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Complex Response to Periodic Inhibition in Simple and Detailed Neuronal Models

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Constant current injection with superimposed periodic inhibition gives rise to phase locking as well as chaotic activity in rat neocortical neurons. Here we compare the behavior of a leaky integrate-and-fire neural model with that of a biophysically realistic model of the rat neuron to determine which membrane properties influence the response to such stimuli. We find that only the biophysical model with voltage-sensitive conductances can produce chaotic behavior.

1 Introduction

We recently reported on the spike patterns of periodically stimulated neurons from rat neocortical slices (Schindler, Bernasconi, Stoop, Goodman, & Douglas, 1997a). Our motivation was to analyze factors that influence the firing patterns of single cells, because of their presumed role in neural information processing (Rieke, Warland, de Ruyter van Steveninck, & Bialek, 1997). In the experiments, we first injected constant current to regularly spiking layer V pyramidal cells and determined the period of the unperturbed activity. We then perturbed the system by superimposing periodic inhibitory pulses and studied the spiking behavior of the cell as a function of the parameter Ω, the ratio between the period of the perturbation and that of the unperturbed activity. Depending on the choice of Ω, regular entrained spike patterns or irregular behavior were observed. The two regimes corresponded to phase-locked and chaotic orbits produced by iteration of a Poincaré map (Guevara, Glass, & Shrier, 1981; Alligood, Sauer, & Yorke, 1997) derived from the experiments that can be used to predict the spiking patterns of the cell.

In this article we explore the cellular mechanisms that could have an influence on the temporal features of the spiking activity under the described stimulation paradigm. We consider first a simple neuronal model, the leaky integrate-and-fire (I&F) unit, and demonstrate its limitations. We then use simulations of a more detailed biophysical model of the rat cell to investigate the factors determining the particular shape of the experimental response to

inhibition and discuss the relevance of voltage-sensitive conductances for the regularity of the induced spike patterns.

2 I&F Unit Driven with Constant Current and Periodic Inhibition

One of the simplest abstractions from the dynamics of a biological spiking cell is the leaky I&F neuron. In spite of its simplicity, this model has been shown to capture many relevant aspects of the temporal dynamics of cortical cells (Knight, 1972; Marsalek, Koch, & Maunsell, 1997).

Under the stimulation of an input current $I(t)$, the dynamics of the subthreshold membrane potential $V(t)$ of an I&F model is governed by (Knight, 1972; Marsalek et al., 1997)

$$\dot{V}(t) = -\frac{V(t)}{\tau} + \frac{I(t)}{C}, \tag{2.1}$$

where C is the membrane capacitance (in the following $C = 1$ will be assumed) and τ the passive time constant. As soon as a voltage threshold θ is reached, a spike is emitted, and thereafter the voltage is clamped to 0 for a refractory period t_r.

If an I&F unit is stimulated with a sufficiently large constant current $I(t) = I_0 > \theta/\tau$, it fires regularly. Integration of equation 2.1 gives the period (time to threshold):

$$T_0 = t_r - \tau \log\left(1 - \frac{\theta}{I_0 \tau}\right).$$

A brief stimulus delivered at time t, at phase $\phi = t/T_0 \pmod 1$, perturbs these orbits (limit cycle), leading to an interspike interval of length $T(\phi)$. The function $T(\phi)/T_0$ is called the phase-response curve (PRC) of the system. In the experimental situation, the PRC could be determined by applying stimuli at various places in the interspike interval and measuring the length of the perturbed interval. For the I&F unit stimulated with a single brief current pulse that displaces the membrane potential by q units, the PRC can be calculated explicitly. Equation 2.1 has to be integrated from 0 to t to calculate the voltage after stimulation; then the additional time required to reach threshold from that voltage can be determined. In the case that the pulse is inhibitory, we have

$$T(\phi)/T_0 = \begin{cases} 1 & \text{if } \phi \in [0, t_r/T_0] \\ \phi + \frac{\tau}{T_0} \log\left(\frac{-q - I_0 \tau e^{-\frac{\phi T_0 - t_r}{\tau}}}{\theta - I_0 \tau}\right) & \text{if } \phi \in]t_r/T_0, 1[\end{cases}. \tag{2.2}$$

Since the return to the limit cycle is immediate after the application of the stimulus, we can now use the PRC to infer the effect of periodic inhibition on the sequence of phases $\{\phi_i\}_{i \in \mathbf{N}}$ produced by the system. For a given

stimulation period t_s, that is, for the corresponding value of the control parameter $\Omega = t_s/T_0$, we have (Guevara et al., 1981; Schindler et al., 1997a):

$$\phi_{i+1} = F(\phi_i) = \phi_i + \Omega - \frac{T(\phi_i)}{T_0} \quad (\mathrm{mod}1). \tag{2.3}$$

The function $F(\phi_i)$ is called the Poincaré map (or the first return map) of the system and expresses the new phase of stimulation as a function of the preceding one. One of the main conclusions from the experiments was that for some values of Ω, the cells and the stimulating oscillator were phase locked, whereas for other values, the spike patterns were chaotic (Schindler et al., 1997a). A necessary condition for chaotic behavior to occur is that the one-dimensional Poincaré map describing the dynamics be noninjective. If we consider trajectories for which the limit cycle exists ($I\tau > \theta$), the derivative with respect to ϕ of the Poincaré map will assume only positive values. As a consequence, the map is monotonic over the entire cycle (see Figure 1A). Chaotic behavior is therefore excluded for the leaky I&F unit. [1]

The I&F neuron has passive membrane properties but lacks the active conductances that dominate the dynamics of the neuronal membrane potential of real cells during spiking activity, and that could contribute to more complex behaviors. We therefore analyzed a biophysically more sophisticated neuronal model in search of cellular properties explaining firing patterns going beyond the dynamics of the I&F unit.

3 Periodic Inhibition of a Biophysical Model of a Regularly Spiking Neocortical Cell

We performed computer simulations of a biologically realistic cell using NEURON (Hines, 1989). In order to mimic the behavior of the particular cells analyzed in the experiments, we modified the model of a simplified neocortical pyramidal cell described in the literature (Bernander, 1993; Rhodes & Gray, 1994). In particular we had to tune several kinetic parameters of the eight active currents of the model and replace one of them to obtain a good match to the interspike trajectory of a regularly discharging neuron. [2]

[1] It can be shown that the Poincaré map remains injective also for a periodic stimulus constituted by sequences $\{p_i\}$ of inhibitory δ pulses, which abruptly discharge the membrane of finite amounts $\{q_i\}$. A similar set of pulses can virtually approximate any kind of inhibitory postsynaptic potential. The only condition for consistency is that the sequence of pulse cannot extend beyond the perturbed period (which is guaranteed, for instance, if each of the pulses is applied at a membrane potential lower than that of the first pulse), or, alternatively, that an intervening spike truncates the sequence of pulses (as it is observed in the experiments). The proof of this proposition, based on the same reasoning applied to the case of the single pulse, is obtained by induction on the number of pulses. It is also easy to show that with excitatory pulses, the system can display only periodic behavior.

[2] The active currents of the model with the respective conductance densities were: I_{na} (fast sodium current), $G_{na} = 500$ mS/cm^2; I_{dr} (delayed rectifier K^+ current), $G_{dr} =$

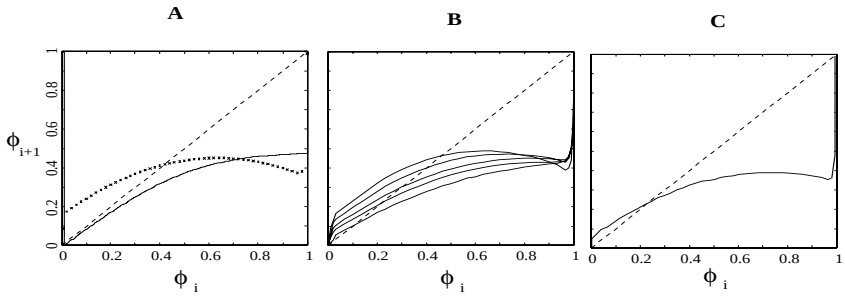

Figure 1: (A) Poincaré map of the I&F neuron (solid line, obtained from equation 2.2) and of a neocortical rat cell (crosses) from the experiments. The parameters of the I&F unit were: $\tau = 10$ ms, $\theta = 1$, $I = 0.103$, $q = -0.06$, $\Omega = 0$. The map is monotonic over the entire cycle. The map of the experimental cell (which was stimulated with DC of 0.7 nA and pulses of 5 ms and -1.5 nA and had an unperturbed interspike interval of 81 ms) was fitted from experimental data. (B) Poincaré maps (obtained with inhibitory pulses of -1.5 nA and 5 ms; $\Omega = 0$) of the biophysical model of the experimental neocortical cell. To obtain the different curves, we stepwise decreased the M-current conductance density from G_m = 2.6 to 1.2 mS/cm^2. The input currents are adjusted (from 0.5 to 0.7 nA) to maintain the unperturbed periods between 83 and 85 ms. The curve with the largest downward curvature is the one with the intact M-current. With decreasing conductance density, the maps become less curved. (C) Poincaré map obtained with synaptic stimulation that reproduced experimental data. The dynamics of the conductance was described by the α-like function $g(t) = g_{\max}(t/\tau)\exp(-(t-\tau)/\tau)$ with maximal value $g_{\max} = 1.5$ pA and time constant τ = 4 ms. The reversal potential of the synapse was -95 mV.

Since the spiking patterns elicited by a periodic stimulus can be predicted by the Poincaré map (see Figure 1B), we examined the factors influencing its properties. The map was relatively insensitive to manipulation of the fast voltage-dependent currents such as those of the spike mechanism, provided that a robust 1 ms action potential was present. The features of the interspike trajectory are important to the Poincaré map, and so modifications of the currents underlying the medium-duration afterhyperpolarization (Schwindt et al., 1988) had most interesting effects.

110 mS/cm^2; I_a (A-type current, taken from Rhodes & Gray, 1994), $G_a = 3$ mS/cm^2; I_m (M-type current), $G_m = 2.4$ mS/cm^2; I_{ahp} (Ca^{++}-dependent K^+ current), $G_{ahp} = 80$ mS/cm^2; I_{ca} (high-threshold calcium current), $G_{ca} = 3.2$ mS/cm^2; $I_{Na,p}$ (persistent Na^+ current), $G_{Na,p} = 1$ mS/cm^2; mS/cm^2; I_{ar} (anomalous rectifier current), $G_{ar} = 1$ mS/cm^2. Further details of the simulation are given in Schindler et al. (1997a).

A distinctive feature of the experimental rat cell was the fact that an inhibitory pulse applied shortly after a spike reduced the length of the interspike interval. This is in agreement with some previous simulations performed by Lytton and Sejnowski (1991) and had important consequences for the behavior of the system. The shortening of the perturbed interval on early stimulation was related to the partial deactivation of slow K^+ conductances by the hyperpolarizing pulse. As a consequence, the K^+ outward current decreased enough to allow the cell to reach threshold earlier. This effect was mainly related to the dynamics of the M-current, so the presence of this particular active conductance conferred the characteristic shape to the PRC and the Poincaré map. The shortening of the interspike interval on early stimulation produced the high initial slope, bringing the map above the identity line. The steepest lengthening of the interspike interval for a pulse applied late in the cycle contributed to the presence of the negative slope of the return map in the second half of the interval.

The role of the M-current was also critical to the expression of chaotic spike patterns. In general, a smaller M-type conductance was associated with a less curved Poincaré map. When we decreased the conductance by more than about 25%, we obtained a monotonic Poincaré map, which lacks a property necessary for chaotic behavior. This result arises for two reasons. First, there was no longer a significant shortening of the perturbed interval; second, the maximal lengthening of the interval decreased slightly, and so did the downward bending of the Poincaré map. These changes are partly due to the shorter duration of the unperturbed period T_0 caused by the decreased total outward current. In order to operate in the same range of frequencies as in the case of intact M-current, we compensated for the missing K^+ conductance by increasing the A-type conductance or the calcium-dependent K^+ conductance or, alternatively, by lowering the input current. Figure 1B shows the effect of a progressive reduction of the conductance of the M-current and a parallel adjustment of the input current to maintain a constant unperturbed interval. None of the described manipulations restored a noninjective Poincaré map. In agreement with the experiments, the original, nonmonotonic map was associated with positive Lyapunov exponents, that is, with unstable, chaotic orbits (Alligood et al., 1997; Peinke, Parisi, Roessler, & Stoop, 1992). Figure 2 illustrates two examples of the behavior of the model for parameters expected to be associated with regular and irregular firing. The manipulation of parameters of other types of active currents (e.g., of kinetic parameters of I_{ahp}, I_a, or I_{ca}), under the constraint of a realistic behavior of the cell and of a physiological choice of the parameters of the currents, could not reverse the effect of a decreased M-type conductance on the return map. In fact, those parameters affected the overall behavior of the neuron (shape of the action potential or of the interspike trajectory, adaptation features, presence of bursts, etc.) more drastically than they affected the Poincaré map.

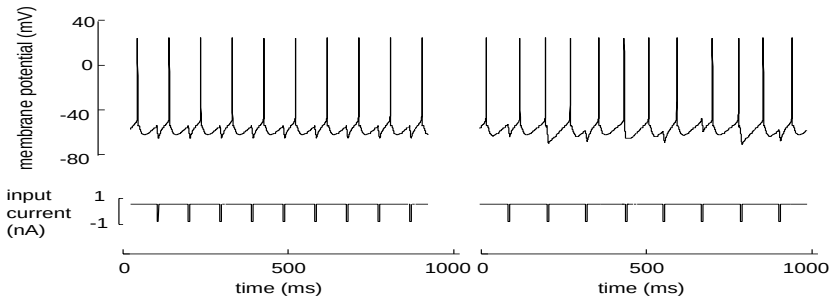

Figure 2: Traces of the membrane potential for two values of the control parameter Ω. The parameters of the simulation are those of the model with intact M-current of Figure 1B. In the left plot, $\Omega = 0.2$ (mod 1) produces phase-locked trajectories. On the right, periodic stimulation with $\Omega = 0.5$ induces irregular spiking patterns. The transition between different firing modes can be described by bifurcations produced by the Poincaré map, which belongs to the class of the one-dimensional circle maps (Stoop et al., 1998).

The effect of the inhibitory input was most prominent when the output frequency of the cell was around 10 to 20 Hz. At these frequencies, perturbations interfere incisively with the dynamics of the M-current, which has an (activation) time constant of 40 ms. There must be a match between firing frequency and kinetic parameters of the current for the mechanism to be effective. However, although the role of the M-current is central in the cases considered, other currents (in particular voltage sensitive currents such as the A-current) also contribute to the shaping of the Poincaré map. The effect of channels with different kinetics might be prevalent at other firing regimes or in other classes of cells with different dynamical properties (e.g, fast spiking cells or intrinsically bursting cells).

To explore more realistic types of inhibition than rectangular current pulses, we also investigated the effect of simulated inhibitory synapses (see Figure 1C). The values of the synaptic dynamics were obtained from experiments in which the afferents to the impaled cell were stimulated with a bipolar electrode, while excitatory synapses were blocked pharmacologically (Schindler et al., 1997b). The effect of this relatively long-lasting inhibition was a reduced shortening of the interspike interval on early stimulation and a larger lengthening on late stimulation. Nevertheless, in agreement with the experiments, the obtained Poincaré map was noninjective. As already noted, the map of an I&F unit stimulated in a similar way does not have this property.

4 Conclusions

Due to its simplicity, the leaky integrate-and-fire neuron is commonly used for large-scale simulations of neural systems and hardware implementations. It is therefore important to know which biological phenomena its dynamics can capture and which it cannot. We have shown that with periodic inhibition, leaky integrate-and-fire neurons cannot generate chaotic spike patterns, whereas more biophysically realistic models with voltage-sensitive conductances have a substantially enriched dynamics, which permit chaotic spike patterns. In particular, the irregular discharge of pyramidal neurons depends crucially on outward currents of a medium duration such as the M-current. Because chaos can mediate between different periodicities, the ability of a neuron to express such activity may be important in the context of synchronization and desynchronization of discharge in biological neural networks. This aspect is under investigation (Stoop et al., 1998).

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