Gomes, J-M., Bedard, C., Valtcheva, S., Nelson, M., Khokhlova, V., Pouget, P., Venance, L., Bal, T. and Destexhe, A. Intracellular impedance measurements reveal non-ohmic properties of the extracellular medium around neurons.
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Supplementary material

A Appendix 1: Integrating the global intracellular impedance in models

In this appendix, we relate the impedance $z_e^{(m)}$ in the generalized cable, to the impedance measurements reported in the present paper. In the generalized cable (Bedard and Destexhe, 2013), the extracellular impedance was modeled by parameter $z_e^{(m)}$. Starting from the expression of the extracellular impedance,

$$Z_e = \frac{z_e^{(m)}}{A_{soma}} = \frac{z_e^{(m)}}{4\pi R_{soma}^2} \tag{A.1}$$

and condisering a single-compartment model, according to Eq. 13, we can write

$$z_e^{(m)} \approx A_{soma} Z_e = A_{soma}[Z_{eq}(\omega) - \frac{R_m}{1 + i\omega\tau_m}] \; . \tag{A.2}$$

Thus, by assuming a typical somatic membrane area, we can estimate Z_e, and thus also estimate $z_e^{(m)}$. The other parameters, R_m, τ_m, Z_{eq}, can also be estimated from the present measurements.

B Appendix 2: Establishing the linearity of the system

In this Appendix, we explain how to determine the linearity of the system, in temporal and frequency space.

B.1 Linearity in Fourier frequency space

In the Fourier frequency domain, the experiments show that the ratio $\Delta V(\omega) \; / \; I^g(\omega)$ is a bounded function for variations around the resting membrane potential. In these conditions, a sinusoid in current gives a sinusoid voltage with the same frequency, and with no additional peak in the spectrum. This is true for relatively small variations (a few millivolts), keeping the membrane far away from spike threshold. As shown in Fig. 1D, a combination of sine-wave currents generates a voltage power spectrum with peaks at the same position in frequency, and where no additional peak or harmonics appear. We can say that in this case, the membrane potential of the neuron is linear in Fourier frequency space. This implies that each component of this system in this space is also linear, and in particular, the V-I relation of ion channels in the membrane are linear, because the membrane capacitance is approximately constant (White, 1970). This is an expression of Ohm's law, in which the ion channels are equivalent to a resistor, with no voltage-dependent effects (see Section B.2).

To demonstrate this, we note that the ratio between V and I^g is a continuous bounded function in Fourier frequency space, with the constraint $V(0) = g(\omega, 0) = 0$ for $\omega \neq 0$ (the latter condition means that the neuron is at rest when the transmembrane current is zero). In these conditions, we have

$$V(\omega) = g(\omega, I^g(\omega)) \, . \tag{B.1}$$

We can develop g in Taylor series relative to the current, because the domain of definition of g is necessarily compact in experimental situations. Consequently, we can write:

$$\begin{aligned} \Delta V(\omega) = V(\omega) - V(0) &= \tfrac{\partial g}{\partial I^g}(\omega, 0) I^g(\omega) + \tfrac{1}{2!}\tfrac{\partial^2 g}{\partial I^{g2}}(\omega, 0) I^{g2}(\omega) + \cdots \\ &= b_1(\omega) I^g(\omega) + b_2(\omega) I^{g2}(\omega) + \cdots \, . \end{aligned} \tag{B.2}$$

The impedance is then given by:

$$Z(\omega) = \frac{\Delta V(\omega)}{I^g(\omega)} = b_1(\omega) + b_2(\omega) I^g(\omega) + \cdots \, . \tag{B.3}$$

We can see that, if the spectrum $I(\omega)$ is a discrete Fourier spectrum composed of Dirac delta functions, then $Z(\omega)$ cannot be a bounded function when $b_n \neq 0$ for $n > 1$. Thus, we obtain

$$\Delta V \omega = b_1(\omega) I^g(\omega) \tag{B.4}$$

when the ratio $V(\omega)/I^g(\omega)$ is a bounded function. In other words, the system is necessarily linear in Frequency space because the V-I relation does not depend on the current amplitude. Note that this independence is only true in the absence of voltage-dependent conductances, so it can apply to the subthreshold range, near the resting membrane potential. Such a linear dependence also implies that the position of spectral lines is necessarily identical between $V(\omega)$ and $I^g(\omega)$.

B.2 Linearity of traditional V-I curves

We now address the question of whether the V-I relation of ion channels is linear when these channels are linear in Fourier frequency space, and *vice-versa*.

In general, for a membrane containing ion channels, we have:

$$V = f(I) \, , \tag{B.5}$$

with $V = f(0) = cst$ for zero current (resting membrane potential).

We can approximate V as precise as we want using a polynomial of the current, because V is necessarily a continuous function of this variable since the electric field is finite ($\vec{E} = -\nabla V$). This is by virtue of the Stone-Weierstrass theorem (Rudin, 1976), which states that every continuous function defined over a closed and bounded domain, can be approximated as close as we want by a polynomial. Thus, for a given population of ion channels, we can write

$$\Delta V(t) = V(t) - V(0) = a_1 I + a_2 I^2 + \cdots \, . \tag{B.6}$$

If we express I as $I(t) = e^{i\omega t}$, we obtain

$$\Delta V(t) = a_1 e^{i\omega t} + a_2 e^{2i\omega t} + \cdots \tag{B.7}$$

such that the Fourier transform of the variations of V around $V(0)$ generally gives a spectrum very different from that of the current. Indeed, applying the Fourier transform gives

$$\Delta V(\omega) = a_1\,\delta(\omega' - \omega) + a_2\,\delta(\omega' - 2\omega) + \cdots \tag{B.8}$$

Thus, it is necessary that $\forall n > 1$ we have $a_n = 0$ if we want that the position of the spectral lines of $\Delta V(\omega)$ is the same as that of $I(\omega)$.

Moreover, it is evident that if the function f is linear, then the position of the spectral lines of $\Delta V(\omega)$ is the same as that of $I(\omega)$.

Thus, the linearity in Fourier frequency space implies linearity of the V-I relation of the ion channels activated in the range of V where $V = f(I)$. The linearity in Fourier frequency space constitutes a full condition of linearity, because the V-I relation can be more complex, for example $V = f(\omega, I)$.

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