Modeling Therapeutic Applications of Electric Currents in the Central Nervous System: understanding the biophysical processes and addressing effectiveness and safety concerns

Sofia Rita Fernandes, Nichal Gentilal, Mariana Pereira, Mamede de Carvalho, Pedro Cavaleiro Miranda

Instituto de Biofísica e Engenharia Biomédica (IBEB) – FCUL
Instituto de Medicina Molecular (iMM) - FMUL

November 3-4, 2020
Overview

1. Electric signals in the CNS
2. Neuronal stimulation techniques
3. Which techniques do we study?
4. Numerical modelling in Neuronal Stimulation
   4.1. Transcranial Magnetic Stimulation (TMS)
   4.2. Transcranial Current Stimulation (tCS)
   4.3. Transcutaneous Spinal Direct Current Stimulation (tsDCS)
   4.4. Tumor Treating Fields (TTFs)
5. “Take home messages”
1. Electric signals in the CNS

Alan Hodgkin and Andrew Huxley won the Nobel Prize for discovering the mechanism of transmission of the nerve impulse. They used the "giant axon" of the squid in studies at the Plymouth Marine Biology Laboratory in 1963.

“Brain is an ‘enchanted loom’ of dynamic ever-changing electric signals”
Neuron – membrane electrically excitable

Membrane electrical properties can be altered by summation of synaptic incoming potentials

Action Potential – electric transmission through the CNS

(Kandel, 2013; VanPutte, 2014)
Techniques that employ electric fields (EF) to stimulate neurons

**Electrical stimulation**
(current applied through electrodes)

**Magnetic stimulation**
(time-varying magnetic field generated by a coil)

**Applications**

- **Diagnostic** – Detect changes in neuronal responses
- **Treatment** – Modulate altered responses due to dysfunction

Cellular stimulation originates responses at a macroscopic level, resulting in changes in central and/or peripheral functions.

Modelling Therapeutic Applications of Electric Currents in the CNS, November 3-4, 2020
srcfernandes@fc.ul.pt
Transcranial magnetic stimulation (TMS): A time-varying magnetic field induces a strong (~100 V/m) short lasting (~1 ms) electric field in the brain.

Transcranial current stimulation (tCS): Long lasting (10-30 minutes), weak (~1 V/m) EF generated by electrodes placed in contact with the scalp. The EF can be either continuous (tDCS) or slowly alternating in time (tACS).

Transcutaneous spinal direct current stimulation (tsDCS): 15-20 minutes transcutaneous DC stimulation over the spinal cord, generating weak EF (< 1 V/m) in the spinal WM and GM.

Tumour treating fields (TTFs): Strong (~100-400 V/m) rapidly oscillating (~200 kHz) EF induced by arrays of electrodes capacitively coupled to the scalp. (not a neuronal stimulation technique)
The effects of these techniques depend directly on the spatial distribution and temporal variation of the EF induced in the brain.

A non-invasive recording of the induced EF is not possible. Modelling is the only viable alternative.

Since analytical solutions to the equations involved are complex (and sometimes not possible to obtain), computational modelling is usually employed.
4. Numerical modelling in neuronal stimulation

Such models require:

- Use of medical imaging to build the geometry of the models.

- Measurements of the dielectric properties of tissues.  
  Gabriel et al. 1996

- Knowledge about the properties of the coils and electrodes employed.  
  Salinas et al., 2007
The neuronal membrane behaviour can be modelled as an electrical circuit:

- **Linear (RC):** passive membrane;
- **Non-linear:** to model action potentials.

(Kandel, 2013)
The variation of the membrane potential $v_m$ for a passive membrane in function of the electric field can be described by the cable equation:

$$\lambda^2 \frac{\partial^2 v_m}{\partial z^2} - \tau \frac{\partial v_m}{\partial t} - v_m = -\lambda^2 \frac{\partial^2 \Phi_e}{\partial z^2}$$

(Plonsey & Barr, 2014)

In DC current stimulation – steady-state, i.e. there is no temporal variation of $v_m$, and considering that the extracellular potential $\Phi_e$ reaches distances larger than $\lambda$:

$$v_m \approx \lambda^2 \frac{\partial^2 \Phi_e}{\partial z^2} = -\lambda^2 \frac{\partial E_z}{\partial z} = A(z)$$

*Activation function of Rattay (1987)*

(a) Extracellular potential

(b) $A(z)$ - anodal stimulation (hyperpolarization)

(c) $A(z)$ for cathodal stimulation (depolarization)

(d) Electrode position
4.1. Transcranial Magnetic Stimulation (TMS)

TMS consists in a strong and short lasting current that flows through a coil located over the scalp, inducing a time varying magnetic field.

This field will induce a time varying EF (~100 V/m, ~1 ms) in the conducting head tissues, according to Faraday’s law of induction.

**TMS main applications**

- **Single pulse TMS**
  - Stimulation of the motor cortex:
    - diagnosis of motor circuitry dysfunctions and degeneration;
    - To study the mechanisms of action of substances.

- **Repetitive TMS (rTMS)**
  - Frequency of rTMS: \( f = \frac{1}{\Delta t} \)
  - Treatment of neuro-psychiatric diseases (e.g. depression)
Numerical modelling in TMS:

- We use the FEM to calculate the EF distribution in the head during TMS in a region of interest (e.g. TMS of the motor cortex).

- Using the values of the estimated EF, we determined the effects in neuronal transmembrane potential by modelling their electrical behaviour.
The cortical EF is induced by a potential difference applied between two electrodes placed in the scalp.

**tCS devices:**
- Electric stimulator with capability to apply ~ 2 mA maximum electric current and a time duration over 10 minutes or more.
- Large electrodes – 9 to 35 cm² area
- Easier to carry and cheaper than TMS devices.

The electrode configuration, geometry and the electric properties of the tissues will determine the EF distribution in the cerebral cortex.
4.2. Transcranial Current Stimulation (tCS)

- Chronic Pain modulation (Fregni et al., 2006)
- Fibromyalgia – sleep modulation (Roizenblatt et al., 2007)
- Stroke recovery and improved motor function in PD (Fregni et al., 2005, 2006)
- Modulation of motor learning processes (Fregni et al., 2006; Hummel et al., 2005)

- Reduction of Depression (Nitsche, 2002)
- Food, alcohol and smoking craving (Boggio, et al. 2008; Fregni et al. 2008)

**Motor Cortex**

- tCS clinical applications

**Pre-frontal Cortex**

![tDCS](chart)
4.2. Transcranial Current Stimulation (tCS)

Numerical modelling in tCS:

- The EF characteristics determined in tCS simulations may predict the success of specific electrode montages, which allows to optimize clinical protocols for a specific target.

Salvador et al., 2015
We apply the same methods to study the application of DC in stimulation of the human spinal cord (tsDCS).

The spinal EF is induced by a potential difference applied between two electrodes placed, one over the vertebral column and the other in a sufficient distant region (e.g. right deltoid area).

Just as in tDCS, the electrode configuration, geometry, polarity and the electric properties of the tissues will determine the spinal EF distribution with strong implications for clinical practice.
Neuromodulation of ascending nociceptive spinal pathways and motor spinal pathways
(Cogiamanian et al., 2008; Cogiamanian et al., 2011; Truini et al., 2011; Winkler et al., 2010)

Neuromodulation of motor spinal pathways
(Winkler et al., 2011; Lamy et al., 2012; Hubli et al., 2013; Bocci et al. 2014)

**Numerical modelling in tsDCS:**
- Modelling studies in tsDCS using MRI-based realistic human models predict that the spatial distribution of the EF depends on stimulation parameters and individual anatomic characteristics (Parazzini et al., 2014; Kuck et al., 2017, Fernandes et al., 2018)
Numerical modelling in tsDCS:

- Predictions of EF distribution match with experimental results observed previously in lumbar stimulation (Pereira et al., 2018)

Modelling Therapeutic Applications of Electric Currents in the CNS, November 3-4, 2020

srcfernandes@fc.ul.pt
Numerical modelling in tsDCS:

- Predictions of EF distribution match with experimental results observed previously in lumbar stimulation (Pereira et al., 2018)

EF < 0.15 V/m
Not sufficient for neuromodulation
Numerical modelling in tsDCS:

- Our main objective is to study the EF for different electrode configurations to optimize tsDCS clinical protocols to treat neurologic dysfunctions, such as muscular weakness and spasticity.

Fernandes et al., 2018
Numerical modelling in tsDCS:

- Results so far suggest that there are optimal configurations for neuromodulation of areas related to upper and lower limb motor and sensory functions.

<table>
<thead>
<tr>
<th>Target regions and functions</th>
<th>Optimal electrode montages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic CS, M, PT, S</td>
<td>T10-rD, L2-rD</td>
</tr>
<tr>
<td>Abdominal CS, M, PT, S</td>
<td>T10-rD, L2-rD, L2-T8, T8-rIC, T8-U</td>
</tr>
<tr>
<td>Middle back CS, M, PT</td>
<td>T10-rD, L2-rD, L2-T8, T8-rIC, T8-U</td>
</tr>
<tr>
<td>Lower back CS, M, PT</td>
<td>L2-T8, T8-rIC, L2-T8, T8-U</td>
</tr>
<tr>
<td>Thigh CS, M</td>
<td>L2-T8, T8-rIC, L2-rD, T8-U, T10-rIC, T10-U</td>
</tr>
<tr>
<td>Hip CS, M</td>
<td>T8-rIC, L2-T8, T10-rIC, T8-U, L2-rD, T10-rIC</td>
</tr>
<tr>
<td>Leg and Foot CS, M</td>
<td>T8-rIC, T10-rIC, L2-T8, T8-U, T10-U, L2-rD</td>
</tr>
<tr>
<td>Pelvic floor CS, M</td>
<td>T10-rIC, T8-rIC, L2-T8, T10-U, T8-U, L2-rD</td>
</tr>
</tbody>
</table>

Fernandes et al., 2018
Numerical modelling in tsDCS:

- Results so far suggest that there are optimal configurations for neuromodulation of areas related to upper and lower limb motor and sensory functions.
Numerical modelling in tsDCS:

- EF > 0.15 V/m in all cervical regions for C3-T3, and only in specific regions for the other electrode montages.

Fernandes et al., 2019, JNER
Experimental protocol based on tsDCS modelling predictions:

**STUDY DESIGN**
Double-blind, crossover, randomized

**SAMPLE**
N = 10 (healthy volunteers)

**PROTOCOL**
- C3-T3
- I = 2.5 mA
- Q = 90 C/cm²

**MEASUREMENTS**
- SEP N9, N13, N18, N20, P22 - latencies
- MEP, F-wave and H-reflex amplitude and latency in the right ADM
- Central and Peripheral Motor Conduction Times (CMCT, PMCT)

Fernandes et al., 2019, JNER
Experimental protocol based on tsDCS modelling predictions:

- Sensory and motor responses neuromodulation
4.4. Tumor Treating Fields (TTFs)

Antimitotic treatment selectively targeting dividing cancer cells at the end of the cell cycle.

TTFs disrupts cellular structures during cell division, causing cell death

TTFs are applied for the treatment of Glioblastoma Multiforme (GBM) through the Optune device.

Numerical modelling in TTFs

Studies on inter-subject variability on the EF distribution in the tumour during TTFs application.

Numerical modelling in TTFs

Determining the TTFs effects on the EF distribution considering different types of tumour cells mixtures.

To study tissue heating due to the passage of current to establishing safety measures during TTFs application:
- Temperature rise might be harmful to biological tissues if excessive and not controlled;
- Average daily usage of TTFields should be at least 18 hours for efficacy – no clear knowledge on tissue heating effects due to prolonged exposure;
- Optune shuts down every time electrodes temperature reaches 41 °C.

Questions to address

How this on/off process affects treatment efficacy
Find ways to deliver TTFS without increasing tissues' temperature by an excessive amount
The Optune device:

- EF generator
- 4 transducer arrays

Current is injected in two perpendicular directions alternately

Studies showed that current should be injected for as long as possible to improve patient’s overall survival:

- Recurrent GBM patients: compliance ≥75%
- Newly diagnosed GBM patients: compliance ≥50%
4.4. Tumor Treating Fields (TTFs)

- Heating is very localized and occurs mainly underneath the regions where the (outer) transducers are placed (Gentilal et al, Phys Med Biol, 2019)

- Heating occurs mainly at the surface of each tissue

- Temperature maxima in each tissue decreases as the distance to the arrays increases

- The maximum temperature is reached in the scalp:
  - Heat flows from the scalp to the deepest tissues and to the gel and transducers

[Brain temperature at the end of the simulation]
According to the literature, some physiological changes are predicted only for the brain:

- Increases in the cerebral blood flow and cerebral metabolic rate
- Changes in the synaptic transmission in the neocortex
- Higher probability of neurotransmitter release

- Blood-brain barrier permeability increase
- Changes in the cerebral blood flow
- Variations in the concentration of GABA, glycine and glutamate
Non-invasive brain and spinal cord stimulation are valuable co-adjuvant therapies to the treatment of psychiatric, sensory and movement dysfunctions of the central nervous system, improving patients’ functional gains in everyday quality of life.

Computational studies on neuronal stimulation techniques are important to address adequate choices of electrode montage and stimulation parameters to achieve a specific clinical purpose.

Realistic models of human tissues and applied electrodes could improve the accuracy of predictions about the EF distribution and resulting neuromodulatory effects, guiding clinical application.

This can open new perspectives for non-invasive stimulation designed for patient’s specific needs.
Acknowledgements

“Brain and Spinal Cord Stimulation” team members

Experimental team
Mamede Alves de Carvalho (iMM)
Mariana Pereira (iMM)

Modelling team
Pedro Cavaleiro Miranda
(P.I., IBEB)

External collaborators
Mª Amparo Callejón Leblic
(doctorate researcher, Universitat de Sevilla)
Ricardo Salvador (Neuroelectrics)
Cornelia Wenger (Novocure)

Nichal Gentilal (PhD student, IBEB)
Sofia Fernandes (doctorate researcher, IBEB, CDRSP)
References

• Bocci et al. 2014 Cathodal transcutaneous spinal direct current stimulation (tsDCS) improves motor unit recruitment in healthy subjects Neurosci Lett 578: 75-79
• Cogiamanian F, et al. 2011 Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings Pain 152(2): 370-375
• Cogiamanian F, et al. 2012 Transcutaneous spinal direct current stimulation Front Psychiatry 3: 63
• Fregni et al. 2006 Movement Disorders, 2006
• Lamy JC and Boaeye M 2013 BDNF Val66Met polymorphism alters spinal DC stimulation-induced plasticity in humans J Neurophysiol 110(1): 109-116
• Miranda P C, Mekonnen A, Salvador R and Ruffini G 2013 The electric field in the cortex during transcranial current stimulation. Neuroimage 70 48-58
• Nitsche MA 2002 Bipolar Disorders
• Roizenblatt et al. 2007 Pain Practise
• Salinas FS, Lancaster JL and Fox PT 2007 Phys Med Biol 52(10): 2879-2892
• Truini et al, 2012 European Journal of Pain
• Wenger C, Salvador R, Bassier PJ, Miranda PC. The electric field distribution in the brain during TTFIELDS therapy and its dependence on tissue dielectric properties and anatomy: a computational study. Phys Med Biol. 2015;60(18):7339-7357