# *Synaptic dynamics*

*John D. Murray*

A dynamical model for synaptic gating variables is presented. We use this to study the saturation of synaptic gating at high firing rate. Shunting inhibition and the voltage dependence of NMDA synapses are also covered.

When the pre-synaptic cell fires an action potential, vesicles release transmitter across the synaptic cleft. Transmitter binds to the receptors on the post-synaptic side of the synapse. This binding causes the receptors to open, allowing current to flow across the post-synaptic membrane.

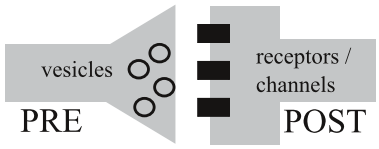


Figure 1: Schematic of a synapse.

## *Synaptic currents*

The synaptic current $I_{syn}$ is described by:

$$I_{syn} = g_{syn} S (V - E_{syn}) \tag{1}$$

where $g_{syn}$ is the conductance, $E_{syn}$ is the reversal potential specific for a receptor type, $V$ is the membrane potential, and $S$ is the *synaptic gating variable*. For excitatory glutamatergic receptors, AMPA and NMDA, $E_{syn} = 0\,\text{mV}$. Receptors at inhibitory synapses have $E_{syn} = -70\,\text{mV}$ for $\text{GABA}_\text{A}$ and $E_{syn} = -90\,\text{mV}$ for $\text{GABA}_\text{B}$. $S$ gates the synaptic current.

## *Simple model of the synaptic gating variable*

Each receptor channel in a synapse is in one of two possible states: closed or open. $S$ is the fraction of channels that are open. Each synapse has many receptor channels, so the gating variable takes values between 0 and 1.

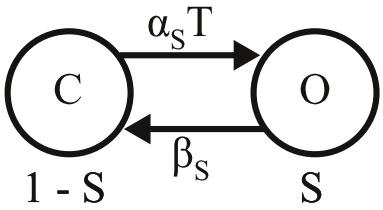


Figure 2: Schematic synaptic receptor dynamics. Receptors can be in either a closed (C) or open (O) state, with transition rates between the two states.

### *First-order kinetics*

Following a presynaptic spike, neurotransmitter is present in the synaptic cleft for a short period of time. $T$ denotes the concentration of neurotransmitter. We model synaptic dynamics as follows. The transition rate from closed to open is proportional to $T$, and the rate from open to closed is independent of $T$ (Figure 2). The fraction of open channels $S$ is then given by the linear differential equation:

$$\frac{dS}{dt} = \alpha_s T (1 - S) - \beta_s S \tag{2}$$

We approximate the time course $T(t)$ as a brief pulse, with $T = T_{max}$ for a short duration $\Delta t$, after which $T$ returns to 0 (Figure 3).

During the pulse, $dS/dt = -(S - S_\infty)/\tau$, where $\tau = 1/(\alpha_s T_{max} + \beta_s)$, $S_\infty = T_{max}/(T_{max} + K_s)$, and $K_s = \beta_s/\alpha_s$. At the end of the pulse, $S$ has the value:

$$S_{post} = S_\infty + (S_{pre} - S_\infty)e^{-\Delta t/\tau} \tag{3}$$

If the transmitter pulse is short ($\Delta t \approx 1$ ms), $S$ cannot reach steady state. We now take the limit $\Delta t \to 0$, while $T_{max} \to \infty$ to keep constant the area under the $T(t)$ curve, $T_{max}\Delta t = \overline{T}$. For example, take $\gamma \equiv \alpha_s \overline{T} = 1$, so that $S_\infty \to 1$. We define:

$$S_- \equiv S \text{ just } \textit{before} \text{ T pulse, at time } t_- \tag{4}$$
$$S_+ \equiv S \text{ just } \textit{after} \text{ T pulse, at time } t_+ \tag{5}$$

Then by integrating Eq. 2, we have:

$$S_+ = S_- + (1 - S_-)(1 - e^{-\gamma}) \tag{6}$$

For the first spike in a train ($S_- = 0$), $S_+ = 1 - e^{-\gamma} = 1 - e^{-1} \simeq 0.63$, so $S_+$ does not saturate at 1 after a single spike.

After the spike, $S$ decays exponentially:

$$S(t) = S_+ e^{-t/\tau_s} \tag{7}$$

where $\tau_s \equiv 1/\beta_s$ is the synaptic *time constant*. Eqs. 6 and 7 describe the spike-time increment and decay, respectively, of $S$. These dynamics are described as *first-order kinetics* and are encapsulated by the equation:

$$\frac{dS}{dt} = \alpha \sum_i \delta(t - t_i)(1 - S) - S/\tau_s \tag{8}$$

where $\{t_i\}$ are the spike times.

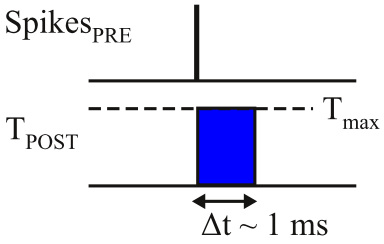


Figure 3: Schematic of the time course of neurotransmitter concentration following a presynaptic spike.

## *Saturation of synaptic gating*

Because $S$ is bounded between 0 and 1, it will saturate if driven by a very high firing rate. We want to study how the mean value of $S$, $\langle S \rangle$, depends on firing rate $r$. Consider a periodic spike train (Figure 4).

We solve for $S_-$ and $S_+$ self-consistently:

$$S_- = S_+ e^{-1/(r\tau_s)} \tag{9}$$
$$S_+ = \frac{1 - e^{-\alpha}}{1 - e^{-\alpha - 1/(r\tau_s)}} \tag{10}$$

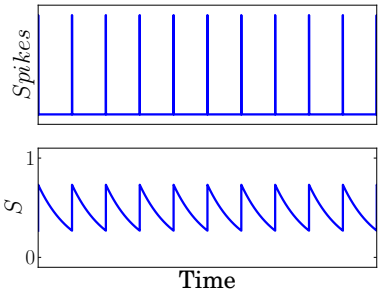


Figure 4: Time course of $S$ in response to a periodic spike train.

Integrate over the period $1/r$ to compute $\langle S \rangle$:

$$\langle S \rangle = r \int_0^{1/r} S(t) dt \tag{11}$$

$$= S_+ r\tau_s \left(1 - e^{-1/(r\tau_s)}\right) \tag{12}$$

$$\langle S \rangle = \frac{r\tau_s \left(1 - e^{-1/(r\tau_s)}\right)\left(1 - e^{-\alpha}\right)}{\left(1 - e^{-\alpha - 1/(r\tau_s)}\right)} \tag{13}$$

We can use Eq. 13 to plot $\langle S \rangle$ as a function of rate $r$ for different values of $\tau_s$ (Figure 5). For fast receptors (e.g., $\tau_s = 2$ ms for AMPA receptors), $\langle S \rangle$ depends linearly on $r$ with no saturation in the physiological range of $r$. However, for slow receptors (e.g., $\tau_s = 100$ ms for NMDA receptors), the $\langle S \rangle$ vs. $r$ curve is nonlinear and shows saturation at $r \approx 10$'s of Hz.

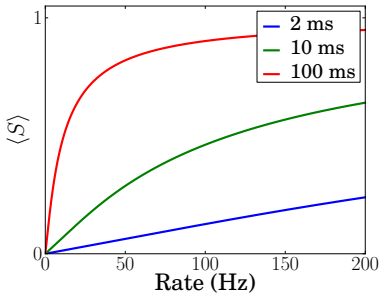


Figure 5: The mean synaptic gating variable $\langle S \rangle$ deviates from a linear response and starts to saturate when presynaptic firing rate $r$ is much larger the $1/\tau_s$.

### *Incorporating latency and rise time*

We can relax the approximation that synapses are opened instantaneously when a presynaptic action potential occurs, to make the synaptic time course continuous and more realistic (Figure 6). A smooth *rise time* can be modeled using *second-order kinetics*. In this form, an additional variable $x$ follows first-order kinetics and is increased instantaneously at the time of a spike, and $x$ gates the activation of $S$. A synaptic *latency* $\tau_L$ can be easily incorporated as a delay in the update of $x$. The equations for the synaptic dynamics are:

$$\frac{dx}{dt} = \alpha_x \sum_i \delta\left(t - t_i - \tau_L\right) - \frac{x}{\tau_x} \tag{14}$$

$$\frac{dS}{dt} = \alpha_s x(1 - S) - \frac{S}{\tau_s} \tag{15}$$

If saturation can be neglected, $S$ is described by:

$$S(t) = \text{const.} \left(e^{-t/\tau_x} - e^{-t/\tau_s}\right) \tag{16}$$

and the time-to-peak $= \ln(\tau_s/\tau_x)/(1/\tau_x - 1/\tau_s)$.[1]

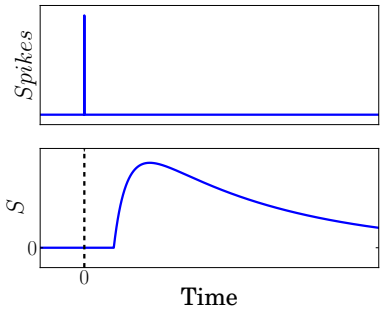


Figure 6: Synaptic response following second-order kinetics and a latency.

[1] Time-to-peak is $\approx 0.3 - 0.5$ ms for AMPA, $0.5 - 1$ ms for $GABA_A$, and 3 ms for NMDA receptors.

## *Shunting inhibition*

Synaptic inhibition can be described as having a *shunting* effect on a cell, i.e., the effect is equivalent to increasing the leak conductance on the cell. The reversal potential of $GABA_A$ receptors is approximately equal to the rest potential of the cell, $E_I \simeq E_L$. The equation governing the membrane potential can then be written:

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_I(V - E_I) + I_{inj} \quad (17)$$
$$\simeq -\hat{g}(V - E_L) + I_{inj} \quad (18)$$

where $\hat{g} = g_L + g_I$. The steady-state voltage $V_{ss} = I/\hat{g} + E_L$, indicating that inhibition has a *divisive* effect on the response of $V_{ss}$ to $I_{inj}$ (Figure 7, top). The membrane time constant decreases as $\tau_m = C_m/\hat{g}$.

However, inhibition has a *subtractive* effect on the firing rate $r$ of an integrate-and-fire cell (with firing threshold $V_{th}$) (Figure 7, bottom):

$$r \simeq \frac{I}{C_m(V_{th} - E_L)} - \frac{\hat{g}}{2C_m(V_{th} - E_L)}\left[(V_{th} - E_L) + (V_{reset} - E_L)\right] \quad (19)$$

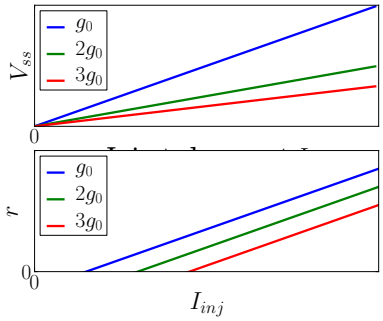


Figure 7: Effects of shunting inhibition on a cell's response to injected current $I_{inj}$, for three values of $g_I$. *Top:* Divisive effect on steady-state membrane potential $V_{ss}$, seen as a decrease in slope of the curve without a change in y-intercept. *Bottom:* Subtractive effect on firing rate $r$, seen as a downward vertical shift of the curve without a change in slope.

## *Voltage dependence of NMDA channels*

NMDA receptors have a voltage-dependent activation, due to a block of the receptor channels by extracellular $Mg^{2+}$ ions. At hyperpolarized post-synaptic membrane potential, NMDA receptors are blocked, and they are unblocked at depolarized potential. We can include this dependence in the synaptic current on post-synaptic potential by including a multiplicative term $F(V_{post})$:

$$I_{NMDA} = g_{NMDA} F(V_{post}) S_{NMDA}(V - E_{syn}) \quad (20)$$

$F(V_{post})$ is a sigmoidal function of $V_{post}$ (Figure 8):

$$F(V) = \frac{1}{1 + \frac{[Mg^{2+}]}{3.57} e^{-V/16.13}} \quad (21)$$
$$= \frac{1}{1 + e^{-(V-\theta)/k}} \quad (22)$$

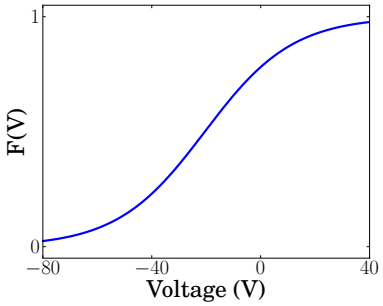


Figure 8: Voltage dependence $F(V_{post})$.

$k = 16.13$; for typical extracellular concentration $[Mg^{2+}]_o = 1$ mM, $\theta = 20.52$ mV

## *Temporal coincidence detection*

The voltage dependence of NMDA receptors display a type of *coincidence detection*. $I_{NMDA}$ is only large if both $S$ is activated and the post-synaptic membrane potential $V_{post}$ is depolarized simultaneously. Moreover, the long time constant for NMDA receptors makes $I_{NMDA}$ sensitive to the order of the pre-synaptic spikes and post-synaptic depolarization.

In Figure 9 *Left*, pre-synaptic spikes precede post-synaptic depolarization. The spikes increase $S$, which is still at a high value at the

time $V_{post}$ is raised. This coincidence of high $S$ and $F(V_{post})$ causes a large $I_{NMDA}$. Alternatively, in Figure 8 *Right*, post-synaptic depolarization precedes pre-synaptic spikes. $F(V_{post})$ is therefore low when $S$ is high, so the channels are under magnesium block while $S$ is high, preventing a large $I_{NMDA}$.

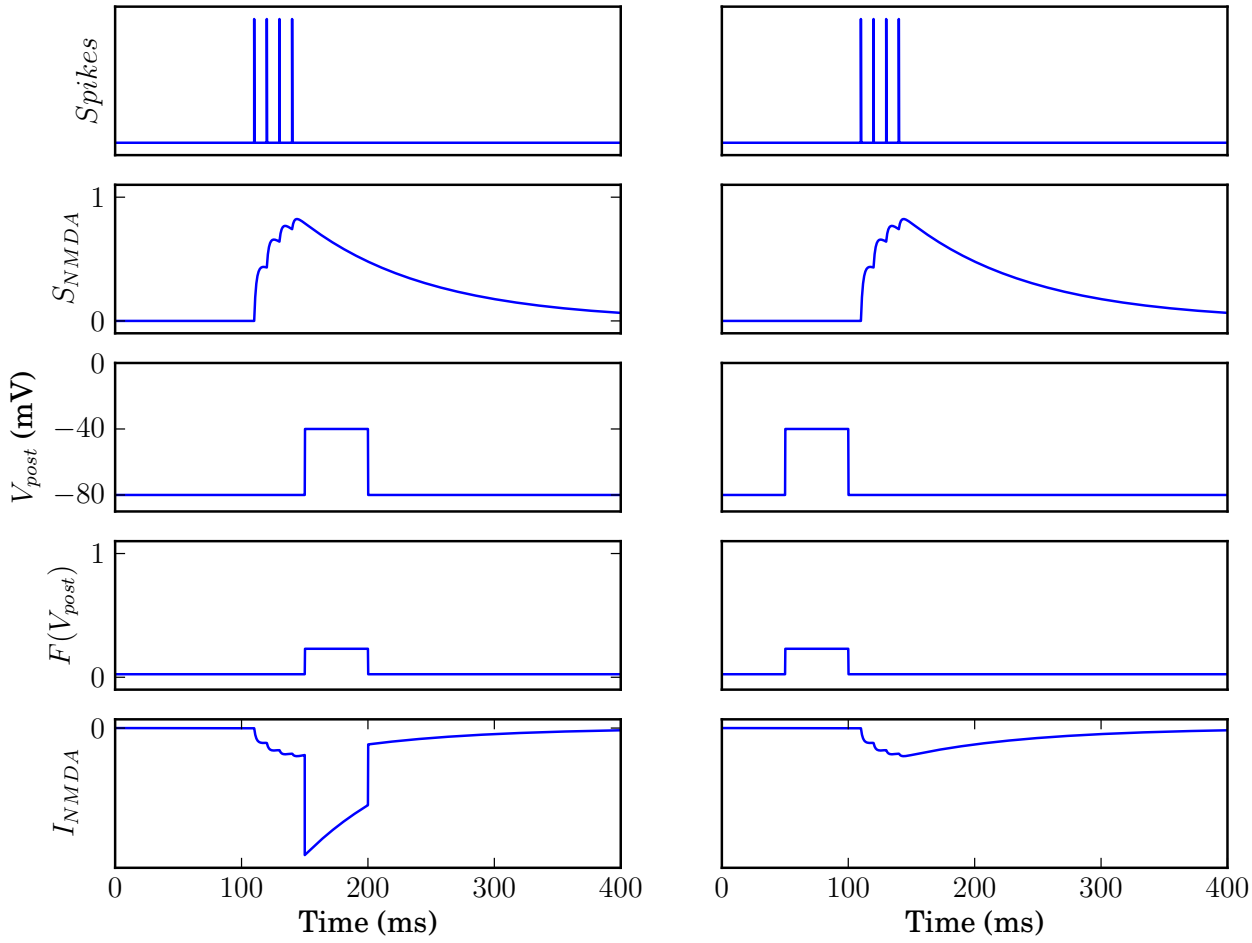


Figure 9: NMDA receptors detect the coincidence of pre-synaptic spikes and post-synaptic depolarization. *Left:* Pre-synaptic spikes before post-synaptic depolarization induces a large $I_{NMDA}$. *Right:* Post-synaptic depolarization before pre-synaptic spikes induces only a small $I_{NMDA}$.