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HYBRID FES-ROBOTIC REHABILITATION SYSTEM FOR LOWER LIMB NEUROREHABILITATION

DESIGN AND EVALUATION

BY
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PhD Thesis 2024

AALBORG UNIVERSITY
DENMARK

Hybrid FES-Robotic Rehabilitation System for Lower Limb Neurorehabilitation

Design and evaluation

Ph.D. Dissertation
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PhD Thesis 2024

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Abstract

The demographic change in the world is leading to a higher proportion of elderly people, who are at a greater risk of developing chronic disease, which is detrimental to their quality of life, and a considerable burden on society. Stroke is of particular concern, as the prevalence of stroke is on the rise, and the rehabilitation needed to regain lost motor skills following a stroke, is often intensive and long-lasting. In the early days following a stroke, the neural system has increased capacity for neuroplastic changes which may be utilized for recovery. Yet, for those severely affected by their stroke who must remain bedridden rehabilitation options are limited.

This PhD study developed and evaluated three components for a hybrid functional electrical stimulation(FES)-robotic rehabilitation system of the lower limb, usable while in bed: 1) A brain computer interface (BCI) to allow for intention-based triggering of the administration of FES, 2) an assist-as-needed (AAN) control paradigm for adjusting the assistance provided by the system to match the capability of the patient, to promote active participation, and 3) a dynamic controller to adjust FES stimulation parameters online to achieve a target movement velocity.

The three studies of the PhD evaluated each system component, respectively, in able-bodied participants and demonstrated their technical performance. The first study demonstrated that the developed BCI was capable of single-trial detections with subsequent administration of FES, in an out-of-lab setting. The second study demonstrated that the developed AAN control method could identify different states in the users' exercise capability, and adjust the assistance provided accordingly. Additionally, the second study evaluated the AAN control method in two stroke patients and showed that the system was capable of appropriately adapting to the capability of the patients, and that the adaptive exercise was well tolerated. The third study demonstrated that the developed FES-controller was able to adjust the stimulation parameters online, when the utilized stimulation parameters were no longer the best suitable to reach the target movement velocity.

The designed components may be used individually or collectively to provide novel hybrid FES-robotic rehabilitation of the lower limb while bedridden. The system collectively demonstrated that bedside rehabilitation with a hybrid FES-robotic rehabilitation system is possible and may be pursued further in the future.

Resumé

De demografiske ændringer i verden fører til en større andel af ældre i befolkningen, der har en højere risiko for at udvikle en kronisk sygdom, hvilket reducerer den enkeltes livskvalitet og udgør en betydelig byrde for samfundet. Stroke er særligt bekymrende, da forekomsten er i fremgang og da den rehabilitering der er nødvendig for at genskabe tabt førlighed efter et stroke, ofte er intensiv og langvarig. I de tidlige dage efter et stroke, har nervesystemet en øget kapacitet for neuroplastiske ændringer, hvilket kan udnyttes i rehabiliteringen. Men, for de der er svært påvirket af et stroke og må forblive sengeliggende er rehabiliteringsmulighederne begrænset.

Dette PhD studie udviklede og evaluerede tre komponenter af et hybridt funktionelt elektrisk stimulering (FES)-robot rehabiliteringssystem til underekstremiteterne, der kan bruges i en seng: 1) Et brain-computer interface (BCI) der tillader selv-initieret aktivering af FES, 2) et assist-as-needed (AAN) styresystem, der justerer mængden af assistance der gives fra system, tilpasset patientens evner, for at promoverer aktiv deltagelse, og 3) en dynamisk controller til online justering af FES stimuleringsparametre, med målet om at vedholde en bestemt bevægelseshastighed.

De tre studier i PhD'en evaluerede hver system komponent hver for sig i raske forsøgspersoner og demonstrerede deres tekniske egenskaber. Det første studie demonstrerede at det udviklede BCI var i stand til, at lave detekteringer baseret på live data, og efterfølgende aktiverer FES, i et ud-af-laboratoriet miljø. Det andet studie demonstrerede, at det udviklede AAN styresystem kunne identificere forskellige niveauer i testpersonernes træningsevner, og justerede mængden af assistance derefter. Yderligere testede det andet studie AAN-styresystemet med to stroke patienter, og viste at systemet var i stand til hensigtsmæssigt at justere assistancen til patienternes behov, og at patienterne tolererede den adaptive træning godt. Det tredje studie demonstrerede at den udviklede FES-controller var i stand til at justere stimuleringsparametrene online, når de brugte stimuleringsparametre ikke længere var de bedst egnede til at opretholde den bestemte bevægelseshastighed.

De designede komponenter kan bruges individuelt eller samlet til at give innovativ hybrid FES-robot rehabilitering af underekstremiteter mens patienten er sengeliggende. Systemet demonstrerer samlet at sengeliggende rehabilitering med et hybridt FES-robotisk rehabiliteringssystem er muligt, og kan forfølges yderligere i fremtiden.

Acknowledgement

A big thank you to all who have supported me on the journey, that was this PhD. Seven years it took to finalize this work – that has got to be some sort of record! Regardless, I am very privileged to have been surrounded by supportive and encouraging people during this time.

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Contents

Chapter 1: Introduction

The world population is getting older [1]. The consequence of such demographic change is an increased burden on the healthcare system, as the elderly have an increased risk of developing chronic diseases, such as stroke, Parkinson's, Alzheimer's disease, etc. [2], and a tremendous impact on the affected individuals' quality of life [2, 3]. In this context, stroke is of great concern, as it is increasingly prevalent [4], it requires intensive and long-lasting interventions to reclaim and maintain quality of life [5, 6], and it is a considerable burden on society, costing an estimated 2.7 billion DKK annually in Denmark alone [7, 8], and resulted in 143 million disease-adjusted life years globally (in 2019) [4].

An estimated 35% of stroke survivors with some degree of impaired lower limb function, will show no motor recovery [9]. For stroke survivors that are severely affected by the stroke and consequently are restricted to a bed in the early days following their stroke, intensive rehabilitation options are limited [1]. Yet, in the early days following a stroke, the neural system is particularly receptive to neuroplastic changes, which may be utilized to promote recovery [10, 11]. These neuroplastic changes may be facilitated by engaging in exercise [10, 12–16]. Therefore, there is great potential for improving the outcome of rehabilitation for severely affected stroke survivors, by facilitating exercising in the early days following their stroke, regardless of their limitations [10, 12, 13, 15, 16].

The above reasons all contribute to an interest in developing technologies to facilitate exercise for severely affected stroke survivors. Technologies such as robotics can provide intensive and repetitive exercise for stroke patients [14, 17, 18], which may lead to improved recovery and the quality of life [19–21]. Additionally, robotics may relieve the strain on healthcare personnel administering therapy [22], as robotics can replace the manual labor of the therapist [23].

1.1 Robotics for early lower limb rehabilitation

Robotics may be used in rehabilitation to facilitate exercise of the lower limbs of patients, which has previously been demonstrated by many [5, 16, 24–26]. The use of robotics allows for longer and more intense durations of exercise [14, 17, 18], as they do

not tire as human therapists would. Additionally, robotics can reproduce exact movements, meaning that the quality of exercise provided is identical to all patients and independent of physiotherapist skill [16]. Robotics that can be used without therapist intervention during exercise, i.e., the therapist does not need to constantly support or observe the use of the technology to ensure, e.g., safety and efficacy, allow said therapists to spent time on other important work [23]. Additionally, it may be possible for a single therapist to supervise several patients exercising at once, in cases where multiple robotic devices facilitating exercise are in close proximity (for safety), boosting efficiency. Finally, providing manual therapy, i.e., repetitively moving the patients' limbs to facilitate exercise [5, 22], constitutes a considerable risk to the therapist, as 55-91% of therapists have reported injuries in the lower back, neck, upper back or shoulders, while 2.8-21% have reported requiring sick leave following their injury [22]. Hence, the use of robotics could reduce the risk of such injuries [14, 20, 22] and help combat the increased demand for therapy [2, 4, 27].

Robotics is a great candidate to facilitate neurorehabilitation principles (NP) shown to optimize rehabilitation outcomes, such as:

I Massed practice [28],

II Progressive increase in difficulty [28],

III Variable practice [28–30], and

IV Active participation [29, 31, 32].

'Massed practice' refers to a period of time during which the patient does repetitive practice of the same exercise or skill [28]. In this regard robotics can facilitate exercise for a prolonged period compared to human therapists [14, 17, 18], and they may simultaneously be used to quantify the completed exercise, using the variety of sensors available in robotic devices. 'Progressive increase in difficulty' refers to the exercise task having to be challenging for optimal rehabilitative outcomes, and to be increasingly more difficult as patients improve, to continuously be optimal [28]. In robotics, this could be achieved by adjusting the resistance or assistance provided, making the exercise task more or less difficult for the patient [33]. 'Variable practice' refers to exercises which allow room for error, such as deviation from a defined movement trajectory, which has been shown to improve motor learning compared to strictly following the moving trajectory [29, 30]. Here robotics may utilize a so-called "virtual tunnel" to impose a region of free movability around the defined movement trajectory and thereby allow error in performing the exercise [29, 34]. 'Active participation' simply refers to the need for patients to be actively involved in the exercise to facilitate motor learning, as alternative to having their limbs passively moved around by e.g., a robotic device [29, 31]. Although passive movement of the limbs is effective to promote recovery [35–37], the active involvement of the patient produces better rehabilitative results [29, 31]. The

assistance provided by robotics during exercise is thus a drawback for neurorehabilitation, as even during active participation of patients, the assistance of robotic devices has been shown to limit the effort of the patients involuntarily, a phenomenon referred to as "slacking" [19, 32]. However, by monitoring the capability of the patient and limiting the assistance provided to only the necessary amount, "slacking" can be avoided. Additionally, to be fully compliant with the fourth NP, it is important that the exercise is coupled with the patient's *intention* of movement [5, 33, 38, 39]. Hence, NP IV is comprised of two components: the active participation of the patients muscles, and the active participation of their mind [5, 29, 31–33, 38, 39]. It is possible to determine the patient's intention of movement by monitoring biosignals, such as electromyography (EMG) in individuals with sufficient remaining voluntary muscle control [40, 41], or electroencephalography (EEG) through the use of a brain-computer interface (BCI) in individuals with no voluntary muscle control [42, 43]. When coupling the intention of patients to the performed exercise, to facilitate neurorehabilitation, it is important to do it per repetition, i.e., each repetition of exercise should be driven by the patients' intention [44, 45]. Hence, the intention-detection algorithm (regardless of whether it is based on EMG or EEG), should be able to work on single trials, i.e., individual attempts by the patient of moving.

The monitoring of patients' capabilities and subsequently adjusting the assistance provided to the patients' specific needs, has been made into a field of study within rehabilitation, under the term "Assist-as-needed" (AAN) [33, 46]. AAN is an exercise principle/control strategy, in which the patient achieves a certain target nr. of repetitions, movement velocity, movement trajectory, etc., with minimum assistance from the system [33, 47] (henceforth referred to as the 'AAN principle'). This in turn promotes that patients use their own internal resources to the greatest extent possible, which is suggested to boost rehabilitative outcomes [33, 47], based on NPs II and IV, as their active participation and high effort is facilitated/promoted by the system [33, 38, 39, 47]. Generally, AAN is implemented in one of two ways: A) by reducing or increasing the direct physical demand on patients during exercise, or B) by reducing or increasing enforcement of a specific movement pattern or behavior. The physical demand on patients may be altered, e.g., by adjusting the torque used to help the patient complete the exercise [38, 40, 47–50] or the body-weight support provided to the patient during exercise [19, 38]. The enforcement of a specific movement pattern or behavior may be adjusted, e.g., by increasing the size of a virtual tunnel, which proportionally applies corrective forces according to the patient's deviation from a desired trajectory [29, 34], thereby allowing more or less error in the movement trajectory, or by facilitating/restricting the movement speed of the exercise [48]. For AAN to be implemented successfully, it is essential that the system can assess or estimate the current capability of the exercising patient, through e.g., force sensors [34, 47, 50] or biosignals [40, 49], to adapt appropriately to the patient's capability.

Even though AAN may optimize the assistance provided, it infers that patients are

able to contribute to the exercise at all. In severe cases, patients may have little-to-no voluntary muscle control [9]. Yet, in these cases active participation of the patients' muscles can be facilitated using Functional Electrical Stimulation (FES). FES is the artificial activation of motor nerves, which relies on the use of electrical stimulation trains applied to the motor points of muscles of interest [51–54]). Thus, FES constitutes a way of activating patients' muscles, even if they have no voluntary ability to do so. By using FES in combination with robotics, as a hybrid FES-robotic system, it will also diminish the "slacking" effect of systems only utilizing robotics. A downside of FES is the rapid induction of fatigue resulting in less force production during stimulation [51, 52]. However, the induction of fatigue by FES may be mitigated by the robotic part of the hybrid system, as the robot may reduce the need for force produced by the FES, resulting in a reduced amplitude/intensity/frequency of FES and thereby fatigue [55, 56].

Therefore, it is proposed that the best option for early rehabilitation of severely affected stroke patients, is a hybrid rehabilitation system combining robotics and FES, incorporating AAN while being able to match the patients' intentions with the exercise on a repetition-per-repetition basis. Such system would also relieve the therapist involved in the therapy of stroke patients, and potentially help mitigate the demand for therapy. Development of such system is the topic of this thesis.

1.2 State-of-the-art hybrid FES-robotic systems for in-bed exercising

In the following a state-of-the-art of identified FES-robotic hybrid systems for bedridden patients is presented. For the purpose of this overview FES-cycling devices will be omitted, as there is a focus on robotic devices for severely affected stroke patients [57], which may also facilitate specific exercises for severely affected stroke patients, such as knee extension for standing and ankle dorsal flexion for relieving foot drop, which FES-cycling cannot.

The identified hybrid FES-robotic rehabilitation systems, which may be used while in bed for severely affected stroke survivors are listed in table 1.1.

Kuznetsov et al. 2013, Calabro et al. 2015, and Sarabadani et al. 2017, all utilized the robotic tilt table ERIGO combined with FES [58–60]. The system is fully functional while the patient is in a supine position, although it does require transfer from the patient's bed onto the tilt table [58–60]. The system provides mechanical stepping-like movement of the patients' legs through moving footplates, and FES with fixed stimulation parameters synchronized to the movement of the patients' legs [58–60]. As the system can facilitate repetitive exercise, and has the option of loading the trainees leg for increased exercise intensity, the system abide by NP I and II [58–60]. However, the system provided cyclic movements, with little variation [58–60], hence NP III was

Table 1.1: Overview of existing hybrid robotic-FES rehabilitation systems applicable to severely affected stroke survivors while in bed. In bed use – indicates whether the system is usable while in bed/supine position. Exercises - indicates which exercises are possible with the respective system. NP - refers to which of the four outlined NP the respective system abide to. AAN – indicates whether the system utilizes AAN control strategies. Intention based – indicates whether the system monitors the intention of the user in the performed exercise. () - indicates that the respective system was not intended for bed-use.

Reference	Description	In bed use	Exercises	NP	AAN	Intention based
[58–60]	Robotic tilt table w. or without resistance + FES synchronized to leg movement	✓	Stepping movements	I and II		
[61]	Motorized knee extension exercise machine combined with FES	(✓)	Knee extension	I and II		
[50]	Robotic knee extension machine coupled with FES	(✓)	Knee extension	I and II		
[62]	End-effector robot coupled with EMG-triggered delivery	✓	Any exercise definable in ROBERT®'s workspace	I, II, III, and IV		✓

not adhered to. The system did not consider the capability of the exercising patients, nor their intention, and indiscriminately applied FES synchronized to the movement of the patient's legs [58–60]. Thus, it does not incorporate NP IV, the AAN principle of providing the least amount of necessary assistance, and it is not intention-based. These shortcomings may limit the rehabilitative capacity of the system [29, 31, 32, 47].

Kirsch et al. 2018 introduced a modified knee-extension exercise machine paired with FES (denoted 'Hybrid neuroprosthesis'), as a hybrid FES-robotic rehabilitation system [61]. The system itself was not intended for in-bed use [61], but in the context of this overview, it is considered probable that the system may be usable in bed. The system worked by varying the proportion of torque produced by the motor and FES, based on the estimated fatigue of the trainee's muscles, according to a fatigue model [61]. As the system can facilitate repetitive exercise [61], and it is deemed feasible that the system may facilitate difficult high effort exercise, i.e., by limiting the provided assistance, it

abides with NP I and II. Similarly to [29, 31, 32, 47] the system was rigid in terms of error allowed during exercising, i.e., trainees are strapped to the system whish has a single degree of freedom [61]. Hence the system did not abide by NP III. Since the system was tested with a participant instructed to remain passive [61], the system did not abide by NP IV, the AAN principle, and was not intention-based [61], which may diminish the systems rehabilitative capacity [5, 14, 33, 38, 39].

Zhang et al. 2017 developed a hybrid FES-robotic knee exoskeleton "FEXO knee", for facilitating knee extension exercise [50]. The exoskeleton comprised a circular brace attached to the shank of a trainee, and all residual mechanical and electrical parts being mounted on a base bench, to be fixed on a table [50]. The FEXO knee was designed to be used in a sitting position [50], but in the context of this review, it is considered probable to utilize the system while in bed. The system would split the torque required to follow a reference trajectory between the electrical motor and FES in the system [50]. In the study, the proportion of torque to be produced by FES was chosen arbitrarily to be 30-70% [50]. A model was used to determine which pulse duration would produce the FES proportion of the necessary system torque, and the torque required by the electrical motor, would be the remainder [50]. Finally, the system would increase the proportion of torque provided by the electrical motor, in the presence of muscular fatigue, estimated as the difference between desired and actual torque [50]. Since the system was capable of providing repetitive exercise, with varying degrees of assistance, [50] NP I and II are adhered to. Similarly to [61], the system was rigid in terms of the error possible in the system with one degree of freedom [50], and hence, the system does not abide to NP III. The system was tested with the participants remaining completely still, and thus, it did not comply with NP IV, the AAN principle, and was not intention-based. Additionally, the extensive modeling in the system, required several calibration steps, including manual parameter identifications [50]. Such procedures can be time consuming (time undisclosed in [50]) and may not be appropriate for clinical practice where limited time is available per patient session (≈95 minutes average session length [63], with 16-47 minutes of active patient time per session [64].

Finally, Petersen et al. 2020 introduced a hybrid system consisting of the seven degree of freedom (DoF) end-effector robot ROBERT® (based on KUKA; Life Science Robotics, Denmark) combined with an EMG-triggered FES system [62]. This system was fully capable of being used with patients in their own beds and supported knee extension and ankle dorsal flexion exercises, but could in principle facilitate any exercise in ROBERT®'s workspace, based on its ability to follow a manually defined exercise trajectory [62]. The robotic device provided the movement trajectory, resistance to the completion of the exercise trajectory, and the automatic return of the lower limb to the starting position of the exercise, when an exercise repetition had been completed [62]. The system monitored EMG of the trainees and applied FES when a set threshold for EMG had been reached [62]. The FES facilitated completion of the exercise trajectory and was terminated upon reaching the end of the trajectory [62]. As the system could

facilitate repetitive exercise, had a changeable resistance, and provided end-effector based exercise with room for error, [62] the system abides to NP I-III. As the exercise was intention-based [62], the system furthermore complied with NP IV. However, the hybrid system did not comply with the AAN principles, as it indiscriminately applied FES, regardless of the capability of the trainees [62], which may compromise the possible rehabilitative power of the system [33, 38, 39, 47].

It should be noted that the few identified hybrid FES-robotic systems in this overview (Kuznetsov et al. 2013, Calabro et al. 2015, Tafreshi et al. 2017, Kirsch et al. 2018, Zhang et al. 2017, and Petersen et al. 2020 [50, 58–62]), does not reflect the absence of hybrid FES-robotic systems in general. However, it does reflect that the efforts in developing hybrid FES-robotic systems are generally focused on out-of-bed systems, of which there are numerous [65], such as a treadmill and body weight supported hip-knee exoskeleton coupled with FES [23], a powered ankle-foot orthosis for overground walking coupled with FES [66], or the Kinesis exoskeleton coupled with FES [55].

Some studies were identified which related to the development of the control strategies for hybrid FES-robotic rehabilitation systems [67–69]. However, as these studies did not realize the system, only the control strategy, it was not included in this review.

From table 1.1 it is evident that no hybrid rehabilitation system exists for use while in bed, which utilizes all the outlined NP (see section 1.1) and the AAN principle, while being intention-based. Further, no identified system utilized a BCI, allowing for intention-based exercise for severely affected patients. Additionally, no identified system utilized the AAN principle at all, allowing the assistance to be adjusted depending on the patients capability. Of the identified robotic devices, only ROBERT® used by Petersen et al. 2020, was able to support different exercise movements [62]. Additionally, ROBERT® was the only device used in a hybrid system that was truly usable in bed (without need for transfers) [62]. Hence, there is untapped potential for recovery of severely affected stroke patients, which may be facilitated by developing the system proposed in section 1.1, and the best identified robotic candidate to base this system on is the ROBERT® device.

Thus, the identified gaps in the state-of-the-art are:

1. No hybrid FES-Robotics system for bedridden patients provide intention-based exercise using a BCI.

2. No hybrid FES-Robotics system for bedridden patients utilized an AAN control strategy.

1.3 Requirements for a hybrid FES-robotic rehabilitation system

As there is untapped potential for facilitating recovery in severely affected stroke patients, by use of hybrid FES-robotic rehabilitation systems while in bed, and since no system has been identified that utilized a BCI or the AAN principle, developing such a system was the focus of this thesis. Based on the presented literature the following requirements for a rehabilitation system for early in-bed rehabilitation of the lower limb following a stroke are defined:

1. Firstly, the system should be able to comply with the four outlined NPs. For this the system should be hybrid, combining a robotic device and a FES delivery system. This is to ensure the facilitation of exercise in paralyzed patients, while actively involving their muscles in the exercise. Such system can facilitate recovery through NP I-IV as outlined in section 1.1.
    (a) The best identified robotic device to base such a system on is ROBERT®, as it was found possible to comply with all four NPs using this device, and due to it being truly usable while in bed in a hybrid configuration, and capable of various exercises.
2. According to the identified gap 1 in the state-of-the-art (section 1.2), the system should facilitate intention-based exercise of the lower limb on a repetition-per-repetition basis, utilizing a BCI. This will facilitate that the exercise may comply with NP IV, as outlined in section 1.1.
    (a) Generally, intention-based exercise should be implemented in the system, using biosignals, i.e., using EMG-based triggers when voluntary muscle activity is present, and using a BCI, when no voluntary muscle activity is present.
        i. For a biosignal-based implementations it is important that the systems work in an out-of-lab setting. Particularly BCI's are usually developed in labs where EEG-signal quality is optimal [70]. However, the EEG-signal quality remains a challenge outside of laboratories, such as in the context of providing rehabilitation in a clinical setting [70]. Therefore, the biosignal-based implementations should be able to work in an out-of-lab setting.
3. According to the identified gap 2 in the state-of-the-art (section 1.2), the system should utilize an AAN control strategy, as this was not present in the current state-of-the-art. Such a control strategy will constitute a strong rehabilitation platform that minimizes the assistance provided to the patient during exercise, to promote the use of the patient's own internal resources to the highest degree possible.

4. While rehabilitation systems, particularly those with more than one source of power production (e.g., robotics and FES) [40, 49], may be complex in nature, it is considered important that they remain simple to use. Complex systems may require specialized skills to use and may take a long time to setup or calibrate, which will all hinder the systems adoption in clinical practice, where limited time is available per patient session (16-95 minutes) [63, 64]. Hence the overall design of each system component should be concerned with reducing complexity of setup, calibration, and use, while being quick to setup.

Chapter 2: Aim and objectives

The aim of this Ph. D. project was to design, implement, and evaluate a hybrid FES-robotic rehabilitation system as outlined in section 1.3, targeting early lower limb rehabilitation for stroke patients in a supine position.

To fulfill this aim, three research questions were formulated:

RQ1 *How can a BCI be designed to provide intention-based exercise with a hybrid FES-robotic rehabilitation system?*

RQ2 *How can an AAN control strategy be designed for a hybrid FES-robotic rehabilitation system?*

RQ3 *How can FES stimulation parameters be controlled to improve the AAN control strategy for a hybrid rehabilitation system?*

To address these research questions, the thesis was divided into three main studies with the following objectives:

A) Design and evaluate a BCI based intention detection method for control of a FES-robotic rehabilitation system:
This study sought to answer the research question RQ1. In very severe cases, stroke survivors may be unable to produce voluntary movement following their neurological insult, even though it may still be possible to produce EEG potentials related to the intended movement. In that case, a BCI should be designed to allow for intention-based exercising. For the BCI to comply with the NP of 'active participation' (IV), the BCI must work on single trials. Finally, the BCI must be designed to control the hybrid FES-robotic rehabilitation system, in an out-of-lab setting.

B) Design and evaluate the feasibility of an assist-as-needed approach for the FES-robotic rehabilitation system:
This study sought to answer the research question RQ2. To comply with NP of 'active participation' (IV), the hybrid FES-robotic rehabilitation system should allow trainees to exercise to the fullest of their capability, i.e., exercise voluntarily

if possible, and provide a minimal amount of assistance when necessary. Hence, a control strategy should be designed that can track the exercise capability of the patient and adapt the assistance provided accordingly.

C) Design and evaluate a controller for adjusting stimulation parameters of FES in the hybrid FES-robotic rehabilitation system for improved AAN control:
This study sought to answer the research question RQ3. Fixing FES stimulation parameters, such as the pulse duration, may over time result in the FES provided not being effective for what is necessary to complete the target exercise, due to fatigue. Additionally, the AAN principle dictates (see section 1.1) that only the minimally required assistance should be provided to complete an exercise repetition, i.e., FES should be applied in a manner that is not excessively assisting the patient. Hence, an FES controller should be designed to alter stimulation parameters to allow for continued exercising, while minimizing the stimulation parameters to the necessary level. Such controller would allow the AAN control strategy to better utilize FES for torque production in line with NP IV.

2.1 Dissertation overview

This thesis presents the design and evaluation of a hybrid FES-robotic rehabilitation system for early exercise of the lower limb, capable of providing intention-based exercise, by use of a BCI or an EMG-trigger, utilizing a novel AAN control paradigm.

Chapter 3 presents the design of the hybrid FES-robotic rehabilitation system and its sub-components. Chapter 4 presents a summary of the three experimental studies focusing on the sub-components of the hybrid FES-robotic rehabilitation system, described in the three above mentioned main objectives of the thesis, and published or submitted as the three main articles of the PhD project, namely:

Study I. Design and demonstration of a hybrid FES-BCI based robotic neurorehabilitation system for lower limbs. [71]
This study fulfills objective A) of the thesis and presents the experimental evaluation of the BCI-controlled version of the hybrid FES-robotic rehabilitation system, conducted in healthy participants.

Study II. A robot-based hybrid lower limb system for Assist-As-Needed rehabilitation of stroke patients: Technical evaluation and clinical feasibility. [72]
This study fulfills objective B) of the thesis and presents the experimental evaluation of the EMG-triggered version of the hybrid FES-robotic rehabilitation system employing an AAN control strategy. The system was technically

evaluated in able-bodied participants and feasibility was preliminary assessed in two stroke patients.

Study III. Dynamic Multi-level Control of Electrical Stimulation During Hybrid FES-robotic Exercise. [73]
This study fulfills objective C) of the thesis. Following the design and test of the system in study II, this study aimed at expanding the AAN control strategy by including a controller for grading the provided FES, for better control of the FES-provided muscular output.

Chapter 5 concludes the thesis, where the main findings and the future considerations are discussed.

Chapter 3: Design and implementation of the hybrid FES-robotic rehabilitation system

The hybrid rehabilitation system at the core of this work utilized several sub-systems, which will be outlined in this chapter. First the robotic device ROBERT®, the FES delivery system and the EMG recording system will be introduced (henceforth referred to as the base system). Then the three sub-systems developed during this Ph.D. work will be presented: 1) The BCI, 2) the AAN control strategy, and 3) the Adaptive FES-Velocity Controller (AFVC).

3.1 The base system: ROBERT®, FES and EMG

ROBERT® (Life Science Robotics ApS, Denmark) is an end effector robot classified as a Class IIa medical device [74], capable of recording and repeating movement patterns of the lower limb while in bed [62, 74], thereby relieving manual strenuous physiotherapy (See ROBERT® in figure 3.1). The robot has 7 DoF with impedance control [72] and is rated for patients up to 165 kg [74]. The robot offers gravity compensation of the lower limb, passive or resistive exercise with automatic return to the start of the exercise trajectory, and a virtual tunnel (promoting a specific movement pattern with room for variation) [72, 74]. These features allow ROBERT® to comply with NP I-III. Following the work done in relation to this PhD, ROBERT® now also offers an AAN functionality ('sensing and stimulation - SAS') [75]

FES was delivered using a NoxiSTIM stimulator (JNI Biomedical, Denmark) employing two stimulation electrodes (8 x 13 cm, Durastick Premium, CefarCompex) [71–73]. The stimulation was provided using a unipolar square pulse, with fixed stimulation parameters for study I and study II: 200 µs pulse duration, at 50 Hz, and an individually calibrated stimulation amplitude [71, 72]. For study III, the pulse duration was variable and controlled by the AFVC [73].

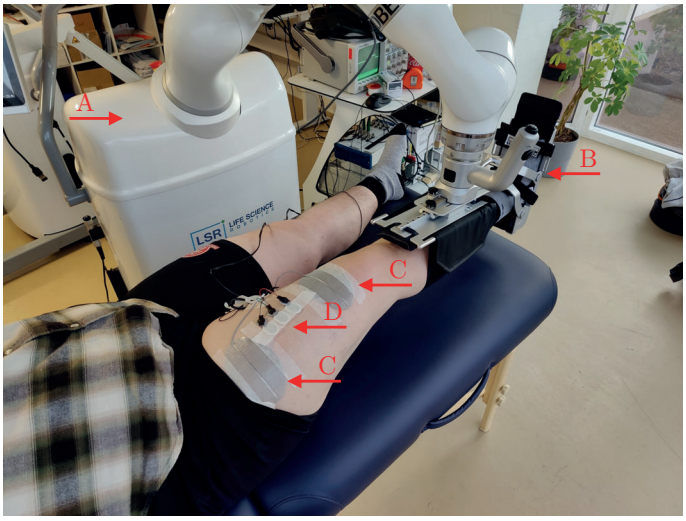


Fig. 3.1: Overview of the base-system, comprising A) the robotic device ROBERT® attached to a trainee through B) a custom brace, and C) stimulation electrodes placed on the trainee's thigh, to facilitate knee extension. Note that D) EMG electrodes are not part of the base system.

The combination of ROBERT® and the FES-delivery system fulfills system requirements 1, and 1a (see section 1.3).

3.2 The BCI Control of the hybrid FES-robotic rehabilitation system

To address objective A) and research question RQ1, a BCI for facilitating intention-based exercise with the hybrid FES-robotic rehabilitation system was introduced in Leerskov et al. 2024A [71]. The purpose of the BCI was to allow those with little to no voluntary movement/EMG production, to actively participate in exercise and promote recovery [71] (NP IV, system requirement 2, and 2a). The BCI was designed to detect the intention to perform a movement of the lower limb (knee extension), by determining the presence of a movement-related cortical potential (MRCP) and then trigger delivery of FES to facilitate the movement [71].

The BCI only utilized five EEG electrodes placed at positions Fz, C3, Cz, C4, and Pz [71], as these are positioned over the sensorimotor cortex of the lower limb [76, 77], and commonly involved in the detection of MRCPs of the lower limb [78]. The limit of five electrodes was set out of consideration for the limited time available per patient [71]

(system requirement 4, see section 1.3), and since there is a limited acceptable time (15 min) for setting up an electrode cap for BCI-use [79]. Since EEG electrode preparation can be time consuming, reducing the number of electrodes necessary would save time.

The EEG was sampled at 250 Hz and streamed from the EEG-headset to a computer wirelessly for processing using the OpenBCI Cyton board [71]. The BCI itself was implemented in MATLAB R2019a and was calibrated to classify EEG into either idling or movement-intention [71]. See an overview of the BCI functioning in figure 3.2. This was done by the following procedure [71]:

a) Filtering EEG with a second order Butterworth lowpass filter with cutoff frequency of 12 Hz.

b) Downsampling the EEG data to 25 Hz.

c) Bandpass filtering the EEG using a second order Butterworth lowpass filter, and a second order Butterworth highpass filter, with cutoff frequencies of 5 and 0.1 Hz, respectively.

d) Splitting the EEG into epochs of 'signal and 'noise' using a cue, which was presented during acquiring calibration data.

e) Removing epochs with outlier EEG values, maintaining a balance in number of 'signal' (movement intention) and 'noise' (idling) epochs.

f) Constructing an Optimized Spatial Filter (OSF) (Niazi et al., 2011), which optimized the signal-to-noise ratio between 'signal' and 'noise' epochs and produced a single spatially filtered EEG channel.

g) Using the OSF on the EEG.

h) Generating an average 'signal' epoch, referred to as a 'Template'.

i) Calculating a feature based on the max cross-correlation between EEG epochs and the template (template matching).

j) Identifying the highest threshold value could discriminate 'signal' from 'noise' epochs based on the template matching feature, with a maximum false positive rate of 0.2.

During online use, the preprocessing described in a), b), c), and g) was applied to newly recorded EEG [71]. For classifying new EEG as being related to a movement intention, the template matching feature was calculated (i), and the threshold value identified in j) was used [71]. To introduce robustness in the detection of movement intention, the BCI utilized a "best-of-three" approach, where two of three consecutive decisions (one per 120ms) should indicate a movement intention before it was accepted,

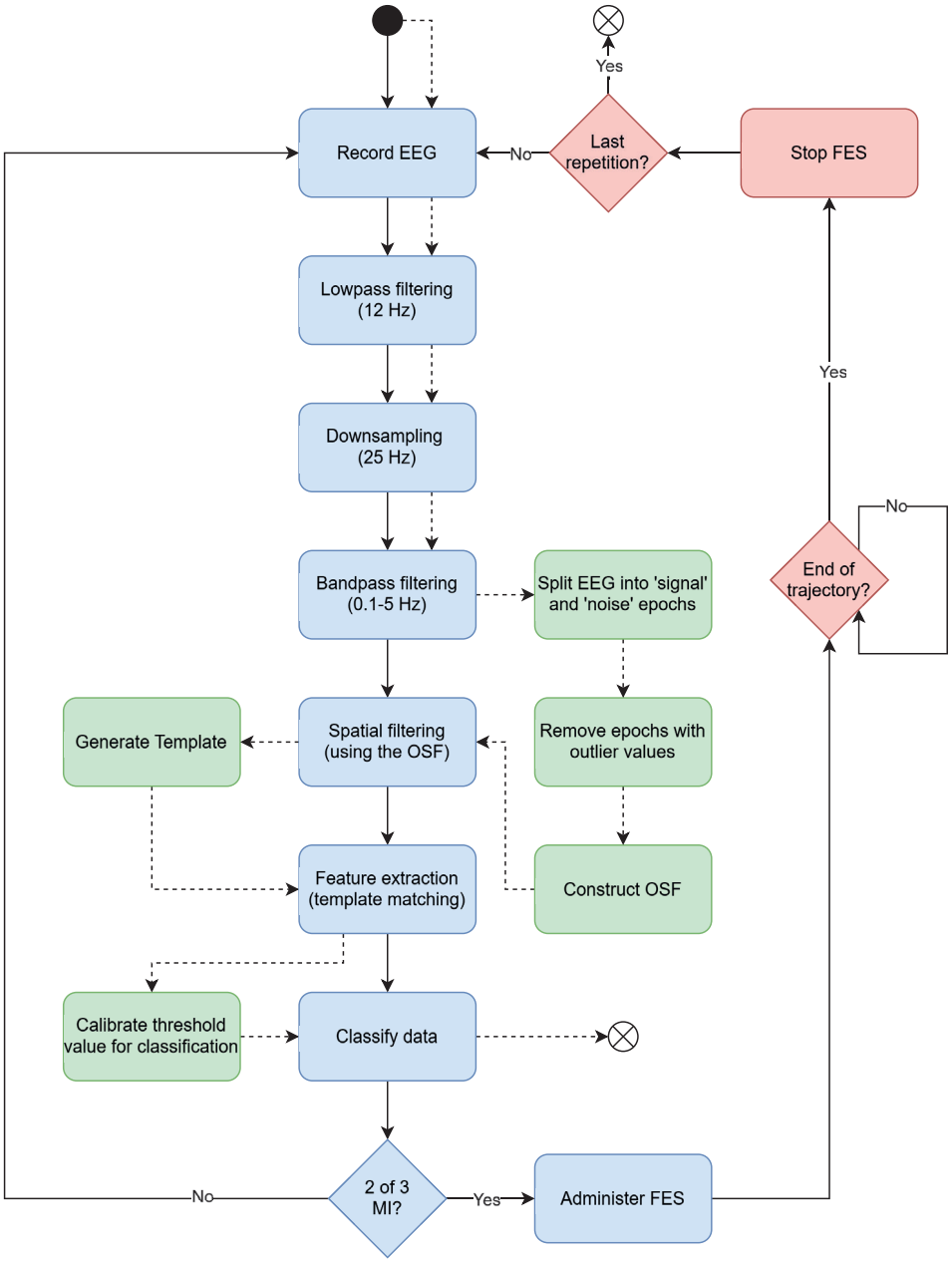


Fig. 3.2: Overview of the BCI functioning during online use and during calibration. Blue elements and solid arrows signify the primary processes of the BCI during online use. Green elements signify processes exclusive to the BCI calibration, and the total calibration process is outlined using dashed arrows. Red elements signify processes relevant to the functioning of the system, which are handled outside in the remaining system control (not BCI related). The processes start at the filled circle, and end with the crossed circle. OSF: Optimized Spatial Filter; 2 of 3 MI: two out of three classifications of the BCI should indicate a movement intention (MI) before FES was administered. Inspired from [71].

and FES was applied [71]. The BCI only interfaced with the FES-delivery system [71]. Hence, ROBERT® worked as described in section 3.1, without interference from the BCI. Upon reaching the endpoint of the movement trajectory, the FES was automatically terminated [71]. During online use it was possible to adjust the threshold for the classifier, using a 'factor', in effect making the BCI more or less likely to classify incoming EEG as movement intention [71]. During pilot testing, it was found that the BCI could become unresponsive/too responsive over time. This was hypothesized to be a result of mental fatigue, concentration issues, or the out-of-lab environment in which the BCI was tested [71]. Hence there was a need for being able to counteract these scenarios. This was done by implementing the 'factor', which was multiplied with the set classification threshold value (j), which could be changed online by the experimenter [71]. This implementation addressed the system requirement 2(a)i (see section 1.3). Finally, the BCI only classified EEG data in a time window of one second prior to one second after a cue was presented to the trainee [71]. This was done, as the BCI would likely result in false triggers, if it continuously classified all incoming EEG, resulting in a great likelihood of administering FES when the trainee was not intending it to happen [71], leading to discomfort and neglecting NP IV.

3.3 Assist-as-needed control paradigm

To address objective B) and research question RQ2, a novel AAN control method was developed in Leerskov et al. 2024A for the hybrid robot-FES system [72].

The purpose of the AAN was to use the minimally required assistance to allow trainees of the system to complete the exercise trajectories (system requirement 3, see section 1.3) [72]. The AAN control strategy was implemented as a state machine in MATLAB R2021a and interfaced with ROBERT® through an ethernet cable, and the FES-delivery system and a custom EMG recording system (Aalborg University, Denmark) through a data acquisition and signal generation device (National Instruments USB-6212) [72].

In the developed system, a state machine was constructed to differentiate between four scenarios of patient capability [72]:

'Vol': The patient was fully capable of exercising on their own.

'FES Trig': The patient was able to initiate movement but not complete the exercise trajectory, prompting FES to be administered.

'FES Auto': The patient was not moving at all (presumably they were unable to do so on their own), prompting FES to be applied.

'FES & Mech': FES was being applied but the patient was not progressing in the exercise at an acceptable velocity (presumably they were too fatigued), prompting mechanical assistance to be applied by ROBERT®.

These scenarios fully encompassed all possible exercising scenarios and provided appropriate responses to them, minimizing the necessary assistance provided (AAN principle), with the goal of enabling and increasing the dose of exercise (NP I), in an intention-based manner (NP IV) [72].

The state machine is illustrated in figure 3.3. To change between the states, the state machine monitored the end-effector velocity of ROBERT® and the EMG [72]. The state machine "asked" a total of three questions to determine the appropriate state-transitions [72]. Starting in state 'Vol', the first question, Q1, was: "Is there any EMG activity in the next 10 sec.?" [72]. If 'Yes', the next question, Q2, was: "Is the movement velocity above 20 mm/s?" [72]. If Q2 was answered 'Yes', no assistance was needed; if Q2 was answered 'No', the state machine would transition to state 'FES Trig' and administer FES [72]. If Q1 was answered 'No', the state machine would transition to state 'FES Auto' and administer FES [72]. When the state machine was in either state 'FES Trig' or 'FES Auto', it would ask the last question, Q3: "Is the movement velocity above 20 mm/s?" [72]. If Q3 was answered 'Yes', no additional assistance was provided; if Q3 was answered 'No', the state machine would transition to state 'FES & Mech', and mechanical assistance was added in addition to FES [72].

The presence of EMG activity was determined by using an EMG-threshold, based on the average ± three times the standard deviation of three seconds resting EMG (referred to as 'SDx3') [72]. This EMG threshold was tested for the relevant hybrid system with other EMG detection algorithms in Rikhof et al. 2022 [80]. It was concluded that the algorithm 'SDx2' (same as 'SDx3', with two times standard deviation, rather than three) was the most successful, as it was more accurate in detecting the movement intentions of subacute stroke patients [80]. However, the study was completed in a lab-setting [80], whereas the testing of the AAN state machine was done in a non-lab setting [72] (system requirement 2(a)i). In this out-of-lab setting, 'SDx2' was deemed too sensitive, and 'SDx3' was thus employed [72].

The '10 sec.' in Q1, was chosen under the assumption that patients unable to generate EMG reaching a detectable level in 10 sec., would not be able to do so during the current exercise repetition [72]. The velocity threshold of '20 mm/s' in Q2 and Q3, was based on the average of 2 sec. of velocity data [72] and determined to be appropriate in able-bodied participants during pilot testing. Later, the appropriate values for stroke patients were found to be '5 sec.', and '1-5 mm/s', respectively, in pilot testing on patients [72]. It was found that the '10 sec.' wait to transition from 'Vol' to 'FES Auto' was too long when the dose of exercise was important [72] (NP I). Additionally, it was found that stroke patients were able to exercise voluntarily at lower velocities (5 mm/s during knee extension and 1 mm/s during dorsal flexion) during the pilot test [72]. This led to the conclusion that the original threshold of 20 mm/s was too high, and would result in unnecessary application of FES, in conflict with the AAN principle [72].

During use the AAN state machine would always start in the 'Vol' state, and progress to provide either FES or FES + mechanical assistance according to the answers for Q1-

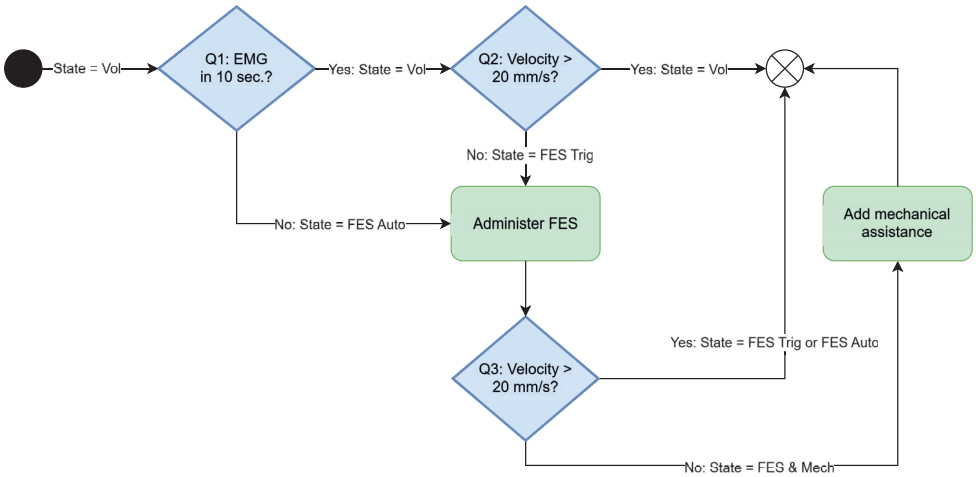


Fig. 3.3: Overview of the AAN state-machine functioning on a repetition-per-repetition basis. Each new exercise repetition begins at the filled circle in state Vol and ends with the crossed circle. Using Q1 ("Is there any EMG activity in the next 10 sec"), the state-machine either progress to state FES Auto and administer FES or remain in state Vol and progresses to Q2. Q2 ("Is the movement velocity above 20 mm/s?") is used to either progress to state FES Trig and administer FES or remain in state Vol and complete the exercise repetition with no assistance. When administering FES, the state-machine progresses to Q3 ("Is the movement velocity above 20 mm/s?"). From here the state-machine either progresses to state FES & Mech and administer mechanical assistance on top of FES, or remains in either state FES Auto or FES Trig, and completes the exercise repetition with pure FES assistance. If mechanical assistance is provided, the exercise repetition is guaranteed to complete in this state. Note that Q1-Q3 are continuously asked until either a state transition occurs, or the exercise repetition is completed. Inspired from [72].

Q3 [72]. Upon reaching the exercise trajectory endpoint, the provided assistance would be terminated, and the next repetition of exercise would begin again in the 'Vol' state, until the end of the exercise session [72].

3.4 Adaptive FES-parameter controller based on movement velocity

To address objective C) and research question RQ3, a novel controller capable of dynamically changing stimulation intensity on a repetition per repetition basis, the AFVC, was developed. Despite successfully considering the capabilities of the patient, and thereby theoretically facilitating recovery [33, 34, 38, 39], the AAN system of Leerskov et al. 2024B, did not fully comply with the AAN principle as it provided FES with fixed

stimulation parameters [72]. Hence, the adaptive FES velocity controller (AFVC) was introduced in Leerskov et al. 2024C [73].

The purpose of the AFVC was to expand the AAN capability of the system introduced in Leerskov et al. 2024B [72], by utilizing multiple stimulation levels with varying pulse durations, rather than fixed FES [73]. This would serve to limit the FES provided to the necessary level (AAN principle) and avoid excessive electrical stimulation [73]. Theoretically, it could simply be inserted into the state machine outlined in section 3.3, as a substitution of the fixed FES employed in Leerskov et al. 2024B [72]. The AFVC was implemented in MATLAB R2022a interface with ROBERT® through an ethernet cable and with the FES-delivery system through a data acquisition and signal generation device (National Instruments USB-6212) [73].

The AFVC employed a database mapping a stimulation level (a specific pulse duration) with an expected induced movement velocity profile (velocity samples over the course of the exercise trajectory) [73]. The specific stimulation levels to be used in the AFVC for an individual trainee, had to be explored manually, finding the limits of FES reliably being able to complete the exercise movement (lower boundary), and trainee tolerance/comfort (upper boundary) [73]. During calibration of the AFVC database, the stimulation levels deemed acceptable for an individual would be administered three times to generate the velocity data necessary to obtain an expected velocity profile of each stimulation level [73]. Hereafter, additional stimulation levels and their associated expected velocity profiles would be 'constructed', i.e., estimated as the average of adjacent stimulation levels (one above and one below) [73]. This procedure was chosen to minimize the time necessary for calibration, in accordance with system requirement 4, and reduced the calibration time necessary by half [73].

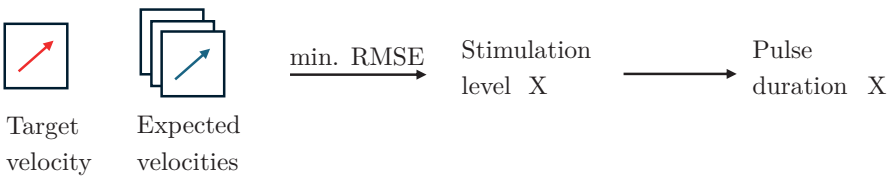
The goal of the AFVC was to minimize the error between a desired target movement velocity profile of the limb-robot contact point, and the movement velocity induced by the chosen stimulation level [73]. A target velocity profile was chosen rather than a target position/movement trajectory due to NP III ('variable practice', see section 1.1), emphasizing the need for variance in the movement pattern [73]. Hence, it would be suboptimal to target the reproduction of a specific movement pattern. The AFVC would choose the necessary stimulation level based on the RMSE between the expected velocity profiles of all stimulation levels, and the target velocity profile [73]. The stimulation level with the lowest RMSE between the expected and target velocity profile, was chosen for the next exercise repetition [73]. See an overview of the AFVC in figure 3.4.

During online use, the database would continuously update the expected velocity of a stimulation level, when new exercise repetitions were completed utilizing the respective stimulation level, and new velocity data was available [73]. Simply, the expected velocity of any given stimulation level, was the average velocity of the three most recent repetitions of movement completed using that stimulation level [73]. The RMSE to be used for determining the appropriate stimulation level would be recalculated before every exercise repetition [73]. Hence, the choice of stimulation level by the AFVC, was

A) Database:

Stimulation level :	Pulse duration :	Origin :	Velocity data:	Expected velocity :
Level 1	300 µs	Calibration	D1	V1
Level 2	312.5 µs	Constructed	D2	V2
Level 3	325 µs	Calibration	D3	V3
...	...	...	...	...
Level X	X: Y µs	Calibration	DX	VX

B) Choosing stimulation level :



C) Updating AFVC:

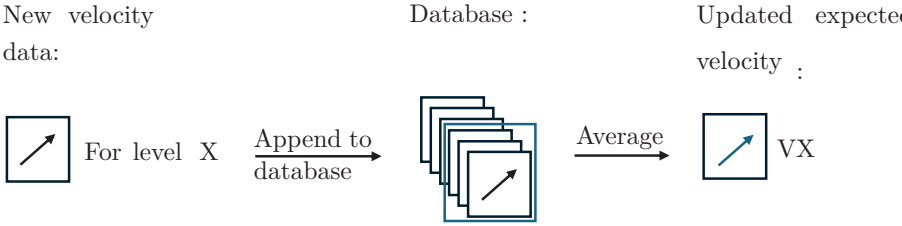


Fig. 3.4: An overview of A) the AFVC database, B) the choice of stimulation level, and C) the update mechanics of the AFVC. A) During calibration the database were constructed based on the recorded velocity data (D1-Dx). From this data, expected velocity profiles (V1-VX) were calculated for each stimulation level (nr. of levels and specific pulse durations depended on the pulse duration boundaries of each trainee) and matched with its corresponding stimulation level and thereby pulse duration, in the database. To save time during calibration, every other stimulation level's data was constructed. B) For every new repetition of exercise, the AFVC calculated the RMSE between the target velocity profile and each expected velocity profile in the database. The stimulation level associated with the lowest RMSE was applied for that exercise repetition. C) When a repetition of exercise had been completed, the velocity data recorded during the repetition was appended to the database. The expected velocity profile for the used stimulation level was updated, as the average of the three most recent velocity data entries in the database. Modified from [73].

always based on the most recent movement velocities obtained by each stimulation level [73].

The need for the adaptive nature of the AFVC was planned out of consideration for fatigue reducing the effectiveness of a given stimulation level. It was, however, further emphasized during unreported pilots showing a considerable degree of decrease and increase in the pilots' response to FES during exercising with the system. Later, a small study on the degree of change during exercising with the system was made, showing that velocity could change in the range -41% to 31% [81].

3.5 The overall system

The developed hybrid FES-robotic system allows for intention-based exercise, with FES being delivered upon detecting the intention of the patient to perform an exercise movement, in the form of a BCI-trigger (objective A) [71], or an EMG-trigger [72, 73]. The system actively considers the capability of the patient, allowing them to exercise voluntarily without any assistance if they are able, and providing assistance in the form of FES or FES+mechanical assistance, only if it is necessary to complete the exercise repetition (objective B) [72]. Finally, the system may adjust the stimulation intensity to maintain a selected movement velocity (objective C) [73]. These features may be used together with the base system in any combination, with minor modifications, e.g., the BCI- and the EMG-trigger may not work together, and velocity data recorded while mechanical assistance is provided, may not be appropriately used to update the expected velocity of stimulation levels in the AFVC. Finally, several design choices were made to reduce the time needed to setup and use the system, out of consideration for the limited time available during patient sessions [71–73]. Thus, the developed system constitutes a versatile hybrid FES-robotic rehabilitation platform, fulfilling the requirements listed in section 1.3.

Chapter 4: Thesis experimental studies and findings

In this chapter the experimental work of the three studies constituting this Ph.D. thesis is outlined. Study I developed and evaluated the BCI (outlined in section 3.2) for intention-based control of the FES-delivery in a hybrid FES-robotic rehabilitation system, in an out-of-lab setting. Study II developed and evaluated the AAN control strategy (outlined in section 3.3) for providing the minimal required assistance during exercising with a hybrid FES-robotic rehabilitation system. Finally, study III developed and evaluated a FES-controller (the AFVC, outlined in section 3.4) for limiting the pulse duration of FES to the necessary level while reaching a target velocity, during exercising in a hybrid FES-robotic rehabilitation system.

4.1 Study I

Title: Design and demonstration of a hybrid FES-BCI based robotic neurorehabilitation system for lower limbs. [71]

Authors: Kasper S. Leerskov, Erika G. Spaich, M. Jochumsen and Lotte N. S. Andreasen Struijk.

Journal: Article in preparation for submission to Biomedical Signal Processing and Control.

Study I concerned objective A) of the thesis "Design and evaluate a BCI based intention detection method for control of a FES-robotic rehabilitation system" and research question RQ1: "How can a BCI be designed to provide intention-based exercise with a Hybrid FES-Robotic rehabilitation system". Thus, it primarily concerned the development and test of the hybrid FES-robotic rehabilitation system with BCI-triggered administration of FES. The reasoning behind the BCI was to allow patients with no

voluntary muscle activity to engage actively in exercise by intentionally triggering the delivery of FES, contributing to and improving the expected outcome of the exercise (NP IV).

10 able-bodied participants were recruited for the experiment, which was conducted in an out-of-lab environment (office setting). Following the mounting of EEG and EMG electrodes (over the rectus femoris), as well as the calibration of the base system (ROBERT® movement trajectory and resistance, and FES amplitude), participants were asked to complete 50 repetitions of a 'minor knee extension movement', to obtain data for calibrating the BCI. A 'minor knee extension movement' was defined as reaching two times the participant's resting EMG level briefly during initiation of a knee extension movement (feedback on EMG amplitude was provided) and relax. Each repetition of the movement during calibration was separated by 10 sec., guided by a cue presented to the participant. Following recording of 50 repetitions of the movement, the BCI was calibrated (see section 3.2).

Participants were then asked to complete as many BCI-triggered exercise repetitions as possible in 60 min, with small breaks every 20 repetitions. During the online use of the BCI, the same 'minor knee extension movement' was used. Participants were prompted to attempt BCI activation by a cue, which was presented after a) 10 sec., if the BCI was unsuccessful in detecting the movement intention of the previous repetition, or b) 3 sec. following the return of the participant's leg to the start of the exercise trajectory, if the BCI had detected the movement intention, activated FES, and the participant had completed an exercise repetition.

Before the calibration of the BCI and after the 60 minutes of BCI-triggered exercising, neurological measurements were taken to quantify any acute neuroplastic changes. This was motivated by previous BCI-triggered electrical stimulation interventions showing remarkable acute changes [82, 83], despite the concrete intervention was considerably different. Measurements were taken related to changes in the movement-related cortical potential, somatosensory evoked potentials, and conditioned H-reflexes (homosynaptic depression, presynaptic inhibition, and reciprocal inhibition) [84]. No trend for changes was found for any change within these measurements – hence they were not reported.

The study included quantifying: the performance of the BCI, the time needed to use the system, and the participants' perception of exercising with the system. The true positive rate (TPR) of the BCI classification was on average of 62.9 ± 9.2% and was in the range 41-75% (see figure 4.1). The latency of the BCI, defined as the difference between the detection of movement intention of the BCI and the time of peak negativity in the movement-related cortical potential of the participants, was on average of -700 ms, ranging from -978 to -436 ms. On average 31.5 ± 3.3 minutes were spent on setting up and calibrating the system by the PhD student, until it was ready for use. Participants found the system moderately taxing to use (NASA TLX total score of 8.5 out of 20), with performance and mental load being the primary contributors with a median NASA TLX score of 45.0 (interquartile range (IQR): 46.0) and 37.5 (IQR: 18.0), respectively.

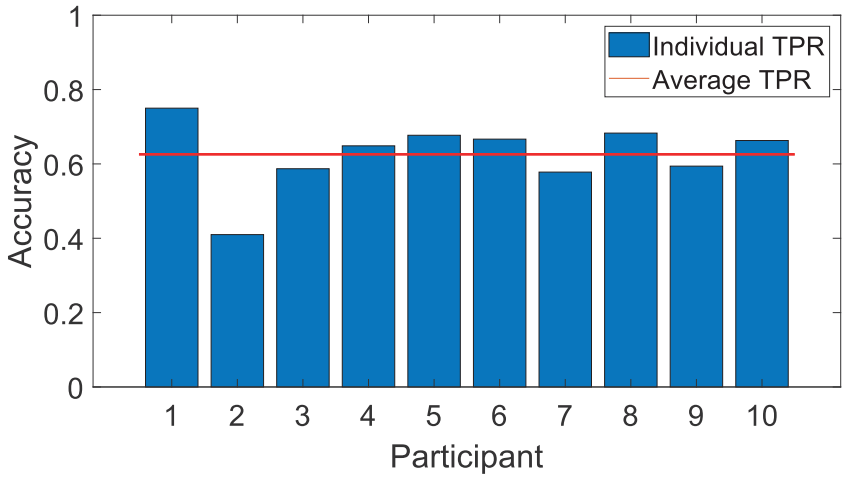


Fig. 4.1: Visual representation of individual TPR achieved during use of the BCI. The red line indicates the mean TPR across participants.

However, participants still indicated moderately high median level of comfort (6.0, IQR: 3.3), enjoyment (5.5, IQR: 3.0) and 'no pain' (5.5, IQR: 4.0) associated with the exercise, with a moderately low median level of tiredness (1.5, IQR: 5.0).

Thus, the study demonstrated that it was possible to use a BCI for intention-based triggering of FES in a hybrid FES-robotic exercise system for in-bed use, in an out-of-lab environment, for able-bodied participants. Hence, study I demonstrated the feasibility of utilizing a BCI to engage trainees in active intention-based exercise with a hybrid FES-robotic rehabilitation system. Such a system would allow those with little-to-no muscular control to pair their active participation with the executed movement/exercise, which is essential for motor learning (NP IV). The study emphasized that the modest TPR may be boosted with using more EEG channels or better/more complex algorithms for processing and classifying the EEG. Yet, this should be balanced with the simplicity of using the system, which may overall hinder the adoption of the system in any clinical setting, where specific BCI knowledge may not be available, and time for setup and calibration of a BCI is a limited resource. The study also highlighted that the amount of time spent setting the system up could be a hindrance for clinical use, but, as the system represents an advanced rehabilitative option for patients with little to no other alternatives, the inappropriate setup time would likely be worthwhile.

4.2 Study II

Title: A Robot-Based Hybrid Lower Limb System for Assist-As-Needed Rehabilitation of Stroke Patients: Technical Evaluation and Clinical Feasibility. [72]

Authors: Kasper S. Leerskov, Cindy J. H. Rikhof, Erika G. Spaich, Strahinja Dosen, Gerdienke B. Prange-Lasonder, Erik C. Prinsen, Johan S. Rietman and Lotte N. S. Andreasen Struijk.

Journal: Computers in Biology and Medicine, vol. 179., DOI: 10.1016/j.compbiomed.2024.108839

Study II was concerned with objective B) of the thesis "Design and evaluate the feasibility of an assist-as-needed approach for the FES-robotic rehabilitation system" and research question RQ2: "How can an AAN control strategy be designed for a hybrid FES-robotic rehabilitation system?".

Hence, the study was concerned with developing an AAN functionality for the hybrid FES-robotic rehabilitation system. This was motivated by several consideration. Firstly, albeit the system primarily targeted patients with some degree of muscular control, it should be useable for any patient no matter their functional capability. Specifically, the system was developed for stroke patients, who may present very differently despite being affected in similar cortical areas. Furthermore, patients exercising with the system may be prone to fatigue, and thus changing their physical capability rapidly during a single exercise session. Thus, depending on their initial state and how patients would progress during exercise, the system had to adapt to the patients' capabilities, for the exercising to continuously be optimal from a rehabilitation point of view, i.e., provide the minimal necessary assistance (AAN principle). If the system provided too much assistance, "slacking" could become an issue and rehabilitation outcomes could be compromised; If the system provided too little assistance, no meaningful exercise would be completed. Hence, the AAN for the hybrid FES-robotic rehabilitation system (see section 3.3) usable for in-bed rehabilitation was developed and tested.

The study was split in two: a technical validation study on 10 able-bodied participants in an out-of-lab setting, and a clinical feasibility test on two stroke patients in a lab-setting.

During the technical validation study, participants were asked to simulate specific behavior, mimicking that of patients with varying degrees of physical capability, to trigger each of the system's four different states 10 times each, for both knee extension and ankle dorsal flexion exercise. This test should reveal if the system could reliably detect the different levels of physical capability, and act appropriately. To trigger the four different states, the participants were asked to:

- During 'Vol': Exercise with their own non-influenced effort in the entire exercise trajectory.
- During 'FES Trig: Make a small initial movement, simulating a "movement attempt" and then remain still until the system administered FES.
- During 'FES Auto: To remain completely still and await the system to administer FES.
- During 'FES & Mech: To remain completely still and await the system to administer FES, although FES would be turned off during this test. Hence, no movement would be produced, prompting the system to administer mechanical assistance.

The study included quantified: the accuracy of the AAN state machine in providing the correct assistance to the simulated behavior of able-bodied participants, describing the progression of the assistance provided for the patients during exercise, and the fatigue experienced by the patients during exercise. The test showed that the system indeed recognized the simulated behavior of the able-bodied participants and changed state appropriately in 97.2 ± 2.2% and 96.6 ± 5.3% of repetitions, for knee extension and dorsal flexion, respectively (see figure 4.2).

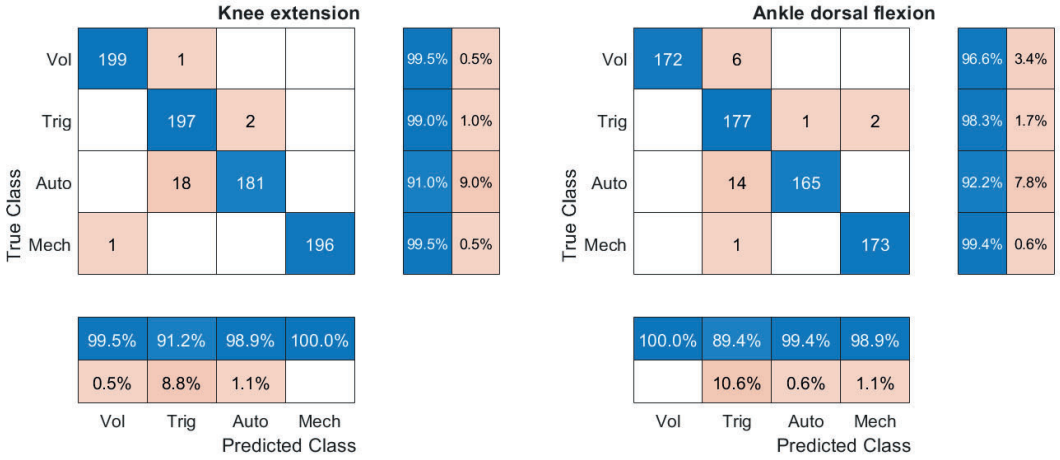


Fig. 4.2: Confusion matrix describing AAN state-machine transitions during testing of the four states, for both knee extension and ankle dorsal flexion exercises. The vertical column to the right of the confusion matrices describes how many percent of the true class occurrences were correctly classified (resulted in the right state transition). The horizontal column under the confusion matrices describes how many percent of the predicted classes were belonging to the true class (resulted in the right state transition). 'Trig': FES Trig. 'Auto': FES Auto. 'Mech': FES & Mech. Modified from [72].

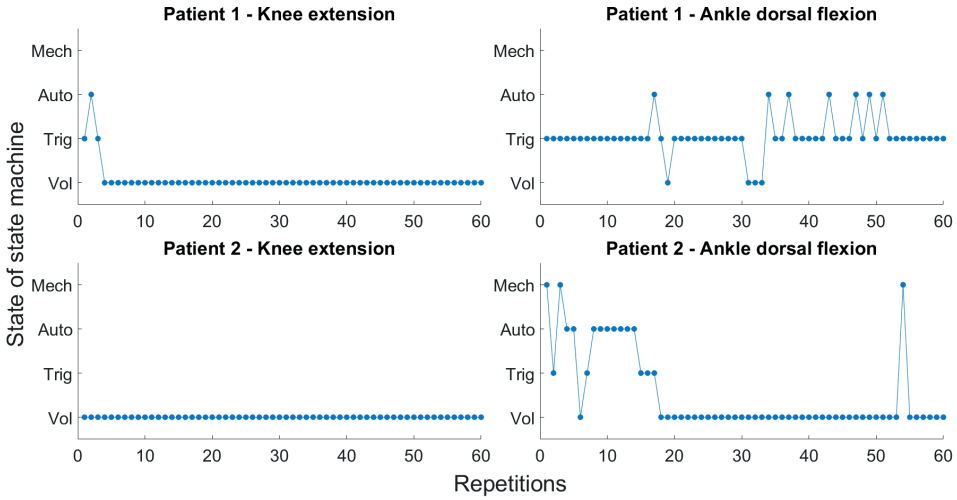


Fig. 4.3: AAn overview of the AAN state-machine transitions during knee extension and ankle dorsal flexion exercise of the two patients. Modified from [72].

During the clinical feasibility test two stroke patients exercised with the system naturally, meaning that they did not simulate any specific behavior and were not asked to do anything other than exercise to the extent of their ability. Two surprising results came from this test. Firstly, patient 1 had a Motricity Index of 0 for the lower extremity, yet they could complete 95% of the knee extension exercise repetitions of the study, without any assistance by the system (see figure 4.3). It should be noted that this was resistive exercise. Secondly, patient 2 started their dorsal flexion exercise requiring extensive assistance, notably the state 'FES Auto' was used a 9 out of the first 17 repetitions, suggesting that the patient was unable to produce detectable EMG during this time. Hereafter, however, patient 2 progressed to exercise without any assistance of the remaining 43 repetitions (except for one). Additionally, the two patients tolerated the exercise with the system well, providing a mean fatigue score of 2 and 2 (out of 10), respectively, for the knee extension exercise, and 4 and 5.5 (out of 10), respectively, for ankle dorsal flexion exercise.

The study demonstrated that the developed AAN could adjust the assistance provided to both able-bodied participants and stroke patients, providing the least amount of assistance necessary for completing the exercise. This ensures a high level of active participation in the exercise, important to facilitate recovery (NP IV). It was highlighted that the additive way of providing a combination of FES and mechanical assistance in the developed AAN control strategy, bypassed the need for complex control systems

needed to balance the torque product of either assistance modality. This in turn reduced the necessary calibration steps required, and thereby the setup time of the system.

4.3 Study III

Title: Dynamic Multi-level Control of Electrical Stimulation During Hybrid FES-robotic Exercise. [73]

Authors: Kasper S. Leerskov, Lotte N. S. Andreasen Struijk, Strahinja Dosen and Erika G. Spaich.

Journal: Article in preparation for submission to Biomedical Signal Processing and Control.

Study III was concerned with objective C) of the thesis "C) Design and evaluate a controller for adjusting stimulation parameters of FES in the hybrid FES-robotic rehabilitation system for improved AAN control" and research question RQ3: "How can FES stimulation parameters be controlled to improve the AAN control strategy for a hybrid rehabilitation system?".

The need for a controller to adapt the stimulation parameters of the FES provided in an AAN context, was brought on by the fact that FES induced fatigue, and hence, unadjusted stimulation parameters would eventually be inadequate to produce the same movement. Additionally, the result of study II showing that patient 2 needed less assistance over time, implied that fixed stimulation parameters may also constitute assistance that is more than necessary. Hence, the FES-controller (AFVC) was developed (see section 3.4).

The AFVC was tested in 10 able-bodied participants, in an out-of-lab setting. Immediately following calibration of the AFVC, the expected velocity profiles of each stimulation level were saved and used as the velocity target profiles for the test. Therefore, the velocity target profiles, and the number of tests was determined for each participant individually. Since the expected velocity profiles and target velocity profiles following the calibration were identical, the same stimulation level would be utilized through the entire test of its respective corresponding target velocity profile, if no change in the participants' responses to FES occurred. Each velocity target profile was used in a randomized order as the target, in 10 successive exercise repetitions. The updated expected velocity profiles from previous exercise repetitions carried over, whenever the target velocity profile changed.

The AFVC was able to maintain an average induced movement velocity with 7.1 $\pm$ 11.3% deviation from the average target velocity, across all participants (see figure 4.4). This, however, was despite the response to FES changed significantly in the experiment. Participants were split into two groups based on whether they experienced an average increase or an average decrease in the induced movement velocity. The velocity of each stimulation level for the two groups changed either an average of 18.8 $\pm$ 19.1%, or -10.6 $\pm$ 12.6% from the initial to the final repetitions of stimulation. To cope with this, the

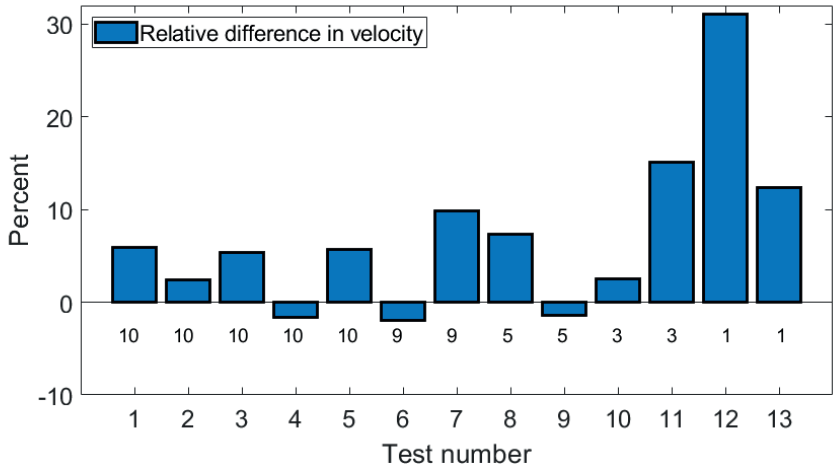


Fig. 4.4: The average percentage difference between the target velocity and the achieved velocity across participants, during testing of the AFVC. Each bar represents the average velocity difference for 10 repetitions of exercise across participants. The total number of tests for each participant was determined individually and followed the number of target velocity profiles for the participant. Hence, the number under each bar represents the number of participants who completed the respective number of tests. Modified from [73].

AFVC only chose the stimulation level associated with the target following calibration in 23.5 ± 9.1% of the repetitions, and in 20.2 ± 13.4% of the repetitions it deviated more than two stimulation levels from the one associated to the target. Finally, the whole setup of the system, including calibrating the AFVC, took 20.5 minutes.

The study showed that the AFVC could maintain a target velocity with an error of 7.1 ± 11.3%, and that it was able to adapt (update expected velocities) and change pulse duration to keep up with the changing responses to FES. Hence, the AFVC could adjust the assistance provided, as needed (i.e., providing longer or shorter pulse durations; the AAN principle), resulting in a nearly maintained target velocity. It was highlighted that the changes in response to repeated FES observed while exercising with the hybrid FES-robotic system, were surprising. Particularly, that the positive changes were observed, i.e., velocity of movement increased rather than decreased, as would be expected with induced fatigue. The study also highlighted that the cause of the positive changes in response to FES is yet unknown but hypothesized to be due to potentiation.

Chapter 5: Discussion

5.1 Main findings

This PhD concerned the development of a hybrid FES-robotic rehabilitation system for severely impaired patients, usable while in bed. In that respect, a BCI was developed to allow weak patients to do intention-based exercise for facilitating motor learning, through their active participation (through intent) in the movements produced by the system [71]. Additionally, to improve the motor learning facilitating capabilities of the system, an AAN control strategy was developed and tested in able-bodied participants and in a pilot study with stroke patients [72]. This was done in a novel way by additively combining FES and mechanical assistance, controlled by a state machine [72]. Finally, an automatic controller for the adjustment of the FES intensity, i.e., the AFVC, was developed, to further elaborate the AAN capability of the system, and minimize the FES employed by the system, to the minimum required for maintaining a target velocity [73].

5.1.1 Design and evaluate a BCI based intention detection method for control of a FES-robotic rehabilitation system

The BCI was designed to detect the presence of a MRCP of the lower limb and subsequently deliver FES (see section 3.2). This way the trainee's intention of moving was coupled with the movement produced by the FES, thereby facilitating intention-based exercise [71].

The BCI was found to be successful in controlling the delivery of FES in the hybrid FES-robotic rehabilitation system [71]. Yet, the modest TPR of $62.9 \pm 9.2\%$ is relatively low [71]. Yet, another study with a TPR of $67.15 \pm 7.87\%$ found acute neuroplastic effects following their BCI-electrical-stimulation based intervention [82], suggesting that it is feasible that TPR of the BCI of this thesis is sufficient to induce neuroplastic effects [71]. However, an extensive protocol of neuroplastic investigations [84] were conducted to see if the coupling of participants' intent to the induced movements would be sufficient to show some degree of acute plasticity, following the exercise [71]. These investigations were ultimately unsuccessful in finding any trends of acute changes [71].

Although other studies did find impressive acute differences following relatively short BCI-electrical stimulation-based interventions [82, 85], it was found that the differences in the studies' methodology were too great to be of appropriate comparison [71]. Likely, acute neuroplastic changes were unreasonable for the intervention, as most studies using similar technology and exercising with multiple joints and muscles have intervention times ranging from several days to several months [15, 24, 71].

The BCI was found to be feasible from a technical point of view, while the feasibility of employing the BCI-controlled version of the system in a clinical setting was found to be ambiguous [71]. The ambiguity stems from the consideration that the BCI is time-consuming to set up, despite only using five electrodes, and to calibrate (total setup and calibration time: 31.5 ± 3.3 minutes), which may be incompatible with clinical practice where time is a scarce resource [63, 64, 71]. Yet, the system facilitated intention-based exercise, which in accordance with NP IV ('active participation') should facilitate recovery [5, 33, 38, 39], and the target group for the system have few to no alternatives for this type of exercising [71]. Hence, there is an argument to be made that the BCI version of the system may be worthwhile, despite the considerable setup and calibration time [71].

5.1.2 Design and evaluate the feasibility of an assist-as-needed approach for the FES-robotic rehabilitation system

The AAN control was designed to additively provide assistance to trainees, based on four states/scenarios [72]: Vol: The trainee was able to exercise without assistance; FES Trig: The trainee was able to initiate a movement but not complete it, resulting in the delivery of FES; FES Auto: The trainee was unable to initiate a movement, resulting in the delivery of FES; FES & Mech: The trainee was unable to complete the movement despite assistance in the form of FES, resulting in the delivery of mechanical assistance [72].

The AAN control strategy was found to be technically sound as it applied the correct assistance to simulated behavior in 97.2 ± 2.2% and 96.6 ± 5.3%, for knee extension and ankle dorsal flexion, respectively [72]. Additionally, the AAN was found to be clinically feasible, as exercising with the developed system was well tolerated in stroke patients, and even found to facilitate better the utilization of the patients' own resources [72].

The improvements found in the stroke patients, i.e., their decreased need of assistance by the system, may be caused by a multitude of factors, such as the phosphorylation of myosin regulatory light chains (main mechanism of 'potentiation', i.e., increased torque production following previous muscular contraction), temperature increases, increased excitability of motoneurons, increased recruitment of motor units, acute elevations in plasma catecholamines levels, increases in the circulating concentration of testosterone after exercise, learning effect and familiarization with the task, placebo effect and subject motivation, and finally changes in pennation angle [86, 87]. However, the finding of less

need for assistance of study II were later verified in a larger cohort of stroke patients [88]. Rikhof et al. 2024, tested the AAN controlled hybrid FES-robotic rehabilitation system in eight stroke patients [88]. The data related to stroke patients in study II, was taken from the cohort of patients in Rikhof et al. 2024 [72], hence the exercise procedure of the patients where the same [72, 88]. In Rikhof et al. 2024, it was found that the patients overall required some degree of assistance during the first set of 30 repetitions of knee-extension exercise, while no assistance was required in the second set (9% $\rightarrow$ 0%) [88]. Similarly, the number of repetitions requiring assistance during dorsal flexion exercise dropped considerably (56% $\rightarrow$ 33%) [88]. The median reported fatigue was 2, and 4 for knee-extension and dorsal flexion respectively [88], comparable to the mean of 2.0 ± 0.0 and 4.8 ± 1.0 reported for knee-extension and dorsal flexion, respectively, in study II [72]. These results suggest that the AAN control strategy can facilitate great utilization of patients' own resources for exercise [72], which according to NP IV would be ideal for promoting recovery [33, 34, 38, 39].

The AAN control strategy designed in study II provided two types of assistance: FES, or FES + mechanical assistance, and was deemed technically and feasibly sound [72]. Other systems combining FES and robotics working in unison, need to balance the contribution of force from either source during use, requiring several calibration steps [40, 49]. This was not necessary with the described implementation, leading it to be require less time to set up [72], making it more feasible for clinical use due to simplicity and time preservation. However, the simple design of the AAN makes it less compliant with the AAN ideology of "minimally required assistance" during exercising, as it lacks dimensionality in the provided assistance [72]. Hence, it was decided to pursue the development of a FES controller (AFVC) for grading the FES applied during exercise (study III) [72, 73].

Finally, since the AAN control designed requires no more setup or calibration than the base system (see section 3.3), it is as feasible in a clinical setting as the base system [72]. This is validated by the fact that the base system is currently being used in clinical settings, and recently implemented the developed AAN control as part of product by Life Science Robotics ApS [75].

5.1.3 Design and evaluate a controller for adjusting stimulation parameters of FES in the hybrid FES-robotic rehabilitation system for improved AAN control

Study III introduced the AFVC; a FES controller that was designed to be implemented in the AAN control strategy of study II [73]. The AFVC worked by utilizing a database associating a stimulation level (pulse duration) with an expected velocity profile and updating respective velocity profiles whenever new data was available [73]. By calculating the RMSE between a desired target velocity profile, and the expected velocity profiles, the AFVC could choose the optimal stimulation level to approach the target

velocity profile, for each exercise repetition [73].

The AFVC was found to be successful in maintaining a target velocity, albeit with a 7.1 ± 11.3% error, by choosing the most appropriate stimulation levels to reach the target velocity profile [73]. It was also found that participants had significantly different responses to FES between the exercise repetitions used during calibration, to the last of the test repetitions [73]. The participants' responses to FES changed either to an increased movement velocity, on average 18.8 ± 19.1%, or a decreased movement velocity, on average -10.6 ± 12.6% [73]. This was partly expected, which is why the AFVC was designed to be adaptable [73]. However, the adaptability of the AFVC was introduced as a consideration of modest levels of fatigue, which would reduce the achievable velocity of a given stimulation level [73]. However, the study demonstrated that significant increases in velocity occurred, which was surprising [73]. Additionally, the changes in response to FES was of such considerable magnitude, that in some cases, the target velocity ended up being unobtainable, as no stimulation level of the AFVC was able to reach it [73]. Just prior to participating in the experimental procedure of study III, participants were asked to sit idle through 50 repetitions of FES, as a familiarization/warm-up period [73]. The changes observed during those 50 repetitions were reported in Leerskov et al. 2022 [81]. Leerskov et al. 2022 also observed significant changes of movement velocity in a positive direction (18.6, standard error of mean: 4.9) [81]. These results, combined with the increased exercise capability of patients observed in Leerskov et al. 2024B [72] and Rikhof et al. 2024 [88], infers that the hybrid FES-robotic rehabilitation system developed in this work can promote, at least temporarily, an increased muscular output, voluntarily and elicited by FES [73]. As previously highlighted, the mechanism of this is not clear, but it is hypothesized to be partly explained by potentiation, an increase in muscular output followed by repeated voluntary or stimulation-based activation of muscles [73, 86, 87]. Furthermore, despite the changes in movement velocity of either 18.8 ± 19.1% or -10.6 ± 12.6%, the AFVC deviated from the target velocity profile with only 7.1 ± 11.3% [73]. This was deemed indicative of the AFVC's ability to alter stimulation parameters appropriately to reach the desired target velocity profile [73].

Additionally, the design of the AFVC allowed a reduced calibration time, as the internal model for stimulation levels were partly "constructed", reducing the need for obtaining data for calibration [73]. The AFVC in its current state required 7.2 minutes longer to set up, compared to the base system, with potential to reduce this if the "construction" capability of the AFVC calibration procedure was expanded, further reducing the required data and time to obtain the full AFVC database [73].

5.1.4 The overall system

Study I, II, and III, all required design and implementation, and was concerned with testing of the individual sub-systems [71–73]. However, a focus was that the three systems were possible to combine. Hence, the BCI could work as a replacement of the

EMG trigger in the base system, regardless of whether the AAN and/or AFVC was implemented in the same version of the system. Despite this focus, time and resources did not allow for the combined testing of the sub-systems developed in the three studies, although this would have been interesting to pursue.

It should be noted that the highlighted concerns with the systems in terms of setup time and complexity, would be additive in a full combined system. It is therefore uncertain how truly feasible the complete system (combining sub-systems of study I – III) would be, with the current state of each sub-system. There is, however, tremendous opportunity for optimization and development of automatized sub-components, which would reduce the need for manual control and calibration of the sub-systems (true for most complex systems), that may make the complete system, or the individual sub-systems, more suitable for clinical practices.

5.2 Limitations

The sub-systems developed in studies I (BCI) and III (AFVC), were designed to be used for patients [71, 73]. Despite this the studies were completed in an able-bodied group [71, 73]. This is a necessary first step for any development process, to make sure that the systems are functional and safe, prior to testing in a patient group. However, the applicability of the results of these studies for the intended patient group, is limited [71, 73]. Yet arguably the feasibility results related to setup times are fairly transferable for patients that may tolerate FES, and where spasticity is not overly prominent. It would have been ideal to do, at least, feasibility testing of study I and III in stroke patients, however, study I was conducted during the COVID-19 pandemic, where patient contact was extremely limited, and it was not possible to recruit patients for study III, due to limited time and resources.

Despite all sub-systems being successfully implemented [71–73], certain aspects could be improved in each. For the BCI, it would be ideal to improve the TPR [71]. This, however, should be achieved in a way that does not add considerably to the setup and calibration time. Likely, this is achievable using more complex but automated processing techniques, including pre-processing, feature extraction and classifiers [71]. For the AAN, in line with the development of the AFVC in study III, it would be interesting to pursue a graded approach to the mechanical assistance, to further improve the AAN aspect of exercising with the system [72]. For the AFVC, the adaptive capability of the controller should be finetuned, including updating of the learning effect from newly available data, and the adaptation of all stimulation levels upon arrival of new data, rather than just the corresponding stimulation level [73]. However, all these improvements require further development and mandate new studies for verification.

Despite a focus on simplicity and feasibility of the designed sub-systems to be used in clinical settings, some degree of manual calibration was still necessary, limiting simplic-

ity and feasibility. In the BCI, a factor could be adjusted for making intention detection more or less likely [71] and in the AAN, parameters for the state machine transitions could be altered [72]. This will limit the use of the systems to the personnel that are trained in using the system and comfortable altering these variables, if necessary. Additionally, if adjustments are frequently required, the potential self-governed exercising possible with the systems are compromised. Additionally, no study assessed healthcare personnel's acceptability of the sub-systems, which would have validated whether the systems truly are feasible.

Finally, spasticity was considered during the development of the sub-systems, however, little-to-no features were implemented to cope with spasticity during use of the system [72]. This was in part due to the focus of the study, and partly due to the base system already having a "safe-mode" in which the leg of the trainee is locked in place, with room for limited movability in all directions, designed to limit adverse movements and risk of injury [72]. Still, spasticity and how to manage it should be further considered for the developed systems.

5.3 Conclusion

This PhD developed and evaluated the first BCI, and AAN control system, for a hybrid FES-robotic rehabilitation system targeting severely affected patients, allowing for in-bed exercise. Throughout the PhD, 30 able-bodied participants and two stroke patients have been participating in tests of the implemented sub-systems. It has contributed to a better understanding of the possibilities within hybrid rehabilitation systems, as well as highlighted important aspects and considerations for designing future hybrid systems. Following the aims of the PhD, the conclusions are:

A) Design and evaluate a BCI based intention detection method for control of a FES-robotic rehabilitation system: The implemented BCI obtained a TPR of 62.9 ± 9.2% in an out-of-lab setting. This TPR was deemed sufficient for driving neuroplastic changes, based on another study showing similar TPR with documented upregulation of MEPs following a single intervention session. Hence, the BCI was successfully capable of facilitating intention-based exercise in the hybrid FES-robotic rehabilitation system, with the potential to promote recovery. The feasibility of the developed system is uncertain, due to the long setup and calibration time (31.5 ± 3.3 minutes). Yet the system is deemed relevant, as it may facilitate intention-based exercising with a hybrid FES-robotic rehabilitation system, in a population with limited alternative hybrid therapies. Hence, the proposed BCI was deemed a success for providing intention-based exercise in a hybrid FES-robotic rehabilitation system.

b) Design and evaluate the feasibility of an assist-as-needed approach for the FES-robotic rehabilitation system: The developed AAN control strategy

was deemed successful in adjusting the necessary assistance to match capability of the trainee, as I correctly identified and provided the appropriate assistance to simulated behavior of able-bodied participants (97.2 ± 2.2% and 96.6 ± 5.3%, for knee extension and ankle dorsal flexion, respectively). Additionally, the AAN was deemed clinically feasible, as two stroke patients exercised with the system, which changed the assistance provided according to their exercise capability, and even facilitated more assistance-free exercising in patient 2. The exercising with the system was well tolerated by both stroke patients (average fatigue score of 2, and 4.75, for knee extension and ankle dorsal flexion, respectively). Hence, the proposed AAN control strategy for a hybrid FES-robotic rehabilitation system was overall deemed a success.

C) **Design and evaluate a controller for adjusting stimulation parameters of FES in the hybrid FES-robotic rehabilitation system for improved AAN control:** The AFVC was deemed successful in adjusting the pulse duration of the administered FES to reach a specific target velocity (with a deviation of 7.1 ± 11.3%). This was accepted as the trainee's average responses to FES changed either 18.8 ± 19.1% (for those exhibiting an increased response), or -10.6 ± 12.6% (for those exhibiting a decreased response). Thereby, the AFVC adjusted the stimulation parameters to maintain a target velocity profile more efficiently than fixed FES, effectively providing FES as needed. Hence, the proposed AFVC was deemed a success for changing the stimulation parameters of FES in a hybrid FES-robotic rehabilitation system, to improve the AAN capability of the system.

5.4 Future perspectives

The sub-systems developed in study I and III should be tested in stroke patients, to validate the applicability of these systems in the appropriate target group [71, 73]. Likewise, all sub-systems should be tested in a real clinical context, to appropriately gauge the feasibility (for study I and III; feasibility of the AAN was established by Rikhof et al. 2024 [88]) and effect of using them in a clinical context [71–73]. Additionally, healthcare personnel should be introduced to the systems and their acceptability of the systems should be assessed, as well as the level of manual calibration that would be appropriate when using such complex systems.

As highlighted previously, certain aspects of the sub-systems may be improved to boost their efficacy and/or clinical feasibility. This includes assessing the possibility of making the manually adjusted parameters automatically calibrated, including assessing the feasibility of such automated procedures. The manually adjusted parameters, which may be candidate for automation, all relate to when FES should be applied or not. Whether it is feasible, let alone ethical, to automatize calibration/adjustment of such parameters, is up to debate. However, if achieved, the use of the system would be more

self-governed by the patient, and it would be more feasible that the healthcare personnel in charge will be able to attend several patients' exercise at the same time, compared to the current implementation.

Spasticity coping needs to be addressed in the future versions of the system. As an estimated 39.5% of stroke patients suffer from spasticity [89, 90], it is essential that the system can be used safely, even in the presence of spasticity. Alternatively, the level of spasticity that should be considered a contraindication of exercise with the system and its sub-systems, should be assessed [72], although this may affect the relevance of the system.

Finally, the strength of the developed system is its ability to perform intention-based, AAN-controlled exercise in a population unable to get out of bed [72]. However, the system may just as well be used in other populations not bound by a bed, such as less severely affected stroke and spinal cord injured patients [72]. Demonstrating the feasibility and relevance of the system in these groups would of great interest for scalability of the system [72].

References

[1] Simone Pittaccio, Lorenzo Garavaglia, Erika Molteni, Eleonora Guanziroli, Filippo Zappasodi, Elena Beretta, Sandra Strazzer, Franco Molteni, Elena Villa, and Francesca Passaretti. Can passive mobilization provide clinically-relevant brain stimulation? a pilot eeg and nirs study on healthy subjects. In *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pages 3547–3550. IEEE, 7 2013. ISBN 978-1-4577-0216-7. doi: 10.1109/EMBC.2013.6610308. URL http://ieeexplore.ieee.org/document/6610308/.

[2] Alarcos Cieza, Kate Causey, Kaloyan Kamenov, Sarah Wulf Hanson, Somnath Chatterji, and Theo Vos. Global estimates of the need for rehabilitation based on the global burden of disease study 2019: a systematic analysis for the global burden of disease study 2019. *The Lancet*, 396:2006–2017, 12 2020. ISSN 1474547X. doi: 10.1016/S0140-6736(20)32340-0.

[3] Kalliopi Megari. Quality of life in chronic disease patients quality of life. *Health Psychology Research*, 2013. doi: 10.4082/hpr.2013.e27.

[4] Valery L Feigin, Benjamin A Stark, Catherine Owens Johnson, Gregory A Roth, Catherine Bisignano, Gdiom Gebreheat Abady, Mitra Abbasifard, Mohsen Abbasi-Kangevari, Foad Abd-Allah, ..., and Christopher J L Murray. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *The Lancet Neurology*, 20:795–820, 10 2021. ISSN 14744422. doi: 10.1016/S1474-4422(21)00252-0. URL https://linkinghub.elsevier.com/retrieve/pii/S1474442221002520.

[5] Roger Gassert and Volker Dietz. Rehabilitation robots for the treatment of sensorimotor deficits: A neurophysiological perspective. *Journal of NeuroEngineering and Rehabilitation*, 15:1–15, 2018. ISSN 17430003. doi: 10.1186/s12984-018-0383-x.

[6] Sheng Li, Gerard E. Francisco, and Ping Zhou. Post-stroke hemiplegic gait: New perspective and insights. *Frontiers in Physiology*, 9:1–8, 2018. ISSN 1664-042X. doi: 10.3389/fphys.2018.01021. URL https://www.frontiersin.org/article/10.3389/fphys.2018.01021/full.

[7] Eurostat. Persons reporting a chronic disease by level of disability (activity limitation), sex and age. https://ec.europa.eu/eurostat/databrowser/view/HLTH_EHIS_CD1D__custom_3209094/default/table?lang=en. (Accessed 8 November 2024).

[8] Poul Jennum, Helle K. Iversen, Rikke Ibsen, and Jakob Kjellberg. Cost of stroke: A controlled national study evaluating societal effects on patients and their partners. *BMC Health Services Research*, 15, 10 2015. ISSN 14726963. doi: 10.1186/s12913-015-1100-0.

[9] Henk T. Hendricks, Jacques Van Limbeek, Alexander C. Geurts, and Machiel J. Zwarts. Motor recovery after stroke: A systematic review of the literature. *Archives of Physical Medicine and Rehabilitation*, 83:1629–1637, 11 2002. ISSN 00039993. doi: 10.1053/apmr.2002.35473.

[10] Julie Bernhardt, Kathryn S. Hayward, Gert Kwakkel, Nick S. Ward, Steven L. Wolf, Karen Borschmann, John W. Krakauer, Lara A. Boyd, S. Thomas Carmichael, Dale Corbett, and Steven C. Cramer. Agreed definitions and a shared vision for new standards in stroke recovery research: The stroke recovery and rehabilitation roundtable taskforce. *International Journal of Stroke*, 12:444–450, 2017. ISSN 17474949. doi: 10.1177/1747493017711816. URL https://doi.org/10.1177/1747493017711816.

[11] Peter Langhorne, Janice M. Collier, Patricia J. Bate, Matthew N.T. Thuy, and Julie Bernhardt. Very early versus delayed mobilisation after stroke. *Cochrane Database of Systematic Reviews*, 2018, 10 2018. ISSN 1469493X. doi: 10.1002/14651858.CD006187.pub3.

[12] Julie Bernhardt, Erin Godecke, Liam Johnson, and Peter Langhorne. Early rehabilitation after stroke. *Current Opinion in Neurology*, 30:48–54, 2 2017. ISSN 1350-7540. doi: 10.1097/WCO.0000000000000404. URL https://journals.lww.com/00019052-201702000-00008.

[13] Remy Cardoso, Vitor Parola, Hugo Neves, Rafael A. Bernardes, Filipa Margarida Duque, Carla A. Mendes, Mónica Pimentel, Pedro Caetano, Fernando Petronilho, Carlos Albuquerque, Liliana B. Sousa, Cândida Malça, Rúben Durães, William Xavier, Pedro Parreira, João Apóstolo, and Arménio Cruz. Review physical rehabilitation programs for bedridden patients with prolonged immobility: A scoping review. *International Journal of Environmental Research and Public Health*, 19, 2022. ISSN 16604601. doi: 10.3390/ijerph19116420.

[14] Volker Dietz. *Clinical Aspects for the Application of Robotics in Locomotor Neurorehabilitation*, pages 209–222. Springer International Publishing, 2016. doi: 10.1007/978-3-319-28603-7_11. URL http://link.springer.com/10.1007/978-3-319-28603-7_11.

[15] Jan Mehrholz, Simone Thomas, Joachim Kugler, Marcus Pohl, and Bernhard Elsner. Electromechanical-assisted training for walking after stroke. *Cochrane Database of Systematic Reviews*, 2020, 10 2020. ISSN 14651858. doi: 10.1002/14651858.CD006185.pub5.

[16] Vaishnavi Warutkar, Ragini Dadgal, and Utkarsha R Mangulkar. Use of robotics in gait rehabilitation following stroke: A review. *Cureus*, 11 2022. doi: 10.7759/cureus.31075.

[17] Salheddine Ayad, Mohammed Ayad, Abdelkader Megueni, Erika G. Spaich, and Lotte N.S.Andreasen Struijk. Toward standardizing the classification of robotic gait rehabilitation systems. *IEEE Reviews in Biomedical Engineering*, 12:138–153, 2019. ISSN 19411189. doi: 10.1109/RBME.2018.2886228.

[18] Dennis R. Louie and Janice J. Eng. Powered robotic exoskeletons in post-stroke rehabilitation of gait: A scoping review. *Journal of NeuroEngineering and Rehabilitation*, 13, 6 2016. ISSN 17430003. doi: 10.1186/s12984-016-0162-5.

[19] Joseph Hidler, Diane Nichols, Marlena Pelliccio, Kathy Brady, Donielle D. Campbell, Jennifer H. Kahn, and T. George Hornby. Multicenter randomized clinical trial evaluating the effectiveness of the lokomat in subacute stroke. *Neurorehabilitation and Neural Repair*, 23:5–13, 1 2009. ISSN 15459683. doi: 10.1177/1545968308326632.

[20] Yong Hwa Park, Dae Hwan Lee, and Jung Ho Lee. A comprehensive review: Robot-assisted treatments for gait rehabilitation in stroke patients. *Medicina (Lithuania)*, 60, 4 2024. ISSN 16489144. doi: 10.3390/medicina60040620.

[21] Francesco Zanatta, Naima Z. Farhane-Medina, Roberta Adorni, Patrizia Steca, Anna Giardini, Marco D'Addario, and Antonia Pierobon. Combining robot-assisted therapy with virtual reality or using it alone? a systematic review on health-related quality of life in neurological patients. *Health and Quality of Life Outcomes*, 21, 12 2023. ISSN 14777525. doi: 10.1186/s12955-023-02097-y.

[22] Mohammad Milhem, Leonid Kalichman, David Ezra, and Deborah Alperovitch-Najenson. Work-related musculoskeletal disorders among physical therapists: A comprehensive narrative review. *International Journal of Occupational Medicine and Environmental Health*, 29:735–747, 2016. ISSN 1896494X. doi: 10.13075/ijomeh.1896.00620.

[23] Xikai Tu, Jian Huang, and Jiping He. Leg hybrid rehabilitation based on hip-knee exoskeleton and ankle motion induced by fes. *ICARM 2016 - 2016 International Conference on Advanced Robotics and Mechatronics*, pages 237–242, 2016. doi: 10.1109/ICARM.2016.7606925.

[24] Ana R. C. Donati, Solaiman Shokur, Edgard Morya, Debora S. F. Campos, Renan C. Moioli, Claudia M. Gitti, Patricia B. Augusto, Sandra Tripodi, Cristhiane G. Pires, Gislaine A. Pereira, Fabricio L. Brasil, Simone Gallo, Anthony A. Lin, Angelo K. Takigami, Maria A. Aratanha, Sanjay Joshi, Hannes Bleuler, Gordon Cheng, Alan Rudolph, and Miguel A. L. Nicolelis. Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. *Scientific Reports*, 6:30383, 9 2016. ISSN 2045-2322. doi: 10.1038/srep30383. URL http://www.nature.com/articles/srep30383.

[25] Jeremy L. Emken, Raul Benitez, and David J. Reinkensmeyer. Human-robot cooperative movement training: Learning a novel sensory motor transformation during walking with robotic assistance-as-needed. *Journal of NeuroEngineering and Rehabilitation*, 4, 2007. ISSN 17430003. doi: 10.1186/1743-0003-4-8.

[26] Yukiyo Shimizu, Hiroshi Kamada, Masataka Sakane, Shizu Aikawa, Hirotaka Mutsuzaki, Kenta Tanaka, Hajime Mishima, Akihiro Kanamori, Tomofumi Nishino, Naoyuki Ochiai, and Masashi Yamazaki. A novel exercise device for venous thromboembolism prophylaxis improves venous flow in bed versus ankle movement exercises in healthy volunteers. *Journal of Orthopaedic Surgery*, 25:1–7, 2017. ISSN 23094990. doi: 10.1177/2309499017739477.

[27] Janice L. Zimbelman, Stephen P. Juraschek, Xiaoming Zhang, and Vernon W.H. Lin. Physical therapy workforce in the united states: Forecasting nationwide shortages. *PM and R*, 2:1021–1029, 11 2010. ISSN 19341482. doi: 10.1016/j.pmrj.2010.06.015.

[28] Martina Maier, Belén Rubio Ballester, and Paul F.M.J. Verschure. Principles of neurorehabilitation after stroke based on motor learning and brain plasticity mechanisms. *Frontiers in Systems Neuroscience*, 13, 12 2019. ISSN 16625137. doi: 10.3389/fnsys.2019.00074.

[29] Tabea Aurich-Schuler, Fabienne Grob, Hubertus J.A. Van Hedel, and Rob Labruyère. Can lokomat therapy with children and adolescents be improved? an adaptive clinical pilot trial comparing guidance force, path control, and freed. *Journal of NeuroEngineering and Rehabilitation*, 14, 7 2017. ISSN 17430003. doi: 10.1186/s12984-017-0287-1.

[30] Lance L. Cai, Andy J. Fong, Chad K. Otoshi, Yongqiang Liang, Joel W. Burdick, Roland R. Roy, and V. Reggie Edgerton. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. *Journal of Neuroscience*, 26:10564–10568, 10 2006. ISSN 02706474. doi: 10.1523/JNEUROSCI.2266-06.2006.

[31] Martin Lotze, Christoph Braun, Niels Birbaumer, Silke Anders, and Leonardo G. Cohen. Motor learning elicited by voluntary drive. *Brain*, 126:866–872, 4 2003. ISSN 00068950. doi: 10.1093/brain/awg079.

[32] D.J. Reinkensmeyer, O.M. Akoner, D.P. Ferris, and K.E. Gordon. Slacking by the human motor system: Computational models and implications for robotic orthoses. In *2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 2129–2132. IEEE, 9 2009. doi: 10.1109/IEMBS.2009.5333978. URL http://ieeexplore.ieee.org/document/5333978/.

[33] Jesús de Miguel-Fernández, Joan Lobo-Prat, Erik Prinsen, Josep M. Font-Llagunes, and Laura Marchal-Crespo. Control strategies used in lower limb exoskeletons for gait rehabilitation after brain injury: a systematic review and analysis of clinical effectiveness. *Journal of NeuroEngineering and Rehabilitation*, 20:1–28, 2023. ISSN 17430003. doi: 10.1186/s12984-023-01144-5. URL https://doi.org/10.1186/s12984-023-01144-5.

[34] Shraddha Srivastava and Pei Chun Kao. Robotic assist-as-needed as an alternative to therapist-assisted gait rehabilitation. *International Journal of Physical Medicine & Rehabilitation*, 4, 2016. doi: 10.4172/2329-9096.1000370.

[35] Ingrid Brenner and Trent University. Effects of passive exercise training in hemiplegic stroke patients: A mini-review open access. *Sports Medicine and Rehabilitation Journal*, 3:1036, 2018.

[36] Gregory Brusola, Erica Garcia, Meagan Albosta, Audrey Daly, Konstandinos Kafes, and Michael Furtado. Effectiveness of physical therapy interventions on post-stroke spasticity: An umbrella review. *NeuroRehabilitation*, 52:349–363, 2023. ISSN 18786448. doi: 10.3233/NRE-220275.

[37] Alex Todhunter-Brown, Gillian Baer, Pauline Campbell, Pei Ling Choo, Anne Forster, Jacqui Morris, Valerie M Pomeroy, and Peter Langhorne. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database of Systematic Reviews*, 2023, 4 2014. ISSN 14651858. doi: 10.1002/14651858.CD001920.pub3. URL http://doi.wiley.com/10.1002/14651858.CD001920.pub3.

[38] J. F. Alingh, B. M. Fleerkotte, B. E. Groen, J. S. Rietman, V. Weerdesteyn, E. H.F. van Asseldonk, A. C.H. Geurts, and J. H. Buurke. Effect of assist-as-needed robotic

gait training on the gait pattern post stroke: a randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, 18, 12 2021. ISSN 17430003. doi: 10.1186/s12984-020-00800-4.

[39] Gilbert Masengo, Xiaodong Zhang, Runlin Dong, Ahmad B. Alhassan, Khaled Hamza, and Emmanuel Mudaheranwa. Lower limb exoskeleton robot and its cooperative control: A review, trends, and challenges for future research. *Frontiers in Neurorobotics*, 16, 1 2023. ISSN 1662-5218. doi: 10.3389/fnbot.2022.913748. URL https://www.frontiersin.org/articles/10.3389/fnbot.2022.913748/full.

[40] Di Ao, Rong Song, and Jinwu Gao. Movement performance of human-robot cooperation control based on emg-driven hill-type and proportional models for an ankle power-assist exoskeleton robot. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 25:1125–1134, 8 2017. ISSN 15344320. doi: 10.1109/TNSRE.2016.2583464.

[41] Kensuke Takenaka, Keisuke Shima, and Koji Shimatani. Hybrid rehabilitation system with motion estimation based on emg signals. *IEEE International Conference on Rehabilitation Robotics*, pages 1–6, 2023. ISSN 19457901. doi: 10.1109/ICORR58425.2023.10304746.

[42] Anusha Venkatakrishnan, Gerard E. Francisco, and Jose L. Contreras-Vidal. Applications of brain–machine interface systems in stroke recovery and rehabilitation. *Current Physical Medicine and Rehabilitation Reports*, 2:93–105, 2014. ISSN 2167-4833. doi: 10.1007/s40141-014-0051-4. URL http://link.springer.com/10.1007/s40141-014-0051-4.

[43] Ren Xu, Ning Jiang, Aleksandra Vuckovic, Muhammad Hasan, Natalie Mrachacz-Kersting, David Allan, Matthew Fraser, Bahman Nasseroleslami, Bernie Conway, Kim Dremstrup, and Dario Farina. Movement-related cortical potentials in paraplegic patients: Abnormal patterns and considerations for bci-rehabilitation. *Frontiers in Neuroengineering*, 7, 8 2014. ISSN 16626443. doi: 10.3389/fneng.2014.00035.

[44] Colin M. McCrimmon, Po T. Wang, Zoran Nenadic, and An H. Do. *BCI-Based Neuroprostheses and Physiotherapies for Stroke Motor Rehabilitation*, pages 617–627. Springer International Publishing, 2016. doi: 10.1007/978-3-319-28603-7_30. URL http://link.springer.com/10.1007/978-3-319-28603-7_30.

[45] Steven C. McGie, José Zariffa, Milos R. Popovic, and Mary K. Nagai. Short-term neuroplastic effects of brain-controlled and muscle-controlled electrical stimulation. *Neuromodulation*, 18:233–240, 2015. ISSN 15251403. doi: 10.1111/ner.12185.

[46] Alberto Plaza, Mar Hernandez, Gonzalo Puyuelo, Elena Garces, and Elena Garcia. Lower-limb medical and rehabilitation exoskeletons: A review of the current designs. *IEEE Reviews in Biomedical Engineering*, 16:278–291, 2023. ISSN 1937-3333. doi: 10.1109/RBME.2021.3078001. URL https://ieeexplore.ieee.org/document/9425437/.

[47] Eric T. Wolbrecht, Vicky Chan, David J. Reinkensmeyer, and James E. Bobrow. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 16:286–297, 6 2008. ISSN 15344320. doi: 10.1109/TNSRE.2008.918389.

[48] Urs Keller, Georg Rauter, and Robert Riener. Assist-as-needed path control for the pascal rehabilitation robot. In *IEEE International Conference on Rehabilitation Robotics*, 2013. ISBN 9781467360241. doi: 10.1109/ICORR.2013.6650475.

[49] Renyu Yang, Zhihang Shen, Yueling Lyu, Yu Zhuang, Le Li, and Rong Song. Voluntary assist-as-needed controller for an ankle power-assist rehabilitation robot. *IEEE Transactions on Biomedical Engineering*, 70:1795–1803, 6 2023. ISSN 0018-9294. doi: 10.1109/TBME.2022.3228070. URL https://ieeexplore.ieee.org/document/9978653/.

[50] Dingguo Zhang, Yong Ren, Kai Gui, Jie Jia, and Wendong Xu. Cooperative control for a hybrid rehabilitation system combining functional electrical stimulation and robotic exoskeleton. *Frontiers in Neuroscience*, 11, 12 2017. ISSN 1662453X. doi: 10.3389/fnins.2017.00725.

[51] Barbara M Doucet, Amy Lam, and Lisa Griffin. Neuromuscular electrical stimulation for skeletal muscle function. *The Yale journal of biology and medicine*, 85:201–15, 6 2012. ISSN 1551-4056. URL http://www.ncbi.nlm.nih.gov/pubmed/22737049http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3375668.

[52] K.J. Hunt, J. Fang, J. Saengsuwan, M. Grob, and M. Laubacher. On the efficiency of fes cycling: A framework and systematic review. *Technology and Health Care*, 20:395–422, 9 2012. ISSN 09287329. doi: 10.3233/THC-2012-0689. URL https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/THC-2012-0689.

[53] Ethne L. Nussbaum, Pamela Houghton, Joseph Anthony, Sandy Rennie, Barbara L. Shay, and Alison M. Hoens. Neuromuscular electrical stimulation for treatment of muscle impairment: Critical review and recommendations for clinical practice. *Physiotherapy Canada*, 69:1–76, 2017. ISSN 03000508. doi: 10.3138/ptc.2015-88.

[54] Xiuyuan Zheng, Danfeng Chen, Tiebin Yan, Dongmei Jin, Zhiqiang Zhuang, Zhimei Tan, and Wei Wu. A randomized clinical trial of a functional electrical stimulation mimic to gait promotes motor recovery and brain remodeling in acute stroke. *Behavioural Neurology*, 2018, 2018. ISSN 18758584. doi: 10.1155/2018/8923520.

[55] Antonio J. Del-Ama, Ángel Gil-Agudo, Elisabeth Bravo-Esteban, Soraya Pérez-Nombela, José L. Pons, and Juan C. Moreno. Hybrid therapy of walking with kinesis overground robot for persons with incomplete spinal cord injury: A feasibility study. *Robotics and Autonomous Systems*, 73:44–58, 2015. ISSN 09218890. doi: 10.1016/j.robot.2014.10.014. URL http://dx.doi.org/10.1016/j.robot.2014.10.014.

[56] Nicholas Kirsch, Naji Alibeji, Lee Fisher, Chris Gregory, and Nitin Sharma. A semi-active hybrid neuroprosthesis for restoring lower limb function in paraplegics. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, pages 2557–2560, 2014. doi: 10.1109/EMBC.2014.6944144.

[57] Klaus Martin Stephan and Dominic Pérennou. *Mobility after stroke: Relearning to walk*, pages 123–147. Springer International Publishing, 1 2021. ISBN 9783030585051. doi: 10.1007/978-3-030-58505-1_8.

[58] Rocco Salvatore Calabrò, Antonino Naro, Margherita Russo, Antonino Leo, Tina Balletta, Ileana Saccá, Rosaria De Luca, and Placido Bramanti. Do post-stroke patients benefit from robotic verticalization? a pilot-study focusing on a novel neurophysiological approach. *Restorative Neurology and Neuroscience*, 33:671–681, 2015. ISSN 18783627. doi: 10.3233/RNN-140475.

[59] Alexey N. Kuznetsov, Natalia V. Rybalko, Vadim D. Daminov, and Andreas R. Luft. Early poststroke rehabilitation using a robotic tilt-table stepper and functional electrical stimulation. *Stroke Research and Treatment*, 2013. ISSN 20420056. doi: 10.1155/2013/946056.

[60] Amirehsan Sarabadani Tafreshi, Jan Okle, Verena Klamroth-Marganska, and Robert Riener. Modeling the effect of tilting, passive leg exercise, and functional electrical stimulation on the human cardiovascular system. *Medical and Biological Engineering and Computing*, 55:1693–1708, 2017. ISSN 17410444. doi: 10.1007/s11517-017-1628-8.

[61] Nicholas A. Kirsch, Xuefeng Bao, Naji A. Alibeji, Brad E. Dicianno, and Nitin Sharma. Model-based dynamic control allocation in a hybrid neuroprosthesis. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 26:224–232, 1 2018. ISSN 15344320. doi: 10.1109/TNSRE.2017.2756023.

[62] Inga Lypunova Petersen, Weronika Nowakowska, Christian Ulrich, and Lotte N.S.Andreasen Struijk. A novel semg triggered fes-hybrid robotic lower limb rehabilitation system for stroke patients. *IEEE Transactions on Medical Robotics and Bionics*, 2:631–638, 11 2020. ISSN 25763202. doi: 10.1109/TMRB.2020.3019081.

[63] Beth Clark, Jill Whitall, Gert Kwakkel, Jan Mehrholz, Sean Ewings, and Jane Burridge. The effect of time spent in rehabilitation on activity limitation and impairment after stroke. *Cochrane Database of Systematic Reviews*, 2021, 10 2021. ISSN 14651858. doi: 10.1002/14651858.CD012612.pub2. URL http://doi.wiley.com/10.1002/14651858.CD012612.pub2.

[64] Helen H. Host, Catherine E. Lang, Mary W. Hildebrand, Dequan Zou, Ellen F. Binder, Carolyn M. Baum, Kenneth E. Freedland, Nancy Morrow-Howell, and Eric J. Lenze. Patient active time during therapy sessions in postacute rehabilitation: Development and validation of a new measure. *Physical and Occupational Therapy in Geriatrics*, 32:169–178, 2014. ISSN 15413152. doi: 10.3109/02703181.2014.915282.

[65] Francisco Anaya, Pavithra Thangavel, and Haoyong Yu. Hybrid fes–robotic gait rehabilitation technologies: a review on mechanical design, actuation, and control strategies. *International Journal of Intelligent Robotics and Applications*, 2:1–28, 2018. ISSN 2366598X. doi: 10.1007/s41315-017-0042-6. URL https://doi.org/10.1007/s41315-017-0042-6.

[66] Suhun Jung, Jae Hwan Bong, Keri Kim, and Shinsuk Park. Machine-learning-based coordination of powered ankle–foot orthosis and functional electrical stimulation for gait control. *Frontiers in Bioengineering and Biotechnology*, 11, 2023. ISSN 22964185. doi: 10.3389/fbioe.2023.1272693.

[67] Naji A. Alibeji, Nicholas Andrew Kirsch, and Nitin Sharma. A muscle synergy-inspired adaptive control scheme for a hybrid walking neuroprosthesis. *Frontiers in Bioengineering and Biotechnology*, 3, 12 2015. ISSN 22964185. doi: 10.3389/fbioe.2015.00203.

[68] Yixiong Chen, Jin Hu, Weiqun Wang, Liang Peng, Long Peng, and Zeng Guang Hou. An fes-assisted training strategy combined with impedance control for a lower limb rehabilitation robot. *2013 IEEE International Conference on Robotics and Biomimetics, ROBIO 2013*, pages 2037–2042, 2013. doi: 10.1109/ROBIO.2013.6739769.

[69] Mojdeh Rastegar and Hamid Reza Kobravi. A hybrid-fes based control system for knee joint movement control. *Basic and Clinical Neuroscience*, 12:441–452, 7 2021. ISSN 22287442. doi: 10.32598/bcn.2021.173.3.

[70] Jane E. Huggins, Christoph Guger, Mounia Ziat, Thorsten O. Zander, Denise Taylor, Michael Tangermann, Aureli Soria-Frisch, John Simeral, Reinhold Scherer, Rüdiger Rupp, Giulio Ruffini, Douglas K.R. Robinson, Nick F. Ramsey, Anton Nijholt, Gernot Müller-Putz, Dennis J. McFarland, Donatella Mattia, Brent J. Lance, Pieter Jan Kindermans, Iñaki Iturrate, Christian Herff, Disha Gupta, An H. Do, Jennifer L. Collinger, Ricardo Chavarriaga, Steven M. Chase, Martin G. Bleichner, Aaron Batista, Charles W. Anderson, and Erik J. Aarnoutse. Workshops of the sixth international brain–computer interface meeting: brain–computer interfaces past, present, and future. *Brain-Computer Interfaces*, 4:3–36, 4 2017. ISSN 23262621. doi: 10.1080/2326263X.2016.1275488.

[71] Kasper S. Leerskov, Erika G. Spaich, Mads R. Jochumsen, and Lotte N. S. Andreasen Struijk. Design and demonstration of a hybrid fes-bci based robotic neurorehabilitation system for lower limbs. 2024. In preparation.

[72] Kasper S. Leerskov, Cindy J.H. Rikhof, Erika G. Spaich, Strahinja Dosen, Gerdienke B. Prange-Lasonder, Erik C. Prinsen, Johan S. Rietman, and Lotte N.S. Andreasen Struijk. A robot-based hybrid lower limb system for assist-as-needed rehabilitation of stroke patients: Technical evaluation and clinical feasibility. *Computers in Biology and Medicine*, 179: 108839, 9 2024. ISSN 00104825. doi: 10.1016/j.compbiomed.2024.108839. URL https://linkinghub.elsevier.com/retrieve/pii/S0010482524009247.

[73] Kasper S. Leerskov, Lotte N. S. Andreasen Struijk, Strahinja Dosen, and Erika G. Spaich. Dynamic multi-level control of electrical stimulation during hybrid robotic-fes exercise. 2024. In preparation.

[74] Life Science Robotics ApS. Lower extremities. https://www.lifescience-robotics.com/solutions/lower-extremities/, 2024. Accessed 8 November 2024.

[75] Life Science Robotics ApS. Emg-triggered fes. https://www.lifescience-robotics.com/solutions/sas/, 2024. Accessed 8 November 2024.

[76] Carina C.J.M. De Klerk, Mark H. Johnson, and Victoria Southgate. An eeg study on the somatotopic organisation of sensorimotor cortex activation during action execution and observation in infancy. *Developmental Cognitive Neuroscience*, 15:1–10, 10 2015. ISSN 18789307. doi: 10.1016/j.dcn.2015.08.004.

[77] S. R. Sreeja, Joytirmoy Rabha, Debasis Samanta, Pabitra Mitra, and Monalisa Sarma. Classification of motor imagery based eeg signals using sparsity approach. In *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, volume 10688 LNCS, pages 47–59. Springer Verlag, 2017. ISBN 9783319720371. doi: 10.1007/978-3-319-72038-8_5.

[78] Sharon Olsen, Gemma Alder, Mitra Williams, Seth Chambers, Mads Jochumsen, Nada Signal, Usman Rashid, Imran Khan Niazi, and Denise Taylor. Electroencephalographic recording of the movement-related cortical potential in ecologically valid movements: A scoping review. *Frontiers in Neuroscience*, 15, 9 2021. ISSN 1662453X. doi: 10.3389/fnins.2021.721387.

[79] Mads Jochumsen, Hendrik Knoche, Preben Kidmose, Troels Wesenberg Kjær, and Birthe Irene Dinesen. Evaluation of eeg headset mounting for brain-computer interface-based stroke rehabilitation by patients, therapists, and relatives. *Frontiers in Human Neuroscience*, 14, 2 2020. ISSN 16625161. doi: 10.3389/fnhum.2020.00013.

[80] Cindy J.H. Rikhof, Gerdienke B. Prange-Lasonder, Erik C. Prinsen, Jaap H. Buurke, and Johan S. Rietman. Comparing different detection thresholds for actively-triggered electrostimulation combined with robotic support of leg movements in sub-acute stroke. In *2022 International 17th Conference on Rehabilitation Robotics (ICORR)*, 2022.

[81] Kasper S. Leerskov, Strahinja Dosen, Erika G. Spaich, and Lotte N.S.Andreasen Struijk. Increase and decrease in velocity and force during exercise with a hybrid robotic-fes rehabilitation system. In *IEEE International Conference on Rehabilitation Robotics*, volume 2022-July. IEEE Computer Society, 2022. ISBN 9781665488297. doi: 10.1109/ICORR55369.2022.9896600.

[82] Imran Khan Niazi, Natalie Mrachacz-Kersting, Ning Jiang, Kim Dremstrup, and Dario Farina. Peripheral electrical stimulation triggered by self-paced detection of motor intention enhances motor evoked potentials. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 20:595–604, 2012. ISSN 15344320. doi: 10.1109/TNSRE.2012.2194309.

[83] Ren Xu, Ning Jiang, Natalie Mrachacz-Kersting, Chuang Lin, Guillermo Asin Prieto, Juan C. Moreno, Jose L. Pons, Kim Dremstrup, and Dario Farina. A closed-loop brain-computer interface triggering an active ankle-foot orthosis for inducing cortical neural plasticity. *IEEE Transactions on Biomedical Engineering*, 61:2092–2101, 2014. ISSN 15582531. doi: 10.1109/TBME.2014.2313867. URL `http://www.ncbi.nlm.nih.gov/pubmed/24686231`.

[84] Kasper K. Leerskov, Lotte N.S.Andreasen Struijk, and Erika G. Spaich. *Assessment of Plastic Changes Following Bio-Robotic Rehabilitation of Spinal Cord Injured Individuals – A Protocol Proposal*, volume 21, pages 866–870. Springer International Publishing, 2019. doi: 10.1007/978-3-030-01845-0_174.

[85] Natalie Mrachacz-Kersting, Signe Rom Kristensen, Imran Khan Niazi, and Dario Farina. Precise temporal association between cortical potentials evoked by motor imagination and

afference induces cortical plasticity. *Journal of Physiology*, 590:1669–1682, 2012. ISSN 00223751. doi: 10.1113/jphysiol.2011.222851.

[86] Neale Tillin and David J. Bishop. Factors modulating post-activation potentiation and its effects on performance. *Sports Medicine*, 39:147–166, 2009.

[87] Haiko Bruno Zimmermann, Brian R. Macintosh, and Juliano Dal Pupo. Does postactivation potentiation (pap) increase voluntary performance? *Applied Physiology, Nutrition and Metabolism*, 45:349–356, 2020. ISSN 17155320. doi: 10.1139/apnm-2019-0406.

[88] Cindy J.H. Rikhof, Kasper S. Leerskov, Gerdienke B. Prange-Lasonder, Erik C. Prinsen, Erika G. Spaich, Strahinja Dosen, Lotte N.S.Andreasen Struijk, Jaap H. Buurke, and Johan S. Rietman. Combining robotics and functional electrical stimulation for assist-as-needed support of leg movements in stroke patients: A feasibility study. *Medical Engineering Physics*, 130:104216, 8 2024. ISSN 13504533. doi: 10.1016/j.medengphy.2024.104216. URL https://linkinghub.elsevier.com/retrieve/pii/S1350453324001176.

[89] Chih Lin Kuo and Gwo Chi Hu. Post-stroke spasticity: A review of epidemiology, pathophysiology, and treatments. *International Journal of Gerontology*, 12:280–284, 12 2018. ISSN 1873958X. doi: 10.1016/j.ijge.2018.05.005.

[90] Huangling Zeng, Jian Chen, Yang Guo, and Sheng Tan. Prevalence and risk factors for spasticity after stroke: A systematic review and meta-analysis. *Frontiers in Neurology*, 11, 1 2021. ISSN 16642295. doi: 10.3389/fneur.2020.616097.