Dynamics of Electrosensory Feedback: Short-Term Plasticity and Inhibition in a Parallel Fiber Pathway

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Lewis, John. E and Leonard Maler. Dynamics of electrosensory feedback: short-term plasticity and inhibition in a parallel fiber pathway. J Neurophysiol 88: 1695–1706, 2002; 10.1152/jn.00171.2002. The dynamics of neuronal feedback pathways are generally not well understood. This is due to the complexity arising from the combined dynamics of closed-loop feedback systems and the synaptic plasticity of feedback connections. Here, we investigate the short-term synaptic dynamics underlying the parallel fiber feedback pathway to a primary electrosensory nucleus in the weakly electric fish, Apteronotus leptorhynhus. In open-loop conditions, the dynamics of this pathway arise from a monosynaptic excitatory connection and a disynaptic (feed-forward) inhibitory connection to pyramidal neurons in the electrosensory lateral line lobe (ELL). In a brain slice preparation of the ELL, we characterized the synaptic responses of pyramidal neurons to short trains of electrical stimuli delivered to the parallel fibers of the dorsal molecular layer. Stimulus trains consisted of 20 pulses, at either random intervals or constant intervals, with varying mean frequencies. With random trains, pyramidal neuron responses were well described by a single exponential function of the inter-stimulus interval—suggesting a single facilitation-like process underlies these synaptic dynamics. However, responses to periodic (constant interval) trains deviated from this simple description. Random and periodic stimulus trains delivered when the feed-forward inhibitory component of this pathway was pharmacologically blocked revealed that inhibition and depression also contribute to the observed dynamics. We formulated a simple model of the parallel fiber synaptic dynamics that provided an accurate description of our data. The model dynamics resulted from a combination of three distinct processes. Two of the processes are the classically-described synaptic facilitation and depression, and the third is a novel description of feed-forward inhibition. An analysis of this model suggests that synaptic pathways combining plasticity with feed-forward inhibition can be easily tuned to signal different types of transient stimuli and thus lead to diverse and nonintuitive filtering properties.

INTRODUCTION

Neuronal feedback is a ubiquitous component of nervous system organization. In many brain structures, feedback projections greatly outnumber primary input projections. Their functional role in information processing is, however, not well understood. In dynamic situations, such as during sensory processing, the analysis of neural systems with feedback is complex. Confounding such analyses are aspects of synaptic plasticity: many feedback synapses exhibit time- and stimulus-dependent dynamics. The development of simple and accurate models of these systems will be critical for understanding the detailed functions of feedback in processing dynamic sensory stimuli.

Neuronal feedback pathways are necessary for effective electrosensory processing (Bastian 1986; Bell 2001). Weakly electric fish use an active electric sense to detect nearby objects and to communicate with one another—behaviors called electrolocation and electrocommunication, respectively (Heiligenberg 1991). These fish generate an electric field that can be distorted by objects or the electric organ discharges (EOD) of other fish. Such distortions are encoded by electrorceptors distributed over the skin surface. In the gymnotid electric fish considered here, sensory afferents from these receptors terminate in the electrosensory lateral line lobe (ELL), making either mono- or disynaptic connections with the basal dendrites and somata of pyramidal neurons. The activity in these pyramidal neurons is the primary source of electrosensory information for higher brain areas.

In addition to sensory afferent inputs, ELL pyramidal neurons receive, via their apical dendrites, two sources of feedback input: the direct and indirect (Fig. 1A) pathways (Berman and Maler 1999). Here, we focus on the indirect feedback from the parallel fibers (PF) of cerebellar granule cells (Berman and Maler 1998a); another recent study has focused on the direct feedback pathway (Oswald et al. 2002). Parallel fibers in the dorsal molecular layer of the ELL make monosynaptic excitatory contacts with pyramidal neuron apical dendrites, as well as disynaptic inhibitory contacts, via three types of inhibitory interneurons (Fig. 1A). While long-term changes (>10 min) in the efficacy of this pathway are well established (Bastian 1998a), there is relatively little known about its short-term dynamics on time scales of less than 1 s —important time scales for electrolocation (Maclver et al. 2001; Nelson and Maclver 1999) and electrocommunication (Bastian et al. 2001; Metzner 1999; Zupanc and Maler 1993). Indeed, plasticity on these time scales is prevalent in the higher order electrosensory neurons of the midbrain (Fortune and Rose 2000). Because short-term changes in efficacy of feedback synapses could greatly influence the responses of pyramidal neurons to electrosensory input, a better understanding of feedback dynamics is necessary to fully understand the function of ELL in processing electrosensory information.

In this paper, we present a quantitative description of the
short-term dynamics underlying the PF feedback to ELL in the weakly electric fish, *Apteronotus leptorhynchus*. An important aspect of our study is that we consider the dynamics arising from inhibitory mechanisms in addition to those associated with traditional short-term synaptic plasticity (i.e., facilitation and depression). We extend a previous model of facilitation and depression at a cerebellar parallel fiber synapse (Dittman et al. 2000) by including a novel description of feed-forward inhibition. This new model, which we refer to as an FDI model because it includes facilitation (F), depression (D), and inhibition (I), provides an accurate description of the PF synapse in the ELL under our experimental conditions. A detailed analysis of our model suggests that not only can this synapse be tuned to exhibit different levels of gain control, but that it also may be tuned to transmit different types of transient stimuli. These diverse filtering characteristics suggest that the PF feedback pathway could play an important role in adaptive sensory processing in the ELL.

**METHODS**

**ELL slice preparation**

The gymnotiform fish, *Apteronotus leptorhynchus* (male or female, 10–15 cm in length) were anesthetized in oxygenated water containing 0.2% 3-aminobenzoic ethyl ester (MS-222; Sigma). Surgical procedures and slice preparation were performed as previously described (Berman and Maler 1998b; Mathieson and Maler 1988). True-transverse 350-μm slices of the ELL were obtained and transferred to an interface-type slice chamber. Slices were perfused (2 ml/min) with bubbled (95% O2 -5% CO2), room-temperature (20°C) artificial cerebrospinal fluid (ACSF) containing (in mM) 124 NaCl, 24 NaHCO3, 10 d-glucose, 1.25 KH2PO4, 2 KCl, 2 CaCl2, and 2 MgSO4. A recovery period of 1–2 h was allowed before recordings were made. In experiments aimed at assessing the effects of GABA-A-mediated inhibition, the GABA-A antagonist SR-95531 (Tocris Cookson) was bath-applied (5 μM in ACSF). All protocols were approved by the University of Ottawa Animal Care Committee.

**Stimulation and recording**

The ELL comprises several morphologically and functionally distinct layers (Berman and Maler 1999; Maler and Mugnaini 1994): dorsal molecular layer (DML), ventral molecular layer (VML), stratum fibrosum (StF), pyramidal cell layer (PCL), granule cell layer (GCL), deep neuropil layer (DNL), and the deep fiber layer (DFL). There are three main inputs to ELL neurons: 1) the primary afferents, which run through the DFL and then form synapses with granule cells and pyramidal cells in the DNL (Fig. 1A), 2) the direct-feedback fibers of the StF, which originate in the nucleus praeminentialis (nP) and form synapses in the VML (not shown), and 3) the cerebellar PF of the indirect feedback pathway, which form synapses in the DML (Fig. 1A). The PFs originate from granule cells in the caudal region of the cerebellum [eminentia granularis posterior (EGp)] and course through the DML perpendicular to the orientation of the apical dendrites of the ELL pyramidal neurons, as they do in the cerebellar molecular layer (Maler 1979; Maler et al. 1981).

Parallel fibers in the DML were stimulated through a stimulus isolation unit (Digitimer; 20–25 V) using two tungsten microelectrodes (2–4 MΩ; FHC, Inc.) in a bipolar configuration, placed in the more dorsal half of the DML and about 300–400 μm lateral to the recording site. The electrode pairs were oriented perpendicular to the parallel fibers, about 100 μm apart. Trains of 20 stimulus pulses were delivered with either constant intervals (periodic trains) or randomly distributed intervals (random trains). The random intervals were computer generated from exponential distributions that were truncated to have a minimum interval of 10 ms (intervals smaller than this made it difficult to resolve the synaptic response). Three different random sequences were generated for each of two mean frequencies, 4 and 16 Hz. Each random train was repeated three times in each slice, with the mean responses over these trials taken as the response for that slice. Depending on the experiment, slice data from periodic trains was a mean of one to three individual trials. The different trains were delivered in a randomized block pattern, with ≥2 min between the delivery of successive trains.

Field potential recordings of the synaptic responses to stimulus trains were recorded using glass microelectrodes (3–10 MΩ) filled with 1 M NaCl) as in previous studies (Berman et al. 1997). The electrode tips were placed in the DML of the centromedial segment (CMS) of the ELL at a depth of 30–60 μm and along the parallel fiber.
axis, medial to the stimulation site. Intracellular recordings were made using sharp microelectrodes beveled to 60–80 MΩ (filled with 3 M KAc) with tips placed in the PCL of the centromedial segment. Both field and intracellular recordings were amplified and filtered (DC-1 kHz, Axoclamp-2A; Axon Instruments), digitized at 5 kHz (ITC-16; Instrutech, Greatneck, NY), and acquired using Pulse Control (Instrutech) and Igor Pro (Wavemetrics, Lake Oswego, OR) software running on a Power Macintosh 7100. We quantified the synaptic responses in both types of recordings by measuring the peak deflection from baseline. The baseline was taken as the average potential in a 2-ms window just previous to stimulus onset. All amplitudes are expressed as mean ± SE in either absolute or normalized units (unless otherwise noted).

Model description

In this paper, we discuss short-term synaptic plasticity (transient facilitation- and depression-like processes) having time scales less than 1 s. Typically, such processes are modeled using so-called FD models (Dayan and Abbott 2001; Fisher et al. 1997). In an FD model, a stimulus-evoked postsynaptic potential (PSP) is typically described by a combination of processes that can either increase (F processes) or decrease (D processes) the PSP amplitude relative to its control value (A). After each stimulus arrives, the values of F and D change by discrete amounts (the update magnitudes) and then decay exponentially, between stimuli, toward a resting value. This general formalism has been used to describe many different synapses with the details of implementation varying among these cases (e.g., Dittman et al. 2000; Hempel et al. 2000; Tsodyks and Markram 1997; Varela et al. 1997).

Because a conventional FD model was not able to capture all features of our data resulting from both periodic and random stimulus protocols, we modified a previous FD model of a cerebellar parallel fiber synapse (Dittman et al. 2000) and added a depression-like term that describes the inhibition due to PF activation of interneurons in the ELL molecular layer—we refer to this model as the FDI model. The response of the FDI model to the ith stimulus delivered at a time ti is given by a combination of three different processes (Eq. 1)

\[
PSP_i = A_i \cdot F(t_i) \cdot D(t_i) \cdot I(t)
\]

Equation 1

The basic formulation of the FD portion of our model has been described in detail previously (Dittman et al. 2000), so we simply outline our modifications in the following sections.

FACILITATION. As in the original model of Dittman et al. (2000), our model uses a single facilitation term (F) whose value is given by Fc passed through a squashing function (Eq. 3) such that F varies between a minimum value of Fa at rest and a maximum value of one (i.e., the maximum release probability). The process Fc has conventional FD model dynamics (Eq. 2) and is associated with the calcium-dependent vesicle release process. Here, and in all further discussion, the times (in seconds) of stimulus arrival are given by ti. At each time ti, the value of Fc is increased by the update magnitude ΔF and then recovers exponentially to its resting value of zero. The parameter τF was the only free parameter for the fitting process because the two other parameters were held constant (the recovery time constant τF = 0.1 s; and the baseline release probability Fa = 0.1) at values close to those of the original model (Dittman et al. 2000)

\[
\frac{dF_c(t)}{dt} = -\frac{F_c(t)}{\tau_F}
\]

Equation 2

\[
F_c(t) \rightarrow F_c(t) + \Delta_F \quad \text{when} \quad t = t_i
\]

\[
F(t) = F_a + \frac{1 - F_a}{1 + (1/F_c(t))}
\]

Equation 3

In principle, we could describe the data presented in this paper using Eq. 2 alone, but we chose Dittman’s original formulation (using both Eqs. 2 and 3) because it will enable us, in future studies, to evaluate the dynamic effects of changing the baseline release probability F_a.

DEPRESSION. In addition to a single facilitation term, our model contains a single depression term that is identical to that described in Dittman et al. (2000), except that it does not include a calcium-dependent time constant (Eq. 4). We have no data in our system suggesting that this time constant may vary, so τD was set to 0.083 s (a value close to the initial conditions used in the Dittman model) and did not depend on stimulus history. The dynamics of this D process are similar to those of the F process. The difference is that when D is updated at every stimulus, it is decreased by an amount equal to the product FD (see Dittman et al. 2000 for more details). The result of this update rule is that the larger F becomes the more prone the synapse becomes to depression

\[
\frac{dD(t)}{dt} = \frac{1 - D(t)}{\tau_D}
\]

Equation 4

\[
D(t) \rightarrow D(t) - F(t)D(t) \quad \text{when} \quad t = t_i
\]

Equation 5

INHIBITION. Most models of short-term synaptic plasticity are focused on the dynamics of presynaptic inputs and therefore the experimental conditions usually involve blocking inhibition. However, the combination of presynaptic plasticity and feed-forward inhibition can result in diverse computational properties (e.g., Buonomano 2000; Buonomano and Merzenich 1998). Inhibition associated with PF input to ELL acts on a time-scale of less than 1 s (Berman and Maler 1998a), and so its transient dynamics may be important for ELL processing of transient stimuli. Thus we wished to have a description of the short-term dynamics of the PF synapse in ELL that included inhibition, yet that was of the same level of complexity as conventional FD models.

In ELL, parallel fibers synapse with both pyramidal neurons and inhibitory interneurons in the DML (Fig. 1A). We assume that this input is identical for both types of neurons and that its dynamics are given by the product of the (presumed presynaptic) facilitation and depression terms, F(t) · D(t). In other words, the input to the interneurons (sI) is proportional to F(t) · D(t), and it is this that determines the update magnitude for inhibition Δi at each stimulus pulse (Eqs. 5 and 6). The scaling term related to this input, ki, is a free parameter that we refer to as the gain of inhibition. The dynamics of this inhibition (I), assumed to be a lumped contribution of the three interneuron types, are modeled as a conventional FD process (Eq. 7).

This formulation is such that the inhibition acts to scale the amplitude of the PSP (see Eq. 1) (Berman and Maler 1998a). The duration of this inhibitory effect was found to be approximately 300 ms (Berman and Maler 1998a), so τI = 0.3 s. Note that the inhibition at these synapses in ELL is GABA_A-mediated and GABA_B antagonists have no effect (Berman and Maler 1998a)

\[
s_I = k_F F(t) D(s)
\]

Equation 6

\[
\Delta_i = \frac{\exp(2(4 - s_I))}{1 + \exp(2(4 - s_I))}
\]

Equation 7

\[
\frac{dI(t)}{dt} = \frac{1 - I(t)}{\tau_I}
\]

Equation 8

\[
I(t) \rightarrow \Delta_I(t) \quad \text{when} \quad t = t_i
\]

Equation 9

At each stimulus (t = t_i), the value of I is decreased by the fraction Δi and then decays exponentially to a resting value of one. The input to the inhibitory process, sI (Eq. 5), determines the value of Δi through the input-output function in Eq. 6; for small sI, Δi is close to one, resulting in a small inhibitory effect, and for large sI, Δi is close to zero, resulting in a large inhibitory effect.
Simulations

To assess the impact of the dynamics of this synapse on signal transmission, we consider a situation in which 100 presynaptic inputs are delivered to a simple "postsynaptic" neuron. Each input consists of a poisson-distributed spike train with a given mean frequency. The postsynaptic neuron is a simple linear integrator \((\tau_n = 5 \text{ ms})\) that sums all the PSPs produced by the active inputs at each simulated time step (Eq. 8). The set of spike times for the \(j^{th}\) input is given by \(\{t_i\}\)

\[
\frac{dV(t)}{dt} = -\frac{V(t)}{\tau_n} + \sum_{j=1}^{100} \text{PSP}_j(t)\delta(t - t_i)
\]  

(8)

We considered three different scenarios for the dynamics controlling the amplitude of each input (PSP): 1) no plasticity condition, where PSP is equal to one and does not vary throughout the simulation; 2) FDI condition, where PSP is given by the dynamics of \(F\) and \(D\) processes alone (analogous to blocking inhibition in the full FDI model or setting \(E\) equal to one); and 3) FDI condition, where PSP is given by the dynamics of the full FDI model.

For the results shown in Fig. 8, the mean and variance of \(V(t)\), under each condition, were calculated over 10 s of simulation time after all transient behavior had decayed. To assess the relative performance of the model under the different conditions, the signal-to-noise ratio (SNR, Eq. 9) was calculated for the responses to two types of transient inputs: step changes and Gaussian changes in the mean frequency of the poisson inputs. For the results shown in Fig. 10, the mean \(\mu_v\) and variance \(\sigma_v^2\) of \(V(t)\) was estimated at two time points, \(t_1\) and \(t_2\) (see Fig. 9)

\[
\text{SNR} = \frac{(\mu_v(t_1) - \mu_v(t_2))^2}{\sigma_v^2(t_1) + \sigma_v^2(t_2)}
\]  

(9)

For step changes, the time at which the step occurs was denoted as \(t = 0\) s, \(t_1 = 0.005\) s and \(t_2 = 1\) s. This choice of comparison points was chosen such that a larger SNR would result when the system produced larger transient responses to stimuli and very little responses to constant changes (i.e., a system with gain control would in general do better than one that simply followed the stimulus time course). For Gaussian changes, the time at which the Gaussian peak occurs was denoted as \(t = 0\) s, \(t_1 = -1\) s and \(t_2 = 0\) s. Estimates of \(\mu_v\) and \(\sigma_v^2\) were calculated from the sample means and variances of 30 independent simulation trials at each time point.

RESULTS

In this paper, we characterize the short-term dynamics of the parallel fiber synapses that form the indirect feedback pathway to pyramidal neurons in the ELL. These synapses consist of an excitatory component and a feed-forward inhibitory component (see Fig. 1A). Our goal is to formulate a quantitative model of this pathway that captures the dynamics during short periods of activity. Such a model can then be used in larger scale models aimed at understanding the role of dynamic feedback in ELL function. To this end, we delivered stimulus trains of constant (periodic) and randomly distributed (random) intervals to PFs, while synaptic responses were measured using field potential recordings, and in some cases, intracellular recordings.

Responses to short stimulus trains

The synaptic responses from PF stimulation depended on the particular sequence of inter-stimulus intervals. Figure 1B shows the field potentials (fEPSPs) recorded during excerpts of random stimulation at two different mean frequencies in the same slice. In this slice, the control response was 0.97 ± 0.04 mV (8 trials), but for some closely spaced stimuli, the responses increased more than twofold in magnitude.

Figure 2A shows the mean normalized fEPSP (relative to the control amplitude, i.e., the first PSP in the train; 0.73 ± 0.06 mV; \(n = 9\) slices) as a function of the preceding stimulus interval for 4- and 16-Hz random trains. These data, although variable, are fit well by a single exponential (\(R = 0.86\), suggesting that a single facilitation-like process may underlie the dynamics of the PF synapse. For such a process, \(F^*\) having dynamics similar to \(F\) (Eq. 2), the relationship between the successive values of \(F^*\) and the previous interval can be derived (Eq. 10)

\[
F^*(i + 1) = 1 + (\Delta_s + F^*(i - 1))e^{-\alpha(t_i - t_{i-1})}
\]  

(10)

where the \(\{t_i\}\) are the stimulus times, the \(F^*(i)\) are the values of \(F^*\) at each stimulus, and the other parameters are similar to those defined for Eq. 2 (update magnitude \(\Delta_s\), and time constant \(\tau_s\)). Now, if the value of \(F^*(i)\) is close to one [i.e., recovery from the \((i - 1)^{th}\) stimulus is nearly complete], then \(F^*(i + 1)\) is a simple exponential function of the stimulus interval, \(t_{i+1} - t_i\) (Eq. 10). This provides a simple explanation for the exponential curve fits in Fig. 2. These results suggest that as long as multiple high-frequency events are rare (as is the case for these random trains), then the data can be explained by a facilitation process alone. However, other processes come into play under different stimulus conditions. Plotted in Fig. 2B are the mean responses to the 3rd and 20th stimuli of periodic trains (4–64 Hz; see following for details). The amplitude of the third PSP follows the simple exponential relationship with stimulus interval. However, by the 20th stimulus in a periodic train, the responses deviate significantly from this predicted behavior for the two smallest stimulus intervals. As successive

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FIG. 2. A: normalized response amplitudes (fEPSPs, from random stimulation (4 and 16 Hz mean frequency) plotted vs. the previous stimulus interval \((t_i - t_{i-1})\), from 9 different slices. The curve fit is a single exponential suggesting that the underlying dynamics involve a single facilitation-like process under these stimulus conditions: \(\text{fEPSP} = 1 + 0.98 e^{f(t_i - t_{i-1})/0.12}\) (\(R = 0.86\). B: normalized response amplitudes (mean ± SE; 9 slices) from the 3rd (left panel) and 20th (right panel) stimuli of a periodic train (frequencies of 4, 8, 16, 32, and 64 Hz). Curve is a single exponential: \(\text{fEPSP} = 1 + 0.65 e^{f(t_i - t_{i-1})/0.12}\) where \(f\) is the stimulation frequency.
high-frequency events occur, as in the case of these periodic trains, other processes exert a greater influence on the overall synaptic responses. This observation necessitated the formulation of a more complicated model that included the effects of inhibition and/or synaptic depression.

Contribution of inhibition to synaptic dynamics

The inhibitory component of the feedback in DML (Fig. 1A) is provided predominantly by the GABAergic stellate and vml interneurons (with a smaller contribution from the GC2 neurons) and mediated by GABA_A receptors on ELL pyramidal neurons (Berman and Maler 1998a; Maler and Mugnaini 1994). To determine the contribution of this inhibition to the synaptic responses to PF stimulation, we bath-applied the GABA_A-antagonist SR-95531 (5 μM) and delivered a 32-Hz periodic train and a 4-Hz random train (identical pattern of interstimulus intervals in all trials). Blocking inhibition in this way resulted in a significant increase (17%) in the amplitude of the first PSP of all trains (for both control and SR conditions) was equal to one. Comparing these re-normalized trains allows the dynamics to be compared independent of the scaling component. Blocking inhibition still had a significant effect on the responses (2-way ANOVA, $P < 10^{-5}$ for random train and $P < 10^{-7}$ for periodic train). Thus the dynamics of inhibition influence the pattern of responses to train stimulation at pyramidal neuron feedback synapses. Note also that for the periodic train in the SR-treated condition, there is a slight decrease in response magnitude during the later part of the train (Fig. 3B), suggesting that a component of synaptic depression remains after inhibition is blocked.

Quantitative model of the PF synapse

We have shown that a model of the PF synapse in ELL must include the dynamics of feed-forward inhibition. We attempted to fit the data with a conventional FD model (see METHODS), in which an independent depression-like process was used to model inhibition. With such models, we could not account for the responses to both random and periodic trains with the same parameter sets. So, we modified a recently described FD model of a cerebellar parallel fiber synapse (Dittman et al. 2000; see METHODS for details) to include feed-forward inhibition. A schematic of our model illustrates the three important processes underlying the synaptic dynamics (Fig. 4). The first two, $F$ and $D$, are essentially the same as those described in the previous model (Dittman et al. 2000). As motivated by our results in the previous section, the model also includes the influence of an inhibitory process ($I$). Because of the feed-forward nature of the inhibition (see Fig. 1A), we assume that the inhibitory process is driven by the same excitatory processes as the postsynaptic pyramidal neuron (given by the product $FD$). This is a critical assumption, but as yet, we have no data on the specific dynamics of either the presynaptic inputs to the inhibitory interneurons or the interneurons’ release dynamics. It should be noted however, that in cortex there can be differential plasticity at synapses among pyramidal neurons and inhibitory interneurons (Galarreta and Hestrin 1998; Reyes et al. 1998).

The model involves two free parameters: $\Delta_F$, the update magnitude of the $F$ process, and $k_I$, the gain of the inhibition. The accuracy of the model in describing a particular data set is given by the root-mean-squared difference (RMS error) between the two. We used a subset of the data to fit the model and another subset to test the model. We considered a fit to be adequate when the RMS error was less than the SD of the individual responses (Hunter and Milton 2001). On average, this trial-to-trial variation was 14% (SD; 9 slices).

Fitting the model

The first step in the fitting process was to consider the data from experiments where inhibition was blocked (Fig. 3). In these cases, the parameter $k_I$ was set to zero and the model consisted of $F$ and $D$ processes alone. For simplicity, the data were normalized to the amplitude of the first response in all cases (so $A_0 = 1/F_0$). The mean data from periodic stimulation (Fig. 3B, ○) was well described by the model ($\Delta_F = 0.13; \text{RMS error} = 3.2\%$). The model, with this parameter set, was then tested on the data from random stimulation without inhibition (Fig. 3A, ○). The resulting RMS error of 8.8% suggests that the model provides a good overall description of the dynamics of this synapse in the absence of inhibition.

In the next step of the fitting process, we considered the control data shown in Fig. 3 (●). The parameter $\Delta_F$ was held constant at the value from the previous fit ($\Delta_F = 0.13$), and $k_I$ was a free parameter. Again, the model provided a good fit to the periodic data ($k_I = 10.4; \text{RMS error} = 2.6\%$). Testing this
parameter set on the random stimulation data produced an RMS error of 9.2%. These results suggest that the short-term dynamics of the PF synapse can be accounted for by the combination of three simple processes, facilitation (\(F\)), depression (\(D\)), and inhibition (\(I\)).

We also tested the model on an additional set of data in which periodic trains were delivered at various frequencies (Figs. 5 and 6). With both \(\Delta_F\) and \(k_I\) allowed to vary, we fit data from 4, 16, and 64 Hz simultaneously and then tested the fit on data from 8- and 32-Hz stimulation. For this data set as well, the model performed well (the combined RMS error for the fits to 4, 16, and 64 Hz data was 6.4% and those for 8 and 32 Hz were 2.4% and 2.6%, respectively). Figure 6 summarizes these data and the model performance for the responses to the 3rd and 20th stimuli of the periodic trains. An interesting feature of the dynamics here is that on the shorter term (3rd pulse) the synapse is high-pass, whereas in the longer term (20th pulse) it is band-pass. This suggests that the PF synapse may be particularly sensitive to burst-like input, where short-duration high-frequency events are separated by periods of relative inactivity.

The conclusions made from field potential recordings were confirmed using intracellular recordings during stimulation with periodic trains of 4, 8, 16, and 32 Hz (3 cells in 3 different slices, data not shown). Overall the means of the intracellular PSPs were well correlated with those recorded using field potentials (\(R = 0.75\)). This is in line with previous studies of the direct feedback pathway to ELL, where good agreement between field potential and intracellular recordings was also found (Berman et al. 1997; Oswald et al. 2002).

Accounting for variations in the mean responses

Thus far, the performance of the model has been discussed with respect to data that have been averaged over many individual slices. It is also important to consider the model’s ability to account for the responses observed in individual slices. Therefore we fit the model to these data, from both random and periodic stimulation (60 response sets in 21 slices), with the same two free parameters, \(\Delta_F\) and \(k_I\). Overall, the average RMS error was 9% and only seven response sets (out of 60) did not meet the criterion for an adequate fit. The resulting values for the two parameters varied over the different response sets (\(\Delta_F = 0.11 \pm 0.08; k_I = 13.4 \pm 7.2; \text{mean} \pm \text{SD}\), reflecting the variability of the response sets. However, the ability of the model to account for these variations provides further support that the model captures the important features of the short-term synaptic dynamics of the PF synapse.

**FDI model: frequency tuning of inhibition**

Having a simple description of the PF synapse allows us to assess the contributions of the individual components to the overall synaptic dynamics. Figure 7A shows the responses of \(F\) and \(I\) components separately during periodic trains of different frequencies. At frequencies below 32 Hz, the \(F\) component shows no depression and hence the response of the

![FIG. 4. Schematic of the different processes involved in the FDI model. The boxed-in region represents the original model (FD model) from Dittman et al. (2000). We have modified the model and added an inhibitory process to account for our experimental observations. At each stimulus, the 3 main processes (\(F, D, \text{and } I\)) are updated according to the different rules: the update of \(F\) depends on the parameter \(\Delta_F\), and \(F\) depends on \(F\) through a squashing function (Eq. 3); the update of \(D\) depends on \(\Delta_F\) through a squashing function (Eq. 3); and that of \(I\) depends on the product \(FD\) (Eqs. 5–7). See METHODS for more details.](image)

![FIG. 5. A–D: mean normalized responses to periodic trains of different frequencies (\(n = 8, 7, 12, 8\) slices for 8, 16, 32, and 64 Hz, respectively). Solid curves represent responses of the model to the same stimulus trains (\(\Delta_F = 0.077\) and \(k_I = 13.3\)).](image)
inhibitory component $I$ increases with frequency. The inhibitory response at 64 Hz, however, is less than that produced at 32 Hz (at least for the later pulses); at this frequency there is evidence of a prominent depression in the $FD$ response, and because this is the input to the inhibitory component, inhibition decreases when the $FD$ component is more depressed. These dynamics may play a critical role in signal processing, as we shall see later. Figure 7B summarizes the tuning of inhibition for both the 3rd pulse and the 20th pulse of periodic trains at different frequencies, for a range of values of inhibitory gain ($k_i$) corresponding to that found in our data (see Accounting for variations in the mean responses). The level of inhibition at the third pulse is relatively small, resulting in a decrease in the PSP of only a few percent for intermediate values of $k_i$. However, by the 20th pulse, the influence of inhibition is substantial and for large values of $k_i$ can result in more than a 70% reduction in the control PSP amplitude.

**Impact of FDI model dynamics on synaptic inputs**

In this section, we consider the effects of 100 independent Poisson trains of inputs onto a simple model neuron and evaluate how the dynamics underlying these inputs can affect the neuron’s response. In a biophysically realistic model, the effects of synaptic inputs would be a combination of direct effects on membrane voltage and those due to changes in membrane conductance (Hô and Destexhe 2000). But here, as a first step in evaluating the complex effects of the synaptic dynamics due to an FDI model, we chose a simplified approach where the postsynaptic neuron is nonspiking and whose synaptic inputs affect only its membrane voltage.

**STEADY-STATE GAIN CONTROL.** First, we investigated the response of the model neuron under steady-state input conditions. In these simulations, the mean frequency of the Poisson inputs was held constant and the neuron’s behavior was characterized over 10 s of simulation time, after transient behavior had decayed (about 1 s). This was done for three different conditions on the dynamics of the inputs: no plasticity, $FD$ dynamics, and $FDI$ dynamics (see METHODS and Fig. 8 legend). It is important to realize that the $FD$ and $FDI$ conditions represent a range of conditions most likely present in ELL, as the gain of inhibition can itself be a dynamic variable, albeit over much longer time scales than those considered here (Bastian 1998a). Figure 8 shows the normalized mean and normalized variance of the voltage trace as a function of mean input frequency for each condition (both measures are normalized to the mean voltage at 1 Hz). For low-input frequencies, the mean voltage increases similarly with frequency in all conditions. In the no plasticity condition, the mean scales linearly with the mean input frequency, as is theoretically predicted by Campbell’s theorem (Papoulis 1991). However, beyond a certain frequency, both the $FD$ and $FDI$ (but not the no plasticity) conditions show behavior characteristic of the gain control found in classic models of synaptic depression (e.g., Abbott et al. 1997). The transition to the gain control regime is different in each case, occurring at about $30–40$ Hz for the $FD$ condition and at about $8–10$ Hz for the $FDI$ condition. Overall, the $FDI$ condition results in gain control over a much larger frequency range than the standard $FD$ condition. Thus by simply varying the level of inhibition, the ELL can systematically vary the gain and frequency filtering of its feedback inputs.

The variance of the neuron’s voltage also varies with input frequency in a manner dependent on the conditions of the input dynamics. In the no plasticity condition, the variance increases linearly with input frequency, again as predicted by Campbell’s theorem (Papoulis 1991). However, in the $FD$ and $FDI$ conditions, the variance increases to a maximum and then decreases at higher input frequencies; it begins at lower frequencies and ends with a lower final value in the $FDI$ conditions. This is a direct consequence of the gain control behavior of the $D$ and $I$ processes, and it may have important implications for the function of this feedback pathway in a closed loop situation (see DISCUSSION).

**DETECTION OF TRANSIENT SIGNALS.** In addition to characterizing the steady-state behavior of this model system, we also tested its responses to two types of transient stimuli: 1) step changes and 2) Gaussian changes in mean input frequency. The first stimulus type (step changes) was chosen because synapses that depress are particularly well suited to signal proportional changes in input (e.g., Abbott et al. 1997; Tsodyks and Markram 1997). To effectively do this, accurate steady-state gain control is required, so this type of stimulus allows us to evaluate the impact of the different input conditions on transient signaling and gain control simultaneously. This type of input may occur in social contexts, during electrocommunication. The second stimulus type (Gaussian changes) was chosen because this is the time-course of input expected from the typical prey of these fish or from self-motion (Bastian 1995; Lewis and Maler 2001; MacIver et al. 2001; Nelson and MacIver 1999). Also, because the input frequency returns to the original baseline after the transient increase, gain control is not critical in the processing of this type of stimulus.
Figure 9 shows responses to the two types of stimuli for the FD and FDI conditions. The step response in the FD condition shows the behavior typical of a depression-dominated synapse: transient increase and return to baseline (Fig. 9A, middle trace). We begin to see the complexity of the FDI model when its step response is considered (Fig. 9A, bottom trace). Here, the step is signaled by a brief transient, but because the synapse becomes depressed (i.e., due to the FD component), inhibition is actually relieved, so the net response eventually increases to a value proportional to the step stimulus. The Gaussian response in the FD condition is essentially nil (Fig. 9B, middle trace); the stimulus is slow enough to be filtered out by the depression process. In the FDI condition, however, the voltage response follows the stimulus very well. Again, this is due to a reduction of inhibition; the FD component becomes transiently smaller due to a relatively greater influence of depression (compared with facilitation), thus decreasing the input to the inhibitory process and allowing a larger net input. It must be emphasized that the behavior of these synapses depends very much on the baseline input frequency (which determines the initial values of $F$, $D$, and $I$), as well as the gain of inhibition $k_I$, so the previous examples should not necessarily be considered representative.

Now, we present a more general description of the responses to these stimuli as a function of baseline input frequency. To quantify the responses, we calculate the SNR (see Eq. 9) between the voltages at two time points (indicated by the arrows in Fig. 9; see Methods for details). The SNR provides a measure of how reliably a signal can be distinguished from a background level. In the case of the step stimulus, we chose our “background” at a time after the step occurred; the SNR calculated in this way takes into account not only the signaling of the transient step but also the ability of the synapse to cancel out constant stimuli (i.e., perform gain control). A more conventional approach for signal detection would be to compare the transient response to the activity before the stimulus. Such an analysis would produce results different from those presented here, because it would emphasize the response transient and not the role of gain control. Figure 10, A and B, shows the SNR for both step and Gaussian stimuli under the three different input conditions. The ability of FD synapses to signal step transients at high baseline frequencies is reflected in a large SNR (Fig. 10A, ○), but the FDI synapse performs relatively poorly in this situation (Fig. 10A, ●). Conversely, the FDI synapses out-perform the FD synapses when Gaussian stimuli are given against a high baseline frequency (Fig. 10B). These are the conditions discussed in the context of Fig. 9 (i.e., high baseline frequency). For low baseline frequencies, the FDI synapse is better than the FD synapse at signaling step transients, whereas the opposite is true for Gaussian transients. While the dynamics considered here always improves the signaling of step changes in input frequency, the no plasticity condition out-performs both the FD and the FDI synapses when Gaussian transients are presented. However, the no plasticity condition would be prone to the effects of saturation of the output neuron, but we have not considered such nonlinearities in the present analysis. In summary, depending on the level of background activity, the level of inhibition (i.e., no inhibition corresponds to the FD condition) can determine what types of signals are best transmitted by these synapses. This potential for differential stimulus filtering at different levels of baseline activity and inhibitory gain is intriguing, but we do not yet understand how it will impact the behavior of ELL pyramidal neurons in a closed-loop situation. Under such conditions, the pyramidal neurons’ activity would be governed by sensory input, as well as direct and indirect feedback inputs.

**Discussion**

In this paper, we have characterized the short-term dynamics of a PF feedback pathway to a primary electrosensory nucleus (ELL). By repeating different patterns of PF stimulation, under
control conditions and when inhibition was pharmacologically blocked, we were able to determine the contribution of inhibition to the overall synaptic dynamics. Thus our description includes the contribution of inhibition, as well as that of classic forms of synaptic plasticity (i.e., facilitation and depression). This is in contrast to many traditional studies of short-term synaptic plasticity in which inhibition is either blocked or analyzed independently of facilitation and depression. We have developed a simple model of the PF synapse (FDI model), that combines previously described features of synaptic facilitation and depression (Dittman et al. 2000), with a novel method of describing feed-forward inhibition. Our analyses show that the combination of these three processes confers diverse and non-intuitive filtering properties to this synapse.

Model of the PF synapse combining facilitation, depression, and inhibition

The indirect feedback pathway of the ELL consists of PFs arising from cerebellar granule cells in the eminentia granularis posterior (EGr) of the cerebellum (Maler 1979; Maler et al. 1981). In ELL, they make monosynaptic excitatory contacts with pyramidal neurons and three types of inhibitory interneurons (Fig. 1A). These interneurons then synapse onto the pyramidal neurons, forming a feed-forward inhibitory component to the PF synapse. The parallel fibers in ELL are ultrastructurally similar in every way to those in mammalian cerebellum (Maler 1979; Maler et al. 1981). Therefore, as a starting point for our model description of the PF synapse, we chose a previous model of short-term presynaptic plasticity in rat cerebellar parallel fibers (Dittman et al. 2000). This model consists of a facilitation process and a depression process, and by choosing different parameters, it was shown to account for a variety of different synapses (Dittman et al. 2000). We chose parameters similar to those found for the PF synapse (see METHODS). In doing so, we have assumed that the facilitation and depression occurring in ELL PFs is presynaptic in nature and similar to that observed in rat cerebellum. In addition, our data (when inhibition is blocked) suggest that this is the minimum number of processes that underlie PF synapse short-term plasticity in ELL.

In extending the previous model to include the effects of inhibition, we wished to maintain a similar level of simplicity to make a detailed understanding of the model possible and to allow its practical implementation in network simulations.

![Figure 8](http://jn.physiology.org/)

**FIG. 8.** Steady-state characterization of the model neuron’s voltage response to 100 inputs as a function of mean poisson input frequency: mean level (A) and variance (B) of V, calculated from 10 s of simulation time (transients excluded). Both measures are normalized to the mean value of V at 1 Hz. Three different conditions on the input dynamics are considered: 1) no plasticity, where the amplitude of each input is constant throughout the simulation, 2) FD, where FD dynamics alone control the amplitude of the inputs (i.e., inhibition blocked; $\Delta_0 = 0.1$), and 3) FDI, where the full FDI model describes the dynamics of each input ($\Delta_0 = 0.1$ and $k = 20$).

![Figure 9](http://jn.physiology.org/)

**FIG. 9.** Examples of the model neuron’s voltage responses to (A) step and (B) Gaussian ($\sigma = 0.15$ s) changes in frequency (baseline mean frequency of inputs is 70 Hz). Amplitude of the step is $\pm 70$ Hz and the peak amplitude of the Gaussian change is $\pm 70$ Hz (i.e., the contrast is equal to 1). Arrows indicate the time points, $t_1$ and $t_2$, that were used for signal-to-noise ratio (SNR) measurements. In A, the time at which the step occurs was denoted as $t = 0$ s, the left arrow at $t_1 = 0.005$ s and the right arrow at $t_2 = 1$ s. In B, the time at which the Gaussian peak occurs was denoted as $t = 0$ s, the left arrow at $t_1 = -1$ s and the right arrow at $t_2 = 0$ s. Vertical scale bars are 0.1 and 0.025 (arbitrary units) for the FD and FDI cases, respectively, and apply to both A and B. The duration of all traces is 2 s.

![Figure 10](http://jn.physiology.org/)

**FIG. 10.** Summary of the model responses to the 2 types of transient inputs described in Fig. 9. The performance, measured as the SNR, is plotted vs. baseline mean frequency of the poisson inputs. The step size and the peak change in frequency for the Gaussian was equal to 50% of the baseline frequency (i.e., the contrast was equal to 0.5). Three conditions are evaluated as in Fig. 8, and results are plotted with closed circles (FDI), open circles (FD), and a solid line (no plasticity). Values plotted are mean ± SE over 5 different simulations (see METHODS for more details).
aimed at an understanding of neuronal feedback in closed-loop conditions. We thus made two important assumptions: 1) inhibition scales the amplitude of the PF-evoked PSP in pyramidal neurons (see Eq. 1) and 2) the direct “input” to the inhibitory process is the same as that received by the postsynaptic pyramidal neuron (i.e., the product of $F_D$, see Fig. 4). The first assumption is not unreasonable because feed-forward inhibition has a gain control mechanism built-in: the larger the excitatory input, the larger the inhibitory input. In addition, previous data from ELL pyramidal neuron responses to single PF stimulus pulses showed the smaller IPSP overlapped in time with the larger EPSP so that when inhibition was blocked, the net excitatory PSP simply increased in amplitude (Berman and Maler 1998a). In other words, the major effect of inhibitory inputs appears to be to control EPSP amplitude. Of course, because the inhibitory process is dynamic, the effect on the EPSP will vary with stimulus history. The second assumption is justifiable only on the basis that it is the simplest situation—we have no data in our system that can separate the PF input to the interneurons and the interneurons input to the pyramidal neurons. However, in the cortex, excitatory and inhibitory synapses among pyramidal cells and interneurons can exhibit differential synaptic plasticity (Galarreta and Hestrin 1998; Reyes et al. 1998). It remains to be seen if this is also the case for the PF synapse in ELL; for the present purpose, we assume that is not.

The manner in which we implement the feed-forward inhibitory process in our $FDI$ model is similar to how an independent depression process would be implemented if we had not pharmacologically isolated the contributions of inhibition. In other words, the overall dynamics of the $FDI$ model could be similar to that of a pure $FD$ model with two depression terms (i.e., $F, D_1, D_2$). However, we were not able to fit such a model to our data. It is likely that the feed-forward nature of the inhibitory input (i.e., that its influence is controlled by the product $FD$) would confer different dynamics to the $FDI$ model unless the $D_2$ term depended on both $F$ and $D_1$, which is typically not the case in such models. One advantage of having inhibition control synaptic dynamics rather than an additional depression term is that it may be easier to regulate. As we show in this paper, simply changing the gain of inhibition can have a significant effect on synaptic filtering. In addition, experimental manipulation of inhibition is easier (i.e., through specific pharmacological blockers) compared with those aimed at presynaptic processes underlying short-term depression—this bodes well for future in vivo experiments aimed at determining the role of feedback inhibition in a closed loop situation.

Gain control in the ELL

In a series of elegant studies (Bastian 1986; Bastian 1998a), the indirect feedback pathway to ELL was shown to be critical for long-term gain control. Long-term synaptic depression (LTD) has been shown to underlie this gain control (Bastian 1998a), and at least in part, this depression is mediated through postsynaptic mechanisms in pyramidal neurons (Bastian 1998b). It is not clear however whether the “depression” is due to increased inhibition, decreased excitation, or both (Bastian 1998a; Roberts 2000).

Our results on the short-term changes at this synapse reveal another form of gain control (Fig. 8). This is due to the steady-state dynamics of the $FDI$ model. A consequence of this is that the variability of this feedback actually goes down with increasing activity in the parallel fibers (Fig. 8B). An interesting and potentially critical aspect of this gain control is evident when this plasticity is considered in the context of an intact feedback pathway. As previously discussed, gain control is critical in the ELL and is mediated by the indirect feedback pathway. At high levels of sensory input, the feedback pathways are presumably (at least transiently) subject to higher activity levels (Bastian 1993; Bastian and Bratton 1990). Such increased activity would result in more “noise” being injected into the system through the increasingly noisy feedback, potentially resulting in deleterious effects on sensory coding at high levels of sensory input. This would be prevented by the intrinsic gain control mechanisms we describe (due to $FDI$ dynamics), which also results in noise control, i.e., reduction in net synaptic variance at high-input frequencies.

Signal processing in the ELL

The activity in the indirect feedback pathway can be influenced by a number of sensory stimuli. During tail-bending behavior (that occurs over a 200- to 500-ms time period), PF activity is likely to be modulated both by proprioceptive input and by the resulting broad-field changes in the fish’s electric field (Bastian 1995). Communication signals, or “chirping” events, may also influence the activity of indirect feedback; these are active high-frequency step-like modulations in electric organ discharge (EOD) (Bastian et al. 2001; Metzner 1999; Zupanc and Maler 1993). In addition, it is possible that local modulations in the electric field, such as those produced by small objects, also influence this feedback pathway (Bastian 1993).

It is not known in detail how these different sensory stimuli are reflected in the firing frequency of the PFs in the indirect feedback pathway. Reversibly blocking the EGp connections to ELL produced complicated effects on pyramidal neurons that cannot be completely explained by the role of this pathway in gain control; the responses of pyramidal neurons to moving objects increased but their baseline firing rates decreased slightly (Bastian 1986). In another study, pharmacologically blocking either glutamatergic or GABAergic input from feedback fibers within the DML did not affect baseline firing, although it strongly affected pyramidal neuron responses to electrostimulatory stimuli (Bastian 1993). This suggests that the steady-state influence of the indirect feedback pathway is minimal. The nP multipolar neurons that project to EGp granule cells show bursty spontaneous firing rates around 70 Hz, but they can fire as high as 700 Hz during stimuli such as step changes in EOD amplitude (Bastian and Bratton 1990). Additional input to EGp granule cells comes from proprioceptive neurons, which can fire at 50–250 Hz during tail bending (Bastian 1995). Thus it seems reasonable to assume that the parallel fibers have a large range of firing frequencies and may often exhibit burst-like firing at high mean frequencies. Cerebellar granule neurons in turtles can fire at rates higher than 100 Hz and are particularly responsive to bursty inputs (Gabbiani et al. 1994). It will be important to characterize the baseline and evoked firing statistics of EGp granule cells, because this will allow the $FDI$ model to better predict the
dynamics of the parallel fiber feedback pathway under in vivo conditions.

To provide insight into the possible functional roles of the feedback dynamics described here, we explored the responses of a simple model neuron to two different types of transient stimuli (Fig. 9): step changes and Gaussian changes in the mean frequency of poisson firing presynaptic inputs. These two types of stimuli can be loosely compared with the stimuli discussed above, namely those produced by chirs, and tail-bending or small objects, respectively. Interestingly, stimuli due to predictable events such as tail-bending are gradually filtered out by active mechanisms that involve the indirect feedback pathway (Bastian 1995; Bell 2001). Inspection of the simple example in Fig. 9 suggests a nonintuitive mechanism for such filtering, specifically that the response to a Gaussian-type transient can be eliminated by the down-regulation of inhibition. This simple example emphasizes the complexity that can result from the combined dynamics of synaptic plasticity and inhibition in an FDI-type synapse.

Another interesting aspect of an FDI-type synapse is that its mean level of activity can result in diverse filtering properties. For low levels of background activity, the FDI synapse is relatively unresponsive to transient changes in input. This can also be the case for high background activity, depending on the level of inhibition. Low levels of inhibition (as for the FD condition of Fig. 10A) result in extremely effective signaling of step-like stimuli; high levels of inhibition result in effective signaling of Gaussian-like stimuli (Fig. 10B). Recently, the dynamics of primary afferent neuron firing has been shown to influence the ability of these neurons to encode dynamic stimuli (Chacron et al. 2001). In this light, it will be interesting to see how such afferent encoding dynamics combine with the dynamics of direct (Oswald et al. 2002) and indirect (the present paper) feedback to influence the encoding properties of ELL pyramidal neurons.

Dynamic role of neuronal feedback

Feedback pathways are prevalent at all levels of the nervous system and they appear to play diverse functional roles. In corticothalamic pathways, feedback can control neuronal firing mode (Sherman 2001), synchronize and control oscillatory discharge (Bal et al. 2000; Blumenfeld and McCormick 2000), contribute to velocity tuning (Hillenbrand and van Hemmen 2001), and provide gain control in orientation tuning networks (Ferster and Miller 2000). In the somatosensory system, feedback has been implicated in transforming a timing code to a rate code (Ahissar et al. 2000). However, how synaptic plasticity affects and contributes to the roles of neuronal feedback is largely unknown. Flexibility of these circuits is undoubtedly crucial, and thus synaptic plasticity over a wide range of time scales must be an essential feature of feedback pathways. An understanding of the detailed mechanisms of feedback control will benefit from a dissection of the different components of the networks involved but will ultimately require the investigation of these networks under closed-loop and dynamic stimulus conditions.

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