On the Limits of Molecular Communication with Coexisting Biological Systems Towards the Internet of Bio-Nano Things

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***Abstract*—Interference is a key challenge for communication systems, whether wireless for the Internet of Things or emerging approaches for the Internet of Bio-Nano Things. In the case of molecular communication between biochemical systems, interference can impact not only other communication systems, but also any nearby biological system. This leads to a different coexistence problem, where communication is constrained such that the function of the biological system is preserved. In this paper, we develop a new model for the interactions between the communication and biological systems, incorporating memory in the channel between the communication and biological systems. We then obtain an impossibility result limiting the amount of information that can be transmitted. In particular, the number of messages scales as $\sqrt{n}$ with the blocklength n.**

I. Introduction

A key challenge for wireless communication networks in the Internet of Things (IoT) is interference. That is, how should devices communicate in such a way that nearby communication networks can still operate reliably or *coexist*? As part of the emerging *Internet of Bio-Nano Things*, the coexistence problem in the IoT is in fact characteristic of communication in other regimes. This is particularly true in nano or micro-scale systems exploiting molecular communications.

Although ubiquitous in biological systems, information exchange via the transfer of molecules—known as *molecular communications*—has only recently been studied as a potential mechanism in artificial communication systems [1]. One of the most popular molecular communication methods is via diffusion [2], where information is encoded in the state of one or molecules which then diffuse through a fluid medium to a receiving device.

Due to the fact that diffusion of a finite number of molecules follows a random walk, the motion of each molecule may lead it to the receiver in an unpredictable fashion. A consequence is that interference may arise when multiple transmissions from different transmitters occur at the same time. This kind of interference can be seen as analogous to the interference that arises in wireless networks, and a number of methods have been proposed to minimize the impact [3].

However, the coexistence problem in molecular communications is further complicated by another factor. Unlike most wireless networks, molecular communication systems have often been proposed to operate in complex biochemical systems, which may be sensitive to the information-carrying molecules. Therefore, it is critical to understand not only how to limit interference between molecular communication networks, but also the impact of the communication mechanism on its environment. For example, many biological systems are sensitive to changes in Ca^{2+} concentrations, which have been proposed as a communication mechanism [4]. In particular, varying the Ca^{2+} concentration near a cell can cause structural changes to the membrane [5].

Recently, the problem of coexistence with the environment has been formalized by the first author in [6], [7]. In this formalization, external biochemical systems are modeled by deterministic chemical reaction systems. The impact of the molecular communication system is then evaluated in terms of changes to steady-state concentrations of chemicals inside the biological system, which are often intimately tied to the function of the biological system [8]. In the model developed in [7], an additional coexistence constraint was shown to have a dramatic effect on the rate of data transmission via a new connection to the problem of covert communications [7].

Nevertheless in [7], a number of simplifying assumptions were made. In particular, it was assumed that the biological system operated near the thermodynamic limit—justifying a deterministic model for the evolution of the quantity of each chemical. However, in many biological systems, it is now understood that random fluctuations play a crucial role [9]. As such, a stochastic model based on the chemical master equation is necessary. A further assumption in [7] was that the state of the biological system was reset between every transmission by the molecular communication system. In reality, this assumption is unlikely to hold for most systems.

In this paper, we propose a new formalization of the coexistence problem between a molecular communication system and its environment. Our formalization introduces both stochasticity into the state of the biological system and removes the reset assumption, allowing for the state to depend on previous transmissions. This overcomes two key issues in the model proposed in [7].

In the new model, we show that establishing fundamental limits of communication under a coexistence constraint remains closely tied to the problem of covert communications. Nevertheless a key difference in our model is that the channel between the transmitting device and the biological system is Markovian; i.e., the channel has memory. In this setting, we derive new limits on the amount of transmitted information. In

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particular, when the channel between the transmitter and the biological system is governed by a time-homogeneous Markov chain, the maximum amount of transmitted information can be no better than the $\sqrt{n}$ law (where n is the blocklength) also obtained under the model in [7].

II. System Model

In this section, we formalize the problem of molecular communication near a biological system. Due to the presence of these two systems, we introduce models both for their individual behavior and also interactions between them. In particular, we adopt an established model for the molecular communication network exploiting diffusion. On the other hand, to model the biological system we exploit an approach widely adopted within systems biology, where the biological system is viewed as a stochastic chemical reaction network. We remark that, with the exception of the model for the biological system, our setup is consistent with [7].

A. Molecular Communication Network Model

We now present the model for the molecular communication network, which is consistent with existing work (see e.g., [10], [11]). In this model, information is communicated from the transmitting device to the receiver via the modulation of the number of molecules that are emitted, known as concentration shift keying (CSK) [2]. We assume that symbols are sent at the beginning of a time slot of duration T and the transmitter and receiver are separated by a distance d.

The molecular communication network seeks to transmit a message $m \in \mathcal{M} = \{1, \ldots, M\}$ over n time slots. To do this, the system is equipped with an encoder $\mathcal{E} : \mathcal{M} \to \mathcal{X}^n$, where $\mathcal{X} = \{x_0, x_1\}$ corresponds to the set of symbols. Due to fact that CSK is employed, each symbol is the number of information molecules emitted by the molecular communication network. The chemical species corresponding to each information molecule is assumed to be the same in each transmission. Moreover, the symbol x_0 is assumed to be an *innocent symbol*. For example, the innocent symbol may correspond to the case where the transmitter does not emit any molecules. We remark that the innocent symbol may still carry information.

We model the channel between the transmitter and the receiver in time slot i by the transmition probability $P_{Y_i|X_i}$, where X_i is the number of molecules emitted in time slot i and Y_i is the number of information molecules observed at the receiver. When a molecule arrives at the receiver, we assume that it is absorbed, corresponding to the absorbing receiver [2].

In general, the transition probability $P_{Y_i|X_i}$ may depend on i due to the presence of inter-symbol interference. In this work, we assume that this is not the case (i.e., all information molecules are absorbed by the end of the time slot), which arises when the symbol period is sufficiently long. As such, the channel between the transmitter and the receiver is memoryless and determined by the transition probability $P_{Y|X}$, independent of the time slot. As a consequence, the system is modeled by a discrete memoryless channel $(\mathcal{X}, P_{Y|X}, \mathcal{Y})$.

The receiver in the molecular communication network is equipped with a decoder $\mathcal{D} : \mathcal{Y}^n \to \mathcal{M}$. After observations from n time slots, the decoder forms an estimate of the transmitted message $m \in \mathcal{M}$, denoted by $\hat{m} \in \mathcal{M}$. For codewords of length n, the decoder has an average probability of error given by

$$P_{err}^{(n)} = \frac{1}{M} \Pr(\hat{m} \neq m | m \text{ sent}). \tag{1}$$

B. Stochastic Chemical Reaction Networks

Due to the fact that biological systems only contain a finite number of molecules within a finite volume, a probabilistic model for the time that individual reactions occur is typically more realistic than the deterministic model. To this end, suppose that there are r_0 chemical reactions involving s_0 chemical species $S_1, \ldots, S_{s_0}$. The network of chemical reactions is given by

$$\sum_{i=1}^{s_0} \nu_{ik} S_i \to \sum_{i=1}^{s_0} \nu'_{ik} S_i, \;\; k = 1, \ldots, r_0, \tag{2}$$

where $\nu_{ik}, \nu'_{ik} \in \mathbb{Z}_{\geq 0}$. We denote $\nu_k = [\nu_{1k}, \ldots, \nu_{s_0 k}]^T$ and $\nu'_k = [\nu'_{1k}, \ldots, \nu'_{s_0 k}]^T$.

At time t, the number of molecules for each species is described by a component of the random vector $\mathbf{X}(t)$. To account for the fact that reactions require individual molecules of each chemical species to be in close proximity, the rate that the k-th reaction occurs when the quantity of molecules for each species is given by $\mathbf{x}$ is denoted by $\lambda_k(\mathbf{x})$, called the *propensity*. If the k-th reaction occurs at time t, the new state is then

$$\mathbf{X}(t) = \mathbf{X}(t-) + \nu'_k - \nu_k. \tag{3}$$

Following [12], the number of times the k-th reaction occurs by time t is given by the counting process

$$R_k(t) = Y_k \left(\int_0^t \lambda_k(\mathbf{X}(s)) ds \right), \tag{4}$$

where the $Y_k, \;\; k = 1, \ldots, r_0$ are independent unit rate Poisson processes. As such, the state of the system at time t is given by

$$\mathbf{X}(t) = \mathbf{X}(0) + \sum_{k=1}^{r_0} R_k(t)(\nu'_k - \nu_k). \tag{5}$$

Unlike deterministic chemical reaction networks, stochastic chemical reaction networks do not generally converge to a unique steady-state with probability one. Instead, the steady-state behavior is described, when it exists, by a stationary measure. A characterization of the stationary measure for a large class of stochastic chemical reaction networks is given in [12].

C. Biological System Model

We now turn to the model of the biological system, which exploits a chemosensing mechanism in order to adapt to its environment; modeled via a stochastic chemical reaction network. In this mechanism, exemplified by EnvZ in bacteria chemotaxis [8], molecules bind to receptors on the surface of the receiving device and through phosphorylation are converted to molecules used internally for regulation.

In this paper, we assume that the chemosensing mechanism is sensitive to the molecules used to transmit information in the molecular communication network. Due to the fact that some molecules from the communication network may diffuse to the biological system, the behavior of the biological system may be affected.

The chemosensing mechanism of a biological system can also be sensitive to more than one type of chemical species; for example, this is the case for bacteria chemotaxis [8]. We assume that the phosphorylation processes for molecules bound to the receptors occurs slower than the time for information molecules to reach the biological system. As a consequence, we associate to each symbol period the total number of molecules bound to receptors before the phosphorylation process begins, denoted by Z_i. In particular,

$$Z_i = Z_{back,i} + Z_{inf,i} + Z_{rev,i}, \tag{6}$$

where $Z_{inf,i}$ corresponds to the number of bound information molecules and $Z_{back,i}$ is the number of naturally occuring molecules to which the chemosensing mechanism is sensitive. We assume that the $Z_{back,i}$, $i = 1, 2, \ldots$ are mutually independent. The term $Z_{rev,i}$ is the number of molecules bound to the receptors due to reverse leakage reactions, where phosphorylated molecules are converted back to molecules bound to the receptors.

We assume that the stochastic chemical reaction network modeling the biological system admits a stationary measure, and is in the steady-state before the end of each symbol period. Let $\mathbf{W}_0$ be the initial quantity of each species *inside* the biological system at the beginning of communication. As such, the stationary measure of any species S internal to the biological system is denoted by $\pi_{\mathsf{S}}(Z^n, \mathbf{W}_0)$, dependent on $Z^n = (Z_1, \ldots, Z_n)$ and $\mathbf{W}_0$ and the random variable $\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)$ denotes the quantity of molecules of species S at any given time n when the biologial system reaches the steady-state.

In many biological systems, there is a species that has a particularly significant impact on behavior. For example, CheY in bacterial chemotaxis [8]. As such, we assume that the species S plays this role.

III. Coexistence Constraints and Connections with Covert Communications

A. Communication Constraints

Our goal is to design a communication strategy such that the molecular communication network is reliable and the function of the biological system is not disrupted; that is, the two systems coexist. The reliability requirement is modeled by the constraint

$$\lim_{n\to\infty} P_{err}^{(n)} = 0, \tag{7}$$

where $P_{err}^{(n)}$ is the average probability of error using a code with blocklength n (we formally define this probability of error in the following section).

Due to the importance of steady-state concentrations on biological function, we formalize the coexistence constraint as follows. Recall that $\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)$ is the random variable corresponding to the steady-state concentration of the chemical species S affecting the function of the biological system, with distribution $P_{\Phi_{\mathsf{S}}(Z^n,\mathbf{W}_0)}$, and Z_i is the quantity of molecules bound to receptors during time slot i. At time n, a natural approach to provide coexistence is therefore to ensure that for some $\delta > 0$,

$$|\mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)] - \mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)|X^n = x_0^n]| < \delta \tag{8}$$

where we adopt the notation $x^n = (x_1, \ldots, x_n)$.

In (8), $P_{\Phi_{\mathsf{S}}(Z^n,\mathbf{W}_0)}$ is the distribution of the quantity of molecules of S at the steady-state within time slot n when there is a transmission. Similarly, $P_{\Phi_{\mathsf{S}}(Z^n,\mathbf{W}_0)|X^n=x_0^n}$ is the distribution of the number of molecules that are observed by the biological system when nothing is transmitted by the molecular communication network. The condition requires that the expected steady-state concentration within the biological system with communication must not differ significantly from the expected steady-state concentration without communication.

Due to the difficulty in characterizing the steady-state distribution for S, it is desirable to obtain a bound for (8) in terms of the distribution of Z^n. To this end, let $\Phi_{\max} = \max\{\Phi_S(z^n, \mathbf{w}_0) : z^n \in \mathcal{Z}^n\}$, determined by the maximum number of information molecules, background molecules, and molecules inside the biological system. Following an argument similar to [7], the following result holds. Due to space constraints the proof is omitted.

Theorem 1. *Let $P_{\Phi_{\mathsf{S}}(Z^n,\mathbf{W}_0)}$ be the distribution of the quantity of molecules of S at the steady-state within time slot i when there is a transmission. Similarly, $P_{\Phi_{\mathsf{S}}(Z^n,\mathbf{W}_0)|X^n=x_0^n}$ is the distribution of the number of molecules that are observed by the biological system when n copies of the innocent symbol x_0^n are transmitted by the molecular communication network. Then,*

$$\begin{aligned}&|\mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)] - \mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)|X^n = x_0^n]| \\ &\leq \Phi_{\max}\sqrt{2D(P_{Z^n}||P_{Z^n|X^n=x_0^n})},\end{aligned} \tag{9}$$

where $D(\cdot||\cdot)$ denotes the Kullback-Leibler divergence.

An appropriate coexistence constraint is therefore that

$$\lim_{n\to\infty} D(P_{Z^n}||P_{Z^n|X^n=x_0^n}) = 0. \tag{10}$$

A key observation is that the constraint in (10) bears a strong similarity to the main constraint in the problem of covert

communications or communication with a low probability of detection. Next, we review this connection initially observed in [7].

B. Connections with Covert Communications

The standard covert communication problem (studied, for example, in [13]) involves two legitimate users who attempt to transmit over a discrete memoryless channel $(\mathcal{X}, P_{Y|X}, \mathcal{Y})$ without being detected by a warden, who observes the signals through another discrete memoryless channel $(\mathcal{X}, P_{Z|X}, \mathcal{Z})$. The key assumptions in this problem are [13]:

- There exists an innocent symbol $x_0 \in \mathcal{X}$, corresponding to the input of the channel when no communication takes place. The distributions on the outputs of the two channels in this case are
$$P_0 = P_{Y|X=x_0},\ Q_0 = P_{Z|X=x_0}. \tag{11}$$
- There exists another symbol $x_1 \in \mathcal{X}$ with $x_1 \neq x_0$, inducing output distributions
$$P_1 = P_{Y|X=x_1},\ Q_1 = P_{Z|X=x_1}. \tag{12}$$
- $Q_1 \ll Q_0$ and $Q_1 \neq Q_0$, which[1] excludes the situations where either the warden would always detect a transmission with non-vanishing probability or would never detect it.
- $P_1 \ll P_0$, which guarantees that the receiver does not have an unfair advantage over the warden.

In the problem of covert communications, the transmitter aims to transmit a message W uniformly distributed on $[1, M]$ by encoding it into a codeword $\mathbf{X} = (X_1, \ldots, X_n)$ of n symbols with the help of a secret key S uniformly distributed on $[1, K]$. In particular, at the beginning of a block of n channel uses, the transmitter sets a switch T:

- if $T = 1$, the input is connected to the channel;
- otherwise the innocent symbol x_0 is sent n times.

Upon observing a noisy version $\mathbf{Y} = (Y_1, \ldots, Y_n)$ of $\mathbf{X}$ and knowing S, the objective is for the receiver to form reliable estimates $\hat{T}$ and $\hat{W}$ of T and W. For a codeword of length n, the error is defined as

$$P_{err}^{(n)} = \mathbb{E}_S[\Pr(W \neq \hat{W}|S, T = 1)] + \Pr(\hat{T} \neq 0|T = 0). \tag{13}$$

The goal in covert communications is then to establish scalings of $\log M$ and $\log K$ with n for which

$$\lim_{n\to\infty} P_{err}^{(n)} = 0 \tag{14}$$

and

$$\lim_{n\to\infty} D(\hat{Q}^n||Q_0^{\otimes n}) = 0, \tag{15}$$

where $Q_0^{\otimes n} = \prod_{i=1}^n Q_0$ and $\hat{Q}^n$ is the output distribution when communication takes place.

[1]Let Q, P be two probability measures. Then, $Q \ll P$ denotes that Q is absolutely continuous with respect to P.

It is now straightforward to identify an equivalence between the covert communication problem and our formalization of the molecular communication strategy. First observe that, for all n,

$$D(\hat{Q}^n||Q_0^{\otimes n}) = D(P_{Z^n}||P_{Z^n|X^n=x_0^n}). \tag{16}$$

Moreover, under the assumption that the switching strategy detailed above is used, the probability of error in (14) is precisely the probability of error in (7).

As noted in [7], the connection between the coexistence problem in molecular communications and covert communications provides a basis to establish fundamental limits of communication. However, until this point, covert communications has only been studied under the assumption of a *memoryless* channel between the transmitter and the warden. Since the analogous channel between the transmitter and the biological system in the molecular communication problem has memory, these results cannot be carried over. In the following section, we study this more general problem.

IV. Fundamental Limits

In this section, we establish fundamental limits of communication in the presence of constraints on the probability of error and the distribution of Z^n at the biological system. In particular, in our analysis we assume the switching strategy in Section III-B is employed. As such, the reliability and coexistence requirements are defined by (14), (15) and (16). There are three cases of interest: insensitive biological systems; the non-reversible model for the biological system; and biological systems governed by a Markov chain model.

A. Insensitive Model

In the case of insensitive biological systems, the presence of information molecules does not change the internal state of the biological system. Formally, this means that

$$|\mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)] - \mathbb{E}[\Phi_{\mathsf{S}}(Z^n, \mathbf{W}_0)|X^n = x_0^n]| = 0. \tag{17}$$

As such, the bound in Theorem 1 is not required. Moreover, there is no coexistence constraint on communication. Since the channel between the transmitter and receiver is memoryless, this means that

$$\lim_{n\to\infty} \frac{\log M}{n} < \sup_{P_X} I(X; Y), \tag{18}$$

where X and Y are equal in distribution to X_i, Y_i, respectively, for all i.

This scenario arises, for example, in systems that either have no chemosensing mechanism or admit robust adaptation [8]. In particular, in robust adaptation the initial quantities of chemical species in the biological system reach a minimum amount, the internal state of the biological system does not change. Hence, communication does not have an impact as long as the Z_{back} is sufficiently large and the initial transmission is delayed until the biological system's internal state is constant.

B. Non-Reversible Model

The case of non-reversible biological systems concerns the scenario where the chemosensing mechanism is non-reversible; that is, $Z_{rev,i} = 0,\ i = 1, 2, \ldots, n$. In this case, the internal state of the biological system does not affect the number of molecules of Z_i. Since the background quantities of $Z_{back,i}$ are assumed to be independent and identically distributed at each symbol period, it follows that the channel between the transmitter and the biological system is memoryless and the result in [6] based on [13] holds. In particular,

$$\lim_{n\to\infty} \frac{\log M}{\sqrt{nD(P_{Z^n}||P_{Z^n|X^n=x_0^n})}} \leq \sqrt{\frac{2}{\chi_2(P_{Z|X=x_1}||P_{Z|X=x_0})}} D(P_{Y|X=x_1}||P_{Y|X=x_0}), \quad (19)$$

where

$$\chi_2(P_{Z|X=x_1}||P_{Z|X=x_0}) = \sum_{z\in\mathcal{Z}} \frac{(P_{Z|X=x_1}(z) - P_{Z|X=x_0}(z))^2}{P_{Z|X=x_0}(z)}. \quad (20)$$

C. Markovian Model

A yet more general model for the biological system is the Markovian model. In this case, the quantity Z^n can be decomposed in the form

$$Z^n = Z^n_{back} + Z^n_{inf} + Z^n_{rev}, \quad (21)$$

as detailed in Section II-C. Due to the fact that the biological system is governed by the chemical master equation, there is dependence between $Z_{rev,i}$ and $Z_{rev,i-1}$. As such, the channel between the transmitter and the biological system is not memoryless. A key question is whether an analogous result to (19) holds. We provide a partial answer to this question when the output process $(Z_i,\ i = 1, 2, \ldots)$ forms a time homogeneous Markov chain. In particular, the following theorem gives an impossibility result for molecular communication systems that must coexist with a nearby biological system. Due to space constraints, the proof which closely follows [13], is omitted.

Theorem 2. *Consider a system with a memoryless channel $P_{Y^n|X^n}$ and a channel between the transmitter and the biological system $P_{Z^n|X^n}$ where $(Z_i,\ i = 1, 2, \ldots)$ forms a time homogeneous Markov chain. Further, we assume that for all i, $P_{Y_i|X_i=x_1} \ll P_{Y_i|X_i=x_0}$, $P_{Z_i|X_i=x_1} \ll P_{Z_i|X_i=x_0}$, and $P_{Z_i|X_i=x_1} \neq P_{Z_i|X_i=x_0}$. Consider a sequence of communication schemes with increasing blocklength n characterized by $\epsilon_n = P^{(n)}_{err}$ and $\delta_n = D(P_{Z^n}||P_{Z^n|X^n=x_0^n})$. If $\lim_{n\to\infty}\epsilon_n = \lim_{n\to\infty}\delta_n = 0$, we have*

$$\lim_{n\to\infty} \frac{\log M}{\sqrt{nD(P_{Z^n}||P_{Z^n|X^n=x_0^n})}} \leq D(P_{Y|X=x_0}||P_{Y|X=x_1}) \times \sqrt{\frac{2}{\mathbb{E}_{P^*_{Z_1}}\left[\chi_2(P_{Z_2|Z_1,X_2=x_1}, P_{Z_2|Z_1,X_2=x_0})\right]}}, \quad (22)$$

where $P^*_{Z_1}$ minimizes the expectation.

Theorem 2 provides an impossibility result, which means that no scheme satisfying both the probability of error and the coexistence constraint can have $\log M$ scaling faster than $O(\sqrt{n})$.

V. Conclusions

We have developed a new model for the coexistence problem in molecular communications. A key feature of this model is that it accounts for memory inherent in the state of biological systems governed by stochastic chemical reaction networks. These models are ubiquitous in a wide range of biochemical systems and therefore our approach should be applicable in many scenarios.

Nevertheless, memory in the channel introduces new challenges in information and communication theoretic characterizations of molecular communication strategies. We have established a connection to the covert communication problem for the new model, extending our prior work in [7]. Nevertheless, standard covert communication models assume memoryless channels. Accounting for the presence of memory, we have established an impossibility result for the amount for information that can be transmitted reliably in n channel uses such that the function of the biological system is preserved.

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