INTERSPIKE MODEL OF IMPULSE ACTIVITY OF ISOLATED NEURON

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Model of stationary activity of single neurons

The transient function of neuronal generation, which is usually used in formal models of a neuronal net, may be simply obtained by "ramp" protocol in patch-clamp experiment with slow increase of inward current. From records of membrane potential, we calculate the values of interspike intervals (ISI) between peak times of adjacent action potentials (AP) as a function of the mean inward current in this interspike interval (Fig. 1, *a*). Such a set of ISI points may be approximated by rational function with three parameters, that is, the dependence of ISI values Δt on the inward current I_{in} is given experimentally as

$$\Delta t\,(I_{in}) = p_1 + \frac{1}{p_2 \cdot (p_3 + I_{in})},$$

where at constant outer calcium parameters p_1, p_2 and p_3 are also constant.

Change in the outer calcium concentration does not change the type of dependence, but makes effect on parameters p_1 and p_3, but not on p_2. With the first-order dependence of parameters from outer calcium concentration $[Ca]_{out}$, we obtain equation

$$\Delta t(I_{in},[Ca]_{out}) = a_1 + a_2 \cdot [Ca]_{out} + \frac{1}{p_2 \cdot (a_3 - a_4 \cdot [Ca]_{out} + I_{in})},$$

where a_1, a_2, a_3 and a_4 are positive constants.

If inward current I_{in} is sufficiently high (> 30 pA), then the equation can be simplified. In case of $[Ca]_{out}$ = 2 mM and given experimentally typical values a_4 = 2.4 and a_3 = 7, it can be transformed for linear calcium dependence with an ISI error below 0.5 ms in such a way:

$$\Delta t\,(I_{in},[Ca]_{out}) = (a_1 + \frac{1}{p_2 \cdot (a_3 + I_{in})}) + [Ca]_{out} \cdot \left(a_2 + \frac{a_4}{p_2 \cdot (a_3 + I_{in})^2} \right),$$

This equation gives the value of stationary interspike interval, or a period of generation, in relation to outer calcium concentration and inward current, but with accommodation not taken into account.

Model of accommodation of single neuron

Accommodation can be observed in many types of neurons as a gradual decrease of own activity in response to long-lasting depolarizing stimuli. In patch-clamp protocol with flat step of inward current, neuron may generate repetitive action potential peaks, which can be calculated into a set of growing ISI values. We investigate the dependence of ISI on the number of action potentials, because only generation causes the accommodation, rather than the time during which the neuron generates an action potential.

Analysis of accommodative sequence shows that the increase of ISI values is well described by an exponential function with saturation. Type of function does not depend on the input current or an external calcium concentration (Fig. 1B), which affect only the parameter values. After applying the stimulus, the dependence of the ISI values *Δt* on the corresponding AP number *n* has the approximation:

$$\Delta t(n) = T_{stat} - (T_{stat} - T_{init}) \cdot \epsilon^{-\frac{V_A}{T_{stat} - T_{init}} \cdot n},$$

where T_{init} is the first interspike interval immediately after the application of stimulus, T_{stat} is the stationary ISI during long-lasting generation of neuron, V_A is the initial "speed" of accommodation defined as a gradient of the dependence at the initial point.

We assume that the mechanism of accommodation can mainly be attributed to an increase in intracellular concentration of "active" calcium

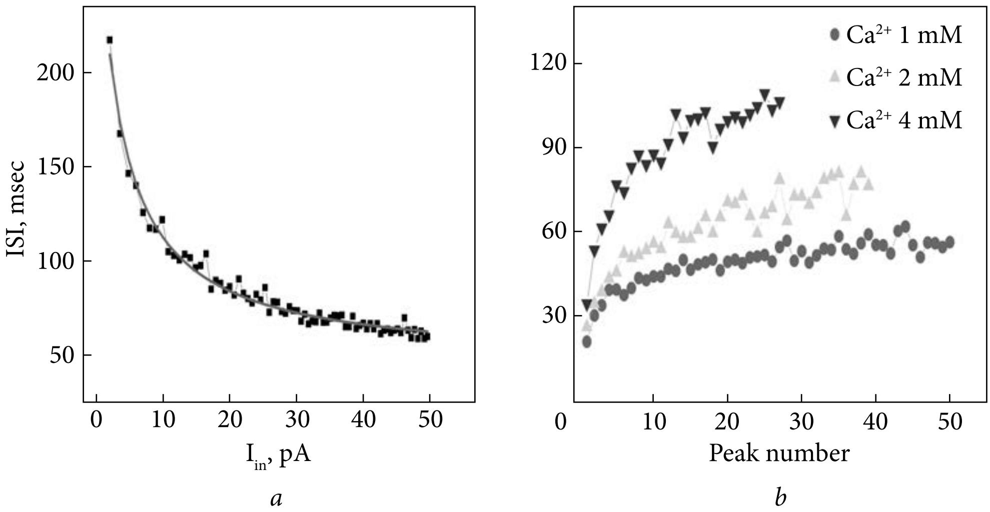

Fig. 1. Interspike interval representation of neuron activity in two protocols: *a* — ISI values decline with increasing inward current, this and other curves in "ramp" protocols can be approximated by rational equation with tree parameters. *b* — nterspike interval curves of accommodating neuron in "step" protocol, when applied outer calcium concentration is 1, 2, and 4 mM. Injected inward current is 60 pA. The dependence retains as an exponential function with saturation

ions, due to the entrance of calcium into the cell during AP generation. Increased calcium delays the generation of next AP, for example, through the activation of Ca-dependent potassium channels or other mechanisms. When generating the AP number n, the accommodation factor $[Ca]_n$ is represented by an active calcium which could influence the generation (or effective amount of intracellular calcium), and is described by the equation of balance:

$$[Ca]_n = [Ca]_{n-1} + A_{Ca} - J_{Ca} \cdot (\Delta t_n - \Delta t_{\min}),$$

where A_{Ca} is the amount of calcium, recruited to the total active calcium inside the cell during AP generation, J_{Ca} is reduction of active calcium per time unit, which can be explained by transport of calcium outside the cell, binding active calcium diffusion in the "inactive" state, mitochondria uptake, and so on, $\Delta t_n = t_n - t_{n-1}$ is the interspike interval between the adjacent action potentials with numbers n-1 and n from the beginning of neuron generation, Δt_{min} is the minimal time of neuron generation, needed to match the physical sense of the balance equation to experimental data.

Values of A_{Ca}, J_{Ca} and Δt_{min} are constants, characteristic for a given neuron with a constant amplitude of the inward current. Δt_{min} can be included into constant A_{Ca} without changing the equation meaning.

When accommodation influences neuron, we suggest the applicability of the dynamic system of equations:

$$\begin{cases} \Delta t = a'_1 + a'_2 \cdot [Ca]_n + \dfrac{1}{p_2 \cdot (a'_3 - a'_4 \cdot [Ca]_n + I_{in})}, \\ [Ca]_n = [Ca]_{n-1} + A_{Ca} - J_{Ca} \cdot \Delta t \end{cases}$$

with the dependence of A_{Ca} from outer calcium.

For given inward stimuli protocol and accommodation constants of given neuron, this system of equations allows to calculate a spikes generation in the form of a set of interspike interval values. This neuronal model differs from conductance-based Hodgkin-Huxley-type models. Instead of reproducing all of the ionic currents, the model reproduces only firing responses.

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