Simulating In Vivo Background Activity in a Slice with the Dynamic Clamp

Frances Chance

Department of Neurobiology and Behavior
University of California, Irvine
Irvine, CA 92697 and

L. F. Abbott

Center for Neuroscience
Department of Physiology and Cellular Biophysics
Columbia University College of Physicians and Surgeons
New York NY 10032-2695 USA

Abstract

Neurons *in vivo* receive a large amount of internally generated "background" activity in addition to synaptic input directly driven by an external stimulus. Stimulus-driven and background synaptic inputs interact, through the nonlinearities of neuronal integration, in interesting ways. The dynamic clamp can be used *in vitro* to duplicate background input, allowing the experimenter to take advantage of the accessibility of neurons *in vitro* while still studying them under *in vivo* conditions. In this chapter we discuss some results from experiments in which a neuron is driven by current injection that simulates a stimulus-driven input as well as dynamic-clamp-generated background activity. One of the effects uncovered in this way is multiplicative gain modulation, achieved by varying the level of background synaptic input. We discuss how the dynamic clamp was used to discover this effect and also how to choose parameters to simulate *in vivo* background synaptic input in slice neurons.

1. Introduction

Much of what we know about the response properties of neurons comes from studies done in fairly inactive slices or in cell cultures. These preparations are ideal for exploring basic electrophysiological characteristics, but they do not duplicate *in vivo* conditions. Neurons in a living brain are subject to a continual barrage of activity arising from both nearby and distal sources. The synaptic input from this background barrage is highly irregular (Softky and Koch, 1993; Shadlen and Newsome, 1994; Troyer and Miller, 1997; Stevens and Zador, 1998; Jaeger and Bower, 1999; Santamaria et al., 2002; Wolfart et al., 2005; Desai and Walcott, 2006), so it acts as a source of noise that introduces variability into the stimulus-evoked responses of neurons (Schiller et al., 1976; Heggelund and Albus, 1978; Vogels et al., 1989; Holt et al., 1996). As would be expected, noise from background input limits the sensitivity and precision of stimulus-driven responses, but in some cases it can actually have an enhancing effect (Troyer and Miller, 1997; Hô and Destexhe, 2000; Anderson et al., 2000; Shu et al., 2003; Wenning et al., 2005) . In addition, background synaptic input is thought to significantly increase the membrane conductance of neurons (Borg-Graham et al., 1998; Hirsch et al., 1998; Destexhe and Paré, 1999, but see Waters and Helmchen, 2006), which affects their input integration properties (Destexhe and Paré, 1999; Azouz, 2005; Zsiros and Hestrin, 2005). The "noise" effects of background input can be mimicked *in vitro* by injecting a fluctuating current into the neuron being recorded, but this does not replicate conductance changes. Fortunately, the dynamic clamp can be used to simulate both the noise and conductance effects of background synaptic input, allowing us to bridge the gap between typically silent slice preparations and active, functioning neural circuits.

Although the summed background input to a neuron *in vivo* can be quite large, it does not, in the absence of stimulus-dependent or other drive, cause neurons to fire at high rates, nor does it hyperpolarize the neuron far below threshold. Reconciling this high level of synaptic input with a relatively small change in mean membrane potential requires the excitatory effects of background input to consist of a well-balanced combination of excitation and inhibition (Shadlen and Newsome, 1994; Shu et al., 2003; Haider et al., 2006; Baca et al., 2008; Okun and Lampl, 2008). Thus, background input to a neuron consists of large amounts of excitation and inhibition that, to a large extent, cancel each other. Cancellation between two large, random sources of opposite sign generates input currents with small means and large variances. However, in spite of the large variance of the fluctuating conductances, the membrane potential fluctuations are limited by the reversal potentials of the synaptic input currents. Attempting to mimic background synaptic input by current injection can result in unrealistically and even excessively large hyperpolarizations of the neuron, a problem that is eliminated by using the dynamic clamp.

It is convenient to divide the total synaptic input to a neuron into a component that controls the total synaptic current, which we call the driving input, and a balanced component that affects both the total synaptic conductance and the input variance arising from the synaptic input but makes little contribution to the total synaptic current. The total synaptic current to the neuron is proportional to the driving component because, by definition, synaptic currents generated by the balanced component are small. On the other hand, because the total synaptic drive consists of two large, essentially canceling terms, the total synaptic conductance and the variability of the synaptic current are dominated by the balanced component. These two components of the synaptic input can act as two independent signal-carrying channels. The driving component can be modulated by changing excitatory and inhibitory drive in opposite directions, increasing excitation and decreasing inhibition, for example. The balanced component can be modified by changing excitation and inhibition in parallel, such as increasing both excitatory and inhibitory input. Often the synaptic input to a neuron is modeled as consisting of a variable stimulus-dependent driving component and a fixed, though large, balanced component. Some studies, however, have considered the impact of modulating the balanced component of synaptic input, with interesting results. Changes in balanced input provide an alternative way of modulating neural responses (Silberberg et al., 2004; Fourcaud-Trocmé and Brunel, 2005; Khorsand and Chance, 2008) or of modifying neuronal gain, defined by the relationship between firing rate and input current (Doiron et al., 2001; Chance et al., 2002; Fellous et al., 2003; Prescott and De Koninck, 2003) or EPSP rate (Mitchell and Silver, 2003), or spiking probability and EPSC size (Hô and Destexhe, 2000; Shu et al., 2003; Chance, 2007). The gain modulation effect relies, in particular, on the impact of the conductance introduced by background synaptic input. Reproducing this effect in slice experiments therefore requires the dynamic clamp. We focus on this effect in this chapter.

In addition to demonstrating the gain modulation effect that arises from simulated background activity, we discuss in this chapter how the dynamic clamp can be used, in general, to simulate the input that a neuron might receive *in vivo* (Destexhe et al., 2001; Chance et al., 2002). In the latter part of this chapter, we focus on calculations needed to adjust the parameters of the dynamic clamp input to reproduce desired values for the mean and variance of the conductance and membrane potential.

2. Gain Modulation from Dynamic Clamp Input

The dynamic clamp allows any combination of conductance changes and current injections to be introduced into a recorded neuron. In this section, we discuss the effects of introducing a fluctuating conductance and current, similar to what would be generated by spontaneous activity *in vivo*, into a cortical neuron recorded in a slice preparation. We also analyze separate conductance and current effects by considering them independently.

2.1 Generating the Dynamic Clamp Input

The essential feature that allows conductances to be mimicked by the dynamic clamp is that the current it injects into a neuron depends on the membrane potential of the neuron.

To duplicate the effects of time-dependent excitatory and inhibitory synaptic conductances $G_{\text{ex}}(t)$ and $G_{\text{in}}(t)$ with reversal potentials E_{ex} and E_{in} respectively, the current injected by the dynamic clamp should be

$$I = G_{\text{ex}}(t)(E_{\text{ex}} - V) + G_{\text{in}}(t)(E_{\text{in}} - V)\,,$$

where V is the membrane potential of the neuron. Given computer generated values of $G_{\text{ex}}(t)$ and $G_{\text{in}}(t)$ and preset values of E_{ex} and E_{in}, this is exactly what the dynamic clamp does. We have a good idea of the values of the reversal potentials of excitatory and inhibitory synaptic conductances, so the problem of duplicating *in vivo* synaptic input lies in mimicking the time-dependent conductances that real synaptic input generates.

One way to generate a time-dependent synaptic conductance mimicking the total conductance produced by a set of afferents to a neuron is to model the spike trains carried by those afferents. Typically, these are assumed to have Poisson statistics. The dynamic clamp attempts to reproduce the effects of synapses distributed across the dendritic arbor by simulating a conductance located at the site of an electrode. Within this unavoidable approximation, the effects of all the afferents on a given conductance (excitatory or inhibitory) add linearly and the Poisson model is similarly additive, we can simply generate spikes at a rate obtained by adding together the rates on all of the afferents. This is done, for a desired total firing rate R, by generating an action potential at each small time step Δt with a probability $R\Delta t$. These Poisson-generated action potentials are then fed into a model of the synaptic conductance. A simple model, for example, increments the total conductance by an amount that represents the unitary maximal synaptic conductance every time a spike is generated, and allows it to decay exponentially back toward zero between spikes. In mathematical terms, we compute G_{ex} and G_{in} by integrating the differential equations

$$\tau_{\text{ex}} \frac{dG_{\text{ex}}}{dt} = -G_{\text{ex}} \quad \text{and} \quad \tau_{\text{in}} \frac{dG_{\text{in}}}{dt} = -G_{\text{in}}\,,$$

where τ_{ex} and τ_{in} are the decay time constants for the excitatory and inhibitory synaptic conductances, and we increment these conductances by

$$G_{\text{ex}} \rightarrow G_{\text{ex}} + g_{\text{ex}} \quad \text{and} \quad G_{\text{in}} \rightarrow G_{\text{in}} + g_{\text{in}}$$

every time an excitatory (left equation) or inhibitory (right equation) action potential is generated by the Poisson model. This model works well (with a small but inessential rise time included, see Chance et al., 2002), but later in this chapter we discuss another procedure that has the virtue of being convenient for mathematical analysis.

It is a good idea to use two recording electrodes when duplicating synaptic input with the dynamic clamp in this way: one electrode to record the membrane potential and a second to inject the computed dynamic-clamp current. Using two electrodes eliminates artifacts that can be introduced into the membrane potential measurements by the injection of rapidly fluctuating current. Figure 1a shows the membrane potential of a neuron recorded from

Figure 1: Intracellular recordings from a layer 5 pyramidal neuron in a slice of rat somatosensory cortex with and without simulated background activity. In both cases, constant current was injected to drive the neuron at approximately 5 Hz. a) The membrane potential of the spiking neuron in the absence of simulated background activity. b) The dynamic clamp was used to simulate 1X background activity. (Adapted from Chance et al., 2002.)

a slice of somatosensory cortex driven to fire by a constant injected current without any additional dynamic clamp input. The firing pattern is regular and the membrane potential shows no significant fluctuations due to the relative silence of this slice preparation. For Figure 1b, excitatory inputs were simulated at a total rate of 7000 Hz and inhibitory inputs at a total rate of 3000 Hz, representing the summed effects of many simulated afferents. The arrival times of these synaptic inputs were randomly generated with Poisson statistics. The unitary synaptic conductance for each synaptic input was set to 2% of the measured resting membrane conductance for excitatory input and 6% of the resting conductance for inhibitory input. The synaptic time constants were $\tau_{\mathrm{ex}} = 5$ ms and $\tau_{\mathrm{in}} = 10$ ms. In the following discussion, we refer to this as the 1X condition (see filled circles in Figure 2), and we will consider 2X and 3X conditions produced by doubling or tripling the rates of both the excitatory and inhibitory synaptic inputs. These parameters were chosen to achieve realistic conductance changes and levels of noise, and to put the synaptic inputs into a configuration in which excitation approximately balanced inhibition. Because of the balance between excitation and inhibition, the background synaptic activity by itself was not very effective at driving the recorded neuron. Instead, the dominant effect of this background activity was to increase the effective membrane conductance and also to introduce noise into the neuronal response, as illustrated in Figure 1b.

2.2 Multiplicative Gain Modulation in a Slice

Varying the level of dynamic-clamp background activity, by multiplying excitatory and inhibitory input rates by factors of 0, 1, 2 or 3, for example, has an interesting effect on the firing properties of a neuron. We characterize firing by plotting firing rates as a function of constant injected current. Multiple firing-rate curves are obtained by measuring the firing rate as a function of driving current for different levels of background activity. Gain is defined as the slope of the non-zero portion of the firing-rate curve. Figure 2A shows firing-rate curves of the same neuron under four different levels of background activity. For the open circles, no background activity was present. The filled circles, open squares, and filled squares are firing-rate curves recorded under 1X, 2X, and 3X conditions, respectively. The solid lines are the best linear fits to these data. The curves show that increasing background input led to a reduction of the firing rate, but did not significantly change the minimum threshold current required to fire the neuron. The dominant effect of changing the level of background activity was to divisively scale the curve of firing-rate versus input current for the neuron. This indicates a change of gain.

To create Figure 2B, the constant current input for the 1X, 2X and 3X cases were divisively scaled by appropriate factors to make the corresponding firing-rate curves overlay the control (0X or no background activity) curve (open circles). The good match between the resulting curves indicates that the gain modulation effect is, indeed, divisive (or equivalently multiplicative if we invert the scaling factors). Two different possibilities exist, however, for how the divisive effect can be realized. A firing rate function of input current, $r = f(I)$ can be scaled, as in Figure 2B, by dividing the input current by a factor c, so that $r = f(I/c)$. Alternatively, the rate itself can be scaled by a factor, $r = f(I)/c$. In either case, c takes different values for each condition. In Figure 2C, the firing rates of the control, 1X and 2X firing-rate curves were divisively scaled to overlay the 3X firing-rate curve (filled squares). This shows that the results are accounted for equally well by a scaling of the rate. In fact, it is impossible to determine whether the gain modulation effect illustrated here represents input gain control (where the input is divisively scaled) or response gain control (where the firing rates are divisively scaled). This ambiguity arises because of the linearity of the neuron firing-rate curves, but analysis of the effect suggests that raising the level of background activity results in changes in both response-gain and input-gain (Chance et al., 2002).

We summarize the effect of background activity on 18 different neurons in Figure 2D. For each neuron, the slope of the firing-rate curve for each level of background input was measured and then normalized by the gain in the 1X condition. Mean gain (averaged across all neurons recorded in each condition) is plotted as a function of rate factor (the factor multiplying the excitatory and inhibitory firing rates, i.e. the 1, 2 or 3 in the 1X, 2X or 3X conditions) in Figure 2D. The numbers under each data point describe the number of cells that were recorded in each condition.

Figure 2: Effects of background activity on the firing-rate curves of neurons. A) Firing rate-curves under 0X (no background activity, open circles), 1X (filled circles), 2X (open squares) and 3X (filled squares) conditions. Lines are linear fits. B) The firing-rate curves from (A) except that the driving currents of the 1X, 2X, and 3X firing-rate curves were scaled so that the firing-rate curves overlay the firing-rate curve in the 0X condition. C) The firing-rate curves from (A) with the firing rates of the 0X, 1X, and 2X curves divisively scaled to overlay the 3X firing-rate curve. D) Slope of the firing-rate curves, normalized to the slope of the 1X firing-rate curve, plotted as a function of rate factor. (Adapted from Chance et al., 2002.)

Although gain modulation arises through this mechanism in part because of increased variance in the neuronal input, gain modulation occurs without a corresponding change in response variability. This is illustrated in Figure 3A, where variability is measured either as the coefficient of variation of the interspike intervals (filled triangles) or the standard deviation of the membrane potential (open triangles) under different levels of background activity. This relative constancy of variability occurs because the effect of the increased variance of the synaptic current is cancelled by the increased conductance of the neuron (see Chance et al., 2002 for a more detailed explanation). This is an example of an effect for which the ability of the dynamic clamp to mimic conductances is essential.

Figure 3: Effects of background activity on the firing of neurons. A) Standard deviation of subthreshold membrane potential fluctuations (open triangles) or coefficient of variation of interspike intervals (filled triangles) as a function of rate factor. For the open triangles, constant current was injected to drive the neuron at 20 Hz. B) Firing-rate curves in the 1X condition (open circles) and with 3X current variance but 1X conductance changes (filled squares). C) Firing-rate curves in the absence of background activity (open circles) and with 32 nS of additional conductance (filled squares). D) Firing-rate curves of a neuron in the 1X (open circles) or the 3X (filled squares) condition. (Adapted from Chance et al., 2002.)

By Ohm's law, increases in membrane conductance will have a divisive effect on the subthreshold membrane potential fluctuations arising from fluctuating input current. However, the multiplicative effect on firing rate illustrated here is not simply a result of the increased conductance induced by the dynamic-clamp simulated input (see Chance et al., 2002 for a full explanation). Two fundamental components of synaptic input increase when background synaptic activity is increased: the variance of the synaptic current entering the neuron and the overall membrane conductance of the neuron.

Increasing the variance of the input current leads to an increase in neuronal firing rate. Of particular relevance is that the elevation in firing rate is also associated with a decrease in gain. The firing-rate curve of a neuron in the 1X condition is plotted in Figure 3B with open circles. To produce the filled squares, the size of the unitary synaptic conductance change associated with a particular synaptic input was tripled while the input rates were divided by three. This increased the variance of the synaptic input current without changing the average synaptic conductance. Thus, the variance of the input current was equivalent to the variance of the input current in the 3X condition, but the average conductance was unchanged from the 1X case. The effect of the increased current variance alone is a decrease in gain combined with an additive (leftward) shift in firing rate. This is equivalent to what would be obtained simply by adding fluctuating current to the input.

In figure 3C, the open circles are the firing-rate curve of a neuron with no simulated background activity. To produce the filled squares, an additional constant conductance of 32 nS was added (the reversal potential of the resulting current was set to -57 mV, the effective reversal potential of the simulated background inputs). The effect of this additional conductance was subtractive, so it shifted the firing-rate curve along the driving current axis. This result is consistent with previous studies examining the effects of increased conductance on the firing-rate curves of neurons (Gabbiani et al., 1994; Holt and Koch, 1997, Chance et al., 2002).

When the rate of background synaptic input is increased, the effect of the increased input current variance illustrated in Figure 3B is combined with the effect of the increased membrane conductance illustrated in Figure 3C. For a certain parameter range, the subtractive effect of the conductance increase cancels the additive effect of the current variance increase, leaving a divisive gain change. The effect of increasing background input from 1X to 3X is illustrated in Figure 3D.

If excitation and inhibition arising from the background input are not appropriately balanced, mixed multiplicative/divisive and additive/subtractive effects occur. For example, if inhibition is slightly stronger than excitation, a subtractive shift (shifting the curve to the right along the input axis) will accompany the divisive modulation. Therefore, mixed multiplicative and additive effects can arise from this mechanism through non-balanced background activity. This implies that we should not think of firing-rate curves plotted as a function of a single variable (the mean input current or, equivalently, the driving input), but as firing-rate surfaces in a two-dimensional plot with the two variables being driving input and balanced input (Abbott and Chance, 2005).

3. Computing the Dynamic Clamp Input

In this section, we present another model for generating dynamic clamp input that is very similar to the input discussed in the previous section, but the model is more analytically tractable, allowing us to discuss how the appropriate parameters of the dynamic clamp model are determined for a given application (see also Rudolph and Destexhe, 2003). To begin our discussion, we consider a single, generic conductance and only later discuss the effects of both excitation and inhibition. Thus, in the initial discussion that follows, the conductance G_s can represent either an excitatory (G_ex) or an inhibitory (G_in) conductance.

3.1 Driving the Synaptic Conductance with White-Noise Input

The alternative approach we now consider is to approximate the Poisson spike train used in the previous section with white noise. This approximation has been used in a number of studies (Destexhe et al., 2001; Fellous et al., 2003; Wolfart et al., 2005; Desai and Walcott, 2006; Piwkowska et al., 2008). According to this method, we determine the total synaptic conductance from the stochastic differential equation

$$\tau_\text{s}\frac{dG_\text{s}(t)}{dt} = -G_\text{s}(t) + \overline{G}_\text{s} + \sqrt{2D_\text{s}}\eta(t)\,,$$

where $\overline{G}_\text{s}$ and D_s are parameters, and $\eta(t)$ is a stochastic term satisfying

$$\langle\eta(t)\rangle = 0 \quad \text{and} \quad \langle\eta(t)\eta(t')\rangle = \delta(t-t')\,,$$

where the angle brackets denote time averages. In practice, $\eta(t)$ is generated randomly at discrete times that are integer multiples of a minimum time interval Δt from a Gaussian distribution with zero mean and variance equal to $1/\Delta t$. The parameters $\overline{G}_\text{s}$, which is the time-average of $G_\text{s}(t)$, and D_s are related to the unitary synaptic conductance g_s and the total afferent firing rate R of the Poisson model discussed in the previous section by

$$\overline{G}_\text{s} = g_\text{s}\tau_\text{s}R \quad \text{and} \quad D_\text{s} = \frac{1}{2}g_\text{s}^2\tau_\text{s}^2R\,.$$

Note that $\overline{G}_\text{s}$ and D_s can be varied independently by adjusting g_s and R. The white-noise driven model therefore defines a two-parameter model of a synaptic conductance. When we include both excitation and inhibition, this will become a four-parameter model described by $\overline{G}_\text{ex}$, $\overline{G}_\text{in}$, D_ex and D_in. The problem we discuss is how to constrain these four parameters.

3.2 Determining the White-Noise Parameters

The autocorrelation function of the conductance determined by the equation above is

$$\Big\langle(G_\text{s}(t) - \overline{G}_\text{s})(G_\text{s}(t') - \overline{G}_\text{s})\Big\rangle = \frac{D_\text{s}}{\tau_\text{s}}\exp(-|t-t'|/\tau_\text{s})\,.$$

The variance of the conductance is just this correlation function evaluated at zero, which is

$$\sigma_G^2 = \frac{D_\text{s}}{\tau_\text{s}}\,.$$

To determine the effects of this conductance on the membrane potential, we use a passive RC model with membrane capacitance C_m, resting conductance (in the absence of synaptic input) G_rest, and resting potential V_rest. The resulting mean membrane potential is

$$\overline{V} = \frac{1}{G_\text{tot}}\left(G_\text{rest}V_\text{rest} + \overline{G}_\text{s}E_\text{s}\right)\,,$$

where

$$G_\text{tot} = G_\text{rest} + \overline{G}_\text{s}$$

is the average total conductance of the neuron. We can also compute the autocorrelation function for the voltage and, from this, the variance of the membrane potential,

$$\sigma_V^2 = \frac{D_\text{s}(\overline{V} - E_\text{s})^2}{G_\text{tot}(C_\text{m} + G_\text{tot}\tau_\text{s})}\,.$$

In performing this calculation, we have used the approximation that V stays close to the value $\overline{V}$. If there are excitatory and inhibitory synapses, their variances simply add together to give the total variance.

3.3 Determining the Dynamic Clamp Parameters

We show how to determine the parameters of the underlying model that drives the dynamic clamp from the simulated electrophysiological properties. When we have both excitatory and inhibitory conductances, the parameters $\overline{G}_{\text{ex}}$, $\overline{G}_{\text{in}}$, D_{ex} and D_{in} can be determined in terms of more biophysically relevant variables using the equations and approximations discussed above. $\overline{G}_{\text{ex}}$ and $\overline{G}_{\text{in}}$ determine the average total conductance of the neuron,

$$G_{\text{tot}} = G_{\text{rest}} + \overline{G}_{\text{ex}} + \overline{G}_{\text{in}} \, ,$$

and the average potential is given by

$$\overline{V} = \frac{1}{G_{\text{tot}}} \left(G_{\text{rest}} V_{\text{rest}} + \overline{G}_{\text{ex}} E_{\text{ex}} + \overline{G}_{\text{in}} E_{\text{in}} \right) \, .$$

If we know the values of G_{tot} and $\overline{V}$ that we want to simulate, we can determine the parameters we need,

$$\overline{G}_{\text{ex}} = \frac{G_{\text{tot}}(\overline{V} - E_{\text{in}}) - G_{\text{rest}}(V_{\text{rest}} - E_{\text{in}})}{E_{\text{ex}} - E_{\text{in}}} \quad \text{and} \quad \overline{G}_{\text{in}} = \frac{G_{\text{tot}}(\overline{V} - E_{\text{ex}}) - G_{\text{rest}}(V_{\text{rest}} - E_{\text{ex}})}{E_{\text{in}} - E_{\text{ex}}} \, .$$

To determine D_{ex} and D_{in}, we relate them to the variances of the synaptic conductance and the membrane potential. From the above equations, the variance of the conductance is

$$\sigma_G^2 = \frac{D_{\text{ex}}^2}{\tau_{\text{ex}}} + \frac{D_{\text{in}}^2}{\tau_{\text{in}}}$$

and the variance of the membrane potential is

$$\sigma_V^2 = \frac{D_{\text{ex}}(\overline{V} - E_{\text{ex}})^2}{G_{\text{tot}}(C_{\text{m}} + G_{\text{tot}}\tau_{\text{ex}})} + \frac{D_{\text{in}}(\overline{V} - E_{\text{in}})^2}{G_{\text{tot}}(C_{\text{m}} + G_{\text{tot}}\tau_{\text{in}})} \, .$$

These equations are sufficient to determine both parameters. If we define

$$\alpha_{\text{ex}} = \frac{G_{\text{tot}}(C_{\text{m}} + G_{\text{tot}}\tau_{\text{ex}})}{(\overline{V} - E_{\text{ex}})^2} \quad \text{and} \quad \alpha_{\text{in}} = \frac{G_{\text{tot}}(C_{\text{m}} + G_{\text{tot}}\tau_{\text{in}})}{(\overline{V} - E_{\text{in}})^2} \, ,$$

the variance parameters of the white-noise driven model are given by

$$D_{\text{ex}} = \frac{\alpha_{\text{ex}}\tau_{\text{ex}}(\alpha_{\text{in}}\sigma_V^2 - \tau_{\text{in}}\sigma_G^2)}{\alpha_{\text{in}}\tau_{\text{ex}} - \alpha_{\text{ex}}\tau_{\text{in}}} \quad \text{and} \quad D_{\text{ex}} = \frac{\alpha_{\text{in}}\tau_{\text{in}}(\alpha_{\text{ex}}\sigma_V^2 - \tau_{\text{in}}\sigma_G^2)}{\alpha_{\text{in}}\tau_{\text{ex}} - \alpha_{\text{ex}}\tau_{\text{in}}} \, .$$

Using the above equations, all of the parameters of the dynamic clamp can be determined on the basis of the total synaptic conductance, mean membrane potential, and variances of the synaptic conductance and membrane potential that are desired. If all of these are not known, other assumptions, such as fixing g_{ex} or g_{in} to experimentally constrained values, can by used to reduce the number of free parameters. If the Poisson model is used instead, the unitary conductances and firing rates can be obtained from the conversion formulas between these parameters and G_{ex}, D_{ex}, G_{in}, and D_{in}.

4. Conclusions

The dynamic clamp is an effective means of mimicking *in vivo* conditions *in vitro*. This allows us to take advantage of the accessibility of neurons in the slice for recording without losing the background synaptic input that strongly affects their response properties in an intact animal. We have discussed the impact of background activity on neuronal gain, but it would be extremely interesting to examine a number of other phenomena, including dendritic integration, dendritic spiking and synaptic plasticity, in the presence of dynamic-clamp simulated background synaptic input.

Acknowledgments

Research supported by the National Institute of Mental Health (MH-58754) an NIH Director's Pioneer Award, part of the NIH Roadmap for Medical Research, through grant number 5-DP1-OD114-02 to LFA and by NSF-IOB-0446129, funds provided by the University of California and an Alfred P. Sloan Foundation Research Fellowship to FSC.

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