Finite Element Modeling of Strategies to Reduce the Foreign Body Response to Neural Electrodes Chronically Implanted in Brain Tissue

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Statement of Purpose: Microelectrodes have the potential to provide persons with disabilities volitional control over prosthetic devices. However, a major issue with these devices is unreliable long-term recording of neural signals from brain tissue. It is widely believed that the foreign body response (FBR) mounted against electrodes negatively impacts recording performance. Therefore, strategies to reduce the FBR are expected to improve the reliability of microelectrodes and help bring this technology to the clinic. Using finite element modeling, we have identified two strategies – reducing device surface area and coatings that enhance soluble factor clearance – that may reduce the predicted local concentrations of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and thereby reduce the severity of the FBR. We have validated the model *in vivo* using immunohistochemical evaluation of brain tissue surrounding electrodes implanted in rats and cats. Based on these findings, we can predictively model simple modifications to existing devices that would greatly reduce their FBR.

Methods: Finite element modeling was performed in COMSOL (COMSOL Group, Stockholm, SE) assuming isotropic Fickian diffusion, closed boundaries at the top surface of the brain and open boundaries elsewhere, a 10 µm thick activated immune cell layer covering all device surfaces producing such soluble factors as TNF-α at a constant rate, and first-order decay of such factors with short half-lifes. Parameters for TNF-α production, diffusion, and decay were based on literature values (Biran R. Exp Neurol. 2005;195(1):115-26, Kim YT. J Control Release. 2007;118(3):340-7, Cheong R. J Biol Chem. 2006;281(5):2945-50). *In vivo* validation was performed in adult male Sprague-Dawley rats with approval from the University of Utah Institutional Animal Care and Use Committee. Planar silicon microelectrodes having either a solid or lattice structure were fabricated by the Center for Wireless Integrated Microsystems at the University of Michigan, Ann Arbor, MI. For solid electrodes coated in alginate, coatings were applied using a repetitive dipping process on cleaned, silanized electrodes. Electrodes were implanted stereotaxically into motor cortex and secured to the skull using a custom-fabricated polyurethane grommet. After long time periods for the lattice and alginate studies, respectively, rats were perfused transcardially and their brains postfixed for 24 h with 4% paraformaldehyde. 30 µm horizontal sections were obtained using a cryostat, stained for ED-1 (AbD Serotec, Raleigh, NC), GFAP (Dako North America, Carpinteria, CA), IgG (Life Technologies, Grand Island, NY), and NeuN (EMD Millipore, Billerica, MA) using standard immunohistochemical techniques, and imaged on an upright microscope. Recording experiments are progress. Cats implanted with Utah Electrode Arrays (UEAs) for 240 to 511 days were received from the Neural Engineering Laboratory at the University of Utah, Salt Lake City, UT and processed in a similar fashion.

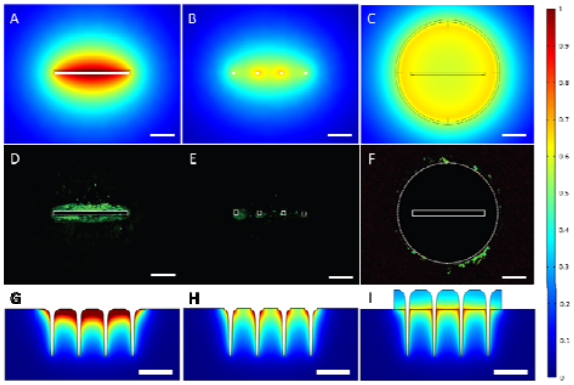

Figure 1. Horizontal cross section of normalized predicted TNF-α concentrations surrounding solid planar (A), lattice (B), and alginate-coated (C) electrodes. Corresponding representative images of ED-1 staining (D-F). Vertical cross section of normalized predicted TNF-α concentrations for plain UEA (G), UEA with 300-µm diameter holes through the base (H), and UEA with alginate-coated base (I). Color scale shown at right. Scale bars 100 µm in A-F, 500 µm in G-I.

Results: Simulated TNF-α distributions for solid, lattice, and alginate-coated electrodes are shown in Figure 1 A-C. Both the reduced surface area of the lattice electrode and the permeability of the alginate coating were effective in reducing simulated TNF-α concentrations. *In vivo*, horizontal sections showed reduced immunofluorescence for ED-1 (activated macrophages and microglia), GFAP (astrocyte cytoskeleton) and IgG (blood-brain barrier disruption) in the vicinity of the implant, as well as increased neuronal cell density as assessed by NeuN staining, compared with controls. Representative images of ED-1 staining are shown in Figure 1 D-F. Finally, we established these strategies can be applied to more complex geometries such as the UEA by simulating the TNF-α distributions surrounding plain and modified UEAs. Plain UEAs had very high TNF-α concentrations near the base (Figure 1 G), in agreement with histological observations that the FBR is also most severe near the base (not shown). Predicted TNF-α concentrations were greatly reduced, however, by creating holes in the base or by incorporating applying a permeable alginate coating on the base (Figure 1 H-I).

Conclusions: We have examined the effects of reduced surface area and increased permeability in our finite element model and validated both strategies *in vivo*. Our finite element model serves as a useful tool for understanding, predicting, and ultimately engineering new ways of reducing the FBR to implanted microelectrodes.