A 3D Simulation of the Diffusion Profile of Brain Derived Neurotrophic Factor in the Inner Ear Using the COMSOL Multiphysics® Software

S. Bharadwaj[1], A. Oleksijew[1], J. Fernandez[2], C. Miller[1], K. Coots[1], K. Nella[1], H. T. Chang[1], C. P. Richter[3], J. Kessler[1], A. Matsuoka[1]

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[2]Department of Chemical Engineering, Northwestern University, Chicago, IL, USA
[3]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA / Resonance Medical, LLC., Chicago, IL, USA

Abstract

Sensorineural hearing loss, which is the most common type of hearing impairment, originates from damaged inner ear nerves. However, this can be treated in many cases by regenerating the synaptic connections between the extant Spiral Ganglion Neurons (SGNs) and transplanted human stem cell derived SGNs. Brain-Derived Neurotrophic Factor (BDNF) that plays an essential role in directing the growth of both types of SGN neurites towards one another. Thus, determining the characteristics of the diffusion profile of BDNF as it is released from Polyhedrin Delivery System (PODS®, Cell Guidance Systems, Cambridge, UK) can help estimate parameters for desired experimental conditions in vivo. Using COMSOL Multiphysics® simulation software, we have developed a finite element model to analyze the diffusion profile of varying initial concentrations of BDNF inside a 3D surface model of a murine scala tympani recreated from micro-computed tomography images.

Mouse cochlea tissue samples were scanned at Advanced Photon Source (Argonne National Laboratory, Argonne, IL). The images were then converted to binary and cleaned of noise via Fiji imaging software. The scala tympani at each cross-section was isolated to create an image stack that was used to construct a 3D surface. The surface was then exported to Autodesk Meshmixer (AUTODESK, San Rafael, CA) for modifications.

The Coefficient Form feature of the Partial Differential Equation Interface of COMSOL Multiphysics® software can be used to create a mathematical model of the problem. The diffusivity coefficient of BDNF in the scala tympani was approximated through the diffusivity of b-Lactoglobulin, a protein of similar size as BDNF. The reaction kinetics of BDNF from the PODS and its subsequent degradation was estimated from data of PODS containing Leukemia Inducing Factor (LIF). A MATLAB® curve-fitting algorithm was used to fit the concentration-time data from the LIF experiment and obtain kinetic constants for the model. The release of BDNF can be represented as a source term, and the degradation constant of BDNF will be used as the absorption coefficient. A time dependent study will be run for 14 days.

The initial results from the scala tympani 3D surface model revealed the concentration diffusion profile of 50 million PODS crystals being inserted at the base of the scala tympani. Standard estimates showed that 10 ng/ml of BDNF is needed for optimal neurite growth in vitro. Our simulation will show whether this concentration can be reached and sustained over a period of time throughout the scala tympani. Further results will be obtained using COMSOL Multiphysics® software and presented at the conference.

Our computational models can help predict the optimal initial parameters needed to achieve desired experimental conditions in vivo. From the simulation results, it can be determined whether the desired BDNF concentration across the scala tympani can be achieved with 50 million crystals. Further simulations on COMSOL Multiphysics® software, which will be iteratively improved with empirical experiments, will be used to test other combinations of number of crystals and number of days that the simulation is run.