Computational Model of Angiogenesis in Wet Age-Related Macular Degeneration

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I. Background

Age-Related Macular Degeneration (AMD)

- Leads to vision loss and blindness
- Localized to subretinal layers (**Figure 1.**)

AMD Disease Mechanism

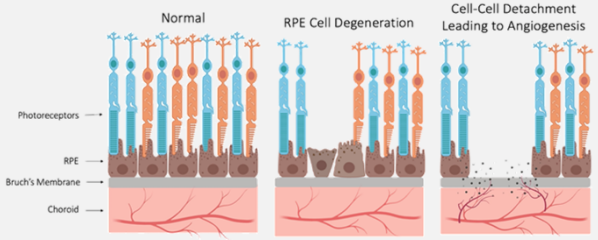

Figure 1. AMD disease mechanism: (left) normal human sub-retina, (center) RPE degeneration, and (right) cell detachment leading to pro-angiogenic factor overexpression and subretinal blood vessel invasion. Diagrams created using BioRender.

(1) Mechanical stress and RPE degeneration

(2) Overexpression of pro-angiogenic factors (especially vascular endothelial growth factor, VEGF)

(3) Subretinal blood vessel invasion

II. Approach

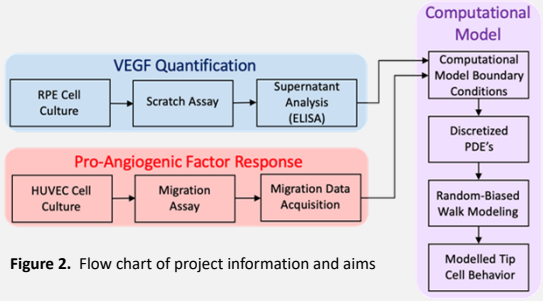

Figure 2. Flow chart of project information and aims

III. Computational Model

- Cell moves in a biased random direction each iteration
- Direction of random movement is influenced by surrounding concentration of VEGF, fibronectin, and protease

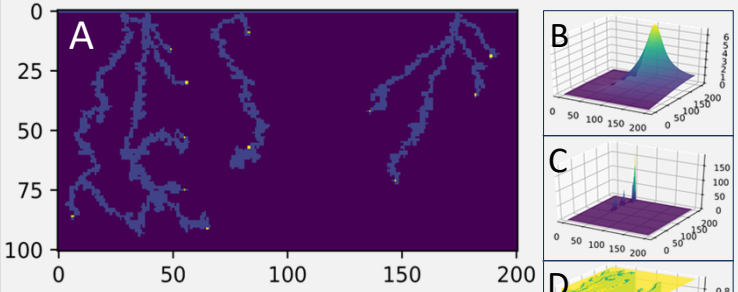

Figure 3. Computation model outputs (A) cell migration pattern (B) 3D VEGF concentration profile (C) 3D fibronectin concentration profile (D) protease concentration profile

Table 1. Comparison of experimental and computational migration patterns. Metrics include forward migratory index (FMI), directness, distance, and velocity. Experimental data (HUVECs with 10% FCS (fetal calm serum) as a chemoattractant) adapted from [3]

	Experimental Model	Computational Model
$FMI^{\parallel}$	0.13	0.14 ± 0.03
$FMI^{\perp}$	0.02	0.02 ± 0.08
Directness	0.23	0.16 ± 0.04
Euclidean distance [μm]	196.78	42.6 ± 2.9
Velocity [μm/min]	1.16	421 ± 309

References

1. Farjood F, Vargis E. Physical disruption of cell-cell contact induces VEGF expression in RPE cells. Mol Vis. 2017;23:431–46.
2. Plank MJ. A reinforced random walk model of tumour angiogenesis and anti-angiogenic strategies. Mathematical Medicine and Biology [Internet]. 2003 [cited 2021 Mar 30];20:135–81. Available from: https://academic.oup.com/imammb/article-lookup/doi/10.1093/imammb/20.2.135
3. Chemotaxis of HUVEC in 2D and 3D [Internet]. ibidi GmbH; 2015. Available from: https://ibidi.com/img/cms/support/AN/AN34_Chemotaxis_2D_3D_HUVEC.pdf

IV. VEGF Quantification

- Scratch assay performed on ARPE-19 to simulate cell-cell detachment, and released VEGF was measured through ELISAs
- Obtained VEGF concentrations to tailor the computational model to AMD-like conditions

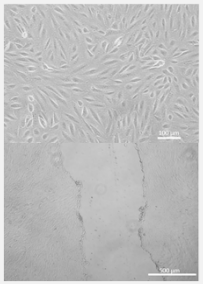

Figure 4. Unscratched (top) and scratched (bottom) ARPE-19

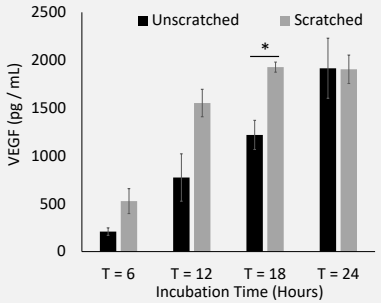

Figure 5. ELISA revealed higher VEGF production in scratched cells. * $p < 0.05$, two-tailed Student's t-test.

V. Pro-Angiogenic Factor Response

- Endothelial migration assays will be done using ARPE-19 supernatants
- Outputs of experimental and computational migration assays will be quantitively and qualitatively compared

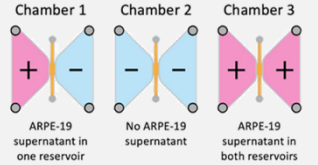

Figure 6. Migration assay setup adapted from [3] with ARPE-19 Scratch assay supernatant (+) and DMEM F-12 with 5% fetal bovine serum (FBS) (−)

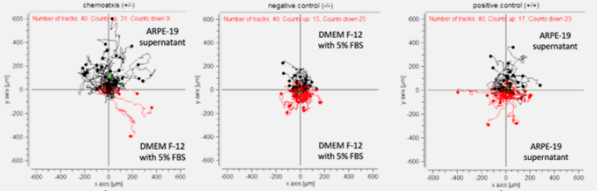

Figure 7. Expected migration assay outputs using ARPE-19 supernatant as chemoattractant adapted from [3]

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