Prova d'esame n. 1

Definizione, obiettivi e target audience di "Outreach Communication", di "Scientific dissemination" e di "IP Exploitation" in H2020;

Testo 1

As another notable application, relevant for dysfunctional glutamatergic transmission, we remind that excitatory synaptic transmission too is highly modulated by extracellular ionic concentrations. NMDA-receptors are in fact strongly inhibited – at resting potentials – by a high concentration of extracellular Mg2+, similar to Ca+2, a well-known modulator of the neurotransmitter release.

Supported by device modelling (Fig. 3), our first order calculations of diffusion transients - triggered by pulsed ion injection in a 20-100nm electrolyte layer between the ion emitter and the neuron - suggest very rapid propagation times ($t_p \propto t_{el}^2/D$) between 0.01 and 1 µs depending on electrolyte thickness (tel) and diffusivity (D), which is faster than most neuronal cellular machinery. We will consider one of the most common iontronic polymers for ionic transport (K+, Ca2+, Mg+): PEDOT:PSS and small biomolecules such as GABA as a contingency plan.

Prova d'esame n. 2

La preparazione e conduzione del kick-off meeting di progetto;

Testo 2

IN-FET aims towards iontronic delivery devices, to control the release of ions, at specific locations and times, via a voltage-controlled integrated device platform. Neuronal excitability will be modulated by changing the local extracellular concentration of certain ionic species. Let's consider the case of K+ ions, dispersed in the extracellular milieu at a concentration x100 lower than in the cytoplasm. As the membrane is permeable at rest to K+, this large chemical gradient induces spontaneous diffusion from the inside to the outside of the cell. At equilibrium, this gradient is balanced by a large electrostatic gradient of -70mV across the membrane, due to repulsive drift forces occurring simultaneously (Fig.2). If the concentration increases outside the cell (Fig. 3), both chemical gradient and electrostatic gradients decrease, becoming more positive.

Prova d'esame n. 3

La stesura di un report scientifico periodico di progetto;

Testo 3

IN-FET's ambition departs significantly from even the most advanced miniaturized microfluidic ion pump, demonstrated so far for in situ electrophoretic delivery for seizure control.

IN-FET will in fact enable us to (1) ionically control neurons and synapses at a much more refined spatial scale than by pumps, to (2) avoid pharmacology or extra-synaptic receptors mediation in neuronal modulation, to (3) reverse the "polarity" of modulation by the same hardware and without the need for separate chemicals and external reservoirs, (4) operate in close-loop, modulating rather than "blasting" cells and circuits.

In addition, IN-FET's strong interdisciplinarity involves a combination of advanced nanotechnology, polymer science and electrochemistry underpinned by strong modelling and simulation in multi-physics and neurobiology. Moreover, the presence of an industrial partner (MCS), will enable integration into a standard microelectronic amplification system for electrophysiology.

Prova d'esame n. 4

Il ruolo del coordinatore in un progetto europeo;

Testo 4

Epilepsy is a widespread brain disorder, with high societal costs. Advances in 'omics', gene editing, and deep-phenotyping techniques promise to bring precision, personalized, pharmacological interventions closer to the patient, but drug treatment is often ineffective. Surgical focal resection of brain tissue, identified by stereo-electroencephalography and assisted by stereotactic navigation, bears risks of cognitive impairment. Despite this, invasive interventions by implanted intracranial strip and/or microelectrodes for stimulation of the neck's (peripheral) left *vagus* nerve, thalamic deep brain and "responsive" neurostimulation have however gathered significant interest. The last is an example of a closed-loop strategy, where an array of metallic leads - placed in up to two seizure onset areas – is used to detect the incipient seizure and respond with electrical counter stimulation.

Prova d'esame n. 5

La gestione del flusso di comunicazione all'interno di un partenariato internazionale;

Testo 5

In IN-FET, we envision a novel class of micro- and nanotechnological neuromodulators, operating on a principle never exploited before: the local, intelligent, closed-loop manipulation of ionic concentrations, surrounding brain circuits and cells. IN-FET unites participants from neuroscience, bio-chemistry, semiconductor technology and simulation to exploit novel technologies for the ionic actuation of neurons and circuits.

These will be demonstrated *in vitro*, in a proof-of-principle integrated platform also featuring high-resolution nanoscale sensing of neuronal activity.

Our long-term breakthrough vision is of a novel neurotechnology, suited for a revolutionary treatment of epileptic seizures and based on (i) high-resolution on-board detection of waves of synchronous neuronal activity and (ii) their on-the-fly disruption by altering the ionic concentrations of key ions in the extracellular space around those neuronal networks, via closed-loop control of cellular excitability. IN-FET will revolutionize neuromodulation, specifically advancing *electroceutics* by going beyond electrical stimulation, with none of the limitations of genetic approaches.