Chapter 7
Synaptic Channels

So far, we have restricted our modeling and analysis efforts to single neurons. To begin to develop networks and the theoretical background for networks, we need to introduce an additional class of membrane channels. We have already looked at voltage- and ion-gated channels. However, there are many other channels on the surface of nerve cells which respond to various substances. Among the most important of these, at least in computational neuroscience, are synaptic channels.

The events leading to the opening of synaptic channels involve several steps. The action potential travels down the axon and terminates at many presynaptic sites invading regions called synaptic terminals. These terminals contain calcium channels. When these are depolarized they cause release of calcium. The calcium then activates a calcium binding protein, which promotes transmitter release by binding to vesicles containing the transmitter. These "docked" vesicles release their transmitter into the synaptic cleft. The transmitter diffuses through the cleft, where it binds to various receptors on the postsynaptic neuron (often on protuberances on the dendrites called spines). These receptors open channels which either depolarize or hyperpolarize the neuron depending on the nature of the transmitter.

Transmitter release can become quite complex for there are sometimes presynaptic receptors near the site of transmission which can be modulated by various chemicals. Furthermore, the release of transmitter is probabilistic and occurs in discrete amounts called *quanta.* Presynaptic stimulation can lead to more vesicles becoming docked to the membrane, so on the next presynaptic spike more transmitter is released than on the first spike. This increase is called *potentiation* or *facilitation*. Additionally, after several presynaptic spikes, the transmitter release per spike can decrease through various means (such as depletion) and take some time to recover. Decrease of transmitter over successive firings of action potentials is called synaptic *depression*.

The consequences of synaptic dynamics and short-term plasticity (e.g., depression and facilitation) have not been thoroughly explored in terms of dynamical systems theory. Here, we will develop several models for both synaptic release and the plasticity of synaptic release. In Chap. 11, we will show some interesting behavior which occurs because of synaptic depression.

G.B. Ermentrout and D.H. Terman, *Mathematical Foundations of Neuroscience*, Interdisciplinary Applied Mathematics 35, DOI 10.1007/978-0-387-87708-2_7,

7.1 Synaptic Dynamics

In this section, we deal with the five most common classes of synaptic dynamics. The main transmitters associated with cortical neurons are glutamate and γ-aminobutyric acid (GABA). A good rule of thumb is that glutamate excites the postsynaptic cell, whereas GABA inhibits it. However, the reversal potential of some GABA receptors is mainly dependent on chloride concentration, so it can be close to rest and even above rest. Thus, (particularly, early in development) some GABA synapses can be excitatory. Like other currents, we model the synaptic currents as the product of a conductance with a voltage difference:

$$I_{\text{syn}} = g(t)(V_{\text{post}} - V_{\text{rev}}).$$

Unlike our previously studied channels, the conductance $g(t)$ depends on the presynaptic neuron.

There are several ways to model the conductance $g(t)$. A popular method among computational neuroscientists is to assume $g(t)$ is the sum of fixed functions which depend only on the times at which that the presynaptic cell has spiked:

$$g(t) = \bar{g} \sum_k \alpha(t - t_k) \equiv \bar{g} z(t), \tag{7.1}$$

where $\bar{g}$ is a constant conductance and $\alpha(t)$ is a prescribed function of time, vanishing for $t < 0$ and positive for $t > 0$. The times t_k are when the presynaptic cell has spiked. The most general form for the function $\alpha(t)$ is

$$\alpha(t) = \frac{a_d a_r}{a_r - a_d}(\mathrm{e}^{-a_d t} - \mathrm{e}^{-a_r t}). \tag{7.2}$$

The parameter a_r characterizes the rise rate of the synaptic conductance and a_d characterizes the decay. Many modelers assume $a_d = a_r$, in which case the function has the form

$$\alpha(t) = a_d^2 t \mathrm{e}^{-a_d t}.$$

Letting $a_r \to \infty$ reduces the model to a single exponential. The maximum of $\alpha(t)$ occurs at $t^* = \ln(a_r/a_d)/(a_r - a_d)$. The constants multiplying these functions are chosen so that the area under $\alpha(t)$ is 1. Other normalizations are possible; for example, choosing the value of $\alpha(t^*) = 1$ for some $t^* > 0$.

If one uses alpha functions in simulations, then (7.1) implies that it is necessary to keep track of all the incoming spikes at times t_k. Since $z(t)$ in (7.1) is the solution to a second-order linear differential equation,

$$z'' + (a_r + a_d)z' + a_r a_d z = 0, \tag{7.3}$$

we need only solve this equation in time with the proviso that each time t_k that a presynaptic spike arises, $z'(t)$ is increased by an amount $a_d a_r$. Formally, we can write

$$z'' + (a_r + a_d)z' + a_r a_d z = a_r a_d \sum_k \delta(t - t_k).$$

If the spike train is random (say, Poisson) with a time-varying rate, $\nu(t)$, then we can formally average this equation to obtain

$$z'' + (a_r + a_d)z' + a_r a_d z = a_r a_d \nu(t). \tag{7.4}$$

The solution to this linear equation provides a formula for the average net synaptic input for a time-varying random stimulus.

Choosing a fixed function $\alpha(t)$ for the synaptic response has some advantages which will become apparent when we study networks. However, from a physical point of view, the use of alpha functions is unsatisfactory. First, as noted above, we need to track the time of a spike which could be ambiguous. Furthermore, this approach does not connect well with our notion of voltage- and ligand-gated channels. We now introduce a simple model for synapses which is identical to the formalism that we previously described for voltage-gated ionic channels. Let $[T]$ denote the concentration of transmitter released into the synaptic cleft by a presynaptic spike. Note that $[T]$ will be time-dependent since synaptic transmitter is rapidly taken up and/or degraded. Then the conductance $g(t) = \bar{g}s(t)$, where $s(t)$ denotes the fraction of open channels. $s(t)$ satisfies

$$\frac{\mathrm{d}s}{\mathrm{d}t} = a_r[T](1-s) - a_d s. \tag{7.5}$$

Suppose at $t = t_0$, $[T]$ jumps to $T_{\max}$ and at $t = t_1$, $[T]$ falls back to 0. Then

$$s(t - t_0) = s_\infty + (s(t_0) - s_\infty)\mathrm{e}^{-(t-t_0)/\tau_s}, \quad \text{for } t_0 < t < t_1,$$

where

$$s_\infty = \frac{a_r T_{\max}}{a_r T_{\max} + a_d} \quad \text{and} \quad \tau_s = \frac{1}{a_r T_{\max} + a_d}.$$

After the pulse of transmitter has gone, $s(t)$ decays as

$$s(t) = s(t_1)\mathrm{e}^{-a_d(t-t_1)}.$$

Although it may appear that, like the alpha function, there is a rise rate and a decay rate, the formula for τ_s shows that the rates are not independent. If $a_r T_{\max}$ is large, the synapse will saturate near 1, so it is not possible to make this rise rate arbitrary. However, by varying the residence time of the transmitter, $t_1 - t_0$, we can mimic the alpha function quite closely. We now must connect the transmitter release $[T]$ with the presynaptic neuron. We assume a model of the form

$$[T](V_{\text{pre}}) = \frac{T_{\max}}{1 + \exp(-(V_{\text{pre}} - V_{\text{T}})/K_p)}. \tag{7.6}$$

Destexhe et al. [62] suggest $T_{\max}$ =1 mM, $V_{\mathrm{T}} = 2$, and $K_p = 5$ mV. As this synaptic channel is gated by the *presynaptic* spike, there could be some transmission delay due to the propagation of the presynaptic spike down the axon to the postsynaptic receptor. Thus, modelers often include a delay term; that is, the term $V_{\mathrm{pre}}(t)$ is replaced by $V_{\mathrm{pre}}(t - t_{\mathrm{delay}})$ in (7.6). Synaptic delays can be fixed or depend on the distance between the presynaptic and the postsynaptic neuron to account for the finite propagation speed down the axon (see Chap. 6).

We now have a complete model of the conductance changes of a simple synapse connected to the presynaptic voltage. We turn next to the four main classes of synaptic transmission used in models of cortical neurons. Figure 7.1 shows the conductance changes due to each of our four model synapses.

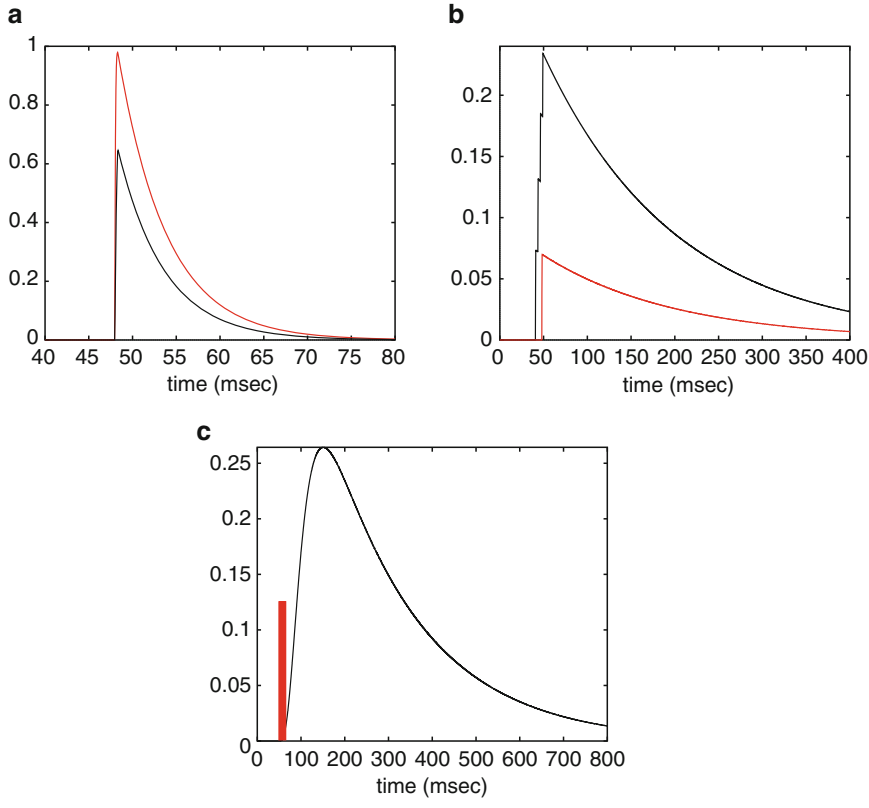

Fig. 7.1 Model synaptic conductances. (**a**) AMPA (*black*) and $\mathrm{GABA_A}$ (*red*) conductance due to a single presynaptic spike. (**b**) NMDA conductance due to a single spike (*red*) and a burst of four spikes (*black*). (**c**) $\mathrm{GABA_B}$ conductance due to a burst of eight spikes. Single spike response is negligible

7.1.1 Glutamate

The neurotransmitter glutamate activates two different kinds of receptors: AMPA/kainate, which are very fast, and NMDA, which is implicated in memory and long-term potentiation of synapses. Both of these receptors lead to excitation of the membrane.

7.1.1.1 AMPA/Kainate

The current from a fast AMPA synapse is

$$I_{\text{AMPA}} = \bar{g}_{\text{AMPA}} s (V - V_{\text{AMPA}}), \tag{7.7}$$

where $V_{\text{AMPA}} = 0$ mV. For the synapse shown in Fig. 7.1a, s satisfies (7.5) and (7.6) with $a_r = 1.1\ \text{mM}^{-1}\ \text{ms}^{-1}$ and $a_d = 0.19\ \text{ms}^{-1}$.

The AMPA synapses can be very fast. For example, in some auditory nuclei, they have submillisecond rise and decay times. In typical cortical cells, the rise time is 0.4–0.8 ms. Using the above model with a transmitter concentration of 1 mM, the rise time would be $1/(1.1 + 0.19) = 0.8$ ms. The decay is about 5 ms. As a final note, AMPA receptors on inhibitory interneurons have rise and fall times about twice as fast as those on excitatory neurons.

Real AMPA synapses show quite strong depression. That is, the peak amplitude of the AMPA current decreases with each subsequent spike. We will address this short-term plasticity in the next section. Figure 7.1a shows the conductance change for a single presynaptic spike.

7.1.1.2 NMDA

The NMDA receptor is also sensitive to glutamate but has effects that last considerably longer than those of AMPA. However, under normal physiological conditions, the NMDA receptor is partially blocked by magnesium ions. The magnesium block can be removed if the postsynaptic neuron is depolarized and, of course, if the neuron is bathed in a low magnesium medium. Thus, if the postsynaptic cell is already active, then the NMDA receptor opens and the effect of the current will be long-lasting. Because of the property that both the presynaptic and the postsynaptic cells must be active for the NMDA current to flow, the presence of these receptors is believed to be necessary for many types of long-term changes in the synapses which presumably encode memories. Indeed, one of the ions carried by NMDA current is calcium, which is a main player in long-term changes in neurons. This synaptic current is also thought to play a role in maintaining persistent activity required for short-term memory (see [182] and Chap. 12). The NMDA current is modeled as

$$I_{\text{NMDA}} = \bar{g}_{\text{NMDA}} s B(V) (V - V_{\text{NMDA}}), \tag{7.8}$$

where s obeys (7.5) and (7.6) and $B(V)$ represents the magnesium block [138]:

$$B(V) = \frac{1}{1 + \mathrm{e}^{-0.062V}[\mathrm{Mg}^{2+}]/3.57}.$$

It is convenient to rewrite this as

$$B(V) = \frac{1}{1 + \mathrm{e}^{-(V-V_\mathrm{T})/16.13}},$$

where V_T is the half activation and is given by

$$V_\mathrm{T} = 16.13 \ln \frac{[\mathrm{Mg}^{2+}]}{3.57}.$$

At the physiological concentration of 2 mM, $V_\mathrm{T} \approx -10$ mV, so the postsynaptic cell has to be quite depolarized. Even at the relatively low concentration of 1 mM, $V_\mathrm{T} \approx -20$ mV. The synaptic parameters for s are well fit by the choices $a_r = 0.072\ \mathrm{mM}^{-1}\,\mathrm{ms}^{-1}$, $a_d = 0.0066$, and $V_\mathrm{NMDA} = 0$ mV. Figure 7.1b shows the conductance change for a model NMDA synapse when there is a single spike and when there are four spikes. The rise time is fast enough such that each spike can be seen in the model trace.

Sometimes it is desirable to implement the NMDA channel so that there is greater flexibility in the rise time. In this case, the channel is modeled by two variables,

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \alpha_1 T(V)(1-x) - \beta_1 x, \\ \frac{\mathrm{d}s}{\mathrm{d}t} &= \alpha_2 x(1-s) - s/\tau, \end{aligned} \tag{7.9}$$

so that the first-order s in (7.8) is replaced by the s in (7.9).

7.1.2 γ-Aminobutyric Acid

GABA is the principal inhibitory neurotransmitter in the cortex. There are two main receptors for GABA: $\mathrm{GABA_A}$ and $\mathrm{GABA_B}$.

7.1.2.1 $\mathrm{GABA_A}$

$\mathrm{GABA_A}$ is responsible for fast inhibition and, like AMPA and NMDA, requires a single presynaptic spike to be evoked. The current is

$$I_{\mathrm{GABA_A}} = \bar{g}_{\mathrm{GABA_A}} s(V - V_{\mathrm{GABA_A}}), \tag{7.10}$$

where s obeys (7.5) and (7.6) with $a_r = 5\ \text{mM}^{-1}\,\text{ms}^{-1}$, $a_d = 0.18\ \text{ms}^{-1}$, and V_{GABA_A} varying between -81 and -60 mV. This GABA current is carried by chloride (among other ions) and thus there is a wide range of values depending on the physiological conditions and the developmental stage of the neurons. (Early in development GABA is mainly depolarizing with a reversal potential well above rest.) In many models in the literature, $V_{\text{GABA}_\text{A}} = -75$ mV. Figure 7.1a shows the conductance change for our model GABA_A synapse.

7.1.2.2 GABA_B

The three synapses described so far (AMPA/kainate, NMDA, and GABA_A) share the common feature that the ion channel and the receptor are the same protein. Thus, the effect of transmitter on these synaptic receptors is *direct.* However, there are other synaptic events which are *indirect* in that the activation of the receptor sets off a cascade of intracellular events which eventually alter the conductivity of an ion channel. The GABA_B receptor is an example of this indirect effect: transmitter binds to a receptor protein which activates an intracellular complex called a G-protein, which in turn activates a potassium channel to hyperpolarize the membrane. Such indirect effects can have several consequences. The responses can be (1) nonlinear, (2) slow to activate, and (3) long-lasting. There are several models for the activation of GABA_B synapses; we will consider only the simplest one. There is a receptor r which is activated exactly as described by (7.5) and (7.6). This receptor activates the ion channel, s, and results in the GABA_B current. The current is a nonlinear saturating function of s. Thus, the model for GABA_B is

$$
\begin{aligned}
I_{\text{GABA}_\text{B}} &= \bar{g}_{\text{GABA}_\text{B}} \frac{s^n}{K_d + s^n}(V - E_K), \qquad (7.11)\\
\frac{\mathrm{d}r}{\mathrm{d}t} &= a_r[T](1 - r) - b_r r,\\
\frac{\mathrm{d}s}{\mathrm{d}t} &= K_3 r - K_4 s.
\end{aligned}
$$

For the synapse shown in Fig. 7.1c, $a_r = 0.09\ \text{mM}^{-1}\text{ms}^{-1}$, $a_d = 0.0012\ \text{ms}^{-1}$, $n = 4$, $K_d = 100$, $K_3 = 0.18\ \text{ms}^{-1}$, and $K_4 = 0.034\ \text{ms}^{-1}$. We use the same function (7.6) for the transmitter release, T, as we have in the other synaptic models. The nonlinearity in (7.11) means s must become large enough for the synapse to take effect. GABA_B is more effective when several action potentials occur in a row. Note also that the reversal potential is that of potassium; in a cortical cell this can be around -90 to -105 mV. GABA_B is unambiguously hyperpolarizing. Figure 7.1c shows the effective synaptic conductance, $s_{\text{eff}} = s^4/(s^4 + K_d)$, for a burst of eight spikes. The conductance for a single spike is very close to 0.

7.1.3 Gap or Electrical Junctions

Many cells can directly communicate with each other via tight junctions between their membranes. These act as resistors connecting compartments in two different cells and are called either electrical or gap junctions. The difference between gap junctions and chemical synapses is that the former always keep the cells in communication, whereas the latter occur only when there is a presynaptic action potential. (Although there are some neurons which release transmitter in a graded fashion, these are rare and atypical. The granule cells in the olfactory bulb of mammals are the best known example.) We model the current for this type of synapse as

$$I_{\text{gap}} = \bar{g}_{\text{gap}}(V_{\text{post}} - V_{\text{pre}}), \tag{7.12}$$

where g_{gap} is the conductance. Gap junctions may play an important role in synchronizing the spiking of inhibitory neurons in the cerebral cortex [4, 12, 101, 102].

7.2 Short-Term Plasticity

Our conceptual model for synapses treats them as though there is no history dependence. That is, the magnitude of the postsynaptic current is independent of how many times that it has been invoked in recent history. However, the experimental work of many groups over the years shows that many synapses exhibit *short-term plasticity.* Here, the emphasis is on the phrase *short-term* as opposed to long-term changes that are associated with learning and memory. Short-term plasticity occurs over timescales of the order of milliseconds to minutes and takes the form of short-term depression (the magnitude of successive postsynaptic currents decreases), facilitation (the magnitude of successive postsynaptic currents increases), or possibly both. We point out that the GABA_{B} model shows facilitation in that several closely timed action potentials lead to a much larger current. Beierlein and Gibson [12], Castro-Alamancos [36], and Markram et al. [191] have quantified synaptic plasticity in mammalian brains. Varela et al. [279] were among the first to recognize the computational consequences of short-term plasticity. Here, we briefly describe some models and some consequences of this plasticity. Later, we will see that the effects on networks or neurons can be much more interesting.

Figure 7.2a shows examples of synaptic depression and synaptic facilitation in cortical neurons. We now describe phenomenological and mechanistic models for short-term plasticity. The phenomenological model is due to Dayan and Abbott but is closely related to many other models. Suppose we want to characterize the magnitude, $M(t)$, of synaptic release per presynaptic spike. We write this magnitude as the product of two factors, the depression $q(t)$ and the facilitation $f(t)$, so that

$$M(t) = q(t)\, f(t).$$

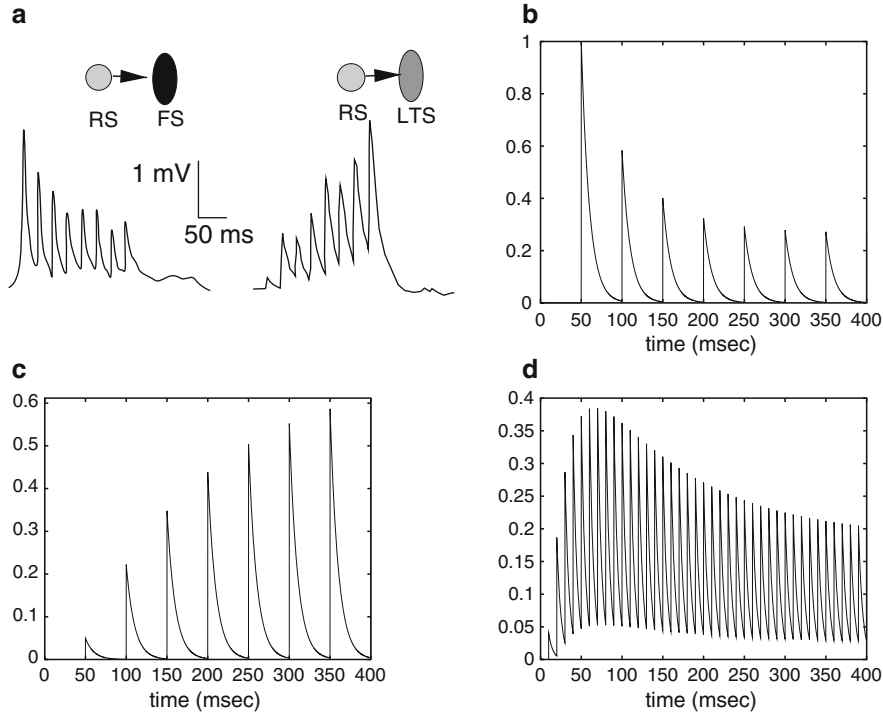

Fig. 7.2 (**a**) Short-term synaptic plasticity in cortical neurons (from [12]). Connections between cortical excitatory cells (RS) and cortical fast spike units (inhibitory) show synaptic depression for 20-Hz stimuli, whereas connections between cortical excitatory cells and low threshold spike (LTS) inhibitory cells show facilitation. (**b–d**) Simulations of (7.13) and (7.14) to periodic stimuli. The parameters for (**b**) are $\tau_d = 300$, $a_d = 0.5$, $d_0 = 1$, $\tau = 10$ and there is no facilitation. The parameters for (**c**) are $\tau_f = 500$, $a_f = 0.2$, $f_0 = 0$, $\tau = 10$ with no depression. The frequency is 20 Hz. (**d**) Both depression and facilitation with $f_0 = 0, d_0 = 1, \tau_f = 50, \tau_d = 400$, $a_f = 0.2, a_d = 0.05$, and $\tau = 5$. The frequency is 100 Hz

We could also call $M(t)$ the probability of release if we were interested in treating the process stochastically. Both $f(t)$ and $q(t)$ lie between 0 and 1 and each has a resting value of f_0 and d_0, respectively, to which it returns with time constant τ_f and τ_d, respectively. Thus, in absence of any inputs,

$$\tau_f \frac{\mathrm{d}f}{\mathrm{d}t} = f_0 - f \quad \text{and} \quad \tau_d \frac{\mathrm{d}q}{\mathrm{d}t} = d_0 - q.$$

Each time there is a spike, $f(t)$ is increased by an amount $a_f(1 - f)$ and $q(t)$ is decreased by an amount $a_d d$. In both cases, the change is multiplied by a factor

which keeps the variables bounded between 0 and 1. We assume both a_f and a_d are less than 1. Formally, we can write the facilitation equation as

$$\frac{\mathrm{d}f}{\mathrm{d}t} = \frac{f_0 - f}{\tau_f} + \left(\sum_j \delta(t - t_j)\right) a_f(1 - f), \tag{7.13}$$

where t_j are the times of the incoming spikes. Similarly, for the depression equation, we have

$$\frac{\mathrm{d}q}{\mathrm{d}t} = \frac{d_0 - q}{\tau_d} - \left(\sum_j \delta(t - t_j)\right) a_d q. \tag{7.14}$$

We leave the analysis of these equations when stimuli are periodic as an exercise. Figure 7.2b–d shows the results of a simulation of these equations when there is a periodic input. Each time a stimulus comes in, the synaptic variable $s(t)$ is increased by $M(t)$ and both $q(t)$ and $f(t)$ are updated. Between stimuli, $s(t)$ decays exponentially with a time constant of τ.

Suppose the inputs to the synapse are Poisson with rate r. (see Chap. 10, Sect. 4 for a definition of Poisson) Averaging (7.13), we obtain

$$\frac{\mathrm{d}f}{\mathrm{d}t} = (f_0 - f)/\tau_f + a_f r(1 - f).$$

The steady-state value of f is

$$f_{\mathrm{ss}} = \frac{f_0 + a_f \tau_f r}{1 + a_f \tau_f r}.$$

A similar calculation for q yields

$$q_{\mathrm{ss}} = \frac{d_0}{1 + a_d \tau_d r}.$$

The effective average rate is

$$r_{\mathrm{eff}} = r f_{\mathrm{ss}} d_{\mathrm{ss}} = r d_0 \frac{f_0 + a_f \tau_f r}{(1 + a_f \tau_f r)(1 + a_d \tau_d r)}.$$

If there is depression, then this function saturates as the true rate goes to infinity.

Varela et al. [279] pointed out that synaptic depression has a useful computational property in that it emphasizes changes in input rates. That is, starting at a low rate and jumping to a high rate results in a huge jump of r_{eff}. Suppose $d_0 = 1$ and the input jumps from r_{lo} to r_{hi}. At the moment before the jump

$$r_{\mathrm{eff}}^{-} = \frac{r_{\mathrm{lo}}}{1 + a_d \tau_d r_{\mathrm{lo}}}.$$

Right after the jump,

$$r_{\text{eff}}^{+} = \frac{r_{\text{hi}}}{1 + a_d \tau_d r_{\text{lo}}}$$

since the depression has not had a chance to take effect. That is, the denominator is still that for the low rate. Over time, the effective rate will decrease to the steady state:

$$r_{\text{eff}} = \frac{r_{\text{hi}}}{1 + a_d \tau_d r_{\text{hi}}}.$$

By the same argument, if the rate is suddenly lowered again, the effective rate will be very small since the denominator is large from the high prior rate. Thus, synaptic depression behaves much like a differentiator of the input rate and allows for very strong temporal contrast. We note that Bertram [14] called our depression model a *vesicle depletion mechanism* as one can regard the variable d as the amount of transmitter available for release.

7.2.1 Other Models

The models discussed so far for plasticity require that one track the time of spikes. In this sense, they are analogous to using alpha functions for synapses rather than the mechanistic models. Manor et al. [190] used a channel-like model for synaptic depression. They combined an activation model like (7.5) with a depression model of the form

$$\frac{\mathrm{d}q}{\mathrm{d}t} = \frac{q_\infty(V) - q}{\tau_1 + \tau_2 q_\infty(V)},$$

where

$$q_\infty(V) = \frac{1}{1 + \mathrm{e}^{k(V - V_{\text{thr}})}}$$

and $k > 0$ and V_{thr} are parameters. The threshold is set close to $V = 0$ and k is somewhat large so that when V is near rest, $q_\infty(V)$ is close to 1 and $q(t)$ will relax to 1 with a time constant roughly like $\tau_1 + \tau_2$. When the neuron spikes, q_∞ is nearly 0 and $q(t)$ will decay to 0 with a time constant of τ_1. Thus, $1/\tau_1$ is like a_d and τ_2 is like τ_d in the heuristic model. Given the equation for $q(t)$ and a model such as (7.5) for $s(t)$, the total synaptic conductance is $\bar{g}s(t)q(t)$. Similar models can be built for potentiation of synapses, but with $k < 0$ so that at rest the potentiation variable goes to a low value which is increased with each spike. A more direct mapping is

$$\frac{\mathrm{d}q}{\mathrm{d}t} = (d_0 - q)/\tau_d - a_d(V)q,$$

where

$$a_d(V) = \frac{a}{1 + \mathrm{e}^{-k(V - V_{\text{thr}})}}.$$

When the neuron spikes $a_d(V)$ is large, otherwise it is negative.

We close this section with a three-state model for depression which is based on a simple physical model:

$$A \longrightarrow S,$$
$$S \longrightarrow U,$$
$$U \longrightarrow A.$$

A is the available transmitter, S is the conducting state which produces the synaptic conductance, and U is the transmitter which is unavailable for release. Since $A + S + U$ is conserved, we can eliminate A and obtain the following pair of differential equations:

$$\frac{\mathrm{d}s}{\mathrm{d}t} = \alpha(V)(1 - s - u) - \beta s \quad \text{and} \quad \frac{\mathrm{d}u}{\mathrm{d}t} = \beta s - \beta_2 u.$$

By varying β_2, we can incorporate various degrees of synaptic depression. This simple model does not have the degree of freedom that other models have; there is only one free parameter β_2 since β determines the decay rate of the synapse and $\alpha(V)$ is voltage-dependent.

7.3 Long-Term Plasticity

One of the main hypotheses in neuroscience is that memories are encoded in the strengths of synapses between neurons. There are dozens of "rules" for strengthening the connections between pair of neurons, far more than we can analyze in depth in this book. Dayan and Abbott [53] (Chap. 8) gives a nice summary of so-called Hebb and timing-based rules along with different ways to normalize the synaptic strengths. Hebb rules strengthen or weaken connections depending on whether or not the presynaptic and postsynaptic neurons are active. (For example, in one implementation, if both neurons are active, the synapse is strengthened; if the postsynaptic neuron is silent, nothing is changed and if the postsynaptic neuron is active but the presynaptic is silent, the synapse is weakened.) The problem with many Hebb rules is that they can lead to runaway excitation since strengthening of (excitatory) synapses results in more activity and thus greater strengthening. Thus, in typical implementations of long-term plasticity, some normalization is applied. For example, the total input to a neuron may be constrained to some constant value. This results in competition between inputs. Exercise 9 provides an example of such competition by developing a very simple model.

Timing-dependent inputs strength the synapse if presynaptic spikes precede the spikes of the postsynaptic cell and weaken if vice versa. Such plasticity can be used to develop networks of unidirectionally coupled neurons that can learn sequences.

7.4 Bibliography

Destexhe et al. [62] were the first to systematically derive a set of differential equation models for synapses where they were treated like other channels. Varela et al. [279] devised a number of short-term plasticity models and emphasized several useful computational features of this kind of plasticity.

7.5 Exercises

1. Simulate and recreate all of Fig. 7.1 using the parameters in the text.
2. If inputs come into a synapse periodically, determine the steady-state values of $q(t)$ and $f(t)$ at the moment after a stimulus has arrived.
3. What rate r maximizes the probability of release for a synapse which has both facilitation ($f_0 = 0$) and depression ($d_0 = 1$)?
4. Simulate
$$\frac{\mathrm{d}q}{\mathrm{d}t} = \frac{1-q}{\tau_d} - a_d r(t) q$$
with $a_d = 0.4$, $\tau_d = 500$ ms, and $r(t)$ changes as follows: for the first 200 ms, it is 25 Hz, it jumps to 100 Hz for the next 300 ms, then it falls to 10 Hz, and at t=1,000 ms it jumps to 40 Hz. Plot the effective firing rate $d(t)r(t)$.
5. Castro-Alamancos [36] described a synapse with the following properties. The ratio of the first spike to the second spike is 0.6 when the time between spikes is 50 ms. If the time between spikes is 25 ms, the ratio is 0.4. Given $d_0 = 1$, find the parameters a_d and τ_d which match this assuming there is no potentiation.
6. Given an alpha function (7.2), compute the steady-state value of $s(t)$ assuming the presynaptic spikes, $t_k = kP$, are periodic with period P.
7. Suppose $v(t)$ in (7.4) is sinusoidal, $v(t) = \sin \omega t$. Find $z(t)$. Find the magnitude of the response.
8. Gulledge and Stuart [113] demonstrated an interesting example of GABA enhancing the postsynaptic response to an excitatory synapse. They recorded from pyramidal neurons in rat somatosensory cortex and produced both dendritic and somatic GABA stimulation. Create a two-compartment passive model with a resting potential of -78 mV, a leak of $0.05\,\mathrm{mS/cm^2}$, and a capacitance of $1\,\mu\mathrm{F/cm^2}$. Suppose the reversal potential of AMPA is 0 mV and that of GABA is -68 mV. Apply a dendritic inhibitory postsynaptic current (use a synapse model for GABA) and measure the depolarization in the soma. Apply an AMPA excitatory postsynaptic current to the soma. Measure the deviation. Now apply both simultaneously and arrange the parameters so that the sum is bigger than either current by itself. Now apply the inhibitory postsynaptic current in the soma along with the same excitatory postsynaptic current. You should get a smaller net depolarization owing to the shunting effects of the inhibitory postsynaptic current. In other words, try to mimic Fig. 3 in the Gulledge and Stuart [113] paper.

9. *Synaptic competition.* Consider a single linear neuron which receives inputs from two different sources, I_1 and I_2, with weights w_1 and w_2:

$$\tau \frac{\mathrm{d}V}{\mathrm{d}t} = -V + w_1 I_1(t) + w_2 I_2(t).$$

Hebbian learning is a mechanism for strengthening the weights according to whether or not presynaptic and postsynaptic cells are active. In a typical model

$$\Delta w = k I_{\mathrm{pre}} V_{\mathrm{post}},$$

where I is the input and V is the output. Many neural models use such a mechanism to strengthen the weights between two cells or between an input and an output neuron. The problem with this kind of learning rule is that all synapses will grow since there is nothing to reduce the weight of the synapse. Thus, in this simple model, synaptic weights can also decay at a rate that is proportional to the activity of the postsynaptic cell, V. As the inputs change randomly, we will look at the averages and build a model based on them. Look at the averages

$$\langle I_1 V \rangle = \langle I_1 (I_1 w_1 + I_2 w_2) \rangle \approx \langle I_1 I_1 \rangle w_1 + \langle I_1 I_2 \rangle w_2.$$

This approximation is valid if the weights change slowly compared with the inputs. The terms in the brackets are just the correlations between the two inputs; we will call them C_{s} and C_{d}, respectively, corresponding to the same and different stimuli, respectively. It should be expected that $C_{\mathrm{s}} > C_{\mathrm{d}}$. On the other hand, the average postsynaptic activity is approximately $\langle I_1 \rangle w_1 + \langle I_2 \rangle w_2$. We assume the average inputs are the same and that the change in weights is a function of the averages:

$$\begin{aligned} \frac{\mathrm{d}w_1}{\mathrm{d}t} &= f(C_s w_1 + C_{\mathrm{d}} w_2)(1 - w_1) - g(w_1 + w_2) w_1, \\ \frac{\mathrm{d}w_2}{\mathrm{d}t} &= f(C_s w_2 + C_{\mathrm{d}} w_1)(1 - w_2) - g(w_1 + w_2) w_2. \end{aligned}$$

The first term represents the growth of the weights to a maximum of 1 and the second term represents the decay. (They are thus constrained to lie between $0 < w_j < 1$ when f and g are positive.) Take $C_{\mathrm{s}} = 0.8$, $C_{\mathrm{d}} = 0.2$, and

$$\begin{aligned} f(x) &= 1/(1 + \exp(-\alpha(x - 1/2))), \\ g(x) &= 1/(1 + \exp(-\beta(x - 1))). \end{aligned}$$

a. Prove $w_1 = w_2 = 1/2$ is always a fixed point of this system.
b. Analyze the stability as a function of α and β.
c. Compute the bifurcation diagram as you vary α and hold $\beta = 5$.
d. Sketch the nullclines for $\alpha = 10$, 12, 15, and 20 and describe all the possible qualitative behaviors.