Final Programme

STW Perspective programme

System Identification and Parameter Estimation of Neurophysiological Systems (NeuroSIPE)

NeuroSIPE: diagnostic tools for neurological disorders

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1 Executive Summary

The goal of the NeuroSIPE program (System Identification and Parameter Estimation of Neurophysiological Systems) is to improve and develop new diagnostic tools for neurological disorders, through the use of closed-loop system identification techniques for the peripheral and central nervous system.

The central nervous system controls body functions and initiates actions through an integrated system of multiple control (or feedback) loops. The challenge in NeuroSIPE is to assess the functioning of an intact feedback system **in vivo**, since cause and effect are intermingled. A closed-loop system identification approach is essential to assess the separate feedback loops of the CNS in an intact functional system, and to quantify the parameters of the feedback loop..

The primary focus of NeuroSIPE will be on, but not limited to, four application domains, i.e. the neuromuscular system, the autonomous cardiovascular system, the thermoregulation system and the pain regulating system. The socio-economic impact of neurological disorders on society is huge, given the high incidence and prevalence. NeuroSIPE is unique in the sense that it focuses on a system's approach and not on a specific neurological disease or subsystem. This approach used across the NeuroSIPE program will bring together technical and medical specialists from different fields and application domains, which will enhance cross-fertilization required for the necessary breakthroughs in neurophysiological assessment.
Companies involved in the NeuroSIPE program have a background in mechatronics, electronics, software development, mechanics, etc., and are typically high tech, innovative SMEs. A number of these companies have experience in the biomedical engineering field and some companies seek opportunities to use their expertise to enter this market. Participating companies may be able to commercialize the equipment, protocols and software interfaces as developed in NeuroSIPE for rehabilitation centers and neurological units in order to quantify the disease progress and the effect of medication, and eventually to diagnose patients with neurological disorders. Another user group are the clinical researchers e.g. in pharmaceutical studies, who can use more accurate and objective data to decrease the cohort size in clinical trials.

The ambition of the NeuroSIPE program in short is expressed as:

- Development of key technology that meets the demands for advanced closed-loop system identification and parameter estimation applicable in the neurophysiological domain.
- Methodological development of perturbation equipment and recording equipment useful for system identification methods applied to the neurophysiological domain.
- Establishing a research community in the Netherlands that enables the dissemination and exchange of design methods, technology and prototypes of NeuroSIPE.
- The initiation of a national center of excellence on neurophysiological recording methods that will grow to one of the world leading centers.

2 Technology landscape

2.1 Introduction to NeuroSIPE

The central nervous system (CNS) is the initiating and regulating organ in the human body. Many feedback loops are present, with sensors and actuators, to control the behavior in many organs, e.g. in the heart, the musculoskeletal system, blood pressure, bladder, and skin. The combination of controller, actuator, plant (system to be controlled) and sensor form a closed-loop system, in which the dynamic behavior can be quite unpredictable from the dynamic behavior of the individual components. Still, only very few studies take the closed-loop character of the CNS into account when recording signals and assessing the function of subsystems of the CNS. As an example, increased joint stiffness in stroke patients can be caused by increased stiffness of muscle tissue or increased muscle activation through feedback from stretch sensors. In case of the former, surgical intervention may be applied while for the latter case administration of anti-spastic drugs are to be chosen. Unfortunately, in daily clinical practice increased joint resistance is assessed by manual movement of the joint using ordinal scales (Ashworth and Tardieu tests) from which the different subsystems (muscular and neural in this example) can not be discerned.

The impact of neurological disorders on the society is huge, given the incidence per year and prevalence in the Netherlands[1-7] of well-known diseases like stroke (incidence 32000, increase 30-45% expected in 2015, prevalence 217000), Parkinson's disease (incidence 2400, prevalence 12000), children with cerebral palsy (2 per 1000 births), Multiple Sclerosis (incidence 1500, prevalence 15000), ALS (incidence 300, prevalence 1000) and Alzheimer's disease (incidence 31000, prevalence 180000). Also for less well-known diseases disturbing the control of (urine) continence, blood pressure, renal function, etc., are still in the early years of discovering the regulating role of the CNS. Furthermore pain related diseases like CRPS, RSI, whiplash, low back pain and fibromyalgia etc., are still in the infancy to discover the (dys)function of the regulating system.

The last decades strong research efforts were made especially in the field of neuro-imaging, in order to understand more of the special functions of the brain. Imaging techniques are more descriptive in nature and can visualize brain activity. The activity of certain brain areas is visualized through measurements of the oxygen depletion of the blood using fMRI (functional MRI), or the course of nerve pathways using DTI (Diffusion Tensor Imaging). Despite all these efforts, many brain diseases are still poorly understood. Many stroke patients suffer from spasticity, yet the cause of spasticity is not clear. Patients with Parkinson's disease have severe tremors and stiffness at the same time, both caused by dysfunction of particular brain areas (especially the basal ganglia), but the exact cause-effect and inter-relationships still need to be revealed.

Currently, symptoms of neurological disorders are often assessed in a qualitative and subjective way through simple tests and questionnaires. Current neurophysiological assessment techniques do give objective measures, but in general: a) use passive conditions, b) use artificial stimulation and c) measure only parts of the system. The challenge in NeuroSIPE is to assess the functioning of an intact feedback system **in**

vivo, where cause and effect are intermingled.

2.2 International landscape of NeuroSIPE

Worldwide there are only a few research groups who combine the expertise in system and control engineering with neurophysiological knowledge. Table 1 gives and overview of the most important neuroscience research groups. Arguably, the largest concentration of such neuroscience research groups is located in Chicago, USA, at Northwestern University. There is a close collaboration between Delft University of Technology and Northwestern University. Prof. F.C.T. van der Helm has an adjunct professorship at NWU, and prof. J. Dewald is intended to become part-time professor at Delft.

Table 1: Overview of the most important international neuroscience research groups

Key research areas in the field:

- Neuroscience and motor control
    - Northwestern University and Rehabilitation institute of Chicago, USA
        - Zev Rymer, Eric Perreault, Fernando Mussa-Ivaldi (Sensory Motor Performance Program)
        - Jules Dewald (Neuro-imaging and motor control laboratory)
        - Todd Kuiken (Neural engineering Center for artificial Limbs)
        - Lee Miller (Dept. of Physiology, Feinberg School of Medicine)
        - CJ Heckman (Animal studies)
        - James Houk (Proprioceptive studies)
        - Norman Hardin (CRPS)
    - John Hopkins Hospital, Baltimore, USA
        - Reza Shadmehr (Motor control)
    - University of Copenhagen, Denmark
        - Jens Bo Nielsen (Institute of Exercise and Sport Science & Dept. of Medical Physiology)
    - Sensorimotor institute (SMI), Aalborg, Denmark
        - Thomas Sinkjaer: Neuromuscular control
        - Lars Arendt-Nielsen: Pain
- Human Balance Control
    - John Jeka & Tim Kiemel (Univ. of Maryland, USA)
    - Bob Peterka (Oregon Health & Science University, Portland , USA)
    - Thomas Mergner (Univ. Freiburg, GER)
    - Ian Loram & Martin Lakie (Manchester Metropolitan University, Mancherster,UK)
- Assessment of stroke:
    - Neville Hogan, Hermano Krebs (MIT, USA)
    - Mehdi M. Mirbagheri (Northwestern University, Chicago, USA)
- Spinal cord injury:
    - Joe Hidler, National Rehabilitation Hospital, Washington DC, USA
    - Bob Kirsch, Case Western Reserve University, Cleveland, USA.
- System identification of the neuromuscular system:
    - Bob Kearney (McGill University, Montreal, CAN)
    - Etienne Burdet (Imperial College London, UK)
    - Mitsuo Kawato (Computational Neuroscience, ATR Institute, Kyoto, Japan)

2.3 Distinctive character of NeuroSIPE

Two aspects make NeuroSIPE a unique program. First, NeuroSIPE combines the stateof-the-art insights in system identification and control engineering with the knowledge of the central nervous system and modern measurement instrumentation, which is only done by very few research groups in the world. Second, NeuroSIPE focuses on a system's approach and not on a specific neurological disease or subsystem.

Unique in the world, we have assembled a multi-disciplinary group of researchers with the desired expertise: neurologists and rehabilitation physicians who have knowledge of the CNS and it's effect on behavior, neurophysiologist who have knowledge about neurophysiological measurement assessment techniques, and control engineers who are experts in system identification, and also have ample experience in collaborating with medical scientists. In addition, world-wide market-leading companies in force-controlled robot manipulators (a.o. MOOG FCS, ForceLink, Demcon), behavioral neurological recording equipment (a.o. Noldus IT b.v., Motek Medical b.v.) and electrophysiological equipment (a.o. ANT, Medtronic, Philips, TMSi) are present, which will strengthen the know-how within the community of interest and the application worldwide. The challenge will be to combine this body of knowledge for a new and innovative methodological approach to neurological measurement instruments.

NeuroSIPE does focus on a system's approach and not a specific neurological disorder or application domain. This will enhance cross-fertilization of methods between the different application domain (neuromuscular, cardiovascular, thermal, pain). The NeuroSIPE program offers the opportunity to increase the size and momentum of the neurophysiological, neuro-engineering and neuro-rehabilitation research communities in a unique program, which is likely to provide the Netherlands a leading position in the development of neurophysiological measurement techniques and experimental protocols for clinical studies.

In many scientific publications, electrophysiological signals measured inside the feedback loop are processed without acknowledging the closed-loop properties. Then, the cause-and-effect of the signals can not be assessed. For example, EMG (representing muscle activity) and force / position are being recorded during a motion. EMG activity will result in the muscle force, but muscle force and change of position as picked up by muscle sensors (muscle spindles, Golgi tendon organs) will result in change of EMG activity as well through the Central Nervous System. In order to solve this circular causal problem, closed-loop system identification theory dictates that an independent perturbation signal with well-known properties should be injected in the feedback loop. The resulting change in measured signals will enable to distinguish cause-and-effect in the forward and backward path, and moreover, to estimate the dynamic transfer function of elements in the feedback loop.

Van der Kooij et al. (2005), participating in the NeuroSIPE program, showed that about 75% of balance control studies published in the international scientific journals neglected the closed-loop system properties, leading to erroneous results and misinterpretations[8]. This opens the opportunity for the NeuroSIPE participants to work at the frontiers of science. In the NeuroSIPE program, international leaders in system identification and parameter estimation (e.g. Verhaegen) collaborate with human motor control specialists (e.g. van der Helm, van der Kooij, van Dieen, Harlaar, Schouten), electrophysiological signal processing specialists (e.g. Veltink, Buitenweg) and medical specialists in the neurological field (e.g. van Hilten), rehabilitation medicine (e.g. Arendzen, Geurts) and pain (e.g. Huygen). These medical and technical specialists know each other well, and have the potential to bring the program to a new scientific level.

3 Goals and Ambition

The goal of the NeuroSIPE program (System Identification and Parameter Estimation of Neurophysiological Systems) is to improve and develop new diagnostic tools for neurological disorders, through the use of closed-loop system identification techniques of the peripheral and central nervous system. The CNS controls body functions and initiates actions through an integrated system of multiple control (or feedback) loops. The challenge in NeuroSIPE is to assess the functioning of an intact feedback system **in vivo**, where cause and effect are intermingled. A closed-loop system identification approach is essential to asses the separate feedback loops of the CNS in an intact functional system.

The ambition of the NeuroSIPE program in short is expressed as:

- Development of key technology that meets the demands for advanced closed-loop system identification and parameter estimation applicable in the neurophysiological domain.
- Methodological development of perturbation equipment and recording equipment useful for system identification methods applied to the neurophysiological domain.
- Establishing a research community in the Netherlands that enables the dissemination and exchange of design methods, technology and prototypes of NeuroSIPE.
- The initiation of a national center of excellence on neurophysiological recording methods that will grow to one of the world leading centers.

The projects in the NeuroSIPE program will have in common the mathematical and control engineering approach to tackle the complex problems associated with closed-loop system identification. Similar perturbation signals must be designed, and high-end recording equipment must be developed for in vivo recordings inside the feedback loop. The participating groups will profit from the broad body of knowledge in the NeuroSIPE community, and from the potential to use inventions in one application area also for the other application areas.

Milestones for the NeuroSIPE program will be:

- Application of the newest development in system identification techniques for time-varying (adapting) and non-linear control systems.
- Quantification of measures for motoric disorders like spasticity, dystonia and tremor.
- One diagnostic method for a patient group with neurological disorder, which can be used in a Randomized Clinical Trial.
- For each of the specified application areas: A model structure of the feedback control loop, and a methodology (perturbation and recording equipment) to estimate the model parameters.
- About 4-5 patents enabling companies to enter a new market in neurophysiological measurements.

3.1 The envisaged trend change in NeuroSIPE development strategy

The central nervous system acts as the controller in many feedback loops, regulating for example the neuromuscular, cardiovascular, thermal and pain function. In the control engineering field, many techniques have been developed which deals with the system identification and parameter estimation of closed-loop systems. However, existing techniques in measuring neurophysiological functions are based on an open-loop approach to the feedback loop, or only measure parts of the feedback loop, and therefore might lead to erroneous results[8-9].

Examples of existing techniques are:

- Deep tendon reflex: By tapping on the muscle tendon, a reflexive (i.e. feedback driven) contraction is evoked. Mostly the reaction is subjectively classified, sometimes EMG (electrical activity of the muscle) responses are recorded.
- Hoffman-reflex (H-reflex): By electrical stimulation of the peripheral nervous the sensory as well as the motoric nerve fibers are stimulated. The H-reflex is calculated as the quotient between the H-wave (EMG activity due to indirect stimulation of the muscle, passed through the sensory nerve fibers and the spinal cord) and the M-wave (EMG activity due to direct stimulation of the muscle through the motoric nerve fibers). Though often used during tasks, the H-reflex passes the sensors in the muscles and the skin, and therefore it does not differentiate between position, velocity and force feedback.
- Thermography: Temperature recordings of the skin.
- Somatosensory Evoked Potential (SSEP): Recording of electrical activity in the spinal cord and/or cortex due to electrical stimulation of the sensory nerve fibers. Often used in patients to demonstrate the continuity of afferent nerve fibers, but it is not used in a functional context.
- Transcranial Magnetic Stimulation (TMS): By transcranial magnetic stimulation, the primary motor neurons in the cortex can be stimulated, which will result in muscle contraction. TMS shows the continuity of the motoric nerve fibers, but it is seldom used in a functional context.

There is a demand for a new technology, in which the neurophysiological control behavior of the central nervous system can be measured during functional tasks, using a correct mathematical approach in order to avoid errors. Some existing techniques for the different application domains have proven successful in accuracy and discriminate ability. Clustered by their application these techniques comprise robot induced joint movements for sensory-motor research[10-15],neural conduction properties using electrical stimulation[16,17] and thermal perturbations using thermal plates for blood flow regulation[18]. These techniques should also be possible to apply for the cardiovascular and pain system.

Four basic steps are necessary in the closed-loop system identification approach:

1. The function of an intact feedback loop can only be assessed through the application of an **external perturbation signal, or stimulus,** with well-known properties, e.g. force perturbations using robot manipulators to investigate neuromuscular control, or a cold plate for thermoregulation.
2. Subsequently, the effects, or **response**, of this external perturbation at various points inside the feedback loop must be **measured**, e.g. position, force and EMG measurements, or thermography.
3. Advanced closed-loop system identification techniques make it possible to quantify the **dynamic transfer function** between the external perturbation and the internal signals inside the feedback loop.
4. Subsequently, **dynamic models** of the controller, sensors, actuators and the controlled system (skeletal, heart, thermodynamics, etc.) are required to obtain quantitative and physically interpretable parameters from the identified transfer functions

3.2 Methodological and Technological Challenges

Major limitation is that all existing techniques to quantify neurophysiological function ignore one or more of the following features that are characteristic for neurophysiological systems in vivo:

- Closed loop interaction between organs and sensors
- Nonlinear response to the imposed perturbation
- Adaptation in time to the imposed perturbation.
- Appropriate perturbation methods

As a consequence, it is not possible to quantify behavior over a wide range of physiological conditions which hampers our understanding of behavioral changes when external condition varies, such as occur in the natural situation.

Technical advances to be made are:

1. **Closed loop approach**. Application of closed loop identification paradigms to neural control of physiological systems, which will require a change of mindset from the clinicians to deal with control engineering issues, and from the technicians to deal with the variability and adaptability of the biological system. A variety of mathematical techniques will have to be tuned for applications in the medical domain.
2. **Nonlinear models**. Development of nonlinear physiological models that capture a wide range of behavior and able to be parameterized from recorded data. Nonlinear models do exists for various parts of the human system (muscle models, muscle spindle models, neural network models of the CNS) but these models are mainly used for simulation having a numerous amount of parameters. Main challenge will be to build models having a minimum number of parameters without loosing much of its descriptive ability and that these parameters can be uniquely estimated from recorded data.
3. **Time variant (TV) behavior**. Identification of physiological properties that change over time are hard to identify. Time-varying identification algorithms are very new and have not yet been applied for biological systems.
4. **Perturbation equipment**. Design of perturbation systems for application of the required test stimuli needed for persistent identification of the physiological system. As dynamic properties may be on a short timescale from e.g. from fast neurochemical processes, stiff tissues or fast pressure waves, system states (position, force, temperature etc) must be changes on a comparable fast time scale. This impose certain design constraints on active devices, being high bandwidth and powerful.

The NeuroSIPE program has adopted the viewpoint that neurophysiological functioning in its widest sense can only be understood when identification techniques deal with the aforementioned fundamental physiological features. Information from the medical, neurophysiological and control engineering research fields needs to be integrated to develop the next generation of identification paradigms that are able to identify nonlinear and time variant behavior in the closed loop. Such new paradigms will quantify physiological parameters that are meaningful to whole system performance and establish the bridge between etiology and impairment.

Two major methodological steps are discerned at arrive to new techniques that are scientifically warranted, applicable for usage as full clinical application as a new diagnostic tool.

1. **Additional diagnostic value** of any new technique must be proven against an existing golden standard of measurement. The NeuroSIPE program aims at the identification of physiological properties into quantitative numbers while existing standards are often expressed in ordinal or nominal units that are rather fuzzy and subjective. Almost by definition, this makes comparison with, and possible substitution of, existing measures difficult. Most challenging is to prove the new technique is better than existing techniques based on validation studies, using the improved predictive value of the new methodology.
2. **Improvement of existing treatment** modalities when using new identification techniques. Ultimately, it must be tested whether and to what extent the newly developed identification techniques contribute to improvement of function. Ultimately, the developments from the NeuroSIPE program should be validated in longitudinal cohort studies (e.g. RCT's) comparing existing standards and the new identification techniques.

Strategy of the NeuroSIPE program is to facilitate technique development in different subsequent stages from baseline theory development to full clinical application/testing to be ready for prospective clinical studies, i.e. selecting treatment modalities and longitudinal monitoring of the patient's progress.

4 Application fields

The primary focus will be on four application domains of the CNS (although other application domains are not excluded), see Figure 2:

- Neuromuscular system
- Autonomous cardiovascular system
- Thermoregulation system
- Pain system

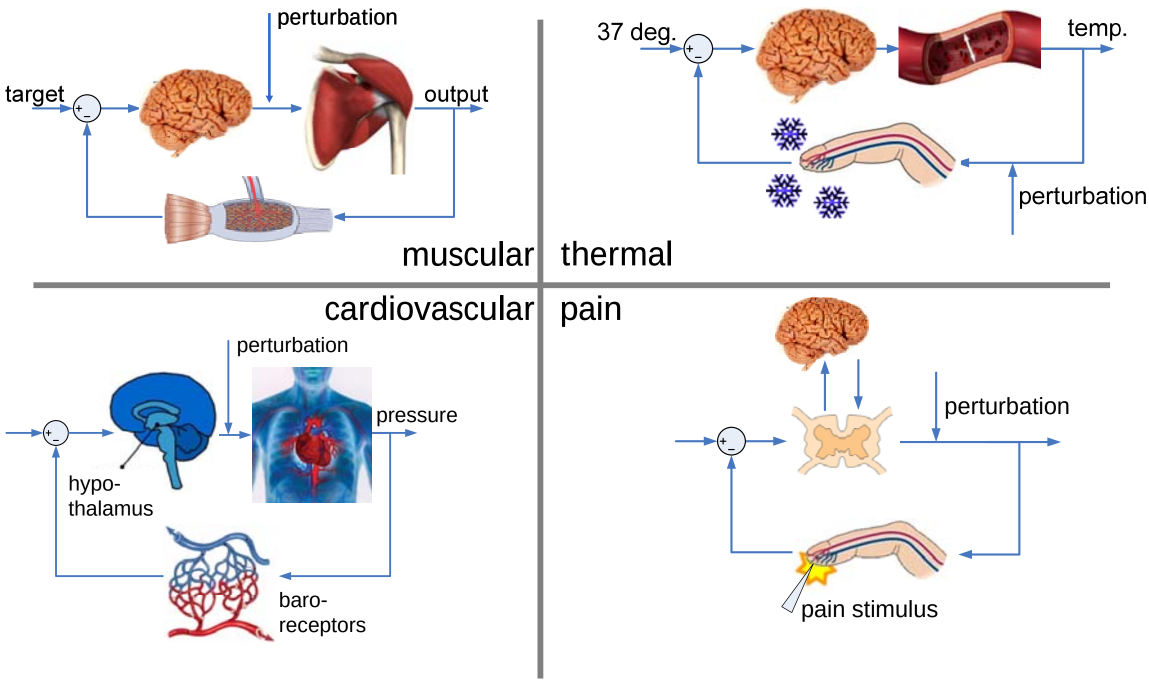

Figure 2: The CNS as the controller of the muscular, thermal, cardiovascular and pain system.

Four developmental phases of techniques development are discerned:

1. **Initial**: The measuring protocol needs to be tested on healthy subjects. Important aspects are: instrument safety, patient-machine interfacing (experiment information, application of perturbations), measurement accuracy, test-retest reliability
2. **Potential**: The relationship with neurological disorders needs to be determined in small groups of patients. Central issue is the relationship of the new measurement technique with existing measures. Important aspects are: sensitivity to separate patients from healthy subjects on the group level, relationship of new parameters to existing parameters and scales, relevance of parameters for therapeutic programs.
3. **Quantitative**: The quantitative relationship with neurological disorders needs to be determined within the patient, e.g. in monitoring the progression of the disease and the effect of medication (cross sectional effect studies).
4. **Diagnostic**: The clinimetric value for neurological disorders needs to be determined, e.g. for diagnosis. Larger patient cohorts are required in longitudinal studies, e.g. in a Randomized Clinical Trials (RCT). Important aspect is the value of the technique in therapy guidance; what therapy (exercise, drug, surgery) need to be chosen from the identified parameters? Is the new technique prevalent to existing measures? High sensitivity and specificity of the measurement tool are required (see STARD initiative (Standards for Reporting of Diagnostic Accuracy)[18]).

The division of each project in phases is very helpful to decide what should be the outcome of the current research phase, what tests should be done, and when the project is ready to enter the next phase. Presumably, each project in the NeuroSIPE program will cover about two phases. For example, in a matured application area like neuromuscular control, equipment will be made ready for commercialization and phase 3 and phase 4 studies will indicate useful clinical parameters to score the patient's symptoms. In other application areas like pain, the methodology should first be tested in healthy subjects, and next it should be shown that it does measure a distinguishing factor between patients and healthy subjects. In the NeuroSIPE program, it is envisaged that there will be about two to three projects in each phase. Clinical testing in phase 4 will fit in the program, in order to make the first steps towards evidence-based medicine. However, for a full-size RCT study funding should be obtained elsewhere.

Most likely, the developed equipment and protocols can be commercialized for clinical applications when phase 3 or phase 4 has been finished. For research applications, also phase 2 may be sufficient to sell equipment to academic and industrial research groups.

4.1 Interdisciplinary work and synergy

For the various focus areas (neuromuscular, cardiovascular, thermoregulation, pain) there is a clear overlap in NeuroSIPE challenges. This will enable the cross-fertilization between different projects within the program. Furthermore, the program's focus on a system's approach will bring together the specialists from different fields and application domains, like e.g. the mechanical engineer, control engineer, bio-medical specialist, neurologists, neurophysiologists, rehabilitation physician, etc. This will result in the necessary breakthroughs for the next generation of neurophysiological assessment systems which is not possible within individual projects that focus on the optimization of a subpart. The presence of a multitude of disciplines researchers within one project will be mandatory for success. To further enhance cross fertilization, the program aims at the development of demonstrators for each of the different application domains, i.e. neuromuscular system, cardiovascular system, pain system and thermoregulation system.

Also stimulation measures between the projects are taken, such as an active coordination action of the program committee during the selection process and regularly during the course of the program. Meetings at least twice a year with the principal investigators of all granted projects will be held. Furthermore, a yearly congress will be organized that brings together the projects and researchers of NeuroSIPE and the international field. These measures to stimulate knowledge exchange between different projects, the research partners and the industrial participants will create a research momentum and knowledge mass that exceeds by far that what could be brought together in an individual project. A workshop at a large international conference or the organization of an international symposium in the last year will be organized to present the finding of the NeuroSIPE program to the international research community.

5 Industrial relevance and utilization

5.1 Economic impact of NeuroSIPE

The development and improvement of new measurement equipment and techniques designed for patients with neurological disorders requires a wide variety of skills and topics. Companies involved in the NeuroSIPE program have a background in mechatronics, electronics, software development, mechanics, etc. A number of these companies have experience in the biomedical engineering field and some companies seek opportunities to use their expertise to enter this market. Thus far, a number of companies have expressed their interest to participate in the NeuroSIPE program, by signing a letter of intent or by joining the workshop:

- Mechatronics:
  - Moog FCS inc. (http://www.moog.com/simulationandtesting/)
  - Demcon b.v. (http://www.demcon.nl/)
  - ForceLink b.v. (http://www.forcelink.nl/)
  - Motek Medical b.v. (http://www.motekmedical.com/)
- ICT
  - Noldus IT b.v. (http://www.noldus.com/)
  - Motek Medical b.v. (http://www.motekmedical.com/)
- Medical electronics and software
  - Advanced Neuro Technology (ANT) b.v (http://www.ant-neuro.com/)
  - ESAOTE (http://www.esaote.nl)
  - Medtronics (http://www.medtronic.nl/NL/)
  - Viasys (http://www.viasyshealthcare.com/)
  - TMSi (http://www.tmsi.nl/)
  - Judex (http://www.judex.dk/)
  - Tiql (http://www.tiql.nl)
- Thermographics
  - FLIR (http://www.flir.com/NL/)
- Drug development
  - Centre for Human Drug Research (CHDR), (http://www.chdr.nl/)
  - Allergan (http://www.allergan.nl/)
- Research institutes
  - Roessingh Research & Development b.v. (http://www.rrd.nl)
  - St. Maartenskliniek (http://www.maartenskliniek.nl/)
  - TNO (www.tno.nl)

In the Netherlands there are no large industrial players in neurophysiological instrumentation. Instead, there are a number of SME which are very innovative and high tech. The market for medical devices is a very special market, and smaller companies tend to be able to quickly shift their momentum to incorporate the newest technology. Another opportunity in the NeuroSIPE program is that we explicitly will support MSc and PhD students to start their own company (Technostarters). Technostarters have shown that they are very knowledgeable about the technology involved, and that they are willing to invest in bringing this technology to the market, where larger companies tend to hesitate. NeuroSIPE will stimulate and support PhD students to submit proposal for the STW valorization grants.

There is potentially a large market for equipment for objective assessment of neurological disorders. Currently, neurologists and rehabilitation physicians have hardly any technological equipment for diagnosing and monitoring their patients. Most patients are solely examined by the clinician, without any objective data being recorded. In paragraph 1.1 the incidence and prevalence of various patient groups with neurological disorders have been described. In total, there are hundred thousands of patients requiring a clinical examination. It is envisaged that in a number of hospitals in the Netherlands and worldwide tools and equipment as developed in the NeuroSIPE program will be acquired, in order to monitor and diagnose patients with stroke, Parkinson's disease, CRPS, Multiple Sclerose, ALS, etc. In the Netherlands there are more than 160 specialized rehabilitation hospitals or hospitals with a rehabilitation unit.

One should think of equipment for imposing perturbations (robot manipulators, thermic perturbations using thermoplates, electrical stimulation, motion platforms, instrumented treadmills), recording physiological signals (EMG, ECG, EEG, microneurography, fMRI, cameras for thermography, sensory testing for pain, etc) and the development of protocols and user interfaces.

The Netherlands is in the lead in the development of advanced neurophysiological recording methods.. A potential market are research groups worldwide, who need commercial equipment for getting involved in new recording methodology, rather than developing the equipment themselves. Another potential market is the use of objective recording equipment for pharmaceutical trials. By accurately monitoring the progress of patients after administering medication will increase the power of statistical testing, and will therefore reduce the number of patients needed for clinical experiments.

5.2 Utilization

Utilization of equipment, protocols and user interfaces will be done in each project separately, through the user's committee. It is strongly recommended to include representatives of a non-academic hospital, a medical insurance company, the patient's society and the medical specialist's society in the user's committee. The time-to-market is long for medical equipment, due to all regulations and safety measures.
Currently, in the regular neurological unit, outpatient pain clinic or rehabilitation hospital there are few instruments to objectively measure the neurophysiological control function of the CNS. However, objective data are necessary for the development of evidence-based medicine which becomes more and more best practice in the Netherlands and outside. There is a new and large initial market with only a few business competitors present. With help of the NeuroSIPE program, Dutch companies can take the lead in commercialization of new equipment.
In each project proposal, a preliminary business plan should be added, in which it is described how many patients should be treated in order to make it profitable, the total number of patients in the Netherlands and worldwide, and the likelihood that use of the equipment will be reimbursed by insurance companies. In general, equipment for neurophysiological measurement should be useful for several neurological disorders. In paragraph 2.1 the incidence and prevalence of some neurological disorders have been indicated. In total, the potential market for neurological disorders is large, covering at least more than 200 000 patients.
The medical market is a very international market, partly because of the high research and development costs. In collaboration with the participating companies, an international market scan should be made, taking into account the differences in the healthcare system and insurance system in the various countries inside and outside the EU.
More than 15 SMEs have already indicated to participate in NeuroSIPE. These companies are in general high-tech, innovative companies, which employ many academically educated employees. The SMEs are very flexible to adapt to the swiftly changing requirements of the medical field, which require short lines between the customer and the research department of the company.
Usually, there are no separate OEMs with supplying companies in this field. Every company covers the whole traject between R&D and market sales. Sometimes, special commercial representative companies are instrumental for the successful marketing and distribution of equipment.

Knowledge dissemination is very important for acceptance of new methods by medical specialists. Therefore, the medical partners in the project should plan presentations for societies of specialists, in order to include the protocols in the guidelines. Also patient's societies have an important role in the medical field. They inform their members and the general public about the best practice in diagnosis and treatment, and may demand certain standards from the medical specialists. A good relation with the patient's society, including regular presentations, is mandatory for a successful commercialization. Regular meetings in the NeuroSIPE program between companies will be helpful to discuss the best practice to enter the market, and to learn from each other.

6 NeuroSIPE program and community

NeuroSIPE is unique in the sense that it focuses on a system's approach and not on a specific neurological disease or subsystem. This approach will bring together specialists from different fields and application domains, which are required for the necessary breakthroughs in neurophysiological assessment systems. Companies involved in the NeuroSIPE program have a background in mechatronics, electronics, software development, mechanics, etc.

6.1 Relevance for the Netherlands

Based on the information related to NeuroSIPE in a Dutch perspective, the following SWOT analysis is made.

<u>Strength</u>

- Build on proven Dutch expertise (neurophysiology, system identification, neuromuscular control)
- Application areas are built on Dutch strength (innovative medical technologies)
- Innovative companies in the Netherlands (a.o. ANT, TMSi, Noldus IT b.v., MOOG- FCS, ESAOTE)

<u>Weakness</u>

- No large industrial players in neurophysiological instrumentation in the NL
- Scattered field

<u>Opportunity</u>

- Realizing a number one position in neurophysiological equipment and protocols world wide
- Realizing a new high potential industry segment in the Netherlands
- Bringing together a unique multi-disciplinary group of experts
- Growing market to serve an expanding global position of healthcare

<u>Threat</u>

- Limited industrial momentum
  This is dealt with by involving many SMEs with a high innovative potential
- Losing focus
  This is dealt with by both a focused medical and technical scope and establishing a coherent research community.

6.2 NeuroSIPE community

The NeuroSIPE program aims to unite neurophysiological research in various academic medical centers (o.a. AMC, VUmc, LUMC, ErasmusMC, UMC Utrecht, Radboud University MC Nijmegen) with the technological and control engineering research in the (technical) universities. Medical disciplines involved are a.o. Neurology, Neurophysiology, Rehabilitation Medicine and Anaesthesiology. Many close ties already existed, which resulted in the research community who wrote the STW perspective pre-proposal. The participating groups are shown in Figure 1, though other groups are welcome to join the community.

Figure 1: Overview of the current NeuroSIPE research community.

Participating medical and technical research groups have long-lasting collaborations, as can be seen in the formal collaborations such as 'Medical Delta' (Leiden University Medical Center, Erasmus Medical Center, Delft University of Technology) and 'Health Valley' (Radboud University Nijmegen, University of Twente). The Nijmegen research groups also participate in the Center for Neuroscience of the Donders Institute for Brain, Cognition and Behaviour. An overview of all the prospective academic partners of the NeuroSIPE program is given in Annex 1.

6.3 Coherence and knowledge transfer

To guarantee the coherence and optimize knowledge transfer between the projects within the program, the program committee with support of STW will:

- Organize a NeuroSIPE workshop each year to exchange knowledge,
- Investigate links between the projects and project partners,
- Coordinate interactions between principal investigators of the different projects,
- Coordinate interactions between the users committees of the different projects,
- Actively informs the general public through a professional website,
- Stimulate new spin-off companies to implement new NeuroSIPE ideas.

6.4 First NeuroSIPE workshop

On November 10 2008 the NeuroSIPE program initiators organized a workshop at the

Delft University of Technology to bring together experts from Dutch academia and industry. In total 40 people visited the workshop (see annex 2), which was given the short time frame a good result. Both academia (Delft University of Technology, VU Amsterdam, Universiteit Twente), academic medical centers (Erasmus MC, VUmc, UMC Utrecht, LUMC, UMC St. Radboud, AMC Amstedam) and industry (Motek Medical, Noldus IT, TMSi, Esaote Europe, Tigl BV, Forcelink, MOOG FCS) contributed to the success of the workshop.

The workshop introduced the goals of the NeuroSIPE program. STW gave a short overview of the granting conditions within a STW program. In one large session six selected possible participants from industry expressed interest in the NeuroSIPE program in general, demonstrated their specific interests and gave examples of previous government granted projects in which they participated. This meeting brought together industry and academia which of some were unfamiliar to each other and possible collaborations were already discussed after the meeting.

6.5 Related initiatives

NeuroSIPE is unique in the sense that it focuses on a system's approach and not on a specific neurological disease or subsystems. This approach will bring together specialists from different fields and application domains, which are required for the necessary breakthroughs in neurophysiological assessment systems.

The NeuroSIPE program will be complementary to the following national initiatives:
Ti-GO: 'TopInstituut Gezond en Succesvol Ouder worden' (Top Institute for Healthy Ageing). FES initiative of academic hospitals and technical universities.
TI Pharma: FES consortium for pharmaceutical research.
BrainGain: FES consortium for brain-computer interfacing and brain stimulation.
TREND: BSIK consortium, focussing on Complex Regional Pain Syndrome.
EXPLICIT-stroke: NWO-Medical Sciences funded project on Neural plasticity after stroke.

<u>Ti-GO</u>
Het TopInstituut Gezond en Succesvol Ouder Worden (Ti-GO) (Top Institute for Healthy Ageing) is a public-private partnership between knowledge institutes, companies and societal organisations. The goals of Ti-GO can be summarized as "science and technology for healthy ageing and extended participation in the society". The focus of Ti-GO is improving the active and independent functioning of elderly people. The elderly people are central, and are incorporated in the strategic input for the institute. The primary task of Ti-GO is the generation of knowledge and translation of this knowledge in innovative applications in the society.

<u>TI Pharma</u>
Top Institute Pharma (TI Pharma) aims to achieve leadership in research and education in areas that are critical for the international competitive position of the pharmaceutical industry. The Institute conducts groundbreaking, cross-disciplinary research and offers advanced training programs focused on improving the efficiency of the entire process of drug discovery and development. This will eventually reduce the 'time- & cost-to-patient' of new medicines and contribute to the well-being of society. TI Pharma devotes special attention to the Priority Medicines project of the World Health Organization.

BrainGain
Detecting and modifying brain activity is currently one of the fastest developing areas of research. It promises to bring applications that have long been thought to be only science fiction, ranging from mind-controlled computer games to so-called mental prostheses and treatment for conditions previously thought untreatable. BrainGain is a Dutch research consortium consisting of researchers, industry and potential users of Brain-Computer and Computer-Brain interfaces. The program started in September 2007 and is funded by SmartMix, a Dutch initiative to support applied research. BrainGain is researching possibilities of applications for both ill and healthy users, and aims to eventually manufacture off-the-shelf products making use of their research results.

TREND
TREND (Trauma REIated Neuronal Dysfunction) is a consortium of Dutch medical and technical universities and industrial companies, in which research on Complex Regional Pain Syndrome type 1 (CRPS-1) is integrated. More recently TREND started successful collaborations with other medical research institutes in the United Kingdom, Germany and the United States. Starting from a multidisciplinary approach TREND aims at combining strong points and expertise from several backgrounds in order to be able to offer an important contribution to the research within the domain of CRPS-1.

EXPLICIT-stroke
Explicit-stroke stands for Explaining Plasticity after stroke. The program is Dutch multicenter collaboration investigating Brain Plasticity in relation to functional recovery of the upper limb after a first-ever ischemic stroke. Over the course of 5 years, 2008-2013, 2 Randomized Clinical Trials and several subprojects will be conducted.

Relation between NeuroSIPE and other initiatives
The NeuroSIPE program has a special focus on the development of new methods, equipment and applications. Products of the NeuroSIPE program can be used in consortia such as Ti-GO, TREND and EXPLICIT. In BrainGain the one of the focus areas is Deep Brain Stimulation, with electrodes inside the brain. The effectiveness of treatments like DBS can be assessed with tools developed in the NeuroSIPE program. In drug development and testing, huge cohorts are sometimes necessary to accurately determine the effectiveness of new treatment. If the outcome will be recorded more accurately, smaller patient cohorts are required in order to obtain the same power of statistical testing. In NeuroSIPE drug development and testing companies like CHDR and ALLERGAN have already expressed their interest. Whenever deemed useful, contacts will be made with TI Pharma in order to contact other pharmaceutical companies, or to enter projects in TI Pharma.

6.6 International initiatives, anchoring

There is a good relation with the international research groups as mentioned in paragraph 2.2. NeuroSIPE will actively seek international collaboration and funding, e.g. through organization of and participation in EU consortia, and together with USA colleagues in NIH funded projects. It will be aimed that the close ties of the NeuroSIPE programme will remain after the 5-year period of NeuroSIPE, and that NeuroSIPE will be instrumental to obtain funding for further research projects with academic partners and companies.

7 Organization of the program and budget

For the details of the time planning, proposal application and selection process please see the call for pre-proposals.

7.1 Budget

For this call a budget of M€ 5.25 is available which must be matched by the contributions of potential technology users (companies/institutes) to a total of at least M€ 7. The maximum of contribution that can be requested from STW is € 750.000 per project. For this program the minimum STW contribution is € 300.000 per project in order to avoid too many small projects. A contribution of potential "users" (companies) of the project results of at least 25% of the total project budget is compulsory, resulting in a minimum project size of € 400.000. The industrial participants do not have to co-finance up-front in the program but may contribute in-kind (materials, equipment, facilities etc.) and/or financially in the project wherein they will participate.

The NeuroSIPE programme will last for a period of five years. It is anticipated that between 10 to 12 projects will be initiated in the NeuroSIPE program. The budget will be divided over the various focus areas (neuromuscular, cardiovascular, thermoregulation, pain), and other interesting applications if submitted. Currently, there is most experience in the neuromuscular application area, therefore roughly 4 projects in the neuromuscular area, and 2-3 projects in each of the other areas are expected. Since some neuromuscular projects will also involve (pre-RCT) clinical testing, the size of these projects will be close to the maximal budget.

A total amount of € 70 000 will be reserved for program activities in order to strengthen the NeuroSIPE community. This budget will be used for the organization of the annual symposium, a professional website, the invitation of international key-note speakers for the annual symposium, and the organization of meeting between users committees of the different projects.
- Organization of annual conference, incl. international keynote speaker: € 10 000 a year, total € 50 000 for 5 years
- Professional website and PR: € 2 000 a year, total € 10 000
- Inter user committee meetings € 2 000 a year, total € 10 000

All other costs for the participating groups should be incorporated in the project budget plan.

7.2 Program Committee

The program committee consists of the following experts:

- Prof.dr. F.C.T. van der Helm (Delft University of Technology), chair
  Biomechatronics and BioRobotics
- Prof.dr.ir. M. Verhaegen (Delft University of Technology)
  Delft Center for Systems and Control

- Dr.ir. H. van der Kooij (University of Twente, Delft University of Technology) Biomechanical Engineering
- Prof.dr. J.H. Arendzen (Leiden University Medical Center) Rehabilitation Medicine
- Prof.dr. J.J. van Hilten (Leiden University Medical Center) Neurology
- Prof.dr. D.C. Stegeman (Radboud University Nijmegen, Vrije Universiteit Amsterdam) Medical Physics / Applied electrophysiology
- Dr. F.J.P.M. Huygen (Erasmus Medical Center Rotterdam) Anesthesiology
- Dr. L. Noldus (Noldus IT b.v.) ICT
- Drs. P. Lammertse (MOOG FCS) Haptic interfaces and robotics

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Annex 1. Participating groups in the NeuroSIPE community

One of the goals of the NeuroSIPE program is to build a community with research groups dedicated to the closed-loop system identification approach of neurophysiological systems. Thus far, a number of groups have expressed their interest to participate in the community. However, the community is open to other groups who want to join. Only the scientific partners are mentioned, the participating companies have been mentioned in chapter 5.

Medical

- CVA (stroke)
  - Dept. of Rehabilitation Medicine, Leiden University Medical Center, Leiden, The Netherlands, Prof. dr. J. H. Arendzen
- Parkinsons Disease, Complex Regional Pain Syndrome
  - Dept. of Neurology, Leiden University Medical Center, Leiden, The Netherlands, Prof. dr. J. J. van Hilten
  - Dept. of Neurology, University Medical Centre St Radboud, Nijmegen, The Netherlands, Dr. Bas Bloem
  - Dept. of Clinical Neurophysiology, Leiden University Medical Center, Leiden, The Netherlands, Prof.dr. J.G. van Dijk
- Dystonia
  - Dept. of neurology, Amsterdam Medical Center, dr. Marina de Koning-Tijssen, Dr. F. van Rootselaar, Dr.ir. L. Bour)
- Cerebral Palsy
  - Dept. of Rehabilitation Medicine, VU University Medical Center, Amsterdam, The Netherlands, dr. ir. J. Harlaar
- Low back, neck, shoulder pain
  - Fac. of Human Movement Science, VU University Amsterdam, The Netherlands, Prof. dr. J. H. van Dieën
- Neurotechnology and neurostimulation
  - Rehabilitation technology, Roessingh Research and Development, Enschede, The Netherlands, Prof. dr. J. S. Rietman
  - Dept. of Clinical Neurophysiology, Erasmus Medical Center Rotterdam, Dr. G.H. Visser, Dr.ir. J. Blok
  - Dept.of Clinical Neurophysiology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Dr. P.L. Oey
- Animal studies for neural processes
  - Leiden Institute of Advanced Computer Science: LIACS, University of Leiden, dr.ir. F.J. Verbeek.

Technical

- System identification
  - Delft Center for Systems and Control, Dept. of Mechanical Engineering, Delft University of Technology, The Netherlands, Prof. dr. ir. M. Verhaegen
- Human Motion Control
  - Delft Laboratory for Neuromuscular Control, Biomechanical Engineering, Dept. of Mechanical Engineering, Delft University of Technology, The Netherlands, Prof. dr. F. C. T.. van der Helm
  - University of Twente, Dept. of Biomechanical Engineering, Enschede, The Netherlands, dr. ir. H. van der Kooij
- Cardiovascular control, neural stimulation
  - Dept. of Biological Signals and Systems, Fac. Of Electrical Engineering, University of Twente, Prof.dr.ir. P.H. Veltink, dr.ir. J. Buitenweg
- Neural Networks
  - Dept. of Applied Mathematics, prof.dr.ir. S.A. van Gils

Annex 2. NeuroSIPE workshop participants

On November 10 2008 the NeuroSIPE program initiators organized a workshop at the Delft University of Technology the following experts participated in the workshop.

Naam	**Voornaam**	**Organisatie**
Dr. F. Huygen	Frank	Erasmus MC
Ir. M. Westermann MBA	Michiel	Motek Medical BV
Dr. Ir. J. Harlaar	Jaap	VUmc, afd. Revalidatie Amsterdam
Dr. J.H. Blok	Joleen	Erasmus MC
Dr. L. Noldus	Lucas	Noldus Information Technology BV
Dr. G.H. Visser	Gerard	Erasmus MC, klin neurofysiol
Dr. P. Liam Oey	Liam	UMC Utrecht, Neuroloog/kl. Neurofysioloog
Dr. J. Marinus	Han	Leids Universitair Med. Centrum
Pfor. Dr. Ir. D. Stegeman	Dick	UMC St. Radboud Nijmegen
		Fac. Beweg. Wetenschap VU Amsterdam
Dr. A.F. van Rootselaar	Fleur	AMC Amsterdam
Dr. Ir. L. Bour	Lo	AMC Amsterdam
Dr. H.E.J. Veeger	Dirk Jan	VU FBW / TU-BME
Dr. Ir. E. de Vlugt	Erwin	TU Delft, Biomechanica
Dr. Ir. R. Happee	Riender	TU Delft
Prof. Dr. J. van Dieen	Jaap	VUA (FBW)
Ir. J. Peuscher	Jan	TMS – international
Ir. P. Lammertse	Piet	Moog-FCS
Dr. Ir. H. van de Kooij		UT - BW, TU Delft, BME
Dr. Ir. A.C. Schouten	Alfred	TU Delft, BME UT - CTW-BW
Ir. J. Meuleman	Jos	Moog-FCS
Ir. J.W. van Wingerden	Jan-Willem	TU Delft – DCSC
Prof. M. Verhaegen	Michel	TU Delft – DCSC
Dr. Ir. L. Kallenberg	Laura	Roessingh Research & development
Dr. H. Slijper	Harm	Erasmus MC
Dr. V. Weerdesteyn	Vivian	UMC Radboud, afd. Revalidatie
Ir. J. Schuurmans	Jasper	TU Delft
Ir. W. Mugge	Wilfred	TU Delft
Drs. E. Abbers	Erwin	Motek Medical BV
Dr. C.P. Botha	Charl	TU Delft / LUMC
Ir. F. Nieuwenhuis	Frank	Forcelink BV
Prof. Dr. S.A. van Gils	Stephen	Universiteit Twente
Dr. Ir. J.R. Buitenweg	Jan	Universiteit Twente
Prof. Dr. Ir. P.H. Veltink	Peter	Universiteit Twente
Prof. Dr. J.H. Arendzen	Hans	LUMC, revalidatie
Dr. C.G.M. Meskers	Carel	LUMC, revalidatie
Dr. P.J. Brands	Peter	Esaote Europe