

Neuroengineering 2020/21

COMPUTATIONAL NEUROSCIENCE 1 - Motor control, high level models and neural basis of motor control

1

Neuroengineering 2020/21

COMPUTATIONAL NEUROSCIENCE 1 –
Part 1- Introduction to Motor Control and Learning

2



“General brain objective is to generate the movement”



Why movement is a complex task?



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Why movement is a complex task?

- DELAYS:

fast movements (300ms)
visuomotor feedback (200ms)

- NOISE (intrinsic neural noise)
Noise on the sensory data
(resolution limit)



Noise on the motor command
(imit)

The SD of noise is about 10% and
25% of the mean activity of a
motor neuron [Harris and Wolpert,
Nature 1998]

PREDICTION and a PLANNING are NECESSARY -> feedforward controller

Why movement is a complex task?

- NOT STATIONARY

Long term scale: growth



Short term scale: different objects

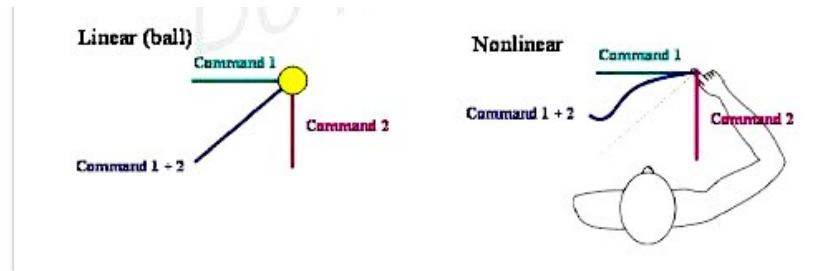


LEARNING IS NECESSARY

Why movement is a complex task?

- NON LINEARITY

Linearity=>effects overlapping
But... Sum of two sequences of motor commands
 \neq sum of the two movements!



Why movement is a complex task?

-MULTIDIMENSIONAL

-Million of inputs

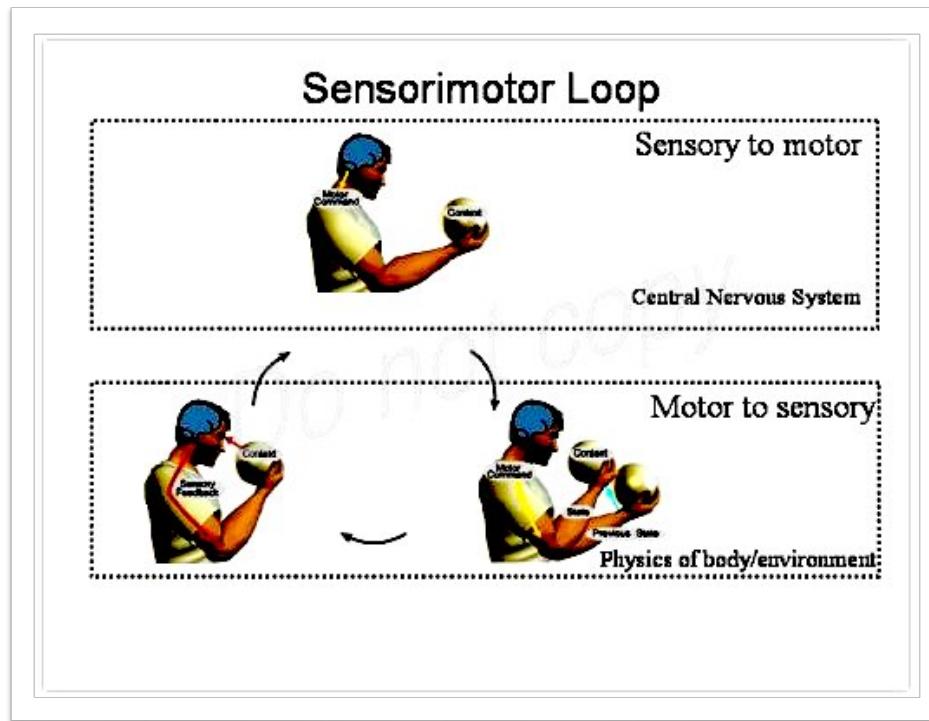


- Million of outputs



SYNERGIES AND MOTOR PROGRAMS ARE NECESSARY

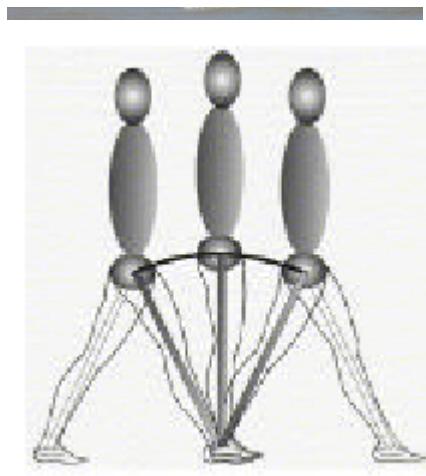
Sensorimotor integration



Motor learning

To adequate the behavior of the action according to the interaction with the environment

OBJECTIVE: improve the performance



Motor learning

COMPROMISE

Innate capacities

- hard-wired

- robust

- fast

Learned capacities

- adaptable

- slow

- flexible



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Motor learning

Simple species don't have any motor learning.



The necessity of motor learning appear in the species in which

- The environment,
 - The anatomic characteristics
 - The objectives
- can change

FLEXIBILITY of the control system



Motor learning

Does the man start from a tabula rasa?

There exist innate motor behaviors

Starting point for the future motor learning



Note: motor learning can require a decrease in the rigid synergies
(for instance neonatal reflexes)

Motor learning

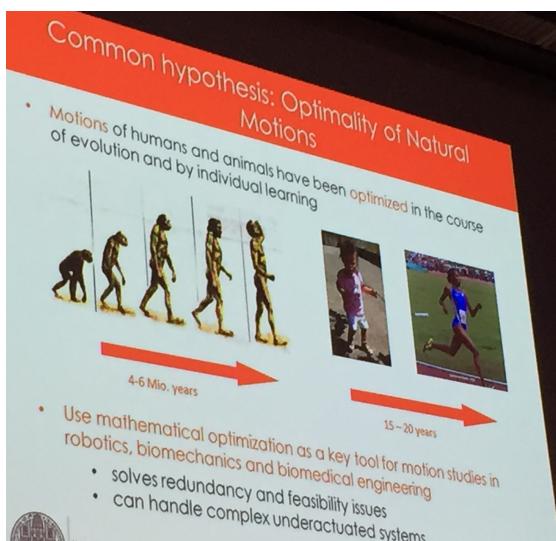
Anatomic structure

Co-adaptation of:

Neural machine



Human motor learning



The man is the unique species living everywhere all over the Earth

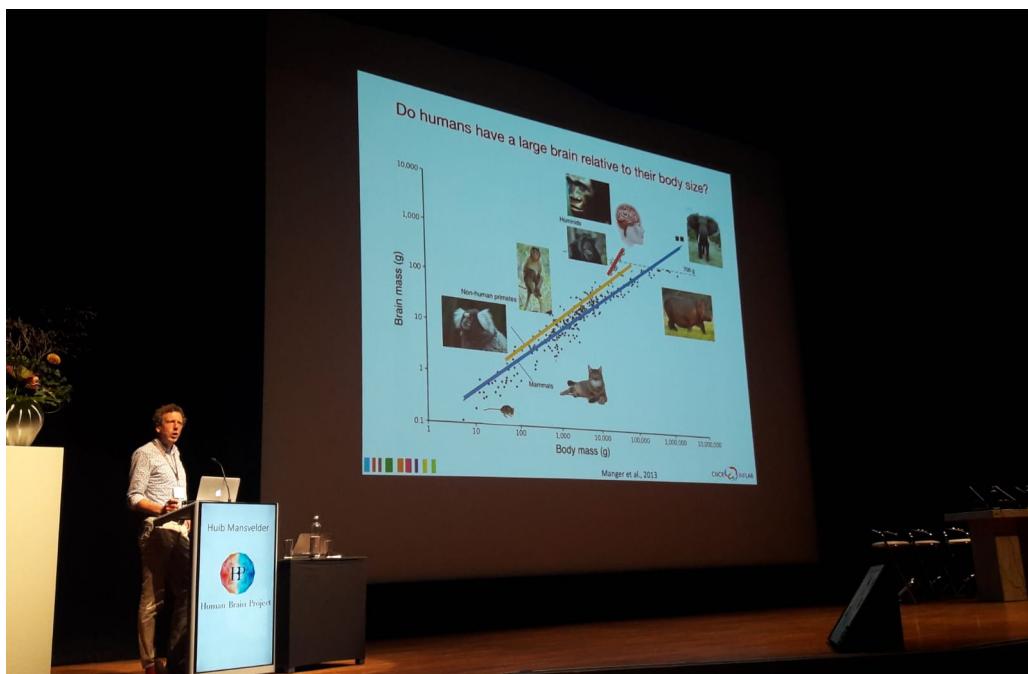
Human characteristics:

- Not specialized (it is able to adapt to changes and not to things)
- Polyvalent

Removability + multifunctionality+ cosmopolitism= exodarwinism

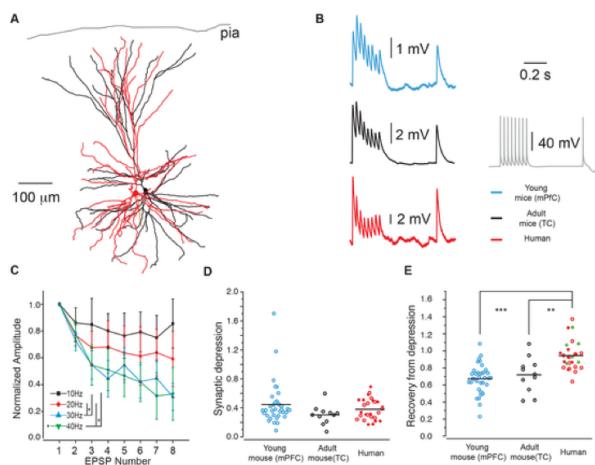
The time scale changes in the evolution

Brain and species - HBP Summit Oct 2018



Prof. Mansvelder Univ. Amsterdam

Figure 1. Synapses in the adult human neocortex rapidly recover from depression.

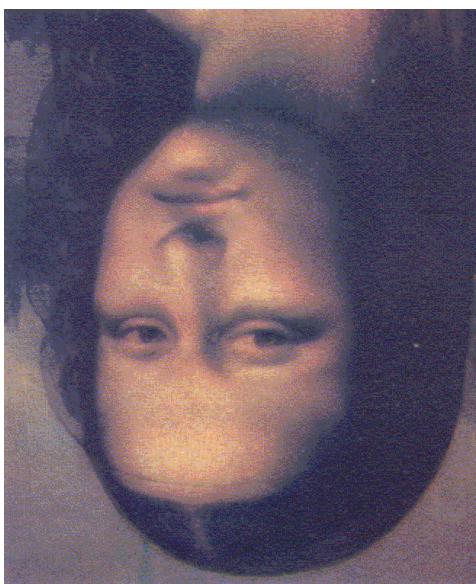


adult human neurons
show a three to four
times faster recovery
from depression.

Testa-Silva G, Verhoog MB, Linaro D, de Kock CPJ, Baayen JC, et al. (2014) High Bandwidth Synaptic Communication and Frequency Tracking in Human Neocortex. PLOS Biology 12(11): e1002007. https://doi.org/10.1371/journal.pbio.1002007
<https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002007>



Top down in perception



The learning and experience become guides to the acquisition of sensorial data and they both affect perception.

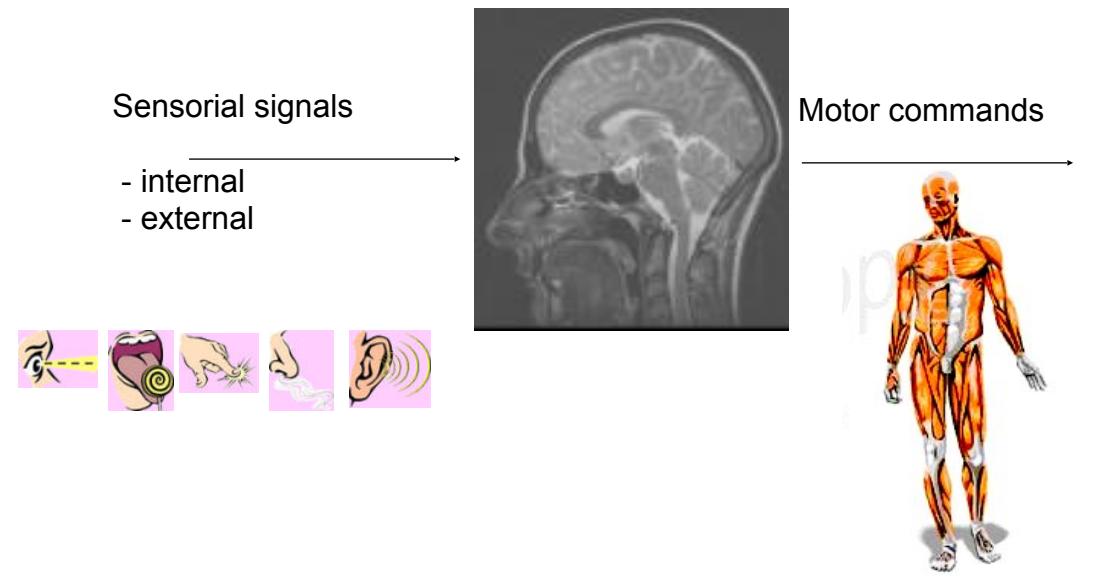
Top down and bottom-up in perception



Top down and bottom-up in perception



Sensory-motor integration



Sensori-motor integration



Kinematic Transformation: conversion between the system coordinates



Dynamic Transformation: it translates the coordinates in motor command, force to apply in order to obtain the desired movement

Kinematics + dynamic transformations

Movements happen through a transformation cascade

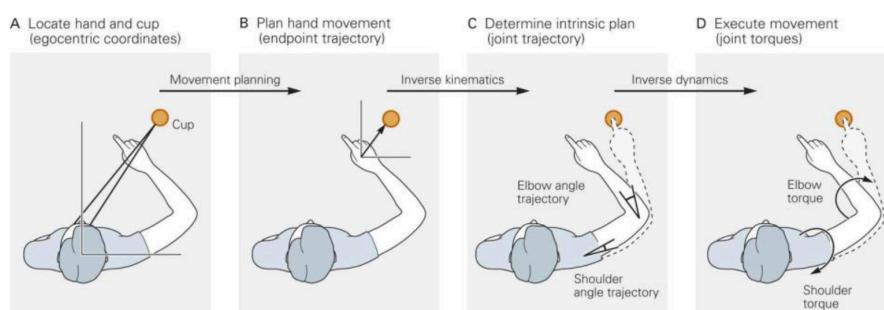


Figure 1.2: Sensorimotor transformations in a reaching movement: (A) **Spatial orientation.** To reach for an object, the object and hand are first located visually in a coordinate system relative to the head (egocentric coordinates). (B) **Movement planning.** The direction and the distance that hand must move to reach the object (the endpoint trajectory) are determined based on visual and proprioceptive information about the current locations of the arm and object. (C) **Inverse kinematic transformation.** The joint trajectories that will achieve the hand path are determined. The transformation from a desired hand movement to the joint trajectory depends on the kinematic properties of the arm, such as the lengths of the arm's segments. (D) **Inverse dynamic transformation.** The joint torques or muscle activities that are necessary to achieve the desired joint trajectories are determined. The joint torques required to achieve a desired change in joint angles depend on the dynamic properties of the arm such as the mass of the segments. (From [1])

Reflexes vs voluntary movements

- Reflexes= simple transformation, hard wired, automatic.

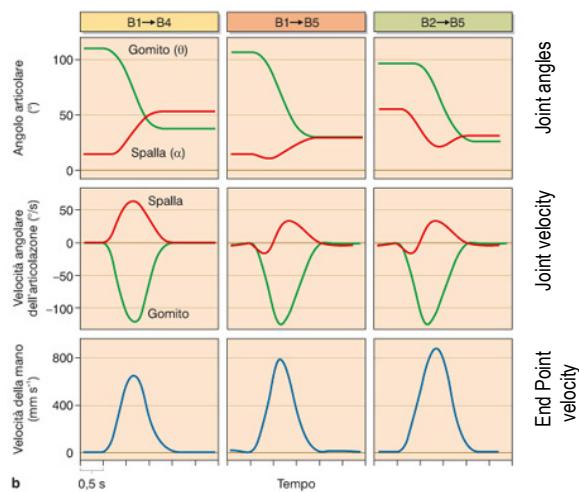
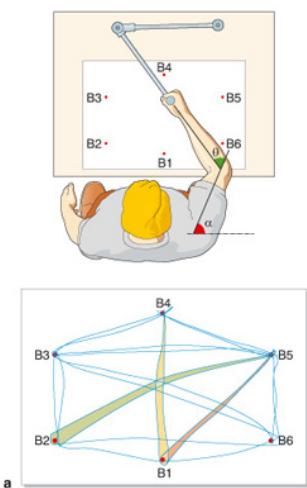
- Input causes the direct output
- Tendon jerk reflex

- Voluntary movement:

- Goal directed
- Independence of the effector
- Response time depends on the amount of information to process
- Execution speed is inversely correlated to the accuracy
- Learned by experience

We have to circumscribe our investigation: we will primarily cover voluntary motor control.

Voluntary movements



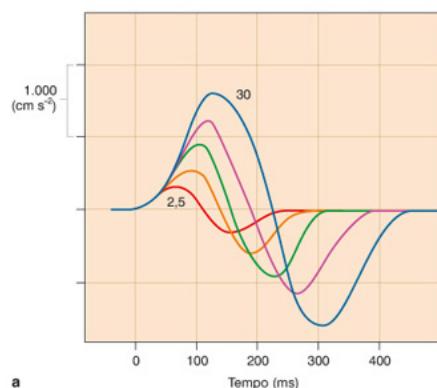
Panels a) The subject is required to make reaching tasks to multiple targets on the horizontal plane. Lower plot: The trajectories of the End Point are quite rectilinear.

Panels b) Different shoulder rotation (red traces) are used to get to the different targets, while very similar elbow joint traces (green) are shown (first raw). Also the joint velocity (second row) are modulated to achieve a very similar end-point velocity (third row).

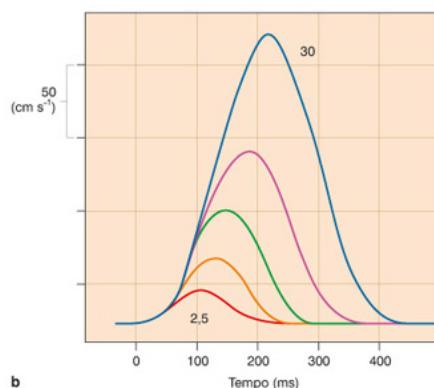
Voluntary movements

The motor plan is the sequence of tasks to accomplish the target, including the amplitude , the kinematics and the dynamics of the movement.

Velocity and acceleration change with the distance of the target.



a



b

OOBA © 2006 edi.ermes milano

a) Hand acceleration over time

b) Hand velocity over time

(Colours: Target distance from 2,5 to 30 cm)

Laws of voluntary movements

I law:

Voluntary movements show invariant features

- Motor Equivalence (Hebb, 1950)
- Independence from the effector
- Writing: Velocity varies as a continuous function of the curvature raised to the 2/3 power

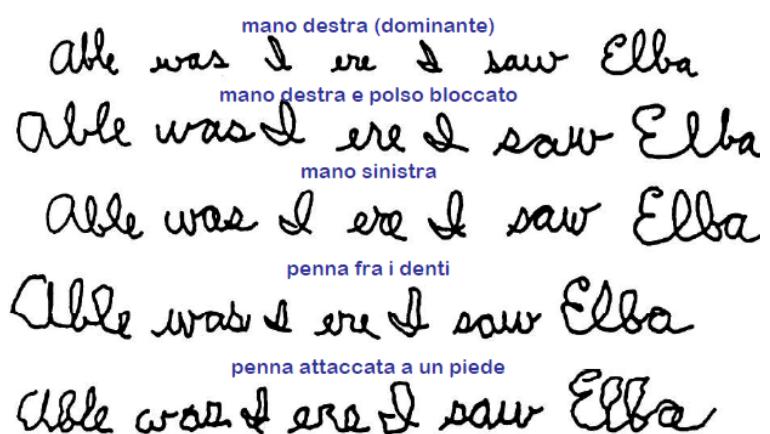
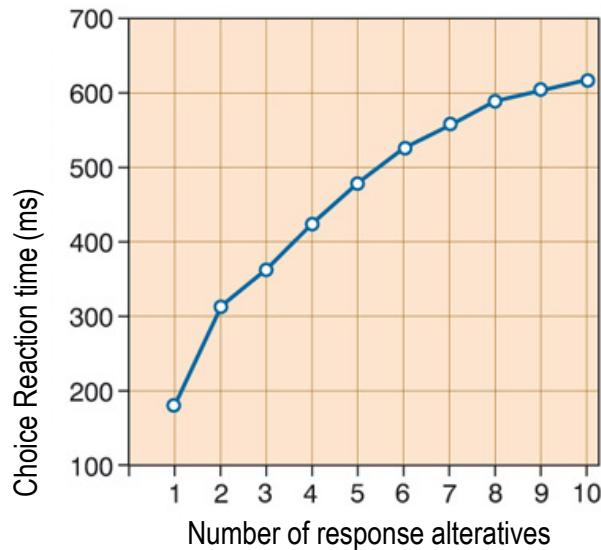


Figure: It is possible to write using different parts of the body. The examples shown in figure are written with the right hand (A), with the right hand but with the wrist fixed (B), with the left hand (C), with the pen between the teeth (D), and with the pen fixed to the foot (E). The capacity to perform the same motor behavior with different muscular groups is called motor equivalence

Laws of voluntary movements

II law: reaction time increases with the information to be processed

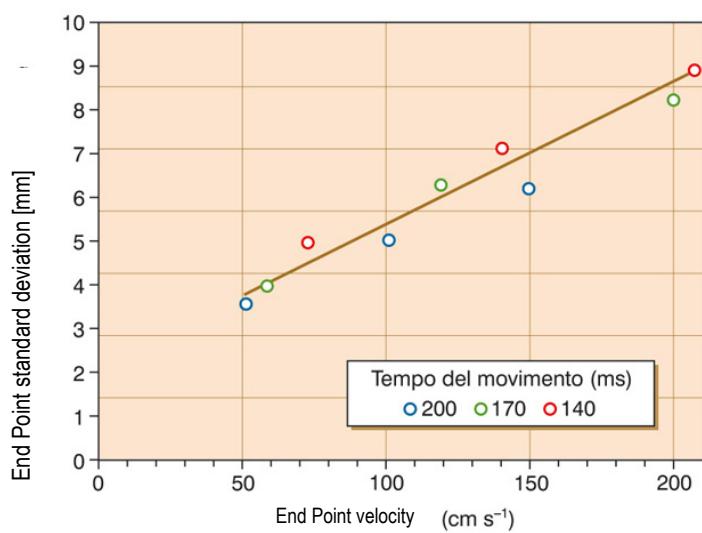
Reaction time increases nonlinearly with the number of response alternatives available to the subject.



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Laws of voluntary movements

III Law: Speed-accuracy tradeoff – Fitt's law

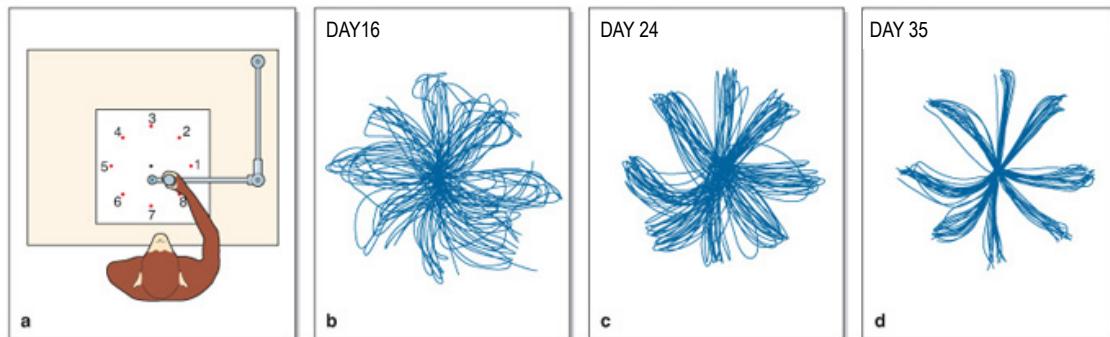


Short time -> no feedback corrections

This tradeoff is linked to signal-dependent noise: higher speed → more recruited motor units(EMGs) → higher signal-dependent noise → lower accuracy

Laws of voluntary movements

IV law: Movement efficacy grows with experience and learning



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Learning induced by repetitive training
(motor memory results from trial and error)

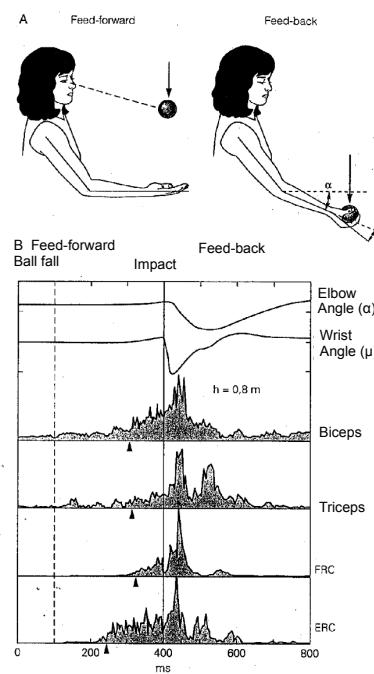
Feedback control / feedforward control

Feedforward:

- Anticipatory control
- Sensorial information + previous experience

Feedback:

- Actual control
- Dependent on the actual sensory information
- Comparison with a reference signal
- Characterized by a gain



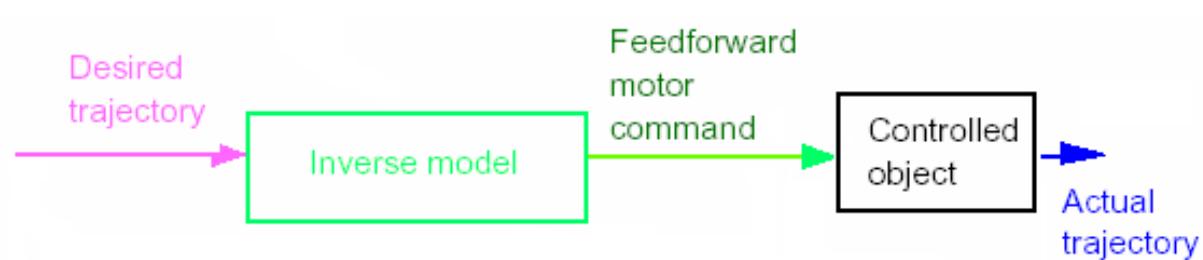
Modelling brain functions in motor control: Internal models

INTERNAL MODELS

Representations of the sensorimotor and motor sensory transformations that occur within our brain

They mimic, inside our brain, the functions of the system to be controlled

Feedforward control: INVERSE MODEL

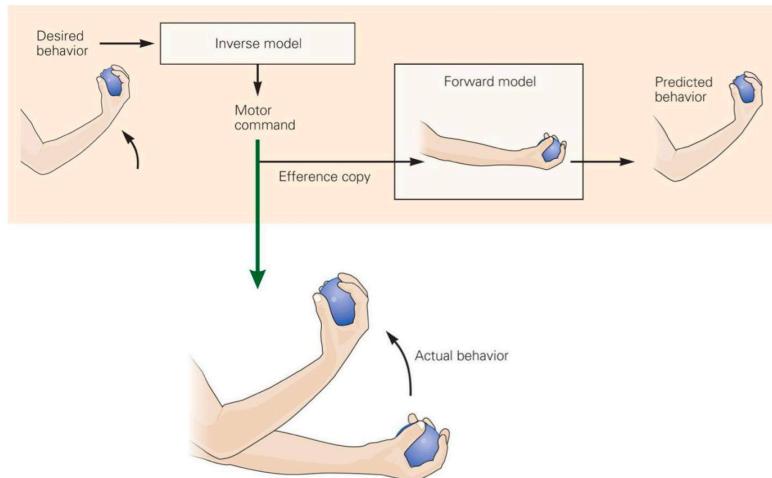


Inverse model: estimates the motor commands required to achieve the desired sensory feedback (anticausal direction)

- It is fast, cancels delays
- It is not able to correct the movement on errors occurring because of its inaccuracy or because of unexpected disturbances

Ballistic movements

Inverse model+ Efference copy + Forward model



Forward model
Maps motor commands
in the sensory space

Inverse model
estimates motor
commands to obtain a
desired sensory
feedback

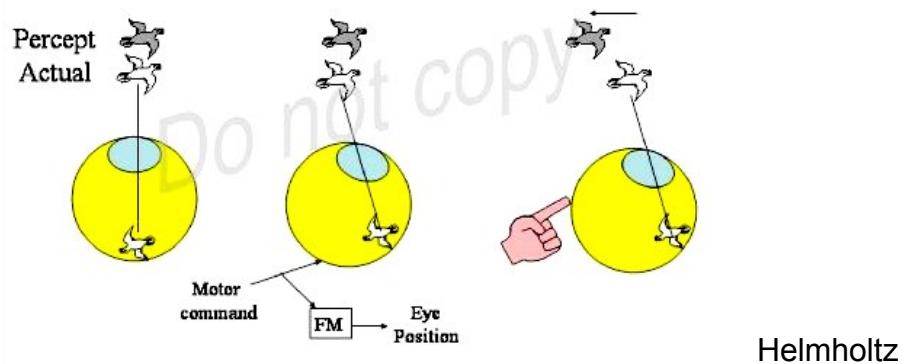
Figure 1.12: **Inverse and Forward model:** Forward model maps motor commands in the sensory space; Inverse model estimates motor commands to obtain a desired sensory feedback. (From [1]).

FORWARD MODEL: state estimation

Efference copy + forward model allows us to distinguish between our own actions and external events

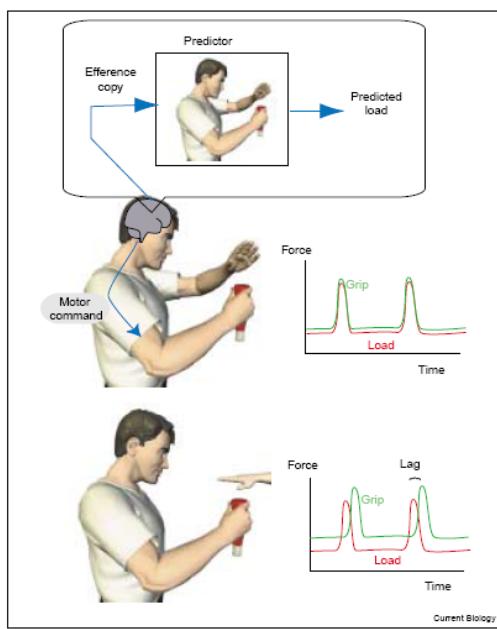
GOALS:

- Detecting the consequences of our own actions
- Perceptual stability
- Modulate attention



Efference copy + forward model

Figure 1



To prevent a ketchup bottle from slipping, sufficient grip force must be exerted to counteract the load. When the load is increased in a self-generated manner (left hand strikes the ketchup bottle top), a predictor can use an efference copy of the motor command to anticipate the upcoming load force and thereby generate grip which

parallels load force with no delay. However, when the load is externally generated (another person strikes the bottle, bottom), then it cannot be accurately predicted. As a consequence, the grip force lags behind the load force and the baseline grip force is increased to compensate and prevent slippage.

Motor prediction

Daniel M. Wolpert* and
J. Randall Flanagan†
Current Biology Vol 11
No 18, 2001

Two eyes for an eye



Two Eyes for an Eye: The Neuroscience of Force Escalation

Shergill, Bays, Frith, Wolpert
Science 11 Jul 2003:
Vol. 301, Issue 5630, pp. 187
DOI: 10.1126/science.1085327

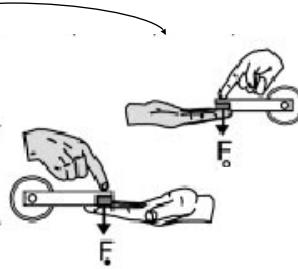
Tit for tat experiment:

Physical conflicts tend to escalate

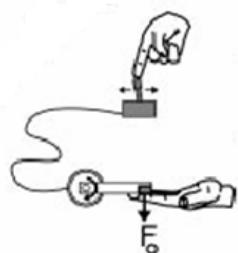
Two eyes for an eye

EXPERIMENTAL PROTOCOL

Cond. 1:
Each person in the couple is required to exert the same level of force he/she receives



Cond. 2:
The motor exerts a force and the subject has to reproduce the same force with the other finger



Cond. 3:
The motor exerts a force on the left finger and the right finger controls the motor with a joystick to reproduce the same force



Two eyes for an eye

RESULTS: escalation of force

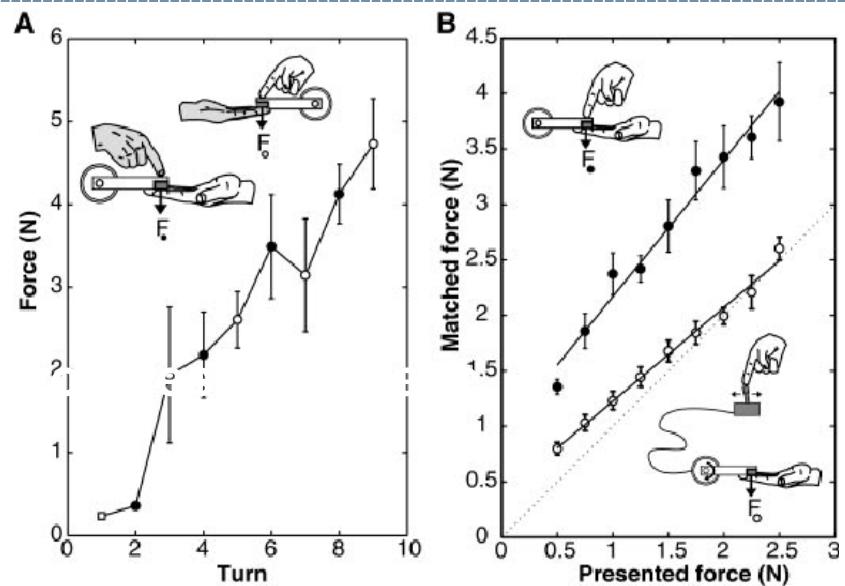


Fig. 1. (A) Force escalation in a typical pair (participant 1, solid circles; participant 2, empty circles; mean \pm SE across four trials). The initial force (white square) was generated on participant 1 by the torque motor.

(B) Matching force generated using the right finger (solid circles) and joystick (white circles) as a function of the externally generated force (mean \pm SE across participants). Dotted line, perfect performance. On each trial, the torque motor generated a force between 0.5 and 2.75 N for 3 s (40 pseudo-randomized trials). Each participant experienced both conditions in a counterbalanced order (participant 1, gray hands and solid circles; participant 2, white hands and open circles; mean \pm SE across four trials).

Why can't you tickle yourself?

(Blakemore et al., Neuroreport 2000)

Use of the efference copy to reduce the sensory feedback due to our own actions

Goal: augment attention on external unexpected perturbations

Experimental evidence:

The consequences of our own actions are perceived differently from the same input due to external actions (Why can't you tickle yourself?)

Why can't you tickle yourself?

Cond .1: robot generates movement (external tickling)

Cond. 2: robot is moved by the left hand of the subject (=self tickling)

Cond. 3: robot is moved by the left hand but with a delay (100, 200, 300 ms)

Cond. 4: robot is moved by the left hand but the robot motion is rotated with respect to the hand motion



Why can't you tickle yourself?

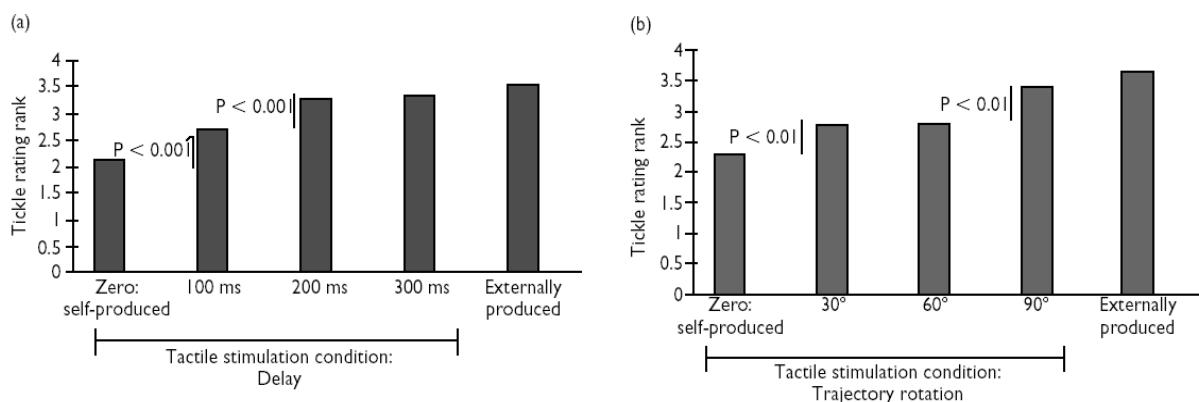
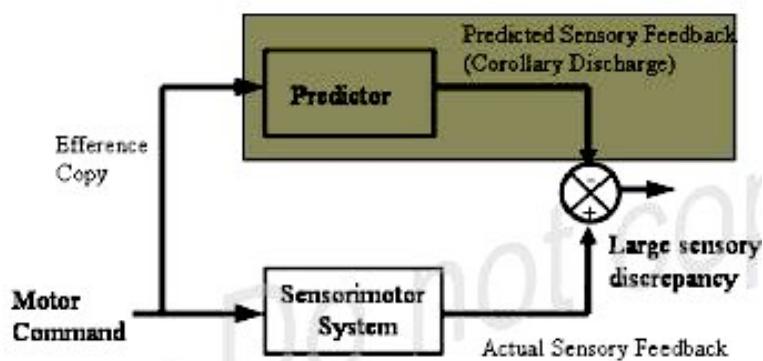


Fig. 2. Graph to show that the tickliness of a tactile stimulus increases with increasing delay (a) and trajectory rotation (b) between the movement of the left hand and the tactile stimulus on the right palm. These results suggest that the perceptual attenuation of self-produced tactile stimulation is based on specific sensory predictions made by a forward model.

Further proof: pathological behaviour

Schizophrenia:
auditory hallucinations /passivity of experiences: first rank features of schizophrenia



Further proof: pathological behaviour

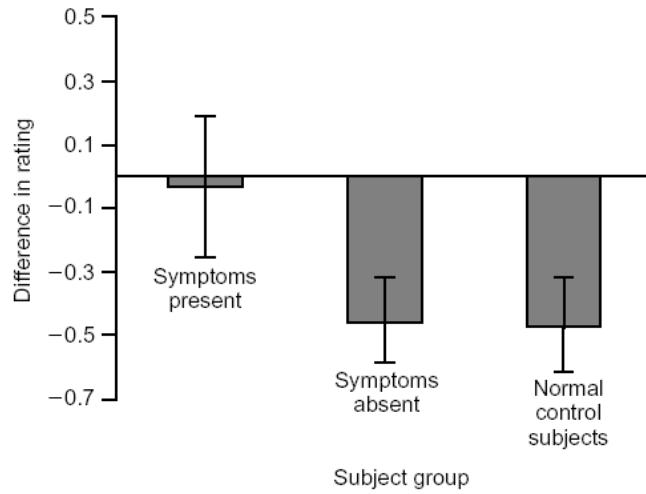
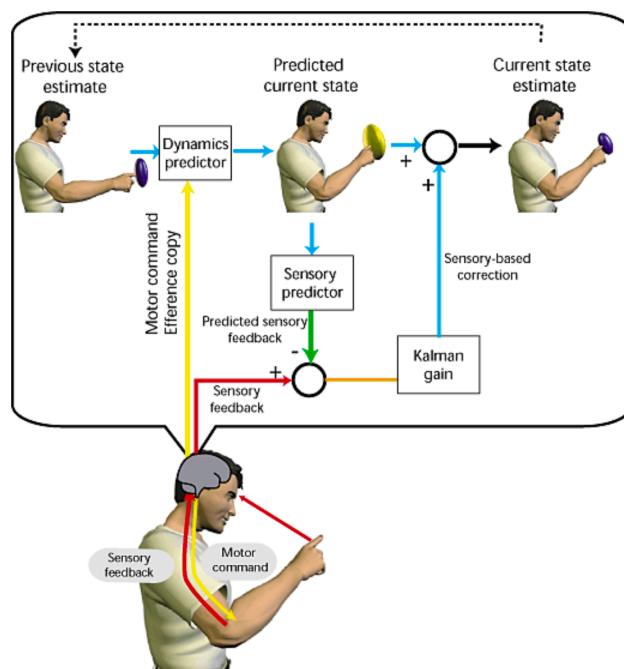


Fig. 6. Graph showing the mean (tickly, pleasant and intense combined) perceptual rating difference between self-produced and externally produced tactile stimulation conditions for the three subject groups: patients with auditory hallucinations and/or passivity, patients without these symptoms and normal control subjects. There was no significant difference between the perceptual ratings in the two conditions for patients with auditory hallucinations and/or passivity, hence the mean rating difference was close to zero. In contrast, there was a significant difference between the perceptual ratings in the two conditions for patients without these symptoms and in normal control subjects: both groups rated self-produced stimulation as less tickly, intense and pleasant than externally produced stimulation.

Blackmore et al. Nature Neuroscience 1998

Summary

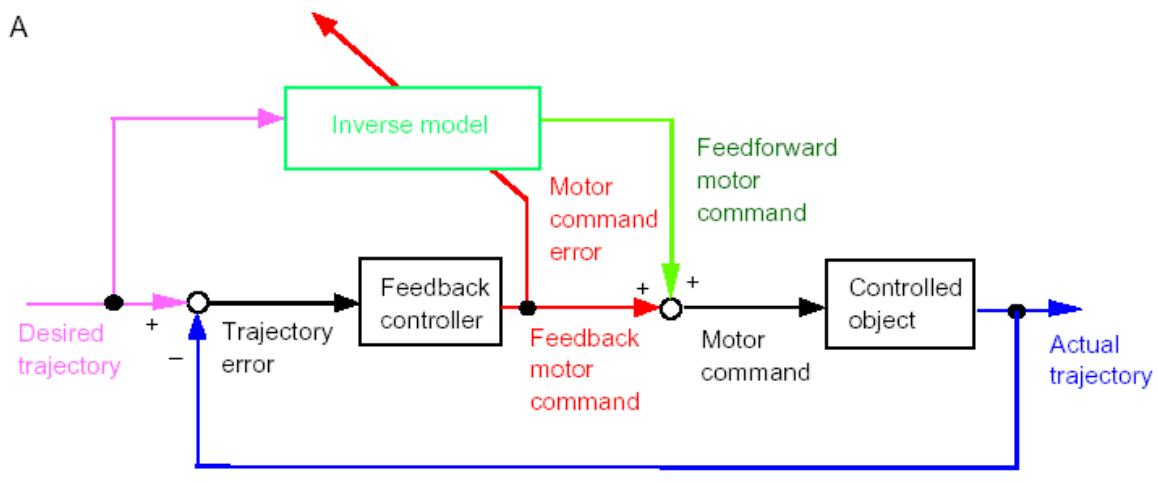


Re-afference and Kalman filter

Claim that initial movement is feedforward and the final part is feedback
Optimal state is a mixture of :
- Predictive estimation(FF)
Sensory feedback (FB)

Figure 1.22: Re-afference and Kalman Filter (From [16].)

How to train the inverse model?

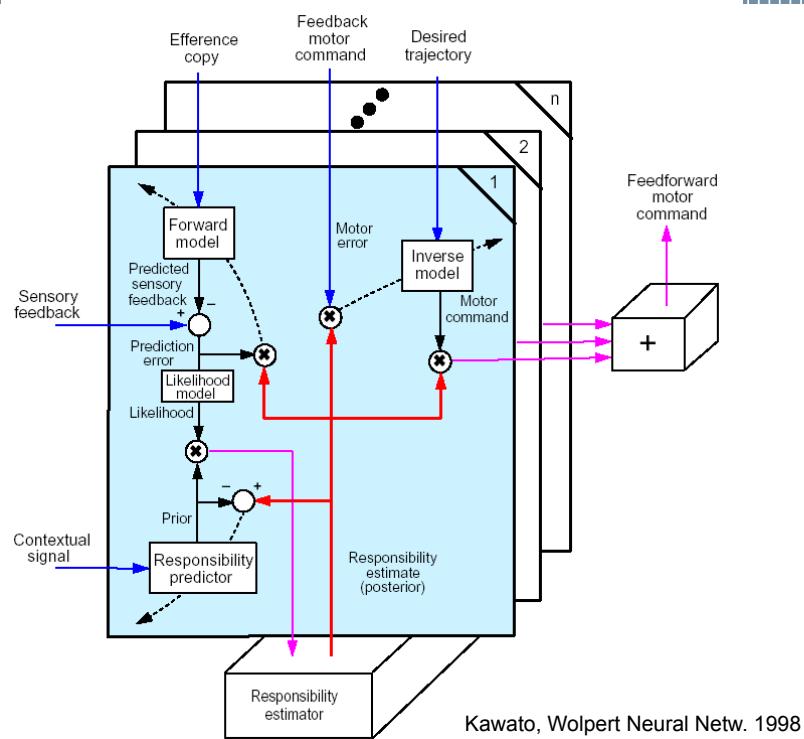


Da Wolpert et al. Trends in cognitive sciences 1998

TRAIN INVERSE MODEL = IDENTIFY FEEDFORWARD CONTROLLER

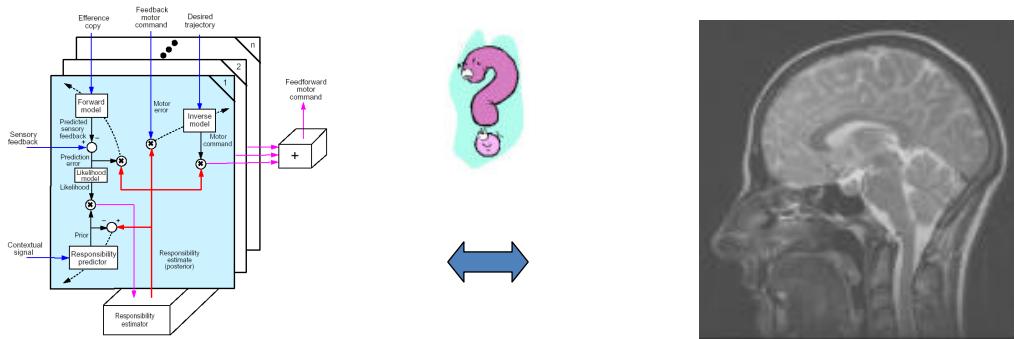
Multiple paired forward-inverse model

Forward models include the correspondence of a certain module to the current context and, accordingly, the corresponding inverse model contributes to the formation of the overall feedforward motor command



Kawato, Wolpert Neural Netw. 1998

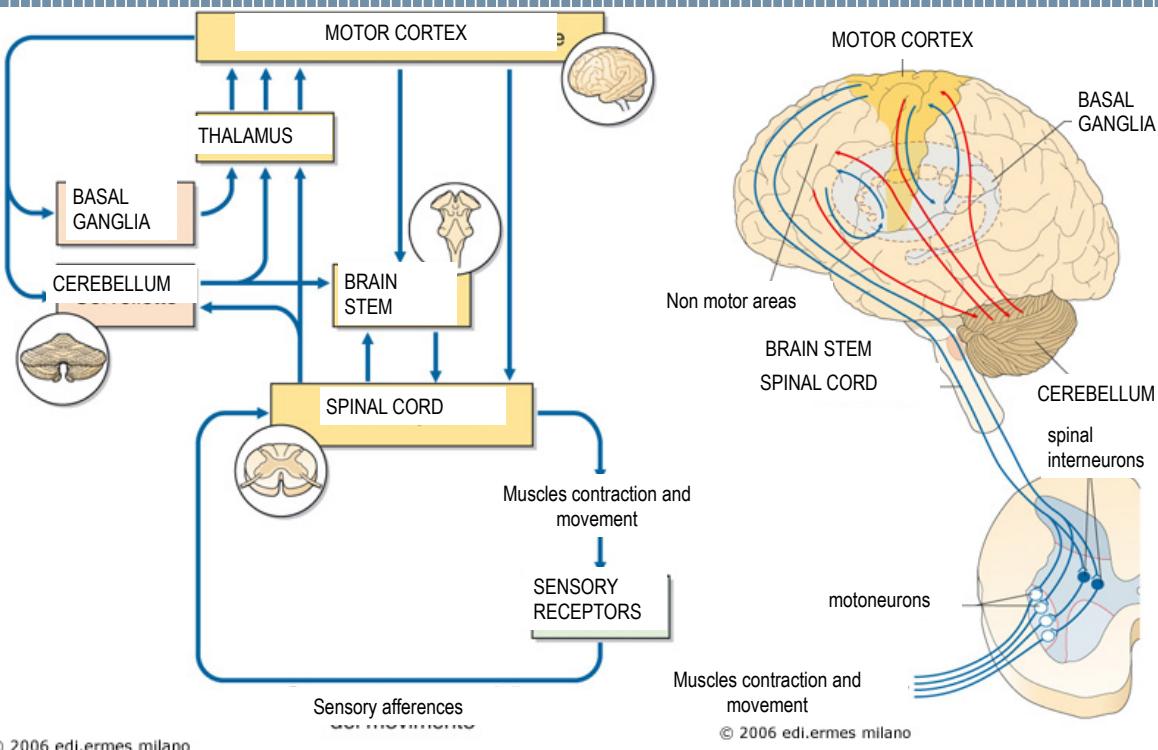
Do these models actually exist?



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COMPUTATIONAL NEUROSCIENCE 1 –
Part 2- Neural bases of Motor Control

Brain areas involved in motor control

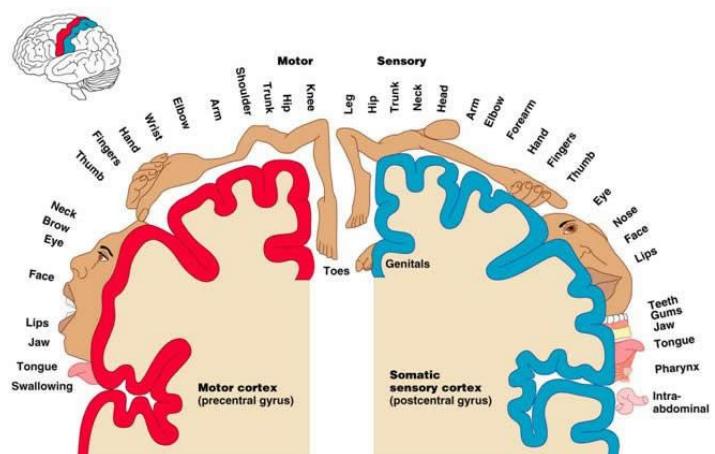


Primary Motor Cortex

Primary motor cortex: area from which it is possible to evoke movements with the minimum stimulation intensity

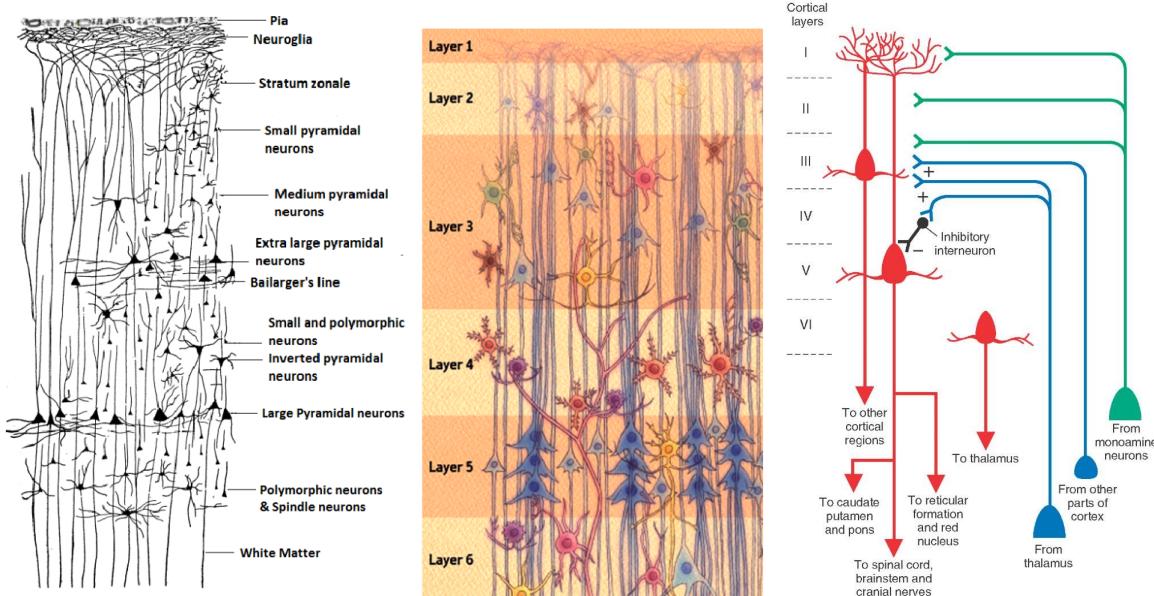
- Low intensity stimuli can activate a single muscle (natural activation of a single muscle is rare)
- One muscle can be activated by the stimulation of different cortical sites
- Most of the stimuli activate different muscles
- Primary Somatosensitive cortex afference + area 5 posterior parietal cortex (sensorial integration)
- Afference from basal nuclei and cerebellum

Figure 2.4: Cortical Homunculus: somatotopic organization (From <http://www.tulane.edu/~howard/BrLg/Cortex.html#id38>)



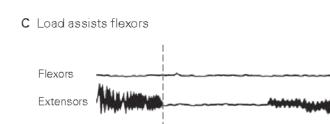
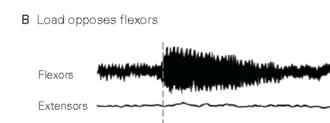
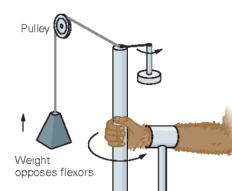
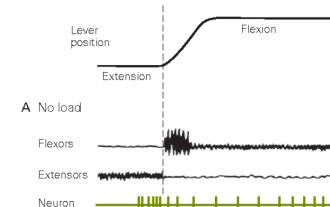
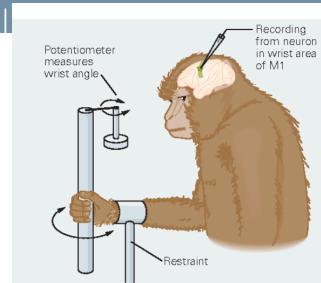
Cortex histological structure

Histological Structure of the Cerebral Cortex



Primary Motor cortex

Force coding
Evarts 1968



When a load-assisting flexion was applied, the neuron fell silent (C). In all three conditions the wrist displacement was the same but the neuronal activity changed as the load changed. Thus the firing of the corticospinal neuron in this experiment is related to the force exerted during a movement and not to the displacement of the wrist. (M1 single neurons activity is correlated to muscular force and it has been observed that there are some activities where the force firing frequency relationship is

Primary Motor cortex

The nature of the motor task changes the neurons activated also if the involved muscles are the same

Maier 1993

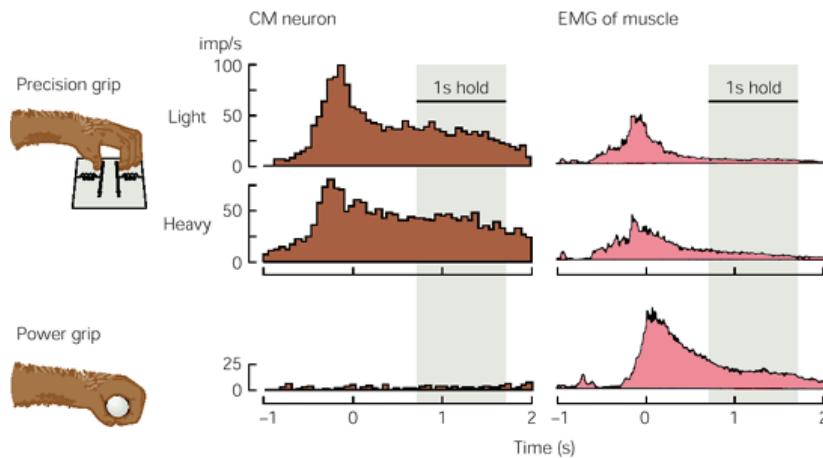


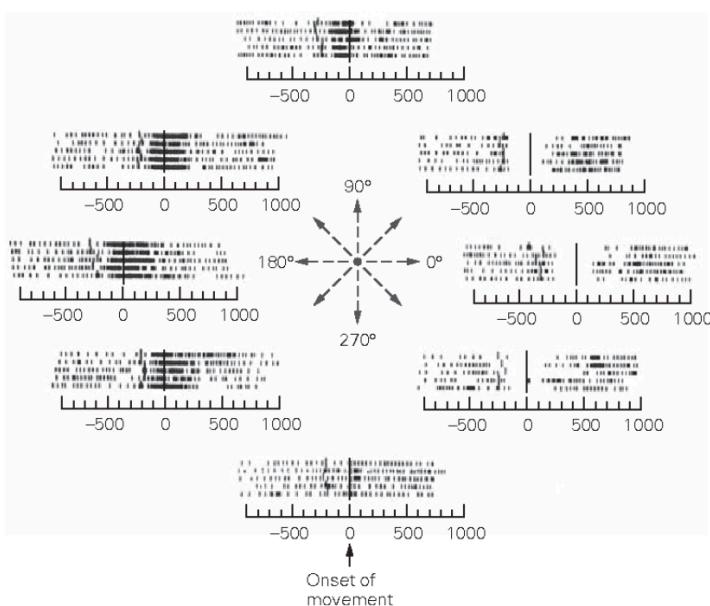
Figure 38-16 Whether an individual corticotononeuronal (CM) cell is active depends on the motor task. The activity of a CM cell and the activity in its target muscle are not directly related. Cumulative histograms show the activity of a single neuron during a precision grip and a power grip. During the precision grip the neuron's activity is the same whether overall force is light or heavy and the level of electromyographic (EMG) activity in the target muscle is similar for both forces. During the power grip there is almost no activity in the neuron despite a greater amount of EMG activity in the muscle. **Thus, even if a given motor neuron is monosynaptically connected to a given CM cell, their firing patterns do not have to parallel each other because the multiplicity of connections to motor neurons allows task flexibility.** (imp/s = impulses per second.) (Maier et al 1993.)

Primary Motor cortex

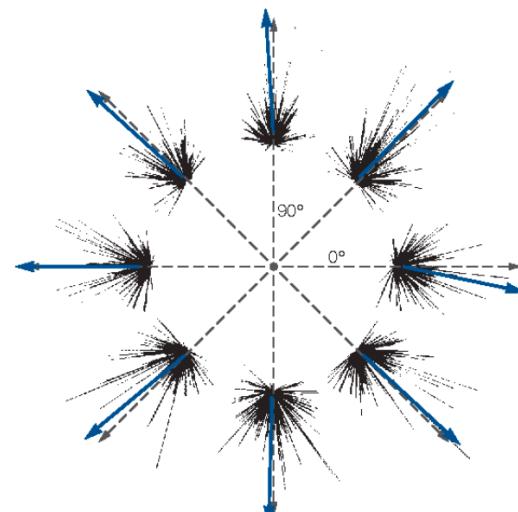
Population vector

Georgopoulos et al.1982

A Single primary motor cortex neuron



B Motor cortex neuronal population



Summary: Primary Motor Cortex

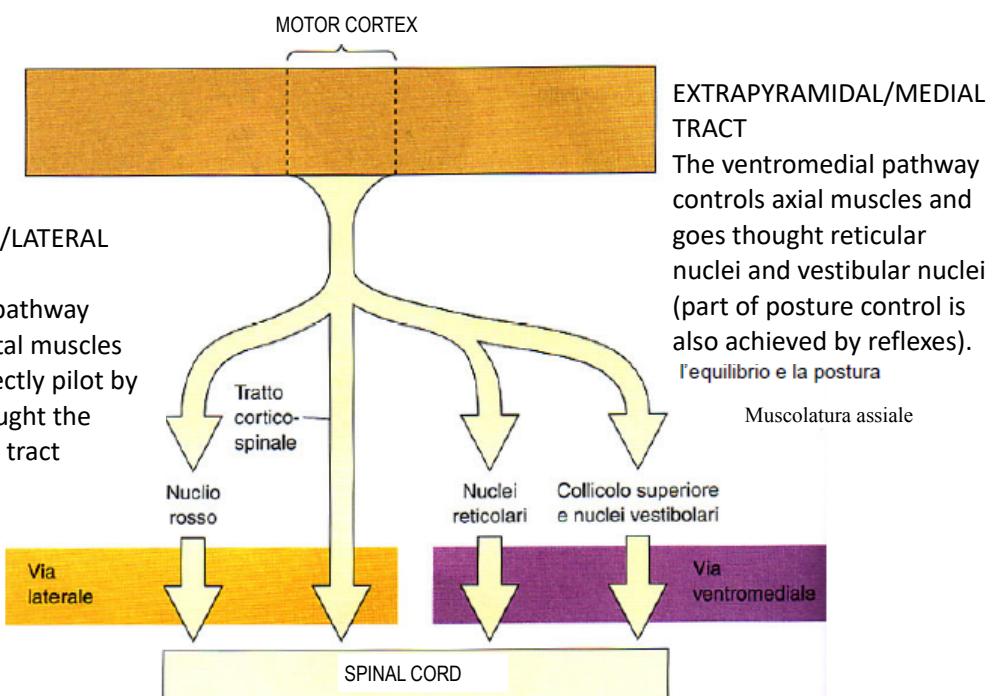
Primary Motor Cortex has a doublefold control

- A low level control of single muscles (homunculus)
- A high level control of multiple muscles depending on High content motor parameters

Exercise and training modify both functions

Spinal cord

PYRAMIDAL/LATERAL TRACT
The lateral pathway controls distal muscles and it is directly pilot by PMC or thought the Rubrospinal tract

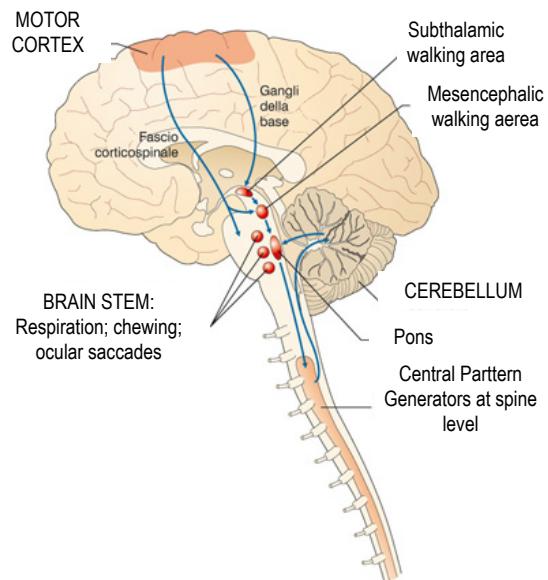


Spinal cord

Control of cyclic motor tasks

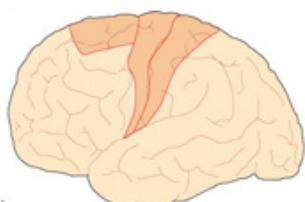
Rhythmic tasks are a combination of voluntary tasks and reflexes. The trigger is, usually, volitional while the continuation is based on spinal reflexes.

CENTRAL PATTERN GENERATORS:
oscillatory generators at high level

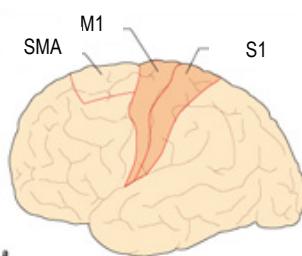


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Supplementary Motor Areas

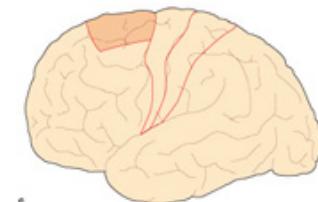


Simple finger flexion
•(M1)
•A (S1)



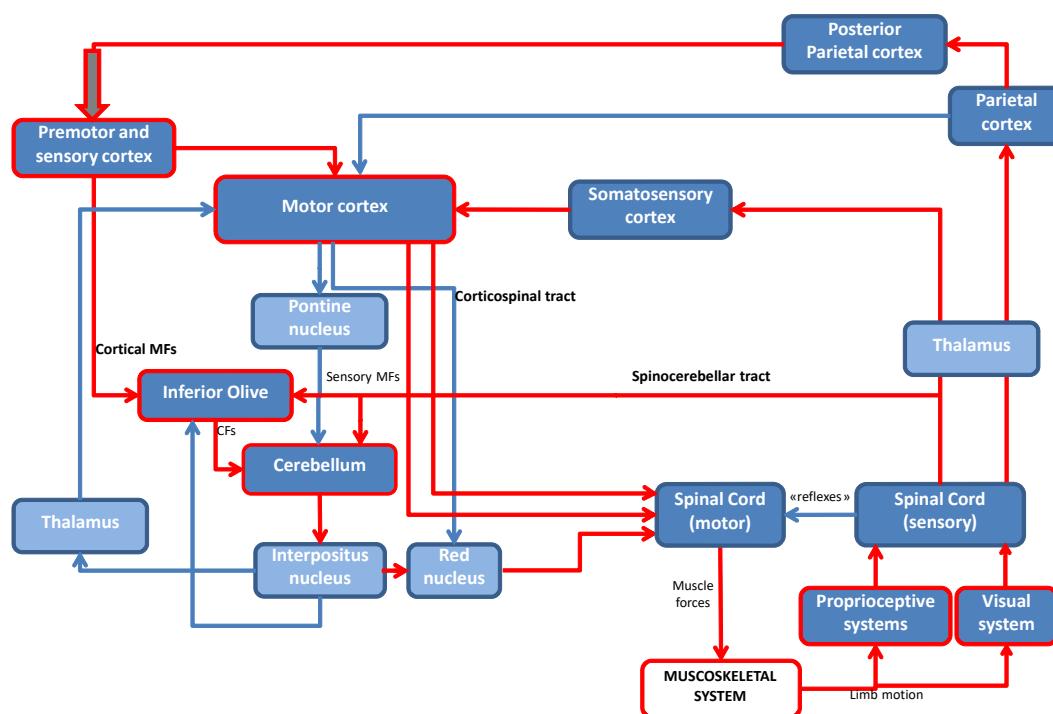
Sequential finger tapping
• (M1)
• (S1)
•PMC or SMA

Mental repetition of sequential finger tapping
•SMA PMC



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Simplified distributed motor control

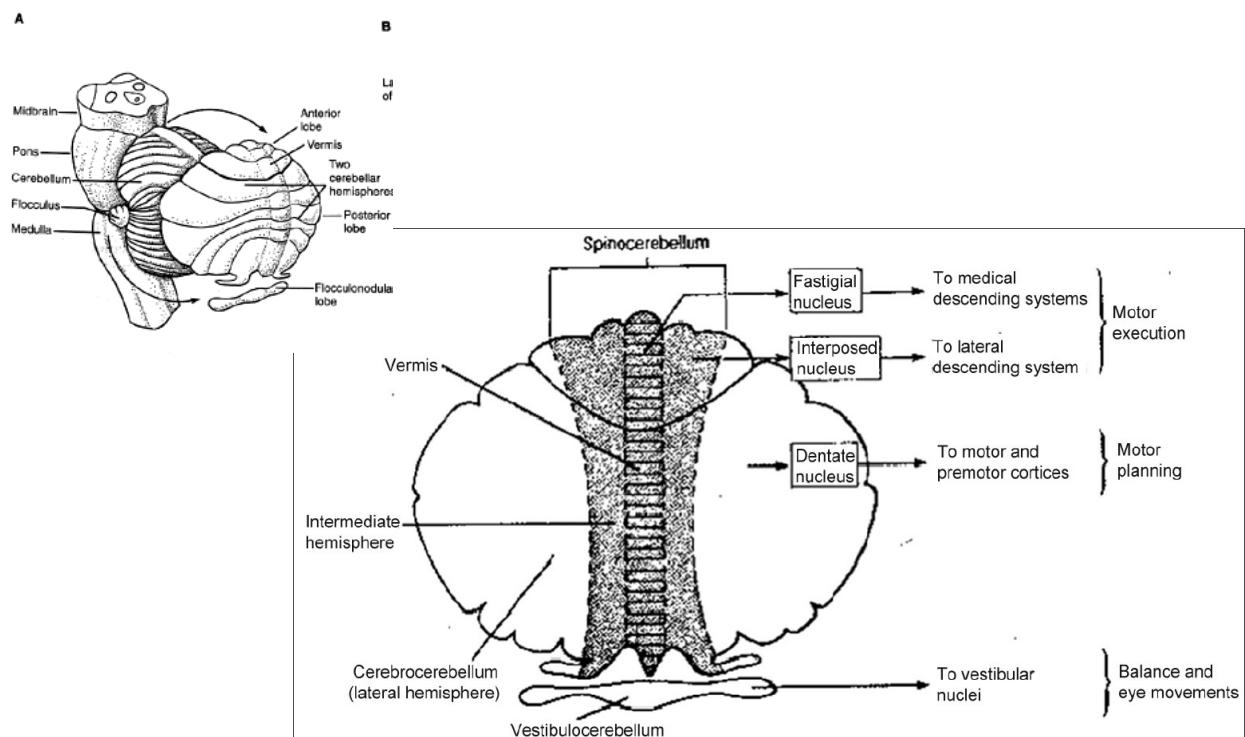


Neuroengineering 2019/20

COMPUTATIONAL NEUROSCIENCE 1 –
Part 3- Neural bases of Motor Control – Focus on the
Cerebellum

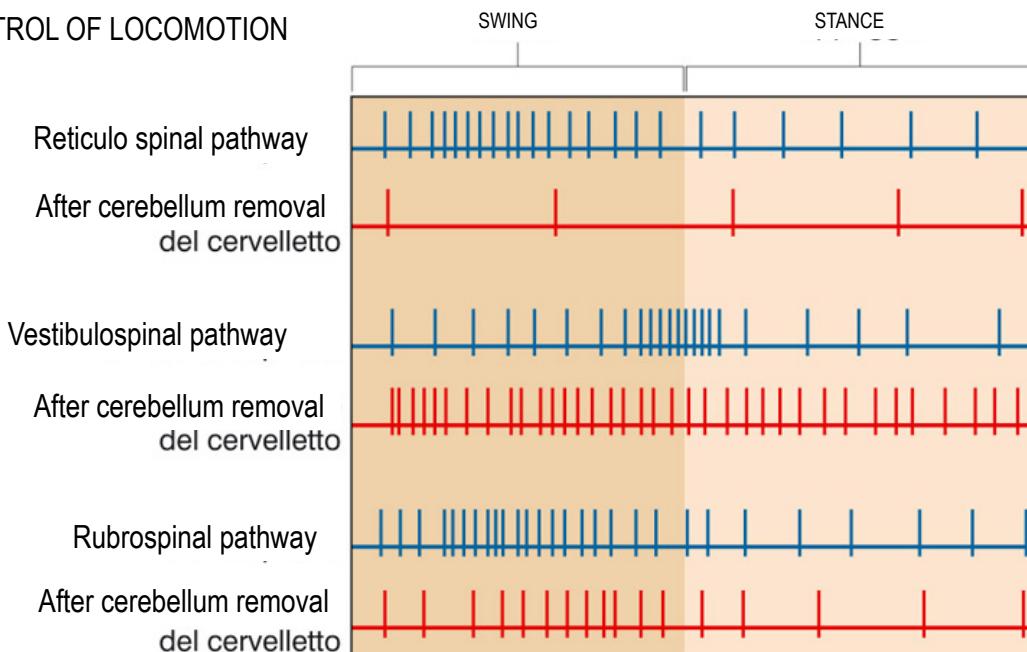
- What does it receive as input? (Inputs=40*outputs)
 - Info on the objective of motor actions
 - Info on the motor commands
 - Sensorial feedback signals associated to the planning and execution of movements
- What does it produce as output?
 - The output projections of the cerebellum are focused mainly on the premotor and motor systems of the cerebral cortex and brain stem, systems that control spinal interneurons, and motor neurons directly
- It has the property of modulation of the input/output connections (adaptation and motor learning: synaptic plasticity)

Anatomical structure



Effects of cerebellar removal

CONTROL OF LOCOMOTION



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Cerebellar microcircuits

The two main inputs are represented by mossy fibers (mf) originating in various brain stem and spinal cord nuclei, and by climbing fibers (cf) originating from the IO.

The structure of the cerebellum is formed by the granular layer (containing GrC bodies and GoC) and the molecular layer (containing PC, SC, and BC) and the parallel fibers (pf- axons of GrC).

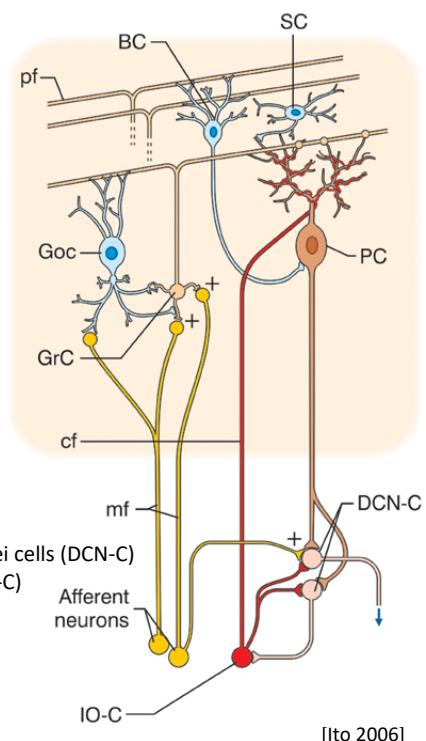
The cerebellar cortical circuit is organized as a feedforward excitatory chain assisted by inhibitory loops: mfs excite GrCs, which activate all the other cortical elements.

In the granular layer, inhibition is provided by GoC, in the molecular layer by SC and BC.

Finally, PCs inhibit DCN.

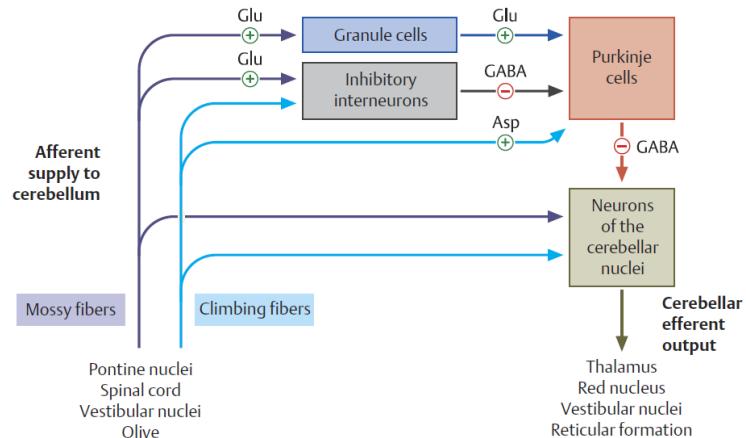
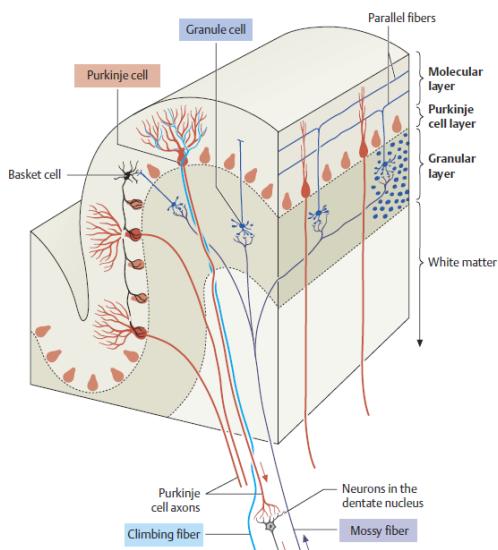
The IO, which is also activated by brain stem and spinal cord nuclei, controls PC activity through a single powerful synapse. Thus, the whole system can be seen as a complex mechanism controlling the DCN output.

Deep Cerebellar Nuclei cells (DCN-C)
Inferior Olive cells (IO-C)
Granule cells (GrC),
Golgi cells (GoC),
Purkinje cells (PC),
Stellate cells(SC)
Basket cells (BC).



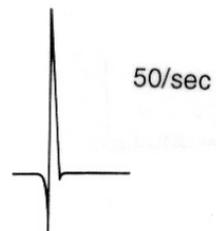
[Ito 2006]

Cerebellum cytology



Cerebellum - input

- **Mossy fibers**
 - They originate from:
 - nuclei in the spinal cord and brain stem carrying sensory information from the periphery
 - the cerebral cortex (cortical MFs) carrying motor commands (efference copy)
 - They have excitatory synapses on the dendrites of granule cells (state generator; not-recurrent; sparse coding: high divergence rate of connections)
- **Granule Cells**
 - Granules excite large numbers of Purkinje inducing a constant simple spike (SS)
 - The frequency of the SS could codify the intensity and the duration of the peripheral or the behaviors generated by the CNS
 - They have a center-surround coding



Cerebellum - input

Climbing fibers (IO)

- They have excitatory synapses on the Purkinje cells (generating complex spike, CS)
 - each Purkinje neuron receives only one climbing fiber
 - They generate low frequency CS;
 - The CS could codify the temporal features of the peripheral events and/or act as starting signals for behavioral actions

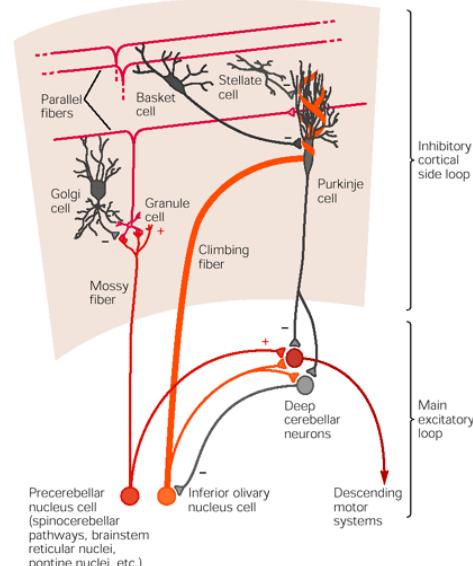
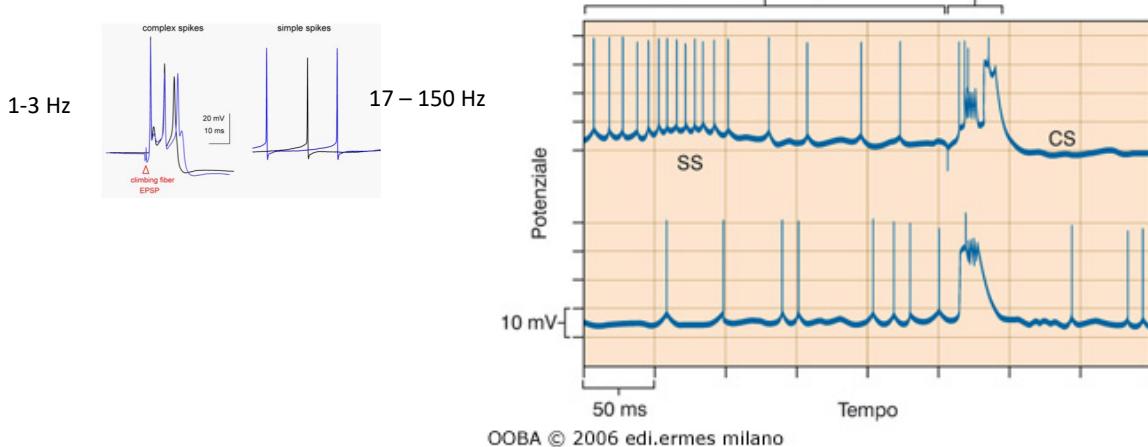


Figure 42-6 Synaptic organization of the basic cerebellar circuit module. Mossy and climbing fibers convey output from the cerebellum via a main excitatory loop through the deep nuclei. This loop is modulated by an inhibitory side-loop passing through the cerebellar cortex. This figure shows the excitatory (+) and inhibitory (-) connections among the cell types.

Cerebellum output



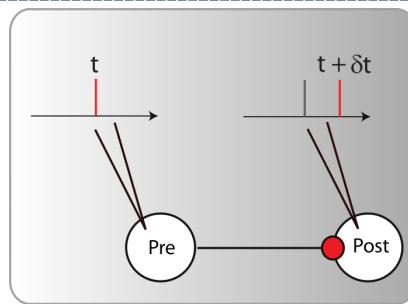
Hebbian plasticity: Spike Timing Dependent Plasticity (STDP)

Hebb hypothesis 1949

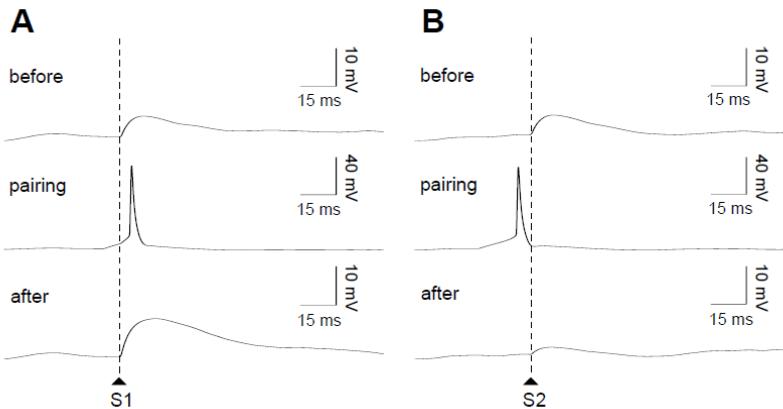
Experimental proofs:

Bi 1998, Markram 1997,

Gerstner 1996



Experimental protocol of Spike Timing Dependent Plasticity in vitro. Pre and Post synaptic neurons are patched and forced to fire with a time difference, while the modification of the synaptic strength is monitored



excitatory postsynaptic potentials EPSP

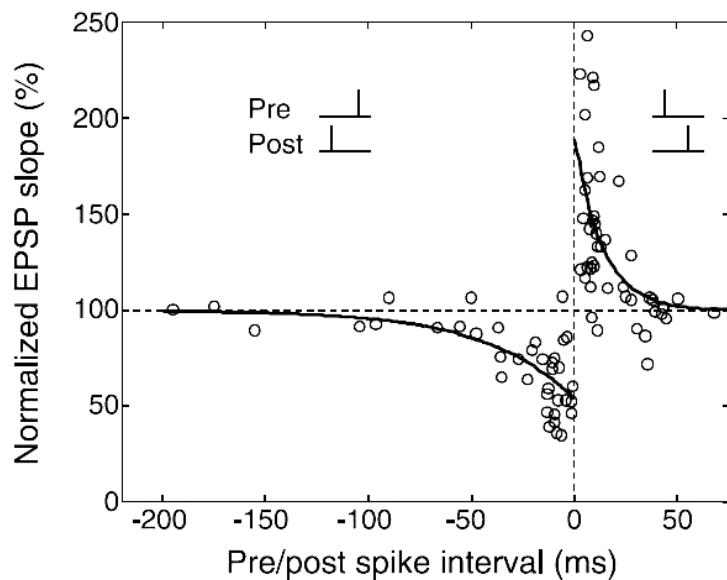
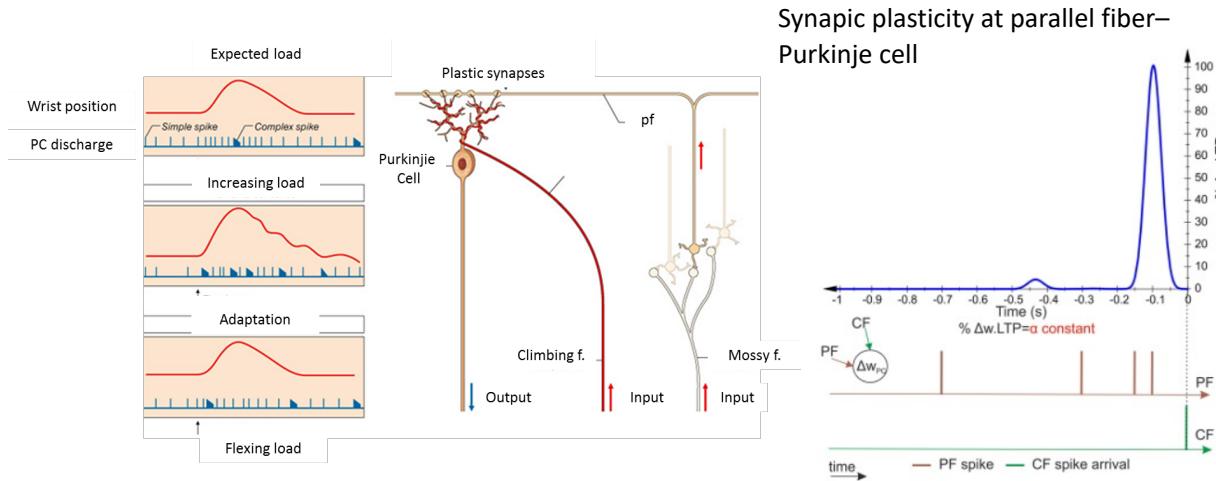


Illustration of spike timing dependent plasticity time windows, taken from (Bi et al, 1998). Depending on the precise time difference between a post- and a pre-synaptic spike, the synaptic weight can be either depressed or potentiated (excitatory postsynaptic potentials EPSP)

Cerebellum output



Changes in the strengths of parallel fiber–Purkinje cell synapses could store stimulus-response associations by linking inputs with appropriate motor outputs, following a **Hebbian learning** approach but **with supervision of Cf discharge**.

Summary

Structure and organization of the brain suggest computational analogies:

- INFORMATION STORAGE: Physical and chemical structure of neurons and synapses
- INFORMATION TRANSMISSION: electrical and chemical signaling
- PRIMARY COMPUTING ELEMENT: the neuron
- COMPUTATIONAL BASIS: still unknown!!!

Summary

- What is motor control and motor learning and high level models of motor control by the Human Brain
- The human brain areas involved in motor control
- Focus on Cerebellum
- The physiology of the cerebellum accounting for its functional features



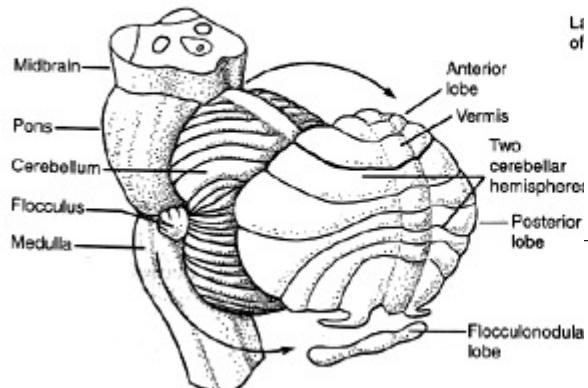
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COMPUTATIONAL NEUROSCIENCE 1 –
Part 3- Neural bases of Motor Control – Focus on the
Cerebellum

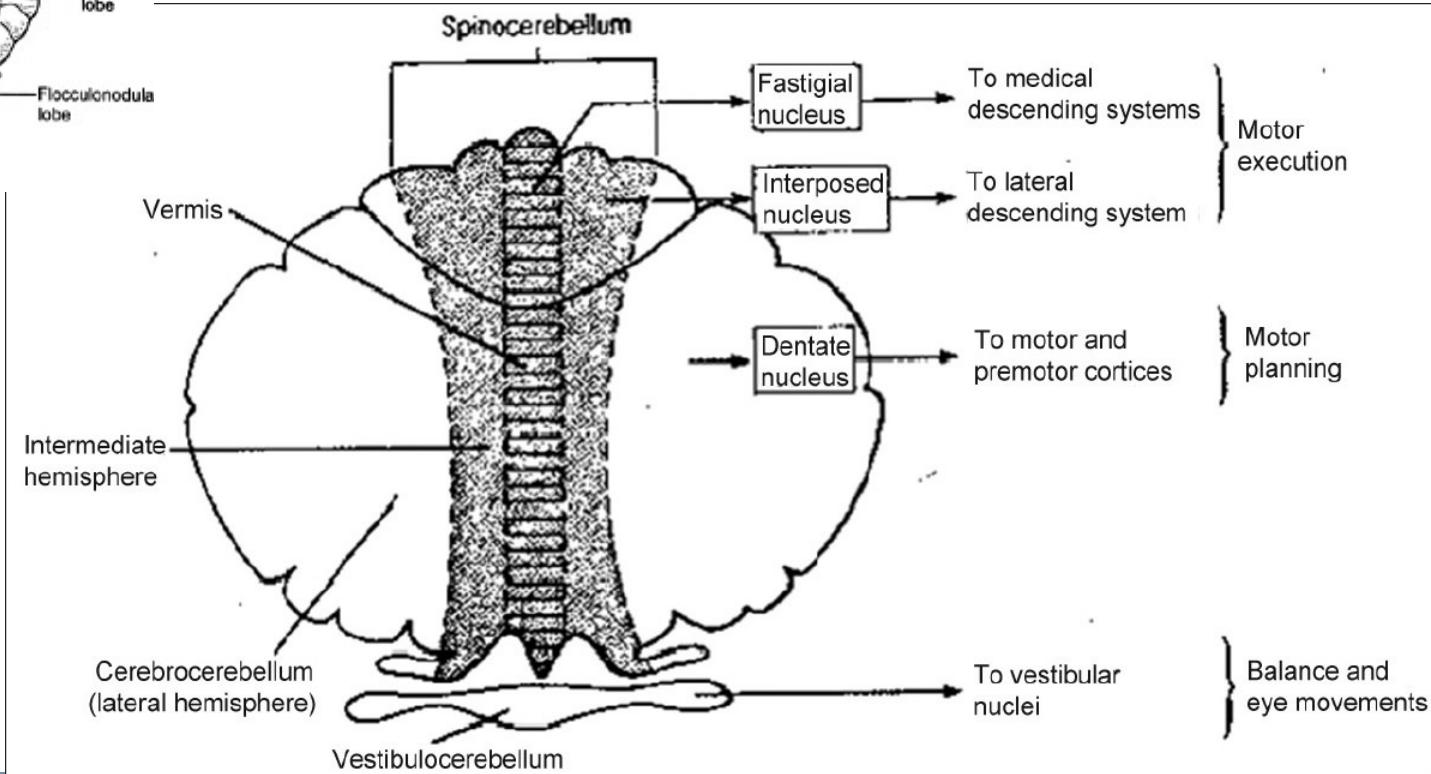
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- It has the property of modulation of the input/output connections (adaptation and motor learning: synaptic plasticity)
- The cerebellum makes up only about 10 percent of the mass of the human brain but contains more than half of its neurons. Stretched out, its surface area would be nearly 80% that of the cerebral cortex.

Anatomical structure

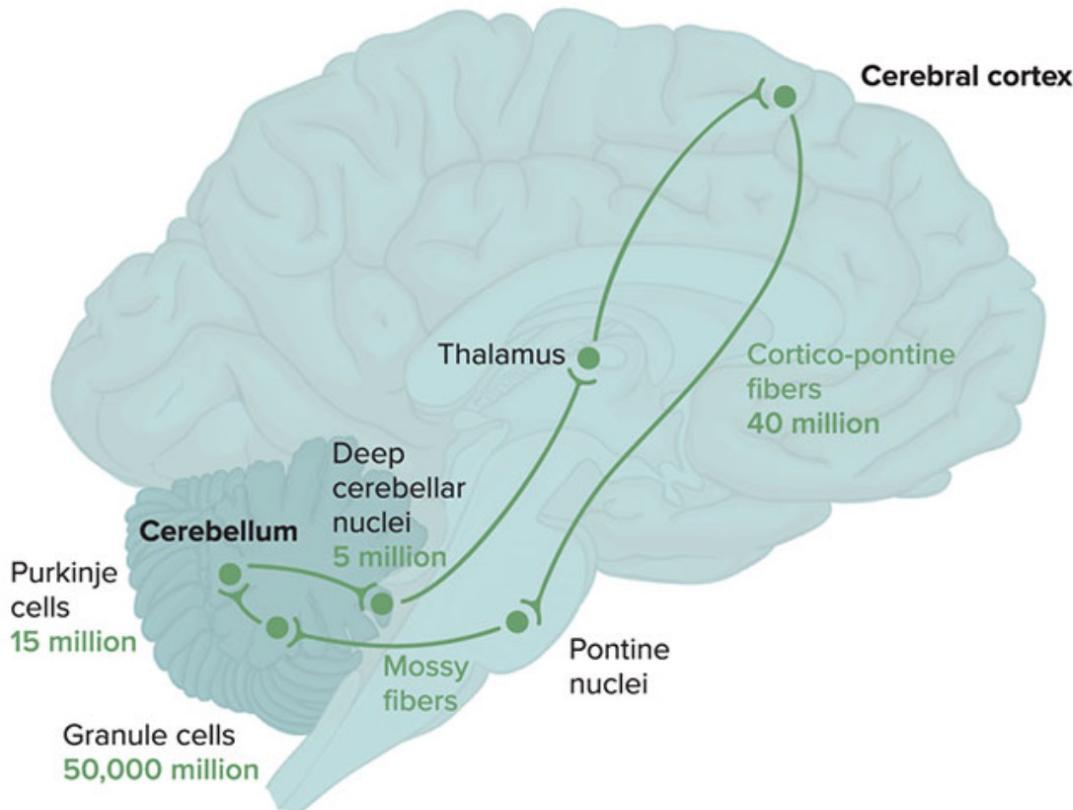
A



B



The cerebellum-cerebral cortex loop



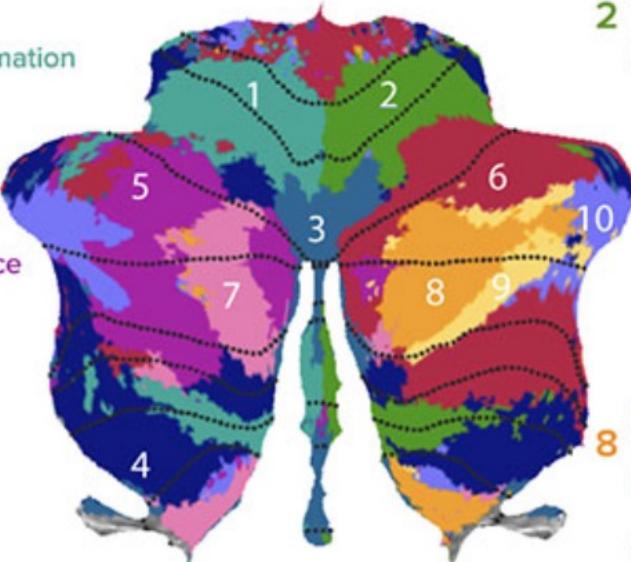
SOURCE: J. DIEDRICHSEN ET AL / NEURON 2019

KNOWABLE MAGAZINE

While the cerebral cortex's role in cognition has long been recognized, the cerebellum's role has largely been ignored. But these two parts of the brain share an elaborate network of connections. Some 40 million neurons in the cerebral cortex have fiber-like axons extending to the pontine nuclei in the brainstem, an area intimately connected to the cerebellum. Extensive connections go in the other direction, too, from the cerebellum up to the cortex.

Functions of the cerebellum

- Motor planning
- 1 Left hand movements**
Resolution of conflicting information
- Visual working memory
- 3 Rapid eye movements**
Visual letter recognition
- Active information maintenance
- 5 Divided attention**
Mental arithmetic
- Emotion processing
- 7 Narrative**
Language processing
- Word comprehension
- 9 Verbal fluency**
Mental arithmetic



- Motor planning
- 2 Right hand movements**
Divided attention
- Divided attention
- 4 Action observation**
Motor planning
- Active information maintenance
- 6 Divided attention**
Verbal fluency
- Language processing
- 8 Word comprehension**
Narrative
- Visual letter recognition
- 10 Autobiographical recall**
Resolution of conflicting information

SOURCE: M. KING ET AL / NATURE NEUROSCIENCE 2019

KNOWABLE MAGAZINE

The cerebellum plays a role in several motor and cognitive tasks. Neuroscientists used functional magnetic resonance imaging to scan people's brains while they carried out a wide variety of activities. The researchers then mapped key functions associated with different regions of the cerebellum. Stronger associations are indicated by larger text in this flattened version of the cerebellum's surface.

<https://www.brainfacts.org/brain-anatomy-and-function/anatomy/2020/the-mysterious-multifaceted-cerebellum-120320>

Effects of cerebellar removal

CONTROL OF LOCOMOTION

Reticulo spinal pathway

After cerebellum removal

Vestibulospinal pathway

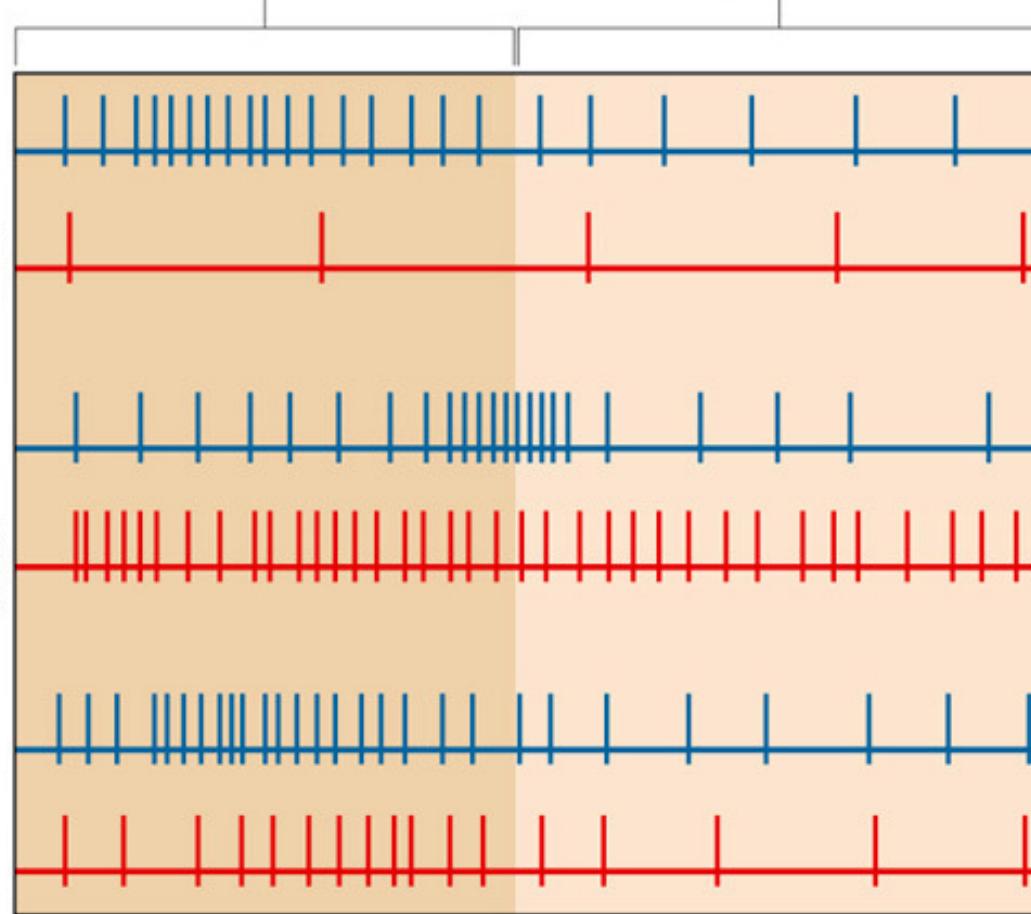
After cerebellum removal

Rubrospinal pathway

After cerebellum removal

SWING

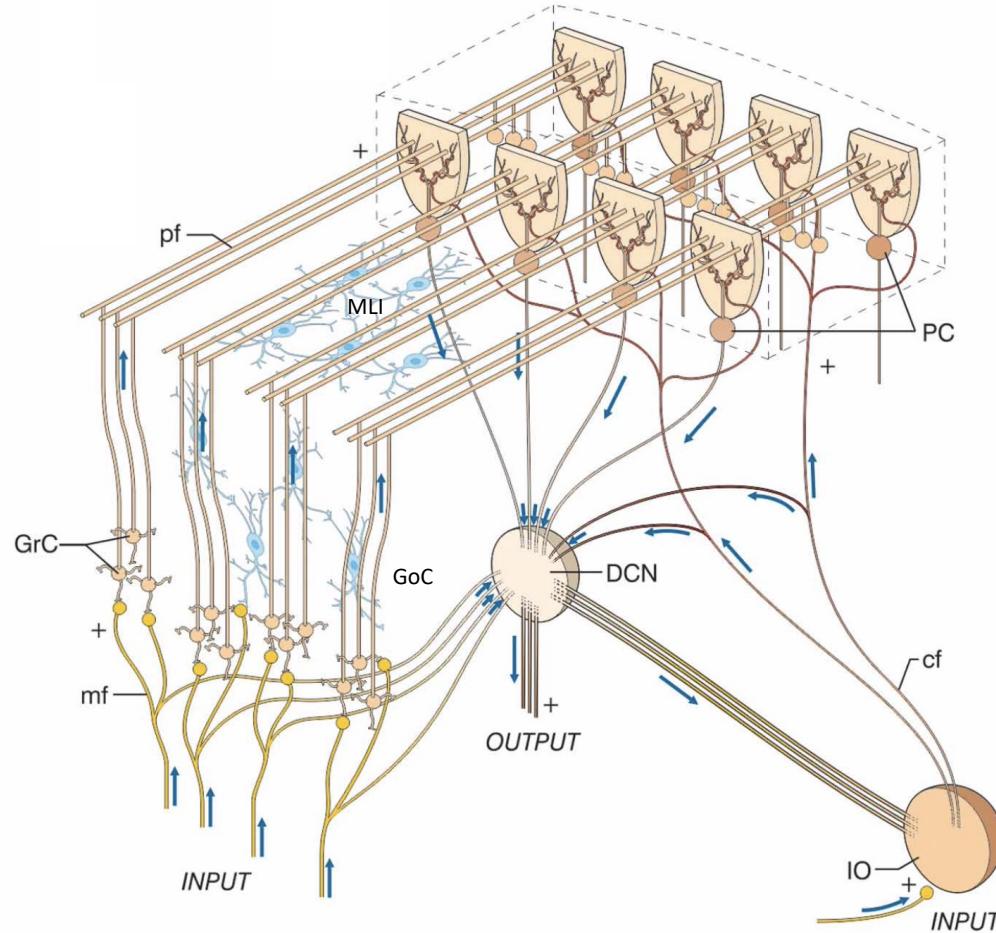
STANCE



Ooba © 2006 edi.ermes milano

Cerebellar microcircuits

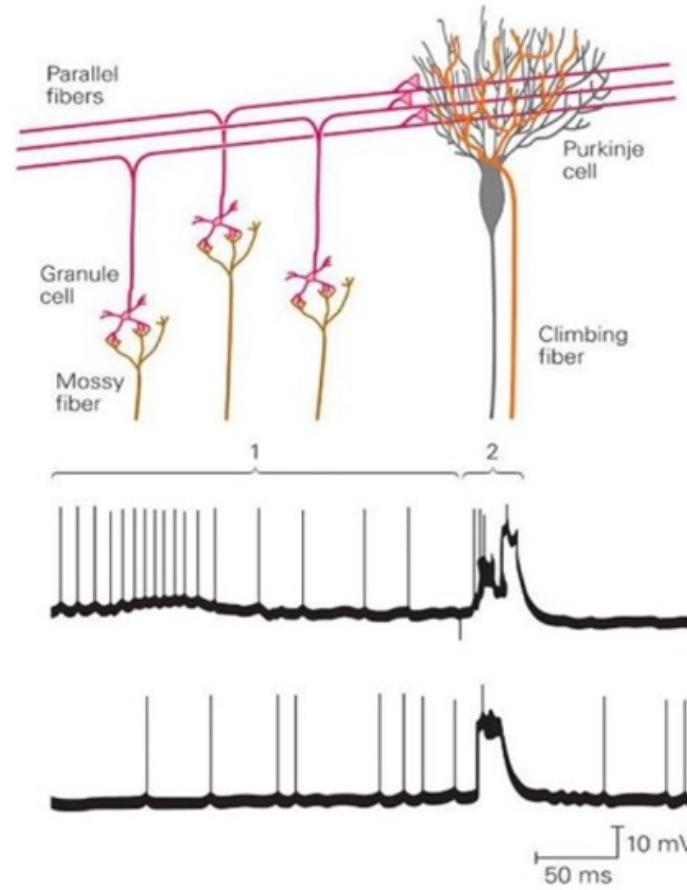
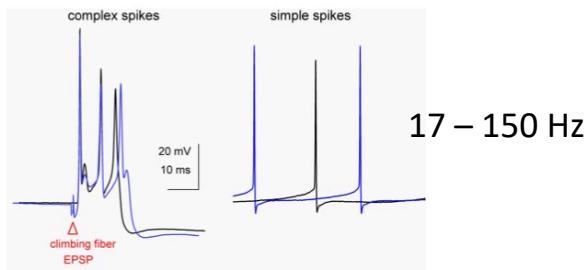
Mossy Fibers (mf)
Granule cells (GrC),
parallel fibers (pf)
Golgi cells (GoC),
Molecular Interneurons (MLI)
Stellate cells(SC)
Basket cells (BC).
Inferior Olive cells (IO-C)
Purkinje cells (PC),
Deep Cerebellar Nuclei cells (DCN-C)



[Ito 2006]

Electrical Activity of Purkinje Cells

1-3 Hz

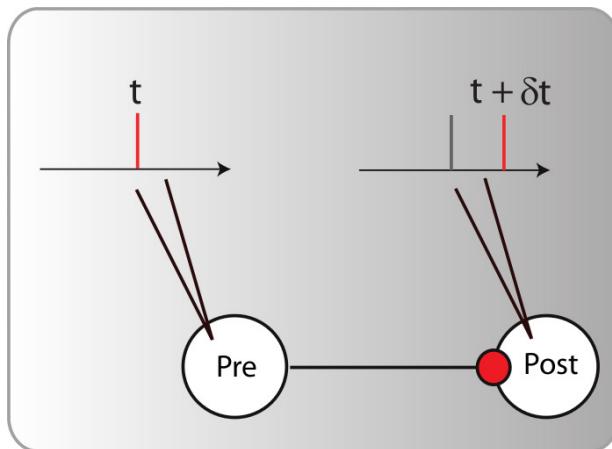


Hebbian plasticity: Spike Timing Dependent Plasticity (STDP)

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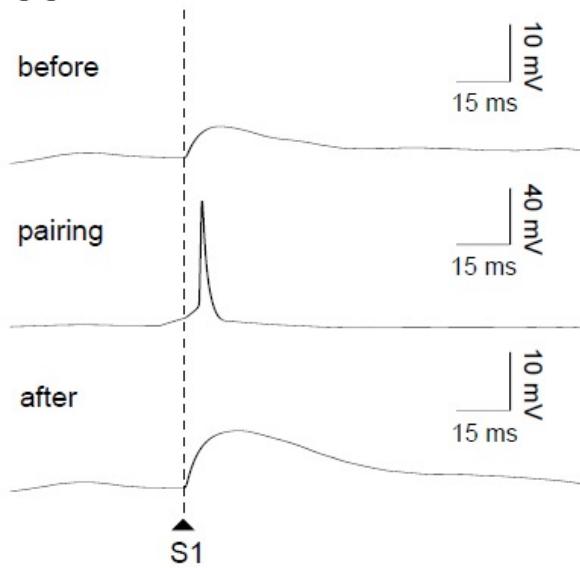
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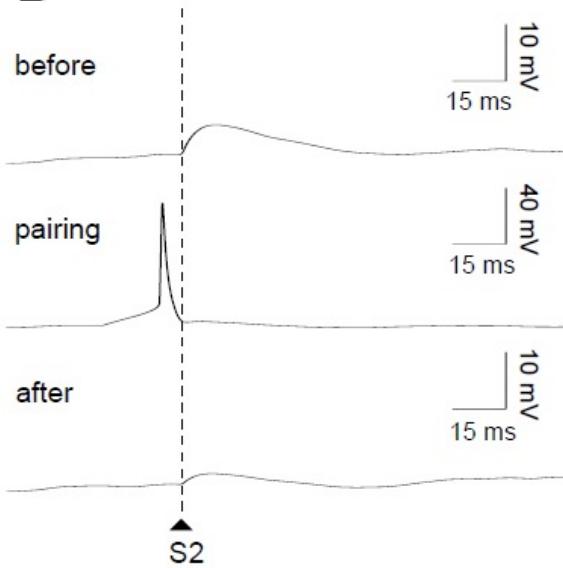


Experimental protocol of Spike Timing Dependent Plasticity in vitro. Pre and Post synaptic neurons are patched and forced to fire with a time difference, while the modification of the synaptic strength is monitored

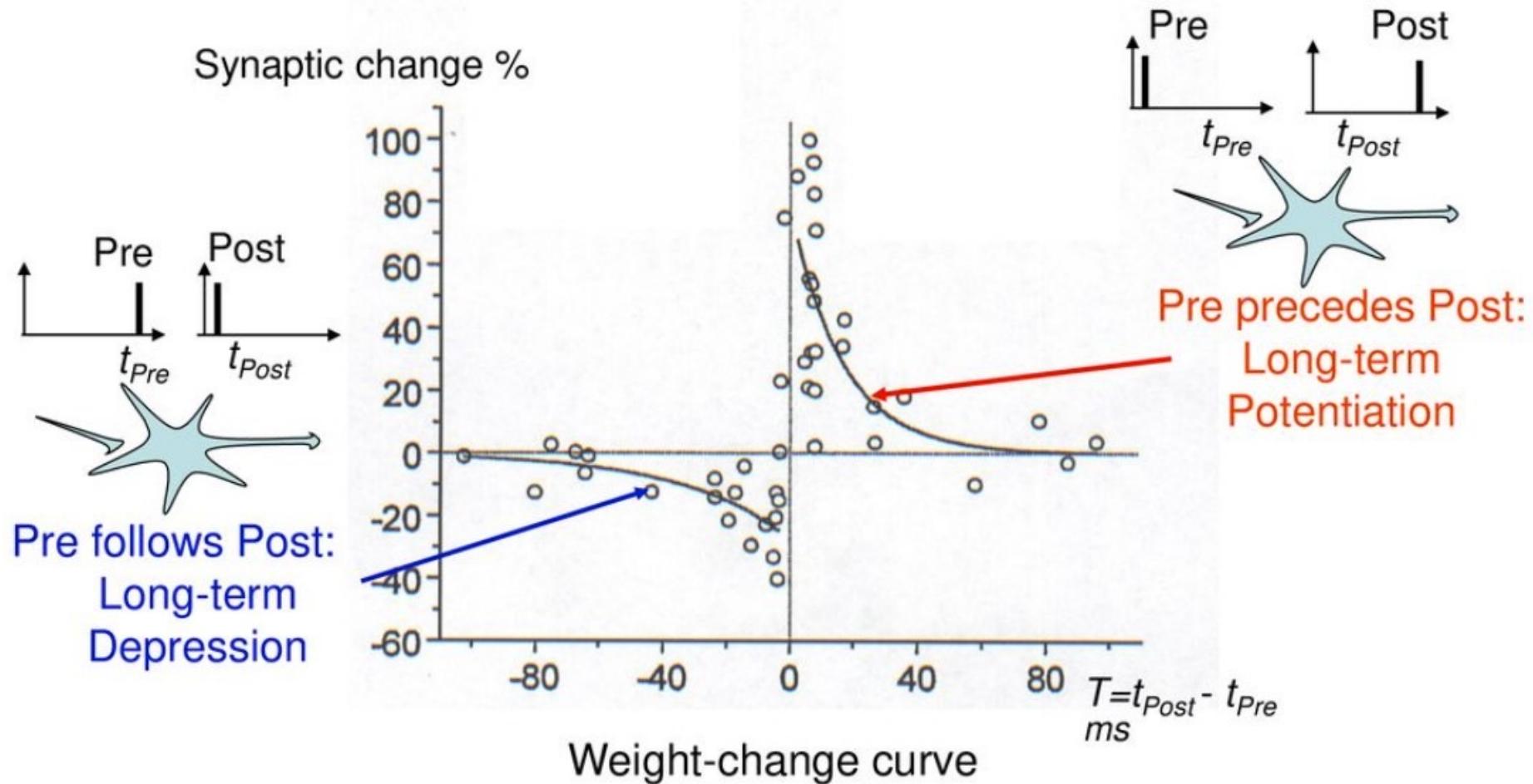
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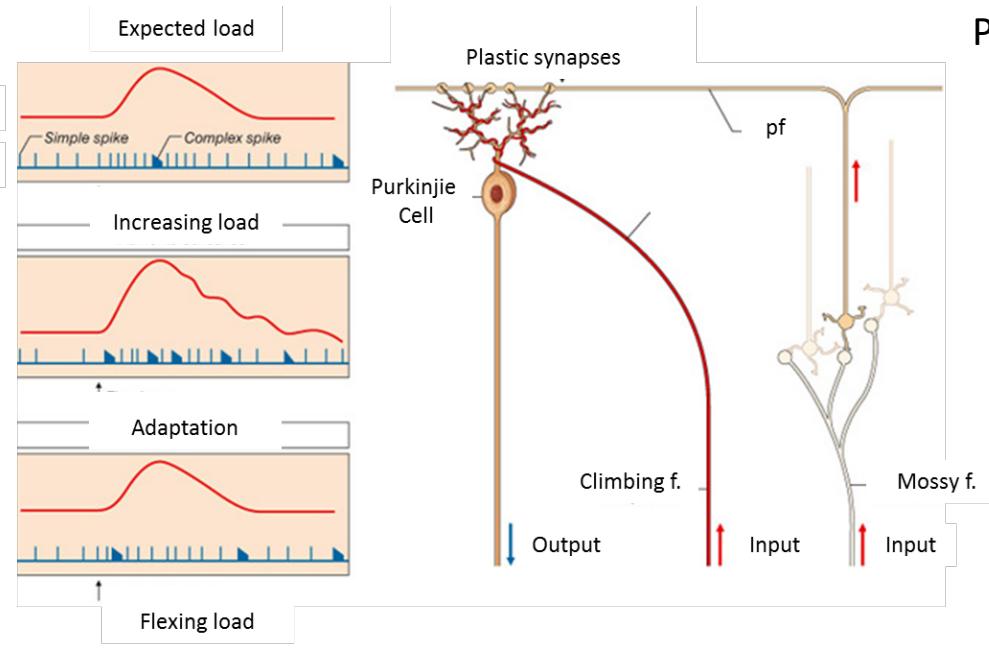
B



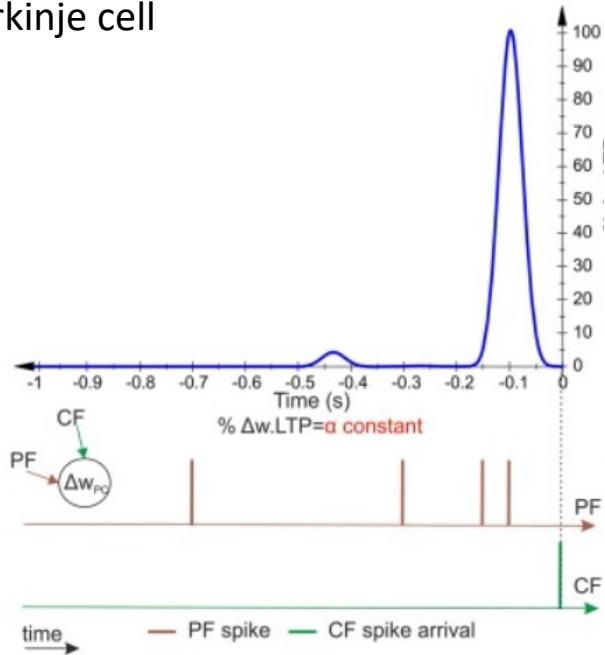
STDP



Cerebellum output



Synaptic plasticity at parallel fiber–Purkinje cell



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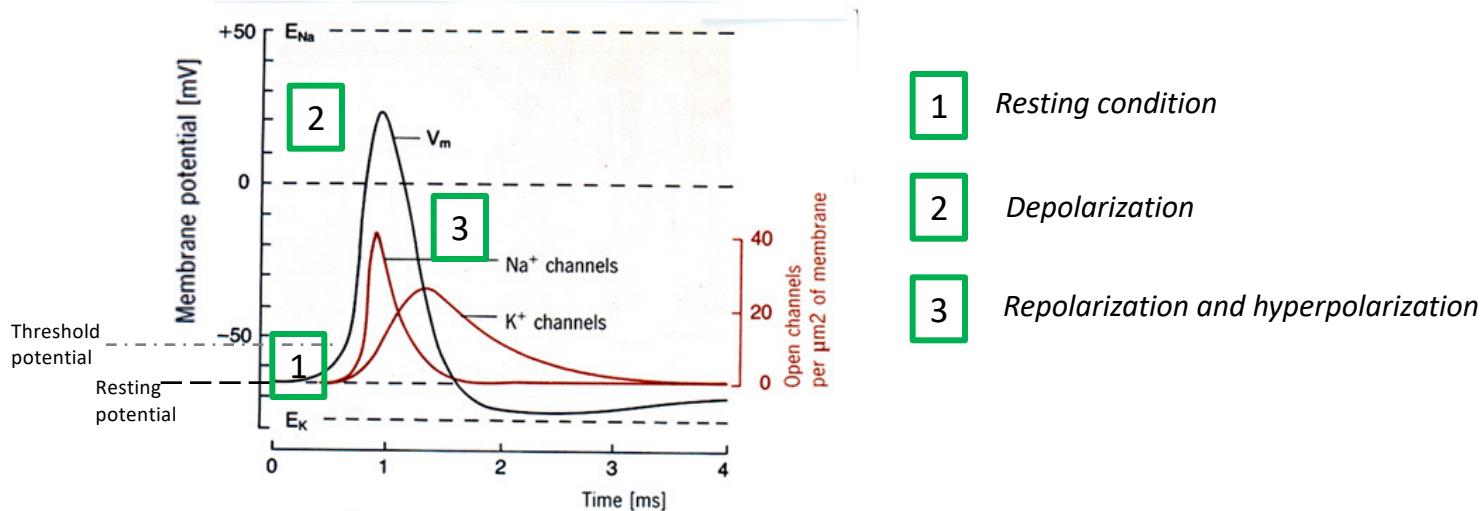


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COMPUTATIONAL NEUROSCIENCE - Part 4 Modelling and Simulations

Neuronal communication: the Action Potential

Neurons communicate through Action Potentials (AP) = change in membrane voltage depending on subcellular ion channel-mediated mechanisms

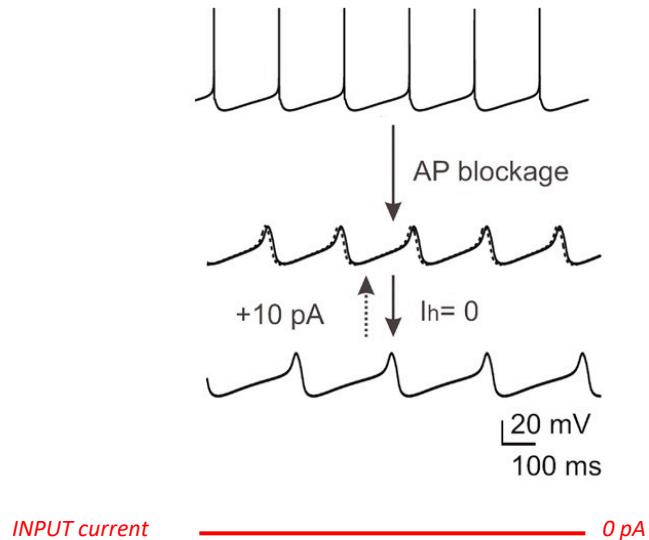


AP can be approximated with SPIKES, the basic units of neuronal coding

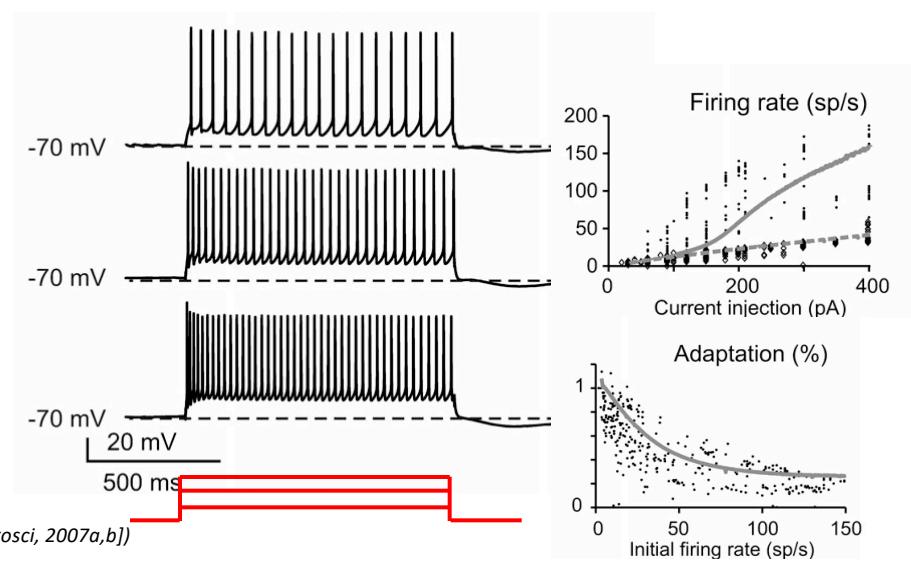
Neuronal communication: single neuron dynamics

Neurons can exhibit different **spiking** patterns (**electroresponsive properties**):

- Autorhythm = spontaneous firing of neurons due to neurons' intrinsic electro-responsiveness
- SubThreshold Oscillations (STO) = sinusoidal oscillations of the membrane potential around the threshold potential value
- Depolarization induced bursting = increased firing rate of neurons following the starting of a depolarizing external stimulation
- Linear current-frequency relationship
- Spike-Frequency Adaptation (SFA) = Decrease in the neuron's firing rate when stimulated with a constant input.



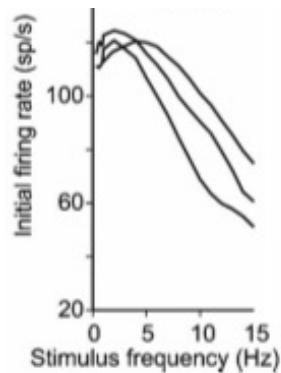
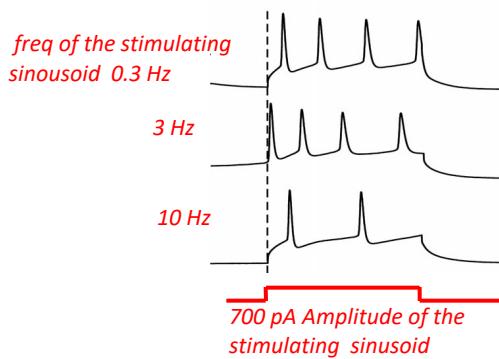
Membrane voltage of a cerebellar Golgi cell (adapted from [Solinas et al, Front Cell Neurosci, 2007a,b])



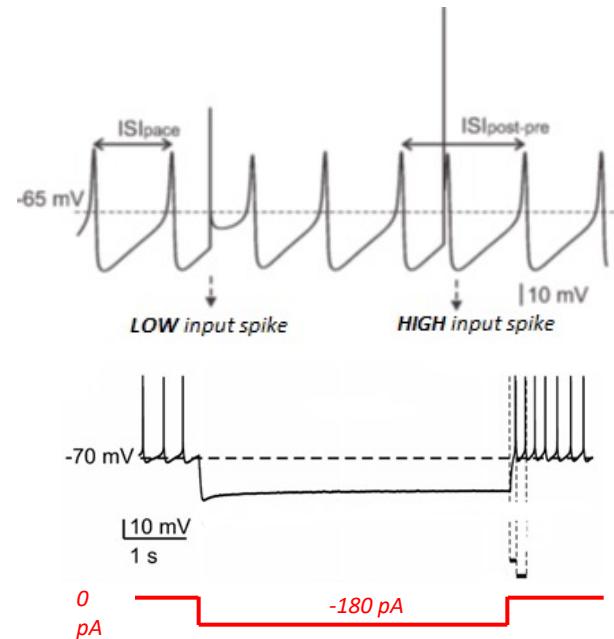
Neuronal communication: single neuron dynamics

Neurons can exhibit different **spiking** patterns
(electroresponsive properties):

- Phase reset
- Post-inhibitory rebound burst = increased firing rate following the end of a negative hyperpolarizing input (amplitude and duration of the negative input are fundamental to cause the rebound burst)
- Resonance = maximum firing response of a neuron at a preferred frequency of the input current stimulus



Initial firing rate is the inverse of the ISI between the first two spikes after the stimulus



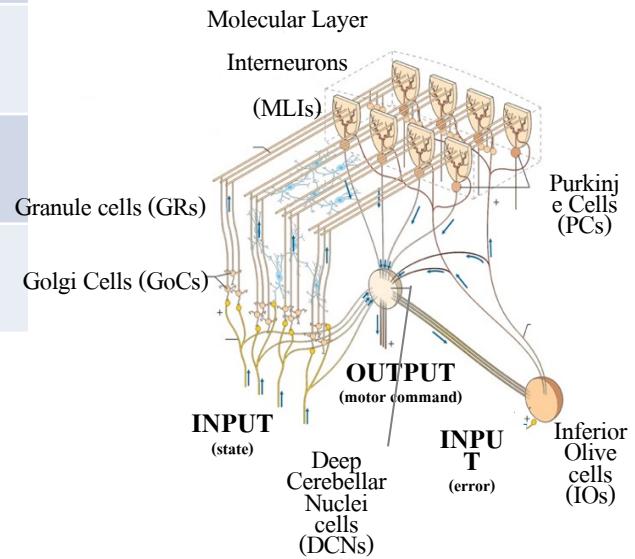
FUNDAMENTAL for:

- ✓ Generating network dynamics
- ✓ Noise filtering
- ✓ Plasticity enhancement
- ✓ Communication within and among brain areas

Cerebellar single neuron dynamics

<u>CEREBELLAR CELLS</u>	Auto-rhythm	Sub-Threshold Oscillations	Depolarization-induced burst	SFA	Phase reset	Post-inhibitory rebound burst	Resonance
Golgi Cell	✓ 5-15 Hz	✓	✓	✓	✓	✓	✓ (θ band)
Granule Cell	-	✓	-	-	-	-	✓ θ band)
Purkinje Cell	✓ 40-80 Hz	-	✓	-	-	-	-
Molecular Layer Interneurons	✓ 10-20 Hz	-	-	-	-	-	-
Deep Cerebellar Nuclei	✓ 10-30 Hz	-	✓	✓	-	✓	-
Inferior Olive cells	-	✓ 1-4 Hz	n.a.	n.a.	✓	-	-

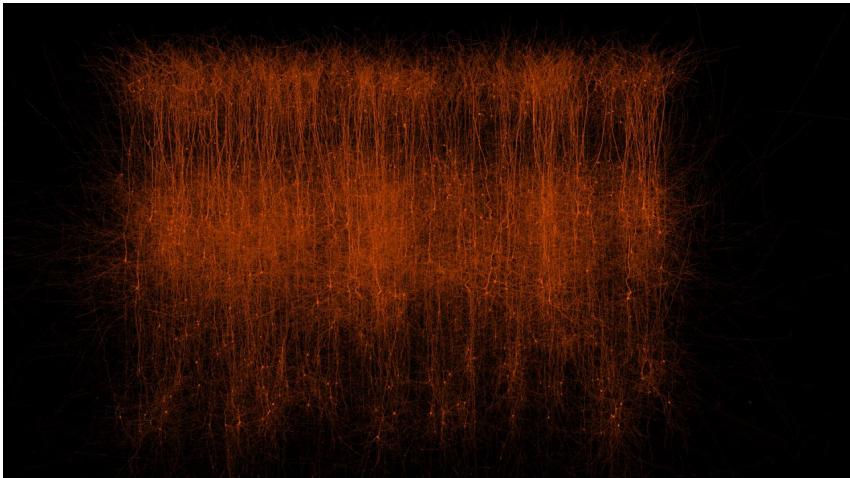
θ band = 1-4 Hz; fundamental for brain oscillations and communication with the cerebral cortex



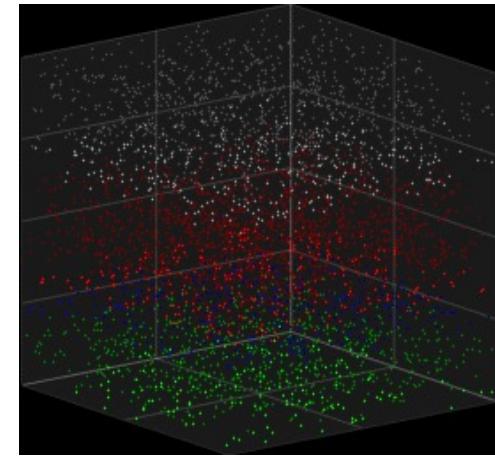
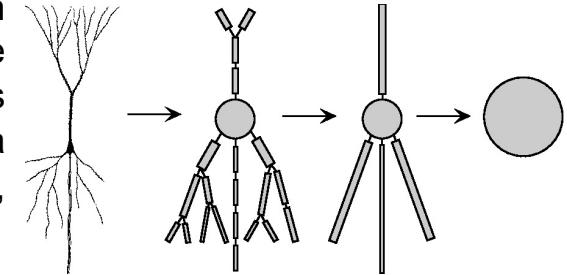
Modelling single neurons

Different levels of morphological detail: from multi-compartment to point neuron models

Multi-compartment neuron models describe the activity of each neuron element (dendrites, axons, ...) taking into account morphological features. Example from the neo-cortex microcircuit [Markram et al., *Cell Reports*, 2015]:



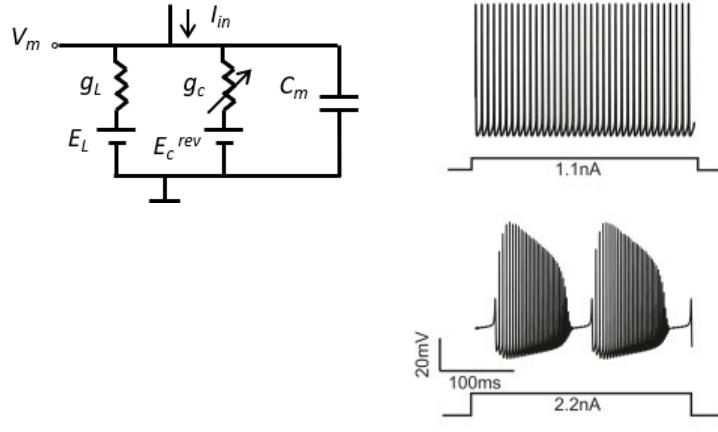
Point neuron models describe the activity of neurons as collapsed in a single point, neglecting compartment differences and morphological features. They represent more the computational properties of neurons, than the electrical activity and its spatial distribution



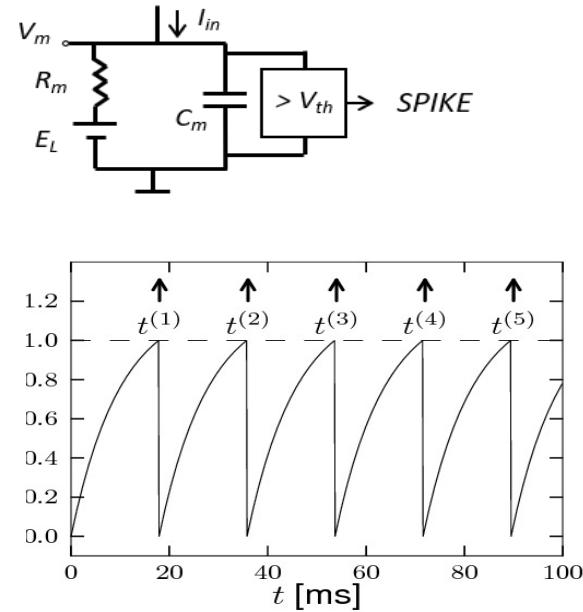
Modelling single neurons

Different levels of electrical detail: Hodgkin-Huxley (HH) and Leaky Integrate-and-Fire (LIF)

HH: membrane potential V_m computed considering the resting potential (E_L) and the contribution of each membrane **ion channel** (represented by the conductance g_c and reversal potential E_c^{rev}).



LIF: Only **passive** membrane properties are considered (capacitance C_m and resistance R_m). The output is a spike train, corresponding to time instants of threshold overcoming



Modelling the neuron: HH Compartmental models

The above HH description is for a single compartment. If one wants to describes propagation of the spike in the axon, one has to couple the compartments like we did in the cable equation. The equation holds for each compartment in the axon.

HIGH PERFORMING COMPUTERS (CINECA)

Stefano Masoli, Sergio Solinas, and Egidio D'Angelo

Front Cell Neurosci. 2015; 9: 47.

In each compartment, membrane voltage was obtained as the time integral of the equation (Yamada, [1989](#)):

$$\frac{dV}{dt} = -\frac{1}{C_m} * \left\{ \sum [g_i * (V - V_i)] + i_{inj} \right\}$$

Adjacent compartments communicated through an internal coupling resistance (Diwakar et al., [2009](#)).

Modelling the Purkinje Cell (PC): HH Compartmental models

Section name	Diameter (μm)	Length (μm)	Nº sections
Dendrites	0.67–9.22	1–10	1599
Soma	29.8	29.8	1
AIS Axon Initial Segment	0.97	17	1
ParaAIS	0.97	4	1
Myelin	0.73	100	4
Ranvier Nodes	0.73	4	3
Collateral	0.6	100	2

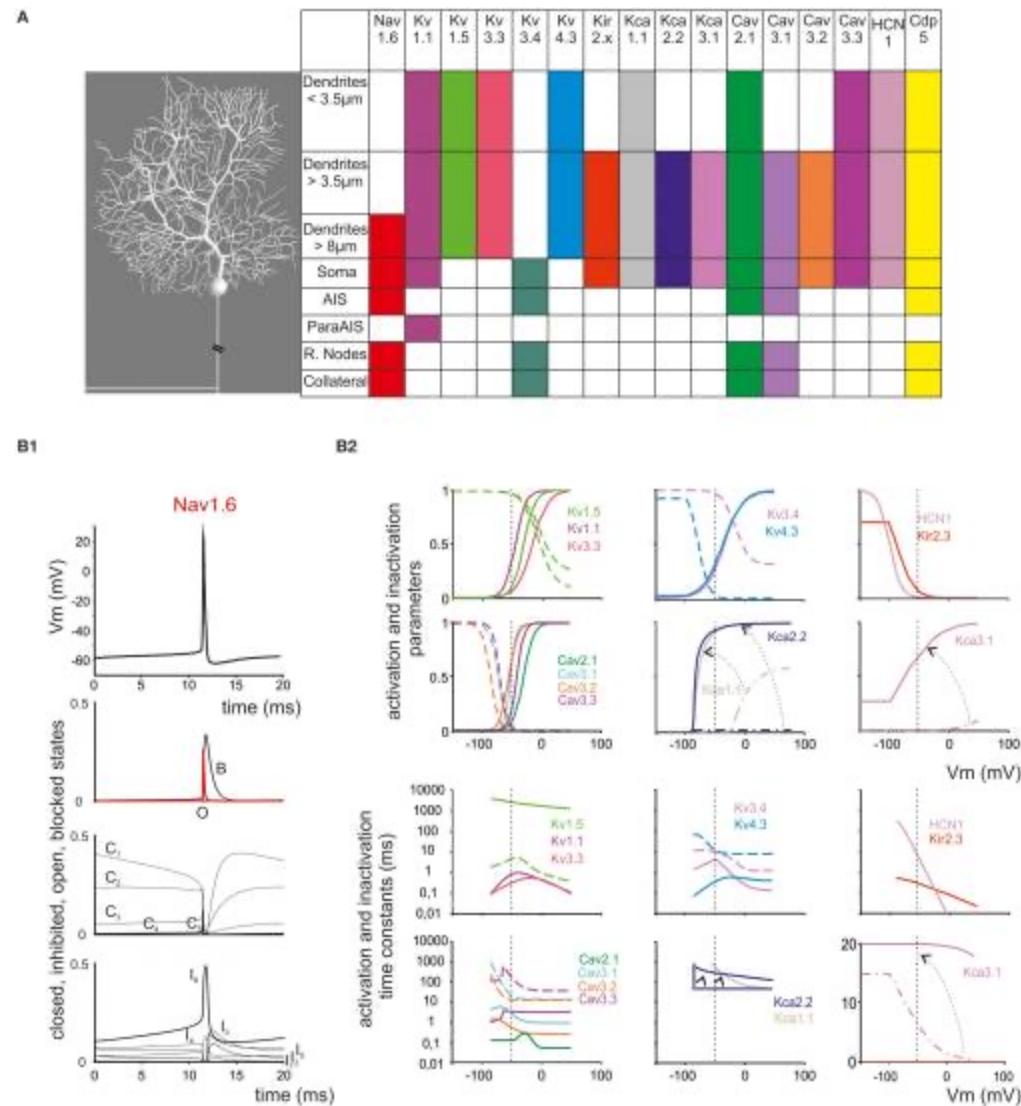


Table 1 -Electrotonic compartments in the PC model.

The table shows the sections of the PC model along with their number, diameter and length.

Modelling PC: HH Compartmental models

Table 2

Ionic mechanisms in the PC model: I.

The table shows ionic channel localization, maximum conductance and reversal potential. Gating equations were written either in Hodgkin-Huxley (HH) style or Markovian style according to indicated references.

Conductance/Location	Gmax (S/cm^2)	Erev (mV)	Description of channel (H.H or Markovian)	References
Na CHANNEL				
Nav1.6	Dendrites	0.016	60	Markovian 13 states
	Soma	0.214		Raman and Bean, 2001
	AIS	0.5		
	Nodes	0.03		
	Collateral	0.03		

Modelling PC: HH Compartmental models

Conductance/Location	Gmax (S/cm ²)	Erev (mV)	Description of channel (H.H or Markovian)	References
K CHANNELS				
Kv1.1	Dendrites	0.0012	-88	HH Akemann and Knopfel, 2006
	Soma	0.002		
	ParaAIS	0.01		
Kv1.5	Dendrites	$1.3 \cdot 10^{-4}$	-88	HH Courtemanche et al., 1998
Kv3.3	Dendrites	0.01	-88	HH Akemann and Knopfel, 2006
Kv3.4	Soma	0.05	-88	HH Raman and Bean, 2001 ; Khalil et al., 2003
	AIS	0.01		
	Nodes	0.01		
	Collateral	0.02		
Kv4.3	Dendrites	0.001	-88	HH Diwakar et al., 2009
Kir2.x	Dendrites	0.00001	-88	HH Diwakar et al., 2009
	Soma	0.00003		

Modelling PC: HH Compartmental models

Conductance/Location		Gmax (S/cm ²)	Erev (mV)	Description of channel (H.H or Markovian)	References
Ca DEPENDENT K CHANNELS					
Kca1.1	Dendrites	3.5×10^{-2}	-88	Markovian	Anwar et al., 2010
	Soma	0.01			
Kca2.2	Dendrites	1×10^{-3}	-88	Markovian	Solinas et al., 2007a,b
	Soma	1×10^{-3}			
Kca3.1	Dendrites	0.002	-88	HH	Rubin and Cleland, 2006
	Soma	0.01			
Ca CHANNELS					
Cav2.1	Dendrites	1×10^{-3}	137.5	HH	Swensen and Bean, 2005 ; Anwar et al., 2010
	Soma	2.2×10^{-4}			
	AIS	2.2×10^{-4}			
	Nodes	2.2×10^{-4}			
	Collateral	2.2×10^{-4}			

Modelling PC: HH Compartmental models

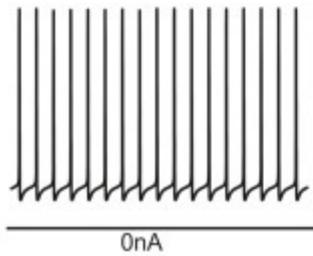
Conductance/Location Ca CHANNELS		Gmax (S/cm ²)	Erev (mV)	Description of channel (H.H or Markovian)	References
Cav2.1	Dendrites	$1*10^{-3}$	137.5	HH	Swensen and Bean, 2005 ; Anwar et al., 2010
	Soma	$2.2*10^{-4}$			
	AIS	$2.2*10^{-4}$			
	Nodes	$2.2*10^{-4}$			
	Collateral	$2.2*10^{-4}$			
Cav3.1	Dendrites	$5*10^{-6}$	137.5	HH	Anwar et al., 2010
	Soma	$7*10^{-6}$			
	AIS	$1*10^{-5}$			
	Nodes	$1*10^{-5}$			
	Collateral	$1*10^{-5}$			
Cav3.2	Dendrites	0.0012	137.5	HH	Huguenard and McCormick, 1992
	Soma	0.0008			
Cav3.3	Dendrites	0.0001	137.5	HH	Xu and Clancy, 2008
	Soma	0.0001			

Modelling PC: HH Compartmental models

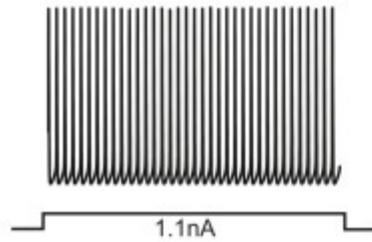
Conductance/Location	Gmax (S/cm ²)	Erev (mV)	Description of channel (H.H or Markovian)	References
MIXED CATIONIC CHANNEL				
HCN1	Dendrites	0.000004	-34.4	HH Angelo et al., 2007 ; Larkum et al., 2009
	Soma	0.0004		
CALCIUM BUFFER—PUMPS DENSITY				
Ca Buffer	Dendrites	$2 \cdot 10^{-8}$	Markovian	Anwar et al., 2010
	Soma	$5 \cdot 10^{-8}$		
	AIS	$5 \cdot 10^{-8}$		
	Nodes	$5 \cdot 10^{-7}$		
	Collateral	$5 \cdot 10^{-8}$		

Modelling PC: HH Compartmental models

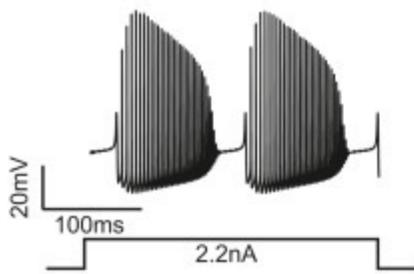
A
Auto-rhythmic properties no current injection



Simple spikes: low somatic current injection

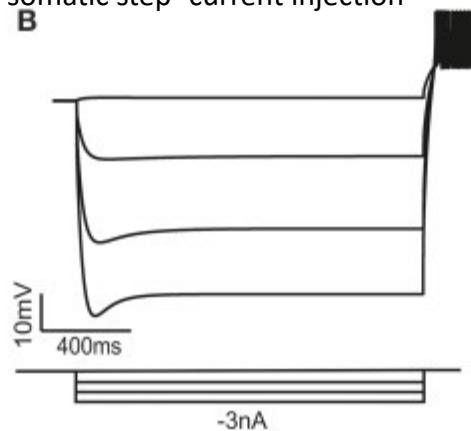


Complex spikes: high somatic current injection



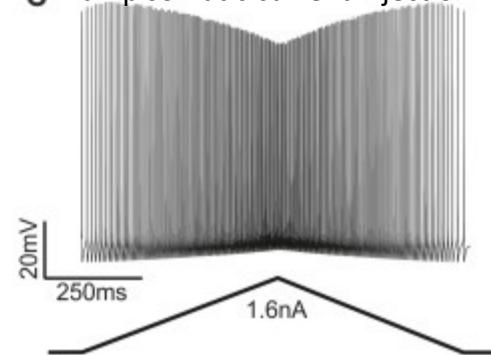
sag and rebound depolarization: Negative somatic step -current injection

B



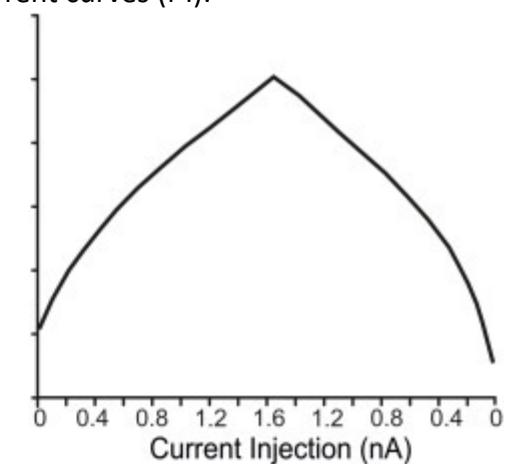
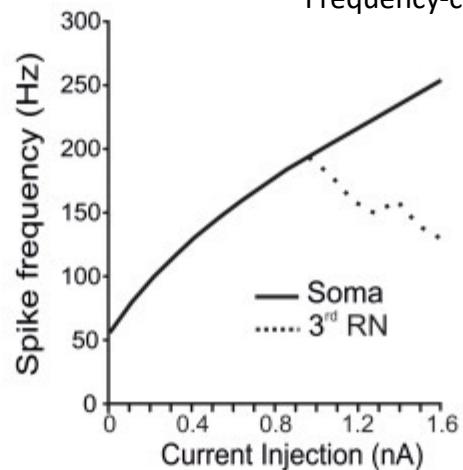
Frequency modulation:
C Ramp somatic current injection

C



D

Frequency-current curves (f-I):



ramp current induces a linear frequency modulation of Soma (up to about 300Hz while RNs are unable to sustain firing frequencies above 200 Hz)

up and down ramp current non perfectly symmetrical

Modelling single neurons: the Leaky Integrate and Fire neuron

In the Leaky Integrate-and-Fire (LIF) neuron, the subthreshold dynamics of the membrane potential is modelled through a single passive term:

Membrane potential dynamics

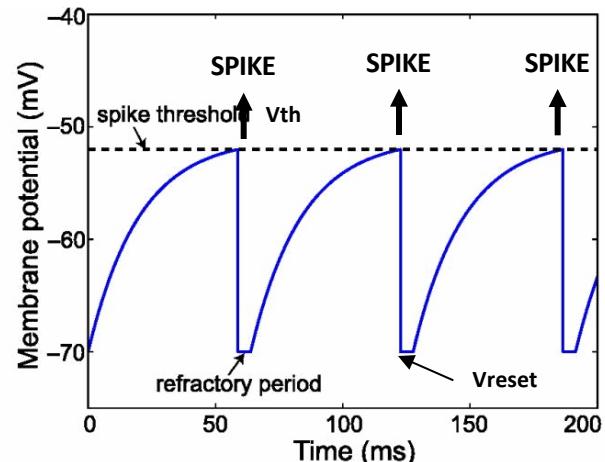
$$\rightarrow \tau_m \frac{dV_m(t)}{dt} = -(V_m(t) - E_L) + R_m \cdot I_{in}(t)$$

Spike condition

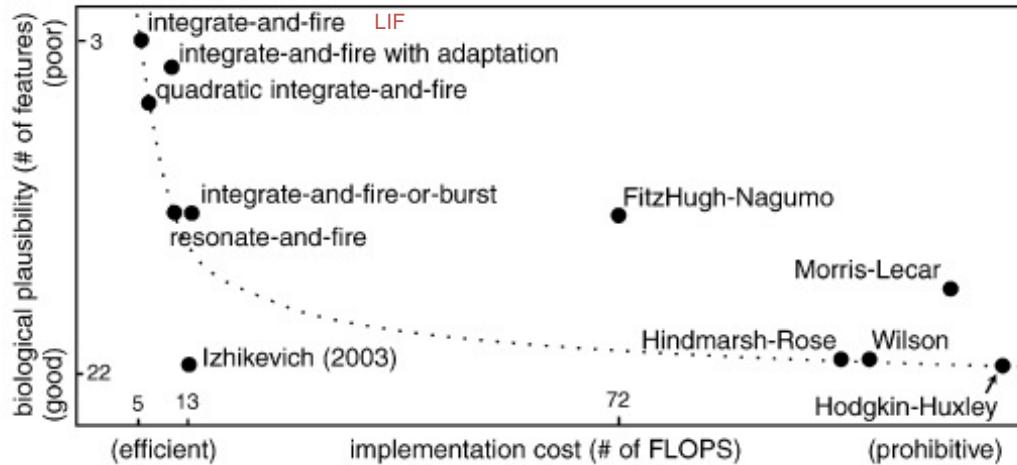
$$\rightarrow \text{If } V_m > V_{th}, \text{ then } V_m = V_{reset}$$

- τ_m is the membrane time constant ($\tau_m = R_m \cdot C_m$, where R_m and C_m are the membrane resistance and capacitance, respectively), and it accounts for how fast the V_m curve increases
- E_L is the resting potential and it represents the steady-state value of V_m in absence of external input current
- I_{in} is the input current.

Action potentials are approximated as **single spike instants**: whenever V_m reaches a firing threshold V_{th} , the membrane potential is reset to a fixed value V_{reset} . After the spike, V_m remains at V_{reset} value (constant) during the refractory period and it is not possible to emit spikes.



Modelling single neurons: biological plausibility vs computational load



[Izhikevich, *IEEE Trans Neural Networks*, 2003]

Compromise between biological plausibility and implementation cost:

- HH multi-compartment models with morphology representation ✓ biological plausibility ✗ computational load
- LIF point neuron models ✗ biological plausibility ✓ computational load
- Multi-dimensional LIF models:
 - Izhikevich (non linear)
 - Adaptive Exponential Leaky Integrate and Fire (LIF) model (non linear)
 - Generalized LIF (linear)
- Fitting with experimental traces for OPTIMIZATION – also optimization has a cost!

Multi-dimensional LIF models: Izhikevich neuron

$$\begin{cases} \frac{dV_m(t)}{dt} = 0.04 * V_m^2(t) + 5 * V_m] + 150 - u(t) + 1 \\ \frac{du(t)}{dt} = a * b(V_m(t) - u(t)) \end{cases}$$

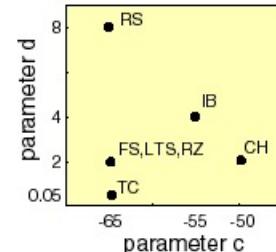
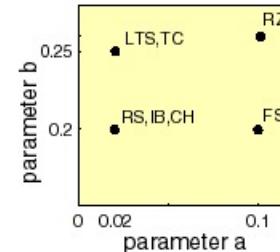
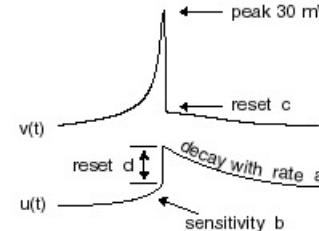
Membrane Potential

Membrane Recovery variable $u(t)$

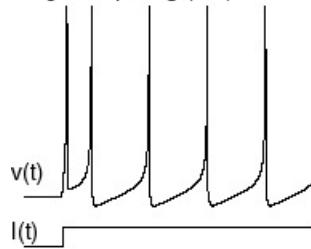
If $V(t) > 30mV \rightarrow$ Spikes.

$$\begin{cases} V_m(t+1) = c \\ u(t+1) = u(t) + d \end{cases}$$

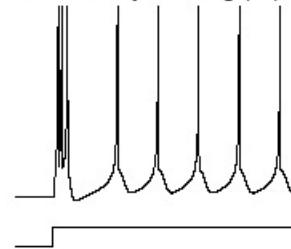
$v' = 0.04v^2 + 5v + 140 - u + 1$
 $u' = a(bv - u)$
if $v = 30$ mV,
then $v \leftarrow c$, $u \leftarrow u + d$



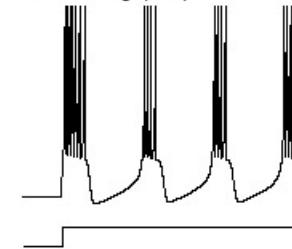
regular spiking (RS)



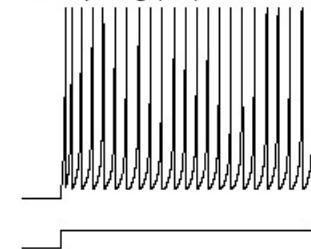
intrinsically bursting (IB)



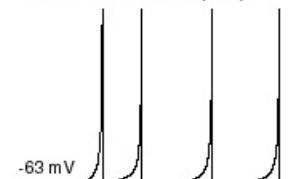
chattering (CH)



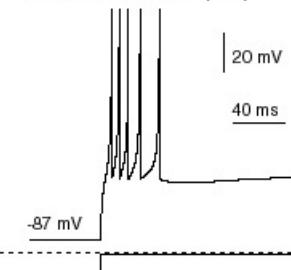
fast spiking (FS)



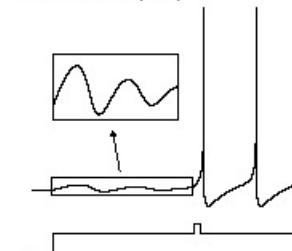
thalamo-cortical (TC)



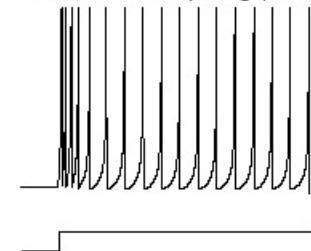
thalamo-cortical (TC)



resonator (RZ)



low-threshold spiking (LTS)



[Izhikevich, IEEE Trans Neural Networks, 2003]

Multi-dimensional LIF models: Adaptive Exponential LIF neuron

The model:

$$\begin{cases} C_m \cdot V_m'(t) = -g_L \cdot (V_m(t) - E_L) + g_L \cdot \Delta_T \cdot e^{\frac{V_m(t)-V_{th}}{\Delta_T}} - w(t) + I_m(t) & V_m(t) \text{ Membrane Potential} \\ \tau_w \cdot w'(t) = a \cdot (V(t) - E_L) - w(t) & w(t) \text{ Adaptive current} \end{cases}$$

If $V_m(t) \geq V_{th} \rightarrow SPIKE:$

$$\begin{cases} V_m(t+1) = V_r \\ w(t+1) = w(t) + b \end{cases}$$

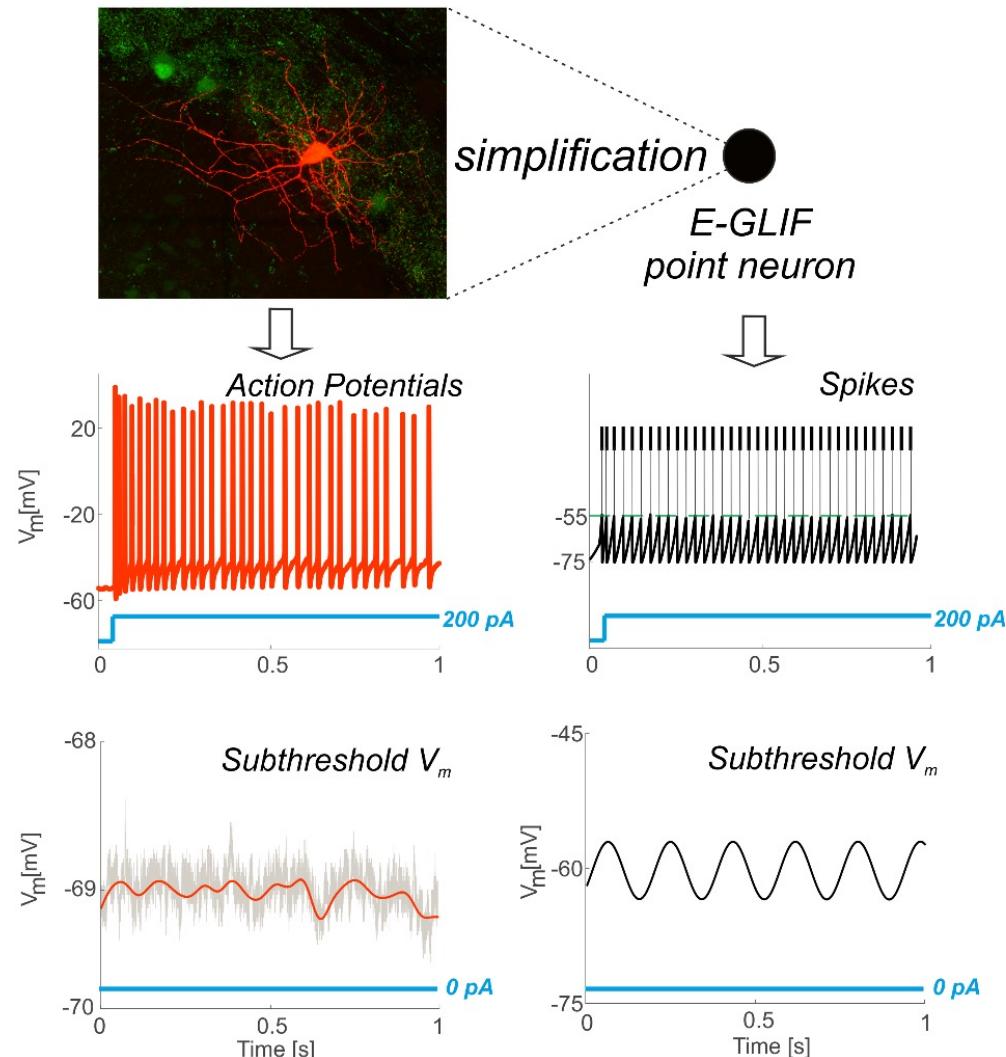
Properties:

- multiple electroresponsive properties based on parameter values
- replacement of the strict voltage threshold by a more realistic smooth spike initiation zone.
- subthreshold resonances or adaptation as in the Izhikevich model.

[Brette and Gerstner, *J Neurophysiol*, 2005]

Towards a unified point neuron model for cerebellar neurons

- Aim: a model able to reproduce all the cerebellar electroresponsive mechanisms, while keeping:
 - **Neurophysiological realism** (elements in the model \leftrightarrow biophysical mechanisms)
 - **Low computational load** (\rightarrow linear and analytically solvable, to increase simulation step without loosing precision within large-scale Spiking Neural Networks - SNNs)
 - **Generalized features** (not fitting on single traces)
 - Different **sets of parameters** for different cells, reproducing **all** the electrophysiological properties of each population, i.e. **spike patterns** more than sub/supra-threshold mechanisms (since within SNN)



Extended-Generalized LIF neuron model (E-GLIF)

Membrane potential V_m

Adaptive current I_{adapt}

Spike-triggered depolarizing current I_{dep}

Biological quantities/parameters

Artificial parameter

$$\begin{cases} V'_m(t) = \frac{1}{C_m} \left(\frac{C_m}{\tau_m} (V_m(t) - E_L) + I_{stim} + I_e + I_{dep}(t) - I_{adapt}(t) \right) \\ I'_{adapt}(t) = k_{adapt} (V_m(t) - E_L) - k_2 I_{adapt}(t) \\ I'_{dep}(t) = -k_1 I_{dep}(t) \end{cases}$$

Refractory period T_{ref}

Stochasticity in spike generation

$$\begin{cases} t_{spk} \notin \Delta t_{ref} \\ rng < (1 - e^{-\lambda(t_{spk})t_{spk}}) \end{cases} \quad \lambda(t) = \lambda_0 e^{\frac{V_m(t) - V_{th}}{\tau_V}}$$

Updates at spike event

$$\begin{cases} V_m(t_{spk}) \leftarrow V_r \\ I_{dep}(t_{spk}) \leftarrow A_1 \\ I_{adapt}(t_{spk}) \leftarrow I_{adapt}(t_{spk} - 1) + A_2 \end{cases}$$

I_{stim} = external stimulation current;

C_m = membrane capacitance;

τ_m = membrane time constant;

E_L = resting potential;

I_e = endogenous current;

k_{adapt}, k_2 = adaptation constants;

k_1 = I_{dep} decay rate;

V_{th} = threshold potential;

λ_0, τ_V = escape rate parameters;

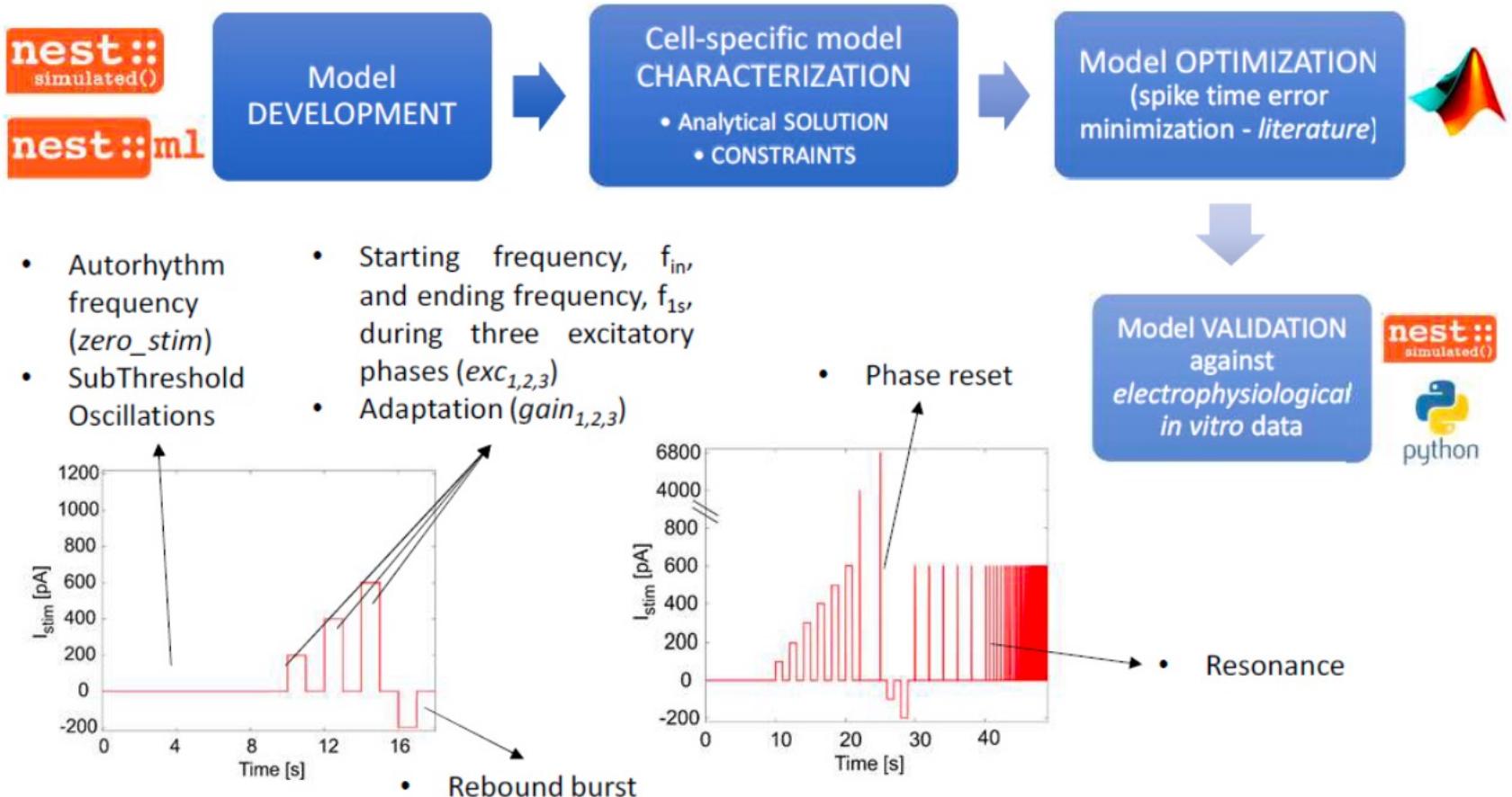
t_{spk}^+ = time instant immediately following the spike

V_r = reset potential;

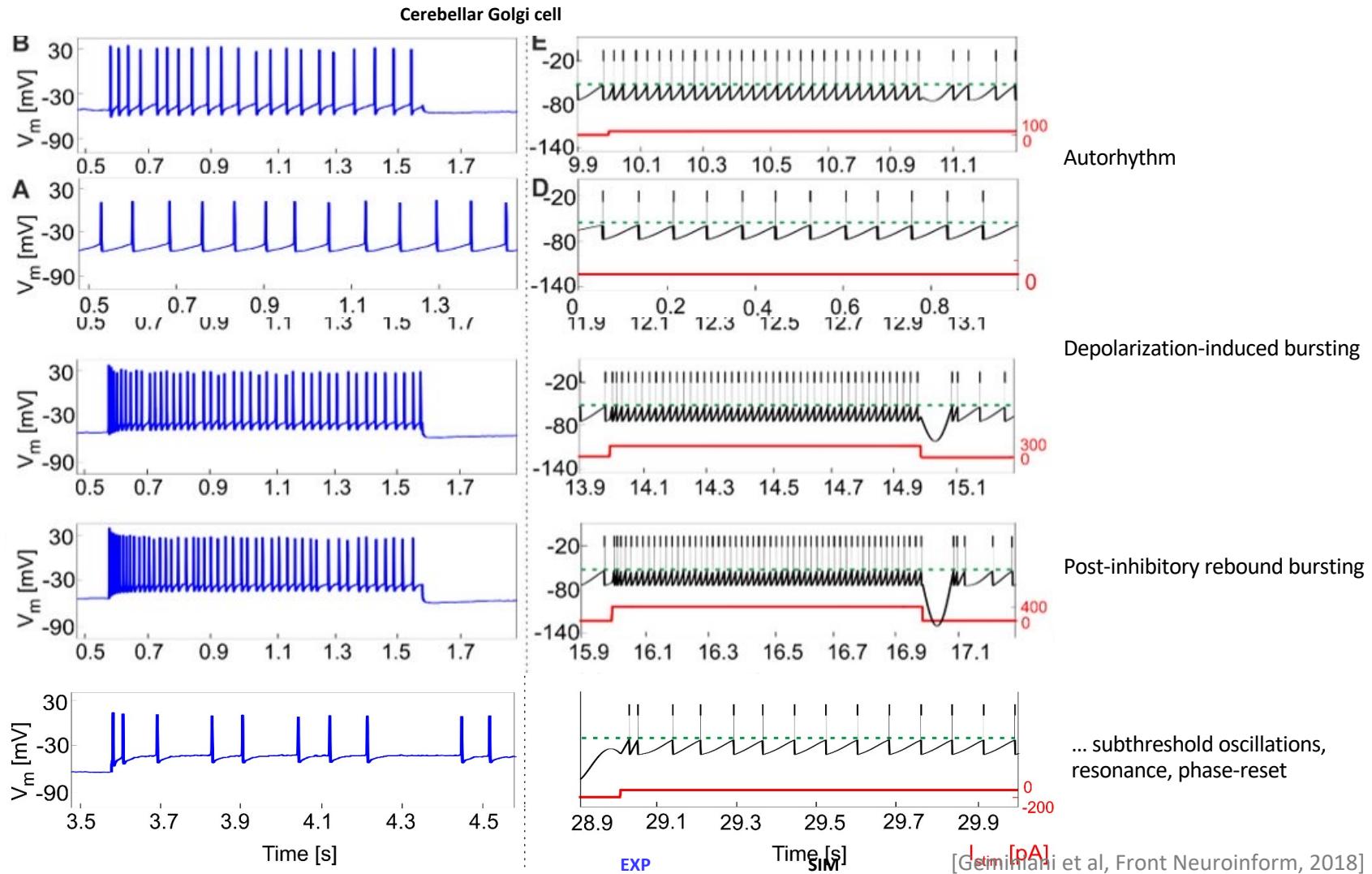
A_2, A_1 = model currents update constants.

[Geminiani et al, *Front Neuroinform*, 2018]

E-GLIF – implementation, optimization and validation

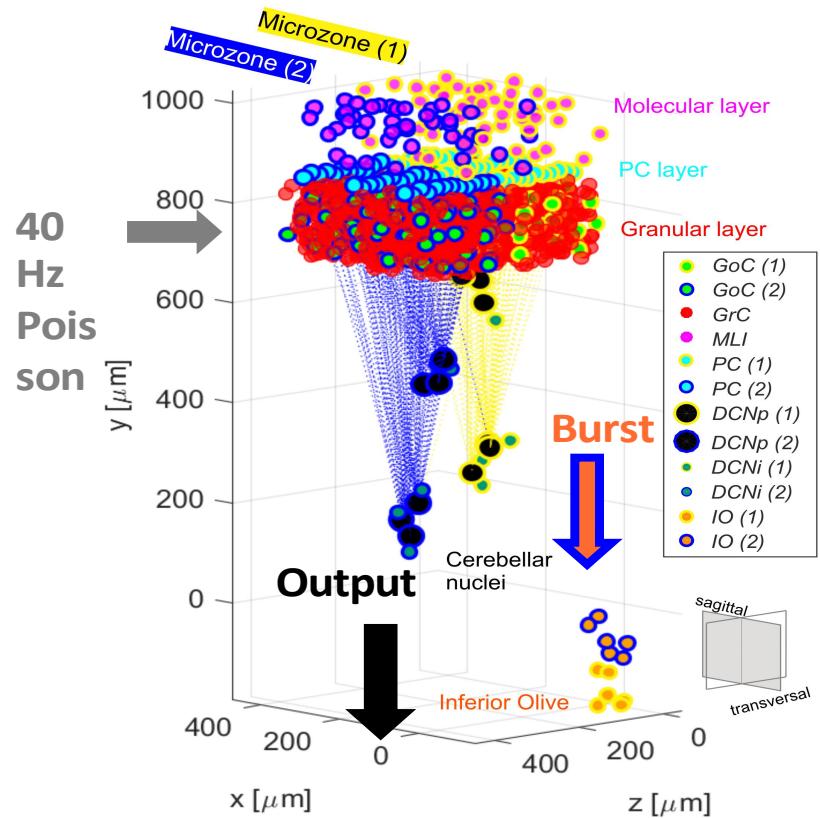
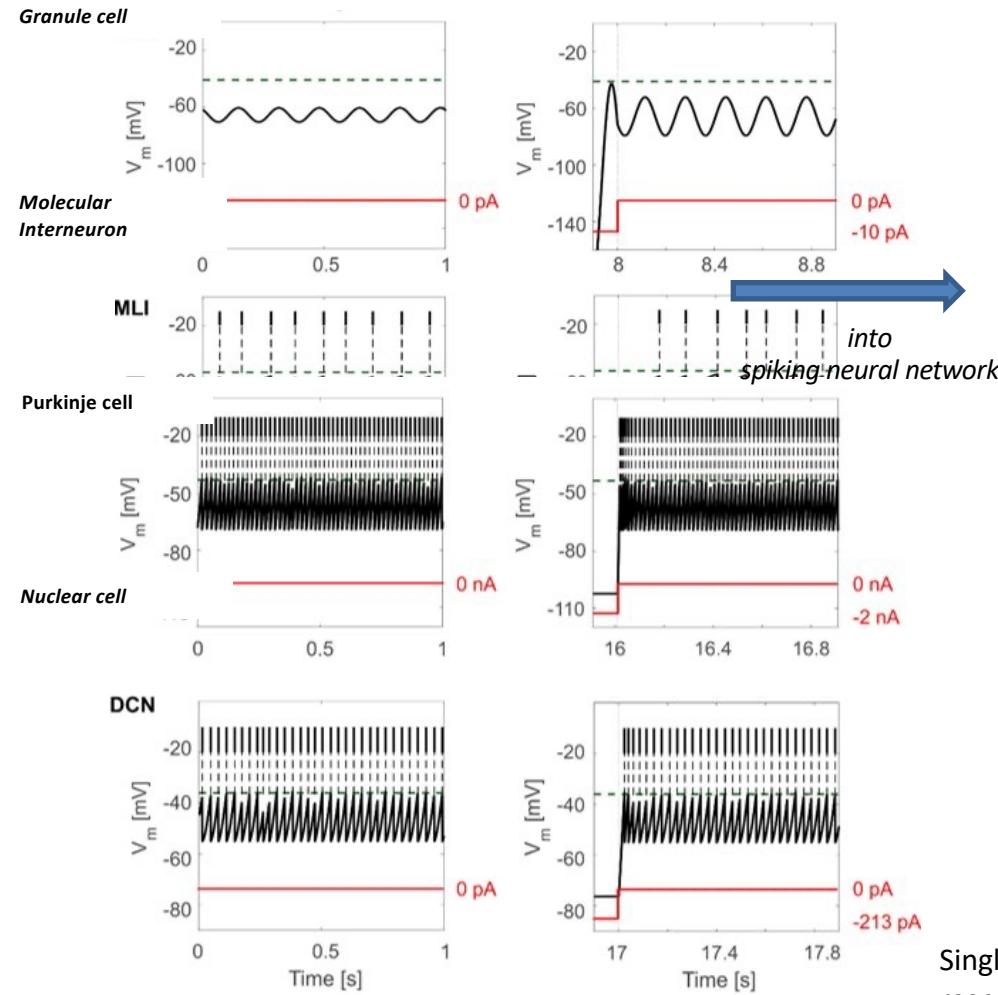


E-GLIF for cerebellar Golgi cells: validation against experimental data



E-GLIF for other cerebellar neurons

Tuned on experimental data for the **other cerebellar neurons**



Single neuron properties propagate to network dynamics: pause-burst responses enhance the time precision of the output

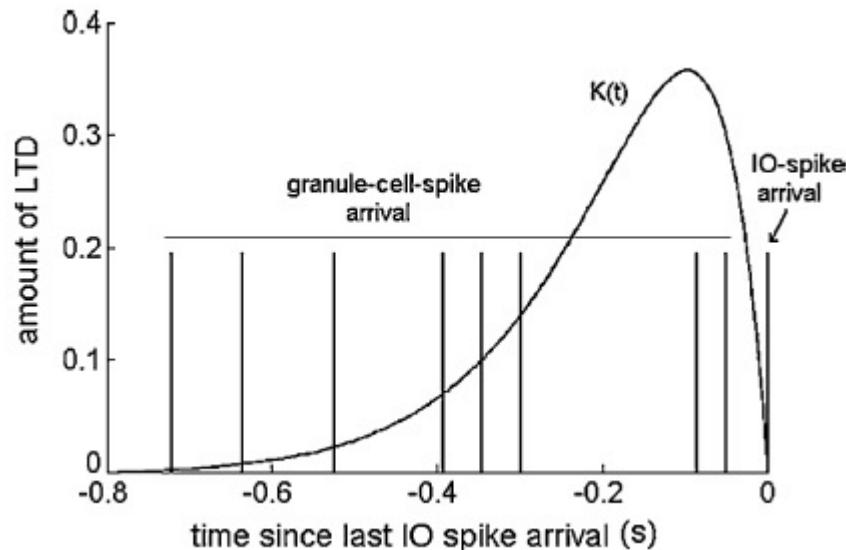
Modelling plasticities (pf-PC)

LTD

$$\Delta w_i = \beta \int_{-\infty}^{t_{IOSPIKE}} k(t_{IOSPIKE} - t) h(t)_{PF_i} dt$$
$$k(t) = e^{-\left(\frac{t-t_0}{\tau}\right)} \sin\left(2\pi\left(\frac{t-t_0}{\tau}\right)\right)^{20}$$
$$h(t) \begin{cases} 1 & \text{if } PF_i \text{ is active at time } t \\ 0 & \text{otherwise} \end{cases}$$

LTP

$$\Delta w_i = \alpha$$



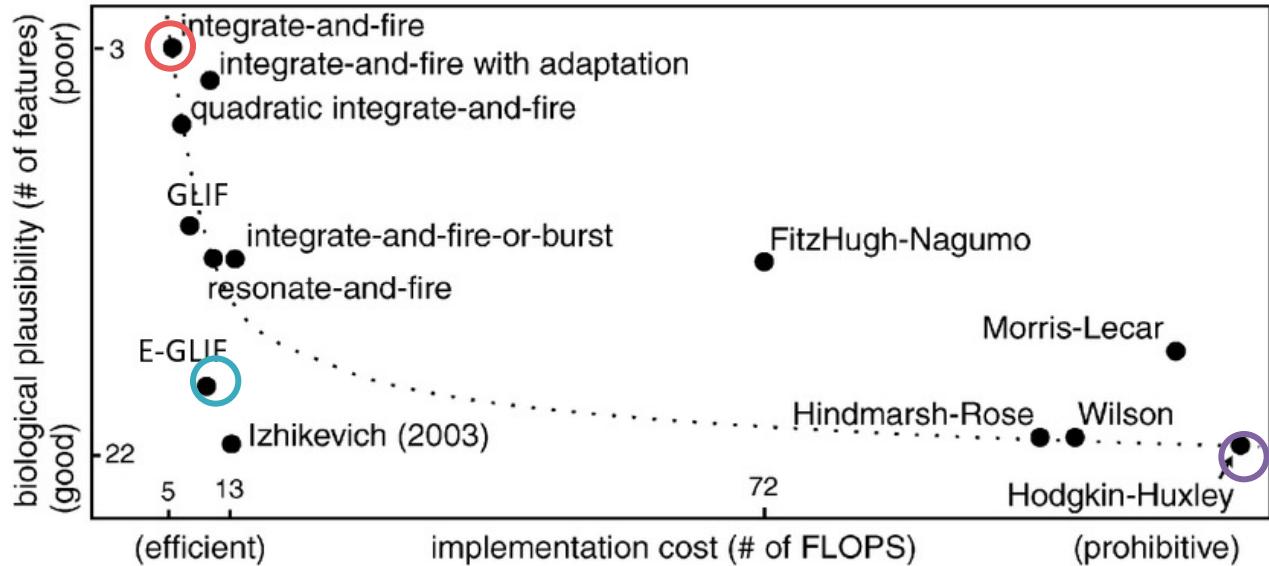


Figure 2.1 Trade-off between biological plausibility and computational load in single neuron models. Basic IF and HH models are at the two extreme cases. GLIF and E-GLIF approximate values have been added. The E-GLIF simplifies the action potential representation, but approaches the Izhikevich and HH precision in terms of firing patterns, outperforming the other multidimensional LIF models. In multi-compartment models, the HH representation remains the standard and amplifies by orders of magnitude both computational capability and biological plausibility. Modified from ([Izhikevich, 2004](#)).

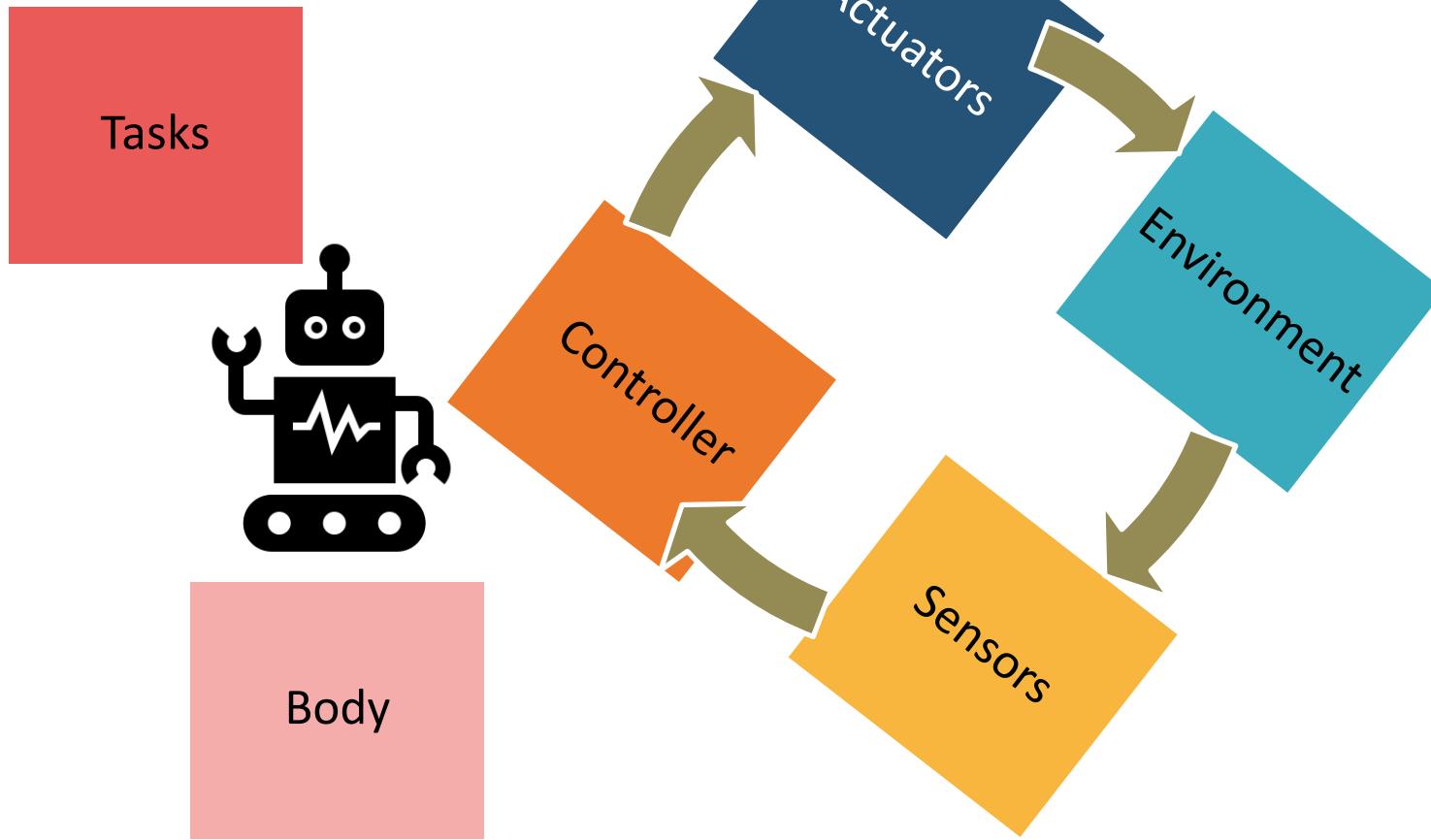


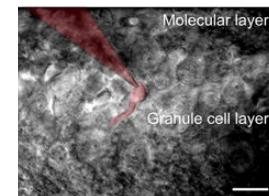
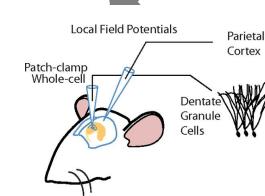
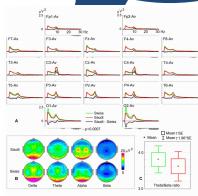
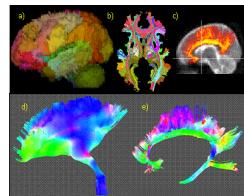
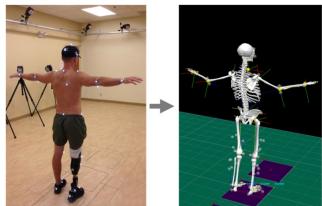
Neuroengineering 2021/22

COMPUTATIONAL NEUROSCIENCE - Part 5 Neurorobotics

Neurorobotics

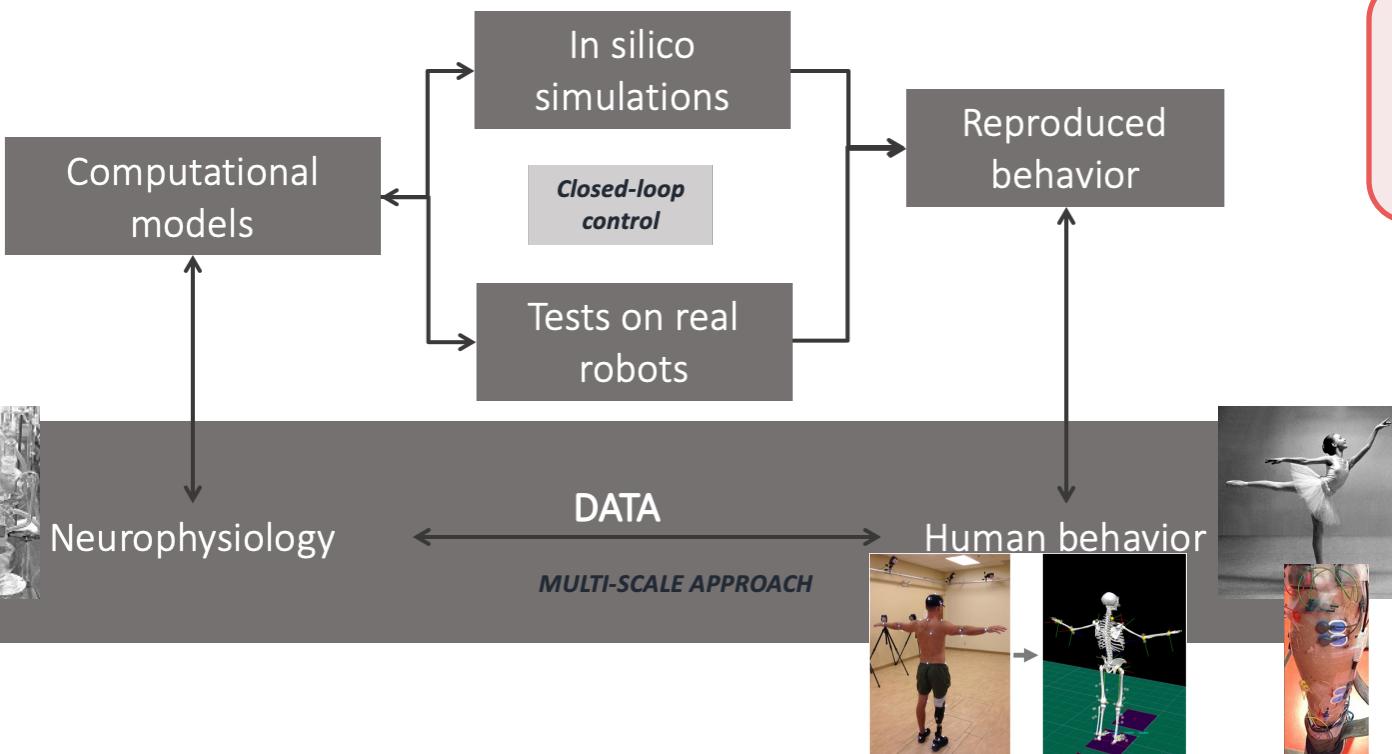
Human Brain Project





Approaches to neurorobotics design

Human Brain Project



D'Angelo et al. Funct. Neurol 2013

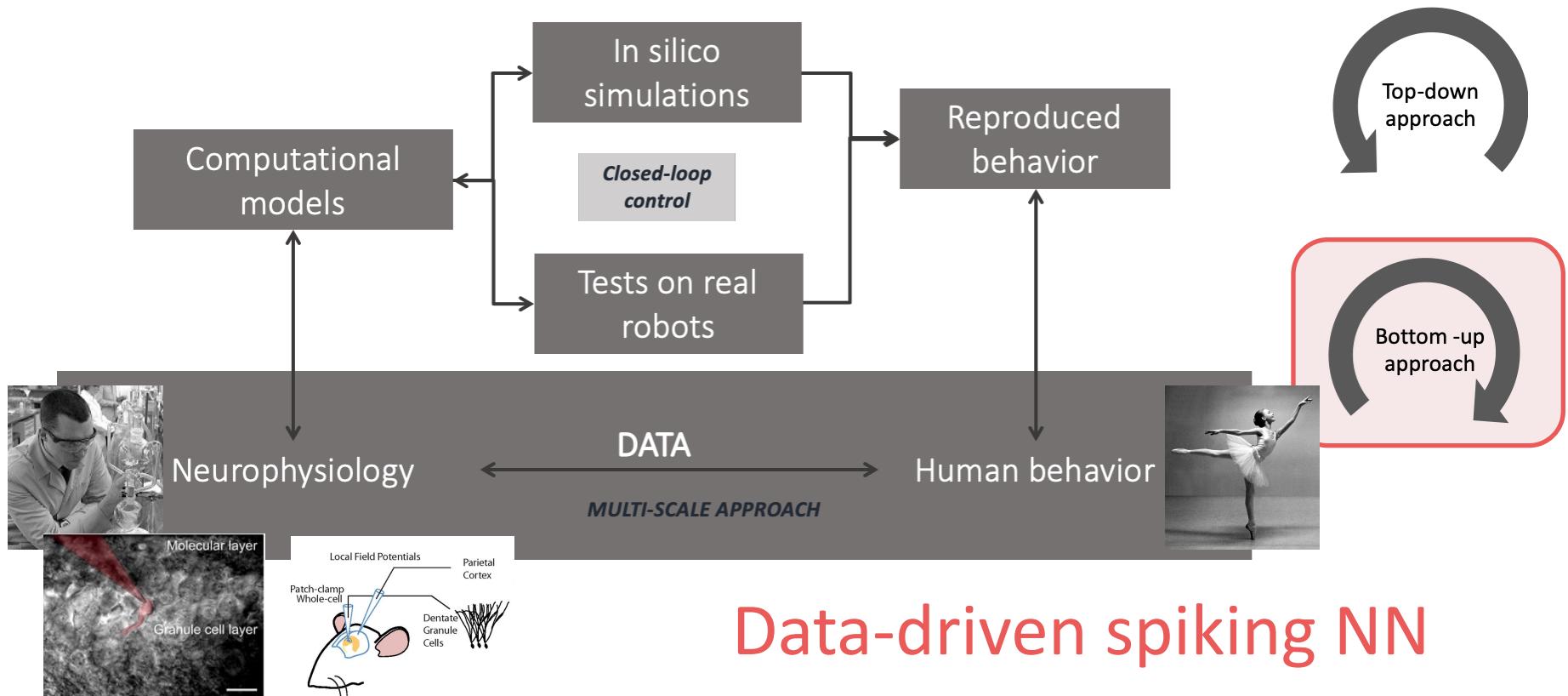
D'Angelo et al. Front. Cell. Neuroscience, 2016

Approaches to neurorobotics design

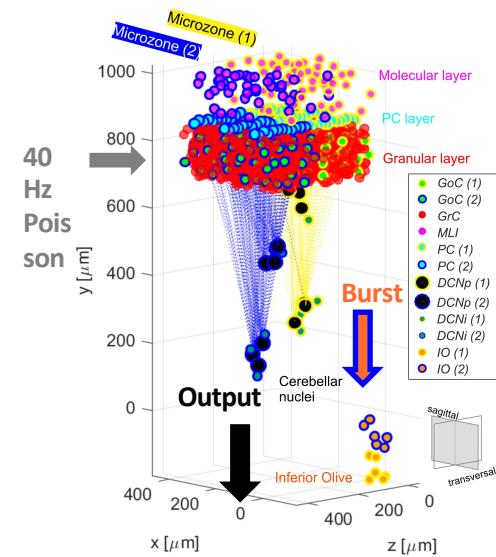
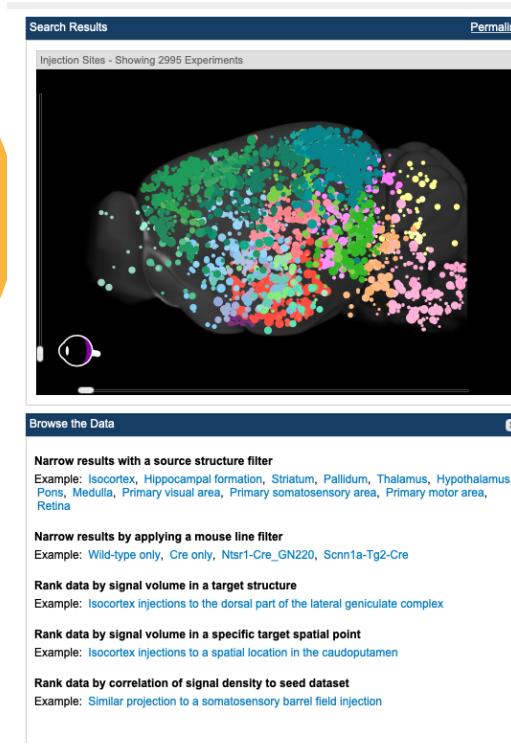
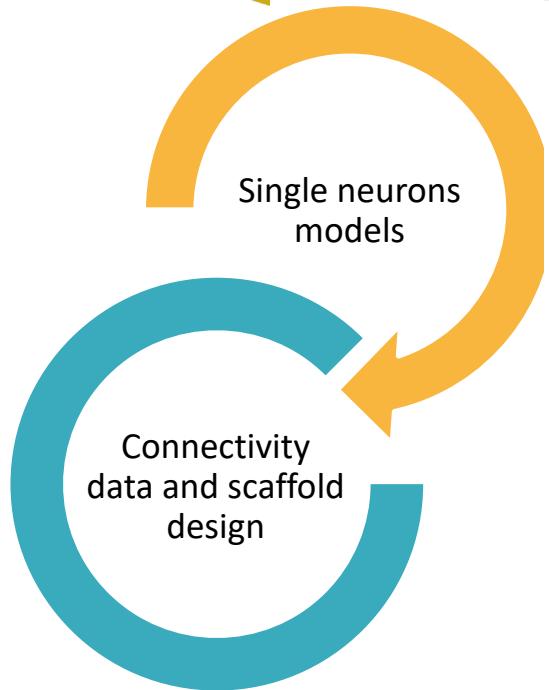
Human Brain Project

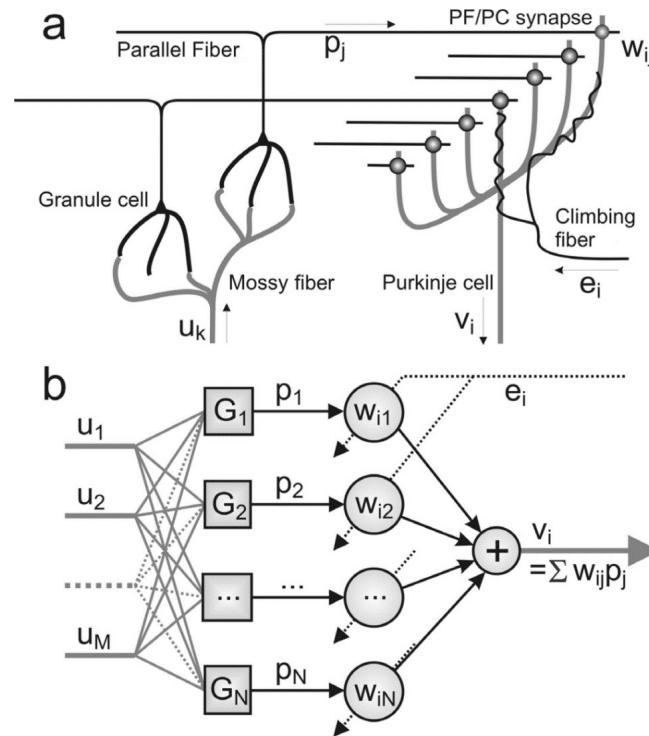
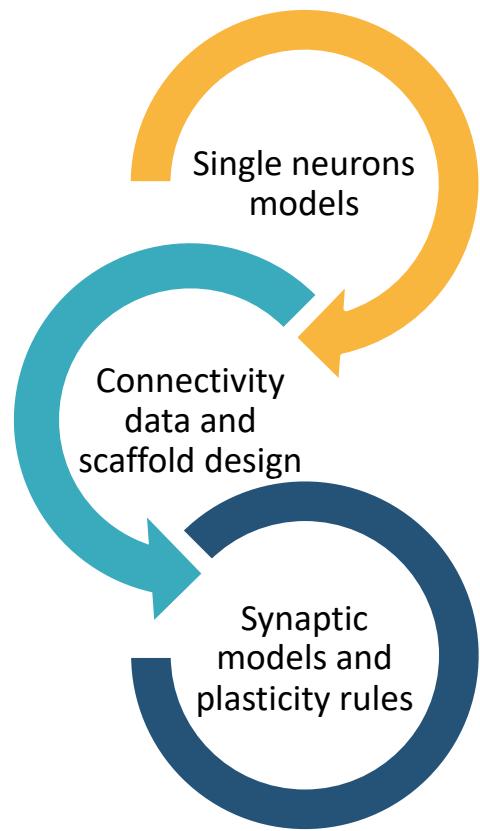


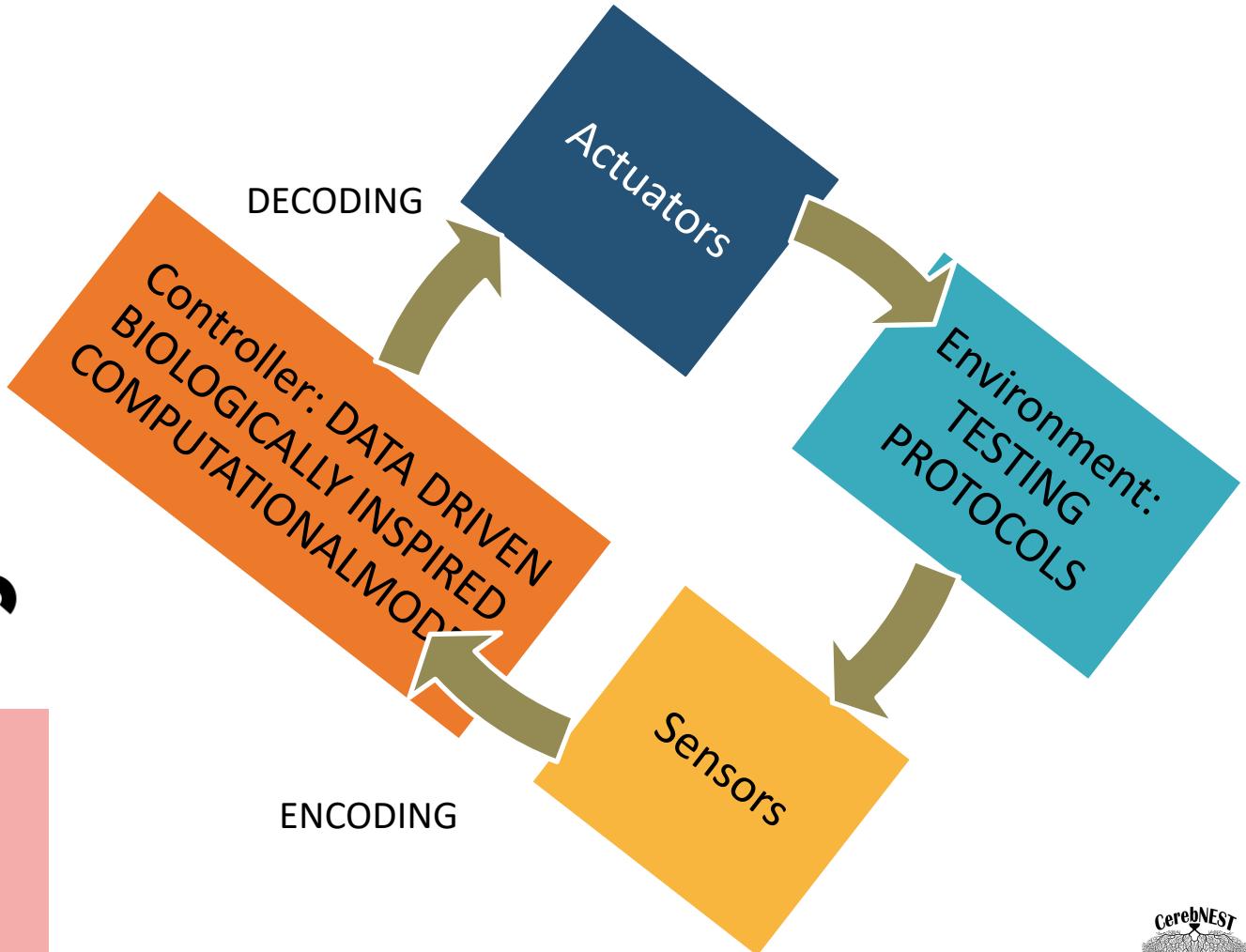
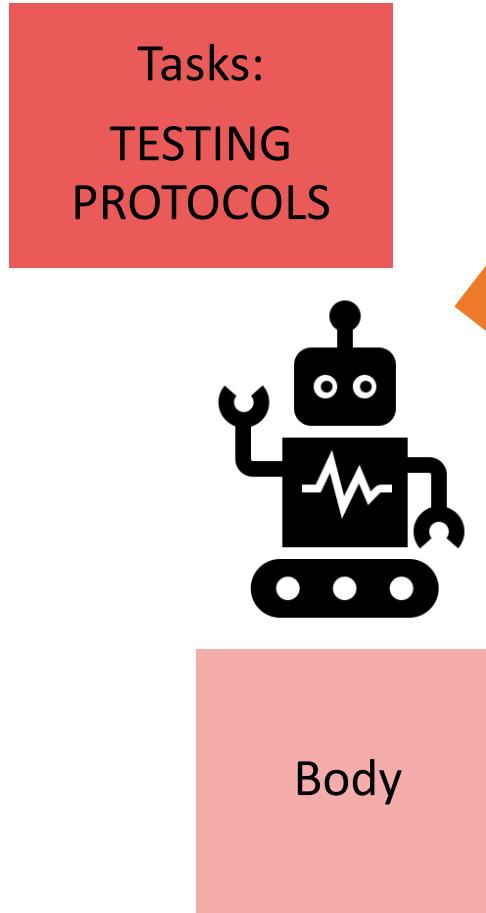
D'Angelo et al. Funct. Neurol 2013
D'Angelo et al. Front. Cell. Neuroscience, 2016



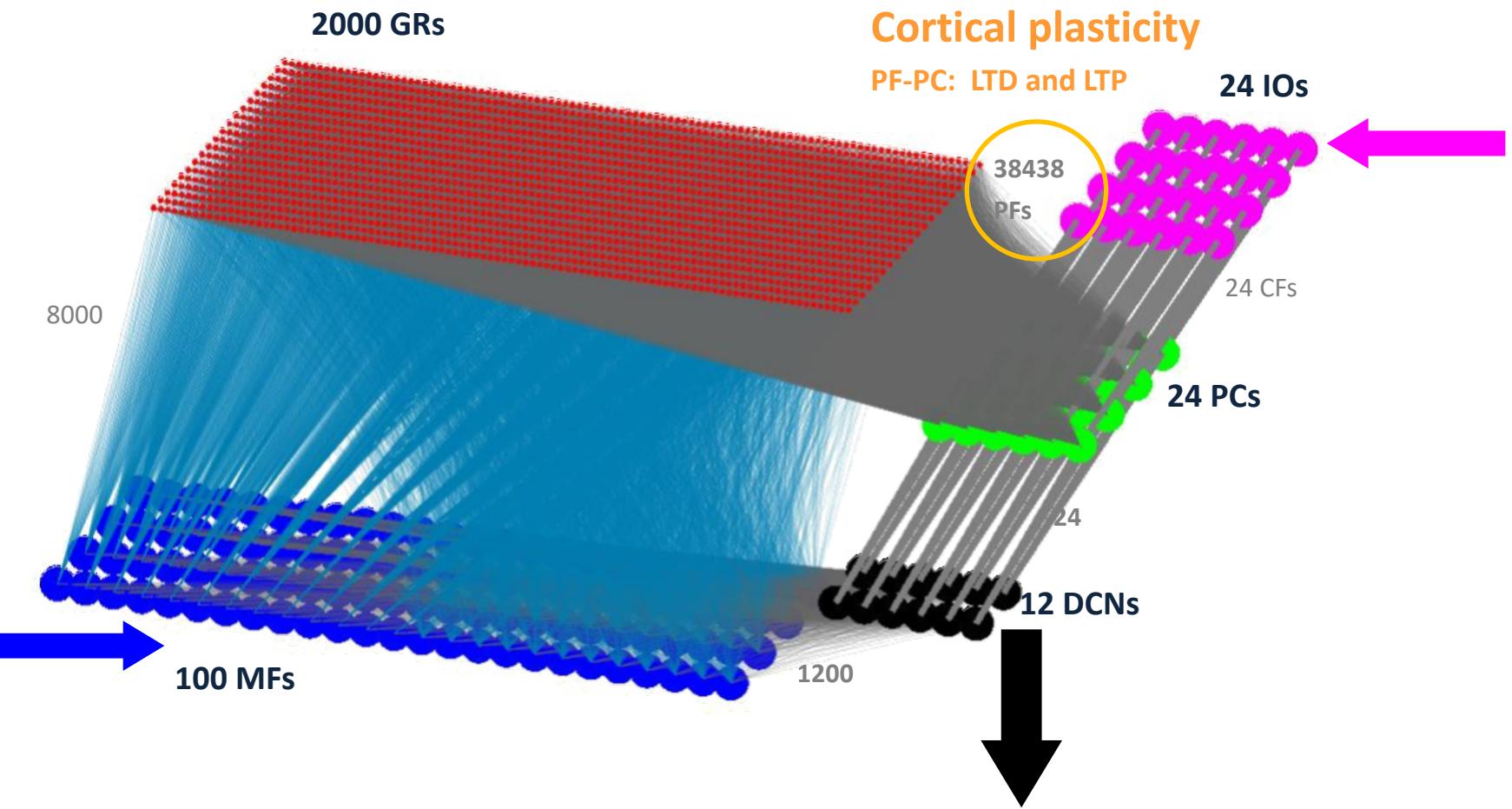
Data-driven spiking NN







Cerebellar spiking NN

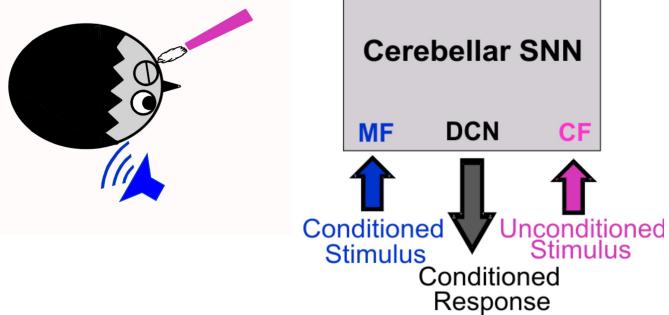


Spiking Neural Network (EDLUT-based)

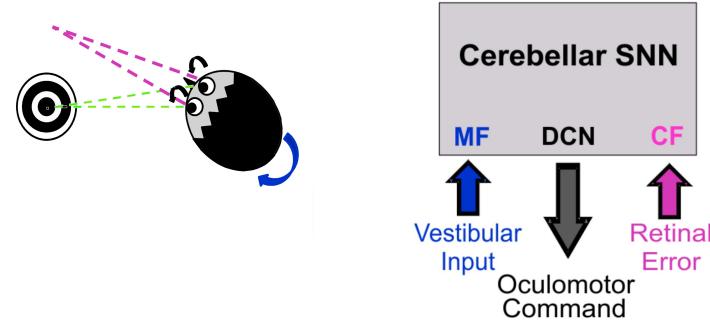
Testing protocols of the Cerebellar Models

Casellato et al., PlosOne 2014;
Antonietti et al., IEEE TMBE 2015

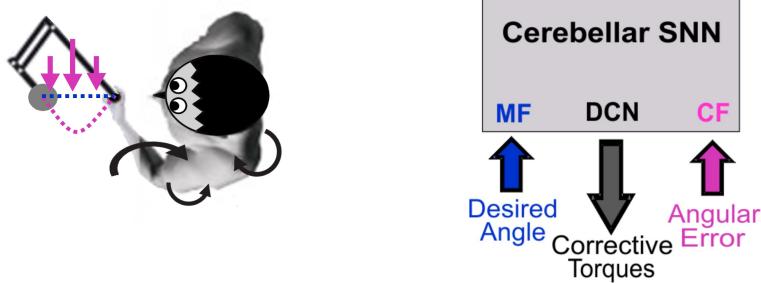
Eye Blink Classical Conditioning (EBCC)



Vestibulo-Ocular Reflex (VOR)



Movements perturbed by Force Fields (FF)



LEARNING FEATURES EMERGE
FROM PLASTICITY CHANGES IN THE SNN

Embodiment with real robots



Ros et al. Neural Computation 2006
Luque et al. Int. J. Neural Syst. 2011
Antonietti et al., IEEE TMBC 2015
Antonietti et al. IEEE TNNLS 2018

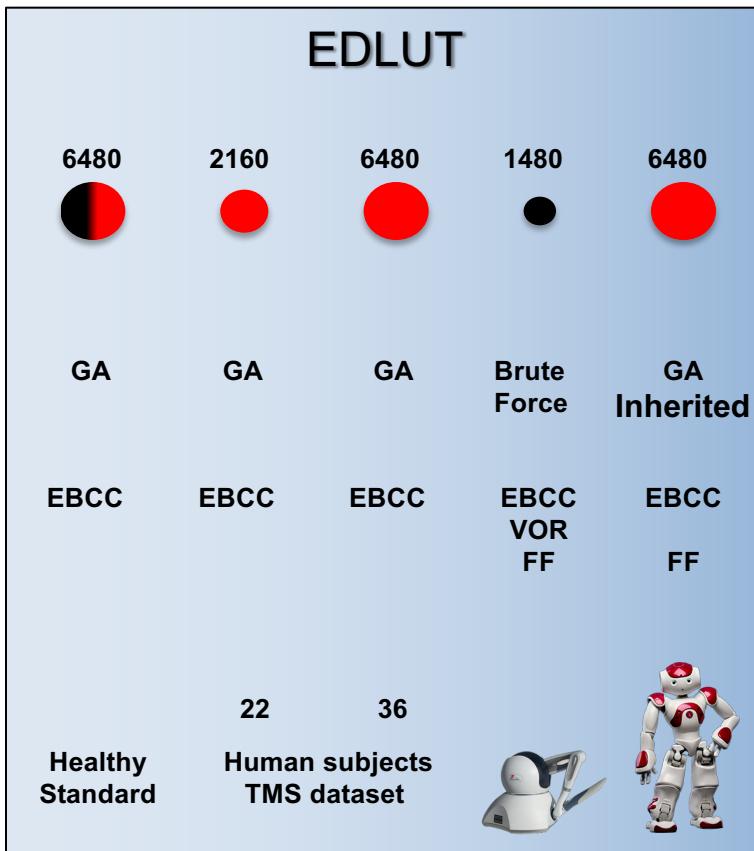
Simulator

Number of Neurons Plasticity (1 vs 3)

Parameter Optimization

Testing paradigms

Embedding or Data Fitting



Embodiment with real robots



Ros et al. Neural Computation 2006
Luque et al. Int. J. Neural Syst. 2011
Antonietti et al., IEEE TMBE 2015
Antonietti et al. IEEE TNNLS 2018

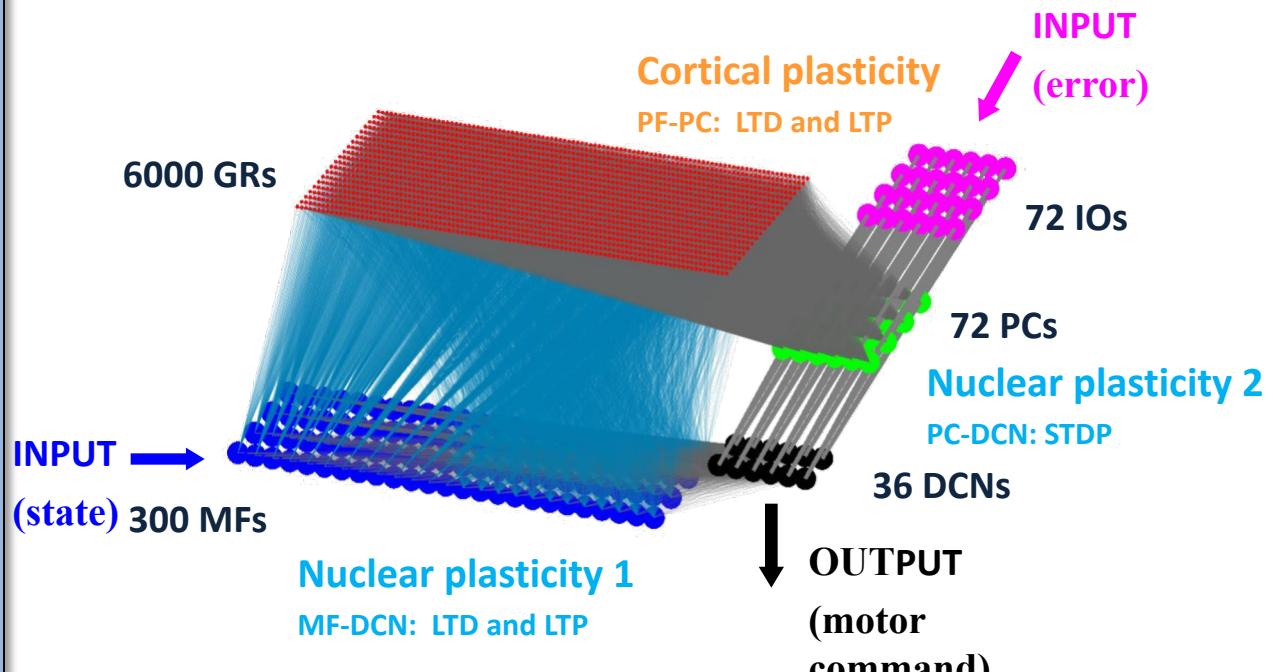
Simulator

Number of Neurons
Plasticity (1 vs 3)

Parameter
Optimization

Testing paradigms

Embedding or
Data Fitting

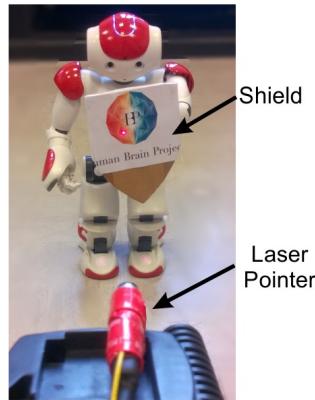


EBCC with Nao robot



Antonietti et al., IEEE TMBE 2015;
Antonietti et al., IEEE TNNLS 2018

NAO Robot

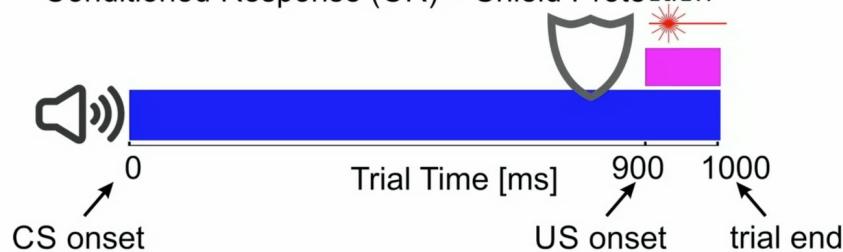


During the Acquisition Phase (13 Trials)

Conditioned Stimulus (CS) = Tone

Unconditioned Stimulus (US) = Laser Beam

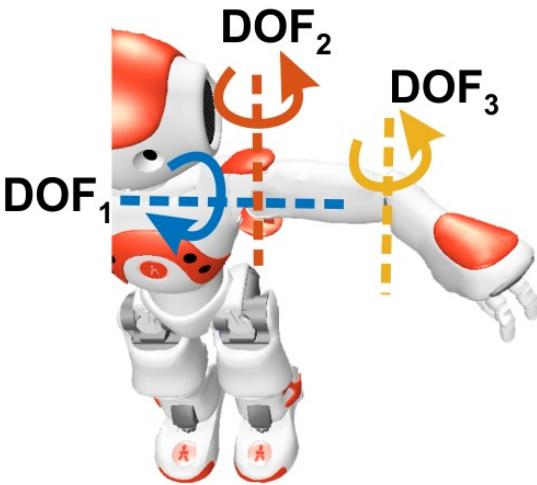
Conditioned Response (CR) = Shield Protection



NAO wants to protect himself from the US

Robotic Embodiment of the Cerebellar Models: FF with NAO Robot

Multi-joint Force Field with NAO Robot

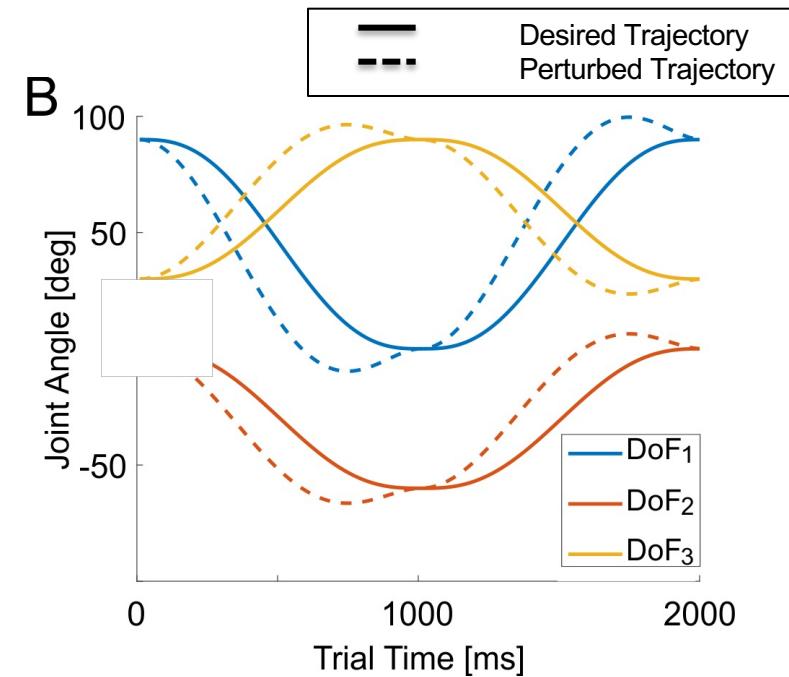


Protocol

5 trials of Baseline
(No perturbation)

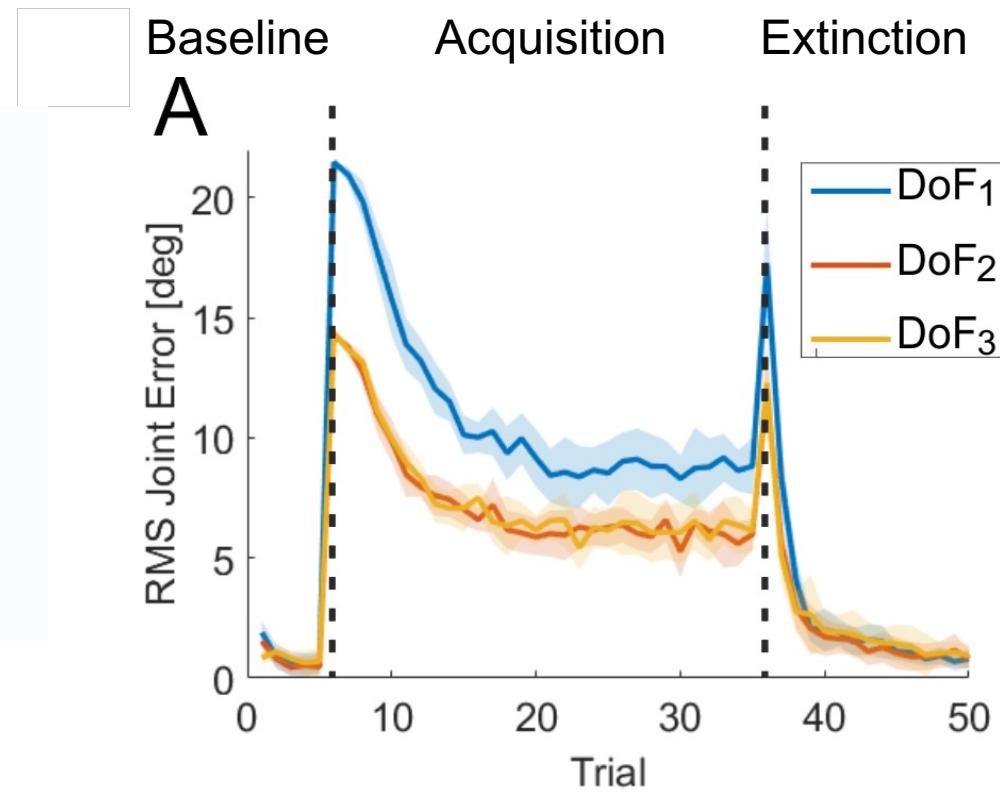
30 trials of Acquisition
(Perturbation starts)

15 trials of Extinction
(Perturbation ends)



Robotic Embodiment of the Cerebellar Models: MC with NAO Robot

5 trials of Baseline
(No perturbation)





Antonietti et al., Comp. Int. And Neurosc. 2019;

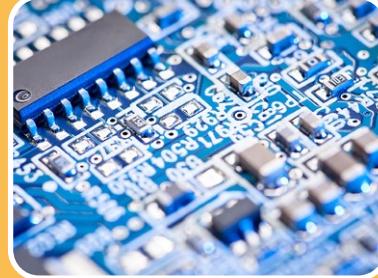
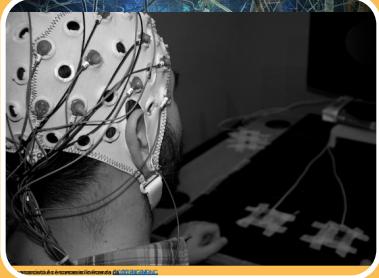


Embodiment with virtual robots: NRP

- Brain simulators at increasing computation load (more features, more neurons, more plasticity,...)
- Physics simulator (virtual robots)
- Robot controller
- Experiment pipeline



Impacts



Impacts on
Basic
Neuroscience

Impacts on
Applied
Neuroscience

Impacts on
Robotics and
Computer
Science

Impacts on basic neuroscience

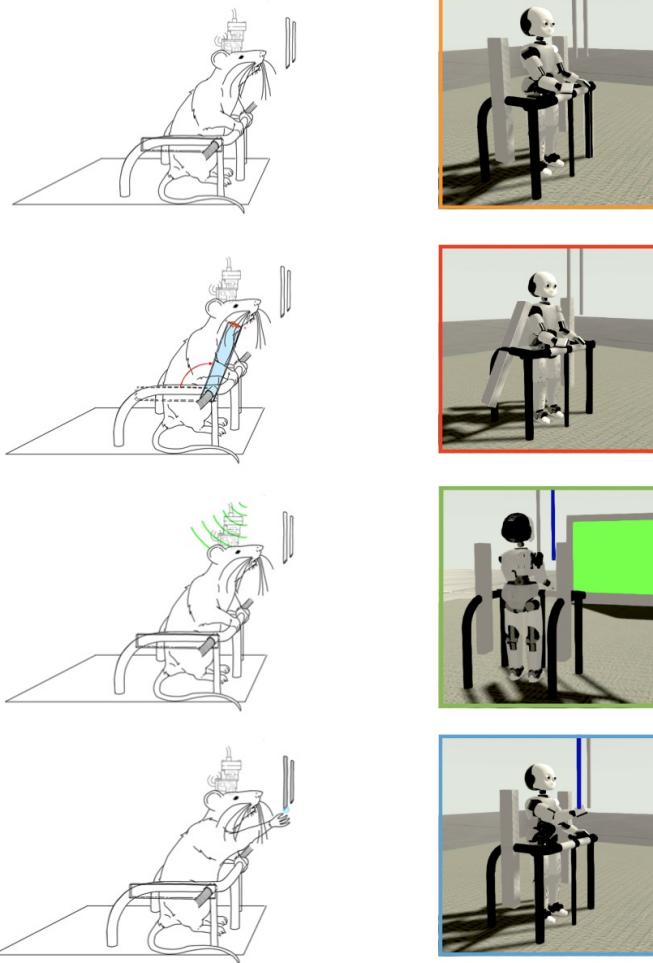


Figure 9: *In vivo* and *in silico* protocol co-execution. The robotic subject successfully performs the protocol as it was designed to be executed *in vivo*. The colored frames are used to mark a temporal reference on the spiking plot in Figure 8.

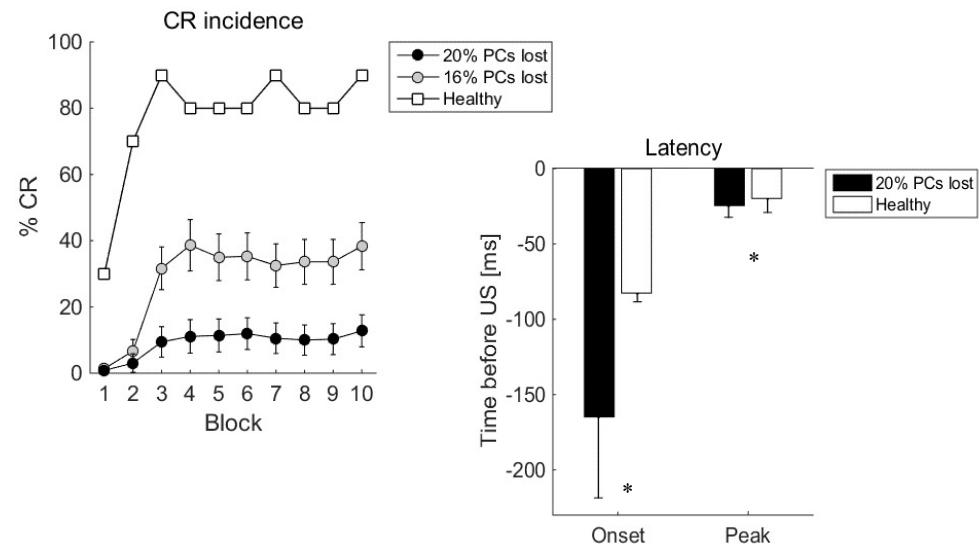
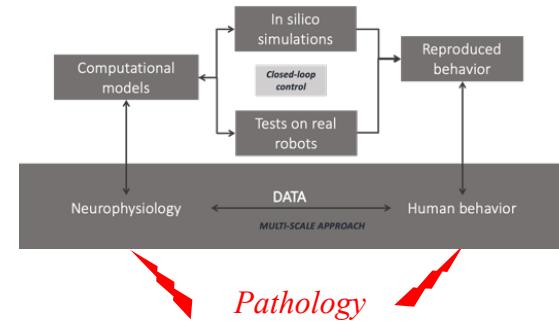
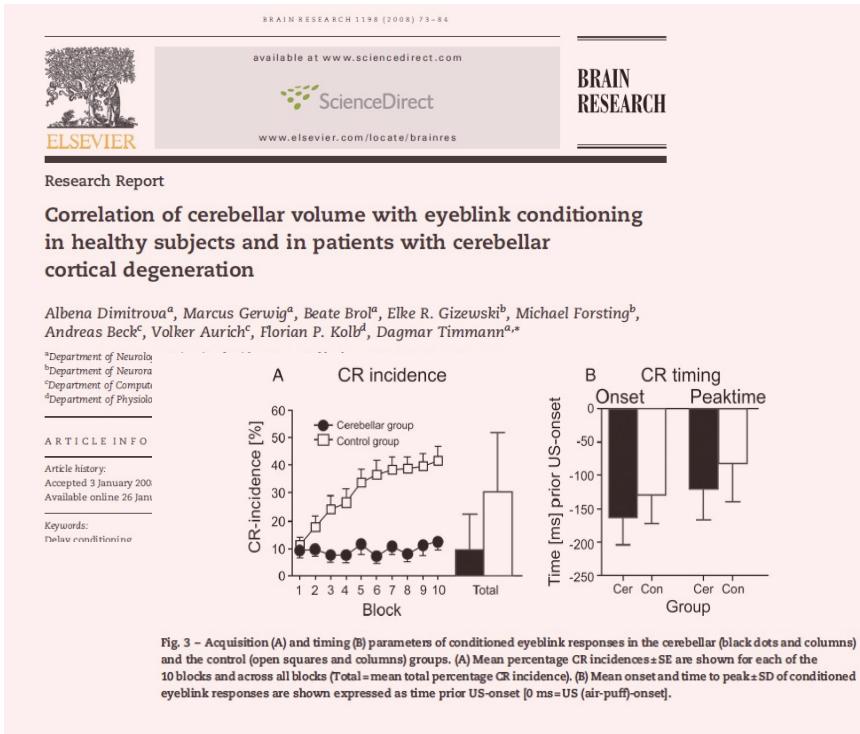
Impacts on applied neuroscience



EBRAINS

Geminiani et al., Int J Neural Syst 2018

- From physiological to pathological models

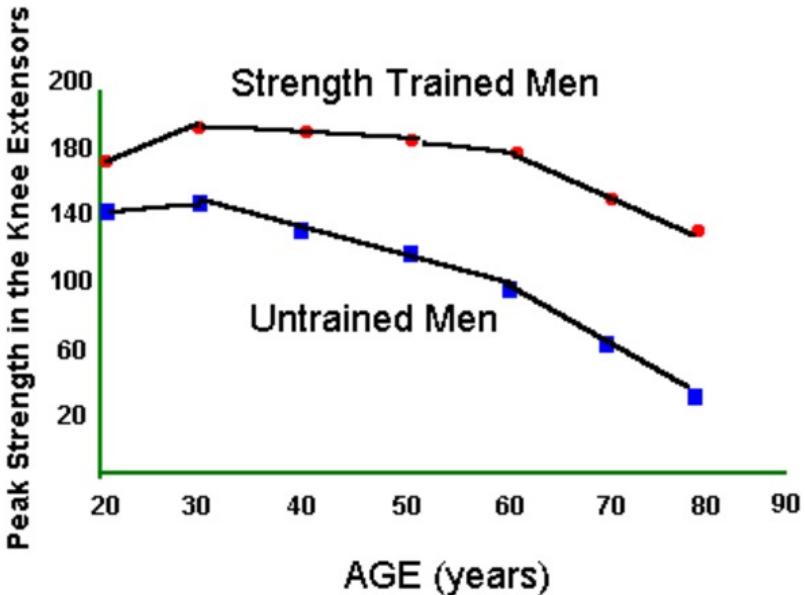




Neuroengineering 2020/21

REHABILITATION ROBOTICS –
Robots for rehabilitation

Context /Impact



Prevalence (US data @2008) :

795000 new stroke every year

- 350000 people with MS

- 250000 with SCI

- 1 million with PD

- 1,7 million with TBI

- 2,8 % children with CP

improvement in acute care

-> more rehabilitation request

Ageing

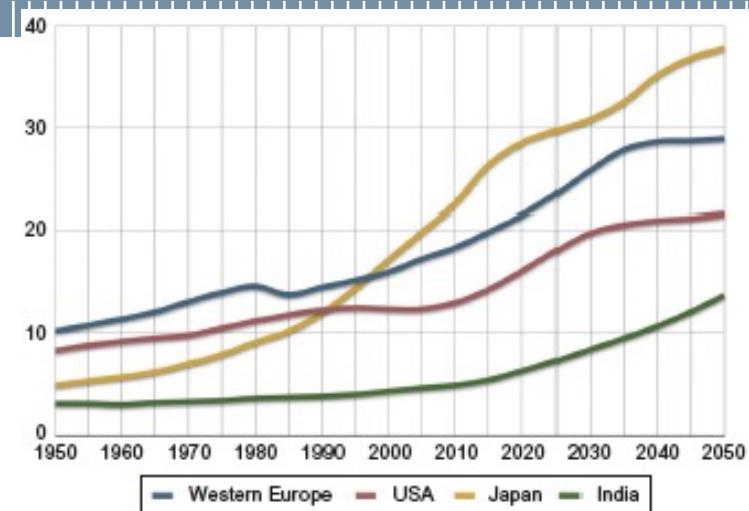
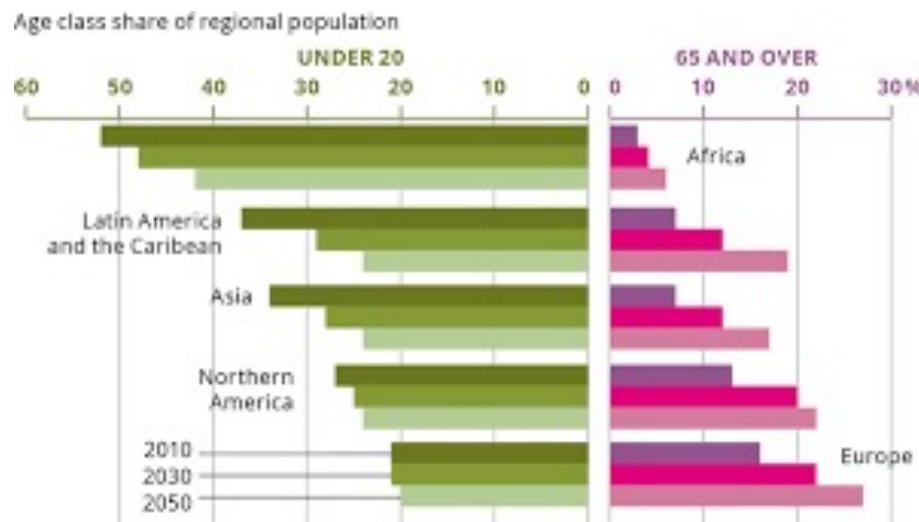


Fig. 23.1. Percentage of population above 65 years of age (UN 2008 Data Series). (Courtesy of IEEE Robotics and Automation Magazine and Professor Henrik Christensen: IEEE, 2010.)



- Rehabilitation robotics
 - tools to assist the clinicians in promoting rehabilitation of an individual so that he/she can interact with the environment unassisted
- Orthotics
 - Aim at improving functions in people with a weak limb due to a neurological disorder who cannot properly control it when interacting with the environment (Assistive technologies)
 - Orthoses are designed to work in cooperation with the intact body and either control or assist movement

Orthotics: Robotic Exoskeletons

- Enhance strength of user
 - Compensate for muscular degenerative disease
 - Provide superhuman capabilities
- Early work
 - 1965: General Electric Research & Development: Hardiman 1
 - Weighed 680 kg
 - Could lift 340 kg
 - Attempting to operate both legs at once leads to “violent and uncontrollable motion”



Stroke

= fast cerebral functionality loss due to a improvise blood flow interruption or haemorragy.

- Immediately after the stroke, 80% of the patients is affected by hemiparesis (loss of muscular tone), 35% maintain a partial disability even after the rehabilitation treatment.
- Functional deficit is controlateral in respect of the cerebral lesion.
- Motor functional recovery has an exponential trend.
- Initial recovery is due to resolution of local ischemia, anoxia, diaschisis, and edema reabsorption.
- Afterwards functional recovery occurs at the same time with a dynamic **process of cortical and subcortical reorganization** (post- acute phase - about 6 months after the accident)
- Chronic phase (low and slow recovery)

Neuroplasticity

Brain plasticity defines all the modifications in the organization of neural components occurring in the central nervous system during the entire life span of an individual

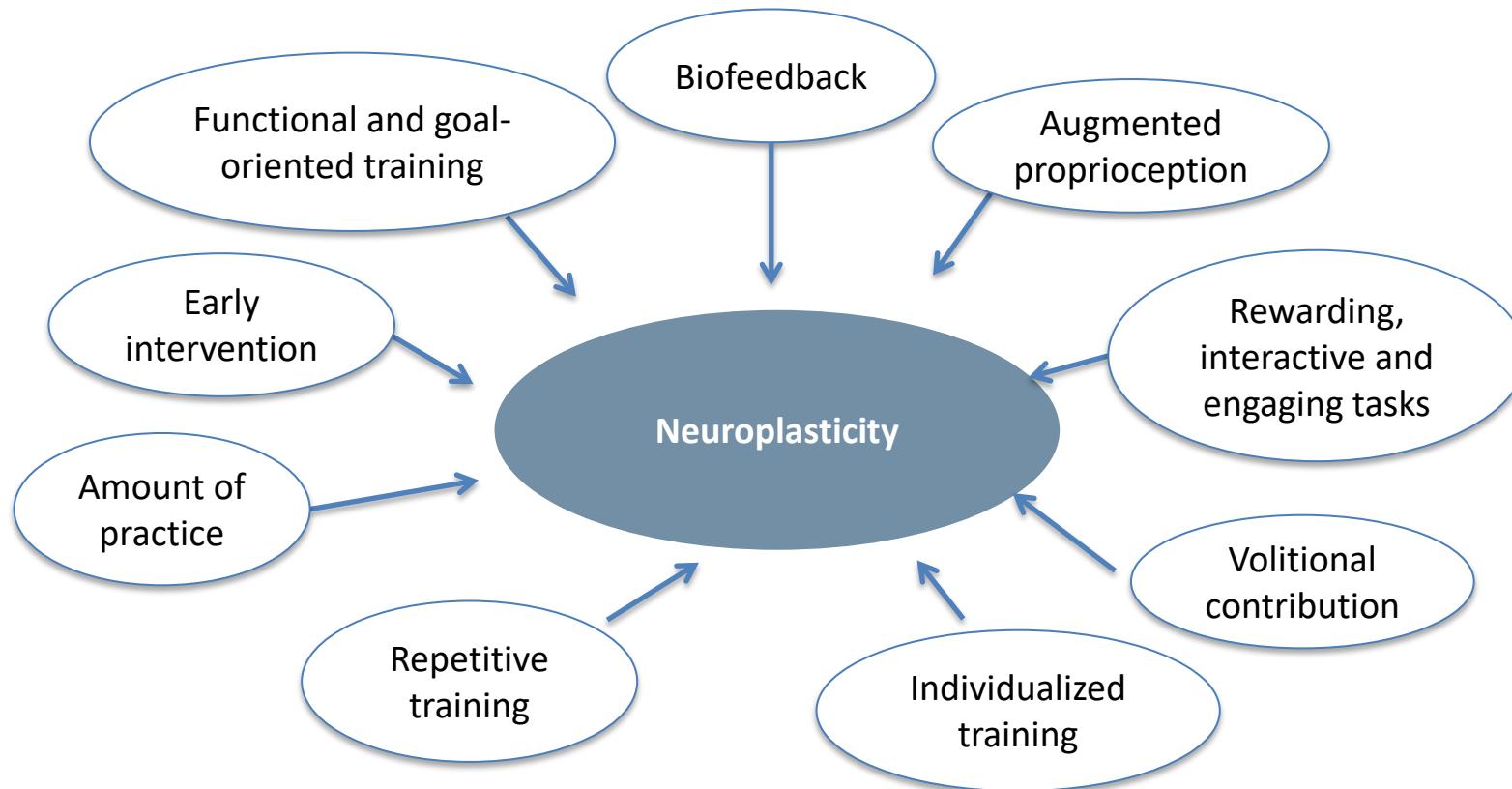
Training enhances lesion induced reorganization of the brain (Liepert et al., 2004; Askim et al., 2009; Lindberg et al., 2009)

Potential for re-organization persists even in chronic stroke patients (Luft et al., 2004)

Active training is better than passive movements (Xiu et al., 2009)

Vicariation, compensatory and substitutive movements can become «Maladaptive plasticity»
How to facilitate brain plasticity?- Drugs; - NIBS/TMS/Tes (increase excitability of damaged areas)

Key ingredients of motor re-learning



[Barsi et al. 2008, Bergquist et al. 2011, Huang et al. 2006, Krakauer et al. 2006]

Key elements for motor recovery

These data indicate that increased practice leads to greater skill, as long as practice is **challenging, progressive, and skill based**

Key factors

- Functional training
- Active participation
- Self-initiated movements
- Training intensity: regular
- The more practice , the greater success



Stroke patient forced to use his impaired arm for training

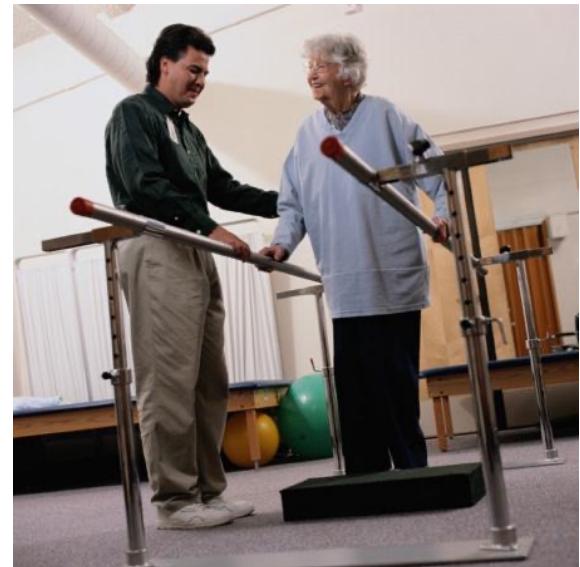
Picture courtesy of Rheinburg Klinik Walzenhausen

Lohse et al, Stroke 2014: We interpret these results as strong evidence of a positive relationship between dose and response. We were able to see a positive dose-response relationship across studies rehabilitating different impairments and functions, using different interventions, and measuring outcomes with different tools.

Preferable measures of dose would be active time in therapy or repetitions of an exercise.

Limitations of conventional therapy

- Poor motivation (depending on personal interaction with therapist)
- Limited by availability of therapists (low dose)
- Limited number of repetitions of exercises
- Unclear feedback regarding therapy progress
- Limited modulation of therapy



The goals

The design and **clinical translation** of **safe, simple, immersive and functional devices** is needed for assuring the **maximal recovery** during the hospitalization as long as in the continuation of the rehabilitation after discharge (at the point of need) and eventually at **home**.

Evidence-based assessment of rehabilitation therapies' alternatives (including neurorobotics assisted therapy, training adopting neuroprostheses and hybrid assistive devices as well as conventional treatments) is a milestone in the view of the **customization** of treatments on single patient.

What is rehabilitation robotics? And why?

Rehabilitation robotics is a field of research dedicated to **understanding** and **augmenting** rehabilitation through the application of robotic devices. Rehabilitation robotics includes development of robotic therapies, and the use of robots as therapy aids instead of solely as assistive devices .

(Wikipedia, July 2012, Oct 2021)

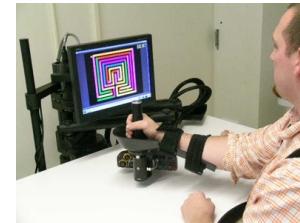
Rehabilitation robots: COMMERCIAL DEVICES

END-EFFECTOR

Definition: apply mechanical forces to the distal segments of the limbs

Advantage: easy to setup and control

Disadvantage: no control of proximal joints, possibility of abnormal movement patterns



MIT manus



Reo Go, Motorika

EXOSKELETON

Definition: robot axes are aligned with the anatomical axes of the subject

Advantage: direct control of individual joints; minimization of abnormal posture

Disadvantage: more complex and expensive



ArmeoPower, HOCOMA

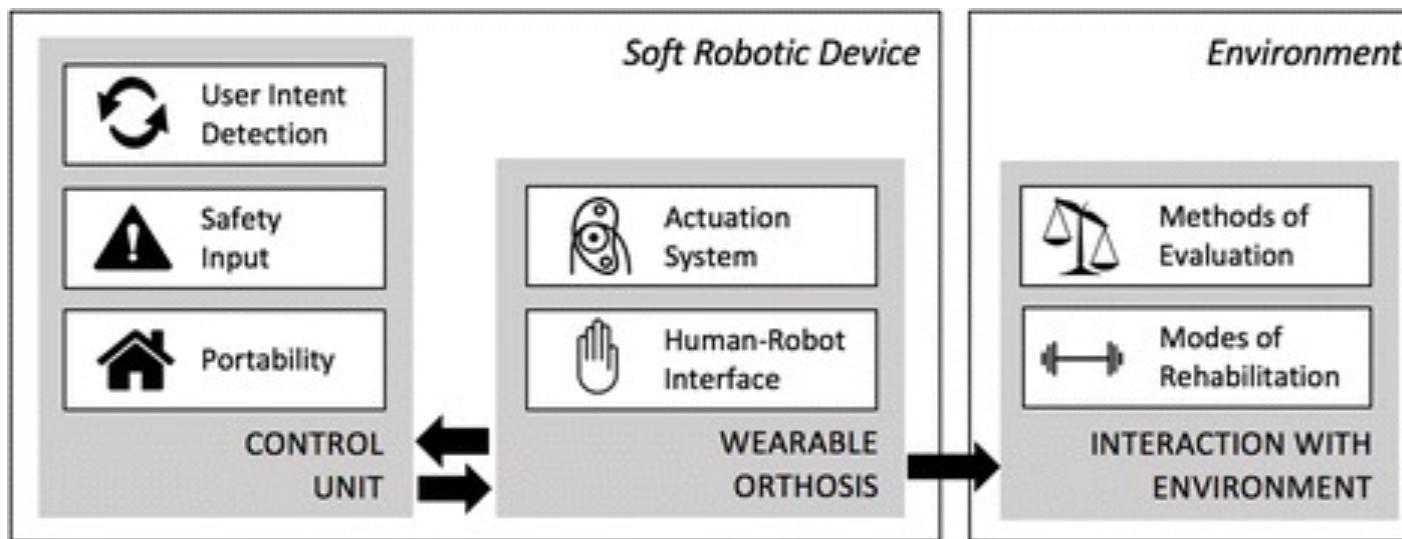


Alex, Wearable robotics

Soft robotics for hand and upper limbs

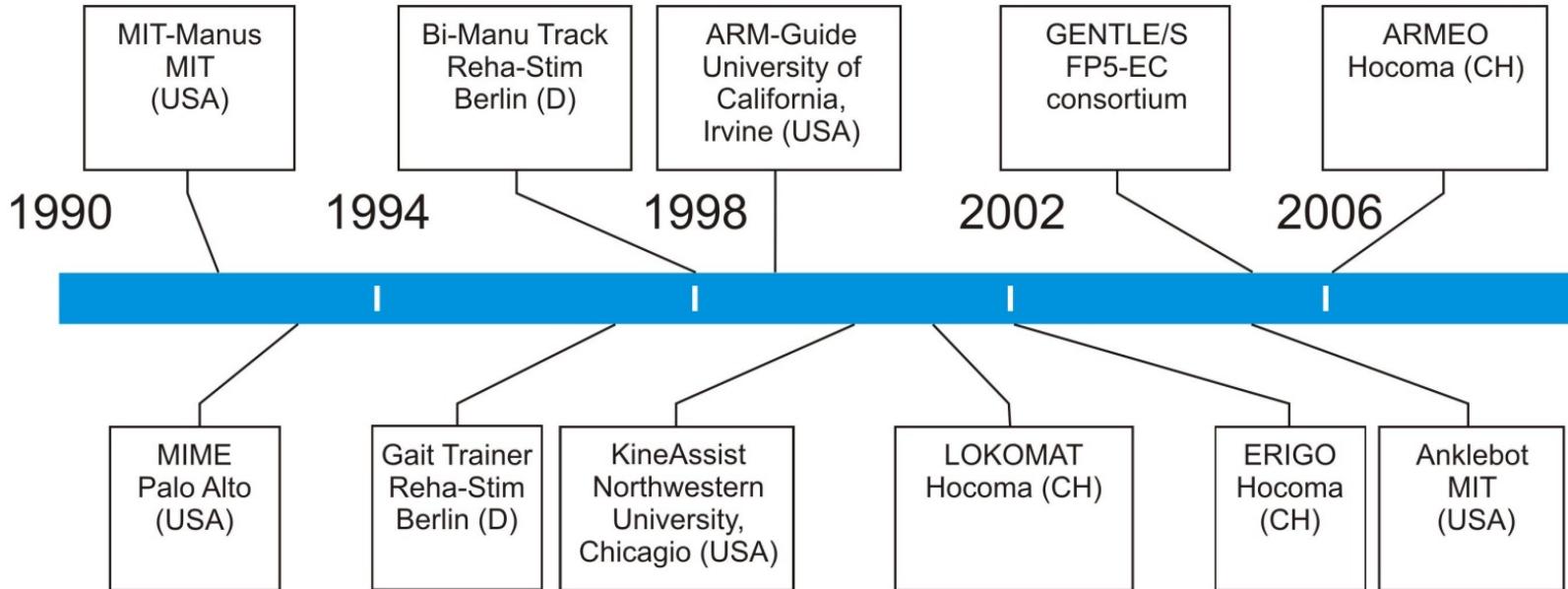
Soft robot: No rigid components on the robot-human interface or minimal rigid components that will not impose physical restraints on joint motions

Our discussion of the schematic is broken into two parts: the first part deals with the design of the robotic device while the second part deals with how the device interacts with the environment.



Chia-Ye Chu and Rita M. Patterson
Journal of NeuroEngineering and Rehabilitation 2018 15:9

Rehabilitation robotics: the first twenty years



Robotics for Upper limbs

Completely different approaches for arm, wrist and hand are available



Tail Wind



YouRehab



NX



ReJoyce



Reo Go



InMotion



Amadeus



BiManuTrack



Gloreha



Armeo Power

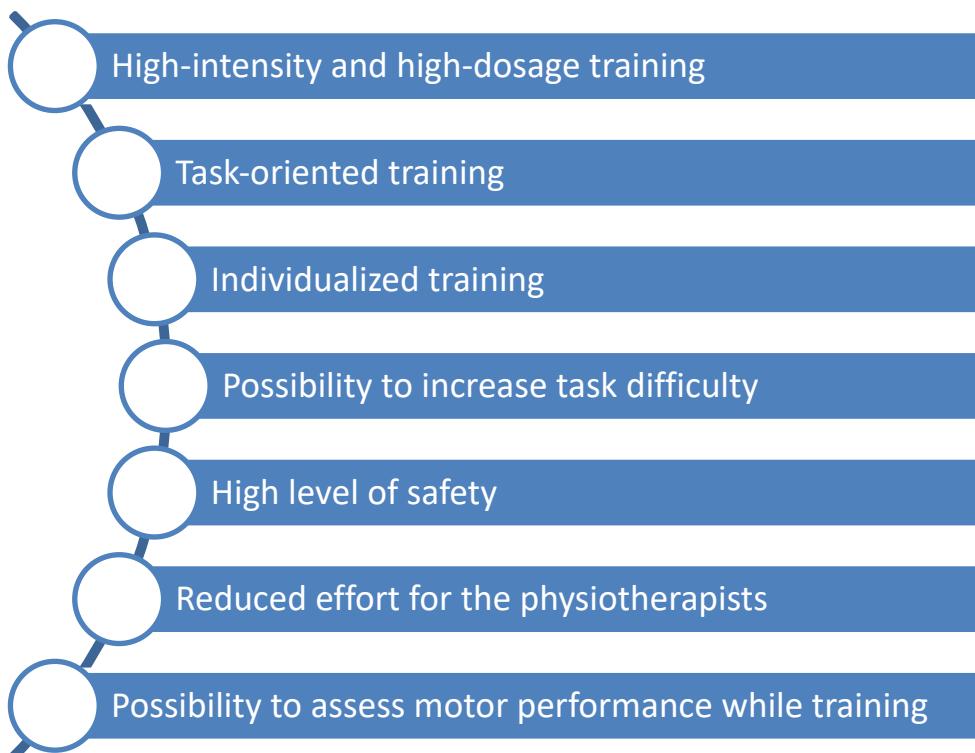


Alex

Rehabilitation robots: a critical view – upper limb

The reasons why...

But...



No clear evidence from clinical studies

RATULS trial (n=770 patients; Rodgers, H. et al. *Lancet Lond Engl.* **394**, 51–62 2019)

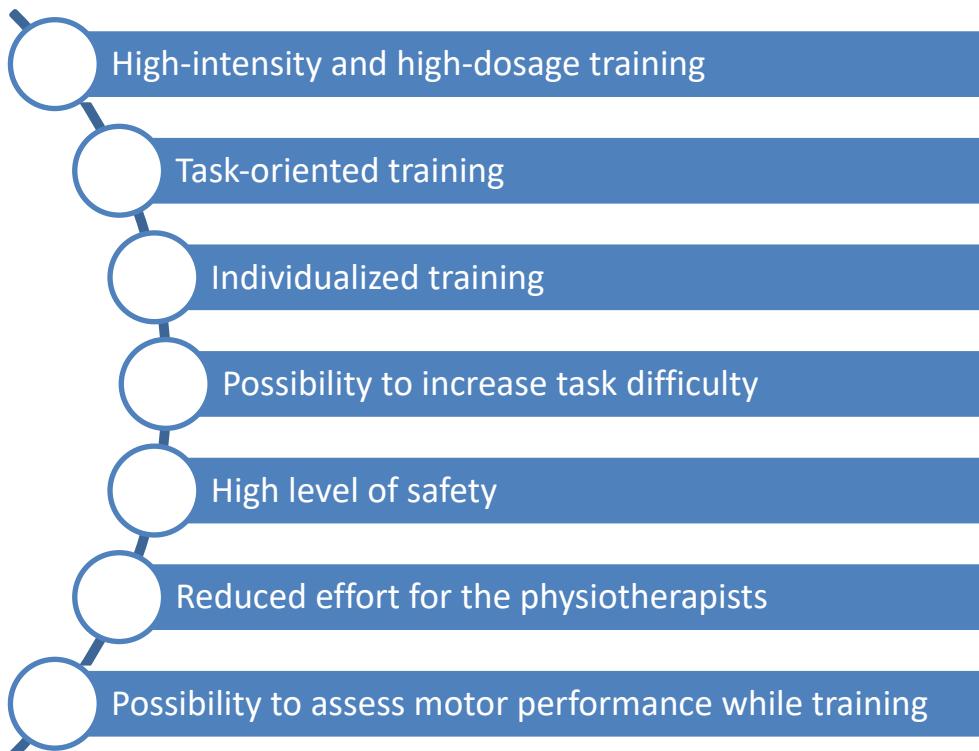
MIT-manus based **robotic training**

Enhanced Upper Limb Therapy, EULT, in which training specifically focused on daily activities and functional tasks, led to

Rehabilitation robots: a critical view

The reasons why...

But...



No clear evidence from clinical studies

RATULS trial (n=770 patients; Rodgers, H. et al. *Lancet Lond Engl.* **394**, 51–62 2019)

MIT-manus based **robotic training** led to

- improvement in upper limb impairment (**FMA motor subscale**) compared with usual care (**Body Structure and Function domain**)
- not improvements in upper limb function or ADL (**Activity domain**).

Enhanced Upper Limb Therapy, EULT, led to

- improvements compared with usual care for both **Body Structure and Activity domains** (**FMA motor subscale and SIS**)

International Classification of Functioning, Disability and Health (ICF)

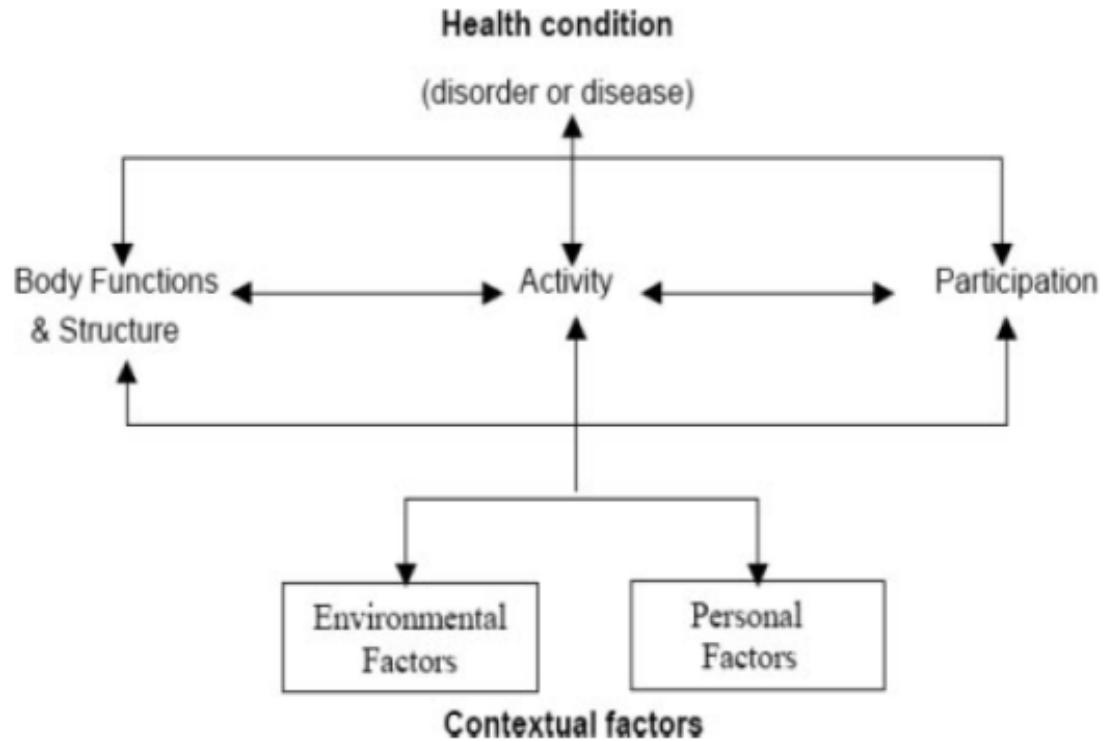


Figure. Diagrammatic representation of the WHO's ICF,⁸ reflecting interactions between the consequences of disease and contextual factors.

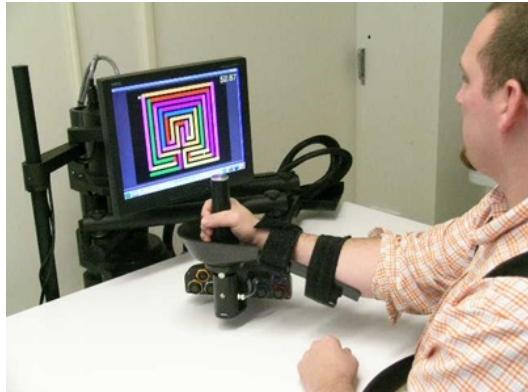
One point of view...

Body Structure and Function

Activity Domains

Participation

In clinical settings robotic therapy should focus on impairment training , combined with therapist transition-to-task training, to translate the impairment gains into function



Duret, C., Grosmaire, A.-G. & Krebs, H. I. Robot-Assisted Therapy in Upper Extremity Hemiparesis: Overview of an Evidence-Based Approach. *Front. Neurol.* **10**, 412 (2019).

Some commercial devices....

Product

- Re Ambulator, Autoambulator (Motorika)
- Gait Trainer (Reha-Stim)
- Gait system, G-EO-System (Reha Technologies)
- LokoHelp (LokoHelp Group)
- Walkbot (P & S Mechanics)
- Robogait



The Armeo® Therapy Concept



Improved arm and hand rehabilitation

- 1 Arm Weight Support in 3D workspace
- 2 Augmented Performance Feedback
- 3 Self-initiated, active, repetitive Training
- 4 Improved therapy efficiency
- 5 Assessment Tools
- 6 Modular Therapy Concept



Sensory – Locomotor learning



Key facts

- Functional training helps recover function
- More training leads to greater success
- Training beyond the present capability
- Afferent feedback is stimulating reorganization of the CNS
- Active participation
- Motivation is the key!



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Free Walking Device

- HAL from Cyberdyne
- ReWalk from ARGO MedTec
- Ekso-Bionics from Berkeley
- ...



ReWalk: Structure





InMotion2 Shoulder-Elbow Robot

- End-effector based, driven system , no guidance for elbow and shoulder
- 2D workspace
- No pro-/supination
- Only assessment of end-point performance possible



ReoGo

- End-effector based, driven system, no guidance for elbow and shoulder
- Limited 3D workspace
- Pro-/supination & grip sensing as additional accessories
- Only assessment of end-point performance possible

Myomo mPower 1000
not CE approved
at the moment



The mPower 1000 is a neuro-robotic arm brace that fits like a sleeve on a person's arm. The arm brace has sensors that sit on the skin's surface and detect even a very faint muscle signal. When a person with a weak or partially paralyzed arm tries to move their arm and a muscle signal fires, the robotics in the mPower 1000 engage to assist in completing the desired movement

Amadeo®

tyromotion

- > Hand rehabilitation system for stroke survivors
 - > Passive motion
 - > Assistive motion
 - > Active motion
- > Force measurement
- > Biofeedback



Possibilities

- > Adaptable to every type of hand
 - > Spastic
 - > Limb
- > Adaptable to every patient
 - > Wheelchair user friendly
- > Created on newest medical knowledge
- > 6 independent axes
- > Motivating therapy programmes

tyromotion



21



Computer controlled device that:

- Follows patient from behind in over-ground walking
- Provides body weight support
- Allows independent motion of torso and pelvis
- Allows therapist's free access to legs
- Complementary to treadmill training



KineAssist™ technology benefits:

Assist clinicians in gait & balance training, in a functional context

Challenge clients to their maximum limits without increasing the risk of falls

Maintain consistency with current practice and infrastructure

Allow more therapy, by minimizing set up time

44

Currently being developed for the market, but no CE Mark or EU presence

Features

- Sophisticated software powers the ReoAmbulator through its integrated computer system, while sensors track numerous functions, continuously monitoring and adjusting power and speed according to each patient's physical requirements.
- Allow the patients to contribute to the movement but provide remaining force necessary for walking
- Adjust the amount of weight bearing
- Walking speed can be varied



Reha-Stim, Reha Technologies



Gait Trainer (**Reha-Stim**)



Gait system, G-EO-System (**Reha Technologies**)

LokoHelp Group



LokoHelp

(LokoHelp Group)



MotionMaker™ is a medical device intended for handicapped and hemiplegic patients so that maximum mobility and autonomy are recovered. It is a stationary device, a robotic system with electro-stimulation for an active mobilisation of the lower limbs.

Its main functions are investigation, diagnostics, training and rehabilitation of muscular strength and endurance, as well as articular mobility and movement coordination.



ZeroG is the most advanced gait and balance training system in the world. With ZeroG, patients can begin practicing a wide range of walking activities, balance tasks, and other Activities of Daily Living early after neurological injuries in a safe controlled environment.

P & S Mechanics



[Walkbot \(P & S Mechanics\)](#)

Eu roadmap Robotics for health care [Butter et al., Tech Rep. 2008]

Robotic assisted motor therapy

Robot assisted physical training

robot assisted mental, cognitive and social therapy

individually adjust the rehabilitative training protocol with accuracy, replication and congruity with residual motor function and treatment targets [Krebs et al. IEEE Trans Rehabil Eng, 1998; Casadio et al. Clin Rehab, 2009]

quantitatively assess baseline conditions and monitor changes during training

extend the application at home under remote control, reducing costs and making the access possible to patients who are technology illiterates [Krebs et al. J Rehabil Res De, 2000].

Reccomendations level of evidence- Guidelines AHA 2016

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				Procedure/ Test	Treatment
	CLASS I <i>Benefit >> Risk</i> Procedure/Treatment SHOULD be performed/ administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>		
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses 	COR III: No benefit	Not Helpful No Proven Benefit
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies 	COR III: Harm	Excess Cost w/o Benefit or Harmful Harmful to Patients
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care 		
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit	COR III: Harm	
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective	potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other	

Recommendations: Rehabilitation Interventions in the Inpatient Hospital Setting	Class	Level of Evidence
It is recommended that early rehabilitation for hospitalized stroke patients be provided in environments with organized, interprofessional stroke care.	I	A
It is recommended that stroke survivors receive rehabilitation at an intensity commensurate with anticipated benefit and tolerance.	I	B
High-dose, very early mobilization within 24 hours of stroke onset can reduce the odds of a favorable outcome at 3 months and is not recommended.	III	A

Recommendations: Nondrug Therapies for Cognitive Impairment, Including Memory (Continued)	Class	Level of Evidence
Exercise may be considered as adjunctive therapy to improve cognition and memory after stroke.	IIb	C
Virtual reality training may be considered for verbal, visual, and spatial learning, but its efficacy is not well established.	IIb	C
Anodal tDCS over the left dorsolateral prefrontal cortex to improve language-based complex attention (working memory) remains experimental.	III	B

Recommendations: Assessment of Motor Impairment, Activity, and Mobility	Class	Level of Evidence
Motor impairment assessments (paresis/muscle strength, tone, individuated finger movements, coordination) with standardized tools may be useful.	IIb	C
Upper extremity activity/function assessment with a standardized tool may be useful.	IIb	C
Balance assessment with a standardized tool may be useful.	IIb	C
Mobility assessment with a standardized tool may be useful.	IIb	C
The use of standardized questionnaires to assess stroke survivor perception of motor impairments, activity limitations, and participation may be considered.	IIb	C
The use of technology (accelerometers, step-activity monitors, pedometers) as an objective means of assessing real-world activity and participation may be considered.	IIb	C
Periodic assessments with the same standardized tools to document progress in rehabilitation may be useful.	IIb	C

AHA guidelines 2016: spasticity and balance

Recommendations: Spasticity	Class	Level of Evidence	Recommendations: Balance and Ataxia	Class	Level of Evidence
Targeted injection of botulinum toxin into localized upper limb muscles is recommended to reduce spasticity, to improve passive or active range of motion, and to improve dressing, hygiene, and limb positioning.	I	A	Individuals with stroke who have poor balance, low balance confidence, and fear of falls or are at risk for falls should be provided with a balance training program.	I	A
Targeted injection of botulinum toxin into lower limb muscles is recommended to reduce spasticity that interferes with gait function.	I	A	Individuals with stroke should be prescribed and fit with an assistive device or orthosis if appropriate to improve balance.	I	A
Oral antispasticity agents can be useful for generalized spastic dystonia but may result in dose-limiting sedation or other side effects.	IIa	A	Individuals with stroke should be evaluated for balance, balance confidence, and fall risk.	I	C
Physical modalities such as NMES or vibration applied to spastic muscles may be reasonable to improve spasticity temporarily as an adjunct to rehabilitation therapy.	IIb	A	Postural training and task-oriented therapy may be considered for rehabilitation of ataxia.	IIb	C
Intrathecal baclofen therapy may be useful for severe spastic hypertonia that does not respond to other interventions.	IIb	A			
Postural training and task-oriented therapy may be considered for rehabilitation of ataxia.	IIb	C			
The use of splints and taping are not recommended for prevention of wrist and finger spasticity after stroke.	III	B			

AHA guidelines 2016: Mobility (gait)

Recommendations: Mobility	Class	Level of Evidence		
Intensive, repetitive, mobility- task training is recommended for all individuals with gait limitations after stroke.	I	A		
An AFO after stroke is recommended in individuals with remediable gait impairments (eg, foot drop) to compensate for foot drop and to improve mobility and paretic ankle and knee kinematics, kinetics, and energy cost of walking.	I	A	Practice walking with either a treadmill (with or without body-weight support) or overground walking exercise training combined with conventional rehabilitation may be reasonable for recovery of walking function.	IIb A
Group therapy with circuit training is a reasonable approach to improve walking.	IIa	A	Robot-assisted movement training to improve motor function and mobility after stroke in combination with conventional therapy may be considered.	IIb A
Incorporating cardiovascular exercise and strengthening interventions is reasonable to consider for recovery of gait capacity and gait-related mobility tasks.	IIa	A	Mechanically assisted walking (treadmill, electromechanical gait trainer, robotic device, servo-motor) with body weight support may be considered for patients who are nonambulatory or have low ambulatory ability early after stroke.	IIb A
NMES is reasonable to consider as an alternative to an AFO for foot drop.	IIa	A	There is insufficient evidence to recommend acupuncture for facilitating motor recovery and walking mobility.	IIb B

Recommendations: Mobility (Continued)	Class	Level of Evidence
The effectiveness of TENS in conjunction with everyday activities for improving mobility, lower extremity strength, and gait speed is uncertain.	IIb	B
The effectiveness of rhythmic auditory cueing to improve walking speed and coordination is uncertain.	IIb	B
The usefulness of electromyography biofeedback during gait training in patients after stroke is uncertain.	IIb	B
Virtual reality may be beneficial for the improvement of gait.	IIb	B
The effectiveness of neurophysiological approaches (ie, neurodevelopmental therapy, proprioceptive neuromuscular facilitation) compared with other treatment approaches for motor retraining after an acute stroke has not been established.	IIb	B
The effectiveness of water-based exercise for motor recovery after an acute stroke is unclear.	IIb	B
The effectiveness of fluoxetine or other SSRIs to enhance motor recovery is not well established.	IIb	B
The effectiveness of levodopa to enhance motor recovery is not well established.	IIb	B
The use of dextroamphetamine or methylphenidate to facilitate motor recovery is not recommended.	III	B

Recommendations: Upper Extremity Activity, Including ADLs, IADLs, Touch, and Proprioception (Continued)	Class	Level of Evidence
Somatosensory retraining to improve sensory discrimination may be considered for stroke survivors with somatosensory loss.	IIb	B
Bilateral training paradigms may be useful for upper limb therapy.	IIb	A
Acupuncture is not recommended for the improvement of ADLs and upper extremity activity.	III	A

AHA guidelines 2016: Upper limb training

Recommendations: Upper Extremity Activity, Including ADLs, IADLs, Touch, and Proprioception	Class	Level of Evidence		
Functional tasks should be practiced; that is, task-specific training, in which the tasks are graded to challenge individual capabilities, practiced repeatedly, and progressed in difficulty on a frequent basis.	I	A	CIMT or its modified version is reasonable to consider for eligible stroke survivors.	IIa A
All individuals with stroke should receive ADL training tailored to individual needs and eventual discharge setting.	I	A	Robotic therapy is reasonable to consider to deliver more intensive practice for individuals with moderate to severe upper limb paresis.	IIa A
All individuals with stroke should receive IADL training tailored to individual needs and eventual discharge setting.	I	B	NMES is reasonable to consider for individuals with minimal volitional movement within the first few months after stroke or for individuals with shoulder subluxation.	IIa A
CIMT or its modified version is reasonable to consider for eligible stroke survivors.	IIa	A	Mental practice is reasonable to consider as an adjunct to upper extremity rehabilitation services.	IIa A
			Strengthening exercises are reasonable to consider as an adjunct to functional task practice.	IIa B
			Virtual reality is reasonable to consider as a method for delivering upper extremity movement practice.	IIa B

AHA reccomendations 2016: assistive devices

Recommendations: Adaptive Equipment, Durable Medical Devices, Orthotics, and Wheelchairs	Class	Level of Evidence
Ambulatory assistive devices (eg, cane, walker) should be used to help with gait and balance impairments, as well as mobility efficiency and safety, when needed.	I	B
AFOs should be used for ankle instability or dorsiflexor weakness.	I	B
Wheelchairs should be used for nonambulatory individuals or those with limited walking ability.	I	C
Adaptive and assistive devices should be used for safety and function if other methods of performing the task/activity are not available or cannot be learned or if the patient's safety is a concern.	I	C

AHA guidelines 2016: Continuity of care

Recommendations: Chronic Care Management: Home- and Community-Based Participation	Class	Level of Evidence	Recommendations: Social and Family Caregiver Support	Class	Level of Evidence
After successful screening, an individually tailored exercise program is indicated to enhance cardiorespiratory fitness and to reduce the risk of stroke recurrence.	I	A (for improved fitness); B (for reduction of stroke risk)	It may be useful for the family/caregiver to be an integral component of stroke rehabilitation.	IIb	A
After completion of formal stroke rehabilitation, participation in a program of exercise or physical activity at home or in the community is recommended.	I	A	It may be reasonable that family/caregiver support include some or all of the following on a regular basis:	IIb	A
Recommendation: Ensuring Medical and Rehabilitation Continuity Through the Rehabilitation Process and Into the Community	Class	Level of Evidence	Education		
It is reasonable to consider individualized discharge planning in the transition from hospital to home.	IIa	B	Training		
It is reasonable to consider alternative methods of communication and support (eg, telephone visits, telehealth, or Web-based support), particularly for patients in rural settings.	IIa	B	Counseling		
			Development of a support structure		
			Financial assistance		
			It may be useful to have the family/caregiver involved in decision making and treatment planning as early as possible and throughout the duration of the rehabilitation process.	IIb	B

The rehab pathways

Phase	Admission	Length of Stay (Mean±SD)
Hospital-based care		
Acute intensive care	Onset to hours	Subarachnoid hemorrhage: 9.2 ±12.3 h Intracerebral hemorrhage: 5.1 ±9.2 h Ischemic stroke: 1.8 ±12.3 h
Acute care	2–3 d	Subarachnoid hemorrhage: 11.3 ±11.6 d Intracerebral hemorrhage: 8.0 ±9.2 d Ischemic stroke: 6.3 ±6.8 d
Inpatient rehabilitation care	5–7 d	Mean of 8–30 d; median of 15 d
		and in Italy?
Skilled nursing facility care		
Inpatient SNF rehabilitation	5–7 d after stroke	Dependent on individual stroke severity (with maximum of 100 d)
Long-term care	Dependent on stroke severity, individual resources, multiple comorbidities	Variable depending on care needs (eg, long-term care vs palliative/end-of-life)
Community-based rehabilitation, including home health care		
Early supported discharge services	20–30 d	1–44 mo
Chronic outpatient rehabilitation	>4–6 mo Variable onset based on individual resources and functional needs	Variable termination based on individual resources and functional needs

AHA/ASA SCIENTIFIC STATEMENT Primary Care of Adult Patients After Stroke: A Scientific Statement From the American Heart Association/American Stroke Association

Kernan et al 2021
Stroke Volume 52, Issue 9, September
2021; Pages e558-e571

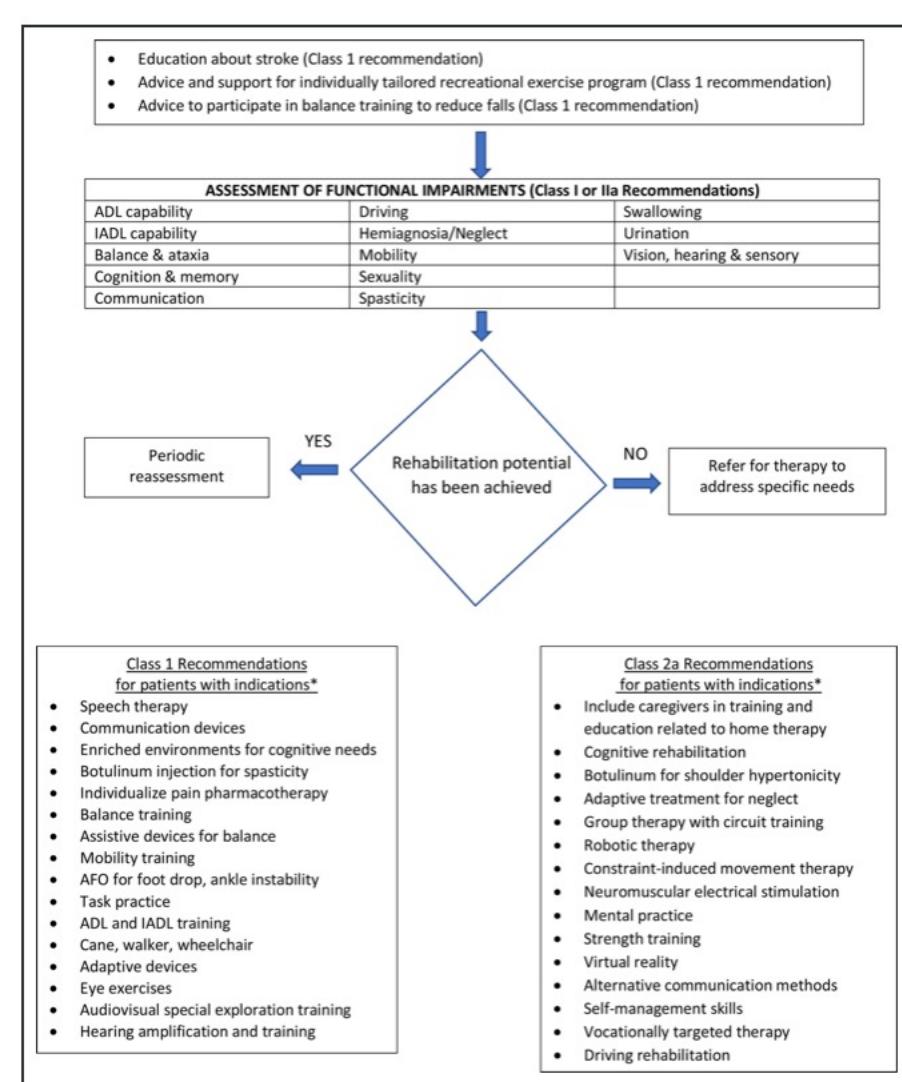


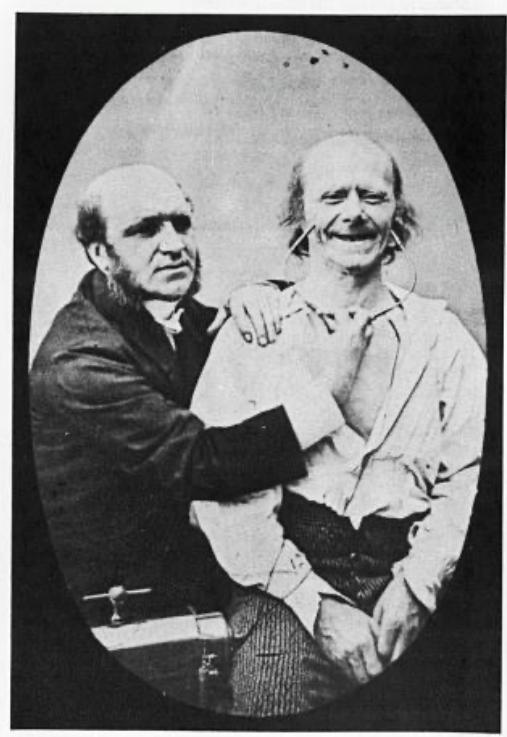
Figure 2. An algorithm for screening and management of poststroke physical rehabilitation needs in primary care. Class or recommendations from the 2016 AHA poststroke rehabilitation guidelines.⁹² ADL indicates activities of daily living; AFO, ankle-foot orthosis; and IADL, instrumental activities of daily living.



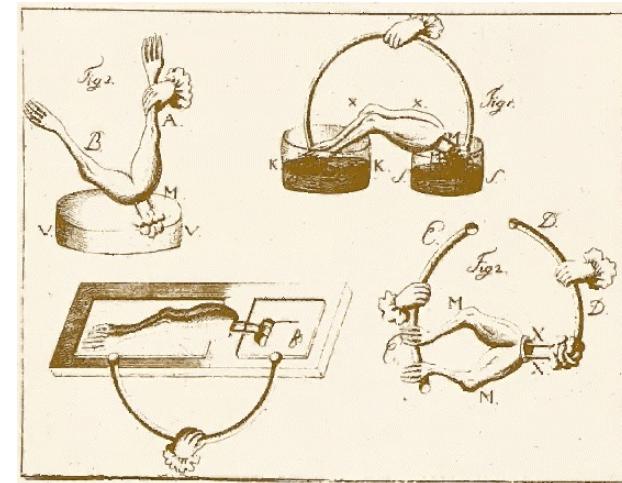
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Section 1- FUNDAMENTALS OF FUNCTIONAL
ELECTRICAL STIMULATION

Electrical Stimulation



- Use of torpedoes
- Galvani 1780
- Duchenne 1862
- Liberson 1961



Marcello Bracale: “Electrical and magnetic stimulation”
In: History of Bioengineering Treatment - E. Biondi and C. Cobelli
2001 - Patron Editore, Bologna, 299-324.

Functional electrical stimulation

“FES is the stimulation able to induce the contraction in a muscle without its neuronal control, in order to obtain a useful functional movement”

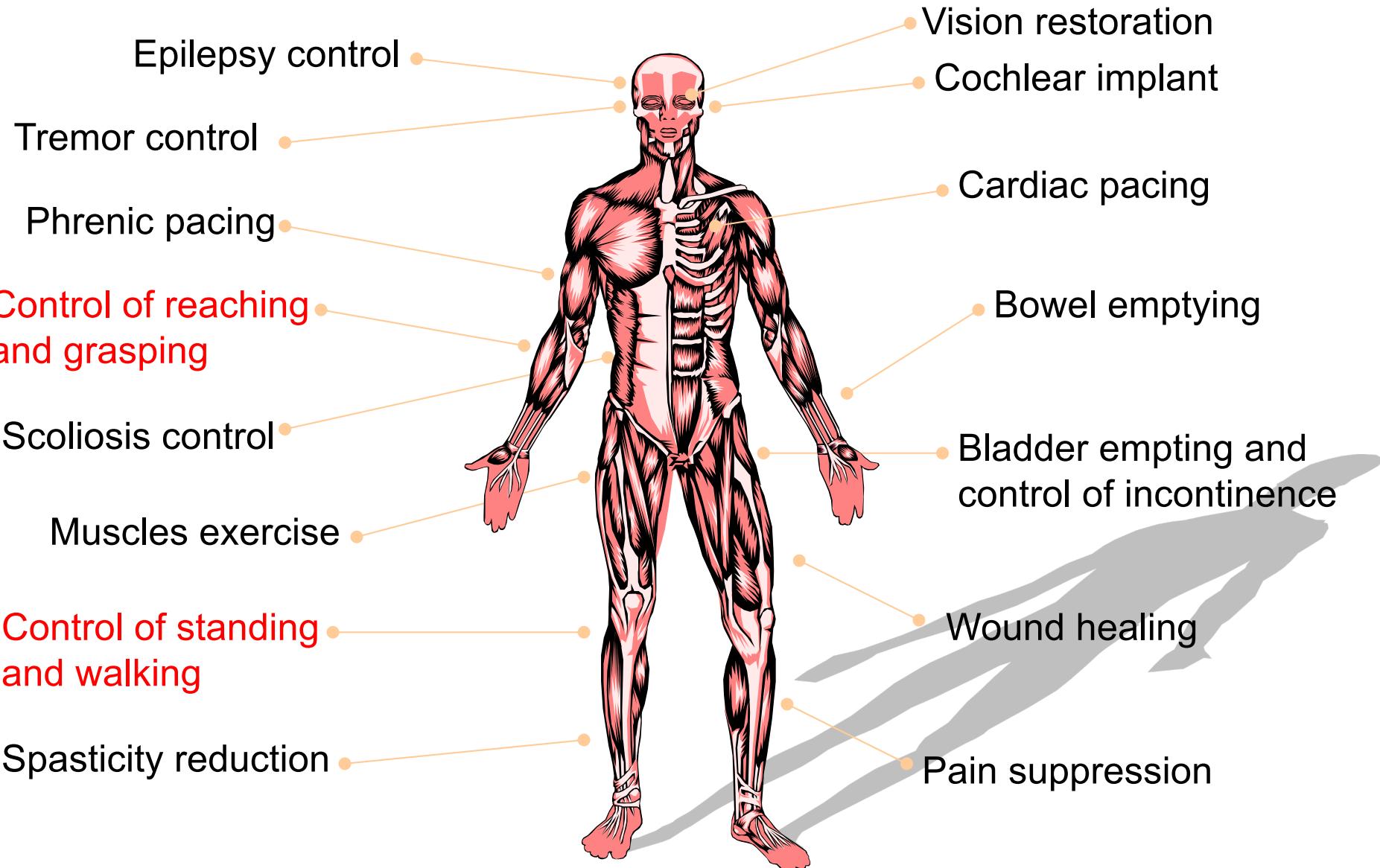
Vodovnik, L. 1971. Functional Electrical Stimulation of Extremities. In Advances in Electronics and Electron Physics, Academic Press.

“Functional electrical stimulation (FES) is the technique of applying safe levels of electric current to activate the damaged or disabled neuromuscular system in a coordinated manner in order to achieve the lost function. Neuro-prosthesis is a device that uses electrical stimulation to activate the nervous system. These initiate a physiological-like stimulation in the intact peripheral nerves, providing functional restoration of various body organs in the neurologically impaired individuals.”

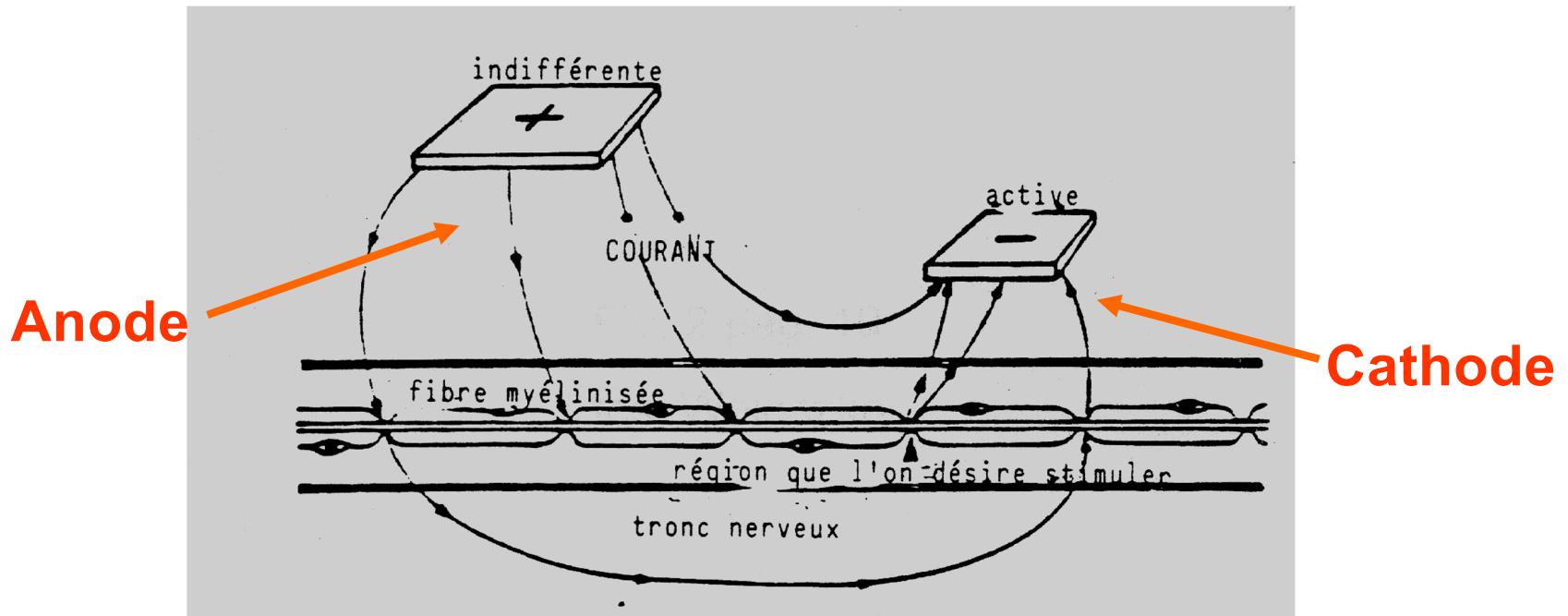
Hamid S, Hayek R. Role of electrical stimulation for rehabilitation and regeneration after spinal cord injury: an overview. *Eur Spine J.* 2008;17(9):1256–1269. doi:10.1007/s00586-008-0729-3

ES interventions and target disabilities

Applications of Electrical Stimulation



FES: Working Principle



Anode:

It sends a positive charge to the membrane which is HYPERPOLARIZED under the anode

Cathode:

The positive charge exits from the cathode; the membrane is DEPOLARIZED under the cathode

DEPOLARIZATION OVER THE THRESHOLD



Action Potential

Stimulation Parameters

- **Current Amplitude [A]**

(it excites the nerve; there is a current threshold)

- **Pulse width (PW, [μ s])**

(the alternative parameter able to adjust the charge)

- **Tension [V]**

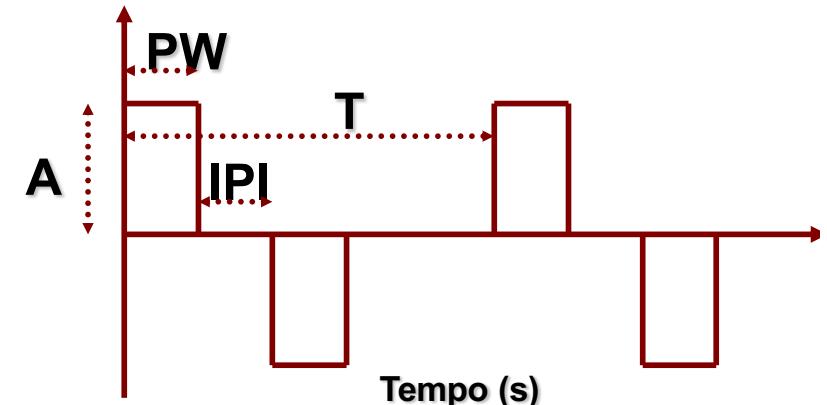
(it supports the current erogation)

- **Stimulus Frequency (1/T) [Hz]**

(it regulates the force of the mechanical action)

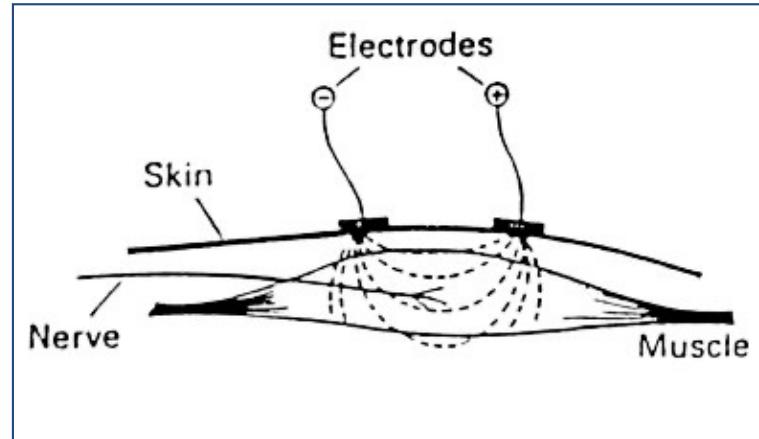
- **Stimuli shape**

(it limits possible tissue damage)



Technological Aspects: Electrodes

SURFACE



PERCUTANEUS

Monopolar Percutaneous Needle



Bipolar Percutaneous Hooks



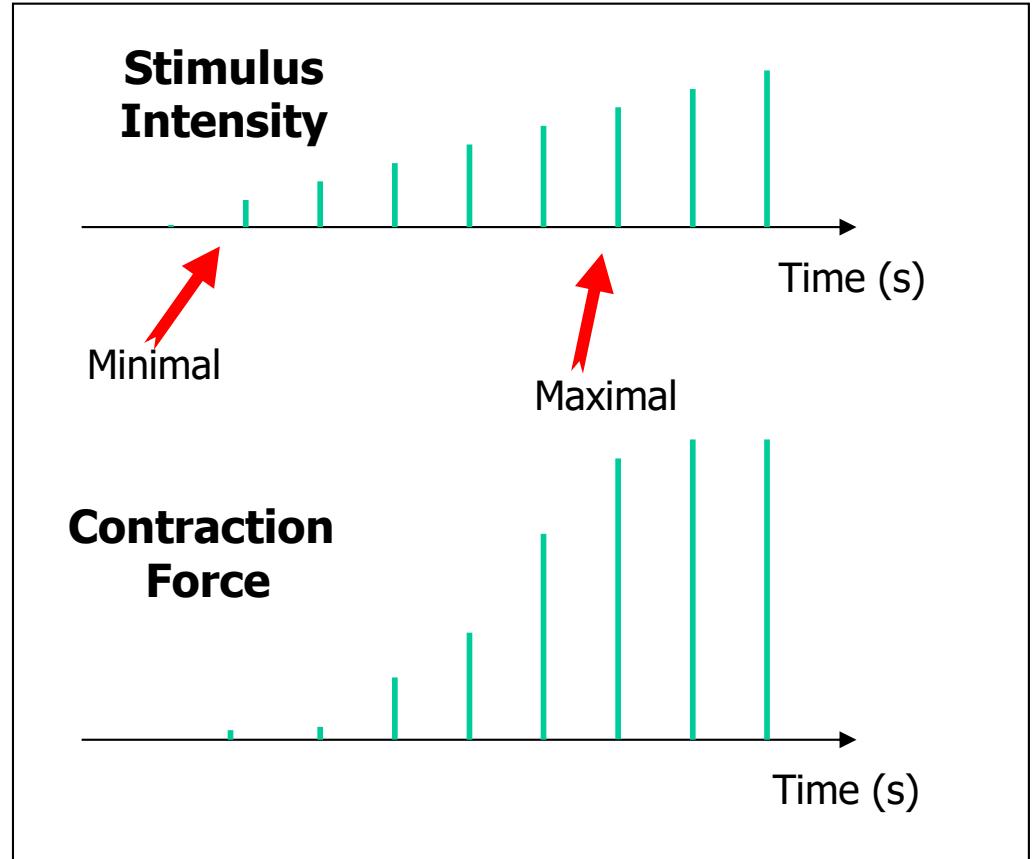
Natural Muscular Contraction

FORCE GENERATED
BY THE MUSCLE

$$F(t) = \sum_{i=1}^N F_i(t)$$

i: index of motor units

N = total number of motor units



Spatial summation

Natural Muscular contraction

- ASYNCHRONOUS ACTIVATION:

Force modulation

Turn over in the fiber activation

A continuous force is obtained with $f = 10 \text{ Hz}$

- PROGRESSIVE ACTIVATION



Type I Fibers

Type IIa Fibers

Type IIb Fibers

Type I fibers:

- Small diameter
- Deep
- Slow contraction
- Limited force (0.6 kg/cm^2)
- Aerobic metabolism (oxidative)



SHORT RECOVERY PERIODS



RESISTANT TO FATIGUE

Type IIa fibers:

- Relatively big diameter
- Relatively fast contraction
- High Force (~~2,6-2,9 kg/cm²~~)
- Anaerobic and aerobic metabolism (glicolitic and oxidative)



MEDIUM RECOVERY PERIODS



MEDIUM RESISTANCE TO MUSCLE FATIGUE

Type IIb fibers:

- Big diameter
- Closer to Surface
- Fast contraction
- High force ($1,5-2 \text{ kg/cm}^2$)
- Anaerobic metabolism (glicolitic)



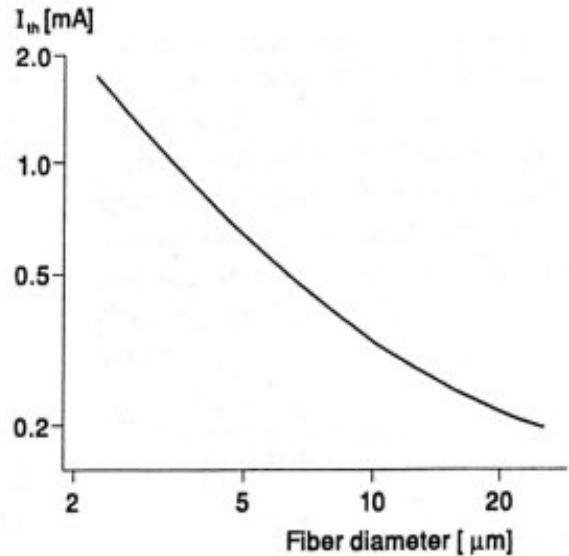
LONG RECOVERY PERIODS



FAST MUSCULAR FATIGUE

Artificial Muscular contraction

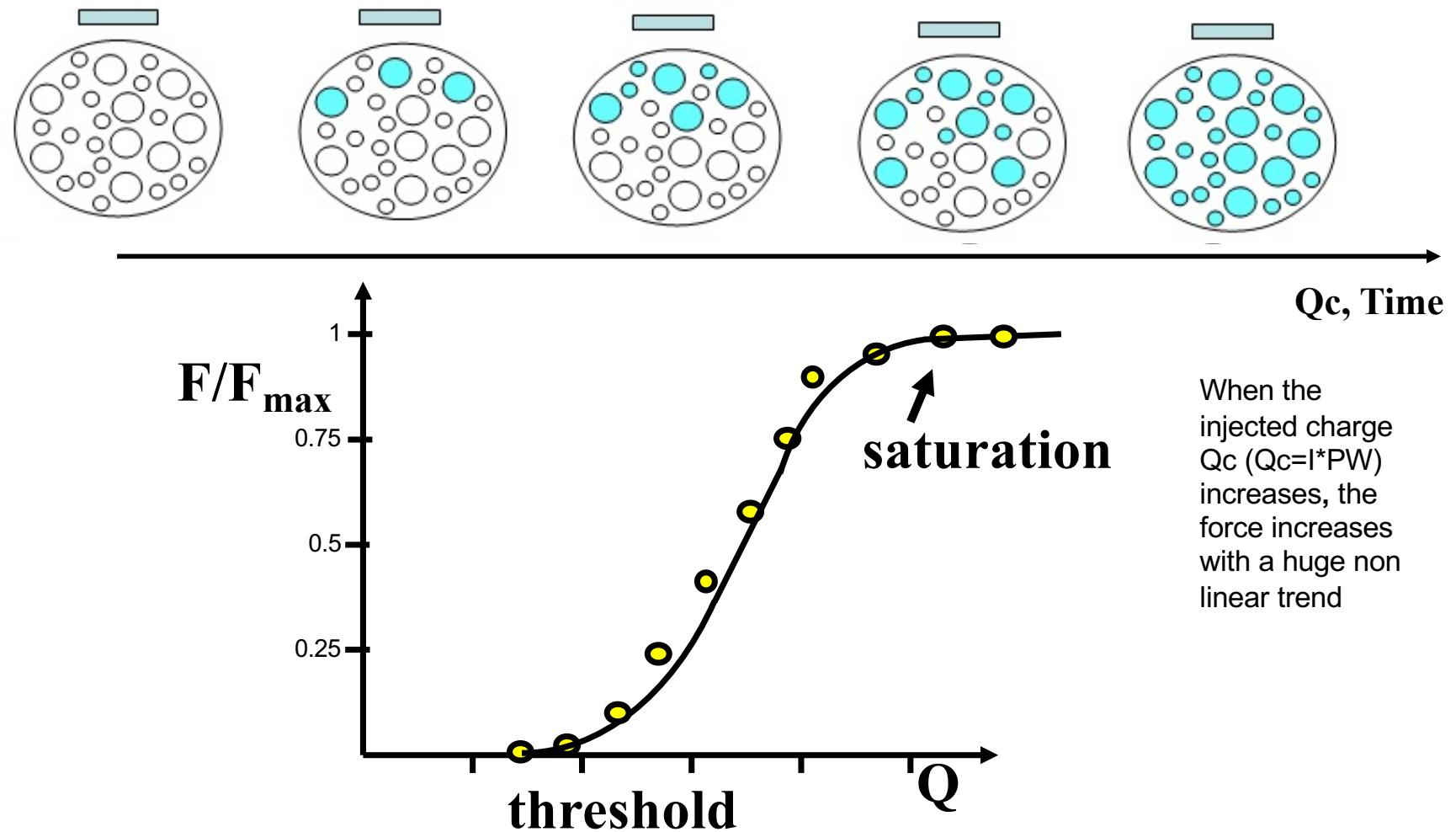
- Electrical stimulation activates the motor neuron (healthy!)
- Generation of an action potential that is not distinguishable from the physiological one



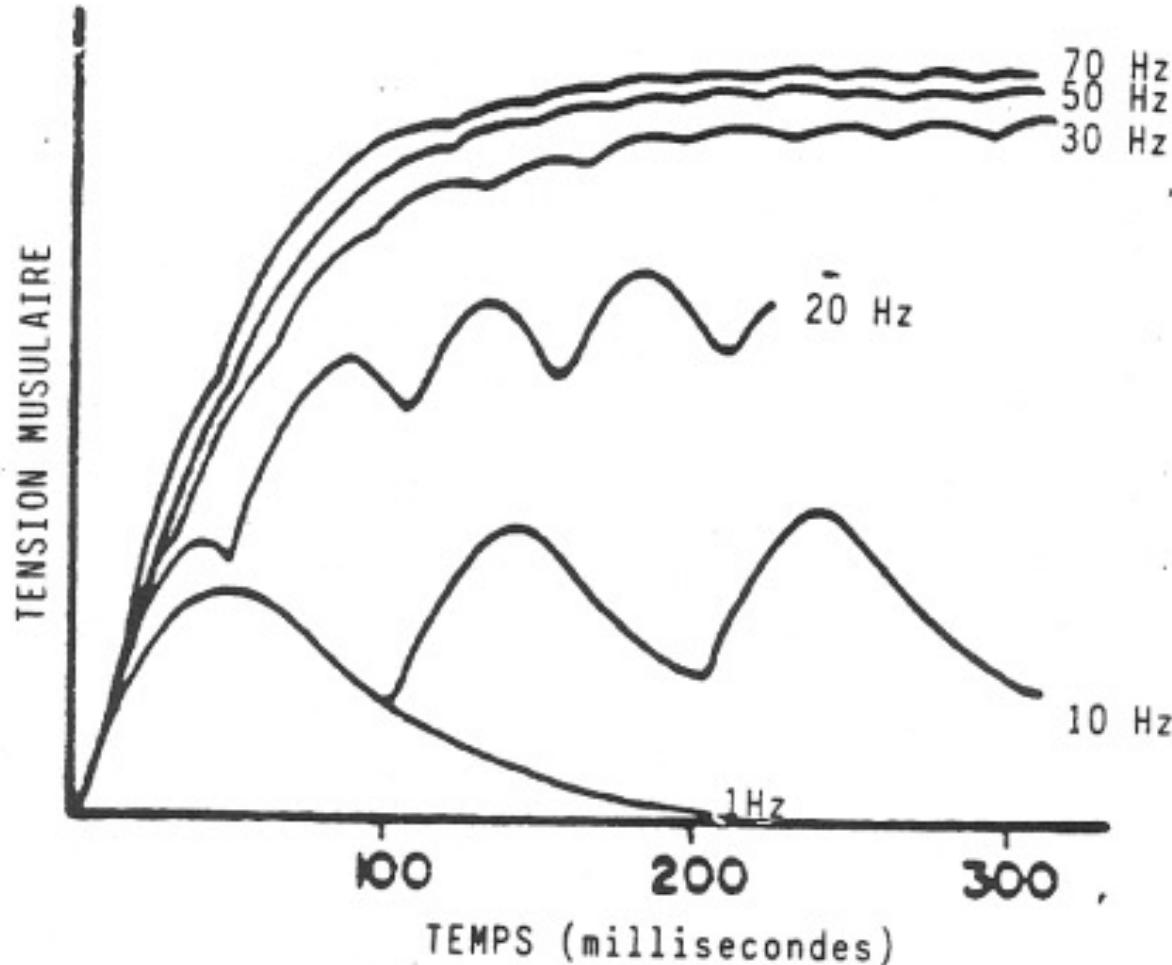
BUT

The artificial stimulation recruits fibers in a non-selective and spatially-fixed way and synchronously.

ARTIFICIAL FIBER RECRUITMENT



Force as a function of frequency



Temporal summation

NOTE: natural stable contraction is achieved by motor units recruitment at 10 Hz

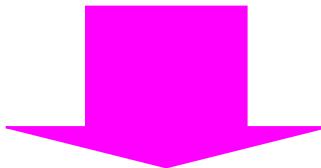
Comparison

ARTIFICIAL

- Synchronous fiber activation
- There is no “turn over” of motor units
- Recruitment order spatially fixed and (II - I)

PHYSIOLOGICAL

- Asynchronous fiber activation
- There is a “turn over” of the motor units
- Recruitment order (I-IIa-IIb)

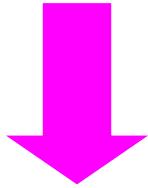


ARTIFICIAL ACTIVATION LIMITS

- Muscular fatigue
- It is difficult to modulate contractions

Changes for paretic muscles

- Reduction of the muscular fiber cross section (ATROPHY)
- Conversion of fibers: from type I (slow) to type II (fast)



NEED A MUSCULAR TRAINING PERIOD THROUGH
FES IN ORDER TO:

- Increase the muscular force and volume
- Increase the resistance to fatigue



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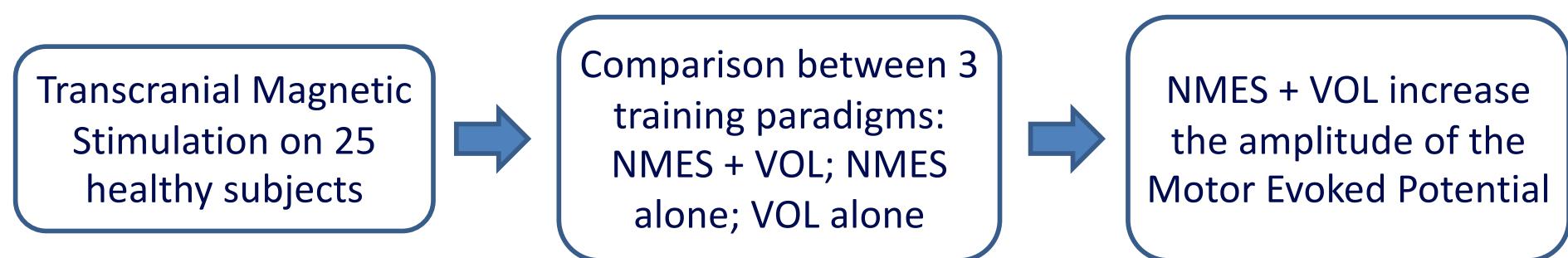
Section 2- THE NEURAL BASES OF FES FOR BRAIN PLASTICITY

FES EFFECTS FOR BRAIN PLASTICITY

NEUROPHYSIOLOGICAL HYPOTHESIS FOR IMPROVED MOTOR LEARNING

CORTICAL LEVEL

- 1) NMES-augmented voluntary activations increase cortical excitability with respect to voluntary activations alone or passive NMES [Barsi, 2008]



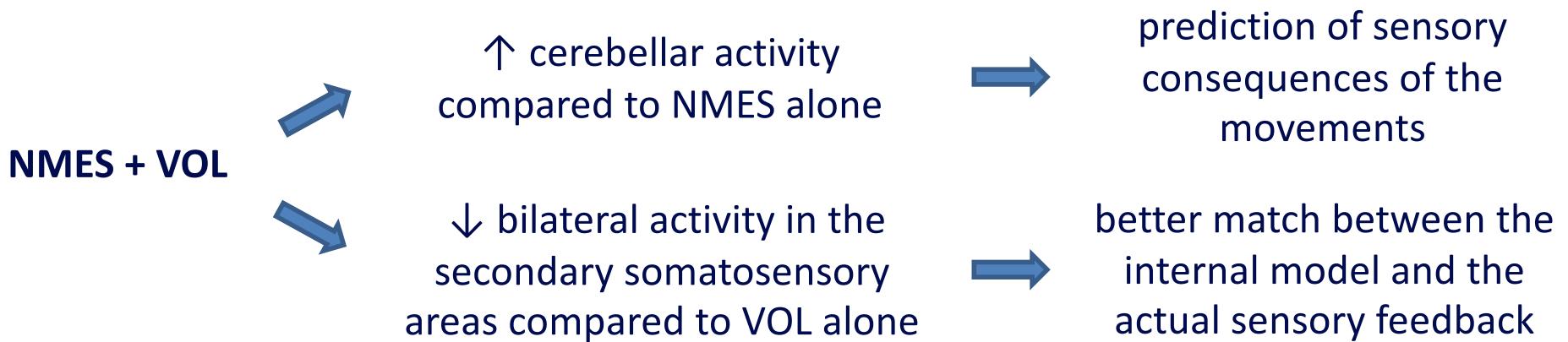
Cortical effects of FES and FES+VOL

NEUROPHYSIOLOGICAL HYPOTHESIS FOR IMPROVED MOTOR LEARNING

CORTICAL LEVEL

- 2) NMES combined with voluntary effort improves the prediction of sensory consequences of motor commands [Iftime-Nielsen, 2012]

fMRI study on 17 healthy subjects to compare cortical activity induced by NMES + VOL, NMES alone and VOL alone.

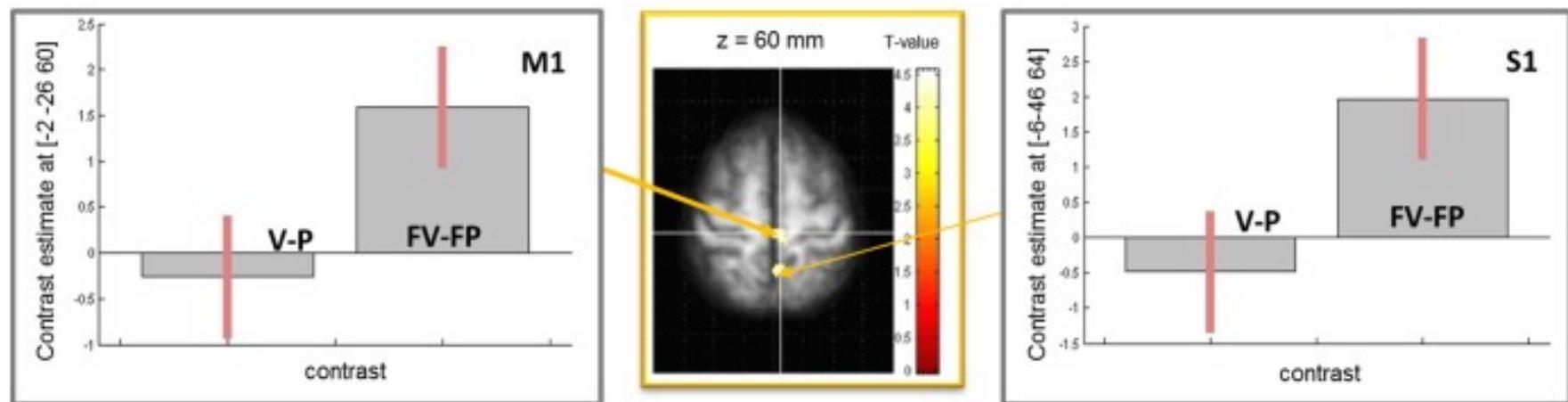


Neurophysiological hypothesis for improved motor learning

CORTICAL LEVEL

- 3) The NMES- augmented proprioception in the context of volitional intent produced a higher activation than NMES-augmented proprioception in the absence of volitional movement [Gandolla et al, 2014]

- ✓ fMRI study on 17 healthy subjects during ankle dorsi-flexion
- ✓ 2x2 factorial design, with volitional intention and NMES as factors:
 - V: only volitional; P: only passive; PV: passive + NMES; FV: volitional + NMES

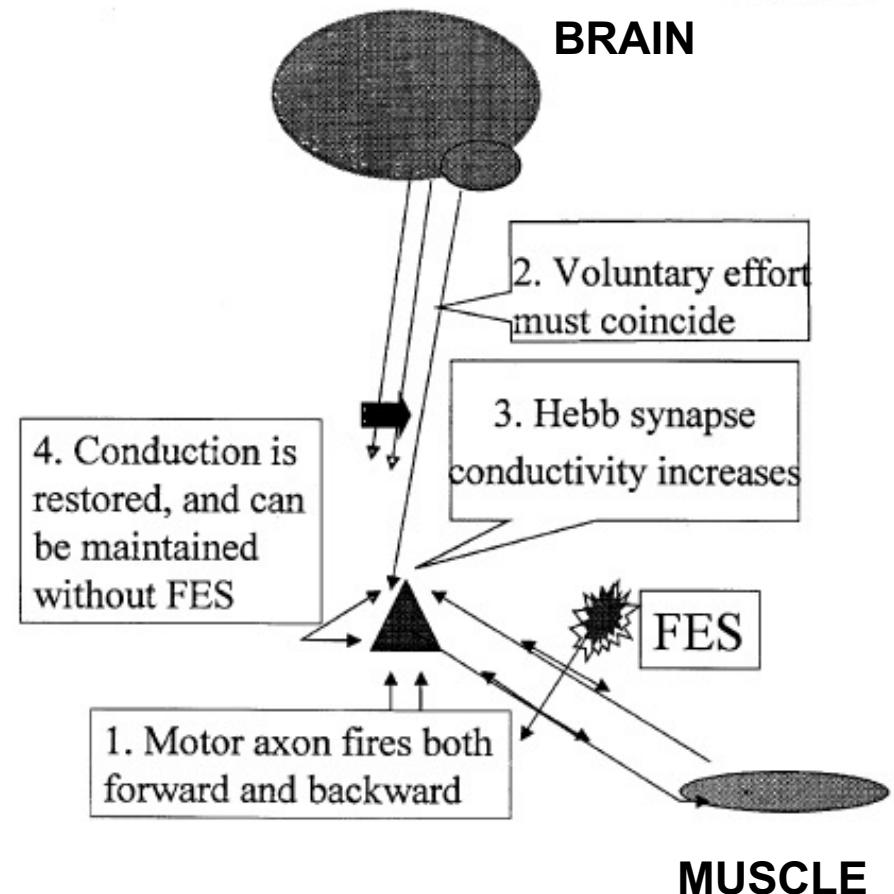


Neurophysiological hypothesis for improved motor learning

NMES antidromic impulses combined with coincident voluntary effort synchronize pre-synaptic and post-synaptic activity of the anterior horn cells



Restorative synaptic modifications at spinal level [Rushton, 2003]

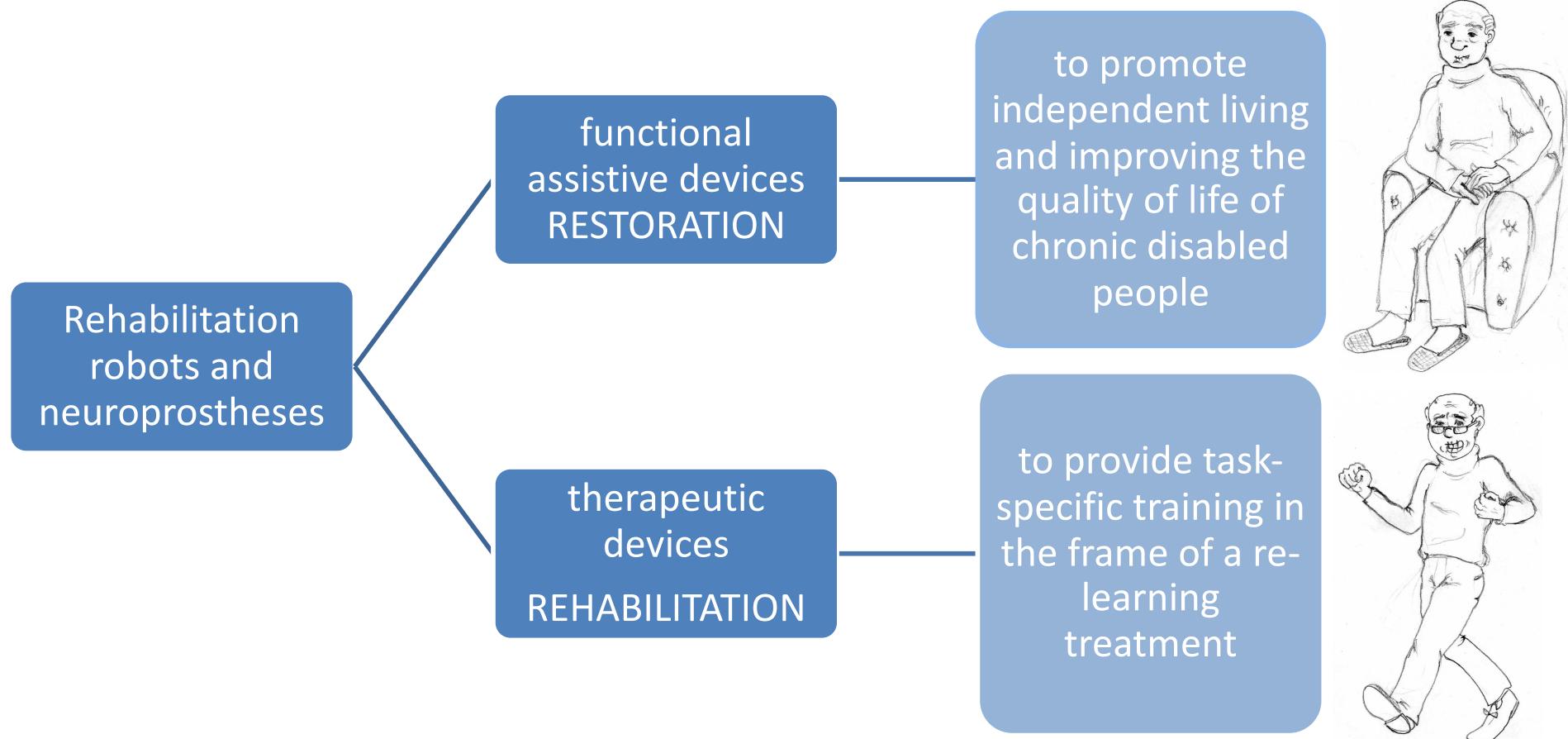




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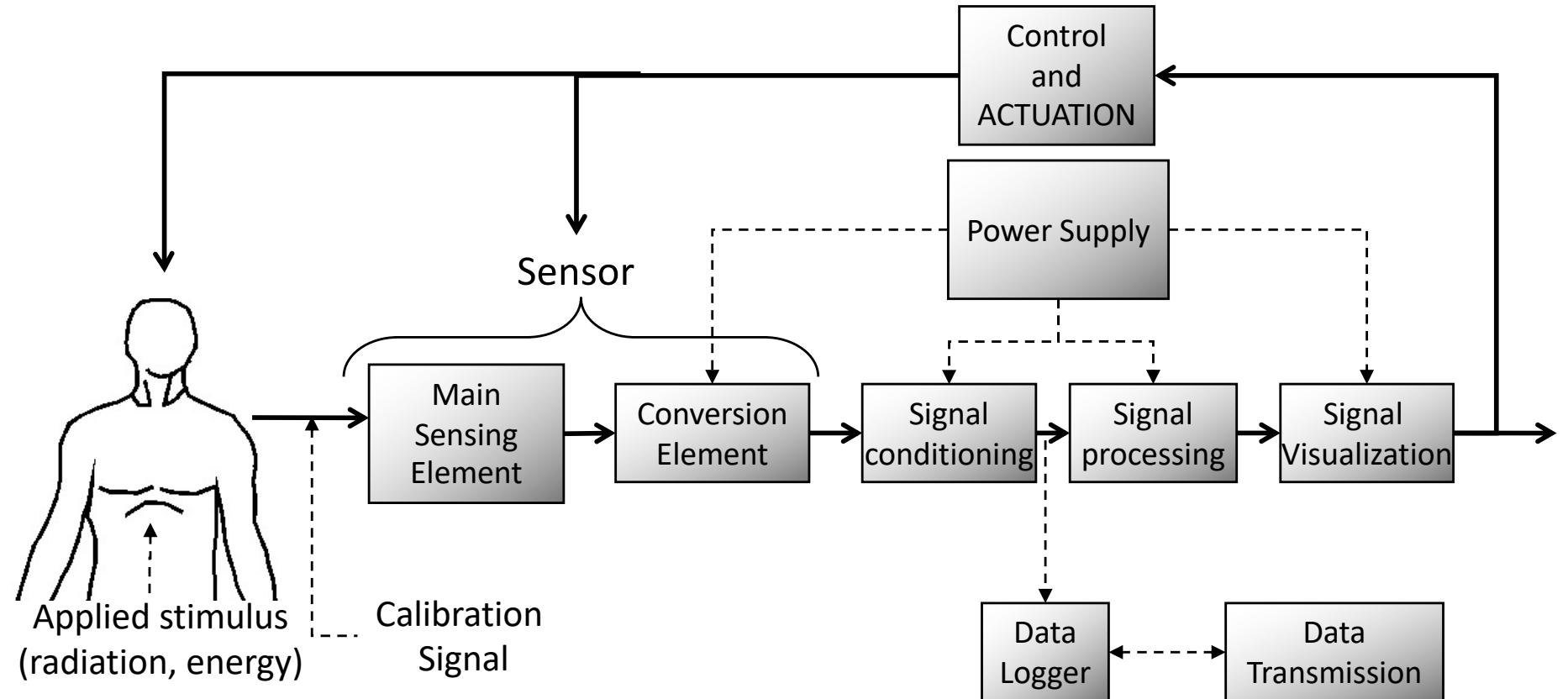
Section 3- HUMAN_MACHINE INTERACTION
INTERFACING NEUROPROSTHESES AND ROBOTS TO
SUBJECT INTENTION

Rehabilitation robotics: framework



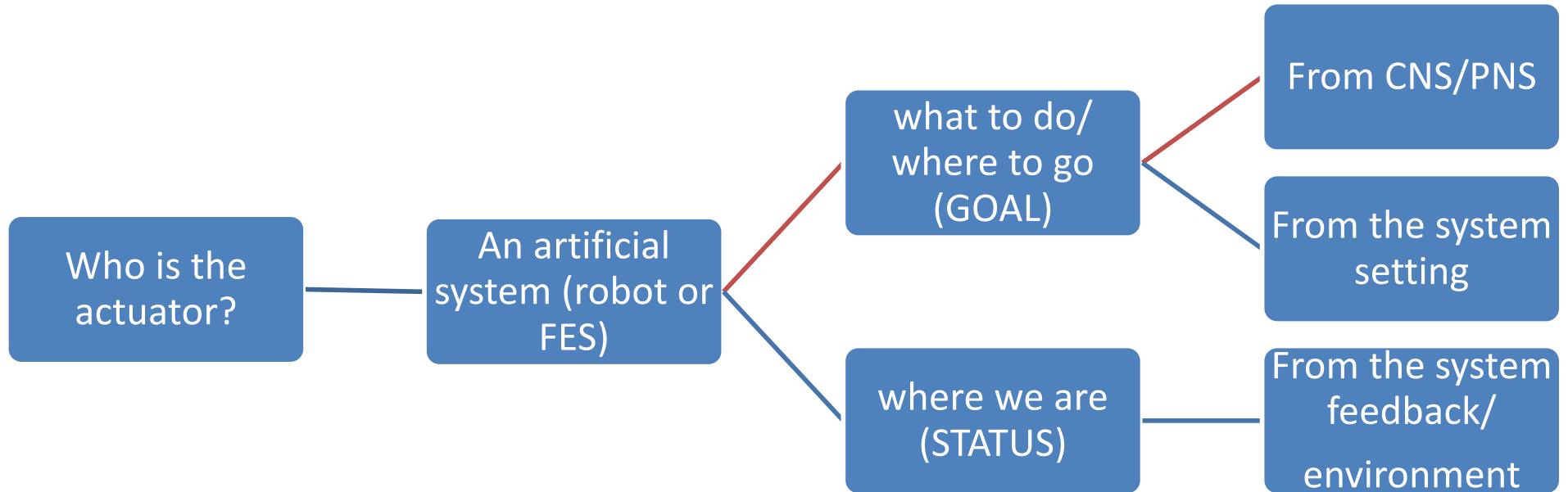
Interfacing devices (NP and ROBOTS) with subject: Sensors

Sensor: device able to convert a physical stimuli into a measureable and recordable signal



Adapted from Webster Medical Instrumentation

Neuroprostheses and robots



Goal of rehabilitation robotics and NP

Neuroplasticity: intrinsic capability of the nervous system to learn



goal of rehabilitation: effective use of neuroplasticity for functional recovery



Training aims people at

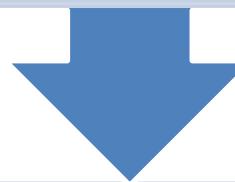
Practicing a task more intensively and safely

Progressing automatically in task difficulty

Achieving the desired movements

Motivating repetitive, intensive practice

reconnecting "intention" to "action"



ROBOTS + NEUROPROSTHESES

Goal of Assistive Neuroprostheses

Chronic damage inducing disability and preventing independent living

goal of restoration: provide the subject with a natural control of an efficient function

Assistive Neuroprostheses aim people at

Long-term regain of independent functions

reconnecting "intention" to "action"

Psychological benefits of natural control

ROBOTS+ NEUROPROSTHESES

Sensors to collect the motor command

Electroencephalogram
(EEG)

Field potential
recorded by scalp
electrodes
(BCI)

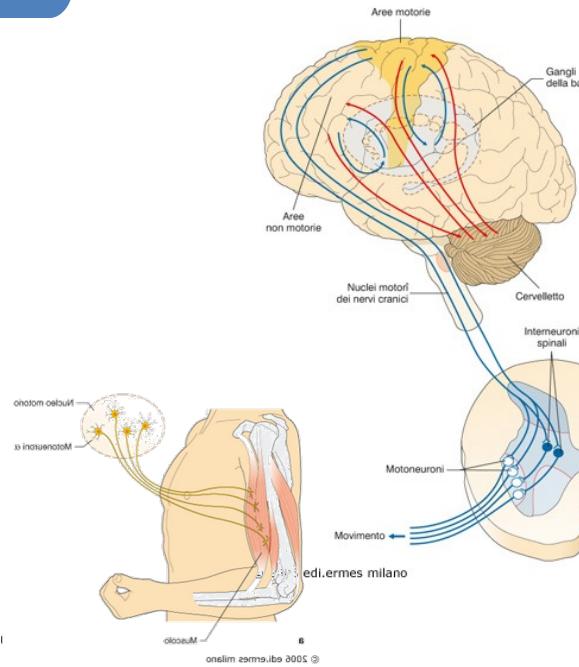
Electrocorticograms
(ECoG)

Field potentials
recorded by skull,
epidural or subdural
electrodes (Local FP)

Implantes Brain Arrays
(MEA)

Multiple single units
recordings or neural
population recording
(BMI)

Electromyogram
(EMG)



Electroneurogram
(ENG)

An overall picture

A Brain

Resolution:
Major benefit:
Clinical trials:

① EEG

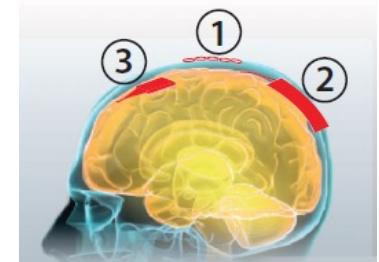
10 mm
No surgery
-236

② ECoG

2 mm
Clinical product
-5

③ Brain array

0.1 mm
Single neuron specificity
-6



B Peripheral nerves



Cuff electrode

Surface activation

LIFE electrode

Longitudinal activation

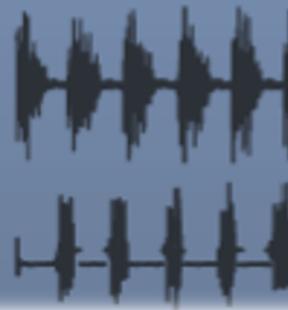
TIME electrode

Transverse activation

Selectivity →

C Muscles and kinematics

EMG sensors



Kinematic reconstruction



Implantable sensors



Adapted from Borton et al Sci Transl Med 5, 210 rv2, 2013

EEG-controlled Neuroprostheses (BCI)

Setting

Scalp electrodes
(wet or dry)

International electrodes
positioning 10-20

Signal pre-processing
(bandpass DC-100 Hz)

Data processing

Natural brain rhythms
modulation (motor
imagery) Event related
Synch/desync ERD/ERS

Movement related
potentials (MRP)

Visual Event
potential(SSVEP)

Event- related Potential
(P300)

Problems/Challenges

Time for setting up

Each session calibration
(about 30 minutes)

Required training of the
subject

BCI illiteracy

Multi Electrodes Arrays controlled robots (BMI)

Setting

Cortical arrays of electrodes
(4x4mm)

One single implantation in M1 (hand area, Hochberg; two for Collinger)

Signal pre-processing (spike detection, spike sorting , spike classification)

Data processing

Spike decoding
observation-based seven dimensional neural decoder of firing rate

model that linearly related neural firing rate to movement velocity

orthoimpedance attenuated the brain-command component perpendicular to the ideal seven-dimensional trajectory

Problems/challenges

Surgery

Each session calibration
(about 15 minutes)

Required training of the subject (three times per week for 13 weeks; each session was about 4 h, Collinger et al)

Illiteracy? few tested people so far

Is the simplest, cheapest and most usable solution?

BMI Some examples



Collinger et al Lancet 2013; 381: 557–64



Hochberg LR et al Nature 2012; 485: 372–75

ENG-controlled robots

Setting

Peripheral nerves activity

Cuff electrodes /transversal
Electrodes

Data processing

Triggering of Drop foot
stimulations

Control of hand
neuroprostheses (Tombini
et al): efferent fibers
MOTOR NP

Problems/Challenges

Surgery

Required training of the
subject

Illiteracy? few tested people
so far

EMG-controlled robots

Setting

Signal generated by muscular contraction

(Mostly) Surface electrodes

Band 10-500Hz

Data processing

Triggering of Impedance control robots

Triggering of FES by other muscles

Triggering of FES by the same target muscle
(Blanking circuit)

Myocontrolled NP
(Blanking circuit + extraction of volitional control)

Problems

Electrodes positioning, electrode-skin contact instability and calibration at each session (about 15 min)

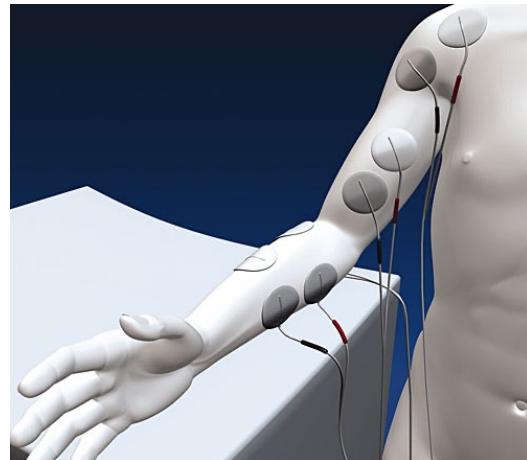
Crosstalk from adjacent muscles

Same muscle control only if a weak but functional activation is still present

In the case of other muscles control the resulting task is rather unnatural

EMG triggered FES

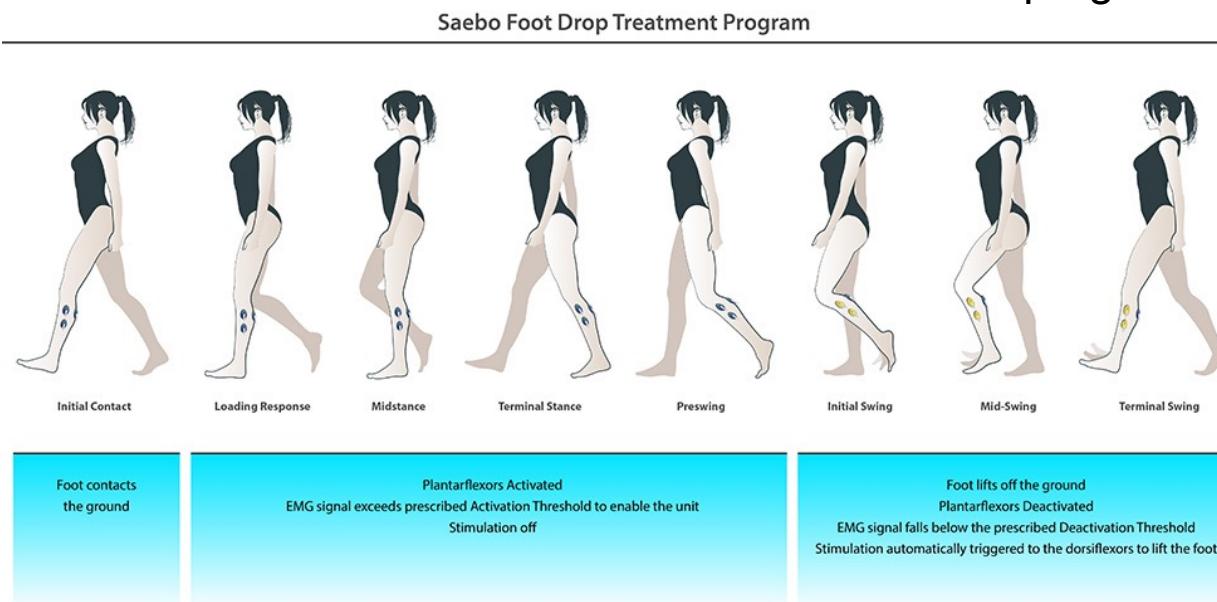
STIWELLmed4
EMG trigger of 4
channel
stimulation



Biomove



Saebo Myotrac Infinity
EMG trigger +
Reciprocal EMG Triggered Stimulation
program.



Technical challenges to make myocontrolled NP

TWO DIFFERENT SOLUTIONS OF MYOCONTROLLED NEUROPROSTHESES

1) *EMG-TRIGGERED NMES*

Residual volitional EMG is used to **trigger** the onset of a **predetermined simulation sequence** applied in an **open-loop modality** to the same muscle used for control.

2) *EMG-CONTROLLED NMES*

Residual volitional EMG is used to **modulate the stimulation intensity** in a **closed-loop modality** to the same muscle used for control.

Myocontrolled NP

TWO DIFFERENT SOLUTIONS OF MYOCONTROLLED NEUROPROSTHESIS

	EMG-TRIGGERED NMES	EMG-CONTROLLED NMES
PROS	Simple to implement → EMG signal is measured only before NMES starts	Assure the synchronization between NMES and voluntary effort
CONS	No guarantees about the synchronization between NMES and voluntary effort	More complex technological solutions are needed for the design

EMG signal during hybrid muscle contractions

Hybrid muscle activations: muscle contractions both volitional and electrically induced [Langzam, 2006]

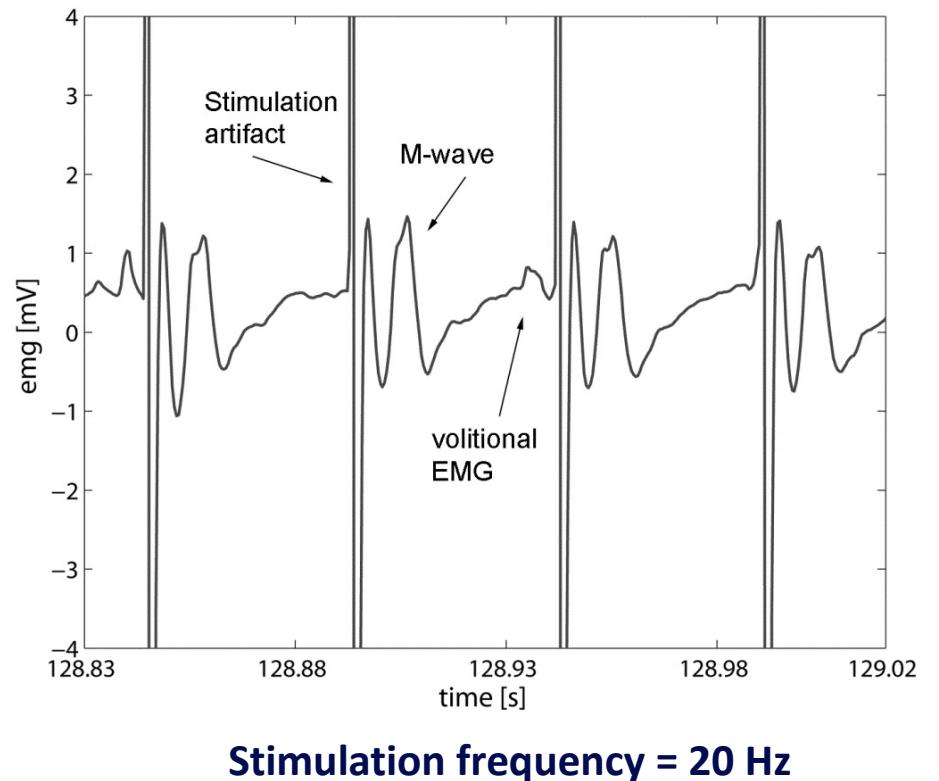
Stimulation artifact: spike lasting few ms due to the electric field generated by the stimulation current

M-wave: compound action potential due to the synchronous firing of the electrically elicited muscle fibers (some mV)

H-reflex: second waveform determined by the orthodromic sensory volley

F-wave: small second compound action potential due to the antidromic efferent stimuli

Volitional EMG: stochastic signal with an amplitude of at least one magnitude less than the M-wave



Devices for EMG recording during FES

Standard amplification unit for EMG recordings can not be used in the presence of NMES



The **stimulation artifact** is the result of a potential difference produced by the stimulation current between the EMG electrodes → it **can not be rejected by the differential amplifier**

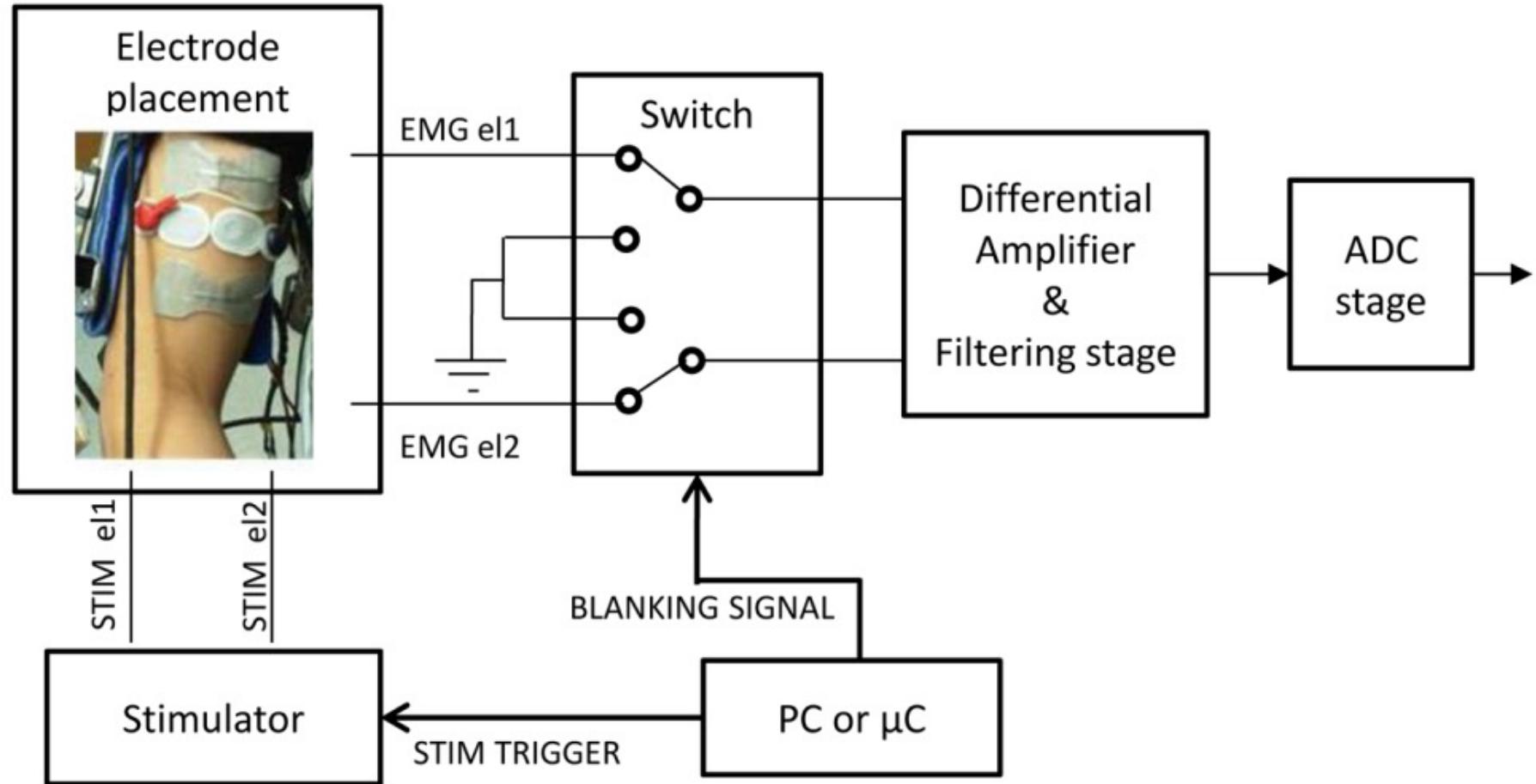


Since its amplitude is one to three orders greater than the M-wave, it can **saturate or even damage the amplifier of a standard EMG circuit**

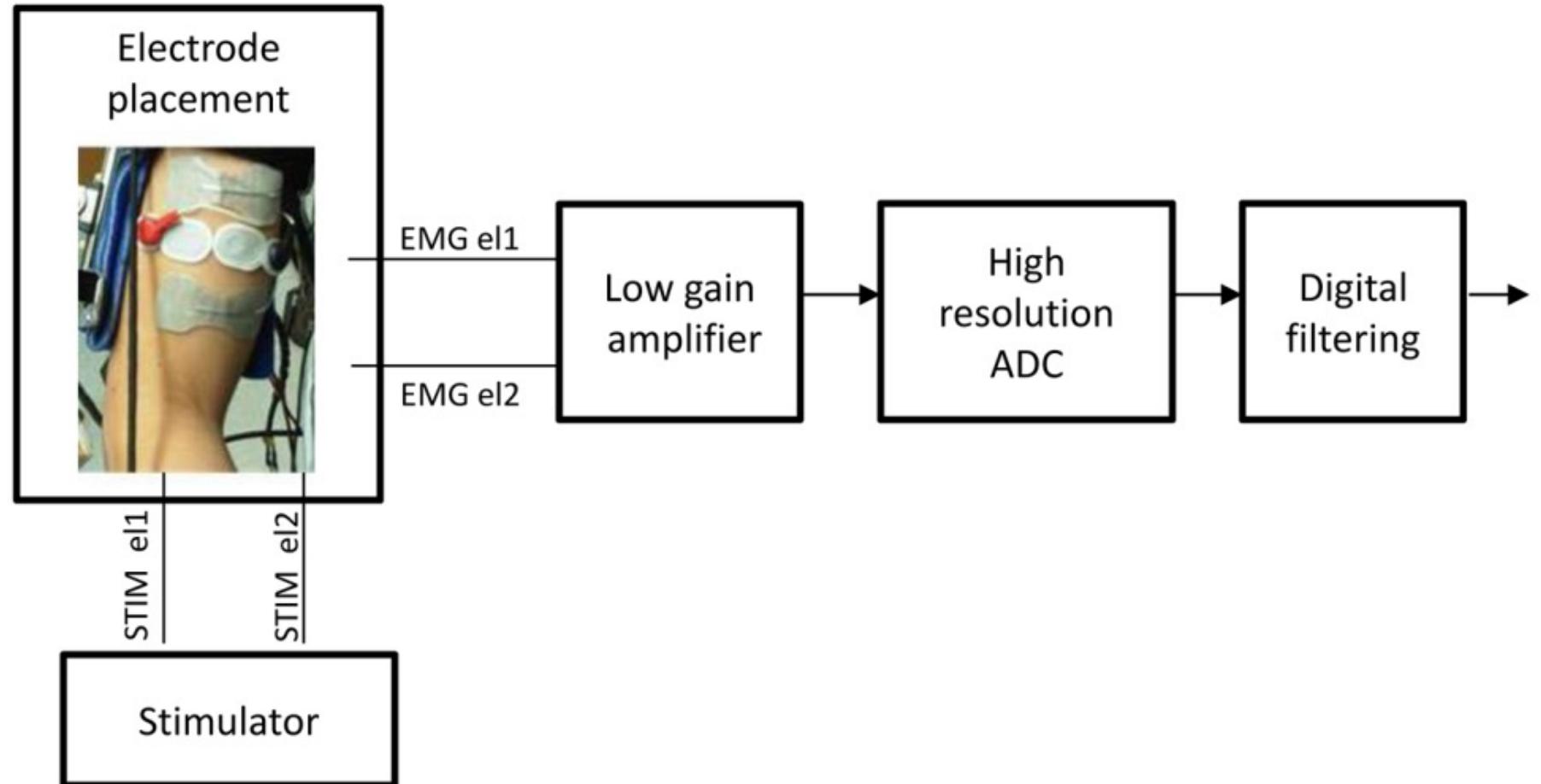


Different solutions have been proposed to face the problem of the **suppression of the stimulation artifact**.

Devices for EMG recording during FES - Blanking



Devices for EMG recording during FES – low gain amplifier



Devices for EMG recording during FES

RECORDING AND STIMULATION ELECTRODE

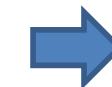
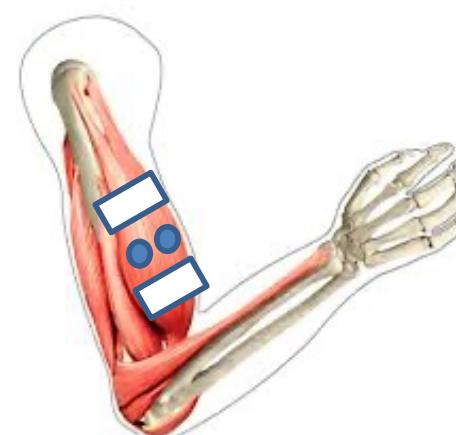
Standard solution: separate recording and stimulation electrodes

The relative placement of the electrodes affect the capability of the system to suppress the stimulation artifact

Regular placement for
EMG recordings
(SENIAM guidelines)



This placement is
preferred in the presence
of NMES [Frigo, 2000]



Higher common mode
component of the
stimulation artifact

- Stimulation electrode
- Recording electrode

Extract volitional EMG from hybrid contraction recording

Blocking window [Langzam, 2006]

The signal is zeroed for the first 20 or 25 ms of each inter-pulse period.

The volitional EMG is estimated from the remaining part of the inter-pulse period.

→ The M-wave is not completely removed

High-Pass filter [Muraoka, 2002; Schauer, 2004]

Assumption: 20-30 ms after the stimulation pulse, only low-frequency electrically-induced components superpose the volitional EMG

Blocking window + high-pass filter with a cut-off frequency between 200 and 330 Hz

Extract volitional EMG from hybrid contraction recording

Linear Prediction Adaptive filter [Sennels, 1997]

Assumption: the volitional EMG is a band-limited Gaussian signal and the M-wave is time-variant

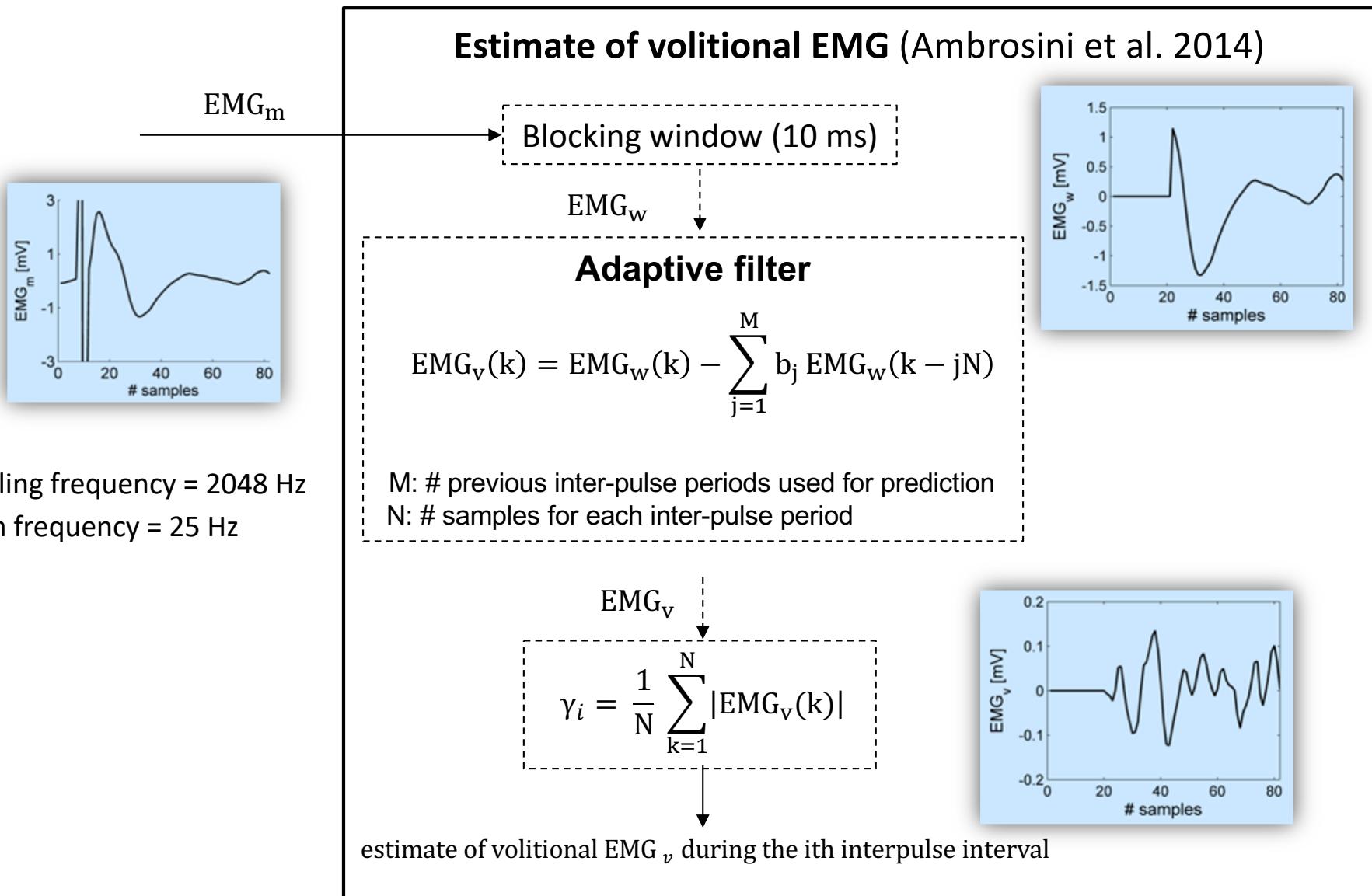
$$EMG_v(n) = EMG_r(n) - \sum_{j=1}^M b_j EMG_r(n - jN)$$

M number of previous inter-pulse periods used for prediction (6)

b_j filter coefficients computed by solving a least square algorithm that minimizes the output energy of the current inter-pulse period

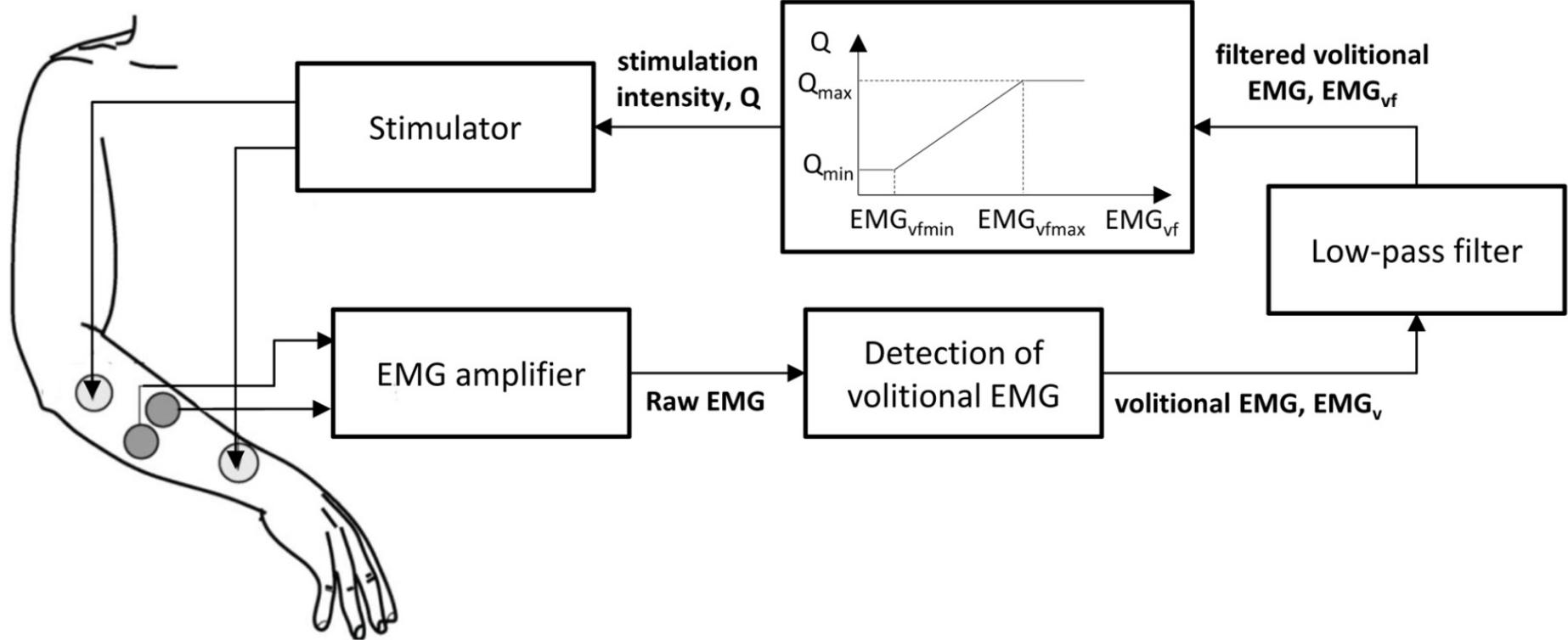
b_j are updated at a rate equal to the stimulation frequency

Linear prediction adaptive filter



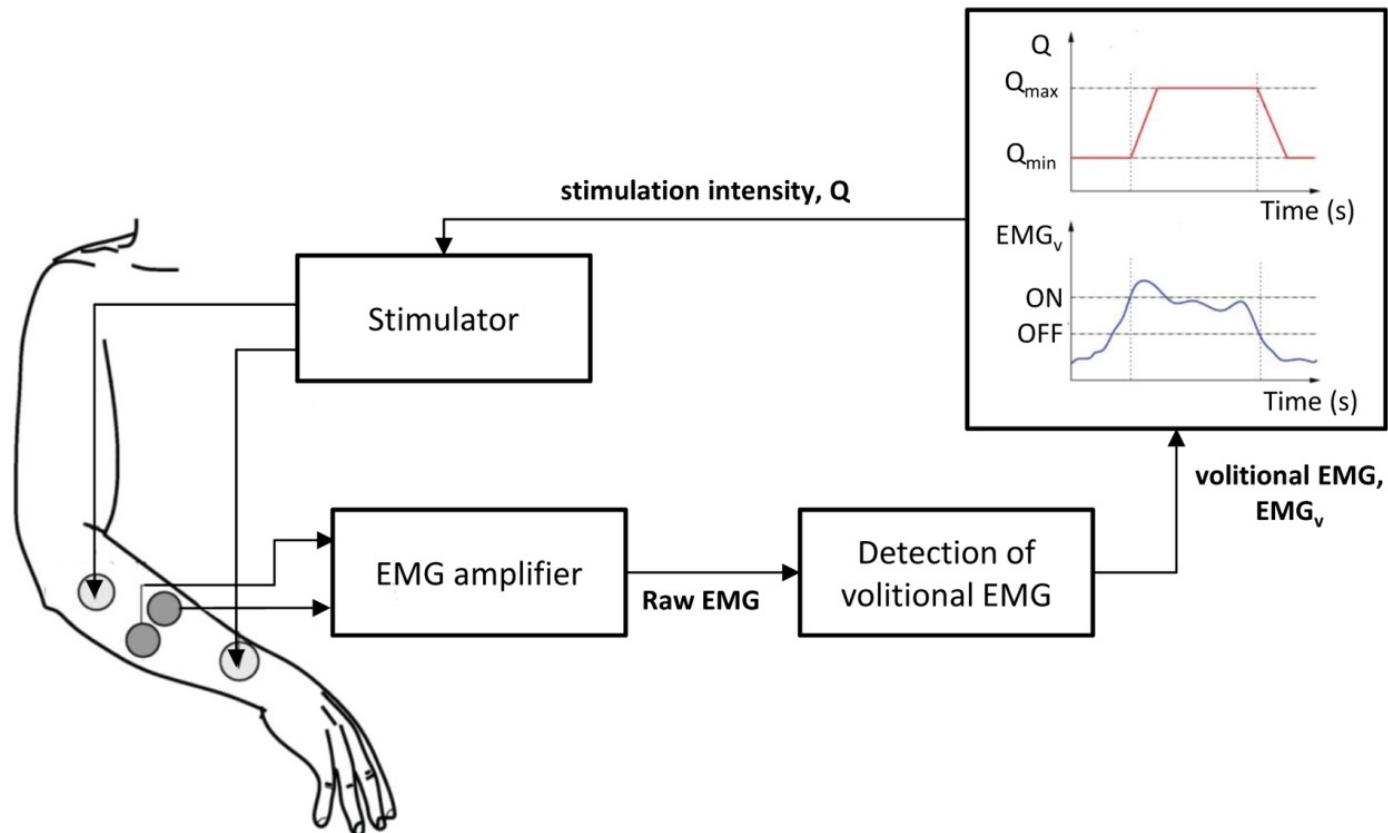
Design myocontrolled NP: control strategies

PROPORTIONAL CONTROLLER



Design myocontrolled NP: control strategies

ON/OFF CONTROLLER



Design myocontrolled NP: control strategies

Only few clinical applications of EMG-controlled neuroprostheses exist.

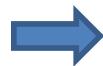
- 1) EMG-proportional controller supports hand functions during daily life activities in people with Spinal Cord Injury [Thorsen 1999, 2001, 2006]



assistive system

stimulation of a muscle closed to the one used for control

- 2) EMG-proportional controller improves hand functions in post-stroke patients [Fujiwara 2009; Shindo 2011]



rehabilitative purposes

same electrodes for stimulation and recordings

stimulation of the same muscle used for control

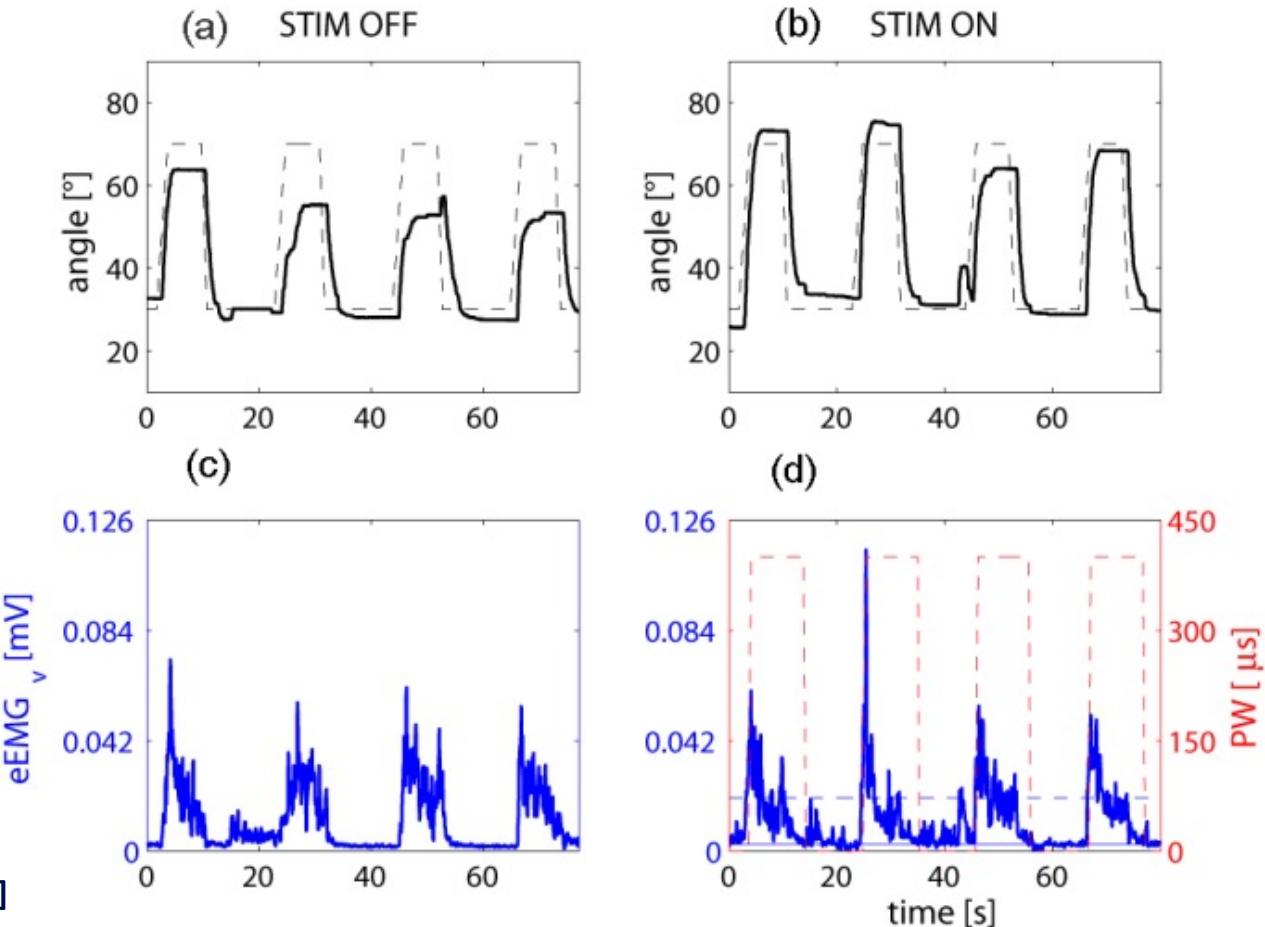
Example of applications

Test of the ON/OFF controller

Task: elbow flexion-extension with and without myocontrolled-NMES support

Participants: 2 healthy subjects and 3 people with Spinal Cord Injury

The neuroprosthesis was integrated with a passive exoskeleton for weight relief to further support the patients.



[Ambrosini et al, JEK, 2014]

Conclusions

Restoration /rehabilitation

Sensors to connect intention to action: neuroprostheses

- Motor NP/Robots
 - EEG controlled NP
 - MEA controlled NP
 - ENG controlled NP
 - EMG controlled NP

TAKE HOME MESSAGES

The main resource is always brain neuroplasticity

The optimal sensor and NP solution depends on the target of the application and the disability

BCI neuroprostheses and Artificial Intelligence (Sept 2018)

Brain–computer interface (BCI) neurotechnology has the potential to reduce disability associated with paralysis by translating neural activity into control of assistive devices. Surveys of potential end-users have identified key BCI system features, including high accuracy, minimal daily setup, rapid response times, and multifunctionality. These performance characteristics are primarily influenced by the BCI’s neural decoding algorithm, which is trained to associate neural activation patterns with intended user actions. Here, we introduce a new deep neural network decoding framework for BCI systems enabling discrete movements that addresses these four key performance characteristics. Using intracortical data from a participant with tetraplegia, we provide offline results demonstrating that our decoder is highly accurate, sustains this performance beyond a year without explicit daily retraining by combining it with an unsupervised updating procedure, responds faster than competing methods, and can increase functionality with minimal retraining by using a technique known as transfer learning. We then show that our participant can use the decoder in real-time to reanimate his paralyzed forearm with functional electrical stimulation (FES), enabling accurate manipulation of three objects from the grasp and release test (GRT). These results demonstrate that deep neural network decoders can advance the clinical translation of BCI technology.



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Section 4- CONTROLLERS FOR NEUROPROSTHESES,
MANAGING FATIGUE USING ANN CONTROLLERS

AIM

To modulate the current stimulus during the movement according to the characteristics of the biological systems to control (non linearity and time variability) so to achieve an accurate, smooth and robust task completion

EXISTING CONTROL STRATEGIES :

- FEEDFORWARD
- FEEDBACK
- MODEL BASED
- ADAPTIVE CONTROLLERS
- CONTROLLERS BASED ON ARTIFICIAL NEURAL NETWORKS

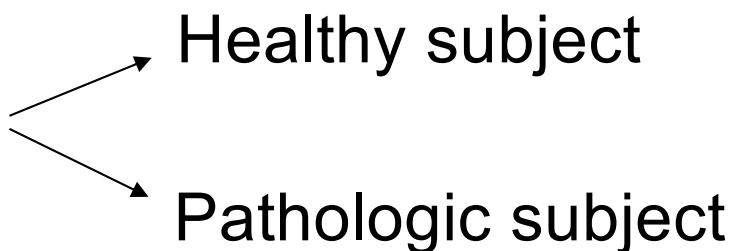
Choose a simple movement

Develop a novel control system

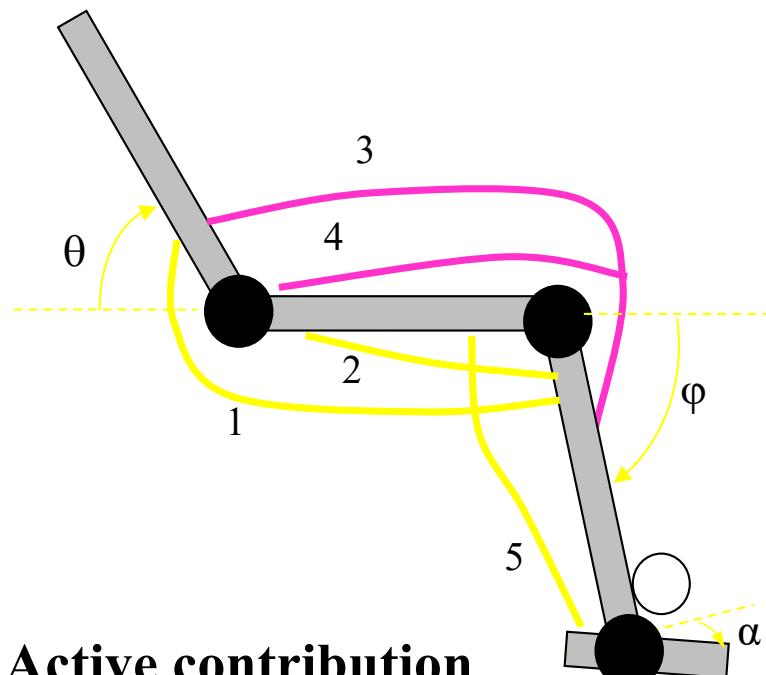
TWO STEPS:

1) Simulation trials

2) Experimental trials



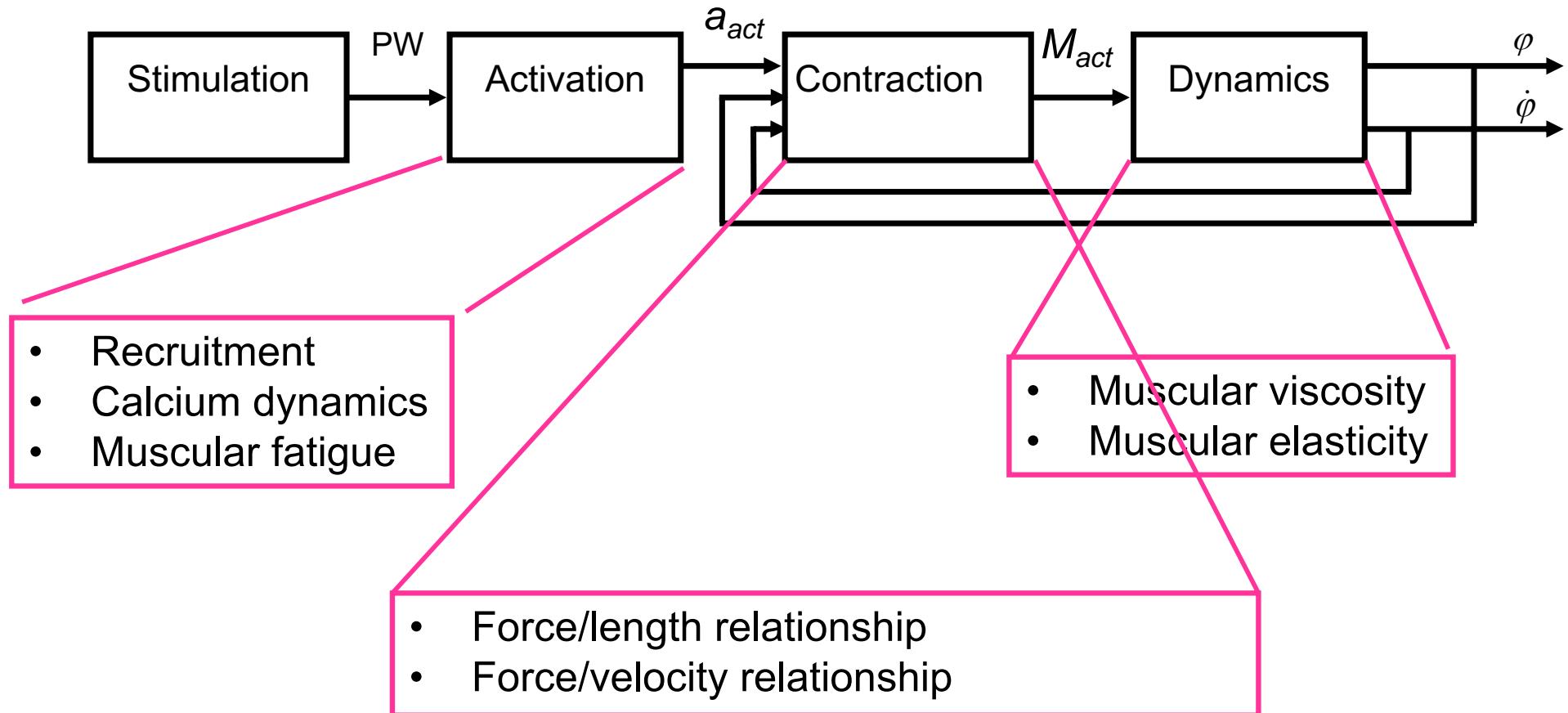
PLANT



Active contribution
Passive contribution

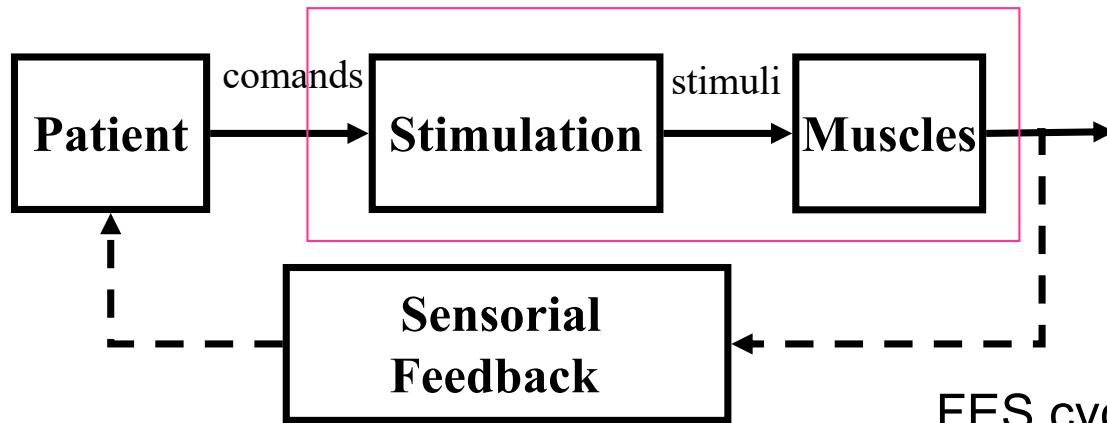
1. Biceps femoris caput lungum,
semitendinosus, semimembranosus
2. Biceps femoris caput brevis
3. Rectus femoris
4. Vasti
5. Lateral and medialis gastrocnemius

Simulation: biomechanical neuro-muscular model



Riener et al., 1997

Feed-forward Control (OPEN LOOP)



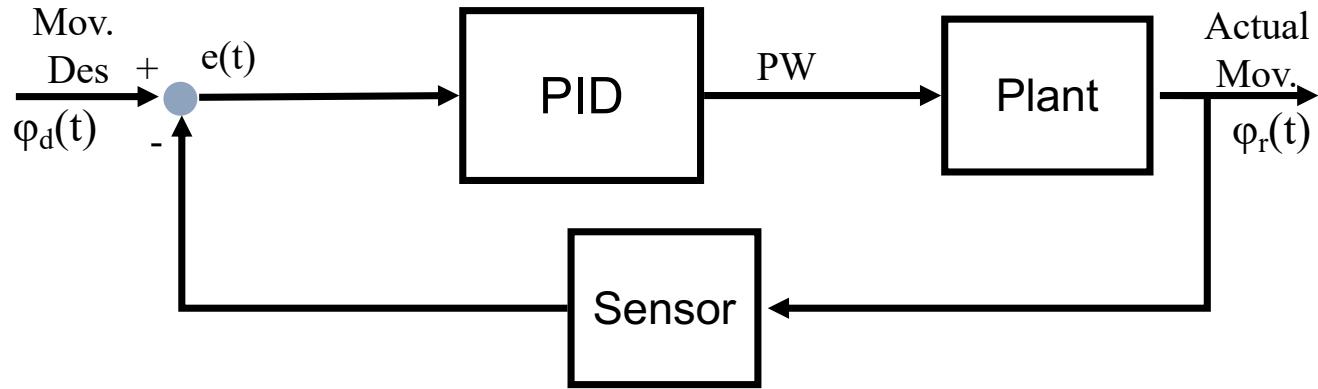
FES cycling controlled on crank angle is a feedforward automatic controller....

Fixed Stimulation trains

Stimulation triggered by manual or heel switches or measures of the task

- No disturbances' compensation
- Necessity of direct control by the patient
- Produces fixed and jerky movements
- Not adaptable to fatiguing muscles

PID controller

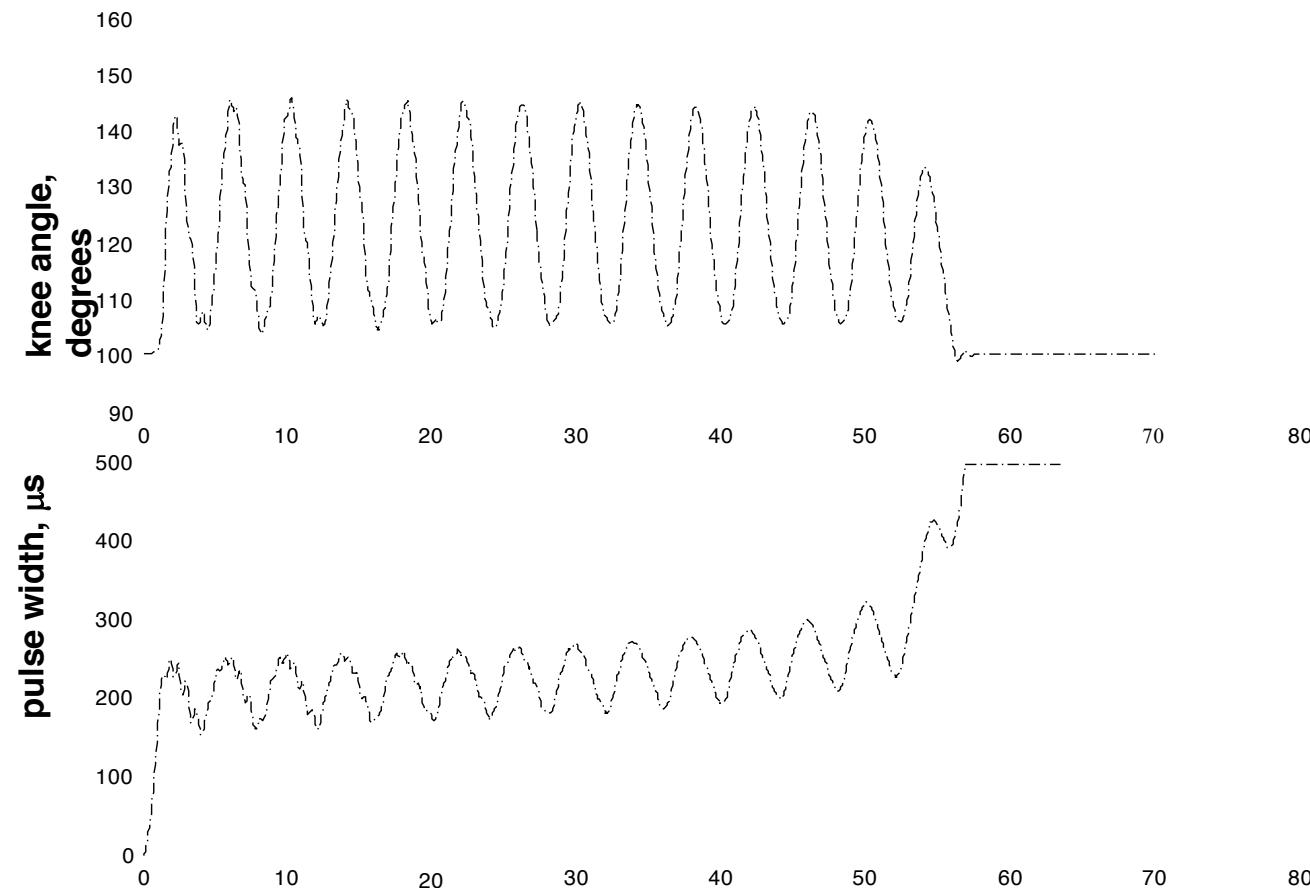


Stimulation changes according to the error between the desired and obtained signal

Compensation of unforeseen events

$$pw(t) = K_p \cdot e(t) + K_d \frac{de(t)}{dt} + K_i \cdot \int_0^t e(t) dt$$

Feedback controller

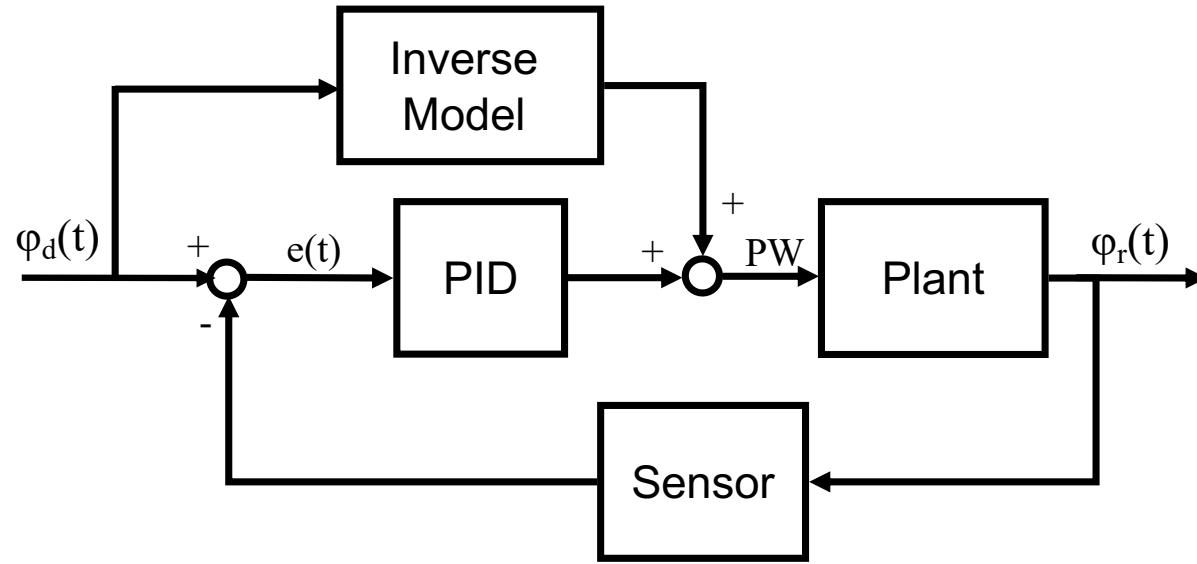


LIMITS

- Linear controller to pilot a non linear and time variant system
- Difficult identification of the controller coefficients
- Delay in the control due to the dominant pole to stabilize the feedback

Impossible to compensate fast disturbances

Model-based control

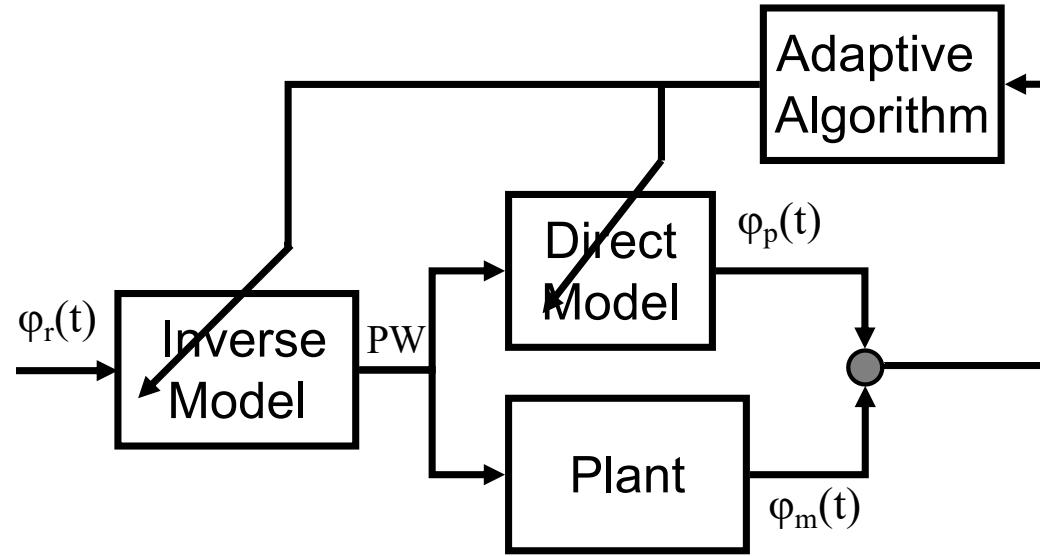


Reduction of the controller delay thanks to the introduction of the feedforward inverse model

LIMITS

- Inversion of the neuro-musculo-skeletal system
- Modellization with fixed parameters of a time variant system
- Difficultly to customize on a single subject

Adaptive controllers



Adaptive systems can follow angular trajectories when they are affected by muscular fatigue or external disturbances

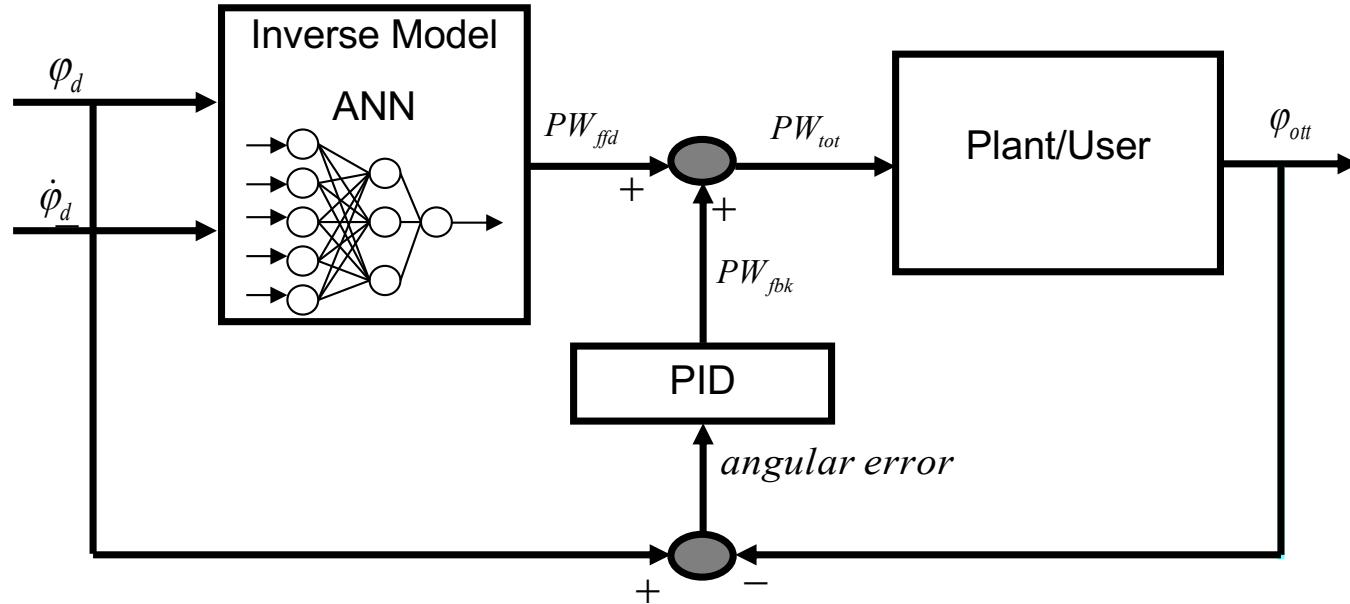
LIMITS

- Inversion of the neuro-musculo-skeletal system
- Convergence problems of the algorithm used to estimate the parameters

WHY?

- ✓ Black Box approach
- ✓ Generalization
- ✓ Adaptability
- ✓ Identification and control of non linear and time variant systems
- ✓ Availability of training set data?

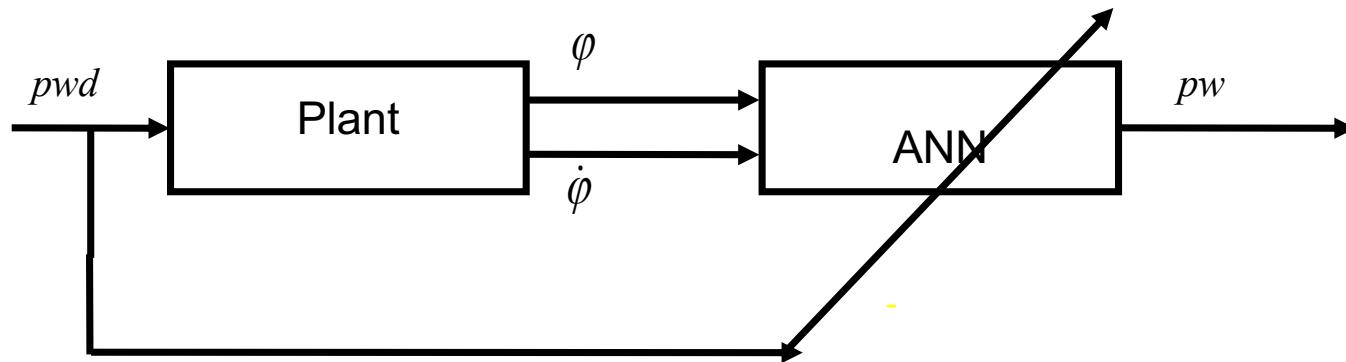
Neural Inverse Model



- ✓ Quadriceps Stimulation for knee flexion/extension
- ✓ GOAL: assure repetitions of knee flex/ext for muscular conditioning
 - ✓ Problem of fatigue controls more than trajectory tracking!
- ✓ Can we collect a training set ?

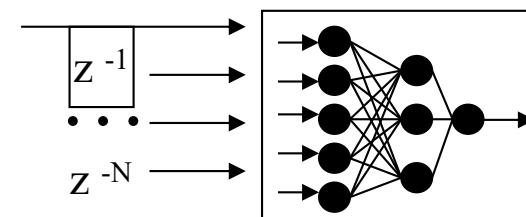
Inverse model identification: NN training set collection

TRAINING

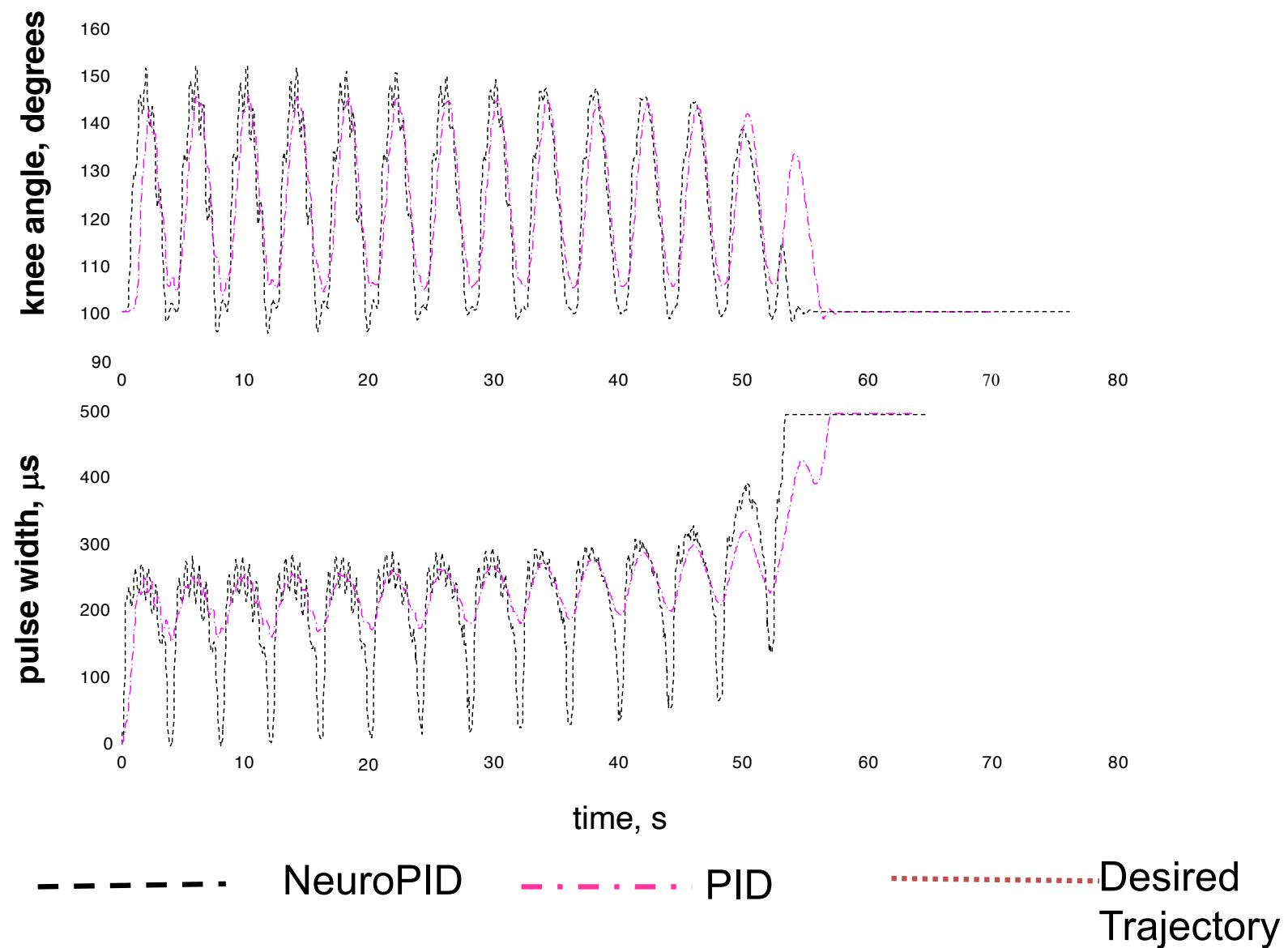


NETWORK CHOICE

- ✓ Multi layer perceptron with time delay in the inputs in order to identify the system time variability

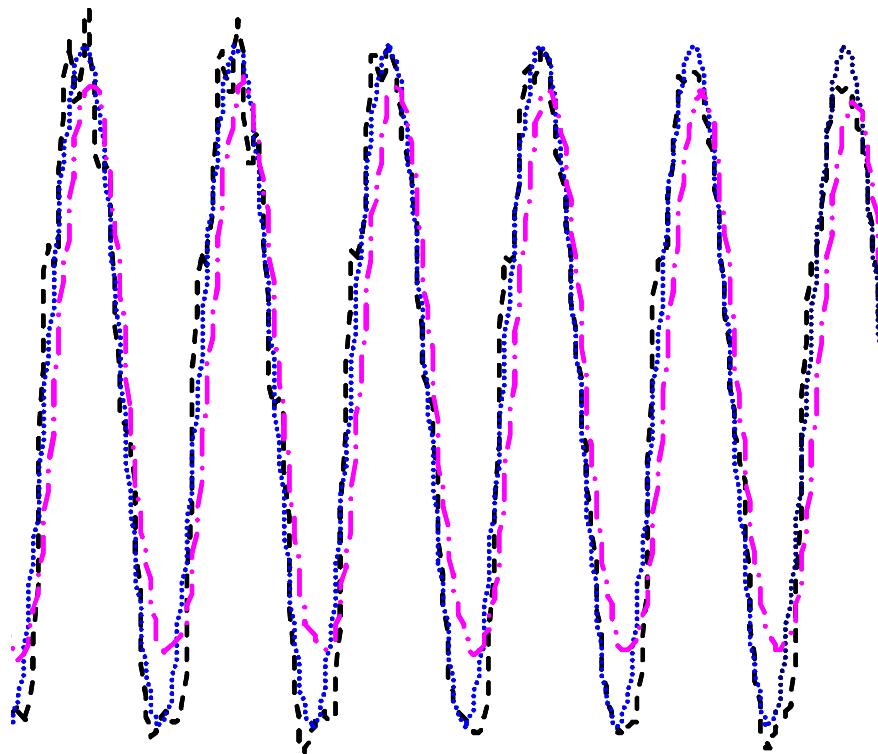


PID vs NeuroPID

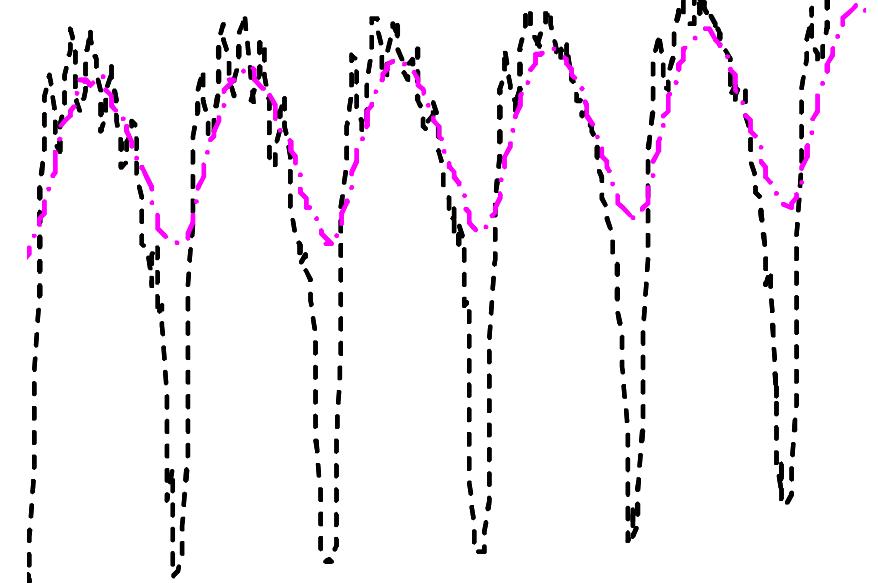


PID vs Neuro PID

Angle



Pulsewidth



----- NeuroPID

- - - - - PID

Desired
trajectory

It comprises a neural inverse model and a PID as a feedback controller

- Reduces the delay effect of the PID controller
- Overstresses the system in order to follow the desired trajectory
- Overcomes the problem of intermediate solicitations

However....

- A huge improvement with respect to the PID alone is not obtained and instead the training of the ANN inverse model is required

ERROR MAPPING CONTROLLER

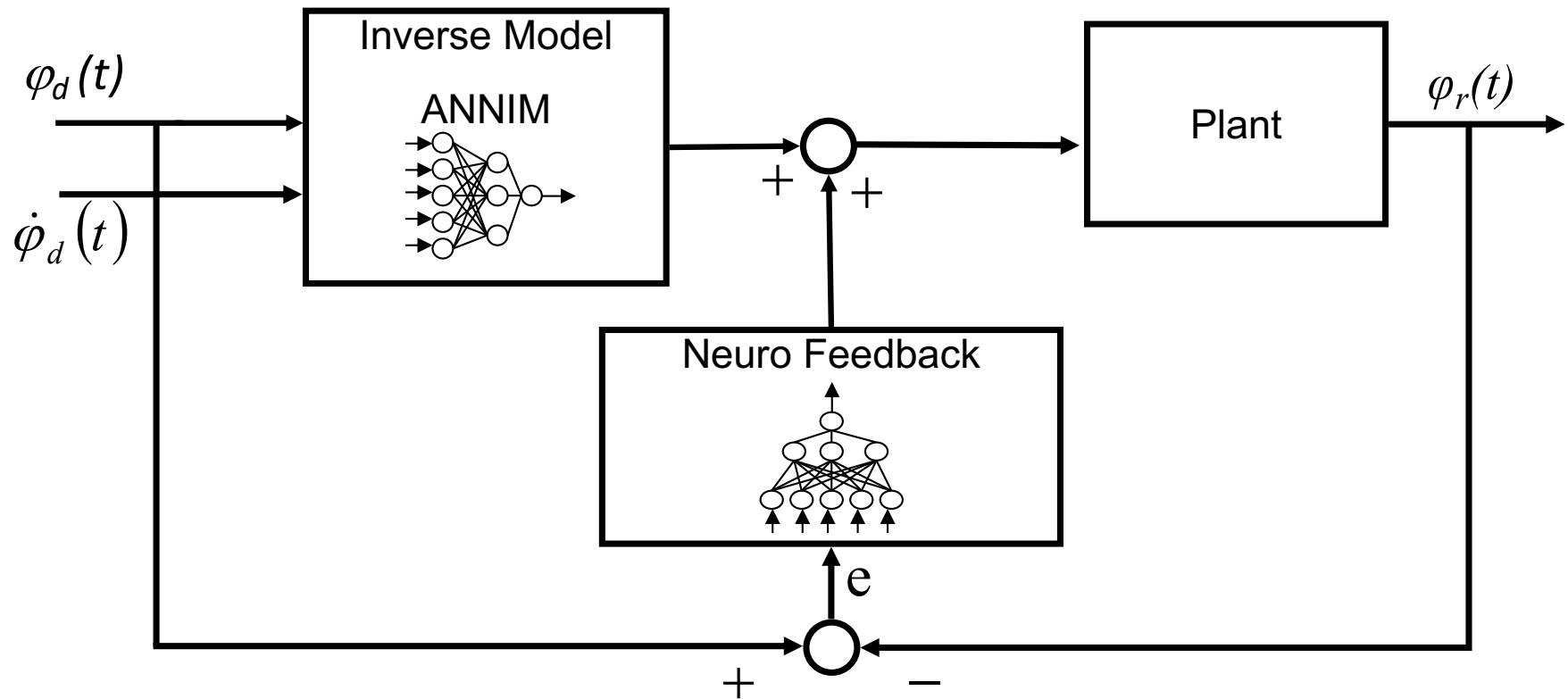
OBJECTIVE:

To make the control system able to map the muscular fatigue of the subject and not only the trajectory tracking problem

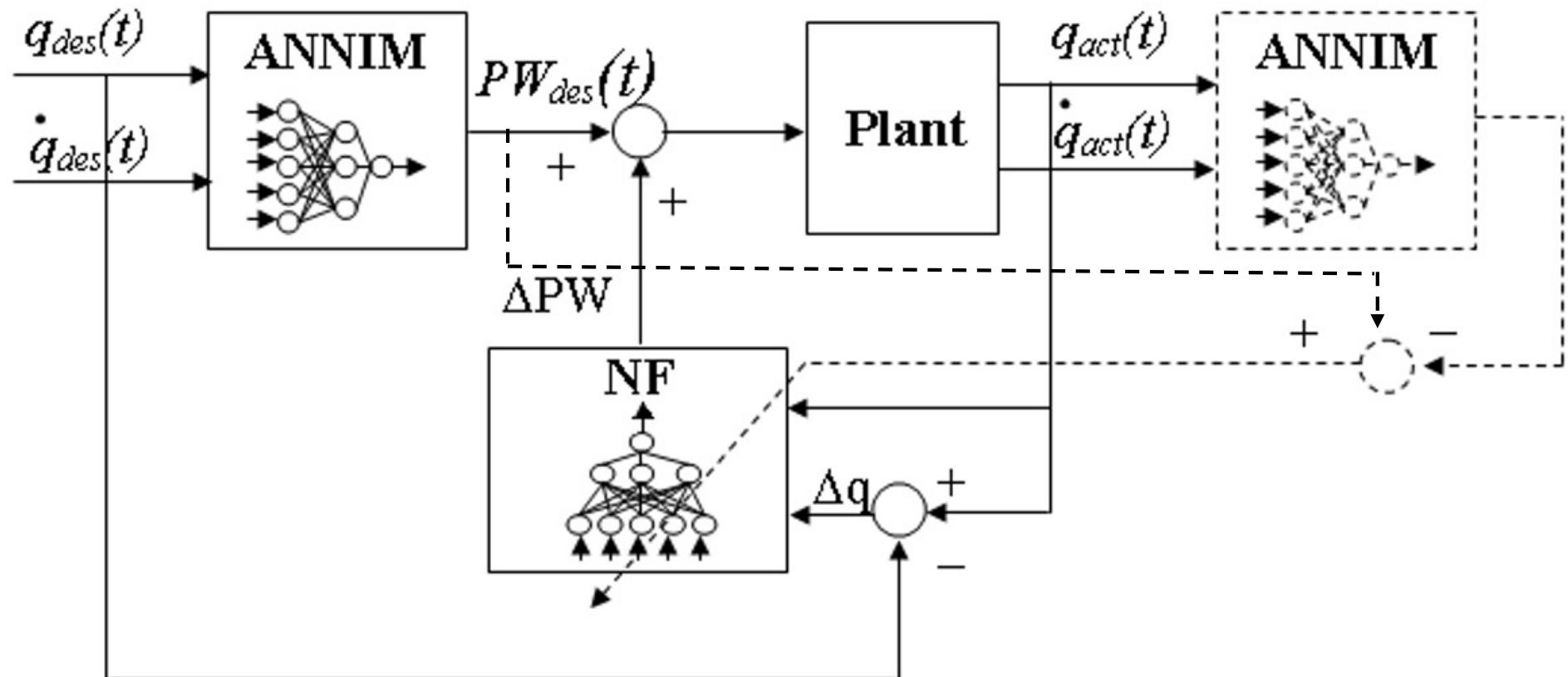
<http://www.jneuroengrehab.com/content/3/1/25>

Neurofeedback

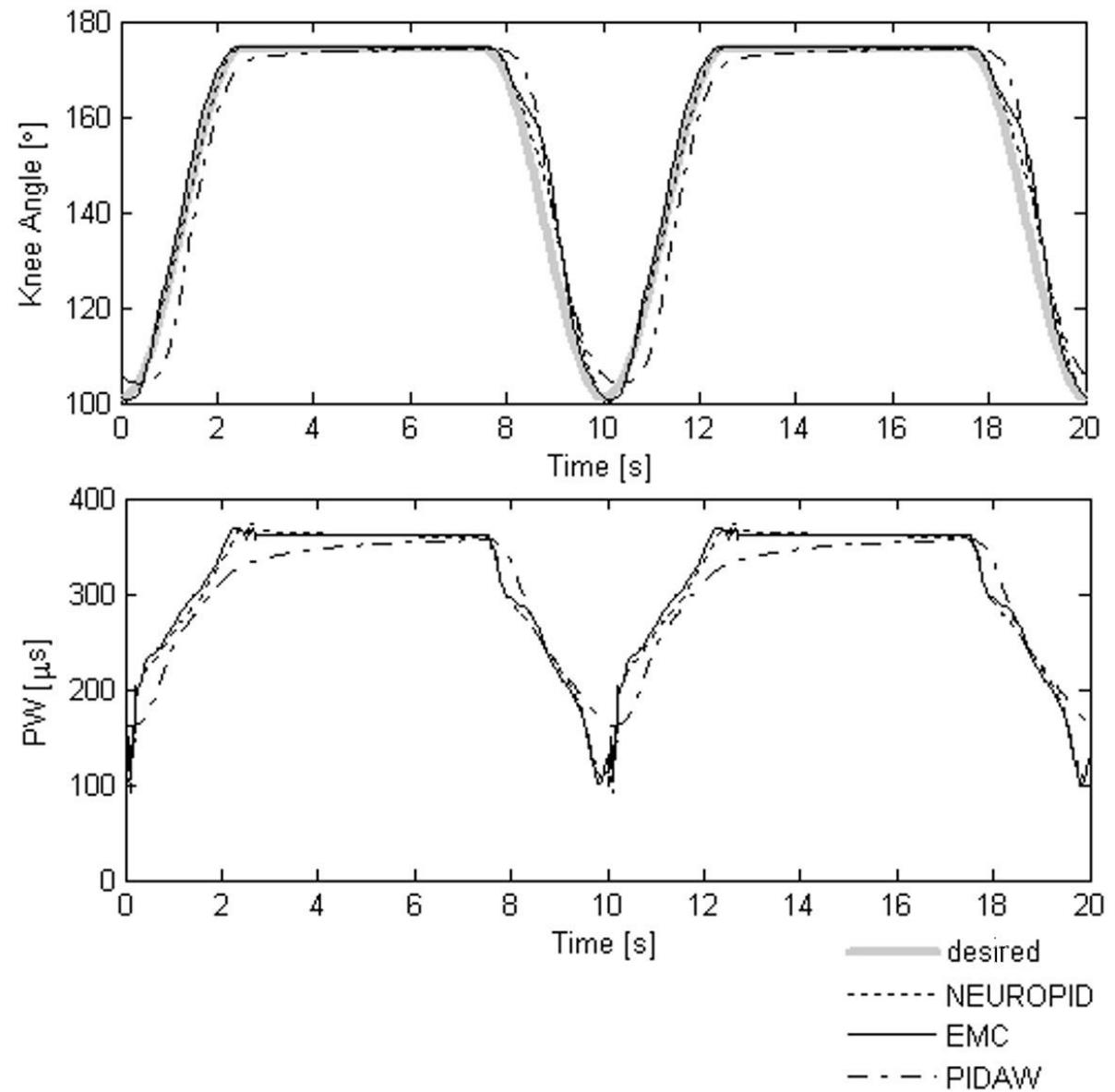
Control the stimulation patterns adapting the **time variability** to the muscular properties of a **single subject**



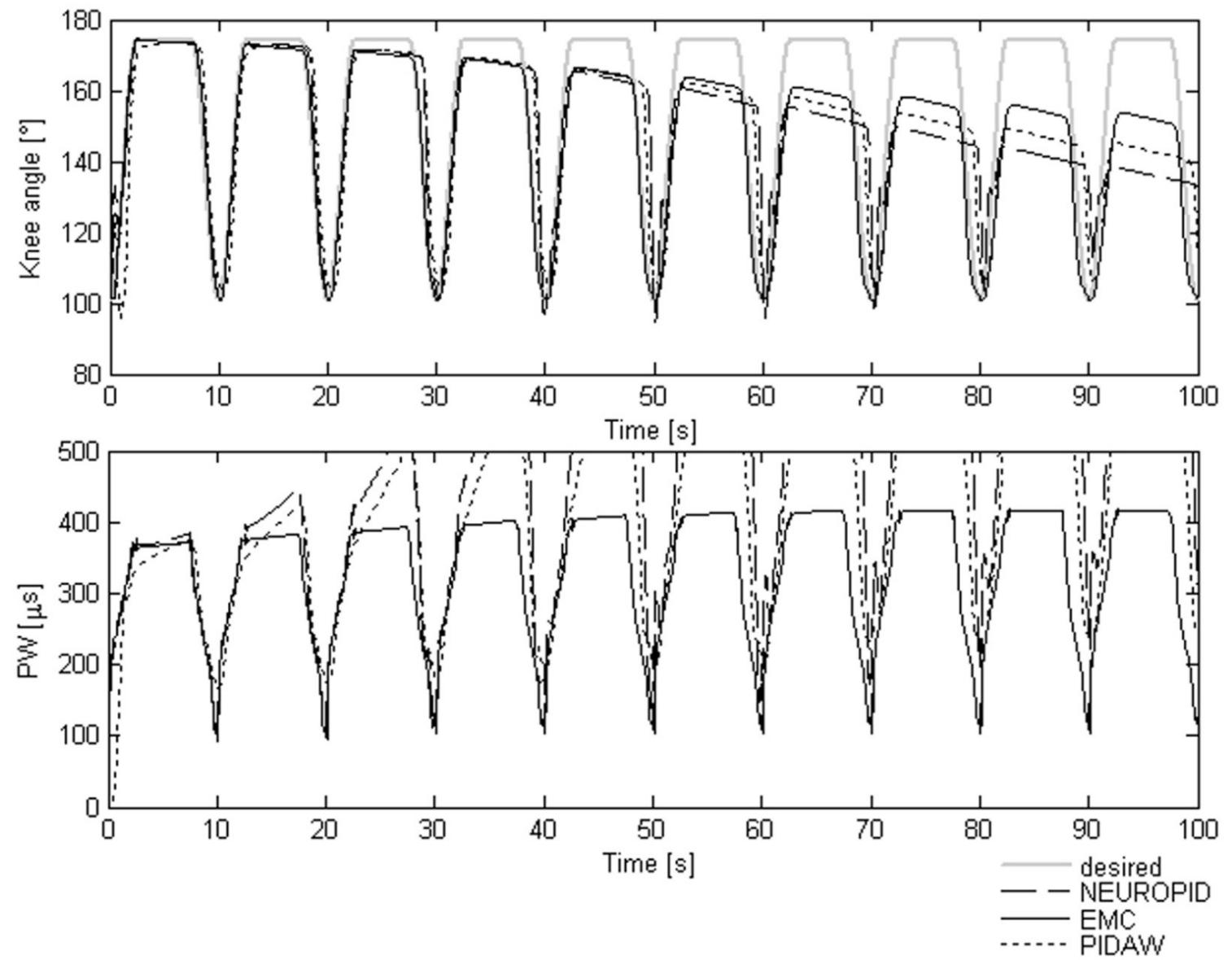
Training Problem



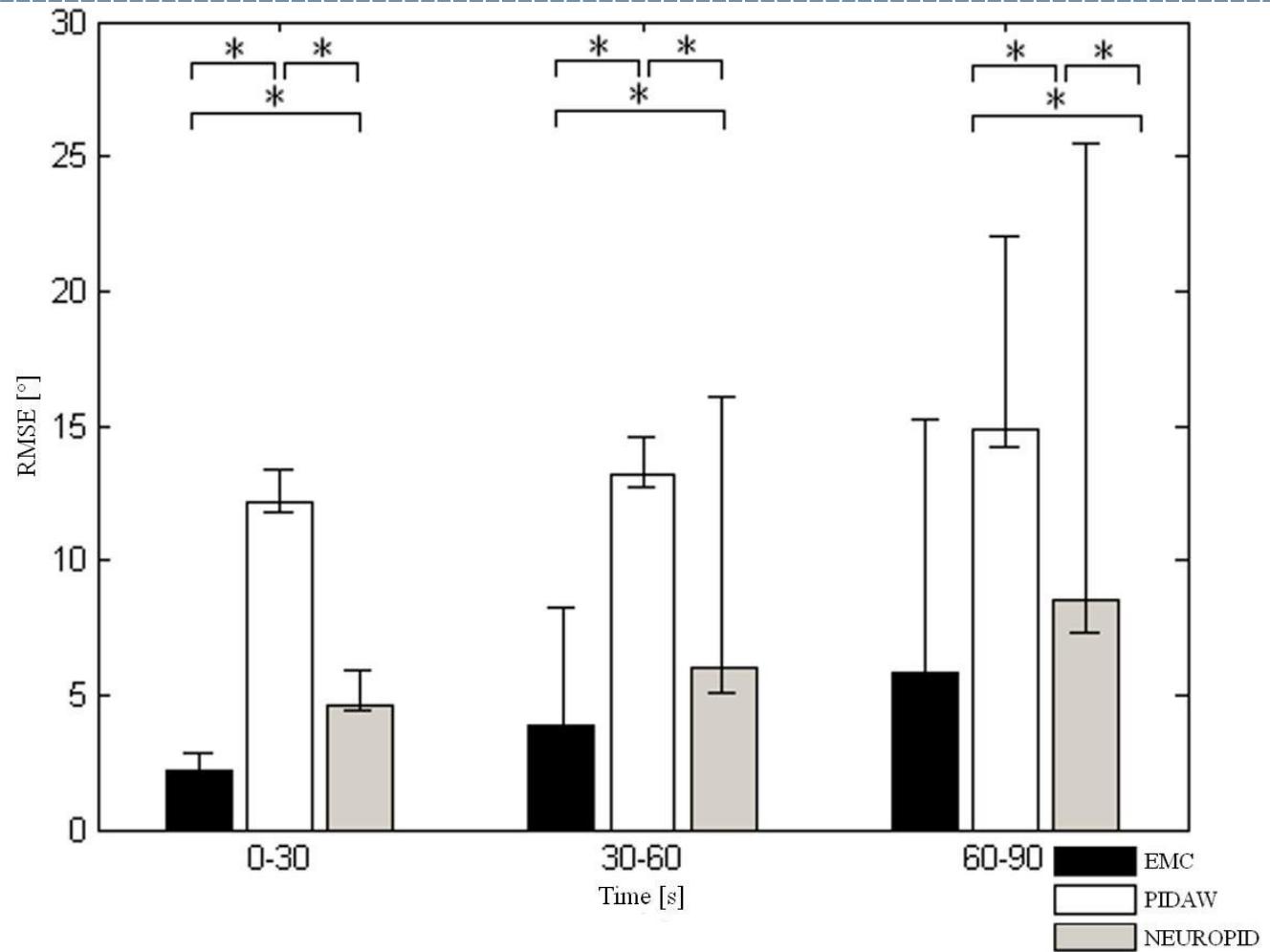
Tracking ability



How to manage muscular fatigue



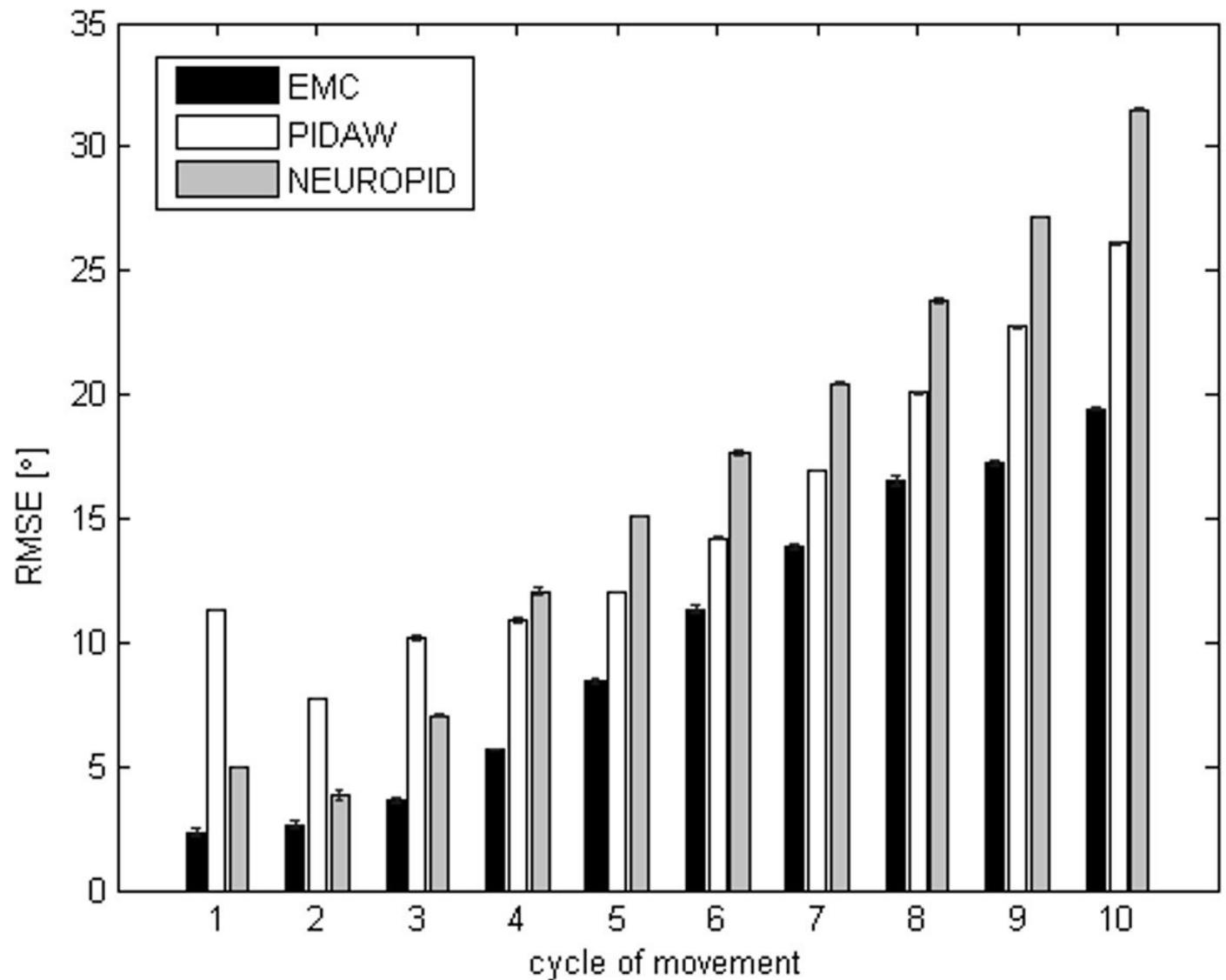
How to manage muscular fatigue



Evaluation of untrained disturbances

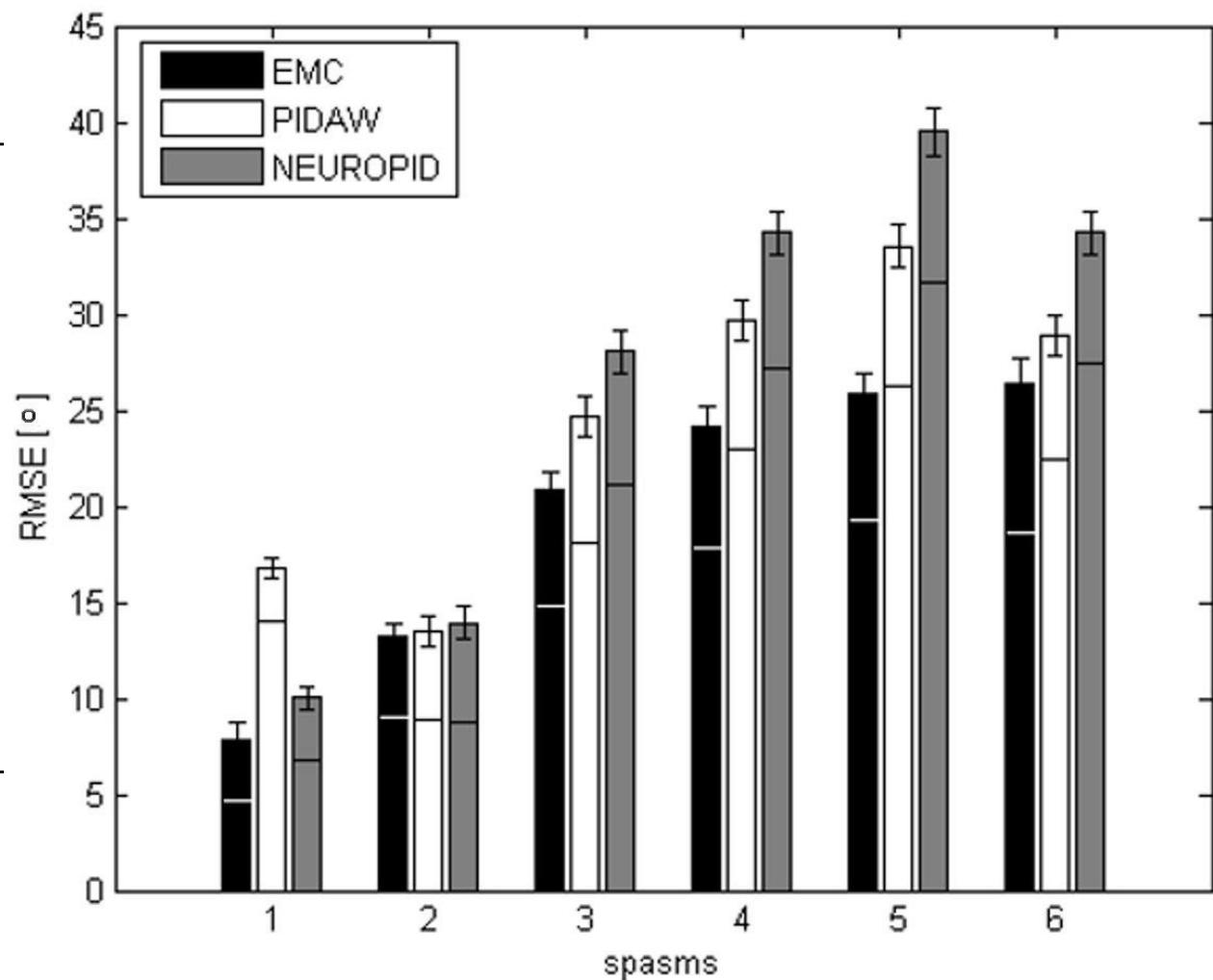
1)Distributed noise

Erroneous placement of electrodes, not well stucked electrodes, changes in the muscular condition, erroneous placement of the electro-goniometer



2) Spasms

SPASM	start (s)	Phase of movement
1	1.5	Raising/ext
2	20	Raising
3	38	Return
4	52	Extension
5	64	Extension
6	75	Extension



The angular error increase is due to the spasm (second part of each bar) and it is the same for all the controllers independently on the instant in which the spasm is simulated during the movement; also the ANN , even if the spasms where not presented in the TS, showed good generalization ability on spasms

Inter and intra- subject variability

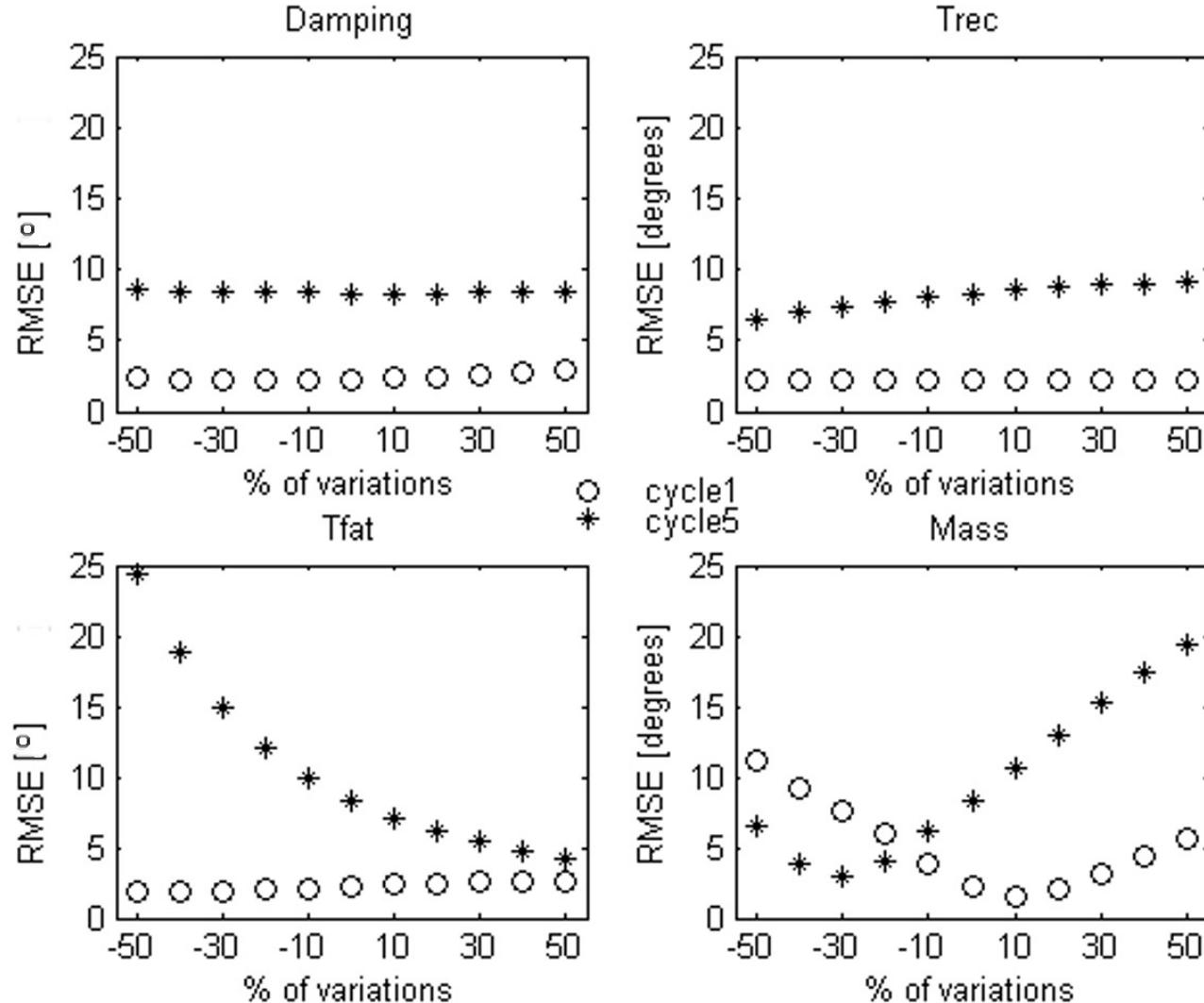
Objective:

When the subject changes and when the session day changes, the features of the system to be controlled also change...

RE-CALIBRATION TIME and/or GENERALIZATION CAPACITY

1) ROBUSTNESS

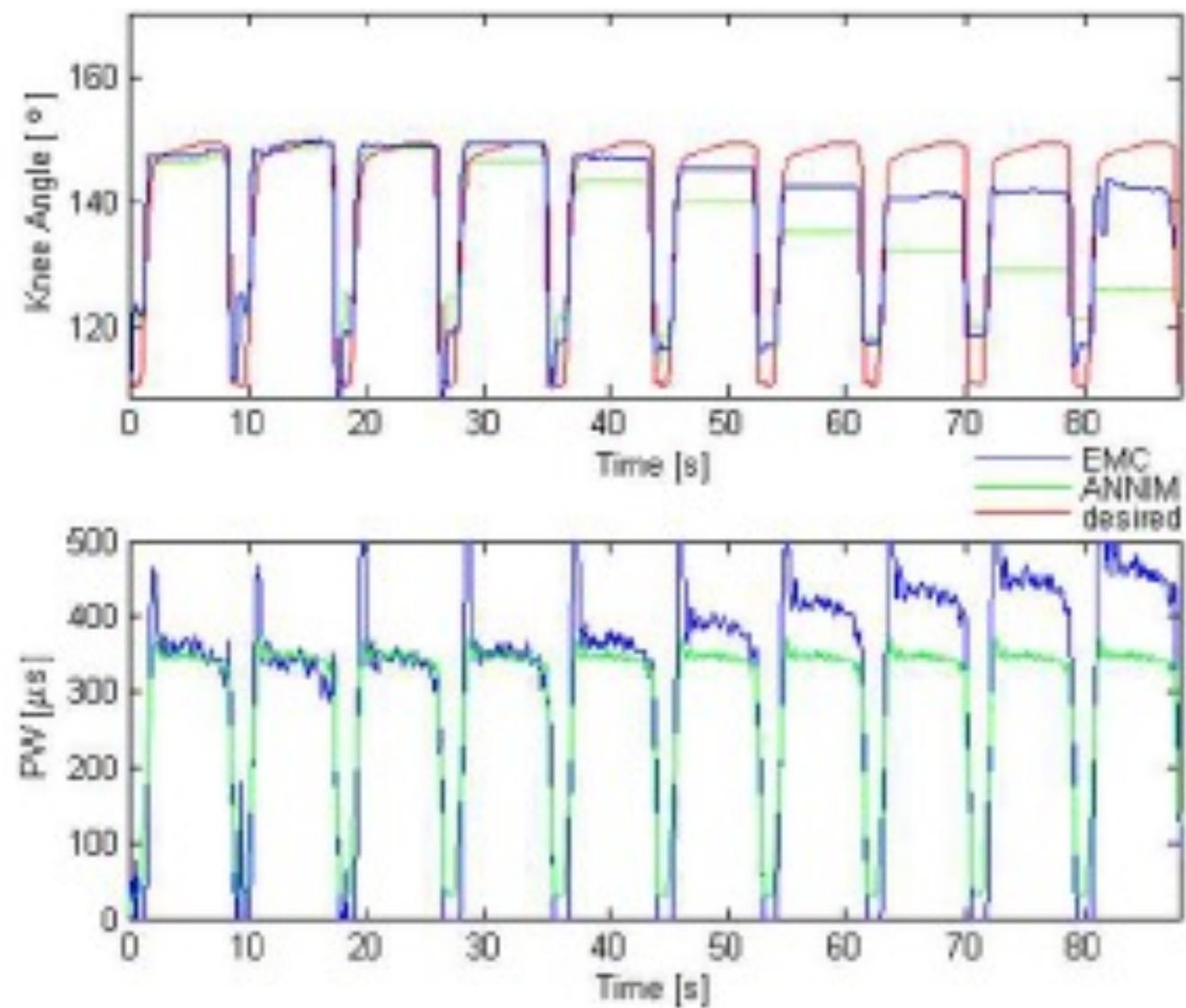
To verify what is the effect of a percentage change of some parameters of the plant (Damping coefficient, Trec and Tfat are the time constant of fatigue, Mass) on the tracking error in the first (without fatigue) and last movement of the knee (with fatigue)



2) SINGLE SESSION Calibration

After an electrode replacement, the current amplitude used by the controller has to be re-calibrated...

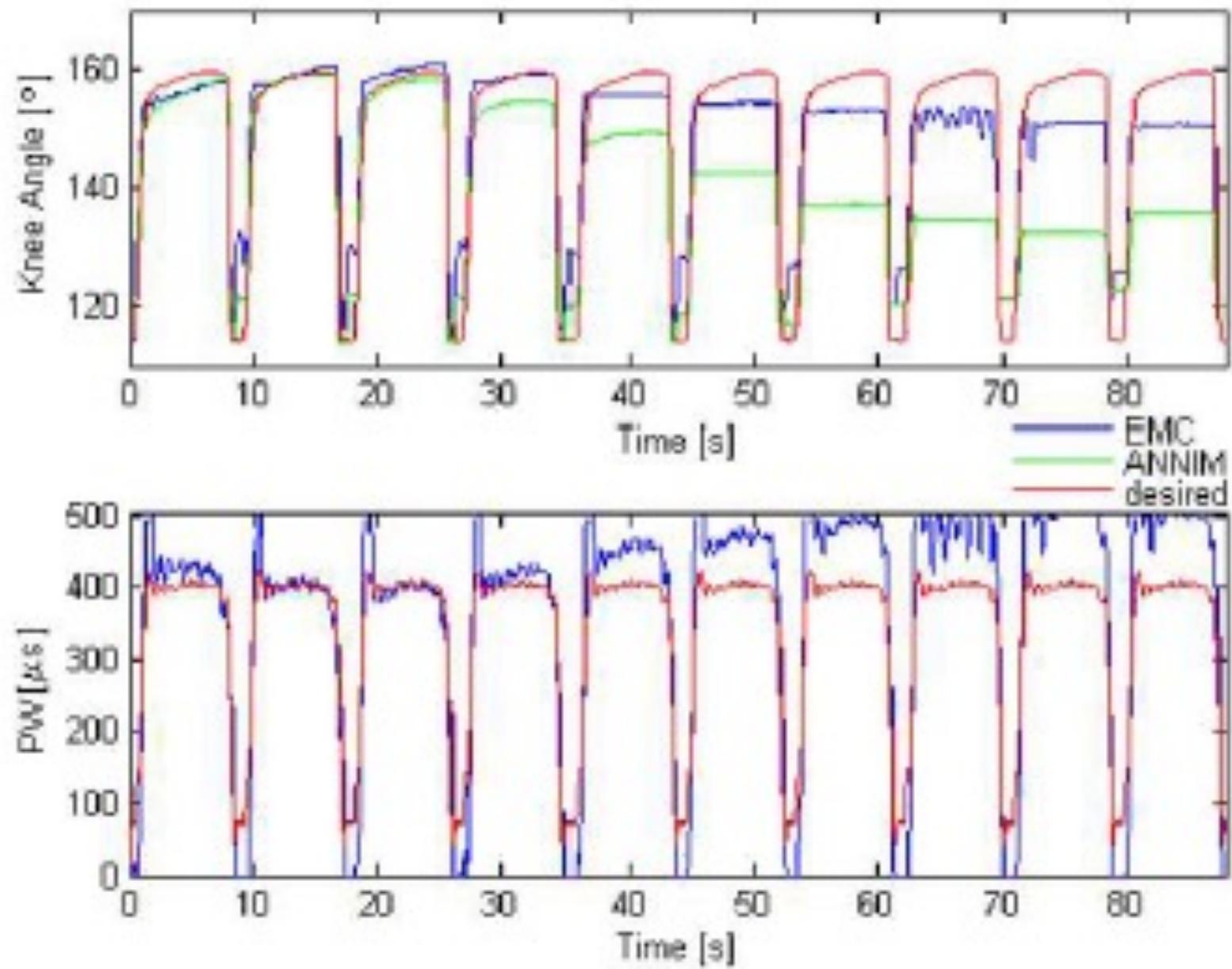
Experiments on one patient



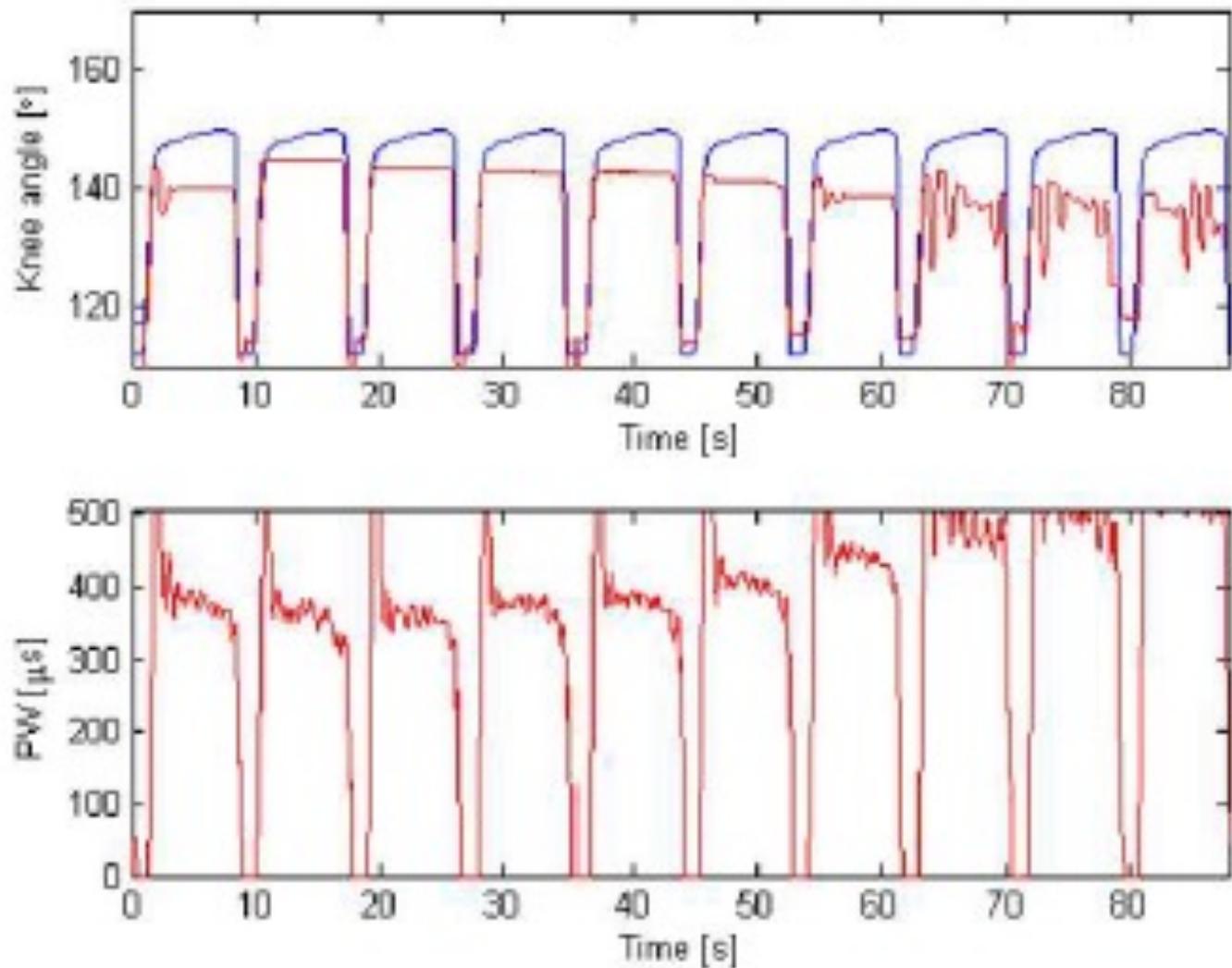


Experiments on one patient

Testing signal



Experiments on one patient Load 0,5Kg

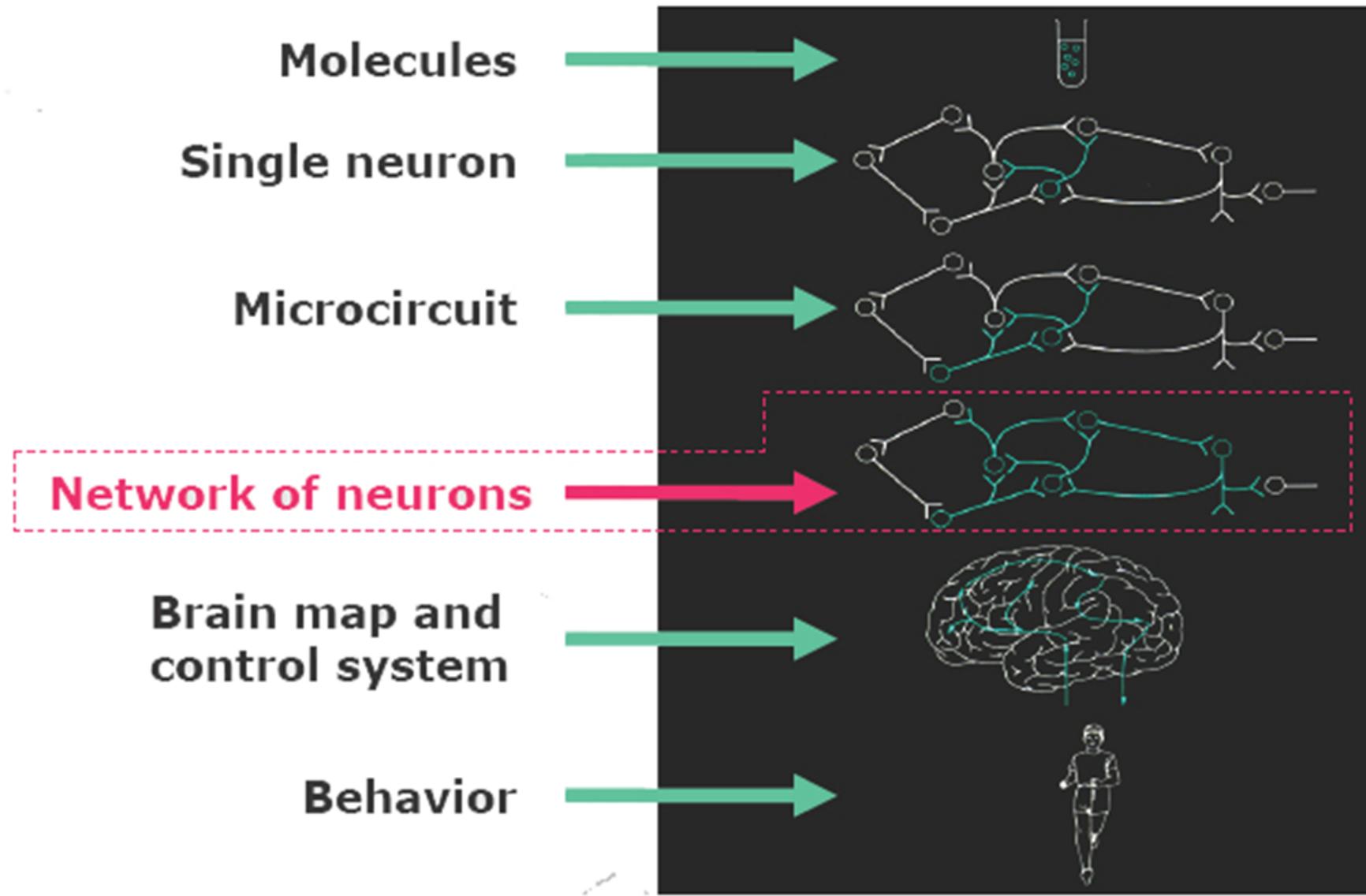




Neuroengineering 2021/22

NEUROENGINEERING FOR BIOLOGY 1-
Electronical tools to interface neuronal networks

Functional scale



GOAL

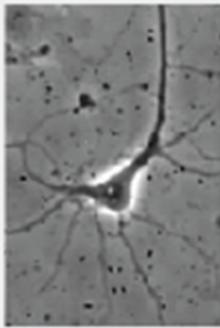
Both the single-neuron level and the CNS-level are well known but the dynamics of neural networks is still far from elucidated. For this reason, studies at this level of analysis are essential to deeply understanding neural pathways.

This question opens some very interesting technological challenges

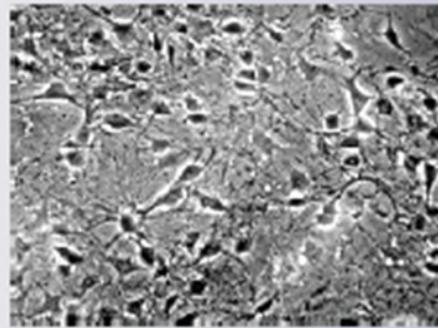
In vitro and In Vivo EXPERIMENTS

in-vitro

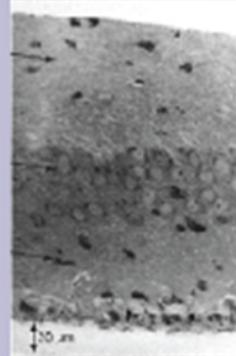
single-neuron
level



neuronal networks of
dissociated cells



brain
slices

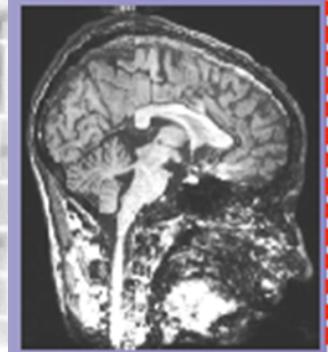


in-vivo

CNS, PNS
level



CNS, PNS
level



Functional connectivity
Modelling complexity
Reduced access

In VITRO EXPERIMENTS

- In-vitro experiments can be used to study the small functional cellular structures:
 - Slices: are functional naturally grown tissues extracted from the brain and then analyzed
 - Cultured neurons: are embryonic dissociated neuronal cells which are cultured in vitro and built the neuronal network directly in vitro. The system is then completely autonomous but it is only a model of natural functional networks.
 - Human patient specific IPS cells differentiated to neuron-like... great challenge for future research!
- **Multimodal approach is pursued to get the maximal information rate usually the different approaches are consecutive in time (depending on the goal)**

Technical specifications

The users' requirements:

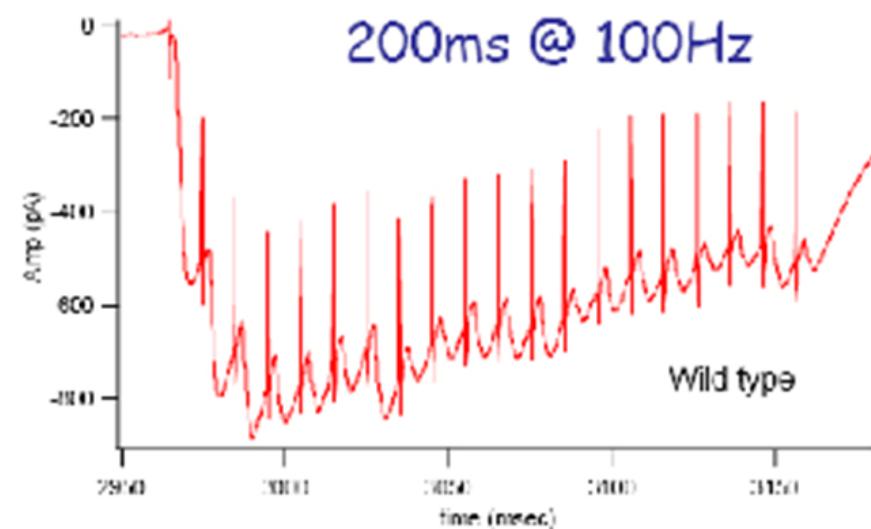
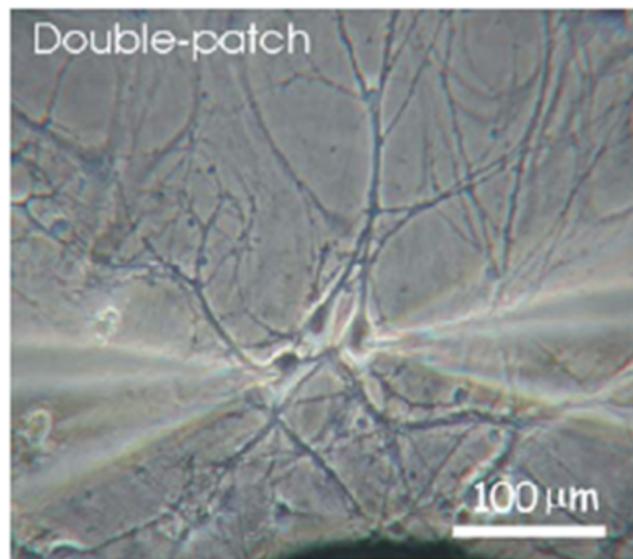
1. Simultaneous record + stimulate of **hundreds individual** neurons
2. Long acquisitions (days and months): maintain stable contact
3. Monitor transmembrane potentials (-80;+30mV)
4. SNR able to catch subthreshold transmembrane potentials ($\pm 0.5\text{--}10$ mV with a rise time of <1 ms and a slow decay time of 100–1,000 ms), and spike occurrence and spike oscillations (up to 50Hz)
5. record APs with amplitudes of ~100 mV and duration of 1–500 ms (long APs for recording from cardiomyocytes).

SPIRA AND HAI Multi-electrode array
technologies for neuroscience and
cardiology NATURE NANOTECHNOLOGY
VOL 8 FEBRUARY 2013

Intracellular electrophysiology

Traditionally...

The functional properties of neurons have been investigated using conventional electrodes , such as glass micropipettes, thus allowing neurophysiologists to disclose a detailed picture about the single cell properties, e.g. the receptor sensitivity and ion channel gating



Intracellular electrophysiology: patch clamp

Complete description of cause-effects links

Correspondence between morphology and function

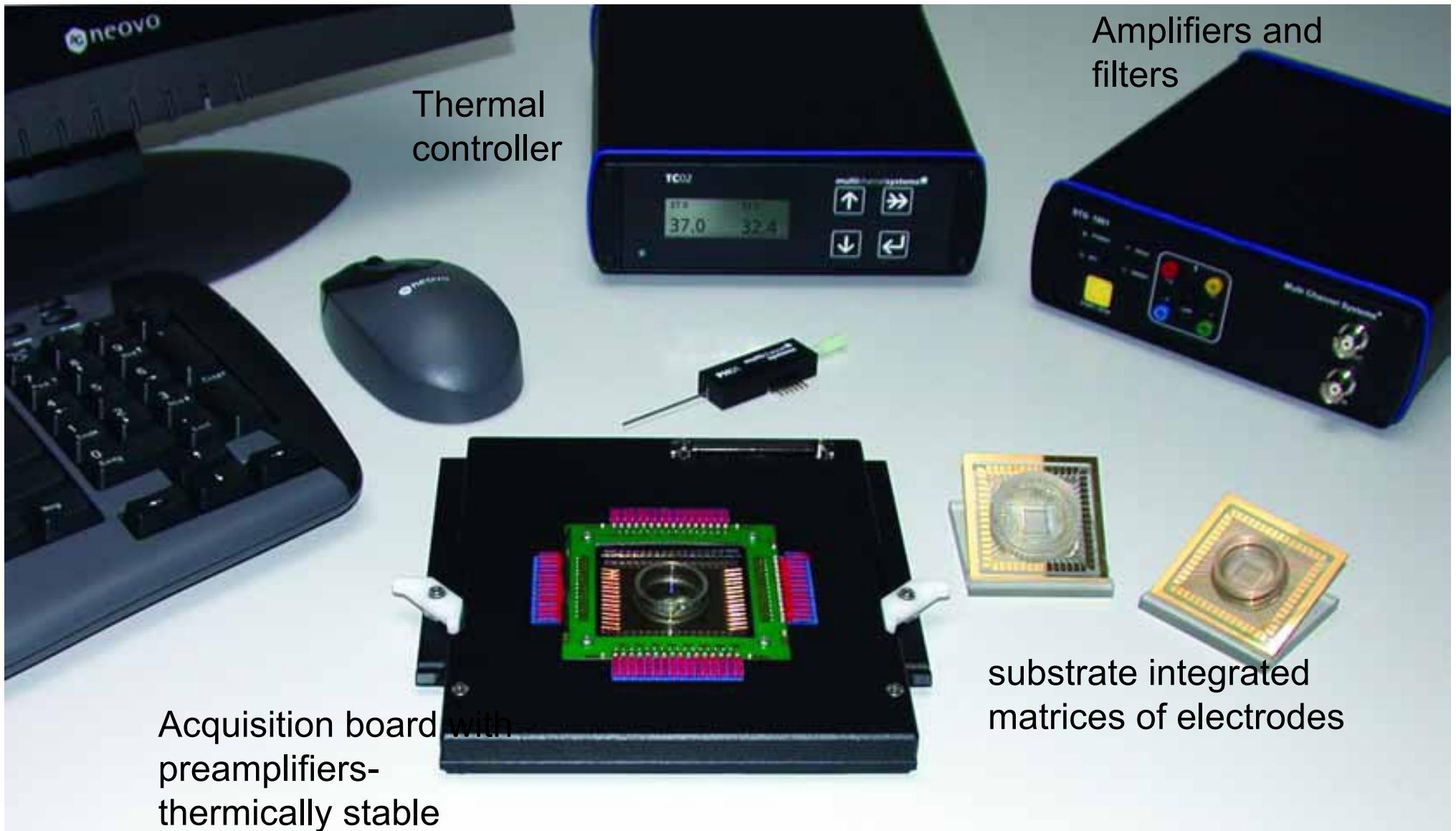
Accurate readout of the entire dynamic range of voltages without distortion

Invasivity -> short registration, non repeated

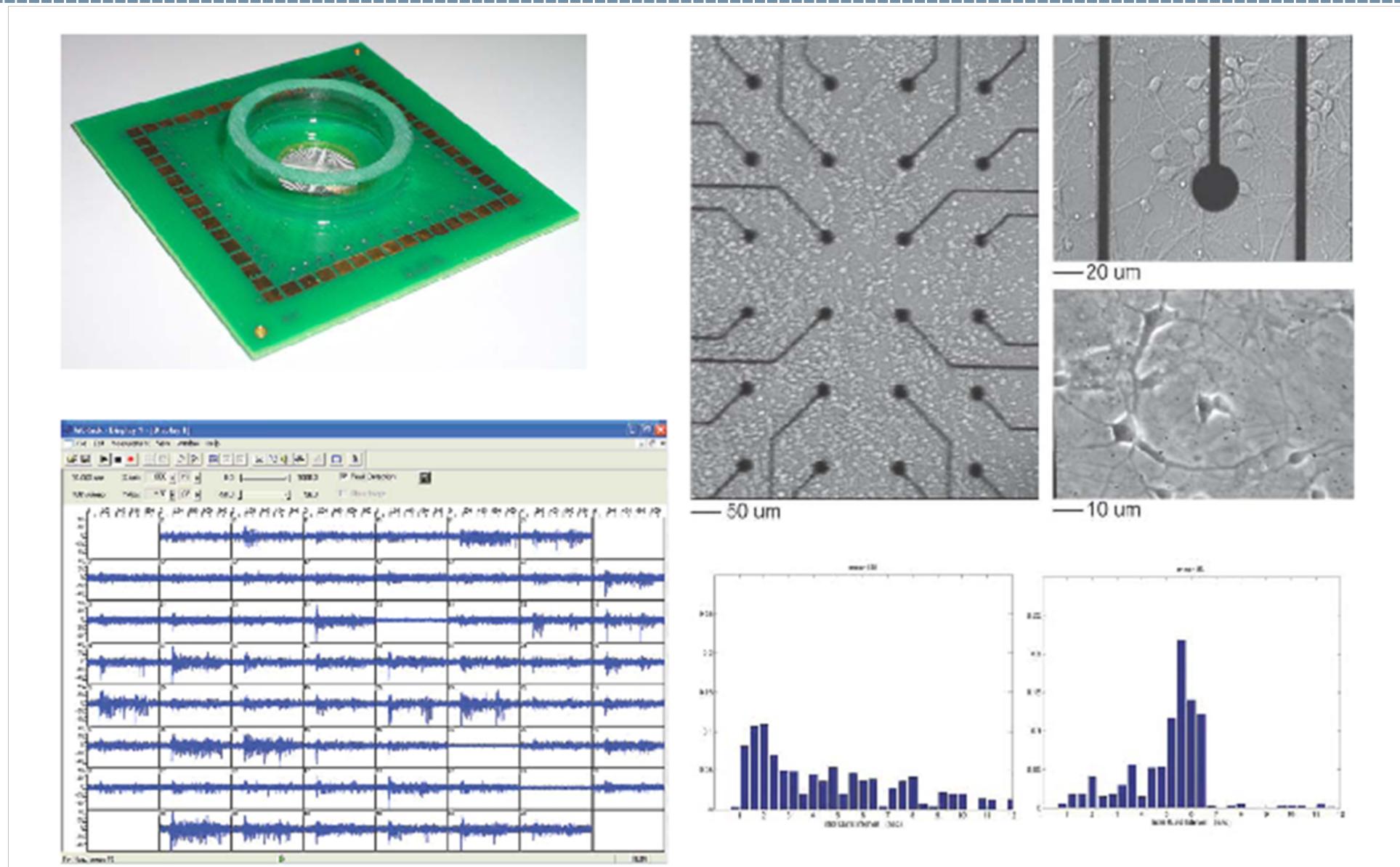
Encumbrance of manipulators -> contemporary registration of few neurons

Mechanical and biophysical instability -> cannot be used to monitor long-term electrophysiological correlates of plasticity

Multi electrodes arrays (MEA)



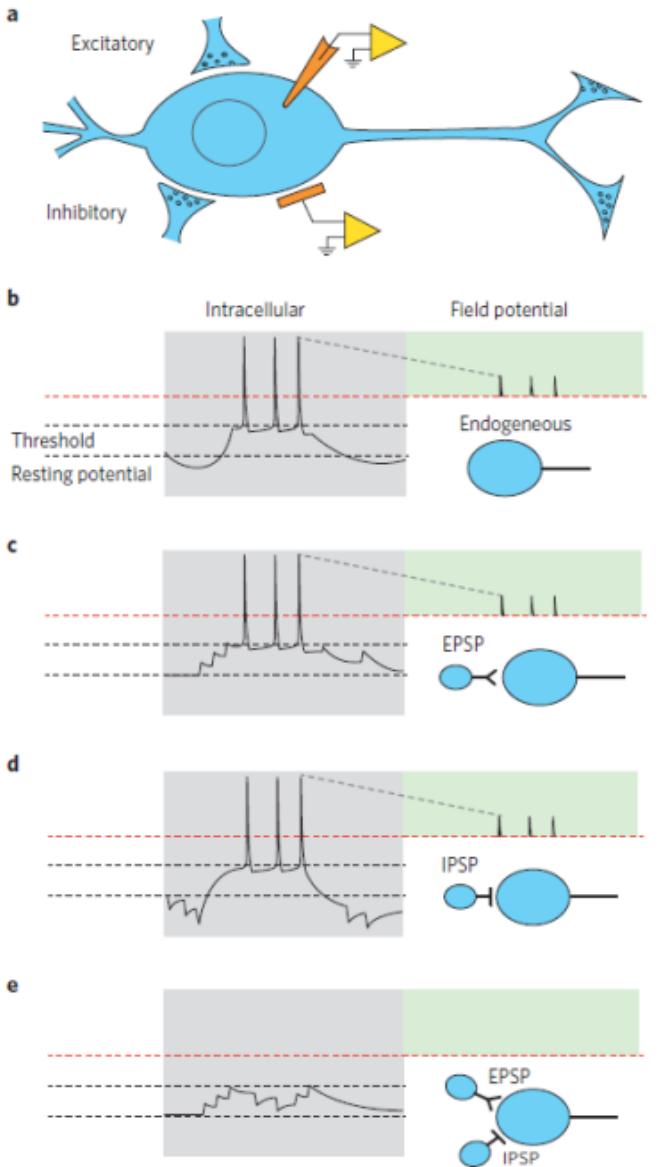
Non-implantable MEA recordings



The extracellular space is conductive as well, and although the resistance is very low, it is not zero.

According to Ohm's law ($V=R*I$), the extracellular current results in a small voltage that can be measured with extracellular electrodes. Extracellular signals are smaller than transmembrane potentials, depending on the distance of the signal source to the electrode.

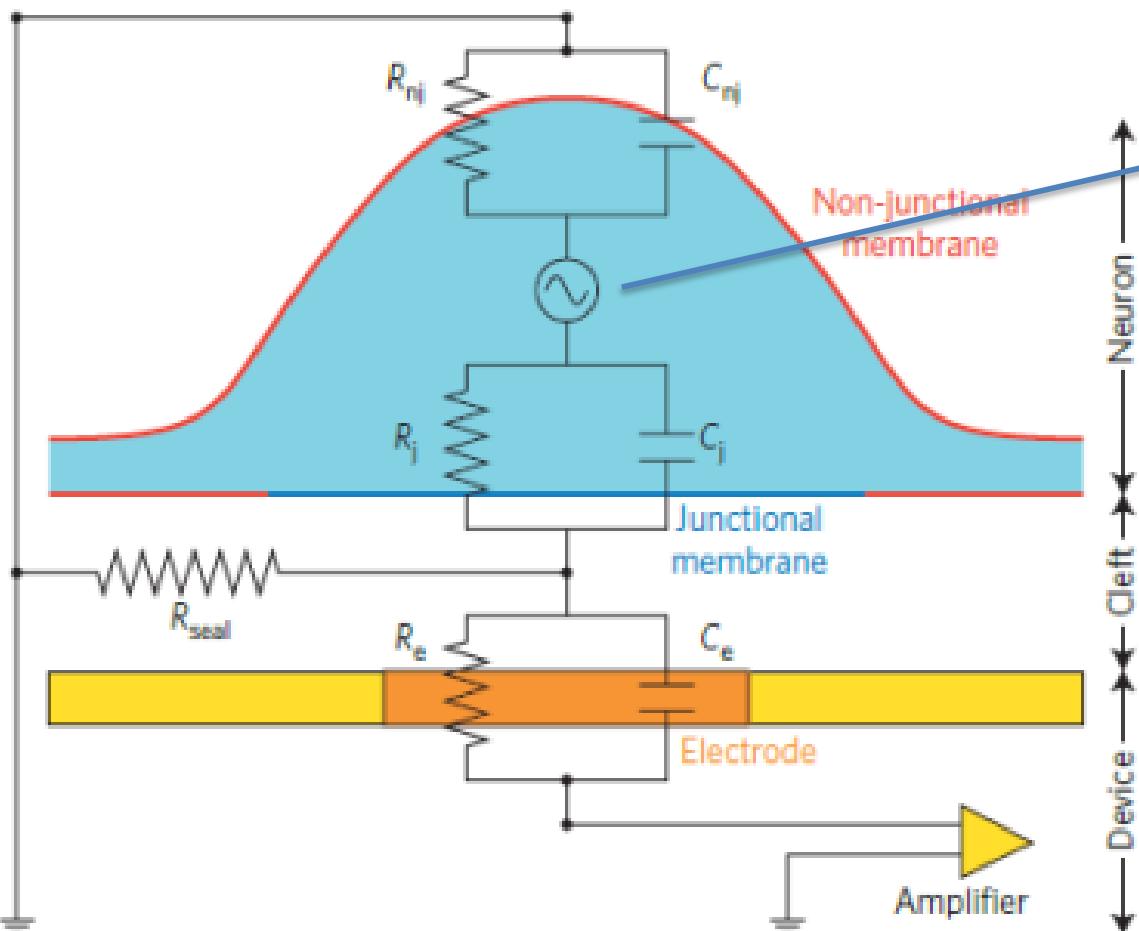
Extracellular recording: the problem of dark neurons



“Whatever sorting algorithm is applied, it remains the limit that MEA recordings could not provide information on as to whether a firing of an individual neuron is triggered by endogenous mechanisms, a barrage of incoming excitatory inputs or the cessation of inhibition... this information is typically available only to intracellular recordings across neuron membrane.”

Spira and Hai, 2013

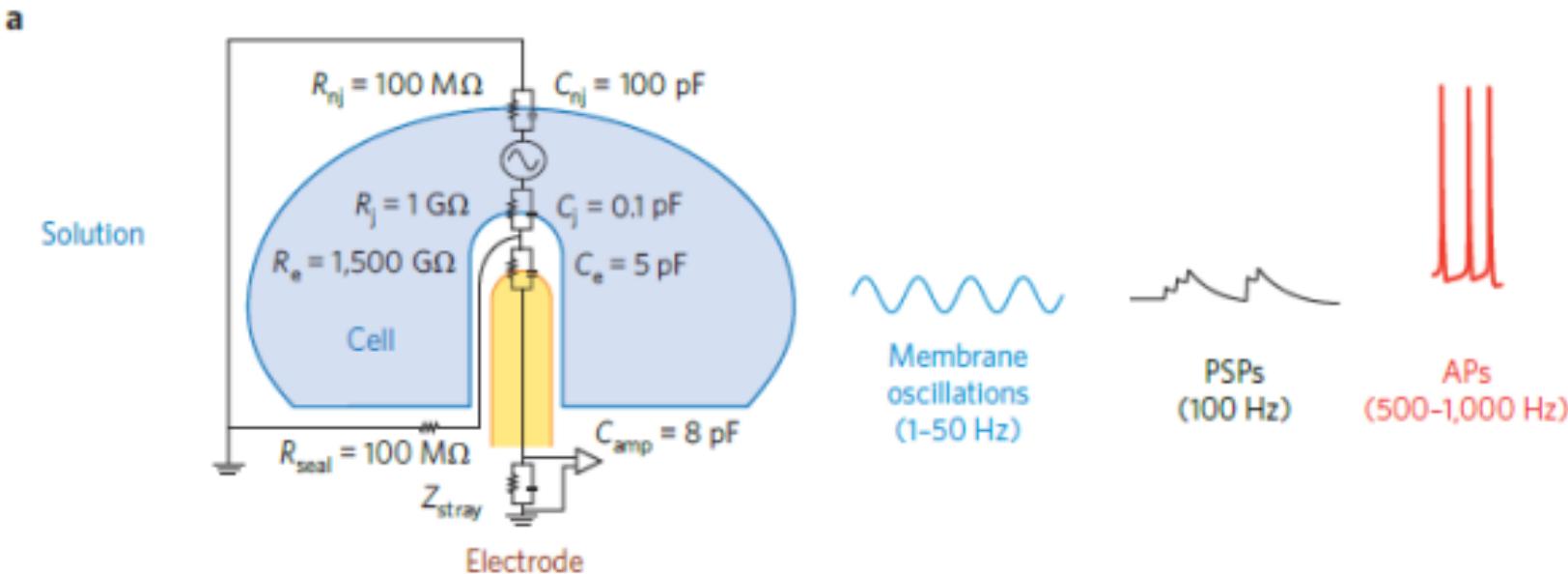
Electrical circuit analogue of neuron/electrode interface



Current generator
which simulates the
action potential

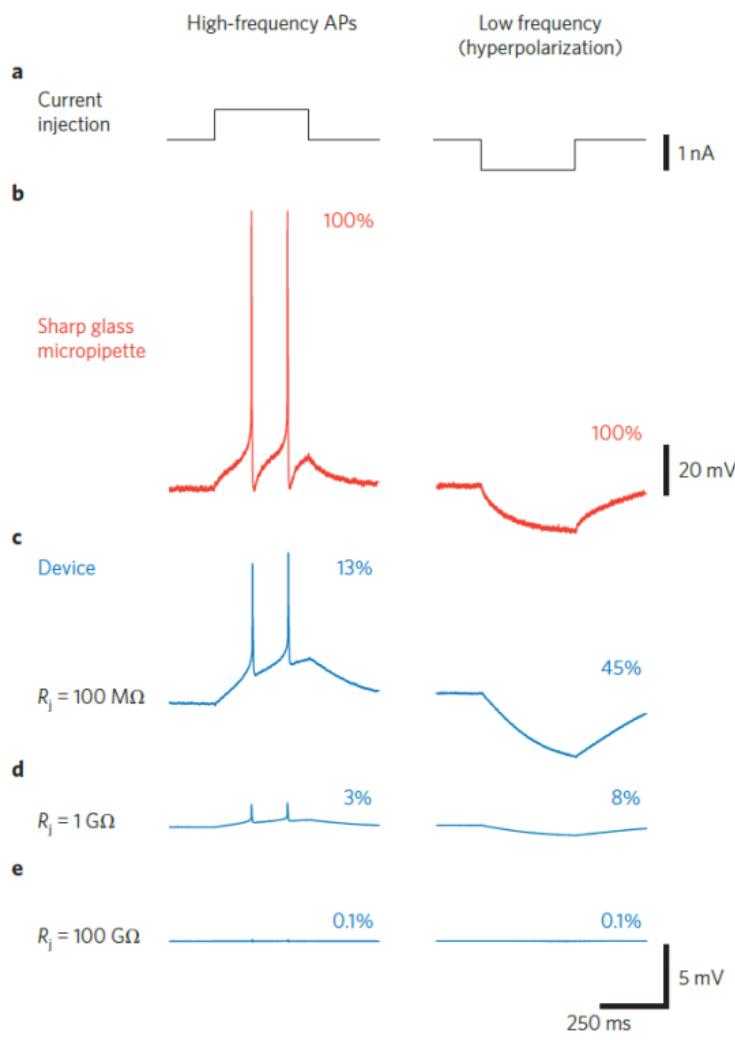
The adherence of the junctional
membrane on the electrode pads
improves the SNR

MEA: SNR and distortion



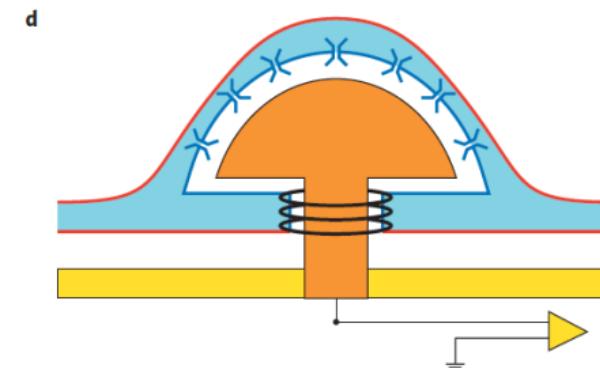
COUPLING: ratio between the maximal voltages recorded by the device in response to the maximal voltage generated by an excitable cell.

SNR and electrode impedance



↑ SNR
↓ Electrode Impedance
↑ Size of electrodes (size of the junctional membrane)
↓ spatial resolution

POSSIBLE IMPROVEMENT IN ELECTRODE:
gold Mushroom-shaped protruding microElectrode gM μ E-based

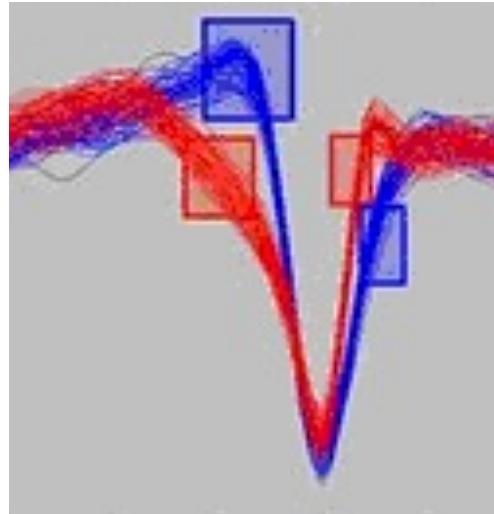


Spike sorting

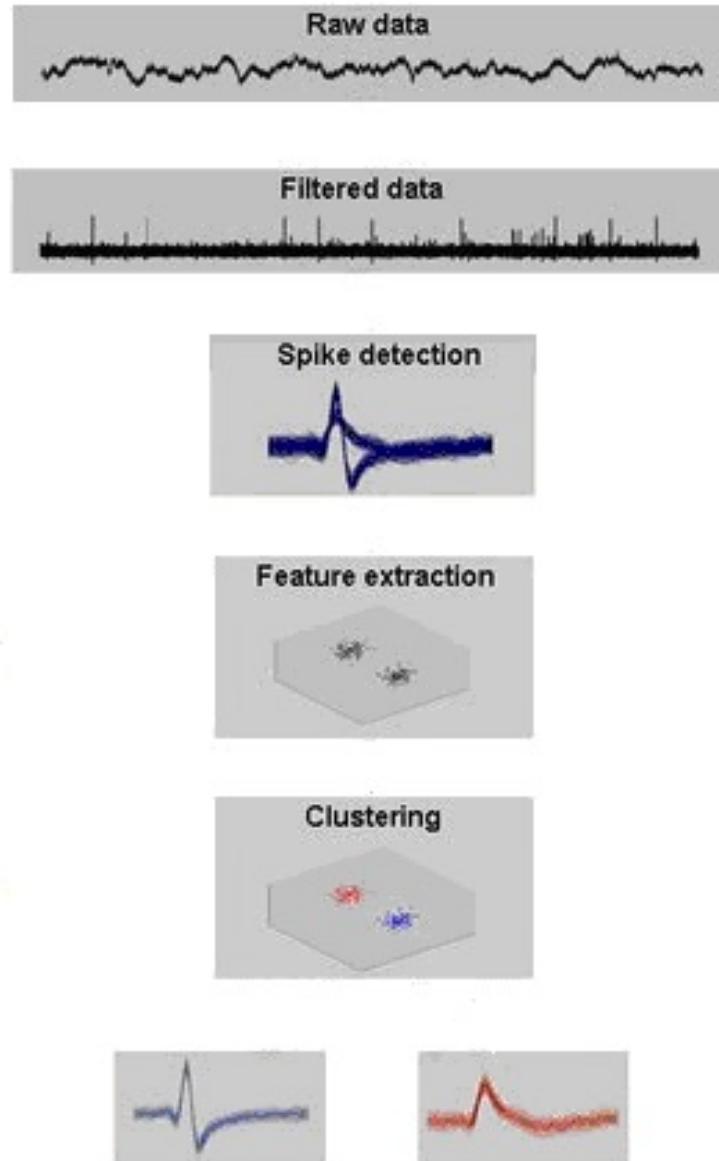
Two cells afferent to the same electrode will in general have a different covered area.

Even if they cover the electrode in the same way, their spike waveform will be different because in general they have a different nature and ionic channel density (V_j).

Assumption: the shape of the spike of each neuron is stationary



Spike sorting

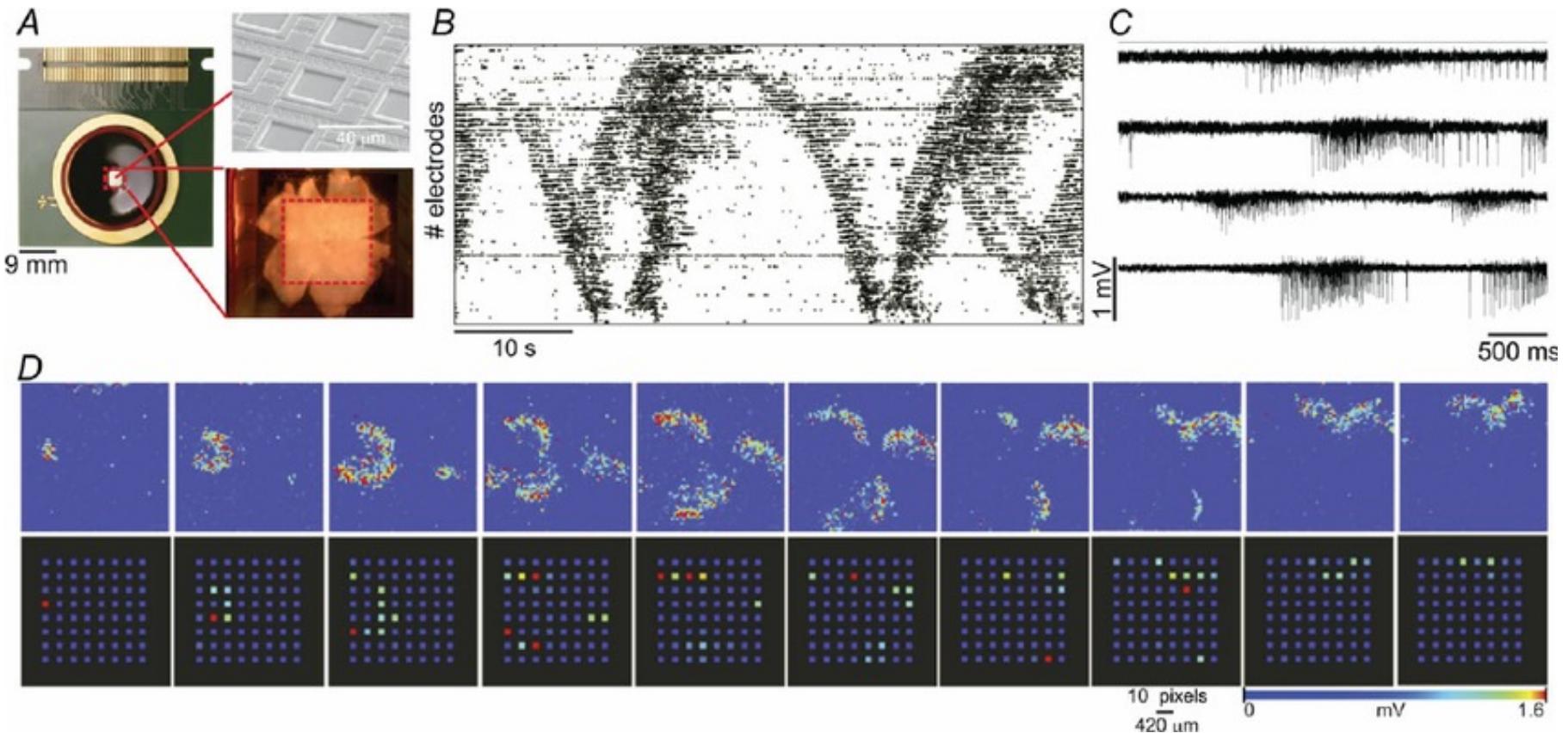


High density MEA (Active Pixel Sensor APS MEA)

GOAL: increase the spatial resolution

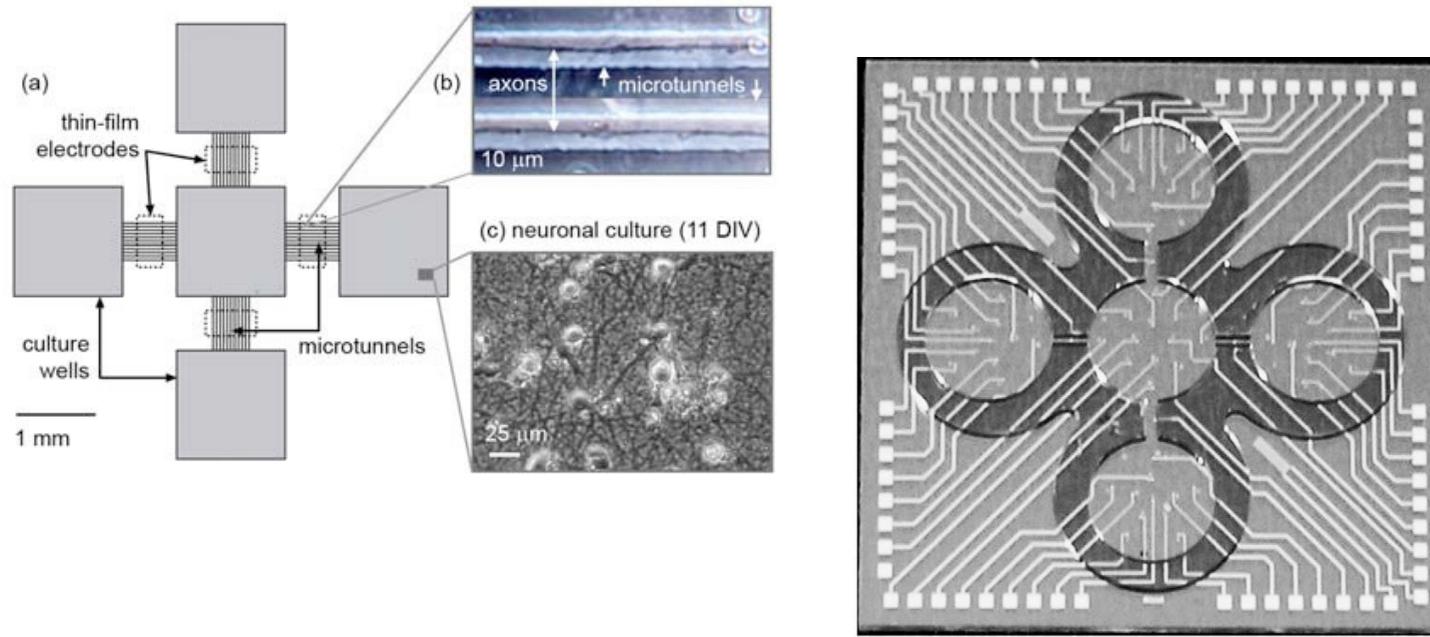
WEAKNESSES:

- worsen the signal-to-noise ratio
- Great deal of computational power to extract data and to sort them out



MEA stimulation

Low selectivity: medium is conductive
Clustering microfluidic solutions to confine stimulus



Pros and Cons

Spatio-temporal recordings of network activity

Large scale acquisitions (network level): modulation of local properties and impact at the network level

Long and repetitive time recordings (up to about one hour)

Low correspondence between morphology and function

High temporal resolution, low spatial resolution

Low selectivity in stimulation

No registration of subthresholds potentials (low SNR) -
>Dark neurons



Neuroengineering 2021/22

NEUROENGINEERING FOR BIOLOGY 2 –
Optical tools for studying neuronal networks

Optical stimulation

Science 1971: Fork Direct laser stimulation

Science 1983: Farber and Grinvald dye mediated stimulation

Neuron 2002: GENETIC METHODS FOR PHOTOSTIMULATION. Another approach to increase the sensitivity of neurons to light is to express a genetically engineered photoactivated sensor in them. (Zemelman et al. 2002)

Cage compounds are molecules that are rendered inactive by the addition of chemical groups, typically nitrobenzyl groups, which are broken up by the absorption of light.

In 2010, optogenetics was chosen as the "Method of the Year" across all fields of science and engineering by the interdisciplinary research journal [Nature Methods](#). At the same time, optogenetics was highlighted in the article on "Breakthroughs of the Decade" in the academic research journal [Science](#). These journals also referenced recent public-access general-interest video [Method of the year video](#) and textual [SciAm](#) summaries of optogenetics.

«But will optogenetics ever be used to treat disease? Several clinical trials are already underway, the results of which are anticipated eagerly. However, rather than optogenetics being used to treat patients directly, it is more likely that new treatments for brain disorders (and other disorders) will derive from the kinds of fundamental discovery research made possible by optogenetics.» ([Josselyn](#) eLife 2018)



Neuroengineering 2021/22

NEUROENGINEERING FOR BIOLOGY 2 –

Optical tools for studying neuronal networks

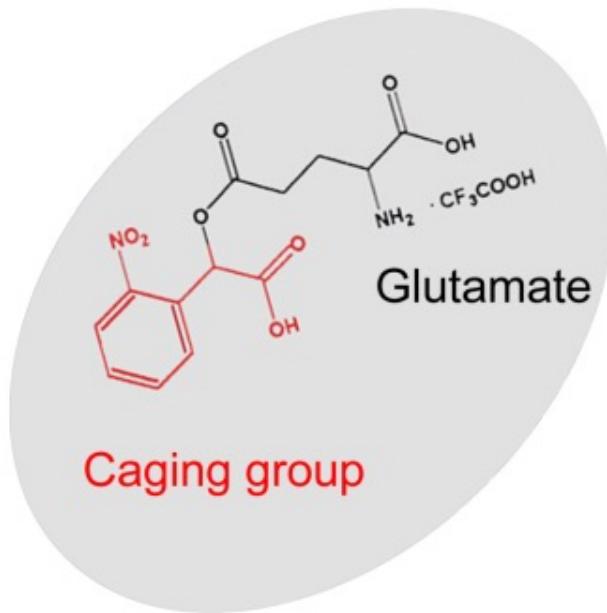
PART 1 –

Optical stimulation of in vitro neuronal cultures

ONE-PHOTON UNCAGING

The basic approach is to cage the compound (Black) with a blocking group (red). Thus, caged compound can be switched into the active form by short UV pulses.

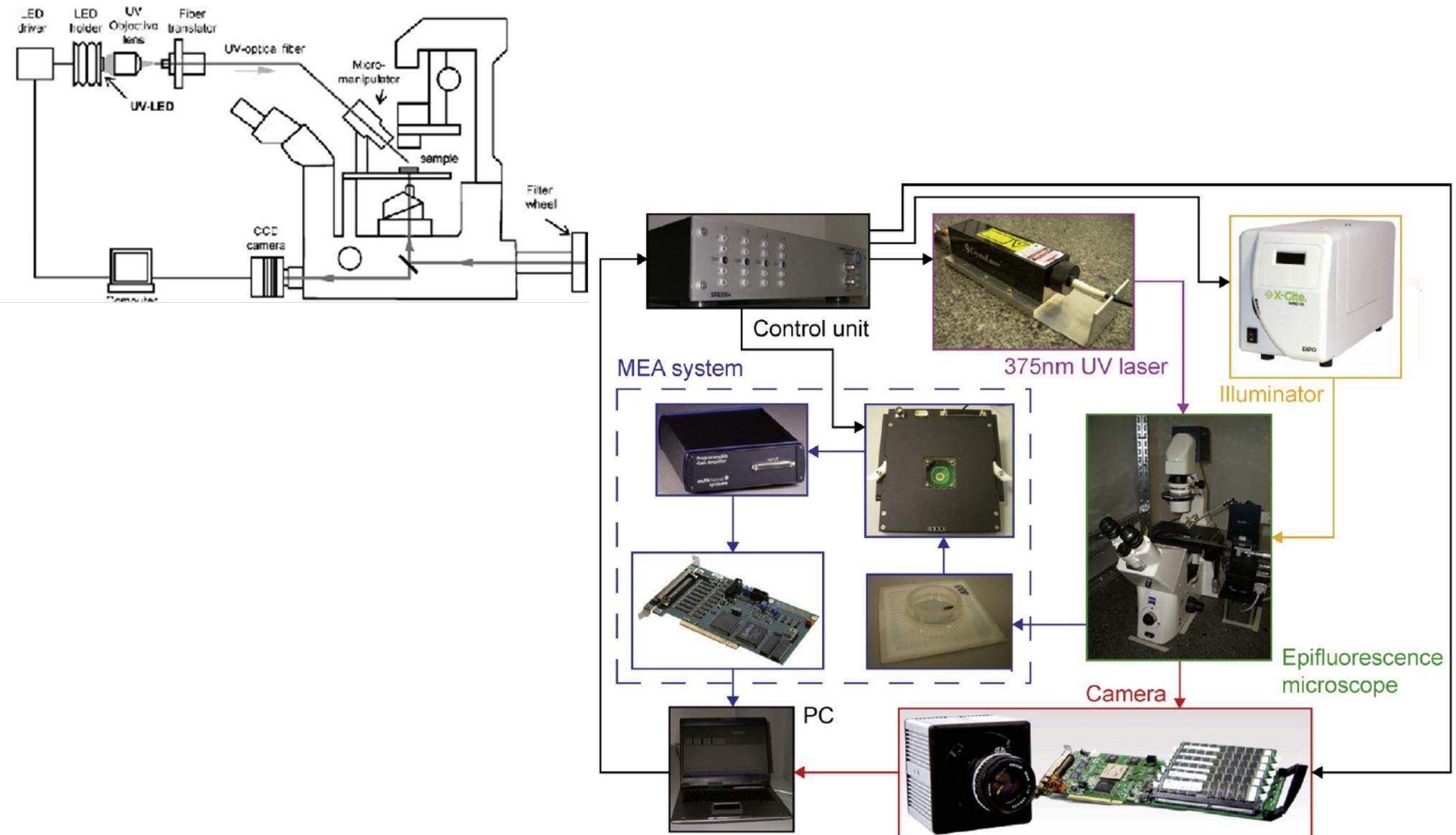
This allows us to obtain high spatial and temporal control during stimulation.



PROS

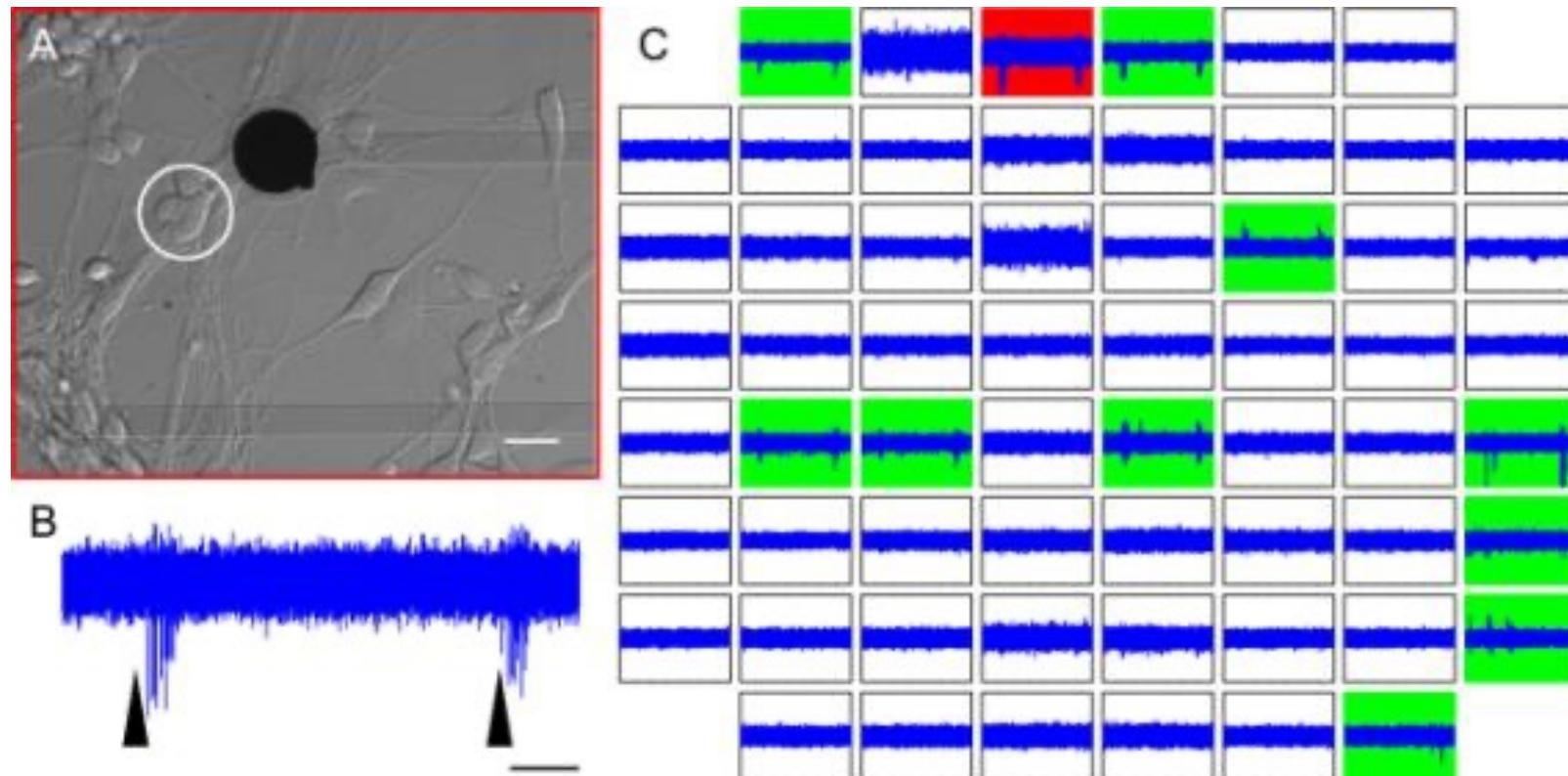
- Glutamate is one of the most common neurotransmitters in the CNS
 - Physiological stimulation
- The UV pulse can be highly focused
 - High selectivity

Setup: opt. Stim by optical fiber

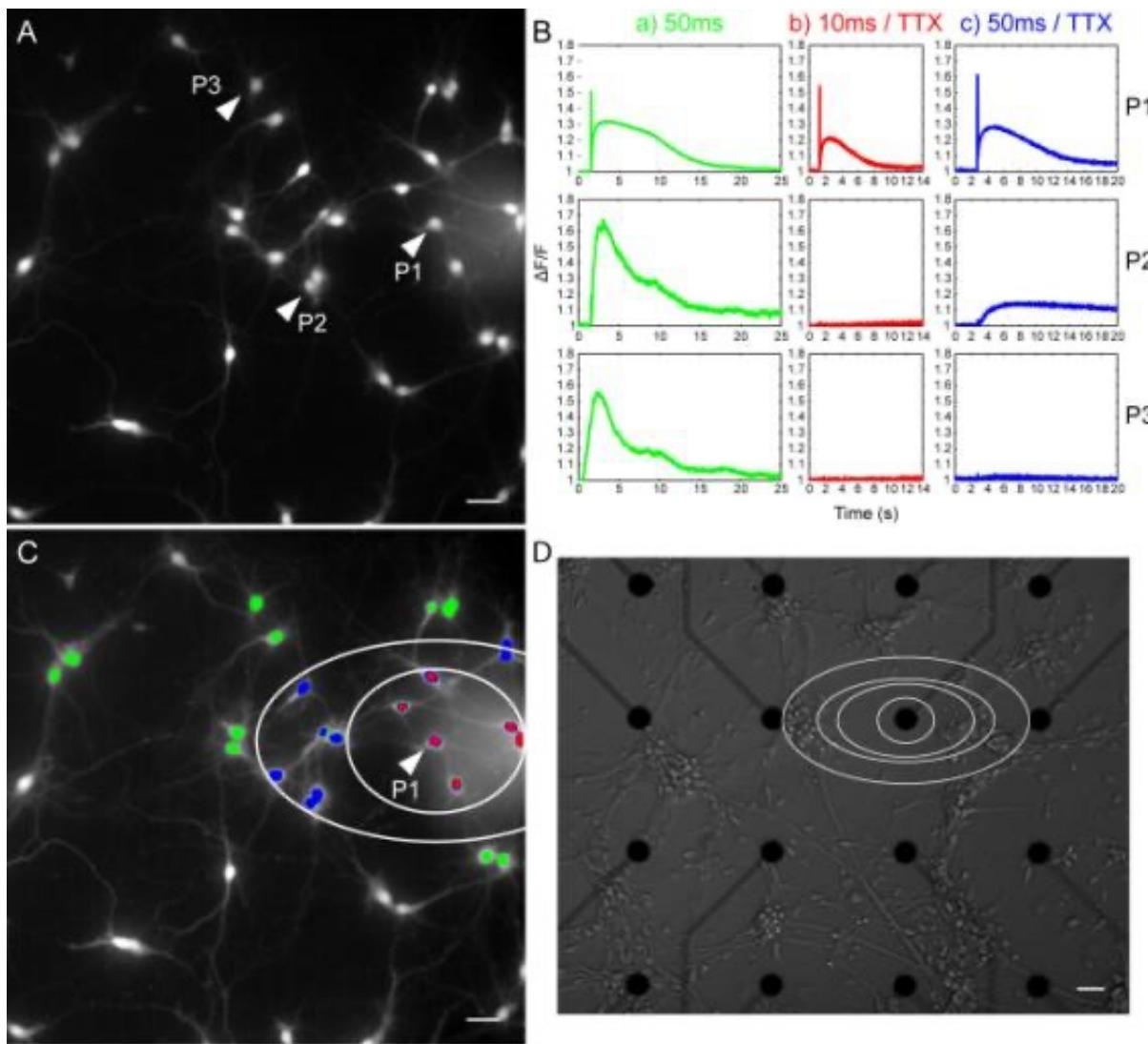


Optical stimulation

Stimulation:
by light caged compounds
Recording:
MEA



Optical stimulation + Ca optical recording



Stimulation:
by light caged
compounds
Recording:
Ca⁺⁺ optical
recording

Optical stimulation
can be confined in
an area of about a
couple of MEA
electrodes.



Neuroengineering 2021/22

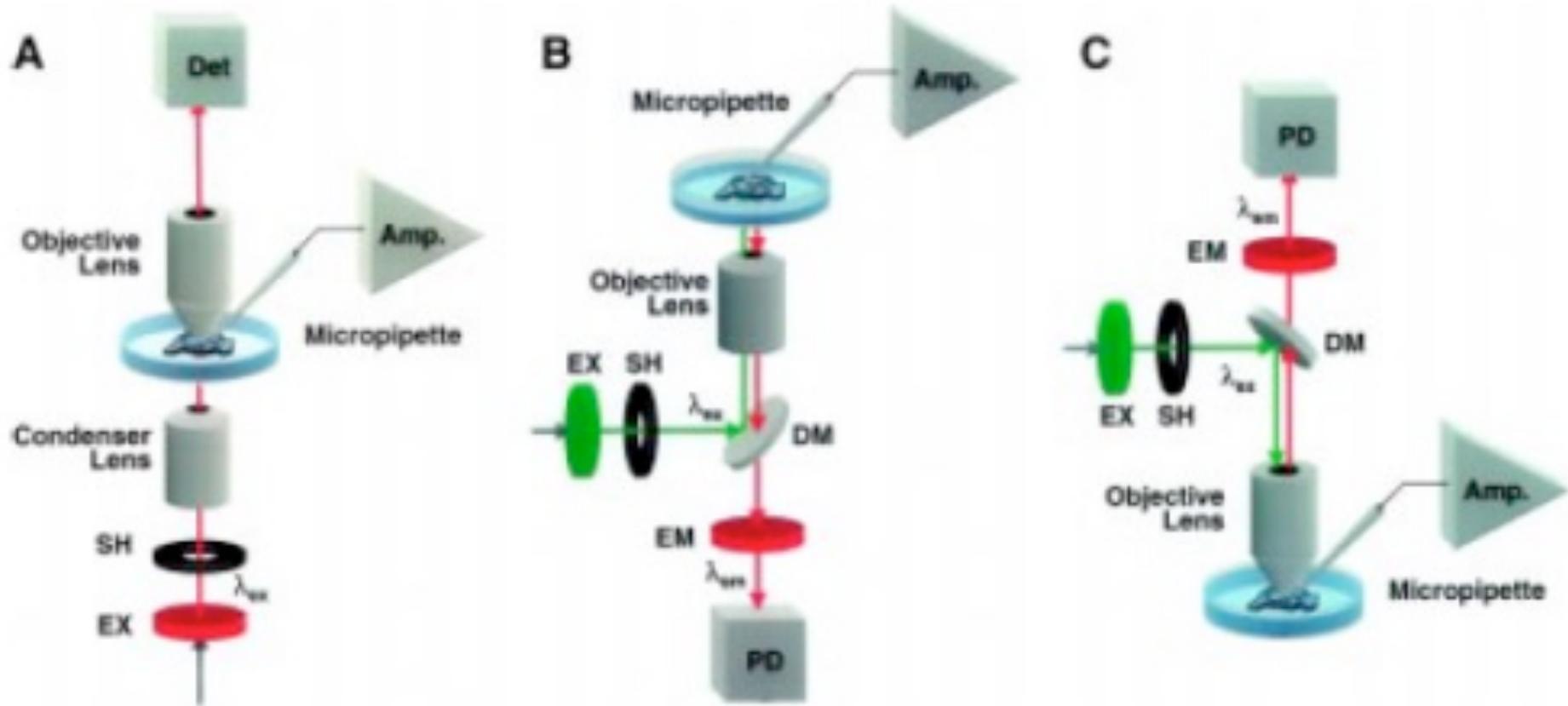
NEUROENGINEERING FOR BIOLOGY 2 –

Optical tools for studying neuronal networks

PART 2–

Optical recording of in vitro neuronal cultures activity

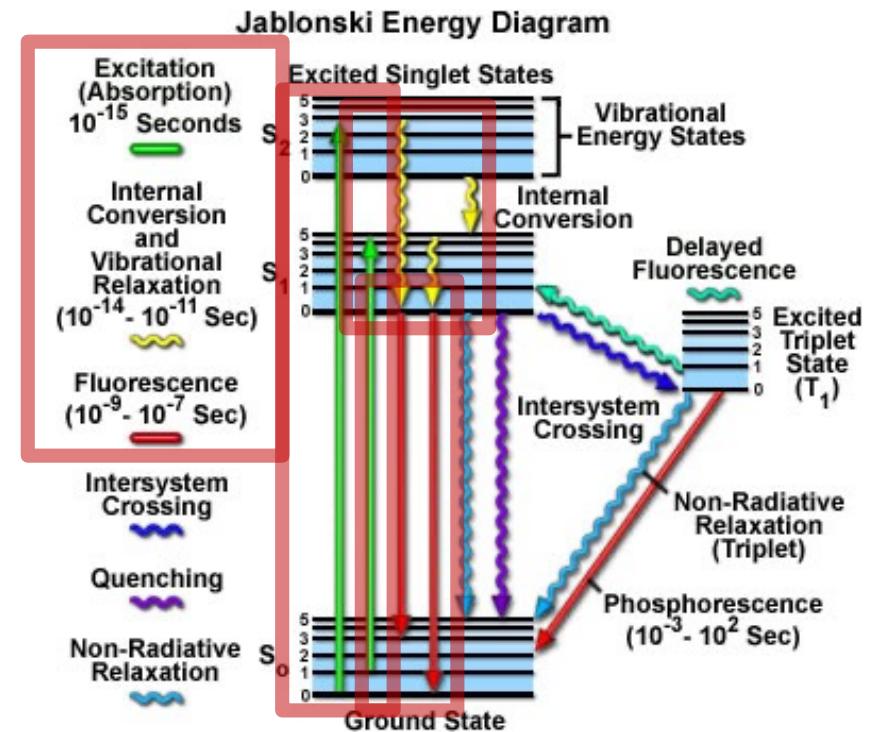
Type of microscopes



Fluorescence

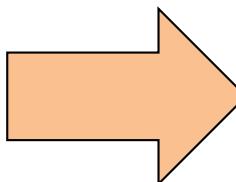
Fluorescence is governed by three events:

- Excitation (or absorption)
- Vibrational relaxation
- Emission



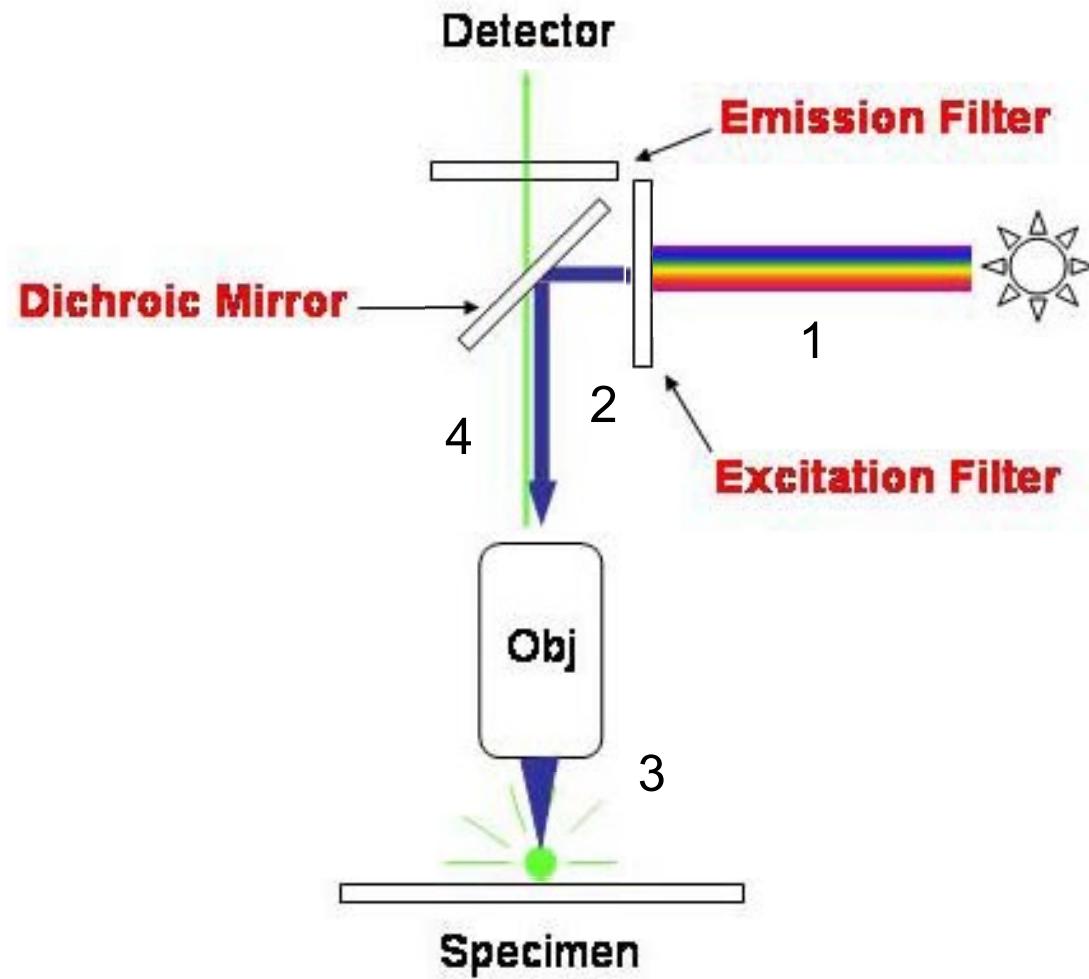
Fluorescence is a quick process: it is measured in billionths of seconds

Energy loss in vibrational relaxation
causes emitted photon to have less
energy than absorbed one



Emitted photon has a different
wavelength (“color”) than absorbed one

Fluorescence microscopy

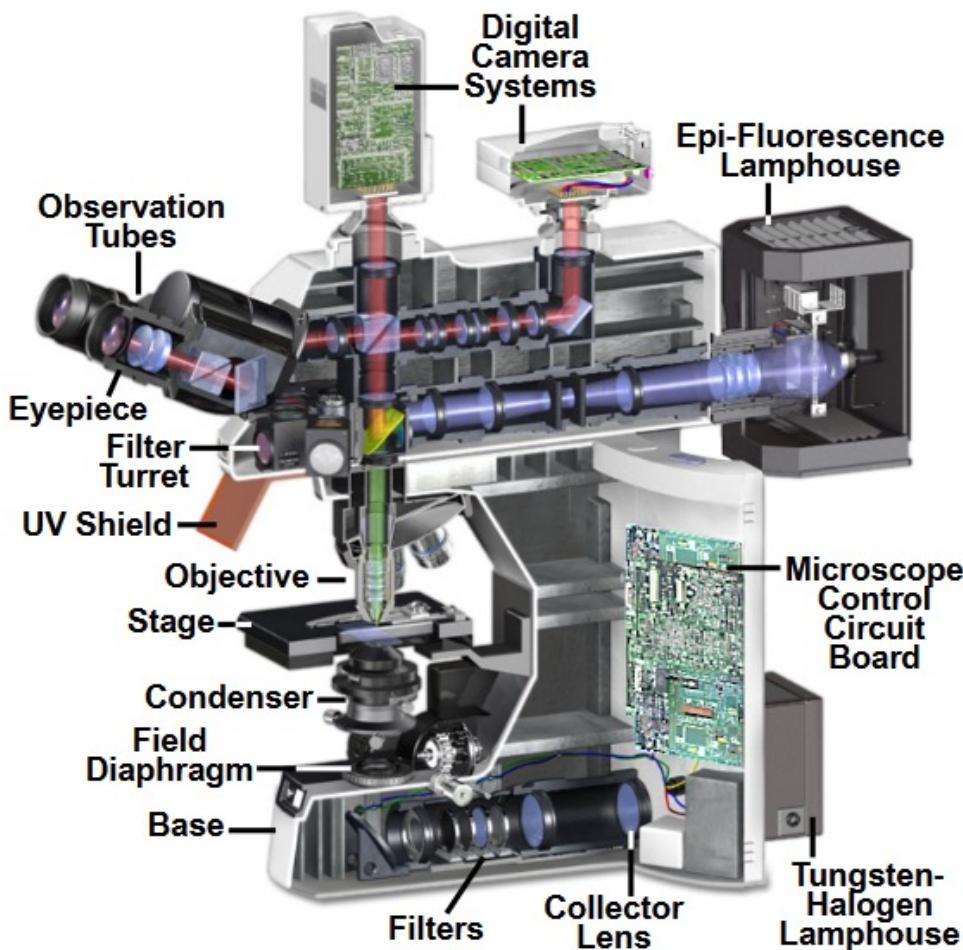


Fluorescence microscopy:

1. White beam from source to excitation filter
2. Monochromatic beam ($\text{wavelength} = \lambda_1$) from excitation filter to sample
3. Absorption and monochromatic beam emission ($\text{wl} = \lambda_2$, $\lambda_2 > \lambda_1$)
4. Monochromatic beam from sample to detector

Epifluorescence microscopy

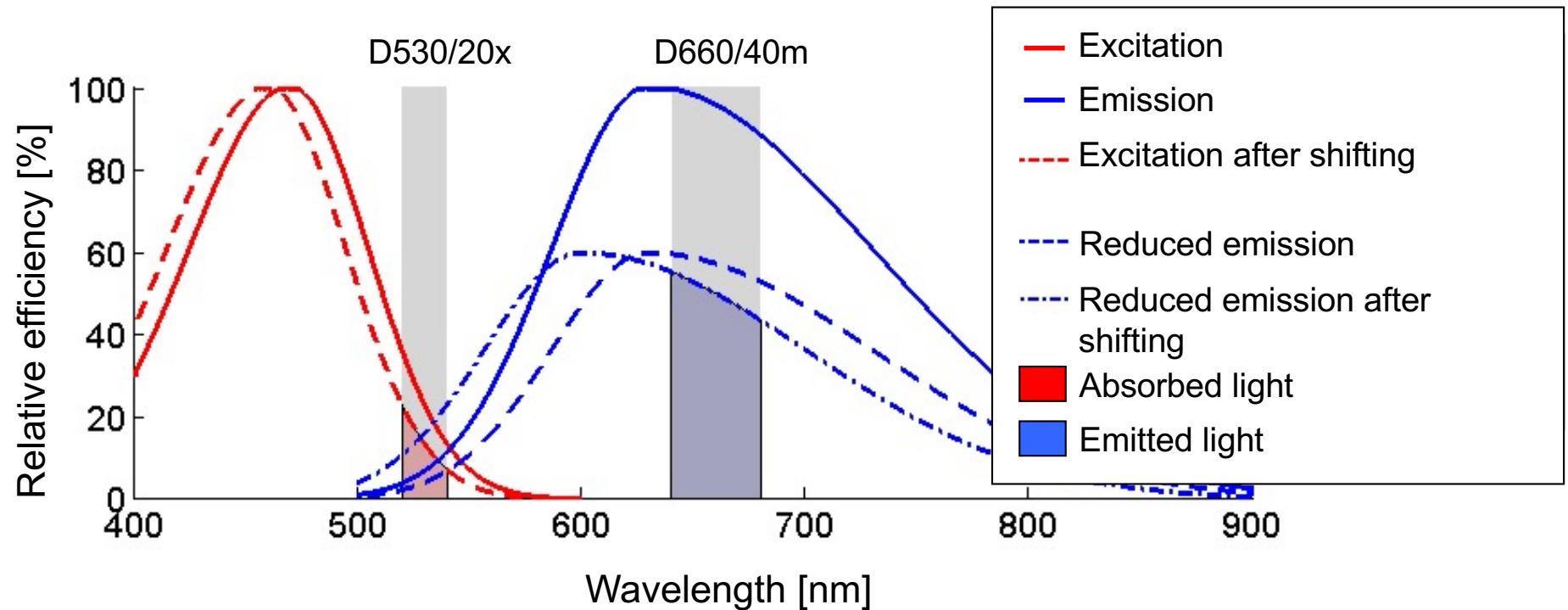
Figure 1 - Epi-Fluorescence Microscope



Epi-fluorescence microscope equipped for both transmitted and reflected fluorescence microscopy

VSDs: principle of working

VSDs allow OPTICAL detection of ELECTRICAL activity



VSDs efficiency is a function of local electrical voltage.

If excitation light is constant, output light intensity depends only on sample electrical properties.

Comparison of technologies for Neuronal culture reading

	Patch clamp	Mea	VSDs
Temporal resolution	+++	+++	Depends on camera, could limit the spatial resolution
Spatial resolution	Single neuron	Pool of neurons around the same electrode (partially improved by post processing)	Single neuron ...depends on the trade-off with the field of view (objective)
Field of view	Max few neurons	Full coverslip culture	Trade off with spatial resolution
SNR	Subthreshold potentials	Spikes (dark neuron)	Spikes (on neurons compartments)
Link activity and morphology	Perfect for the recorded neurons	NA	Good in the field of view
Difficulty	+++	++	+
....			