Is There a Benefit of Randomness in Synaptic Vesicle Release?

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Idealized Model with an Unlimited Number of Docking Sites

$\alpha_0$

$p_0$
Rate of action potentials

Rate of vesicle release (p=1)
rate of action potentials

rate of vesicle release (p=0.5)
rate of action potentials

rate of vesicle release (p=0.1)
docked vesicle

with probability $p$ on each action potential

with probability per unit time $\alpha$

fused vesicle
Fernandez-Alfonso T and Ryan TA:
The Kinetics of Synaptic Vesicle Pool Depletion at CNS Synaptic Terminals.
Neuron 41: 943-953, 2004
Modeling the Experiment of Fernandez-Alfonso & Ryan

Summary of the experiment

- Start with a synapse that has been at rest for some time
- Apply a sequence of 300 equally spaced action potentials
- Observe the fraction of fused vesicles as a function of time during and after the spike train
- Repeat for a variety of interspike intervals

Model of the experiment

- All docking sites are occupied at $t = 0$.
- Action potential arrival times are $t_k = kT$ for $k = 0, \ldots, n-1$ with $n = 300$ and $T =$ interspike interval of the experiment.
- Let $p$ be the probability of fusion of any docked vesicle upon arrival of an action potential. We assume that $p$ is constant during any one experiment, but that it depends (because of facilitation) on the rate of arrival of action potentials, and therefore varies from one experiment to another.
- Let $\alpha$ be the rate constant for reformation of a docked vesicle from a fused vesicle. We find that $\alpha$ is constant across all of the experiments.

Let $f(t)$ be the expected fraction of fused vesicles at time $t$. Then

$$f(t_0^-) = 0 \quad (1)$$

$$f(t_k^+) = f(t_k^-) + p \left( 1 - f(t_k^-) \right), \quad k = 0, \ldots, n-1 \quad (2)$$

Between the arrival times of action potentials, and also after the arrival of the last action potential, we have the following differential equation for $f(t)$:

$$\frac{df}{dt} = -\alpha f \quad (3)$$
From the decay of $f(t)$ following the end of the train of action potentials, we can check whether the decay is indeed exponential and identify the parameter $\alpha$. We get a good fit to all of the individual experiments with

$$\alpha = 0.02/s$$  \hspace{1cm} (4)

To evaluate $p$, which we expect to be different in each experiment, we use the fraction of fused vesicles immediately following the last action potential in the spike train. This is given by

$$f(t^+_n) = p \frac{1 - ((1 - p) \exp(-\alpha T))^n}{1 - (1 - p) \exp(-\alpha T)}$$  \hspace{1cm} (5)

The left-hand side is a number in $(0, 1)$ that is experimentally determined, and everything on the right-hand side is known except for $p$. It is straightforward to show that there is a unique $p \in (0, 1)$ that satisfies (5) and we find that value numerically. With $\alpha$ and $p$ determined, we can evaluate $f(t)$ for any $t$ by solving (1-3) and compare to the experimental results. The comparison is shown in the following figures.
Model Results

300 AP at
- 2 Hz
- 5 Hz
- 10 Hz
- 20 Hz
- 30 Hz
- 1800 AP @ 30 Hz

% of fused vesicles vs. time (sec)
Model Results & Experimental Results Superimposed

\[ \Delta F_{spH} \]

![Graph showing model results and experimental results superimposed](image)

- 300AP at 2Hz, 5Hz, 10Hz, 20Hz, 30Hz
- 1800AP at 30Hz in Baf

Time (sec)
Fitting $p_0$ to the data reported by Fernandez-Alfonso and Ryan (2004)
Interaction of facilitation/depression

\[ \frac{dn}{dt} = \alpha (n_s - n(t)) - r(t) \]

\[ \frac{dp}{dt} = \gamma \left( \frac{s(t)}{s_l} - p(t) \right) \]

\[ r(t) = s(t) \cdot p(t) \cdot n(t) \]

\[ s(t) = \text{rate of arrival of action potentials} \]

\[ p(t) = \text{probability of release for each docked vesicle when an action potential arrives} \]

\[ n(t) = \text{number of docked vesicles} \]

\[ r(t) = \text{rate of vesicle release} \]
Parameters

\( n_5 = \# \text{ of docking sites} \)

\( \alpha = \text{rate constant for refill of empty site (0.02/second)} \)

\( \nu = \text{rate constant for adaptation of facilitation} \)

\( S_1 = \text{extrapolated rate of arrival of action potentials that would make } P = 1 \)

\( (6000/\text{second}) \)
Sensitivity of output to input:
\[
\frac{\Delta r}{r} = \frac{\Delta s}{s}
\]

- Sensitivity to sudden changes is equal to 1, since \(n\) and \(p\) cannot change abruptly.

- Sensitivity to slow changes is equal to

\[
2 \left( \frac{n^*}{n_s} \right) = 2 \left( \frac{1}{1 + \frac{(S^*)^2}{\alpha S_1}} \right)
\]

where \(\sqrt{\alpha S_1} \approx 10/\text{second}\)
Frequency response of the synapse to small-amplitude modulation of a regular spike train:

\[
\left( \frac{\hat{r}}{r^*} \right) = \frac{1}{1 + \frac{1}{1 + \frac{1}{1 + i\omega/\alpha}}} \left( \frac{\hat{S}}{S^*} \right)
\]

\[
1 + \frac{(S^*)^2}{\alpha s_1} \left( \frac{1}{1 + i\omega/\alpha} \right)
\]

High-frequency gain = 1

Low-frequency gain =

\[
2 \left( \frac{1}{1 + \frac{(S^*)^2}{\alpha s_1}} \right)
\]
If \( \alpha \ll \omega \ll \nu \), then

\[
\left( \frac{r^1}{r^*} \right) = \frac{2i\omega}{i\omega + \frac{(S^*)^2}{s^1}} \left( \frac{s^1}{s^*} \right)
\]

\[
= \frac{2}{1 + \frac{i\omega s_1}{(s^*)^2}} \left( \frac{s^1}{s^*} \right)
\]

and this is the transfer function of a pseudo-differentiator.
References on Stochastic Aspects of Synaptic Vesicle Dynamics

Zhang C and Peskin CS:
Improved signaling as a result of randomness in synaptic vesicle release.
Proceedings of the National Academy of Sciences USA 112(48): 14954-14959, 2015

Zhang C and Peskin CS:
Analysis, simulation, and optimization of stochastic vesicle dynamics in synaptic transmission.