SUMMARY

CDI TYPE I: A Communications Theory Approach to Morphogenesis and Architecture Maintenance

The assertion that biological systems are communication networks would draw no rebuke from biologists – the terms *signaling*, *communication*, and *network* are deeply embedded parts of the biology parlance. However, the more profound meanings of information and communication are often overlooked when considering biological systems. Information can be quantified, its flow can be measured and tight bounds exist for its representation and conveyance between transmitters and receivers in a variety of settings. Furthermore, communications theory is about *efficient* communication where energy is at a premium – as is often the case in organisms. But perhaps most important, information theory allows mechanism-blind bounds on decisions and information flow. That is, the physics of a system allows determination of limits that *any* method of information description, delivery or processing must obey.

Thus, rigorous application of communication theory to complex multi-cellular biological systems seems both attractive and obvious as an organizing principle – a way to tease order from the myriad engineering solutions that comprise biological systems. Likewise, study of biological systems – engineering solutions evolved over eons – might yield new communication and computation theory. Yet so far, a communications-theoretic approach to multi-cellular biology has received scant, if any, attention. We therefore propose to explore this interdisciplinary intellectual gap under the auspices of the NSF CDI program.

The **intellectual merit** of the proposed research lies in *careful and rigorous* exploration of communications theory concepts applied to signaling between and within cells in *multi-cellular networks*. Energy consumption is a key feature in both biological networking problems and in the formal specification of communications problems and for this reason we believe that a communications theory perspective may help illuminate biological mechanisms in specific areas such as tissue biology, cancer biology, the biology of aging, and microbial ecosystems as well as other areas where a formal network perspective may be appropriate. Likewise, we suspect that the existence proof provided by living things, in combination with a communication-theoretic perspective, can provide new approaches to biological and non-biological engineering problems.

The **broader impact** of developing an effective communications framework for biological systems which can both explain and predict the general behavior of multi-cellular systems over time is difficult to overestimate. The most obvious impact areas are embryology, development, aging and age-related diseases such as cancer in biology, and distributed specification and assembly of robust structures in engineering, but a multitude of other applications in biology and engineering are clearly possible. A more modest, but still potentially profound and important impact of the proposed work would be to delineate the limits of key biological communications methods. For instance, are signaling methods such as chemical gradients necessary and sufficient to rigorously explain tissue development, organization, maintenance and aging? For any given method can we derive bounds on how much cells can possibly say to one another and how they might say it? We expect the answers will be of great interest to both the multi-cellular biological community and the communications theory community.

Christopher Rose
Wireless Information Network Lab
Rutgers University

I. Saira Mian
Life Sciences Division
E.O. Lawrence Berkeley National Laboratory

1 Introduction

The assertion that biological systems are communication networks would draw no rebuke from biologists – the terms *signaling*, *communication*, and *network* are deeply embedded parts of the biology parlance. However, the more profound meanings of information and communication are often overlooked when considering biological systems. Information can be quantified, its flow can be measured and tight bounds exist for its representation and conveyance between transmitters and receivers in a variety of settings. Furthermore, communications theory is about *efficient* communication where energy is at a premium – as is often the case in organisms. But perhaps most important, information theory allows mechanism-blind bounds on decisions and information flow. That is, the physics of a system allows determination of limits that *any* method of information description, delivery or processing must obey.

Thus, rigorous application of communication theory to complex multi-cellular biological systems seems both attractive and obvious as an organizing principle – a way to tease order from the myriad engineering solutions that comprise biological systems. Likewise, study of biological systems – engineering solutions evolved over eons – might yield new communication and computation theory. Yet so far, a communications-theoretic approach to multi-cellular biology has received scant, if any, attention. We therefore propose to explore this interdisciplinary intellectual gap under the auspices of the NSF CDI program.

We begin with a roadmap to this multi- and inter-disciplinary proposal. Unlike area-specific work where the general problems are understood and widely accepted, this proposal spans at least two major topics and a number of subdisciplines within these major areas. Thus, rather than stating research goals and reviewing previous work at the outset as is normally done, we have taken a somewhat spiral approach. In section 2 we cover necessary background material while introducing the ideas underlying the proposed research. In section 3 we begin to explore basic research questions and revisit them in increasing detail until descriptions of specific mathematical biological communications problems can be considered. A brief review of related prior work follows in section 4 and allows us to compare previous approaches to what we propose. Then in section 5 our research goals are listed. We felt this organization would allow the widest range of readers to more easily evaluate the proposed work.

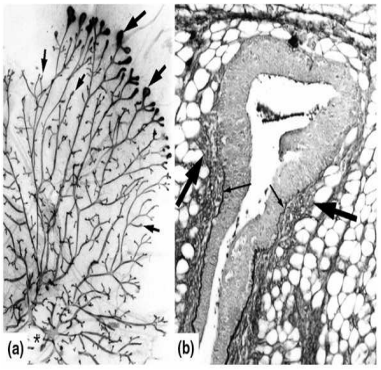
It is also worth mentioning here that although we have deliberately taken a more communications theoretic approach to multi-cellular communication, we are aware of the many complexities inherent in and manifested by real-world multi-cellular systems [1–21]. The PIs have experience deriving and applying mathematical models of biological systems using a variety of descriptive (phenomenological) approaches [22–31] and statistical machine learning (data-driven) approaches [32–50]. However, with this work, rather than starting with observed phenomena and providing *descriptions* [51], we seek to first establish inviolable bounds on communication that all biological systems must obey and thereby make *predictions* about what biological systems *must* do under basic physical assumptions. We will then circle back through heterogeneous, publicly available, Web-based databases and resources to identify existing (or uncover new) data, information and knowledge that support our results, a process that will almost certainly suggest new experiments designed to assess the validity of particularly important predictions. (See, for example, our previous integrated computational-experimental studies [10, 12, 16, 52–68].)

Or more simply put, we will seek basic physical models into which signaling schemes must fit and then pursue their implications for the development and maintenance of form and function in multi-cellular biological systems – that is, the communications theory aspects of *morphogenesis* and tissue architecture. Of course, there exists a danger that simple models will only lead to trite conclusions. However, we will see in later sections that with even minimal attention to modeling detail, interesting organizational and operational principles emerge that can guide biological experimentation and discovery.

2 Background

2.1 Signaling in Biological Systems

Any organism composed of more than one cell is by definition a communications network. Such networks span the range of complexity from microbial ecosystems such as biofilms, microbiomes and bacterial mats to animal and plant tissues, organs, organisms, populations and ecosystems. Two examples of multi-cellular systems at the tissue- and organism-level are provided in FIGURE 1 to familiarize non-biologists with the stunning complexity (and beauty) of biological matter at the cellular level. As if by magic, a seemingly non-descript clump of cells becomes an organism through a sequence of distributed yet carefully choreographed decisions. Signaling within and between cells is accomplished through a variety of chemical, electrical, mechanical and other means so that individual cells can sense their cellular and non-cellular environment to make appropriate functional and behavioral choices.



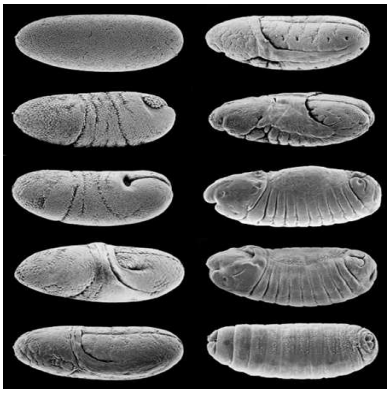


Figure 1: Photomicrographs of complex biological systems comprised of multiple heterogeneous intercommunicating cells. LEFT: Adult mammary gland tissue showing (a) part of the ductal tree and (b) a cross-section through the duct and acinus of a terminal end bud. RIGHT: Development of a *Drosophila* embryo (gastrulation) [69] starting from a cellular blastoderm (upper left). Individual cells visible.

Signals can be conveyed using chemicals (hormones, cytokines, growth factors, ions, drugs, small molecules, neurotransmitters, peptides, proteins, lipids, carbohydrates), mechanical forces, pressure, temperature, light, electrical potentials and magnetic flux. Stimuli may trigger various responses occurring over different time scales such as an alteration in cell metabolism, a change in cell membrane voltage, activation of gene expression (transcription in the nucleus) and cell locomotion, to name a few. Often such signal transduction involves a sequence of biochemical or other reactions whereby one molecular species is converted to another which in turn constitutes the input for the next reaction. This sequence of events is often called a *signaling pathway* and the collection of intercommunicating pathways results in *signaling networks*. The behavior of a given signaling pathway and hence signaling networks may be modulated by different stimuli. (A variety of Web-based portals have been developed to help navigate and understand the vast body of work on cellular interpretation of signals in context-dependent manners – see, for example [70–72].)

Although this basic network analogy can be pursued at a number of levels, from ecosystems to populations to organisms to organs to tissues to cells to molecules, we will focus on cells as the fundamental unit of organization. There are a number of reasons for this choice with perhaps the most obvious being that cells are discrete entities with clearly definable boundaries. Furthermore, cells are specialized, self-contained, self-powered, sensing and communication platforms that organize themselves into myriad complex systems. In addition, since elucidating the full repertoire and function(s) of the molecular components of cells is an integral part of genome biology and an important component of many other fields, a careful investigation of the form and function of tissues comprised by cells seems a reasonable next step and one which has so far received considerably less attention. We will also focus primarily on epithelial tissue because it exemplifies the interplay between morphogenesis, architecture, and disease, a feature that has been demonstrated most comprehensively for the mammary gland where studies have shown that its cells communicate in spatially precise ways to both attain structure (morphogenesis) and maintain structure in the face of various insults, both gross and genetic [73–80].

2.2 Mechanics of Intercell Signaling

Intercellular communication occurs through mechanisms and structures mediated by the cell membrane. A *gap junction* is an area of apposed cell membranes containing *connexons*, proteins that bridge the extracellular space between two cells and allow the cytoplasm of one cell to communicate directly with that of the other via chemical and/or electrical means. Some categories of chemical signals, for example a gas such as nitric oxide, simply diffuse across the cell membrane into the cytoplasm and then, possibly, into the interior of a membrane-bound intracellular organelle (nucleus, mitochondrion, lysosome, endoplasmic reticulum) where they effect a response.

In receptor-mediated signaling – perhaps the most important form of communication between cells in a tissue – chemical signals, often small protein ligands such as *hormones*, diffuse through some medium and bind to a specific protein located in the cell membrane. Alternatively, the signal might reduce the concentration of specific ligands local to the target cell. In either case, the ligand-receptor complex mediates the transmission of extracellular signals to the interior of a cell. The reverse process (sometimes using the same structures, sometimes not) conveys intracellular signals to the exterior. Receptor-mediated signaling involving hormones can be roughly divided into *endocrine*: a signal which travels through some extracellular medium to distant cells, *paracrine*: a signal received only by cells in the same vicinity, *autocrine*: a signal received by cells of the same type or the sender cell itself, and *juxtacrine*: a signal which travels along or through the cell membrane and is received by the sender cell itself or a physically adjacent cell.

A cell interacts dynamically and reciprocally with its cellular and non-cellular environments at many levels. Locally within its niche, a cell responds and is responsive to neighboring cells, the extracellular matrix, and soluble factors. In a tissue, cells/niches are influenced by myriad hormonal and chemical signals. The systemic milieu affects the tissue and this in turn is affected by external environmental influences. Overall, endocrine, paracrine, autocrine and juxtacrine signals are chemical signals that play critical roles in communication within and between layers of this organizational hierarchy. Also, as might be expected in biological systems where evolution parsimoniously reuses and adapts basic themes to fit different purposes, communications methods can be assemblages or cascades of more basic methods – such as auditory signal transduction in hair cells which incorporates mechanical, chemical and electrical means to relay sound stimuli to nerve fibers.

Our particular focus will be on the communications aspects of form and function development in multi-cellular systems (morphogenesis). However our overall goal will be to understand the capabilities and limitations of information transfer within multi-cellular systems. To this end, we now provide a brief overview of relevant communications theory concepts.

2.3 A Communications Theory Primer

Shannon theory [81–84] enables specification of two inviolable bounds – the lowest information rate needed to faithfully represent a message source, and the highest rate of reliable message delivery through some medium under transmission energy constraints. These bounds are the *source entropy rate* and the *channel capacity*, respectively. *Rate distortion theory* [83, 84], specifies how much information is necessary to approximate an information source under some fidelity criterion when a complete source specification is too large. These basic communications ideas (and associated bounds) fall under the general topic of *information theory* and are applicable to any scenario comprised of message sources, channels through which messages can be conveyed, and receivers that care about the messages. This use of the plural – sources, channel*s* and receiver*s* – is deliberate. Information theory, and the maturing area of network information theory, deal with all manner of intercommunicating elements [84]. However, we will confine ourselves here to the basic concepts with a single source, channel and receiver.

Entropy is a measure of what one does not know about a given random observable X having probability density $f_X(x)$. Entropy is formally defined as

$$H(X) = -\sum_x f_X(x) \log f_X(x) \tag{1}$$

for discrete X and as an integral for continuous X. The base of the $\log()$ determines the units; i.e., if natural log is used, the units are "nats" while if base 2 is used, the units are "bits." Besides having a number of desirable and intuitive mathematical properties, the definition is completely consonant with thermodynamic entropy via statistical mechanics. Furthermore, the idea can be extended to *entropy rate* if X is a time-varying correlated stochastic sequence rather than a single random variable.

For discrete X, mapping X to Y compactly and losslessly is called *source coding* and the associated landmark result is that for any number of code bits per symbol R (called a code rate) which exceeds the source entropy $H(X)$, we can find a code which losslessly encodes the message source X. From a resource use perspective, it is often useful to make R as small as possible. However, the converse to the coding theorem states that if $R < H(X)$ then loss is inevitable. Thus, we have a first inkling of what the term *mechanism blind* implies. The coding theorem states that any rate above $H(X)$ can be achieved losslessly and that any rate below cannot. The mechanism by which one might build good codes is not relevant to the bounds obtained through the coding theorem and thus frees us from having to consider the details of each possible coding method. But perhaps the most important point of the coding theorem is the converse, which keeps us from seeking the "perpetual motion" solution of coding rates below the source entropy.

Understanding information delivery leads to the concept of *mutual information* – the amount of *information* observations of Z provide about Y. The formal definition is rather intuitive:

$$I(Y;Z) = H(Y) - H(Y|Z) \tag{2}$$

or the average amount by which knowing Z reduces the initial uncertainty about (entropy of) Y. In a communications context, we often assume causality $Y \rightarrow Z$, in which case the stochastic mapping from random variable Y to random variable Z is called the communications *channel*.

The *data processing theorem* – $I(X;Y) \geq I(X;g(Y))$ – will prove extremely useful. It states that no amount of "processing" (represented by the function $g()$) can increase the mutual information between X and Y. That is, all the information we can possibly obtain about X is contained in Y and loosely speaking the best we can do is to preserve it. The data processing theorem seems particularly important when considering multi-cellular biological systems since the constituent units, cells, can be machines of dizzying complexity. However, in conveyance of information *between* cells, the theorem applies no matter what the cellular complexity and therein lies its simplifying utility.

Mutual information also allows quantitative consideration of continuous sources X which do not have finite descriptions. For example, a finite number of bits cannot exactly represent every real number on the interval $[0,1]$ and we must accept some error. If we quantify the error with a *distortion measure* $d(x,q(x))$ where $q(x)$ is a finite representation of x, we can then ask how many bits per source symbol, $R(\epsilon)$, are required on average to represent an *information source* X under an average acceptable distortion constraint ϵ. *Rate distortion theory* tells us that

$$R(\epsilon) = \min_{q(),E[d(X,q(X))]\leq\epsilon} I(X;q(X)) \tag{3}$$

Just as important, rate distortion theory also tells us that any coding rate below $R(\epsilon)$ results in unacceptable average distortion.

Perhaps the most famous information theoretic result is the channel capacity theorem which states that the maximum rate at which information can be delivered *reliably* (error free) over a channel defined by the probabilistic mapping $f_{Z|Y}(z|y)$ is

$$C = \max_{f_Y(),\mathcal{E}_Y\leq P} I(Y;Z) \tag{4}$$

in bits per channel use. The maximization is over the channel input distribution $f_Y()$ subject to an input energy constraint $\mathcal{E}_Y < P$ since Y is assumed to represent a real physical quantity. Similar to the source coding theorem and rate distortion theory, the converse states that if a transmission rate $R > C$ is attempted, error is unavoidable. This result, in combination with the source coding theorem where Y is derived via coding X (or $q(X)$ if X is continuous) implies that for $H(X) < C$, reliable transmission is possible – and

impossible if $H(X) > C$. Once again it is important to note that the result is mechanism blind. The best coding and transmission methods are either error free or they are not.

There are, of course, caveats. The source coding theorem and the channel capacity theorem are asymptotic in nature. The bounds assume coding and transmission done over an infinite number of symbols. Put another way, for any finite number of symbols, the probability of error is non-zero for any non-trivial channel. However, the convergence toward zero probability of error is exponential in sequence length, so this issue if often more technical than practical. Furthermore, we will not (at least at first) seek to posit actual coding methods for biological systems, but rather, seek inviolable bounds based on the physics which all multi-cellular systems must obey.

Another caveat concerns channels with feedback. Homeostatic (and other) feedback mechanisms abound in biological systems. If the channel is memoryless (where previous channel inputs do not affect future outputs) the capacity theorem holds even if the receiver provides feedback to the source. However, for channels with memory, the feedback capacity can exceed the bound of equation (4). This issue is often addressed by modifying signal representations so that from the perspective of the transformed system, the channel (or a decomposed channel ensemble) is again memoryless.

This possible need for signal transformations leads to the last topic in this primer – the concept of a *signal space*. It is often convenient to represent signals $s(t)$ as $s(t) = \sum_k s_k \phi_k(t)$ where the s_k are the *projections* of the signal $s(t)$ onto the *orthogonal basis functions* $\{\phi_k(t)\}$. Just as we represent a point in physical space using three perpendicular (orthogonal) coordinates (also called *degrees of freedom*), we can represent functions as projections onto sets of orthogonal functions. The idea can be extended to joint space-time signal variations as well. The utility of a signal space approach stems from both how signals propagate through channels and in how source signals are represented in terms of information. Notably, signal space methods are used in combination with equation (4) to derive Shannon's famous Gaussian channel capacity theorem and its extension to channels with memory.

2.4 A Multi-Cellular Communication Framework

In the multi-cellular biological context, a message can be any information the environment, a sender cell (or group of cells) seeks to convey. The most fundamental and ubiquitous intercellular communication method is chemical signaling whereby cells produce signaling agents that are selectively sensed by specialized receiver structures on the same or other cells. Development of signal space models for the temporal and spatial variation of such signals is relatively straightforward. Chemical properties of ligands and receptors as well as genetic features (such as splice variants of a gene) also constitute degrees of freedom that might be amenable to some form of signal space representation. The channel is the physics that allows transport of signaling agents as well as the set of actuators between where the message resides (transmitting cell(s)) and where action is taken (receiving cell(s)).

Identification of specific biological signaling agents and molecular mechanisms is a daunting experimental task and one which already consumes a significant part of the research community. However, though such details are necessary to understand (and influence – i.e., pharmacologically) specific biological systems, the beauty of a communications theory approach is that the detailed methods by which information is conveyed do not affect the bounds on how much information there is or how rapidly it can be reliably delivered. Put another way, in pursuing a communications-theoretic approach to biological signaling, we need not assume that biological systems practice any particular style of coding or transmission. Rather, communications theory places fundamental limits on *any* method biological systems use to perform information transfer. Once the physical substrate is described, communications theory provides *mechanism-blind* bounds.

The signal to noise ratio (SNR) is a simple but illustrative example of mechanism-blindness in telecommunications theory. For a channel described by $r(t) = s(t) + w(t)$ where $s(t)$ is the information-bearing signal, $w(t)$ is noise and $r(t)$ is the received signal, there is an infinity of potential signal and receiver structures to carry information over the channel. However, if $w(t)$ is white Gaussian noise, communications theory tells us that the figure of merit is the energy carried by signal $s(t)$ relative the noise energy in the

signal space occupied by $s(t)$ – the SNR [84–87]. The detailed structure of the receiver and signal do not affect the theoretical bounds on information flow.

A variety of similar bounds exist for networks of communicating elements [84]. It is this generality and implicit reduction of complexity that constitutes the power of a communications-theoretic lens. Therefore, by analyzing channel physics and using energy-efficiency as an organizing principle, communications theory may help refine and extend our understanding of multi-cellular communications and its role in morphogenesis, tissue maintenance, aging and disease – all complex systems where in health, cells communicate in spatially precise ways to reliably develop and maintain tissue structures.

3 Research Plan

3.1 The Limits of Cellular Conversations

The most obvious question regards how information is coded and delivered in multi-cellular systems. The ubiquity of diffusive signaling agents suggests that elaborating the details of various diffusion channels – including those with multiple signaling species and multiple spatially distinct receptors – is necessary to help answer questions about how rapidly information can be reliably delivered via diffusion and also suggest signaling mechanisms (diffusive or otherwise) which can be explicitly sought (or ruled out) by experimental biologists.

For instance, understanding the capacities of diffusive channels could illuminate known phenomena in tissue development such as the occurrence of repeatably abrupt boundaries amidst a more gently varying spatial profile of *morphogenic* (shape inducing) signaling agents [88]. The usual explanation of such behavior is that cells are endowed with special processing capabilities (particular thresholds and nonlinearities, for instance [88, 89]). In contrast, a communications theory analysis provides that either the appropriate information can be reliably delivered to cells in the requisite spatially specific manner or it cannot. Thus, communications theory may help illuminate the surprising robustness observed in most developing systems even amid the tangle of known and emerging microbiological detail about cell behavior. That is, even the complex "black boxes" that are cells are subject to the data processing theorem. Without the right information at the right time in the right place, no amount of processing can make development reliable.

Consider then that tissues form communities of intercommunicating cells – intricately organized three-dimensional structures from bacterial mats to mammalian epithelia [90–93]. How do such ensembles maintain structure and function even under environmental insults? It is well known that many signaling agents and associated receptors are not "orthogonal" in that a receptor may bind more than one type of ligand. Indeed, such "cross-talk" between receptors and ligands is a hallmark of signaling networks. Response overlap implies signal interference that could disrupt signals which convey architectural information. Or perhaps overlap enhances signaling through multi-cell cooperation. By investigating the network information theoretic bounds [84] on what cells and groups of cells can possibly say to one another, we can narrow the possibilities for system connectivity, and perhaps even anticipate connections between components of multi-cellular communities that may have previously been obscured or overlooked.

Furthermore, examining communications issues in a multi-cellular biology context might also provide new network information-theoretic insights especially for such modern contrivances as sensor networks [94–96] which arguably operate under similarly severe energy constraints. Specifically, network information theory is as yet only partially understood and multi-cellular biological systems have had ages to optimize performance under the common constraint of energy usage. Cellular systems of decision making components exhibit remarkable resilience - a tradeoff between efficiency and persistence, constancy and change, and predictability and unpredictability. Under normal circumstances, an adult tissue tolerates disturbance without collapsing into a qualitatively different state and can withstand shocks and rebuild itself when necessary. Perhaps in trying to understand how cells communicate within a community, some biomemitic opportunities for human-engineered systems could become evident.

3.2 What Do Cells Talk About?

Suppose we can obtain a reasonable understanding of bounds on signaling rates between cells in a multi-cellular community. A number of vital structural/functional questions immediately follow. For instance, in a mammary epithelium, how does a given cell know it is part of an acinus and needs to secrete milk into the lumen and not in the other direction? How do genotypically malignant breast cells know to behave "normally" when placed in an appropriate three-dimensional tissue microenvironment [93, 97–99]. These sorts of questions – of which there are many examples from bacterial mats to organisms with billions of cells – are at heart, the developmental biology question. How is a "complex" structure elaborated from a single cell and maintained and how is spatial/architectural information conveyed.

Much effort has been devoted to the study of pattern formation and the emergence of complexity in biology (reviewed in [88, 89, 100–102] and for a recent experimental and computational study of tissues see [103, 104]). Nonetheless, we know of no study that asks what *rate of information flow* between cells is necessary to allow cells to develop and maintain a complex functioning structure. Specifically, cells assess their environments, and based on incoming information make *decisions*. A large (and rapidly increasingly) number of these decisions can be probed experimentally using modern biological methods. Via source coding (including rate distortion theory) these decisions can be quantified to some number (say B) of bits, a variable which depends upon the circumstances.

These B bits might require delivery by some deadline T (as when a cell has to decide its fate) or may need refreshing at some average rate R in order to perform one of 2^B possible behaviors. That is, cells of an organism respond to their environments by behaving in different ways. Furthermore, even in a strictly developmental context after fate has been decided, isolated cells express themselves differently than when they are part of a community and over time [92, 105]. So, information is constantly collected for appropriate decision making, at least in healthy cellular communities. Thus, simply speaking, the rate of information flow into a cell must be at least B/T where a deadline must be met, or RB when a series of behavioral decisions must be made.

A communications framework then allows us to ask whether the signaling rates culled from the physics of known biology comport with the spatially-specific limits imposed by the signaling physics or whether other mechanisms must be invoked. Can a given cell possibly receive the information it needs under given channel assumptions or does the information required greatly exceed the system capacity? Such studies will almost certainly enhance understanding and suggest new avenues of exploration in experimental multi-cellular biology.

There are also specific biological questions about tissues that lend themselves to a communications theory framework. Does the lowest information rate needed to faithfully represent a message source (source coding) and the highest rate of reliable message delivery through some medium (channel capacity) change during the generation (development and morphogenesis), maintenance (regeneration and replacement), and decline (aging) of the biological system? For these disparate tissue-level processes, how much information is necessary to approximate an information source under some fidelity criterion given that the complete source specification is extremely large (rate distortion theory)? Is the progressive decline in cell and tissue form and function seen in aging a consequence of a reduction in the fidelity of transmission, increasing lack of knowledge about a message (capacity diminution), inability to encode a message compactly and losslessly (source coding)? Do these phenomena vary from cell to cell? Could the loss of resilience of a multi-cellular system with age and/or in disease be due to the transmission of information with increasingly higher levels of loss and/or error? Is a diseased multi-cellular system one where the signal space is distorted through mutations in signal-producing genes?

It is also possible to pose the abstract question. Rather than seeking to explain how known biology achieves complex structure, we might ask in general what minimal information flows are necessary between identically programmed units which must cooperate to become an arbitrary structure. Is there some minimal information flow necessary to support such a given function? What are the requisite signaling methods? This question is similar to one asked in "amorphous computing" and pattern formation studies [106, 107] but ours will be an information-theoretic as opposed to computational approach.

3.3 What Can a Cell Say?

Diffusion of signaling agents through some medium is a ubiquitous form of intercellular communication. However, manufacture of signaling compounds can be metabolically costly. A moderate-sized 100-amino acid signaling molecule requires approximately 400 ATP to manufacture [108] which is significant even in comparison to an elevated 6×10^4 ATP/sec total energy budget during cell replication (E. Coli [109]) since many signaling molecules must be produced. Furthermore, the receptor structures sensitive to signaling agents also require energy for upkeep and operation (a feature only coming to be appreciated recently in telecommunications systems with modern sensor networks [94]).

Interestingly, communications theory suggests that the ubiquity of chemical signaling in multi-cellular biology is not accidental. It can be shown that *inscribed-matter* communication – of which chemical signaling is an instance – is often stunningly more energy-efficient than electromagnetic (or acoustic) methods in a surprising variety of contexts [110–112]. Notably, such messaging is not limited to passive diffusion methods in biological systems but is also prominent in active forms. For instance, tactile communication through filopodial extension [11], cell migration [88, 102] and perhaps most obviously, sexual reproduction all constitute forms of inscribed-matter messaging. Each requires energy not only to compose the message but also to deliver and to interpret it as well. With energy efficiency as a driver for many aspects of evolution, the various forms of inscribed-matter messaging in multi-cellular systems thus warrant close inspection.

We can begin by asking a simple and precise question. How rapidly can information be reliably sent over a *diffusion channel*? Here we examine two facets of the problem which we think provide some insight into how cells may (or may not) communicate over distance in complex tissues and organisms.

The diffusion equation in an isotropic medium is

$$\frac{\partial \rho}{\partial t} = \mathcal{D}\nabla^2 \rho \tag{5}$$

where $\mathcal{D}$ is the diffusion coefficient, a measure of how rapidly a diffusing species can flow as function of concentration gradients ($\nabla\rho$). Equation (5) is linear and time-invariant, so assuming variable-separable solutions we obtain a complex exponential fundamental solution

$$g(x, y, z, t) = e^{-k^2 t} e^{j\sqrt{k_x^2 \mathcal{D}}x} e^{j\sqrt{k_y^2 \mathcal{D}}y} e^{j\sqrt{k_z^2 \mathcal{D}}z} \tag{6}$$

where k^2 is some positive constant (for stability in time) and $k_x^2 + k_y^2 + k_z^2 = k^2$. Linearity allows us to form

$$\rho(x, y, z, t) = \int dk \int_{\mathcal{Z}(k)} R(k_x, k_y, k_z) e^{-k^2 t} e^{jk_x\sqrt{\mathcal{D}}x} e^{jk_y\sqrt{\mathcal{D}}y} e^{jk_z\sqrt{\mathcal{D}}z} dk_x dk_y dk_z \tag{7}$$

for some complex function $R(k_x, k_y, k_z)$ where $\mathcal{Z}(k)$ is the region where $k_x^2 + k_y^2 + k_z^2 = k^2$.

For simplicity, consider one dimension and a specific initial condition of $\rho(x, t = 0) = \delta(x)$ which corresponds to an impulse of signaling agent concentration injected into the system at $x = t = 0$. This leads to

$$\delta(x) = \int_{-\infty}^{\infty} R(k) e^{jk\sqrt{\mathcal{D}}x} dk$$

which implies $R(k) = \frac{1}{2\pi}$. Thus, the impulse response is the well-known Gaussian diffusion profile

$$h(x, t) = \int_{-\infty}^{\infty} R(k) e^{-k^2 t} e^{jk\sqrt{\mathcal{D}}x} dk = \frac{1}{\sqrt{4\pi\mathcal{D}t}} e^{-\frac{x^2}{4\mathcal{D}t}} u(t) \tag{8}$$

where $u(t)$ is the unit step function. The Fourier transform of $h(x, t)$ has magnitude

$$|H(x, f)| = \frac{1}{\sqrt{8\mathcal{D}\pi f}} e^{-\sqrt{\frac{\pi f x^2}{\mathcal{D}}}} \tag{9}$$

and characterizes the effect of a time-varying point-source at the origin on a receiver at position x.

To explicitly compute channel capacity, a few more steps are necessary – receptor noise levels must be determined (see [113–115] and section 3.4 for details) and considered in light of signaling molecule manufacture energy budgets. Furthermore, we have deliberately ignored issues such as signal degradation, active transport, mediated transport or multiple interacting signaling species, to mention only a few [108]. Nonetheless, the forms of equation (8) and equation (9) are telling. Specifically, we see as with any "wireless channel" that signal strength decreases with increasing distance x. However, this diminution is particularly severe – the impulse response of equation (8) is doubly exponential in distance x as opposed to the power law dependence of an acoustic or electromagnetic system. In addition, equation (9) shows that bandwidth also decreases exponentially with distance. A diminution of bandwidth serves to decrease the number of degrees of freedom available for communication and even further depresses capacity with increasing distance. These features can be seen in FIGURE 2 for step applications of signal at biologically relevant diffusivities $\mathcal{D}$, distances r, and signal application times T in seconds.

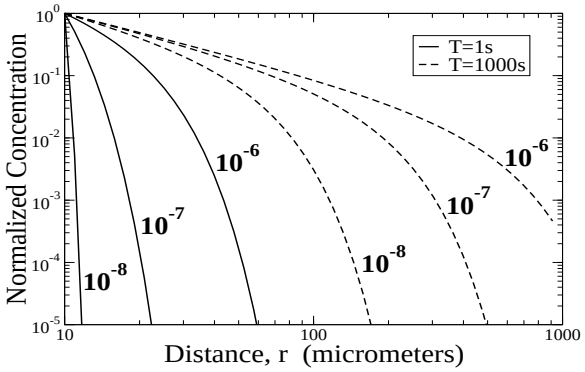


Figure 2: Normalized signal concentration versus distance r from a steadily applied point source (in three dimensions). $\mathcal{D} = \{10^{-8}, 10^{-7}, 10^{-6}\}$ cm^2/sec. Typical eukaryotic cells diameters are on the order of tens of micrometers (μm). Notice sharp decrease in concentration with increasing distance and with shorter application time $T = 1s$ and smaller diffusivities, $\mathcal{D}$. Ordinate: $\rho(r, T)/\rho(10\mu m, T)$.

A communications theory lens suggests that the channel physics heavily penalizes long distance communication via simple diffusion. Furthermore, imposing temporal structure on signals carries a significant penalty as well. This latter point speaks directly to the question of whether gradients convey information via time-variation [88, 89] and implies that if simple diffusion is the transport method, then static or very slowly varying gradients may be the most likely signaling method, even over relatively short distances. We must close, however, with a caveat. Unless signaling agents are "gettered" with antagonists (as in synaptic clefts) or the signaling interval is long enough to restore pre-signaling conditions, the diffusion channel is far from memoryless. Thus, the implicit potential for capacity-increasing feedback must be considered.

3.4 What Can a Cell Hear?

The cascades of cellular events that can be evoked by signals are daunting in both their complexity and variety [116]. However, signal cascades are themselves communications channels which convey degraded versions of the information present at the cell's boundary. Thus, by considering only the information present at the initial receptor sites (some of which may be internal for species which diffuse through the cell membrane) and applying a communications theory perspective (via the coding, channel and data processing theorems) we can reasonably ask: *what can a cell possibly hear?*

The fundamental event at a ligand-receptor complex is the binding of the ligand. At the molecular level, the process is stochastic owing both to diffusion and to the ligand-receptor kinetics. Furthermore, a given ligand may have multiple binding states at a receptor. However, for simplicity we will assume receptor occupation is a binary random variable X and that the probability p a receptor is occupied is some monotone increasing function of the ligand concentration ρ_ℓ [113–115]. The exact relationship between p and ρ_ℓ depends on a number of factors, including the ligand-receptor kinetics, which could in principle be calculated or measured. Further, we will assume that if a cell carries N receptors, sampling at some time instant provides N iid binary random variables X_i [115]. Finally, assume that the receptors are indistinguishable so

that the effective information variable accessible to the cell is the number of bound receptor sites K, which for large N is approximately Gaussian with mean Np and variance $Np(1-p)$.

To obtain a measure of the amount of information that could theoretically be conveyed through the ensemble of N receptors, we seek the maximum mutual information between ρ_ℓ and the X_i. However, if we assume p is an invertible function of ρ_ℓ we can equivalently seek

$$C = \max_{f_P(p),\mathcal{E}_P} I(K;P) = \max_{f_P(p),\mathcal{E}_P} H(K) - E_P\left[\frac{1}{2}\log\left(2\pi eNp(1-p)\right)\right] \tag{10}$$

where $f_P(p)$ is the input distribution (invertibly related to ρ_ℓ) and $\mathcal{E}_P$ is an "energy constraint" on p related to the signal manufacture cost of producing a ligand concentration ρ_ℓ at the receptor array. We note that the signal might be the particular ligand, but it might also be an enzyme which affects the native concentration of the ligand local to the target receptors.

For simplicity, we first ignore the energy constraint on signal manufacture and assume that any distribution on p is admissible. For $f_P(p)$ uniform and N large, the marginal distribution on K is almost exactly uniform itself. Thus, we can say (approximately) that

$$C \geq \log N - \int_0^1 \frac{1}{2}\log\left(2\pi eNp(1-p)\right)dp = \frac{1}{2}\left(\log N - 0.837\right) = \left(\frac{1}{2}\log_2 N - 0.6\right) \text{ bits.} \tag{11}$$

For a relatively large $N = 10^5$ receptors [115, 117, 118], a sequence of measurements could convey about 8 bits of information per measurement on average. For a more conservative $N = 1000$ [113], over 4 bits per measurement is theoretically possible.

If the ligand concentration ρ_ℓ could be changed as rapidly as desired and the interval between measurements were governed only by receptor activation/deactivation times, perhaps many observations could be made per second per signaling agent. (Nicotinic-cholinergic receptors, for instance, operate on a tens of milliseconds time scale [119, 120].) Thus, the incoming data rate to a cell could in principle be hundreds of bits per second. In light of this observation, it is easy to imagine single cells as information-gathering engines – as may have been useful in a free-foraging evolutionary past, as may have been re-used in multi-cellular developmental contexts, and perhaps as may be used by, say, malignant cells that rip free of their moorings.

However, in a multi-cellular system, the maximum theoretical input rate is only a part of the whole picture. ρ_ℓ is driven by other cells and though the data rate present just after surface receptors can be theoretically large, our previous consideration of the diffusion channel suggests that driving signal concentration levels rapidly over distance can be metabolically prohibitive. What may be a severe mismatch between sending and receiving capabilities in multi-cellular systems is interesting and will be explored.

Ultimately, deriving the channel capacity will require "closing the loop" by explicitly modeling $p(\rho_\ell)$. A direct approach is possible and will be pursued, but the results may depend strongly on specifics of the ligand-receptor kinetics among other highly variable and perhaps difficult to isolate and measure parameters. However, as in other areas of communication theory, it is often possible to find useful bounds under basic physical assumptions – such as receiver noise temperature and the worst case nature of white Gaussian processes for additive channels [83, 84]. Thus, part of our work will be investigation of bounds and bounding processes for the biological noise processes we consider – such as receptor noise.

3.5 Cells As Relays and Routers

If diffusion has limited range as a signaling method, then how do cells many cell-lengths away intercommunicate in spatially precise ways? The most obvious alternative mechanism to passive diffusion is active mixing. However, such mixing is usually chaotic which can destroy spatially specific information necessary for tissue architecture development and maintenance. A more spatially stable alternative might have individual cells relay information by up-regulating their production of signaling compounds in response to incoming signals. However, up-regulation of a signal constitutes processing and by the data processing

theorem, the information content of the up-regulated signal can only degrade the input information. This leads to a version of a well-studied communications problem – the relay channel. We intend to formulate the relay channel in a multi-cellular communications context and also to identify instances of relay channels in biology [121].

Relay channels figure prominently in human-engineered systems such as sensor networks [94–96]. Likewise, distributed sensing can be a primary function of some tissues and systems (inflammatory response, immune system). Via the Sleppian-Wolf theorem [84] information theory provides a basic analytic framework. However, from the perspective of implementation, the study of such biological systems in general and paracrine, autocrine and juxtacrine signaling in particular could reveal new ways of thinking about the sensing problem. Similarly, the detection and response to DNA damage is both a cell- and tissue-level phenomenon, so exploring the signaling involved in this critical function may provide insights about the design and construction of resilient systems – as one would like sensor networks to be.

Relaying might also be directed as opposed to diffuse. That is, the spatial differentiation seen in developing organisms suggests the possibility that cells can release signaling agents anisotropically to produce or enhance spatial specificity. The idea that cells might behave effectively as *routers* is at once both obvious and exciting. Obviously cells have structure and orientation themselves. A hair cell has stereocilia at one end and neural contacts at the other. Neurons have axons and dendrites. Mammary epithelial cells secrete milk on only on the lumen side of an acinus. However, the notion that an individual cell (or a small group) during morphogenesis might receive incoming signals and route information in spatially distinct ways like a router seems an interesting line of research to pursue.

Also, keeping an open mind about information transfer mechanisms is certainly necessary. For instance, it is known that sense organ precursor cells in developing Drosophila can forge direct long range contact with other cells by extending filopodia [11]. Simple diffusion and cell-cell relay methods have been ruled out experimentally. This delightfully direct method of communication is extremely spatial-specific, but at the metabolic cost of constructing and extending the filopodia. Additionally, once this possibility of gross motion in the service of communication is broached, a number of other phenomena spring to mind. The epithelial-mesenchymal transition (EMT) is a cellular program characterized by loss of cell adhesion and increased cell mobility that is highly spatially specific and essential for numerous developmental processes. The initiation of tumor metastasis, a process that involves invasion, has many phenotypic similarities to EMT, including loss of cell-cell adhesion. Since nature is seldom frivolous with energy, it will be interesting to analyze these and other phenomena as communications problems under energy constraints.

3.6 A Signal Space for Structural Information

One of the key problems in biology is how a genetic code (along with initial conditions imprinted on an ovum) is reliably elaborated into a complete organism. However, as scientists and engineers, we are often presented with the reverse problem – to determine the amount of information necessary to code specific structures – and it is tempting to simply apply that familiar methodology. Thus, standard signal space methods might be employed to represent any tissue volume, much as Fourier transforms, wavelets or any number of other orthogonal methods might be used to represent the image in a photograph.

Communications theorists often seek "minimal" representations subject to some distortion measure. However, discovering such representations among the infinity of possibilities for even "simple" problems like image coding seems more art than science. It seems especially daunting in the context of directly discovering the tissue-structure component of genetic codes. So instead, we initially plan to view known biology-driven approaches through a communications theory lens, and then examine other possible representations of structure based on known physics and observed behavior [102].

As one example, the *morphogenic gradient* is an accepted (if somewhat mysterious) mechanism in developmental biology whose discovery garnered the 1995 Nobel Prize in Medicine [88]. The basic premise is that during development, external gradients of signaling agents (*morphogens*) signal the clump of cells which comprise the blastula and cause it to differentiate into various precursor structures as the first step toward gastrulation. The implication is that the cells recursively impose their own morphogenic gradients

on the developing embryo and the process drives formation of the mature organism. A reasonably large literature has developed around this basic idea in the mathematical biology literature [89]. However, to our knowledge, there is no morphogenic gradient analog to the notion of signal space – a corresponding "structure space" accessible using morphogenic gradients as the basic operator. Thus, it is unclear what range of structures can be elaborated by morphogenic gradients even in the absence of signaling noise.

We will therefore seek suitable decomposable mathematical representations for structures. Previous work in this general area [100, 122] has had limited success, and a brute force approach (using forms of vector quantization, for instance) might also be attempted but would have the same problems as finding suitable basis sets for images. Thus, one of our first investigations will be to consider models based explicitly on morphogenic gradients and known developmental *primitives* such as proliferation, migration, folding, branching, apoptosis and the like [102]. Of course, any approach that includes potentially iterative non-linear operations (such as folding) literally invites chaos. However, the incredible reliability of development in biological systems gives us hope that should there be chaos, there must also be some mechanism which can be included in any candidate "structure space" approach that can keep incipient chaos tightly in check. That is, successful development provides a clear existence proof of reliable code-to-structure transformations – even though almost certainly a dash of genetic chaos drives evolution.

The true utility of a structural space, however, lies in how it can be used to quantify the information content of structures. That is, we suspect that analogous to the development of communications theory, determining some space of "elaborable structures" along with a decomposable mathematical description, and considering it in the context of intercellular signaling capacity, should allow us to express the information necessary to reliably encode structures and aid our understanding of the mechanisms by which multi-cellular systems could recover from environmental insults. Thus, whether we succeed in developing a powerful structure space method or not, we plan to apply a communications theory lens to the candidates we do consider.

3.7 Scaling

Although cell membrane-bound ligand-receptor channels are important in the exchange of information between the interior and exterior of cells, ligand-receptor complexes perform similar functions when present in the membranes of intracellular organelles such as the nucleus, mitochondria, lysosomes, and endoplasmic reticulum. While there is only one nucleus per cell, there many more copies of the other organelles. Thus, the ideas we develop for intercellular signaling will almost certainly have application to *intra*cellular signaling as well. Likewise, the assemblages of tissues that comprise organisms are also communications networks as are populations and ecologies. We view such questions as potential targets of opportunity depending upon the success of our multi-cellular inquiries. That is, the potential for communications theory as a scale-spanning organizing principle deserves at least some attention as part of this study.

3.8 Mining the Biological Info-Space

Standard biophysical, biochemical, molecular biology and cell biology experimental techniques permit many aspects of the structure and behavior of receptors to be measured and monitored over time (the binding of ligands, conformational changes, the generation of second messengers, etc.). New technologies are pushing the boundaries so that, for example, behavior can be measured at the level of individual cells as opposed to populations of cells. Clearly the potential application of emerging techniques to our problem area is exciting and we will keep a close watch on such methods and relevant results. However, direct experimentation is not the only avenue open to exploration of biological systems.

For instance, consider the following questions: Is the information conveyed by one mouse cell to another mouse cell the same as that transmitted by one human cell to another? Within a given species, what information does one cell type convey to another? We can attempt to answer the first question using comparative genomics, for example, by utilizing readily available whole genome and proteome sequence data [123–126] to determine whether the mouse genome encodes the same type and/or number of signaling molecules as

the human genome. The second question can be addressed using functional genomics, for example, by performing retrospective analyses of transcript profiling data housed in public repositories [127, 128] to determine whether a human mammary gland epithelial cell expresses the same type and/or number of signaling molecules as a human brain cell. Such questions can be answered for "normal," "senescent," and "tumor" cells as well as cells treated with drugs or other agents. As discussed earlier, ligand-receptor interactions are key to intercellular communication but under some circumstances, one or the other but not both components of the system may be expressed by a cell type. For example, communication may be subverted (or perverted) if a given receptor is present in the cell membrane but the ligand is not expressed.

A ligand-receptor complex does not exist in isolation but is subject to numerous control and feedback mechanisms from channels of the same or different type. Public resources dedicated to signaling and other molecules, pathways and networks [70–72, 129–132] will allow us to collate and organize information about signaling mechanisms and agents. Web-based text analysis tools [133–135] should facilitate our ability to distill existing research and formulate general concepts that will allow us to start addressing concepts such as channels and signal space in realistic ways. Although some mutations in signaling proteins may inactivate the molecule so that it is unable to function properly, others may alter its effectiveness to transmit a signal without loss and/or error. For example, the ability of a receptor to transmit information may be enhanced, diminished or conditioned on some other factors. By examining the basic biology of engineered and naturally occurring [136] mutations, we may be able to uncover the relevance of our communication theory ideas to health and disease.

In addition to the public and Web-based resources and databases mentioned above, we will perform more sophisticated analyses of molecular sequence (protein, DNA, RNA), molecular profiling (gene expression), biomedical text and organismal phenotype data as and when needed using a variety of software and tools, including many with which we are already familiar [32–50].

4 Previous Applications of Information Theory to Biology

There are a variety communications/information theory applications to biological systems and the literature is far too broad to reasonably survey here. Nonetheless, it seems useful to describe general classes of previous work and provide examples so as to place what we propose in better context. To start, the broadest application of communications theory to biology is somewhat "thermodynamic" in nature and applied at the molecular/genetic level. Such work (e.g., [137–141]) typically draws quantitative analogies between chemical energy changes and system information gain or loss. In contrast, another class of work considers nearly explicit communications analogs in biological systems (e.g., [142–145]).

The neural transmission and storage of information (as typified by [146, 147]) has also been of great interest. Neuroscience has perhaps the longest association with communications theory, perhaps because information theory and the physics of neural transmission were roughly simultaneous intellectual breakthroughs [81, 82, 148–152]. Recently, communications theory – in the form of model parameter estimation – has been successfully applied to studying brain function [153–155], allowing researchers to infer behavioral states from multiterminal recordings, a holy grail of sorts. Sensorineural transduction and coding has also held a particular fascination for communications scientists. Probably the most relevant to our proposed work is the study of source-channel matching done in sensory transduction (see [156] for a review) which examines the behavior of sensorineural systems in an information theoretic way without trying to force mainstream communications theory onto biology. That is, sometimes channel-matched but uncoded transmission is optimal [157] (or near-optimal which seems far more important to living systems than true optimality [156]).

Arguably, the most successful application of communications theory ideas to biology has been genomics research [141]. The inherently digital representation of information in molecular sequences (DNA, RNA, protein) allows comparisons across the entire biome, a feature which can be of clinical significance. For instance, a recent information-theoretic analysis was performed to measure the joint effect of a high frequency germline genetic variant of the p53 tumor suppressor pathway and gender on clinical cancer phe-

notypes [158]. Though we will certainly make use of such biome-wide associations as part of our work, our approach is perhaps more literal and based on the physics of interaction as opposed to abstractions of interaction.

The work closest in spirit to what we propose is a recent study of chemotaxis – the ability of a motile single-celled organism to seek greater concentrations of nutrients [159,160]. Using an information-theoretic rate distortion approach [160] seeks to understand the decisions cells make (in terms of chemotactic motion) using available concentration gradient information. The underlying premise is that the environment communicates with the cell through variations in nutrient concentration via surface receptors. This communication results in readily measurable cellular decisions whereby cells move toward greater concentration of the sensed nutrients. The marriage of mutual information and rate distortion theory along with channel physics and measurable response pursued in [160] is exactly the sort of approach we hope to use in our proposed multi-cellular studies.

5 Research Goals

We can now formally state our research goals:

- Study the fundamental communications physics of intercellular signaling
- Derive capacity/distortion bounds for intercellular communication
- Derive capacity/distortion bounds for signaling *across* cell membranes
- Explore biological implications of communications-theoretic bounds
- Exercise theory on web-mined biological data
- Study intercellular information flow as it relates to tissue morphogenisis, maintenance and aging
- Explore biomimesis for distributed sensor and auto-assembly networks
- Explore the scaling properties of a communications theory framework

We also expect to identify appropriate experimental preparations and techniques that can be used to not only test our results, but that could form the basis of subsequent larger efforts in which communications theory is used as an explicit tool for biological system exploration. (Also see section 7.)

6 Research Impact

Assuming success, the broader impact of developing an effective communications framework for biological systems which can both explain and predict general multi-cellular network behavior is difficult to overestimate. Certainly such a framework would be pivotal in quantifying the process by which genetic codes are translated into organisms or understanding disease and aging as information network disorders. Likewise, distributed specification and assembly of robust structures in engineering as well as a multitude of other applications in biology and engineering are clearly possible.

We expect this work will interest both communications theorists and multi-cellular biologists. Likely communications theory journals include IEEE Transactions such as *Information Theory* and *Communications* or the more biologically oriented *Biomedical Engineering* and *Systems Man and Cybernetics*. Likely biological journals include *Cell*, *Developmental Biology*, *Journal of Theoretical Biology*, *Biophysical Journal* and widely-read high-impact multidisciplinary journals such as **PLoS Biology**, **Nature** and **Science**.

Finally, it is worth mentioning that we envision this proposal as the first in a series under the CDI program which builds a moderately large, diverse and cohesive team of communications theorists and experimental biologists. That is, the ultimate goal is to help create a new scientific discipline which integrates

biology and communications theory via biophysics. This first step will explore the subject and lay solid theoretical groundwork which can then inform and enhance bench biological experimentation.

7 Educational Impacts

As a general rule, biologists are not trained in communications theory, and communications theorists are not trained in biology or biophysics. In fact, the classical relationship between biology and physics – of which communications theory is a descendant – has arguably been one of mutual distrust:

> *" ... but I happen to know that most biologists consider the physicists' obsession with certainty and correctness to be exasperatingly childish and evidence of their limited mental capacities. Physicists, in contrast, consider tolerance of uncertainty to be an excuse for second-rate experimentation and a potential source of false claims.*" R. Laughin, **A Different Universe** [161].

Only relatively recently have portions of communications and information theory begun to take hold on the larger biological research enterprise, but as previously discussed, the most prevalent applications have been statistical and inferential as opposed to as explicit as we propose – where interactions between biological elements are modeled as information flows and the actions taken by cells as formal decisions all quantified using the machinery of communications theory.

Should communications theory prove an effective organizing principle for studying multi-cellular biological systems, the ultimate goal would be to teach multi-cellular biology from a communications theory standpoint [137] and *vice versa* – that is, make communications theory part of the biological education mainstream. There would then be an obvious need for a cohort of students, graduate and undergraduate, whose training explicitly spanned the divide between biology and communications theory. However, with a single grant of this size, it is not credible to claim anything as large as a program or "cohort" could be produced. Nonetheless, we envision this grant as the first in a series and have therefore thought reasonably carefully about the educational component writ larger than a few supported graduate students.

At the undergraduate level, Rose will develop a senior level elective course on biological communication geared toward communications theory concentrators and at the graduate level he and Mian will knit together offerings from biology and communications theory to develop a coherent course of study in multi-cellular biological communications. We also plan to develop an introductory course in biological communications theory for biologists – most likely as a seminar at first – which can serve as a cross pollination vehicle for biologists and communications scientists. As part of this effort, Rose plans to conduct what might called "mini sabbaticals" during the summers with various developmental biologists at key laboratories, not only to gain first hand experience with modern experimental cellular biological techniques, but also to understand how best to infect young biologists with formal communications theory concepts.

8 Results from Prior NSF Support

Christopher Rose has served as PI and co-PI on a number of previous NSF grants; (PI) NCR-9206148 [162], CCR-98-14104 [163] and CCR-99-73012 [164]; (co-PI) NCR-9506505 [165], NCR-97-29863 [166], ITR/CCR-00-85986 [167], ITR/CCR 02-05362 [168], NeTS-0434854 [169], NeTS-0435370 [170] and CNS-0716400 [171]. The work completed on these grants has addressed a broad range of problems associated with optimizing the use of radio resources in communications systems. Call admission for wireless systems was studied in [172–175]. Fundamental algorithms for paging and registration of mobile nodes were established in [176–187]. Recent work has been focused on understanding the U-NII [163, 188, 189], opportunistic transmission methods and associated delivery protocols [190–192], and developing interference avoidance methods for a variety of communications problems [193–220] as well as non-standard communications models [110–112, 221, 222]. The work described in [111] is featured on the NSF *Discoveries* web page. Most recently **I. Saira Mian** and Rose collaborated on the exploratory grant CCF-0703708 [223], one result of which is the material and approach of the current proposal.

Coordination Plan

The PI (Rose) is a communications theorist with a background in biophysical theory and experimentation. The Co-PI (Mian) is a physical chemist and biologist with a strong computational biology background. We both have experience deriving and applying mathematical models of biological systems using a variety of descriptive (phenomenological) approaches [22–31] and statistical machine learning (data-driven) approaches [32–50]. Our complementary skills are important, but equally important is enough disciplinary overlap to allow more fruitful collaboration than were a communications theorist vaguely interested in biology paired with a biologist vaguely interested in communication theory. That is, the PIs speak a common "technical tongue."

Aside from obvious and necessary telephone and Internet collaboration methods, we also plan to meet quarterly, face-to-face, to discuss results and plan subsequent research. Some of these meetings (summer) will include extended visits by Rose at Mian's home institution (LBNL) which is a primary nexus of activity on the architectural aspects mammary epithelium in health and disease. We suspect that the meeting format will be short (i.e., morning or afternoon) workshops on the topics where interested parties could attend and contribute if desired. Should this model prove especially successful and other researchers at other institutions/laboratories wish to join the effort, larger workshops might be planned.

In addition, we will build a Web site using Wiki software MediaWiki [224]. The project wiki will have multiple pages and sections and serve as the main vehicle for describing and disseminating the results of the proposed research. Users will be able to freely download experimental/technical details, primary/processed data, positive (and negative) results, and conclusions.

In order to facilitate collaboration and sharing among the project personnel as well as with members of the biomedical, scientific and engineering community and/or general public, other second generation web-based communities and hosted services relevant to the research will be created, notably social networking services (the building and verifying of communities of people who share interests and activities pertinent to the proposed research) and "folksonomies" (collaborative tagging or the practice and method of creating and managing collaboratively tags to annotate and categorize content). This seems especially important in light of our desire to cobble together a community of researchers interested in applying communications theory to multi-cellular systems as well as those seeking to learn how such techniques might be applied to their own biological (or engineering) research. The wiki will support registered logins with scoped administrative access. User groups will be utilized in combination with administrative scoping to ensure that project personnel can edit and publish documents in the appropriate sections of the site.

It should be noted that our focus is fundamental and exploratory research at the interface of communication theory and multi-cellular biology rather than the formulation of novel algorithms and robust software implementing them. Thus, we will use open-source and freely-available tools, software, and resources for any data modeling and analysis we might need to perform. Similarly, our aim is to submit results for publication in both high impact scientific/engineering journals as well as open access journals. In all cases, we will make complete methods, software, data and results available as supplementary material.

References

[1] I.S. Mian, A.R. Bradwell, and A.J. Olson. Structure, function and properties of antibody binding sites. *J Mol Biol*, 217:133–151, 1991.

[2] J.Z. Dalgaard, M.J. Moser, R. Hughey, and I.S. Mian. Statistical modeling, phylogenetic analysis and structure prediction of a protein splicing domain common to inteins and hedgehog proteins. *J Comput Biol*, 4:193–214, 1997.

[3] M.J. Moser, W.R. Holley, A. Chatterjee, and I.S. Mian. The proofreading domain of *Escherichia coli* DNA polymerase I and other DNA and/or RNA exonuclease domains. *Nucleic Acids Res*, 25:5110–5118, 1997.

[4] J.Z. Dalgaard, A. Klar, M.J. Moser, W.R. Holley, A. Chatterjee, and I.S. Mian. Statistical modeling and analysis of the LAGLIDADG family of site-specific endonucleases and identification of an intein that encodes a site-specific endonuclease of the HNH family. *Nucleic Acids Res*, 25:4626–4638, 1997.

[5] G.M. Martin and I.S. Mian. Ageing. New mice for old questions. *Nature*, 390:18–19, 1997.

[6] I.S. Mian, M.J. Moser, W.R. Holley, and A. Chatterjee. Statistical modelling and phylogenetic analysis of a deaminase domain. *J Comput Biol*, 5:57–72, 1998.

[7] I.S. Mian. Sequence, structural, functional and phylogenetic analysis of three glycosidase families. *Blood Cells Mol Dis*, 24:83–100, 1998.

[8] M.J. Bissell, I.S. Mian, D. Radisky, and E. Turley. Tissue-specificity: Structural cues allow diverse phenotypes from a constant genotype. In S.A. Newman and G.B. Müller, editors, *Origination of Organismal Form: Toward a postgenomic synthesis*. Vienna Series in Theoretical Biology. MIT Press, 2001.

[9] C.-S. Lim, I.S. Mian, A.F. Dernburg, and J. Campisi. A new regulator of telomere metabolism in *C. elegans*, encoded by the life span regulator *clk-2*. *Curr Biol*, 11:1706–1710, 2001.

[10] D.N. Everly Jr., P. Feng, I.S. Mian, and G.S. Read. mRNA degradation by the virion host shutoff (VHS) protein of Herpes Simplex virus: genetic and biochemical evidence that VHS is a nuclease. *J Virol*, 76:8560–8571, 2002.

[11] C. de Joussineau, J. Soule, M. Martin, C Anguille, P. Montcourrier, and D. Alexandre. Delta-Promoted Filopodia Mediate Long-Range Lateral Inhibition in Drosophila. *Nature*, 426:555–559, December 4 2003.

[12] J.A. Chekanova, J.A. Dutko, I.S. Mian, and D.A. Belostotsky. *Arabadopsis thaliana* exosome subunit AtRrp4p is a hydrolytic $3' \rightarrow 5'$ exonuclease containing S1 and KH RNA binding domains. *Nucleic Acids Res*, 30:695–700, 2002.

[13] M.J. Bissell, A. Rizki, and I.S. Mian. Tissue architecture: the ultimate regulator of breast function. *Curr Opin Cell Biol*, 15:753–762, 2003.

[14] E.A. Worthey, A. Schnaufer, I.S. Mian, K. Stuart, and R. Salavati. Comparative analysis of editosome proteins in trypanosomatids. *Nucleic Acids Res*, 31:6392–6408, 2003.

[15] D. Chen, Q. Lin, I.S. Mian, J. Reed, and E.E. Medrano. The multiple roles of the oncogenic protein SKI in human malignant melanoma. In V. Hearing and S. Leong, editors, *From Melanocytes to Malignant Melanoma*. Humana Press, 2004.

[16] Y. Nakayama, I.S. Mian, T. Kohwi-Shigematsu, and T. Ogawa. A nuclear targeting determinant for SATB1, a genome organizer in the T cell lineage. *Cell Cycle*, 4:1099–1106, 2005.

[17] C.K. Patil, I.S. Mian, and J. Campisi. The thorny path linking cellular senescence to organismal aging. *Mech Ageing Dev*, 126:1040–1045, 2005.

[18] J.A. Reed, Q. Lin, D. Chen, I.S. Mian, and E.E. Medrano. SKI pathways inducing progression of human melanoma. *Cancer Metastasis Rev*, 24:265–272, 2005.

[19] I.S. Mian, E.A. Worthey, and R. Salavati. Taking u out, with two nucleases? *BMC Bioinformatics*, 7:305, 2006.

[20] S. Huang, L. Lee, N.B. Hanson, C. Lenaerts, H. Hoehn, M. Poot, C.D. Rubin, D.F. Chen, C.C. Yang, H. Juch, T. Dorn, R. Spiegel, E.A. Oral, M. Abid, C. Battisti, E. Lucci-Cordisco, G. Neri, E.H. Steed, A. Kidd, W. Isley, D. Showalter, J.L. Vittone, A. Konstantinow, J. Ring, P. Meyer, S.L. Wenger, A. von Herbay, U. Wollina, M. Schuelke, C.R. Huizenga, D.F. Leistritz, G.M. Martin, I.S. Mian, and J. Oshima. The spectrum of WRN mutations in Werner syndrome patients. *Hum Mutat*, 27:558–567, 2006.

[21] A. Rizki, V.M. Weaver, S.Y. Lee, G.I. Rozenberg, K. Chin, C.A. Myers, J.L. Bascom, J.D. Mott, J.R. Semeiks, L.R. Grate, I.S. Mian, A.D. Borowsky, R.A. Jensen, M.O. Idowu, F. Chen, D.J. Chen, O.W. Petersen, J.W. Gray, and M.J. Bissell. A human breast cell model of preinvasive to invasive transition. *Cancer Res*, 68:1378–1387, 2008.

[22] C. Rose. *An Orthosis for Reduction of Parkinsonian Tremor*. Bachelor's thesis, M.I.T. Department of Electrical Engineering and Computer Science, June, 1979.

[23] C. Rose. *A Silicon-Based Regeneration Electrode for Implantation in Amphibia*. Master's thesis, M.I.T. Department of Electrical Engineering and Computer Science, June 1981. (http://dspace.mit.edu/bitstream/1721.1/34295/1/08277008.pdf).

[24] C. Rose. *Methods of Frequency Selectivity and Synchronization Measurement in Single Auditory Nerve Fibers: application to the alligator lizard*. PhD thesis, M.I.T. Department of Electrical Engineering and Computer Science, June 1985. (http://dspace.mit.edu/bitstream/1721.1/34301/1/13296339.pdf).

[25] C. Rose and T.F. Weiss. Frequency Dependence of Synchronization of Cochlear Nerve Fibers in the Alligator Lizard: evidence for a cochlear origin of timing and non-timing neural pathways. *Hearing Research*, 33:151–166, 1988.

[26] T.F. Weiss and C. Rose. Stages of Degradation of Timing Information in the Cochlea: a comparison of hair-cell and nerve-fiber responses in the alligator lizard. *Hearing Research*, 33:167–174, 1988.

[27] T.F. Weiss and C. Rose. A Comparison of Synchronization Filters in Different Auditory Receptor Organs. *Hearing Research*, 33:175–179, 1988.

[28] I.S. Mian and W.G. Richards. Theoretical binding energies of inhibitors to enzymes. *Biochim Biophys Acta*, 87:177–179, 1986.

[29] D.S. Goodsell, I.S. Mian, and A.J. Olson. Rendering of volumetric data in molecular systems. *J Mol Graph*, 7:41–47, 1989.

[30] W.R. Holley, I.S. Mian, S.J. Park, B. Rydberg, and A. Chatterjee. A model for interphase chromosomes and evaluation of radiation induced aberrations. *Radiat Res*, 158:568–580, 2002.

[31] R.B. Calder, R.B. Beems, H. van Steeg, I.S. Mian, P.H.M. Lohman, and J. Vijg. MPHASYS: A mouse phenotype analysis system. *BMC Bioinformatics*, 8:183, 2007.

[32] A. Krogh, M. Brown, I.S. Mian, K. Sjölander, and D. Haussler. Hidden Markov models in computational biology: Applications to protein modelling. *J Mol Biol*, 235:1501–1531, 1994.

[33] Y. Sakakibara, M. Brown, R. Hughey, I.S. Mian, K. Sjölander, R.C. Underwood, and D. Haussler. Stochastic context-free grammars for tRNA modelling. *Nucleic Acids Res*, 22:5112–5120, 1994.

[34] A. Krogh, I.S. Mian, and D. Haussler. A hidden Markov model that finds genes in *E. coli* DNA. *Nucleic Acids Res*, 22:4768–4778, 1994.

[35] K. Sjölander, K. Karplus, M. Brown, R. Hughey, A. Krogh, I.S. Mian, and D. Haussler. Dirichlet mixtures: a method for improving detection of weak but significant protein sequence homology. *Computer Applications in the Biosciences (CABIOS)*, 12:327–345, 1996.

[36] K. Murphy and I.S. Mian. Modelling gene expression data using Dynamic Bayesian Networks. Technical report, Department of Computer Science, University of California Berkeley, 1999. `http://www.cs.ubc.ca/~murphyk/papers.html#techreports`.

[37] E.J. Moler, M.L. Chow, and I.S. Mian. Analysis of molecular profile data using generative and discriminative methods. *Physiol Genomics*, 4:109–126, 2000.

[38] E.J. Moler, D.C. Radisky, and I.S. Mian. Integrating naïve Bayes models and external knowledge to examine copper and iron homeostasis in *Saccharomyces cerevisiae*. *Physiol Genomics*, 4:127–135, 2000.

[39] I.S. Mian and I. Dubchak. Representing, and reasoning about protein families: combining generative and discriminative methods derived from different projections of a family. *J Comput Biol*, 7:849–862, 2000.

[40] M.L. Chow, E.J. Moler, and I.S. Mian. Identifying marker genes in transcription profile data using a mixture of feature relevance experts. *Physiol Genomics*, 5:99–111, 2001.

[41] H. Bengtsson, B. Calder, I.S. Mian, M. Callow, E. Rubin, and T.P. Speed. Identifying differentially expressed genes in cDNA microarray experiments. *Sci Aging Knowledge Environ*, 12:8, 2001.

[42] C. Bhattacharyya, L.R. Grate, A. Rizki, D.C. Radisky, F.J. Molina, M.I. Jordan, M.J. Bissell, and I.S. Mian. Simultaneous classification and relevant feature identification in high-dimensional spaces: application to molecular profiling data. *Signal Processing*, 83:729–743, 2003.

[43] A.V. Loguinov, I.S. Mian, and C.D. Vulpe. Exploratory differential gene expression analysis in microarray experiments with no or limited replication. *Genome Biol*, 5:R18, 2004.

[44] C. Bhattacharyya, L.R. Grate, L. El Ghaoui, M.I. Jordan, and I.S. Mian. Robust sparse hyperplane classifiers: application to uncertain molecular profiling data. *J Comput Biol*, 11:1073–1089, 2004.

[45] J.R. Semeiks, L.R. Grate, and I.S. Mian. Networks of genetic loci and the scientific literature. In *International Conference on Complex Systems (ICCS 2004)*, 2004.

[46] J.R. Semeiks, L.R. Grate, and I.S. Mian. Text-Based Analysis of Genes, Proteins, Cancer, and Aging. *Mech Ageing Dev*, 126:193–208, 2005.

[47] W. Wu, E.P. Xing, I.S. Mian, and M.J. Bissell. Evaluation of normalization methods for cdna microarray data by classification. *BMC Bioinformatics*, 6:191, 2005.

[48] D.M. Blei, K. Franks, M.I. Jordan, and I.S. Mian. Statistical Modeling of Biomedical Corpora: mining the *Caenorhabditis* Genetic Center Bibliography for genes related to aging. *BMC Bioinformatics*, 7:250, 2006.

[49] J.R. Semeiks, A. Rizki, M.J. Bissell, and I.S. Mian. Ensemble attribute profile clustering: discovering and characterizing groups of genes with similar patterns of biological features. *BMC Bioinformatics*, 7:147, 2006.

[50] S. Bhadra, C. Bhattacharyya, N. Chandra, and I.S. Mian. A linear programming approach for estimating the structure of a sparse linear genetic network from transcript profiling data. *Algorithms in Molecular Biology*, 2008. Submitted.

[51] C.J. Tomlin and J.D. Axelrod. Biology by numbers: mathematical modelling in developmental biology. *Nature Reviews Genetics*, 8:331–340, May 2007.

[52] A. Herbert, J. Alfken, Y.-G. Kim, I.S. Mian, K. Nishijura, and A. Rich. A Z-DNA binding domain present in human editing enzyme, double-stranded RNA adenosine deaminase. *Proc Natl Acad Sci USA*, 94:8421–8426, 1997.

[53] S. Huang, B. Li, M.D. Gray, J. Oshima, I.S. Mian, and J. Campisi. The premature aging syndrome protein, Wrn, is a $3'$ to $5'$ exonuclease. *Nat Genet*, 20:114–116, 1998.

[54] B. Rydberg, W.R. Holley, I.S. Mian, and A. Chatterjee. Chromatin conformation in living cells: support for a zig-zag model of the 30 nm chromatin fiber. *J Mol Biol*, 284:71–84, 1998.

[55] J. Xia, Y. Peng, I.S. Mian, and N.F. Lue. Identification of functionally important conserved and non-conserved domains in the N-terminal region of telomerase reverse transcriptase. *Mol Cell Biol*, 20:5196–5207, 2000.

[56] E.A. Gross, G.-R. Li, Z.-Y. Lin, S.E. Ruuska, J.H. Boatright, I.S. Mian, and J.M. Nickerson. Prediction of structural and functional relationships of Repeat 1 of human interphotoreceptor retinoid-binding protein (IRBP) with other proteins. *Mol Vis*, 6:30–39, 2000.

[57] E.A. Gross, G.-R. Li, S.E. Ruuska, J.H. Boatright, I.S. Mian, and J.M. Nickerson. Effects of dispersed point substitutions in Repeat 1 of human interphotoreceptor retinoid-binding protein (IRBP). *Mol Vis*, 6:40–50, 2000.

[58] G.S.C. Dance, P. Beemiller, Y. Yang, D. van Mater, I.S. Mian, and H.F. Smith. Identification of the yeast cytidine deaminase CDD1 as an orphan C to U RNA editase. *Nucleic Acids Res*, 29:1772–1780, 2001.

[59] Y. Peng, I.S. Mian, and N.F. Lue. Analysis of telomerase processivity: mechanistic similarity to HIV-1 reverse transcriptase and role in telomere maintenance. *Mol Cell*, 7:1201–1211, 2001.

[60] S. Glande, L.A. Dickinson, I.S. Mian, M. Sikorska, and T. Kohwi-Shigematsu. SATB1 cleavage by caspase 6 disrupts PDZ domain-mediated dimerization causing detachment from chromatin early in T-cell apotosis. *Mol Cell Biol*, 21:5591–5604, 2001.

[61] V. Hegde, M.R. Kelley, X. Y, I.S. Mian, and W.A. Deutsch. Conversion of the *Drosophila* S3 bifunctional 8-oxoguanine/β/δ AP DNA repair activities into the human S3 monofunctional β-elimination catalyst through a single amino acid change. *J Biol Chem*, 276:27591–27596, 2001.

[62] S. Singh, O. Steinberg-Neifach, I.S. Mian, and N.F. Lue. Analysis of catalytic and non-catalytic subunits of telomerase in *Candida albicans*: a direct role for Est1p in telomere extension. *Eukaryot Cell*, 1:967–977, 2002.

[63] A.M. Earl, M.M. Mohundro, I.S. Mian, and J.R. Battista. The IrrE protein of *Deinococcus radiodurans* R1 is a novel regulator of *recA* expression. *J Bacteriol*, 184:6216–6224, 2002.

[64] N.F. Lue, Y.-C. Lin, and I.S. Mian. A conserved telomerase motif within the catalytic domain of TERT is specifically required for repeat addition processivity. *Mol Cell Biol*, 23:8440–8449, 2003.

[65] D. Bosoy, Y. Peng, I.S. Mian, and N.F. Lue. Conserved N-terminal motifs of telomerase reverse transcriptase required for ribonucleoprotein assembly *in vivo*. *J Biol Chem*, 278:3882–3890, 2003.

[66] P.C. Abad, I.S. Mian, C. Plachot, A. Nelpurackal, C. Bator-Kelly, and S.A. Lelièvre. The C-terminus of the nuclear protein NuMA: phylogenetic distribution and structure. *Protein Sci*, 13:2573 – 2577, 2004.

[67] V. Hegde, M. Wang, I.S. Mian, L. Spyres, and W.A. Deutsch. The high binding affinity of human ribosomal protein S3 to 7,8-dihydro-8-oxoguanine is abrogated by a single amino acid change. *DNA Repair*, 5:810–815, 2006.

[68] P.C. Abad, J. Lewis, I.S. Mian, D. Knowles, J. Sturgis, S. Badve, J. Xie, and S.A. Lelièvre. NuMA influences higher order chromatin organization in human mammary epithelium. *Mol Biol Cell*, 18:348–361, 2007.

[69] Parkust Lab: Fred Hutchinson Cancer Research Center. Drosophila Embryo Morphogenesis, 2008. http://www.fhcrc.org/science/labs/parkhurst/embryo.html.

[70] The Alliance for Cellular Signaling (AfCS): an effort to understand as completely as possible the relationships between sets of inputs and outputs in signaling cells that vary both temporally and spatially. `http://www.afcs.org/`.

[71] The UCSD-Nature Signaling Gateway: a comprehensive and up-to-the-minute resource for researchers interested in signal transduction. `http://www.signaling-gateway.org`.

[72] NCI-Nature Pathway Interaction Database: biomolecular interactions and cellular processes assembled into authoritative human signaling pathways. `http://pid.nci.nih.gov/`.

[73] W. Mueller-Klieser. Three-dimensional cell cultures: from molecular mechanisms to clinical applications. *Am J Physiol*, 273:C1109–C1123, 1997.

[74] J.B. Kim, R. Stein, and M.J. O'Hare. Three-dimensional *in vitro* tissue culture models of breast cancer - a review. *Breast Cancer Res Treat*, 85:281–291, 2004.

[75] J. Debnath and J.S. Brugge. Modelling glandular epithelial cancers in three-dimensional cultures. *Nat Rev Cancer*, 5:675–688, 2005.

[76] C.M. Nelson and M.J. Bissell. Modeling dynamic reciprocity: engineering three-dimensional culture models of breast architecture, function, and neoplastic transformation. *Semin Cancer Biol*, 15:342–352, 2005.

[77] G.Y. Lee, P.A. Kenny, E.H. Lee, and M.J. Bissell. Three-dimensional culture models of normal and malignant breast epithelial cells. *Nat Methods*, 4:359–365, 2007.

[78] P.A. Kenny, G.Y. Lee, C.A. Myers, R.M. Neve, J.R. Semeiks, P.T. Spellman, K. Lorenz, E.H. Lee, M.H. Barcellos-Hoff, O.W. Petersen, J.W. Gray, and M.J. Bissell. The morphologies of breast cancer cell lines cultured in three-dimensional assays correlate with their profiles of gene expression. *Molecular Oncology*, 1:84–96, 2007.

[79] M.J. Bissell. Modelling molecular mechanisms of breast cancer and invasion: lessons from the normal gland. *Biochem Soc Trans*, 35:18–22, 2007.

[80] M.A. LaBarge, O.W. Petersen, and M.J. Bissell. Of microenvironments and mammary stem cells. *Stem Cell Rev*, 3:137–146, 2007.

[81] C. Shannon. A Mathematical Theory of Communication. *Bell System Technical Journal*, 27:279–423 & 623–656, July & October 1948.

[82] C. Shannon. The Zero-Error Capacity of a Noisy Channel. *IRE Transactions on Information Theory*, IT-2:8–19, 1956.

[83] R.G. Gallager. *Information Theory and Reliable Communication*. Wiley, 1968.

[84] T. M. Cover and J. A. Thomas. *Elements of Information Theory*. Wiley-Interscience, New York, NY, 1991.

[85] J.M. Wozencraft and I.M Jacobs. *Principles of Communication Engineering*. Wiley, 1965.

[86] H.L. Van Trees. *Detection, Estimation, and Modulation Theory, Part I*. Wiley, New York, 1968.

[87] S. Haykin. *Communication Systems*. John Wiley & Sons, 1994.

[88] C. Nusslein-Volhard. *Coming to Life: how genes drive development*. Kales Press, 2006.

[89] A.D. Lander. Morpheus Unbound: Reimaging the Morphogen Gradient. *Cell*, 128:245–256, January 2007.

[90] J.R. Spear, R.E. Ley, A.B. Berger, and N.R. Pace. Complexity in Natural Microbial Ecosystems: the Guerrero Negro experience. *Biol Bull.*, 204:168–173, 2003.

[91] R.E. Ley, J.K. Harris, J. Wilcox, J.R. Spear, S.R. Miller, B.M. Bebout, J.A. Maresca, D.A. Bryant, M.L. Sogin, and N.R. Pace. Unexpected Diversity and Complexity of the Guerrero Negro Hypersaline Microbial Mat. *Appl Environ Microbiol*, 72:3685–3695, 2006.

[92] M.J. Friedrich. Studying cancer in 3 dimensions. 3-D models foster new insights into tumorigenesis. *JAMA*, 290:1977–1979, 2003.

[93] M.J. Bissell and M.A. Labarge. Context, tissue plasticity, and cancer: are tumor stem cells also regulated by the microenvironment? *Cancer Cell*, 7:17–23, 2005.

[94] I.F. Akyildiz, W. Su, Y Sankarasubramaniam, and E. Cayirci. A Survey on Sensor Networks. *IEEE Communication Magazine*, 40(8):102–116, 2002.

[95] D. Estrin, D. Culler, K. Pister, and G Sukhatme. Connecting the Physical World with Pervasive Networks. *IEEE Pervasive Computing*, 1(1):59–69, March 2002.

[96] M. Tubaishat and S. Madria. Sensor Networks: an overview. *IEEE Potentials*, 22(2):20–23, April 2003.

[97] M.J. Bissell. The differentiated state of normal and malignant cells or how to define a "normal" cell in culture. *Int. Rev. Cytol*, 70:27–100, 1981.

[98] V.M. Weaver, O.W. Petersen, F. Wang, C.A. Larabell, P. Briand, C. Damsky, and M.J. Bissell. Reversion of the malignant phenotype of human breast cells in three-dimensional culture and *in vivo* by integrin blocking antibodies. *Journal of Cell Biology*, 137:231–245, 1997.

[99] V. Weaver, S. Lelièvre, J. Lakins, M. Chrenek, J. Jones, F. Giancotti, Z. Werb, and M. Bissell. β4 integrin-dependent formation of polarized three-dimensional architecture confers resistance to apoptosis in normal and malignant mammary epithelium. *Cancer Cell*, 2:205–216, 2002.

[100] A. Gierer. Generation of Biological Patterns and Form: some physical, mathematical, and logical aspects. *Prog. Biophys. Molec. Biol.*, 37:1–47, 1981.

[101] M.A.J. Chaplain, G.D. Singh, and J.C. McLachlan, editors. *On Growth and Form: Spatio-temporal pattern formation in biology*. John Wiley & Sons Ltd, New York, 1999.

[102] J.A. Davies. *Mechanisms of Morphogenesis: the creation of biological form*. Elsevier, 2005. ISBN 13:978-0-12-204651-3.

[103] J.A. Axelrod. Cell Shape in Proliferating Epithelia: A Multifaceted Problem. *Cell*, 126:643–645, August 25 2006.

[104] R. Nagpal M.C. Gibson, A.B. Patel and N. Perrimon. The emergence of geometric order in proliferating metazoan epithelia. *Nature*, 442:1038–1040, August 31 2006.

[105] R. Bahar, C.H. Hartmann, K.A. Rodriguez, A.D. Denny, R.A. Busuttil, M.E.T. Dollé, R.B. Calder, G.B Chisholm, B.H. Pollock, C.A Klein, and J. Vijg. Increased cell-to-cell variation in gene expression in ageing mouse heart. *Nature*, 441:1011–1014, 2006.

[106] H. Abelson, D. Allen, D. Coore, C. Hanson, G. Homsy, Jr. T.F. Knight, R. Nagpal, E. Rauch, G.J. Sussman, and R. Weiss. Amorphous Computing. *Communications of the ACM*, 43(5):74–82, May 2000.

[107] D. Yamins. Towards a Theory of Local to Global in Distributed Multi-Agent Systems (I). In *Proc.*4^{th} *International Joint Conference on Autonomous Agents & Multiagent Systems (AAMAS)*, pages 183–190, July 2005.

[108] D.L. Nelson and M.M. Cox. *Lehninger Principles of Biochemistry*. Freeman, 2005. 4th Ed.

[109] A. Lehninger. *Biochemistry: the Molecular Basis of Cell Structure and Function*. Worth Publishing, 1975.

[110] C. Rose. Write or Radiate? In *IEEE Vehicular Technology Conference*, October 2003. Orlando.

[111] C. Rose and G. Wright. Inscribed Matter As An Energy-Efficient Means Of Communication With An Extraterrestrial Civilization. *Nature*, 431:47–49, 2004.

[112] C. Rose and G. Wright. Will ET Write or Radiate: inscribed mass vs. electromagnetic channels. In *Asilomar*, October 2004. Pacific Grove, CA.

[113] H.C. Berg and E.W. Purcell. Physics of Chemoreception. *Biophysical Journal*, 20:193–219, 1977.

[114] W. Bialek and S. Setayeshgar. Physical Limits to Biochemical Signaling. *PNAS*, 102(29):10040–10045, July 2005.

[115] K. Wang, W-J Rappel, R. Kerr, and H. Levine. Quantifying Noise Levels of Intercellular Signals. *Phys. Rev. E*, 75(6), June 2007. (061905).

[116] A.R. Asthagiri and D.A. Lauffenburger. Bioengineering Models of Cell Signaling. *Annual Review of Biomedical Engineering*, 2:31–53, 2000.

[117] R.H. Weisbart, D.W. Golde, and J.C. Gasson. Biosynthetic human GM-CSF modulates the number and affinity of neutrophil f-Met-Leu-Phe receptors. *J. Immunology*, 137:3584, 1986.

[118] S.D. Tennenberg, F.P. Zelman, and J.S. Solomkin. Characterization of N-formyl-methionyl-leucyl-phenylalanine receptors on human neutrophils. Effects of isolation and temperature on receptor expression and functional activity. *J. Immunology*, 141:3937, 1988.

[119] E. Neher, B. Sakmann1, and J.H. Steinbach. The extracellular patch clamp: A method for resolving currents through individual open channels in biological membranes. *Pflugers Archiv European Journal of Physiology*, 375(2):219–228, July 1978.

[120] N. Bocquet, L. Prado de Carvalho1, J. Cartaud, J. Neyton, C Le Poupon, A. Taly, T. Grutter, J-P Changeux, and P-J Corringer. A prokaryotic proton-gated ion channel from the nicotinic acetylcholine receptor family. *Nature*, pages 116–119, January 4, 2007.

[121] S. Soyaland P.M. Ismail, J. Li, B. Mulac-Jericevic, O.M. Conneely, and J.P. Lydon. Progesterone receptors - animal models and cell signaling in breast cancer: Progesterone's role in mammary gland development and tumorigenesis as disclosed by experimental mouse genetics. *Breast Cancer Research*, 4:191–196, 2002.

[122] R. Nagpal. *Programmable Self-Assembly: constructing global shape using biologically-inspired local interactions and origami mathematics*. PhD thesis, M.I.T. Department of Electrical Engineering and Computer Science, June 2001.
(http://dspace.mit.edu/bitstream/1721.1/7076/2/AITR-2001-008.pdf).

[123] NCBI Genome: genomic biology tools and resources, including organism-specific pages that include links to many web sites and databases relevant to that species. `http://www.ncbi.nlm.nih.gov/Genomes/`.

[124] Ensembl: a software system which produces and maintains automatic annotation on selected eukaryotic genomes. access to all the data produced by the project, and to the software used to analyse and present it, is provided free and without constraints. `http://www.ensembl.org`.

[125] UCSC Genome Browser: a site that contains the reference sequence and working draft assemblies for a large collection of genomes and provides a portal to the ENCODE project. The primary Web-based tools used to explore these sequences are the Genome Browser (zoom and scroll over chromosome showing the work of annotators worldwide) and the Gene Sorter (show expression, homology and other information on groups of genes that can be related in many ways). `http://genome.ucsc.edu`.

[126] Entrez Gene: a database for gene-specific information (nomenclature, map location, gene products and their attributes, markers, phenotypes), and links to citations, sequences, variation details, maps, expression, homologs, protein domains and external databases. `http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene`.

[127] Gene Expression Omnibus (GEO):. `http://www.ncbi.nlm.nih.gov/geo/`.

[128] ArrayExpress. `http://www.ebi.ac.uk/arrayexpress/`.

[129] The Pfam database: a large collection of protein families, each represented by multiple sequence alignments and hidden Markov models (HMMs). `http://pfam.sanger.ac.uk/`.

[130] Treefam: a curated database of phylogenetic trees of animal gene families. `http://www.treefam.org`.

[131] Kyoto Encylopedia of Genes and Genomes (KEGG): a biological systems database integrating both molecular building block information and higher-level systemic information. `http://www.genome.jp/kegg`.

[132] Reactome, a curated knowledgebase of biological pathways. `http://www.reactome.org/`.

[133] ihop (information hyperlinked over proteins): a gene network for navigating the literture. `http://www.ihop-net.org/UniPub/iHOP/`.

[134] Pubgene: navigate gene and protein networks for biological literature associations. `http://www.pubgene.org/`.

[135] Chilibot: mining pubmed for relationships. `http://www.chilibot.net/`.

[136] V.A. McKusick. Online Mendelian Inheritance in Man, OMIM^{Tm}. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). `http://www.ncbi.nlm.nih.gov/omim/`, 2000.

[137] T. D. Schneider. Claude Shannon: Biologist. *IEEE Engineering in Medicine and Biology Magazine*, 25(1):30–33, 2006.

[138] T. D. Schneider. Sequence Logos, Machine/Channel Capacity, Maxwell's Demon, and Molecular Computers: a Review of the Theory of Molecular Machines. *Nanotechnology*, 5:1–18, 1994. http://www.lecb.ncifcrf.gov/˜toms/paper/nano2/ http://www.lecb.ncifcrf.gov/˜toms/paper/nano2/.

[139] T. D. Schneider. Theory of Molecular Machines I. Channel Capacity of Molecular Machines. *J. Theor. Biol.*, 148:83–123, 1991.

[140] T. D. Schneider. Theory of molecular machines. II. Energy dissipation from molecular machines. *J. Theor. Biol.*, 148:125–137, 1991.

[141] R.A. Gatenby and B.R. Frieden. Information Theory in Living Systems, Methods, Applications and Challenges. *Bulletin of Math. Biol.*, 69:635–657, 2007.

[142] T.D. Schneider and R.M. Stephens. Sequence logos: a new way to display consensus sequences. *Nucleic Acids Research*, 18:6097–6100, 1990.

[143] D. A. MacDonaill. A parity code interpretation of nucleotide alphabet composition. *Chem. Commun.*, 18:2062–2063, 2002.

[144] D. A. MacDonaill. Why nature chose A, C, G and U/T: an error-coding perspective of nucleotide alphabet composition. *Orig Life Evol Biosph*, 33:433–455, 2003.

[145] E.E. May, M.A. Vouk, and D.L. Bitzer. Classification of Escherichia coli K-12 ribosome binding sites. An error-control coding model. *IEEE Eng Med Biol Mag*, 25(1):90–97, 2006.

[146] D. Goldberg and A. Andreou. Spike communication of dynamic stimuli: rate decoding versus temporal decoding. *Neurocomputing*, 58-60:101–107, June 2004.

[147] D. Goldberg, A. Shripati, and A. Andreou. Energy efficiency in a channel model for the spiking axon. *Neurocomputing*, 52-54:39–44, June 2003.

[148] A.L. Hodgkin, A.F. Huxley, and B. Katz. Measurement of current-voltage relations in the membrane of the giant axon of Loligo. *J. Physiol.*, 116:424–448, 1952.

[149] A.L. Hodgkin and A.F. Huxley. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *J. Physiol.*, 116:449–472, 1952.

[150] A.L. Hodgkin and A.F. Huxley. The components of membrane conductance in the giant axon of Loligo. *J. Physiol.*, 116:473–496, 1952.

[151] A.L. Hodgkin and A.F. Huxley. The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. *J. Physiol.*, 116:497–506, 1952.

[152] A.L. Hodgkin and A.F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.*, 117(4):500–544, 1952.

[153] A.C. Smith, A. Wirth, W. Suzuki, and E.N. Brown. Bayesian analysis of interleaved learning and response bias in behavioral experiments. *Journal of Neurophysiology*, 97(3):2516–2524, Mar 2007.

[154] L. Srinivasan and E.N. Brown. A state-space framework for movement control to dynamic goals through brain-driven interfaces. *IEEE Transactions on Biomedical Engineering*, 54(3):526–535, 2007.

[155] A. Ergun, R Barbieri, U.T. Eden, M.A. Wilson, and E.N. Brown. Construction of point process adaptive filter algorithms for neural systems using sequential Monte Carlo methods. *IEEE Transactions on Biomedical Engineering*, 54(3):419–428, 2007.

[156] Toby Berger. Living Information Theory. *IEEE Information Theory Society Newsletter*, 53(1):1, March 2003. `http://www.itsoc.org/publications/nltr/it0303web.pdf`.

[157] M. Gastpar, B. Rimoldi, and M. Vetterli. To Code, or Not to Code: Lossy Source-Channel Communication Revisited. *it*, 49(5):1147–1158, May 2003.

[158] G.S. Atwal, R. Rabadán, G. Lozano, L.C. Strong, M.W. Ruijs, M.K. Schmidt, L.J. van't Veer, H. Nevanlinna, J. Tommiska, K. Aittomäki, G. Bougeard, T. Frebourg, A.J. Levine, and G.L. Bond. An information-theoretic analysis of genetics, gender and age in cancer patients. *PLoS ONE*, 3:e1951, 2008.

[159] P.A. Iglesias and P.N. Devreotes. Navigating Through Models of Chemotaxis. *Current Opinion in Cell Biology*, 20(1):35–40, Feb. 2008.

[160] B.W. Andrews and P.A Iglesias. An Information-Theoretic Characterization of the Optimal Gradient Sensing Reponse of Cells. *PLoS Computational Biology*, 3:1489–1497, August 2007.

[161] Robert B. Laughlin. *A Different Universe: reinventing physics from the bottom down*. Basic Books, 2005. (page 9).

[162] C. Rose and R. Yates. Searching for Good Call Admission Policies in Communications Networks. NSF grant NCRI 92-06148, $416,000.

[163] C. Rose, A.T. Ogielski, and D. Goodman. WINLAB FOCUS'98: A Workshop to Study Peaceful Coexistence in the Unlicensed National Information Infrastructure. NSF grant CCR 98-14104.

[164] C. Rose and R. Yates. Interference Avoidance in Wireless Systems. NSF grant CCR 99-73012, $430,000.

[165] R. Yates and C. Rose. Power Control for Packet Radio Networks. NSF grant NCRI 95-06505, $469,897.

[166] D. Goodman, N. Mandayam, A. Ogielski, C. Rose, and R. Yates. Parallel computing for wireless networking research. NSF CISE Instrumentation grant NCR 97-29863. 11/1/97.

[167] R. D. Yates, N. B. Mandayam, and C. Rose. "Free" Bits: The Challenge of the Wireless Internet. NSF grant ITR 00-85986, $860,000.

[168] R. Yates, N. Mandayam, D. Raychaudhuri, C. Rose, and P. Spasojevic. ITR: Collaborative Research: Achieving Innovative and Reliable Services in Unlicensed Spectrum. NSF grant CCR-0205362 ($866,411), in collaboration with Michigan State (CCR-0205362) and Cornell (CCR-0205431).

[169] N. Mandayam (PI), C. Rose, P. Spasojevic, and R. Yates. NeTS-ProWin: Cognitive Radios for Open Access to Spectrum. National Science Foundation NeTS-0434854, $670k.

[170] B. Ackland (PI), M. Bushnell, D. Raychaudhuri, C. Rose, and T. Sizer. NeTs-ProWin: High Performance Cognitive Radio Platform with Integrated Physical and Network Layer Capabilities. National Science Foundation NeTS-0435370, $1.2M.

[171] W. Trappe, C. Rose, and Y. Zhang. Collaborative Research: CT-T: TRIESTE: A Trusted Radio Infrastructure for Enforcing Spectrum Etiquettes. NSF grant CNS-0716400, $50,000.

[172] A. Yener and C. Rose. Genetic Algorithms Applied to the Cellular Call Admission Problem: Local Policies. *IEEE Transactions on Vehicular Technology*, 46(1), February 1997.

[173] C. Rose and R. Yates. Genetic Algorithms and Call Admission to Telecommunications Networks. *Computers and Operations Research*, 23(5):485–499, May 1996.

[174] A. Yener and C. Rose. Near-Optimal Call Admission Policies for Cellular Networks Using Genetic Algorithms. *IEEE Wireless'94*, July 1994. Calgary.

[175] R. Yates, S. Gupta, C. Rose, and S. Sohn. Soft dropping power control. In *Proceedings of The IEEE Vehicular Technology Conference VTC 97*, May 1997.

[176] C. Rose and R. Yates. Minimizing the average cost of paging under delay constraints. *ACM Wireless Networks*, 1(2):211–219, 1995.

[177] C. Rose. Minimizing the average cost of paging and registration: A timer-based method. *ACM Wireless Networks*, 2(2):109–116, June 1996.

[178] C. Rose and R. Yates. Ensemble polling strategies for increased paging capacity in mobile communications networks. *ACM Wireless Networks*, 3(2):159–167, 1997.

[179] C. Rose and R. Yates. Location uncertainty in mobile networks: a theoretical framework. *IEEE Communications Magazine*, 35(2):94–101, February 1997.

[180] C. Rose. A Greedy Method of State-Based Registration. In *IEEE International Conference on Communications ICC'96*, June 1996. Dallas, TX.

[181] C. Rose. State-based paging/registration: A greedy technique. Winlab-TR 92, Rutgers University, December 1994.

[182] R. Yates, C. Rose, S. Rajagopalan, and B. Badrinath. Analysis of a mobile-assisted adaptive location management strategy. *ACM Mobile Networks and Applications (MONET)*, 1(2):105–112, 1996.

[183] C. Rose and A. Yener. Highly mobile users and paging: optimal polling strategies. *IEEE Transactions on Vehicular Technology*, 47(4):1251–1257, 1998.

[184] C. U. Saraydar and C. Rose. Minimizing the paging channel bandwidth for cellular traffic. In *ICUPC'96, Boston*, pages 941–945, October 1996.

[185] Z. Lei and C. Rose. *Wireless Subscriber Mobility Management using Adaptive Individual Location Areas for PCS Systems*. *ICC'98*, 1998.

[186] Z. Lei and C. Rose. A Probability Criterion Based Location Tracking Method. *Proceedings of Globecom 97*, 2:977–981, Nov. 1997. Phoenix, AZ.

[187] C. Rose. Paging and Registration in Mobile Networks. In *Wiley Encyclopedia of Telecommunications*, 2002. J.Proakis, Ed.

[188] C. Rose and A.T. Ogielski. WINLAB Focus'98 on the U-NII. *ACM, MC^2R*, 2(4):20, October 1998. 6/98 in Long Branch NJ (also see `www.winlab.rutgers.edu/Focus98`).

[189] C. Rose and A.T. Ogielski. WINLAB Focus'99 on Radio Networks for Everything. *ACM, MC^2R*, 3(3):24–25, July 1999. 5/99 in New Brunswick NJ (also see `www.winlab.rutgers.edu/Focus99`).

[190] A. Iacono and C. Rose. Bounds on file delivery delay in an infostations system. In *Vehicular Technology Conference*, pages 6.11–3, May 2000. Tokyo.

[191] A. Iacono and C. Rose. Infostations: New Perspectives On Wireless Data Networks. In *Next Generation Wireless Networks*. Kluwer Academic, May 2000. Editor: S. Tekinay.

[192] A. Iacono and C. Rose. MINE MINE MINE: Information Theory, Infostation Networks and Resource Sharing. In *WCNC 2000*, September 2000. Chicago, IL.

[193] C. Rose, S. Ulukus, and R. Yates. Interference Avoidance in Wireless Systems. *IEEE Transactions on Wireless Communications*, 1(3):415–428, July 2002.

[194] D. C. Popescu and C. Rose. Interference Avoidance and Dispersive Channels. A New Look at Multicarrier Modulation. In *Proc. 37th Allerton Conf. on Communication, Control, and Computing*, pages 505–514, Monticello, IL, September 1999.

[195] C. Rose. Cdma codeword optimization: interference avoidance and convergence via class warfare. *IEEE Transactions on Information Theory*, 47(7):2368–2382, September 2001.

[196] C. Rose. Sum capacity and interference avoidance: convergence via class warfare. In *CISS 2000*, March 2000. Princeton.

[197] D. Popescu and C. Rose. Codeword Optimization for Asynchronous CDMA Systems Through Interference Avoidance. In *CISS 2002*, March 2002. (available at `http://www.winlab.rutgers.edu/~crose/papers/async4.ps`.

[198] D. C. Popescu and C. Rose. Codeword Quantization for Interference Avoidance. In *Proc. 2000 Int. Conf. on Acoustics, Speech, and Signal Processing - ICASSP 2000*, volume 6, pages 3670–3673, June 2000. Istanbul.

[199] C. Rose, S. Ulukus, and R. Yates. Interference avoidance for wireless systems. In *Vehicular Technology Conference*, pages 2.05–3, May 2000. Tokyo.

[200] D. C. Popescu and C. Rose. Interference Avoidance for Multiaccess Vector Channels. In *2002 IEEE International Symposium on Information Theory - ISIT'02*, Lausanne, Switzerland, July 2002.

[201] D. C. Popescu, O. Popescu, and C. Rose. Interference Avoidance and Multiaccess Vector Channels. *ieeecomm*, 55(8):1466–1471, August 2007.

[202] D. C. Popescu and C. Rose. Interference avoidance and multiaccess dispersive channels. In *35th Annual Asilomar Conference on Signals, Systems, and Computers*, Nov 4-7 2001. Pacific Grove, CA.

[203] O. Popescu and C. Rose. Minimizing total square correlation with multiple receivers. In *39th Allerton Conference on Communication, Control, and Computing*, pages 1063–1072, October 3-5 2001. Monticello, Illinois.

[204] O. Popescu and C. Rose. Interference avoidance and sum capacity for multibase systems. In *39th Allerton Conference on Communication, Control, and Computing*, pages 1036–1035, October 3-5 2001. Monticello, IL.

[205] D.C Popescu and C. Rose. A new approach to multiple antenna systems. In *CISS'01*, March 2001. Baltimore, MD.

[206] D. C. Popescu and C. Rose. Fading Channels and Interference Avoidance. In *Proc. 39th Allerton Conf. on Communication, Control, and Computing*, pages 1073–1074, Monticello, IL, September 2001. (available at `http://www.winlab.rutgers.edu/~cripop/papers`).

[207] D. C. Popescu and C. Rose. Codeword Optimzation for Uplink CDMA Dispersive Channels. *IEEE Transactions on Wireless Communications*, 4(4):1563–1574, July 2005.

[208] D. C. Popescu and C. Rose. Interference Avoidance and Multiuser MIMO Systems. *International Journal of Satellite Communications*, 15(1):1–19, January 2003.

[209] D. C. Popescu and C. Rose. Interference Avoidance. In *Wiley Encyclopedia of Telecommunications*, 2002. J.Proakis, Ed.

[210] O. Popescu, C. Rose, and D. C. Popescu. Maximizing the Determinant for a Special Class of Block-Partitioned Matrices. *Mathematical Problems in Engineering*, 1:49–61, 2004.

[211] J. Singh and C. Rose. Distributed Incremental Interference Avoidance. In *IEEE Globecom 2003*, San Francisco, December 2003.

[212] O. Popescu and C. Rose. Waterfilling May Not Good Neighbors Make. In *Globecom 2003*, December 2003. San Francisco.

[213] C. Popescu and C. Rose. Interference Avoidance and Power Control for Uplink CDMA Systems. In *IEEE Vehicular Technology Conference*, October 2003. Orlando.

[214] O. Popescu, C. Rose, and D.C. Popescu. Strong Interference and Spectrum Warfare. In *CISS'04*, Princeton, NJ, March 2004.

[215] D. C. Popescu and C. Rose. *Interference Avoidance Methods for Wireless Systems*. Kluwer Academic Publishers, New York, NY, 2004.

[216] O. Popescu and C. Rose. Greedy SINR Maximization in Collaborative Multi-Base Wireless Systems. *EURASIP Journal on Wireless Communications Networking*, 2:201–209, 2004.

[217] O. Popescu and C. Rose. Sum Capacity and TSC Bounds in Collaborative Multi-Base Wireless Systems. *IEEE Transactions on Information Theory*, 50(10):2433–2438, October 2004.

[218] N. Clemens and C. Rose. Intelligent power allocation strategies in an unlicensed spectrum. In *Proc. IEEE DySPAN 2005*, 2005. Baltimore, MD.

[219] O. Popescu, D. C. Popescu, and C. Rose. Simultaneous Water Filling in Mutually Interfering Systems. *IEEE Transactions on Wireless Communications*, 6(3):1102–1113, March 2007.

[220] J. Singh and C. Rose. Channel Probing Under a Power Budget. In *CISS'06*, Princeton, March 2006.

[221] F. Atay and C. Rose. Exploiting Mobility in Multi-hop Infostation Networks to Decrease Transmit Power. In *IEEE WCNC'04*, Atlanta, GA, March 2004.

[222] F. Atay and C. Rose. Threshold Based Policies in Infostations Networks. In *CISS'04*, Princeton, NJ, March 2004.

[223] C. Rose and I.S. Mian. SGER: Communications Theory & Multicellular Biology. NSF grant CCF-0703708, $99,422.

[224] Mediawiki: a wiki engine or software which provides a web site that contains user-editable pages. http://www.mediawiki.org.