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Brain-Computer Interface Technologies

Accelerating Neuro-Technology for Human Benefit

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To our patients, who give us so much
motivation to continue.
To all my colleagues at the Wyss Center for
Bio and Neuroengineering and to all the
people I worked with in the past 30 years in
the field of active implantable devices.
Geneva, June 3, 2019

Preface

If we were able to sneak along our spinal cord and nerves, or to slip through by the interface of our ears or eyes, we would enter in the limitless cosmos of the billions of neurons living in our body which are making us as we are. The ancients were thinking that our heart was the center of our emotions. It is not true. The heart is the machine our body needs to preserve life, but what characterizes human beings, personal features, sensations, emotions, and feelings resides in our nervous system where, in a majestic dynamic ballet, interconnections change, neurons die and appear, and areas damaged by a traumatism receive help from other sections of the brain. The way our synapses interleave is in a continuous evolution, and we ignore the rules governing these changes.

For a long time, we could not do much more than "listen" to the brain by collecting tiny electrical signals at the surface of the scalp using the well-known electroencephalograms (EEG). These receivers, kept distant from the brain by the skin, scalp, skull, and dura-mater, hear only a remote murmur: the choir of billion neurons.

Since the end of the 1980s, the advent of technologies in the field of active implants has allowed us to place electrodes on or in the brain. We are now able to hear, in detail, what the brain is saying. In our thirst of understanding everything, neurosciences were first trying to grasp the overall complexity of the brain, even to model or simulate it. We realize now that we should not compare the brain to a computer. Connections between neurons are not governed by a binary system but rather by multidimensional nonlinear relations of chaotic nature. This is the miracle: from chaos appear motor actions, perceptions, emotions, feelings, memories, and ideas. Today, and probably for many more years, we are not able to "program" soft human particularities like love, attraction for another individual, survival instinct, or duty to reproduce. Science does not explain falling in love, genius, or creation of a unique piece of art.

Nevertheless, we have discovered that electrical signals, injected at appropriate locations, may inhibit, modify, or influence the relations between the brain and its environment. Clinical tests have shown that implanting electrodes in the nervous system may treat a large variety of conditions, including cognitive, affective, and psychiatric disorders. It raises fundamental questions in terms of ethics and society.

Is “emotionally augmented human” a sustainable concept? Do we want to annihilate our differences and our personal characteristics?

We know that we will never reach the confines of our universe. We should also realize that we should remain modest in our conquest of the brain. Finding rationality in the never-ending dance of neurons is maybe a vain challenge. Shall we keep untouched those mysteries which make us unique and unpredictable?

Genève, Switzerland Claude Clément

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About the Author

Claude Clément born in 1955, is from the French-speaking part of Switzerland. He has first worked in R&D for the watch industry (Swatch Group) as head of the transducers and actuators development group. He entered the world of medical technologies by heading the diversification activities of Swatch in the field of wearable programmable drug delivery pumps. Afterward, he spent 27 years in the field of active implantable medical devices, as director of Manufacturing Engineering at Intermedics (now Boston Scientific), as plant manager of the Swiss Operations at Medtronic, and later as a consultant for major companies, mainly in the field of pacemakers, and for various highly innovative start-ups. Starting 1996, he put in place and ramped up the highly automated factory of Medtronic in Lake Geneva area. This plant is the world's largest site for the assembly of active implantable medical devices, producing large volumes of pacemakers, defibrillators, and neurostimulators. Until 2014, he was CEO of MyoPowers, a start-up company developing an electromechanical implant to treat severe incontinence. Beginning of 2015, he joined the Wyss Center for Bio and Neuroengineering as CTO. He is or was founder, chairman, or board member of several start-ups and small businesses. He is chairman of the BioAlps Association, a diversified life science cluster in Western Switzerland. He holds a master's degree in Electrical Engineering from the Swiss Federal Institute of Technology (EPFL) in Lausanne and an MBA from HEC at the University of Lausanne (Switzerland).

Abbreviations and Acronyms

510k	Premarket submission to the FDA, substantially equivalent to a legally marketed device
5G	Fifth generation of cellular network technology
AB	Advanced Bionics
AC	Alternating Current
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
AI	Artificial Intelligence
AIMD	Active Implantable Medical Device
ALD	Atomic Layer Deposition
ALS	Amyotrophic Lateral Sclerosis
AMF	Alfred Mann Foundation
BAHA	Bone-Anchored Hearing Aid
BCI	Brain Computer Interface
BD	Big Data
BGA	Ball Grid Array
BMI	Brain Machine Interface
BSc	Boston Scientific
CBP	Chronic Back Pain
CDRH	Center for Devices and Radiological Health (FDA)
CE	Conformité Européenne
CHUV	Centre Hospitalier Universitaire Vaudois
CI	Cochlear Implant
CLIS	Completely Locked-In Syndrome
CMOS	Complementary Metal Oxide Semiconductor
CNS	Central Nervous System
CoC	Chip-on-Chip
CoGS	Cost of Goods Sold
CoNQ	Cost of Non-quality
COTS	Component of the Self
CRM	Cardiac Rhythm Management

CSEM	Centre Suisse d'Electronique et de Microtechnique
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DARPA	Defense Advanced Research Projects Agency
DBS	Deep Brain Stimulation
DC	Direct Current
EAP	Expedited Access Pathway
EC	Ethics Committee
ECAPS	Evoked Compound Action Potential Signal
ECG	Electrocardiogram
ECoG	Electrocortical Grid
EEG	Electroencephalogram
EFS	Early Feasibility Study
EMD	Electromagnetic Disturbance
EMG	Electromyogram
EOL	End of Life
EPFL	Ecole Polytechnique Fédérale de Lausanne
EtO	Ethylene Oxide
FBSS	Failed Back Surgery Syndrome
FCB	Flip Chip Bonding
FCC	Federal Communications Commission
FDA	Food and Drug Administration
FES	Functional Electrical Stimulation
FI	Fecal Incontinence
FIH	First in Human
fMRI	Functional Magnetic Resonance Imaging
FPGA	Field Programmable Gate Array
FT	Feedthrough
FtO	Freedom to Operate
GES	Gastric Electrical Stimulation
GNS	Gastric Nerve Stimulation
HDE	Humanitarian Device Exception
HF	High Frequency
IC	Integrated Circuit
ICD	Implantable Cardiac Defibrillator
IDE	Investigational Device Exemption
IMMG	Intramuscular Myogram
IMS	Intramuscular Stimulation
IoE	Internet-of-Everything
IoMT	Internet-of-Medical-Things
IoT	Internet-of-Things
IP	Intellectual Property
IPA	Isopropyl Alcohol
IPG	Implantable Pulse Generator
IR	Infrared Light

ITU	International Telecommunication Union
LCP	Liquid Crystal Polymer
LED	Light-Emitting Diode
LIFUS	Low-Intensity Focused Ultrasounds
M2M	Machine-to-Machine Communication
MDD	Major Depressive Disorder
MDR	Medical Device Regulation
MDT	Medtronic
MEA	Microelectrode Array
MEG	Magnetoencephalogram
MIL-STD	Military Standard
MMI	Mind-Machine Interface
MPE	Maximum Permissible Exposure
MRI	Magnetic Resonance Investigation
NB	Notified Body
NESD	Neural Engineering System Design
NI	Neural Interface
NIR	Near Infrared Light
NNP	Networked Neuroprosthetics System
OAB	Overactive Bladder
OCD	Obsessive-Compulsive Disorder
OEM	Original Equipment Manufacturer
OR	Operation Room
OSA	Obstructive Sleep Apnea
PBS	Phosphate Buffered Saline
PCA	Patient-Controlled Analgesia
PCB	Printed Circuit Board
PD	Parkinson's Disease
PET	Positron Emission Tomography
PI	Principal Investigator
PM	Personalized Medicine/Program/Project Manager
PMA	Pre-market Approval
PMA-S	Pre-market Approval Supplement
PMS	Pain Management System/Post-market Surveillance
PNS	Peripheral Nerve Stimulation
PVD	Physical Vapor Deposition
QA	Quality Assurance
QMS	Quality Management System
RA	Regulatory Affairs
RAA	Reactive Accelerated Aging
RF	Radio Frequency
RGA	Residual Gas Analysis
RI	Retinal Implant
RNS	Responsive Neurostimulator System
ROS	Reactive Oxygen Species

RR	Rate Responsive
SAR	Specific Absorption Rate
SCI	Spinal Cord Injury
SCS	Spinal Cord Stimulation
SEM	Scanning Electronic Microscope
SNR	Signal-to-Noise Ratio
SNS	Sacral Nerve Stimulation
SoC	System-on-Chip
TACS	Transdermal Alternating Current Stimulation
TDCS	Transdermal Direct Current Stimulation
TENS	Transdermal Electrical Nerve Stimulation
TESS	Targeted Epidural Spinal Stimulation
TNS	Tibial Nerve Stimulation
UE	European Union
UEA	Utah Electrode Array
UI	Urinary Incontinence/Urge Incontinence
US	Ultrasounds
UV	Ultraviolet Light
V&V	Verification and Validation
VCSEL	Vertical Cavity Surface Emitting Laser
VNS	Vagal Nerve Stimulation
WB	Wire Bonding
WLAN	Wireless Local Area Network
WP	Work Package
YAG	Yttrium Aluminum Garnet

Chapter 1
Introduction

The objective of this book is to provide a general overview, in easy language, not scientific, of neuro-technologies, in the context of translational medicine, from concept to human clinical applications. Deep explanations on the physiological and clinical aspects of neurological disorders are not the purpose of this book. An abundant literature is available for a more scientific and medical understanding.

The subtitle of the book is *How to build the brain-computer interface of the future*. The keyword is *build*, and the emphasis will be put on the translational development, from concept to patient, with a special focus on how to practically execute projects in the field of active implantable medical devices applied to neurological indications. *Build* also concretely means that our intent is to design, manufacture, and commercialize devices which will provide improvements in the quality of life of patients suffering from neurological disorders of various origins, from birth defects, accidents, diseases, degeneration, or age-related degradation.

1.1 Brain-Computer Interface (BCI)

There are several definitions of brain-computer interfaces, which sometime have other names like brain-machine interface (BMI), mind-machine interface (MMI), or neural interface (NI). The most global definition of BCI is a direct interaction between the neural system and electronic systems. Some authors limit the use of the term "BCI" to bidirectional communications with the brain only. The term BCI made its first appearance at the University of California in the 1970s.

Other notions, like neuromodulation and neuroprosthetics, may somehow overlap with the terminology BCI. As this book is focused on technologies, we will not have any restrictive definition of what a BCI is. We will cover the technical challenges of any system intended to enter in contact with the entire nervous system and senses (see Fig. 1.1a).

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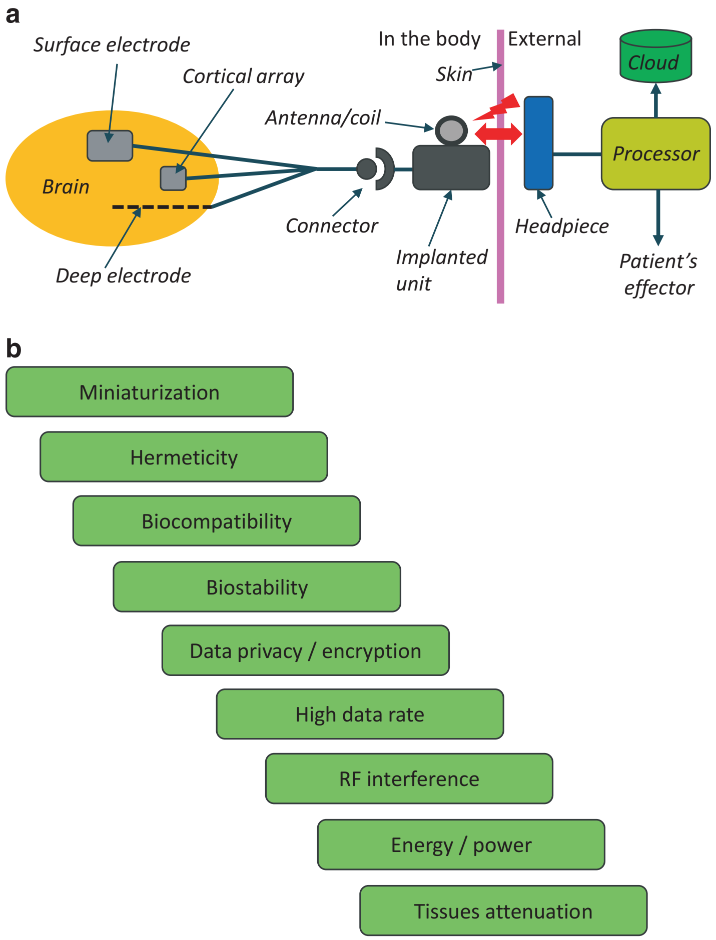

Fig. 1.1 (**a**) Global description of a bidirectional BCI. (**b**) Main challenges in building BCI systems

We will see along the various chapters of this book that interfacing with the brain is a very complex task, mainly due to the nature of the human body. A thorough easy-to-access article on BCIs has been published by the economist [12]. It is a good introduction to understand the global context. At page 7 of this document, the quote says: *"The brain is not the right place to do technology."* We'll explain this statement in this book and cover the main challenges (see Fig. 1.1b) involved in the building of devices interfacing with the brain and the nervous system.

In a first stage, BCI systems are unidirectional, limited to "reading" the brain (see Fig. 1.2). There are plenty of possible configurations of BCI for collecting signals from the brain.

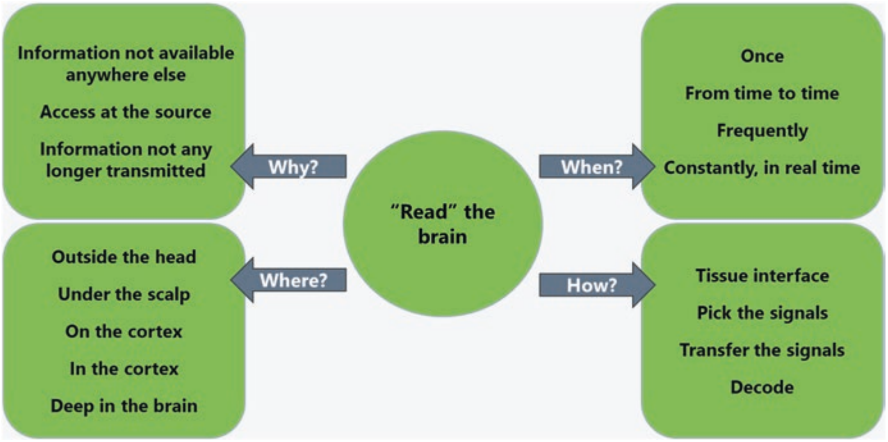

Fig. 1.2 Reading the brain

1.2 Technology Versus Science

Technologies are now available and make it possible to interact with the human brain and nervous system. This book covers the past achievements, the current work, and the future perspectives of BCI and other interactions between medical devices and the human nervous system. Repairing and rehabilitating patients suffering from neurologic impairments, from paralysis to movement disorders and epilepsy, are described in detail, from a pragmatic point of view. Whenever possible, we try to interact with the nervous system without breaking the skin barrier. Nevertheless, such severe disorders often require an invasive solution, based on an implanted device. This book explains the unique and special environment of active implants electrically interfacing with the brain, spinal cord, peripheral nerves, and organs.

BCI should be understood as a wide concept:

- B: Brain, but also central nervous system, spinal cord, vagal nerve, peripheral nervous system, senses, and various organs.
- C: Computer, but also "machines" (BMI: brain-machine interface), implanted electronics, and external electronics.
- I: Sensing and/or stimulating from electrodes or tissue interfaces.

Active implantable medical devices (AIMDs) have been available from the 1960s, mainly to treat cardiac disorders. Pacemakers and implantable defibrillators are now very mature, reliable, and efficient devices, several of them being implanted in patients every minute all over the planet. Using similar technologies, based on hermetically sealed electrical stimulators and sensing devices, the industry of active implants started to address other unmet medical needs at other locations in the body, like deep brain stimulation (DBS) cancelling the symptoms of the Parkinson's disease (PD) or cochlear implant (CI) to mainly restore hearing in children born deaf. Already hundreds of thousands of patients benefit from these advanced technologies.

Today, new technologies make it possible to interact more efficiently with organs. Devices with hundreds of sensing/stimulating electrodes, connected with powerful electronics and wireless communication systems, allow engineers and clinicians to explore new therapies and to push out the frontiers of neuro-technologies.

The rapid progresses of neuro-technologies are described mainly in scientific papers and articles. This high-level literature is difficult to understand for the healthcare community, for the developers of new clinical solutions, and for the industry. The objective of this book is to simplify the understanding of such a complex field and to present, in a clear language, the extraordinary revolution that neurotechnologies will contribute to healthcare and quality-of-life improvement.

Every day, scientists and researchers progress in their knowledge of the extraordinary complexity of our nervous system, rising hopes and expectations for better therapies, more accurate diagnostics, and coverage of unmet medical needs.

This constantly improving grasp of the interactions between cells, neurons, brain circuits, and organs paves the way to new technological solutions. The main goal of this book is to describe how to translate the considerable progress of neurosciences, in devices, tools, interfaces, software, and other technological steps, which will give patients a better life.

Experts in translational neuro-medicine must be bilingual. They need to understand the language of neuroscientists and to be able to translate it properly in technological needs, specifications, and human factors. Working together, scientists and engineers have the power to assess the technical limitations, the physics of implants in the human body, and the realistic long-term perspectives.

This book will provide down-to-earth global analysis of neuro-technology for human benefit, including science, technology, regulatory, clinical, reimbursement, patient's acceptance, surgical aspects, and long-term perspectives. We will review the evolution of the AIMD industry, moving from cardiac to neuro-applications. A critical analysis on the pioneer implantable neuro-indications will also show that many people already benefit from neuro-technologies. Reviewing "who-is-doing-what" in this field will confirm the statement that "the next decades are going to be the age of neuro-technologies."

1.3 This Is Not Science Fiction

Neuro-technology is not science fiction. Since the 1980s, millions of people have benefitted from implants not related to cardiac disorders. Every day, in the streets or public transportation systems of large cities, you meet somebody who has a neuro-device implanted, but you do not even notice it. This is a proof that the neuro-industry has already succeeded in repairing people to a level that the other bypassers do not know anything of the problem. Let's quickly mention some successful therapies and corresponding devices related to the nervous system. A deeper review of some of them can be found in Sect. 3.2.

1.3.1 Cochlear Implants (CI)

Interfacing directly with neuroreceptors of the inner ear was the first commercial achievement of neuro-technologies. CIs are mainly implanted in children born with a nonfunctioning conduction of the sound waves from the eardrum to the cochlear, often due to malformation of the middle ear. CIs are also indicated for the treatment of severe deafness of adults and elderly people. A tiny electrode is introduced in the cochlear and stimulates the natural neuroreceptors of the inner ear. The electrode is connected to an implanted electronic in a hermetic housing which receives signals from an external sound processor positioned on the scalp, at the rear of the ear. Natural sounds are picked by a microphone and processed by the external unit. CI will be described in more details in Sect. 3.3.1.

1.3.2 Deep Brain Stimulation (DBS)

Available since the end of the 1980s, DBS systems consist of electrodes placed in specific areas deep in the brain, mainly to treat movement disorders like Parkinson's disease, dystonia, or essential tremors. The leads are tunneled under the scalp and then along the neck to be connected to an implantable pulse stimulator (IPG) located in the pectoral area. The electrical signals applied in the brain block the symptoms characteristic to PD like uncontrolled movements and tremor of the upper limbs. Details on DBS will be covered in Sect. 3.3.2.

1.3.3 Spinal Cord Stimulation (SCS)

SCS represents about 50% of the overall market of neurological implants. Electrical signals are sent to selected area of the spinal cord, mainly for the treatment of chronic back pain. Paddle electrodes are connected to an IPG located in the back. Electrical stimulation blocks the pain signals at the root of the nerves and prevents them to reach the brain. Technical aspects of SCS can be found in Sect. 3.3.3.

1.3.4 Sacral Nerve Stimulation (SNS)

Stimulation of the sacral nerve permits to treat mild to moderate forms of urinary and fecal incontinence. Sacral nerves control functions of the pelvic area. Stimulating them with electrodes placed nearby, connected to an IPG, provide remote control of the bladder and sphincters. More details on urinary incontinence in Sect. 3.3.5.

1.3.5 Vagal Nerve Stimulation (VNS)

The vagal nerve is the second "communication neurohighway," after the spinal cord. It includes afferent and efferent fibers. Stimulating it permits some control on epilepsy, treatment-resistant major depressive disorders (TR-MDD), and other treatments of organs related disorders. Stimulation of the vagal nerve is done either by placing a cuff electrode around the nerve, connected to an IPG, or by transcutaneous stimulation.

1.3.6 Various Devices

In addition, several devices have been developed and approved to treat diseases related to the nervous system. Some examples:

- Programmable implantable drug delivery pumps for intrathecal injection (in the cerebrospinal fluid (CSF)) to treat chronic pain, end-of-life pain, and tremors.
- Gastric nerve stimulation (GNS) is aiming to treat obesity by electrical stimulation of the upper part of the stomach.
- Retinal implants have proven efficient to give some visual perception to totally blind patients (more details in Sect. 3.3.4).
- Tibial nerve stimulation (TNS) has shown potential to treat mild urinary incontinence by stimulating the tibial nerve, by external or implanted stimulation.
- Functional electrical stimulation (FES) is already used by some groups to directly apply electrical stimulation to nerves or muscles for the restoration of simple movements for paralyzed patients.

1.4 Pioneers, Doers, and Dreamers

1.4.1 Pioneers

We will see later in this book that most of the technical developments related to electrical interactions with the human body find their origins in cardiac applications. It is known since centuries [1] that muscles and nerves react to electrical stimulation. Implantable systems could only be realized when transistors, integrated electronics, and small batteries became available in the late 1950s. First came the pacemakers and about 30 years later implantable defibrillators which needed much more sophisticated electronics. Then, in the late 1980s, the first neuromodulation devices appeared: deep brain stimulation and spinal cord stimulation. At the same period, CIs made their way to market. Early neuro-devices are not strictly speaking BCI but rather stimulators interacting with the nervous system. In this sense, spending some time to understand how they developed is also part of the objectives of this book: how to build the BCI of the future.

1.4.1.1 Pacemakers

Early pacemakers [2], in the later 1950s, were simple pulse generators, with fixed pulse rate, basic non-programmable electronics, and mercury batteries potted in epoxy or silicone rubber. Long-term reliability was poor, as epoxy encapsulation did not provide long-term hermeticity. Nevertheless, those simple devices opened the door to an entire industry by providing acceptable life-supporting solutions to thousands of people with serious cardiac disorders.

In the 1970s, the first laser welded hermetic titanium-encapsulated pacemakers paved the way for high reliability implants with sophisticated, programmable, and integrated electronics. Hermetic sealing achieved two major steps in the field of implantable devices:

- Protection of the patient in case of battery leakage.
- Protection of the implanted electronics from moisture and body fluids.

The pacemaker industry has set the fundamental grounds of active implants. Early devices were not hermetically encapsulated, meaning that sooner or later, electronic components will be exposed to moisture. At that time, the electronics of the implants were based on discreet components like simple transistors, resistors, and capacitors, assembled with a comfortable distance between them. In this configuration, diffusion of moisture through the plastic encapsulation was not critical.

When electronics became more integrated, with thousands of transistors on integrated circuits (ICs) and short distance between components, simple epoxy or silicone encapsulations were not enough to provide long-term reliability. Total hermeticity was required to avoid exposure of sensitive electronic components to moisture and oxygen. Laser seam welding of titanium housing provided the solution for long-term reliable high-tech implants. Feedthroughs are key components to build hermetic packaging. They consist in one or several conductive wires sealed in an insulator, itself brazed in the packaging. These wire connections allow communication between the electronics in the package and the tissue interfaces. These technologies could then be applied to other indications.

The pacemaker industry is now a mature technological field with very high reliability. About 1.5 million pacemakers are implanted every year.

1.4.1.2 Implantable Cardiac Defibrillators (ICDs)

The first ICDs appeared in the early 1990s. Compared to pacemakers which generate low-voltage pulses to stimulate, resynchronize, or assist the heart, ICDs are designed to provide high-voltage high-energy electrical shocks in case of sudden cardiac arrest, severe tachycardia, or ventricular fibrillation. ICDs include advanced electronics and high-voltage circuits which require hermetic encapsulation. As ICDs are life-supporting devices, they cannot rely on rechargeable batteries, which might be depleted when needed. The primary battery being at low voltage (3.5 V), a complex voltage multiplier rises it to about 700 V, necessary to generate high-energy shock, in the range of up to 40 J. This large amount of energy cannot be continuously stored in the implant. Therefore, when electrodes detect a situation of fibrillation or a heart stop, the multiplier starts loading a capacitor with the appropriate energy for the shock. It takes 10–20 seconds before the ICD is ready to fire.

Modern ICDs have been miniaturized and are now used in large numbers of cardiac indications, combining regular stimulation and defibrillation. Hundreds of thousands ICDs are implanted every year.

1.4.1.3 Cochlear Implants

As mentioned earlier, CIs have been a major contributor to the evolution of active implants. They are the first neurological active implanted devices to have reached a large population. Unlike pacemakers and ICDs, CIs are battery-less devices. The implanted electronics get its energy through transdermal inductive magnetic coupling of an implanted coil and an external coil. The acoustic signal is transmitted through the same inductive coupling.

In the last 30 years, about 700–800 thousand CIs have been implanted in children with congenital deafness or in older patients with severe hearing disorders.

1.4.1.4 Deep Brain Stimulation

In the late 1980s, DBS became the first therapy interacting directly with the brain. Patient's benefits were amazing even if the understanding of the effects of electrical stimulation on the thalamus were then not totally understood. Today, more than 200,000 patients are well treated, having no visible symptoms of Parkinson's any longer. Compared to more drastic surgery, like tissue ablation, DBS has the advantage of being controllable and reversible.

1.4.1.5 Spinal Cord Stimulation

A few years after DBS, it was understood that stimulation electrodes could be placed on the spinal cord where afferent nerve merges to it. Applying mild current at this location allows a substantial reduction of the perception of pain, for example, in cases of chronic back pain (CBP) or lower limbs pain. Compared to other methods for treating pain, like drugs, SCS has the advantage of have no side effect and to be reversible.

1.4.2 Doers

The pioneer indications are going on growing and serving more and more patients. More recently several products made their way to the market to treat other patients' needs. There is currently a formidable energy focused on applying technology to treat neurological disorders. Some projects are leveraging the technologies of the pioneers to treat new indications. Other groups are pushing the former technologies further with the objective to meet medical needs which were not so far reachable. Here below, you'll find a brief description of recent (last two decades) and ongoing initiatives with promising outcomes.

1.4.2.1 Spinal Cord Stimulation

SCS has been described as a pioneer technology, but, because of its success, it also belongs to this chapter. SCS is the largest indication in the field of neuro-technologies. Its impact in terms of quality of life and societal benefit is clear. The therapy is expected to improve. New projects, using high-frequency stimulation, show promising results, even if the scientific rational is not yet fully understood. Controlling pain through electrical stimulation is a high-potential target. A lot of progress is expected in this domain.

1.4.2.2 Sacral Nerve Stimulation

Like SCS, SNS is a therapy which is mainly unknown of by the population, but hundreds of thousand patients have already benefited of SNS for a better control of urinary incontinence. Originally, the indication was limited to mild forms of urge incontinence (UI) and overactive bladder (OAB). Medtronic was a pioneer in this indication [3]. Today, we see new companies like Axonics [4] and Nuvectra [5] entering in this field and an extension of indications in the direction of fecal incontinence. So far, SNS is not able to treat severe forms of incontinence, like post-prostatectomy incontinence and older women severe incontinence, which remain real unmet medical needs.

1.4.2.3 Vagal Nerve Stimulation

Cyberonics (now LivaNova) [6] was first to attempt stimulating the vagal nerve in order to control epilepsy. It demonstrated that a lot can be achieved by interfacing with the vagal nerve. VNS is still one of the only therapy available for the treatment of some forms of epilepsy. There are several other initiatives aiming to stimulating the vagal nerve for other indications. In neurology, it has been shown that VNS might be efficient to treat forms of depression, like major depressive disorders (MMD), without understanding all the brain mechanisms associated with these results.

Other applications of VNS, not strictly neurological, have been developed, for example, for the treatment of morbid obesity through gastric electrical stimulation (GES). Original work in this direction has been done by EnteroMedics [7] which has now merged with ReShape Lifesciences [8] providing a gastric band for the same purpose. VNS as proposed by EnteroMedics failed in proving to be superior to other solutions.

1.4.2.4 Retinal Implants

Three to four companies are achieving tremendous successes in their endeavor to provide some sense of vision to blind people. Retinal implants are still limited to hundreds of pixels. It is small compared to the performance of a healthy retina. But, getting some basic visual perception is an enormous improvement for blind people. From the ongoing work, we can anticipate substantial achievements. Several teams are currently progressing fast on other neuro-interfaces to restore vision, where electrodes are not located in the eyes but rather on the optic nerve or on the visual cortex.

1.4.2.5 Peripheral Nerve Stimulation (PNS)

Stimulation of nerves outside the brain and spinal cord domain has shown a high potential. Several companies are working in the field of PNS with exciting successes. Among them SNS can be considered as PNS. Other therapies, like gastric nerve stimulation (GNS), for fighting obesity also belong to the PNS group. FES and TNS, already described above, are addressing specific medical needs with several approved devices.

1.4.2.6 Intelligent Prosthesis for Amputees

Various ongoing projects are aiming to connect intelligent prosthesis with the remaining nerves at the root of the lost limbs, either to be able to activate the prosthesis directly from the patient's nerves or to provide a sensory feedback (haptic) from sensors placed in the prosthesis and connected to the nerves. The number of patients who benefit from these devices is still limited, but large progresses will come soon, especially when lower limbs amputees would become eligible.

1.4.2.7 Diagnostic and Monitoring of Epileptic Patients

The common approach to assess occurrence, intensity, frequency, and localization of epileptic seizure is to use electroencephalography (EEG). Unfortunately, EEG caps cannot be worn for extended periods of time. Home-based accurate long-term monitoring is not available yet, with the exception to NeuroPace RNS system (see Sect. 3.4.7). It consists in an implantable recorder, inserted in a craniotomy, and connected to 8–16 electrodes (paddle cortical electrodes or penetrating electrodes). Several groups are currently developing less invasive implantable system for medium- to long-term diagnostic and monitoring of epileptic patients, with objectives of being able to forecast or event predict seizures. An example is UNEEG [9], a Danish company part of the Widex Group [10], a hearing aid supplier.

1.4.2.8 BCI for Sensing Motor Areas of the Cortex

Since more than a decade, the BrainGate Initiative [11] gathers five US institutions in a consortium which leads the way of research and development in the domain of reading movement intentions of paralyzed patients. Sensing the cortical activity is mainly done through the so-called blackrock array or Utah array (see Fig. 1.3), a microelectrode array (MAE) [12]. This tiny tissue interface of up to 100 fine electrodes penetrates about 1.5 mm in the motor cortex.

So far, the electrodes are connected to a bundle of thin gold wires and a transdermal connector called pedestal (see Fig. 1.4). The pedestal is attached to the skull.

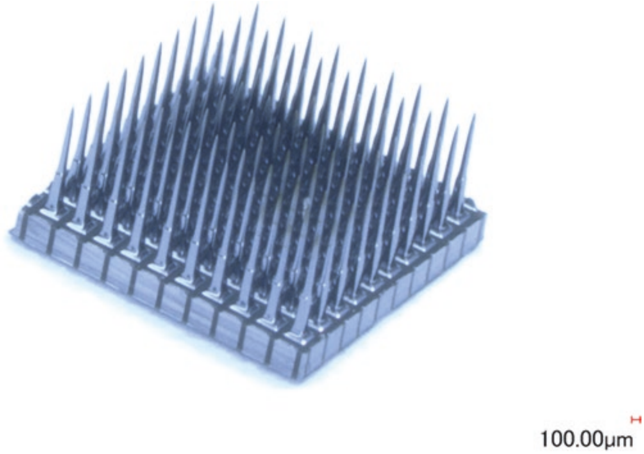

Fig. 1.3 Utah or blackrock array. *(Courtesy: Blackrock Microsystems LLC)*

Fig. 1.4 Utah array connected to a transdermal pedestal. (*Courtesy of Blackrock Microsystems LLC)*

Until now, around 15–20 paralyzed patients have had 1 or 2 Utah arrays inserted on their motor cortex. The greatest challenge resides in the real-time decoding of the movement intentions. Early work enabled a paralyzed patient to successfully move, by his/her thoughts only, a cursor (2D) on a screen, click on icons, use a speller, and conduct other tasks similarly to the activation of a computer mouse. Later, it became possible to decode and extract information corresponding to more complex movements, up to a dozen degrees of freedom. “Move, Reach, and Grasp” movement intentions of the arm have been decoded successfully, allowing the activation of a robot arm for simple tasks like drinking from a bottle or taking food in a bowl with a fork. Recently, the robot arm was replaced by direct FES stimulation of the paralyzed patient’s arm.

Current work (see Sect. 7.3.6) is using the same type of BCI to regain contact with people with completely lock-in patient syndrome (CLIS).

1.4.2.9 Others

Several developments related to innovative devices for interfacing with the nervous system are going on around the planet. To cite just a few:

- Simulation of the spinal cord for reactivate walk in paralyzed patients or for rehabilitation after stroke.
- Stent-like electrodes placed in brain blood vessels for sensing brain signals.
- Stimulation of the inner ear to repair vestibular disorders.
- Stimulation of the optic nerve or on the visual cortex to treat blindness.
- Steerable DBS for a more accurate treatment of PD.
- Use DBS for other syndromes like obsessive-compulsive disorders (OCD), chronic depression, migraine, Tourette's syndrome, obesity, addictions, epilepsy, etc.
- PNS to treat amputees' phantom pain.
- Mirror restoration of unilateral facial paralysis.
- Neurofeedback for tinnitus.
- Hypoglossal nerve stimulation to treat sleep apnea.
- Gastric nerve stimulation for gastroparesis, nausea, and vomiting.
- Brain re-synchronization for dyslexia or certain speech disorders.
- Wired and wireless networks of implants for FES.
- ….

The ongoing development efforts in neuro-technologies will have a considerable impact on health and quality of life. Some improvements are done step-by-step. Some will be disruptive and revolutionary. Learning from the work of the pioneers is essential to execute good research and development today. Anticipating the trends and changes in our environment induces us to also listen to the "dreamers."

1.4.3 Dreamers

Pioneers and "doers" in neuro-technologies were or are mainly physicians, healthcare specialists, surgeons, engineers, regulators, scientists, and researchers. Their focus is on improving therapies and diagnostics, with patients in the center.

A new category of players appeared recently: dreamers. Their goals are to use BCI for nonmedical applications. They usually do not have a full understanding of the specificities of the human body. They also underestimate the technical challenges related to interfacing with the brain.

They are successful, wealthy, and young entrepreneurs who founded and grew immense companies, mainly in communication, Internet, software, online commerce, or electrical cars. Their capacity to reinvent entire industries is amazing. As such, doers should listen to dreamers and grasp opportunities whenever possible.

Dreamers want to push BCI beyond its current stage, aimed to repairing people with neurological disorders. They want to distribute BCI over the entire volume of