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CHAPTER 11

Drivers and modulators from push-pull and balanced synaptic input

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Abstract: In 1998, Sherman and Guillery proposed that there are two types of inputs to cortical neurons; drivers and modulators. These two forms of input are required to explain how, for example, sensory driven responses are controlled and modified by attention and other internally generated gating signals. One might imagine that driver signals are carried by fast ionotropic receptors, whereas modulators correspond to slower metabotropic receptors. Instead, we have proposed a novel mechanism by which both driver and modulator inputs could be carried by transmission through the same types of ionotropic receptors. In this scheme, the distinction between driver and modulator inputs is functional and changeable rather than anatomical and fixed. Driver inputs are carried by excitation and inhibition acting in a push-pull manner. This means that increases in excitation are accompanied by decreases in inhibition and vice versa. Modulators correspond to excitation and inhibition that covary so that they increase or decrease together. Theoretical and experimental work has shown that such an arrangement modulates the gain of a neuron, rather than driving it to respond. Constructing drivers and modulators in this manner allows individual excitatory synaptic inputs to play either role, and indeed to switch between roles, depending on how they are linked with inhibition.

Introduction

Cognitive processing often relies on one region of the brain controlling and modulating the actions of another. One mechanism for such control is gain modulation, a prominent feature of neural activity recorded in behaving animals (Salinas and Thier, 2000). Gain modulation is a multiplicative (or divisive) scaling effect on neuronal responses, equivalent to a change in slope of the firing rate versus current (f-I) curve, that is distinct from the additive (or subtractive) shifts in the firing rate produced by pure excitation or inhibition acting as a driving input (Gabbiani et al., 1994; Holt and Koch, 1997).

The distinction between driver and modulator inputs (Sherman and Guillery, 1998), is illustrated in Fig. 1. Figure 1A shows the well-known effect of increasing either the excitatory or inhibitory component of the total synaptic input to a model neuron, which is a left- or rightward shift of the f-I curve. This additive or subtractive effect of excitation or inhibition corresponds to a driving input. In contrast, Fig. 1B illustrates a multiplicative alteration in the f-I curve (the curves are approximate multiples of each other), the signature characteristic of gain modulation. It is important to appreciate that gain modulation is a change in the sensitivity of a neuron, similar to adjusting the volume control on an amplifier, not simply an additive enhancement or subtractive

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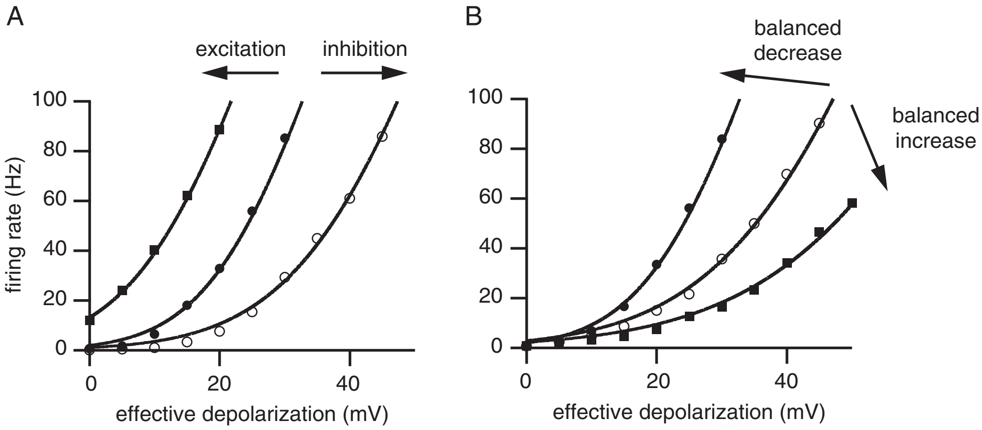

Fig. 1. Effects of excitatory and inhibitory input on the firing rate versus input current (f-I) curve of an integrate and fire model neuron. Input current is plotted in terms of the equivalent amount of depolarization produced in the resting neuron with spiking blocked, a convenient measure. (A) The effect of increased excitation is a leftward shift of the f-I curve, while increased inhibition produces a rightward shift. (B) Modifying levels of both excitation and inhibition in a balanced manner produces a multiplicative enhancement (reduced excitation and inhibition) or a divisive reduction (increased excitation and inhibition) in the firing rate. In both figures, dots are simulation results and solid curves are a fit using Eq. 3.

diminution of its response. This change of sensitivity is the key to its usefulness as a mechanism for switching and modifying neural circuits.

Gain modulation appears to be a primary mechanism by which cortical neurons non-linearly combine input signals. It shows up in a wide range of contexts including the gaze-direction dependence of visual neurons in posterior parietal cortex (Andersen and Mountcastle, 1983; Andersen et al., 1985, Murphy and Miller, 2003), the effects of attention on visually responsive neurons (Connor et al., 1996, 1997; McAdams and Maunsell, 1999a,b; Treue and Martínez-Trujillo, 1999), auditory processing in birds (Peña and Konishi, 2001), and visual escape responses in locusts (Gabbiani et al., 1999). Gain modulation is seen in early visual processing (Weyland and Malpeli, 1993; Pouget and Sejnowski, 1994, 1997; Trotter and Celebrini, 1999), and it has been proposed as a mechanism for generating a variety of non-classical receptive field effects for neurons in primary visual cortex (Heeger, 1992, 1993; Carandini and Heeger, 1994; Carrandini et al., 1997; Tolhurst and Heeger, 1997) and for the decorrelation of natural images (Simoncelli and Schwartz, 1999; Schwartz and Simoncelli, 2001a,b). The neural computations required for coordinate transformations during reaching tasks (Zipser and Andersen, 1988; Salinas and Abbott, 1995; Pouget and Sejnowski, 1997) and for object recognition (Salinas and Abbott, 1997) also appear to involve gain modulation.

Although the importance of gain modulation (and multiplicative interactions in general) in neurons has been appreciated for many years (Mel and Koch, 1990; Koch and Poggio, 1992; Pouget et al., 1993, Pouget and Sejnowski, 1994, 1997; Salinas and Abbott, 1995, 1997), it has proven difficult to uncover a realistic biophysical mechanism by which it can occur. (It is important to note that, despite comments in the literature to the contrary, divisive inhibition of neuronal responses cannot arise from so called shunting inhibition. As has been shown both theoretically (Gabbiani et al., 1994; Holt and Koch, 1997) and experimentally (Chance et al., 2002), inhibition has the same subtractive effect on firing rates whether it is of the shunting or hyperpolarizing variety. Thus, shunting inhibition does not provide a plausible mechanism for neuronal gain modulation.) In particular, it has not been known how restrictive gain modulation might be; for example, whether it requires relatively non-specific neuromodulatory systems (Marder and Calabrese, 1996), relies on slow metabotropic receptors (Sherman and Guillery, 1998), or requires blocks of neurons to be modulated together (Salinas and Abbott, 1996; Hahnloser et al., 2000). Despite a number of attempts (Srinivasan and Bernard, 1976; Koch and Ullman, 1985; Koch and Poggio, 1992; Mel, 1993; Salinas and Abbott, 1996; Koch, 1998; Hahnloser et al., 2000), no really satisfactory proposal existed until recently (Doiron et al., 2001; Chance et al., 2002; Prescott and De Koninck, 2003; Mitchell and Silver, 2003).

Gain modulation from balanced synaptic input

Neurons typically receive a massive barrage of excitatory and inhibitory synaptic input. The functional role of this noisy background activity has been a long-standing puzzle in neuroscience. Background activity dramatically affects neuronal response properties (Bernander et al., 1991; Douglass et al., 1993; Collins et al., 1996; Levin and Miller, 1996; Nozaki et al., 1999; Destexhe and Paré, 1999; Hô and Destexhe, 2000; Anderson et al., 2000a; Tiesinga et al., 2001; Destexhe et al., 2001) in part by increasing overall conductance (Rapp et al., 1992; Borg-Graham, 1998; Hirsch et al., 1998; Destexhe and Paré, 1999; Shelley et al., 2002).

Cortical neurons exhibit a remarkably high level of response variability (Burns and Webb, 1976; Dean, 1981; Softky and Koch, 1992, 1994; Holt et al., 1996; Anderson et al., 2000a). This led to the suggestion that, in addition to the push-pull excitation and inhibition (Anderson et al., 2000b) that drives or suppresses their responses, cortical neurons receive a high degree of parallel excitation and inhibition (Shadlen and Newsome, 1994, 1998; Tsodyks and Sejnowski, 1995; van Vreeswijk and Sompolinsky, 1996; Troyer and Miller, 1997, Stevens and Zador, 1998). Although this so-called balanced synaptic input generates little mean overall current, due to the cancellation of excitatory and inhibitory components, it produces a highly fluctuating input that contributes to response variability.

Previous work has treated the balanced component of synaptic input as a constant source of noise that continuously underlies the stimulus-evoked increases in excitation that drive neuronal responses. However, when the overall level of background activity is varied, an interesting thing happens. The example of gain modulation shown in Fig. 1B was obtained from an integrate-and-fire model neuron receiving large amounts of excitation and inhibition in a balanced configuration. The responsiveness of the model neuron was investigated by plotting the firing rate evoked by various levels of injected current (the f-I curve). The difference between the three curves lies in the different levels of balanced excitation and inhibition that the neuron received.

The gain modulating effect of balanced synaptic input has also been seen in neurons in layer 5 of rat somatosensory cortex (Chance et al., 2002). In these experiments, the dynamic clamp was used to simulate, within in the normally quiescent slice preparation, the high conductance changes and fluctuations in membrane potential that are characteristic of in vivo cortex. For the parameters that achieved realistic conductance changes and levels of noise, the synaptic inputs were in a configuration in which excitation approximately balanced inhibition. In particular, to simulate typical in vivo conditions, excitatory inputs were generated at a rate of 7000 Hz and inhibitory inputs at a rate of 3000 Hz, representing the summed effects of many simulated afferents. The arrival times of these synaptic inputs were randomly generated with Poisson statistics. The unitary synaptic conductance for each synaptic input was calculated as a difference of exponentials, with time constants of 0.1 ms for the rising phase and either 5 ms (excitatory) or 10 ms (inhibitory) for the falling phase. The peak unitary synaptic conductances were set to 2% (excitatory) or 6% (inhibitory) of the measured resting membrane conductance.

The balanced background synaptic activity introduced with the dynamic clamp was not very effective at driving the recorded neuron. Instead, the dominant effect of this background activity was to introduce noise into the neuronal response, as illustrated in Fig. 2. The level of variability matched quite well with levels seen in vivo (Fig. 2).

Varying the level of background activity had a significant effect on the gain of the neuron as measured by driving it with different levels of constant injected current (the driving current) in addition to the simulated background synaptic activity. In other words, the firing rate was measured as a function of driving current for different levels of

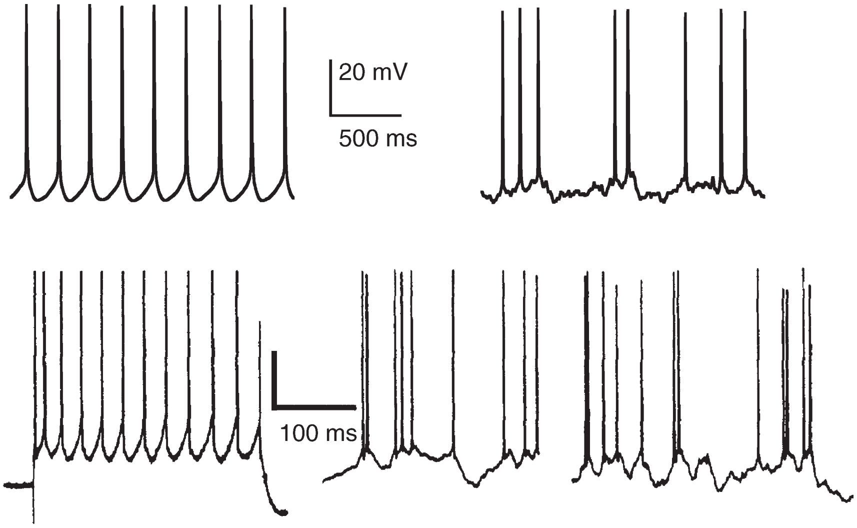

Fig. 2. Top panels: (adapted from Chance et al., 2002) Intracellular recordings from a layer 5 pyramidal neuron in a slice of rat somatosensory cortex. Constant current was injected to drive the neuron at approximately 5 Hz. The two traces represent the firing of the neuron with (right) and without (left) simulated background activity. For comparison, the bottom traces (adapted from Holt et al., 1996) are intracellular recordings from pyramidal neurons of cat visual cortex driven with constant current in slice (left) or in vivo (middle), and when driven by visual activity in vivo (right).

background activity. The dominant effect of changing the level of background activity was to multiplicatively scale the curve of firing-rate versus input current for the neuron (Fig. 3). This effect is equivalent to changing the gain of the neuron, where gain is defined as the slope of the firing rate curve.

Through this mechanism, gain modulation occurs without a corresponding change in firing rate variability (measured as the coefficient of variation of the interspike intervals). The multiplicative effect is not simply a result of the increased conductance induced by the dynamic clamp simulated input (see Chance et al., 2002 for more details). Briefly, two fundamental components of synaptic input increase when background synaptic activity is increased: the overall conductance and the variance of the synaptic current entering the neuron. The increase in conductance has a subtractive effect on the firing rate curve of the neuron (Gabbiani et al., 1994; Holt and Koch, 1997, Chance et al., 2002) while the increase in synaptic current variance leads to a decrease in gain, along with an additive effect (Chance et al., 2002). When the rate of background synaptic input is increased, these effects combine. For a certain parameter range, the subtractive effect of the conductance increase cancels the additive effect of the current variance increase, leaving the divisive gain change.

Of relevance for the connection with the idea of driver and modulator inputs (Sherman and Guillery, 1998) is the fact that mixed multiplicative/divisive and additive/subtractive effects are obtained if the levels of excitation and inhibition in the background synaptic activity is not completely balanced. For example, in the right panel of Fig. 3, inhibition was slightly stronger than excitation. As background synaptic activity was increased, this produced a subtractive effect (shifting of the curve to the right along the input axis) as well as a divisive effect. Therefore, mixed multiplicative and additive effects can arise from this mechanism through non-balanced synaptic input.

A firing-rate description of gain modulation

Many network models in neuroscience are constructed by using firing rates to characterize neuronal activity. The use of firing-rate descriptions (Wilson and Cowan, 1972; Dayan and Abbott, 2001) is

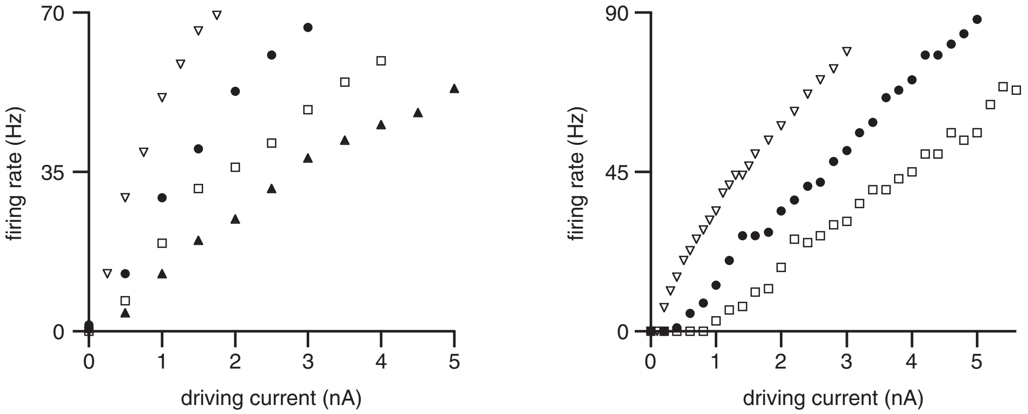

Fig. 3. Gain modulation by background synaptic activity for two different neurons (adapted from Chance et al., 2002). Firing rate plotted against driving current for different levels of background activity. Open inverted triangles represent the responses of the neuron in the absence of any background synaptic activity. The filled circles represent the responses recorded in the standard condition (see text and Chance et al., 2002). To produce the open squares and filled triangles, the input rates of the background excitatory and inhibitory synaptic inputs were doubled and tripled, respectively.

standard practice in network modeling because it greatly accelerates the construction of networks and facilitates our understanding of what they are doing. By having an accurate expression for the firing rate of a spiking neuron, it is possible to build network models rapidly, analyze their behavior and then, if the network seems interesting, build the corresponding spiking network model. The latter is obviously more realistic and more interesting from a biological standpoint, but more difficult to construct from scratch. A commonly used form for the f-I curve in such models is the threshold-linear function. It is actually easier for what follows to express the firing rate r in terms of the steady-state membrane potential, V_{ss}, that the neuron would obtain in response to the given input current if it was held constant and the spiking mechanisms of the neuron was inactivated. In terms of this steady-state voltage, which is typically related in a linear manner to the input current, and a threshold potential V_{th},

$$r = \frac{(V_{\text{ss}} - V_{\text{th}})\Theta(V_{\text{ss}} - V_{\text{th}})}{\tau(V_{\text{th}} - V_{\text{reset}})}, \tag{1}$$

where τ is an arbitrary constant, although in many models it corresponds to the membrane time constant, and $\Theta(x)$ is a step function that takes the value 1 if $x > 0$ and zero otherwise.

Equation 1 gives the firing rate in terms of an input current, or equivalently the effective steady-state potential it produces. This formula is valid in the absence of "noise", which means non-variable synaptic input. This result should be extended to the case where this variable input causes fluctuations in the membrane potential. The magnitude of these fluctuations is characterized by their standard deviation denoted by σ_V. It is well-known that such fluctuations "soften" the threshold present in Eq. 1. In other words, when its membrane potential fluctuates, a neuron can fire even when the steady-state potential V_{ss} is less than the threshold potential V_{th}. To account for this effect, the Θ function should be "softened" in Eq. 1. The function required for this purpose must satisfy a number of conditions. First, it should go to 0 when $(V_{\text{ss}} - V_{\text{th}})/\sigma_V \ll 0$ because in this limit the noise level is insufficient to make the neuron fire. Second, it should go to 1 when $(V_{\text{ss}} - V_{\text{th}})/\sigma_V \gg 0$ because over this range the noise is irrelevant. Third, if the neuron is to fire when $V_{\text{ss}} = V_{\text{th}}$, the factor that replaces the Θ function in Eq. 1 must grow without bound proportional to $1/(V_{\text{ss}} - V_{\text{th}})$ near the point where $V_{\text{ss}} = V_{\text{th}}$. Finally, this function should approach a Θ function in the limit of no noise, $\sigma_V \to 0$.

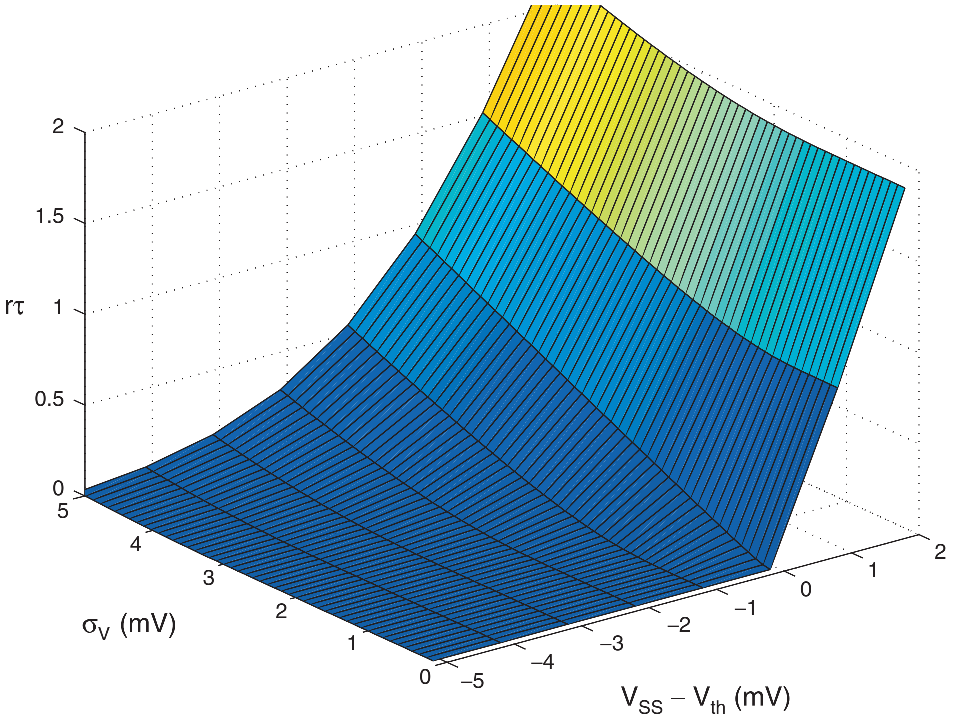

Fig. 4. The firing of Eq. 3 times the constant τ plotted as a function of the steady-state voltage minus the threshold voltage and the standard deviation of the membrane potential fluctuations.

If one sticks to using standard functions, it is clear that the replacement one wants to make in order to satisfy these conditions is

$$\Theta(V_{\rm ss} - V_{\rm th}) \to \frac{1}{1 - \exp\Big(- a(V_{\rm ss} - V_{\rm th})/\sigma_V\Big)}, \tag{2}$$

where a is a constant parameter. Making this replacement in Eq. 1 leads to the functional form proposed for describing how the firing rate in the presence of variable input depends on both the mean steady-state potential and the standard deviation of the membrane potential,

$$r = \frac{(V_{\rm ss} - V_{\rm th})}{\tau(V_{\rm th} - V_{\rm reset})\Big(1 - \exp(-a(V_{\rm ss} - V_{\rm th})/\sigma_V)\Big)}. \tag{3}$$

This formula, suggested as a simpler alternative for an exact expression for the firing rate of an integrate-and-fire model neuron receiving a white noise input (Ricciardi, 1977; Tuckwell, 1988), works quite well in all the cases where it has been tried. For example, the solid lines in Fig. 1 were generated using Eq. 3. Figure 4, displays how the firing rate given by this formula depends on the steady-state membrane potential and membrane potential variance over a range of values.

Discussion

High levels of highly variable synaptic input are a distinctive and puzzling feature of cortical circuitry. Previous work has treated this input purely as a source of noise and response variance. The results reported show that, in real cortical neurons, high levels of synaptic input can produce a more interesting effect, modulating the gain of neuronal responses.

Given the high levels of synaptic activity in cortical circuitry, modulatory effects are inevitable, so it is important to characterize them fully and to understand their roles in cortical processing. We suggest Eq. 3 as one such compact and useful description.

We propose that the driving and modulatory inputs that Sherman and Guillery (1998) suggested neurons in cortical circuits receive are not distinguished anatomically, they are distinguished functionally. In the present study both classes of inputs operate through ordinary AMPA- and GABA-mediated fast, ionotropic conductances, which allows modulatory inputs to be as specific and rapid as driving inputs. Driving inputs to the neuron are carried along excitatory and inhibitory afferents that operate in an opposing, push–pull manner (Anderson et al., 2000b). Modulatory inputs consist of excitatory and inhibitory afferents in a balanced configuration (Shadlen and Newsome, 1994, 1998; Troyer and Miller, 1997) that produces little net drive to the neuron. If the balance between the excitatory and inhibitory components is modified, this produces an additive or subtractive shift in the responsiveness of the neuron, corresponding to conventional excitation and inhibition. If the excitatory and inhibitory components are varied in parallel, maintaining the balance between excitation and inhibition, this produces a multiplicative or divisive modulation in the gain or sensitivity of the neuronal response. Together, these two forms of response modulation provide a powerful mechanism for modifying and switching network function. Furthermore, specific excitatory afferents can rapidly switch from one type to the other by changing their correlation with associated inhibitory inputs.

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