A Chemical Master Equation Model for Synaptic Molecular Communication

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Abstract—In synaptic molecular communication, the activation of postsynaptic receptors by neurotransmitters (NTs) is governed by a stochastic reaction-diffusion process and, hence, inherently random. It is currently not fully understood how this randomness impacts downstream signaling in the target cell and, ultimately, neural computation and learning. The statistical characterization of the reaction-diffusion process is difficult because the reversible bi-molecular reaction of NTs and receptors renders the system nonlinear. Consequently, existing models for the receptor occupancy in the synaptic cleft rely on simplifying assumptions and approximations which limit their practical applicability. In this work, we propose a novel statistical model for the reaction-diffusion process governing synaptic signal transmission in terms of the chemical master equation (CME). We show how to compute the CME efficiently and verify the accuracy of the obtained results with stochastic particle-based computer simulations (PBSs). Furthermore, we compare the proposed model to two benchmark models proposed in the literature and show that it provides more accurate results when compared to PBSs. Finally, the proposed model is used to study the impact of the system parameters on the statistical dependence between binding events of NTs and receptors. In summary, the proposed model provides a step forward towards a complete statistical characterization of synaptic signal transmission.

I. INTRODUCTION

Diffusive molecular communication (DMC) is a novel communication paradigm inspired by the exchange of information between biological entities by means of diffusing molecules [1]. It is envisioned that DMC will enable revolutionary applications in the field of intra-body nanoscale communications based on and interfacing with natural molecular communication (MC) systems, such as the synaptic DMC system [2]. Since the synaptic DMC system enables complex processes such as learning and memory, understanding its design is key to the development of synthetic neural applications such as neural prostheses and brain-machine interfaces [2]. However, despite considerable research efforts, our picture of synaptic communication is not complete to date.

In synaptic DMC, information is conveyed from the presynaptic cell to the postsynaptic cell by means of diffusing molecules called neurotransmitters (NTs). NTs are sensed by the postsynaptic cell using membrane-bound receptors and may be degraded by enzymes while diffusing in the extracellular medium [3]. One central open question regarding synaptic DMC concerns the role of different kinds of signaling noise for the signal transmission [2]. In particular, it is not fully understood, whether the randomness in synaptic communication due to the random propagation and reaction of NTs with enzymes and postsynaptic receptors makes synaptic communication more or less reliable [4].

Synaptic DMC has been studied in the MC community with emphasis on different aspects, such as information theoretic limits [5], the design of artificial synapses [6], and the long-term average signal decay [7], see also literature overviews in [2], [8]. Mean-field models, i.e., deterministic models for the average receptor activation valid in the large system limit, have been developed for synapses employing enzymatic degradation [7], [9] and other channel clearance mechanisms [6], [8], [10]. However, stochastic fluctuations in the postsynaptic receptor activation have been considered only recently [9]. Yet, the statistical model proposed in [9] does not account for the randomness of the enzymatic degradation of NTs and relies on the simplifying assumption that either NTs compete for postsynaptic receptors or postsynaptic receptors compete for NTs. Hence, the scope and applicability of the model in [9] is limited to a specific range of parameter values. Other statistical models for ligand receptors in the MC literature assume statistical independence of the receptors [11]. As already shown in [9], this assumption is in general not justified.

In this paper, we propose a novel statistical signal model for synaptic DMC in terms of the chemical master equation (CME). The proposed model characterizes the joint statistics of the postsynaptic receptor occupancy and the enzymatic degradation process for the first time in the MC literature. Furthermore, in contrast to existing models, it does not rely on simplifying assumptions with respect to the statistical (in)dependence between receptors and/or NTs. Since the CME model in its original form is computationally intractable, a novel adaptive state reduction scheme is proposed which allows the efficient computation of the proposed model. The proposed state reduction scheme exploits knowledge of the first-order statistics of the considered process and, in contrast to common approximation methods for the CME found in the literature [12], the approximation error is explicitly characterized and can, hence, be controlled. Finally, the results of the proposed model are compared to stochastic particle-based computer simulations (PBSs) to verify both the assumptions made to arrive at the proposed CME model and the accuracy of the proposed state reduction scheme. In summary, the proposed model allows for an accurate statistical characterization of the synaptic noise due to NT binding and degradation outperforming existing models. It hence provides a step forward towards a comprehensive statistical analysis of the noise in synaptic DMC.

The remainder of this paper is organized as follows. The system model in terms of the CME is introduced in Section II. In Section III, a state reduction scheme for the computation of the CME is provided. In Section IV, the proposed model is used to study the statistics of synaptic

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communication for selected, biologically relevant parameter regimes and numerical results from PBS are presented which validate the model. Section [VI] concludes the paper with a brief summary of the main findings and an outlook towards future research directions.

II. SYSTEM MODEL

In synaptic communication, NTs are released into the synaptic cleft by exocytosis of presynaptic vesicles. After release, NTs propagate by Brownian motion and react with postsynaptic transmembrane receptors and degradative enzymes, cf. Fig. 1. Since both reactions and the diffusion of NTs are random, the number of activated postsynaptic receptors at time \( t \), \( O(t) \), and the total number of (non-degraded) NTs at time \( t \), \( N(t) \), are random processes.

A. Mean-Field Model

For synaptic DMC systems satisfying the assumptions discussed in [9] Sec. II-A, i.e., synapses that employ enzymatic degradation as channel clearance mechanism and are either of large extent or confined by surrounding cells, the expected concentration of NTs after a single release into the synaptic cleft is described by the following partial differential equation [9]

\[
\partial_t c(x, t) = D \partial_x^2 c(x, t) - \kappa_c c(x, t), \quad 0 < x < a,
\]

where the synaptic cleft is represented by the one-dimensional spatial domain \([0, a]\), \( c(x, t) \) denotes the expected concentration of solute NTs at time \( t \) and spatial coordinate \( x \) in \( \mu m^{-1} \). \( D \) and \( \kappa_c \) denote the diffusion coefficient for NTs in \( \mu m^2 \mu s^{-1} \) and the enzymatic degradation rate in \( \mu s^{-1} \), respectively, and \( \partial_t \) and \( \partial_x \) denote the first partial derivative with respect to time \( t \) and the second partial derivative with respect to space \( x \), respectively. The reversible binding of NTs to postsynaptic receptors is modeled as a boundary condition at \( x = a \) [9]

\[
-D \partial_x c(x, t) \big|_{x=a} = \kappa_a \left( 1 - \frac{\alpha(t)}{C} \right) c(a, t) - \kappa_d o(t),
\]

where \( C \) and \( \alpha(t) \) denote the total number of postsynaptic receptors and the expected number of postsynaptic receptors occupied at time \( t \), respectively, \( \kappa_a \) and \( \kappa_d \) denote the microscopic binding rate of NTs to postsynaptic receptors in \( \mu m \mu s^{-1} \) and the unbinding rate of NTs from postsynaptic receptors in \( \mu s^{-1} \), respectively, and \( \partial_x \) denotes the first partial derivative with respect to \( x \). The model is completed by the initial and boundary conditions [9]

\[
c(x, 0) = N_0 \delta(x) \quad \text{and} \quad \partial_x c(x, t) \big|_{x=0} = 0,
\]

respectively, where \( N_0 \) and \( \delta(x) \) denote the number of released NTs and the Dirac delta distribution, respectively. Furthermore, \( o(t) \) is related to \( c(x, t) \) by the equation

\[
o(t) = \int_0^t -D \partial_x c(x, \tau) \big|_{x=a} d\tau.
\]

Since boundary condition [2] is nonlinear, a closed-form solution to the boundary value problem [1]–[3] cannot be obtained. Instead, a state space model is used in [9] to compute \( o(t) \) iteratively in the transfer function domain. We call this model \( S \) and it is defined by a state equation [9] Eq. (42)] and an output equation [9] Eq. (31)].

Now, let \( n(t) \) denote the expected total number of NTs, i.e., the expected number of solute NTs and bound NTs, at time \( t \). When \( S \) is computed, we obtain not only \( o(t) \), but also \( c(x, t) \) and \( n(t) \) [9 Sec. III-C-3].

In the following, we will use these quantities to compute the macroscopic absorption rate for NTs to postsynaptic receptors.

B. Macroscopic Binding Rate

In the mean-field model [1]–[4], the binding rate of NTs to postsynaptic receptors is given by constant \( \kappa_a \). In fact, \( \kappa_a \) results from mapping the actual three-dimensional reaction-diffusion process to the one-dimensional process in [1]–[4]. According to [9] Sec. V-A, \( \kappa_a \) can be written as

\[
\kappa_a = \bar{\kappa}_{a0} C,
\]

where \( \bar{\kappa}_{a0} \) is a constant depending on the intrinsic binding rate of one NT to one receptor and the ratio of the receptor area to the postsynaptic membrane surface area. Hence, the activation of postsynaptic receptors can be written as the following reversible bi-molecular reaction [2]

\[
S_a + R \xrightleftharpoons{\kappa_a}{\kappa_d} O,
\]

where \( R \) denotes unoccupied postsynaptic receptors and \( S_a \) denotes the solute NTs located in an (infinitesimally) small volume close to the postsynaptic membrane.

Now, denoting by \( S(t) \) the total number of solute molecules at time \( t \) and assuming that the ratio \( S_a(t)/S(t) \) is well-approximated by the ratio of the corresponding mean values obtained from [1]–[4], i.e.,

\[
\frac{S_a(t)}{S(t)} \approx \frac{E[S_a(t)]}{E[S(t)]} = \frac{c(a, t)}{\int_0^a c(x, t) dx},
\]

where \( E[\cdot] \) denotes the expectation operator, we can write the change in \( O \) due to the binding and unbinding of NTs in the large system limit as

\[
\frac{dO(t)}{dt} = \bar{\kappa}_{a0} S(t) \frac{c(a, t)}{\int_0^a c(x, t) dx} R(t) - \kappa_d O(t).
\]

Hence, defining the time-dependent macroscopic binding rate \( \kappa_a(t) \) as \( \kappa_a(t) = \bar{\kappa}_{a0} c(a, t)/\int_0^a c(x, t) dx \), we obtain the reaction

\[
S + \frac{\kappa_a(t)}{\kappa_d} \xrightleftharpoons{} \kappa_a(t) O.
\]

1By “one-dimensional”, we refer to spatial dimensions, excluding the temporal dimension.
Eq. [9] provides a space-independent description of the reaction of NTs with postsynaptic receptors. However, in contrast to space-independent models with constant reaction rates [12], we do not assume that the reaction volume is well-mixed. Instead, the spatially heterogeneous and time-dependent distribution of solute NTs is represented by $\kappa_a(t)$. The accuracy of this model as compared to the actual reaction-diffusion process depends on the validity of (7).

Eq. (7) in turn is justified if the number of solute NTs is not too small and diffusion is relatively fast as compared to the chemical reactions. We will see in Section IV that (9) provides a very accurate model for different, biologically relevant ranges of parameter values.

C. The Chemical Master Equation

In this section, we formulate a statistical model for the random processes $O(t)$ and $N(t)$ in terms of the CME.

First, besides the reaction of NTs with postsynaptic receptors defined in (9), solute NTs are exposed to enzymatic degradation which is modeled as a uni-molecular reaction in (1). This degradation reaction is described as follows

$$S \xrightarrow{\kappa_d} \emptyset,$$  \hspace{1cm} (10)

where $\emptyset$ denotes any species that does not react with NTs and postsynaptic receptors.

Next, we note that the state of the system described by (9) is in general not possible [13]. Hence, in this section, we aim at computing $P(n, o, t)$ as defined in (11) numerically. As we will see, even the numerical evaluation of (11) poses a severe challenge.

A. Formal Solution

According to (11), there exist $M = (N_0 + 1) \times (C + 1)$ different system states. We organize these states in a level-dependent manner where the total number of NTs, $n$, determines the level. This means, we define the probability vector $\pi(t) \in [0, 1]^M$ as

$$\pi(t) = [\pi_{n,0}(t), \pi_{n-1,0}(t), \ldots, \pi_0(t)]^T,$$  \hspace{1cm} (12)

where $[\cdot]^T$ denotes transposition and the $N_0 + 1$ vectors $\pi_n(t) \in [0, 1]^{(C+1)}$ are defined as $P(n, o, t) = [P(n, 0, t), P(n, 1, t), \ldots, P(n, C, t)]$.

In a similar fashion, we collect all transition probabilities from (11) in the time-dependent transition matrix $A(t) \in \mathbb{R}^{M \times M}$. $A(t)$ is a block-bidiagonal matrix consisting of $(N_0 + 1)^2 (C + 1) \times (C + 1)$ matrices with all sub-matrices equal to the quadratic all-zero matrix $0_{(C+1)}$, except for the matrices on the main diagonal and the lower diagonal which we denote as

$$A_{i,i} = Q_{N_0-i+1}, \quad 1 \leq i \leq N_0 + 1,$$  \hspace{1cm} (13)

and

$$A_{i,i-1} = D_{N_0-i+1}, \quad 2 \leq i \leq N_0 + 1,$$  \hspace{1cm} (14)

respectively. Matrices $Q_n$ and $D_n$ collect the level-dependent transition rates for the binding and the degradation reactions. The $Q_n$ are tridiagonal matrices with the diagonals defined as follows

$$(Q_n)_{i+1,i+1} = -[\kappa_d i \kappa_n(n - i)]$$  \hspace{1cm} (15)

$$(Q_n)_{i+1,i} = \kappa_a(t)(n - i)(C - i), \quad 0 \leq i \leq C,$$  \hspace{1cm} (16)

$$(Q_n)_{i,i+2} = \kappa_d(i + 1), \quad 0 \leq i \leq C - 1.$$  \hspace{1cm} (17)

The $D_n$ are diagonal matrices with diagonals defined as follows

$$(D_n)_{i,i+1} = \kappa_e(n + 1 - i), \quad 0 \leq i \leq C.$$  \hspace{1cm} (18)

With these definitions, we can write (11) in vector form as the following system of differential equations

$$\frac{d\pi}{dt} = A(t)\pi(t),$$  \hspace{1cm} (19)

the formal solution of which is given as

$$\pi(t) = \exp \left( \int_0^t A(\tau)d\tau \right) \pi_0,$$  \hspace{1cm} (20)

where $\exp(M)$ denotes the matrix exponential of square matrix $M$ and, according to (3), $\pi_0 = \pi(0)$ is given by the $M$-dimensional vector $[1, 0, \ldots, 0]^T$.

B. Computational Issues and Approximation Schemes

Since the dimension of $A(t)$ grows quadratically with both the number of released NTs and the number of receptors, computing the matrix exponential in (20) is intractable [14]. Indeed, even for the moderate number of 500 released NTs and 200 receptors, the number of elements of $A(t)$ is of order $\sim 10^{10}$.

This problem is common to many applications using the CME as modeling tool and, consequently, several methods have been proposed to approximate the solution of the CME [13]. Two of the most frequently used approximation schemes are moment closure schemes and schemes exploiting some kind of system size expansion, the most popular among the latter being the linear noise approximation (LNA) [13]. Both of these approaches have their strengths and limitations, the discussion of which would go far beyond the scope of this paper. Here, it suffices to say that due to the bimolecular reaction [9] both methods cannot be used without further simplifications or approximations to obtain the statistics of $N(t)$ and $O(t)$.

Another commonly used method for computing high-dimensional CMEs is to approximate the CME on a lower-
The restriction of \( \pi_t \) and the restriction of \( \pi_t \) to the indices of the elements of reduced state space \([12]\). In the following section, we show how to exploit our knowledge of the first-order statistics of \( N(t) \) and \( O(t) \) given by \( n(t) \) and \( o(t) \), respectively, to adapt the state space iteratively while computing the CME. We show that this adaptive scheme allows to compute \([20]\) efficiently and, at the same time, control the approximation error.

### C. Adaptive State Reduction

To introduce the proposed adaptive state reduction scheme, we first discretize time into subsequent intervals of length \( \Delta t \), such that the \( k \)th interval is \( I_k = [t_k, t_{k+1}] \), where \( t_k = (k-1)\Delta t \) and \( k \) is from the set of positive integers \( \mathbb{N} \). The idea is to compute \( \pi(t) \) iteratively for each interval \( k \) while discarding the states \( (n, o) \) which do not contribute significant probability mass in interval \( k \).

To this end, we first define the respective marginal distributions of \( N(t) \) and \( O(t) \) at time \( t \) as

\[
P_N(n, t) = \sum_{o=0}^{C} P(n, o, t) \quad \text{and} \quad P_O(o, t) = \sum_{n=0}^{N} P(n, o, t),
\]

and the full state space of \( (11) \) as

\[
S_0 = \{ (n, o) | 0 \leq n \leq N, 0 \leq o \leq C \}. \tag{22}
\]

Furthermore, let \( P_B(n, p) \) denote the probability mass function of a binomial random variable with parameters \( n \) and \( p, \epsilon > 0 \), and define

\[
N_{\text{min}}(k) = \max \left\{ n \left| \sum_{o=0}^{C} P_B \left( n', n_0, \frac{n(t_k+1)}{N_0} \right) < \epsilon \right. \right\}, \tag{23}
\]

\[
N_{\text{max}}(k) = \min \left\{ n \left| \sum_{o=0}^{N} P_B \left( n', t_k \right) < \epsilon \right. \right\}, \tag{24}
\]

\[
O_{\text{min}}(k) = \max \left\{ o \left| \max_{t \in I_k} \sum_{i'=0}^{C} P_B \left( o', C, \frac{i(t)}{C} \right) < \epsilon \right. \right\}, \tag{25}
\]

\[
O_{\text{max}}(k) = \min \left\{ o \left| \max_{t \in I_k} \sum_{i'=0}^{C} P_B \left( o', C, \frac{i(t)}{C} \right) < \epsilon \right. \right\}. \tag{26}
\]

We define the reduced state space in interval \( k \) as follows

\[
S_k = \{ (n, o) | N_{\text{min}}(k) \leq n \leq N_{\text{max}}(k), \ O_{\text{min}}(k) \leq o \leq O_{\text{max}}(k) \}, \tag{27}
\]

and the restriction of \( \pi(t) \) to \( S_k \) as

\[
\pi(t)|_{S_k} = [\pi_{(N_{\text{min}}(k))}|_{S_k}, \ldots, \pi_{(N_{\text{max}}(k))}|_{S_k}], \tag{28}
\]

where

\[
\pi_n(t)|_{S_k} = [P(n, O_{\text{min}}(k), t), \ldots, P(n, O_{\text{max}}(k), t)]. \tag{29}
\]

The restriction of \( \pi(t) \) to \( S_k \), \( \pi(t)|_{S_k} \), is obtained by discarding the rows and the columns of \( \pi(t) \) corresponding to the indices of the elements of \( \pi(t) \) discarded in \( \pi(t)|_{S_k} \). Finally, we define the approximate solution of \( (19) \) in \( S_k \) by

\[
\tilde{\pi}(t)(n, o, t) = \left\{ \begin{array}{ll}
\pi(t)(n, o, t), & (n, o) \in S_k, \\
0, & \text{otherwise}.
\end{array} \right. \tag{30}
\]

This dependence remains implicit for notational simplicity.

### Algorithm 1 Iterative computation of \( \pi(t) \)

1. initialize: \( k = 1, K = [t/\Delta t], \tilde{\pi}(0)(0) = \pi_0, \Delta t, \epsilon \).
2. while \( k \leq K \) do
3. Compute \( S_k \) according to \([23]-[27]\).
4. Set \( \pi(k)(k) = \tilde{\pi}(k-1)(k) \).
5. Compute \( \tilde{\pi}(k)(t) \) for \( t \in I_k \) by solving \([30]\).
6. Set \( k = k + 1 \).
7. end while
8. Return \( \tilde{\pi}(K)(t) \).

### IV. Numerical Results

In this section, we present numerical results for the statistics of \( N(t) \) and \( O(t) \) obtained with Alg. \([1]\) and compare
these results with two reference models for $O(t)$, one reference model for $N(t)$, and stochastic PBS. The reference models for $O(t)$ are the statistical models based on the hypergeometric distribution proposed in [9], denoted by $\mathcal{H}(o)$, and the binomial model obtained by assuming statistical independence of the receptors, $\mathcal{B}(o) = P_B(o; C, o(t)/C)$, where $P_B$ was defined in Section III-C. The implementation details of the PBS, we refer the reader to [8], [9]. To compare the PBS with the results obtained with Alg. 1 we compute the empirical distribution of $N(t)$ and $O(t)$ at some time $t$ based on 6,000 PBS realizations.

For the numerical analysis, we consider three sets of parameter values, $\Sigma_0$, $\Sigma_1$, and $\Sigma_2$, listed in Table I. Further model parameters relevant for the PBS and the state space model $S$ but not for the CME model considered in this paper are set according to [9], Table I.

$\Sigma_1$ is used to model synapses in which the competition of NTs for receptors is relatively small as compared to $\Sigma_0$ as it is the case in the neuromuscular junction where more receptors are present than in central synapses [15]. In this case, the assumption underlying the model proposed in [9] is not fulfilled. $\Sigma_2$ models a scenario in which many receptors compete for relatively few NTs. Although NTs are usually more abundant than receptors, this situation may occur as a consequence of impaired vesicle loading [16].

### A. Receptor Occupancy Statistics

Fig. 2 shows $P_O(t)$ at $t = 1$ ms as obtained by Alg. 1 and the reference models $\mathcal{H}$ and $\mathcal{B}$, as well as the results obtained by PBS, for $\Sigma_0$, $\Sigma_1$, and $\Sigma_2$. We observe from Fig. 2 that the model proposed in Sections II and III matches the empirical distribution obtained by PBS accurately for all considered sets of parameters. Also, both reference models $\mathcal{H}$ and $\mathcal{B}$ match the PBS data for $\Sigma_0$. However, $\mathcal{H}$ fails to reproduce $P_O(t)$ for $\Sigma_1$. The reason for this is that due to the large abundance of both NTs and receptors in $\Sigma_1$, there is neither competition of NTs for receptors nor competition of receptors for NTs and the main assumption for $\mathcal{H}$ is not fulfilled. On the other hand, $\mathcal{B}$ fails to reproduce $P_O(t)$ for $\Sigma_2$, the reason being that for $\Sigma_2$, the independence assumption underlying $\mathcal{B}$ is not fulfilled. We conclude that the statistical model for $O(t)$ proposed in this paper is more robust towards parameter variations than previous models.

Finally, we observe from Fig. 2 that the variance of $O(t)$ and, consequently, the statistical dependence between the activation of different postsynaptic receptors depends largely on the choice of the synaptic parameters. While correlation between receptors is rather strong in $\Sigma_2$, it is almost negligible in $\Sigma_0$ and $\Sigma_1$. In $\Sigma_0$, on the other hand, competition of NTs for receptors is stronger compared to $\Sigma_1$.

### B. Neurotransmitter Degradation Statistics

Now, we consider the statistics of $N(t)$. Fig. 3 shows the statistics of $N(t)$ as obtained by Alg. 1 for reference model $\mathcal{N}$, and PBS data at different time instants $t = 0.5$ ms, 0.75 ms, 1 ms for parameter values $\Sigma_1$. First, we observe from Fig. 3 that the results obtained by Alg. 1 match the empirical distribution of $N(t)$ very well for all considered time instants. Furthermore, we observe from Fig. 3 that the degradation of single NTs is negatively correlated, since $P_N(t)$ as obtained by Alg. 1 is more concentrated compared to the binomial model $\mathcal{N}$.

From these results, we conclude that the proposed model can be used to gain novel insights into the impact of the various synaptic parameters on the statistics of synaptic signaling.

### V. Conclusion

In this paper, we proposed a novel statistical model for the receptor occupancy and the neurotransmitter degradation in the synaptic DMC system. The proposed model is superior to existing models, because its applicability is not compromised by the simplifying assumptions underlying these models; neither does it require statistical independence of the receptors as the binomial model does, nor does it require competition of NTs for receptors or receptors for NTs as the model proposed in [9] does. Furthermore, in contrast to existing models, the proposed model yields the joint distribution of the number of occupied receptors and the number of surviving NTs which fully characterizes the system state at each time instant. The comparison with PBS results underlines the high accuracy of the proposed model and the validity of the assumptions made to arrive at this model. In summary, the proposed model provides a step forward towards a complete statistical characterization of the synaptic MC system.

We conclude noting that the CME model proposed in this paper can be used to study the depolarization of the postsynaptic membrane resulting from the stochastic activation of postsynaptic receptors [4]. However, due to space constraints, discussion and further investigation of this point is left for future work.

### APPENDIX

#### Proof of Theorem 1

From the structure of $A(t)$, cf. (13), (14), we know that there is only probability flux from level $n + 1$ to level $n$, not vice versa. Hence, we conclude that

$$\sum_{n=n_0}^{N} P_N(n, t+\Delta t) \leq \sum_{n=n_0}^{N} P_N(n, t),$$  \hspace{1cm} (35)\n
for any $n_0 \in \{0, \ldots, N\}$, $\Delta t > 0$. Eq. (35) provides an upper tail bound for $P_N(n, t+\Delta t)$ in terms of $P_N(n, t)$. On the other hand, by the same argument

$$\sum_{n=0}^{n_0} P_N(n, t) \leq \sum_{n=0}^{n_0} P_N(n, t+\Delta t).$$  \hspace{1cm} (36)\n
Let us consider the interval $I_k$. By assumption, we know $P_N(n, t_k)$. Then, with $N_{\max}^{(k)}$ as defined in (24), we conclude
Figure 2. Probability mass function of $O(t)$ at $t = 1$ ms as predicted by the model proposed in Sections [II] and [III] (red), the statistical model proposed in [9] (orange), and the binomial model (brown). Results from PBSs are shown in blue. The three subfigures correspond to the different scenarios $\mathcal{S}_0$, $\mathcal{S}_1$, and $\mathcal{S}_2$, respectively, as defined in Table [I].

Figure 3. $P_N(n,t)$ at different time instants $t$ for $\mathcal{S}_1$. The figure shows the CME model proposed in this paper (red), the binomial model $\mathcal{N}$ (brown) and results from PBSs (blue).

from [35] that $\sum_{n=n_{\min}}^{N} P_N(n',t) < \epsilon$ for any $t \in I_k$. Now, let us consider the assumption that the NTs are degraded independently of each other. Under this assumption, since all NTs are identical, $N(t)$ follows a binomial distribution with parameters $N_0$ and $\mathbb{E}[N(t)]/N_0 = n(t)/N_0$. Indeed, this is a worst-case assumption with respect to the spread of $P_N(n,t)$, since in reality, the degradation of NTs is negatively correlated ⁵ i.e.,

$$\sum_{n=0}^{N_0} P_N(n,t) \leq \sum_{n=0}^{N_{(n,k)}} P_B(n,n_{(n,k)}/N_0), (37)$$

where $P_B(:,n,p)$ as defined in Section [III-C] [17]. Now, with $N_{(n,k)}$ as defined in [34], we conclude from (37) and (36) that $\sum_{n=0}^{N'} P_N(n',t) < \epsilon$ for any $t \in I_k$. Since the binding of NTs to receptors is also negatively correlated [9], the upper and lower tail bounds for $O(t)$ follow from the same line of argumentation as (37). This concludes the proof.

⁵To see the negative dependence of degradation events, consider one NT $N_i$. The more NTs are degraded by time $t$, the more likely it is that $N_i$ binds to a free receptor and thus cannot be degraded by enzymes. On the other hand, the fewer NTs are degraded, the more NTs compete for receptors and it is less likely that $N_i$ finds a free receptor that prevents it from being degraded. This conclusion is also confirmed by the results presented in Fig. 1.