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Differential Filtering of Two Presynaptic Depression Mechanisms

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The filtering of input signals carried out at synapses is key to the information processing performed by networks of neurons. Two forms of presynaptic depression, vesicle depletion and G-protein inhibition of Ca^{2+} channels, can play important roles in the presynaptic processing of information. Using computational models, we demonstrate that these two forms of depression filter information in very different ways. G-protein inhibition acts as a high-pass filter, preferentially transmitting high-frequency input signals to the postsynaptic cell, while vesicle depletion acts as a low-pass filter. We examine how these forms of depression separately and together affect the steady-state postsynaptic responses to trains of stimuli over a range of frequencies. Finally, we demonstrate how differential filtering permits the multiplexing of information within a single impulse train.

1 Introduction

Synapses are subject to a wide range of activity-dependent short-term and long-term changes in efficacy. These changes can potentiate or depress the synapse and have both presynaptic and postsynaptic sites of induction and expression. Forms of synaptic enhancement include facilitation, augmentation, posttetanic potentiation, long-term facilitation (Magleby, 1987; Zucker, 1996), and long-term potentiation (Gustaffson, Wigstrom, Abraham, & Huang, 1987). Forms of synaptic depression include postsynaptic desensitization (Hestrin, 1992), vesicle depletion (Dobrunz, Huang, & Stevens, 1997), G-protein-mediated presynaptic inhibition (Bean, 1989), and long-term depression (Stanton & Sejnowski, 1989). While the long-term forms of plasticity are thought to be linked to learning and memory (Bliss & Collingridge, 1993), the short-term forms likely act as filters. That is, short-term plasticity acts as a frequency-dependent filter of the presynaptic signal, where the selectivity is determined by the type of short-term plasticity exhibited by the particular synapse. The focus of this article is on the differential filtering actions of two forms of short-term depression, vesicle depletion and G-protein-mediated presynaptic inhibition, which both have presynaptic sites of induction and action but involve very different mechanisms.

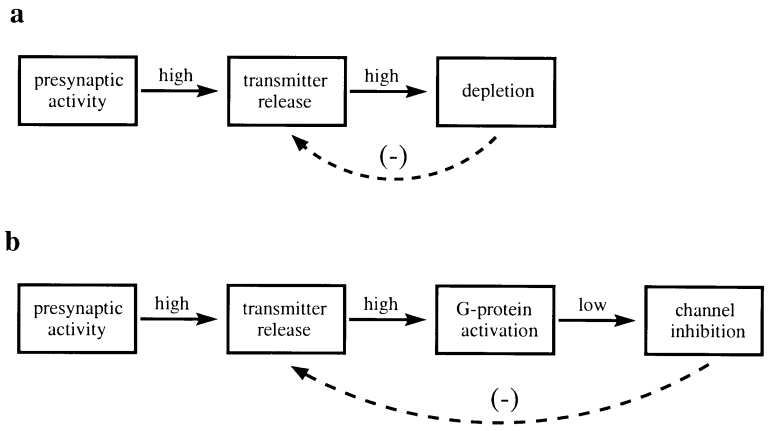

Figure 1: The steps involved in depression induced by vesicle depletion (a) and G-protein inhibition of release (b). High-frequency presynaptic stimuli increase transmitter release, which increases both depletion and G-protein activation. In contrast, low-frequency stimuli are most effective in mediating Ca^{2+} channel inhibition by activated G-proteins. Both depletion and channel inhibition reduce transmitter release during subsequent impulses.

Release of transmitter occurs when Ca^{2+} brought into the terminal through voltage-dependent channels binds to release sites in a readily releasable vesicle pool (Rosenmund & Stevens, 1996). During a train of impulses, this pool may deplete, reducing the probability of vesicle fusion later in the train. This form of depression is most severe during high-frequency stimulus trains (see Figure 1a).

The mechanism of G-protein inhibition is more complicated (Dolphin, 1998). This occurs when chemical messengers such as GABA, adenosine, glutamate, dopamine, or serotonin bind to receptors in the presynaptic terminals that activate G-proteins. Major targets of these activated G-proteins are Ca^{2+} channels, primarily the P- and N-type found in presynaptic terminals (Boland & Bean, 1993; Chen & van den Pol, 1998; Stanley & Mirotznik, 1997), although there are other targets (Dittman & Regehr, 1996; Vaughan, Ingram, Connor, & Christie, 1997). Data indicate that $G_{\beta\gamma}$ subunits of activated G-proteins bind to the $\alpha 1$ subunit of a Ca^{2+} channel, putting the channel into a "reluctant" state where the probability of opening is greatly reduced (Bean, 1989; De Waard et al., 1997). As a result, less Ca^{2+} enters the terminal during an action potential and the probability of transmitter release is reduced. An important characteristic of G-protein inhibition of Ca^{2+} channels is that it is often relieved by depolarization (Bean, 1989; Zamponi & Snutch, 1998). We will demonstrate that this is crucial to the filtering properties of this type of synaptic depression.

Receptors for G-protein agonists may respond to transmitter molecules released from neighboring synapses (Dittman & Regehr, 1997) or from the target synapse itself. This receptor binding leads to heterosynaptic or homosynaptic inhibition, respectively. The latter seems to be ubiquitous, since metabotropic transmitter autoreceptors have been found in many different presynaptic terminals (Chen & van den Pol, 1998; Langer, 1987; Starke, Gothert, & Kilbinger, 1989). The filtering properties of G-protein inhibition are not obvious. The amount of transmitter released and the subsequent G-protein activation are greatest during high-frequency trains. However, because activated G-proteins unbind from channels when the presynaptic terminal is depolarized, the binding affinity of G-proteins to Ca^{2+} channels is greatest at hyperpolarized potentials. Thus, G-protein activation is maximized by high-frequency stimulus trains, while the binding of activated G-proteins to Ca^{2+} channels is maximized by low-frequency trains (see Figure 1b).

In this article, we use simple computational models of vesicle depletion and G-protein inhibition, coupled with a simple model of a postsynaptic cell with active membrane currents, to study the filtering properties of depletion and G-protein inhibition. We find that depletion acts as a low-pass filter, preferentially transmitting low-frequency presynaptic stimuli to the postsynaptic cell. In contrast, G-protein inhibition acts as a high-pass filter in this model, filtering out low-frequency stimuli while reliably transmitting high-frequency trains.

We next voltage-clamp the model postsynaptic cell and compute the synaptic current during presynaptic impulse trains of different frequencies. We find that for a model synapse exhibiting both forms of depression, the steady-state frequency-response curve is flat over a large range of frequencies. This is consistent with data from auditory glutamatergic synapses, which show strong depression due to both vesicle depletion and presynaptic inhibition mediated by $GABA_B$ receptors (Brenowitz, David, & Trussell, 1998). In contrast, cortical synapses show a steady-state excitatory postsynaptic current (EPSC) amplitude that is inversely proportional to the stimulus frequency (Abbott, Varela, Sen, & Nelson, 1997; Tsodyks & Markram, 1997), suggestive of depression due solely to vesicle depletion. With a flat frequency-response curve, the total synaptic signal transmitted (the product of stimulus frequency and EPSC amplitude) increases roughly linearly with stimulus frequency, while with a frequency-response curve that decays as the inverse of frequency, the total signal is relatively insensitive to stimulus frequency (Abbott et al., 1997; Tsodyks & Markram, 1997). Thus, it appears that G-protein inhibition can remove the gain control introduced by vesicle depletion.

Finally, we show that by taking advantage of the differential filtering performed by depletion and G-protein inhibition, information can be multiplexed within a single impulse train. This is accomplished by encoding one stream of information at a low frequency and a second stream at a

high frequency. The information transmitted at a particular synapse is then determined by the dominant form of synaptic depression at that synapse. Information multiplexing is a particularly efficient means of increasing the information content in limited neural circuitry.

2 Methods

We consider a simple two-compartment representation of a population of synaptic connections between one or more presynaptic neurons (subject to identical input stimuli) and a postsynaptic neuron. A brief description of the presynaptic and postsynaptic models is provided here; all equations and parameter values are provided in the appendix. A complete description of a similar presynaptic model (which includes an additional mechanism for synaptic facilitation) is given in Bertram and Behan (1999).

2.1 Presynaptic Models. We assume that each docked vesicle is associated with a single Ca^{2+} channel located 10 nm away. We assume further that each vesicle has a single low-affinity Ca^{2+} binding site ($K_D = 170$ μM) that is influenced by the microdomain of high Ca^{2+} concentration that forms at the inner mouth of the colocalized open channel. This site has a high Ca^{2+} unbinding rate and free intraterminal Ca^{2+} does not accumulate, so there is no facilitation of release. More complex models for the probability of transmitter release have been developed (Bertram, Sherman, & Stanley, 1996; Bertram, Smith, & Sherman, 1999; Fogelson & Zucker, 1985; Parnas, Dudel, & Parnas, 1986; Yamada & Zucker, 1992), but are not needed here.

In the absence of G-protein binding, the state of the colocalized Ca^{2+} channel is determined by a five-state kinetic scheme based on an N-type Ca^{2+} channel (Boland & Bean, 1993). This represents a "willing" Ca^{2+} channel. A channel that is bound by a G-protein is in a "reluctant" state and has a significantly lower opening probability. The transition rate from a willing state to a reluctant state increases with the fraction of activated G-proteins, while the transition rate from a reluctant state to a willing state increases with depolarization.

The binding of a transmitter molecule to a presynaptic autoreceptor, activating a G-protein, is modeled by a first-order kinetic scheme, assuming that the mean transmitter concentration is proportional to the probability of release. The proportionality constant ($\overline{T}$) was chosen so that the mean transmitter concentration during an impulse peaks at ~ 0.4 mM.

Vesicle depletion is modeled as a first-order process with a forward rate proportional to the transmitter concentration. Forward and backward kinetic rates were chosen so that there would be significant depletion during a 70 Hz stimulus train, but not during a 5 Hz train. The refilling of the readily releasable pool is intended to represent transfer of filled vesicles from a reserve pool (Worden, Bykhovskaia, & Hackett, 1997). With the depletion model, the transmitter concentration is $T = \overline{T}(1 - D)R$, where D is the frac-

tion of vesicles depleted from the readily releasable pool and R is the release probability.

2.2 Postsynaptic Model. The postsynaptic membrane potential (V_{post}), like the presynaptic potential, is described by the Hodgkin-Huxley equations (Hodgkin & Huxley, 1952), with an excitatory synaptic current added to the voltage equation. Binding of transmitter to postsynaptic receptors is assumed to be a first-order process, with forward rate proportional to the transmitter concentration. Receptor desensitization is not included in the model.

3 Results

Two presynaptic models for the probability of transmitter release are used initially: one that allows for vesicle depletion and one that allows for G-protein inhibition. The depletion model includes a variable, D, that describes the depletion of vesicles from the readily releasable pool, and the G-protein inhibition model includes a variable C_G that is the fraction of Ca^{2+} channels in a reluctant state. Thus, both D and C_G are measures of processes that depress transmitter release.

3.1 Differential Filtering Properties. We first examine the presynaptic responses to low- and high-frequency stimuli using 5 Hz and 70 Hz depolarizing current trains to induce presynaptic action potentials. During the high-frequency (70 Hz) stimulus, there is significant vesicle depletion since subsequent impulses occur before the pool is refilled by vesicles from a reserve pool (see Figure 2a). In the G-protein model, the high-frequency train releases a great deal of transmitter that binds to autoreceptors, producing a large fraction of activated G-proteins (see curve A in Figure 2b). However, there is little binding of activated G-proteins to Ca^{2+} channels (see curve C_G in Figure 2b) due to the frequent depolarization. As a result, G-protein inhibition is minimal.

The converse is true with low-frequency (5 Hz) stimuli. In the depletion model, the longer time between stimuli gives the readily releasable pool time to refill, so there is little depletion at the time of the subsequent stimulus (see Figure 2c). In the G-protein model, even though the fraction of G-proteins activated is less than during the high-frequency train, the longer periods of hyperpolarization between stimuli provide ample opportunity for activated G-proteins to bind to Ca^{2+} channels and put them into a reluctant state (see Figure 2d), reducing the Ca^{2+} influx, and thus the transmitter release, during subsequent stimuli.

The postsynaptic responses to the high- and low-frequency trains for both presynaptic models are shown in Figures 3 and 4. The postsynaptic cell, at rest in the absence of synaptic input, generates a train of impulses in response to presynaptic action potentials when there is neither deple-

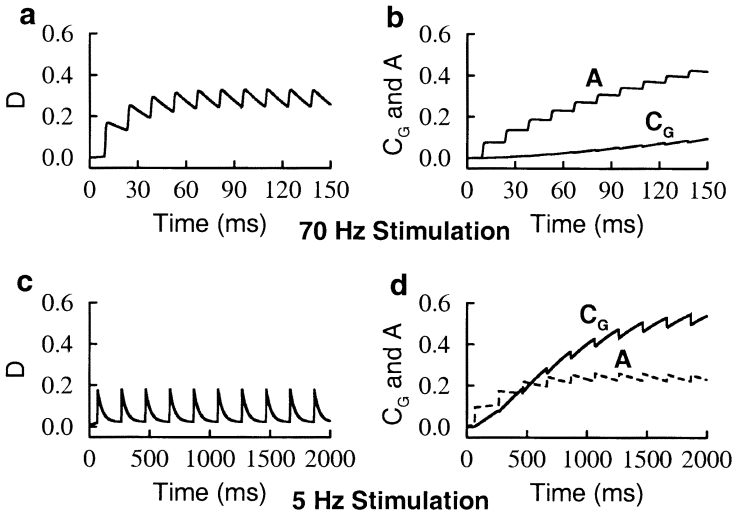

Figure 2: Vesicle depletion (D) occurs during a (a) high-frequency stimulus train but not during a (c) low-frequency train. The fraction of activated G-proteins (A) accumulates more during the (b) high-frequency train than during the (d) low-frequency train, but the fraction of Ca^{2+} channels in a reluctant state (C_G) increases to a much higher level during the low-frequency train.

tion nor G-protein inhibition (see Figures 3a and 4a). However, during the high-frequency train, the postsynaptic voltage in the depleting synapse population fails to reach the spike threshold after the second stimulus, so only two postsynaptic impulses are generated (see Figure 3b). At this frequency, the postsynaptic voltage of the synapse population subject to G-protein inhibition reaches spike threshold with each stimulus, so the full input signal is faithfully transmitted (see Figure 3c). The opposite is true during low-frequency stimulation. In this case, the depleting synapse population faithfully transmits the input signal (see Figure 4b), while the population subject to G-protein inhibition transmits only the first two impulses (see Figure 4c).

These simulations suggest that G-protein inhibition acts as a high-pass filter, while vesicle depletion acts as a low-pass filter. We examine this further using steady-state responses over a range of stimulus frequencies, using models with depletion or G-protein inhibition alone and a model with both forms of depression.

3.2 Steady-State Responses. The active postsynaptic currents ($I_{Na,post}$ and $I_{K,post}$) provide a voltage threshold that must be crossed for an action potential to be generated. To study the steady-state effects of depletion and

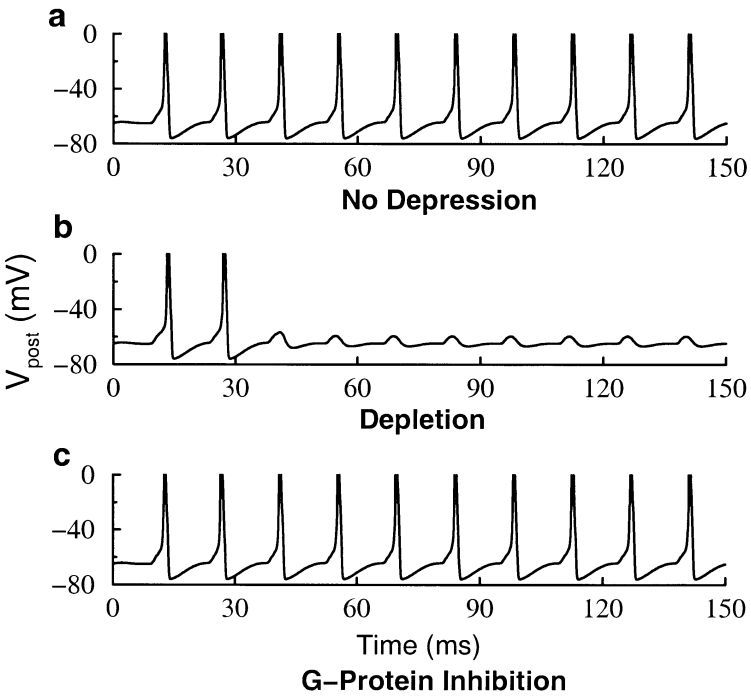

Figure 3: Postsynaptic response to a 70 Hz train of presynaptic action potentials. The input signal is transmitted reliably to the postsynaptic cell when (a) there is no presynaptic depression or (c) transmitter release is subject to G-protein inhibition. However, the signal is not transmitted when (b) vesicle depletion occurs. Postsynaptic impulses have been chopped at 0 mV.

G-protein inhibition, it is useful to exclude this extra nonlinearity, so we focus now on the synaptic current (I_{syn}) induced by presynaptic impulses when the postsynaptic cell is voltage clamped at -30 mV. Our goal is to determine the steady-state I_{syn} over a range of stimulus frequencies (5–100 Hz), so at each frequency the presynaptic cell is stimulated for a length of time sufficient to ensure that the amplitude of the postsynaptic current has reached steady state (see Figure 5a).

The steady-state responses with different depression mechanisms are shown in Figure 5b. In the presence of depletion alone, I_{syn} decreases with higher-stimulus frequencies (open circles). This is consistent with the low-pass filtering demonstrated earlier and the downward trend in steady-state excitatory postsynaptic potential (EPSP) amplitude observed in cortical neurons (Abbott et al., 1997; Tsodyks & Markram, 1997). A similar downward trend was shown in EPSC recordings from glutamatergic auditory

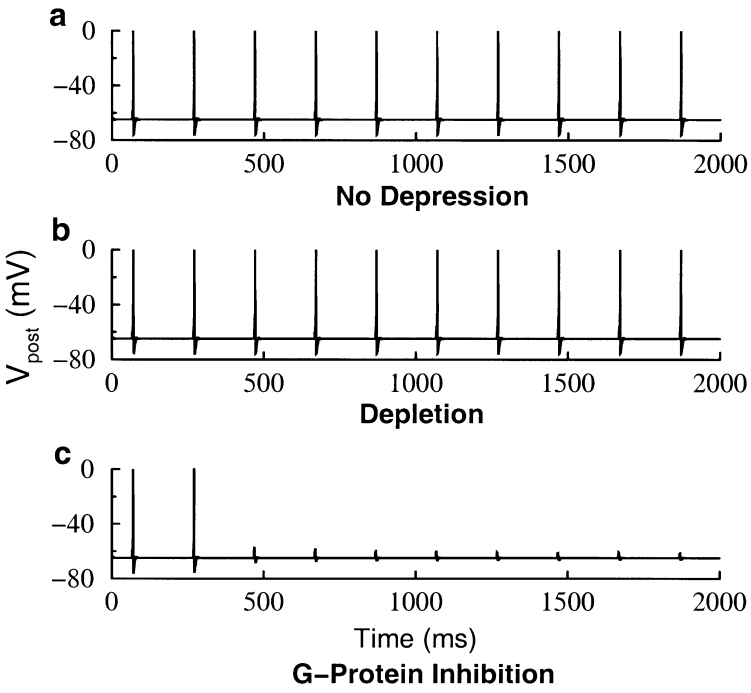

Figure 4: Postsynaptic response to a 5 Hz stimulus train. As before, the input signal is transmitted reliably when there is no depression (a). However, the signal is now also transmitted when transmitter release is subject to vesicle depletion (b), but not when it is subject to G-protein inhibition (c), in contrast to the high-frequency response (see Figure 3).

synapses in the absence of the $GABA_B$ agonist baclofen (Brenowitz et al., 1998), a condition where depletion is thought to be the only form of depression.

With G-protein inhibition alone, I_{syn} is an increasing function of stimulus frequency (open squares in Figure 5b), reflecting the high-pass filtering performed by this form of depression. When both depletion and G-protein inhibition are included in the model, I_{syn} first increases and then remains relatively constant over a large range of frequencies (the closed triangles in Figure 5b). Thus, the combination of these forms of depression results in a steady-state response that is relatively insensitive to stimulus frequency. Similar insensitivity was observed in auditory synapses when presynaptic G-proteins were activated by the $GABA_B$ agonist baclofen, so that vesicle depletion was supplemented by some form of G-protein inhibition (Brenowitz et al., 1998). Implications of this insensitivity, and its contrast to the linear de-

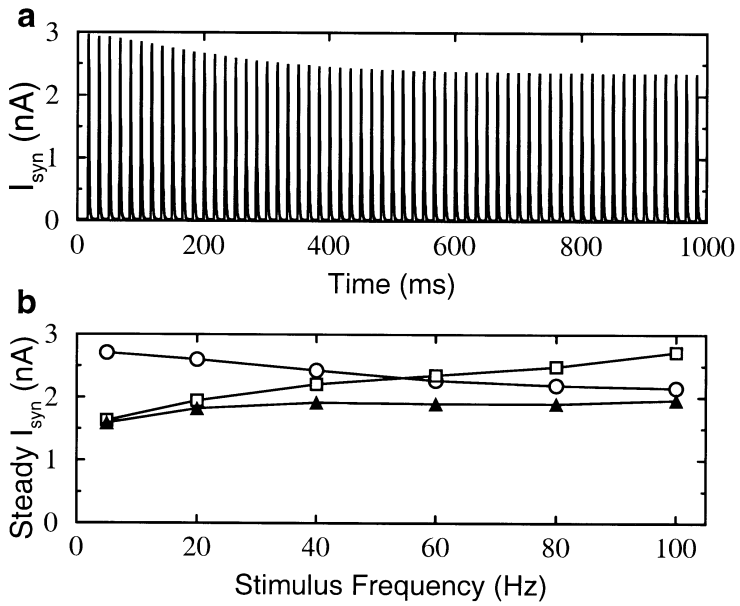

Figure 5: Synaptic current produced by long trains of presynaptic impulses. (a) Time course of I_{syn} during a 70 Hz train of presynaptic impulses with G-protein inhibition but no depletion. The amplitude of the last peak is used as the steady-state value. (b) Steady-state I_{syn} over a range of stimulus frequencies. The maximum occurs at 5 Hz when the model synapse is subject to depletion alone (open circles). The maximum occurs at 100 Hz when G-protein inhibition is the only depression mechanism (open squares). When both depression mechanisms are included in the model (closed triangles), the response is relatively insensitive to stimulus frequencies between 40 and 100 Hz.

cline observed in cortical neurons (Abbott et al., 1997; Tsodyks & Markram, 1997), will be discussed shortly.

3.3 Information Multiplexing. Finally, we examine how synapses subject to depletion or G-protein inhibition would process an input signal with an initial low-frequency component followed by a high-frequency component. These components may be thought of as the concatenation of two independent streams of information. As was done earlier, we examine the voltage response of a postsynaptic cell with active membrane currents.

Figure 6a shows the voltage response, in the absence of depression, to a train of presynaptic impulses at 10 Hz followed by a burst of impulses at 100 Hz (only the last four low-frequency responses are shown). If the model synapse is subject to depletion, the low-frequency component is transmit-

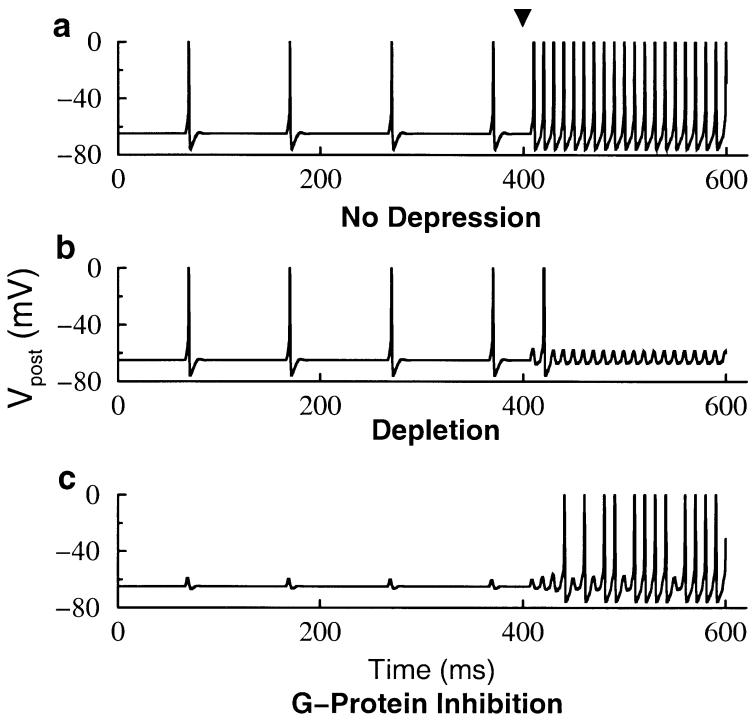

Figure 6: Postsynaptic voltage response to a presynaptic input signal consisting of a low-frequency (10 Hz) component followed by a high-frequency (100 Hz) component. (a) Both components are transmitted when the synapse is not subject to depression. The response to the last four low-frequency stimuli is shown, followed (at the arrow) by the high-frequency response. (b) The high-frequency component is filtered out by vesicle depletion, while the low-frequency component is transmitted. (c) G-protein inhibition filters out the low-frequency component, while the high-frequency component is transmitted.

ted, while the high-frequency component is filtered out (see Figure 6b). Thus, only information encoded at the low frequency is transmitted, while information encoded at the high frequency is ignored. Conversely, when the model synapse is subject to G-protein inhibition alone, only the high-frequency component of the signal is transmitted, while information at the low frequency is ignored (see Figure 6c). Thus, one way to transmit two independent streams of information on the same input line (a presynaptic cell) is to encode one at a low frequency and the other at a high frequency. The filtering performed at a particular synapse then determines which stream of information is transmitted by that synapse.

4 Discussion

The way that synapses filter input signals is key to the information processing done by networks of neurons. Using computational models, we have demonstrated that two forms of presynaptic depression, vesicle depletion and G-protein inhibition of Ca^{2+} channels, filter input signals in very different ways. Vesicle depletion acts as a low-pass filter, filtering out high-frequency signals while reliably transmitting low-frequency signals. G-protein inhibition acts as a high-pass filter, filtering out low-frequency signals while reliably transmitting high-frequency signals. This unusual filtering property is due to the depolarization-induced relief of Ca^{2+} channel inhibition that is typical of G-protein-mediated Ca^{2+} channel inhibition (Bean, 1989; Zamponi & Snutch, 1998). The differential filtering performed by vesicle depletion and G-protein inhibition provides a means for the multiplexing of neuronal information, whereby information encoded at low frequencies is transmitted by synapses in which vesicle depletion is the primary depression mechanism, and information encoded at high frequencies is transmitted preferentially by those in which G-protein inhibition of Ca^{2+} channels is the dominant depression mechanism. This is a particularly efficient means of increasing the information content in neural circuitry. Furthermore, alterations in gene expression of the various proteins involved in vesicle depletion and G-protein inhibition can alter the mix of these forms of depression, modifying the type of information that is transmitted by the synapse. This provides flexibility without changing the connectivity of the neural circuitry and is different from, but complementary to, systematic changes in synaptic strength.

We have shown that the combination of the two forms of depression can produce a steady-state frequency-response curve that is flat over a large range of frequencies. Thus, the effects of G-protein inhibition remove the gain control observed in some cortical neurons, where the steady-state EPSP amplitude decays at a rate inversely proportional to the stimulus frequency (Abbott et al., 1997; Tsodyks & Markram, 1997). A flat frequency-response curve has been observed in auditory neurons, where baclofen was used to activate presynaptic $GABA_B$ receptors (Brenowitz et al., 1998). Binding to this type of receptor typically activates G-proteins and has been shown to produce inhibition in different neurons using different targets, including Ca^{2+} channels (Chen & van den Pol, 1998; Dittman & Regehr, 1996; Takahashi, Kajikawa, & Tsujimoto, 1998; Wu & Saggau, 1995), K^+ channels (Thompson & Gähwiler, 1992; Vaughan et al., 1997), or proteins downstream of those responsible for depolarization and Ca^{2+} entry (Dittman & Regehr, 1996). In the Brenowitz study, the G-protein target was not investigated, and indeed in our model with Ca^{2+} channels as the target, we were unable to produce a postsynaptic response that was greater in the presence of agonist than in its absence, as was shown in the auditory neuron. Whatever the target, the insensitivity of response amplitude implies that the total

synaptic response (frequency × EPSC amplitude) increases roughly linearly with stimulus frequency, unlike the frequency-independent total responses produced by synapses exhibiting vesicle depletion but no G-protein inhibition (Abbott et al., 1997; Tsodyks & Markram, 1997). As discussed by these groups, frequency-independent total responses provide gain control, so that low-frequency input to a postsynaptic cell is not dominated by high-frequency input from a different synapse. Our model predicts that this gain control is removed by G-protein inhibition, allowing high-frequency input to dominate input of lower frequency.

The details of this study depend quantitatively on the choice of parameter values. Of particular importance here are the rate of refilling of readily releasable stores from a reserve pool of vesicles (k_d^-) and the rate at which activated G-proteins become inactive (k_a^-). We have investigated the effects on the frequency-response curve of varying these two parameters. In the depletion model, reducing the refilling rate causes the steady-state frequency-response curve for depletion (see Figure 5b) to decay more rapidly and reach a lower value. Increasing k_d^- has the opposite effect. In the G-protein inhibition model, reducing the G-protein inactivation rate results in extra accumulation of activated G-proteins during low-frequency stimulus trains, and consequently the steady-state frequency-response curve for G-protein inhibition is lower at low frequencies than that shown in Figure 5b. Increasing k_a^- has the opposite effect. When either k_d^- or k_a^- is increased or decreased by a factor of two, the steady-state frequency-response curve of a model with both forms of depression remains flat over most frequencies tested. Indeed, the range of frequencies where the response is flat is extended by reducing k_d^- or increasing k_a^-.

In a previous computational study (Bertram & Behan, 1999), we investigated the effects of G-protein inhibition and the depolarization-induced relief of inhibition on synaptic facilitation. The main result was that facilitation can be greatly enhanced as Ca^{2+} channels move from a reluctant state to a willing state, so some of the facilitation generally attributed to accumulation of free or bound Ca^{2+} may actually be due to the relief of basal G-protein inhibition. Another point made in this earlier report was that at very low stimulus frequencies (lower than the frequencies used in this article), there will be no accumulation of activated G-proteins. This implies that G-protein inhibition acts as a low-pass filter at these very low frequencies. When the frequency is very low, activated G-proteins do not accumulate and the signal is transmitted, but at higher frequencies there is sufficient G-protein accumulation and Ca^{2+} channel binding to block the input signal. Thus, in our model, G-protein inhibition allows the transmission of signals at a very low frequency and at a high frequency, but filters out those with frequency in between.

It has been demonstrated previously that in the absence of depletion, bursts of high-frequency presynaptic stimuli are more efficiently transmitted than are lower-frequency trains (Lisman, 1997). This is due to facilitation,

the potentiation of transmitter release that often occurs when one stimulus is preceded by one or more conditioning stimuli. Since facilitation is greater at high stimulus frequencies than at low frequencies, it acts like a high-frequency amplifier. In the light of this, our results suggest that G-protein inhibition and presynaptic facilitation have similar signal processing properties in that both preferentially transmit high-frequency signals; the former filters out low-frequency signals, while the latter amplifies high-frequency signals. The signal processing performed by these two forms of short-term plasticity contrasts greatly with the low-pass filtering carried out by vesicle depletion.

Appendix

A.1 Equations for Presynaptic Membrane Potential. Presynaptic action potentials were generated with the Hodgkin-Huxley (1952) equations by applying periodic 1 ms current pulses of magnitude $I_{ap} = 30\ \mu\text{Acm}^{-2}$. The equations are:

$$C_m \frac{dV}{dt} = -[\bar{g}_{Na}\, x^3\, h\,(V - V_{Na}) + \bar{g}_K\, n^4\,(V - V_K) + \bar{g}_l\,(V - V_l) - I_{ap}] \quad \text{(A.1)}$$

$$\frac{dx}{dt} = (x_\infty(V) - x)/\tau_x(V) \quad \text{(A.2)}$$

$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V) \quad \text{(A.3)}$$

$$\frac{dh}{dt} = (h_\infty(V) - h)/\tau_h(V) \quad \text{(A.4)}$$

where $x_\infty(V) = \alpha_x/(\alpha_x + \beta_x)$, $\tau_x(V) = 1/(\alpha_x + \beta_x)$ (similarly for n_∞, h_∞, τ_n, and τ_h) and $\alpha_x = 0.2(V + 40)/[1 - e^{-(V+40)/10}]$, $\beta_x = 8\,e^{-(V+65)/18}$, $\alpha_n = 0.02(V + 55)/[1 - e^{-(V+55)/10}]$, $\beta_n = 0.25\,e^{-(V+65)/80}$, $\alpha_h = 0.14\,e^{-(V+65)/20}$, and $\beta_h = 2/[1 + e^{-(V+35)/10}]$. Capacitance, maximum conductance values, and reversal potentials are $C_m = 1\ \mu\text{Fcm}^{-2}$, $\bar{g}_{Na} = 120$, $\bar{g}_K = 36$, $\bar{g}_l = 0.3$ (mScm^{-2}), and $V_{Na} = 50$, $V_K = -77$, and $V_l = -54$ (mV). It is assumed that Ca^{2+} current does not affect presynaptic voltage.

A.2 Equations for the Presynaptic Ca^{2+} Channel and Secretion Models. The equations for the G-protein-regulated presynaptic Ca^{2+} channels are described in detail in Bertram and Behan (1999). Briefly, the model channel has three G-protein-bound or "reluctant" closed states (C_{Gi}), four unbound or "willing" closed states (C_i), and a single open state. Equations for closed-state probabilities are:

$$\frac{dC_1}{dt} = \beta C_2 + l C_{G1} - (4\alpha + k)\, C_1 \quad \text{(A.5)}$$

$$\frac{dC_2}{dt} = 4\alpha C_1 + 2\beta C_3 + 64 l C_{G2} - (\beta + 3\alpha + k)\, C_2 \quad \text{(A.6)}$$

$$\frac{dC_3}{dt} = 3\alpha C_2 + 3\beta C_4 + (64)^2 l C_{G3} - (2\beta + 2\alpha + k)\, C_3 \tag{A.7}$$

$$\frac{dC_4}{dt} = 2\alpha C_3 + 4\beta m - (3\beta + \alpha)\, C_4 \tag{A.8}$$

$$\frac{dC_{G1}}{dt} = \beta' C_{G2} + k C_1 - (4\alpha' + l)\, C_{G1} \tag{A.9}$$

$$\frac{dC_{G2}}{dt} = 4\alpha' C_{G1} + 2\beta' C_{G3} + k C_2 - (\beta' + 3\alpha' + 64l)\, C_{G2} \tag{A.10}$$

$$\frac{dC_{G3}}{dt} = 3\alpha' C_{G2} + k C_3 - (2\beta' + (64)^2 l)\, C_{G3}. \tag{A.11}$$

The probability that a channel is open is given by the conservation relation $m = 1 - C_1 - C_2 - C_3 - C_4 - C_{G1} - C_{G2} - C_{G3}$. The fraction of channels in a reluctant state, $C_G = C_{G1} + C_{G2} + C_{G3}$, is plotted in Figure 2.

Voltage-dependent forward (α) and backward (β) kinetic rates are (in ms^{-1}):

$$\alpha = 0.9e^{V/22}, \qquad \beta = 0.03e^{-V/14} \tag{A.12}$$

$$\alpha' = \alpha/8, \qquad \beta' = 8\beta. \tag{A.13}$$

The G protein unbinding and binding rates are (in ms^{-1}) $l = 0.00025$ and:

$$k = \frac{0.3A}{68 + 32A}\,, \tag{A.14}$$

where A is the fraction of activated G-proteins or the fraction of presynaptic autoreceptors bound by neurotransmitter. This fraction changes in time according to:

$$\frac{dA}{dt} = k_a^+ T(1 - A) - k_a^- A, \tag{A.15}$$

where T is the transmitter concentration and $k_a^+ = 0.2\ \text{mM}^{-1}\text{ms}^{-1}$, $k_a^- = 0.0015\ \text{ms}^{-1}$.

For simplicity, it is assumed that transmitter release sites have a single Ca^{2+} binding site and that presynaptic Ca^{2+} does not accumulate. The release probability (R) is given by:

$$\frac{dR}{dt} = k_r^+ Ca_d(1 - R) - k_r^- R, \tag{A.16}$$

where $k_r^+ = 0.015\ \mu\text{M}^{-1}\text{ms}^{-1}$, $k_r^- = 2.5\ \text{ms}^{-1}$, and Ca_d is the domain Ca^{2+} concentration (in μM) at the mouth of an open Ca^{2+} channel.

Depletion of releasable vesicles, D, is described by:

$$\frac{dD}{dt} = k_d^+ T(1 - D) - k_d^- D, \tag{A.17}$$

where $T = \overline{T}(1 - D)R$ is the transmitter concentration released during an impulse, $\overline{T} = 2$ mM is a proportionality constant, and $k_d^+ = 0.5\ \mathrm{mM}^{-1}\mathrm{ms}^{-1}$, $k_d^- = 0.025\ \mathrm{ms}^{-1}$.

A.3 Equations for Postsynaptic Membrane Potential. The equations for postsynaptic potential are similar to equations A.1–A.4, with the addition of a synaptic current in the voltage (V_{post}) equation:

$$C_m \frac{dV_{post}}{dt} = -(I_{Na,post} + I_{K,post} + I_{l,post} + I_{syn}), \tag{A.18}$$

where $I_{Na,post}$, $I_{K,post}$, and $I_{l,post}$ are functions of V_{post} and are similar to their presynaptic counterparts. The synaptic current is $I_{syn} = \bar{g}_{syn} b(V_{post} - V_{syn})$, where $\bar{g}_{syn} = 0.3\ \mathrm{mScm}^{-2}$ is the maximum synaptic conductance, $V_{syn} = 0$ mV is the reversal potential, and b is the fraction of bound receptors, given by:

$$\frac{db}{dt} = k_b^+ T(1 - b) - k_b^- b. \tag{A.19}$$

The binding and unbinding rates, $k_b^+ = 2\ \mathrm{mM}^{-1}\mathrm{ms}^{-1}$ and $k_b^- = 1\ \mathrm{ms}^{-1}$, are appropriate for "fast" receptors (Destexhe, Mainen, & Sejnowski, 1994). All differential equations were solved numerically using the software package XPPAUT (Ermentrout, 1996).

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