UNIVERSITÀ DEGLI STUDI DI SALERNO

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Ministero dell'Istruzione, dell'Università e della Ricerca

Dottorato di Ricerca in Ingegneria dell'Informazione

Facoltà di Ingegneria
Dipartimento di Ingegneria dell'Informazione ed Elettrica e Matematica Applicata

A neurocomputational model of reaching movements

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Anno Accademico 2014-2015, XIII Ciclo – Nuova Serie

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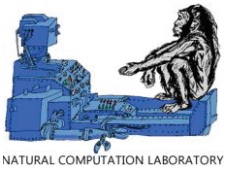

NATURAL COMPUTATION LABORATORY

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TESI DI DOTTORATO

A neurocomputational model of reaching movements

CANDIDATO: **ANTONIO PARZIALE**

COORDINATORE: **PROF. MAURIZIO LONGO**

TUTOR: **PROF. ANGELO MARCELLI**

Anno Accademico 2014 – 2015

To my mother Teresa,
my father Elio and
my sister Margherita

Acknowledgments

One's Personal Legend is what you have always wanted to accomplish. Everyone, when they are young, knows what their Personal Legend is. At that point in their lives, everything is clear and everything is possible. They are not afraid to dream, and to yearn for everything they would like to see happen to them in their lives. But, as time passes, a mysterious force begins to convince them that it will be impossible for them to realize their Personal Legend [...] whoever you are, or whatever it is that you do, when you really want something, it's because that desire originated in the soul of the universe. It's your mission on earth

...

The alchemist
Paulo Coelho (1988)

A long time ago I was strolling with my family and some friends along the streets of my city. A man in a wheelchair needed to get on the sidewalk and my father helped him. I was seven years old and I promised to myself to become a doctor for helping people as that man.

The ways of destiny are strange and even if I became an engineer, I have spent the last four years of my life studying how brain controls the execution of movement, one of the key questions that researchers attempt to answer for helping people with movement impairment.

I don't know if it is really my *Personal Legend*, but I want to

thank all the people I met over these years.
First, I want to thank Prof. Angelo Marcelli, my mentor. If it had not been for him, I would never start my Ph.D. because of my doubts and worries. Thanks to him I met people from different countries and I lived experiences that improved me a lot. I owe prof. Marcelli my personal and professional growth.
I thank Adolfo Santoro and Rosa Senatore, my colleagues and friends, for the beautiful moments spent together since my master degree. We had the opportunity to do special things together and I hope new ones will come.
I thank Prof. Antonio Della Cioppa, for introducing me to the evolutionary computation and the interesting discussions on research.
I thank Prof. Claudio De Stefano, for the opportunity to work together on another interesting research topic as the character recognition.
I thank Canio Di Cairano, the irreplaceable friend of the last years always ready to support me.
I thank Gianmarco Ragognetti, the friend and the artist that painted the cover of this thesis.
I thank Antonio Genovese, Luca Aquino, Raffaele Raimo, Antonio Festa, Eustachio Caliano and Carmine Mazza, my long-time friends always present.
I thank Luca Greco, Donato Barbuzzi, Cristina Carmona Duarte, Moises Diaz Cabrera and all the people that I met in the Natural Computation Laboratory, for the interesting and amusing conversations and the nice days spent together.
Eventually, I thank my family for all the support and love they gave me. They taught me that to love, to be kind and to smile are the simplest and the rightest ways to accomplish our *mission on earth*.

25th april 2016,

Antonio Parziale

Contents

Introduction

How the brain controls movement is a question that has fascinated researchers from different areas as neuroscience, robotics and psychology. The relationship between life and movement is so strong that scientists belive that movement is the reason behind our evolution [SW04]:

> *The vertebrate central nervous system evolved to learn how, when, and where to move. The basic neuronal and synaptic mechanisms that evolved to do that job also support other forms of learning, and therefore provide the basis for all knowledge.*

Similarly, the neuroscientist Daniel Wolpert argues that the brain is not evolved to think or to feel but to control movement [Wol11]:

> *We have a brain for one reason and one reason only, and that's to produce adaptable and complex movements. There is no other reason to have a brain. Think about it. Movement is the only way you have of affecting the world around you. [...] Everything goes through contractions of muscles. [...] So think about communication: speech, gestures, writing, sign language. They're all mediated through contractions of your muscles.*

The ease with which we perform movements efficiently and effortlessly hides complex neural processes that subserve movement execution and that are only partially understood. The simplest

action, as reaching for an object, requires the activation of tens of different muscles, each of which is made up of many muscle fibers receiving neural inputs via their own nerve fiber.

It has been hypothesized that the central nervous system simplified the control of movement thanks to a hierarchical and modular architecture. The spinal cord is the lowest level of hierarchy that hosts a group of cells (the interneurons) that are organized in functional modules, each of which activates a set of muscles [BA15]. Cortical motor areas are the higher levels of the hierarchy that recruit and combine the spinal modules to control different movements [dT07]. However, how the higher levels activate the spinal cord to execute a specific movement is still not clear and it needs to be investigated.

In order to properly plan movements and to activate muscles for executing the desired action, highly interconnected brain regions have to integrate sensory information from several sources. The major cortical area involved in the generation signals for activating spinal cord modules is the primary motor cortex.

A longstanding controversy concerns whether the neural activity of this brain area codes kinematic or the kinetic parameters of the movement. This issue is of fundamental importance in different field of application, from neuroprosthetic to the design of pattern recognition systems. To understand how we move is not only an intellectual challenge, but it is important for finding new strategies for nursing people with movement diseases, for rehabilitation and to develop new robotic technology.

People that have lost control of voluntary movements due to spinal cord injury, brainstem stroke and amyotrophic lateral sclerosis can recover mobility and independence thanks to brain machine interfaces (BMIs) that translate neuronal activity recorded from the primary motor cortex directly into control signals for assistive devices [HBJ+12] [SHY+14]. An approach to recover lost sensory and motor abilities in amputees and patients with tetraplegia is to supply them with implants that provide a direct interface with the CNS allowing to control the movement of a cursor or robotic limb, while another interface conveys sensory information

about the consequences of these movements back to the patient [RCP+14]. In this scenario, to understand what kind of parameters is encoded by the motor cortex is very important in order to design a good decoder that transforms the neural activity of the patient into the movements of the artificial arm. In fact, if the discharge of primary motor cortex neurons carry kinetic information, then a kinematic decoder that predicts only the movement trajectory may show an unpredictable behaviour if the user attempts to pick up a load [BM14]. Despite decades of research, we are still far from detecting the patient's intent and transforming it into an effective control signals [CBNvdS15].

Understanding which kind of parameters are encoded by the brain for controlling movements can be very useful in the design of new handwriting recognition and signature verification systems: it is possible to define a new set of features and new similarity measures that take into account the complex generation process underlying the production of the patterns [MSP+14] [PM14].

In order to understand how the brain controls voluntary movements and to encompass the controversy about kinematic and kinetic parameters, it has been proposed to combine the efforts of physiologists, molecular biologists, and computational neuroscientists [BA15] [ALP07]. In particular ***computational models*** can be used to simulate movement tasks for comparing simulated with real behaviours, and for evaluating new hypothesis of how brain signals are processed to achieve sophisticated motor control [Kat03].

The complexity of neural networks within anatomical structures of the sensorimotor system makes it impossible to characterize how they work and their input-output transformation. Computational models are therefore essential for predicting these non-intuitive interactions and provide insight into the possible transformations that a neural network can apply to a range of input signal patterns [LT15].

The research presented in this thesis aims at understanding how primary motor cortex and spinal cord cooperate to execute a reaching movement, and whether a modular organization of the

spinal cord can be exploited for controlling the movement.

We propose that the execution of voluntary movements results from the cooperation of different clusters of neurons distributed in the rostral and caudal regions of primary motor cortex, each of which activates different functional modules in the spinal cord. In particular, both kinetic and kinematic aspects of movement are represented by primary motor cortex, and the descending corticospinal impulses specify the activation of modules in the spinal cord. In order to validate our hypothesis we have developed a computational model of the spinal cord circuitry and of its interaction with supraspinal areas.
The thesis is organized as follows:

- *Chapter 1* reviews the different point of views about how and what the primary motor cortex encodes. Furthermore, it presents new physiological findings showing that primary motor cortex is organized in two different areas: the rostral one contributes to motor output by activating spinal interneuron, the caudal one directly activates alpha motoneurons.

- *Chapter 2* analyzes what is known about the interaction between spinal and supraspinal networks from studies on the modular organization of the motor system. It presents the proposed model of the spinal cord and its differences respect to other models in literature.

- *Chapter 3* presents a functional modules organization of the spinal cord interneurons modules. The chapter describes experiments showing that it is possible to move an arm to a desired position by recruiting spinal modules using different strategies. The results of experiments suggest that the central nervous system can adopt a simple solution to controlling the large number of muscle fibers by selecting and combining the right spinal interneuronal modules. This chapter also shows that the correction of an ongoing movement can be executed in time by properly modify the recruitment of the functional module that hosts propriospinal interneurons.

- *Chapter 4* exploits the Fitts' law and the proposed computational model to get more insights about how brain encodes movements and to unveil the role played by the different area of the primary motor cortex in determining the trade-off between speed and accuracy.
- *Appendix A* presents the neuromusculoskeletal model used in the experiments to simulate the execution of an elbow flexion movement performed by a human upper-arm.
- *Appendix B* presents the Sigma Lognormal model, a model used in this thesis to verify that the movements generated by the proposed model were human-like.

Chapter 1

The movement representation problem

1.1 Introduction

The primary motor cortex (M1) is a major source of descending motor commands for voluntary movements. While there is an agreement about its role in the execution of voluntary movements, what features of movement are actually encoded (and how) by the neural activity of this brain area is still debated. As a matter of fact M1 appears to convey a multiplicity of information, from the force that has to be generated by a particular muscle to the displacement or position of the limb.
The movement representation problem is a longstanding controversy between the supporters of kinematic parameters and the supporters of kinetic parameters. In this chapter we will review the different point of views about what (and how) is encoded by the neural activity of the motor cortex. On the basis of new findings about the primary motor cortex organization, we will show it is possible to argue that both the representations are used in parallel.

1.2 The origin of the controversy

The motor cortex is the most examined brain area from anatomical, physiological and functional perspectives since 1870, when Gustav Fritsch and Edvard Hitzing discovered that the electrical stimulation of a dog's cerebral cortex produces movements [FH09]. Their central findings were that:

- the stimulation elicits contractions of the muscles on the contralateral side of the body;
- movements were evoked only by stimulating the frontal lobe of the cortex but not the posterior one;
- the stimulation of specific parts of the cortex activated specific muscles, the excitable sites forming a map of body movements;
- the lesion of a site of the motor cortex impaired the movements produced by the stimulation of that site.

Three years later, David Ferrer obtained the same findings by stimulating the cerebral cortex of a monkey [Fer74]. Both those seminal studies were the first experimental demonstration that the cerebral cortex was electrically excitable and that a circumscribed region of the cortex was devoted to the control of movement. As described in [TG03], the two studies had considerable differences in the methods, results and interpretation of experiments. Fritsch and Hitzig stimulated the cortex with low galvanic currents and described the resulting motor responses as spastic twitch-like contractions of one or a few muscles. In contrast, Ferrier used a faradaic stimulation, which allows to apply longer stimulus durations without damaging the tissue, and reported evoked responses that looked like coordinated multi-joint fragments of natural behaviors.

These investigations were the beginning of a debate about the nature of *the representation of movement in the motor cortex* that continues still today: does the motor cortex control the contractile

activity of groups of muscles or the coordinated muscle activity required for reaching? The electrical stimulation of the cortex showed that the twitch evoking sites were organized in rough map of the body.

The view of a motor cortex as set of muscles arranged in a topographic order was confirmed by the studies on human motor cortex performed by Penfield in 1937 [PB37], which showed that the musculature involved in fine motor control occupies more space than the other muscles. Mapping experiments performed with brief, low-intensity stimuli, led to argue that motor cortex is a mosaic of individual columns, each controlling a single muscle [Asa75].

Other experiments showed that motor cortex is not organized in a muscle-by-muscle map but instead the activity of each neuron affects the activation of many muscles crossing many joints [CF85]. Eventually, in the last decade, the use of prolonged electrical or optogenetic stimulation has suggested an organization of motor cortex according to classes of behavior [GTM02] [HAM12].

1.3 Neural Encoding

"The motor code hunt" began in earnest with the development of single unit recording in behaving monkey [Jas58] and its use in the primary motor cortex [Eva66]. The study of how information is represented by the electrical activity of neurons or networks of neurons is known as *neural encoding*. These studies aim to characterize the relationship between neural activity in term of action potential firing and sensory stimuli or behavioural output. According to [HSM10] there are at least three definitions of neural encodings that can be derived from literature. The most common definition is that a feature is encoded by a neural structure if there is **correlation** between the responses of neurons within the neural structure and the values that the feature can take. A second definition of encoding requires the **invariance** and the **uniqueness** of the mapping between the neural structure activity and

the feature it encodes. Therefore a parameter is encoded by the motor cortex if it is specified in the same way regardless of the behavioural context. A third definition of neural encoding is based upon the **causality** between neural activity and what it encodes. In [HSM10] the authors suggest that this kind of definition is not appropriate in the context of the motor cortex because a significant number of motor cortical neurons do not make direct monosynaptic connections with motor neuron in the spinal cord, therefore it could be difficult to demonstrate a causal role in the activation of muscles.

Two main approaches have been used for examining neural coding in the primary motor cortex [SS09]:

- to correlate the **single cell activity** to parameters of movement;
- to correlate the **activity of a population of neurons** to parameters of movement.

To study the movement tuning of a neuron n in motor cortex means to describe the firing rate $r_n(t)$ as a function of various parameters:

$$r_n(t) = f_n(p_1(t), p_2(t), p_3(t), ...) \tag{1.1}$$

The first study that evaluated the properties of single neurons activity in the primary motor cortex of monkey was performed by Evarts in 1968 [Eva68]. The result of his experiment was that the activity of single neurons in the motor cortex is better correlated with isometric force than with limb position. Those findings together with the dense connections between the pyramidal tract neurons and spinal cord lead to the interpretation that primary motor cortex controls muscle force or activation [Eva11]. Numerous other parameters have been suggested to be encoded by single neural activity, as for example direction of movement [GKCM82], speed and direction [MS99], distance to target [FSE93] [FFCE95], acceleration [AG94], static joint angles [Tha78]. Furthermore, it was pointed out that the activity of single cells is related to multiple parameters of movement (end-point force, position, acceler-

ation, velocity) and the correlation with each parameter vary in time and is influenced by the motor behavioral context [JME01].

In [GKCM82] the authors recorded the activity of single cells in motor cortex while monkeys made arm movements in eight directions and showed that the cell discharge rate d is coarsely tuned to the direction of reaching $\mathbf{M}$. In particular, the neuron firing rate varies as a linear function of the cosine of the angle θ_{CM} between the preferred direction of the cell (i.e. the direction for which the discharge rate of the cell is highest) and the direction of reaching:

$$d(\mathbf{M}) = b + kcos(\theta_{CM}) \tag{1.2}$$

where b and k are cell-specific regression coefficients.

An experimental and conceptual shift occurred in the 1980s, when neuroscientists begun to examine more complex and natural movements as multi-joint and whole arm movements [Kal09]. The traditional view that movement parameters were encoded within the firing of a neuron was juxtaposed with the view that parameters are encoded across populations of neurons. This population-code view was born thanks to a series of pioneering work led by Georgopoulos and colleagues [GKC$^+$84][GSK86]. As wrote in [Geo92]

> *The idea is that any single neuron carries only partial information about a movement parameter which is therefore uniquely represented only in the whole neuronal ensemble.*

The idea behind the population code approach is that a movement arise from the combination of the activities of different cortical neurons each of which contributes by "voting" for its "preferred" movement. In [GKC$^+$84] the authors showed that the movement direction $\mathbf{M}$ is coded by the discharge of a population of directionally tuned neurons, each of which contributes to the movement. The contribution of the ith neuron is represented by a vector that points in the cell's preferred direction $\mathbf{C}_i$ and has an amplitude $w_i(\mathbf{M})$ proportional to the cell's frequency of discharge $d(\mathbf{M})$. The vector sum of these neuronal contributions is the *population vector*

$P(\mathbf{M})$ that points in the direction of the movement $\mathbf{M}$ for discrete movements in 2D and 3D space:

$$P(\mathbf{M}) = \sum_{i}^{N} w_i(\mathbf{M})\mathbf{C}_i \tag{1.3}$$

where N is the number of cells in the population.

Other encodings have been suggested in the framework of the population-code approach. It has been shown that the neural discharge is tuned to both the direction of a planar arm movement and the direction of a static load pulled by the arm. In both cases it can be described by a linear summation of the movement-related discharge without any loads, and the change in tonic activity of the population caused by the load [KCHP89]. In [Kal91] it has been suggested that population vector encodes a kinetic parameter, such as the direction of force.

The single cell and the population level approach are both focused on the representation employed by the motor cortex for controlling the movement and some authors refer to them as the **representational view** of the motor cortex. In the last decade, it has been argued that the evolution of neural activity should be best captured not in terms of movement parameter evolution, but in terms of the dynamical rules by which the current state causes the next state [SSC13]. According to this new hypothesis the motor cortex may constitute a dynamical system that generates a pattern of activity that encodes movement trajectories [HXA07] [CCK+12]. The cortical activity can be expressed as:

$$\dot{\mathbf{r}}(t) = g(\mathbf{r}(t)) + \mathbf{u}(t) \tag{1.4}$$

where $\mathbf{r}$ is a time-varying vector describing the firing rate of all neurons (the population response), $\dot{\mathbf{r}}$ is its derivative, $\mathbf{u}(t)$ is an input that arrives from other cortical areas and g is an unknown function.

1.4 Kinematic versus Kinetic Control

As emerged from previous sections, there is a fierce debate on whether the motor cortex activity encodes kinematic or kinetic variables.

These two positions have been summarized in [Ash05] by speaking of two groups of scientists, one supporting the idea that motor cortex "*knows nothing of muscles*" and another one believing that "*motor cortex knows nothing of movements*".
The view of a **kinematic control of movement** was born with the finding of direction tuning of motor cortex neurons [GKCM82] [GKC+84]. In addition to the direction of the movement, other kinematic parameters as position, velocity and acceleration have been shown to covary with the M1 activation [MS99] [AG94]. This position has also been supported in the last years by the results obtained in the field of brain-machine interface. For example it has been shown in many studies that the position of a robotic limb, or of a cursor on a screen, can be controlled in real time by recording neuronal activation [HSF+06] [HBJ+12].
However, it is not possible to argue by these results that the discharge of M1 neurons is exclusively determined by movement kinematics. In [SK95] [SK97] the authors recorded the motor cortex activity of a monkey that performed the same reaching movements with two different arm postures. They found that the cell activity in the motor cortex is highly sensitive to changes in arm posture even though hand trajectory remained similar. Thus, they conclude that the neuronal activity was not exclusively tuned to the movement direction, but it reflected also other aspects of the arm movement related to the arm posture, as for example angles of joint or contraction of individual muscles. This experiment is at the center of the controversy on whether motor cortex neurons control high-level variables, such as hand direction (sometimes referred as *extrinsic coordinates*), or low-level variables, such as joint angles and muscle forces (sometimes referred as *intrinsic coordinates*).
The view of a **kinetic control of movement** arises from the

notion that primary motor cortex neurons project to the spinal cord and some of them have monosynaptic connections to alpha motoneurons that activate muscles. It follows that the greater the neuronal activity, the greater the muscle activation. It is therefore obvious to hypothesize as control variable the force generated by muscles, as confirmed by the experiment performed in [Eva68]. Since then, a lot of studies have shown relations between M1 activation and kinetic parameters as torque, direction and magnitude of force [HKC+07] [KCHP89]. Furthermore, it has been shown that the patterns of muscle activity can be reconstructed with a weighted linear sum of activities of neurons in the primary motor cortex [MM03] [TPL06].
On the other hand, theoretical studies have shown that the directional tuning of a population of M1 neurons can also result from a system that fundamentally codes muscle shortening [MI88]. In [Tod00] the author showed that population vectors tend to point in the direction of movement because of geometry of the limb, its inertial properties and the presence of external loads. The author suggested that the directional tuning of M1 activity is an epiphenomenon emerging from the complexity of the musculoskeletal system. Furthermore, in [SFB04] it has been shown that it is computationally possible that extrinsic and intrinsic neurons can control the same variables, as for example the muscle activation, in parallel.
Due to this long standing controversy, in the last year a new view of the motor cortex function, known as the **action map view**, has been proposed [Gra06]. According to this new view, neurons in motor cortex do not control one type of parameter but instead they control mixtures of all variables relevant to the execution of ethologically categories of behaviour, such as hand to mouth actions, defensive actions, reaching, etc.

1.5 The problem of correlated parameters

Behind the multiplicity of control variables proposed in literature there is the statistical dependencies among movement parameters: neurons could appear to encode a parameter p_1 but instead the cortex is encoding a parameter p_2 to which the first one is related to.
In motor control experiments, it is difficult to investigate parameters independently because the movement is executed by the subject, and it is not under the full control of the experimenter and movement parameters are naturally correlated. The sources of correlation can be grouped in three classes [HSM10] [RH09]:

- **biological constraints**, as for example the minimization of jerk, the two-thirds power law between velocity and curvature and the Fitt's law that describes the tradeoff between speed and accuracy. These are regularities originating by the way the movement is controlled by the neural structures;

- **physical constraints**, as for example the presence of interaction torques between different joints, the restrictions on trajectories due to joint geometry, the relationship between acceleration and force imposed by the Newton's second law, the restrictions on torques and joint angles due to passive muscle properties;

- **behavioral constraints**, which are introduced by the experiment set up for studying the motor system;

Some of these correlations can be removed or reduced with proper controls, but it is clearly not possible to uncouple all movement parameters. It may be possible to train a subject to violate the biological constraints but it's not possible to eliminate the dependencies due to physical constraints.

1.6 A proposal to overcome the problem

Some experiments have shown that two subpopulations of neurons coexist in M1: neurons that capture kinematics properties of the movement and neurons that encode kinetic properties. As for example, the experiment described in [KHS99] demonstrated that extrinsic and intrinsic coordinates are both represented in motor cortex. The existence of both populations of cells within M1 led the authors to propose that neurons showing different functional properties may be connected in a network performing a transformation from abstract to intrinsic representation according to a *serial processing scheme*. Instead, the model presented in [SFB04] suggests that the two populations of M1 neurons may be organized according to a *series-parallel processing scheme*. The difference between the serial and the series-parallel processing scheme is that in the first one the only cortical source involved in the recruitment of spinal motoneurons are the M1 cells encoding kinetic properties while in the second scheme spinal motoneurons can be recruited directly also by the neurons encoding extrinsic-like properties of the movement.

To resume what has been described in this chapter, it is reasonable to assume that primary motor cortex encodes both movement's parameters and patterns of muscle activation. We believe that to better understand the "code" used for executing voluntary movements the activity of primary motor cortex must be evaluated taking into account its interaction with other brain regions and the spinal cord. In particular, in this thesis, we will investigate the interaction between motor cortex and the spinal cord that is the main recipient of the descending signals departing from M1 neurons. The opinion of studying the activity of primary motor cortex by understanding its relations with others brain regions is not new [Sco03] but in the last years new insights arose to support this point of view. In our opinion the findings reported in [RS09] and [SHPK05] are the pillars for hypothesizing that M1 controls different variables of a motor task and that this property emerges

from the organization of its cells and the way they are connected with the cells hosted in the spinal cord.

The main source of motor commands sent by the primary motor cortex are the corticospinal (CST) neurons, which are located in the cortical layer V and have axons that reach neurons in the spinal cord. Using a retrograde transneuronal transport of rabies virus from single muscle, it has been shown in [RS09] that CST neurons can be divided into two classes: neurons that project their axons to spinal interneurons located into the intermediate zone of the spinal cord, and neurons that makes monosynaptic connections with motoneurons in the ventral horn of the spinal cord. Neurons belonging to the latter class are also termed *cortico-motoneuronal (CM) cells*, because they have direct connections with the alpha motoneurons. The experiment performed in [RS09] has shown that:

- CM cells are almost entirely segregated to the caudal region of M1. These CM cells are connected not only to motoneurons that excite muscles of fingers, but also to motoneurons exciting muscles of the shoulder and elbow (see Figure 1.1). Therefore, the caudal region of M1 has direct access to motoneurons that control proximal as well as distal muscles;

- The caudal portion of M1 shows a proximal to distal (medial to lateral) topography of arm representation (see Figure 1.2), similar to the map of arm representation obtained in experiments based on intracortical stimulation of the caudal M1 [KMMW78]. So, CM cells exhibit a somatotopic organization;

- The different populations of CM cells are intermingled (see Figure 1.3).

From these findings results that primary motor cortex is subdivided into two regions, the rostral and the caudal one. In macaques, the rostral region is located on the crest of the precentral gyrus, whereas the caudal region is buried in the anterior bank of the central sulcus (CS). CST neurons in the rostral region control alpha

motoneurons activation through disynaptic or polysynaptic pathways, while CST neurons in the caudal region have direct control over motor output thanks to their monosynaptic connections with motoneurons. While the rostral region is present in many mammals, CM cells are peculiar of Old and New World monkeys, great apes and humans so it is a new area arose during the evolution. Furthermore, the intermingling of CM cells for different muscles suggests that populations of CM cells create muscle synergies for controlling multijoint as well as single-joint movements.

In [SHPK05] the authors recorded the activity of neurons in caudal part of primary motor cortex related to movements of the proximal arm and they showed a correlation with both the temporal pattern of force production and the dynamics of motor output. Furthermore, studies on local field potentials in the motor cortex have shown the propagation of beta oscillations across the arm area of the motor cortex and along the rostral to caudal axis, during both the motor preparatory period and the movement execution. It has been hypothesized that these high-frequency oscillations may subserve intra- and inter-cortical information transfer during movement preparation and execution [RRH06] [HSM10].

On the basis of that, we argue that the execution of voluntary movements results from the cooperation of different clusters of neurons distributed in the rostral and caudal regions of primary motor cortex, each of which represents different aspects of the ongoing movement. In particular, kinetic aspects of movement are directly represented by the caudal part of primary motor cortex as activations of alpha motoneurons, while kinematic aspects of the movement are encoded by the rostral region and are translated by spinal cord interneurons into alpha motoneurons activation.

So, in order to support and to know more about the code used by the motor cortex, a model of spinal cord and its connections with supraspinal brain areas are presented in the next chapter.

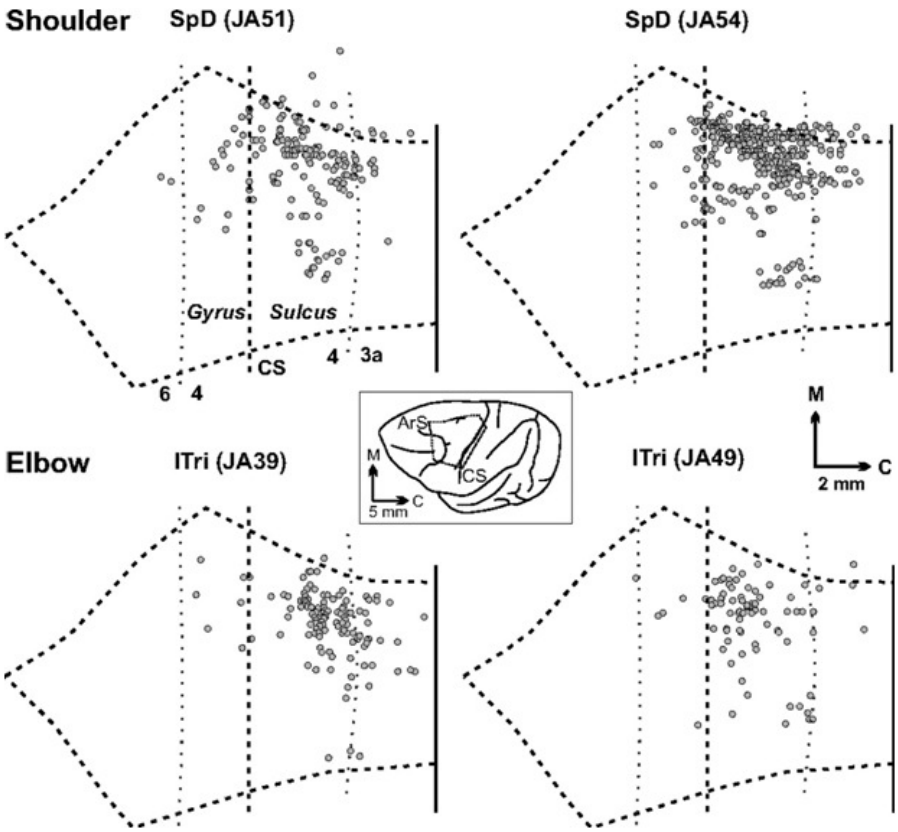


Figure 1.1 Distribution of CM cells innervating the motoneurons of a shoulder or an elbow muscle. Each map shows an unfolded reconstruction of layer V from an experimental case. Each dot represents a labeled CM cell. The central Inset shows the general location of the reconstructed area on a lateral view of the macaque cerebral hemisphere.C, caudal; M, medial; Gyrus, crest of the precentral gyrus; Sulcus, anterior bank of the CS. *This figure is taken from [RS09]. Courtesy of PNAS.*

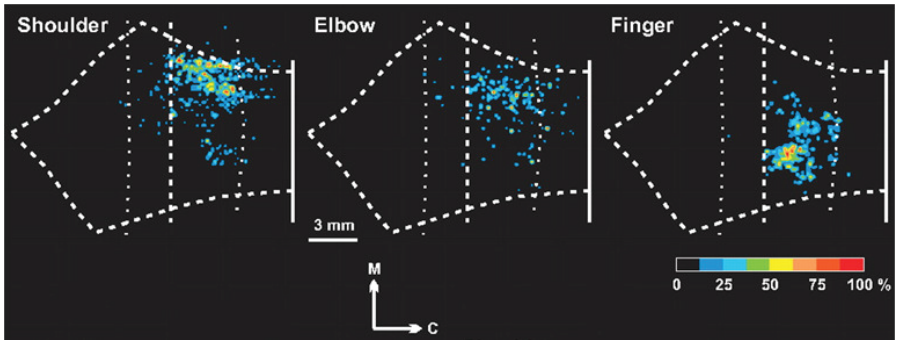


Figure 1.2 Topographic organization of CM cells in M1. (Upper) Density analysis of CM cells innervating shoulder (Left), elbow (Center), or finger (Right) motoneurons. The color scale at the right indicates the density of labeled neurons as percentages relative to the maximum peak density. *This figure is taken from [RS09]. Courtesy of PNAS.*

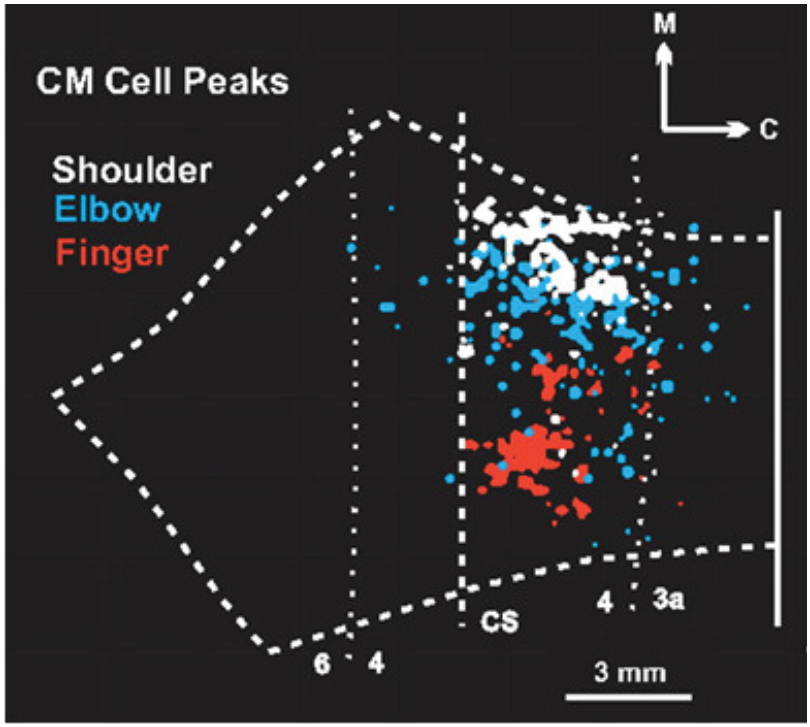


Figure 1.3 Density peaks of shoulder (white), elbow (blue), and finger (red) CM cells. There is considerable intermingling of the different populations of CM cells. *This figure is taken from [RS09]. Courtesy of PNAS.*

Chapter 2

The interaction between Motor Cortex and Spinal cord

2.1 Introduction

The control of goal-directed limb movements needs the generation of the appropriate muscle activation patterns for coordinating the complex multijoint musculoskeletal system and the online compensation of errors due to noise and perturbations. Experimental evidences suggest that the central nervous system (CNS) is able to built a representation of the dynamic properties of the limbs thanks to elementary building block hosted by the spinal cord [MIB00]. Spinal circuitries are fundamental for motor execution, as they provide different mechanisms for movement and control. Their precise role in motor control is still not clear and three questions need to receive a clear and definitive answer [GhU12]:

- What are the relative roles between brain and spinal cord circuitry?

- What are the relative roles between peripheral inputs and descending commands in organizing spinal behaviours?

- Are the spinal behaviours organized in a modular fashion and is this organization exploited in executing skilled voluntary movements?

Starting from studies on the modular organization of the motor system, in this chapter we try to summarize what is known about the interaction between spinal and supraspinal networks with a computational model based upon muscle synergies.

Commonly, muscle synergies are suggested as a strategy for the simplification of control that overcomes the degrees of freedom problem faced in motor control and it is debated if these primitives take the form of time-invariant muscle coactivations (spatial synergies) or time-varying muscle commands (spatiotemporal synergies). Instead, we interpret synergies as neural structures that provide a translation between task level goals and execution commands to accomplish those goals. In the proposed model two levels of muscle synergies are hypothesized and these neural structures are the joining link between kinematic and kinetic representations of the movement.

2.2 Modularity in motor control: Motor Primitives and Motor Synergies

Everyday we experience our ability to build complex behaviours and complex representations by combining simple elements in different ways. For example we compose words articulating phonemes (*behaviour*) and we compose sentences from words (*representation*). This ability is fundamental also for visual perception, action and cognition: there are evidences suggesting that our visual recognition system is based upon a hierarchy of cortical stages that combines responses from neurons tuned to simpler features [PB04].

On the basis of studies on vertebrate and invertebrate motor systems and taking into account that the execution of even

the simplest movement requires the activation of many thousands of motor units in numerous muscles, different investigators have hypothesized that the central nervous system executes voluntary movements by exploiting a hierarchical architecture based upon discrete building blocks activated simultaneously or serially in time [FH05]. Different **motor primitives** have been proposed in literature (for a complete review [FH05] [GPH07] [GHS10] [Gis15]) and they can be divided in two classes:

- *kinematic primitives*, as strokes and submovements, that are patterns of motion without regard to force or mass. For example, hand trajectory has been decomposed in velocity primitives represented with minimum-jerk or log-normal functions;
- *kinetic or dynamic primitives*, as for example static force fields, muscle and joint torque synergies, neural drive synergy;

Electrophysiological studies in spinalized frogs [BMIG91] and rats [TSB99] suggested that the spinal cord provides the central nervous system with a "vocabulary" of motor primitives to be superimposed for generating a wide repertoire of motor behaviors. These studies provided evidence that neural circuits in the spinal cord are organized into a set of distinct functional modules whose activation induces a specific force field. As described in [BCd+08]:

> *A spinal module is a functional unit in the spinal cord that generates a specific motor output by imposing a specific pattern of muscle activation.*

Those modules control groups of coactive and linearly covarying muscles that generate force fields [GMIB93] [MIGB94]. It was shown that the simultaneous activation of multiple modules leads to the vectorial summation of the fields generated by each site separately [MIGB94] [MIB00]. Vector summation of force fields implies that a motor behaviour can be controlled and learned through the *linear combination* of motor primitives/spinal modules activations, so the non-linearities that characterize neurons and muscles

are eliminated. Motor primitives have been defined as *compositional elements for movement construction* [Gis15] that are recruited by impulses conveyed by supraspinal pathways, and/or by the reflex pathways.

Another kind of "basis functions" whose combinations explain the motion generation are the **muscle synergies**. They are defined as coordinated activations of a group of muscles and therefore they embrace a wide range of muscle recruitment strategies: activation of muscles by a common drive, muscles recruited at the same time but controlled separately, or muscles controlled in a stereotypic temporal pattern. These different implementations of the abstract concept of muscle synergies implies different motor patterns, underlying circuitry and subsequent force generation [GHS10]. Regularities observed in the electromyographic activities of several species [BCd$^+$08] have provided evidence for the *muscle synergy hypothesis*: a set of synergies are encoded by the CNS and are combined in a task-dependent fashion in order to generate the muscle contractions that will results into the desired movement [ADN$^+$13].

Given M muscles, the concept of muscle synergy has been formalized in a variety of mathematical models, two of which are the **synchronous synergies** and the **time-varying synergies**. A *synchronous synergy* is expressed as an M-dimensional vector $\mathbf{w}$ of coefficients specifying the relative activation level of the muscles. Therefore, the activations of M muscles are computed through the linear combination of a set of N synchronous synergies $\mathbf{w}_i, i = 1, ..N$:

$$\mathbf{m}(t) = \sum_{i=1}^{N} c_i(t) * \mathbf{w}_i \tag{2.1}$$

In equation 2.1 $\mathbf{m}(t)$ is a M-dimensional vector that specifies the activation of each muscle at time t and $c_i(t)$ is the time-varying coefficient. Across movement conditions, either the synergies $\mathbf{w}_i$ or the activation coefficients $c_i(t)$ may be invariant and we can speak respectively of synchronous synergy model and temporal synergy model [ADN$^+$13].

A *time-varying synergy* is instead represented by a collection of muscle waveforms expressed as a time-varying M-dimensional vector $\mathbf{w}(t)$. In this case, the generation of muscle pattern is modeled by the recruitment of N time-varying synergies each of which can be scaled in amplitude and shifted in time by means of the coefficients c_i and t_i :

$$\mathbf{m}(t) = \sum_{i=1}^{N} c_i * \mathbf{w}_i(t - t_i) \tag{2.2}$$

c_i and t_i representing the commands used to accomplish the desired task.
The two models have two main differences:

- the synchronous synergies model doesn't allow temporal delay between different muscles, so all muscles within a synergy are active at the same time, while within a time-varying synergy muscle activations do not necessarily covary;

- the synchronous model adopts a continuous control scheme, as the command is a time-varying function, while time-varying one adopts a discrete scheme, as the command is a constant.

The muscle synergies models have been successfully used in characterizing the muscle contractions during human reaching movements. Muscle patterns recorded during fast movements in different directions [dPFL06] and speed [dFPL08] were accurately reconstructed by appropriate linear combinations of synergies, which appeared very similar between subjects. In [dPFL06] synergies extracted from muscle activities during unloaded reaching were used for reconstructing EMG signals obtained during loaded conditions. Furthermore, it has been shown that the recruitment and the onset time of the individual synergies were modulated with movement direction and did not change significantly with movement speed. The study performed in [MBdF10] showed that a large set of multijoint movements in different directions could be generated by a

small set of synchronous synergies. In [dPL11] the authors investigated whether the muscle patterns to correct ongoing reaching movements are generated by the superposition of the same set of time-varying muscle synergies used for reaching movements. The results they obtained suggest that a common modular architecture is used for the control of unperturbed arm movement and for its visually guided online correction. In order to execute an online correction experimental results suggests that the CNS may either modulate existing synergies [dPL11], or reprogram new ones [FBB10].
Eventually, even within the framework of equilibrium point control it has been argued that the brain may control complex movements through flexible combination of motor primitives, where each primitive is an element of computation in a sensorimotor map that transforms desired limb trajectories into motor commands [TS00].

One of the main critiques of experiments supporting the muscle synergy hypothesis is that they reflect task constraints rather than a neural control strategy [TJ09]. Furthermore some analyses of variability in motor patterns have provided evidence against the existence of muscle synergies and suggest that the nervous system preferentially controls task-relevant parameters on the muscle level [VCVT09].
From a computational point of view, a modular organization of the motor system is very attractive because it simplifies motor control and learning, and it may contribute to the adaptability observed in biological systems. For these reasons, the hypothesis of muscle synergies inspires methods to control artificial systems [ADN+13].

Nevertheless, some aspects about motor primitive plasticity and their reuse are still not clear. The degree of stability of spinal motor primitives through development, their plasticity are still open questions and it is speculated that in humans the need of executing novel skills requires novel motor primitives that have perhaps never been used before in evolutionary history [Gis15].

2.3 The neural basis of muscle synergies

Researchers in the field of motor control work to reverse engineering the design of the biological controller leading the movement execution. Two complementary approaches can be used for fulfilling this aim: the *structural* and the *behavioral* approach. While the first one requires to gain access to the neural circuitry and decoding the neural representation of the controller, the latter one requires access only to the controller's output and is less difficult to put in practice [dT07]. Therefore, the basic procedure used in the experiments cited in the previous section is:

- to measure EMGs from a large number of muscles during a complex behavior;
- to identify a set of synergies from the recorded EMGs using computational analysis such as non-negative matrix factorization;
- to evaluate to which extent the observed EMGs fit with one of the synergy models presented before.

Using this method the presence of synergistic structures within the CNS can only be inferred and it is not clear whether and in which areas the muscle organization is neurally implemented. Some experiments and simulations challenge the hypothesis that muscle synergies are a neural strategy by showing that they may originate from biomechanical couplings and task constraints [KVC12]. Therefore investigating the neural mechanisms that select the muscle activation patterns required to achieve a behavioral goal is of paramount importance [DCB10].

Some studies in monkey supported for the existence of neural substrates of muscle synergies in primary motor cortex [HM02], while studies on frogs supported for neural populations of interneurons in the spinal cord as neural basis of synergies [HG10] [DCB10].

In [LHH$^+$14] a population of interneurons that could support motor primitives in mammals was identify in the mouse spinal cord

and it was named motor synergy encoder (MSE) by the authors. This population receives direct inputs from the motor cortex and sensory pathways and, in turn, has monosynaptic outputs to spinal motoneurons. Its optical stimulation drove reliable patterns of activity in multiple motor groups and the authors speculated that MSE may encode coordinated motor output programs.

In [OdR+15] the authors investigated whether populations of motor cortical neurons reflect recruitment of motor primitives in the form of spatiotemporal synergies. They compared EMG derived spatiotemporal [OdRB08] and spatial [OdCB12] synergies extracted from forelimb muscle in rhesus macaques with synergies derived from cortical data recorded in primary motor cortex, in dorsal and ventral premotor cortex. Their results show that, at the population level, motor cortical units in the primate brain exhibit the recruitment of spatiotemporal synergies whose dimensionality, timing, and amplitude modulation correspond with synergies independently inferred from muscle recordings. Furthermore, it is shown that these spatiotemporal synergies could be reconstructed as sequential activations of spatial synergies both at the muscular and neural levels. These results suggest a hierarchical relationship between the two levels of synergies: spatial synergies may be hard-wired and recruited together in the form of higher-level spatiotemporal synergies.

These findings support the hypothesis that voluntary movements are executed by a complex interaction between the motor cortex and the spinal interneurons. The cortex may select and combine the proper spinal interneuronal modules, and provides them the suitable temporal patterns of activation for the behavior being executed [BC13]. Studies on a group of humans with lesions in the motor cortical areas due to a stroke have shown that it is possible to extract similar muscle synergies from both stroke-affected and unaffected arm even if motor performance between the arms were substantially different [CPA+09]. These results match the idea that muscle synergies are implemented in spinal cord circuitry and are recruited by descending commands from supraspinal area. In fact, after a stroke the descending com-

mands are altered and the motor behaviour is abnormal due to an improper activation of synergies [BC13]. It is plausible to think that the right temporal activations of primitives are learned gradually as the individual grows from being a neonate to an adult. In fact, in [DIC+11] the authors found that two basic patterns of stepping neonates are retained through development while other are added over the years.

Eventually, it is also plausible that highly skilled movements are encoded by muscle synergies implemented directly by ensembles of neurons in the motor cortex [RS06].

2.4 Skilled Movements

Skilled movements are the result of the interaction between efferent neural pathways, which produce muscle contraction, and the feedback pathways that report the effects of motor commands. The role of feedback pathways is fundamental for signaling error and correcting motor output. There are two types of feedback projections used for comparing the planned and the performed actions [AA15]:

- the **external feedback pathways**: proprioception and vision convey information about the state of muscle contraction and the position of limb in the space. These pathways are affected by temporal delay that complicates the control of movement. In fact, delays in feedback may induce oscillations and limit the rapidity with which motor commands can be modified;

- the **internal feedback pathways**: a copy of the motor commands, often referred as *efference copy*, is delivered to the cerebellum in order to built a *forward model* of the limb movement that will allows the rapid prediction of the sensory outcome of motor action.

Both the proprioception signals and the internal copies of motor commands are transmitted from the spinal cord to the cerebellum

through the spino-cerebellar pathways. A direct spino-cerebellar pathway, the cuneo-cerebellar tract, carries proprioceptive information from the upper limbs to the cerebellum and it is mainly dedicated to rhythmic motor acts. The indirect spino-lateral reticular nucleus-cerebellar pathway is relevant to the execution and coordination of dexterous limb movements. The lateral reticular nucleus (LRN), a precerebellar centre located in the brainstem, is a major mossy fiber relay of information from the spinal cord, motor cortex and superior colliculus [AE13] projecting to cerebellar cortex and sending collaterals to the deep cerebellar nuclei (DCN). Three major ascending systems from the spinal cord to the LRN have been described in the cat: the bilateral ventral flexor reflex tract (bVFRT), the ipsilateral forelimb tract (iFT) and the C3-C4 propriospinal neurones. These systems could signal information respectively about posture, grasping and reaching. In [AE15] [AE13] the authors investigate the convergence of these three systems onto LRN neurones and they suggest that an elaborate process of descending and ascending synaptic integration occurs before the mossy fiber output to the cerebellum. The authors proposed that the convergence in the LRN might contribute to the coordination of posture, reaching and grasping into coherent and smooth movements.
The C3-C4 propriospinal neurons (PNs) represent the best characterized internal copy circuit. Their function has been investigated in behavioral experiments, revealing a role in mediating the voluntary command for visually guided forelimb reaching in the cat and additionally for precision grip in the macaque monkey [AI12]. The C3-C4 PNs are not the unique type of spinal interneurons projecting to the LRN. In fact, the experimentation presented in [PESA14] reveal the existence of a spatial map within the LRN: spinal neurons of different single progenitor-domain origin establish distinct axonal terminations in the LRN.
Moreover, LRN receives projection from motor cortex via a population of cortico-reticular neurons terminating in the brainstem but not from collaterals of corticospinal fibers [AE15].
LRN mossy fibers project at the same time to cerebellar granule

cells and to deep cerebellar nuclei. Granule cells provide a potential location for the convergence of sensory and copy information [AFJ14]. The result of the Granule cells integration is then transmitted by the Purkinje cells toward the deep cerebellar nuclei, which modulate the activity of several descending brainstem nuclei (reticulospinal nuclei, vestibular nucleus, red nucleus). Eventually, the brain steam nuclei deliver the updated motor command to the spinal cord.
Therefore, the spinal cord-LRN-cerebellum-deep cerebellar nuclei loop is closed via the rubro- and reticulospinal systems and allows to update descending pathways in a timely fashion with ongoing activity from the spinal cord. This idea was recently supported by a combined electrophysiological, optogenetic and behavioral study in the mouse, in which the ascending branch from V2a PNs to the LRN could be selectively activated [AFJ14].
During visual control of upper limb reaching, two pathways are available for updating the motor commands sent to the spinal cord: one involves cortical structures as the posterior parietal cortex (PPC) while the other involves subcortical regions as the bulbospinal system, part of reticulospinal tract. Both the pathways need the efference copy sent to the LRN and the visual information for correcting the movement. In humans, cortical visual pathways correct the ongoing movement with latencies longer than 200 ms, instead subcortical structures are involved in the fastest adjustments of the trajectory with latencies in the range of 120-160 ms [DL00] or even shorter (around 100 ms) [PKB$^+$10]. It follows that the fastest pathway may be used for the online correction of the ongoing movement when for example a target jump happens, while the slowest pathway involving cortical areas may be used for replanning the movement. As discussed in [SM15] one pathway may be preferred respect to the other on the basis of task conditions: if spatiotemporal restrictions are placed in the execution of the task it has been shown that the correction through the fastest pathway is performed.

2.5 The proposed model

2.5.1 The architecture

On the basis of the studies on motor cortex and spinal cord presented in this and in the previous chapter, we propose the model in Figure 2.1 that may explain how brain and spinal cord interact for controlling a reaching movement. In Figure 2.2 are pointed out the connections between the cerebellum and the brainstem and the connections coming from the primary motor cortex and the spinal cord.
In our model *motor commands* are represented by the activations of clusters of neurons in the rostral and in the caudal part of M1 cortex. Their selection is regulated by the cortical loop through the Basal Ganglia, whereas the cerebellum is involved in their timing and coordination.
Motor commands travel down the corticospinal tract (CST) to synapse on interneurons and motor neurons in the spinal cord. In particular, neurons located in the rostral region of the M1 cortex make monosynaptic connections with interneurons in the intermediate zone of the spinal cord, while the neurons in the caudal part have direct connections with alpha motor neurons. The density of CST neurons in both the regions of M1 is comparable [RS09].

We propose that neurons in the rostral M1 are organized in clusters devoted to the activation of different subpopulations of interneurons in the spinal cord. In turn, interneurons are organized in functional modules, each of which regulates the activity of a subset of muscles working around one or more joints. These spinal functional modules are interneurons networks that implement hard-wired muscle synergies recruited by the rostral M1 cortex or by subcortical nuclei of the brainstem. The way a module regulates the muscles activations is related to its structural properties, as for example the connections between the neurons belonging to it, the type, the number and the synaptic weight of its inputs. The recruitment of an hard-wired synergy concerns to the supraspinal

regions but their activation is modulated by sensory inflow. The modulation due to sensory inputs could explain immediate motor adjustments and the adaptation to constraints imposed by the task. Nevertheless, supraspinal regions can increase or decrease the sensory inflow into a synergy by the presynaptic gains modulation, directly on indirectly through inhibitory interneuron population [MPD98] [BME10] [FCH+14]. The variation of the presynaptic gains is a strategy adopted by the CNS for modulating the strength of many spinal reflexes during both locomotor and voluntary motor behaviors [Loe13].

We propose that the population of cortico-motoneuron (CM) cells in the caudal part of M1 create muscle synergies for a direct control of muscle activity. This hypothesis is supported by the findings in [RS09] showing that there is an overlap and an intermingling of CM cells connected to motoneurons exciting different muscles and by the evidence that presynaptic inhibition of these direct projections is absent [LKM+04]. The population of CM cells may implement new collections of synergies useful to execute highly novel skills that require a direct control of multijoint and single-joint movements by the CNS.

As already argued, the two families of motor cortex neurons cooperate in order to accomplish different requirements of a complex behaviour. The control of movement execution through the recruitment of interneurons networks is simpler because local networks linearize the complex mechanical properties of the musculoskeletal system, instead the direct regulation of alpha motoneurons activity allows a more flexible control.
The variability observed in the motor execution of a complex task may be due to the variability in the sensory inflow that modulates the hard-wired synergy activation rather than to poor planning or control. In fact, information from sensory organs are affected by the psychophysical state of the subject, by the initial conditions of the movement and by the state of the external environment. The CNS may correct the motor variability introduced by sensory

variability by directly regulating the pattern of muscle activity through the caudal M1 cortex. As proposed by the uncontrolled manifold hypothesis [Lat12] the CNS has to correct for variability that prevents the accomplishment of the task goals and it can skip the variability that does not affect them.

We argue that hard-wired primitives are available at birth and infants use them to organize initial movements and to explore the environment. Babies learn to generate visually guided reaching by mixing submovements produced by the activation of motor primitives, which contribute to the ontogenetic construction of more complex motor acts [Kon05]. At the beginning, the movements produced by the baby toward different objects are inaccurate but as he develops the precision increases. The improvement of the movement accuracy is due to not only a maturation of the nervous system but also to a better calibration in the recruitment of motor primitives [GW04] and in our model this calibration correspond to a tuning of rostral M1 cells activation.

In our model, LRN receives and integrates information from collaterals of spinal interneurons and from motor cortex via a population of cortico-reticular neurons terminating in the brainstem as suggested in [AE15]. Cerebellum receives information from sensory organs and from the LRN and may built an internal representations of the movement as combination of modular primitives in the spinal cord. Recently, it has been suggested that one of the role of the motor cortex is in "tutoring" subcortical circuits during skill learning [KMP$^+$15]: motor cortex executes movements as combination of motor primitives and the cerebellum learn how to execute a movement receiving information about the motor commands, the activity of spinal interneurons and the sensory feedback.

Correction to the ongoing movement due to visual information can be performed through the pathway involving the posterior parietal cortex, the primary motor cortex or the pathway involving subcortical nuclei.
On the basis of the task requirements subcortical nuclei can modify voluntary movement through interneuronal circuits in the spine

and through projections to cortical motor regions.
In the following subsection the model of spinal circuitry is described.

2.5.2 The circuitry of the Spinal Cord

As described before, the experimental studies published in the last years confirm that a neural basis of the modular organization of motor system exists and that the basic modules recruited for the execution of a movement are hosted, at least in part, in the spinal cord. The spinal cord is not a simple relay station for transmitting information to and from supraspinal centers but, as defined by [Bur08]:

> *It is a highly evolved and complex part of the CNS that has considerable computational ability.*

Limb movements are planned and initiated by the brain but they cannot be performed without a spinal cord and the intricate feedback systems that reside within it [PDB12]. The cord is divided into segments along its length, each with a separate pair of dorsal and ventral nerve roots. The dorsal roots contain the afferent sensory nerve fibers carrying information from the body to the CNS, while the ventral roots carry the efferent nerve fibers that control the muscles. There are many types of afferent signals carrying different information about the external environment, the position and movement of the body. *The spindles* are sensory receptors arranged parallel to the muscle fibers that provide information about the muscle length through both Ia (primary) and II (secondary) afferent fibers, and information about the rate of muscle length change through the secondary afferent fibers. *Golgi tendon organs* (GTOs) are sensory receptors located at muscle-tendon junctions that through Ib afferent convey information about the force produced by the muscle during its contraction.

The spinal cord is divided into segments containing motor neurons and interneurons, and cervical segments are devoted to the innervation of arm muscles. The spinal cord contains many types

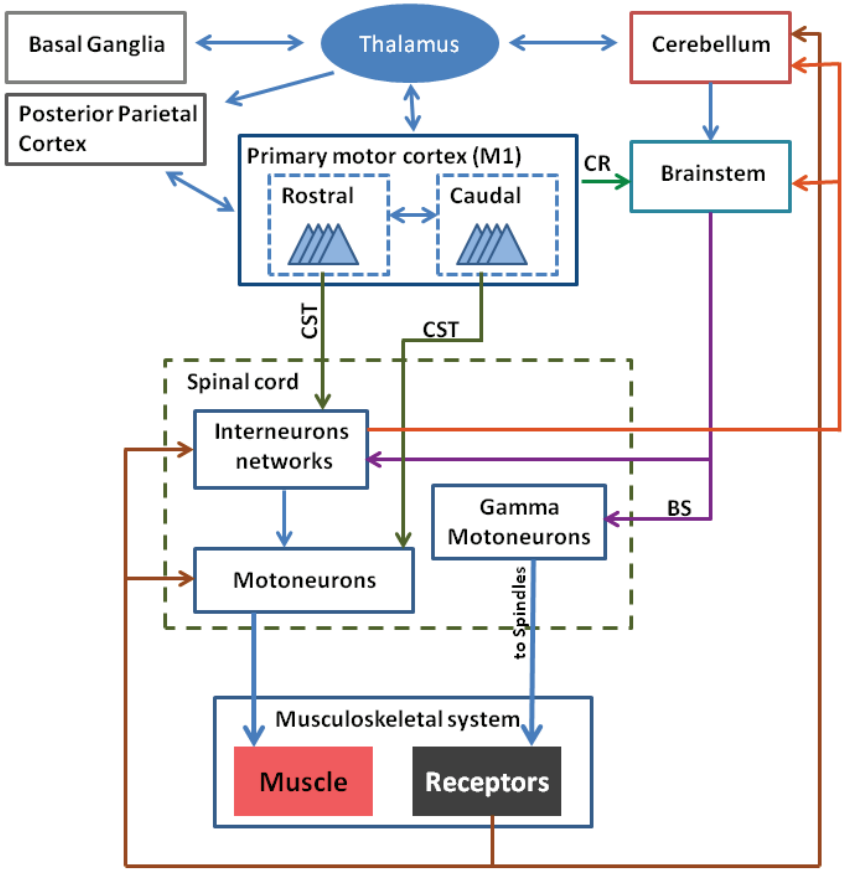


Figure 2.1 The architecture of the proposed model. In figure are pointed out the connections between spinal cord, motor cortex and subcortical nuclei. Gamma motoneurons regulate the sensitivity of muscle spindles. *BS*: Bulbospinal tract, *CR*: Cortico-reticular tract, *CST*: Corticospinal tract

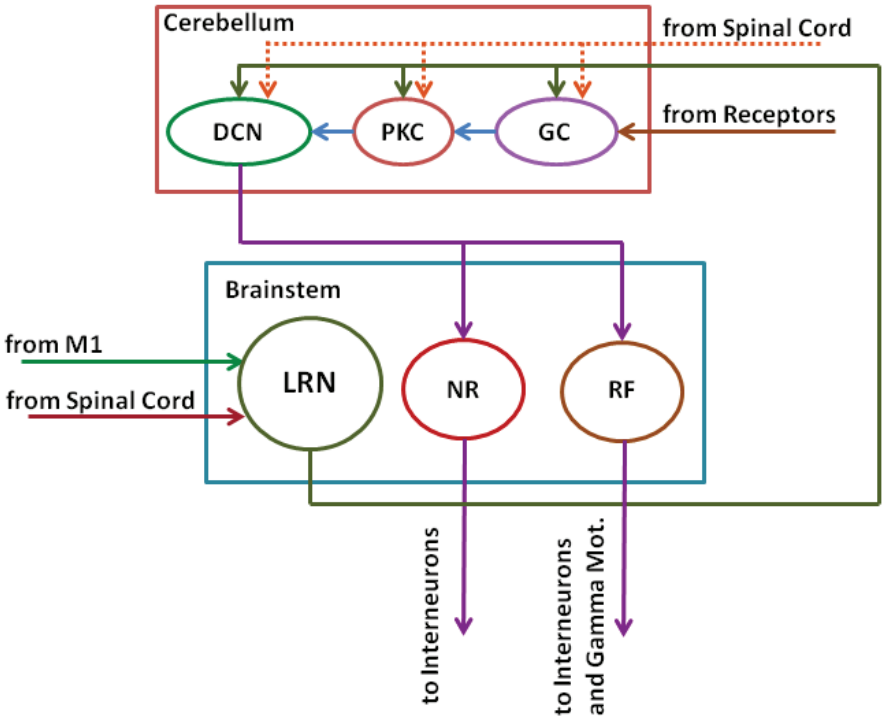


Figure 2.2 Connections between the cerebellum, the brainstem and the spinal cord. Dotted lines represent connections for whom contradictory evidence are reported in literature. *DCN*: Deep Cerebellar Nuclei, *PKC*: Purkinje cells, *GC*: Granule cells, *LRN*: Lateral Reticular Nucleus, *NR*: Nucleus Ruber, *RF*: Reticular Formation

of interneurons that are strongly interconnected and that can be classified according to anatomical, physiological and molecular criteria. Recently, it has been demonstrated that spinal neurons can be subdivided into 11 cardinal classes based on their progenitor-domain origin (dorsal dI1-dI6; ventral V0-V3; spinal motor neurons MN), and a variety of distinct roles of corresponding neuronal subpopulations has been revealed [PESA14].

Spinal interneurons receive input from different areas of the brain, as for example cerebral cortex, brain stem and tectum. The specific location of source input and how these are distributed within the interneuron networks are poorly understood. We have modeled the main and well-known pathways in the spinal cord that are described in literature [PDB12] and we have adopted the convention of naming the interneurons on the basis of their dominant input. The modeled pathways, interneurons and connections are reported below. For the sake of clarity, it's important to point out that when we perform a movement a lot of different muscles are recruited to complete it. Each muscle plays one of the following roles during a particular movement:

- *agonist* is the muscle that causes a movement to occur through its contraction;
- *antagonist* is the muscle counterbalancing the agonist that is involved in decelerating and stabilizing the movement;
- *synergist* is the muscle that helps the agonist to perform the joint motion;

As suggested by [Loe13], given an axis of motion around one joint (e.g., flexion/extension of the elbow joint), it is possible to describe all the muscles that create a positive moment as synergists and all that create a negative moment as antagonists.

Alpha and gamma motor neurons Alpha and gamma motor neurons are the two types of motor neurons in the spine. Each alpha motor neuron innervates any number of myofibrils, each of

which is innervated just by one motor neuron. The alpha motor neuron, its axon and the muscle fibers it innervates constitute a functional unit called *motor unit*. The size of the motor units and the number of myofibrils that are innervated contribute to the force of the muscle contraction.

A single motor neuron in the spine can receive thousands of inputs from the cortical motor regions, the subcortical motor regions and also through interneurons in the spine. In our model alpha motoneurons receive inputs from the local circuitry below (as shown in Figures 2.3, 2.5, 2.6 and 2.4), and from CM cells in the caudal part of M1 cortex. While synaptic inputs from interneurons can be both excitatory and inhibitory, projections from CM cells are only excitatory: in fact, there is no evidence for CM-evoked monosynaptic inhibition [LKM$^+$04]. In addition to corticospinal tract, several descending pathways have been shown to produce monosynaptic actions on motoneurons, including fibers running in the rubro-, reticulo-, vestibulo- tracts, but their functional role is not clear and we do not model them.

Gamma motor neurons are another type of motor neurons that innervate fibers within the muscle spindles (intrafusal fibers) and make them contract. This contraction regulates the sensitivity of the intrafusal fibers to muscle stretch. Little is known about the mechanisms of gamma motoneuron activation during goal-directed movements; all we know is inferred from muscle spindle afferent activity [Sco03], and it is agreed that the activation of gamma motor neurons is modulated on the basis of task requirements. The gamma efferent system is excited specifically by signals from the bulboreticular facilitatory region of the brain stem and, secondarily, by impulses transmitted into the bulboreticular area from the cerebellum, the basal ganglia, and the cerebral cortex [GH06].

Monosynaptic Ia excitation and Ia Interneurons Group Ia fibers from the primary endings of spindles can synapse monosynaptically with alpha motoneurons that innervate the same muscle (also called *homonymous muscle*) or with alpha motoneurons that innervate a synergist. These monosynaptic connections allow

a rapid response, with the shortest possible time delay, to unexpected increase in muscle length, know as *stretch reflex*. Whenever a muscle is stretched suddenly, excitation of the spindles causes reflex contraction of the muscle fibers of the stretched muscle and also of synergistic muscles.

Furthermore, the Ia afferents are the main input of Ia inhibitory spinal interneurons that form inhibitory synapses to the motoneurons of antagonist muscles (also called *heteronymous* muscle). These interneurons implements the *reciprocal inhibition* mechanism: they tend to inhibit the antagonist muscles when the agonist ones are stretched in order to avoid that the activity of antagonist muscles is opposed to the excitatory stretch reflex.

The inhibitory input from Renshaw cells is what distinguishes Ia interneurons from other interneurons. The connection from Renshaw cells and its supraspinal control may be used to ensure coactivation of antagonist muscles by decreasing reciprocal inhibition. The local circuitry that involves the Ia interneurons is shown in Figure 2.3.

Renshaw Cells These interneurons are excited by homonymous and synergist alpha motoneurons while their axons ramify and contact primarily the alpha motoneurons related to agonists and antagonists muscles. Renshaw cells inhibit the same alpha motoneurons that excite them and this mechanism is also known as *recurrent inhibition*. How strongly Renshaw cells respond to the excitation from the alpha motoneurons is regulated by inputs from supraspinal regions.

Further, the Renshaw cells inhibit the Ia inhibitory interneurons of the homonymous muscle mediating the reciprocal inhibition mechanism, i.e. resulting in a disinhibition of the antagonist motoneurons. The functional role of the Renshaw cells is controversial, but these cells seem important to regulate the temporal pattern of action potential sent from the alpha motoneurons and to balance the activation of antagonist muscles by adjusting the degree of Ia reciprocal inhibition. The local circuitry that involves the Renshaw cells is shown in Figure 2.4.

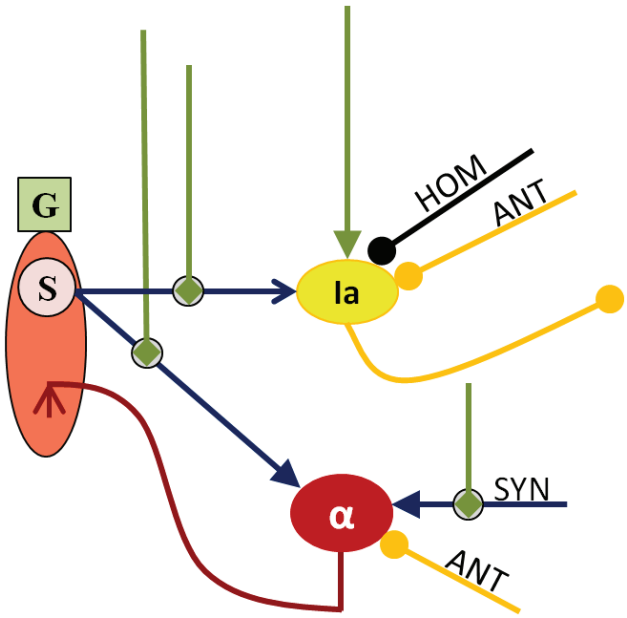


Figure 2.3 Descending and peripheral inputs converging on an Ia interneuron. Information from spindles, M1 cortex, Renshaw cell are represented in blue, green and black respectively. The blue arrow named SYN came from the spindles of the synergistic muscle. The black connection named HOM came from the Renshaw cell regulating the activity of the homonymous alpha motoneurons. The yellow connections named ANT came from the Ia interneuron receiving Ia fibers from the spindles of the antagonistic muscle. Filled dots represent inhibitory synapses, arrows represent excitatory synapses, while diamonds represent axo-axonic synapses.

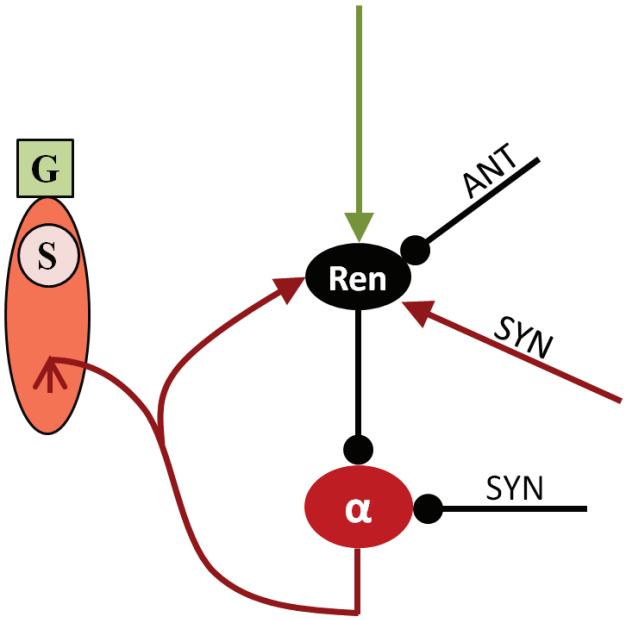


Figure 2.4 Descending and peripheral inputs converging on a Renshaw cell. Information from M1 cortex is represented in green. The red connection named SYN came from the alpha motoneurons innervating the synergistic muscle, while the black connections named ANT and SYN came from Renshaw cells regulating the activity of the synergistic and antagonist muscles respectively. Filled dots represent inhibitory synapses, while arrows represent excitatory synapses

Ib Interneurons These inhibitory interneurons receive monosynaptic excitation from corticospinal tract and the periphery. Inputs from the periphery include a wide range of cutaneous and proprioceptive afferents but we chose to model only the Ib afferents because they are the dominant ones. The absence of inhibitory projections from Renshaw cells is what distinguishes these cells from Ia interneurons. Furthermore, in [Lun71] is hypothesized that these interneurons project to the cerebellum.

Ib interneurons receive excitatory Ib afferents from many of the muscles controlled by the section of the spinal cord to which the interneurons belong to, not only from the ones the interneurons is directly connected through the motoneurons [Jan92].

These interneurons project to both synergistic and antagonistic motoneurons. Their projection to antagonist motor neurons is excitatory, whereas that to homonymous and synergistic motor neurons could be excitatory or inhibitory due to the existence of alternative pathways involving other segmental interneurons. Thus, individual motoneurons can be either excited or inhibited by Ib afferents. As described in [Loe13], the final effect depends on which interneuronal pathway is activated by the descending commands sent to Ib interneurons and segmental interneurons placed along the pathway from the GTO to the motoneuron. The final effect can result in positive, self-reinforcing feedback loops [Loe13].

The functional role of Ib interneurons during voluntary contraction is to keep a smooth profile of force development, to avoid jerky movements, to prevent the overcontraction of an agonist muscle and to facilitate the contraction of antagonist. The local circuitry that involves the Ib interneurons is shown in Figure 2.5.

Propriospinal (PN) Interneurons They are a population of spinal cord interneurons that connect multiple spinal cord segments and participate in complex motor reflexes. In fact these interneurons receive direct excitatory projections from Ia and Ib afferents, as well as monosynaptic excitation from the motor cortex, nucleus ruber (NR), reticular formation (RF) and superior

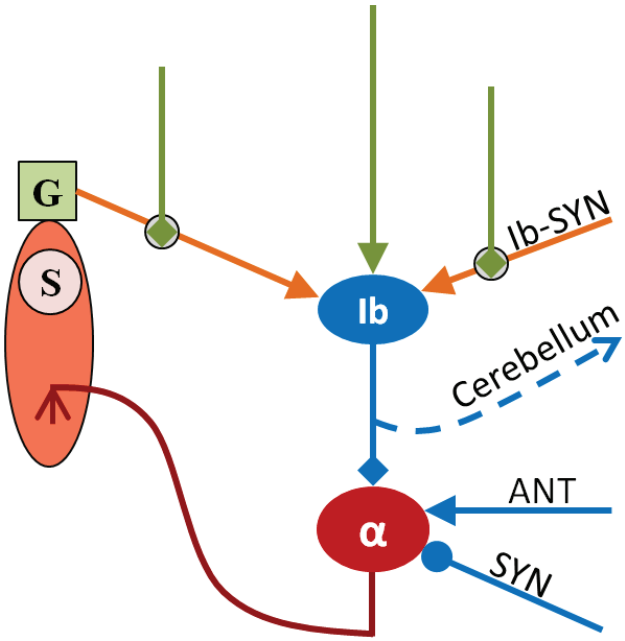


Figure 2.5 Descending and peripheral inputs converging on an Ib interneuron. Information from GTO and M1 cortex are represented in orange and green respectively. The orange connection named Ib-SYN came from the GTO of the synergistic muscle. The connections named SYN and ANT came from Ib interneurons regulating the activation of the synergistic and antagonist muscles, respectively. Filled dots represent inhibitory synapses, arrows represent excitatory synapses, while green diamonds represent axo-axonic synapses. The blue arrow terminating with a diamond represent a path that could be excitatory or inhibitory on the base of a descending input (not shown in figure).

colliculus (SC). Some of these descending connections can mediate disynaptic inhibition of PNs via feed-forward and feed-back inhibitory interneurons.

The PN interneurons in turn project to motor neurones located in the C6-Th1 segments innervating upper arm muscles. In addition, as described in the previous sections, these neurons have ascending axon collaterals to neurones in the lateral reticular nucleus, which provide cerebellum with an efferent copy of the signal to the motor neurons.

The rubro and reticulospinal neurons with projection to these interneurons receive input from the motor cortex and the deep cerebellar nuclei [AI12], therefore it is likely that projections from these subcortical regions are used to the online correction of the movement.

The functional role of propriospinal interneurons is probably to integrate the descending command and afferent feedback from the limb during the movement in order to modulate or to update the descending command during the execution of a movement, depending on the task requirements and the state of the external environment. The local circuitry that involves the PN interneurons is shown in Figure 2.6.

Presynaptic modulation A feature of the spinal circuits is the presence of 'axo-axonic' synapses, which allow the modulation of the activity of just an afferent axon terminal that reaches a neuron. These presynaptic pathways may exert either a depolarizing modulation, which has the effect of inhibiting transmitter, or an hyperpolarizing modulation, which facilitates the transmitter [Loe13]. We have modeled these facilitation and inhibition effects for each synapse between a sensory input and an interneurons or motoneurons, as shown in Figures 2.3, 2.5, 2.6 and 2.4. For example, the modulation of monosynaptic Ia excitation directed to alpha motoneurons allows the CNS to regulate the strength of the stretch reflex.

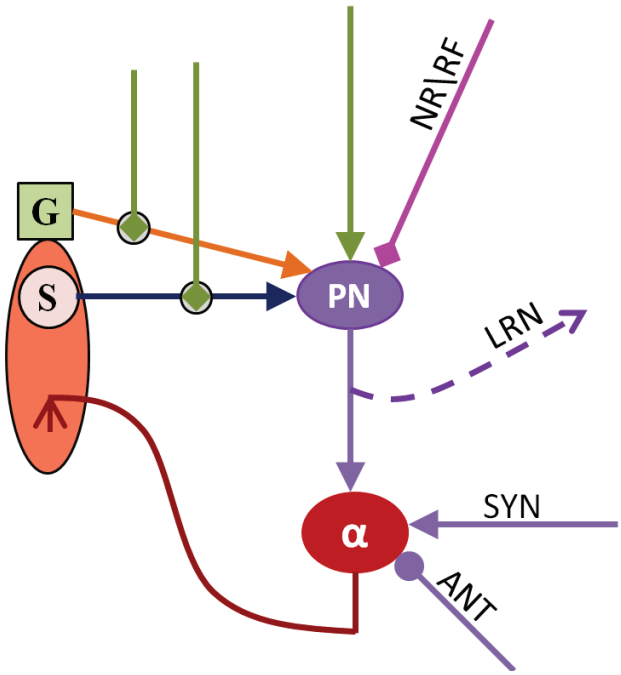


Figure 2.6 Descending and peripheral inputs converging on a PN interneuron. Information from GTO, spindles, M1 cortex, Nucleus Ruber and Reticular Formation are represented in orange, blue, green and magenta, respectively. Filled dots present inhibitory synapses, arrows represent excitatory synapses, while diamonds represent axo-axonic synapses. The connection named SYN and ANT came from PN interneurons regulating the activity of the synergistic and the antagonist muscle respectively.

2.5.3 Related works

In the last years, computational models have been devised in order to improve our understanding about how movements are performed and to overcome the difficulty of recording in vivo data during behavior. The state of art in this field suggests that quite similar models of spinal circuitry have been used for understanding different aspects of movement.

FLETE [BG89] was one of the first models of spinal circuitry introduced in 1988 by Bullock and Grossberg in order to explain the role of the spinal cord in the translation from motor intention to motor execution.

In more recent years, Tsianos and colleagues [TGL14] investigated the role of spinal cord in sensorimotor control and learning of movements using a detailed model of the spinal circuitry connected to a two degree of freedom arm. The same authors in [TRL11] used a model of spinal circuitry to investigate the role of cocontraction in learning to resist to a perturbation.

Raphael and colleagues [RTL10] used a model of spinal cord for investigating how the supraspinal centers can control the cord for stabilizing the responses of a four-muscle wrist joint to force perturbations, for executing rapid movement to reach a spatial target and for evaluating command adaptation when viscous curl force fields were applied.

Buhrmann and Di Paolo [BDP14] have used a model of spinal circuits for providing evidence that CNS can plan and control movements without a representation of complex bodily dynamics, because the creation and coordination of dynamic muscle forces is entrusted to the spinal feedback mechanisms.

Li and colleagues [LZH$^+$15] used a model of spinal circuitry for investigating how the central nervous system coordinates the activation of both alpha and gamma motoneurons during movement and posture, which is still an open question in the field of neuroscience [PE12]. Li and colleagues [HHX$^+$13] investigated also the role of propriospinal neurons in transmitting the cortical oscillatory signals to peripheral muscles in Parkinsonian tremor. The

distinct feature of the computational model used in both papers is the division of the descending commands into a static and a dynamic set that can be coordinated to obtain an accurate control of movement dynamics and stable maintenance of posture.

In [PFM15] we presented a model of the spinal cord simpler than the model described here that was able to regulate the position of a one degree-of-freedom arm by integrating commands from CNS and signals from proprioceptors and it was able to mediate the same reflex actions showed by the human. We showed that weight of synapse connections could be computed by requiring that the spinal cord model was capable of exhibiting the stretch and the autogenic inhibition reflexes.

Eventually, in [SG14] the authors evaluated whether a controller based on a simplified model of spinal cord permits complex behaviors in multi-muscle, multi-joint limb control. They demonstrated that their controller could smoothly accomplish reaching tasks in 2-D space, and it can manipulate highly nonlinear biological-like actuators and facilitate robust behaviors.

The model used in thesis presents some differences respect to the models in [TRL11], [TGL14] and [RTL10], both from an architectural and a behavioral perspective. In our model:

- each alpha motoneuron receives a monosynaptic input from corticospinal neurons, consistenting with the findings that cortico-motoneuronal cells in the primary motor cortex make monosynaptic connections with motoneurons innervating elbow, shoulder and finger muscles [RS09];

- Ib interneurons are excited by the Ib afferents coming from the homonymous and the synergistic muscles but these interneurons do not project to each other;

- the descending inputs direct to the interneurons and motoneurons are excitatory because they represent the commands coming from the corticospinal tract. In fact, it is widely accepted that the dominating descending input across the corticospinal tract is excitatory because glutamate is the

likely neurotransmitter released by this tract [NSDR05]. Instead, inputs from the rubro- and the reticulo- spinal tracts converging on PN interneurons can be both excitatory and inhibitory due to local inhibitory mechanisms, as for example the feedforward inhibition [PDB12]. In the other models each descending input can be both excitatory and inhibitory in order to represent the overall effect of the different tracts. In our opinion, the effect of all the descending tracts cannot be represented with just one command that can be both excitatory and inhibitory because commands from different descending tracts can be sent in different moments during the execution of a movement. For instance, the descending tract from the bulbospinal system is used for the online correction of the movement after the onset due to commands from the corticospinal tract;

- each descending input is a step function and, differently from the other models, inputs that regulate different functional modules are activated in different times;

- each neurons integrate its input with delay. More information about how neurons are modeled are reported in the appendix to this thesis.

Respect to the other models differences are in:

- the strategies adopted for controlling the activity of spinal cord;

- the model used for describing the activity of a neuron;

- the way the synaptic weights are computed.

Chapter 3

Experimental Evaluations: Execution of a movement

3.1 Introduction

In the previous chapter we have hypothesized that a movement is executed by mixing the activations of clusters of neurons within the M1 cortex. These clusters, in turn, regulate the activation of different spinal circuitries and generate movements with different characteristics. In this chapter we want to validate this hypothesis by showing that it is possible to move an arm to a desired position by recruiting spinal circuitries with different strategies.
Furthermore, we have verified that the correction of an ongoing movement can be executed in time through the loop involving the brainstem nuclei, as described in the literature and in the proposed model.

3.2 Experimental setup

The experiments presented and discussed in this and in the next chapter refer to the execution of an ***elbow flexion movement*** performed by the musculoskeletal model described in the Appendix A.

The arm movement is actuated by three muscles: the *Biceps Short*, the *Brachialis* and the *Triceps Lateral*. In the elbow flexion the Biceps Short, the Brachialis and the Triceps Lateral perform the role of agonist, synergistic and antagonist muscle, respectively.
The spinal circuitry and the descending inputs that regulate the contraction of these three muscles are shown in Figure 3.1.
We have hypothesized that these circuitries are organized in the 9 *functional modules* described in Table 3.1, each of which can be activated independently at any time. Each module receives inputs that regulate the firing of neurons and the gains of proprioceptive afferents. Because there is still disagreement on the way the CNS uses γ motoneurons to control the sensitivity of muscle spindles during voluntary movement [PE12], we adopted the strategy of activating γ_s together with the α motoneurons and the γ_d together with the PN interneurons, as proposed in [LZH$^+$15].
Overall, when a movement is performed by activating all the 9 functional modules it is needed to specify 52 parameters: 43 inputs and 9 activation times.
In the experiments we want the system to learn how to move the simulated arm from the initial fully extended position $\theta_{elbow}(t_{start})$ = 0 rad to the final position $\theta_{elbow}(t_{end})$ = 1.0472 rad (i.e. from 0° to 60°), by fulfilling some requirements on the *accuracy*, the *energy consumption* and the *duration* of the movement.
Thus, learning a movement is equivalent to solve a multiobjective optimization problem. As humans acquire a new motor ability by repeating the movement till the required performances are reached, the model learns to control the simulated arm by repeating the elbow flexion till the desired position is reached with the minimum consumption of metabolic energy. To implement such a trial-and-error process, we have used an evolutionary algorithm for learning the best values of the model parameters. In particular, we have chosen to use the *Differential Evolution* (DE) algorithm [SP97] because it is fairly fast and efficient in finding the global optima of non differentiable, non linear and multimodal functions, and requires few control parameters. In our implementation, each individual in the population is a vector whose elements are the

values of the model parameters for one execution of the elbow flexion. The DE works with a one-, two- or three-objective optimization problem depending on the experiment. The values of DE parameters used in the experiments are as follows:

- *maximum number of generations*: between 250 and 550. We chose this parameter on the basis of the difficulty of each experiment;
- *population size*: $10 * (number\ of\ objectives)$;
- *scaling factor*: 0.5;
- *crossover probability*: 0.2.

Each simulation of the arm movement lasts 6 seconds:

- from $t_{simulation} = 0\ s$ to $t_{simulation} = t_{start} = 1\ s$ the arm is at rest and the inputs modulating the gains of sensory feedback are set to -0.5 in order to ensure the stability of the arm, while all the other descending inputs are set to 0;
- from $t_{simulation} = 1\ s$ to $t_{simulation} = 2\ s$ the descending inputs change according to the values provided by the DE algorithm;
- from $t_{simulation} = 2\ s$ until the end of simulation $t_{end} = 6\ s$ the inputs under cortical control do not change.

In each simulation the position profile $\theta_{elbow}(t)$, i.e. the time evolution of the elbow angle, and the velocity profile $v(t)$ are computed and the distance from the target, the energy consumption, the duration of the movement and the cocontraction indexes are measured.
The **distance from the target** e is a measure of the **accuracy** of the movement: the smaller the distance, the higher accuracy. The distance is computed as the difference between the target position θ_{tp} and the position of the arm θ_{rp} when the movement has been

completed, i.e. when its velocity becomes and remains smaller than 0.0025 rad/s and the arm appears to be in a steady position.

$$e = \theta_{tp} - \theta_{rp} \tag{3.1}$$

where

$$\theta_{rp} = \theta_{elbow}(t_{rp}),\ t_{rp} = \inf(t \in [t_{start}, t_{end}] : v(t) \leq 0.0025\ rad/s)$$

The **energy consumption** is evaluated as the sum of the metabolic energy consumed by the three muscles during the last five seconds of the simulation.

$$E_c = \int_{t_{start}}^{t_{start}+5} [E_{BI}(t) + E_{BRA}(t) + E_{TRI}(t)]\mathrm{d}t \tag{3.2}$$

The **duration of movement** Δ_{tm} is defined as the time elapsed from the activation t_{st} of the first functional module to the time t_f at which the arm has entered and remained within the range $[\theta_{elbow}(t_{rp}) - 3°, \theta_{elbow}(t_{rp}) + 3°]$. In fact, as discussed in [OLB05], humans and non-human primates can make reliable discriminations only among trajectories that differ for more than 2° or 3° in direction.

$$\Delta_{tm} = t_{st} - t_f \tag{3.3}$$

$$t_{st} = \min(t_{PN-BI}, t_{PN-BRA}, t_{PN-TRI}, t_{\alpha-BI}, t_{\alpha-BRA}, t_{\alpha-TRI}, t_{IA}, t_{IB}, t_{REN}) \tag{3.4}$$

where

$$t_f = \inf(t \in [t_{start}, t_{end}] : \theta_{elbow}(t) \in [\theta_{elbow}(t_{rp}) - 3°, \theta_{elbow}(t_{rp}) + 3°])$$

Two **cocontraction indexes**, CCI_a and CCI_b, are computed to describe the simultaneous activity of the muscles acting around the elbow joint. The CCI_a index is determined in the form suggested by [KBP+03]:

$$CCI_a = \frac{F_{TRI}(t_{end})}{F_{BI}(t_{end}) + F_{BRA}(t_{end})} \tag{3.5}$$

where $F_{BI}(t_{end}), F_{BRA}(t_{end}), F_{TRI}(t_{end})$ are the forces exerted by the three muscles around the elbow joint at the end of simulation. Instead the CCI_b index describes the level of cocontraction over the entire movement and it is quantified as the product of the activation levels of the agonist and antagonist muscles, as suggested by [RTL10]:

$$CCI_b = \int [(\alpha_{BI}(t) + \alpha_{BRA}(t)) * \alpha_{TRI}(t)] \mathrm{d}t \tag{3.6}$$

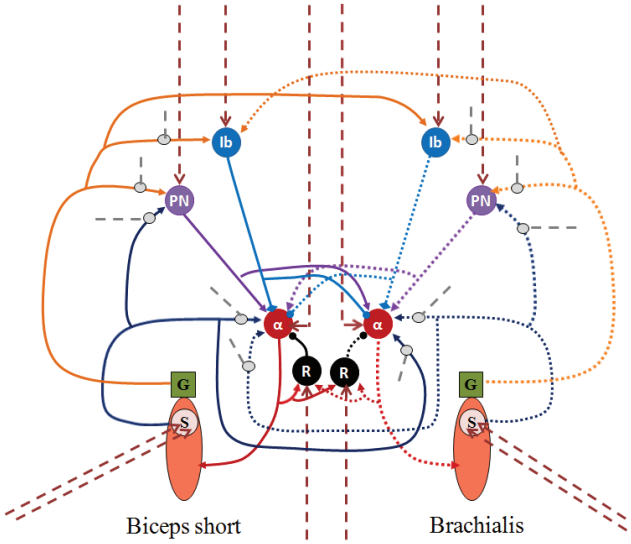
Eventually, in order to evaluate if a movement executed by our system is human-like we compared its velocity profile with the velocity profile foreseen by the Kinematic Theory of rapid human movements, described in Appendix B. This choice is supported by several psychophysical studies that have shown that the velocity profile of a rapid reaching movement is strongly stereotypical and it has an asymmetric bell shape [PAYL93].

3.3 Movement execution by functional modules combination

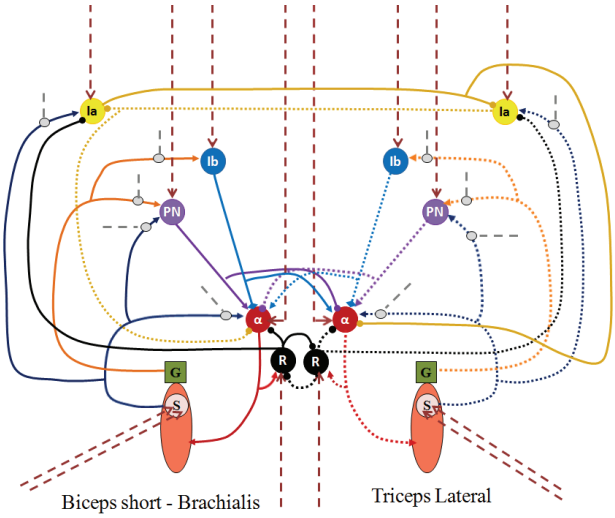
In this section we show that it is possible to execute a human-like movement by adopting different strategies in the recruitment of the functional modules listed in Table 3.1. When a functional module is not recruited, the inputs sent to it are kept to their starting values: the descending inputs, which can vary between 0 and 1, are set to 0 and the inputs modulating the presynaptic gains, which can vary between -1 and 1, are set to -0.5.

3.3.1 Activation of the PN functional modules

The goal of this experiment is to move the simulated arm from the initial position to the final one by activating only the functional modules $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ under the constraint of minimizing both the distance from the target and



(a) Spinal network regulating the contraction of a pair of synergistic muscles



(b) Spinal network regulating the contraction of a pair of antagonistic muscles

Figure 3.1 The spinal cord circuitry. The brown dashed lines represent the descending inputs from the corticospinal tract, while the grey dashed lines represent the presynaptic inputs that modulate the gains of proprioceptive afferents. S and G are for spindles and Golgi tendon organs respectively.

Table 3.1 Functional modules

Name: $fmPN_{BI}$	*Activation time*: t_{PN-BI}	*Number of inputs*: 4
The PN interneurons receiving afferents from the Biceps and the γ_d motoneurons exciting the intrafusal fibers of the same muscle belong to this functional module. It receives descending inputs that regulate the firing of the neurons and presynaptic inputs regulating the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Biceps.		
Name: $fmPN_{BRA}$	*Activation time*: t_{PN-BRA}	*Number of inputs*: 4
The PN interneurons receiving afferents from the Brachialis and the γ_d motoneurons exciting the intrafusal fibers of the same muscle belong to this functional module. It receives inputs that regulate the firing of the neurons and presynaptic inputs regulating the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Brachialis.		
Name: $fmPN_{TRI}$	*Activation time*: t_{PN-TRI}	*Number of inputs*: 4
The PN interneurons receiving afferents from the Triceps and the γ_d motoneurons exciting the intrafusal fibers of the same muscle belong to this functional module. It receives descending inputs that regulate the firing of the neurons and presynaptic inputs regulating the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Triceps.		
Name: $fm\alpha_{BI}$	*Activation time*: $t_{\alpha-BI}$	*Number of inputs*: 2
The α and the γ_s motoneurons innervating the extra and the intrafusal fibers of the Biceps belong to this functional module. The module receives descending inputs regulating the background activity of the neurons.		
Name: $fm\alpha_{BRA}$	*Activation time*: $t_{\alpha-BRA}$	*Number of inputs*: 2
The α and the γ_s motoneurons innervating the extra and the intrafusal fibers of the Brachialis belong to this functional module. The module receives descending inputs regulating the background activity of the neurons.		
Name: $fm\alpha_{TRI}$	*Activation time*: $t_{\alpha-TRI}$	*Number of inputs*: 2
The α and the γ_s motoneurons innervating the extra and the intrafusal fibers of the Triceps belong to this functional module. The module receives descending inputs regulating the background activity of the neurons.		
Name: $fmIA$	*Activation time*: t_{IA}	*Number of inputs*: 11
All the IA interneurons belong to this functional module. It receives inputs that regulate the firing activity of the IA interneurons and presynaptic inputs that regulate the gain of proprioceptive afferents having a synaptic connection with the IA interneurons and the α motoneurons.		
Name: $fmREN$	*Activation time*: t_{REN}	*Number of inputs*: 3
All the Renshaw cells belong to this functional module. It receives inputs that regulate the firing activity of the Renshaw cells.		
Name: $fmIB$	*Activation time*: t_{IB}	*Number of inputs*: 11
All the IB interneurons belong to this functional module. It receives inputs that regulate the firing activity of the IB interneurons and presynaptic inputs that regulate the gain of proprioceptive afferents having a synaptic connection with the IB interneurons.		

Table 3.2 Activation of the PN functional modules: Sigma-Lognormal Parameters.

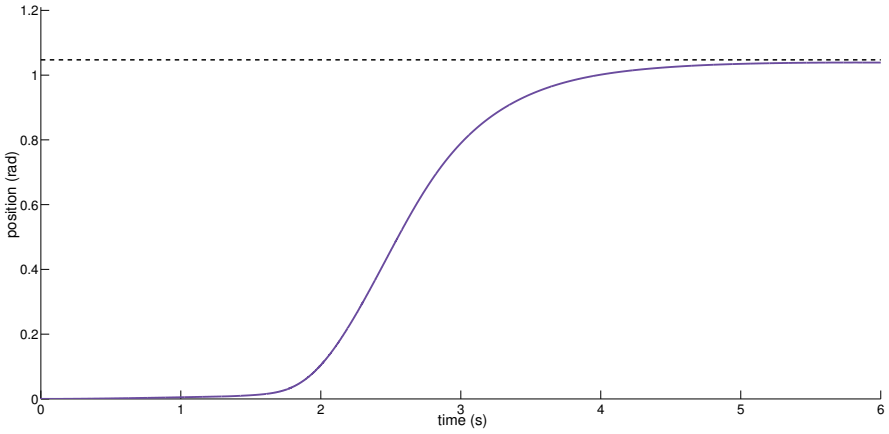
t_0	D	μ	σ	θ_s	θ_e
0.979	21.924	-0.076	0.173	-0.0448	-0.073
1.554	181.995	-0.010	0.436	-0.0487	-0.097

the consumption of metabolic energy. Therefore, the DE algorithm works with a two-objective optimization problem searching for best values of 15 parameters. After 400 generations, the DE algorithm provided 4 Pareto optimal solutions, i.e. 4 solutions for which none of the two objective functions can be improved in value without degrading the other one. In Figure 3.2 are shown the position and the velocity profiles of the solution with the minimum distance from target. For this solution $e = 0.01\ rad$, $\Delta_{tm} = 2.39\ s$ and $E_c = 3.7\ J$.

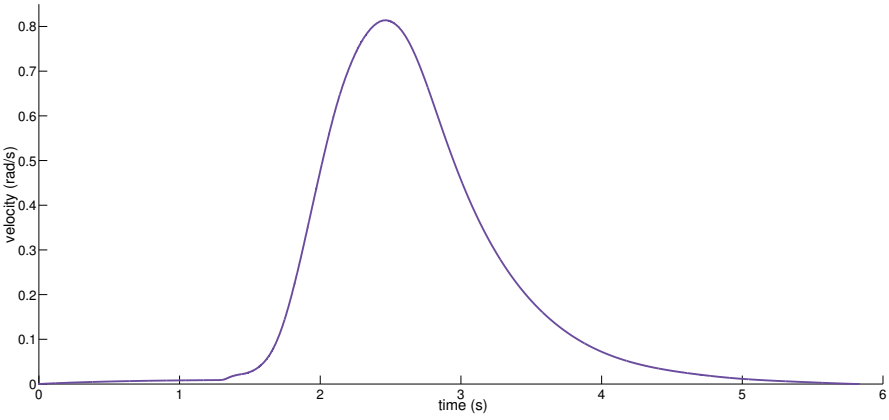
By activating only the three PN functional modules, it is possible to generate slow movements with a small energy consumption. An interesting property of this solution is that the activation profiles of the agonist and the synergistic muscles are equal, as if they were a single muscle and the movement was executed by a pair of agonist and antagonist muscles.

We have verified that the speed profile of this solution could be reconstructed by the Sigma-Lognormal model. We used the XzeroROBUSTE software [OP09a] for the automatic extraction of the Sigma-Lognormal parameters. This software reconstructed the speed profile generated by our model by the time superimposition of two lognormal functions whose parameters are reported in Table 3.2. As shown in Figure 3.3, the speed profile was reconstructed with a SNR equal to 29 dB.

The extraction of two lognormal primitives seems to confirm that the Biceps and the Brachialis are working as a single agonist muscle.



(a) Position Profile



(b) Velocity Profile

Figure 3.2 Position and velocity profiles of the best movement executed by activating only the PN functional modules. The dashed line represents the target position.

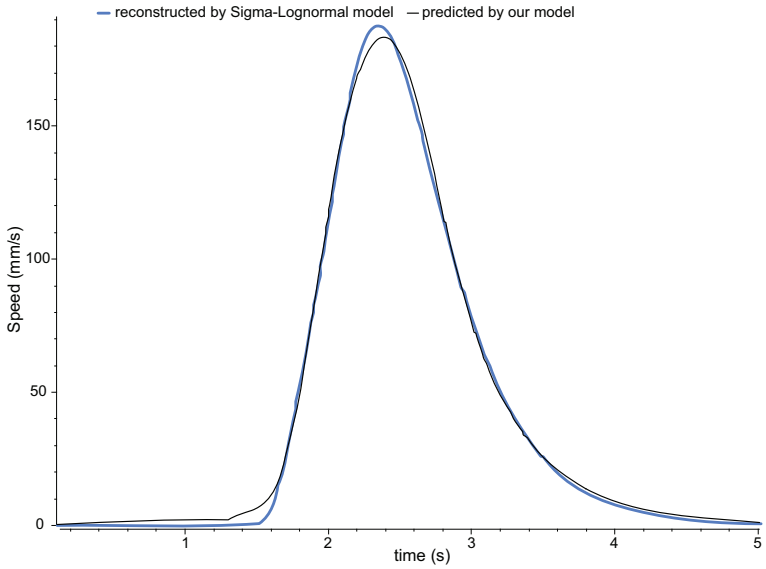


Figure 3.3 Speed profile of the movement executed by activating only PN functional modules (in *black*) and its reconstruction by Sigma-Lognormal model (in *blue*). The fitting has a SNR equal to 29 dB.

3.3.2 Activation of the PN, IA, IB, REN functional modules

Starting from a learned PN activation The goal of this experiment is to move the arm toward the final position by:

- activating the functional modules $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ by using the 15 parameters learned in the previous experiment and corresponding to the more accurate solution, as shown in Figure 3.2;

- searching for the best values of 28 parameters that regulate the activity of the functional modules $fmIA$, $fmREN$ and $fmIB$.

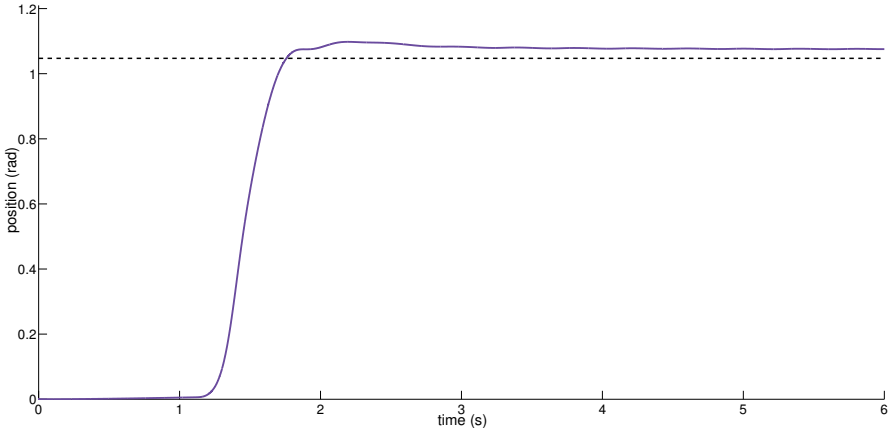
In this experiment, the aim is to find the parameters that minimize the distance from the target, the consumption of metabolic energy and the duration of the movement. Therefore, the DE algorithm

Table 3.3 Activation of the PN, IA, IB, REN functional modules, starting from a learned PN activation: Sigma-Lognormal Parameters.

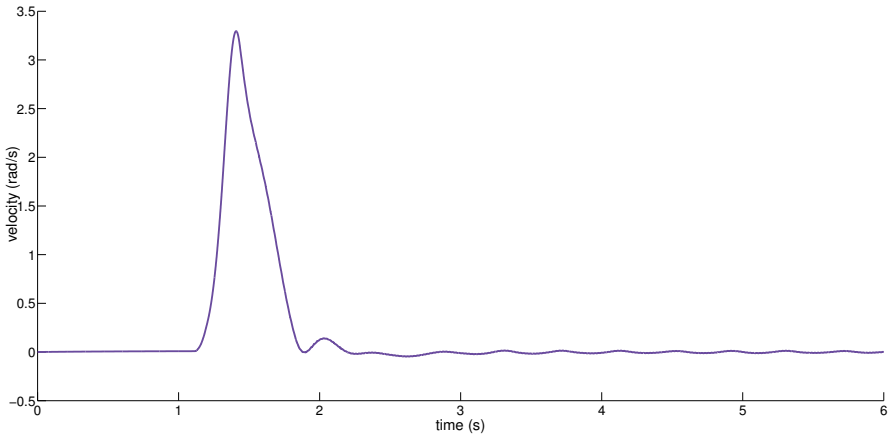
t_0	D	μ	σ	θ_s	θ_e
0.665	49.967	-0.420	0.103	-0.045	-0.077
1.229	147.117	-1.454	0.444	-0.050	-0.098
1.235	16.219	-0.935	0.190	-0.072	-0.156

works with a three-objective optimization problem. After 400 generations, the DE algorithm provided 20 Pareto optimal solutions, with different levels of accuracy, energy consumption and time duration. The fastest solution has $e = 0.028\ rad$, $\Delta_{tm} = 0.72\ s$ and $E_c = 409\ J$ and it is shown in Figure 3.4. The XzeroROBUSTE software [OP09a] reconstructed the speed profile of this solution through the time superimposition of three lognormal functions whose parameters are reported in Table 3.3. The reconstructed speed profile fits the profile predicted by our model with a SNR equal to 31.1 dB, as shown in Figure 3.5.
Eventually, we repeated this experiment without the activation of the $fmIB$ functional module in order to understand which is the role played by this module in the execution of a movement. Taking into account the movements with a distance from the target less than 0.06 rad, the energy consumption is equal to $220 \pm 201\ J$ when the $fmIB$ module is activated while is equal to $4 \pm 2\ J$ when it is not activated. Moreover, the duration of movement is equal to $1.5 \pm 0.7\ s$ when the module is activated and it is equal to $2 \pm 0.1\ s$ when it is not activated. Therefore, the activation of the $fmIB$ module allows to execute faster movements with an increase in the energy consumption. This suggests that in order to fulfill the requirements of minimizing both the distance from the target and the duration of movement the descending commands activated the interneuronal pathway by means of which Ib interneurons implement a positive force feedback loop.

Searching for all the parameters Unlike in the previous one, in this experiment we want to move the arm toward the final position by searching for the best values of 43 parameters that regulate



(a) Position Profile



(b) Velocity Profile

Figure 3.4 Position and velocity profiles of a movement executed by activating the PN, IA, IB, REN functional modules and starting from a learned PN activation. The dashed line represents the target position.

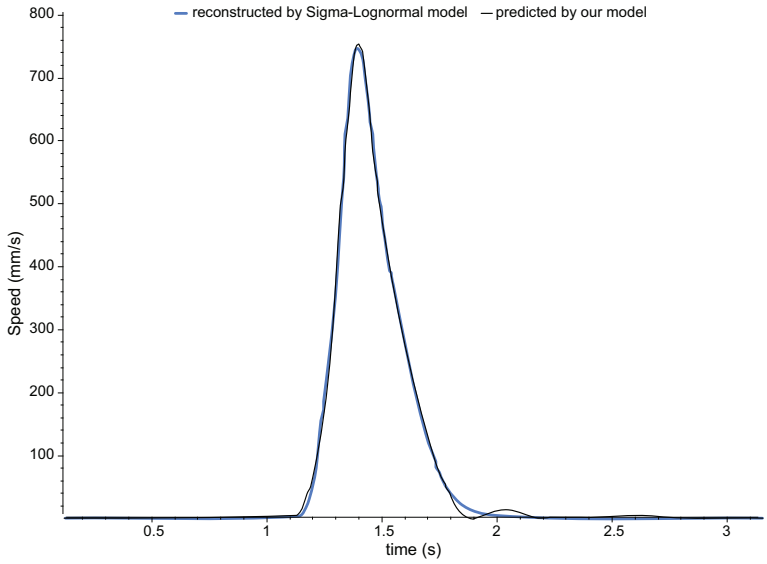


Figure 3.5 Speed profile of the movement executed by activating the PN, IA, IB, REN functional modules and starting from a learned PN activation (in *black*) and its reconstruction by Sigma-Lognormal model (in *blue*). The fitting has a SNR equal to 31.1 dB.

the activity of the functional modules $fmIA$, $fmREN$, $fmIB$, $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$, without using the previously learned parameters for $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$. The DE algorithm works with a three-objective optimization problem also in this case. After 550 generations, the DE algorithm provided 14 Pareto optimal solutions, with different levels of accuracy, energy consumption and time duration. In Figure 3.6 the three fastest solutions are depicted in red, orange and blue while the solution less energetically wasteful is represented in green. The characteristics of these solutions are summarized in Table 3.4. The solution depicted in red is faster than the blue one that has a bigger velocity and reaches the steady state sooner, because it has a shorter latency between the activation of the first functional module $t_{st} = 1.18\ s$ and the beginning of the movement $t_{bm} = 1.22\ s$. Instead the blue solution shows a latency about ten times bigger, in fact $t_{st} = 1.25\ s$ and $t_{bm} = 1.7\ s$. The XzeroROBUSTE software [OP09a] reconstructed the speed profile of the red solution

Table 3.4 Activation of the PN, IA, IB, REN functional modules: Best movements.

Solution	Distance from the target (rad)	Energy (J)	Duration (ms)
Red Trace	$\mathbf{3.9 * 10^{-3}}$	**251**	**870**
Orange Trace	$5.4 * 10^{-4}$	436	900
Blue Trace	$1.4 * 10^{-3}$	325	1040
Green Trace	$8.5 * 10^{-3}$	2.2	2670

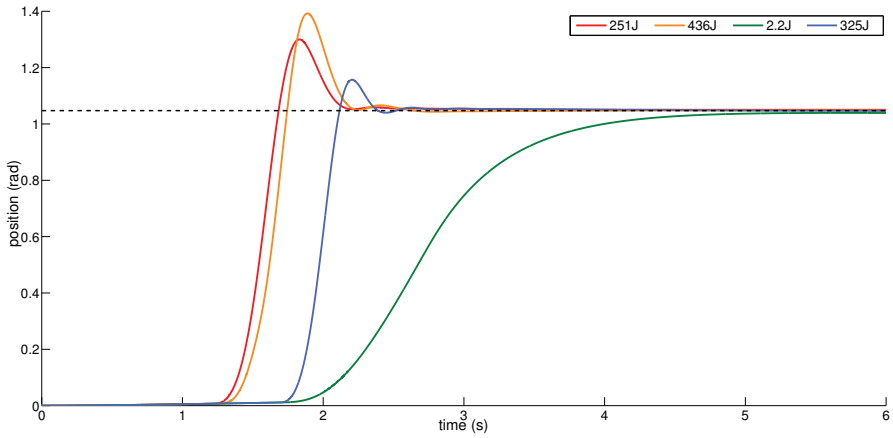
Table 3.5 Activation of the PN, IA, IB, REN functional modules: Sigma-Lognormal Parameters.

t_0	D	μ	σ	θ_s	θ_e
0.59	245.752	-0.035	0.140	-0.045	-0.120
1.365	14.75	-1.494	0.253	0.035	-0.103
0.93	53.089	-0.055	0.172	-9.47	-9.584

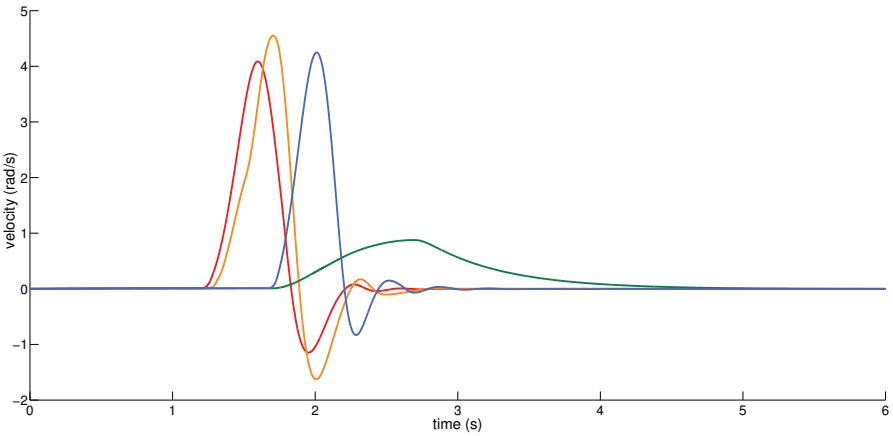
through the time superimposition of three lognormal functions whose parameters are reported in Table 3.5. The reconstructed speed profile fits the profile predicted by our model with a SNR equal to 29 dB, as shown in Figure 3.7.

We repeated the experiment of moving the arm by activating the functional modules $fmIA$, $fmREN$, $fmIB$, $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ without the objective of minimizing the energy consumption in order to understand how this constraint influences the search for the best strategy for controlling the arm. After 550 generations, the DE algorithm provided only 4 Pareto optimal solutions with an energy consumption equal to 321 ± 69.5 J, a time duration equal on average to 0.95 ± 0.24 s and the bigger time duration equal to 1.3 s. When it was required to minimize the energy consumption the Pareto solutions with a duration of movement less than 1.3 s had an energy consumption equal to 299 ± 116 J.

The amount of metabolic energy expenditure is roughly the same whether or not the energy consumption is one of the objective to fulfill. This result may suggest that the minimization of energy is an intrinsic property of the spinal cord circuitry, as if the evolution had built spinal circuitries in a way that minimizes the energy consumption per se.



(a) Position Profiles



(b) Velocity Profiles

Figure 3.6 Position and velocity profiles of the best movements executed by the activation of the PN, IA, IB, REN functional modules. The dashed line represents the target position.

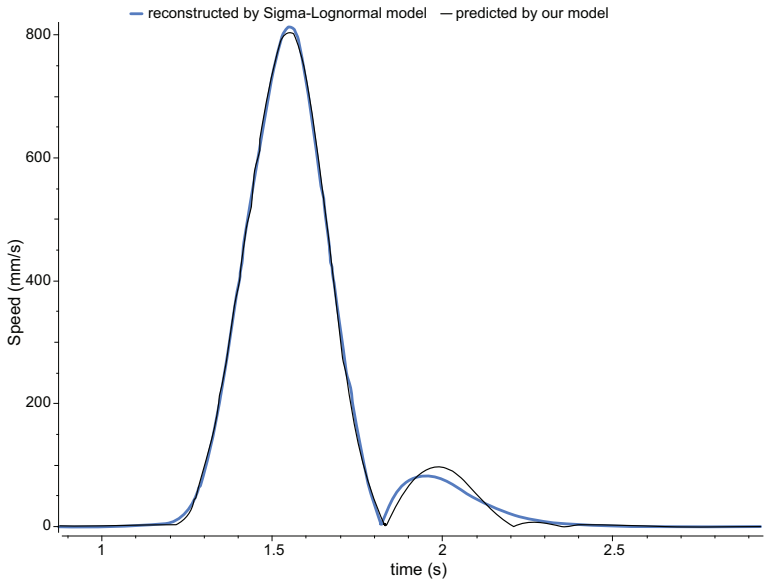


Figure 3.7 Speed profile of the movement executed by activating the PN, IA, IB, REN functional modules (in *black*) and its reconstruction by Sigma-Lognormal model (in *blue*). The fitting has a SNR equal to 29 dB.

3.3.3 Activation of the ALFA functional modules

The goal of this experiment is to move the arm toward the target position by activating the $fmIA$, $fmREN$, $fmIB$, $fm\alpha_{BI}$, $fm\alpha_{BRA}$ and $fm\alpha_{TRI}$ modules and by minimizing the distance from the target, the consumption of metabolic energy and the duration of the movement. The DE algorithm has to search for the best values of 37 parameters in a three-objective optimization problem. After 550 generations, the DE algorithm provided 11 Pareto optimal solutions that are shown in Figure 3.8 over the Pareto frontier. Movements obtained by actuating three of the Pareto solutions are shown in Figure 3.9 and their characteristics are reported in Table 3.6. Moreover, for the five fastest movements we have evaluated the relationship between the CCI_a index and the accuracy, and the relationships between the CCI_b index and the energy consumption and the duration of the movement,

Table 3.6 Activation of the PN, IA, IB, REN functional modules: Best movements.

Solution	Distance from the target (rad)	Energy (J)	Duration (ms)
Red Trace	$\mathbf{5.6 * 10^{-3}}$	**418.5**	**790**
Green Trace	$1.4 * 10^{-3}$	290.6	880
Purple Trace	$28.8 * 10^{-3}$	191.5	960

as shown in Figure 3.10.
Figure 3.10.(a) shows that the CCI_a index, a measure of the cocontraction at the end of the movement, increases with the increasing of the accuracy. The same relationship has been described in an experimental study presented in [GMCM03], even if the cocontraction is measured in a different way.
Furthermore, it is interesting to note that CCI_b, a measure of the cocontraction during all the movement, increases with the increasing of the energy consumption and decreases with the increasing of the movement duration. The faster solution (the red trace in Figure 3.9 and the filled dot labeled 'C' in Figure 3.10) is the movement with the greater CCI_b and the greater energy expenditure. The results shown in Figure 3.10.(b) and 3.10.(c) suggest that in order to execute a faster movement it is needed to increase the activation levels of the three muscles and therefore to increase the energy consumption.
The XzeroROBUSTE software [OP09a] reconstructed the speed profile of this solution through the time superimposition of three lognormal functions whose parameters are reported in Table 3.7. The reconstructed speed profile fits the profile predicted by our model with a SNR equal to 30.4 dB, as shown in Figure 3.11.

Table 3.7 Activation of the ALFA, IA, IB, REN functional modules Sigma-Lognormal Parameters.

t_0	D	μ	σ	θ_s	θ_e
0.974	12.812	-1.024	0.128	-0.056	-0.035
1.025	265.295	-0.702	0.238	-0.054	-0.099
1.505	75.039	-1.420	0.665	-9.425	-9.610

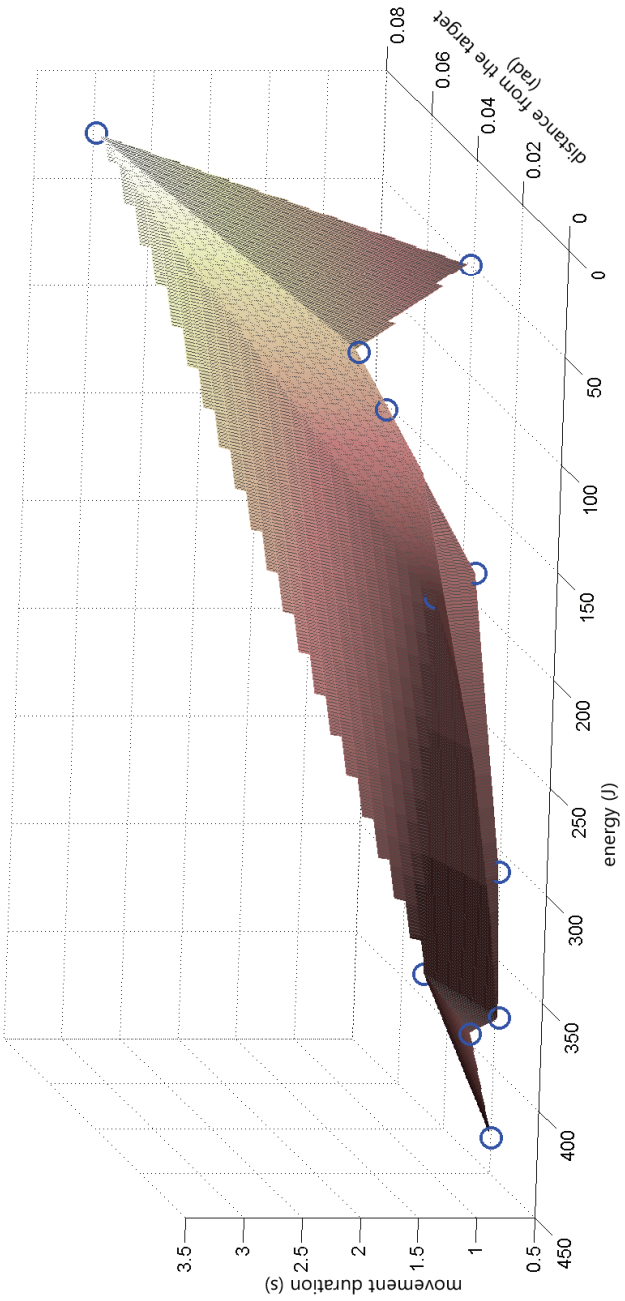
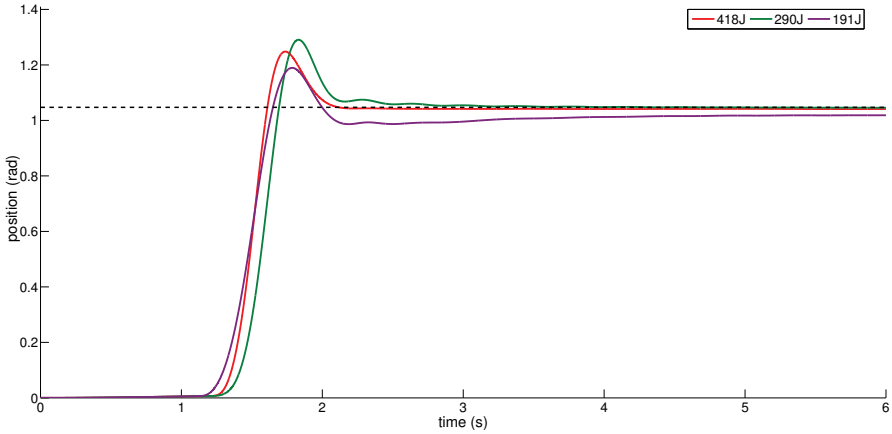
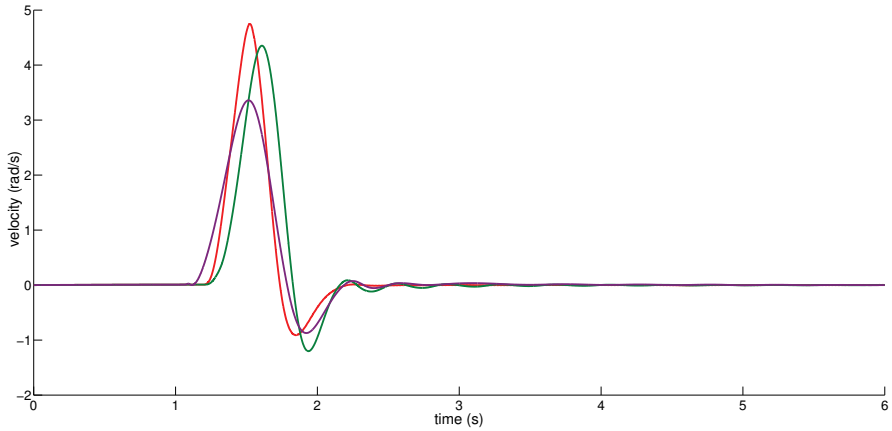


Figure 3.8 Pareto frontier obtained by activating the ALFA, IA, IB, REN functional modules. The 11 Pareto optimal solutions are depicted with blue circles.

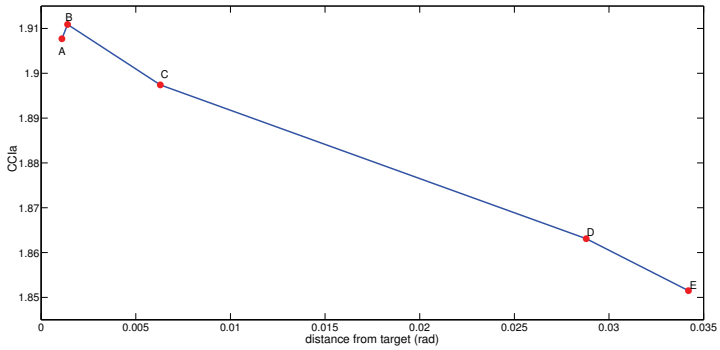


(a) Position Profiles

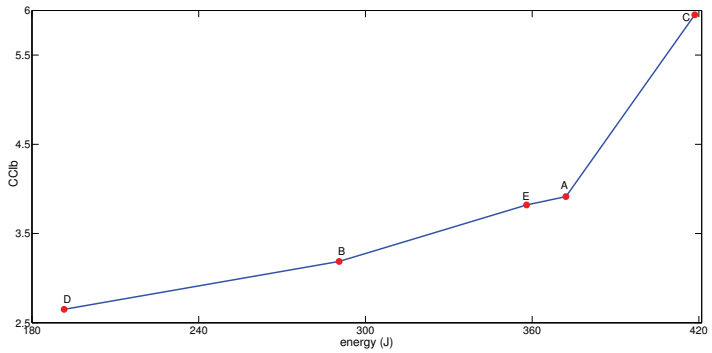


(b) Velocity Profiles

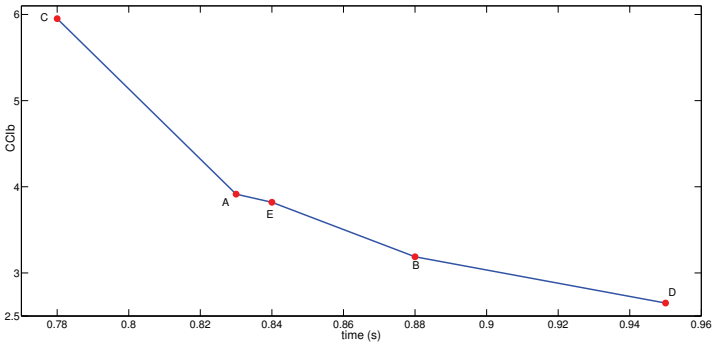
Figure 3.9 Position and velocity profiles of some movements executed by the activation of the ALFA, IA, IB, REN functional modules. The dashed line represents the target position.



(a) CCI_a vs distance from target



(b) CCI_b vs energy consumption



(c) CCI_b vs duration of the movement

Figure 3.10 Relationships between the cocontraction indexes and the (a) the distance from the target, (b) the energy consumption and (c) the duration of movement by activating of the ALFA, IA, IB, REN functional modules.

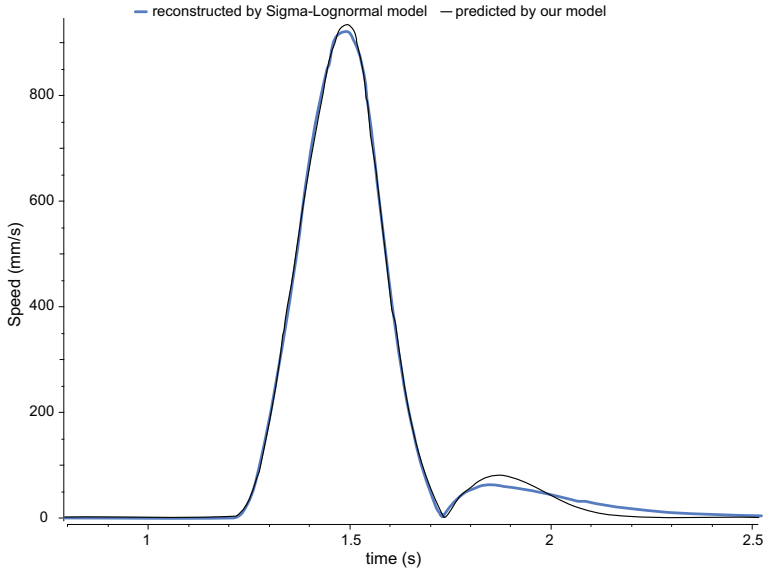
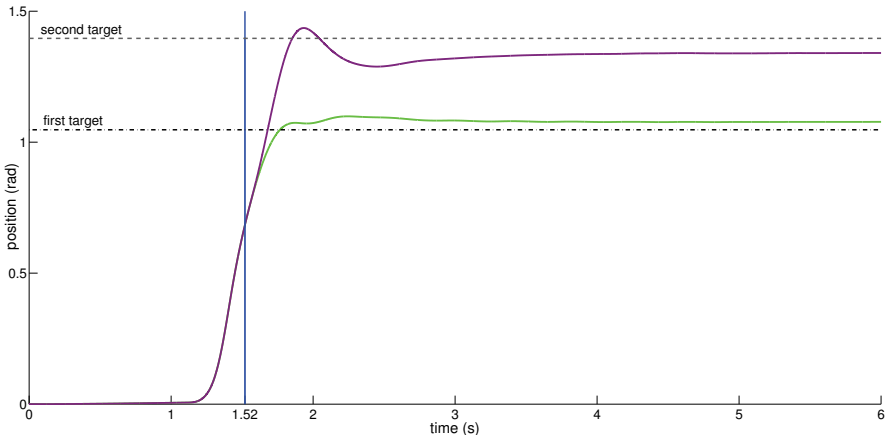


Figure 3.11 Speed profile of the movement executed by activating the ALFA, IA, IB, REN functional modules (in *black*) and its reconstruction by Sigma-Lognormal model (in *blue*). The fitting has a SNR equal to 30.4 dB.

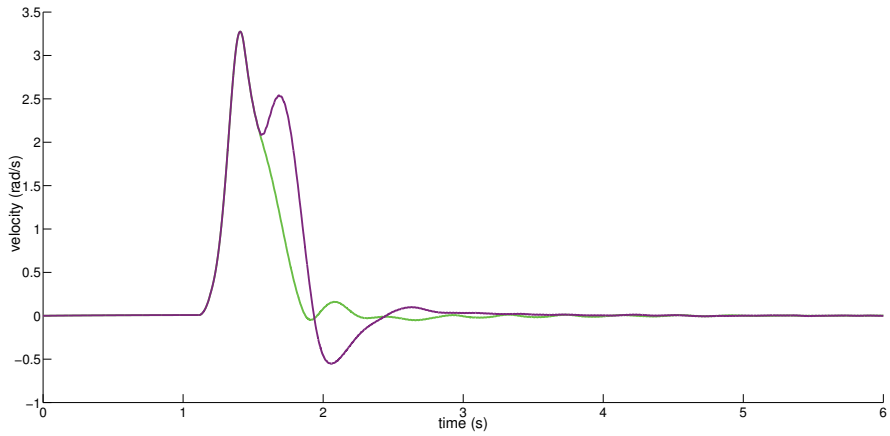
3.4 Switching the direction of an ongoing movement

In [AGLP90] the ability of cats to switch the direction of an ongoing target-reaching forelimb movement was investigated. Cats were positioned in front of two horizontal tubes containing a morsel of food and they were trained to make a fast visually guided reaching movement toward the tube indicated by a light. After the training stage, the behaviour of cats was evaluated when the light was switched off in one tube and switched on in the other tube during an ongoing movement. The illumination was shifted to the other tube randomly after 25-75 ms, and the latency to the earliest change in movement trajectory was measured. The mean switching latency in four cats ranged from 83 to 118 ms. The observed latencies are too short for a visual processing at the cortical level and for producing a new cortical command, therefore the authors proposed that a motor command sent from the motor cortex could

be updated by commands given via the brainstem system to the C3-C4 PN interneurons (*updating hypothesis*), as explained in the previous chapter.
In this section, we show that it is possible to reproduce with our model the behaviour observed in the cats by updating the activation of the C3-C4 PN interneurons through the subcortical connections coming from Nucleus Ruber and Reticular Formation.
We chose as learned movement the one shown in Figure 3.4 and directed toward a target in the position $\theta_{tp} = 1.047\ rad$, because it was the fastest movement obtained by regulating only the activities of spinal interneurons. In fact, it is important to point out that cats lack CM projections [LKM+04], therefore we cannot use movements executed by the direct activation of alpha motoneurons in order to reproduce the *in vivo* experiment. Moreover, the tubes used in the experiment had an internal diameter equal to 30 mm and were positioned with an intercenter distance equal to 60 mm. Therefore, we positioned the second target at $\theta_{tp} = 1.396\ rad$ (i.e. 80°) in order to have an arc length distance between the two target equal to 101 mm.
In our simulation the switching latency was set equal to 100 ms and the illumination was shifted to the second target 420 ms after $t = t_{start}$. We used the DE algorithm for finding the values of commands from subcortical systems for activating or inhibiting C3-C4 PN interneurons. In Figure 3.12 is shown in purple the fastest movement found by the DE algorithm after 300 generations: the arm reached the new target 530 ms after the updating commands from the brainstem system, with an error equal to 0.055 rad and an energy consumption equal to 337 J. This movement was obtained by decreasing the activation of PN interneurons that excite the biceps and the triceps and by increasing the activation of the PN interneuron that excites the brachialis.
The XzeroROBUSTE software [OP09a] reconstructed the speed profile of the movement through the time superimposition of four lognormal functions whose parameters are reported in Table 3.8. The reconstructed speed profile fits the profile predicted by our model with a SNR equal to 31.2 dB, as shown in Figure 3.13.



(a) Position Profiles



(b) Velocity Profiles

Figure 3.12 The position and the velocity profiles of the planned movement are depicted in green. The position and the velocity profiles of the executed movement are depicted in purple. The target position was shifted at $t = 1420\ ms$ and after 100 ms the executed movement started to move away from the planned one due to the updating of the motor commands.

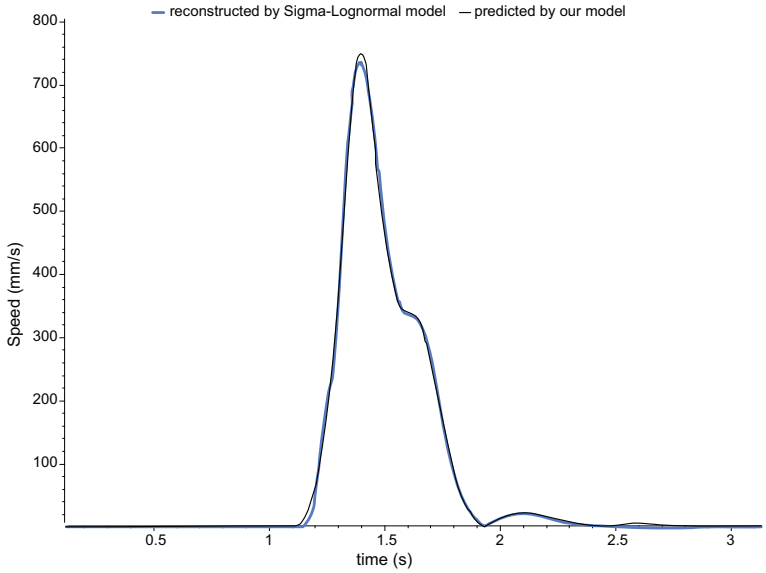


Figure 3.13 Speed profile of the movement executed with the updating of the motor commands (in *black*) and its reconstruction by Sigma-Lognormal model (in *blue*). The fitting has a SNR equal to 31.2 dB.

Table 3.8 Movement executed with the updating of the motor commands: Sigma-Lognormal Parameters.

t_0	D	μ	σ	θ_s	θ_e
0.819	25.10	-0.773	0.103	-0.044	-0.076
1.219	173.02	-1.475	0.466	-0.047	-0.101
0.714	38.92	-0.035	0.081	-6.322	-6.523
1.105	8.36	-0.010	0.141	-9.364	-9.686

3.5 Discussion

In this chapter we have used the Sigma-Lognormal model to verify whether the movements produced by our *computational model* are human-like. Sigma-Lognormal model is a *behavioral model* predicted by the Kinematic Theory of rapid human movements [Pla95]. This theory models the behaviour of the motor control and the neuromuscular system involved in the production of rapid movements and it has been experimentally supported in numerous physiologically tests. While the Kinematic Theory provides a parametric representation of the motor control behavior, our model describes how the neuronal networks work for producing a behaviour. The kinematic theory describes the global properties of the neuromuscular networks involved in a synergistic action and it predicts that a complex trajectory results from the time superimposition of lognormal functions.
It is interesting to note that in the experiments presented before, except the last one, the number of lognormal functions predicted by the Sigma-Lognormal model for a movement is equal to the number of muscles that are activated for executing the movement. In particular, the number of lognormal functions is equal to the number of muscles that receive a different excitation pattern. In the last experiment there are four lognormal functions instead of three because there is a correction of the ongoing movement that in the Sigma-Lognormal model correspond to superimpose a new basic primitive (i.e. a lognormal) for reaching a new target point. However, a relationship between the parameters of the two models seems to exist and in the future this aspect has to be investigated.

Chapter 4

Experimental Evaluations: Fitts' law

4.1 Introduction

Fitts' law is an empirical phenomenon that has been used to verify the validity of many computational models. Despite the constraints provided by the Fitts' law are too general to give clear suggestions about the organization of the nervous system [Sch02], we exploited this law and our model to get more insights about how brain encodes movements and to unveil the role played by the different area of the brain in determining the trade-off between speed and accuracy in reaching movements.

4.2 Fitts' Law

One of the aspects of human movement that has been deeply investigated is the tradeoff between speed and accuracy in reaching movements. Such a tradeoff, indeed, had been investigated since the 19th century in psychology, when response time was considered as a mean to unveil the inner functioning of the mind [Hei14]. However, the investigations were carried out in "extreme" conditions, i.e. spatially constrained tasks, emphasizing high accuracy

without concern for the response time, or temporally constrained tasks, examining the ability to produce predefined responses to simple stimuli without paying attention to the accuracy of the movement itself.

It was only in the middle of 20th century that Fitts considered the two aspects simultaneously [Fit92]. Fitts considered reaching movements between rectangular targets, as representative of typical (at the time of his investigation) industrial tasks, such as installing parts on an assembly line or stamping envelopes in an office. In Fitts' experiments, human subjects were requested to move a stylus back and forth between two fixed targets as quickly as possible for 15 s. Fitts measured the average time MT required to execute the movements depending on the width W of the targets and the distance, he called amplitude, A between them, and, in the light of the information theory formulated by Shannon a few years before, fitted a logarithmic model to the data, yielding the equation that later was referred to as "Fitts' Law":

$$MT = a + b * \log_2(\frac{2A}{W}) \tag{4.1}$$

where a and b are constants whose values were determined empirically.

In the following decades, a large number of experiments and studies have provided more and more empirical support, thus contributing to boost the the popularity of Fitts' law. They envisaged a variety of movements, limbs and muscle groups, experimental conditions, manipulating devices, subjects, and a wide range of performance indices.

4.3 Experimental setup

The experiments presented and discussed in this chapter are aimed at verifying if the elbow flexion movements executed by the musculoskeletal model described in the Appendix A satisfy the tradeoff between speed and accuracy predicted by the Fitts' law.

We supposed that when a human has to produce a previously learned movement faster his brain retrieves the motor commands, i.e. the set of descending inputs, used for executing the learned movement and then changes some of the commands for increasing the speed of the movement.
On the basis of the connections between the neurons located in the primary motor cortex and the neurons within the spinal cord, we have hypothesized different strategies that may be implemented by the brain for the execution of a faster movement starting from a learned one. The proposed strategies will be presented in the next two sections.
In order to reproduce the Fitts' experiment, we fixed the position of the two targets in $\theta_{elbow}(t_{start}) = 0\ rad$ and $\theta_{elbow}(t_{end}) = \theta_{des} = 1.0472\ rad$ and we varied the motor commands when different levels of accuracy for the desired position were accepted: $W = (5°, 10°, 20°)$. In particular, defined a circular target centered on θ_{des} and with a diameter equal to W, a movement fulfills the constraint on the accuracy if the arm never oversteps the target and its position at t_{end} is within the circle. In each experiment, we used the DE algorithm for setting the values of motor commands so as to generate faster repetitions of an elbow flexion: a learned movement was used as individual of the initial population, and the DE is aimed at minimizing the time duration of the motion over 250 generations. Each simulation is set-up as in the previous chapter and when a movement didn't fulfill the required level of accuracy it was not accepted as a solution for the task.
For each experiment, we computed the mean time duration of the movements corresponding to the best solutions provided at each generation. So, for each strategy we had three pairs of accuracy and mean time duration values and then we computed the parameters of Fitts' law that best fit the data by using the Trusted Region algorithm [BCL99].

4.4 Exploring the Fitts' law by recruiting networks of homogeneous interneurons

4.4.1 Learning the execution of accurate movements

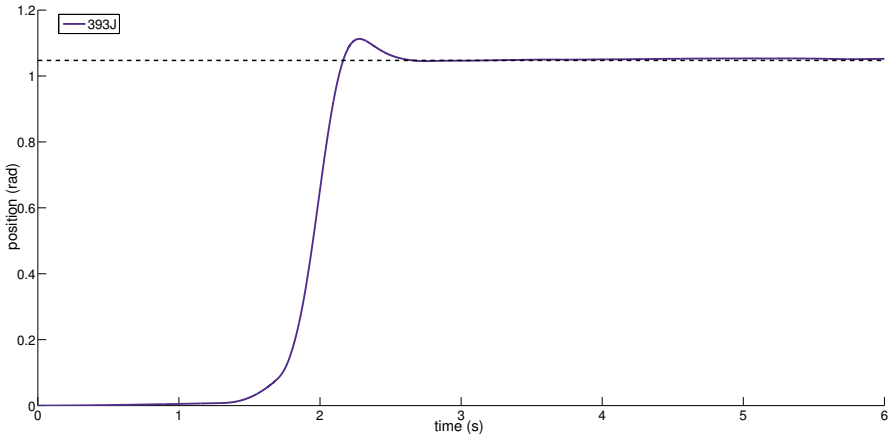
In this experiment we want the system to learn how to move the simulated arm from the initial position to the final one without the activation of the corticomotoneuron cells, minimizing the distance from the target and the energy consumption. The DE algorithm works with a two-objective optimization problem over 500 generations by searching for the best values of 43 parameters (37 inputs and 6 activation times) that regulate the activity of the functional modules $fmIA$, $fmREN$, $fmIB$, $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ described in Table 3.1. These modules are networks of homogeneous interneurons (i.e. interneurons belonging to the same class). The fastest movement that reaches the desired position is the one shown in Figure 4.1 and its properties are $e = 4.4 * 10^{-3}\ rad$, $\Delta_{tm} =\ 1.08\ s$ and $E_c =\ 393\ J$.

4.4.2 Execution of faster movements

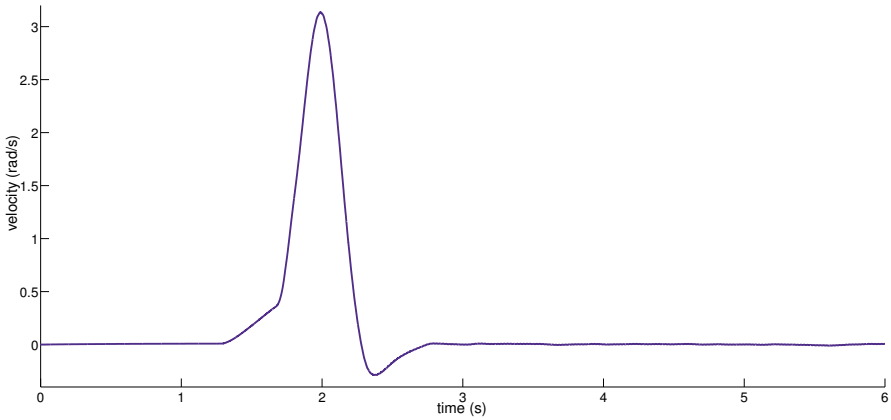
We have hypothesized that in order to execute an elbow flexion faster than a learned one, the brain may adopt the following strategies for varying the motor commands memorized during the learning process:

- *Strategy A*: to recruit the $fm\alpha_{BI}$, $fm\alpha_{BRA}$ and $fm\alpha_{TRI}$ modules without changing the activation of the other modules. This strategy corresponds to the activation of clusters of cortical neurons located in the caudal part of the M1 cortex and, in our simulation, requires to compute 9 parameters;

- *Strategy B*: to modify the input sent to the $fmIA$, $fmREN$, $fmIB$, $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ modules with-



(a) Position profile of the fastest movement



(b) Velocity profile of the fastest movement

Figure 4.1 Position and velocity profiles of the fastest movement that minimizes the distance from the target and the energy consumption. The movement is actuated by recruiting networks of homogeneous interneurons. The dashed line represents the target position.

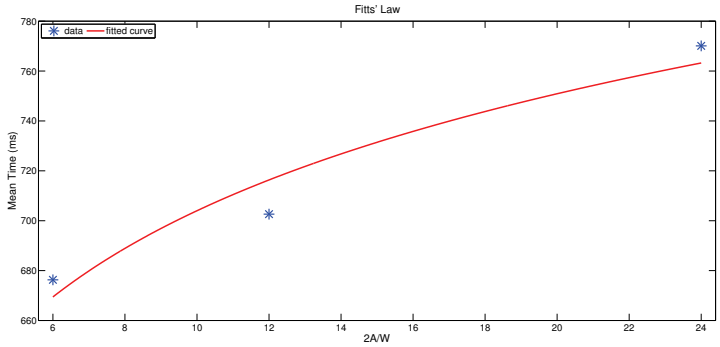
Table 4.1 Coefficients of the Fitts' law for the three strategies described in section 4.4.2 and measure of goodness of the fitting

Strategy	Model coefficients		R^2
	a	b	
Strategy A	548.2	47	0.94
Strategy B	815	37	0.75
Strategy C	544.2	12.35	0.87

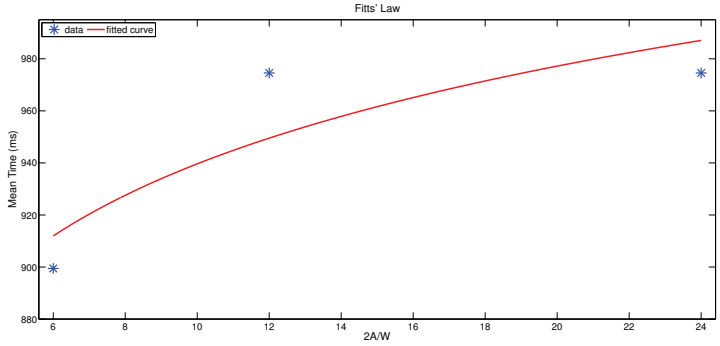
out varying the activation times. This strategy corresponds to a variation in the activation of clusters of cortical neurons located in the rostral part of the M1 cortex and, in our simulation, requires to vary 37 values;

- *Strategy C*: to modify the activation times of the $fmIA$, $fmREN$, $fmIB$, $fmPN_{BI}$, $fmPN_{BRA}$ and $fmPN_{TRI}$ modules without varying the inputs sent to them. This strategy corresponds to a variation in the activation of the cerebellum cells that regulate the timing of motor commands and, in our simulation, requires to vary 6 values.

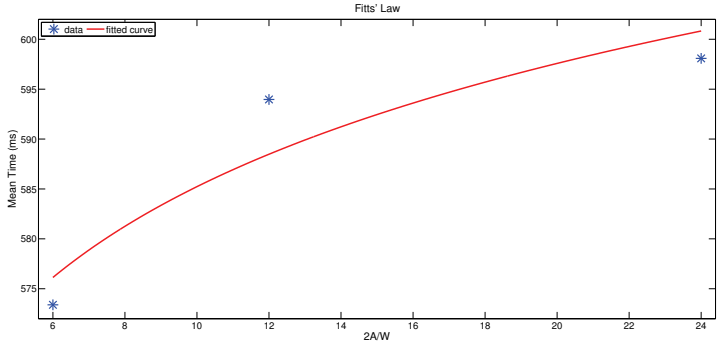
For each strategy, the Fitts' experiment has been reproduced using the three targets with different width. The set of parameters actuating the movement shown in Figure 4.1 and learned in the previous subsection was used as individual of the initial population of the DE algorithm.
The experimental data and the Fitts' law fitted to them are shown for each strategy in Figure 4.2 while the R^2 values for evaluating the goodness of each fit is reported in Table 4.1. The results show that *Strategy A* is the best one and that exhibits an almost perfect fit with Fitts' law.



(a) Strategy A



(b) Strategy B



(c) Strategy C

Figure 4.2 The experimental data obtained by adopting *Strategy A*, *Strategy B* and *Strategy C* are shown in blue while the prediction of Fitts' law is represented in red.

4.5 Exploring the Fitts' law by recruiting networks of heterogeneous interneurons

In this section we propose a different view of the spinal circuitry shown in Figure 3.1. Now, we suppose that the spinal circuitry is controlled as the 3 *networks of heterogeneous interneurons* described in Table 4.2. Differently from the previous experiment, in which the interneurons were divided on the basis of the class they belong to, here the interneurons are divided taking into account which muscle is influenced by their firing activity or which muscle is the source of their sensory inputs. Furthermore, γ_s and γ_d are coactivated with the interneurons of the modules they belong to. Overall, when a movement is performed by activating all the 3 networks it is needed to specify 46 parameters: 43 inputs and 3 activation times.
As in the previous scenario, the values of the parameters for moving the arm toward the desired position are learned, and then it is evaluated which set of motor commands has to be modified in order to obtain faster movements that satisfy the speed-accuracy tradeoff.

4.5.1 Learning the execution of accurate movements

As before, the arm has to be flexed from $\theta_{elbow}(t_{start}) = 0\ rad$ to $\theta_{elbow}(t_{end}) = 1.0472\ rad$ by reaching the final position as close as possible and by minimizing the metabolic energy expenditure. The system has to execute the movement by activating only the clusters of neurons within the rostral part of the primary motor cortex, so without the activation of the corticomotoneuron cells.
The DE algorithm has to find the set parameters that regulate the activity of the functional modules fm_{BI}, fm_{BRA}, fm_{TRI} by solving a two-objective optimization problem over 400 generations. Because we required that in this motor task the neurons in the

Table 4.2 Functional modules

Name: fm_{BI}	*Activation time*: t_{BI}	*Number of inputs*: 15
Belong to this functional modules: the PN and the IA interneurons receiving afferents from the Biceps, the α, the γ_s and γ_d motoneurons exciting the extrafusal and intrafusal fibers of the Biceps, the Renshaw cells excited by the α belonging to this functional module and, eventually, the IB interneurons that inhibit the Brachialis. This module receives descending inputs that regulate the firing of its interneurons and the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Biceps.		
Name: fm_{BRA}	*Activation time*: t_{BRA}	*Number of inputs*: 15
Belong to this functional modules: the PN and the IA interneurons receiving afferents from the Brachialis, the α, the γ_s and γ_d motoneurons exciting the extrafusal and intrafusal fibers of the Brachialis, the Renshaw cells excited by the α belonging to this functional module and, eventually, the IB interneurons that inhibit the Biceps. This module receives descending inputs that regulate the firing of its interneurons and the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Brachialis.		
Name: fm_{TRI}	*Activation time*: t_{TRI}	*Number of inputs*: 13
Belong to this functional modules: the PN and the IA interneurons receiving afferents from the Triceps, the α, the γ_s and γ_d motoneurons exciting the extrafusal and intrafusal fibers of the Triceps, the Renshaw cells excited by the α belonging to this functional module and, eventually, the IB interneurons that excite the Biceps and the Brachialis. This module receives descending inputs that regulate the firing of its interneurons and the gain of the Ia and Ib proprioceptive afferents coming from the sensory receptors of the Triceps.		

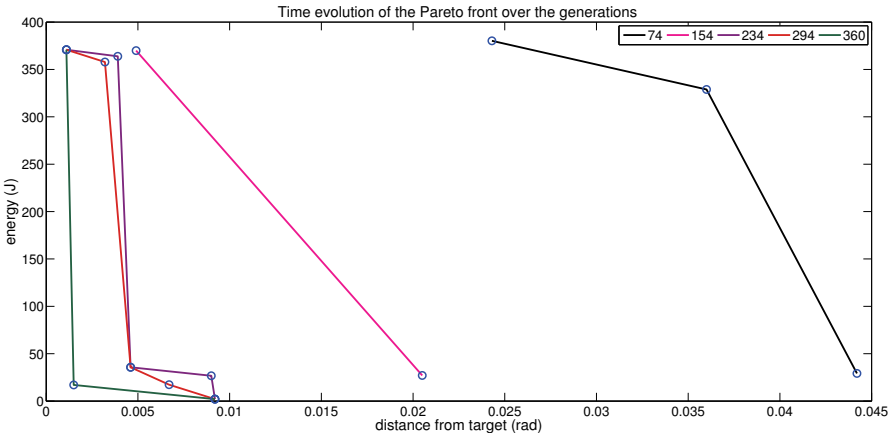
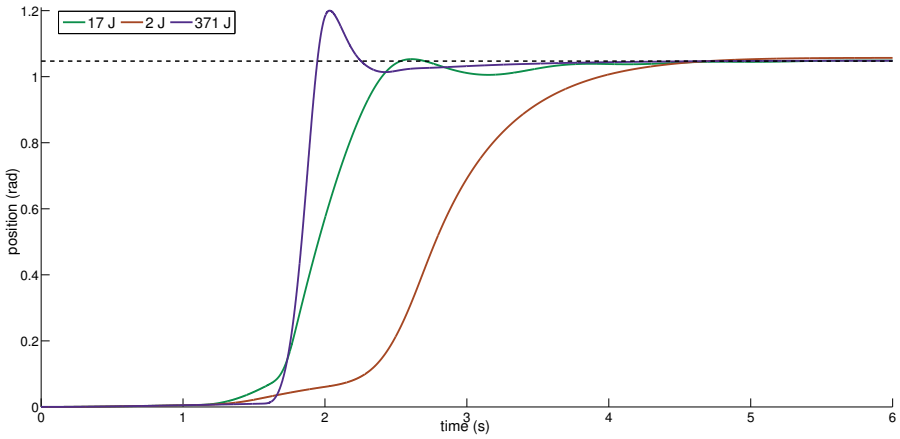
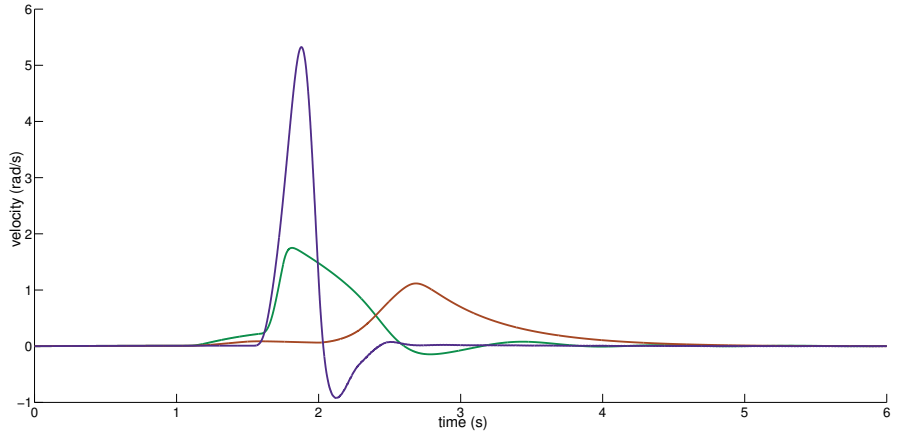


Figure 4.3 The most significant variation of the Pareto frontier over the generation. The circles represent the Pareto solutions.

caudal part of M1 were inactive, the DE has to search for the best values of 43 parameters (40 inputs and 3 activation times).
In Figure 4.3 it is shown how the Pareto frontier will move over the generations. The movements obtained by actuating the three solutions located on the Pareto frontier of the last generation are plotted in Figure 4.4, while in Table 4.3 are reported their properties in term of accuracy, duration and energy consumption.
It's worth to note that the solutions corresponding to the fastest and the slowest movements are found by the DE algorithm only after 236 generations, at the half of the evolution process.
Furthermore, independently of the recruiting strategy (i.e. the type of functional modules) faster movements involve bigger energy consumption.
The XzeroROBUSTE software [OP09a] reconstructed the speed profiles of both the fastest and slowest movements through the time superimposition of three lognormal functions whose parameters are reported in Table 4.4 and in Table 4.5, respectively. The speed profile of the fastest movement is fitted with a SNR equal to 33.2 dB while the speed profile of the slowest movement is fitted with a SNR equal to 27.6 dB, as shown in Figure 4.5.



(a) Position Profile



(b) Velocity Profile

Figure 4.4 Position and velocity profiles of the movements obtained by recruiting networks of heterogeneous interneurons and corresponding to the Pareto optimal solutions that minimize the distance from the target and the energy consumption. The dashed line represents the target position.

Table 4.3 Properties of the movements actuated by recruiting networks of heterogeneous interneurons and that minimize both the distance from the target and the energy consumption.

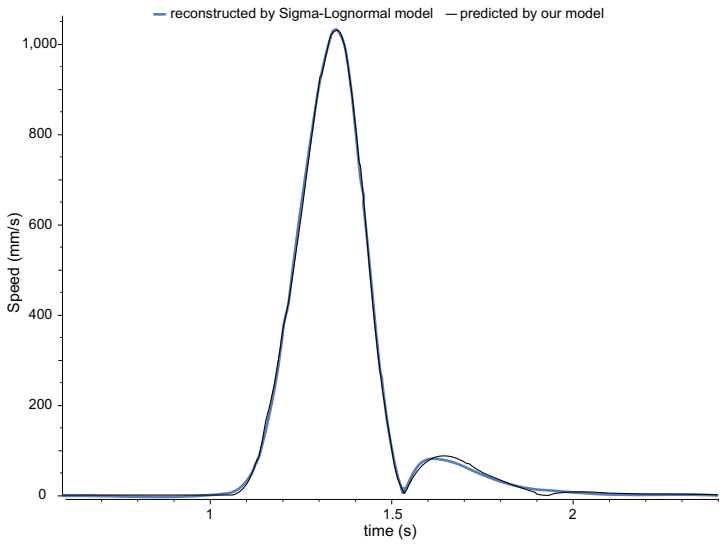
Solution	Distance from the target (rad)	Energy (J)	Duration (ms)
Violet Trace	$\mathbf{1.1 * 10^{-3}}$	**371**	**647**
Green Trace	$1.5 * 10^{-3}$	17	1390
Brown Trace	$9.2 * 10^{-3}$	2	2970

Table 4.4 Sigma Lognormal Parameters of the fastest movement in Figure 4.4

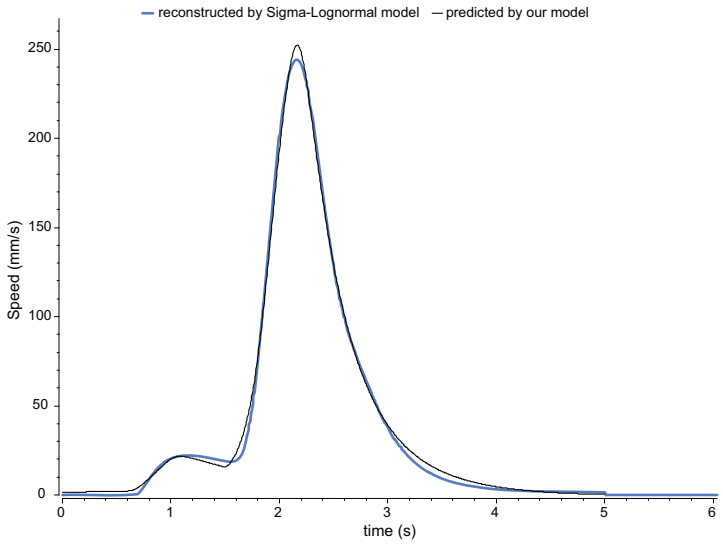
t_0	D	μ	σ	θ_s	θ_e
0.34	215.77	-0.0001	0.104	6.231	6.211
1.045	33.41	-1.101	0.169	6.183	6.07
1.325	46.04	-1.391	0.478	3.136	2.97

Table 4.5 Sigma Lognormal Parameters of the slowest movement in Figure 4.4

t_0	D	μ	σ	θ_s	θ_e
0.66	33.51	-0.010	0.855	6.24	6.170
1.29	188.06	-0.010	0.339	6.233	6.187
1.54	14.53	-0.020	0.173	3.051	3.065



(a) Speed profile of the fastest movement



(b) Speed profile of the slowest movement

Figure 4.5 Real and reconstructed speed profiles of (a) the fastest and (b) the slowest movements shown in Figure 4.4

4.5.2 Execution of faster movements

We have hypothesized four strategies that may be adopted by the brain for executing a faster flexion starting from a learned movement and by exploiting the functional modules described in Table 4.2:

- *Strategy 1*: to activate the α motoneurons belonging to the three modules. This strategy corresponds to the activation of clusters of cortical neurons located in the caudal part of the M1 cortex and, in our simulation, requires to compute 3 parameters;

- *Strategy 2*: to modify the activation times of the three subsets of motor commands with respect to the learned solution. This strategy corresponds to the activation of the cerebellum cells that regulate the timing of motor commands and, in our simulation, requires to vary 3 values;

- *Strategy 3*: to modify the motor commands sent to the three modules without varying their activation times. This strategy corresponds to the activation of clusters of cortical neurons located in the rostral part of the M1 cortex and, in our simulation, requires to vary 37 values;

- *Strategy 4*: to modify the activation times and the values of the motor commands sent to the three modules. This strategy corresponds to the activation of the cerebellum cells and of the cortical neurons in the rostral M1 and, in our simulation, requires to vary 43 parameters.

For each strategy, the Fitts' experiment has been reproduced using the three targets of different width. The fastest movement obtained in the previous subsection was the learned movement used as individual of the initial population of the DE algorithm. The experimental data and the prediction of Fitts' law are shown in Figure 4.6 and Figure 4.7 while the values of R^2 are in Table 4.6. The results show that *Strategy 2* exhibits an almost perfect

Table 4.6 Coefficients of the Fitts' law and measure of goodness of the fitting for the four strategies described in section 4.5.2 starting from the fastest movement in Figure 4.4

Strategy	Model coefficients		R^2
	a	b	
Strategy 1	505	31	0.94
Strategy 2	710	96	0.99
Strategy 3	1414	110	0.92
Strategy 4	615	135	0.88

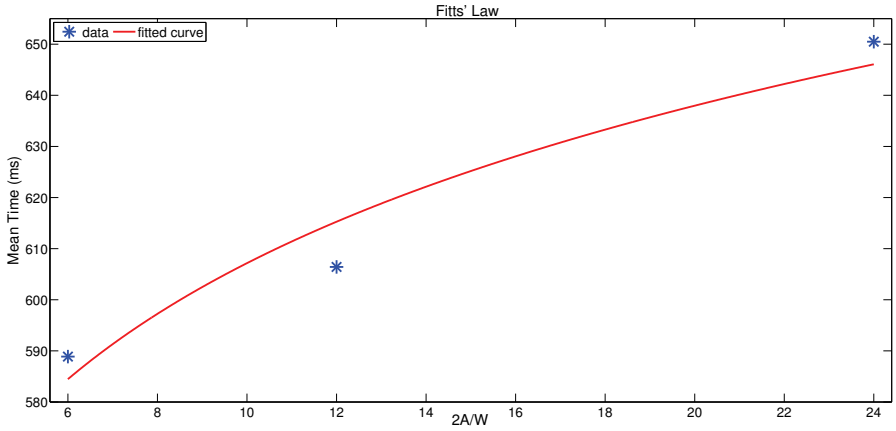
Table 4.7 Coefficients of the Fitts' law and measure of goodness of the fitting for the first two strategies described in section 4.5.2 starting from the slowest movement in Figure 4.4

Strategy	Model coefficients		R^2
	a	b	
Strategy 1	869	407	0.97
Strategy 2	1781	135	0.95

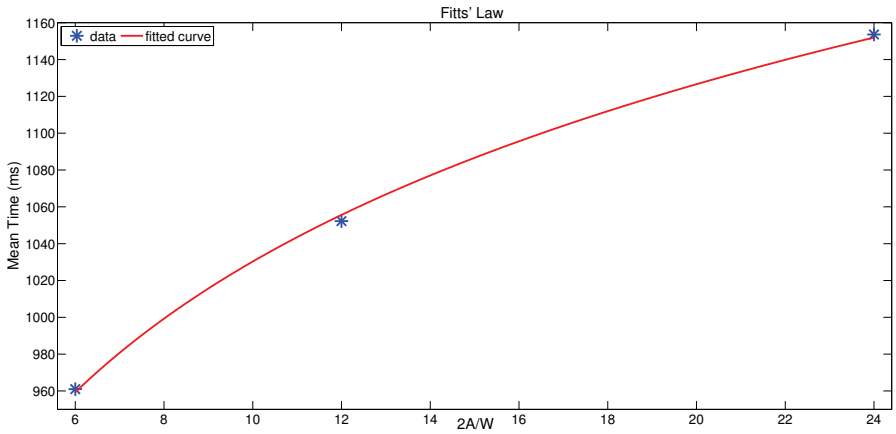
fit with Fitt's law prediction, and that *Strategy 4* is the one that performs worst. In Figure 4.8 the position profiles of the faster movements as the target size changes are shown for the two best strategies. It is worth to note that even if the Fitts' law is fitted slightly better by adopting *Strategy 2* rather than *Strategy 1*, movements obtained with the latter strategy are approximately twice faster.

An interesting aspect pointed out by this experiment is that the system learned to produce faster movement than the learned one with the required accuracy even when the learned movement presents an overshoot bigger than the required accuracy (i.e. its overshoot is bigger than $W/2$)

In order to verify if the goodness of the fitting has been influenced by the properties of the learned movement we have evaluated the fitting when the learned movement is the slowest flexion in Table 4.3. The values of the R^2 for *Strategy 1* and *Strategy 2* are reported in Table 4.7 while the experimental data and the Fitts' law fitted to them are shown in Figure 4.9. *Strategy 1* is confirmed to be the best one for producing faster movements with the required accuracy.

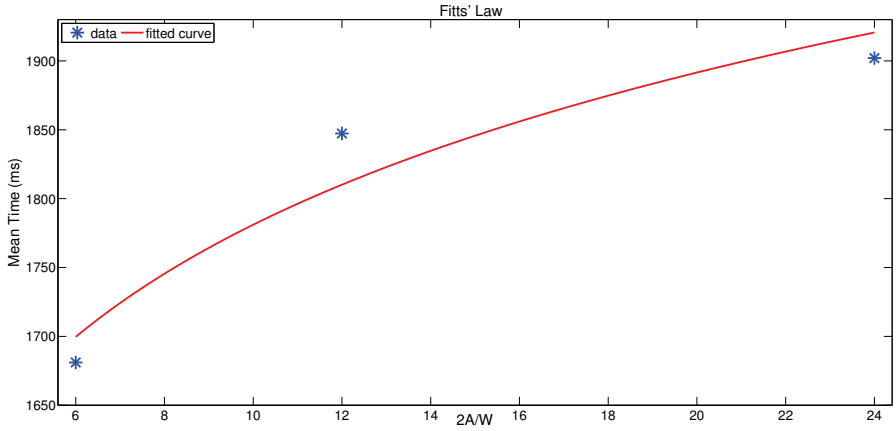


(a) *Strategy 1*

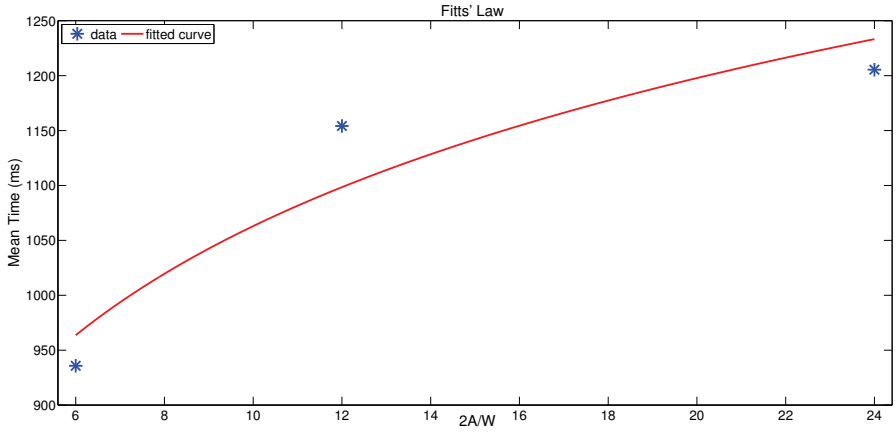


(b) *Strategy 2*

Figure 4.6 The experimental data obtained by adopting *Strategy 1* and *Strategy 2* are shown in blue while the prediction of Fitts' law is represented in red. The starting movement is the fastest one in Figure 4.4.

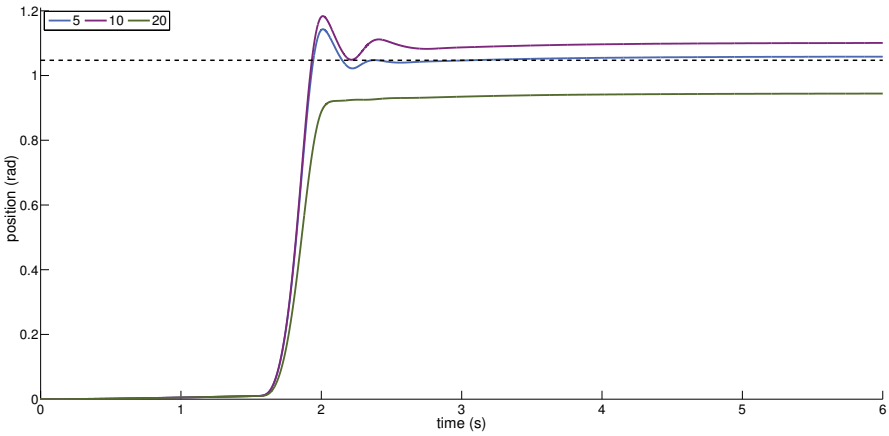


(a) *Strategy 3*

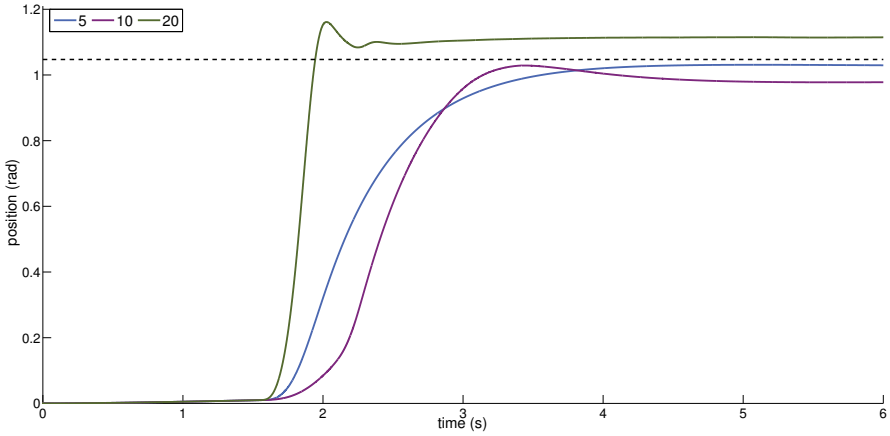


(b) *Strategy 4*

Figure 4.7 The experimental data obtained by adopting *Strategy 3* and *Strategy 4* are shown in blue while the prediction of Fitts' law is represented in red. The starting movement is the fastest one in Figure 4.4.

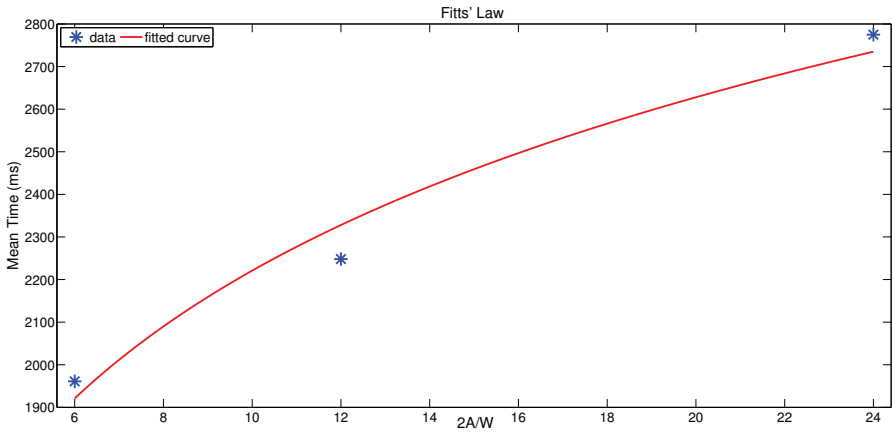


(a) *Strategy 1*

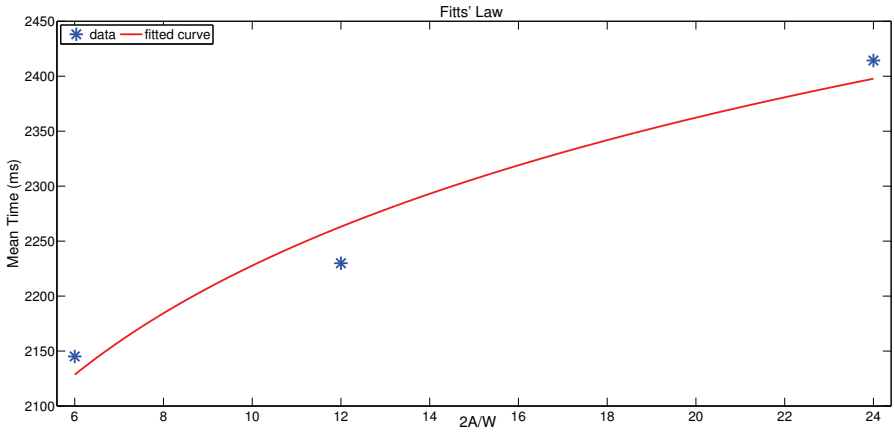


(b) *Strategy 2*

Figure 4.8 The position profiles of the faster movements that are executed adopting (a) the *Strategy 1* and (b) the *Strategy 2* as the target size changes.



(a) *Strategy 1*



(b) *Strategy 2*

Figure 4.9 The experimental data obtained by adopting *Strategy 1* and *Strategy 2* are shown in blue while the prediction of Fitts' law is represented in red. The starting movement is the slowest one in Figure 4.4.

4.6 Discussion

The results in subsections 4.4.1 and 4.5.1 show that, independently of the functional modules organization, the model learns by a trail-and-error process, driven by two goals: reaching the desired position and minimizing the metabolic energy consumption to perform the movement. Under those constraints, the system executes fast movements consuming more metabolic energy than in case of slow movements.
The experiments presented in subsections 4.4.2 and 4.5.2 provide a neuro-physiological foundation of the speed-accuracy tradeoff observed by Fitts. The results show that movements produced by *Strategy A* and *Strategy 1* are faster than those executed with the other strategies and they exhibit an almost perfect fit with Fitts' law. Both the strategies increase the speed of the movements by directly regulating the activity of the α motoneurons through the corticomotoneuronal pathway. This results are in accordance with those reported in [BWFN10], where the authors conclude that:

> *the results from brain-imaging and neurophysiological studies suggest that speed-accuracy tradeoff is implemented by changes in the baseline activity of integrator neurons.*

It's important to note that in our experiments the learned movements are executed by the activation of the clusters cells in the rostral part of M1, without the intervention of the caudal part. This aspect combined with the results of the fitting experiments suggests that the brain may use the clusters of neurons in the rostral M1 for encoding the direction of the movement and the clusters of CM cells in the caudal M1 for regulating the tradeoff between speed and accuracy.
In his paper, and in the light of information theory recently (at the time) introduced by Shannon [Sha01], Fitts' concluded that the speed-accuracy tradeoff was a consequence of the limited information processing of the human motor system. The results reported in Table 4.3 show that the system is able to produce

faster movements preserving the accuracy. This suggests that the limited information capacity does not follow from the structure of the system, but arises from the strategy adopted to produce faster movements, by modifying only the activations of the integrator neurons and starting from the configuration corresponding to the execution of a pre-learned movement. We conclude that the speed-accuracy tradeoff is a behavioral trait that emerges from both the structure of the motor system and the strategy adopted to perform *faster-than-usual* movements.

Conclusions

This thesis investigates how motor cortex commands the execution of reaching movements by exploiting the spinal cord circuitry. The beginning purpose of our research was to discover which parameters were encoded by the brain to control a movement. The analysis of the state of art, reported in *Chapter 1*, showed an agreement about the major role of the primary motor cortex in the control of voluntary movement and a longstanding controversy about what kind of parameters are encoded. The difficulty of understanding how movements are represented, despite the considerable amount of experiments evaluating the correlation between neuronal firing and movement kinematics and kinetic, led to speak about this problem as the *holy grail of the neuroscience*.

New findings [RS09] about the subdivision of M1 into two regions, each of which has different connection with the motoneurons within the spinal cord, encouraged us to investigate the interaction between motor cortex and the spinal cord in order to understand the "code" used for executing voluntary movements.

We have proposed that a movement is commanded by the activation of different clusters of neurons distributed in the rostral and caudal regions of primary motor cortex. Clusters of neurons in the rostral region have connections with spinal cord interneurons that translate cortical commands into motoneurons activations, instead clusters of neurons in the caudal part have monosynaptic connections with the alpha motoneurons. The activation of a cortical cluster corresponds to the recruitment of one of the functional modules in which spinal interneurons and motoneurons are organized. When a movement is planned, the cortical loop through the

basal ganglia and the cerebellum regulates the selection of clusters to be activated with the right timing.

To test these hypotheses we have developed the computational model of the spinal cord circuitry described in *Chapter 2*, where the synaptic connections between interneurons implement hard-wired synergies. In *Chapter 3* we have verified that the recruitment of spinal modules by clusters of cortical neurons allows to execute movements with different properties. Eventually, in *Chapter 4* we have verified that the cortical clusters of neurons in the rostral and caudal part of M1 may cooperate to determine the trade-off between speed and accuracy in reaching movements. In particular, results show that the rostral M1 may encode the direction of the movement, while the CM cells in the caudal M1 regulate the force production of the muscles involved in the execution of the motor task, thus defining the tradeoff between speed and accuracy.

The results obtained using our computational model confirm what has been hypothesized in literature [dGI+15]: modularity may be the organizational principle that the central nervous system exploits in motor control. In humans, the central nervous system can execute motor tasks by recruiting the motor primitives in the spinal cord or by learning new collections of synergies essential for executing novel skills typical of our society, as for example to play an instrument, by exploiting the clusters of neurons in the caudal M1 that directly regulates the contraction of muscles working around one or more joints.

The hypothesis that movements are executed by combining the activation of basic modules hosted in the spinal cord can explain how movements change from the neonatal to the adult stage. Infants are able to explore the environment since their birth exploiting these modules. The spontaneous motions, the early goal-directed movements and the primitive reflexes showed by infants could be temporal assemblies of the motor primitives hard-wired in his spinal cord [Kon05]. These movements are very imprecise but as the baby grows he becomes able to execute more complex motor behaviours thanks to learning. Motor experience during

early postnatal life is essential both for the corticospinal tract development [MCPM04] [Mar05] and for learning new pattern of activation of the spinal modules.
Furthermore, it is plausible to argue that during the developmental process proprioceptive feedback modifies spinal interneuronal circuitry to tune spinal circuitry to the limb biomechanics of the individual [BA15].

The hypothesis that hard-wired synergies are tailored to the biomechanics of the effector controlled by them and that the central nervous system recruits these motor primitives by regulating both the level and the time of activation confirms the needed of a double representation of movements in the brain in order to explain the phenomenon of the *motor equivalence*. As explained in [Sen12], movements are stored in the brain as both a sequence of target points that have to be reached and as a sequence of motor commands that generate the muscular contractions needed to reach the target points. The representation of movement as sequence of target points is independent of effector, while the representation through motor commands is effector dependent. Because hard-wired synergies are tuned to the effector to be controlled, the central nervous system needs to learn motor commands specific for each effector even if the sequence of target points that has to be reached is the same.

To summarize our position, we argue that the evolution has designed a biological system that is aimed to move in order to interact with the environment. This system has to use a set of modules to fulfill its aim but how these modules changes during the individual life, and which strategies can be adopted for using these modules depends upon the motor experience and the interaction with the environment. An interesting example is how the speech apparatus allows the production of different phonemes. Newborns are able to produce any sound because the evolution provides them with all the motor primitives needed for controlling the speech apparatus. As speech is learned, humans are no longer able to reproduce sounds that do not occur in their daily language because they have not developed the connections and the strategies to

recruit the motor primitives producing those sounds. An adult can reproduce sounds different from those learned during the early years of life by learning strategies for combining sounds for which motor primitives exist: an example is the native chinese speaker that need practice in combining sounds for producing the sound of 'r' [He14] [GW04].

The idea that some properties of the motor primitives are defined by the evolutionary process fits well with what we observed in our experiments about the energy consumption. In particular, the results presented in *Chapter 3* suggests that the layout of neurons in the spinal cord are shaped by the evolution to subserve the general principle of minimizing the metabolic energy consumption. It means that spinal circuitry is organized to limit the energy consumption per se and the observed difference in the energetic consumption between different movements is related to the way circuitry is controlled and to the requirements of the behavioural task to execute. For example, we have observed in the experiments that the energy consumption increases significantly if the goal of the motor task is to execute a fast reaching movement.

Physiological studies show that the evolutionary process defined important species differences in the organization of corticospinal transmission to motoneurons. For example, the direct corticomotoneuronal pathway becomes prominent for the control of the upper limb in the primates needing for manual dexterity while it lacks in lower species as in the cat [AI12]. This observation has lead to hypothesize that transmission of corticospinal excitation through C3-C4 PNs is relatively unimportant in humans. Nevertheless, it is difficult to find conclusive evidence for or against the use of C3-C4 system during motor task due to indirect nature of the experiments in human subjects [LKM$^+$04]. The experiments performed with our computational model suggest that the activation of PN interneurons can be exploited by human subjects when it is required to perform slow movements or to limit the energy consumption. Furthermore, the activation of PN interneurons together with the activation of other interneurons allows to execute fast movements and subcortical nuclei can

switch the direction of an ongoing movement just by regulating the activity of the PN interneurons.

Eventually, we have shown in this thesis that it is plausible to support the hypothesis that movements are executed thanks to the cooperation of two different areas of the primary motor cortex. One area recruits the hard-wired motor primitives hosted in the spinal cord as spatiotemporal synergies, while the other one has direct access to the alpha motoneuron and may build new synergies for the execution of very demanding movements. The existence of these two areas regulating directly and indirectly the muscle activity can explain the controversy about what kind of parameter is encoded by the brain. The simulation performed with our computational model have shown that the activation of an area cannot exclude the activation of the other one but, on the contrary, both the activations are needed to have a simulated behaviour that fits the real behaviour, as in the case of the trade-off between speed and accuracy.

All these findings, if will be verified *in vivo*, may have important implications for the development of neural prostheses. In fact, the possibility that complex motor behaviors may be executed by combining the activation of motor primitives may lead to the design of brain-machine interface based upon a decoder that takes into account this modular strategy for commanding a movement. The research performed in this thesis is a contribution toward the understanding of how voluntary movements are executed. Still, there is a question that we did not consider here: how the information provided by proprioceptive and sensory input are represented and used to modify the motor behaviour during learning. We plan to address this crucial issue in our future research.

Appendix A

Neuromusculoskeletal model

A.1 Introduction

To control a movement, the central nervous system generates motor commands that led muscles to contract. The observed movement is the result of the interaction of the forces generated by the muscles with inertia and external forces that may be acting on the body. Moreover, the central nervous system is able to control a movement because it receives information about forces and movements of the musculoskeletal system measured by various proprioceptive sensors. Therefore, in order to validate a model of the motor control system it isn't possible to ignore the properties of the musculoskeletal system that it must control.
This appendix describes the models of the muscles, of the skeleton and of the neurons used for building up a musculoskeletal model useful to validate the hypothesis formulated in this thesis.

A.2 Muscle model

Each muscle has been modeled with Virtual Muscle [SRLL08] [CBL00], a model that represents the anatomical structures and

Table A.1 Muscles architectural parameters

	Biceps	Brachialis	Triceps Lateral
Optimal Fascicle Length (cm)	21	10	11.38
Optimal Tendon Length (cm)	16	8	9.8
Mass (g)	200	282	237
Fiber Type	50% Slow, 50% Fast	50% Slow, 50% Fast	50% Slow, 50% Fast

the physiological processes that are typical of mammalian skeletal muscles. It combines the advantages of phenomenological (Hill-type) and mechanistic (Huxley-type) models. In particular, Virtual Muscle groups a set of phenomenological models, each of which describes a major physiological process underlying muscle contraction. The muscle model requires a set of morphometric and architectural parameters including muscle mass, optimal fascicle length, maximum musculotendon length, optimal tendon length and the fraction of fiber type distribution; the values for this parameters are reported in Table A.1. Furthermore, the model requires other parameters describing the properties of individual fiber type; the values for these parameters were estimated for human fiber types in [CBL00]. By selecting appropriate parameters, the model can be used to represent any specific normal or pathological muscle.

The model estimates force and rate of metabolic energy consumption as a function of time in response to neural excitation, muscle length and velocity [TRL12].

Another convenient features of Virtual Muscle is that it is equipped with realistic models of spindles [MBLL06] and Golgi tendon organs [ML06]. In particular, the spindle model consists of three nonlinear intrafusal fiber models, each of which responds to the fascicle length and to the drive from the gamma static and gamma dynamic motoneurons.

A.3 Neuron Model

The activity of the spinal cord model depends on the connectivity of its circuitry and on the biophysical properties of the neurons belonging to it. The way neurons are modeled in this thesis was taken from [TGL14], where the authors chose to capture only the major computational properties while minimizing the number of arbitrary parameters and computational load. We chose to adopt the same model in order to compare our results with the results described in literature.
Neurons of the spinal cord show a transduction property simpler than cortical neurons [TGL14], thus the axonal output of a neuron is simply computed as by summing the firing rates of all input axons rather than integrating postsynaptic potentials generated by individual spikes. In other words, actual neurons communicate via action potential spiking, but we model this communication with the **rate code approximation**, where the neuron continuously outputs a single value, between 0 and 1, that reflects the overall rate of spiking that the neuron should be exhibiting given the level of inputs it is receiving. As explained in [OMF+12], by a biological point of view the rate code represents the output of a small population of neurons that are generally receiving the same inputs, and giving similar output response. So, we are assuming that information is conveyed by the frequency of the firing and not by the precise timings of the spikes.
Based on this approximation, in order to represent the frequency of the spikes along the axon, we model the ***activation function*** of each neuron with a sigmoid function:

$$y = \frac{1}{1 + \exp(-a(\sum_i p_i x_i - b))} \tag{A.1}$$

where x_i is the i-th synaptic input, p_i is the related weight that could be positive or negative depending on whether the input is excitatory or inhibitory, a is the gain and b is the bias. It is also assumed that the weight p_i of a synaptic connection formed by the axon of a transmitter neuron n_t on the soma of a receiver neuron n_r depends on:

- the type of connection (inhibitory or excitatory);
- the total number of excitatory synaptic inputs syn_{exc} and the total number of inhibitory synaptic inputs syn_{inh} on the soma of the n_r cell;
- the maximal allowable hyperpolarization and overdrive of the neuron;
- what kind of neuron is n_t, i.e. it is an interneuron, an alfa motoneuron, a cortical neuron or a sensor neuron.

Thus,

$$p_i = \begin{cases} 1, & \text{if the source is the CST} \\ \omega, & \text{for sensory input and local collaterals} \end{cases} \tag{A.2}$$

where

$$\omega = \begin{cases} -\dfrac{HYP}{syn_{inh}}, & \text{for an inhibitory connection} \\ \dfrac{1+OD}{syn_{exc}}, & \text{for an excitatory connection} \end{cases} \tag{A.3}$$

where HYP and OD are the maximal hyperpolarization and overdrive limits and are both set to 2, as in [TGL14], in order to produce the most physiological results.
When the source of a synaptic input x_i^* is a sensory afferent its value is modulated by a presynaptic input PI_i as shown in equation A.4:

$$x_i = \frac{1}{1+\exp(-a(x_i^* + PI_i) + b)} \tag{A.4}$$

The value of each PI_i varies between -1 and 1 and is controlled directly or indirectly by cortical areas.
In A.1 and A.4 a and b are set to 11 and -0.5 respectively as suggested in [TGL14].

A.3.1 Reflex Latency

The reflex arc consists of an afferent neuron that senses an external stimulus, a central processing unit (i.e. one or more neurons that process the stimulus) and an efferent neuron that induces a muscle contraction. Each reflex involves a time delay between the stimulus and the reaction. This time delay is called **reflex latency** that consists of three components [Lat08]:

- *time of afferent conduction* T_a, which depends on the speed of the action potential propagation along the involved neural fibers and on the length of the fibers;
- *central delay* T_c, which depends mostly on the number of synapses involved in processing the afferent volley and in generating an efferent command: increasing the number of synapses leads to a proportional increase in the central delay;
- *time of efferent conduction* T_e, which is the synaptic delay at the motor end plate;

These three time components are subject specific and vary for each muscle. We set $T_a = 10\ ms$, $T_e = 10\ ms$ and $T_c = 0.5\ ms$ in order to obtain a stretch reflex latency equal to 20.5 ms and a golgi tendon reflex latency equal to 21 ms, which are plausible values for both the reflex latencies [HR] [Bro10] [PDB12].

A.4 Skeletal model

The musculoskeletal model used in this study is a one degree-of-freedom arm whose motion is restricted to the extension/flexion of the elbow. In fact, the shoulder and the wrist joints are grounded while the elbow joint is modeled as a hinge-like joint.
The skeleton is made up of the upper arm, to which belongs the *humerus*, and the forearm, to which belongs the *ulna*, the *radius* and the *hand*. The physical and the inertial parameters used for the bones are reported in Table A.2 and Table A.3.

Table A.2 Bones physical parameters

	Mass	Length
Upper Arm	1.86 Kg	29 cm
Forearm and hand	1.53 Kg	40 cm

Table A.3 Inertial parameters

	Mass center (cm)			Inertia ($Kg * cm^2$)	
	x	y	z	I_t	I_l
Upper Arm	0	18.04	0	148.1	45.51
Forearm and hand	0	18.14	0	192.81	15.71

The position of the shoulder joint (humerus reference system) respect to the ground (absolute reference system), and the position of the elbow joint (ulna reference system) respect to the humerus reference system are reported in Table A.4. The three reference systems are shown in Figure A.1.
In our model the forearm is extended and flexed by three muscles: *Biceps Short*, *Brachialis* and *Triceps Lateral*. The muscle origin and insertion points and the musculotendon paths reported in Table A.5 have been chosen according to anatomical constraints at joints and they have been adapted from [HMD05] [SLLG08].
A cylindrical wrapping object is used to model the bony surfaces over which the Brachialis muscle wraps and to ensure the right calculation and application of the muscle forces produced by the muscle on the skeletal system.
The arm model has been developed in the MSMS simulator [DL11] and it is depicted in Figure A.1.

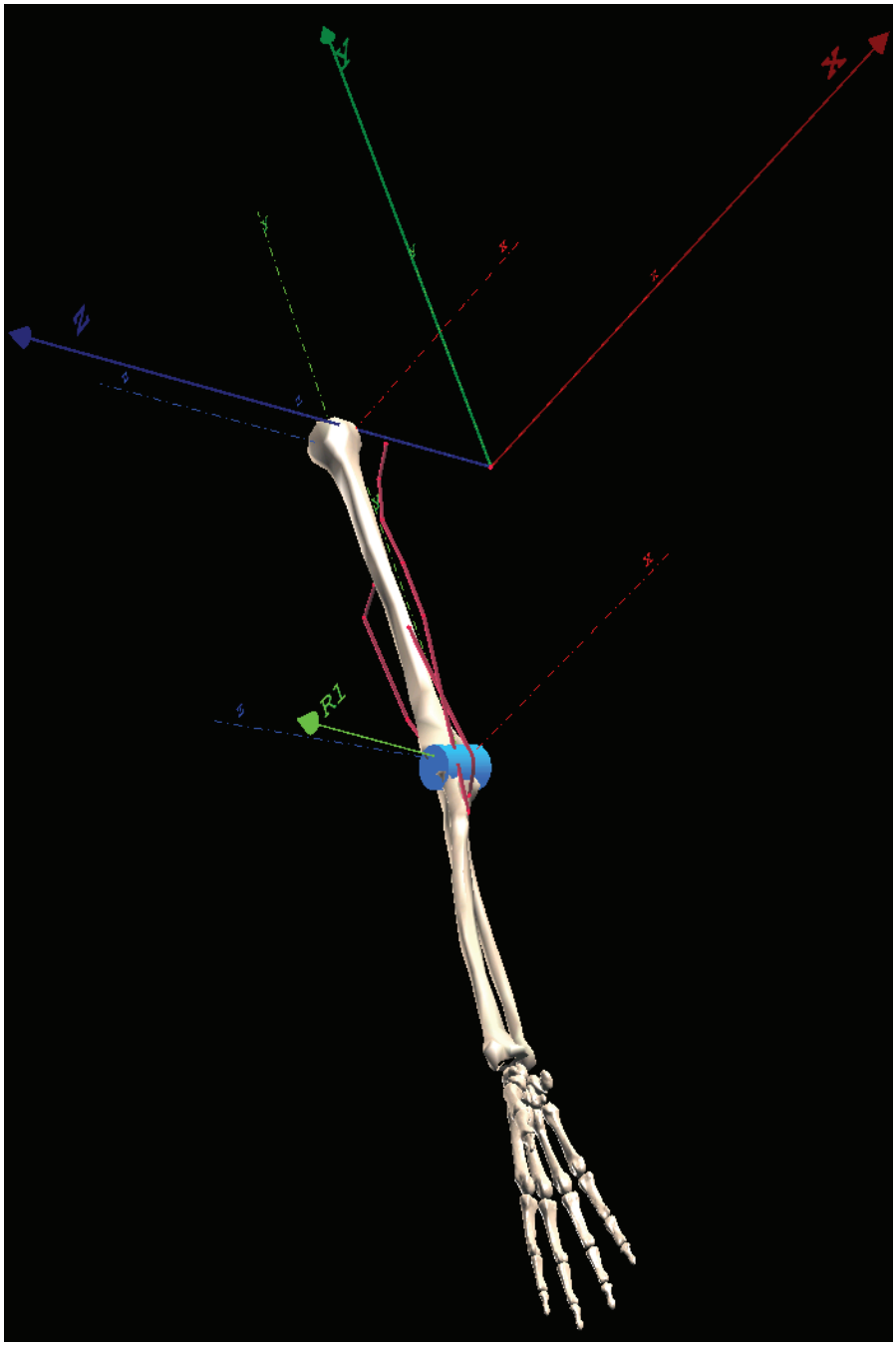


Figure A.1 Musculoskeletal model in MSMS. The ground, humerus and ulna coordinate systems are reported in figure. The elbow rotation axis is highlighted.

Table A.4 Joint Center Offset

	Proximal segment	Joint Type	Center offset (cm)		
			x	y	z
Shoulder Joint (Humerus Reference System)	ground	Weld	-1.75	-0.7	17
Elbow Joint (Ulna Reference System)	Humerus	Pin/Revolute	0.61	-29.04	-1.23

Table A.5 Muscles path

Muscle	Coordinates			Reference Segment
	x	y	z	
Biceps	0.005	-0.012	0.135	ground
	-0.007	-0.04	0.145	ground
	-0.011	-0.076	-0.011	Humerus
	0.017	-0.121	-0.011	Humerus
	0.023	-0.175	-0.006	Humerus
	0.008	-0.048	0.022	Ulna
Triceps	-0.00599	-0.12646	0.00428	Humerus
	-0.02344	-0.14528	0.00928	Humerus
	-0.03184	-0.22637	-0.01217	Humerus
	-0.01743	-0.26757	-0.01208	Humerus
	-0.0219	0.01046	-0.00078	Ulna
Brachialis	0.0068	-0.1739	-0.0036	Humerus
	0.0028	-0.2919	-0.0069	Humerus
	-0.0032	-0.0239	0.0009	Ulna

Appendix B

The Kinematic Theory of rapid human movements

B.1 Introduction

Different models have been proposed to explain how the central nervous system generates and controls human movements. Among them, the Kinematic Theory of rapid human movements [Pla95], from which the Sigma-Lognormal model [PD06] were developed, provides the best performance in reconstructing human movement [PAYL93].
In order to verify that the movements generated by our model were human-like we have compared the velocity profile of these movements with the velocity profile foreseen by the Kinematic Theory.

B.2 Sigma-Lognormal Model

By a mathematical point of view, the Sigma-Lognormal model considers the velocity of the end-effector $\vec{v}(t)$ as a vectorial summation (B.1) of N lognormal primitives (B.2)

$$\vec{v}(t) = \sum_{i=1}^{N} \vec{v_i}(t) = \sum_{i=1}^{N} \vec{D_i}(t)\Lambda_i(t, t_{0i}, \mu_i, \sigma_i^2); N \geq 2 \qquad \text{(B.1)}$$

Table B.1 The Sigma Lognormal parameters

Parameter	Unit	Description
D	meter	Amplitude of the command given for the generation of a neuromuscular component
μ	ln(s)	Time delay of a neuromuscular impulse response on a logarithmic time scale.
σ	ln(s)	Response time of a neuromuscular impulse response on a logarithmic time scale.
t_0	second	Time of command emission.
θ_s	radian	Starting angle of the trajectory.
θ_e	radian	Ending angle of the trajectory.

$$\Lambda_i(t, t_{0i}, \mu_i, \sigma_i^2) = \frac{1}{\sigma_i\sqrt{2\pi}(t - t_{0i})} exp(\frac{-[\ln(t - t_{0i}) - \mu_i]^2}{2\sigma_i^2}) \quad \text{(B.2)}$$

Each of these primitives is assumed to occur around a pivot, and the evolution of the angular position of the trajectory (B.3) is calculated using an error function erf:

$$\theta_i(t) = \theta_{si} + \frac{(\theta_{ei} - \theta_{si})}{2}[1 + erf(\frac{[\ln(t - t_{0i}) - \mu_i]}{\sigma_i\sqrt{2}})] \quad \text{(B.3)}$$

Each primitive is characterized by 6 parameters that are summarized in Table B.1. In particular, μ and σ are two parameters that characterize the neuromuscular systems, while D, t_0, θ_s and θ_e are command parameters.

B.3 Sigma-Lognormal Parameter Extraction

Given the velocity signals recorded during an experimentation (v_{xe}, v_{ye}) some algorithms [POG+14] have been defined in order to extract the lognormal parameters that most adequately fit the experimental data. Sigma-Lognormal parameters are considered to be well estimated and fitted for statistical analysis if the SNR, defined in (B.4), is over 20 dB [POG+14]:

$$SNR = 10\log(\frac{\int v_{xe}^2 + v_{ye}^2 \mathrm{d}t}{\int (v_{xe} - v_{xm})^2 + (v_{ye} - v_{ym})^2 \mathrm{d}t}) \quad \text{(B.4)}$$

In equation (B.4) (v_{xm}, v_{ym}) are the velocity signals of the sigma-lognormal reconstruction. We have used the ScriptStudio Software [OP09b] for the automatic extraction of Sigma-Lognormal parameters from the velocity signals recorded during the simulation of our model.

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