Is There a Benefit of Randomness in Synaptic Vesicle Release?

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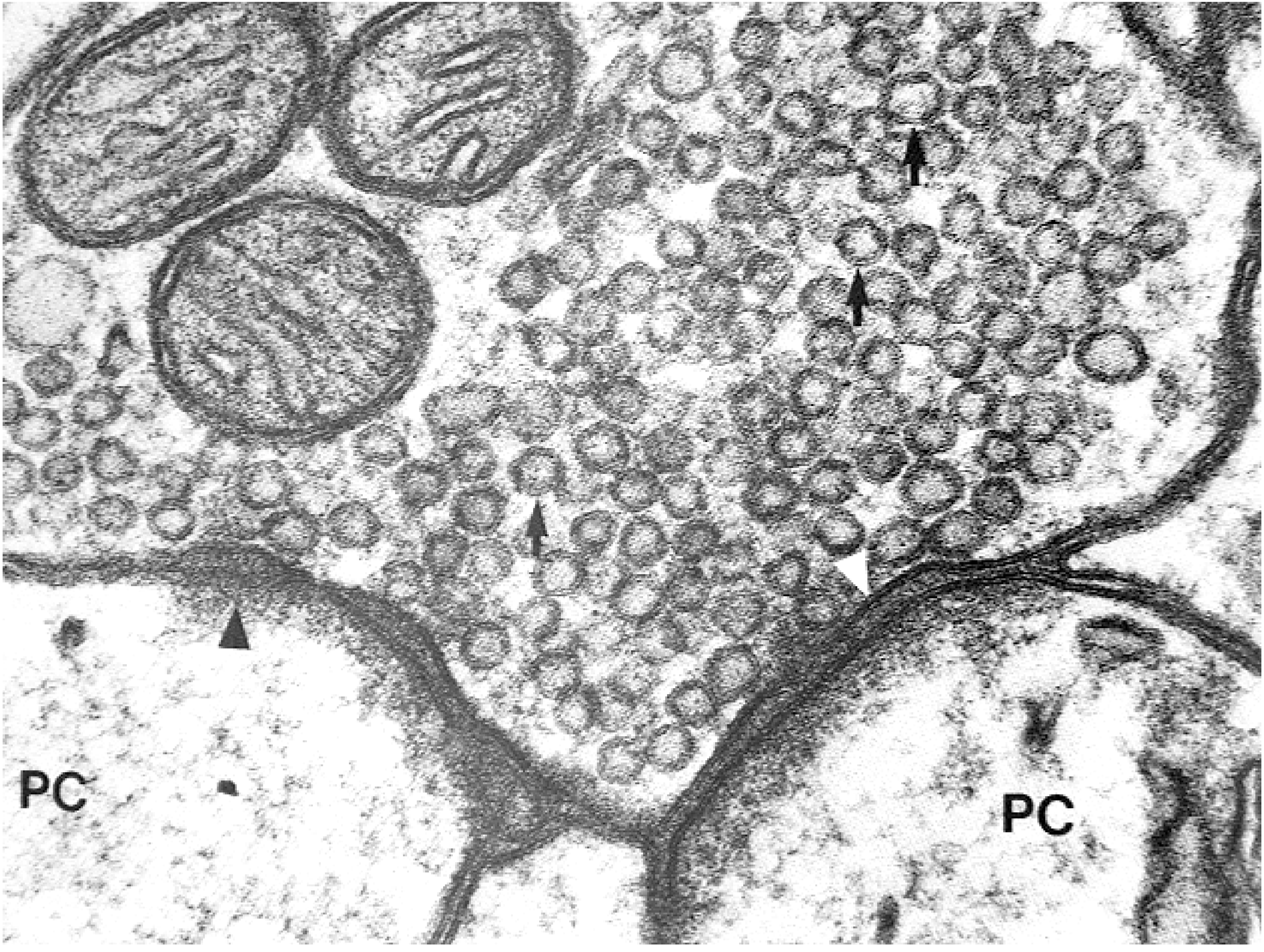
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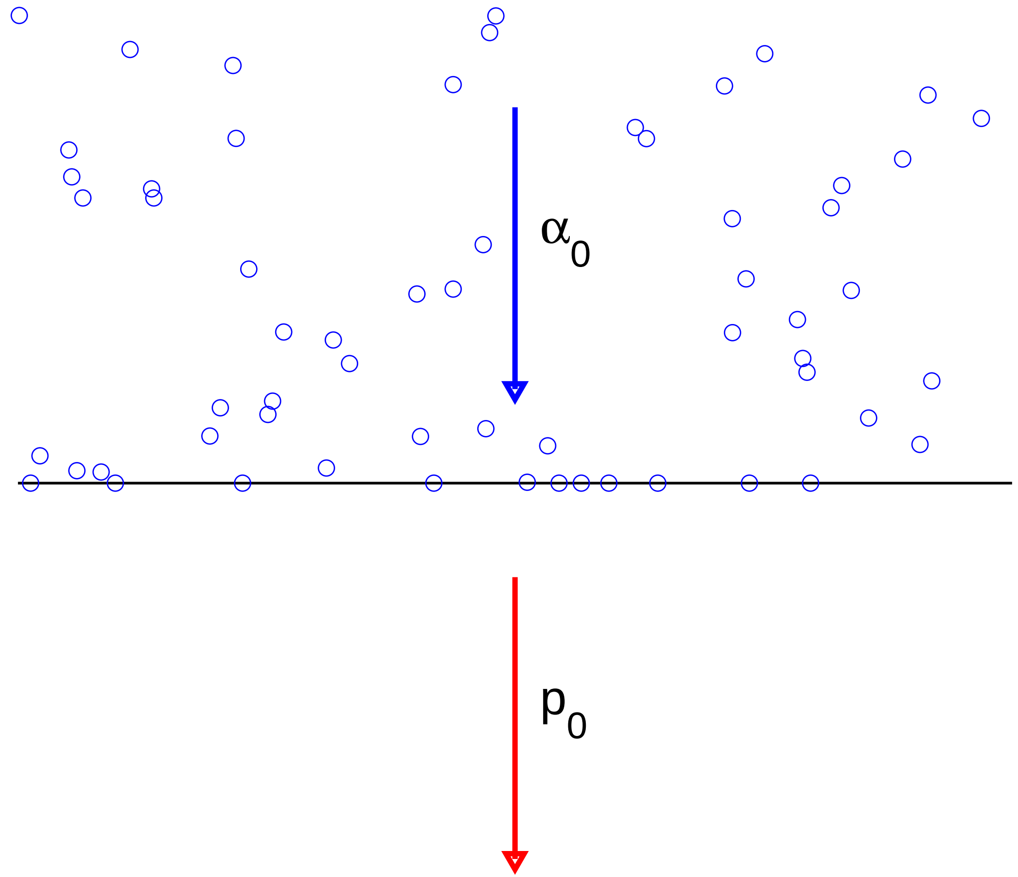
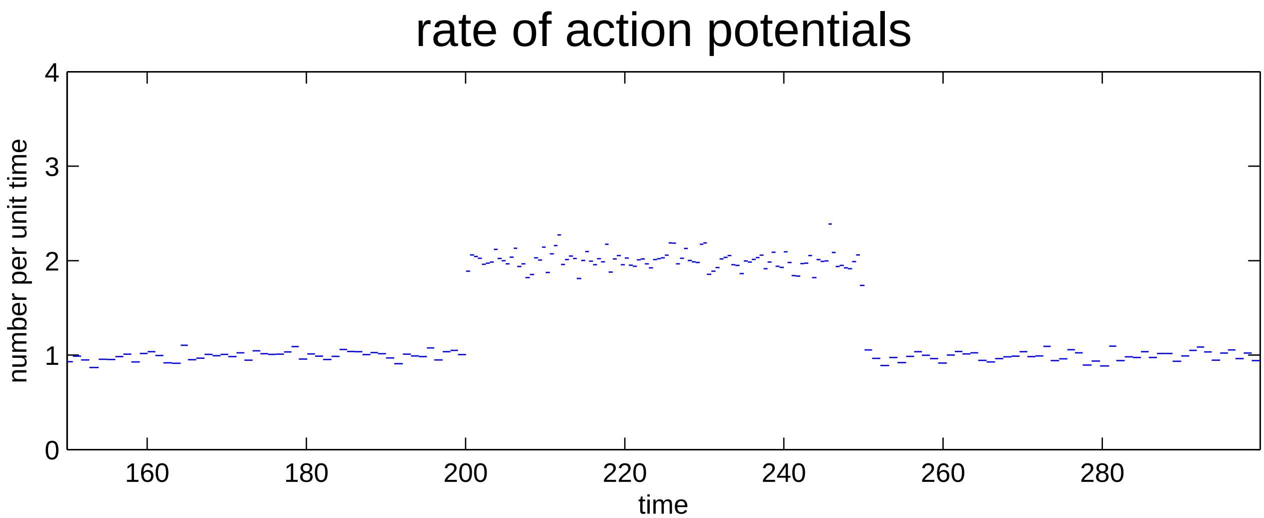
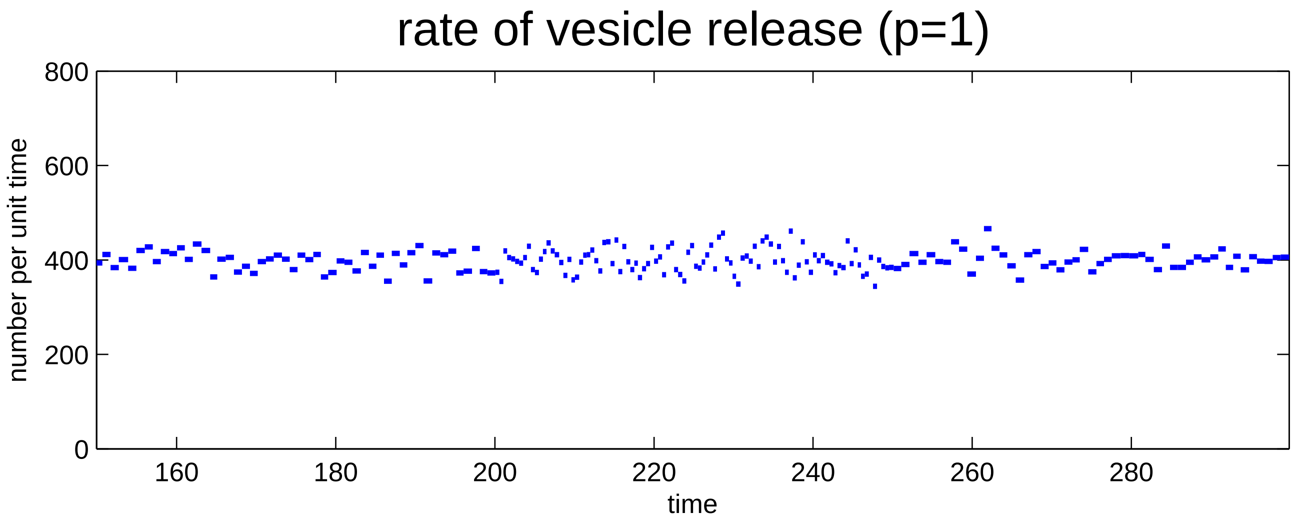
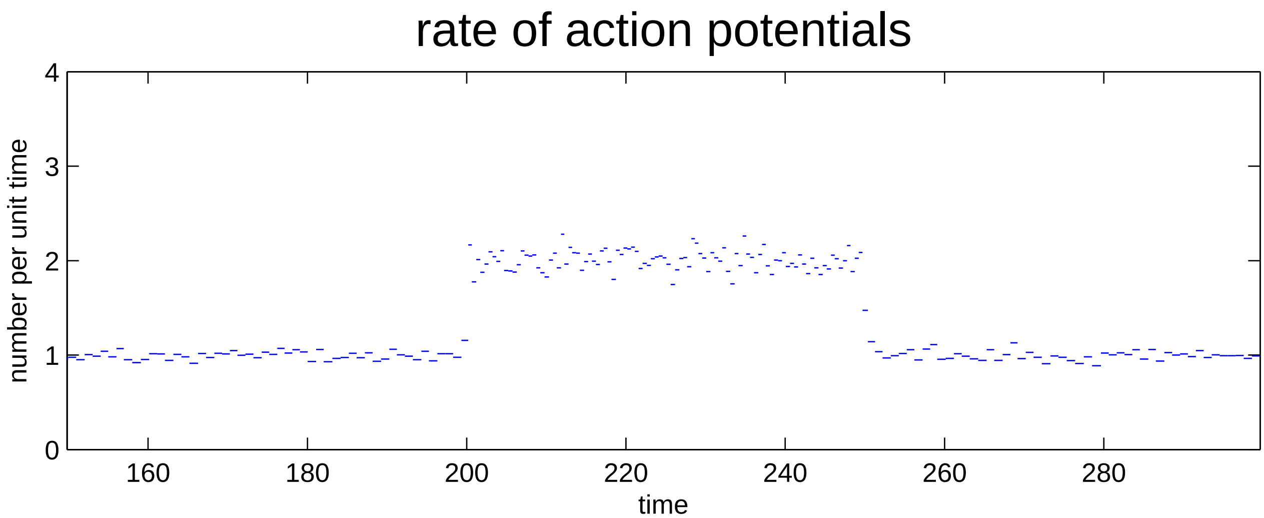
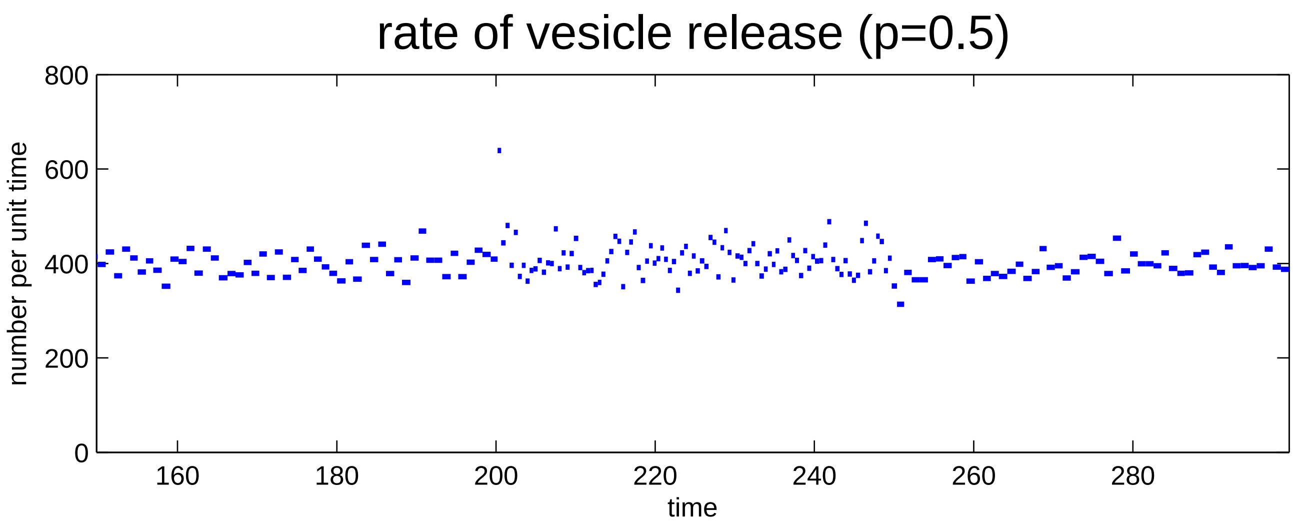
Idealized Model with an Unlimited Number of Docking Sites

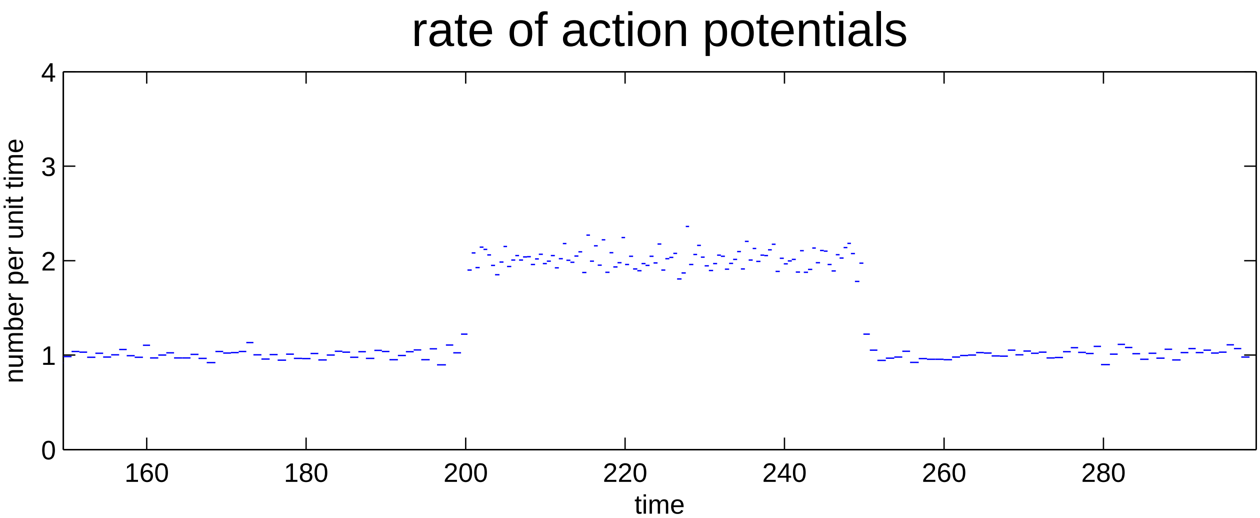


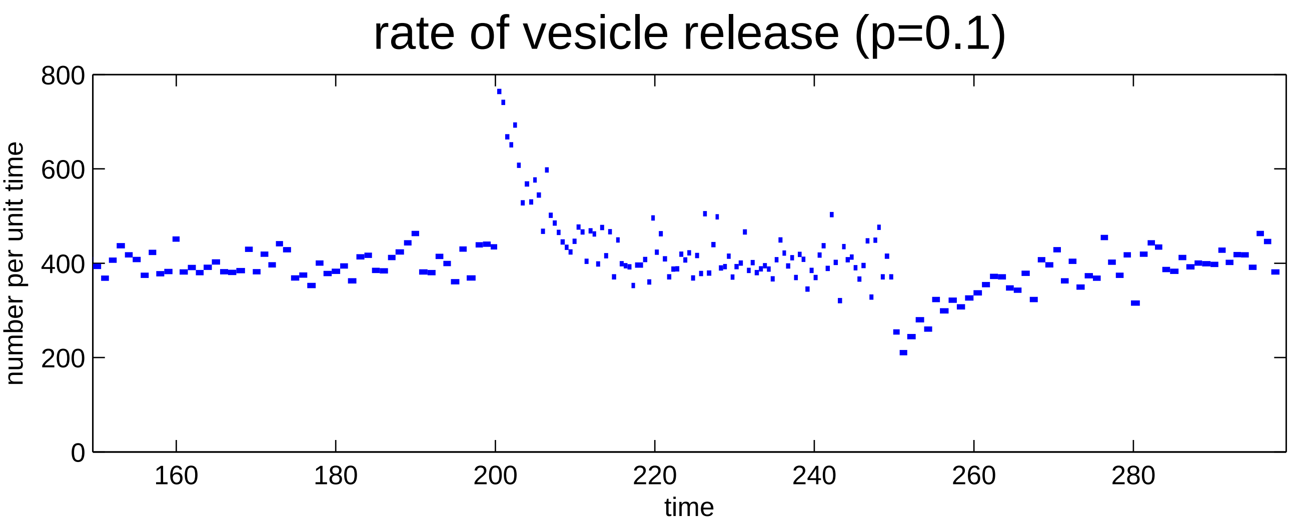

rate of action potentials
number per unit time
0
1
2
3
4
160
180
200
220
240
260
280
time

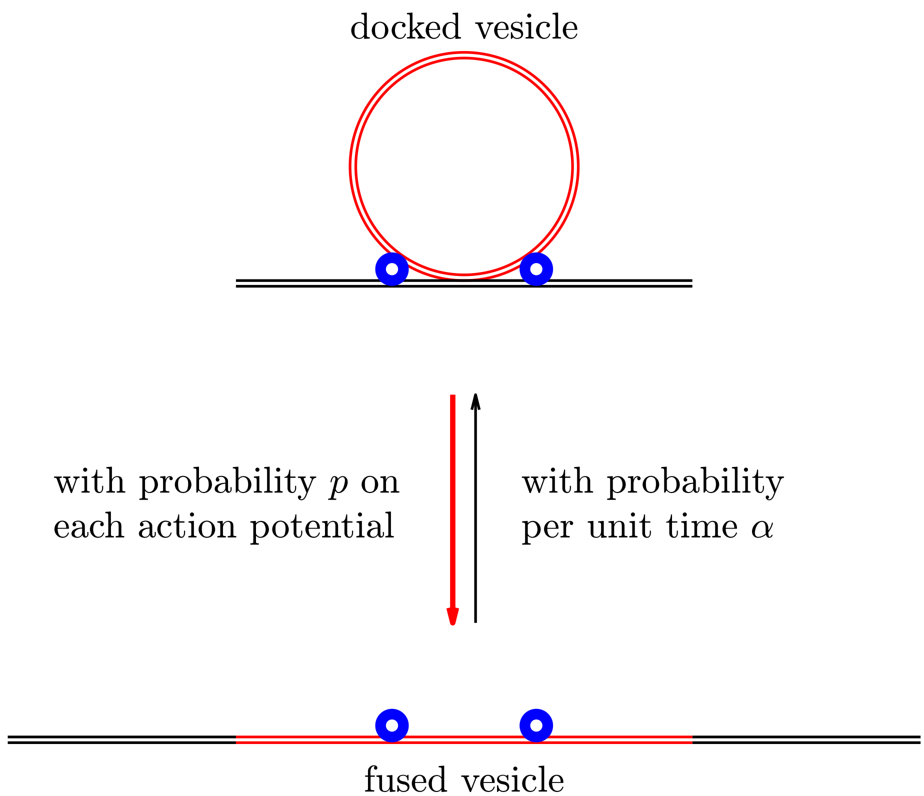

rate of vesicle release (p=1)
number per unit time
0
200
400
600
800
160
180
200
220
240
260
280
time


rate of action potentials
number per unit time
0
1
2
3
4
160
180
200
220
240
260
280
time

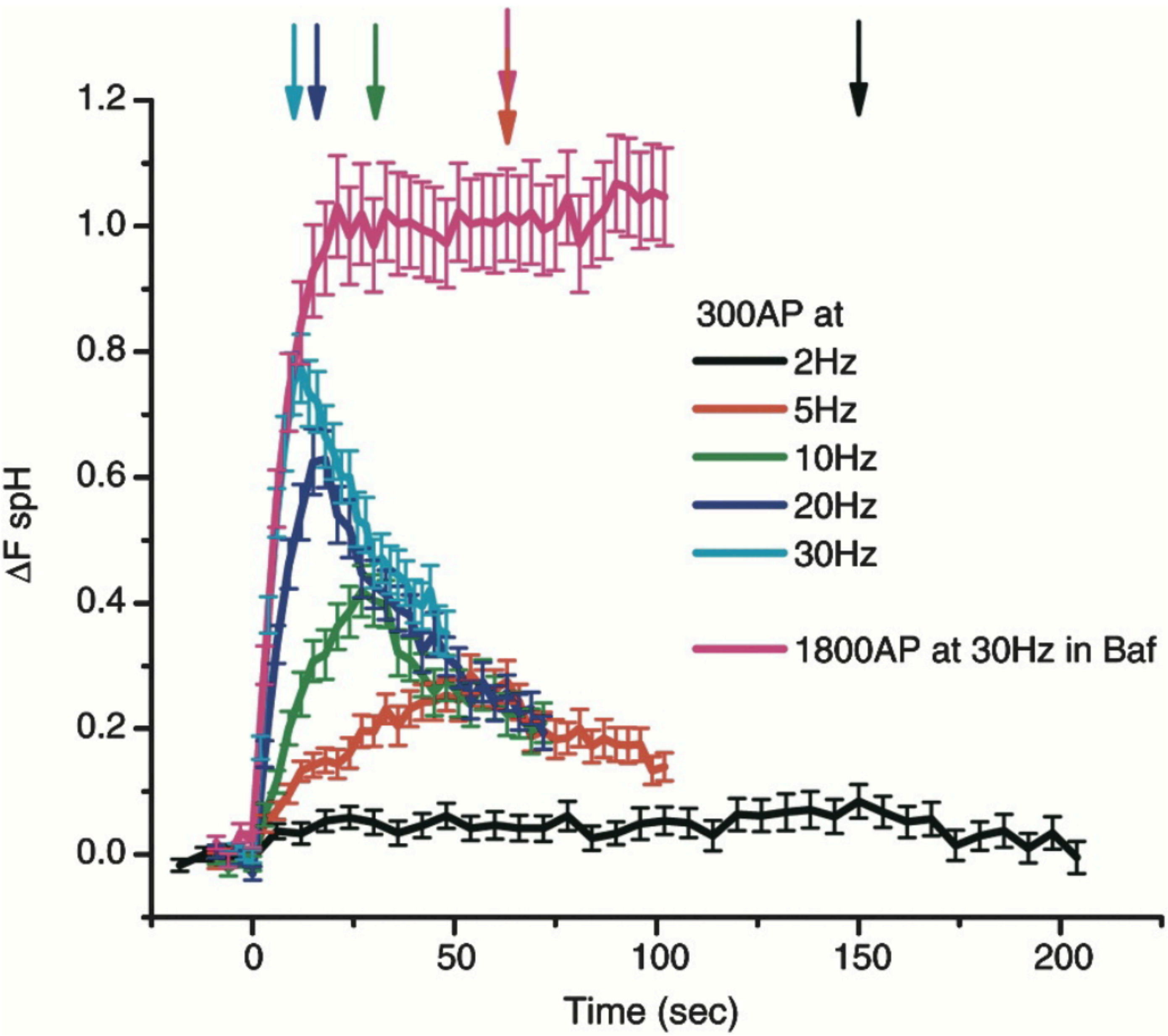

rate of vesicle release (p=0.5)
number per unit time
0
200
400
600
800
160
180
200
220
240
260
280
time


rate of action potentials
number per unit time
time
0
1
2
3
4
160
180
200
220
240
260
280


rate of vesicle release (p=0.1)
number per unit time
time
0
200
400
600
800
160
180
200
220
240
260
280


docked vesicle
with probability p on each action potential
with probability per unit time α
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 α be the rate constant for reformation of a docked vesicle from a fused vesicle. We find that α is constant across all of the experiments.

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

$$f(t_0^-) = 0 \qquad (1)$$
$$f(t_k^+) = f(t_k^-) + p\left(1 - f(t_k^-)\right), \quad k = 0, \ldots, n-1 \qquad (2)$$

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

$$\frac{df}{dt} = -\alpha f \qquad (3)$$

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 α. We get a good fit to all of the individual experiments with

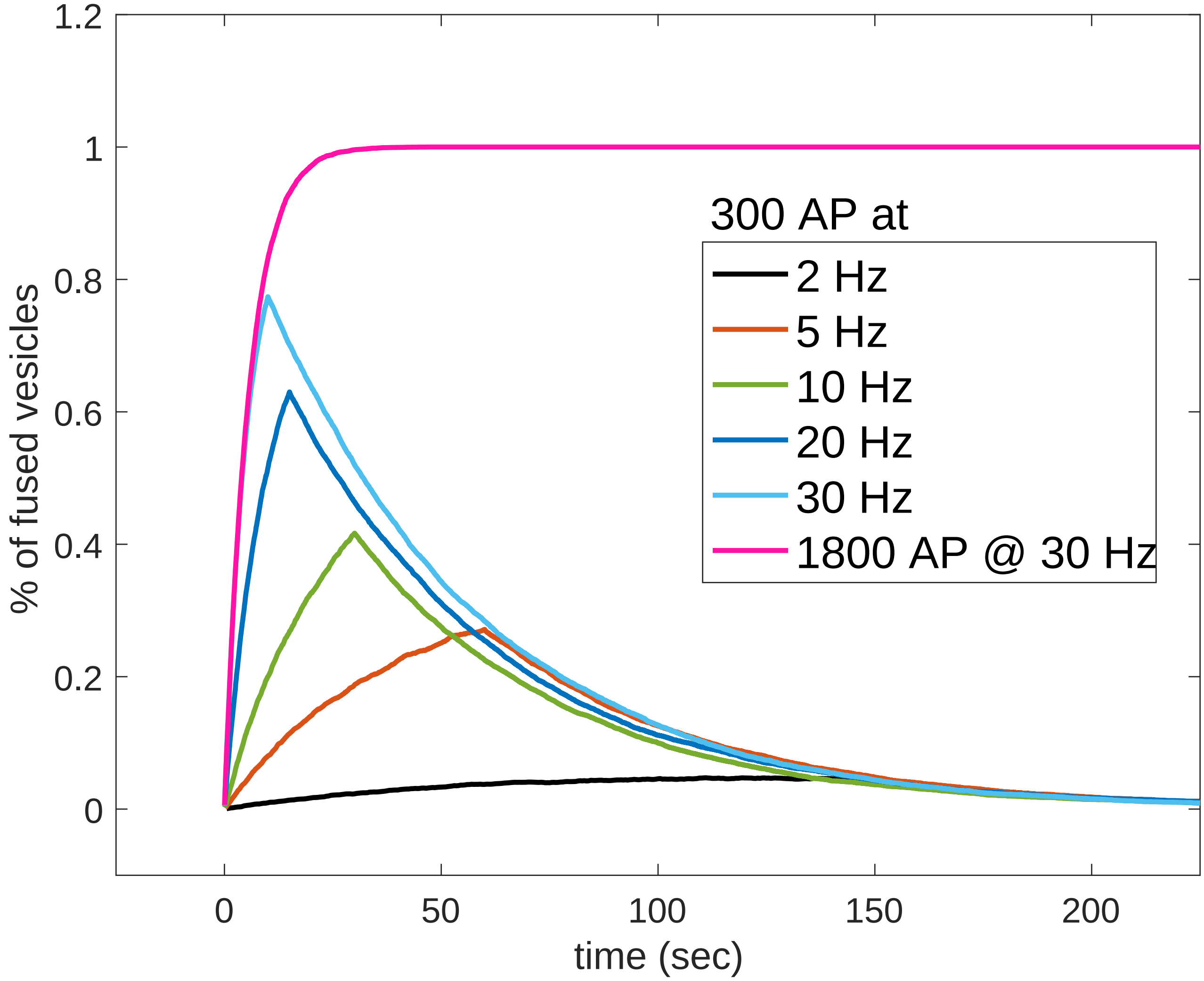
$$\alpha = 0.02/\mathrm{s} \tag{4}$$

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

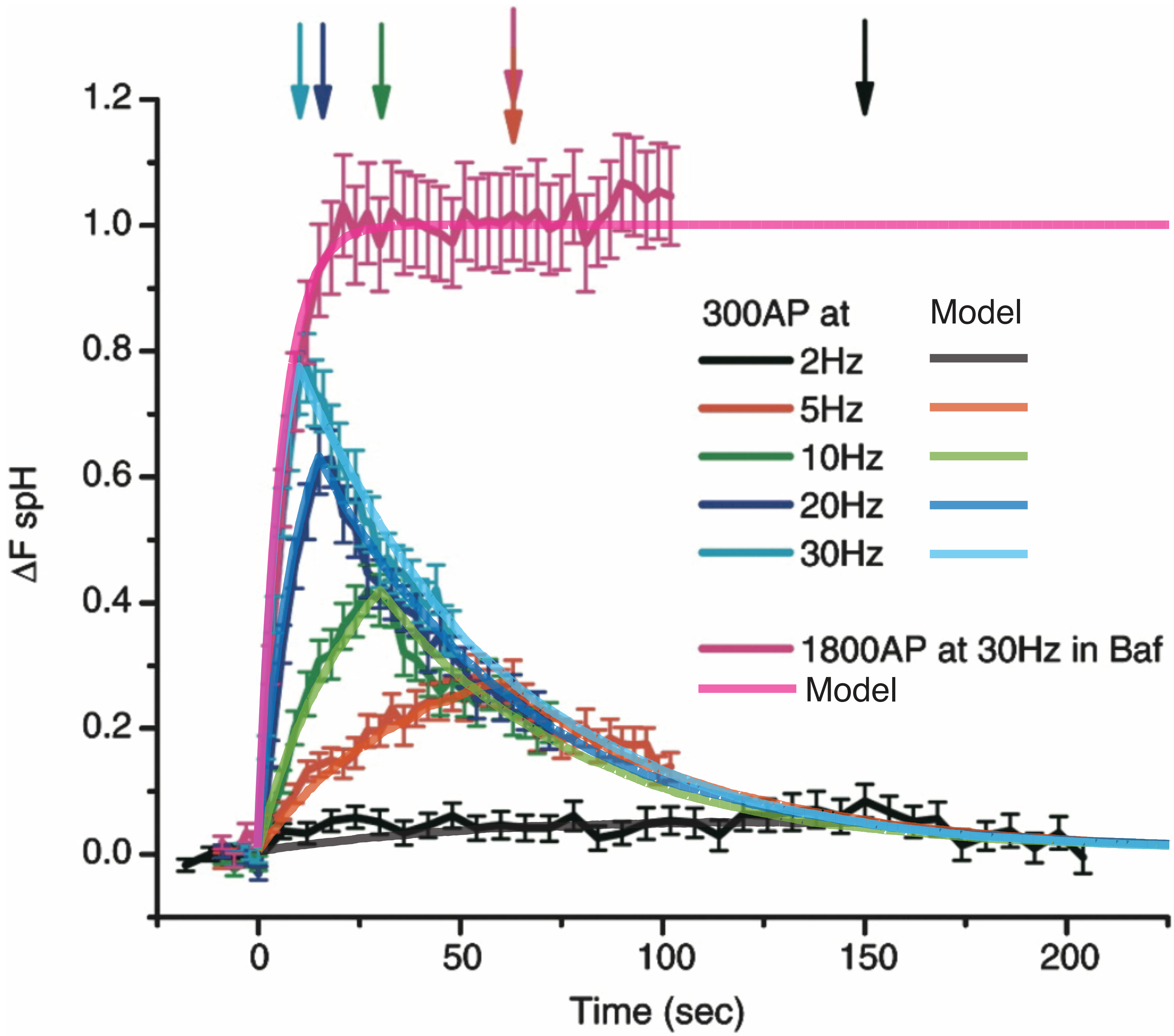
$$f(t_{n-1}^{+}) = p\frac{1 - ((1-p)\exp(-\alpha T))^{n}}{1 - (1-p)\exp(-\alpha T)} \tag{5}$$

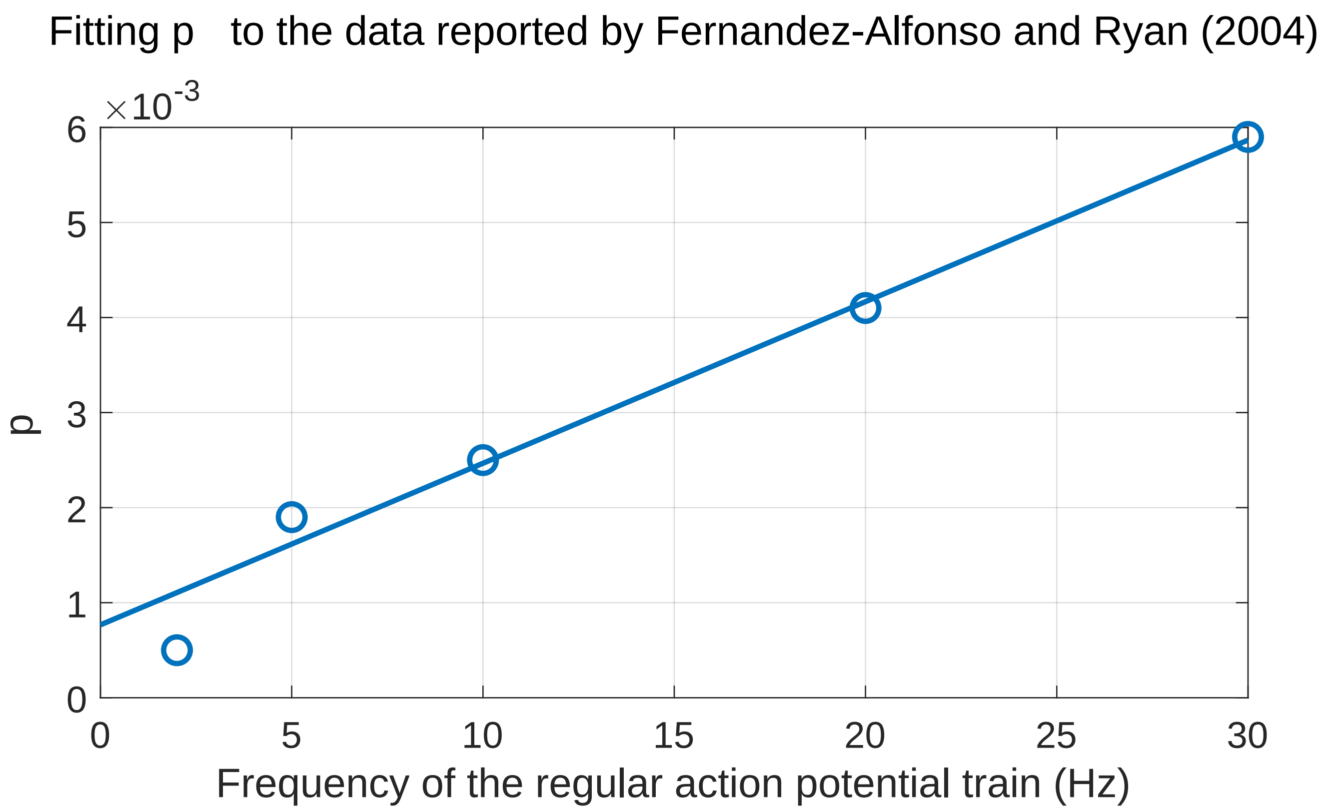
The left-hand side is a number in $(0, 1)$ that is experimentally determined, and everything on the right-hand side is known except for p. It is straightforward to show that there is a unique $p \in (0, 1)$ that satisfies (5) and we find that value numerically. With α and p determined, we can evaluate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

Model Results



Model Results & Experimental Results Superimposed




Fitting p   to the data reported by Fernandez-Alfonso and Ryan (2004)
×10^-3
6
5
4
3
2
1
0
p
0
5
10
15
20
25
30
Frequency of the regular action potential train (Hz)

Interaction of facilitation/depression

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

$$\frac{dp}{dt} = \nu\left(\frac{s(t)}{s_1} - p(t)\right)$$

$$r(t) = s(t)\,p(t)\,n(t)$$

$s(t)$ = rate of arrival of action potentials

$p(t)$ = probability of release for each docked vesicle when an action potential arrives

$n(t)$ = number of docked vesicles

$r(t)$ = rate of vesicle release

Parameters

n_s = # of docking sites

α = rate constant for refill of empty site (0.02/second)

ν = rate constant for adaptation of facilitation

S_1 = extrapolated rate of arrival of action potentials that would make $p = 1$ (6000/second)

Sensitivity of output to input:

$$\frac{\Delta r / r}{\Delta s / s}$$

- 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 $\sqrt{\alpha S_1} \cong 10/\text{second}$

Frequency response of the synapse to small-amplitude modulation of a regular spike train:

$$\left(\frac{\hat{r}}{r^*}\right) = \frac{1 + \dfrac{1}{1 + i\omega/\nu}}{1 + \dfrac{\frac{(S^*)^2}{\alpha S_1}}{1 + i\omega/\alpha}} \left(\frac{\hat{S}}{S^*}\right)$$

High-frequency gain $= 1$

Low-frequency gain $=$

$$2\left(\frac{1}{1 + \frac{(S^*)^2}{\alpha S_1}}\right)$$

If $\alpha << \omega << \nu$, then

$$\left(\frac{\hat{r}}{r^*}\right) = \frac{2 i\omega}{i\omega + \frac{(s^*)^2}{s_1}} \left(\frac{\hat{s}}{s^*}\right)$$

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

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.
Communications on Pure and Applied Mathematics 73(1): 3-62, 2020