BioCom²: NSF Workshop on Biological Computations and Communications

Boston, Massachusetts, November 8-9, 2012

Funded under NSF award CNS 1057955
Co-funded by the College of Computer and Information Science
Northeastern University

**Principal Investigators**
Dr. Guevara Noubir, Northeastern University
Dr. Bernardo Barbiellini, Northeastern University

**Organizing Committee**
Bernardo Barbiellini, Northeastern University (Physics)
Douglas Densmore, Boston University (ECE)
Christopher King, Northeastern University (Math)
Guevara Noubir, Northeastern University (CS)
Gemma Reguera, Michigan State University (Biology)
Thorsten Ritz, University of California Irvine (Physics)

**NSF Program Officers**
Dr. Alhussein Abouzeid, NSF CISE/CNS
Dr. Sajal Das, NSF CISE/CNS
Dr. Min Song, NSF CISE/CNS
The second iteration of the workshop, BioCom\textsuperscript{2}, retained the goal of bringing together researchers with broad interests in computation and communication in the bio-nano world. Nevertheless, it concentrated on four specific topics, namely engineering synthetic biological circuits with communication interfaces, microbial communication networks, wireless energy transfer at the nanoscale, and quantum coherence in biological systems. The workshop was again successful in attracting a mix of scientists from often polarized fields such as Computer Science, Bioengineering, Mathematics, and Physics to foster inter-disciplinary discussions and collaborations. It was held in Boston on November 8-9, 2012 and attracted 31 researchers most of whom gave presentations organized in six sessions Synthetic Biology, Microbial Communications, Bio-Nano Communications, Quantum Coherence and Sensing in Biological Systems, Communication and Computations from Micro to Nanoscale, and Bio-Signaling. In the following we summarize the presentations, discussions, and suggestions for future research directions. Additional information can be found on the workshop website:

http://madrid.ccs.neu.edu/biocom2

Synthetic Biology

This session reported on enhancing the field of synthetic biology specifically in terms of robustness and scalability. The first presentation by Douglas Densmore (Boston University) illustrated tools such as computer aided design to address the complexity and robustness challenges of the specification, design, and assembly of synthetic biology devices and systems. The following two presentations by Monica Ortiz (Stanford University) and Peter Carr (MIT/Lincoln Lab) focussed on high capacity robust communication strategies for synthetic biology.

Synthetic Biology Overview
Douglas Densmore, Boston University

Densmore started with an overview of synthetic biology, describing some of the currently envisioned applications spanning from bio-therapeutics, bio-energy to education. This was followed by an introduction to the basic techniques and procedures of synthetic biology. The talk emphasized the importance of design tools to overcome the challenges of capacity and robustness. Current designs are within the range of 20 kb with dozens of components significantly smaller than the target of 8 mb with thousands of components. The analogy with integrated circuits design was noted with the quote of Richard Newton, Former UC Berkeley Dean of Engineering and Electronic Design Automation Pioneer “Synthetic biology is the new semiconductor industry”.

Synthetic Biology Overview
Douglas Densmore, Boston University

Densmore started with an overview of synthetic biology, describing some of the currently envisioned applications spanning from bio-therapeutics, bio-energy to education. This was followed by an introduction to the basic techniques and procedures of synthetic biology. The talk emphasized the importance of design tools to overcome the challenges of capacity and robustness. Current designs are within the range of 20 kb with dozens of components significantly smaller than the target of 8 mb with thousands of components. The analogy with integrated circuits design was noted with the quote of Richard Newton, Former UC Berkeley Dean of Engineering and Electronic Design Automation Pioneer “Synthetic biology is the new semiconductor industry”.

Synthetic Biology Overview
Douglas Densmore, Boston University

Densmore started with an overview of synthetic biology, describing some of the currently envisioned applications spanning from bio-therapeutics, bio-energy to education. This was followed by an introduction to the basic techniques and procedures of synthetic biology. The talk emphasized the importance of design tools to overcome the challenges of capacity and robustness. Current designs are within the range of 20 kb with dozens of components significantly smaller than the target of 8 mb with thousands of components. The analogy with integrated circuits design was noted with the quote of Richard Newton, Former UC Berkeley Dean of Engineering and Electronic Design Automation Pioneer “Synthetic biology is the new semiconductor industry”.

Synthetic Biology Overview
Douglas Densmore, Boston University

Densmore started with an overview of synthetic biology, describing some of the currently envisioned applications spanning from bio-therapeutics, bio-energy to education. This was followed by an introduction to the basic techniques and procedures of synthetic biology. The talk emphasized the importance of design tools to overcome the challenges of capacity and robustness. Current designs are within the range of 20 kb with dozens of components significantly smaller than the target of 8 mb with thousands of components. The analogy with integrated circuits design was noted with the quote of Richard Newton, Former UC Berkeley Dean of Engineering and Electronic Design Automation Pioneer “Synthetic biology is the new semiconductor industry”.
Figure 1. Synthetic biology has applications in areas from bio-therapeutics, to bio-energy, to education.

The talk provided also an overview of the echo system of existing and under development design tools in the area. These tools span the specification, modeling, design, assembly, simulation, and data management. Developing such tools with adequate interfacing and “cross-compiler” capabilities is viewed as essential to make synthetic biology move forward as an engineering discipline and bridge the gap between current devices/systems and more useful and complex systems [Beal et al., 2012].
Many tools were developed to support the specification, modeling, design, assembly, simulation, and data management in synthetic biology.

Cell-Cell Communication via Transmission of DNA Messages among Bacteria

Monica Ortiz, Stanford University

The talk of Monica Ortiz’s (Endy Lab at Stanford University) reported about enhancing the communication capabilities of cell-cell communication. The standard Quorum Sensing cell-cell communication based on N-Acyl Homoserine Lactones (AHL) is in fact rather limited since, viewed as a communication channel, it uses only the density of AHL molecules as the message (therefore is limited to a single message) and it couples the message to the channel (i.e. changing molecule changes the channel). Ortiz’s recent work led to the development and the prototyping of several new communication paradigms to overcome such limitations [Ortiz et al., 2012]. The single-message limitation is overcome by using nucleic acids to encode any user-defined information or biochemical function. The message-channel coupling is overcome by using a phage (M13) to packet and carry any user-defined sequence reaching a capacity of 40 kb+ DNA per bacteriophage. M13 has the additional advantage of being non-lytic. Thus, this first set of mechanisms extends the capacity of the channel, but relies on diffusion which can be a rather slow process more adequate for short range communication. Therefore, in order to extend the range, chemotaxis was coupled with the message.
transmission.

**Figure 3.** DNA messaging through bacteriophage transport and chemotaxis are promising approaches to scale synthetic cell-cell communication.

Other results discussed consisted of programming small amounts of memory, logic gates with decoupled input/output, A-to-D conversion, and transmission of biological logic functions to be activated in the receiving cells [Bonnet et al., 2013]. This is opening up new areas of research such as Biological FPGA denoted by Boolean Integrate Logic Gates.

**Genetic Cell-Cell Communication by Bacterial Conjugation**

Peter Carr, MIT Lincoln Laboratory

Peter Carr presented an alternative approach to cell-cell communication based on bacterial conjugation, which is one of the important horizontal gene transfer mechanisms (sometimes referred to as bacterial mating). The others being transformation (i.e., uptake of short fragments of naked DNA by naturally transformable bacteria), and translation/transduction (i.e., transfer of DNA from one bacteria to another through bacteriophage as exploited and presented in Ortiz’s talk).

**Figure 4.** Bacterial conjugation with new genetic codes allows scalable cell-cell communication without infection risks of natural organisms.

Carr also introduced MAGIC an in vivo genetic method for the rapid construction of recombinant DNA molecules. It has the advantage of eliminating the need for restriction
enzymes, DNA ligases, preparation of DNA and all in vitro manipulations required for subcloning. He also talked about MAGE (Multiplex Automated Genome Engineering) and CAGE (Conjugation-Assisted Genome Engineering), which are approaches to the engineering and prototyping of new genetic codes with both the potential to plug-and-play biological functions in a cell but also the genetic isolation between engineered and natural organisms [Wang et al., 2009]. Making the genetic code unique to an organism has the key advantage of blocking infection since a virus needs to be compatible with the host genetic code to correctly interpret its DNA and replicate [Isaacs et al., 2011].

**Bacterial Communications & Bio-Signaling**

Bacterial communications and bio-signaling extended over two days. The presentations focused on the modeling and analysis of naturally occurring bacterial communications. The session was introduced by Gemma Reguera (Michigan State University) providing an overview of a diverse modes and processes of bacterial communication. The introduction set the stage for three presentations, the first by Brian Hammer (Georgia Institute of Technology) on quorum sensing, the second by Paul Bogdan (Carnegie Mellon University) on modeling, analysis, and optimization in biological networks, and the third by Gemma Reguera on electronic bacterial communications. On the second day, Yuri Gorby (University of Southern California) presented synergetic results in understanding, analyzing and exploiting electronic communication in microbial communities. The final talk under this theme was given by Lars Dietrick (Columbia University), who presented results on understanding intercellular signaling and community behavior via phenazines.

**Cell-Cell Signalling via Quorum Sensing**

Brian Hammer, Georgia Institute of Technology

Brian Hammer started with an overview of cell-cell communication based on Quorum Sensing. Bacteria using Quorum Sensing monitor the presence and density of other bacteria in their vicinity by sensing and producing signaling molecules called auto inducers (AI). Once the concentration of AI exceeds a certain threshold, the activation of transcription in target genes is triggered. This mechanism allows bacteria to behave differently in groups from when they are isolated.
Figure 5. Quorum Sensing in Vibrio cholerae.

Hammer also presented two major types of Quorum Sensing: the Gram-negative LuxIR circuits based on the acyl-homoserine lactone (AHL) autoinducer and the Gram-positive based on autoinducing oligopeptides. For example, the LuxI-LuxR quorum sensing systems regulate bioluminescence in Vibrio fischeri, virulence factors and biofilms in Pseudomonas aeruginosa, and mating and transfer of mobile DNA in Agrobacterium tumefaciens. Hammer went on describing current research in his group relating to the role of Quorum Sensing in the human pathogen Vibrio cholerae, and the engineering of synthetic Quorum Sensing systems as a tool to model molecular communication networks [Bardill et al., 2011], [Hammer et al., 2009].

Communication Modeling, Analysis and Optimization in Biological Networks
Paul Bogdan, Carnegie Mellon University

Paul Bogdan illustrated recent work that aims at understanding biological communication processes [Bogdan et al., 2012]. Such processes represent a web of interactions at both intra-cellular and inter-cellular levels between biological organisms connected via a dynamic networked infrastructure. From the chemical activation of the bacteria motor in Escherichia Coli to the global swarm dynamics in response to attractive/repulsive cues, these biological communication processes have been considered random in nature and, hence, hard to understand, model and optimize. With the advent of information technology and the availability of a large amount of biological measurements, it has been acknowledged that biological communication is not in fact so random in nature: it can exhibit complex, yet
predictable spatio-temporal patterns. The existence of these patterns poses new challenges for both modeling and optimizing biological networked infrastructures. For instance, it is still a major challenge to identify the crucial chemicals and their critical amounts inhibiting Quorum Sensing in microbial communication networks as a function of population size while avoiding the pollution of the environment.

Given the importance of these complex spatio-temporal patterns of biological communication processes, Bogdan introduced a novel dynamic game capturing two essential aspects of both biological systems and their networked infrastructure: i) the fractal behavior of biological systems; ii) the dynamics of biological agents through a fractal structure. These two principles enable the development of a statistical physics description of a dynamical game that can be used to model and optimize the dynamics of biological networks.

**Electronic Microbial Networks and Interfaces**

Gemma Reguera, Michigan State University

Gemma Reguera focussed on recent discoveries in microbial communication beyond the well investigated chemical communication (e.g., Quorum Sensing). Such alternative communication mechanisms called physical communication extend over acoustic waves, electromagnetic waves, and electric currents [Reguera et al., 2005], [Reguera, 2011], [Reguera, 2012]. The existence of bacterial acoustic/electromagnetic communication is supported by the evidence that acoustic waves stimulate the growth of B. carboniphilus, the recording of sound waves emitted by Bacillus subtilis, the demonstrated interaction with biophotons between E. Coli colonies, and the conversion of electromagnetic waves to acoustic in growth medium with carbon materials, such as graphite or activated charcoal. Most of the presentation focussed on Reguera and her colleagues’s work on electronic communication starting with the recent discoveries of microbial nano-wires and their role as cellular electronic conduits in Geobacter sulfurreducens. The role of nano-wires in the coupling biogeochemical processes across marine sediments, from oxygen consumption in the aerobic layers (i.e., $O_2 \rightarrow H_2O$) to hydrogen sulphide ($H_2S \rightarrow S$) and organic carbon oxidation in the deep, anaerobic sediment layers [El-Naggar et al., 2010]. Such nanowires exhibit electrical potentials across centimetre distances as a result of the chemical reactions carried out across the sediment. In contrast with chemical communications such as Quorum Sensing, electronic communication has the advantage of being more energy efficient, long range, and do not suffer from the limitations of diffusion. Reguera discussed technological application of nanowires and electronic microbial communications such as for batteries.
Intercellular signalling and community behavior via phenazines
Lars Dietrich, Columbia University

Lars Dietrich showed recent results on the understanding of bio-film morphogenesis in multicellular communities such as in Gram-negative pathogen Pseudomonas aeruginosa [Dietrich et al., 2013]. This bacterium produces phenazines, colorful redox-active antibiotics that shuttle in and out of the cell. Dietrich’s team results indicate that *P. aeruginosa* can make use of phenazines as signaling molecules to regulate the expression of target genes such as Fur (Fe(III) uptake), SoxR (superoxide response regulator), and cell aggregation genes. In the absence of these signals the bacteria aggregate into visually striking, wrinkled colonies, while wild-type colonies are smooth. Experimental data suggests that the increased surface-to-volume ratio of the wrinkled colonies is an adaptation to oxygen limitation. It also suggests functions for redox-active pigments that extend beyond their antibiotic properties and are critical to the maintenance of intracellular redox homeostasis. These physiological effects determine the developmental processes of bacterial communities.
Bio-Nano Communications

This session concerned the capacity, reliability, and security of bio-nano communication systems. Andrew Eckford (York University) and Christopher Rose (Rutgers University) reported about information theoretic modeling and analysis of bio-nano systems while Falko Dressler (University of Innsbruck) described security issues. Finally Radu Marculescu's (Carnegie Mellon University) talk showed how to study the dynamic of large bacteria populations.

Models and Capacities of Molecular Communication
Andrew Eckford, York University

Andrew Eckford started noticing that nanorobot construction is within the current capabilities of engineering, but getting them to cooperate in an intelligent way is not. Molecular communication is a promising technology that could enable this cooperation, unlocking disruptive applications in nanomedicine, such as targeted drug delivery and minimally invasive surgery. Eckford work concerns the mathematical modeling of molecular communication channels, which allows detailed analysis and optimization using the many tools from communication theory [Srinivas et al, 2012]. After a basic review of information theoretical approaches to channel capacity analysis, he noted that the channel modeling problem is an important one for molecular communication, as it can be shown that the channel has an unusual memory structure that makes it difficult to calculate the conditional probability of outputs given inputs. Thus, high-fidelity but low-complexity channel models are an important topic of research. He presented results of the channel models he developed (in collaboration with others) including the additive inverse Gaussian noise channel, which models communication using individual molecules with drift; and the delay-selector channel,

Figure 7. Microbial species such as pathogen Pseudomonas aeruginosa form multicellular communities with complex bio-film morphogenesis through phenazines signaling.
which models groups of indistinguishable molecules under arbitrary diffusion [Srinivas et al., 2012].

**Timing Channels with Identical Quanta**  
Christopher Rose, Rutgers University/ WINLAB

Christopher Rose presented work in collaboration with Saira Mian from the Lawrence Berkeley National Laboratory. He first noted that biological systems are networks of intercommunicating elements at any level one might want to consider – (macro)molecules, cells, tissues, organisms, populations, microbiomes, ecosystems, etc... This explains the interests of communication theorists in this rich field. However, identifying the underlying mechanisms (signaling modality, signaling agent, signal transport, and so on) as well as the molecules and structures implementing the mechanisms is a very challenging task. He noted that typically, the application of communication theory to biology starts by selecting a candidate system whose components and operations have been already elucidated to varying degrees using methods in the experimental and/or computational biology toolbox and then applying communication theoretic methods. However, he stressed, that communication theory in general and information theory in particular are not merely system analysis tools for biology. That is, given the energy constraints and some general physics of the problem, an information-theoretic treatment can be used to provide outer bounds on information transfer in a mechanism-blind manner. Thus, rather than simply elucidating and quantifying known biology, communication theory can winnow the plethora of possibilities (or even suggest new ones) amenable to experimental and computational pursuit. He then specifically considered the problem of signaling over distance using messenger molecules in biological systems [Mian et al., 2011]. He presented results of the analysis of mutual information between release times and capture times for a set of $M$ identical quanta traveling independently from a source to a target. The quanta are immediately captured upon arrival, first-passage times are assumed independent and identically distributed and the quantum emission times are constrained by a deadline. The primary application area is intended to be inter/intracellular molecular signaling in biological systems whereby an organelle, cell or group of cells must deliver some message (such as transcription or developmental instructions) over distance with reasonable certainty to another organelles, cells or group of cells [Mian et al., 2011].

**Security in Nano Communication: Related Challenges and Open Issue**  
Falko Dressler, University of Innsbruck

Falko Dressler started with an overview of recent progress achieved in developing nano-machines supporting the needs in healthcare through nanomedicine and other application scenarios. He stressed that interaction among nano-machines is necessary to
address the very complex requirements in the field. Drug delivery and environmental control are only two of the many interesting application domains, which, at the same time, pose many new challenging problems. Very relevant communication concepts have been investigated such as electromagnetic wave communication in the terahertz band or molecular communication based on transmitter molecules. He noted that the nano-communication security has been largely absent in most discussions: will it be possible to protect such systems from manipulation by malicious parties? He shared some first insights into the security challenges and highlighted some of the open research challenges in this field.

*Figure 8. New concepts: Biochemical cryptography.*

The main observation is that especially for molecular communication existing security and cryptographic solutions might not be applicable. He coined the term biochemical cryptography as a fundamental component of molecular communication. He also pointed out to relevant problems that have similarities with typical network architectures but also completely new challenges [Dressler et al., 2012].

**Modeling the Collective Dynamics of Large Bacteria Populations Targeting Diagnostic and Drug Delivery Applications**  
Radu Marculescu, Carnegie Mellon University

Marculescu’s talk was presented by Paul Bogdan, who introduced mathematical models for describing the dynamics of a large number (or teams) of self-driven micro-robots (i.e., bacteria propelled capsules) able to swim and access small regions of the human body in a non-invasive manner due to micro-robots dimensions [Bogdan et al., 2012]. Such engineered micro-robots can perform massively parallel and distributed tasks related to diagnostic or drug delivery purposes. For example, given the affinity of chemotactic bacteria to high oxygen consumption around tumors, the micro-robots can sense and swim through the interstitial spaces towards the affected regions. In particular micro-robotic swarms can swim in the spinal cord and can sense the environment for detecting potential cancer risks.
Quantum Coherence and Sensing in Biological Systems

Quantum mechanics and Biology seem to be very different fields [Ball, 2012]. The former is usually observed in special laboratory environment involving high vacuum and low temperatures while the latter is studied in warmer and less controlled conditions. According to a common belief, the quantum phenomenon of coherence and its wave-like behavior are strongly damped inside the viscous domains of the cell. Nevertheless, recent studies have suggested that some coherent quantum processes may exist in the natural world. Possible examples range from the mechanism of photosynthesis and resonant energy transfer to the ability of birds to navigate using Earth’s magnetic field. The session entitled "Quantum Coherence and Sensing in Biological Systems" has explored these examples and has reviewed state of the art techniques at the nanometer scale for sensing in biological systems.

Remarks on Resonances in Open Quantum Systems
Christopher King, Northeastern University

It has long been known that near-field electrodynamics allows energy transfer without emission of real photons. Nowadays, the phenomenon of non-radiative decay is of great scientific interest in many different fields of Physics and Chemistry. In particular, new paradigms for solar energy conversion make use of non-radiative coupling for direct transfer of energy from the excitons created in the solar absorber to high mobility charge carriers. The mechanism for this transfer relies on the near-field resonance of electric dipoles, and is generally known as Forster Resonance Energy Transfer (FRET). In its simplest formulation, FRET is the quantum version of a classical resonance phenomenon, whereby oscillating electric dipoles exchange energy through their mutual electric fields. However, the quantum version is richer and can also include the possibility of coherent interactions between the dipoles. King et al. have considered a simple model for FRET [King et al., 2012], which incorporates both electronic and vibronic effects. The model applies in situations where the donor molecule is rigid, with weak coupling between its electronic and vibronic states, while the acceptor has strong electronic-vibronic coupling in its excited state. In this situation, the model is exactly solvable and thus allows a comparison with the perturbative formulas derived by Forster and others. In particular, King, Barbiellini, Moser and Renugopalakrishnan have derived exact formulas for FRET efficiency and the Forster radius and have compared these to the well-known Forster formulas. Furthermore, the model is fully quantum mechanical and predicts coherent oscillations between donor and acceptor under strong FRET conditions.
Figure 9. Left: Schematic model for FRET. The donor (D) is a quantum dot (QD), while the acceptor is an optoelectric protein such as bacteriorhodopsin (bR). Right: Top, efficiency for QD-bR as a function of the separation, the arrows indicate the FRET range for two values of a parameter of the model. Bottom, Occupation probability of the initial excited state as the function of time.

Quantum Biology
Thorsten Ritz, UC Irvine

There have been many suggestions that quantum mechanics plays a crucial role in biology, beyond providing the composition and the structure of biomolecules and their interactions such as FRET. These hypotheses range from Schrödinger’s hypothesis that quantum fluctuations produce mutations to a more recent suggestion that quantum coherence in some chemical reaction is linked to the compass of birds and other animals [Ritz et al., 2014]. This chemical compass could be activated by light striking the bird’s retina. The incoming photon creates a pair of free radicals, each with an unpaired electron with a given spin, that can be reoriented by a magnetic field. As the radicals separate, the unpaired electron on one is primarily influenced by the magnetism of a nearby atomic nucleus, whereas the unpaired electron on the other is further away from the nucleus, and feels mostly the Earth’s magnetic field. The difference in the fields puts the radical pair between two quantum states (singlet and triplet) with differing chemical reactivity. Some chemical could be synthesized in the bird, retinal cells when the system is in the singlet state, but not when it is in the triplet state. Thus, the chemical concentration reflects the Earth’s magnetic field orientation. Therefore, reactions involving free radical pairs provide a possible application of weak magnetic fields detection. The rate of free radical formation can change depending on the magnetic field value. Magnetic processes based on the spin dynamics of the radicals develop much faster than the thermodynamic equilibrium. Therefore, the spins can move coherently and no thermal equilibrium exists within spin lifetimes of the order of 1-10 ns. Radio frequency magnetic fields will also affect radical pairs via resonances if the field is strong enough and has right frequencies: resonances with hyperfine interaction (0.1-50 MHz) and free electron Larmor-frequency for 50 mT (1.4 MHz).
Array-Based Sensing of Biosystems
Vincent Rotello, UMass Amherst

A key issue in the use of nanomaterials is controlling the interfacial interactions of these systems. Most biomolecular recognition processes in biology occur via specific interactions. Sensory processes such as taste and smell, however, use “differential” binding through pattern recognition technique where the receptors bind to their analytes by different binding characteristics that are selective rather than specific. The “chemical nose/tongue” approach presents a potential alternative to specific recognition and separations techniques. In this approach a sensor array is generated to provide differential interaction with analytes via selective receptors, generating a stimulus response pattern that can be statistically analyzed and used for the identification of individual target analytes and also analysis of complex mixtures. Therefore, the tunability of nanoparticles makes them excellent candidates for this sensor strategy [Saha et al., 2012]. In Rotello talk a sensor array containing non-covalent gold nanoparticle-fluorescent polymer assemblies was considered in order to identify and to quantify protein, bacteria, and cancerous cells. In this setup, the polymer fluorescence is quenched by gold nanoparticles whereas proteins, bacteria, or cancerous cells disrupt the nanoparticle-polymer interaction producing distinct fluorescence response patterns.
Figure 11. A) Schematic of array-based sensing of biomacromolecules using displacement of conjugated polymer reporter groups. B) Schematic of the distinct fluorescence response patterns for analytes. C) Canonical score plot by LDA for the first two factors of simplified fluorescence response patterns obtained with NP-PPE.

Computational Biology

The second day of the workshop started with a tutorial on Computational Biology. Computational biologists are presently changing paradigms in medicine, environmental science, fuel technology and agriculture. They are not only accelerating the drug discovery process but they are also developing synthetic viruses to attack cancer cells, creating biosensors to detect poisons in drinking water, developing biofuels, and designing algae that process carbon dioxide to reduce power plant emissions. As a result, computational biology is not only a scientific discipline but also an engineering one. Nevertheless, most biological systems are extremely complex therefore it takes a huge amount of reverse-engineering to gather enough information and insight to model them. Faced with these obstacles, many computational biologists have developed ingenious bioinformatics methods outlined in the overview talk given by Matteo Pellegrini.

Computational Tools for Algal Genomics
Matteo Pellegrini, University of California Los Angeles

Algae are a promising source of biofuel, due to their rapid growth rates compared to land plants. However, to optimize the production of algal biofuels it is important to characterize the molecular pathways that are responsible for lipid production [Lopez et al., 2011]. Understanding the natural variation in these pathways across algal species could enhance our
understanding of their components and thus facilitate their optimization. Pellegrini has begun to compile genome-wide data across three algae: *Chlamydomonas reinhardtii*, *Chlorella NC64A* and *Cyclotella Cryptica*. To collect genome-wide transcriptional data it is first necessary to assemble the genomes of these organisms, predict their genes and assign functions to these, and only then is it possible to measure changes in transcript levels in response to lipid producing conditions using approaches such as RNA-seq. Pellegrini’s group has been developing and applying tools to accomplish this task. As an example, Matteo Pellegrini presented the efforts to assemble the genome of *Cyclotella cryptica*, a marine diatom with high lipid yields, using data from paired-end libraries with different insert lengths. He has discussed the RNA-seq based gene prediction pipeline that have been constructed. He has also presented the Pathway Algal Annotation Tool, a web portal that performs functional annotations of predicted protein sequences, and permits users to analyze lists of genes from transcriptomic projects. This approach also highlights the fundamental flow of biological information from DNA to RNA to proteins, and illustrates how this information flow can now be determined more than ever using next-generation sequencing platforms. The ultimate goal is to optimize these analysis pipelines so that they may be efficiently applied to hundreds of as yet unstudied algal species, to determine the enzymes that are most strongly associated with large lipid yields.

**Communication and Computations from Micro to Nanoscale**

The confluence of Nanotechnology, Physics, Chemistry, Biology and Computer Science is creating new fields of science such as novel branches of medicine, where various treatments could be controlled remotely. In fact, wirelessly activated medication could provide fast on-off switches compared to conventional drugs that take much longer time to act in the body. For this purpose nanoscale resonators can couple RF signals to a biosystem. Interestingly nanoscale resonators exhibit resonance behavior involving the mechanical vibration of system elements. The natural frequencies of such resonances will, generally, be in the radio frequency range. Some of these systems will be coupled to the electromagnetic field by the charge distributions or by their magnetic moment they carry.

![Image](image_url)

*Figure 12. Left: Possible application of a Nanoresonator coupling RF signal to a bio-system. Right: magnetosome in magnetotatic bacteria.*
Magnetic nanoparticles (MNP), among various classes of magnetic materials, make a strong candidate for use in nanoresonators. Small size in addition to the fact that they can easily be encapsulated in different protein coatings allow them to attach to virtually all receptors on the cell membrane without undesired consequences on receptors’ functionality and cell’s health. Most importantly, MNP can easily be manipulated by alternating electromagnetic (EM) fields via thermal and mechanical effects. While thermal effects of EM exposure on MNPs are well understood and being used in medical procedures such as hyperthermia, details and validity of controlled mechanical interactions of EM fields and MNPs are yet to be fully understood. Mechanical manipulation of MNPs can be classified based on the use of magnetic force or torque. Since the dimensions of the MNP are often much smaller than wavelength of the EM signal, the gradient of the magnetic field along the body of the particle is negligible. Therefore, the torque mechanisms, which depend on the amplitude of the field instead of its gradient, are preferable.

Biogenic magnetite nanoparticles called magnetosomes, first discovered in magnetotactic bacteria, are also found in the brain of many animals and are believed to participate in determining the orientation in several species such as migratory birds. Interestingly, magnetosomes consist of magnetite particles of radius 50–100 nm, and are embedded in the cytoskeleton bound to a viscoelastic system formed by a net of protein fibers. Because magnetic nanoparticles of such size are single-domain with high coercivity, the magnetosome can be represented as a torsional nanoresonator with magnetic coupling.

Clearly, nanoscale wireless systems have tremendous potential for medical applications. Moreover, new powerful tools for communication and computations are fostered by the research reported in the session entitled "Communication and Computations from Micro to Nanoscale".

Communication Engineering and Information Theory in Microbial Molecular Nanonetworks
Massimiliano Pierobon, Georgia Institute of Technology

Molecular Communication (MC) is a promising paradigm for nano-device interconnections, or nanonetworks, and it is based on the exchange of molecules, through which information is transmitted, propagated and received. Pierobon and collaborators have applied tools from communication engineering and information theory to study MC inspired by the communication strategies adopted by cells for intra- and intercellular communication, where message-carrying molecules are synthesized, emitted, collected and converted to cellular responses through biochemical processes. Given the tight integration of MC within the biological environment and its feasibility at the cellular scale (nm), they have studied MC not only as a candidate for nanonetwork communication, but also as a possible tool for the future nanonetworks to interact with the living organisms and their biological processes. Disease
control and infectious agent detection, smart drug delivery systems, bacterial bio-film monitoring and control and automated surveillance systems against biological and chemical attacks are among the potential practical applications of MC-enabled nanonetworks.

**Energy Transfer Performance of Magnetically-Coupled Mechanical Nanoresonators**

Hooman Javaheri, Northeastern University

Javaheri, Barbiellini and Noubir have considered the energy transfer performance in electrically and magnetically coupled mechanical nanoresonators [Javaheri et al., 2012]. Using the resonant scattering theory, they have shown that magnetically coupled resonators can achieve the same energy transfer performance as for their electrically coupled counterparts, or even outperform them within the scale of interest. Magnetic and electric coupling were compared in the Nanotube Radio, a realistic example of a nano-scale mechanical resonator. The energy transfer performance has also been considered for a newly proposed nanoresonator composed of a magnetosomes coated with a net of protein fibers.

![Resonant energy transfer model](image)

**Figure 13.** Resonant energy transfer model by Javaheri, Barbiellini and Noubir [Javaheri et al., 2012].
Photonic biocommunication and cellular bioelectrodynamics
Michal Cifra, Institute of Photonics and Electronics, Academy of Sciences of the Czech Republic

Vibrational eigenmodes of proteins may play an important role in protein’s reactivity and chemical kinetics. This includes not only mechanically caused conformational changes, but also oscillatory movement of bounded charge of the protein. Moreover, many proteins in living cell are only subunits establishing larger structures. The vibrational behavior of these rather complex formations can be studied as well, but the biophysical consequences of these vibrations are not well understood. One of the consequences of vibration of polar molecular structures is a convective high-frequency current of oscillating bounded charge which would generate electromagnetic field with a high spatial order. Cifra has presented results of computational analysis of electric field generated by mechanically vibrating microtubule, which are cytoskeleton structures present in almost every eukaryotic cells. Their vibration modes range from kHz to the GHz region and their energy supply can be provided from the GTP-hydrolysis. In the approximation of microtubule subunits (tubulin molecules) as rigid particles, Cifra and collaborators have calculate the electric field generated by the optical branch of axial longitudinal vibration modes. These modes are the most efficient for generating electromagnetic field, since they possess low damping (due to organized water around microtubules in vivo) and tubulin heterodimers behave as oscillatory electric dipoles. One can show that depending on the mode number the generated electric field acquires various geometries and may play various roles in the cellular organization by spatial redistribution of molecules and organelles.

Figure 14: Structure of a microtubule which is a sub-component of the cell cytoskeleton.
The research conducted by Cifra and collaborators [Cifra, 2012] is aimed for new medical diagnostic methods. It is based on the characterization of parameters of endogenous cellular nanoscopic electrodynamic field using new nanoelectronic sensors and for bioinspired photonic communication protocols. It focuses on the following topics: development of nanoelectronic sensors for detection of endogenous high frequency oscillations (kHz - THz) of living cells, theoretical modeling of coherent cellular processes (cytoskeleton oscillations) which generate electrodynamic field and electromagnetic cellular communication/interaction through endogenous biological photon emission.

**Communications and Energy-Harvesting in Nanosensor Networks**
Michele Weigle, Old Dominion University

Nanoscale sensor networks can be used detect chemical compounds in concentrations as low as one part per billion or the presence of different infectious agents such as viruses or harmful bacteria. These networks are composed of thousands of nanoscale nodes. Communication among these nodes and with the external world is an exciting new topic in networking. So far, two methods of communication have been proposed for these nanosensors: molecular communication and electromagnetic communication. Because of the limitations in molecular communication (mainly its low speed), Weigle has concentrated her effort on electromagnetic communication where pulse-based communications in the Terahertz band have been proposed as the communications method for these nanosensors [Akyildiz & Jornet, 2010]. Because of this, new medium access protocols must be developed as existing ones for carrier-sensing based systems are not applicable. One advantage to using short pulses for communication in a high bandwidth channel is that the probability of collision of the pulses is very small.

A significant challenge is that these nodes will have relatively small power supplies (and computation engines) due to their nanometer size. It has been estimated that the maximum capacity of a nano battery would be on the order of 800 pJ and that the transmission of a single short pulse will expend 1 pJ of energy. If one maps a pulse to a single bit, then a nanosensor can send at most an 800-bit packet before needing to harvest energy. Using vibration for energy-harvesting, this could take on the order of seconds (50 sec from vibrations from an A/C vent) to minutes (42 min from human heartbeat) [Jornet & Akyildiz, 2012].

Because of the long duration of energy-harvesting, multi-hop communication becomes an issue. For a nanosensor to successfully deliver a packet to a data sink, at least some neighboring nodes must be awake and have sufficient power to receive the message and forward it. If there are no awake neighbors, then the packet may need to be retransmitted later, wasting precious energy and reducing the quality of service in terms of delay and throughput. Therefore, energy harvesting-aware protocols for communication among nanosensors are required. Moreover, the stochastic behavior of the energy-harvesting sources should be taken into account, as some sources such as thermoelectric or RF may not be available all the time.
We are interested in developing intelligent, energy-harvesting aware scheduling strategies for communications between nanosensors. To do this, we are modeling the energy usage of communicating nanosensors. We are also building upon previous research to develop efficient pulse-based encoding schemes that can use silence as well as pulses for communication, thus saving energy. On top of this, we will develop a medium access protocol using repetition and retransmission for data delivery with an acceptable rate of reliability.

Bio-inspired Wireless Sensor Networking
Preetam Ghosh, Virginia Commonwealth University

Ghosh has presented strategies to design robust autonomic, self-managing wireless sensor networks (WSNs) based on simple bio-inspired rules [Nazi et al., 2013]. He has observed that the robustness inherent in biological systems can provide key insights to address common wireless network design issues such as scalability, heterogeneity, complexity and dynamical considerations. A bio-inspired mechanism should ideally possess important properties (e.g., scalability with nodes, self-organizing capability, simplicity in control rules, adaptability, and robustness to dynamically changing environments) that are sought in engineered systems including WSNs. In particular, he has applied principles of genomic robustness to engineer robust WSNs. The robustness and adaptability of biological (cellular) functions arises from the optimized structures of their gene regulatory networks (GRNs), among others. The main hypothesis is that such GRNs will serve as efficient schemes and tools to (a) design novel network topologies and routing strategies, (b) identify critical nodes, and (c) determine sensor-failure mitigation and packet loss strategies in WSNs.

Recommendations

The objective of the Biocom² workshop was to investigate if fundamental principles in Life Sciences can be applied to built computational and communication networks at the nano-scale. In particular, a crucial question explored at the workshop was how these nano-networks could function. Clearly, due to their size, standard solutions will not work, but fortunately, unique phenomena emerging at the nano-scale enable novel applications not feasible when working with bulk materials or even single atoms and molecules. Some nano-scale devices (e.g. nano-resonators) already exist, but they must still be improved in order to work efficiently and reliably. These devices also need robust communication and computation algorithms, protocols and software in order to collaborate and develop some collective intelligence.

One of our main recommendations is therefore to turn the attention towards the bio-nano world for inspiration since some of these nanomachines we are looking for already exist in nature. For instance, cells and bacteria are good examples of nano-machines. We therefore
suggest that a good strategy is to study bacterial behavior and communication. It is already known that *Quorum Sensing* enables some bacteria to communicate via signaling molecules while other bacteria produce nanowires through which they communicate electronically. Therefore, another important recommendation is to encourage the search, discovery, and exploitation of new types of bacterial communication using physical signals such as microwave radiation, magnetic fields, and sound waves. In particular, biological systems could be electrically excited to vibrate at particular frequencies. Synthetic biology made significant progress both in terms of tools and mechanisms to scale robustness and communication capacity through computer aided design tools and new mechanisms for cell-cell communication based on DNA bacteriophage transport and conjugation.

At a fundamental level, the flow of energy and information across the proposed nano-networks could be either a wavelike (coherent) process or a diffusion (incoherent) process. Coherent and massively parallel processes are usually the most efficient ones, but require special conditions in order to protect their coherence from the thermal noise. We therefore strongly suggest to support the interdisciplinary research in the area of Quantum Mechanics which addresses novel aspects of coherence and decoherence in the bio-nano realm.

We would also like to reiterate the suggestions of previous years related NSF funded workshops in terms of support for education, interdisciplinary collaborations between biology, computer science, engineering, and physics. For instance, by organizing integrative conferences, workshops and lectures to disseminate new knowledge and by promoting facilities for interdisciplinary research of biological communications technology: micro/nano fabrication and characterization facilities; high performance computing; biological model systems and experimental data. Computational and networking approaches are already playing a major role in accelerating the pace discovery in traditional scientific disciplines. We argue that the interdisciplinary nature of the research proposed in these workshops requires long term investments. One can note that today’s digital revolution is the result of decades of cross-fertilizing efforts across physics, material science, electrical engineering, and computer science (i.e., from solid state physics, to electronic chips, to software systems) and that today’s Internet was not born in a day but took decades to gradually harness the technological progress in many scientific fields.

**Acknowledgements**

We would like to express our gratitude to the NSF for making this fruitful interdisciplinary event possible. In particular we acknowledge the encouragements and help of the three program directors we interacted with Dr. Alhussein Abouzeid, Dr. Sajal Das, and Dr. Min Song. We would like to thank all the workshop participants for their enthusiasm and unique input. We are specially indebted to the organizing committee who was crucial in attracting leading researchers with such diverse backgrounds still at the heart of the theme of the workshop. This final report is based on the sessions’ and talk’ summaries and we take responsibility for all inaccuracies and misinterpretations.
References


Communications (MoNaCom 2012), Ottawa, Canada, June 2012.


<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
</table>
| 08:30 - 09:00 AM | Opening Remarks & Workshop Themes  
Guevara Noubir, Northeastern University |
| 09:00 - 10:30 AM | Synthetic Biology  
*Synthetic Biology Overview [Slides]*  
Douglas Denismore, Boston University  
*Cell-Cell Communication via Transmission of DNA Messages among Bacteria [Slides]*  
Monica Ortiz, Stanford University |
| 10:30 - 11:00 AM | Break |
| 11:00 - 12:30 PM | Microbial Communications  
*Cell-Cell Signalling via Quorum Sensing [Slides]*  
Brian Hammer, Georgia Institute of Technology  
*Communication Modeling, Analysis and Optimization in Biological Networks*  
Paul Bogdan, Carnegie Mellon University  
*Electronic Microbial Networks and Interfaces*  
Gemma Reguera, Michigan State University |
| 12:30 - 01:30 PM | Lunch Buffet |
| 01:30 - 05:00 PM | Bio-Nano Communications  
*Models and Capacities of Molecular Communication*  
Andrew Eckford, York University  
*Security in Nano Communication: Related Challenges and Open Issues [Slides]*  
Falko Dressler, University of Innsbruck  
*Timing Channels with Identical Quanta [Slides]*  
Christopher Rose, Rutgers University/ WINLAB  
*Modeling the Collective Dynamics of Large Bacteria Populations Targeting Diagnostic and Drug Delivery Applications*  
Radu Marculescu, Carnegie Mellon University |
| 03:00 - 03:30 PM | Break |
| 03:30 - 05:00 PM | Quantum Coherence and Sensing in Biological Systems  
*Remarks on Resonances in Open Quantum Systems*  
Christopher King, Northeastern University  
*Quantum Biology*  
Thorsten Ritz, UC Irvine  
*Array-Based Sensing of Biosystems*  
Vincent Rotello, UMass Amherst |
<p>| 05:00 - 06:00 PM | Breakout Sessions |
| 06:30 PM | Dinner at Brasserie Joe and General Talk |</p>
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/09/2012</td>
<td><strong>Overview Talk on Computational Biology</strong></td>
</tr>
<tr>
<td></td>
<td><em>Matteo Pellegrini, UC Los Angeles</em></td>
</tr>
<tr>
<td>09:00 - 09:30 AM</td>
<td><strong>Communication and Computations from Micro to Nanoscale</strong></td>
</tr>
<tr>
<td>09:30 - 10:45 PM</td>
<td><strong>Communication Engineering and Information Theory in Microbial Molecular Nanonetworks</strong> [Slides]</td>
</tr>
<tr>
<td></td>
<td><em>Massimiliano Pierobon, Georgia Institute of Technology</em></td>
</tr>
<tr>
<td></td>
<td><strong>Energy Transfer Performance of Magnetically-Coupled Mechanical Nanoresonators</strong></td>
</tr>
<tr>
<td></td>
<td><em>Hooman Javaheri, Northeastern University</em></td>
</tr>
<tr>
<td></td>
<td><strong>Photonic biocommunication and cellular bioelectrodynamics</strong></td>
</tr>
<tr>
<td></td>
<td><em>Michal Ofra, Institute of Photonics and Electronics, Academy of Sciences of the Czech Republic</em></td>
</tr>
<tr>
<td></td>
<td><strong>Communications and Energy-Harvesting in Nanosensor Networks</strong> [Slides]</td>
</tr>
<tr>
<td></td>
<td><em>Michele Weigle, Old Dominion University</em></td>
</tr>
<tr>
<td></td>
<td><strong>Bio-inspired Wireless Sensor Networking</strong></td>
</tr>
<tr>
<td></td>
<td><em>Preetam Ghosh, Virginia Commonwealth University</em></td>
</tr>
<tr>
<td>10:45 - 11:00 AM</td>
<td><strong>Coffee Break</strong></td>
</tr>
<tr>
<td>11:00 - 12:15 AM</td>
<td><strong>Bio-Signaling</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intercellular signalling and community behavior via phenazines</strong> [Slides]</td>
</tr>
<tr>
<td></td>
<td><em>Lars Dietrich, Columbia University</em></td>
</tr>
<tr>
<td></td>
<td><strong>Charge Transfer and Electrical Communication in Microbial Communities</strong></td>
</tr>
<tr>
<td></td>
<td><em>Yuri Gorby, University of Southern California</em></td>
</tr>
<tr>
<td></td>
<td><strong>Sub-neuronal modeling of brain signals</strong></td>
</tr>
<tr>
<td></td>
<td><em>Aftab Ahmad, Norfolk State University</em></td>
</tr>
<tr>
<td>12:15 - 02:00 PM</td>
<td><strong>Networking and Scheduling in Neuron-based Molecular Communication</strong></td>
</tr>
<tr>
<td></td>
<td><em>Jun Suzuki, UMass Boston</em></td>
</tr>
<tr>
<td>02:00 - 04:00 PM</td>
<td><strong>Report from Breakout Sessions &amp; Wrap-up</strong></td>
</tr>
</tbody>
</table>
## Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaron Adler</td>
<td>BBN Technologies</td>
</tr>
<tr>
<td>Aftab Ahmad</td>
<td>Norfolk State University, Department of Computer Science</td>
</tr>
<tr>
<td>Bernardo Barbiellini</td>
<td>Northeastern University, Department of Physics</td>
</tr>
<tr>
<td>Paul Bogdan</td>
<td>Carnegie Mellon University, Department of Electrical and Computer Engineering</td>
</tr>
<tr>
<td>Peter Carr</td>
<td>MIT, Lincoln Laboratory</td>
</tr>
<tr>
<td>Michal Cifra</td>
<td>Acad. of Sci. of Czech Rep., Institute of Photonics and Electronics</td>
</tr>
<tr>
<td>Sajal Das</td>
<td>Univ. of Texas at Arlington, Department of Computer Science and Engineering</td>
</tr>
<tr>
<td>Douglas Densmore</td>
<td>Boston University, Electrical and Computer Engineering</td>
</tr>
<tr>
<td>Lars Dietrich</td>
<td>Columbia University, Department of Biological Sciences</td>
</tr>
<tr>
<td>Falko Dressler</td>
<td>University of Innsbruck, Institute of Computer Science</td>
</tr>
<tr>
<td>Andrew Eckford</td>
<td>York University, Department of EECS</td>
</tr>
<tr>
<td>Preetam Ghosh</td>
<td>Virginia Commonwealth U., Department of Computer Science</td>
</tr>
<tr>
<td>Brian Hammer</td>
<td>Georgia Tech, Institute for Bioengineering &amp; Bioscience</td>
</tr>
<tr>
<td>Hooman Javaheri</td>
<td>Northeastern University, College of Computer and Information Science</td>
</tr>
<tr>
<td>Chris King</td>
<td>Northeastern University, Department of Mathematics</td>
</tr>
<tr>
<td>Radu Marculescu</td>
<td>Carnegie Mellon University, Department of Computer Science</td>
</tr>
<tr>
<td>Saira Mian</td>
<td>Laurence Berkeley Nat. Lab., Computational Science and Engineering</td>
</tr>
<tr>
<td>Tamer Nadeem</td>
<td>Old Dominion University, Department of Computer Science</td>
</tr>
<tr>
<td>Guevara Nouibir</td>
<td>Northeastern University, College of Computer and Information Science</td>
</tr>
<tr>
<td>Monica Ortiz</td>
<td>Stanford University, Department of Bioengineering</td>
</tr>
<tr>
<td>Matteo Pellegrini</td>
<td>UC Los Angeles, Dept. of Molecular Cellular and Development Biology</td>
</tr>
<tr>
<td>Massimiliano Pierobon</td>
<td>Georgia Tech, Department of EECS</td>
</tr>
<tr>
<td>Vince Rotello</td>
<td>UMass Amherst, Department of Chemistry</td>
</tr>
<tr>
<td>Gemma Reguera</td>
<td>Michigan State University, Department of Microbiology and Molecular Genetics</td>
</tr>
<tr>
<td>Thorsten Ritz</td>
<td>UC Irvine, Department of Physics</td>
</tr>
<tr>
<td>Chris Rose</td>
<td>Rutgers University, Electrical and Computer Engineering</td>
</tr>
<tr>
<td>Jun Suzuki</td>
<td>UMass Boston, Department of Computer Science</td>
</tr>
<tr>
<td>Vlatko Vedral</td>
<td>University of Oxford, Department of Physics</td>
</tr>
<tr>
<td>Michele Weigle</td>
<td>Old Dominion University, Department of Computer Science</td>
</tr>
<tr>
<td>Fusun Yaman</td>
<td>BBN Technologies</td>
</tr>
</tbody>
</table>