# 10

# Future Applications of the TIME

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The development of TIME electrodes was driven by the goal to investigate the treatment of phantom limb pain in upper limb amputees by selective intraneural stimulation. Can the experience with the approach be transferred in other applications? What lessons have been learned with the approach of intraneural thin-film-based stimulation electrodes embedded in polymer substrates with respect to other implantation sites, stimulation paradigms, and even other designs?

This chapter will discuss the most obvious next applications and speculate about transfer in other treatment and rehabilitation scenarios in which flexible but mechanically robust nerve interfaces could be advantageous.

Electrical stimulation to deliver sensory feedback (Pasluosta, 2017) is not only limited to patients with limb loss after amputation. Evoked somatosensory potentials (Granata, 2018) of the phantom hand cannot only be used to diminish phantom limb pain (Stieglitz, 2012) but also to deliver signals for sensory feedback in the control of artificial hand prostheses (Micera, 2016). While the benefit of information about grasp force and object compliance during grasping is beyond discussion and was achieved in a subchronic pilot study (Raspopovic, 2014), improvement of proprioception (D'Anna) and embodiment (Rognini, 2018) based on intraneural sensory stimulation could be shown in chronic implantations in three patients. Since delivery of sensory feedback by intraneural stimulation was beneficial after amputation of the upper limb, the research question arose whether sensory feedback after lower limb amputation would improve the use of leg prostheses. Would there be any additional information beyond the one that leg prostheses users get by mechanical interaction of the stump with the prosthesis socket? Preliminary results from studies over up to 4 months in three patients indicate that sensory feedback delivered via four TIME in the residual nerves in the stump does not only reduce energy consume during walking and decreases phantom limb pain (Petrini, 2017 and 2019) but also restores the dexterity, confidence, and ownership in lower-limb amputees (Raspopovic, 2017).

Further transfer scenarios have not been studied yet but include all approaches in which nerves allow transversal implantation by pulling from anatomical access and structure. Linear arrangements or arrays might cover the cross-sectional area of any medium-sized mono- or multifascicular nerve or selectively address subset of fibers in muscles for recording (Farina, 2008) or stimulation. These scenarios include both, control and drive of artificial limb prostheses as well as neuroprothetic control of paralyzed limbs. While early suggestions of double-sided electrode arrays where pure technological design studies (Stieglitz, 2001) on the nerve interface, current technology, and manufacturing readiness levels have matured and allowed chronic first-in-human studies. The requirement of electrode sites on both sides of the implanted probe can be achieved by folding of the thin substrate instead of using complex processes that drive manufacturing costs and quite often result in low yield (Stieglitz, 2002; Poppendieck, 2014). However, for clinical applications wireless systems without the need of percutaneous wires have to be developed and delivered. If the electrode array with many channels and the hermetic package housing electronic circuitry are rather concentrated like in cochlear implants (Lenarz, 2018), direct connection of the array and the hermetic package can be envisioned given that reliable pad-to-pad insulation is delivered over the life-time of the implant (Khan, 2018).

Experiences made with clinical implants that experience mechanical forces due to limb or muscle movements like cardiac pacemakers and deep brain stimulators indicate the necessity of solvable connections to minimize the invasiveness of the surgical procedure and allow for replacement of implant components in the case of (wire) failures. The lack of implantable connectors with about 16 channels or more is currently challenging research groups as well as companies to develop fully implantable systems that would be able to drive several TIMEs at a time with a single implantable pulse generator. Stimulator, package, and feedthrough technology is available (Kohler, 2017) desperately awaiting innovation in the connector development. Challenges in the course of increasing the technology readiness level and commercialization address mainly aspects of longevity. Thin-film electrodes embedded into polyimide substrates have been working reliably over up to 5 months under electrical stimulation in human studies and for more than 2 years in recording studies in nonhuman primates (unpublished data) but they still have to prove their stability. The transition between the micromachined substrate and "real" cables is one of the critical transitions known from many medical and nonmedical developments. Scalability with respect to cables and connectors is very specific for implants since approaches from telecommunication and automotive lack solutions for insulation in humid and salty environment or size restrictions. A possible solution lies in the integration of electronics with multiplexing capabilities and wireless data transmission and energy supply close to the electrode array. Technology is available and solutions could be developed with state of the art knowledge. This work, however, needs more time and money that can regularly be allocated in research project based on public funding. Private-public-partnerships, for example, made in the framework of either strategic or venture capital-based start-up companies, look for prefer to look for application with large patient numbers and high therapeutic need to be able to transfer research ideas into a "mass market" product and have a realistic chance for break even. Different levels of translational research can be foreseen in the preclinical research market or in clinical studies and application. The lowest hanging fruits include the development of flexible probes for the neuroscientific research community that mainly addresses cortical or subcortical structures in rodent animal models. Using insertion tools, polyimide-based probes show foreign body reactions that are comparable to established microprobes or even below (Boehler, 2017). When hearing research goes beyond cochlear implants toward the acoustic nerve (Lenarz, 2018), the TIME approach delivers a good combination of robustness in handling and flexibility at the material-tissue interface. It has all prerequisites to deliver spatiotemporal stimulation patterns in a resolution adequate to restore hearing at a better quality than currently existing auditory brainstem implants. Huge patient numbers would benefit from solutions in the field of bioelectronics medicine (Bouton, 2017). Widespread diseases in aging societies include diabetes, hypertension, rheumatic arthritis, and asthma with patient numbers far above those of neuronal disorders. The vision to interface target nerves close to the end organs or interfere with the autonomous nervous system via the vagus nerve opens many scenarios in which the TIME concept can deliver highly selective nerve interfaces with relatively low degree of invasiveness. However, proof-of-concept studies in small animal models have to validate the general concepts in this relatively new field or research until translational studies can bring hope and new treatment options to these patients.

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