Summary Report for the

SRC/NSF WORKSHOP ON MICROSYSTEMS FOR BIOELECTRONIC MEDICINE

Workshop Dates:	April 12-13, 2017
Workshop Location:	IBM Conference Center, Washington, DC
Sponsors:	Semiconductor Research Corporation National Science Foundation IBM Corporation National Institute of Standards and Technology

Workshop Organizing Committee

Jamu Alford, Medtronic

Rashid Bashir, U Illinois

Rizwan Bashirullah, Galvani Bioelectronics

Chad Bouton, The Feinstein Institute for Medical Research

Andreas Cangellaris, U Illinois

Gary Carpenter, ARM

Bryan Clark, Boston Scientific

Brian Cunningham, U Illinois

Ronald Dekker, Philips

Timothy Denison, Medtronic

Barun Dutta, IMEC

Farzin Guilak, Intel

Ken Hansen, SRC

Juan Hincapie, Boston Scientific

Roy Katso, Galvani Bioelectronics

Richard Kemkers, Philips

Laszlo Kiss, Pfizer

Qinghuang Lin, IBM

Heather Orser, Medtronic

Jordi Parramon, Boston Scientific

Ajit Sharma, Texas Instruments

Jonathan Sporn, Pfizer

Usha Varshney, NSF

David Wallach, SRC

James Weiland, U Michigan

Michael Wolfson, NIH/NIBIB

Paul Young, Pfizer

Victor Zhirnov, SRC

Executive Summary

Bioelectronic medicine will revolutionize how we practice medicine and dramatically improve the outcome of healthcare. It employs electrical, magnetic, optical, ultrasound, etc. pulses to affect and modify body functions as an alternative to drug-based interventions. Furthermore, it provides the opportunity for targeted personalized treatment in closed-loop control system.

This document is based on the input from the Workshop on Microsystems for Bioelectronic Medicine that was held on April 12-13, 2017 at IBM Conference Center in Washington, DC. The workshop emphasized the potential for commercial and societal impact of electroceutical technologies. Workshop participants included representatives from Industry (Biomed, Pharma, and Semi), Health Providers, Academia, and Government Agencies.

Industry:	GSK/Galvani, Medtronic, Boston Scientific, Intel, TI, IBM, Novartis, Mallinckrodt, Philips, ARM, ON Semiconductor, CooperVision, 3M, Inspire Medical Systems, SRC, IMEC
Health Providers:	Northwell Health
Universities:	TU Delft, Harvard U, Stanford U, UC Berkeley, Duke U, U Michigan, UPenn, National U Singapore, U Illinois, CMU, Georgia Tech, UT Dallas, U Delaware
Government:	NIH, NSF, DARPA, FDA

Technical discussions at the workshop covered all aspects of next-generation microsystems for bioelectronic medicine, including electronic signal treatment for therapeutic applications, fundamental physics limits of essential components of bioelectronic devices, and interfaces between biological systems and artificial devices. The overall presentations and discussions create a foundation for the Bioelectronic Roadmap. The consensus of the workshop discussions was that a collaborative multi-disciplinary research program is instrumental for the acceleration of development of next-generation bioelectromedical technologies.

Call for Action: *Innovation explosion is always at the intersection of two scientific disciplines*. It has become increasingly clear that information processing plays a central role in enabling the functionality of biological systems from the molecular level to the body scale. As such, a joint research effort of practitioners in medical and semiconductor disciplines is needed that will result in unprecedented breakthroughs in both the understanding of the nervous system, from central to peripheral, as an information system and the development of technology and electronics to interface with the nervous system. New developments in semiconductor technology will provide revolutionary tools and instrumentation for fundamental biological discovery and medical applications. Sophisticated software strategies will provide the logical "glue" between instrumentation, samples and the data sets they produce. A new collaborative research initiative is envisioned to harness and accelerate the synergies between the electronic and biomedical domains. Direct involvement of industry in fundamental research is a proven strategy for accelerating new discoveries. The proposed action is to build world-class research centers focused on the development of tools and technologies for Bio-Electronic Medicine. These centers will bring together investigators with expertise in neural stimulation, semiconductor circuits and systems, and modeling/simulation of biological systems. This will be a new, previously unexplored model of collaboration between several industries.

1. Introduction

This report summarizes the main findings and recommendations from the *Workshop on Microsystems for Bioelectronic Medicine* that was held on April 12-13, 2017 at the IBM Conference Center in Washington, DC. The Workshop featured contributions from a selected group of experts from industry and academia. The agenda and presentation materials can be found at https://www.src.org/calendar/e006247 (log-in required).

The first session examined fundamentals and application perspectives for bioelectronic medicine. The speakers stressed that the bioelectronic medicine is a complex and highly interdisciplinary endeavor. Expertise and know-how from biology, chemistry, engineering, ethics, materials science, medicine, neuroscience, regulatory compliance, etc. are needed and must be coordinated with more obvious electronics and engineered systems to ensure success. This complex bioelectronic medicine research requires coordination and collaboration to roadmap potential applications, fundamental understanding, technology needs, and timeline as well as identifying funding mechanisms. On bioelectronics side, there will have to be technology push to achieve the performance, such as low noise level in sub-microvolt level, and power levels amenable to sub-mm miniaturization of the systems, which are at or beyond current state of the art.

The second session provided an assessment of electronic signals treatment for therapeutic applications that may be able to replace/supplement existing pharmaceuticals methods. It has been stressed that electrical neuromodulation should be regarded as an information delivery process, that requires a deep understanding of the underlying mechanisms. Further, such a system needs to be bidirectional, e.g. sensing and stimulation in a closed look to achieve neural control of organs for future neuromodulation therapies. On the sensory side, both the electronics and computing platform will need to incorporate signal processing as well.

Session 3 discussed where we are today with mm scale computing systems and what are the challenges to further scaling the technology. The smallest electronic system demonstrated by 2017 is 1 mm^3 in volume, and scaling it further, e.g. to 100um^3 will require a major effort in circuit design, new energy sources and communication schemes. As it was highlighted in this session, the communication solution may shift from RF to other energy modalities such as ultrasonic for sub-mm system sizes due to fundamental physics. One can expect that the sub-mm systems will possess a considerable on-node intelligence to avoid communication costs, i.e. increased IQ/mm^3.

Interfaces between the electronic and biological systems is a challenging environment. A new materials base may be needed for future electronic implants, which would be biocompatible and support chronic stability. Session 4 focused on materials that have interesting electrical and mechanical properties that exhibit ‘smart’ or adaptable behavior in biological environment. Biological matter itself, even living cells, can be part of the machine. This critical interface issue provides many opportunities for new innovations and materials but also opportunities for collaboration between multiple organizations to solve these problems.

Session 5 addressed the question of an optimum trajectory for successful implementation of bioelectronic medical systems from research to commercialization. Developing microsystems

for therapeutic applications takes place in a heavily regulated environment which requires assessment of device safety and efficacy. Also, research and ultimately development and commercialization of bioelectronic medical devices requires multidisciplinary knowledge and skills, including neuroscience, medicine, systems engineering, materials, electronics, etc. Industrial consortia specializing in management of industry-relevant fundamental research offer a proper vehicle to accelerated innovation, workforce training, and transfer the research results to industry.

2. Fundamentals and Application Perspectives (Session I)

Session Keynote:

Rizwan Bashirullah, Galvani Bioelectronics

Bioelectronic Medicines: A Research Roadmap

Session Panelists:

Nitish Thakor, Natl University of Singapore

Implantable neurotechnologies: electrical stimulation and applications

Chad Bouton, Northwell Health,

Bioelectronic Medicine: Molecular mechanisms

Wouter Serdijn, Delft University

Challenges and perspectives of injectable neurostimulators

Guosong Hong, Harvard University

Chronic Interface at Single-Neuron Level

Session Chair:

Qinghuang Lin, IBM

Microsystems for Bioelectronic Medicine are envisioned as medical devices that employ electrical (or magnetic, optical, ultrasound, etc.) pulses to affect and modify body functions as an alternative to drug-based interventions (this group of emerging devices is sometimes referred to as 'electroceuticals' in the literature[1,2,3]). Research in the field is at its early stages, and it is expected that advanced semiconductor technologies will enable the development of novel devices and therapies. In contrast to the existing drug-based treatments, the emerging bioelectronic medicine will employ sophisticated closed—loop control strategies to modulate physiological (and psychological) regulations of human body for more precise and effective treatments.

Bioelectronic Medicines: A Research Roadmap

Bioelectronic medicine could revolutionize how we practice medicine and dramatically improve the outcome of healthcare. Major challenges of bioelectronic medicine are (1) understanding the underlying mechanisms of the electrical control of organs and precise mapping the electrical activity of nerves with functioning of different organs and (2) development of safe, low-power, scalable bioelectronic microsystems capable of two-way interactions with a high selectivity (in some cases down to a single axon precision).

Examples of the state of the art commercial neural interface products include deep brain stimulator by Medtronic and spinal cord stimulators by Boston Scientific. They are employed to treat tremor, movement disorder and chronic pain, respectively. These technologies are also often referred to as neurostimulation or neuromodulation technologies. Examples of other emerging commercial neural interfaces are for the peripheral and visceral nervous system, as evidenced by vagal stimulators by Cyberonic and Checkpoint.

In order to fully realize the potential of bioelectronic medicine, neuromodulation devices need to be improved considerably in the spatial and temporal precision and the adherence

throughout implantation. Device miniaturization is one of the key success factors of future bioelectronic medicine[4]. Next-generation neuromodulation devices are expected to improve three key areas:

- ***Sensivitivity,*** i.e. able to sense signals from neurons in the cortex and nerve fascicles and fibers in the periphery, in a highly sensitive manner against other background interference
- ***Selectivity,*** i.e. able to precisely target nerves near visceral organs central in chronic diseases with clear endpoints
- ***Responsiveness,*** i.e. form closed-loop around recording of neural signatures and detection of biomarkers (several communicating devices may be needed for the close-loop biomarker detection and stimulation)
- ***Acceptance,*** i.e. miniaturized low power devices that can be delivered with minimally invasive implantation thereby reducing patient burden and improving access

An essential task in developing future bioelectronic medicine technologies is preparing a comprehensive technology roadmap with participation of broader community[5]. The roadmap should address three major components:

1. Creation of a visceral nerve atlas
2. Advancement of neural interfacing technology
3. Early establishment of therapeutic feasibility

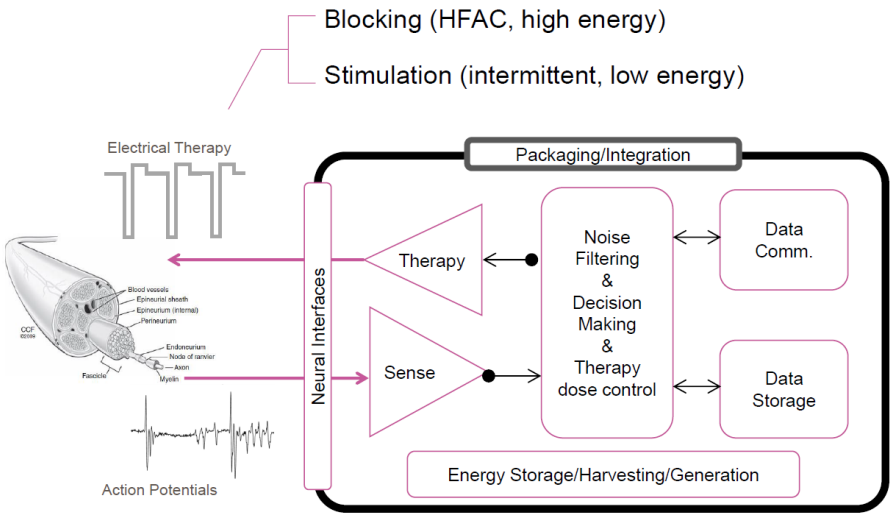


Fig. 1.1. A generic block diagram of an implantable neuromodulation device[4].

A generic block diagram of an implantable neuromodulation device is shown on Fig. 1.1. The neuromodulation system technology needs (Fig. 1.2) include:

- Miniaturization of implantable devices requires new technologies at different levels
- Precise sensing and control of neural signals
- Low-power, low-noise, & low-voltage circuit design
- Efficient energy harvesting / generation, storage and delivery in a small form factor

- High bandwidth and low-power two-way communication
- Biocompatible and flexible packaging technologies,
- Safety and long-term reliability of implantable neuromodulation device, etc.

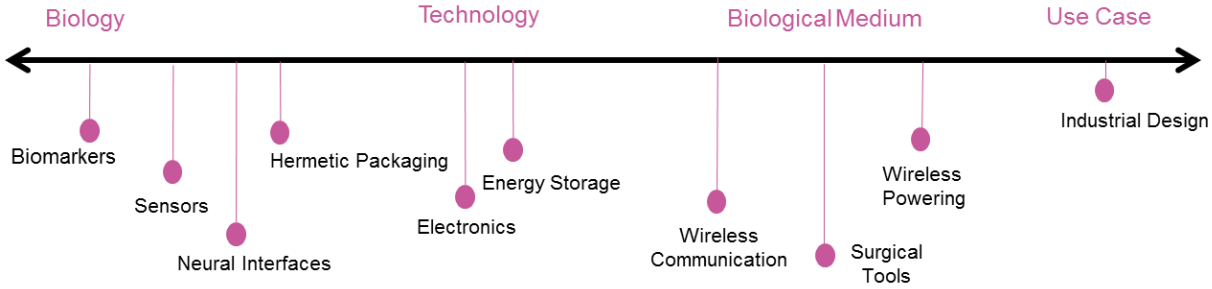


Figure 1.2. Neuromodulation system technology needs[4]

In most application scenarios, implantable neuromodulation devices need to operate under severe energy constraints due to overall system size limitations, difficulties of deep-tissue power transfer and safety[6]. Therefore, novel low power circuits are needed both in stimulation/blocking[7] and signal processing[8] to reduce the overall energy consumption of the closed-loop therapeutic neuromodulation devices. In addition, energy storage, wireless powering and communication plays a critical role in the usability of the devices (e.g. the way the patient interacts with the device to deliver therapy) and burden placed on the patients (e.g. frequency of charging and impact on lifestyle).

To develop a comprehensive Roadmap for Bioelectronic Medicine, joint efforts of experts from different disciplines are needed: biology, chemistry, computer science, electrical engineering, materials science, medicine, neuroscience, physics, semiconductor technology, etc. are needed. Advances in semiconductor industry offer critical enabling technologies for bioelectronic materials, components, subsystems and processes. These include cutting edge semiconductor technologies that are state of the art, working at the limits of power, noise, power harvesting and bidirectional data communication and other performance metrics. In addition, signal processing, data analytics, privacy, security and ethics should be a substantial part of the roadmap. Ancillary technologies such as surgical tools, visualization technologies, biomarker research, etc. should also be considered. Finally, establishment of a multidisciplinary workforce to drive research is a key success factor for Bioelectronic Medicine[4].

Implantable neurotechnologies: electrical stimulation and applications

Currently, neurostimulation using electrical pulses is the popular mode of neural interface both in functional therapies and as an experimental tool for neuroscience applications. Neural stimulators are expected to play a profound role in implantable neural devices that treat disorders and help restore functions in injured or disabled nervous system[9,10]. Nerve stimulation is currently applied for the treatment of many conditions, such as the treatment of sensory, motor, bladder, respiratory or other visceral disorders[10].

In spite of a number of successful demonstrations, the field of implantable neurostimulators is far from being mature, and a massive research effort is needed to address a number of difficult challenges, some of which are outlined below.

Overall, we need to develop a set of technologies for "modulating" the nervous system. High-level research needs here include mapping the nerves that target different organs, nerve-organ interactions, separating the sensory and motor or anterograde and retrograde communications, establishing reliable interfaces to nerves from extra-neural electrodes to fascicles to fibers, and understanding electrical and chemical mechanisms of stimulation and blocking[10].

Another important direction for research is closed-loop stimulation using bidirectional interfaces that transfer information into and out of the nervous system as illustrated in Fig. 1.3[11]. At this point, our understanding of the use role and use of bidirectional interfaces for therapeutic applications is largely speculative and preliminary. Significant advancements are needed in the understanding of neural processing and coding so that input information is decoded, and more effective therapeutic closed-loop strategies so that output in terms of modulating the organ function can be developed[11].

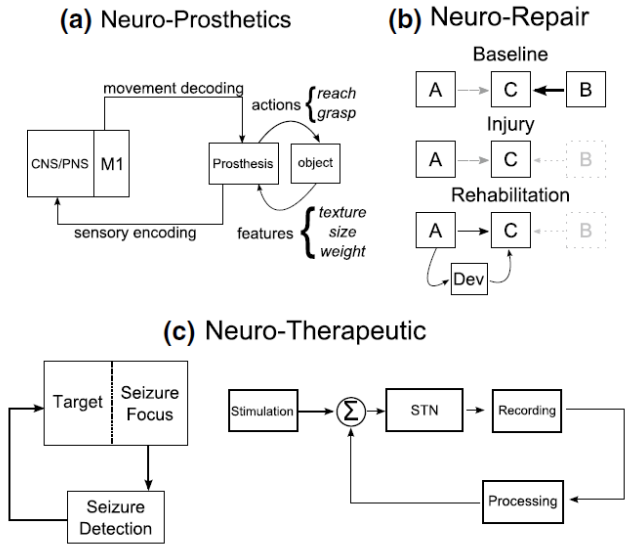


Fig. 1.3. Block diagrams of bidirectional neural interfaces[11].

"Chronic" physical interfaces are critical parts of technological advances that will be needed for implantable neural devices to become a widespread therapeutic means. Research tasks include hermetically sealed packaging, insulation, feedthrough, motion compliance, etc.[10]

Successful development of implantable neural devices requires multidisciplinary teaming of both engineers and biomedical scientists as well as university-industry partnership to facilitate benc-to-bedside transition. A roadmap for Bioelectronic Medicine should include numerical targets (the strawman target goals for bioelectromedical microcell discussed at the workshop are given in Appendix).

Bioelectronic Medicine: Molecular mechanisms

Two million adverse drug reactions are observed each year and they are 4th leading cause of death, ahead of pulmonary disease, diabetes, automobile deaths[12]. What if we could treat disease and injury without drugs? Bioelectronic Medicine can offer such opportunities, in fact neurological devices is today fastest growing segment of the medical device market[12], and many diseases can be, in principle, treated by a precise stimulation of nerves (Fig. 1.4).

The development of new tools and technology to tap into the nervous system should occur in parallel with understanding of molecular mechanisms of neural control. The key questions include:

- What is the target (both anatomical and molecular)?
- What is the neural pathway related to the specific target?
- What technology should be used to modulate the pathway?
- What technology should be used to acquire and decode the signaling of the pathway?

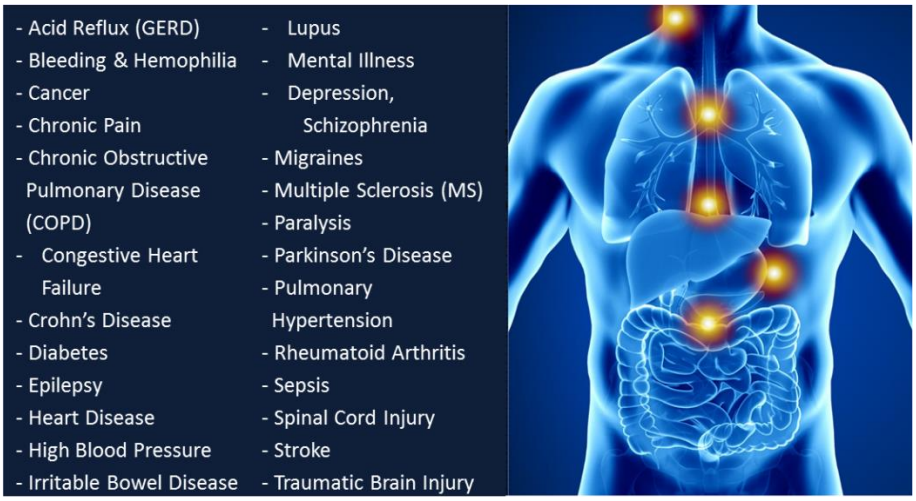


Fig. 1.4. Examples of diseases that are potential targets for Bioelectronic Medicine[12]

The above questions should always be considered in the context of clinical embodiment. One example of a successful therapy based on understanding of molecular mechanisms of neural control is non-physiologic (i.e. bioelectronic) control of inflammation as illustrated in Fig. 1.5[12].

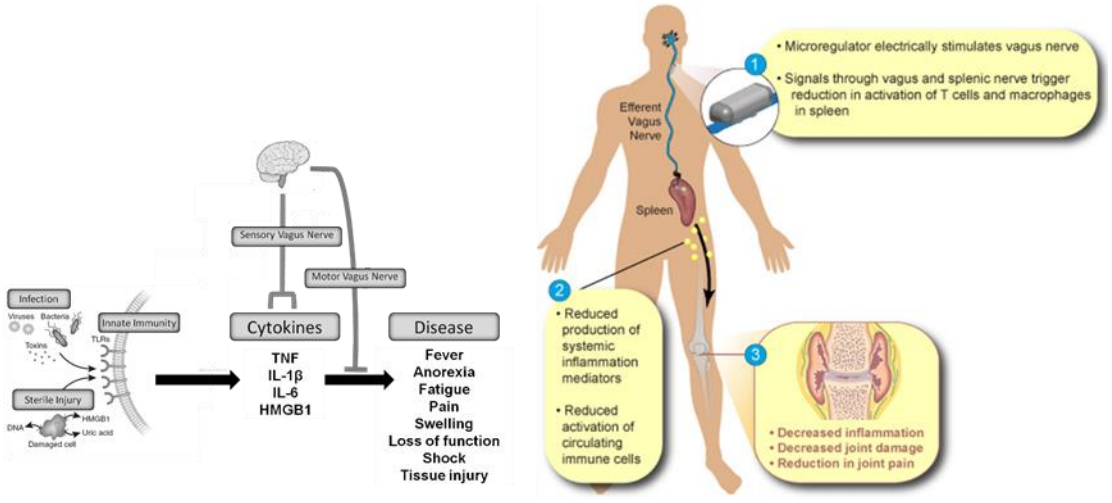


Fig. 1.5. Bioelectronic control of inflammation[12]

Challenges and perspectives of injectable neurostimulators

In addition to therapeutic neurostimulators that are implanted in the body by surgery, there are also injectable models that are implanted through a syringe, for example Bion™ from Boston Scientific[13]. The injectable neurostimulators under development promise extreme miniaturization[14].

The next generation of injectable neurostimulators should have form factor small enough to enable direct injection into nerve or muscle sites by means of middle-gauge needles, e.g., 17G (outer and inner needle diameters 1.473mm and 1.067mm respectively). The preferred size of the neurostimulator should be similar to that of the stimulating tissue, to cut down stimulating current and compliance voltage. It is also very important that the electrodes, core, and case should be soft, flexible, and bendable such that the device can conform to the body's anatomy and reach regions that were previously inaccessible[15].

Fig. 1.6 displays a conceptual architecture of the next-generation injectable neurostimulator that fits a cylindrical case 5mm long and 1mm in diameter (total volume 4×10^{-3} cm^3). To build ultra-small injectable neurostimulators, state-of-the-art nanometer complementary metal oxide semiconductor (CMOS) technology, combined with other nanotechniques and approaches, should be employed to miniaturize each of the functional building blocks of the neurostimulator[15].

Powering such an ultra-small implant to sustain a long stimulation time appears to be one the key challenges, and one key focus of future research should be on evolution of injectable or renewable power sources with high power density, novel injectable antennas to transfer data and energy efficiently in vivo[14]. Other important questions include:

- How do we minimize the size of the (active part of the) implant?
- How do we ensure proper recording, even while stimulating?
- How do operate the implant from a single supply?
- How do we ensure security of the device?
- Is there a need / room for optogenetic stimulation?, etc.[14]

It should also be noted that currently the injectable stimulators do not have the precision that will likely be needed for highly selective interfaces (this of course depends on the target nerve).

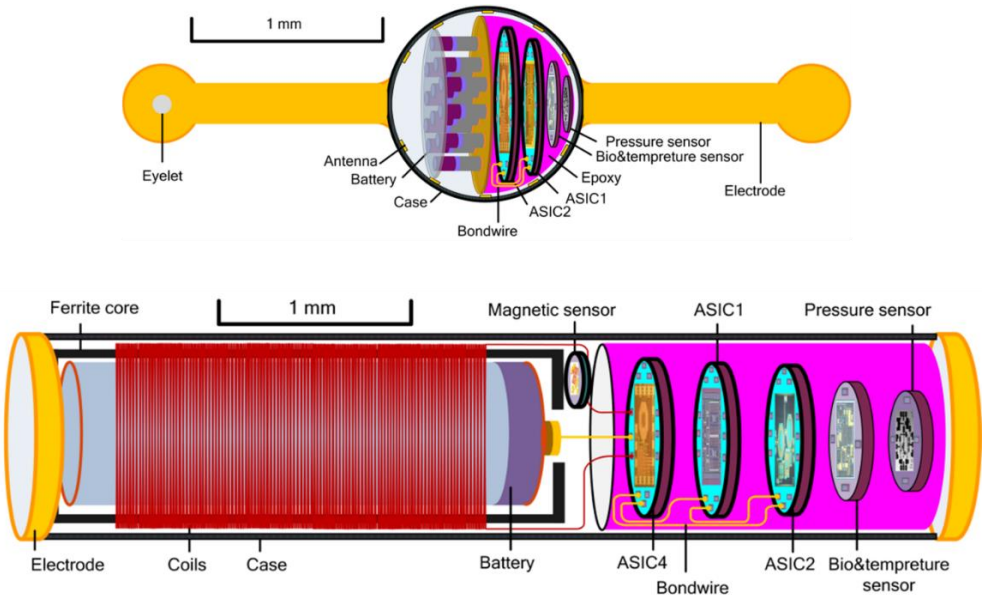


Fig. 1.6. Conceptual architecture of the new generation of injectable neurostimulators[15]

(Abbreviations: ASIC, application-specific integrated chip; FBBS, functional building blocks; ICL, inductively coupled link; InNS, injectable neurostimulator; RF, radio-frequency; RFEH, RF energy harvester.)

Chronic Interface at Single-Neuron Level

Stable in vivo mapping and modulation of the same neurons (centrally) or nerve fibers (in the periphery) over extended periods is critical to both neuroscience and medicine. While current electrical implants offer single-neuron spatiotemporal resolution, however, mechanical mismatch and chronic immune responses result in shear motion, glial scar formation and neuron depletion at neural interfaces, which leads to degradation of recording and stimulation capabilities typically over days to weeks[16].

Factors contributing to chronic instability of implanted probes include size and mechanical mismatch with neurons and neural tissue (Fig. 1.7) [17]. Associated problem is that of micromotion of the cortex, or large organ movement and deformation of the nerves in the periphery in awake, behaving subjects. Reducing the probe size or a compliant design may allow it to adapt to the motion to reduced deleterious immune responses, but these smaller probes still exhibit substantial mechanical mismatch due to highly different Young's modulus of current generation of probes and the neural tissue. Achieving stable long-term seamless neural-electronics integration is one of the Grand Goals of the Bioelectronic Medicine, and a key question here is whether we can blur the distinction between neuronal and electronic interface whereby such coupling and compliance would be natural?

To address these mechanical mismatch issues, a strategy towards "brain-like" electronics has been introduced based on 3D macroporous network structures with similar flexibility as the brain, which can reduce chronic glial scar formation and micromotion. A nascent technology, termed syringe-injectable mesh electronics with micrometer feature sizes comparable to neuron somata and effective bending stiffness values comparable to those of dense neural tissue, has been demonstrated[18]. Chronic recording and stimulation in live rodent and primate

brains with mesh electronics was demonstrated to have enabled consistent and reproducible recording from and stimulation of the same individual neurons in vivo for at least 8 months.

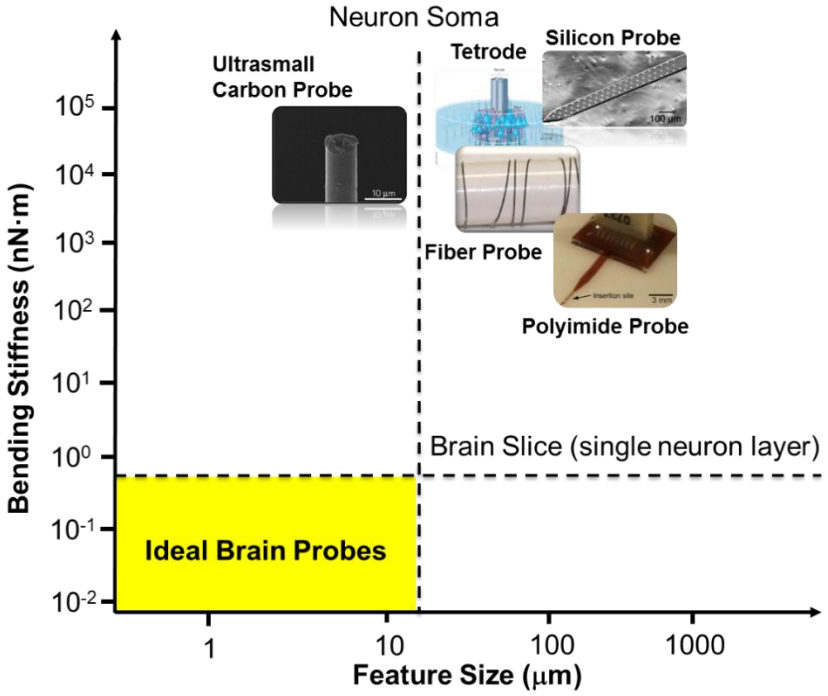


Fig. 1.7. Mechanical incompatibility between the nervous tissues and man-made electrode materials[17].

Session I Roundtable Discussion Summary

- Bioelectronic medicine is a complex and highly interdisciplinary endeavor. Expertise and know-how from biology, chemistry, engineering, ethics, materials science, medicine, neuroscience, regulatory compliance, etc. are needed and coordinated to ensure success.
- This complex bioelectronic medicine research requires coordination and collaboration to roadmap potential applications, fundamental mechanistic understanding, technology needs, timeline as well as funding mechanisms.
- While, in general, we want to miniaturize the devices to achieve greater patient access, we must be cognizant of possible tradeoffs imposed on other important aspects such as selectivity, responsiveness and patient burden.
- Partial List of Research Opportunities
    - Neuro circuit mapping and correlation to organ functions
    - Minimally or non-invasive delivery technique
    - Scalable, mechanically matched, and reliable lead/probe for bidirectional interactions with neurons or nerve fibers

- Hermetically sealed and low-power microsystems with sensing, date storage, computing and communication capabilities
- Power generation / harvesting, storage, and delivery
- Signal analysis and algorithms for decoding neural information and for bidirectional control
- Reduction of inflammation, gliosis, and other immune response and improving biocompatibility
- Innovative materials for safe and reliable neural interfaces

3. Electronic Signals Treatment for Therapeutic Applications (Session II)

Session Keynote:

Tim Dennison, Medtronic

From stimulators to restorative nervous system

Session Panelists:

Warren M. Grill, Duke University

Model-Based Design of Optimal Stimulation Signals for Bioelectronic Medicines

Jack Judy, University of Florida,

Bioelectronic Medicine Interfaces and Packaging

Barun Dutta, IMEC

Si Based Probes for Neuroscience and Implantables

Session Chair:

Bryan Clark, Boston Scientific

Almost all organs and functions in the human body are regulated by networks of neurons communicating through electrical impulses. Therefore, instead of targeting cells with a drug, an electrical pulse could be sent to alter the commands an organ receives, and thereby control its function. For a successful implementation of this concept, it would be highly advantageous to identify one or more reasonably well understood organs and disease states to demonstrate viability of treating disease with bioelectronics solutions. The approach could then be extended to a wider variety of diseases and different organs. The three key success factors here are: (1) Development of miniaturized and remotely controlled instrumentation, (2) Development of low-power, high-bandwidth biocompatible implantable wireless communication technology and (3) Creation of good test methods and approaches to optimize the new bioelectronic solution concepts.

From stimulators to restorative nervous system

Defining longer-term items of the Roadmap for Bioelectronic Medicine is a fearless forecast of the technology future. A Grand Mission for future-generation neuromodulation therapy is technology development for *rebuilding/functional replacement of nervous system to restore full health*[19].

The therapeutic purpose of neuromodulation is alteration of nerve activity through targeted delivery of a stimulus to normalize/restore functions of organs. Recent demonstrations of deep brain stimulation set a benchmark of the state-of-the-art of neuromodulation (referred here as to '*Neuromodulation 1.0*'). While very impressive results of neural stimulation have been reported, there is plenty of room for improvement. First of all, the *Neuromodulation 1.0* can be characterized by imprecise probe location that has empirically evolved from functional neurosurgery and classical lesioning targets, simple stimuli (constant or simple cycling, decoupled from physiology), tonic pattern of stimulation with an unknown mechanism of action, etc.

In order to bridge the gap from *Neuromodulation 1.0* to future therapy concepts, electrical neuromodulation should be regarded as an information delivery process, where understanding the underlying mechanisms of the neural control of organs is a key (Fig. 2.1). Thus, a central question for future neuromodulation therapies is how to modulate precisely signals in the nervous system to restore function. Key attributes include the following:

- Neural codes must be delivered to the right location
- Neural codes must contain the right pattern of stimulation
- Neural codes must be provided at the right time
- Neural codes must be personalized

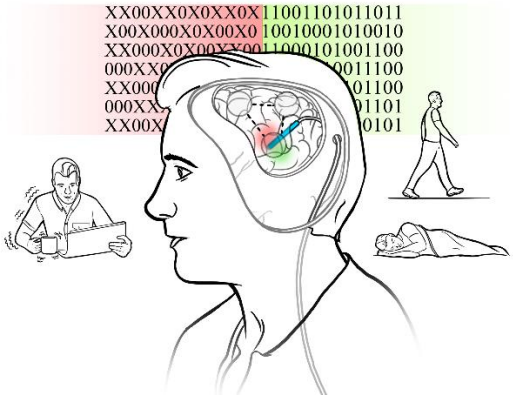


Fig. 2.1. Neuromodulation as information delivery[19]

A taxonomy of system engineering models for "duplex" neuromodulation devices for *Neuromodulation 2.0* is shown in Fig. 2.2[19]. In addition to direct therapeutic actions, the *Neuromodulation 2.0* devices will also augment human capabilities, and thus act as 'neural co-processors'. Two recent impressive demonstrations are described in the following examples. In one example[20], communication by a patient with late stage Amyotrophic Lateral Sclerosis (ALS) has been demonstrated through a fully implanted brain–computer interface. The implant, combined with automated decoding software, enabled communication via typing. The patient was able to use the system at home. In another example[21], deep brain stimulation was applied for treating Essential Tremor, the most common neurological movement disorder. For the first time, neural sensing of movement was used to enable or disable electrical stimulation for Essential Tremor; thereby reducing the total stimulation applied, and potentially extending the lifetime of surgically-implanted batteries (the batteries require surgical replacement). While the current development targets mainly clinical uses, in the future such brain coprocessors could assist in high-level human cognition or complex decision making[22].

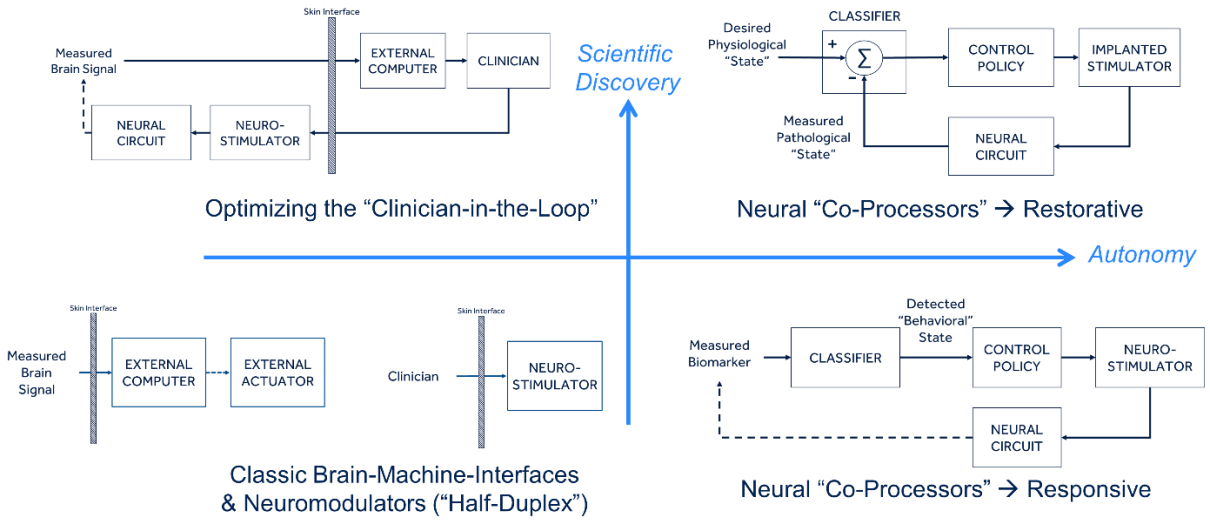


Fig.2.2. System engineering models for neuromodulation devices[19]

The complexity of the human nervous system and the challenge of providing a *Neuromodulation 2.0* systems requires multidisciplinary science and engineering skills, and building a full collaborative ecosystem is an important success factor. Public-private partnerships play an important role in research tool development and in translation prototypes to product (a recent example is the Brain Initiative[23])

Model-Based Design of Optimal Stimulation Signals for Bioelectronic Medicines

The energy efficiency of stimulation is an important consideration for battery-powered implantable stimulators[24,25]. Up to now, the stimulation parameters used for neurostimulation are selected empirically. For example, in case of deep brain stimulation (DBS), the signals consist of short-duration (60 to 180μs), high-frequency (typically 130 to 185Hz) pulses of electrical stimulation to ameliorate symptoms. The efficacy of DBS is strongly dependent on the frequency of stimulation: low-frequency stimulation (<50 Hz) is ineffective or exacerbates symptoms, whereas high-frequency stimulation produces symptomatic benefit. Unfortunately, high stimulation frequencies consume more energy, leading to frequent surgical replacement of battery-powered, implanted pulse generators (IPGs). IPG replacement surgeries are expensive and carry risks, including infection and misprogramming[26].

Earlier studies of the effects of the waveform shape on efficiency all concluded that the energy-optimal waveform shape is a rising exponential. However, in *in vivo* experiments, the rising exponential waveform was no more energy efficient than rectangular, ramp or decaying exponential waveforms[25]. Also, the current neuromodulation systems deliver a regular temporal pattern of stimulation, where inter-pulse intervals do not vary as a function of time. There are, however, indications that the effects of neurostimulation on symptoms depend both on the waveforms shape and temporal pattern of stimulation. Therefore the design of optimal waveform shapes and temporal patterns of stimulation (Fig. 2.3) based on realistic biophysics-

based models may increase the energy efficiency and symptomatic efficacy of *Neuromodulation 2.0* systems.

Model-based computational evolution (Fig. 2.4) can be used to design an optimized waveform and temporal pattern of stimulation that reduced the average stimulation energy and preserved efficacy. Genetic algorithms (GA) were designed and coupled to computational models of stimulation of mammalian myelinated axon[25] and basal ganglia[26] to optimize the waveform shape and temporal pattern of stimulation, respectively.

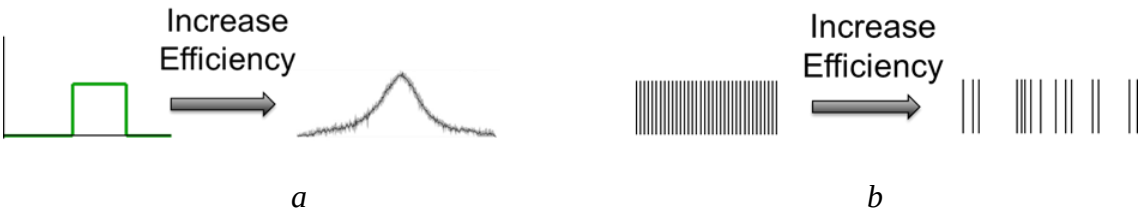


Fig. 2.3. Signal optimization for neuromodulation therapy to optimize stimulation efficiency: (a) waveform optimization; (b) temporal pattern optimization[24].

The GA-derived waveforms were more energy efficient than the conventional stimulation waveform shapes for all pulse widths (PWs). For PW $\leq$ 0.2 ms, the GA waveforms were slightly more energy efficient (<20%) than the other waveform shapes (Fig. 2.5). Between PW = 0.2 ms and 0.5 ms, the differences in energy efficiency between GA waveforms and the conventional shapes increased considerably, and these differences increased further with PW for all but the exponential waveforms. Further, for biphasic stimuli, typically used to minimize the probability of damage to the electrode or tissue, the GA-derived waveforms reduced stimulation energy by 50%.

Novel temporal patterns of stimulation were also designed via computational evolution[26]. The resulting optimized temporal pattern achieved efficacy at a low average frequency (45Hz) that

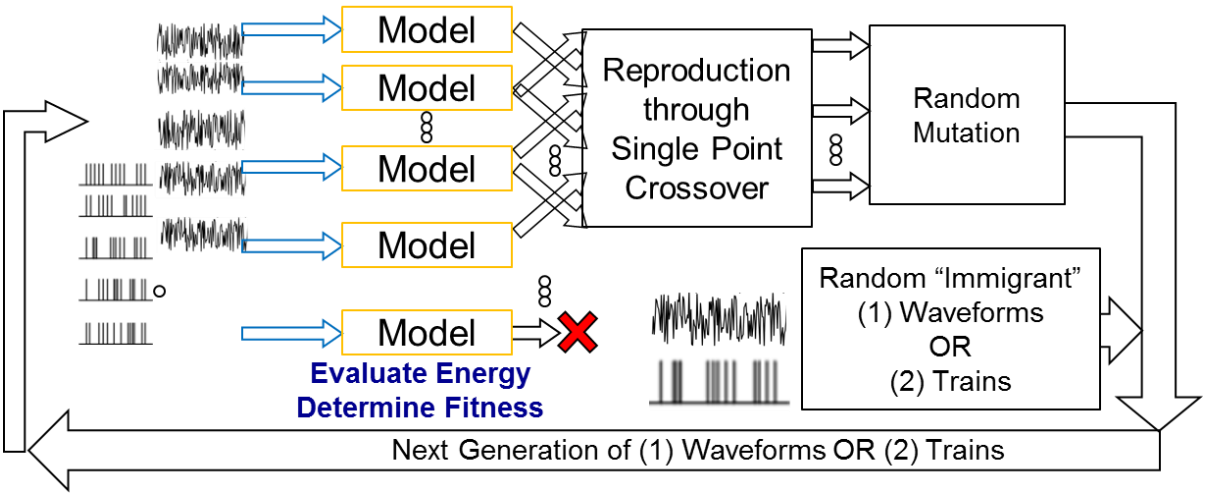


Fig. 2.4. Optimization of Waveform Shape and Temporal Patterns via Computational Evolution[24]

was not effective during non-patterned stimulation. This low-frequency optimized pattern of stimulation offers considerable energy savings over conventional temporally regular high-frequency DBS (typically 130 to 185 Hz)[26].

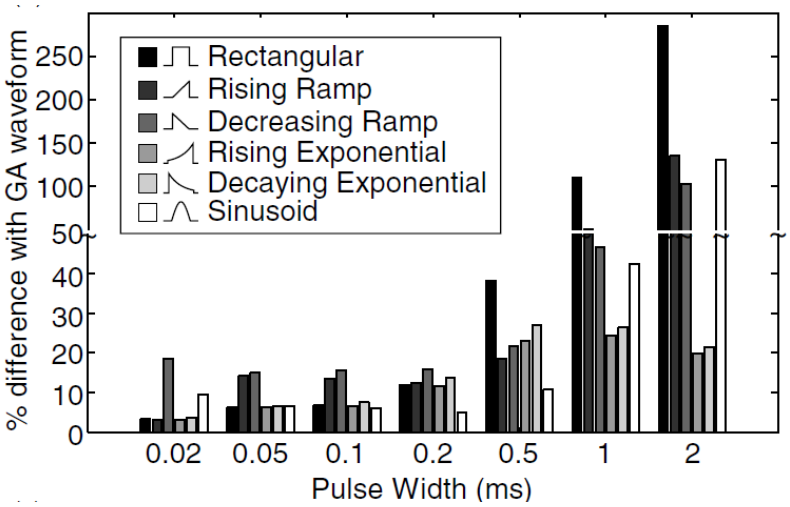


Fig. 2.5. Energy efficiency of GA waveforms compared to conventional waveform shapes used in neural stimulation[25]

Bioelectronic Medicine Interfaces and Packaging

Interfaces and packaging are among the key research topics for future neurotechnology products[27]. The existing Clinical Nerve Interfaces share several common characteristics:

- Low Channel Count
- Large Size (entire nerve)
- Low Selectivity
- Low Invasiveness

The overall interface challenges Include:

1) Surgical Access nerves varies tremendously with anatomical target.
2) Selectivity of stimulation and recording depends on application/target, and is not well understood. Off-target stimulation could result in undesirable side effects.
3) Scalability - Targeting/selectivity demands can result in decreasing interface size and channel count (size)
4) Invasiveness (driven by application, anatomical target, and selectivity requirements)
5) Reliability issues:
    i. Biotic: Tissue response (materials, scale, stiffness, surface chemistry/texture, etc.)
    ii. Abiotic: Device failures (engineering): channel isolation, hermeticity, fatigue, etc.

Since key signals for bioelectronic-medicine applications are chemical, on-electrical interfaces may play an important role in future generations of neuromodulation devices. However, today chronically implanted chemical sensors are more unreliable than chronically implanted neural recording.

The overall packaging challenges include:

1) Limited scalability, which impacts channel count density in leads, connectors, and packages
2) Leads tradeoffs for channel count, size, electrical properties, stiffness, fatigue resistance
3) Connectors represent a tremendous bottleneck for high-channel-count approaches
4) Miniaturized enclosures that would allow functional integration, high feedthrough density, power/data transfer, heat transfer etc; emerging clinical nerve packaging should exploit latest technology to push miniaturization.

Si Based Probes for Neuroscience and Implantables

Neurostimulation and recording of neural signals requires the use of high-resolution penetrating probes that would cause minimal tissue damage[28,29,30]. The probes should also be both biocompatible and wafer-scale CMOS Fab compatible.

For neurostimulation, a novel multi-electrode-optrode array has been reported, in which titanium nitride (TiN) electrodes was monolithically integrated with silicon nitride (Si_xN_y) waveguides[29] (Fig. 2.6). The probe contains 24 TiN electrodes and 12 Si_xN_y optrodes (6 blue - 450-490nm and 6 amber - 575-632nm[28]. Thanks to the small size of the blue optrodes (6 × 23µm), single neuron stimulation is possible.

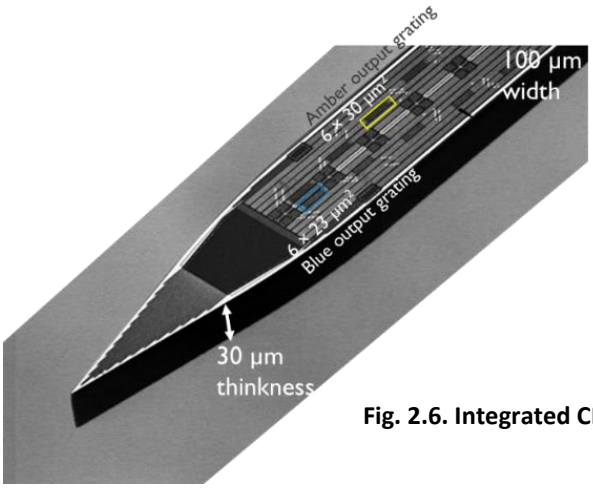


Fig. 2.6. Integrated CMOS-compatible multi-electrode-optrode array[28]

For recording of neural signals, high-density programmable digital probe has been demonstrated[28,30]. The probe was fully-integrated with CMOS circuitry for signal conditioning and digitization. It contained 966 selectable, neuron-sized electrodes (12x12µm^2) densely packed along a narrow (70µm) and thin (20µm) implantable shank. The entire recording pixel occupies 20x30µm^2 and consumes 4.7µW. The probe was fabricated in a 0.13µm SOI Aluminum CMOS technology, using biocompatible, low-impedance TiN electrodes. This example represents the highest reported number of electrodes in a single shank (966) r, the lowest crosssectional area coefficient (1.45µm^2), and the highest number of recording channels (384) integrated in the same probe substrate[30]. The total power consumption of the probe is 18.84mW (1.31mW at the shank and 17.53mW at the base).

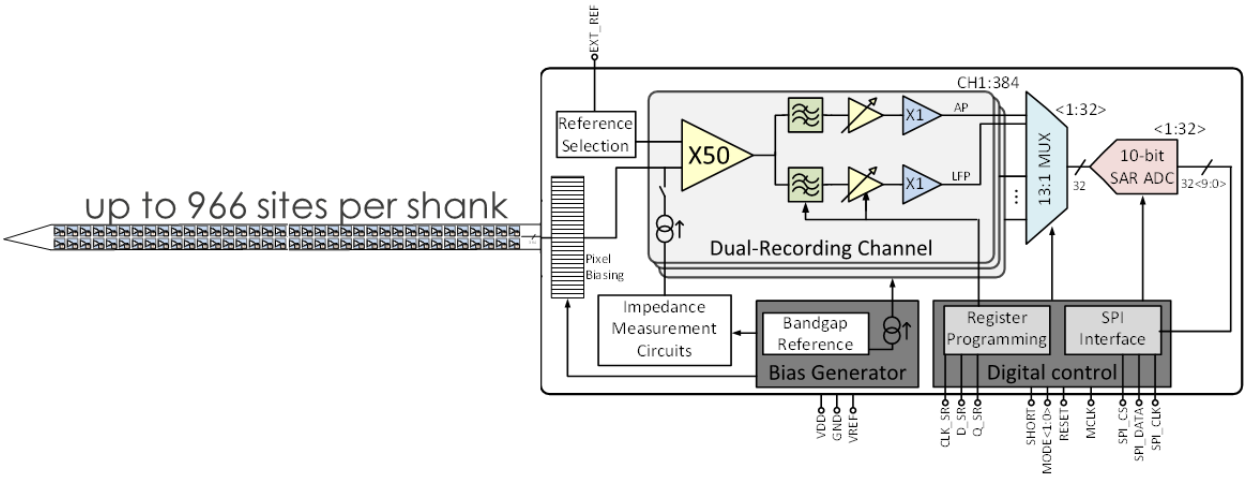


Fig. 2.7. High-density digital probe with integrated CMOS circuitry for signal conditioning and digitization[28]

Session II Roundtable Discussion Summary

- Personalization of neural stimulation offers an approach to improve efficacy
- Energy source is an important consideration in implantable neurostimulators design
- High density biocompatible rechargeable batteries are more important that direct wireless power transfer (there are different opinions on this subject)
- Realistic biophysics-based organ models of neural and organ systems are needed
- Overcome foreign-body response
- Optical stimulation holds a lot of promise
- Intelligent control system models are essential, for closed-loop control and critical to define circuit needs and specs.
- Exploit Latest technology to push miniaturization (epineural to intraneural)
- Need for holistic SOC or SIP design and not discrete component approach to the entire system to be successful
- Business opportunities for the semiconductor companies are not yet obvious (there are different opinions on this subject)

- Partial List of Research Opportunities
    - Reliable implantable chemical sensors integrated into into Bioelectronic-Medicine Systems
    - Stimulation protocol design based on realistic biophysics-based models
    - Scalable implantable connectors; connector Standards for Physician-Driven Interoperability
    - Wafer scale/chip scale bio compatible packaging critical for size and power budget and dissipation

4. Bioelectromedical Microcell – Replacing Drugs by Semiconductor Technologies (Session III)

Session Keynote:

Michael Wolfson, NIH

100 microns: Neurons and Semiconductors

Session Panelists:

Dennis Sylvester, U of Michigan

Ultra-Low Power Millimeter-Scale Systems for Bioelectronics Medicine

Ryan Neely, UC Berkeley,

Wireless power for implantable bioelectronics

Amin Arbabian, Stanford

Ultrasonically Powered Miniaturized Implantable Devices: A Platform Technology

Victor Zhirnov, SRC

Microsystems for Bioelectronic Medicine: Fundamental Limits of Scaling

Session Chair:

Gary Carpenter, ARM

We imagine that it is desirable and feasible to design an 'bioelectromedical cell' whose function, upon injection into the body, or being placed in closed proximity or on the body, is to interact with tissue/ living cells in order to determine the state of the cell and support certain therapeutic actions. We stipulate that for a precise action, a fully functional microsystem should be on the order of the size of a living cell, i.e. a cube of dimensions 100um x 100um x 100um. The purpose of this session was to examine the physical limits and trade-offs for each of the required system components and functions, given such severe volume limitations and constrained operating conditions. In particular, the bioelectromedical microcell cell must have the capability to collect data on the living cell, analyze the data, and make a decision; possibly communicate with an external controlling agent; and finally take corrective action. Such an electronic cell would need its own energy source, sensors, computers, data storage, and communication devices, integrated into a complete system. In this section, a thought problem is considered intended to force consideration of fundamental limits for energy sources, sensors, computing elements, communication components, and actuators as fundamental system dimensions are reduced to the sub-100 micron regime. Can we come up with Figures-of-Merit (FoM) for such a system?

100 microns: Neurons and Semiconductors

In order to understand the effects of neural stimulation with ~100μm spatial resolution it is instructive to consider the structure of a nerve[31]. For example, the Vagus nerve (cranial nerve X), is 5 mm in diameter that consists of many bundles (fascicles) of nerve fibers (axons). Axons range from 0.25 um to 25 um diameter. 80% to 90% of axons are afferent, i.e. they transmit sensory information about state of body's organs to the 'center'. Overall, there is more than 100,000 axon fibers in the vagus nerve (Fig. 3.1). Three main types of nerve fibers are described in Table 3.1.

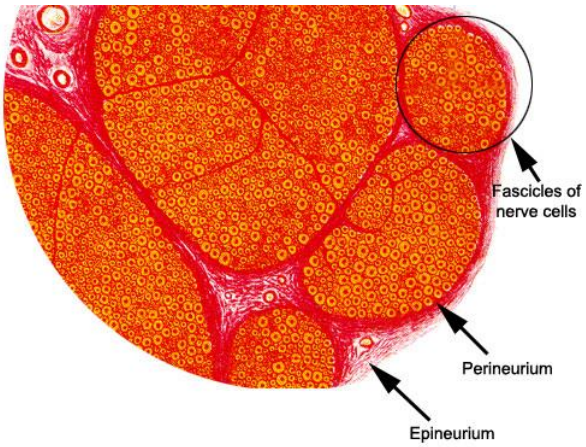


Fig. 3.1. Cross-section of a nerve showing individual nerve bundles and individual axons as distinct circular structures[32].

Table 3.1. Nerve Fiber Types[31]

Fiber Type	Diameter	# of axons in a 100μm nerve	Conduction Velocity	Myelinated	Nervous System
A	5-20 μm	~50	up to ~150 m/s	thickly	somatic (voluntary)
B	2-5 μm	~900	up to~15 m/s	thinly	autonomic (preganglionic)
C	<1-2 μm	~7800	up to~1.5 m/s	no	autonomic (postganglionic)

Biophysically plausible neural models that take into account realistic anatomical and neurophysiological data are important for our understanding of the principles and efficacy of high-resolution. For example, recently a hybrid neural model of the median nerve has been developed, starting from histological pictures and resulting in the solution of voltage distribution within the nerve (Fig. 3.2)[33].

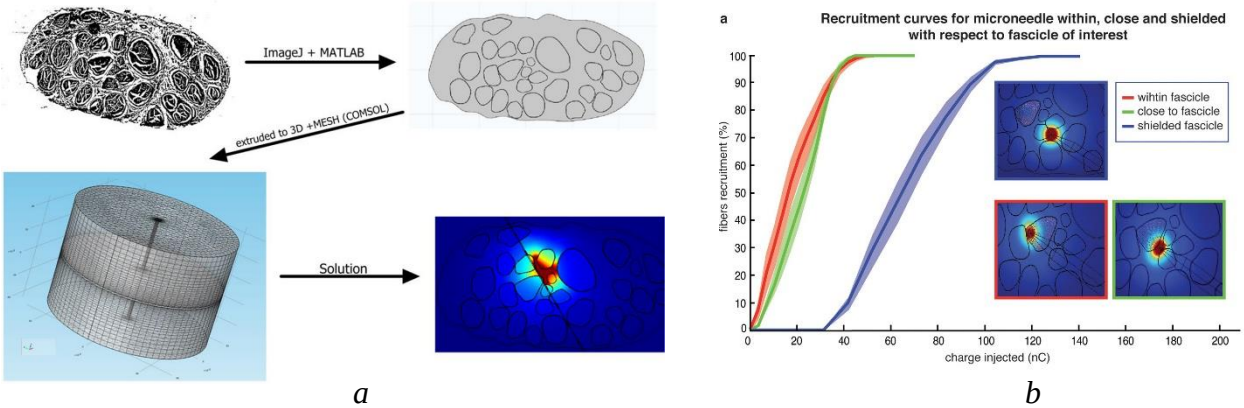


Fig. 3.2. Finite element model for the human median nerve: (a) Model flow, starting from histological pictures and resulting in the solution of voltage distribution within the nerve; (b) Calculated microstimulation effects[33]

What happens when neural stimulation occurs within a 100 µm^3 spot? This is an interesting open question, and the answer to a large extent depends on the location of the stimulus relative to branch points, axons of interest etc. In this example, about 1000 to 10,000 axons are in the accessibility range, but it should be taken into account that on average, 80-90% of the axons are afferent (sensory), which means they are not suitable for a direct stimulation (also there might be interesting opportunities for indirect stimulation).

The next pertinent question is scalability of semiconductor systems to the 100 µm^3 volume. While active semiconductor components can be scaled to the size of several nanometers, passive elements may represent a significant challenge for an extreme scaling. For example, there is inherent inductor size limitation (Fig. 3.3[31]) due to the fundamental laws of physics.[34] This has important implications for the choices of communication and power generation/delivery in small-size systems.

Finally the system-level integration considerations associated with the constrained operating conditions around biocompatibility include heterogeneous packaging, thermal issues, toxicity, device life span, electrochemistry, plasticity, targeting the right axons, regulatory issues etc.[31].

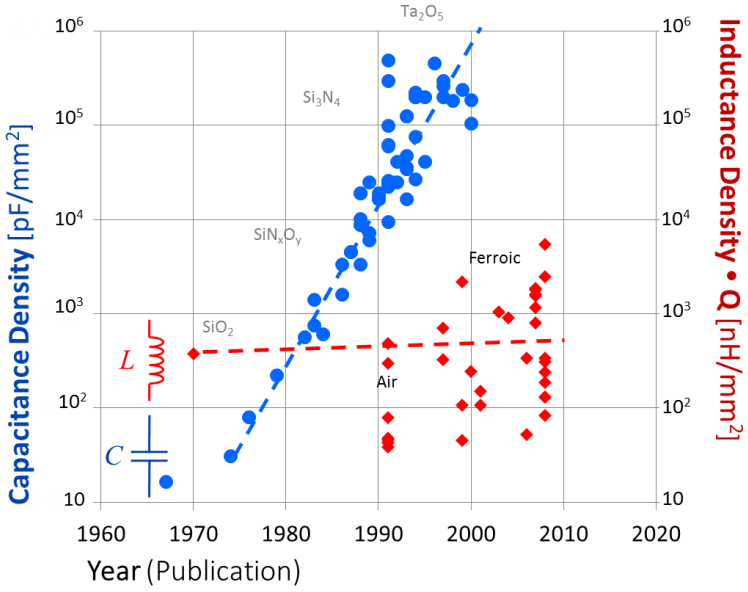


Fig. 3.3. Scaling trends of capacitive and inductive passive elements of integrated circuits[31]

<u>Ultra-Low Power Millimeter-Scale Systems for Bioelectronics Medicine</u>

Wireless sensor nodes (WSNs) will be essential elements for future health monitoring systems. An individual wireless sensor node typically contains sensors, hardware for computation and communication, and a power supply. There have been continuous efforts to address challenges for WSNs such as short lifetime, high power consumption, and bulky volume. The smallest node demonstrated by 2017 is M^3 (Michigan Micro-Mote) is 1 mm^3 in volume without encapsulation (1.1mm×2.21mm×0.4mm)[35]. M^3's layer structure and block diagram are shown in Fig. 3.4[36]. The M^3 capabilities can be summarized as follows[35]:

- Thin-film mm-scale battery, 2-20uAh
- Harvesting with indoor lighting (300lux)

- ADCs, CDCs, incident light measurement
- RF: short-range (sub-m) to medium range (20m)
- Embedded non-volatile memory
- Temperature sensing, pressure sensing, image sensing, audio sensing (ex: voice activity detection)
- Optical RX/TX

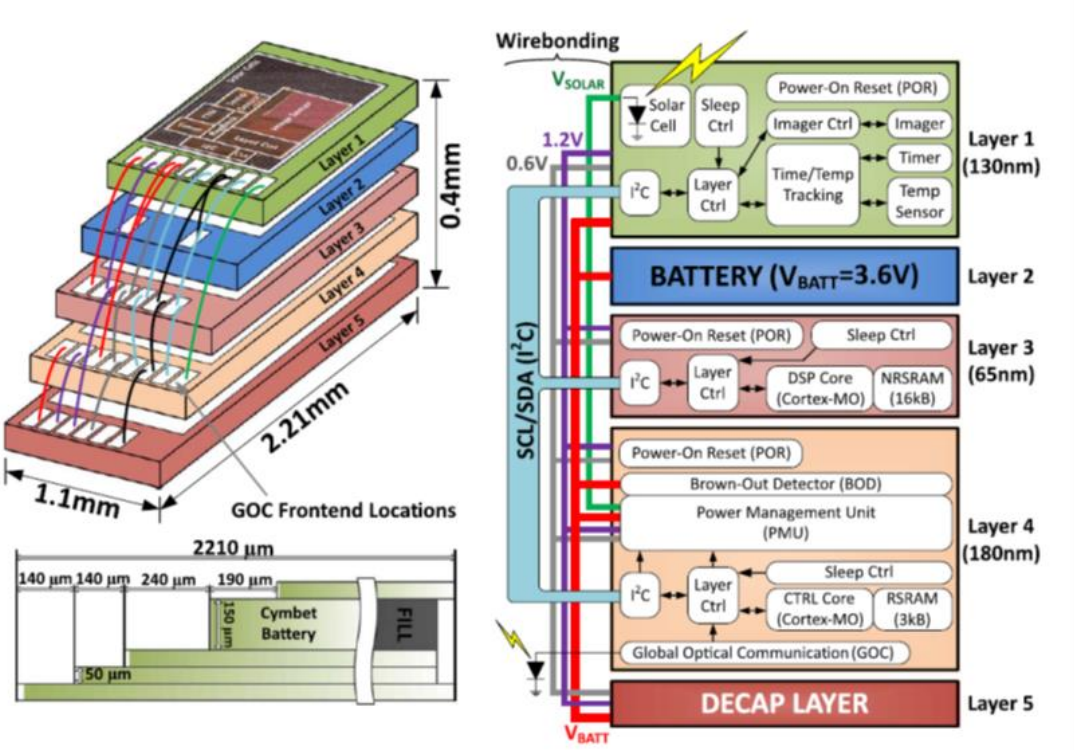


Fig. 3.4. Layer structure and block diagram of custom-designed IC-based sensor nodes in mm^3 volume[36]

Biomedical applications of M^3 explored to date include pressure monitoring in tumors for chemotherapy efficacy, intraocular pressure sensing (glaucoma), and intracranial pressure monitoring (hydrocephalus).

Miniaturizing to 100um^3 will require a major effort in circuit design, new energy sources and communication schemes. The most difficult components to scale are energy sources and RF communication components. Current thin-film mm-scale batteries scale poorly: the energy capacity per volume drops rapidly (Fig. 3.5), and the internal resistance rises, which limits peak power. Possible responses to the battery issues include harvest-only options and ultra-low power circuit design.

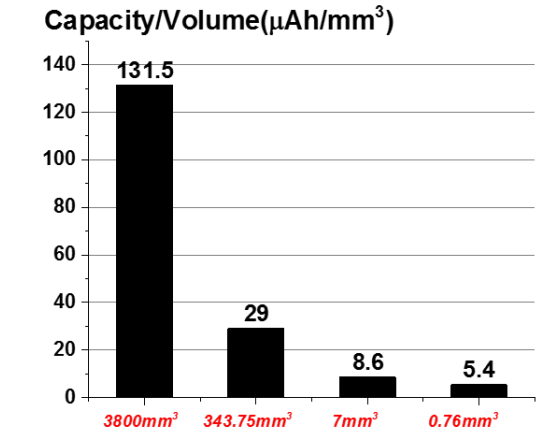


Fig. 3.5. Practical scaling properties of miniaturized batteries[35]

Considering communication options at sub-mm scale, one can argue that RF is poorly suited to communicating in the body: small system size requires very high frequencies, which will result in high path loss and high power consumption (and potentially high exposure).

A plausible alternative to RF could be near-IR optical schemes, as they offer:

- Scalability to very small sizes
- Decent transmission into the body
- Multiple channels via differing frequencies
- Sub-nW wakeup receiver, supports ~Mbps RX data rate
- Can also provide harvested power (~400nW at 100um × 100um)

Overall, the realization of sub-mm microsystems will likely require a true heterogeneous single-chip integration with no discrete components. The technology selection should be driven by highest integration density and lowest leakage (the trade-off space needs to be explored).

One can expect that the sub-mm systems will possess a considerable on-node intelligence (e.g., deep neural networks) to avoid communication costs[35].

Wireless power for implantable bioelectronics

Options for external powering of mm-scale implanted devices include electromagnetic and ultrasound energy transfer[37]. Transfer efficiency for biomedical implants depends on two major factors: implant size and physical properties of tissue. Ultrasound power delivery appears to be a winning technology for sub-mm side dimensions (Fig. 3.6)[37,38].

Not only ultrasound is effective for delivering power to mm-scale devices in tissue; it can also be used for passive, battery-less sensing and communication using backscatter[37,39]. Ultrasound-based neural interface system shows promise for advancing future bioelectronic therapies. It should be noted however that scattering of ultrasound by impedance mismatches, such as bone or air in the transmission path, can be problematic for ultrasound-based approaches.

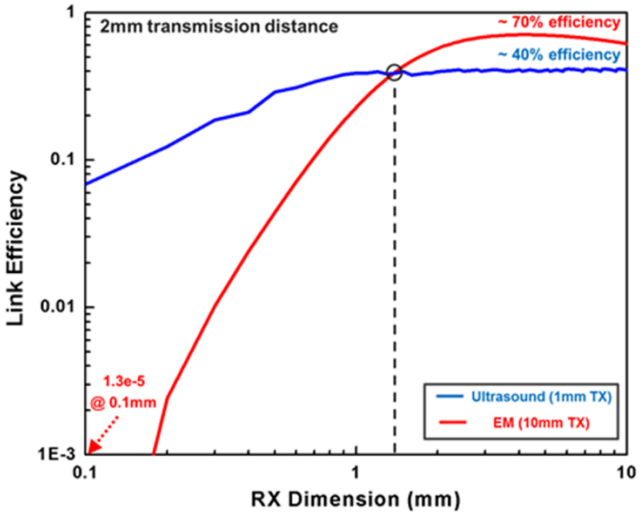


Fig. 3.6. Efficiency comparison of electromagnetic and ultrasound power delivery schemes as a function of receiver size[37]

Ultrasonically Powered Miniaturized Implantable Devices: A Platform Technology

As was stated above, using ultrasound, power and data can be efficiently transferred through the body as its wavelength at MHz frequencies is comparable to a mm-sized receiver, resulting in improved focusing, coupling, and acoustic-to-electrical conversion efficiency[40],[41]. Ultrasound undergoes relatively small propagation losses through tissue (~1 dB/MHz/cm) and has a high FDA-allowed time-averaged intensity (7.2 mW/mm^2), making it ideal for efficient power transmission at great depths (>5 cm). Additionally, ultrasound has small wavelengths in tissue (e.g., 1.5 mm at 1 MHz) allowing for superior energy focusing down to millimeter spots as well as more efficient energy recovery from a ultrasonic receiver[41]. Figure 3.7 depicts a conceptual diagram of the wireless ultrasonic powering system. Such a system can deliver >1mW/mm^2 average power levels at 10cm depth with end-to-end efficiency of >10%[40].

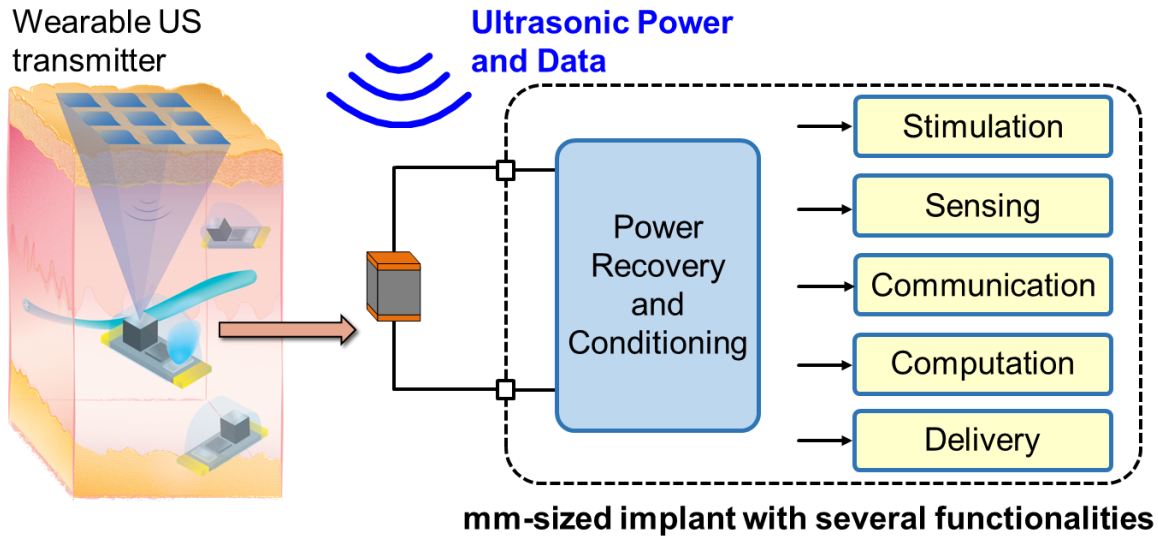


Fig. 3.7. A conceptual diagram of the wireless ultrasonic powering system[40].

Recently, a miniaturized fully packaged implant has been demonstrated that receives both ultrasound power and data and also transmits the ultrasound data for uplink[42]. Both RX and TX are made from piezoelectric materials. The ultrasound Power/Data downlink operates at input frequency f_{in} = 0.95MHz with ~50% acoustic-to-electrical efficiency. The input data rate is ~25 kb/s. The carrier frequency, f_{out}, of the output data is ~2.6× f_{in} to avoid self and external interference from the high-power downlink and its harmonics. The output data rate is ~95 kb/s. The output peak power was 125µW.

A fully wireless end-to-end test with external power/data transmitter and data receiver in castor oil, commonly used as a tissue phantom with loss ~0.6dB/cm/MHz, was performed. Bit error rate (BER) was $<10^{-4}$ for a data rate of 95kb/s. The average signal-to-interference ratio (SIR) is computed to be 27.4 and 15.8dB respectively.

Figure 3.8 shows fully packaged implants and their cross-sections. This device is at least 2.5× smaller and operates 2× deeper in tissue than comparable ultrasound-powered implants[42].

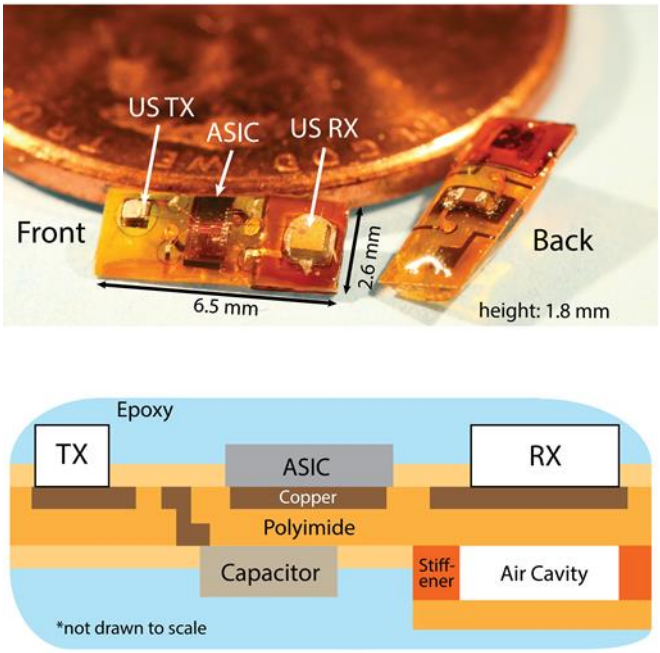


Fig. 3.8. Fully packaged implants and their cross-sections[42].

Microsystems for Bioelectronic Medicine: Fundamental Limits of Scaling

Volume and Energy are two primary design constraints for the bioelectronic microsystems, and they must be very carefully allocated among all functional units. In order to comprehend scaling limits for these microsystems, physics-based scaling and energy limits for different electronic components need to be examined including logic circuits, storage and communication subsystems, etc. Each of the essential units in the system occupies certain volume in space and consume a portion of energy. Therefore, theoretically optimal partitioning within a fixed space and energy envelopes needs to be explored (Fig. 3.9)[43].

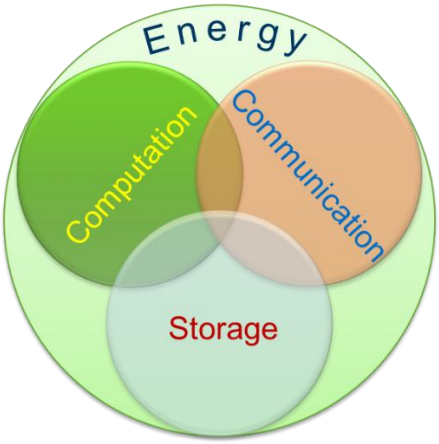


Fig. 3.9. Communication-Storage-Computation Triade: What is theoretically optimal partitioning within fixed space and energy envelopes?

Energy:

In electrochemical (e.g. galvanic) cells, 'atomic fuel' (metal atoms at the negative electrode) are consumed to produce electricity and the total stored energy is directly proportional to the number of metal atoms, thus the volume. An upper bound for energy that can be stored in an electrochemical cell was estimated to be 10^4 J/cm^3, thus at most 10^{-2} J can be available in a 100μm×100μm×100μm volume.[43,44]

Logic:

In principle, the full MPU capabilities can be realized within 100um square (Table 3.2). For example, if 65 nm CMOS semiconductor fabrication process is used, about 6000 logic transistors can be placed on 100μm×100μm footprint[43], which is equivalent to, e.g. the Intel 8080 processor. The circuit-level energy-per-bit for this technology node is ~5×10^{-16} J/bit. The projected limits of scaling of semiconductor transistors are estimated as ~5nm transistor gate length and 2×10^{-18}J per bit[44].

Table 3.2. Logic circuits: the number of transistors in 100μm×100μm area and circuit-level energy per bit.

Technology node	# of transistors in 100μm×100μm area	E_{bit}, J
65nm	6,000 (~Intel 8080)	5×10^{-16}
45nm	12,000 (~Motorola 6809)	2×10^{-16}
22nm	50,000 (~ARM 6)	4×10^{-17}
10nm	250,000 (~Intel i960)	10^{-17}
5nm*	1,000,000 (~Intel 486)	2×10^{-18}*

***projected limits of scaling**

Storage

The scaling limit of electron-based storage (flash) is ~10nm cell size[45]. For flash memory arrays, due to the regular wiring, the energy per bit operation of flash doesn't scale with the cell size, and is determined by charging of the interconnecting array wires. The large operating voltage of flash results in rather large line charging energy, ~$C_{line}V^2$of ~10^{-11} J[45] (in addition, in many flash memory systems large energy is consumed in high-voltage peripheral circuitry, such as

multiplexers and voltage pumps, which can raise the system level write energy to 10^{-9}-10^{-10} J/bit).

Free-Space Single-Photon Limit for Energy in EM Communication

The minimum energy requirements in EM communication can be estimated based on the fact that the radiation can be emitted or absorbed only in discrete increments – photons. This means, among other things, that at least one photon must be absorbed by a receiving device, and the photon energy E_{ph} can be viewed as the absolute lower bound on the energy per bit of EM communication. The photon energy is a function of the wavelength, λ ($E_{ph}=hc/\lambda$), and the size of the transducer (e.g. the antenna) needs to be about the same as the radiated wavelength, $\lambda \sim L$. Next, If the location of the external receiving device relative to the sending device is unknown, then in order to guarantee that at least one photon will reach the detector, the entire sphere of radius r must be 'covered' with N_{ph} photons. The resulting formula for the minimum energy required to transmit one bit of information is[43,44]

$$E_{com} = N_{ph} \cdot E_{ph} \sim \frac{4\pi r^2}{\lambda^2} \cdot \frac{hc}{\lambda} \sim \frac{4\pi hcr^2}{L^3}$$

For L=100μm and the distance between the cell and the receiver r=1 m, the above equation gives E_{com}~2.5x10^{-12} J/bit. Of course, this energy estimate is a lower bound on communication,and it doesn't consider, e.g., absorption efficiencies of the transducer and detector, noise, etc.

As follows from the above, the energy to store or send a bit of data by a sub-mm microsystem is several orders of magnitude larger than the energy per bit in logic circuit. This suggests that the overall design goal should be to minimize communication and to maximize the 'intelligence' of the microsystem.

Session III Roundtable Discussion Summary: On our way to the 100μm microcell for bioelectronics medicine

During the session and in the discussion that followed a few opportunities and gaps emerged:

- Opportunities:
  - There's great potential for leveraging technology advancements from other spaces such as IoT and mobile for this applications space. Many compute / communications/ storage / robustness and security and software needs should map to this space. The challenge will be to identify and communicate these between these domains and bioelectronics medicine microcell teams.
- Gaps:
  - Packaging is an area where the technology requirements in probes, sensors, and device isolation may be unique due to environments and regulations.
  - Communications and systems architectures also may need to be optimized by target application. There are challenges in developing solutions to these gaps.

    - Much discussed was the market and financial model between medicine and Si technology which must be bridged to enable technology development to occur.
    - Also there is a need for identifying the key design parameters for target applications.

- Moving forward some questions to answer include:
    - Should we focus on a roadmap to 100u or reach to 100u to push technology development? One risk highlighted in this session was communications where the solution may shift from RF to ultrasonic at some point between 10mm to .1 mm due to fundamental physics. So which method is best for this program.
    - A better understanding of the application space as well as fundamental requirements for interfacing with nerves (for example, stimulation parameters or recording bandwidth requirements) that apply to a broad range of applications would be a major benefit to defining hardware challenges and goals.
    - What is the makeup of a successful microcell team? Clearly a center with the objective of a microcell will need capabilities in packaging, compute technologies, system architecture, and software to augment applications domain knowledge from the medical and biologic device fields.

5. Biocompatibility issues of technologies for bioelectronic medicines (Session IV)

Session Keynote:

James Weiland, U Michigan

Biocompatibility

Session Panelists:

David Martin, U Delaware

Molecular Design, Synthesis, and Characterization of Conjugated Polymers for Interfacing Biomedical Devices with Living Tissue

Walter Voit, UT Dallas,

Biocompatible Smart Polymers for Neural Interfaces

Christopher Bettinger, CMU

Ultracompliant Electrode Arrays: Polymers and Processing for Hydrogel-based Peripheral Nerve Interfaces

Rashid Bashir / U Illinois

3D Printed Skeletal Muscle-Powered Biological Machines

Session Chair:

Jamu Alford, Medtronic

Microelectromedical devices have a large potential to improve human health, but long term use faces several challenges, including biofouling, maintaining robust electrical connections for external communication, and accessing a continuous source of power. This session explored issues with and approaches to biocompatibility and long-term biostability of the microsystems for bioelectronic medicine.

Biocompatibility

General considerations for chronic packaging include biocompatibility, hermeticity, outgassing of internal materials, wireless communication, package heating, matching coefficients of thermal expansion, and insulating lead coatings.

Biocompatibility is a broad term referring to the interaction between the implanted device and the biological (e.g. neural) tissue. This term covers both the issues of protecting the body from the implant and (equally important) protecting implants from the body[46].

Water constitutes ~65% of human body, and is one of the primary concern factors for protecting bioelectronic implants. Examples of failure modes for electronics exposed to water include corrosion from water deposition on metal and remnant contaminants and electrolytic conduction between bias lines.

Implantable electronic devices require a protective barrier to ensure that neither moisture nor ions reach incorporated electronic circuits. Traditional methods for forming this barrier involve the use of titanium or ceramic cases. The thickness of the case leads to implant external dimensions much larger than the size of the enclosed electronics[47]. In the case of silicones and epoxies, water vapor transmission rates are often too high for enclosure.

Hermetic encapsulation is an important and challenging step in the packaging process. For this, surface cleaning is critical. Any void in the encapsulant is a potential area for water condensation, corrosion, and failure. Metal thin films can be deposited for encapsulation, but in this case fragility is a concern: Microcracks may occur in films deposited both with ALD and with RF sputtering[46]. In addition, the metal encapsulation needs long-term process development effort and is equipment intensive.

Interfacing of the packaged microsystem with external environment occurs by means of *feedthrough*, which is a substrate with multiple isolated conductors penetrating the hermetic package. For the feedthrough conductors Pt, Pt/Ir, Pd, Nb, and Co/Fe/Ni alloys are typically used. Water resistant materials such as glass, zirconia, and alumina are used for feedthrough insulators. The feedthrough body must be mechanically strong and non-corrosive and is typically made of stainless steel or titanium.

After encapsulation, hermeticity testing is needed, which is a nontrivial task. Helium leak detection is a standard test to estimate package lifetime. The He leak rate depends on the water content inside the package, thus the moisture level can be quantified. The sources of leak can be direct transmission (all materials have a finite water vapor transmission rate) or defects (such as bad seals or pinholes). How much moisture can be tolerated? For example, the Department of Defense's Test Method Standard for Microcircuits - Mil-StD 883[48] suggests that 5000 ppm is the limit for moisture inside the case. Of course, the specifications for leak rate will depend on desired lifetime and internal cavity volume. For many microimplants leak rate specifications are sometimes beyond the ability to detect, which represent a test challenge.

The importance of packaging on the performance of bioelectronics products can be illustrated using the example of retinal implants (Table 4.1). The electronics inside of this device allows for light perception, object discrimination, however there is notable longevity vs. visual acuity trade-off. Better visual acuity requires a larger number of channels, which negatively impacts the longevity of the encapsulation and thus the entire implant.

Table 4.1. Packaging trade-offs in visual implants: Better visual acuity requires a larger number of channels, which negatively impacts the longevity of the encapsulation and thus the entire implant.

	Channels	Longevity	Visual Acuity
Argus II (enclosure)	60	10 years+	20/1260
Alpha-IMS (encapsulation)	1500	2 years?	20/546

The current and future packaging needs can be summarized as follows:

- Next generation bioelectronics will be smaller and have more independent channels
- Traditional enclosures and packaging approaches may not scale
- Whether enclosure or encapsulation is used, pre-implant testing may not reveal defects, so redundancy and replacement may be required

Another pertinent topic is the biocompatibility of electrical stimulation. Neurons can be damaged by the stimulation, even if it is within electrochemical safety limits. Pulse rate, duty

cycle, number of active channels all were found to contribute to the harmful effects[46]. Charge density and frequency also play important roles. Also mechanical biocompatibility should be taken into account: while stiff electrodes are good for robustness and insertion, the mismatch in stiffness is suspect for the chronic inflammatory response. Platinum-Iridium electrodes with high surface area co-deposited in electrodeposition process demonstrate an improved biocompatibility and robustness under conditions of use (insertion, stimulation)[46].

One possible way to mitigate the inflammatory response is through a reduced probe footprint[49]. Recently recording electrode array designs using carbon fibers have been demonstarted[49]. Carbon fiber electrodes are small (d = 6.8 µm), and with the addition of a parylene-C insulating coating, the overall diameter is only increased to 8.4 µm. Carbon fiber electrodes demonstrated the ability to chronically record unit activity in the rat motor cortex up to 16 weeks and were found to greatly outperformed silicon electrodes with comparable site sizes[49].

While extracellular recordings from single neurons are typically made using penetrating metal wire or microfabricated microelectrode arrays, single- and multi-unit neuronal recordings have been reported using non-penetrating electrodes placed on the epineural surface of the dorsal root ganglia (DRG). This approach may have advantages over penetrating electrode arrays in terms of clinical acceptability and recording longevity[50].

Another proposed way to mitigate the inflammatory response is through reduced modulus of the implants. Active research in both soft[51] and softening bioelectronics [52]is exploring the effects of modulus as a factor in the chronic inflammatory response in tandem with surface chemistry and device geometry. Packaging devices, especially those that change in stiffness orders of magnitude between insertion and use, presents interesting materials challenges for the community.

Emerging applications for implantable electronic devices, such as brain machine interfaces and visual prostheses, will require packaging technology that is ultraminiature so that the implants can be placed close to target neurons, and yet is still compatible with hundreds of independent conductors. Using traditional technologies, such implants would be unacceptably large.

Molecular Design, Synthesis, and Characterization of Conjugated Polymers for Interfacing Biomedical Devices with Living Tissue.

In developing chronic microstimulation-based devices, there is a major trade-off with electrode miniaturization due to the increase in impedance and charge density requirements. Thus, the development of novel materials with lower interfacial impedance and enhanced charge storage capacity is essential for the development of micro-neural interface-based neuroprostheses[53,54]. Also, there is a need to reliably interface an electrically active, solid, abiotic device with an ion-rich, living, water-laden, dynamic biological environment[55]. Conjugated polymers are being considered for use at such abiotic–biotic device–tissue interfaces. These organic materials have properties that are intermediate to these two extremes, and their chemistry, structure, and performance can be precisely manipulated over a large range. Examples of current interest include copolymers of [poly](3,4-ethylene dioxythiophene)- PEDOT and poly(3,4-propylene dioxythiophene)- ProDOT. These materials are able to accommodate both electronic and ionic

transport. PEDOT is one of the most chemically stable conjugated polymers and can show high conductivities (more than 3000 S/cm in certain cases). When electrochemically deposited onto solid microelectrodes (typically made of gold, iridium, and platinum), PEDOT turns the metallic surface into a soft, conformal, and high–surface area organic interface that supports both electron and ion transport. With PEDOT coatings on the electrodes, the performance of biomedical devices, both in vivo and in vitro, is significantly improved[53]. The use of PEDOT as a neural interface material for microstimulation of small-area iridium electrodes on silicon-substrate arrays results in lower interfacial impedance at physiologically relevant frequencies, (with the 1 kHz impedance magnitude being 23.3 ± 0.7 kΩ, compared to 113.6 ± 3.5 kΩ for iridium oxide (IrOx) on 177 μm^2 sites), enhanced charge storage capacity at 75.6 ± 5.4 mC/cm^2 (compared to 28.8 ± 0.3 mC/cm^2). The PEDOT coatings provide both significantly lower voltages during stimulation (Fig. 4.1b) and a more ohmic representation of the applied current compared to IrO_x. PEDOT coatings were demonstrated to improve the performance of Regenerative Peripheral Nerve Interface (RPNI), which is an internal interface for signal transduction with external electronics of prosthetic limbs, consisting of an electrode and a unit of free muscle that is neurotized by a transected residual peripheral nerve. Adding a conductive PEDOT polymer coating on electrodes improves sensitivity and lowers the operational power[53,56].

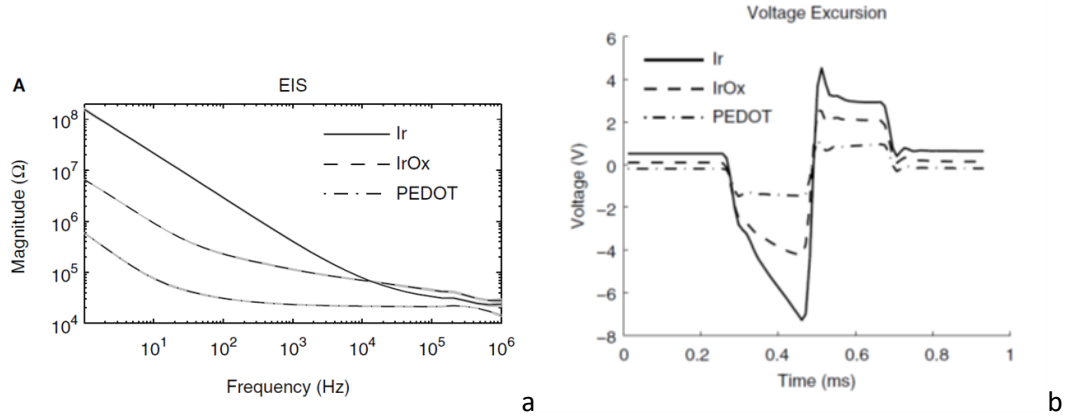


Fig. 4.1. The use of PEDOT as a neural interface material for microstimulation of small-area iridium electrodes results in (a) lower interfacial impedance at physiologically relevant frequencies, and (b) lower voltages during stimulation[53,56].

Biocompatible Smart Polymers for Neural Interfaces

Multi-functional polymers with tunable physiological responses promise to advance the capabilities of medical bioelectronic devices intended to function *in vivo*[57,58]. Polymer networks (such as polyimides or polysiloxanes) succeed in providing either stiff or soft substrates for bioelectronic devices; however, the capability to significantly tune the modulus of such materials is lacking. Within the space of materials with easily modified elastic moduli, thiolene copolymers are a subset of materials that offer a promising solution to build next generation implantable bioelectronics[59].

Softening neural interfaces have been demonstrated, which are implanted stiff to enable precise insertion, and then soften in physiological conditions to minimize modulus mismatch with tissue, and thus attenuate the neuronal damage [57,60]. Accelerated electrical aging tests under simulated physiological conditions have shown that photolithographically defined electrodes on shape memory

polymer neural interface substrates can deliver more than 2 billion symmetric, biphasic, charge balanced pulses[57,60].

Ultracompliant Electrode Arrays: Polymers and Processing for Hydrogel-based Peripheral Nerve Interfaces

Next-generation peripheral nerve interfaces will likely utilize novel materials, form factors, and device fabrication strategies[61]. Hydrogel-based materials can improve the sensing and stimulation of excitable tissue by promoting conformal integration of electronic devices and bridging the abiotic–biotic interface (Fig. 4.2.)[62].

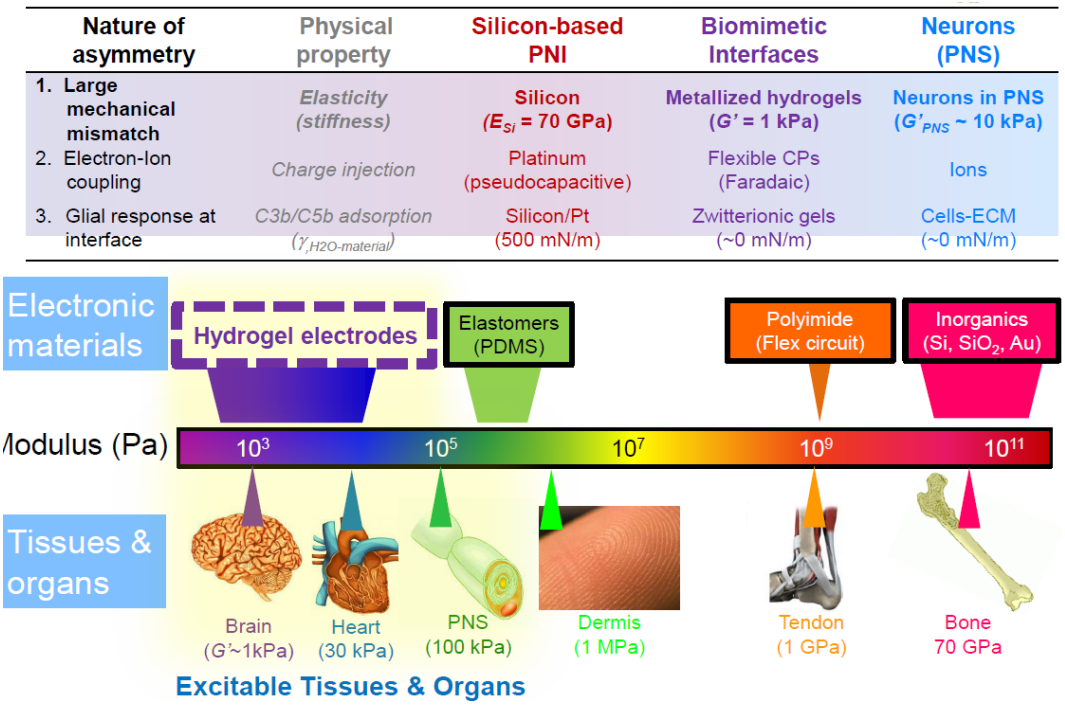


Fig. 4.2. Hydrogel electrodes for tissue-device interface[61]

A challenging task is the direct integration of micro-electronics with hydrogels. Recently, integration of electronic structures directly with adhesive hydrogels through transfer printing has been demonstrated[62]. Adhesion in hydrated environments is a difficult problem that has been solved in part by recent discoveries of adhesion-promoting materials utilizing mussel inspired metal–catechol coordination bonds[63]. Preliminary recording test of the adhesive electrode-based hydrogels on the dorsal root ganglia in feline has been conducted[61].

3D Printed Skeletal Muscle-Powered Biological Machines

Biological materials have the ability to sense, process, and respond to a range of dynamic environmental signals in real time. This capability allows biological systems to demonstrate complex behaviors such as self-assembly, self-organization, self-healing, self-replication, and constant adaptation of composition and functionality to best suit their environment. Recent advances in manufacturing technologies, such as 3D printing, combined with progress in the field of biomaterials, have synergistically produced robust

approaches for manufacturing complex 3D structures from biological materials. This has driven fundamental advances in the fields of tissue engineering and regenerative medicine by providing a method of reverse-engineering native tissues and organs[64,65].
Bio-integrated machines (or bio-bots), built using a combination of biological and synthetic materials have the potential to develop enhanced functional attributes as compared with traditional synthetic materials. Such machines will require biological actuators that can generate force and perform mechanical work. Examples of such millimeter-scale biological actuators include cardiac cell driven micropumps and skeletal muscle cell driven 3D printed hydrogel "bio-bots" powered by the actuation of an engineered mammalian skeletal muscle strip that results in locomotion. The contraction of the cells in the muscle strip can be triggered by electrical or optical stimulation[65].

Session IV Roundtable Discussion Summary

A. General

- It is important to test new technologies in realistic scenarios of integration and application
    - Materials research must consider condition of use, supporting materials for sterilization, storage, and implantation
- When will it make business sense for major semiconductor fabs to contribute?
- How do we balance invasiveness with reliability?
- Can we tolerate the decoupling of scalable components vs. non-scalable components?

B. Interfaces

- The interface between biological systems and artificial devices provides a challenging environment.
    - Both systems are initially diametrically opposite in many properties and each can cause irreversible damage to the other if not mitigated appropriately.
- By changing the material properties of electrodes and electrode coating one can dramatically mediate the interface between the electrodes and tissue.
    - E.g. functionalized EDOT and ProDOT copolymers provide a means for systematic control of chemical composition, charge transport, mechanical properties making it possible to tailor specific interactions with inorganic substrates and biological tissue
    - Possibilities for deposition into gels and living tissue
    - Problem: Long term performance and reliability (fracture, adhesion, wear, fatigue, chemical stability, etc.)
- In future devices adaptive materials can be used to address the mechanical mismatch
    - Material stiffness can be dynamically controlled to allow mechanical matching but also permit surgical placement.
- Interfacing electronics into hydrogels offers interesting opportunities
- Living cells themselves can be part of the machinery by using 3D printed biologically structures that can be controlled by electronics.

C. Packaging

- Packaging appears to be not a “sexy” problem, but is highly critical
- How do we harmonize robust packaging versus mechanical flexibility?
- Should we always demand hermetic packages?
- For higher channel count applications like vision or smaller implants, new, significantly better packaging technology is needed.
    - Implants that must maintain viable recording channels face additional challenges, related to mechanical interface

    - Should we focus on local high-density channel counts or numerous distributed electrodes?

D. Partial List of Research and Collaboration Opportunities

- Tissue reaction related to electrical stimulation mechanical interaction
- Novel electrode materials
- Solutions for chronic connectors
- Robust, rational, or generalizable multi-electrode algorithms
- Development and optimization of standardized, quantitative testing methods for evaluating bioelectronics device failure mechanisms and associated materials performance
- The biotic-abiotic interface challenges provide many opportunities for new innovations and also opportunities for collaboration between multiple organizations to solve these problems.
    - Packaging and feedthroughs seems like a natural point of possible collaboration as it is an issue that must be solved by each entrant in this field.
- Bioelectronic Roadmap should address the following common issues: High-channel count interconnects between hermetic (like titanium or alumina) devices and flexible leads then developing processes to remove the need for the Ti-shell by new methods including cleaning and coating with Si or equivalent.

6. Roadmap from Research to Commercialization (Session V)

Session Keynote I:

Brian Litt, UPenn

Engineering the Next Generation of Neuroscientists

Session Keynote II:

Goran Marnfeldt, Boston Scientific

Growing the neuromodulation/bioelectronics industry from $4B to $40B: Historical insights, challenges and opportunities

Session Panelists:

Emily Caporello, DARPA

Nerve Interface System Development, Human Testing, and Transition to Clinic: Learning from the HAPTIX program

Michael Hoffmann, FDA

Navigating FDA's Regulatory Landscape for Medical Devices

Quan Ni, Inspire Medical Systems

Implanted Hypoglossal Nerve Stimulation for Sleep Apnea

Rashid Bashir / U Illinois

Preparing the Workforce through Pre-Competitive, Cross-disciplinary Research

Ronald Dekker, Philips

Bridging the valley of death with open platforms and pilot lines

Session Chair:

Rizwan Bashirullah, Galvani Bioelectronics

Several challenges need to be addressed for successful implementation of a large-scale research initiative in bioelectronic medical systems. First, unlike consumer and many other electronic devices, developing microsystems for therapeutic applications takes place in a heavily regulated environment which requires assessment of device safety and efficacy. Given the novel nature of bioelectronic microsystems, it would be helpful to develop an experimentation platform for testing new bioelectronic treatments during the research and pre-clinical trial phase.

Second, research and ultimately development and commercialization of bioelectronic medical devices requires multidisciplinary knowledge and skills, including neuroscience, medicine, systems engineering, materials, electronics, etc. Establishment of core technology requirements, cross-disciplinary education, open-source resources, and experiential learning are ways to create a suitably educated workforce and equip future scientists, engineers and doctors to make the next disruptive discoveries.

Third, the subject of bioelectronic medicine, like any new technology, potentially raises ethical and legal issues that need to be understood as research is undertaken.

Growing the neuromodulation/bioelectronics industry from $4B to $40B: Historical insights, challenges and opportunities

Neuromodulation is currently about a $4B business, globally[13]. The market can roughly be split in five major areas:

- Spinal Cord Stimulation: $1.5B-$2B (almost ½ of the market)
- Cochlear Implants: $1B (1/4 of the market)
- Deep Brain Stimulation $0.5B (⅛ of the market)
- Over Active Bladder) $0.5B (⅛ of the market)
- Epilepsy: $0.5B (⅛ of the market)
- Others: $0.5B (⅛ of the market)

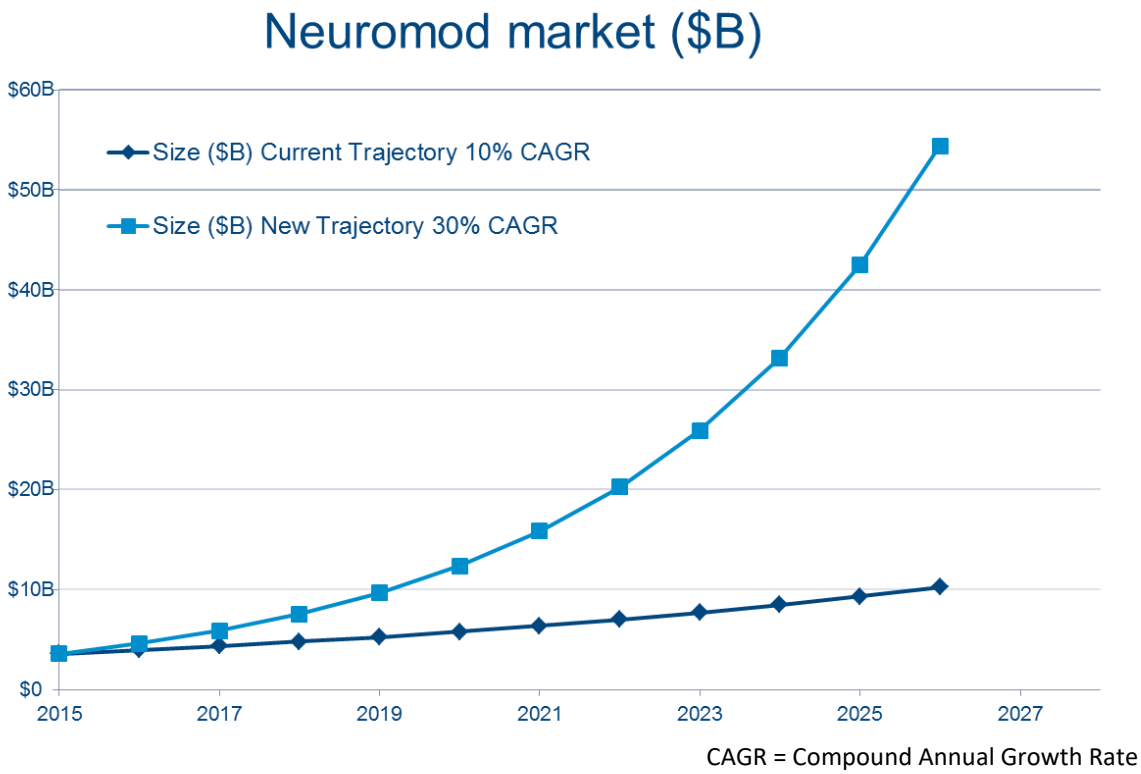


Fig. 5.1. Neuromodulation devices market trends[13]

While the current growth rate for the bioelectronics industry is about 10%, the question is what do we do collectively to change the trajectory from 10% to 30%? One can speculate on several recipes for the trajectory changes:

- Solve new unmet clinical needs – finding a better clinical solution than existing treatment
    - Move from science to clinical evidence
- Changing clinical algorithm
    - By creating the new technology, we must convince the physicians to adopt it, and that it's better than what they are used to

    - One can have the best evidence of the treatment efficacy, and still physicians may be driven by other things, e.g. financial incentives

- Reimbursement strategy (someone has to pay for it)
    - Even with the best evidence of the treatment efficacy, and physicians prepared to change their practice, things will not move on, if no one is willing to pay the bill.
    - New product must be more cost effective than established practice
        - Low-cost product
        - Procedures, cheap to implant
        - Low service cost

Historically, for a startup, it takes roughly 10 years and a $100M investment to bring a new neuromodulation technology to market. If we want change the current trajectory, we need to get there faster and cheaper. In order to do this, we need to:

- Increase Scientific / MOA (= Mechanisms Of Action) understanding
- Reduce risk
    - Fast-to-fail / Cheaper FIH (= First In Human)
        - Put your hypothesis to test early
- Technology leverage
    - Partnerships / Collaborations
        - It's not about competition and beating someone else by a few market share points.
        - The real challenge is to grasp the gigantic uncut cake that's still out there.
        - Expand the market, and don't just compete for what exists today

Considering some examples of success technologies at BSC (defined as developed from zero to over $500M in 12 years since commercialization), they appeared as a result of technology-push strategy, using first-in-tech approach. Examples include Spinal Cord Stimulation (first rechargeable IPG, first wireless, first MICC, first anatomical algorithm, first wireless charger) and Deep Brain Stimulation (first directional lead + MICC system, first cordless charger).

There are also examples of technologies that were not that successful. For example, Bion™ Microstimulator, the first injectable battery-powered neurostimulator for Over Active Bladder, and later for migraine. Overall, the Bion™ Microstimulator was a great technical success. The team started in March 1999, the chip development started in January 2000, and the first human implant happened in Dec 2002. The whole system created by a team of approximately 20 people with less than $10M/year in less than 3 years. Note, that while completed 15 years ago, in 2017 it is still 10 years ahead of its time! The device has outstanding technical parameters: it is ultraminiature (3.3mm x 27mm hermetic cylinder, 0.23cc) and operates at ultra-low power (1 week time-to-recharge for OAB).

However financially the Bion™ was not that successful; it impacted 100 people in a clinical study at an accumulated cost of around $25M and 1 device was sold commercially. The main reason for this was that an injectable device has been developed without understanding the physician's first question, which is: If I inject this into the body, how am I going to take it out? Also, there was not enough clinical evidence for its use. Since the devise is so small, there was a

premise that a better result could be achieved by stimulating the Pudendal nerve vs the Sacral roots. But that was a theoretical assumption, not supported by clinical data. Also, the Bion™ is a single-contact device, thus not offering sufficient flexibility as platform approach; it takes skill and luck to get it in the right place, and it cannot be moved sideways. All these factors contributed to the lack of commercial success of the Bion™.

In finding a new, optimum trajectory different considerations need to be taken into account, as outlined in the following:

1) There is an invasiveness problem, which includes both the psychological burden for the patient, having an implant; and a complicated procedure for the physician.
2) System level considerations must be taken seriously. For example, it doesn't make sense to make a super small chip, if other components dominate size. Also, manufacturable micro-scale hermetic packages represents a difficult challenge with little success so far.
3) How small is small enough? To make a 1 cubic micrometer device today, it would probably take a trillion dollars and require 10 Nobel prizes worthy inventions. But for a larger scale devices, we already do that today, so it's essentially a zero technology development cost. Somewhere in the middle is a "sweet spot", but that spot is moving so aim at where it will be when you're ready for market.
4) Physics helps us with fundamental variables, and in the physics-based view everything starts with *energy*, end energy drives everything else.
    a. Whether it's a central or distributed in/out-body network power, always the patient usability burden needs to be kept in mind
        - E.g. a micro-device might need to be charged more often, so the benefit of less invasiveness is paid for by increased charge burden for patient.
    b. Improve wireless powering
        - Mid-field use antennas for small devices instead of coils. When the source and the receiver are weakly coupled, high frequency midfield wireless powering yields much higher efficiency than near-field systems.
        - Ultrasound allows for large power levels, with no SAR limit, better tissue penetration, but Tx-tissue coupling is a difficult issue.
    c. Better batteries
        - Often primary cells are better suited because they reduce patient burden when size doesn't matter or energy requirements are low
        - New materials in combination with wearables are driving new battery technologies
    d. Energy harvesting or "creation" - there are sources of energy inside the body:
        - Muscle movement – stimulate a muscle and use the resulting movement to drive a piezo generator
        - Electric potential in inner-ear from cochlea
        - Temperature gradients
        - Fuel cells running on glucose and oxygen in blood stream

e. Make a power budget for the full system and see where it makes sense to save
    - Don't kill yourself to e.g. reduce the standby current way below the self discharge of the battery
    - Don't focus too much of cutting microprocessor power if delivery of therapy takes 95% of the energy
    - A higher capacity rechargeable battery will take longer to charge if you can't improve wireless energy transfer. Just more charge power will increase tissue heating!
    - Your power system must meet both power and energy needs. E.g. duty cycling increases instantaneous power needs, but not energy needs
f. **Most important of all**, if you can deliver the therapy in the right spot and the right way, orders of magnitude could be saved!
g. If you can create a latent effect, then you don't need to stimulate 100% of the time, and that's a very easy way to save power

5) Stimulation problem
    a. What are the temporal dynamics of stimulation to maximize benefit? How you talk to the nerves?
    b. How to improve fiber selectivity? Pick the right ones to talk to! Or
    c. More complex field shaping algorithms

6) Control problem
    a. Local (patient) closed loop
        - There are likely biomarkers for most indications that can be sensed. We need to establish them.
        - What does the feedback algorithm look like? General rules vs patient specific
    b. Global (population) closed loop
        - Can aggregated "real-time" population data allow therapy optimization?

7) Scalability problem: How to go from tens of stimulation / sensing sites to thousands, or a million?
    a. Are NIH and DARPA sponsored programs viable?
    b. We need to go to much higher number of channels than we have today
        - Distributed mux architectures? Wired or wirelessly?
        - What are high density interconnect limitations?
        - What is the role of optogenetics and optical selectivity?
        - Differentiate sensing and actuation access technologies? Sense here, but stimulate there
        - What are the signal processing and energy challenges derived from scalability problem?
            - Retinal implants and power / heating density
            - 60 pixels today at e.g. 100 uA
            - HD 1080p with 2 Mpixel would be more than 3 Amps

8) COGS (Cost Of Goods Sold) problem
    a. Can we go from 100,000 patients/users to 10 million?
    b. Could we have a $10 (COGS) implant?

In conclusion, we should be able to change the trajectory. But it takes more of a holistic approach to get there than just better technology, though **technology is an enabler**. We need smarter devices (IQ/mm^3) that can improve treatment, reach new targets, be cheaper, reduce the service burden, and be less invasive.

Engineering the Next Generation of Neuroscientists

New technologies to probe the nervous system are propelling innovation and discovery at blinding speed, but are our trainees prepared to maximize this power? Currently, there is not enough skilled people to practice the discipline of neurostimulation, which requires expertise in both engineering and neuroscience[66,67]. For example, an incomplete list of skills needed for data acquisition in bioelectronic medicine includes:

- Sensors/Electronics/ imaging
- MEA, optical, genetic, molecular
- Digital Signal Processing
- Materials, biocompatibility
- Electrical safety, wireless
- Animal safety/ techniques
- Instrumentation, math, physics, chemistry

Next, data wrangling, i.e. transforming and mapping raw data into another, more suitable format requires skills in:

- Programming (MATLAB and Python)
- Storage, encryption, compression, and transfer of data
- Pipelines
- Cluster and cloud computing
- Code “hygiene” (GitHub, versioning)
- Documentation, etc.

Finally, data analysis and interpretation requires skills in

- Visualization,
- Statistics
- Machine learning
- Modeling, etc.

The growing role of engineering in research, such as materials, computing, electronics, and devices, compels us to rethink neuroscience education. Core technology requirements, cross-disciplinary education, open-source resources, and experiential learning are new ways we can efficiently equip future leaders to make the next disruptive discoveries. The challenge today is that as new technologies become increasingly complex and expensive, it is no longer possible to master them alone in a reasonable amount of time.

Operating instrumentation required for neurostimulation research may, without the right preparation, take years to master. On the other hand, there is a risk of training sophisticated equipment ‘‘operators’’ without a sufficient depth of knowledge. In order to reduce risks of technical and conceptual errors, this group must have the insight to push state of the art tools to their performance limits.

One answer to the technological ‘‘skills gap’’ in neuroscience might be to recruit more students for technologically intensive research laboratories with degrees in electrical engineering, computer science, mathematics, or physics.

Nerve Interface System Development, Human Testing, and Transition to Clinic: Learning from the HAPTIX program

The goal of the DARPA’s HAPTIX program is to create neural interface microsystem that achieves ultimate goal of naturalistic motor and sensory function with advanced prosthetic limbs. HAPTIX will create and demonstrate a system in humans that enables daily use of these advanced limbs in the field. While the primary goal of this program is to create a system that achieves the requirements for our hand prosthesis applications – the expectation is that the technology will be modular and scalable to serve a variety of applications. Academia-private sectors partnership is an important success factor for this program[68].

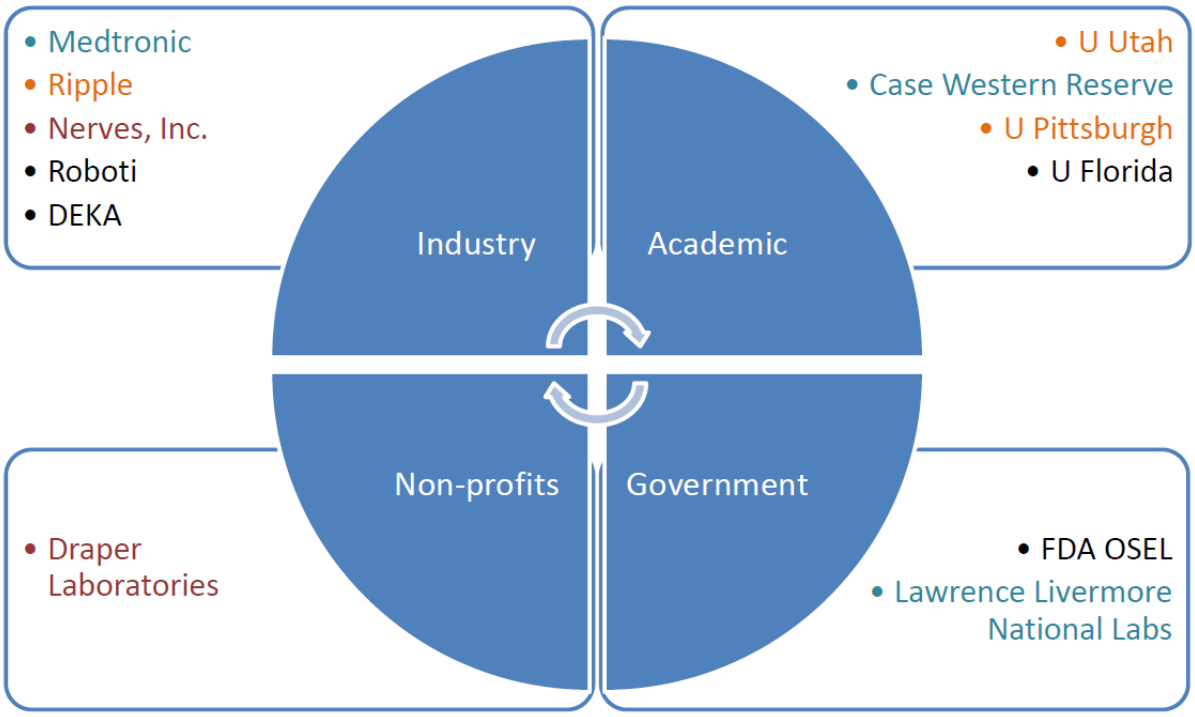


Fig. 5.2. HAPTIX Performer Community[68]

Navigating FDA's Regulatory Landscape for Medical Devices

The U.S. is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety. U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance. Consumers, patients, their caregivers, and providers should have access to understandable science-based information about medical devices and use this information to make health care decisions. There are multiple tools and sources of information from FDA available for the developers of implantable medical devices, and in order to stay on a success trajectory, it is recommended to interact with FDA at earlier stages of development, for example Early Feasibility Study (EFS) can be conducted. EFS permits a more efficient pathway to commercialization, as FDA feedback early in product development may help you improve your development strategy and reduce unnecessary testing. It enables collection of high quality clinical data for, e.g., optimizing device design/operator technique, developing subsequent clinical study protocols, etc. Early engagement with FDA allows for potential issues to be identified earlier. This is particularly useful if there are concerns related to novel technology or testing[69].

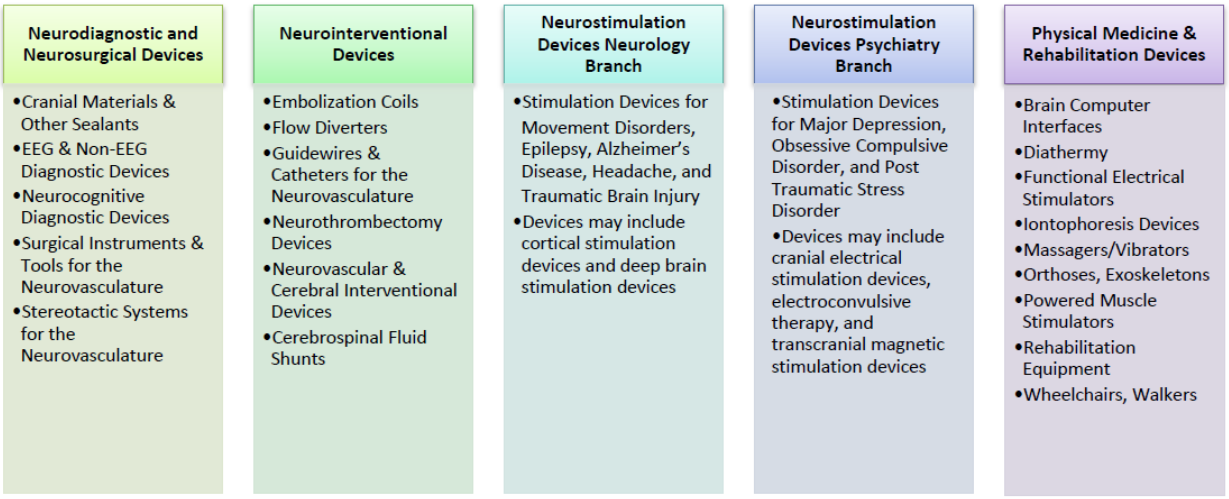


Fig. 5.3. FDA's Division of Neurological and Physical Medicine Devices[69]

Implanted Hypoglossal Nerve Stimulation for Sleep Apnea

Obstructive sleep apnea (OSA) is a sleep disorder that involves cessation or significant decrease in airflow during breathing. With estimated 18 million American having sleep apnea, this is a good target for bioelectronic therap[70]. In the current US healthcare system, new therapy development typically needs to overcome three barriers: clinical, regulatory and reimbursement. The work on implanted neuromodulation devices for OSA treatment has begun in 1996, and in 2014 FDA granted pre-market approval for INSPIRE stimulation system that senses respiration and delivers mild electrical stimulation to the hypoglossal nerve. Approval for this active implantable

neuromodulation device was preceded by a clinical trial whose results were published in the New England Journal of Medicine [71]. Currently, the product is in reimbursement stage. The development pathway for the Inspire's neuromodulation device is shown in Fig. 5.4.

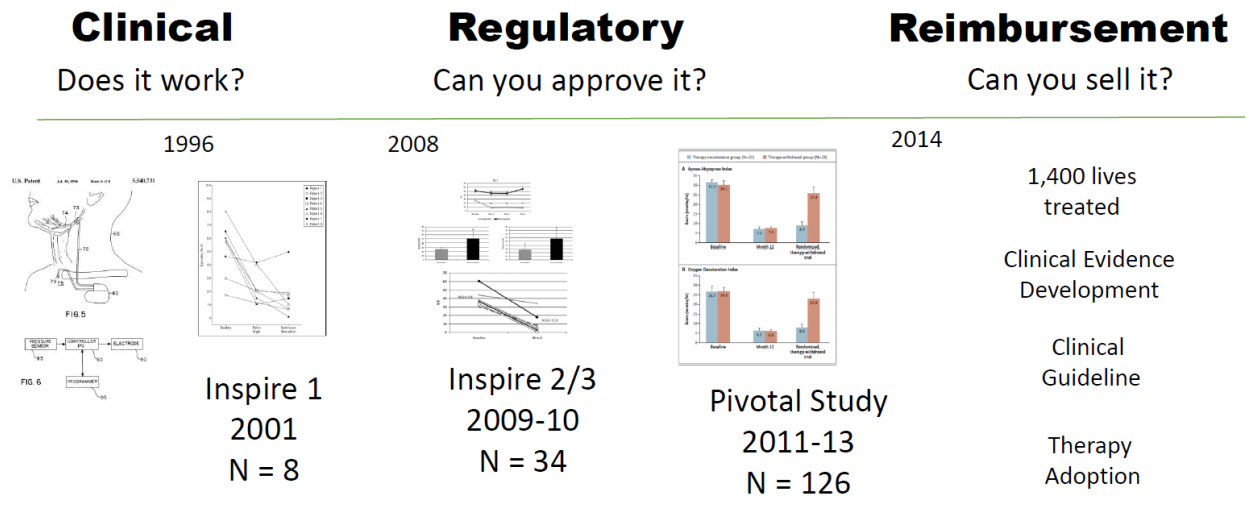


Fig. 5.4. The journey of a new medical device therapy – the case of Inspire's implanted neuromodulation device for Sleep Apnea[70]

Preparing the Workforce through Pre-Competitive, Cross-disciplinary Research

Interdisciplinary research facilities provide the venue and the laboratories for the disciplines to come together and their communities to interact, learn from each other, and inquire and discover together. However, they are lacking in the sustainable funding necessary for the development of the interdisciplinary workforce in solid numbers, expedient translation of discovery to actionable innovation and sustainable growth of the industry. An alliance of the relevant industry stakeholders can help to fill this gap. Industrial consortia specializing in management of industry-relevant fundamental research, such as SRC, offer a proper vehicle to accelerated innovation, workforce training, and transfer the research results to industry[72].

One of the goals of this collaborative research along with new curriculum development is to redefine medical practice and education to become a more quantitative systems-based discipline and move from the current model of examine, diagnose and treat to understanding the etiology and focus on health and wellness (Fig. 5.5). This goal can be achieved scientific and engineering discoveries in areas such as imaging, nanotechnology, computational, electronic health record, materials and device, tissue engineering and bio-manufacturing. A campus-wide effort driven by the college of engineering will have to participate and contribute. An example is being developed at University of Illinois[72].

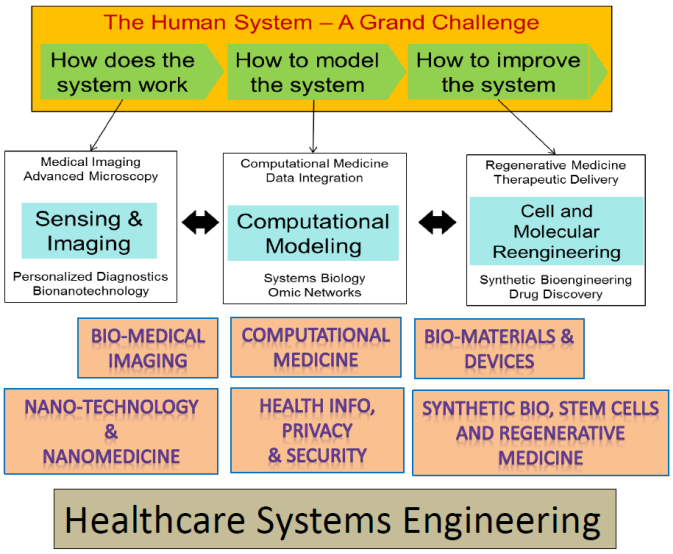


Fig. 5.5. Future of Medical Practice and Education[72]

Bridging the valley of death with open platforms and pilot lines

As catheters are becoming complex electronic systems with wireless connectivity, electronic industry has begun to play a leading role in the development of next-generation catheters. Smart Catheters developments in Europe represent a compelling example of successful public-private partnership[73].

Today's 1st generation smart catheters are analog instruments, use point solutions, and are not integrated in clinical Catheter Labs. The forthcoming 2nd generation of *digital* smart catheters will be built using on state-of-the-art technology and open technology platforms. They are expected to be fully integrated in the Catheter Lab infrastructure.

INCITE (Intelligent Catheters in Advanced Systems for Interventions) is a research project focusing on the development of a technology platform that will enable advanced imaging, sensing (pressure, force, biomarker) and steering functions to be integrated into (sub)millimetre size in-body catheters and surgical instruments for emerging complex minimally invasive cardio-, neuro-, and peripheral vascular interventions. The devices that are developed in the project are expected to accelerate the shift from costly surgical treatments to cost-effective and patient-friendly minimally invasive interventions[74]. INCITE is funded by the ENIAC Joint Undertaking, a public-private partnership for nanoelectronics research, bringing together the ENIAC member states, the European Commission, and the association of R&D actors in this field, to support growth and empower sustainable European competitiveness[74].

Further developments include consortia-building activities targeting a convergence between electronics and pharmaceuticals. One example, which is still in an early planning stage is the "SIMPEL" initiative (Smart Implantable Platform for Electroceuticals)[73].

Session V Roundtable Discussion Summary

A. Science and Technology

- Is science clear enough? Many startups have failed here, and very few people understand the science
- Neuromod is still like fixing a Swiss watch with a sledgehammer
- Technology is an enabler. We need smarter devices (IQ/mm^3) that can improve treatment, reach new targets, be cheaper, reduce the service burden, and be less invasive.
- Neuromodulation has such a broad range of power and energy needs, so there may not be a one size fits all
- Surgical tools can make a big difference. A new device size and implant location can enable new surgical tools, and vice versa.

B. Clinical issues

- On the physician's side, neuromodulation is not a medical discipline. Cardiologists or neurologists are not "neuromodulators". How do we connect the dots in the clinical practices? It's very hard to find a physician who knows how to implant a device! They just don't learn that.
- We need simpler, faster, implant procedures, that can be performed by more physicians at a lower cost.
- Will patients accept therapy? Patients don't want to deal with their device, just want to be healthy
- People in R&D need to go out and talk to patients and physicians, so don't lose sight of reality

C. Education

- Medical schools don't teach neuromodulation - we need Neuromodulation to become a medical discipline

D. Economics

- Changing reimbursement levels issue - You build your business case based on some reimbursement level, and that can change all of a sudden
- To really get COGS down, we need to get volumes up. But to get volumes up, we need to get total price as seen by the payer down

E. Regulations

- Changing regulatory requirements: FDA may change the threshold for acceptability, by e.g. requesting a control study with placebo

F. Partial List of Research and Collaboration Opportunities

- Industrial consortia specializing in management of industry-relevant fundamental research offer a proper vehicle to accelerated innovation, workforce training, and transfer of the research results to industry
- We may need to create a center of excellence, and a discipline of how to implant devices - make sure we get from patient to implanters!

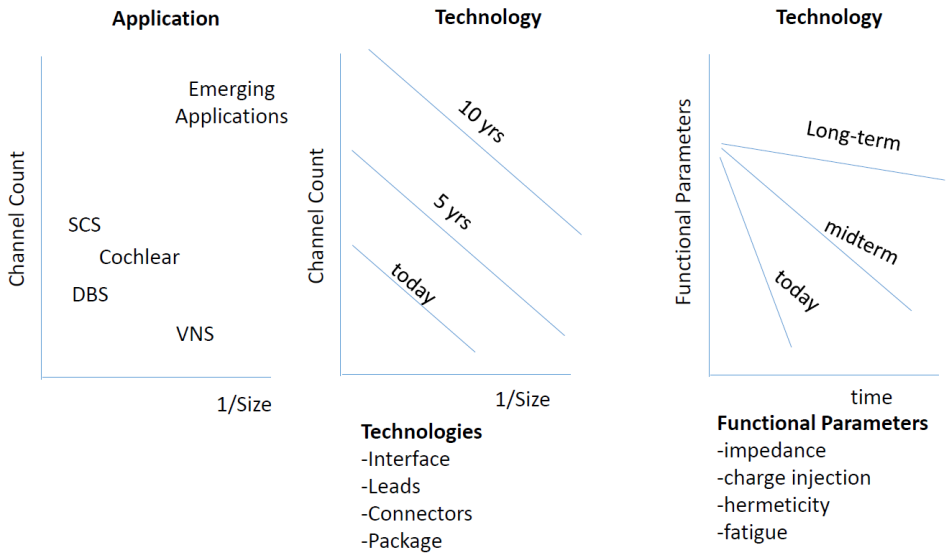
Breakout Groups Reports

Breakout Group 1: Biocompatible Materials for Bioelectronic Interfacing and Packaging

Facilitator: Rizwan Bashirullah - Galvani Bioelectronics

Research Needs:

1. Electrodes
    - Low impedance electrodes
    - High charge injection
    - Ionic interfaces (Hydrogels)
2. Dielectric encapsulation
    - High channel count leads
3. Packages
    - Interface integrated electronics
    - Transparency for telemetry
4. Anchoring methods
5. Accelerated testing
    - Focus on materials and processes
    - Independent evaluation
6. Biophysical modeling tools
7. Other
    - Absorbable materials
    - Drug elution
    - Mechanical compliance matching



Breakout Group 2: Devices, Sensors, Communications and Power Sources

Facilitator: Gene Civillico, NIH

Research Needs:

Three gaps from session yesterday: (1) unique packaging requirements; (2) communication in and out; (3) power.

GET RID OF LEADS.

- Change the processing to bring more onto the wafer so you don't have to bond it out.
- Connecting components inside the can.

SENSORS.

- Graphene, nano, 2D sensors,
- Chemical treatment of recording sites to lower noise
- Multimodal/Multiphysics
- Platforms e.g. Philips talk

POWER/COMMS.

- How do you power a millimeter scale implant that is 10 cm deep? (or, need a dense implantable battery).
- Time between recharges?
- Lifetime in body?

MINIATURIZATION.

- Small is interesting for injectable, etc. but small is not great if you need to modulate a large organ.
- Existing customers don't ask for miniaturization.
- ON semi, devices usually 2000-3000u on a side (stimulation ASICs).
- HAPTIX devices – cm-scale, functional improvements come from > maturity

PACKAGING

- beyond plastic/ceramic, but reconsider hermeticity requirement
- Identify and leverage IoT, technical advancements in software (this depends on solving the gaps above)
-

Option A: create one or more microcell platform technologies targeting needs

- Platform technology
    - Good demo capability to help people look forward
- Eliminate leads
- Impedance-lowering treatments
- Chemical treatments to amplify signal at the interface level
- Carbon fiber electrodes
- Stim and record combined – artifact cancellation
    - Multimodality – multiphysics to avoid interference

Option B: "Trusted middleperson"/module qualification and sharing

- Qualification to a spec – qualify elements for a library of functions.

- Why would TI or whoever, want to do this?
    - Incentive: Your component library is available for many applications
- If Regulatory is the bottleneck, generic materials with design files sitting at FDA -open up translation, Companies get productization going quicker
- More modular approach, design file etc. Record, stimulate, power, communicate
- SRC create a little foundry? Would not be their typical MO -> more like JUMP – DARPA-SRC
- Re-use IP for the medical space?

Option C: what is the next computing substrate?

- What does the next computing substrate look like and should it borrow from biology?
- Note that biological systems don't really separate functions - storage, energy, structure, memory, actuation are done simultaneously by organic molecules. Is this a clue?

Other considerations: education, clinical, roadmap etc.

- Interplay between surgeons and device companies
- How to talk to surgeons about new uses for technology
- New things are tough sells at first
- Create platforms – keep bringing the surgeons to ideate around them.
- Advisory board of innovative surgeons? Reality check.
- Engineering roadmap or grand challenge?
    - Roadmaps don't always have a good endpoint
    - Challenges are good ways to organize centers.
- Vertical centers with cross-cutting horizontal skill groups?
    - e.g. microcell
- Standardization: e.g. how much electrical stimulation is OK?
    - like what IEEE does

Breakout Group 3: System Architecture and Modelling

Facilitator: Ken Hansen - SRC

It was noted multiple times by presentations during the workshop the criticality and importance of taking a system view to a bioelectronic medicine in order to optimize the whole rather than focusing on a particular device or specification. Inherent in this comment is that the system design is application dependent and the requirements vary from one application to another. Furthermore, the ability to model at various abstraction layers has been demonstrated in many industries as the tool to enable innovation, reduce design cycle time and provide for the ability to design extremely complex but robust systems.

The team felt it important to develop a set of roadmaps that would provide for some "short" term successes but with an eye on an ultimate modelling and system design package as this is an extremely complex system consisting of elements from biology, chemistry, physics, electronics mechanics, optics, ultrasound and others. And that the system must be able to model complex interfaces such as the probe/tissue interface where there will be a transport conversion from charge or photons to ions. Further the system is complicated by the dynamics of human body movement and requiring the ability to be robust and non-interfering in the presence of traditional medical diagnosis such as CAT scans and MRIs.

With that as background, the team identified three areas to be roadmapped:

1. Application space
2. Modelling
3. Implementation

It was felt that a target of deep brain stimulation would produce the broadest impact in disease management and therefore be an opportunity for scale. However, there were significant issues with understanding where to locate the probe, probe stability, tolerance to MRIs and unintentional or dangerous consequences in the penetration of the probe to the deep layer. Therefore, this application was identified as a long term goal from a system modelling and architecture perspective. As one example of a shorter term application, the idea of using electroceuticals as a complimentary approach to pharmaceuticals was suggested. For example, the chemotherapy dose in treating some cancers is limited by a side effect of increased insulin release. If a counteractive electroceutical signal could be sent to deter this from happening, then the chemo dose could be increased to more aggressively fight the tumor. The benefits of such an electroceutical is that the battery pack and sensor could be carried outboard and the lifetime of the electroceutical would be 1-3 years both of which would dramatically simplify the system design requirements. It was suggested that an electroceutical that could control insulin, IL6 or dopamines to name a few could have many applications. Lastly it was suggested a target in the intermediate timescale should be focused at lifestyle diseases such as obesity or chronic pain management where there is not a life threatening immediate treatment required and there is a large volume opportunity. While with further study or understanding perhaps other applications would show higher promise, but the intent is to focus on a series of challenges with increasing difficulty where the challenge and the system design know-how are comparable.

As biologic systems are not well understood, modelling should have short term goals of developing high level models. At the same an effort should commence to develop deeper levels of abstraction such as at the cell level where the expectation is that success will be demonstrated further out in time. It was suggested that creation of the macro level biologic models should take advantage of data sets that are being collected. One example is to use the work in the NIH SPARC program that is building an atlas of nerve highways. From a modelling perspective, it's important not just to capture the path but the amplitude and phase of the signal such that a transfer function model can be built. As part of this effort, it was suggested that new modalities for data visualization be investigated, both as part of instrumentation for studying cause and effect and as post processing of simulation results such that it becomes possible for the human mind to grasp the impact of a proposed electroceutical.

Lastly, it was felt that for implementation in the shorter term that the equivalent of a PDK should be built that would consist of building blocks that are well known in various domains such as packaging, imaging, waveform generation, sensing, etc. This will provide a common understanding and a basis for collecting data from which more sophisticated models and/or PDK elements can be built. Having such a design kit provides the elements for building a platform that can be used in higher volume with a consistency and robustness from one electroceutical to another. Furthermore, as part of the PDK there should be any additional elements that would provide for an instrumentation set such that real time data collection is possible. As the maturity of models progress, the PDK elements would eventually include those level of abstractions allowing for simulation as well as prototyping.

From these roadmap desires, clear research needs drop out. It should be noted that some approaches to pursue for lower level model abstraction were defined well in Jamu's group 4 presentation. In addition, there is a need to establish metrics so comparisons of different approaches of a treatment can be accurately judged and absolute performance can be measured. A couple of examples where bioelectronics medicines are being utilized but yet no consistent metric exists are levels of pain and tremor attenuation.
To summarize, the vision of the team would be to create a biophysics co-simulation CAD environment with underlying models that supports design of bioelectronics medicines at multiple levels of abstraction such that system level to "component" level design, analysis and verification can be accurately performed. Achieving this goal is highly ambitious and thus it is team's recommendation to work both from the top down and the bottom up, take advantage of results understanding their limitations in accuracy as soon as possible, and apply them to simpler but impactful applications first.

Breakout Group 4: Targeting, Implants and Anchoring Methods

Facilitator: Jamu Alford - Medtronic

Alternate title: Where to put the device, how to get it there and how to keep it there?

Question 1: What is the relationship between size of the device and

- Implant location?
- Efficacy?
- Side-effects?
- Anchoring methods and forces?
- Sensing (noise, LFP vs. single neuron)?
- Patient motion?

Question 2: What is the patient risk related to

- Anchor failure?
- Wrong location – due to faulty targeting or placement or other?
- Due to plasticity does the location/efficacy change over time?
- Removability – short term vs. long term (degradable, disable-able (turn it off)
- Surface

Question 3: What imaging technology needs to be developed for visualizing during placement or presurgical planning?

- Unmet needs:
    - Needs of precision medicine to understand the spatial relationship of the target nerve(s) and/or regions for a the particular person at the time of implant. *Stealth Station* for bioelectric medicine.

Question 4: Feasibility of injectable devices which 'auto-locate' targets?

<u>Research Needs:</u>

- Predictable (electrical) model of neuronal vs electrode size/pattern, electrical fields and current density
- Predictable (mechanical) model of forces and motion (would be location dependent)
- Predictable model of tissue immune/damage response – tethered vs. free – non linear need to have a graph of size/response – in brain, near peripheral nerves, spinal cord, in organs. Including the biology of glial cells or other cell types beside the neurons. Including surface coatings to develop bioactive and stealth interfaces and drug eluting/delivery and dynamically changing devices
- Create artificial cells that provide neuronal interfaces – synthetic biology.

Notes:

- Neural interface and packaging may be separate dynamics
- Modular devices – dynamically change the number of or size of channels

Targets for the next 5 years, 10 years, and 15-20 years

A. Develop, validate and disseminate models (mathematical or computational) that accurately predict the long-term response of miniaturized devices. Models should have:

- Electrical model of neuronal activation vs electrode size/pattern, include electrical fields and current density (5-years down to 100um; 10-years down to 50 um; 20-years 10um) – both stimulation and record. Needs to describe the temporal variation in the target nerve structure (axon level adaptability)
- Mechanical model of forces and motion of tissues and devices as a function of size (5-years small animal; 10-years in human)
- Tissue immune/damage response model (tethered vs. free) with non-linear response – in brain, peripheral nerves, spinal cord, in organs. Including the biology of glial cells or other cell types as well as the neurons (5-years small animal). Model to include surface coatings to develop bioactive and stealth interfaces and drug eluting/delivery and dynamically changing devices (10-years in humans).

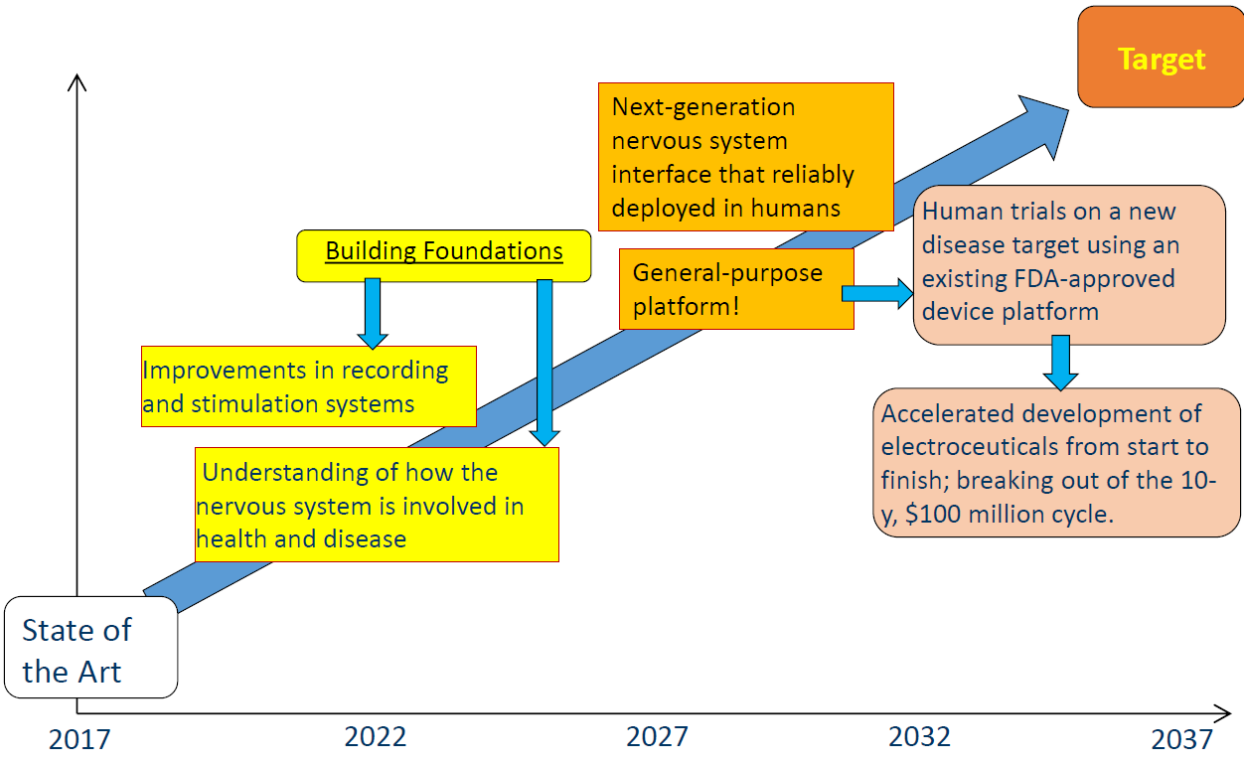
B. Enabled by these models

- Define optimum size/electrode patterns and materials for various targets
- Determine energy requirements and storage vs harvesting
- Select optimal materials and/coating
- Determine appropriate anchoring needs
- Understanding of the dynamics of the system and implant needs
- Quantify differences between animal model and human patient

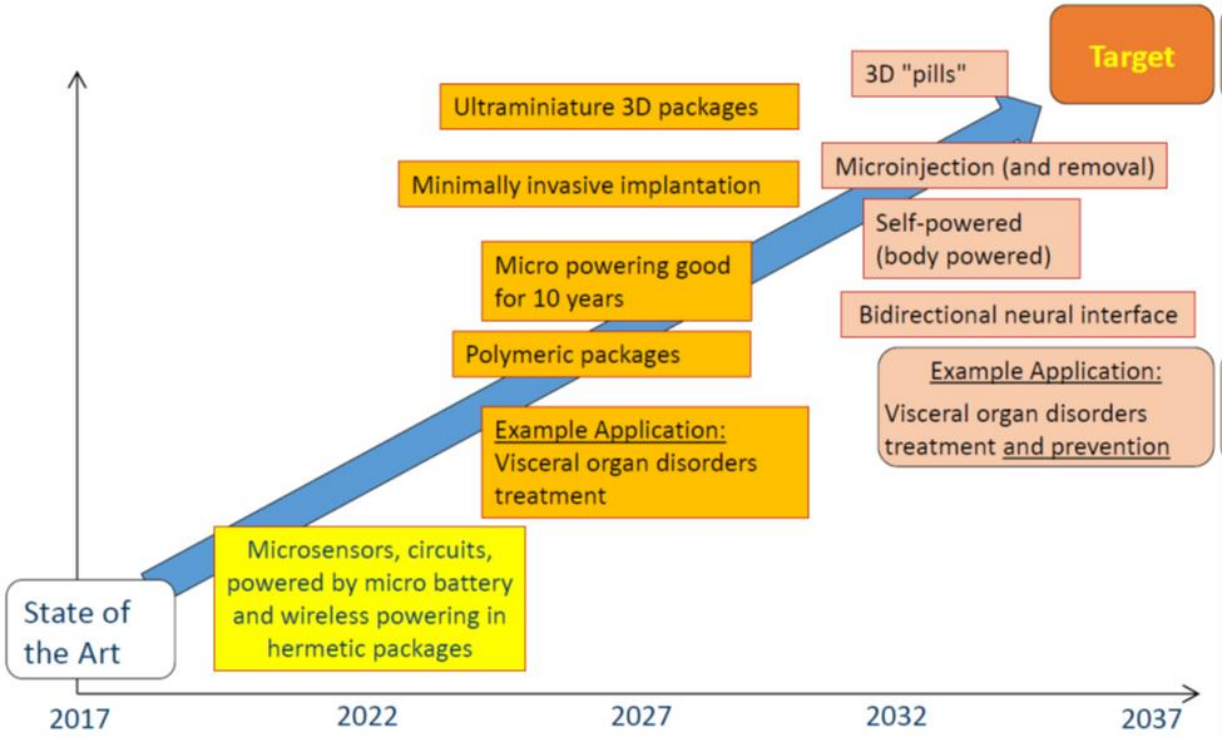
Roadmapping

In the following, a collection of very preliminary Bioelectronic Medicine (BEM) 'roadmap' charts is shown, based on the input from the workshop participants. Although incomplete, the roadmaps do identify important subelements of the bioelectronic medicine field and provide a high-level vision to drive forward. As a next step, these roadmaps will be expanded with more detailed steps and quantifiable measures.

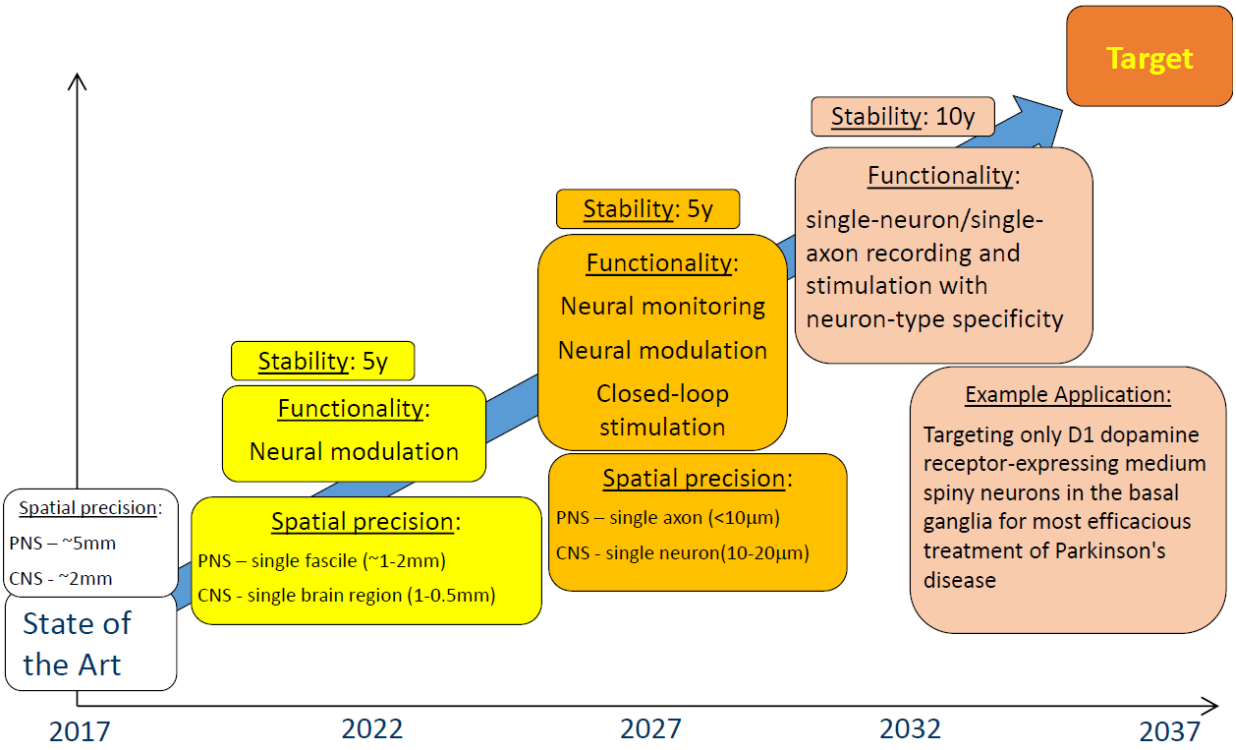
A. BEM Platform Roadmap



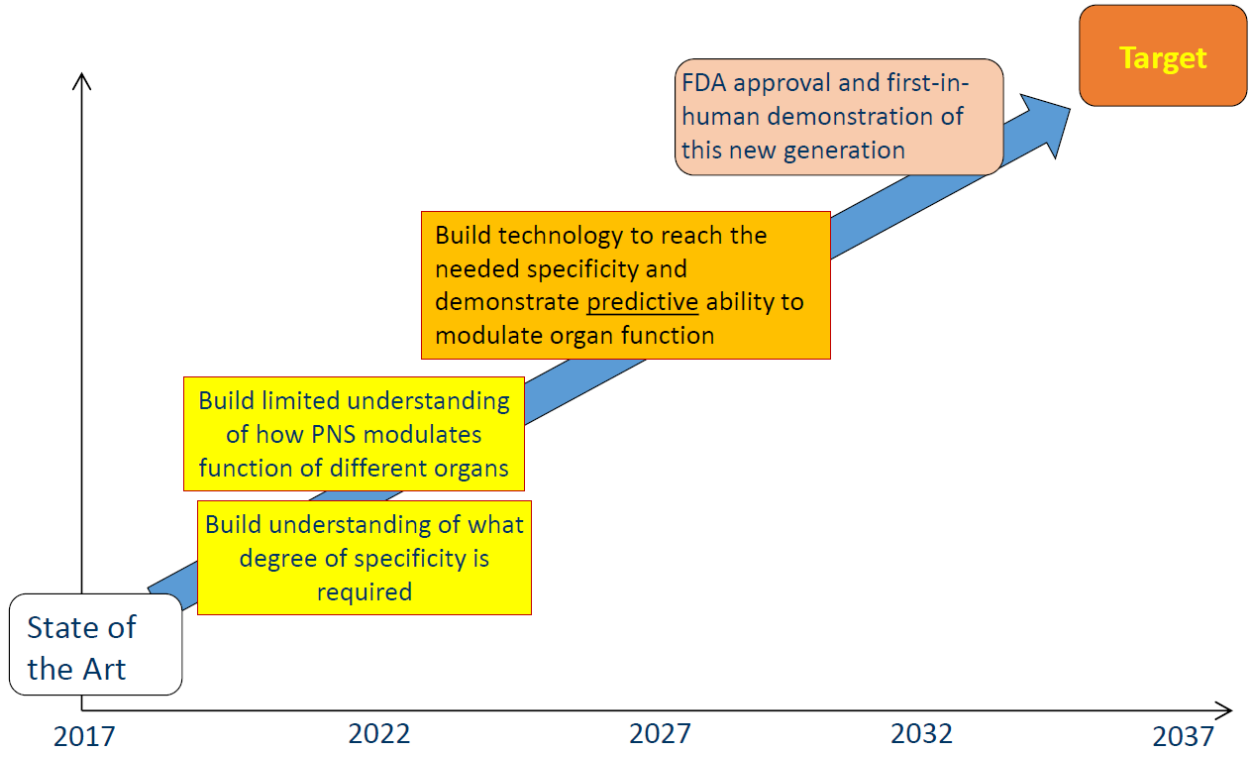
B. Miniaturization and Functionality

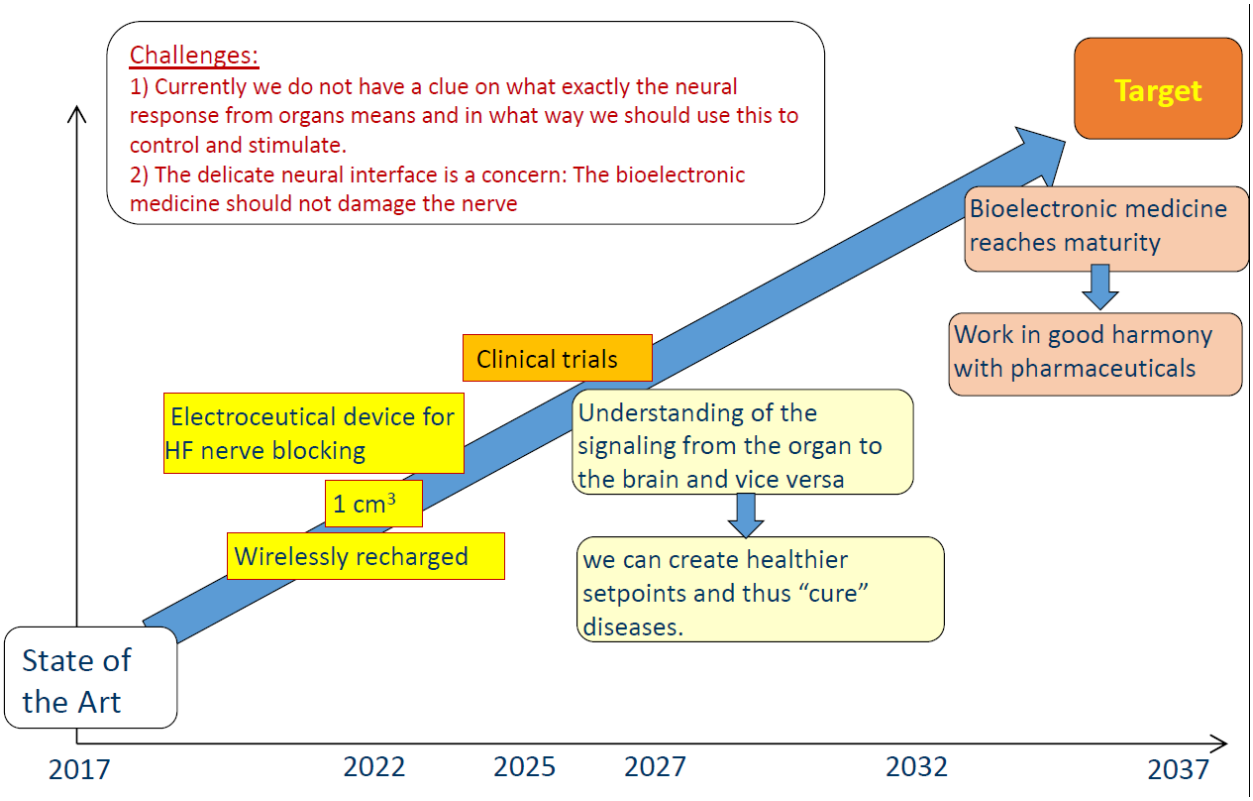


C. Target Precision

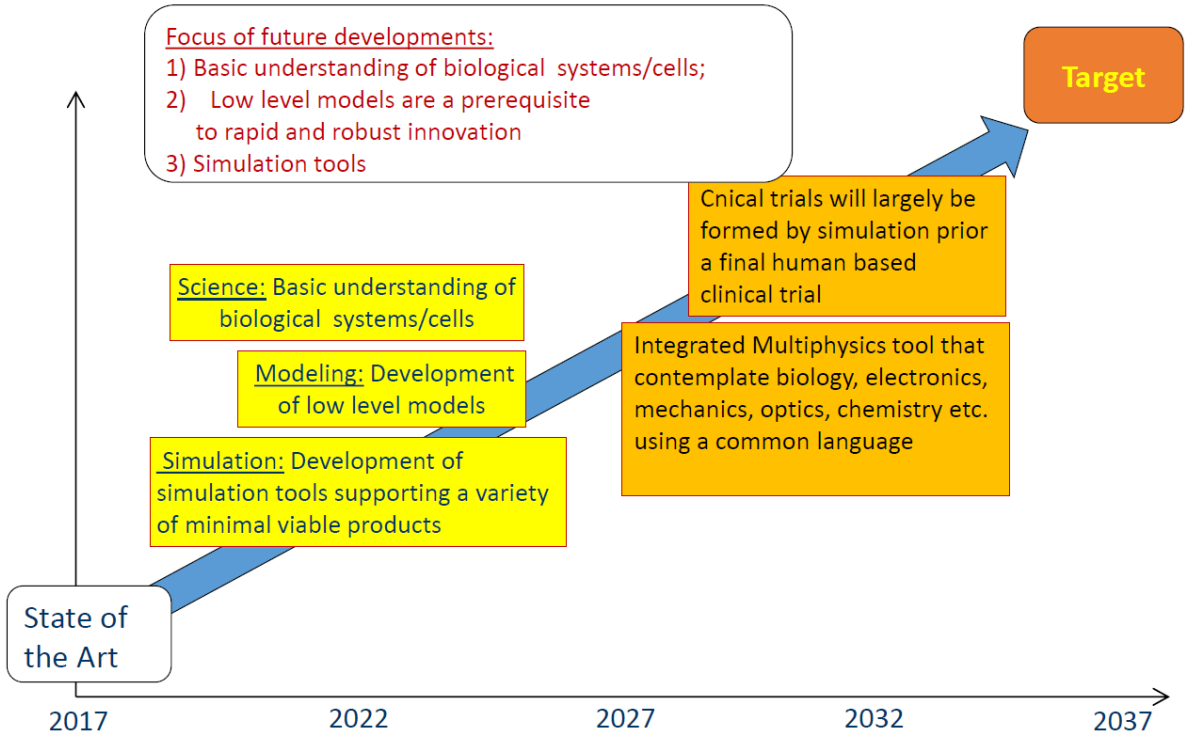


D. Instrumentation Capabilities

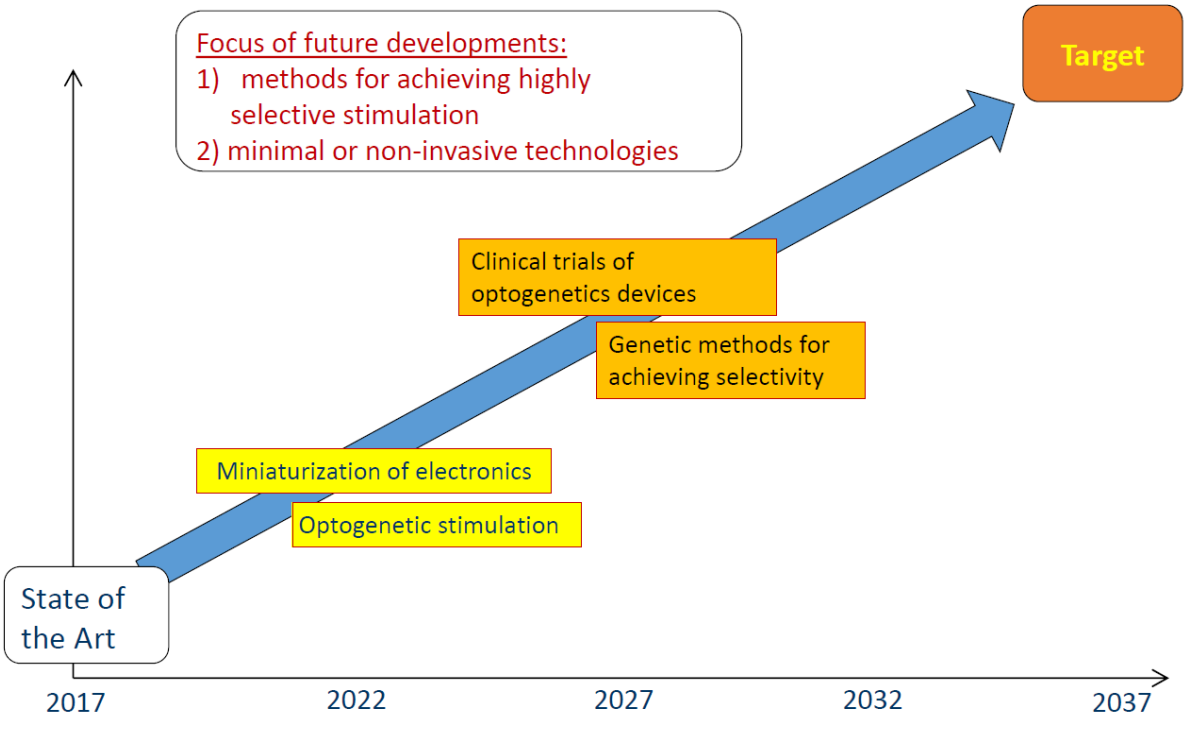




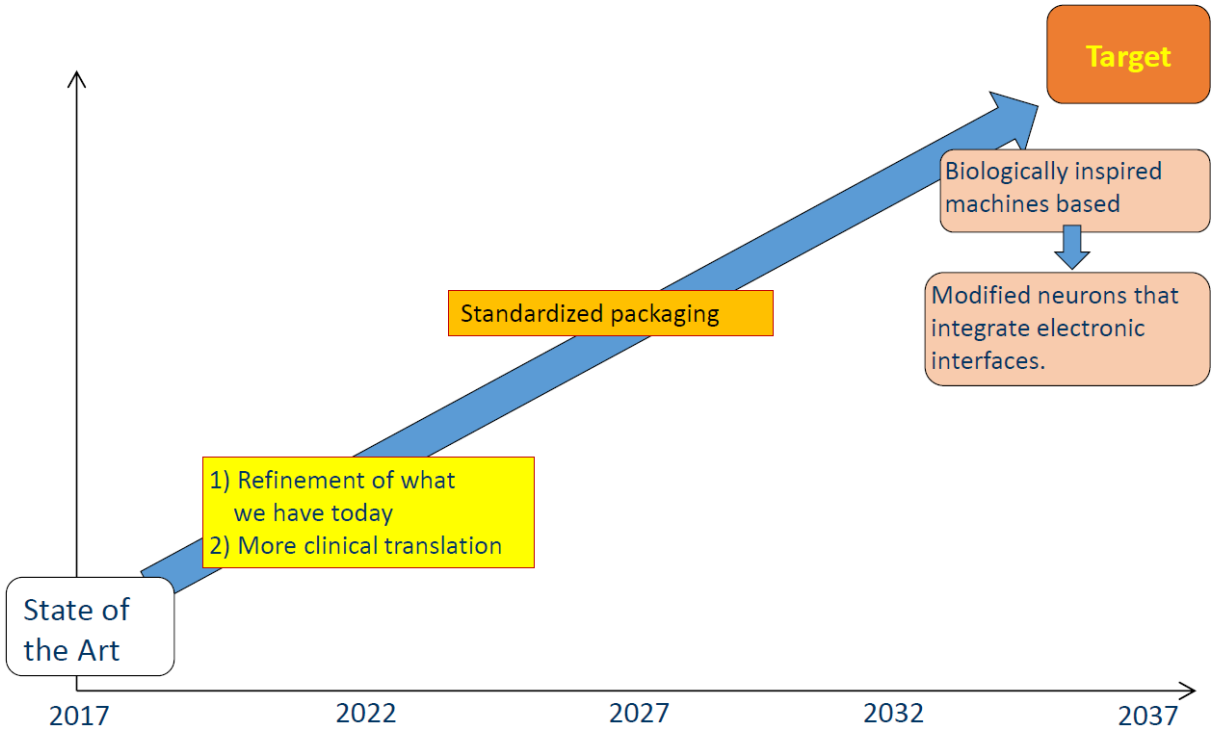
E. BEM Design Automation



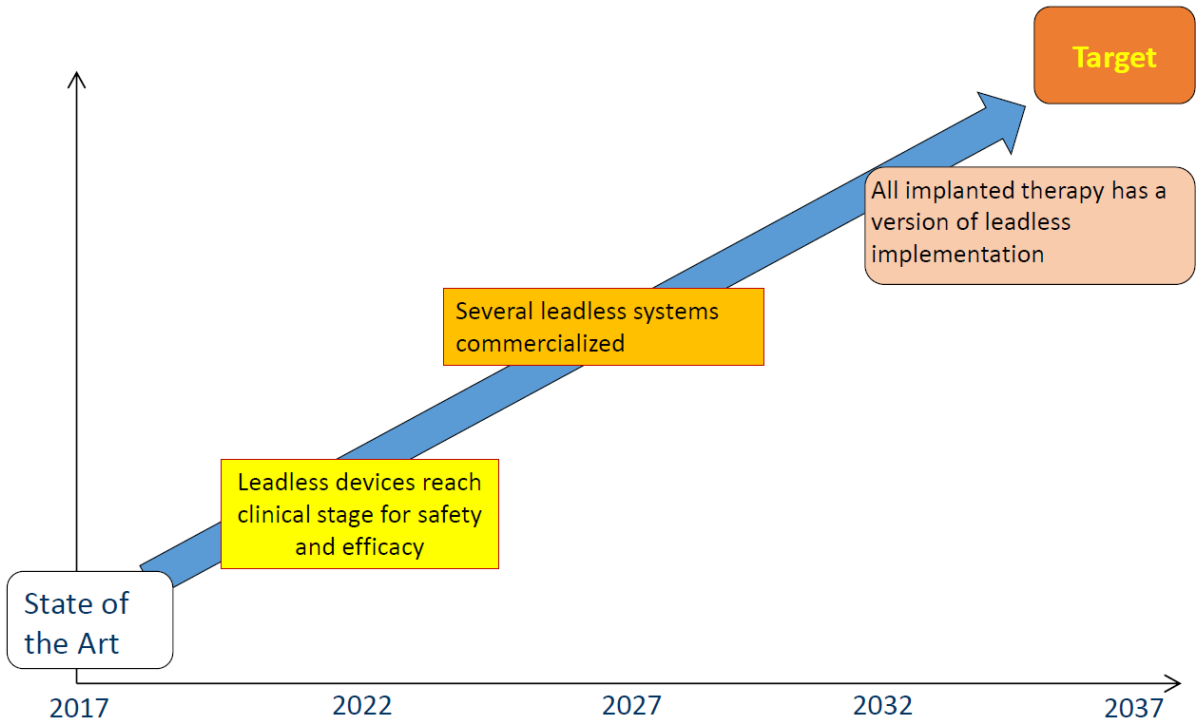
F. Highly selective Non-Invasive Stimulation



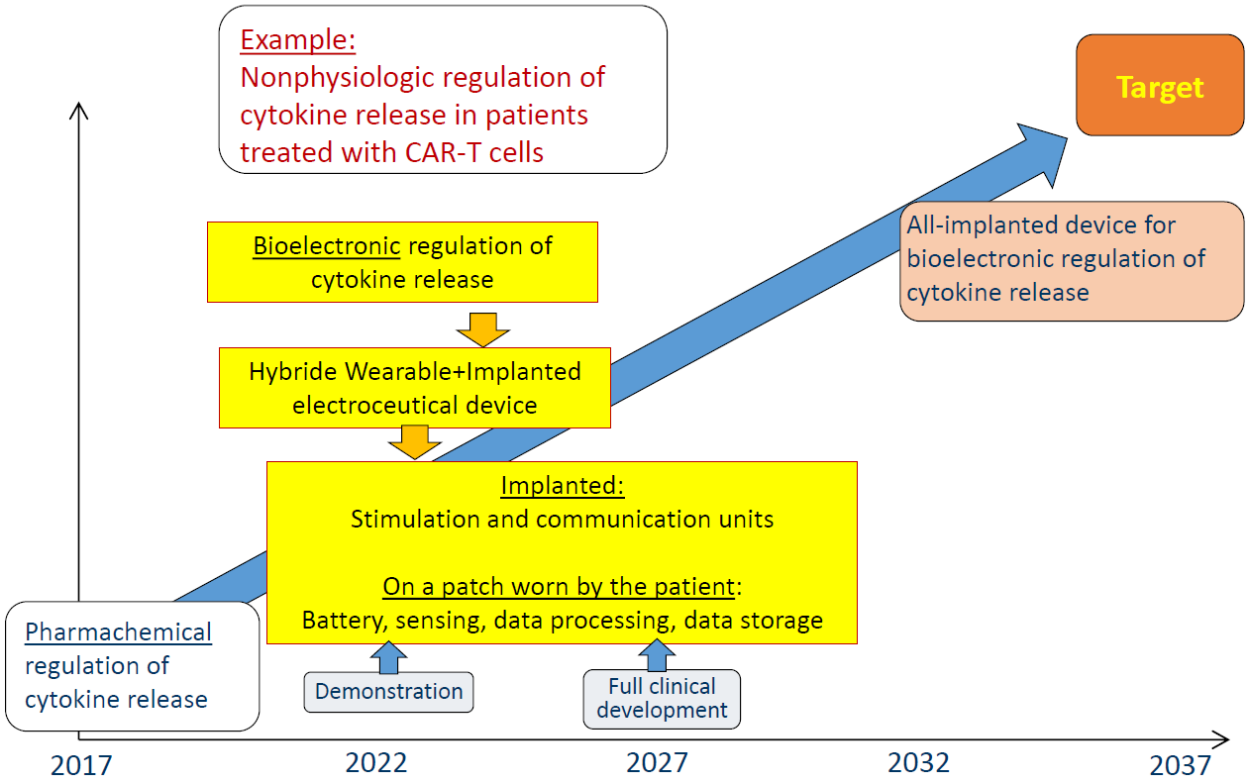
G. Biocompatible Packaging



H. Electrodes



I. Minimal Viable Product Roadmap (Example)



APPENDIX: Feedback from Participants

At the end of the workshop, all participants were asked to briefly answer the following 4 questions

- What is the major technical challenges?
- What is the major technical issue that you are interested in addressing?
- What is your view and vision for the next 5 years, 10 years, and 15-20 years?
- What is your take-home message from this workshop on bio-nanofabrication?

The responses are collected in this section.

1) **What is the major technical challenges?**

Unfortunately the entire system (engineering, biology and physics) are all still challenging. No part is 'easy'

The major technical challenges are mainly at the physical interface between device and tissue. For example, how to package a micro-scale implanted device? How to anchor a mm-scale or sub-mm device at a nerve? How to maintain a high-fidelity signal in the face of electrode or sensor movement, encapsulation, or degradation? How to deploy devices in the correct location? Other technical challenges that need to be addressed are mainly power and communication. Can rechargeable and wireless approaches become as reliable and user-friendly as primary batteries? Can we get high enough data transfer rates from small, deep-tissue implants without relying on wires or leads?

I believe the major technical challenges in the field of bioelectronics are: chronic stability, power delivery, data storage/communication, and targeting precision (specific region and specific types of nerves/neurons);

For the technical challenges, I will defer to the experts. On a macro level, I would note that the interplay between "technical advances" and "clinical utility" will be of great important to advance the field overall. This is an iterative process, and so regular coordination between the two is of critical importance.

The major technical challenges include the lack of understanding at electrochemical response at the electrode-tissue interface. The system approach for miniaturization for a leadless device is another major challenge.

Developing small, selective devices that also meet the reliability standards (say, at least 1 year) that are necessary for an implanted device in humans. From a HAPTIX perspective, many rounds of optimization and testing are necessary to achieve this.

Major technical challenges:

- Probe to tissue interface – mechanical stability and electrical signal transfer
- Packaging – corrosion sensitivity of the electronics (hermiticity) and diffusion of what's becoming the periodic table from the electronics to the human
- Dissolvability when useful life is complete
- Basic understanding of biological systems/cells such that no low level models exist which are an impediment to rapid and robust innovation

Major technical challenges:

- Building fully, chronically implanted systems (that integrate all aspects, sensors, circuits, power, packaging)
- Accelerating animal testing to human implant (with regulatory approval)

Technical challenge is to take a systems engineering approach to building a system when the target (biology) is so poorly understood and the research community does not understand systems engineering. Specifically, if you ask a neuroscientist what gizmo they want, they'll ask for absolutely everything and be completely unable to prioritize or make tradeoffs in capability (storage vs size vs heat vs compressibility of data).

As they are tiny, in the order of 1 cm^3 or even 1 mm^3, the amount of discrete and bulky components needs to be reduced drastically. This includes the use of coupling capacitors, batteries, packaging material, connectors, electrodes, antennas, etc. As they operate in a closed-loop manner, the tiny signals received from the sensors and the electrodes need to be acquired without too much noise and interference and converted into the digital domain, after which they are cleaned up further and classified and clustered before an appropriate electrical or optogenetic stimulation control action can be taken. Moreover, as there is no room for a battery that can support the electroceutical over its life time, alternative forms of energy generation, transfer and management need to be developed to power the implant. Finally, new forms of biocompatible packaging and encapsulation techniques need to be introduced that are more compliant with the body and will not damage the nerve cells that the electroceutical is in contact with and has to stay in contact with for many years.

2) **<u>What is the major technical issue that you are interested in addressing?</u>**

Create a standard high-channel feedthrough. This would have a technical specification, and if possible a manufacturer that all bioelectric companies could buy from.

I am personally interested in investigating how to incorporate wireless power and communication into a minimalistic, monolithic, and distributed system. I think that working to

build such a platform can give some insight into how to address more specifically some of the issues at the device-tissue interface.

I am most interested in addressing the following challenges: improving chronic stability by reducing the glial scarring at the neural/electronic interface, and improving the targeting precision via both mechanical and biochemical advances.

From a clinical utility perspective, I think if we can solve the technical challenge around "modulation" and "comms" on the implanted device, and keep the other components (battery, sensing, data processing, data storage) outside (e.g. on a patch worn by the patient), then we have a "minimum viable product" with a path to the clinic (example use case: regulate cytokine release in patients treated with CAR-T cells https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119809/).

I am interested in addressing the system requirement for a miniaturized leadless device for peripheral nerve stimulation.

Neural interface designs that are capable of providing highly selective stimulation of targeted nerve fibers. Ideally, this would include the ability to stimulate both anatomically defined regions of the nerve (potentially down to the single fiber), as well as the ability to target specific fiber types.

Modelling and system simulation
- Developing novel sensors and circuits to develop "bidirectional" interfaces for neuromodulation
- Developing suitable animal models and clinical partnerships for rapid translation

I'm addressing mechanistic understanding of underlying nervous system. Building technology to understand and interface with the PNS.

I feel very comfortable with the electronic aspects of energy harvesting, neural stimulation, neural recording, wireless power transfer. Think of RF energy harvesting with greatly enhanced efficiency because of antenna-electronics co-design, power efficient neural stimulation from the same voltage supply as the one being used for neural recording (single voltage domain), recording on top of the stimulus and artifact and optogenetic stimulation. My direct colleague Vasili Giagka feels equally comfortable with flexible encapsulation and packaging and monitoring of the reliability of the implant. We will work on these aspects further.

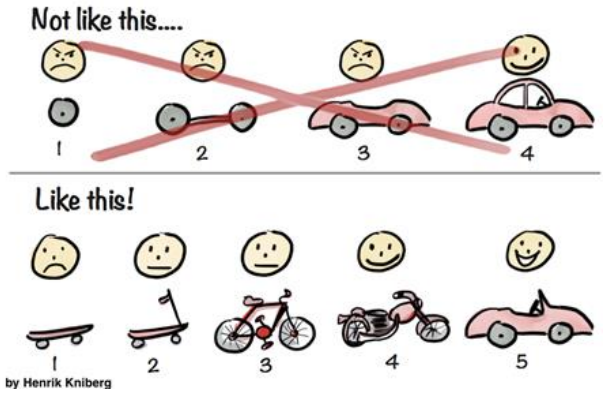
3) **What is your view and vision for the next 5 years, 10 years, and 15-20 years?**

5-years refinement of what we have today plus more clinical translation; 10-years standardized packaging; 20-years is biologically inspired machines based – e.g. modified neurons that integrate electronic interfaces.

I think in the next 5 years, we need to begin building foundations both from the bottom-up and top-down. By this, I mean designing better recording and stimulation systems, but also using them to improve our understanding of how the nervous system is involved in health and disease, which should in turn drive more specific design goals for future devices. In 10-15 years, we should have a next-generation nervous system interface that can be reliably deployed in humans. Having a general-purpose platform is key: if we can move into human trials on a new disease target using an existing FDA-approved device platform, we can really start to accelerate the pace of electroceutical development from start to finish, and break out of the 10-year, $100 million cycle.

My view and vision for the next 5, 10 and 15-20 years: in 5 years from now, I envisage 5-year chronically stable interface for neural modulation with spatial precision at the level of single fascicle in PNS or single brain region in CNS; in 10 years from now, I envisage 5-year chronically stable interface for both neural activity monitoring and modulation (with closed-loop stimulation) with spatial precision at the level of single axons in PNS or single neuron in CNS; in 15-20 years from now, I envisage 10-year chronically stable interface for both single-neuron/single-axon recording and stimulation with neuron-type specificity (such as targeting only D1 dopamine receptor-expressing medium spiny neurons in the basal ganglia for most efficacious treatment of Parkinson's disease).

I would suggest we should strive for having a minimal viable product / platform within 5 years. I.e. that is has the minimum viable functionality with path to clinic (see above), while it's OK that some longer term design goals are not yet met. And also that it's a platform i.e. a device that has the inherent potential of modulating multiple nerves, perhaps even multiple nervous system, rather than single purpose device. Within 10 years these should be in full clinical development.
See illustration below



In 5 years, a leadless device will reach clinical stage for safety and efficacy; in 10 years, several leadless systems will be commercialized. In 20 years, all implanted therapy will have a version of leadless implementation.

I think a focus of future development should be on methods for achieving highly selective stimulation with minimal or non-invasive technologies. This could be accomplished through the

miniaturization of electronics, as many are pursuing now, and by continuing to vet alternative approaches. In the research domain, for instance, optogenetics is a strong, established method for achieving highly selective fiber stimulation. On a ten year scale I think it is important to watch the progression of clinical trials in the optogenetics space, and keep an eye on potential opportunities to incorporate genetic methods for achieving selectivity.

The opportunity for alternative treatments is huge but taking advantage of those opportunities will be limited/accelerated by the amount of research the combination of industry and government are willing to invest. It is likely there will be benefits for other applications that at the moment are hard/impossible to predict. To move forward, within 5 years a challenge that would focus and organize the effort should be placed towards which the combined interests can tackle. In the 15-20 year timeframe models should be sophisticated enough that innovation is only limited by creativity and that clinical trials should largely be formed by simulation until a final human based clinical trial is performed (in necessary), but those should normally pass with no issues.

5 years: Microsensors, circuits, powered by micro battery and wireless powering in hermetic packages
10 years: Minimally invasive implantation of ultraminiature 3D packages of compliant sensors and circuits with micro powering good for 10 years in polymeric packages to treat visceral organ disorders
20 years: Microinjection (and removal) of 3D "pills" to treat visceral organ disorders through bidirectional neural interface that are self-powered (body powered) to treat or prevent visceral organ disorders.

5 years: build limited understanding of how PNS modulates function of a handful of organs, build understanding of what degree of specificity is required
10 years: build technology to reach that specificity and demonstrate predictive ability to modulate organ function
15 years: FDA approval and first-in-human demonstration of this new generation

It will need quite some water under the bridge (in the Netherlands we say water in the Rhine River) before the devices that some of us target will become a reality. Currently we do not have a clue on what exactly the neural response from organs means (the decoding) and in what way we should use this to control and stimulate. Also, the precious and delicate neural interface is a concern. A bioelectronic medicine should not damage the nerve bundle/fascicles/fibers. However, that said, I believe we might have a prototype of a 1cm^3 HF [high-frequency (2–10 kHz) sinusoidal currents] blocking [nerve] electroceutical that is wirelessly recharged in 5 years and that is going into clinical trials in about 8 years. In 10-15 years, we probably will understand much more, perhaps even exactly how the signaling from the organ to the brain and vice versa is being done and thus how we can create healthier setpoints and thus “cure” diseases. In 20 years from now the bioelectronic medicine have reached maturity and will work in good harmony with pharmaceuticals.

4) **What is your take-home message from this workshop on bioelectonic medicine?**

This will not be easy since the application/therapy space is so large.

I think there were two points that resonated strongly with me after this workshop. First, we don't have a good sense of the application space, and what specs (from a device design perspective) are really NECESSARY to succeed. In other words, its hard to design interfaces for a biological system that we don't really understand. Secondly, technical success isn't enough to make electroceuticals a reality. A holistic approach is necessary- considering human factors, device lifetimes, financial considerations and even public perception. Without all the pieces of the puzzle, it will be an uphill battle to get bioelectronic medicine off the ground. However, I still believe that we may be at the beginning of a tipping point for broad adoption of nervous system interfaces, and the sooner we can corral these elements together the sooner the vision can be realized.

I really learned a lot from all the talks given by experts in this field, in particular your talk, at this workshop. The biggest take-home message to me is that, when designing next-generation bioelectronics for medical applications, the underlying physical principles, such as the energy density of battery material, information/bit density of storage material, permeability and biocompatibility of the packaging material, should always be taken into consideration, especially when one is faced with the pressing need for miniaturization and longevity of the implantable devices.

Tremendous advances in engineering, and rapidly progressing insights in electronic signaling pathways of the human physiology are driving great progress in bioelectronics medicine.

An opportunity for the pre-competition collaboration on bioelectronic medicine is to develop comprehensive models of electrode-tissue interface.

There are a lot of really wonderful concepts and proof-of-principle technologies for overcoming a number of the technological challenges that have been discussed in this meeting. I think a lot of work needs to be done vetting and optimizing potentially viable approaches, pushing for reliability, and testing in animals and humans. We should be cognizant that funding for this phase of device development is the hardest to get. I think we should also take a close look at technology needs on a condition by condition basis. What conditions can be treated with existing, low channel count, clinically available devices? What conditions require advances (smaller form factor, higher selectivity, longer battery life) and can mature preclinical devices (such as those in the HAPTIX program) be hijacked for these purposes? Given the cost and time required to mature technologies, I think it is important to make sure the technology advancements that are invested in are clearly meeting the needs of treatment and filling gaps in the field.

There is a lot of exciting work going on. We collectively need to harness and focus it to demonstrate short term but meaningful impact to build momentum beyond the small community that sees the possibilities today.

This is truly a multi-disciplinary initiative that needs complementary expertise to address grand challenges through academia-industry-clinician partnership.

Take-home message: Great promise through integration of technology to build a new kind of medicine, but it's important to set realistic expectations.

A great network! The noses have been put into the same direction. There is a common sense of urgency. We are on the right track. Bioelectronic medicine has still a lot of hurdles to overcome, but there seem to be no fundamental brick walls. We will do a special issue on electroceuticals to inform the community. Who else in the world (apart from the US and 2 from Europe and ½ from Singapore) are they working on this? As an educator, how do I prepare my students in Biomedical Engineering and Microelectroncis for this exciting career best?

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