Functional Electrical Stimulation (FES):

1.1 describe the principle of working.

The functional electrical stimulation (FES) consists of applying a voltage between two electrodes in order to obtain a muscular contraction of the muscles underneath the electrodes. It can be applied both whether or not the subject has partial neuronal activation from higher centres, it is mandatory that the subject still have innervation of the muscle. Two electrodes are used (anode and cathode): the cathode provides a negative current that hyperpolarizes, through the induced ionic currents the area below it; the ions "flow" from the area below the anode that will be depolarized, thus a ionic current flows between the two electrodes. If the depolarization is sufficient to exceed a certain threshold an action potential will be generated causing a muscle contraction with similar dynamic to that generated by a higher command.

1.2 describe the possible areas of application for disabled people.

The electrical stimulation can be used in different areas, for example in the cochlear stimulation for deaf people, in the deep brain stimulation for people with Parkinson Disease or it can be used to help the recovery of a function in a subject who presents neuromotor impariments (neuro-prosthesis), both as assistive devices or for functional recovery. The neuro-prosthesis can be used for different pathologies, such as Spinal Cord Injury, Stroke, Ataxia and Multiple Sclerosis.

1.3 Discuss one application example where the use of artificial neural networks (ANN) could be a good solution for the control of FES. Properly justify and explain your choice.

An ANN can be a good solution if the model we are considering is a complex model, if the laws that regulate it are not known and if it is possible to collect a sufficiently redundant training set.

An application example is the use of an ANN to provide the feedforward control in a single joint movement, elbow flex-extension. The muscle to be stimulated is the biceps, the subject is sit and the arm is extended along the trunk side. We aim at properly stimulate the biceps so to control the elbow angle time profile. The goal is to train the muscle and to improve fine control. The target population could be MS. The network can be trained to behave like the inverse model (linking the desired movement- angle kinematics time profile- to the correspondent FES sequence of stimuli (controlled for example in PW). This inverse neuromuscular model is complex, nonlinear, strongly personalized and difficult to be inverted, so it is reasonable to explore the use ANN.

The collection of the training set could be done by stimulating the subject in the final configuration with a sequence of exploratory FES stimulation profiles and collecting the correspondent achieved angle time profile.

The network can be trained on the collected data by using the time profile as input and the sequence of stimulation as output.

The collection of training set does not imply difficult operation by the subject and the therapist and can be seen as a preliminary phase of the treatment. Data collection of training set can be amle but anyway, after each therapeutic training the new data collected can be offline used to futher update the ANN so to adapt it to the user’s progression or decrease.

1.4 discuss one application example where the use of ANN would not properly cope with the goal. Properly justify and explain your choice.

In the case of gait- assisted FES the use of an inverse model ANN-based approach to build the feedforward controller is quite inapplicable because the system has three kinematic degrees of freedom (hip, knee and ankle angle) and multiple muscles to be stimulated (about 8 groups including bilateral muscles). The selection of an exploratory sequence of stimulation a priori to collect the training set could expose the subject to configuration of possible falls or difficult posture. Feedforward controllers based on stereotyped EMG physiological contractions (biomimentic controllers) are much more feasible in such condition.

2.1 List the parameters used to modulate the contraction

Parameters to control the stimulation:

- Amplitude (A) of the current pulse, [mA]
- Stimulation frequency (1/period→ 1/T)
- Pulse width (PW): width in time of each current pulse [□s]
- Monopolar or biphasic pulse Waveform

2.2 Discuss the differences between the artificial contraction elicited by FES and the natural muscular contraction

1) Muscle fibers are recruited synchronously with the current pulse stimuli – no turnover of fibers. Higher frequency of activation is mandatory to avoid twitches.

2) The recruitment of the muscle fibers is spatially fixed and depends on the quantity of charge delivered at the electrodes (it cannot be changed once the parameters of the stimulus are set) – this is exacerbated by the fact that axon threshold are inversely proportional to the diameter of the fiber, inducing a faster activation of Type B fibers, which are larger but are less resistant to fatigue.

3) Using external superficial electrodes, the working volume is quite large limiting the capability to control fine smooth movements. Often cross-stimulation to nearby muscles is induced.

4) Using intraneural electrodes, the stimuli are more selective but problems of invasiveness and stability of the implant become paramount.

Rehabilitation Robotics:

1.1 Define rehabilitation robotics (for rehabilitation purpose and not for restorative purpose)**.**
Rehabilitation robotics refers to the use of robots to help the physicians in rehabilitation of body parts or functions, which are impaired in patients. The aim is that the functionality is at least partially recovered and the patient can get back moving without being assisted.

1.2 Which are the key elements for motor recovery in rehabilitation?
The key elements are: frequency and intensity of rehabilitation sessions, functional goal oriented movements, patient active participation.

1.3 Which are the main limits of conventional therapy?

1) Limited resources for intensive training (one-to-one coupling between therapist and patient) for cost sustainability and organizational reasons in the hospital

2) Lack of quantitative evaluation of patient's improvements, which is necessarily subjective and not precise and limit the capability to tailor the treatment to single patients.

3) In addition, some therapies can be difficult to deliver, for example in case of particular movements for overweight people.

4) Safety of treatments limits the tasks, which can be trained, so reducing the challenging to the user and the motivation. The training of functional complex tasks is postponed until safety is assured.

5) Once patients are discharged from hospital, the continuation of therapy is usually very limited by costs.

1.4 How can robot-based rehabilitation tackle the key elements for motor recovery mentioned above?
The frequency and intensity of sessions are easy to take on because they depend only on the number of available robots and the therapist supervision can be shared by two/three patients. In addition, after training in the hospital, the patient can use the devices (or simple version of them) at home under remote supervision so to allow continuity of care at home.
Robots can assist the patient in goal-oriented tasks, by modulating the difficulty of the tasks and the level of assistance on patient's current conditions, always assuring proper safety.
Patient active participation can be assured in different ways: EMG-based assistance, or "assistance as needed", with the aim of avoiding the slacking problem. Further training exercises can be immersed in attracting virtual environments or can be designed as games so to sustain subject's motivation and attention.

2.1 discuss the major advantages of the use of robots for the rehabilitation of post-stroke patients.

1) Safety in performing also complex tasks since very early after the trauma

2) Immersivity and motivation (fancy exercises/games)

3) Continuous Monitoring and consequently single user tailoring of therapy.

4) Reward: scaling of goal of therapy and assistance by the robot so to assure the completion of the tasks, avoiding frustration and sustaining motivation

5) Intensity of repetitive training (for neuroplasticity remapping repetition is crucial)

6) Continuity of care: execution of exercises at home under partial/remote supervision after hospital discharge

2.1 Robots with impedance controllers: Describe the design of the control solution and the reason for its application.
An assistive robot performs a kinematics motion control: as long as the patient's movement remains within the desired trajectory (represented by a proper tunnel around the desired trajectory), there is no correction; when he/she deviates from the ideal tunnel, the robot exerts a force on the patient's limb in order to bring it back to the desired position.
The control mechanism is based on a threshold system, which shall cause the robot to intervene if a parameter of interest (distance from the desired path) exceeds a certain threshold (tunnel size).
Since the human movements have some variability during the performance of a task, a dead-band (or tunnel) is used: the robot does not correct the motion in case of slight variations from the desired trajectory.
The desired position is usually considered as spatial position but also as temporal profile, so that if the patient gets stuck in the tunnel or goes too slow the robot assist the acceleration of the task (back wall assistance).

An implementation of this kind of assistance could be the use of adaptive algorithms that tune the control according to the patient's performance so that the subject is constantly forced to make an effort.
A control algorithm could be: $P_{i+1} = f*P_i + g*e_i$ where P_{i+1} is the parameter at the successive instant, f is the forgetting factor, g is the gain, and e_i is the error at the i-th instant.
They are used for the motor re-learning of patients suffering from brain damage, but with a residual capacity of nervous control.

2.2 discuss the limitations and drawbacks of the use of robots for the rehabilitation of post-stroke patients.

1) limited exploration of compensatory strategies (the robot teaches the "target" trajectory and not any possible compensatory alternative), variety of solutions is limited.

2) limited translatability of results into daily activities: assistance by the robot simplifies the task execution (for example gravity relief) but at the end of the therapy the goal is to transfer the acquired skills into daily activities performances.

3) The subject can learn to let the robot do the movement on his/her behalf: slacking hypothesis.

2.3 select one drawback and present the design of a controller for robots which could limit the impact of such drawback.

1) Considering the limited translatability: the robotic assisted treatment should be designed so to reduce the assistance as soon as the user is improving till the non-assistance condition, which is the daily living target. The controller should be adaptable and a modulation of assistance (level of antigravity support for example) should scaled of a YY percentage (parameter YY: e.g. -2%) automatically every time the subject succeeds in performing the task in XX trials running (parameter XX: e.g. 5). At the end of each training session, the initial level of assistance and the final one are given back to the therapist/clinician to inform about the progression and to let him/her scale the parameters of the automatic controller XX and YY.

2) Considering slacking hypothesis:

a. a tunnel-based with backward-wall impedance controller could limit the problem of slacking (describe the principle)

b. a proportional myocontroller could help assuring the subject participation throughout the whole task execution. (describe the principle)

In-vitro neuronal models:

1.1 Report the two main types of in-vitro models used to obtain neuronal networks. Discuss advantages and disadvantages for each of them.

1) In vitro cultured neurons: Cultured neurons can be taken directly from embryonic brain tissue and grow in vitro under proper environmental conditions and nutrients delivery. In vitro cultured neurons over time form synapses and grow in network similar to brain tissues.

a. Adv:

i. the formation of the network can be analysed over time and for long periods (for example studying the pathology pathways or pharmacological kinetics.

b. Disadv:

i. The network is not natural. Very confined in space and formed by one type of neuron (not mimicking the complex connection between brain areas)

2) Brain slices: the slices are taken directly from brain tissue and then put into proper culture medium to preserve the activity of the neurons.

a. Adv:

i. The network is the very physiological one (or pathological), its formation has not been artificially modified.

b. Disadv:

i. The slice is extracted from the brain and then its connection to the rest of the brain are cut, this can modify the functioning also of the preserved neurons.

ii. The external layers of the slices are the cut dead neurons, they can partly mask the activity of the inside alive neurons (for example in case of MEA recording)

iii. Slices can be studied for short term (not possible to use for example for studies on synapses formation or of long term effects of drugs)

1.2 Report at least two of the available technologies used to investigate intracellular electrophysiology from in-vitro models.

Intracellular electrophysiology can be studied by

1) patch clamp electrodes

2) Voltage sensitive dyes optical studies

(Please note that MEAs record extracellular electrical activities: specific neurons and electrodes coupling models allow to infer information about intracellular electrophysiology from MEA recordings but this should have been clearly clarified in the answer)

1.3 Pick one of the two technologies: describe its working principle and discuss its advantages and disadvantages.

The first method consists of reading the electrical signals developed by the neuronal units. This technique is useful both for morphological and functional aspects. Unfortunately, the voltage difference given to the cell membrane leads to its degeneration and death. Therefore, this technique is not repeatable and it cannot be made on large scale.

For this reason, we moved to the use of MEA (and subsequently to the photoMEA), which are arrays of many electrodes (60 for the old technology, more than 1000 with the latest generation of CMOS). Thanks to a conductive interlude, these allow to study the synapses of neural networks in a bigger scale than with patch clamping. They have another advantage: a high time resolution and high repeatability. On the contrary, they have low selectivity (4-5 neurons per electrode) and no longer morphological meaning as in patch clamping.

Cerebellum:

1.1 Report its physiological structure (inputs, outputs, cells that make up the tissue and their interconnections)

The cerebellum is a structure located at the base of the skull and has many functions. One of the main ones is creating internal models for movement, balance, posture and in general, adaptation and learning in motor control. It contains about half of the total neurons of the brain, with a ratio of INPUT = 40 * OUTPUT.
It is organized in repetitive circuit units, microcomplexes, which can be easily recognized.
It includes 3 layers:
1) The top layer is the molecular layer, characterized by Stellate cells, Basket cells with inhibitory function and very small dimensions, Parallel fibers, which are made of axonal structures of the underlying Granular cells, over which the dendrites of the Purkinje cells create their synapses.
2) The middle layer is characterized by the presence of Purkinje cells somata, with inhibitory function on the output cerebellar neurons, the Deep Cerebellar Nuclei cells. They receive information from climbing fibers and from the parallel fibers (Granuli). Every cell of Purkinje receives only one climbing fiber but the same climbing fibers form synapses with more than one Purkinje cells and receive multiple parallel fibers spatially organized.
3) The last layer, i.e. the Granular layer, includes Granular cells that are inhibited by Golgi cells and excited by the Mossy fibers. These are the inputs of the system, carrying sensorial and passage-of-time information, which is processed through a spatio-temporal filtering in this layer.
The Mossy fibers also form connections with Deep Cerebellar Nuclei. Instead, the Climbing fibers originate from the Inferior Olivary cells, which are close to the brain stem and carry information on the motor gesture delay and error signals, providing a teaching signal that controls synaptic plasticity.

1.2 Explain the reason why the cerebellum represents a relevant test bench for computational neuroscience.

The cerebellum has significant plasticity properties and constitutes a key element in motor learning; this makes it very interesting for neuroscience.
There are two considerations, which makes it a special test bench for computational models in neuroscience:
1) very paradigmatic but, at the same time, simple experiments can be used to test cerebellum properties in simulation or even with real robots: pavlovian association protocols, such as timing association (e.g. Eye Blinking classical Conditioning) or Vestibulo-ocular reflex experiments or reaching experiments under modulation of force fields, that requires continuous tuning of corrective movements.

2) Its structure includes a limited number of cell types (see point above) and their geometrical modular organization as well as their connectivity are rather well known. The level of knowledge of the cerebellum neurophysiology is much higher with respect to other brain areas. In addition, there is a solid literature on the use of computational models to investigate cerebellar learning.

Computational Neuroscience:

1.1 What is Computational Neuroscience;

Computational neuroscience is the study of neurophysiology or neuropathology, investigating cognitive brain information processing features, through the use of computational models with the double goal of

- Understanding better the brain functioning
- Advancing computational control solutions mimicking brain performances.

1.2 Present one example of the cerebellum computational model, identifying the characteristics of the computational model, the similarities with the cerebellum physiology, and the possible testing methods.

The cerebellum acts as a feedback/forward controller including an adaptive learning module that allows adjusting the different motor actions.

The cerebellum can be schematized with different models. For example, it can be modelled as an inverse model that can be updated thanks to the use of feedback signals (see Figure below). In fact, as known from neurophysiology, the output of the cerebellum (representing motor commands) can be tuned under the supervision of a teaching/error signal encoded by neurons from the Inferior Olive and the corresponding Climbing Fibers. This happens thanks to synaptic plasticity.

Embedding the model into a closed-loop circuit reproducing the main cerebellum-driven tasks is fundamental to test the model functioning (therefore, using a simulated or real robotic platform).

Example protocols:

- Eye-Blinking Classical Conditioning (EBCC): by providing a Conditioned Stimulus, CS (e.g. a sound) and an Unconditioned Stimulus, US (e.g. an air puff, thus a perturbation) with a precise timing, after a learning period, the system learns to provide a conditioned response, eye-blinking, anticipating the US onset.
- Vestibulo-Ocular Reflex (VOR): it consists of a movement of the head while looking at a fixed or moving object. Thanks to the adaptive cerebellar module, the system after training will learn that the rotational movement of the head needs a compensatory movement of the eyes in the opposite direction that allows keeping the gaze fixed on the target.
- Reaching under external viscous force: while executing a reaching task, if an external force perturbs the movement, the systems learns to produce a compensatory torque to perform successfully the reaching task.

Correction depending on the external force is:

Gradually the system learns to counterbalance the external force, decreasing the error between the real and ideal trajectory.

2.1 Create a block diagram that associates the functioning of the different internal models discussed throughout the course.

Motor control is a highly complex physiological mechanism characterized by non-linearity, non-stationarity, noise and multi-dimensionality. This complex process is decomposed by the CNS in different functional modules, each one with different input-output features. An engineering modelling of this mechanism must be based on the distinction into modules as close as possible to the real ones. Two of the best-known internal models are:

• The inverse dynamic model: a mechanism that allows generating the torques to be applied to the body segments from a desired trajectory. This is also known as the feedforward controller because it represents the "open-loop control" of the motor control.

• The forward model, also called state estimator: it allows to estimate the sensory feedback generated by a certain motor command, in order to subtract the contribution of the patient's own movements from the sensory feedback.

The feedback controller is then the internal model converting the error as fed back to the brain in terms of afferences discrepancies to the error in motor commands. Kalman filter can be added to this network to mimic the capability of our brain to base the action either on current afferences or on a-priori models depending on the current reliability of the afferences.

(Also HONDA model can be described to answer this question)