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Computerized “Psychophysical Testing Platform” to Control and Evaluate Multichannel Electrical Stimulation-Based Sensory Feedback

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8.1 Introduction

Use of electrical stimulation through implanted neural interfaces makes it possible to selectively activate afferent neurons and provide natural sensory feedback. However, effective stimulation patterns for creating natural sensory feedback are not uniquely characterized in the literature. Thus, there is often a need to evaluate various combinations of different stimulation parameters for specific applications, which can produce a wide range of possible stimulation patterns in a multichannel stimulation system. It makes the use of sensory feedback an impracticable and time-consuming task. We therefore designed and implemented a computerized tool referred to as a “Psychophysical Testing Platform” to easily control multichannel stimulation and characterize the evoked sensations. The tool was tested in a clinical trial including one amputee with the aim to relieve his phantom limb pain (PLP) by manipulation

of phantom sensation using intraneural stimulation. The tool may also be utilized in systems based on surface electrical stimulation.

8.2 Sensory Feedback

Amputation of a limb involves the complete transection of afferent and efferent nerves innervated the removed limb. Sensory feedback from the missing part of the limb is thus severely impaired. While most amputees experience that the absent limbs still exist (Kooijman et al., 2000), artificial activation of the residual afferent neurons likely enhances the sensory feedback by creating more specific sensations, e.g., joint position or finger movement. The enhanced sensory feedback may be utilized in prosthetic hand control or PLP treatment (see, e.g., Flor et al., 2001; Rossini et al., 2010; Dietrich et al., 2012).

Electrical stimulation has been recognized as one of the feasible approaches to artificially activate sensory neurons, which can, according to where the stimulation is applied, broadly be grouped into two types: cutaneous stimulation and direct nerve stimulation (Riso, 1999). Cutaneous stimulation may substitute impaired sensibilities by accessing the tactile senses in the skin (Szeto and Saunders, 1982). Users are typically provided with coded stimuli (such as modulation of pulse rate) and learn to relate these codes to specific sensory information, e.g., pinch force (Shannon, 1979). However, intensive cognitive load is usually required for a user to correctly interpret the coded signal (Prior et al., 1976).

Stimulation directly applied to the peripheral nerves through implanted nerve-electrode interfaces makes it possible to generate natural sensations and provide more intuitive sensory feedback (Anani and Korner, 1979; Dhillon et al., 2005). It has been demonstrated that intraneural stimulation via implanted microelectrodes was capable of evoking sensation of touch, joint position, and movement referred to the amputated limb (Dhillon et al., 2005; Rossini et al., 2010). The orientation of the stimulation sites of the implanted electrodes is usually blinded due to complex histological characteristics of peripheral nerves as well as due to some limitations of the current surgical procedures (Stewart, 2003; Harreby et al., 2012; Kundu et al., 2012). As previously mentioned, the stimulation patterns capable of producing natural sensory feedback are not well documented in the literature. Therefore, there

is a need to consider a variety of possible combinations of stimulation parameters that may generate sensations such as touch/pressure, finger movement, and vibration (Dhillon and Horch, 2005) or tingle, touch, vibration, buzz, pinch in cutaneous stimulation (Kaczmarek et al., 1991; Pfeiffer, 1968).

The magnitude of a sensation is commonly estimated using scaling methods by assigning a number to the perceptual event such as sensation (Stevens, 1957). A 10-point visual analogue scale (VAS) is widely used, with 0 representing “no sensation” and 10 “the upper limit of a sensation or pain.” There are also a number of other types of linear scales such as Likert scale and Borg scale. A particular scaling method may outperform the others in specific circumstances (Grant et al., 1999).

8.3 Sensory Feedback for Phantom Limb Pain Treatment

In 50–80% of amputees, pain occurs in the missing limb, known as PLP (Weeks et al., 2010). There are no effective, long-lasting treatments currently available for PLP and it has not been completely understood why and how the phantom pain develops. However, cortical reorganization has been discussed as a plausible cause for the development of PLP (Ramachandran et al., 1992; Flor et al., 1995) and a positive relation was found between the amount of plasticity in the primary somatosensory cortex (S1) and the severity of PLP (Florence et al., 2000; Lotze et al., 2001; Karl et al., 2004).

Several studies demonstrated a positive effect of enhancing sensory feedback on reversal of cortical changes and relief of PLP. For instance, the patients who received daily training in sensory discrimination of surface electrical stimuli applied to the stump, experienced reduction of PLP after 2 weeks (Flor et al., 2001). In another study, training in control of a robotic hand with limited amount of sensory feedback significantly reduced PLP in a human amputee implanted with four intrafascicular electrodes in the nerve stump. The reduction in PLP lasted several weeks after removal of the electrodes and changes in sensorimotor cortex topography were shown (Rossini et al., 2010). A recent study found that use of a prosthesis that provides somatosensory feedback on the grip strength effectively alleviated PLP (Dietrich et al., 2012). The evidence suggested the likelihood to suppress PLP by providing intensive, natural sensory feedback to amputee patients.

8.4 Psychophysical Testing Platform Design Strategy and Principles

The psychophysical testing platform was designed as a part of the “TIME prototype system” to efficiently test, deliver, and evaluate generated sensory feedback (see introduction).

The aim of the TIME (transverse intrafascicular multichannel electrodes) project was to develop an implantable neural prosthesis system with sufficient stimulation selectivity to generate phantom sensations and explore the possibility of using the method as a potentially effective treatment for PLP. The project hypothesized that manipulating phantom sensations using selective stimulation of the nerve stump may reverse cortical reorganization and consequently mitigate PLP.

TIME electrodes, each consisting of 12 stimulation sites, were designed and manufactured by IMTEK (University of Freiburg, Germany) based on micromachining technologies on flexible polymeric substrates (Boretius et al., 2010) were used as the interface for the peripheral nerves, see also Chapter 3. A customized 12-channel stimulator was developed (Montpellier Laboratory of Informatics, Robotics, and Microelectronics and MXM Neuromedics, France) to deliver the electrical stimulation, see also Chapter 7.

The psychophysical testing platform consisted of two computers interacting with each other – i.e., subject performs psychophysical tests for characterization of the delivered sensory feedback on Computer #1 and the experimenter controls and monitors the stimulation process on computer #2.

Definition of the system functionalities was based on the experimental tasks to be conducted. Three main experimental tasks were identified: (1) determination of threshold, (2) characterization of sensation, and (3) repeated application of “useful” stimulation.

- *Experimental Task 1: Determination of the sensation threshold and upper limit of sensation.* Before applying stimulation for pain relief treatment, it is necessary to determine which of the TIME electrode active sites are functional and how much electricity should be injected into each active site to elicit natural sensations referred to the phantom hand. Therefore, the sensation threshold and the upper limit of a sensation first needs to be determined. The sensation threshold is defined as the current level where subject can just barely detect that a stimulus is delivered. The upper limit of a sensation is defined as the current level where the nature or the location of the sensation changes, or when the sensation becomes uncomfortable or painful. To determine the

sensation threshold, the intensity of the stimuli presented to the subject should initially be sufficiently weak and then increase in successive steps. Different psychophysical methods can be adopted to identify the sensation threshold and the upper limit of the sensation (Ehrenstein et al., 1999).

- *Experimental Task 2: Sensation characterization.* After thresholds are determined, the perceived location, type, and intensity of the sensation should be characterized for those active sites that were defined as functional in Experimental Task 1. This task is important to identify the stimulation patterns that can produce natural phantom sensations which are interpreted as meaningful by the subject. The range of current between the sensation threshold and the upper limit of sensation are applied. Other parameters that are interested include: pulse duration, pulse frequency, single-pulse vs. pulse train, number of pulses, monopolar vs. bipolar, as well as stimulation site combinations.
- *Experimental Task 3: Repeated application of natural sensory feedback.* Repeated application of the stimulation patterns that were identified as “meaningful” in Task 2 may reinforce the effect of sensory feedback on cortical plasticity and PLP. A subset of optimal stimulation patterns selected based on the results in the Task 2 is repeatedly applied in the experimental task.

Four main functionalities were defined according to the tasks above described.

- *Functionality 1: Decide stimulation parameters.* An interface is needed for the experimenter to configure the stimulation parameters to be varied. Each stimulus usually needs to be repeated multiple times and randomized to obtain a data set that later can be statistically analyzed. The interface should thus allow repeated configuration of one or a series of stimuli, as well as randomization of stimuli.
- *Functionality 2: Determine thresholds.* Threshold is usually determined by delivering a set of stimuli with an intensity in the vicinity of the threshold. An interface is developed for the subject to indicate whether or not the stimulus just delivered was perceived or perceived as the upper limit. The subject’s response and corresponding stimulation parameters need to be tracked for later calculation of threshold.
- *Functionality 3: Characterize sensations.* A sensation can be characterized by three main attributes: location, type, and intensity. An interface is needed for this psychophysical testing, which comprises a questionnaire

presented to the subject for evaluating the three sensation attributes. The subject’s response and corresponding stimulation parameters is tracked for later identification of optimal stimulation patterns, or analysis of the relation between a parameter and evoked sensation.

- *Functionality 4: Automated repetition of stimulation and characterization.* The large amount of stimulus patterns to be investigated to determine the thresholds or characterize the sensations requires an efficient way to deliver stimuli and characterize the evoked sensation. An automated process of stimulus delivering, sensation characterization, and data collection is the solution to address the issue. The system supports the automated process, in which each session proceeds as illustrated in Figure 8.2.

8.5 Software Components

The software was developed in the LabVIEW environment (National Instruments). Control of the electrical stimulator was implemented through accessing a set of application programming interface (API) functions built in dynamic linked libraries provided by the stimulator developer.

The specified functionalities were implemented in two subsystems, i.e., the stimulator and experiment control (SEC) subsystem (located in Computer #1, see Figure 8.1) and the interactive subject interface (ISI) subsystem (located in Computer #2, see Figure 8.2).

Stimulator and experiment control (SEC): The SEC subsystem provides a tool for the experimenter to configure stimulation parameters, and monitor

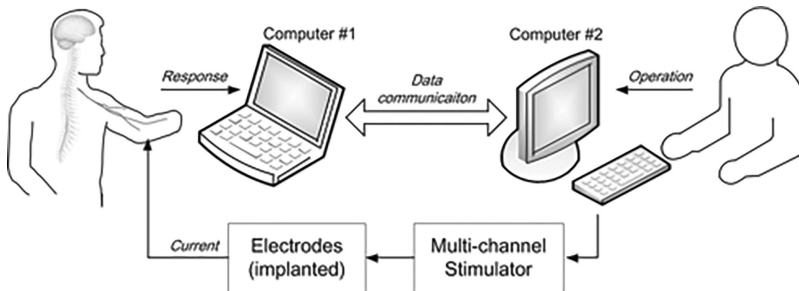


Figure 8.1 Prototype system in the TIME project. The psychophysical testing platform was implemented on Computer #1 and Computer #2 to interact with the experimenter and the subject.

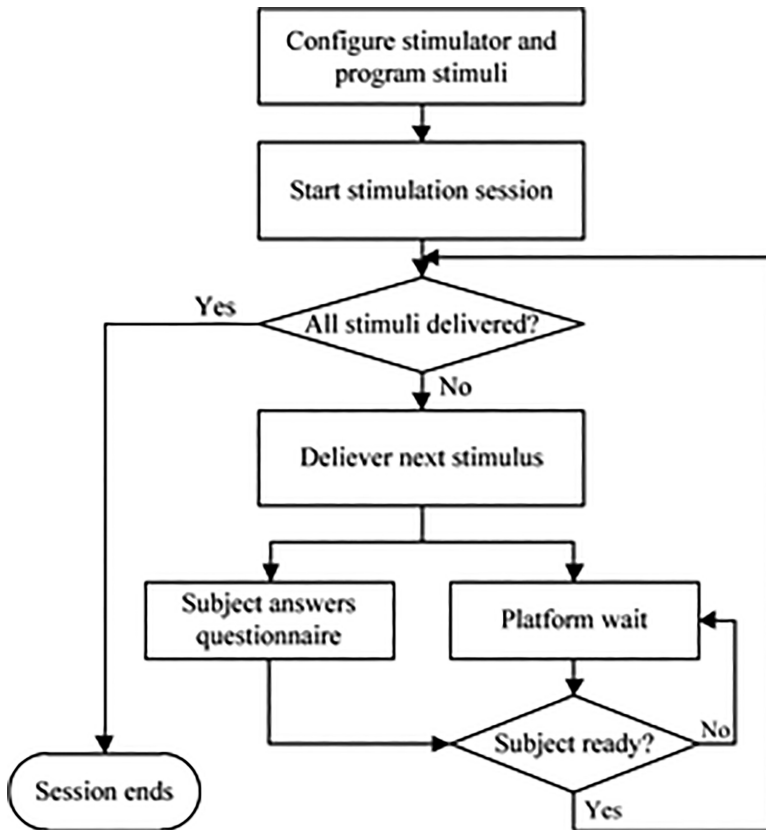


Figure 8.2 Flow chart showing automated process of stimulus delivering and sensation measurement in one stimulation session.

stimulation process and experimental progress. To secure safe delivery of the electrical stimulation it is possible for the experimenter to override the otherwise automated stimulation process.

Interactive subject interface (ISI): The ISI subsystem provides the interface to perform psychophysical testing with the subject, i.e., threshold determination and sensation characterization. This subsystem also collects all the subject's responses for later data analysis.

The functionalities defined for the SEC were implemented in five modules physically grouped in the main graphical user interface (GUI), as shown in the screenshot (Figure 8.3). The five modules are described in details as follow.

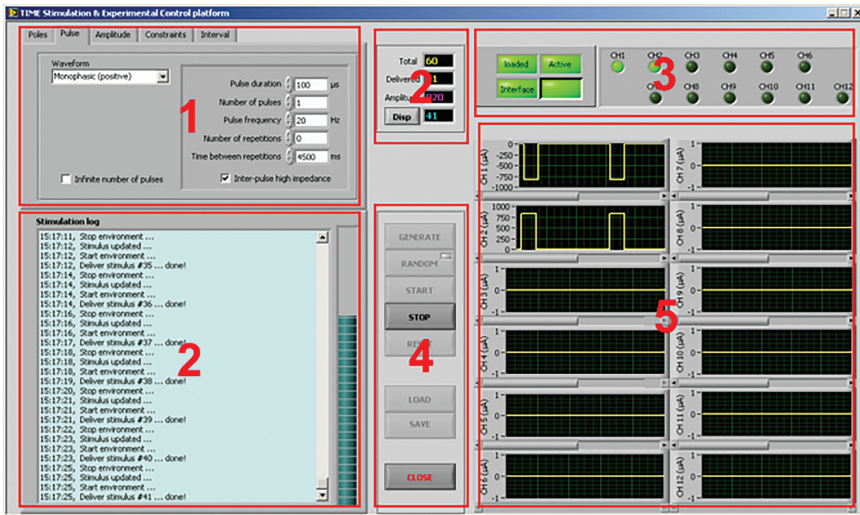


Figure 8.3 Screenshot of the main GUI of the SEC software with the five modules identified (i.e., the module numbers are shown in the center of each module box).

Table 8.1 A list of stimulation parameters implemented in SEC software

Parameter	Range	Step Size
Pulse waveform	Monophasic (negative or positive) Biphasic (symmetric, positive following negative) Biphasic (symmetric, negative following positive) Biphasic (arbitrary amplitude and pulse duration)	N/A
Amplitude	5 mA	20 μ s
Pulse duration	500 μ s	1 μ s
Number of pulses	1–5000 pulses	1
Frequency	1–1000 Hz	1 Hz

Module 1: Stimulation parameter configuration. In this module different parameters can be configured in a panel consisting of several pages. Table 8.1 is a summary of the range and step size of each stimulation parameter. The panel also includes a page where the stimulation constraints can be configured to ensure the safety. If a stimulus violates the constraints, the stimulation session will stop.

Module 2: Progress monitoring. A progress bar is used to indicate how far a stimulation session has progressed. A textual indicator (light blue box) shows specific status information of the stimulation session (e.g., which stimulus was just delivered, waiting for a response from the subject). This information is automatically saved in a log file. In addition, four numeric

indicators are used to respectively display: (1) the total number of stimuli in the ongoing stimulation session, (2) the number of stimuli already delivered, (3) the current level of the stimulus just delivered, and (4) the index of the stimulus just delivered.

Module 3: Stimulator status monitoring. Four squared “LED” indicators are used to indicate the status of interaction between the software and the stimulator. These four indicators are used for trouble-shooting if the stimulation process accidentally stops or hangs during communicating with the stimulator. Twelve round-shape “LED” indicators are used to indicate active cathode channels (i.e., light up when active).

Module 4: Experimental control. This module allows to control the experiment and choose the way that the configured stimuli are delivered. The commands include:

- Add one or a series of increasing stimuli with constant step size.
- Randomize the order of the stimuli to be delivered.
- Start/stop/continue a stimulation session.
- Save the stimulus configurations to an external text file.
- Load stimulus configurations from a previously saved file.
- Clear and reset the stimuli.

Module 5: Graphical display. This module provides a graphical display of the stimulus waveform just delivered in the 12 stimulator output channels.

8.6 Implementation of ISI Subsystem

The ISI subsystem software includes two main user interfaces: the interface for threshold determination and the interface for sensation characterization. The interface for threshold determination provides the subjects with a YES or NO choice on whether or not the stimulation was perceived, or whether or not the stimulation was perceived as the upper limit of a sensation (Figure 8.4).

In the interface for sensation characterization, three questions are implemented with regard to the sensation type, location, and magnitude, respectively (see Figure 8.5).

Question 1: Please choose one or more words to describe the sensation you felt. A list of words describing possible evoked sensation types is predefined based on previous studies (Dhillon et al., 2005; Dhillon and Horch, 2005; Rossini et al., 2010). The list includes touch/pressure, vibration, tugging, spider crawling, pinch, pain, wrist flexion, wrist extension finger flexion, finger extension, cold and warm. One or more types can be selected.

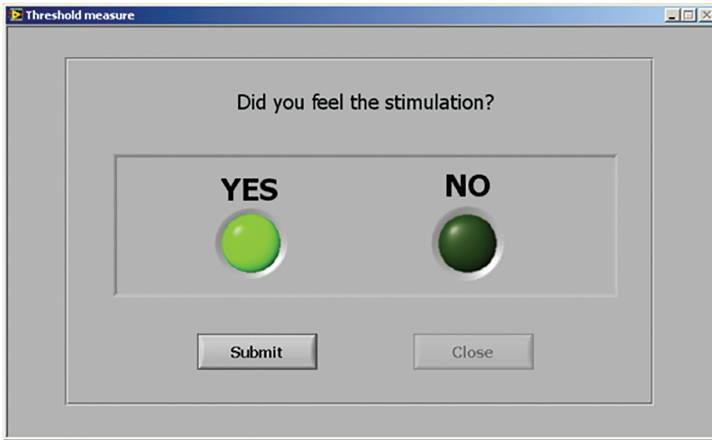


Figure 8.4 Screenshot of user interface for threshold determination.

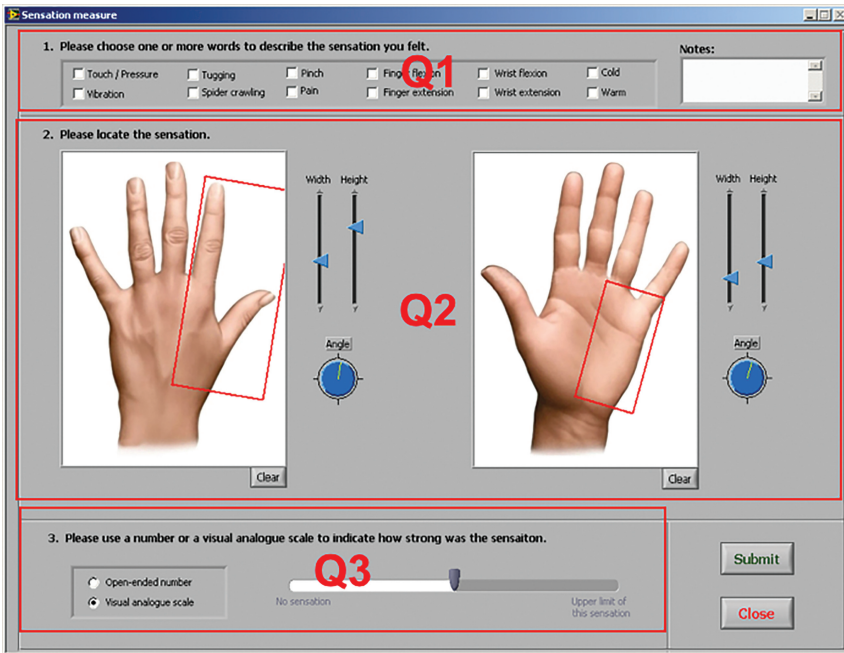


Figure 8.5 Screenshot of user interface for characterization of the sensation type, location, and magnitude, each corresponding to a question in the red box.

In case the perceived sensation is not covered by the list, an option of making a note is provided to the subject.

Question 2: Please locate the sensation. Two pictures of the front and back view of a human hand are provided for the subject to locate the evoked sensation. The subject needs to point the cursor to the center of the perceived region using the mouse. A red-color rectangular box will then be marked on the hand picture. The width, length and angle of the box can be adjusted.

Question 3: Please use a number or a visual analogue scale to indicate how strong you felt the sensation. Two approaches of measuring the sensation strength were implemented: visual analogue scale (VAS) and open-ended number. A VAS is a horizontal bar anchored by word descriptors at each end (left end: no sensation, right end: upper limit of a sensation). The subject can mark a point by moving the slider, to indicate how strong the sensation is. The VAS score is then determined by the distance from the left end of the bar to the point that the subject marks. Alternatively, the subject can use an open-end number to indicate the magnitude of a sensation.

8.7 Communication Between SEC and ISI

The SEC and ISI software are able to communicate and exchange data through a local area network to achieve the automated process of stimulation and evaluation. The physical substrate of the communication is an Ethernet crossover cable, which directly connects the two computers allowing data transfer across the network. The LabVIEW DataSocket has been used to realize data communication between two applications residing in two computers.

8.8 Use of the Psychophysical Testing Platform

Training of amputee subject. One amputee volunteer was recruited for the clinical test of the TIME prototype system (see also Chapter 9). Before the subject had the electrodes implanted he went through a training session to familiarize him with the automated stimulation-characterization procedure, as well as the interactive interfaces for psychophysical testing. Comparing the use of paper-based psychophysical questionnaire, the subject reported that the system assisted and promoted the process of the psychophysical testing, which helped him concentrate more on the actual experiments.

Evaluation by clinical doctors. A questionnaire was used to evaluate the usability of the software and user satisfaction of the interfaces. It was developed based on a modification of IBM The Post-Study System Usability Questionnaire (Lewis, 1995) and the Questionnaire for User Interface Satisfaction (Chin et al., 1988). Only relevant questions from the original questionnaires were included in our evaluation. This questionnaire was given to our clinical partner who was using the software in clinical experiments. The response to the questionnaire helped us understand what aspects of the software they were particularly concerned about and satisfied with.

Use in clinical trials. When the electrodes were implanted in two main nerves in the subject’s forearm (i.e., the median and ulnar nerve), the software part of the TIME prototype system was used for clinical tests. SEC was used to define specific stimulation sequences, define, and control the delivery of the electrical stimulation, and monitor the progress of the experiment. ISI was used to perform psychophysical testing, where the subject filled in questionnaires to describe and quantify the perceived sensation referred in the phantom hand (see Chapter 9).

8.9 Discussion

Following amputation, the complete truncation of afferent and efferent nerves leads to lack of sensory feedback from the missing limb, and this can produce a phantom pain effect. Artificial activation of sensory neurons may then be considered as a solution to recover the impaired sensibility. Microfabricated neural interfaces enable direct nerve stimulation with high selectivity. However, morphological complexity and limited knowledge about optimal stimulation strategies make it necessary to investigate a large number of different combinations of stimulation parameters. To overcome these limitations, a computerized tool may be used to efficiently evaluate the sensory feedback in a multichannel, intraneural stimulation setting as described here.

We sought to evaluate the usability and user satisfaction of the software. However, the evaluation was limited due to the simple fact that the system was only used with one amputee subject.

Based on the experience obtained from the clinical tests, we believe that the psychophysical testing platform may be improved in the following aspects. For instance, a resizable, rotatable rectangular box was used to localize a sensation, since the perceived region could be in an irregular shape. An improved tool should instead allow arbitrary drawing to localize

the sensation more precisely and speed up the process further. Moreover, bilateral upper-extremity amputees may not be able to control a computer mouse conveniently. Using a touch screen could be easier, especially for above-elbow amputees.

The platform was designed to collect the data from threshold and sensation measure experiments. However, to counteract cortical plasticity and consequently relieve PLP, it is necessary to carry out repeated, intensive stimulation sessions. Therefore, a set of optimal stimulation patterns should be identified based on the results in sensation characterization. The optimal stimulation patterns is defined as those capable of eliciting clear, meaningful, distinct sensation referred to the phantom hand, e.g., finger movement, touch, joint position, etc. As such, a module that can automatically select optimal stimulation patterns can be considered in future development.

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