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Physica A 314 (2002) 61–68

PHYSICA A

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Reliability of neural encoding

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Abstract

The reliability with which a neuron is able to create the same firing pattern when presented with the same stimulus is of critical importance to the understanding of neuronal information processing. We show that reliability is closely related to the process of phaselocking. Experimental results for the reliability of neuronal firing in the spinal cord of rat are presented and compared to results from an integrate and fire model.

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PACS: 87.10.e+; 87.19.La; 87.80.Jg; 87.80.Tq; 87.80.Vt

Keywords: Integrate a Fire model (IF-model); Neural encoding; Phase locking; Reliability; Spike timing

Experimental techniques make it possible to measure intracellularly from neurons while injecting a command current through the membrane. This makes it possible to examine the spike time encoding of neurons of the mammalian nervous system. One intriguing question is of the reliability of this neural encoding. In several studies a high variability for subsequent measurements [1,2] has been observed, and the reliability seems highly dependent on the injected signal [3–5]. The reliability of the encoding of information in the nervous system is of high importance to our understanding of how this information is processed.

In this article, we present a series of experiments performed on neurons of the spinal cord of neonatal rats. By comparing with a simple model of neuronal firing we show that high reliability requires that the neuron phaselocks to the incoming signal.

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This also means that for two neurons to be able to communicate reliably, their time constants have to be closely related. For experimental procedures, see Ref. [6].

Whole cell patch clamping was performed on 24 cells with all synaptic activity blocked, and different command currents were injected. The voltage trace $V(t)$ was recorded (Fig. 1a–c, middle) and this was repeated 10 times for each command current $I(t)$. The firing times were detected and could be compared for each of the 10 runs. Plotting the firing times above each other, gives an indication of how reliable the firing is (Fig. 1a–c, top).

Injecting a constant current into a cell without synaptic activity (Fig. 1a), causes the cell to fire with a high variability, i.e., low reliability, even though the mean rate of fire is kept constant. Changing the input to a sinewave current (Fig. 1b), aligns the firing times much better although the cell is unable to fire in a complete one to one correspondence with the input current. However, increasing the current the cell may fire at a one to one correspondence with the input current (Fig. 1c), and the firing times are now almost perfectly aligned indicating a very high reliability.

To explain the phenomenon we consider a version of an Integrate-and-Fire model (see, e.g. Ref. [7]) given by

$$RC \frac{dV(t)}{dt} + V(t) - V_{rest} = RI(t), \quad (1)$$

where R is the resistance and C is the conductance of the cell membrane. When the voltage $V(t)$ reaches a certain value V_{thr} at some time t_0 it is reset to its resting potential V_{rest} , that is

$$\text{if } V(t_0) = V_{thr} \text{ then } V(t_0^+) = V_{rest}.$$

We add a “spike” at the time of firing. This is done by adding a term $V_2(t)$ to the solution of Eq. (1):

$$V_2(t) = B \exp(-(t - t_0)/\gamma)$$

with γ chosen so that $V_2 \sim 0$ after 2 ms and B chosen to be of a realistic size of a spike. For our experiments relevant parameters are $\gamma = 6.25$ ms and $B = 90$ mV.

For a constant current $I(t) = I_0$ Eq. (1) has the solution

$$V(t) = RI_0(1 - e^{-(t-t_0)/\tau}) + V_{rest} \quad (2)$$

with $\tau = RC$ and $V(t_0) = V_{rest}$. The voltage charges up towards a value $RI_0 + V_{rest}$ and it approaches this value asymptotically if it is below the threshold V_{thr} . For a nonconstant current $I(t) = A \sin(2\pi vt)$, we choose to reset to a value $V(t_0) = V_{thr} - A\beta R$ and have the solution

$$V(t) = A\beta R[\sin(2\pi vt - \phi) - e^{-(t-t_0)/\tau}] + V_{rest} \quad (3)$$

with

$$\beta = \frac{1}{\sqrt{1 + (2\pi v\tau)^2}} \quad (4)$$

Fig. 1. (a–c) Experimental measurements from an interneuron in the spinal cord of neonatal rat; (d–f) theoretical simulations. At the bottom of each figure is the command current, center is the measured voltage and the top of the figure shows the firing times for each subsequent stimulation; (a and d) constant injected current $I_0 = 75$ pA; (b and e) injected sinewave current $I = A \sin(2\pi\nu t)$ with $A = 75$ pA and $\nu = 3.125$ Hz; (c and f) injected sinewave current $I = A \sin(2\pi\nu t)$ with $A = 85$ pA and $\nu = 3.125$ Hz. Stimulating frequencies were between 0.3 and 18.75 Hz and the current was between 10 and 200 pA.

Fig. 2. The effect of the lowpass filter on the amplitude of the command current, from two cells. Higher frequencies are attenuated, while lower frequencies are unchanged. The cut-off frequency and its corresponding value are marked by the vertical and horizontal lines. The timeconstant for these cells were $\tau = RC = 77$ ms (lower) and $\tau = RC = 50$ ms (upper). The time constant, τ was generally between 50 and 100 ms, while the resistance was between 200 and 500 M Ω .

and

$$\phi = \arctan(2\pi\nu\tau) \quad (5)$$

Eq. (3) is just a sinewave with a phaseshift, minus a transient.

Before we can use the model we need to establish the parameters of the system. The resting potential V_{rest} can be measured directly and the threshold for firing, V_{thr} can be found by depolarizing the cell slowly until firing begins. However in order to find the resistance R and the conductance C another technique was used.

It is well known that the cell membrane of a neuron in many ways acts like a lowpass filter, attenuating the higher frequencies (see, e.g., Ref. [8]). This is also seen from Fig. 2. To test this we injected a command current $I(t)$ into one cell, with a constant amplitude but an increasing frequency. After each period of the sinewave, the frequency was increased by 10%. By measuring the resulting amplitude of the voltage response $V_{amp} = A\beta R$, we could get an estimate of the lowpass effect. For the low frequencies there is no attenuation of the amplitude, and the resulting amplitude V_{amp} and resistance R is simply given by Ohms law

$$V_{amp} = RA \quad (\nu \rightarrow 0). \quad (6)$$

The resulting amplitude, V_{amp} , obtained at high frequencies, was divided by this value to give the attenuation of the lowpass effect β , plotted in Fig. 2 along with the theoretical curve given by Eq. (4).

The cut-off frequency, defined as the frequency for which $\beta^2 = 1/2$, i.e., where $2\pi\nu\tau = 1$, is used to determine the time constant $\tau = RC$ of the system. Note that the experimental values lie above the theoretical curve frequencies above 10 Hz. This is

probably due to a frequency dependency of the time constant, a feature we have chosen not to include in our simple model.

The time varying input causes the unit to be unable to fire in part of the period [9,10]. This creates large areas in parameter space of phaselocking [11,12]. Consider the rotation number N defined as the mean rate of firing ψ divided by the stimulating frequency ν .

$$N = \psi/\nu. \quad (7)$$

As the system is now in a phase locked situation, changing the frequency ν or the amplitude A of stimulation will not necessarily change the rotation number.

It can be shown that the noiseless system is in a situation where there is phaselocking for almost all parameters (except for a set of Lebesgue measure zero [13]). The Poincaré mapping, i.e., the potential of the model, $V(t + 1/\nu)$, as a function of the potential one period of the stimulation frequency earlier, $V(t)$, has a gap.

Fig. 3 shows the phase plot A and ν . The large areas of constant rotation number are termed Arnold tongues. These areas are robust for minor changes in parameters. Changing the amplitude A of the incoming signal slightly will not change the type of phaselocking, if the neuron is firing in the middle of one of the large tongues.

Real neurons are parts of a biological system influenced by a myriad of external factors causing a certain instability of the parameters of the system, here just modeled as noise. This instability will move the point in phase space about causing it to drift around some average value. If situated deep within a tongue this will not change the firing pattern, whereas a position close to the border of a tongue will cause the cell to fire irregularly.

We can therefore establish a connection between the concept of reliability and phaselocking. When there is a clear phaselocking in a large area of the phase plot (e.g. $N=1$ in Fig. 3b), the system should fire with a high reliability. When the phaselocking is of a rotation number with a smaller area in the phase plot (e.g. $N=3/2$), this will result in a low reliability. This insight can be used to compare the model to the experimental data and explain the changes in reliability we have seen.

To make a direct comparison between the model and the experimental results, a noise term is added to the voltage output V_{noise} , a noise term composed of gaussian distributed noise with zero mean and a standard deviation of $\sigma=0.9$ mV. The standard deviation was chosen by fitting the numerical results to the experimental data from one neuron, see Fig. 3a.

Using the same stimulus on the model as in the experimental setup, creates theoretical outputs very similar to those found experimentally (Fig. 1d–f). The constant current leads to the lowest reliability (Fig. 1d), the nonconstant current yields a better reliability (Fig. 1e) and the reliability is at its highest for a 1:1 phaselocking (Fig. 1f).

Now we introduce a quantitative measure for the reliability P (see also Ref. [6]), by making a histogram of the firing times with bin size 3 ms and define the reliability P as the total number of firings in bins containing more than 1 firing divided by the sum of all firings. In this way a reliability of 0 will mean that the cell never fired twice in the same timebin and a reliability of 1 means that every firing occurred within the same timebin as at least one other; i.e., no bins contain only one firing.

Fig. 3. (a) Reliability (upper) and rotation number (lower) as a function of the amplitude of the resulting voltage $A\beta R$ for one cell normalized by the difference between the threshold and the resting potential. ($V_{rest} = -40$ mV, $V_{thr} = -28$ mV, $RC = 50$ ms, $R = 215$ M Ω). The theoretical values are shown as lines and the experimental values are points (x/+). The noise level in the system was chosen by fitting the form of the theoretical curve for the rotation numbers to the experimental values. (b) Phaseplot of the model with noise. The frequency ν has been normalized with the timeconstant τ . The areas of integer rotation number have been grayshaded and the value has been indicated. The largest area is for $N = 1$. The line indicates the cut through the figure followed in figure (a). The experimental values of $\nu\tau$ was between 0.05 and 0.8.

We have done a series of experiments where we have varied the amplitude A of the input sinewave for a fixed frequency and measured the reliability for each set of parameters. This corresponds to making a horizontal cut in the phase plane (line in Fig. 3b). The resulting experimental and numerical values are shown in Fig. 3a.

As the amplitude increases, the numerical reliability (the line) also increases while the rotation number reaches a plateau at the 1 to 1 phaselocking. Increasing the

Fig. 4. Reliability as a function of the rotation number for one cell (same as Fig. 3(a)). Experimental data are shown as points (+) while the simulation is the dotted line. The inset shows all the experimental data for 7 different neurons stimulated with frequencies ν between 1.25 and 18.75 Hz and amplitudes A between 20 and 135 pA.

amplitude further causes the rotation number to increase to 2. The reliability drops as the rotation number is between integer values and increases again as the rotation number reaches 2.

This seems to fit very well with the experimental results (+) although the increase in reliability as the rotation number reaches 2 is hard to see in the experimental values due to lack of data in this area. It does however seem to confirm the claim that a high value of reliability P is found for rotation numbers $N = 1$ and 2.

Another way of showing this is by plotting the reliability as a function of the rotation number. This is shown in Fig. 4, for the same cell as in Fig. 3a. It is clear to see that there is a peak at $N = 1$ but the peak at $N = 2$ is only visible for the numerical data.

In the inset of Fig. 4 all our experimental data from different cells and different command currents are put into the same plot. It is here quite easy to see that there is a peak at $N = 1$ and 2, signifying that the 1:1 and 2:1 phaselocking are necessary to create the highest levels of reliability.

Our results provide evidence for a strong connection between phaselocking and the reliability of firing. This acts as a stabilizer as opposed to the noise of the system and enables the cell to fire with a very low variability. Phaselocking ensures that the signals can be transmitted reliably. This also sets some natural boundaries on the signals used for transmitting information of the spinal cord, especially in combination with the lowpass effect which attenuates the higher frequencies. For a further discussion of this subject see Ref. [6].

This phaselocking requirement for reliable signal transmission, depends on the time-constant of the cell, which can vary drastically between different types of neurons, severely influencing the signal transmission between different celltypes. Signal transmission in cortical neurons would therefore be much faster, and directly incompatible, with the signals transmitted in neurons of the spinal cord.

The connectivity between cells at the border between these areas would therefore have to take this into account, by dynamically changing the firing frequencies to ensure the reliable transfer of the signal.

Although the present study uses an analytical tractable integrate and fire model, we expect similar results should be found for more delicate neuronal models which use a recharging membrane potential such as the Hodgkin–Huxley model [14].

PA acknowledges support from CORE.

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