The balance between pre-synaptic short-term facilitation and depression explains the variability of observable responses in striato-striatal GABAergic terminals.

1 Simple model of short-term plasticity

Assume that a presynaptic cell fires action potentials at times t_k, $k = 0, 1, ..., N$, with interspike intervals $y_k = t_k - t_{k-1}$, $k = 1, ..., N$. Let x be the occupancy of the readily releasable pool and p the probability of release. The presynaptic release can then be described by two variables with dynamics given by

$$\partial_t x = \frac{x\,(1-x)}{\tau_r} - px \sum_{i=1}^{N} \phi\,(t - t_i)\,, \tag{1}$$

$$\partial_t p = \frac{p_\infty - p}{\tau_f} + (1-p) \sum_{i=1}^{N} h_i \phi\,(t - t_i)\,, \tag{2}$$

where x_∞, p_∞, τ_r and τ_f, represent the steady state occupancy, the steady state probability of release, and the recovery and facilitation time constants, respectively. Note the equation for occupancy has logistic dynamics between pulses with two limiting values 0 and x_∞, which are, respectively, repelling and attractor states for x. The occupancy and probability of release can be thought of as the depression and facilitation variables, respectively. The function ϕ is a small pulse triggered by presynaptic action potentials that enables changes in both, the occupancy and the probability of release. The increase in p at a spike time t_i is a fraction h_i of $1 - p$ and could, a priori, depend on the interval of time between the current, and the last presynaptic action potential (see Hennig, 2013, for a review).

The steady states x_∞ and p_∞ could increase or decrease to model long-term enhancement or depression, respectively. Note that setting the steady state value of occupancy to one, is equivalent to assume that long term enhancement could be due only to an increase in the steady state probability of release. Note then that the dynamics of x capture depression by depletion of the readily releaseable pool of vesicles, whereas the dynamics of p capture facilitation by accumulation of calcium or some other factor that increases the probability of vesicle release.

1.1 Enhancement dynamics

Between action potentials, the dynamics of p are given by

$$p(t) = p_\infty - (p_\infty - p_0) \exp\left(-t/\tau_p\right) \tag{3}$$

where p_0 is the initial condition. Assume that $p(0) = p_\infty$ and that presynaptic actions potentials occur at a times $0 < t_0 < t_1 < ... < t_n$, after a long time without firing. The probability of release does not change after the first action potential. At each action potential after t_0,

$$p \mapsto p + h_1(1-p) = h_1 + (1-h_1)p.$$

Then,

$$p(t_1) = h_1 + (1-h_1)p_\infty \tag{4}$$

which represents a new initial contidion for p. For $t \in (t_1, t_2)$, the dynamics of p are then given by

$$\begin{aligned} p(t) &= p_\infty - (p_\infty - p(t_1)) \exp\left(-\frac{t-t_1}{\tau_p}\right), && (5) \\ &= p_\infty - [p_\infty - p_\infty - h_1(1-p_\infty)] \exp\left(-\frac{t-t_1}{\tau_p}\right), && (6) \\ &= p_\infty + h_1(1-p_\infty) \exp\left(-\frac{t-t_1}{\tau_p}\right). && (7) \end{aligned}$$

At $t = t_2$, p jumps to $p + (1-p)h_2 = h_2 + (1-h_2)p$, so that

$$p(t_2) = h_2 + (1-h_2)\left[p_\infty + h_1(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right]. \quad (8)$$

The resulting dynamics for $t \in (t_2, t_3)$ are then

$$\begin{aligned} p(t) &= p_\infty - (p_\infty - p(t_2)) \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty - \left\{p_\infty - h_2 - (1-h_2)\left[p_\infty + h_1(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right]\right\} \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty - \left\{p_\infty - h_2 - (1-h_2)p_\infty - h_1(1-h_2)(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right\} \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty - \left[-h_2 + p_\infty(1-(1-h_2)) - h_1(1-h_2)(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right] \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty + \left[h_2 - p_\infty h_2 + h_1(1-h_2)(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right] \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty + \left[h_2(1-p_\infty) + h_1(1-h_2)(1-p_\infty) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right] \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty + (1-p_\infty)\left[h_2 + h_1(1-h_2) \exp\left(-\frac{t_2-t_1}{\tau_p}\right)\right] \exp\left(-\frac{t-t_2}{\tau_p}\right), \\ &= p_\infty + (1-p_\infty)\left[h_2 \exp\left(-\frac{t-t_2}{\tau_p}\right) + h_1(1-h_2) \exp\left(-\frac{t-t_1}{\tau_p}\right)\right]. \quad (9) \end{aligned}$$

Once again, for the action potential at time $t = t_3$,

$$p(t_3) = h_3 + (1-h_3)\left\{p_\infty + (1-p_\infty)\left[h_2 \exp\left(-\frac{t_3-t_2}{\tau_p}\right) + h_1(1-h_2)\exp\left(-\frac{t_3-t_1}{\tau_p}\right)\right]\right\} \tag{10}$$

and for $t \in (t_3, t_4)$,

$$\begin{aligned}
p(t) &= p_\infty - (p_\infty - p(t_3))\exp\left(-\frac{t-t_3}{\tau_p}\right), \\
&= p_\infty - \left(p_\infty - h_3 - (1-h_3)\left\{p_\infty + (1-p_\infty)\left[h_2 \exp\left(-\frac{t_3-t_2}{\tau_p}\right) + h_1(1-h_2)\exp\left(-\frac{t_3-t_1}{\tau_p}\right)\right]\right\}\right)\exp\left(-\frac{t-t_3}{\tau_p}\right), \\
&= p_\infty - \left(p_\infty - h_3 - (1-h_3)p_\infty - (1-h_3)(1-p_\infty)\left[h_2 \exp\left(-\frac{t_3-t_2}{\tau_p}\right) + h_1(1-h_2)\exp\left(-\frac{t_3-t_1}{\tau_p}\right)\right]\right)\exp\left(-\frac{t-t_3}{\tau_p}\right), \\
&= p_\infty - \left(p_\infty h_3 - h_3 - (1-h_3)(1-p_\infty)\left[h_2 \exp\left(-\frac{t_3-t_2}{\tau_p}\right) + h_1(1-h_2)\exp\left(-\frac{t_3-t_1}{\tau_p}\right)\right]\right)\exp\left(-\frac{t-t_3}{\tau_p}\right), \\
&= p_\infty + \left(h_3(1-p_\infty) + (1-h_3)(1-p_\infty)\left[h_2 \exp\left(-\frac{t_3-t_2}{\tau_p}\right) + h_1(1-h_2)\exp\left(-\frac{t_3-t_1}{\tau_p}\right)\right]\right)\exp\left(-\frac{t-t_3}{\tau_p}\right), \\
&= p_\infty + (1-p_\infty)\left[h_3 \exp\left(-\frac{t-t_3}{\tau_p}\right) + h_2(1-h_3)\exp\left(-\frac{t-t_2}{\tau_p}\right) + h_1(1-h_2)(1-h_3)\exp\left(-\frac{t-t_1}{\tau_p}\right)\right].
\end{aligned} \tag{11}$$

In general, for $t \in (t_m, t_{m+1})$

$$p(t) = p_\infty + (1-p_\infty)\sum_{k=1}^{m} h_k \left[\prod_{l=k+1}^{m}(1-h_l)\right]\exp\left(-\frac{t-t_k}{\tau_p}\right). \tag{12}$$

At $t = t_{m+1}$,

$$p(t_{m+1}) = h_{m+1} + (1-h_{m+1})\left\{p_\infty + (1-p_\infty)\sum_{k=1}^{m} h_k \left[\prod_{l=k+1}^{m}(1-h_l)\right]\exp\left(-\frac{t_{m+1}-t_k}{\tau_p}\right)\right\}. \tag{13}$$

Simplification. Assume that $h_k = h$ for $k = 1, ..., n$. Then, between action potentials occuring at times t_m and t_{m+1}, equation (12) simplifies to

$$\begin{aligned}
p(t) &= p_\infty + (1-p_\infty)\sum_{k=1}^{m} h \left[\prod_{l=k+1}^{m}(1-h)\right]\exp\left(-\frac{t-t_k}{\tau_p}\right). \\
&= p_\infty + (1-p_\infty)h\sum_{k=1}^{m}(1-h)^{m-k}\exp\left(-\frac{t-t_k}{\tau_p}\right).
\end{aligned} \tag{14}$$

At $t = t_{m+1}$, the probability of release is

$$p(t_{m+1}) = p_\infty + (1-p_\infty)h\sum_{k=1}^{m}(1-h)^{m-k}\exp\left(-\frac{t_{m+1}-t_k}{\tau_p}\right). \tag{15}$$

If the interspike intervals are such that $\delta = t_m - t_{m-1}$ for all $m \in \{1, ..., n\}$, then equation (12) simplifies further to

$$\begin{aligned}
p(t) &= p_\infty + (1-p_\infty)h\exp\left(-\frac{t-t_m}{\tau_p}\right)\sum_{k=1}^{m}(1-h)^{m-k}\exp\left(-(m-k)\frac{\delta}{\tau_p}\right) \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)h\,(1-h)^m\exp\left(-\frac{m\delta}{\tau_p}\right)\sum_{k=1}^{m}(1-h)^{-k}\exp\left(\frac{k\delta}{\tau_p}\right) \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)h\,(1-h)^m\exp\left(-\frac{m\delta}{\tau_p}\right)\sum_{k=1}^{m}\left(\frac{\exp\left(\delta/\tau_p\right)}{1-h}\right)^k \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)h\,(1-h)^m\exp\left(-\frac{m\delta}{\tau_p}\right)\frac{1-\frac{\exp((m+1)\delta/\tau_p)}{(1-h)^{m+1}}}{1-\frac{\exp(\delta/\tau_p)}{1-h}} \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)h\frac{(1-h)^m\exp\left(-m\delta/\tau_p\right)-\frac{\exp(\delta/\tau_p)}{(1-h)}}{1-\frac{\exp(\delta/\tau_p)}{1-h}} \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)h\frac{(1-h)^{m+1}\exp\left(-m\delta/\tau_p\right)-\exp\left(\delta/\tau_p\right)}{(1-h)-\exp\left(\delta/\tau_p\right)} \\
&= p_\infty + (1-p_\infty)\exp\left(-\frac{t-t_m}{\tau_p}\right)F(h,\delta,m) \qquad (16)
\end{aligned}$$

where

$$F(h,\delta,m) = h\frac{(1-h)^{m+1}\exp\left(-m\delta/\tau_p\right)-\exp\left(\delta/\tau_p\right)}{(1-h)-\exp\left(\delta/\tau_p\right)} \qquad (17)$$

At $t = t_{m+1}$,

$$p(t_{m+1}) = \qquad (18)$$

1.1.1 Frequency-dependent enhancement

Consider first Eqn. (2) with frequency-dependent increase in the probability of release given by

$$h_i = g(h_i) = \frac{h_0}{h_0 + h_i}, \qquad (19)$$

where h_0 is the interspike interval at which the increase in the probability of release is half of its current value.

1.2 Analysis of occupancy (depression)

For simplicity in the analysis, let ϕ be an instantaneous pulse for each presynaptic spike. Also, assume the probability of release and the facilitation factor h are constant and an initial state of occupancy $x(0) = x_\infty$. Under those conditions, the occupancy of readily releasable sites after the the

nth pulse is given

$$x_n = \frac{x_\infty (1-p)^{n+1}}{(1-p)^n + p\sum_{k=1}^{n}(1-p)^{n-k}\exp\left[-(t_n - t_{n-k})r_x\right]} \quad (20)$$

$$= \frac{x_\infty (1-p)}{1 + p\sum_{k=1}^{n}\frac{\exp[-(t_n - t_{n-k})r_x]}{(1-p)^k}} \quad (21)$$

Triggering pulses. A more realistic approach would be to define ϕ so that its time course resembles that of calcium activation, during which neurotransmitter is released, the occupancy of vesicle docking sites drops, and the probability of release changes. One such function could be

$$\phi(y) = H(y)\frac{y}{\tau_\alpha}\exp\left(-\frac{y}{\tau_\alpha}\right) \quad (22)$$

where $H(y)$ is the heavy-side function, taking the value 0 if for $y < 0$, and 1 otherwise.

Enhancement as a function of interspike intervals. Facilitation (*i.e.* increase in p), can be assumed to depend on the presynaptic interspike intervals $h_k = t_k - t_{k-1}$ for $k = 2, 3, ...$ For instance,

$$q(h) = \bar{q}\frac{h}{\tau_q}e^{(h-h_*)/\tau_q} \quad (23)$$

where τ_q can be regarded as a facilitation time constant, h_* as an optimal interspike interval for facilitation, and $\bar{q}$ is the maximum increase in the probability of release.

2 Mathematical details

Let $(x_k, p_k) = (x(t_k), p(t_k))$ represent the states of the system at the time of arrival of the kth pulse. From (1)-(2), the dynamics of (x, p) for $t \in (t_i, t_{i+1})$ satisfy

$$x(t) = \frac{x_\infty x_i}{x_i + (x_\infty - x_i)\exp\left(-(t-t_i)x_\infty/\tau_x\right)}, \tag{24}$$

$$p(t) = p_\infty - (p_\infty - p_i)\exp\left(-\frac{(t-t_i)}{\tau_p}\right). \tag{25}$$

At $t = t_{k+1}$, the time of the $(k+1)$th spike, the state $(x, p)(t)$ jumps to the value

$$x_{k+1} = \frac{x_\infty x_k\,(1-p_{k+1})}{x_k + (x_\infty - x_k)\exp\left(-(t_{k+1}-t_k)x_\infty/\tau_x\right)} \tag{26}$$

$$p_{k+1} = \left[p_k + (p_\infty - p_k)\exp\left(-(t_{k+1}-t_k)/\tau_p\right)\right](1 - p_{k+1}x_{k+1}) \tag{27}$$

2.1 Analysis of occupancy (depression) in response to δ-pulses for constant p

At $t = t_{i+1}$, the time of the $(i+1)$th pulse, the occupancy jumps to the value

$$x_{i+1} = \frac{x_\infty x_i\,(1-p)}{x_i + (x_\infty - x_i)\exp\left(-(t_{i+1}-t_i)x_\infty/\tau_x\right)} \tag{28}$$

for $i \in \{0, ..., N-1\}$.

The general expression in (28) can be used recursively to investigate the behavior of the occupancy after a series of pulses. To do so, let $i = 1$, $r_x = x_\infty/\tau_x$, and replace the occupancy $x_0 = x_\infty(1-p)$ after the first pulse into Eqn. (28). Then, the occupancy at $t = t_1$ is

$$\begin{aligned} x_1 &= \frac{x_\infty\,(1-p)}{1 + \left[\frac{x_\infty}{x_0} - 1\right]\exp\left[-(t_1-t_0)r_x\right]} \\ &= \frac{x_\infty\,(1-p)}{1 + \left[\frac{x_\infty}{x_\infty(1-p)} - 1\right]\exp\left[-(t_1-t_0)r_x\right]} \\ &= \frac{x_\infty\,(1-p)}{1 + \left(\frac{p}{1-p}\right)\exp\left[-(t_1-t_0)r_x\right]} \\ &= \frac{x_\infty\,(1-p)^2}{(1-p) + p\exp\left[-(t_1-t_0)r_x\right]} \end{aligned} \tag{29}$$

The occupancy at $t = t_2$ is

$$
\begin{aligned}
x_2 &= \frac{x_\infty (1-p)}{1 + \left[\frac{x_\infty}{x_1} - 1\right] \exp\left[-(t_2 - t_1) r_x\right]} \\
&= \frac{x_\infty (1-p)}{1 + \left[\frac{x_\infty}{\frac{x_\infty (1-p)^2}{(1-p) + p \exp[-(t_1 - t_0) r_x]}} - 1\right] \exp\left[-(t_2 - t_1) r_x\right]} \\
&= \frac{x_\infty (1-p)}{1 + \left[\frac{(1-p) + p \exp[-(t_1 - t_0) r_x]}{(1-p)^2} - 1\right] \exp\left[-(t_2 - t_1) r_x\right]} \\
&= \frac{x_\infty (1-p)^3}{(1-p)^2 + \left[(1-p) + p \exp\left[-(t_1 - t_0) r_x\right] - (1-p)^2\right] \exp\left[-(t_2 - t_1) r_x\right]} \\
&= \frac{x_\infty (1-p)^3}{(1-p)^2 + \left[\left((1-p) - (1-p)^2\right) \exp\left[-(t_2 - t_1) r_x\right] + p \exp\left[-(t_2 - t_0) r_x\right]\right]} \\
&= \frac{x_\infty (1-p)^3}{(1-p)^2 + p(1-p) \exp\left[-(t_2 - t_1) r_x\right] + p \exp\left[-(t_2 - t_0) r_x\right]},
\end{aligned}
\tag{30}
$$

from which it is clear that a pattern starts to emerge. The occupancy at $t = t_3$ is then

$$
\begin{aligned}
x_3 &= \frac{x_\infty (1-p)}{1 + \left[\frac{x_\infty}{x_2} - 1\right] \exp\left[-(t_3 - t_2) r_x\right]} \\
&= \frac{x_\infty (1-p)}{1 + \left[\frac{x_\infty}{\frac{x_\infty (1-p)^3}{(1-p)^2 + p(1-p) \exp[-(t_2 - t_1) r_x] + p \exp[-(t_2 - t_0) r_x]}} - 1\right] \exp\left[-(t_3 - t_2) r_x\right]} \\
&= \frac{x_\infty (1-p)}{1 + \left[\frac{(1-p)^2 + p(1-p) \exp[-(t_2 - t_1) r_x] + p \exp[-(t_2 - t_0) r_x]}{(1-p)^3} - 1\right] \exp\left[-(t_3 - t_2) r_x\right]} \\
&= \frac{x_\infty (1-p)^4}{(1-p)^3 + \left[(1-p)^2 + p(1-p) \exp\left[-(t_2 - t_1) r_x\right] + p \exp\left[-(t_2 - t_0) r_x\right] - (1-p)^3\right] \exp\left[-(t_3 - t_2) r_x\right]} \\
&= \frac{x_\infty (1-p)^4}{(1-p)^3 + p(1-p)^2 \exp\left[-(t_3 - t_2) r_x\right] + p(1-p) \exp\left[-(t_3 - t_1) r_x\right] + p \exp\left[-(t_3 - t_0) r_x\right]}
\end{aligned}
\tag{31}
$$

In general, for the nth pulse,

$$x_n = \frac{x_\infty (1-p)^{n+1}}{(1-p)^n + p\sum_{i=1}^{n}(1-p)^{n-i}\exp\left[-(t_n - t_{n-i})r_x\right]} \tag{32}$$

$$= \frac{x_\infty (1-p)}{1 + p\sum_{i=1}^{n}(1-p)^{-i}\exp\left[-(t_n - t_{n-i})r_x\right]} \tag{33}$$

$$= \frac{x_\infty (1-p)}{1 + p\exp\left[-t_n r_x\right]\sum_{i=1}^{n}(1-p)^{-i}\exp\left[t_{n-i} r_x\right]} \tag{34}$$

3 Abstract from Barroso, Herrera-Valdez, and Bargas

The neostriatal neuronal population is composed mainly by spiny projection neurons (SPNs), which make synapses with each other via their local axon collaterals (approx. 100mm long) shaping the activity of a localized feedback inhibitory circuit. The other 5-10% of the neuronal population is composed by different classes of interneurons, mainly GABAergic. The synapses between GABAergic interneurons and SPNs form a feedforward inhibitory circuit in the striatum by connecting hundreds of SPNs, which may be as far as 1 mm. Both inhibitory circuits are richly inervated by dopaminergic neurons from the substantia nigra pars compacta (SNc), and therefore both circuits are affected by dopamine (DA) loss, like in Parkinson disease. However, little is known of how the dopamine loss affects each synapse form the feedforward inhibitory circuit. To asses this question, we favor the feedforward circuit by using intraestriatal field stimulation 1 mm away from the SPN recorded. We show that using field stimulation it is possible to distinguish between synapses of the feedforward circuit characterized by their short term synaptic plasticity (STSP); finding that there are at least three different types of inhibition in the feedforward circuit: depressing synapses (putative fast spiking (FS) to SPN synapse), facilitating synapses (putative ???(LTS) to SPN synapse) and a novel combination of facilitating/depressing synapses (possibly yet another kind of LTS-SPN). In addition, we use intensity-amplitude experiments to reveal different properties of each synapse. We then found using cluster analysis that each response corresponds to a different kind of synapse. Using the 6-hydroxydopamine (6-OHDA) rodent model of Parkinsonism we demonstrate how each of this synapses are differentially affected, showing that depressing synapses are the less affected by DA deprivation, whereas the inhibition form both facilitating and facilitating/depressing synapses are enhanced (statistical significance). Moreover, evoked IPSCs after DA loss in facilitating and facilitating/depressing synapse are more likely to occur than in control conditions. Taken together, our observations suggest that these synapses take control of the feedforward inhibitory circuit in Parkinsonism and depressing synapses dominate such a circuit in control conditions.

References

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