# 2018 BioElectronic Medicine Roadmap

Semiconductor Research Corporation

NIST

# Message from the Editorial Team

We are delighted to introduce the 1st Edition of the Bioelectronic Medicine (BEM) Technology Roadmap, a collective work by many dedicated contributors from industry, academia and government. It can be argued that innovation explosions often occur at the intersection of scientific disciplines, and BEM is an excellent example of this. The BEM Roadmap is intended to catalyze rapid technological advances that provide new capabilities for the benefit of humankind.

## Editorial Team

**Renée St. Amant**
*Staff Research Engineer (Arm)*

**Victor Zhirnov**
*Chief Scientist (SRC)*

**Ken Hansen**
*President and CEO (SRC)*

**Daniel (Rašić) Rasic**
*Research Scientist (SRC)*

# Table of Contents

# Acronym Definitions

| | |
|---|---|
| 1D | One-Dimensional |
| 2D | Two-Dimensional |
| 3D | Three-Dimensional |
| A/D | Analog-to-Digital |
| ADC | Analog-to-Digital Converter |
| AFE | Analog Front-End |
| AI | Artificial Intelligence |
| ALD | Atomic Layer Deposition |
| AMS | Analog-Mixed-Signal |
| ANS | Autonomic Nervous System |
| ASIC | Application-Specific Integrated Circuit |
| AWG | Arbitrary Waveform Generator |
| BEM | Bioelectronic Medicine |
| BER | Bit Error Rate |
| BJT | Bipolar-Junction Transistor |
| CAV2 | Canine Adeno Virus (serotype 2) |
| CMAP | Compound Motor Action Potentials |
| CMOS | Complementary Metal-Oxide-Semiconductor |
| CNS | Central Nervous System |
| DARPA | Defense Advanced Research Project Agency |
| DBS | Deep Brain Stimulation |
| DNA | Deoxyribonucleic Acid |
| DR | Dynamic Range |
| EEG | Electroencephalogram |
| EKG | Electrocardiogram |
| EMG | Electromyography |
| EMR | Electronic Medical Record |
| ESD | Electrostatic Discharge |
| FCC | Federal Communications Commission |
| FDA | Food and Drug Administration |
| FF | Form-Factor |
| FOM | Figure of Merit |
| FRAM | Ferroelectric Random-Access Memory |
| GDP | Gross Domestic Product |
| HW | Hardware |
| IC | Integrated Circuit |
| IDE | Investigational Device Exemption |
| I/O | Input/Output |
| IPG | Implantable Pulse Generators |
| ISM band | Industrial, Scientific and Medical radio bands |
| JFET | Junction Gate Field-Effect Transistor |
| LUT | Lookup Table |
| MIPS | Million Instructions Per Second |
| ML | Machine Learning |
| MRAM | Magnetic Random-Access Memory |
| MRI | Magnetic Resonance Imaging |
| MVP | Minimum Viable Product |
| NEF | Noise Efficiency |
| NESD | Neural Engineering System Design |
| NIST | National Institute of Standards and Technology |
| NVM | Nonvolatile Memory |
| OCD | Obsessive-Compulsive Disorder |
| PNS | Peripheral Nervous System |
| PCRAM | Phase-Change Random-Access Memory |
| PDMS | Polydimethylsiloxane |
| PEDOT | Poly(3,4-ethylenedioxythiophene) |
| PET | Positron Emission Tomography |
| PMA | Pre-Market Application |
| R&D | Research and Development |
| RF | Radio-Frequency |
| RNS | Responsive Stimulation System |
| RRAM | Resistive Random-Access Memory |
| SEMISYNBIO | Semiconductor Synthetic Biology |
| SNR | Signal-to-Noise Ratio |
| SRC | Semiconductor Research Corporation |
| SW | Software |
| TWG | Technical Working Group |
| VCO | Voltage-Controlled Oscillator |
| VNS | Vagus Nerve Stimulation |
| WDT | Wireless Data Telemetry |
| WPT | Wireless Power Transfer |

# Introduction

## Who We Are & What We Do

*Bioelectronic Medicine (BEM) can revolutionize how we practice medicine and dramatically improve the outcomes of healthcare. It employs electrical, magnetic, optical, ultrasound, etc. pulses to affect and modify neurological behavior which in turn impacts body functions as an alternative to drug-based interventions. Furthermore, it provides the opportunity for targeted and personalized treatments of neurological based diseases and conditions in closed-loop control systems. Bioelectronic medicine aims to dramatically improve the outcomes and reduce the cost of healthcare.*

A grand societal and technology challenge as the population grows and ages is to sustain and improve the quality of life for the 7.6 billion people on the Earth. Domestically, healthcare expenditure accounts for more than 17% of gross domestic product (GDP), or more than 3.2 trillion U.S. dollars, and is projected to grow to more than 20% by 2020. Remarkably by one estimate, up to 40% of this healthcare expenditure is wasteful. We envision a future where bioelectronic medicine will revolutionize how we practice medicine and dramatically improve the outcome and reduce the cost of healthcare.

Innovation explosions have increasingly occurred at the intersection of scientific disciplines. In the case of BEM, it has become increasingly clear that the intersection of information processing with our understanding of biological systems from the molecular level to body scale will be an important area of innovation and growth. Today at this intersection, various information processing approaches to disease treatments through sensory and diagnostic interfaces and therapeutic solutions, such as electrical neuromodulation, have been developed.

In both the diagnostic and therapeutic space, semiconductors play key roles in the design. As such, a joint research effort of practitioners in medical and semiconductor disciplines is needed. This joint effort is expected to result in unprecedented breakthroughs in both the understanding of the nervous system as an information system and the development of electronics technology to interface with the nervous system.

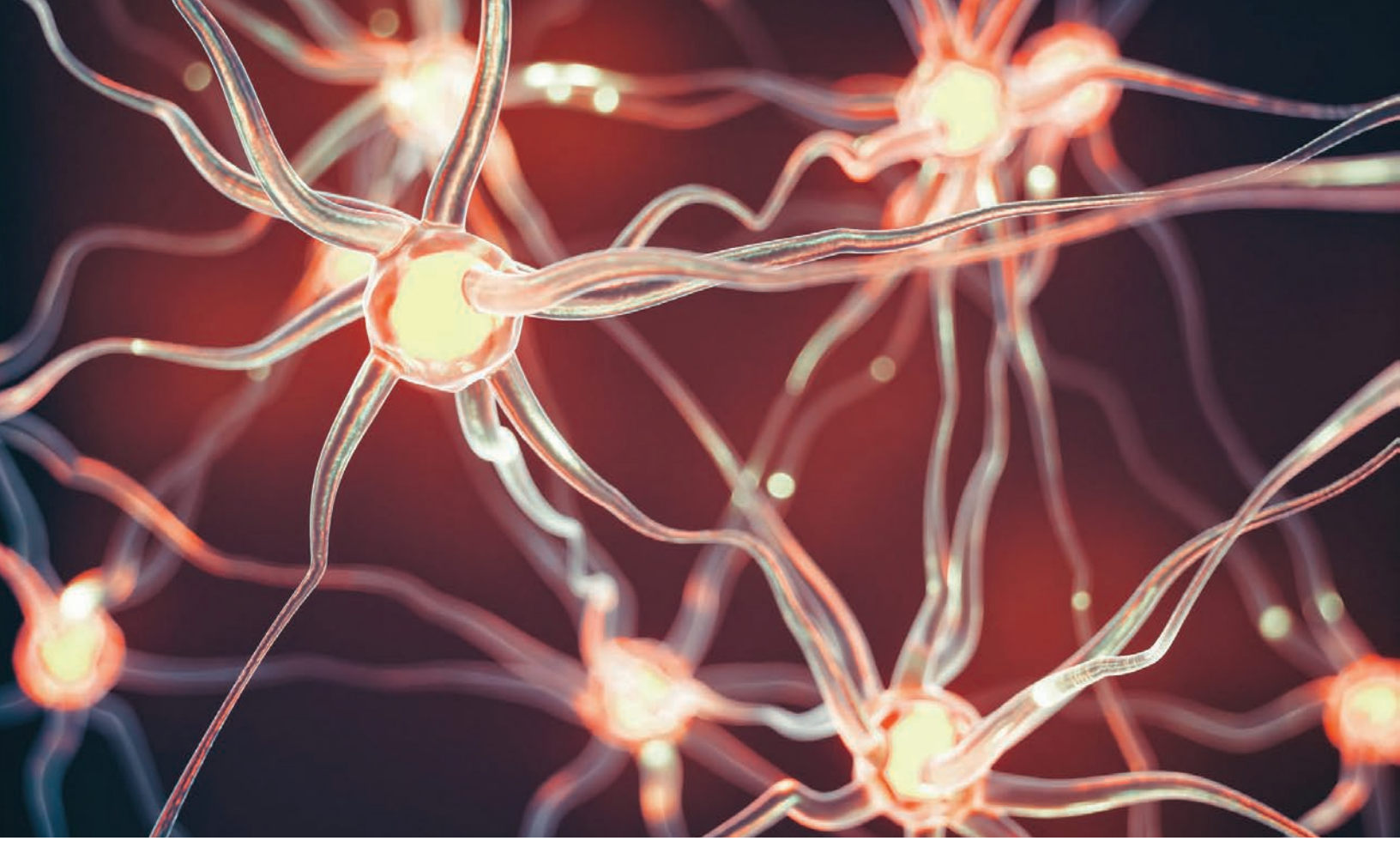
New developments in semiconductor technology will provide revolutionary tools and instrumentation for fundamental biological discoveries and medical applications. Novel materials will provide packaging solutions for ultra-miniature bioelectronics devices readied for chronic implantation. Sophisticated software strategies will provide the logical “glue” between biology and semiconductors. Any Bioelectronic Medicine solution must, of course, interface to human organs (particularly the nervous system) and effectively affect functions, treat a specific disease, disorder or injury, and avoid any complications or side effects.

A critical activity for the emerging Bioelectronic Medicine has been the development of a BEM Technology Roadmap. This Roadmap is intended to serve as a planning tool that connects the societal trends and challenges facing a product or industry with the technologies needed to address them. It is also intended to help guide the future investments in this emerging field of medicine.

The Technology Roadmap for Bioelectronic Medicine covers neuromodulation for therapeutic applications, fundamental physics limits of the essential components of bioelectronic devices, and interfaces between biological systems and bioelectronic devices. It also highlights challenges of developing closed-loop bioelectronic microsystems for personalized treatments and offers directions for future research and development in this emerging field of medicine.

To develop a comprehensive Technology Roadmap for Bioelectronic Medicine, joint efforts of experts from different disciplines have been employed: biology, chemistry, computer science, electrical engineering, materials science, medicine, neuroscience, neurosurgery, physics, and semiconductor technology.

The BEM Technology Roadmap addresses a 10-20-year timeframe, embracing both current and projected needs. It serves as a guide for university researchers who will train the entrepreneurs, engineers and scientists who will lead the creation of this new industry. It is expected that many startups emerge from the research to commercialize these new approaches.



Chapter 1

# BEM Roadmap Overview

## 1.1 Introduction

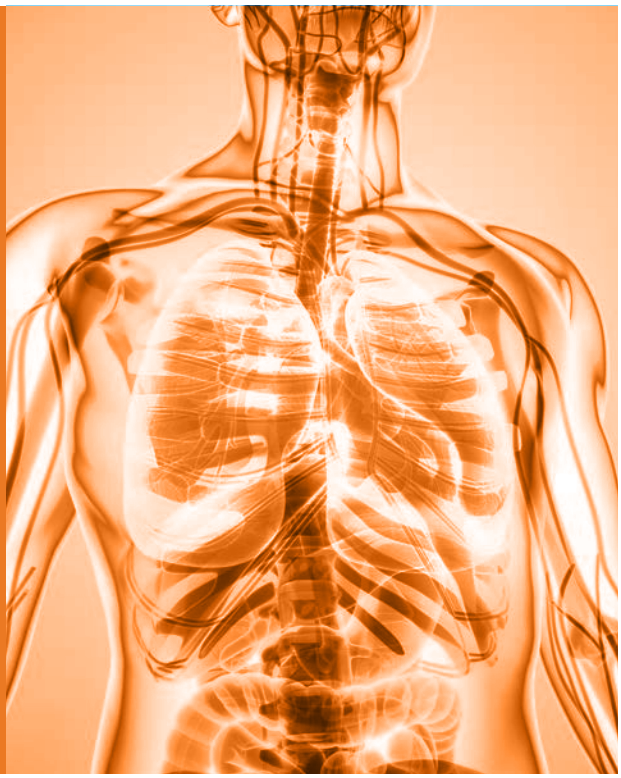
Two million adverse drug reactions are observed in the U.S. each year. They are the 4th leading cause of death, ahead of pulmonary disease, diabetes, and automobile deaths [1]. What if we could treat disease and injury without drugs? Bioelectronic Medicine (BEM), which uses neurotechnologies to interface with the nervous system, can offer such opportunities. Neurotechnologies are among the fastest growing segments of the medical device market [1]. Many diseases can be treated, in principle, by precise modulation of the body's nerve signals **(Figure 1.1)**.

Bioelectronic Medicine can revolutionize how we practice medicine, reduce cost and dramatically improve the outcomes of healthcare. It employs electrical, magnetic, optical, ultrasound, etc. pulses to affect and modify nerve behavior, which in turn impacts body functions as an alternative or supplement to drug-based interventions. Furthermore, it provides the opportunity for targeted and personalized treatments of diseases and conditions with closed-loop control systems.

The purpose of the BEM Technology Roadmap is to capture the high-level work necessary to meaningfully advance neurotechnology-based diagnosis and treatment of diseases at an accelerated rate with intermediate steps defined along the path. It also provides a view of the gaps or misalignments which may need to receive greater research attention and funding support. This Roadmap is intended to provide best estimates of current capabilities, projections of technology needs, research priorities and direction for supporting industries and institutions on necessary collaboration to achieve the expected benefits.

**Figure 1.1** Examples of diseases that are potential targets for Bioelectronic Medicine [adapted from 1]

- Acid Reflux (GERD)
- Bleeding & Hemophilia
- Cancer
- Chronic Pain
- Chronic Obstructive Pulmonary Disease (COPD)
- Congestive Heart Failure
- Crohn's Disease
- Diabetes
- Epilepsy
- Heard Disease
- High Blood Pressure
- Irritable Bowel Disease
- Lupus
- Mental Illness
- Depression, Schizophrenia
- Migraines
- Multiple Sclerosis (MS)
- Paralysis
- Parkinson's Disease
- Pulmonary Hypertension
- Rheumatoid Arthritis
- Sepsis
- Spinal Cord Injury
- Stroke
- Traumatic Brain Injury



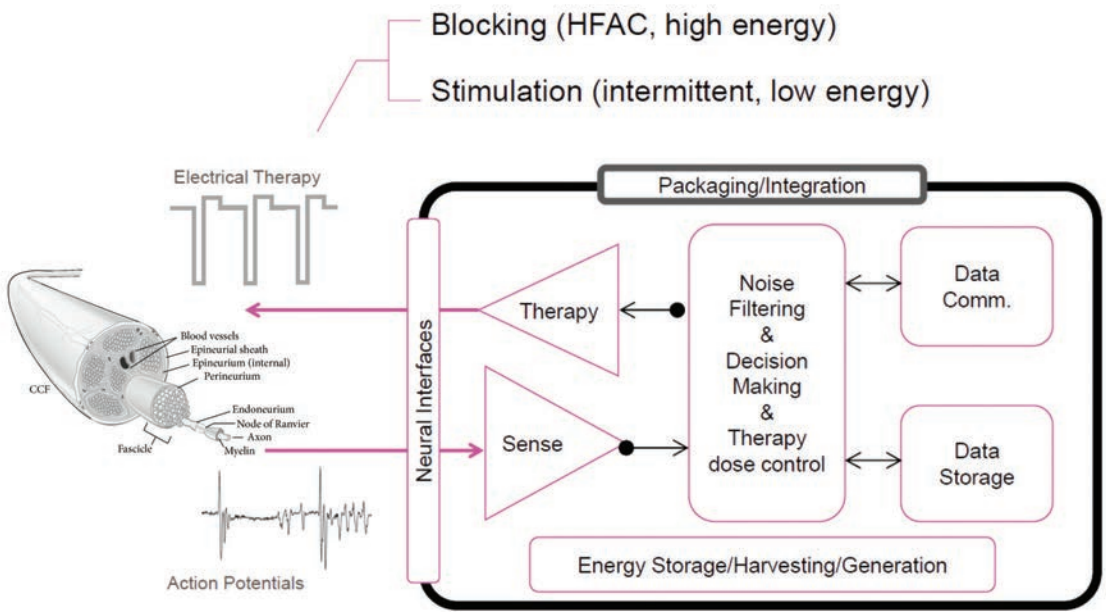
## 1.2 BEM success factors

In order to meet the goals of advancing BEM therapy, the following goals need to be achieved:

- Targeted diseases and conditions must be identified as good candidates for bioelectronic medicine.
- Investigative devices to understand underlying mechanisms are required. For investigative devices, it will be critical to understand what to measure and how to measure it, as well as how it can be integrated in a complete therapy to understand what gaps remain.
- Cross-disciplinary collaborations are needed to efficiently address challenges between biologic/medical/computing disciplines. There is the need to create a synergistic partnership among the scientific researchers, technology developers, and clinical translators.
- The foundation of the work must be built on understanding the biology of the system and the disease.
  - System models including biological, chemical, electrical, and mechanical interactions for normal and disease state behavior are required.
  - Disease state focus is required to understand and treat the states of disease relative to the normative state.

*What if we could treat disease and injury without drugs? Bioelectronic Medicine (BEM), which uses neurotechnologies to interface with the nervous system, can offer such opportunities.*

Figure 1.2 A generic block diagram of an implantable neuromodulation device [2]




## 1.3 BEM Microsystem

The main functional blocks of a closed-loop BEM microsystem are shown in **Figure 1.2**. An implantable electrode senses biosignals, which are filtered and analyzed. A device reacts to those processed signals via neural interface that stimulates or blocks nerve activity. The resulting data may be stored in the implantable device or communicated externally.

Device miniaturization is one of the key success factors of future bioelectronic medicine [2]. Next-generation neuromodulation devices are expected to improve the current state of the art in five key areas:

- ***Sensitivity:*** i.e. able to sense and decode signals from neurons in a highly sensitive manner against other background interference
- ***Selectivity:*** i.e. able to precisely target specific nuclei in the brain or nerves in the periphery, while avoiding off-target neurons; such targeting should have clear endpoints
- ***Responsiveness:*** i.e. able to capture the neural signatures and to detect biomarkers (a variety of sensors may be needed, both electrical and biochemical, as biomarkers for detection and stimulation effectiveness)
- ***Acceptance:*** i.e. miniaturized low-power devices that can be delivered with minimally invasive implantation, thereby reducing patient burden and improving access
- ***Closing the loop:*** i.e. form a closed-loop system to record and stimulate, block, or more generally neuromodulate to achieve the targeted function consistently

A number of technologies are critical to the BEM Technology Roadmap **(Figure 1.3)**:

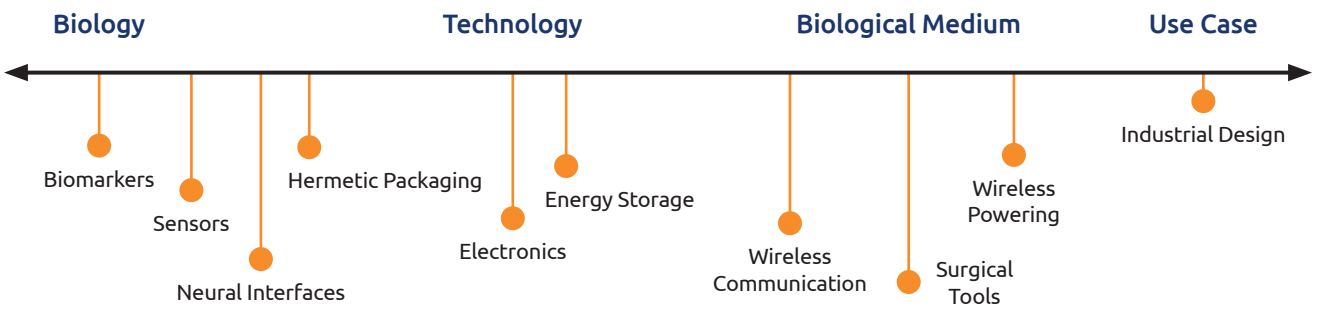
- Miniaturization of implantable devices including the sensors, circuits, and powering devices
- Precise sensing of biosignals, including nerve signals
- Low-power, low-noise, and low-voltage circuit design
- Efficient energy harvesting / generation, storage and delivery in a small form factor
- High bandwidth and low-power two-way communication
- Biocompatible and flexible packaging technologies
- Safety and long-term reliability

## 1.4 Roadmap Organization

The BEM Technology Roadmap is organized into eight chapters:

- **Chapter 1** (BEM Roadmap Overview)
- **Chapter 2** (BEM Platform Functionality) addresses the 'BEM platform,' which is defined as a combination of electronic hardware pieces (such as an energy source, communication unit, nonvolatile memory etc.) and algorithms integrated in a system that determines the system's basic operational characteristics.

**Figure 1.3** Neuromodulation system technology needs [2]




- **Chapter 3** (Instrumentation Capabilities) is focused on instrumentation to support functional organ-nerve mapping and, more generally, further understanding of the nervous system as an information system. New developments in semiconductor technology are expected to provide the revolutionary tools and instrumentation for fundamental biological discovery and medical applications. Also, sophisticated software strategies will provide the logical "glue" between instrumentation, samples and the data sets they produce.
- **Chapter 4** (Modeling and Simulation) describes the modeling and simulation priorities for bioelectronic medicine. Design productivity, robustness and probability of success of BEM systems critically depend on models at various levels of abstraction coupled to simulation tools capable of handling large-scale multi-domain systems to convert the raw data results to understandable and actionable information.
- **Chapter 5** (Neural Interfaces) deals with the topics of neural modulation and recording for therapeutic purposes. Topics include an introduction to the autonomic nervous system, neuromodulation modalities, neural recording, types of neural interfaces, and target precision.
- **Chapter 6** (Biocompatible Packaging) focuses on various aspects of packaging of BEM devices: BEM implants will require packaging technology that is ultraminiature so that, e.g. the implants can be placed close to target neurons and still provide the capacity for thousands of independent conductors.
- **Chapter 7** addresses the topic of Clinical Translation and aims to accelerate the translation of research into practice. Accelerating that translation is greatly beneficial for patients, as it provides more efficient therapies, and for the healthcare system in general, as it potentially reduces the cost of the disease.
- **Chapter 8** defines the concept and gives examples of a Minimum Viable Product. In addition to "mono-therapeutic" applications of BEM, i.e. those exploring clinical opportunities for the use of BEM technologies as a single or primary therapeutic intervention, there may also lay great clinical value and business opportunity in combining BEM with pharmacological intervention, i.e. to treat a single indication with a combination of BEM (for therapeutic modulation of the nervous system) and drug treatment (for intervention in the systems biology).

The BEM Technology Roadmap elicits an optimum trajectory for the successful implementation of bioelectronic medical systems and their translation 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, and more. Industrial consortia specializing in the management of industry-relevant fundamental research offer a proper vehicle to accelerated innovation, workforce training, and fluid transfer of research results to industry.

# References

[1] Chad Bouton, "Bioelectronic Medicine: Molecular mechanisms", SRC/NSF Workshop on Microsystems for Bioelectronic Medicine, April 12 & 13, 2017, IBM Conference Center, Washington, DC

[2] Rizwan Bashirullah, "Bioelectronic Medicines: A Research Roadmap", SRC/NSF Workshop on Microsystems for Bioelectronic Medicine, April 12 & 13, 2017, IBM Conference Center, Washington, DC

Chapter 2

# Platform Functionality

## 2.1 BEM Platform: Types and Organization

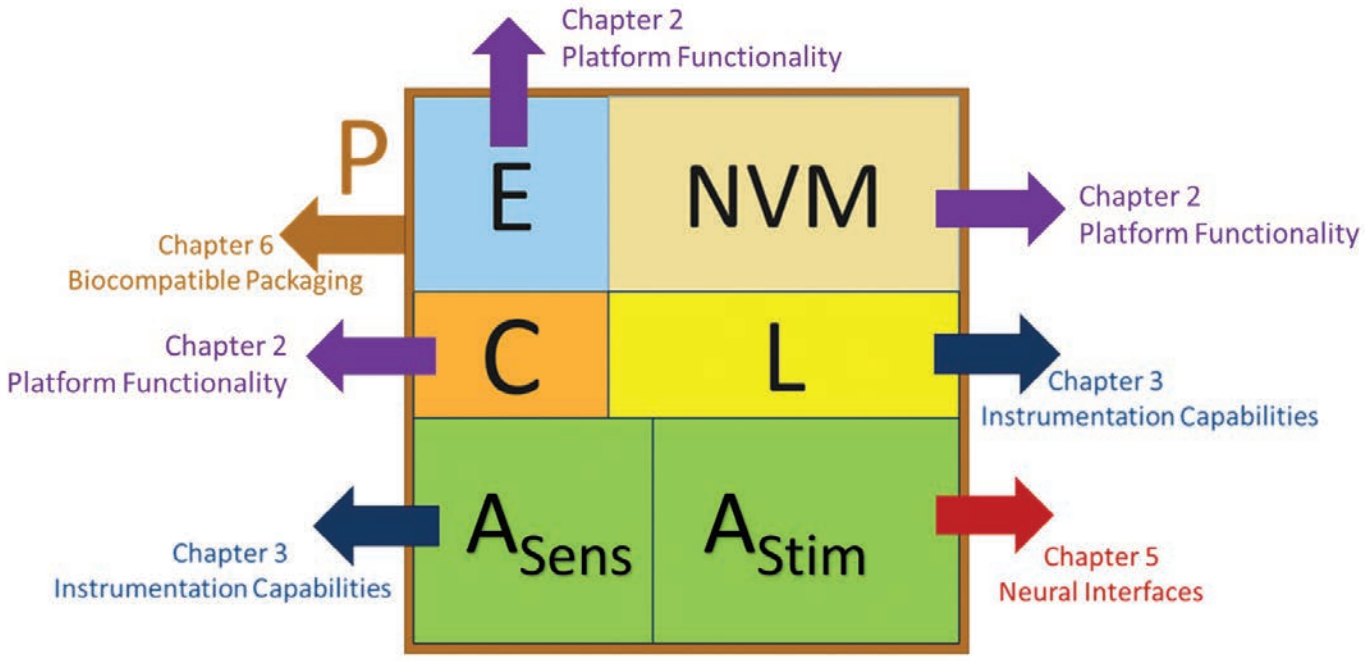
A platform, in engineering terms, is a shared set of common design, engineering, and production efforts, as well as major components supporting a number of distinct product models. This concept provides a manufacturer a capability for cost-effective, product-family scaling and the acceleration of product development.

In this document, the BEM platform is defined as a combination of electronic hardware components and algorithms integrated in a way that defines the system's basic operational characteristics. **Figure 2.1** describes the building blocks of a BEM microsystem and their relationships to the subsequent chapters: energy source (E), analog blocks (A) for data collection and stimulation, communication unit (C), logic unit (L), nonvolatile memory (NVM) and packaging enclosure/encapsulation (P). Each of the building blocks is critical for building a fully-implantable system and is covered in significant detail in the subsequent chapters.

## 2.2 BEM System Scaling

Volume and energy are two primary design constraints for bioelectronic microsystems, and the tradeoffs between the two must be very carefully considered among all functional units. In order to better understand the scaling limits for these microsystems, it is helpful to consider physics-based scaling and energy limits for the different electronic components. Each of the essential components in the system occupies a certain volume in space and consume a portion of the total available energy. Therefore, an optimal partitioning within a fixed volume and energy envelope needs to be explored.

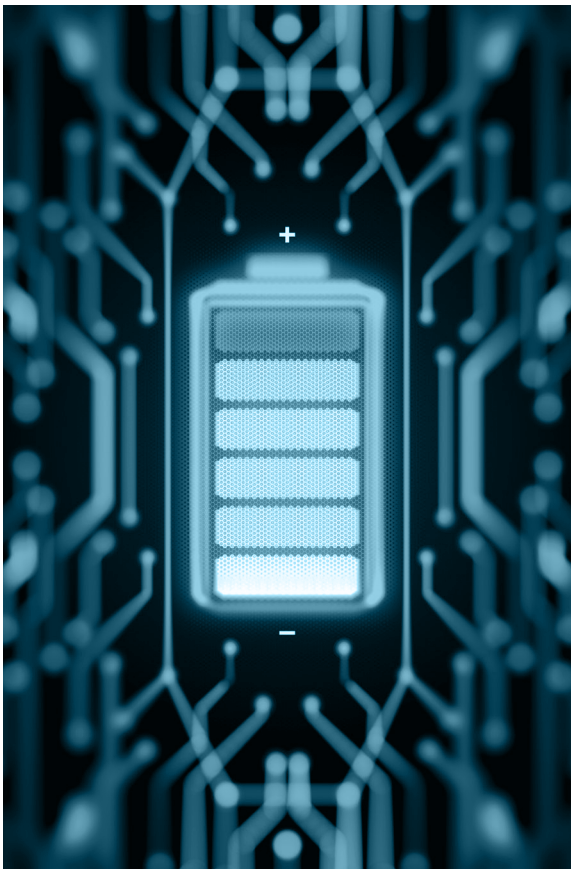
Figure 2.1 The main functional blocks of a BEM platform: A–analog sensing and stimulation, C–communication unit, E–energy source, L–logic unit, NVM–nonvolatile memory, P–packaging



## 2.3 BEM Platform Functional Blocks

### 2.3.1 Power Sources

Embedded energy sources are a key enabler for applications with limited or no physical access to external energy supplies. For BEM microsystems, the available volume for on-board energy supplies is very limited. Thus, the capacity of an energy supply, in terms of both energy stored and the rate at which it can deliver energy, can place severe constraints on system operation. Powering implants to sustain a long stimulation time appears to be one of the key challenges, and one key focus of future research should be on the evolution of injectable or renewable power sources with high power density, as well as novel solutions to transfer energy efficiently in vivo. **Table 2.1** gives information on the platform development and projected specification of the form factor and power consumption expectations.




*Volume and energy are two primary design constraints for bioelectronic microsystems, and the tradeoffs between the two must be very carefully considered among all functional units.*

**Table 2.1** General Platform Characteristics

| Year | 2018 | 2023 | 2028 | 2033 |
|---|---|---|---|---|
| Min. volume ($mm^3$)/ Form factor (mm) | 1000/10 | 10/2 | 1/1 | 0.001/0.1 |
| Average power consumption | <100mW | 10mW | <1 mW | <20 µW |
| Operational lifetime* | ~1 year | 5 years | 10 years | >10 years |
| Attributes/properties | Require surgical insertion | Minimally invasive surgical implant; MRI compatibility up to 3T | Non-invasive removal and insertion (e.g. ingested); Noninvasive body surface imaging; MRI compatible up to 7T | Capablity for accurate positioning/ repositioning remotely within the body; Bio-degradable; Secure, i.e., cannot be hacked easily |

*Can be application specific; for example, the device can be required to stay operational for the life of the patient or bioresorbable /easily removable otherwise

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

### 2.3.2 Microbatteries (Table 2.2)

In electrochemical (e.g. galvanic) cells, individual metal atoms are consumed at the negative electrode to produce an electrical potential, and the total stored energy in the cell is directly proportional to the number of metal atoms, and thus the volume. An upper bound for energy that can be stored in an electrochemical cell was estimated to be ~$10^4$ J/cm$^3$ [1].

Current thin-film mm-scale batteries scale poorly, and the energy capacity per volume drops rapidly **(Figure 2.2)** [2]. Encapsulation may be the most important issue for the very small batteries. As a possible solution, caseless microbatteries were proposed for bioimplantable applications that consist of only two electrodes immersed in physiological fluids, such as the subcutaneous interstitial fluid, blood, serum etc. [3].

### 2.3.3 Energy Harvesting Solutions (Table 2.2)

In the context of the BEM system, energy harvesting refers to the collection of energy from external sources and its conversion into electrical form to power the system [4, 5, 6].

**Figure 2.2** Practical scaling properties of miniaturized batteries [2]

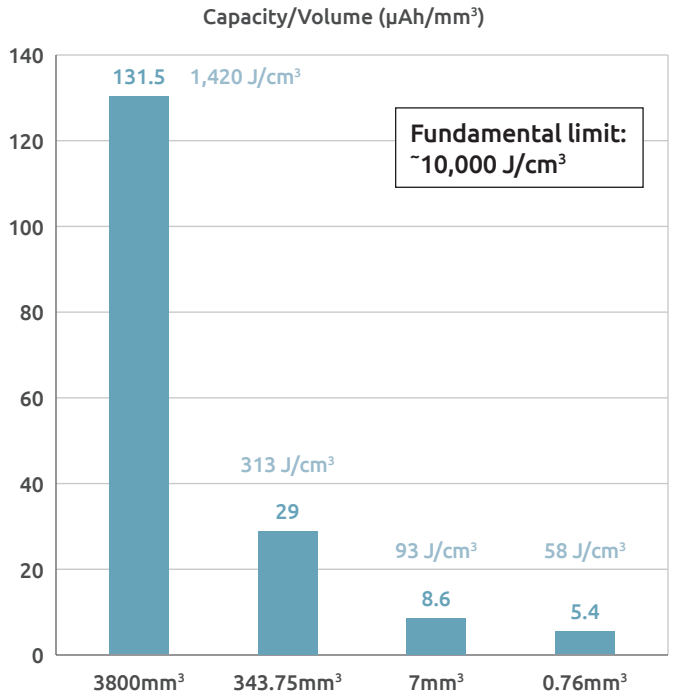



**Table 2.2** Power Sources

| Year | 2018 | 2023 | 2028 | 2033 |
|---|---|---|---|---|
| ***Microbatteries*** | | | | |
| Volume, mm3 | 23 | 5* | 0.5* | $5{\cdot}10^{-4}$* |
| Output voltage, V | 3.8 | 1 | 0.5 | <0.5 |
| Capacity, J | 0.16 | $5{\cdot}10^{-2}$ | $5{\cdot}10^{-3}$ | $10^{-3}$ |
| Attributes/properties | Rechargeable with a large number of charge cycles<br>Lithium battery solution | Rechargeable with a large number of charge cycles<br>Lithium battery solution | Non-Li caseless solutions | Non-Li caseless solutions |
| ***Energy Harvesting Solutions*** | | | | |
| Volume*, mm$^3$ | ~500 | 5 | 0.5 | $5{\cdot}10^{-4}$ |
| Output voltage, V | ~1 | 1 | 0.5 | <0.5 |
| Delivered power, W | <0.5 | $10^{-1}$ | $10^{-3}$ | $10^{-5}$ |
| Power delivery/ harvesting schemes | Inductive | Capacitive, Ultrasound | Ultrasound, Light, Biofuel cells | Ultrasound, Light, Temperature gradients, Biofuel cells, Electric potentials of body organs |

*Can be application specific; for example, the device can be required to stay operational for the life of the patient or bioresorbable /easily removable otherwise

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

Energy can be harvested from intentional sources that transmit energy to an implant for conversion and conditioning. The external energy accessible for harvesting can be in the form of radiation (light, RF), mechanical energy (ultrasound, vibrations), thermal energy, etc. Generally speaking, the amount of energy available for harvesting is fundamentally limited by the level of energy available in the 'safe' ambient environment, e. g. as defined by various regulatory agencies. Energy transfer efficiency for biomedical implants depends on two major factors: implant size and the physical properties of tissue.

In addition to external energy sources, there are other unexplored sources of energy inside the body, which constitute an important direction for research. Examples include:

- Muscle/organ movement that can drive e.g. a piezo-generator,
- Electric potential in inner-ear from cochlea,
- Temperature gradients,
- Fuel cells, e.g. running on glucose and oxygen in blood stream, etc.

## 2.4 Logic and Analog/Mixed Signal Circuits (see **Table 3.1**)

The capability of the BEM electronic unit is determined by its complexity (e.g. the device count) and the energy required for its operation. The system's 'intelligence', e.g. defined as its capability to locally make valid decisions regarding actuation (using a combination of analog/mixed signal, logic and memory elements), needs to be maximized to reduce the communication costs and latency (incurred if a decision is made by an external control unit).

BEM Logic and Analog/Mixed Signal Circuits Challenges:

- Dramatic supply voltage reduction
- Noise levels of electronics suitable for single fascicle and fiber level recording
- Signal processing in implanted circuits to denoise, filter, separate fascicular and fiber signals, and extract features to be used for machine learning classification
- Machine learning algorithms used to drive actuation using features derived from monitored signals as well as treatment protocols
- Single voltage domain for both digital and AMS parts
- Increased leakage in advanced technology nodes
- Cost-effective manufacturing, e.g. the ability to 3D print the housing
- Flexible internal wiring as well as flexible electronics
- Substantial architecture change is required for 100μm-scale systems

## 2.5 Nonvolatile Memory (Table 2.3)

A BEM system needs data storage capabilities to collect sensory data, store process instructions, etc. Long life time and reliability are the two most essential attributes of a BEM memory unit. Currently, flash memory is a mainstream solution for long-term storage. Ferroelectric random-access memory (FRAM) technology has significant potential for applications in implantable medical electronics, as it enables high speed, low power and virtually unlimited endurance [7]. Other imaging memories can be considered such as:

**Table 2.3** BEM Nonvolatile Memory Unit

| Year | 2018 | 2023 | 2028 | 2033 |
|---|---|---|---|---|
| Max chip size, $mm^2$ | 100 | 4 | 1 | 0.1 |
| Memory type | NOR Flash | NOR Flash<br>FRAM | FRAM<br>MRAM<br>PCRAM | FRAM |
| Attributes/ properties | Low-speed,<br>Low-endurance | Low-energy<br>High-speed<br>High-endurance | High density | Dissolvable/biodegradable [8] |

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

i) magnetic (MRAM), ii) phase-changing (PCRAM) and iii) resistive (RRAM) memory technologies.

## 2.6 Communication (Table 2.4)

Ubiquitous communication with the external monitoring/control equipment is an essential function of BEM microsystems. While most wireless implants use RF communication, this becomes inefficient in very small systems. Based on the physics of electromagnetic radiation, the primary physical parameter, which determines the scaling limits of the communication system, is the *radiation wavelength* $\lambda$ compared with the characteristic size of the BEM system or form-factor (FF). A condition for an efficient electromagnetic wave transmission is $\lambda/4$~FF, and therefore the form-factor pre-determines the choice of the radiation wavelength used for communication. The optimal FF×4 frequencies for different sizes of a BEM system are given in Table 2.4. For example, for FF=1mm, the FF×4 frequency is 75 GHz. At these frequencies, the radiation losses in biological tissues significantly increase, and thus RF communication may become inefficient. Therefore, the communication solution is likely to shift from RF to other energy modalities, such as ultrasonic for mm- and sub-mm sized systems.

Ultrasound is typically operated at MHz frequencies, which is compatible with a mm-sized receiver [9] and undergoes relatively small propagation losses through tissue (1 dB/MHz/cm). The FDA permits a time-averaged ultrasound intensity of 7.2 mW/mm$^2$. Ultrasound can also be used for passive, battery-less communication using backscatter [10].

Challenges of ultrasonic communication include:

- Scattering of ultrasound by impedance mismatches, such as bone or air in the transmission path, can be problematic
- Due to lower frequency, the data rate in ultrasonic communication is likely to be much lower than in RF

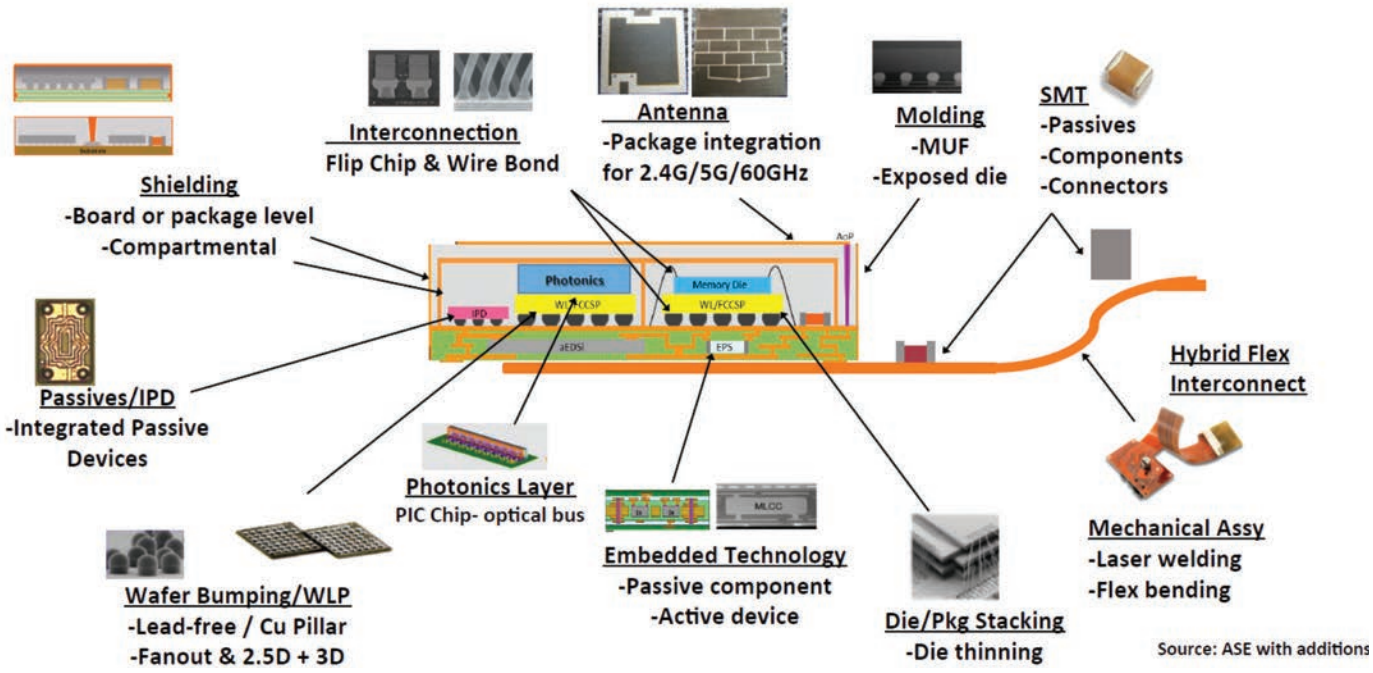
**Table 2.4** BEM Communication

| Year | 2018 | 2023 | 2028 | 2033 |
|---|---|---|---|---|
| ***RF communication*** | | | | |
| Nominal minimal form-factor (MFF), mm | 10 | 2 | 1 | 0.1 |
| Operation frequency, GHz | 0.402-0.405<br>0.420-0.450<br>0.863-0.870<br>0.902-0.928<br>0.950-0.958<br>2.36-2.40<br>2.40-2.48<br>3.49-4.49<br>6.49-9.98* | 10-60** | 75** | unknown |
| MFF×4 frequency, GHz | 7.5 | 37.5 | 75.0 | 750 |
| ***Ultrasound communication*** | | | | |
| Operation frequency, MHz | 1-18*** | 1-18*** | 1-18.5*** | <0.1-18.5*** |
| MFF×4 frequency, MHz | 0.039 | 0.19 | 0.39 | 3.85 |

*IEEE802.15.6 standard, ISM bands **would need regulatory approval from both the FDA and FCC ***medical ultrasound frequency range

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

Figure 2.3 Heterogeneous vertical integration




Another alternative to RF could be near-IR optical communication schemes [11], as they offer:

- Scalability to very small sizes
- Sufficient transmission through tissue
- Frequency-based multiplexing
- Ultra-low power standby mode (sub-nW)
- High data rates (> Mbps)

## 2.7 Electronic Packaging

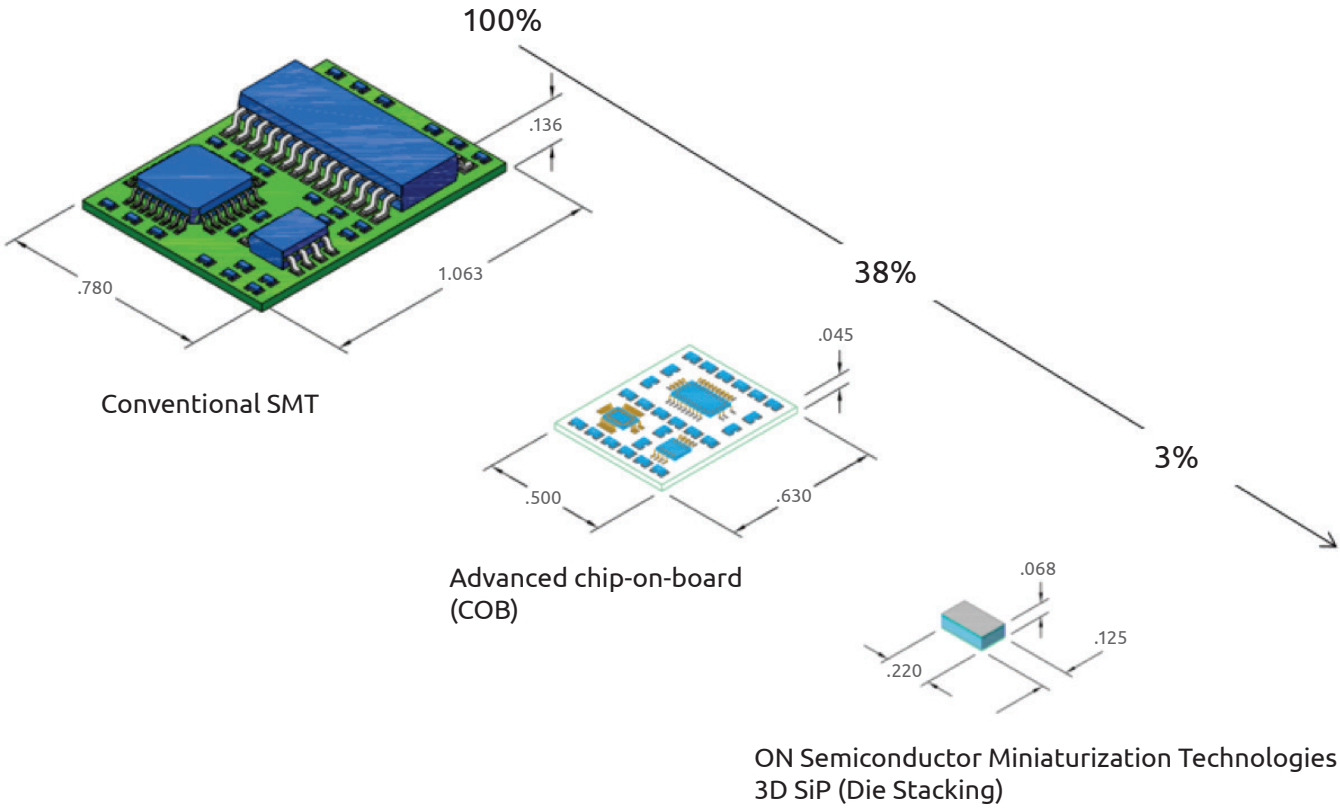
Multiple electronic components form the electronics module. Connection of ICs, off-chip components (capacitors, inductors, crystal oscillators) is an important area of research. Furthermore, there is a growing demand for increased sophistication and complexity of the electronics at the edge to enable much greater local compute and decision making capability. Currently, printed circuit boards are still used to integrate components for many applications. In order to minimize the difficulty in surgically implanting and the likelihood of inflammation or rejection by the human body, generally a smaller packaged device is preferred. Since the size of the enclosure will be determined in part by the size of the electronics module, miniaturization of the electronics module will enable reduction in package size.

A systems level approach to electronics packaging must be taken with consideration given to partitioning of components and I/O interfacing. This has led to research and advanced development of heterogeneous vertical or fanout integration (see Figure 2.3) where interconnects are made at or near silicon scale.

As each I/O on an IC requires ESD protection and a bond pad to exit, careful design of the integrated functions is necessary to prevent the area consumed by I/O from dictating the die size. Design approaches to address this include bond over active (incorporating the ESD circuitry under the bond pad), aggressive bond pad sizes and spacings, 2.5D/3D interconnects and staggered bond pads.

An example of the size reduction obtainable by taking a systems level design approach in a heterogeneous integration solution is shown in Figure 2.4 where a 33X footprint size reduction is achieved. Key enablers for the deployment of Bioelectronic Devices will be optimized systems design based electronic modules taking advantage of heterogeneously integrated circuits and discretes.

Figure 2.4 Electronic packaging miniaturization (Provided by ON Semiconductor)




# References


[1] V. V. Zhirnov and R. K. Cavin, Microsystems for Bioelectronics: Scaling and Performance Limits – 2nd Edition (Elsevier 2015)

[2] Dennis Sylvester, "Ultra-Low Power Millimeter-Scale Systems for Bioelectronics Medicine", SRC/NSF Workshop on Microsystems for Bioelectronic Medicine, April 12 & 13, 2017, IBM Conference Center, Washington, DC

[3] E. F. Garay and R. Bashirullah, "Biofluid Activated Microbattery for Disposable Microsystems", *J. Microelectromech. Syst.* 24 (2015) 70-79

[4] H. B. Radousky and H. Liang, "Energy harvesting: an integrated view of materials, devices and applications", *Nanotechnology* 23 (2012) 502001

[5] N. S. Hudak and G. G. Amatucci, "Small-scale energy harvesting through thermoelectric, vibration, and radiofrequency power conversion", *J. Appl. Phys.* 103 (2008) 101301-24.

[6] G. Zhou, L. Huang, W. Li, and Z. Zhu "Harvesting ambient environmental energy for wireless sensor networks: A Survey", *J. Sensors* (2014) 815467

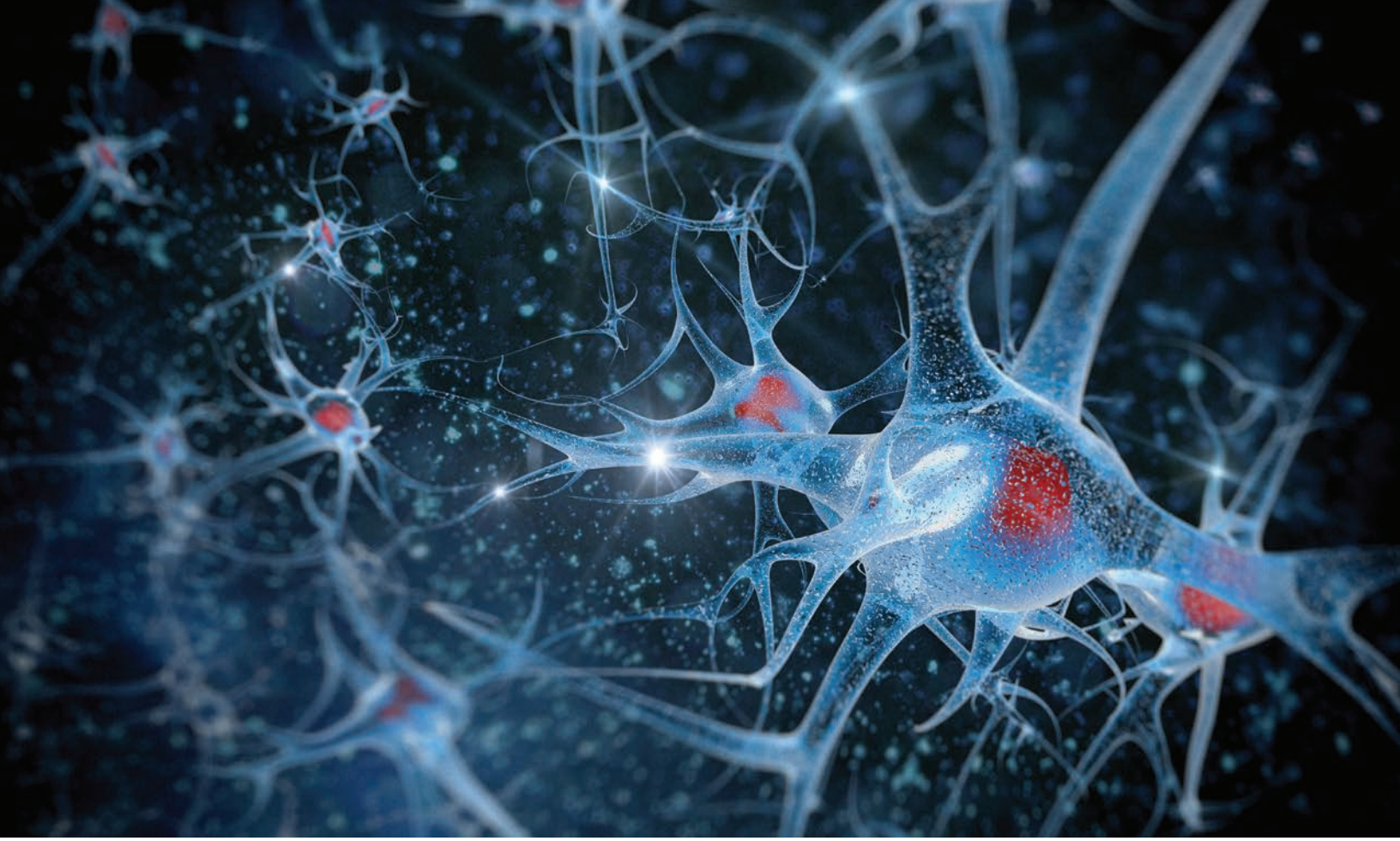
[7] http://www.ti.com/corp/docs/innovation/innovation-stories/medical/medical-FRAM.html

[8] S. Wu, H. Wang, J. Sun, F. Song, Z. Wang, M. Yang, H. Xi, Y. Xie, H. Gao, J. Ma, X. Ma, Y. Hao, "Dissolvable and Biodegradable Resistive Switching Memory Based on Magnesium Oxide", *IEEE Electr. Dev. Lett.* 37 (2016) 990-993

[9] T-C. Chang, M. J. Weber, M. L. Wang, J. Charthad, B. T. Khuri-Yakub, A. Arbabian, "Design of Tunable Ultrasonic Receivers for Efficient Powering of Implantable Medical Devices with Reconfigurable Power Loads", *IEEE Trans. Ultrasonics Ferroelectrics and Frequency Control* 63 (2016) 1554-1562

[10] D. Seo, R. M. Neely, K. Shen, U. Singha, E. Alon, J. M. Rabaey, J. M. Carmena, M. M. Maharbiz, "Wireless Recording in the Peripheral Nervous System with Ultrasonic Neural Dust", *Neuron* 91 (2016) 529–539.

[11] M. Mujeeb-U-Rahman, D. Adalian, C-F. Chang, A. Scherer, "Optical power transfer and communication methods for wireless implantable sensing platforms", J. Biomedical Optics 2 0 (2015) 095012



Chapter 3

# Instrumentation Capabilities

## 3.1 Introduction

New developments in semiconductor technology are expected to provide revolutionary tools and instrumentation for fundamental biological discovery and medical applications. This chapter focuses on the electronic instrumentation inside a BEM device that supports in-vivo sensing of biological parameters, signal processing, intelligent decision making, communication and transduction. In addition to hardware advancements, sophisticated software strategies will provide the logical "glue" between instrumentation, samples, and the data sets that they produce.

**Figure 3.1** below shows a detailed block diagram of the mixed signal electronic instrumentation sub-systems within a BEM device.

**Table 3.1** outlines the key metrics of the instrumentation sub-systems and provides a scaling roadmap for future research.

This chapter is organized as follows: **Section 6.2** discusses the various sensing modalities by which biological signals are converted into electrical signals. **Section 6. 3** discusses challenges for the electronic front ends that amplify and process these minute signals for subsequent post processing. **Section 6. 4** outlines system intelligence, as, in order to be an effective long-term therapeutic aid, some level of system intelligence for on-the-fly decision making and adaptation without the physician interference is critical, given the multiple variables impacting in-vivo signal recording (surrounding tissue types, aging of cellular structures, variations in pH, etc.). **Section 6. 5** deals with data transmission both out of and back into the body, and **Section 6. 6** highlights figures-of-merit (FoM) for various instrumentation sub-systems. Finally, **Section 6. 7** discusses pre-competitive research tools.

**Figure 3.1** Block diagram of various instrumentation sub-blocks in a BEM device. Image of nerve fiber from [10]

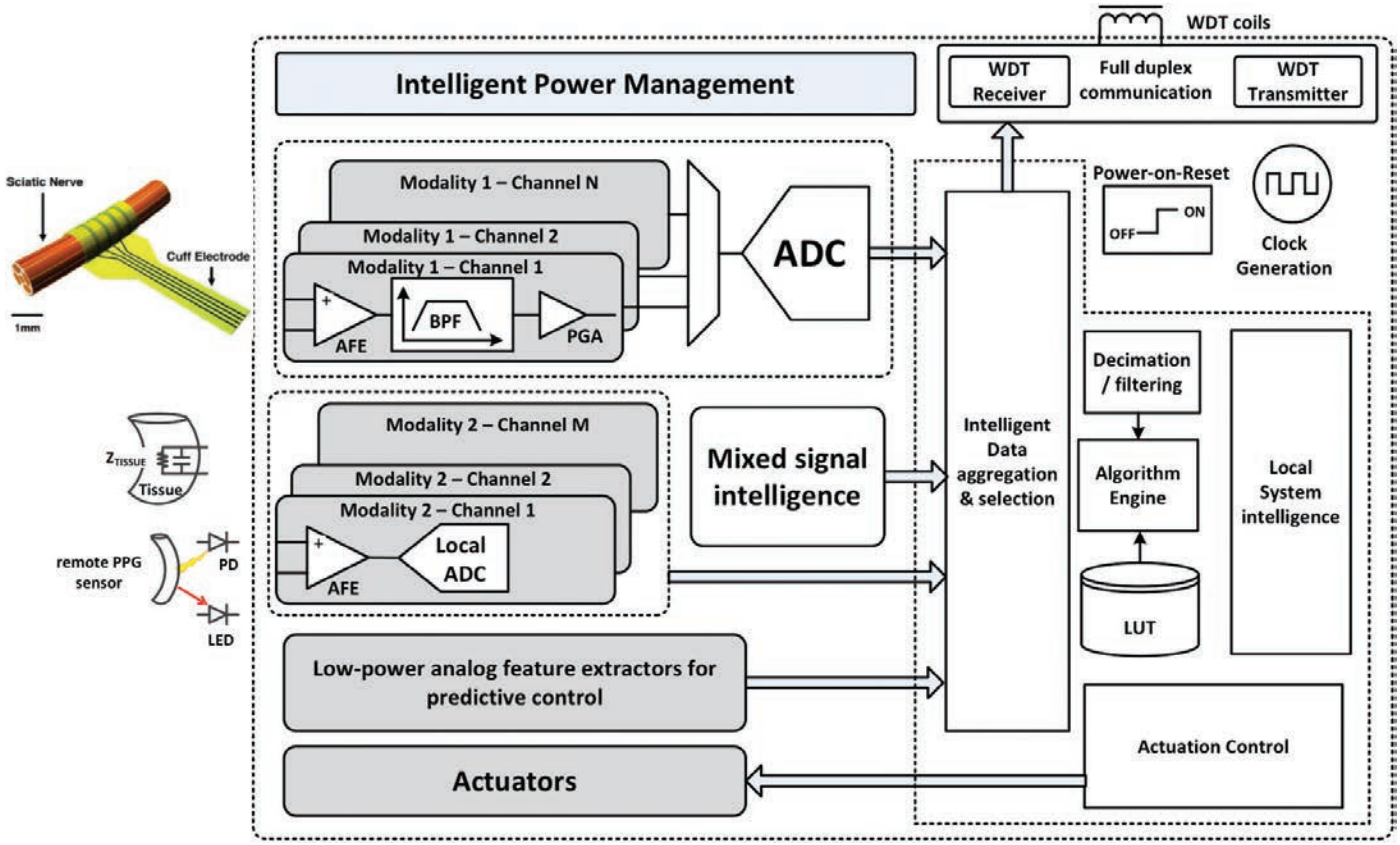



**Table 3.1** Electronic Instrumentation Targets

| Parameter | 2018 | 2023 | 2028 |
|---|---|---|---|
| Chip Size | 10mm2 | < 4mm2 | < 1mm2 |
| Technology Node | 0.18um | 90nm | 45nm |
| Supply Voltage | 1.8V/ 3.3V | 1.2V/ 1V | 0.6V |
| Power | 1mW | 100uW | < 20μW |
| Signal Bandwidth | 0.1 – 10kHz | 0.1 – 10kHz | 0.1 – 100kHz |
| Input Referred Noise | 3uVrms | 1uVrms | < 1uVrms |
| ADC Resolution | 10 bits | 12 bits | 14 – 16 bits |
| Stimulation | Fixed | AWG that is LUT-based, moderate intelligence | AWG that is continuously adapted |
| On-Board Intelligence | Limited | Able to perform electrical self-calibration | Able to perform bio-electronic self-calibration |

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

## 3.2 Biosensing and Remote Biosensors

It is envisioned that instrumentation to support functional organ-nerve mapping will, to a large extent, rely on remote biosensors implanted or worn at different locations of the human body. Therefore, the instrumentation platform should be capable of receiving and integrating information from multiple sources.

The primary function of biosensors is to receive and transform biological signals into an electrical form for subsequent communication processing and analysis to provide a basis for further actions. The state of a living system can be monitored by sensing different physical parameters e.g. chemical, electrical, optical, thermal, mechanical, etc. A typical task for biosensors is to monitor biological processes by detecting the reagents or products of biochemical reactions, such as DNA fragments, proteins, pH, etc.

It appears that the 1D and 2D structures, such as graphene layers, silicon nanowires and carbon nanotubes, might be essential for biosensing, as they potentially offer better sensitivity than other types of devices and allow for the detection of femtomolar concentrations and even single biomolecules. In addition, 1D structures with very small diameters could be used to explore the intriguing possibility of electrically monitoring processes inside individual cells. Neuronal electrical signals are usually recorded with an electrode in close proximity to neurons. Typical neuronal electrical signals are on the order of a few to hundreds of μV at a neuron firing frequency of a few kHz. Important metrics of neural recording include sensitivity, specificity, signal-to-noise ratio, spatial and temporal resolutions of the signals, as well as long-term stability and reliability of the signals.

The Grand Challenge for in-vivo biosensing is sensor biodegradation, e.g. due to biofouling, which is caused by the accumulation of proteins or cells on the sensing surface. For example a “foreign body capsule” typically surrounds devices implanted in the human body. Biodegradation causes unpredictable changes in the sensor’s response characteristics (e.g. sensitivity, baseline, selectivity, etc.) and may lead to a rapid device failure. Thus, one of the primary tasks in biosensor research is to devise sensors that work remotely in hostile locations (e.g. inside the body) for very long periods of time (years) at an acceptable unit cost. Sensor lifetime can be significantly increased if a periodic testing of small samples is used instead of direct sensing. For sensors, operating in an autonomous mode implies that sampling machinery would be embedded into the sensors, such as microfluidic devices — pumps, valves, etc.

## 3.3 Electronic Front-End

The analog front end (AFE) of the instrumentation forms one critical interface between the biological world and the electrical domain. The transducers such as neural probes, electro-chemical electrodes, biosensors, etc. convert the biological signals and chemical processes into an electrical quantity, such as voltage, current or charge.

Since neural signals are typically from tens to hundreds of microvolts in amplitude, the first role for on-chip circuitry is to amplify the recorded signals and lower their impedance levels to make them less vulnerable to externally introduced noise. A second role is to multiplex the signals so that many sites can be monitored from only a few external leads [26]. The requirement to pick up extremely weak in-vivo signals — for example, picking up a neural signal of 1uVrms — have often determined the noise floor and hence dynamic range (DR) of the AFE. Motion artifacts, subtle changes in pH and chemistry around the implant, and biodegradation and bio-fouling as discussed earlier all show up as unwanted interferers and/or drifts that place additional stringent requirements on the AFE dynamic range. Any power-vs-dynamic range trade-offs that could have been previously anticipated for short-term implants must now be re-evaluated when designing an AFE for long-term bioelectronic therapy.

In conventional therapy, the physician/diagnostician reviews patient data and relies on subtle changes in morphology of the recorded signal (ECG, SpO2 level, etc.) as an indicator of disease and/or to determine a course of treatment. This implies that very accurate signal recording is needed, which directly translates to the noise floor of the AFE, dynamic range of the entire signal chain and the resolution of the A/D converter that is used in the recording system. These constraints get exponentially amplified due to the limited area, voltage and power budgets available in the BEM device.

**Table 3.2** lists some of the key challenges in designing silicon electronic front ends for bioelectronic medicine.

Keeping the above-mentioned challenges in mind, a substantial front-end architecture change is required for 100μm-scale systems that will enable future bioelectronic medicine platforms.

**Table 3.2** Key challenges in designing silicon electronic front ends for bioelectronic medicine

| Challenges in design of the AFE | Impact to BEM device | Possible solutions/ Research Opportunities |
|---|---|---|
| Decreased supply voltage | • Lower headroom for CMOS transistors<br>• Reduced dynamic range | • Current-mode circuits<br>• Low-$V_T$ processes |
| High 1/f noise | • Lower DR especially between 0.1–1kHz band, lower resolution<br>• Larger area/current required to meet required resolution | • Advanced circuit techniques<br>• Improved CMOS processes and /or integration of BJT's/ JFETs |
| Need for advanced signal processing | • Places stringent requirements on MIPS/ clock frequency available<br>• Typically needs more on-chip/ on-board memory | • Intelligent use of feature extractors [18] to alleviate data deluge<br>• Tightly coupled algorithms that vary analog parameters along with signal [18] |
| Multiple voltage domains to cater to analog, digital and actuation | • reduced over-all efficiency leading to decreased lifetime of implant<br>• Large board space/ volume for additional power modules | • Single supply operation across analog and digital domains |
| Increased leakage in smaller geometry processes | • Reduced battery life<br>• Offset drift | • Develop low-leakage libraries and processes<br>• Circuit techniques to recycle/ store leakage charge |

## 3.4 System Intelligence: Machine Learning and Models

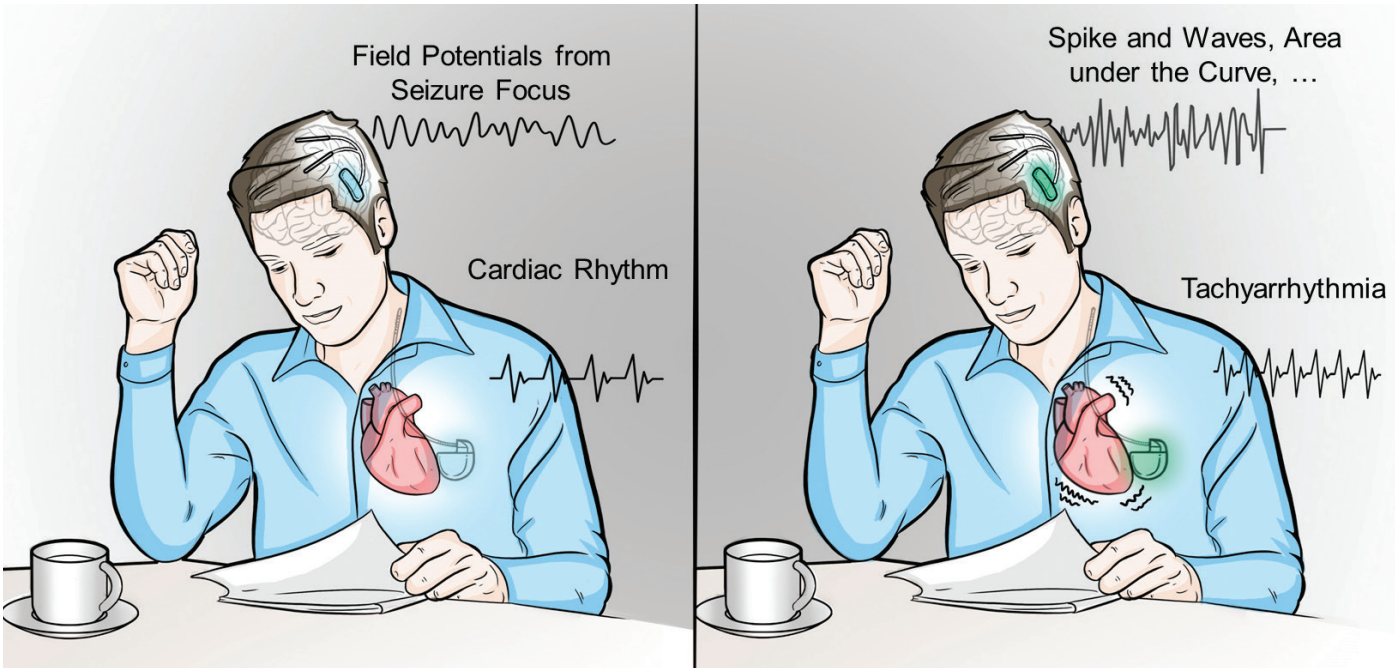
A closed-loop system that includes both sensing and stimulation allows for feedback information to be used in an intelligent fashion. This information can, for example, be utilized for fault detection and correction, classification, false alarm minimization, timing optimizations, circuit adaptation, learning, or prediction. The Bioelectronic Medicine Technology roadmap moves us toward an increasingly intelligent closed-loop system that maintains energy efficiency, efficacy, and safety while providing patient-personalized stimulation that adapts over time to changing environments and/or device degradation.

The incorporation of machine learning, modeling and statistical techniques is one avenue toward increased system intelligence [17], [27], [14], [19], [21]. Shoaran et al., for example, utilize on-chip decision trees for more accurate classification of neural features as compared to traditional thresholding techniques [19]. Pilot work in epilepsy therapy devices are also making in-roads for system intelligence. As illustrated in **Figure 3.2**, responsive systems for using both neural and cardiac signals are approved and continue to be refined using machine learning techniques. In both cases,

*New developments in semiconductor technology are expected to provide revolutionary tools and instrumentation for fundamental biological discovery and medical applications.*

the baseline physiological signals are complex and subject to natural variations like circadian rhythms which impede accurate detection of the pathological state. One strategy for overcoming these natural variations might be to constrain what is considered normal physiological behavior and define anything outside those bounds as pathological—for example, when the physiomarker exceeds an acceptable threshold actuation is enabled. The sensors for these systems include biopotentials from seizure focus, network electrodes, and cardiac events. The classifiers are sensor-dependent, but examples include line lengths, power in band, or entropy from neural field potentials, or tachyarthymia events derived from cardiac signals. The best location and stimulation method for actuation remains an area of research.

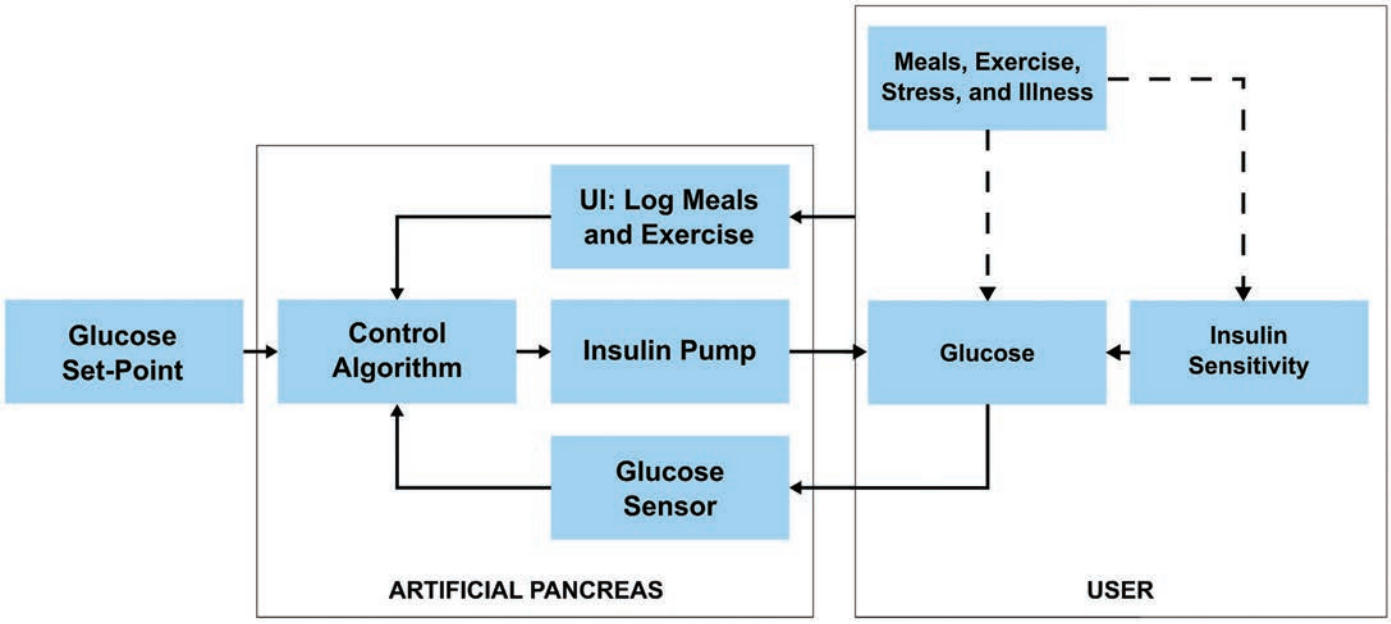
**Figure 3.2** Responsive stimulators for the treatment of epilepsy. Existing adaptive systems use the detection of either transient cardiac arrhythmias or localized neural fluctuations to trigger stimulation to restore normal brain processes.




System Intelligence implemented with bioelectronics is also being developed for diabetes. Diabetes is a disease characterized by significant blood glucose variation due to partial or absolute deficiency in insulin secretion, lack of gluco-regulatory action of insulin, or both [2]. The lack, or absence, of endogenous insulin can be supplemented with exogenous insulin, in the form of subcutaneous injections. Without insulin, glucose levels in the bloodstream can become dangerously elevated (hyperglycemia) leading to diabetic ketoacidosis [13], [3]. Prolong hyperglycemia can also cause long term complications, such as cardio-vascular disease, neuropathy, nephropathy, loss of vision, etc. [13], [3]. Conversely, too much insulin can lead to severe hypoglycemia or low blood sugar levels, causing dizziness, unconsciousness, coma, or even death [13], [3]. Continuous subcutaneous delivery of insulin through the use of pumps and infusion sets, and continuous measurement of interstitial glucose through sensors has become routine in recent years. This has enabled the development of the "Artificial Pancreas", or closed-loop control of insulin delivery through glucose sensor feedback in order to produce tighter glucose control [24].

Data derived from these glucose management devices has allowed simulation of physiologic models of Diabetes and closed-loop control algorithms [9]. Two main types of control strategies currently under development are single-hormone with insulin only as the manipulating variable to decrease and maintain glucose levels [4], [23], or dual-hormone with insulin and glucagon as the manipulating variables to decrease or increase glucose levels, respectively, as per requirement [16]. The adaptive closed-loop systems drive sensor glucose level toward a set-point, with disturbances arising mainly from ingestion of meals, exercise, stress, or illness **(Figure 3.3)**. The single or dual control systems compensate for each event using sensor feedback and system predictions. Due to the physiologic delays associated with gluco-regulatory action of subcutaneously administered insulin, both systems (single or dual hormone) still require user input in terms of meal/exercise announcement as a feed-forward signal in order to achieve the most effective disturbance rejection. These dynamics highlight the need to consider machine learning methods at multiple timescales and the synthesis of multiple sensor sources.

**Figure 3.3** Flow diagram of an artificial pancreas system leveraging a continuous blood glucose sensor and implantable insulin pump.




The physiologic model allows rapid algorithm prototyping and testing prior to human use. Future work may include the use of databases of collected information to predict personalized settings. Several companies and researchers are racing toward human testing and product commercialization in this rapidly evolving field [24].

As a final note, the design of an "intelligent" implant requires thoughtful consideration for the characteristics of the integrated bioelectronic-physiological system. These considerations are well captured by the IEC 60601-1-10 standard: *general requirements for basic safety and essential performance—collateral standard: requirements for the development of physiologic closed loop controllers* [5]. Although intended for external controllers, using this standard as a guiding set of principles can help ensure robust operation of any bioelectronic system.

## 3.5 Data Transmission

Wireless transmission of power and data circumvents problems associated with failure and infection due to cables between the implant and the outside world. Wireless Power Transfer (WPT) and Wireless Data Telemetry (WDT) are expected to remain the *defacto* mode of power delivery and data transmission for future bioelectronic implants. Typically, both power and data signals can be transmitted using electromagnetic radio frequency (RF), infrared, optical, or acoustic energy. The power delivery aspects have been discussed Chapter 2 and this section will focus on telemetry considerations. When considering a WDT link, multiple factors must be considered.

1. **Size and Modality:** The modality of communication primarily determines the size of the WDT. The literature demonstrates Optical [22], RF/inductive [6] and Ultrasonic [12] modes of WDT. With advances in wireless charging and portable communication devices, RF wireless telemetry based on RF transmission between two closely coupled coils (inductive coupling) is becoming the most commonly used scheme of data transmission.

2. **Range:** The required range of the WDT depends on the application and location of the implant. Previously, for transdermal and prosthetic implants, a range of a few centimeters was deemed adequate. However, with neural stimulation extending deeper into the body, a range of up to 20-30 cm needs to be considered.

3. **Data Rate:** The wireless link should provide a high data-transfer rate (bandwidth) both into the body (forward telemetry) as well as out of the body (back telemetry). This requirement is also application dependent, although in most emerging recording and stimulating systems, bandwidths in excess of 10–20 Mb/s are needed owing to increases in the number of sites that need to be simultaneously recorded.

**Table 3.3** Comparison of state-of-the-art inductive links.

| Work | Mandal2008 [11] | Rush2012 [15] | Kiani2013 [7] | Kiani2015 [8] | Yeon2017 [28] | Future |
|---|---|---|---|---|---|---|
| CMOS Technology | 0.5µm CMOS | 0.8µm CMOS | 0.35µm CMOS | 0.35µm CMOS | 0.35µm CMOS | 65nm CMOS |
| Application | | | | | | |
| Modulation | LSK | FSK | PHM | PDM | OOK | |
| Range (mm) | 20 | 20 | 10 | 10 | 18 | 150 |
| Carrier freq (MHz) /single/multiple carrier | 25/single carrier | 5/single carrier | 66.5/single carrier | 50/Multiple carrier | 131/Multiple carrier | > 200/Multiple carrier |
| Data rate (Mbps) | 2.8 | 1.25 | 20 | 13.56 | 1 | 200 |
| TX/ RX power (pJ/bit) | 35.7/1250 | - | 345/294 | 960/162 | 8.86 | 250/50 |
| Tx/ Rx Area (mm2) | 2.2/ 2.2 | - | 0.1/0.5 | 0.34/0.37 | 1 | 0.25/0.25 |
| BER | ~ $10^{-6}$ | - | 8.7 x $10^{-7}$ | 4.3 x $10^{-7}$ | ~ $10^{-6}$ | 1 x $10^{-8}$ |

4. **Robustness:** The telemetry approach chosen should be immune to most in-vivo environmental conditions and should be able to pass through tissue. In addition, it must remain immune to interference from the power delivery that mostly will occur simultaneously.

5. **Energy Dissipated:** The amount of energy that is dissipated into the surrounding tissue during data transmission needs to meet specified standards [5]. This energy dissipation must also consider any heating on the body surface of the patient to avoid undue discomfort or injury.

6. **Accuracy:** The next consideration for the WDT link is accuracy and/or error. The error in data transmission is typically specified in terms of a bit error rate (BER) and lowering the BER improves overall energy efficiency of the bioelectronicimplant.

7. **Energy Efficiency:** The energy efficiency of the link – especially in back telemetry – is critical in determining how much energy needs to be stored on the implant itself and has ramifications for battery and inductive coil sizes. The efficacy of the telemetry link is expressed in the amount of energy (typically in pJ) it takes to transmit one bit (pJ/bit) of data. This directly impacts both necessary power storage (and thereby volume of the implant) as well as the amount of energy dissipated into the surrounding tissue.

8. **Adaptability:** Finally, the wireless link should be adaptable so it can satisfy the needs of different applications as well as variations in the biological tissue over time.

**Table 3.3** compares some of the literature in the field over the last decade and provides a target for WDTs for the future BEM device.

## 3.6 Figures-of-Merit

Given the inherent complexity of the electronic instrumentation necessary in a BEM device, defining a single Figure-of-merit (FoM) might not be possible, or even useful. Instead, having a FoM for each of the major instrumentation sub-systems offers a more intuitive and practical solution.

For the AFE, noise efficiency (NEF) per channel is a useful FoM. NEF of an electric front-end recording amplifier is given by:

$$NEF = V_{rms}\sqrt{\frac{2\times I_{total}}{\pi\times V_T\times 4kT\times Bandwidth}}$$

Where $V_{rms}$ is the input referred noise of the recording signal chain, $I_{total}$ is the total current consumption and *Bandwidth* refers to the signal bandwidth that can be processed.

For A/D's in the BEM device, we can use the standard Walden FoM [25] that quantifies the efficiency of A/D conversion, expressing it as the energy consumed to compute each bit:

$$FoM_{ADC} = \frac{Power}{2^{ENOB}\times BW}\ Units: [pJ/bit]$$

**Table 3.4** Parameters of interest in various instrumentation sub-systems

| Instrumentation Sub-System Domain | Parameter | Unit |
|---|---|---|
| **Recording/ front-end** | Number of recording channels | - |
| | Channel Gain | dB |
| | ADC ENOB | Bits |
| | Signal bandwidth | Hz |
| | Sampling rate | MHz |
| | Signal path /recording latency | µs |
| | Input Referred Noise | µVrms |
| | NEF of front-end | |
| | ADC Walden FoM | pJ/bit |
| | Power/channel | µW/ch |
| **Processing & System Intelligence** | Programming language (C) | - |
| | Processor type (RISC, etc.) | |
| | Algorithm (CNN, etc.) & # of layers | - |
| | Parallelism | # of MACs |
| | # of data fetches | # |
| | Max. Throughput | GOPS |
| | Pattern Recognition Accuracy | % |
| | Memory size | kBytes |
| | I/O data compression | Y/N |
| | Range of precision scaling | Bits |
| | Energy efficiency i.e. Energy/operation | TOPS/W |
| **Data Transmission** | Full Duplex data telemetry | Y/N |
| | Forward Data Rate | Mbit/s |
| | Reverse Data Rate | Mbit/s |
| | Antenna size | mm2 |
| | Bit Error Rate (BER) | Bit errors/s |
| | Signal to Interference Ratio (SIR) | dB |
| | Bit Error Ratio (bit errors/total number of bits) | - |
| | Transmission efficiency/power consumption | pJ/bit |
| | Telemetry distance | cm |
| **Physical Parameters** | ASIC power dissipation | mW |
| | Process | µm |
| | Chip size | mm x mm |
| | Implant volume | cm3 |
| | Weight of ASIC + supporting passives | g |
| | Thermal resistance of ASIC package | °C/W |

Where *Power* is the average power consumption of the ADC in Watts [W], *ENOB* is the effective number of bits (bits), and *BW* is the bandwidth of the ADC in Hz. This FoM is independent of the topology of the ADC used—whether successive approximation, time domain/VCO based, ΔΣ or pipe-lined.

**Table 3.4** summarizes the key parameters of interest for each sub-system.

The concept of the Walden FoM can be extended to the entire bio-signal processing signal chain. This effective signal chain FoM quantifies the energy efficiency of obtaining a final value of the biological parameter being sensed,for instance a pulse-plethysmograph (PPG) sample [18]. The effective FoM can then expressed as:

$$FoM_{SIGNAL} = \frac{Power_{AFE} + Power_{ADC} + Power_{DataTx}}{2^{ENOB} \times BW} \; Units: [pJ/bit]$$

From a data-transmission angle, to compare various telemetry units, it is intuitive to normalize the energy it takes to transmit and receive a bit (energy/bit) to the overall bit error ratio (not to be confused with Bit-error rate). This can be expressed as:

$$FoM_{telemetry} = \frac{Energy/_{bit}}{Bit\ Error\ Ratio} \; Units: [pJ/bit]$$

## 3.7 Precompetitive Research Tools

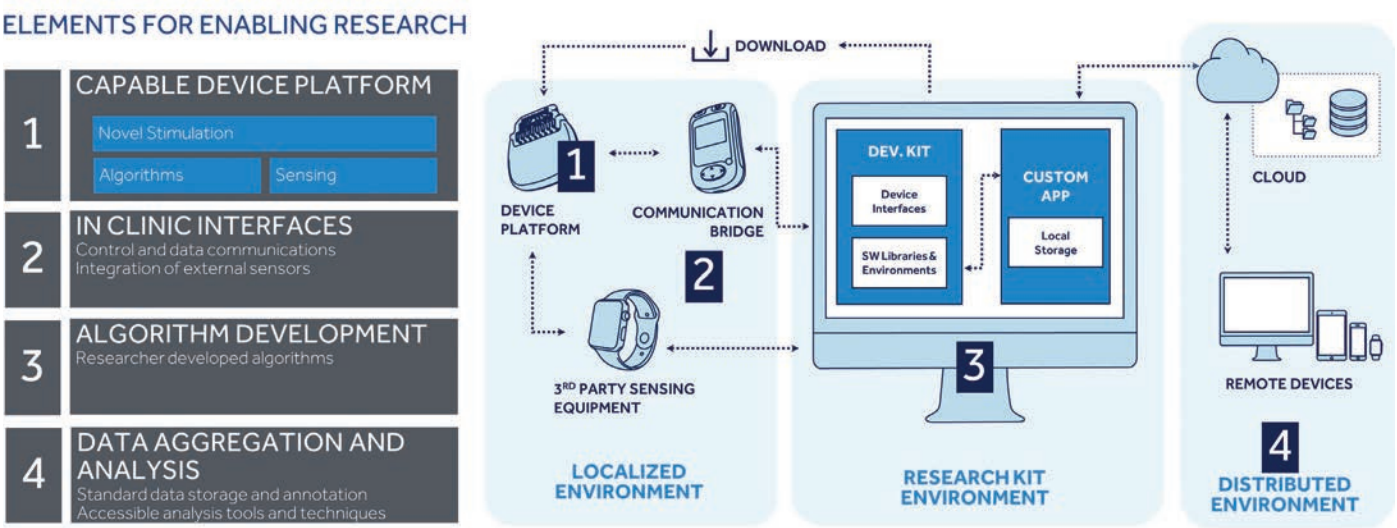
Precompetitive research tools do not have a specific application or disease defined. Instead, the goal is to understand the "core of the problem" and mechanisms of a biological system. One example currently deployed in multiple feasibility trials is the Activa PC+S; this Ce-marked system allows for gathering of key neuroscience data and prototyping closed-loop algorithms (system intelligence) while providing an established therapy [1]. These tools are expected to be capable of assessing the fundamentals of a biological system and will be used to develop/inform biological models and understand potential therapy solutions.

Current chronic research capability for humans is highly limited for invasive applications and it is expected that externals and wearables will be much more accessible. The overall ecosystem for a research system is captured in **Figure 3.4**, which highlights the key attributes for a mature toolkit.

Key attributes of a precompetitive tool include:

- Ensure safety of patient while providing enough potential benefit to warrant the risk
- Ideally, be supported for the life of the patient if they benefit from the research
- Be adaptable to needs of a study, including updating the device configuration
- Be capable of integrating information from multiple sources
- Provide a data analysis and algorithm development environment for iterative learning
- Ability to store large datasets for annotation, analysis, and cross-validation

**Figure 3.4** Key attributes of a pre-competitive research tool



Research tools with these attributes are currently supporting on-going feasibility studies across multiple disease states—in human subjects (hundreds of "pt-years" and growing, exponentially)—supported in part by public-private partnerships like the NIH BRAIN initiative.

The next generation of tools should support greater modularity and interchangeability of tools, connected through APIs; such an architecture allows for the integration of networks of systems, but also require up-front collaboration for system architecture definition, risk and hazard assessments, and system-level mitigations.

# References


[1] Activa PC neurostimulator, http://www.medtronic.com/us-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems/activa-pc.html

[2] American Diabetes Association, Standards of medical care in diabetes–2008. *Diabetes Care.* 31 Suppl 1, S12-54 (2008).

[3] The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes.* 45, 1289–1298 (1996).

[4] B. Grosman et al., Hybrid Closed-Loop Insulin Delivery in Type 1 Diabetes During Supervised Outpatient Conditions. *J Diabetes Sci Technol* (2016), doi:10.1177/1932296816631568.

[5] IEC 60601-1-10 standard: *General requirements for basic safety and essential performance—collateral standard: requirements for the development of physiologic closed loop controllers.*

[6] Y. Jia, et al., "A mm-Sized Free-Floating Wirelessly Powered Implantable Optical Stimulating System-on-a-Chip,: ISSCC Tech. Digest., 2018, pp. 468–469, Feb 2018.

[7] M. Kiani, M. Ghovanloo, "A 20Mbps pulse harmonic modulation transceiver for wideband near-field data transmission," IEEE Trans. Circuits and Systems – II, vol. 60, pp. 382–386, July 2013.

[8] M. Kiani, M. Ghovanloo, "A 13.56-Mbps pulse delay modulation based transceiver for simultaneous near-field power and data transmission," IEEE Trans. Biomed. Circuits and Systems, vol. 9, pp. 1–11, Feb 2015.

[9]. B. P. Kovatchev, M. Breton, C. D. Man, C. Cobelli, In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *J Diabetes Sci Technol.* 3, 44–55 (2009).

[10]. Hyun Lee, Soo & Hwan Jung, Jung & Mee Chae, Youn & Suh, Jun-Kyo & Kang, Ji. (2010). Fabrication and characterization of implantable and flexible nerve cuff electrodes with Pt, Ir and IrOx films deposited by RF sputtering. Journal of Micromechanics and Microengineering. 20. 035015. 10.1088/0960-1317/20/3/035015.

[11] S. Mandal, R. Sarpeshkar, "Power efficient impedance-modulation wireless data links for biomedical implants," IEEE Trans. Biomed. Circuits and Systems, vol. 2, pp.301–315, Dec 2008.

[12] F. Mazzilli, M. Peisino, R. Mitouassiwou, B. Cotte, P. Thoppay, C. Lafon, P. Favre, E. Meurville, C. Delhollain, In-vitro platform to study ultrasound as source for wireless energy transfer and communication for implanted medical devices, Annual International Conference of the IEEE Engineering in Medicine and Biology, 2010, pp. 3751–3754.

[13]. The Diabetes Control Complications Trial Research Group, The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *New England Journal of Medicine.* 329, 977–986 (1993).

[14] O'Leary et al. A recursive-memory brain-state classifier with 32-channel track-and-zoom Δ2 Σ ADCs and Charge-Balanced Programmable Waveform Neurostimulators. IEEE International Solid-State Circuits Conference (ISSCC). 2018.

[15] A. Rush, P. Troyk, "A power and data link for a wireless-implanted neural recording system," IEEE Trans. Biomed. Circuits and Systems, vol. 59, pp.355-3262, Nov 2012.

[16] S. J. Russell *et al.*, Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N. Engl. J. Med.* 371, 313–325 (2014).

[17] Mehdi Sadi, Gustavo K. Contreras, Jifeng Chen, LeRoy Winemberg, Mark Tehranipoor. Design of Reliable SoCs With BIST Hardware and Machine Learning. IEEE Transactions on Very Large Scale Integration (VLSI) Systems (Volume: 25, Issue: 11, Nov. 2017).

[18] A. Sharma, A. Polley, S.B. Lee, S. Narayanan, W. Li, T. Sculley, S. Ramaswamy, "A sub-60uA Multi-modal Smart Bio-sensing SoC with >80dB SNR, 35uA Photo Plethysmography Signal Chain," *IEEE J. Solid-State Circuits,* April 2017

[19] Shoaran et al. Efficient Feature Extraction and Classification Methods in Neural Interfaces. Winter Bridge on Frontiers of Engineering. 47. 2017.

[20] Robert Stengel. Intelligent failure-tolerant control. *IEEE Control Systems Magazine.* 1990.

[21] Vivienne Sze. Designing Hardware for Machine Learning: The Important Role Played by Circuit Designers. IEEE Solid-State Circuits Magazine (Volume: 9, Issue: 4, Fall 2017)

[22] H. Takehara, et al., "Implantable micro-sized image sensor for data transmission with intra-vital optical communication, Journal of Engineering, vol. 2017, Iss. 1, pp. 4–6, 2017.

[23]. H. Thabit *et al.*, Home Use of an Artificial Beta Cell in Type 1 Diabetes. *N. Engl. J. Med.* 373, 2129–2140 (2015).

[24]. S. Trevitt, S. Simpson, A. Wood, Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development? *J Diabetes Sci Technol* (2015), doi:10.1177/1932296815617968.

[25] R. Walden, "Analog-to-digital conversion in the early twenty-first century," *Wiley Encyclopedia of Computer Science and Engineering*, pp. 126–138, Wiley, 2008.

[26] K. D. Wise, D. J. Anderson, J.F. Hetke, D.R. Kipke, K. Najafi, "Wireless Implantable Microsystems: High-Density Electronic Interfaces to the Nervous System" Proceedings of the IEEE, vol. 92, No. 1, Jan 2004.

[27] Jintao Zhang, Liechao Huang, Zhuo Wang, Naveen Verma. A seizure-detection IC employing machine learning to overcome data-conversion and analog-processing non-idealities. IEEE Custom Integrated Circuits Conference (CICC). 2015.

[28] P. Yeon, S. A. Mirbozorgi, J Lim, M. Ghovanloo, "Feasibility study on active back telemetry and power transmission through an inductive link for millimeter-sized biomedical implants," IEEE Trans. Biomed. Circuits and Systems, vol. 11, No. 6, Dec 2017.

Chapter 4

# Modeling and Simulation

## 4.1 Introduction

Humans are incredibly complex systems, with a nearly impenetrable panoply of feedback loops spanning biochemical, neural, and mechanical domains. While it may not be currently possible to simulate this extraordinary complexity, there are untapped opportunities to abstract, validate, and gain greater understanding of the interplay between these domains through computational methods.

To accelerate the development of Bioelectronic Medicine (BEM) systems, models at various levels of abstraction coupled to simulation tools capable of handling large-scale, multi-domain systems operating over disparate time and spatial scales with intuitive graphical user interface need to be developed in order to convert the raw sensor data into understandable and actionable information.

Not only is the simulation environment extraordinarily complex, but techniques developed in other disciplines have not been fully brought to bear, thus current modeling suffers from a lack of standards in parameter extraction and experimental data for model validation has not been centralized nor made open to the scientific community. It is imperative to address these roadblocks to enable rapid advancement in model development.

As in many other scientific domains, the key to rapid innovation is to step away from a trial and error phenomenological exploration to experimentation informed by simulation utilizing accurate models. Thus, it is vital for the BEM community to rally around a Modelling and Simulation Roadmap.

Due to interdependencies with all other Roadmap chapters, the requirements for this chapter are derived from a thorough analysis of the requirements of the other Roadmap chapters, especially regarding the technological options chosen and the time schedules. Furthermore, development of a model for a particular disease state (from the list in **Figure 1.1**) will serve to develop an understanding of system dynamics, provide valuable patient feedback and comparisons to the norm for model enhancements, and pave the way for exploration through simulation.

## 4.2 Modeling of Biological Systems

The BEM Roadmap recognizes the need for the development of both cell-level and organ-level biological models from a theoretical biology perspective, as well as highly abstracted models based on transfer functions obtained from measuring responses due to a variety of stimuli. Multiscale models spanning several layers of biological organization from intracellular molecular networks and cell-to-cell interactions to interacting tissues and organs of the whole body need to be developed. Models should allow for experimental validation of the mechanisms they propose. Their components should be at a level of description that allows for the design and inclusion of experimental perturbations using current experimental techniques. Some considerations for modelling are identified below.

**Levels of abstraction**

- From rigorous biology/biochemistry based to empirical observation-based models
- Minimal (reduced, compact, etc.) models that accurately describe a piece of the biology but at the potential price of being too narrowly focused.
- Consistent levels of abstraction supporting a mix and match strategy for hierarchal level simulation

**Methods to create models**

- From theoretical biology to experimental stimulus/response based
- Standards for measuring modeling parameters to enable model accuracy comparison and thus rapid model improvement

**Model interfaces**

- Neural to electrical, mechanical, biochemical, etc.
- Translational to conventional diagnostic tools such as imaging (MRI, ultrasound, etc.)
- Disease state specific

## 4.3 BEM Design Automation

Full-scale computer-aided tools will be needed for reliable simulation of larger and more complex systems, such as whole-cell and whole-organ models. In contrast with modern electronic design automation (EDA), biological simulation tools are currently fragmented and task-specific. New methodologies and design principles are needed that embrace the complexity of multi-scaled electronic-biological systems integration. This section identifies the necessary elements required of a BEM design automation simulation toolset.

**Multi-science/Multi-domain mixed-mode simulator**

- Biology, Physics, Electrical, Mechanical, Chemical

**Hierarchical simulator**

**Libraries**

- Components (e.g. dendrites, axons or neurons)
- Subsystems (e.g. probe/neuron interface, communications link, vagus nerve, etc.)

**Computational complexities**

- Large matrices with non-zero elements
- Time/scale resolution variability
- Accuracy

**Algorithms**

- Time/scale resolution variability
- Accuracy

**Artificial Intelligence/Machine Learning (AI/ML)**

**Graphical User Interface to facilitate design entry**

**Synthesis tools to auto generate HW/SW solutions that meet the complex biological-electronic systems specifications**

**Verification tools**

**Visualization tools for results in various domains**

**Filters and other processing elements**

**Design aids**

Models in a sophisticated simulation environment facilitate further insight and understanding of complex biological systems. As an example, a high-level understanding of tremor response associated with Parkinson's disease to deep brain stimulation has been gained by utilizing fairly simple electrical models representing the biological functions implemented in a control loop. With this knowledge enhancements in both the models and the ultimate treatment can be made. Applying new techniques such as AI/ML may provide the means for personalizing otherwise generic models. Furthermore, through the use of models, additional parameters which are not directly accessible in any other way are exposed and/or can be derived.

**Table 4.1** High level Modeling & Simulation Roadmap

| Year | 2018 | 2023 | 2028 | 2033 |
|---|---|---|---|---|
| Science | Basic understanding of biological systems/cells | Theory for how to integrate model selection with constraint propagation across several layers of biological organization | Theory developed for human body response to attachment of a probe/ stimulus to a neuron | Theoretical understanding of neurostimulation waveform requirements accounting for variability amongst individuals |
| Modeling | Fragmented, Specific, and Non-standard | Development of low-level models<br>Formal methods of model selection | Variability models for neurons<br>Catalogue of simulated signal neural patterns for organs | Validated hierarchical models translating neuron models to organ stimulation |
| Simulation | Fragmented, Specific, and Non-standard | Development of simulation tools supporting a variety of minimal viable products | Integrated multi-physics tool that contemplate biology, electronics, mechanics, optics, chemistry etc. using a common language | Clinical trials are largely formed by simulation prior to a final human-based clinical trial |

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

## 4.4 Modeling & Simulation Roadmaps

**Table 4.1** presents a high-level roadmap of modeling, simulation, and scientific insight. The first step is to work on standardization and open data for model development. Subsequent to that, more detailed roadmaps should be defined to align with the priorities of the BEM community.

## 4.5 Challenges in BEM Modelling and Simulation

Critical modelling and simulation topics are outlined below in accordance with the various BEM Technology Roadmap chapters.

### Platform Functionality

- Transducer attach and energy conversion for
  - Muscle/organ movement, electric potential in inner-ear from cochlea, temperature gradients or fuel cells running on glucose and oxygen in the blood stream

### Instrumentation Capabilities

- In-body electromagnetics
  - Implanted antennas, inductive wireless links, optoelectronics inside a human body
- Biosensors
  - Sensitivity, selectivity, degradation over time (biofouling)
  - Data fusion of multiple sensors
- Nerve model including stimulus, nerve conduction, coupling to/from neighbors

### Neural Interfaces

- Precise signal parameters for neurostimulation
- Computational models incorporating the disturbances in the response simply due to the attachment of an electrode
- Deep brain stimulation of how and which neurons are modulated
- Ultra large-scale recording with single neuron precision
- Neural signal degradation over time as a function of tissue injury, micro movement, toxicity and formation of glial scars
- Vagus nerve axons mapped to organs including propagation loss, pulse shaping, etc. to stimulus as seen at receptor
- Computational models of neuromodulation that incorporate variability due to individual subject differences
- Computational models for non-invasive nerve stimulation technologies
- Computational models predictive of side effects
- Computational models to correlate in-vitro to in-vivo response

### Biocompatible Packaging

- Biomedical surface science/Cell-material interactions
- Battery encapsulant protection/seal to the electrochemical reaction
- Mechanical biocompatibility
  - Inflammatory response as a function of Young's modulus and size of package and electrodes
  - Temporal response (inflammation, electrical contact) of a system with dynamic flexibility

### Minimal Viable Products

- Interaction between a pharmaceutical and a BEM stimulus to ensure the unwanted response from the pharmaceutical is canceled by the application of some sort of neuromodulation

### Clinical Translation

- Accelerated life test
- Computational models to translate dimension-dependent and anatomy-dependent parameters to animal models then to humans and vice-versa
- Algorithms for multisensory data fusion to collect/integrate indicators of certain biological state or condition from multiple sources
- Models to relate integrated multisensory data and medical imaging
- Modeling of the clinical system

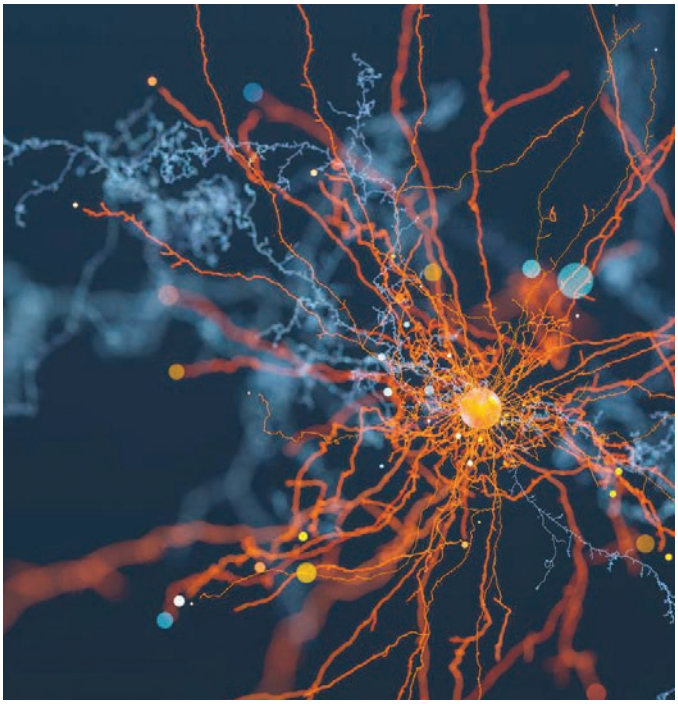
## References


[1] V. V. Shah, S. Goyal, H. J. Palanthandalam-Madapusi, "A Possible Explanation of How High-Frequency Deep Brain Stimulation Suppresses Low-Frequency Tremors in Parkinson's Disease", IEEE TRANS. NEURAL SYST. REHAB. ENG. 25 (2017) 2498-2508

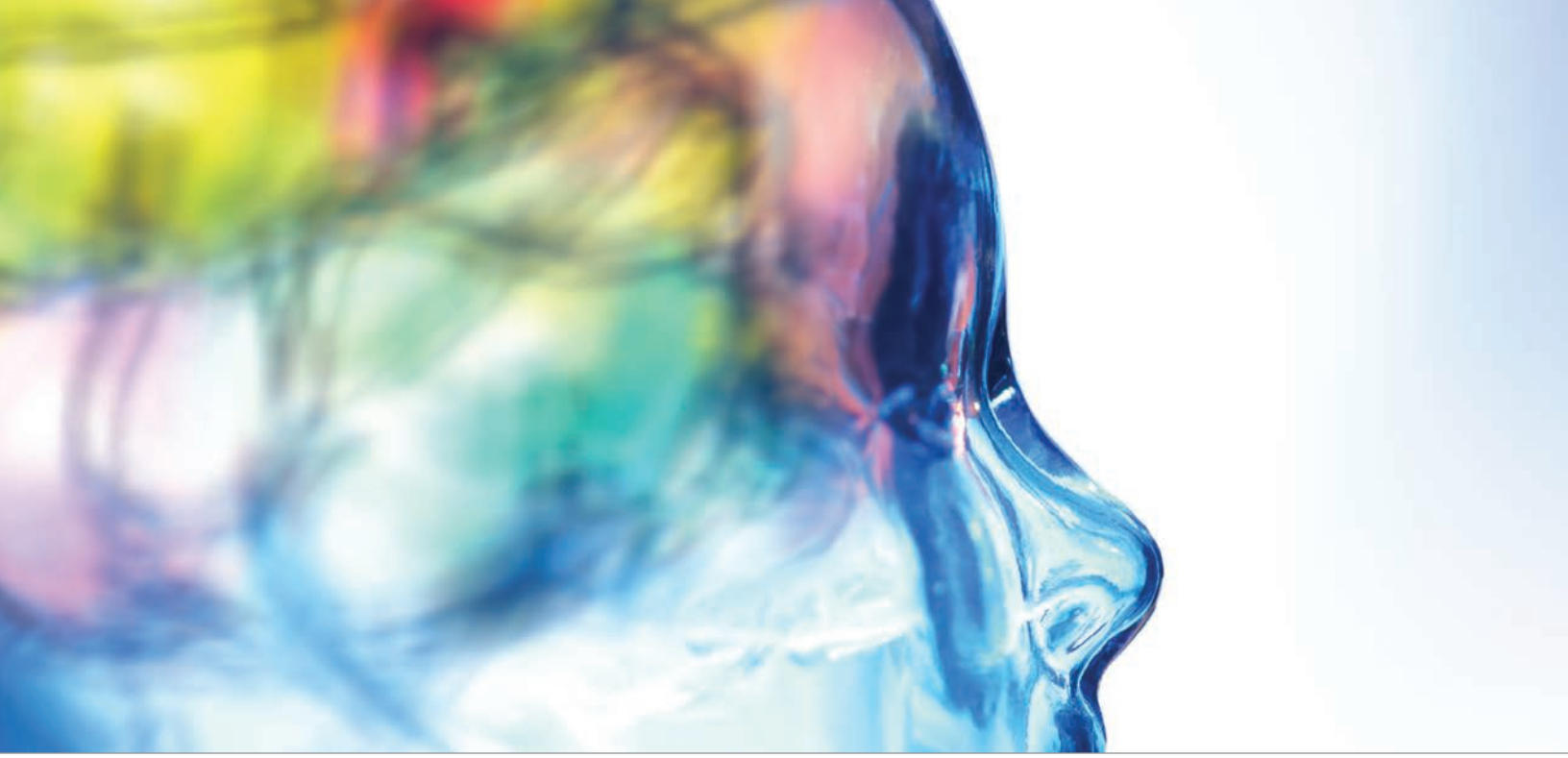
[2] E. Kayvanpour, T. Mansi, F. Sedaghat-Hamedani, A. Ali, D. Neumann, B. Georgescu, P. Seegerer, A. Kamen, J. Haas, K. S. Frese, M. Irawati, E. Wirsz, V. King, S. Buss, D. Mereles, E. Zitron, A. Keller, H. A. Katus, D. Comaniciu, B. Meder, "Towards Personalized Cardiology: Multi-Scale Modeling of the Failing Heart", PLoS One 10 (2015) e0134869.

[3] R. J. White, G. C. Y. Peng, S. S. Demir, "Multiscale Modeling of Biomedical, Biological, and Behavioral Systems (Part I)", IEEE ENG. IN MEDICINE AND BIOL. MAG. 28 (2009) 12-13

[4] M. R. Maurya and S. Subramaniam, "Computational Challenges in Systems Biology", in: Systems Biomedicine: Concepts and Perspectives (ELSEVIER 2010)

*Humans are incredibly complex systems, with a nearly impenetrable panoply of feedback loops spanning biochemical, neural, and mechanical domains. While it may not be currently possible to simulate this extraordinary complexity, there are untapped opportunities to abstract, validate, and gain greater understanding of the interplay between these domains through computational methods.*



Chapter 5

# Neural Interfaces

## 5.1 Nerve and Organ Function

The human body contains more than 70 organs, which work together in groups (systems) to execute specific body functions. The respiratory system, for example, includes organs such as the lungs, pharynx, trachea, and diaphragm, which serve to control breathing. Internal organ function is largely regulated by a complex network of nerves that facilitate bidirectional communication between the organs, spinal cord, and brain. This network is known as the autonomic nervous system (ANS) because it operates without voluntary input. The primary role of the ANS is to control visceral reflexes and help maintain homeostasis, for example regulating key biological processes such as blood pressure, body temperature, and metabolism. Autonomic dysfunction has been associated with a variety of conditions including congestive heart failure and panic disorder.

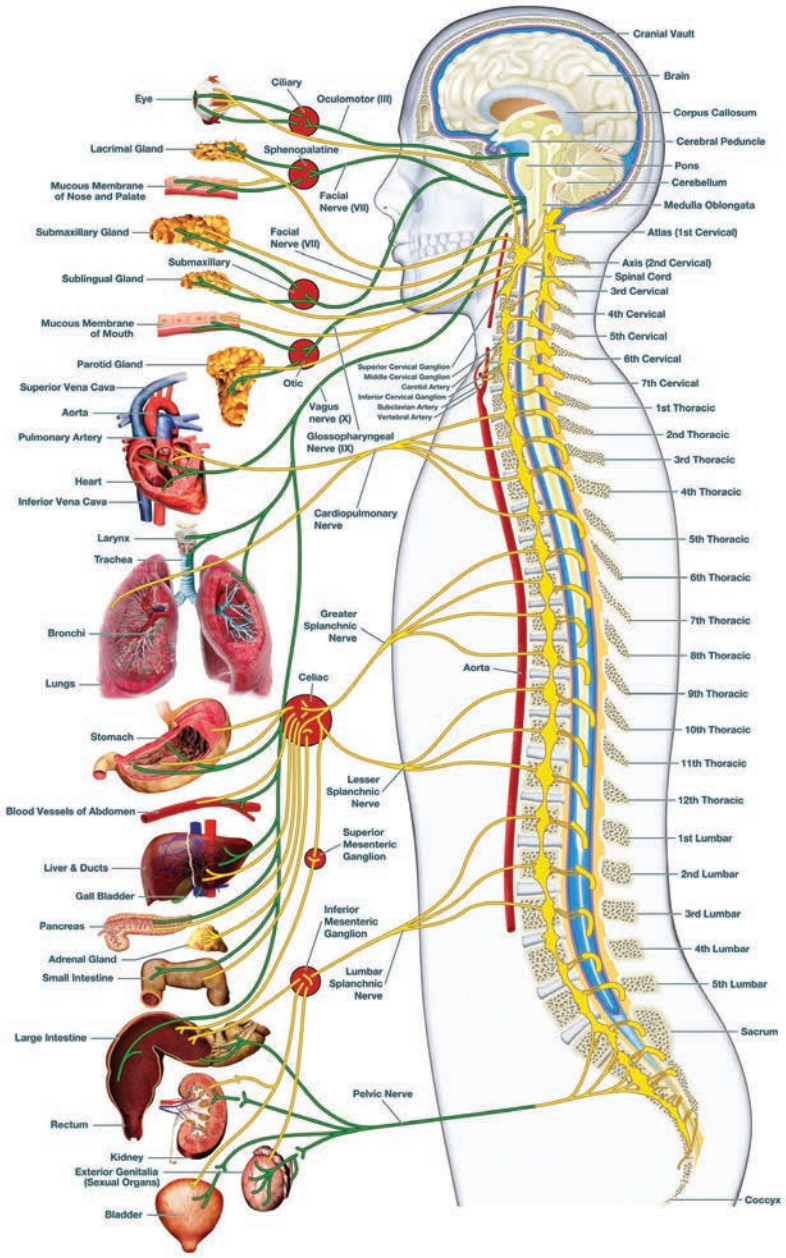
The ANS carries impulses from the brain and spinal cord to organs through efferent pathways consisting of neurons. These neurons bridge the central nervous system (CNS) and the peripheral nervous system (PNS) in ganglia, which are clusters of nerve cell bodies that lie outside the CNS. Sensory information from organs is then transmitted back to the CNS. Near the organs, efferent and afferent axons (projections of the neurons) often organize into branching networks called plexuses or plexi.

The ANS can be divided into three anatomically and functionally distinct divisions: sympathetic, parasympathetic, and enteric. The sympathetic nervous system controls responses such as a reaction to a perceived threat ("fight or flight") while the parasympathetic nervous system controls responses such as salivation ("rest and digest"). Finally, the enteric nervous system controls gastrointestinal function, including gut motility and secretion [1].

## 5.2 Nerves: Types, Sizes, and Spatial Organization

A nerve, for example the vagus nerve (cranial nerve X), is approximately 3-5 mm in diameter in humans, and consists of bundles (fascicles) of nerve fibers (axons). Axons range from 0.25 µm to 25 µm in diameter. Out of ~100,000 axons in the vagus nerve **(Figure 5.1)**, approximately 80% to 90% are afferent, i.e. they transmit sensory information about the state of the body's organs to the central nervous system. Three main types of axons are described in **Table 5.1**. [2]–[4]

**Figure 5.1** Nervous system and organs functions




# 5.3 Neuromodulation Modalities

Common ways to modulate neural activity is through the application of electrical or magnetic stimulation. The electrical stimulation uses either invasive or non-invasive electrodes while the magnetic stimulation is performed by a non-invasive magnetic coil. At the single-cell level, the mechanisms of stimulation are reasonably well characterized. There are well-defined guidelines for the optimal placement of electrodes, and the electrochemical and biochemical effects of cathodal and anodal stimulation can be accurately modeled. For example, the most effective way to activate a cell was found by placing a cathode close to the axon hillock or node of Ranvier [5]. Some recent models can predict which and how many nerve fibers are modulated by an applied electrical field in a nerve. Since the brain consists of complex networks of excitatory and inhibitory neurons with complex geometries and 3D structure, it is extremely difficult to fully understand how and which neurons of specific brain networks are modulated. However, some empirically determined therapeutic effects of brain stimulation can be observed in cases such as Parkinson's disease, epilepsy, chronic pain, and others.

With more control over type and amount of cells that are modulated by electrical

**Table 5.1** Axon Types

| Axon Type | Diameter | Conduction Velocity | Myelinated | Nervous System |
|---|---|---|---|---|
| A | 5-20 μm | up to ~150 m/s | thickly | Somatic (voluntary) |
| B | 2-5 μm | up to ~15 m/s | thinly | Autonomic (preganglionic) |
| C | <1-2 μm | up to ~1.5 m/s | no | Autonomic (postganglionic) |

stimulation, better therapeutic effects can be expected. One anticipated approach would be to use more sophisticated electrodes that allow steering of electrical fields. Another approach that shows promise is optogenetics, where neurons are genetically modified to express light-sensitive ion channels (opsins). Upon activation by light of a specific wavelength, the opsins allow passage of specific ions or activate intracellular signaling pathways. In vivo, this is mostly done using non-pathogenic viral vectors. For example, canine adeno virus (serotype 2) (CAV2) preferentially transduces neurons, mainly at presynaptic endings, and traffic retrogradely along the axon to the cell body. So injecting the CAV2 at a target organ would transduce the nerve ending(s) that innervate the organ. About two weeks later, light could be used to selectively activate the nerve fibers innervating the target organ of interest. [6]

The net effect is that specific neurons can be modulated (e.g. activated/inhibited) by light. If the opsin expression is driven by specific promotor systems, it is possible to selectively render different subtypes of neurons that are sensitive to specific light frequencies. With this approach, it is possible to selectively inhibit excitatory neurons with red light and at the same time excite inhibitory neurons with blue light. These approaches have been shown to successfully interrupt ongoing seizures in animals [7]. Taken together, optogenetics is a tool that can be used to modulate the activity of neural networks with revolutionary temporal, spatial and cellular specificity. However, optogenetics presents several challenges that need to be addressed before clinical application becomes a possibility. **Table 5.2** outlines these challenges and suggests possible solutions.

One intermediate step towards the introduction of this technology could be optopharmacology , or the use of drugs that can be activated by illumination. This approach does not involve gene therapy and might find its way to clinic much faster than optogenetics. [8], [9]

## 5.4 Neural Recording / Biosensing

Biosensing is a critical component of any effective closed-loop neuromodulation treatment system. These signals serve as indispensable information for adaptive and personalized treatments or interventions. Biosensing signals can broadly be categorized into three types: i) neuronal electrical signal in the form of action potential, ii) biochemical signals such as concentrations of biomarkers, e.g. neurotransmitters, and iii) environmental signals such as local temperature, pH values, etc. Important metrics for each of these biosensing modalities include sensitivity, specificity, signal-to-noise ratio, spatial and temporal resolutions of the signals, areal coverage, as well as the long-term stability and reliability of the signals.

Neuronal electrical signals are usually recorded with an electrode made of an electrically conductive metal or polymer implanted next to the targeted neurons. These electrodes also often serve as stimulating electrodes. Neuronal electrical signals of action potentials are usually on the order of a few to hundreds of micro volts, and individual neurons may fire at a frequency of up to one kHz.

State-of-the-art neural interfaces may have tens up to thousands of neural electrodes, each with dimensions ranging from a few micrometers (the size of a neuron) to a few millimeters. The recorded neuronal electrical signals are aggregated measurements of the environment near the electrode. Sophisticated algorithms are needed to pinpoint signals from specific neurons, a process called spike sorting. In the future, larger scale and more precise neural probes, along with advanced machine learning algorithms, are needed to achieve large scale neural recoding with single-neuron precision.

**Table 5.2** Challenges and possible solutions in optogenetics

| Challenges | Suggested Solutions |
|---|---|
| Toxicity related to opsin expression and long-term efficiency | Select promotor systems that allow chronic, non-toxic levels of opsin expression |
| Insertional lesions by optic probes | Less invasive approaches; transcranial, epidural, transvascular |
| Phototoxicity | Triggered illumination in closed-loop design |
| Controlling spatial extend of modulation | Determine optimal injection method, viral vector serotype, volume volume and titer of viral vector |
| Possibility for chronic modulation | Dependent on the application |

Key challenges of neural recording include achieving and maintaining a high signal-to-noise ratio (>5) over the entire lifetime of a neural implant (in years). Unfortunately, extant electrodes are subject to signal degradation caused by tissue injuries during probe insertion and micromovement, formation of glial scars, and other side effects. Development of neural probes that match the mechanical properties of the neural tissues and improvement in biocompatibility of the materials will be the key to solving these challenges.

Aside from measuring individual neuron activity, it is important to have biosensing of neurotransmitters and other biomarkers that are important to a particular disease or condition. Neurotransmitters carry information among neurons through electrochemical reactions. Major neurotransmitters include amino acids, monoamines, peptides and purines, etc. Other relevant biomarkers include glucose, glutamates, pressure, acidity, etc.

For example, dopamine is a monoamine neurotransmitter. It modulates arousal and motivation in humans and animals. It plays a central role in the brain's "reward" system. Its dysregulation is implicated in several debilitating disorders, such as addiction, depression, Parkinson's disease, and schizophrenia. The release of dopamine occurs in a sub-second regime. The dynamics of dopamine neurotransmission have been probed using electrically conductive carbon materials, such as carbon fibers, glassy carbon, etc. using techniques such as fast-scan cyclic voltammetry.

Ultimately, to precisely control the effective closed-loop neuromodulation therapies, further research in biosensing is critical.

## 5.5 Types of Neural Interfaces

Neurostimulation therapies are used to treat a wide range of conditions by engaging neural targets. For example, through delivery of electrical pulses from an implantable pulse generator (IPG) to chronic neural interfaces with electrical contacts. Neural interfaces must be fit-for-purpose to achieve therapeutic effect, and they vary in type depending on the desired anatomical target, implant location and surgical access requirements. The following are some common examples:

- **Spinal cord leads** are used to deliver neurostimulation to the spinal cord. For example, to mask pain signals to the brain or to engage sacral roots for treatment of bowel and bladder dysfunction. There are two basic styles of spinal cord stimulation (SCS) interfaces: leads and paddles. Leads are cylindrical PtIr electrode rings, typically 4-16 contacts, spaced by insulating material such as silicone, whereas paddles, as the name implies, comprise electrodes stamped onto paddle-shaped silicone backing.
- **Deep brain leads** are conceptually similar to spinal cord leads but for the brain targets that control unwanted neurological or psychological symptoms, such as essential tremor, Parkinson's disease, dystonia, refractory epilepsy and depression. Deep brain stimulation (DBS) leads will commonly comprise of 4-8 segmented contacts, but more complex multi-contact investigational leads with up to 40 contacts have been demonstrated by Medtronic-Sapiens.
- **Cuffs electrodes** are made to encircle nerves and thus they have the potential to achieve a more direct control over discrete nerves. For example, a two-contact spiral cuff from Cyberonics is used to interface with the vagus nerve to treat intractable epilepsy. Multi-contact cuffs, such as Imthera's six contact cuff is used to selectively activate the hypoglossal nerve to treat sleep apnea. [10], [11]
- **Cortical grids** are neural interfaces similar in concept to paddle electrodes and commonly used for mapping or monitoring brain function in specific areas of the cortex.
- **Patch electrodes** are similar to cortical grids but typically much smaller and with one to few electrodes, and they can be used to target nerve plexuses such as the carotid body.
- **Leadless stimulators** are two electrode contacts that are integral to the IPG body in a very small form factor. The BION is an example of a leadless stimulator originally developed for functional electrical stimulation (FES). More recent examples include SetPoint Medical's cervical vagus nerve interface for treatment of rheumatoid arthritis and BlueWind's tibial nerve stimulator for overactive bladder. [3], [12]
- **Penetrating electrodes** such as FINE or LIFE interfaces can be used to penetrate the nerve epineurium to achieve improved selectivity and/or low thresholds of activation; however, these electrodes have not been used in chronic clinical applications.

## 5.6 Target Precision

### 5.6.1 Current neural interface spatial precision

As a starting point, target precision capabilities of neurostimulation devices and interfaces need to be defined. These include 1) invasive interfaces for nerve stimulation (such as cuff, LIFE and TIME electrodes) and for brain stimulation such as surface grid/strip electrodes and intracranial depth

electrodes and 2) non-invasive interfaces for nerve stimulation, such as electroCore's gammaCore device, the NET-2000 device of Auri-Stim Medical, the Parasym® system of Parasym Health, etc.), and for brain stimulation such as transcranial direct/alternating current stimulation. In addition to neurostimulation, spatial precision of various recording techniques such as electrical field recording, electrical impedance tomography, calcium imaging, etc., need further clarification. The spatial precision that can be achieved with current state-of-the-art techniques is ~3 mm for PNS and ~2 mm for CNS.

### 5.6.2 Improving spatial precision

Several approaches have been developed to improve spatial resolution, some of which have been used clinically (e.g., TIME and LIFE electrodes). New methods are needed to improve target precision in steering and focusing, targeting afferent and efferent fibers separately, etc. For example, optogenetic could allow for single-axon targeting. However, single-axon precision may not be necessary for achieving the desired therapeutic effect. New experiments and clinical studies are needed to establish the required target precision for a given application (and likely in a given individual). More specifically, identifying pathways of axons in the cervical vagus nerve will allow for organ/disease specific treatments. Furthermore, establishing animal models and biosensors for measuring and mapping the effects of neural stimulation is necessary. Finally, optimizing the stimulus with a closed-loop neuromodulation creates an opportunity for machine learning utilization. **Table 5.3** shows the current and projected spatial resolutions for neural stimulation and recording.

### 5.6.3 Surgical advances that are needed to enable better target precision

Current surgical spatial precision is ~1 mm. New surgical methods may be needed to enable finer precision for positioning micro-scale neural interfaces in a reliable and reproducible manner. It will also be important to understand the anatomical variability among individuals.

Examples include:

- Contrast agents to help visualize nerves, ganglia, and plexuses during surgery
- Surgical tools that allow for a more accurate and reliable positioning of neural interfaces
- Robotic surgery for placement of neural interfaces
- Methods to limit neural interface movement and encapsulation over time
- Methods to target specific fiber types
- Real-time methods to determine if nerves are damaged during surgery

## 5.7 State of the Art / Product Examples

The neurostimulation market is composed of four major segments: i) spinal cord stimulation (SCS) for the treatment of chronic intractable pain, ii) deep brain stimulation (DBS) for brain related disorders, iii) vagal nerve stimulation (VNS) for intractable epilepsy and iv) sacral nerve stimulation (SNS) for bladder and incontinence. Four major companies, Medtronic, St. Jude Medical (acquired by Abbott in 2017), Boston Scientific and LivaNova, collectively represent more than 98% of neurostimulation market worldwide. Below are some examples of emerging products in DBS, SCS and VNS that have market approval or are in the clinical trials:

- **The Vercise DBS system** from Boston Scientific is a USFDA approved device for precise neural targeting in patients with Parkinson's disease, primary and secondary dystonia, and essential tremor. It features a rechargeable IPG with Multiple Independent Current Control (MICC) and dedicated power sources for each of the eight electrodes on the lead to allow for accurate targeting stimulation and minimize unwanted side effects.

**Table 5.3** Target precision for neural stimulation and recording

| Target precision goals (spatial resolution) | Current | 5 years | 10 years | 15 years |
|---|---|---|---|---|
| Stimulation/Recording | PNS: 3 mm<br>CNS: 2 mm | PNS: ~1-2mm (single fascicle)<br>CNS: ~0.5-1mm (single brain region) | PNS: 100µm<br>CNS: 100µm | PNS: <10um (single axon)<br>CNS: 10-20um (single neuron) |

Commercial solutions exist, and are being used  Commercial solutions are known and are being tested/optimized  Commercial solutions do not exist

**Table 5.4** Neurostimulation and Recording Technologies*

| Year | 2018 | 2023 | 2028 |
|---|---|---|---|
| Neuromodulation Modalities | Electrical, Magnetic, Optical | Electrical Optical, Acoustic | Thermal, Mechanical, Chemical |
| Recording/Sensing Modalities | Electrical | Electrical Impedance Tomography, Optical Imaging | Biomolecular markers |
| Interfacing Methods | Cuff Electrodes, Penetrating Electrodes (TIME/LIFE/FINE), TENS, tDCS, Spinal Paddle Arrays, DBS Electrodes, TMS Coils | Optrodes, Ultrasonic Phased Arrays, Infrared Light | Optogenetics, Two-way chemical communication |
| Attributes/Properties | Open-loop neuromodulation | Closed-loop neuromodulation (via biosensing) to optimize the stimulus | Cell-type specificity |

*The BEM Technology Roadmap tables distinguish between different maturity or confidence levels, represented by colors in there tables, for the roadmap targets:

Commercial solutions exist, and are being used  Commercial solutions are known and are being tested/optimized  Commercial solutions do not exist

- **The Evoke™ Spinal Cord Stimulation System** from Saluda Medical is an investigational device for the treatment of chronic pain that is designed to continuously measure the body's response to stimulation by incorporating sensing capability of the evoked compound activity potentials to automatically adjust stimulation levels to the patient's preferred level.
- **SetPoint Medical** has investigational device with USFDA approval for treating patients with inflammatory diseases such as Crohn's Disease and rheumatoid arthritis. It uses a proprietary implantable platform designed to interface with the cervical vagus and consists of a miniature rechargeable implantable microregulator, wireless charger and iPad prescription pad application.

## 5.8 Summary and Outlook

The state-of-the art capabilities in neural interfaces were outlined in this chapter. While most of the current neurostimulation technologies use open-loop configuration, it is expected that new closed-loop technologies will be used in the near future. **Table 5.4** shows some examples of anticipated future neural interface technologies.

# References


[1] K. Ludwig, E. Ross, N. Langhals, D. Weber, J. Luis Lujan, and D. Georgakopoulos, "The Autonomic Nervous System," 2017, pp. 12–39.

[2] J. Erlanger and H. S. Gasser, "THE ACTION POTENTIAL IN FIBERS OF SLOW CONDUCTION IN SPINAL ROOTS AND SOMATIC NERVES," *Am. J. Physiol. Content*, vol. 92, no. 1, pp. 43–82, Feb. 1930.

[3] F. A. Koopman et al., "Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis," *Proc. Natl. Acad. Sci.*, vol. 113, no. 29, pp. 8284–8289, 2016.

[4] S. L. Helmers et al., "Application of a computational model of vagus nerve stimulation," *Acta Neurol.* Scand., vol. 126, no. 5, pp. 336–343, Nov. 2012.

[5] J. B. Ranck, "Which elements are excited in electrical stimulation of mammalian central nervous system: A review," *Brain Research*, vol. 98, no. 3. Elsevier, pp. 417–440, 21-Nov-1975.

[6] O. Yizhar, L. E. Fenno, T. J. Davidson, M. Mogri, and K. Deisseroth, "Optogenetics in Neural Systems," *Neuron*, vol. 71, no. 1. Cell Press, pp. 9–34, 14-Jul-2011.

[7] E. Krook-Magnuson, C. Armstrong, M. Oijala, and I. Soltesz, "On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy.," *Nat Commun*, vol. 4, p. 1376, 2013.

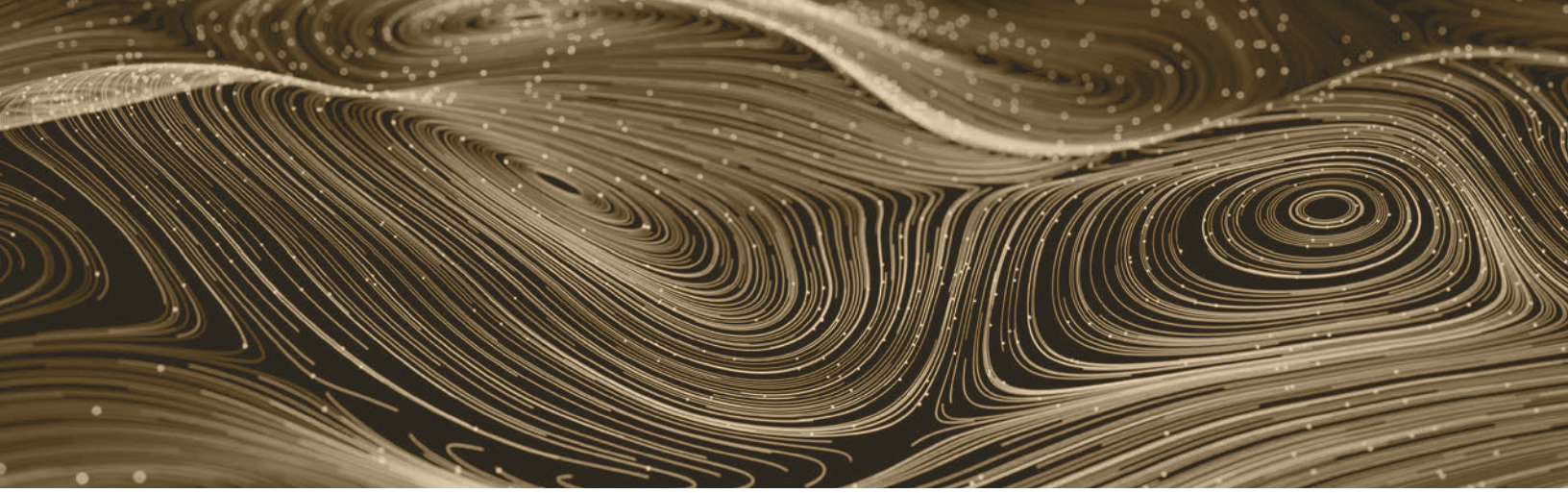
[8] C. Zussy *et al.*, "Optical activation of endogenous metabotropic glutamate receptor 4 (mGlu4) in the amygdala dynamically regulates symptoms associated with persistent inflammatory pain," *Mol. Psychiatry*, vol. 23, no. 3, pp. 489–489, Mar. 2018.

[9] J. Font et al., "Correction: Optical control of pain in vivo with a photoactive mGlu5 receptor negative allosteric modulator," *Elife*, vol. 7, 2018.

[10] E. Ben-Menachem, D. Revesz, B. J. Simon, and S. Silberstein, "Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability," *Eur. J. Neurol.*, vol. 22, no. 9, pp. 1260–1268, Sep. 2015.

[11] G. B. Mwenge, P. Rombaux, M. Dury, B. Lengelé, and D. Rodenstein, "Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study."

[12] H. M. K. van Breda, F. M. J. Martens, J. Tromp, and J. P. F. A. Heesakkers, "A New Implanted Posterior Tibial Nerve Stimulator for the Treatment of Overactive Bladder Syndrome: 3-Month Results of a Novel Therapy at a Single Center," *J. Urol.*, vol. 198, no. 1, pp. 205–210, Jul. 2017.



Chapter 6

# Biocompatible Packaging

## 6.1 Introduction

Present day bioelectronics implants are large relative to the size of the electronics module. Emerging applications for implantable electronic devices will require packaging technology that is ultra-miniature so that the implants can be placed, for example, close to the targeted neurons and still provide the capacity for thousands of independent conductors. Using traditional technologies such as implants would be unacceptably large. In this section, current packaging technologies and their scalability issues are reviewed. Finally, possible technical solutions are discussed and a roadmap for implementation is presented. For a more comprehensive overview of packaging technology, the reader is referred to [1] and [2].

## 6.2 Two Types of Packaging for Medical Implants

Implantable electronic devices require a protective barrier to ensure that neither moisture nor ions reach the electronic circuits. Protective barriers **(Figure 6.1)** are currently formed by two main methods: enclosures (primary method for medical implants) or encapsulation (used for experimental devices).

### 6.2.1 Current neural interface spatial precision

Enclosures are the traditional method used in clinical devices and involve the use of titanium or ceramic cases. The thickness of the case leads to implant with external dimensions much larger than the size of the enclosed electronics [3]. Hermetic enclosures are the current gold-standard for protecting implanted electronics. Industry standard practices include a titanium-case brazed to a ceramic-feedthrough component (see **Section 6.3**). Careful assembly of the components must consider i) matching of the coefficients of thermal expansion (since brazing is a high-temperature process), and ii) removing as much water vapor from inside the enclosure as possible using heating and vacuum processes [1]. Residual water vapor inside the enclosure can condense, which leads to liquid water on the electronics and a corrosion-related failure mode. Once assembled, enclosures can be evaluated for quality using helium leak testing (per Mil-Std 883), although for smaller enclosures such testing is of limited use **(Section 6.4)**. The two examples of currently available medical implants that utilize enclosures are shown in **Figure 6.2**.

### 6.2.2 Encapsulation

Encapsulation involves coating the electronics, typically with a polymer such as silicone or parylene to prevent water and ion ingress. Encapsulation is highly dependent on process control. For an encapsulation approach to packaging, 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 [4]. In addition, the metal encapsulation needs long-term process development effort and is equipment intensive. However, demonstrations of long-lasting implants with polymer encapsulants do exist: a retinal prosthesis prototype was implanted for 18 months

**Figure 6.1** Cross section of two types of packaging. (Top) Enclosures use a cap attached to a feedthrough platform, where the empty space inside the enclosure is a vacuum or filled with inert gas. (Bottom) Encapsulation uses a conformal coating as a barrier to moisture and ions.

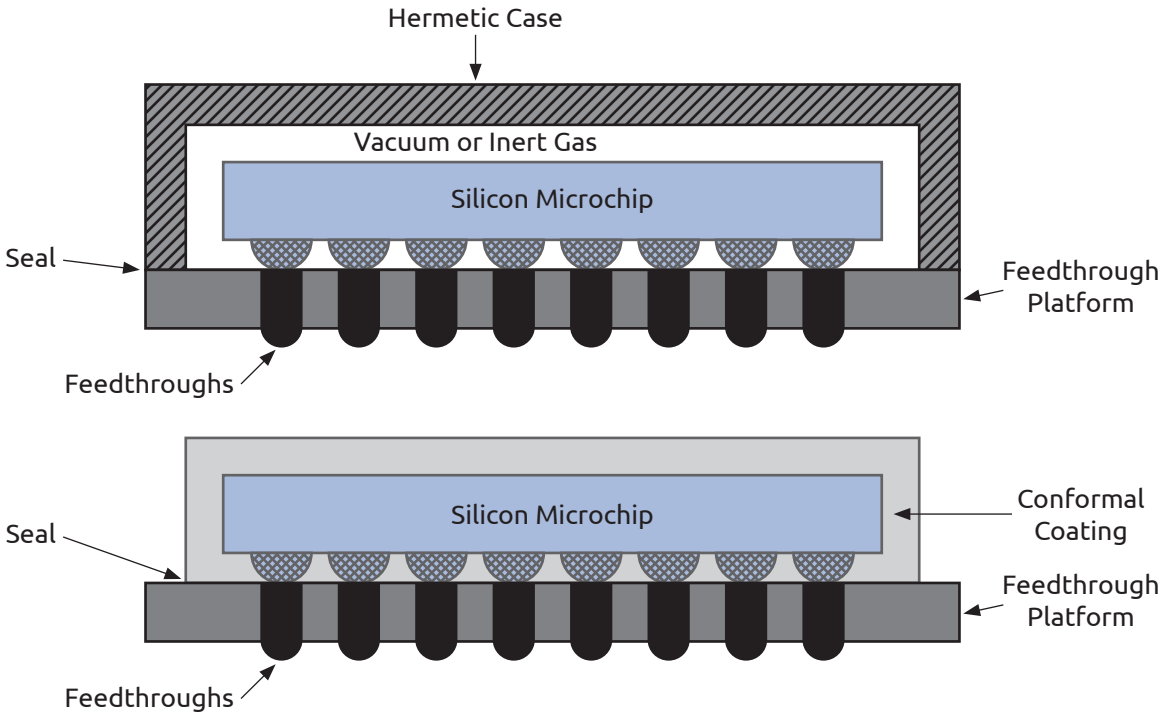



**Figure 6.2** Two examples of medical implants that use enclosures. (Left) Argus II Retinal Implant (external system not shown). Feedthroughs for the Argus II are on the other side of the silver case and are not visible in this picture. (Right) Medtronic Intellis—smallest fully-implantable spinal cord neurostimulator.


and remained functional using polymer encapsulation [5]. However, the prototype was only active several times during the 18 months, so the device was primarily passive. It is known that powered circuits degrade much faster due to the driving force of voltage. Alpha-AMS is a commercially available (in Europe under CE Mark) retinal prosthesis that uses an encapsulation approach for protection of a sub-retinal micro-photodiode array. The estimated median lifetime of this device is 3.3 years (based on clinical results) or 4.7 years (based on laboratory results) [6].

## 6.3 Feedthroughs

The interface between the packaged microsystem and the external environment (for example, with a neural interface array) traditionally occurs by means of feedthrough, which is a substrate with multiple isolated conductors penetrating the hermetic package. The feedthrough isolates individual conductors to allow independent stimulation channels. Modern DBS systems have 8-10 feedthroughs, cochlear implants have 20-32, and retinal implants 60-150. Feedthrough conductors typically use Pt, Pt/Ir, Pd, Nb, and Co/Fe/Ni alloys. 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.

Currently, visual prostheses have achieved the highest density feedthroughs. For example, the Argus II Retinal Prosthesis has 60 independent channels and its hermetic package is 1 cm in diameter. The IRIS II Retinal Prosthesis (Pixium Vision, Inc.) has 150 channels and its package is 13 mm in diameter. These devices have both received regulatory approval. While the spacing of the individual channels in the feedthrough is not spread evenly over the package, the spacing is still few hundred microns (determined by the available manufacturing processes).

**Figure 6.3** A traditional feedthrough comprised of a flange to mechanical stability, frits for insulation between the conducting

## 6.4 Testing

After packaging, hermeticity testing is needed, which is a nontrivial task. Helium leak detection is a standard test to estimate package lifetime. The helium leak rate depends on the water content inside the package, thus the moisture level can be quantified. The sources of leak can either be from the diffusion (diffusion rate is dependent on the vapor pressure) or mechanical defects (such as bad seals or pinholes). To gauge how much moisture can be tolerated, the Department of Defense's Test Method Standard for Microcircuits (Mil-StD 883 [7]) results indicate that 5000 parts-per-million (ppm) is the limit for moisture inside the case. Of course, the tolerable leak rate will depend on the desired lifetime of the device and the volume of the internal cavity. However, for many micro-implants, leak rates are sometimes beyond the detection limit, which represent a testing challenge. Thus, leaks that are tolerated by larger packages are not by smaller (< 1 $cm^3$) packages , as smaller leaks may not be detectable using the current method of mass spectrometry of slowly leaking helium [2].

Another important consideration is that the encapsulated devices cannot be tested in the same way as enclosures. Encapsulation relies on the absence of any voids between the encapsulant material and the electronics, since a void will result in water accumulation, corrosion, and eventual failure. The lack of voids means helium leak testing cannot occur. Since soak testing implants is destructive or will reduce lifetime, implants that are encapsulated depend on a well-controlled process to achieve adequate protection. This is possible, but a small percentage of devices will fail due to the inherent randomness in any manufacturing process. Currently, the inability to screen for such devices is a major limitation to the encapsulation approach. Moving forward, on-chip safety sensors might be used to monitor temperature, moisture etc. inside the package and warn of impending failure [8].

## 6.5 Other Packaging Considerations

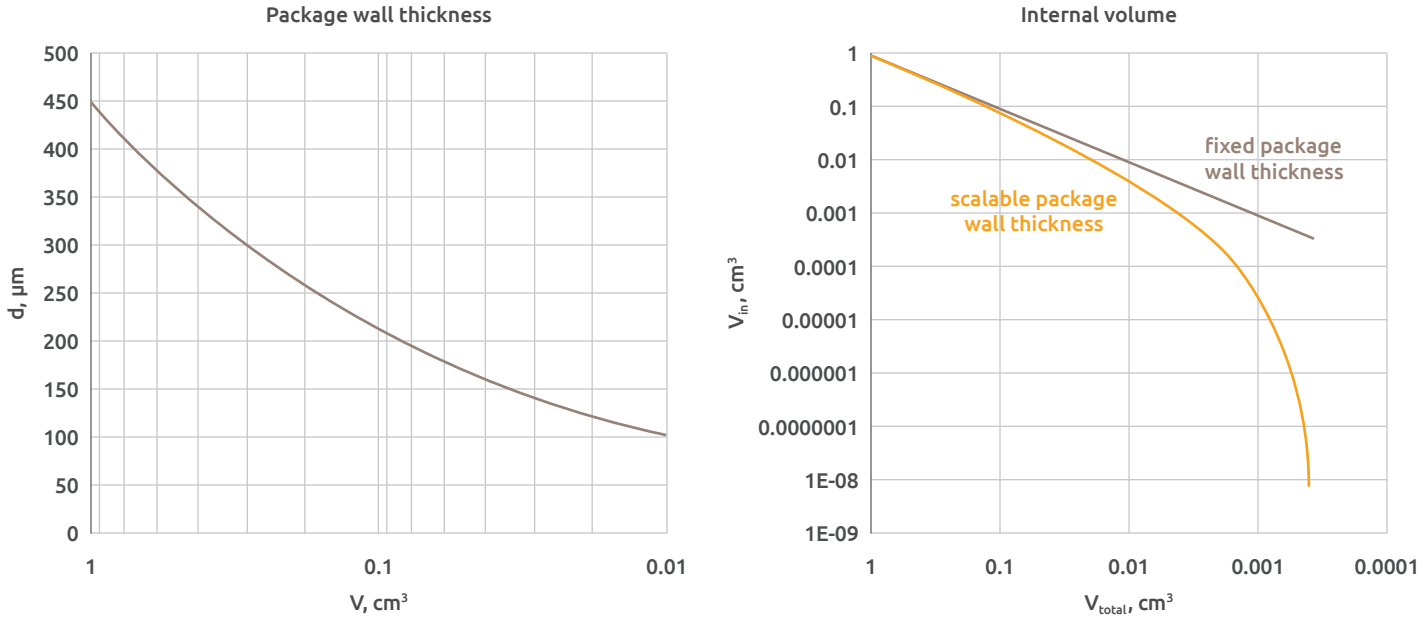
Biocompatibility reflects the nature and degree of interaction between the package and the host tissue. Biocompatibility can be defined as the ability of a package to perform with an appropriate host response in a specific application [9]. There are two elements of biocompatibility: **(i) biosafety**, (i.e., appropriate host response) and **(ii) biofunctionality** (i.e., the ability of the material to perform the specific task for which it is intended). Biocompatibility entails mechanical, chemical, thermal, etc. compatibility. In current implants, the specific tasks of the package is primarily protective. It provides a critical water and ion barrier while also mechanically shielding the electronics from impact. This task is not affected by a normal foreign body response. A secondary function of device packaging is as a current return or system ground. Since the device is large relative to the microelectrode, the presence of fibrous tissue growth does not affect this function. However, as device sizes shrink and the package and neural interface becomes co-located or even integrated, foreign body response becomes an important issue. Discussion of this topic can be found in the **Chapter 5: Neural Interfaces**.

Multiple electronic components form the electronics module, and the connection of silicon ICs, off-chip components (e.g. capacitors, inductors, crystal oscillators) is a critical area of research. Currently, printed circuit boards are still used to integrate components for many applications. Since the size of the enclosure will be determined, in part, by the size of the electronics module, miniaturization of the electronics module will enable a reduction in package size. A more detailed discussion of electronic packaging can be found in **Chapter 2**.

## 6.6 Limitations with Current Technology

Enclosures can protect electronics for decades; however, physical scaling limitations suggest the need for an alternative approach for the massively-parallel interfaces envisioned for

**Figure 6.4 (a)** Package wall thickness as a function of total volume of a BEM implant (assumes that the package volume is 20% of the total volume). **(b)** Internal vs. total volume of a BEM implant for scalable and fix-wall thickness (the fixed wall thickness is assumed to be ~450µm).




next generation bioelectronics. Current implant architectures, such as deep brain stimulators, place the enclosure in the chest and use a long, multi-wire cable to deliver stimulus current to deep-brain structure. Future bioelectronics will have more parallel channels, making a long cable impractical. It is possible to use multiple hermetic modules with smaller modules used for multiplexing, but even the multiplexing module must provide adequate feedthroughs for every independent channel. Both the size of the feedthrough and the size of the enclosure to illustrate the lack of scalability of current technology needs to be considered.

The IRIS II retinal prosthesis has 150 feedthroughs in a 13 mm diameter case. The goal of DARPA's NESD program is to demonstrate 10,000 channel implants [10, 11]. A simple calculation shows that if the feedthrough area in the IRIS occupies only ½ of the case area (on one side), a 10,000-channel feedthrough would be about 50 mm in diameter. An implant of that size would be difficult to implant on brain cortex given the convoluted nature of the brain. Thus, radically new technologies will be needed to achieve a 10,000-channel interface; however, this progression comes at the cost of increased complexity of wireless transmission, and it mandates redundant power supplies for each module.

Enclosure size is also a concern; enclosures are typically a cap or a lid that mates with the feedthrough. In the IRIS and Argus implant, the cap is a short cylinder, while DBS implant the "cap" is more like an envelope, with the feedthrough at one end to close the envelope. While thinner metal cases may maintain sufficient barrier properties, mechanical strength is needed to maintain operation in case of impact-per-device standards [12]. Thus, cap size is determined by the thickness of the wall, the cross section of the feedthrough, and the shape of the electronics module which must be covered by the cap. This may include a battery. Inductive coils can be outside the enclosure, since the wire coil does not require hermetic packaging. The trade-off in choosing wall thickness is packaging strength vs. size and available internal volume **(Figures 6.4 a and b)**. If the package wall thickness cannot be decreased (e.g. due to reliability concerns), the internal volume available for the enclosed electronics will be dramatically decreased for smaller sizes of BEM implants. Therefore, for 1 mm³-scale BEM devices soft 'protection' methods will be required even if hermeticity is compromised. Reliable packaging solutions for small implantable electronics is a critical BEM research topic.

## 6.7 Challenges and Future Packaging Needs

From the discussion, we can make the following conclusions:

- 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 using traditional techniques such as helium leak testing may not reveal defective devices
- Encapsulation approaches are the most likely path to meet channel count and size goals

## 6.8 Possible solutions to these technical issues

Encapsulation processes must be tightly controlled to yield high-quality films

The effects of failed encapsulation can be mitigated by

- On-chip sensors that detect ions and/or moisture and warn of impending failure
- Replaceable components

High-density wiring to connect output of IC to feedthrough

Flexible internal wiring, as well as flexible electronics

Active packaging

- Drug-eluting encapsulation materials to modify tissue response / reduce scaring around implant
- Electrical control of porosity, hydrophobic characteristics of encapsulation, etc.
- Polymers that change stiffness with temperature/ humidity

Packaging beyond titanium:

- hermetic-sealed ceramic/glass, or biotic insulation and packaging
- flexible uni-body design such as PDMS (as it has a Young's modulus near that of body tissue)

Minimally-invasive surgery and imaging

- For implantation
- For removal and repositioning
- Implantation of hybrid electrodes and their repositioning

Cost-effective manufacturing (e.g. the ability to 3D print the housing)

Finally, current state-of-the art and future technology projections for BEM packaging and suggested materials of choice are summarized in the **Tables 6.1 and 6.2**.

**Table 6.1** BEM packaging technology projections

| Year | 2018 | 2023 | 2028 | 2033 | 2038 |
|---|---|---|---|---|---|
| Form Factor | Separate system and leads | Separate system and leads | Integrated system and leads | Integrated system and leads | Integrated system and leads |
| Total volume, $cm^3$ | 1 | 0.5 | 0.1 | $10^{-2}$ | $10^{-3}$ |
| Ext. dimensions, cm | 1 | 0.8 | 0.5 | 0.2 | 0.1 |
| Operational lifetime | Lifetime of the patient | Lifetime of the patient | Biostable for life of patient or easily removable otherwise | | |
| Package thickness, µm | 450 | 350 | 200 | 100 | 40 |
| Number of feedthroughs | 150 | 1000 | 10,000 | 10,000 | 10,000 |
| Feedthrough density, $cm^{-2}$ | 20 | 300 | 9600 | $4.5 \cdot 10^4$ | $2 \cdot 10^5$ |
| Attributes/ properties | Transparency for telemetry, MRI conditional | Transparency for optical signals | Self-repairing barrier | | Case-less device |
| Testing | Hermeticity test using mass spectrometry of slowly leaking helium | Accelerated life-test methods | Non-destructive imaging to detect encapsulation flaws<br>On-chip sensors detecting impending failure, Replaceable implant | On-chip sensors detecting impending failure, Redundant electronics | On-chip sensors detecting impending failure, Wet electronics |

Commercial solutions exist, and are being optimized  Commercial solutions are known  Commercial solutions are not known

**Table 6.2** BEM packaging materials

| Year | 2018 | 2023 | 2028 | 2033 | 2038 |
|---|---|---|---|---|---|
| Water Barrier | Silicone, parylene, polyimide | Shape memory polymers, Silk-based, Transient/Biodegradable materials | | | Biomaterials extracted from living tissues and organs. |
| Conductor | Ti, Pt, Au, $Ir_2O_3$, TiN, NiCr, PEDOT | Polymers, metal nanowires | Carbon nanotubes Graphene | | |

■ Commercial solutions exist, and are being optimized ■ Commercial solutions are known ■ Commercial solutions are not known

# References


[1] G. Jiang and David D. Zhou. "Technology advances and challenges in hermetic packaging for implantable medical devices." *In Implantable Neural Prostheses 2*, pp. 27-61. Springer, New York, NY, 2009.

[2] A. Vanhoestenberghe and N. Donaldson, "Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices", *Journal of Neural Engineering* 10, no. 3 (2013): 031002.

[3] J. D. Weiland, F. M. Kimock, J. E. Yehoda, E. Gill, B. P. Mclntosh, P. J. Nasiatka, A. R. Tanguay, "Chip-Scale Packaging for Bioelectronic Implants", 6th Annual International IEEE EMBS Conference on Neural Engineering, San Diego, California, 6 - 8 November, 2013, 931-936

[4] X. Xie, L. Rieth, R. Caldwell, S. Negi, R. Bhandari, R. Sharma, P. Tathireddy, and F. Solzbacher. "Effect of bias voltage and temperature on lifetime of wireless neural interfaces with Al 2 O 3 and parylene bilayer encapsulation." *Biomedical microdevices* 17, no. 1 (2015): 1.

[5] R. Hornig, M. Dapper, E. L. Joliff, R. Hill, K. Ishaque, C. Posch, R. Benosman, Y. LeMer, J-A. Sahel, and S. Picaud. "Pixium vision: first clinical results and innovative developments." In Artificial Vision, pp. 99-113. Springer, Cham, 2017.

[6] K. Stingl, R. Schippert, K. U. Bartz-Schmidt, D. Besch, C. L. Cottriall, T. L. Edwards, F. Gekeler et al. "Interim results of a multicenter trial with the new electronic subretinal implant Alpha AMS in 15 patients blind from inherited retinal degenerations." Frontiers in neuroscience 11 (2017): 445.

[7] http://scipp.ucsc.edu/groups/fermi/electronics/mil-std-883.pdf

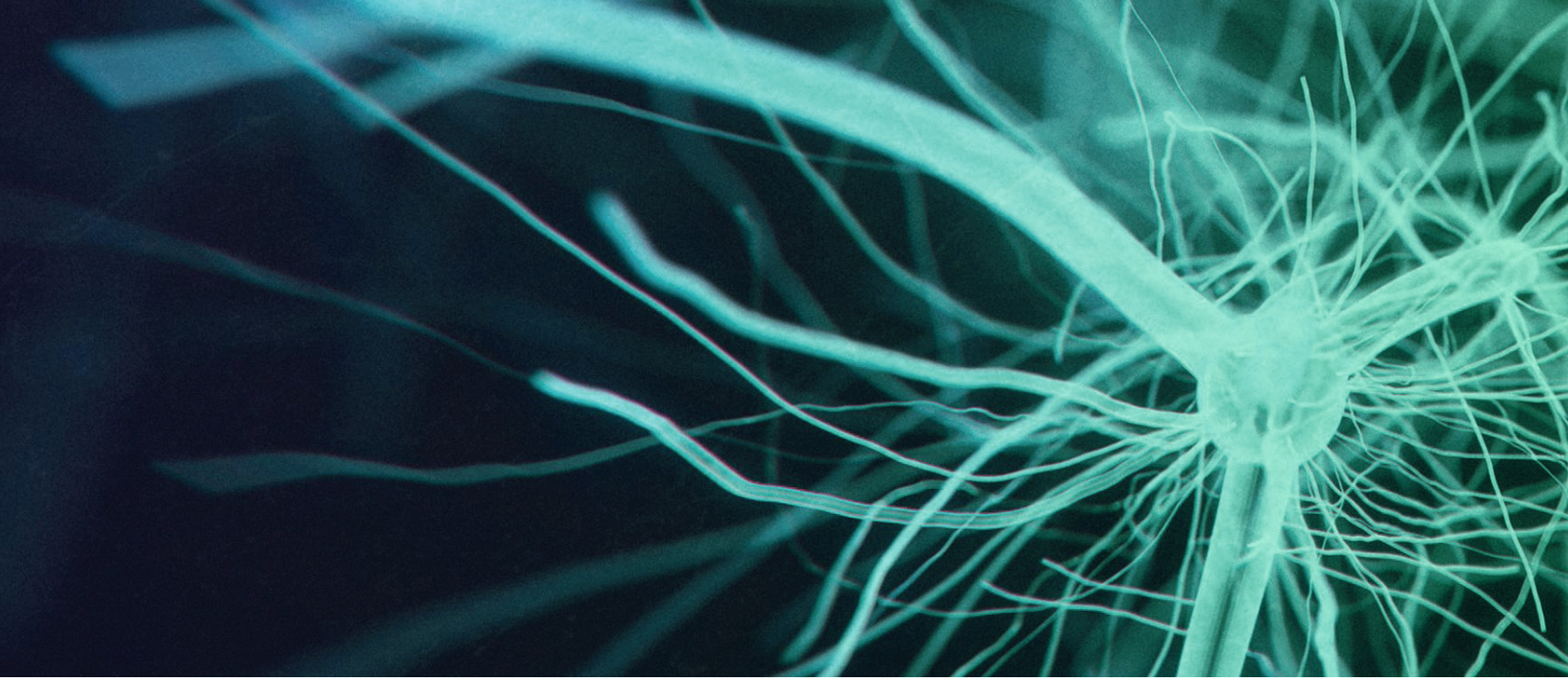
[8] X. Liu, V. Valente, Z. Zong, D. Jiang, N. Donaldson, A. Demosthenous, "An Implantable Stimulator with Safety Sensors in Standard CMOS Process for Active Blocks", IEEE Sensors J. 16 (2016) 7161-7172

[9] J. M. Morais, F. Papadimitrakopoulos, D. J. Burgess, "Biomaterials/Tissue Interactions: Possible Solutions to Overcome Foreign Body Response", AAPS J. 12 (2010) 188-196

[10] https://www.darpa.mil/program/neural-engineering-system-design, accessed July 12, 2018

[11] https://engineering.columbia.edu/news/ken-shepard-brain-computer-interface, accessed July 12, 2018

[12] EN 45502-2-3:2010. Active Implantable Medical Devices. Particular Requirements for Cochlear and Auditory Brainstem Implant Systems.



Chapter 7

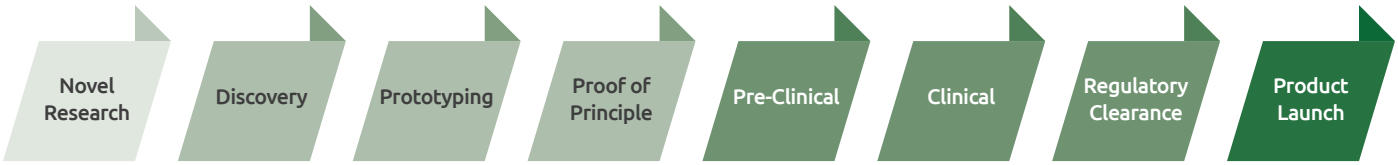
# Clinical Translation and Pharmacological Intervention

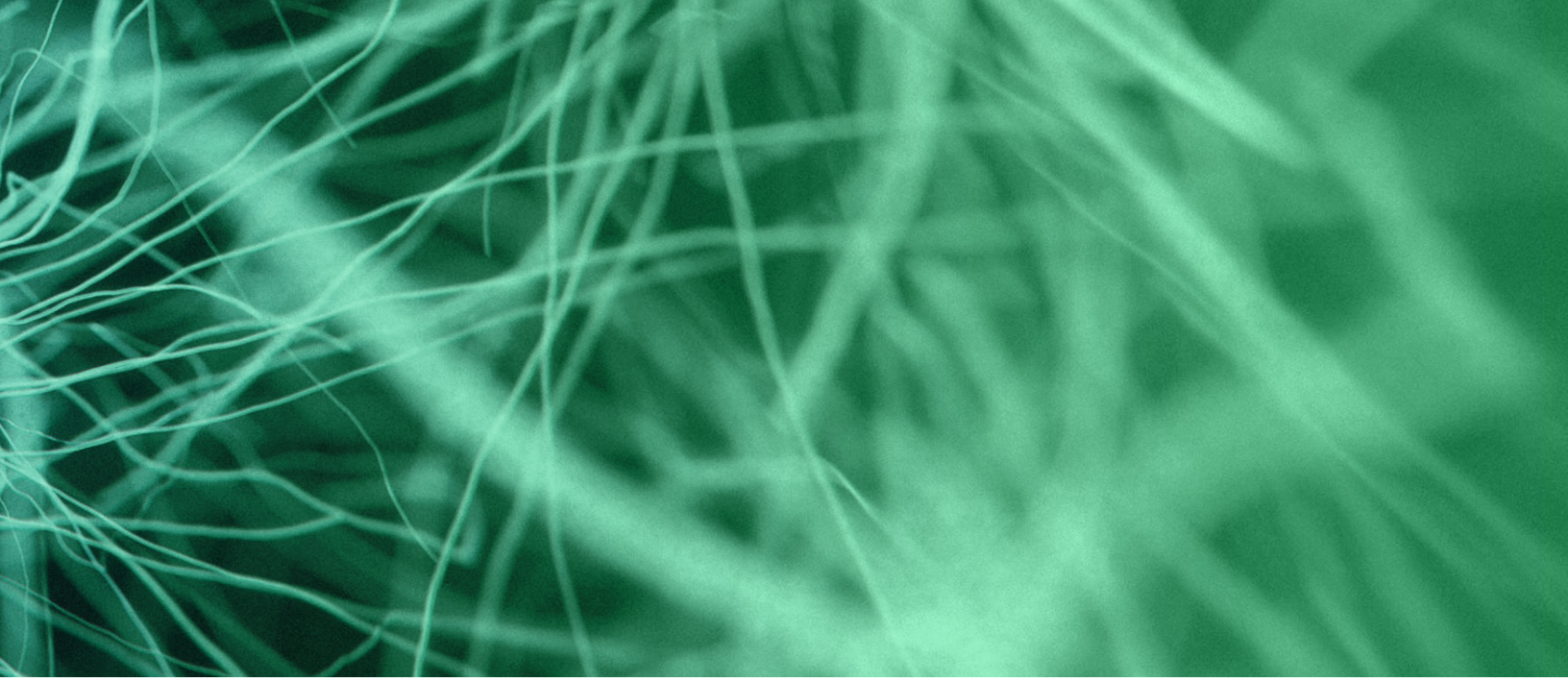
An ultimate goal of Bioelectronic Medicine (BEM) is clinical translation (advancing technologies from the laboratory through preclinical testing in animal models and into patients).

## 7.1 Introduction

The goals of clinical translation are straight-forward: to improve diagnosis, treatment, outcome, ease of use, and to reduce side effects and cost. Today, innovation in medical technology is exploding worldwide, reducing what used to be a lag from "bench to bedside" of approximately 17 years to considerably shorter time periods [1]. The medical innovation pipeline has well defined stages as shown in **Figure 7.1**. At each stage, the goal for clinical translation is to conquer "go-no-go" milestones that will pass forward or kill new technologies quickly, so as to keep pipeline throughput steady and optimize the use of resources. "Real" clinical translation starts with proof or principle testing, building a functioning prototype and then preclinical testing in animals. What ultimately will determine uptake for many worthy devices is the type of regulatory approval granted, its indications, and if insurers are willing to pay for the product/ services.

**Figure 7.1** The Medical Innovation Pipeline. Darkness of shading corresponds to the amount of clinical relevance and impact of each stage. (Figure courtesy of Victoria Berenholz, Penn Health-Tech, University of Pennsylvania.)





Bioelectronic Medicine has many potential novel applications [2], and the list is expanding as new neural pathways are discovered. **Table 7.1** lists some applications of these therapies, along with estimated time horizons for development, the major challenges they face, and their potential impact.

**Table 7.1** A sample of applications for bioelectronic devices.

| Application | Impact | Challenges | Est. Time |
|---|---|---|---|
| **Hypertension** — modulate or ablate renal or carotid plexus | 1/3 of population, ~12% Medication resistant, 1,000 die/ day in the US | Map renal nerves, ablation targets, perfect technique, reduce cost | Clinical trials are ongoing, likely ~5 years |
| **Diabetes** — modulate islet cell function | ~10% of US pop., ~30% on insulin | Map nerves, Control, interface | ~10-15 years |
| **Migraine** — neural modulation of cranial nerves/ pain | 14.7% of pop., 2% of world pop. Mx protein resistant | Mechanism, map circuits, spreading depression, targets | External devices in clinical trials, some FDA approved |
| **Autoimmune Disease** — neural modulation | 20% of US pop., varies by disease | Mechanism, more targets, validate case reports | In early trials. ~3-5 years for results |
| **Epilepsy** — detect, predict, stim to stop or prevent seizures | 1% of population worldwide | Improve targeting, algorithms, implants, platforms | VNS has been used for 20 yrs, robust pipeline |
| **Stroke** — modulate blood clotting, vessel response | 7% prevalence in US | Mechanism/ targets interfaces | ~5-10 years |
| **Asthma** — control airways via neuromodulation | 8.3% in US alone | Map nerves, interface, decoding | ~5-10 years |

Major challenges to translating bioelectronic technologies into clinical care fall into two spheres:

### A. Technical

1. Building robust, durable tissue-electrode interfaces that do not deteriorate over time
2. Miniaturizing sensors and effectors (e.g. electrical recording and stimulation circuitry, or other novel modalities for neural recording and activation)
3. Biocompatibility
4. Satisfying increasing power demands of more complex, chronically implanted devices
5. Electrode number and resolution
6. Signal bandwidth for digitization, buffering and transmission
7. On-board storage, processing
8. Two-way wireless transmission
9. Algorithms for detection, prediction and control
10. Localization, targeting, resolving anatomy to individual variability and normal variant patterns: personalization of hardware, software and interface.
11. Building devices compatible with body imaging

### B. Biological

1. Peripheral nervous system: Mapping neural anatomy—nerve and bundle location, functional composition (e.g. sensory, motor, autonomic, etc.)
2. Central nervous system: Mapping functional neural anatomy—circuits, white matter connectivity locally and at a distance, by Broadman area (cortical), subcortical (nuclei level) and subfield resolution
3. Functional circuit neuroanatomy and network physiology/ topology
4. Functional circuit anatomy by neuronal subtype (neurotransmitter, excitatory, inhibitory, interneuron, etc.)
5. Neural encoding and decoding
6. Stimulation or modulation coding
7. Understanding disease mechanisms
8. Imaging that correlates to function and higher resolution

These challenges, to a large degree, will determine the timeline for translating technologies to address specific clinical applications and domains. **Table 7.2** provides an estimate of potential time latency to specific applications in light of the above considerations, and what is known anatomically and mechanistically about some specific disorders that are, at least in part, neurologically mediated. It is important to note that the topic of the brain-computer interfaces for motor and sensory dysfunction, while being a vital part of the BEM, is not fully discussed in this roadmap.

## 7.2 Technology Considerations

Chapters 2-6 of this Roadmap explore the predicted evolution of spatial precision of BEM devices, the invasiveness of device and therapy delivery, and broader characteristics of complete devices over time. These chapters depict the important interplay between technology development and clinical implementation, which is an iterative process. Technology innovation typically gives rise to successive generations of devices that improve efficacy, usability and eventually reduce cost to allow the increase in the device uptake in the community.

At present, many standard devices consist of sensors/ electrodes for recording and stimulation that are invasively

**Table 7.2** Applications timelines for clinical translation. These are projected numbers and variable amounts of progress have been made in many of these areas. Delays in implementation relate largely to challenges in neuroscience, understanding brain and peripheral networks and enervation. Diseases currently most amenable to BEM therapy are those in which functional anatomical networks are best understood, at least to the degree where interventions are having a measurable impact.

| | Current | >5 years | >10 Years |
|---|---|---|---|
| Disease/ Condition | Movement disorders, chronic pain, epilepsy, depression, headache, cardiac dysfunction, motor paralysis | Arthritis, chronic inflammatory diseases, sleep disorders<br>Neural repair/stroke<br>Depression/OCD, sensory loss | Language, diabetes, depression, hypertension, memory loss, obesity<br>Addiction<br>Schizophrenia |

introduced to specific targets, either percutaneously or through open procedures, and connected to implantable pulse generators (IPGs) that contain sensing and stimulation hardware. Implantation may require surgical incisions, endoscopic deployment, etc., depending upon target location. Such placement is sometimes guided by functional localization, such as neural stimulation or evoked response testing, in order to functionally verify the target. Sensors, electrodes, wires, and other device components are then typically tunneled under the skin to connect to an IPG (installed in a pocket in the muscle either under the clavicle, under the arm, in the abdomen or elsewhere) where it can be accessed (by inductive coupling with programming hardware to either download data or upload commands). This hardware is gradually shrinking, as implanted devices, most importantly batteries, are becoming smaller, rechargeable, more energy efficient and sophisticated—with increasing channel number and data throughput. It is expected that over time devices will continue to become smaller, and more frequently introduced percutaneously through minimally invasive procedures [3]. Procedures will utilize and perhaps be performed in imaging suites, such as MRI, for better anatomical targeting. It is possible that some of these device components may eventually be delivered serially through novel methods, such as magnetic targeting of intravascularly infused nanoparticles and click chemistry [4], [5]. Newer technologies, such as silk and transient devices [6] may also obviate the need for removing devices after clinical applications are completed, reducing cost and eliminating the need for second invasive procedure after therapy.

## 7.3 The Translation Pipeline—One Approach to Testing

Once a device prototype is made and basic operation is confirmed, it then becomes vital to demonstrate proof of principle, safety and efficacy of the new technology or device. The order of these investigations may vary slightly by application, but typically proceeds in a predictable sequence, in each case accompanied by appropriate safety assessment and documentation:

1. **In-Vitro Testing:** Proof of principle of sensor or effector in vitro, for example cellular activation or inhibition in cell culture, tissue slide, organoid or similar construct, carefully measuring the amount of cellular injury or death to perfect parameters for in-vivo testing

2. **Initial In-Vivo Prototype—Small Animal:** Testing of a non-final, often externalized prototype in-vivo, usually in a small animal, such as a murine control or disease model, where device function can be observed, measured and biological effects measured via tissue analysis post mortem.

3. **In-Vivo, Large Animal Model:** Next is usually escalation to a more realistic human-scale version of the device, potentially externalized or implanted in a large animal model, preferably with some relation to the disease process. Examples of large animal models used for specific types of devices include:

   i. **pigs** (commonly used for cardiovascular devices)

   ii. **minipigs** (easy to work with due to small size but very comparable to humans in experiments for human lipid metabolism, vascular system, immune responses, response to therapy and microbial sensitivity)

   iii. **dogs** (long history of use for testing cardiac and neurodevices),

   iv. **sheep** (cardiovascular and peripheral central nervous system devices)

   v. **cats** (neurodevices, such as cochlear implants),

   vi. **primates** (CNS neurostimulation, particularly for realistic models of human disease for example in movement disorders/Parkinson's disease with MPTP monkeys [7]. In this phase human cadaver testing might also be done if exact modelling of human dimensions is a necessity. This type of testing is of particular importance when testing new invasive techniques for inserting and removing devices.

   Data from successful studies 1 through 3 are used as supportive evidence for submission to obtain an Investigational Device Exemption (IDE) submission to the FDA in the United States (slightly different when pursuing a CE Mark in Europe). These data, indicating safety and the potential for efficacy, must also be accompanied by stringent safety data from ISO testing (see **Section 7.3.3** Preclinical Testing, ISO and European Guidelines), when submitting an IDE. IDE submission may be held either by the company making the device and sponsoring the clinical trial, or in the case of a university, it may be held by the academic institution and investigator conducting the trial, provided they do not have a conflict of interest precluding this.

4. **Limited Human Pilot Testing—Intraoperative (requires IDE):** Limited human testing is next, usually in a fashion that limits exposure and risk. Initial human experiments may be conducted under very controlled circumstances,

such as in the operating room for a few minutes, often in tissue that is marked for resection. Such studies provide very low risk and at the same time pathological verification of safety. Following such testing, investigators will often next opt for limited bedside testing in hospital inpatients where only sensors/effectors are implanted but not full devices. An example of such trajectory is the testing of NeuroPace's Responsive Stimulation System (RNS) that was tested in externalized form in patients already being monitored invasively with intracranial electrodes during evaluation for epilepsy surgery [8] In this example, patients were connected to an externalized prototype device that performed responsive brain stimulation after normal patient evaluation was completed, followed by the system removal during the electrode de-plantation at the end of the monitoring period. Adding on the existing procedures provides an easy way to recruit patients and reduce cost in a well-controlled, safe setting.

5. **Human Safety Pilot (requires IDE):** This phase of testing usually follows a meeting with the FDA in which, depending upon the "class" (I-III) of the invasive device, permission is usually granted for a small human pilot safety study, often on the order of 5-10 patients. Such trials are not powered to prove efficacy of the device, though they provide supportive data. The main purpose of these studies is to provide data that the proposed device is safe and well tolerated, paving the way, if successfully completed, for a pivotal human clinical trial, powered to prove efficacy. More involved safety analysis is included in this study. If this study is well conducted, with positive results and limited adverse events, it may be sufficient to support an application for approval for the device from the FDA via the Pre-Market Application (PMA) or its equivalent, the 510k application process. It is important that this study be carefully designed to support approval for the indication for which the device is intended, as FDA approval is indication specific. Once a device is approved, it may sometimes be prescribed by clinicians for off-label indications where the labeled indication is the one supported by the pivotal trial, but not marketed for these by the manufacturer. It is important to note that implantation location is often a strict part of indications for which a device may be marketed as "FDA approved," so that implantation of a brain stimulation in the subthalamic nucleus for treating Parkinson's disease does not provide FDA approval for implantation of the same exact device in the anterior thalamic nucleus a few centimeters away for treatment of epilepsy. This same restriction of indication and approval will likely also be extrapolated to applications in the peripheral nervous system, though the authors want to be clear that the final decision for such issues is the purview of the FDA and other appropriate regulatory bodies in such cases.

6. **Reimbursement:** This step is the critical final hurdlein device translation, and it depends upon a number of factors, including a demonstration of equivalence or hopefully superiority to existing therapy, preferably at reduced cost or increased value.

### 7.3.1 Computational Models

There is a strong history of using computational models to determine parameters for neural recording and stimulation, such as in neurostimulation for Parkinson's Disease [7]. These models are typically used to guide pilot and early phase clinical trials, particularly when working out methods. They can be applied later, after device approval, and throughout the translational testing pipeline to help improve safety, efficacy and tolerability. In several cases, commercial software for this purpose has become part of device systems that are sold to health industry. Models for charging and reimbursing for these services, particularly if they are to be used on an ongoing basis, are yet to be developed in many countries.

### 7.3.2 Biomarkers

Safety, efficacy and tolerability studies, and their outcome, are highly dependent upon the biomarkers chosen as endpoints. It is of vital importance that these are as objective as possible, easily quantifiable, obtainable with sufficient fidelity, in sufficient quantity and at frequent enough intervals while being minimally invasive. Biomarkers must be reproducible and preferably with a high signal-to-noise ratio, meaning that they are stable over time and with repeated measurements.

Examples of some frequently used biomarkers are listed below:

1. **Physiological**—blood pressure, heart rate, urine output, temperature, etc.
2. **Electrophysiology**—EEG, Evoked Potentials, compound motor action potentials (CMAPs), EKG, EMG measure, nerve conduction amplitude and latency, TMS-probed cortical excitability
3. **Serological**—electrolytes, glucose, blood counts, proteins or reactive substances measured in blood or from body fluids, exosomes, gene or transcription products, etc.

4. **Behavioral, clinical/ other** — quantitative (e.g. clinical rating scales for movement, pain and mood, though the last two are notoriously subjective, tremor, walking speed, range of motion)
5. **Imaging** — (MRI, fMRI, x-ray, CT scan, objective video of clinical events or movement
6. **PET scans** — either a global measure or focusing on single organs, such as brain
7. **Micro-dialysis** for sampling of neurotransmitters and other substances in near real time.

Safety biomarkers also fall into similar categories, but include more subjective reporting or variables such as pain, discomfort, measures of tissue injury, infection, and recording serious adverse events etc.

Biomarkers or measures of efficacy may also fall within similar categories as those listed above, though they are more often measures of function and capability, such as the ability to walk, elimination of pathological events like arrhythmias or seizures, independence in specific activities, such as activities of daily living, etc. Correlation of therapeutic intervention with one or more measurable quantities is the ideal approach to assessing new devices and technologies.

*Important note: A well thought plan for measuring and monitoring a range of biomarkers in each category, efficient data handling, sharing, analysis and archiving/ preserving these measurements and analyses for later review is vital.* ***Investigators should note that all records kept throughout the development and translation pathway are potentially relevant to regulator (e.g. FDA) review and submission both at the IDE phase and later in the approval process. Meticulous record-keeping and data organization are absolutely key to this process, as are adhering strictly to well-defined protocols published by these agencies.***

### 7.3.3 Preclinical Testing, ISO and European Guidelines

There are well defined safety and biocompatibility testing guidelines for medical devices published by the US Food and Drug Administration (FDA). There are comparable guidelines for the European Union and other countries, some of which draw on similar resources. These guidelines provide an important gateway on assessing risk of device implantation and operation, in-vitro, in-vivo toxicity, degradation of the device and its constituent materials, and different mechanisms for injury [9]–[11].

### 7.3.4 Modeling a Clinical System

When designing devices for clinical translation, it is important to understand the basic classification of devices, their approval process and how requirements for device approval vary depending upon their risk profiles, invasiveness and whether or not they are life sustaining. It is also important to note that devices, in the eyes of regulatory authorities, consist not only of hardware, but also the entire system for their delivery, operation, monitoring, recharging and removal. Software and systems for recording, transmitting, viewing, annotating and analyzing data for clinical applications are also considered part of medical devices as well. Below is an example of components that must be tested, certified and approved for medical device systems:

- Implant
- Electrodes/ sensor
- Hardware for processing, power, data recording, transmission, stimulation, etc.
- Software, both within the implantable and outside
- Patient facing components/ clinical system: device readers, software displays etc.
- Software, hardware and systems for tracking devices, performance, reporting, compliance, programming, security and privacy
- Systems for device insertion and removal
- Battery, charging, replacement indicators, systems for testing, impedance testing
- Systems for device failure monitoring, auto-safety modes, shut down and alert/ event reporting, forensics

### 7.3.5 Device Classes and the FDA

In the United States the FDA has a wide array of presentations and tools that enable innovators and industry to determine if their product is considered a medical device and in what class it falls. An excellent introduction to these concepts can be found in an FDA slide presentation by William Sutton, Deputy Director Division of Industry and Consumer Education Office of Communication and Education Center for Devices and Radiological Health U.S. Food and Drug Administration [12].

As of 2015, there were 1700 generic groups of devices listed within 16 separate medical specialties, as labeled by the FDA. Devices roughly fall into 3 classes:

**Class I:** Low risk, e.g. a tongue depressor, Band-Aid or sun glasses. For these devices "general controls," such

as registration, listing, proper labeling, etc. are deemed sufficient to guarantee safety to the public.

**Class II:** Moderate risk, e.g. syringe, surgical mask, powered wheelchair. For these devices, general controls are not deemed sufficient to guarantee safe use. Special controls are required such as special labeling, mandatory performance standards, and special guidelines for use. These products require considerable testing and documentation to support these controls.

**Class III:** High risk, e.g. cardiac pacemakers, robotic surgery devices, implantable neurostimulators, heart valves. These devices are life sustaining and general and special controls are not deemed sufficient to guarantee safety and efficacy. These devices must go through the PMA, or its equivalent, for example 510k, if there are already predicate devices that utilize the relevant technology, components and materials that are approved and on the market.

There are considerable nuances to determining the classification of a particular device and requirements for approval. For this reason, in the United States, the FDA provides a rich set of online tools for determining this, including an extensive database of devices already approved that can be searched to inform new applicants [13].

## 7.4 Examples of Strategies for Device Approval: Practical Approaches:

- **Pursue an Indication to Satisfy an Acute Need First:** Successful approaches for getting new medical devices to market follow a number of patterns. Some, like cardiac defibrillators, focus on special populations, such as patients with end-stage ischemic disease, specific syndromes or hereditary disorders with a high risk of death and disability. Focusing on populations in direct need of new therapies (also called "compassionate use") as first indications can pave the way to expedited proof of principle testing, review, and approval. After the device is approved for this indication, it then becomes more straightforward to test and adapt this platform for secondary indications that may involve larger markets with less acute need, such as those for whom risk of sudden death is much lower, who might also require pacing or in whom risk of toxicity from medications is much greater than risk of device implantation.
- **Pursue a Platform Technology:** In this approach a device platform, consisting of an implantable, support software, hardware, delivery system, tracking and other required components are constructed that could be turned toward a variety of applications and indications. A non-life sustaining indication might be pursued first in a PMA application, and, once approved, the platform is applied serially or in parallel to a variety of other indications that can be pursued through the 510k or similar path that leverages experience, safety and performance data from the platform in the initial trial. An example of such an approach was the development of straight-forward, open loop spinal cord stimulators developed to treat chronic pain that, once approved, were applied to many other stimulation applications, such as DBS for movement disorders, OCD, Dystonia, Epilepsy etc., focusing on different indications and targets.
- **One-Off Devices and Applications:** This is a common strategy for smaller start-ups or innovators who are focused on single applications. Possible directions for such efforts might include the sale of the technology to a larger company that could build it into a platform or an initial public offering that may make a commercial effort initially focused on a single clinical application. This pathway certainly allows for building a platform, however the initial deployment, application and market would need to be of sufficient size to sustain a new commercial effort or be sufficiently novel to be attractive to an established industry partner to enable acquisition and development.

## 7.5 The Future of Clinical Translation

Devices for Bioelectronic Medicine are moving forward rapidly, particularly if one includes existing applications in the central nervous system in this category. As the field evolves, innovation in hardware, software, computing and medical informatics will drive different models and applications that will likely change day to day care. Some of these changes may include:

- Incorporating informatics, learning and personalization of device technologies, utilizing not only individual anatomy and physiology, but likely genetics, Electronic Medical Record (EMR) information and tracking performance over time.
- Stratifying patients by their individual characteristics and historical responsiveness to various treatment modalities to get individual patients to optimal therapy faster, while identifying patient characteristics that make device use ill advised. This strategy will be vital, not only to optimizing utilization of new BEM devices, but also to dramatically accelerating and decreasing the cost of clinical trials.
- Understanding and modelling human diversity in target populations and making devices available to patient groups

that might be good candidates for therapy but who are currently excluded either socioeconomically or through decreased access to care due to geography or for other reasons. Taking on such issues is a vital part of being socially responsible when developing new healthcare technologies.

- The need for feedback of information on cost, user friendliness, outcome, quality of life and therapy performance in order to assess the role of devices in total value care. These models dictate risk sharing for device cost and maintenance between patients, caregivers, health systems and insurers so that technology use is based upon strong indication data.
- The need for HIPAA compliant, likely cloud-based systems and Software-as-a-Service models to inform and guide care. At present, there are scant billing codes available for such services, but there are precedents in home monitoring devices and implantable cardiac arrhythmia monitors that allow reimbursement for devices that may reduce hospitalizations and increase overall utilization of healthcare resources. Such services will likely interface directly with the EMR and include an infrastructure for data that includes clinical outcomes, imaging, time series, other modalities and analytics to govern the application and utilization of technologies.

## 7.6 Summary

One of Bioelectronic Medicine's primary goals is clinical translation — taking cutting edge science and transporting it to treat human disease and improve quality of life. This chapter described elements of the translational pathway leading from prototype development to pivotal clinical trials. These approaches are well established for CNS devices, of which there are already a considerable number on the market. It is assumed that the pathway to clinical translation for peripheral devices will approximately be the same. However, there are fewer predicate devices on which to base submissions for approval and from which predictions of possible pitfalls can be made to prevent potential pitfalls in guiding the device development. This chapter provided a brief overview of important parts of this process, potential challenges and an estimated timeline for the technological evolution of specific BEM applications. Some translations are already underway, such as Vagus Nerve Stimulation for epilepsy and stimulation of specific brain pathways. Other devices, such as those that require large amounts of technological innovation or new biological knowledge, seem much farther away. Examples include developing nerve-computer interfaces and miniaturized implants capable of high-resolution recording, processing, and stimulation through large numbers of channels. These devices may be removed from translation for 5-10 years or more, while their safety, materials, electronics and power challenges are being addressed, among other things. Finally, a wide array of disparate technologies that demonstrate current state-of-the art were mentioned and promising areas for early proof-of-principle translation are discussed.

## References


[1] Z. S. Morris, S. Wooding, and J. Grant, "The answer is 17 years, what is the question: understanding time lags in translational research," *J. R. Soc. Med.*, vol. 104, no. 12, pp. 510–520, Dec. 2011.

[2] E. Waltz, "A spark at the periphery," *Nat. Biotechnol.*, vol. 34, p. 904, Sep. 2016.

[3] T. G. Schuhmann, J. Yao, G. Hong, T.-M. Fu, and C. M. Lieber, "Syringe-Injectable Electronics with a Plug-and-Play Input/Output Interface," *Nano Lett.*, vol. 17, no. 9, pp. 5836–5842, Sep. 2017.

[4] B. Litt, "Targeted Therapy with Nanodevices - Brain Research Foundation," 2013. [Online]. Available: https://www.thebrf.org/scientific-innovations-award/2013-scientific-innovations-award/targeted-therapy-nanodevices/. [Accessed: 16-Aug-2018].

[5] "The Quarterly," *RESEARCH DISCOVERIES IN THE NEWS*, vol. 5, 2013.

[6] S.-W. Hwang et al., "Materials and Fabrication Processes for Transient and Bioresorbable High-Performance Electronics," *Adv. Funct. Mater.*, vol. 23, no. 33, pp. 4087–4093, Apr. 2013.

[7] H. Bergman, T. Wichmann, B. Karmon, and M. R. DeLong, "The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism," *J. Neurophysiol.*, vol. 72, no. 2, pp. 507–520, Aug. 1994.

[8] E. H. Kossoff et al., "Effect of an External Responsive Neurostimulator on Seizures and Electrographic Discharges during Subdural Electrode Monitoring," *Epilepsia*, vol. 45, no. 12, pp. 1560–1567, Nov. 2004.

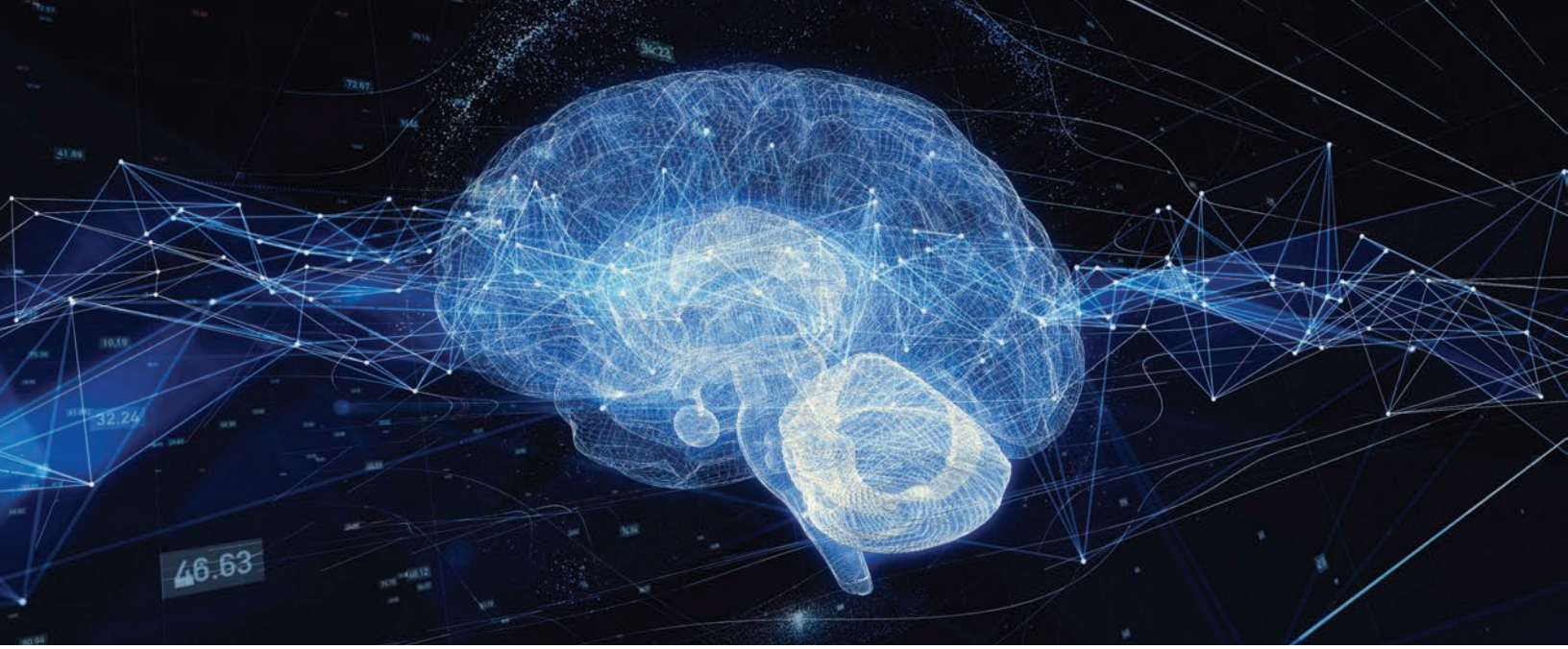
[9] C. for D. and R. Health, "Investigational Device Exemption (IDE) - IDE Application." [Online]. Available: https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046706.htm#reqele. [Accessed: 16-Aug-2018].

[10] E. Underwood, "Cadaver study challenges brain stimulation methods," *Science (80-. ).*, vol. 352, no. 6284, p. 397 LP-397, Apr. 2016.

[11] "Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process," 2016.

[12] S. Spring and W. M. Sutton, "Classification Overview," 2015. [Online]. Available: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466473.pdf. [Accessed: 16-Aug-2018].

[13] C. A. Bowsher, "Medical devices," *Society*, 1991. [Online]. Available: https://www.fda.gov/MedicalDevices/default.htm. [Accessed: 16-Aug-2018].



Chapter 8

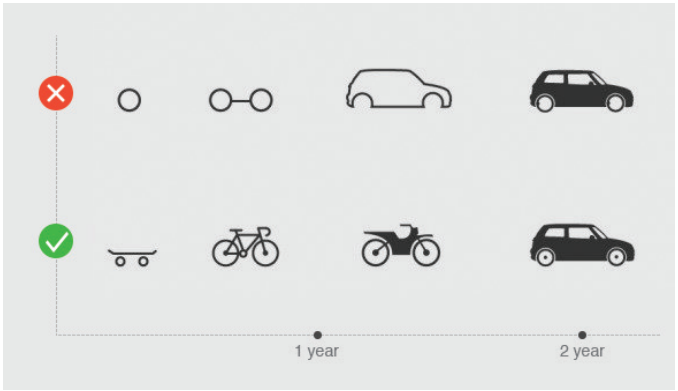
# Minimum Viable Products

## 8.1 Introduction

A minimum viable product (MVP) can be defined as a development procedure where for any commercially viable idea, a minimum requirement is that the cost of the initial investment (intellectual and/or monetary) coincides with the quantifiable return that allows for second round of developments, thus creating a product.

This concept of Minimum Viable Products is illustrated in the figure below:

**Figure 8.1** Illustration of the concept Minimum Viable Products (MVP). What MVPs can we define for BEM?




As illustrated in the example above, we believe such earlier version of BEM devices will find even greater clinical utility, and thus viability, when indicated in combination with pharmacological therapy.

Therefore, this chapter focuses on addressing the following questions:

- Which therapeutic indications could benefit from the combination of a BEM device (for the therapeutic modulation of the nerve system) and drug treatment (for intervention in the systems biology)? These are the scenarios or "use cases" where BEM + CAR-T is one example.
- What are the minimum set of *sufficient* features of the BEM device that are required to treat the indication in this scenario?
- Answers to these questions will be summarized as "Target Product Profiles" (TPPs) – blueprints for such BEM devices identifying its required (minimal and sufficient) feature set as well as its clinical utility.
- Moreover, such TPPs can be used as a strategic planning tool for the further technical development and clinical development of the BEM device. These TPPs will be shared in the public domain in an attempt to drive further R&D activity in those devices.

In the Bioelectronics Medicine Roadmap, MVP refers to the concept of developing BEM products with *sufficient* features for clinical utility in such scenarios as illustrated here, such that the investment and feedback on those early products advance the overall BEM feature set.

Bioelectronic Medicine holds tremendous promise as a therapeutic intervention in and of itself. Beyond mono-therapeutic applications of BEM (i.e. beyond exploring clinical opportunities for the use of BEM technologies as a single or primary therapeutic intervention), there may also be great clinical value and business opportunity in combining BEM with pharmacological intervention (i.e. to treat a single indication with a combination of BEM) for therapeutic modulation of the nerve system and drug treatment (for intervention in the systems biology).

One example might be a pharmacological intervention that uses CAR-T Cell therapies to treat a variety of cancers [1]. CAR-T therapies hold great promise in the treatment of a variety of cancers and may in some cases even lead to complete remission in patients that have no further treatment options. At the same time, one of the greatest risks in the delivery of CAR-T treatment is that it may trigger an exaggerated response of the immune system—causing serious adverse reactions [2]. This immune system response could potentially be modulated by a therapeutic intervention with a BEM device.

The use of a BEM device in such scenarios has two important implications:

- The design requirements for this scenario, i.e. the requirements for a BEM device to be used in a short-term episode for the treatment of hospitalized patients who likely has no further treatment options, are probably less stringent and less-complex to engineer compared to, for example, a wearable or implanted BEM device for the continuous management of a chronic condition in the patient's daily life.
- If a BEM device in this scenario were feasible, it could benefit from the tremendous attention and resources invested in the development of novel CAR-T therapies. These resources would themselves drive the evolution of BEM devices to a next generation of BEM devices with superior designs.

Opportunities for the application of BEM devices in combination with pharmacotherapy include:

- Spinal cord stimulation for chronic pain
- Deep brain stimulation for movement disorders
- Vagus nerve stimulation for epilepsy and depression
- Repetitive transcranial magnetic stimulation for major depression
- Sacral nerve stimulation for urinary incontinence
- Hypoglossal nerve stimulation for obstructive sleep apnea

## 8.2 Scope

The scope of this chapter can be categorized in three sections: i) identifying applications outside clinical translations, ii) utilizing modulation of nerve therapy in combination with pharmacological therapy and iii) collaborating with regulatory agencies and experts in fast-tracking the development of viable products.

I. **Scope of scenarios / use cases.** **Chapter 7** on Clinical Translation focuses on translating advances in BEM technology to the clinic. This chapter seeks to further advance development in BEM technology by identifying supplemental use cases of combination therapies, where BEM technologies are co-prescribed with pharmacological treatment. We expect that for set combination therapies, we can identify minimum viable BEM products with a subset of features that would be required for a fully self-sufficient stand-alone BEM therapy.

II. **Modulation vs sensing of nerve activity.** This chapter focuses on the combination of BEM for the *modulation* of nerve therapy with pharmacological therapy. Other "drug device" combinations can be envisaged that only *sense* nerve activity; e.g. in the example of CAR-T treatment—one could envisage a closed-loop therapy where the drug therapy is effectively titrated based on measured nerve activity. Although such approaches may have great clinical utility (and require fewer BEM features), this chapter focuses on opportunities that utilize modulation, as modulation is a core component of the BEM systems described in this roadmap.

III. **Regulatory perspectives.** Based on the interest and proactive support that many regulatory agencies have been extending towards the development of therapeutic medical devices, we are hopeful to find accelerated paths to clinic through the identification of minimum viable

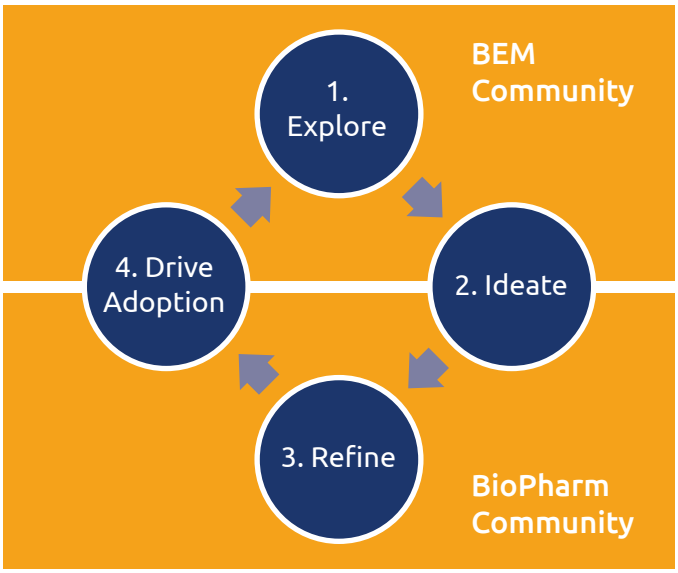
BEM products. Additionally, the the activities described in this chapter may typically predate the involvement of such regulatory authorities. As such, we count on the participating BEM community and biopharmaceutical community to inject regulatory expertise in the activities of this chapter, though we also welcome direct involvement of regulatory agencies should they have the interest and bandwidth to participate.

## 8.3 Goals and Approaches

The goal of this chapter is to outline an approach for developing TPPs for minimum viable BEM devices. This approach includes fostering active dialogue and identifying common research interests between BEM and biopharmaceutical R&D communities.

We believe such common interests to exist when unmet medical need can be addressed by treating a single indication with a combination of BEM (for therapeutic modulation of the nerve system) and drug treatment (for intervention in the systems biology).

**Figure 8.2** Proposed approach for the development of TTPs for Minimum Viable BEM Products




The proposed approach seeks to foster active dialogue and collaboration between BEM and Biopharmaceutical R&D communities by undertaking the following activities:

1. **Explore:** Explore the features of BEM devices for the "present timeframe"—i.e. features of BEM devices that can be made to function reliably, under investigational device exemption, within the next 3-5 years. Explore what biophysical responses can be effectively modulated with such devices.

2. **Ideate:** Organize facilitated, multidisciplinary, facilitated workshops to identify for which indications these features would suffice as a clinically useful and therefore viable BEM product—in combination with a drug therapy. Define high-level outlines of a corresponding Target Product Profile.

3. **Refine:** Refine the high-level TPPs from the ideation workshop with relevant subject matter experts, detailing the unifying definitions for the technical development, clinical development, and commercialization potential of such interventions. This refinement phase may typically entail small and focused research studies to validate and refine key concepts identified in the Ideation step.

4. **Drive Adoption:** Promote the (refined) TPPs in the public domain. Collect feedback from the public domain to feed in to the next Exploration cycle. Drive and track the adoption of TPPs by third parties (BEM companies, Biopharmaceutical companies, consortia), as the ultimate success measure will be the number of TPPs that are ultimately used for bringing novel combination therapies into the clinic. We propose results of the annual workshops are published in peer-review literature and that reference materials are made available through the BEM public forums (website and other).

## References

[1] NIH National Cancer Institute. (2017, December 14). *CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers*. Retrieved from NIH National Cancer Institute: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

[2] Bonifant, C., Jackson, H., Brentjens, R., & Curran, K. (2016, April 20). Toxicity and management in CAR T-cell therapy. *Mol Ther Oncolytics*. doi:10.1038/mto.2016.11.

Chapter 9

# Workforce Development

One of the strategic objectives of the BEM Technology Roadmap is to foster integration of research and workforce development to stimulate and create a new industry. **Semiconductor Research Corporation (SRC)**, a recipient of the National Medal of Technology, is a non-profit consortium of firms in semiconductor and related industries. As the premier technology research consortium for more thirty years, SRC sponsors pre-competitive university research on behalf of its members. Having developed efficient tools and processes, SRC makes a critical contribution to the R&D activities. Since its inception, SRC has invested over $2 billion in cutting-edge, pre-competitive university research, supporting over 10,000 students at more than 250 universities. Many of today's semiconductor industry leaders are former SRC supported students. Because its industry members are actively engaged in shaping the research program, providing oversight of and extracting value from SRC-funded research, SRC represents a particularly effective vehicle for technology transfer, commercialization, and workforce development.

# Acknowledgments


## BEM Roadmap Editorial Team

Renée St. Amant (Arm), Victor Zhirnov (SRC), Leslie Faiers (SRC), Ken Hansen (SRC), Daniel (Rašić) Rasic (SRC).

## Bioelectronic Medicine Roadmap Committee

Jamu Alford (Kernel), Rizwan Bashirullah[3,5] (Galvani Bioelectronics), Gary Carpenter[1] (Arm), Frederik Ceyssen (KU Leuven), Bryan Clark[8] (Boston Scientific), Juan Cueva[6] (Applied Materials), Veerle De Colvenaer (DSP Valley), Ronald Dekker (Philips Research Labs), Timothy Denison[3,7] (Medtronic), Farzin Guilak[2], (Intel), Ken Hansen[4,8] (SRC), Qinghuang Lin[1,5,6] (IBM), Brian Litt[3,7] (Univ. of Pennsylvania), Goran Marnfeldt (Boston Scientific), Heather Orser[1,4] (Medtronic), Robrecht Raedt[5,7] (Univ. Gent), Daniel (Rašić) Rasic (SRC), Juan Rey[4] (Mentor Graphics/Siemens), Anthony Samir[7] (Harvard Univ.), Wouter Serdijn (Delft Univ.), Ajit Sharma[3] (Texas Instruments), Patrick Smith[1,3,8] (ON Semi), Renée St. Amant[3] (Arm), Michael Stewart[6] (Applied Materials), Johanna Swan[6] (Intel), Nitish Thakor[2] (NUS), Dieter Therssen (DSP Valley), Joris Van Dam[8] (Novartis), Carl Van Himbeeck (Cochlear), Annelies Vandamme (IMEC), Kristl Vonck[5,7] (Univ. Gent), David Wallach (SRC), James Weiland[5] (Univ. of Michigan), Andrew Weitz[5] (NIH), Michael Wolfson[4,5] (NIH), Victor Zhirnov[2,5] (SRC).

## Technical Working Groups (TWG)

| | |
|---|---|
| [1]TWG#1 on BEM Roadmap Overview | (Chair – Heather Orser / Medtronic) |
| [2]TWG#2 on Platform Functionality | (Chair – Nitish Thakor / National University of Singapore) |
| [3]TWG#3 on Instrumentation Capabilities | (Chair – Ajit Sharma / Texas Instruments) |
| [4]TWG#4 on Modeling and Simulation: | (Chair – Ken Hansen / SRC) |
| [5]TWG#5 on Neural Interfaces | (Chair – Rizwan Bashirullah / Galvani Bioelectrinics) |
| [6]TWG#6 on Biocompatible Packaging | (Chair – James Weiland / University of Michigan) |
| [7]TWG#7 on Clinical Translation | (Chair – Brian Litt / University of Pennsylvania) |
| [8]TWG#8 on Minimum Viable Product: | (Chair – Joris VanDam / Novartis) |

Semiconductor
Research
Corporation

4819 Emperor Blvd
Suite 300
Durham, NC 27703

919.941.9400
www.src.org

100 Bureau Drive
Gaithersburg, MD 20899

301.975.2000
www.nist.gov