Modeling Synaptic Dynamics with Randomness and Plasticitiy

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Introduction

A simple model of synaptic vesicle release (SVR)

A more general model of SVR

Simulation of synaptic vesicle dynamics and its optimal filtering

Determination of model parameters

Outline

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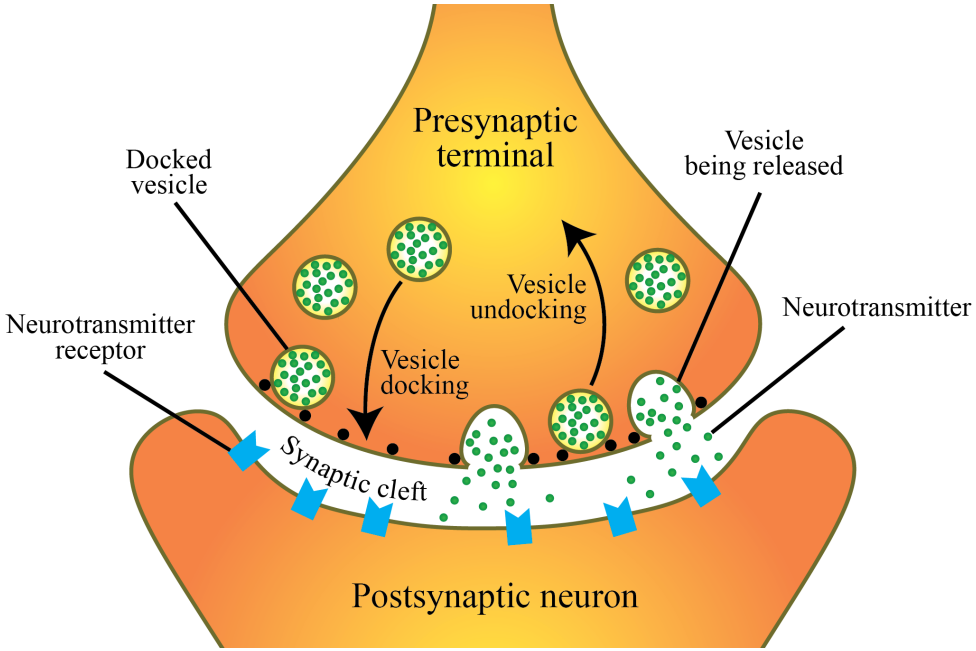
Introduction

Motivation and Overview

- Neurons form complex networks via synapses through which information propagates.
- Here, we consider *chemical synapses*: one neuron influences another through the release of neurotransmitters, which are small molecules packed inside synaptic vesicles (SV).

Introduction

Motivation and Overview



- *At the presynaptic terminal:* Action potential triggers synaptic vesicle release (SVR).
- *In the synaptic cleft:* Neurotransmitters bind to receptors, which can open synaptic channels.
- *In the postsynaptic neuron:* Ionic currents flowing through the open synaptic channels displace the membrane potential.

Introduction

Motivation and Overview

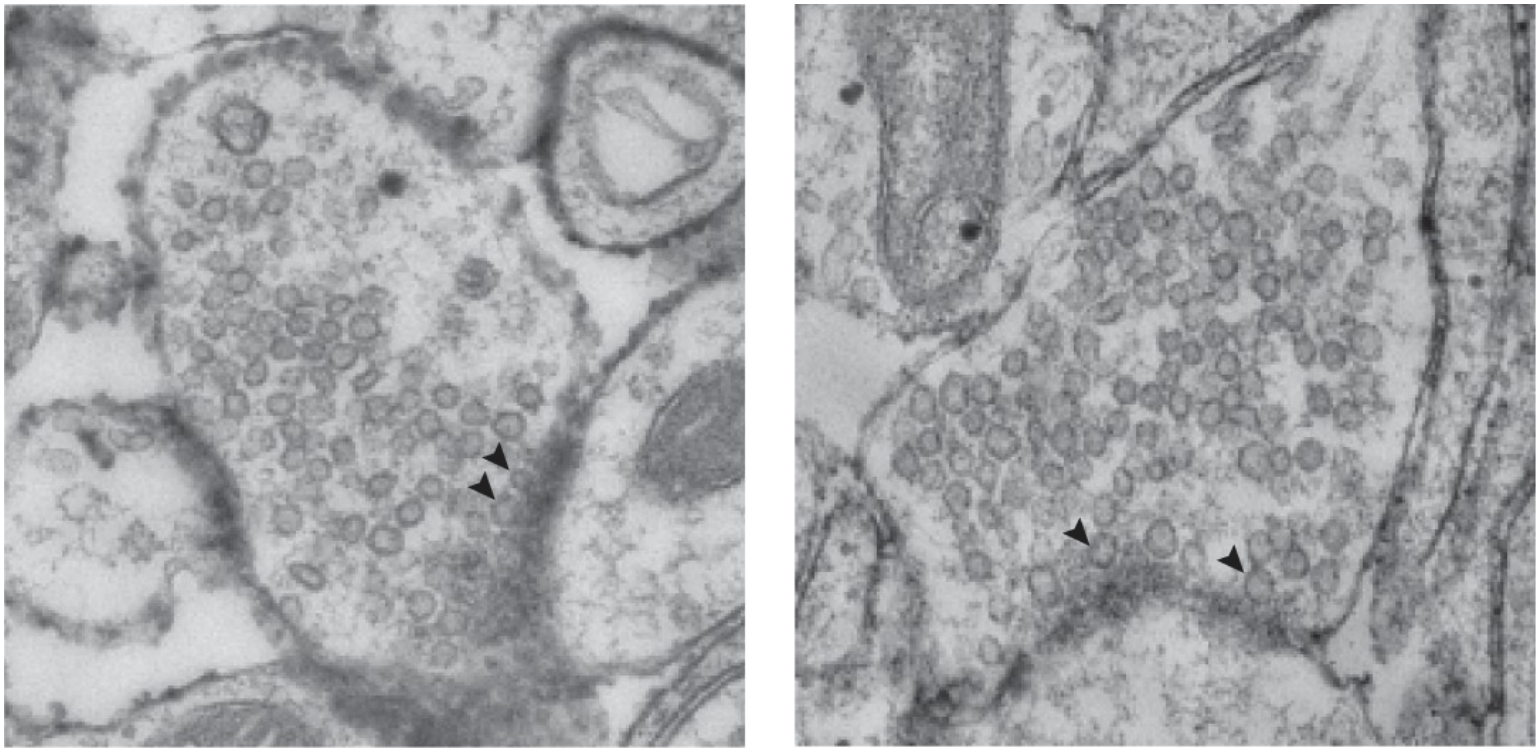


Figure: *Electron microscope cross-sectional images of two synapses of cortical neurons in the mouse brain. Some docked vesicles are indicated by arrows.* *(Images adapted from Wu et al. [28], under the Creative Commons Attribution 4.0 International Public License.)*

Introduction

Motivation and Overview

- Unlike the all-or-none action potential, synaptic transmission is graded.
- The synapse is therefore a favorite site of *hormonal*, *pharmacologic*, and *neural* regulation of nervous activity.
- SVR is stochastic and its likelihood of occurrence is a crucial factor in the regulation of signal propagation in neuronal networks [7, 10, 14, 32].
- SVR is the most significant source of noise in the central nervous system [3, 9].

Introduction

Motivation and Overview

- The synapse is the site at which learning takes place and at which memory is stored [1, 25].
- Modification of the rate of SVR contributes to both *short-term* [18, 32] and *long-term* [23, 24] changes at synapses.
- The rate of SVR has been linked to severe neurological disorders, such as Parkinson's disease [16, 26] and Alzheimer's disease [21, 33].
- A quantitative understanding of how various factors in synaptic transmission determine the rate of SVR is crucial to the understanding of the brain.

Introduction

Existing models of synaptic vesicle release

Based on binomial statistics, the famous model by Katz [2] assumed that there are n_s independent docking sites, **all of which are occupied at all times**, and that the probability of a vesicle undergoes exocytosis (i.e., release) following the arrival of a nerve impulse is p_0. Then the probability that k vesicles are released is

$$\Pr(N = k) = \frac{n_s!}{k!(n_s - k)!} p_0^k (1 - p_0)^{n_s - k}.$$

Introduction

Existing models of synaptic vesicle release

- The assumption that n_s is a constant is not accurate in general.
- Several studies have reported that the number of docked vesicles prior to each action potential is variable [19].
- Barrett & Stevens [5, 6] adopted a different approach: they assumed that vesicle release at each docking site occurs by a Poisson process with a time-dependent rate.
- In recent years, evidence has indicated that in many synapses the statistics of vesicle release does not follow a Poisson distribution [17, 29].
- Attempts to loosen the Poisson assumption led to the development of models of vesicle pool dynamics, in which ODEs are used to describe the replenishment of RRP from recycle and reserve vesicle [8, 15, 20, 27].

Introduction

Recent work by others

- Rosenbaum, et al. [22] showed that stochastic synapses act as a high-pass filter, whereas deterministic synapses encode any frequency equally well.
- Manwani & Koch [12] found that a single stochastic synapse cannot transmit presynaptic spike density $S(t)$ reliably, but redundancy obtained using a small number of multiple synapses leads to a significant improvement in the reconstruction of $S(t)$.

An idealized model of SVR

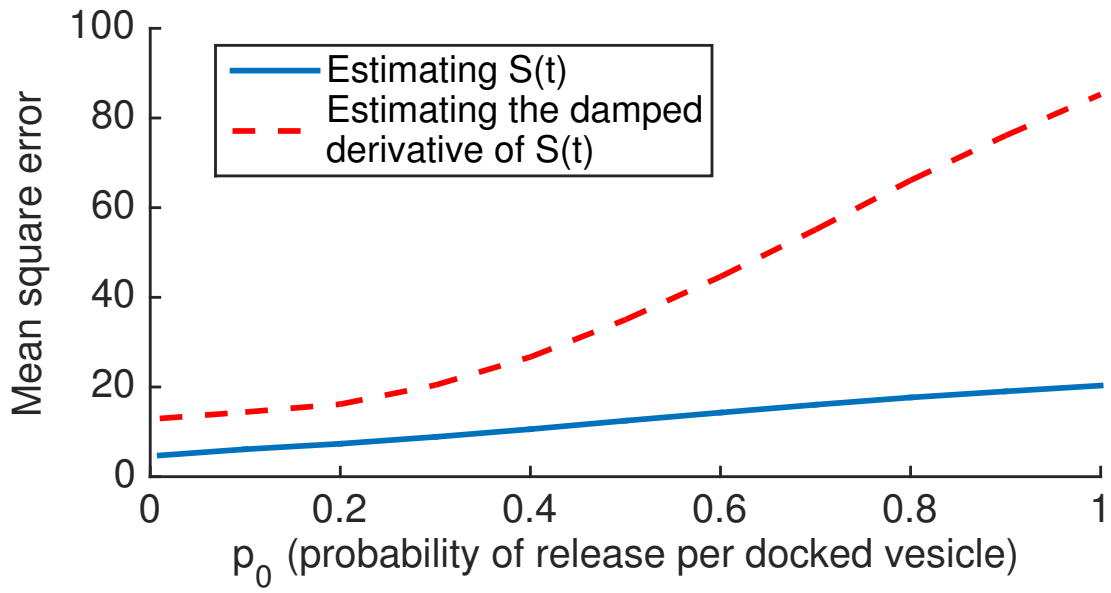
Zhang & Peskin 2015 model with unlimited docking sites

- In a recent paper [30], Peskin and I considered an idealized model synapse, in which we assumed that:
- vesicle docking occurs by a homogeneous Poisson process with mean rate α_0,
- presynaptic action potentials arrive by a stochastic process with mean rate $S(t) > 0$, and
- each vesicle that is docked has a probability p_0 to be released upon the arrival of each action potential, independently of other docked vesicles.

An idealized model of SVR

Zhang & Peskin 2015 model with unlimited docking sites

- In this idealized case, we found that a small p_0 helps reduce the error in the reconstruction of desired signals from the time series of vesicle release events.
- Below, I simulated SVR for 2,500 independent sample paths and used optimal linear filter theory to reconstruct $S(t)$ or its damped derivative. Here, each realization of stochastic process $S(t)$ is a telegraph signal.



An idealized model of SVR

Zhang & Peskin 2015 model with unlimited docking sites

- If we assume that presynaptic action potentials occur by an inhomogeneous Poisson process with mean rate $s(t)$, then the expected rate of vesicle release $r(t)$ conditioned on this $S(t) = s(t)$ is rigorously given by

$$\frac{d}{dt}\left(\frac{r}{s}\right) = p_0\,(\alpha_0 - r)\,. \tag{1}$$

- To our knowledge, Eq. 1 is new. Its linearized form, however, is closely related to the theory of Rosenbaum et al. [22].
- Eq. 1 shows that during any time interval in which the spike density $s(t)$ is constant, the expected rate of vesicle release $r(t)$ approaches the mean rate of vesicle docking α_0.

An idealized model of SVR

Zhang & Peskin 2015 model with unlimited docking sites

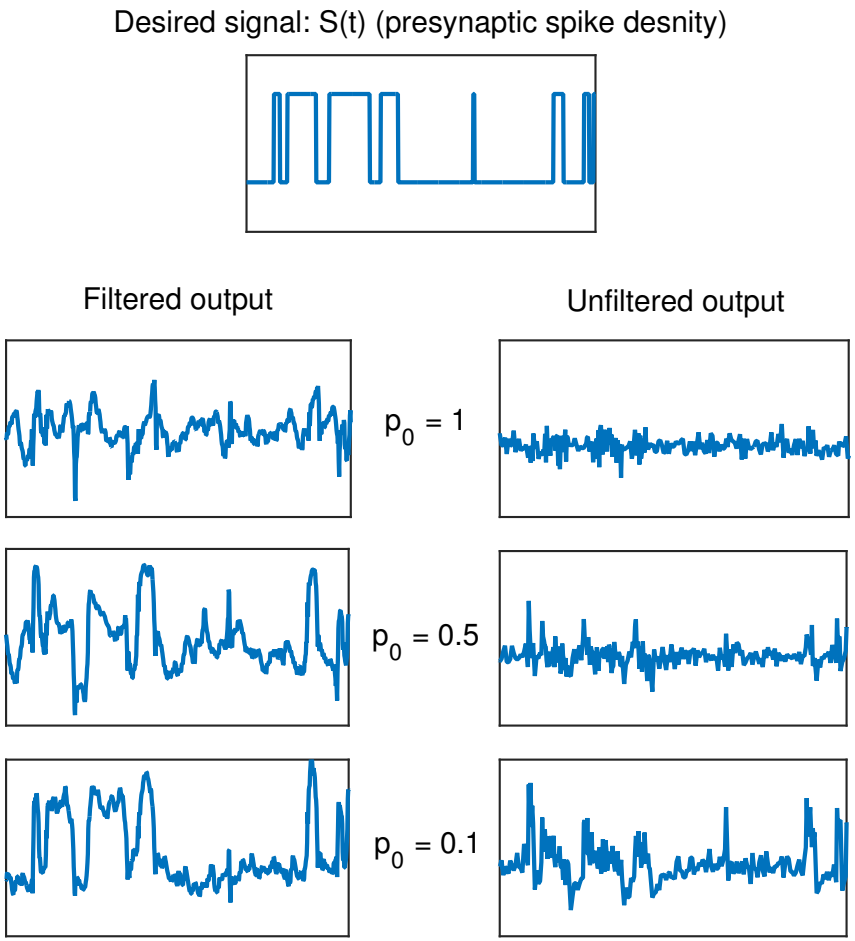
$$\frac{d}{dt}\left(\frac{r}{s}\right) = p_0\left(\alpha_0 - r\right).$$

- When p_0 is large, the rate of vesicle release converges rapidly back to α_0 whenever there is a jump in $s(t)$.
- In the extreme case of $p_0 = 1$, the time constant of the exponential approach is equal to the mean interspike interval after the jump in rate!
- In practice, when $p_0 = 1$, the transient is too fast to be detected by the postsynaptic neuron in the presence of noise.
- In contrast, when p_0 is small, it takes longer for the rate of SVR to get close to α_0, and this makes it easier for the transient to be detected.

An idealized model of SVR

Optimal filtering of SVR

- An example of this phenomenon can be seen below.



- The unfiltered output in the case of $p_0 = 1$ shows essentially no semblance of the original signal.
- Hints of the original signal begin to appear in the unfiltered output as p_0 is reduced.

An idealized model of SVR

Optimal filtering of SVR

- This result is a general feature of our model, and is not dependent on the Poisson assumption.
- This complete insensitivity to the absolute level of stimulation is consistent with several experimental observations [4, 11, 13, 32].
- A similar but less extreme insensitivity to low-frequency signals would occur if we assumed a limited number of docking sites.

An idealized model of SVR

The high-pass nature of SVR

Suppose there are n_s docking sites, and let α be the probability per unit time that an empty docking site becomes filled.

Then Eq. 1 implies that the expected rate of vesicle release $r(t)$ satisfies

$$\frac{d}{dt}\left(\frac{r(t)}{s(t)}\right) + \alpha\frac{r(t)}{s(t)} = p_0\Big(\alpha n_s - r(t)\Big).$$

Now consider a small-amplitude perturbation to $s(t)$ around s_0 and the resulting perturbation to $r(t)$:

$$s(t) = s_0\Big(1+\varepsilon\sigma(t)+o(\varepsilon)\Big), \qquad r(t) = r_0\Big(1+\varepsilon\rho(t)+o(\varepsilon)\Big).$$

Then s_0 and r_0 satisfy the steady-state equation

$$\alpha\frac{r_0}{s_0} = p_0\left(\alpha n_s - r_0\right).$$

An idealized model of SVR

The high-pass nature of SVR

It follows that

$$\frac{r}{s} = \frac{r_0}{s_0}\Big(1 + \varepsilon(\rho - \sigma) + o(\varepsilon)\Big),$$

and the first-order equation is

$$\frac{d}{dt}(\rho - \sigma) + (\alpha + p_0 s_0)(\rho - \sigma) = -p_0 s_0 \sigma.$$

After taking Fourier transforms, this becomes

$$i\omega(\hat{\rho} - \hat{\sigma}) + (\alpha + p_0 s_0)(\hat{\rho} - \hat{\sigma}) = -p_0 s_0 \hat{\sigma},$$

or

$$\hat{\rho} = \frac{i\omega + \alpha}{i\omega + \alpha + p_0 s_0}\hat{\sigma}.$$

An idealized model of SVR

The high-pass nature of SVR

Let

$$G(\omega) = \frac{i\omega + \alpha}{i\omega + \alpha + p_0 s_0}$$

so that

$$\hat{\rho}(\omega) = G(\omega)\hat{\sigma}(\omega),$$

we have

$$G(0) = \frac{\alpha}{\alpha + p_0 s_0} < 1,$$
$$G(\infty) = 1.$$

Thus the system is always *high-pass*, but to make this a strong effect, we require $\alpha \ll p_0 s_0$. If we let p_0 vary with other parameters fixed, we find that the high-pass effect is strongest when $p_0 = 1$, but even then it is only a strong effect if $\alpha \ll s_0$.

An idealized model of SVR

The high-pass nature of SVR

To go back to the case of an unlimited number of docking sites, let

$$n_s \to \infty,$$
$$\alpha \to 0,$$

in such a way that

$$n_s \alpha = \alpha_0.$$

Then $G(0) = 0$ and $G(\infty) = 1$, regardless of the value of p_0.

A more general model of SVR

Model set-up: Zhang & Peskin 2020 model

We consider a more general model of SVR characterized by four parameters [31]:

- the number of docking sites, n_s
- the rate (i.e., probability per unit time) of vesicle docking at each empty site, α
- the rate of undocking for each filled site, β
- the probability of release, p_0, when an action potential arrives, of each vesicle that is docked at that time.

A more general model of SVR

Model set-up: Zhang & Peskin 2020 model

- The input to our model synapse is a sequence of action potential arrival times $\ldots T_k \ldots$.
- The output of the model presynaptic terminal is a sequence of random nonnegative integers, $\ldots N_k \ldots$, each of which is the number of vesicles released by the corresponding action potential.
- Conditioning on $\{T_k\}$, we derive and solve a recursion relation for N_k, and also a correlation function that partially characterizes the statistics of SVR.
- Then we adopt the point of view that $\ldots T_k \ldots$ themselves are generated by a stochastic process and are carrying information about an underlying continuous signal, and we ask to what extent that signal can be reconstructed by linear filtering of $\ldots (T_k, N_k) \ldots$

A more general model of SVR

Model set-up: Zhang & Peskin 2020 model

- We address the filtering question both analytically and numerically.
- In the analytic case, we make simplifying assumptions that are not needed when the problem is tackled numerically.
- In both cases, we focus on the choice of the parameter p_0, and we find that the quality of the best signal reconstruction that can be done depends on this choice.

A more general model of SVR

Model set-up: Zhang & Peskin 2020 model

- Roughly speaking, the result is that p_0 should be equal to 1 when the effective number of docking sites is small, but p_0 should be small when the effective number of docking sites is large.
- The latter case is interesting, since it implies that randomness in vesicle release can be helpful for signal preservation during synaptic transmission.
- The terminology "effective number of docking sites" refers to the influence of the undocking process in setting an upper bound that is smaller than n_s on the expected number of docked vesicles.

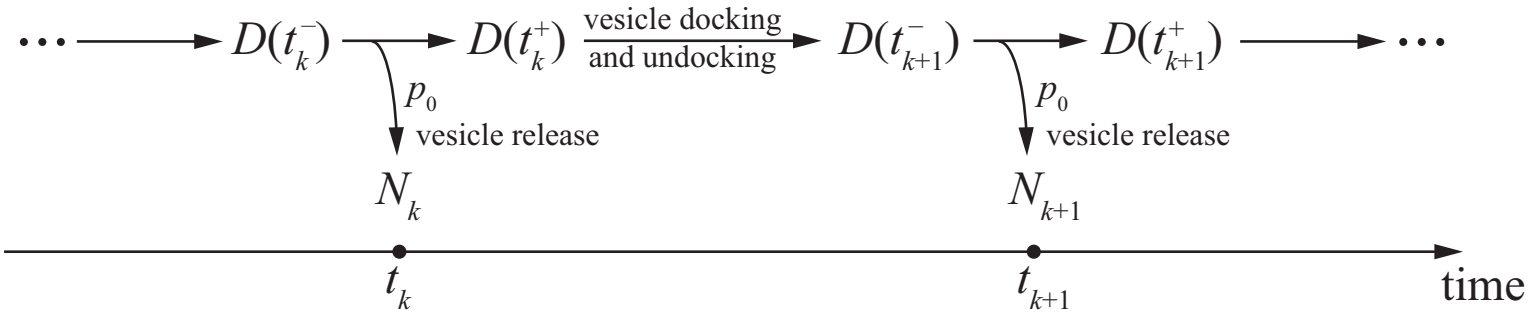
A more general model of SVR

Model set-up: Zhang & Peskin 2020 model

- The optimal choice of p_0 is also influenced by other parameters such as the rate of arrival of action potentials.
- We conclude by showing how the parameters of the model can be identified from experimental data, and also how the model can be tested experimentally.

A more general model of SVR

Zhang & Peskin, 2020, CPAM



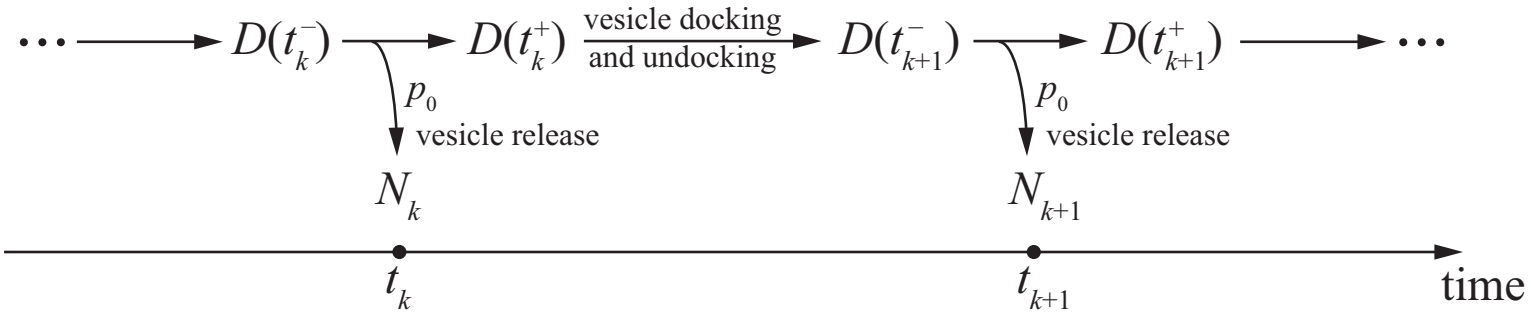
- The input to a synapse is a sequence of action potential arrival times

$$\dots t_{k-1} < t_k \dots$$

(Later, we will use the capital letter $\dots T_k \dots$ when we consider action potential arrival times that are generated by a stochastic process.)

A more general model of SVR

Zhang & Peskin, 2020, CPAM



- The synapse has some number n_s of equivalent vesicle release sites. Any particular site may be occupied or unoccupied by a synaptic vesicle.

A more general model of SVR

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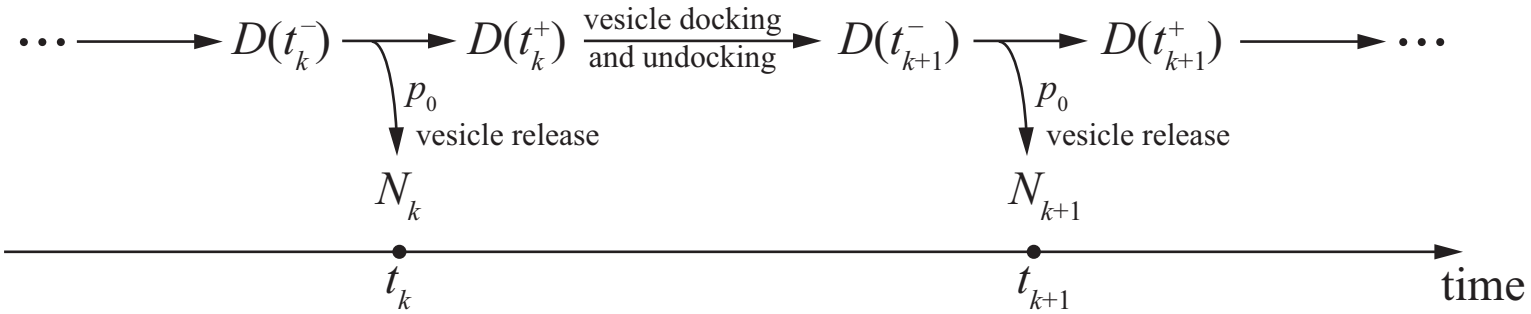
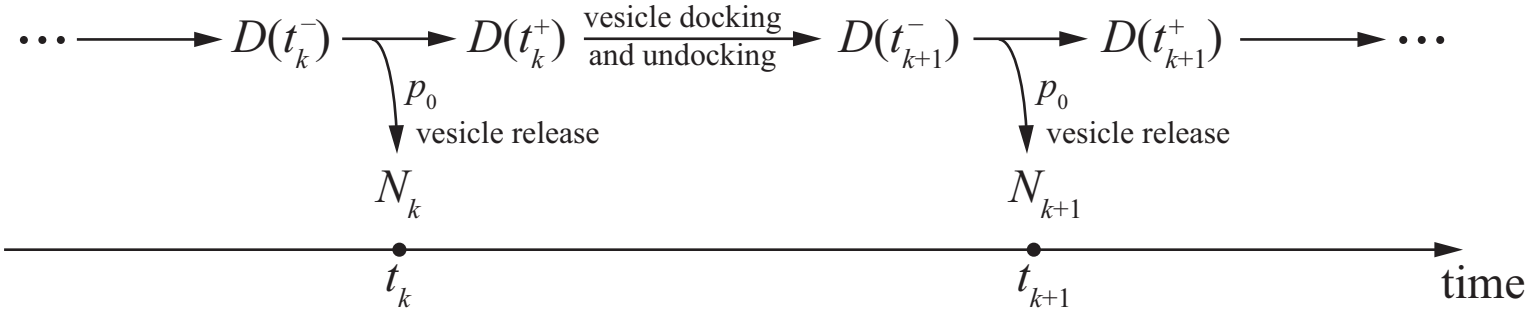


Between action potential arrival times,

- every unoccupied site has a probability per unit time α of becoming occupied, and
- every occupied site has a probability per unit time β of becoming unoccupied.

A more general model of SVR

Zhang & Peskin, 2020, CPAM



- Thus, between action potential arrival times, each site obeys the reaction scheme

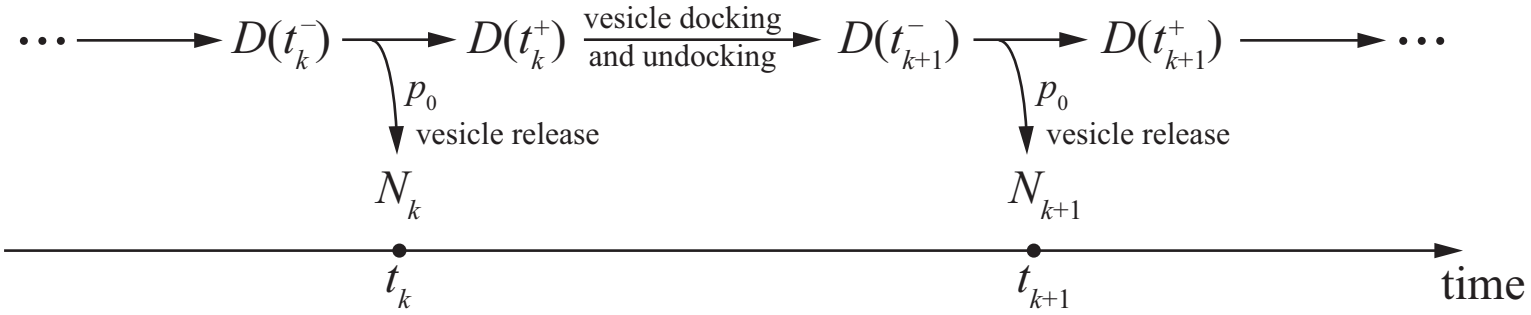
$$0 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} 1$$

in which 0 denotes an unoccupied site and 1 denotes an occupied site.

- The changes that occur at one site are independent of those occurring at any other site.

A more general model of SVR

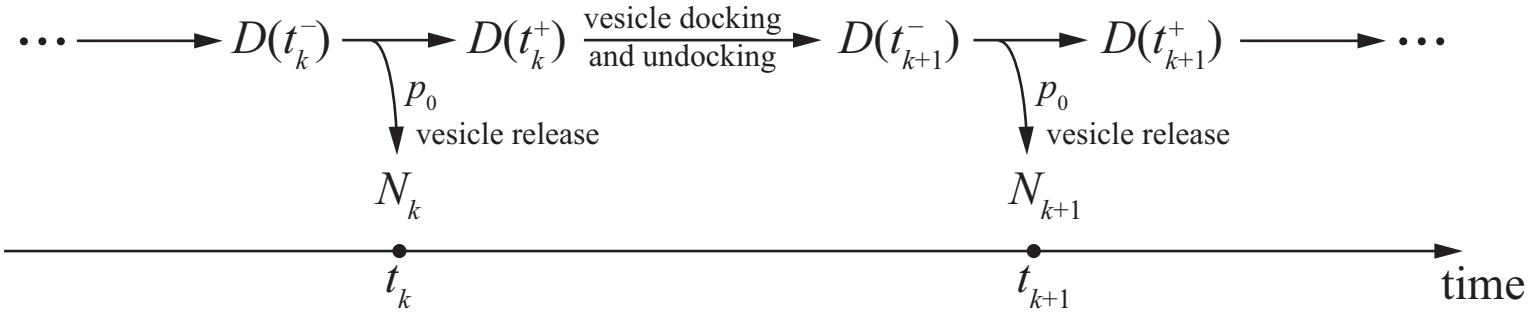
Zhang & Peskin, 2020, CPAM



- At each T_k, every site that is occupied immediately before T_k has the possibility of releasing the contents of its vesicle and thereby becoming an unoccupied site.
- The probability that such release occurs at any particular site is denoted by p_0, and the decision whether to release the vesicle or not is made independently for each site. (p_0 is also known as the vesicle fusion probability.)

A more general model of SVR

Zhang & Peskin, 2020, CPAM



- Let $D(t)$ be the number of docked vesicles at time t.
- Let N_k be the number of vesicles released by the arrival of the k-th action potential.
- At any given time t between action potential arrival times, $D(t)$ changes in steps of ± 1,
- and the probability per unit time that $D(t)$ increases by 1 is $\alpha\big(n_s - D(t)\big)$,
- whereas the probability per unit time that $D(t)$ decreases by 1 is $\beta D(t)$.

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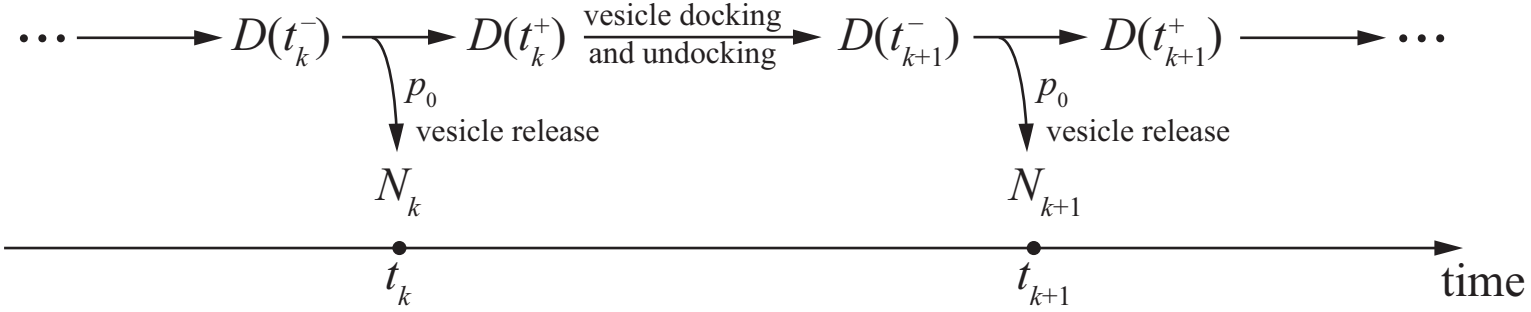
Zhang & Peskin, 2020, CPAM



At the action potential arrival time t_k,

$$\Pr(N_k = n \,|\, D(t_k^-) = d) = \binom{d}{n} p_0^n (1-p_0)^{d-n},$$

and then, of course,

$$D(t_k^+) = D(t_k^-) - N_k.$$

We regard the sequence $\ldots(N_k, T_k)\ldots$ as the output of the synaptic vesicle release process (i.e., the output of the presynaptic terminal).

A more general model of SVR

$\overline{N_k}$, the expected number of vesicles released at each spike conditioned on the spike arrival times

The first result is a recursion formula for $\overline{N_k}$, the expected number of vesicles released at each spike conditioned on the spike arrival times $\ldots t_k \ldots$
Let

$$\gamma = \alpha + \beta,$$
$$n_s^* = \alpha n_s/(\alpha + \beta),$$

then $\overline{N_k}$, conditioned on $\{t_k\}$, is given by the recurrence

$$\overline{N_k} = (1 - p_0)\overline{N_{k-1}} e^{-\gamma(t_k - t_{k-1})} + p_0 n_s^* \left(1 - e^{-\gamma(t_k - t_{k-1})}\right). \tag{2}$$

We call n_s^* the effective number of docking sites.

A more general model of SVR

$\overline{N_k}$, the expected number of vesicles released at each action potential conditioned on the spike arrival times

We can use Eq (2) to express $\overline{N_k}$ in terms of $\overline{N_i}$ for any $i < k$. Multiplying both sides of (2) by the summation factor $e^{\gamma t_k}/(1-p_0)^k$, we obtain

Theorem

(Zhang & Peskin, 2020, CPAM) For any $i < k$, the expected number of vesicles released at each action potential, conditioned on the action potential arrival times $\{t_k\}$, is

$$\overline{N_k} = (1-p_0)^{k-i} e^{-\gamma(t_k - t_i)} \overline{N_i} + p_0 n_s^* \sum_{j=i+1}^{k} (1-p_0)^{k-j} e^{-\gamma(t_k - t_j)} \left(1 - e^{-\gamma(t_j - t_{j-1})}\right). \tag{3}$$

A more general model of SVR

The autocovariance of N_k conditioned on the spike arrival times

Denote by φ_{ik} the autocovariance of N_k:

$$\varphi_{ik} = \overline{N_i N_k} - \overline{N_i}\ \overline{N_k}.$$

The second result is a formula for the autocovariance of N_k conditioned on the action potential arrival times.

Theorem

(Zhang & Peskin, 2020, CPAM) The autocovariance of N_k, conditioned on $\{t_k\}$, is

$$\begin{aligned}\varphi_{ik} =& n_s^* p_0 \sum_{j=-\infty}^{k} (1-p_0)^{k-j} e^{-\gamma(t_k - t_j)} \left(1 - e^{-\gamma(t_j - t_{j-1})}\right) \delta_{ik} \\ & - \frac{(n_s^* p_0)^2}{n_s} \left[\sum_{j=-\infty}^{i} (1-p_0)^{i-j} e^{-\gamma(t_i - t_j)} \left(1 - e^{-\gamma(t_j - t_{j-1})}\right)\right]^2 \cdot \\ & (1-p_0)^{|k-i|} e^{-\gamma|t_k - t_i|} \qquad (4)\end{aligned}$$

for all (i,k), where δ_{ik} is the Kronecker delta.

A more general model of SVR

Example: a regular spike train

Example

Let's consider the special case of a regular spike train. Conditioned on the action potential arrival times $\{t_k\}$, where

$$t_k - t_{k-1} = \begin{cases} (\Delta t)_1 & \text{for } k \leq 0, \\ (\Delta t)_2 & \text{for } k > 0. \end{cases}$$

A more general model of SVR

Example: a regular spike train

The expected number of vesicles released at the time of the k-th action potential is

$$\overline{N_k} = \begin{cases} \overline{N}((\Delta t)_1) & \text{for } k \leq 0, \\ \overline{N}((\Delta t)_2) + \left(\overline{N}((\Delta t)_1) - \overline{N}((\Delta t)_2)\right)(1-p_0)^k e^{-k\gamma(\Delta t)_2} & \text{for } k > 0, \end{cases}$$

where $\overline{N}(\Delta t)$ is the steady-state expected number of vesicles released at each spike under a constant spike train with interspike interval $\Delta t > 0$:

$$\overline{N}(\Delta t) = p_0 n_s^* \frac{1 - e^{-\gamma \Delta t}}{1 - (1-p_0)e^{-\gamma \Delta t}}.$$

A more general model of SVR

Example: a regular spike train

We can re-express everything in terms of the rate of arrival of action potentials and the rate of SVR by making the definitions

$$s_k = \frac{1}{t_k - t_{k-1}}, \quad R_k = \frac{N_k}{t_k - t_{k-1}}, \quad \overline{R_k} = \frac{\overline{N_k}}{t_k - t_{k-1}}.$$

A more general model of SVR

Example: a regular spike train

In terms of these variables,

$$\overline{R_k} = \begin{cases} \overline{R}(s_1) & \text{for } k \leq 0, \\ \overline{R}(s_2) + \left(1 - w^k(s_2)\right) + \overline{R}(s_1)\frac{s_2}{s_1} w^k(s_2) & \text{for } k > 0, \end{cases}$$

where

$$w(s) = (1 - p_0)e^{-\gamma/s},$$

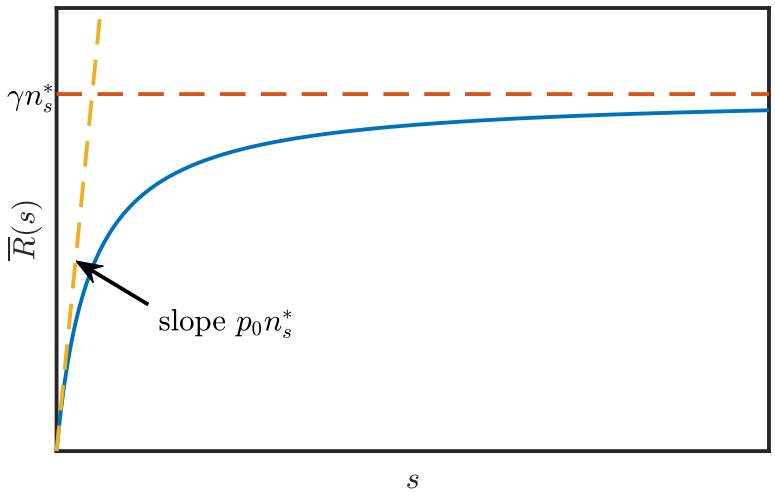
and $\overline{R}(s)$ is the steady-state rate of SVR when the rate of arrival of action potentials is constant and equal to s:

$$\overline{R}(s) = \frac{\overline{N}(s)}{1/s} = p_0 \gamma n_s^* \frac{\frac{1-e^{-\gamma/s}}{\gamma/s}}{1 - (1 - p_0)e^{-\gamma/s}}.$$

A more general model of SVR

Example: a regular spike train

The asymptotic behavior of the steady-state rate of SVR:



- As $s \to \infty$, we have

$$\lim_{s \to \infty} \overline{R}(s) = \gamma n_s^* = \alpha n_s^*.$$

(insensitive to the spike rate when it is large)

- As $s \to 0$, we have

$$\overline{R}(s) \sim p_0 n_s^* s.$$

(proportional to the spike rate when it is small)

A more general model of SVR

Example: a regular spike train

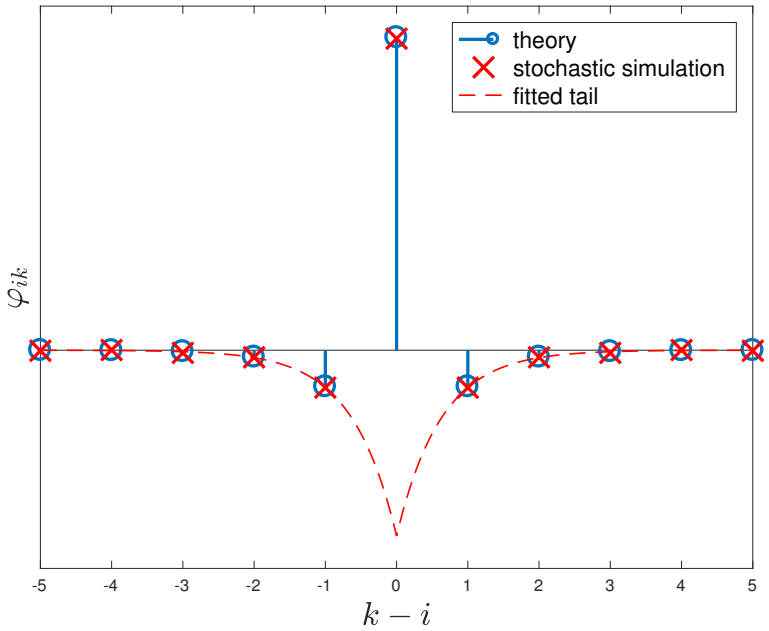
Furthermore, the autocovariance of N_k, given by (4), simplifies to

$$\varphi_{ik} = \overline{N}(\Delta t)\delta_{ik} - \frac{1}{n_s}(\overline{N}(\Delta t))^2 \left((1-p_0)e^{-\gamma \Delta t}\right)^{|k-i|},$$

where δ_{ik} is the Kronecker delta function.

A more general model of SVR

Example: a regular spike train



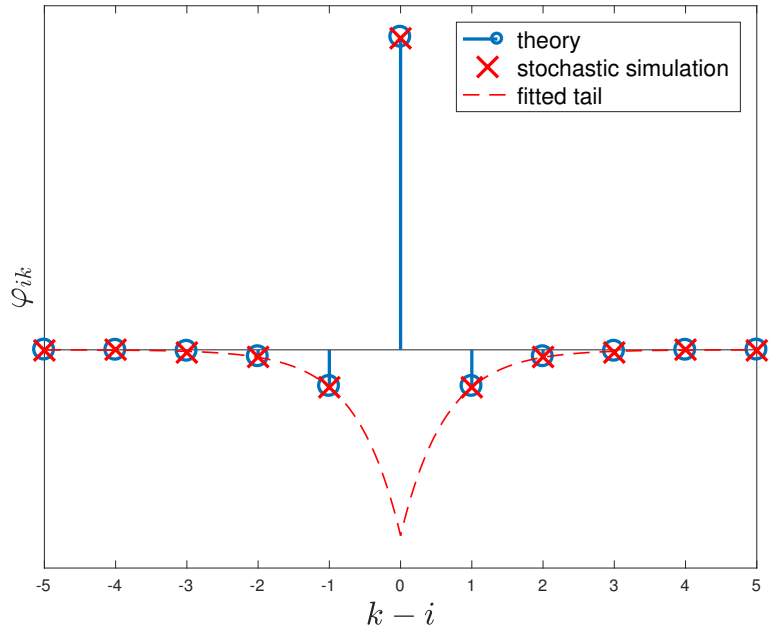
- Note the height of the central peak and the amplitude of the negative tails. Their ratio

$$r = \left(\overline{N} - \frac{(\overline{N})^2}{n_s}\right) \Big/ \frac{(\overline{N})^2}{n_s} = \frac{n_s}{\overline{N}} - 1,$$

can be used as a check for our theory and parameter fitting.

A more general model of SVR

Example: a regular spike train



- If n_s is large, the negative tail of the autocovariance will be undetectable.
- As $n_s \to \infty$, the random variables N_i and N_k are uncorrelated for $i \neq k$.

A more general model of SVR

The conditionally independent Poisson nature of the N_k

The autocovariance of N_k in the Example shows that, as $n_s \to \infty$, the random variables N_i and N_k become uncorrelated for $i \neq k$.

This suggests that $\ldots N_k \ldots$ are independent in a model synapse with an unlimited number of docking sites; this is indeed true, as proven below for arbitrary spike trains.

A more general model of SVR

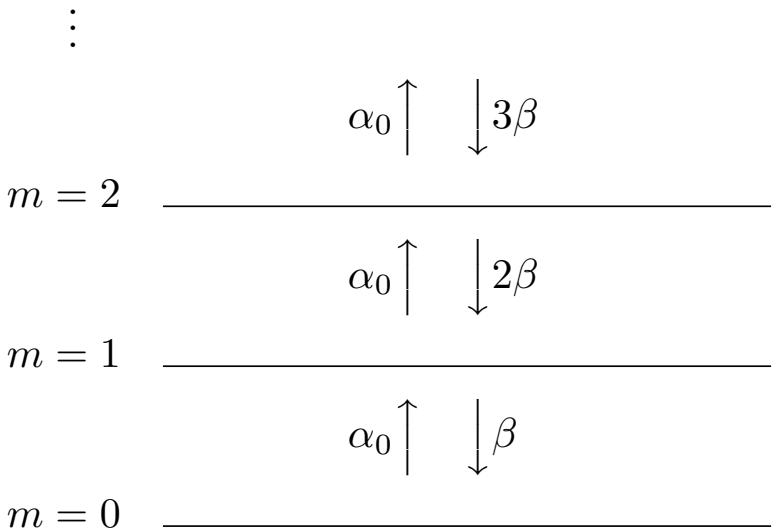
The conditionally independent Poisson nature of the N_k

Idea of the proof:

Let

$$P_D(m,t) = \Pr(D(t) = m), \quad \text{for } m = 0,1,2,\ldots \tag{5}$$

Between action potentials, i.e., on a time interval (t_{k-1}, t_k), the process governing $D(t)$ is described by the diagram below:



A more general model of SVR

The conditionally independent Poisson nature of the N_k

The diagram corresponds to the equation

$$\frac{dP_D}{dt}(m,t) = \alpha_0\Big([m \neq 0]P_D(m-1,t) - P_D(m,t)\Big) + \beta\Big((m+1)P_D(m+1,t) - mP_D(m,t)\Big),$$

where the factor $[m \neq 0]$ is 1 if the statement "$m \neq 0$" is true, and is 0 if "$m \neq 0$" is false.

A more general model of SVR

The conditionally independent Poisson nature of the N_k

We look for a solution in which $P_D(m,t)$ is given by a Poisson distribution with some unknown mean $\mu_D(t)$:

$$P_D(m,t) = \frac{(\mu_D(t))^m}{m!} e^{-\mu_D(t)}.$$

After some derivations, we get

$$\frac{d\mu_D(t)}{dt} = \alpha_0 - \beta\mu_D.$$

Since μ_D is the expected value of D, we have $\mu_D \equiv \overline{D}$.

A more general model of SVR

The conditionally independent Poisson nature of the N_k

- The above shows that if D is Poisson immediately after any action potential, it remains Poisson up to the time of the next action potential.
- But we also know that for every k the random variables N_k and $D(t_k^+)$ are obtained from the random variable $D(t_k^-)$ by binomial splitting.
- Hence, if $D(t_k^-)$ is Poisson then N_k and $D(t_k^+)$ are Poisson and moreover they are independent random variables.

A more general model of SVR

The conditionally independent Poisson nature of the N_k

- Since $D(t_k^+)$ is the only possible link between N_k and the whole future of the process, it follows that the value of N_k has no influence at all upon that future, i.e., that all of the N_k are independent.
- Thus, conditioned on the spike times $\ldots t_k \ldots$, if the process starts with a Poisson distributed number of docked vesicles (e.g., 0), then all of the N_k are Poisson-distributed and independent.
- The expected value of N_k conditioned on $\{t_k\}$ is obtained by letting $\gamma \to \beta$ and $n_s^* \to \alpha_0/\beta$ in the recurrence relation.

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and releases

Theorem

(Zhang & Peskin, 2020, CPAM) In a model synapse with an unlimited number of docking sites obtained by letting $n_s \to \infty$ while keeping $\alpha n_s \equiv \alpha_0$ constant. Then, conditioned on $\{t_k\}$, if the process starts with a Poisson-distributed number of docked vesicles (such as 0), then all of the N_k are independent and Poisson-distributed with mean given by the following recurrence

$$\overline{N_k} = (1-p_0)\overline{N_{k-1}}e^{-\beta(t_k-t_{k-1})} + \frac{p_0\alpha_0}{\beta}\left(1-e^{-\beta(t_k-t_{k-1})}\right). \tag{6}$$

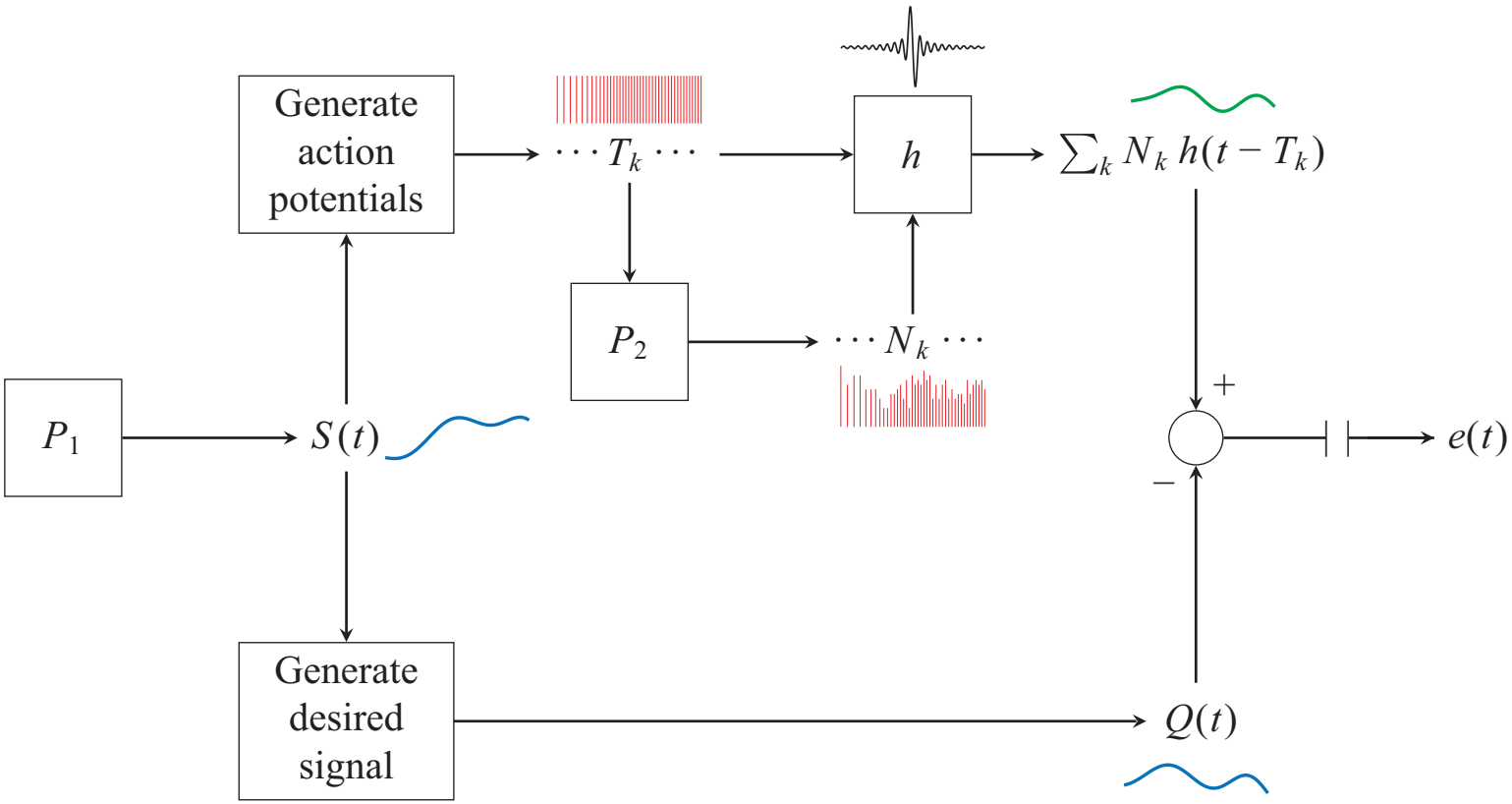
A more general model of SVR

The conditionally independent Poisson nature of the N_k

- It is surprising that the N_k are independent because it may seem that N_k should depend on $D(t_k^-)$, which in turn should depend on N_{k-1}.
- However, the independence of the N_k follows from *the Poisson nature of the numbers of docked vesicles*, and from the behavior of *a Poisson random variable under binomial splitting*.
- Since the statistics of a Poisson-distributed random variable are determined completely by its mean, the Theorem provides a computationally efficient way for large-scale simulation of SVR.
- We emphasize that, however, the independence of the N_k only holds in the limit of an unlimited number of docking sites.

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release



By hypothesis, $Q(t)$ is a desired signal with mean zero generated from $S(t)$; depending on the function of the synapse, $Q(t)$ can be $S(t)$ itself or some other signal derived from $S(t)$.

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

The optimal filtering problem is stated as follows. Let

$$R(t) = \sum_k h(t - T_k) N_k.$$

We seek $h(t)$ to minimize $\mathbb{E}[e^2(t)]$, where

$$e(t) = (R(t) - \mathbb{E}[R(t)]) - Q(t).$$

Thus, we are trying to find an impulse response $h(t)$ of the filter such that $R(t)$ approximates $Q(t)$ the best, but our definition of error ignores mean values.

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

We proved the following result in the limit of small signals (Zhang & Peskin, 2020, CPAM):

Consider a model synapse with an unlimited number of docking sites (possibly with undocking allowed) obtained by letting $n_s \to \infty$ while keeping $\alpha n_s \equiv \alpha_0$ constant. Suppose the sequence of action potential arrival times $\dots T_k \dots$ is a perturbation of a sequence of equally spaced times

$$T_k = k\tau + \varepsilon T_k^{(1)} + \cdots$$

where τ is a given constant (the unperturbed period of the spike train), and ε is a small parameter.

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

Suppose the stochastic process P_1 that generates both $Q(t)$ and the sequence $\dots T_k \dots$ is band-limited in the sense that $\hat{\varphi}_{QT}(\omega)$ is supported on some interval $(-\omega_0, \omega_0)$ with

$$\omega_0 \tau < \pi,$$

in which $\hat{\varphi}_{QT}(\omega)$ is the Fourier transform of the cross-covariance of $Q(t)$ and $\{T_k^{(1)}\}$ defined by

$$\varphi_{QT}(t - k\tau) = \mathbb{E}[Q(t)\, T_k^{(1)}].$$

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

Then the impulse response $h(t)$ of the filter that minimizes the mean square error, to lowest order in ε, has Fourier transform $\hat{h}(\omega)$ given by

$$\hat{h}(\omega) = \frac{\varepsilon}{\tau}\left(\frac{\nu\tau}{\overline{N}(\tau)}\frac{1-e^{i\omega\tau}}{1-\xi e^{i\omega\tau}} + i\omega\tau\right)\hat{\varphi}_{QT}(\omega), \tag{7}$$

in which $\overline{N}(\tau)$ is the mean number of vesicles released by each spike when the spike train is perfectly regular with constant interspike interval τ, and

$$\xi = (1-p_0)e^{-\beta\tau}, \tag{8}$$

$$\nu = e^{-\beta\tau}\frac{\alpha_0 p_0^2}{1-(1-p_0)e^{-\beta\tau}}. \tag{9}$$

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

The corresponding minimal mean square error, to lowest order in ε, is

$$\mathbb{E}[e^2(t)] = \varphi_{QQ}(0) - \frac{\varepsilon^2}{2\pi}\left(\frac{2}{\tau}\right)^3 \frac{\overline{N}(\tau)}{\tau} \cdot$$

$$\int_{-\theta_0}^{\theta_0} \frac{\left(\frac{\nu\tau}{\overline{N}(\tau)}\frac{\sin\theta}{\theta} - (1-\xi)\cos\theta\right)^2 + (1+\xi)^2\sin^2\theta}{(1-\xi)^2\cos^2\theta + (1+\xi)^2\sin^2\theta}\theta^2 \left|\hat{\varphi}_{QT}\left(\frac{2\theta}{\tau}\right)\right|^2 d\theta, \tag{10}$$

in which $\varphi_{QQ}(t)$ is the autocovariance of the desired signal $Q(t)$ defined by

$$\varphi_{QQ}(t'-t'') = \mathbb{E}[Q(t')\,Q(t'')], \tag{11}$$

and

$$\theta_0 = \frac{\omega_0\tau}{2}. \tag{12}$$

A more general model of SVR

The optimal filtering problem for stochastic vesicle docking, undocking, and release

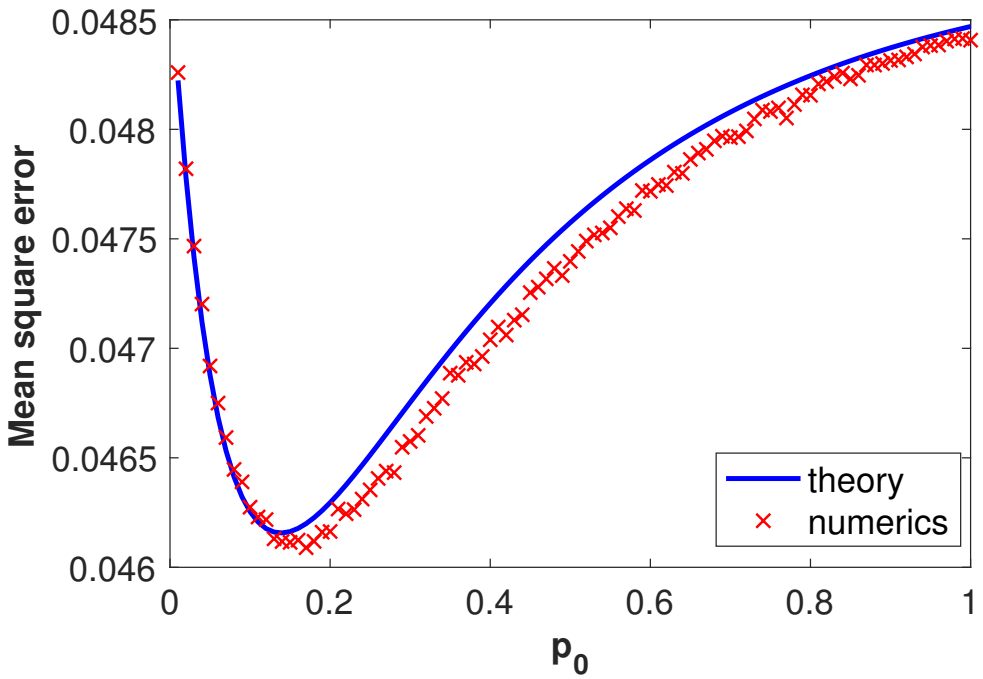


Figure: *Comparing the analytical estimate of the mean square error in Eq.* (10) *to the numerically evaluated mean square error in the regime of small signals* ($\varepsilon = 0.05$). *Here, the desired signal* $Q(t)$ *is the presynaptic spike density* $S(t)$, *which is generated by a smoothed dichotomous jump process.*

A more general model of SVR

The optimal p_0 for synaptic transmission

To make sense of the above result in the context of how p_0 affects the fidelity of synaptic transmission, we proved the following result:

Theorem

(Zhang & Peskin, 2020, CPAM) In a model synapse with undocking ($\beta > 0$) and with an unlimited number of docking sites obtained by letting $n_s \to \infty$ while keeping $\alpha n_s \equiv \alpha_0$ constant, the optimal p_0 is given asymptotically by

$$p_0 \sim \left(\left(\frac{I_0}{I_2} \right) \beta \tau \right)^{1/3} \quad as\, \beta \tau \to 0, \tag{13}$$

provided that the assumptions made in the preceding Theorem hold.

Modeling Synaptic Dynamics with Randomness and Plasticitiy

C. Zhang-Molina

Introduction

A simple model of synaptic vesicle release (SVR)

A more general model of SVR

Simulation of synaptic vesicle dynamics and its optimal filtering

Determination of model parameters

A more general model of SVR

The optimal p_0 for synaptic transmission

- A nonzero undocking rate prevents the unlimited accumulation of docked vesicles, so the above result suggests that, in a synapse with a finite number of docking sites, the best choice of p_0 should be some nonzero number.
- The exact optimal value of p_0 would depend on the parameters of vesicle docking and the statistics of the signal ensemble.
- In the rest of the talk, I provide several numerical examples of the optimal filtering of SVR where the optimal p_0 is a nonzero number under various biologically relevant scenarios.

Simulation of synaptic vesicle dynamics and its optimal filtering

Zhang & Peskin 2020 model

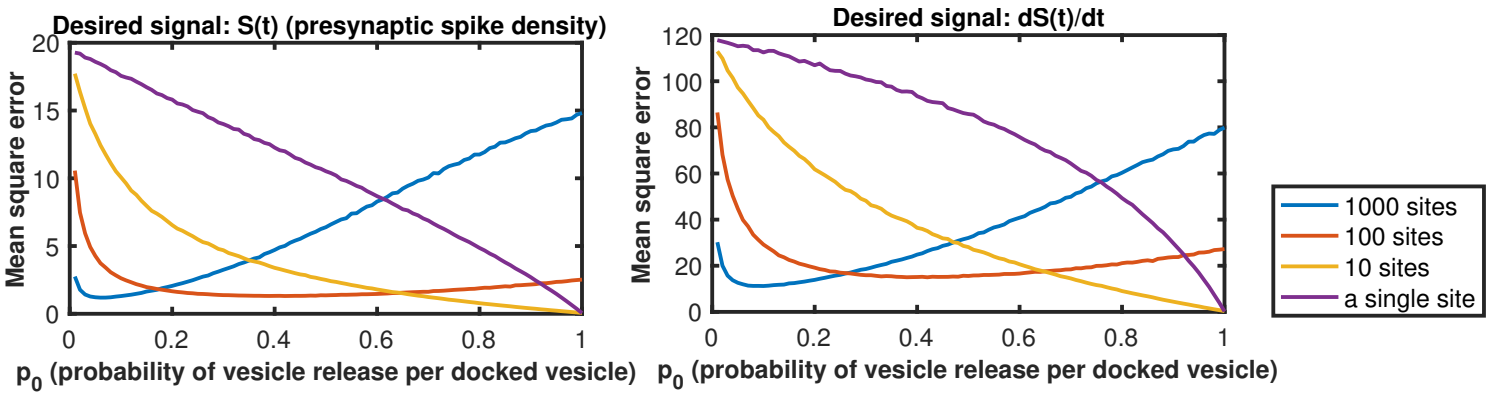


Figure: *Effect of probability of vesicle release per docked vesicle (p_0) on the mean square error ($\mathbb{E}[e^2(t)]$) in the estimation of the presynaptic spike density $S(t)$ and its derivative.*

Simulation of synaptic vesicle dynamics and its optimal filtering

Zhang & Peskin 2020 model

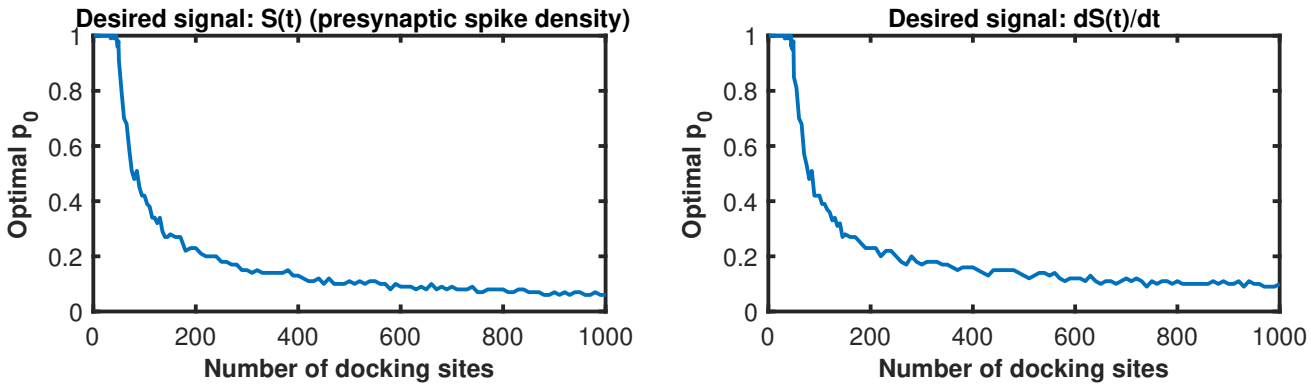


Figure: *Effect of the number of docking sites (n_s) on the optimal probability of vesicle release per docked vesicle (p_0) in the estimation of the presynaptic spike density $S(t)$ and its derivative.*

Simulation of synaptic vesicle dynamics and its optimal filtering

Zhang & Peskin 2020 model

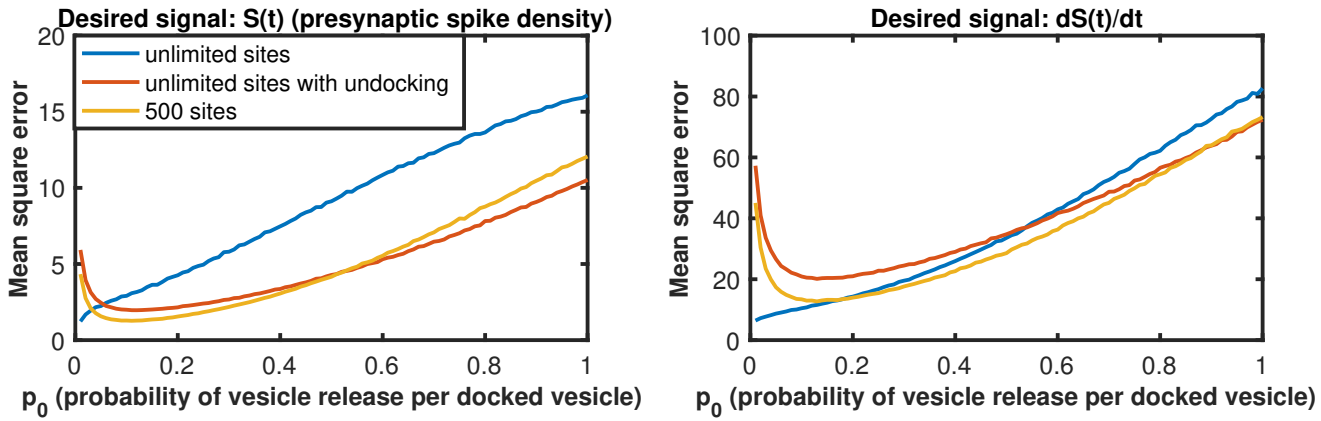


Figure: *Effect of probability of vesicle release per docked vesicle (p_0) on the mean square error ($\mathbb{E}[e^2(t)]$) in the estimation of the presynaptic spike density $S(t)$ and its derivative.*

Simulation of synaptic vesicle dynamics and its optimal filtering

Zhang & Peskin 2020 model

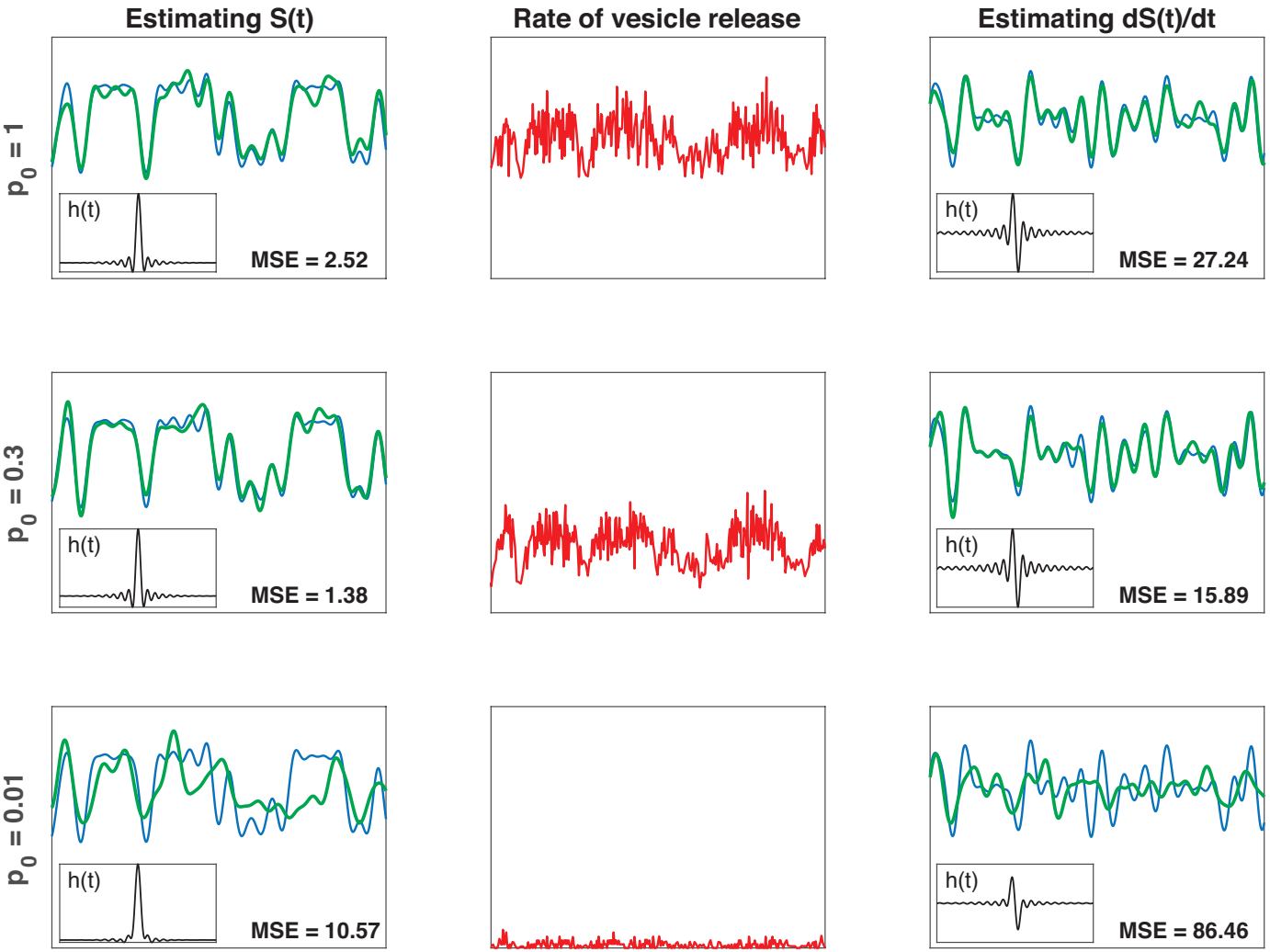


Figure: *A synapse with 100 docking sites and no undocking.*

Determination of model parameters

Zhang & Peskin 2020 model

Consider the inverse problem of estimating model parameters. We first note that if we measure γ and n_s^*, then n_s can be any integer such that

$$n_s \geq n_s^*.$$

Once n_s has been chosen, α and β are then determined by

$$\alpha = \frac{\gamma n_s^*}{n_s},$$
$$\beta = \gamma\left(1 - \frac{n_s^*}{n_s}\right).$$

It is interesting to note that by considering the mean behavior, it is impossible to distinguish models with the same (γ, n_s^*) but different (α, β). Such models, however, produce different statistics.

Determination of model parameters

Zhang & Peskin 2020 model

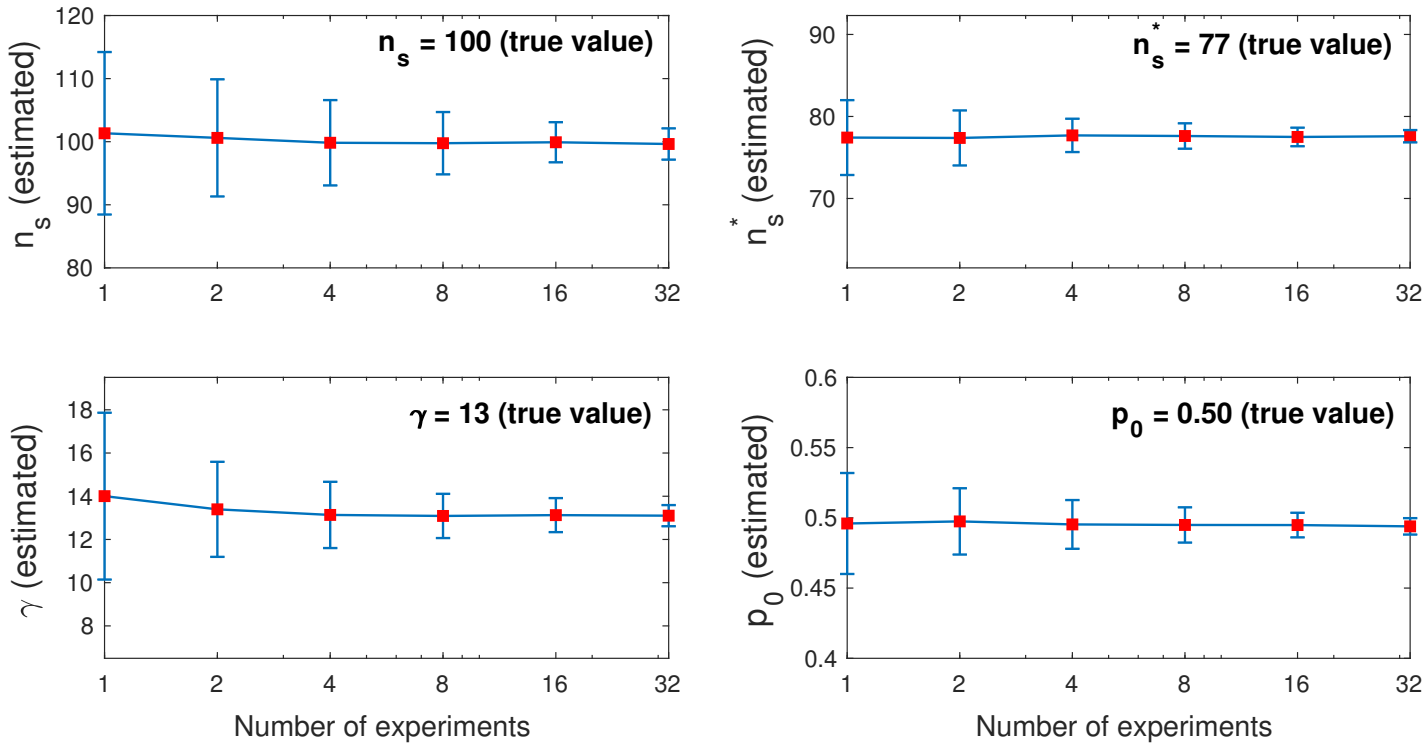


Figure: *Parameter identification using our proposed method for a model synapse with 100 docking sites and undocking.*

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