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FINITE ELEMENT MODELS OF MECHANICAL BEHAVIOUR OF ENDOTHELIAL CELLS

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Abstract: *Recently hybrid models of the endothelial cell were created by using the bendo-tensegrity concept to complete the continuum parts of the cell with an adequate cytoskeleton model. The proposed model of endothelial cell includes a network of actin filaments (AFs) as tension supporting cables and microtubules (MTs) as bended beams supporting primarily compression. It is created by adopting the geometrical shape of a short hexagonal prism with its 12 vertices that results in a nearly isotropic behaviour of the model without a preferred orientation. To achieve the synergistic effect of cytoskeletal components, the elements representing AFs, MTs, and Intermediate filaments (IFs) are sharing the same end nodes (representing focal adhesions) with the cell membrane (CM). The AFs are prestressed (i.e. stressed without application of external load), which is essential for the cell shape stability, while the IFs are wavy, thus not bearing load until straightened. The objective is to create different FE models of endothelial cells which will be used to simulate mechanical responses of the cell under different loading conditions. Endothelial cell dysfunction has been linked to atherosclerosis through their response to mechanical loads, especially hemodynamic forces.*

Keywords: Endothelial cell, Finite element model, Cytoskeleton, Tensegrity, Mechanical behavior.

1. Introduction

Endothelium is a continuous, single cell-thick layer lining blood vessels and forming part of their tunica intima. Its cells rest on a connective tissue basement membrane that connects them to the tunica media (mainly composed of elastin, collagen, and smooth muscle cells). The outermost layer of the vessel wall, the tunica adventitia, is largely composed of connective tissue strengthened by collagen fibres.

Continuous lining of endothelial cells protects the luminal surface of mammalian vessels. In vivo, blood flow pulsations in the arteries produce periodic oscillations in vessel diameter, resulting in a cyclic increase and decrease of stretch of the vessel wall. Additionally, the blood flow causes also oscillating fluid shear stresses upon the endothelial lining. Endothelial cells in arteries are elongated and oriented in the direction of the blood flow (Langille et al., 1981) (Levesque et al., 1986) whereas endothelial cells of large veins are polygonally shaped.

Atherosclerosis can cause narrowing of lumen of blood vessels, commonly known as stenosis, creating pro-thrombotic regions. The shear stress in stenotic regions can stimulate vascular cells as well as blood components. Cellular interactions play a key role in diverse biological processes within the cardiovascular system (Konstantinos et al., 1998) such as development of atheroma or thrombosis. They are highly specific and regulated by different factors, such as hemodynamic forces. The attachment of blood components to the vessel wall depends on the balance between dynamic forces (forces acting on the cells) and adhesive forces (interactions of receptors and ligands from one cell to another). Understanding the interactions between hemodynamic forces and vascular cell biology is crucial to understanding cardiovascular diseases. The created models enable us to investigate the impact of mechanical stimuli on the endothelial cells; such stimuli, to which the vessel wall is exposed in healthy and stenotic arteries, may be circumferential and axial stretch, blood pressure, or shear stress from the blood flow.

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2. Methodology of the model proposal and discussion

The concept of "bendo-tensegrity" was proposed by (Mehrbod et al., 2011) suggesting a modification of contemporary cytoskeletal tensegrity models to consider the flexural response of MTs. This concept was applied recently, in combination with continuum model of cytoplasm, nucleus and cell membrane, for modelling of mechanical behaviour of smooth muscle cells (Bansod et al., 2018); as the first finite element model it enabled one to mimic the transmission of external mechanical stimuli onto the nucleus, where they may stimulate a biochemical response of the cell.

In this paper, three created bendo-tensegrity models of endothelial cell are presented, i.e. flat, spherical, (suspended) and adherent cell models. The endothelial cell model encompasses the nucleus and cytoplasm surrounded by the CM and cytoskeletal components like AFs, MTs, and IFs (see Fig. 1). For the proposed model implementing hybrid modelling approach, the continuum parts (nucleus, cytoplasm) are modelled using continuous (volume) elements circumscribed by a thin layer of shell elements (representing CM) while the cytoskeletal components are modelled using discrete (beam or truss) elements

2.1. FE model of flat endothelial cell

The physiological dimensions of endothelial cells are 0.5 μm thick, 15 μm wide and upto 50 μm long and have a centrally located oval or round nucleus slightly raised compared to the rest of the cell. Endothelial cells are usually flat and elongated in the direction of blood flow (Sumpio et al., 2002). Based on the physiological dimensions and shape, the cell was modelled as a very short (0.5 μm) regular hexagonal prism with the edge length of 12.5 μm as shown in Fig. 1d. Both cytoplasm and nucleus (Fig. 1e) were modelled with eight-node hexahedral isoparametric elements. A thin flexible layer circumscribing the cytoplasm referred to as CM was modelled with four-node quadrilateral shell elements on the outer surface of the cytoplasm, with thickness of 0.01 μm (Rand, 1964) and no bending stiffness. The cytoskeleton is inscribed inside this continuous part as follows: AFs are modelled as truss elements connecting all the corners of the prism representing focal adhesions (FAs) as shown in Fig. 1c. The resist only tensile loads and are internally prestressed (i.e. stressed even without application of an external load); to achieve this in the proposed models, the experimentally measured prestrain of 24 % (equal throughout all the model) (Deguchi et al., 2005) (Kojima et al., 1994) was assigned to them, generating thus an initial force (prestress) essential for the cell shape stability. The elements representing AFs, MTs, and IFs were connected by sharing the same end nodes at the CM representing FAs.

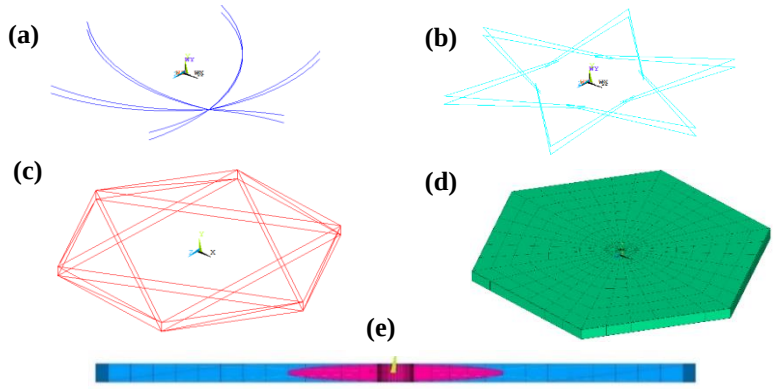

Fig. 1: Computational model of a flat endothelial cell comprising: (a) Microtubules; (b) Intermediate filaments; (c) Actin filaments; (d) Cytoplasm surrounded by cell membrane (CM); (e) Nucleus (pink) in the cytoplasm (sectional view).

In a real cell, MTs (see Fig. 1a) originate from the centrosome located near the nucleus and emanate outward through the cytoplasm till the cortex where they interact with other cytoskeletal filaments at focal adhesions (FAs). It is now evident that MTs do not have compression-only behaviour but they appear highly curved (buckled) in living cells under no external load. This shape reduces highly their stiffness under compressive load, therefore previous tensegrity models gave non-realistic results (see Burša et al., 2012).

IFs are scattered throughout the intracellular space and circumscribe the nucleus to stabilize its position within the cell. The proposed model omits their parts adherent to the nucleus and introduces the IFs only as straight fibres being tangential to the nucleus surface and connecting it with the FAs. When stretched, these filaments become straight and behave stiffer, thus contributing to the cell mechanics only at large

strains (above 20 %) (Janmey et al., 1991) (Wang et al., 2000). To incorporate their waviness, the IFs (their arrangement is shown in Fig. 1b were modelled as truss elements resisting only tensile loads under elongations higher than 20 %, with this limit strain value being equal for all of them.

2.2. FE model of spherical endothelial cell

The experiments (Caille et al., 2002) show a spherical shape of cells suspended in a liquid medium as used in most mechanical tests. In order to enable us validation of some mechanical responses of our endothelial cell model, we rearranged the shape of flat endothelial cell model into the spherical cell model as shown in Fig. 2.

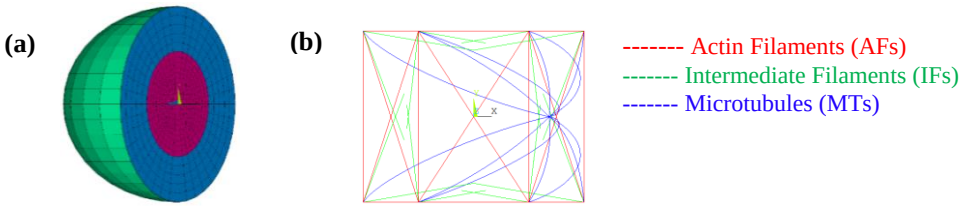

Fig. 2: Spherical model of suspended endothelial cell: (a) sectional view of cytoplasm (blue) with CM (light green) and nucleus (pink); (b) cytoskeleton.

We assumed the same volume of the cell, thus the dimensions are recalculated by equating the volume of regular hexagonal prism to the volume of a sphere. From this, the diameter of cytoplasm is 7.4 μm and diameter of nucleus is 3.0 μm. The topology and arrangement of cytoskeletal elements remains the same as in the flat model (see Fig. 2b).

2.3. FE model of adherent endothelial cell

To enable us simulations of mechanical tests done experimentally with cells adhered to a substrate, such as e.g. indentation test or magnetic tweezer test, the FE model of adherent cell was created (see Fig. 3c) on the basis of the model used in (Bansod, et al., 2018) and applying the rules described by (McGarry et al., 2004). Again it was modified from the suspended cell model by creating an axisymmetric cell model with the shape of a truncated sphere. On the basis of experimental observations in (Jean et al., 2004) and (Caille et al., 2002), we used the cell model with a maximum diameter of 20 microns and a maximum height of 8 microns; the nucleus was modelled as a flat ellipsoid with maximum diameter of 8 microns and height of 4 microns. In contrast to the above endothelial cell models, the adherent cell possesses a thin layer of actin-gel at the cell surface referred to as actin cortex (AC). We used an analogous approach as presented by (Barreto et al., 2013) and modelled the AC (i.e. the CM together with the dense acting network below it) with four-node quadrilateral shell elements having no bending stiffness. The experimentally measured thickness of this cortical layer is 0.2 μm, i.e. 20 times thicker than the cell membrane itself (Unnikrishnan et al., 2007), (Jean et al., 2005); this value is consistent with another study on endothelial cells. Another difference within a cell adhered to a rigid substrate is in arrangement of actin, which is, in contrast to the other cell shapes, arranged in a form of thicker Actin Bundles (ABs) localized at the cell periphery and aligned in the longitudinal direction. These bundles, requiring a different topology and geometry of the model (see Fig. 3a), were modelled using truss elements that resist only tensile loads and are arranged along the AC with both ends anchored to it at FAs together with the elements representing MTs and IFs. As like AFs, the ABs were also internally prestressed by introducing the 24 % prestrain (Deguchi et al., 2005), (Barreto et al., 2013). The topological distribution of both MTs and IFs was retained analogous to that of the suspended cell model. Due to the geometric complexity of cell configuration, both cytoplasm and nucleus were meshed with four-node tetrahedral solid elements.

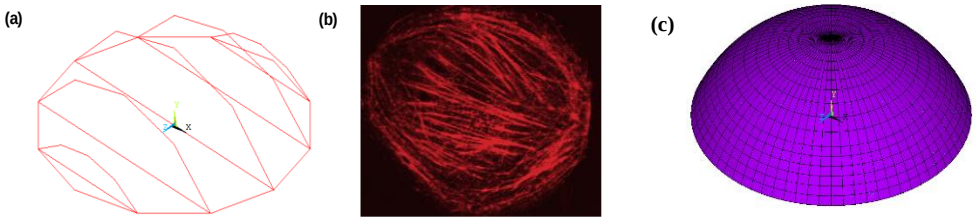

Fig. 3: (a) Computational model of Abs; (b) Microscopic image of Abs (cytoskeleton, Inc); (c) Computational model of adherent cell.

3. Conclusion

The presented work aims at realistic computational modelling of mechanical behaviour of cytoskeleton and the endothelial cell as a whole. The FE hybrid model of smooth muscle cell created in (Bansod et al., 2018) and exploiting bendo-tensegrity principle was modified to mimic specific shapes, properties and cytoskeletal arrangement of endothelium cells. It focuses on cytoskeletal mechanics of the endothelial cell in its suspended, flat and adherent shapes to study its passive behaviour. The proposed FE models of the endothelial cell are intended to be used for simulations of mechanical tests of endothelial cells under different loading conditions to validate the model and to enable us to transform different mechanical stimuli into a chosen unique quantity representing the cell mechanical response under different loading conditions. Endothelial cell dysfunction has been linked to atherosclerosis through their response to mechanical loads, especially hemodynamic forces, and these simulations should contribute to understanding this process.

Acknowledgement

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