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# Multimodal adaptive interfaces for upper limb robot-aided neuro-rehabilitation

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*"Start by doing what's necessary;*
*then do what's possible;*
*and suddenly you are doing the impossible."*

Saint Francis of Assisi

# *Abstract*

## Multimodal adaptive interfaces for upper limb robot-aided neuro-rehabilitation

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Nowadays, stroke is one of the leading cause of permanent disability. Several rehabilitation methodologies can be adopted to counteract stroke motor impairments, but the optimal training approach remains unknown. In this perspective, rehabilitation robotics is one of the most active research fields in the neuro-rehabilitation panorama.

Robotic devices for upper limb treatment may lead to improvements in motor recovery and neuro-plasticity due to their ability to deliver highly-intensive, repeatable, and accurate movement therapy. In addition, robotic machines provide objective measurements for patient assessment, while guaranteeing patient safety and unloading therapist workload with respect to conventional therapy.

This work presents the development of multimodal adaptive interfaces tailored to human's specific needs. Multimodal interfaces represent complex systems characterized by the simultaneous use of multiple human sensory modalities that can support combined input/output modes. They include different subsystems that can operate both as monitoring tools that record various levels of information as well as stimulation techniques (auditive, visual, haptic and neuromodulation). The concept of multimodal interface is then applied to upper limb robot-aided neurorehabilitation with the ambition to maximize the therapeutic effects in post-stroke patients.

Bio-cooperative systems and non-invasive neuromodulation techniques may represent a general extended vision of multimodal interfaces. In particular, bio-cooperative systems include several subsystems that communicate through a customized multimodal interface. They represent the new generation of robotic platforms that collocate the patient in the control loop, by employing his/her physiological, neurological, psychological and biomechanical measures, and automatically adapts the control strategy on the basis of the acquired patient states.

The proposed work consists of two main research areas that include the concept of multimodal interface: i) design criteria of bio-cooperative robotic systems for upper limb rehabilitation, ii) application of multimodal interfaces for investigating effects of robotic therapy combined with non-invasive neuromodulation techniques. Regarding the first area, a novel taxonomy of bio-cooperative systems is proposed.

In addition, the application of bio-cooperative system has been applied to two case studies grounded on end-effector machines (Kuka robotic arm and CBM-Motus). However, the approach can be easily extended to wearable robotic devices as shown in Chapter 5. A special attention has been paid to the design and development of an arm gravity support system integrated in a bio-cooperative upper limb robot-aided rehabilitation system. The bio-cooperative approach and an adaptive control strategy have been then applied to a robotic tele-rehabilitation system.
Furthermore, a modular system aimed to control an upper arm robotic exoskeleton for assistive tasks has been presented and discussed. Finally, the development of a mechanical interfacing system for hand rehabilitation devices and upper arm exoskeletons is reported.
As regards the second area, the concept of multimodal interface has been applied for quantitative assessment of the outcomes related to clinical studies involving stroke patients. These studies have been designed for investigating the effects of neuromodulation techniques paired with upper limb planar robotic therapy.
The outcomes of two clinical studies combining Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) with upper limb robotic therapy are reported and discussed.

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# Chapter 1

# Introduction

Stroke is a sudden, non-convulsive loss of neurological functions due to an ischaemic or haemorrhagic intracranial vascular event [1] and considered one of the leading causes of disability in industrialized countries. Over the past few years, rehabilitation robots have been employed to deal with upper limb motor impairment caused by stroke [2, 3] since robots represent valuable tools for delivering high-intensive and task-specific rehabilitation [4, 5].

The employment of robots in neurorehabilitation is grounded on the brain physiological mechanism called *neuroplasticity*. It represents the capability of the brain to reorganize itself by forming new neural connections and changing the cortical representations of motor actions, in order to compensate for its damaged area [6, 7].

Moreover, robots are able to guarantee patient safety as well as unloading therapist workload with respect to conventional methods. However, typical rehabilitation with robots is mainly *"controlled"* by robot, applying predefined commands, independently of patient needs or characteristics; in this manner, the user is a passive actor and his/her intentions are not considered in the control loop [8, 9].

The concept of *human-in-the-loop* represents the fundamentals of the proposed work. Recent advancements in next-generation interfaces able to combine recording and stimulating capabilities in so-called closed-loop devices have shown the potential to further extend neuroelectronic augmentation of injured motor circuits [10]. In this perspective, the use of multimodal interfaces that are completely shaped on the patient's needs becomes a key element into the rehabilitation process and constitutes the main theme of the proposed work.

Multimodal interfaces represent particular systems characterized by the simultaneous use of multiple human sensory modalities. They include several subsystems that can operate both as monitoring tools that record various levels of information as well as stimulation techniques (auditive, visual, haptic and neuromodulation). In particular, the concept of multimodal interface can be extended to the following items aimed to maximize clinical outcomes of upper limb robot-aided rehabilitation:

i) design and development of bio-cooperative robotic systems for upper limb rehabilitation in clinical centers and at home, through remote rehabilitation, ii) coupled use of robotic therapy and neuromodulation techniques and quantitative assessment through robots.

These two aspects have been widely analyzed and discussed throughout the thesis with the attempt to provide novel solutions and technologies aimed to enhance the *human-centered* approach in the field of rehabilitation and assistive robotics. On the one hand, bio-cooperative systems represent the new generation of robotic platforms that promote a bidirectional interaction between the robot and the patient based on multimodal interfaces; the inclusion of physiological and psychological measurements of the patient's state into the control loop, in addition to biomechanical measurements, makes the system *"Bio-Cooperative"* [11, 12].

The bio-cooperative paradigm has been applied to two case studies with end-effector robotic machines. However, this approach can be easily extended to wearable robots as described in Chapter 5. The use of such systems is expected to promote patient engagement and speed up the recovery process exploiting the concept of human-in-the-loop [9, 13–15].

On the other hand, the application of multimodal interfaces including non-invasive brain stimulation techniques is arising interest in the scientific community. The capability of such techniques to modulate excitability of a targeted brain region non-invasively, using electrical current and magnetic field has demonstrated beneficial effects on motor and functional recovery of stroke patients [16–19].

The neuromodulation techniques present a twofold feature that make them eligible to be employed in a multimodal interfaces scenario. First, together with robotic technologies, non-invasive brain stimulation targets the modulation of brain plasticity (excitatory or inhibitory), individuating a rationale for investigating whether combining these modalities could lead to an additional benefit.

Furthermore, they may operate as an assessment tool thanks to the extraction of indicators related to brain activity. These indicators may contribute to enrich

the multimodal interface and thus increase the contribution of the patient in the rehabilitation loop.
The thesis is therefore structured in two main parts. The first part is dedicated to the development of novel bio-cooperative approaches in robot-aided therapy in clinical centres and at home as explained in the following:

- In Chapter 2, the neurophysiology of stroke, fundamentals of post-stroke physical therapy as well as conventional methods for stroke rehabilitation and assessment are discussed. The current literature on upper limb rehabilitation robotics is analysed; the main technologies and techniques for post stroke robot-mediated therapy and evaluation are presented and discussed. Moreover, the application of multimodal interfaces and bio-cooperative systems into rehabilitation and assistive robotics is introduced.

- In Chapter 3, an overview of bio-cooperative systems and their main features are presented, by introducing a general scheme of bio-cooperative system applied to rehabilitation and assistive robotics. Furthermore, the case study of a bio-cooperative robotic platform for upper limb 3D robotic therapy is presented. It comprises a 7 DoF robotic arm, a multimodal interface and an adaptive control system grounded on biomechanical measurements of patient performance. The functioning is presented and the integration of a custom-designed motorized arm-gravity support system together with its control strategy are discussed.

- In Chapter 4, a general modular tele-rehabilitation architecture based on a bio-cooperative system for upper limb robot-aided therapy is proposed. The same functional architecture is then tailored to CBM-Motus, a planar end-effector based robot conceived for training shoulder/elbow district. A multimodal adaptive control strategy based on performance indicators extracted from kinematics is presented; in addition, feasibility tests of modular architecture on healthy subjects are reported and discussed.

- In Chapter 5 modular integration of software and hardware modules of multimodal interfaces is proposed. A modular software architecture for guaranteeing safe communication among the subsystems composing a multimodal interface has been developed. The multimodal interface controls an upper limb exoskeleton aimed to assist disabled people in accordance with specific user needs. Preliminary results of the proposed architecture are presented.

In addition, a mechanical flange for interfacing upper limb exoskeletons is presented. The designed flange has been employed for integrating a module for hand rehabilitation and the robotic exoskeleton ARMin. The whole system is conceived to be easily adjustable in order to be integrated into several upper arm exoskeletons as the robotic exoskeleton for assistance discussed in the first part of the Chapter.

The second part of the thesis is dedicated to the application of a multimodal interface for the quantitative assessment of outcomes deriving from the adjunct of neuromodulation techniques to robotic therapy aimed to enhance motor and functional recovery after a stroke.

- In Chapter 6, neuromodulation techniques for understanding and treating stroke recovery are presented. Afterwards, a proof-of-concept study on the effects of repetitive TMS combined with shoulder/elbow robotic therapy in chronic stroke patients is reported both with background and methods employed. A quantitative evaluation of the patients based on a multimodal interface is presented and results are reported and discussed.

- In Chapter 7 study background and methods employed in upper limb robotic therapy combined with transcranial Direct Current Stimulation (tDCS) are presented. The multimodal interface is used for the quantitative evaluation of the outcomes of a pilot study carried out at University Campus Bio-Medico of Rome and preliminary results on chronic stroke patients are reported. Moreover, effects of tDCS combined with upper limb robotic treatment are investigated and analyzed throughout the current literature.

- In Chapter 8, conclusions and final considerations are reported.

# Chapter 2

# Rehabilitation robotics and bio-cooperative systems in post stroke treatment: a literature analysis

Currently, stroke is one of the leading causes of disability in industrialised countries leaving affected people with severe and permanent motor impairments. Rehabilitation treatments are proved to be the most effective way to address such disabilities. A great variety of rehabilitative approaches have been proposed throughout years to deal with upper limb impairments after stroke; however, the exact type of therapy leading to effective and optimal results is still unknown.

Furthermore, therapy assessment is often carried out by means of traditional clinical scales which are mainly subjective evaluation's tools, thus suffering from a series of hindrances. Hence, developing new methods for assisting people who suffered a stroke is one of the most active and crucial research field in the neurorehabilitation scenario.

Robotic devices for upper limb treatment can be seen as successful tools handled by therapists in order to enhance motor recovery and neuro-plasticity due to their ability to supply highly-intensive, repeatable, and accurate movement therapy. In addition, robots can provide an objective therapy assessment while guaranteeing patient safety and unloading therapist workload with respect to traditional methods.

Notwithstanding, traditional robotic therapy relies on an "if-then" functioning

mode, which permits to execute only predefined unidirectional action on human subjects without actively including the patient in the control loop and participating in the therapy definition [8, 20–22]. Currently, special attention has been paid to the development of bio-cooperative systems. They represent the new generation of robotic platforms able to promote a bidirectional interaction between the subject and the robot [12, 13]. The inclusion of biomechanical, physiological and psychological measurements of the patient's state into the control loop allows to customize the rehabilitation to the specific user's needs. Such condition, is expected to promote patient engagement and speed up the recovery process more than the previously reported studies [9, 23, 24].

The purpose of this Chapter is to provide the current state-of-the-art in upper limb robot-aided neurorehabilitation with the attempt to propose novel approaches for maximizing the therapeutic effects deriving from robotic therapy. A clear picture of all the possible bio-cooperative systems currently available in the literature has been obtained with the development of a novel modular bio-cooperative scheme that will be discussed in Chapter 3.

This Chapter is structured as follows. The aspects relative to traditional post-stroke treatment and assessment are discussed in Sections 2.1 and 2.2, respectively, while the principal technologies and methodologies for upper limb robot-mediated rehabilitation and evaluation are addressed in Sections 2.3, 2.4 and 2.5.

In Section 2.6 an introduction on bio-cooperative control systems applied in upper limb post-stroke robotic treatment is given. Finally, an explanation regarding the attempt of this thesis to go beyond the current state-of-the-art is provided.

## 2.1 Stroke treatment

Stroke, together with ischemic heart disease, is one of the leading factors of morbidity and mortality worldwide [25]; in low and middle countries of Europe and Central Asia, stroke conditions represent more than a quarter of the total disease burden [26]. In Italy stroke annual incidence varies between 175/100.000 and 360/100.000 in men and between 130/100.000 and 273/100.000 in women [27]. Further, a total of 196.000 individuals are affected each year, of which 80% are new episodes and 20% are elapses. The prevalence of stroke depends primarily on age and gender with an estimation of 1% of world population [26].

Stroke event consists of a sudden loss of neurological function due to an ischemic or

hemorrhagic vascular event [28]. Ischemic stroke, accounting for 87% of all stroke cases, is the main diffused type of stroke event and is caused by rapid obstruction of a brain blood vessel. The remaining cases (13%) are relative to hemorrhagic stroke, related to sudden breakage of a brain vessel.

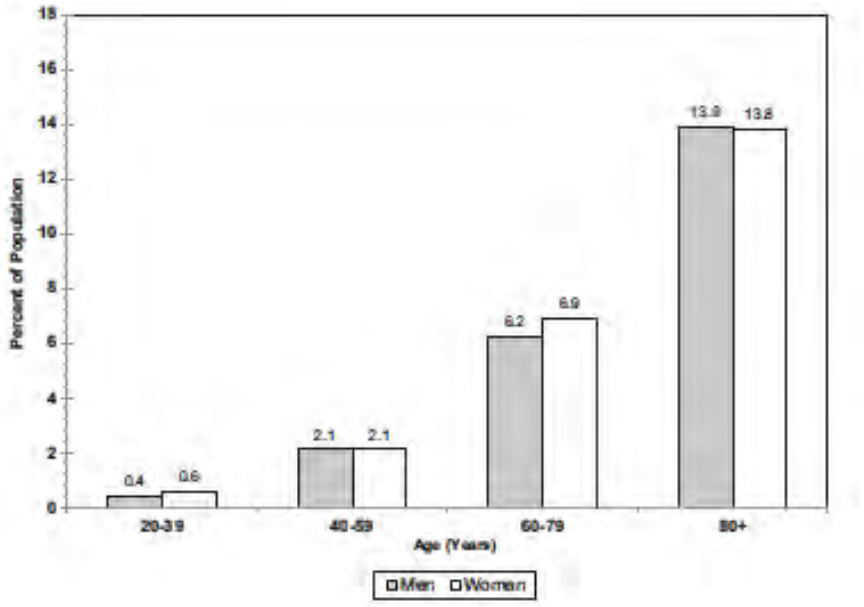


FIGURE 2.1: Worldwide prevalence of stroke by age and sex

In Figure 2.1 is reported the stroke incidence in the world population related to age and sex.
Generally, most people survive stroke but are often left with variety of deficits at different levels (i.e. motor, sensory, cognitive and psychological). Motor impairment secondary to stroke hits about 80% of stroke survivors [29], in most cases affecting the control of face, arm and leg on one side of the body [2]; in addition, upper limb motor impairments are often persistent and difficult to treat. The principal deficits occurring after stroke are listed in the following:

- Physical impairments - Paralysis of one side of the body caused by a brain damage on the contralateral side is called hemiplegia. Such paralysis may affect only one part of face, arm or leg and, in the worst cases, an entire side of body and face. In the case of upper limb deficits, weakness of entire limb and decreased functions of arm and hand, lead to serious difficulties in the execution of simple activities of daily living (ADLs).

- Cognitive and emotional impairments - Stroke may cause issues related to memory, awareness, thinking, attention as well as difficult to control emotions and feelings expressing inappropriate behaviour in specific circumstances. Depression is the most common arising problem.
- Balance and coordination deficits - Damages in the coordination area of the brain may lead to difficulties in performing normal activities like walking, dressing or eating.
- Language impairments - Stroke subjects often have problems to understand and form speeches; such deficit is called aphasia and may also cause problems in reading and writing.
- Pain - Stroke victims may experience limb pain and strange sensations after stroke occurrence.

Right after stroke onset, a spontaneous neurorecovery can be observed. However, due to the physiological differences among patients this recovery is extremely variable, depending on the area of the lesion, the size and the type of lesion. Considering these aspects, spontaneous recovery may take from some days to several months (Figure 2.2).

In Fig.2.2, is depicted a typical recovery trend from stroke and when is worth to intervene with rehabilitation strategies. After an initial phase of spontaneous recovery, a plateau is reached [29]. Despite this trend, there are multiple scientific evidences showing that rehabilitation strategies must be preferred to spontaneous recovery process, no matter which is the chosen therapy. In fact, employing specific therapies tailored to key factors of neural plasticity, may play a fundamental role in the compensation of functional loss [30].
Neural plasticity is defined as the ability of the central nervous system to adapt in response to changes in the environment or lesions. It occurs at many levels from molecules to cortical reorganization [31].
This cortical reorganization may occur in sites close to and/or far from the lesioned area and allows the development of new neural pathways that bypass those damaged by stroke. Finally, therapies based on high-intensive repetitive movements and sensorimotor stimuli may actively enhance neuroplastic changes [32].
It has been estimated that about 80% of stroke survivors are affected by motor control or sensory feedback deficits in the upper-limb of the paretic side [33]; therefore, rehabilitation interventions play a crucial role to counteract upper-limb motor

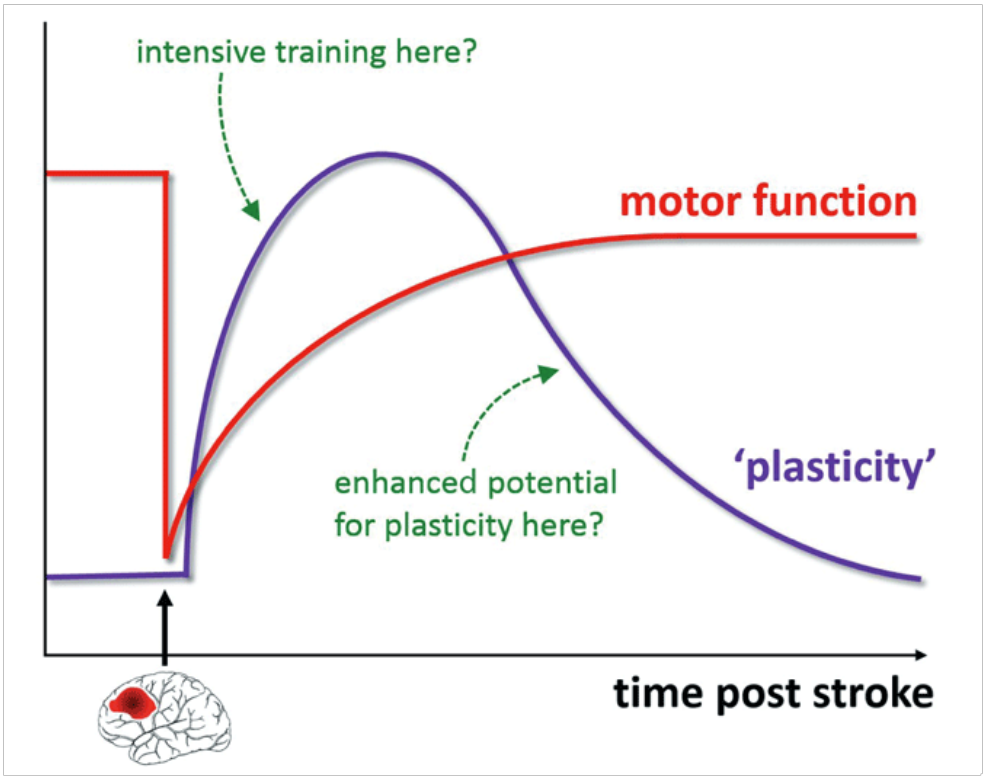


FIGURE 2.2: Stroke trend and spontaneous recovery: how and when is worth to intervene

impairments [29]. Intensive as well as task-specific training can be very effective in rehabilitation treatments after stroke and this training should be repetitive, challenging and functional for the patients, thus involving both arm and hand [34, 35]. In recent decades, a wide number of promising alternative therapies, medications, and experimental treatments have shown benefit to post-stroke patients [36]:

- Selective serotonin receptor inhibitor (SSRI) antidepressants - SSRIs are newer (second-generation) antidepressants which have been introduced in stroke treatments after their FDA approval in 1987. Several trials on SSRI medications after stroke have reported outcomes such as neurologic recovery, functional recovery and independence with ADLs although with mixed results [36–38].

- Constraint-induced movement therapy (CIMT) - The underlying concept of CIMT is that restricting the use of the unaffected upper extremity will force an individual to use the affected limb to complete task-based activities, affecting neuroplastic change and improving upper extremity function over time.

- Noninvasive brain stimulation (NIBS) - These techniques deal with the application of weak electric or magnetic fields to the brain using electrodes on the surface of the scalp with the goal of enhancing or normalizing brain activity [39–41].
  NIBS are predominantly employed in the study of brain physiology and function, neuroplasticity and the functional networks between various brain region. Currently, the available techniques are transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS) together with their modifications.

- Mirror therapy (MT) - This treatment consists in the placement of a mirror in the mid-sagittal plane, allowing the patient to perceive the reflection of the non-affected limb as if it is the affected one. Since the illusory perceptions of the limb would counteract maladaptive neuroplastic changes that may occur after a stroke, MT has been examined as a potential therapeutic modality for stroke victims [42].

- Motor Imagery/Mental Practice - These two practices represent the mental execution of a skilled movement without actually performing the movement ("motor imagery", MI) and the description of a training or therapy task in which an internal representation of the movement is activated and the execution of the movement repeatedly mentally simulated, without physical activity ("motor practice", MP) [43, 44].

Conventional motor rehabilitation sessions consist of individual treatments delivered by a therapist who assists the patient during the execution of dedicated motor exercises [45]. There are four main categories of interaction between patient and therapist:

1. Passive interaction - In this configuration, the patient is "relaxed" while the therapist moves his/her joints. This approach aims to maintain joint's range of motion and flexibility of muscles and tendons.

2. Active-assisted interaction - The therapist assists the patient as needed while he/she attempts to move the paretic limb or joint. Active-assisted strategy is performed in order to allow patients to accomplish movements that cannot complete independently.

3. Active-resisted movement - In this configuration, patient has to perform a movement against some degree of resistance (gravity, additional weights, elastic band, or the therapist's applied force). This approach is typically dedicated to mild-moderate impaired patients.

4. Bilateral interaction - The subject moves the impaired limb repeating the simultaneous movement of the unaffected limb.

Despite the last interesting advancements in this area, with a huge number of new developing technologies to enhance motor recovery after stroke, the type of therapy leading to optimal results remains controversial and elusive, and patients are often left with considerable disabilities [46].

## 2.2 Stroke assessment

Stroke can affect numerous aspects of neural function thus resulting in loss of body function and structure. Many scales have been devised in order to quantify the loss of body function caused by stroke. The scales differ from each other since they may address several rehabilitation assessment aspects, distinguishing among body function/structure, activity and participation in life/society.
Normally post stroke evaluation involves both the motor and the functional domain. While measures of motor impairment provide a quantitative analysis of the post-stroke recovery, functional assessment scales give a numerical value to abstract concepts such as "disability" and they can be used to objectively quantify deficits and track change over time. This can be particularly useful in a rehabilitation setting.
Some of the most common clinical scales for stroke evaluation are reported in Table 2.1 together with a brief description.
Clinical scales are widely recommended as evaluation tools being integral part of the stroke rehabilitation treatments. However, the use of such clinical scales has a series of hindrances that have to be considered. Scales are subjective, i.e. operator-dependent, with discrete scores and limited to specific movement characteristics; in addition, they often have low sensitivity and require time-consuming administration procedures.

Although therapists perceived all these barriers regarding clinical scales, they cannot go without them due to the lack of new affordable instruments for evaluating efficacy of rehabilitative intervention after stroke.

TABLE 2.1: Overview of the common clinical scales for stroke assessment of motor and functional abilities

| Main features | Scale | Strengths | Weaknesses |
|---|---|---|---|
| **Assessment of motor function** | Fugl-Meyer (FM) | Extensively evaluated measure. Good validity and reliability for assessing sensorimotor function and balance | Considered too complex and time-consuming by many. |
| | Modified Ashworth Scale (MAS) | Good, brief assessment of movement and physical mobility. | Reliability assessed only in stable patients. Sensitivity not tested. |
| | Motricity Index (MI) | Brief assessment of motor function of arm, leg, and trunk | Sensitivity not tested. |
| **Measures of disability/activities of daily living (ADL)** | Barthel Index (BI) | Widely used for stroke. Excellent validity and reliability. | Low sensitivity for high-level functioning. |
| | Functional Independence Measure (FIM) | Widely used for stroke. Measures mobility, ADL, cognition, functional communication. | "Ceiling" and "floor" effects. |
| **Stroke Deficit Scales** | NIH Stroke Scale | Brief, reliable, can be administered by non-neurologists. | Low sensitivity. |
| | Canadian Neurological Scale | Brief, valid, reliable. | Some useful measures omitted. |
| **Mental status screening** | Folstein Mini-Mental State Examination | Widely used for screening. | Several functions with summed score. May misclassify patients with aphasia. |
| | Neurobehavioral Cognition Status Exam (NCSE) | Predicts gain in BI scores. Unrelated to age | Does not distinguish right from left hemisphere. No reliability studies in stroke. No studies of factorial structure. Correlates with education. |
| **Assessment of speech and language functions** | Boston Diagnostic Aphasia Examination | Widely used, comprehensive, good standardization data, sound theoretical rationale. | Time to administer long; half of patients cannot be classified. |
| | Porch Index of Communicative Ability (PICA) | Widely used, comprehensive, careful test development and standardization. | Time to administer long. Special training required to administer. Inadequate sampling of language other than one word and single sentences. |
| **Level-of-consciousness scale** | Glasgow Coma Scale | Simple, valid, reliable. | None observed. |
| **Global disability scale** | Rankin Scale | Good for overall assessment of disability. | Walking is the only explicit assessment criterion. Low sensitivity. |
| **Balance Assessment** | Berg Balance Assessment | Simple, well established with stroke patients, sensitive to change. | Sensitivity not tested. |
| **Mobility assessment** | Rivermead Mobility Index | Valid, brief, reliable test of physical mobility. | None observed. |

## 2.3 Therapy robots

The most important feature of traditional stroke therapy is the development of a task-oriented, high-intensive, repetitive and active training. In fact, these characteristics have been proved to be essential for promoting neuroplasticity and speed-up motor re-learning process [47].
In this context, robotics appears to be one of the most active research fields in the neurorehabilitation panorama due to its ability to supply a highly-intensive, repeatable, and accurate movement therapy, while guaranteeing patient safety and unloading therapist workload with respect to traditional methods [9, 11, 20].

The use of robots presents several potential advantages in stroke treatment. In fact, they can provide:

- repeatable and precisely controllable assistance or resistance [30];
- movement constraint's behaviour [48];
- the use of virtual reality and game scenarios in order to enhance patient engagement [49].
- acquisition of kinematic and dynamic measures that may be employed as methods for evaluation of therapy outcomes and residual motor skills as well as tools for personalising therapy grounded on subject's motor performances [50–52].

However, whether robot-aided motor therapy lead to higher motor and functional improvements respect to conventional therapy is still an open question. In the last few years, many clinical trials have been performed regarding this topic showing contrasting results.
In general, upper limb robot-aided treatments have shown the capability to provide at least the same amount of motor and functional recovery respect to intensive traditional therapy [53, 54]. In this context, it appears that robotic interventions may enhance therapy effects only as cooperative tools employed in adjunct to therapist's skills and experience [9, 55, 56].

Robotic devices for upper limb treatments have been classified throughout years in different ways spanning from modes of intervention, modes of application or

modes of operation.
A more detailed way of characterisation is grounded on the following points:

- Mode of intervention: unilateral or bilateral training;
- Proximal or distal upper limb segment;
- End-effector or exoskeleton basis;
- Active or passive training;
- Type of motion: symmetrical, asymmetrical or complex motions;
- Number of involved Degree of Freedom (DOF);
- Commercial availability.

Moreover, robotic devices can be controlled in three different ways that guide, assist or contrast patient movement in line with the types of interaction between patient and therapist. In passive mode, the robotic device is controlled in a way that it moves the patient's arm with full assistance along a predefined trajectory, while the subject is completely relaxed; in active-assisted mode, the patient tries to perform a determined movement while the robot provides the needed assistance in the case the subject is not able to fulfil the movement.
Finally, in the active-resisted mode the robot applies opposite predefined forces to counteract patient movement in the attempt to challenge him/her.
Considering the patient-robot mechanical interface, rehabilitation robots can be categorized as end-effector-based robots and exoskeleton-type robots (Fig 2.3).

End-effector based robots are connected to subject's hand or forearm at one single point; therefore, robot's axes do not correspond with human joint axes. Control of such machines is implemented in Cartesian space and accordingly to the number of active DOF, the human arm can be moved into the operational space. They present some advantages like simple construction, usability and easiness to adapt to different arm lengths.
On the other hand, end-effector robots do not allow to determine the full arm posture or the joint interaction torques since the human-robot interaction is restricted to one single point [57]. There are two main types of end-effector systems, 2D systems (Figure 2.4) and 3D systems (Figure 2.5).

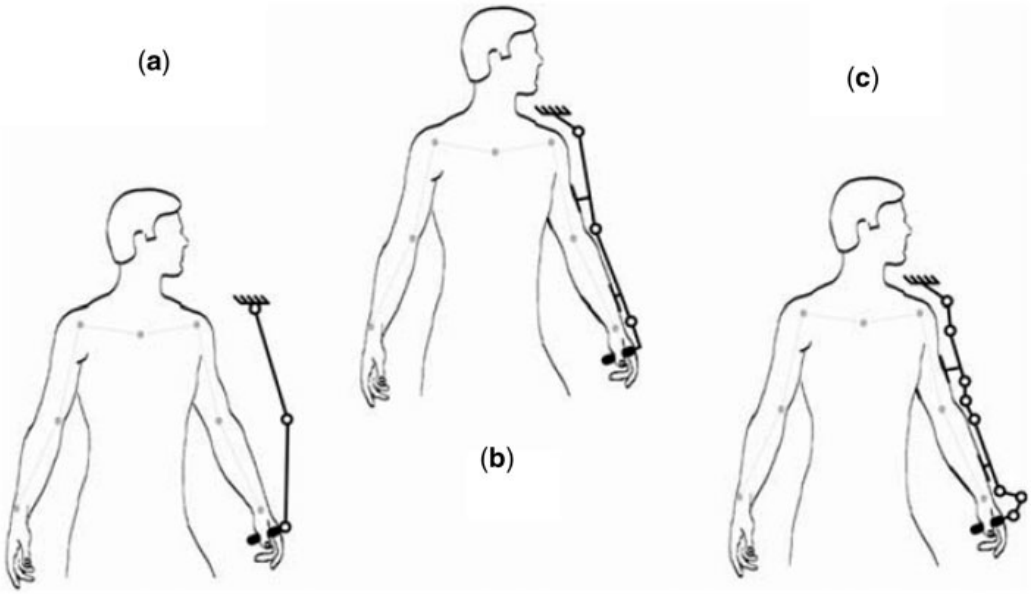


FIGURE 2.3: Modes of interaction between rehabilitation robots and human: a) end-effector based, b) exoskeleton robots with same kinematics of human limb, c) exoskeleton robots kinematically not the same of the human limb [57]

Unilateral robot systems are conceived for training one single limb at a time (e.g Figure 2.4) while bilateral systems allow the user to train both arms simultaneously also using mirror therapy approaches (Figures 2.4c and 2.5a). REHAROB in Figure 2.5d is a 3D multi-robot system which employs two industrial robots for assisting upper arm and forearm separately.

Gentle/S and DIEGO (Tyromotion Inc.) are wire-based systems which allow three-dimensional exercises combining arm orthosis and gravity support suspension mechanisms. The last two devices represent the step between end-effector robots and exoskeleton ones.

Recently, also some end-effector hand rehabilitation devices have been produced as shown in Figures 2.4e and 2.4f. They both allow the user to perform grasping exercises which have been appointed as the most used functional movements regarding the human hand [68].

The exoskeleton robots are built in order to be worn by end-users mimicking the human joint motions; they can be further categorized into two groups: i) exoskeletons with same human kinematics (Figure 2.3b) and ii) exoskeletons kinematically different from human arm (Figure 2.3c).

Exoskeletons allow controlling arm joint motion whereas the DoF of the robot are active (i.e. motorised). Moreover, they need to be lightweight and able to compensate the arm gravity without restricting critically human-limb workspace. On the other hand, exoskeleton robots can be controlled into the joint space and

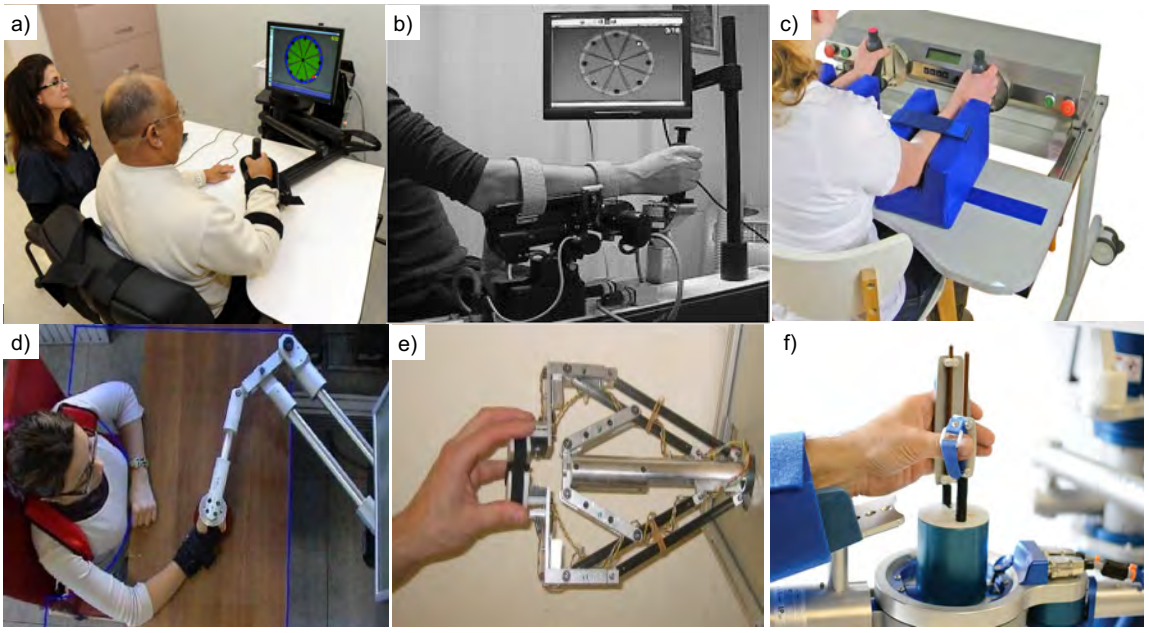


FIGURE 2.4: Some examples of 2D rehabilitative robots: a) InMotion2, InMotion Tech. for shoulder/elbow training [58], b) InMotion3, InMotion Tech. for wrist training [59], c) Bi-Manu Track for forearm and wrist rehabilitation [60], d) Braccio di Ferro [61], planar robot for should/elbow training, e) Haptic Knob [62] and f) InMotion hand [63] for hand training.

thanks to the sensors distributed along the robot, they allow to reconstruct human arm kinematics and dynamics. However, particular attention has to be paid to misalignments between human joint axes and robot joint axes since they may create undesired forces and torques on human joints.

Some examples of upper limb exoskeleton robots are reported in Figure 2.6; among them there are some commercially available devices such as the Armeo Power 2.6e and the Armeo Spring 2.6a manufactured by Hocoma, AG Switzerland. In particular, Armeo Power is the commercial version of ARMin robot 2.6b [69] while Armeo Spring is the commercial replica of the T-WREX [70].

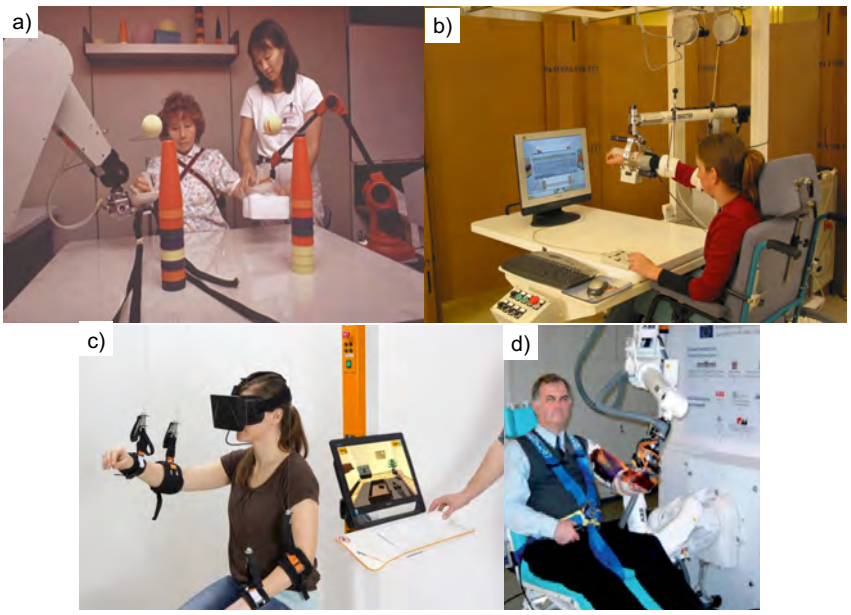


FIGURE 2.5: 3D end-effector based robots: a) MIME [64], b) Gentle/s system [65], c) Diego, Tyromotion Inc. [66], d) REHAROB [67]

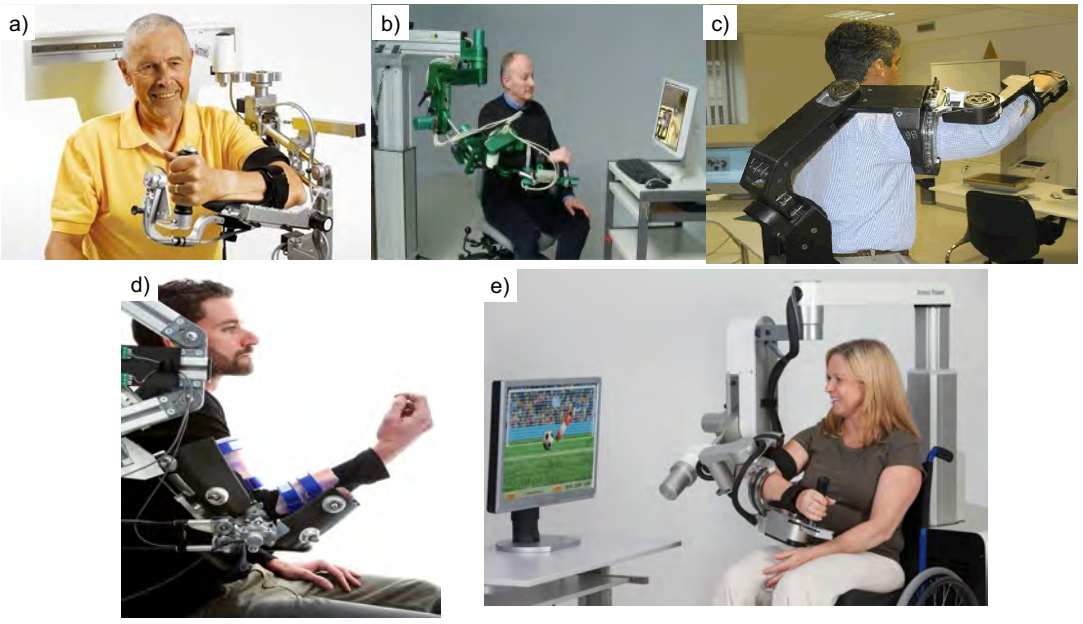


FIGURE 2.6: Exoskeleton based for upper limb training: a) Armeo Spring by Hocoma, AG, Switzerland, b) ARMin robotic system [69], c) L-EXOS [71], d) NEUROExos[72], e) Armeo Power by Hocoma, AG, Switzerland

In addition to the upper arm exoskeletons, also hand exoskeletons have been developed during the last few years. They allow the user to perform different tasks like objects manipulation, individual finger training, different grasping positions; such exercises are of paramount importance for the functional rehabilitation of the hand, especially for performing normal ADLs.

In Figure 2.7 some of the recently developed hand exoskeletons are reported. In particular, the Gloreha robotic glove has been employed also in clinical studies which have proven its feasibility in hand rehabilitation applications [73]. A sum-

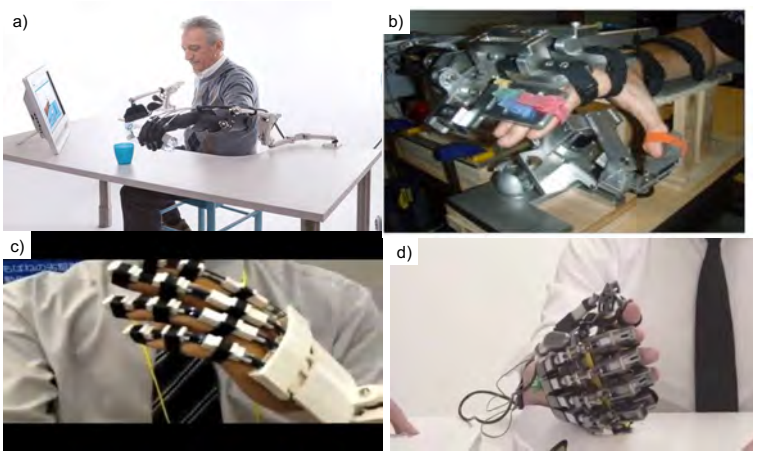


FIGURE 2.7: Exoskeleton devices for hand training: a) Gloreha, Idrogenet srl, Italy [74] b) HEXORR, hand robot exoskeleton [75], c) light-weight hand exoskeleton developed by Arata et al. [76], d) Hand of Hope, robotic hand exoskeleton developed by Rehab Robotics, Ltd

mary of the main robotic devices for upper limb rehabilitation employed in clinics and research are finally reported in this review [77].

## 2.4 Assistive robots

Robotic devices developed for human-robot interaction can be further classified into therapeutic and assistive robots.

Therapeutic robots have been discussed in the previous subsections; they are systems conceived for temporary use (duration of the therapy) while put their emphasis on maximizing the clinical efficacy of the therapy.

Assistive robots are robotic systems conceived for assist disabled people in independent living (assisted activity). Such systems are developed for life-long use with particular emphasis on requirements for maximizing subject autonomy level in executing activities of daily living (ADLs) and, when appropriate, working activities.

In general, assistive robots for upper limb can be intended as manipulation aids. They are further distinguished into manipulation aids on fixed platforms, on moving platforms or integrated on wheelchairs. Recently, also some particular exoskeleton robots can be seen as assistive tools although they have to be specifically

designed to these purposes.

As an example, the European funded project AIDE has the ambition to integrate a complete upper arm exoskeleton (arm plus hand) mounted on a wheelchair in order to assist paralysed people performing ADLs, using an intelligent multimodal system. In Figure 2.8 some of the main assistive robotic systems are reported.

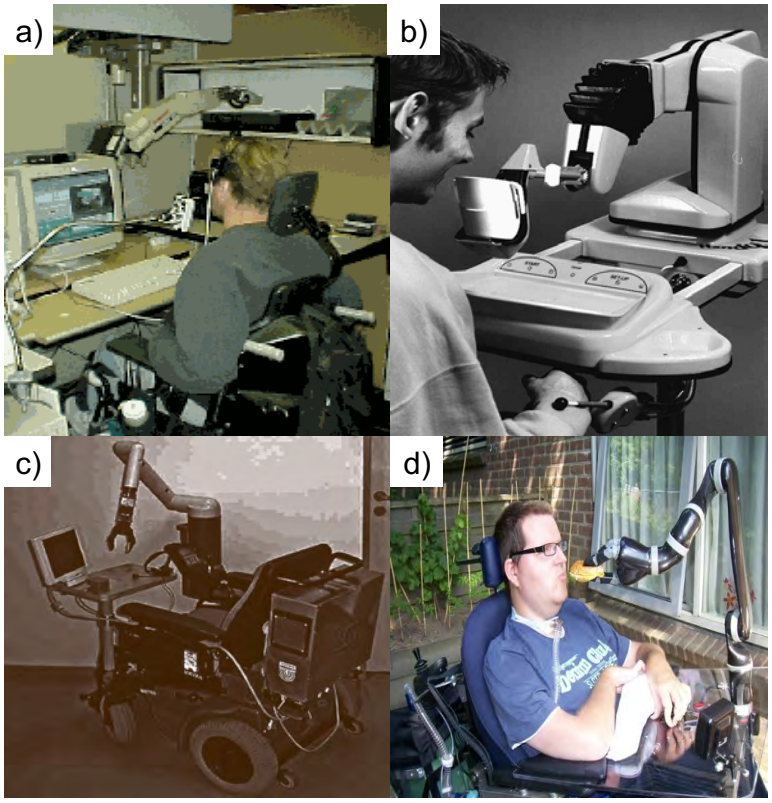


FIGURE 2.8: Robotic manipulator systems for assisting disabled people a) The ProVAR system[78] b) Handy-1, 1st european domestic robot [79], c) the ARM system, previously known as MANUS [80], d) JACO robotic manipulator developed by Kinova (www.kinovarobotics.com)

The ProVAR (Professional Vocational Assistive Robot) is a research prototype based initially on a PUMA-260 robot arm mounted on a 1m transverse overhead track (Figure 2.8a). Such system allows the robot to manipulate objects and operate devices on side shelves and the tabletop, bringing objects (like a glass of water) to the robot's operator [78]. In Europe, the domestic robot with 3 DoF Handy-1 (Figure 2.8b) has been designed in the UK in order to assist people affected by cerebral palsy [79].

The Assistive Robot service Manipulator (ARM), developed by Exact Dynamics in the Netherlands, is a robotic commercial manipulator (previously known as MANUS Figure 2.8c) mounted on a wheelchair controlled via joystick or numeric keyboard included into the system [80]. Recently, Kinova (www.kinovarobotics.com)

developed JACO a new-generation light-weight robotic arm with 6 DoF and a two or three fingers gripper (Figure 2.8d).
JACO is mounted on a wheelchair and assists disabled people during the normal daily activities. Other examples of robotic manipulators are the iARM commercialised by AssistiveInnovations (www.assistive-innovations.com), KARES II [81], the WAM Arm [82] commercialised by Barrett Technology and DLR-LWR III [83].

## 2.5 Robotic assessment

The use of robotic devices into the rehabilitation field can be very important also for evaluation purposes. Although the traditional evaluation of stroke recovery is grounded on clinical scales, they suffer from several drawbacks as previously mentioned in Section 2.2. To this purpose, utilisation of robots as means of assessment is rapidly increasing into rehabilitation community [51, 84].
Rehabilitation robots are equipped with high-resolution sensors that allow accurate measurements of movement kinematics (i.e. upper limb trajectories) and kinetics (i.e. interaction forces). Patient's motion can be accurately monitored and evaluated by means of opportune performance indicators to be used together with the normal clinical scales; such approach may lead to a more exhaustive and complete evaluation of patient's recovery after stroke.
Robot-assisted performance indicators are mainly divided into kinematics, kinetics and neuromechanics indicators [51].
Kinematics indicators quantify subject's movement in spatial and temporal domains and are defined either in Cartesian space or in the arm joint space; kinetic indicators measure the force, work, power and energy consumption exerted by the patient during the movement. Finally neuromechanical indicators allow to estimate viscoelastic characteristics or mechanical impedance of upper limb at rest. However, performance indicators are strictly related to the motor task they are conceived for and the method used for its computation, although there are some of them that can be used for all motor tasks (e.g. Motion duration).

For the sake of clarity, within this dissertation only particular reaching tasks as well as tracking tasks have been addressed. In the reaching tasks user's arm has to move along straight trajectories from already known starting and ending points [21]; in tracking tasks, the patient has to draw specific spatial trajectories like circles or squares [85].

In literature, there are several indicators used in robot-aided therapy for assessment of patient's motor performance. In the following, the main indicators for motor evaluation are reported, rated by specific domains.

- *Motion accuracy* [52, 85] is a kinematic measure that assesses the capability of the patient to perform the required movement. It expresses the difference between the actual user's trajectory and the desired path.
- *Motion direction* quantifies the angular difference between the target direction and the path's direction performed by the subject [52, 86]. This is a kinematic indicator.
- *Smoothness* is a measure of how gradually a movement is changing; it is also characterised by peaks and deep valleys in the speed profile [87]. The more such profile has peaks and valleys the more the movement is not smooth; such trend is typical of post stroke subjects. This indicator can be used in all movement task's evaluation.
- *Movement duration* gives a measure of the time required to accomplish a specific task from the movement onset to movement termination [52, 88]. Movement onset is defined as the time instant when the velocity exceeds a predefined speed threshold of 10% of peak velocity while movement termination is the time instant where velocity goes below the same predefined threshold of 10%. This is a general indicator that can be used in most motor tasks.
- *Efficiency* accounts for the patient's ability to reach predefined targets during reaching tasks [86]. This indicator can be employed in most of the motor tasks.
- *Amount of assistance* quantifies the subject's ability to accomplish motor tasks without robot's assistance. Such indicator is general and can be used in all motor tasks [85, 89].
- *Force direction error* is a kinetic measure which represents the user's ability to apply forces toward desired direction, i.e. the target direction [90–92]. As the last one, also this indicator can be applied to general motor tasks.

Despite the potential advantages that can be obtained combining traditional evaluation methods and robot-based assessment, so far there is no clinical evidence of

such improvements. The lack of standard evaluations procedures, the variety of the patients recruited for the studies, the different methods and tools employed do not lead to objective and affordable post-stroke assessment.
Moreover, is not clear how to translate robot-based measurements to clinical decision making; in fact, there are several robotics metrics which often are not directly transferable to clinical context.
Finally, due to the lack of studies with large number of patients and the different methods and tools employed such topic is still under investigation by the scientific community.

## 2.6 Bio-cooperative robotic systems

Post-stroke robotic rehabilitation is very task-oriented. Usually, the main strategy consists in controlling the robot in a way that it "forces" the patient to follow predefined paths applying corrective unidirectional actions when the subject tends to move outside the desired trajectory. This approach follows a sort of *if-then* algorithm and doesn't involve actively the subject into the therapy thus decreasing the possible recovery chances.
Bio-cooperative systems represent the new generation of robotic platforms that promote a bidirectional interaction between the robot and the patient based on multimodal interfaces. Such an approach would help to personalise therapy for each patient, on the basis of his/her psychophysiological condition [11]. Bio-cooperative systems also aroused interest in the European Commission who has financed many projects on this topic, such as MIMICS [12] and Echord-MAAT [93] in the FP7 and AIDE in the Horizon 2020 programme.
The strength point of the bio-cooperative approach is that the information coming from different sources collocate the user inside the control loop by providing a continuous feedback on his/her global status, i.e. his/her condition, described through user properties, actions, intentions and environmental factors and provided by biomechanical, physiological and psychological measures [12, 13].
The inclusion of physiological and psychological measurements of the patient's state into the control loop, in addition to biomechanical measurements, makes the system "Bio-Cooperative" [11, 12]. Moreover, the multisensory information describing the subject's condition can also be employed simultaneously to quantitatively assess patient's recovery during treatment.

The most used functional scheme of a bio-cooperative system has been previously presented by Riener in [12] as shown in Figure 2.9.

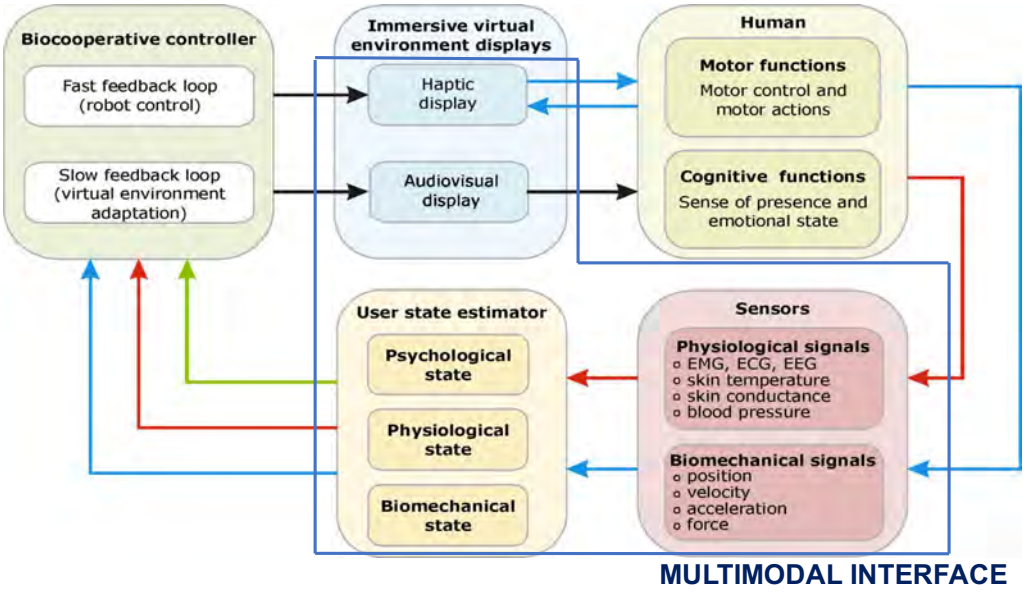


FIGURE 2.9: Functional scheme of a general bio-cooperative rehabilitation robotic system (adapted from the scheme in [12])

Recently, bio-cooperative systems have been extended to include non-invasive Brain Computer Interfaces (BCIs) based on electroencephalography (EEG) and non-cortical interfaces (electrooculography EOG, electromyography EMG and eye-tracking) for detecting subject's movement intentions. Virtual reality environment as well as haptic perception for augmenting patient's sensory feedback have been also employed [9].

Robotic technologies for rehabilitation have been focused for a long time on simple motor tasks (namely analytical tasks) such as reaching actions [94]. In addition, since the focus is on separate joints (either proximal or distal) rather than together, it may have contributed to limit transfer of motor gains to ADLs [9, 95, 96].

Only recently, special attention has been paid to develop functional-oriented tasks which require the arm to move in a 3D workspace mimicking the most common daily life activities such as eating, drinking or grooming. There is strong evidence that real therapy lead to effective improvements in independence of people with sensory-motor impairments [3, 5, 48, 97].

The idea of monitoring stroke patient performances is not completely new in the literature [98]. In [13] a bio-cooperative system for upper limb post stroke rehabilitation is proposed. The main feature of such system is the difficulty adaption of virtual task on the basis of data extracted from biomechanical measurements

and four physiological signals.

In addition, the question of what are the measurements needed for a bio-cooperative feedback loop has been addressed. Experimental trials conducted on sixteen subjects have shown that physiological measurements can only add supplementary information compared to the movement performance analysis. However, the accuracy of the controller is increased when all such information, i.e. biomechanical and physiological, are used concurrently.

Another bio-cooperative system for upper limb stroke rehabilitation is proposed by Guerrero et al. in [14]. Data coming from three physiological channels are used to update task's difficulty in order to maintain therapy level as intensive as possible. Experimental tests on eight healthy subjects showed that the use of a bio-cooperative control system may increase the engagement of the user by modulating motor effort.

The bio-cooperative approach has also been applied to stroke robot-aided gait rehabilitation. In [15] a multimodal interface acquires physiological and biomechanical measurements that modulate the cognitive load during a virtual gait task. Results suggest that the physiological signals acquired are well suited for estimating the task cognitive workload during the robot-aided gait therapy. On the other hand, the addition of the physiological measurements to the performance metrics only lead to few improvements in the estimation of user's needs.

## 2.7 Final considerations

The analysis of the literature performed in this Chapter has revealed that rehabilitation and assistive robotics is becoming one of the most important tool for facing post-stroke intervention. Although the huge efforts put by researchers, robots for rehabilitation are not completely able to substitute conventional therapy as confirmed by multicenter trials [53, 54].

These results have encouraged scientific community to develop novel strategies that collocate the patient in the centre of the rehabilitation cycle. In this context, bio-cooperative systems based on multimodal interfaces have found great visibility in the last years [12, 13, 99].

These systems have demonstrated that the inclusion of various sources of information such as biomechanical, physiological and psychological measurements of the patient's state into the control loop may allow to customize the rehabilitation to

the specific user's needs. Such condition, is expected to promote patient engagement and speed up the recovery process more than the *traditional* robotic therapy that instead follows predefined control strategies.
In addition, the recent introduction of non-invasive cortical interfaces such as BCI and neuromodulation strategies together with the development of augmented feedback such as virtual reality and haptic interfaces, have enriched the potentiality of bio-cooperative systems enhancing patient's engagement. However, the optimal rehabilitation strategy remains still unknown due to the large variability of brain lesions referable to stroke. Such variability may be tackled by neuromodulation strategies that allow at the same time to modulate and quantify patient-specific brain lesions. In this light, future larger studies are suggested in order to determine the more effective rehabilitation strategy.
On the other hand, robots for assistance have gained huge consideration and they are becoming efficient tools for enabling severely impaired people to perform normal ADLs. Multimodal interface approach and bio-cooperative strategy may also be employed in this context with the aim to develop revolutionary robotic platform tailored to specific patient's needs.
This aspect may change substantially the field of assistive robotics thus giving disabled people powerful and autonomous devices able to help them to regain a *quasi-normal* lifestyle.
On the basis of these considerations, the work described in the following Chapters has the aim to propose and discuss novel applications of multimodal interfaces to upper limb rehabilitation and assistive robotics.
These interfaces can actively collocate the subject in the center of the rehabilitative loop exploiting its multisensory information and the modern techniques for modulating and monitoring human brain activity.

# Chapter 3

# Bio-cooperative systems for upper limb robot-aided rehabilitation

The concept of multimodal interface is largely introduced in this chapter. In fact, an overview of bio-cooperative control strategies for upper limb rehabilitation robotics is presented as well as a novel scheme for bio-cooperative system conceived to be extended to generic robotic platforms (Section 3.1).
In addition, a case study of 3D bio-cooperative system for upper limb post stroke treatment is proposed (Section 3.2). In this application, the bio-cooperative strategy is applied to an end-effector robotic machine (Kuka robotic arm) but it can be easily extended to exoskeleton devices. Special attention has been paid to the design and development of a motorised arm-gravity support aimed to sustain the user's arm during the 3D tasks. However, such system is still in a preliminary phase and needs to be validated with human healthy subjects.
The proposed approach based on human multisensory information and novel stimulation techniques is expected to provide a huge contribution to the scientific community for treating neurological diseases such as stroke.

## 3.1 Overview on bio-cooperative control strategies for promoting patient engagement in post stroke upper limb therapy

The use of conventional rehabilitation devices can be unsatisfactory in certain cases, because an efficient interaction between the technical system and the patient is often restricted or difficult. In fact, during such interaction only predefined unidirectional (unilateral) actions are applied to the human and his/her intentions are often ignored [8].
In contrast, novel rehabilitation technologies offer a new approach by placing the human into the loop, promoting a bidirectional interaction between human and robots and taking into account the user's properties, intentions and actions, as well as environmental factors [12]. Therefore, the robot assists the human in a compliant way, with just as much force as needed so that the patient can contribute to the movement with its own voluntary effort.
Psychophysiological integration involves recording and controlling the patient's physiological reactions so that the patient receives appropriate stimuli and is challenged in a moderate, but engaging and motivating way without causing undue stress or harm. Including biomechanical, physiological and psychological measurements into the loop makes the system "Bio-Cooperative" [12].
The general architecture showing the functioning of a bio-cooperative system is shown in Figure 3.1.

This novel diagram is directly derived from the one already proposed in [12]. The aim of the scheme proposed in Figure 3.1 is to provide a clear picture of all the possible bio-cooperative systems currently available in the literature, which can be obtained from the scheme in Figure 3.1 by just eliminating some modules.
The novelty introduced in the proposed functional scheme is the inclusion of non-invasive cortical and non-cortical interfaces (such as Brain Machine Interface (BMI)) as well as environmental factors. Thanks to these interfaces, users become active part of the process since the control inputs can be generated directly from their brain activity.
Besides these aspects, BMI technology may also operate as an effective tool to promote neural plasticity facilitating motor recovery after brain damage like a stroke [100]. In fact, a recent approach for the enhancement of motor recovery is

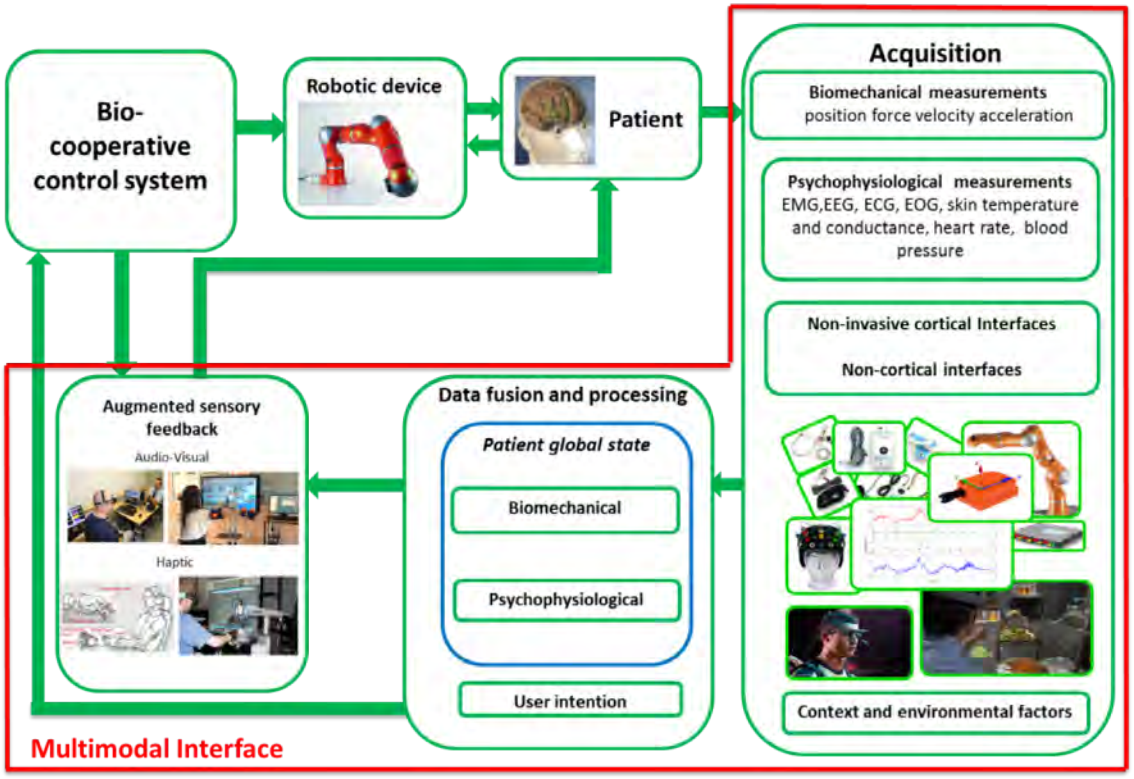


FIGURE 3.1: Computational scheme of the proposed bio-cooperative system for upper limb robotic rehabilitation

represented by non-invasive human brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Such techniques may have the double role of stimulating and monitoring brain activity by means of dedicated neuro-indicators.

In this fashion, the rehabilitation process will improve both from a physical point of view and also from a neurological perspective [101]. The central role is given to the human user who is closed in the control loop thanks to a dedicated multimodal interface that collects and processes data coming from different sources.

Biomechanical, physiological and psychological measurements are used to extract a complete picture of the patient's state during therapy and they represent the main core of the multimodal interface.

Noninvasive cortical (i.e. EEG) and non-cortical interfaces (EMG, EOG, eye tracking, etc.) allow to identify the user's motion intention and to send control commands to robotic devices also representing a powerful way to further increase subject's involvement in the rehabilitative process.

In this context, data fusion and processing algorithms are developed working on the multimodal signals recorded by the acquisition system.

All these information are conjoined together and used to update the sensory feedback to the user (including visual, e.g. virtual reality, audio, and haptic feedback) and the bio-cooperative control in a patient-tailored manner, always guaranteeing safety in human-robot interaction.

### 3.1.1 Bio-cooperative control system

Currently, several control algorithms have been developed for rehabilitation machines; the same controllers are employed also in the bio-cooperative control loop and can be grouped in the following categories.

- Assistive controller - It is the most widely developed control paradigm [21]. Assistive controllers help participants to move their weakened limbs in desired patterns during grasping or reaching tasks, with a strategy similar to "active-assisted" exercises performed by rehabilitation therapists.
  Providing the subject with the minimal robotic assistance for completing the task execution allows the user to be actively involved and put consistent effort into therapy [102, 103].

- Haptic simulation - It is the practice of ADL movements in a virtual environment. Such control offers flexibility, convenience, and safety as advantages compared to practice in a physical environment [104, 105]

- Challenge-based control - It represents the controllers' category opposite to assistive controllers since they make movement tasks more difficult or challenging. Challenge-based controllers provide resistance to the participant's limb movements during exercise, requiring specific patterns of force generation or increasing the size of movement errors with *error amplification* strategies [8].

- Non-contact coaching approach - It is related to robotic devices that do not enter into physical contact with the participant; they play instead the role of non-contact coaches that decide and direct the therapy program and motivate participants. For such devices, it has been hypothesized that physically embodying the automated coaching mechanism has special merit for motivating participants [106].

On the basis of this classification, bio-cooperative control can be considered as a combination of assistive control and haptic simulation. The assist-as-needed control strategies can be further divided into four groups: impedance-based, counterbalance-based, EMG-based and performance-based adaptive assistance.

The impedance-based controllers are simple position controllers based on a proportional action [21, 107, 108]. The desired reference trajectory is normally generated by a minimum jerk trajectory [109, 110] or, in some cases, by an averaged pre-recorded path from healthy subjects. Several studies have shown that giving the patient the possibility to choose its own trajectory can result in muscle tone reduction and improvements in ADL [54, 98].

In addition, radial basis function (RBF) [111], bayesian learning [112] and machine learning techniques [113, 114] have been employed for estimating patient's arm model and establishing the needed assistance depending on patient's impairment level.

EMG-based control can be well suited for subjects who are able to generate muscle activation instead of force or movement, i.e. not highly impaired. EMG can be used as trigger signal in a threshold approach as proposed in [115, 116], while a continuous EMG control method is presented in [117]; here the assistance provided by the robot is proportional to the measured EMG signal.

In the last few years, BCI techniques and body signals have been used to develop a conceptual framework aimed to control robotic devices [118, 119]. For example a novel Brain/Neural-computer interaction (BNCI) system that comprises EEG and EOG has been used to control a robotic hand exoskeleton [120].

Such physiological non-invasive signals are employed as a trigger for initiating and stopping movement therapy intending to provide an online modification/adaptation of robot-aided rehabilitation exercises by continuously monitoring patient's intention.

In this context, BCI-gaze-driven control can be employed in a multimodal platform comprising eye-tracking system and BCI technologies in order to command robotic devices in rehabilitation settings [121].

Performance-based control has been extensively used with InMotion2 robot showing that adapting therapy to specific patient's motor characteristics led to better improvements (although very small) with respect to conventional therapy [53, 98]. Moreover, it has recently been shown that upper-limb 3D training provided by an exoskeleton with a patient-cooperative control can slightly enhance motor function improvement more than conventional therapy in chronic stroke subjects [54].

Such findings seem to confirm the hypothesis that the more the knowledge about the patient's condition is complete the more the bio-cooperative control can meet user's needs during robotic therapy.

### 3.1.2 The acquisition block

The acquisition block collects all the signals that can be extracted from the patient during the robotic treatment, thus allowing the analysis of user needs throughout the therapy sessions.
Position, velocity, acceleration and forces represent the biomechanical data extracted from the subject during the robotic therapy. They can be obtained through sensors embedded into the robot, or else sensors on the subject (e.g. wearable sensors like EMG, magneto-inertial sensors), or else sensors in the environment (e.g. RGB cameras and optoelectronic systems).
Psychophysiological measurements can be extracted from a number of biological signals (Figure 3.1), e.g. EMG, EEG, EOG, heart and respiration rate, skin conductance, temperature and blood pressure. Analysing context and environmental factors that influence people behaviour during a rehabilitation session is a crucial aspect in intelligent virtual reality systems. For instance, RGB cameras and gaze detection systems are often used to select specific actions or monitor user interaction with the robot and the environment.
Human specific behaviors and intentions can be triggered by gaze focalization. To this purpose, Microsoft Kinect represents an affordable solution for performing visual tracking of active objects in the rehabilitation scenario within the 3D workspace where the objects can be reached and located [121].

### 3.1.3 Data fusion

Once data coming from different sources have been collected, data fusion and processing procedures are required to depict the patient's global state and update accordingly the sensory feedback (including the virtual reality as well as audio and haptic feedback) and the bio-cooperative control. In the following the main states composing the patient's global picture are listed.

- *Biomechanical state* - It is estimated through kinematic and dynamic indicators which provide kinematic measures of movement duration, accuracy and smoothness, or else dynamic measures of forces and work expended during therapy. Bio-cooperative controller receives biomechanical feedback able to adapt robot gains and stiffness to specific patient's conditions [52, 122].

- *Psychophysiological state* - Continuously identifying patient cognitive load during the task execution allow to obtain the psychophysiological patient's condition undergoing robotic therapy [123]. The cognitive load can be estimated using physiological measurements like heart rate, respiration rate, skin conductance and blood pressure [13, 15].
  In order to better exploit all these information, machine learning algorithms allow to extract features that can help the robot system to learn the way to automatically update its behavior depending on specific user requirements [124, 125].

- *User intention* - It comprises a bundle of information that together give a picture of the user intention while performing determined tasks. Such information come from non-cortical interfaces that use either biomechanical parameters, such as force, velocity, position, time thresholds for triggering therapy, or electromyography (EMG) and eye-tracking signals [98, 117, 121]. Robot assistance is provided when the signal detecting patient motion intention overcomes a predefined threshold of the trigger-cue. In the same way, BCI systems, may infer the user's intent through neural data acquired from the brain i.e. EEG, exploiting them as input control for robotic assistive device.
  Gathering together BCI with EOG, EMG and eye-tracking signals is also recommended for strengthening system capability to detect patients' intentions.

### 3.1.4 Sensory feedback: visual and haptic

Sensorial feedback are extremely important into rehabilitation process since they give to the patient the perception of "what" and "how" they are doing during therapy. In general, sensory feedback may be either visual or haptic or their combination [126, 127].
Virtual reality (VR) and computer-game techniques represent a useful way to

enhance neuroplasticity [49, 128, 129]. The adjunct of acoustic feedback, together with a virtual reality environment that reproduce a normal rehabilitation scenario results in a more challenging patient sensorimotor engagement thus operating as "augmented feedback" [130].
User's sensorial state can be further enhanced merging together VR, haptic and vibrotactile feedback [131]. These elements provide the perception of the task in a kinesthetic or tactile manner operating directly onto subject's skin in order to guide the arm into the desired target configuration shown on a graphical interface or virtual environment [132].

## 3.2 The proposed bio-cooperative robotic platform for 3D upper limb treatment

In this section, a bio-cooperative system for 3D upper limb rehabilitation, partly developed within the Echord/MAAT project is presented [93, 122, 133]. The system is composed of a 7-DoF robotic arm (Kuka LWR-III), a motorized arm-weight support system, an adaptive interaction control system, and a module for on-line evaluation of patient performance in order to adaptively and dynamically change robot behavior (see Figure 3.2). Although the novel bio-cooperative scheme pro-

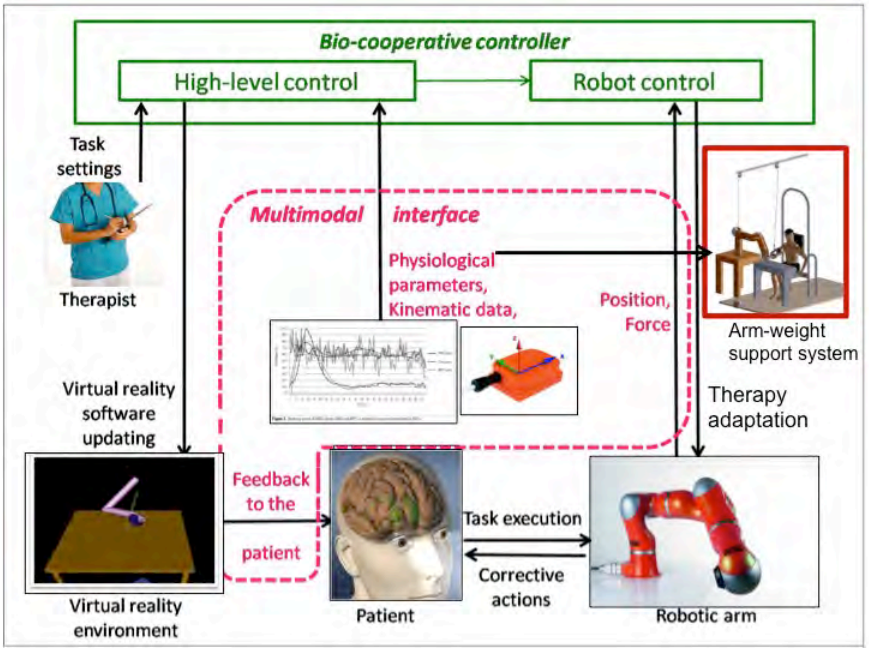


FIGURE 3.2: Overview of the overall MAAT system with the integrated module for arm-weight support

posed in Figure 3.1, has been conceived for any robotic devices, in this application it has been decided to use a Kuka robotic arm since it was one of the robotic machines available in the Laboratory of Biomedical Robotics and Biomicrosystems.
The proposed system represents an illustrative case of bio-cooperative system deriving from the general scheme in Figure 3.1 and it copes with the delicate requirement of introducing an adaptive arm-weight support for 3D rehabilitation with end-effector machine.
Therefore, the motorized arm-weight support can be regarded as the main innovative element of the bio-cooperative system previously developed in [122], aimed to overcome patients' difficulty to self-sustaining their own arm during the motor exercises. The multimodal interface is the central core of the system and is composed of the following sources of information, providing a picture of the patient's condition:

- Robot sensors for hand pose and force;
- Magneto-inertial sensors for reconstructing the user's joint motion;
- EMG electrodes for recording muscular activity;
- A module for on-line evaluation of patient performance that records patient biomechanical data through an unobtrusive, wearable sensory system; it also evaluates patient biomechanical state and updates robot control parameters for modifying the level of assistance and task complexity in the 3D workspace;
- A virtual reality reproducing the selected task is developed for further promoting patient motivation and engagement.

The system is grounded on an end-effector machine that interacts with the user only at the end-effector level while providing assistance in analytical tasks, i.e. point-to-point in 2D and 3D space, as well as in functional tasks of daily living (ADLs).
However, because of the interaction limited to just one point, an additional mechatronic arm-weight support has been developed. It has the fundamental purpose of providing an adaptive level of support, by compensating the gravity force depending on the subject arm configuration in the space. In the following the main modules of the proposed system are discussed.

### 3.2.1 The patient tailored adaptive robotic control

The controller has the main goal of assisting the patient (who is connected to the end-effector of the robot) when he/she is not able to accomplish the task autonomously, with a level of assistance that is tuned on the patient global state. As a result, the robot has to be highly compliant when patient is able to follow the planned path, while it has to change adaptively its behavior when subject moves away from reference trajectory.
To this purpose, an impedance control in the Cartesian space has been selected as the most suitable kind of control for this application. Task duration and robot stiffness are the control parameters updated according to the patient biomechanical state, as reported in Section 3.2.2. The robot control law can be expressed as follows [122].

$$\vec{\tau}_{cmd} = J^T(\vec{q})[K(\vec{x}_p - \vec{x}) + \vec{FT}] + D(d) + \vec{f}_{dyn}(\vec{q}, \dot{\vec{q}}, \ddot{\vec{q}}) \tag{3.1}$$

$J^T$ is the transposed Jacobian matrix, $K$ is the Cartesian stiffness matrix, $\vec{x}_p$ and $\vec{x}$ are the desired and actual Cartesian position vectors, $D(d)$ is the damping term, $\vec{FT}$ is an additional superposed Cartesian force, $\vec{q}$ is the joint vector, $\vec{f}_{dyn}$ is the dynamic model. Furthermore, in order to promote patient involvement and enhancing voluntary efforts, a *dead band* around the reference trajectory is created [8, 98] where no assistance is provided. For 2D and 3D point-to-point movements a minimum-jerk trajectory is planned as reference trajectory; on the other hand, for ADL tasks, pre-recorded trajectories from healthy subjects are used.

### 3.2.2 The module for biomechanical and physiological assessment of patient performance

Patient's biomechanical measures are recorded by means of robot position and force sensors as well as an accelerometer positioned on the patient's arm. EMG electrodes are used to record physiological measures; a data fusion and processing algorithm allow evaluating the patient status through kinematic, dynamic and EMG indicators. Afterwards, control parameters are updated by means of modulation functions that exploit the computed indicators.
Kinematic indicators take into account patient behavior in the Cartesian and in

the joint space. Patient trajectories in the Cartesian space are computed exploiting encoders embedded into the robot; on the other hand, an inverse kinematics algorithm (presented in detail in [134]) based on the patient augmented Jacobian has been developed for reconstructing the patient's joint motion. The algorithm is grounded on to the measures provided by the robot position sensors and the accelerometer located on the subject's arm.
The computed kinematic indicators are presented and explained hereinafter.

- Aiming angle ($\alpha$) [52], i.e. the angle between the target direction and the direction of travel from the starting point up to peak speed. It allows evaluating motion direction and accuracy.
- Mean Arrest Period Ratio (MAPR) [87, 135], defined as the proportion of task duration where movement speed exceeds the 10% of peak speed. It is used to quantify motion smoothness.
- Inter-joint coordination ($q_{corr_{i,j}}$) expresses the correlation index between two upper limb joint angles $q_i$ and $q_j$ [122].

A set of dynamic indicators is extracted exploiting the torque sensors embedded into the robot. These indicators quantify the interaction force between human and robot during the dedicated task. The computed indicators are the following [52]:

- Useful-Mean-Force (UMF) which represents the amount of mean force exerted along the target direction;
- Useful-Peak-Force (UPF) that expresses the peak force along the target direction;
- Total-Work (TW) which is the total work expended during motion;
- Useful-Work (UW) that expresses amount of total expended work along target direction.

In addition, also indicators related to EMG activities of antagonist muscles (pectoral/ deltoid and biceps/triceps muscles) are computed in order to estimate muscular force, power and fatigue expended during robotic therapy. They are expressed in detail as:

- Root Mean Square (RMS), i.e. the quadratic mean of signal amplitude [136];
- Power Spectrum (PS), that is power spectral signal density [137];
- Co-Contraction Index (CCI), i.e. a quantitative measure of the simultaneous activation of antagonist muscles across a joint [138];
- Median Frequency (MF), i.e. the median of frequency distribution of the signal [137, 138].

Performance indicators are then normalized with respect to their maximum and adjusted in order to increase with motor recovery. They are used for a twofold purpose: (a) to assess patient behavior during therapy and evaluate his/her level of recovery; (b) to tailor the therapy to the patient's state by updating control parameters $t$ (i.e. task duration) and $K$ (i.e. robot stiffness).
Two weighted-sum modulation functions are employed in order to adjust the computed performance indicators as expressed by Eq. (3.2) and (3.3).

$$C_t = \sum_{j=1}^{J} w_j PI_j \tag{3.2}$$

$$C_K = \sum_{i=1}^{I} w_i PI_i \tag{3.3}$$

$PI_j$ is the *j-th* performance indicator ($j$ *=0,1,2,..,* $J$) used for the adaptation of the time allotted for task execution; $PI_i$ is the *i-th* performance indicator *(i=0,1,2,.., I)* used for the adaptation of robot stiffness and $w_{i,j}$ is the weight chosen for the selected indicators.
The different weights are chosen with a trial-and-error approach. Several trials have been performed assuming different weights for the selected performance indicators with the aim to identify those that provide more indications of a pathological behaviour versus a healthy behaviour.
For instance the aiming angle is expected to have a greater contribution for the adaptation of robot stiffness $K$ rather than the task duration $t$ since it quantifies accuracy and direction of the fulfilled movement. For this reason, the aiming angle is employed only in $C_K$.
On the other hand, since MAPR quantifies movement smoothness (describing the percentage of stops during task execution) it is expected to have major effects on task duration $t$ and therefore is used only in $C_t$. All the other indicators are

employed in both functions with lower weights.
The modulation functions continuously vary between 0 and 1; a threshold strategy is employed to convert them into discrete performance levels related to predefined value of $t$ and $K$.
To this purpose, three performance levels are identified (1, 2 and 3) corresponding to three intervals of $C_K$ and $C_t$ (i.e. [0, 0.5), [0.5, 0.70) and [0.70,1)) [122]. The robot control automatically associates them to predefined values of robot stiffness and task duration.

### 3.2.3 Design and development of a mechatronic module for arm weight support

Subjects who undergo robotic therapy with end-effector machine may require an arm-weight support to compensate for gravity and fulfill the motion exercises. Patient difficulty to self-sustain arm during robotic treatment is mainly due to neuromuscular damages caused by stroke [139] which produces upper limb muscular weakness, making really challenging for the patient to execute the required tasks.
Providing subjects with arm weight-support has been shown to reduce the abnormal coupling of shoulder abductors and elbow flexors often observed in stroke survivors who are affected by severe motor impairments [5, 69, 140–142].
Robotic devices which supply arm weight-support, have been demonstrated to facilitate arm movements during reaching tasks by reducing the required level of muscle activity, particularly for muscles involved in arm-sustenance against the effect of gravity [143, 144].
These studies, as well as the collaboration with the clinicians have encouraged the development of a novel mechatronic module for online adaptation of arm-weight support. In this subsection, the requirements and the design of the arm-weight support are explained; however, its validation on healthy subjects is intended to be realized as a future application.
The development of the arm-weight module is an extension of the bio-cooperative system developed within the Echord/MAAT project, and plays a key role in the application of the system to clinical trials on post stroke patients. Finally, a preliminary description of the new platform comprising the arm-gravity support system is shown in Figure 3.3.

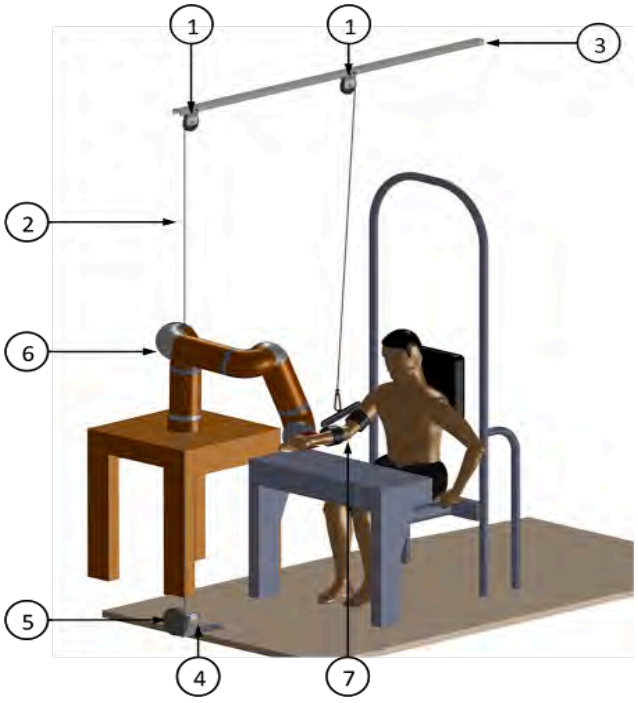


FIGURE 3.3: The developed mechatronic module for arm weight support: (1) pulleys; (2) steel wire; (3) steel bar; (4) actuation system; (5) aluminum drum; (6) 7-DoF KUKA LWR; (7) forearm-belt support

The arm-weight support has to sustain patient's arm during 3D task execution by adapting the level of support to the limb configuration. To this purpose arm weight (i.e. the load), arm moment of inertia, approximate task velocity and required range of motion (ROM) are estimated.

The following values have been chosen in the design phase: arm weight equal to $5kg$ [145], arm moment of inertia is taken equal to 0.0245 $kgm^2$ [145], arm velocity is set as 0.5 $m/s$ [122], arm ROM along z-axis is 0.5 $m$ [122]; for safety reason a factor 2 is used in order to overestimate these values.

As transmission system, a cable-pulley system is chosen driven by a DC motor secured on one extremity of the cable. A specific orthosis for arm/forearm support is fixed at the other cable extremity.

The cable-pulley system in Figure 3.3 is composed of: (1) two pulleys (BNL acetal 25 $mm$ pulley, 18 $mm$ pitch diameter, 102 $mm$ external diameter, 9 $mm$ bore) with ball bearings and bore reduction bush; (2) 4 $mm$ steel wire rope black nylon coated to 5 $mm$, with winding radius equal to 70 $mm$; (3) steel bar equipped with holes for fast choosing of pulley's location, fastened on room ceiling; (4) an actuation system composed of: EC-max 40 brushless Maxon Motor, planetary gearhead Maxon GP 42-C 74:1, Maxon HEDL-5540 encoder and Maxon EPOS2 50/5 control unit; (5) aluminum drum, for enveloping steel rope, (diameter: 140

*mm*) is built-in with motor shaft; (6) 7-DoF KUKA LWR; (7) forearm-belt support, which enables to set correct fitting depending on patient's requirements.
The selected actuation group has been chosen to provide the maximum continuous torque (load acceleration torque and continuous torque for maintaining arm) for sustaining the upper limb, which has been estimated as 4.1 $Nm$. Moreover, the actuation group and the cable-pulley system can be adjusted according to the patient anthropomorphic characteristics and sitting position.
In order to provide the patient with online adaptive arm support during the 3D tasks and ADLs, a position control is currently under development that can command the motor to reel in or else unroll the cable according to the patient's limb configuration.
Such control is obtained on the basis of the already validated inverse kinematics algorithm in [134] which allows to compute in real time the Cartesian position of the elbow. The controlled rotational movement of the motor shaft coupled with drum is expected to induce translational movements to the cable capable of lifting and lowering the patient arm as required by the task.
As future work, the developed system needs to be validated with human healthy subjects for demonstrating the feasibility of the proposed approach.

## 3.3 Discussions and final considerations

This Chapter has presented an overview on bio-cooperative robotic systems in the rehabilitation scenario, proposing a novel functional architecture including new technologies. Moreover, the case study of a bio-cooperative system for upper-limb motor therapy has been described.

The key-issue of a bio-cooperative system is to close the patient in the control loop in two ways:

(a) by feeding back to the robot multimodal information about the patient's global status (through biomechanical, physiological, psychological information);

(b) by returning to the patient the perception of the task being executed (through visual, auditory or haptic feedback).

Hence, a multimodal human-robot interface includes all the modules responsible for acquisition, processing and feedback of such a huge number of signals.
The provided definition of bio-cooperative system together with its functional architecture (Figure 3.1) is extended to include non-invasive human-machine interfaces for detection of human intention, context and environmental factors, and augmented sensory feedback for the patient (in addition to the multimodal signal acquisition for the patient state).
Although all these potential advantages introduced by the bio-cooperative systems, a number of open issues regarding the use of such systems in rehabilitation robotics are still open. For instance the use of multimodal interfaces requires to gather different signals from several sources, thus notably increasing system complexity [11]. This may cause a non negligible computational burden as well as the use of obtrusive equipment for the users. Obtrusiveness is a very delicate issue that can contribute to cause user's stress or unsatisfaction during the therapy. To this purpose, there is the attempt to realize bio-cooperative systems with unobtrusive equipment [122].
Sensory and multimodal enhanced feedback have shown many positive effects such as:

- reduction of the workload during motor task learning;
- facilitating learning of spatial and temporal aspects of the movements, thanks to visual and auditory feedback.

However, it is worth noticing that, despite these promising findings, the augmented feedback still present limitations. For instance, many devices that are required to operate a VR system, with sensory feedback, or to track user behavior, generally requires obtrusive hardware that are a source of distraction and inconvenience.
Real-time synchronization of signals dedicated to reconstruct VR may be delayed due to the large number of required devices. This lead to a bad real-time environmental reconstruction, thus increasing the task difficulty.
Future challenges regarding augmented feedback suggest to examine whether visual, auditory, and haptic feedback can induce similar effects on patients, whereby measuring brain activation in different feedback conditions.
Another potential issue is represented by the use of EMG-based control system. It gives a significant movement freedom to the user, with the consequent drawback that it may enhance pathological movements related to stroke conditions rather

than allow regaining motor and functional skills. Furthermore, the introduction of BCI system and its coupling with physiological signals EEG and EOG may provide multimodal movement-related physiological data, which can be exploited to generate reliable and robust "biomarkers" of motor and functional recovery in patients with neural damages [146]. On the other hand, such systems may introduce several uncertainty due to the unknown efficiency of brain signal's detection and processing.

In conclusion, notwithstanding their potential, bio-cooperative systems still present some open issues that have to be addressed in the future. In fact, their validation in the clinical settings is still very limited (except for a few preliminary studies [14, 54, 99, 122, 124, 147]); such validation represents the real keystone to assess the efficiency of bio-cooperative approach in rehabilitation robotics.

Finally, in Section 3.2 a bio-cooperative system for upper limb robot-aided rehabilitation is presented. The system is composed of a multimodal interface that exploits patient biomechanical and physiological (EMG) performance to update an adaptive robot control system. A specific module for arm-weight support has been implemented to provide the patient with adaptive support against gravity. The module is designed according to clinicians requirements in order to extend therapy to stroke patients and its validation is expected to start very soon.

Further experiments on healthy subjects will be carried out to test the reliability of the complete platform before moving to the clinical validation on post-stroke subjects.

# Chapter 4

# A modular telerehabilitation architecture for bio-cooperative robotic systems

This Chapter intends to extend the concept of multimodal systems to a telerehabilitation application. To this purpose, a case study of a bio-cooperative modular architecture for upper limb robotic telerehabilitation in unilateral configuration has been developed.

In this Chapter, the bio-cooperative approach has been applied to an end-effector machine (CBM-Motus); however, it can be further extended to wearable robotic devices such as exoskeletons. The architecture is designed to be modular and is conceived to be as general as possible, in order to be independent from the specific robotic platform employed for delivering the therapy. The main goal of the developed architecture is to guarantee reliable communication between the therapist and the patient for transmitting therapy data and update the process within the therapy session.

The same architecture is designed to operate in a realistic telerehabilitation scenario where the patient and the therapist interact over the Internet, without a dedicated or special data interconnection.

The developed modular architecture is then applied to a planar end-effector machine for upper limb rehabilitation named CBM-Motus, which is one of the robotic machines available in the Laboratory of Biomedical Robotics and Biomicrosystems. The CBM-Motus is able to provide required assistance thanks to a multimodal interface grounded on a patient-tailored control that can monitor the patient's motor

performance and, accordingly, tune the therapy.
The Chapter is structured as follows. Sections 4.2 and 4.3 present the general modular architecture for upper limb unilateral telerehabilitation and its application to the CBM-Motus planar robot, respectively. Finally, the experimental validation of the proposed telerehabilitation architecture on healthy subjects as well as the results are described in Section 4.4 and final considerations are discussed in Section 4.5.

## 4.1 Background

Several factors may prevent post-stroke subjects from participating in rehabilitation protocols, e.g. geographical location of rehabilitation centers, socioeconomic status, economic burden, lack of logistics surrounding transportation.
Early supported discharge (ESD) from hospitals with continued rehabilitation at home represents a well-defined regimen of post-stroke treatment [148]. It consists of services that aim to accelerate the discharge of patients after a stroke event, and provide a comparable rehabilitation level at the patient's home with conventional hospital care and discharge [149].
The application of this regimen to post-stroke rehabilitation has fostered a growing interest in the development of new technologies for telerehabilitation, able to provide remote delivery and monitoring of rehabilitation services over telecommunication networks and internet.
Furthermore, telerehabilitation can also benefit from the recent advancements of robot-aided rehabilitation, thus providing interactive, repetitive and task-specific activities that can be tailored to the user's needs, and promote motor learning, exploiting neuroplasticity, without the continuous oversight by a therapist [2, 77].
The development of novel robotic control strategies that integrate the human into the loop exploiting biomechanical, physiological and even psychological information derived from patients may further enhance the potential of telerehabilition.
In this context, bio-cooperative systems employed in telerehabilitation scenario give the opportunity to establish patient-tailored rehabilitation protocols shaped on the specific user's needs [11, 12]. Such an aspect, is expected to increase the diffusion of such systems as powerful tools for enhancing motor and functional recovery of stroke subjects treated with in-home rehabilitation strategies.

In the recent years, different telerehabilitation systems have been developed to improve patients' ADLs in the attempt to increase their independent living at home [150–153].
The systems for robot-aided telerehabilitation can be grouped into two different classes [154]:

- *unilateral* configuration systems;
- *bilateral* configuration systems;

In *unilateral* configuration only the patient is connected to the robot while the therapist can remotely communicate with the robot and the patient. The communication between patient and therapist is not required to be real-time; after a predefined time-lapse data are sent to the therapist interface in order to verify the therapy progress and, possibly, modify the treatment.
The JavaTherapy system [155] has been the first developed unilateral system for telerehabilitation purposes. It consists of a wrist trainer system based on a low-cost commercial force feedback designed for home therapy that is remotely monitored and managed by therapist via a low-cost web camera and teleconference software.
Other important devices are the Hand Mentor™ and Foot Mentor™, developed by Kinetic Muscles Inc., that provide hand and foot in-home rehabilitation. Clinical studies have been also performed with these systems in order to investigate the real effectiveness of teletherapy respect to standard home exercise program [156–158]. However, no significant improvements have been found so far.
In the *bilateral* configuration both the patient and therapist interact with a robot and communicate over the Internet through a shared virtual environment (SVE), normally using a *client/server* approach.
The communication is real-time and enables the therapist to modify the current exercise or apply corrective actions during the tasks. Basdogan et al. [159] have developed a multimodal shared virtual environment to study the role of haptic feedback in collaborative tasks using two PHANTOM™ haptic devices (SensAble Technologies Inc, Woburn, Massachusetts).
Studies on ESD have shown the need of in-home rehabilitation delivery system because, when therapy is maintained constant and intense, the increase of the functional recovery can be significant [160]. Robots for telerehabilitation have to address specific requirements related to the application, such as portability and, consequently, lightness, compactness, easiness to set up and ready to use both for

therapists and patients.

Finally, communication architecture has to be reliable guaranteeing robust and safe communication between the patient and the therapist side. In addition, system modularity is also required since different signals and modules could be employed. In this scenario, in Section 4.2 the attempt to develop a pioneer bio-cooperative modular architecture for upper limb telerehabilitation grounded on a multimodal interface is proposed and discussed together with some preliminary results.

## 4.2 The proposed modular architecture for telerehabilitation systems

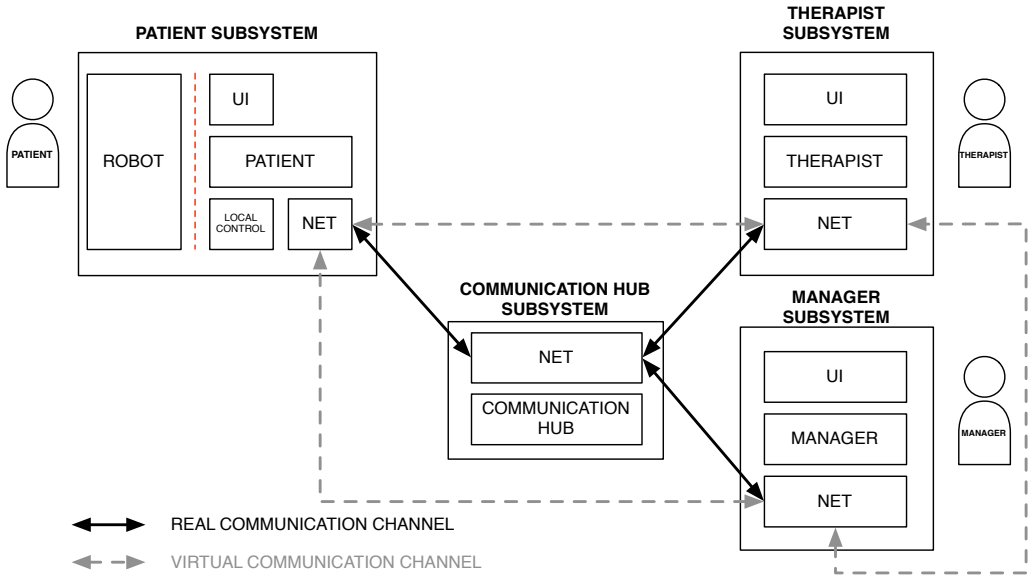


FIGURE 4.1: The proposed general architecture for telerehabilitation robotic systems.

The bio-cooperative modular architecture for telerehabilitation systems is conceived to be a flexible model usable in several rehabilitation scenarios, including remotely controlled robotic systems that deliver in-home rehabilitation treatments and continuously control rehabilitation outcomes [161]. In Figure 4.1 the proposed model is presented.

It comprises four subsystems each with a specific role and functionality.

1. *Patient subsystem* - It is the component that physically interacts with the patient including the robotic system and implements control and communication functionalities.

2. *Therapist subsystem* - It is the component that interacts directly with the therapist also enabling the remote monitoring and control of the patient.

3. *Manager subsystem* - It is the component that interacts directly with one of the system managers. It enables the control and the configuration of other entities, and the management of users.

4. *Communication HUB* - It is the component that provides several services. In particular, it implements all the functionalities required for recognizing the users and allowing them to communicate.

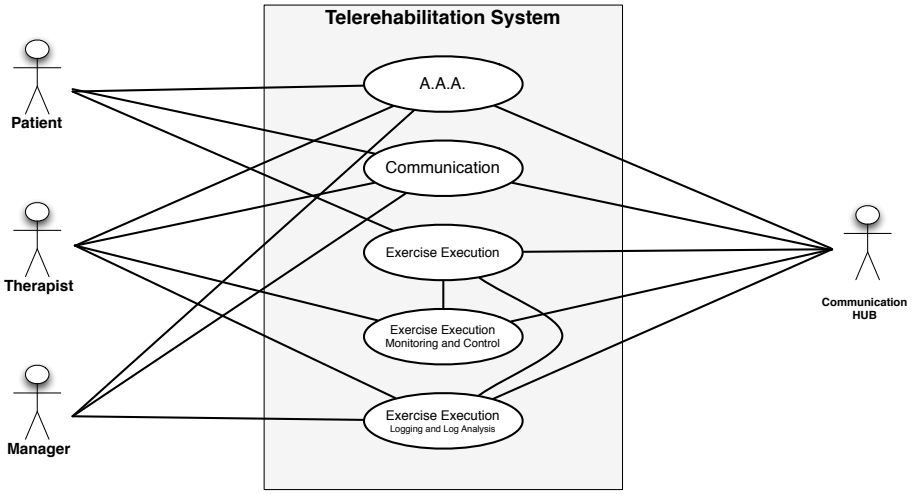


FIGURE 4.2: Telerehabilitation systems main services.

The four subsystems interact each other in order to provide different services as shown in Figure 4.2. An explanation of these services is provided hereinafter.

- *A.A.A.*: *Authentication, Authorization and Accounting* services allow controlling the access to the system. In the proposed model, the Communication HUB is in charge of maintaining information on users (Patient, Therapist and System Managers) and allowing them to log into the system. Historical information on services are recorded and associated to each user for clinical (Patients and Therapist) and system management (Patients, Therapist and Managers) reasons.

- *Communication*: This service is required to enable the data transfer between subsystems. The communications are mediated by the Communication HUB since i) it simplifies the authorization of communications, ii) it disentangles the system from the Internet reachability problem (i.e. the behind NAT (Network Address Translation) problem), when the system shares a public IP address with other devices and it is not directly accessible without an ad-hoc configuration of the router it connects to), and iii) it simplifies the monitoring of all the actions performed on the system.
  It is worth mentioning that drawbacks as Communication HUB overload can be easily solved, for instance by means of system repetition and load balancing.

- *Exercise Execution*: The execution of the rehabilitation exercise is performed by the patient and supported by the Patient subsystem under two possible execution models: (i) patient-alone and (ii) patient-supervised. When executed alone, the patient is not required to access the *A.A.A.* and the *Communication* services.
  Conversely, in the other modality the patient has to identify itself and communicate through the Communication HUB with the Therapist. Even though the patient-alone model does not require access to the *A.A.A.* and the *Communication* services for its execution, the dissemination of collected data through the Communication HUB needs them.

- *Exercise Execution, Monitoring and Control*: In the supervised execution model the system allows the therapist to interact with the patient. This interaction can be limited to the online visualization of the exercise during its execution or it may be extended further, including the online transmission of multimodal data for patient's monitoring and the adaptation and control of rehabilitation parameters. In addition the transmission of these data can be also employed for therapy assessment.
  This service requires that both the patient and the therapist use their local subsystem, and pass through the *A.A.A.* and the *Communication* services.

- *Exercise Execution, Logging and Log Analysis*: Patient performance assessment needs the collection of multimodal data generated during exercises for an offline analysis. Hence, data is collected by the Communication HUB, which implements both a database for data collection and an interface and/or a set of APIs for data retrieval.

The evolution of multimodal patient's performance can be monitored using the Logging and Log Analysis service that are also employed to track and make global studies on the impact of rehabilitation therapies.

## 4.3 The application of the telerehabilitation architecture to CBM-Motus

In this Section the first implementation of the proposed architecture combined with the CBM-Motus rehabilitation robot, including the *Communication*, the *Exercise Execution* and the *Exercise Execution, Monitoring and Control* services is presented.

The CBM-Motus planar robot has been selected for this preliminary study since it is one of the available robotic devices available into the Laboratory of Biomedical Robotics and Biomicrosystems. Further applications of the modular architecture to other robotic devices could be envisaged as future works.

The general scheme for robot-aided telerehabilitation previously presented in Figure 4.1 and 4.2 has been then tailored to the CBM-Motus robotic device as shown in Figure 4.3. The granularity of viable control depends on the latency and the

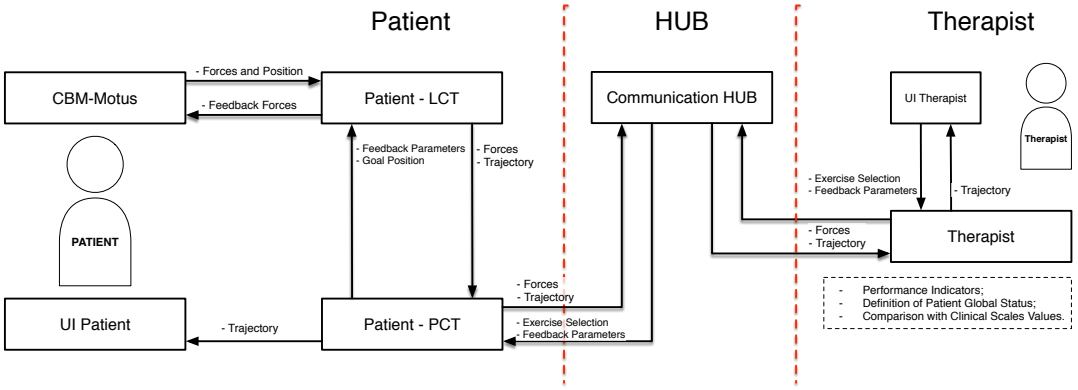


FIGURE 4.3: The modular architecture for telerehabilitation applied to the CBM-Motus rehabilitation robot. The patient side includes the robot and the patient-robot interaction modules; the therapist side includes evaluation and therapy modules, allowing therapy definition based on the evaluation of the patient thanks to quantitative performance indicators and clinical scales.

bandwidth exhibited by the Patient-to-Therapist and Therapist-to-Patient communication channels.
The employed libraries and the software have been tailored to run on cheap hardware settings and, indeed, all the systems developed in this work run seamlessly on Pentium 4 workstation equipped with less than 1GB main memory.
The telerehabilitation system based on the CBM-Motus robot is composed of Patient, Therapist, Manager and Communication HUB software components. The architecture of each software component is outlined in the following subsections.

### 4.3.1 Patient software component

The Patient software component has to fulfil several requirements. First it has to control the robotic system, then it implements the UI for the patient and is responsible of the data communication logic for patient/therapist interaction.
The main architecture of this component is composed of two tiers (Figure 4.4): the Local Control Tier (LCT) that controls the robotic rehabilitation end-point and the Patient Control Tier (PCT) that manages the UI, the interaction with the first tier and the remote exchange of data.
The LCT is a three-layer software component; the lowest layer (HAL - hardware abstraction layer) abstracts the hardware and implements a general software interface, the second layer (Control logic) implements local and time-critical control functionalities for the robot management and the highest layer (Local comm.) provides a communication interface based on standard interprocess communication (IPC), to exchange messages (commands and data) with the other tier.
On the other hand, PCT is a multilayer software component that implements rehabilitation exercises (Local control), the User Interface for the patient (UI Patient) and communication functionalities (Communication Logic and Local Communication). Local communication functionalities are based on standard IPC, whereas the interaction with other rehabilitation systems, mediated by the Communication HUB, is based on the TCP/IP network protocol.

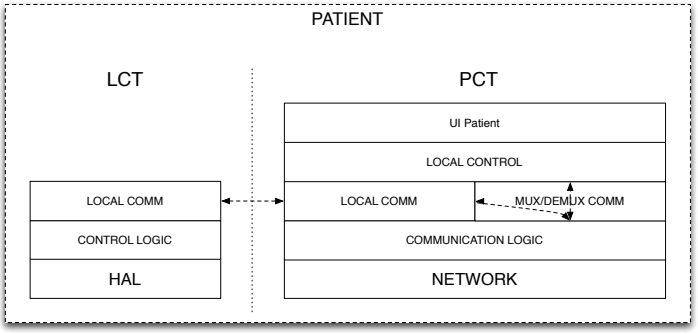


FIGURE 4.4: Patient Component Architecture

### 4.3.2 Therapist, Manager and Communication HUB software components

The other three main software components of the architecture are the Therapist, the Manager and the Communication HUB. The Therapist block allows the therapist to monitor the execution of the patient's exercises and to change exercise parameters online (Figure 4.5a).

From bottom to top, the *Network* layer is in charge of communication functionalities based on the TCP/IP protocol. The *Communication Logic* manages uplink (data) and downlink (control messages) flows, whereas the *Remote Control* layer maps therapist actions to commands for the patient software components. Eventually, the UI Therapist implements the graphical interface that the therapist uses to monitor and issue commands. Data messages to the therapist UI are sent by means of TCP packets at the same rate they are generated for the patient UI.

The Manager software component allows monitoring the execution of exercises concurrently with the therapist. Its architecture is shown in Figure 4.5b and it's the same of the Therapist. Contrary to the Therapist, the Manager cannot issue control operation during exercises but it is enabled to monitor exercises and commands flows. Moreover, the manager takes care of hardware settings that are out of the scope of therapist's actions.

Finally, the Communication HUB relies on a three layer architecture in order to manage the authentication of users, the communications among other software components and to implement a local debug console for system monitoring. As shown in Figure 4.5c the *Network* and the *Communication Logic* layers implement a TCP/IP service to which all the other software components (Patient, Therapist and Manager) can connect.

Finally, the *Auth Logic* sublayer controls if a given software component is allowed

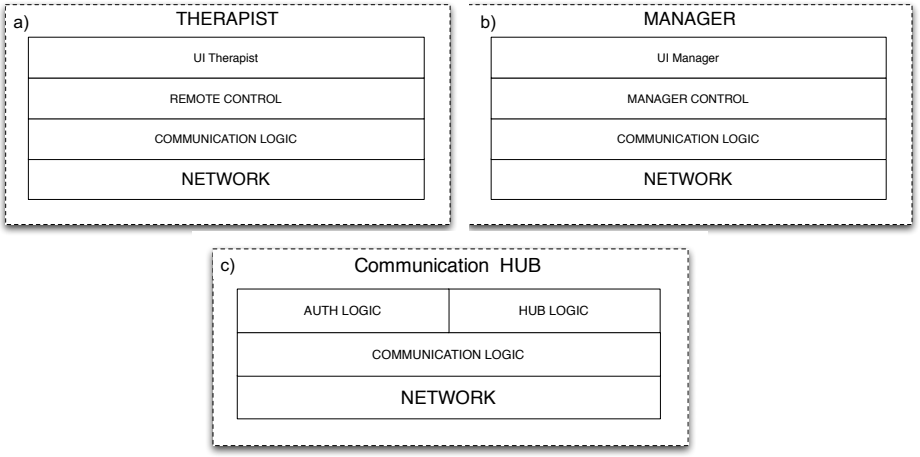


FIGURE 4.5: Software components architecture: Therapist a), Manager b) and Communication HUB c)

to connect and which role it has while the *Hub Logic* dispatches messages (data and commands) among the connected subsystems.

### 4.3.3 The CBM-Motus planar robotic device

The CBM-Motus is a planar end-effector machine for upper limb rehabilitation (Figure 4.6) grounded on a Cartesian kinematic structure consisting of two modules connected by a double prismatic joint. The machine is conceived to address the following main requirements: low and isotropic inertia, simplicity in the mechanical structure, lightness and compactness in order to enable portability and low cost to favour home usage with a total mass less than 30 kg. The kinematic structure ensures a good rigidity of the robot with relatively small moving masses; in addition, thanks to the double prismatic joint, only tensile forces can be transmitted to the belts.

The ends of the bars are equipped with a ball-bearing slider that aims to compensate vertical load and axial forces induced by friction in the prismatic joints [162]. Finally, two DC servomotors (Aerotech BM 250) directly drive the two kinematic modules presenting a rated torque of 2 Nm and peak torque of 5 Nm. These values allow the robot to exert a force of 80 N for each axis with a peak force up to 200 N. However, the maximum exercisable force has been limited via software to 50 N in order to maintain a safe human-robot interaction [163].

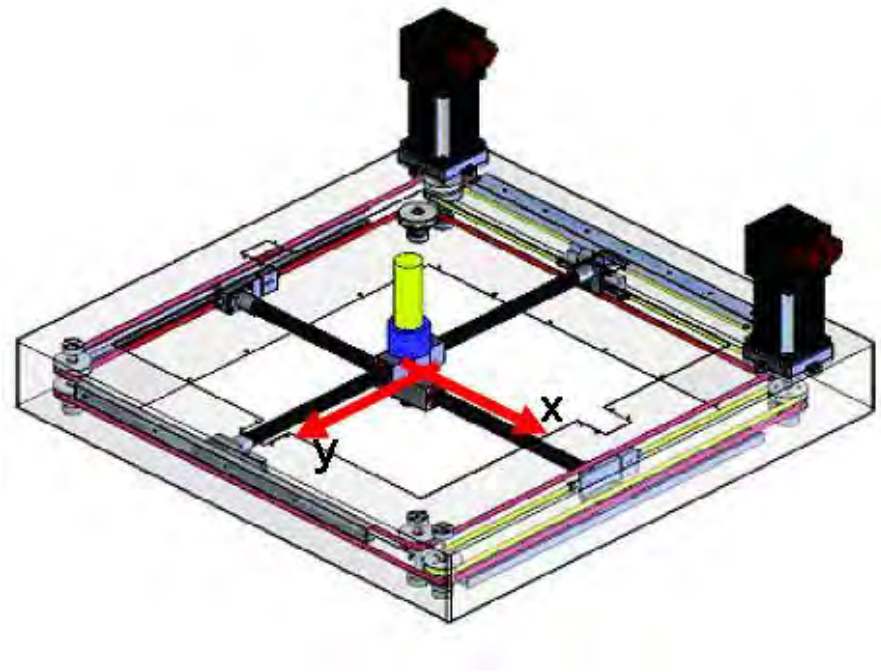


FIGURE 4.6: Overview of CBM-Motus's structure

### 4.3.4 CBM-Motus bio-cooperative control

The bio-cooperative approach is applied for the control of CBM-Motus. Robot control aims at providing the patient with the minimum level of assistance needed to accomplish the task, by monitoring the patient's status by means of multimodal information. To this purpose, positions and velocities of the user's hand are recorded using robot's sensors and employed for the extraction of well-defined performance indicators.

Due to the modularity of the system, the multimodal interface can be further extended adding various sensors for monitoring user's state. For instance, magneto-inertial sensors and psychophysiological measurements can be added in order to obtain information about dynamic and affective states of the subject.

In this application, an impedance control with adjustable parameters has been implemented. It can be written as follows

$$\tau = B(q)y + F_v\dot{q} + F_s sign(\dot{q}) \tag{4.1}$$

with

$$y = M_d^{-1}(M_d\ddot{q}_d + K_P\tilde{q} + K_D\dot{\tilde{q}}), \tag{4.2}$$

In Eq. 4.1 $\tau$ is the torque command, $B$ is the inertia matrix (independent of robot configuration), $F_v\dot{q}$ and $F_s sign(\dot{q})$ are dynamic and static friction torques, which are non negligible in the CBM-Motus dynamics [162]. On the other hand, $y$ represents the stabilizing action that makes the robot acting as a generalized mechanical impedance regulated by mass matrix $M_d$, stiffness matrix $K_P$ and damping matrix $K_D$.

The control is tailored to the subject's motion abilities by updating during the therapy stiffness matrix $K_P$ and time allotted for task execution $t$ [122]. To this purpose, a set of performance indicators have been selected for a quantitative evaluation of the subject's biomechanical behaviour [52] and employed to adjust control parameters. Position and velocity sensors embedded into the robot are employed to record hand position and velocity in the planar space and, later, compute performance indicators.

The two control parameters (i.e. $K_P$ and $t$) are progressively updated, based on the values acquired by modulation functions $C_K$ and $C_t$, expressed as

$$C_K = \frac{3}{5}\alpha + \frac{1}{4}AREA + \frac{1}{4}nMD \tag{4.3}$$

$$C_t = \frac{3}{10}MAPR + \frac{1}{4}SpeedMetric + \frac{1}{6}MD \tag{4.4}$$

Eqs. 4.3 and 4.4 are weighted sums of a few of the aforementioned performance indicators where ($\alpha$) is the *Aiming angle*, $AREA$ is the area between the desired and the actual trajectory performed by the subject, $nMD$ is the normalized Mean Deviation from desired path, $MAPR$ *Mean Arrest Period Ratio* represents the proportion of time (i.e. the percentage of samples) that movement speed exceeds 10 % of the peak speed, $SpeedMetric$ expresses the ratio between mean speed and peak speed and $MD$ is movement duration.

The weights have been chosen through a trial and error approach already described in Section 3.2.2; the *Aiming angle* and the $MAPR$ have greater weights than the others as they are more indicative of a pathological behaviour versus a healthy behaviour in terms of required assistance (through $C_K$) and movement velocity (through $C_t$).

The other indicators have not been employed in this preliminary phase since they provide more general information respect to the selected ones; however, they may be employed in the future development of the online adaptation of the control law

to further increase the strategy tailored to the subject.
The values of control parameters are chosen using a threshold strategy that takes into account that Eqs. 4.3 and 4.4 continuously vary in the interval [0; 1]. Therefore, the discrete levels ($L_i$) of patient performance for updating $K_P$ and $t$ are defined as

$$L_i = \begin{cases} 1 \quad if \quad C_i \in [0, 0.25) \\ 2 \quad if \quad C_i \in [0.25, 0.5) \\ 3 \quad if \quad C_i \in [0.5, 0.75) \\ 4 \quad if \quad C_i \in [0.75, 1] \end{cases}$$

where $i = K$, $t$. Predetermined values of stiffness and task duration are associated to values of $L_k$ and $L_t$. Depending on $L_i$, $K_P$ can assume one of the following four values: 1, 25, 75 or 120 N/m, while task duration $t$ can be equal to 1000, 2000, 2500 or 3000 ms. All these values have been empirically derived, in a way similar to previous studies on a similar topic [122].

## 4.4 Experimental validation and results

The patient-alone configuration of the Patient subsystem has been evaluated with some experimental trials. Seven healthy subjects have been asked to perform typical upper limb robotic exercises, e.g.*clock-game* [21, 53]. Each session consists of 160 point-to-point movements in 8 different directions rotated of $45^o$.
Exercises are grouped into 80 trials performed without assistance, in order to measure subject performance and update control parameters, and 80 trials performed with a level of assistance tailored on the patient status (described through the computed performance indicators). The session of 160 point-to-point movements has been repeated in two different conditions, i.e., i) healthy behaviour, ii) simulated post-stroke behaviour.
In order to make the results comparable among the subjects and ensure repeatability of the performed trials, the simulated post-stroke behaviour is implemented by applying a constraint on the healthy subjects. It consists of an elastic sling

applied on the subject's arm between the forearm (12 cm below the elbow joint) of the ipsilateral arm and the axilla of the contralateral arm.
The resulting elastic force is not exactly quantified due to the unknown elastic constant of the sling. However, it is assumed to be in the range [15, 30] N. The proposed constraint intends to increase the difficulty of elbow flexion/extension movements, which are the most affected movements after a stroke event.
Moreover, elastic force of the band strictly depends on its length and the length of user arm. No adjustments regarding arm-length or subject-based strength have been performed; such an aspect might have introduced an appropriate amount of uncertainty [161].
Hence, subjects are asked to perform 80 point-to-point movements without robot assistance ($K_p = 1$ N/m, and $t = 3000$ ms). Position and velocity acquired by robot sensors are sent from the patient side to the therapist side for computing performance indicators.
The performance indicators have a twofold purpose: (i) evaluation of the therapy progress; (ii) adaptation of the level of assistance to the patient condition, by updating control parameters through Eqs. 4.3-4.4. Afterwards, control parameters $K_p$ and $t$ are sent to the patient side and the block of 80 assisted point-to-point movements is performed again.
It has been decided to carry out calculations at the therapist side in order to give the therapist a complete overview of the therapy process and not to overload the PCT with computational efforts which can be easily carried out on therapist side. Such solution is implemented in this modular way since the application is thought to be employed for in-home rehabilitation sessions where the patient and therapist are not in the same place.
Limits of the proposed architecture in *Internet* scenarios are investigated by means of modelling. Real data obtained from tests are used to fill the model and characterize the system. In particular, the assessment of the Patient-Therapist-Patient control loop has been addressed. The aim is to quantify the level of control that can be applied under realistic communication constraints. The computational time required to calculate performance indicators is reported in the following three different conditions:

- for the single point-to-point movement;
- for a block of 16 movements (i.e. one repetition of the whole clock-game);
- for a block of 80 movements (i.e. five repetitions of the clock-game).

Further, the time required for transmitting data and commands between the Patient and Therapist in the aforementioned three different conditions has been extracted. These times can be used to compute closed loop communication delays and characterize applicable control strategies.
In particular, a single control loop requires:

1. the generation of patient's data: $T_P$;
2. the full transmission of such data to the Communication HUB: $T_{P\rightarrow H}$;
3. reception and decoding of the patient's data: $T_H$ [1];
4. the full forwarding of data to the therapist: $T_{H\rightarrow T}$;
5. the computation of performance indicators and updated parameters: $T_T$;
6. the full transmission of updated parameters to the Communication HUB: $T_{T\rightarrow H}$;
7. reception and decoding of the therapist's data: $T_H$;
8. the full forwarding of data to the patient: $T_{H\rightarrow P}$;
9. the application of new parameters: $T_A$

Assuming that: (i) $T_P \approx 0$, i.e. the generation of data is done while the exercise is executed, (ii) $T_H \approx 0$, i.e. Communication HUB packet forwarding times is negligible[2], and (iii) $T_A \approx 0$, i.e. the update of available parameters has negligible time, is possible to write that

$$T_{LOOP} = T_{P\rightarrow H} + T_{H\rightarrow T} + T_T + T_{T\rightarrow H} + T_{H\rightarrow P} \tag{4.5}$$

This time has to be lower than the maximum waiting time that the patient can accept during exercise phases involved in parameters update.

[1] The Communication HUB identifies the sender and the receiver and dispatches the received packet to its transmission queue.

[2] This time is required to make very few memory accesses and can be easily controlled and maintained negligible with respect to other times.

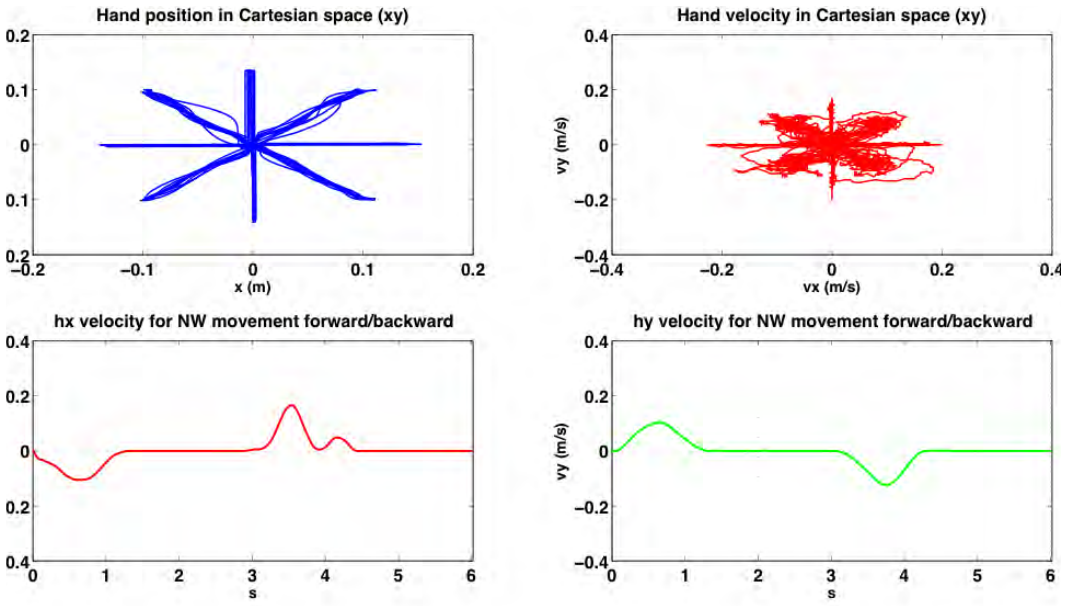


FIGURE 4.7: Subject 1 performing 80 repetitions of the clock game in healthy condition: Cartesian position (upper left side), Cartesian velocity (right upper side), $x$ component of hand velocity over time during NW forward/backward movement (lower left side), $y$ component of hand velocity over time during NW forward/backward movement (lower right side)

### 4.4.1 Experimental validation of the multimodal adaptive interface grounded on performance indicators

In this subection, the results of the multimodal interface applied to the exercises performed with the CBM-Motus are presented.

Hand trajectories and velocities in the Cartesian space of one subject are shown for unassisted healthy, unassisted simulated post-stroke condition and assisted simulated post-stroke behavior (Figures 4.7, 4.8, 4.9).

### 4.4.2 Experimental validation of the communication architecture

The characterization of the Patient-Communication HUB-Therapist control loop is based on data reported in Table 4.1. The table presents mean and standard deviations of computational times required to update robot's control parameters, and the size of data transferred between the patient and the therapist in order to perform this computation and to apply results back into the Patient subsystem.

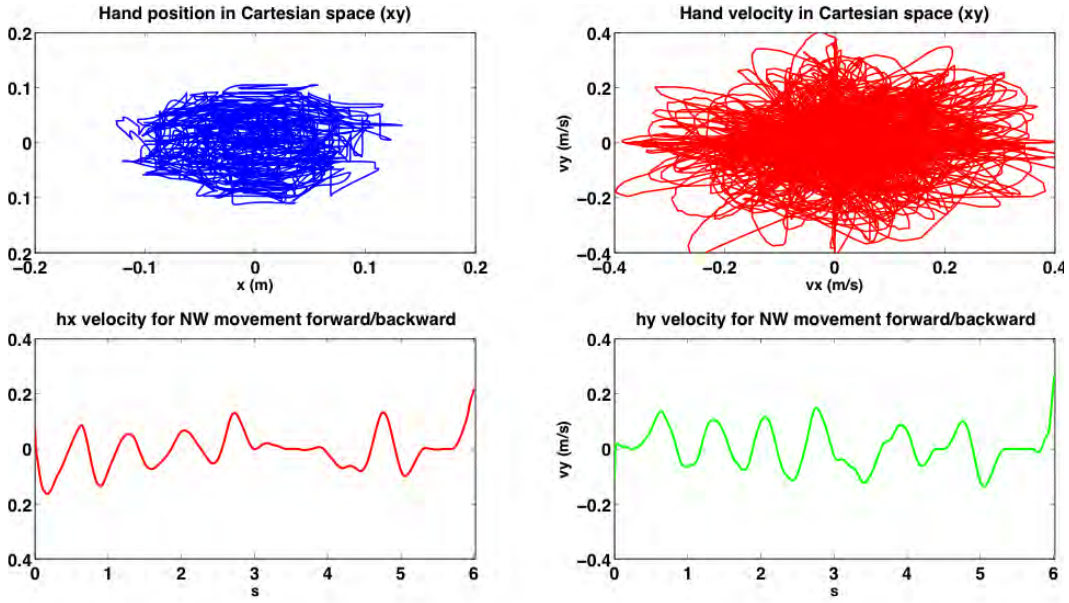


FIGURE 4.8: Subject 1 performing 80 repetitions of the clock game in unassisted simulated post-stroke condition: Cartesian position (upper left side), Cartesian velocity (right upper side), $x$ component of hand velocity over time during NW forward/backward movement (lower left side), $y$ component of hand velocity over time during NW forward/backward movement (lower right side)

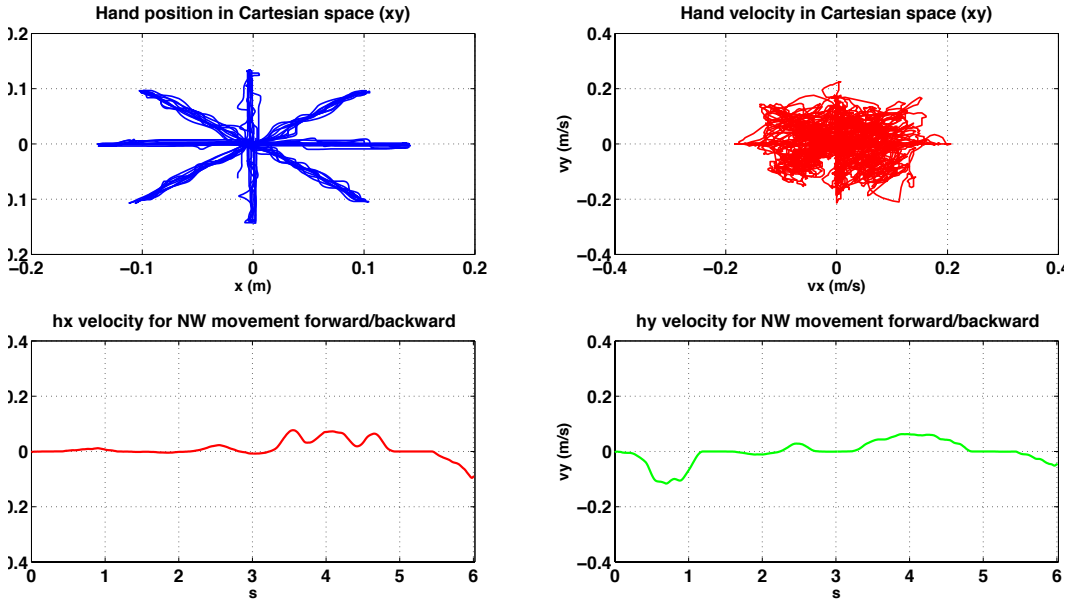


FIGURE 4.9: Subject 1 performing 80 repetitions of the clock game in assisted simulated post-stroke condition: Cartesian position (upper left side), Cartesian velocity (right upper side), $x$ component of hand velocity over time during NW forward/backward movement (lower left side), $y$ component of hand velocity over time during NW forward/backward movement (lower right side)

TABLE 4.1: Architecture validation: Computational time for updating control parameters (mean and standard deviation (SD)) and file size of the information exchanged throughout the architecture blocks

| Trial | Time (mean) | SD | File size P → T | File size from T → P |
|---|---|---|---|---|
| single movement | 0.23 s | 0.01 s | 8 B | $K_P$= 3 B, $t$= 5 B |
| 16 movements | 1.48 s | 0.04 s | 118 kB | $K_P$= 3 B, $t$= 5 B |
| 80 movements | 6.52 s | 0.23 s | 622 kB | $K_P$= 3 B, $t$= 5 B |

TABLE 4.2: Closed Loop Parameters Update Times (single movement)

| | 50 ms | 100 ms | 250 ms | 450 ms |
|---|---|---|---|---|
| 256 kbps | 331 ms | 431 ms | 731 ms | 1131 ms |
| 1 Mbps | 330 ms | 430 ms | 730 ms | 1130 ms |
| 10 Mbps | 330 ms | 430 ms | 730 ms | 1130 ms |

In particular, these data are extracted considering an update operating between the following three groups of elementary actions: i) the single movement scenario, ii) the 16 movements scenario and iii) the 80 movements scenario.
On the basis of these data is allowed to compute an upper bound of the closed loop time for parameters update as

$$T_{LOOP} = 2 \times T_{ping} + 2 \times T^{tx}_{P \to T} + 2 \times T^{tx}_{T \to P} + T_T$$

where Eq. 4.5 has been used assuming that each direct data exchange is composed of two components: $T_{ping}/2$, the time required to send a short packet from two generic entities of the system[3], and $T^{tx}_{Source \to Destination}$ = Message Size/Communication Rate. Being interested in an upper bound, the aforementioned parameters are assumed all equal to those of the worst direct interconnection among subsystems.

Tables 4.2, 4.3 and 4.4 present values regarding the time required for the closed loop update of parameters in the case of the configurations of Table 5.1 and considering different values of $T_{ping}$ (columns) and Communication Rate (rows).

[3]It can be estimated by means of the standard *ping* command.

TABLE 4.3: Closed Loop Parameters Update Times (16 movements)

| | 50 ms | 100 ms | 250 ms | 450 ms |
|---|---|---|---|---|
| 256 kbps | 7.7 s | 7.8 s | 8.1 s | 8.5 s |
| 1 Mbps | 2.2 s | 2.3 s | 2.6 s | 3.0 s |
| 10 Mbps | 0.52 s | 0.62 s | 0.9 s | 1.1 s |

TABLE 4.4: Closed Loop Parameters Update Times (80 movements)

| | 50 ms | 100 ms | 250 ms | 450 ms |
|---|---|---|---|---|
| 256 kbps | 39.2 s | 39.3 s | 39.6 s | 40 s |
| 1 Mbps | 10.3 s | 10.4 s | 10.7 s | 11.1 s |
| 10 Mbps | 1.33 s | 1.42 s | 1.72 s | 2.13 s |

## 4.5 Discussion and final considerations

In this Chapter the concept of multimodal interface has been adapted to design a modular telerehabilitation architecture for bio-cooperative robotic systems. In addition, Section 4.3.4 has reported the application of a bio-cooperative control system to CBM-Motus. The adaptive control strategy has been tailored to the information provided by robot's sensors that compose the multimodal interface. The results obtained from the experimental validation are described in Section 4.3.

As shown in subsection 4.4.1 after adaptation of control parameters, simulated post-stroke behaviour tends to the healthy one in terms of hand trajectories as well as in terms of velocity and smoothness (Figures 4.7-4.9).

Moreover, since post-stroke subjects typically have higher motion difficulty in directions requiring elbow extension, it has been chosen to show NW (NorthWest) hand velocity trajectories to highlight performance improvement after control parameters update.

In Fig. 4.10 a bar-plot of the selected performance indicators is shown both for *unassisted* and *assisted* movements taking into account mean values and standard deviation. Even though no clinical considerations can be extracted from these data, the indicators trend confirms the expected improvements between *unassisted* and *assisted* tasks, especially observing the simulated post-stroke behaviour. Moreover, it shows the efficacy of the control modulated by the therapy side and

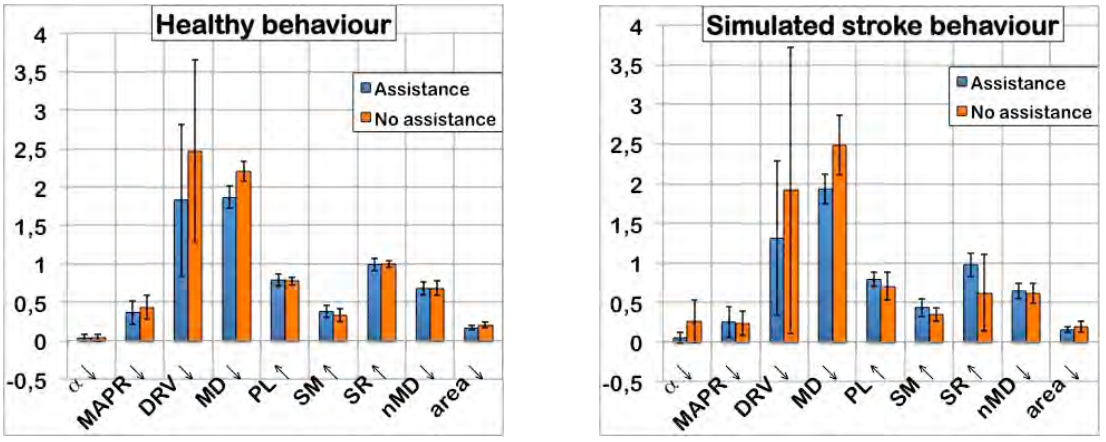


FIGURE 4.10: Mean values and standard deviations of performance indicators for all the subjects before and after updating control parameters. They are reported both for healthy (left) and simulated post-stroke condition (right). The horizontal axis reports the selected performance indicators and the expected trend during motor recovery:
$\alpha$=Aiming angle, $MAPR$=Mean Arrest Period Ratio, $DRV$=Deviation from Ratio Between Velocities, $MD$=Movement Duration, $PL$=Path Length, $SM$=Speed Metric, $SR$=Success Rate, $nMD$=normalized Mean Deviation, $area$

the functioning of the proposed bio-cooperative telerehabilitation architecture. Being a preliminary phase, the computation of performance indicators has been executed in an offline modality and therefore communication stability has been proved by the aforementioned tests. Obvious extension of the proposed bio-cooperative architecture will be the computation of the performance indicators and the update of control parameters in a real-time environment.

This will allow the therapist to monitor and evaluate the therapy in a simultaneous way by setting the type of exercise, the level of difficulty and the needed robot assistance depending on the specific patient's condition.

The characterization of the Patient-Communication HUB-Therapist control loop is based on data reported in Tables 4.2,4.3 and 4.4. The results show that, in the case of updates between single movements, the most critical parameter is the communication delay between systems and, indeed, assuming that the maximum waiting time acceptable between single movement is 500 ms, all the communication rates provide acceptable results, given that $T_{ping}$ = 50 or 100 ms (i.e. given that the communication latency is low enough). When the amount of data communicated between systems increases, the results change and the most critical parameter becomes the transmission rate. In addition, assuming that the maximum waiting time acceptable between 16 movements (80 movements) is 2 s (20 s), all the configurations having a communication rate equal to 10 Mbps (1 or 10

Mbps) are valid, independently of the $T_{ping}$ value.

Results demonstrate the feasibility and limits of the proposed architecture for upper limb robotic telerehabilitation. The implemented system is able to send data and compute performance indicators in a safe and reliable way. In this condition, the subject who is performing the robot-aided exercise has enough time to accomplish the required task being involved also by means of visual feedback.

Moreover, the telerehabilitation architecture has been conceived to be modular and then scalable to various subsystems that may compose the multimodal interface.

Despite the several possible telerehabilitation scenarios, e.g. a single patient communicating with a single therapist, several patients with one therapist or many patients communicating each other, in this context the proposed modular architecture is mainly dedicated to develop reliable communication between a single patient and one therapist. The main goal of the communication architecture is to provide the therapist with the possibility to configure the optimal therapy session for a specific subject according to the performance recorded thanks to the multimodal interface.

In this first application, the therapist still holds an active role since it has the responsibility to monitor therapy trend and change it online on the basis of patient's performance indicators. Such an aspect would allow to tailor the therapy to the specific user's needs.

Future application may address the possibility to perform an automatic assessment of patient performance and then instruct the user via a telemedical system without therapist.

In conclusion, the experimental validation on healthy subjects simulating a post-stroke behaviour has demonstrated the functioning and reliability of the novel architecture, as well as the modularity of the proposed system able to be tailored to different unilateral robot systems. Tests performed with the CBM-Motus encourage the potential use of the implemented bio-cooperative telerehabilitation system in a clinical scenario. To this purpose, future studies on post-stroke subjects' in-home telerehabilitation programmes will be taken into account in order to enhance patients' independence and encourage faster recovery from stroke.

# Chapter 5

# Modular integration of software and hardware modules of multimodal interfaces

A common issue that arises during the application of a multimodal interface is to guarantee safe and reliable interaction between the various subsystems composing the interface. The capability of the multimodal interface to easily exchange the different modules becomes a crucial aspect; moreover, among the several modules that communicate through a multimodal interface is possible to find both hardware and software modules.

In this context, the design of novel systems able to provide modular solutions that allow to facilitate the communication between the different subsystems of the multimodal interface assumes a fundamental importance.

The development of such modular integration systems is grounded on the necessity of creating a multimodal interface that can be easily adaptable to different subsystems and to different user's needs. In this context, the current Chapter has the aim to describe the development of novel modular hardware and software integration strategies.

The first part of the Chapter presents the design of a modular software architecture which allows communication among the different subsystems composing the multimodal adaptive interface of the AIDE project (Adaptive Multimodal Interfaces to Assist Disabled People in Daily Activities). In the second part of the Chapter the design of a mechanical interface that allows the integration of various robotic devices is proposed. The implemented solution is then applied to the integration

of a robotic module for hand rehabilitation and the ARMin exoskeleton.
The Chapter is structured as follows. Section 5.1 presents the recent trends in assistive technology for supporting ADLs, mobility and communication of disabled people as well as the concept and structure of the AIDE project. In Section 5.2 the modular software architecture implemented for guaranteeing communication between the subsystems composing the multimodal interface is presented.
The experimental validation and the preliminary results of the proposed modular software architecture are described in Section 5.3. The design of a mechanical interface that allows interaction between hand robotic devices and upper arm exoskeletons and its application to the ARMin robot are presented and discussed in the Subsection 5.4.

## 5.1 Background

In Europe, around 80 million people have a disability. They are often hindered from full social and economic participation by various barriers related to physical, psychological and social factors. Over 30% of people above the age of 75 are impaired to some extent, and over 20% are severely impaired. The percentage of people with disabilities is set to rise as the European population ages.
Nowadays, the recent trends in assistive technology for supporting disabled people are based on the integration of the capabilities of the user and the employed technologies [164]. The improvement of the interaction and cooperation between user and assistive technologies, can be split in three main areas:
1) improvements of the assistive devices, such as, mechanical parts, and electronic parts;
2) improvements of the user-technology interface;
3) improved shared-control between the user and assistive technology.
The AIDE project (2015-2018) is part of the European Horizon2020-ICT programme and involves nine partners among universities and industries that are spread all over the continent each with a different role.
The ambition of the AIDE project is to strongly contribute to the improvement of the user-technology interface by developing and testing a novel modular and adaptive multimodal interface conceived to be tailored to the individual needs of people with disabilities.
In order to go beyond the current state of the art in assistive devices, AIDE adopts

a participative user centered design. Hence, the main end users (moderately to severely disabled patients) are actively involved throughout the project.

In Figure 5.1 the novel modular bio-cooperative perception system which employs a customized adaptive multimodal interface towards disabled people needs is presented.

The multimodal interface analyses and extracts relevant information from the identification of residual abilities, behaviors, emotional state and intentions of the user, from analysis of the environment and from context factors. Finally, the human-robot cooperative system is designed in accordance with specific user needs. The

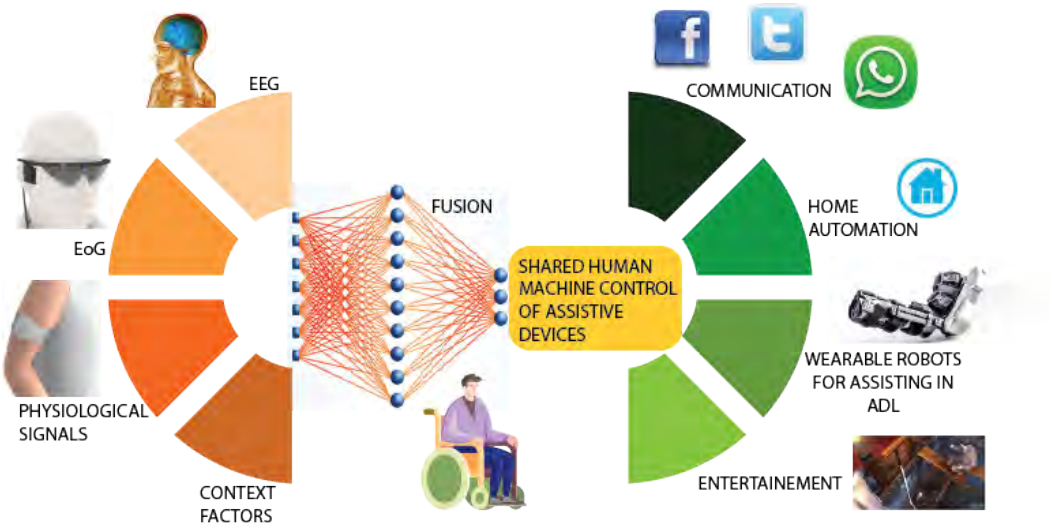


FIGURE 5.1: The AIDE concept with all the single blocks involved: Signal and context factors; Classification and fusion; Shared Human Machine Control of Assistive Devices; Application areas: Communication, Home Automation, Wearable robotic devices and Entertainment

main components of the system are presented hereinafter with the intention of explain the single nodes that have to interact each other thanks to the modular software architecture:

- The novel multimodal interface has the following duties:
  - Detection of user's behaviours and intentions;
  - Estimation of user's affective state;
  - Sensing and understanding the user's environment and context to automatically recognize the necessary abilities for different ADLs;
  - Supervising the performance of the upper-arm powered exoskeleton and the hand exoskeleton as well as the pronation/supination module;

- The shared human-machine control system is in charge of:
  - Fusing the information provided by multimodal interface (behaviours and intentions of the user, estimation of the user's affective state and environment and context factors);
  - Controlling the level of assistance provided by the whole upper-limb powered exoskeleton (arm and hand exoskeletons), allowing the user to voluntarily interact with the environment;
  - Keeping the user in the control loop supervising the operation of the whole upper-limb powered exoskeleton and optimizing the cognitive and physical interaction during the assistance;
  - Developing a self learning approach to adapt the performance of the control system to the user needs;
- The modular multimodal perception system has to provide information and support to the multimodal interface and the human-robot bio-cooperative control. It is composed by:
  - Brain machine interface(BMI) control based on EEG brain activity;
  - Wireless EMG surface system;
  - Wearable physiological sensors to monitor physiological signals such as, heart rate, skin conductance level, temperature and respiration rate;
  - Wearable ElectroOculographic(EOG) system;
  - Eye tracking module to identify the gaze point on a screen where visual feedback of the environment is shown;
  - RGB and depth camera to recognize and track the user and objects in the working area;
  - Kinetic and dynamic information provided by upper limb exoskeleton and hand exoskeleton;

## 5.2 Modular communication architecture of AIDE multimodal interface

In this Section the modular architecture for managing inter-module communication is discussed. The architecture is conceived for guaranteeing the communication among the various modules of the multimodal interface.
An approach based on Component-Based Software Engineer (CBSE) has been chosen and the Yet Another Robot Platform (YARP) has been elected as the most suitable component based software for managing communication among the different subsystems of the platform.
YARP [165] is a middleware for robotics and supports building a robot control system as a collection of programs communicating in a peer-to-peer way, with an extensible family of connection types, such TCP, UDP and multicast that can be swapped in and out to match user needs.
YARP consists in a set of libraries and executable programs that can be installed in a Windows OS environment, permitting it to handle the low level communication with the devices.
Practically, the YARP messaging system allows associating components of the multimodal interface to nodes and connecting/disconnecting them quickly and easily without compromising the system performances. Each node has a name and a specific port number.
The communication protocol, however, can be multiple and is defined at the time of the link between nodes. The YARP server plays the main role; it can be queried at any time to request information and services to the nodes.
A schematic configuration showing the interacting subsystems, the nodes as well as the project's partners responsible for them is reported in Figure 5.2. The whole system is running on a single high-performance computer for managing the whole multimodal interface; the established communication protocol is the TCP/IP since it represents the standard protocol embedded in YARP and it is more stable than UDP communication.
In order to check messages integrity all of them have to pass through the central nodes and then they can be redirected to the correct destination. There are three types of nodes that are possible to use into the YARP environment (Figure 5.3):

- The native YARP node that can send and receive any type of message with any protocol, i.e. full-duplex channel

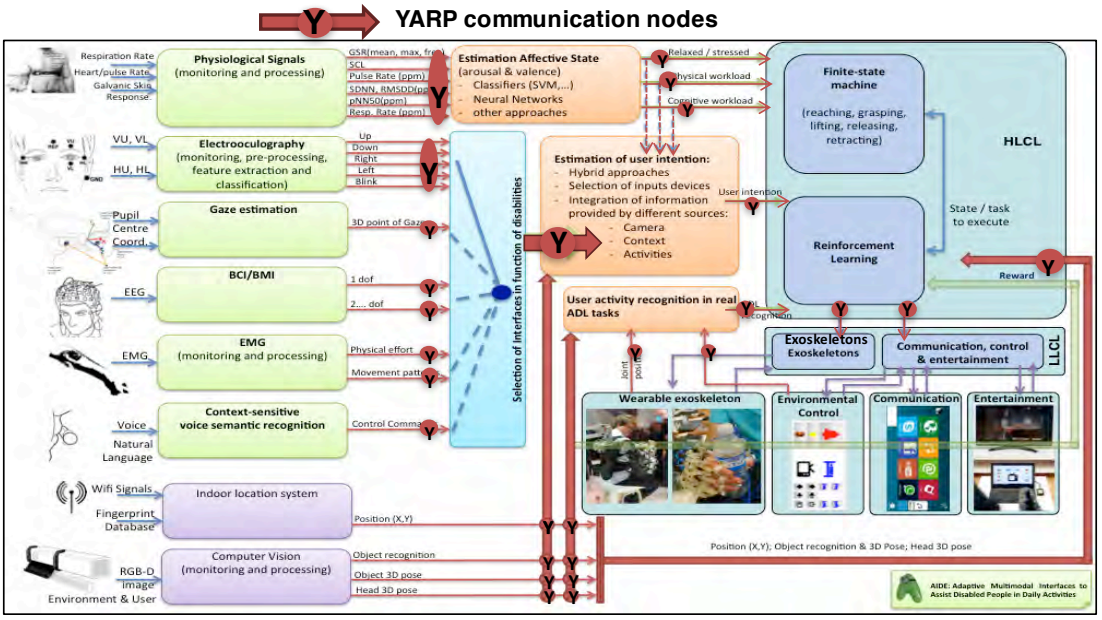


FIGURE 5.2: Schematic representation of the systems that need to communicate through YARP

- The text node, an external node that can be developed in any programming language supporting TCP/UDP socket. Such nodes can send or receive (i.e. half-duplex channel) only ASCII format (i.e. text) messages

- the YARP node, an external node that simulates a native node behaviour. This can be obtained forcing a client/server TCP to behave like a native node; in this way each simulated node can send or receive all the messages or headers as a native node.

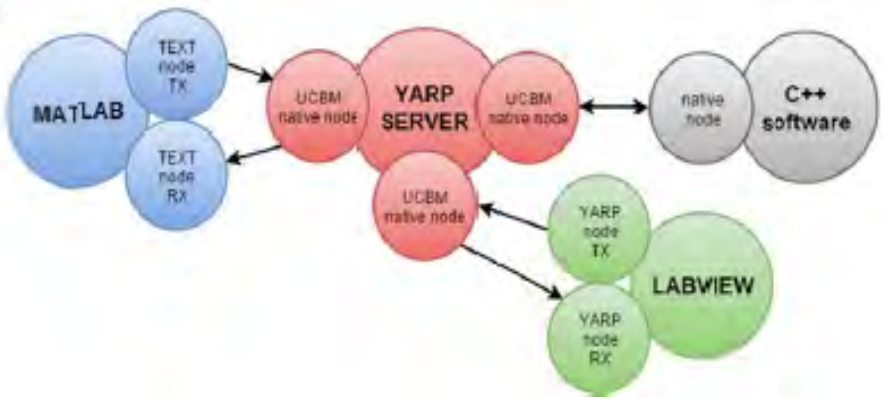


FIGURE 5.3: Example of YARP working principle

To this purpose, the YARP server can transmit and receive messages from the subsystems of the entire platform by using a full-duplex channel and employing

native nodes written in C++. On the other hand, the subsystems developed by other partners can transmit or receive by using one of the aforementioned three types of nodes.
Obviously, the subsystems developed with a language different from C++ need two different nodes, one for receiving and one for transmitting, since they are not employable in bilateral communication.

## 5.3 Experimental validation

Preliminary tests have been performed to verify and assess performance of the proposed software architecture. They have been grouped into two sessions: preliminary tests for assessing performance of communication between the different types of nodes (and consequently extract indications about the most appropriate nodes for a fast enough and reliable communication); subsequently, an experimental validation on healthy subjects has been carried out in order to demonstrate feasibility and reliability of using YARP for communicating with some of the AIDE platform subsystems.

### 5.3.1 Evaluation of communication between the different types of nodes

Preliminary tests have been conducted in order to build a platform enabling correct handling of all the signals composing the multimodal interface. In particular, a test to demonstrate the feasibility and the communication performance through YARP between native nodes and non-native nodes has been performed. The YARP server has been installed on a PC running under Windows 10. During the initial tests, data provided by one of the partner (Scuola Superiore Sant'Anna, Pisa, Italy) about joint positions of the arm exoskeleton have been used.
Two arrays (S_AA_DesiredPosition and S_FE_DesiredPosition) of 10000 elements each one have been transmitted from a Matlab script to the YARP server (Figure 5.4).

The two nodes /matlabY and /matlabT have been created in Matlab. The former is a YARP external node exchanging data through TCP/IP connection with TCP protocol, while the latter is a Text external node exchanging data through

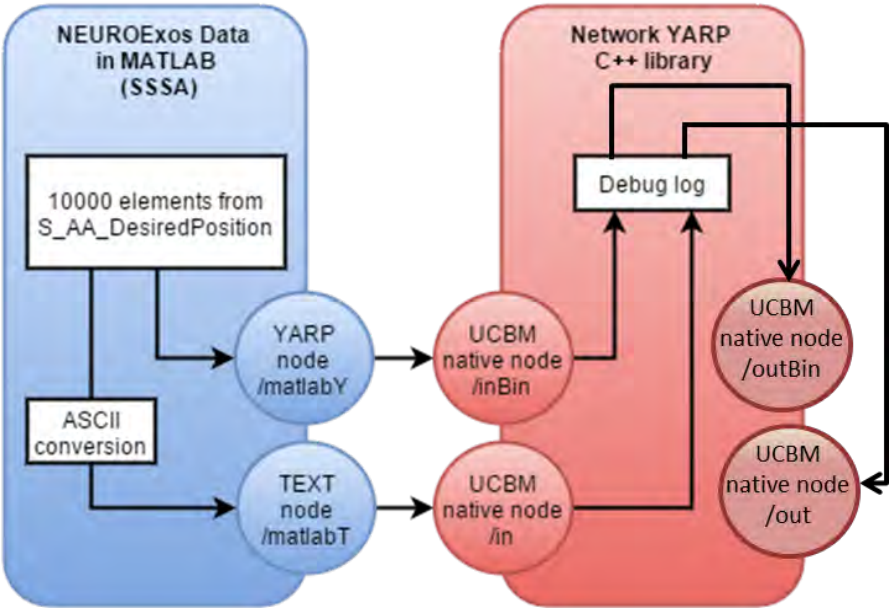


FIGURE 5.4: Example of the YARP Communication implemented in the preliminary phase

TABLE 5.1: Architecture validation: Computational time for updating control parameters (mean and standard deviation (SD)) and file size of the information exchanged throughout the architecture blocks

| TX Node | RX node | Frequency [Hz] | Data lost [msg] | Delay [ms] |
|---|---|---|---|---|
| /matlabY | /inBin | 500 | 0 | 0 |
| /matlabT | /in | 4235 | 35 | 0 |
| /matlabT | /in | 2956 | 0 | 0.2 |

TCP/IP connection with TEXT protocol.

Afterwards, two additional nodes have been created in C++ Visual Studio, corresponding to the previous ones and called /inBin and /in. The first couple of nodes (i.e. /matlabY-/inBin) through TCP/IP connection and TCP-YARP protocol reached 500 msg/s (500 Hz), the second one (i.e. /matlabT-/in) reached 2956 msg/s (2956 Hz) on a TCP/IP connection and Text-YARP protocol.

The obtained performance are summarized in Table 5.1.

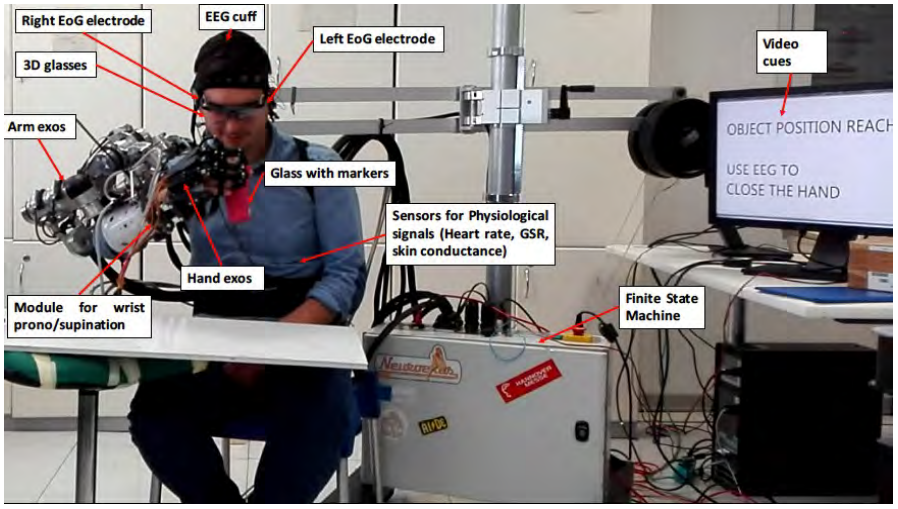


FIGURE 5.5: Experimental scenario with all the components

### 5.3.2 Communication performance during robotic assistance

This experimental session is intended to provide a preliminary evidence of the feasibility to allow a user to drink from a glass thanks to a multimodal robotic system. The whole system is composed by the following components as shown in Figure 5.5 while the communication between them is managed by YARP:

- Shoulder-elbow exoskeleton [72]
- Hand exoskeleton and an active module for wrist pronation/supination
- Biosignal processing and recording system comprised of a wireless EEG recording system, a wearable glasses for EOG acquisition, a device for measuring skin conductivity, a wearable strap placed around the chest for acquiring ECG and a respiratory plethysmography together with a main processing unit
- Gaze tracking and context recognition devices

The employed exoskeleton [72] is a 4 DoF wearable robot developed for assisting shoulder/elbow 3D rehabilitation of post-stroke subjects. The exoskeleton has been integrated mechanically with a hand exoskeleton and with a module for active wrist pronation/supination. In this experimental phase, the control of these devices is separated; future applications foresee to integrate the two control systems into a single unit.

The arm, hand exoskeletons and the wrist module have been adapted to the subject arm and hand. In the starting configuration, the shoulder-elbow and wrist module are placed in a configuration comfortable for the user and the hand exoskeleton is opened.
The gaze tracking glasses and cameras are used to identify the object (i.e. the glass) and its location in the workspace.
EoG Left signal is the trigger that move the arm exoskeleton to the target (the glass or the mouth). The control of the arm exoskeleton ensures the target reaching. After opening the hand the exoskeleton is controlled to move back to the initial position automatically. The EoG Right signal represents the signal that the user could use at any times to stop the execution of the movement and go back to the initial position.
The core of the architecture (i.e. the YARP server) is represented by a Windows 10 OS processing unit that is also the permanent means of communication among the architecture nodes. Due to the different programming languages employed by the interacting subsystems, the YARP external nodes are chosen since they can efficiently work in the communication frequency range without data loss. Moreover, the use of these nodes reduces significantly the computational load required by the text nodes for type casting thus improving the system performance.
An overview of the whole communication system is shown in Figure 5.6 where the labels of each transmitter and receiver nodes are also reported; a TCP/IP connection with TCP protocol is adopted for managing the communication among the external nodes and between external nodes and the YARP server. Each node (in YARP application) presents a specific dedicated thread making the communication a multithread framework in order to make the interaction (i.e. access to a node or its disconnection) with the various nodes decoupled from the main linear loop.
This is a fundamental implementation to make the whole system more dynamic and reactive since each node could be connected or disconnected at any time without causing delays in system communications.
The communication among all the subsystems described above has been tested during the experimental tests on one participant (a volunteer healthy man). He has been asked to identify the object to be grasped (i.e. a glass) and to drink from it for 10 times. For measuring performance of the YARP architecture, the timing of sent and received data has been measured and a screenshot of the obtained values during one trial is shown in Figure 5.7. The messages among the several

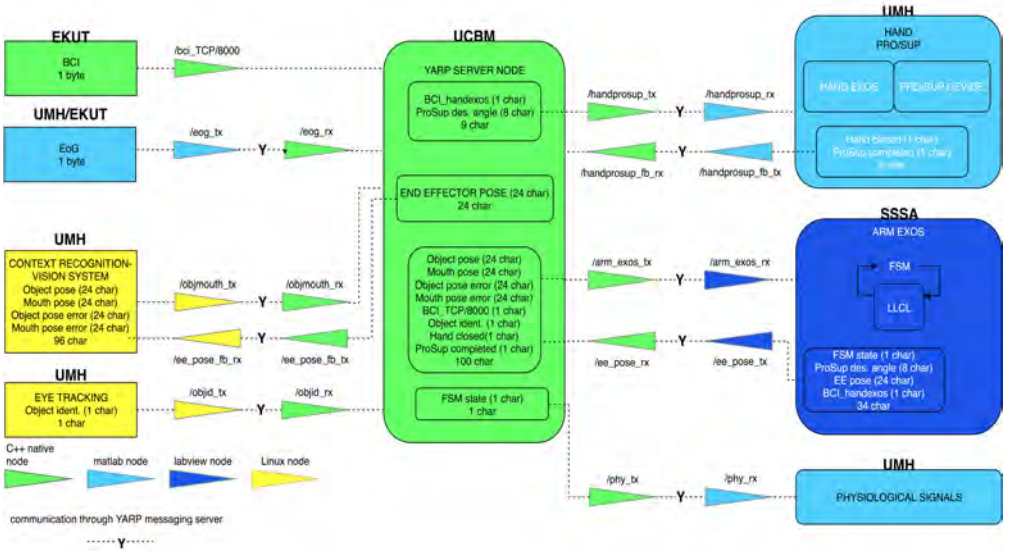


FIGURE 5.6: Overview of the YARP communication system. The native nodes are in green and all the remaining nodes are simulated native nodes written in several programming languages or environment

parts of the assistive platform have been exchanged through TCP at a frequency of about 20 Hz (50 ms), which is the frequency of the arm exoskeleton Finite State Machine (i.e. the lowest frequency in the whole platform). No data have been lost during the trials due to the adopted low frequency.

```
objmouth_period: 0.054000
handprosup_fb_period: 0.053000
ee_pose_period: 0.053000
eog_period: 0.054000
objmouth_period: 0.053000
objid_period: 0.053000
handprosup_fb_period: 0.053000
ee_pose_period: 0.054000
eog_period: 0.053000
handprosup_fb_period: 0.053000
objmouth_period: 0.054000
objid_period: 0.054000
ee_pose_period: 0.053000
eog_period: 0.054000
objid_period: 0.054000
objmouth_period: 0.054000
handprosup_fb_period: 0.054000
ee_pose_period: 0.054000
eog_period: 0.054000
handprosup_fb_period: 0.052000
objmouth_period: 0.053000
objid_period: 0.053000
ee_pose_period: 0.053000
eog_period: 0.053000
```

FIGURE 5.7: Measured time for sending and receiving data during the performed drinking task by an healthy subject. The recorded values are reported in seconds

These preliminary results demonstrate the feasibility and reliability of using YARP for the communication between the platform subsystems. In particular, the communication with YARP server has been tested when all the nodes were running

and exchanging information each other. Finally, such tests have revealed no data loss for data exchange rate around 45-55 ms, imposed by the arm exoskeleton Finite State Machine.

## 5.4 Design of a mechanical flange to integrate robotic exoskeletons

The work presented in this Section has been carried out during the six months spent as visiting PhD student at Sensory Motor Systems Lab, ETH Zurich. The Section deals with the design of a mechanical flange for the integration of a novel module for hand rehabilitation into the ARMin upper arm robotic exoskeleton. The proposed work is included into this Chapter due to the possibility of extending the application of the flange to other upper arm exoskeletons.
For instance, the upper arm exoskeleton and the hand exoskeleton employed in the AIDE project have been integrated by means of a dedicated mechanical system. In this context, the designed flange may be employed as a possible tool for guaranteeing mechanical interaction between the two exoskeletons.
In Subsections 5.4.1 and 5.4.2 a brief overview of the ARMin exoskeleton and the fundamental basis of the hand module are given to define design principles of the mechanical flange, respectively.

### 5.4.1 The ARMin robotic exoskeleton

The ARMin robotic exoskeleton is presented in this Subsection in order to provide the design fundamentals of the mechanical integration flange. As reported in Section 2.3 ARMin belongs to the category of robotic exoskeleton that allows to treat people with upper limb motor impairments [69].
The ARMin is an upper limb robotic exoskeleton that is used for task-oriented repetitive movement therapy for severely impaired patients.
The upper and lower arm of the patient are attached to the device with dedicated cuffs. The hand is fixated to a hand module, which is able to open/close the hand mimicking the parallel extension (Figure 5.8). The latest version of the ARMin robot is named ARMin V and is currently under development. It has

FIGURE 5.8: Rehabilitation session with the ARMin robot

seven actuated degree of freedom (DOF) three for the shoulder, one for the elbow, two for the forearm and wrist and one for the hand. The robot is also equipped with three six-axes high resolution force/torque sensors one for the upper arm, one for the lower arm and the last for the hand.
The use of force/torque sensors and the adjunct of additional potentiometers for estimating length changes in the upper and lower arm, and the adaptation of the shoulder angle independently of patient's anthropometry, are expected to improve global robot control and transparency [166].

### 5.4.2 Hand module concept and its implementation

In Figure 5.9 the previous hand module of the ARMin is reported. The hand

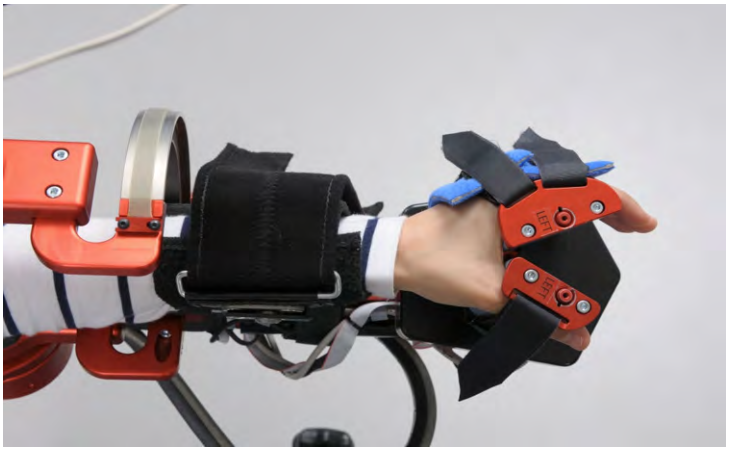

FIGURE 5.9: The previous version of the hand module for the ARMin rehabilitation robot

module of the ARMin robot presents some drawbacks; one of them is the device usability for the therapist and for the patient. In fact, a patient with high spasticity may present several obstacles while attempting to wrap the hand around the hand module. In this condition, the therapist has to relax the muscles before insert the hand into the hand module. For these reasons, the development of a new hand

FIGURE 5.10: The new version of the hand module for the ARMin rehabilitation robot

module has been defined based on the previous work by Masia et al. [63] and Lambercy et al. [62]. The new hand module is a device for hand rehabilitation of severely impaired patients that have a high level of spasticity.
It is similar to a pole with a tip on the top that is able to expand its diameter thanks to six panels aimed to distribute the force of the hand module onto the patient's hand surface evenly (Figure 5.10).
The design of the pole enables some benefits considering the usability of the device; in fact, the therapist can mount the patient's hand on the pole without stretching the arm.
Preliminary control tests of the hand module device, using a simple position control implemented in Matlab environment, have been performed in order to test the capability of the hand module to open and close a human hand in a safe manner. These simple tests on healthy subject have confirmed the possibility to use the device for simulating grasping tasks.

### 5.4.3 Design of a mechanical flange for the ARMin robotic exoskeleton

The design of the mechanical integration flange has the aim to realize a flexible solution that allows integration between the hand module and the ARMin exoskeleton. This solution might be extended to other upper arm exoskeletons for

integrating hand exoskeletons.

The integration has to concern with some potential issues that may arise substituting the old configuration.

Therefore, the following aspects have been taken into account for the design of the mechanical flange:

- The new system has to be easy to use for the therapist;
- The weight's increase of the new system must not afflict the overall robot performances;
- The hand module needs to be easily removed from the new system grounded on the ARMin in order to increase robot's usability;

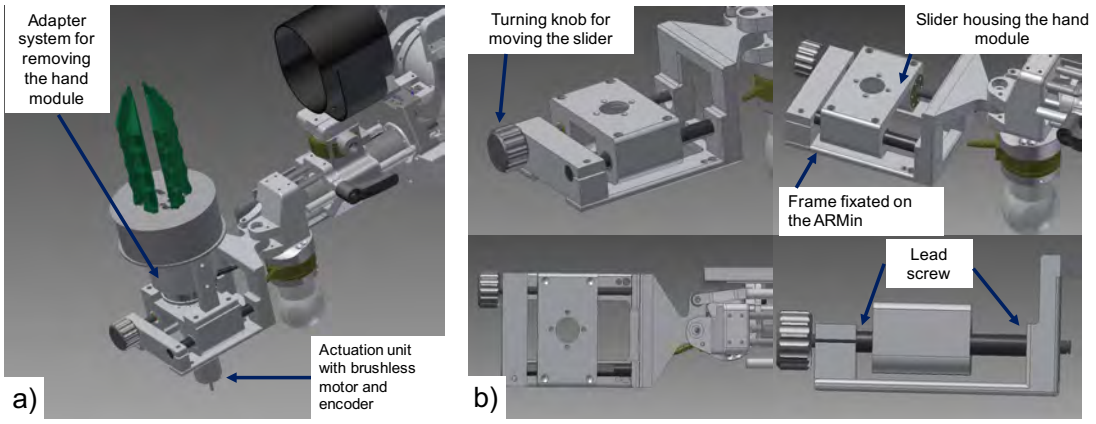


FIGURE 5.11: a) Final integration of the hand module on the ARMin framework. The device is easily removable thanks to the adapter system and can be easily moved in order to adjust for different forearm lengths b) Different views of the mechanical integration on the ARMin

Regarding the usability of the entire device, the flange is designed to guarantee fast set up of the lower arm length while using the hand module into ARMin. To this purpose an approach based on lead screw mechanism has been chosen. In Figure 5.11a different views of the new system are shown; in particular the lead screw mechanism is visible together with the part that allows fixation on ARMin framework and the sliding part on which the hand module and the motor unit are mounted (Figure 5.11b).

Taking into account the weight limitation requirements, the flange has been fabricated in aluminium with a particular shape. In addition, some other parts have been 3D printed in plastic ABS (e.g. the adapter system for quick removing of the hand module) to further reduce weight of the system. Total weight of the entire

system including the flange, the hand module and the adapter system that houses the hand module is 1.65 kg, 0.7 kg more than the old configuration.
Moreover, an adapter system based on a clicking mechanism has been developed in order to fix the hand module to the flange allowing to remove it in an easily and intuitive way. In fact, by pressing two plastic hooks located at both sides of the adapter is possible to take out the hand module.

## 5.5 Final considerations

This Chapter has presented two main parts describing solutions that allow communication among subsystems composing a multimodal interface for assistive robots. The first part has presented a modular architecture for guaranteeing safe and reliable communication among different subsystems composing the AIDE multimodal interface.
Starting from a detailed literature analysis, the YARP system has been chosen as the most appropriate messaging system for satisfying the set of requirements for the AIDE platform. The demanded architecture for the communication among the several subsystems constituting the platform has been developed and successfully tested.
YARP communication among nodes regarding EEG, EoG, physiological signals (i.e. heart rate, GSR, skin conductance), Finite State Machine, gaze tracking and object identification system has been tested using TCP/IP protocol and a frequency rate of 20 Hz. The YARP server and the receiver and transmitter nodes did not report errors that could imply system stop. The dynamic connection and disconnection of the nodes allowed not following a precise order in activating each component.
As shown in Subsections 5.3.1 (Table 5.1) and 5.3.2, when messages are sent through YARP external nodes it is possible to reach a frequency of maximum 500 Hz without losing data. When messages are sent through Text external nodes the maximum frequency without data lost is around 3000 Hz.
Therefore, the performed tests have shown that the TEXT-YARP protocol through TCP/IP connection guarantees the best performance in term of data loss.
Although it has been found that the best performance can be achieved if messages are sent in Text mode (ASCII) up to 3 KHz, the use of YARP external nodes can

reduce the computational burden required by the text nodes for type casting.
Therefore, YARP external nodes seems to be the best compromise between performance and computational burden when the working frequency is low, up to a maximum value of 500 Hz.
The second part of this Chapter has been focused on the development of a mechanical flange conceived to guarantee interaction between an upper arm exoskeleton and a hand module. Particularity of the proposed design is the possibility to extend the application of the flange to several robotic exoskeletons. A brief introduction to ARMin and the design of a novel hand module for increasing ARMin usability have been reported as the design principles of the integration flange.
The new flange has demonstrated to reflect all the requirements set in the design phase as well as increasing the exoskeleton usability and representing an optimal solution to be extended also to different upper arm robotic exoskeletons.
Regarding the new hand module preliminary control tests of the hand module device, using a simple position control implemented in Matlab environment, have demonstrated that the device is feasible to be used in hand rehabilitation settings. Further studies will investigate the feasibility of the hand module for treating stroke patients with discrete-level of spasticity. Despite this achievement, the device presents several issues regarding high friction and perceived inertia by the user while operating. In order to face such issues, future studies will develop a current-based impedance control.
In fact, electric current can be used as an indirect measure of interaction force and fed back in addition to position readings from the encoders. This approach is particularly interesting since (i) it can behave as an impedance control with force feedback; (ii) it does not require force sensors that may complicate the hand module structure and solves problems related to the increase of the apparent inertia perceived by the human [162].

# Chapter 6

# Robotic training coupled with TMS in severe upper limb-impaired chronic stroke patients: a quantitative evaluation through a multimodal interface

This Chapter presents the application of a multimodal interface for the quantitative assessment of a proof-of-principle study that wants to investigate safety and efficacy of combining inhibitory continuous Theta Burst Stimulation (cTBS) with shoulder/elbow robot-assisted therapy.
The present study aims to explore whether the combination of these two approaches might enhance their positive effects on motor recovery.
The primary outcome used for evaluating the post stroke motor recovery following the proposed approach is the Fugl-Meyer Scale. In addition, a robotic assessment grounded on a multimodal interface has been performed by extracting a bundle of performance indicators quantifying the biomechanical features of stroke subjects undergoing robotic therapy. The robotic assessment has the twofold objective of flanking the clinical evaluation and investigating correlation between performance indicators and the clinical scales used for assessment.

Moreover, Transcranial Magnetic Stimulation may be also used for extracting neurophysiological indicators of brain activity. To this purpose, such indicators may be also incorporated in bio-cooperative approach presented in Chapter 3 thus reinforcing the active role of the patient in the rehabilitative loop.
The Chapter is structured as follows. Section 6.1 presents the physiological principles of transcranial magnetic stimulation applied to stroke; in Section 6.2 study design, participants' selection, robotic and stimulation systems are presented.
The outcomes of the proof-of-principle study and the robotic assessment features are described in Section 6.3. Finally, in Section 6.4 the obtained findings are discussed and final considerations are reported.

## 6.1 Background

Severe upper limb impairment in chronic stroke patients does not respond to standard rehabilitation strategies. Nowadays, the need of new treatments that might be effective in patients with drastically limited residual movement capacity has been rapidly increased [86].
Robotic therapy has produced slight improvements in motor recovery of patients with moderate to severe upper-limb impairment [53, 54], as widely discussed in the previous Chapters. Another innovative approach for the enhancement of motor recovery is represented by non-invasive human brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).
These techniques can induce long-lasting changes in the excitability of central motor circuits via long-term potentiation/depression (LTP/LTD)-like phenomena [167]. A recent study reported a mild motor improvement after 10 sessions of rTMS in a group of severe chronic stroke patients [168].
Moreover, rTMS protocols suppressing cortical excitability have been shown to strongly facilitate motor learning in normal subjects [169]. In the context of stroke, delivering a rTMS protocol that induces LTD-like effects on the stroke-affected hemisphere before performing rehabilitation, would luckily result in better relearning [170]. In the proposed study continuous Theta Burst Stimulation (cTBS), a robust form of inhibitory rTMS inducing LTD-like changes lasting for about 1 h, has been delivered on the affected hemisphere. This choice is based on the findings retrieved in [171], which suggested that this inhibitory protocol

can improve the response to physical therapy. The proof-of-concept study herein described aims to explore whether the combination of the two approaches (i.e. robotic therapy and TMS) might enhance their positive effects on motor recovery. The study has been designed as a double blinded semi-randomized sham-controlled trial involving chronic stroke patients.
In addition, a multimodal interface is employed for a quantitative assessment based on robotic measures; aim of this evaluation is to enrich the information derived from the traditional clinical scales thus providing a more detailed picture of patient's recovery.
Finally, no reported studies regarding TMS have investigated physiological interactions with a highly controlled motor training. Therefore, this study represents an innovative approach to understand mechanisms and characteristics of an emerging stroke rehabilitation therapy.

## 6.2 Methodology

### 6.2.1 Study design

The study has been performed according to the Oviedo Convention and approved by the Ethics Committee of University Campus Bio-Medico of Rome and proposed to patients attending the outpatient clinic for cerebrovascular disorders of Campus Bio-Medico University Hospital.
Ten patients have been randomized to robot-assisted therapy associated with real cTBS and ten patients to robot-assisted therapy associated with sham cTBS, through a randomization stratification approach. Moreover, rehabilitation doctors, patients, and researchers involved in data analysis are blind to the type of cTBS delivered (i.e., sham or real), in order to obtain a double-blinded sham-controlled study design.
Each patient receives a session of robotic therapy following the real or sham stimulation everyday for ten consecutive working days. Four evaluation points have been selected: baseline (Baseline), just after the treatment (Post), after 1 (1 Month) and 3 months (3 Months). For all these evaluation points the Fugl-Meyer score is the primary outcome and robotic measures of motor performance are the secondary outcome.
In addition, at baseline also the following clinical scales are used: NIHSS, Rankin

Scale, Barthel Index, and Modified Ashworth Scale (MAS) for assessing spasticity at four different joint of affected arm: shoulder, elbow, wrist, and fingers. The scheme in Figure 6.1 shows the algorithm of the study design, the evaluations carried out and the treatments delivered.

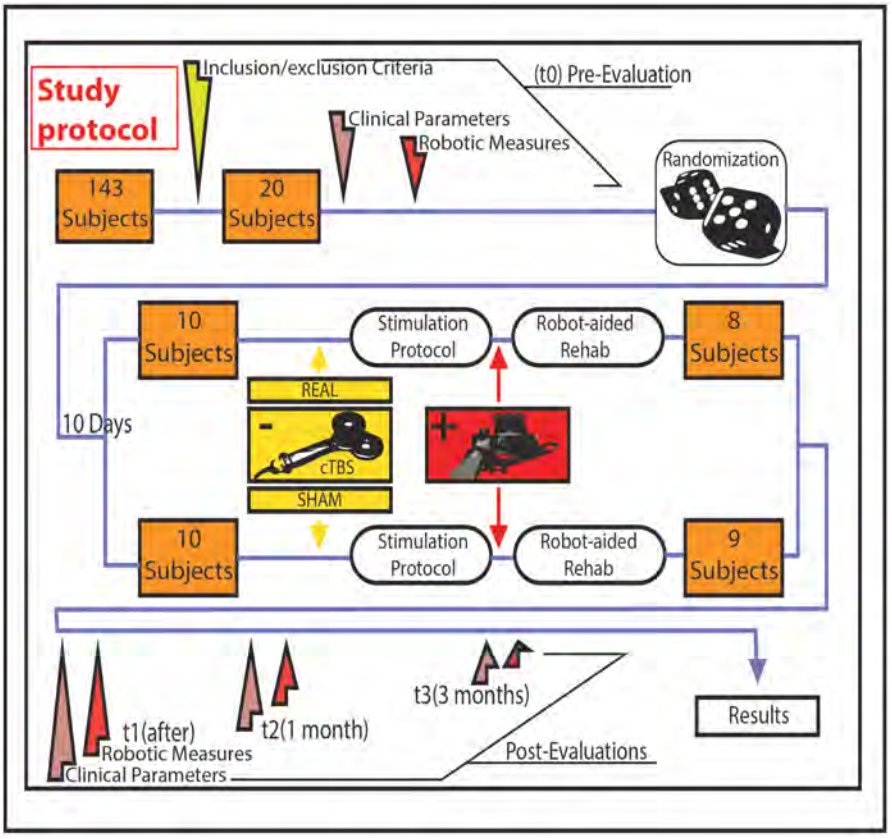


FIGURE 6.1: Figurative illustration representing the algorithm of the study design, the evaluations carried out and the treatments delivered. Treatment (real/sham cTBS + physical robotic therapy) is delivered for 10 consecutive working days. Baseline evaluation is performed in the first day of treatment

The combined effect of robotic rehabilitation and brain stimulation has been evaluated with (a) the Fugl-Meyer score after intervention, as compared to baseline (primary outcome measure of clinical improvement) and (b) robot derived measures of motor performance (secondary outcome measures).
After the two weeks of intervention, patients did not receive any additional physical therapy until the last follow-up visit (at 3 months). Pharmacological therapy remained the same.

### 6.2.2 Subjects

Participants provided written informed consent. The following inclusion criteria have been identified:

(a) First-ever ischemic stroke at least 1 year earlier;

(b) Severe hand function impairment, defined as score of 3-28 on the Fugl-Meyer Assessment of sensory motor recovery after stroke, a scale with scores for upper-limb impairment ranging from 0 (no function) to 66 (normal function);

(c) Ability to give informed consent and comprehend instructions.

With the same method, exclusion criteria have been determined:

(a) Concomitant neurological conditions, including any history of epilepsy and significant comorbidities;

(b) Cognitive impairment or any substantial decrease in alertness, language reception, or attention that might interfere with understanding instructions for motor testing;

(c) Apraxia;

(d) Excessive pain in any joint of the paretic extremity;

(e) Contraindications to TMS such as metal head implants;

(f) Advanced liver, kidney, cardiac or pulmonary disease;

(g) History of significant alcohol or drug abuse;

(h) Depression or use of neuropsychotropic drugs such as antidepressants or benzodiazepines.

Further evaluation of neurological impairment and disability at the enrolment have been performed using The National Institute of Health Stroke Scale (NIHSS) and the Barthel Index (BI).
143 patients have been screened from April the $1^{th}$, 2013, to September the $30^{th}$, 2014; 13 of whom declined, 110 have been excluded, and finally 20 are recruited. Patients characteristics at recruitment phase are reported in Table 6.1.

TABLE 6.1: **Demographic and clinical characteristics of recruited subjects at baseline**
[a]Chi-Square, [b]Mann-Whitney, [c]Two tailed independent samplet-test, [*]Cumulative score obtained by summing the scores obtained at four different joints of affected arm: shoulder, elbow, wrist, and fingers

| | **Real cTBS (n=8)** | **Sham cTBS (n=9)** | ***P*-value** |
|---|---|---|---|
| Age (years) | 57.88 ± 4.434 | 56.78 ± 3.202 | 0.841 |
| Sex (M) | 4 | 4 | 1.000[a] |
| Months since stroke | 63.25 ± 25.437 | 61.33 ± 14.716 | 0.541[b] |
| NIHSS | 5.50 ± 0.779 | 5.00 ± 0.687 | 0.636[c] |
| Rankin | 2.88 ± 0.350 | 3.00 ± 0.333 | 0.815[b] |
| Barthel index | 76.88 ± 7.130 | 77.22 ± 4.648 | 0.743[b] |
| MAS cumulative score[*] | 5.00 ± 0.597 | 7.111 ± 1.160 | 0.140[c] |
| Fugl-Meyer | 14.50 ± 2.428 | 12.56 ± 2.243 | 0.565[c] |

### 6.2.3 Transcranial brain magnetic stimulation

rTMS is applied over the hand motor area of the affected hemisphere using a DUO-MAG XT stimulator (DEYMED Diagnostic, Czech Republic) and a figure-of-eight shaped coil, with the handle pointed posteriorly and approximately perpendicular to the central sulcus. Active rTMS is delivered as cTBS, in which 3 pulses are given at 50 Hz, repeated every 200 ms for a total of 600 pulses.
Stimulation intensity is 80% of the active motor threshold (AMT) of the affected hemisphere, defined as the minimum single pulse intensity required to produce a motor evoked potential $>200\mu$V on more than 5 out of 10 trials from the contracted contralateral first dorsal interosseous muscle.
Whenever AMT over the affected hemisphere could not be determined because TMS at maximum stimulator output (MSO) failed to evoke any response, cTBS intensity is performed at an intensity corresponding to unaffected hemisphere AMT. On the other hand, sham rTMS is performed using the same stimulator at an intensity of 3% of MSO and with the coil tilted at 90°; this intensity of stimulation, with this orientation of the coil, produces auditory sensation similar to the active stimulation, but has no stimulating effect on the cortex.

### 6.2.4 Robotic therapy and assessment

Shoulder-elbow robotic therapy is delivered with the InMotion2 robotic machine (Interactive Motion Technologies, Inc.) [21] that provides two translational degrees of freedom for elbow and forearm motion (Figure 6.2). Impedance control

FIGURE 6.2: The InMotion2 robotic machine (Interactive MotionTechnologies, Inc.) employed in the study

enables the robot to move, guide or perturb the patient's movement.
Absolute encoders at each motor and a six-axis force/torque sensor at the end-effector allow measuring robot joint position, robot Cartesian position (via forward kinematics) and interaction forces.
The robot has a twofold purpose: deliver therapy and record kinematic data about patient's performance which are used for therapy evaluation. In fact, in the evaluation phase the robot is completely passive while position sensors record subject kinematic data.
Each patient is asked to perform five blocks of unassisted 16 point-to-point movements from the center to eight outbound targets along a circle at a distance of 0.14 m, with a self-paced speed in a maximum time slot of 3 s.
Robot data are then offline processed to compute quantitative performance indicators of temporal and spatial features of motor skill recovery (as secondary outcome) [52, 122]. The indicators for robotic evaluation belong to the class of kinematic indicators as reported in Section 2.5. The selected kinematic indicators are presented in the following:

- **Motion Accuracy**

  - *AREA*. It represents the area between the desired and the actual trajectory performed by the patient in the XY plane during the point-to-point motion; it is expected to decrease as movement accuracy increases with recovery.

  - *normalized Mean Deviation (nMD)* [89]. It is the mean absolute value of the distance between the desired path and the curve actually performed by the patient, normalized on the maximum deviation (or on the length of the theoretical path). As the patient recovers, the deviation from the desired path is expected to decrease.

- **Motion Direction**

  - *Aiming angle*. It is the angular difference between the target direction and the direction of the path performed from the starting point up to peak speed point. It is expected to decrease as movement direction improves during recovery.

- **Movement smoothness** [87]

  - *Speed Metric (SM)*. It is expressed as the ratio between mean speed and peak speed. As patient recovers, the normalized mean velocity increases due to the reduction of peaks and valleys in the velocity profile;

  - *Mean Arrest Period Ratio (MAPR)*. It represents the amount of time (i.e., the percentage of samples) that the movement speed exceeds the 10% of the peak speed. The deep valleys (percentage of pauses during the task execution) in the velocity profile of the patient hand are expected to reduce as movement smoothness improves.

- **Speed**

  - *Deviation from Ratio between Velocities (DRV)*. It is a quantification of the speed defined as the absolute deviation of the ratio between peak velocity and mean velocity from the constant value 1.875 (corresponding to the value obtained in the minimum jerk trajectory) [110]. It is expected to reduce when patient velocity tends to the bell-shaped velocity profile of the minimum jerk trajectory.

- **Movement Duration (MD)**

  - It gives a measure of the task execution time, evaluated as the time occurred for performing a point-to-point movement from movement onset to movement termination. Movement onset is defined as the time instant where speed exceeds a predefined threshold of 10% of peak velocity and movement termination is defined as the time instant where velocity goes below a predefined threshold of 10% of peak velocity. As patient recovers, movement duration is expected to decrease as a consequence of the improved efficiency.

- **Efficiency**

  - *Path Length (PL).* It represents the length ratio between the actual patient curve and the desired straight line, and computed as the line integral of the trajectory over the Movement Duration (MD), normalized with respect to the desired path. It is expected that during recovery the actual patient curve tends to the desired path and, hence, their ratio tends to one;
  - *% Successes (SR).* It accounts for the percentage of times that the patient reaches the target during a therapy session of point-to-point movements. The increase of the SR with recovery is expected [92].

Robotic treatment consists of three sessions of 320 assisted point-to-point movements, from the center to eight outbound targets, spaced out by four sessions of 16 unassisted recorded point-to-point movements. Robot assistance at each session is tuned on patients' performance during the 16 point-to-point sessions.
Finally, the aforementioned robotic treatment is delivered daily for ten consecutive working days. A physical and rehabilitation medicine doctors attended and assisted patients both during evaluations and treatments.

## 6.3 Results

Out of the twenty recruited patients, one real patient withdrew consent before the first session of treatment. In addition, one real patient and one sham patient withdrew because of difficulty in reaching the hospital after the third and after

the fifth day of treatment, respectively. Consequently, data of the patients who were withdrawn from the study are not included in the analysis.
A total of 17 patients completed the study including the 3-month follow-up: 8 real cTBS patients (mean age: 57.8 ± 4.4 years) and 9 sham cTBS (mean age: 56.7 ± 3.2 years). The randomised groups have been matched regarding age, sex, time elapsed from stroke onset, and clinical status at baseline as reported in Table 6.1. It is worth to mention that no treatment related to adverse events occurred; in particular patients reported no side effects that could be related either to the robotic treatment (e.g., shoulder, elbow, or wrist pain) or to cTBS (seizure, syncope, transient headache, local pain, neck pain, transient cognitive/neuropsychological changes) [172].

### 6.3.1 Clinical assessment

The primary outcome of the study is the Fugl-Meyer score. In order to compare the scores at baseline respect to the end of the treatment, the ANOVA Mixed Model with Time (four levels: Baseline, Post, 1 Month, 3 Months) as within subject factor and Group (two levels: real cTBS and sham cTBS) as between subjects factor is applied. The analysis shows significant effect of rehabilitation ($p = 0.013$) but no effect of the brain stimulation is observable (*Factor Group and Group by Time interaction:* $p > 0.200$ *consistently*).
Figure 6.3 reveals the outcomes of the statistical analysis. The improvement vs. baseline is statistically significant both soon after the intervention (Post) and at 1-Month follow-up (Bonferroni corrected post-hoc p = 0.30, p = 0.19, respectively). At 3-Month an average additional increase of the Fugl-Meyer score is shown, however the difference respect to Baseline is not significant (Bonferroni corrected post-hoc p = 0.75).

### 6.3.2 Robotic measures for assessment

Robotic measures analysis pointed out a rehabilitation-related improvement of the motor performance across multiple domains, including Motion Accuracy, Motion Direction, Smoothness, Speed, and Movement Duration. In particular all the

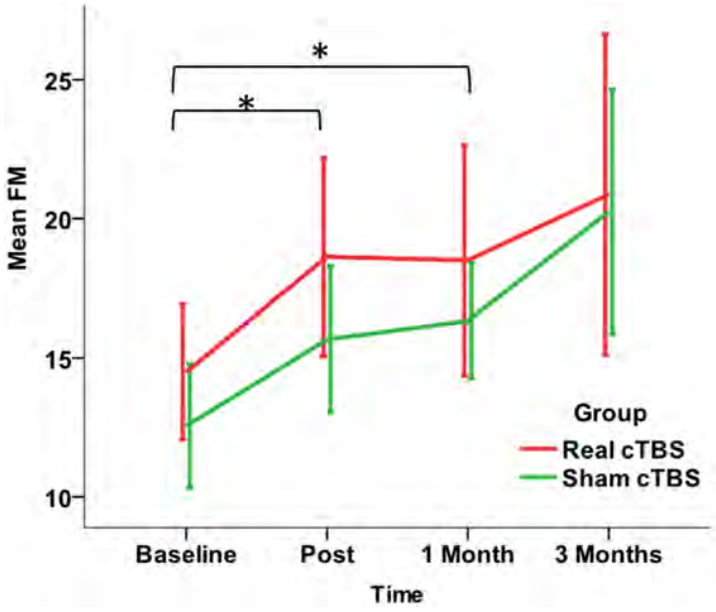


FIGURE 6.3: Changes in the primary Outcome Measure (Fugl-Meyer Assessment score) in the Real (red line) and the Sham (green line) cTBS groups. Compared to Baseline both groups significantly improved at t1 (post-treatment) and t2 (1 month). There is no significant difference between groups. *p $< 0.05$

robot-derived measures, except normalized Mean Deviation (nMD), have consistently shown a significant factor *Time* (Figure 6.4). The Bonferroni corrected comparisons at all the time points toward Baseline has shown a consistent and persistent improvement for all these measures (Post intervention, at 1-Month and at 3-Month, $p < 0.05$ consistently).

The effect of cTBS on these parameters may have caused the lack of significant main factor *Group* and *Group by Time interaction*. The analysis of the indicators that account for Efficiency has pointed out that cTBS over the affected hemisphere has an impact on the improvement of motor performance produced by the robotic treatment. Such effect has not been unveiled by the measure of the path length (PL), for which both main Factors and interaction are not significant, but it has become clear at the analysis of the Success Rate.

Indeed, the number of errors at Baseline (across groups) is 593 and decreases after the intervention, being 342 at Post, 364 at 1-Month, and 313 at 3-Month. Nevertheless, the improvement is different in the two cTBS groups (Chi-Square = 35.576, df = 3, p = 0.0001). The real cTBS group shows a higher error number (337 vs. 256, Std. Residual -2.4) at Baseline.

However, in spite of this, the study of the residuals has revealed that, compared to the cTBS group, the errors are significantly more in the sham at Post (Real cTBS 136, Sham cTBS 206, Std. Residuals >1.9) and 1-Month (Real cTBS 155,

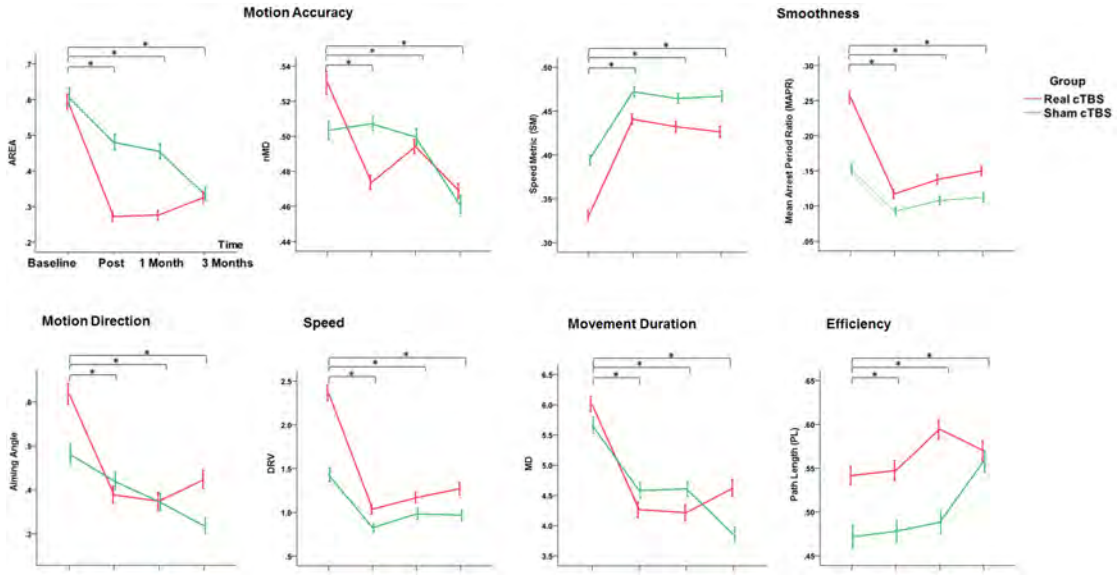


FIGURE 6.4: Changes in the Secondary Outcome Measures (motor performance parameters extracted by the robot) in the Real (red line) and the Sham (green line) cTBS groups. Compared to Baseline both groups significantly improved at t1 (post-treatment), t2 (1 month), and t3 (3 months) *p $< 0.05$. There is no difference between groups

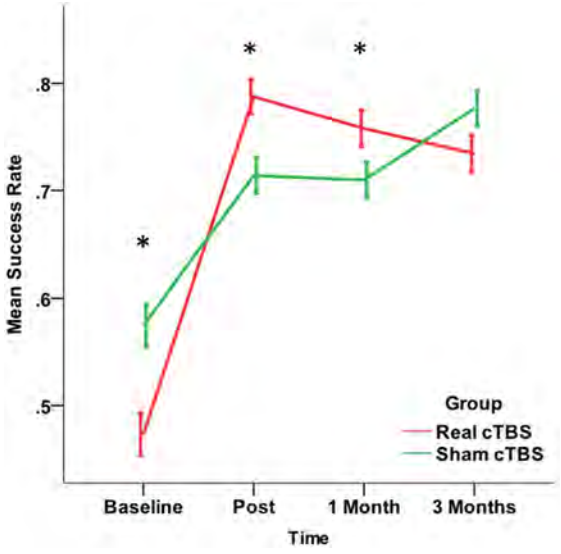


FIGURE 6.5: Changes in the Success Rate, a broader measure of motor performance representing the percentage of times that the patient reaches the target. The improvement in the real cTBS group was higher than in the sham group at t1 (post-treatment) and t2 (1 month). *p $< 0.05$.

Sham cTBS 209, Std residuals = 1.9). Finally, this effect is no more present at 3-Month evaluation (3-Month; Real cTBS 170, Sham cTBS 143, Std residuals = 1.2) as shown in Figure 6.5.

## 6.4 Discussions and conclusions

The present study has shown that a robot-assisted rehabilitation protocol lasting two weeks produces a slight, but significant, clinical improvement in chronic stroke patients with severe upper limb motor deficits. The mean gain in Fugl-Meyer score is rather limited, about 5% (3/4 points). However, this might be considered meaningful in chronic patients, especially in those with severe impairment [53].

On the other hand, it is also pointed out that non-invasive brain stimulation delivered as cTBS over the affected hemisphere does not seem to enhance the clinical gains from this treatment.

Interestingly, the mean improvement in the Fugl-Meyer score is comparable to what has been achieved previously with longer lasting interventions (12 weeks with 36 1-hour/day sessions of robot-assisted rehabilitative therapy [53] and 8 weeks with a total 24 sessions [54]).

In contrast with present findings, a previous study in chronic stroke patients with moderate upper limb deficits suggested that cTBS might enhance the gain from a late rehabilitation with a standardized protocol of physical rehabilitation [171]. One possible explanation for this discrepancy is that robot assisted rehabilitation attains a maximal benefit in patients with severe deficits and this cannot be enhanced by brain stimulation because of a ceiling effect.

Another possibility, is that, as suggested in [173], a more prolonged robotic therapy is needed to obtain a consistent improvement in patients with severe impairment and thus, it cannot be excluded that prolonging the association of robotic treatment and brain stimulation for a longer period might result more effective.

Finally, a further possibility could arise from the fact that the affected and unaffected hemispheres seem to play a different role in mild vs. severe strokes, so that the hemisphere mainly responsible for motor recovery in severe stroke is the unaffected one [167].

If this is the case, in patients with severe brain damage, it may be not useful to attempt promoting ipsilesional reorganization because the manipulation of the excitability of the affected hemisphere may not produce any advantage in terms of promoting relearning from rehabilitation. Instead, in these patients, future efforts should target the unaffected hemisphere being its role in recovery more relevant [167].

It should be considered that, for safety concerns, stimulus intensity has been estimated from the unaffected hemisphere, because this might be hyperexcitable [174].

It might be that this intensity is below the one needed to activate intracortical networks of the affected hemisphere.

Although cTBS after effects are produced by stimulus intensities well below motor threshold [175], and although this intensity produced significant effects in a previous study in patients with less severe stroke [171], it cannot be excluded that higher intensity cTBS could produce a more pronounced effect also in patients with severe stroke.

The application of a multimodal interface with robotic measures of motor performance has guaranteed a more sensitive and accurate evaluation of the effects of robotic rehabilitation and brain stimulation on motor recovery.

These measures complement the clinical scales and show that the proposed rehabilitation strategy achieves a significant benefit up to 3 months after the end of the treatment, confirming the findings of previous studies [5, 48, 53, 54]. Multiple domains of motor control present significant improvements in both groups (Motion accuracy, Motion Direction, Smoothness, Speed, Movement Duration, Success Rate), with no significant difference between groups. Only the Success Rate seems to show a cTBS effect on rehabilitation.

It can be hypothesised that the Success Rate, being a broader measure of motor performance, capitalizes the slight improvements in multiple domains of motor control, resulting statistically significant between groups [52]. Nevertheless, this finding should be taken extremely cautiously, since the other robot-derived measures do not show significant differences. In addition, the success rate values imbalance between groups at baseline might have influenced the changes observed in the two groups.

In the future, the application of non-invasive magnetic stimulation can be also envisaged as a powerful monitoring tool to be applied in a bio-cooperative control strategy. In fact, the extraction of neurophysiological indicators that account for brain activity may enrich the multimodal source of information used for designing a control strategy entirely tailored to the specific patient's needs.

In this context, the neurophysiological indicators represent the neurophysiological state of the patient and therefore they can be included into the bio-cooperative system proposed in Fig. 3.1.

# Chapter 7

# The application of a multimodal interface for the quantitative assessment of upper limb robotic training and tDCS in chronic stroke patients

In this Chapter, the multimodal interface proposed in Chapter 3 is employed for the quantitative evaluation of chronic stroke patients in a small pilot study that investigates the effects of transcranial Direct Current Stimulation (tDCS) coupled with upper limb robotic therapy.
The proposed multimodal interface has two main objectives:

- Flank common clinical evaluation scales with quantitative evaluation of their performance using robotic measurements;
- Investigate the correlation between the selected performance indicators and the clinical scales usually employed for assessment.

In Section 7.1 the principles of tDCS and robotic therapy are discussed; Section 7.2 presents the current studies investigating the effects on motor recovery of tDCS combined with upper limb robot-aided rehabilitation.
On the other hand, Section 7.3 presents the methodology of the pilot study and

the results of the robotic evaluation by means of performance indicators.
Finally in Section 7.4 a discussion on the presented studies and possible future challenges are reported.

## 7.1 Basic principles of tDCS and robot-aided therapy

Activities of daily living (ADLs) strongly depend on arm functioning; this is why upper limb impairments can lead to a poor perception of health-related quality of life [176]. Therefore, one of the goals of post-stroke rehabilitation is to recover arm and hand functions, and enable the patients to perform independently activities of daily living.
Application of robotics in neurorehabilitation represents a key enabling technology for addressing requirements such as task-specific, repetitive, challenging and functional training for post stroke subjects [3]. Despite the interesting advancements in this area, the type of therapy leading to optimal results remains controversial and elusive, and patients are often left with considerable disability.
The adjunct of non-invasive interventions, such as the electrical brain stimulation, might be used to speed-up and maximize the potential benefit of rehabilitation treatment [16]. In particular, transcranial Direct Current Stimulation (tDCS), modulating the excitability of a targeted brain region non-invasively, can be used to favor a normal balance in the interhemispheric interaction and, hence, facilitate the recovery of motor functions of the paretic limb. This suggests that, by coupling tDCS with other interventions, it should be possible to increase the modulatory effects on the motor neural network of those interventions and, thus, increase clinical gain [177].
tDCS consists of applying low-intensity current (1-2 mA) between two electrodes on the scalp (Figure 7.1). There are two possible electrode polarities which cause different effects:

- Anodal stimulation - It induces depolarization of resting membrane potential and increases cortical excitability
- Cathodal stimulation - It causes hyperpolarization of resting membrane potential and decreases cortical excitability.

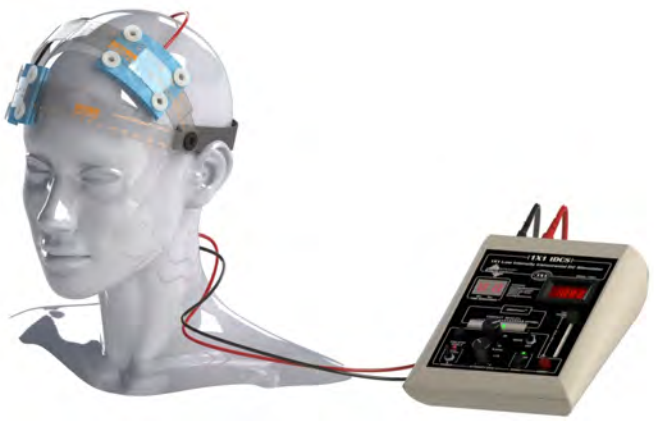

FIGURE 7.1: Common system for applying tDCS

This approach is grounded on the inhibitory competition model; it states that in order to restore the interhemispheric imbalance altered after a stroke, excitability of the affected hemisphere can be increased with anodal tDCS, or decreased it with cathodal tDCS [18].
In addition, using bilateral tDCS (i.e. applying simultaneously anodal electrode on the affected hemisphere and cathodal electrode on the unaffected hemisphere) could also represent an effective strategy to produce interhemispheric rebalancing effects [178].
All these findings have encouraged the scientific community to start investigating the effects of upper limb robot-aided motor training coupled with tDCS in stroke, relying on the adjunct of tDCS to further enhance primary effects of motor recovery in post-stroke patients treated with upper limb robot-assisted therapy (in the following named RT).

## 7.2 tDCS coupled with upper limb robotic therapy: current trends

The study of the effects deriving from the coupled use of tDCS and RT represents a relatively new field of interest. Currently, there are only few studies that have tried to prove the successful combination of this two techniques. All the studies are grounded on the theory of interhemispheric competition where anodal tDCS is delivered on lesioned hemisphere (excitatory protocol) and cathodal tDCS is delivered on contralateral hemisphere (inhibitory protocol).

In addition, the Fugl-Meyer score has been chosen as primary outcome for the majority of the studies, even though other outcomes are also reported.
Although the selected studies share the general objective of assessing the effects of tDCS combined with the RT, the employed investigation methods are different and provide heterogeneous data that are difficult to be analyzed in a systematic way.
However, despite the difficulty to find a global primary outcome measure, interesting common features have been extracted and a list of factors has been identified. For the sake of clearness the retrieved studies are grouped in the following queries to be investigated:

1. Effects of anodal and/or cathodal tDCS coupled with RT in post stroke patients (compared or not with RT alone);
2. Effects of different anodal tDCS delivering time, i.e. before, during or after RT;
3. Effects of anodal tDCS compared to cathodal tDCS when coupled with RT;
4. Effects of anodal tDCS combined with peripheral nervous stimulation (PNS), MI-BCI (Motor Imagery-Brain Computer Interface) and RT.

Regarding the first group five studies have been considered. In [179] the feasibility of anodal tDCS (1.5 mA for 7 minutes) during bilateral RT (20 minutes) with the BiManu Track [60], has been investigated in a pilot study with ten subacute ischemic stroke patients. A significant improvement in Fugl-Meyer scores between pre and post treatment has been shown.
The same group performed a multicenter trial in which 96 subacute stroke patients have been randomized in three groups receiving different treatments [180]. First group received anodal tDCS (2 mA for first 20 min), the second group received cathodal tDCS (2 mA for first 20 min) and the third one received sham stimulation; all groups have received RT with BiManu Track (Figure 7.2a) contemporaneously to brain stimulation. The Fugl-Meyer scores showed an improvement at the end of the treatment for all groups but no significant improvements occurred between groups.
In [181] 23 stroke patients (12 subacute and 11 chronic) have been selected and randomized into two groups: real anodal tDCS (1mA for first 20 minutes) and sham tDCS coupled with Armeo®Spring RT (Figure 7.2d).

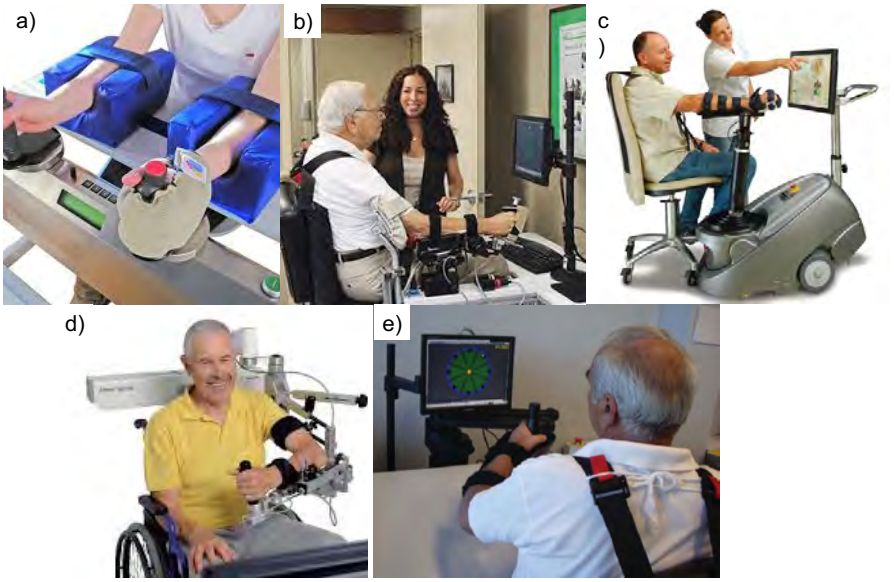


FIGURE 7.2: The different robotic devices employed in the studies investigating coupled effect of robot-aided therapy and tDCS. a) BiManu Track for wrist and forearm training, b) InMotion3 wrist robot, c) REO Therapy System for shoulder/elbow treatment, d) ArmeoSpring, shoulder/elbow exoskeleton, e) InMotion 2 shoulder/elbow robot

Again, the results analysis showed significant improvements in Fugl-Meyer scores for both groups (respect to baseline) while no significant effects of group or group by time interaction have been retrieved. Slight significant changes in Fugl-Meyer scores have been obtained analyzing the proposed treatment (tDCS and RT) respect to the type of stroke, i.e. subacute and chronic.

Effects of anodal tDCS coupled with InMotion3 (Figure 7.2b) wrist robotic training (five sessions per six weeks) have been investigated in twelve subacute stroke patients randomly assigned to experimental (real tDCS) and control (sham tDCS) group [182]. Fugl-Meyer scores evaluated pre/post intervention and a set of kinematic measurements did not change significantly between groups.

Finally, in [183] 23 stroke patients, 14 chronic and 9 subacute, have been selected and then allocated randomly into two groups undergoing bilateral tDCS (1mA for 30 min) and sham tDCS coupled with REO$^{TM}$ RT (Figure 7.2c), a shoulder/elbow robot commercialised by Motorika, Inc., Israel. No significant differences between groups have been retrieved; only adjusting analysis for stroke type and duration revealed a significant interaction effect. In fact, subcortical chronic stroke subjects have benefited more than subacute subjects with cortical lesions.

The effect of tDCS timing on robotic therapy has demonstrated to play an important role in the design of successful clinical protocols [184] as confirmed by

Giacobbe et al. in [185].

In this study, twelve chronic stroke subjects have received anodal tDCS (2mA for 20 minutes) before, during and after a single session of unilateral RT with InMotion3 (20 min). Differently from the previous works, kinematic measurements have been considered as primary outcome instead of Fugl-Meyer scores. Results analysis have showed significant improvements (between pre and post intervention) in movement smoothness only when anodal tDCS is delivered before RT.

The third query investigates the effects of comparison between anodal tDCS and cathodal tDCS both coupled with bilateral RT [186]. The same eighteen chronic stroke patients have received by turns anodal tDCS and cathodal tDCS during the initial 10 minutes of RT with BiManu Track. Fugl-Meyer scores have shown improvements in both interventions, pointing out no significant differences between them. Only a slight significant effect of cathodal tDCS has been found for patients with right hemispheric lesions with respect to anodal tDCS.

Recently, the effects of anodal tDCS and robotic therapy have been further investigated with the adjunct of peripheral nervous stimulation [187] and MI-BCI [188]. In [187] the authors tried to investigate whether timing variations of electrical brain stimulation paired with nerve stimulation and RT may enhance motor recovery in chronic stroke subject.

To this purpose, 10 chronic stroke subjects were recruited and divided into two groups: anodal tDCS has been delivered before (Group A: tDCS pre-PNS group) or after (Group B: tDCS post-PNS group) PNS and followed by shoulder/elbow RT with InMotion2.

Slight significant effect has been observed for Stroke Impact Scale (SIS) in Group A; no significant changes have been retrieved in FMS for Group A and Group B and in SIS for Group B. Moreover, no between groups effects have been obtained both for FMS and SIS.

These findings seem to demonstrate that for moderate-to-severe stroke patients, tDCS at the start, rather than the end, of peripheral nerve stimulation prior to robotic motor training may result in better functional outcomes [187].

On the other hand, in [188] there was the aim to demonstrate the feasibility to use tDCS to facilitate the ability of stroke patients to operate a MI-BCI [189] and, subsequently, the efficacy of the treatment together with robotic feedback in a sham-controlled randomized trial. Nineteen moderate-to-severe chronic stroke patients were randomized in two groups, undergoing 20 minutes of real (sham)

bilateral tDCS before 1 hour of MI-BCI with robotic feedback provided by the InMotion2 robot. Fugl-Meyer scores showed that real tDCS before MI-BCI and RT did not result in additional motor improvements compared to the single treatment (i.e. MI-BCI paired with robotic feedback).

On the other hand, the evaluation of online MI-BCI accuracy may have benefited from tDCS; this supports its potential role in facilitating the operation of motor imagery in chronic stroke subjects (62.9% in the real group, 57.0% in the sham group), as already preliminary analyzed in [190].

A complete overview of the studies together with the main related outcomes is depicted in Figures 7.3-7.4-7.5-7.6-7.7-7.8-7.9.

| Study | Protocol therapy | Patient's number | Diagnosis | Age (Mean±SD) | Time post-stroke | Description of the intervention | Kinematic indicators | Neuro-physiological indicators | Clinical scales |
|---|---|---|---|---|---|---|---|---|---|
| Hesse et al. 2007 | Anodal tDCS +BiManuTrack RT | 1Group: 10 patients | Subacute ischemic stroke | 63.3 years (SD is not directly reported) | 4-8 weeks | 20 min of RT with first 7 minutes of anodal tDCS (1.5 mA). 30 sessions (5 per 6 weeks) | - | - | FMS |
| Hesse et al 2011 | -Anodal tDCS+ Bi ManuTrack RT -Cathodal tDCS + BiManuTrack RT - Sham tDCS+ BiManuTrack RT | 3 Groups: 32 patients for each group | Subacute Ischemic stroke | Group A (real anodal): 63.9 ± 10.5 years Group B (real cathodal): 65.4 ± 8.6 years Group C (sham): 65.6 ± 10.3 years | 3-8 weeks | Group A: 20 min of RT coupled with anodal tDCS (2.0 mA); Group B: 20 min of RT coupled with cathodal tDCS (2.0 mA) Group C: 20 min of RT coupled with SHAM tDCS. 30 sessions (5 per 6 weeks) | - | - | FMS, MAS, BI, MRC, B&B |
| Ochi et al. 2013 | -Anodal tDCS+ BiManuTrack RT -Cathodal tDCS+ BiManuTrack RT | 2 Groups: 9 patients for each group | Chronic: 11 hemorrhagic 7 ischemic stroke | 61.1± 10.0 years | (Mean) 4.4 years | 1 mA anodal tDCS during first 10 min of robotic AT; 1 mA cathodal tDCS during first 10 min of robotic AT. 10 days, multiple sessions spaced out by 2-days rest | - | - | FMS, MAS, MAL |
| Giacobbe et al. 2013 | Anodal Real/Sham tDCS+wrist RT (InMotion3) | 1 group: 12 patients | Chronic ischemic stroke | 64.4 ± 11.7 years | (mean) 4.0 years | TMS delivered for locating correct anodal position; 20 min of wrist RT coupled with: -20 min of REAL tDCS before RT; -20 min of REAL tDCS during RT; -20 min of REAL tDCS after RT; -20 min of SHAM tDCS during RT. 1 single session | Cartesian space: Mean speed, Peak speed, Deviation, Smoothness, Duration, Aim | MEP (FCR, ECR) | FMS |

FIGURE 7.3: Overview of the studies on tDCS combined with robotic upper limb rehabilitation after stroke tDCS. tDCS = Transcranial Direct Current Stimulation; RT = Robotic Training; TMS = Transcranial Magnetic Stimulation; MEP = Motor Evoked Potential; FMS= Fugl-Meyer Score; MAS= Modified Ashworth Scale; BI= Barthel Index; B&B= Box and Block Test; MRC= Medical Research Council; MAL=Motor Activity Log; FCR=Flexor Carpi Radialis; ECR=Extensor Carpi Radialis; SD=Standard Deviation

| Study | Protocol therapy | Patient's number | Diagnosis | Age (Mean±SD) | Time post-stroke | Description of the intervention | Kinematic indicators | Neuro-physiological indicators | Clinical scales |
|---|---|---|---|---|---|---|---|---|---|
| Ang et al., 2015 | -Bilateral Real/Sham tDCS + MI-BCI with robotic feedback (InMotion2) | 2 Groups: 10 patients for real group 9 patients for sham group | Chronic stroke: 13 ischemic 9 hemorrhagic; 18 subcortical 1 cortical | Group A(real): 52.1± 11.7 Group B(sham): 56.3± 9.5 | 9 months | Group A: 10 sessions of 20 minutes of bilateral tDCS (1 mA) before 1 hour of MI-BCI with robotic feedback upper limb stroke rehabilitation for 2 weeks. Group B: 10 sessions of 20 minutes of sham tDCS (1 mA) before 1 hour of MI-BCI with robotic feedback upper limb stroke rehabilitation for 2 weeks. | - | MI-BCI screening | FMS |
| Triccas et al. 2015 | -Anodal Real/Sham tDCS+Armeo Spring RT | 2 Groups: 12 patients for real group 11 patients for sham group | 12 Subacute: 10 ischemic and 2 haemorrhagic stroke; 11 Chronic: 8 ischemic and 3 haemorrhagic stroke | Group A (real): 64.3± 10 years Group B (sham): 62.5± 14.3 years | Subacute stroke: (mean) 8-10 weeks Chronic stroke: (mean) 3.1 years | Group A: anodal tDCS (1.0 mA) during first 20 min of 1 hr RT; Group B: sham tDCS during first 20 min of 1 hr RT; 18 sessions for 8 weeks (2-3 sessions per week) | Hand Path Ratio (HPR) | - | FMS, ARAT, MAL, SIS |
| Powell et al., 2016 | - Anodal tDCS delivered before PNS or after PNS combined with robotic therapy (InMotion2) | 2 Groups: 4 patients for before PNS group 6 patients for after PNS group | Chronic stroke: 7 ischemic 3 hemorrhagic; 6 left side lesion 4 right side lesion | Group A (before PNS): 61.0 ± 6.63 Group B (after PNS): 60.5± 2.95 | 4.5 years | Group A: 10 daily sessions of 20 minutes of anodal tDCS (2 mA) BEFORE 2 hour of PNS followed by 2hr of RT Group B: 10 daily sessions of 20 minutes of anodal tDCS (2 mA) AFTER 2 hour of PNS followed by 2hr of RT | - | Motor map volume of ipsilesional hemisphere, COG | FMS, SIS |
| Straudi et al. 2016 | -Anodal and cathodal Real/Sham tDCS+ReoGo Therapy System RT | 2 Groups: 12 patients for real group 11 patients for sham group | 9 Subacute: 6 cortical and 3 subcortical (9 ischemic and 2 hemorrhagic) 14 Chronic: 8 cortical and 6 subcortical (10 ischemic and 2 hemorrhagic) | Group A (real): 52.7.3± 16 years Group B (sham): 64.3± 9.7 years | Subacute stroke: < 6 months Chronic stroke: > 6 months | Group A: 30 min of RT with anodal and cathodal real tDCS (1.0 mA); Group B: 30 min of RT with anodal and cathodal sham tDCS during first 30 seconds; 10 sessions for 2 weeks (5 sessions per week) | - | - | FMS, SIS |

FIGURE 7.4: Overview of the studies on tDCS combined with robotic upper limb rehabilitation after stroke. tDCS = Transcranial Direct Current Stimulation; RT = Robotic Training; FMS = Fugl-Meyer Score; ARAT = Action Research Arm Test; SIS = Stroke Impact Scale; B&B = Box and Block Test; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; MI = Motricity Index; MI-BCI = Motor Imagery-Brain Computer Interface; COG = Center of Gravity of the lesion; SD = Standard Deviation

| Study | FMS (SD) | BI (SD) | MAS (SD) | MAL (SD) | MRC (SD) | B&B (n≥3) |
|---|---|---|---|---|---|---|
| Hesse, 2007 Baseline | 7.2 ± 3.1 | - | - | - | 3.0 ± 3.1 | - |
| Post treatment* | 18.2 ± 17.2 | | - | - | 7.6 ± 6.9 | - |
| Hesse, 2011 Baseline | Group A tDCS(a): 7.81±3.8<br>Group B tDCS(c) :7.9±3.4<br>Group C tDCS(s) :8.2±4.4 | Group A tDCS(a): 34.1±3.4<br>Group B tDCS(c) :34.2±7.6<br>Group C tDCS(s): 35.0±7.8 | Group A tDCS(a):1.6±2.9<br>Group B tDCS(c) :1.0±1.8<br>Group C tDCS(s) :1.4±2.7 | - | Group A tDCS(a): 3.5±3.6<br>Group B tDCS(c) :2.9±3.4<br>Group C tDCS(s) :3.4±3.2 | Group A tDCS(a): 0<br>Group B tDCS(c): 0<br>Group C tDCS(s): 0 |
| Post treatment** | Group A tDCS(a): 19.1±14.4<br>Group B tDCS(c): 18.9±10.5<br>Group C tDCS(s) :19.2±15.0 | Group A tDCS(a): 53.6±14.5<br>Group B tDCS(c) 59.2±12.4<br>Group C tDCS(s) 56.3±15.5 | Group A tDCS(a): 3.3±3.6<br>Group B tDCS(c) :3.5±4.9<br>Group C tDCS(s) :3.5±4.0 | | Group A tDCS(a): 11.9±12.5<br>Group B tDCS(c): 13.7±10.4<br>Group C tDCS(s): 12.8±12.1 | Group A tDCS(a): 9<br>Group B tDCS(c): 8<br>Group C tDCS(s): 9 |
| Ochi, 2013 Baseline | Group A tDCS(a): 23.2±16.6<br>Group B tDCS(c): 23.6±16.7 | - | Group A tDCS(a): (E) 2.4 ± 1.1<br>(W) 3.0 ± 1.1; (F) 2.8 ± 1.3<br>Group B tDCS(c): (E) 2.5 ± 1.2<br>(W) 2.9 ± 1.1;<br>(F) 2.9 ± 1.2 | Group A tDCS(a): 1.6±2.7<br>Group B tDCS(c): 1.6±2.8 | - | - |
| Post treatment*** | Group A tDCS(a): 23.2±16.6<br>Group B tDCS(c): 23.6±16.7 | - | Group A tDCS(a): (E) 2.4 ± 1.1<br>(W) 3.0 ± 1.1; (F) 2.8 ± 1.3<br>+<br>Group B tDCS(c): (E) 2.5 ± 1.2<br>(W) 2.9 ± 1.1;<br>(F) 2.9 ± 1.2+ | Group A tDCS(a): 1.6±2.7<br>Group B tDCS(c): 1.6±2.8 | - | - |

FIGURE 7.5: Clinical Scales scores; $p<0.05$ has been taken as significant value tDCS = Transcranial Direct Current Stimulation; RT = Robotic Training; FMS = Fugl-Meyer Score; MAS = Modified Ashworth Scale; BI = Barthel Index; B&B = Box and Block; MRC = Medical Research Council; MAL = Motor Activity Log; E = elbow; W = wrist; F=finger; SD = Standard Deviation.
*Significant difference occurred in FMS and MRC assessed between baseline and post treatment, $p=0.018$ and $p=0.027$ respectively.
** No between group differences occurred for all clinical indicators used ($p>0.025$). Significant difference ($p=0.014$) only occurred within the cathodal group (TACI+LACI vs LACI) in terms of ΔFMS (not directly reported in Table 2a).
***Small but significant improvements ($p<0.05$) between pre/post treatment, have been observed for both stimulation protocol in FMS and MAS (not in MAL, $p>0.05$).
+ Between stimulation condition, i.e. tDCS(a) and tDCS(c), only for tDCS(c)+RT a significant improvement in MAS for the fingers has been observed

| Study | FMS (SD) | MAL (SD) | B&B (n≥3) | MAS (SD) | SIS (SD) |
|---|---|---|---|---|---|
| Ang, 2015<br>Baseline | Group A real tDCS:<br>35.3±7.8<br>Group B sham tDCS:<br>32.6±8.1 | - | - | - | - |
| Average improvement between post intervention and baseline ^ | Group A real tDCS:<br>0.9±3.0<br>Group B sham tDCS:<br>2.8±4.0 | - | - | - | - |
| Triccas, 2015<br>Baseline | Group A real tDCS: 24.91±16.01<br>Group B sham tDCS: 37.09±13.57 | - | - | - | - |
| Post treatment**** | Group A real tDCS: 33.64±16.25<br>Group B sham tDCS: 44.82±16.29 | - | - | - | - |
| Powell, 2016<br>Baseline | Group A tDCS pre-PNS: 23.3 ± 15.8<br>Group B tDCS post-PNS: 18.7 ± 8.1 | - | - | - | Group A tDCS pre-PNS:<br>65.3 ± 5.1<br>Group B tDCS post-PNS:<br>60.0 ± 9.7<br><br>Group B sham tDCS: 63.17 ± 8.40 |
| Average improvement between post intervention and baseline ***** | Group A tDCS pre-PNS: 1.5 ± 1.39<br>Group B tDCS post-PNS S: 0.17 ± 1.3 | - | - | - | Group tDCS pre-PNS:<br>6.33 ± 2.21<br>Group B tDCS post-PNS:<br>0.50 ± 1.56 |
| Straudi, 2016<br>Baseline | Group A real anodal/cathodal tDCS: 24.08±16.60<br>Group B sham anodal/cathodal tDCS:<br>21.09±13.19 | Group A real tDCS(a+c) AOM:<br>0.68±0.90<br>Real tDCS(a+c) QOM: 0.69±1.01<br>Group B sham tDCS(a+c) AOM:<br>0.59±1.02<br>Sham tDCS(a+c) QOM: 0.59±1.17 | Group A real<br>anodal/cathodal tDCS:<br>10.42±15.47<br>Group B sham<br>anodal/cathodal tDCS:<br>6.55±11.67 | - | - |
| Post treatment****** | Group A real anodal/cathodal tDCS:<br>28.50±18.96*****<br>Group B sham anodal/cathodal tDCS:<br>26.64±16.12***** | Group A real tDCS(a+c) AOM:<br>1.09±1.36§<br>Real tDCS(a+c) QOM: 1.05±1.43§<br>Group B sham tDCS(a+c) AOM:<br>0.89±1.38<br>Sham tDCS(a+c) QOM: 0.85±1.50 | Group A real<br>anodal/cathodal tDCS:<br>12.67±17.23§<br>Group B sham<br>anodal/cathodal tDCS:<br>8.55±14.07 | - | - |

FIGURE 7.6: Clinical Scales scores; $p<0.05$ was taken as significant value tDCS = Transcranial Direct Current Stimulation; RT = Robotic Training; FMS = Fugl-Meyer Score; B&B = Box and Block; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; MI = Motricity Index; CM = Chedoke Mc-Master Scale; UE = upper limb; AOM = Amount of Movement; QOM = Quality of Movement; SD = Standard Deviation

****Significant difference occurred in FMS assessed between baseline and post treatment, $p<0.001$ in both groups; however, no significant difference between groups have been retrieved.

***** Significant difference occurred in FMS (UE) and MI assessed between baseline and post treatment, $p<0.05$ in both groups; however, no significant difference between groups have been retrieved.

****** No significant difference occurred in FMS assessed between baseline and post treatment in both groups ($p=0.31$ pre-PNS and $p=0.67$ post-PNS); significant difference occurred for the SIS in the tDCS pre-PNS group ($p=0.02$). However, no significant difference between groups have been retrieved for both FMS and SIS $p=0.59$ and $p=0.07$ respectively. § A significant interaction effect ($p<0.05$) was detected regarding stroke duration (subacute vs chronic) and type (cortical versus subcortical).

^ No significant intergroup differences have been observed at any time point

| | **FMS (SD)** | **ARAT (SD)** | **SIS (SD)** | **MAL (SD)** |
|---|---|---|---|---|
| Baseline | Subacute stroke: 36.7±18.4<br>Chronic stroke: 27.55±13.77 | Subacute stroke: 33.5±0.6<br>Chronic stroke:6.0±0.2 | Subacute stroke: 58.0±21.8<br>Chronic stroke:58.1±26.5 | Subacute stroke: 1.3±1.3<br>Chronic stroke:0.5±0.5 |
| Post treatment* | Subacute stroke: 47.0±17.8<br>Chronic stroke: 30.0±10.23 | Subacute stroke: 48.5±0.6<br>Chronic stroke:8.0±0.2 | Subacute stroke: 75.0±15.7<br>Chronic stroke:58.5±23.4 | Subacute stroke: 2.3±1.8<br>Chronic stroke:0.5±0.7 |

FIGURE 7.7: Clinical Scales Scores for [181] regarding treatment effects on subacute vs chronic stroke
FMS = Fugl-Meyer Score; ARAT = Action Research Arm Test; MAL = Motor Activity Log; SIS = Stroke Impact Scale; SD = Standard Deviation
*Significant changes at post-intervention between stage (i.e. subacute vs chronic) per time interaction have been retrieved.

| | | **Mean Speed (rad/s)** | **Peak Speed** | **Deviation (rad)** | **Smoothness** | **Duration (s)** | **Aim (rad)** |
|---|---|---|---|---|---|---|---|
| Expected trend | | | | - | | - | - |
| Sham tDCS during RT | Pre-training | $3.1 \pm 0.1 \times 10^{-1}$ p=0.006** | $13.1 \pm 0.8 \times 10^{-1}$ p=0.009** | $3.6 \pm 0.4 \times 10^{-2}$ p=0.168 | $2.8 \pm 0.1 \times 10^{-1}$ p=0.317 | 3.74 ± 0.23 p=0.432 | $7.9 \pm 0.4 \times 10^{-1}$ p=0.095 |
| | Post-training | $3.7 \pm 0.2 \times 10^{-1}$ p=0.006** | $16.6 \pm 1.1 \times 10^{-1}$ p=0.009** | $4.4 \pm 0.5 \times 10^{-2}$ p=0.168 | $2.6 \pm 0.1 \times 10^{-1}$ p=0.317 | 3.48 ± 0.23 p=0.432 | $8.8 \pm 0.35 \times 10^{-1}$ p=0.095 |
| tDCS before RT | Pre-training | $3.65 \pm 0.2 \times 10^{-1}$ p=0.43 | $16.4 \pm 0.1 \times 10^{-1}$ p=0.297 | $4.7 \pm 0.5 \times 10^{-2}$ p=0.133 | $2.5 \pm 0.1 \times 10^{-1}$ p=0.001** | 3.1 ± 0.3 p=0.062 | $9.3 \pm 0.3 \times 10^{-1}$ p=0.052 |
| | Post-training | $3.8 \pm 0.2 \times 10^{-1}$ p=0.43 | $14.9 \pm 0.1 \times 10^{-1}$ p=0.297 | $3.7 \pm 0.4 \times 10^{-2}$ p=0.133 | $2.9 \pm 0.1 \times 10^{-1}$ p=0.001** | 3.2 ± 0.2 p=0.062 | $8.3 \pm 0.4 \times 10^{-1}$ p=0.052 |
| tDCS during RT | Pre-training | $3.4 \pm 0.2 \times 10^{-1}$ p=0.53 | 13.9 ± 1 x 10-1 p=0.585 | $3.6 \pm 0.3 \times 10^{-2}$ p=0.239 | $2.8 \pm 0.1 \times 10^{-1}$ p=0.554 | 3.01 ± 0.22 p=0.987 | $7.1 \pm 0.3 \times 10^{-1}$ p=0.019* |
| | Post-training | $3.6 \pm 0.2 \times 10^{-1}$ p=0.53 | $14.6 \pm 0.9 \times 10^{-1}$ p=0.585 | $4.2 \pm 0.5 \times 10^{-2}$ p=0.239 | $2.9 \pm 0.1 \times 10^{-1}$ p=0.554 | 3.08 ± 0.21 p=0.987 | $8.2 \pm 0.3 \times 10^{-1}$ p=0.019* |
| tDCS after RT | Pre-training | $4.1 \pm 0.2 \times 10^{-1}$ p=0.032* | $15.7 \pm 0.9 \times 10^{-1}$ p=0.595 | $3.6 \pm 0.4 \times 10^{-2}$ p=0.087 | $3.0 \pm 0.1 \times 10^{-1}$ p=0.529 | 2.58 ± 0.18 p=0.158 | $8.0 \pm 0.4 \times 10^{-1}$ p=0.65 |
| | Post-training | $3.6 \pm 0.2 \times 10^{-1}$ p=0.032* | $15.0 \pm 1 \times 10^{-1}$ p=0.595 | $4.8 \pm 0.5 \times 10^{-2}$ p=0.087 | $2.9 \pm 0.1 \times 10^{-1}$ p=0.529 | 2.94 ± 0.19 p=0.158 | $7.8 \pm 0.3 \times 10^{-1}$ p=0.65 |

FIGURE 7.8: Kinematic indicators for [185]
*Significant REDUCTION in post intervention with respect to baseline (<20%)
** significant INCREASE in post intervention with respect to baseline (p<0.05)

| Study | Mean MEP (SD) Amplitude (FCR, ECR, muscles) | Ipsilesional cortical map volume (normalized MEP amplitude*cm$^2$) (mean) | $COG_x$ (cm) (lateral-medial) | $COG_y$ (cm) (anterior-posterior) |
|---|---|---|---|---|
| Giacobbe et al., 2013 | Increased amplitude %FCR and ECR<br>tDCS pre-RT(n=6)<br>(FCR) 97±9% baseline<br>(ECR) 124±21% baseline<br>tDCS during-RT (n=5)<br>(FCR) 139±43% baseline<br>(ECR) 115±29% baseline<br>tDCS post-RT (n=5)<br>(FCR) 110±19% baseline<br>(ECR) 103±16% baseline | - | - | - |
| Powell et al., 2016* (Baseline vs post intervention) | - | Group A tDCS pre-PNS: 2.1<br>Group B tDCS post-PNS: -6.3 | Group A tDCS pre-PNS: -0.62 (medial)<br>Group B tDCS post-PNS: 0.3 (lateral) | Group A tDCS pre-PNS: 0.48 (anterior)<br>Group B tDCS post-PNS: -0.48 (posterior) |

FIGURE 7.9: Neurophysiological indicators for [185] and [187]
FCR=Flexor Carpi Radialis; ECR=Extensor Carpi Radialis; MEP = Motor Evoked Potential; COGx = ipsilesional Center of Gravity location change; COGy = ipsilesional Center of Gravity location change; SD= standard deviation.
*Only one subject for each group (Powell et al., 2016). Ipsilesional map volume increased in Group A and decreased in Group B. COG location shifted in opposite directions according to stimulation condition.

## 7.3 Quantitative evaluation of chronic stroke patients undergoing tDCS combined with wrist robotic training

The experimental study presented in this Section aims at evaluating the effects of robot-aided wrist training coupled with tDCS on chronic stroke patients. The hypothesis to test is if a training regimen over six weeks can lead to a significant improvement in motor functions. The study has a twofold purpose:

- To propose a novel strategy that can lead to long lasting improvements in motor function of stroke patients, i.e. tDCS coupled with robotic motor training;
- To test if this strategy can be more effective than robotic training alone in promoting motor recovery.

Patient's recovery evaluation is performed through common clinical scales, parameters of cortical excitability and quantitative indicators of motor performance extracted by a multimodal interface.

### 7.3.1 Study design

The experimental study is a double-blind, randomized study in which a total number of 24 chronic stroke patients have been enrolled. Patients are randomized into three groups; all groups receive wrist motor therapy with the InMotion3-Wrist robot (Section 2.3, Figure 2.4b), but they can receive real or sham tDCS, according to the following randomization:

- Group A - Robotic training with InMotion3 and simultaneous tDCS real, followed by tDCS sham
- Group B - Robotic training with InMotion3 and simultaneous tDCS sham, followed by tDCS real;
- Group C - Robotic training with InMotion3 and simultaneous tDCS sham, followed by tDCS sham.

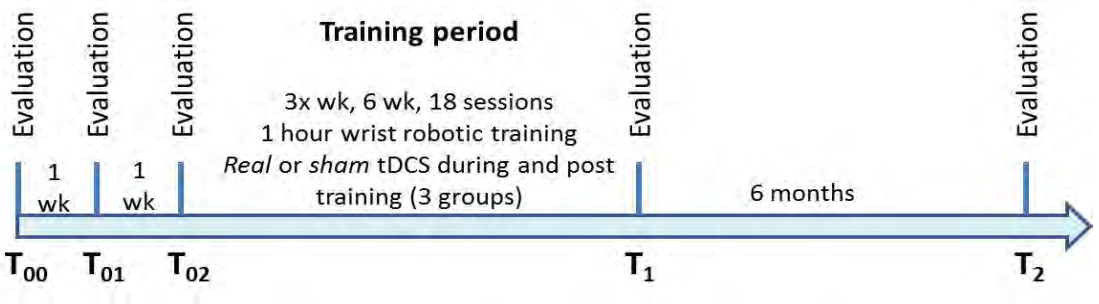


FIGURE 7.10: Graphical representation of the experimental protocol timetable with the evaluation and training phases

Real tDCS is delivered at 1mA for 20 min, while sham tDCS is fictitiously delivered in three steps: 1mA for 30 seconds, 0mA for 19 min and 1mA for 30 seconds. The experimental protocol timetable is shown in Figure 7.10. After patient recruitment, according to the inclusion criteria described in Section 7.3.2 the evaluation phase is carried out three times ($T_{00}$, $T_{01}$ and $T_{02}$), separated by one week, to ensure reliability and stability of measures. The evaluation phase consists of:

- Clinical measures,
- Robot-aided evaluation at InMotion2-Shoulder/Elbow robot (Section 2.3, Figure 2.4a) and InMotion3-Wrist robot and computation of the selected performance indicators through the multimodal interface (Section 7.3.5).

Then, eighteen 1-hour sessions of robotic therapy are administered to the patients three times a week, in alternate days. Finally, the evaluation phase is repeated twice: at the end of the training phase ($T_1$) and after six months ($T_{2\text{-follow up}}$).

### 7.3.2 Subject's recruitment

Patients are recruited on the basis of the following inclusion criteria:

- First single focal unilateral lesion with diagnosis verified by brain imaging (MRI or CT scans), occurred at least 6 months prior;
- Cognitive functions sufficient to understand the experiment and follow instructions, i.e. Mini-Mental Status Examination (see below) of 22 or higher;

- Fugl-Meyer assessment 7 to 36 out of 66 (neither hemiplegic nor fully recovered motor function in the muscles of the shoulder, elbow and wrist);
- Acceptance of the informed consent to participate in the study.

On the other hand, the following criteria have been applied to exclude patients:

- A fixed contraction deformity in the affected limb;
- A complete and total flaccid paralysis of all shoulder and elbow motor performance;
- A hemorrhagic stroke;
- Psychoactive medications, such as stimulants, antidepressants, and antipsychotic medications;
- Additional potential tDCS (or TMS - Transcranial Magnetic Stimulation) risk factors:
  - Damaged skin at the site of stimulation,
  - Presence of an electrically, magnetically or mechanically activated implant (including cardiac pacemaker),
  - Metal in any part of the body (jewels must be removed during stimulation),
  - A history of medication-resistant epilepsy in the family,
  - Past history of seizures or unexplained periods of loss of consciousness.

### 7.3.3 Transcranial Direct Current Stimulation and robotic devices

tDCS is delivered through surface rubber-carbon electrodes (area: 35cm$^2$), equipped with saline soaked sponges (0.9%NaCl), driven by a battery of a constant current stimulator (Figure 7.1). As anticipated, real tDCS consists of 20 min stimulation, with the anode placed over the site for flexor carpi radialis and cathode on the contralateral motor area.
The robots employed for the study are the InMotion3-Wrist robot (Figure 7.11a)

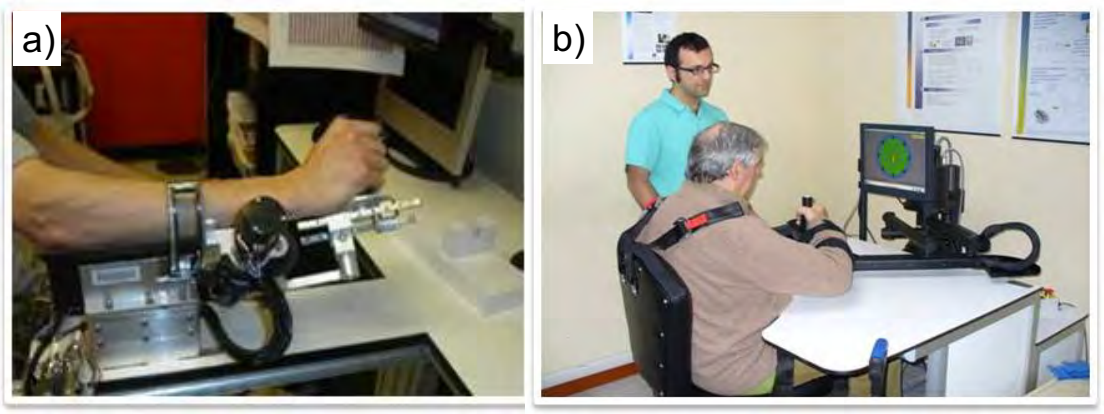


FIGURE 7.11: InMotion 3 wrist robotic training and InMotion 2 for shoulder/elbow training

and InMotion2-Shoulder/Elbow robot (Figure 7.11b) designed to move patient wrist-forearm and shoulder-elbow, respectively, as already explained in Section 2.3 of Chapter 2.

During the treatment the patient seats in a chair, grasping the robot handle and performing a series of point-to-point movements shown on a video screen: motion targets and a cursor tracking patient hand movement are displayed. A single training session consists of different motor tasks during which the robot can either assist, guide or oppose patient motion, according to the planned treatment.

A key feature of the InMotion robots is the low, near isotropic inertia and the reduced friction; the force required to move the robotic arms, in fact, is minimal, compared to moving unrestricted.

The InMotion3-Wrist robot is conceived to train three upper-limb joint angles, i.e. pronation-supination of the forearm, ulnar-radial deviation of the hand and flexion/extension of the hand. In the study here presented, the wrist robot is used in both the training phase and the evaluation phase. The InMotion2-Shoulder/Elbow robot is conceived for proximal training, as it moves shoulder and elbow joints. In the study here presented, this robot is employed only in the evaluation phase for therapy outcome measures.

### 7.3.4 Clinical evaluation

During the evaluation phase at $T_{00}$, patient medical history, personal and anthropometric data are registered. The clinical evaluation includes i) the administration of clinical scales for the evaluation of motor impairment and ii) the applications

of specific magnetic stimulation protocols for the assessment of excitability and plasticity of M1. The following clinical scales are used for motor impairment quantification:

- Mini-Mental Status Examination - It is a brief 30-point questionnaire used to screen for cognitive impairment;
- Fugl-Meyer Assessment Upper Extremity (FMA-UE) - It evaluates upper limb motor impairment through five sub-scales (i.e. Motor, Balance, Sensation, Joint Range of Motion and Pain);
- Motor Power scale (MP) - It evaluates tone and power of upper-limb muscles;
- Modified Ashworth Scale (MAS) - It assesses spasticity by feeling the resistance of the muscles to passive lengthening;
- Nine Hole Peg Test - It evaluates the fine manual dexterity.

Regarding the assessment of excitability and plasticity of M1 specific TMS protocols are employed by neurologists for the evaluation of the functional modifications in motor cortex. Stimulation is delivered through the Magstim 200 (from Magstim), while the position of the TMS coil is controlled by a neuronavigation system.
At the same time, two types of electrical recordings are performed: (i) the EMG activity of hand muscles, (ii) a 32-channels EEG recording, for the assessment of the modifications produced by TMS stimulations on cerebral activity.
Some neurological parameters have been extracted:

- Motor Evoked Potentials (MEP) - They are used to evaluate the basic ipsi and contralesional excitability of M1 after a focal stimulation of the cortical area relative to hand motor control;
- Short Interval Cortical Inhibition (SICI) and Intracortical Facilitation (ICF) - They are used to evaluate intracortical inhibition and facilitation processes.

Finally, in order to evaluate motor cortex response to neuroplastic phenomena, the same neurological parameters are measured after conditioning the lesioned motor cortex through a repetitive stimulation protocol (rTMS) with facilitatory function.

In Figure 7.12 is reported a panoramic of the pilot study including the clinical scales and the performance indicators employed for the quantitative assessment through the multimodal interface.

| **Protocol therapy** | **N** | **Diagnosis** | **Age (Mean±SD)** | **Time postroke** | **Description of intervention** | **Kinematic indicators** | **EMG and neurologic indicators** | **Clinical scales** |
|---|---|---|---|---|---|---|---|---|
| Anodal/ Sham tDCS + Wrist RT (InMotion3) | 2 Groups: 3 patients for each group | Chronic Ischemic stroke | Group A: 60.3 ± 4.1 years Group B: 63.6 ± 5.8 years | > 6 months | Group A – RT coupled with anodal tDCS real (1 mA for 20'), followed by tDCS sham (1mA for 30", 0mA for 19' and 1mA for 30"); 18 sessions (3 per weeks)<br><br>Group B – RT coupled with sham tDCS (1mA for 30", 0mA for 19' and 1mA for 30") followed by sham tDCS (1mA for 30", 0mA for 19' and 1mA for 30"); 18 sessions (3 per weeks) | Cartesian space: f, nMD AREA, SM MAPR, DRV SR, MD, PL, $w_1$ Joint Space: -qcorr$_{i,j}$ | RMS, PS, CCI, MF, FI. MEP, SICI, ICF | FMS, MAS, MP, NHPT, MMSE |

FIGURE 7.12: Overview of the pilot study: tDCS =Transcranial Direct Current Stimulation; RT = Robotic Training; MEP= Motor Evoked Potential; SICI=Short Interval Cortical Inhibition; ICF= Intra Cortical Facilitation; FMS= Fugl-Meyer Score; MP=Motor Power; NHPT= Nine-Hole Peg Test; MMSE= Mini Mental State Examination; MAS= Modified Ashworth Scale; SD= standard deviation; PS= Power Spectrum; RMS= Root Mean Square; CCI= Co-Contraction Index; MF= Median Frequency; FI= Fatigue Index; $\phi$ = Aiming Angle; nMD= normalized Mean Deviation; AREA= area between desired and actual trajectory; SM= Speed Metric; MAPR= Mean Arrest Period Ratio; DRV= Deviation from Ratio between Velocities; SR= Success Rate; MD= Movement Duration; PL= Path Length; $w_1$= Manipulability Index; $q_{corr\ i,j}$= Inter joint coordination

### 7.3.5 Quantitative robotic assessment

A quantitative evaluation of the motor performance of the patients recruited in the experimental study has been carried using the multimodal interface presented in Section 3.2. To this purpose different signals are acquired:

- Motion data from position sensors of InMotion robots - only data relative to unassisted (i.e. robot motors are switched off) clock games are considered;
- Upper arm radial accelerations from a MTx sensor (Xsens) placed on the patient arm - they are used for reconstructing the upper-limb kinematics [134];

- Electromyographyc signals from two couples of antagonist muscles of the upper-limb i) Pectoral muscle and Deltoid muscle (involved in shoulder flexion and extension, respectively) and ii) Biceps muscle and Triceps muscle (responsible of elbow flexion and extension, respectively).

Synchronization between signals is guaranteed through a purposely generated square wave sent from the robot controller to both the EMG acquisition board and the acquisition software of the MTx sensor.
Once processed, data are ready for the extraction of the performance indicators. The selected indicators are the same already employed in Chapter 6, Section 6.2.4 with the addition of some kinematic indicators and some EMG indicators. The additional indicators are listed in the following:

- Manipulability Index ($w_1$) - It represents a kinematic indicator in the Cartesian space. It is expected that the volume of the manipulability ellipsoid of the upper-limb increases as the global hand capacity of velocity generation improves;
- Inter-joint coordination ($q_{corr\ i,j}$) - It is a kinematic indicator in the joint space. It is expected to increase as the coordination between patient upper-limb joint angles improves. The following couples of adjacent joint angles are here considered:
  a) shoulder abduction/adduction and elbow flexion/extension ($q_{corr\ 1,4}$),
  b) shoulder flexion/extension and elbow flexion/extension ($q_{corr\ 2,4}$),
  c) wrist abduction/adduction and wrist flexion/extension ($q_{corr\ 6,7}$),
- EMG indicators:
  - Root Mean Square value (RMS) - It is expected to increase with recovery since patient muscular force increases;
  - Power Spectrum (PS) - As patient recovers, his/her muscular power is expected to increase
  - Co-Contraction Index (CCI) - As patient recovers, it is expected to decrease as the simultaneous activation of antagonist muscles crossing a joint reduces;
  - Median Frequency (MF) - It is expected to increase with patient recovery as his/her muscular force and resistance to fatigue improve;

– Fatigue index (FI) - As patient recovers, his/her fatigue level grows more slowly, so fatigue index is expected to decrease.

### 7.3.6 Preliminary results

Only six patients have completed the whole protocol. Three patients belong to the group underwent real anodal tDCS and wrist robotic training and three patients belong to the sham tDCS group coupled with wrist robotic training, as reported in Figure 7.12.

The analysis of results has shown overall improvements in FMS for both groups and patients who have received real anodal stimulation+RT obtained higher FMS values than patients who have received sham stimulation+RT; on the other hand, opposite trend between the two groups has been observed in MP scores (Figure 7.13).

EMG and kinematic indices followed the expected trend (Figures 7.13-7.14), and higher (even if very moderate) improvements have been retrieved in real tDCS group with respect to control group.

Notwithstanding these preliminary results were in line with FMS scores trend, no statistical analysis could be conducted between experimental (real tDCS+RT) and control group (sham tDCS+RT) since the number of the involved patients is still too narrow for a thorough discussion of the results.

Moreover, a correlation analysis between the computed set of performance indicators and the obtained clinical scores cannot be applied in the current status due to the very small number of patients that have completed the experimental protocol.

| **Clinical scale scores** | **FMS (SD)** | | | **MP (SD)** | |
|---|---|---|---|---|---|
| Baseline | Group A Real: 28.0 ± 5.7<br>Group B Sham: 17.3 ± 2.8 | | | Group A Real: 45.3 ± 7.6<br>Group B Sham: 40.0 ± 7.8 | |
| Post treatment | Group A Real: 35.3 ± 7.7<br>Group B Sham: 18.7 ± 2.3 | | | Group A Real: 48.0 ± 6.3<br>Group B Sham: 43.0 ± 8.7 | |
| | | | | | |
| **EMG indicators (DEL, PECT, TRIC, BIC muscles)** | **RMS [mV] (SD)** | **PS [mV²/Hz] (SD)** | **CCI (SD)** | **MF[Hz] (SD)** | **FI [Hz/s] (SD)** |
| Expected trend | ↑ | ↑ | ↓ | ↑ | ↓ |
| Baseline | Group A: 0.7±0.5<br>Group B: 0.5±0.2 | Group A: (1.4±0.2)*10$^{-6}$<br>Group B: (7.0±3.0)*10$^{-7}$ | Group A: 0.7±0.4<br>Group B: 0.4±0.3 | Group A: 196.0±27.0<br>Group B: 247.0±9.0 | Group A: -0.07±0.05<br>Group B: -0.09±0.07 |
| Post treatment | Group A: 3.0±1.0<br>Group B: 0.6±0.2 | Group A: (4.0±2.0)*10$^{-5}$<br>Group B: (2.0±1.0)*10$^{-5}$ | Group A: 0.4±0.2<br>Group B: 0.4±0.3 | Group A: 231.0±18.0<br>Group B: 238.0±27.0 | Group A: 0.06±0.01<br>Group B: -0.14±0.09 |

FIGURE 7.13: Summary of the preliminary results of the pilot study: Clinical scale scores and EMG indicators.
TMS= Transcranial Magnetic Stimulation; FMS= Fugl-Meyer Score; MP=Motor Power; SD= standard deviation; PS= Power Spectrum; RMS= Root Mean Square; CCI= Co-Contraction Index; MF= Median Frequency; FI= Fatigue Index; DEL= deltoid; PECT= pectorals; TRIC= triceps brachii; BIC= biceps brachii;

| **TMS parameter** | **RMT-UH [% of MSO]** | **MEP-UH [uV]** | **SICI-UH [% of test MEP]** |
|---|---|---|---|
| Expected trend | ↑ | ↓ | ↓ |
| Group A (Real) | | - | |
| Baseline | 59.7±13.4 | 474±408 | 74.0±21.2 |
| Post-treatment | 62.3±15.3 | 268±129 | 13.0±18.4 |
| Group B (Sham) | | | |
| Baseline | 67.3±20.0 | 177±153 | 35.3±14.2 |
| Post-treatment | 66.0±19.1 | 348±129 | 4.7±4.5 |

| **Kinematic indicators** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Expected trend** | ↓ | ↓ | ↓ | ↑ | ↓ | ↓ | ↑ | ↓ | ↓ | ↑ | ↑ | ↑ | ↑ |
| Group A (Real) | $\phi$ (SD) | nMD (SD) | AREA [m²] (SD) | SM (SD) | MAPR (SD) | DRV (SD) | SR(SD) | MD[s] (SD) | PL (SD) | $\omega_1$ (SD) | $q_{corr1,4}$ (SD) | $q_{corr2,4}$ (SD) | $q_{corr6,7}$ (SD) |
| Baseline | 0.16±0.02 | 0.44±0.05 | 0.10±0.02 | 0.46±0.02 | 0.08±0.02 | 0.50±0.09 | 0.98±0.01 | 3.06±0.40 | 0.73±0.09 | 0.034±0.007 | 0.78±0.03 | 0.67±0.04 | 0.53±0.04 |
| Post treatment | 0.13±0.03 | 0.39±0.07 | 0.07±0.01 | 0.49±0.03 | 0.06±0.01 | 0.42±0.08 | 1±0 | 2.48±0.20 | 0.78±0.09 | 0.035±0.006 | 0.81±0.01 | 0.70±0.01 | 0.75±0.02 |
| Group B (Sham) | $\phi$ (SD) | nMD (SD) | AREA[m²] (SD) | SM (SD) | MAPR (SD) | DRV (SD) | SR (SD) | MD[s] (SD) | PL (SD) | $\omega_1$ (SD) | $q_{corr1,4}$ (SD) | $q_{corr2,4}$ (SD) | $q_{corr6,7}$ (SD) |
| Baseline | 0.5±0.2 | 0.56±0.09 | 0.7±0.5 | 0.4±0.1 | 0.19±0.15 | 1.9±1.5 | 0.5±0.3 | 6.0±1.0 | 0.4±0.2 | 0.028±0.003 | 0.72±0.03 | 0.53±0.20 | 0.60±0.10 |
| Post treatment | 0.4±0.2 | 0.5±0.1 | 0.5±0.4 | 0.4±0.1 | 0.18±0.2 | 1.8±1.5 | 0.6±0.4 | 5.0±1.7 | 0.58±0.08 | 0.029±0.002 | 0.80±0.04 | 0.67±0.04 | 0.70±0.10 |

FIGURE 7.14: Summary of the preliminary results of the pilot study: neurophysiological parameters and kinematics indices
TMS= Transcranial Magnetic Stimulation; MEP= Motor Evoked Potential; SICI=Short Interval Cortical Inhibition; ICF= Intra Cortical Facilitation; SD= standard deviation; $\alpha$ = Aiming Angle; nMD= normalized Mean Deviation; AREA= area between desired and actual trajectory; SM= Speed Metric; MAPR= Mean Arrest Period Ratio; DRV= Deviation from Ratio between Velocities; SR= Success Rate; MD= Movement Duration; PL= Path Length; $w_1$= Manipulability Index; $q_{corr\ i,j}$= Inter joint coordination

## 7.4 Achievements and future challenges

The current literature analysis has shown that brain electrical stimulation such as tDCS does not seem to produce a significant improvement in upper limb motor and functional control of post-stroke patients when used together with robotic practice.
It is clear that the very limited number of studies and the variety of methods and tools employed make difficult to compare and provide a clear analysis of the results. Among the possible influence factors, four have been identified as responsible of the large results' variety.

- Several types of intervention and treatment intensity;
- Not unique primary outcome;
- Different type of stroke and patient's lesion;
- Different robotic treatment (wrist and/or shoulder elbow district).

All these factors together contributed to the lack of a standardised intervention protocol about the combined use of tDCS and robot-aided therapy. In fact, from the current studies and despite the aforementioned differences, it seems that there is no evidence of benefits deriving from the coupled use of RT with brain electrical stimulation, in terms of both clinical outcomes and quantitative performance indicators. Nevertheless, despite these limitations, each of the reported studies shows some encouraging findings which would deserve to be investigated by means of large randomized controlled trials with standardized treatment protocols:

- A single session of anodal tDCS during bilateral RT on subacute stroke patients lead to significant improvements in FMS (Hesse et al., 2007);
- Delivering tDCS before RT seems to induce more benefit rather than during or after RT in terms of kinematic performance [185];
- tDCS may enhance the averaged accuracy of classifying the MI of the stroke-affected upper limb [188].
- Combined with RT, cathodal stimulation of the contralateral hemisphere could yield higher effects with respect to anodal tDCS stimulation of the affected hemisphere [186];

- Slight clinical effects of anodal tDCS plus exoskeletal robotic treatment are found in subacute versus chronic stroke patients [181];
- Bilateral tDCS and proximal upper limb RT seem to be more effective in chronic patients with subcortical lesions [183]
- Delivering excitatory tDCS before PNS and RT may enhance the functional outcomes of chronic stroke patients more than applying tDCS after PNS and before RT [187].

Finally, the preliminary pilot study proposed in Section 7.3 has employed a multimodal interface to quantitatively evaluate the effect of anodal tDCS and wrist RT compared to wrist RT alone. Robotic measurements have been used to compute performance indicators that contributed to the quantitative assessment of the proposed therapy, in addition to clinical scales. Results reported in subsection 7.3.6 show higher pre-post intervention improvements in FMS for real tDCS group as well as in all the other outcomes.
In details, the analysis of the computed performance indicators showed that:

- The performance indicators followed the expected trend (as shown at the bottom of Figure 7.13) showing slightly general improvements in post treatment with respect to baseline;
- Improvements of biomechanical and EMG indicators are slightly higher with respect to baseline in patients who received 20 min of real tDCS during wrist robotic practice (Figure 7.14).
- FMS scores do not seem to show an in-line trend with respect to studies analysed in Section 7.2; in fact, pre/post FMS scores in real group are higher than those of sham group (Figure 7.13).

These findings could be explained as a consequence of the non-homogeneous FMS scores of the recruited groups at baseline; even more, the small number of patients does not allow extracting general considerations.
However, kinematic, EMG and neurophysiological parameters of cortical excitability are in-line with the observed trend of FMS. In particular, TMS parameters of cortical excitability has shown a trend at the follow-up that might reflect plastic changes coherent with the interhemispheric inhibitory competition hypothesis, as

indicated by a reduction of cortical excitability of the unaffected hemisphere (as expressed by increased motor threshold, reduced MEP amplitude and reduced intracortical inhibition).

No evaluation can be made about the excitability of the affected hemisphere in this small sample of patients. In fact, the stimulated cortical area was not excitable in most of them at the baseline evaluation and remained not excitable at the follow-up. As previous mentioned, all the studies are based on the inter-hemispheric inhibitory competition model. The rationale behind this approach might not be valid in all conditions for all patients.

A recent study suggests a possible alternative approach of neuromodulation based on the inhibition of the ipsilesional motor cortex as a way to foster motor learning through mechanisms of "homeostatic" plasticity [171].

Furthermore, the bimodal balance-recovery model proposed in [167] asserts that the influence of inter-hemispheric balancing on functional recovery depends on the structural reserve spared by the lesion. All these sources of variability, including lesion location and size as well as impaired connectivity, suggest the development of a patient-tailored approach.

In this context, a multimodal pre-therapy diagnosis could be envisaged, involving the clinical history of the patient, time elapsed after the stroke, topography of the lesion, and type and severity of functional impairment [167]. In future studies, a more individually tailored approach is then required to choose the best approach of tDCS (excitatory and/or inhibitory) and the best possible target (ipsilesional or contralesional hemisphere). Moreover, such studies will help to refine the bimodal balance-recovery model and test whether the efficacy of individualized NIBS therapy combined with robotic therapy might result superior to the current methods. Finally, it is expected that such a patient-tailored approach together with technology advancements in robotic devices may lead to obtain better improvements in motor and functional recovery. As previously mentioned in Chapter 6, the application of electrical brain stimulation can have the double role of stimulating the cortical activity and contribute to the extraction of several neurophysiological indicators (e.g. motor evoked potentials of the muscles involved in the rehabilitative task) that represent the neurophysiological state of the patient which can be included into the bio-cooperative general system proposed in Chapter 3, Fig. 3.1.

# Chapter 8

# Conclusions

The incidence of stroke as one of the worldwide primary causes of mortality has pushed the scientific community to develop new techniques for maximizing therapeutic effects of rehabilitation. The concept of *human-in-the-loop* has gained crucial importance in the neurorehabilitation scenario. Recent advancements in next-generation interfaces able to combine recording and stimulating capabilities in so-called closed-loop devices have shown the potential to further extend neuroelectronic augmentation of injured motor circuits [10].

In this perspective, multimodal interfaces represent an effective way to actively exploit the concept of *human-in-the-loop*; in fact, they are characterized by the simultaneous use of multiple human sensory modalities that can be employed to control complex systems grounded on patient's needs. Such an aspect becomes a key element into the rehabilitation process.

Bio-cooperative systems portray a type of multimodal interfaces since they gather multimodal sensorial information coming from human and environmental factors. Recently, they have been widely employed for administering robot-aided therapy to stroke subjects represents a real innovation into the scientific field. They represent the new generation of robotic platforms that promote a bidirectional interaction between the robot and the patient based on multimodal interfaces.

On the other hand, the recent developments in non-invasive brain stimulation techniques and the concurrent technological improvement of robotic devices has suggested to combine such techniques to further enhance brain plasticity as well as motor and functional recovery of post-stroke subjects. In addition, neurophysiological indicators of brain activity can also be recorded throughout such techniques thus enriching the concept of multimodal interface.

This thesis has examined the application of multimodal interfaces for upper limb robot-aided neurorehabilitation. These strategies have shown the potential to increase and maximize the therapeutic effects in post-stroke treatments and can be grouped into:

1. Design criteria of bio-cooperative systems for upper limb robot-aided therapy,
2. Neuromodulation techniques in upper limb robot-aided neurorehabilitation.

Regarding the first item, an attempt to develop new systems for enhancing post stroke rehabilitation is discussed in Chapter 3.
An overview and a new definition of bio-cooperative systems are provided by integrating new techniques such as Brain Computer Interfaces, augmented sensory feedback and analysis of contextual factors. They offer the real challenge to depict a complete picture of the user and apply this picture to real-time shape the therapy on the user's features.
However, they will need larger clinical studies in order to prove their potential; this represents the real keystone to assess the efficiency of bio-cooperative approach in rehabilitation robotics.
The bio-cooperative approach has been applied to a particular robotic platform for delivering 3D upper limb post stroke treatment. The platform has been integrated with a novel mechatronic arm-gravity support system grounded on a cable-pulley approach. In fact, stroke patients using end-effector machine in rehabilitation context often present lack in arm self-sustaining.
Particularity of this support system is its capability to provide the required assistance in 3D space by controlling a motor to reel in or else unroll the cable according to the patient's limb configuration.
Future activities will be the validation of the final system on healthy and post stroke subjects aimed to the definition of continuous functions (instead of discrete approach) for modulating robot control parameters.
In Chapter 4 the design of modular telerehabilitation architecture, grounded on a bio-cooperative robotic system valid for unilateral upper limb robotic therapy is presented. The architecture has been validated on the CBM-Motus planar robot; an adaptive control strategy grounded on kinematic performance indicators has been implemented on CBM-Motus during execution of state-of-the-art rehabilitative tasks.

Results of the experimental validation carried out on healthy subjects have shown the following aspects:

- Functioning and reliability of system's modularity;
- Capability of the adaptive control system to correctly evaluate subject movements computing the kinematic performance indicators;
- The implemented controller is able to enhance the user's performance driving him/her towards the target, with a level of assistance that is tuned on his/her motor abilities;
- The proposed telerehabilitation architecture is able to send data and compute performance indicators in a safe and reliable way;
- Potential use of the proposed telerehabilitation system in a clinical scenario.

Performance indicators have been offline computed being a preliminary experimental phase. Obvious extension of the proposed modular architecture will be the calculation of the performance indicators and the update of robot control parameters in a real-time environment.
Furthermore, future developments will require the design of in-home telerehabilitation programmes on post-stroke subjects in order to enhance patients' independence and encourage a faster recovery.
The analysis of the first item is completed in Chapter 5 by the description of a new modular software architecture for a multimodal interface. This multimodal interface comprises several subsystems interacting each other with the final goal to assist a disabled subject to perform common ADLs with the help of an upper limb robotic exoskeleton.
The modular communication architecture has been developed in the YARP environment and tested on healthy subjects performing drinking tasks. The results have shown the feasibility and reliability of the system regarding intersystems communication as well as the capability of the exoskeleton to guide the subject accomplishing the required task.
In the same Chapter the design of a mechanical flange able to guarantee integration among upper arm exoskeletons and hand rehabilitation devices is proposed. Principal characteristic of the proposed flange is the possibility to be extended to different robotic exoskeletons (e.g. the one mentioned in the first part of Chapter

5). In particular, the integration between a hand module and an upper arm 7 DoF robotic exoskeleton by means of the mechanical flange has been explained. The development of the mechanical flange, the novel hand module and its integration into the ARMin robot have lead to achieve the following points:

- Fast set-up for therapist and patient;
- Capability to perform hand functional movements;
- Integrate hand and arm therapy with a unique device.

Future activities will be the development of dedicated control strategies for the hand module and the integration of these strategies into the ARMin control system.
The second module has been addressed in the last two chapters. In Chapter 6 a multimodal interface is applied for studying the effects of continuous Theta Burst Stimulation (cTBS) combined with shoulder/elbow robotic therapy in a clinical study with seventeen severely impaired chronic stroke patients, randomised into an experimental (real cTBS) and control (sham cTBS) group.
In addition, a quantitative assessment of the patient's recovery has been performed by means of dedicated kinematic indicators derived by robot's measurements. The results show that non-invasive brain stimulation delivered as cTBS of the affected hemisphere to promote homeostatic metaplasticity, seems to be not effective in patients with severe deficits.
On the other hand, the study confirms that robot-assisted rehabilitative treatment produces a slight improvement years after a stroke and it also shows, for the first time, that an improvement can be obtained even in patients with severe upper-limb impairment treated daily for only ten working days.
Future studies should be more focused on the identification of those subgroups of patients that most likely will respond to a particular intervention.
In Chapter 7 the multimodal interface is employed to quantitatively assess the outcomes of a pilot study that investigates the effects of combining robotic therapy and non-invasive electrical brain stimulation such as tDCS.
In addition, the current trends on the combined use of tDCS and robotic therapy are introduced in the first part of the Chapter. The literature analysis shows that the combined approach might produce slight improvement in motor and functional recovery when different aspects are taken into account separately. However, due to

the restricted number of studies, their heterogeneity and the lack of a standardized method is difficult to draw firm conclusions.
On the other hand, results of the pilot study carried out at University Campus Bio-Medico of Rome suggest slightly general improvements of the combined treatment. This improvements are confirmed both by clinical scales outcomes and by performance indicators analysis.
Finally, all the sources of variability, including lesion locations and size as well as impaired connectivity, suggest the development of a patient-tailored approach. To this purpose, future larger clinical trials will be needed in order to prove or disprove the efficacy of the combined approach.
In conclusion, the application of multimodal interfaces, conveniently enriched by recent technology advancements in bio-cooperative systems and novel neuromodulation approaches has confirmed that put the human actively in the loop may represent the future of robot-aided neurorehabilitation.
On the basis of the results presented in this thesis, future works will be focused on the design and development of a complex innovative robotic platform that will be able to deliver post stroke neurorehabilitation as well as perform robotic assessment of the recovery process.
The future platform will employ a larger multimodal interface including different multisensorial information based on human as well as context and environmental characteristics. All these aspects may represent the key element for designing a real-effective therapy tailored to the specific needs of each single patient.

# List of Publications

## Published

### International peer-reviewed journals

Simonetti, D., Zollo, L., Vollero, L., Iannello, G. and Guglielmelli, E., 2017. A modular telerehabilitation architecture for upper limb robotic therapy. Advances in Mechanical Engineering, 9(2), p.1687814016687252.

Simonetti, D., Zollo, L., Papaleo, E., Carpino, G. and Guglielmelli, E., 2016. Multimodal adaptive interfaces for 3D robot-mediated upper limb neuro-rehabilitation: An overview of bio-cooperative systems. Robotics and Autonomous Systems, Volume 85, Pages 62-72, ISSN 0921-8890.

Di Lazzaro, V., Capone, F., Di Pino, G., Pellegrino, G., Florio, L., Zollo, L., Simonetti, D., Ranieri, F., Brunelli, N., Corbetto, M. and Miccinilli, S., 2016. Combining Robotic Training and Non-Invasive Brain Stimulation in Severe Upper Limb-Impaired Chronic Stroke Patients. Frontiers in neuroscience, 10.

### Peer-reviewed national and international conference proceedings

Simonetti, D., Zollo, L., Vollero, L., Iannello, G., and Guglielmelli, E., 2016. A Modular Architecture for Remote Robotic Rehabilitation. Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the. IEEE, 2016. 1 page paper.

Simonetti, D., Zollo, L., Vollero, L., Iannello, G., and Guglielmelli, E., 2016. A Modular Telerehabilitation Architecture for Upper-limb Robotic Therapy. V Congress Gruppo Nazionale di Bioingegneria. GNB2016, June 20th-22nd 2016, Naples, Italy.

# In Review

## International peer-reviewed journals

Simonetti, D., Zollo, L., Milighetti, S., Miccinilli, S., Bravi, M., Ranieri, F., Magrone, G., Guglielmelli, E., Di Lazzaro, V. and Sterzi, S., 2017. Literature review on the effects of tDCS coupled with robotic therapy in post stroke upper limb rehabilitation. Frontiers in Human Neuroscience.

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