DOTTORATO DI RICERCA IN INGEGNERIA
DELL'ELETTRONICA BIOMEDICA, DELLE
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# "Development of techniques and algorithms for the functional evaluation and assistance in the movements of the upper limb"

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*Thanks to my mentors, my family*

*and my friends…*

# Index

## Sommario

L’evoluzione della medicina nei secoli scorsi ha portato ad un costante aumento dell’aspettativa di vita nelle popolazioni delle nazioni sviluppate. Il miglioramento degli standard di igiene e della pratica clinica ha reso meno pericolose per la vita dell’uomo la maggior parte delle operazioni cliniche e molte malattie considerate ad alta mortalità fino al secolo scorso. Ma mentre l’aumento dell’aspettativa di vita e’ sicuramente un obbiettivo importante per la medicina moderna, il suo raggiungimento ha portato al sorgere di due domande fondamentali: la prima e’ come mantenere uno standard di qualità di vita accettabile durante gli anni “extra”, la seconda e’ se le strutture ed i sistemi sanitari delle nazioni sviluppate possono permettersi i costi all’aumento dell’età media della popolazione.

Da questo punto di vista l’attenzione e’ stata quindi rivolta a quelle affezioni correlate all’età anagrafica, quali per esempio il morbo di Parkinson o l’ictus. Molte di queste malattie colpiscono il paziente degradandone progressivamente le capacità motorie, e limitandone notevolmente la qualità della vita. Inoltre, superato l’evento acuto, questo tipo di malattie non risultano di fatto pericoli immediate per la vita del paziente ed i costi legati alla malattia sono destinati ad aumentare con l’aumentare dell’età del paziente stesso. Nella maggior parte dei casi non esistono reali possibilità di cura per questo genere di patologie, ma è comunque possibile migliorare le funzionalità del paziente anche grazie alla disponibilità di tecnologie per l’assistenza.

Il morbo di Parkinson, in particolare, è una, se non la più frequente, patologia legata all’età. Attualmente ne è affetto circa lo 0.3% della popolazione dei paesi industrializzati, con percentuali fino al 4% per la fascia d’età dagli 80 anni in su.

Questa malattia colpisce, tra le altre cose, le funzioni motorie dei pazienti ed i sintomi motori del morbo di Parkinson rappresentano la principale causa di disabilità dei pazienti. Questi sintomi sono normalmente:

- Tremore muscolare (movimento involontario oscillatorio dei muscoli)
- Bradicinesia (lentezza dei movimenti)
- Rigidità muscolare
- Discinesie ed acinesie
- Mancanza di equilibrio

Inoltre circa il 70-90% dei pazienti presenta disabilità legare alla produzione vocale quali disfonia ed ipofonia che sono normalmente considerate come effetti secondari dei sintomi motori primari precedentemente elencati. In particolare gli effetti di tremore, rigidità e bradicinesia sui muscoli della laringe, del viso e del tronco, che causano una limitata apertura vocale, una respirazione non ottimale ed una ridotta articolazione delle parole, sono generalmente considerati come la causa principale della disfonia dei malati di Parkinson.

La terapia nel morbo di Parkinson è prevalentemente farmacologica con l'obiettivo di aumentare o surrogare la produzione di dopamina, e consiste nella somministrazione del precursore biosintetico levodopa, oppure in quella di altri farmaci in grado di attivare i recettori della dopamina.

Genericamente la terapia farmacologica riduce significativamente la gravità dei sintomi motori nei primi 2-5 anni dalla diagnosi della malattia (periodo chiamato "levodopa honeymoon"), ma la maggior parte dei paziente tende a sviluppare complicazioni motorie come effetto secondario di questo tipo di trattamento.

Queste complicazioni consistono nella perdita momentanea di efficacia della terapia stessa, soprattutto verso la fine del tempo di dosaggio ed in discinesie, ovvero in improvvisi movimenti involontari anche complessi. Queste complicazioni vengono generalmente chiamate fluttuazioni motorie.

Nei casi peggiori, ovvero quando gli effetti collaterali della terapia farmacologica cominciano a diventare troppo invalidanti per il paziente, si è soliti ricorrere alla terapia chirurgica. Un tipico approccio è basato sulla generazione, da parte del chirurgo, di piccole lesioni nell'area subcorticale (nel caso del globo pallido questa tecnica viene chiamata pallidotomia, mentre altre aree normalmente soggette al lesionamento chirurgico possono essere il talamo ed il nucleo subtalamico). Una soluzione molto più comune si basa invece sull'impianto di uno stimolatore elettrico e di un set di elettrodi (2 o 4 a seconda dell'area) nel talamo o nel nucleo subtalamico e questa tecnica viene generalmente chiamata Deep Brain Stimulation. Questo tipo di stimolazione (i valori di tensione utilizzati sono generalmente al di sotto dei 3 V, con frequenze che vanno dai 60 ai 130 Hz) ha l'effetto di alleviare molto i sintomi motori primari (in particolare il tremore) e di permettere quindi la progressiva riduzione della terapia farmacologica, alleviando quindi gli effetti negativi da essa causati. Tuttavia l'estrema invasività della procedura rende sconsigliabile questo tipo di intervento in pazienti in età avanzata. Inoltre gli effetti collaterali causati da una impostazione non ottimale dei parametri di stimolazione (che possono includere allucinazioni e influssi negativi sull'umore del paziente) rendono questo tipo di intervento non praticabile in pazienti con problemi neuropsichiatrici.

Un altro tipo di intervento possibile è quello offerto da dispositivi per l'assistenza indossabili, che vanno ad agire sui sintomi e non sulla causa fisiologica del disordine motorio. Un esempio da questo punto di vista è rappresentato dall'esoscheletro sviluppato nel progetto DRIFTS, che grazie all'utilizzo di due motori alle giunture del gomito e del polso e ad una rete di sensori inerziali per il riconoscimento del tremore, è in grado di contrastare lo stesso sia attivamente (ovvero agendo in controfase ad esso) sia passivamente (ovvero aumentando il carico all'articolazione applicando una piccola forza resistente sui motori). In questo contesto si inserisce anche il progetto europeo TREMOR (in collaborazione con il

quale parte del lavoro di questa tesi è stato svolto), che prevede lo sviluppo di un dispositivo in grado di bloccare il tremor sull'arto superiore attraverso stimolazione elettrica funzionale (FES) dei muscoli dell'arto superiore.

E' anche di fondamentale importanza, nei pazienti affetti da Parkinson, riuscire a valutare correttamente l'evolvere della gravità dei sintomi nel tempo e durante la giornata, soprattutto per pazienti negli stadi finali della malattia e affetti da fluttuazioni motorie. Attualmente il controllo delle fluttuazioni motorie viene effettuato dal medico curante durante le visite di routine ed è principalmente basato sulla valutazione dei cambiamenti nel punteggio UPDRS (Unified Parkinson's Rating Scale, che e' un test standardizzato nel quale al paziente viene chiesto di effettuare dei test di routine ai quali il medico assegna un voto relative alla gravità dei sintomi durante il test) del paziente durante una serie di screening effettuati durante il ciclo di medicazioni e su domande poste al paziente stesso al fine di verificare la percentuale percepita di momenti OFF durante la giornata. L'esito di questa valutazione può portare al cambiamento (in termini di medicinale e di dosaggio) del trattamento farmacologico del paziente.

I difetti di questo tipo di approccio sono essenzialmente legati:

1) alla soggettività intra-operatore dell'analisi basata sullo score UPDRS
2) alla soggettività dell'analisi quantitativa delle tempistiche ON-OFF fornita dal paziente
3) ai costi oggettivi legati alla valutazione in ambiente clinico del paziente, che oltretutto tendono a limitare la frequenza dell'analisi.

In questo contesto quindi, la sfida tecnologica è rappresentata dallo sviluppo di strumenti affidabili per l'analisi quantitativa delle fluttuazioni motorie dei pazienti Parkinsoniani al fine di semplificare l'ausilio clinico, ridurre i costi e, in generale, permettere un intervento più tempestivo e frequente sulla terapia del paziente al fine di limitarne i sintomi invalidanti e migliorare la qualità della vita dei pazienti. Molti studi negli ultimi anni  sono stati focalizzati sull'applicazione di tecniche di data

mining a caratteristiche derivate da grandi dataset di dati cinematici dei pazienti, acquisiti tramite sensori indossabili. E' stato dimostrato come le caratteristiche descriventi la cinematica dei pazienti durante test standardizzati siano altamente correlate con gli score UPDRS dei pazienti stessi, e di come sia possibile ricavare gli score stessi a partire dalle sole caratteristiche. In particolare, i sensori inerziali risultano essere molto utili per il tracking della gravità di sintomi quali tremore, bradichinesia, discinesia e achinesia. Le caratteristiche di rigidità muscolare del paziente, dovute alla malattia, sono invece difficilmente inseguibile tramite l'utilizzo dei soli sensori inerziali.

Lo sviluppo di soluzioni che possano aiutare i pazienti malati di Parkinson, sia durante le attività di tutti i giorni, sia nello spettro più ampio della valutazione sul medio e lungo periodo della loro terapia può quindi rappresentare un valore aggiunto per i pazienti stessi (per esempio lo sviluppo di dispositive in grado di fermare I sintomi motori possono permettere una diminuzione della terapia farmacologica e quindi una diminuzione dei problemi ad essa annessi) e può aiutare a diminuire I costi della terapia (per esempio permettendo visite di routine più frequenti direttamente da casa del paziente).

Lo sviluppo di questo tipo di soluzioni in ambito bioingegneristico, si basa sui seguenti tre step:

- Estrazione di informazioni da misure relative al paziente, che in questo caso possono essere misure relative alla qualità e alle caratteristiche dei suoi movimenti o misure relative alla gravità attuale dei suoi sintomi.

- Integrazione dell'informazione, tramite modelli o metodi in grado di trasformare le informazioni precedentemente ottenute in una più fruibile, sia, per esempio, per il sistema di controllo di uno strumento, o anche per i clinici, nel valutare lo stato del paziente.

- Intervento vero e proprio, che può essere il comandare un sistema in grado di bloccare un sintomo o sfruttare informazione sullo stato del paziente per modificarne la terapia.

In questo lavoro di tesi sono stati sviluppati vari metodi e soluzioni volti allo sviluppo di strumenti per l'assistenza atti alla limitazione del tremore sull'arto superiore. Il focus principale e' stato quello di sviluppare nuovi algoritmi in grado di fornire informazioni utili ed in real-time sui movimenti dei pazienti e modelli in grado di sfruttare questo tipo di informazione in maniera attiva per il controllo del tremore sull'arto superiore.

Nel primo capitolo di questo lavoro di tesi introduce il contesto fisiologico. Vi è dapprima descritta brevemente l'anatomia dell'arto superiore, e a seguire quindi viene illustrata una estesa descrizione della letteratura riguardante i modelli computazionali per il controllo motorio dell'arto superiore. Le principali teorie in letteratura riguardanti il controllo motorio dell'arto superiore sono state studiate e classificate. Le teorie del controllo motorio studiano i meccanismi fisiologici di base che si occupano del controllo dei movimenti (nel caso in esame, dei movimenti dell'arto superiore). Data la complessità di questi meccanismi, è molto difficile, se non impossibile, darne una rappresentazione tramite un approccio algoritmico tradizionale, dove l'evoluzione e il processing delle informazioni atte alla pianificazione ed esecuzione del movimento devono essere sempre chiaramente definite in ogni passaggio. Un'interessante alternativa alle tecniche tradizionali è fornita dalle cosiddette tecniche di "Soft-Computing", nelle quali, piuttosto che definire precisamente ogni parametro del modello da replicare, l'attenzione viene spostata verso la comprensione dei meccanismi fondamentali che ne regolano il comportamento, al fine di costruire relazioni ingresso/uscita basate sulla struttura del fenomeno stesso. Nella teoria del controllo motorio, un modello biologicamente

ispirato è un sistema artificiale capace di imitare le proprietà funzionali di un sistema biologico reale rispetto ai seguenti quattro criteri: 1) Architettura; 2) Apprendimento (inteso come l'acquisizione di abilità motorie); 3) Esecuzione del movimento; 4) Adattività in ambienti dinamici. Le Reti Neurali Artificiali possono essere considerate come l'approccio Soft-Computing più biologicamente ispirato tra quelli offerti in letteratura, grazie alla loro capacità di imitare il comportamento delle Reti Neuronali Biologiche in termini di architettura, acquisizione delle competenze e processing dell'informazione in tempo reale. Lo studio della letteratura ha permesso di classificare i lavori presentati secondo i quattro criteri precedente illustrati, e cioè raggruppando gli studi proposti sulla base della capacità di imitare i sistemi biologici atti alla generazione ed esecuzione del movimento in termini di: architettura, apprendimento, esecuzione del movimento ed adattività all'ambiente di lavoro. Questo studio della letteratura ha permesso di incrementare la comprensione delle problematiche proprie della progettazione di sistemi di controllo intelligenti. A tal fine sono stati anche analizzati alcuni lavori in letteratura in cui sono presenti applicazioni cliniche basate su sistemi di controllo biologicamente ispirati. Infine in questo capitolo viene presentato il contesto pato-fisiologico del morbo di Parkinson's, le principali terapie ed i problemi ad esse correlati.

Il secondo capitolo è stato dedicato alla descrizione delle principali soluzioni nello sviluppo di dispositivi per il controllo del tremore nell'arto superiore. Sono state descritte le due principali strategie per il controllo esterno del tremore nell'arto superiore:

- La strategia attiva, in cui si induce sull'articolazione un movimento oscillatorio in controfase rispetto al tremore stesso per limitarne l'effetto. In questo tipo di strategia si effettua di fatto un filtraggio notch sulle frequenze del tremore.

- La strategia semi-attiva, in cui le caratteristiche biomeccaniche dell'articolazione vengono modificate (in particolare si aumenta la rigidità dell'articolazione stessa) per modificare l'impedenza del braccio e bloccare il tremore. In questo tipo di strategia si effettua un filtraggio passa basso con frequenza di taglio che esclude le frequenze principali del tremore.

Sono state quindi illustrati alcuni dispositivi e metodi sviluppati in letteratura per la limitazione del tremore dell'arto superiore. E' stato descritto un esoscheletro attuato da motori (progetto DRIFT) in grado di riconoscere e limitare il tremore utilizzando sia la strategia attiva che la strategia semi-attiva ed è stato descritto il contesto di limitazione del tremore tramite stimolazione elettrica funzionale dei muscoli dell'arto superiore (progetto TREMOR). Nella parte finale del capitolo è stata infine presentata l'implementazione di un controllore basato su reti neurali artificiali in grado di guidare un sistema di stimolazione elettrica funzionale per la limitazione del tremore dell'arto superiore tramite una strategia semi-attiva. Il sistema di controllo proposto consta di tre blocchi principali:

- Un modello biomeccanico dell'arto superiore, rappresentante la dinamica diretta per i movimenti planari dell'arto superiore, in grado di trasformare i pattern di attivazione muscolare in movimento
- Una cosiddetta "Noise-Box" in grado di generare i pattern di attivazione muscolare relativi ad un movimento affetto da tremore
- Un controllore, in grado di stabilire le attivazioni opportune per limitare il tremore a partire dalle attivazioni muscolari del movimento tremoroso

I risultati ottenuti tramite questo modello di controllore in un contesto simulativo sono quindi stati descritti.

Nel terzo capitolo della tesi descrive il processo di sviluppo di un modello biomeccanico 3D dell'arto superiore da utilizzare come piattaforma di simulazione per lo sviluppo di strumentazione per l'assistenza di disabilitàdell'arto superiore. Tale modello è costituito da un modello scheletrico, in grado di imitare fedelmente le proprietà cinematiche dell'arto superiore, al quale è sovrapposto un modello muscolare. Il modello completo è in grado di simulare i movimenti dell'arto superiore dati in ingresso i pattern di attivazione muscolare ed è completamente modificabile sulle caratteristiche peculiari dei singoli pazienti. Le problematiche progettuali associate allo sviluppo di questo modello sono relative a:

- Scelta del numero di gradi di libertà del modello scheletrico
- Scelta del numero di muscoli da inserire nel modello
- Scelta del modello muscolare adatto alla simulazione del comportamento del singolo muscolo
- Scelta dell'ambiente di sviluppo

Il modello qui sviluppato è stato progettato in modo da simulare fedelmente i gradi di libertà relativi alle articolazioni del gomito (flesso-estensione e prono-supinazione) e del polso (flesso-estensione e add-abduzione). Inoltre, per rendere più realistici i movimenti simulati, sono stati inseriti nel modello anche tre gradi di libertà relativi all'articolazione della spalla (rotazione, flesso-estensione e ab-adduzione), ottenendo così un modello scheletrico a 7 gradi di libertà. Inoltre il modello risultante presenta 12 muscoli costruiti utilizzando una versione modificata del modello muscolare di Hill, che rappresenta il golden standard della letteratura. L'ambiente di sviluppo scelto per la realizzazione del modello è Simulink di Matlab.

Il quarto capitolo descrive una serie di algoritmi per l'estrazione delle caratteristiche dei movimenti tramite l'analisi dei segnali EEG, sEMG ed IMU. Viene descritto inizialmente un algoritmo real-time per la rivelazione degli istanti di attivazione muscolare tramite l'analisi del segnale sEMG di superficie. Questo

algoritmo è di fatto un'implementazione innovativa dell'algoritmo statistico doppia soglia di Bonato e colleghi che rappresenta il golden standard in letteratura. In questa nuova implementazione tale algoritmo è stato reso in grado di operare in real-time ed indipendentemente dal rapporto segnale rumore (SNR) del segnale sEMG.

Vengono quindi descritti una serie di algoritmi per la classificazione dei movimenti volontari ed involontari dell'arto superiore. Questo tipo di informazione è di fondamentale importanza nello sviluppo di dispositivi per la limitazione di movimenti involontari dell'arto superiore quali il tremore. La corretta individuazione di movimenti volontari ed involontari permette la corretta limitazione della componente involontaria senza compromettere l'attività volontaria. Sono stati esplorati due approcci diversi per la valutazione della volontarietà del movimento dell'arto superiore, basati sull'analisi dei segnali EEG ed EMG:

- Coerenza cortico-muscolare
- Event Related Desynchronization Detection (ERD)

La coerenza è un parametro utilizzato per stimare l'accoppiamento lineare tra due segnali nel dominio della frequenza ed è definita come il rapporto tra il quadrato del cross-spettro dei due segnali ed il prodotto dei due auto-spettri. Per coerenza cortico-muscolare si intende la coerenza tra il segnale EEG acquisito nell'area corticale ed il segnale sEMG rettificato. Tale grandezza fornisce un indice della sincronizzazione delle unità motorie a varie frequenze attraverso diverse vie discendenti. Tra gli agenti oscillatori in grado di sincronizzare le unità motorie nell'uomo, quelli in banda beta (15 – 30 Hz) sono solitamente associati all'attività muscolare volontaria durante contrazioni sub-massimali. E' stato quindi realizzato un algoritmo per la stima in real-time della coerenza cortico-muscolare basato su una modellazione Auto-Regressiva dei segnali sotto analisi. In questo approccio, i segnali EEG ed sEMG, opportunamente filtrati, sono modellati tramite un modello Auto-Regressivo Bivariato. Tale approccio, teoricamente applicabile ad una

qualsiasi coppia di segnali, permette di stimare il campione corrente di un segnale sulla base dei campioni passati del segnale stesso e dei campioni passati dell'altro segnale sotto osservazione. La coerenza può essere stimata dai parametri di questo modello auto regressivo in un approccio tempo frequenza. E' stato quindi sviluppato un algoritmo di rivelazione dei contributi coerenza in banda beta ed a tali contributi sono stati associati componenti volontarie del movimento. Risultati ottenuti tramite questo algoritmo su segnali acquisiti da pazienti affetti da morbo di Parkinson sono stati riportati.

Il secondo fenomeno studiato è stato quello della Event Related Desynchronization e Resynchronization (ERD/ERS). Con ERD/ERS si intendono due fenomeni fisiologici legati alla preparazione, all'immaginazione ed all'esecuzione del movimento volontario. Questi due fenomeni consistono, in termini generali, nella diminuzione (desincronizzazione) della potenza nella banda alfa (8-13 Hz) del segnale EEG acquisito nell'area corticale durante la preparazione, l'immaginazione e l'esecuzione di movimenti volontari seguito da un aumento (risincronizzazione) della potenza del segnale nella sopraccitata banda alla fine dell'esecuzione del movimento. Tali variazioni di potenza fanno riferimento ad un potenziale di "riposo" registrato durante l'assenza di movimento. Questo fenomeno può essere considerato causato dalla diminuzione (o dall'aumento durante la risincronizzazione) della sincronia della popolazione neuronale sottostante l'area corticale. La desincronizzazione del segnale EEG è particolarmente visibile in sottobande della banda alfa (8-13 Hz), mentre la risincronizzazione ha contributi maggiori in sottobande della banda beta (15-30 Hz). Sono stati sviluppati una serie di algoritmi in grado di riconoscere i pattern di desincronizzazione e risincronizzazione dal segnale EEG, da solo o rinforzando tale informazione utilizzando caratteristiche estratte dal segnale sEMG o IMU. Sono stati riportati infine risultati ottenuti con questi algoritmi su segnali acquisiti da pazienti affetti da morbo di Parkinson.

L’ultimo capitolo è stato incentrato sullo studio e l’applicazioni di tecnologie basate su sensori indossabili per la valutazione funzionale delle disabilità legate al Morbo di Parkinson. Lo scopo è quello di sviluppare sistemi in grado di permettere uno screening della gravità attuale dei sintomi dei pazienti tramite segnali estratti da sistemi indossabili. Questo tipo di sistemi può essere molto utile nella corretta determinazione dei parametri della terapia del paziente e può aiutare a ridurre i costi legati alla terapia stessa. E’ stato in particolare realizzato e descritto un protocollo per uno studio sulla stima della rigidità muscolare dei pazienti parkinsoniani tramite l’uso di segnali vocali. In questo studio caratteristiche estratte dai segnali vocali dei pazienti vengono modellate tramite tecniche di data mining per ottenere una stima del grado di rigidità muscolare del paziente, partendo dal presupposto fisiologico che la rigidità muscolare modifica sensibilmente le caratteristiche vocali dei pazienti malati di Parkinson. Alcuni risultati preliminari su questo studio vengono infine riportati.

Nell’ultima parte della tesi vengono infine presentate le conclusioni generali di questo lavoro e ne viene illustrato il contributo complessivo nel contesto dello sviluppo di tecniche ed algoritmi per l’ausilio e la valutazione funzionale dei movimenti dell’arto superiore.

# *ABSTRACT*

*This thesis describes some novel techniques and algorithms for the functional evaluation and assistance in the movements of the upper limb.*

*In this context and with particular focus on Parkinson's disease, the framework of the development of innovative solutions is here described and new proposals are presented. Different methods for gathering and exploiting information measured from the patients are deeply investigated and described in this thesis.*

*The main theories and computational models of the motor control of the upper limb are here described and classified depending on their characteristics, in terms of biologically inspired design. This classification helped getting a better understanding of the upper limb control mechanisms for the intelligent design of complementary control systems for assistive devices.*

*The principal findings and some novel approaches in the development of devices for tremor suppression in the upper limb are described and this knowledge is used for the development of a original neural-based control architecture able to limit tremor in the arm using Functional Electrical Stimulation (FES). The importance of models as benchmark platform for the development of assistive devices is highlighted and the principal steps for the development of a biomechanical 3D model of the upper limb as simulative tool for the design of tremor intervention strategies are addressed.*

*Some novel algorithms for the extraction of information on movements are developed and presented. Information about movement timing is extracted in real-time through the analysis of the surface electromyographic signal (sEMG), independently from the level of the noise affecting the signal. Algorithms for the classification in real-time between voluntary and involuntary movements from electroencephalographic and movement-related signal are described and applied to signals extracted from healthy and impaired persons.*

*Finally, a novel approach on the assessment of muscular rigidity through the analysis of voice signals is presented, in the framework of the design of wearable sensors-based solutions for the evaluation of the symptoms of patients affected by Parkinson's disease.*

# Introduction

The evolution of medicine in the past few centuries, together with the spread of the technological era, brought to a steady increase of life expectancy in the population of developed countries. Increase of hygiene standards and methods for clinical practice allows now a high surviving rate for most of surgery intervention. Also the development of vaccines, antibiotics and the overall increase in pharmacological treatment understanding and efficacy allowed to overcome epidemic events and to address as easily curable diseases that have been considered highly life threatening only one century ago. Thus the focus of modern medicine in occidental countries has been, in the last century, to raise life expectancy of the population by counteracting the danger of sudden disease or accident-related adverse events.

However, even though prolonging life is certainly an important goal, its progressive reaching addressed two fundamental questions. The first one is how to maintain an acceptable quality of life in the extra years. The second one, intrinsically related to the first one, is whether and how the healthcare systems, in developed countries, can try to reduce costs related to the ageing of the population, and thus whether and how society can really afford the costs related to the ageing of the population.

Quality of life in elderly people, beside chronic affections, is a concept strictly related to their ability to move and go on performing normal activity of daily living and maintain themselves independent and functioning. The ageing of the population has brought to the attention the rising number of people affected by degenerative disorders, such as Parkinson's disease (PD) [1], or acute events, such as stroke [2], that have negative effects on patient's motor capacities. These disorders, beside non life-threatening per-se (after the acute event, such as for stroke survivors), lead to a

progressive degeneration of the motor abilities of the patients and, in turn, to an overall worsening of their health condition over time. Also, the costs related to clinical care and routine screenings for this kind of disorders tend to increase together with the ageing and number of patients. In fact, it has been estimated, for example, that costs associated to treatment for a PD patient can rise from about 5.000 dollars per year after the diagnosis up to 100.000 dollar per year in late stage of the disease (estimative made by the America *National Institute of Neurological Disorders and Stroke (NINDS),* reported by the Michael Stern PD Research Foundation [3]).

For these reasons, the goal in rehabilitation research has been dedicated, in the past two decades, to the development of assistive technologies focused on reducing the impact of motor disabilities in patients.

This broad goal can be achieved in many different ways, as, for example, developing assistive wearable devices able to help the subjects in their activities of daily living [4] [5], or designing new methods and technologies in order to to improve the rehabilitative therapies of the patients [6] [7], or also developing techniques aiming at simplifying evaluation and routine clinical care practices for these patients [8] [9]. It is out of doubt that all these kind of assistive technologies can have a great impact on both the quality of life of the patients and the associated costs that, both the patients and the healthcare systems have to share for the treatments.

Many examples of this kind of technologies have been described in the literature in the past few years. A number of interesting works have been presented describing novel assistive or rehabilitative methods for improving mobility of the lower limbs [10] [11] [12] or actively detect motor events, such as falls, to which elderly people and motor impaired patients are more prone [13][14].

Relatively to the upper limb, disabilities introduced by degenerative disorders, as the motor symptoms related to Parkinson's disease (such as tremor, bradykinesia and muscular rigidity [15] [16]), or stroke-related impairments in acute events survivors, can deeply affect the capacity of one patient to perform independently simple tasks (e.g. dressing up, driving or preparing meal). These inabilities can mine the overall quality of life of the patients and put them in the situation of needing continuous assistance in everyday life. For this reason, also in the case of upper limb disabilities the proposal of methods and the design of devices for the functional assistance and the assessment have increased in the past years. Most of the new proposed solutions are focused on the enhancement of the rehabilitative practice [7] and on the improvement of the overall mobility of the patients [4] [5].

Since now, many interesting questions on how to cope with motor impairments caused by degenerative disorders have been posed, and some interesting solutions have been presented. Beside the fact that no technique or device in this topic has reached the status of standard in clinical practice so far (although some of the solution presented before, like the MIT manus [7] or the Lokomat [10], have become, in time, useful and assessed research tools), the interest in this area of research remains very high. The reason for that has to be found in the potential impact that these technologies may have, also taking into account that the ageing of population phenomenon is only supposed to grow. Thus the design of subject-based effective technologies for the treatment (in assistive, rehabilitative or screening frameworks) of motor impaired subjects can affect deeply, beside quality of life, the costs related to the increasing number of patients, by limiting and facilitating intervention and follow up procedures.

This thesis's work has been devoted to the development of methods and techniques for the assistance and functional evaluation of movements of the upper limb. The attention has been focused on the development of novel rehabilitative and

classification tools for subjects affected by degenerative disorders, such as Parkinson's disease, mining the proper functioning of the upper limb.

The development of this kind of solution deeply relies on the ability to extract and exploit information on patient's behavior and actual state in the intervention procedure. Ideally this process can be divided, according to a bioengineering approach, in the following steps:

- Gathering of information that is extracting relevant characteristics of patient's current state from measures extracted from the patient itself or his surrounding environment.
- Integration of information, that is building a model-based solution able to project the gathered information into a more reliable and effective one or into a command signal for an assistive device.
- Delivery of assistance, by means of active intervention on patient's actual state through an assistive device or just the effective use of the new information in patient's therapy.

This general approach can be used in either the development of assistive or rehabilitative devices or in the design of therapy-enhancing solutions. As an example of the device-development framework, the European project TREMOR [17], with whom part of the work presented in this thesis has been carried out will be presented as a possible example of novel rehabilitative device for the upper limb. This project has been devoted at the design of a novel device able to track and reduce tremor of the upper limb in patients affected by different causing pathologies. Tremor reduction is performed by means of Functional Electrical Stimulation (FES) [18] of the muscles involved in the movement of the trembling joints. The device's control system has been designed in order to be adaptive and self-learning, and has been based on a multimodal Brain Computer Interface (or Brain-Controlled Interface, that

brings to the same acronym BCI) [19] framework. The device designed in this project can be seen as the example of assistive device for the upper limb and its development followed the three general steps previously presented. The aims of this device are the following:

- detecting the movement intent of the patient, characterizing tremor and separating its effect from voluntary movement (gathering of information) through contemporary analysis of electroencephalographic (EEG), electromyographic (surface EMG) and kinematic signals;
- selecting the most correct intervention strategy given the actual information (integration of information).
- demote Tremor by means of the most appropriate FES pattern (delivery of assistance)

In this thesis, algorithms for extracting information about characteristics of movement of tremor-affected patients will be presented, as example of solutions in the gathering of information phase of a device development. Also the importance of modeling solutions, both in the overall planning of an intervention scheme and in a translational step of the gathered information will be extensively described.

Finally, in the last part of this thesis, this designing approach will be also used for the development of novel methods for the functional evaluation of disabilities of the upper limb. An innovative solution aiming at tracking motor symptoms (with a particular interest on muscular rigidity) of Parkinson's patients by means of the analysis of the characteristics of their voice will be described. In this final part the relations between changes in voice production and motor impairments in PD patients will be described and a new data mining approach for the classification and prediction of severity of motor symptoms from features extracted from the voice of the patients will be presented.

## Thesis Overview

The first chapter describes the physiology of the upper limb and presents a review of the State of the Art relative to computational models for motor control of the upper limb, with a particular interest on biologically inspired models. Also an overview of Parkinson's disease as example of one of the main age-related disorder that can lead to impaired functioning of the arm, and the way in which these disorders affect the motor control of the upper limb will be presented.

The second chapter is specifically devoted to the description of the design of assistive devices for tremor suppression in the upper limb. The background and overall framework of this particular field will be presented, describing existing proposed solutions and novel implementations such as the one developed in the TREMOR project. Also a conceptual example of a biologically inspired model for the tremor control of the upper limb by means of Artificial Neural Networks and Functional Electrical Stimulation will be described.

The third chapter will describe the design process of a biomechanical 3D model of the upper limb that will be used as a simulative tool in the development of assistive devices for the upper limb. All the steps and issues related to the selection of the muscles (and muscular models) and of the proper number of degrees of freedom (DoFs) will be discussed.

The fourth chapter will describe a series of algorithms for the extraction of characteristics of movements such as movement timing and intent by means of the analysis of EMG, EEG and kinematics related signals. Results of the application of these algorithms on healthy subjects and patients affected by tremor will be also reported.

In chapter five the framework of wearable sensor based technologies for the functional evaluation of the motor symptoms of the Parkinson's disease will be described. Also a proposal for a new protocol aiming at the estimation of the severity of muscular rigidity of patients by means of the analysis of the characteristics of their voice will be described.

The last chapter will draw general conclusions on this thesis work.

# Chapter 1

# Physiological and Clinical Background

## 1.1 The Human upper limb

One characteristic that mainly differentiate humans with respect of the majority of all the other mammals is their ability to manipulate objects and interact efficiently with the environment that surrounds them. This is achieved thanks to the precision and adaptability of the human upper limb, which is a result of the evolutionary path that led humans to become bipedal. In the moment in which our far ancestors stopped using their upper limb for locomotion, evolution led to the optimization of the hand, no longer needed as walking aid, for precise manipulative tasks, the final result being the opposable thumb. Hand specialization led also to modification of the whole upper limb and on a refining of the way in which the human brain is able to control it, in order to obtain the precision needed for the human complex manipulative tasks.

The human upper limb is that part of the body from the deltoid region to the hand, comprising also the shoulder. It is often referred to as human arm, beside the fact that the term arm only indicates the part of the limb that goes from the shoulder to the elbow joint. It is then common usage for the term arm to indicate the whole limb, while upper arm, beside the redundancy of the term, is usually used to indicate the shoulder-elbow region.

The upper limb is a highly redundant part of the body that can achieve an amazing number of positions and movements, thanks to its 26 Degrees of Freedom (DoFs) and more than 50 muscles acting on and in it. This high redundancy makes the process of understanding the way in which the brain controls the human arm particularly though. It is well known for example that the trajectory formation during ballistic planar movements is pretty consistent, and that all human-produced movements of this kind share characteristic features, such as bell-shaped hand

velocity profiles. It is then interesting to understand why, among the infinite combination of joint postures and trajectories that the brain can produce to achieve a certain movement, the picked trajectories have these common characteristics. This behavior is a result of the complex coordination among muscles, limbs and neural circuitry that humans achieve through learning in the first phases of their life.

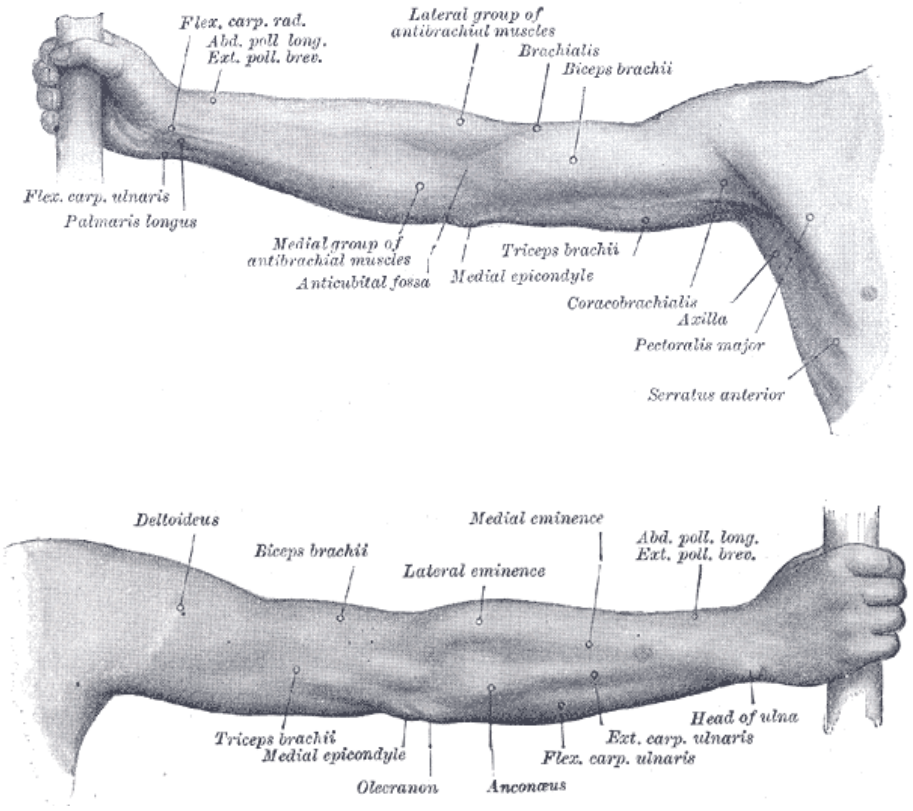



**Figure 1. Front and back depicture of the human upper limb from Gray's Anatomy [20]**

A deeper understanding on the way the brain controls the movements of the upper limb can be an useful piece of information in many fields such as robotics (for the development of biomimetic mechatronical applications), ergonomics (for the

development of more consistent human-based solutions) and, of course, rehabilitation. A comprehensive knowledge, in fact, of all the steps needed for the production of an effective movement by the human upper limb can be of great help when dealing with diseases where some of the sub cited steps is malfunctioning of missing.

The field of Neuroscience studying the way in which the human brain plans and allows the body to execute movements is called *Motor Control*. The mechanisms involved in motor control can be briefly classified in:

- Perception, through the senses (sight in primis) and proprioceptive information from the limbs and body (through Golgi tendon organs, muscle spindles and similar proprioceptive structures).

- Motor Planning that takes place from the motor cortex through the cerebellum.

- Motor Execution that translates the motor planning information to motoneural commands delivered by the spinal cortex.

- Feedback, through senses and proprioceptive organs, that helps to evaluate the outcome of the actions and to eventually correct the movement *"on-line"*.

- Biomechanics that is the limb itself.

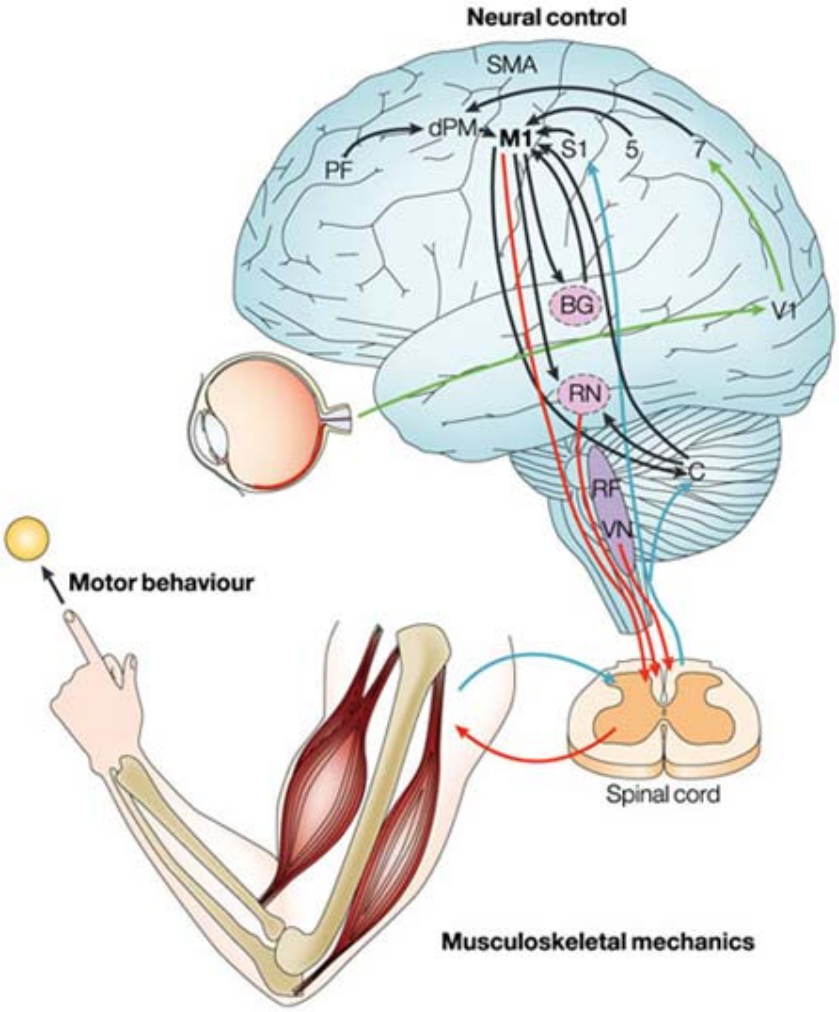



**Figure 2. Motor Control scheme, the integration of all the different mechanisms**.

The actual roles of all these components and the physiological mechanisms related to them have been subject of extensive study in the past five decades.

In the following a review of the principal theories and models for motor control of the upper limb will be presented. Particular attention will be dedicated to works proposing biologically inspired modeling solutions.

## 1.2 State of the art in the study of motor control of the upper limb

In the last years many Neuroscience studies have been focused on investigating the basic physiological mechanisms that the nervous system employs when controlling movements of the upper limb. One of the main issues is to understand as the Central Nervous System (CNS) is able to interact with a complex anatomy in order to achieve the desired movement. In order to do so it is crucial to discover and try to understand the neuronal networks present in the CNS that regulate motor planning and execution. This means to understand how the networks succeed in solving problems of high complexity even if they are composed by units whose single behavior is too simple to explain the acquisition of any competency. To understand how new competencies are learned and adapted to different environments, such as it happens for the motor control of the upper limb, it is necessary to take into account the single units only as part of a bigger entity, from whose structure depends its overall behavior.

In this context, models are an extremely useful tool, and can help to better comprehend the way in which the nervous systems works. In particular, in motor control mechanisms, several neuronal structures (i.e. perceptive, associative, cognitive and motor) are integrated, and computational models have often been used for the study of those singular structures.

It is difficult to represent such a complexity by using a conventional, deterministic, algorithmic approach where the data flow has to be clearly defined in any single instruction. Soft computing techniques [21] offer a viable solution by moving the rationale of the modeling from the mathematic description of a behavior to the understanding of the fundamental mechanisms behind it. Moreover since soft computing methods can achieve statistically varying results, lying in a range of

acceptable solutions, they simulate biological mechanisms in a way that can be considered inspired to real life.

The idea of biologically inspired modeling was used in several works of the motor control literature since the seventies, starting from the well known work proposed by Ito [22]. But what are the parameters that make a model "biologically inspired" with respect to another one that is not considered so?

In motor control theory it can be theorized that a biologically inspired model is an artificial system able to mimic the functional properties of the real biological system with respect to the following four criteria:

1) Architecture

2) Learning behavior (that mean the way in which the model acquire new motor skills)

3) Functioning (in terms of control and execution of movements)

4) Adaptability to different environments (force fields, presence of obstacles, etc.).

If we rely on these four points, Artificial Neural Networks (ANN) should then be considered as the "most biologically inspired" among soft computing approaches. ANNs, in fact, are able to mimic the behavior of biological networks of the CNS with respect to the architecture, the mechanisms of competences acquisition and the real-time processing of the information.

A deeper insight in the different neural typologies can lead to a differentiation between the classic architectures (i.e. Hopfield [23], Multi Layer Perceptron [24]) that are centered on activity levels only and the ones resembling neurophysiologic behavior and including also timing properties such as the Spiking networks [25].

Although there are big differences between different kinds of implementations of ANNs, they all share the same basic principle that is the one of a complex functioning system constituted by extremely simple units that it is able to change its behavior and acquire competencies by modifying the characteristics of the single units. Thus modeling the human motor control mechanisms aims at a clear understanding of the functionality of the motor system, from the learning process to the movement execution.

Also the importance of cognitive capacities has to be taken into account when studying the way in which living organism develop motor control skills, since clearly accuracy and robustness to changing environment and adaptability to altered conditions result from the intrinsic capacity of a biological system to learn from experience, which, in the motor control framework, is its ability to develop a sensorimotor organization model. This is a direct consequence of the neural plasticity which, starting from the birth, allows change at the neuronal and network level and provides refinement of the model during the entire life cycle.

The modeling of these mechanisms can be divided into two main focuses: the first one is the modeling of the kinematics and dynamics of the arm, its main goal being to an optimal simulation of the motor behavior; the second one deals instead with the modeling of higher-level processes and takes into account the relation between the learning and the organization schemes of the movements (i.e. sensorimotor adaptation).

Nevertheless some problems, such as the integration of all the different brain areas that contribute to the computational process of motor skills learning [26] are still far to be clearly disclosed and still under investigation.

In the context of biologically inspired models adaptivity has to be taken into account in the design of the mechanisms for motor control since environmental conditions

and properties of the limbs deeply affect the development of neuromuscular strategies. This phenomenon has been studied experimentally by modifying the environment in several controlled ways, through visual [27] [28] [29] or mechanical distortions [30] [31], stable [32] and unstable [33] interactions produced by haptic interfaces.

Experimental data proved the concept that the CNS is able to compensate dynamically in perturbed and unstable environment. This led to the hypothesis that the CNS may be structured in the so called Internal Models (IM) that basically consist in the feedforward neural mechanisms connecting input and output signal of the sensorimotor system [34].

This appealing theory is based on the concept that IM are nothing less than the keystone upon which the motor control takes shape and dynamically evolves. IM are built and trained and contain information about the mechanical properties of the human body and relate them with both the environment and the subject's experience. From a physiological point of view IM are hypothesized to be structured in the cerebellum [35]. In order to build an efficient IM, two different functions need to be executed by the cerebellum, and they can respectively be associated with the direct internal models (DIM) and the inverse internal models (IIM) [36].

The function of the DIM is to forecast the consequences of an action, from a sensorial output point of view, and assessing the limb future state (i.e. position and velocity) from the knowledge of the actual state and the motor commands to be executed. On the other side the IIM produce the motor commands which modify the state of the end effector(s). This differentiation is main due to these two observations:

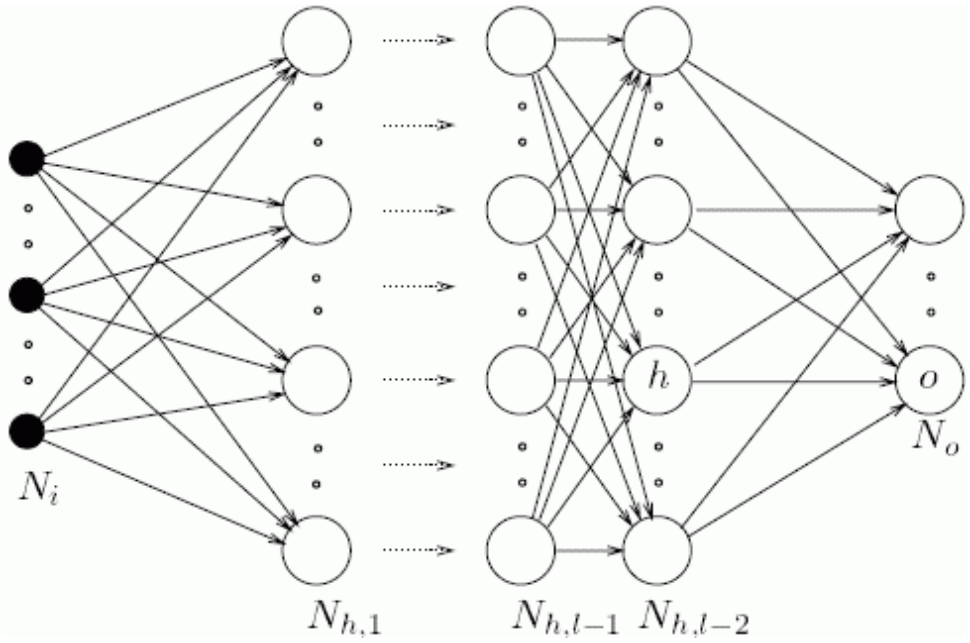
- there is evidence of an anticipative control of the movements

- there is evidence that the central planning before the beginning of the task is connected and followed by corrective processes based on feedback information

The main strategies in control systems are the open-loop (feedforward) and the closed-loop (feedback) control: the former is related to all those systems based on the control of an end-effector without having any information about the state during the control, but on a predetermined sequence of actuator commands; the latter concerns the theories of control in which the information of the state available at any time step modify the flow of the commands in order to correct errors. These two strategies can be easily adapted also to the motor control framework. In this case, the presence of feedforward mechanisms is fundamental since sensorimotor control needs a significant and highly variable amount of time (150–250ms) to elaborate a motor reaction to a sensory feedback stimulus [36]. The ways these feedback and feedforward components of motor control interact has been discussed in several studies and among the possible implementations the ones based on ANN reveal good potentialities.

### 1.2.1 Neural computational models

As it has introduced before, computational models for motor control based on ANN can be considered as biologically inspired with respect to more common deterministic solutions. This derives from the fact that ANN resemble human neuronal structures in architecture, behavior and possible learning paradigms. In fact, neural networks are indeed composed by units connected among them, just as human neuronal networks.



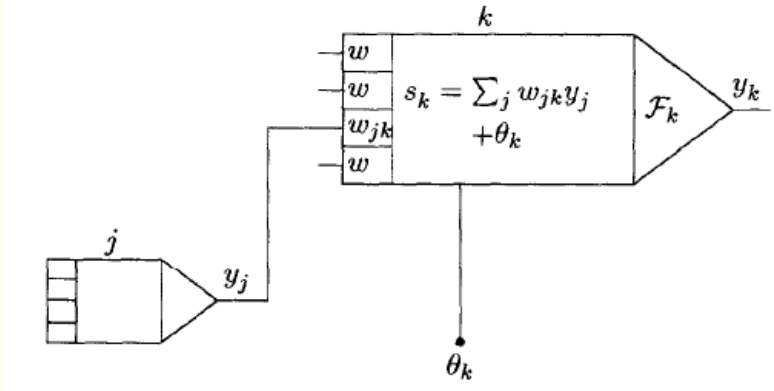




**Figure 3. Top figures shows an example of architecture for a Multi Layer Perceptron Artificial Neural Network; bottom figure shows an example of neuron: the weights *w* are used to change contribution of previous layer outputs and are summed and processed inside the neuron to produce the output *y***

The connections among the single units are weighted and these weights and the architecture of the connections characterize the behavior of the whole neuronal system. Weights and connection are determined and tuned through learning. In the

previous section four main parameters were suggested as main features of biologically inspired models. In the following a classification of the contribution on modeling of motor control presented in literature has been achieved by focusing on which work can be considered as biologically inspired in terms of:

1) Architecture

2) Learning behavior

3) Functioning

4) Adaptivity

Regarding architecture, an example of biologically inspired model in this sense is certainly that proposed by Billard and Mataric [37]. The model consists of a hierarchy of ANN and is composed by modules simulating specific brain regions (i.e. temporal cortex, spinal cord, primary motor cortex, premotor area, cerebellum) involved in visuo-motor learning and control. The learning that is based on an imitation paradigm is addressed to the modules of premotor area and cerebellum, the first one simulating an abstract representation of mirror neurons [38] and the second one allowing to master complex tasks by learning sequences of primitive movements.

Both these modules have been implemented as Dynamical Recurrent Associative Memories (i.e. fully recurrent ANN without hidden units). A Hebbian strategy (that in this case can be resumed as a "the neurons that fire the most have the strongest weights") [39] has been used for learning. This model has been used in simulation, using an 11 DOF human model as end effector, and movements achieved during the testing phase resemble real ones. Integration of sensory information in movement planning has been studied also by Glasius and colleagues in [40]. In this work the issues of trajectory formation and obstacle avoidance are solved using a single

network, built as a two-layers ANN, trained in an unsupervised way. In this model the layers of the networks mimic parts of the brain devoted to motor planning. The first layer represents the sensory map that builds up the activity patterns from sensory information, while the second represents time-evolving motor map, transforming activity patterns into motor commands.

Regarding learning behavior, studies who use ANN to implement IM can be considered as the ones in which learning behavior better resembles that of human motor control. Three main learning paradigms can be defined for ANN: 1) supervised learning: an "external teacher" provides the net with the input-output pairs. The error is used to adapt the synaptic weights; 2) unsupervised learning: the significant features from the input population are self-recognized; 3) reinforcement learning [41]: it is based on the maximization of a reward or a reinforcement parameter, which influences weights modification (increasing the probability of future rewards) and establishes the end of the learning phase. This paradigm in particular is useful when a task can be decomposed into different sub-tasks, whose sequence can influence the overall reward value.

In the work by Kawato and coworkers [42] a computational model for learning and controlling voluntary movements based on Hierarchical ANN is proposed. This scheme uses ANN to implement both a DIM and an IIM: the first provides a feedback signal (regarding the actual state of the end effector) for the training of the second. The IIM is trained by using a feedback error learning algorithm, and provides the motor commands regarding a desired movement when fed by information on the trajectory of the movement in the joints space. A similar approach has been also proposed by Izawa in [43] where an ANN representing the IIM of the upper limb is used as a state predictor in order to stabilize a Reinforcement Learning algorithm for an Actor/Critic ANN controller based on Temporal Difference Learning [41].

Focusing on the upper limb, one of the main purpose in the modeling of motor control systems is biologically inspired functioning, thus the correct imitation of the way in which human move and control their arms. The main problem with the human functioning in upper limb movements is that of the high redundancy of the arm architecture that affects also the movement production. For this reason most biologically inspired model in terms of functioning try to imitate only selected subsets of motor tasks, such as ballistic or planar movements. The works presented in [44] [45] [46] try to mimic the bell-shaped velocity profile of the human movement. Fagg presented in 1997 [44] a heuristic computational model based on ANN that learns simple motor programs in a way similar to that in which infant perform simple reaching strategy, that is bringing an arm to the target and correcting reaching movements. This "trial and error" architecture is able to produce, after some attempts, biologically plausible movements, that are characterized by bell-shaped tangential velocity profiles. Karniel and Inbar [45] proposed a comprehensive neural-based model of the human constituted by a 2 Degrees Of freedom (DOF) manipulator driven by three muscle pairs for the direct dynamic part of the model, and by a control architecture based on ANN generating neural outputs and a pulse generator able to transform the neural outputs into representative motor commands. Also in this case the model is able to provide movements that are consistent with that of the actual human arm, although the working area is restricted to a limited region of the entire workspace and the learning algorithm cannot be considered as properly biologically inspired. Bernabucci [46] proposed a multilayer Perceptron ANN for the representation of an IIM for ballistic planar movements of the upper limb. Movements generated by this controller reproduce the bell-shaped hand velocity profiles.

But while the functioning is a well solved problem, on the other hand, the adaptivity of the models to different environment situations is a far more challenging task.

In the work proposed by Stroeve [47] a multi-layer Perceptron is developed and trained to simulate an IM: a desired task is executed by motor commands which are chosen as adaptively dependent on the working environment. The control is performed by generating signals similar to those extracted from real myoelectric data. The adaptavity of this model has been assessed by comparing real data with the changes in arm impedance of the model to external disturbances. Also in [46] a controller of an upper human arm model has been exposed to altered force environment, showing the adaptation ability environmental modifications such as the insertion of different force fields acting on the end-effector.

All these works pointed out the fact the IIM, together with complete feedforward control schemes, cannot manage sudden changes in the environmental conditions, thus suggesting that a mixed use of forward and inverse models of the dynamics could help solve such a problem.

### 1.2.2 The use of computational models in applications

There are some examples in literature in which computational models for motor control of the upper limb have been moved from the theoretical framework into a more applicative one. These studies aimed at proposing models able to produce acceptable movements in virtual arms. Among the few works successfully applied to real contexts (of these that have been presented so far), the learning and control scheme proposed by Kawato in 1987[42] was used to control an industrial manipulator [48] and the study presented by Glasius [40] was tested to drive both a mechanical manipulator and an artificial arm.

Some works have been using motor control models to drive devices such as Functional Electrical Stimulation (FES) devices that can allow using the actual arm as the end effector, thus canceling some of the problems and limitations brought from the necessity to implement an upper limb simulating model for the testing of the control architecture. Some preliminary attempts to use computational models as FES controllers have been proposed. In this framework, Lan [49] implemented an open-loop controller for a FES muscle stimulator by using a recurrent feedback-feedforward ANN. In this work the net is fed with kinematic information (i.e. desired trends of trajectory and angular velocity) and gives as output both the muscular stiffness and the motor patterns to tune the FES stimulation parameters. The stimulated movements are executed with limited error on the final position of the end-effector, with respect to the desired movement.

Goffredo et al proposed a work [50] presenting the rationale for a novel FES-assisted system devoted to the upper-limb rehabilitation and controlled by a biologically inspired ANN [46] has been presented recently. The system is envisioned as a means to rehabilitate patients affected by hemiplegia: the movement of the paretic upper limb is assisted by an "optimal" stimulation provided by the controller previously trained to associate kinematics to muscular activation patterns. The training is achieved by mimicking the behavior of a set of movements (in terms of the kinematics) executed either by the therapist or by the patient's sound arm in virtual/augmented reality.

These latter works present the idea that computational models for motor control, which are generally developed within theoretical frameworks, can be transferred into applications such as those dealing with rehabilitative devices that is the main focus of this dissertation. In this context, knowing the way in which the brain controls movements of the upper limb can help developing surrogate or complementary control systems in case of "malfunctioning behavior" of the primary

control system. Given the classification previously presented, still no work has been proposed developing a model that can be considered as fully biologically inspired in terms of architecture, learning, functioning and adaptivity, while some partial attempts have been proposed so far.

Assessing the feasibility of the use of soft computing techniques, together with biologically inspired modeling of motor control for the help of control of movements of the upper limb is thus a field still to develop fruitfully.

## 1.3 Motor Disorders

As it has been described in the past paragraph, movement production relies on the contribution of several part of the human body, from the brain, to sensory organs, to the spinal cord and finally to the limb. Neurodegenerative disorders and acute events can disrupt the functioning of one or more of these mechanisms or the flowing of information between the different areas of the body related to movement production.

For example, brain damage caused by ischemic stroke affecting the cerebral cortex may affect movement planning and execution pathways in the motor cortex and cerebellum, thus paralyzing or limiting the functionality of one or more limbs. In PD the motor symptoms are instead caused by the reduced production of dopamine in the brain. Dopamine, among the other things, is responsible in reducing the influence of the indirect pathway while increasing the actions of direct pathway within the basal ganglia. Disruption of the pathway to the motor circuit of the basal ganglia, caused by impaired dopamine level in the system, is the main reason for PD related motor disturbs [15] [16].

In the following a description of causes and pathophysiology of PD, together with a description of the most common intervention strategies will be carried out. This part will serve as an introduction to the description of the development of methods and algorithms for the assistance and functional evaluation of disabilities of the upper limb that will exposed in the next chapters.

### 1.3.1 Parkinson's disease

Parkinson's disease (PD), also referred as primary or idiopathic Parkinsonism, is one of the most common age-related degenerative disorder of the Central Nervous System. It takes its name from James Parkinson, an English physician who first published its detailed description in *An Essay on the Shaking Palsy* in 1817 [1].

It has been estimated that about the 0.3% of the population in developed countries is affected by PD, with a percentage that rises up to 4% for people 80 or older. Taking the United States as example, the overall number of affected subjects is estimated around one million individuals, with about 20 new cases every 100.000 persons every year [16] [51]. In Italy the estimated number of patients is around 200.000 individuals, with about 10.000 new diagnoses every year.

The PD affects particularly the part of the brain structures of the *Basal Ganglia*. The main pathological characteristic of PD is the death of the cells of the *substantia nigra*, with a specific focus in the ventral part of the *pars compacta*. Also, microscopic anatomy of the *substantia nigra* and other brain regions revealed that PD patients show neuronal loss and Lewy bodies in part of the remaining nerve cells. Lewy bodies (that are abnormal aggregates of proteins inside the nerve cells),

are a peculiar characteristic of PD patients. The pathophysiological effects of the death of the cells of the *substantia nigra pars compacta* is the reduced activity of dopamine-secretive cells, that are primarily located in this part of the brain. This leads to a lower level of dopamine in the system that is the cause of the symptoms related to the PD.

PD is considered as a movement disorder, although it often causes also many non-motor dysfunctions such as sensory and sleeps difficulties, impaired cognitive abilities and mood control together with autonomic dysfunctions. Nevertheless the motor symptoms of the PD represent the most disabling effects of the disease. Primary motor symptoms of PD are:

- Tremor, that is an oscillatory involuntary movement in the upper or lower limb. It is the most common motor impairment caused by PD. Usually PD patients show rest tremor that is a kind of tremor that manifests when the patient is not moving, disappearing or diminishing during the execution of voluntary movements. The frequency of rest tremor in PD patients is usually around 4 and 7 Hz.

- Bradykinesia, that is slowness in movements. It is considered associated with problems during the whole motor process, from the planning to the actual execution. It also makes sequential, complex and simultaneous movements difficult to perform for PD patients.

- Rigidity, that is stiffness and passive resistance to movement offered by the patient. It is caused by an increased muscle tone and by continuous contractions of muscles.

- Postural instability, that is typical in late stages of the disease. It is accompained by impaired balance and frequent falls.

A number of other motor symptoms are often present in PD patients, and are labeled as secondary motor symptoms. These symptoms, such as mask-like face, voice disorders, small handwriting, swallowing disturbances and festination, are considered as caused by the primary motor symptoms (e.g. small handwriting is principally caused by bradykinesia in the muscles of the hand and forearm and voice impairments are strongly related to rigidity of the muscles involved in voice production).

Other motor disorders show these kinds of motor symptoms. All the affections characterized by of these symptoms are classified under the name *Parkinsonism* while PD is often referred as primary or idiopathic Parkinsonism, since is not considered to be caused by external causes, although recent researches [52] [53] showed particular genetic patterns in PD patients.

Evaluation of symptoms is performed by clinicians using standardized score on motor tests, as the Unified Parkinson's Disease Rating Scale [54]. During screening visits the patient is asked to perform standard motor tests (such as heel striking, finger to nose, walking, palms pronation supination…) and a score (from 0 to 4) is associated to every item of the test. Also other characteristics, such as speech and cognitive impairments, are analyzed and scored. The UPDRS is used to track the progressing of the disease during screening visits and to thus tune the therapy.

The therapy for PD is mainly pharmacological and its goal is that to augment or surrogate the production of dopamine. The composition of the pharmacological

therapy is mainly based on the biosynthetic dopamine precursor levodopa, or on other active principles able to activate the dopamine receptors [55].

Usually the pharmacological therapy is effective in lowering the gravity of the motor symptoms for the first 2 to 5 years after the beginning of the medicine intake (a period that is generally called *"levodopa honeymoon"*), but most of the patients develop, in time, resistance to the drugs and motor complications as secondary effects of the levodopa treatment [56] [57] [58] [59]. These complications consist mainly in momentary loss of effect of the therapy itself during the medication cycle (a complication often referred to as *"wearing off"*), and dyskinesies, that are sudden involuntary movements. The motor complications caused by the levodopa are generally called *motor fluctuations* [60] [61]. Motor fluctuations and dyskinesies especially, can become in some patients even more invalidating than the therapy itself. Motor fluctuations are difficult to track, since they could change significantly during a single medication cycle. Since is difficult to evaluate motor fluctuations during the screening visits, patients are often asked to keep a diary of their 'off' states during the day.

In the worst cases, when the therapy becomes completely ineffective on the patients or the severity of motor fluctuations become unsustainable, surgical therapy may be needed. Surgery in PD patients usually consists in the generation of small lesions in the sub-cortical area (if this procedure is applied to the *globus pallidus* it is generally referred as pallidotomy [62], while also lesions in the thalamus and subthalamic nucleus may be provoked). Lesions are inducted by using electrical probes to burn and thus create a scar in a selected area. This scar has the effect to reduce the activity in the area in which has been inducted, thus reducing the motor symptoms such as tremor and rigidity. The area in which the probe will be placed and then the scar provoked is selected after accurate analysis of MRI scans of the brain of the patients. This kind of therapy is not indicated for elderly patients and

may have secondary effects, even serious, such as stroke, infections or internal bleeding.

Another solution, based on surgery, is that of the *Deep Brain Stimulation* [63]. In this technique a small electrical stimulator is implanted in the patients. The stimulator has 2 or 4 leads which will be placed either in the thalamus or in the sub-thalamic nucleus. The leads induce a current (through a voltage between 1 and 3 V, at a frequency that can change between 60 and 130 Hz and a pulsewidth of about 100ms) in the area where they are placed, and the electrical stimulator act as a *Pacemaker* for the brain activity in that area [65]. The stimulator alleviates the symptoms of PD, such as tremor and rigidity, allowing the reduction of the medicine intake and reducing the severity of the motor fluctuations [64]. But also in this case, the high invasive nature of the procedure make it unsuitable for elderly patients and severe secondary effects can be present either caused by the surgical procedure (as in the case of the pallidotomy) or by an incorrect setting of the stimulation parameters (such as hallucinations, pain, dyskinesies, mood swings and even suicide attempt). For these reasons patients with neuropsychiatric problems are generally not suitable for this kind of procedure. Little is still known about the way in which the cells of the thalamus and sub-thalamic nucleus are affected by the stimulation [64] [66], and the stimulation parameters are usually selected in a trial and error fashion, with the clinician changing the parameters until he reaches a configuration where the motor complication are minimized and there is no hint of secondary effects [65].

Many studies in literature are focusing on helping the clinician in the selection of the proper parameters for the stimulation [67] [69]. This is necessary since right now the parameters are adjusted during clinical trials depending on the severity of the motor symptoms, but, among the main motor symptoms of PD, only rigidity and tremor respond in real time to the changing of the parameters, while

bradykinesia, dyskinesia and impaired balance have a different response and observation time constant (e.g. bradikynesia may change, dependently from the parameters of the DBS, in one or two weeks [70]). For this reason more sound methods are needed for the setting of DBS devices and some preliminary studies, based on wearable sensors, have been proposed in the last few years [68].

All the main intervention techniques for PD that have been illustrated so far point at reducing the gravity of the motor symptoms by acting on their physiological causes in the brain. This principle is, from one point of view, clinically sound, since a single intervention makes possible the counteraction of all the PD-related motor symptoms. From the other side, as it becomes clear examining the back draws of all these techniques, still more has to be understood on the pathophysiological dynamics in the brain that lead to PD, and the current intervention methods still don't prove to be completely effective in assuring PD patients an acceptable quality of life.

Another "philosophy" of intervention can be that based on the mechanical counteraction of the single motor symptoms. In this case the focus could be to develop *complementary* therapies able to help reducing motor disorders and allowing a less aggressive approach on the main pharmacological therapy, as in the case of DBS. A number of solutions, regarding tremor especially, have been developed in literature so far [71] [72] [73] [74]. Most of these works are based on wearable technologies, thus meaning on devices that have to be worn by the patients and that act on the symptom "in loco", that is directly on the affected limb or limbs.

An example of this kind of technology is the upper limb exoskeleton developed in the DRIFTS project [73] that uses mechanical actuators placed on elbow and wrist joints to deploy the tremor in the arm. The control of the actuators is pursued by means of analysis of data from inertial sensors that can be used to

characterize the tremor (in terms of frequency and amplitude) and the voluntary activity behind it. This device is then able to counteract the tremor either producing an out-of-phase oscillation, with respect to the tremor oscillation, in the joint in a intervention strategy that has been named “active strategy” or by applying a load on the joint through the actuators, that change the mechanical properties of the limb such as stiffness and viscosity and demote small tremor-caused oscillation. This latter counteracting method has been named “semi-active strategy”.

A device like the one developed in the DRIFTS project, certainly can’t represent a realistic approach for tremor suppression, since the complexity of the system and the size of the device itself does not allow a patient to use it on a daily living environment, but represents a prove of concept for the use of wearable technology in the intervention on motor symptoms of PD. Such kind of devices, if soundly developed, can represent an aid for patients on the activities of daily living and can be used to reduce the aggressiveness of the primary intervention (e.g. pharmacological therapy), thus reducing its back draws. In the next chapter a further example of wearable device for tremor suppression, around which has been focused some of the work presented in this dissertation, will be presented.

# Chapter 2

# Design of assistive devices for tremor suppression

## 2.1 Strategies for Tremor control

In the framework of the new methods and techniques for the assistance and functional evaluation of people suffering from impairments of the upper limb, the development of devices for the characterization and mechanical reduction of tremor represents a novel and interesting field to be investigated. As introduced in the previous chapter, tremor, that is one of the main motor symptoms related to age related degenerative disorders like PD, but that can be also due to other disabling events and disorders (e.g. cerebellar syndrome, traumatic events…), is a rhythmic oscillation of the limbs, and can bring to serious difficulties in performing standard activities of daily living. Tremor is usually treated indirectly, by treating the generating disorder, generally by means of drug therapy, but standard treatments don't come out to be effective in all patients (with an estimated 25% of tremor affected people not gaining benefits from drug therapy) and sometimes can lead to even more impairing side effects (e.g. levodopa induced motor fluctuations).

In recent years some solutions have been proposed for the development of wearable devices able to demote tremor mechanically, by applying loads on the affected joints [73] [74] [75], or by generating out-of-phase torques that oppose to the involuntary oscillation [71] [72] [73]. More specifically early works on mechanical tremor suppression [4] have classified external tremor control strategies in two main groups:

- Active tremor control, that is based on the induction of out-of-phase oscillations in the trembling limb with respect of the tremor oscillation; ideally this strategy acts like a selective notch filter on tremor frequencies.

- Semi-active tremor control, that is based on the modification of the mechanical properties of the upper limb such as stiffness, impedance and viscosity for tremor demotion; ideally this strategy acts as a low pass filter up to the tremor frequencies.

Both strategies have been implemented in the WOTAS device (developed in the DRIFTS project [4] [73]), that is a mechanical exoskeleton for the upper limb with electrical actuators acting on the wrist and elbow joints.

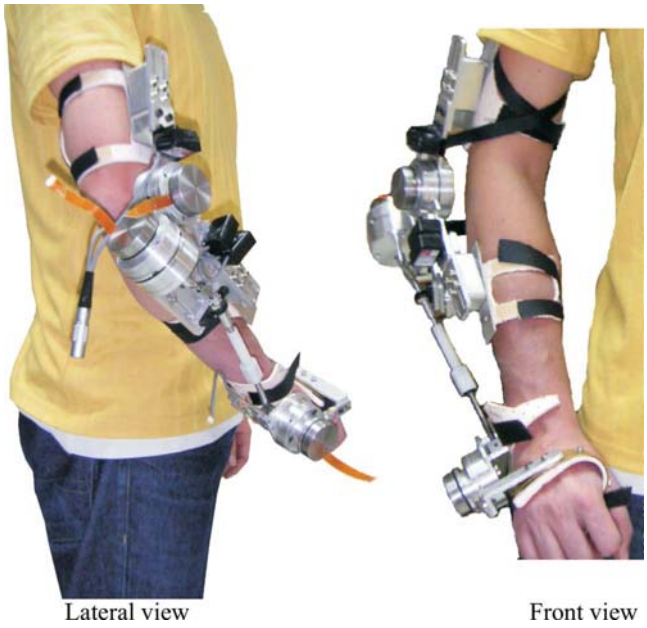



**Figure 5. The WOTAS device, an exoskeleton for mechanical tremor suppression (from [73], added with the permission of the authors)**

In the case of the active control strategy, information on frequency, phase and amplitude of tremor are used for the generation of an out-of-phase oscillation of the limb by means of two electrical actuators. In the WOTAS implementation the active control strategy is constituted by a dual control loop, where the upper loop is

devoted to tremor tracking and suppression, and lower loop is dedicated to the issue of minimizing interaction forces between the device and the arm, that could lead to instability of the control system. This control strategy clearly acts as a notch filter tuned on the individual frequency of the tremor of the patients wearing the device, since it produces (from kinematics point of view) a waveform at the same frequency of the tremor, and by adding it out-of-phase to the arm, only removes the particular frequency mark related to the involuntary oscillation (if properly identified).

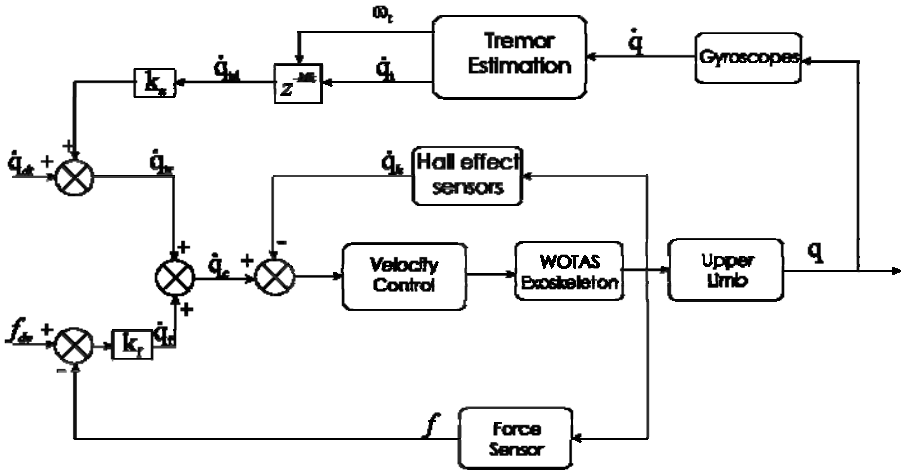



**Figure 6. Active control strategy for tremor suppression as implemented in the WOTAS control system (from [73]), added with the permission of the authors)**

The passive control strategy, on the other hand, is based on the proved concept that acting on limb impedance can have the effect of reducing tremor impairment [75]. Impedance of the arm is constituted by stiffness, viscosity and inertia. All these three components are able to vary the characteristics of tremor on the upper limb. In the control scheme for the semi-active strategy that has been developed in the WOTAS device, amplitude of the tremor is used to evaluate the amount of load that, if applied on the joint, may counteract it. The load is then applied through the

actuators. The application of a load modifies the "transfer function" related to the upper limb (that can be roughly described as a second order system), translating its frequency response towards lower frequencies and dampening higher frequency components of the movement. For this reason the semi-active strategy can be seen as a low pass filter on tremor frequencies.

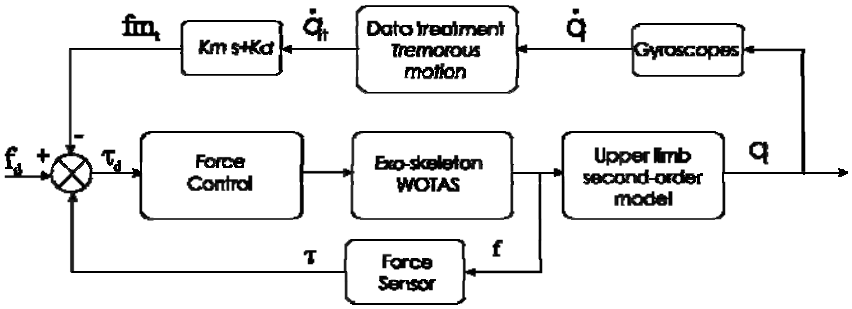



**Figure 7. Semi-active control strategy for tremor suppression as implemented in the WOTAS control system (from [73]), added with the permission of the authors)**

Prochazka et al. [71] implemented a control system that implements the active tremor suppression strategy on the upper limb by means of FES. In this scheme the amplitude of the stimulation is modulated out-of-phase with respect of the oscillation recorded through displacement sensors. This system, despite its simplicity, has been applied to tremor affected patients, showing significant results in terms of tremor reduction [72]. Nevertheless no control architecture has been, by now, proposed for the development of semi-active control strategy using FES. Electrical stimulation for tremor control, implementing both active and semi-active strategies, has been widely studied in the development of the TREMOR device that will be described in the following.

## 2.2 Overview of the TREMOR project

A novel solution for tremor control has been proposed in the European Project TREMOR [17], on whose framework part of the work of this thesis has been carried on. The main focus of this project has been to validate the concept of mechanical suppression of tremor by Functional Electrical Stimulation (FES) based on a multimodal BCI-driven approach for the characterization of involuntary movement and its separation from voluntary activity. The project aimed at studying the feasibility of a system able to:

- Detect and monitor tremor by means of the contemporary analysis of electroencephalographic (EEG), surface electromyographic (sEMG) and kinematic signals (Inertial Measurement Units, IMU) in a framework referred to as *multimodal Brain Computer Interface (BCI)* (gathering of information).
- Select the appropriate tremor intervention strategy given the information on ongoing voluntary and non voluntary activity (integration of information)
- Counteract tremor without affecting the voluntary movement, through a multi-channel array FES system, implementing both active and semi-active tremor control strategies (delivery of assistance).
- Be functional and aesthetically acceptable by the patients.

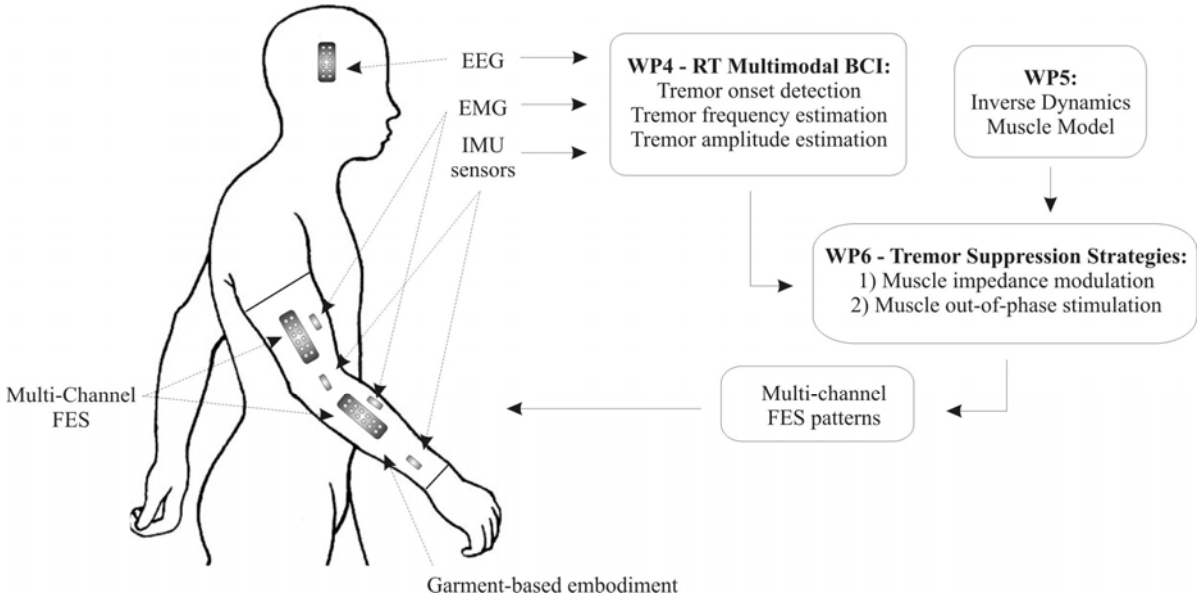



**Figure 4. General Scheme of the tremor device**

The goals of the multimodal BCI control system designed in this project have been primarily two: a) to promptly detect the onset of the tremorous activity and the characteristics of tremor; b) to be able to discriminate tremor and voluntary activity. The first goal has been widely studied in literature. In the DRIFTS project an algorithm for the tracking of tremor from IMU signals was implemented and successfully used in the testing and functioning of the device. The algorithm was based on a Benedict-Bordner dampening filter [76] for the real-time separation of tremorous and voluntary activity, and a Weighted Fourier Linear Combination (WFLC) based algorithm [77][78] for the characterization of tremor phase and frequency from the involuntary contribution to movement. But besides IMU based approaches, also algorithms based on the sEMG signal have been for tremor detection and characterization [79] [80] [81] [82], like the Second Order Moment Function (SOMF) [79].

Regarding the second goal, on the other hand, not many solutions have been proposed so far. For this reason the main role of the EEG signal in this project (from whose use the BCI acronym is mainly derived) has been to allow the device to automatically understand if the movement performed by the patient is voluntary, involuntary or a combination of the two. This feature is of crucial importance since the device is supposed to counteract tremor with a limited (if null) effect on the execution of voluntary activity. This has been achieved by detecting the voluntary activity onset on the basis of the changes in the EEG that are related to the planning and the execution of voluntary movements [83] [84] [85]. Thus the system, once derived the characteristics of the tremor and the eventual presence of voluntary activity, is able to drive the FES stimulator selecting the proper strategy of intervention.

FES directly activates muscles by stimulating motoneurons, and allows regulating the force exerted by varying the amount of current fed to the muscle. FES-driven tremor suppression is not a new concept in literature. A well known pilot study on the argument was developed by Prochazka and co-workers in 1992 [71] [72]. This system was based on a feedback controlled out-of-phase (thus implementing an active tremor suppression strategy) stimulation of the muscles of the wrist. The characteristics of the tremor were identified by filtering the displacement signal of the wrist. This filtered signal was also used for the modulation of the amplitude of the stimulator. This work proved the feasibility of the concept of FES-induced tremor suppression itself, beside the simplicity of the architecture and the limited stability of the closed loop control system of the device. Nevertheless no significant further improvements have been proposed on this subject so far. Also the use of FES in the implementation of a semi-active tremor control strategy is a concept that still has to be properly investigated, and a solution, in this sense, will be presented in the next subchapter.

Finally, the importance of developing an aesthetically acceptable device cannot be underestimated. In fact patients may decide to discard too bulky or voluminous assistive devices, for both functionality reasons or also for the fear of social exclusion. In the TREMOR framework, all the instrumentation that needs to be placed on the arm (sEMG electrodes, IMU sensors, FES electrodes) has been included in an elastic-garment sleeve [86], that is supposed to solve the previously described back draws. In fact the sleeve provides an acceptable visual impact for both the patients and the people around them and do not represent a functional obstacle for the patient. Also, since electrodes and sensors placement is a task that should be normally performed by trained personnel, the use of a tight sleeve with the sensors and electrodes tailored onto it and visual landmarks helping the patient to fit it optimally, represent a solution easily usable by patients, with minimum aid. The device developed in the TREMOR project represents clearly a novel solution for the functional assistance of tremor impaired persons, and will be a useful tool for the further proving of the concept of FES mediated tremor suppression. Also a number of tools, such as biomechanical models of the upper limb, have been developed in this framework, to serve as simulative benchmark platform for the development and testing of the proper intervention strategy for every possible situation. In the following a simulative study for the implementation of semi-active tremor control strategy by means of FES will be described.

## 2.3 FES-based semi-active control strategy implementation

Semi-active control of tremor of the upper limb acts, conceptually, as a low pass-filter whose cutoff frequency is set right before the lowest tremor frequential component. This can be achieved, mechanically, by stiffnening the tremor-affected joint itself by means of damping (either passive or actuated, as in the DRIFT

exoskeleton). When no external mechanical actuator is present, as in a FES-based system, the stiffnening has to be achieved using the natural arm actuators that are the muscles. Co-contraction of agonist and antagonist muscles has the effect of raising the stiffness at the joint where the muscles are acting. During this doctoral work, a system acting as a simulative tool for the study of the feasibility of a FES based semi-active tremor control system for kinetic tremor of the upper limb has been developed. Kinetic (or "action") tremor is an oscillation that is present during the voluntary movement. It is not common in PD patients [87], but is often seen in people affected by cerebellar syndrome or TBI patients. Usually the oscillation frequencies for this kind of tremor are between 8 and 12 Hz.

This system represents the feasibility study of a controller able to deploy tremor basing on information about kinematics of the movement. This system is constituted by three main blocks:

- A Biomechanical Arm Model which solves the dynamic direct problem related to the translation of a neural activation pattern (NAP) in a planar movement of the upper limb.
- A Noise-Box that generates the NAP corresponding to tremorous movements.
- The Controller that generates the NAP able to correct the movement affected by tremor.

The biomechanical arm model has been developed by designing a simplified arm structure consisting of a skeletal model and two pairs of muscles. The skeletal model of the arm has been modeled as a plain structure with two rigid cylinders for the forearm and the upper arm and two ideal hinges for which represent the shoulder and elbow joints. The pairs of muscles are pectoralis major and posterior deltoid for the shoulder joint, biceps brachii long head and triceps brachii lateral head for the

elbow joint [88]. The muscles have been modeled using the Hill's muscle model [89] [90] [91] that allow to calculate the forces acting on the arm joints and to take into account the effect of the dynamics. Due to the nature of the movements that have been considered in this study the gravitational force and the static and viscous friction terms have been neglected in Hill's equations.

The Biomechanical arm model is driven by NAPs that simulate the activation level of the muscles. The force developed by the muscle is calculated as a percentage of the maximum muscle's exertable force.

The Noise-Box is ANN based system able of simulating the NAP of a voluntary movement affected by tremor. Kinetic tremor, which can be interpreted as a noise affecting the movement's torques and has been simulated adding three sine waves in the range 8-12 Hz of varying phase and amplitude to the torques at the shoulder and elbow joints during a planar movement. An artificial neural network trained using reinforcement learning (ANN1) has been developed in order to find which neural activations can reproduce this kind of noise on the torques. ANN1 is a feed-forward neural network with two hidden layers each constituted by 150 neurons. It has four inputs, which are the values of the noise on the torques for the present time-step and for the previous time-step, and four outputs, which are the neural activations for the four muscles of the arm model. The training algorithm is a modified version of the "Associative Reward-Penalty" developed by Sutton and Barto [41]. The training scheme is the following:

- ANN1 is fed with the current values of the noises affecting the torques acting on the shoulder and elbow joints and gives as output the neural activation for the two pair of muscles

- Neural activations are fed into the Biomechanical Arm model that produces two instant values of torque at the joints, in order to reproduce the tremor given as input to ANN1

- The Critic calculates the normalized difference between the actual noise and the produced torque and sums it to the neural activation of the agonist muscle and subtract it to the neural activation of the antagonist muscle

- The newly calculated activations are back- propagated in the network

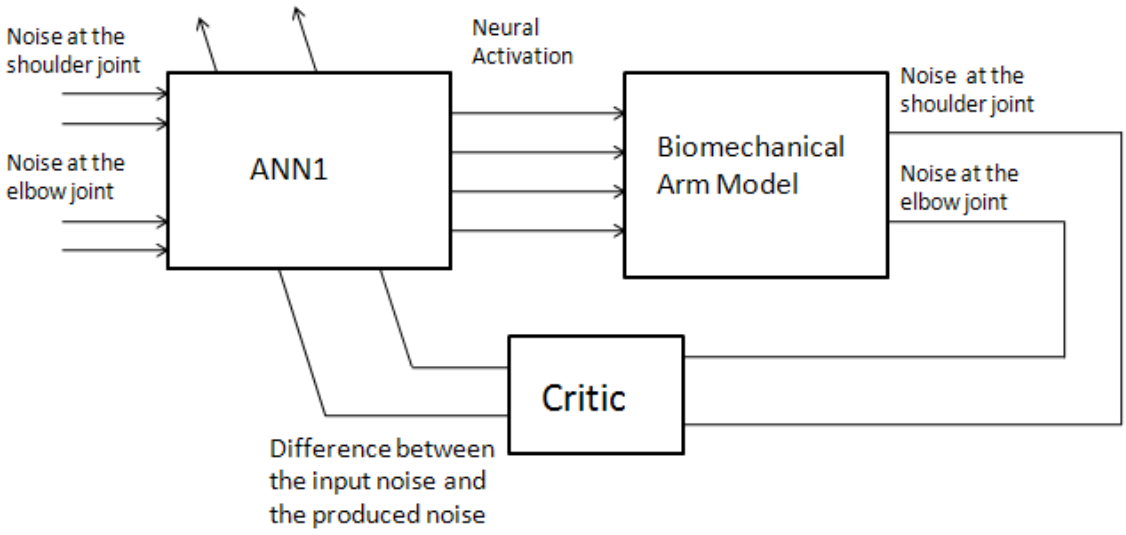



**Figure 8. Scheme of the reinforcement training algorithm for ANN1**

Once ANN1 has produced the NAP of the noise on the torques at the shoulder and elbow joints, those activations are combined with that of a voluntary movement.

Another important feature of the Noise-Box is that of calculating the NAP able to counteract tremor after being added to that of a tremorous movement. This pattern is

then used to train the Controller in a supervised way. This calculation is performed taking the difference between the activations of the voluntary movement and the tremorous movement when at least one movement's activation is non-zero, and inverting the noise activations during the deceleration phase, when only the noise contribution is taken in account, giving for every erroneous firing of an agonist muscle an identical firing to the antagonist.

The Controller is constituted of another Artificial Neural Network, called ANN2 composed of two hidden layers of 150 neurons each. It takes as input the NAP of a movement affected by tremor and gives as output the activations that have to be added to that of the tremorous movement in order to deploy the tremor.

The Controller is trained in a supervised way using the information given by the Noise-Box, that acts like a teacher for the Controller. For every movement to be learned the Noise-box produces the noise's activations, combines them with the activations of the voluntary movement and uses the result to feed the Controller inputs, calculates the correctional activations and back-propagates them through the Controller. It can be thus assumed that this scheme represents an implementation of the semi-active control strategy, since it counteracts tremorous activations of muscles by stimulating the antagonists muscles. This brings to a raise of the level of co-contraction of the muscles acting on the moving joint that increases the stiffness of the joint itself, thus changing the biomechanical properties of the arm.

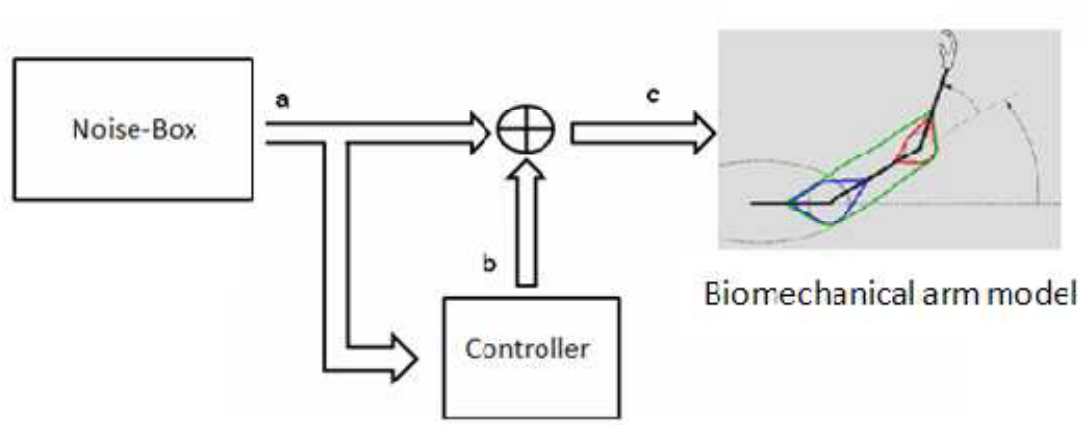



**Figure 9. Overall functioning of the system: The Controller takes as input the NAP of a tremor-affected movement (a) generated by the noise box and gives as output a "correctional" NAP (b) that is summed with (a) in order to obtain the NAP of a movement where tremor has been reduced.**

The implemented system has been trained to simulate and counteract a noise on the torque showing a SNR (where the signal is the torque of the voluntary movement and the noise is the torque of the tremor alone) of 12 dB. Various tests have been performed, in two different frameworks: a "real time framework", in which the system has to counteract tremor in random movements without any a priori information about the movement to execute with different SNR (20, 18, 15 and 12 dB) in order to validate the ability of the system to generalize its behavior; a "rehabilitation framework" in which information about the movement to be performed is used to filter the neural activations furnished by the Controller.

Tests carried on in the real time framework at different level of SNR show that the controller can effectively limit the tremor for SNR levels above 15 dB. Performance has been evaluated by means of the point-to-point trajectory error ant the percentage of difference between the error in the tremorous movement (with respect of the

same movement without tremor) and the corrected movement. Table 2.1 shows the numerical results.

| SNR | Tremorous Movement | Corrected Movement | % Percent of Difference |
|---|---|---|---|
| **20 dB** | 6.72 cm | 2.41 cm | 64.13% |
| **18 dB** | 6.01 cm | 4.13 cm | 31.28% |
| **15 dB** | 5.67 cm | 5.55 cm | 2.11% |
| **12 dB** | 4.67 cm | 8.05 cm | -72.37% |

**Table 2.1. Point-to-point trajectory error on 200 trials**

In the "rehabilitation framework" the system is supposed to be used as an aid in rehabilitation and physical training. In this framework information about the movement to be executed is present and is exploited during the task. In particular, once the movement has been chosen, the NAP of the movement relatively of a non-tremorous arm is calculated and multiplied to the neural pattern produced by the Controller. The original pattern is used to "filter" the activations given by the Controller, in order to help the system to identify correctly the movement to be executed.

In this case only the test with an SNR of 12 dB has been performed, results are shown in Table 2.2 and an example of the correction on the torques is shown in Figure 10.

| SNR | Tremorous Movement | Corrected Movement | % Percent of Difference |
|---|---|---|---|
| **12 dB** | 3.9 cm | 1.1 cm | 71.79% |

**Table 2.2. Point-to-point trajectory error on 200 trials for the rehabilitation framework, SNR 12dB.**

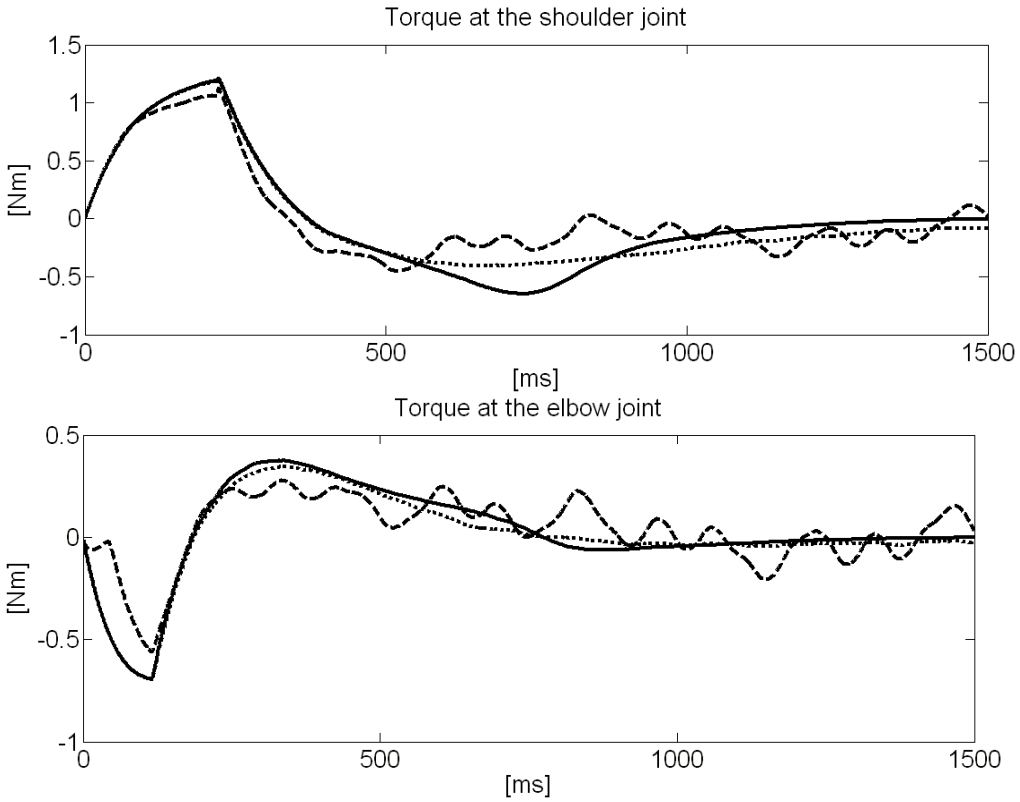



**Figure 10. Example of torques in the rehabilitation framework. The solid lines represent the torques of the original movement, dashed lines those of the tremorous movement and the dotted lines those of the corrected movement**

These results show that the proposed Controller is able to generalize it behavior and to easily deploy the tremor knowing which kind of movement is going to be executed.

This system proves the feasibility of using muscles co-contraction through FES for stiffness augmentation and thus semi-active control of tremor. Of course the presented modeled system is based on a rough representation of the upper limb physiology and functioning. For this reason a more accurate model of the upper limb has been designed as simulation tool to be used for the TREMOR and similar projects. Its implementation will be described in the following chapter.

# Chapter 3

# Design of a 3D Biomechanical Arm Model

## 3.1 Development of a 3D biomechanical arm model, overall design

In the process of designing a new device, especially assistive ones that are intended to be used on patients and should be, therefore, absolutely error-proof, modeling and simulation methods are of crucial importance. These tools allow the investigators first to better plan the designing process and, in second instance, to test the device for every possible functioning situation that may encounter.

For this purpose a 3D biomechanical arm model (BAM) of the upper limb has been developed. This new model can be used as benchmark for the tremor-counteraction strategies, in a way similar to the model described in the previous chapter. This model takes into account a 3D environment and an extended set of degrees of freedom (with respect with extremely simple model shown in chapter 2) of the movement and muscles, together with a more comprehensive muscular model.

The model, as its predecessor, is constituted by a skeletal model, able to replicate accurately the kinematics of the upper limb, with a series of superimposed modeled muscles acting as actuators for the skeletal model. The muscles are fed by muscular activation patterns and feedback information (such as muscle's length).

The design of biomechanical models resembling human limbs for movement and control simulation is a widely studied field, that has found a particular interest in literature both for the lower [92] [93] and upper limbs. Simulative studies always tend to develop models driven by muscles that take as input an estimate of the overall activity of the actual muscle, to be then translated in functional active parameters related to the muscular physiology [94][95][96] [97].

The accuracy of design of a biomechanical model is always related to the variety and nature of the movements that have to be simulated. For example many models in literature are intended to simulate only simple movements such as planar or

ballistic movements [45][46] and present thus simpler architecture with respect of similar models (that can also take into account the same number of DoF) devoted to the simulation of more complex movements [98].

The development of a biomechanical model presents the following design issues:

- Selection of the number of Degrees of Freedom (DOFs) relative to the limb movement to be modeled.
- Selection of the number of muscles to be used inserted in the model
- Selection of the appropriate muscular model to be used for the modeling of each single muscle
- Selection of the computational environment to be used

Since the model that is going to be described has been developed in the framework of the TREMOR project and, in general, tremor limiting devices, as a simulative tool to be used for the validation of both the tremor models and of the strategies for tremor suppression, all four of the presented design issues have been resolved in terms of the needs of the project, in an application driven context.

With reference to the DOFs of the model we have to consider that: i) from the elbow to the fingertips, the human arm has 26 degrees of freedom; ii) the models presented in literature show a varying number of DOFs (from 1 to 13) [99] depending on the requested accuracy.
For the particular requirements of TREMOR, 4 DOFs have been identified as crucial in tremor representation and suppression:

- elbow flexion-extension (Humero-Ulnar Joint)
- elbow prono-supination (Radio-Ulnar Joint)
- wrist flexion-extension (Radio-Carpal Joint)

- wrist adduction-abduction (Radio-Carpal Joint).

These 4 DOFs of the upper limb are considered as those in which tremor is more present [73].Moreover, in order to better simulate the behavior of the upper limb, the biomechanical model includes also 3 DOFs related to the shoulder that are:

- shoulder adduction–abduction (Gleno-Humeral Joint)
- shoulder flexion-extension (Gleno-Humeral Joint)
- shoulder rotation (Gleno-Humeral Joint).

Thus, the proposed skeletal model has 7 DOFs. The bones used for this skeletal model are those of an actual arm: clavicle, humerus, ulna and radius, plus a single body representing the hand. Dimensions and masses have been selected from published data [100] [101] [102], taking into account a standard body structure, but therefore, all the lengths and properties of the bones are designed in order to be completely customizable, depending on the physiology of every single patient. Bones of the skeletal model can assume every pose, accordingly with joint limits.

Regarding the number of muscles, models in literature [94] [95] [99], show a number of muscles spanning from 3 to 36. The presented model has been implemented as constituted by 14 muscles; part of them, namely biceps brachii (long and short head), triceps brachii (long, medial and lateral head), extensor carpi radialis, extensor carpi ulnaris, flexor carpi radialis and flexor carpi ulnaris are the muscles directly involved in the tremor modeling and FES stimulation and have therefore been selected.
The remaining muscles are the brachialis, brachiradialis, pronators (teres and quadratus) and supinator that have been added in order to guarantee a realistic

behavior of the limb because of their passive properties. In fact the biomechanical characteristics of every joint critically depend on that of the muscles acting on it. Every muscle in the model has a specific wrapping object, located between the two bones' attachment points, devoted to simulate the non-linear behavior of the muscle during the movement.

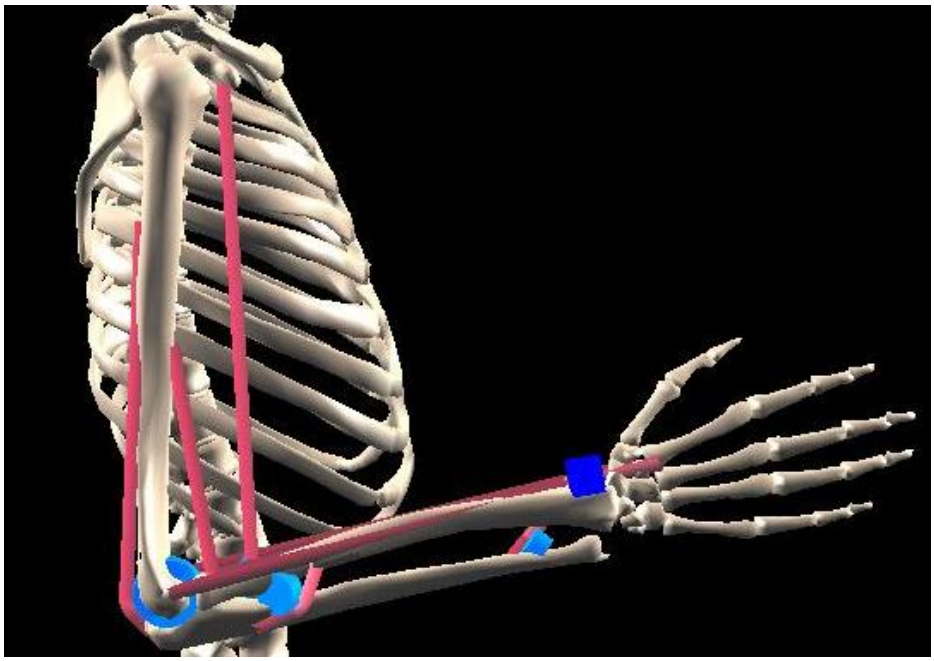


**Figure 11. Close-up of the skeletal model (white) with muscles (red) and wrapping points (blue) superimposed on it.**

## 3.2 Muscular model

One of the most important issues in the development of a dynamic direct model of the upper limb is the modeling of the muscles. Many of the well known solutions appeared in literature are inspired by the Hill's model [89] [90] [91], that set the basis for the conceptual modeling of the mammal's muscles. In this model the muscle is described as a lump circuit constituted by a series elastic element (SE), a

parallel viscous element (PE) and a contractile element (CE) in series with SE defined by a Neural Input Processor (that takes into account the muscular activation level) and a parallel viscous element B(*v*) whose characteristics depend on the shortening velocity *v* of the muscle. The interaction of all these elements gives the output force, F, produced by the muscle as function of its properties and the neural activation.

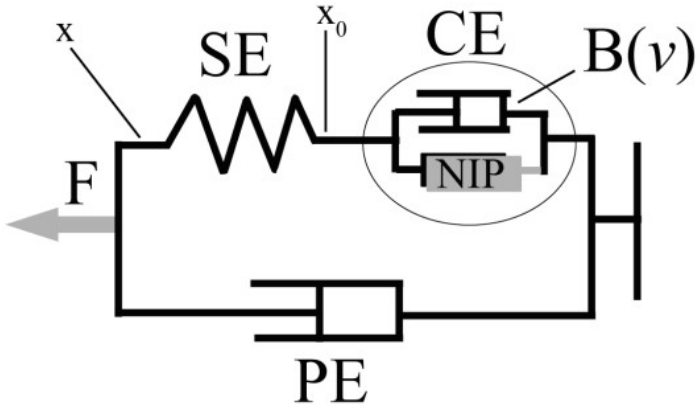



**Figure 12. Schematic reproduction of Hill's Muscle model as a lump circuit.**

The muscular model used for the proposed BAM is also derived from Hill's model and is the one provided in the Virtual Muscle software [103]. In this software muscles are also modeled as a combination of elastic and contractile elements, and the properties of the tendons are also included. Inputs of the model are:

- An activation signal, managing the incremental recruitment and modulating the firing rate of the motor units.

- The actual muscle length, calculated from the muscle path.

The contractile elements produce force as a function of the recruitment of motor units, the frequency modulation, the length and the velocity of the muscles. The viscoelastic elements for passive muscle force are included in the contractile ones while the passive elastic elements represent series-compliance of tendons and aponeuroses. Thus the total force exerted by the muscle is calculated taking into account contributions from:

- Active contractile force;

- Parallel elastic force;

- Series elastic elements;

All these parameters depend on the physical properties of the muscle that can be completely customized in the software. Motor units are responsible for the production of the active contractile force and for parallel elastic force, while series elastic elements are represented by tendons, which share similar properties in every muscle. Motor units can have different properties (in terms of active contractile and parallel elastic force development) among them, depending on their fiber type [104]. Muscular fibers in human striated muscle are in fact usually divided (depending mainly on their size and contraction speed) in Type I (slow), Type IIa (moderate fast, Type IIx (fast) and Type IIb (very fast). The Virtual Muscle model allows user to select the fiber types composing the muscle. Thus the modeling steps for muscles comprehend:

- definition of muscle fibers:
    - types of fibers to take into account
    - properties of each fiber type

- definition of muscle morphometry:
    - number of motor units for each fiber type
    - relative contribution of every fiber type to muscle composition o spatial features of the whole muscle

The muscles in the proposed model have been modeled as composed by Type I, Type IIa and Type IIx fibers, which have been spatially distributed following data published in literature [105] [106]. Even if each type of muscular fiber is characterized by specific features, the model allows a customization by tuning the following parameters:

- main parameters (higher level):
    - $F_{min}$ = minimum firing frequency of each motor unit
    - $F_{max}$ = maximum firing frequency of each motor unit
    - $F_{0.5}$ = frequency needed to produce 50% of maximal isometric force
    - $V_{0.5}$ = velocity of shortening required to produce 50% of maximal exertable force

- additional parameters (lower level):
    - Force-Length Curve
    - Force-Velocity Curve
    - Effective Activation
    - Activation Delay
    - Rise and Fall Times
    - Sag
    - Yield

- Energy Rate

All these values have been also selected following evidences extracted from the literature [105] [106] [107].

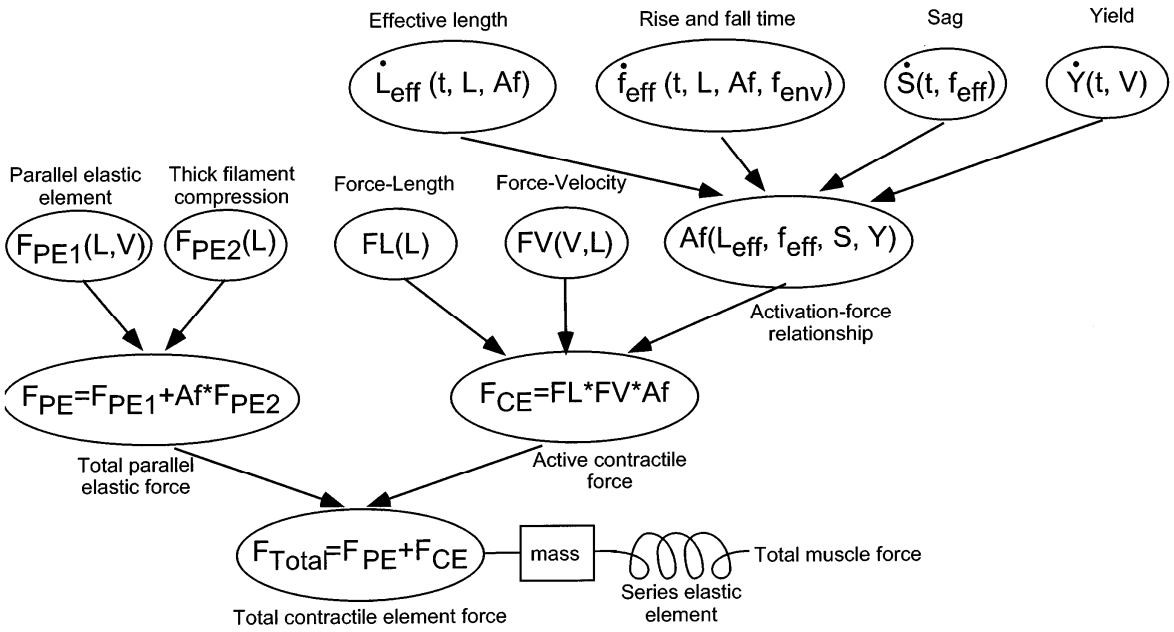



**Figure 13. Parameters linking in the Virtual Muscle model.**

In order to set the number of motor units composing each fiber the Virtual Muscle model allows to select the percent contribution of each fiber type to the whole muscle mass and the number of motor units related to every fiber type. The physiological cross-sectional area (PCSA) of the portion of the muscle represented by a single fiber type is then divided equally among the motor units constituting that fiber. This step is important since it allows reducing the number of motor units to be used in the model thus reducing the overall complexity of the model. Contribution of every kind of fiber type in the muscle mass has been chosen using data on muscle's composition (obtained on cadavers) present in literature [105] [107].

The last step in muscle modeling is related to the dimensional features of the whole muscle, in terms of proportional length of each muscle (and relative tendon) and definition of overall muscle mass (from which maximum exertable force depends). The length and the mass depend on both the total length of the arm and the characteristics (i.e. overall mass, body fat...) of the subject. The model is, also in this case, completely customizable on patient's specifics.

The final development part in the realization of a biomechanical model of the upper limb is the computational environment to be used. Since the Virtual Muscle software is C-based and then easily interface-able to the Matlab Simulink environment, the MSMS software has been selected as the computational tool for the modeling of the skeletal model. This software, in fact, allows the user to design the skeletal structure in a user friendly interface and then export it easily to the Simulink environment.

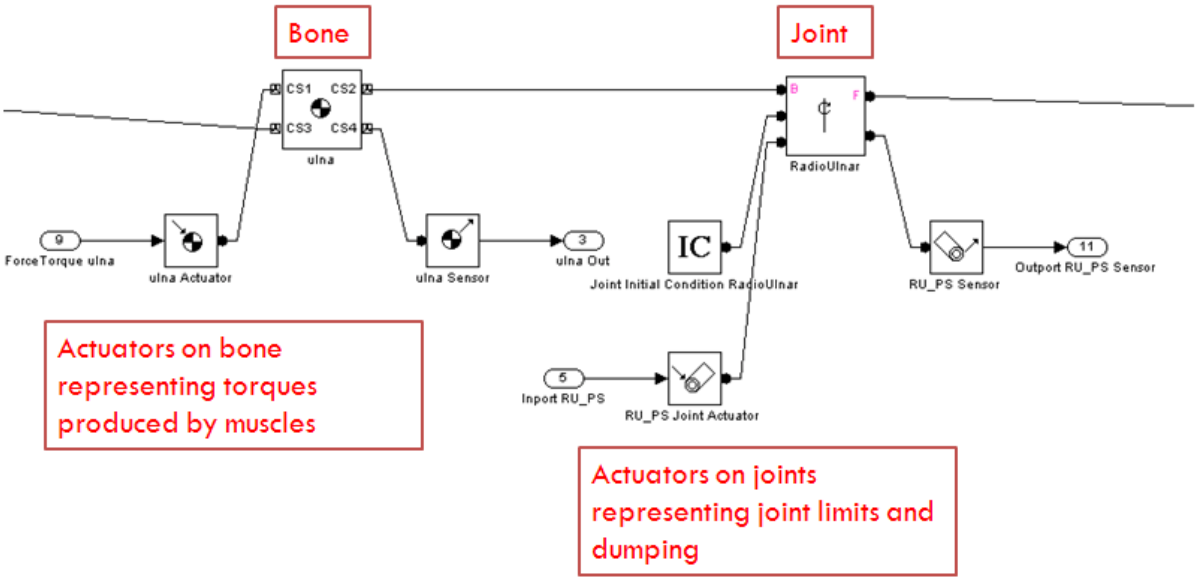



**Figure 14. Example of Simulink structure of wrist Radio-Carpal Joint developed using MSMS**

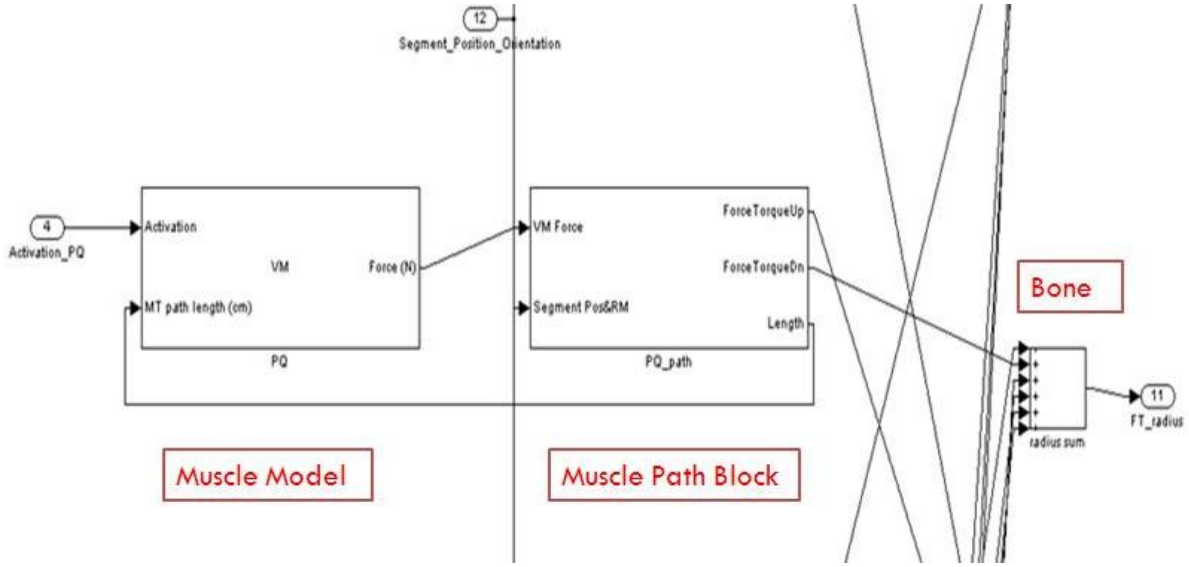



**Figure 15. Simulink block representing muscle and muscle path calculation, acting on a given joint.**

This BAM has then been tested as simulation tool for tremor modeling and characterization of the correct strategies for tremor suppression. Every muscle is controlled by two input parameter:

- the actual muscle length

- the istantaneous muscular activation.

The former is calculated by a block in the Simulink model (figure 15) taking into account the actual position of the bones, joints and wrapping object, thus determining the real muscle length, while the latter is a parameter spanning between 0 and 1 whose value can be set by the user.

A 0-level muscular activation represents a status of no recruitment, while a 1-level is related to a state of maximum muscular recruitment of motor units. All the values between 0 and 1 trigger a percentage of recruitment of motor units according to the activation-recruitment curve of the muscle fiber types.

Tremor is thus easily replicable in this model as a train of 1-0 activation patterns, at the frequency of the movement.

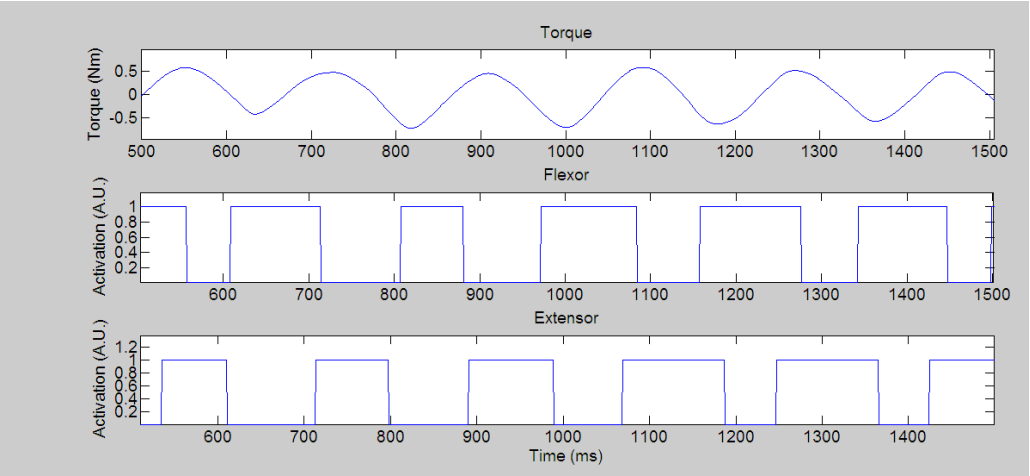



**Figure 16. Tremor replication using 1-0 activation patterns appropriately timed.**

This model act as a direct model able to provide kinematics and dynamics of the arm on the basis of the muscular activation patterns of the muscles. In fact these data can be easily recorded in the Simulink environment placing sensors at any given joint or in every position of a given body. These sensors can record kinematics (position, acceleration and velocity) and dynamics of the given body or joint, allowing then also the calculation of instantaneous impedance characteristics of the virtual arm (stiffness, viscosity).

The model has also been used for the testing of various preliminary implementations of both the active and the semi-active tremor-control schemes. Standard use comprehend tremor-affected movement simulation on the model,

implementation of algorithms able to track and counteract tremor (as the one described in the previous section, acting on a 2D biomechanical model) and application of the results of the algorithms to the control of trembling model in real time.

# Chapter 4

# Development of algorithms for tracking of voluntary activity

## 4.1 Physiological signals for the tracking of movements

In the conceptual design presented in the introduction of this dissertation, the phase of gathering of information represent the primary step in the development of novel solutions in biomedical-field applications. Thus the study and development of techniques and devices that have as primary goal the rehabilitation of the upper limb is a field that deeply relies on the study of the information related to the movement, from the planning to its actual execution that is possible to extract from the biophysiological signals. Many works in literature in fact have been dedicated to the study of physiological signals for the tracking and evaluation of human movements during the rehabilitative path of a patient [108], mostly in order to give the clinician additional information on the effectiveness of the treatment, both in the short term and in the long term. Most of this study relies on the analysis of information from signals from inertial sensors [108] and sEMG [109]. From the point of view of the design of rehabilitative device, this task becomes crucial, since information on the quality and nature of the movement exploited by the patient becomes necessary for the characterization of the device itself [73] and in some cases can be even used as a biofeedback for the enhancement of the rehabilitative process [6] [7]. Moreover in recent times, most of the rehabilitative devices integrate (integration phase) the real time information about the movement in their functioning. The goal is, in this case, controlling the device using the information on the residual or erroneous activity of the patient to actively tune or select the proper intervention [73] [110].

This is the context common to tremor-limiting devices (like the one developed in the TREMOR project), where the information gained from an extensive set of movement-related signals is used in the controller of the device. In the following a series of algorithm developed in this thesis will be presented. These algorithms use

physiological signals such as sEMG and EEG to derive features related to the movement performed, for the purpose of tracking the movement itself or gaining information on its characteristics such as voluntariness. These algorithms are intended to be integral part of a gathering information module for an assistive device for the upper limb.

## 4.2 Movement tracking using biological signals - Estimation of muscular onset-offset from sEMG

The study and the analysis of the information that can be obtained from surface electromyography have found a peculiar importance over the course of the last few decades. Among the different information that is possible to obtain from sEMG about muscle's behavior during the execution of movement and the nature of the movement itself, an important one is the determination of the onset-offset timing of the muscular activity.

Estimation of sEMG activation timing has been proven to be a useful parameter in many fields, such as orthopedics [111] [112] [113], neurophysiology [114] and rehabilitation [115] [116]. Muscle onset estimation is also used as a trigger signal to control a number of different devices, such as orthoses [117], exoskeletons [118] and prostheses [119].

In the early times, when information gained from sEMG first started to be used in clinical practice, onset-offset estimation was performed through visual inspection by trained clinicians [120], while, more recently, the attention has been focused on the development of automatic computer-based methods [121].

The simplest approach is based on single-threshold detectors [122], where an auxiliary variable of known statistics is derived from the signal and the muscle activity is detected once the auxiliary variable passes a selected threshold. The choice of the threshold allows selecting the false alarm probability $P_{fa}$ but does not give control on the detection probability $P_d$, that depends on the SNR of the signal.

Bonato and co-workers [123] developed a double-threshold statistical algorithm that allows the user to select the false alarm and detection probabilities (namely $P_{fa}$ and $P_d$) of the detector, depending on the signal-to-noise ratio (SNR) of the acquired sEMG. Double threshold detectors extend the single threshold detection to a fixed number of subsequent samples ($m$), and detect an activity transition once $r_0$ out of the $m$ samples (the second threshold) pass the first threshold. Given a $P_{fa}$ derived from the first threshold, the introduction of the second threshold allows choosing between $m$ different values of $P_d$ by selecting the value of $r_0$.

More elegant approaches are based on time-frequency analysis such as wavelet transform [124] [125], or on statistically optimal decision criteria [121] [126].

Since the performance of the detectors is strongly affected by the amount of noise superimposed to the signal, many works have been focusing on the description of methods able to operate even at very low SNR values [124], but at present none has been designed in order to deal with situations where the SNR of the sEMG may change during the recording. SNR fluctuations during sEMG acquisition can be principally due to two phenomena: change of the signal power (e.g. changes in the exerted force during isometric trials) or change of the noise power (e.g. due to the variations of the skin-electrode interface characteristics, or due to changes in the ground reference level). The second phenomenon in particular can distort the onset-offset estimation of sEMG signal and can jeopardize the validity of an acquisition. When information about sEMG onset-offset timing is supposed to be used in

devices that has to function as aid in activities of daily living, these phenomena must be taken into account necessarily, since skin-electrode interface characteristics, in example, tend to degrade as time passes by and may be modified by changes in the properties of the skin (temperature, humidity due to sweat and so on). Thus robust methods for detection are necessary in this case.

In order to overcome the limitations associated with changes in the SNR of the sEMG signal over time in Bonato's algorithm, an almost real-time SNR-independent implementation of it is presented in this thesis and its performance are compared with that of the original formulation. This modified version of the algorithm is adaptive with respect to changes of SNR, in the sense that it is able to update the detector thresholds on the basis of the desired $P_d$ and $P_{fa}$ and of the SNR estimation for each muscular activity burst. This particular implementation is also able to give information on the estimated onset and offset timing shortly after the end of every burst of EMG activity (thus the wording pseudo real-time).

### 4.2.1 Theoretical framework of the algorithm

The detector developed by Bonato and colleagues is based on Hogan's modeling of the sEMG signal [127] [128]. This model makes the assumption that a sEMG signal recorded during dynamic contractions may be considered as a realization of a zero-mean non-white Gaussian distributed process $s(t)$ modulated by the muscle activity, with a superimposed zero-mean white Gaussian noise $n(t)$.

In the detection phase, the sEMG temporal series $\{x_i\}$ is whitened by means of an adaptive whitening filter [129], obtaining the series $\{x_{iw}\}$. An auxiliary time series $\{z_i\}$ can then be obtained summing the square of two consecutive samples of the

whitened series. Under the hypothesis that both the signal *s(t)* and the superimposed noise *n(t)* are Gaussian, the consecutive samples of the series $\{xi_w\}$ can be considered as independent and thus $\{z_i\}$ has a $\chi 2$ distribution with two degrees of freedom.

Given the properties of the $\chi 2$ distribution, it is possible to define the probability that a specific noise sample of the series $\{z_i\}$ is above a fixed threshold *th*. This probability can be written as a function of the variance of the superimposed noise $\sigma_{nw}^2$ as in the equation:

$$P_{th} = P[z > th;\ x(t) = n(t)] = e^{-th/2\sigma_{nw}^2} \qquad (1)$$

If noise is superimposed to the signal, the probability that a given sample *k* is above the threshold *th* is then given by:

$$P_{dk} = P[z > th\,; x(t) = s(t) + n(t)] = e^{-th/(2\sigma_{nw}^2 + 2\sigma_{sw}^2)} = e^{-th/[2\sigma_{nw}\left(1+10^{\frac{SNR}{10}}\right)]} \qquad (2)$$

Where $\sigma_{sw}^2$ is the variance of the signal and SNR is the signal to noise ratio of the series.

The probability that $r_0$ successive samples out of *m* are above a given threshold can be derived from the probability associated to a single sample considering a repetition of Bernoulli trials:

$$P_{fa} = \sum_{k=r_0}^{m} \binom{m}{k} P_{th}^{k} (1 - P_{th})^{m-k} \quad (3)$$

$$P_{d} = \sum_{k=r_0}^{m} \binom{m}{k} P_{dk}^{k} (1 - P_{dk})^{m-k} \quad (4)$$

The probabilities expressed in (3) and (4) represent respectively the false alarm probability and the detection probability of the algorithm.

### 4.2.2 Standard implementation of the detector

Given the theoretical framework of the method, the main difference between the standard (ST) and the proposed novel (NV) formulation of the algorithm is in the selection of the detection parameters before (as in the ST implementation) or during (as in the NV one) the trial. Statistical properties of the detector are described by the desired values of $P_{fa}$ and $P_d$ (namely $P_{fad}$ and $P_{dd}$) that, in both the implementations, are selected before the beginning of the analysis and affect the selection of all the other parameters of the algorithm.

In the ST formulation of the algorithm, the tuning and functioning of the detector is based on the following steps:

1) Selection of the length of the observation window *m*. This value is selected depending on the desired time resolution of the analysis. The standard value is $m = 5$, that, since the $\chi 2$ distribution is derived from two consecutive samples of the whitened series, corresponds to a time resolution of 10 ms if a sampling rate of 1000 samples/s is hypothesized.

2) Selection of the second threshold $r_0$. Low values of this parameters lead to higher $P_d$ for a given $P_{fa}$. In the standard formulation of the detector this value is fixed at $r_0 = 1$. Once the values of $m$ and $r_0$ are fixed, a feasibility study is performed in order to check if the values of $P_{fad}$ and $P_{dd}$ are achievable using these parameters and the supposed SNR range of the trial.

3) Selection of the first threshold. This value is obtained after estimating the variance $\sigma_{nw}^2$ of the superimposed noise by solving the equation (3) for $P_{th}$ and the equation (1) for the current threshold *th*. The noise variance is obtained from the estimation of the SNR of the trial under analysis. At each iteration when samples are considered belonging to a burst its variance is considered as noise variance plus signal variance (following Hogan's sEMG model [127] [128]) while interburst samples variance is due only to noise. The procedure is stopped when the relative difference between consecutive SNR estimations is less than a given threshold ($10^{-3}$).

The selected parameters ($m$, $r_0$ and *th*) are then kept fixed for all the detection process of a given sEMG trial. The stochastic nature of the sEMG signal, however, can lead to several erroneous transitions during the analysis, especially for low values of SNR. For this reason in [123] a post-processing technique is added in cascade to the detector. This post-processor cancels detected patterns (labeled by the algorithm as either burst or inter-burst) if they are shorter than a selected duration, by considering them as either false positives or false negatives. The minimum acceptable duration depends on the motor task that is being analyzed (e.g. in gait analysis it has been assumed close to 30 ms).

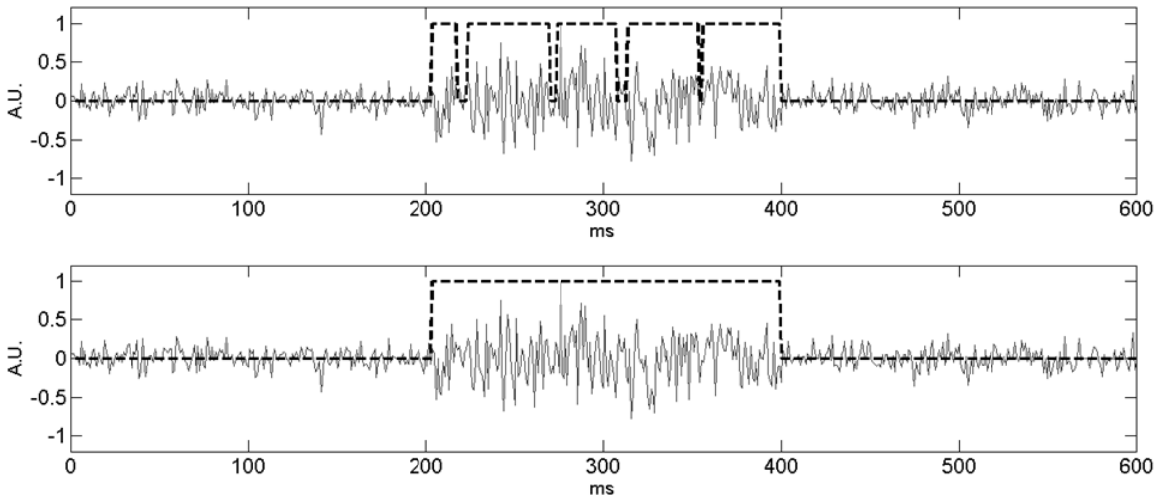



**Figure 17: output of Bonato's algorithm (simulated signal, SNR 10 dB) before (top) and after (bottom) the use of the post-processor for the elimination of short transitions.**

### 4.2.3 Novel Formulation

The main limitation related to the ST formulation of the algorithm is that the SNR estimation provides a value that is an average calculated on the whole signal. This characteristic is not critical for analyses during which the SNR of the signal is not supposed to show major changes. Nevertheless, if the SNR of the signal changes during the analyzed trial, the calculated threshold could be not optimal for bursts whose SNR is far from the estimated mean value. Moreover, sudden changes of the power of the noise during the trial can heavily affect the accuracy of the results.

The NV formulation of the algorithm, whose flowchart is shown in figure 18, is based on a preliminary estimation of the noise variance at the beginning of the trial, followed by a SNR (and thus noise variance) estimation for each detected burst. All the parameters of the detector (except the window analysis *m*, which is kept fixed

for all the trials) are updated accordingly to the $P_{fad}$ and $P_{dd}$ and the current SNR. Specifically:

1) Before the beginning of the analysis, the values of m, $P_{fad}$ and $P_{dd}$ are initialized (standard values are $m$ = 5, $P_{fad}$ = 0.05 and $P_{dd}$= 0.95). Also initial values for SNR and $r_0$ are set (namely SNR = 12 dB and $r_0$= 1).

2) A buffer of the original signal (initialized at the beginning of the analysis with the first 50 ms of the signal) is whitened by means of an adaptive whitening filter. At each sample the buffer is expanded using the current sample of the original time series.

3) A first-guess estimation of the noise variance is performed on the first 50 ms of the signal and the first threshold th is derived from equation (1).

4) A buffer for the analysis is updated at each sample with the current sample of the whitened sEMG signal, and the associated auxiliary variable *{z}* is calculated. The buffered distribution is then analyzed for burst detection using the current parameters, and post-processed.

5) If the analysis has detected the end of a sEMG burst, its SNR and the associated noise variance are calculated (from the variance of the estimated burst and interburst), and the value of $r_0$ and *th* are updated by solving the equations (3), (4) and (2). The burst-detection with the updated parameters is repeated until the SNR converges (i.e. the difference between two consecutive SNR estimates is less than 10-3).

6) Once a burst has been detected the buffer is deleted and the procedure is repeated.

If no value of *th* and $r_0$ can provide the $P_{fad}$ and $P_{dd}$ values, the thresholds are selected in order to minimize (possibly under the desired $P_{fad}$ constrain) the false

alarm probability with the highest possible detection probability. SNR is evaluated for each cycle of the burst analysis using the estimation of the onset-offset timing.

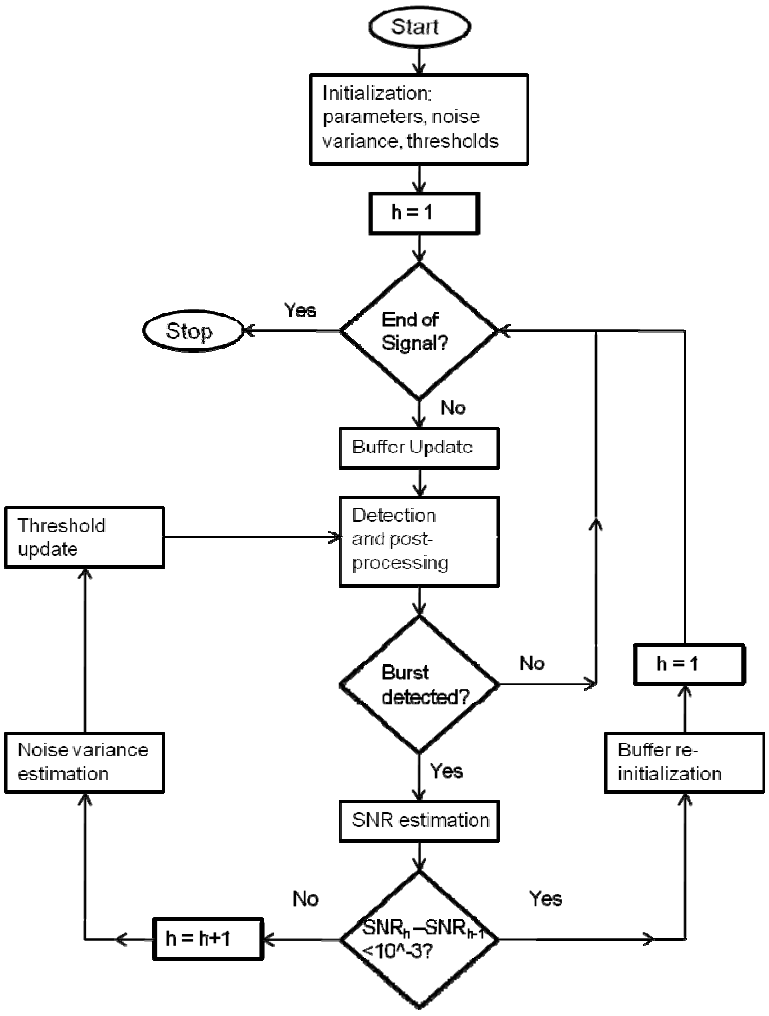



**Figure 18: flow chart of the on-line implementation (NV) of the algorithm**

### 4.2.4 Simulated data

The performance of the NV formulation was tested on simulated data and compared with that of the ST formulation. Simulations took into account both fixed and variable SNR trials.

Simulated sEMG data were synthesized using the sEMG model used for the original evaluation of the standard approach: signals have been generated by modulating zero-mean Gaussian colored noise (obtained applying the Stulen–De Luca filter [130] to white noise series) with a rectangular or Gaussian modulating function, truncated depending on the desired time support for the burst. SNR of the signal is calculated as the mean SNR over the entire burst.

Time support for the Gaussian modulating function with standard deviation equal to $\sigma$ is $\pm\alpha\sigma$, where $\alpha$ is a constant. Zero-mean white Gaussian noise realizations were added to the modulated signals to simulate the noise and to manage the SNR value of each sequence of data.

Constant SNR trials were composed of single movements (one movement per trial) and signals were synthesized at different levels of SNR (namely 26, 20, 16, 13, 10) with different $\alpha$ (1, 1.5 and 2) and $\sigma$ (50, 100 and 150 ms).

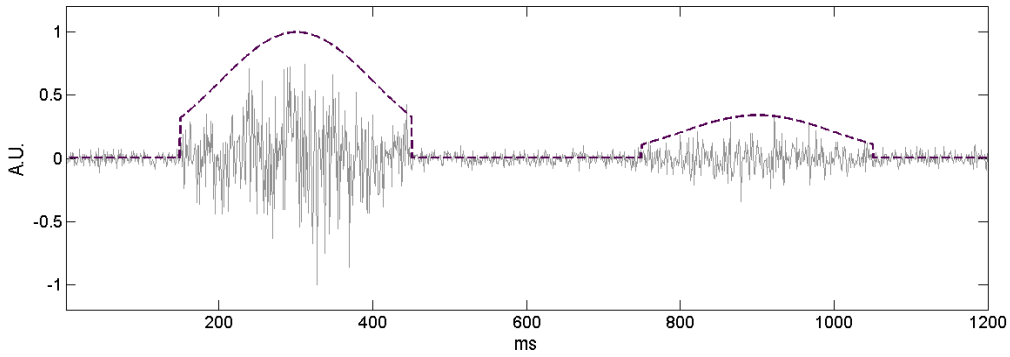



**Figure 19: example of two simulated bursts SNR 20 dB (left) and 10 dB (right), σ = 100 ms, α = 1.5.**

For the time-varying SNR trials, variations in both signal (VS trials) and noise power (VN trials) were considered: VS testing trials were simulated as repetitions of ten rectangular-shaped bursts with different SNR values (random SNR values in a range between 9 and 24 dB), while VN trials were simulated using Gaussian modulating functions with different α and σ as in the constant SNR trials. This difference in the modulating function for VS trials was decided in order to better highlight the difference in performance between the two implementations of the algorithm. VN trials were indeed simulated by modulating, with an exponential function through time, the power of the noise superimposed to the modulated colored noise, thus degrading the quality of the signal. VN Trials are composed of 10 movements with a starting SNR of 25 dB and a final SNR of 15 dB.

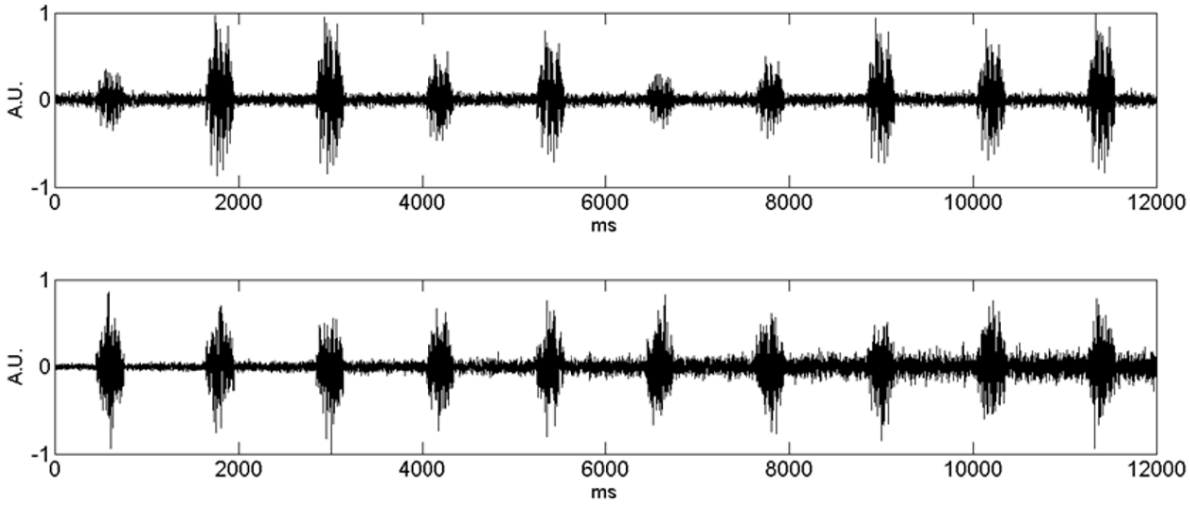



**Figure 20: Example of the two kinds of VS (top) and VN (bottom) trials, used for the evaluation of the algorithm. VS trial in figure is composed of ten rectangular-shaped bursts (300 ms duration) at random levels of power. VN trial in figure has been obtained by adding an exponentially modulated noise to ten Gaussian shaped ($\sigma$ = 100 ms, $\alpha$ = 1.5) bursts for a SNR varying between 25 and 15 dB.**

### 4.2.5 Real data

A protocol for the acquisition of sEMG at various SNR levels was developed for tests on real sEMG data. The protocol was based on isometric triceps medialis contractions executed at different percentages of the MVC during the acquisitions.

The experiments were performed on 5 healthy male adults (age 29 ± 3). The subjects were informed on the experimental protocol and gave their consent to participate. Each subject was seated on a chair with the right shoulder and elbow both flexed at 90˚. Subjects were instructed to push on a load-cell positioned next to their right hand. Before the beginning of the current experimental trial, MVC was calculated for each subject, and two preliminary tests were conducted in order to make the subjects get familiar with the task.

Different levels of MVC during each trial were achieved using a biofeedback of the actual exerted force, based on the desired level of MVC: a screen was positioned in front of the subjects during the trials showing the levels of both the requested and the currently exerted forces. The subjects were asked to perform three isometric contractions for each of the three MVC requested percentages (20, 40 and 60%) and to maintain them for 5 s. The load cell and the sEMG acquisition were electronically triggered for synchronous recording. All data were recorded at 1000 samples per second with the FREEEMG 300, BTS Bioengineering.

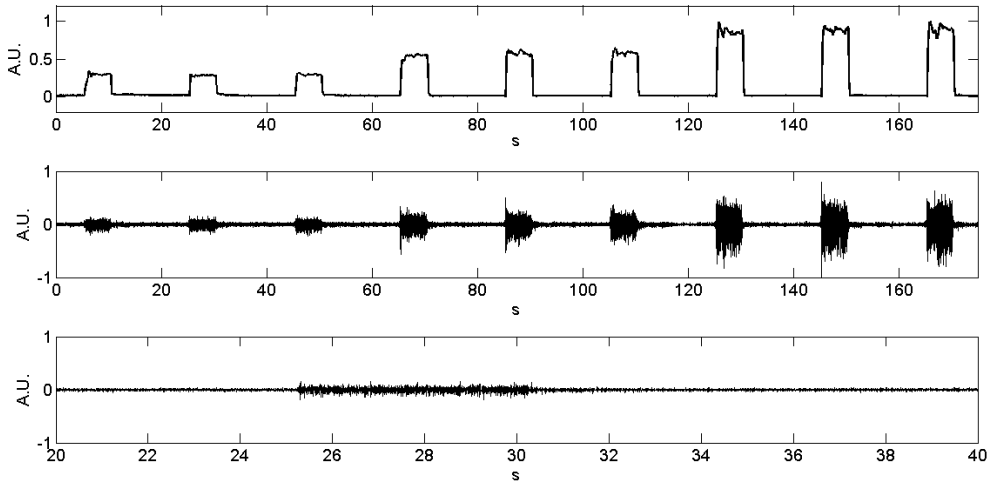



**Figure 21: example of real data acquisition with varying SNR during trial. Top plot shows load cell signal, middle plot shows sEMG recorded on the triceps medialis, bottom plot shows a zoom of the sEMG signal for a low SNR burst (20-40 s).**

### 4.2.6 Evaluation of results

Results for simulated signals were evaluated in terms of:

- Detection percentage (Dp), i.e. the ratio between the number of movements correctly detected and the number of total movements multiplied by 100.
- False Positive percentage (FPp), i.e. the ratio between the number of movements with false positive occurrences and the number of total movements multiplied by 100.
- Bias (B), calculated as the mean difference (in milliseconds) between the estimated and the current onset-offset of the simulated movement
- Standard Deviation (StD), calculated as the standard deviation of the differences between estimated and the actual onsets-offsets.

Results for real signals were evaluated with respect to the load force signal, and in this case, the bias was not taken into account, since it incorporated the delay associated with the electro-mechanical transduction [131]. The standard deviation of the differences between the estimated onsets of sEMG activity and the ones of the load cell signal was used to evaluate results. The onsets of activity in the mechanical signal obtained from the load cell was evaluated as corresponding to the samples in which the load cell signal raises from the zero-level.

### 4.2.7 Experimental Results - Simulated Data

Table 4.1 presents the results of the estimation of the onset of muscular activity (results for the offset are similar), that have been obtained by applying the algorithm to simulated data with constant SNR level, and time support $\pm\alpha\sigma$. For every set of parameters, 100 realizations consisting of one simulated movement were analyzed.

| | σ = 50 ms | | | σ = 100 ms | | | σ = 150 ms | | |
|---|---|---|---|---|---|---|---|---|---|
| | α = 1 | α = 1.5 | α = 2 | α = 1 | α = 1.5 | α = 2 | α = 1 | α = 1.5 | α = 2 |
| SNR = 26 dB | 1.4 ± 0.8 | 2.4 ± 1.6 | 3.4 ± 2.8 | 1.3 ± 1.0 | 1.5 ± 1.6 | 3.6 ± 4.3 | 1.2 ± 0.8 | 2 ± 1.5 | -0.7 ± 7.2 |
| SNR = 20 dB | 1.7 ± 1.8 | 2.9 ± 2.2 | -1.5 ± 8.5 | 1.8 ± 2.6 | 2.8 ± 4.1 | 0 ± 5.8 | 1.5 ± 1.4 | 3 ± 4.2 | -0.2 ± 6.0 |
| SNR = 16 dB | 0 ± 2.6 | 2.4 ± 3.6 | 0.4 ± 6.1 | -0.1 ± 1.9 | 2.2 ± 4.6 | 1.2 ± 8.0 | 0 ± 1.9 | 1.8 ± 3.4 | 4.6 ± 9.9 |
| SNR = 13 dB | 0.5 ± 4.0 | 3.4 ± 4.6 | 2.9 ± 11.6 | 0.7 ± 2.9 | 5.6 ± 8.2 | 9.9 ± 13.8 | 0.8 ± 3.3 | -3.1 ± 7.0 | 17.3 ± 19.5 |
| SNR= 10 dB | -2.9 ± 5.9 | 1.3 ± 7.3 | 2.6 ± 15.6 | -2 ± 5.9 | 3.7 ± 9.1 | 13.6 ± 18.2 | -2.2 ± 6.3 | 2.8 ± 8.2 | 14.1 ± 26.4 |

**Table 4.1: Results (in terms of bias (B) ± standard deviation (StD) in ms) obtained with NV algorithm for fixed SNR trials for different levels of SNR and values of time support ασ.**

Results obtained with this version of the algorithm are consistent with those presented in the original work [123], with the values of the estimation bias below 10 ms in almost all configurations. Neither false positive transitions, nor missed detections occurred during these trials. For high values of SNR and limited time support, results obtained with NV method are better than those obtained with the original ST implementation of the algorithm, since the NV implementation is able to find an optimal value for $P_{th}$ and thus for the second threshold.

From these results it can be noticed that no particular trend is observed in bias for the same time support when the SNR is decreasing. Nevertheless this trend is observable for standard deviation values. This behavior is caused by the fact that the values of *th* and $r_0$ change depending on the current value of the SNR, which is evaluated at each iteration of the burst analysis. This can lead to situations where the $P_d$ and $P_{fa}$ of the detector, despite satisfying the values of $P_{dd}$ and $P_{fad}$, differ consistently between two trials with the same value of time support, mostly due to changes in the values of $r_0$.

The difference between the two formulations is more marked in the VS and VN trials than in constant SNR level trials. The difference between the NV and ST

implementations is that the former updates the SNR and noise variance estimation (and thus the value of the first threshold) for every burst, while the latter estimates fixed values for these parameters for all the trial. For VS trials, simulated as 200 trials constituted by ten rectangular modulated movements with random values of SNR between 9 and 24 dB, results are presented in table 4.2. In this case, the ST formulation estimates an average SNR for all the trials, and the noise variance and thus the first threshold are chosen accordingly. Therefore, the results on the onset, even if satisfactory, are affected by a bias depending on the error on the noise variance estimation and on the non-optimality of the threshold. NV implementation shows markedly lower bias and standard deviation values on the estimation of the burst onset, since the estimated noise-variance, which is updated on a burst-per-burst basis, is closer to the current value.

| ST | |
|---|---|
| B ± StD (ms) | -5.9 ± 3.2 |
| FPp | 1% |
| Dp | 100% |
| NV | |
| B ± StD (ms) | 0.1 ± 1.6 |
| FPp | 1% |
| Dp | 100% |

**Table 4.2: Comparison of results between the standard (ST) and the novel (NV) formulation of the algorithm for VS trials. Results are presented for a single value of time support (150 ms) and are expressed in terms of bias (B) ± standard deviation (StD), false positives percentage (FPp) and detection percentage (Dp).**

This behavior is even more marked in VN trials, i.e. trials where the power of the superimposed noise changes during the acquisition: these trials simulate conditions where e.g. the impedance between the electrode and the skin may change over time. In these trials, ST implementation shows a low detection percentage (around 50% for all the studied combinations {SNR, α, σ}), a high false positive percentage and high values of bias and standard deviation for all the time supports.

| SNR | σ = 50 ms | | |
|---|---|---|---|
| | α = 1 | α = 1.5 | α = 2 |
| ST | - 9 ± 13.8 | - 15 ± 14.0 | -19 ± 20.0 |
| FPp | 7% | 7% | 2% |
| Dp | 53% | 50% | 52% |
| NV | -0.1 ± 0.7 | 4 ± 5.3 | 18 ± 21.0 |
| FPp | 0% | 0% | 0% |
| Dp | 100% | 100% | 100% |
| SNR | σ = 100 ms | | |
| | α = 1 | α = 1.5 | α = 2 |
| ST | -20.3 ± 11.2 | -29.1 ± 16.5 | -16.7 ± 9.0 |
| FPp | 20% | 17% | 11% |
| Dp | 44% | 47% | 48% |
| NV | -0.1 ± 0.9 | 4.4 ± 6.2 | 33.6 ± 38.0 |
| FPp | 0% | 0% | 0% |
| Dp | 100% | 100% | 100% |
| SNR | σ = 150 ms | | |
| | α = 1 | α = 1.5 | α = 2 |
| ST | -24.1 ± 13.1 | -25 ± 14.7 | -16.8 ± 9.1 |
| FPp | 32% | 27% | 11% |
| Dp | 42% | 41% | 44% |
| NV | 0.1 ± 0.9 | 5.8 ± 7.2 | 49.9 ± 53.6 |
| FPp | 0% | 0% | 1% |
| Dp | 100% | 100% | 100% |

**Table 4.3: Comparison of results between standard (ST) and novel (NV) implementations of the algorithm for VN trials. Results are presented for different time supports and are expressed in terms of bias (B) ± standard deviation (StD), false pattern percentage (FPp) with respect of the total number of movements and detection percentage (Dp).**

This is due to the fact that changes in the noise level can lead to situations where the threshold calculated for the whole signal falls below the inter-burst level, even if $P_d$ and $P_{fa}$ values are satisfied with the current level of SNR.

On the other hand, NV implementation shows a 100% detection percentage for every value of time support, and a very low false positive percentage (Table 4.3). Also bias and standard deviation values are acceptable in most configurations. As shown in figures 22 and 23, NV implementation is able to track and adapt to the local SNR of the sEMG signal with a low estimation error.

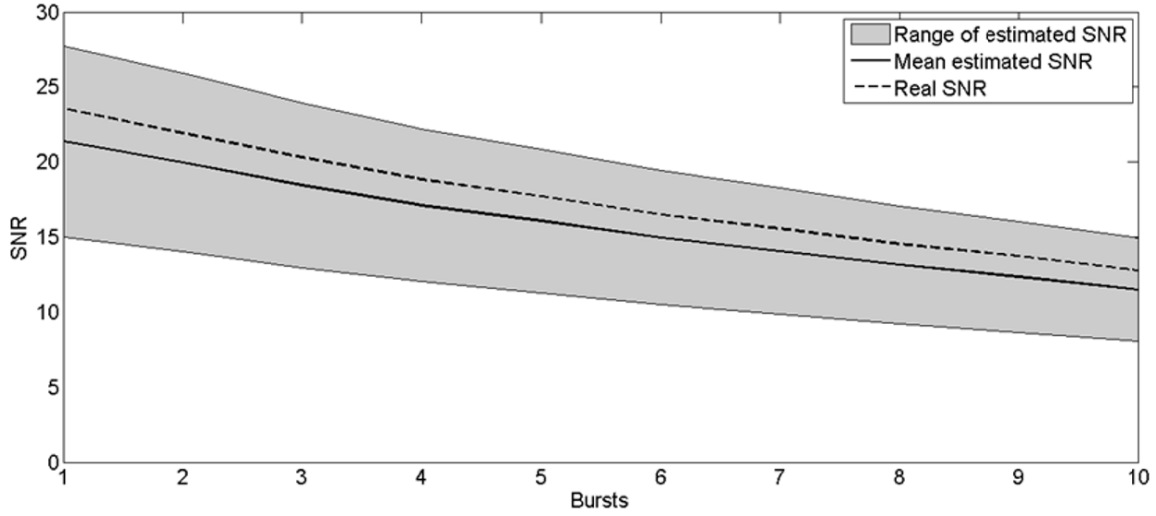



**Figure 22: SNR estimation for VN trials. Dashed line represents real SNR of the trials while solid line and grey bands represent respectively the mean value ± the standard deviation of the SNR estimation on all the trial for a fixed value of time support ($\sigma$ = 100 $\alpha$ = 1.5)**

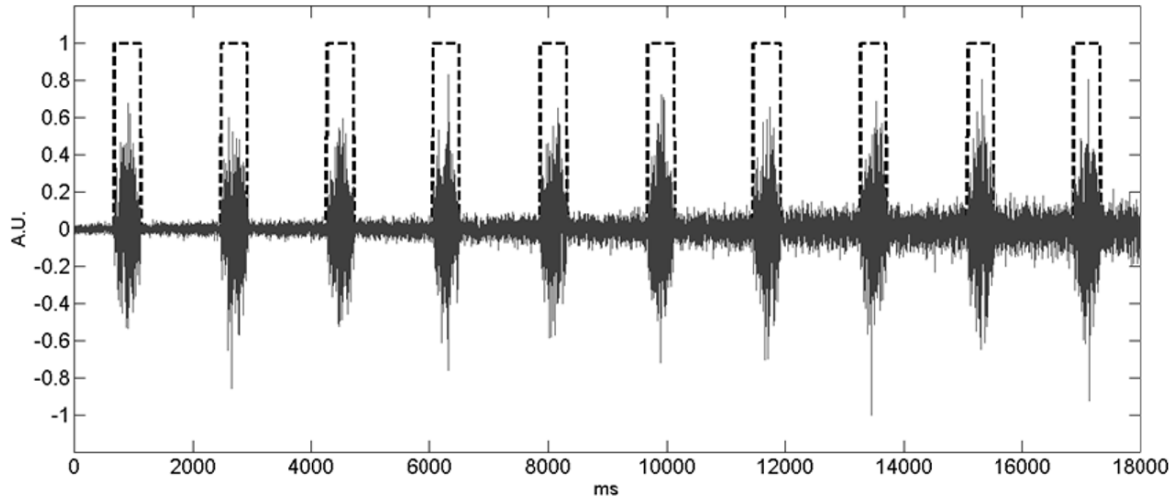



**Figure 23: Example of results obtained with the novel implementation of the algorithm on a VN trial ($\sigma = 100$, $\alpha = 1.5$).**

### 4.2.8 Experimental data

Results have been evaluated in terms of standard deviation of the differences between the onsets of the estimated muscular activity and those of the load cell (the bias due to the electromechanical delay has not been taken into account). As shown in table 4.4, the NV formulation gives lower values of StD in the estimation of the onset of muscular activity, if compared with the ST formulation. The percentage of false positive transitions is always below 10%. The standard implementation instead presents a high number of false positive transitions. Moreover, the proposed method is automatic and limits the number of selections to be preliminarily made by the operator and the pseudo real-time detection allowed by this formulation can be profitably exploited by biofeedback applications based on myoelectric information.

| | Sub1 | Sub2 | Sub3 | Sub4 | Sub5 |
|---|---|---|---|---|---|
| ST –StD(ms) | 343 | 70 | 123 | 61 | 73 |
| FP % | 12% | 20% | 50% | 16% | 10% |
| NV– StD(ms) | 55 | 38 | 35 | 41 | 42 |
| FP % | 5% | 2% | 0% | 0% | 3% |

**Table 4.4: Comparison of results between standard (ST) and novel (NV) implementations of the algorithm for VS trials on real signals. Values are expressed as the standard deviation (StD) of the difference between the onset of the sEMG and that of the load cell (in ms). For every subject the percentage of false positive transitions with respect to the total number of movements is shown.**

### 4.2.9 Conclusions

A method like one that has just been exposed could represent an interesting improvement for technologies that relies on information on timing of the residual sEMG activity for the driving of rehabilitative or assistive devices [110]. In fact, in this kind of framework, the effective device should be designed in a way in which its functioning can remain consistent during all the time in which it is supposed to be used (that can span from few hours to a whole day). Nevertheless changing on electrode-skin contact impedance due to degradation of the conductive medium used or sweating or in general changing of the characteristics of the skin lead to a degradation of the SNR. For this reason, a tracking algorithm able to follow these changes of SNR over time, thus maintaining the same standard of behavior of the device, becomes necessary. The presented algorithm is an example of viable solution for this issue. This algorithm can be integrated in various kind of assistive device for the upper limb. It can be used either as control signal on low-level

residual sEMG activity, as, e.g., in the device described in [118] [119] or it can also be applied to the tracking of low-SNR tremor burst with respect to high SNR voluntary movements in the context of tremor limiting devices.

## 4.3 Movement tracking using EEG - Algorithms for the detection of movement intent from the EEG signal

A novel approach in the study of movement-related physiological signals consists on the exploitation of information that is directly related to the execution of the movement, but not gained from the parts of the body directly involved in it, as, for example, the information obtained from the EEG signal on movement preparation, planning and intent [83] [84] [85].

One of the main issues in the development of assistive device that have to limit involuntary expressions of movement like tremor is how to develop a device that is able to counteract the symptom on the upper limb without affecting the execution of user's voluntary movements. This can be achieved by:

a) Distinguish between voluntary and non-voluntary activity

b) Distinguish between voluntary and non-voluntary components (tremor) during the execution of voluntary activity

While the second point has been addressed in this context in the past, and algorithms for tremor separation in IMU sensors have been proposed [73] [132], the first one has been extensive objective of study during the work that led to this thesis.

An approach that has been gaining particular attention in the last years for enhancing information about characteristics of movement in assistive and rehabilitative devices is that of Brain Computer Interface (BCI) based algorithm design; BCI is intended as a specialized interface that, using particular features extracted from the electrical activity of the brain, allows a subject to communicate directly to a computer or a computer-controlled device [133]. The results of BCI studies have been mainly devoted to the development of applications for assisting subjects affected by severe movement-related disabilities [134]. Even if a unifying framework for the development and planning of BCI devices has not yet been agreed, because of the absence of international standardized guidelines in this context, the common elements of a BCI design are: an acquisition unit, a feature extraction and translation unit, a control interface and a controller for the device to be driven [135]. The most varied part of this scheme is generally represented by the feature extraction and translation unit, due to the possibility of using different features of the EEG signal in a control application. Many BCIs derive commands from signals located over the sensorimotor areas of the cortex. Some of them, such as the one developed by Pfurtscheller in Graz [136] and the one by Wolpaw in Albany [137] use the information obtained from the changes in the mu (8-13 Hz) and beta (15-30 Hz) rhythms of the EEG signal to move cursors on the screen. Other approaches employ signals coming from sensors overlying the motor areas, such as that presented by Birbaumer [138] or the low frequency-asynchronous switch design developed by Mason and Birch [139]. Other BCIs use instead signals acquired from outside the motor cortex, such as that presented by Lauer [140].

A common characteristic of all these BCI systems is that, in order for them to be sufficiently accurate, they need the patient to be trained on how to control the assistive device, by voluntarily modulating the brain activity related to particular tasks. A different approach consists of extracting the information or the control

signals for the assistive device directly from the natural brain activity, so preserving the patient from the training effort [141] [142] and allowing him to use the device as a natural extension. In this thesis work and in collaboration with the TREMOR project [17], this latter kind of approach has been investigated and integrated. The aim in this case is to have the device automatically tuned on patient's intention in order to promote voluntary movement and demote tremor. This can be achieved by integrating signals from the Central Nervous System (EEG) with their "manifestation" in the peripherical part of the body, such as sEMG and IMU signals that are in some way generated by the primitive CNS activity, in a context that takes the name of Multimodal BCI (MBCI).

In this chapter two different approaches, both based on the cross-analysis of EEG signals and movement related signals (sEMG and IMU) will be shown:

- Cortico Muscular Coherence

- Event Related Desynchronization

## 4.4 Cortico Muscular Coherence

Spectral coherence is an index of the coupling of two signals in the frequency domain and can be used to assess the common drives present in contemporary recordings of the two signals under analysis. If those signals are coming from cortical areas and muscular fibers, the term used is Cortico-Muscular Coherence (CMC) [143] [144]. From a physiological point of view, CMC reflects the synchronization of motor units discharge at different frequencies by several descending drives.

Magnetoencephalographic recordings (MEG) in man show CMC between the controlateral cortical signal from the primary motor cortex and EMG activity in the beta band (15-30 Hz) during weak contractions of forearm and hand muscles [145]. These results have been obtained also using EEG signals [144]. The oscillatory drives in the beta band have been associated to voluntary muscular activity during submaximal contractions [143] [144]. As presented by Brown in [146], results obtained in this sense suggest that the rhythmic drive to human muscles in the beta band may originate in the primary motor cortex and contributes to the overall μ rhythm (8-12 Hz) recorded from the motor cortex. This rhythm disappears during voluntary movements, although some rhythmic activity re-appears during isometric contractions [147]. Coherence contribution in the band between 5 and 12 Hz seems instead to be related to the central elements of physiological tremor and pulsatile organization of movement [148], although no convincing evidence of motor cortex drive has been proven and only occasionally sub-peaks at these frequencies have been seen in coherence spectra of the MEG signal from the motor cortex and EMG activity [145].

In order to estimate CMC, many methods have been developed in the past years: the standard approach to coherence estimation is represented by Welch's Fourier-based periodogram [143] [144] [149], while also time-frequency approaches based on wavelet analysis have been used to investigate coherence evolution during arm or finger movements [147] [150]. Autoregressive modeling of the signals [151] for CMC estimation has also been studied.

Since these CMC contributions can be caused either by cortical commands to the muscles or by the afferent feedback from the contracting muscles [149], auto-regressive multivariate methods for signal analysis have been applied in order to study the directional coherence contributions.

If the assessment of the time evolution of the CMC is used to timely drive an assistive technology appliance, a real-time CMC estimation is needed. In this case, the standard Fourier-based method shows limitations due to the use of an analysis window whose length represents a critical issue.

In order to overcome the limitations of the standard Welch [153] approach, a method based on bivariate auto-regressive (BAR) modeling [152] for the estimation of time-frequency CMC has been developed in this work. In this formulation, CMC can be calculated from the parameters of the BAR model through a closed-loop representation of their generation. Besides being an alternative and efficient way to investigate time-frequency CMC contributions, the BAR approach can be tested as a component of a multimodal Brain Computer Interface (BCI) able to gain information on voluntary activity from CMC occurrences in the beta band. In order to make the BCI systems sufficiently accurate, the patient needs to be trained on how to control the assistive device, by voluntarily modulating the brain activity related to particular tasks. A different approach consists of extracting the control signals for the assistive device directly from the spontaneous brain activity, thus avoiding the training effort of the patient [141] [142]. CMC is then proposed as a solution for the detection of movement intent in tremor-affected patients and healthy subjects.

### 4.4.1 Coherence Estimation

Spectral coherence represents the correlation between two signals in the frequency domain. Coherence can be expressed by using its squared form that is defined as in (1):

$$|R_{12}(\omega)|^2 = |P_{12}(\omega)|^2 / P_{11}(\omega)P_{22}(\omega) \qquad (1)$$

Where $P_{12}(\omega)$ is the cross spectral density of the two processes $x_1(n)$ and $x_2(n)$, and $P_{11}(\omega)$ and $P_{22}(\omega)$ are the corresponding auto-spectral densities.

The estimation of $R_{12}(\omega)$ for time-limited real signals can be obtained by either non-parametric [153] or parametric approaches. In the following, the focus will be on parametric techniques for CMC estimation, thus labeling EEG signal samples as $x_1(n)$, and EMG signal samples as $x_2(n)$.

### 4.4.2 Signal Modeling

CMC can be estimated by using a BAR model of EEG and EMG signals. It has been chosen in order to overcome the time-frequency resolution problems of the Fourier-based methods, and to benefit from a modeling approach in terms of understanding the interconnections between two signals during their generation process. In BAR models, the current sample of each signal depends on past inputs of the signal itself and past inputs of the other signal, plus a White Gaussian Noise (WGN) realization sample of a given variance, thus making the generation of the two processes strongly interconnected, as described in (2).

$$x_1(n) = -\sum_{k=1}^{p} a_{11}(k)x_1(n-k) - \sum_{k=1}^{p} a_{12}(k)x_2(n-k) + u_1(n)$$

$$x_2(n) = -\sum_{k=1}^{p} a_{21}(k)x_1(n-k) - \sum_{k=1}^{p} a_{22}(k)x_2(n-k) + u_2(n) \qquad (2)$$

where $a_{ij}$ represent the coefficients of the BAR model, $u_{1,2}$ represent the WGN realizations used as inputs, and p is the order of the BAR model, that for the sake of simplicity has been chosen as the same for all the AR blocks.

Each set of coefficients ($a_{ij}$) can be represented in the z-domain by (3):

$$A_{ii}(z) = -\sum_{k=1}^{p} a_{ii}(k)z^{-k}, A_{ij}(z) = -\sum_{k=0}^{p} a_{ij}(k)z^{-k} \qquad (3)$$

These functions are then used to calculate the squared coherence between the two processes by means of a closed-loop representation of the whole process as explained in [152].

### 4.4.3 Closed-loop representation and coherence estimation

The transfer functions of the closed loop are represented in figure 24, and can be characterized from the coefficients of the autoregressive model (as in equation 3). The closed-loop blocks can be obtained from:

$$H_i(z) = 1/(1 - A_{ii}(z)) \qquad (4)$$

$$G_{ij}(z) = A_{ij}(z)/(1 - A_{ii}(z)) \qquad (5)$$

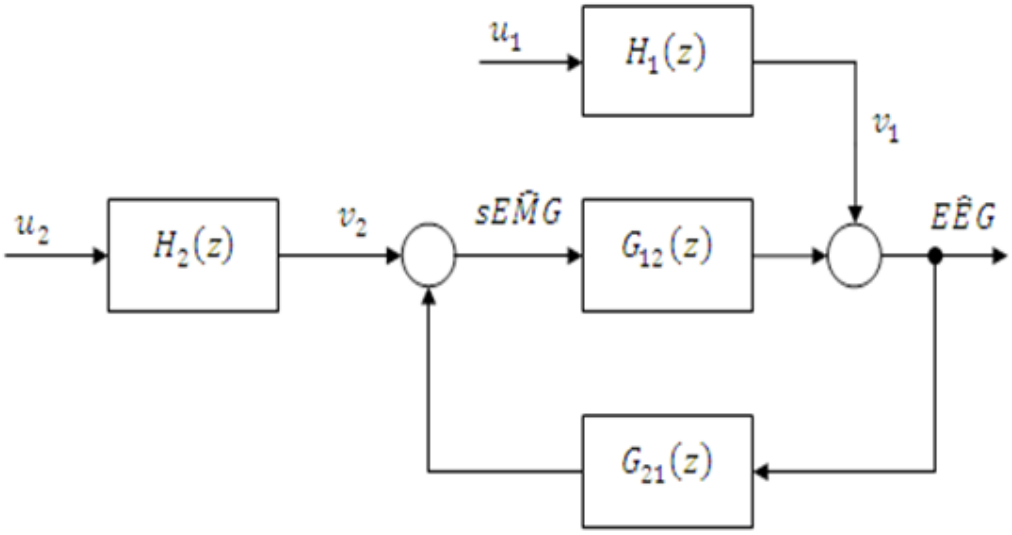



**Figure 24. Closed-loop representation of EEG and EMG signals generation**

From these, the sensitivity function S is defined as:

$$S(z) = (1 - G_{12}(z)G_{21}(z))^{-1} \qquad (6)$$

The auto-spectra and the cross-spectrum, and consequently the squared coherence in the frequency domain, can be obtained from the parameters just calculated as in equations 7, 8 and 9:

$$P_{11}(\omega) = \left|S(e^{j\omega})H_{11}(e^{j\omega})\right|^2\gamma_1 + \left|G_{12}(e^{j\omega})S(e^{j\omega})H_{22}(e^{j\omega})\right|^2\gamma_2 \quad (7)$$

$$P_{22}(\omega) = \left|S(e^{j\omega})H_{22}(e^{j\omega})\right|^2\gamma_2 + \left|G_{21}(e^{j\omega})S(e^{j\omega})H_{11}(e^{j\omega})\right|^2\gamma_1 \quad (8)$$

$$P_{12}(\omega) = G_{21}(e^{-j\omega})\left|S(e^{j\omega})H_{11}(e^{j\omega})\right|^2\gamma_1 + G_{12}(e^{j\omega})\left|S(e^{j\omega})H_{22}(e^{j\omega})\right|^2\gamma_2 \quad (9)$$

Where $\gamma_1$and $\gamma_2$ are the covariance values of the two WGN realizations $u_1$ and $u_2$ feeding the closed-loop. Following the definition of coherence, it is then possible to estimate the squared coherence as in (1).

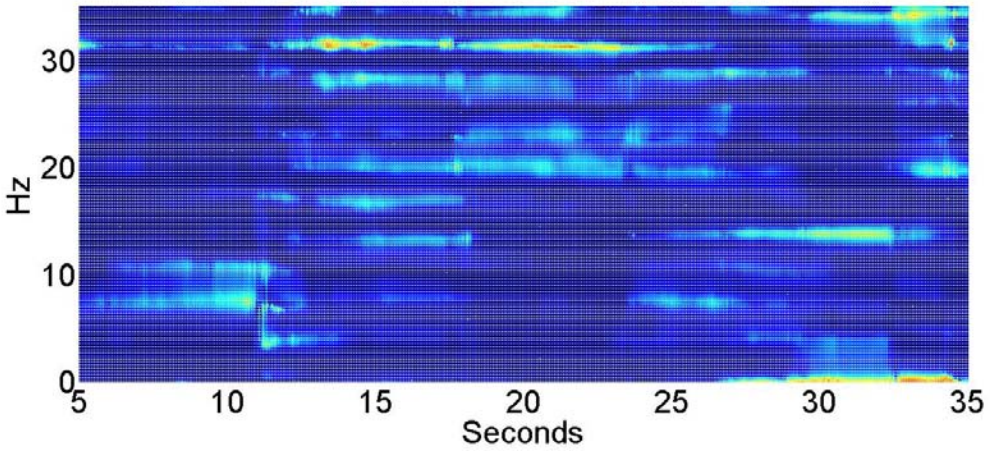
This closed-loop representation of the EEG-EMG generation offers the possibility to estimate also the directional coherences, by alternatively zeroing the transfer functions of the blocks representing the cross-dependencies of the signals (namely $G_{12}$ and $G_{21}$), thus splitting the contributions of spectral coherence between the two cause-effect directions.

### 4.4.4 Time-frequency analysis

In order to assess the time evolution of CMC, the analysis has been implemented by segmenting the signals through an observation window sliding at fixed time steps. The window length and time shift are respectively 2.5 s and 0.06 s. For each segment, the coefficients of a BAR model are estimated, and the coherence is correspondingly calculated, thus building a CMC time-frequency map. For the calculation of the AR parameters of the signals under examination, the package ARFIT [154] [155] has been used. The order of the bivariate AR process has been set at $p = 13$ .

### 4.4.5 Significance Level Estimation

Significance level estimation needs to be assessed in coherence estimation. In the Welch's approach, significance level is obtained according to [144] that depend on both the number of non-overlapping windows used to estimate the spectrum and the expected level of significance for the null hypothesis. In the case of AR spectral estimation, an alternative way of calculating the significance level is needed. An elegant solution in these regards is based on surrogate data analysis as presented in [156]: for each original signal pair, 40 surrogate pairs are calculated, randomly permuting the phase information of the Fourier transform of the series, thus destroying the original coherence coupling. Coherence is then obtained for each pair of the surrogate series, and, for each frequency value, the probability density function of the surrogate data values is estimated. The threshold is then set at the 100(1-$\alpha$) percentile, with $\alpha$ being the significance level chosen (in this case 0.05). The values of CMC that are below the threshold are considered as not significant and are thus zeroed in the final coherence map.



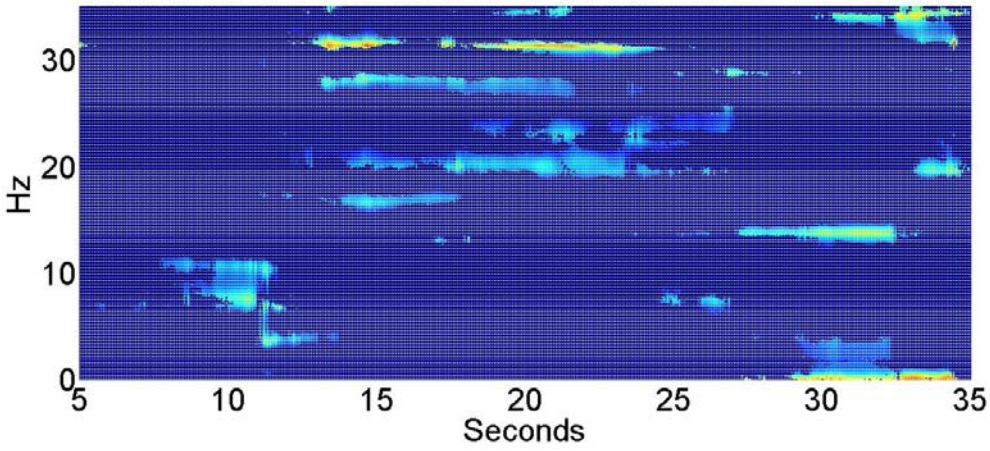



**Figure 25. Top plot shows a coherence map before significance estimation, bottom plot shows the same map after significance assessment by means of surrogate data analysis**

### 4.4.6 Detection Algorithm

After assessing the significance level for the coherence map, a detection algorithm is performed in order to extract a digital signal where the level "high" indicates the presence of coherence contributions in the beta band. A threshold value equal to the mean value plus two times the standard deviation of the whole contribution of the coherence in the beta band in a given time step is calculated. For every time step, if the average of all the coherence values in the beta band exceeds the threshold, the control signal is set at the "high" level. If state transitions (both high and low) are shorter than 50 ms the algorithm does not take them into account.

### 4.4.7 Performance on simulated data

The first analysis performed on this method compares the time-frequency maps obtained by the BAR approach with those obtained by the Welch's periodogram on a set of simulated data. EEG signal has been simulated as a colored noise with frequency content between 0.5 and 100 Hz, while EMG signal has been generated by modeling white noise through the Stulen-De Luca filter [130]. A common drive of narrow-band (4 Hz) noise series has been added to both signals in the beta band in order to simulate CMC contributions for a fixed amount of time (11 s).

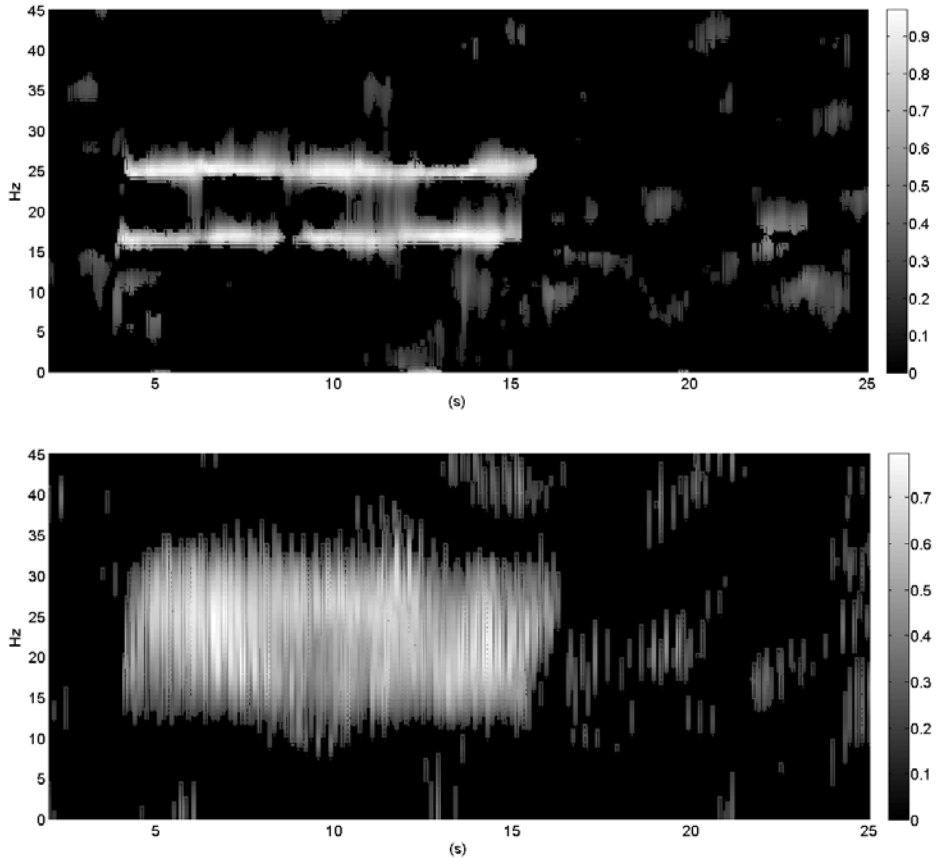



**Figure 26. Time-frequency coherence analysis performed using the proposed method (top figure) and the standard Welch's algorithm (bottom figure). Analysis has been performed on simulated EEG and EMG signals with two common narrowband (4 Hz) at 17 and 23 Hz noise series between 4 and 15 seconds. Grayscale is used to better highlight separation in top figure.**

Simulated time series have been processed in a time-frequency framework by using Welch's approach and the proposed BAR method. The length of the observation window and the time-step was the same for both analyses (2.5 s and 0.06 s, respectively). Both CMC maps underwent significance level estimation according to the method explained in section 2.5.It can be noticed from figure 26 that the BAR approach offers a better frequency resolution as compared to than the Welch's approach. In the BAR analysis the noise series common to both signal are recognizable, while in Welch's coherence analysis they cannot be distinguished.

### 4.4.8 Performance on experimental data and experimental protocol

The method previously explained has then been used to analyze movements performed by two healthy subjects and four patients affected by rest tremor (4-6 Hz) and postural tremor (5-8 Hz).

Data have been recorded during three different motor tasks: a wrist task (WT), in which the subject is still in sitting position and performs a single wrist flexion-extension movement; an arms outstretched task (AOT), in which the subject is required to raise her/his arms and then maintain both the arms outstretched; a finger to nose task (FNT), in which the subject, starting from a rest position, has to move her/his finger to the nose 10 times. AOT and FNT tasks are preceded by a single wrist extension movement that has been used as a common reference between patients and tasks for the detection of actual movement intent. An acoustic cue was used to warn the subjects about the beginning of every task. All the recording sessions last between 30 and 50 s.

EEG signals have been acquired at a sampling frequency of 1000 samples per second using tin electrodes; then they have been notch filtered at 50 Hz and low-pass filtered at 60 Hz. The EMG signals have been recorded using two matrices of 6 electrodes [157] with an inter-electrode distance of 8 mm. The best electrode (in terms of SNR) has been chosen and processed for each array. The muscles analyzed in this work, depending on the tasks previously indicated, are the Extensor Carpi Ulnaris (ECU), the Flexor Carpi Ulnaris (FCU) and the Biceps Brachii (BIC). The EMG signal has been notch filtered at 50 Hz, rectified and then low-pass filtered at 60 Hz in order to maintain relevant CMC contributions in this band. Finally all the signals have been sub-sampled at a frequency of 150 samples per second. CMC has then been estimated by using EEG signals from C3 or C4 electrodes, (in a controlateral configuration with respect to the EMG) depending on the arm (right arm – C3; left arm – C4) and using EMG signals from the best electrode of the most relevant muscle involved in each task. A total of 33 trials have been analyzed.

In order to compare the timing of the coherence contributions in the beta band with the actual occurrence of the voluntary movement, standard implementation of Bonato's algorithm for the detection of muscular activation from the EMG signal has been used [123].

### 4.4.9 Analysis on experimental data

Figures 27 to 29 present three different examples of time-frequency CMC maps for the tasks taken into account, together with a rectified EMG plot for every map used as a timing reference for the actual movement.

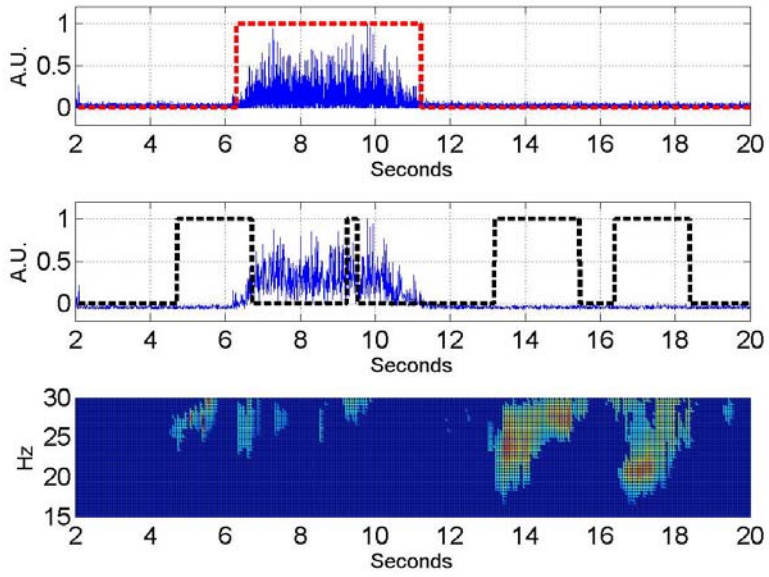



**Figure 27. Top panel represents coherence analysis between C3 electrode and EMG at the right ECU on a rest task for patient 01. Middle panel represents the digital output of the algorithm highlighting CMC contributions in the beta band. Bottom panel shows the corresponding EMG activity estimated using Bonato's algorithm.**

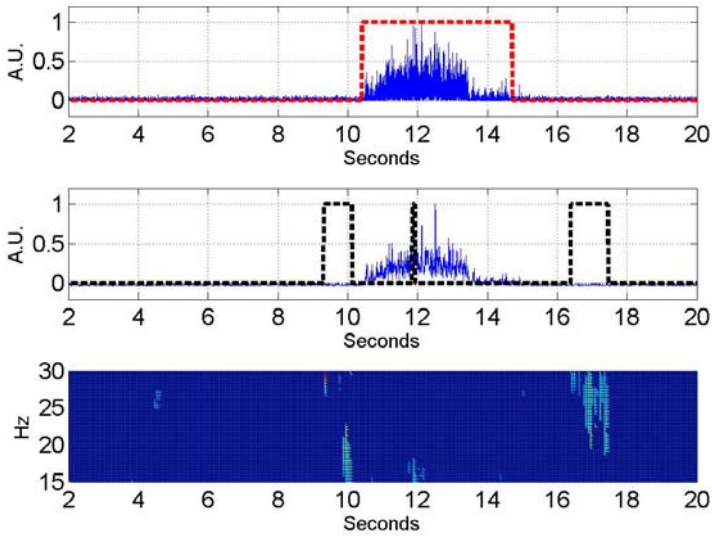



**Figure 28. Top panel represents coherence analysis between C3 electrode and EMG at the right ECU on a rest task for patient 02. Middle panel represents the digital output of the algorithm highlighting CMC contributions in the beta band. Bottom panel shows the corresponding EMG activity estimated using Bonato's algorithm.**

As previously shown, CMC contributions in the beta band have been associated to the planning and execution of the voluntary movement. So the aim of this analysis is to detect coherence intervals in this band before and during the actual movement, and to identify possible recurring patterns in patients and healthy subjects. It can be noticed from the figures that distinctive significant coherence values can be detected in the beta band right before (0.5 s to 2.5 s) the beginning of the first (wrist) movement in the tasks taken into account.

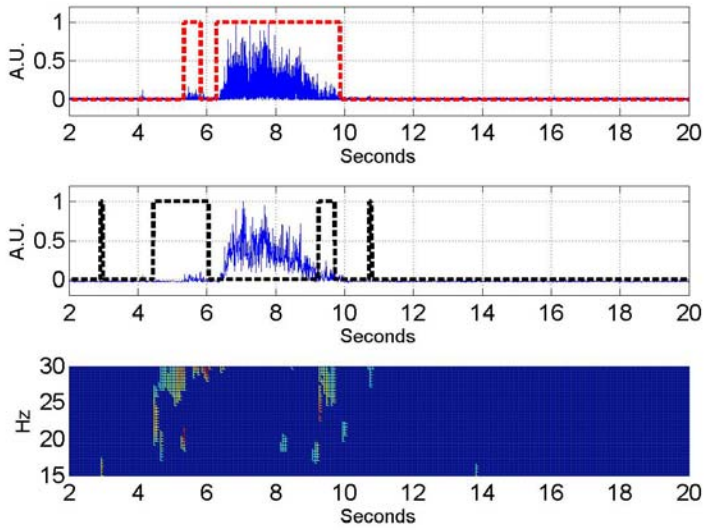



**Figure 29. Top panel represents coherence analysis between C3 electrode and EMG at the right BIC on a FN task for patient 04 during two consecutive movements. Middle panel represents the digital output of the algorithm highlighting CMC contributions in the beta band. Bottom panel shows the corresponding EMG activity estimated using Bonato's algorithm.**

This behavior has been observed in 79 % of the analyzed trials (83 % in controls, 77 % in patients) with a mean value of anticipation of 1.35 s with respect to the actual movement, and a standard deviation of 0.45 s (see table 4.5).

| | Mean Anticipation | Standard Deviation | Observed Percentage |
|---|---|---|---|
| **Patients** | 1.41 s | 0.47 s | 77% |
| **Controls** | 1.06 s | 0.28 s | 83% |
| **Overall** | 1.35 s | 0.45 s | 79% |

**Table 4.5: Mean value, standard deviation and observed percentage on trials values for CMC contributions anticipating the execution of the first movement.**

Also in 50 % of the analyzed trials no significant CMC contributions in the beta band have been observed during the execution of the first (wrist). As observed in literature [144] [149], sustained movements present high beta-band coherence contributions during the execution (as shown in figure 27). Nevertheless, in tasks where several abrupt movements are present, it is not possible to distinguish among CMC changes associated with each single movement.

In conclusion results on simulated signals show that this method is able to provide better results in the time-frequency domain with respect to the Welch's approach. Analysis on data from experimental trials shows how coherence contributions in the beta-band, which have been linked in literature to the execution of voluntary movements, show significant values before and during the actual execution of the tasks. It can be speculated that CMC contributions preceding the beginning of the current movement could be caused by the descending drives modulating tonic muscular activity, triggered by the acoustic cue indicating the beginning of the task [158]. Nevertheless, it is not possible to gain stable information in abrupt movements. No particular differences have been noticed between healthy subjects and tremor affected patients in the tasks taken into account, although it has to be pointed out that no major tremor episodes were present during these trials.

The algorithm that has been presented proves the validity of the use of a BAR approach in the estimation of CMC. The information obtained using this method can be integrated with information regarding muscular activations (related both to tremor and voluntary movement), obtained from the algorithm described in the previous subchapter, and with that coming from kinematic and kinetic sensors. In particular, CMC contributions in the beta band prior to the execution of a given movement can be used as an index of the beginning of voluntary activity, thus putting the basis for the possible integration of this method in a multimodal BCI-driven control system able to drive an assistive device to demote involuntary

components of movement such as tremor without affecting the underlying voluntary activity.

## 4.5 Event Related Desynchronization

Another physiological manifestation of voluntary activity observable through surface EEG analysis is the Event Related Desynchronization and Resynchronization (ERD/ERS). ERD and ERS are two physiological phenomena visible in the EEG activity during the preparation, imagination and execution of voluntary movements. They consist of a decrease of EEG signal power (desynchronization) in the alpha band (8-13 Hz) before the beginning of voluntary movement (or its imagination) from a given baseline calculated during a relaxation status, followed by an increase (resynchronization) in the signal power in the beta band (15-30 Hz) after the end of the execution [159]. These phenomena are considered as caused by the decrease (or increase) in synchronization in the neuronal population underneath the cortical area that reflexes in a decrease of the EEG signal over that area, since the EEG signal can be seen as a "summation" of all the electrical activity going on under the electrode. ERD detection can be used as an index of the onset of movement-related voluntary activity prior to movement execution. During the work on this thesis, three algorithms for the detection of voluntary activity during movement of the upper limb based on ERD/ERS detection have been developed:

- EEG solo algorithm: this algorithm uses only the contribution from the EEG signal to determine the beginning and the end of the voluntary activity; ERD occurrences are taken as onset of the voluntary activity, while ERS occurrences are considered the offset

- EEG-EMG algorithm: this algorithm uses the information obtained from the EMG signal to determine the end of the voluntary activity

- EEG-IMU algorithm: this algorithm uses the information obtained from the IMU signal to determine the end of the voluntary activity

All these algorithms use the EEG signal form electrodes in the cortical area (generally C3 and C4, controlaterally with respect to the moving limb). These electrodes are dereferenced using a spatial laplacian filter that is subtracting the contribution of the 4 surrounding electrodes, opportunely weighted by their relative distance from the electrode under analysis [160].

In the EEG solo algorithm, the signal is filtered and squared in sub-bands within the alpha and beta bands. An observation window l second long is moved over the two versions of the signal. For each version of the signal a value calculated as $\sqrt{2}/2*r$ (where r is the range of the filtered signal in the observation window) is assigned to the central sample of the observation window. The presence of voluntary activity is evaluated on these reference signals by means of a dynamic threshold algorithm. The initial threshold is calculated as the mean of the reference signal in a time-span where no movement has been performed. The movement onset is detected when alpha band reference signal decreases by at least 50% of its power with respect of its baseline for a time interval indicated as *minimum activation time* (*mat*, that is the minimum biological activation time and is used to avoid erroneous transitions). The offset of the movement is detected when beta band reference signal increases by at least 200% for at least the *mat*. After ERS occurrence, new baselines for both alpha and beta band are calculated. This algorithm has been designed in

order to be real-time functioning, with a minimum buffer depending on the length of the observation window used for the non-linear filtering of the signal. The main disadvantage of this approach is related to the variability of the phenomenon under observation. This algorithm has been tested on data acquired from three tremor-affected patients during simple wrist movements. Every patient performed three trials. The algorithm is able to detect the beginning of the voluntary activity before the beginning of the actual movement in all the trials with a mean anticipation of 1.07 s.

Figure 30 shows an example of functioning of the algorithm, while figure 31 shows results obtained on six of the nine trials.

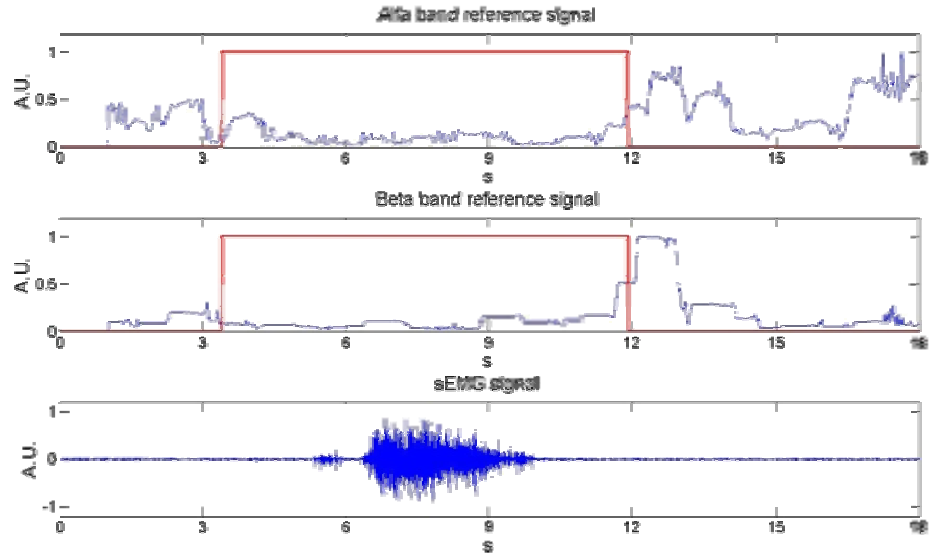



**Figure 30. Example of functioning for the EEG solo dynamic threshold algorithm. Signal in red represents the output of the algorithm, signals in blue represents, from top to bottom, the alpha reference signal, the beta reference signal and the sEMG of the extensor carpi ulnaris (used as reference for the actual voluntary movement).**

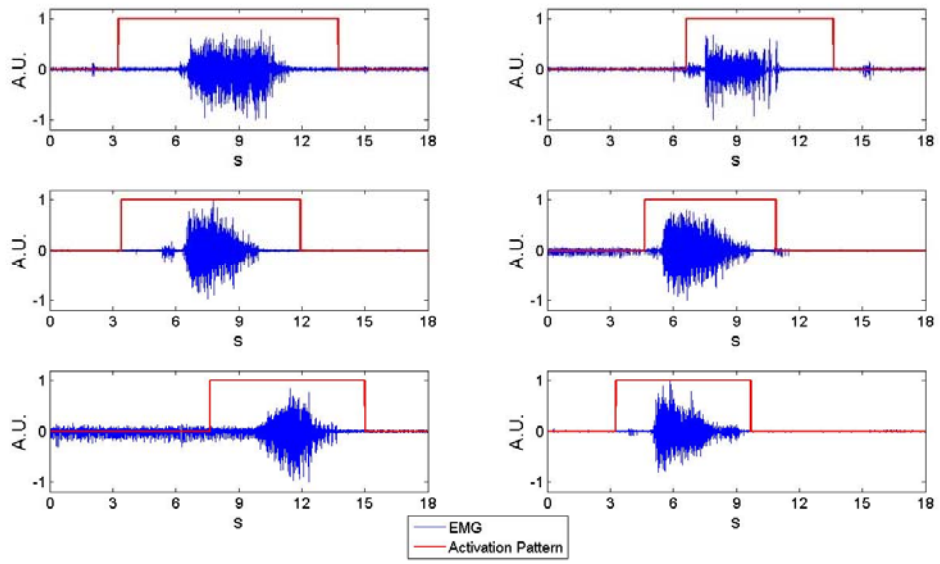



**Figure 31. Results obtained with the EEG solo dynamic threshold algorithm on six of the nine trials analyzed**

The second algorithm, named EEG-EMG, is de-facto a modification of the EEG solo algorithm that uses information from the sEMG signal to correctly estimate the offset of the voluntary movement. This modification allows a better estimation of the baseline power that will be used to determine the ERD event and then the onset of the voluntary activity. In fact, the estimation of the baseline power critically depends from the estimation of the offset of the movement, since the baseline is updated after every detection in order to correctly follow the activity of the cortical area. In this sense EMG signal is able to furnish a more easily detectable index for the end of the voluntary movement. In this algorithm only the contribution of the alpha band of the EEG signal is taken into account and used for ERD detection. The signal filtered in the alpha band is squared and then low pass filtered twice (the first filter being the range filter previously explained, the second one a first order Butterworth filter with a cut-off frequency of 0.1 Hz). The signal thus processed is used for the calculation of the reference power and for the detection of ERD events,

following the same scheme used for the ERD solo algorithm. Surface EMG signal is jointly analyzed by means of an algorithm for the detection of muscular activation intervals (Hodge's algorithm [122], but also the novel implementation of Bonato's algorithm can be used in this framework). Once an ERD event is detected, and with it the onset of a voluntary activity, the offset is then estimated as the offset of the next muscular activation detected on the sEMG signal. Once the offset has been detected, the baseline power is re-calculated. This algorithm has been tested on 3 tremor affected patients. All the signals (EEG and sEMG) have been acquired with a sampling frequency of 1000 samples/s. Every registration consisted of series (8 to 11 movements) of finger to nose (FTN) movements performed in a sitting position. The movements have been triggered by an acoustic signal.

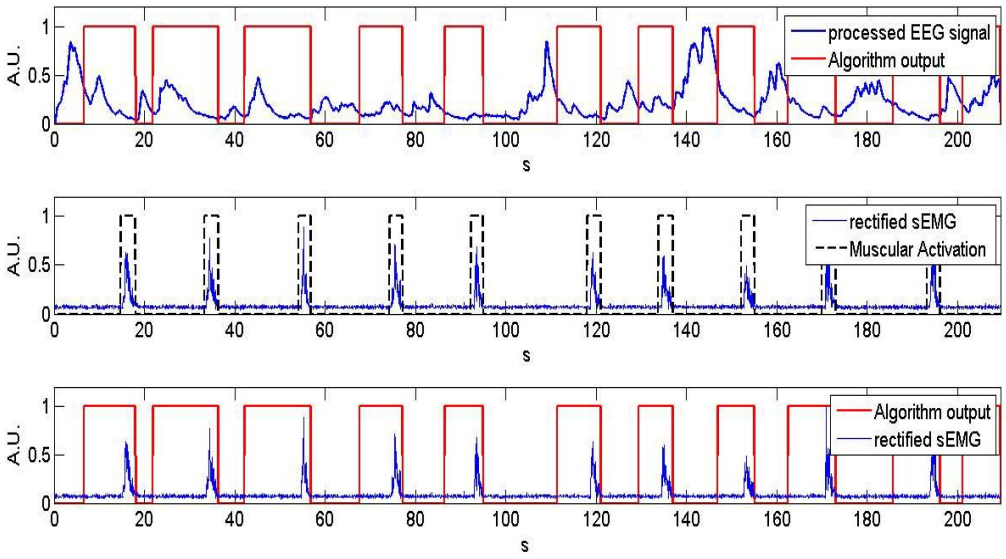



**Figure 32. Example of results for the EEG-EMG algorithm for the detection of voluntary activity in the upper limb. Top figure shows the envelope of the EEG signal in the alpha band used for the ERD detection (blue) and the output of the algorithm (red). Middle figure shows the rectified sEMG signal (blue) together with the output of Hodge's algorithm (black). Bottom figure shows sEMG signal (blue) , as reference for the actual movement, together with the output of the EEG – EMG algorithm (red).**

The patients have been instructed to start every movement some seconds after the acoustic trigger. Time-span between two consecutive movements is about 20 s. Figure 32 show an example of the results obtained using this algorithm. Results, in terms of percentage of correct detections indicate that about 60% of the movements are correctly detected with a mean anticipation of 5 s and a standard deviation of 2.3 s. The other movements are often detected but with a too large anticipation. Since all the movements have been triggered by an acoustic signal, after which the patients were instructed to wait some seconds (3-4 s) and then move, it is not possible to say if the actual ERD occurrence depends on the trigger or on the movement. The percentage of correct detections underlines and confirms the high variability of the ERD phenomenon also in heavily controlled experimental conditions. Onset occurring prior to 8 s to the actual muscular activation has been considered as not caused by an ERD event but as related to standard oscillations of the power of the EEG signal.

The third algorithm (EEG-IMU) directly derives from the EEG – EMG just shown. In this case activity detected form the IMU sensors substitute the information gained from the sEMG signal for the estimation of the offset of the voluntary activity. A simple peak picking algorithm is used for the determination of the offset of the movement from the IMU sensors, while ERD occurrences, estimated as in the previous two algorithms, are used for the determination of the onset of the voluntary activity. Also this algorithm has been tested on a set of data recorded on tremor affected patients. The algorithm has been tested on four patients. Each patient executed 6 trials constituted by 12 movements each. Results in this case have been evaluated in terms of sensitivity and precision of the algorithm [161], already used in BCI systems. The predicted Activation Units (AU, intended as the time interval related to the execution of a single movement, as estimated by the algorithm) were compared against the actual ones determined by gyroscope signal activity. True

positives (TP) were considered when the onset of the predicted AU anticipates the execution of the movement, otherwise the transition was considered as a False Positive (FP). False Negatives (FN) occur when a movement is not detected. Sensitivity rate is then calculated as (TP/(TP + FN)) while precision as (TP/(TP + FP)). The anticipation, for each movement, was also calculated (results in Table 4.6).

| Patient | Precision | Sensitivity | Mean Anticipation |
|---|---|---|---|
| **1** | 69% | 69% | 2.03 s |
| **2** | 91% | 83% | 2.15 s |
| **3** | 66% | 67% | 2.42 s |
| **4** | 68% | 74% | 2.15 s |
| **Group Average** | 73.5% | 73.3% | 2.18 |

**Table 4.6. Precision(TP/(TP + FP)), sensitivity(TP/(TP + FN)) and mean anticipation results obtained using the EEG-IMU algorithm on data recorded on 4 tremor affected patients.**

The main advantage of this algorithm with respect with the EEG-EMG one is that IMU sensors are easier to place with respect to EMG sensors. The former, in fact, only require the user to individuate the right spot on the limb (that can be easily indicated in, e.g., a reference on the sleeve), while the latter requires the correct identification of the muscle belly, that it's not always easy, especially on elderly

subject, and the preparation of the skin. Also kinematic information on one limb represent an integration of all movements going on that body segment, while sEMG activity is only relative to the muscle on whom the sensor is placed on (if not taking into account crosstalk from other muscles). On the other end, information from sEMG sensors is more "on time" than that obtained from IMU sensors, since kinematic expression of movement suffers from electromechanical delay, with respect to sEMG detection. This delay can affect baseline calculation in an approach as the one described above.

In this part of the chapter it has been shown that the cross analysis of EEG and other movement-related physiological signals such as sEMG and IMUs allows early detection of the movement intent, prior to the actual execution of the movement. This has been achieved in two ways:

- Investigating the presence of the descending drives from the part of the brain where they generate up to their manifestation in the muscles of the arm through the Cortico Muscular coherence approach.

- Using the changes in the brain activity due to the generation of a motor plan and of the motor commands and reinforcing this information with that related to the actual execution of the movement, through the ERD based algorithms.

The results that have been shown prove the feasibility, in the context of the development of devices able to limit involuntary activity in the upper limb such as tremor, of a MBCI platform that can give information to the device controller for the not trivial problem of demoting involuntary activity without affecting voluntary movement.

# Chapter 5

# Developement of Methods for the Functional Evaluation of patients

## 5.1 Wearable sensors for the functional evaluation of Parkinson's patients

The last part of this doctoral work has been carried out in the Motion Analysis Lab of the Spaulding Rehabilitation Hospital (Physical Medicine & Rehabilitation Department, Harvard Medical School, Boston), and has been focused on the study and application of wearable sensor based technologies to the functional evaluation of the motor symptoms of the Parkinson's Disease. The term "wearable sensors" [162] is intended to include all those technologies that can be used and worn by patients during the normal activities of daily living.

Classical examples of this kind of sensors are inertial sensors (IMUs, accelerometers, gyroscope) or vocal transducers (microphones). These sensors are nowadays integrated in most of the mobile devices commonly used in everyday life, such as mobile phones, smart phones, tablets, computers and video games.

Inertial sensors give information on patient's kinematics and thus on its activity and functionalities. This makes them a useful tool for the evaluation of patient's disabilities during everyday activities. As introduced in chapter 1, the evaluation of the progressing of Parkinson's disease is generally performed by the clinician during routine screening visits. During these visits the patients are asked to report about their condition (with the help also of patient's diary, to track changes of the symptoms during the day) and to perform standard motor tests and questionnaires. These tools are then scored by the clinicians using standardized rating scales such as the Unified Parkinson's Disease Rating Scale [54] (that scores single features and tests performed by patients in a scale of severity from 0 to 4).

A number of studies [163] [164] have recently proved that information gained from data extracted from wearable sensors can be reliably used in predicting clinical

evaluation scores (such UPDRS scores in the case of PD patients) given by clinicians during routine visits. This kind of evaluation tool, if translated in devices for home monitoring of patients to be used in standard clinical practice, may have a positive effect on the quality of life of patients and on the simplification of the clinical care. In fact, the development of tools that can be used directly by the patients in their home for the evaluation of the ongoing status of their disease can:

a) Reduce the number of clinical visits

b) Reduce the related costs

c) Allow a more frequent evaluation of the patient's status.

All these benefits can positively affect the clinical therapy for both patients and clinical structures. In the particular case of PD, wearable sensors have been also used for the evaluation of motor fluctuations during the day. The term "motor fluctuations" refers to all the motor complications and changes in the severity of motor symptoms in patients during a medication cycle. Motor fluctuations shows up in a significant percentage of PD patients after some years of levodopa therapy. They consist often of wearing off periods of the therapy during the day and in unpredictable dyskinesies. All these complications cannot be easily evaluated during standard routine clinical visits (since the transition between a "normal state" and a fluctuation event should happen right during the clinician's visit in order to be tracked) and their tracking is based on patient's reports and diaries (where the patient has to report, for example, the amount of time he spends in the OFF state during the day). These instruments lack of the necessary objectivity for a sound clinical evaluation. An alternative solution could be to perform multiple continuous

screenings of the patient by the clinician during the whole medication cycle that can be costly. Moreover scoring such as UPDRS suffers from inter-operator subjectivity [165].

In this framework wearable sensors can be used for tracking the changes in the motor behavior of the patients during the whole day, thus reporting information on the frequency and gravity of motor fluctuations. This can be an useful information for physician that can decide to change ore better tune the pharmacological therapy of the patient depending on the evolution of the symptoms, reducing the costs of the therapy and increasing its quality and with that, that of the life of the patients [8] [9].

Many studies in the last years [166] [167] [168] [169] have been focused on the use of data mining techniques to features derived from large datasets of patient's kinematics, acquired using wearable sensors. It has been demonstrated that features describing kinematics of the patients during standardized tests are highly correlated with the clinical scores (e.g. UPDRS) that clinicians derive from such tests. These features can be standard descriptive statistics ones (such as mean value, median, standard deviation), frequency features (such as peak frequency, useful for the evaluation of tremor), or also statistical properties of the signals (such as entropy). The signals used in these kinds of studies are usually accelerometric signals acquired from sensors placed on the lower and upper part of the limbs of the patients and on their waist and trunk, in order to catch changes in status in all the body segments without losing postural information. The features derived are then usually rated (in order to promote features carrying the most information) and then "fed" to data mining model for status classification or scores prediction. Ideally the information on the scores can be useful for the clinician to track changes in the state of the patients during the medication cycle and tune the therapy accordingly.

This design scheme follows the general framework in biomedical engineering of information gathering (features extraction), integration of information (data mining techniques applied to the features) and delivery of assistance (the clinician knows the current state of the patient and changes the therapy accordingly) presented in the introduction. It has been shown that inertial sensors are in particular well suited for the tracking of motor symptoms such as tremor, bradykinesia, dyskinesia and akinesia. Nevertheless muscular rigidity, that is one of the primary motor symptoms in PD, is not easily observed using only this kind of sensor.

But kinematical data are not the only kind of data acquirable from wearable sensors that can carry information related to the motor symptoms of PD. Recently some studies demonstrated the feasibility of using data mining techniques on features extracted from datasets of vocal signals acquired from PD patients for the estimation of their motor UPDRS scores [163][164]. In fact, one of the secondary PD symptoms, directly related to the primary motor symptoms, is the degradation of the quality of patient's voice, both in terms of phonation and production of syllables and words. This drop in quality of voice is mainly caused by tremor and rigidity in the muscles involved in the production of voice in the larynx and in the mouth and is often indicated by patients as a major reason for discomfort [170] [171] [172] [173].

It is then fair to assume that, since voice degradation has been linked to muscular rigidity, the parallel use of signals regarding the kinematics of the patients (e.g. accelerometers) and vocal signals can represent a viable solution for the development of new wearable sensors based platforms for the correct evaluation of the primary motor symptoms related to PD in the household. In fact, while inertial sensors have been proved to be a useful tool for the estimation of symptoms such as tremor and bradykinesia, in such framework the vocal signals can be used for the

estimation of rigidity impairment level. During this thesis work a protocol for a feasibility study on such kind of platform has therefore been developed.

## 5.2 Development of a protocol for the evaluation of patients PD symptoms using vocal signals.

The design of the proposed protocol is based on the analysis of vocal, accelerometric and force signals from a sample of about 10 late stage PD patients. The analysis will be based on features extracted (gathering) from these signals and the application of data mining techniques (integration) on these features for the study of the correlation of the characteristics of vocal signals with patient's UPDRS scores, giving particular attention on muscular rigidity (delivery). This kind of framework is similar to that presented in Patel et al. [163] for the estimation of UPDRS from inertial sensors.

Some studies have shown that particular features extracted from the vocal signals are significantly different between PD patients and normal subjects, and can be used to correctly discriminate between controls and patients [171] [172] [173]. Also, more specific works showed that a number of speech features change in PD patients with respect to healthy subjects, and theorized the relation between the primary motor symptoms and the direction of the change in these features [171].
One example is the Fundamental Frequency of the voice (that is the principal frequency component of the voice during speech) during elaborate passages. Parkinsonian patient's voice is often labeled "monotonal" since the effects of their impairment on the vocal tract do not allow them to change voice intonation easily. Thus fundamental frequency has less variation during speech. A selection of the features investigated in these works has been chosen for the estimation of muscular

rigidity in the proposed protocol. Tremor and rigidity in the laryngeal and pharyngeal muscles can cause a loss of elasticity and impaired activation timing in these muscles, affecting the vowel production capacity of patients. Thus one of the tasks that the patients will be asked to perform is vowel production (four corner vowels each for three seconds). Features that will be extracted during vowel production are:

- Mean and median fundamental frequency (for the vowels /a/ and / i/)
- Range and Standard deviation of the fundamental frequency
- Jitter (that is the instantaneous change in the fundamental frequency) expressed both in percentage and as absolute value
- Shimmer (that is the instantaneous change in the voice intensity) expressed both in percentage and as absolute value
- Noise to Harmonics ratio
- Harmonics to Noise ratio
- Intensity
- Vowel Area (that is the area of the quadrilateral obtained plotting the first two formants of the four fundamental vowels /a, i, o, u/
- Non-linear features [174], that are features shown to be unrelated to the morphological characteristics of the patients, such a pitch period entropy, D2 coefficient, recurred period density entropy and de-trended fluctuations analysis)
- Cepstral Coefficients [175] (that are coefficients often used in speech recognition)

Primary motor symptoms (rigidity and tremor) in the facial muscles can cause instead problems in the production of syllables and words. For this reason a standard test in voice analysis of PD patients is based on the reading of standardized passages (such as the *Rainbow Passage*) or phrases. The features that will be extracted from these tasks are:

- Mean fundamental frequency during all the passage
- Jitter
- Percentage of voiced time with respect to pause time
- Fundamental frequency changes during the onset and offset of a mute consonant such as /f/ [173]
- Voice onset timing, that is the time that passes between the end of a consonant (such as /p/, /t/ or /k/) and the beginning of the following vowel

These tests will be performed for at least 5 sessions with a 30 minutes interval between consecutive sessions.

During the process that led to design of this protocol, some preliminary analysis have been carried out on a dataset of voice signal acquired from PD patients, in order to determine if this set of feature is able to discriminate between healthy control subjects and PD patients and to eventually track changes in vocal characteristics of patients during the medication cycle.

This preliminary analysis took into account 2 late stage PD patients and 1 healthy subject. Vowels and passage tests have been performed 7 times in a 4 hours span, with a 30 minutes interval between two consecutive tests, in order to catch variations inside a medication cycle.

Vocal features have been derived from the voice signals recorded during the tests and a preliminary reduction and projection of the dataset has been performed using Principal Component Analysis [177] and Sammon's maps [176] on the features sets.

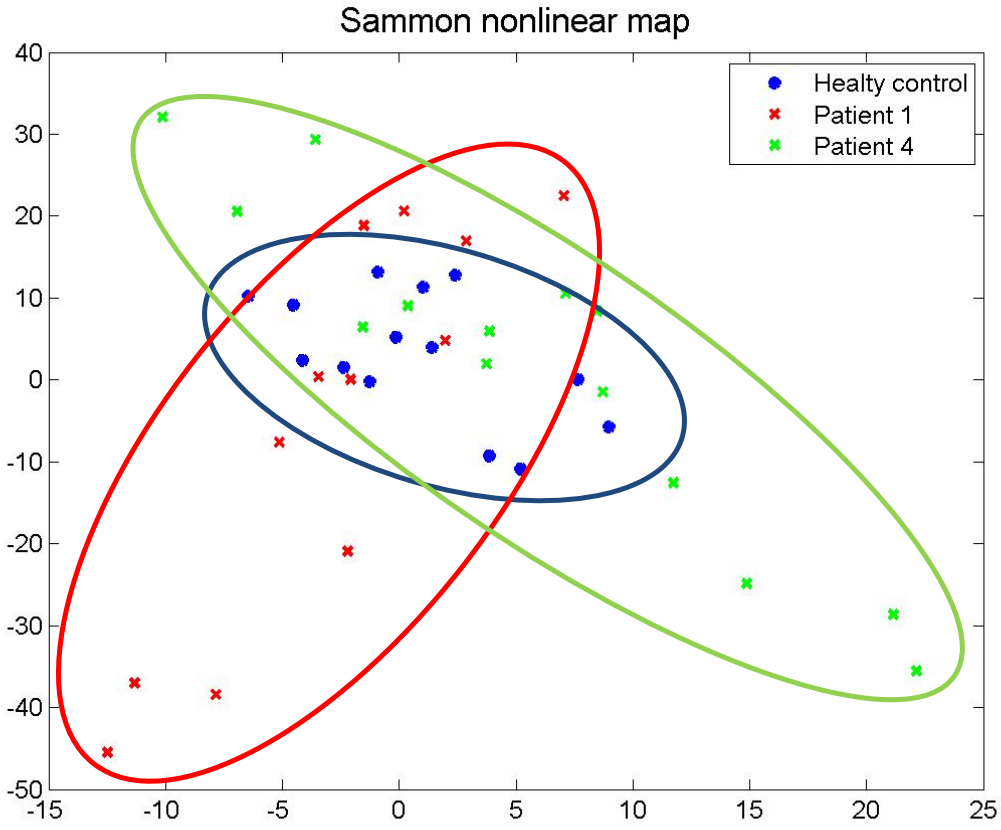



**Figure 33. Sammon maps obtained from the features of the two patients and the control subject.**

The map that has been obtained (shown in figure 33) highlights that the dimensionality of the feature projection in the Sammon space is much more extended for the PD patients than for the healthy subject. Also it has been highlighted that tasks "closer", in the Sammon space, to the area described by the features of the healthy subject are the tasks executed in time intervals right after the

intake of medication, when PD symptoms are generally lower in patients affected by motor fluctuations.

Similar results have been obtained from the study of the dispersion of the first principal component of the features space. In patients the first principal component obtained from the features (that describe in this case the 95% of the overall variance) has a higher variance during the 7 trials with respect of the same analysis performed on the features of the healthy patients.

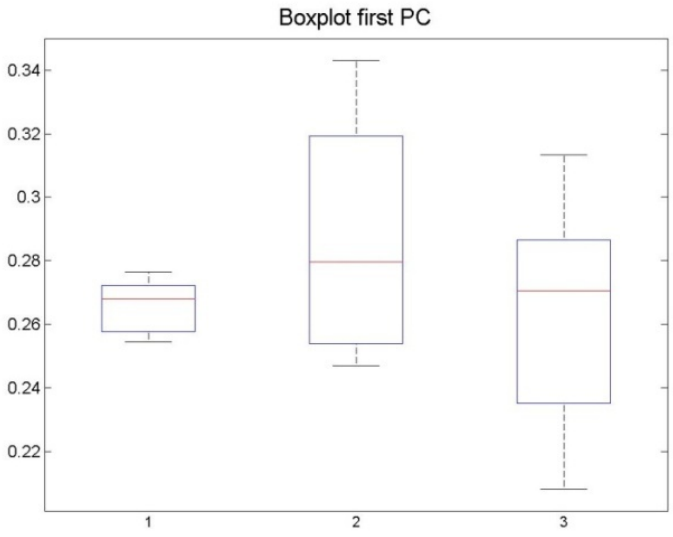



**Figure 34. Box plot of the mean value and variance of the first principal component obtained from the vocal features during the seven trails for the healthy subject (1) and the two PD patients (2 and 3).**

Thus the set of features that has been selected has been demonstrated to be able to classify between healthy subjects and PD patients. During the tests motor impairment will be measured using accelerometers and UPDRS scores during standard motor tasks used in PD evaluation. Also a numeric estimation of rigidity

will be evaluated from the UPDRS and from data obtained using the isokinetic device Biodex System 2. This device will be used to induce passive elbow flexion-extension movements to the patient. The resistance (in terms of torque and joint stiffness) expressed by the patient during this test will be used for a numerical estimation of the rigidity. The patient will be asked to lay his arm on a support, his wrist strapped on it and its elbow centered on the rotation center of the device. The limb of the patient will be moved by the machine at different speeds (20, 40 and 60 degrees per seconds) in a range of motion going from 45 to 140 degrees. Joint stiffness during the movement will be evaluated as the slope of the angle-torque curve between 100 and 120 degrees [178].

**Figure 35. The Biodex device**

Classification and regression techniques will be then used on vocal features (or on subsets of them) in order to discriminate and eventually try to predict the rigidity level of the patients. If this goal will be achieved with the desired precision, it will be then possible to integrate the information about rigidity obtained from speech

signals to that of bradykinesia, tremor and dyskinesia obtained from inertial sensors. This information can be used to gain a better estimation of the state of the patients, in terms of progression of the symptoms and discontinuity of treatment. This proposed system represents a novel solution for the evaluation of impairments in the upper-limb caused by PD and inserts in the framework of the proposal of new methods whose primary goal is to help clinical staff in managing and evaluating patients.

# Conclusions

The progressive ageing of the population in the developed countries has raised the attention on degenerative disorders that affect people in the late stages of their life. These disorders, such as the Parkinson's Disease, and the consequent motor impairments they bring, can be non-life threatening, but affect deeply the quality of life of the patients, reducing their ability to move freely or perform tasks that are common in the activity of daily living. Also the costs associated to the clinical care of this kind of patients rise over-time.

In this context, the development of new techniques and devices able to produce a positive effect on the quality of life in disabled elderly and to simplify and reduce the costs of the clinical care is a matter of importance. These new tools can be devices designed for helping patients during their normal activities, devices studied to enhance the rehabilitation outcome, or also methods that can help clinician in better evaluating the overall progressing of the patients. In this framework, the results presented in this dissertation show some examples of new methods and technologies for helping people with disabilities of the upper limb.

In this context, the development of novel solutions is based on a general scheme consisting of these steps: extract valuable information about the actual characteristics of the disability; integrate this information into a more usable one and finally use it to deliver assistance to the patient. In this dissertation, this scheme has been applied on both the development of assistive devices for tracking and limiting involuntary expressions of movement of the upper limb and the design of new evaluation techniques for estimating patient's actual level of impairment. Some novel devices designed for the counteraction of tremor in the upper limb have been presented, such as the TREMOR device. Also many of the key aspects related to the

design of the latter and similar devices have been addressed and described such as, for example:

- The proper classification between involuntary and voluntary activity using physioelectrical signals such as EEG and EMG, as information to be exploited in the functioning of the device

- The study of the principles of biologically inspired motor control as a mean for an intelligent design of the overall control architecture

- The development of simulative tools for the testing and implementing of the tremor control strategies, for integration of information and delivery of assistance

The first point is of particular importance. The framework of the development of automatic and adaptive assistive devices of the upper limb, in fact, deeply relies on sound information about the actual (residual or impaired) activity of the patient. As a matter of fact, if the goal is to design solutions that are supposed to be used by patients during activities of daily living, these devices need to be effective and consistent in their behavior in all the possible situations. This can be achieved only maximizing the flow of information on ongoing movements by means of a multivariate analysis of the biggest possible number (the limit being the design of the device) movement-related signals. Also the reliability of this information has to maintainacceptable levels during the projected functioning time of the device. In the framework of tremor-limiting devices the most information to be extracted are those about:

- The tracking of tremor, in terms of tremor temporal and spatial characteristics.

- The proper classification between voluntary activity and tremor itself.

The first point has been investigated extensively in literature and has been addressed in this work by proposing a novel implementation for a statistical method for the evaluation of muscular activation patterns in muscles. Information about the timing of sEMG activity can be easily used for the tracking of movements and of tremor, with a small anticipation with respect of kinematics signals given by the electromechanical delay. Thus a stable and error-resistant (with respect to dynamical recording conditions such as changes in the SNR of the signal) detection algorithms can represent a useful tool in the context of providing reliable information about actual movement to assistive devices control systems.

Regarding the classification between voluntary and involuntary activity, two different techniques for the estimation of movement intent using the EEG signal, together with other movement-related signals such as sEMG and IMUs, as in a multimodal BCI framework, have been described. It has been shown that these signals together, are able to give insights on the onset of voluntary activity before the actual execution of the movement. This timing information can be crucial for the correct tuning of a rehabilitative device that has to promote correct voluntary activity and demote disability-related movements. It has been then shown in this work that integration of information of different nature but related to the same event could represent a viable solution for this issue. All the algorithms proposed in this work are, from the methodological point of view, completely novel, but all exploit well-known theoretical frameworks (such the one behind the sEMG detector) or clinically known and well observed physiological phenomena (such as Cortico Muscular Coherence and Event Related Desynchronization) in a solution-oriented approach.

Regarding the second aspect, that is the study of the motor control system of the brain as a replicable model, a comprehensive study and classification of the literature has been carried out. It has been shown that soft computing techniques, such as artificial neural networks, can mimic the overall architecture and functioning of the actual networks involved in the generation of the human motor behavior. Moreover, it has been shown the way neural networks can be used in the development of biologically inspired control systems for tremor reduction devices. The concept behind this part of the work is that in order to develop sound technologies able to help motor impaired persons, a deeper understanding on the biological mechanisms driving motor control is surely needed. Even if the field of mechanism for motor control is still far to be completely uncovered, and the review work pointed out that it is also in continuous evolution, many modeling solutions for these functional structures have been proposed in the past few decades. The development of biologically inspired models can help in both understanding better the mechanisms behind motor production, simplifying the task with respect to an unrealistic deterministic approach, and designing applications that can help restoring movement execution in impaired persons by using the same functional principles exploited by the human motor control system. These applications will have to serve as complementary neural control system for the malfunctioning one in the brain.

Finally, the importance of modeling solutions for the integration of information and as benchmark platforms in the development of novel devices has been pointed out. A biologically inspired control system for tremor limitation on the upper limb by means of FES has been implemented during this work and described in this dissertation. This system proves the feasibility of developing a biologically inspired control system able to translate information about voluntary and involuntary components of the movement into a control signal for an “assistance delivery system” that, in this case, is represented by the theoretical FES system applied on a

biomechanical arm model. Moreover, dealing with patients whose impairments can be particularly different from case to case, fully customizable simulative tools are helpful for the correct design and testing of a device or even for a theoretical intervention principle. All the design problems related to the development of a biomechanical 3D model of the upper limb have been addressed and discussed.

In the last part of this dissertation an insight of the design of methods for the classification of motor disabilities level and the estimation of clinical scores (such as UPDRS) has been shown. These methods, if effective, can improve the quality of life of patients and simplify the clinical care, thus reducing its overall costs, by:

- allowing more frequents screening visits

- allowing the clinician to adjust medication intake depending on patient's current status
- diminishing the number of visits to the clinical facilities by the patients by mean of remote home screening

In the particular case of Parkinson's disease, motor fluctuations related to the levodopa treatment can highly affect the quality of life of late stage patients. In order to limit this counter effects of the pharmacological therapy, medicine intake needs to be properly regulated with respect of the frequency and gravity of the motor fluctuations events. It has been demonstrated in literature that it is possible to estimate clinical scores relative to UPDRS tasks by means of inertial sensors. The latter can easily track changes in tremor, bradykinesia and dyskinesia gravity during the medication cycle, but cannot reliably estimate muscular rigidity features of the patients. In the final part of this thesis a new protocol for the estimation of muscular rigidity, both in terms of UPDRS scores and quantitative measures, has been presented. The rationale of this proposed study is based on the concept that

muscular rigidity deeply affects the vocal ability of the patients, both in terms of phonation and syllables and words production. Thus, it has been hypothesized that the study of changes in vocal characteristics of patients during the medication cycle can be related to their rigidity level. Hence, a new evaluation method has been proposed. The aim of this novel proposal is to design a system able to gather information from voice signals and translate it into a clinically usable one.
This information, together with that obtained from inertial sensors, can allow clinicians to have a complete and precise screening of the patients.
These kinds of techniques, together with the ease-of-use of these sensors and with the fact that nowadays many devices normally used in daily activities include these sensors such as microphones and accelerometers, can help the future design of effective home monitoring systems for patients. In such kind of systems the clinician, by having the possibility to access more frequent screening of the patient, is able to deliver the assistance by correctly and timely tuning the therapy in time.

The framework of rehabilitation of the upper limb, with a particular interest to age related disabilities such as Parkinson's Disease is a field in continuous evolution, thanks to availability of always newer, smaller and cheaper technologies. Beside none of the solutions that have been developed so far in the literature and exposed in this thesis has reached the goal to be a standard in clinical practice, some developing guidelines can be extracted in this framework from this and previous works. In this work some of these guidelines have been shown and novel solutions have been proposed. In particular, in the first part of the thesis, the importance of modeling solutions in the understanding of movement production and the development of assistive solutions has been pointed out, while in the second part, a whole of algorithms and methods for gathering and integrating different information coming from different biological signals for the evaluation of patients' status and activity have been exposed.

The methods and results shown in this work could hopefully represent an extension of the knowledge in this field, and could, thereby, favor the design and development of new assistive devices and evaluative techniques.

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