A COMSOL Multiphysics® Finite Element Model of the Diffusion Profile of Brain Derived Neurotrophic Factor: Biological Validation through a Microfluidics Device

S. Bharadwaj[1], K. Nella[1], A. Oleksijew[1], J. Fernandez[1], C. Miller[1], K. Coots[1], R. Heuer[1], H. Chang[1], C. Richter[1], J. Kessler[2], A. Matsuoka[1]

1. Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

2. Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

INTRODUCTION:

Sensorineural hearing loss can be treated in many cases by regenerating the synaptic connections between the extant Auditory Neurons (ANs) and transplanted human stem cell-derived ANs. One growth factor that plays an essential role in this paradigm is Brain-Derived Neurotrophic Factor (BDNF), integral to both cell survival and directed growth of AN peripheral processes (neurites). Using COMSOL Multiphysics® simulation software, we have developed a finite element model to analyze the diffusion profile of varying concentrations of BDNF released from the Polyhedrin Delivery System (PODS™) (Cell Guidance System, Cambridge, U.K) within a Xona Microfluidics device. We will then compare it to empirical experiments using immunohistochemistry as a measurement tool to assess for cell survival, migration and directed neurite growth.

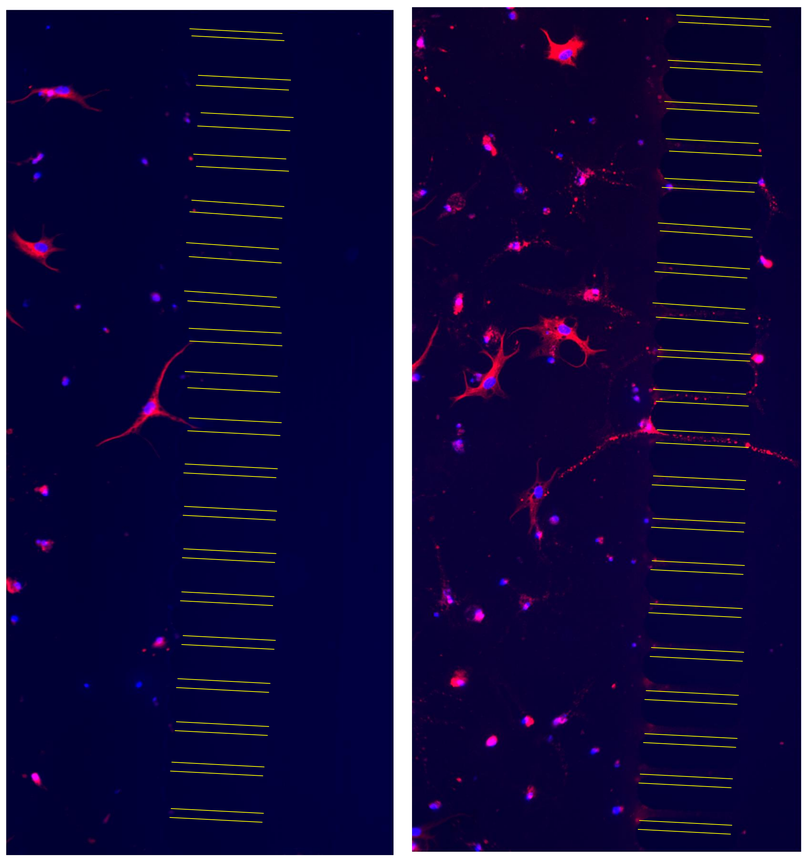

Figure 1: XC150 Immunocytochemistry (after 7 days culture). Stained with DAPI and β-III Tubulin. *(A) Image of differentiated auditory neurons of positive control (cells with exogenous human recombinant BDNF). Image shows minimal cell migration and neurite extension through microchannels. (B) Image of differentiated auditory neurons of experimental condition (cells with 3.5 million PODS). Image shows marked cell migration and neurite extension along the device.*

COMPUTATIONAL METHODS:

The geometry for the mesh was created using the native geometry builder of the COMSOL Multiphysics® software. We characterized the reaction that describes the breakdown of the polyhedrin-BDNF peptide link as a heterogenous chemical reaction occurring at a predefined surface, in which the reactants are in distinct phases (e.g. solid phase and liquid phase), for which the Chemical Reaction Engineering module is directly applicable. The BDNF PODS (reactant) were modeled as being adsorbed to the predefined surface boundary, while the cell-secreted proteases (catalyst) were modeled as a bulk species. The second reaction is the subsequent natural degradation of the product (free BDNF). Rate constants for either reaction were approximated by regression analysis performed on quantitative data attained by measuring the sustained release profile of BDNF released by PODS, and as well as the degradation of recombinant BDNF over time. The simulation was computed using the chemistry, transport of diluted species, and surface reaction interphases in a time-dependent study.

RESULTS:

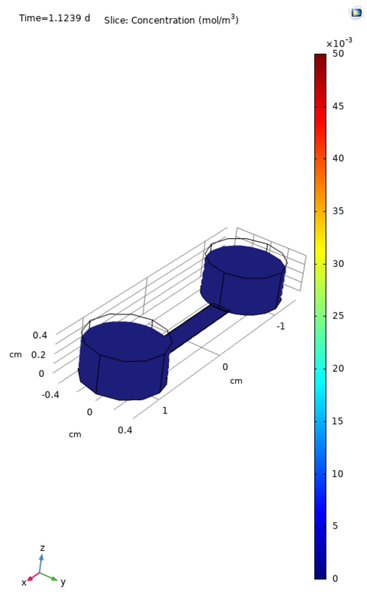

Figure 2a. Day 1

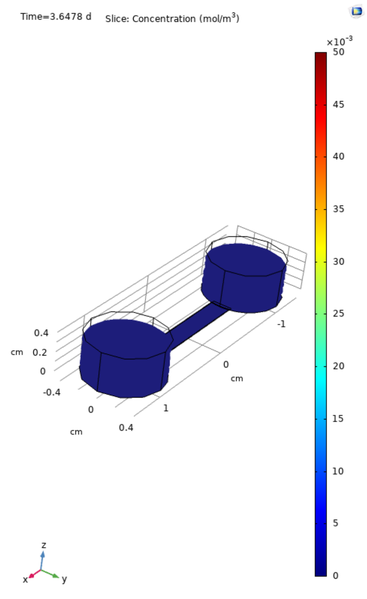

Figure 2b. Day 4

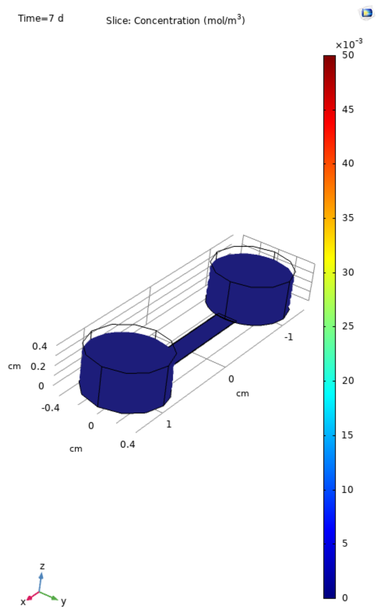

Figure 2c. Day 7

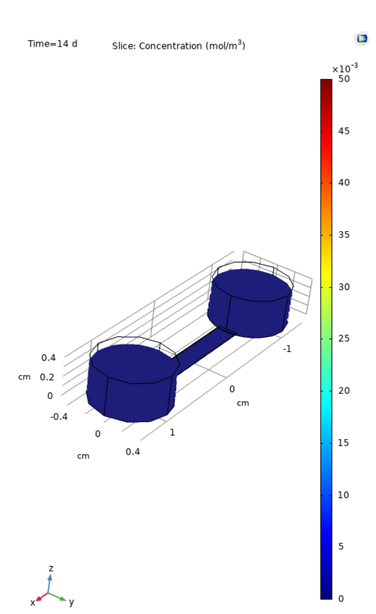

Figure 2d. Day 14

CONCLUSIONS:

Our computational models can help predict the optimal parameters needed to achieve AN neurite growth *in vivo.* Standard estimates state that 10 ng/mL of BDNF is needed for sustained neurite growth, so the parameters in our simulation experiment would work with that. Future directions of the work involve conducting similar simulations using the geometry of the inner ear with validation by empirical *in vivo* experiments in live mice.

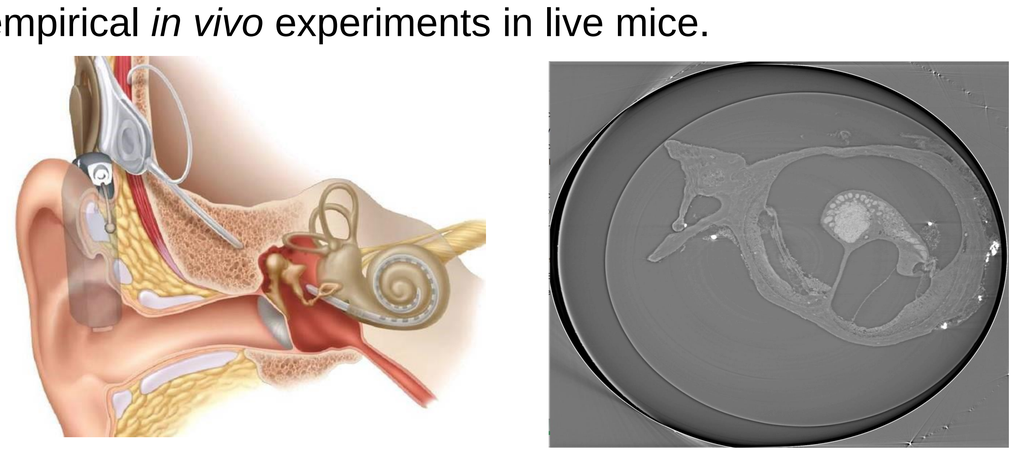

Fig 3: (a): Conventional cochlear implant (Cochlear, LTD). (b): Mouse cochlear tissue sample that was imaged using 22 keV X0rays at Argonne National Laboratory.

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