Improving Receiver Performance of Diffusive Molecular Communication with Enzymes

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Abstract—In this paper, we perform receiver analysis for a diffusive molecular communication system that uses diffusing enzymes in the propagation environment to mitigate intersymbol interference. The enzymes form reaction intermediates with information molecules and then degrade them so that they cannot interfere with future transmissions. We derive a lower bound expression on the expected number of molecules recognized at the receiver. We design a simple binary receiver detection scheme where the number of observed molecules is sampled at the time when the greatest number of molecules is expected, and provide insight into the selection of an appropriate bit interval. We then derive a recursive expression for the expected bit error probability as a function of the current and all previously transmitted bits. Simulation results show the accuracy of the bit error probability expression and the improvement in communication performance by having active enzymes present.

I. INTRODUCTION

Recent interest in the design of nanonetworks, where communicating devices have functional components that are on the order of nanometers in size, has emerged for applications in areas such as biomedicine, environmental monitoring, and manufacturing; see [2], [3]. The devices themselves could share information over potentially longer distances, on the micrometer scale and further. This communication capability is essential if the entire devices themselves are very small since they would have limited individual processing capacity. Molecular communication is a nanonetwork design strategy where a transmitter emits information molecules that are carried to an intended receiver. It is a bio-hybrid approach that can take advantage of the many mechanisms in cells and subcellular structures that already use the emission of molecules for communication. By utilizing bio-hybrid components, such as genetically modified cells, we might hope to design networks that are inherently biocompatible for implementation inside of living organisms.

The simplest propagation method using molecules is free diffusion, which can be modeled as a random walk. Small molecules that are released by a transmitter can freely diffuse away without any external energy or infrastructure requirements. Diffusion can be very fast over short distances, and is a common means of communication in nature; many cellular processes rely on diffusion for limited quantities of small molecules to efficiently propagate both within and between cells, as described in [4, Ch. 16]. Many researchers have also adopted diffusion for the design of molecular communication networks, cf. e.g. [5]–[17].

The average distance travelled by a diffusing molecule is proportional to the square root of the time that it takes to diffuse. So, molecular communication systems have to deal with increasingly longer propagation times as the receiver is placed further away. The general lack of control over where molecules diffuse means that a large number of molecules is required to ensure that a sufficient number arrive at the receiver instead of diffusing away. Furthermore, the receiver’s ability to differentiate between the arrival of the same type of molecule emitted at different times is reduced by how long it takes for those molecules to leave the proximity of the transmitter and receiver. Unless there is a mechanism in place to remove excess information molecules from the environment, the transmission rate between a single transmitter and receiver is limited by the on-going proximity of previously emitted molecules, i.e., intersymbol interference (ISI).

Communications capacity can be significantly improved by adding a mechanism that actively transforms information molecules so that they are no longer recognized by the receiver. In general, chemical reactant molecules could perform this role, but then they must be provided in stoichiometric excess relative to the information molecules, otherwise their capacity to transform the information molecules will degrade over time. Catalysts, on the other hand, lower the activation energy for biochemical reactions but do not appear in the stoichiometric expression of the complete transformative reaction; unlike reactants, catalysts are not consumed. Specifically, enzymes are catalytic biomolecules that can have the advantage of very high selectivity for their substrates; see [4, Ch. 16]. Some enzymes are already used in nature for the purpose of reducing ISI; for example, acetylcholinesterase is an enzyme in the neuromuscular junction that hydrolyzes acetylcholine as it diffuses to its destination, as described in detail in [18, Ch. 12]. Furthermore, another mechanism regenerates acetylcholine at the transmitter from its hydrolyzed components so that it can be re-used in future emissions.

We are interested in using enzymes in the propagation environment due to their selectivity and because a single enzyme can be recycled to react many times. No additional complexity at either the transmitter or receiver is required. The reduction in ISI would enable transmitters to release molecules more often, simultaneously increasing the data rate and decreasing the probability of erroneous transmission. There would also be
less interference from neighbouring communication links, so independent transmitter-receiver pairs could be placed closer together than in an environment dominated by diffusion alone.

The current literature on diffusion-based molecular communication has primarily dealt with ISI via passive strategies where the transmitter must wait sufficiently long for previously-emitted information molecules to diffuse away before it can release more molecules, thereby limiting the maximum transmission rate. For example, ISI has often been ignored, as in [5]–[9], or it has been assumed that interfering molecules are released no earlier than the previous bit interval, as in [10]–[13]. ISI from all transmissions has been considered in [14], where the Viterbi algorithm is applied at the receiver to optimally detect emissions from a transmitter that uses molecule shift keying. However, the Viterbi algorithm may be too complex for practical implementation in small bio-hybrid devices.

In addition, the potential for information molecules to participate in a chemical reaction mechanism has usually been considered only at the receiver, as in [9], [15]. Two works that have considered information molecules reacting in the propagation environment are [16], [17]. In [16], the spontaneous destruction and duplication of information molecules are treated as noise sources but were not deliberately imposed to improve communication. In [17], the exponential decay of information molecules was considered via simulation as a method to reduce ISI. However, information was measured as the total number of molecules to reach the receiver, so the achievable information rate actually decreased when information molecules were allowed to decay.

In this paper, we present a model for analyzing diffusion-based molecular communication systems when there are enzymes present throughout the entire propagation environment. The enzymes react with the information molecules via the Michaelis-Menten reaction mechanism, which is a common mechanism for enzymatic reactions; see [19] Ch. 10. We first introduced this scenario in [1], where we derived a lower bound on the expected number of information molecules observed at a receiver placed some distance from a transmitter that emits impulses of molecules. We justified a particle-based simulation framework and presented preliminary simulation results that showed that the addition of enzymes can drastically reduce the number of information molecules that remain in the vicinity of the receiver. Effectively, the enzymes reduce the “tail” created when we rely on diffusion alone. This paper expands the work presented in [1] with the following new contributions:

1) We derive the time at which the maximum number of information molecules is expected, both with and without enzymes, and then derive an upper bound expression on the time required for the number of molecules expected to decrease to some fraction of the maximum number. This analytically shows that, for a given level of ISI, a shorter bit interval can be achieved by adding enzymes. This also provides insight into the selection of an appropriate bit interval.

2) We design a simple receiver scheme where the receiver counts the number of molecules observed at the instant when the number of molecules is expected to be maximum and the number observed is compared to a binary decision threshold.

3) We derive the bit error rate of this scheme for the first emission by the transmitter and then as a function of the current and all previous emissions. This strategy is more generalized than the current practice in the literature of either assuming that only the immediately previous transmission can interfere with the current one or that all ISI is negligible. With the exception of [14], ISI from all transmissions has been previously considered via simulation only, as in [20].

The rest of this paper is organized as follows. In Section II we introduce our system model for transmission between a single transmitter and receiver. A lower bound expression on the number of observed molecules at the receiver is derived in Section III. The performance analysis of the receiver, where we calculate the signal degradation time and derive the bit error rate for the simple detection scheme, is presented in Section IV. In Section V we describe the simulation framework and provide some insight into the selection of appropriate parameter values. In Section VI we present numerical and simulation results and discussion. Conclusions and the ongoing direction of our research are described in Section VII.

II. Physical Model

There is a transmitter fixed at the origin of an unbounded 3-dimensional aqueous environment. The receiver is an observer with a fixed volume of size \( V_{obs} \), centered at location \( \{x_0, y_0, z_0\} \) where \( \vec{r}_0 \) is the vector from the origin to \( \{x_0, y_0, z_0\} \), and a sphere with radius \( |\vec{r}_{obs}| \). The receiver is a passive observer; molecules can diffuse through it as they do through the entire environment.

There are three mobile species in the system that we are interested in: \( A \) molecules, \( E \) molecules, and \( EA \) molecules. \( A \) molecules are the information molecules that are released by the transmitter. These molecules have a natural degradation rate that is negligible over the time scale of interest, but they are able to act as substrates with enzyme \( E \) molecules. We apply the Michaelis-Menten reaction mechanism to the \( A \) and \( E \) molecules (which is generally accepted as the fundamental mechanism for enzymatic reactions; see [18], [19]):

\[
E + A \xrightarrow{k_1} EA, \quad (1)
\]

\[
EA \xrightarrow{k_{-1}} E + A, \quad (2)
\]

\[
EA \xrightarrow{k_2} E + A_P, \quad (3)
\]

where \( EA \) is the intermediate formed by the binding of an \( A \) molecule to an enzyme molecule, \( A_P \) is the degraded (product) \( A \) molecule, and \( k_1, k_{-1}, \) and \( k_2 \) are the reaction rates for the reactions as shown with units molecule\(^{-1}\) m\(^3\) s\(^{-1}\), s\(^{-1}\), and s\(^{-1}\), respectively. We see that \( A \) molecules are irreversibly degraded by reaction (5) while the enzymes are released intact so that they can participate in future reactions. \( A_P \) molecules are ignored once they are formed because they cannot participate in future reactions and they are not recognized by the receiver.
(we do not consider the re-generation of A molecules from $A_p$ molecules at the transmitter).

The number of molecules of species $S$ is given by $N_S$, and its concentration at the point defined by vector $\vec{r}$ and at time $t$ in molecule $\cdot m^{-3}$ is $C_S(\vec{r}, t)$. For compactness, we will generally write $C_S(\vec{r}, t) = C_S$. We assume that every molecule of each species $S$ diffuses independently of all other molecules. We assume that all free molecules are spherical in shape so that we can state that each molecule diffuses with diffusion constant $D_S$, found using the Einstein relation as [18, Eq. 4.16]

$$D_S = \frac{k_BT}{6\pi\eta R_S}, \quad (4)$$

where $k_B$ is the Boltzmann constant ($k_B = 1.38 \times 10^{-23}$ J/K), $T$ is the temperature in kelvin, $\eta$ is the viscosity of the medium in which the particle is diffusing ($\eta \approx 10^{-3}$ kg $\cdot$ m$^{-1}$s$^{-1}$ for water at 25°C), and $R_S$ is the molecule radius. Thus, the units for $D_S$ are m$^2$/s. The diffusion of a single molecule along one dimension has variance $2D_S t$, where $t$ is the diffusing time in seconds [18, Eq. 4.6].

Communication occurs as follows. The transmitter emits impulses of $A$ molecules, where the number of molecules emitted is $N_A$ (not to be confused with Avogadro’s Number, $6.02 \times 10^{23}$). This is a common emission scheme in the molecular communication literature; see, for example, [8], [15], [21], [22]. We deploy binary modulation with constant molecular communication literature; see, for example, [19, Ch. 9]) to the Michaelis-Menten

$$C_A = \frac{N_A}{4\pi D_A t \frac{3}{2}} \exp \left( \frac{-|\vec{r}|^2}{4D_A t} \right). \quad (6)$$

Eq. (6) is the form that is typically used in molecular communication to describe the local concentration at the receiver (where $\vec{r} = \vec{r}_0$); the receiver is assumed to be a point observer, as in [20], [23], at the position of the receiver. Assuming the A molecules are released from the origin at $t = 0$, we then have [18, Eq. 4.28]

$$C_A = \frac{N_A}{4\pi D_A t \frac{3}{2}} \exp \left( \frac{-|\vec{r}|^2}{4D_A t} \right). \quad (6)$$

for species $S$. Closed-form analytical solutions for partial differential equations are not always possible and depend on the boundary conditions that are imposed. Currently, we have no E molecules, so there are also no $E_A$ molecules, and we immediately have $C_E = C_{EA} = 0$ for all $\vec{r}$, $t$. Assuming that the $A$ molecules are released from the origin at $t = 0$, we then have [18, Eq. 4.28]

$$C_A = \frac{N_A}{4\pi D_A t \frac{3}{2}} \exp \left( \frac{-|\vec{r}|^2}{4D_A t} \right). \quad (6)$$

III. OBSERVATIONS AT THE RECEIVER

Generally, the spatiotemporal behavior of the three mobile species can be described using a system of reaction-diffusion partial differential equations. Even though these equations are deterministic, they will enable stochastic simulation. In this section, we use the deterministic, but we assume perfect passive counting in order to focus on the propagation environment.

B. Reaction-Diffusion

We now include active enzymes in our analysis. The general reaction-diffusion equation for species $S$ is [24, Eq. 8.12.1]

$$\frac{\partial C_S}{\partial t} = D_S \nabla^2 C_S + f(C_S, \vec{r}, t), \quad (7)$$

where $f(\cdot)$ is the reaction term. Applying the principles of chemical kinetics (see [19, Ch. 9]) to the Michaelis-Menten
mechanism in (1)-(3), we write the complete partial differential equations for the species in our environment as

\[ \frac{\partial C_A}{\partial t} = D_A \nabla^2 C_A - k_1 C_A C_E + k_{-1} C_{EA}, \]

\[ \frac{\partial C_E}{\partial t} = D_E \nabla^2 C_E - k_1 C_A C_E + k_{-1} C_{EA} + k_2 C_{EA}, \]

\[ \frac{\partial C_{EA}}{\partial t} = D_A \nabla^2 C_{EA} + k_1 C_A C_E - k_{-1} C_{EA} - k_2 C_{EA}. \]

We can readily convert these concentrations into the expected number of observed A molecules at the receiver, \( \bar{N}_{A,obs}(t) = C_A(\bar{r}_0, t)V_{obs} \), if we assume that the concentration throughout the receiver is uniform, which we do for the remainder of this paper.

IV. RECEIVER PERFORMANCE ANALYSIS

In this section, we first consider the signal degradation with enzymes and provide a method to calculate an appropriate bit interval \( T_B \). Then, we derive the bit error rate of our receiver and provide approximations that facilitate closed-form expressions. We design the reception mechanism such that the receiver counts the number of free A molecules observed within \( V_{obs} \), at the instant when the expected number of molecules is maximal (assuming that the transmitter emitted molecules at the start of the bit interval). A single decision threshold is used for the receiver to determine whether a binary 1 or binary 0 was sent by the transmitter. This is a relatively simple reception mechanism that facilitates analysis but is physically justifiable. If a biochemical response mechanism were triggered at the receiver when the information molecule concentration reached a threshold level, then such a detection scheme is analogous to the scheme described here.

A. Signal Degradation with Enzymes

Assuming that the concentration of molecules within \( V_{obs} \) is uniform and equal to that expected at the center of the receiver, then the expected number of A molecules in \( V_{obs} \), \( \bar{N}_{A,obs}(t) \), is given by multiplying (12) by the receiver volume \( V_{obs} \) and setting \( \bar{r} = \bar{r}_0 \), i.e.,

\[ \bar{N}_{A,obs}(t) \geq \frac{V_{obs} N_A}{(4\pi D_At)^{3/2}} \exp \left( -k_1 C_{EA} t - \frac{|\bar{r}_0|^2}{4D_At} \right), \]

assuming that the transmitter releases the A molecules at \( t = 0 \). It is straightforward to take the derivative of (13) with respect to \( t \) to find the time, \( t_{max} \), at which the maximum number of molecules is expected, found as

\[ t_{max} = \frac{-3 + \sqrt{9 + (4k_1 C_{EA} t_0^2)/D_A}}{4k_1 C_{EA}}, \]

where we only consider non-negative finite time. The maximum number of expected molecules at the receiver, \( N_{A,max} \), is then found by substituting (14) into (13). By comparison, when there are no enzymes present, i.e., \( C_{EA} = 0 \), the maximum number of molecules is expected at time

\[ t_{max} \bigg|_{C_{EA}=0} = \frac{|\bar{r}_0|^2}{6D_A}, \]

and it is straightforward to show that, for all valid (i.e., non-negative) parameter values, \( t_{max} \leq t_{max} \bigg|_{C_{EA}=0} \). So, when enzymes are added, the maximum number of molecules is expected no later than when enzymes are not added.

By inspection of (13), we also observe that, for a given \( t \), we expect to observe fewer A molecules when enzymes are present, i.e., \( \bar{N}_{A,obs}(t) \leq \bar{N}_{A,obs}(t) \bigg|_{C_{EA}=0} \forall t \). Thus, we immediately have that \( \bar{N}_{A,max} \leq \bar{N}_{A,max} \bigg|_{C_{EA}=0} \). In
addition, when enzymes are present, the expected number of molecules will decrease to any value sooner than when enzymes are absent, i.e., ISI must decrease. In order to consider the selection of an appropriate bit interval $T_B$, we are interested in solving for the time required for $N_{A_{obs}}(t)$ to decrease to some threshold value, i.e., find $t_\alpha$ that satisfies

$$\frac{N_{A_{obs}}(t_\alpha)}{N_{A_{max}}} \leq \alpha,$$

(16)

where $0 < \alpha < 1$ is a threshold fraction of the maximum expected number of molecules and $t_\alpha > t_{max}$. There are two issues with solving (16). First, it cannot be strictly satisfied because we only have a lower bound on $\frac{N_{A_{obs}}(t)}{N_{A_{max}}}$; showing that the lower bound is lower than $\alpha N_{A_{max}}$ does not satisfy (16). For now, we assume that (13), the lower bound on $\frac{N_{A_{obs}}(t)}{N_{A_{max}}}$, is sufficiently accurate as we will show in Section VII. Second, an analytical solution using the lower bound is not possible; further bounding will be required to obtain a closed-form expression for $t_\alpha$. Of course, we can solve (16) numerically using (13) without any further bounding by initializing $t_\alpha = t_{max}$ and gradually incrementing $t_\alpha$.

To derive the bound for $t_\alpha$ satisfying (16) where (13) is used for $N_{A_{obs}}(t_\alpha)$, we first note that the exponential portion of (13) decays much slower with $t_\alpha$ than $t_\alpha^{-\frac{2}{3}}$ decays with $t_\alpha$ for the range of values of $t_\alpha$ that we are interested in, so we upper-bound the exponential with its maximum over time. It is easy to show that the exponential term is maximized when $t_\alpha = |r_0^2|/4k_1 C_{E_{tot}}D_A$, so that the exponential term in (13) is upper-bounded by $\exp\left(|r_0^2|\sqrt{k_1 C_{E_{tot}}/D_A}\right)$, \forall $t_\alpha$.

We then solve for $t_\alpha$ and find that

$$t_\alpha \geq \frac{1}{4\pi D_A} \left(\frac{V_{obs} N_A}{\alpha N_{A_{max}}} \right)^{\frac{2}{3}} \exp\left(-\frac{2}{3} |r_0^2| \sqrt{\frac{k_1 C_{E_{tot}}}{D_A}}\right),$$

(17)

satisfies (16). In addition, we can guarantee that $t_\alpha > t_{max}$ because we used the upper-bound on the exponential term. Similarly, for the case without enzymes present, we upper bound the exponential term with 1 and find that

$$t_\alpha \bigg|_{C_{E_{tot}}=0} \geq \frac{1}{4\pi D_A} \left(\frac{V_{obs} N_A}{\alpha N_{A_{max}}|_{C_{E_{tot}}=0}} \right)^{\frac{2}{3}}$$

(18)

satisfies (16). A strict comparison between (17) and (18) is not fair due to the issues previously mentioned. However, these expressions do provide some guidance in the selection of an appropriate bit interval.

B. Error Rate at the Receiver

In our simple detection scheme, the receiver counts the number of free $A$ molecules at time $t_{max}$ after the start of the bit interval and compares that number with decision threshold $\xi$. We assume that there is perfect synchronization between the transmitter and receiver to emphasize the limitations of intersymbol interference. Recalling that $T_B$ is the bit interval time, the decision sampling time for the $j$th bit interval is $(j-1)T_B + t_{max}$.

Let $W[j]$ be the $j$th information bit sent by the transmitter, i.e., sent at the beginning of the $j$th bit interval, and let $Pr(W[j] = 1) = P_t$ and $Pr(W[j] = 0) = P_0 = 1 - P_t$, where $Pr(\cdot)$ denotes probability. Let $\hat{W}[j]$ be the $j$th received bit at the receiver. Thus, the reception mechanism can be written as

$$\hat{W}[j] = \begin{cases} 1 & \text{if } N_{A_{obs}}((j-1)T_B + t_{max}) \geq \xi, \\ 0 & \text{if } N_{A_{obs}}((j-1)T_B + t_{max}) < \xi. \end{cases}$$

(19)

It is clear that an error occurs if $W[j] \neq \hat{W}[j]$, and we define the error probability of the $j$th bit $P_e[j] = Pr(W[j] \neq \hat{W}[j])$. So, we are interested in evaluating $Pr(N_{A_{obs}}((j-1)T_B + t_{max}) \geq \xi)$, a function of the current and all previous emissions by the transmitter. We begin by considering the first bit, i.e., $j = 1$, and then extend the result to any $j$th bit in the transmission. Generally, bits transmitted later will have a higher probability of being detected in error because there are more previous bits to create ISI.

Consider the first bit for the case $W[1] = 1$ (of course, for the case $W[1] = 0$, there are no $A$ molecules anywhere in the system and so there will be none observed at the receiver). The lower bound on the expected number of observed molecules is also a lower bound on the probability density function (PDF) over all time and space for a single molecule if we set $N_A = 1$ and assume that the location and state of any one $A$ molecule is independent of the other $A$ molecules. Therefore, a lower bound on the probability $P_{obs}(t)$ that a given molecule is observed within $V_{obs}$ at time $t$ is found by integrating (12) over $V_{obs}$. We assume that the concentration of molecules within the receiver is uniform and equal to that expected at the center of the receiver. Thus, we write

$$P_{obs}(t) \geq \frac{V_{obs}}{(4\pi D_A t)^{3/2}} \exp\left(-k_1 C_{E_{tot}} t \frac{|r_0|^2}{4D_A t}\right),$$

(20)

and we will assume that (20) is met with equality. Generally, we have $N_A$ molecules, and each molecule is either inside $V_{obs}$ at a given time or outside, so the number of observed molecules follows the binomial distribution. Thus, we can write (25) Ch. 3]

$$Pr(N_{A_{obs}}(t) \geq \xi) = \sum_{w=0}^{N_A} \left(\begin{array}{c} N_A \\ w \end{array}\right) P_{obs}(t)^w (1 - P_{obs}(t))^{N_A-w}.$$  

(21)

Eq. (21) is exact for a given $P_{obs}(t)$ but is difficult to evaluate for large values of $N_A$. However, as noted in (10), we can write (21) in an equivalent form as

$$Pr(N_{A_{obs}}(t) \geq \xi) = I_{P_{obs}}(\xi, N_A - \xi + 1),$$

(22)

where $I_{P_{obs}}(\xi, \cdot)$ is the regularized incomplete beta function based on individual probability $P_{obs}(t)$; see (26) Eq. 8.392). Furthermore, we also note that

$$Pr(N_{A_{obs}}(t) = w) = I_{P_{obs}}(w, N_A - w + 1) - I_{P_{obs}}(w + 1, N_A - w).$$

(23)

Eqs. (22) and (23) can be evaluated numerically but the incomplete beta function does not easily lend itself to optimization. For example, its derivative cannot be written in closed form. We consider two approximations of the binomial distribution. For infinitely large $N_A$ and infinitely small
$P_{obt}(t)$, such that their product is a finite positive number, then the binomial distribution approaches the Poisson distribution with mean $N_AP_{obs}(t)$, and we can write [25, Ch. 3] \[
\Pr(N_{Aobs}(t) = w)_{\text{Poisson}} = \frac{(N_{A}P_{obs}(t))^w}{w!} \exp\left(-N_{A}P_{obs}(t)\right),
\]
and so \[
\Pr(N_{Aobs}(t) \geq \xi)_{\text{Poisson}} = 1 - \exp\left(-N_{A}P_{obs}(t)\right) \times \sum_{w=0}^{\xi-1} \frac{(N_{A}P_{obs}(t))^w}{w!}. \tag{25}
\]

Alternatively, we can approximate the binomial distribution with a Gaussian distribution with mean $N_{A}P_{obs}(t)$ and variance $N_{A}P_{obs}(t)(1 - P_{obs}(t))$. This approximation has been applied by other authors for molecular communication, cf. e.g. [11], [15], and is valid when $P_{obs}(t)$ is not close to one or zero and $N_{A}P_{obs}(t)$ is sufficiently large. Generally, this approximation will not be as accurate as using the Poisson distribution because we will tend to have very small values for $P_{obs}(t)$. We still consider the Gaussian distribution because it does not include any factorials and so can be more computationally efficient than the Poisson distribution. The Gaussian approximation enables us to write \[
\Pr(N_{Aobs}(t) = w)_{\text{Gauss}} = \frac{\exp\left(\frac{(w - N_{A}P_{obs}(t))^2}{2N_{A}P_{obs}(t)(1-P_{obs}(t))}\right)}{\sqrt{2\pi N_{A}P_{obs}(t)(1-P_{obs}(t))}}, \tag{26}
\]
and by using the error function [27, p. 406] we can show that \[
\Pr(N_{Aobs}(t) \geq \xi)_{\text{Gauss}} = \frac{1}{2} \left[1 - \text{erf}\left(\frac{\xi - N_{A}P_{obs}(t)}{\sqrt{2N_{A}P_{obs}(t)(1-P_{obs}(t))}}\right)\right]. \tag{27}
\]

To evaluate the error probability for the first bit, we use either of (26), (25), or (27). As noted, an error in $W[1]$ is possible only when $W[1] = 1$. Thus, the probability of error in the first bit is \[
P_e[1] = P_t[1 - \Pr(N_{Aobs}(t_{max}) \geq \xi)]. \tag{28}
\]

The probability of error of the $j$th bit is a function of all of the first $j$ bits, since $A$ molecules can remain in the propagation environment from any of the previous emissions by the transmitter. The common practice when deriving error rates in the molecular communication literature is to assume that information molecules remain in the environment for no more than two transmission intervals, cf. e.g. [9]–[13]. We will not begin with this assumption in order to present the general bit error expression, which has not yet been developed in the literature. However, we will assume that the number of $A$ molecules, observed at some time $t$, that were emitted at the start of the $j$th bit interval, are independent of the number of molecules, also observed at that time $t$, that were emitted at the start of any other bit interval. We note that this is not strictly true because an $E$ molecule that is bound to an $A$ molecule is temporarily unavailable to bind to the $A$ molecules of other transmissions (the mean time of unavailability is set by the value of $k_2$). We write the expected number of molecules observed at the receiver at time $t$ as \[
N_{Aobs}(t) = N_A \sum_{j=1}^{\left\lfloor \frac{t}{TB} \right\rfloor} W[j] P_{obs}(t - (j - 1)TB). \tag{29}
\]

We emphasize that any molecule observed within $V_{obs}$ could have been emitted during the current or any previous bit interval. We define $N_{Aobs}[j] = N_{Aobs}(j - 1)TB + T_{max}$, i.e., all $A$ molecules observed at the optimal time in the $j$th bit interval. We define $N_{Aobs}[j; i; 1], 1 \leq i \leq j$, as the number of molecules that had been originally emitted by the transmitter in only the $i$th bit interval, i.e., at time $t = (i - 1)TB$, and then observed by the receiver at the optimal time in the $j$th bit interval. Furthermore, we define $N_{Aobs}[j; i; 1], 1 \leq i \leq j$, as the number of molecules that had been emitted by the transmitter in all of the first $i$ bit intervals and then observed in the $j$th bit interval, such that \[
\sum_{n=1}^{i} N_{Aobs}[j; n; 1] = N_{Aobs}[j; i], \quad \tag{30}
\]
and $N_{Aobs}[j; j] = N_{Aobs}[j]$. \[
\Pr(N_{Aobs}[j; i; 1] = w) \quad \text{can be evaluated from (26), (25), or (27), where } t = (j - i)TB + T_{max}. \]

Analogously, $\Pr(N_{Aobs}[j; i; 1] \geq \xi)$ can be evaluated from (25), (26), or (27). It is easy to see that $\Pr(N_{Aobs}[j; i; 1] \geq 1) = 1, \forall i, j$, and if $W[i] = 0$, then $\Pr(N_{Aobs}[j; i; 1] \geq 0) = 0, \forall j$. Of course, any observed molecule is more likely to have been emitted at the beginning of more recent bit intervals. We propose a recursive form for evaluating $P_e[j]$ that reflects this. First, we claim that \[
\Pr(N_{Aobs}[j; i] \geq \xi) = P_t[1 - \Pr(N_{Aobs}(t_{max}) \geq \xi)] + \sum_{w=1}^{\xi} \Pr(N_{Aobs}[j; i; 1] = \xi - w) \times \Pr(N_{Aobs}[j; i - 1] \geq w), \tag{31}
\]
where we initialize the left-hand side with $N_{Aobs}[j; j] = N_{Aobs}[j]$. Eq. (31) says that molecules observed in the $j$th bit interval that were emitted within the first $i$ bit intervals were either all emitted in the $i$th bit interval or some of the molecules were emitted in the $i$th bit interval and the rest were emitted in the first $i - 1$ intervals. The complete recursion would stop when $i = 1$, since no molecules could have been emitted before the first bit interval. In practice, we can stop the recursion when $\Pr(N_{Aobs}[j; i; 1] \geq 1)$ becomes sufficiently small such that it is extremely unlikely that we will be observing molecules emitted in the $i$th bit interval or earlier. In practice, we will stop recursion when $\Pr(N_{Aobs}[j; i; 1] \geq 1) < 10^{-8}$ or once a specified number of recursions have taken place (whichever occurs first).

Eq. (31) uses no knowledge of $W[i], i \leq j$, but $P_e[j]$ can be evaluated either with or without the a priori knowledge of $W[i]$. If we do not use the a priori knowledge of $W[i]$, then $P_e[j]$ is averaged over every possible permutation of $W[i]$. We consider this case first and write \[
P_e[j] = P_t[\Pr(N_{Aobs}[j] < \xi | W[j] = 1, W[i], i < j) + P_0 \Pr(N_{Aobs}[j] \geq \xi | W[j] = 0, W[i], i < j), \tag{32}
\]
We emphasize that we stop the recursive evaluation of \((36)\) when \(\Pr (N_{A_{obs}} [j; i] \geq 1) < 10^{-8}\) or once a specified number of recursions have taken place.

The common practices in the literature of either ignoring ISI or only considering the interference caused by emission in the previous bit interval, e.g. \([9] - [11], [13]\), can both be evaluated as special cases of \((32)\) by limiting the recursion. Specifically, we set \(\Pr (N_{A_{obs}} [j, i] \geq 1 | i < j) = 0\) to ignore ISI and set \(\Pr (N_{A_{obs}} [j, i] \geq 1 | i < j - 1) = 0\) to only consider ISI from the previous bit interval.

**V. Simulation Framework**

This section describes the framework used to perform stochastic simulations of the system of equations described by \((8) - (10)\).

**A. Choice of Framework**

Our simulation framework uses a particle-based method, where the precise locations of all individual molecules are known. Every free molecule diffuses independently along each dimension. Such methods require a constant global time step \(\Delta t\) and there is a separation in the simulation of reaction and diffusion; see \([28]\). First, all free molecules are independently diffused along each dimension by generating normal random variables with variance \(2D_{w} \Delta t\). Next, potential reactions are evaluated to see whether they would have occurred during \(\Delta t\). For bimolecular reactions, a binding radius \(r_{B}\) is defined as how close the centers of two reactant molecules need to be at the end of \(\Delta t\) in order to assume that the two molecules collided and bound during \(\Delta t\). For unimolecular reactions, a random number is generated using the rate constant to declare whether the reaction occurred during \(\Delta t\).

Particle-based methods tend to be less computationally efficient than subvolume-based methods, but they do not have to meet the latter’s well-stirred requirement, where every subvolume should have many more nonreactive molecule collisions than reactive collisions, as described in \([29], [30]\). A general criterion for subvolume size is that the typical diffusion time for each species should be much less than the typical reaction time; see \([31]\). In order to satisfy this criterion, we would need to use very small subvolume sizes relative to the total size of the environment under consideration. If we used such small subvolumes, then we would not gain in computational efficiency and, for small (nanoscale) environments, the subvolume size would not be much greater than the size of individual molecules. Thus, we proceed with a particle-based method.

**B. Simulating Reactions**

The bimolecular reaction \((11)\) (the binding of \(E\) and \(A\) to form \(EA\)) is reversible, so we must be careful in our choice of binding radius \(r_{B}\), time step \(\Delta t\), and what we assume when \(EA\) reverts back to \(E\) and \(A\) molecules. A relevant metric is the root mean square step length, \(r_{rms}\), between \(E\) and \(A\) molecules, given as \([28], \text{Eq. 23}\)

\[
r_{rms} = \sqrt{2 (D_{A} + D_{E}) \Delta t}.
\]  

**TABLE I**

**WORKFLOW FOR THE EVALUATION OF \(P_{c} [j]\) AS GIVEN BY \((32)\).**

| Eqn. | Solve As |
|------|----------|
| \((32)\) | \[
P_{i} (1 - \xi) + P_{0} \xi, \text{if } W [j] \text{ unknown}
1 - \xi, \text{if } W [j] = 1
\xi, \text{if } W [j] = 0
\]
| \((33)\) | Evaluate \((36)\) using \(i - 1\) as \(i\) for every conditional probability in \(\sum_{w=1}^{\xi}\), evaluate \((36)\) using \(i - 1\) as \(i\) |
| \((34)\) | \[
P_{i} \xi + P_{0} (1 - \xi), \text{if } W [i] \text{ unknown}
\xi, \text{if } W [i] = 1
\xi, \text{if } W [i] = 0
\]

where

\[\Pr (N_{A_{obs}} [j, i] < \xi | W [j] = 1, W [i], i < j) = 1 - \Pr (N_{A_{obs}} [j, i] \geq \xi | W [j] = 1, W [i], i < j).\] (33)

We see that \((32)\) branches into two terms according to the possible values of \(W [j]\). Each of these two terms branches into recursive summations according to the possible values of \(W [i], i < j\). Specifically, from \((31)\) we have

\[\Pr (N_{A_{obs}} [j, i] \geq \xi | W [i] = 0, W [n], n < i) = \Pr (N_{A_{obs}} [j; i - 1] \geq \xi | W [n], n < i),\] (34)

and

\[\Pr (N_{A_{obs}} [j, i] \geq \xi | W [i] = 1, W [n], n < i) = \Pr (N_{A_{obs}} [j; i - 1] \geq \xi) + \sum_{w=1}^{\xi} \Pr (N_{A_{obs}} [j; i - 1] = \xi - w) \times \Pr (N_{A_{obs}} [j; i - 1] \geq w | W [n], n < i),\] (35)

where each recursive term in \((34)\) and \((35)\) branches as

\[\Pr (N_{A_{obs}} [j, i] \geq \xi | W [1], \ldots, W [i]) = P_{i} \Pr (N_{A_{obs}} [j, i] \geq \xi | W [i] = 1, W [n], n < i) + P_{0} \Pr (N_{A_{obs}} [j, i] \geq \xi | W [i] = 0, W [n], n < i).\] (36)

Thus, the conditional probabilities in \((34)\) and \((35)\) refer to molecules emitted in prior bit intervals \((i - 1 < j)\) and are evaluated using \((36)\), whereas \((36)\) is evaluated for the \(i\)th interval using \((34)\) and \((35)\). If we do have a priori knowledge of \(W [i]\), then we know \(P_{i}, P_{0}, \forall i\) is either 0 or 1 and we only take one term from each branch in \((32)\) and \((36)\). Thus, the complete evaluation of \(P_{c} [j]\), where we recurse back to \(W [1]\), is much faster when using a priori knowledge of \(W [i]\). A summary of the recursive evaluation of \(P_{c} [j]\) with or without a priori knowledge is presented in Table I.
If reaction (2) occurs, then the root mean square separation of the product molecules \( A \) and \( E \) along each dimension is \( r_{rms} \). Unless \( r_{rms} \gg r_B \), then these two reactants will likely undergo reaction (1) in the next time step. Generally, we need to define an unbinding radius that specifies the initial separation of the \( A \) and \( E \) molecules when reaction (2) occurs. However, in the long time step limit, we can define \( r_B \) as

\[
r_B = \left( \frac{3k_B \Delta t}{4\pi} \right)^{\frac{1}{2}}, \quad (38)
\]

and this is valid only when \( r_{rms} \gg r_B \). Thus, if \( r_{rms} \) is much greater than \( r_B \) as found by \( 38 \), which we can impose by our selection of \( k_1 \) and \( \Delta t \), then we do not need to implement an unbinding radius. We will select parameters so that \( r_{rms} \gg r_B \) is satisfied, so we simply use \( 38 \). If we find a pair of \( A \) and \( E \) molecules that are close enough, then we move both of them to the midpoint of the line between their centers and re-label them as a single \( EA \) molecule.

The two unimolecular reactions have the same reactant, \( EA \), so we must consider both of them when calculating the probability of either reaction occuring. For (2), we have \( 28 \) Eq. 14

\[
Pr(\text{Reaction } 2) = \frac{k_{-1}}{k_{-1} + k_2} \left[ 1 - \exp \left( -\Delta t \left( k_{-1} + k_2 \right) \right) \right], \quad (39)
\]

where \( 3 \) has an analogous expression by switching \( k_{-1} \) and \( k_2 \). A single random number uniformly distributed between 0 and 1 can then be used to determine whether a given \( EA \) molecule reacts, and, if so, which reaction occurs. If the reaction occurs, then we place the products at the same coordinates as the reactant \( EA \) molecule.

C. Simulating the Transmitter and Receiver

We simulate emissions at the transmitter by initializing \( N_A \) \( A \) molecules centered at the origin and with a separation of \( 2R_A \) between adjacent molecules so that together they form a spherical shape. The receiver can make observations only at integer multiples of time step \( \Delta t \), so for detection we round \( t_{max} \) to the nearest multiple of \( \Delta t \). When an observation is made, all free \( A \) molecules whose centers are within \( V_{obs} \) are counted.

D. Selecting Component Parameters

Most enzymes are proteins and are usually on the order of less than 10 nm in diameter; see \( 4 \) Ch. 4. From \( 4 \), smaller molecules diffuse faster, so we favor small molecules as information molecules. Many common small organic molecules, such as glucose, amino acids, and nucleotides, are about 1 nm in diameter. In the limit, single covalent bonds between two atoms are about 0.15 nm long; see \( 4 \) Ch. 2.

Higher rate constants imply faster reactions. Bimolecular rate constants can be no greater than the collision frequency between the two reactants, i.e., every collision results in a reaction. The largest possible value of \( k_1 \) is on the order of \( 1.66 \times 10^{-19} \text{moleculer}^{-1}\text{m}^{-3}\text{s}^{-1} \); see \( 19 \) Ch. 10] where the limiting rate is listed as on the order of \( 10^8 \text{L/mol/s} \). \( k_2 \) usually varies between 1 and \( 10^5 \text{s}^{-1} \), with values as high as \( 10^7 \text{s}^{-1} \). In theory, we are not entirely limited to pre-existing enzyme-substrate pairs; protein and ribozyme engineering techniques can be used to modify and optimize the enzyme reaction rate, specificity, or thermal stability, or modify enzyme function in the presence of solvents; see \( 4 \) Ch. 10.

VI. Numerical and Simulation Results

We present simulation results based on the analysis that we have performed in this paper. We assume that the environment has a viscosity of \( 10^{-3} \text{kg} \cdot \text{m}^{-1}\text{s}^{-1} \) and temperature of 25 °C. We compare three sets of system parameters, as described in Table II. System 3 is identical to System 1 except for a larger value of \( N_A \). \( N_E \) is chosen so that the enzyme concentration in all systems is equivalent to 166 \( \mu \text{M} \), which is high for a cellular enzyme; see \( 12 \). In comparison to the limiting values of reaction rate constants \( k_1 \) and \( k_2 \) discussed in the previous section, the reaction rate constants for Systems 1 and 3 are relatively high. The numbers of molecules \( N_A \) and the size of the environments of Systems 1 and 2 are kept deliberately low in order to ease computation time.

A. Accuracy of Expected Number of Molecules

In Fig. 2, we compare the observed number of molecules for Systems 1 and 2 due to a single transmission. The observed number of \( A \) molecules via simulation is averaged over at least 6000 independent emissions by the transmitter at \( t = 0 \). We measure the number of information molecules observed over time, in comparison to the lower bound expression \( 13 \) and the expected number without enzymes in the environment as given by \( 13 \) for \( C_{Enz} = 0 \).

We clearly see in Fig. 2 that the receivers in Systems 1 and 2 have the same lower bound on \( N_{Aobs} (t) \), the expected number of observed information molecules, when we account for System 2’s longer diffusion time as its receiver is placed further away. The simulated number of observed molecules of both systems over time is close to the derived lower bound.

---

| Parameter | System 1 | System 2 | System 3 |
|-----------|-----------|-----------|-----------|
| \( V_{enr} \) \( \mu\text{m}^3 \) | 1 | 37 | 1 |
| \( N_A \) | \( 5 \times 10^3 \) | \( 5 \times 10^3 \) | \( 2 \times 10^4 \) |
| \( N_{Enz} \) | \( 10^5 \) | \( 3.7 \times 10^6 \) | \( 10^6 \) |
| \( k_1 \) \( \text{molecule}^{-1}\text{s}^{-1} \) | \( 2 \times 10^{-19} \) | \( 1.79 \times 10^{-20} \) | \( 2 \times 10^{-19} \) |
| \( k_{-1} \) \( \text{s}^{-1} \) | \( 10^4 \) | \( 900 \) | \( 10^4 \) |
| \( k_2 \) \( \text{s}^{-1} \) | \( 10^6 \) | \( 9 \times 10^4 \) | \( 10^6 \) |
| \( |\vec{r}_0| \) \( \text{nm} \) | 300 | 1000 | 300 |
| \( |\vec{r}_{obs}| \) \( \text{nm} \) | 45 | 150 | 45 |
| \( R_A \) \( \text{nm} \) | 0.5 | 0.5 | 0.5 |
| \( R_E \) \( \text{nm} \) | 2.5 | 2.5 | 2.5 |
| \( R_{EA} \) \( \text{nm} \) | 3 | 3 | 3 |
| \( \Delta t \) \( \mu\text{s} \) | 0.5 | 5 | 0.5 |
reactivity and the number of molecules) on the accuracy of the effect of the environmental parameters (including chemical expression than that for System 1. We leave further study of the maximum number of expected molecules for System 2 is visibly closer to the analytical lower bound expression for future work.

For most of the remaining results, we focus on System 1 because it has a less accurate lower bound on the expected number of observed molecules and also because it has overall fewer molecules in the system so that its simulations can be executed more efficiently.

B. Selection of Bit Interval

From (14) and (15) (or by observation of Fig. 2), we calculate that the maximum number of expected molecules for System 1 should be observed at times $t_{max} = 25.68 \mu s$ and $t_{max}|_{C_{Enzyme}=0} = 34.36 \mu s$ with and without active enzymes, respectively. At these times, the expected number of observed molecules is $N_{A_{max}} = 2.92$ and $N_{A_{max}|_{C_{Enzyme}=0}} = 5.20$, respectively. We are interested in solving (16) to get a sense of how long we should wait after an emission from the transmitter before sending another bit.

In Fig. 2, we solve (16) for the cases of enzymes present and absent by using upper bounds (17) and (18), respectively. We also solve (16) numerically. We see that the bound (17), for enzymes present, is quite accurate if the fraction of molecules expected at the end of the interval is between 30% and 80% of the expected maximum (representing between 1 and 2.3 molecules expected on average), whereas the bound (18), for enzymes absent, improves with time as fewer molecules are expected.

Whether comparing the bounds or the numerical solutions, Fig. 3 shows that the transmitter can emit much more frequently with less risk of ISI if enzymes are present. For example, we may desire to have no more than 30% of $N_{A_{max}}$ within the receiver at the end of the bit interval. Using the numerical solution, we see that we would need to wait about 170 $\mu s$ if there were no enzymes present, but only about 70 $\mu s$ with enzymes present. This result suggests that we can increase the data rate by about 150% with a comparable level of relative ISI. For lower levels of ISI, the numerical solutions suggest even higher increases in data transmission. We emphasize that solving (16) is insufficient in evaluating the ISI for a given set of system parameters, but it allows us to get a sense of what an appropriate $T_B$ might be.

C. Detection Probability of One Bit Interval

Before we consider the bit error rate over a lengthy data transmission, we consider the detection probability for the first emission by the transmitter. This enables us to focus on evaluating the accuracy of our expressions derived for the probability of the observed number of molecules being equal to or above some threshold; namely, we consider the binomial distribution (21), which is exact for a given $P_{obs}(t)$ (recall that we have (20), a lower bound on $P_{obs}(t)$), with the Poisson and Gaussian approximations (25) and (27), respectively. We evaluate the detection probabilities at time $t_{max} \approx 25.5 \mu s$ since we have to make observations at multiples of $\Delta t$, and we compare with the number of $A$ molecules observed via simulation as averaged over 6000 independent emissions by the transmitter at $t = 0$. The results are presented in Fig. 4 for $1 \leq \xi \leq 5$.

In Fig. 4 we see that the detection probability can be kept above 0.5 for $\xi \leq 3$, which we expect since $N_{A_{max}} = 2.92$.
The binomial distribution based on $P_{obs}(t)$ from (20) returns detection probabilities that are comparable to those found via simulation; for $\xi = 2$, the detection probability found via simulation and via the binomial distribution are both about 0.8. We also see that the Poisson approximation is indistinguishable from the binomial distribution, whereas the Gaussian approximation has a notable loss in accuracy.

**D. Bit Error Rate of Multiple Intervals**

We now assess the bit error probability for System 1 transmitting multiple bits by comparing the recursive evaluation of (32) with simulation results. We choose the Poisson approximation for evaluating the expected $P_e[j]$ because of its high accuracy to the binomial distribution for System 1. We also select either $T_B = 50 \mu s$ or $T_B = 120 \mu s$. For $T_B = 120 \mu s$, we see from Fig. 3 that the expected number of molecules at the end of a bit interval due to a single emission of molecules is less than 20% of the maximum when enzymes are present but more than 40% of the maximum when there are no enzymes. For $T_B = 50 \mu s$, the expected ISI is even higher.

First, we consider a known data sequence in order to compare the accuracy of missed detection (incorrectly detecting a 1 instead of a 0) versus false alarm (incorrectly detecting a 0 instead of a 1). The transmitter emits molecules according to a sequence of five consecutive 1s followed by five consecutive 0s. In Fig. 5 we track the receiver error probability $P_e[j]$ over time for $T_B = 120 \mu s$, where the simulation results are averaged over 35000 independent transmissions. Receiver errors within the first five bit intervals are missed detections, whereas errors within the last five bit intervals are false alarms.

We evaluate the error probability using only knowledge of the current bit (no recursion), using knowledge of the current and previous bits (one level of recursion), and using knowledge of the current and all previous bits (up to nine). We set decision threshold $\xi = 1$ as we will later see that it is the optimal threshold for System 1 when $T_B = 120 \mu s$.

In Fig. 5 we see via both simulation and evaluation of (32) that the error probability reaches a floor on missed detection with repeated 1s and tends to zero on false alarm with repeated 0s, which is an intuitive result. Note that, when the transmitted bit changes at interval 6, the error probability assuming no ISI immediately drops to zero whereas all other results spike showing a high probability of false alarm when a 0 is transmitted after a 1. The error probability using knowledge of only the current and previous bits drops to zero by interval 7, even though the error measured via simulation and evaluated by considering the current and all previous bits shows a non-negligible error probability of about 1%. All evaluations of (32) appear to over-estimate missed detection and under-estimate false alarm; this makes sense since the underlying probability of observing an information molecule is a lower bound. Thus, the accuracy of the expected error probability, even when considering all previous bits, becomes quite poor when consecutive zeros are transmitted. However, we will next see that this does not have a noticeable effect on the average bit error probability for a random transmission in System 1.

We now assess the mean receiver error probability, $\overline{P}_e$, as a function of the bit decision threshold where we generate a long random source transmission (50 bits). We assume no a priori knowledge of the transmitted data when calculating the expected error probability $P_e[j]$ from (32), and $\overline{P}_e$ is evaluated by averaging $P_e[j]$ over all $j$. The results are presented in Fig. 6 for $T_B = 50 \mu s$ and $T_B = 120 \mu s$ where we set $P_1 = P_0 = 0.5$. We also consider $T_B = 120 \mu s$ when there are no enzymes present. We use the current and seven previous bit intervals when evaluating (32) with enzymes, and up to nine previous bit intervals when evaluating (32) without enzymes. Simulation results are averaged over 6000 independent transmissions.

We see that in Fig. 6 the optimal decision threshold for System 1 and $T_B = 120 \mu s$ is $\xi = 1$ with enzymes and $\xi = 5$ without enzymes, whereas the optimal threshold when $T_B = 50 \mu s$ is $\xi = 2$. These differences make intuitive sense; when the bit interval is shorter or enzymes are not present, there is more ISI from previous bits such that a lower decision threshold can result in many more false alarms. The
minimum error probability is much lower for $T_B = 120 \, \mu s$ with enzymes; just over 0.05 versus over 0.12 for $T_B = 120 \, \mu s$ without enzymes and for $T_B = 50 \, \mu s$.

The difference in Fig. 6 between the curve generated via simulation and the error expected by the evaluation of (32) for the case of $T_B = 120 \, \mu s$ without enzymes is because nine previous intervals is still insufficient for accurately evaluating (32) in this case. We do not evaluate more previous intervals because the evaluation time grows with decision threshold $\xi$ and with the number of previous intervals. However, the error expected by the evaluation of (32) with enzymes is much more accurate than what we might expect from Fig. 5 alone; a long sequence of consecutive zeros is unlikely in a random transmission, and the slight over-estimation of missed detection is on average balanced by the under-estimation of false alarm. The primary observation in Fig. 6 is that, by adding enzymes, the data transmission rate can be significantly increased (more than doubled here) while maintaining the same expected error probability, or the error probability can be improved significantly for the same data transmission rate.

Finally, we note that the error probabilities presented in this section are not very low in the context of information transmission. By deliberately selecting a system with a low number of molecules, we were limited by a low expected maximum number of information molecules $N_{A_{max}}$. For contrast, we consider System 3, for which we can expect $N_{A_{max}} = 11.69$ molecules to be observed at $t_{max} = 25.68 \, \mu s$ when there is a single emission. We evaluate the average error probability $P_e$ when the transmitter in System 3 emits a stream of 50 bits with $T_B = 120 \, \mu s$. We use the current and one previous bit interval when evaluating (32), because for this system the expected error probability does not significantly improve by adding more bits. The results are plotted in Fig. 7 where we see that for the optimal threshold $\xi = 4$, the expected error probability is about $1.5 \times 10^{-3}$, much less than those observed for System 1, and the observed error probability is about $10^{-5}$. The larger deviation between expected and simulated results for System 3 relative to System 1 is because the lower bound expression on the PDF (20) is not as tight for System 3; the over-estimation of missed detection and the under-estimation of false alarm are more evident for System 3 than they are for System 1 as shown in Fig. 6. We reiterate that further study on the effect of environmental parameters on the accuracy of the analytical lower expression is left for future work.

VII. CONCLUSIONS AND FUTURE WORK

In this paper, we expanded upon the physical system model that we developed in [1] for transmitter impulses of molecules being released into a propagation environment that contains diffusing enzymes. We derived a lower bound expression on the expected number of information molecules at the receiver. We showed how the expected signal degradation can be used to predict an appropriate bit interval length. We then derived the expected error rate for a simple receiver scheme as a recursive function of the current and all previous emissions. Our results showed that the expected probability of error can be accurately represented by the Poisson approximation and agrees with the error probabilities observed via simulation. The accuracy of the bit error probability can be improved to some maximum by increasing the number of previous bits that are included in the recursive error probability evaluation.

Our on-going work includes dimensional analysis to show the scalability of our model and to generalize the accuracy of the lower bound expression on the expected number of information molecules. We are also performing the formal development of a tractable optimization problem to find the bit decision threshold that minimizes the bit error probability for a given data rate or maximizes the data rate for a given bit error probability. More robust detection schemes for the receiver are being considered, such as an adaptive decision threshold.

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