

# Sensing Nature's Electric Fields: Ion Channels as Active Elements of Linear Amplification

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**Abstract.** Given the parameters of familiar cellular elements – voltage-sensitive ion channels, carriers, pumps, phospholipid insulators, and electrolytic conductors – is it possible to construct an amplifier whose sensitivity matches the 5 nV/cm threshold found in behavioral experiments on elasmobranch fish? Or, in addition to clever circuitry that uses commonly known elements and principles, do we need something else to understand this sensitivity? The resolution of this question is important not only for studies in sensory biophysics seeking to reveal underlying mechanisms and molecular structures. More generally, it deepens our appreciation of the stochastic nature of inter- and intra-cellular circuits. Here I analyze a simplified circuit involving negative differential resistance of voltage-sensitive ion channels. The analysis establishes an off-equilibrium criterion for amplification, shows that ion channels are the dominant noise sources, and, by minimizing channel noise within the given constraints, demonstrates that generic voltage-sensitive ion channels are likely candidates for the active elements of the linear cellular amplifiers. Finally, I highlight a number of unsolved issues.

## INTRODUCTION

The crucial role of voltage-sensitive ion channels in *non-linear* amplification is well established. These channels provide the macromolecular basis of nerve excitation where over-threshold stimuli give rise to full-sized action potentials. However, their possible involvement in *linear* amplification has never been analyzed quantitatively. Here I explore the feasibility of linear amplification by considering a cellular system with graded positive feedback employing 'generic ion channels' with parameters typical of voltage-sensitive ion channels in excitable membranes, such as gating charge, conductance, and dwell time in the open state.

As explained in the preceding chapter [1], the crucial element of a cellular amplifier is a membrane with a negative differential resistance. Since the pioneering work by Ehrenstein, Lecar, and Nossal [2] it has been known that properly biased voltage-sensitive ion channels behave like a negative resistor. That is, for sufficiently slow and small changes in voltage, the increase in voltage bias decreases the average current through the channels.

Contrary to ion carriers, which transfer ions one by one, channels regulate ion flow by gating large fluxes on a millisecond time scale – fluxes of about  $10^7$  ions per second at 'physiological voltages' of about 0.1 V. This leads to a quantization of charge transfer at approximately  $10^4$  electronic charges per single event of channel opening and, consequently, to a proportionally larger mean-square noise level.

Therefore, in view of the astounding sensitivity of the ampulla's receptor cells [1], relying on ion channels as active elements raises the issue of amplifier noise.

## RESULTS AND DISCUSSION

### Ion Channels as Dominant Noise Sources

Shot noise reveals the random character of charge transfer and is intimately related to the discreteness of charge. When charge is (unidirectionally) transported by independent univalent ions, its low-frequency spectral density is described by the Schottky formula [3]:

$$S_{sh} = 2e\langle I \rangle, \quad (1)$$

where  $e$  is the electron charge and  $\langle I \rangle$  is the average current.

On the other hand, the low-frequency noise of ion channels that follow single-exponential statistics at low open channel probability can be expressed as:

$$S_{ch} = 4Q\langle I \rangle, \quad (2)$$

where  $Q$  is the average charge transported through a channel during its transient open state:

$$Q = h\tau_o(V - E_N). \quad (3)$$

Here,  $h$  is the channel conductance,  $E_N$  is the Nernst potential pertinent to the particular channel,  $V$  is the actual voltage across the membrane, and  $\tau_o$  is the mean dwell time in the open conformation. Although they give similar dependences on average current, Equations (1) and (2) differ greatly in their numerical factors, which state that the noise introduced by ion channels is  $2Q/e$  times larger than the noise expected from ion carriers. The factor 2 reflects the difference in statistical properties of the two processes. In single-electron (or single-ion) shot process elementary events are exactly the same; in noise generation by channels elementary events themselves are random.

To obtain expression (2) we start with the original Machlup formula [4] for the power spectral density,  $S_i(f)$ , of current fluctuations in a two-state Markov process

$$S_i(f) = \frac{4i^2\tau^2}{\tau_o + \tau_c} \frac{1}{1 + (2\pi f\tau)^2}, \quad (4)$$

where  $f$  is frequency,  $i$  is the current in the open channel state,  $\tau_o$  is the mean dwell time in the open state, and  $\tau_c$  is the mean dwell time in the closed state. The 'relaxation time'  $\tau$  is defined by  $\tau = \tau_o\tau_c/(\tau_o + \tau_c)$ . The Lorentzian spectrum described by this equation gives a 'white' (that is, frequency-independent) spectral density for frequencies that are smaller than the inverse of  $2\pi\tau$ . We are interested in the frequency range below 10 Hz [1], while the typical relaxation times for voltage-

sensitive ion channels are on the order of milliseconds. Therefore, we can neglect the last multiplier. The probability  $p_o$  to find the channel in the open state is  $p_o = \tau_o/(\tau_o + \tau_c)$  and the current through the open channel is  $i = h(V - E_N)$ . Substituting these values into Equation (4) and multiplying by the total number of channels,  $N$ , for the low-frequency spectral density of the channel current noise,  $S_I(0)$ , we have

$$S_I(0) = 4N(h(V - E_N))^2 \tau_o p_o (1 - p_o)^2. \quad (5)$$

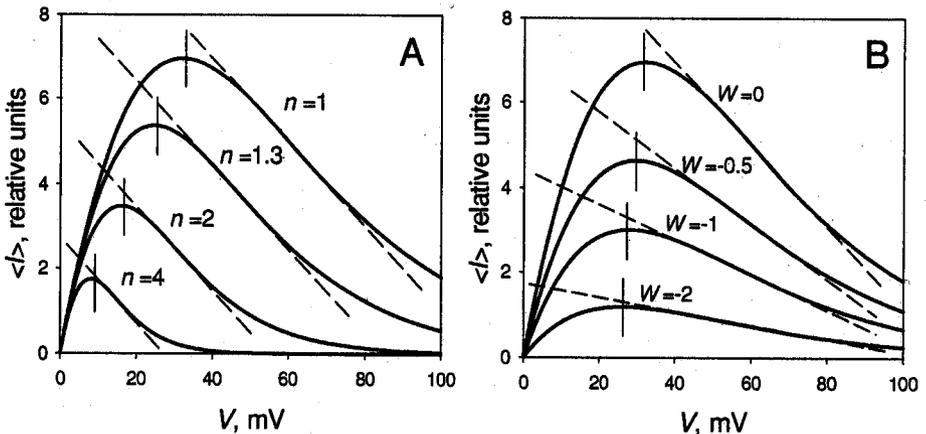
We can leave out the last multiplier when the open channel probability is much smaller than one. Then, by taking into account that the average current through the channels is given by

$$\langle I \rangle = Nhp_o(V - E_N), \quad (6)$$

we arrive to Equation (2). Although the open channel probability does not have to be small to exhibit negative resistance, our analysis of noise minimization (see below) shows that at the optimal noise performance this probability is always smaller than 0.5, so that Equation (2) gives a good order-of-magnitude estimate for the channel noise.

### Off-Equilibrium Criterion for Amplification

From Equation (2) it follows that the mean-square noise level is proportional to the total charge passing through the channel during each single transient opening. Therefore, a simple solution of the noise problem would be to reduce the number of ions per transient channel opening by reducing the voltage bias. To be specific, if it were possible to reduce the normal voltage bias corresponding to  $10^4$  ions per single



**FIGURE 1.** Average current through voltage-sensitive channels as a function of applied voltage at  $E_N = 0$ . **A:** Changing the gating charge,  $n$ , at zero free energy difference,  $W = 0$ , and zero Nernst potential,  $E_N = 0$ , changes the crossover voltage (vertical solid lines) but does not influence the maximal negative slope (interrupted lines). **B:** Changing the free energy difference,  $W$ , at the constant gating charge,  $n = 1$ , and  $E_N = 0$  changes both the crossover voltage and the maximal negative slope.

channel opening by ten thousand times, channel noise would be reduced to the mere level of shot noise. The closer the bias is to equilibrium, the smaller is the channel noise. However, to show negative conductance, ion channels must be kept at a certain voltage distance from equilibrium.

Indeed, the average current through a population of voltage-sensitive ion channels, Equation (6), is proportional to the probability to find a channel in its open state [2]

$$p_o = \left[ 1 + \exp\left(\frac{neV - W}{kT}\right) \right]^{-1}, \tag{7}$$

where  $n$  is the channel gating charge,  $W$  is the difference in free energy between closed and open channel conformations at  $V = 0$ , and  $k$  and  $T$  are the Boltzmann constant and the absolute temperature. Figure 1 gives  $I$ - $V$  curves for differing gating charge (A) and free energy difference (B) at  $E_N = 0$ . To account for differing Nernst potentials, it can be shown that the  $I$ - $V$  curves are exactly the same as in Figure 1B if a new independent variable,  $V - E_N$ , and new free energy,  $W - enE_N$ , are introduced. The voltage  $V^*$  of crossover between positive and negative differential conductance regimes ( $d\langle I \rangle/dV > 0$  or  $< 0$ ) and the maximal negative slope depend on all these parameters.

Therefore, the distance from equilibrium, that is, the difference between the crossover voltage  $V^*$  and the Nernst potential  $E_N$ , is a function of the gating charge and of the combination of the conformational energy difference and the scaled Nernst potential,  $W - enE_N$ . Further analysis shows that whatever this combination is, in order to exhibit negative resistance the channels should be biased in excess of  $kT/ne$ :

$$V^* - E_N > kT/ne. \tag{8}$$

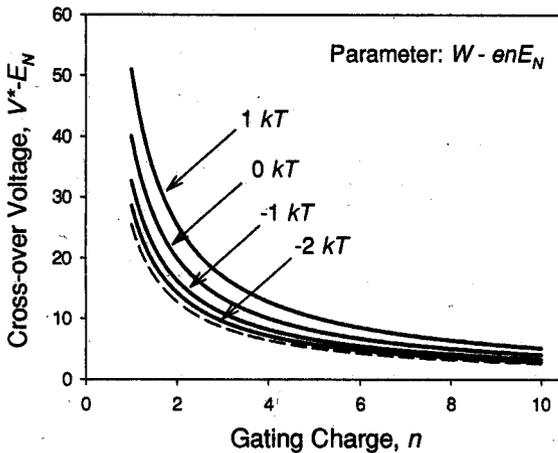


FIGURE 2. Crossover voltage – the voltage bias separating regimes of positive and negative resistance – is a decreasing function of the gating charge. To exhibit negative resistance, ion channels should be driven off equilibrium by at least  $kT/ne$  (interrupted line). This limiting value is approached at large negative combinations  $W - enE_N$ .

Figure 2 shows the dependence of  $V^* - E_N$  on the gating charge for different  $W - neE_N$  combinations. The maximal negative slope occurs for a bias approximately equal to twice the crossover bias.

These off-equilibrium constraints constitute the criterion of amplification and, according to Equation (2), impose limitations on amplifier noise performance.

### Noise Performance of Cellular Amplifier

The minimal equivalent circuit of a cellular amplifier is shown in Figure 3 (see ref. [1] for details). It is a series connection of three elements: canal resistance,  $R_c$ , apical membrane resistance,  $R_a$ , and basal membrane resistance,  $R_b$ . To amplify, the circuit must contain negative resistance. This property is assigned to the channels of the apical membrane. The input voltage,  $\Delta V_{in}$ , acts on the canal opening; the output voltage,  $\Delta V_{out}$ , is applied to the basal membrane.

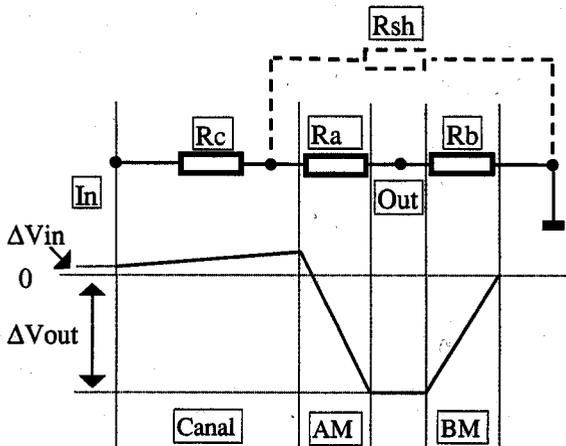


FIGURE 3. The minimal circuit of a voltage amplifier is a series connection of positive resistances of the canal and the basal membrane (BM) and a negative resistance of the apical membrane (AM). The role of the shunt resistance (part of the circuit shown by the interrupted line) is not considered here.

For slow and small signals the system can be linearized and the amplification coefficient can be calculated from Ohm's law as

$$K \equiv \frac{\Delta V_{out}}{\Delta V_{in}} = \frac{R_b}{R_c + R_a^{diff} + R_b}, \quad (9)$$

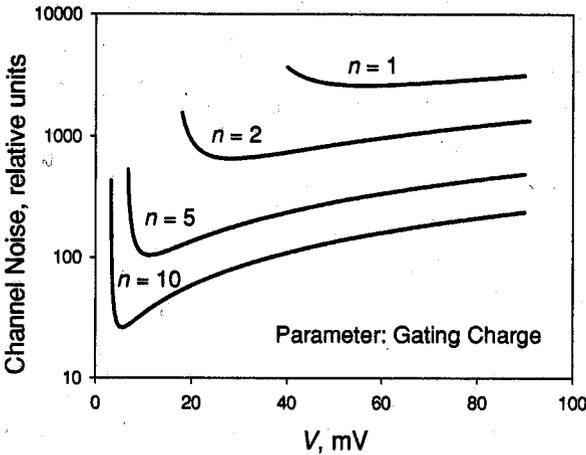
where  $R_a^{diff}$  is the differential resistance of properly biased voltage-sensitive channels of the apical membrane, which can be calculated from Equations (6) and (7). For the sake of simplicity I assume that both the canal and the basal membrane are linear devices so that their differential resistances coincide with their integral resistances  $R_c$  and  $R_b$ . Electrophysiological data [1] and the requirement of high amplification

suggest that in this circuit canal resistance has to be much smaller than the basal membrane resistance,  $R_c \ll R_b$ . Therefore, from Equation (9) it follows that high amplification is achieved when  $R_a^{diff} \cong -R_b$ . This condition allows us to find the total number of voltage-sensitive channels  $N$  as a function of given voltage bias and  $R_b$ .

Taking into account that at low frequencies the voltage and current power spectral densities are related by  $S_V(0) = S_I(0)R^2$ , and using Equation (5) to calculate channel noise, for the equivalent generator of voltage noise of the apical membrane we find

$$S_V(0) \cong 4h\tau_o R_b \frac{(V')^2}{\frac{neV'}{kT} - 1 - \exp\left(\frac{W' - neV'}{kT}\right)} \frac{1}{1 + \exp\left(\frac{W' - neV'}{kT}\right)}. \quad (10)$$

Here,  $V'$  is the distance from the equilibrium voltage, that is, the difference between the actual voltage at the apical membrane and channel Nernst potential,  $V' = V - E_N$ , and  $W'$  is a modified free energy,  $W' = W - enE_N$ .



**FIGURE 4.** Noise of voltage-sensitive ion channels of the apical membrane, Equation (10), as a function of transmembrane voltage at four different gating charge values if  $W = E_N = 0$ . For simplicity,  $\tau_o$  is considered to be constant.

For a high-gain cellular amplifier that adjusts the total number of negative-differential-resistance channels to match the resistance of the basal membrane, the channel-induced noise depends strongly and non-monotonically on voltage (Figure 4). Channel noise at the optimal voltages is reduced proportionally to the square of the gating charge. Thus, the results of the system noise analysis summarized by Equation (10) demonstrate that the channel noise can be minimized by increasing the channel gating charge and by reducing its conductance and dwell time in the open state. Interestingly, varying  $W'$  through  $E_N$  and  $W$  does not reduce noise in the minima. Rather, as our analysis shows, it changes the optimal open probability of the channels

within the limits  $0 < p_o < 0.5$ , consequently changing the 'working point' of the amplifier.

At optimal voltages that give the smallest channel noise, the product of the last two multipliers in Equation (10) is  $4(kT/ne)^2$ . This gives the following expression for the minimal spectral density of the channel-induced voltage noise of the circuit

$$S_V(0) \cong 16h\tau_o R_b (kT/ne)^2. \quad (11)$$

To obtain the root-mean-square noise value one has to account for the effective frequency band

$$\text{Noise}_{rms} \cong \sqrt{S_V(0)\Delta f} \cong 4(kT/ne)\sqrt{h\tau_o R_b \Delta f}. \quad (12)$$

It is interesting to note that Equation (11) can be presented in a form that expresses the channel-generated noise as a product of the basal membrane thermal noise [5],  $4kTR_b$ , and a dimensionless "excess noise factor",  $\theta_e$

$$\theta_e = 4kTh\tau_o/(ne)^2. \quad (13)$$

Plugging in parameters for a generic channel [6]: conductance  $h = 10^{-11}$  S, channel dwell-time in the open state  $\tau_o = 10^{-3}$  s, gating charge  $ne = 10e$ , one finds that  $\theta_e \cong 60$ . For the root-mean-square noise this recalculates into a factor of 8. Therefore, analysis of channel noise of the cellular amplifier permits its minimization to a level that is only an order of magnitude higher than the basic thermal noise. Equation (13) also demonstrates that further reduction of the excess noise factor can be achieved by decreasing the channel conductance and the mean open time and, most significantly, by increasing the gating charge.

## CONCLUSIONS

It is widely appreciated that the ability of organisms to detect weak signals is limited by intrinsic fluctuations occurring at the cellular and sub-cellular levels [7-15]. While the idea per se has enjoyed proper attention and has been investigated by many authors, to my knowledge intrinsic noise has never been analyzed for a cellular system capable of *linear signal amplification*.

Here I have considered sensory signal amplification based on negative resistance provided by voltage-sensitive ion channels. The goal was not to analyze any particular type of channels with elaborate gating characteristics and typical voltage-biases [6]. Rather, playing with all these parameters, I was trying to establish the fundamental constraints on the amplifier noise performance.

The main results of this study are: (i) there exists an off-equilibrium criterion for amplification with voltage-sensitive ion channels; to serve as amplifiers, ion-selective channels must be driven away from their equilibrium potential  $E_N$  by at least  $kT/ne$ , where  $n$  is the channel gating charge; (ii) due to the randomness of channel gating, this off-equilibrium condition sets an inescapable restriction on system noise performance; (iii) however, when properly minimized, the root-mean-square excess noise of channels with generic parameters is only one order of magnitude higher than the basic

limit imposed by the thermal noise. This makes voltage-sensitive ion channels likely candidates for the active elements of signal amplification by electroreceptor cells.

Nevertheless, the transducer issue remains unsolved. Leaving aside the stability problem, the simplified circuit of Figure 3 appears not to suffice in view of noise considerations. The electrophysiological data [1], and the requirement for significant amplification to prepare the weak electrical input signal for synaptic transduction, would call for prohibitively high values of the negative and positive resistances of the apical and basal receptor-cell membranes. However, by taking into account the accessory-cell shunt resistances of the ampulla proper (part of the circuit shown by interrupted lines in Figure 1, equivalent circuits in ref. [1]), one can explore the possibility of implementing a system with sufficiently low resistances to attain the desired low-noise performance. To get a definite answer, we will have to ask the animals in properly designed experiments.

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