INVESTIGATION OF THE IMPACT OF THE ENDOTHELIAL SURFACE LAYER ON THE CAPILLARY VESSELS THROUGH MULTISCALE MODELING AND SIMULATIONS

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ABSTRACT
The effect of the macromolecular layer covering the luminal surface of the vascular endothelium, called endothelial surface layer (ESL), on microcirculation has become increasingly interesting, since it has been described as the main mechanosensor and transducer of fluid shear-stress on endothelial cells. In this study, we investigate the ability of ESL to allow fluid transition (permeability) through an extensive multiscale simulation of blood flow in capillaries which is the most common level linked to the vasculature pathophysiology. Modelling the glycocalyx as an ideal spatial arrangement of protein fibres we accurately calculate the core-plasma interface shear stress as well as the macroscopic geometry-defined permeability. The investigation extends to a more realistic model through a microscopic approach incorporating the interaction between blood plasma and glycocalyx fibres.

INTRODUCTION
Functions such as the control and regulation of vascular tone, haemostasis, fluid and solute exchange and coagulation and inflammatory responses depend on phenomena occurring at the ESL. Many research studies[1-2] show and visualize the existence of a hairy-like pericellular network that resides in ESL, namely Endothelial Glycocalyx (EG) which is mainly composed by membrane-bound glycoprotein and glycolipid chains[3]. Over the past decades, insight has been gained into the role of EG which has been described as the main mechanosensor and mechanotransducer of fluid shear-stress on endothelial cells limiting access of circulating blood plasma components to Endothelial cell membrane[4] as well as affecting drug delivery process since it controls the capillary permeability[5]. Recently, Mitchel & King investigated EG contribution to the spreading of cancer metastasis[6] extending the importance of EG in fields such as pathophysiology. Other research studies on their effort to examine glycocalyx's role in biologic mechanisms, focused on the study of its geometric structure. Specifically, Squire et al[7] presented a geometric model representing EG as a quasiperiodic ultrastructural arrangement yet to be developed by Weinbaum et al[8] into an ideal periodic bush structure model with distinct spatial characteristics. In hemodynamics, where effective medium theory has been used to model blood plasma flow in the porous ESL, these findings proved significant and constituted the basis in the evaluation of ESL's rheological properties such as the permeability; the capability of a layer to allow fluid transmission. Led by the work of Sangani & Acrivos[9] , determination of a geometry-defined permeability constant in flows past hexagonal cylindric solid arrays has been conducted in many scientific studies finding application in the idealized geometric representation of EG. These approaches contributed in the understanding of mechanisms which include endothelium's response to shear forces imposed by the blood flow arising in pathological states. However, glycocalyx is treated as a rigid non-deformable structure and few have considered its elastic properties and the effect they may have in the determination of its apparent permeability. In the present study, we account for EG's mechanical properties (elasticity, compressibility) and through a microscopic simulation we investigate in-detail the interaction between blood plasma and glycocalyx solid structure to determine ESL apparent permeability

METHODOLOGY
Initially, we consider a one-dimensional multiphase blood flow through a microvessel, where we develop a three-phase moving interface model[10] with the three phases being: (a) the rich-in-RBCs

(Red Blood Cells) core represented by an elastoviscoplastic constitutive equation[11], a novel model which associates the aggregation effects of erythrocytes with yield stress at low shear rates, (b) a dynamically predictable cell-free layer (CFL) rich in plasmatic proteins close to the vessel walls[12] , and (c) a porous medium of about 150-500 nm thickness which corresponds to the glycocalyx layer of the ESL. Glycocalyx is modelled as an ideal spatial arrangement of protein fibres in order to accurately calculate the core-plasma interface shear stress as well as the macroscopic geometry-defined permeability of the ESL. In order to determine the ESL apparent permeability, the interaction between blood plasma and glycocalyx fibres is examined through simulations at the microscopic level. The Fluid-Structure-Interaction (FSI) problem is defined on a three-dimensional periodic domain utilizing the shear stress and CFL thickness extracted from the macroscopic simulations.

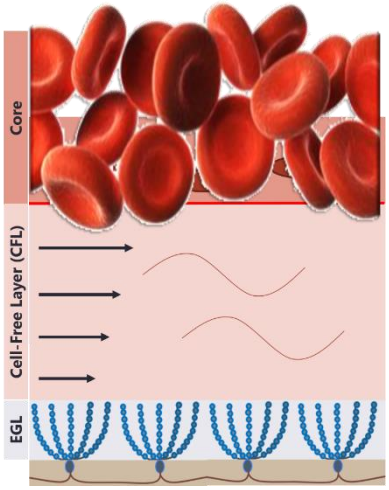

Figure 1. *Three-phase moving interface model*

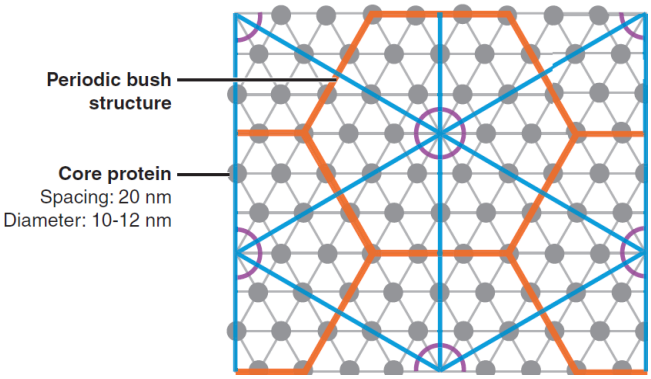

Figure 2. *Idealized hexagonal periodic bush-structure model (Weinbaum et al.)*

GOVERNING EQUATIONS

The glycocalyx fibres are assumed to be deformable elastic solids described by mechanical properties (Young's modulus, Poisson's ratio), while blood plasma is treated as a Newtonian fluid. The governing equations for this simulation are presented below.

Plasma Domain

Continuity: $$\nabla \cdot \underline{u}_f = 0 \quad [1]$$

Momentum Balance: $$\rho_f \left(\frac{\partial \underline{u}_f}{\partial t} + \left(\underline{u}_f - \underline{w}_f \right) \cdot \nabla \underline{u}_f \right) = \nabla \cdot \underline{\underline{\sigma}}_f \quad [2]$$

Mesh Motion: $$\nabla^2 \underline{d}_f = 0 \quad , \quad \frac{\partial \underline{d}_f}{\partial t} = \underline{w}_f \quad [3]$$

Where ρ, $\underline{u}$, $\underline{w}$, $\underline{d}$ are the density, velocity vector, mesh velocity vector and mesh displacement vector respectively. The subscripts f and s denote the fluid and solid domains. The Cauchy stress tensor $\underline{\underline{\sigma}}_f$ follows the Newtonian Constitutive Law: $\underline{\underline{\sigma}}_f = -p_f \underline{\underline{I}} + \eta_f \left(\nabla \underline{u}_f + \nabla \underline{u}_f{}^T \right)$ with p_f, η_f being the pressure and dynamic viscosity of plasma.

EG (solid) Domain

Momentum Balance: $\rho_s \left(\frac{\partial \underline{u}_s}{\partial t} + \underline{u}_s \cdot \nabla \underline{u}_s\right) = \nabla \cdot \underline{\underline{\sigma}}_s$ [4]

Mesh Motion: $\frac{\partial \underline{d}_s}{\partial t} = \underline{u}_s$ [5]

In this study EG is considered a hyperelastic solid following Saint Vernant-Kirchoff model which is expressed via 2nd Piola-Kirchoff stress tensor as $\underline{\underline{S}}_s = \lambda \left(tr\underline{\underline{E}}\right) \underline{\underline{I}} + 2\mu \underline{\underline{E}}$ where λ, μ are the so-called Lame's constants and $\underline{\underline{E}}$ the Green strain tensor. The Cauchy stress tensor is related to $\underline{\underline{S}}_s$ with the expression $\underline{\underline{\sigma}}_s = \frac{1}{J} \underline{\underline{F}} \cdot \underline{\underline{S}}_s \cdot \underline{\underline{F}}^T$ where $\underline{\underline{F}}$ the deformation gradient tensor and J its determinant. Lame's constants incorporate solid's mechanical properties of elasticity and compressibility through the relations:

$\mu = \frac{E}{2(1+\nu)}$ [6]

$\lambda = \frac{\nu E}{(1+\nu)(1-2\nu)}$ [7]

Where E and ν are Young's moduli and Poisson ratio respectively.

PROBLEM FORMULATION

Based on the quasiperiodic ultrastructural model of Squire et al[7] and the periodic bush-structure model of Weinbaum et al[8] for the geometric representation of glycocalyx, we construct a realistic detailed 3D domain for the solid phase with distinct spatial characteristics.

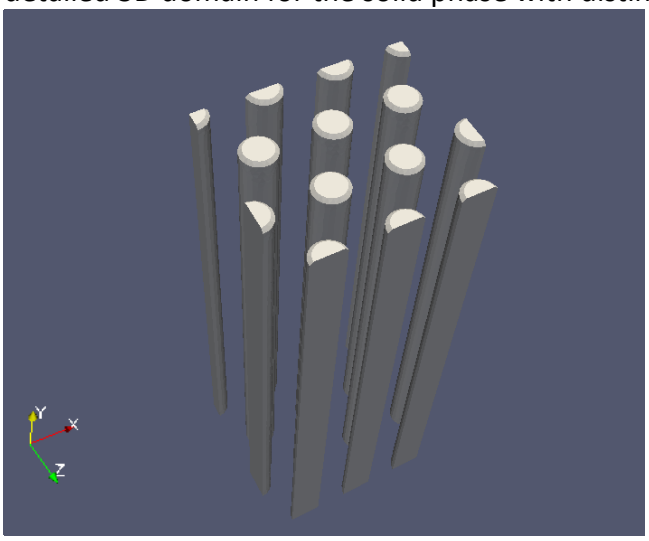

Figure 3. *EG 3D representation*

Geometry Properties
CFL thickness = $2\ (\mu m)$
Fiber height = $0.1 \sim 0.5 (\mu m)$
Distance between fibers = $0.02\ (\mu m)$
Fiber radius = $0.005\ (\mu m)$

RESULTS

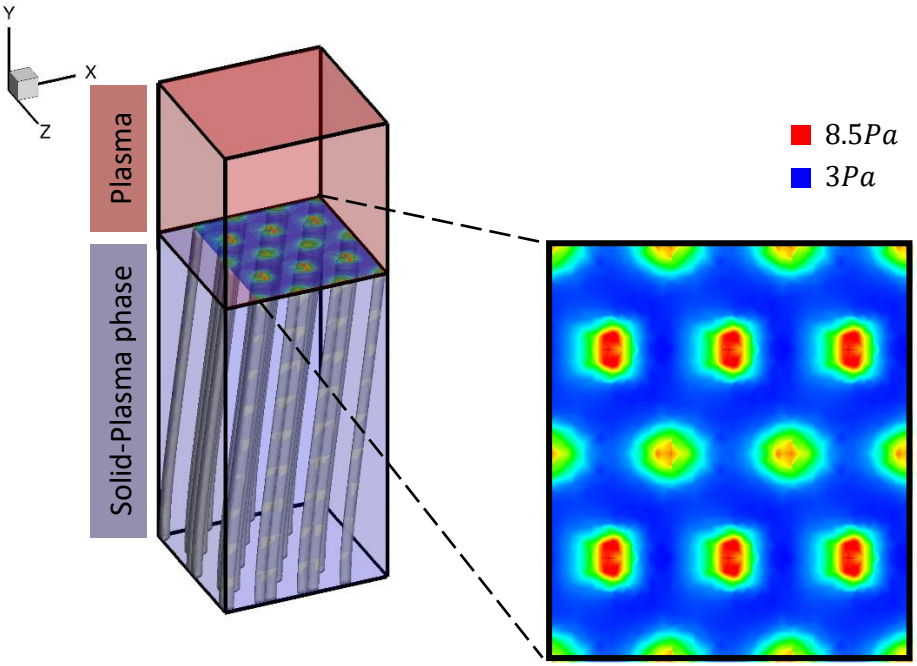

Figure 4. *Shear (τ_{xy}) stress field on the tip of EG at steady state for $E = 5\ (kPa)$, Fibre height = $0.15\ (\mu m)$. Field follows a hexagonal pattern as the spatial arrangement of fibers. Max values appear just above the fiber tip–plasma interface.*

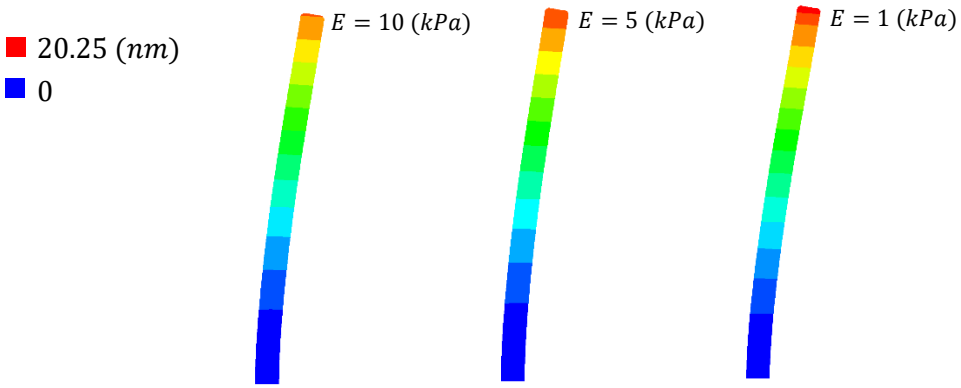

Figure 5. *Fiber displacement (d_x) for varying E, Fibre height = $0.15\ (\mu m)$*

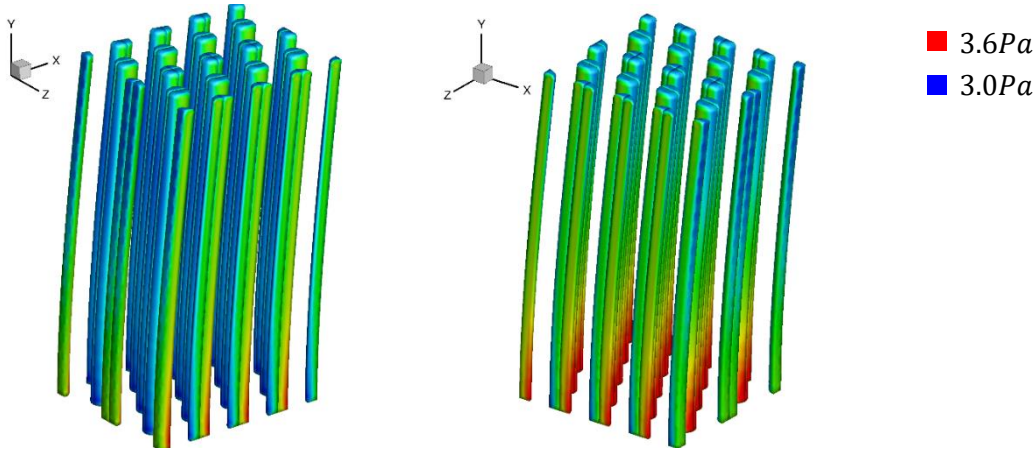

Figure 6. *Fiber stress magnitude. Max value appears at the bottom of the structure in direction of the deformation (x-direction).*

CONCLUSIONS

Our results on the stress fields, developed by the plasma flow past the glycocalyx fibers, verify the role of EG as a mechanosensor and transducer of plasma shear stress at the endothelium.
Accounting for the elasticity, and consequently the deformation, of the fibers we find that EG's spatial characteristics, even though they are considered idealized, present a transient behavior. As a result, a constant geometry-defined permeability cannot accurately describe glycocalyx ability to allow fluid transition.

ACKNOWLEDGMENTS

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REFERENCES

[1] J. H. Luft (1966) Fed Proc 25:1773–1783
[2] E. E. Ebong, F. P. Macaluso, D. C. Spray, J. M. Tarbell (2011) Arterioscler Thromb Vasc Biol 31(8): 1908–1915
[3] S. Reitsma, D. W. Slaaf, H. Vink, M. A. M. J. van Zandvoort, M. G. A. oude Egbrink (2007) Pflügers Arch 454(3):345–359
[4] Ye Zeng, E.E. Ebong, Bingmei M. Fu, J. M. Tarbell (2012) PLoS One 7(8): e43168
[5] D. Chappell, K. Hofmann-Kiefer, M. Jacob, M. Rehm, J. Briegel, U. Welsch, P. Conzen, B.F. Becker (2009) Basic Res Cardiol 104(1):78-89
[6] M. J. Mitchell & M. R. King (2013) Am J Physiol Cell Physiol 306(2):C89-C97
[7] J. M. Squire, M. Chew, G. Nneji, C. Neal, J. Barry, C. Michel J Struct Biol. (2001) 136 (3):239-55
[8] S. Weinbaum, X. Zhang, Y. Han, H. Vink, S.C. Cowing (2003) Proc Natl Acad Sci U S A 100(13):7988-95
[9] A. S. Sangani & A. Acrivos (1982) Int J Multiphase Flow 8(4):343-360
[10]K. Sriram, M. Intaglietta, D.M. Tartakovsky (2014) Microcirculation 21(7):628-39
[11]Y. Dimakopoulos & J. Tsamopoulos (2017) J Vasc Res 54-71
[12]S. Varchanis, Y. Dimakopoulos, C. Wagner, J. Tsamopoulos(2018) Soft matter 14(21):4238-4251