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Cybernetics

The Chemistry of Cyborgs—Interfacing Technical Devices with Organisms

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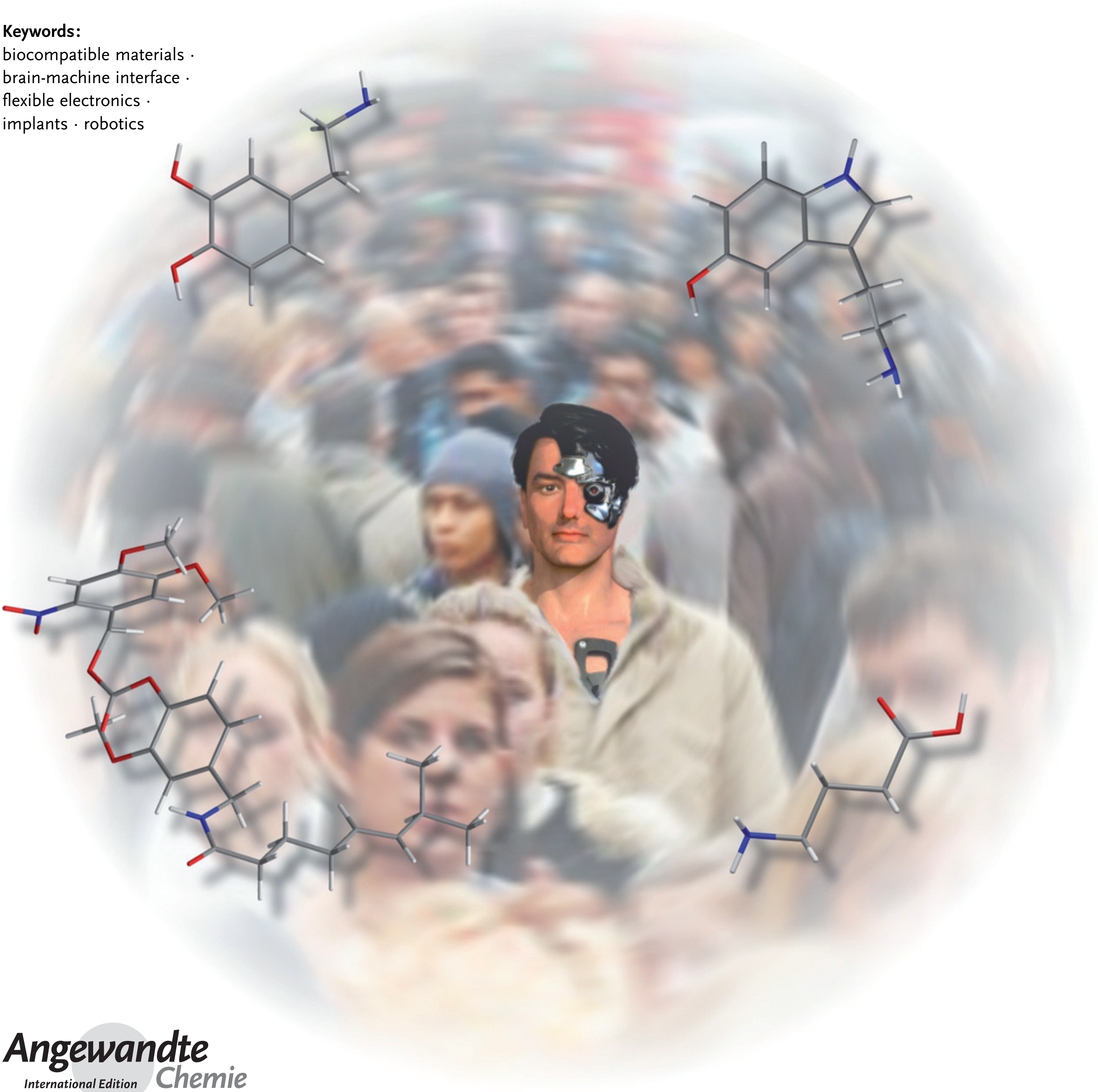

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The term "cyborg" refers to a cybernetic organism, which characterizes the chimera of a living organism and a machine. Owing to the widespread application of intracorporeal medical devices, cyborgs are no longer exclusively a subject of science fiction novels, but technically they already exist in our society. In this review, we briefly summarize the development of modern prosthetics and the evolution of brain–machine interfaces, and discuss the latest technical developments of implantable devices, in particular, biocompatible integrated electronics and microfluidics used for communication and control of living organisms. Recent examples of animal cyborgs and their relevance to fundamental and applied biomedical research and bioethics in this novel and exciting field at the crossroads of chemistry, biomedicine, and the engineering sciences are presented.

From the Contents

1. Introduction

The term "cyborg" had already been coined in 1960 to refer to a cybernetic organism. It characterizes the chimera of a living organism and a machine and it was defined by Clynes and Kline as: "*The Cyborg deliberately incorporates exogenous components extending the self-regulatory control function of the organism in order to adapt it to new environments.*"[1] Cyborgs were considered the logical expansion of "*man's bodily functions to meet the requirements of extraterrestrial environments.*"[1] Today, the widespread public image of cyborgs comes from numerous science fiction novels, where cyborgs often appear as beings with supernatural ability and power, frequently used to harm humanity. Given the fact that a significant number of individuals are nowadays using intracorporeal medical devices, such as pacemakers, complex prosthetics, or cochlea and retina implants, this part of mankind can technically already be considered as cyborgs. In this review, we will summarize recent developments on the interfacing of technical devices with higher organisms. In Section 2 we give a brief survey of the state-of-the-art of modern implants, which describes that implantation technology has been under development for more than 1000 years, but has made tremendenous progress in the past 10 years. This has enabled the development of sophisticated implantable brain–machine interfaces (Section 3) which provide a means to extract, and even inject, electrical signals from and into the brain. Such devices are under development and are already being used, for example, for medical action-from-thoughts applications where paralyzed individuals instruct robotic instrumentation by mere thinking. More than a decade of work on animal cyborgs has not only contributed significantly to these cutting-edge medical applications. The so-called biobots, such as large insects with implanted electronic and fluidic control units, are also considered as an approach to a novel generation of tools, such as small aircrafts for observation and search missions. Moreover, the external control of animal muscle and neural tissue by hand-held devices aims to increase our fundamental understanding of neuroscience. It is outlined in Section 4 that the developments of biocompatible flexible electronics, chimeric device–tissue interfaces, novel fluidic and optical brain–machine interfaces, as well as the concept of harvesting energy from the host organism to operate implants represent key aspects of the ongoing research and development of cyborg technology for medical and other applications.

2. From static prosthetics to smart implants

The original idea of cybernetic organisms has been dramatically pushed forward in the past couple of years, primarily by urgent needs in biomedicine and tremendous advances in micro- and nanotechnologies. As a matter of fact, totally or partially implanted technical aids and prostheses have long been used to compensate for defects and impairments resulting from traumatic events or diseases. The Romans, for example, had already used wrought iron artificial tooth constructs, which were most likely produced by a hot-hammering and folding process, in the first or second century AD as dental implants to replace lost teeth.[2] Although, metal-based materials are far from being ideally suited for dental implants, those prostheses might have been functional because of their osseointegration and correct anatomical position.

More than a century ago, the history of modern mechanical prosthesis and arthroplasty started with emerging techniques to treat joint disorders by replacing parts of the human body by either animal-derived tissues and materials, or by technical constructs. These approaches eventually enabled, for example, the first total hip replacement in 1938.[3] However, these early attempts were characterized by a low

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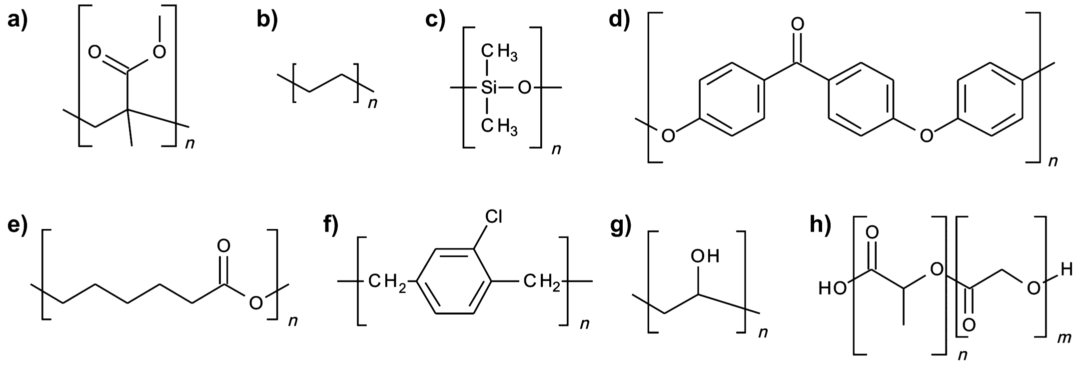


Figure 1. Polymer structures of commonly used polymeric materials for implants: a) poly(methylmethacrylate), b) poly(ethylene), c) poly(dimethylsiloxane), d) poly(etheretherketone), e) poly(caprolactone), f) parylene C, g) poly(vinylalcohol), h) poly(lactide-co-glycolide).

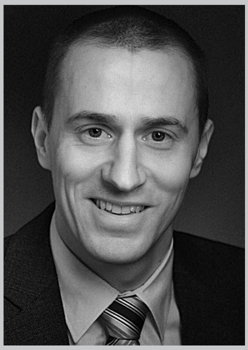
success rate owing to non-physiological designs and, in particular, the lack of suitable materials with sufficient mechanical strength, durability, and surface properties that provided both low-friction and biocompatible tissue integration properties.

Plates, screws, or marrow nails of metal-based materials were used in the early days of hip, knee or shoulder prostheses, or for the fixation of fractures. Whereas noble metals such as gold, silver, and platinum show a comparably good biocompatibility with only moderate irritation and body reactions owing to their high corrosion resistance, they are limited to only a few medical applications because of their low mechanical strength. Stronger metals such as iron, brass, or copper are not applicable because of their low biocompatibility. In the early 20th century and later, new alloys, such as chrome–nickel steels and titanium alloys, which exhibit improved mechanical properties and biocompatibility, have been identified as alternatives and are now widely used for medical implants.[4]

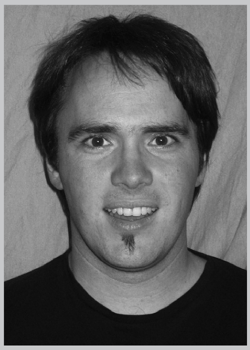
Later, synthetic polymers found their way into clinical applications. Typical examples of modern polymers include poly(methyl methacrylate) (PMMA; Figure 1 a) for bone cement or intraocular lenses, polyethylene (Figure 1 b) for the reconstruction of low-friction joint sockets, polysiloxane (Figure 1 c) for breast implants, or poly(etheretherketone) for osteosynthesis plates (Figure 1 d). Of additional importance for medical applications are ceramics and composite materials. Typical representatives include aluminum or zirconium oxides, calcium phosphates, and glass ceramics, which are mainly used for prostheses, as well as carbon- and fiber-reinforced composites.

In the last couple of decades, a lot of progress has been made in this field by developing novel so-called "smart materials" with responsive properties.[5] This has been accomplished through the use of computer-aided design and the fabrication of implants, such as through 3D-printing based on MRI data sets (Figure 2),[6] and, in particular, advanced surface modification of complex shaped free-form surfaces, to warrant improved host tissue integration.[7]

The chemistry of implant surfaces is tightly linked with successful tissue integration and the prevention of inflammatory response and unwanted foreign body reactions. New methods have been developed that allow for the creation of patterned surface coatings with non-fouling or even bioactive properties.[8] Thin-film and thick-film technologies, such as chemical and physical vapor deposition or plasma spraying, are also being employed to generate functional coatings for improved tissue integration. Examples include parylene (Figure 1 f) coatings, produced by pyrolysis of [2,2]-paracyclophanes, or calcium carbonate (hydroxylapatite) ceramic coatings.[4] Owing to their chemical inertness, mechanical resilience, and high biocompatibility, parylenes are now widely used as ISO-10993 compatible coating materials for implants, electrodes, and probes in living organisms. Recently, Zhang et al. have developed a coating for implants from ultra-low-fouling biomaterials to prevent nonspecific protein adsorp-



Stefan Giselbrecht studied Biology at the Friedrich-Alexander University, Erlangen, and the University of Saarbrücken. He received his doctoral degree from the Institute of Microstructure Technology at the University of Karlsruhe under the supervision of Professor Saile. Subsequently, he has been a research associate at the Institute for Biological Interfaces 1, where he was appointed as leader of the working group "Biomimetic Microdevices" in 2007. His research focuses on the development of new, especially polymer-film-based, technologies for the fabrication of functionalized micro- and nanostructures for biomedical and biotechnological applications.



Bastian E. Rapp studied mechanical engineering at the University of Karlsruhe, where he finished his PhD on biosensors for biomedical diagnostics in 2008. He is now head of a Young Investigator Group at the Institute of Microstructure Technology (IMT) of the Karlsruhe Institute of Technology. His research focuses on the development of microfluidic analytical systems and instrumentation for biomedical applications and biotechnology. He has been awarded, among others, the Edison Award of the General Electric (GE) Foundation, the REHAU award and the Südwestmetallförderpreis award, for his work.

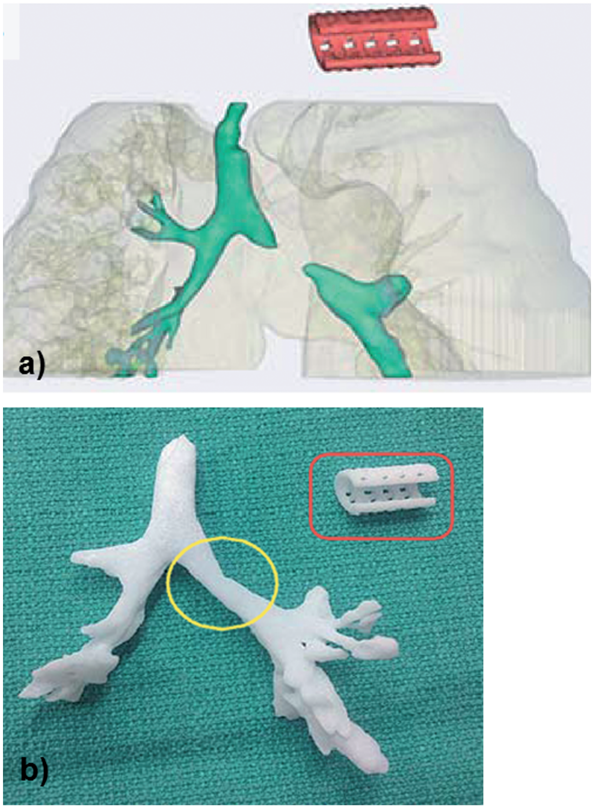


Figure 2. A biodegradable airway splint produced by rapid prototyping from poly(caprolactone) (see also Figure 1 e). a) A computed tomography-based design of the splint (red). b) The printed splint (red frame) was implanted to prevent the collapse of the malacic left mainstem bronchial segment (yellow frame) of a few-weeks-old patient.[6b]

tion,[9] which seems to be highly correlated with implant lifetime. They used zwitterionic hydrogels produced from carboxybetaine-based monomers and cross-linkers. Subcutaneous implantation into mice revealed that the hydrogel coatings prevented the formation of a dense collagenous capsule for at least three months.[9]

Remarkably rapid progress has occurred in the field of implantable electronic devices, which particularly benefited from the immense progress made in microelectronics and semiconductor technology. Since Luigi Galvani showed in the late 18th century that nerve conduction and muscle contraction are based on electrical signals,[10] many approaches have been developed to establish and exploit electrical communication for interfacing technical and biological systems. This strategy aims to either control, restore, or improve functions of the human body, as well as to control prostheses and even external robotic devices by signals derived from nerves or muscles.[11] The most prominent and widely applied example in the medical field is the portable and fully implanted cardiac pacemaker, which was successfully implanted for the first time by Senning in 1958.[12] Another established application is based on retinal implants, which play an increasingly important role in medicine, particularly because the first FDA-approval of a retinal implant for treating patients with advanced retinitis pigmentosa was granted at the beginning of this year. Additional auxiliary equipment for medical applications are cochlea implants for hearing-disabled persons, and implants for deep brain stimulation for pain treatment of drug-resistant patients or treatment of Parkinson's disease.[13] These and other examples are further described in Section 3.1.

Christof M. Niemeyer studied chemistry at the University of Marburg and received his PhD at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr with Manfred T. Reetz. After a postdoctoral fellowship at the Center for Advanced Biotechnology in Boston (USA) with Charles R. Cantor, he received his habilitation from the University of Bremen in 2000. From 2002–2012 he has held the chair of Biological and Chemical Microstructuring at TU Dortmund before he moved to the Karlsruhe Institute of Technology, where he is now professor of Chemical Biology and director of the Institute for Biological Interfaces. His research focuses on the chemistry and applications of bioconjugates.

Bioelectronic devices are nowadays merged with the field of robotics, in particular, to develop sophisticated neuroprosthetic devices.[14] To this end, so-called "brain–machine interfaces" (BMI) are currently being developed, which have already shown significant relief for the symptoms of medical disorders. As we will describe in Section 3, humans benefit greatly from the huge and increasingly detailed three-dimensional data sets obtained from sophisticated brain-mapping methods.[15] Notably, progress in the field of BMI also strongly affects the development of animal cyborgs or biobots,[16] where much effort has been spent in the last decade on integrating electronic devices into insects or molluscs to realize the remote control of living systems[17] (see Section 3.4). These approaches were conducted with small animals but they are coming more and more into the spotlight for applications in higher organisms, even humans. The technical hurdles in this area consist of the questions of high data transfer rates, size, and integration density down to the cellular length scale, intimate functional interfacing of soft three-dimensional tissue, and power consumption and supply.[18] Although we will discuss these issues in Section 4, it is worth mentioning here that long-proposed concepts, such as harvesting energy from the host organism by the aid of biofuel cells (see Section 4.4) or miniaturized implantable drug delivery systems previously considered for in vivo delivery of insulin,[19] are currently opening up new avenues for the remote control of organism behavior based on chemical signaling (see Section 4.3). Notably, the latter approach might further evolve by learning from Nature where certain parasites are able to change the complex behavior of their host through the secretion of neuromodulators.[20]

3. Interfacing brain and machine

As described above, recent years have seen leaps in functional implant technology, with a multitude of new and emerging manufacturing and functionalization technologies. Today the degree of coexistence and functional cooperation of living tissue and technical systems has reached an astonishing level of complexity. Modern technical systems are capable of keeping living organisms alive through the replacement of essential bodily functions (pacemakers), they help by compensating for reduced sensory perception (cochlear implants), and they also complete missing or non-functional body components such as arms and legs, which can be partially or entirely replaced by technical prosthesis. If a technical system is to replace complex body functions, such as grabbing, it is essential that the system is tightly interconnected with the living organism. Ideally, the technical system should be capable of receiving and transducing motion and control signals directly from the central nervous systems, most prominently the brain itself. Such hardware/wetware interfaces are commonly referred to as brain–machine interfaces (BMI). They provide the interface to the brain from which technical systems receive control commands, and to which technical systems may deliver feedback or stimulation.

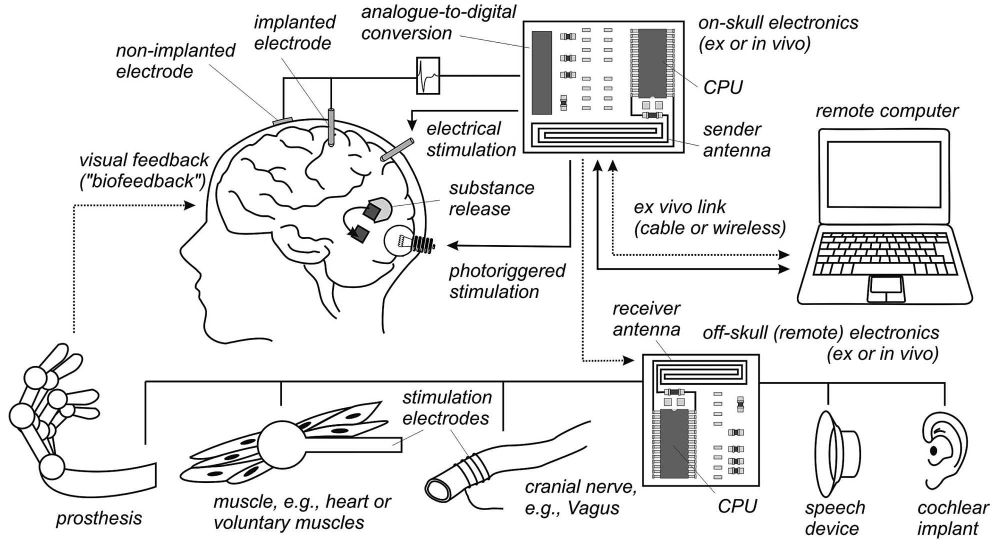


Figure 3. Principle setup of brain–machine interfaces (BMI). A set of electrodes (implanted or non-implanted) is continuously sampled by suitable on-skull electronics (potentially also including analog-to-digital conversion and algorithmic complexity reduction), resulting in motion and control commands. These commands are either communicated to off-skull electronics for direct control of, for example, a prosthesis, a loudspeaker (speech device) or electrodes located in proximity to muscles or nerves (for example, cranial nerves such as the Vagus nerve). The on-skull electronics may also directly communicate with a remote PC. Remote control of on-skull electronics can be used to inject signals into the brain, primarily using electrical stimulation. Recent developments also describe controlled substance release through microfluidics or light. The off-skull electronics may also be acting autonomously, as is the case with, for example, cochlear implants (which are triggered by an off-skull microphone) or pacemakers (which are controlled by the CPU clock cycle). Cable-based signal transduction is indicated by solid lines, whereas wireless signal transduction is indicated by dotted lines.

3.1. What are brain–machine interfaces?

The term brain–machine interface is used in reference to technical means of accessing and contacting the brain, that is, the nerve cells, of living organisms. Compared to computer-vision-based approaches relying on visual data for gesture recognition,[21] BMIs are designed to directly interface, and thus allow sampling of the electrical potentials of the living brain (Figure 3). The fact that the human body uses electrical potentials (so-called action potentials) for signal transduction and muscle activation has been known since the 18th century. Recording such action potentials is technically not a complicated task, because these signals can be picked up by simple circuitry and amplified. This can be achieved non-invasively with low spatial resolution, as is the case in electroencephalography (EEG). Interestingly, low-cost instrumentation for sampling action potentials from nerves and amplification to audio signals is nowadays accessible even for non-expert researchers, as illustrated by the so-called SpikerBox, which is commercially available from the company Backyard Brains.

There are two main types of BMIs: invasive and non-invasive. Invasive BMIs rely on electrodes permanently or temporarily implanted directly into a living brain, whereas non-invasive BMIs work with electrodes placed closely onto the skull, as with an EEG. Implanted electrodes are usually positioned subdurally atop the relevant cortex of the brain, and the method is then referred to as electrocorticography (ECoG). Implanted electrodes usually allow signal acquisition at higher data rates and significantly higher signal-to-noise ratios, as compared to non-invasive electrodes. This is due to the fact that each additional layer of tissue and bone acts as low-pass filter with high attenuation. Non-invasive BMIs are usually restricted to data rates of 20–30 bits per minute, whereas invasive BMIs outperform these values by at least one order of magnitude.[22] However, numerous commercially successful applications have been established using non-invasive BMIs. Most prominently, they have been used for decades for recording EEGs. The technique was first demonstrated by Berger in 1925,[23] and it is nowadays a routine technique in medical diagnostics. Another prominent example of non-invasive BMIs was introduced as a "thought translation device" in 1999 by Birbaumer et al.[24] to assist paralyzed patients in verbal communication.

Invasive BMIs were introduced in the late 1960s by Fetz during his seminal work on monkeys.[25] Implanting electrodes directly into the brain of a living organism carries all the risks associated with open brain surgery. Additionally, this procedure raises significant ethical concerns due to the fact that it is possible for such BMIs to not be operated solely as classical signal output devices for acquiring electrical potential data from the brain. Instead, BMIs can technically also be used to inject signals into the brain. This technique is generally referred to as deep brain stimulation (DBS). Even though this is an ethically highly disputed field, DBS is already being applied in the treatment of a wide range of medical conditions, which include chronic pain, tremors, and Parkinson's disease,[26] as well as numerous neurological and psychiatric disorders, such as epilepsy, anxiety disorders, and even chronic depression, which is treated by stimulation of the Vagus nerve. Interestingly, the first medical reports on DBS in humans date back to 1974,[27] only five years after the first electrodes were successfully implanted into the brain of a monkey. Typical examples of BMIs used for stimulating non-cranial nerves are pacemakers, which are among the oldest autonomous body implants in humans, as the first pacemaker was successfully implanted in 1958.[12b]

During the last two decades, BMIs have become a vital tool for medical engineering as means of extracting motion and control signals from the human brain, an application that is usable for the actuation of prostheses and implants; as such, they are key to replacing lost bodily functions, such as for paralyzed patients or amputees. In addition, BMIs enable insights into the brain and its underlying functional connections, and are thus a vital tool for modern neurology. In the course of their development, BMIs have been equipped with increasingly complex circuitry and processor capacity, which has been made possible by progresses in device and electronic miniaturization. Some of the most advanced BMIs today are almost autonomous systems with integrated microprocessors, suitable antennas, and interfaces for remote control. Designing suitable BMIs for a specific application is usually a highly transdisciplinary endeavor involving microelectronics, neuroscience, and robotics, as well as biomedical engineering and computer science.

3.2. Signal acquisition: the gateway to the brain

The main task of BMIs is accessing and translating raw neuronal signals into a technically processable format. Neuronal signals are analogue signals that need to be sampled at a sufficiently high sampling rate, filtered, and converted into digital signals (analog-to-digital conversion, ADC). Depending on the complexity of the BMIs, the device may either perform these operations autonomously or simply delegate this task to a remote computer. Usually the latter type of BMI is operated with a cable connection in order to transfer the complex analog signals with minimal quality losses. If the circuitry for autonomous ADC is located in close proximity to the electrodes, for example, if the BMI is installed on the skull (either ex vivo or in vivo), higher signal-to-noise ratios can be obtained and reduced amounts of data need to be transferred. Such on-skull electronics are often designed such that they support wireless communication with a remote computer or other electronic devices, such as prosthesis actuator electronics.

Signals may be acquired either by implanted electrodes or by electrodes located on the skull, closely on top of the respective brain cortex. In general, single electrodes do not provide signals of sufficient significance. This is due to the fact that action potentials of several hundreds to thousands of cells are involved in complex movement patterns. Therefore, only combined data analysis on larger groups of cells from different regions of the brain allow the derivation of stable control signals. It is also very important that these electrodes, especially if implanted, must sustain long-term operation without significant change in their surface impedance and biocompatibility. As rather classical systems based on, for example, high-density silicon micro-needle arrays[28] are still the benchmark for laboratory-scale experiments (but still suffer from limitations for usage as long-term implants), this aspect of BMI development offers plenty of room for further developments in materials science. Signals acquired from such electrode arrays are usually complex, and thus means to reduce complexity, such as artificial neuronal networks, support-vector machines, or hidden Markov models, have to be employed to generate signals suitable for actuator control. Some modern BMIs already support such functionality, albeit in reduced format, which allows them to become self-controlled units that may only intermittently require input from a remote computer.

Depending on the application, BMIs may also be operated with intact and accessible nerve or muscles cells that are still actively connected to the central nervous systems. This is often the case for partially paralyzed patients or amputees. Accessing electrical potentials from these sources may also suffice for obtaining body motion and control signals of sufficient quality.

3.3. Actions from thoughts: what to do with control signals?

The primary application of BMIs is deriving motion and control signals, which allow one to link neuronal activity in a certain brain cortex to the "control commands" issued to instruct a certain body part or limb. In most higher organisms, the brain is a highly evolved and very complex organ capable of extensive remapping of functions. For example, experiments on primates indicated that an animal can learn to control a robotic arm merely by thought.[29] Animals are even able to perform self-feeding under restriction of arm movement in such a setting, as demonstrated by Velliste et al.[29b] This not only indicates that motion and control signals of sufficient quality can be derived from raw neural activity data, but also that the animal becomes aware of its ability to control the robotic arm merely by thought. In this type of experiment, an animal is first trained to move a robotic arm while sampling the brain activity during animal movement. In the second stage of such experiments, the arm of the animal is fixed and the robotic arm is controlled exclusively by the action potential sampled from the animal's brain. Seminal experiments of this type date back to 1999 and were performed by Chapin et al.,[30] using rodents as model systems. In fact, this was the first demonstration that it is possible to derive control signals of sufficient quality from raw neural activity. These experiments also indicate that, if visual feedback is provided, the brain undergoes extensive functional remapping to gain better control over the robotic device. This process is often referred to as "brain plasticity" and it is one of the many examples of functional adaptability of the brain. If the control signal derivation of the BMI is imperfect, the brain neuronal signals result in incorrect operation of the technical system. Visual feedback allows the brain to adapt to the imperfect technical interface, thus issuing "better" control signals and gaining better control over the technical system. Hence, brain plasticity is the brain-derived correction of the technical limitation of the BMI.

The experiments on animal models served well for knowledge acquisition and system development, but application of such complex BMI systems in humans is a yet more challenging task. Nevertheless, numerous examples have meanwhile proven the successfully implantation of prosthesis with BMIs to the nerve system and to voluntary muscles, as realized in speech devices for paralyzed patients,[24] and hand prostheses.[31] In addition, research on directly connecting remote-controlled robotic instruments to the human brain has led to astonishing progress in recent years. Hochberg et al. demonstrated restoration of the ability to grab objects in patients suffering from tetraplegia (the most severe form of paralysis in which patients lose the ability to control all limbs) using a robotic system directly connected to the brain of the patient by an implanted BMI (Figure 4).[32] They implanted a 96-channel electrode array manufactured from silicon and coated with parylene C (Figure 1 f) into the head of a patient, directly into the motor cortex. Selecting a subset of the 96 channels, those channels with the lowest firing rate for best signal-to-noise ratios, allowed extraction of brain activity signals and derivation of motion and control signals using a cable-connected remote computer for data analysis. Motion and control signals were translated to a robotic arm designed for grabbing and moving objects. Using this setup, tetraplegic patients were able to grab a coffee and serve themselves, merely by thought control of the robotic arm. Naturally, further miniaturization of the sampling electrodes, as well as integrated signal processing by on-skull electronics and remote control of a robotic system would need to be implemented in such systems to render them applicable outside of the lab. Nonetheless, the convincing results of such in-lab setups clearly indicate that "actions-from-thoughts" technology is working and that ongoing research is paving the way for functional artificial limb replacements with direct connection to the central nervous system. It goes without saying that this technology offers enormous potential to reduce the suffering of disabled individuals.

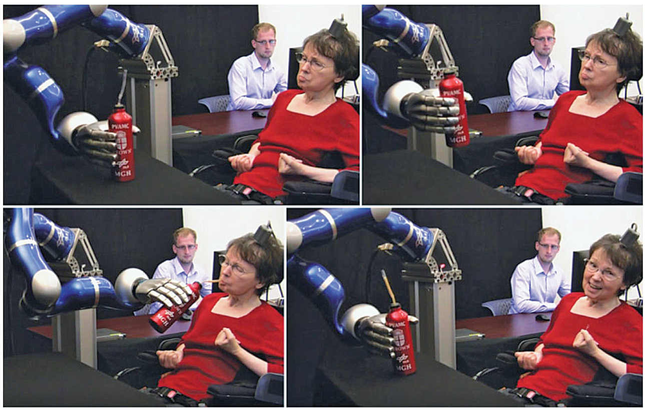


Figure 4. A demonstration of thought-controlled device operation. A patient with tetraplegia (who is unable to use her arms) has a multichannel electrode array implanted directly into the motor cortex. A remote computer continuously samples the raw neural signal, extracting motion commands for the robotic arm. This system allows her to serve herself a drink (images taken from [32]).

3.4. Signal injection: BMIs as input devices

BMIs are mostly conceived as data sources. However, this gateway to the brain can, of course, also be used to inject signals into the brain. This option represents a highly controversial ethical issue, and this new technology presents totally new challenges in bioethics.[33] One should be aware that implanted BMIs that inject signals into the nerve system or directly into the brain are already in routine use, for example, in pacemakers or DBS devices (see Section 3.1) Presently, however, these signals are neither intended nor suitable for controlling the entire organism, a scenario suggested in numerous examples of cyborg fiction. The brains of most living organism are too complex to precisely link the injection of a certain signal pattern to a certain limb actuation or movement.

The control of entire organisms is significantly simpler to achieve in lower organisms, such as insects. Respective studies have already been conducted with cockroaches, beetles,[34] moths,[16,35,36] and locusts[37] (Figure 5). In general, the brains of insects are of lower complexity and signal injection can indeed trigger a certain motion program, such as flight or movement. Studies on the use of self-sustained on-skull electronics with implanted electrodes have shown that insects can be controlled with operation times of up to 3 h. These studies have coined the term "Cyborg beetle". Part of the motivation to work on engineering insect cyborgs stems from the need for downscaling traditional aircraft designs for applications required by military, industrial, and academic communities; insects represent the gold standard in terms of aerodynamics, payload capacity, energy efficiency, and biochemical sensing capabilities. Insect cyborgs can also be controlled using freely accessible nerves, for example, sensitive neurons located in the antennae of cockroaches. By suitable microstimulation, the animal can be tricked into believing that a certain path is blocked by an obstacle, this leads the animal to change direction. Notably, devices to produce these so-called "RoboRoaches" are currently being commercialized by Backyard Brains.

Attempts to perform remote control on higher organisms, such as pigeons and rats,[38] were also conducted, and control over distances of up to 300 meters has been reported.[39] However, because signal injection into complex brains is less straight-forward, the animals were usually directed by a virtual punishment and reward strategy, through microstimulation of the medial forebrain bundle of the animals. Spatially confined stimulation may trigger directional flight of the animal, thus allowing for a certain degree of control over

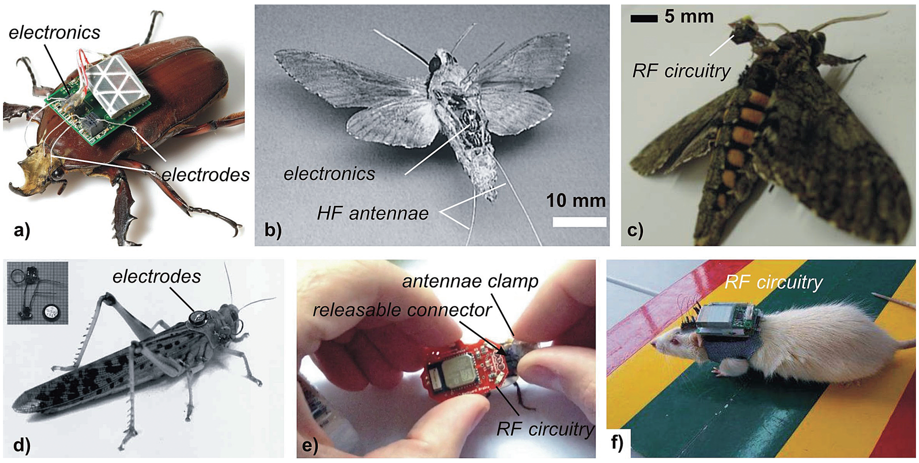


Figure 5. Examples of signal injection for the control of animal behavior. a) Cyborg beetle of *Mecynorhina polyphemus* or *Mecynorhina torquat*, for which flight control has been demonstrated.[34a] Signals are injected from the electronics mounted onto the back of the animal (adapted from [40]). b) Hawkmoth with mounted dual-channel FM transmitter, which directly connects to the flight muscles of the animal, thus allowing for control during flight (adapted from [35]). c) *Manduca sexta* moth with embedded circuitry for remote control by direct stimulation of the flight muscles. The electronics even include a microheater, which allows prewarming of the thorax prior to lift-off, thus allowing quicker takeoff (adapted from [36]). d) Locust with added telemetry system for recording and manipulation of muscle activity during flight (adapted from [37]). e) "RoboRoach" cockroach, as commercialized by Backyard Brains. Circuitry is mounted onto the back of the animal to be temporarily connected by a plug to a permanently mounted antennae clamp. The circuitry can be controlled remotely by a smart phone to stimulate the antennae, thus tricking the cockroach into believing it would run against an obstacle (image courtesy of Backyard Brains). f) A remote-controlled ratbot carrying an HF-receiver backpack that allows the operator to deliver pulses directly to the medial forebrain bundle of the animal (adapted from [41]). This approach follows the virtual punishment or reward strategy (see text for details).

its movement. It is important to distinguish that this stimulation strategy does not trigger a motion program as in insects, but it rather punishes or rewards the animal when following a designated movement pattern. Envisioned applications of such cyborg animals include observation and search-and-rescue mission tasks in hostile territory, during hostage situations or natural disaster. Obviously, the rationale and ethical aspects of such "biobots" are highly disputed.

It should be stressed that the majority of BMI research on signal injection into the central nervous system is not motivated by gaining control of movement. In medical applications, DBS has proven a suitable strategy for treatment of numerous diseases, including Parkinson's disease, epilepsy, and some psychiatric disorders. In the case of epilepsy, certain patterns of cortical activity occur seconds to minutes before an immanent seizure. Picking up these signals can trigger an autonomous BMI to induce a certain DBS pattern, usually at the Vagus or trigeminal nerves, to interrupt the epileptic process. This approach has proven to significantly reduce the risk of a seizure.[42] Cochlear implants are another example; BMIs can inject signals received from an external microphone directly into the auditory nerve. Similarly, retina implants inject signals obtained from a charge-coupled device (CCD) or light-emitting diode (LED) arrays into the optic nerve or even directly into the visual cortex of the brain. Additional examples of similar BMIs can be found in applied medicine and they have already proven their capability to increase the life quality of millions of patients.

Only two physiochemical means are currently known to inject signals into the brain, either by application of electrical potentials or by release of chemical substances. As described above, the former has been harnessed in the majority of previous work, because the sampling electrodes of an implanted BMI can be used directly for signal injection. However, the number of electrodes that can be implanted into the brain is physically limited. Therefore, extensive work is currently underway regarding the technical improvement of such devices, which is outlined below in Section 4. There, we will also highlight an alternative means of signal injection, which is based on substance release. This approach takes advantage of implantable microfluidic devices, and has also been achieved by the aid of LEDs that induce the uncaging of neuroactive substances.

4. Chemistry and Engineering of Interfaces

The aforementioned quantum leaps in complexity and performance of implantable devices are intimately linked to advances in chemistry and engineering. Two important aspects of interfacing the technical device with an organism need to be considered here: On the one hand, the interface should enable the closest possible contact between the biological and man-made systems. This calls for soft, stretchable, and biocompatible materials as carriers for electronic circuits. On the other hand, the machine should ideally be interfaced with the biological tissue such that contact points meet the length scale of functional entities of the biological unit. Such functional units of organs, tissues, and cells span dimensions from centimeters (for the nerves in muscle tissue) to tens of nanometers (for the ion channels of individual nerve cells or the synapses between neurons), and because the quality of organism–machine communication increases with an increasing number of focal points, this calls for advanced engineering of devices bearing arrays of micro- and nanosized electrodes. Recent advances in materials science indicate that both demands can be met with a steadily increasing level of sophistication.

4.1. Flexible electronics

As described above, the collection of high quality electric signals from organs, nerves, and the brain requires an intimate contact between the biological tissue and the transducer electrodes, and therefore the implantation of electrode arrays at the inside of the inner table of the skull and below the dural membrane is most desirable for ECoG to obtain high frequency signals (>30 Hz). To meet the requirements of irregularly shaped, soft, deformable tissue, arrays of electrodes mounted on flexible and stretchable carrier materials are currently being developed, and the group of John Rogers has made numerous high-impact contributions to this field. For example, they developed a stretchable form of single-crystal silicon suitable for electronic devices on rubber substrates,[43] and they established printing procedures that allow the combination of various dissimilar materials, for example, combining single-walled carbon nanotubes and single-crystal micro- and nanoscale wires and ribbons of gallium nitride, silicon, and gallium arsenide with high-performance integrated electronics on rigid and flexible substrates.[44]

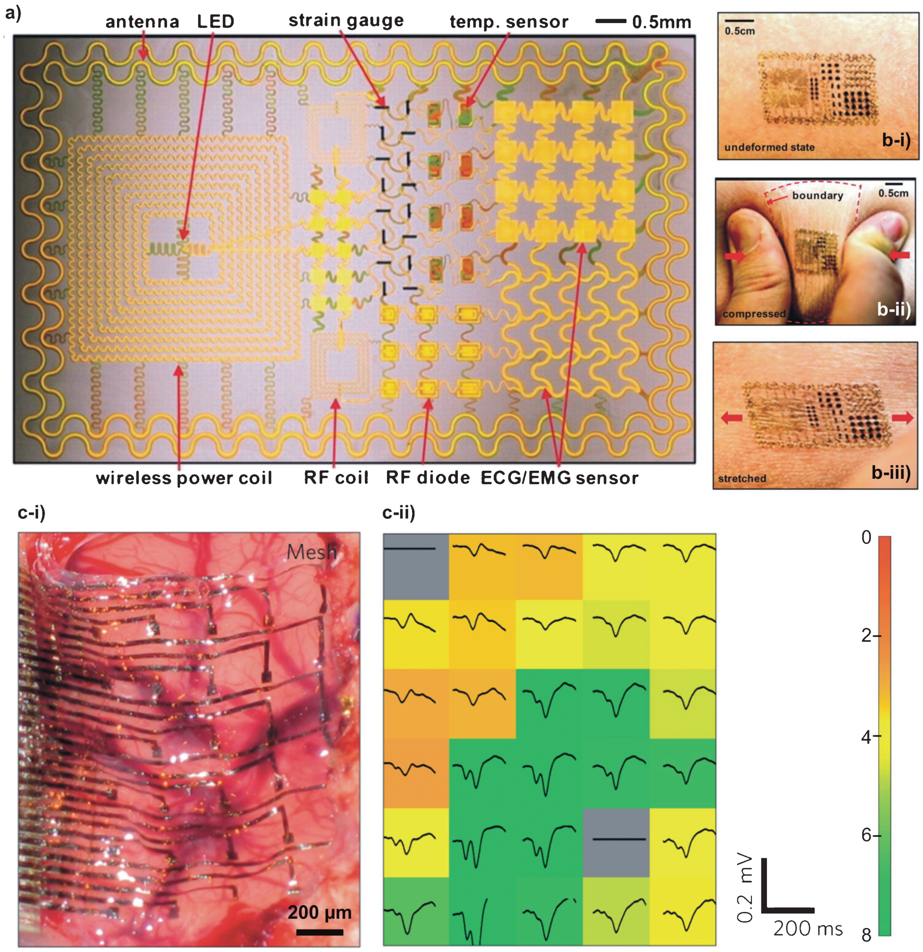


Figure 6. Stretchable electronics. a) A demonstration platform for multifunctional epidermal electronic systems (EES).[45] b) Multifunctional EES on skin in undeformed (b-i), compressed (b-ii), and stretched (b-iii) states.[45] c) An electrode array on silk fibroin on a feline brain (c-i) and the average evoked response from each electrode (c-ii), with the color showing the ratio of the root-mean-square amplitude of each average electrode response in the 200 ms window immediately after the presentation of a visual stimulus.[47]

More recently, the Rogers group has developed multifunctional epidermal electronic systems (EES), which include a variety of microelectronic elements, such as electrophysiological, temperature, and strain sensors, transistors, light-emitting diodes, photodetectors, radio frequency inductors, capacitors, oscillators, rectifying diodes, and even solar cells and wireless coils for power supply, all of which are mounted on biocompatible soft substrates (Figure 6a).[45] The active elements were fabricated in ultrathin layouts of <7 µm thickness from electronic materials, such as silicon and gallium arsenide, in the form of filamentary serpentine nanoribbons and micro- and nanomembranes, on elastomeric polyester sheets and water-soluble sheets of polyvinylalcohol (PVA; see Figure 1g). The latter were used as a temporary support for the manual mounting of devices onto the skin, similar to the transfer of a temporary tattoo. The PVA can be removed by washing and peeling, leading to perfect conformal contact of the multifunctional web-like devices with the skin through van der Waals interactions. Because of their extreme deformability and skin-like physical properties (Figure 6b), the microelectronic systems cannot be mechanically sensed by the user. Devices worn on the arm, neck, forehead, cheek, and chin were stable for several days and did not irritate the skin. The authors applied their EES to measure electrical activity produced by the heart, brain, and skeletal muscles. They also demonstrated that a device mounted on the throat of a human can noninvasively monitor muscle activity to deliver data containing sufficient information to control a computer strategy game.[45] This technology opens up entirely novel ways for non-invasive measurements of biogenic signals with a quality far beyond those of conventional, point contact electrode interfaces to the skin, and recent advances demonstrate that EES can even be printed onto the skin with conformal lamination.[46]

To minimize unwanted side-effects of such devices, the increased biocompatibility of carrier materials plays an important role, in particular, for intracorporeal applications. Based on previous work regarding the use of silk films as a substrate for transistors[48] and photonic devices,[49] Roger's group established silk fibroin as a carrier material for electronics, because it is soft, deformable, and bioresorbable.[47] They prepared ultrathin arrays (150 nm thick) of gold electrodes by photolithography on ultrathin, spin-cast films of polyimide (PI), which were then transferred to a silk film (20–

50 μm thick). The silk film allowed for convenient manual implantation onto exposed feline brain. Flushing with saline to dissolve the silk spontaneously induced conformal wrapping and intimate contact between the wrinkled brain tissue and the mesh-like device, which had a thickness of < 2.5 μm. Functionality was demonstrated by in vivo neural mapping experiments, which revealed well-resolved patterns of visually evoked action potentials from the visual cortex covered with the electrode arrays (Figure 6c).[47] In a recent continuation of this approach, the silk-based devices were used as sensor and actuator webs for large-area complex geometry cardiac mapping and therapy, as illustrated by in vivo studies in rabbit and pig models.[50] These reports impressively demonstrate that the interfacing of biological and man-made tissue can be achieved through the combined approaches of chemistry and engineering.

4.2. Chimeric device–tissue interfaces

Whereas the aforementioned developments of flexible electronics are primarily aiming towards interfacing pre-grown, mature tissue with electrical contact pads to establish effective communication between technical elements and living organisms, even more sophisticated developments are underway to establish real chimeric bioelectronic tissue. These efforts strive to combine generic concepts of 3D tissue engineering with nanowire-based nanoelectronics to eventually access the dimensionality of individual cells in living tissue, to maximize communication, and to establish complementarity between biotic and abiotic systems.[51] This direction of research and development takes advantage of properties of nanowires made from silicon and other semiconductor materials, as well as of inert metals such as gold, which can nowadays almost routinely be fabricated in any desired shape and composition, and which show enhanced coupling to artificial membranes, cells, and tissue. As the state-of-the-art of nanowire nanoelectronics for building interfaces with tissue and cells,[51] as well as nanotechnological strategies for engineering complex tissues[52] have recently been surveyed by Lieber and Langer, respectively, we will here only briefly describe two recent examples of these two groups.

Langer and co-workers have reported on semisynthetic nanowired three-dimensional cardiac patches that may have potential for the treatment of damaged heart tissue.[53] They prepared millimeter-length gold nanowires with diameters of 30 nm by anisotropic gold seed elongation and incorporated them into scaffolds produced from alginate. This nanocomposite scaffold was used for the growth of primary cardiac cells, cardiomyocytes, and fibroblasts, which were isolated from neonatal rat hearts. It was observed that the gold nanowires bridge the electrically resistant pore walls of the alginate matrix, leading to increased electrical communication between adjacent cells. As a consequence, the tissues grown in the composite material were thicker, better aligned, and contained higher levels of the proteins involved in muscle contraction and electrical coupling than cells cultured in the control alginate matrices, which lacked the gold nanowires.[53]

Lieber's group has recently reported on macroporous nanowire nanoelectronic bioactive scaffolds for the growth of semisynthetic tissue useful for applications in cellular biophysics and regenerative medicine.[54] To electrically probe the physicochemical and biological microenvironments of living tissue they developed macroporous, flexible, and free-standing nanowire nanoelectronic scaffolds (nanoES), which mimic the structure of natural tissues and contain a number of silicon nanowire field-effect transistors (FET). FETs are active detectors that respond to variations in potential at the surface of the transistor channel region. Arrayed FETs incorporated in a biocompatible carrier are thus capable of recording both extracellular and intracellular signals with subcellular resolution. The fabrication process of nanoES was based on the self-organization of coplanar reticular networks of FETs with built-in strain, which roll up into tubular 3D structures. The tubes possess nano- and microscaled features with an extremely high porosity of larger 99% (Figure 7). The particular steps of the process included: 1) Chemical synthesis of uniform silicon nanowires, which were then deposited in patterns to form single-nanowire FETs. 2) Lithographic patterning, metallization, and epoxy passivation of single-nanowire FETs to generate free-standing macroporous 3D scaffolds (nanoES). 3) Coating of the nanoES with traditional extracellular matrix (ECM) components, such as macroporous collagen, alginate, or poly(lactic-co-glycolic acid) (Figure 1h). 4) The subsequent incorporation of cells. The resulting sensor network differs from both the more conventional miniaturized 2D electrode arrays and the flexible electrodes described in Section 4.1, because the nanoES is 3D, flexible, and macroporous, therefore ideal for use as a scaffold for 3D cultivation of cells. It was shown that the seeding and cultivation of rat hippocampal neurons or cardiomyocytes (heart muscle cells), indeed led to the formation of bioelectronic hybrid tissue. The ingrown electronic sensor array allows the detection of electrical potentials from (in principle) individual cells. For example, simultaneous recordings from four nanowire FETs demonstrated multiplexed sensing of a coherently beating cardiac patch, with submillisecond time resolution.

Although the reported nanoES device had a relatively sparse density of about 60 individual FET sensor elements over an area of about 3.5×1.5 cm^2, the authors suggested that further developments could lead to much higher sensor densities, which could allow mapping of the electrical activity of tissue with high spatial resolution in three dimensions. It was explicitly noted that an additional area to develop concerns the tuning of cell interactions with nanoES through the aid of biomolecular growth determinants.[52] It seems obvious that modern methods of bioorthogonal chemical coupling[55] in combination with spatially resolved immobilization techniques[56] will provide a means for decorating such synthetic scaffolds in two and three dimensions with sophisticated patterns of biomolecular entities.

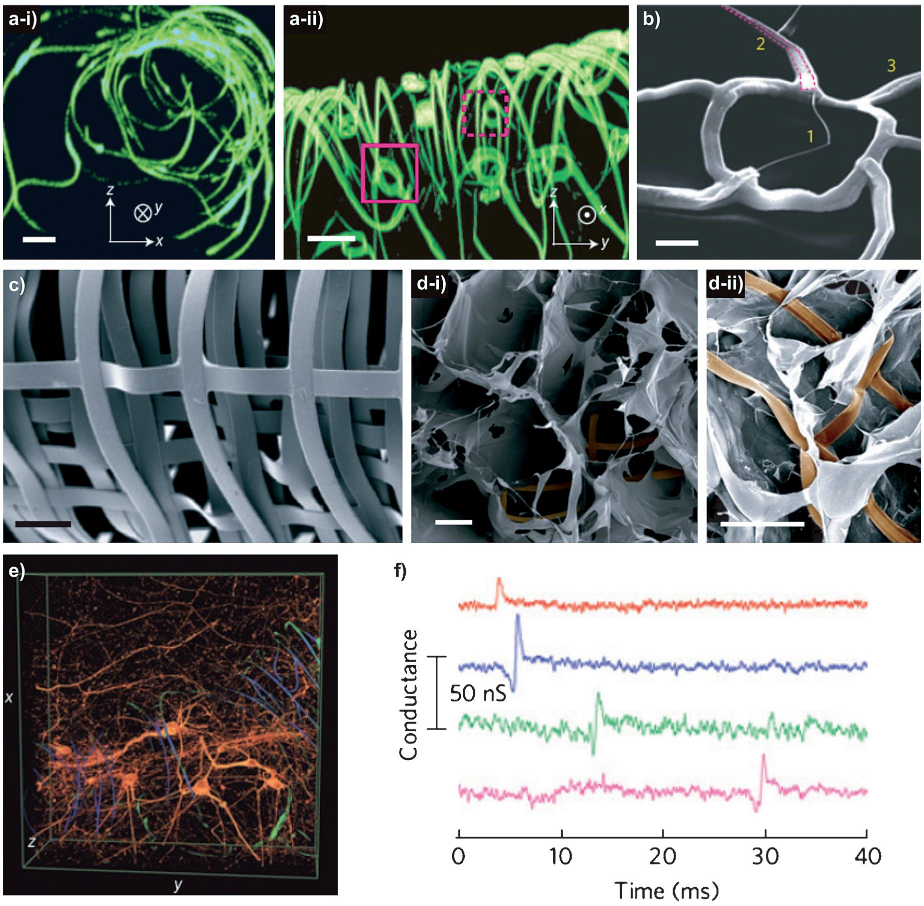


Figure 7. a) Reconstructed confocal fluorescence micrographs of a nanoES scaffold, labeled with rhodamine 6G and viewed along the *y* (a-i) and *x* (a-ii) axes. b) SEM image of a single-kinked-nanowire FET within a reticular scaffold, showing the kinked nanowire (1), the metallic interconnects (2; dashed magenta lines) and the SU-8 backbone (3). c) SEM image of a loosely packed mesh nanoES, showing the macroporous structure. d) SEM top- (d-i) and side-view (d-ii) images of a mesh nanoES/alginate scaffold; the epoxy ribbons from nanoES are false-colored in brown for clarity. e) 3D reconstructed confocal images of rat hippocampal neurons after a two-week culture inside a nanoES. f) Multiplex electrical recording of extracellular field potentials from four nanowire FETs in a mesh nanoES. Data are conductance vs. time traces of a single spike recorded at each nanowire FET (images taken from [54]).

4.3. Fluidic and optical devices

In addition to using electrical signals as output and/or input for communication between organisms and man-made instrumentation, the spatiotemporal controlled release of substances from implanted micro- and nanofluidic elements can also be harnessed to establish remote control over living organisms. Based on decades of research and development of implants for drug release, such as insulin, micro- and nanofabrication of porous silicon and its associated dielectrics (silicon dioxide and silicon nitride, among others) is now sufficiently matured to enable the engineering of nanochannel drug delivery implants or multistage logic embedded vectors for the targeted systemic distribution of therapeutic and imaging contrast reagents.[57] As discussed in Section 3.4, the majority of approaches for controlling the flight of insects have taken advantage of electrical stimulation. Implantation of highly miniaturized fluidic devices has been explored by Erickson and colleagues for controlling the flight behavior of insects.[17] The implantation of microfluidics promises not only a more intimate way of exerting control over insect flight, for example, by the administration of neuroactive reagents, but it might also allow for a more sophisticated interconnection with the animal's metabolism, which would be useful for sensing applications. For example, microfluidics were implanted in immature *M. sexta* moth pupae to enable on-command modulation of the internal levels of L-glutamic and L-aspartate acid levels in the animals, thereby inducing changes in activity behavior ranging from retarded motion to complete, reversible paralysis.[17] These chemical control schemes have recently been married in hybrid systems with implanted electrodes,[58] such that the electrical component of the system initiates and maintains flight by applying electrical pulses and the implanted drug delivery component modulates flight output power by administering neurotransmitter doses to the central nervous system.[58]

Besides applying a substance using microfluidic/electronic circuitry, controlled light-induced release of a suitably protected, metabolically active effector inside of the brain can also be used to modulate animal behavior.[59] Phototriggered release of neuroactive reagents is a very elegant way of signal injection into nerves and the brain, and this approach is even being studied as an alternative to DBS for brain repair and trauma therapy in humans.[60] Triggering the release of biochemically active molecules by means of light is a key concept in optogenetics, and this relatively young field of research has already found many applications in recent years.[61] In the ground-breaking research of Miesenböck and collegues,[62] the released substance triggers secondary effects in the host organisms, eventually leading to predictable changes in brain chemistry. Effectors may be based on existing pathways, such as the dopamine reward pathway, or ligand-gated ion channels, such as the ATP-gated calcium channel P2X2.

Specific approaches often take advantage of the genetic introduction of receptors that can be targeted with chemical effectors. For example, the ligand-gated cation channel TRPV1, which can be desensitized with the chemical effector capsaicin (Figure 8c), can be genetically introduced into

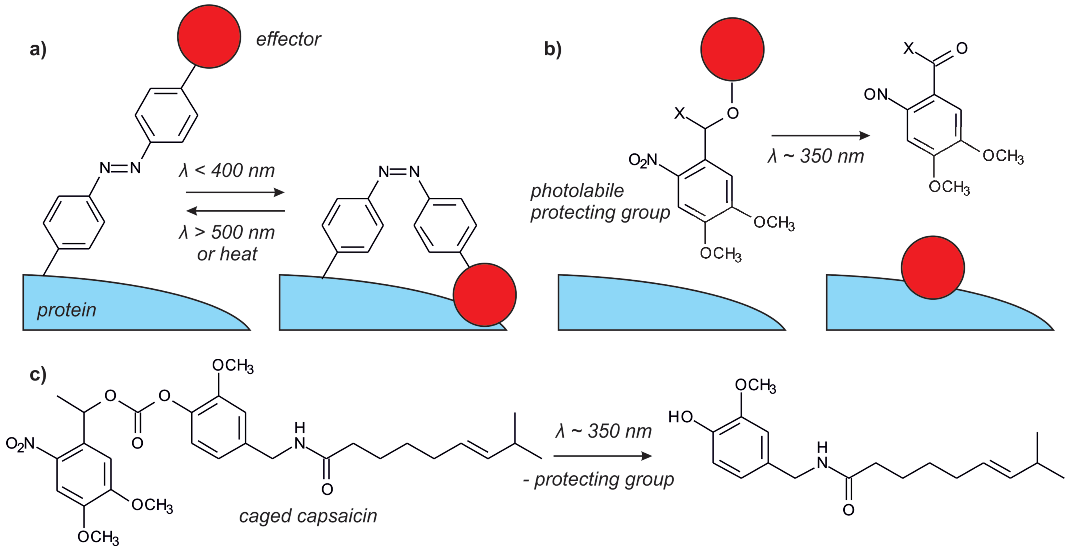


Figure 8. Representative probes used in optogenetics. Probes are commonly based either on phototriggered conformational changes (a) or photodeprotection (b) chemistry. a) Effector bound to a photoisomerizable tethered azo ligand. Irradiation with light (<400 nm) leads to photoisomerization, which brings the effector close to the target (here, a protein). The isomerization of the azo compound can be reversed by thermal relaxation or by exposure to light (>500 nm). b) General principle of caged effectors, in this case bound to the photolabile protecting group *o*-nitroveratryloxycarbonyl (NVOC; X=H). Upon irradiation (usually with light in the near ultraviolet), the effector is released. c) Caged capsaicin effector, which is released upon irradiation.

transgenic animals, such that they express the capsaicin receptor in dopaminergic neurons. Removal of the protecting group from caged capsaicin by light exposure frees the effector and triggers action potentials. This approach has been extensively studied in transgenic *Drosophila*,[63] using caged capsaicin and similar photoresponsive effectors. This controlled photorelease as well as phototriggered changes in the conformation and, thus, accessibility of binding sites of ligands (Figure 8a), are tools that have been used for quite some time.[64] The sheer number of applications arising from these two principles is highly impressive and the reader is referred to excellent reviews on the chemistry of these photoactive probes.[59b,61]

Fruit flies have the advantage of being optically transparent, thus bright-field illumination of the entire animal can be employed as means of triggering photouncaging, and thus signal injection. Interestingly, Miesenböck and colleagues showed in their seminal work that triggering of motor programs in fruit flies is even possible when the animal is decapitated.[62] However, optogenetics is less straightforward on rodents and higher organisms, which are not optically transparent. Here, in order to allow spatially controlled substance release, light exposure must be transferred to regions inside of the brain. In a very recent example, Kim et al. used an implanted wirelessly controllable on-skull electronic device containing LEDs for uncaging and signal injection into the dopamine reward pathways of rodents (Figure 9).[65] By temporal release of dopamine, the movement patterns of mice could be manipulated by reward-

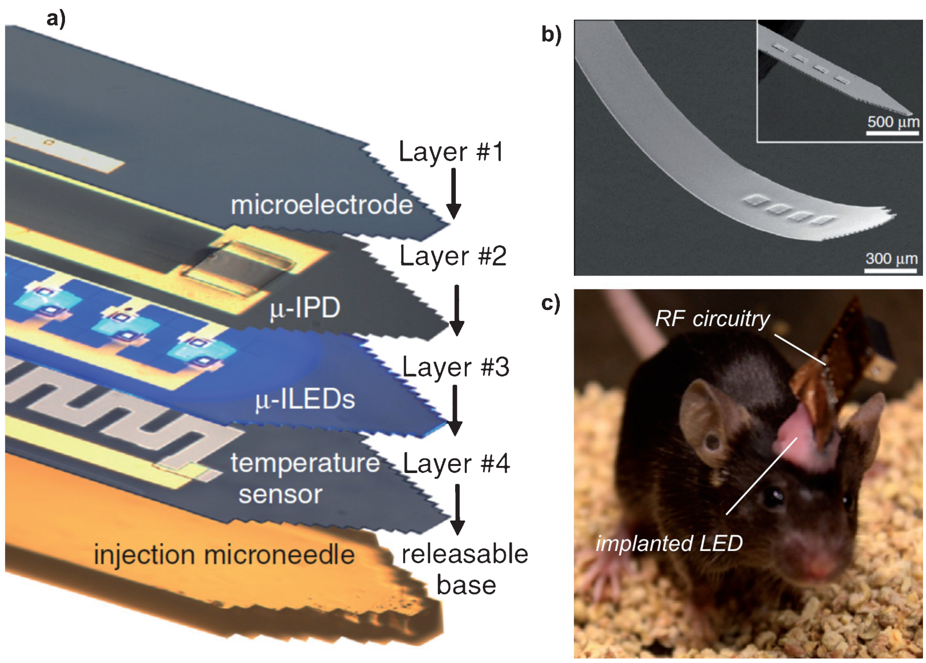


Figure 9. Electrically actuated signal injection using optogenetic tools in mice. a) Exploded view of a device to be implanted into a mouse brain. The setup consists of multiple layers with inorganic light emitting diodes (ILEDs) as the central component. The ILEDs can be actuated remotely for controlled photochemical release of effectors, which induce phasic neuronal firing of ventral tegmental area dopaminergic neurons. This enables control over the behavior of the animal. b) Scanning electron micrograph of the actual device prior to mounting onto the releasable base. The latter is only used as support during implantation. c) A mouse with the implant (adapted from [65]).

ing correct choices in its movement direction. This approach suggests that higher organisms may effectively be controlled by optogenetic tools that are remotely triggered by suitable electronics. Hence this work goes beyond that of the above-described ratbots (Section 3.4), where electrical nerve stimulation was used for virtual reward and punishment strategies. The recent work[65] combines electrical signal transmission, potentially including, but not relying exclusively on, electrostimulation, with biochemical signal injection, which acts in a more subtle and less disruptive way in the brain chemistry of the host organism.

4.4. Energy supply

In view of envisaged applications of the long-term operation of implants bearing diverse functional parts and a logic controller, the supply of energy for these devices will most likely play a key role. In the 20th century, various methods to supply implants with energy have been developed. Permanent connection to an external power source brings with it numerous severe drawbacks because a transcutaneous connection often leads to inflammation, infection, and other problems. To avoid these obstacles, wireless energy transfer, such as resonant inductive coupling, has been used to recharge the implantable batteries of, for example, cardiac pacemakers. Since this technology is not applicable for all medical applications, power consumption or supply, as well as the total size of an implant, still represent major critical issues of active implants. Fortunately, the storage of electrical energy has made significant progress in recent years. New battery technology and a tremendous reduction in power consumption of modern microelectronic systems have opened up the possibility to run electrically active implants for a long time. For example, the batteries of modern cardiac pacemakers now last for up to ten years before needing to be replaced.[66] It seems reasonable that this approach is also applicable for long-term brain implants.

The continuous harvesting of energy from the patient would represent an elegant means to energize implanted devices. The principle sources of energy in the body that have been considered thus far are thermal, kinetic, electrical, and chemical energy. The first ideas and concepts of implantable energy harvesters to create autarkic systems already appeared in the middle of the 20th century. For example, in 1966 Kennedy et al. presented a strategy of a self-powered cardiac pacemaker using piezoelectric ceramics, which were able to convert the mechanical energy of the myocard into electrical power.[67] More recently, Pfenniger et al. demonstrated a novel concept for harvesting energy from the pressure-driven deformation of an artery by using a magneto-hydrodynamic generator to theoretically generate up to 135 μW.[68] Very recently, Mercier et al. showed the possibility of using the electrical energy of the human inner ear to energize implants. They designed an ultra-low quiescent-power energy harvesting chip to harvest 1.12 nW of electrical power from the endocochlear potential for up to 5 h in a guinea pig. The harvested power was sufficient to power the chip with an integrated sensor to monitor the endocochlear potential and to transmit the measurements at 2.4 GHz.[69]

To harvest chemical energy from a body, Reynolds et al. implanted platinum electrodes into different tissues of a rat to generate approximately 0.02–0.2 μW, taking advantage of the concentration cell concept.[70] Biogalvanic cells, which are based on the implantation of a pair of different metal electrodes into the body fluid, were already utilized in the 1970s. In early attempts, zinc was used as a sacrificial anode material in combination with AgCl or Pt-black electrodes.[71] To enable a power supply of 100 μW for an implanted cardiac pacemaker over a duration of 10 years, 15 g zinc electrodes and AgCl electrodes were implanted subcutaneously in adipose tissue and into the pectoralis major muscle of human patients. Although the pacemakers could be powered over a longer period of time, the amount of zinc ions released into the patient's body, especially in the subcutaneous region, led to severe local toxic events and painful tissue reactions. Therefore the implants had to already be removed after a few months.[71,72] Another approach, which is still under development, focuses on the realization of glucose biofuel cells. This concept is based on the enzymatic oxidation of glucose on biocatalytic electrodes to harvest chemical energy.[73] These examples illustrate that numerous original approaches have already been explored to harvest energy from the host of an implant. As no suitable technology has yet been identified, this aspect again represents a wide field for chemists and engineers to develop innovative solutions for urgent medical needs.

5. Conclusions

The strategies and examples described above, as well as recent commentaries,[74] clearly indicate that the cyborg era has already begun. The widespread use of pacemakers, intracorporeal autonomous body implants with onboard logic circuits, has been firmly established for more than two decades. Similar technical aids and prosthesis, such as cochlea and retina implants, or even neuroprosthetic devices, are becoming routine parts for use in regenerative medicine. The development of so-called brain–machine interfaces (BMI), which provide means to extract signals for device operation from nerves and the brain, and which are even capable of signal injection, represents a key technology for further advancements of the field. Particular aspects of ongoing BMI developments involve, on the one hand, dimensional matching between the man-made system and the biological organism, where functional unit dimensions range from centimeters to tens of nanometers. On the other hand, the functional interfacing of technological and biological systems is of paramount importance for increasing complexity and performance. Both topics are intimately connected with the chemical sciences, be it the development of biocompatible and bioresorbable scaffolds, or the fabrication of soft, stretchable electronic parts through materials science; the micro- and nanostructuring of contact units through self-assembly and supramolecular chemistry; the development of sophisticated biointerfaces bearing biomolecular growth determinants through bioconjugation chemistry; or the establishment of novel ways of communication through biochemistry and chemical biology. As an example, biomolecular bottom-up techniques, such as those provided by structural DNA nanotechnology[75] might contribute to biointerface developments, as they offer the potential for high spatial control on the nanometer length scale combined with the perfect biocompatibility of the construction material. Owing to the fact that DNA can be processed by molecular tools of biotic origin, such as nucleases, polymerases, and other enzymes, this may even enable autonomous dynamic adjustments of technical parts in response to cellular conditions.

The development of BMI and deep-brain stimulation has already led to astonishingly complex applications in the medical sciences, most notably devices to prevent epileptic seizures or action-from-thought systems where paralyzed individuals instruct robotic instrumentation by thinking. Decades of work on animals are the foundation for these modern achievements, and the more recent work on animal cyborgs is not only contributing to our fundamental understanding of how to functionally interconnect nerve and muscle tissue with electronic, fluidic, optical, and mechanical devices. The development of these biobots also aims at the establishment of an entirely novel generation of tools, such as biohybrid robots for observation, search, supply, and rescue missions. Additional applications of the research on modern implants and cyborgs may arise from the novel approach of "electroceuticals", currently initiated by academic research institutions and the pharmaceutical industry, which are aiming to develop medicines that use electrical impulses to modulate the neural circuits of the body.[76]

The research and development activities summarized here clearly raise significant social and ethical concerns, in particular, when it comes to the use of BMIs for signal injection into humans, which may lead to modulation or even control of behavior. The ethical issues of this new technology have been discussed in the excellent commentary of Jens Clausen,[33] which we highly recommend for further reading. The recently described engineering of a synthetic polymer construct, which is capable of propulsion in water through a collection of adhered rat cardiomyocytes,[77] a "medusoid" also described as a "cyborg jellyfish with a rat heart", brings up an additional ethical aspect. The motivation of the work was to reverse-engineer muscular pumps, and it thus represents fundamental research in tissue engineering for biomedical applications. However, it is also an impressive, early demonstration that autonomous control of technical devices can be achieved through small populations of cells or microtissues. It seems reasonable that future developments along this line will strive, for example, to control complex robots through the use of brain tissue. Given the fact that the robots of today are already capable of autonomously performing complex missions, even in unknown territories,[78] this approach might indeed pave the way for yet another entirely new generation of cybernetic organisms.

In summary, the ongoing advances in the interfacing of technical devices with organisms are indicative of the fascinating and revolutionary potential of this technology. Owing to its immediate impact on human society, we should not neglect social and ethical concerns, because cyborgs certainly bear both opportunities and risks, as all groundbreaking technologies do.

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