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Wireless electrical stimulation induced by a 3D biofriendly polymer-based magnetoelectric graft: an in silico study

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Abstract

Electrical stimulation promotes the repair of nerve injuries, however, their large-scale application in vivo is still limited due to the issues related to invasive and not-mechanically compliant commonly-used stimulators.
Recently, magnetoelectric nanoparticles (MENPs) have been proposed thanks to their ability to locally generate electricity, when activated by external and low intensity magnetic fields. Here, a new paradigm based on the use of MENPs-loaded 3D polymeric graft has been demonstrated through a multi-scale *in silico* framework. In particular the stimulation ability of a millimetric, biomechanically compliant, magnetoelectric graft was functionally assessed in a realistic model of human peripheral nerve.
Our results pave the way for a remote and wireless electricity generation by using novel magnetoelectric-based biomaterials, able to deliver the extremely localized effects of individual MENPs to elicit neurons electrical stimulation.

1. Introduction

External electric stimulation is a powerful tool to induce recovery from nerve injuries [1]. However, the traditional approach relies on the use of implanted electrodes, which are invasive and often cause interface effects, secondary damages and inflammatory responses, due to their not-biologically and mechanically compliant physics-chemical properties [2]. Therefore, an alternative strategy for remote and biofriendly electrical stimulation is needed.
Magnetoelectric materials may offer possible solutions, thanks to their dual piezoelectric and magnetostrictive nature, which allow the generation of extremely local electric fields by mild external magnetic stimulation [3]. Recently, magnetoelectric/polymeric composites have been gaining popularity, since they can be easily fabricated by using well-established biomaterials processing techniques, such as 3D printing and electrospinning. Nevertheless, polymeric-based structures are generally tissue mechanically compliant, besides showing tunable biodegradability and biocompatibility [4]. Poly(3-hexylthiophene (P3HT) is a conductive polymer with low cytotoxicity and good physical and chemical stability in the biological environments[5]. Moreover, it shows higher values of softness and stretchability, if compared with standard metal-based electrodes, thus making it a good candidate to assemble neuronal biointerfaces [6]. Therefore, we here built a multi-scale in silico model to estimate the electrical in vivo performance of a novel nano-structured material composed of MENPs embedded in a 3D P3HT polymeric matrix for wirelessly modulating neural pathways.
Overall, our approach predicts the stimulation ability of a millimetric, soft and wireless electrode in a clinically mimicking virtual scenario, starting from the modeling of the magnetoelectric sources at the nanoscale.

2. Methods

2.1 Sim4Life model of the magnetoelectric base unit

Sim4Life (ZMT Zurich Med Tech AG, Zurich, Switzerland) was adopted to model the nanometric unit composed by MENPs embedded in a P3HT matrix (18w/V% MENPs/P3HT). The model was composed of three different subdomains: (i) the 3D MENPs; (ii) the polymeric matrix (cube: 400 nm side); (iii) the surrounding tissue (nerve, cube: 800 nm side). Leveraging on the COMSOL Multiphysics results previously published [7,8] about the electric potential generated by a 90nm diameter Cobalt Ferrite/Barrium Titante MENP when stimulated by an external static magnetic field above the magnetic saturation (Ms), each MENP was modelled as two hemispheres, one with a positive electric potential of +2.25 mV and one with a negative potential of -2.25 mV (Dirichlet boundary conditions, with a total charge of 4.5 mV), separated by an insulating layer of Techotane 75D ($V = 0$, $\sigma = 0$, $\varepsilon = 3.4$, and $\mu = 1$). All MENPs were hypothesized to be aligned all in the same direction, i.e. the one of the external magnetic field. Properties related to the polymeric matrixes and their surrounding nerve tissue are summarized in Table 1.

Table 1. Electrical features of P3HT and the surrounding nerve tissue.

Mat.	Electrical Conductivity, σ (S/m)	Rel. permittivity, ε	Relative permeability, μ
P3HT	$2.24 * 10^{4}$	3	0.92
NERVE	$3.48 * 10^{-1}$	466016	1

An ohmic quasi-static approximation was set with 100 Hz as stimulation frequency. Dirichlet boundary conditions (V = 0) were set at the borders of the computational domain.
A more clinically consistent millimetric graft (1x1 mm) with the same electrical features of the nanometric unit base set above was then modelled. Firstly, it was positioned within the nervous tissue, whose properties are resumed in Table 1, and the E_{field} distribution was evaluated by solving the Laplace equation. Then, a more realistic model of peripheral nerve cylindrically-shaped nerve with a diameter equal to 1.3 mm, containing different structural and functional domains (blood vessels, connective tissue, axon fascicles and interstitial tissue), was considered. Some simplifications were adopted: (i) all the structures present circular symmetry, with (ii) diameter, myelination and material density constant along all the axon length; (iii) fascicles and fibers show no tortuosity (iv) all the fascicles are modeled by using the MRG model of mammalian peripheral nerve and considering fiber diameter equal to 5.7 μm.
The designed, soft graft is placed in contact with the nerve model, encapsulated in a silicone layer to ensure that the electric charges are directed towards the nerve fibers (Figure 2A). Results are used as sources for the neuronal stimulation (by means of the NEURON dynamic solver). In fact, the ability of our graft to trigger nerves action potentials was evaluated. To this end, Sim4Life is coupled with the NEURON solver (Yale University, CT, USA, https://www.neuron.yale.edu/neuron/) to model the effect of the generated currents on the neuronal dynamics. Two sides of our cubic ME-patch were placed in contact with the nerve, and a reference node was identified in correspondence of the most external fascicle. A sinusoidal type source with a frequency of 100 Hz, sine amplitude equal to the amplitude of the electric field obtained by the electromagnetic simulation and 50 milliseconds of duration, was considered. The action potential was registered at one reference axon (spline 0) and at the one location of the fiber (the nearest node to the graft side center).

3. Results

The electrical features on the outer surface of a 3D MENP/P3HTgraft were assessed through the Sim4life Biophysics tool. In particular, MENPs were modelled only in terms of their electrical features (maximum and minimum electric potential of +/- 2.25 mV derived at the their surface from the COMSOL framework previously published by our group [7,8]). Current density distribution (J) at the external surface of the graft and within the material cross-section (Figure 1A) was obtained. From the color maps and the quantitative analyses (Figure 1A) the electrical field generated by individual MENPs is transferred through the polymeric matrix, which therefore acts as a soft nano-structured electric source.
Surely, the MENPs positioning within the matrix may condition the effective electric stimulation at the outer surface of the P3HT, especially when dealing with very few particles concentration. In this regard, we have considered a 18% w/V of particle concentration (i.e 6 MENPs with our unit base), because it should guarantee an effective electrical stimulation, while preserving the rheological properties of the overall system, as well as its processability.
The electrical behavior obtained at the nanoscale was reproduced on a more clinically-size millimetric patch, properly modelled as repeated replicates of the unit base previously studied. This approach agrees with the definition of "volume dipole moment density function" to model the electric potential on the surface of a source containing repetitions of individual dipoles [9, 10]. The electric field distribution within the biological surrounding, represented by nerve tissue, was then derived. Figure 1B reports the resulting spatial distribution of E_{field} on a specific reference plane (xy). Simulations were performed in all possible reference planes (data not shown). Results show that the electric pulse decays rather quickly with the distance from the graft. However, the plot (Figure1B) shows that the E_{field} is higher than threshold values commonly considered necessary to trigger a neuron response [11,12].

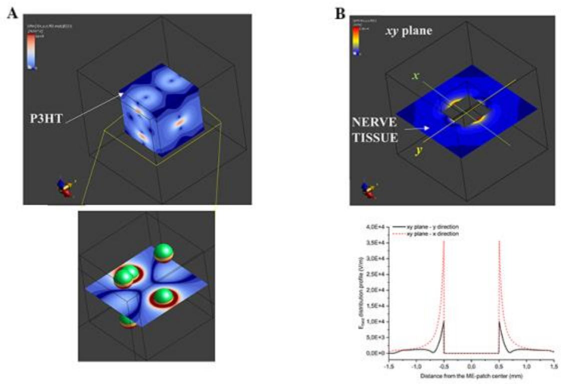

Figure 1. A) Sim4Life 3D rendering and quantitative evaluation of the current density distributions (J, expressed as A/m^2) at the surface and at the center (xy plane) of the 3D graft nanometric unit. B) Color map of E_{field} (V/m) generated by the P3HT surface, which propagates within the nerve tissue (xy reference plane). E_{field} profiles have been extrapolated along directions of references and compared (xy plane in y direction vs xy plane in x direction).

Therefore, in the last part of the study, Sim4Life was coupled with the NEURON solver to model the neuronal activation. The validation of our 3D MENPs-P3HT graft was performed by using the Yoon-sun arm model from the neuro-functionalized virtual population model library of Sim4Life.
Two sides were alternatively positioned in contact with the nerve model and used for the stimulation assessment (Figure2). Results show that the E_{field} profile within the nerve cross-section propagates accordingly with i) the different positioning, ii) the electrical features of the biological structures encountered (Figure 2A). These results are used as input for the NEURON solver. Figure 2B shows that the local E_{field} provided by our 3D magnetoelectric graft is sufficient to trigger an action potential presenting periodical spikes of magnitudes up to 30 mV, thus indicating the functional effectiveness of the proposed approach.

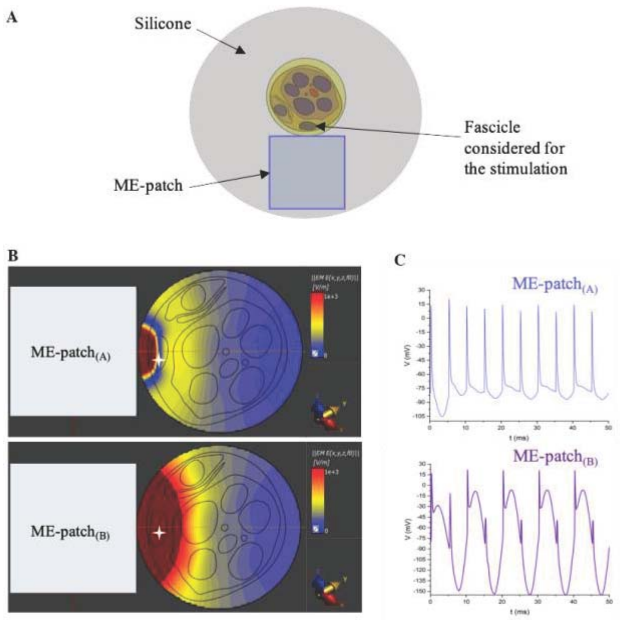

Figure 2. (A) Sketch showing the millimetric, cubic ME-patch positioning in contact with the nerve embedded in a silicon wrap, to isolate it from the surroundings. B) E_{field} profiles developed within the nerve cross-sections, when in contact with two different specific sides of the graft. White stars identify the fascicles considered. C) Nerve transmembrane potential (V) during the electromagnetic stimulation (carried out for 50 ms, with a E_{field} of 100 Hz).

4. Conclusions

This work establishes a computational multi-scale framework for the design of a novel non-invasive wireless electrical stimulation technology, able to effectively trigger a neuronal response. The model encompasses an analysis at the nanometric scale to then simulate the electric stimulation capability of a millimetric and mechanically compliant MENPS-based graft in a virtual in vivo scenario. Overall, our results simulate the efficacy of a new bionic structure to activate neuronal action potentials by delivering and dissipating individual MENPs electricity onto a biofriendly 3D wireless system.

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