In Silico Optimization of Microporous Annealed Particle Hydrogel for Endothelial Cell Migration

Lauren Pruett[1], Alex Taing[1], Neharika Singh[1], Donald Griffin[1,2]
[1]Department of Biomedical Engineering, [2]Department of Chemical Engineering, University of Virginia

Statement of Purpose: Active promotion of cell migration is essential to successful regenerative biomaterials. Specifically, endothelial cell migration is necessary for angiogenesis and significant new tissue formation. We have used the microporous annealed particle (MAP) platform[1] to heterogeneously include spatially isolated heparin-modified microgels (heparin µislands), which can sequester and release growth factors[2]. Using *in vitro* endothelial cell spheroid sprouting assays we tested 1%, 10%, and 100% ratios of heparin µislands to total microgels and observed a parabolic relationship (i.e. 10% of microgels containing heparin promoted more migration than 1% or 100%)[2]. Due to the low number of conditions tested, we expect the percent heparin µislands can be further optimized. Rather than testing experimentally, we approached this challenge using agent-based modeling, which is a computational method used commonly in biologic study of angiogenesis. We hypothesize the distribution of heparin µislands can be optimized using agent-based modeling to increase endothelial cell migration.

Methods: A two-dimensional hybrid agent-based model (ABM) was developed using Hybrid Automata Library (HAL), which is a java-based library that couples a spatial ABM with partial differential equation components to model diffusion. Particles are 80µm and modeled as perfect packing with a 15µm pore diameter (Fig. 1A). Heparin particles are randomly distributed within the scaffold at a programmable percentage and act as a constant growth factor source. Endothelial cell sprouting from a spheroid is modeled using literature derived rules consisting of proliferation, tip cell migration, and branching. The frequency of branching actions depends on growth factor density in the local environment and endothelial cell migration is in the direction of the highest growth factor gradient. Growth factor diffusion profiles were modeled using a calculated diffusion coefficient for Vascular Endothelial Growth Factor (VEGF). VEGF degradation is simulated using the known half-life of 90 minutes. The same total amount of growth factor was loaded for each model configuration. Four parameters were unable to be derived from experimental or literature values, therefore we calculated sensitivity coefficients by varying the values 50% above and below the anticipated baseline values. Due to computational constraints, the two most sensitive parameters were fitted using manual parameter estimation and varying both parameters simultaneously to determine the combination with the least error compared to experimental results for the 10% µisland condition. Simulation outputs were fold change in area, total blood vessel length, and maximum head cell distance from the center. After parameter fitting to match 10% µislands, 100 simulations were run for every 5% from 0 to 100% µislands. Once the best 10% range was determined, every 1% was run 100 times to determine the percentage resulting in the highest blood vessel length. Following model simulations, an endothelial cell spheroid sprouting assay was conducted with 10%, 100%, and the computationally determined percentage of heparin µislands. Spheroids were imaged every 24 hours and ImageJ was used to calculate fold change from Day 0.

Results: A 2-D model of sprouting angiogenesis in a MAP scaffold was developed where percentage of heparin µislands was the changing variable (Fig. 1A). A sensitivity analysis of four parameters indicated the model was highly sensitive to two parameters including VEGF sensitivity, which was the minimum VEGF necessary for an endothelial cell to be activated, and VEGF uptake by endothelial cells (Fig. 1B). Both parameters were manually fitted. After parameter fitting, each percentage was run 100 times in the model and a parabolic relationship was observed between percentage of µislands and total blood vessel length, consistent with our experimental findings[2] (Fig. 1C). 25%-35% µislands was determined to be the best range, with 27% resulting in the highest blood vessel length. In a validation experiment, we observed that 27% µislands promoted significantly more endothelial cell migration compared to 10% µislands and model results matched experimental results (Fig. 1D).

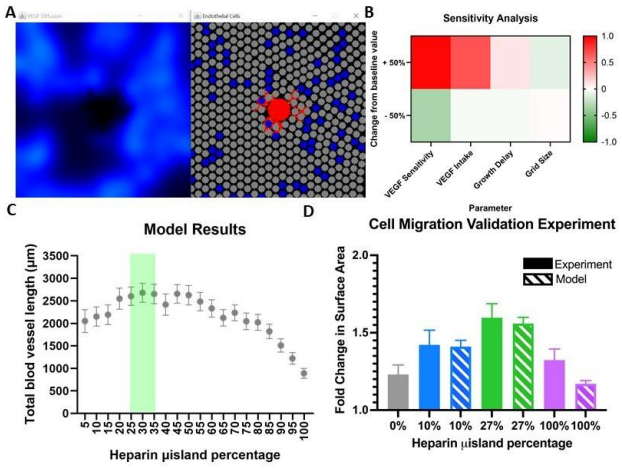

Figure 1. A) Model framework with the growth factor diffusion on the left and sprouting angiogenesis on the right. B) Sensitivity analysis. C) Model results for 5-100% µislands at 24 hours. D) Cell migration validation experiment matches model results at 24 hours.

Conclusions: Importantly, we present the first agent-based model of microporous annealed particle (MAP) hydrogel to optimize the ratio of heparin µislands. We present the model can accurately predict cell migration trends in *vitro* and these studies provide insight on how computational modeling can be used to improve and accelerate the design of biomaterials.

References: : [1]Griffin, et. al. Nat Mater. 2015; 14(7)L737-744. [2]Pruett, et. al. *Adv Funct Mater.* 2020. 31(35).