URSI GASS 2021, Rome, Italy, 28 August - 4 September 2021

Non-contact DC field effects on glioma cells migration: *in vitro* and *in silico* studies

Laura Caramazza*[(1,2)], Nicolò Lauciello[(2)], Annalisa De Angelis[(1,2)], Daniel Remondini[(3)], Gastone Castellani[(4)], Micaela Liberti[(1,2)], Francesca Apollonio[(1,2)], and Isabella Zironi[(3)]
(1) CLNS@Sapienza, Istituto Italiano di Tecnologia, Rome, Italy, 00161; corr. e-mail: laura.caramazza@iit.it
(2) DIET@Sapienza University of Rome, Italy, 00184; corr. e-mail: francesca.apollonio@uniroma1.it
(3) DIFA@University of Bologna, Italy, 40126; corr. e-mail: isabella.zironi@unibo.it
(4) DIMES@University of Bologna, Italy, 40126; e-mail: gastone.castellani@unibo.it

The migration of cells plays a critical role in maintaining in a variety of processes that are physiologically relevant for maintaining and developing multicellular organisms, such as embryogenesis, neurogenesis, tumor metastases and wound healing [1]. Usually, the mechanisms could involve both a dynamic interaction between various cell types and a regulated production of cytokines and mediators [2,3]. In this context, the application of external electric fields (EF) can affect cell migration, overriding most chemical gradients, thus promoting electrotactic response, termed galvanotaxis. Considering that different cell types show subtly different response to EF, most cells seem to migrate once exposed to EF=200 V/m but can sense as low as 10 – 25 V/m [4]. As regards, the concept of a non-contact force capable of directing cell migration is interesting for brain cancer therapy and seems promising to treat *in vivo* the deadly brain tumor glioblastoma multiforme (GBM) [5]. In this context, the majority of the *in vitro* galvanotaxis studies in literature [6] are performed in a "contact mode". Hence, *in vitro* "non-contact" galvanotaxis studies to remotely guide cells migration could be promising to fully understand the involved phenomena, avoiding the interaction between electrodes and cell cultures.
In this work, authors provide an experimental study on the mobility of cells exposed to a direct currents (DC) EF in a "non-contact" mode using two different configurations setup, supported by a suitable numerical modeling of the experimental bench. To this end, glioma cells were plated on two different Petri dishes with: a polystyrene bottom as 1st setup; a glass bottom microwell of 10 (ø) mm as 2nd setup. Cells were maintained for 48 h in Eagle's Minimum Essential Medium, then a scrape wound assay was performed. Finally, the cells were exposed to a static EF, acquiring phase contrast micrographs of multiple visual fields up to 20 h. Results show that cells migration of exposed samples start accelerating after 2.5 h, almost reaching a complete closure in half the time compared to the sham samples.
Numerical simulations of the exposure system were carried out with COMSOL Multiphysics v. 5.3 in order to support the experimental evidence obtained. In accordance with *in vitro* experiments, in numerical results the EF distribution on the adherent cells plane differs in terms of both intensity values and distribution.
Here authors demonstrate that average EF intensities ranging from 50 to 60 V/m, applied in a "non-contact" mode, together with a resulting current density values in line with literature [7], determine an effective galvanotactic stimulus, increasing the collective migration velocity of glioma cells (T98G) involved in a wound healing process. Finally, *in silico* studies demonstrate that a larger gradient together with higher EF intensity values on cells determine an increase of the electrical stimulus efficacy.

References

[1] Trepat X, Chen Z, Jacobson K. Cell migration. Compr Physiol. 2012;2(4):2369-92. doi: 10.1002/cphy.c110012.
[2] Te Boekhorst V., Preziosi L. and Friedl P., "Plasticity of cell migration in vivo and in silico," Annu Rev Cell Dev Biol. 2016 Oct 6; 32:491-526.
[3] Funk, R.H.W. "Endogenous electric fields as guiding cue for cell migration," Front. Physiol. 6, Article n. 143 (2015).
[4] Balint R, Cassidy NJ, Cartmell SH. Electrical stimulation: a novel tool for tissue engineering. Tissue Eng Part B Rev. 2013 Feb;19(1):48-57. doi: 10.1089/ten.TEB.2012.0183.
[5] Mun E.J., Babiker H.M., Weinberg U. and Von Hoff D.D., "Tumour-treating fields: A fourth modality in cancer treatment," Clin. Cancer Res., 24 (2), 266–275, (2018).
[6] Cohen D. J, Nelson W.J., Maharbiz M.M., "Galvanotactic control of collective cell migration in epithelial monolayers," Nat. Mater. 13 (4) 409-417, (2014).
[7] Tsai, H., Cheng, J., Chang, H., Yamamoto, T., & Shen, A. Q. (2016). Uniform electric field generation in circular multi-well culture plates using polymeric inserts. Nature Publishing Group, October 2015, 1–11. https://doi.org/10.1038/srep26222