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Analysis and Design of Two-Hop Diffusion-Based Molecular Communication With Ligand Receptors

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ABSTRACT This work presents a performance analysis of a decode-and-forward (DF) relay-assisted diffusion-based molecular communication system consisting of one nanotransmitter, one nanoreceiver and one nanotransceiver acting as relay. We consider cases using one molecule in our two-hop relay network (1M2H), and using two molecules (2M2H). Inspired by the biological signal transduction systems, the ligand-receptor binding mechanism is introduced for the receptors on the surface of receiver. Inter-symbol interference (ISI) and self-interference (SI) can be identified as the performance-limiting effects in our relaying network. The number of received molecules can be approximated by the normal distribution, and using this approximation, a closed-form expression of bit error probability for the relay-assisted network is derived. Then, we put forward an optimization problem for minimizing the bit error probability, and solve it using an algorithm based on the gradient descent to find the optimal detection threshold. In addition, the expression of channel capacity is obtained for two-hop molecular communication with ligand receptors. Numerical results show that the 2M2H network has greater capacity than the 1M2H network.

INDEX TERMS Two-hop network, ligand-receptor, bit error probability, gradient descent, self-interference.

I. INTRODUCTION

Molecular communication (MC), a biologically-inspired technique in which information is transferred via molecules, is an emerging technique for communication among so-called nanomachines in a nanonetwork. Due to the potential advantages of MC, which include biocompatibility and energy efficiency, it is a preferred communication option for wireless body area networks among nanomachines. Hence, it is a key to enabling applications in areas such as biological engineering, medicine, industry, and environment [1], [2].

Inspired by the communication mechanism used by living cells, several different MC architectures can be used for information exchange, including the transport of molecules by molecular motors [3] and self-propelled microorganisms [4], as well as molecular communication via diffusion (MCvD) [5]. MCvD systems are the primary form for communication in cell biology and have been widely studied by

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scholars. Common examples include the diffusion of calcium ions for cellular signalling among cells, neurotransmission between adjacent neurons, and pheromonal communication which triggers a social response among members of the same species. Because of Brownian diffusion, some of the messenger molecules may not reach the receiver in the current symbol interval, and instead may interfere with the subsequent transmission of molecules, which will cause *inter-symbol interference* (ISI) [6]. That is, these residual molecules can interfere with the current signal, which leads to signal detection error. In addition, when the receiver does not know whether the messenger molecules are from a given transmitter or from other sources with the same type of molecules, *multi-source interference* (MSI) will occur.

In diffusion-based MC systems, the propagation time is proportional to the square of the distance. If the transmission distance is far, then the communication process may fail. Relaying is a good option to improve the reliability and performance of these networks. Relay networks in which the relay node both receives and emits the same type of

molecules may suffer *self-interference* (SI) [7]. The authors in [8] consider two ways to mitigate self-interference. One is for the relay node to use an adjustable decision threshold, while the other is to adopt a half-duplex relaying scheme.

A. RELATED WORK

Signal transduction is the most common molecular communication system in biological cell. Using signal transduction, an extracellular signaling molecule collides a particular receptor on the surface of cell [9]. Living cells communicate with one another through such *signal transduction networks* [10], [11]. The cells can perceive and react to chemical stimuli in the biochemical systems [12]. There are many examples in biology, e.g., calcium signaling transduction in the postsynaptic spines [13], migratory cells locating pathogens [14], and guiding growth cones during neuronal growth [15].

Signal transduction networks, and other biological communication systems, often exploit relaying to ensure information is successfully conveyed to distant receivers. For example, the release of calcium from one cell can lead to a wave of calcium emissions from neighbouring cells [16], [17]. Several papers have extensively studied the bacteria relaying mechanism in both fields of biological physics and cell biology [18]. Chemotaxis performs a mechanical relaying function by picking up plasmids as information molecules and transmitting them to the receiver [19]. In [4], flagellated bacteria are used for transporting DNA encoded in a nanonetwork architecture, which reveals the relaying process of molecular communication with bacteria [20].

Cooperative protocols are usually divided into three main categories: decode-and-forward (DF), amplify-and-forward (AF), and compress-and-forward (CF) [21], [22]. In DF schemes, the relay node decodes molecules released from the source node, re-encodes, and emits the molecules to the destination node. Since DF relaying can avoid the influence of ISI and noise on the subsequent sequence, DF relaying achieves better performance than AF relaying. Several works in the existing literature model relay-assisted MC system and analyze the network performance. In [23], the expression of average error probability for a relay-assisted MC network is derived, and mitigation techniques for the SI (due to the same type of molecules is detection and emission at the relay) are proposed. The authors in [24], [25] consider a repeater cells with calcium junction channels; calcium ions are used as signal molecules for transmission, amplification and absorption. In [26], a relay-assisted network with an M-ary modulation scheme is considered, where these nodes are made up of a group of biological agents. This work also confirms that the optimal combination of relaying schemes can significantly improve the network reliability. The authors in [27] derive the error probability of two-hop MC network with DF relaying. In particular, the time-varying molecular concentrations are affected by ISI and noise. Further, in [28], [29], the proposed multi-hop MC nanonetworks consider bacteria and virus particles as symbol carriers. These papers also study the

biological characteristics of bacteria and viruses. In [30], the authors investigate a relay-assisted MC network inside a blood vessel of a human body, and also propose an optimization problem to minimize the BER by considering the algorithm of bisection. Considering the ISI, SI, and counting errors in [31], multi-hop MC systems are analyzed, while the optimal decision rules are obtained by utilizing a likelihood ratio test (LRT). In our own previous work [32], we propose a relay-assisted MC system that uses a ligand-receptor binding mechanism, called the relay BIND channel. The BIND channel is a discrete time, two state Markov channel, which represents the signal reception at the receiver.

The current research on relay-assisted cooperative MC can be divided into two aspects. The first aspect mainly focuses on the engineering perspective, such as exploring special applications of MC. Based on communication theory and statistical tools, [23], [27], [30], [31] propose a relay network model, then analyze the performance of the network, and derive ideal mathematical formulas. However, these research often ignore the biological mechanism of the system. The second kind of research focuses on the biological mechanism of MC, such as ligand-receptor systems, bacterial migration and conjugation, chemotactic signalling systems, and neuronal signalling. In [24]–[26], [28], [29], the authors focus on the communication mechanism between biological cells through a network of biochemical interactions. The biochemical systems allow individual cells to perceive, evaluate and react to chemical stimuli. However, these works tend to lack complete mathematical analysis.

B. CONTRIBUTIONS

In this paper, we study the combination of biology and engineering. First, we introduce the biological fundamentals of signal transduction. Second, we analyze the system performance in detail based on the proposed relay-assisted network. Finally, we present an optimization threshold to achieve better network performance. The main contributions of this paper are as follows:

- 1) We model the reception of molecules as a ligand-receptor binding mechanism, which considers all possible noise sources in the two-hop MC system.
- 2) We derive a closed-form analytical expression for the expected error probability of the DF relay-assisted diffusion-based MC system, in which we consider two cases: Two-Molecule Two-Hop (2M2H) network and Single-Molecule Two-Hop (1M2H) network.
- 3) In order to minimize the bit error probability, we propose an optimization problem and utilize the algorithm of gradient descent to solve the joint optimal detection threshold. This method is used to select the most suitable detection threshold with the given system parameters.
- 4) Based on these results, we evaluate the channel capacity of our proposed relay-assisted MC network with ligand receptors.

The rest of this paper is organized as follows. In Section II, we describe the biological fundamentals, system model and

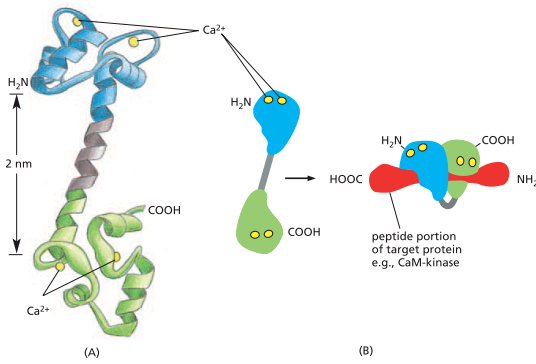


FIGURE 1. Calmodulin and the shape-changing of the calmodulin protein with calcium binding. (A) Calmodulin has a dumbbell shape with two globular domains connected by a flexible helix, there are two Ca^{2+} binding domains at each region. (B) The structure of the conformational changes when Ca^{2+} /calmodulin binds to an isolated fragment of the protein [9].

preliminaries. In Section III we derive the expected error probability of the 2M2H network. In Section IV we derive the expected error probability of the 1M2H network. In Section V we establish the optimization problems of the relay-assisted MC network. In Section VI we give the analysis of channel capacity. In Section VII we show numerical results. Finally, the conclusion is given in section VIII.

II. SYSTEM MODEL

A. BIOLOGICAL FUNDAMENTALS

Our relaying scheme is inspired by cooperation in biological signal transduction systems. We use calmodulin (CaM), a calcium-sensitive receptor with multiple cooperative binding sites, as a motivating example.

Calcium ions are often used as a signal through which stimuli evoke cellular responses. Calcium, a diffusible second messenger, involve in intracellular signaling system. Many kinds of proteins are sensitive to calcium levels inside and outside cells. CaM is the most widely distributed and the most versatile member of a family of calcium-binding proteins which serve as receptors and signal transducers for the Ca^{2+} signal. CaM plays a key role in a number of diverse physiological process such as cell division, inflammation, contraction, fertilization, neurotransmission, immune response, and metabolism [33].

CaM is a small dumbbell-shaped protein. The protein has two symmetrical globular domains connected by a flexible linker region (helix). Each domain contains a pair of EF hand motifs (the N- and C- domain), and each hand motif can sense intracellular calcium levels by binding a Ca^{2+} ion. When Ca^{2+} binds to CaM, the protein undergoes a conformational change that allow it to interact with multiple target proteins in the cell, see Figure 1 [9].

CaM plays an important role in the physiological process of animals and plants. To stimulate smooth muscle contraction, the front end of the myosin light chain (MLC) should be phosphorylated. CaM can activate the MLC kinase when it is bound to calcium, and causes smooth muscle contraction

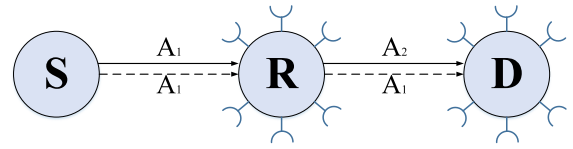


FIGURE 2. System model of a two-hop MC network with ligand receptors. 2M2H and 1M2H schemes are showed with solid and dashed arrows, respectively.

when calcium ions are present, through the activation of MLC kinase and the binding of CaM. CaM also plays a fundamental role in plant development and growth, and the reproductive development of plants can be controlled by CaM binding proteins. For example, the CaM-binding protein kinase plays a role as a negative regulator of flowering in tobacco. The shoot apical meristem in tobacco also contains the CaM-binding protein kinase. For the plant, a large amount of kinases in the meristem leads to a delayed transition to flowering.

B. SYSTEM OVERVIEW

Inspired by the biological process of calmodulin, the relay-assisted MC system consists of a source nanomachine (node S), a destination nanomachine (node D) and a relay nanomachine (node R). The relay R is placed between node S and node D, and is used to support the communication between these nodes, as shown in Figure 2. Suppose node R and node D are spherical, and their radiuses (and volumes) are r_R (V_R) and r_D (V_D), respectively.

We adopt a full-duplex relaying protocol for two-hop transmission. The relay R receives and transmits information bits in the same time. In other words, in each time slot, relay R captures the messenger molecules from node S, and emits the messenger molecules decoded in the previous time slot to node D. We use the on-off keying (OOK) modulation technique in the transmission node (S and R) and a fixed interval duration T_S .

We consider two relaying schemes in our relay network: first, a two-molecule two-hop (2M2H) network; and second, a single-molecule two-hop (1M2H) network. The 2M2H scheme assumes that two different types of molecules are used in node S and node R, while the 1M2H scheme assumes that only one type of molecule is available. In the 1M2H scheme, relay R emits molecules at the beginning of the interval, then some of the molecules are absorbed inside V_R during the subsequent interval. We refer to this effect as *self-interference* [23]. Thus, the 1M2H scheme suffers from inter symbol interference (ISI) and self-interference (SI). However, the 2M2H scheme can avoid SI completely.

The communication process in this architecture consists of three main phases: emission, propagation, and reception. There are R_T receptors on the surface of receiver nodes (R and D), while the reception of molecules is governed by the ligand-receptor binding mechanism. The parameters and notations are summarized in Table 1.

C. MATHEMATICAL MODEL

We assume a communication link between transmitting node m and receiving node n , where $m \in \{S, R\}$, $n \in \{R, D\}$.

TABLE 1. Summary of notation.

Notation	Description
$Z_{m,n}^{A_i}[l]$	The number of captured A_i molecules by node n emitted by node m in the l^{th} time slot, where $m \in \{S, R\}$, $n \in \{R, D\}$.
$Z_{m,n}^{Signal,A_i}[l]$	The number of A_i molecules emitted and captured in the current symbol duration (signal).
$Z_{m,n}^{ISI,A_i}[l]$	The number of A_i molecules emitted in the previous symbol durations and captured in the current duration (ISI).
$Z_{m,n}^{Noise}[l]$	The number of molecules from other sources (noise).
$C_{m,n}^{A_i}[l]$	The concentration of A_i molecules captured by node n emitted by node m in the l^{th} time slot.
$C_{m,n}^{Signal,A_i}[l]$	The concentration of A_i molecules emitted and captured in the current symbol duration (signal).
$C_{m,n}^{ISI,A_i}[l]$	The concentration of A_i molecules emitted in the previous symbol durations and captured in the current duration (ISI).
$C_{R,R}^{ST,A_i}[l]$	The concentration of A_i molecules emitted and captured by relay R (SI).
$x_m[l]$	Information bit transmitted by node m in the l^{th} time slot.
$\hat{x}_n[l]$	Information bit detected by node n in the l^{th} time slot.
ξ_n	Decision threshold of node n .
ξ_n^*	Optimal decision threshold of node n .
$N(\mu_{0m,n}, \sigma_{0m,n}^2)$	Normal distribution with mean $\mu_{0m,n}$ and variance $\sigma_{0m,n}^2$ for bit 0.
$N(\mu_{1m,n}, \sigma_{1m,n}^2)$	Normal distribution with mean $\mu_{1m,n}$ and variance $\sigma_{1m,n}^2$ for bit 1.
$d^{(k)}$	Gradient direction.
λ_k	Step size.
R_T	The number of receptors on the surface of receiver.
$B_n(t)$	The number of bound receptors on node n .
$R_n(t)$	The number of unbound receptors on node n .
k_f	Rate constant for association reaction.
k_r	Rate constant for disassociation reaction.
K_D	Equilibrium dissociation constant.

The diffusion phenomenon in the fluid environment is primarily dominated by Fick's second law [34], which characterizes the macroscopic behaviour of molecular movement. Under the law, the concentration of A molecules at location \vec{r}_n and at time t (denoted by $C_{m,n}^A(\vec{r}_n, t)$) is described as

$$\frac{\partial C_{m,n}^A(\vec{r}_n, t)}{\partial t} = D_A \nabla^2 C_{m,n}^A(\vec{r}_n, t) \quad (1)$$

where D_A is the diffusion coefficient of A molecules which is related to the viscosity of the propagation medium. When the number of the molecules is large enough, the molecular concentration can be regarded as a function of time and space. If the transmitter m is a point source, and releases Q_A molecules defined by vector at the point \vec{r}_m at the instant $t = 0$, then the molecular concentration at the point defined by \vec{r}_n in a 3-dimensional space can be written as [34]:

$$C_{m,n}^A(\vec{r}_n, t) = \frac{Q_A}{(4\pi D_A t)^{\frac{3}{2}}} \exp\left(-\frac{|\vec{r}_n - \vec{r}_m|^2}{4D_A t}\right) \quad (2)$$

By (2), we can define impulse response $h_{m,n}^A(\vec{r}_n, t)$ as $h_{m,n}^A(\vec{r}_n, t) = \frac{1}{(4\pi D_A t)^{\frac{3}{2}}} \exp\left(-\frac{|\vec{r}_n - \vec{r}_m|^2}{4D_A t}\right)$.

The receiver is a bio-inspired nanomachine, which has receptors on its surface and captures molecules dominated

by the ligand-receptor binding mechanism. In our ligand-receptor binding model, a ligand L reversibly binds to a receptor R to form a ligand-receptor complex B as in the following chemical reaction [35], [36]:



In our system, we assume that ligands and receptors have only one binding site, so that more than one ligand could not bind to the same receptor. This also implies that ligands cannot bind to the receptor until the receptor unbinds from the ligand.

To get the analytical expressions, the following assumptions are given:

- 1) The ligands move fast enough so the reception is not limited to mass transport. This assumption is made to ensure that the received ligands are uniformly distributed over the receptor, and each of the receptors can sense the same value of concentration.
- 2) We assume that ligand concentration is much higher than the concentration of receptors, and even though the ligand-receptor reactions are happening, the ligand concentration in the reception space remains almost constant.

These assumptions are widely adopted in both research of MC and biosensors [37].

The signal from the surrounding medium transmitted to cell take the form of the time-varying concentration $C_{m,n}^A(\vec{r}_n, t)$. There are R_T receptors on the receiver surface. The following differential equation describes the feature that the ligand-receptor complex density $B_n(t)$ is a function of the ligand concentration $C_{m,n}^A(\vec{r}_n, t)$ and the free receptor number $R_n(t)$ as [35], [36]:

$$\frac{dB_n(t)}{dt} = k_f R_n(t) C_{m,n}^A(\vec{r}_n, t) - k_r B_n(t) \quad (4)$$

where k_f and k_r are the rate constants for the forward (association) and backward (disassociation) reaction, respectively. Because of the forward and backward reactions, the numbers of ligands and receptors change with time t . Obviously, the total number of unbound and bound receptors is a fixed value in a cell, i.e., $R_T = R_n(t) + B_n(t)$.

For analysis, the reaction-limited operation is simplified, the transient phase between adjacent concentration of ligand can be ignored, e.g., $C_{m,n}^A(\vec{r}_n, t) = C_{m,n}^A[l]$ for $t \in [t_l, t_l + T_S]$, where $C_{m,n}^A[l]$ represents the ligand concentration of current symbol in the l^{th} time slot, t_l is the transmission time from the $(l - 1)^{th}$ time slot to the l^{th} time slot, and T_S is the interval duration. We can obtain that the reception space of the receiver n has a constant concentration of ligand $C_{m,n}^A[l]$ for $t \in [t_l, t_l + T_S]$.

While give the initial condition $B_n(t_l - \epsilon) = B_n[l - 1]$ with $\epsilon \rightarrow 0$, we can obtain the solution of (4) as [38], [39]

$$B_n(t) = B_n^{ss}[l] + (B_n[l - 1] - B_n^{ss}[l])e^{-(k_f C_{m,n}^A[l] + k_r)(t - t_l)} \quad (5)$$

for $t \in [t_l, t_l + T_S]$, where $B_n^{ss}[l]$ represents the mean number of bound receptors at steady-state for

$dB_n(t)/dt = 0$. Although the level of $C_{m,n}^A[l]$ varies around the receiver, the receptors should take a certain time to accommodate the concentration level of the subsequent symbol. The reaction timescale controls when a steady-state is reached, i.e., $\tau = (k_f C_{m,n}^A[l] + k_r)^{-1}$. The mean number of bound receptors of receiver n at steady-state can be written as [40]

$$B_n^{ss}[l] = \frac{k_f R_T C_{m,n}^A[l]}{k_f C_{m,n}^A[l] + k_r} = \frac{R_T C_{m,n}^A[l]}{C_{m,n}^A[l] + K_D} \quad (6)$$

where $K_D = k_r/k_f$ is the equilibrium dissociation constant.

We assume that the receiver samples the state of receptors at steady-state. Hence, the mean number of bound receptors represents in the l^{th} time slot can be written as

$$B_n(t) = B_n^{ss}[l] = \frac{R_T C_{m,n}^A[l]}{C_{m,n}^A[l] + K_D} \quad (7)$$

For the purpose of identifying the state of receptor n , let b_n be the Bernoulli random variable, i.e., $b_n \sim \mathcal{B}(1, p)$, where p is the occupancy probability and be written as

$$p = \frac{C_{m,n}^A[l]}{C_{m,n}^A[l] + K_D} \quad (8)$$

Hence, the number of bound receptors is

$$B_n^A(t) = R_T \cdot p = \frac{R_T C_{m,n}^A[l]}{C_{m,n}^A[l] + K_D} \quad (9)$$

On the other hand, the number of occupied receptors can be described as a binomial random variable $Z \sim \mathcal{B}(R_T, p)$

$$\Lambda(k; R_T, p) = \binom{R_T}{k} p^k (1-p)^{R_T-k} \quad (10)$$

We assume that the number of receptors R_T is sufficiently large, then $\mathcal{B}(R_T, p)$ can be approximated by a normal distribution $\mathcal{N}(\mu, \sigma^2)$, i.e.,

$$Z_{m,n}^A[l] \sim \mathcal{N}\left(\frac{R_T C_{m,n}^A[l]}{C_{m,n}^A[l] + K_D}, \frac{R_T C_{m,n}^A[l] K_D}{(C_{m,n}^A[l] + K_D)^2}\right) \quad (11)$$

If the transmitter m emits two different levels of ligand concentration around the receiver n , i.e., higher concentration $C_{m,n}^{A,1}[l]$ and lower concentration $C_{m,n}^{A,2}[l]$ represent bit 1 and bit 0, respectively. Different concentration can cause different occupancy probabilities, i.e.,

$$p_i = \frac{C_{m,n}^{A,i}[l]}{C_{m,n}^{A,i}[l] + K_D} \quad (12)$$

where $i = 1, 2$. Hence, the number of molecules absorbed by the receiver can be expressed as a normal distribution

$$Z_{m,n}^{A,i}[l] \sim \mathcal{N}\left(\frac{R_T C_{m,n}^{A,i}[l]}{C_{m,n}^{A,i}[l] + K_D}, \frac{R_T C_{m,n}^{A,i}[l] K_D}{(C_{m,n}^{A,i}[l] + K_D)^2}\right) \quad (13)$$

For detection, we take the maximum-a-posterior (MAP) method. Compare the total number of captured molecules

$Z_{m,n}^A[l]$ with a decision threshold. The information bit $\hat{x}_n[l]$ detected by node n in the l^{th} time slot is given as

$$\hat{x}_n[l] = \begin{cases} 1 & \text{if } Z_{m,n}^A[l] \geq \xi_n, \\ 0 & \text{if } Z_{m,n}^A[l] < \xi_n \end{cases} \quad (14)$$

where ξ_n is the detection threshold of node n .

The error probability of the l^{th} bit when $x = 1$ can be calculated as

$$\begin{aligned} P_{e1}[l] &= Pr(Z[l] < \xi | x''[l] = 1) \\ &= \frac{1}{\sqrt{2\pi\sigma_1^2}} \int_0^\xi \exp\left(-\frac{(Z - \mu_1)^2}{2\sigma_1^2}\right) dZ \\ &= \frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi - \mu_1)}{\sqrt{2\sigma_1^2}}\right) \end{aligned} \quad (15)$$

Similarly, the error probability when $x = 0$ as

$$\begin{aligned} P_{e0}[l] &= Pr(Z[l] > \xi | x''[l] = 0) \\ &= \frac{1}{\sqrt{2\pi\sigma_0^2}} \int_\xi^\infty \exp\left(-\frac{(Z - \mu_0)^2}{2\sigma_0^2}\right) dZ \\ &= \frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi - \mu_0)}{\sqrt{2\sigma_0^2}}\right) \\ &= \frac{1}{2} \operatorname{erfc}\left(\frac{(\xi - \mu_0)}{\sqrt{2\sigma_0^2}}\right) \end{aligned} \quad (16)$$

Therefore, the average error probability for point-to-point communication system, which refers to a communications link between a transmitting node and a receiving node. Let transmission probability $p_1 = p_0 = \frac{1}{2}$, it can be calculated as

$$\begin{aligned} P_e[l] &= p_1 Pr(Z[l] < \xi | x''[l] = 1) + p_0 Pr(Z[l] > \xi | x''[l] = 0) \\ &= p_1 \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi - \mu_1)}{\sqrt{2\sigma_1^2}}\right)\right) \\ &\quad + p_0 \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi - \mu_0)}{\sqrt{2\sigma_0^2}}\right)\right) \\ &= \frac{1}{2} + \frac{1}{4} \operatorname{erf}\left(\frac{(\xi - \mu_1)}{\sqrt{2\sigma_1^2}}\right) - \frac{1}{4} \operatorname{erf}\left(\frac{(\xi - \mu_0)}{\sqrt{2\sigma_0^2}}\right) \end{aligned} \quad (17)$$

III. TWO-MOLECULE TWO-HOP NETWORK

In the two-molecule two-hop network, node S emits type A_1 molecules, which are absorbed by node R. Subsequently, relay node R emits type A_2 molecules, which are absorbed by node D. Because A_1 and A_2 are different types of molecules, they do not interfere with each other.

In our model, the concentration of molecules at the receiver is measured by its surface receptors, while the detection process is dominated by the ligand-receptor mechanism. The number of captured type $A_i (i = 1, 2)$ molecules by node n emitted from node m in the l^{th} time slot be denoted as $Z_{m,n}^{A_i}[l]$.

$Z_{m,n}^{A_i}[l]$ consists of the number of molecules transmitted and captured during the current time slot (signal molecules), denoted by $Z_{m,n}^{Signal,A_i}[l]$, the number of molecules transmitted in the previous slot $l-1, l-2, \dots, l-M$ and captured during the current slot l , (ISI molecules), denoted by $Z_{m,n}^{ISI,A_i}[l]$, and the number of molecules from other sources, also known as noise molecules which may result in MSI, denoted by $Z_{m,n}^{Noise}[l]$. Therefore, the total number of captured molecules $Z_{m,n}^{A_i}[l]$ can be expressed as

$$Z_{m,n}^{A_i}[l] = Z_{m,n}^{Signal,A_i}[l] + Z_{m,n}^{ISI,A_i}[l] + Z_{m,n}^{Noise}[l] \quad (18)$$

The number of signal molecules captured by the receiver $Z_{m,n}^{Signal,A_i}[l]$ follows a binomial distribution, i.e.,

$$Z_{m,n}^{Signal,A_i}[l] \sim \mathcal{N}\left(\frac{R_T C_{m,n}^{Signal,A_i}[l]}{C_{m,n}^{A_i}[l] + K_D}, \frac{R_T C_{m,n}^{Signal,A_i}[l] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2}\right) \quad (19)$$

where $C_{m,n}^{Signal,A_i}[l]$ is the concentration of signal molecules in the l^{th} time slot. Since the effect of ISI can be negligible after a finite number of previous transmission bits, the ISI length of channel is set to a finite value M . $C_{m,n}^{ISI,A_i}[l]$ is the concentration of ISI and the number of ISI molecules is also characterized normal random variable, i.e.,

$$Z_{m,n}^{ISI,A_i}[l] \sim \mathcal{N}\left(\sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k]}{C_{m,n}^{A_i}[l] + K_D}, \sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2}\right) \quad (20)$$

We also assume that the number of noise molecules obeys the normal distribution as follows [41]

$$Z_{m,n}^{Noise}[l] \sim \mathcal{N}(\mu_{Noise}, \sigma_{Noise}^2) \quad (21)$$

From the above discussion, and formulas (18)-(21), we can write the total number of captured A_i molecules by node n as follows:

$$\begin{aligned} Z_{m,n}^{A_i}[l] &\sim \mathcal{N}\left(\frac{R_T C_{m,n}^{Signal,A_i}[l]}{C_{m,n}^{A_i}[l] + K_D}, \frac{R_T C_{m,n}^{Signal,A_i}[l] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2}\right) \\ &+ \sum_{k=1}^M \mathcal{N}\left(\frac{R_T C_{m,n}^{ISI,A_i}[l-k]}{C_{m,n}^{A_i}[l] + K_D}, \frac{R_T C_{m,n}^{ISI,A_i}[l-k] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2}\right) \\ &+ \mathcal{N}(\mu_{Noise}, \sigma_{Noise}^2) \end{aligned} \quad (22)$$

Therefore, $Z_{m,n}^{A_i}[l]$ obeys the following normal distribution

$$Pr(Z_{m,n}^{A_i}[l] | x_m''[l] = 0) \sim \mathcal{N}(\mu_{0m,n}, \sigma_{0m,n}^2) \quad (23)$$

$$Pr(Z_{m,n}^{A_i}[l] | x_m''[l] = 1) \sim \mathcal{N}(\mu_{1m,n}, \sigma_{1m,n}^2) \quad (24)$$

where the mean and variance can be written as

$$\mu_{0m,n} = p_1 \sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k]}{C_{m,n}^{A_i}[l] + K_D} + \mu_{Noise} \quad (25)$$

$$\begin{aligned} \mu_{1m,n} &= \frac{R_T C_{m,n}^{Signal,A_i}[l]}{C_{m,n}^{A_i}[l] + K_D} \\ &+ p_1 \sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k]}{C_{m,n}^{A_i}[l] + K_D} + \mu_{Noise} \end{aligned} \quad (26)$$

$$\begin{aligned} \sigma_{0m,n}^2 &= p_1 \sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2} \\ &+ p_1 p_0 \sum_{k=1}^M \frac{R_T^2 C_{m,n}^{ISI,A_i}^2[l-k]}{(C_{m,n}^{A_i}[l] + K_D)^2} + \sigma_{Noise}^2 \end{aligned} \quad (27)$$

$$\begin{aligned} \sigma_{1m,n}^2 &= \frac{R_T C_{m,n}^{Signal,A_i}[l] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2} + p_1 \sum_{k=1}^M \frac{R_T C_{m,n}^{ISI,A_i}[l-k] K_D}{(C_{m,n}^{A_i}[l] + K_D)^2} \\ &+ p_1 p_0 \sum_{k=1}^M \frac{R_T^2 C_{m,n}^{ISI,A_i}^2[l-k]}{(C_{m,n}^{A_i}[l] + K_D)^2} + \sigma_{Noise}^2 \end{aligned} \quad (28)$$

where $Pr(x_S''[l] = 1) = p_1$ and $Pr(x_S''[l] = 0) = p_0$.

If $x_S''[l]$ is given, the error probability of the l^{th} bit when $x_S''[l] = 1$ and $x_S''[l] = 0$ can be written as

$$\begin{aligned} P_e[l | x_S''[l] = 1] &= Pr(Z_R^{A_1}[l] < \xi_R | x_S''[l] = 1) \\ &\times Pr(Z_D^{A_2}[l+1] < \xi_D | x_R''[l+1] = 0) \\ &+ Pr(Z_R^{A_1}[l] \geq \xi_R | x_S''[l] = 1) \mu_{Noise} \\ &\times Pr(Z_D^{A_2}[l+1] < \xi_D | x_R''[l+1] = 1) \\ &= \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf} \mu_{Noise} \left(\frac{\xi_R - \mu_{1S,R}}{\sqrt{2\sigma_{1S,R}^2}}\right)\right) \\ &\times \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right)\right) \\ &+ \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_R - \mu_{1S,R})}{\sqrt{2\sigma_{1S,R}^2}}\right)\right) \\ &\times \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right)\right) \end{aligned} \quad (29)$$

and

$$\begin{aligned} P_e[l | x_S''[l] = 0] &= Pr(Z_R^{A_1}[l] \geq \xi_R | x_S''[l] = 0) \\ &\times Pr(Z_D^{A_2}[l+1] \geq \xi_D | x_R''[l+1] = 1) \\ &+ Pr(Z_R^{A_1}[l] < \xi_R | x_S''[l] = 0) \\ &\times Pr(Z_D^{A_2}[l+1] \geq \xi_D | x_R''[l+1] = 0) \\ &= \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right)\right) \\ &\times \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_D - \mu_{1R,D})}{\sqrt{2\sigma_{1R,D}^2}}\right)\right) \\ &+ \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right)\right) \\ &\times \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf} \left(\frac{(\xi_D - \mu_{1R,D})}{\sqrt{2\sigma_{1R,D}^2}}\right)\right) \end{aligned} \quad (30)$$

In our relay-assisted communication link, if the detection is erroneous in either node R or node D, then an error will occur, e.g., an error occurs in the $(l + 1)^{th}$ time slot when $x_S''[l]$ is given, if $\hat{x}_R[l] \neq x_S''[l]$ and $\hat{x}_D[l + 1] = x_R''[l + 1]$, or $\hat{x}_R[l] = x_S''[l]$ and $\hat{x}_D[l + 1] \neq x_R''[l + 1]$. Setting $p_1 = p_0 = \frac{1}{2}$, we can obtain the error probability of the l^{th} bit as follows

$$\begin{aligned}
 P_e[l | x_S''[l]] &= p_1 P_e[l | x_S''[l] = 1] + p_0 P_e[l | x_S''[l] = 0] \\
 &= \frac{1}{2} + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1S,R})}{\sqrt{2\sigma_{1S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_S - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1S,R})}{\sqrt{2\sigma_{1S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1R,D})}{\sqrt{2\sigma_{1R,D}^2}}\right) \\
 &\quad + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1R,D})}{\sqrt{2\sigma_{1R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right). \quad (31)
 \end{aligned}$$

IV. SINGLE-MOLECULE TWO-HOP NETWORK

Now we analyze a single-molecule two-hop network, in which the same type of molecule A_1 is used by node S and node R. Relay node R uses the same type of molecule for transmission and reception, which can cause self-interference as well as inter-symbol interference.

The number of captured A_1 molecules by the node R emitted from node S in the l^{th} time slot be denoted as $Z_{S,R}^{A_1}[l]$. $Z_{S,R}^{A_1}[l]$ consists of the number of signal molecules $Z_{S,R}^{Signal,A_1}[l]$, the number of ISI molecules $Z_{S,R}^{ISI,A_1}[l]$, the number of self-interference molecules $Z_{R,R}^{SI,A_1}[l]$ and the number of noise molecules (MSI) $Z_{S,R}^{Noise}[l]$. Therefore, the total number of captured molecules $Z_{S,R}^{A_1}[l]$ can be written as

$$Z_{S,R}^{A_1}[l] = Z_{S,R}^{Signal,A_1}[l] + Z_{S,R}^{ISI,A_1}[l] + Z_{R,R}^{SI,A_1}[l] + Z_{S,R}^{Noise}[l] \quad (32)$$

where the self-interference $Z_{R,R}^{SI,A_1}(t)$ is the number of captured molecules within V_R emitted by relay R. The concentration of self-interference $C_{R,R}^{SI,A_1}(t)$ is given by l'Hôpital's rule as [42]

$$C_{R,R}^{SI,A_1}(t) = \operatorname{erf}\left(\frac{r_R}{2\sqrt{Dt}} - \frac{r_R \exp\left(\frac{-r_R^2}{4Dt}\right)}{\sqrt{\pi Dt}}\right) \quad (33)$$

The number of self-interference molecules is also characterized as a normal random variable, i.e.,

$$Z_{R,R}^{SI,A_1}[l] \sim \mathcal{N}\left(\frac{R_T C_{R,R}^{SI,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D}, \frac{R_T C_{R,R}^{SI,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2}\right) \quad (34)$$

The total number of captured A_1 molecules by node R is given as follows:

$$\begin{aligned}
 &Z_{S,R}^{A_1}[l] \\
 &\sim \mathcal{N}\left(\frac{R_T C_{S,R}^{Signal,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D}, \frac{R_T C_{S,R}^{Signal,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2}\right)
 \end{aligned}$$

$$\begin{aligned}
 &+ \sum_{k=1}^M \mathcal{N}\left(\frac{R_T C_{S,R}^{ISI,A_1}[l-k]}{C_{S,R}^{A_1}[l] + K_D}, \frac{R_T C_{S,R}^{ISI,A_1}[l-k] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2}\right) \\
 &+ \mathcal{N}\left(\frac{R_T C_{R,R}^{SI,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D}, \frac{R_T C_{R,R}^{SI,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2}\right) \\
 &+ \mathcal{N}(\mu_{Noise}, \sigma_{Noise}^2) \quad (35)
 \end{aligned}$$

Therefore, $Z_{S,R}^{A_1}[l]$ obeys the following normal distribution

$$Pr(Z_{S,R}^{A_1}[l] | x_S''[l] = 0) \sim \mathcal{N}(\mu_{0S,R}, \sigma_{0S,R}^2) \quad (36)$$

$$Pr(Z_{S,R}^{A_1}[l] | x_S''[l] = 1) \sim \mathcal{N}(\mu_{1S,R}, \sigma_{1S,R}^2) \quad (37)$$

where the mean and variance can be written as

$$\mu_{0S,R} = p_1 \sum_{k=1}^M \frac{R_T C_{S,R}^{ISI,A_1}[l-k]}{C_{S,R}^{A_1}[l] + K_D} + \frac{R_T C_{S,R}^{SI,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D} + \mu_{Noise} \quad (38)$$

$$\begin{aligned}
 \mu_{1S,R} &= \frac{R_T C_{S,R}^{Signal,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D} + p_1 \sum_{k=1}^M \frac{R_T C_{S,R}^{ISI,A_1}[l-k]}{C_{S,R}^{A_1}[l] + K_D} \\
 &\quad + \frac{R_T C_{R,R}^{SI,A_1}[l]}{C_{S,R}^{A_1}[l] + K_D} + \mu_{Noise} \quad (39)
 \end{aligned}$$

$$\begin{aligned}
 \sigma_{0S,R}^2 &= p_1 \sum_{k=1}^M \frac{R_T C_{S,R}^{ISI,A_1}[l-k] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2} + p_1 p_0 \sum_{k=1}^M \\
 &\quad \times \frac{R_T^2 C_{S,R}^{ISI,A_1}^2[l-k]}{(C_{S,R}^{A_1}[l] + K_D)^2} + \frac{R_T C_{R,R}^{SI,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2} + \sigma_{Noise}^2 \quad (40)
 \end{aligned}$$

$$\begin{aligned}
 \sigma_{1S,R}^2 &= \frac{R_T C_{S,R}^{Signal,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2} + p_1 \sum_{k=1}^M \\
 &\quad \times \frac{R_T C_{S,R}^{ISI,A_1}[l-k] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2} \\
 &\quad + p_1 p_0 \sum_{k=1}^M \frac{R_T^2 C_{S,R}^{ISI,A_1}^2[l-k]}{(C_{S,R}^{A_1}[l] + K_D)^2} \\
 &\quad + \frac{R_T C_{R,R}^{SI,A_1}[l] K_D}{(C_{S,R}^{A_1}[l] + K_D)^2} + \sigma_{Noise}^2 \quad (41)
 \end{aligned}$$

Similarly, we assume that $Z_{R,D}^{A_1}[l + 1]$ denotes the number of molecules emitted from node R and captured by node D in the $(l + 1)^{th}$ time slot. $Z_{R,D}^{A_1}[l + 1]$ consists of the number of signal molecules $Z_{R,D}^{Signal,A_1}[l + 1]$, the number of captured ISI molecules $Z_{R,D}^{ISI,A_1}[l + 1]$ from node R, the number of captured ISI molecules $Z_{S,D}^{ISI,A_1}[l + 1]$ transmitted in the previous interval $l, l - 1, \dots, l - R + 1$ from node S, and the number of noise molecules (MSI) $Z_{R,D}^{Noise}[l + 1]$. Therefore, the total number of captured molecules $Z_{R,D}^{A_1}[l + 1]$ can be expressed as

$$\begin{aligned}
 Z_{R,D}^{A_1}[l + 1] &= Z_{R,D}^{Signal,A_1}[l + 1] + Z_{R,D}^{ISI,A_1}[l + 1] \\
 &\quad + Z_{S,D}^{ISI,A_1}[l + 1] + Z_{R,D}^{Noise}[l + 1] \quad (42)
 \end{aligned}$$

The total number of captured A_1 molecules by node D is given as follows:

$$\begin{aligned}
 & Z_{R,D}^{A_1}[l+1] \\
 & \sim \mathcal{N}\left(\frac{R_T C_{R,D}^{Signal,A_1}[l+1]}{C_{R,D}^{A_1}[l+1] + K_D}, \frac{R_T C_{R,D}^{Signal,A_1}[l+1]K_D}{(C_{R,D}^{A_1}[l+1] + K_D)^2}\right) \\
 & + \sum_{j=1}^M \mathcal{N}\left(\frac{R_T C_{R,D}^{ISI,A_1}[l-j+1]}{C_{R,D}^{A_1}[l+1] + K_D}, \frac{R_T C_{R,D}^{ISI,A_1}[l-j+1]K_D}{(C_{R,D}^{A_1}[l+1] + K_D)^2}\right) \\
 & + \sum_{k=1}^R \mathcal{N}\left(\frac{R_T C_{S,D}^{ISI,A_1}[l-k+1]}{C_{S,D}^{A_1}[l+1] + K_D}, \frac{R_T C_{S,D}^{ISI,A_1}[l-k+1]K_D}{(C_{S,D}^{A_1}[l+1] + K_D)^2}\right) \\
 & + \mathcal{N}(\mu_{Noise}, \sigma_{Noise}^2) \quad (43)
 \end{aligned}$$

Here $Z_{R,D}^{A_1}[l+1]$ obeys the following normal distribution

$$Pr(Z_{R,D}^{A_1}[l+1] | x_R''[l+1] = 0) \sim \mathcal{N}(\mu_{0R,D}, \sigma_{0R,D}^2) \quad (44)$$

$$Pr(Z_{R,D}^{A_1}[l+1] | x_R''[l+1] = 1) \sim \mathcal{N}(\mu_{1R,D}, \sigma_{1R,D}^2) \quad (45)$$

where the mean and variance can be written as

$$\begin{aligned}
 \mu_{0R,D} &= p_1 \sum_{k=1}^M \frac{R_T C_{R,D}^{ISI,A_1}[l-k+1]}{C_{R,D}^{A_1}[l+1] + K_D} \\
 &+ p_1 \sum_{j=1}^R \frac{R_T C_{S,D}^{ISI,A_1}[l-j+1]}{C_{S,D}^{A_1}[l+1] + K_D} + \mu_{Noise} \quad (46)
 \end{aligned}$$

$$\begin{aligned}
 \mu_{1R,D} &= \frac{R_T C_{R,D}^{Signal,A_1}[l+1]}{C_{R,D}^{A_1}[l+1] + K_D} \\
 &+ p_1 \sum_{k=1}^M \frac{R_T C_{R,D}^{ISI,A_1}[l-k+1]}{C_{R,D}^{A_1}[l+1] + K_D} \\
 &+ p_1 \sum_{j=1}^R \frac{R_T C_{S,D}^{ISI,A_1}[l-j+1]}{C_{S,D}^{A_1}[l+1] + K_D} + \mu_{Noise} \quad (47)
 \end{aligned}$$

$$\begin{aligned}
 \sigma_{0R,D}^2 &= p_1 \sum_{k=1}^M \frac{R_T C_{R,D}^{ISI,A_1}[l-k+1]K_D}{(C_{R,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 p_0 \sum_{k=1}^M \frac{R_T^2 C_{R,D}^{ISI,A_1}^2[l-k+1]}{(C_{R,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 \sum_{j=1}^R \frac{R_T C_{S,D}^{ISI,A_1}[l-j+1]K_D}{(C_{S,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 p_0 \sum_{j=1}^R \frac{R_T^2 C_{S,D}^{ISI,A_1}^2[l-j+1]}{(C_{S,D}^{A_1}[l+1] + K_D)^2} + \sigma_{Noise}^2 \quad (48)
 \end{aligned}$$

$$\begin{aligned}
 \sigma_{1R,D}^2 &= \frac{R_T C_{R,D}^{Signal,A_1}[l+1]K_D}{(C_{R,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 \sum_{k=1}^M \frac{R_T C_{R,D}^{ISI,A_1}[l-k+1]K_D}{(C_{R,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 p_0 \sum_{k=1}^M \frac{R_T^2 C_{R,D}^{ISI,A_1}^2[l-k+1]}{(C_{R,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 \sum_{j=1}^R \frac{R_T C_{S,D}^{ISI,A_1}[l-j+1]K_D}{(C_{S,D}^{A_1}[l+1] + K_D)^2} \\
 &+ p_1 p_0 \sum_{j=1}^R \frac{R_T^2 C_{S,D}^{ISI,A_1}^2[l-j+1]}{(C_{S,D}^{A_1}[l+1] + K_D)^2} + \sigma_{Noise}^2 \quad (49)
 \end{aligned}$$

Similarly, the error probability of the l^{th} bit when $x_S''[l] = 1$ and $x_S''[l] = 0$ is given as

$$\begin{aligned}
 P_e[l | x_S''[l] = 1] &= Pr(\mathcal{Z}_R^{A_1}[l] < \xi_R | x_S''[l] = 1) \\
 &\times Pr(\mathcal{Z}_D^{A_1}[l+1] < \xi_D | x_R''[l+1] = 0) \\
 &+ Pr(\mathcal{Z}_R^{A_1}[l] \geq \xi_R | x_S''[l] = 1) \\
 &\times Pr(\mathcal{Z}_D^{A_1}[l+1] < \xi_D | x_R''[l+1] = 1) \\
 &= \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1S,R})}{\sqrt{2\sigma_{1S,R}^2}}\right)\right) \\
 &\times \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right)\right) \\
 &+ \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1S,R})}{\sqrt{2\sigma_{1S,R}^2}}\right)\right) \\
 &\times \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right)\right) \quad (50)
 \end{aligned}$$

and

$$\begin{aligned}
 P_e[l | x_S''[l] = 0] &= Pr(\mathcal{Z}_R^{A_1}[l] \geq \xi_R | x_S''[l] = 0) \\
 &\times Pr(\mathcal{Z}_D^{A_1}[l+1] \geq \xi_D | x_R''[l+1] = 1) \\
 &+ Pr(\mathcal{Z}_R^{A_1}[l] < \xi_R | x_S''[l] = 0) \\
 &\times Pr(\mathcal{Z}_D^{A_1}[l+1] \geq \xi_D | x_R''[l+1] = 0) \\
 &= \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right)\right) \\
 &\times \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_D - \mu_{1R,D})}{\sqrt{2\sigma_{1R,D}^2}}\right)\right) \\
 &+ \left(\frac{1}{2} + \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0S,R})}{\sqrt{2\sigma_{0S,R}^2}}\right)\right) \\
 &\times \left(\frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{(\xi_D - \mu_{0R,D})}{\sqrt{2\sigma_{0R,D}^2}}\right)\right) \quad (51)
 \end{aligned}$$

Finally, the error probability of the l^{th} bit can be derived as

$$\begin{aligned}
 P_e[l | x_S''[l]] &= p_1 P_e[l | x_S''[l] = 1] + p_0 P_e[l | x_S''[l] = 0] \\
 &= \frac{1}{2} + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right)
 \end{aligned} \tag{52}$$

V. DETECTION THRESHOLD OPTIMIZATION

In the previous section we obtained the bit error probability of a decode-and-forward (DF) two-hop diffusion-based MC system. It is clear that the error probability $P_e[l]$ is a function of ξ_R and ξ_D (i.e., the detection thresholds). Here we propose to find the optimal detection threshold; our goal is to minimize the error probability $P_e[l]$ by solving the joint optimization problem to find ξ_R^* and ξ_D^* . The optimization problem is formulated as follows:

$$\begin{aligned}
 \min_{\xi_R, \xi_D} P_e[l] &= \frac{1}{2} + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad + \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right) \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right)
 \end{aligned} \tag{53}$$

Now we introduce gradient descent, which is a first-order iterative optimization algorithm to find the extremum of a function. In order to find the local minimum value, we need to take steps proportional to the negative gradient of the function at the current point [43]. First, we can define a multi-variable function $P_e(\xi^{(k)})$, which is differentiable in the neighborhood of a point $\xi^{(k)}$ at iteration k . On this basis, we can take gradient descent. Then, at the point $\xi^{(k)}$, along the direction $d^{(k)}$ of the negative gradient of $P_e(\xi^{(k)})$, one can observe that $P_e(\xi^{(k)})$ decreases fastest. The following result can be obtained

$$\xi^{(k+1)} = \xi^{(k)} + \lambda_k d^{(k)} \tag{54}$$

for $\lambda_k \in \mathbb{R}$, and we have $P_e(\xi^{(k)}) \geq P_e(\xi^{(k+1)})$. It is clear that the term $\lambda_k d^{(k)}$ is subtracted from $\xi^{(k)}$ since our goal is to move against the gradient, toward the minimum. Note that

the value of the negative gradient direction $d^{(k)}$ is allowed to change at each iteration, which satisfies

$$d^{(k)} = -\frac{\nabla P_e(\xi^{(k)})}{\|\nabla P_e(\xi^{(k)})\|} \tag{55}$$

where the gradient is given by

$$\nabla P_e(\xi^{(k)}) = \left[\frac{\partial P_e(\xi^{(k)})}{\partial \xi_R}, \frac{\partial P_e(\xi^{(k)})}{\partial \xi_D} \right]^T \tag{56}$$

According to the formula $\frac{d}{dx} \operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \exp(-x^2)$, the derivative of (53) with respect to the optimization variable, i.e., ξ_R and ξ_D are equal to

$$\begin{aligned}
 \frac{\partial P_e(\xi^{(k)})}{\partial \xi_R} &= \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{1,S,R}^2}} \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{1,S,R}^2}} \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad + \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{0,S,R}^2}} \operatorname{erf}\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right) \\
 &\quad - \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{0,S,R}^2}} \operatorname{erf}\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right)
 \end{aligned} \tag{57}$$

and

$$\begin{aligned}
 \frac{\partial P_e(\xi^{(k)})}{\partial \xi_D} &= \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_D - \mu_{0,R,D})}{\sqrt{2\sigma_{0,R,D}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{0,R,D}^2}} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \\
 &\quad - \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{1,R,D}^2}} \operatorname{erf}\left(\frac{(\xi_R - \mu_{1,S,R})}{\sqrt{2\sigma_{1,S,R}^2}}\right) \\
 &\quad + \frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{(\xi_D - \mu_{1,R,D})}{\sqrt{2\sigma_{1,R,D}^2}}\right)^2\right) \\
 &\quad \times \frac{1}{\sqrt{2\sigma_{1,R,D}^2}} \operatorname{erf}\left(\frac{(\xi_R - \mu_{0,S,R})}{\sqrt{2\sigma_{0,S,R}^2}}\right)
 \end{aligned}$$

$$-\frac{1}{8} \frac{2}{\sqrt{\pi}} \exp\left(-\left(\frac{\xi_D - \mu_{0,R,D}}{\sqrt{2\sigma_{0,R,D}^2}}\right)^2\right) \times \frac{1}{\sqrt{2\sigma_{0,R,D}^2}} \operatorname{erf}\left(\frac{\xi_R - \mu_{0,S,R}}{\sqrt{2\sigma_{0,S,R}^2}}\right) \quad (58)$$

We also know that the value of the step size λ_k can be changed at each iteration, which can be obtained as

$$P_e(\xi^{(k)} + \lambda_k d^{(k)}) = \min_{\lambda \geq 0} P_e(\xi^{(k)} + \lambda d^{(k)}) \quad (59)$$

In our problem, we set the initial iteration $k = 1$ and initial point $\xi^{(1)} = (0, 0)^T$. Then, we calculate the gradient $\nabla P_e(\xi^{(k)})$, magnitude of gradient $\|\nabla P_e(\xi^{(k)})\|$, and gradient direction d^k . If $\|d^{(k)}\| \leq \varepsilon$, the algorithm stops, and we obtain the optimal point $\xi^* = \xi^{(k)}$ with minimum bit error probability $P_e(\xi^*) = P_e(\xi^{(k)})$. Otherwise, we set $k := k + 1$ and $\xi^{(k+1)} = \xi^{(k)} + \lambda_k d^{(k)}$, and this process is repeated until the gradient magnitude is small enough. The proposed algorithm based on the gradient descent method for solving our optimization problem is shown in **Algorithm 1**.

Algorithm 1 Iterative Minimum Error Probability Optimal Algorithm

- Step1:** Initialization: set $\xi^{(1)} = (0, 0)^T \in \mathbb{R}^n$, $\varepsilon > 0$ and $k = 1$;
- Step2:** Calculate search direction: $d^{(k)} = -\nabla P_e(\xi^{(k)})$;
- Step3:** If $\|d^{(k)}\| \leq \varepsilon$, stop;
Otherwise, Starting from $\xi^{(k)}$, we use one dimensional search along $d^{(k)}$, then calculate λ_k , make $P_e(\xi^{(k)} + \lambda_k d^{(k)}) = \min_{\lambda \geq 0} P_e(\xi^{(k)} + \lambda d^{(k)})$
- Step4:** Let $\xi^{(k+1)} = \xi^{(k)} + \lambda_k d^{(k)}$, set $k := k + 1$, go step 2.
- return** ξ^* , $P_e(\xi^*)$;

Gradient descent can be applied to multi-dimensional space for solving an optimization problem. In particular, it can work in infinite-dimensional space. The search space can be regarded as a function space, and the descent direction is obtained by taking the Fréchet derivative of the function and minimizing it. If the curvature of the presented function differs greatly in different directions, then the gradient descent can calculate the local minimum through multiple iterations to achieve a required accuracy. Preconditioning is a good choice to analyze this function. It can change the geometric structure of the space, making the shape of the function level sets like concentric circles. However, the cost of preconditioning is relatively high in the construction and calculation [44].

VI. CAPACITY ANALYSIS

The capacity is defined as the maximum mutual information, which is one of the central results of information theory. By mapping the information into the corresponding ‘‘symbol interval’’ transmission sequence to the channel, we can

TABLE 2. System parameters for simulations.

Parameter	Symbol	Value
Probability of bit 1	P_1	$\frac{1}{2}$
Diffusion coefficient	D	$4.365 \times 10^{-10} m^2/s$
Radius of node R	r_R	5nm
Radius of node D	r_D	5nm

reconstruct the source message at the output reliably, i.e., with very low error probability, even in the presence of noise. The capacity is the highest information rate at which reliable communication can be achieved [45]. The authors in [31], [46] derive the capacity expressions of dual-hop and multi-hop diffusion-based MC networks with ISI, MSI, and errors.

We analyze the capacity of relay-assisted MC system, which includes the impact of ISI, SI, and noise. For tractability, we make assumptions on the capacity similar to those in [31], [46]. First, we consider a binary channel, with inputs $X[l]$ and corresponding outputs $Y[l + 1]$ in the l^{th} time slot. The mutual information is given as

$$I(X[l], Y[l + 1]) = \sum_{x[l] \in \{0, 1\}} \sum_{y[l+1] \in \{0, 1\}} Pr(x[l], y[l + 1]) \times \log_2 \frac{Pr(y[l + 1] | x[l])}{Pr(y[l + 1])} \quad (60)$$

The joint probability $Pr(x[l], y[l + 1])$ and marginal probability $y[l + 1]$ can be written as

$$Pr(x[l], y[l + 1]) = Pr(y[l + 1] | x[l])Pr(x[l])$$

$$Pr(y[l + 1]) = \sum_{x[l] \in \{0, 1\}} Pr(y[l + 1] | x[l])Pr(x[l]) \quad (61)$$

Substituting (61) into (60), the mutual information is given in the expression (62), as shown at the bottom of the next page, where the conditional probabilities $P_e[l | x_S''[l]]$ can be written in term of $P_{FA}^{S,D}[l + 1]$ and $P_D^{S,D}[l + 1]$ as

$$Pr(y[l + 1] = 1 | x[l] = 0) = P_{FA}^{S,D}[l + 1] = P_e[l | x_S''[l] = 0]$$

$$Pr(y[l + 1] = 0 | x[l] = 0) = 1 - P_{FA}^{S,D}[l + 1] = 1 - P_e[l | x_S''[l] = 0]$$

$$Pr(y[l + 1] = 1 | x[l] = 1) = P_D^{S,D}[l + 1] = 1 - P_e[l | x_S''[l] = 1]$$

$$Pr(y[l + 1] = 0 | x[l] = 1) = 1 - P_D^{S,D}[l + 1] = P_e[l | x_S''[l] = 1] \quad (63)$$

The capacity of the relay-assisted channel with ligand-receptor binding can be calculated by maximizing the average mutual information $I(X[l], Y[l + 1])$ as [47]

$$C = \max_{p_1} I(X[l], Y[l + 1]) \text{ bits/slot} \quad (64)$$

where the maximization is taken over the set of the probability distributions p_1 for the discrete input. Generally, the capacity of relay-assisted MC is achieved by a uniform distribution on the discrete inputs, e.g., $p_1 = p_0 = \frac{1}{2}$.

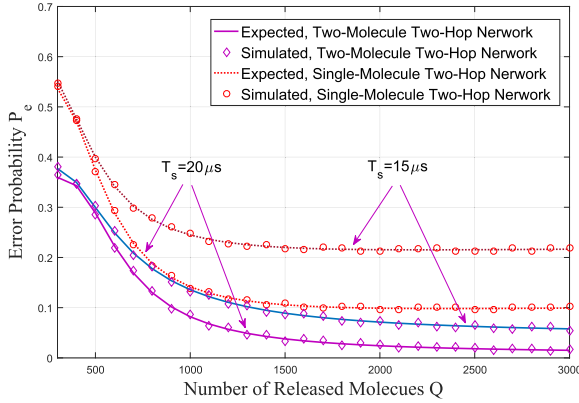


FIGURE 3. Error rate probability of the two-hop diffusion-based MC system for a varying released molecules Q with $D = 4.365 \times 10^{-10} m^2/s$, $d_{S,R} = d_{R,D} = 1.5nm$, $\xi_R = \xi_D = 500$, $T_S = 20\mu s$ and $T_S = 15\mu s$.

VII. RESULTS AND DISCUSSIONS

In this section, we present the analytical and simulation results to evaluate the performance of the proposed two-hop network. A particle-based stochastic simulator is used in our simulations [42]. Molecules undergo Brownian random motion in each time step. We use the error probability and capacity as the performance metric and reveal the effect of the number of molecules and detection threshold.

To compare the performance of different relaying schemes, we set the physical parameters of the two-hop network to be constant in the theoretical analysis and simulation. We list the model parameters in Table 2. In the simulation, we divide the time into small steps and track the positions of messenger molecules in the released medium. The motion of the molecules is independent at each time step. We assume that source node and relay node emit the same number of messenger molecules, and that the two types of molecules have the same diffusion coefficient D . The parameters that we can change during the simulation are the number of released molecules Q , detection threshold ξ , and noise variance σ_{Noise}^2 .

Figure 3 shows the error probabilities of the 2M2H scheme and the 1M2H scheme versus the number of released molecules Q . In these results, we set the number of receptors on nodes R and D $R_{T_R} = R_{T_D} = 1000$, detection threshold $\xi_R = \xi_D = 500$, and time slots T_S equal to $20\mu s$ and $15\mu s$. First, the simulation values are in good agreement with the theoretical curves, which indicate that our theoretical analysis is accurate. It shows that the error probability P_e is a

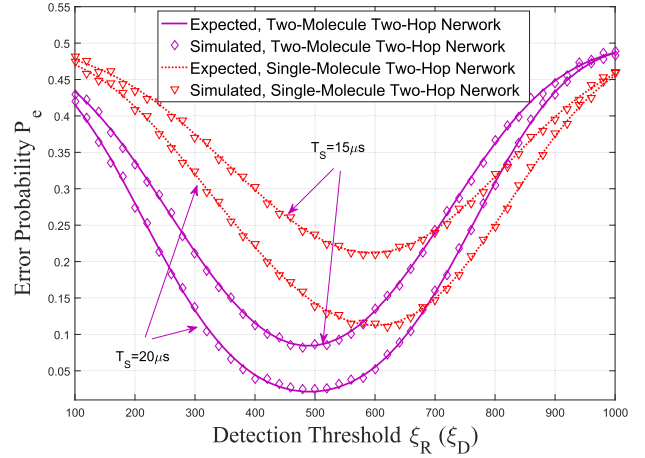


FIGURE 4. Error rate of diffusion-based two-hop MC systems versus detection threshold with $D = 4.365 \times 10^{-10} m^2/s$, $d_{S,R} = d_{R,D} = 1.5nm$, $Q = 3000$, $T_S = 20\mu s$ and $T_S = 15\mu s$.

decreasing function of released molecules Q . With the increase of the number of released molecules, the error probability slowly decreases. Since the 2M2H scheme has two types of molecules for signal transmission, it has no self-interference (SI). However, the 1M2H scheme has not only SI, but also ISI from the source node. Hence, the 2M2H scheme has better system performance than the 1M2H scheme. The results also show that increasing time slot T_S can improve the performance of the two relaying schemes, because increasing T_S can reduce the impact of ISI.

Figure 4 shows the error probability of two-hop network versus detection threshold. We illustrate the performances of the 2M2H scheme and the 1M2H scheme for $Q = 3000$, $R_{T_R} = R_{T_D} = 1000$, $\xi_R = \xi_D = \xi$ and time slots T_S equal to $20\mu s$ and $15\mu s$. The simulation results reveal that the 2M2H scheme has better performance than the 1M2H scheme in most cases. That is because the 2M2H network can effectively mitigate the ISI, but the 1M2H network is seriously affected by ISI and self-interference. Hence, the 2M2H network performs significantly better than the 1M2H network. It is also very interesting that the networks have different optimal thresholds for the 2M2H and the 1M2H, respectively. Further, these relaying schemes in $T_S = 20\mu s$ achieve lower error probability in comparison to the relaying schemes in $T_S = 15\mu s$.

Figure 5 shows the capacity of a two-hop MC system as a function of the released molecules Q , for time slots T_S

$$\begin{aligned}
 & I(X[l], Y[l + 1]) \\
 &= p_1 Pr(y[l + 1] = 0 | x[l] = 1) \log_2 \frac{Pr(y[l + 1] = 0 | x[l] = 1)}{p_0 Pr(y[l + 1] = 0 | x[l] = 0) + p_1 Pr(y[l + 1] = 0 | x[l] = 1)} \\
 &+ p_1 Pr(y[l + 1] = 1 | x[l] = 1) \log_2 \frac{Pr(y[l + 1] = 1 | x[l] = 1)}{p_0 Pr(y[l + 1] = 1 | x[l] = 0) + p_1 Pr(y[l + 1] = 1 | x[l] = 1)} \\
 &+ p_0 Pr(y[l + 1] = 0 | x[l] = 0) \log_2 \frac{Pr(y[l + 1] = 0 | x[l] = 0)}{p_0 Pr(y[l + 1] = 0 | x[l] = 0) + p_1 Pr(y[l + 1] = 0 | x[l] = 1)} \\
 &+ p_0 Pr(y[l + 1] = 1 | x[l] = 0) \log_2 \frac{Pr(y[l + 1] = 1 | x[l] = 0)}{p_0 Pr(y[l + 1] = 1 | x[l] = 0) + p_1 Pr(y[l + 1] = 1 | x[l] = 1)} \tag{62}
 \end{aligned}$$

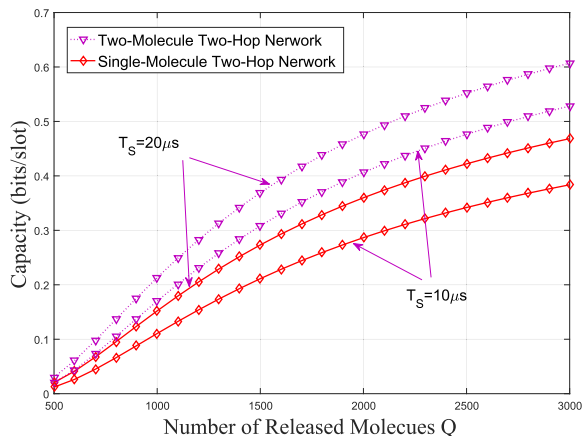


FIGURE 5. Capacity of diffusion-based two-hop MC system for a varying released molecules Q with $D = 4.365 \times 10^{-10} m^2/s$, $d_{S,R} = d_{R,D} = 1.5nm$, $\xi_R = \xi_D = 500$, $T_S = 20\mu s$ and $T_S = 10\mu s$.

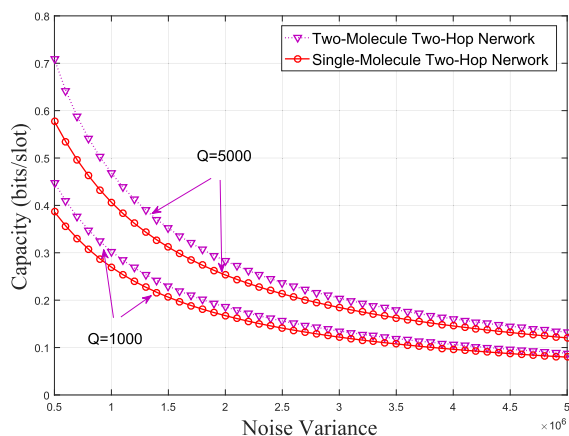


FIGURE 6. Capacity of diffusion-based two-hop MC system for a varying noise variance σ_{Noise}^2 with $D = 4.365 \times 10^{-10} m^2/s$, $d_{S,R} = d_{R,D} = 1.5nm$, $Q = 1000$ and $Q = 5000$.

equal to $20\mu s$ and $15\mu s$. The maximum mutual information is achieved when the probabilities of information symbol are equal, *i.e.*, $P_1 = P_0 = 0.5$. Equation (64) is used for the theoretical analysis of capacity. It is clear that the capacity of MC systems significantly increases with the increase of the number of released molecules. That is because increasing the number of transmission molecules increases the energy in the signal. Compared with the 1M2H system, the 2M2H system can achieve greater capacity values. Because the 1M2H system is affected by ISI and SI, which has a deleterious effect on performance. In addition, increasing the time slot T_S can achieve greater capacity.

Figure 6 shows the capacity of two-hop molecular communication system. It is clear that the capacity of relay-assisted MC systems significantly decreases with the increase of the noise variance σ_{Noise}^2 . In addition, we can also conclude that the 2M2H system achieves greater capacity values in comparison to the 1M2H system for $Q = 1000$ and $Q = 5000$. This is because the 2M2H system eliminates SI. Furthermore, as noted previously, more released molecules means greater channel capacity.

VIII. CONCLUSION

In order to improve the range of diffusion-based molecular communication systems, we present a relay-assisted communication network in this paper. We assume that two different types of molecules and one type of molecule are utilized in 2M2H scheme and 1M2H scheme, respectively. The receiver is a bio-inspired nanomachine whose surface receptors capture molecules dominated by the ligand-receptor binding mechanism. We derive a closed-form expression of bit error probability for the relay-assisted network. We propose an optimization problem and solve it using an algorithm based on the gradient descent method to find the joint optimal detection threshold. In addition, we obtain an expression for channel capacity for two-hop molecular communication scenario. Numerical results confirm the accuracy of the derived expression of error probability, and show that the 2M2H relay scheme has better performance than 1M2H scheme.

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