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Activation in vesicle-mediated signaling shaped by batch arrival statistics

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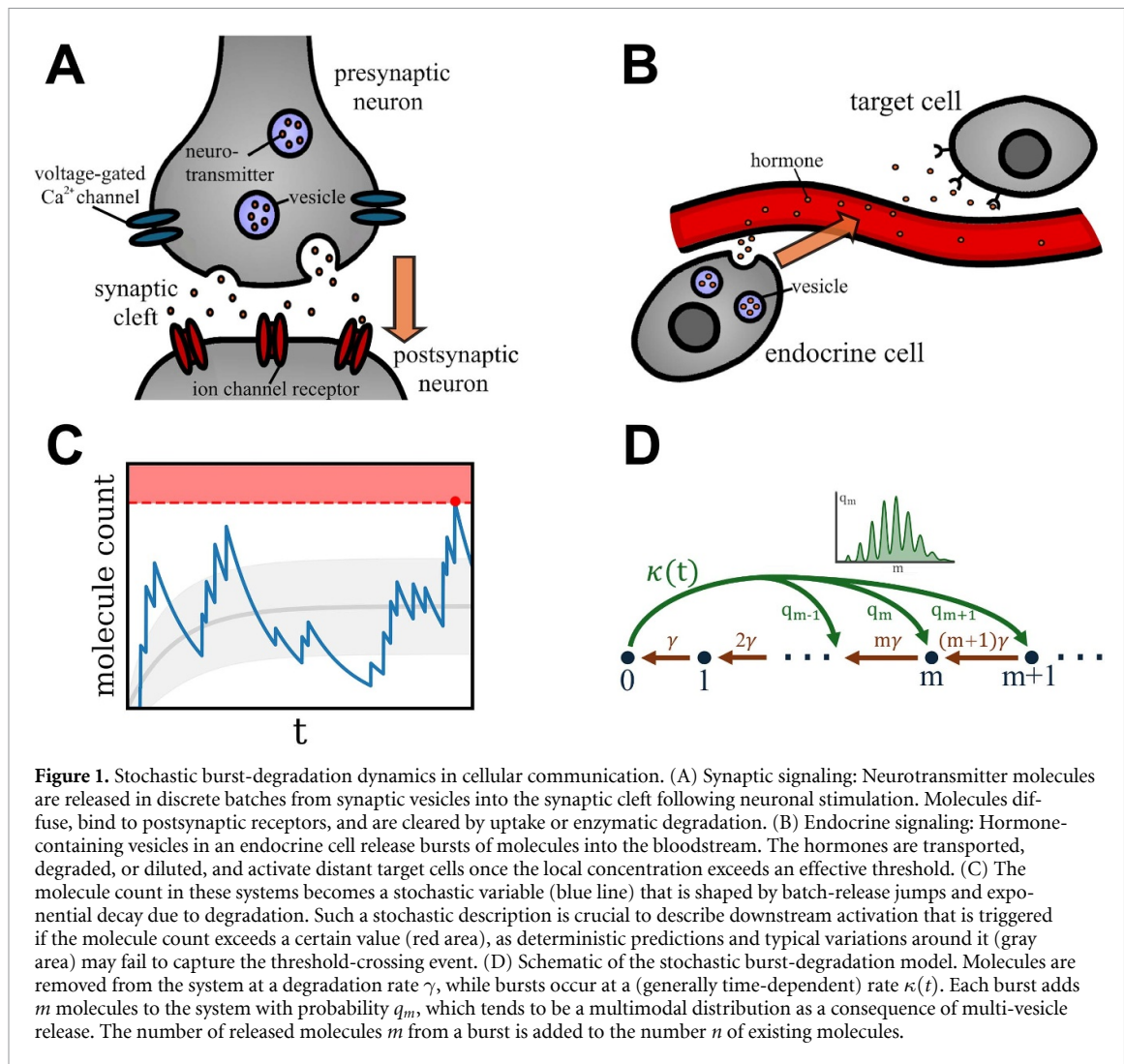
E-mail: schwarz@thphys.uni-heidelberg.de**Keywords:** vesicle release, master equation, first-passage timeSupplementary material for this article is available [online](#)

Abstract

Vesicle-mediated secretion of ions or molecules is a central mechanism of cellular communication, for example in processes such as neurotransmission or hormone release. These events are inherently stochastic: vesicle fusions lead to bursts of variable sizes, releasing discrete packets of transmitters that are subsequently cleared or degraded. The dynamics are intrinsically time-directed due to the interplay of spontaneous bursts and continuous degradation. Using generating functions and a recursion relation, we derive an exact solution for the full time-dependent probability distribution of a general batch arrival-degradation model. This framework also enables a full analysis of first-passage times to a concentration threshold representing downstream activation. We show that activation kinetics are not determined by mean dynamics alone, but depend sensitively on the temporal statistics of arrival events, batch-size variability, and degradation. In particular, different arrival processes with identical mean rates can lead to qualitatively distinct first-passage behavior, reflecting the role of time-asymmetric fluctuations. We also discuss extensions incorporating vesicle depletion. Our results provide a transparent link between stochastic release dynamics and activation timing in vesicle-mediated signaling.

1. Introduction

Biological cells communicate through many different channels, including biochemical, adhesive and mechanical signals [1]. The prototypical type of cell–cell communication is the release of a biochemical signal, e.g. a growth factor or a cytokine, into the surrounding medium, which is then sensed and processed by other cells [2]. In some biological situations of interest, the release process occurs through vesicle secretion, such that large numbers of molecules are released at the same time. One example is the neuronal synapse, where signaling is very local, from the presynaptic to the postsynaptic cell, as shown schematically in figure 1(A) [3–5]. Another example is endocrine signaling, where hormones are released into the bloodstream for long-range signaling in the body, as shown schematically in figure 1(B) [6]. In either case, signaling molecules are released through stochastic vesicle fusion events, leading to a discrete, quantized increase in the local molecular count, and are removed through transport and degradation processes [7]. The resulting dynamics are therefore shaped by spontaneous increases (bursts) rather than showing smooth deterministic trajectories [8–11]. Bursts of activity also occur in gene expression, where bursts arise from intermittent promoter activity and finite mRNA lifetimes [12–18], as described by appropriate stochastic equations [19–24]. However, in marked contrast to vesicle-mediated release, transcriptional or translational burst sizes of gene expression are geometrically distributed, often with time-homogeneous production and degradation rates [25, 26], while the molecular count of a single vesicle is more naturally described by binomial statistics, reflecting the finite number of release sites and probabilistic vesicle fusion [9, 27–30].



Postsynaptic neurons or hormone-receiving cells respond once the molecular count exceeds a certain threshold, making the timing of such threshold crossings a central observable [31–34] (figure 1(C)). From a physical perspective, vesicle-mediated signaling is an example of a strongly non-equilibrium transport process, where the molecular count is shaped by spontaneous burst events and continuous degradation. This leads to intrinsically time-directed dynamics, which are not described well by mean production and degradation rates alone.

The problem of the molecule count reaching a critical threshold can be naturally formulated in terms of first-passage times (FPTs) describing the stochastic time required to reach a target for the first time [35–37]. While FPTs are relatively well studied for diffusion processes and continuous stochastic dynamics [38, 39], the burst-driven systems require a discrete description shaped by the interplay of spontaneous releases, burst size statistics and molecular degradation. Recent work has made significant progress in understanding these contributions, including a derivation of exact FPT distributions in stochastic protein accumulation models [21] and analytical descriptions of quantal release statistics in synaptic transmission [40]. These studies highlighted the importance of stochasticity in such burst-degradation systems, but primarily focused on steady-state or time-homogeneous settings. However, a general model that incorporates both arbitrary release statistics and time-dependent rates to describe stochastic molecule counts and threshold-crossing events has not been analyzed yet.

To incorporate these aspects into a general framework, we here study a general batch arrival-degradation process as a minimal mathematical model for such systems [41–43]. The molecule count is described as a stochastic variable, which is increased in discrete jumps due to spontaneous release events and decreased by ongoing degradation (figure 1(D)). The framework analyzed here allows us to consider arbitrary burst profiles, including binomial distributions describing single-vesicle releases, but also more complex and potentially multimodal distributions, which can arise due to multivesicular release and heterogeneity in release probability or vesicle content [44, 45]. Moreover, for neurons in particular,

the vesicle release rate is generally time- and history-dependent, reflecting short-term memory driven by presynaptic Ca^{2+} dynamics and vesicle-pool depletion [46, 47]. In an extension of our model, we show that vesicle depletion can be included in the description by treating the number of docked vesicles (which are the vesicles that are already positioned at the membrane and which can readily fuse upon the arrival of an action potential) as an additional stochastic variable, typically with a constant replenishment rate [40, 48–54], although extensions to include molecule-dependent rates, vesicle undocking and repair steps have also been proposed [55–59].

A central question that our model allows us to address is how different batch arrival statistics lead to qualitatively different downstream activation profiles as a consequence of non-trivial threshold-crossing behavior. In particular, we investigate how different time statistics of bursts shape activation for processes with identical mean behavior but different arrival statistics. We find that these differences alone can lead to qualitatively distinct activation profiles, highlighting the role of the batch-arrival statistics for FPTs in these systems. Hence, the resulting activation cannot be predicted from deterministic dynamics alone and requires a careful mathematical treatment of the resulting FPT distributions. These findings are complementary to recent work which has highlighted that intrinsic noise can be decisive in predicting the timing of cellular events [21, 60]. In particular, Ham *et al* [22] demonstrate that stochasticity can accelerate or delay the mean FPT relative to deterministic predictions.

Our paper is organized as follows. In section 2, we introduce our model. In section 3, we apply the generating function method to derive a general analytical solution for the time-dependent probability distribution, in terms of a recurrence relation between the occupation probabilities. In section 4, we then express conditional threshold-crossing probabilities as a convolution of stochastic decay and the burst size distribution and specify the latter in terms of vesicle release statistics and quantal variability. We then apply this framework to several biologically relevant scenarios: we compare fixed-interval and homogeneous Poisson spike trains and cover the example of an exponentially decaying release rate and show that variability in the timing of release events strongly facilitates threshold crossing. Moreover, we illustrate that stochastic trajectories can reach thresholds significantly earlier than suggested by their deterministic dynamics. Lastly, section 5 extends the description to incorporate the effect of vesicle depletion and captures its impact as a correction to the release statistics and activation dynamics. We finally close with a summary and discussion in section 6.

2. Model

We study a model in which vesicle release is assumed to occur independently at a (potentially time-dependent) rate $\kappa(t)$, corresponding to a general time-inhomogeneous Poisson process. Each vesicle fusion event triggers the release of m molecules with probability q_m . In interneuronal signal transmission, the triggering event for vesicle releases is the arrival of an action potential (which is a traveling wave of a transient reversal in the membrane potential) in the presynaptic neuron. This can release multiple vesicles, so the release size distribution q depends both on the number of vesicles released and the number of molecules per vesicle. The molecules are subsequently removed by dilution, absorption or degradation, occurring at a rate γ per molecule, so that the total loss rate is proportional to the molecular count. This leads to the reaction network for a burst shown in figure 1(D). Note that each burst adds m molecules to the existing number n of molecules. The resulting dynamics are intrinsically asymmetric: the increase of the molecular count is driven by spontaneous bursts while it decreases as a result of ongoing degradation, leading to asymmetric stochastic dynamics with unidirectional transitions.

The probability $p_n(t)$ of having n molecules in the environment at time t obeys the following master equation:

$$\frac{dp_n}{dt} = -(\kappa + \gamma n)p_n + \gamma(n+1)p_{n+1} + \kappa(q * p)[n] . \quad (1)$$

In the last term, we use the discrete convolution to represent the different burst sizes:

$$(q * p)[n] = \sum_{m=0}^n p_{n-m} q_m = \sum_{m=0}^{\infty} p_{n-m} q_m . \quad (2)$$

Note that the sum can be extended because $p_n(t) = 0$ if $n < 0$. While the two terms in equation (1) with γ correspond to a simple one-step process of continuous degradation, the two terms with κ correspond to the bursts and balance each other, because each burst takes from the state n and gives to the state $n + m$.

One can non-dimensionalize time by rescaling it as $\gamma t \rightarrow t$, introducing the dimensionless parameter $\lambda(t) := \frac{\kappa(t)}{\gamma}$, to obtain:

$$\frac{dp_n}{dt} = -(n + \lambda)p_n + (n + 1)p_{n+1} + \lambda(q * p)[n], \quad (3)$$

leaving $\lambda(t)$ as the only free parameter of the system. Multiplying by n and summing over n on both sides of the master equation yields a differential equation for the mean molecule count:

$$\frac{d}{dt}\langle n \rangle = -\langle n \rangle + \lambda(t)\langle m \rangle, \quad (4)$$

where $\langle m \rangle = \sum_{m=0}^{\infty} mq_m$ denotes the average forward jump size. This is solved by

$$\langle n \rangle(t) = n_0 e^{-t} + \langle m \rangle \int_0^t ds \lambda(s) e^{s-t}. \quad (5)$$

For constant λ , this becomes

$$\langle n \rangle(t) = n_0 e^{-t} + \langle m \rangle \lambda (1 - e^{-t}) \quad (6)$$

and the deterministic long-time limit is $\langle m \rangle \lambda$. However, as illustrated in figure 1(C), stochastic trajectories fluctuate around this mean and can transiently reach molecule counts significantly above the deterministic limit. This implies that random activation of downstream processes with higher thresholds becomes possible, highlighting the need for a full stochastic description to capture the system's behavior accurately.

In the general framework as formulated here, one can choose any release size distribution q of interest. We briefly discuss some common modeling choices. Following the paradigmatic example of vesicle release in a neuronal synapse, we decompose q into the distribution $q^{(V)}$ of the count of released vesicles (*quantal count*) and the distribution $q^{(C)}$ of the molecular vesicle content (*quantal size*). Given that ν vesicles are released, the probability that m molecules are released is $(q^{(C)})_m^{*\nu}$, where $(q^{(C)})^{*\nu}$ is the ν -fold discrete convolution of the quantal size distribution $q^{(C)}$. Taking the expectation over the quantal count distribution $q^{(V)}$, one obtains

$$q_m = \sum_{\nu=0}^{\infty} (q^{(C)})_m^{*\nu} (q^{(V)})_{\nu}. \quad (7)$$

As can be easily verified, the mean release size $\langle m \rangle$ is the product of the mean quantal count $\langle \nu \rangle$ and the mean quantal size $\langle c \rangle$.

The widely adopted binomial model [28, 61] assumes that upon the arrival of an action potential, vesicles fuse independently of each other, resulting in a binomial distribution $q_{\nu}^{(V)} = \text{Binom}(\nu | V, \rho)$, where V is the number of docked vesicles and ρ is the individual probability for a docked vesicle to be released. For now, we assume V to be constant. An extension to settings where the rate of vesicle replenishment is on the order of the release rate, meaning that V itself has to be interpreted as a stochastic variable [62], is given in section 5.

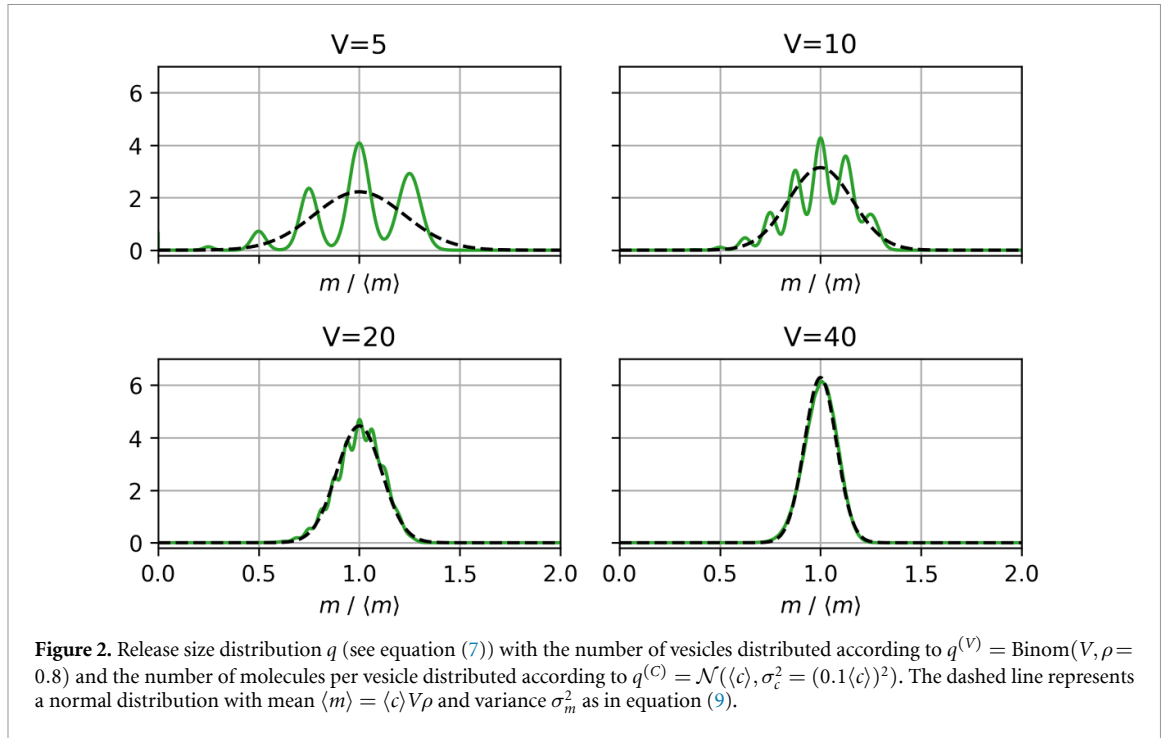
It is important to note that the quantal size is subject to fluctuations [63], and its exact distribution is experimentally only partially accessible [64]. The variance σ_c^2 of the quantal size modifies the variance σ_m^2 of the total release size according to

$$\frac{\sigma_m^2}{\langle m \rangle^2} = \frac{\sigma_{\nu}^2}{\langle \nu \rangle^2} + \frac{1}{\langle \nu \rangle} \frac{\sigma_c^2}{\langle c \rangle^2}. \quad (8)$$

For a binomial quantal count distribution $q^{(V)}$, this specializes to:

$$\frac{\sigma_m^2}{\langle m \rangle^2} = \frac{1}{V\rho} \left(1 - \rho + \frac{\sigma_c^2}{\langle c \rangle^2} \right). \quad (9)$$

According to the binomial limit theorem, if the number of releasable vesicles V is not too small, one may approximate q by a normal distribution with mean $\langle m \rangle$ and variance σ_m^2 (see figure 2).



3. Probability distribution of the molecule count

The generating function of the probability distribution is defined as $G(z, t) := \sum_{n=0}^{\infty} p_n(t) z^n$ [65]. Applying this transformation to equation (3) converts the master equation into a partial differential equation for $G(z, t)$:

$$\partial_t \ln G = (1 - z) \partial_z \ln G + \lambda(t) \left(\sum_{m=0}^{\infty} q_m z^m - 1 \right). \quad (10)$$

The solution for $G(z, t)$ subject to the boundary conditions $G(z = 1, t) = 1$ (for normalization) and for no initial molecular count ($p_n(t = 0) = \delta_{n,0}$) is given by:

$$\ln G(z, t) = \sum_{k=0}^{\infty} \sum_{m=k}^{\infty} q_m (\lambda * \mathcal{B}_k^m)(t) z^k - \int_0^t ds \lambda(s), \quad (11)$$

where $*$ denotes the convolution in time and

$$\mathcal{B}_k^m(t) := \binom{m}{k} e^{-kt} (1 - e^{-t})^{m-k} \quad (12)$$

is the binomial probability that k out of m molecules remain after time t . See supplement IA for details on the derivation. For an arbitrary initial condition $p_n(t = 0) = \delta_{n,n_0}$, this result generalizes to:

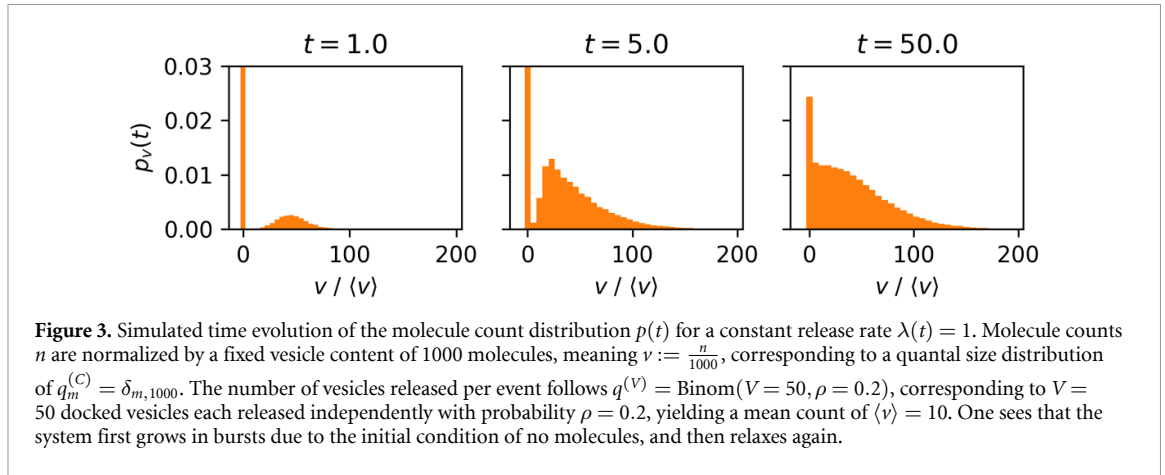
$$\ln G_{n_0}(z, t) = \ln G(z, t) + n_0 \ln((z - 1)e^{-t} + 1). \quad (13)$$

Observe that the k -th derivative of $\ln G(z, t)$ in $z = 0$ is given by:

$$\frac{\partial^k}{\partial z^k} \ln G \Big|_{z=0} = k! (\lambda * Q_k)(t), \quad (14)$$

where

$$Q_k(t) = \sum_{m=0}^{\infty} q_m \mathcal{B}_k^m(t) \quad (15)$$



is the probability that a single burst results in k molecules remaining after time t . From this, the probability distribution follows as:

$$p_0(t) = \exp\left((\lambda * Q_0)(t) - \int_0^t ds \lambda(s)\right), \quad (16)$$

$$p_n(t) = \frac{1}{n!} \frac{\partial^n}{\partial z^n} G(z, t) \Big|_{z=0} \quad (17)$$

$$= \frac{1}{n!} B_n(1!(\lambda * Q_1)(t), \dots, n!(\lambda * Q_n)(t)) p_0(t), \quad (18)$$

where $B_n(x_1, \dots, x_n)$ denotes the Bell polynomials [66], which satisfy the following recurrence relation:

$$B_{n+1}(x_1, \dots, x_{n+1}) = \sum_{i=0}^n \binom{n}{i} B_{n-i}(x_1, \dots, x_{n-i}) x_{i+1}. \quad (19)$$

This implies the following recurrence relation for $p_n(t)$:

$$p_n(t) = \frac{1}{n} \sum_{k=1}^n k p_{n-k}(t) (\lambda * Q_k)(t), \quad (20)$$

which allows for an efficient evaluation of the distribution. Figure 3 shows an example plot for $\lambda = \text{const}$.

Equation (20) makes explicit that the dynamics are governed by two ingredients: the statistics of burst arrivals and the subsequent decay, encoded in the kernels $Q_k(t)$, which represent the effective contribution of bursts generating k molecules that survive up to time t , leading to a compact recursive relation between the occupation probabilities at all times.

If λ is constant, corresponding to a homogeneous Poisson process and denoted as (P) , one may take the limit $t \rightarrow \infty$ of equation (20) and obtain the following steady state probabilities (Supplement IB):

$$\begin{aligned} \pi_0^{(P)} &= \exp\left(-\lambda \sum_{m=1}^{\infty} q_m H_m\right), \\ \pi_n^{(P)} &= \frac{\lambda}{n} \sum_{k=0}^{n-1} \pi_k \sum_{l=n-k}^{\infty} q_l, \end{aligned} \quad (21)$$

where $H_m := \sum_{k=1}^m \frac{1}{k}$ are the harmonic numbers. From the cumulant generating function $K(x) = \ln G(e^x, t \rightarrow \infty)$, the steady-state cumulants follow as:

$$\kappa_{\pi, l}^{(P)} = \lambda \sum_{m=1}^{\infty} q_m \sum_{k=1}^m k^{l-1}. \quad (22)$$

4. First passage to a threshold

4.1. Conditional hitting probability

As illustrated by the results in the previous section, the stochastic dynamics separate intrinsically into the statistics of release events and molecular degradation in between. We now use this to characterize the activation of downstream processes as a result of the molecule count exceeding a given threshold. The FPT probability density, i.e. the distribution of times when a certain threshold is crossed for the first time, is only accessible via stochastic sampling methods (examples below). As a simpler yet insightful quantity, we introduce the probability $p_{n|n_0}^+(t)$ that the next release will result in a molecule count of n , given that the previous release at time t brought the count to n_0 . We refer to this quantity as the *conditional hitting probability* or *conditional post-release distribution*. Intuitively, it allows us to analyze the hitting of thresholds not on a continuous-time basis, but on a per-release basis: rather than tracking exactly when the molecule count crosses a threshold, we ask for the probability of a given release event to bring the count above it. We can rewrite $p_{n|n_0}^+(t)$ as the discrete convolution

$$p_{n|n_0}^+(t) = \sum_{j=0}^n q_{n-j} p_{j|n_0}^-(t), \quad (23)$$

of the release size distribution q introduced in section 2 and the *conditional pre-release distribution* $p_{j|n_0}^-(t)$, i.e. the probability of having j molecules right before the release. Between release events, molecules degrade independently with rate unity, meaning that the molecule count follows a linear decay process, starting at time t with count n_0 . Given that a time period τ passes between releases, the number of remaining molecules then follows a binomial distribution with $N = n_0$ and $p = e^{-\tau}$, again denoted as $\mathcal{B}_j^{n_0}(\tau)$. Taking into account that τ is randomly distributed according to a distribution $f(\tau)$, we find

$$\begin{aligned} p_{j|n_0}^-(t) &= \int_0^\infty d\tau f(t+\tau) \mathcal{B}_j^{n_0}(\tau) \\ &:= \left\langle \mathcal{B}_j^{n_0}(\tau) \right\rangle_{\tau \sim f(t)}. \end{aligned} \quad (24)$$

If, as assumed previously in sections 2 and 3, the release events follow a time-inhomogeneous Poisson process with rate $\lambda(t)$, we have $f(t) = \lambda(t) \exp\left(-\int_0^t \lambda(s) ds\right)$. From the convolution in equation (23), we can read that the mean molecule count after the next release is

$$\mu_{+|n_0}(t) = \langle m \rangle + n_0 \langle e^{-\tau} \rangle_{\tau \sim f(t)}, \quad (25)$$

where $\langle m \rangle$ is the average size of the incoming burst and $n_0 \langle e^{-\tau} \rangle_{\tau \sim f(t)}$ is the expected number of molecules that survived up to this point. Similarly, also all higher cumulants of the post-release distribution $p_{j|n_0}^-(t)$ decompose into two separate contributions from the burst size and the degradation process. A particularly useful case, illustrated in the following example, arises when the conditional hitting probability $p_{j|n_0}^-(t)$ loses its time dependence, enabling the analysis of the steady state and the mean recurrence time.

4.2. Homogeneous Poisson train and fixed-interval train

As a simple and illustrative example, we discuss the release dynamics of a spike train of action potentials at a constant mean rate λ . Figure 4(A) schematically shows the situation as an action potential arrives at a synapse. Two limiting cases are particularly relevant [67, 68]: First, the time-homogeneous Poisson train (P) introduced in section 3, where releases are uncorrelated in time, which may apply to spontaneous or irregular neuronal activity. Second, the fixed-interval train (F), in which stimulation is perfectly periodic with inter-spike interval $\frac{1}{\lambda}$, as is typical in controlled experimental settings. Example trajectories of both cases are shown in figure 4(B). Note that the master equation treatment in sections 2 and 3 implicitly assumes events to follow a (time-inhomogeneous) Poisson process and therefore does not apply to the fixed-interval train. Instead, in supplement ID and IE, we derive formulas for the steady-state dynamics using an alternative generating function technique.

Here, we again focus on the first-passage problem. We begin by revisiting the conditional pre-release distribution $p_{j|n_0}^-$ as introduced in equation (24). For the fixed train, we simply have a binomial distribution with $N = n_0$ and $p = e^{-1/\lambda}$:

$$p_{j|n_0}^{-(F)} = \mathcal{B}_j^{n_0}(1/\lambda). \quad (26)$$

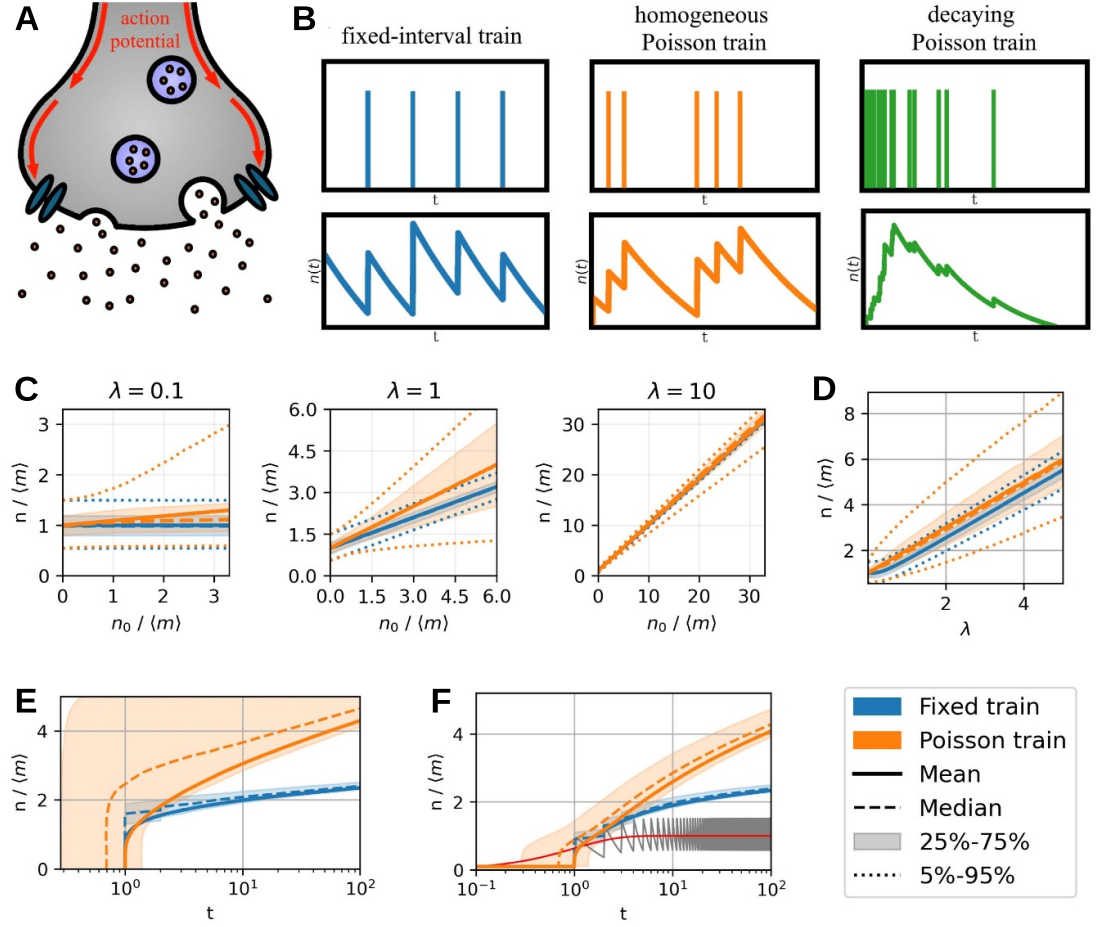


Figure 4. Comparison of the hitting statistics of a fixed-interval spike train and a homogeneous Poisson spike train with the same mean release rate λ . The count of released vesicles is assumed to follow a binomial distribution $q^{(V)} = \text{Binom}(V, \rho)$ with $V = 50$ releasable vesicles and release probability $\rho = 0.2$. The quantal size distribution $q^{(C)}$ is normal with mean $\langle c \rangle = 1000$ molecules per vesicle and $\sigma_c = 0.2\langle c \rangle$. The quantiles of the shown distributions were obtained from stochastic sampling (see supplement III). (A) Upon arrival of a spike, each docked vesicle at the active zone fuses and releases its contents with a certain probability ρ . (B) Qualitative comparison of the trajectories, in the case of releases occurring in fixed intervals (blue) or according to a homogeneous Poisson process (orange). The inhomogeneous Poisson process with exponentially-decaying rate (green) is treated separately in section 4.3. (C) Conditional post-release distribution $p_{n_0}^+$ of the molecule count (normalized by the mean release size $\langle m \rangle$), depending on the previous post-release count n_0 . (D) Steady state post-release distribution π^+ plotted against the release rate λ . (E) Distribution of times between subsequent hits of the same threshold (recurrence time), for $\lambda = 1$. Note that a hit is also recorded if the process crosses the threshold and remains above it until the next jump. (F) FPT from $n_0 = 0$ to n , for $\lambda = 1$. For comparison, the transient of the mean molecule count is plotted in gray for the fixed-interval train, and in red for the Poisson train.

For the Poisson train, we instead find

$$\begin{aligned}
 p_{j|n_0}^{-(P)} &= \int_0^\infty \lambda e^{-\lambda\tau} \mathcal{B}_j^{n_0}(\tau) d\tau \\
 &= \lambda \binom{n_0}{j} \text{Beta}(j + \lambda, n_0 - j + 1),
 \end{aligned} \tag{27}$$

corresponding to a Beta-Binomial($n_0, \lambda, 1$) distribution. The cumulants of both distributions are well known, and according to equation (23), adding to them the cumulants of the release size distribution q yields the cumulants of the post-release distribution $p_{|n_0}^+$. For example, we find for mean $\mu_{+|n_0}$ and variance $\sigma_{+|n_0}^2$:

$$\mu_{+|n_0}^{(F)} = n_0 e^{-1/\lambda} + \langle m \rangle, \tag{28}$$

$$\sigma_{+|n_0}^{2(F)} = n_0 e^{-1/\lambda} \left(1 - e^{-1/\lambda} \right) + \sigma_m^2, \tag{29}$$

$$\mu_{+|n_0}^{(P)} = n_0 \frac{\lambda}{\lambda + 1} + \langle m \rangle, \quad (30)$$

$$\sigma_{+|n_0}^{2(P)} = n_0 \frac{\left(\frac{n_0}{\lambda+1} + 1\right) \lambda}{(\lambda+1)(\lambda+2)} + \sigma_m^2, \quad (31)$$

where $\langle m \rangle$ is the mean and σ_m^2 is the variance of the release size. In particular, the mean post-release count $\mu_{+|n_0}$ is strictly smaller for the fixed train than for the Poisson train, despite the release rate λ and the release size being the same. Note that this is a direct consequence of the different decay probabilities between releases, as described by equations (26) and (27). Similarly, the variance $\sigma_{+|n_0}^2$ scales as $O(n_0)$ for the fixed train and as $O(n_0^2)$ for the Poisson train, implying substantially greater post-release variability from the Poisson train when the count is far above the steady-state mean. In figure 4(C) we plot the conditional post-release distributions for different rates λ , including the median and quartiles to illustrate the different shapes of the distributions. $p_{|n_0}^{+(P)}$ appears skewed for low and high release rates, while $p_{|n_0}^{+(F)}$ is approximately normal (see supplement IE for a formal argument on why this is the case).

By interpreting $p_{n|n_0}^+$ as a transition probability of a discrete-time stochastic process (Supplements IC and ID), we obtain analytical expressions for the cumulants of the post-release distribution in steady state π^+ . In other words, we examine the distribution π^+ of the molecule count after a release without making an assumption on the molecule count n_0 after the previous release. In figure 4(D), we plot the mean and quartiles of π^+ over the release rate λ . We observe that the findings for the conditional distribution essentially also apply to the steady state, with the post-release mean for the fixed train

$$\mu_+^{(F)} = \frac{\langle m \rangle}{1 - e^{-1/\lambda}} \quad (32)$$

being strictly lower than the post-release mean of the Poisson train

$$\mu_+^{(P)} = (\lambda + 1) \langle m \rangle \quad (33)$$

and the Poisson train showing a higher variance.

With the steady state results for the post-release distribution, we turn to the recurrence time to a threshold, defined as the waiting time between successive release events at which the molecule count reaches or exceeds a threshold n . According to a standard theorem in Markov chain theory [69], the mean number of release events needed to reach a molecule count equal to or higher than n is $1/\pi_{\geq n}^+$, where $\pi_{\geq n}^+ = \sum_{k=n}^{\infty} \pi_k^+$. Since the mean time between release events is $1/\lambda$, the mean recurrence time is $\langle \tau_n \rangle = 1/(\lambda \pi_{\geq n}^+)$. As shown in figure 4(E), this time grows super-exponentially with threshold n and is generally higher for the fixed-interval train compared to the Poisson train, reflecting the lower mean and variance in the post-release count. As for the post-release distribution, the variability in inter-event timing causes the recurrence time distribution to be broader for the Poisson train than for the fixed-interval train.

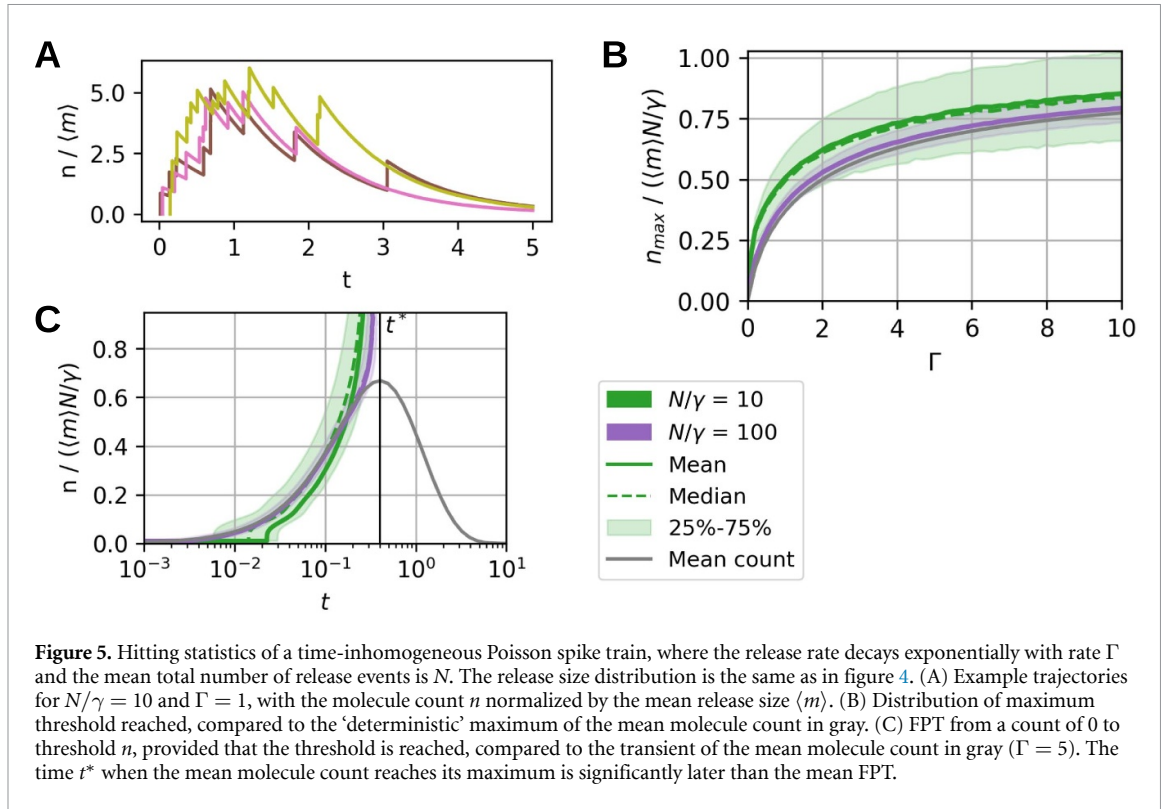
The same super-exponential growth with threshold, and the contrast between Poisson and fixed-interval trains, holds qualitatively for the FPT from any lower initial count. As an example, consider a neuron that is initially inactive ($n_0 = 0$) and begins receiving stimulation at $t = 0$. The FPT is then the time for the molecule count to first reach a threshold value n . As a reference, we compare the FPT distribution against the transient evolution of the mean molecule count. For the Poisson train, we apply equation (5) and find

$$\langle n^{(P)} \rangle(t) = \langle m \rangle \lambda (1 - e^{-t}). \quad (34)$$

For the fixed-interval train, the mean molecule count after the N th release event is $\langle n \rangle_N = \langle m \rangle + e^{-1/\lambda} \langle n \rangle_{N-1}$, where $\langle n \rangle_0 = 0$ and each step accounts for degradation between releases. Solving the recursion and including exponential decay between releases yields

$$\langle n^{(F)} \rangle(t) = \langle m \rangle \frac{1 - e^{-[\lambda t]/\lambda}}{1 - e^{-1/\lambda}} e^{-T}, \quad (35)$$

where $T = t - [\lambda t]/\lambda$ is the time since the last release. In figure 4(F), we compare this to the sampled FPT distribution. The mean FPT curve (blue and orange) and the transient mean molecule count (red and gray) intersect at a threshold value below the steady-state mean. For low thresholds, the FPT exceeds the transient mean time, since some finite time must elapse before the first jump occurs in the stochastic setting. For high thresholds, the stochastic process reaches the threshold earlier and the mean FPT



approaches the mean recurrence time (figure 4(E)), as the influence of the initial condition diminishes. We also observe that both the recurrence and the FPT distributions for high thresholds converge to a memoryless exponential distribution. This likely reflects that many individual attempts have to be made to cross a threshold, and has been rigorously proven in the case of exponential release size distributions [70].

The results above for the Poisson and fixed-interval trains illustrate how stochasticity in both release size and release timing shapes the activation of downstream processes. Beyond that, they provide the foundation for more elaborate models. In supplement IC and IIC, we generalize the results for the pre- and post-release distribution to the case of gamma-distributed inter-arrival times, which may be used to model bunched or anti-bunched spike trains. Section 5 extends the results to changing vesicle-pool sizes.

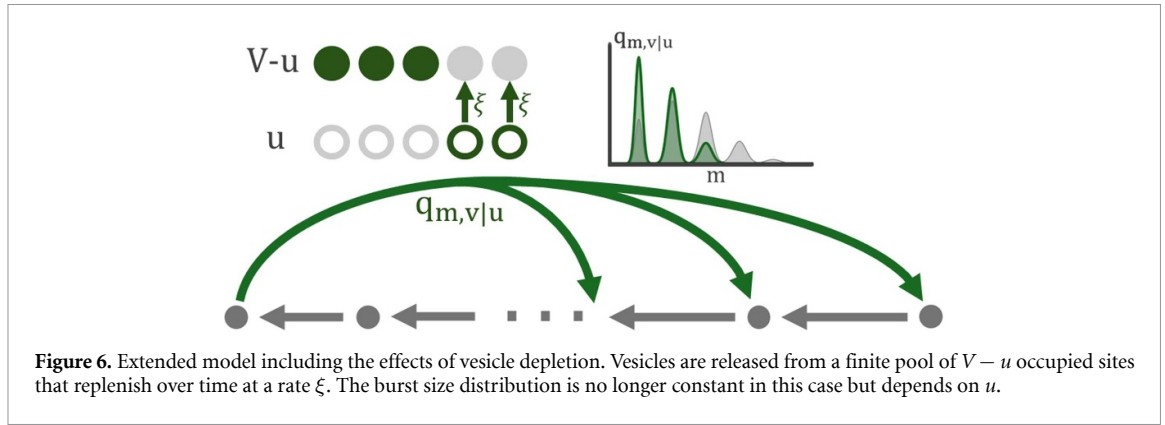
4.3. Poisson train with exponentially decaying release rate

As a second example, we study a case in which the release rate is time-dependent. Neuronal activity often occurs in transient bursts, for example, following a stimulus or during short periods of elevated excitability [67, 68]. To capture this behavior, we consider a neuron that is inactive for $t < 0$ and for $t > 0$ releases vesicles according to a time-inhomogeneous Poisson process with rate $\kappa(t) = N\Gamma e^{-\Gamma t}$, where $N = \int_0^\infty \kappa(t)dt$ is the mean total number of release events and Γ is a relaxation rate. To avoid vesicle depletion (see section 5), we assume $\kappa(t)$ to be much smaller than the rate of vesicle replenishment. As in section 2, we can non-dimensionalize the release rate by rescaling time as $\gamma t \rightarrow t$, where γ is the rate of degradation of molecules, and introduce $\lambda(t) = \frac{\kappa(t)}{\gamma}$.

Figure 5(A) shows example trajectories of the molecule count for this case, and figure 4(B) compares them qualitatively to the fixed-interval and the time-homogeneous Poisson train. From equation (5), we find

$$\langle n(t) \rangle = \frac{\langle m \rangle N \Gamma}{\gamma} \frac{(e^{-t} - e^{-\Gamma t})}{\Gamma - 1} \quad (36)$$

for the time evolution of the mean. At $t^* = \ln(\Gamma)/(\Gamma - 1)$, this becomes maximal with $\langle n(t^*) \rangle = \langle m \rangle \frac{N}{\gamma} \exp(-\ln \Gamma / (\Gamma - 1))$. In figure 5(B), we compare $\langle n(t^*) \rangle$ to the mean of the actual maximum molecule count reached by the stochastic process. For all relaxation rates Γ , the true stochastic maximum is strictly higher, particularly when N/γ is small, which corresponds to the case of few release events or fast degradation. In figure 5(C), we compare the transient of the mean molecule count to the



distribution of the FPT to a threshold, given that the threshold is actually reached. We observe that thresholds around $\langle n(t^*) \rangle$ and higher thresholds are in fact reached significantly before t^* . For lower thresholds, the dynamics of the mean are only representative if N/γ is large. Together, these results highlight that the mean molecule count can be misleading in the case of few release events or fast degradation, underestimating the maximum count reached and overestimating the time until a threshold is crossed.

5. Vesicle depletion

For high release rates, the pool of releasable vesicles can be depleted, and the mathematical description therefore requires a release size distribution q depending on previous release events. Let V be the total number of release sites and u the number of empty release sites. Following previous work by other authors [40, 48–54], we assume a constant replenishment rate ξ per released vesicle (see figure 6), which we again non-dimensionalize by applying $\xi/\gamma \rightarrow \xi$, where γ is the molecular degradation rate.

The extended version of equation (3) then reads

$$\frac{dp_{n,u}}{dt} = -(n + \lambda + \xi u)p_{n,u} + (n + 1)p_{n+1,u} + \xi(u + 1)p_{n,u+1} + \lambda \sum_{m,v} q_{m,v|u-v} p_{n-m,u-v}, \quad (37)$$

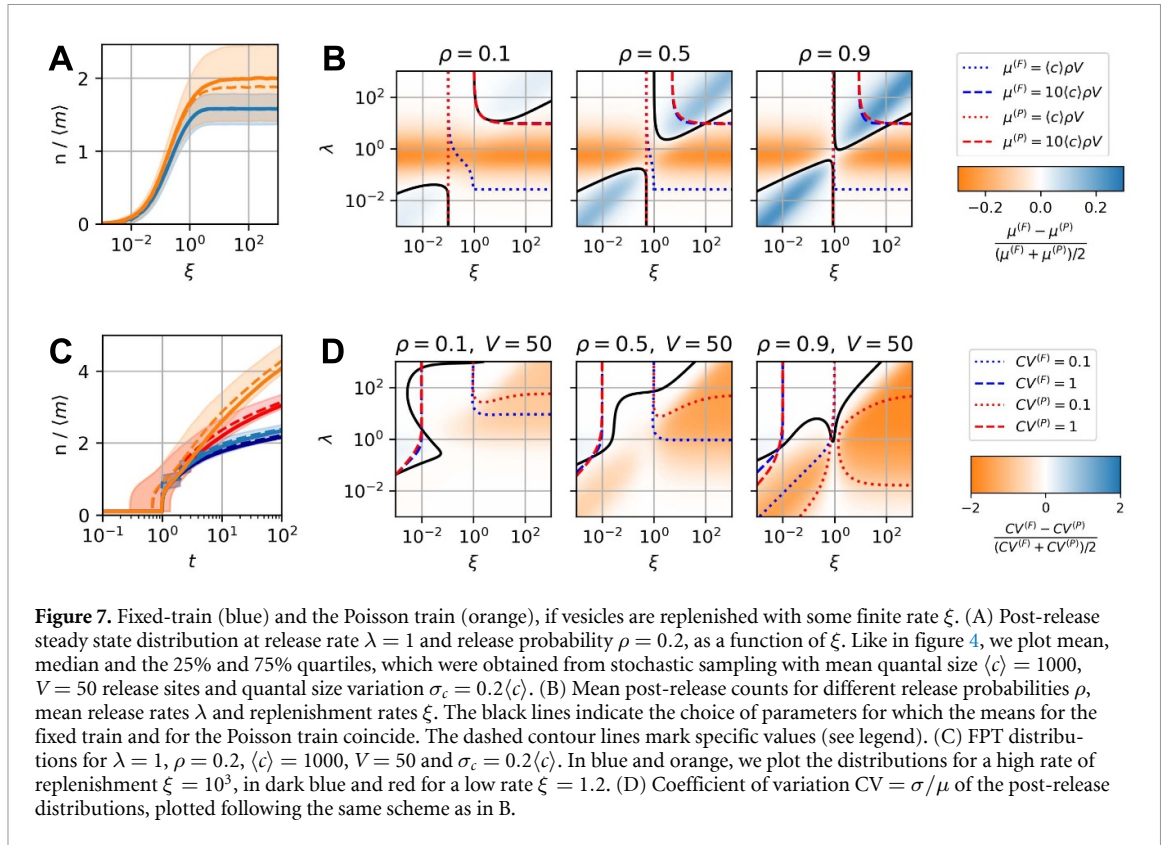
where $q_{m,v|u_0}$ now is the probability of releasing m molecules distributed across v vesicles, provided that $V - u_0$ vesicles are available for release. In accordance with the binomial model, we choose

$$q_{m,v|u_0} = \left(q^{(C)} \right)_m^{*v} \text{Binom}(v | V - u_0, \rho), \quad (38)$$

where $q^{(C)}$ is the quantal size distribution with mean $\langle c \rangle$ and variance σ_c^2 . We note that a simpler version of this model, where the quantal size is fixed to $\langle c \rangle$, has been covered in recent work by Rijal *et al* [40] and other authors [53, 54]. In supplement II, we extend their moment and generating function analysis to account for a non-vanishing release size variance σ_c^2 and provide generalized formulas for the mean molecule count and the post-release distribution.

The steady-state distributions for both the fixed-train and the Poisson train (cf section 4.2) can change substantially under the influence of vesicle depletion. For example, figure 7(A) shows that for $\lambda = 1$ and even a low release probability of $\rho = 0.2$, the mean and variance of the post-release distribution are significantly altered if the replenishment rate ξ is on the order of magnitude of the release rate λ . This is also true for the FPTs to thresholds above the steady state mean, which are plotted in figure 7(C).

In supplement IIC, we derive the mean and variance of the modified post-release distributions p^+ . It turns out that the previous equations (32) and (33) for the steady-state mean μ_+ with constant vesicle pool remain valid if the mean release size $\langle m \rangle$ is treated as a function of the release rate λ and the rate of replenishment ξ . Concretely, $\langle m \rangle$ factorizes into the mean burst size for a full pool $\langle c \rangle V \rho$ times the fraction of occupied vesicle sites in the (model-dependent) steady state. Since the release and degradation rates remain unchanged, the prefactors in equations (32) and (33) are unaffected. For the fixed



train, one finds

$$\langle m^{(F)}(\lambda, \xi) \rangle = \langle c \rangle V \rho \cdot \frac{1 - e^{-\xi/\lambda}}{1 - (1 - \rho)e^{-\xi/\lambda}}, \quad (39)$$

while for the Poisson train

$$\langle m^{(P)}(\lambda, \xi) \rangle = \langle c \rangle V \rho \cdot \frac{\xi}{\xi + \lambda \rho}, \quad (40)$$

which is always smaller than the value for the fixed train.

As a consequence, the steady state mean may be higher either for the fixed train or for the Poisson train, depending on the choice of λ , ξ and ρ . In figure 7(B), we plot the difference between the respective means μ_+ of the post-release distribution for different parameter choices. As indicated by the dashed contour lines, the mean generally increases with both λ and ξ . In a region where $10^{-1} \lesssim \lambda \lesssim 10^1$ (orange shade), the Poisson train tends to give a higher mean, while in a region $\lambda \approx \xi$ (blue shade), it is the fixed train. Where both regions intersect (black line), it depends on the release probability per vesicle ρ , with high ρ favoring the fixed train. This makes intuitive sense, since the Poisson train yields higher means for a given release size (cf section 4.2), especially for intermediate λ , but also exhibits clustering of release events and therefore lower mean release sizes compared to the fixed train. This matters especially for high ρ , i.e. if many of the available vesicles are released.

If the release sizes are generally small ($\lambda > \xi$ and small V), the variability of the post-release distribution, quantified by the coefficient of variation σ/μ , may also become near-identical between fixed train and Poisson train or even slightly higher for the fixed train. Otherwise, as seen in figure 7(D) for the example $V = 50$, the variability of the Poisson train is significantly higher.

6. Summary and discussion

In this work, we have derived an exact solution for the fully time-dependent occupation probabilities of a general batch arrival-degradation model and shown that the activation timing is not determined by the

mean burst frequency alone, but also by the time statistics of the bursts. Our model for vesicle-mediated signaling combines the effects of burst-like releases at generally time-dependent rates, arbitrary release size distributions and molecular degradation. By solving the corresponding master equation with the generating function approach, we obtained an exact representation of the full time-dependent probability distribution that could be used to derive an interpretable recurrence relation to evaluate the dynamics.

To study the activation of downstream processes, such as the activation of a postsynaptic neuron or a hormone-sensing target cell, we introduced the conditional threshold crossing probability and studied the FPT to a prescribed target for multimodal burst size distributions reflecting the effect of multi-vesicle releases. We compared the two experimentally relevant cases of a fixed spike train and a homogeneous Poisson spike train with the same mean vesicle-release frequency, reflecting the cases of periodic and irregular excitation of the presynaptic neuron, respectively. Our results show that the two activation profiles show qualitatively distinct FPT behaviors, due to different fluctuations in the timing of release events determining the probability of rare fluctuations that result in sufficiently high molecule counts for threshold crossing. In particular, this illustrates that the mean vesicle-release frequency is insufficient to fully capture activation profiles. Moreover, this effect also persists for time-dependent release rates, such as an exponentially decaying activity after an initial stimulus, where threshold crossing is dominated by early stochastic events and can occur significantly before the maximum of the mean molecule count.

Lastly, we also investigated an extension of the model that incorporates vesicle depletion due to a finite replenishment rate. In this extended model, the number of available vesicles becomes a dynamical variable coupling the burst size distribution to previous release events. Qualitatively, the influence of stochasticity persists, but depletion can alter the differences between activation profiles, depending on the replenishment rate and the release probability. This demonstrates that burst statistics have a robust influence that nevertheless depends on the conditions of the system.

Including the number of available vesicles as a second stochastic variable introduces memory to the system. Without it, the burst-events are Poisson-like, i.e. memoryless, which is only valid for high replenishment rates of the vesicles ready for release. This assumption can also be relaxed by allowing for non-exponentially distributed release times, which we discuss for the analytically tractable case of a gamma distribution of the release times in supplement IC and IIC for the simple model and the model including vesicle depletion, respectively.

Our results complement and extend previous work on stochastic burst-degradation processes and FPTs. While earlier studies have largely focused on steady state distributions or specific burst size distributions such as geometric distributions in gene expression [21, 24, 26, 71], our framework allows for arbitrary release statistics and time-dependent burst rates, which are both reflected in our analytical expression for the time-dependent occupation probabilities. Recent work has shown that the prediction of mean activation times for noisy systems can differ profoundly from deterministic expectations [22], a fact that is also well-known for diffusion problems in complex environments, where the means fail to capture the broadness or heterogeneity of the FPT distribution [39, 72, 73]. Extending this idea, our FPT analysis also reveals that different stochastic systems such as the fixed-interval and homogeneous Poisson train vesicle release models can lead to distinct activation behavior despite sharing the same mean burst frequency. Similar qualitative results were obtained for time-dependent release rates and also under the inclusion of vesicle depletion, indicating that the statistical nature of release events constitutes a key parameter of activation dynamics.

From a biological perspective, these findings suggest that variability in neuronal or endocrine signaling may not merely reflect a noisy environment but could actively shape downstream processes, and irregular or burst-like activation patterns could enhance responsiveness by increasing the probability of fast activation, while vesicle depletion provides a mechanism to regulate this effect.

So far, our model assumes independent release events and linear degradation, neglecting feedback mechanisms, spatial transport and receptor dynamics [53, 54, 74]. Extending the framework to include such effects and potentially interacting signaling pathways may provide further insight into how stochasticity shapes cellular communication in realistic biological settings. More broadly, our framework suggests that asymmetric dynamics on the microscopic level give rise to emergent activation dynamics at the macroscopic scale.

Finally, our analysis was restricted to a single type of molecule with a single activation threshold, while in practice vesicle releases often feature more than one species, which may serve as different downstream signals [75]. In the future, extensions of our mathematical model to d -dimensional vectors of molecular counts for d different species may allow us to further explore correlations between their individual FPTs. For molecular species that are co-packaged, these correlations are expected to be particularly strong and future research may explore how correlations change due to individual degradation and diffusion patterns, including in comparison to conventional diffusion.

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Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: <https://github.com/HaukeJan/vesicle-release> [76].

Supplemental text available at: <http://doi.org/10.1088/1367-2630/ae98a6/data1>.

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