

Improved signaling as a result of randomness in synaptic vesicle release

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The probabilistic nature of neurotransmitter release in synapses is believed to be one of the most significant sources of noise in the central nervous system. We show how p_0 , the probability of release per docked vesicle when an action potential arrives, affects the dynamics of the rate of vesicle release in response to changes in the rate of arrival of action potentials. Furthermore, we examine the theoretical capability of a synapse in the estimation of desired signals using information from the stochastic vesicle release events under the framework of optimal linear filter theory. We find that a small p_0 , such as 0.1, reduces the error in the reconstruction of the input, or in the reconstruction of the time derivative of the input, from the time series of vesicle release events. Our results imply that the probabilistic nature of synaptic vesicle release plays a direct functional role in synaptic transmission.

synaptic transmission | stochastic vesicle release |
release probability | optimal filter

Randomness is present in almost all levels of all nervous systems, such as in ionic channels of individual neurons, in synapses between neurons, and in environmental stimuli. The probabilistic nature of the synaptic vesicle release process is believed to be one of the most significant sources of randomness. Stochastic vesicle release affects information transfer from a presynaptic neuron to a postsynaptic neuron, and hence may play not only an important role in synaptic plasticity (1, 2) but also a significant role in determining the functionality of certain synapses, a point we will argue in this article. The functional role of stochastic vesicle release in synaptic transmission is likely to be more significant in those synapses in the central nervous system, where the size of the readily releasable vesicle pool is usually smaller than those in the periphery.

Synaptic vesicle release has only recently been studied in a probabilistic or information-theoretic manner (3–5). A systematic perspective on how stochastic vesicle release affects neural code processing at synapses is still lacking. On the experimental front, a comprehensive, quantitative knowledge about the nature of vesicle docking, priming, fusing, undocking, replenishing, and recycling is far from complete, and hence a biophysically detailed model of the entire vesicle release process is not yet possible.

Despite current limited understanding of the synaptic vesicle release process, a probabilistic model that captures the essential elements of that process can still be built to study the effect of various sources of randomness on synaptic transmission. Rosenbaum et al. (3) recently constructed such a model to study how variability in vesicle dynamics affects information transfer from one neuron to another. They found that the depletion of docked vesicles at higher rates of arrival of action potentials makes the synapse act as a high-pass filter from a signal processing point of view. Motivated by Rosenbaum et al.'s (3) model of the presynaptic vesicle release process, we here build a probabilistic model that includes four stochastic subprocesses involved in synaptic vesicle release: the stochastic process that generates the presynaptic spike density $S(t)$, the randomness of the interspike intervals in the presynaptic spike train, the randomness in vesicle docking, and the probabilistic nature of vesicle release. Based on this presynaptic model, we use optimal linear filter theory to determine the best possible linear response of the postsynaptic neuron to each vesicle release

event with the aim of reconstructing desired signals derived from $S(t)$. This optimization approach contrasts with that of Manwani and Koch (4), in which biophysical details are used to formulate a model of the postsynaptic response. Instead, we ask what the best response is given the goal to reconstruct some aspect of the input signal $S(t)$. For example, if the function of this synapse is to simply relay and preserve the original presynaptic signal $S(t)$, then our model answers the question of how various sources of randomness in the vesicle release process affect the theoretical capability of the synapse in the reconstruction of $S(t)$. As another example, if this synapse serves as an edge detector, then our model can be used to study how various sources of randomness in the vesicle release process affect the reconstruction of the derivative of $S(t)$. In both cases we find that a smaller probability of release per docked vesicle, such as 0.1, is preferable to a larger probability of release, such as 0.5 or 1.

More generally, we provide a systematic framework, based on a cascade of stochastic models of the presynaptic vesicle docking and release processes coupled with optimal linear filter theory, to address how various sources of randomness in synaptic vesicle release affect synaptic transmission between two neurons. We believe that our model framework can be further extended or modified to incorporate biophysical details of the synaptic vesicle release process, or by changing the objective function used in the optimal filter theory, to study various issues in synaptic transmission.

The Presynaptic Model of Synaptic Vesicle Release

We first build a model of stochastic vesicle release in the presynaptic neuron.

A key assumption of our model is that we allow for an unlimited number of docking sites. Let vesicle docking occur by a homogeneous Poisson process with mean rate α_0 , so that α_0 is the probability per unit time that the number of docked vesicles increases by one. Note that α_0 is the rate at which the total number of docked vesicles in the entire synapse increases in the absence of vesicle release. In fact, if a given neuron makes multiple synapses

Significance

Noise is not only a source of disturbance, but it also can be beneficial for neuronal information processing. The release of neurotransmitter vesicles in synapses is an unreliable process, especially in the central nervous system. Here we show that the probabilistic nature of neurotransmitter release directly influences the functional role of a synapse, and that a small probability of release per docked vesicle helps reduce the error in the reconstruction of desired signals from the time series of vesicle release events.

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onto a given postsynaptic neuron, then, under the assumption of our model, these synapses may be regarded as one large model synapse with a parameter α_0 that is the sum of the individual α_0 's.

Let presynaptic action potentials occur by a stochastic process with mean rate $s(t) > 0$, so that $s(t)$ is the probability per unit time of the occurrence of action potentials in the presynaptic neuron [i.e., $s(t)$ is the presynaptic spike density]. Of course, the rate $s(t)$ does not fully characterize the statistics of the spike train. We consider some particular cases later. Denote the time of the k th presynaptic action potential by T_k , $k = 1, 2, \dots$. Later, we shall regard $s(t)$ as a sample of a stochastic process $S(t)$, but when we write lowercase $s(t)$, we are conditioning on $S(t) = s(t)$, for all t . The vesicle docking process and the process that generates action potentials are independent of each other, regardless of whether we condition on S ; this is a consequence of the assumption of an unlimited number of docking sites. Otherwise, vesicle release by action potentials would increase the rate of docking by making more sites available.

When an action potential occurs in the presynaptic neuron, each vesicle that is docked has a probability p_0 of being released, this choice being made independently for all of the vesicles that happen to be docked at that moment. Note that p_0 is not the same as p_r , which is commonly used to refer to the probability of vesicle release for the entire synapse (6). In fact, p_r is the probability that at least one vesicle is released when an action potential occurs, whereas p_0 is the probability of release per docked vesicle when an action potential occurs. Hence, $p_r = 1 - (1 - p_0)^n$, where n is the number of docked vesicles when the action potential occurs.

The Expected Rate of Synaptic Vesicle Release

Using the above model of the presynaptic vesicle docking and release processes, we first study how p_0 , the probability of release per docked vesicle when an action potential occurs, affects the expected rate of synaptic vesicle release. In this section only, we assume that the presynaptic action potentials occur by an inhomogeneous Poisson process with a given mean rate $s(t)$.

Let $\bar{V}(t)$ be the expected number of vesicles that dock during (t_0, t) , and let $\bar{R}(t)$ be the expected number of vesicles that are released during (t_0, t) . Then $\bar{V}(t) - \bar{R}(t)$ is the expected number of vesicles that are docked at time t , and the expected rate of vesicle release ($d\bar{R}/dt$) satisfies the differential equation

$$\frac{d\bar{R}}{dt} = p_0 s(t) (\bar{V}(t) - \bar{R}(t)), \quad \bar{R}(t_0) = 0. \quad [1]$$

On the right-hand side of Eq. 1, the product of $(\bar{V}(t) - \bar{R}(t))$ and p_0 gives the expected number of vesicles released when a single action potential arrives in the presynaptic neuron at time t . Further multiplying this product by the spike density $s(t)$ gives us the expected rate of vesicle release, $d\bar{R}/dt$, at time t .

If we differentiate Eq. 1 with respect to time on both sides and make use of $d\bar{V}/dt = \alpha_0$, we get

$$\begin{aligned} \frac{d^2\bar{R}}{dt^2} &= p_0 \frac{ds}{dt} (\bar{V} - \bar{R}) + p_0 s \left(\alpha_0 - \frac{d\bar{R}}{dt} \right), \\ &= \frac{1}{s} \frac{ds}{dt} \frac{d\bar{R}}{dt} + p_0 s \left(\alpha_0 - \frac{d\bar{R}}{dt} \right). \end{aligned} \quad [2]$$

Let $r = d\bar{R}/dt$, then Eq. 2 becomes

$$\frac{dr}{dt} = \frac{r}{s} \frac{ds}{dt} + p_0 s (\alpha_0 - r). \quad [3]$$

Dividing both sides by $s(t)$ [recall that $s(t) > 0$] and rearranging the terms, we see that Eq. 3 can be written simply as

$$\frac{d}{dt} \left(\frac{r}{s} \right) = p_0 (\alpha_0 - r). \quad [4]$$

Although the above derivation is informal, Eq. 4 is rigorously correct given our assumptions, including the assumption of a Poisson spike train; it can be derived, for example, from the master equation for the process by taking first moments to get expected values.

To our knowledge, Eq. 4 is new. In its linearized form, however, it is closely related to the theory of Rosenbaum et al. (3). Eq. 4 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 . However, if $s(t)$ jumps, Eq. 4 shows that the variable r/s must be continuous, so $r(t)$ also jumps proportionally, which shows that the stochastic vesicle release process provides a synaptic mechanism through which the Weber–Fechner principle (7) in the sensory system can be realized.

Plotted in Fig. 1 are the probability per unit time of an action potential in the presynaptic neuron [blue curve, also referred to as the presynaptic spike density $s(t)$] and the corresponding expected rate of vesicle release [red curve, $r(t)$] under three values of p_0 : 1, 0.5, and 0.1. For all three cases, the expected rate of vesicle release exponentially approaches the vesicle docking rate α_0 when the presynaptic spike density $s(t)$ remains constant. The rate constant for the approach to the steady level α_0 is $s(t)p_0$. In particular, the rate constant is larger during the transient following the upward jump in $s(t)$ and smaller during the transient following the downward jump. 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, when $p_0 = 1$, the time constant of the exponential approach is equal to the mean interspike interval after the jump in rate, and this means in practice that 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 vesicle release to get close to α_0 , and this makes it easier for the

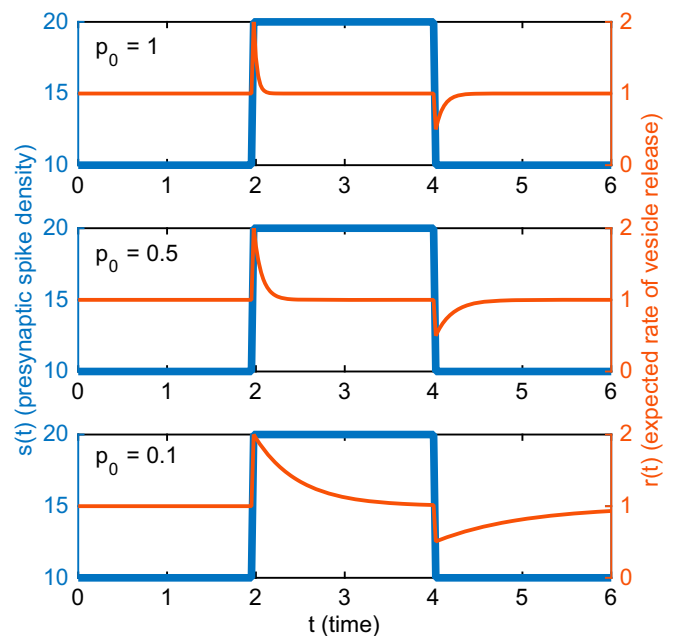


Fig. 1. Effect of probability of release per docked vesicle (p_0) on the expected rate of vesicle release (r) for a spike train generated by an inhomogeneous Poisson process with mean rate $s(t)$. Results for $p_0 = 1, 0.5$, and 0.1 are plotted in *Top*, *Middle*, and *Bottom*, respectively. $s(t)$ is plotted in blue, and $r(t)$ is plotted in red. Parameters used: $s(t) = 10 \text{ s}^{-1}$ for $0 \leq t < 2 \text{ s}$ and $4 \text{ s} < t \leq 6 \text{ s}$, $s(t) = 20 \text{ s}^{-1}$ for $2 \text{ s} \leq t \leq 4 \text{ s}$; $\alpha_0 = 1 \text{ s}^{-1}$.

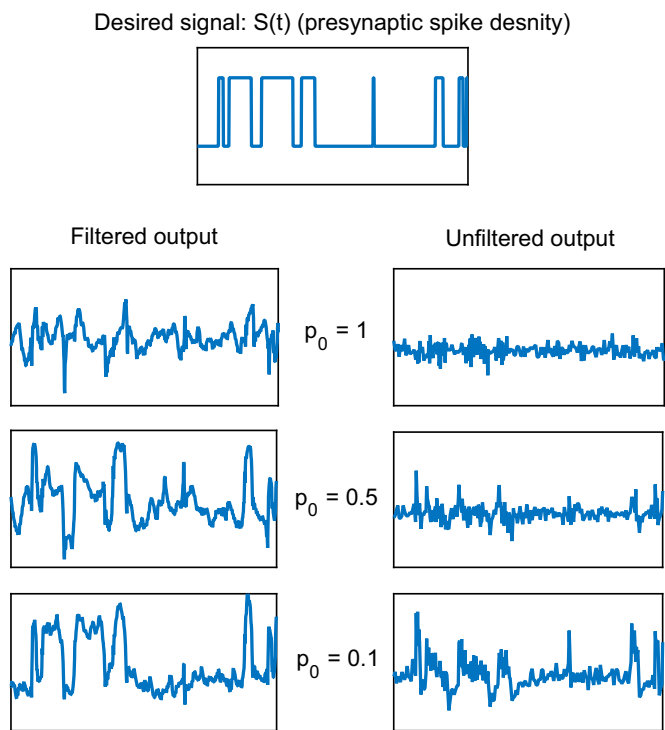


Fig. 2. Effect of probability of release per docked vesicle (p_0) on the synapse's ability to estimate the presynaptic spike density $S(t)$. In this numerical experiment, the goal of the synapse is to simply relay and preserve the presynaptic spike density $S(t)$, plotted in the topmost frame. We repeat this experiment for $p_0 = 1, 0.5$, and 0.1 ; results are shown in two columns: (Left) estimation $f(t)$ of $S(t)$ from Eq. 5 (filtered output), obtained by applying the optimal filter to the rate of vesicle release $dR(t)/dt$; (Right) instantaneous rate of vesicle release (unfiltered output), defined (13) by $N_k/(T_k - T_{k-1})$, where N_k is the number of vesicles released at the k th action potential, and T_k is the time of the occurrence that action potential. Note that the optimal filter is different for each p_0 (see *SI Materials and Methods* for the shape of the optimal filter). The design of the optimal filter is based upon the statistical properties of the ensemble of the presynaptic spike density, the spike generation, and the vesicle docking and release processes, but not upon the particular presynaptic spike density $S(t)$ used in the experiment. Data shown are for a time duration of 20 s, with $s_1 = 10 \text{ s}^{-1}$, $s_2 = 20 \text{ s}^{-1}$, $\nu_{12} = \nu_{21} = 10 \text{ s}^{-1}$, $\alpha_0 = 1,000 \text{ s}^{-1}$. All panels in this figure cover the time interval (65 s, 85 s).

transient to be detected. An example of this phenomenon can be seen in Fig. 2. Note in particular that the unfiltered output in the case of $p_0 = 1$ shows essentially no semblance of the original signal, and that hints of the original signal begin to appear in the unfiltered output as p_0 is reduced.

Note that in our model, any steady level $s(t) = \text{constant}$ leads eventually to the same vesicle release rate α_0 ; this is because, in any steady state, the rate of vesicle release must equal the rate of vesicle docking. This result is a general feature of our model, and is not dependent on the Poisson assumption used in this section; it is a consequence, however, of our assumption that there is an unlimited number of docking sites available. The functional significance of this feature of our model is that the model synapse is completely insensitive to the steady level of stimulation and communicates only transient changes in the level of stimulation to the postsynaptic neuron. A similar but less extreme insensitivity to low-frequency signals would occur if we assumed a limited number of docking sites (*SI Materials and Methods*) (3).

Synapse as an Optimal Filter

So far we have only discussed the effect of randomness on the expected rate of vesicle release. In this section, we address the

theoretical capability of a postsynaptic neuron in using the time series of vesicle release events to estimate the instantaneous rate of action potentials in the presynaptic spike train $S(t)$, or the time derivative of $S(t)$; the ability of the synapse to do so involves not only the expected rate of vesicle release but also the noise in the vesicle docking and release processes and the noise in the stochastic processes for generating the presynaptic spike density and the spike train.

We consider the optimal filtering of the rate of synaptic vesicle release dR/dt , where $R(t)$ is the number of vesicles that have been released during (t_0, t) . From here on, we regard the presynaptic spike density $s(t)$ as a realization of a stochastic process $S(t)$. Note that $R(t)$ is a continuous-time, nondecreasing, integer-valued time series determined by the entire stochastic vesicle release process that includes four sequential subprocesses: the randomness in the presynaptic spike density $S(t)$, the randomness of interspike intervals in the presynaptic spike train, the randomness in vesicle docking, and the probabilistic release of docked vesicles when an action potential arrives in the postsynaptic neuron.

Let $x(\cdot)$ and $y(\cdot)$ describe filters that are applied to dR/dt and $S(t)$, respectively. The outputs of these filters are

$$f(t) = \int_{t_0}^{\infty} x(t-t') \frac{dR}{dt}(t') dt' \quad [5]$$

and

$$g(t) = \int_{t_0}^{\infty} y(t-t') S(t') dt'. \quad [6]$$

The filtered output $f(t)$ is the actual output signal produced by the postsynaptic neuron, whereas $g(t)$ is the desired output signal that we prescribe. $f(t)$ can be thought of as the postsynaptic membrane potential. Note that f is actually a sum, because dR/dt is a sum of Dirac delta functions at the action potential times weighted by the numbers of vesicles released at those times. $g(t)$ gives different desired output signals for different choices of $y(\cdot)$. For example, if $y(t)$ is the Dirac delta function $\delta(t)$, then $g(t)$ gives the presynaptic spike density $S(t)$ itself, and if $y(t)$ is the derivative of $\delta(t)$, then $g(t)$ gives the derivative of $S(t)$.

Note also that we do not impose any causality constraint on the optimal filter $x(\cdot)$; i.e., $x(t)$ can take nonzero values for all t because we are idealizing the postsynaptic neuron as an observer who can record the vesicle release events and process them at leisure to reconstruct the desired signal. It is well known in optimal filter theory that such an ideal observer can be approximated by a real observer whose task is to produce the desired signal after some specified delay. The approximation improves as the delay increases (8).

The actual postsynaptic neuron, of course, does not have this luxury. In future work we shall consider the causal case in which $x(t) = 0$ for $t < 0$.

The point of view here is that we are given $y(\cdot)$, and we seek $x(\cdot)$ to make $f(t)$ and $g(t)$ as close as possible. In defining the error, however, we ignore the mean values. Thus, we let

$$e(t) = \int_{t_0}^{\infty} x(t-t') \frac{d\tilde{R}}{dt}(t') dt' - \int_{t_0}^{\infty} y(t-t') \tilde{S}(t') dt', \quad [7]$$

where $\tilde{R}(t) = R(t) - \mathbb{E}[R(t)]$ and $\tilde{S}(t) = S(t) - \mathbb{E}[S(t)]$, in which $\mathbb{E}[\cdot]$ means the expectation of the corresponding random variable.

Two remarks are of importance here. First, the optimization problem is not fully specified until we define the stochastic processes that generate the presynaptic spike density $S(t)$ and

interspike intervals. The second remark is that we seem to have a separate optimization problem for each time t at which we choose to minimize the error. This difficulty will disappear, however, if we take the limit $t_0 \rightarrow -\infty$ and also assume that $S(t)$ is generated by a stationary stochastic process.

The mean square error $\mathbb{E}[e^2(t)]$ is minimized when $x(\cdot)$ satisfies the following equation (*Materials and Methods*):

$$\int_{-\infty}^{\infty} x(t-s)\varphi_{RR}(s)ds = \int_{-\infty}^{\infty} y(t-s)\varphi_{RS}(s)ds, \quad [8]$$

in which

$$\varphi_{RR}(t''-t') = \lim_{t_0 \rightarrow -\infty} \mathbb{E} \left[\frac{d\tilde{R}}{dt}(t') \frac{d\tilde{R}}{dt}(t'') \right], \quad [9]$$

$$\varphi_{RS}(t''-t') = \lim_{t_0 \rightarrow -\infty} \mathbb{E} \left[\frac{d\tilde{R}}{dt}(t') \tilde{S}(t'') \right]. \quad [10]$$

Taking Fourier transforms on both sides of Eq. 8, we get

$$\hat{x} = \hat{y} \frac{\hat{\varphi}_{RS}}{\hat{\varphi}_{RR}}, \quad [11]$$

in which $\hat{x}, \hat{y}, \hat{\varphi}_{RR}, \hat{\varphi}_{RS}$ are the Fourier transforms of their respective original variables, $\hat{\varphi}_{RR}$ is known as the auto power spectral density of $d\tilde{R}/dt$, and $\hat{\varphi}_{RS}$ is known as the cross-power spectral density of $d\tilde{R}/dt$ and \tilde{S} .

Therefore, to find the optimal filter $x(\cdot)$, we need to evaluate the expressions on the right-hand sides of Eqs. 9 and 10; this can be done semianalytically for some specific choices of the stochastic processes for vesicle docking and release by first finding the right-hand sides of Eqs. 9 and 10 conditioned on $S(t)$ and then taking a numerical average over a sufficiently large number of samples of $S(t)$. The optimal filter can also be obtained entirely numerically by simulating the stochastic vesicle release process for a sufficiently large number of samples of $S(t)$.

Once we obtain the optimal filter $x(\cdot)$ for the synapse, we can evaluate the mean square error $\mathbb{E}[e^2(t)]$ over the ensemble of the presynaptic spike density $S(t)$. $\mathbb{E}[e^2(t)]$ measures the accuracy of the estimation of a desired signal from the rate of vesicle release events and is a property of the stochastic processes for generating $S(t)$, interspike intervals, vesicle docking, and vesicle release. The filtering property of an actual synapse is determined by various factors, such as the shape of postsynaptic potentials and the molecular mechanisms of exocytosis of synaptic vesicles (9).

The perspective we adopt here is to provide a theoretical upper bound on how well the synapse can possibly perform in the estimation of a desired signal in the mean square sense under optimal linear filter theory. Using this method, we can address how various sources of randomness in synaptic vesicle release affect the fidelity of synaptic transmission.

A Small p_0 Enhances Synaptic Transmission

In this section, we show that a small value of p_0 , the probability of release per docked vesicle when a presynaptic action potential occurs, enhances the fidelity of synaptic transmission. Recall that the determination of the optimal filter is not possible until we specify the stochastic processes that generate the presynaptic spike density $S(t)$ and interspike intervals.

We assume that the presynaptic spike density $S(t)$ is generated by a dichotomous jump process, i.e., a process with two discrete levels: s_1 and s_2 with $0 < s_1 < s_2$. Let $S(t_0) = s_1$, and we define ν_{12} to be the probability per unit time that $S(t)$ jumps up from s_1 to s_2 ,

and ν_{21} to be the probability per unit time that $S(t)$ jumps down from s_2 to s_1 .

We assume that the presynaptic spike train $\{T_k\}_{k=1}^{\infty}$, where T_k is the time of the k th action potential, is generated using the following two steps: first, generate a provisional spike train $\{\tilde{T}_k\}_{k=1}^{\infty}$ such that the interspike interval is chosen from a prescribed distribution and has a mean of one unit of time, i.e., let $\tilde{T}_k = \tilde{T}_{k-1} + \mathcal{D}_k$, where $T_0 = t_0$ and the \mathcal{D}_k are independent, identically distributed random variables with mean $\mu = 1$. Second, rescale the time variable by $S(t)dt = dt'$, where t' is the old time variable in the provisional spike train and t is the new (physical) time variable. Then our desired spike train $\{T_k\}$ with a time-dependent spike density $S(t)$, under the new time variable t , is given by

$$\int_{t_0}^{T_k} S(t)dt = \tilde{T}_k, \quad k = 1, 2, \dots \quad [12]$$

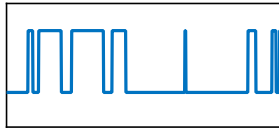
This rescale of time variable accelerates time when the spike density is high and decelerates time when the spike density is low so that under the new time variable the neuron has an instantaneous spike density $S(t)$. This way of generating synaptic spike times from the spike density is also known as the “faithful copy” property introduced by Knight (10) and analyzed by Sirovich (11) (see also ref. 12). Experimental evidence of neurons that follow the faithful copy property is also presented in ref. 11. A faithful copy neuron allows the user to generate a spike train with expected spike rate equal to $S(t)$, independent of the user’s choice of the shape of the interspike interval distribution. In the examples used in this section, we assume that the interspike intervals in the provisional spike train are normally distributed, i.e., we choose $\mathcal{D}_k \sim \mathcal{N}(\mu, \sigma)$, where $\mathcal{N}(\mu, \sigma)$ is the normal distribution with mean $\mu = 1$ and SD $\sigma = 0.01$, such that the intervals \mathcal{D}_k always happen to be positive numbers. A spike train generated by an inhomogeneous Poisson process with mean rate $S(t)$ is another special case of the output of a faithful copy neuron, but such a spike train is too irregular for the performance of the optimal filter to be satisfactory, especially if the goal is to estimate the derivative of $S(t)$.

We simulate numerically the stochastic synaptic vesicle release process defined above at different values of p_0 . A direct simulation of the vesicle docking and release processes can be computationally prohibitive because one needs to keep track of the status of each individual vesicle. Instead, we simulate the vesicle docking and release events using an efficient method relying on our theory that the number of vesicles released at each action potential conditioned on the spike times is independent and Poisson distributed (*Materials and Methods*). For each p_0 , we calculate the optimal estimations of two different desired signals: the presynaptic spike density $S(t)$ and the damped derivative (defined below) of $S(t)$. Results are shown in Figs. 2 and 3, respectively.

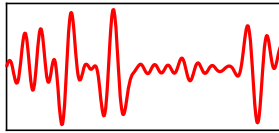
The filtered outputs in Fig. 2 clearly show the gradual improvement of the estimation of the presynaptic spike density $S(t)$ as p_0 is lowered. Note that the square bumps are already present at $p_0 = 0.5$; such bumps are not easy to discern at $p_0 = 1$. In Fig. 3, a good estimation of the damped derivative of the presynaptic spike density also emerges at $p_0 = 0.5$. Note that because $S(t)$ is discontinuous at the jump times, we have defined the damped derivative of $S(t)$ by removing frequency components higher than the mean frequency of jump events in $S(t)$, which is 1 Hz in these examples, so that the damped derivative of $S(t)$ is bounded and continuous.

Fig. 4 plots the mean square error $\mathbb{E}[e^2(t)]$ as a function of p_0 in the estimation of $S(t)$ (blue solid curve) and in the estimation of the damped derivative of $S(t)$ (red dashed curve). As p_0 approaches 0 (but not reaching 0), $\mathbb{E}[e^2(t)]$ monotonically decreases

S(t) (presynaptic spike density)



Desired output: damped derivative of S(t)



Filtered output

Unfiltered output

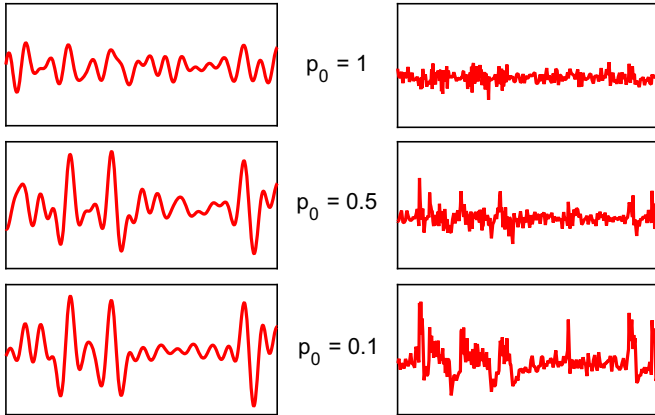


Fig. 3. Effect of probability of release per docked vesicle (p_0) on the synapse's ability to estimate the damped derivative of the presynaptic spike density, plotted in the second frame. Layout of panels and parameter values are as in Fig. 2.

for both cases. A smaller value of $\mathbb{E}[e^2(t)]$ indicates a more accurate estimation of the desired signal.

The perspective adopted in this paper is that we do not presume the biophysical details of a synapse's postsynaptic response to the presynaptic vesicle release events, but instead we use optimal linear filter theory to address the ability of our idealized postsynaptic neuron to estimate a desired signal derived from the presynaptic rate of arrival of action potentials as a function of time, given that we know the statistical properties of the ensemble from which the presynaptic rate of arrival of action potentials as a function of time has been drawn. We have shown in this paper how the optimal filter is calculated, and that a lower probability of release per docked vesicle upon arrival of a presynaptic spike leads to a more accurate estimation of two kinds of desired signals; we believe that this result goes a long way to explain why synaptic vesicle release is a random process.

Materials and Methods

Derivation of the Optimal Linear Filter. Our goal is to find an optimal linear filter $x(\cdot)$ that minimizes the mean square error

$$\begin{aligned} \mathbb{E}[e^2(t)] = & \int_{t_0}^{\infty} \int_{t_0}^{\infty} x(t-t')x(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \frac{d\bar{R}}{dt}(t'') \right] dt' dt'' \\ & - 2 \int_{t_0}^{\infty} \int_{t_0}^{\infty} x(t-t')y(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \bar{S}(t'') \right] dt' dt'' \\ & + \int_{t_0}^{\infty} \int_{t_0}^{\infty} y(t-t')y(t-t'') \mathbb{E} \left[\bar{S}(t') \bar{S}(t'') \right] dt' dt''. \end{aligned} \quad [13]$$

If $x(\cdot)$ minimizes $\mathbb{E}[e^2(t)]$, then for arbitrary $\delta x(\cdot)$ we have, to first order in $\delta x(\cdot)$,

$$0 = \delta \mathbb{E}[e^2(t)] = 2 \int_{t_0}^{\infty} \delta x(t-t') \int_{t_0}^{\infty} \left(x(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \frac{d\bar{R}}{dt}(t'') \right] - y(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \bar{S}(t'') \right] \right) dt'' dt'. \quad [14]$$

Because $\delta x(\cdot)$ is arbitrary, we must have

$$\int_{t_0}^{\infty} x(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \frac{d\bar{R}}{dt}(t'') \right] dt'' = \int_{t_0}^{\infty} y(t-t'') \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \bar{S}(t'') \right] dt''. \quad [15]$$

Note that $\delta x(\cdot)$ here is a perturbation to $x(\cdot)$, not to be confused with the Dirac delta function $\delta(t)$ used previously.

Now take the limit $t_0 \rightarrow -\infty$, and make the assumption that there exists functions φ_{RR} and φ_{RS} , each of one variable, such that

$$\lim_{t_0 \rightarrow -\infty} \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \frac{d\bar{R}}{dt}(t'') \right] = \varphi_{RR}(t''-t'), \quad [16]$$

$$\lim_{t_0 \rightarrow -\infty} \mathbb{E} \left[\frac{d\bar{R}}{dt}(t') \bar{S}(t'') \right] = \varphi_{RS}(t''-t'). \quad [17]$$

Then Eq. 15 becomes

$$\int_{-\infty}^{\infty} x(t-t'') \varphi_{RR}(t''-t') dt'' = \int_{-\infty}^{\infty} y(t-t'') \varphi_{RS}(t''-t') dt''. \quad [18]$$

It is easy to check that Eq. 18 holds for all (t, t') if and only if it holds for $t' = 0$. Thus, $\mathbb{E}[e^2(t)]$ is minimized when $x(\cdot)$ satisfies Eq. 8.

Simulation of the Vesicle Docking and Release Processes. Under the assumption that vesicle docking occurs by a homogeneous Poisson process, we show that N_{kj} , the number of vesicles that are released at the k th action potential, are independent and Poisson distributed, conditioned on the presynaptic spike times $\{T_k\}_{k=1}^{\infty}$. This fact allows us to simulate the vesicle release events in an efficient manner without the need to directly simulate the docking and release process by tracking the status of each individual vesicle.

To see this fact, let us first define R_{jk} ($j \leq k$) to be the number of vesicles released at the k th action potential that docked during the time interval (T_{j-1}, T_j) . Recall that T_j is the time of the j th action potential, presumed to be given. Then $N_k = \sum_{j=1}^k R_{jk}$.

The process that generates the numbers R_{jk} for a fixed j can be described as follows: first, choose D from Poisson distribution with mean $\mu = \alpha_0 (T_j - T_{j-1})$. Second, let each of the D vesicles independently undergo a branching process such that each unreleased vesicle has a probability of p_0 to be released whenever an action potential occurs. For each individual vesicle, suppose there are K possible outcomes; there are $K-1$ action potentials under consideration and the K possible outcomes are release on any one of those, and nonrelease.

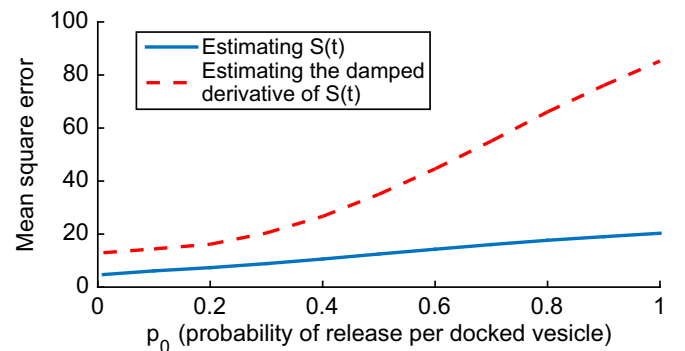


Fig. 4. Effect of probability of release per docked vesicle (p_0) on the mean square error $\mathbb{E}[e^2(t)]$ in the estimation of the presynaptic spike density $S(t)$ and its damped derivative. The units of $\mathbb{E}[e^2(t)]$ are s^{-2} in the case of estimation of $S(t)$ and s^{-4} in the case of estimation of the damped derivative of $S(t)$. $\mathbb{E}[e^2(t)]$ is obtained numerically by simulating the stochastic vesicle release process for 2,500 independent sample paths, each of which lasts 100 s. Parameter values are as in Fig. 2.

Let p_k be the probability of the k th outcome, and M_k be the number of individual vesicles that are released on the k th action potential ($k = 1, 2, \dots, K - 1$), or not released (outcome K). Then, $\sum_{k=1}^K p_k = 1$ and $\sum_{k=1}^K M_k = D$.

For any integers m_1, m_2, \dots, m_K , let $m = \sum_{k=1}^K m_k$, then

$$\begin{aligned} \Pr(M_1 = m_1, M_2 = m_2, \dots, M_K = m_K) \\ = \Pr(D = m) \frac{m!}{m_1! m_2! \dots m_K!} p_1^{m_1} p_2^{m_2} \dots p_K^{m_K} \\ = \frac{\mu^m}{m!} e^{-\mu} \frac{m!}{m_1! m_2! \dots m_K!} p_1^{m_1} p_2^{m_2} \dots p_K^{m_K}. \end{aligned} \quad [19]$$

Noting that

$$\mu^m = \mu^{m_1} \mu^{m_2} \dots \mu^{m_K}, \quad [20]$$

$$e^{-\mu} = e^{-\mu(p_1 + p_2 + \dots + p_K)} = e^{-\mu p_1} e^{-\mu p_2} \dots e^{-\mu p_K}, \quad [21]$$

we have

$$\begin{aligned} \Pr(M_1 = m_1, M_2 = m_2, \dots, M_K = m_K) &= \prod_{k=1}^K \frac{(\mu p_k)^{m_k}}{m_k!} e^{-\mu p_k} \\ &= \prod_{k=1}^K \Pr(M_k = m_k), \end{aligned} \quad [22]$$

where $\Pr(M_k = m_k) = (\mu p_k)^{m_k} / m_k! e^{-\mu p_k}$; this shows that M_k is Poisson distributed with mean μp_k , and that M_1, M_2, \dots, M_K are independent random

variables. Therefore, for each j , $\{R_{jk}\}_{k=j}^\infty$ are independent and Poisson distributed with

$$\mathbb{E}[R_{jk}] = \alpha_0 (T_j - T_{j-1}) p_0 (1 - p_0)^{k-j}. \quad [23]$$

Note that the random variables R_{jk} are also independent for different j , because different j refers to different cohort of vesicles, and both docking and release are independent for different vesicles. Because the sum of independent, Poisson-distributed random variables is a Poisson-distributed random variable with its mean equal to the sum of the means of the original Poisson-distributed random variables, we conclude that $\{N_k\}_{k=1}^\infty$ are independent and Poisson distributed. Also,

$$\mathbb{E}[N_k] = \sum_{j=-\infty}^k \mathbb{E}[R_{jk}] = \alpha_0 p_0 \sum_{j=-\infty}^k (T_j - T_{j-1}) (1 - p_0)^{k-j}. \quad [24]$$

Hence, given the presynaptic spike times $\{T_k\}_{k=1}^\infty$, the number of vesicles released at the k th action potential can be simulated in an efficient manner by drawing a number from Poisson distribution with its mean defined by the above Eq. 24.

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