

# Treatment planning for electrochemotherapy and irreversible electroporation: optimization of voltage and electrode position

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Duration of the experiments: 90 min

Max. number of participants: 6

Location: Laboratory of Biocybernetics

Level: Basic

## PREREQUISITES

No specific knowledge is required for this laboratory exercise.

## THEORETICAL BACKGROUND

Electrochemotherapy (ECT) is an efficient local treatment of cutaneous and subcutaneous tumors, which combines the delivery of nonpermeant, cytotoxic chemotherapeutics (e.g. bleomycin, cisplatin) and short high-voltage electric pulses. The pulses induce electric fields inside the tissue, thereby increasing cell membrane permeability in tissue (electropermeabilization) to otherwise nonpermeant chemotherapeutics. ECT requires the electric field inside the tumor to be higher than the threshold value needed for reversible electroporation ( $E_{rev}$ ) while irreversible electroporation ( $E_{irrev}$ ) in nearby critical structures should be limited. For IRE, the electric field in the entire tumor volume needs to be above the irreversible electroporation threshold. It is not necessary that the whole tumor is electropermeabilized by one pulse or pulse sequence - sometimes a combination of several pulse sequences or a combination of different electrodes is required.

**The aim** of this laboratory practice is to learn how to use optimization techniques to achieve suitable electric field distribution for electrochemotherapy experimental planning and treatment planning.

## EXPERIMENT

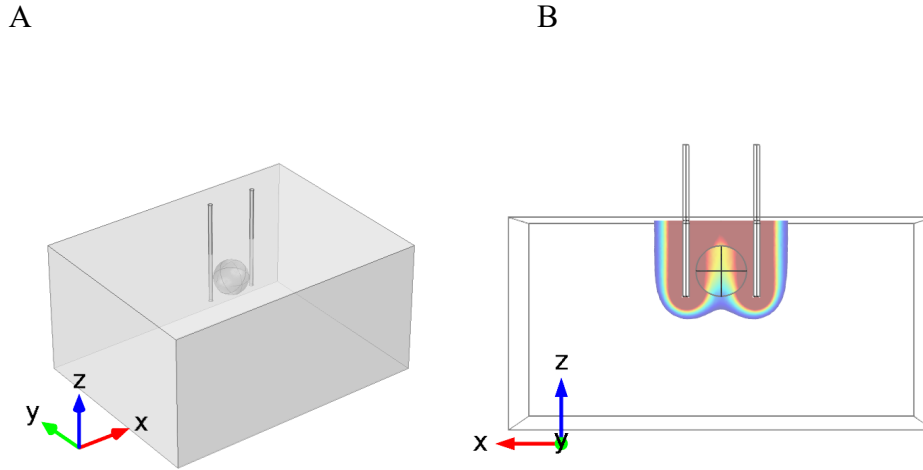
A finite element based numerical modeling program package COMSOL Multiphysics version 5.4 (COMSOL AB, Stockholm, Sweden) will be used to optimize voltage between the electrodes and position of the electrodes on a simple 3D model of a spherical subcutaneous tumor and surrounding tissue (Figure 1a). Electrode positions and the applied voltage should be chosen, so that the following objectives are fulfilled:

- For electrochemotherapy: the tumor is permeabilized ( $E_{tumor} > E_{rev} = 400 \text{ V/cm}$ ),
- For irreversible electroporation: the tumor is permeabilized above the irreversible threshold ( $E_{tumor} > E_{irrev} = 600 \text{ V/cm}$ ),
- the damage to healthy tissue is kept to a minimum.

We will calculate the electric field distribution in the model after each change of the electrode placement or voltage. The final goal of this exercise is to achieve 100 %  $E_{tumor} > E_{rev}$  (or 100 %  $E_{tumor} > E_{irr}$  when planning for IRE) and minimize  $E_{irr}$  in healthy tissue.

**Protocol:** Build the 3-d model by following the lecturer's instructions and take into account your tissue-specific electric properties. Solve the model and evaluate the initial solution. In case, the initial solution is inappropriate (see e.g., Figure 1b), try to improve on the solution by changing electrode positions and voltage between the electrodes. Calculate the electric field distribution in the model after changing the

electrode positions or voltage and then determine the coverage of tumor tissue with  $E_{tumor} > (E_{rev} \text{ or } E_{irrev})$  and determine damage to healthy tissue due to irreversible electroporation. Repeat the process, until the quality of your solution reaches the set goals. Compare the results with others, who have used different tissue properties. Use a parametric study to find the lowest voltage which achieves the objective for the selected electrode geometry.



**Figure 1:** (A) Simple 3D model of tumor and needle electrodes in healthy tissue; (B) electric field over reversible threshold inside the healthy tissue and the tumor.

### FURTHER READING:

- Miklavčič D, Čorović S, Pucihar G, Pavšelj N. Importance of tumor coverage by sufficiently high local electric field for effective electrochemotherapy. *EJC Supplements*, 4: 45-51, 2006.
- Čorović S, Županič A, Miklavčič D. Numerical modeling and optimization of electric field distribution in subcutaneous tumor treated with electrochemotherapy using needle electrodes. *IEEE Trans. Plasma Sci.*, 36: 1665-1672, 2008.
- Županič A, Čorović S, Miklavčič D. Optimization of electrode position and electric pulse amplitude in electrochemotherapy. *Radiol. Oncol.*, 42: 93-101, 2008.
- Edd JF, Davalos RV. Mathematical modeling of irreversible electroporation for treatment planning, *Technol. Cancer Res. Treat.*, 6: 275-286, 2007.
- Kos B, Zupanic A, Kotnik T, Snoj M, Sersa G, Miklavcic D. Robustness of Treatment Planning for Electrochemotherapy of Deep-Seated Tumors, *Journal of Membrane Biology* 236: 147-153, 2010.
- Cukjati, D, Batiuskaite D, Andre F, Miklavcic D, Mir L. Real Time Electroporation Control for Accurate and Safe in Vivo Non-viral Gene Therapy. *Bioelectrochemistry* 70: 501–507, 2007.

### NOTES & RESULTS

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