A Framework for

BIOELECTRONICS

Discovery and Innovation

February 2009

Report prepared by:

Glenn M. Walker
Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill and North Carolina State University

J. Michael Ramsey
Department of Chemistry and the Center for Genome Sciences at the University of North Carolina at Chapel Hill and the Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill and North Carolina State University

Ralph K. Cavin, III
Semiconductor Research Corporation

Daniel J.C. Herr
Semiconductor Research Corporation

Celia I. Merzbacher
Semiconductor Research Corporation

Victor Zhirnov
Semiconductor Research Corporation

Acknowledgements

The participants of the Bioelectronics Roundtable are thanked for their contributions at the Bioelectronics Roundtable held November 4, 2008 in Research Triangle Park, North Carolina and their input to this report. In particular, Madoo Varma of Intel Corporation provided graphic material and thoughtful feedback that greatly improved the report. Reviews by Dr. William C. Tang, Dr. John Carruthers, and Dr. Christina Ahn are gratefully acknowledged. Stacey Shirland is thanked for her support of both the workshop and the preparation of the report.

This study was sponsored by the Semiconductor Electronics Division at the National Institute of Standards and Technology, an agency of the U.S. Department of Commerce.

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Executive Summary: Bringing the Benefits of Moore's Law to Medicine

Motivation

There is an opportunity for dramatically increased synergy between electronics and biology, fostered by the march of electronics technologies to the atomic scale and rapid advances in system, cell, and molecular biology. In the next decade, it may become possible to restore vision or reverse the effects of spinal cord injury or disease; for a lab-on-a-chip to allow medical diagnoses without a clinic or instantaneous biological agent detection. Bioelectronics is the discipline resulting from the convergence of biology and electronics and it has the potential to significantly impact many areas important to the nation's economy and well-being, including healthcare and medicine, homeland security, forensics, and protecting the environment and the food supply. Not only can advances in electronics impact biology and medicine, but conversely understanding biology may provide powerful insights into efficient assembly processes, devices, and architectures for nanoelectronics technologies, as physical limits of existing technologies are approached. This report develops the thesis that advances in bioelectronics can offer new and improved methods and tools while simultaneously reducing their costs, due to the continuing exponential gains in functionality-per-unit-cost in nanoelectronics (aka Moore's Law[a]). These gains drove the cost per transistor down by a factor of *one million* between 1970 and 2008 (for comparison, over the same period, the average cost of a new car rose from $3,900 to $26,000) and enabled unprecedented increases in productivity.

In this report, a number of emerging opportunities in bioelectronics are identified. Although, it is difficult to project the financial benefits at this early stage of research, the following figures for the costs of just a few diseases that could be impacted by bioelectronics provides a sense of the magnitude of potential markets and of the benefits to individuals and society in the healthcare sector alone.

- In 2008, an estimated 1.4 million new cases of cancer were diagnosed and over 560,000 cancer deaths were reported in the United States, costing nearly $90 billion in direct medical expenses and $130 billion more in lost productivity.
- An estimated 22 million Americans suffer from heart disease and about 460,000 die from heart attacks each year (about 1 in 5 deaths). In 2008, heart disease cost $172.8 billion in direct medical expenses and an additional $114.5 billion in indirect costs.
- An estimated 7.2 million Americans are diagnosed with Type 2 diabetes and millions more are undiagnosed. The American Diabetes Association estimates that medical costs associated with diabetes were $116 billion in 2007, with an additional $58 billion in indirect costs.

The overarching technical drivers pushing bioelectronics are the constant advances in semiconductor technology and in surface chemistry related to the interface of biology and man-made devices. At the same time, understanding biological systems and processes at the macro- to nano-scale is growing rapidly.

Research Challenges and Opportunities

Realizing the promise of bioelectronics requires research that crosses disciplines, such as electrical engineering, biology, chemistry, physics, and materials science. Challenges and opportunities were discussed at a roundtable in November 2008 that brought together experts from industry, government, and academia, including representatives from IBM, Intel, Texas Instruments, Tokyo Electron Ltd.,

[a] Moore's Law, which was first observed by the founder of Intel Corporation, Gordon E. Moore, states that the size of integrated circuits decreases by one half every 18-24 months.

Freescale, and Abbott Laboratories. Also participating were representatives from the National Institute of Standards and Technology (NIST), National Science Foundation (NSF), and National Institutes for Health (NIH), and several academic research institutions. Research areas identified at the roundtable include the following:

1. Understanding molecule/cell-electronics interfaces;
2. Understanding cellular responses—and their variabilities—to stimulation (electrical, mechanical, chemical, thermal, and the like);
3. Ability to collect and analyze essential data on the state of biomolecules and cells (chemical, physical, structural, functional);
4. Ability to monitor, in real-time, the biochemistry of a single cell or a population of cells, which requires comprehension of interaction between molecules;
5. Ability to deliver appropriate therapeutic materials and stimuli in real-time; and
6. Ability to detect, identify, and quantify thousands of different biomarkers simultaneously.

Transitioning the results of this multidisciplinary research to commercial products will be expedited through collaboration at early stages between the electronics industry and the biomedical device industry, along with the academic and government research communities. Government, industry, and academic leaders from different sectors and disciplines who do not necessarily speak the same 'language' must be willing to commit to joint efforts where interdisciplinary contributions are necessary for success.

Observations and Recommendations

The application of electronics technology to biology and medicine is not new. Examples include pacemakers and virtually the entire medical imaging industry. Research that enabled these applications grew out of many disciplines of science and engineering; however, recently, the term "bioelectronics" is being used more widely to describe this multidisciplinary field. A survey of publications that use the term in the title or abstract captures on a fraction of the actual research, but suggests that the center of activity is in Europe (43 percent of publications), followed by Asia (23 percent) and the United States (20 percent). With outstanding research expertise in both biomedicine and semiconductors, the United States is in a position to become a leader in the field with appropriate and directed investments in the areas outlined in this report.

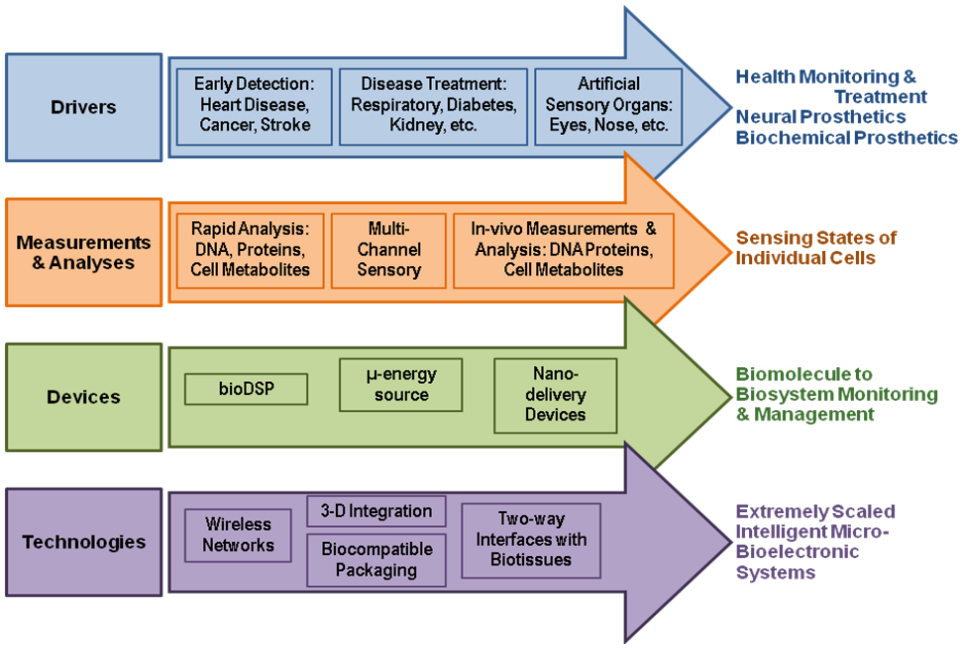
Science and technology experts representing the nano-electronics and biotechnology communities provided inputs for this report. Collectively, the participants identified a wide range of opportunities and challenges for the field, which are listed in the table below. The strategic drivers that were most frequently cited were: disease detection, disease prevention, and prosthetics. The technologies and devices that will enable applications in these areas will impact other vital areas, such as homeland and national security, forensics, and the environment. Progress in all of these sectors requires innovation in crosscutting areas, including measurement and characterization, fabrication, and power sources.

As a next step, stakeholders from government, academic, and industry should jointly develop a detailed bioelectronics roadmap, which can serve to facilitate effective planning and resource management for increasing the productivity and commercializaition of bioelectronics research and development. Such an exercise would define and clarify projected application-specific research metrics and metrology gaps and needs; timelines for research, development, and prototyping; and emerging market and commercialization insertion opportunities. The International Technology Roadmap for Semiconductors (www.itrs.net) , especially its Working Groups on Emerging Research Materials and on Emerging Research Devices may serve as useful templates for the proposed roadmapping exercise.

Category	Highest Priority Research Challenges [Priority, where 1.0 = max.]
Drivers	• Prosthetics, including tissue and neural implants, i.e. vision, hearing, etc. [0.91] • Disease Prevention, including neural degeneration, cancer, etc. [0.82] • Disease Detection, including neural degeneration, cancer, etc. [0.82]
Devices	• Lab on a chip [0.64] • Protein and DNA chips [0.64] • Imaging, including cellular [0.64] • Telemonitoring [0.55]
Measurements and Analyses	• Noninvasive physical sensing, e.g. vital functions [0.73] • Concentration of analyte and metabolites, etc. [0.73] • Real-time & time dependent measurements [0.64] • Single bio-molecule detection, e.g. in Lab-on-Chip environment (including mass, size, chemical, optical, etc.) [0.64]
Technologies	• Molecular recognition [0.73] • Signal processing algorithms [0.73] • DNA sequencing [0.64] • Fabrication (electrodes, devices), including patterning [0.64] • Thin film technology [0.64]

The figure below shows a framework for bioelectronics research, based on input from experts engaged for this study. This proposed framework is intended to catalyze further analyses and a comprehensive road-mapping exercise.

The field of bioelectronics is poised for exponential growth. The Federal government's expertise in critical areas of science and technology, including sensors, nanoelectronics, and metrology should be harnessed and coordinated, along with expertise from academia and industry to firmly establish the United States as a leader in this high impact area of research and development.



1. Introduction

Electronic devices have been revolutionizing biology and medicine over the past several generations. The development of the electrocardiograph (i.e., recording the electrical activity of the heart) approximately 100 years ago was one of the defining moments that helped establish the field of cardiology and is now an integral part of clinical practice [1]. Today, defibrillators are implanted at a rate of 160,000 per year in the US alone to restore proper electrical activity to diseased hearts, once again changing the practice of medicine and creating a new market worth $5 billion per year [2]. Electronic systems have also been critical to the development of the field of radiology, which has evolved from a single modality (X-ray) to include magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), among others. MRI has made possible the imaging of soft tissue to help treat physical injuries. CT now allows 3D visualization of anatomical features, facilitating surgical planning. The medical imaging equipment market is expected to be worth $11.4 billion by 2012 [3]. In short, the application of electronics to medicine has transformed medical practice and will continue to do so.

In this report, a number of emerging opportunities in bioelectronics are identified. Although, it is difficult to project the financial benefits at this early stage of research, the following figures for the costs of just a few diseases that could be impacted by bioelectronics provides a sense of the magnitude of potential markets and of the benefits to individuals and society in the healthcare sector alone.

1. In 2008, domestic health care spending reached $2.4 trillion, or 17 percent of the gross domestic product (GDP). This spending is projected to increase to $4.3 trillion in 2016.[b]
2. In 2008, an estimated 1.4 million new cases of cancer were diagnosed and over 560,000 cancer deaths were reported in the United States. The National Institutes of Health (NIH) estimates these cases cost nearly $90 billion in direct medical expenses plus $130 billion more in lost productivity to the U.S. economy.
3. An estimated 22 million Americans suffer from heart disease and about 460,000 die from heart attacks each year (about 1 in 5 deaths). NIH estimates the direct cost of heart disease in the United States in 2008 to be $172.8 billion and the additional indirect cost due to lost productivity was $114.5 billion.
4. An estimated 7.2 million Americans are diagnosed with Type 2 diabetes and millions more are undiagnosed. Diabetes leads to a range of debilitating complications, including blindness, nerve damage and amputation of toes or feet. The American Diabetes Association estimates that medical costs associated with diabetes were $116 billion in 2007, with an additional $58 billion in indirect costs.

The study of biology also has been transformed by electronics. In the late 1940s and early 1950s, understanding the molecular basis of nerve and muscle function was achieved with the use of high-impedance amplifiers. Those studies led to a new era of quantitative biology and practical clinical neuroscience. The patch clamp, which allowed researchers to measure the ionic current through single ion channels gave further insight into nerve action. These studies led directly to three Nobel Prizes and ultimately seven more. The electron microscope is also an example of applying electronics to biological problems. First demonstrated in the 1930s and developed over the next decade, the electron microscope allowed scientists to visualize the miniscule world of cells at an entirely new level of detail [4]. Much of modern cell biology is built on information captured from these indispensible tools.

[b] S. Keehan et al. “Health Spending projections through 2017”, Health Affairs Web Exclusive W146: 21 Feb. 2008

Given the profound impact electronics has had on medicine and biology in the past, it is easy to imagine that integrating modern electronics (i.e., semiconductor technology) with biology and medicine will result in equally profound quantum leaps. The ongoing miniaturization of semiconductor devices is leading to new opportunities in biomedical research and commercial medical applications. In medicine, healthcare costs could be drastically reduced and presently untreatable diseases could be cured. The medical problems of today could have commonplace solutions in the future. Nanoscale bioelectronics will be an enabler for the development of molecular-based personalized medicine. In particular, the use of nanoscale electrical measurements will be important in genomics and proteomics for identifying the function of proteins and their reaction pathways inside cells, as well as on and through cell membranes.

The length scale of features that can reliably be manufactured by semiconductor technology is now sufficiently small that novel devices can be envisioned to probe cells or biomolecules either *in vitro* or *in vivo*. Advances in integration and packaging mean that circuitry can be integrated with sensors, actuators, and computers. These enabling technologies will allow the creation of devices and systems that can intelligently probe biological systems from the molecule to cell to whole organism levels and thereby open up new areas of basic biological research and new market opportunities for commercialization. Highly integrated systems also make possible the creation of implantable devices that can sense their environment and actively choose an appropriate response, as in intelligent drug delivery chips. Numerous other applications will emerge from the continued integration of electronics with biology that will result in new revolutionary biomedical advances Moreover, the development of nanoscale metrologies for the semiconductor industry may well find applications in various biological and biomedical research areas.

2. Research Activity

The application of electronics technology to biology and medicine is not new, however research activity in this convergent field is growing rapidly. A proxy for activity, especially in academia, is publications. In order to assess bioelectronics research activity, an analysis of publications was made using the *Science Citation Index Expanded™* (SCIE), available through the *Web of Science®*. The SCIE includes information from more than 10,000 of the world's leading scholarly science and technical journals in more than 100 disciplines. It also contains papers from over 110,000 conference proceedings. The database is updated weekly and contains citations dating back to 1900. Publications that contained the word ‘bioelectronic’ or ‘bioelectronics’ in their title or abstract were identified. The total number of such papers is 548, published from 1912 through January 2009. It should be noted that the absolute number of publications on bioelectronic topics (without using the term bioelectronics in the title or abstract) is undoubtedly much larger; however, this analysis provides a sample that is believed to be representative of the related activities in the field.

Although publications referencing bioelectronics concepts were published even before 1912, 516 of the 548 papers that use the term in the title or abstract were published since 1990. Figure 1 shows the number of publications by year. The number of papers per year increased markedly in 2005 over the previous year (from about 25 to 50) and by and large has continued to grow. Moreover, the number of citations to the papers identified has increased exponentially (Figure 2). Because many papers related to bioelectronics do not use the term in the title or abstract, the absolute number of papers underestimates the actual level of activity; however, it is clearly increasing over time.

Figure 3 shows the geographical distribution of the location of the authors’ research institutions, which suggests that, although U.S. authors have published more papers than authors from any other

country, the center of activity is in Europe (43 percent of publications), followed by Asia (23 percent) and the United States (20 percent).

The SCIE study also revealed fifteen papers in the bioelectronics area that have received one hundred or more citations, which is on the order of the number of citations received by Nobel laureates in the semiconductor sciences. The number of publications each year and the number of citations received by bioelectronics papers are growing rapidly, indicative of an area of expanding activity. Table 1 lists the fifteen most influential papers in bioelectronics since 1993.

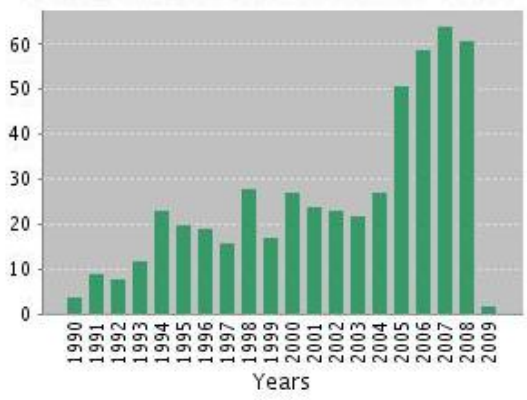


Figure 1: *Number of publications with 'bioelectronic(s)' in the title or abstract by year. [Source: Science Citation Index Expanded™]*

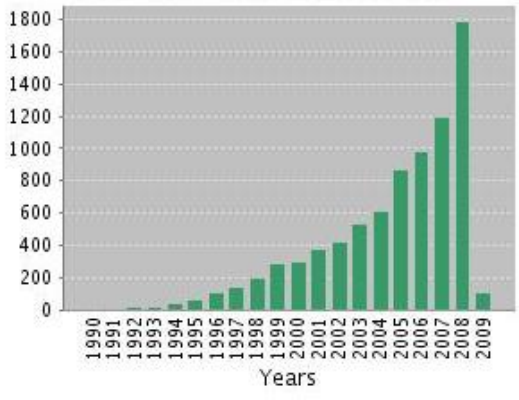
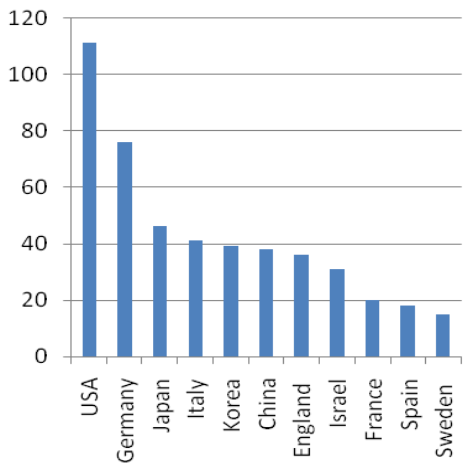


Figure 2: *Number of citations to a publication with 'bioelectronic(s)' in the title or abstract by year. [Source: Science Citation Index Expanded™]*



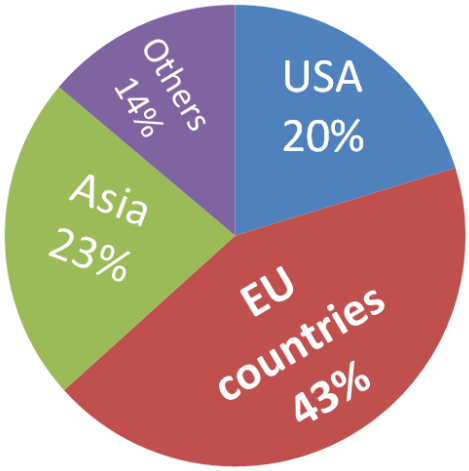


Figure 3: *Number of publications with 'bioelectronic(s)' in the title or abstract by country (left). Distribution of bioelectronics publications by region (right).*

Table 1. *Influential publications in bioelectronics*[c]

	Publication	Author(s)	Citations
1	"Integration of layered redox proteins and conductive supports for bioelectronic applications", Angew. Chem.-Int. Ed. 39 (2000) 1180	I. Willner and E. Katz Hebrew University Jerusalem, Israel	417
2	"Biological surface science", Surface Science 500 (2002) 656	B. Kasemo Chalmers Univ. Technology Gothenburg, Sweden	260
3	"Probing biomolecular interactions at conductive and semiconductive surfaces by impedance spectroscopy: Routes to impedimetric immunosensors, DNA-Sensors, and enzyme biosensors", Electroanalysis 15 (2003) 913	E. Katz and I. Willner Hebrew University Jerusalem, Israel	233
4	"Control of the structure and functions of biomaterials by light", Angew. Chem.-Int. Ed. 35 (1996) 367	E. Katz and I. Willner Hebrew University Jerusalem, Israel	203
5	Supramolecular self-assembly of lipid derivatives on carbon nanotubes, Science 300 (2003) 775	CEA Saclay Inst Genet&Biol , Mol&Cell. Univ Strasbourg, France	200
6	Toward bioelectronics: Specific DNA recognition based on an oligonucleotide-functionalized polypyrrole, J. Am. Chem. Soc. 119 (1997) 7388	H. Korri Youssoufi, et al. CNRS, France	192
7	Preparation and hybridization analysis of DNA/RNA from E-coli on microfabricated bioelectronic chips, Nature Biotechnology 16 (1998) 541	J. Cheng et al. Nanogen, Inc., San Diego CA	161
8	Dielectrophoretic assembly of electrically functional microwires from nanoparticle suspensions, Science 294 (2001) 5544	O. D. Velev et al. NCSU, Raleigh, NC and Univ. Delaware , Newark, DE	146
9	Towards genoelectronics: Electrochemical biosensing of DNA hybridization, Chemistry- Eur. J. 5 (1999) 1681	J. Wang NM State University Albuquerque, NM	142
10	Electrical contact of redox enzyme layers associated with electrodes: Routes to amperometric biosensors, Electroanalysis 9 (1997) 965	I. Willner, et al. Hebrew University Jerusalem, Israel	126
11	"Biomolecular electronics: Protein-based associative processors and volumetric memories", J. Phys. Chem. 103 (1999) 10746	R. R. Birge et al. Syracuse University Syracuse, NY	120
12	The application of conducting polymers in biosensors, Synthetic Metals 61 (1993) 15	P. N. Bartlett & P. R. Birkin Univ. Southampton, England	116
13	Chip and solution detection of DNA hybridization using a luminescent zwitterionic polythiophene derivative, Nature Materials 2 (2003) 419	KPR Nilsson and O. Inganas Linkoping Univ, Sweden	106
14	Bioelectrocatalyzed amperometric transduction of recorded optical signals using monolayer-modified Au-electrodes, J. Amer. Chem. Soc. 117 (1995) 6581	I. Willner, et al. Hebrew University Jerusalem, Israel	105
15	Microchips, microarrays, biochips and nanochips: personal laboratories for the 21st century, Clinica Chimica Acta 307 (2001) 219	LJ Kricka U. Pennsylvania Philadelphia, PA	100

[c] Note the citations given are as of 1/28/2009

Comparing Table 1 and Figure 3, we note that 1) Israel and the United States each have five of the fifteen most cited papers; 2) the United States has more than three times the number of papers than Israel overall; and 3) the nationality of other authors shown in Table 1—England, Israel, France, and Sweden—are ranked 7th, 8th, 9th, and 11th in Figure 3 . The fact that publication rates and citation rates are not correlated may be due to the relatively small number of active research groups to date. In addition to the highly cited papers shown in Table 1, there are many publications that do not use the term 'bioelectronics' in the title or abstract and yet must be considered fundamental to the field. Examples of such seminal publications include reports on electrical activity of neurons and development of technologies for characterization of biomaterials, including cells [5-10].

3. Bioelectronics: A Taxonomy

The first reference to bioelectronics, published in 1912, focused on measurement of electrical signals generated by the body, which is the basis of the electrocardiogram. In the 1960s two new trends in bioelectronics began to appear. One trend, enabled by the invention of the transistor, centered on the development of implantable electronic devices and systems to stimulate organs, e.g., the pacemaker. In the same time frame, fundamental studies were beginning to be reported on electron transfer in electrochemical reactions. Today, these three areas of endeavor are converging to enable multi-signal recording and stimulation at the cell level, i.e., there is a kind of physical scaling law that is moving over time from the organ level toward cellular dimensions. At the same time, studies at the molecular level are leading to new understanding of cell performance. The analogy with nanoelectronics is striking; top-down scaling is being abetted by device design from the atomic level.

Bioelectronics encompasses a range of topics at the interface of biology and electronics. One aspect of bioelectronics is the application of electronics to problems in biology, medicine, and security. This includes electronics for both detection and characterization of biological materials, such as on the cellular and subcellular level. Another aspect of bioelectronics is using biological systems in electronic applications (e.g., processing novel electronic components from DNA, nerves, or cells). Bioelectronics also focuses on physically interfacing electronic devices with biological systems (e.g., brain-machine, cell-electrode, or protein-electrode). Applications in this area include assistive technologies for individuals with brain-related disease or injury, such as paralysis, artificial retinas, and new technologies for protein structure-function measurements. The identified publications were organized into several topical areas, as shown in Figure 4.

Examples of research papers in each of the topical areas are given below:

Measurements (35%) – Works on sensors, monitoring systems and metrology. Several distinct categories were identified:

- Sensors (9%) - fabrication and properties of biosensors, biological, and chemical sensors
- Biochemical measurements (7%) - application of biosensors
- "Bio-electronic Nose" (6%) – Efforts focused on system integration for one targeted application
- Neural recording (2%) – Focus on microelectrode arrays and their interfaces with neurons
- BioFET (4%) – Field-Effect-Transistor-like devices for bio-sensing
- Bio-electronic Instrumentation (7%) – Practical (e.g. clinical) application of bio-electronic devices

Biomaterials (29%) - Materials and fabrication techniques for bio-electronic devices, medical implants, 3D assembly, self-assembly, nano-particles, nano-tubes, nano-wires, etc.

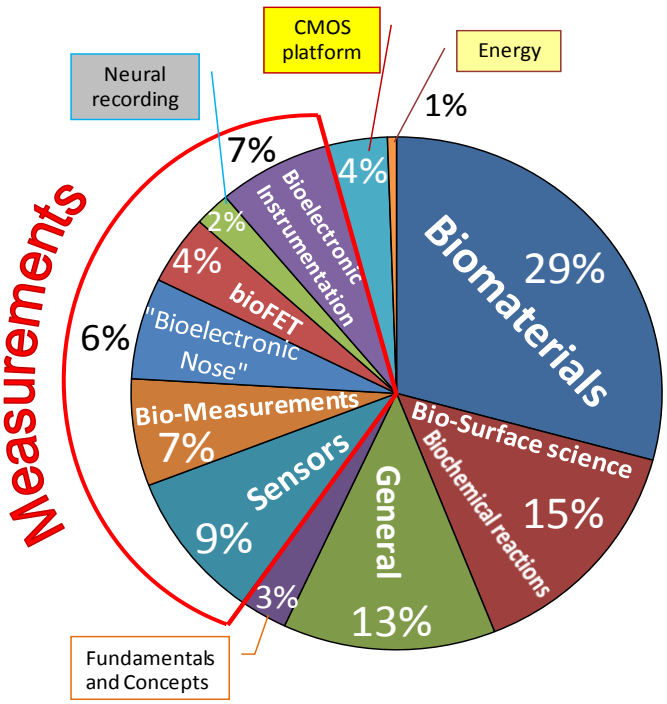


Figure 4: *Distribution of bioelectronics publications by topical area.*

Bio-surface science/biochemical reactions (15%) - Research focused on the interaction between bio-molecules and solid surfaces. Examples include bio-molecule immobilization, electron transfer in biochemical reactions and between bio-objects (bio-molecules or cells) and the solid surface. The latter is often referred as "bio-electronic interface". This definition is narrower than broader concept of bio-electronic interface as interaction between electronic devices and bio-objects.

General (13%) -Articles including forewords, short abstracts, program descriptions, status reports, surveys, patent analyses, etc.

CMOS/Semiconductor Platform (4%) – Electronic components of bioelectronic systems and integration issues. Topics include:

- Low-power implantable devices
- On-chip integration of sensors
- DSP for real-time processing of multi-parametric bioelectronic signals
- CMOS IC/microfluidic hybrid systems for cell manipulation and electrochemical analysis
- Micro-photodiodes arrays for retinal stimulation
- 3D chip integration and packaging

Fundamentals and Concepts (3%) – Models, simulation, and new concepts related to bioelectronics.

Energy Sources (1%) – Only three papers were identified and these focused on bio-fuel cells.

The analysis of bioelectronics publications revealed a wide range of research programs spanning many related thrust areas. Although it is clear that micro- and nanoelectronics is playing an important role in bioelectronics, via direct application of semiconductor industry products, an evident lack of semiconductor-related bioelectronic research is very visible. For example, only a small percentage of the surveyed work dealt with semiconductor platforms for biological applications. Moreover, the critical area of autonomous (e. g. implantable) energy sources doesn't appear to have received much attention

in the context of bioelectronics. There is an opportunity, therefore, for a concerted research effort directed toward the utilization of the semiconductor industry's capabilities to provide bioelectronic-specific tools and systems.

4. Examples of Technical Areas of Opportunity for Bioelectronics

The overarching technical drivers for bioelectronics are the constant advances in semiconductor technology coupled with advances in surface chemistry and their application to life sciences research. Much of the work that has been done in the bioelectronics field since the 1990s has been focused on creating better biosensors by integrating biomolecules with semiconductors [11]. For decades, semiconductor technology has advanced at an exponential rate and is described by Moore's law, which states that the number of features in a given area of substrate doubles every 18–24 months. A result of Moore's law is that the computing power and capabilities increase with each generation of device while the cost per function decreases.

As Moore's law has progressed, so have the number of semiconductor applications in the life sciences. In particular, significant effort has gone into developing surface chemistries that can be used to attach biological molecules to semiconductor substrates [12]. Two examples are biosensors that use enzymes covalently linked to electrode surfaces [13] and DNA recognition based on surface-bound DNA-functionalized polypyrrole molecules [14]. Although advances have been made in binding biological molecules to substrates, no truly biomimetic synthetic surfaces yet exist (e.g., for use in implants). The following are examples of technical areas or opportunities that will impact bioelectronics:

Real-Time and Massively Parallel Molecular and Cellular Characterization for Systems Biology

The nascent field of systems biology—using systems engineering approaches to analyze cellular function—is driving the development of new technology that can monitor multiple aspects of cellular behavior over many timepoints. Systems biology embodies a new perspective from which to view biological systems and knowledge culled from its approaches could lead to advances in medicine and security. However, significant investment is needed to develop tools and associated standards and metrology that can characterize and continuously monitor the states of cells at sub-cellular resolutions [15]. Advances in micro- and nano-fluidic systems that can monitor many cell populations in parallel are beginning to address this need [16, 17].

Biologically-based Sensors and Fabrication

Another driver of bioelectronics is that cells and their components can be used as biological transducers for measurements or as components in building novel materials or circuits. In other words, components of cells have been used for novel applications outside of their originally observed purpose. Cells are sensitive to many environmental cues. For example, identifying the response of a cell to a known toxin could allow it to be used as a "canary in a coal mine" to detect toxic substances in captured air samples [18]. Biomolecules, in particular antibodies, can also be used as transducers, via their exquisite specificity for complementary molecules. Coupling antibodies with emerging nano-scale technologies could result in ultra-sensitive detection methods [19]. Bio-inspired fabrication shows promise for constructing nanoscale assemblies, which could lead to significant advances in sensor design and materials technology [20].

Protection and Restoration of Health

The development of new technology that can protect lives (e.g., by preventing bioterrorism) and restore health (e.g., by developing novel implantable therapeutic devices) is also driving the

development of bioelectronics. National security demands new technology for monitoring chemical or biological threats, and advances in lab-on-a-chip technology have been developed to address this need [21]. Further miniaturization of these technologies will likely result in smaller units with increasing capabilities. Advances in miniaturization and power transmission, storage, and generation have allowed implantable medical devices to emerge [22]. The artificial retina, which is a first step toward restoring sight in people with degenerative diseases of the retina, is representative of these advancements [23]. Implantable drug delivery devices, based on micro-electro-mechanical systems (MEMS), are beginning to emerge, and the next generation of drug delivery devices are likely to be "smart" and to have embedded transceivers (i.e., able to sense and respond to their environment and transmit and receive data) instead of passively delivering drugs at pre-defined intervals [24].

The health and safety issues associated with the synthesis and use of nano-materials in semiconductor manufacturing will be informed by the understanding that will come from using bioelectronics to study toxicity effects at the cellular and molecular levels. These data will allow exposure limits to be determined and guide standards for environmental monitoring.

5. Cross-cutting Challenges

Moving bioelectronics forward requires innovation among the broad areas of measurements and analyses, fabrication, biocompatibility, and power sources. In general, these cross-cutting challenges either stem from a lack of technology, biological understanding, or a combination of both. Expertise that is resident across government agencies, academic research institutions, and industry will need to be coordinated and brought to bear in order to to achieve the necessary innovations.

Cellular and Biomolecular Measurements and Analyses

New methods are needed for the detection, identification, and quantification of DNA, proteins, and other biomolecules. These methods would also provide a more accurate measurement of cell phenotype (e.g., DNA sequence, surface markers, etc.) and enable high throughput real-time information about cellular behavior.

Biomolecular measurements are increasingly focused on higher bandwidth measurements (i.e., multiple analytes measured at increasingly high frequency). The biomolecules of interest usually have very low concentrations, on the order of nanomolar to femtomolar. When considering protein analysis of single cells, the concentration of even highly expressed molecules becomes very small. As more cellular and biomolecular measurements are needed to paint a comprehensive picture of cell behavior *in situ*, larger numbers of measurements per observation will be needed at increasingly smaller concentrations per molecule. Figure 5 summarizes the parameter space. Metabolic measurements of cells occupy the upper-left portion of the graph, while the protein and DNA characterization of cells occupy the lower-right corner.

The fundamental challenge facing DNA analysis is the ability to rapidly and accurately determine the sequence. Sequencing technologies have advanced significantly, with three generations of disruptive innovations already productized. But an ultimate goal is a method that can rapidly and inexpensively sequence DNA from a small and complex sample without need for sample manipulation. Single molecule and nanopore sequencing are promising approaches that may provide a solution [25]. A secondary challenge of DNA analysis is determining which genes are active. Gene expression can be quantified by measuring messenger RNA (mRNA) expression as a surrogate using DNA arrays or gene chips. While gene chips are currently the best way to provide a comprehensive picture of gene expression, DNA hybridization arrays require sample amplification, which adds time to the assay and can lead to

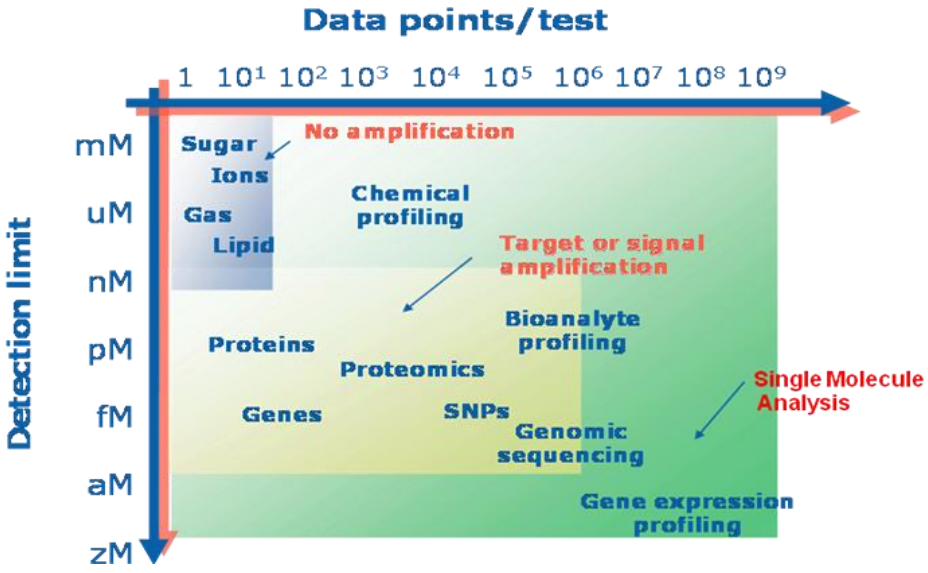


Figure 5: *Trade-offs between measurement sensitivity and measurement time are due to the increasing need for information-rich data.*

increased levels of noise, due to PCR errors introduced into the DNA [26]. Furthermore, collecting gene expression data over many time points (e.g., minutes or hours) is tedious. An ideal technique forquantifying gene expression would require minimal human intervention (i.e., sample manipulation) and allow multiple time point measurements within the same inexpensive, reusable device. Electrochemical methods show promise for creating highly sensitive and integrated (e.g., in a lab-on-a-chip device) DNA arrays [27].

The challenges for cellular and molecular measurements are based on a lack of adequate metrological tools. To address these challenges, new devices in combination with other techniques (multi-modal metrologies) need to be developed that can:

- Rapidly determine whole genome and RNA sequences;
- Quantify the up or down regulation of multiple genes over many timepoints;
- Identify biomarkers for disease states (e.g., DNA, RNA, proteins, polysaccharides, metabolites) in both serum and actual blood and tissue samples;
- Identify and quantify biomarkers in real-time at sensitivity levels equal to or better than existing lab techniques such as enzyme linked immunoassays (ELISA) and also be reusable;
- Monitor multiple intracellular events in real-time;
- Simultaneously determine membrane protein structure and function in an *in-vivo*-like environment;
- Identify the chemical and mechanical cues that drive stem cell differentiation;
- Recapitulate physicochemical cellular microenvironments; and
- Implement ion channels, ion channel-like devices, as sensors for improved molecular recognition and sensitivity.

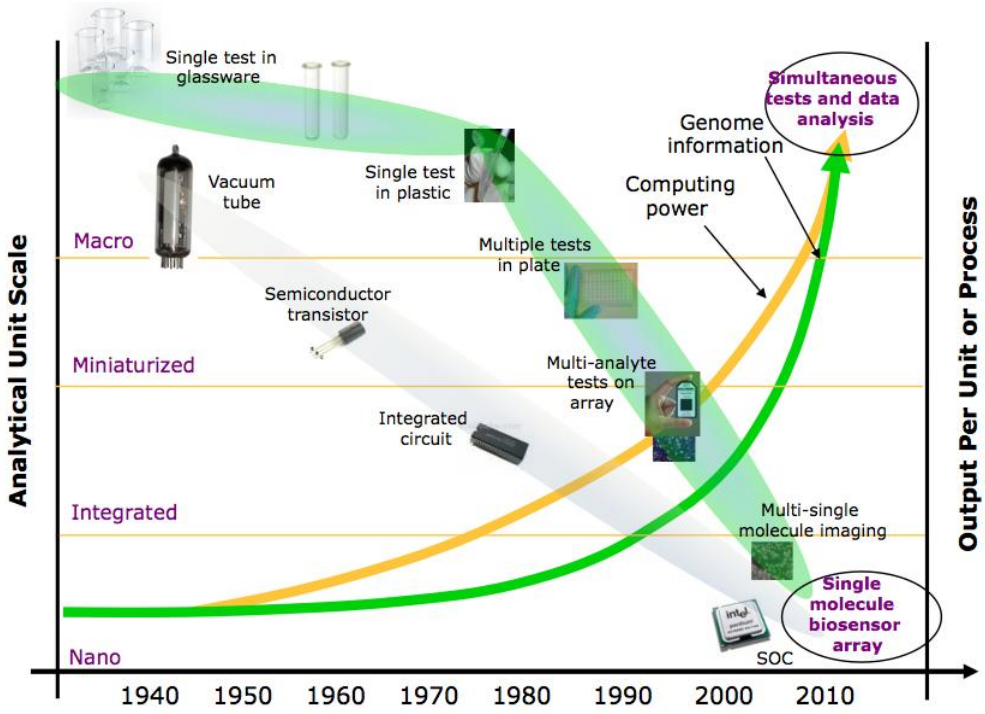


Figure 6: *Increasing the density of semiconductor features will ultimately allow arrays of single-molecule measurements. Courtesy of Madoo Varma, Intel Corporation.*

Fabrication

Fabrication challenges include creating better sensors and developing novel fabrication techniques. Integrating multiple sensing technologies with integrated circuit (IC) technologies also presents a challenge. Biosensors will play a key role in meeting future bioelectronics demands and improvements to increase bandwidth and lower detection limits are needed. Massive parallelization of sensors is necessary to see the same benefits from future bioelectronics devices that now exist in ICs because of Moore's law. Figure 6 illustrates how the miniaturization of semiconductor technology has led to acommensurate decrease in the size of liquid volumes used for biological assays. As technology continues to advance, high throughput nanofabricated arrays capable of quantifying single molecules in solution will become commonplace.

The challenges faced in realizing single molecule biosensor arrays are based in part on a lack of fabrication technologies. New methods are needed to fabricate structures reliably at the nanoscale, and new metrology and standards are needed to characterize these structures. To date, the vast majority of nano-fluidic devices have been characterized by planar surfaces and simple features defined by one, two, or at most several device depths [28]. As the functionality of a nano-fluidic device is determined by its dimensionality and complexity, the development of more intricate three dimensional structures would lead to enhanced control over nanometer scale fluidic environments and analytes, which could result in new or improved device utility. Progress in this regard has been limited by conventional nanofabrication processes, which are inherently planar and become increasingly restrictive, when many layers of high resolution lithography are performed in a research facility. Figure 7 shows how nano-fluidic devices relate to some of the more popular methods for molecular analysis.

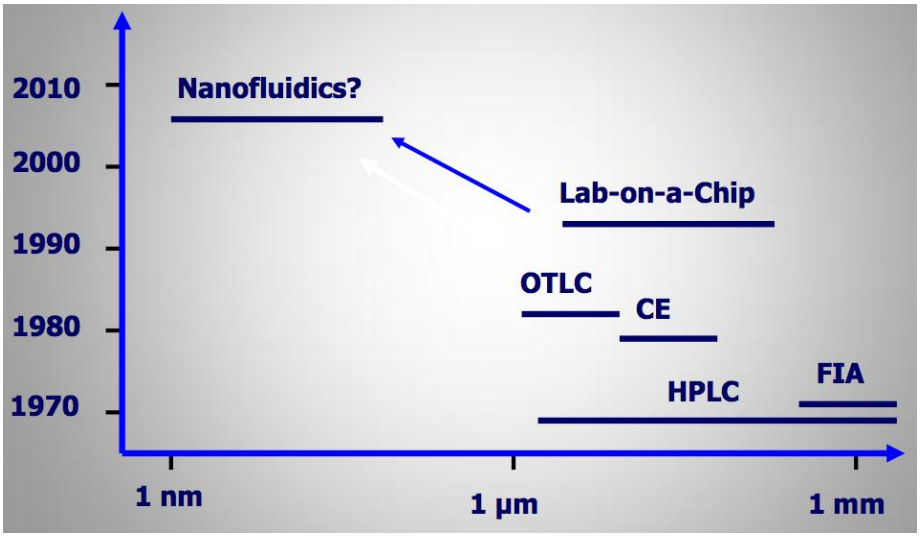


Figure 7: *New fabrication technologies will be required to fabricate nano-fluidic devices that have single-molecule sensitivity. Current technologies include lab-on-a-chip, open tubular liquid chromatography (OTLC), capillary electrophoresis (CE), high-pressure liquid chromatography (HPLC), and flow injection analysis (FIA).*

The fabrication of nano-materials and nanoscale devices raises health and safety concerns that will need to be addressed [29]. The technologies developed in response to challenges in the previous section can be used to address the concerns associated with the synthesis and use of nano-materials and nano-devices in semiconductor manufacturing.

Fabrication challenges that need to be overcome include:

- Improving fabrication techniques for on-chip integrated optical excitation and detection in nanoliter-femtoliter volumes;
- Endowing electrochemical sensors with sub-zeptomole sensitivity;
- Developing electronics with a sensitivity of < 1 pA and a bandwidth of hundreds of MHz;
- Integrating high-density photodiode arrays into substrates;
- Harnessing biological assemblies for nanoscale fabrication;
- Fabrication of complex physical features into substrates with critical dimensions ≥ 1 nm;
- Developing metrology tools for test and measurement of nanoscale features. Developing surfaces for control of antibody and antigen binding;
- Immobilization of electrode surfaces for control of antibody and antigen binding. This requires extensive development of the needed biochemistries.

Device and Material Biocompatibility

Accurate bioelectronic measurements and safe use in patients demand that the device surface not inhibit or cause deleterious effects on the biological system. One of the most critical issues in realizing the potential of bioelectronic devices is to understand how they perturb the local environment and

cellular response, which includes but is not limited to physical contact and radiation effects. Improving biocompatibility, via surface chemistry, is critical for enabling future implantable bioelectronic devices, such as insulin delivery systems or chronic neurological implants [12]. The optimization of the material biocompatibility, however, cannot come at the loss of device or measurement functionality. The surface modification or coating must allow for adequate environmental sampling for timely and accurate electronic measurements.

Key challenges include:

- Implementing biocompatible materials that do not kill tissue or cells and maintain the native structure of biomolecules, while not compromising device operation.
- Limiting implant rejection by maintaining and stimulating tissue integrity.
- Minimizing the amount of tissue heating that occurs from electromagnetic radiation (e.g., during the transmission of power).

Power Sources

New methods for harvesting and storing energy to power mobile and implantable devices are required [30]. Next-generation devices will need power sources that offer prolonged device life with minimal intervention (e.g., through multiple surgeries) and minimal increase in device size. Methods for producing energy from biological or bio-inspired sources will also be needed to meet future domestic energy demands. One example is using microbial fuel cells to generate electricity [31].

High-level challenges include:

- Improving the efficiency of RF power transmission to devices within the body while minimizing tissue damage;
- Improving battery energy density;
- Developing alternative energy generation strategies for devices such as kinetic power production (e.g., power harvested from body motion);
- Developing alternative energy strategies that use biological or bio-inspired approaches, such as synthetic photosynthesis (light harvesting) or microbial energy generation.

6. Current Capabilities and State-of-the-Art

Current technologies for cell and biomolecular measurements, fabrication, device biocompatibility, power sources, and implantable devices are briefly reviewed. Where applicable, drawbacks of the current approaches are pointed out.

Cellular and Biomolecular Measurements and Analyses

DNA and proteins can be studied either in their native state within a living organism (*in vivo*) or extracted from their native environment (*in vitro*). Cellular measurements are typically conducted *in vitro* in artificial microenvironments to identify a particular cellular state, through the characterization of DNA, proteins, and other components. However, a growing number of researchers are realizing that studying cells in these artificial environments can skew experimental results [32]. A common drawback to all current capabilities is that they do not allow the simultaneous measurement of biological function (DNA, proteins, cells, etc.) over multiple timepoints in an *in-vivo*-like environment.

DNA

DNA has been studied for decades but the three largest areas of emphases have been to develop rapid methods for (1) sequencing DNA, (2) recognizing short strands, and (3) detecting single nucleotide variations. Current methods include slab gel electrophoresis, capillary gel electrophoresis, and DNA microarrays.

The ability to amplify the number of DNA copies via the polymerase chain reaction (PCR) has been critical to the growth of genetics research. The traditional method for DNA sequencing involves polymerase amplification of DNA fragments followed by sizing, using electrophoretic separation (Sanger method). Separation of DNA using electrophoresis in agarose slabs is the traditional approach for sizing biopolymers and is used to size polymerase-generated DNA fragments, which allows determination of DNA sequence. The small capillary diameters (< 100 μm) used in capillary gel electrophoresis provide improved thermal transport, allowing the use of higher electric field strengths to correspondingly reduce separation times.

Although sensitive and reliable, high-end setups are large, expensive, and require optical (laser) systems to accurately read data. The classic approach to DNA sequencing also requires a large time investment for sequencing whole genomes and large amounts of sample. Current methods of DNA analysis lack the speed and ease of use that is desired for personalized medicine and systems biology, among other applications. DNA detection methods used in biomedical research are continually improving, but are still slow and cumbersome to use for monitoring gene expression over multiple time points with multiple cell types. For example, real-time PCR can be used to monitor gene expression over time, and looking at a single cell line expressing a single gene or protein is a routine process. Looking at multiple cell lines (e.g., as in a co-culture) expressing more than a handful of genes or proteins over time is currently impractical.

Next generation DNA sequencing tools have become available in the past couple of years that have reduced whole genome sequencing costs by several orders of magnitude. Some of these new sequencing techniques are classified as sequencing by synthesis methods, which generally use DNA polymerases that allow incorporation of recognizable deoxynucleotide triphosphates, one at a time [33]. Synthesis of complementary strands of template DNA fragments is done in a massively parallel (10^5) fashion to increase speed and reduce costs.

Current methods for direct sequencing of DNA eliminate the need for PCR and, thus, significantly reduce the time needed for genomic analysis. However, these methods, such as electrical detection of sequence pairs when DNA molecules are translocated through nanopores, need major engineering development.

Proteins

Useful characteristics of proteins include their structure, function, sequence, concentration, and binding characteristics. A significant number of proteins, especially those of interest to the pharmaceutical industry, are embedded in the cellular membrane, which confers on them a particular three-dimensional structure [34]. To date, no method exists that can determine both the structure and function of membrane proteins in their *in vivo* conformation. Common methods of protein characterization include slab gel separations, mass spectrometry, fluorescence imaging, x-ray crystallography, and NMR spectroscopy.

While 2D slab gel separations reveal size and charge information for proteins, and have historically been the lab workhorse for analyzing proteins (e.g., Western blots), they do not provide any information about polypeptide sequence, which is needed for identifying unknown proteins. Mass spectrometry is a

powerful tool, but high concentrations of common biological proteins that may also be present in a sample, such as albumin, can mask signals from less concentrated proteins important to cellular activity. Fluorescence methods can reveal useful information, but preparing fluorescent markers is often time-consuming, tedious, and expensive. Because a large number of proteins cannot be monitored easily with these techniques, the throughput of discovery and monitoring of complex intracellular interactions is limited.

Mass spectrometry is a rapidly evolving field in which proteins are characterized wholly or by digesting them into smaller fragments (peptides), further fragmenting the peptides in the gas phase, and determining the molecular weight of the gas phase components. The gas phase fragmentation of peptides generates a mixture of peptides that differ by one amino acid residue and yields the peptide sequence. Comparing this peptide sequence information with genomic sequence information often reveals the identity of a unique protein. Information on expression levels (concentration) of the proteins is simultaneously determined. A recent development in size (or mass) spectrometry of individual molecules in the aqueous phase may prove useful for protein fragment analysis [35].

Genetic engineering can be used to incorporate fluorescent protein (e.g., GFP) sequence information next to unidentified target proteins so that their production within a cell can be monitored. Optical fluorescence techniques, such as fluorescence recovery after photobleaching (FRAP), can be used to monitor protein production within a cell. Fluorescence resonance energy transfer (FRET) can be used to monitor protein-protein interactions. However, these altered proteins can take months to prepare and are limited in their throughput once they have been incorporated into the cell(s) being studied.

X-ray crystallography and NMR spectroscopy are used to infer the structure of proteins, but cannot provide information on function. Furthermore, neither method can capture the conformation of the protein in its native (i.e., within a cell or on a cellular membrane) state. NMR does offer the advantage that protein structure can be observed within an aqueous solution.

Cell Phenotype

Cell phenotype is determined through the interaction of the genome with the environment. The phenotype can be quantified by measuring the genome, proteome, secretome, metabolic state, electrical characteristics, and mechanical characteristics of the cell. Techniques commonly used to quantify cells include:

- Optical and fluorescence microscopy,
- DNA analysis,
- Protein analysis,
- Patch clamps,
- Cell deformation

Optical and fluorescence microscopy are the most common method of observing cell phenotype. Cells can be visually inspected with optical microscopy to reveal distinguishing physical characteristics, such as unique structural features, and to observe cell movement. Cell migration studies, which are key to many fields, including cancer metastasis, are performed with temporal snapshots of cell position on a substrate. Fluorescence microscopy provides more detailed cellular information in that dyes are used that can highlight particular features of cells. For instance, the presence of metabolic activity within a cell can be observed using the proper dye, which in some cases offers better spatial resolution and easier implementation than electrochemical methods. Cell viability is also routinely measured using fluorescent live/dead assays. Fluorescent probes exist for hundreds of cellular characteristics, but they

suffer from three main drawbacks. First, most dyes cannot be used over multiple timepoints—cells often need to be fixed in order to be stained. Second, fluorescent dyes are subject to photobleaching. Third, probes for proteins that are expressed in very small quantities may not give a detectable signal. Semiconductor quantum dots with protein and fluorescent tags address some of these issues but their toxicity remains an issue for deployment *in vivo*.

Cell phenotype can also be determined by DNA array chips through the identification of mRNA. Proteins are synthesized from translation of the mRNA sequence into a specific amino acid polymer. Measurement of mRNA expression levels in cells is an indirect way to determine probable protein expression. DNA array chips can rapidly provide a global snapshot of cell activity. However, the sequences of interest must be known to some degree (to provide a complimentary binding site). DNA chips also provide only a single snapshot of which genes are up- or down-regulated. Multiple timepoints of cell state, which would be more valuable to biologists, are tedious to measure with current techniques.

The proteome, the protein catalog expressed by a cell, is quantified by lysing the cell and detecting the complement of expressed proteins. Mass spectrometry combined with various chemical separation techniques is used to determine the partial proteome of cells, although larger volumes are required to identify low-concentration proteins. Comprehensive proteome analysis strategies still remain elusive. Fluorescently tagging of proteins is a way to identify protein expression and interaction within cells but this method suffers from the drawbacks mentioned previously.

The secretome is the catalog of all proteins secreted into the extracellular environment. There is a growing realization among researchers of its importance in determining and regulating cell behavior [36]. Also important is the uptake of proteins and other small molecules by cells. With the exception of well-known proteins like insulin or certain neurotransmitters, no widely accessible techniques exist to readily identify or characterize the secretome of cells.

Electrochemical methods have historically been used to determine the metabolic state of a cell by measuring the uptake or secretion of metabolites and waste such as O_2, CO_2, glucose, and NH_4. The state of electrically active cells, such as neurons, is measured by electrochemically detecting intracellular ion concentrations. Transport of small molecules across the cell membrane is an active area of research that impacts both basic cell biology and the development of pharmaceuticals. Broadly speaking, electrochemical measurements rely on electron transfer at an electrode surface to generate a current that can then be recorded. Electrochemical measurements are attractive because electrodes can be miniaturized and integrated with semiconductor processes.

Disadvantages of electrochemical measurements include the impact of electrode degradation (e.g., through chemical reactions or adsorption of proteins) on signal quality and limitations on the types of molecules that can be monitored [37]. The types of molecules that can be electrochemically measured depend on the technique used and the electroactivity of the molecule. These issues will be addressed with further advances in surface chemistry.

Mechanical characteristics of cells include cell deformation, cell adhesion, and cell migration. Cell deformation studies are performed by aspirating cells into a micropipette tip and observing the deformation at a given pressure. Cell deformation is increasingly being viewed as a viable marker for cell behavior and has recently been studied as a metric for identifying differentiated stem cells and cancer cells [38, 39]. Cell deformation is also increasingly being used as a way to drive stem cells down specific differentiation pathways [40]. Cell adhesion studies seek to characterize how strongly a cell is attached to a substrate. Common methods for measuring adhesion include pulling on cells with optical tweezers or an atomic force microscope tip or even quantifying interference patterns on a flexible substrate [41].

Adhesion studies, along with cell migration studies, are used to determine how a cell generates force when moving and how it responds to external stimuli.

The drawback to all mechanical cell studies is the relatively low throughput and imprecise nature of the measurement tools. Large numbers of replicates are required to validate biological claims. The tedious nature of most cell-based mechanical experiments means that the throughput of discovery is relatively low and the cost per useful outcome relatively high.

Another important opportunity for bioelectronics is to study the ion channels needed for protein transport through cell membrane walls. These features are poorly understood but are critical to proper cell function and successful drug deployment.

Fabrication

Fabrication methods for the semiconductor industry are optimized for minimizing trace widths and feature sizes. Current high volume fabrication limits are 45 nm for minimum center-to-center distance between interconnect lines and 25 nm for physical transistor gate length. In addition, a wide variety of materials has been incorporated into fabrication processes with an eye towards increasing the performance and density of ICs, while lowering cost.

In contrast to IC fabrication, methods for building micro-devices used in biology, medicine, and security applications are not well established. In particular, reliability remains a concern [42]. Most micro-fabricated bio-electronic devices are either fabricated by small custom suppliers or are made in academic facilities. Examples of devices include multi-electrode arrays, integrated micro-fluidics sensors, and more recently micro-fabricated actuators to probe cellular function. Micro-fabricated biomedical devices are defined not so much by minimum feature size or density as in the IC industry, but rather by sensing and actuation functions [43]. Packaging is usually an issue with micro-fabricated biomedical devices because of liquid interfacing, biocompatibility, reliability, and durability.

While semiconductor technologies can be used to fabricate incredibly small features, they are not yet able to fabricate complex biosensors in bulk [44]. A biosensor is defined as any sensor that uses a biological element. For example, sensors that incorporate antibodies to bind specific molecules for detection are biosensors. A sensor that measures the pH within a cell culture is not a biosensor but rather a biological sensor, since it is being used for a biological application but does not contain any biological components. Biosensors are necessary to achieve the level of molecular specificity required in certain applications (e.g., testing for blood-borne pathogens) [45]. For biosensors to become widely available, traditional semiconductor fabrication approaches must be integrated with biotechnology manufacturing practices. In the meantime, biological sensors can be integrated into current microfabricated devices, but they often are not an appropriate substitute for biosensors.

Device/Material Biocompatibility

Broadly speaking, a biotic/abiotic interface is any interface at which a biological molecule or component (e.g., cell) comes in contact with a non-biological surface. The field of biomaterials is concerned with studying this interface—namely, the biocompatibility of artificial surfaces with tissue, cells, and molecules. Significant effort is being put into creating materials with improved biocompatibility and that will elicit the appropriate host response [46]. However, the field is not based on first-principles, and often discovery of better biomaterials relies on brute-force methods of screening instead of design. Biomaterials research can broadly be organized into studying two surface properties: composition and texture.

Surface Composition

The chemical composition of a material is a major contributor to how well it will support biological systems. Devices' surfaces can be decorated with a variety of molecules that will minimize the body's immune response or modulate the behavior of cells *ex-vivo*. Many basic materials like titanium and some polymers/co-polymers are well-known biocompatible materials. Incompatible surfaces can be modified via covalently bonding molecular species, adsorbing proteins or oxygen plasma treatment to elicit a biocompatible response [12]. State-of-the-art materials include bio-compatible polymers such as poly lactic-co-glycolic acid (PLGA) [47]. Current research is also aimed at decorating polymers with the appropriate signaling molecules to elicit a specific cellular response [48]. Surface composition is critical for the development of biosensors. The biochemistry associated with effective binding of biomolecules to electrode surfaces is a research area that is relatively new but critical to the success of any bioelectronic measurement method.

Surface Immobilization

The biochemistry associated with effective binding of biomolecules to electrode surfaces is a research area that is relatively new but critical to success of any bioelectronic measurement method.

Surface Texture

The topology of a surface also dictates cell behavior. Evidence suggests that restricting biocompatible regions into particular geometric features or submicron roughness can control cellular behaviors [49]. Cell viability, cell differentiation, and axonal outgrowth are just a few of the cellular behaviors that can be directed through surface texturing. A significant challenge in controlling surface texture is the fabrication of complex or non-planar three dimensional surface topographies with submicrometer and nanometer scale dimensions. Such structures would enable increased surface functionality and more elaborate control over cellular behaviors. The fabrication of these complex structures is currently limited by conventional planar micro-fabrication and nanofabrication processes.

Power Sources

Batteries are currently the only readily available power source for implantable devices. Among battery technologies, lithium-ion provides the highest energy density at approximately 150 (Wh/kg) [30]. Batteries will likely be the main power supply for implantable and portable devices for the foreseeable future. Lithium-based batteries are used in implantable devices such as pacemakers and typically last 5 to 10 years depending on the type of device and the amount of use.

Implantable Devices

The cardiac pacemaker is implanted in 600,000 people per year [50]. Moore's law has been key to the success of modern pacemakers because increasing circuit density has allowed more features to be included in each device generation. The earliest pacemakers were simply oscillators that delivered pulses at a constant frequency. Modern pacemakers can sense when a person is climbing stairs or exercising, for example, and deliver the appropriate treatment. While semiconductor technology can be used to create implantable devices that are intelligent, the main obstacle remains biofouling. Biofouling affects pacemakers by altering the electrical properties of the electrodes attached to the heart, making sensing and actuation difficult. Future implantable devices (e.g., implantable devices for diabetes treatment) will also face biofouling challenges. New methods will need to be developed to overcome, or attenuate, sensor fouling.

The key issue is the interface between living tissues and man-made implantable devices. Cochlear implants, retinal implants, implantable neural electrodes, muscle implants, and other must perform

their functions by directly interacting with the respective organs to elicit the sensation of sound, sight, neurological functions, and muscle contractions, respectively. The artificially generated electrical pulses in each of these cases must be engineered within the context of the physiological system and its biological characteristics. The state-of-the-art approaches are far from representing a seamless interface, in which the implantable devices would mimic or restore the deteriorated or lost neurological functions that they are intended to replace or augment. Because of the high level of sophistication of digital electronics, the core of the signal processing in each of these cases is far more advanced than the front-end analog interface with the biological world, which is orthogonally different from the digital domain.

7. Emerging Trends

Emerging trends will also drive new developments in the bioelectronics field. The following areas were identified during discussions at the Bioelectronics Roundtable held in November 2008.

Systems Biology

- Systems biology is the study of biological complexity through the systematic study of complex interactions in biological systems. The promise of systems biology is that it will revolutionize medicine through a quantitative understanding of cellular behavior. The following technical challenges were identified by The Institute for Systems Biology, a world-class research institute that focuses on systems biology, and are worth quoting directly [51].

- Sensitive tools for identifying and quantifying the concentrations, fluxes, and interactions of various types of molecules at high resolution both in space and time are required. These dynamic measurements must be made in the appropriate context of specific networks, cells, and organisms.

- Miniaturized and automated micro-fluidics/nanotechnology platforms, capable of parallel multi-parameter analysis that integrates operations such as cell sorting and single-cell gene and protein profiling, are necessary. In addition, nano-mechanical and nano-electronic devices will also permit the quantification of the forces and kinetics associated with protein/protein, protein/DNA, and protein/drug interactions.

Imaging will need to be extended to dynamic, spatial, multi-parameter measurements within single cells. Furthermore, hypotheses must ultimately be tested in whole animals. Such testing requires advances in molecular imaging, ranging from bioluminescence and fluorescence to positron emission tomography (PET) and magnetic resonance imaging (MRI).

Many of the key challenges of systems biology are the same as for bioelectronics, as identified in Section 5. These challenges center around creating better ways to measure and quantify cells and biomolecules. Thus, the development of the systems biology field is directly linked to the growth of bioelectronics.

Forensics

There is a significant need for advancements in DNA typing for forensics applications. In particular, a backlog of over 800,000 DNA samples remains untested throughout the nation at the state and federal level [52]. Research groups are beginning to develop miniaturized devices targeting DNA analysis for forensics applications [53, 54]. New lab-on-a-chip devices that can perform rapid DNA analysis will help address this backlog, for example by allowing law enforcement officials to conduct testing at the scene of the crime. Lab-on-a-chip systems require much smaller sample volumes than traditional DNA analysis

protocols and the amount of sample handling required is minimized by incorporating processing procedures, thus reducing contamination and chain of custody issues.

Homeland Security

The 9/11 terrorist attacks added to the urgency of developing a new generation of sensors capable of detecting chemical and biological warfare (CBW) agents. Although sensor development has been ongoing for years, a deployable sensor network that can accurately discriminate among multiple CBW agents does not yet exist [55]. New molecular recognition elements with improved specificity are needed for biological warfare agents [45]. Bioelectronics could improve the state-of-the-art by creating novel sensors that have increased specificity and sensitivity and that can be tightly integrated with semiconductor technology, making distributed sensor networks a reality.

Another need in the homeland security arena is novel therapeutics in the event of a CBW attack. Bioelectronics could facilitate this too, by enabling new screening and detection tools for identifying promising drug leads. Among the areas in which bioelectronics can play an important role are:

- Detecting chemical or biological agents,
- Discovering the mechanism of action for agents, and
- Helping develop novel therapeutics, rapidly.

Medicine

Clinical interventions are increasingly dependent on advances in fields that impact bioelectronics. Areas of activity that incorporate these advances include implantable medical devices and point-of-care diagnostics.

Implantable micro-fabricated devices: Some implantable micro-fabricated medical devices treat disease by delivering drugs or restoring tissue function. Micro-fabrication has enabled the development of implantable MEMS-based drug delivery devices and commercial products have been developed using this technology (e.g., MicroCHIPS™, www.mchips.com) [24]. Implantable medical devices can also restore function by integrating with non-damaged tissue within an organ. Examples of current devices under development include the artificial retina, which records light intensity and then transmits this information to nerves within the retina [23], and the development of implantable nerve stimulation arrays. These devices promise to allow selective stimulation of particular regions of the brain to restore patient function (e.g., to enable neural control of prosthetic limbs) [56]. Nerve chips are implantable devices that interact directly with the human nervous system *in vivo* (e.g., cochlear implants). Future implants have a more ambitious objective, namely to restore the function of more complex organs. Advances in bioelectronics will result in new surface chemistries and signal processing capabilities that will positively impact the field of implantable medical devices.

Cochlear implants have been successfully deployed to 160,000 patients worldwide, restoring the ability to hear and understand speech in patients suffering from profound deafness. Its success is enabled by the availability of sophisticated digital signal processors and advances in the understanding of how electrical signals can encode both frequencies and loudness of sound, and with a microelectrode array implanted into the cochlea to stimulate the surviving spiral ganglion nerve cells. The electronics developed for 16-channel cochlear implants were borrowed directly to be used for retinal implants in the early-stage development, and thus first-generation retinal implants provided only 16 pixels of resolution. Now, with better understanding on artificially elicited sight, advanced skills of surgical procedure, and the broad of use of ultra-low-power electronics, retinal implants with pixel counts exceeding several hundred are being pursued.

Point-of-care diagnostics: Recent advances in lab-on-a-chip technology allow new systems to be developed that can provide diagnostic information in a handheld device. The most popular commercial example of this is the i-STAT® blood gas analyzer, (www.i-stat.com), which provides information on patient blood samples in a handheld unit. Point-of-care (POC) devices are being developed that can analyze patient samples for a variety of molecular biomarkers. Applications demonstrated include detection of circulating tumor cells [57], activation of signaling pathways associated with malignancies, chemical and biological warfare agent exposure [58], detection of food poisoning [59], and the detection of influenza [60].

8. Vision for Ten Years Out

Bioelectronics has the potential to changes peoples' lives, but key challenges must be overcome. Input from microelectronics and biotechnology experts, with a diversity of expertise, was gathered during a wide ranging discussion of long-term opportunities at the Bioelectronics Roundtable meeting.[d] Subsequently, the Roundtable participants were asked to identify the highest priority research need areas in bioelectronics from a list of over 90 topics. Topics identified by multiple respondents are shown below as "Highest Priority", whereas those that received fewer votes are listed as "Other Topics of Interest". A more complete summary of their responses may be found in Appendix D. Even if research is already underway, realization of any one of the technologies or capabilities listed below is envisioned to take ten years or more, based on the ten to twelve year innovation period that is typically required to take a novel research discovery through to commercialization [61].

Highest Priority Topics:

- Prosthetics, including tissue, i.e. artificial pancreas, and neural implants, i.e. vision, hearing, etc.
- Disease prevention, including neural degeneration, cancer, etc.
- Disease detection, including neural degeneration, cancer, etc.
- Lab-on-a-chip
- Electronic protein and DNA chips
- Imaging, including cellular
- Tele-monitoring
- Noninvasive physical sensing, e.g. vital functions
- Concentration of analyte and metabolites, etc.
- Real-time and time dependent measurements
- Single bio-molecule detection, including mass, size, chemical, optical, etc.
- Molecular recognition
- Signal processing algorithms
- DNA sequencing
- Nanofabrication (electrodes, devices), including patterning
- Thin film technology

Other Significant Topics:

- Health monitoring and compliance, real time
- Replacement tissue

[d] The Bioelectronics Roundtable agenda and list of attendees are shown in Appendix C. Copies of the Roundtable presentations are available at http://www.src.org/member/event/e003426/default.asp

- Drug Discovery
- Drug Delivery
- Drug dose, delivery verification
- Energy Scavenging
- Batteries
- Adverse effects
- Nano-delivery and sensing, such as long-term implantable glucose monitors
- Detection-transduction-signal processing
- High resolution (spatial & temporal) imaging (anatomical, functional, & molecular)
- Surface characterization
- Protein produced in cells
- Nanopores and nano-membranes
- Neural modeling
- Single-use disposable technologies
- Packaging
- Rehabilitation, including home healthcare and independent living
- Monitoring
- Cell Biology
- Novel power generators that will extend the life of implanted devices
- Real time, personalized medicine, via customizable chips

The highest priority challenges, listed above, were categorized within four cross-cutting topical areas: application drivers, devices, measurements and analysis, or technologies, as shown in Figure 8. These topical areas, and the corresponding challenges, align and map into the framework described in in the next section of this report.

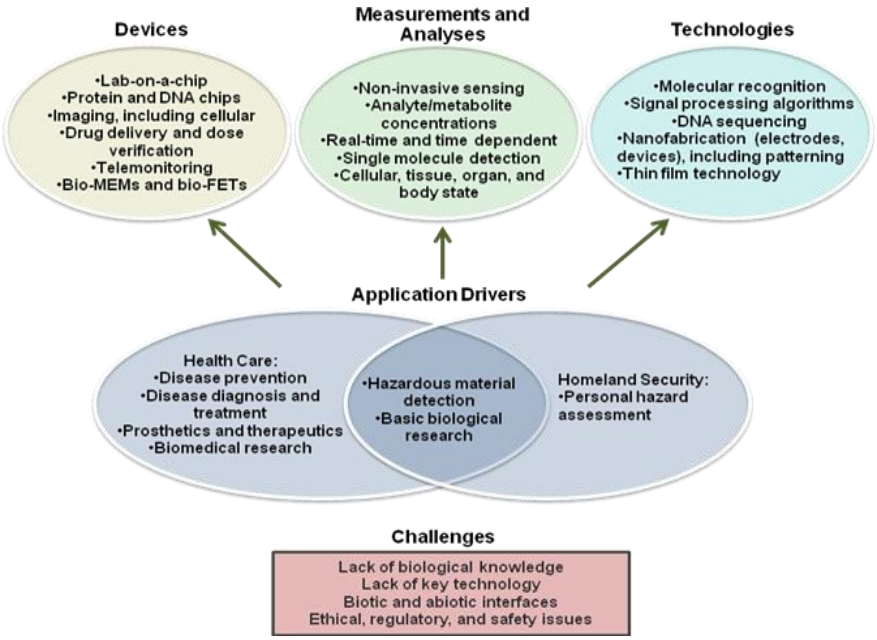


Figure 8: *Cross-cutting drivers address critical challenges, through the creation of new bio-electronic related devices, measurement capabilities, and technologies.*

9. Five-Year Major Goals

Specific clinical diagnostic ideas and devices that are currently being researched and exhibit potential for commercial use in five years include:

- Point-of-care micro-flow cytometry devices with high throughput and accuracy
- Micro-chemical cytometry (Cellular protein expression and activation) devices
- Devices for isolation and identification of rare circulating tumor cells (CTC)
- Massively parallel micro-fluidics immunoassays
- Point-of-care metabolomics (Miniaturized LC/ESI/MS systems)

10. Framework for Action

A framework for a 'Biolectronics Roadmap' is presented in Figure 9, based on input from the experts attending the roundtable. The framework provides a basis for a program that strategically addresses the research that is detailed fully in this report. The taxonomy in this framework can serve to organize and guide a research program. It consists of four themes: Drivers, Biomeasurements and Analyses, Devices, and Technologies.

Drivers: Drivers are clusters of targeted bioelectronic technology applications. Examples include:

- Health monitoring, e.g. for cancer detection, diabetes treatment, early stroke warning, etc.;
- Neural prosthetics, e.g., artificial retinas;
- Biochemical prosthetics, e.g. artificial tissues and organs.

Measurements and Analyses: Measurement plays a pivotal role in most bioelectronics applications, often at the sub-cellular level with spatial resolutions of less than 10 µm. Today, cell-related measurements typically are conducted *in vitro*, in artificial micro-environments. However, it often is a challenge to ensure that *in vitro* data are representative of actual cellular responses. A related challenge is to simultaneously measure multiple biological functions over time in an *in-vivo*-like environment. Significant efforts are needed to develop metrology tools and associated standards to characterize and continuously monitor cell dynamics at sub-cellular resolution.

Measurement targets include: high sensitivity, e. g. single biomolecule detection; speed, e.g. real-time monitoring of biochemical processes; and molecular selectivity.

Devices: Many bioelectronic devices will be needed to integrate a variety of signals (electrical, chemical, optical, etc.) to achieve the desired functionality, in contrast to conventional information processing devices, which primarily handle electrical signals. Moreover, complexity of the signals and the environment pose further obstacles. For example, monitoring of the electrical activity among multiple neurons represents a significant technology and circuit design challenge [62]. Typically, very weak signals must be processed, i.e. amplified, filtered, digitized etc., by ultra-low-noise circuitry placed very close to sensing electrodes. Thus, special digital signal processing (DSP) circuitries need to be developed, and are referred to as 'bioDSP' in Figure 9. Micro-scale energy sources, listed as 'µ-energy sources' in Figure 9, represent one of the biggest obstacles facing many high potential impact *in vivo* devices and applications, due to limited energy density or re-charging challenges [63]. Additionally, nanoscale delivery devices are important components of many bioelectronics applications, including on-demand drug delivery, biochemical prosthetics, and cell-to-cell chemical communications.

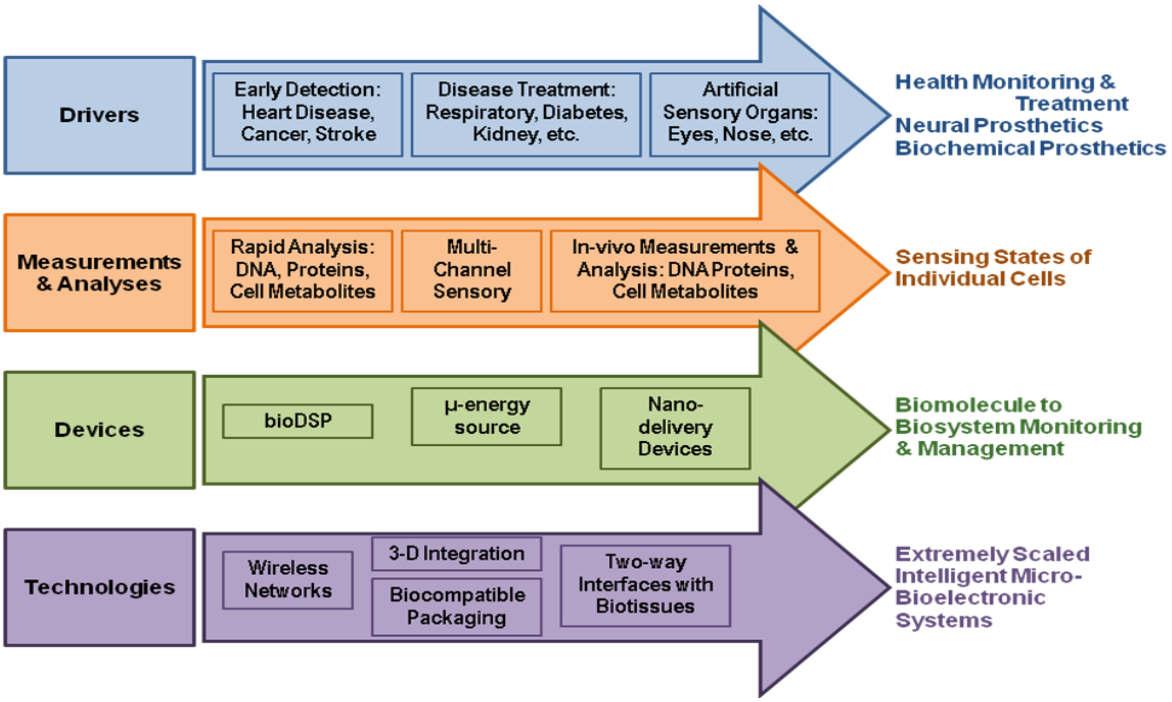


Figure 9. *A framework for the Bioelectronic Roadmap (temporal ordering of indicated R&D activities is not implied).*

Technologies: The realization of many bioelectronic application opportunities requires the development of a number of critical technologies. One example of an ultimate technology target would be extremely scaled intelligent bio-electronic micro-systems for *in vivo* operations. This requires the convergence of several technologies, such as 3D integration, wireless networks, and two-way interfacing with tissues such as neurons and other cells, as well as organs. In general, *technology* encompasses the fabrication and design processes required to construct a functional bioelectronics system; e.g., semiconductor manufacturing, computer-aided design, packaging and system integration, etc.

An illustrative example of a driver and related measurements, devices, and technologies is a personalized medicine system to monitor an individual's wellness, detect disease at the earliest stage, and measure the effectiveness of therapies. Using a systems biology approach, such an application will require the development of massively parallel bioelectronic sensor systems that have the capability of detecting, identifying, and quantifying a wide range of biomarkers (e.g., RNA, DNA, proteins, metabolites, growth factors, hormones, etc.). The convergence of the best attributes of semiconductor electronics (amplifiers, DSPs, memory, displays, systems integration, scalability) and biology (specific recognition of biomolecules, nanometer-length scales, self-assembly, and complexity) could someday lead to a true personalized medical device that can be implanted in the body. Similar systems could also be used in the research domain to provide a fundamental understanding of how single cells and populations of cells work.

11. Summary and Recommendation

Thirty microelectronic and biology related science and technology experts met in Research Triangle Park, N.C. in November 2008 and agreed that now is the time to act and develop a program that involves collaboration among industry, academia and government institutions. The discussion highlighted the diversity of applications and of research needed to realize them. As a next step, stakeholders from government, academia, and industry should jointly develop a detailed Bioelectronics Roadmap, which can serve to facilitate effective planning and management of bioelectronics research and development. Such an exercise would define and clarify projected application-specific research metrics and metrology gaps and needs; timelines for research, development, and prototyping; and emerging market and commercialization insertion opportunities. The International Technology Roadmap for Semiconductors (www.itrs.net) , and its Working Groups on Emerging Research Materials[e] and on Emerging Research Devices[f] may serve as useful guides for the proposed bioelectronics roadmap to accelerate innovations and commercialization in this exciting field .

It is clear that the eventual commercialization of bioelectronics will require expertise from both the biomedical and electronics industries. The biomedical device industry understands the healthcare market and its regulatory framework and business model. It also has experience in making products that are compatible with the body and that can be used safely and reliably when lives are at stake.

Traditionally, the semiconductor industry has focused on applications and products for which it can provide significant added value, for example in information and communications technologies. The semiconductor industry also benefits from its ability to manufacture complex nanoscale structures in large volumes. Clearly there are medical applications to which the semiconductor industry can add substantial value. However, the number and types of applications requiring significant volume production (and hence cost reduction), which are compatible with the business models and regulatory framework, need to be identified to induce interest by the semiconductor industry.

Today, the field of bioelectronics is poised for exponential growth. The Federal government's expertise in critical areas of science and technology, including sensors, nanoelectronics, and metrology should be harnessed and coordinated, along with expertise from academia and industry to firmly establish the United States as a leader in this high impact areas of research and development.

[e] Information available at http://www.itrs.net/Links/2007ITRS/2007_Chapters/2007_ERM.pdf

[f] Information available at http://www.itrs.net/Links/2007ITRS/2007_Chapters/2007_ERD.pdf

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Appendix A: Acronyms

DNA – deoxyribonucleic acid

POC – point of care

PCR – polymerase chain reaction

MRI – magnetic resonance imaging

CT – computed tomography

PET – positron emission tomography

MEMS – micro-electro-mechanical systems

mRNA – messenger RNA

ELISA – enzyme linked immunosorbent assay

IC – integrated circuit

GFP – green fluorescent protein

FRAP – fluorescence recovery after photobleaching

FRET – fluorescence resonance energy transfer

NMR – nuclear magnetic resonance

PLGA – poly lactic-co-glycolic acid

CBW – chemical and biological warfare

OTLC – open tubular liquid chromatography

CE – capillary electrophoresis

HPLC – high-pressure liquid chromatography

FIA – flow injection analysis

Appendix B: Bioelectronics in Academia, Industry, and Government

The following list includes centers, funding organizations, and other metrics of bioelectronics research activity; it should not be considered comprehensive.

Research Centers

Clemson University-Center for bioelectronics, biosensors, and biochips
http://www.clemson.edu/c3b/

Arizona State University – Center for Bioelectronics and Biosensors
http://www.biodesign.asu.edu/centers/bb/

Fraunhofer Institute for Biomedical Engineering - Molecular Bioanalytics and Bioelectronics
http://www.ibmt.fraunhofer.de/fhg/ibmt_en/biomedical_engineering/molecular_bioanalytics_bioelectronics/index.jsp

Seoul National University - Nano-Bioelectronics & SYstems (NBS) Research Center
http://nanobio.snu.ac.kr/eng/index.html

Degree Programs

New Jersey Institute of Technology - MS in Bioelectronics
http://www.njit.edu/features/sceneandheard/ms-bioelectronics.php

St. Louis University – Undergraduate focus in bioelectronics within electrical engineering
http://www.slu.edu/x26421.xml

North Carolina State University - Undergraduate focus in bioelectronics in electrical and computer engineering http://www.ece.ncsu.edu/research/bee/

Marquette University – Bioelectronics track within Biomedical Engineering
http://www.marquette.edu/engineering/pages/AllYouNeed/Biomedical/Programs/Bioelectronics.html

University of Hasselt – Bioelectronics and Nanotechnology degree program of the Master in Biomedical Sciences http://www.uhasselt.be/bioelectronics-master/english/

Government Programs

The Department of Energy has within its Office of Basic Energy Sciences multidisciplinary programs that fund projects at national laboratories and universities.
http://www.science.doe.gov/Program_Offices/BES.htm

The Food and Drug Administration (FDA) has programs related to the multidisciplinary aspects of applying bioelectronics to protecting the environment. The FDA Office of Science and Enginnering Laboratories has several divisions that contribute to bioelectronics.
http://www.fda.gov/cdrh/osel/researchlabs/

The National Insitutes for Health (NIH) has many intramural and extramural programs involving bioelectronics. Examples include:

National Institute for Biomedical Imaging and Bioengineering
http://www.nibib.nih.gov/Research/Intramural
http://www.nibib.nih.gov/Research/ProgramAreas

National Cancer Institute Network for Translational Research:
http://imaging.cancer.gov ; http://proteomics.cancer.gov

National Institute of Diabetes and Digestive and Kidney Diseases:
http://www2.niddk.nih.gov/AboutNIDDK/ResearchAndPlanning/Type1Diabetes/

National Institute of Standards and Technology (NIST) has bioelectronics projects in many of its laboratories, such as those involved with electronics and electrical engineering, chemistry, physics, materials research, and information technologies. Examples include:

http://www.eeel.nist.gov/812/nanobio/index.html
http://www.cstl.nist.gov/biotech/Biotechnology_Div.htm
http://www.itl.nist.gov/iad/894.05/biochange2005/Biochange2008-webpage.html
http://www.nist.gov/msel/biomaterials.cfm

The National Science Foundation currently supports bioelectronics research in the Electronics, Photonics, and DeviceTechnologies (EPDT) program.

http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=13379

Symposia

Industry-Academia Workshop on Bioelectronic System-On-Package (BioSOP) First Workshop: September 18, 2008 (GaTECH--Maysam) Conference cited by Nocoli in 1993.

http://www.prc.gatech.edu/events/biosop/index.html

Books

Willner, I. and E. Katz (eds.), *Bioelectronics: From Theory to Applications*, Wiley-VCH, Weinheim, Germany, 2005. http://www.amazon.com/Bioelectronics-Theory-Applications-Itamar-Willner/dp/3527306900/ref=sr_1_1?ie=UTF8&s=books&qid=1229293104

Market reports

SRI Consulting Business Intelligence -- Next-generation technologies: Bioelectronics

http://www.sric-bi.com/Explorer/NGT-BE.shtml

Venn Research, Inc. -- Worldwide Biosensor and Bioelectronic Market

http://www.marketresearch.com/map/prod/1343053.html

BCC Research - Biotechnology: Biosensors and Bioelectronics

http://www.bccresearch.com/report/BIO039B.html

Appendix C: Agenda and Attendee List for Bioelectronics Roundtable Meeting

Bioelectronics Roundtable
November 4, 2008
Research Triangle Park, NC

Agenda

8:30	a.m.	8:45	a.m.	Welcome	Dr. Rudy Juliano Univ. of North Carolina, Chapel Hill
8:45	a.m.	9:00	a.m.	NIST's Perspective on Bioelectronics	Dr. David Seiler NIST
9:00	a.m.	10:00	a.m.	Bioelectronics Overview: State of Science, Opportunities and Challenges	Dr. Glenn Walker, NCSU Dr. Mike Ramsey, Univ. of North Carolina, Chapel Hill
10:00	a.m.	10:30	a.m.	Break	
10:30	a.m.	11:00	a.m.	Vision of Science & Technology at the Biology-Electronics Interface	Dr. John Kasianowicz NIST
1:30	p.m.	2:00	p.m.	Nanoparticles and Cancer Therapy	Dr. Mary Napier Univ. of North Carolina, Chapel Hill
11:30	a.m.	12:00	p.m.	Technology Needs from a Biological Perspective	Dr. Laurence Clark NIH / NCI
12:00	p.m.	12:30	p.m.	Semiconductor Industry Perspective	Dr. Madoo Varma Intel Corporation
12:30	p.m.	1:30	p.m.	Lunch	
11:00	a.m.	11:30	a.m.	Aspects of Electronic Systems that Relate to Bioelectronics	Dr. Wentai Liu Univ. of California, Santa Barbara
2:00	p.m.	2:15	p.m.	Introduction to Roadmaps	Dr. Ralph Cavin Semiconductor Research Corp.
2:15	p.m.	4:30	p.m.	Discussion	Open Forum
4:30	p.m.	5:00	p.m.	Summary	Dr. Ralph Cavin Semiconductor Research Corp.

Bioelectronics Roundtable Participants

Name	Title
Christina Ahn	Director Faculty Enrichment Programs, Duke University School of Medicine
M. Ashraf Alam	Professor of Electrical and Computer Engineering, Purdue University
Anne Andrews	Associate Professor of Molecular Toxicology, Dept of Veterinary & Biomedical Sciences, Penn. State Neuroscience Institute, Pennsylvania State University
Kevin Arikado	Fellow, Tokyo Electron
Sankar Basu	Program Director, CISE/CCF Division, National Science Foundation
Ralph Cavin	Chief Scientist, Semiconductor Research Corporation
Laurence Clark	Branch Chief, Imaging Technology Development, Cancer Imaging Program, National Institute of Health/National Cancer Institute
Mark Cronjaeger	University Programs Manager, Medical Business Unit, High Performance Analog, Texas Instruments
Anand Dabak	Fellow, DSPS Research and Development Center, Texas Instruments
Barbara Goldstein	Associate Director, Electronics & Electrical Engineering Laboratory, National Institute of Standards and Technology
Daniel Herr	Director of Nano-manufacturing Sciences, Semiconductor Research Corporation
William Holton	Joint Professor of N.C. State University and University of North Carolina, Chapel Hill
Rudy Juliano	Professor and Associate Dean for Research and Graduate Education, UNC Eshelman School of Pharmacy
John Kasianowicz	Group Leader, Nano-Biotechnology Project, National Institute of Standards and Technology
Wentai Liu	Professor / Campus Director of NSF-ERC on Biomimetic MicroElectronics Systems, Baskin School of Engineering, UC Santa Cruz
Celia Merzbacher	Vice President Innovative Partnerships, Semiconductor Research Corporation
Renee Mitchell	Director, Business & Technology Incubator, Corporate Strategy & Business Transformation, Freescale
Troy Nagle	Professor and Founding Chair, Joint Department of Biomedical Engineering University of Chapel Hill and N.C. State University
Mary E. Napier	Senior Research Associate, Department of Chemistry, University of North Carolina, Chapel Hill
Faran Nouri	Director, New Business Development Group, CTO Office, Applied Materials
Michael Ramsey	Professor , Department of Chemistry, Center for Genome Sciences, University of North Carolina at Chapel Hill and Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and N.C. State University
James Ryan	Founding Dean of the Joint School of Nano-science and Nano-engineering of University of N.C., Greensboro & N.C. Agricultural and Technical State University
David Seiler	Chief, Semiconductor Electronics Division, National Institute of Standards and Technology
Dorel Toma	Director of U.S. Technology Development Center, Tokyo Electron US Holding
Yuji Tsukamoto	Senior Manager of Development Planning Department, Tokyo Electron
Madoo Varma	Director, Research & Business Operations, Integrated Bio-Systems Programs, Intel Research
Glenn Walker	Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill and North Carolina State University
Kevin Warnke	Systems Integration Manager, Abbott Labs
Sufi Zafar	Research Staff Member, R.J. Waston Research Center, IBM
Victor Zhirnov	Cross-Disciplinary Science Research Program Manager, SRC

Appendix D: Survey Results Describing the Relative Importance of Topics in Bioelectronics Research Areas

During the Bioelectronics Roundtable discussion, participants identified more than ninety topics of interest that were assigned to four broad categories: Drivers, device attributes, measurements, and technologies. Subsequently, participants were asked to identify top priority areas in each category by approval voting. The table below reflects the feedback to date. Items listed in Tier 1 and Tier 2 categories reflect those areas receiving the most votes (number is shown in brackets) by the roundtable participants. (Because of differing numbers of votes across the categories, the absolute number of votes separating Tier 1 from Tier 2 varies.) The highest priority 'Drivers' include prosthetics, disease prevention, and disease detection. The highest priority 'Device', 'Measurements', and 'Technology' related needs and interests focus on monitoring and analysis functions, which are aligned most closely with disease detection and prevention. Priorities identified for the latter two topics, i.e. 'Measurements' and 'Technologies', also would support an emphasis on prosthetics. This feedback appears to be self consistent and well aligned. Note that this information is not statistically meaningful and is intended to catalyze further discussion and serve as support for this report's recommendations.

Priority Drivers, Devices, Measurements and Technologies. Number of respondents who chose each topic (out of a total of 11 responses to date) is shown in brackets.

Category	Tier I	Tier II
Drivers	• Prosthetics, including tissue and neural implants, i.e. vision, hearing, etc. [9] • Disease Prevention, including neural degeneration, cancer, etc. [8] • Disease Detection, including neural degeneration, cancer, etc. [8]	• Health Monitoring and Compliance, Real Time [6] • Replacement Tissue [6] • Drug Delivery [5] • Drug Discovery [4] • Rehabilitation, including home healthcare and independent living [4] • Monitoring [4] • Cell Biology [4]
Devices	• Lab on a chip [7] • Protein and DNA chips [7] • Imaging, including cellular [6] • Telemonitoring [6]	• Drug dose, delivery verification [5] • Energy Scavenging [4] • Batteries [4] • Nanodelivery [4] • Adverse effects [4]
Measurements and Analyses	• Noninvasive physical sensing, e.g. vital functions [7] • Concentration of analyte and metabolites, etc. [7] • Real-time & time dependent measurements [7] • Single bio-molecule detection, e.g. in Lab-on-Chip environment (including mass, size, chemical, optical, etc.) [6]	• Detection-transduction-signal processing [5] • High res (spatial & temporal) imaging (anatomical, functional, & molecular) [5] • Protein produced in cells [5] • Surface characterization [5]
Technologies	• Molecular recognition [8] • Signal processing algorithms [8] • DNA sequencing [7] • Fabrication (electrodes, devices), including patterning [7] • Thin film technology [7]	• Nanopores & nanomembranes [6] • Neural modeling [6] • Single-use disposable technologies [5] • Packaging [4] • Neural modeling [6] • Single-use disposable technologies [5]