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Workshop on

Biologically-Enabled Wireless Networks Design and Modeling

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Executive Summary

The National Science Foundation Workshop on Biologically-Enabled Wireless Networks Design and Modeling took place in Arlington, VA, on July 19-20, 2011. The meeting attracted 29 researchers from several science and engineering disciplines pertaining to the theme of the workshop including Bio-Engineering, Chemical Engineering, Computer Science, Electrical Engineering, and Physics. About ten NSF officials also attended the workshop. One of the declared goals of the workshop was to bring together several scientific communities and discuss potential synergies across disciplines. The two-days event included two sessions of disciplinary presentations and several inter-disciplinary breakout sessions on *Wireless to Bio Transduction*, *Molecular Computing*, *Synthetic Biology*, *Nanoscience for Bio-Synthetic Wireless Sensor Networks*, *Wireless Control of Nano-Structures and Bio-Networks in Healthcare and Medicine*, and *Information Collection for Complex Biological Systems*. While, the presentations gave an overview of the state of the art in specific discipline from different angles, the breakout sessions followed by reporting sessions provided an opportunity for interaction between the researchers. The workshop discussions crystallized both potential short-term to medium-term research collaborations and long-term basic research opportunities. Several recommendations were given, and some of the most promising ideas are summarized at the end of the this document. The present report is based on the input from the workshop participants, and in particular the group leaders of the breakout sessions consisting of summary slides and report documents. Additional information is available on the workshop website including speakers presentations, participants white papers, and breakout session summary reports and slides: `http://nsfbw11.ccs.neu.edu/nsfbw11/`. The structure of this document is as follows: Section 1 provides a background on the themes of the workshop, Section 2 defines some basic concepts and terminology, Sections 3-8 summarize the subjects covered in the breakout sessions. Section 9, give our main suggestions for future research directions. The report ends with Appendices including the workshop agenda, and list of participants.

1 Introduction

Over the last decade, wireless communication networks have achieved many major successes and emerged as the key technology for enabling ubiquitous access to information. However, several challenges remain, energy-efficiency being one of the most notable [1]. At the same time, biological systems are well known to be extremely energy efficient. From the brain, which performs outstandingly complex tasks with only few tens of watts, to the ear, which can carry out the equivalent of a billion floating-point operations per second, biological systems are many orders of magnitude more efficient than our state of the art wireless systems. Such an efficiency gap can be explained by the fact that today's electronic systems rely on transistors (∼30nm) to perform very basic functions, while biological systems rely on nano-level machines (e.g., proteins) to perform specialized and complex functions. A natural, although clearly challenging question is if we can build biologically-enabled wireless networks [1]. This quantum leap in efficiency is analogous to the improvements from Pascal's mechanical calculators to electronic calculators. One can argue that recent advances in nanotechnology and bio-engineering will dramatically expand the frontier of wireless communication research.

An example of systems that can benefit from such research is a wireless sensor network. Most wireless sensor nodes rely on a periodic wakeup to be paged for requests. This results in significant energy consumption and increased delay. A Bio-enabled Sensor Network (BSN) composed of a nano-power sensing device that can go into a full sleep mode but can still be woken up using a fairly long-range RF signal could solve this problem. The idea is to transduce a weak Electro-Magnetic (EM) signal into biological signals and use a biological device to demodulate the information embedded in the original EM signal [2].

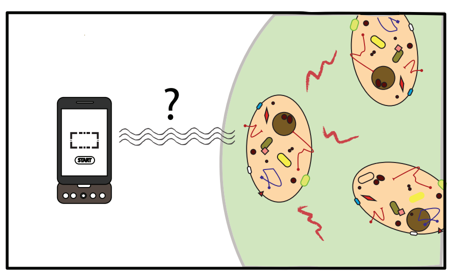

Figure 1: Electromagnetic interactions with biological materials are not yet fully understood.

Other examples include the synthesis and self-assembly of a protein/polymer-based radio receiver that diffuses through the body and targets specific cells such as cancerous cells, liver cells, or even neurons [3, 4] to allow the remote monitoring, manipulation (e.g., opening/closing ion channels as demonstrated in the

[1]The theme of this research is bio-enabled mechanisms which are fundamentally different from bio-inspired techniques.

remote control of C. Elegans worms [5]), and even destruction (e.g, by triggering apoptosis processes) of the targeted cells.

2 Basic Concepts and Illustrating Example

Computation and communication are the basic operations of a wireless network. Biological computing and communication operate on various scales and substrates. Protein folding is an instance of molecular computing, while interactions of specially constructed RNA strands is another example. Yet another is design of genetic networks within biological cells and even beyond that one can speak of interactions between such cells or colonies of such cells. Thus, though the fundamental operations are carried out at a molecular level, the ultimate realizable system architectures can span six or more orders of magnitude [6].

Likewise, wireless specifically conjures images of EM field-mediated interactions (from optical to radio frequency). However, perhaps the key issue when it comes to interconnectivity is the existence (or lack) of space-filling dedicated physical superstructures along which information is passed – of which a *wire* is an example. Thus, matter-mediated interactions over distance such as the release, diffusion and uptake of signalling quanta also constitute wireless communication. Therefore, two appropriate definitions emerge.

Molecular Computing: An ability to program functions over some domain, in this case using molecular scale building blocks and perhaps biased toward the increasingly well understood existence proof of biological engines that perform "atomic" computational operations.

Wireless Communication: Communication in the absence of dedicated solid structures which physically connect the sender and receiver.

It is with these definitions in mind that we next discuss the possibilities of biologically-enabled networks.

As an example, one could think of cells as biological devices where inputs and outputs denote external stimuli and cell responses respectively. Interfacing with cells should provide an efficient channel to exchange *information* and *energy*. It should not perturb the functionality of either side. Ideally, the interface does not concern how information is processed at its endpoints. Figure 2 illustrates a simple two-way interface between a wireless node and a cell. The information flow consists of the following two links:

Cell to node: The response of the cell alters the state of the surrounding micro-environment. Therefore, a wireless node equipped with a properly designed bio-sensor can observe this effect in the extracellular environment in a non-invasive fashion.

Node to cell: To trigger any cell response, the corresponding combination of stimuli should be present. Either propagation of EM signals directly produces a stimulation in the extracellular space, triggering a transduction process, or the cell perceives a secondary effect of the EM signal delivered by auxiliary nano-devices or chemical reactions.

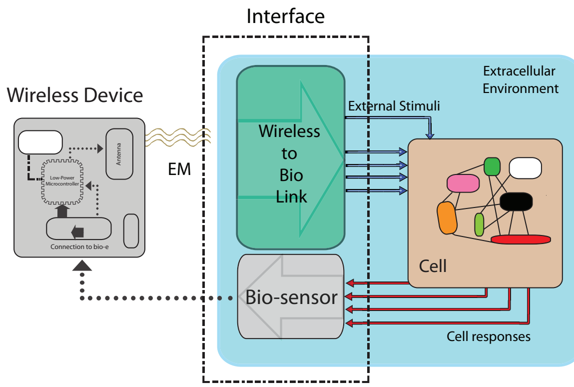

Figure 2: Illustrative example: components of a simple interface between a cell and a wireless device.

The possibilities and challenges to create the link from wireless device to biological system will be discussed in more detail in the following sections.

3 Wireless to Bio Transducers

A transducer is a device that converts one type of energy to another. Energy types include (but are not limited to) electrical, mechanical, electromagnetic (including RF and light), chemical, acoustic or thermal energy. An antenna for example converts electromagnetic waves into electric current and vice versa. At the hearth of biologically enabled wireless communication there should be interfacing mechanisms able to couple EM field to bio-elements such as enzymes and antibodies whose goal is to produce physical and chemical changes resulting in biological signals [1]. In the following, several ways to couple biological signals to electromagnetic fields are outlined.

One key element for efficient transduction is resonance. However, the possibility that biological systems coupled to the electromagnetic field can exhibit classical resonance at radio-wave frequencies remains unclear [7, 8]. The difficulty in explaining this effect is related to the fact that for resonance in order to have an important effect on biology, the system must in principle absorb energy in excess of that from thermal noise $k_B T$, where k_B is the Boltzman constant and T is the temperature. Analysis performed by Adair suggest that the damping of the vibratory motion by biological fluids severely restricts such possibilities because typical systems may not be coupled to the electromagnetic fields with sufficient strength to allow significant energy transfers. This problem is known in the literature as the 'kT problem'. However, in engineering, the kT problem is generally not so acute. For example, detecting extremely weak magnetic field can be performed by converting it into an electrical signal using a superconducting quantum interference device (SQUID) then, the electrical signal is integrated using well-known techniques up to the level exceeding that of the thermal noise. Low intensity electromagnetic fluxes can affect biology through changes in chemical concentrations produced by changes in the rates of chemical reactions. Thus, in comparison with the aforementioned physical measurements, a weak magnetic signal could also be detected in a biological system with a chemical converter. Furthermore, nano-technology opens-up new and sometimes unique avenues for Wireless to Bio transduction. The diameters of nanostructures are comparable to the sizes of biological and chemical species being sensed, and thus intuitively represent excellent primary transducers for producing signals that ultimately interface with macroscopic instruments. Inorganic nanowires and nanocrystals exhibit unique electrical, magnetic and optical properties that can be exploited for sensing. For example, the size-tunable colors of semiconductor nanocrystals, together with their highly robust emission properties, are opening up opportunities for labeling and optical-based detection of biological species that offer advantages compared with conventional organic molecular dyes widely used today. Specific transduction mechanisms are discussed in Section 6.

4 Molecular Computing

One could imagine molecular computing as nano/meso/macro structural specification and assembly (designer molecules/materials or even growing a dwelling from a "seed"), sensing and actuation based on molecular level events (environmental sensing, in-body monitoring) and concomitant better identification and control of biological/ecological disease states. Biological systems offer promising massively parallel, low power consumption molecular computation platforms and enable calculations that are not currently possible using today's silicon-based technology. In addition, the potential applications are equally if not more exciting since biological systems provide an existence proof of coding for physical structure and interacting with the macroscopic (and microscopic) world.

As an example, consider that a typical biological cell (say, bacterium) is transcribing roughly 20% of its genome at any given time, and that a typical bacterial cell carries $4,000$ genes [9]. Thus, a single bacterium such as *E. Coli* whose rod-like dimensions are roughly 2μm long with a diameter of $1u$m, could be "running" 800 genetic pathways (which might loosely be analogous to "operations") in parallel. Likewise, a typical cell consumes on the order of 10^7 ATP per second which at 8×10^{-20}J per ATP is 8×10^{-13} watts.

Thus, a 1cm^3 block of *E. Coli* "paste" with a packing of roughly 0.125 cells per μm^3 (with gaps to allow nutrient/waste flow) would contain 1.25×10^{11} cells, perform 10^{14} operations in parallel and consume on the order of 100 milliwatts. With a "cycle time" on the order of 100 seconds, the implicit raw computational power is on the order of a 10^{12}op/second. Coupled to the existence proof that biological structures can be grown from the interaction of many-like-programmed units [10], the notion of molecular computing, cell-based or not deserves deeper study.

The previous discussion of raw computational power, however simplistic, begs the question of how one might build a molecular computer to do one's bidding. One can identify several key issues that must be addressed in order to build such an implicitly general purpose "machine."

4.1 The Machine

By analogy to silicon-based systems, the discovery, construction and standardization of system *blocks* seems key. Though, we do not know yet if molecular computing systems will follow the same architecture that current silicon-based technology. In any case, there is a need for operational building blocks be they specific molecular components or genes to be inserted into a host bacterium. Currently, results are not reproducible and interoperable enough. A standard set of methods and bank of *parts* would help solve this problem.

Likewise, given the size scales of such systems and the tantalizing possibility to construct them naturally in three dimensions, some degree of machine auto-assembly seems important and requires new technologies. Such assembly might be in physical space or one could imagine it in some *signal space* specified by the molecular interactions.

The structural issue leads to perhaps the most important and so far unrealized aspect of molecular computing – interconnection of blocks. While some recent progress was made in DNA-based molecular computers interconnects, and serves as an existence proof [11]. However, given the somewhat heroic effort of the work, the simplicity of the system it ultimately describes and what appears to be a lack of scalability, the road toward a large molecular computer seems daunting without breakthroughs in our ability to interconnect functional blocks and reason about their communication capability.

Once we have a basic structure of *processors* and *interconnects*, key higher level questions arise. How can one program such machines? What is the functional description one might use? What is the best structure for molecular computers? Should the structure itself be static or dynamic? These types of considerations seem to open up a novel and potentially deep new area in computer science, and especially computer architecture tailored to the strengths of molecular-based systems. Architecture for unreliable and/or short-lived components seems key.

4.2 Input, Output and Control

To be useful a computer must interact with its environment. This involves the physics of Input/Output (I/O) with and within a molecular machine. In particular, there is the issue of how one might control the internal blocks, how they should be structured and how they behave. The specific issue of I/O is already under intense scrutiny, but not necessarily from the perspective of building molecular computers. The ability to actuate and measure response at molecular levels is of obvious utility to biological study which seeks to elucidate structure and function. A number of different modalities for interacting with tissue and molecules was presented at the workshop from photonic coupling targeted at molecular bonds and processes to radio frequency transmission of power and information into more macro-scale devices. In between were hybrid notions of tailoring cells to express components that would respond to magnetic fields, physical touch or molecular (matter-mediated) signals. None of the currently used methods seem perfect for molecular computer I/O and ongoing research will be necessary to figure out the best methods for coupling information (and sometimes powering-energy) into and out of molecular computers, of whatever type and size they happen to be.

5 Synthetic Biology

Synthetic biology is an emerging field focused on the development of engineering principles and their application to the design, construction, and characterization of biological systems [12, 13, 14]. It is also viewed as one of the promising approaches to enable molecular computing. On the other hand, electronic systems communicating as networked devices have the ability to perform powerful computation and transmit data over long distances. The design of biological agents that interact with these electronic systems has the potential to introduce transformative capabilities in sensing, materials production techniques, and therapeutics.

Traditional Electronic Engineering (EE) and Synthetic Biology (SB) have complementing advantages. Electronic systems are fast, highly engineerable, and can usually be accurately modelled, they are however difficult to noninvasively integrate in biological environments and to adapt to extreme conditions. Biological systems on the other hand can work noninvasively in cellular/organismal environments, and are able to self-replicate, self-repair, self-renew and operate in parallel. They are limited by their speed, mutation and evolution rates, and difficulty to accurately model.

SB products can go into the human body more easily. They may also be able to go into extreme environments that have characteristics unfavorable to electronics (e.g. high heat, magnetic fields, etc). EE devices can go within extreme environments that have characteristics unfavorable to specific organisms (e.g. high salinity, lack of oxygen, lack of light). In general there is a need to examine the chemical properties of the parts (both SB and EE) and where they might operate (i.e., proteins that are more thermostable, more resistant to radiation, high salt). Some of the applications of hybrid bio-electronic devices are:

- Remote sensing and report from inside tissues and control of tissues.
- High energy efficiency wireless sensors.
- Communication between cells.
- Biological memory.

- Solid state memory device interfacing with brain for memory enhancement.
- Monitoring biological agents.
- Novel bio-computing platforms (e.g., Protozoan/ciliates, flip DNA)

The integration of SB and EE requires the development of two specific areas. The first area is to develop tools and building blocks upon which the applications can be realized. They must be characterized regarding their cost (e.g., size, energy use, metabolic impact, harmful interactions). These tools can support and enable varied technologies such as DNA constructs, RNA, or small molecules. The second area is that of applications, which would determine a desired behavior (e.g., produce a chemical signal in response to environmental stress) and provide a set of performance requirements (e.g., chemical signal X must be at Y concentration and produced in Z time units). Applications should take advantage of the unique strengths of biology and electronics, while leveraging these advantages against each others weaknesses.

The design problem then becomes engineering a system that meets the behavior and performance requirements of the application given the costs of the individual tools used to create the system. This approach can be thought of as a combination of bottom up tool development and top down application specification. This is analogous to the concept of platform-based design in embedded systems. Design approaches in synthetic biology such as BioBricks also reflect this compositional, standardized approach.

While synthetic biology has made progress over the last decade, the current state of the art is characterized by a limited modelling accuracy, a genetic circuits complexity of tens of genes, fast individual reactions but overall slow cellular communications, an assembly capability of 10^7 base pair segments, and few hybrid I/O interfaces that are asymmetric (e.g., optogenetics, triggered microfluidics, optical fluorescent readouts). Some of the Grand Challenges in this field are:

- Assembly: develop cost effective synthesis.
- Characterization: enable predictability and robustness.
- Scaling: explore the limits of robustness scaling and composition, load on cell, pathway architecture, context, interference, noise.
- Parts: generate new biological functions and scale to different chassis and contexts.
- Computing and communication: develop integrated elements; develop models that reflects the semantics of biological computation and communication.

6 Nanoscience for Bio-Synthetic Wireless Sensor Networks

This section explores the problem of networking among nano-scale nodes. Each node of a sensor network has typically several parts: a radio transceiver with an internal antenna and an embedded form of energy provisioning. Nanoscience is the most promising route to facilitate the signal conversion in the biological environment and to enable wireless networks for ultra-immersive sensing applications. Some of the challenges are to mitigate the effects of noise, provide efficient energy and information transfer, and enable robustness and scalability for a high density of low-cost and low-power elements. As a matter of fact, all the required components of a wireless sensor node, i.e., a sensing unit, a processing unit, a transceiver unit, and a power unit have already been demonstrated with nanoelements, such as carbon nanotubes [15]. However, a lot of work remains to make these components suitable for nanosize wireless sensor networks that have not been possible before. Some promising avenues are in field of directed self-assembly involving tiles and scaffolds (e.g., DNA tile complexes [16]). Nanotechnology also offers new possibilities for synthesis of inorganic nano-devices and novel biological sensors. For instance radical enhancements of the performance could come from magnetic nanoparticles. The key challenge remains to interface biological components to the electromagnetic field. In the following, possible solutions are presented using either magnetic nanoparticles (magnetosomes) or chemical reactions resonating with electro-magnetic fields. Physical and chemical communications implemented in bacterial networks are also discussed.

6.1 Magnetic Nanoparticles and Magnetosomes

Magnetic fields, in contrast to electric fields, are not affected by strong attenuation, thus can penetrate deep in biological media. Magnetic nanoparticles (MNP), among various classes of magnetic materials, make a strong candidate for use in bio-devices. They are small size, can easily be encapsulated in different protein coatings to attach to virtually all receptors on the cell membrane without undesired consequences on receptors' functionality. Most importantly, MNP can easily be manipulated by alternating EM fields via *thermal* and *mechanical* effects (i.e., torque and force). 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. MNPs are no-strangers to biological systems. In fact nano-magnetite crystals called *magnetosomes* are found in bacteria and brain tissues of many animals and humans. They proved to have a biogenic origin and could therefore be synthesized and utilized in-vivo. In birds the magnetosome is believed to be useful for navigation. The energy of a 100 nm magnetosome in the geomagnetic field H_{geo} is approximately 24 $k_B T$ which can cause a biological response. Furthermore, it was shown that

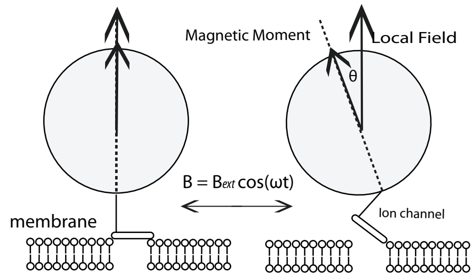

Figure 3: An illustration of using torque to open an ion-channel [18].

the biologically detectable level of the magnetic field may be even tenfold less if magnetosomes rotate in a double-well energy potential [17]. In this case, the thermal fluctuations contribute to the capability of a weak magnetic stimulus to cause a response (stochastic dynamics).

6.2 Resonant Energy Transfer

A key question in interfacing biological components with electromagnetic fields is understanding the efficiency of energy transfer. A particular efficient mechanism to deliver energy is to couple the incoming EM-wave with the receiver in a resonant regime. Using the resonant scattering theory [19], one can show that the magnetic nano-resonator of Figure 3 can achieve a significant energy transfer at a resonant frequency of about 1MHz provided that the quality factor Q is of order 100 [20]. However, mechanical resonance is not the only possibility, chemical reactions involving free radical pairs provide another possible resonant target for the incoming electromagnetic radiation. This chemical process involves the quantum evolution of a spatially-separated pair of electron spins and such a model has been used to explain the compass used by birds for their orientation. By manipulating a captive bird's magnetic environment and recording its response, one can make inferences about the mechanism of the magnetic sensor [21]. Specifically, European Robins are only sensitive to the inclination and not the polarization of the magnetic field and this sensor is evidently activated by photons entering the bird's eye. Importantly, a very small oscillating magnetic field (with a frequency of about 1 MHz) can disrupt the bird's ability to orientate. The basic idea of the Radical Pair model is as follows: there are molecular structures in the bird's eye which can each absorb an optical photon and give rise to a spatially separated electron pair in a singlet spin state. Because of the differing local environments of the two electron spins, a singlet-triplet evolution occurs. This evolution depends on the inclination of the molecule with respect to the Earth's magnetic field. Recombination occurs either from the singlet or triplet state, leading to different chemical end products. The concentration of these products constitutes a chemical signal correlated to the Earth's field orientation. The specific molecule involved is still unknown but the results are consistent with a resonance effect on singlet-triplet transitions. Magnetic processes based on spin dynamics of the radicals develop so quickly that the thermodynamic equilibrium has no time to be established. This means spins move coherently and no temperature of spins exists within the spin lifetime of the order of 1-10 ns. Thus magnetic fields produce coherent spin motion and change the probability of the pair recombination. Interestingly, the magnetic field produced by magnetosomes can be rather intense and it is of the order of 0.1 T in the vicinity of the magnetosome surface. Therefore, its rotation can distinctly affect the rate of free-radical reactions. Moreover, new paradigms for optical energy conversion, inspired by photosynthesis in leaves, use non-radiative dipole-dipole coupling for direct transfer of energy also called Forster resonance energy transfer (FRET) [22]. A similar principle applied to radio waves provides efficient wireless non-radiative energy transfer. *WiTricity* [23, 24], based on resonant inductive coupling, demonstrates the transfer of high amount of energy (∼60 W) over a distance of 2m at remarkably high efficiency (∼40%). Although the size of the implemented system (coils of radius 40 cm) is a great deal larger than MNP dimensions, the theoretical analysis supports the possibility of similar resonant coupling in nano-scale [24]. It is possible to couple an external resonator to an engineered nanocoil attached to a targeted receptor, creating an exclusive and efficient channel of energy from outside to the biological system.

6.3 Bacterial communication and networks

Bacteria appear as small vessels filled with DNA and an amorphous cytoplasm, they are, however, highly sophisticated creatures that can communicate between themselves and form networks. *Quorum sensing* (Bassler) enables some bacteria to communicate via signaling molecules, whereas other bacteria produce nanowires through which they communicate electronically. Recent work shows that the anaerobic bacterium Geobacter sulfurreducens can conduct electricity along filaments attached to the cell membrane. Composed of the protein pilin, the filaments only 35 nm wide and up to tens of microns longhave metal-like properties akin to those of synthetic organic conductors. Nanowires provide two distinct electron-flow pathways for Geobacter sulfurreducens cells, one for fast electron flow at high voltages and the other a high-resistance path reflecting metabolic status. However, these microbial nanowires studies are not the first to suggest a role for electronic signals in cell- cell communication. In fact other reports suggest that bacteria may communicate using physical signals such as microwave radiation, magnetic fields, and sound waves. For example, sound waves stimulate Bacillus cells to produce physical signals, possibly sonic in nature that trigger nearby cells to grow. For example, those sonic signatures could arise from the vibrational modes of individual cells in a colony. Biological systems could be also electrically excited to vibrate at particular frequencies. Metabolic energy can make the cell wall of Saccharomyces cerevisae yeast oscillate at frequencies ranging from 0.8 to 1.6 kHz. Other possible wireless forms of communication have been suggested [25], however, these claims still remain controversial.

7 Wireless Control of Nano-Structures and Bio-Networks in Healthcare and Medicine

There already exists multiple examples of clinical technologies that include one or more of the design concepts from wireless control, nanostructures, and bio-networks. In particular, telemedicine and distributed health care are emerging as important paradigms, particularly in the management of chronic diseases and in the delivery of health care to the developing world. For example, longitudinal monitoring of cardiac biometrics (e.g., weight, blood pressure, EKG) are key components of management of heart failure; however many of these measurements require a clinic visit and thus invite low compliance. A variety of clinical trials are underway in which patients take these measurements at home and then relay them to their health care provider using traditional communications networks. As another example, automated implantable cardioverter-defibrillators (AICDs) are surgically-implanted devices that continuously monitor heart rhythm, and when specific types of arrhythmia occur can deliver an electric shock to the myocardium to resynchronize beating. Multiple clinical trials have shown or strongly suggested that these devices provide a survival benefit over conventional anti-arrhythmic drugs. Finally, magnetic nanoparticles have long been approved as contrast agents for MRI, and the group discussed whether it might be desirable to take advantage of this fact and use these particles for some sort of delivery or actuation function (see below). Other emerging technologies, including contact lens-based retinal imaging systems and nanotechnologies that could be RF-induced to assemble in specific target cells to deliver some therapeutic payload.

Nanotechnology is no stranger to oncology, liposomes are early examples of cancer nanotherapeutics, and nanoscale-targeted magnetic resonance imaging contrast agents illustrate the application of nanotechnology to diagnostics [26, 27]. This field enable advances in early detection, diagnostics, prognostics. Good examples of detection nanotechnologies are arrays of nanocantilevers, nanowires and nanotubes.

Many of these existing technologies could be improved by incorporating wireless sensing, actuation, or power components, and by reducing size scale. The long-term vision here, articulated in greater detail below, is to develop noninvasive micro- or nanotechnologies that could be introduced into the body and continuously monitor and report on specific health metrics and perhaps even be remotely induced to carry out therapeutic functions when needed (nanoscale theranostics).

There are several key challenges faced by these technologies. First, it is not clear that conventional sensing components that have been created and validated on the macro- or micro-levels could be readily scaled to the nano-level. At the same time, as nanoscale devices become more common in the health care space, new technologies would be needed to assess device performance on the nanoscale, such as nanoscale temperature, pressure, and chemo-sensors. Furthermore, biological signals potentially sensed on this length scale are likely to be very weak relative to conventional electrical signals, which would require the development of very high-performance transducers that could operate on the micro- or nanoscale. An important challenge is to make biochemical systems talk to electrical devices. The greatest initial traction is likely to be gained with biological signals that are already intrinsically electrical signals, such as EKG and EEG.

7.1 Paradigm shift in healthcare and medicine

The are at least two main promising directions that could lead to significant advancement in healthcare and medicine.

The first is represented by wireless in vivo diagnostics and therapeutic treatments realized using micro- and nano-machines that can move, deliver drugs, and collect information inside the human body. In these emerging and promising technologies, an I/O interface is needed to exchange information with an external controller. All regions of the electromagnetic spectrum, not only radiofrequencies, should be explored for the realization of such interface. An important aspect is related to the source of energy needed to power up such micro and nano machines. The miniaturization down to the nano-scale could be particularly difficult in this respect. Energy transfer using methods would work best in the GHz range and devices would be limited to the micro scale. On the other hand, in using nanostructures these technologies could take advantage of self-assembly that can be actuated and controlled through the I/O interface. Examples include the manipulation and controlled assembly of magnetic nanoparticles, and nanostructures that could be used to improve the resolution and accuracy of opto-genetic techniques. All these technologies will lead to non invasive diagnosis and monitoring of patients, and could revolutionize medical decision-making and risk stratification.

A second promising direction involves the use of bio-networks and concepts from complex systems control to enhance drug discovery and enable personalized medicine. In particular, the idea of combinatorial therapies was mentioned. The paradigm that a single drug should target a single component in a single pathway of a complex biological system has shown its limitations in recent years. The application of computational and algorithmic methods to complex biological systems, often described using complex bio-networks representations, could lead to new transformative approaches for optimizing pharmacological interventions. Traditional in-vivo and ex-vivo diagnostics tools and the new wireless technologies discussed above could be used to collect data to optimize such pharmacological interventions on a single patient basis, an approach known as personalized medicine.

7.2 Economic, ethical, and social issues

The safety and toxicity of the new in vivo devices and therapeutic methods should be a priority, even at the initial research development stages. In particular, toxicity should be addressed both from the point of view of the patient and in a broader sense including the public and the environment. Privacy of wireless-transmitted personal health data is also a concern related to the development of wireless technologies in healthcare and medicine. As these technologies become more common, new and adaptable security strategies will need to be developed.

A final important issue is the public perception of new technologies aiming at controlling life such as genetic engineering and synthetic biology. There is a need of educating the public, and in particular students at all levels, through outreach activities addressing and explaining in simple terms the risk and the benefits associated with such emerging technologies.

8 Information Collection for Complex Biological Systems

Ultra-immersive high density wireless sensor networks can enable real-time and local information analysis and decision making in a variety of bio-related applications. They can operate at various scales and in various modalities (e.g., brain networks, protein networks, organs, bacterial networks, populations). The massive and distributed data collection at high throughput raises several architectural and algorithmic issues. For example, what type of networks, topologies, sensing and communication interfaces, and feedback mechanisms should be used? Understanding this massive amount of heterogeneity and complexity requires appropriate techniques from multiple disciplines. For example community detection techniques draw from physics and information theory to understand the stability of network structure and function under external perturbations [28]. Such methods have been applied to numerous networks including those of dolphins, C-elegans, anthropological systems, hierarchical and random networks with billions of links, and the analysis of chemical and physical systems with 10000 atoms and therefore seem useful for the type and amount of data gathered through high-density multi-scale sensor networks. It is however, important to understand the limits of any method because complex system interfaces are difficult to define since the issues in the systems may be data/information driven and statistically defined. Another illustrative example are biological control networks whose understanding can lead to new combinatorial therapies [29].

9 Recommendations

One of the directions revealed by this year's workshop is that wireless nanoscale systems have tremendous potential to contribute to both medical diagnostics and therapeutics, as hinted by the widespread use and rapid adoption of automated implantable devices and telemedicine. However, the absence of true nanoscale wireless technologies in practical use illustrates the fact that it is difficult to get all parts of the system sensing, transduction, actuation, processing and power delivery in a single integrated system. Thus, significant additional investment is needed in basic research and development to integrate these components and potentially develop new control and computational architectures capable of interfacing with these new technologies and optimally managing what is sure to be an enormous amount of streaming data.

We first outline our suggestions to the general theme of the workshop namely the interfacing of communications and biological systems. We advocate the need for patience and perseverance to develop reliable technology and deeper understanding of the fundamental mechanisms underlying the communication and computation, energy transfer, molecular biology, and physics of such systems. There are already several indicators that we are at turning point enabled by progress in nanotechnology, synthetic biology [13, 12, 30], DNA-assembly [16], recent discovery of quantum coherence in biology [31], electronic bacterial communication [10], and efficient resonant energy transfer [23]. These advances will allow to tackle fundamental problems in health science through nano-medicine, energy demand, and the next frontier for ubiquitous computing.

We suggest support for enabling inter-disciplinary research with potential for both short-term and long-term impact. Some of the exciting directions discussed at the workshop include:

- Assembly and characterization of bio-nano products: develop cost effective synthesis with appropriate predictability and robustness (e.g., DNA-assembly scaffolds, bio-parts, nano-resonators).

- Computing and communication: develop integrated elements and models that reflect the semantics of biological computation and communication and allow the understanding and harnessing of biological mechanisms such as quantum coherence and bacterial communication.

- Scaling: explore the limits of robustness scaling and composition, architectures, interference, noise-mitigation in molecular computation and communication, and develop multi-scale approaches for massive data processing.

This recommended research addresses both the thermal noise (referred to as the 'kT problem' in the bio-physics community) and opens new possibilities for denser circuitry and networks, which can operate at a much smaller scale than current wireless networks. Moreover, micro/nano-robots and small biological parts at the nano-scale, which are currently being developed, should soon perform massively parallel operations culminating in a new era of industrial production and unprecedented computing power.

One of the most challenging problems identified at the workshop is how to effectively realize a reliable and high-rate interface between wireless signals and bio-systems. The understanding and the mastering of coherence in biology is a very promising research direction in this connection. The consequences of coherence in biological systems are remarkable, making systems insensitive to thermal noise and enabling efficient energy transfer [31]. Another area of potential application is in quantum computing where the main challenge is to maintain qubits coherence. Some biological systems may have already solved this problem, for example as Ritz has presented in the workshop on how the birds compass might protect itself from decoherence. These recent discoveries will give new clues in the quest of quantum technologies.

We would also like to reiterate the suggestions of previous years related NSF funded workshops [32, 33] in terms of support for education, inter-disciplinary 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 inter-disciplinary 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.

10 Acknowledgements

We would like to express our gratitude to the NSF for making this fruitful inter-disciplinary 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 breakout sessions chairs who led the discussions and synthesized the group slides and reports, which are available at the workshop website. Their work and dedication made our task much easier. This final report is based on the sessions' summaries and we take responsibility for all inaccuracies and misinterpretations.

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11 Workshop Agenda

Tuesday 7/19/2011

07:30–08:30	**Registration and Breakfast**
08:30–09:00	**Welcome and Overview:** *Bernardo Barbiellini (Northeastern University, Physics)* *Guevara Noubir (Northeastern University, CS)* **Opening Remarks:** *Keith Marzullo, Division Director, NSF CISE/CNS* *Susanne Hambrusch, Division Director, NSF CISE/CCF* *Anne Maglia, Program Director, NSF BIO/DBI* *Sajal Das, Program Director, NSF CISE/CNS* **Perspective Presentations I**
09:00–09:20	New Approaches for Remote, Contact-less Control of Stimulatory Cells in-Vivo, *Arnd Pralle (University of Buffalo, Biophysics)*
09:20–09:40	DNA Meta-Molecules: Synthetic Biology via DNA Nanostructures & Hybridization Reactions, *John Reif (Duke University, CS)*
09:40–10:00	Molecular Information Theory, Energy Efficiency and Molecular Computing, *Thomas Schneider (National Institutes of Health, NCI-Frederick)*
10:00–10:20	Synthetic Biology: the Next Generation of Biotechnology, *Christina Smolke (Stanford University , Bio Eng)*
10:20–10:50	**Coffee Break**
10:50–12:30	**Disciplinary Breakout Sessions** Wireless-to-Bio Transductions *Group leaders: Ada Poon (Stanford University, EE), Arnd Pralle (University of Buffalo, Physics)* Synthetic Biology *Group leaders: Douglas Densmore (Boston University, ECE), Christina Smolke (Stanford University, Bio Eng)* Molecular Computing *Group leaders: Christopher Rose (Rutgers University, ECE), Thomas Schneider (NIH, NIC)*

12:30–01:30	**Working Lunch (breakout sessions continued)**
01:30–02:30	**Group Leaders Report from Disciplinary Breakout Sessions** (State of the Art, Recent Breakthroughs, Challenges, Directions)
02:30–03:00	**General Discussion and Synthesis of Unifying Themes** *Moderator: Guevara Noubir (Northeastern University, CS)*
03:00–03:30	**Coffee Break**
03:30–05:30	**Breakout Sessions on Unifying Themes** Nanoscience for Bio-Synthetic Wireless Sensor Networks *Group Leaders: John Reif (Duke University, CS), Christof Teuscher (Portland State University, CS)* Wireless Control of Nano-Structures and Bio-Networks in Healthcare and Medicine *Group Leaders: Sanjay Kumar (UC Berkeley, Bio Eng), Carlo Piermarocchi (Michigan State University, Physics)* Information Collection for Complex Biological Systems *Group Leaders: Kalyan Basu (CARLBio), Jung-chih Chiao (University of Texas at Arlington, EE)*
05:30–6:00	**Group Leaders Preliminary Report from Unifying Themes Sessions**
06:00–06:30	**Report Generation and Expectations**
07:00–09:00	**Working Dinner:** Daring Opinions and Visionary Ideas Shared Organizing Principles in the Computing and Biological Sciences Recapitulating the NSF Workshop held in May, 2010, *Mitra Basu (NSF, CISE/CCF)* *Moderators: Manu Prakash (Stanford University, Bio Eng), Christopher Rose (Rutgers University, ECE)*

Wednesday 7/20/2011

07:30–08:30	**Breakfast**

08:30–08:50	**Welcome Remarks:** Suzanne Iacono, Deputy Assistant Director (Acting) , NSF CISE **Recap:** Bernardo Barbiellini, Guevara Noubir (Northeastern University)
	Perspective Presentations II
08:50–09:10	Biophysical Strategies for Graded and Dynamic Actuation of Cellular Signaling, *Sanjay Kumar (UC Berkeley, Bio Eng)*
09:10–09:30	Wireless Locomotive Micro Implant: Translating EM torque into controlled motion, *Ada Poon (Stanford University, EE)*
09:30–09:50	Magnetic Orientation and Radio-Frequency Oscillating electromagnetic fields: Possible Mechanisms of Interaction, *Thorsten Ritz (UC Irvine, Physics)*
09:50–10:10	Structure and Stability of Networks and Ways Towards their Improvement using Biologically Inspired Tools, *Zohar Nussinov (Washington University in St. Louis, Physics)*
10:10–10:30	**Coffee Break**
10:30–12:00	**Breakout Sessions on Unifying Themes (continued with optional participants reshuffling)**
12:30–01:30	**Working Lunch (breakout sessions continued)**
01:00–01:30	A Potential Unifying Theme Based on Disciplinary Breakout Sessions, *Douglas Densmore (Boston University, ECE), Christopher Rose (Rutgers University, ECE)*
01:30–02:00	**Remarks and Discussions** *Farnam Jahanian, Assistant Director, NSF CISE*
02:00–02:30	**Reports on Unifying Themes Breakout Sessions** (Grand Challenges, Game Changing Breakthroughs, Perspectives)
02:30–03:00	**General Discussion:** Strategy and Directions *Moderator: Bernardo Barbiellini (Northeastern University)*

12 Workshop Participants

Name	Affiliation
Ada Poon	Stanford University
Al-Hussein Abouzeid	Rensselaer Polytechnic Institute
Arnd Pralle	University of Buffalo
Bernardo Barbiellini	Northeastern University
Carlo Piermarocchi	Michigan State University
Chengde Mao Purdue	University
Christina D. Smolke	Stanford University
Christof Teuscher	Portland State University
Christopher Rose	Rutgers University
Dinesh Bhatia	University of Texas, Dallas
Douglas Densmore	Boston University
Guevara Noubir	Northeastern University
Herbert Sauro	University of Washington
Hooman Javaheri	Northeastern University
Jinglin Fu	Arizona State University
John Reif	Duke University
Jung-chih Chiao	University of Texas at Arlington
Kalyan Basu	CARLBio Ltd.
Manu Prakash	Stanford University
Marc Riedel	University of Minnesota
Nitin S. Baliga	Institute for Systems Biology
Preetam Ghosh	Virginia Commonwealth University
Radha Poovendran	University of Washington
Reshma Shetty	Ginkgo BioWorks
Sanjay Kumar	University of California, Berkeley
Thomas Schneider	National Institutes of Health
Thorsten Ritz	University of California, Irvine
Timothy Lu	Massachusetts Institute of Technology
Zohar Nussinov	Washington University in St. Louis

Registered NSF Participants

Name	Affiliation
Anne Maglia	National Science Foundation, BIO/DBI
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Min Song	National Science Foundation, CISE/CNS
Mitra Basu	National Science Foundation, CISE/CCF
Mohamed Gouda	National Science Foundation, CISE/CSR
Sajal Das	National Science Foundation, CISE/CNS
William Barkis	National Science Foundation, CISE