A Fundamental Framework for Molecular Communication Channels: timing & payload

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Abstract—As system sizes shrink, the usual macroscopic methods of communication using electromagnetic and acoustic waves become increasingly less efficient owing to mismatches between realizable antenna sizes and the propagation characteristics of the medium. Thus, at the scale of microns and below, communication methods which utilize molecular messengers become attractive, a notion supported by the ubiquity of molecular signaling in biological systems, sometimes using identical molecules (tokens) and sometimes using tokens with embedded payloads such as, for instance, m-RNA. Here we consider a wide range of molecular signaling techniques used by biological systems, and by applying simple information-theoretic concepts seek to develop an outer-bound model which distills the plethora of channel details to (1) timing, and (2) molecular "packet" payloads as the information-bearing agents. We find that both bits/joule and bits/sec/joule efficiencies are greatly increased by using tokens with only 1-bit payloads and that overall information carriage efficiency (and consequently, bit rate) is best served by using tokens with large payloads.

Index Terms—Diffusion channel capacity, molecular signaling, timing channel capacity

I. INTRODUCTION

Biological systems are networks of intercommunicating elements at whatever level one cares to consider – (macro)molecules, cells, tissues, organisms, populations, microbiomes, ecosystems, and so on. It is therefore no wonder that communication theorists have plied their trade heavily in this scientific domain (for a recent review, see [1]). Biological systems offer a dizzying array of processes and phenomena through which the same and different tasks, communication or otherwise, might be accomplished (see, for example, [2]–[8]). Identifying the underlying mechanisms (signaling modality, signaling agent, signal transport, and so on) as well as the molecules and structures implementing the mechanisms is no small undertaking. Consequently, experimental biologists use a combination of prior knowledge and what can only be called instinct to choose those systems on which to expend effort. Guidance may be sought from evolutionary developmental biology – a field that compares the developmental processes of different organisms to determine their ancestral relationship and to discover how developmental processes evolved. Insights may be gained by using statistical machine learning techniques to analyze heterogeneous data such as the biomedical literature and the output of so-called "omics" technologies – genomics (genes, regulatory, and non-coding sequences), transcriptomics (RNA and gene expression), proteomics (protein expression), metabolomics (metabolites and metabolic networks), pharmacogenomics (how genetics affects hosts' responses to drugs), and physiomics (physiological dynamics and functions of whole organisms).

Typically, the application of communication theory to biology starts by selecting a candidate system whose components and operations have been already elucidated to varying degrees using methods in the experimental and/or computational biology toolbox [9], [10] and then applying communication

theoretic methods [1], [7], [11]–[13]. However, we believe that communication theory in general and information theory in particular are not merely system analysis tools for biology. That is, given energy constraints and some general physics of the problem, an information-theoretic treatment can be used to provide outer bounds on information transfer in a *mechanism-blind* manner. Thus, rather than simply elucidating and quantifying known biology, communication theory can winnow the plethora of possibilities (or even suggest new ones) amenable to experimental and computational pursuit. Likewise, general application of communication-theoretic principles to biology affords a new set of application areas for communication theorists. Some aspects of the potential for communication theory as a new lens on biological systems are explored in [14].

In this light, here we seek to devise an abstraction that encompasses the myriad biological processes and phenomena, utilize it to devise a simpler model suitable for communication-theoretic investigations, and analyze the resultant model. Specifically, numerous scenarios in biology that involve the transmission of information can be synthesized and summarized as "inscribed matter" [15] is sent by an emitter, moves through a medium, and arrives eventually at its destination receptor where it is interpreted. Scenarios illustrating the complexity and diversity that our abstraction attempts to capture include the following:

- Messenger RNA molecules (mRNAs) that are transcribed from the genome migrate from the nucleus to the cytoplasm where they are translated by the ribosome into proteins.
- Molecules of the neurotransmitter acetylcholine (Ach) that are released by the presynaptic neuron terminal diffuse through the synaptic cleft and bind to nicotinic Ach receptors on the motor end plate.
- Ions, molecules, organelles, bacteria and viruses that are present in one cell are shipped through a thin membrane channel (tunneling nanotube) to the connected cell where they elicit a physiological response.
- Membrane-bound vesicles that contain a variety of materials and substances translocate through the cytoplasm to the cell membrane where release their contents into the extracellular environment.
- Malignant cells that have escaped the confines of a tissue circulate through the bloodstream to other sites where they re-penetrate the vessel walls and can seed a new tumor.
- Chemicals factors that are secreted or excreted by an individual travel outside the body where they are sensed by a member of the same species triggering a social or behavioral response.

We argue that the key common physical features of all these examples from an information transfer perspective are:

- Molecule emission and reception times – inscribed matter (token) timing information
- Variable molecule structure/composition – token information payload

Now, although the abstraction accommodates a wide range of spatiotemporal scale and types of emitters, inscribed matter, and receptors, we recognize that it also neglects many biologically important features. For example, the suite of signaling quanta – molecules, macromolecular complexes, organelles, cells, and so on – that are released is not necessarily the same as that which reaches the target because some may be changed (eukaryotic mRNAs are modified post-transcriptionally), some may be removed (Ach can be degraded by the enzyme Ach-esterase), some never arrives (the random path produced by diffusion may result in a trajectory that leads away from the target), and some may be detected (bound) multiple times at a receptor surface. In addition, the movement of inscribed matter may be passive or active, may or may not require energy and so on.

However, despite these real complications, the idea of token timing information and token information payloads still pertains as illustrated in FIGURE 1. That is, tokens are released at the transmitter and captured by a receiver after transport through some medium. The information flow between emitter and receiver is bounded from above by the information content of each token (payload) and the first-passage time of tokens from emitter to the arbitrarily close dashed receiver boundary. Tokens may be distinguishable, partially distinguishable, indistinguishable or any combination. However, we will assume that transport is i.i.d. for all tokens of a given type – a specific signaling protein, ionic species or the like. However, once tokens are constructed (or harvested)
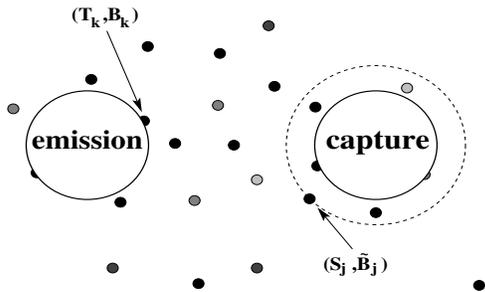
Fig. 1. **Point-to-Point Molecular Signaling Channel Abstraction:** An emitted token with payload B_k emitted at time T_k is "processed" by the channel to produce a token which pierces the dashed reception boundary at corresponding time S_k (not shown) with (possibly modified) payload $\tilde{B}_k$ (not shown). Also shown is the arrival of another token launched at time T_j and arriving at time S_j with correspondingly corrupted payload $\tilde{B}_j$.

and emitted by the transmitter, the channel between the sender and receiver (which may include the receptor structure – hence the inclusion of the dashed boundary around the receiver in FIGURE 1) cannot increase the information carried *no matter how the tokens are "processed"* either by the medium or by the capture mechanism and receiver [16]. Thus, by considering *only* timing and payload, we can derive upper bounds for point to point molecular communication.

Furthermore, it should also be noted that this "finest grain" timing/payload abstraction encompasses the more usual signal concentration abstraction favored in most biological communication (i.e., [7]) as well as communication-theoretic work (i.e.,

[17]–[23]). That is, if time resolution is sufficiently coarsened, the detailed timing structure is lost and we are left with tokens received per unit time – or time-varying concentration.

Thus, we argue that token timing and payload are *the most basic information carriers for molecular communication systems*. Therefore, the mutual information between token release and capture as well as the mutual information between emitted payload and captured payload provide inviolable upper bounds for information carriage rates between senders and receivers of molecular messages.

Of course, the existence of two fundamental communication modalities raises an obvious question: *What is the interplay between payload and timing information for molecular channels?* To understand this interplay, we must first consider timing channels with identical tokens [20], [24]–[29]. We will then show how the identical token model extends to a model with distinguishable tokens carrying information payloads [20]. We will then consider the energetics of token construction and examine the effects of timing and payload in the carriage of information over molecular channels.

II. PAPER ORGANIZATION

We begin with a problem overview and description taken from our previous work [26]–[30] which (re)introduces the necessary mathematical machinery (sections III and IV). Since the ideas associated with identical token channels are not yet mainstream, we feel this background must be included here for our arguments to be at all comprehensible. For this we apologize in advance. That said, for clarity we omit proofs of previous results. We then describe the energetics/cost of molecular channels (section VI) and show how previous identical-token channel results can be used to derive the capacities per unit cost (section VIII) on systems with token playloads. We conclude with a discussion of channel use regimes for which timing, payload and/or both mechanisms are energetically favorable.

III. PROBLEM OVERVIEW & NOTATION

Let us begin by assuming that M indistinguishable tokens are emitted at times $\{T_m\}$, $m = 1, 2, ..., M$ and each is captured by the receiver at times $\{S_m\}$. Note that under this assumption, the tokens themselves can carry no information payload since if they did, they would be, almost by definition, distinguishable in some way. The duration of token m's passage between source and destination is a random variable D_m. For a given species of token, these D_m are assumed i.i.d. with $f_{D_m}(d) = g(d) = G'(d)$ where $g()$ is some causal probability density with mean $\frac{1}{\mu}$ and CDF (cumulative distribution function) $G()$. We also assume that $g()$ contains no singularities.

Thus, the first portion of the channel is modeled as a sum of random M-vectors

$$\mathbf{S} = \mathbf{T} + \mathbf{D} \qquad (1)$$

for which we have

$$f_{\mathbf{S}}(\mathbf{s}) = \int_{\mathbf{0}}^{\mathbf{s}} f_{\mathbf{T}}(\mathbf{t})\mathbf{g}(\mathbf{s} - \mathbf{t})d\mathbf{t} \qquad (2)$$

where $\mathbf{g}(\mathbf{s} - \mathbf{t}) = \prod_{m=1}^{M} g(s_m - t_m)$ and we impose an emission deadline, $T_m \leq \tau(M)$, $\forall m \in \{1, 2, ..., M\}$.

At this point it is tempting make a direct analogy to *Bits Through Queues* [31]. However, since the tokens are identical

we cannot necessarily determine which arrival corresponds to which emission time. Thus, the final output of the channel is a reordering of the $\{S_m\}$ to obtain a set $\{\vec{S}_m\}$ where $\vec{S}_m \leq \vec{S}_{m+1}$, $m = 1, 2, ..., M - 1$. We write this relationship as

$$\vec{\mathbf{S}} = P_\Omega(\mathbf{S}) \tag{3}$$

where $P_k()$, $k = 1, 2, \cdots, M!$, is a permutation operator and Ω is a permutation index which produces an arrival-time-ordered $\vec{\mathbf{S}}$ from the argument $\mathbf{S}$. That is, $\mathbf{S}$ is sorted by arrival time to produce $\vec{\mathbf{S}}$. The associated emission time ensemble probability density $f_\mathbf{T}(\mathbf{t})$ is assumed causal, but otherwise arbitrary. We define the launch and capture of M tokens as a "channel use" and if we assume multiple independent channel uses, then the usual coding theorems apply [16] and the channel's figure of merit is the mutual information between $\mathbf{T}$ and $\vec{\mathbf{S}}$, $I(\vec{\mathbf{S}}; \mathbf{T})$.

We note that the event $S_i = S_j$ $(i \neq j)$ is of zero measure owing to the no-singularity assumption on $g()$, Thus, for analytic convenience we will assume that $f_\mathbf{S}(\mathbf{s}) = 0$ whenever two or more of the s_m are equal. This assumption also assures that the Ω which produces $\vec{\mathbf{S}}$ in equation (3) is unique.

Thus, the density $f_{\vec{\mathbf{S}}}(\vec{\mathbf{s}})$ can be found by "folding" the density $f_\mathbf{S}(\mathbf{s})$ about the hyperplanes described by one or more of the s_m equal until the resulting probability density is nonzero only on the region where $s_m < s_{m+1}$, $m = 1, 2, ..., M - 1$. Analytically we have

$$f_{\vec{\mathbf{S}}}(\vec{\mathbf{s}}) = \begin{cases} \sum_{n=1}^{M!} f_\mathbf{S}(P_n(\vec{\mathbf{s}})) & \vec{s}_1 < \vec{s}_2 < \cdots < \vec{s}_m \\ 0 & \text{otherwise} \end{cases} \tag{4}$$

We can likewise describe $f_{\vec{\mathbf{S}}|\mathbf{T}}(\mathbf{s}|\mathbf{t})$ as

$$f_{\vec{\mathbf{S}}|\mathbf{T}}(\vec{\mathbf{s}}|\mathbf{t}) = \begin{cases} \sum_{n=1}^{M!} f_{\mathbf{S}|\mathbf{T}}(P_n(\mathbf{s})|\mathbf{t}) & \vec{s}_1 < \vec{s}_2 < \cdots < \vec{s}_m \\ 0 & \text{otherwise} \end{cases} \tag{5}$$

which to emphasize the assumed causality of $g()$ we rewrite as

$$f_{\vec{\mathbf{S}}|\mathbf{T}}(\mathbf{s}|\mathbf{t}) = \begin{cases} \sum_{n=1}^{M!} \mathbf{g}(P_n(\mathbf{s}) - \mathbf{t})\mathbf{u}(P_n(\mathbf{s}) - \mathbf{t}) & \text{ordered } s_i \\ 0 & \text{o.w.} \end{cases} \tag{6}$$

where $\mathbf{u}(P_n(\mathbf{s}) - \mathbf{t}) = \prod_{m=1}^{M} u([P_n(\mathbf{s})]_m - t_m)$ and $u()$ is the usual unit step function. (Note that $[P_n(\mathbf{s})]_m$ is the mth component of the vector $P_n(\mathbf{s})$.)

With these preliminaries done, we can now begin to examine the mutual information between $\mathbf{T}$, $\mathbf{S}$ and $\vec{\mathbf{S}}$.

IV. Mutual Information Between $\mathbf{T}$ and $\vec{\mathbf{S}}$

The mutual information between $\mathbf{T}$ and $\mathbf{S}$ is

$$I(\mathbf{S}; \mathbf{T}) = h(\mathbf{S}) - h(\mathbf{S}|\mathbf{T}) \tag{7}$$

where $h()$ is differential entropy. Since the S_i given the T_i are mutually independent, $h(\mathbf{S}|\mathbf{T})$ does not depend on $f_\mathbf{T}(\mathbf{t})$. Thus, maximization of equation (7) is simply a maximization of the marginal $h(S)$ over the marginal $f_T(t)$, a problem explicitly considered and solved for a mean T_m constraint in [31] and under a deadline constraint with exponential i.i.d. $\{D_m\}$ in [26].

The corresponding expression for the mutual information between $\mathbf{T}$ and $\vec{\mathbf{S}}$ is

$$I(\vec{\mathbf{S}}; \mathbf{T}) = h(\vec{\mathbf{S}}) - h(\vec{\mathbf{S}}|\mathbf{T}) \tag{8}$$

Unfortunately, $h(\vec{\mathbf{S}}|\mathbf{T})$ now *does* depend on the input distribution and the optimal form of $h(\vec{\mathbf{S}})$ is non-obvious. So, rather than attempting a brute force optimization of equation (8) by deriving order distributions [20], [25], we invoke simplifying symmetries as in [28], [29]. First, we may assume [28], [29] that

$$f_\mathbf{T}(\mathbf{t}) = f_\mathbf{T}(P_n(\mathbf{t})) \quad \forall n \tag{9}$$

so that

$$f_\mathbf{S}(\mathbf{s}) = f_\mathbf{S}(P_n(\mathbf{s})) \quad \forall n \tag{10}$$

That is, $f_\mathbf{T}()$ and $f_\mathbf{S}()$ are "hypersymmetric". Coupled to the assumption that the first-passage density is continuous we have the following theorem, taken from [28], [29]:

Theorem 1:

If $f_\mathbf{T}()$ is a hypersymmetric probability density function on emission times $\{T_m\}$, $m = 1, 2, .., M$, and the first-passage density is non-singular, then the entropy of the size-ordered outputs $\vec{\mathbf{S}}$ is

$$h(\vec{\mathbf{S}}) = h(\mathbf{S}) - \log M!$$

and the conditional entropy of the size-ordered outputs is

$$h(\vec{\mathbf{S}}|\mathbf{T}) = h(\mathbf{S}|\mathbf{T}) - H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$$

where $H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$ is the uncertainty about which index Ω produces $P_\Omega(\mathbf{S}) = \vec{\mathbf{S}}$ given both $\mathbf{T}$ and $\vec{\mathbf{S}}$.

We note that $0 \leq H(\Omega|\vec{\mathbf{S}}, \mathbf{T}) \leq \log M!$ with equality on the right for any density where all the T_m are equal. Thus, for $f_\mathbf{T}()$ hypersymmetric and nonsingular first-passage densities we can write the ordered mutual information as [28], [29]:

Theorem 2:

$$I(\vec{\mathbf{S}}; \mathbf{T}) = I(\mathbf{S}; \mathbf{T}) - \left(\log M! - H(\Omega|\vec{\mathbf{S}}, \mathbf{T}) \right) \tag{11}$$

That is, an information degradation of size $\log M! - H(\Omega|\vec{\mathbf{S}}, \mathbf{T}) \geq 0$ is introduced by the sorting operation. It is also important to note that $H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$ represents the minimum average amount of information per channel use necessary to establish the correct one-to-one mapping between the elements of $\mathbf{T}$ and $\vec{\mathbf{S}}$.

V. Maximizing $I(\vec{\mathbf{S}}; \mathbf{T})$ for the Timing Channel

Since $h(\mathbf{S}|\mathbf{T})$ is a constant with respect to $f_\mathbf{T}(\mathbf{t})$, maximization of equation (11) requires we maximize $h(\mathbf{S}) + H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$. Mutual information is convex in $f_\mathbf{T}(\mathbf{t})$ and the space $\mathcal{F}_\mathbf{T}$ of feasible hypersymmetric $f_\mathbf{T}(\mathbf{t})$ is clearly convex. Thus, we can in principle apply variational [32] techniques to find that hypersymmetric $f_\mathbf{T}()$ which attains the unique maximum of equation (8). However in practice, direct application of this method can lead to grossly infeasible $f_\mathbf{T}()$, implying that the optimizing $f_\mathbf{T}()$ lies along some "edge" or in some "corner" of the convex search space.

After considering important technical details [29] which establish appropriate definitions of channel use and which re-

quire finite-mean first-passage distributions $G()$[1] we can then (with some effort [29], [30]) obtain the following key theorem about channel capacity C_m, the maximum information transfer rate in nats/token:

Theorem 3: If the first-passage density $f_D()$ is exponential with parameter μ and ρ is the constant average rate at which tokens are released ($\rho \equiv \lim_{M\to\infty} \frac{M}{\tau(M)}$) then the capacity [29] per token, C_m, obeys

$$C_m \geq \log \chi + e^{-\frac{1}{\chi}} \sum_{k=1}^{\infty} \left(\frac{1}{\chi}\right)^k (k\chi - 1)\frac{\log k!}{k!} \qquad (12)$$

where $\chi \equiv \frac{\mu}{\rho}$.

We can rewrite equation (12) more compactly by noting that

$$\sum_{k=1}^{\infty}\left(\frac{1}{\chi}\right)^k (k\chi-1)\frac{\log k!}{k!} = \sum_{\ell=1}^{\infty}\log\ell\sum_{k=\ell}^{\infty}\left(\frac{1}{\chi}\right)^k \frac{(k\chi-1)}{k!}$$

Then

$$\sum_{k=\ell}^{\infty}\left(\frac{1}{\chi}\right)^k \frac{1}{k!} = e^{\frac{1}{\chi}} - \sum_{k=0}^{\ell-1}\left(\frac{1}{\chi}\right)^k \frac{1}{k!}$$

and

$$\sum_{k=\ell}^{\infty} k\chi \left(\frac{1}{\chi}\right)^k \frac{1}{k!} = \sum_{k=\ell-1}^{\infty}\left(\frac{1}{\chi}\right)^k \frac{1}{k!}$$

can be used to obtain

$$\sum_{k=\ell}^{\infty}\left(\frac{1}{\chi}\right)^k \frac{(k\chi-1)}{k!} = \frac{1}{(\ell-1)!}\left(\frac{1}{\chi}\right)^{\ell-1} = \ell\left(\frac{1}{\chi}\right)^{\ell}\frac{\chi}{\ell!}$$

We can then define the probability mass function $p_\ell = e^{-\frac{1}{\chi}}\left(\frac{1}{\chi}\right)^{\ell}\frac{1}{\ell!}$, $\ell = 0, 1, \cdots, \infty$ to obtain the more compact

$$\sum_{k=1}^{\infty}\left(\frac{1}{\chi}\right)^k (k\chi-1)\frac{\log k!}{k!} = E_\ell\left[\chi(\ell\log\ell)\right] \qquad (13)$$

so that equation (12) becomes

$$C_m \geq \log \chi + E_\ell\left[\chi(\ell\log\ell)\right] \qquad (14)$$

VI. Token Construction Cost

From a real-world perspective, channel capacity is a meaningless concept without the notion of a limited resource which must be expended for communication. All such considerations arguably boil down to energy constraints. Thus, we will assume a biologically-inspired – but generally plausible for *any* engineered system – cost structure associated with signaling tokens and examine the capacity per joule of molecular communication channels that use timing and/or payload carriage for information transfer.

First-consider tokens without information payloads. In biological systems, small molecules and single ionic species are often used as messengers which do not themselves carry information payloads. Larger more complex molecules such as specific proteins, glycans and the like can also serve as such messengers. In the case of ionic species, the cost of a message might include collection, sequestration or even construction/extraction of the relevant molecule/ion from chemical

precursors. For more complex molecules similar considerations apply, but the idea is that for a given species, the construction cost is fixed. We will here denote the cost of construction for the jth species without payload as $c_0(j)$ in joules.

Now consider tokens *with* information payloads. Oligomers are molecules that can be constructed by concatenation of standard elements called monomers chosen from some "alphabet." Proteins are composed from an amino acid alphabet, m-RNA is composed from a nucleotide alphabet and glycans are a branched and re-entrant complex composed of a monosaccharide (sugar) alphabet. For proteins, the cost of adding an amino acid to an existing chain is roughly 4 ATP (32×10^{-20} joules) [33] and similar energy costs can be derived for other oligomers both biological and not. To model the cost of signaling oligomer construction we posit a base cost $c_1(j)$ for the "superstructure" (allowing the possibility that $c_1(j) = 0$) and an incremental cost $\Delta c_1(j)$ which represents cost of adding a monomer to the chain. Both quantities in in joules. For simplicity but with no loss of generality we will assume binary alphabets so that monomer addition adds one bit of information to the structure. That said, we will here completely ignore the more complex structural information issue associated with branched/re-entrant "colored graphs" such as glycans.

Thus, a token without payload "costs" $c_0(j)$. Of course, we note that we may have $c_0(j) = c_1(j) + L\Delta c_1(j)$ where L is the number of monomers used to form each identical token. So, a cost of $c_0(j)$ is a sufficient description. Similarly, payload-carrying tokens cost $c_1(j) + B\Delta c_1(j)$ where B is the number of bits in the token "information payload." A more details accounting of energy can be found in [34].

VII. Payload-Laden Token Ordering Overhead

Human-engineered packet networks require a sequence of tokens carrying information payloads to be "strung together" in some way to recover the original message. To be placed in sequence, *each token must be identifiable*. In packet networks, a sequence number is used for this purpose and we could in principle adopt a similar construction here by appending $\log M$ bits to each token in a given signaling interval. Alternatively, one could theoretically avoid overhead completely by sending token-strings of lengths $1, 2, \cdots, K$ where $M = K(K+1)/2$, but from a practical perspective, the string sizes could become cumbersome under such a discipline with large M. Nonetheless, there are perhaps other ways to send along structural "side information" but we do not consider those here. Regardless, $\log M$ is a rather pessimistic imposition of overhead if it is unlikely that tokens will arrive out of order – as might be the case for rapid first-passage compared to low average token launch rate (i.e., $\chi \gg 1$). So, we must ask what is the minimum amount of information necessary to establish token order. $H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$ provides a way to determine this minimum overhead.

Remember that $H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$ is a measure of the reordering-entropy given the arrivals $\vec{\mathbf{S}}$ and the *known* departures, $\mathbf{t}$. Under the assumption of hypersymmetric $f_{\mathbf{T}}()$, $\mathbf{t}$ is not known at the receiver, *even after decoding* because any of $M!$ by-design equiprobable (and indistinguishable once launched into the channel) $\mathbf{t}$ could have been sent. Thus, $H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$ seems of little use in determining bounds on the "sequencing

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[1]Free-space diffusion processes do *not* have finite mean first-passage times. However, for any real system, finite extent dictates that a finite mean first-passage time must exist.

information" necessary to ensure proper reconstruction of the message.

However, consider the timing-only channel for a moment. From [28], [29] we see that for every hypersymmetric distribution which maximizes the mutual information $I(\vec{\mathbf{S}}; \mathbf{T})$ there exists an equivalent "folded" distribution where the $\{t_m\}$, $m = 1, 2, \cdots, M$ are strictly ordered and which also maximizes $I(\vec{\mathbf{S}}; \mathbf{T})$. This ordered distribution could theoretically be employed to construct codebooks (i.e., using jointly typical coding [16]) which asymptotically achieve capacity – and for which decoding of received $\vec{s}$ sequences would reveal the proper codeword $\mathbf{t}$. And since given $\mathbf{t}$ the uncertainty about which $\vec{s}_j$ corresponds to which t_i is quantified by $H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$, we have $\frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$ as the absolute minimum average information which must be sent along with each token to ensure proper reording at the receiver, a result we summarize as a theorem:

Theorem 4: To ensure correct message reconstruction using payload-laden tokens at the receiver, departure times must be ordered $t_1 \leq t_2 \leq t_3 \leq \cdots \leq t_M$. Then, the minimum amount of information which must be appended to each payload-carrying token to ensure correct sequencing at the receiver is $\frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{T})$.

In the next section we provide expressions for capacity-per-joule with identical tokens and payload-laden tokens. For simplicity we assume no payload corruption, but note that such potential corruption would simply produce additional coding overhead and consequently a marginally larger payload.

VIII. PAYLOAD + TIMING ENERGY EFFICIENCY

The arguments of the previous section lead to the following theorems.

Theorem 5: If information is conveyed only through timing of identical tokens, then the capacity in bits per joule, $\mathcal{C}_T$, obeys

$$\mathcal{C}_T \geq \frac{1}{c_0}\left(\log\chi + E_\ell\left[\chi(\ell\log\ell)\right]\right) \quad (15)$$

Theorem (5) results from direct application of Theorem (3) and the cost structure.

If information is conveyed using both timing and payload, then for a B-bit payload, the timing+payload capacity is given by the following theorem:

Theorem 6:

$$\mathcal{C}_{P+T}(M) = \max_{f_{\mathbf{T}}()} \frac{I(\vec{\mathbf{S}}; \mathbf{T}) + MB}{M\left(c_1 + \Delta c_1\left(B + \frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{T})\right)\right)} \quad (16)$$

Theorem (6) follows directly from Theorem (4) and the cost structure. However, the optimization of equation (16) seems at least as difficult as maximizing $I(\vec{\mathbf{S}}; \mathbf{T})$ for identical tokens. But since we have assumed exponential first-passage, we can apply equation (12) to obtain:

Theorem 7: Let $f_{\mathbf{T}}^*() = \prod_m f_{T_m}^*()$ be the token launch density that maximizes the timing channel $I(S; T)$ for exponential first passage as derived in [26]. Then for $M \to \infty$, application of $f_{\mathbf{T}}^*()$ produces rate

$$\mathcal{R}_{P+T} = \frac{\log\chi + E_\ell\left[\chi(\ell\log\ell)\right] + B}{c_1 + \Delta c_1\left(B + E_\ell\left[\chi(\ell\log\ell)\right]\right)} \quad (17)$$

where $\mathcal{R}_{P+T} \leq \mathcal{C}_{P+T}$.

Proof: Theorem (7) Application of any specific density $f_{\mathbf{T}}()$ cannot produce a rate which exceeds capacity. Via Theorem (3) and equation (13) we have

$$\max_{f_{\mathbf{T}}()} \frac{1}{M}I(\vec{\mathbf{S}}; \mathbf{T}) = C_m \geq \log\chi + E_\ell\left[\chi(\ell\log\ell)\right].$$

From [29] and equation (13) we know application of $f_{\mathbf{T}}^*()$ produces $\lim_{M\to\infty} \frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{T}) = E_\ell\left[\chi(\ell\log\ell)\right]$ which completes the proof. ●

For information carried via payload only (and exponential first passage), we have the following theorem:

Theorem 8:

$$\mathcal{C}_P = \frac{B}{c_1 + \Delta c_1\left(B + \min_{\mathbf{t}} \frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{t})\right)} \quad (18)$$

whose proof follows directly from direct application of Theorem (3) and the cost structure. For payload-only, no decoding of the fixed ($\min_{\mathbf{t}} \frac{1}{M}H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$ minimizing) launch times $\mathbf{t}$ is required. But since minimization of $H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$ in $\mathbf{t}$ is non-trivial, the following lemma is useful:

Lemma 1:

$$\mathcal{C}_P \geq \frac{B}{c_1 + \Delta c_1\left(B + E_\ell\left[\chi(\ell\log\ell)\right]\right)} \quad (19)$$

whose proof follows directly from Theorem (7), equation (13) and that $H(\Omega|\vec{\mathbf{S}}, \mathbf{T}) \geq \min_{\mathbf{t}} H(\Omega|\vec{\mathbf{S}}, \mathbf{t})$.

IX. DISCUSSION

Human-engineered packet networks generally require the payload B to be much larger than the maximum sequencing overhead $\frac{1}{M}\log M!$ of an M-packet message. By analogy, equation (18) reduces to $\approx \frac{1}{\Delta c_1}$ if we also assume $c_1 \ll B\Delta c_1$. It is also worth noting that care should be taken with payload sequence overhead. If the sequence overhead is chosen simply as $\frac{1}{M}\log M!$, both timing+payload and payload-only capacities approach 0 as $M \to \infty$.

In FIGURES 2 and 3 we compare equation (15), equation (17) and equation (19) by assuming c_1, the "substrate" cost for payload-carrying tokens, is negligible relative the term in Δc_1. We also set both c_0 and Δc_1 to 1 since adjustment of c_0 relative Δc_1 will simply scale the $\mathcal{C}_T$ curve. We see in
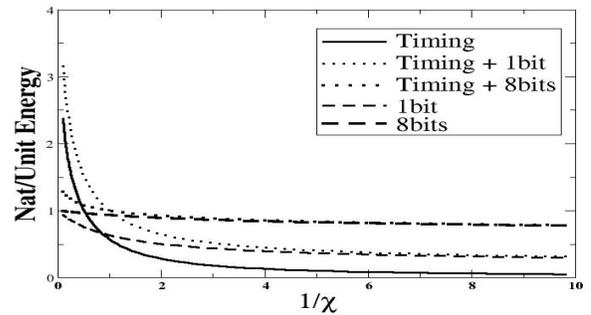
Fig. 2. **Nats per unit energy vs. $1/\chi$:** c_1 "substrate cost" assumed negligible and $c_0 = \Delta c_1 = 1$.

FIGURE 2 that information per unit energy increases as the rate at which tokens are launched into the system increases (increasing $1/\chi$). Also, the relative efficiency of payload-only and timing+payload channels approach each other. Of particular note, the relative efficiency of adding a single bit of payload outstrips the timing-only channel efficiency at low
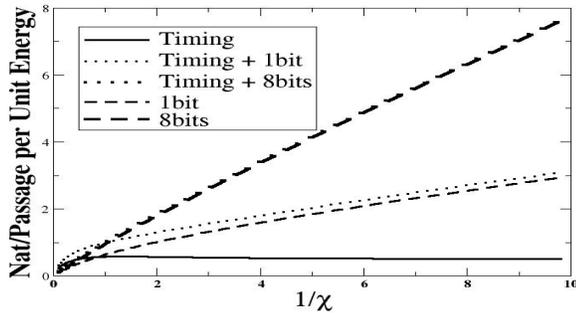
Fig. 3. **Nats per passage per unit energy vs. $1/\chi$:** c_1 "substrate cost" assumed negligible and $c_0 = \Delta c_1 = 1$.

token launch rates. Likewise, timing-only becomes the least efficient for larger $1/\chi$. We see similar behavior in FIGURE 3 where bits/passage-time per unit energy is plotted against $1/\chi$ The timing-only channel becomes the least efficient for larger $1/\chi$, approaching 0.5 nats/passage/unit energy as $1/\chi \to \infty$.

X. CONCLUSION

Alhough molecular transport and first-passage results constitute only the first link the a molecular communication chain, the results do provide some guidance by setting bounds on rates assuming perfect information transfer through subsequent processing steps such as signal molecule capture and transduction. Overall, timing-only or $B = 1$ (i.e., two species of token) timing+payload channels may offer the most energy-efficient delivery of bits at low token launch rates while payload and payload+timing channels may offer more efficient bit *rate* delivery at higher token intensities. From a biological (or nano-engineering) perspective, if energy is limited, the results may suggest that low bit rate traffic might be most efficiently carried via simple tokens and timing only (which includes signaling through temporal variation in signal concentration such as endocrine systems). Where higher rates are required (as with, say, genetic material replication or protein synthesis), traffic carriage via timing + tokens with payloads (such as m-RNA) might be the more energy-efficient choice. And of particular note, if (as we suspect) the timing-only lower bound is close to the corresponding upper bound, launching copious tokens into the system (increasing $1/\chi$ or "concentration") confers no increase in bit rate efficiency (or bit rate) past approximately 1.3 times the first passage rate.

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