NEUWalk Explores New Horizons in Neuroprosthetics

Novel approaches may in future allow to alleviate the burden of paraplegia and Parkinson's disease

At present, paraplegia, as a result of severe injury of the spinal cord, can barely be cured on existing rehabilitation methods. Readdressing the denervated but intact neural circuits being involved in locomotion and other fundamental body functions is not yet feasible. Hence, the diagnosis of paraplegia is a fatal burden in many ways for the affected individuals.

> About 2.5 million people worldwide live with spinal cord injury

Implementation of efficient methods to recover voluntary motor function after severe spinal cord injury (SCI) is thus not only an utmost ethical concern but also of considerable socio-economic relevance.

NEUWalk, equipped with a total budget of 11.3 Mio Euros, targets an entirely novel approach for restoring limb function in paraplegic SCI individuals: locomotor-related information is extracted from the cortical signals and used to directly engage spinal neuronal networks by electrical stimulation. Related to this, NEUWalk also investigates the potential of this method for an efficient strategy to alleviate the symptoms of Parkinson's disease (PD). Potentially, the basic

> NEUWalk opens the horizons for a completely new generation of neuroprosthetic systems for treatment of severe SCI and PD

NEUWalk concepts may also apply to other neurodegenerative diseases.

The European integrated project NEUWalk was kicked off on June 1st 2010 and is scheduled for 4 years. The consortium comprises 9 partners from leading European organizations from neuroscience and neural rehabilitation research, microelectronics, micro technology and medical industry.

> One year after kick-off, NEUWalk is on the right tracks.

During the first year the conceptual design of the NEUWalk neuroprosthetic systems including stimulator, feedback and monitoring devices have been set up. Appropriate design control guidance and auditing processes have been implemented to ensure compliance with current regulatory directives for medical products. To meet the complex demands for the chronically implantable, flexible multi-

Dr. Peter Detemple, IMM
NEUWalk Project Coordinator

Extensive experience in R&D projects for the implementation of devices for electrophysiological diagnostics and therapy of neurodegenerative disorders.

site microelectrode arrays (FMEAs) with respect to geometry, electrode density and mechanical and biological durability, alternative manufacturing technologies are under investigation.

Implementation of a Brain-Spinal Interface (BSI) is one of NEUWalk's main challenges. Here, considerable progress has been achieved in analysing the relationship between neuronal excitation patterns of the motor cortex and the provoked hindlimb gait. Related to that, a first model to predict gait-specific spinal stimulation patterns has been set up. On rats with clinically relevant SCI it could be demonstrated impressively, that voluntary locomotion can be regained when combined electrical and pharmaceutical stimulations are applied to the spinal cord.

The research leading to these results has received funding from the European Community's Seventh Framework Programme [FP7/2007-2013] under grant agreement no. CP-IP 258654

Biocompatible neuroprostheses for spinal cord stimulation in paraplegia

Figure 1:Our first FMEA with 6 electrodes on a rat spinal cord. The square-shaped contact pads are visible on the left and connected to the electrodes (Ø 200µm) via intersecting serpentine traces that provide greater elasticity than straight traces.

Development of flexible multi-electrode array (FMEA) implants

Recent studies in animal models show impressively that epidural stimulation with implanted electrodes is a first step towards restoration of walking ability. By means of methodical refinement of stimulus application and concomitant use of neuro-pharmaceuticals even more powerful movements with a higher weight bearing capacity can be achieved. In combination with repeated physiotherapy the course of rehabilitation can be further optimized (Courtine et al. 2009). Thus, also for paraplegic patients a glimmer of hope is available now, similar to the impressive success with cochlear implants or recent retinal implants. Even the motor control of artificial arms or keyboards via Brain-Computer Interface (BCI) is possible now in humans.

Biocompatible FMEAs to encode the walking mode.

The animal model with spinal cord implant allows the first systematic analysis of the relationship between various excitation patterns of afferent pathways and the response of the network with intrinsic spinal cord interneurons and afferent sensory feedback fibers. The pattern of excitation of afferent motor pathways can be experimentally varied through the implanted FMEA module and optimized with regard to the intended movement. A recent study in a chronically paralyzed paraplegic man (Harkema et al., 2011, The Lancet) has revealed the tremendous potential of this therapeutic approach. These first promising results emphasize the need to optimize spinal neuroprosthesis and stimulation protocols in animal models. For the development of high-performance and adaptable neural prostheses it is elementary to elucidate the network functionality in the spinal cord.

In the NEUWalk project, Prof. Vörös and A. Larmagnac engage primarily with the development and optimization of biocompatible FMEAs. Prof. Micera and Prof. Courtine together with their research groups investigate the use of such FMEAs in an animal model for deciphering the relevant network features, which encode the walking mode and allow a fine-tuned walking. This cooperation will accelerate application of FMEAs in later clinical studies and advance the process of rehabilitation. It is known already that the ability to walk again can be improved by active training. In combination with simultaneous epidural stimulation this physiotherapy process could be even faster and also allow for a more stable walking.

Currently, the focus is on novel powerful multi-electrode systems. The objective is clear: the neuroprosthesis must be flexible in order to adapt perfectly to the anatomy of the spinal cord. It must be biocompatible and must not cause any tissue damage. Ideally, the device should also offer a number of stimulating electrodes (currently a maximum of 6) to allow specific multisite activation. The aim of the development is powerful FMEA spinal implants that allow accelerating human rehabilitation. The ultimate goal is the fine tuning of complex walking- and stepping movements or stair walking, respectively. Initial data from animal models are promising. Adapted FMEAs for first clinical testing are already expected in about two years.

Reference:

Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, Song B, Ao Y, Ichiyama RM, Lavrov I, Roy RR, Sofroniew MV, Edgerton VR. Nature Neuroscience 2009 Oct; 12(10):1333-42.

Prof. Janos Vörös, University and ETH Zurich

With his team, the Laboratory for Biosensors and Bioelectronics, he studies the interface between electronic devices and their biological environment.

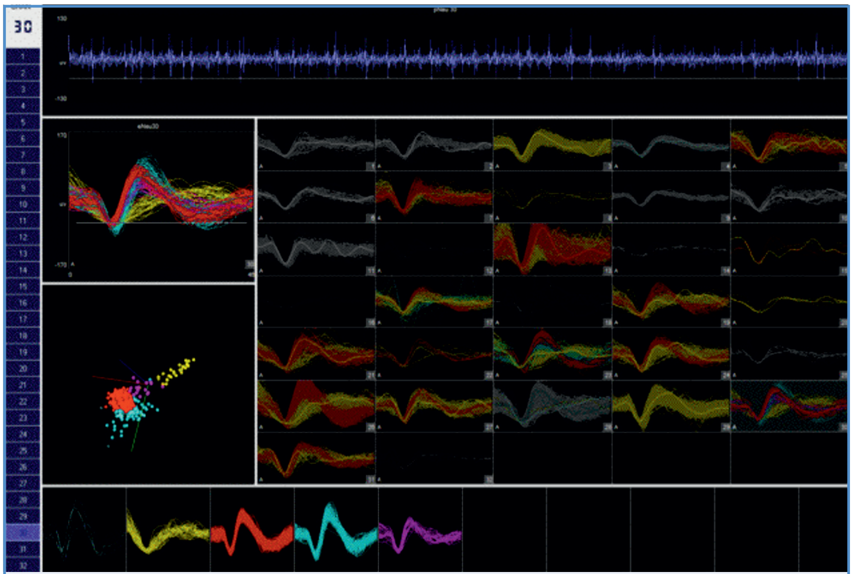
Alexandre Larmagnac, ETH Zurich

Since 2008 he is researching cell/electrode interactions and implantable devices with embedded electronics in Prof. Vörös team.

Brain-Spinal Interface (BSI) for voluntary control of goal-directed locomotion

Development of a BSI after spinal cord injury – Decoding of supra-spinal afferent excitation patterns

Intrinsic spinal cord circuits can be reactivated using a combination of epidural electric stimulation, pharmacological stimulation and physiotherapy. In animal models with experimental spinal cord injury (SCI) this technology allows for simple walking activity (Courtine et al., 2009). According to these studies, central neuron pattern generators at the spinal cord level can thus be excited which then are modulated by proprioreceptive feedback input from the extremities. Animals are even capable of partially supporting their own body weight in these experiments. In healthy animals, afferents from motor cortex converge on these circuits providing central nervous control and coordination for spinal neurons. Yet little information is available on the principles of higher supraspinal coding in the motor cortex, particularly in light of various voluntary motor tasks. Still unknown for example, is how the descending afferents modulate these circuits. Or, which cortical excitation patterns initiate a certain voluntary movement of legs and then accurately control the variety of complex movement types.



Decoding of cortical signals with spike analysis programs for identification of movement specific algorithms used in BSIs.

For development of effective neural prostheses these questions of cortical coding of voluntary locomotor movements are of fundamental importance. They are a key element for functional programming novel BSIs aimed to restore independent walking in spinal cord injury. It is known from neurophysiological studies that the essential signals for voluntary movement are caused by distributed coding in the complex network of the cortex. These highly integrated neuronal excitation patterns are passed then via descending pathways to the neuronal switching stations in the spinal cord. As part of NEUWalk project the research group led by Prof. Micera and Dr. DiGiovanna examines the decoding of such central nervous system patterns in the motor cortex, especially complex movements such as climbing of steps and overcoming of obstacles. Based partially on these data, algorithms for a powerful neuroprosthetic BSI can be developed enabling the voluntary motor control by epidural electrical stimulation.

Currently, the studies focus on the neuronal decoding based on multi-site recording in the motor cortex of healthy rats. As a first step healthy animals are conditioned to specific locomotor tasks. Then, the associated neural excitation patterns are read out in neurophysiological experiments via electrodes permanently implanted in the motor cortex. The data include relevant partial information about the desired coding patterns that correlate with specific locomotion types. Long-term recordings and statistical analysis ensure that an accurate mapping exists between a particular locomotion task – e.g. the movement of the leg by a certain angle – and a particular neural code.

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Prof. Dr. Silvestro Micera, Swiss Federal Institute of Technology Zurich

Hybrid neuroprosthetics for the restoration and assessment of sensory-motor function in disabled persons is his devotion. He received the Early Career Achievement Award of the IEEE Engineering in Medicine and Biology Society.

Dr. Jack DiGiovanna, ETH Zurich

As part of Prof. Miceras Neuroprosthetics Control Group at the Automatic Control Laboratory of ETH Zurich he focuses on learning prosthetic control and interactions between natural and artificial beings.

Brain-Spinal Interface for voluntary control...

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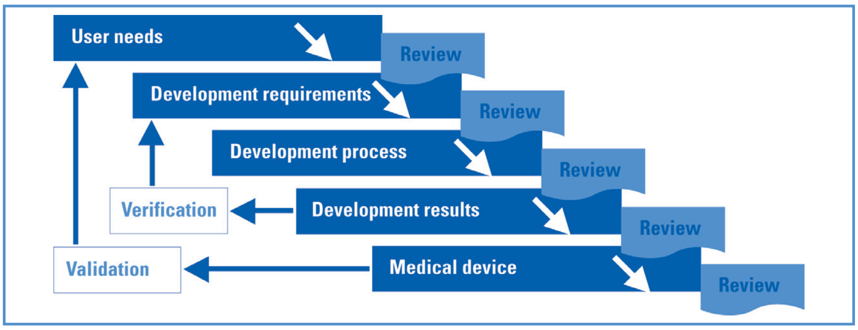
This analysis requires sophisticated mathematical and statistical tools. A first step in finding complex neuronal response patterns is to detect and classify extracellular action potentials. This spike sorting can be done with commercially available programs and also custom analysis tools have been developed and applied for more precise sorting. The decoding of various parameters of locomotion can provide first conclusions about which decoding algorithms will be compatible with a BSI. The functionality of these algorithms will then be checked in a second step in an animal with induced SCI: Using an implanted BSI the coding patterns for specific voluntary motor actions are transmitted back to the spinal cord in form of electrical stimuli in order to control spinal circuits. After appropriate training, the quality of the identified algorithms can be verified.

Decoding useful control signals will allow us to 'close the loop', thus permitting the rat to modulate spinal stimulation through her motor cortex. This will provide the BSI with an additional excellent decoder – the brain. We hope that demonstrating this adaptation and control will motivate developing such strategies in future therapeutic approaches.

Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, Song B, Ao Y, Ichiyama RM, Lavrov I, Roy RR, Sofroniew MV, Edgerton VR. Nature Neuroscience 2009 Oct;12(10):1333-42.

From Ideas to Real Products



Designing and developing new medical devices is a very complex task. And implants are the most complex medical devices. To establish an implant prototype for clinical trials, regulatory affairs have to be implemented in an early stage. A helping tool can be the **design requirements** and **design control guides**. For the success of NEUWalk it is essential that all particular subsystems are technically integrated into a complete and implantable technical system. Therefore it is mandatory to establish essential requirements from the very first plans and development activities. The product design has to comply with safety and performance to the design guidelines, which themselves comply with the design control guidance for medical device for manufacturers according e.g. to FDA 21 CFR 820.30.

Within NEUWalk the industrial partners inomed Medizintechnik GmbH and Mega electronics are focusing on the identification and adaption of the specifications and the interfaces between all single work packages taking into account the necessary requirements for medical products. The industrial partner Finetech Medical is contributing through their long experience in human implants.

In the first months of the project a design control guide was implemented to assure that all partners design and develop according to the requirements of the Medical Device Directive (MDD) 93/42/EEC and the active implantable medical devices directive (AIMD) 90/385/EEC.

In year one an internal questionnaire had been developed to collect ideas, possible solutions and opinions about the development requirement specifications from different NEUWalk partners, emphasising the feedback of the clinical partners. This questionnaire led to the Requirement Specification. The questions covered the functionality of the implant, if the implant electronics are passive (powered from outside) or active (internally powered, e.g. battery), the size of the implant and the duration of the implantation. Questions about the number, size and alignment of the electrode arrays are also of great importance. All regulatory documents are frequently updated and support the agreement on certain crucial design parameters of the implant. Thus marking the first step of many for a medical product to help mankind.

Thilo Krüger, inomed

Krüger studied technical cybernetics and focused with his PhD in biomedical engineering. His interests are in the interface between human and machine and monitoring nervous structures.

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CONTACT
Institut für Mikrotechnik Mainz GmbH
Carl-Zeiss-Straße 18-20, D-55129 Mainz
Dr. Peter Detemple
Tel: +49 (0)6131 990-318, E-Mail: detemple@imm-mainz.de

Design - Layout
FeinDesign Silke Wolter
Tel: +49 (0)6196 523 69 46, E-Mail: swolter@t-online.de