram (ISIH), may incorrectly indicate the presence of SR (Giacomelli et al. 1999). Therefore it is necessary to adequately account for the effect of the particular output SNR index used in any study of SR. For neurobiological systems, where system output is determined from action potential discharge, one of the most commonly used indices is SNR_{ISIH}. SNR_{ISIH} is the probability of an action potential occurring once within each stimulus period. Consequently, in the absence of any periodic stimulus, SNR_{ISIH} may falsely indicate the presence of SR because the ISIH changes shape according to the noise amplitude (Choi et al. 1998). This led Marchesoni et al. (2000) to use a variation of SNR_{ISIH} based on the difference between the noise-alone ISIH and the ISIH produced with a combination of a subthreshold periodic stimulus and noise, $SNR_{ISIHDIF}$. However, the amount of data required for this index is often in the order
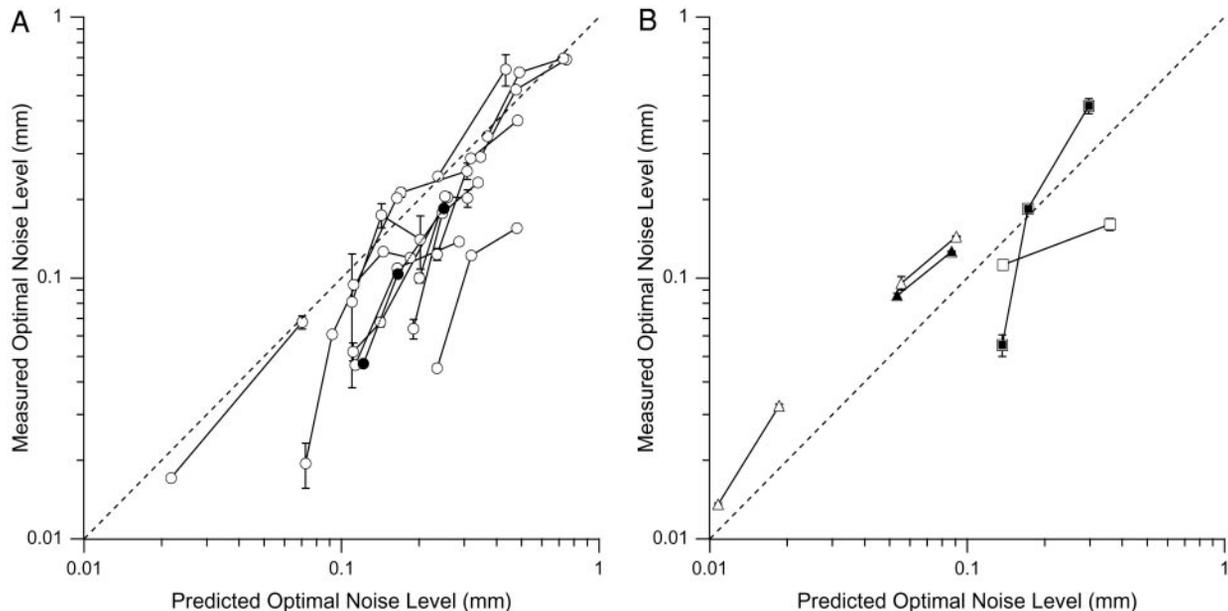

FIG. 6. Pooled data from 15 Golgi tendon organs (*A*), 2 muscle spindle primary endings (*B*, squares), and 3 muscle spindle secondary endings (*B*, triangles), together with the line of proportionality (dashed line) predicted by stochastic resonance theory. Values for D_{OPT} are shown with an estimate of their associated error. Results for each receptor are joined by a solid line to show the positive correlation between D_{OPT} and D_{PRE} for each unit. Filled symbols represent data shown in Figs. 3, 4, and 5 for a single Golgi tendon organ, muscle spindle primary ending, and muscle spindle secondary ending, respectively.

of several hundred thousand action potentials, and it is therefore impracticable in experimental situations. Consequently, this study used a novel index based on cycle histograms, SNR_{CYCLE}, which could be computed from relatively few action potentials but is still sensitive enough to observe fully tuneable stochastic resonance in the Hodgkin-Huxley model (unpublished observations).

A system's optimum output SNR, resulting from fully tuneable stochastic resonance, in response to noise and subthreshold periodic input, can be observed either by tuning the frequency of the subthreshold periodic stimulus while holding amplitude of noise constant or by tuning the amplitude of the noise while holding the frequency of the subthreshold periodic stimulus constant (see Fig. 1). However, to qualify the responsible mechanism as fully tuneable stochastic resonance further requires that the effect be co-dependent on the amplitude of the noise and the frequency of the periodic input. That is, higher frequency periodic stimuli will require larger noise amplitudes to maximize the output SNR, if the increase in output SNR is the result of fully tuneable stochastic resonance. In addition, for a given frequency of subthreshold periodic stimulation, the empirically determined noise amplitude required to optimize the system's SNR should correlate with that predicated from the system's response to noise alone.

In the reports generated from crayfish multi-modal interneurons (Pei et al. 1996b), a visual perception task (Chialvo and Apkarian 1993), and mechanoreceptors in humans (Ivey et al. 1998), data were obtained that supports the assumption that an increase in output SNR with the addition of noise occurred as a result of fully tuneable stochastic resonance. However, fully tuneable stochastic resonance has not been unequivocally demonstrated in any of the previous reports from biological systems. Using SNR_{CYCLE}, this study demonstrates that both Golgi tendon organ and muscle spindle afferents exhibit all of the characteristics of fully tuneable stochastic resonance. The frequency-dependent nature of fully tuneable stochastic resonance is observed by stimulating the receptors with multiple frequencies of subthreshold periodic stimuli. An increase in the frequency of the subthreshold periodic stimulus resulted in the requirement for a larger noise amplitude to maximize the output SNR for all receptors studied. In addition, the predicted and measured optimal noise amplitudes were correlated (Fig. 6). Consequently, the data presented here provides the first rigorous evidence of fully tuneable stochastic resonance in a biological system, specifically sensory receptors in mammalian muscle.

It was possible to observe stochastic resonance in all Golgi tendon organs and muscle spindles for which a subthreshold periodic and suprathreshold noise stimulus could be reliably imposed through changes in muscle length. However, only a limited number of muscle spindles could be studied under these conditions, as the majority of muscle spindles had a maintained discharge in the absence of any length stimuli. In the cat, muscle spindles are known to have different rates of ongoing impulse activity according to the recent length and contraction history of their surrounding extrafusal muscle (Morgan et al. 1984). For this reason, all muscle spindles were studied after "hold test" conditioning and at muscle lengths long enough to prevent the muscle falling slack, thereby ensuring that the length stimuli were actually imposed on the muscle. Muscle spindles with a maintained discharge after hold test condition-

ing responded to small sinusoidal length changes of 5 μm, which was the lower limit for the amplitude of sinusoidal length changes available with our equipment. It is possible to silence muscle spindles using a "hold long" conditioning to introduce slack into the intrafusal muscle fibers (Proske et al. 1993); however, the rapid length changes resulting from the noise movements removes the effect of hold long conditioning. This would have resulted in the threshold changing in an unpredictable manner for different amplitudes of noise. The majority of muscle spindles therefore could not be tested for fully tuneable stochastic resonance, because a subthreshold periodic stimulus is a prerequisite for the experiment.

Cordo et al. (1996) reported that muscle spindles innervating wrist and hand muscles exhibit SR. A subthreshold sinusoidal rotation of the wrist was used as the periodic input while various amplitudes of noise were applied via the tendon of the muscle of interest. An output SNR measure based on the power spectrum of the afferent response was calculated, and some subjects exhibited an increase in output SNR with the addition of noise. It is difficult to determine whether this increase in sensitivity is a result of fully tuneable stochastic resonance, or some other noise effect such as threshold SR, as only a single frequency of sinusoidal stimuli was tested. Consequently, it is not possible to observe the distinguishing feature of fully tuneable stochastic resonance, a matching of time scales. Similarly, a noise-alone response was not provided, so it is also not possible to determine the relationship between the measured optimal noise amplitude, D_{OPT}, and predicted optimal noise amplitude, D_{PRE}, or the noise threshold.

Fully tuneable stochastic resonance is a possible mechanism whereby noise could be used to increase the sensitivity of a biological system rather than reduce it. Fully tuneable stochastic resonance, however, is not the only mechanism whereby noise can increase the sensitivity of a system. Threshold SR is another mechanism by which noise can be used to increase the sensitivity of a system. A system using threshold SR will have an increased sensitivity to all frequencies of signals, including aperiodic signals such as ramp-and-hold stimuli. It is for this reason that dithering, a closely related phenomenon, has found considerable practical use in the electronics industry. Using similar effects as those that contribute to threshold SR, it is possible to add near threshold deterministic signals, such as sinusoids, rather than random "noise" signals to the input to achieve the increase in output SNR (Matthews and Watson 1981). Another related phenomena is "spatial averaging," which Milgram and Inbar (1976) have suggested may be used by CNS networks to improve SNR.

In contrast, fully tuneable SR requires that the noise amplitude be tuned to the frequency of the subthreshold periodic signal of interest or vice versa. Once tuned, the system will be most sensitive to a narrow range of frequencies and will therefore act as a crude type of filter. A possible scenario whereby SR filtering could be utilized biologically is in the detection of muscle tremor. The "noise" produced by asynchronous contractions of extrafusal muscle fibers could be utilized to preferentially increase the sensitivity of Golgi tendon organs to a specific range of frequencies. (Similarly, the noise produced by asynchronous contraction of intrafusal muscle fibers, particularly chain fibers, could be utilized by muscle spindles). As whole muscle force increases, the amount of noise would be expected to increase as more and larger motor

units are recruited. This would result in a shift in the frequency range of maximal receptor sensitivity toward higher frequencies. The natural frequency of the muscular-skeleto system would also be expected to increase as a result of the increased stiffness of the muscle. Therefore it is possible that the range of frequencies to which Golgi tendon organs (and/or muscle spindles) are most sensitive may track the natural frequency.

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