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Bioelectronic medicine – promises and challenges

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Electrical active implants that overwrite signals of natural sensors and organs in the body might offer alternative treatment options to conventional pharmaceutical solutions. “Electroceuticals”, “electronic pills” and “bioelectonic medicine” are terms that describe approaches of neural interfaces and implants in that field of research. Widespread diseases in ageing societies like diabetes, rheumatic arthritis, asthma but also hypertension, autoimmune deficiencies like Crohn’s disease are on the research agenda of biomedical engineering groups and small and large size start-up companies. Promises have been made and have to be kept withing the next years.
An overview of the basic ideas and approaches of the field of bioelectronics medicice will be given including the different physical modalities that have been proposed to interface with the nervous system: electrical signals, optogenetic modifications, nanoparticles and ultrasound are the most prominient ones. The pathophysiological of the most often targeted diseases will be discussed with respect to the envisioned methodologies how the bioelectronics approach will target and influence the origin or symptoms of the specific disease. Target specifications of required implants will be derived and mirrored commercially available and approved implantable medical devices in clinical practice. Progress of research will be critically reviewed with respect to fundamental knowledge of the interaction mechanism. Technology readiness levels will be assessed of interfaces and implants from both, academic research groups commercial companies at an international level. New approaches do not only need novel medical devices but also further education of the medical personnel since not only pharmacological expertise is needed but also profound knowledge in electrophysiology and biomedical engineering. This overview will be concluded with a discussion of the challenges and the promised time lines as well as aspects of reimbursement of novel therapies in the health system.
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Nerve cuff electrodes for electrically interfacing with the peripheral nervous system

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Bioelectronic medicine focusses on treating conditions such as rheumatic arthritis, diabetes, hypertension, infertility and others by electrically modulating disordered circuitry of the peripheral nervous system. For doing so, the targeted nerves need to be connected to an electrical interface. Cuff electrodes provide such an interface. They consist of an electrically insulating cylinder installed around the nerve having one or multiple electrical contacts facing towards the neural tissue. Passing an electrical current through the contacts will either artificially excite fibers of the nerve, inhibit natural signal traffic to travel along the nerve or modulate the natural neural signals. We developed a flexible method for making multi-contact nerve cuffs for nerve diameters ranging from 0.1 mm to 10.0 mm diameter applying laser-micromachining of medical grade silicone rubber and high-purity platinum-iridium foil. Depending on the nerve diameter and the location of implantation (deep cavities or rather superficial locations) the cuff closure mechanism has to be adapted. The closure mechanism is responsible for 1.) a reliable fixation of the cuff to the nerve, preventing it from slipping off, and 2.) ensuring electrical insulation between the inside (nerve) and the outside (surrounding tissue) area of the cuff, which is desired for electrical stimulation, and absolutely crucial for electrical recording of nerve signals. Four closure mechanisms have been developed: a) Buckle and belt closure for very small nerves, so called 'sling cuffs', b) Self-closing split-cylinder with dual-sealing lips, called 'tunnel cuffs' c) Self-closing split-cylinder cuffs without extra seals and d) self-wrapping spiral cuff electrodes.
The cuffs have been used extensively in animal studies, providing stable electrical stimulation and recording properties, as well as in human studies for fascicle-selective nerve stimulation.

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Bioelectronic approach for diabetes therapy

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State of the art blood glucose monitoring bases on electrochemical measurements of blood droplets or via implanted sensors. The determination of the blood glucose level is a crucial parameter for type 2 diabetes mellitus (T2DM) patients. Electrochemical sensors are prone to sensor drift due to immune reactions which are hard to predict. In the body the physiological glucose sensor is located in the pancreas, i.e. in the beta cells encapsulated in the islets of Langerhans. The glucose metabolisation within these cells results in characteristic electrophysiological patterns. Phases of activity and phases of rest alternate, the duty cycle of this sum signal depends on the metabolism. As the ratio of activity to non-activity encodes the information rather than the amplitude of the signal, this method is stable and drift-free. Thus, recording the electrical activity of islets of Langerhans can be used to determine the blood glucose level. Furthermore this electrical activity directly links to the amount of insulin secreted by the very same beta cells.
Long term malnutrition results in increased activity of the beta cells. This overactivity can lead to cell damage due to the production of reactive oxygen species (ROS), one mechanism of T2DM. Alternatively, electrical stimulation of beta cells also causes secretion of insulin. This artificially induced insulin release does not induce damaging metabolism-dependent ROS production. Combining the two approaches of using beta cells in situ as glucose sensors and electrical stimulation is a novel concept to treat T2DM. In a project funded by the ministry of economics and finance Baden-Württemberg (AZ 7-4332.62-NMI/49), institutes of the innBW consortium aim on developing implant prototypes, investigate the biological basics and design the hard- and software to evaluate this therapy.

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Baroloop – selective vagal stimulation to treat hypertension

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In recent years, hypertension has become a major threat to both, patience life expectancy and healthcare systems. While many patients can be treated pharmaceutically, a larger percentage shows no response to this treatment. The human body is capable to adjust the BP to the actual demands by means of several, independent pathways. Using selective vagal stimulation, with our patented multichannel cuff electrode, we were able to modulate the inherent blood pressure signals of rats, sheep and pigs. This neuromodulatory procedure triggers the baroreflex, a body's own negative feedback loop, which decreases the blood pressure. The selectivity of our approach is a result of the geometry of our electrodes as well as the stimulation paradigm. Our Baroloop implant, which currently undergoes chronic test runs, will become a smart implant, capable to use the heart rate as a loop back control and safety feature. Our cuff electrode is manufactured in thin film technology to support superior structural solution and mass production capability, alike.

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Device-mediated-therapy – a neurosurgeon's perspective on implant design and device location

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In the recent years, non-medical treatment of common diseases like epilepsy, parkinson's and hypertension has moved in focus of research, with many different deviced being developed. Beside meeting the technical criteria for governmental approval, practical aspects for implantation should be kept in mind in order to assure the easiest and safest surgical procedure. Implantable devices should be packed in at least two sterile bags to avoid accidental contamination if one bag is damaged during opening. In the operation room, the medical assisting staff must be able to unpack the devices comfortably with minimal risk of improper, contaminating opening of the packaging. During development of an implantable device, different areas of implantation should be provided in case a patient's condition does not allow the device being placed at the standard location. If a cable needs to be positioned subcutaneously, a bidirection tunneling device should be provided in order to assure clean and safe implantation with minimal cutaneous incisions. In thin patients, a bulky device with sharp edges can cause severe impaired wound healing with possibly catastrophic consequences like infection and sepsis. In contrast, a deep subcutaneous implantation in an obese patient can compromise telemetric communication. In the clinical routine it is desirable that an implant and its MRI compatibility is easy to identify via x-ray and that sufficient information on the implant is available via Internet.