

**WHEN BACTERIA TALK : TIME ELAPSE
COMMUNICATION FOR SUPER SLOW NETWORKS**

A Thesis
Presented to
The Academic Faculty

by

Bhuvana Krishnaswamy

In Partial Fulfillment
of the Requirements for the Degree
Master's Thesis in the
School of Electrical and Computer Engineering

Georgia Institute of Technology
December 2013

Copyright © 2013 by Bhuvana Krishnaswamy

**WHEN BACTERIA TALK : TIME ELAPSE
COMMUNICATION FOR SUPER SLOW NETWORKS**

Approved by:

Professor Raghupathy Sivakumar, Advisor
School of Electrical and Computer
Engineering
Georgia Institute of Technology

Professor Ian Akyildiz
School of Electrical and Computer
Engineering
Georgia Institute of Technology

Professor Faramarz Fekri
School of Electrical and Computer
Engineering
Georgia Institute of Technology

Date Approved: May 2013

TABLE OF CONTENTS

LIST OF FIGURES	v
SUMMARY	vi
I INTRODUCTION	1
II EXPERIMENTAL SYSTEM DESIGN	4
2.1 Modified E. coli Bacteria	4
2.2 Microfluidic System	5
III MOTIVATION	7
3.1 On-Off Keying	7
3.2 Related Work	8
IV TIME-ELAPSE COMMUNICATION	10
4.1 Problem Statement	10
4.1.1 Promise of TEC	11
4.1.2 Limitations of TEC	13
4.2 TEC-SMART : TEC for Non-Zero Error Conditions	13
4.2.1 Error Curtailment/Differentiation	14
4.2.2 Differential Coding (DC)	17
4.2.3 Piggybacked Ordering (DC_P)	18
4.2.4 DC for unbounded noise - DC_U	19
4.2.5 Summary	21
V THEORETICAL ANALYSIS OF CAPACITY	22
5.1 Uniform Distribution of Noise	22
5.2 Exponential Distribution of Noise	25
VI NUMERICAL ANALYSIS OF TEC	27
6.1 Frame Size	27
6.2 Bit Period	28

6.3	Frequency	28
6.4	Error	29
6.4.1	Bounded Error	29
6.4.2	Unbounded Error	30
VII	CONCLUSION	32
7.1	Conclusion	32
7.2	Future Work	32
REFERENCES	34

LIST OF FIGURES

1	<p>(a) A constitutive promoter (P_{on}) that is always on drives expression of the <i>luxR</i> gene that codes for the C6-HSL receptor, LuxR. When the C6-HSL signal reaches the receiver cells, it diffuses into the cell, and binds to LuxR. The LuxR/C6-HSL complex activates the <i>lux</i> promoter (PLux), resulting in expression of the GFP gene carrying a degradation tag, and production of green fluorescent protein (GFP). Engineered in this manner, receiver cells will become fluorescent in response to C6-HSL, and will stop being fluorescent when C6-HSL is no longer present.</p> <p>(b) Bacteria are housed in rectangular trapping chambers that are in fluidic contact to the main flow channel. As C6-HSL flows through the main channel, the C6-HSL diffuses across the trapping chamber, which leads to the fluorescent response in the bacteria (fluorescent image inset). In the absence of C6-HSL, there is no fluorescence (bright field image).</p> <p>(c) Two inputs and two outputs are used in the microfluidic device adapted from Danino et al. [7]. Input A supplies media with AHL, while input B provides media alone. Both outputs are used to remove waste. (Photo of microfluidic device inset.)</p>	3
2	Response of Bacteria to Input signal	5
3	Illustration of modulation schemes	10
4	Performance of <i>TEC</i> under ideal zero error conditions	12
6	Fall-time error correction	14
6	Illustration of rise and fall time error correction	14
7	Simulation based capacity	25
8	Theoretical analysis of capacity	26
9	Performance of <i>TEC-SMART</i> and <i>TEC-SIMPLE</i> with varying n and t_b	27
10	Performance of <i>TEC-SMART</i> and <i>TEC-SIMPLE</i> under varying error conditions.	29
11	Performance of <i>TEC-SMART</i> (DC_U) under exponential noise in the channel.	30

SUMMARY

In this work we consider nano-scale communication using bacterial populations as transceivers. We demonstrate using a microfluidic test-bed and a population of genetically engineered *Escherichia coli* bacteria serving as the communication receiver that a simple modulation like on-off keying (*OOK*) is indeed achievable, but suffers from very poor data-rates. We explore an alternative communication strategy called time elapse communication (*TEC*) that uses the time period between signals to encode information. We identify the severe limitations of *TEC* under practical non-zero error conditions in the target environment, and propose an advanced communication strategy called smart time elapse communication (*TEC-SMART*) that achieves over a 10x improvement in data-rate over *OOK*. The thesis is organized as follows.

Chapter 2 presents a detailed description of the bacterial strain used and the microfluidic system that houses the bacteria. Chapter 3 presents the results from microfluidic experiments with *E. coli* bacteria and establishes the motivation for time-elapse communication in *super-slow networks*. Chapter 4 presents the key design principles of time-elapse communication. Chapter 5 presents the theoretical maximum achievable data-rate using time-elapse communication and Chapter 6 shows the simulation results of time-elapse communication along with the optimization proposed. Chapter 7 concludes the paper with proposed future work.

CHAPTER I

INTRODUCTION

Nano-scale communication strategies can be categorized into two broad domains depending upon their target environment: *electromagnetic communication (EM)* at the nano-scale involves the extension of traditional EM based communication techniques for use in inorganic or non-biological applications [2,8]; and *molecular communication* involves strategies (typically bio-inspired) for use in biological applications [1,9,17]. In recent years, bacteria have emerged as promising candidates for nano-machines in biological applications [7]. Bacteria are prokaryotic microorganisms, typically about 1 μm in size, that are well-studied and understood in terms of morphology, structure, behavior, and genetics. Genetic engineering of bacteria to introduce or delete DNA for specific traits (e.g., bioluminescence, motility, adhesion, etc.) has enabled recent advancements in synthetic biology [10]. Many bacteria utilize a process called quorum sensing, whereby bacterial cells naturally behave as transceivers that interact with one another, relaying signals by transmitting and receiving chemical signal molecules [4,11]. Using the power of synthetic biology and the inherent transceiver properties, bacterial nano-machines hold much promise to be used in biological applications such as toxicology, biofouling, and biosensing. For example, receiver bacteria have been used as biosensors to detect the presence of metals [5], and to detect arsenic pollution [16].

The context for this work is thus molecular communication between bacterial populations. Specifically, we consider a system in which bacterial populations are used as transceivers connected through pathways for molecular signals. The focus of this

work is to study the communication performance between the transceivers and develop strategies to improve the same. To this end, we make three major contributions:

First, we use *Escherichia coli* (*E. coli*) bacteria genetically engineered to exhibit fluorescence upon the receipt of a specific signal molecule (N-(3-Oxyhexanoyl)-L-homoserine lactone, or C6-HSL). A microfluidic experimental system houses bacterial populations within micrometer sized chambers fed by channels that provide both nutrients and controllable levels of C6-HSL, to demonstrate that a chemical signal at the sender can be reproduced as a fluorescence signal at the receiver reliably. Specifically, we demonstrate that it is indeed feasible to realize a simple modulation technique such as *On-Off Keying (OOK)* for communication between the bacterial populations, but the consequent data rates achievable is as low as 10^{-5} bps. We term such environments where the transmission rates are very low as *super-slow networks*.

Second, we introduce a new communication strategy called *time-elapse communication (TEC)* for *super-slow networks* that relies on the time interval between two signals to encode information. Thus offloading some of the communication burden to the sender and receiver (in the form of measuring time periods), we show that *TEC* under idealized conditions can deliver data-rate improvements of an order of magnitude in the target environment. We also evaluate *TEC* under realistic conditions that involve non-zero error and show that the performance of *TEC* reduces to being marginally better than *OOK*. We propose an improved communication strategy called *smart time-elapse communication (TEC-SMART)* that uses a combination of mechanisms that improve how information is represented and how error is interpreted.

Third, we derive the maximum achievable capacity using time based communication like *TEC*. We present an analysis of capacity for different distribution of noise viz., a uniformly distributed noise and an exponentially distributed noise in the microfluidic channel. Using simulations driven by experimental data, we also

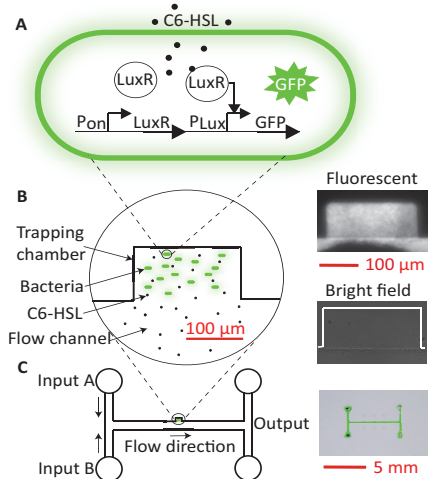


Figure 1: (a) A constitutive promoter (P_{on}) that is always on drives expression of the *luxR* gene that codes for the C6-HSL receptor, LuxR. When the C6-HSL signal reaches the receiver cells, it diffuses into the cell, and binds to LuxR. The LuxR/C6-HSL complex activates the *lux* promoter (P_{Lux}), resulting in expression of the GFP gene carrying a degradation tag, and production of green fluorescent protein (GFP). Engineered in this manner, receiver cells will become fluorescent in response to C6-HSL, and will stop being fluorescent when C6-HSL is no longer present. (b) Bacteria are housed in rectangular trapping chambers that are in fluidic contact to the main flow channel. As C6-HSL flows through the main channel, the C6-HSL diffuses across the trapping chamber, which leads to the fluorescent response in the bacteria (fluorescent image inset). In the absence of C6-HSL, there is no fluorescence (bright field image). (c) Two inputs and two outputs are used in the microfluidic device adapted from Danino et al. [7]. Input A supplies media with AHL, while input B provides media alone. Both outputs are used to remove waste. (Photo of microfluidic device inset.)

show that *TEC-SMART* approaches the original promise of *TEC* even under realistic conditions involving non-zero error. We identify data-rate as a function of different parameters and perform a sensitivity analysis to analyze the impact of each parameter.

CHAPTER II

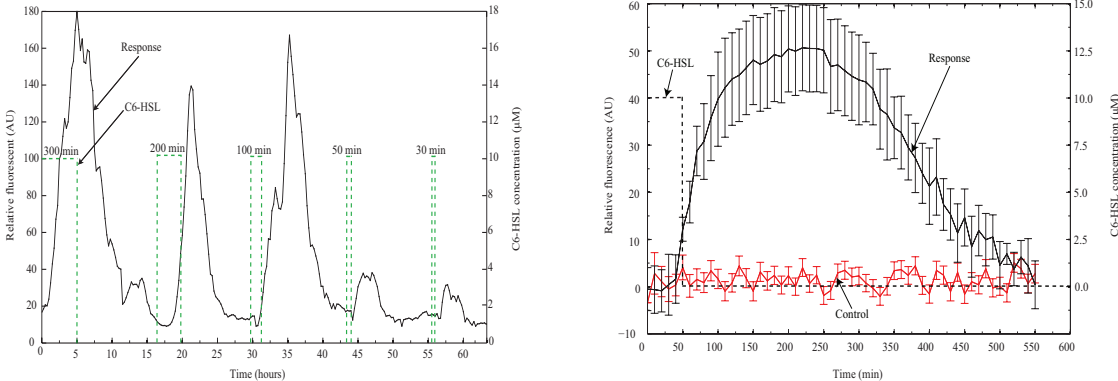
EXPERIMENTAL SYSTEM DESIGN

The illustration in Figure 1 presents the set-up we consider in this work. The sender has access to a "sender" bacterial population that acts as a transceiver, and which when provided the appropriate stimulation by the sender releases molecular signals. The signals propagate along a predefined pathway toward the bacterial population that acts as the transceiver at the receiver. The "receiver" bacterial population, on receipt of the molecular signals, responds with fluorescence, which then is detected and interpreted by the receiver. Thus, the sender is able to convey information to the receiver using the bacterial populations as the transceivers and the pathway as the channel in-between. In this work we focus exclusively on the communication between the bacterial populations without regard to the specific nature of the sender and receiver. We now briefly describe the experimental set-up used for the motivation results.

2.1 Modified E. coli Bacteria

The *E. coli* bacteria was genetically engineered in the Hammer Lab by Dr. Patrick bardill by Dr. Patrick bardill under the guidance of Dr. Brian Hammer. The bacterium *E. coli* was engineered to serve as a receiver in the test bed. *E. coli* is an extensively-studied, widely used model organism with genetic tools available to modify its DNA and resulting characteristics. *E. coli* does not carry the molecular communication described here. However, it was modified to serve as a receiver of signal molecules naturally transmitted and received by the marine bacterium *Vibrio fischeri* (*V. fischeri*) which generates light (bioluminescence) when in large populations through a phenomenon called quorum sensing. Natural *V. fischeri* cells have DNA

allowing them to serve as transceivers of C6-HSL signal molecules [4]. *E. coli* was engineered to carry *V. fischeri* DNA with a promoter (P_{on}) that is always on and drives the gene encoding the C6-HSL receptor protein, LuxR; thus these receiver cells can respond to, but do not transmit, C6-HSL. In our simple model here, rather than utilizing transmitter cells, purified C6-HSL is injected into the channel and flows to the receiver cell population in the chamber (described below). When C6-HSL enters the cells and binds LuxR, there is activation of the P_{lux} promoter to produce green fluorescent protein (GFP), allowing detection by fluorescence microscopy (Figure 1).



(a) Bacteria relative fluorescence was measured in response to varying pulse inputs (300, 200, 100, 50 and 30 min) of C6-HSL. A typical response is shown.

(b) Bacteria relative fluorescence was measured in response to pulse input of duration 50 min of C6-HSL (Number of experiments=10), as compared to a reference (Number of experiments=4). Error bars represent one standard deviation.

Figure 2: Response of Bacteria to Input signal

2.2 Microfluidic System

The experiments involving bacteria in a microfluidic system were performed in the Precision BioSystems Laboratory by Caitlin Henegar under the guidance of Dr. Craig Forest. The microfluidic system enables the measurement of the bacterial response to C6-HSL while keeping the bacterial population alive and stable within a chamber. In operation, $\approx 10^5$ bacteria are first grown to a stable population within the chamber

(100 μm x 150 μm x 5 μm) for a duration of 1 day by delivering Luria-Bertani (LB) medium containing ampicillin at 10 $\mu\text{g}/\text{ml}$ at a flow rate of 350 $\mu\text{l}/\text{hr}$ using a syringe pump (Harvard Apparatus) connected by tygon tubing to a flow channel on the microfluidic chip. The flow channel (250 μm x 10 μm) is in direct fluidic contact with the chamber as depicted in Figure 1. The media flow delivers necessary nutrients for bacterial growth while the ampicillin maintains the plasmid carrying the *V. fischeri* DNA. The flow rate ensures that bacteria growth beyond the chamber dimensions is washed away. Following this growth phase, C6-HSL can be applied to the bacteria for a desired duration (e.g., 30 min) by similarly flowing media containing C6-HSL at 0.01 mM at 10 $\mu\text{l}/\text{hr}$ in LB medium. In response to C6-HSL, the bacteria express GFP. The microfluidic system is mounted on a microscope (Nikon TE 2000) such that these proteins can be optically excited and their emitted fluorescence can be imaged every 15 min and analyzed using MATLAB.

CHAPTER III

MOTIVATION

The experiments in the microfluidic system demonstrate that *OOK* is (a) achievable in the target environment; and (b) has a data-rate performance that is quite low.

3.1 On-Off Keying

Using the genetically engineered bacteria in the microfluidic system imaged in Figure 1(c), we were able to elicit a fluorescent response to C6-HSL and image it with the fluorescence microscope (See Figure 1(b)). At steady state (e.g., 1 hr) fluorescent bacteria (number of experiments=10, SNR=20) was imaged, and returned to non-fluorescing state by removing C6-HSL from the flow channel (number of experiments=10, SNR<1). The C6-HSL input signal as a pulse with 10 μM concentration for a variety of durations was experimented. As shown in Figure 2(a), the bacteria respond to this input pulse with varying widths.

In order to select an appropriate input pulse width, an experiment was run with varying pulses of 10 μM C6-HSL to determine the minimum pulse width that fit our requirements for a distinguishable signal. To be considered as a signal, the response must have an SNR ≥ 5 , and a plateau region of sustained fluorescence above this SNR threshold of duration greater than 10% of the total signal time. Shown in Figure 2(a), the bacteria were exposed for 300, 200, 100, 50 and 30 mins with periods of pure media in between. The 50 min pulse was the shortest pulse that met these requirements, and was therefore used in the following experiments. The bacteria were exposed to C6-HSL for a 50 min pulse for all results shown in Figure 2(b). For ten samples, the average response time, defined as the time from when the bacteria begin to fluoresce until the time they stop, was found to be 435 min. with a standard deviation of 47.

The average delay time, characterized as the time between when the bacteria start to receive the C6-HSL until they begin to fluoresce, was 31 min. with a standard deviation of 11. The average SNR was 7.9.

It can be seen that the receive signals clearly follow the ON-OFF patterns at the sending side, albeit offset by the propagation delay in the environment. While the above results demonstrate that *OOK* can indeed be relied upon for conveying information from the sender to the receiver, we now proceed to derive the achievable data-rates using *OOK* based on parameters extracted from the experiments. The key parameter of interest in determining the achievable data-rate is the *bit period*. The bit period at the receiver is greater than that at the sending side due to the biological processing at the receiver bacteria. We define the maximum of the two bit periods as the effective bit period t_b . As mentioned before, we restrict our study to an input signal of pulse width 50 min and the corresponding average bit period of 435 min. The data-rate of *OOK* is thus $\frac{1}{t_b}$, which for a t_b of 435 min is $3.8 * 10^{-5}$ bps. In the rest of the thesis, we introduce and describe strategies that are aimed toward improving the achievable data-rates in *super-slow networks*.

3.2 Related Work

The notion of encoding information in time periods is not new to this work. *Timing channels* rely on such a notion to achieve covert information transfer [3], while *Pulse-Position Modulation (PPM)* relies on conveying information through the relative position of pulses in environments where there is little or no error conditions. In addition to timing channels and PPM, there are few other approaches related to *TEC*. The key difference between such techniques and this work is significant: the domain of interest - bacterial communication - raises unique and considerable challenges in how a technique like *TEC* can be realized in the target environment, and hence the solutions we propose to adapt *TEC* are in turn unique and fundamentally

tailored to the domain. We discuss some of these approaches below:

Timing Channels: In [14] mechanisms to improve the data-rate of timing channel have been proposed. However, the proposed techniques are not targeted for the context of bacterial communication. Specifically, this work involves the use of static and complex coding tables unsuitable for the target environment. More importantly, it does not deal with large error rates and hence will perform similar to *TEC* without any optimization.

Communication through Silence: A solution to use silent periods in sensor networks to communicate information was presented in [18]. The primary goal is to reduce the energy consumption, but non-zero error conditions are not considered and data-rate improvement is not the primary focus.

Timing modulation in fluid channel: An information theoretic approach to the timing modulation in molecular communication has been studied in [15]. Absolute timing is relied upon and hence the solution requires strict clock synchronization. Further, data-rate improvement is not a focus of this work.

CHAPTER IV

TIME-ELAPSE COMMUNICATION

4.1 Problem Statement

The data-rate performance of *OOK* in bacterial communication is low due to the inordinately large bit period involved. Hence, in this work we explore a communication strategy called *time-elapse communication (TEC)*, wherein information is encoded in the time period between two consecutive signals. A pictorial representation of *TEC* and *OOK* is presented in Figures 3(a) and 3(b). The number of molecular signals generated always remains at two (the start and the stop respectively) independent of the actual information. *TEC* requires the clock rates at the sender and receiver respectively to be the same, although no clock synchronization is required. Intuitively, *TEC* improves the data-rate over *OOK* by reducing the number of communication signals that need to be conveyed per unit of information.

More precisely, if the clock rate at the sender and receiver is f_c , information v is represented by the sender as $|v|/f_c$ time units separating a *start* signal and a *stop* signal, where $|v|$ is the magnitude of v . If the communication involves conveying a series of such values, the *stop* signal of a particular value is used as the *start* signal of

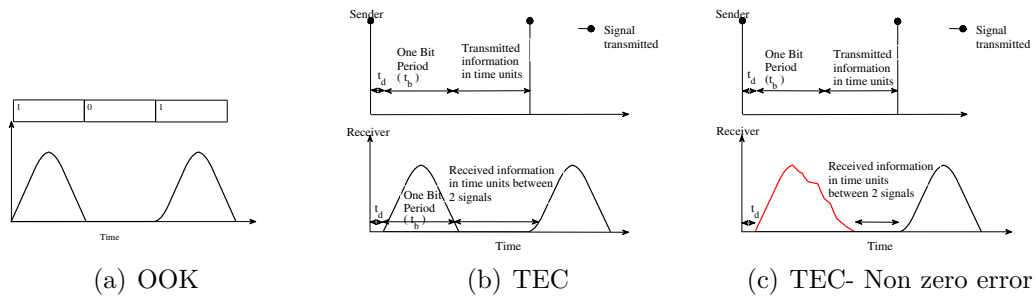


Figure 3: Illustration of modulation schemes

the next, and hence the number of communication signals per unit of information is amortized to just one. In *OOK*, an information value $|v|$ would be represented using approximately $\log_2 |v|$ bits. As illustrated in Figure 3(a), a value of 5 is represented using 3 bits and requires $3t_b$ time units to convey a value of 5. However, in *TEC*, the information value $|v|$ is represented using $|v|$ clock cycles, and hence the clock rate has to be exponentially larger than the underlying *OOK* data-rate in order for *TEC* to exhibit superior performance. Revisiting the set-up in 3.2, for an *OOK* data-rate of $3.8 * 10^{-5}$ bps and a clock rate of 1 Hz, under idealized channel conditions, *TEC* will provide an average data-rate of $3.9 * 10^{-4}$ bps, a 10.3x improvement over *OOK*. In general, consider a decimal data i being sent, the total delay required to communicate this data using *TEC* is the sum of one bit period using molecular signaling and the information delay (say $t_{info} = \frac{i}{f_c}$) corresponding to the wait time for the data. Thus, it takes *TEC* a maximum of $t_b + \frac{2^n - 1}{f_c}$ time to transmit a n bit data. The data-rate of *TEC* is thus given by the following:

$$R_{TEC} = \frac{n}{t_b + \frac{i}{f_c}} : i \in \{0, 1, \dots, 2^n - 1\}. \quad (1)$$

4.1.1 Promise of TEC

We now use numerical analysis of the data-rate equations of *OOK* and *TEC* to study the promise of *TEC* under variations of different parameters. Unless otherwise specified, we use a molecular signaling bit period t_b of 435 min based on the experimental results presented in 3.2, and a clock rate of 1 Hz. The data-rates of *OOK* and *TEC* as a function of the bit period t_b is shown in Figure 4(a), while Figure 4(b) presents the relative performance improvement of *TEC* with respect to *OOK*. With an increasing t_b , *TEC*'s improvement over *OOK* increases since the dependency of *TEC*'s performance on the parameter is relatively smaller. Figure 4(c) presents the relative performance improvement of *TEC* with respect to the number of bits n . It can be observed that the relative performance of *TEC* initially improves as the numerator

grows in Equation (1), but eventually the waiting term in the denominator begins dominating the performance, leading to a reduction in the relative performance. Thus, for a given set of t_b and f_c , there is an optimal value of n that should be used in *TEC*. Finally, if the clock rate is higher, the waiting time between signals corresponding to the data value will be smaller. It can be observed from Figure 4(d) that *TEC*'s relative performance with respect to *OOK* improves with higher f_c . Note that while a higher f_c is always better under idealized zero error conditions, any skew in clock rates between the sender and the receiver will be exacerbated under realistic non-zero error conditions. We discuss this later in the work motivating a balanced approach to the selection of f_c .

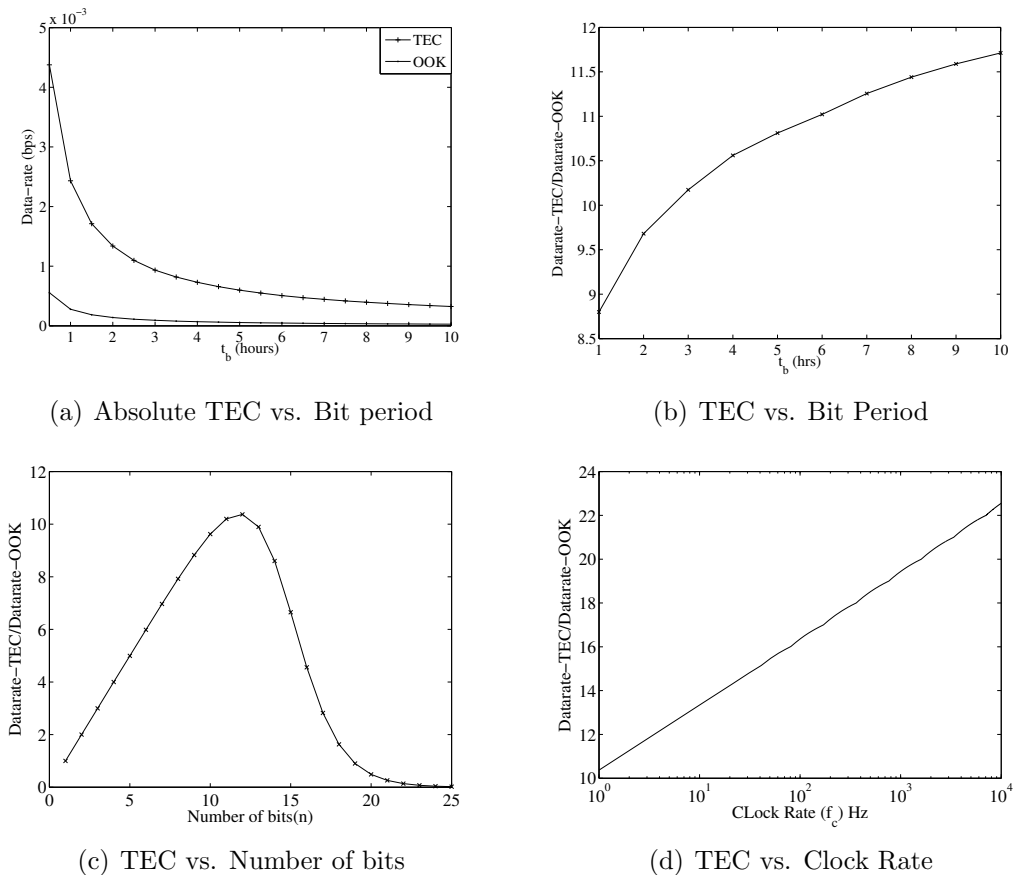


Figure 4: Performance of *TEC* under ideal zero error conditions

4.1.2 Limitations of TEC

Thus far, we have explored the performance of *TEC* under idealized zero error conditions. In reality, the responses of biological systems will vary across time. Figure 3(c) illustrates a deviation from ideal behavior. The start signal in Figure 3(c) gets delayed and hence the time elapsed between the signals is different leading to bit errors. To the best of our knowledge, there has not been any work that models the statistical distribution of the delay in the response of bacteria to molecular signals. Hence, we consider a simple uniform distribution $U(t_b - \epsilon, t_b + \epsilon)$ to model the real response time of receiver bacteria. On an average, one bit period is t_b with a bounded error that is uniformly distributed $U(-\epsilon, +\epsilon)$. Any deviation from the average is termed as error. The net error ϵ is the sum of all errors from the time of introduction of molecules into the medium to the detection of fluorescence output. Given that the error is bounded, it is possible for the receiver to decode with 100% accuracy by the simple technique of increasing the minimum distance between messages. A message is defined by both the *start* and the *stop* signals, and both these signals can be subject to an error of $\pm \epsilon$. If the minimum distance between adjacent messages is at least 4ϵ , the receiver can decode messages correctly in spite of any errors. We refer to *TEC* with simple error correction as *TEC-SIMPLE*. Figure 9(a) that the relative data-rate performance of *TEC-SIMPLE* in a realistic system has reduced to approximately 1.8x *OOK* (for an error of 10% in t_b). Thus, the introduction of error in the system has brought down the performance of *TEC* considerably.

4.2 *TEC-SMART : TEC for Non-Zero Error Conditions*

In this section we propose multiple techniques that in tandem improve the performance of *TEC* under non-zero error conditions. Specifically, we present (i) an error curtailment/differentiation strategy that reduces the impact of error on *TEC's* performance; (ii) a differential coding strategy that is uniquely targeted towards amortizing

the cost of t_b across multiple pieces of information; (iii) an optimization to the differential coding strategy that reduces overheads and (iv) an optimization to detect error in case of unbounded channel noise.. We refer to a communication strategy that uses *TEC* along with the aforementioned mechanisms as *smart time-elapse communication (TEC-SMART)*.

4.2.1 Error Curtailment/Differentiation

The uniformly distributed error $U(-\epsilon, +\epsilon)$ is actually the sum of multiple error components: propagation-time error e_d , rise-time error e_r , and fall-time error e_f corresponding to the propagation of molecules through the medium, the ramp-up of fluorescence, and the ramp-down of fluorescence respectively. Instead of handling the composite error in its entirety, we propose handling the error in two independent stages by introducing redundancy in the *bit period* to handle e_r and e_f , and by introducing redundancy in the *information delay* to handle e_d .

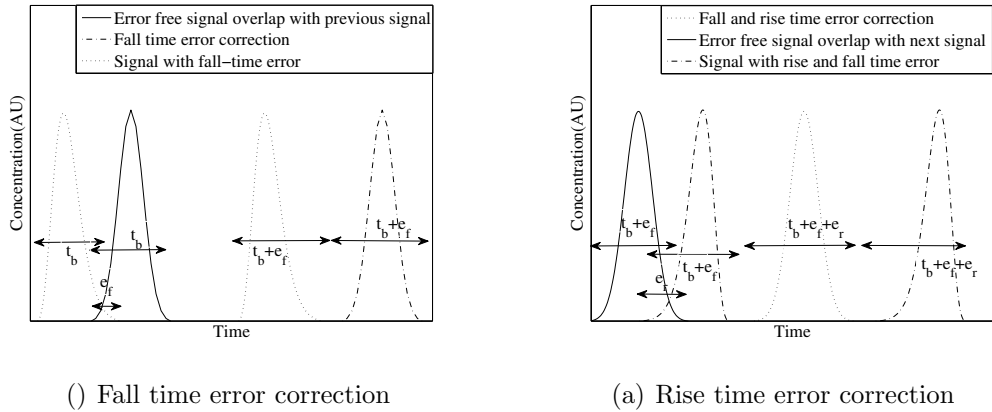


Figure 6: Illustration of rise and fall time error correction

Fall-Time Error Correction

The time period between the end of the i^{th} signal and the start of the $i + 1^{th}$ signal at the receiver represents the i^{th} message. Any deviation from the estimated fall-time alters the stop of the current message, in-turn changing the absolute value of

the data. Such an error in fall-time can be corrected by a proper choice of the sampling point. Assuming all other processes to be without error, it is sufficient to start measuring the time period in the rise phase of the receiver response and stop measuring upon the onset of the next rise phase. On subtracting the bit period from the total measured time, the actual message is retrieved. The fall-time error is thus absorbed in the time measurement phase. Such a correction can potentially lead to inter-symbol interference (ISI). The first 2 output signals in Figure 5(a), illustrate interference between signals due to fall-time error in signal 1. To overcome ISI, the bit period is increased from t_b to $t_b + e_f$. The last 2 output signals in Figure 5(a) have an increased bit period thus overcoming ISI.

Rise-Time Error Correction

The fall-time error correction was based on the assumption that all other timing components are error-free. An accurate ramp-up phase is thus essential in correcting fall-time error. If the propagation delay is error-free, the time at which the leading edge of signal reaches the receiver is error-free. Thus, assuming that the propagation delay is error-free, the response of the receiver is extrapolated to identify the time at which leading edge of signal reached the receiver. The receiver adds (or subtracts) the difference between the actual and estimated times of arrival to its time measure. Again, in order to ensure that two adjacent signals do not interfere, the bit period is further increased from $t_b + e_f$ to $t_b + e_f + e_r$. Figure 6(a) illustrates rise-time error and correction. The rise-time error in signal 1 causes interference between signals 1 and 2. Increase in bit period resolves this as seen in third and fourth signals in Figure 6(a). Thus, both rise-time and fall-time errors are corrected by simply increasing the bit period. The information to be transmitted remains unaltered.

Propagation Error Correction

The propagation delay determines the time at which the leading edge of a signal reaches the receiver, which in turn conveys the start of a message. Therefore, error in the propagation time is corrected by introducing redundancy in the message as in the simple error correction scheme with the minimum distance between messages being $4e_d$ instead of $4(e_d + e_f + e_r)$.

Assuming the first signal in a communication to be error-free, it is possible to decode with zero error for a reduced minimum distance of $2e_d$ as every signal is corrected based on the received and decoded messages i.e., if the *start* signal is received correct, only the *stop* signal can be erroneous. Since we decode with 100% accuracy, the error introduced is predicted and the *stop* is adjusted such that the error does not propagate. The transmission of first signal is restricted to slots of width one bit period ensuring an error-free start signal. In the following sections we assume the first signal to be error-free. The data-rate incorporating smart error correction mechanisms is as follows:

$$R_{TEC} = \frac{n}{t_b + t_{info}}. \quad (2)$$

TEC-SIMPLE performs error correction by multiplying each message by $2(e_d + e_f + e_r)$ which allows receiver to correct upto $e_d + e_f + e_r$. Therefore, the information delay (t_{info}) for *TEC-SIMPLE*, referred as t_{simple} is

$$t_{simple} = \frac{i(2(e_d + e_f + e_r)f_c + 1)}{f_c} : i \in \{0, 1 \dots 2^n - 1\}.$$

The data-rate is,

$$R_{SIMPLE} = \frac{n}{t_b + t_{simple}}. \quad (3)$$

Employing *TEC-SMART*, each message is multiplied by $2e_d$ while one bit period is increased from t_b to $t_b + e_f + e_r$. The information delay in this case is given by t_{smart}

as,

$$t_{smart} = \frac{i(2e_d f_c + 1)}{f_c} : i \in \{0, 1 \dots 2^n - 1\}. \text{The data-rate is,}$$

$$R_{SMART} = \frac{n}{t_b + e_f + e_r + t_{smart}}. \quad (4)$$

4.2.2 Differential Coding (DC)

From Equation (3), it is evident that while curtailing the impact of error has a distinct benefit on the performance of *TEC*, the impact of t_b still remains as-is. We thus propose a differential coding (*DC*) mechanism that leverages correlation between the values of consecutive messages to amortize the impact of t_b across them. The messages at the source are assumed to be independent and identically distributed. Dependence is introduced by taking the differences of pairs of adjacent messages such that every message in the new sequence is smaller in value compared to that of the original. Since the message is encoded in time, the transmitted values cannot be negative. A sequence of m messages is hence arranged in increasing order, and a new sequence constituting differences between adjacent values is formed so that each element in the new sequence is positive and smaller than its value in the original sequence. Since the ordering of elements in the original sequence is altered by virtue of the rearrangement, the actual order must be transmitted as a separate message. If a table of different orders is shared by the end systems, where the table has all possible orders for m messages (i.e., $m!$ entries), a message of size $\lceil \log_2 m! \rceil$ bits is required to transmit the order. Consider an example to understand the aspects of *DC*. Let the messages to be transmitted by the source be 10(0), 30(1), 5(2), 25(3), 3(4) where the numbers in the bracket denote the position of the message in the sequence. Differential coding is performed in 2 steps. In step 1, the messages are arranged in increasing order. Here, in this example it is 3(4), 5(2), 10(0), 25(3), 30(1). The ordered messages are then passed through differential encoder block that takes difference of adjacent messages giving an output 3, 2, 5, 15, 5 for the above example. Since the messages are arranged

in increasing order, the sequence at the output of differential encoder contains only positive values. The position of corresponding order in the table maintained by end systems is transmitted as another message. Let us say the order 4,2,0,3,1 is at position 10 in the table. In this example, the total delay is “40” clock ticks+ $6t_b$ as against the “73” clock ticks+ $5t_b$ without coding. The number of clock ticks per message is reduced with the use of *DC* that in turn translates to a higher data-rate.

The sum of elements in the new sequence is equal to the largest element in the original sequence and hence the total waiting time is the sum of the waiting time to transmit the largest message in the sequence and the corresponding ordering. The information delay per sequence of m messages t_{dc} is

$$t_{dc} = \frac{(i+j)(2e_d f_c + 1)}{f_c} : i \in \{0, 1..2^n - 1\}, j \in \{0, 1..m\}$$

The data-rate for *DC* is thus,

$$R_{DC} = \frac{mn}{(m+1)(t_b + e_f + e_r) + t_{dc}}. \quad (5)$$

The receiver has to wait till the end of sequence to receive all m messages. Thus, the delay in *DC* is higher than that in *TEC-SMART* without coding but is close to that of *OOK*. For an n -bit message, *OOK* takes nt_b time units while *DC* transmits mn bits in a maximum of $mt_b + t_{info}$ time units. The delay in *DC* is close to nt_b units if m is close to n (as $t_{info} \ll t_b$). It has been observed that m is close to n over different values of t_b .

4.2.3 Piggybacked Ordering (*DC_P*)

Recall that *DC* adds one extra message per sequence to convey the ordering of messages in the sequence. *DC_P* is an optimization technique that eliminates the extra message in *DC* for conveying the ordering of messages. We refer to this variant as *TEC-SMART(DC_P)*. To keep the number of signals equal to the number of messages, the order is conveyed embedded within the message. Thus, one pair of (bit

period + delay corresponding to order) is eliminated at the cost of increased waiting time per message. Every message (the difference) is multiplied by a constant k_1 and a portion of the ordering information is added. Redundancy in information delay and bit period is then introduced to the resultant message for error correction. The receiver, after performing error correction divides the number by the same constant k_1 so that the quotient is the message and the remainder is the portion of ordering. In this fashion, the receiver is able to recreate the ordering message that is embedded in the data messages. The order embedded in each message is k_2 . The information delay in case of DC_P is,

$$t_{dcp} = \frac{(ik_1 + k_2)(2e_d f_c + 1)}{f_c} : i \in \{0, 1, \dots, 2^n - 1\}$$

The data-rate using DC_P is thus,

$$R_{DC_P} = \frac{mn}{m * (t_b + e_f + e_r) + t_{dcp}}. \quad (6)$$

The constant k_1 is chosen such that $k_1 \geq \frac{\log_2(m!)}{m}$ i.e., the constant should be able to indicate the number of extra bits per message to represent the order. Considering $m = 8$, the number of bits required to represent $8!$ is 16 and hence *2 bits per message* making $k_1 = 4$. k_1 cannot be arbitrarily large; the larger the value of k_1 , the higher the waiting delay per message. An optimization to choose the best possible value of k_1 , given t_b and m must be performed.

4.2.4 DC for unbounded noise - DC_U

We proposed *TEC-SMART*, that uses error differentiation and piggybacked ordering to improve data-rate performance in a bounded noise channel. We considered a simple case of uniformly distributed additive channel noise. In this section, we analyze *TEC-SMART* in the case of unbounded noise. We propose an optimization to detect error in an unbounded noise channel. When noise distribution is unbounded, it is not possible to achieve 100% error correction. We propose DC_U as an optimization that

can detect error in case of unbounded noise. DC_U gives a percentage of correctable, detectable and undetectable error for a given noise distribution. In the rest of the thesis, we refer to this variant as $TEC-SMART(DC_U)$.

As described in 4.2.3, $TEC-SMART(DC_P)$ requires the sender and receiver to share a list of ordering. For a sequence of m messages, a list of $m!$ entries is shared by sender and receiver. The location of order in the list is appended to the actual message. Noise in the channel alters the location of the order and not the actual ordering. As every received location maps to a valid order, a timing error more than ϵ cannot be detected.

$TEC-SMART(DC_U)$ detects errors by appending the absolute ordering to the message. In order to represent the order of m messages, each message requires an additional $\log_2 m$ bits. The order in each message is distinct and takes only values from 1 to m . Each message in the new sequence is then multiplied by 2ϵ . If the error is greater than ϵ , the order appended is changed. Absence of m unique order at the receiver indicates an uncorrected error. DC_U also avoids the need for a list of order to be shared by sender and receiver. No extra memory is required. The implementation is the same as DC except the steps to add order to the message .

Thus, if an error greater than ϵ is added to the message, the order as decoded by receiver will not have m distinct numbers thus indicating the presence of an error. In the following conditions, error detection is not possible:

1. Error in each message such that there are m distinct orders but at different positions
2. Large enough ϵ such that order still remains but message is altered

For a sequence of m messages, there are $m!$ distinct ordering, of which only one is correct. There will be $m! - 1$ possibilities of wrong reception with DC_U . But the total number of erroneous reception can be m^m . Of the m^m possibilities, $m! - 1$ cannot

be detected. The rest can be detected. $\frac{(m!-1)*100}{m^m}$ gives the percentage undetectable error. The choice of ϵ determines the percentage of correctable error and choice of m determines the percentage of detectable error.

4.2.5 Summary

Thus far in this section we have presented *TEC-SMART*, a communication approach to improve data-rate performance of bacterial communication under non-zero error conditions. In the following section, we use both theoretical and numerical analysis to evaluate *TEC-SIMPLE* and *TEC-SMART*.

CHAPTER V

THEORETICAL ANALYSIS OF CAPACITY

Capacity of a channel is given by the maximum mutual information $I(X : Y)$ between input X and output Y , maximized over all input distributions.

$$C = \lambda \max_{f_X(x)} I(X : Y) \quad (7)$$

where, $\lambda = \frac{1}{E(Y)}$ is the inter-arrival rate at the receiver. To the best of our knowledge, existing works do not characterize the channel delay of a molecular communication system. Therefore, following the approach in [13], we derive the maximum achievable data-rate for uniform and exponential distribution of channel delay.

5.1 Uniform Distribution of Noise

Let N be the channel delay. N is uniformly distributed with mean t_b . $N \sim U(t_b - \epsilon, t_b + \epsilon)$. Since information is conveyed in time intervals, there is no parameter analogous to signal power [15]. Therefore, constraint on the input can be mean or peak. Let X be the inter-arrival delays at the sender end and Y be the inter-arrival delays at the receiver end. Consider $x_1 \in X$ be the message to be transmitted. Due to the response time at receiver bacteria, the receiver observes y_1 in Y as $y_1 = x_1 + N_1$, where $N_1 = t_b + n_1$ is the error introduced by the channel and t_b is the average time required by bacteria to respond to a signal. Upon reception, the receiver subtracts the average response time of receiver from the observed time and the received message is $y_1 - t_b$. Thus, the system can be modeled using the following equation,

$$Y = X + N - t_b \quad (8)$$

We derive the capacity of timing channel using differential entropy of Y and N.

$$I(X : Y) = h(Y) - h(Y|X) \quad (9)$$

$$= h(Y) - h(X + N|X) \quad (10)$$

$$h(X + N|X) = h(N|X) , \text{ as X and N are independent} \quad (11)$$

$$I(X : Y) = h(Y) - h(N|X) \quad (12)$$

$$= h(Y) - h(N) \quad (13)$$

Case 1: Peak-Constraint

$X \sim [0, t_x]$. Since X and N are bounded, Y is also bounded. [6] shows that among all bounded distributions, uniform has maximum entropy. Thus, uniform distribution is the entropy maximizing distribution. $Y \sim U(-\epsilon, t_x + \epsilon)$. The differential entropy of uniform distribution is given by, $h(Y) = \ln(t_x + 2\epsilon)$ and $h(N) = \ln(2\epsilon)$. Substituting in equation 9,

$$I(X : Y) = \ln(t_x + 2\epsilon) - \ln(2\epsilon) \quad (14)$$

$$C \leq \lambda \ln \frac{t_x + 2\epsilon}{2\epsilon} \quad (15)$$

Capacity per average delay of channel is obtained by,

$$C \leq \lambda t_b \ln \frac{t_x + 2\epsilon}{2\epsilon} \quad (16)$$

where, $\lambda = \frac{1}{t_b + E(Y)}$ is the average inter-arrival rate at the receiver. Since $E(Y) \geq 0$, λt_b varies from 0 to 1. As shown in Figure 8(a), maximum capacity is achieved when $\lambda t_b = 1$. Also, capacity increases with increasing t_x . Note that λt_b is strictly less than 1, as $E(Y) = E(X)$ and $E(X) \geq 0$. The different colors in 8(a) denote different values of λt_b . For a given t_x , depending on the error correction mechanism and modulation, the system approaches a certain ratio of λt_b . The higher the value of λt_b is, the better the algorithm is, in achieving the maximum data-rate. The smaller the value

of $E(X)$, higher the ratio λt_b i.e., for small values of $E(X)$, $E(Y) \approx t_b$. The delay at the receiver end is thus dominated by bit period leading to an increased data-rate. If $\epsilon \ll t_x$, then an approximation for entropy maximizing input distribution can be derived. Assume $X \sim U(0, t_x)$. We assumed $N \sim U(t_b - \epsilon, t_b + \epsilon)$. The distribution of sum of 2 independent random variables is the convolution of 2 distributions [12]. Here, both X and N are uniformly distributed. Convolution of these 2 uniform pulses gives a trapezium. The slope of the sides of the trapezium is very high if $\epsilon \ll t_x$, which we can approximate to a uniform distribution. Hence, for peak constrained input in a uniform noise distribution channel such that $\epsilon \ll t_x$, uniformly distributed input maximizes channel capacity.

Case 2: Mean-Constraint

$E(X) \leq k$ where k is an arbitrary constant. The mean of the input distribution is constrained. Since $Y = X + N - t_b$, $E(Y) = E(X)$, Y is also mean-constrained. Note that $Y + t_b$ is the time between 2 receptions and hence is positive. Among all mean-constrained, positive distributions, exponential distribution gives the maximum entropy. Thus, capacity is upper bounded when $Y + t_b$ and hence Y follows exponential distribution. Since entropy does not change with linear translation, $h(Y) = 1 - \ln \frac{1}{E(Y)}$. Similar to case 1,

$$I(X : Y) = 1 - \ln \frac{1}{E(Y)} - \ln(2\epsilon) \text{ as } E(Y)=E(X), \quad (17)$$

$$C \leq \lambda \left(1 + \ln \frac{E(X)}{2\epsilon}\right) \quad (18)$$

Total delay per reception is $E(Y) + t_b$. Thus, the capacity per average delay of channel is,

$$C \leq \lambda t_b \left(1 + \ln \frac{E(X)}{2\epsilon}\right) \quad (19)$$

Figure 8(b) shows the capacity as a function of mean of the input with $t_b = 435\text{min}$ and $\epsilon = 0.6\text{s}$. With increasing mean, the capacity increases to a maximum and then

decreases. Till the peak, total delay is dominated by t_b after which, the delay increases linearly whereas the number of bits represented increases logarithmically. Thus the net data-rate decreases.

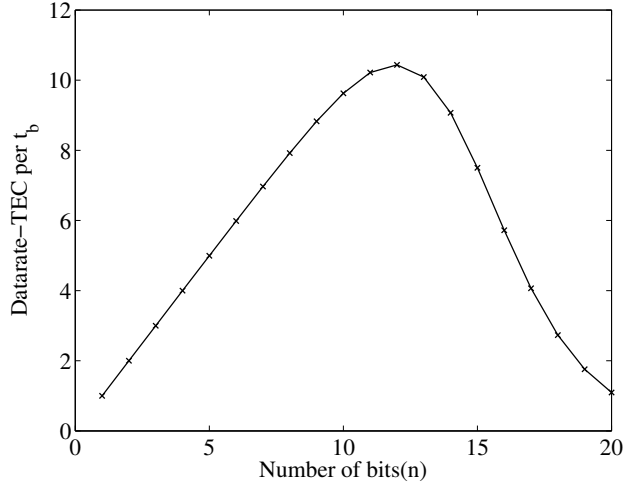


Figure 7: Simulation based capacity

5.2 Exponential Distribution of Noise

In case of unbounded distribution, peak-constraint for input is not tractable. Therefore, we consider a mean-constrained input. Let N follow exponential distribution with mean t_b . Following the case 2 of uniformly distributed noise, Y should follow exponential distribution with mean $E(Y) = E(X)$.

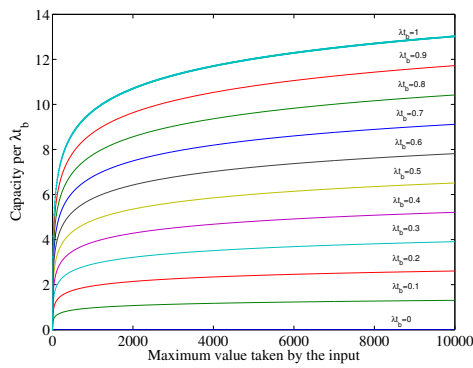
$$I(X : Y) = 1 - \ln \frac{1}{E(Y)} - 1 + \ln \frac{1}{t_b} \quad (20)$$

$$C \leq \lambda \ln \frac{E(X)}{t_b} \quad (21)$$

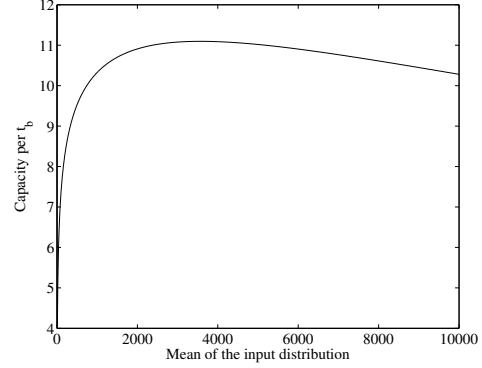
Capacity per average delay of channel is obtained by,

$$C \leq \lambda t_b \ln \frac{E(X)}{t_b} \quad (22)$$

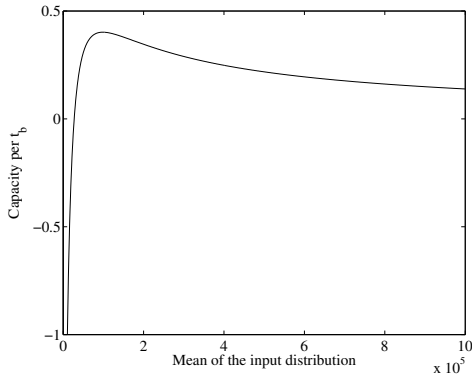
Following the theoretical analysis, the maximum achievable data-rate under different constraints on input distribution for uniform and exponential noise distribution has



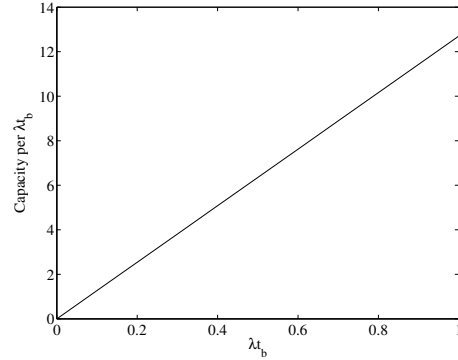
(a) Bounded channel delay with peak-constrained input



(b) Bounded channel delay with mean-constrained input



(c) Unbounded channel delay with mean-constrained input



(d) Bounded channel delay for a given input mean

Figure 8: Theoretical analysis of capacity

been derived. The performance of proposed error correction scheme along with timing modulation is compared against channel capacity. The simulation results do not include the differential encoder block as data-rate across channel is compared. Figure 7 shows the data-rate performance based on simulation results. The results show that the proposed error correction has $10.5X$ improvement over OOK with peak constraint on input at 2^{12} . The input was uniformly distributed and the noise was uniformly distributed. Under the given conditions, maximum achievable capacity is $11.7X$ over OOK. The data-rate of the proposed solution is 90% of that of the maximum achievable data-rate.

CHAPTER VI

NUMERICAL ANALYSIS OF TEC

We now perform numerical analysis of Equations (1) to (6) using MATLAB. The specific values for the parameters and the ranges for parameters used are driven by the experimental results presented in 3.2. Unless otherwise specified we use the following values: $t_b = 435$ min, $t_d = 6$ sec, $e_f + e_r = 0.1t_b$, $e_d = 0.1t_d$. Since the performance of *TEC-SMART* is dependent on the message size, the bit period, error introduced by the channel and the clock rate, we study the sensitivity of its performance to these different parameters. We present only relative performance results for *TEC* and its variants with respect to *OOK*. Every data point is obtained by taking an average of data-rate corresponding to all messages of frame size n .

6.1 Frame Size

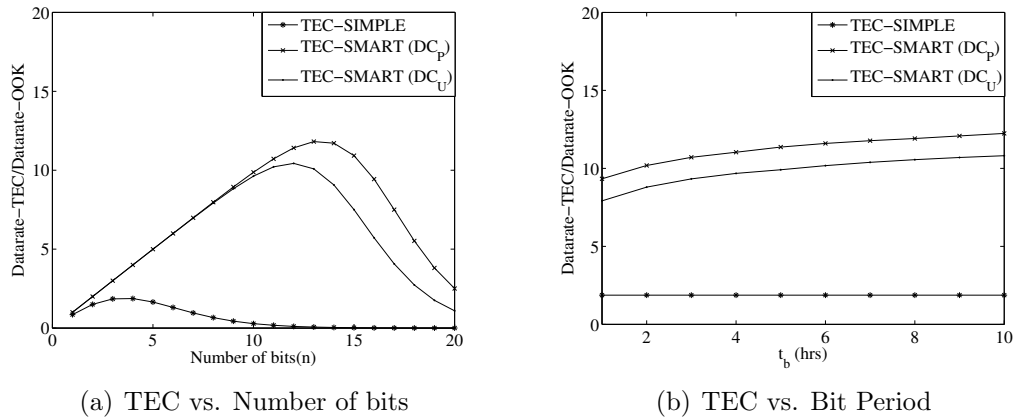


Figure 9: Performance of *TEC-SMART* and *TEC-SIMPLE* with varying n and t_b

Unlike other modulation techniques, the data-rate of *TEC* varies with the number of bits per message or the frame size n . The total delay involved in a transmission varies with the absolute value of the message. For small values of n , information

delay t_{info} is negligible compared to the bit period t_b . Thus, the data-rate increases with increasing n . Once t_{info} is comparable to t_b , the data-rate begins to decrease as the t_{info} starts dominating. The relative data-rate performance of *TEC-SIMPLE*, *TEC-SMART(DC_P)* and *TEC-SMART(DC_U)* is presented in Figure 9(a). This motivates the need for an appropriate selection of the frame size given a target environment. The performance of *TEC-SMART(DC_U)* is for an unbounded channel delay distribution. The goal of *TEC-SMART(DC_U)* is to detect error in the presence of unbounded noise and hence the maximum data-rate achievable is smaller than *TEC-SMART(DC_P)*, which cannot correct or detect any error greater than e_d .

6.2 Bit Period

Figure 9(b) presents the data-rate performance for *TEC*, *TEC-SMART(DC_P)* and *TEC-SMART(DC_U)* for different bit period. The value of t_b is varied from 1 to 20 hours. It can be observed from the results that while *TEC* is impacted heavily in its performance by an increase in t_b , *TEC-SMART(DC_P)* and *TEC-SMART(DC_U)* is considerably more resilient to larger values of t_b . This is due to the amortization of the t_b overhead over multiple messages.

6.3 Frequency

Figure 4(d) shows an increase in the data-rate with increasing clock frequency. With the introduction of error in the system, the clock rate loses its significance. Recall that the transmitter and the receiver measure the number of e_d time units between the start and stop signals. Hence, however high the clock rate is, the time slot is now in terms of error and hence the data-rate performance does not change with frequency once the error correction is introduced.

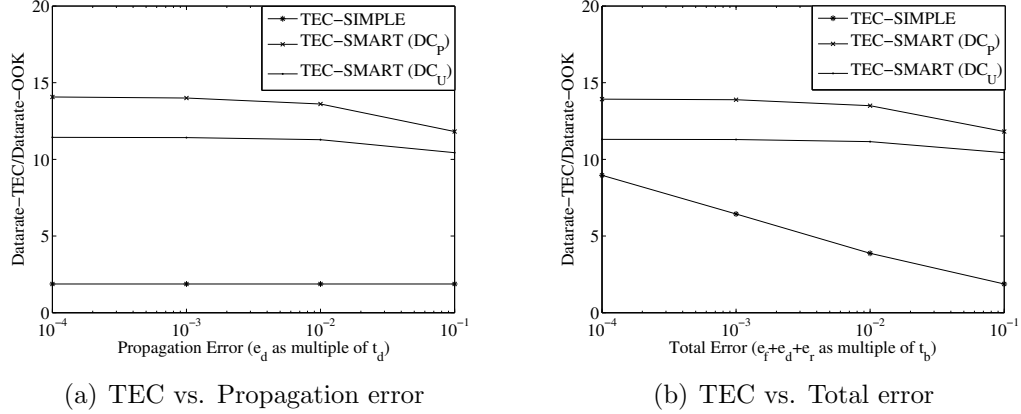


Figure 10: Performance of *TEC-SMART* and *TEC-SIMPLE* under varying error conditions.

6.4 Error

We proposed *TEC-SMART* as a better error correction strategy. *TEC-SMART* considers both bounded and unbounded error and proposes strategies to detect uncorrected error with high probability in case of unbounded error. We analyze the performance of *TEC-SMART* under bounded and unbounded error for varying error conditions.

6.4.1 Bounded Error

Recall from 4.2.5 that the performance of *TEC-SIMPLE* reduced to being marginally better than that of *OOK* under non-zero error conditions. However, *TEC-SMART* is explicitly designed to handle error conditions better by virtue of its error curtailing and differentiation mechanisms. Thus, the increase in *rise-time error* and *fall-time error* has minimal impact on the overall performance of *TEC-SMART*. In this section, we analyze the results in a bounded error. As seen in Figure 10(a), *TEC-SMART(DC_P)* can deliver a data-rate of over 10x even when the the total error is large ($0.1t_b + e_d$). Data-rate with respect to varying error components is presented in Figures 10(a)-10(b). Overall, the results demonstrate the better error resiliency exhibited by *TEC-SMART(DC_P)*. The data-rate delivered by *TEC-SMART(DC_U)*

is smaller than $TEC-SMART(DC_P)$ but the former can detect error greater than e_d .

6.4.2 Unbounded Error

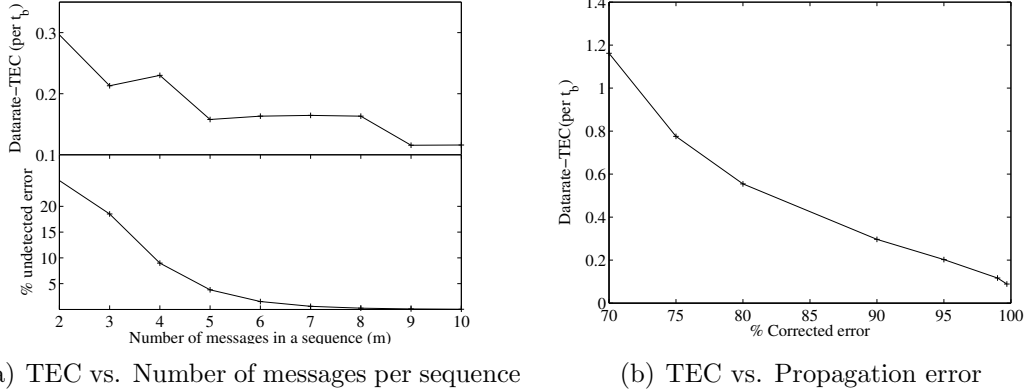


Figure 11: Performance of $TEC-SMART(DC_U)$ under exponential noise in the channel.

In the case of positive valued unbounded channel delay, exponential distribution can be considered as a general case, similar to Gaussian distribution in energy based communication. Figure 11 shows the performance of $TEC-SMART(DC_U)$ under exponential channel delay. The percentage of correctable error is increased by increasing ϵ but this reduces the data-rate due to the increase in redundancy. Figure 11(b) shows the decrease in data-rate with increasing ϵ . The following analysis is used to estimate ϵ for a given % of error correction. Let a be the fraction of error to be corrected and $f(x)$ be the probability distribution of exponential error. For e.g, $a = 0.9$ for 90% error correction

$$\int_0^\epsilon f(x) dx = a$$

For an exponential distribution,

$$F(\epsilon) = a \text{ where, } F(x) \text{ is the cumulative distribution function}$$

$$1 - e^{-\lambda\epsilon} = a$$

$$e^{-\lambda\epsilon} = 1 - a$$

$$\epsilon = -\lambda(\ln(1 - a))$$

Figure 11(a) shows the variation of data-rate and percentage of undetected error with increasing m . The correctable error is set to 90%. The value of ϵ to be multiplied to the message is obtained from the probability distribution of channel noise as explained above.

From the capacity analysis and numerical analysis, we observe that *TEC* is suitable for *super-slow networks*. Depending on the application and the target environment, the optimum value of n , ϵ and m for a given t_b is identified a priori using the analysis presented above. In a bounded error, *TEC* provides over an order of magnitude improvement over *OOK* in data-rate performance while in an unbounded error, it can still detect uncorrected error.

CHAPTER VII

CONCLUSION

7.1 Conclusion

In this work, using state-of-art advancements in genetic engineering and microfluidics we have argued with results from an experimental test-bed that a modulation technique like *OOK* is indeed achievable for communication between bacterial populations relying on molecular signaling. We also have shown that the data-rate performance of *OOK* is dismally low because of the large bit periods. We propose a communication strategy called time-elapse communication with a set of optimization mechanisms that improves the data-rate over *OOK* by more than an order of magnitude. We derived the maximum achievable capacity of time based communication for a uniformly distributed noise and an exponentially distributed noise channel.

7.2 Future Work

While we have achieved improvement in data-rate performance, there are other problems to be considered for future work like,

1. Effect of error propagation: TEC relies on the correctness of previous message. In case of unbounded noise, error greater than ϵ can only be detected. Thus, error in one message will cause an error in the following messages. The impact of error propagation is not studied.
2. The entropy maximizing input distribution is not derived. Capacity derivation give an entropy maximizing output distribution. Simulation results use uniform input distribution.

3. Resource consumption: The energy consumption of *TEC* is not discussed, as the resource bottleneck is not identified. Identifying the bottleneck resource and analysing the performance of *TEC* will be an interesting future work.

Following the analysis in energy based communication, the energy consumption is directly proportional to the number of signals transmitted into the channel. *TEC*, by principle, is designed to reduce the number of signals transmitted. Irrespective of the number of bits per message, only 2 signals are transmitted viz., *start* and *stop*. Also, *stop* of present message acts as *start* of next message. Thus, *TEC* uses one signal message. Therefore, the energy consumed is $\frac{1}{\text{Framelength}}$ times energy consumed for OOK. But, in a molecular communication system, resources required to transmit a signal is approximately the same as that required to keep the receiver alive. Thus, energy per transmission is negligible. One possible solution to reduce energy can be to reduce the time a receiver is awake.

REFERENCES

- [1] AKYILDIZ, I. F., FEKRI, F., FOREST, C. R., HAMMER, B. K., and SIVAKUMAR, R., “Monaco: Fundamentals of molecular nano-communication networks (invited paper),” *IEEE Wireless Communications Magazine, Special Issue on Wireless Communications at the Nano-Scale*, 2012.
- [2] AKYILDIZ, I. F. and JORNET, J. M., “Electromagnetic wireless nanosensor networks,” *Nano Communication Networks*, 2010.
- [3] ANANTHARAM, V. and VERDÚ, S., “Bits through queues,” *IEEE Transactions on Information Theory*, 1996.
- [4] BASSLER, B. L., “How bacteria talk to each other: regulation of gene expression by quorum sensing,” *Current Opinion in Microbiology*, 1999.
- [5] CHARRIER and OTHERS, “A multi-channel bioluminescent bacterial biosensor for the on-line detection of metals and toxicity. part ii: technical development and proof of concept of the biosensor,” *Analytical and Bioanalytical Chemistry*, vol. 400, pp. 1061–1070, 2011.
- [6] COVER, T. M. and THOMAS, J. A., *Elements of Information Theory (Wiley Series in Telecommunications and Signal Processing)*.
- [7] DANINO and OTHERS, “A synchronized quorum of genetic clocks,” *Nature*, vol. 463, pp. 326–330, Jan. 2010.
- [8] DELIGEORGIS, G. and OTHERS, “Microwave propagation in graphene,” *Applied Physics Letters*, 2009.
- [9] ECKFORD, A. W., “Molecular communication: Physically realistic models and achievable information rates,” *arXiv:0812.1554v1*.
- [10] ENDY, D., “Foundations for engineering biology,” *Nature*, vol. 438, no. 7067, pp. 449–453, 1111.
- [11] MELKE, P., SAHLIN, P., LEVCHENKO, A., and JÖNSSON, H., “A cell-based model for quorum sensing in heterogeneous bacterial colonies,” *PLoS Computational Biology*, 2010.
- [12] PAPOULIS, A. and PILLAI, U. S., *Probability, Random Variables and Stochastic Processes*. Dec. 2001.
- [13] SELLKE and OTHERS, “Timing channel capacity for uniform and gaussian servers,” in *Forty-Fourth Annual Allerton Conference on Communication, Control, and Computing*, 2006.

- [14] SELLKE, S., WANG, C., BAGCHI, S., and SHROFF, N., “TCP/IP timing channels: Theory to implementation,” *INFOCOM*, 2009.
- [15] SRINIVAS, K. V., ECKFORD, A. W., and ADVE, R. S., “Molecular communication in fluid media: The additive inverse gaussian noise channel,” *IEEE Transactions on Information Theory*, 2012.
- [16] STOCKER and OTHERS, “Development of a set of simple bacterial biosensors for quantitative and rapid measurements of arsenite and arsenate in potable water,” *Environmental Science & Technology*, vol. 37, no. 20, pp. 4743–4750, 2003.
- [17] SUDA, T. and OTHERS, “Exploratory research on molecular communication between nanomachines,” in *GECCO 2005*.
- [18] ZHU, Y. and SIVAKUMAR, R., “Challenges: communication through silence in wireless sensor networks,” in *MobiCom*, 2005.