Auditory sensitivity may require dynamically unstable spike generators: Evidence from a model of electrical stimulation

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Abstract: The response of the auditory nerve to electrical stimulation is highly sensitive to small modulations ($<0.5\%$). This report demonstrates that dynamical instability (i.e., a positive Lyapunov exponent) can account for this sensitivity in a modified FitzHugh-Nagumo model of spike generation, so long as the input noise is not too large. This finding suggests both that spike generator instability is necessary to account for auditory nerve sensitivity and that the amplitude of physiological noise, such as that produced by the random behavior of voltage-gated sodium channels, is small. Based on these results with direct electrical stimulation, it is hypothesized that spike generator instability may be the mechanism that reconciles high sensitivity with the cross-fiber independence observed under acoustic stimulation.

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1. Introduction

Most cochlear implants excite neural spike generators with a sequence of shocks (current pulses), and information about speech is represented by a modulation of the amplitude of these shocks (e.g., Wilson and Dorman¹). Based on these facts, one would expect that the mechanism that determines the spike generator's sensitivity to amplitude modulations plays a critical role in the encoding of speech in the neural discharge pattern of cochlear implantees. Indeed, Fu² has shown that implantees' abilities to recognize speech sounds are strongly correlated with their abilities to detect a small modulation imposed upon a shock train. While modulation sensitivity evidently plays a major role in the neural encoding of speech, the mechanism that produces this sensitivity has not been elucidated.

Many discussions of the neural mechanism of modulation sensitivity have emphasized the role of physiological noise, suggesting that physiological noise contributes positively or constructively to the modulation sensitivity via "stochastic resonance."³⁻¹¹ Yet, neural models with large input noise have not been demonstrated to account for the extremely high modulation sensitivity recorded in electrically stimulated auditory nerve fibers. In particular, high-noise models have not been shown to account for the prominent spike synchronization induced by a 0.5% modulation in the amplitude of a high rate (5 kHz) shock train.⁸

A previous study¹² showed that these high rate shock trains produce dynamical instability in the simple FitzHugh-Nagumo model and that this instability reproduces prominent features of the non-Poisson-like firing irregularity exhibited by electrically stimulated auditory

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nerve fibers,^{6,13} but that these non-Poisson-like features are abolished by a large input noise. That study also noted that dynamical instability produces both high sensitivity to step increments in the pulse amplitude and cross-fiber statistical independence in the absence of ongoing noise. The present study uses a modification of this FitzHugh-Nagumo model (mFN) to determine whether dynamical instability can account for the experimentally measured neural sensitivity to amplitude modulations and to investigate the effect of additive membrane noise on modulation sensitivity.

The degree of dynamical instability is quantified by the Lyapunov exponent, a number that measures the sensitivity of a system to a small perturbation.¹⁴ When the Lyapunov exponent is positive, the effect of a small perturbation is amplified over time, whereas when the Lyapunov exponent is negative, the effect of a perturbation decays over time.

2. Brief methods

The FitzHugh-Nagumo model approximates the time course of excitation and refractoriness predicted by more complex biophysical models such as the Hodgkin-Huxley model.^{15,16} Hindmarsh and Rose¹⁷ modified the differential equations that specify the FitzHugh-Nagumo model to better account for the refractory properties of real neurons. This study uses a simplified version of these Hindmarsh and Rose equations. The parameters of this simplified model were adjusted to produce a relative refractory time that is similar to the auditory nerve. Standard numerical techniques are used to solve these modified FitzHugh-Nagumo equations (mFN) in response to sequences of delta function pulses that represent the stimulating current shocks. To simulate the effect of the noise generated by the random opening and closing of voltage-gated sodium channels, a Gaussian noise current $I_{\text{noise}}(t)$ was added to the input. In some simulations, this ongoing noise current was set to zero [$I_{\text{noise}}(t) \equiv 0$] and the height of the stimulating pulses were randomly jittered. This study is limited to a stimulus condition studied by Litvak *et al.*⁸ Specifically, the driving pulse rate is fixed at 5 kHz, corresponding to an interpulse time of 0.2 ms. The amplitude of the pulse train is adjusted to produce a discharge rate of 50 spikes/sec in the absence of an applied sinusoidal amplitude modulation ($m=0$). A 0.5 percent sinusoidal modulation ($m=0.005$) is then applied to the pulse height. The modulation frequency is 416.67 Hz. The methods are described more extensively in the Detailed Methods.¹⁸

3. Results

The left side of Fig. 1 shows histograms of firing times during the modulation period (2.4 ms) for the noise-free simulation using the mFN model (Panel A), for the auditory nerve data (Litvak *et al.*⁸ shown here in Panel B), and for the mFN model with additive noise (Panel C). In all these cases, the pulse train amplitude A_{carrier} was adjusted to produce a discharge rate of approximately 50 spikes/sec in the absence of modulation and a 0.5 percent modulation ($m=0.005$) was then applied. In both the noise-free simulation and the empirical response, the firings occur synchronized to the modulation to similar degrees. In contrast, the addition of noise with an RMS amplitude that is equal to the RMS modulation amplitude flattens the histogram to a large degree, showing a substantial reduction in the strength of synchronization.

The amount of synchrony induced by the modulation can be quantified by the vector strength or synchronization index (SI).¹⁹ An SI of unity indicates that all the spiking occurs at a certain phase of the modulator, whereas an SI of zero indicates no phase preference. The filled circles in Fig. 1(D) represent the SI as a function of the input noise level for the mFN model. At the lowest noise levels ($0 \leq \text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}} \leq 0.1$, demarcated by a vertical gray line and denoted Region I), the SI is above the range of values measured in auditory nerve fibers and falls slowly with increasing noise amplitude. At somewhat higher noise levels ($0.1 < \text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}} < 0.2$), the SI falls rapidly with increasing noise level, dropping below the physiological range at about $\text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}} = 0.2$. The synchrony continues to decrease markedly throughout Region II ($0.1 \leq \text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}} < 1.1$). In Region III ($1.1 \leq \text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}} < 1.8$), the SI is roughly constant and comparable in magnitude to the “noise floor,” which is determined by calculating the SI in the absence of any applied modulation.

Fig. 1. (Color online) The responses of an auditory nerve fiber and of the noise-free modified FitzHugh-Nagumo (mFN) model synchronize prominently to a small modulation applied to the pulse amplitude. Period histograms showing the distribution of spike times during a sinusoidal amplitude modulation for the noise-free mFN model (A), an auditory nerve fiber (B), and the mFN model with an applied ongoing noise current whose RMS amplitude equals that of the sinusoidal modulation (C). The right side of the figure shows the synchronization index (SI) (D) and the Lyapunov exponent (λ) of the mFN model (E) as a function of the input noise level (filled circles). The amplitude of the input noise is expressed relative to the amplitude of the modulation (RMS_{noise}/RMS_{mod}). For values of RMS_{noise}/RMS_{mod} less than 0.42, black lines superimposed on the filled circles indicate the standard deviation computed from six sequential time segments. The shaded gray region indicates the range of SI's recorded in the three units studied in Litvak *et al.*⁸ Vertical lines demarcate the three regions discussed in the text. Gray open symbols indicate results with pulse-amplitude jitter but zero additive noise current (open triangles, Euler method; open circles, adaptive NDSolve method). The amplitude of the modulation is 0.5 percent of the carrier pulse height ($m=0.005$). The carrier rate is 5 kHz and the frequency of the applied modulation is 417.67 Hz. Note the phase of the response of the mFN model (A and C) was shifted to account for the propagation delay between the spike generation site and the recording electrode. The histogram of the auditory nerve response (B) was taken from Fig. 4 of Litvak *et al.*⁸

The corresponding value of the Lyapunov exponent (λ), computed from the mFN model, is shown in Fig. 1(E). A comparison of Fig. 1(D) with Fig. 1(E) reveals that the SI is correlated with the Lyapunov exponent. Specifically, in Region I, where the SI is falling slowly with increasing noise, the Lyapunov exponent is roughly constant. In Region II, where the SI falls rapidly, the Lyapunov exponent, though still positive ($\lambda > 0$), is also falling rapidly. Finally, in Region III, where the SI is comparable to the noise floor, the Lyapunov exponent is negative ($\lambda < 0$).

The open symbols in Fig. 1(D) and Fig. 1(E) represent results obtained in the presence of a random jitter applied to the pulse amplitude but with zero ongoing noise [$I_{noise}(t) \equiv 0$]. These results demonstrate that in the absence of intrinsic noise at the spike generator, stimulus jitter

comparable in amplitude to the small applied modulation can reduce the synchrony so that it falls within the range of measured values. [Note that because the random signal which jitters the pulse height is identically equal to zero between the pulses, the power in the jitter signal is much smaller than the ongoing noise signal at the same RMS, and this accounts for the comparatively smaller effect of the jitter on the SI apparent in Fig. 1(D). When the noise is expressed in terms of power rather than RMS amplitude (supplemental Fig. S1¹⁸), the synchrony falls more quickly in response to jitter than it does in response to the ongoing noise. The reason for the greater influence of the jitter, at a given noise power, is that regions of the phase plane where the short-term Lyapunov exponent is large and positive are visited immediately after a stimulus pulse (see Figs. 2, 7A, and 7B of O’Gorman *et al.*¹²), and, hence, random fluctuations that are timed to coincide with the stimulus pulses are maximally amplified.]

4. Discussion and conclusions

This report demonstrates that a dynamically unstable spike generator ($\lambda > 0$) produces realistically high sensitivity to small applied modulations, but only when the noise acting on the spike generator is small. Specifically, when the ratio $\text{RMS}_{\text{noise}}/\text{RMS}_{\text{mod}}$ is greater than about 0.2, the dynamically unstable spike generator is no longer able to account for the high degree of synchronization to the modulator that is observed experimentally.

Although the Lyapunov exponent by definition characterizes the sensitivity to a small perturbation of the initial condition, this report demonstrates that the Lyapunov exponent correlates with the sensitivity to amplitude modulation [Figs. 1(D) and 1(E)]. Specifically, at low noise levels, when the Lyapunov exponent is positive ($\lambda > 0$) and roughly constant, the synchrony to an applied sinusoidal modulation is high and decays relatively gradually with increasing noise, whereas when the Lyapunov exponent falls rapidly at higher noise levels, the synchrony to the modulation similarly declines rapidly. Finally, when the noise is sufficiently intense to abolish dynamical instability ($\lambda < 0$), the synchrony is comparable to the noise floor and no longer depends strongly on the noise level.

The reduction in the Lyapunov exponent with increasing noise intensity apparent in Regions II and III of Fig. 1(E) is consistent with the smoothing-by-noise mechanism described in O’Gorman *et al.*¹² (Fig. 8 and related discussion). Specifically, at stimulus levels that produce low firing rates, the Lyapunov exponent is close to its maximum value. Sufficiently intense noise, however, causes nearby regions of the phase-plane that are associated with smaller Lyapunov exponents to be visited, hence lowering the value of the Lyapunov exponent. The slow fall-off of the Lyapunov exponent at the lowest noise levels (Region I) is consistent with noise-induced sampling of very nearby trajectories that have a Lyapunov exponent that is similar to the noise-free response.

A similar relationship between synchrony and the Lyapunov exponent is produced by pulse jitter acting on an otherwise deterministic spike generator [open symbols; Figs. 1(D) and 1(E), and Fig. S1¹⁸]. The implication of this finding is that stochastic differential equations may not be needed to approximate the main effects of physiological noise on the neural response to pulses, assuming an appropriate level of jitter is applied to the pulse height. Thus, for studying dynamical instability and modulation sensitivity, deterministic models might be more useful than their more complicated stochastic counterparts, such as the stochastic Hodgkin-Huxley model that explicitly represents the random motion of individual gating particles (e.g., Rubinstein *et al.*⁵).

Dynamical instability ($\lambda > 0$) accounts for cases of high modulation sensitivity, but it is also the case that dynamical *stability* indicated by a negative Lyapunov exponent ($\lambda < 0$) can account for cases in which high modulation sensitivity is not observed, as in the “transient” units that failed to respond in a sustained fashion⁷ or in cases in which the discharge rate is much larger than the spontaneous discharge rate of healthy fibers.^{6,20} Supplemental Fig. S2¹⁸ illustrates these two dynamically stable ($\lambda < 0$) response types in the mFN model. One possible explanation for the poor representation of sinusoidal modulations in the auditory cortex²¹ for high rate carriers like those used in the studies by Litvak *et al.* is that the modulations are poorly

represented in the auditory nerve population itself, due to a large fraction of spike generators being dynamically stable. A large population of dynamically stable spike generators might similarly explain why the modulation sensitivity of cochlear implantees is typically poorer at these high carrier rates than at lower carrier rates (e.g., Pfungst *et al.*²²) and why high rate carriers do not consistently provide an advantage in speech perception (e.g., Friesen *et al.*²³) despite the fact that high rate carriers sample the speech waveform more rapidly, and hence provide a more detailed representation of the temporal fluctuations of speech. Further elucidating the relationship between (1) the Lyapunov exponent; (2) the properties of spike generator; and (3) the timing, amplitude, and shape of the stimulating pulses may allow for the systematic optimization, across the neural population, of the representation of information-bearing modulations that are essential to speech perception.

Finally, we speculate on the implication of low-noise, dynamically unstable spike generators for healthy acoustic responses. An unresolved issue in the physiology of acoustic hearing is the mechanism that generates the high sensitivity of primary auditory nerve fibers²⁴ in a way that simultaneously maintains a high degree of statistical independence across nearby fibers whose mechanically driven input is presumably highly correlated.²⁵ Kiang²⁶ listed this co-existence of high sensitivity and statistical independence as an important unexplained phenomenon (“curious oddment”) in auditory nerve physiology. Electrophysiological recordings near the afferent terminal of auditory nerve fibers are difficult to obtain,^{27,28} and existing data do not yet provide a detailed picture of the synaptic input to the auditory nerve’s spike generators. The synaptic input is typically assumed to be noise dominated,^{4,5} yet the ongoing spontaneous activity of healthy fibers is exceedingly sensitive to very small changes in the RMS inner hair cell voltage²⁹ produced by, for example, a low-intensity tone presented in quiet.²⁴ In a previous paper,¹² it was speculated that spike-generator instability produces the statistical independence exhibited by pairs of closely spaced auditory nerve fibers. The results presented here are consistent with this spike-generator-instability hypothesis because they suggest that the noise level internal to the spike generator is low. A low-noise, dynamically unstable spike generator not only can account for statistical independence (Fig. 11 of O’Gorman *et al.*¹²), but also high sensitivity (Fig. 1), whereas Johnson and Kiang’s spike-generator-noise explanation would seem to account only for the statistical independence of similarly driven fibers and not their extraordinary sensitivity, because a large amount of noise acting on the spike generator would abolish sensitivity.

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