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Coupling Computational Fluid Dynamics and Agent Based Modelling in Analysing the Progression of Stenosis in Blood Flow

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ABSTRACT

Coronary artery disease is one of the cardiovascular diseases caused by stenosis that forms in the artery due to fatty substances and cholesterol. This condition can lead to death. The development and progression of stenosis significantly depend on the blood flow within the artery. The present study aims to simulate the interaction between the progression of stenosis and blood flow using the Agent-Based Modelling (ABM) technique. ABM, widely utilized in social science and dynamical systems, is applied here to simulate this progression. COMSOL Multiphysics is used to compute the behaviour of blood flow in the artery. The essential data generated, such as wall shear stress, is then incorporated into the ABM to simulate the developmental progression of stenosis. The results reveal that ABM can effectively simulate the progression of stenosis due to blood flow. Additionally, changes in the geometry of the stenosis alter the characteristics of the blood flow passing through it. Understanding the interaction between blood flow and stenosis progression is crucial for developing advanced treatments for coronary artery disease.

1. Introduction

The failure of the cardiovascular system can lead to health risks that underscore the potential for every individual to be susceptible to arterial diseases. When a mild stenosis emerges, the arterial lumen constricts, prompting changes in the regional rheological behavior of blood. These alterations further contribute to the progression and heightened severity of these diseases [1]. Despite this, a significant number of people remain unaware of this health issue. Risk factors such as dietary fat, blood cholesterol, high blood pressure, and smoking are pivotal in fostering atherosclerosis infection. In essence, the development of this disease is closely intertwined with an individual's lifestyle choices [2]. Consequently, there arises an urgent need to explore the rheological behavior of blood and delineate the fluid dynamic properties of blood flow. This pursuit aims to establish fundamental insights into the diagnosis and treatment of coronary artery disease, enabling greater awareness among many individuals regarding their susceptibility to these ailments.

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Coronary artery disease is caused by atherosclerosis, a process started by the buildup of fatty cellular waste products, smooth muscle cells, cholesterol, and chemicals within the arterial wall [3]. Stenosis, characterized by localized plaque formation, results in the narrowing of the vessel wall, inducing changes in flow patterns. Consequently, the flow of fluid to other organs and tissues diminishes [1]. This stenosis also induces the hardening and constriction of vessel walls [4]. Atherosclerosis can remain asymptomatic for extended periods, even starting as early as adolescence. However, symptoms and health issues typically manifest later in adulthood, as the stenosis becomes more severe. The formed plaque can trigger the formation of blood clots and potentially rupture into smaller fragments, which subsequently travel downstream to narrower vessels. In this context, the smaller vessels can become entirely obstructed as given in [5, 6]. Consequently, individuals may experience conditions such as strokes, heart attacks, and peripheral vascular diseases [7].

Utilizing numerical methods, Computational Fluid Dynamics (CFD) solves the underlying nonlinear differential equations that depict fluid flow, encompassing the Navier-Stokes equations and related counterparts. This approach is employed for predefined geometries and boundary conditions, bringing about cost and time savings while yielding dependable outcomes. In the realm of medical applications, computational simulations play a pivotal role in forecasting surgical outcomes and comprehending the hemodynamics of blood circulation [8]. Employing numerical modeling techniques, CFD simulations have been instrumental in characterizing flow within the carotid artery. These simulations offer a point of reference for validating other interconnected studies [9]. Consequently, the utilization of CFD simulations in simulations has significantly contributed to the identification of sites susceptible to the formation of atherosclerotic lesions [5].

Agent-based modelling (ABM) has demonstrated its prowess as a potent tool for predictive biological modeling in the past [10]. The effectiveness of ABMs in exploring overarching patterns that arise from localized cell-environment interactions renders them particularly well-suited for applications in tissue engineering. ABM is a subcategory of computational modelling. That anticipates the progression of a dynamic system by emulating the actions of self-governing cellular components, referred to as 'agents.' These agents adhere to predefined 'rules' dictating their responses to shifts in their internal or environmental attributes. This dynamic framework facilitates the emergence of intricate phenomena through the interplay of straightforward, rule-based behaviors exhibited by the agents. ABM is a computational technique in which decision-making agents interact with their surroundings using a set of predetermined rules [11]. The conduct of cells or agents is dictated by the regulations that govern their surrounding or environment, ultimately giving rise to global behavior at the system level as an outcome of these local interactions. Dhange *et al.,* [12] conducted a mathematical analysis of blood flow within an inclined artery featuring stenosis and dilatation. The blood flow was modeled using the Casson model, and the study investigated the impact of a magnetic field on this scenario.

ABMs have found extensive applications in modeling diverse systems, ranging from social and economic to biological systems. Furthermore, the integration of computational models that encompass plaque growth and wall shear stress (WSS) through the utilization of ABM presents significant contemporary challenges. An investigation into the dynamics of vein graft remodeling triggered by hemodynamic forces was conducted by Hwang *et al.,* [13]. Expanding on their earlier work, they incorporated rule-based modeling techniques, including agent-based modeling, which leverages foundational insights into individual components to anticipate emergent behaviors within intricate systems. Multiple methodologies have been employed to elucidate cellular activities within the vascular wall [14]. They devised a dynamic system to explore vein graft adaptation while also evaluating the intricate interplay between biomechanics and cell/matrix kinetics. To address this

limitation, they proposed a hybrid approach combining Partial Differential Equations (PDEs) and ABM, explicitly capturing tissue adaptation at the cellular level.

To project the advancement of stenosis within arteries and comprehend the development of atherosclerosis diseases, an analysis of wall shear stress at various levels becomes imperative. Consequently, Bhui and Hayenga [15] introduced a period of time during which WSS is transmitted from the CFD model to the ABM. This integration simulates pulsatile flow and produces a model that incorporates WSS requirements associated with plaque growth and remodeling. Their findings emphasize that combining this ABM with a blood flow model improves understanding of the spatial and temporal hemodynamic impacts on plaque development. In line with this, Garbey *et al.,* [16, 17] replicated clinical evidence utilizing ABM, capturing patterns of cellular events primarily driving restenosis. Particularly, their focus lies on intimal mitosis induced by shear stress alterations. Their ABM, rooted in cellular automata principles, examines the temporal evolution of variables tracked within the dynamic system, including wall compartment thickness and radius. Additionally, the investigation of atherosclerotic plaque development through ABM, employing a multiscale modeling framework and parameter sensitivity analysis, was undertaken by Corti *et al.,* [18, 19]. Their conclusions underscore the ABM's outputs as predominantly influenced by cell and extracellular matrix (ECM) dynamics, with notable impact on the lumen area. They pinpoint a subset of parameters that influence the final lipid core size, without substantially affecting trends related to cell/ECM or lumen area.

Saghian *et al.,* [20] employed Agent-Based Modeling (ABM) to explore how blood flow impacts the plugging of spiral arteries and to uncover the underlying mechanisms of endovascular trophoblast invasion within the spiral artery lumen. Using ABM, the authors effectively simulated and visualized the biological blood flow system within these arteries. This approach provided valuable insights for complementing in vivo experiments. Utilizing analytical data on the macroscopic behavior of biological tissue, Kakhaia *et al.,* [21] applied the ABM approach to investigate interaction forces within arterial tissue. The results indicate that the model accurately represents the authentic mechanical behavior of biological tissue. Recently, [22] employed ABM to study the eruption process of tumor cells, a process involving the chemoattraction of blood platelets. The outcomes demonstrated consistent alignment with the experimental observations. A comprehensive exploration of the use of ABM in biological systems modeling and its potential for spaceflight biology studies was presented by Millar-Wilson *et al.,* [23].

The above literature survey has discussed the role of cardiovascular diseases, particularly coronary artery disease induced by atherosclerosis, which leads to death. The use of Agent-Based Modeling (ABM) in predictive biological modeling is highlighted. The present study focuses on utilizing ABM's applicability for tissue engineering applications and its potential to simulate complex interactions between cellular components. We aim to bridge the gap by exploring the connection between blood flow and the progression of stenosis using ABM. The objective is to create a computational framework that captures the dynamics of vascular growth and remodeling by incorporating blood flow and the spatial variation of arterial stress. By integrating ABM, generated using MATLAB software, and Finite Element Analysis (FEA) implemented in COMSOL Multiphysics, the study seeks to provide a more comprehensive understanding of how blood flow impacts the development of stenosis, offering insights into the intricate processes underlying arterial disease progression.

2. Mathematical Formulation

2.1 Governing Equations

Steady and incompressible laminar blood flow through an artery with stenosis is being considered. To simplify the complexity of the problem, the fluid flow is considered to be two dimensions and axisymmetric, and the schematic diagram of the geometry is presented in Figure 1.

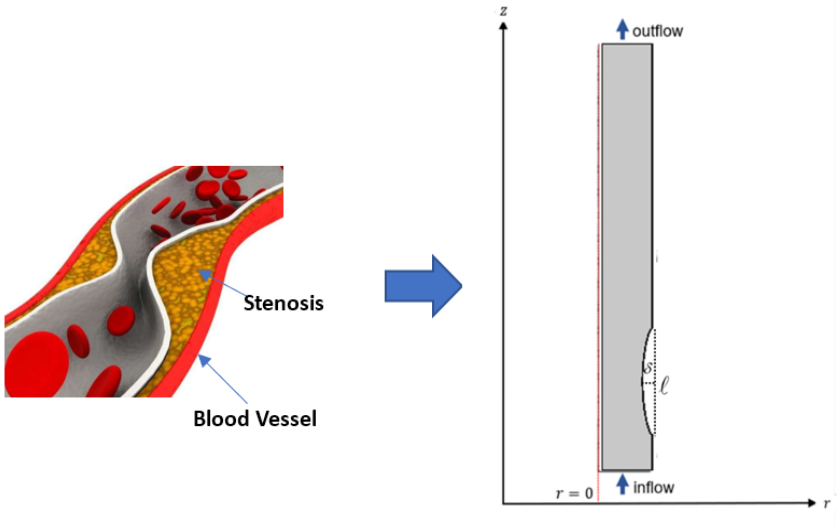


Fig. 1. Schematic diagram of coronary artery disease with stenosis

The non-dimensional governing equations for the flow in a cylindrical coordinates system are written as follows [24-28]:

$$\frac{1}{r}\frac{\partial(ru)}{\partial r}+\frac{\partial w}{\partial z}=0, \tag{1}$$

$$u\frac{\partial w}{\partial r}+w\frac{\partial w}{\partial z}+\frac{\partial p}{\partial z}=\frac{1}{\mathrm{Re}}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial w}{\partial r}\right)+\frac{\partial^2 w}{\partial z^2}\right], \tag{2}$$

$$u\frac{\partial u}{\partial r}+w\frac{\partial u}{\partial z}+\frac{\partial p}{\partial r}=\frac{1}{\mathrm{Re}}\left[\frac{\partial}{\partial r}\left(\frac{1}{r}\frac{\partial(ru)}{\partial r}\right)+\frac{\partial^2 u}{\partial z^2}\right], \tag{3}$$

Where,

$$\mathrm{Re}=\frac{\rho U_0 R_0}{\mu}. \tag{4}$$

u and w represent the radial and axial velocity components, respectively, r is the radius of the daughter artery. The generalized Reynolds number, Re is defined accordingly in Eq. (4). R_0 is the radius of the artery in the non-stenotic region, $U_\circ$ is the flow speed, ρ is the density of blood, μ is the viscosity and p is the pressure distribution acting on the surface.

2.1.1 Boundary conditions

Since the arterial wall is considered to be stiff, the bloodstream's velocity boundary conditions on the wall are the conventional no-slip conditions provided by [1], where $r = R(z)$ is the radius of the arterial segment in the stenotic region [24-28].

$$u(r,z) = v(r,z) = w(r,z) = 0 \quad on\ r = R(z) \tag{5}$$

The radial and micro rotational flow in the direction of the axis, as well as the fluid's axial velocity gradient, are assumed to be zero, which can be expressed mathematically as,

$$v(r,z) = 0,\ w(r,z) = 0,\ \frac{\partial u(r,z)}{\partial r} = 0,\ on\ \ r = 0 \tag{6}$$

It is also assumed that no flow occurs at first while the system is at rest, except for fully developed parabolic velocity (Hagen-Poiseuille) [1]. A parabolic velocity profile is enforced at the inlet [9] as below:

$$\text{At } z = 0; \quad u(r,0) = 0, \text{ and } \ w(r,0) = u\_\max\left(1 - \left(\frac{r}{a}\right)^2\right) \text{(parabolic inlet)} \tag{7}$$

On the blood-wall interfaces, a natural traction equilibrium, a no-slip boundary condition, and displacement continuity are established. It is critical to analyze the significance of the contact between blood flow and the artery wall on both sides. Hence, at the outlet, a traction-free condition is applied [9], which can be defined as,

$$\left(-pI + \tau\right)\boldsymbol{n} = 0. \tag{8}$$

3. Methodology

3.1 Computational Fluid Dynamics (CFD) Simulation in COMSOL

A two-dimensional axisymmetric, laminar, steady, incompressible, and Newtonian fluid in nature is considered [Xenos and Tzirtzilakis]. The schematic diagram of mild arterial stenosis is shown in Figure 2 where the radius of the artery is denoted as $a = 0.5$. $\delta = a - \left(0.2a\right)$ and $\ell = 1$ are the respective depth for the severity of the stenosis and the lengths of stenosis. Following [27, 28], the flow parameter Re=400, ρ=1050 kgm^{-3} and μ=0.0035kgm^{-1}s^{-1} are applied to compute the numerical solutions. The implementation of CFD simulation using COMSOL Multiphysics utilized quadratic shape functions for the velocity and linear shape functions for the pressure. The implementation involves several steps: Firstly, the problem is formulated by creating a geometrical model depicting blood flow in a stenosed artery, as outlined in Figure 2. Subsequently, the model's geometry is established, and relevant settings are defined. Material properties are assigned, and the model is configured accordingly. The simulation considers the laminar flow nature. A mesh is then set up to discretize the domain effectively. Finally, the results are computed and analyzed, encompassing parameters such as blood flow velocity, pressure drops, and wall shear stress.

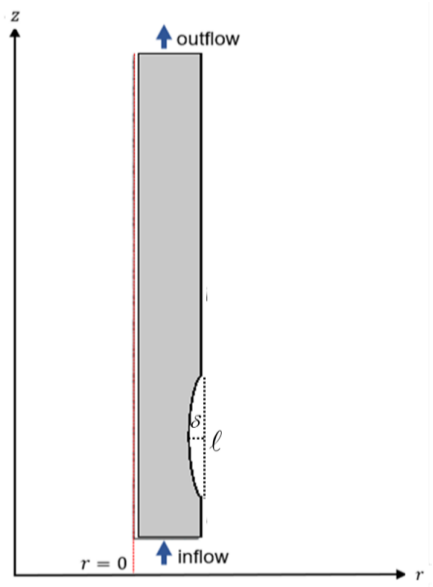
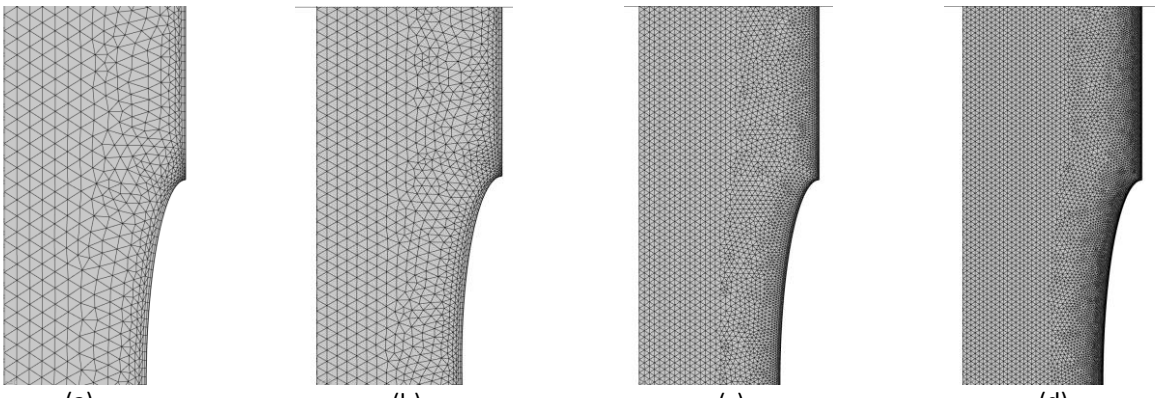


Fig. 2. Schematic diagram of mild arterial stenosis

3.1.1 Computational mesh test

The intention of mesh test is to show that the findings are not dependent on the number of elements. To mesh the geometry, the triangular element is used as the default setting in COMSOL Multiphysics for the fluid flow problem. Table 1 provides information about the number of elements and the maximum velocity for each mesh. Figure 3 depicts the saturation of the mesh with various element sizes. As indicated in Table 1, there is a minor error in the maximum velocity value as the number of elements increases. The average error 4.47×10^{-3} falls within a certain range, and the variability in the location of the maximum velocity is not significant. This suggests that the results are unaffected by the meshing. Consequently, due to time and computational complexity considerations, we will utilize Mesh 3 for computing the results in the subsequent analysis.



(a) (b) (c) (d)

Fig. 3. Mesh with various element sizes with partially magnified section. (a) Mesh 1, normal element size (b) Mesh 2, fine element size (c) Mesh 3 with a finer element size (d) Mesh 4, extra fine element size

Table 1
The mesh test and the generated maximum velocity

Mesh	Number of elements	Maximum velocity, V	Location of the Max. velocity (*r, z*)
Mesh 1	2718	2.03971	(0, 1.2400)
Mesh 2	7356	2.04626	(0, 1.2308)
Mesh 3	15639	2.05251	(0, 1.2209)
Mesh 4	32809	2.05317	(0, 1.2258)

3.2 Agent Based Modelling (ABM) Simulation

The study begins by simplifying the representation of blood flow through an arterial stenosis using basic geometry as shown in Figure 1. Subsequently, Computational Fluid Dynamics (CFD) is employed through the COMSOL software to simulate blood flow within the simplified artery featuring the stenosis (refer to Section 3.1 for implementation specifics). This simulation produces the pattern of wall shear stress (WSS) generated by flowing blood on the inner surface of the artery. The obtained WSS data is then utilized within an Agent-Based Model (ABM) constructed using MATLAB. This ABM emulates the evolution of the stenosis as influenced by blood flow. As changes occur, a modified geometry is generated to reflect the evolving state. This updated geometry is integrated back into COMSOL to generate new WSS patterns. This cyclic process continues iteratively until a predefined stopping condition is met, allowing for comprehensive study of the stenosis progression based on the interplay between blood flow dynamics and geometric changes. The flowchart illustrating the process is depicted in Figure 4.

ABM is a computational modeling technique used to simulate interactions between agents and the environment based on given conditions. Each agent typically adheres to a predefined set of rules or behaviors, enabling them to engage with other agents and adapt to changes within their environment. Thus, we begin by identifying agents and environment to model the progression of stenosis using ABM. The agents are defined as the stenosis in the artery, while the environment is defined as the blood flow passing through it. Subsequently, the neighboring environment affected by the agents is also defined. To detect the impacted environment, the WSS generated in COMSOL is applied to the ABM simulation. The WSS values on the environment are then defined as $Wss_{i,j}$. The environment is divided into a grid, with each node denoted by indices *i* and *j*. For a preliminary exploration of using ABM to simulate the progressive development of stenosis, a basic level of dysfunction Wss is computed.

$$\begin{aligned} Wss &= \left| Wss_{i+a,j+b} - Wss_{i,j} \right| \qquad if \quad Wss_{i+a,j+b} > Wss_{i,j}, \\ Wss &= 0, \qquad\qquad\qquad\qquad for \;\; elsewhere, \end{aligned} \tag{9}$$

Where a = 0 or 1, and b = 0 or 1 represent the grid nodes of the neighboring environment. The dysfunction profile of Wss for the environment is generated, and the region exposed to Wss greater than 0 exhibits a more pronounced stenosis area. This indicates that the environment with $Wss > 0$ will be converted into agents.

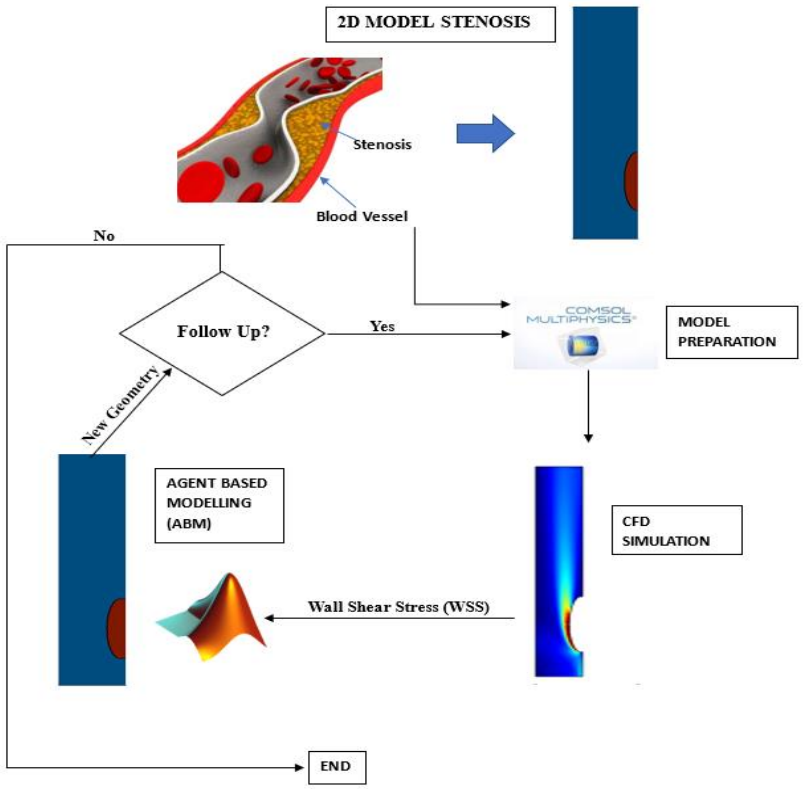


Fig. 4. Couple computational framework. Combining computational fluid dynamics (CFD) simulation using COMSOL Multiphysics and agent-based modelling (ABM) simulation using MATLAB to examine the development of stenosis in blood flow

3. Results

By applying the ABM, the progression and development of the stenosis, along with the corresponding changes in blood flow within the artery, are demonstrated. Figure 5 illustrates the evolution of stenosis progression attributed to the wall shear stress (WSS) of arterial blood flow. The initial stage of stenosis is depicted in Figure 5(a), where the blood flow through the narrowed artery is computed and simulated using COMSOL. The blood flow within the stenosis is analysed and the outcomes are visualized in Figure 6(a). The resulting WSS pattern is depicted in Figure 7(a), with the WSS data subsequently utilized in an Agent-Based Model (ABM) implemented in MATLAB to simulate the advancement of the stenosis. Subsequently, the newly formed geometry, as illustrated in Figure 6(b), is employed once again in COMSOL under the same conditions to compute a new set of fluid field results. The outcomes of the primary computational iteration are presented in Figure 6(b) for the velocity profile and in Figure 7(b) for the WSS distribution. The process is typically repeated until the stenosis completely occupies the artery. However, the objective of the current study is to showcase the capacity of utilizing the ABM to simulate the developmental progression of stenosis caused by blood flow.

Furthermore, changes in the structure of the stenosis do indeed influence the behaviour of blood flow. As observed in Figure 6, the maximum velocity increases as the stenosis develops. Additionally, the point of maximum velocity occurs within the narrowed region created by the stenosis due to the pressure distribution (see Figure 8). As the size of the stenosis increases, the pressure at the blood inflow area also rises well agree with the Bernoulli principle. This is because the reduced area for blood flow in the stenotic region increases resistance, hindering the passage of blood. Consequently,

more force is generated to drive the blood through. To be more specific, the line-cut plot for the WSS at z = 1 is demonstrated in Figure 9. It is clear to be seen in Figure 9(b) that, along the progression of the stenosis, the WSS near the surface of the stenosis is increasing. Advanced treatments could be devised if the progression of stenosis due to blood flow is comprehensively analysed. Furthermore, understanding the repercussions of blood flow behaviour due to stenosis severity might offer an alternative means for early detection of coronary artery disease, bypassing the complexities of traditional methods.

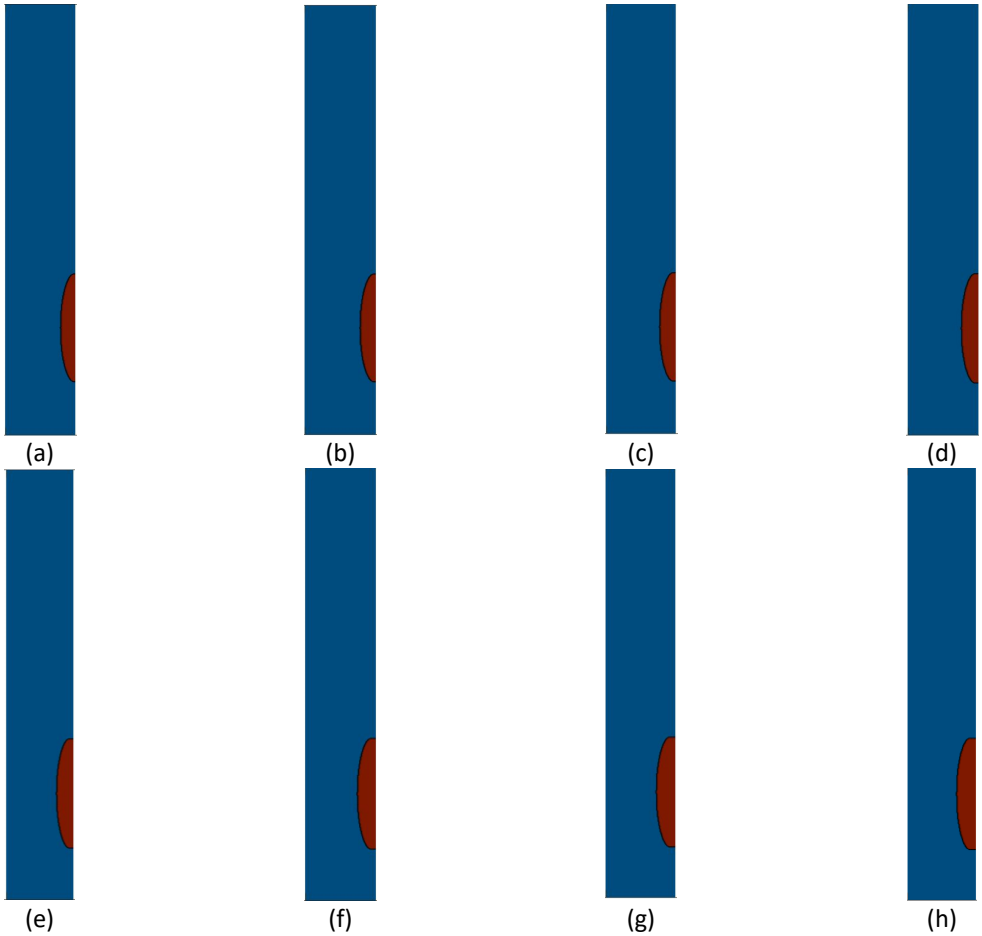
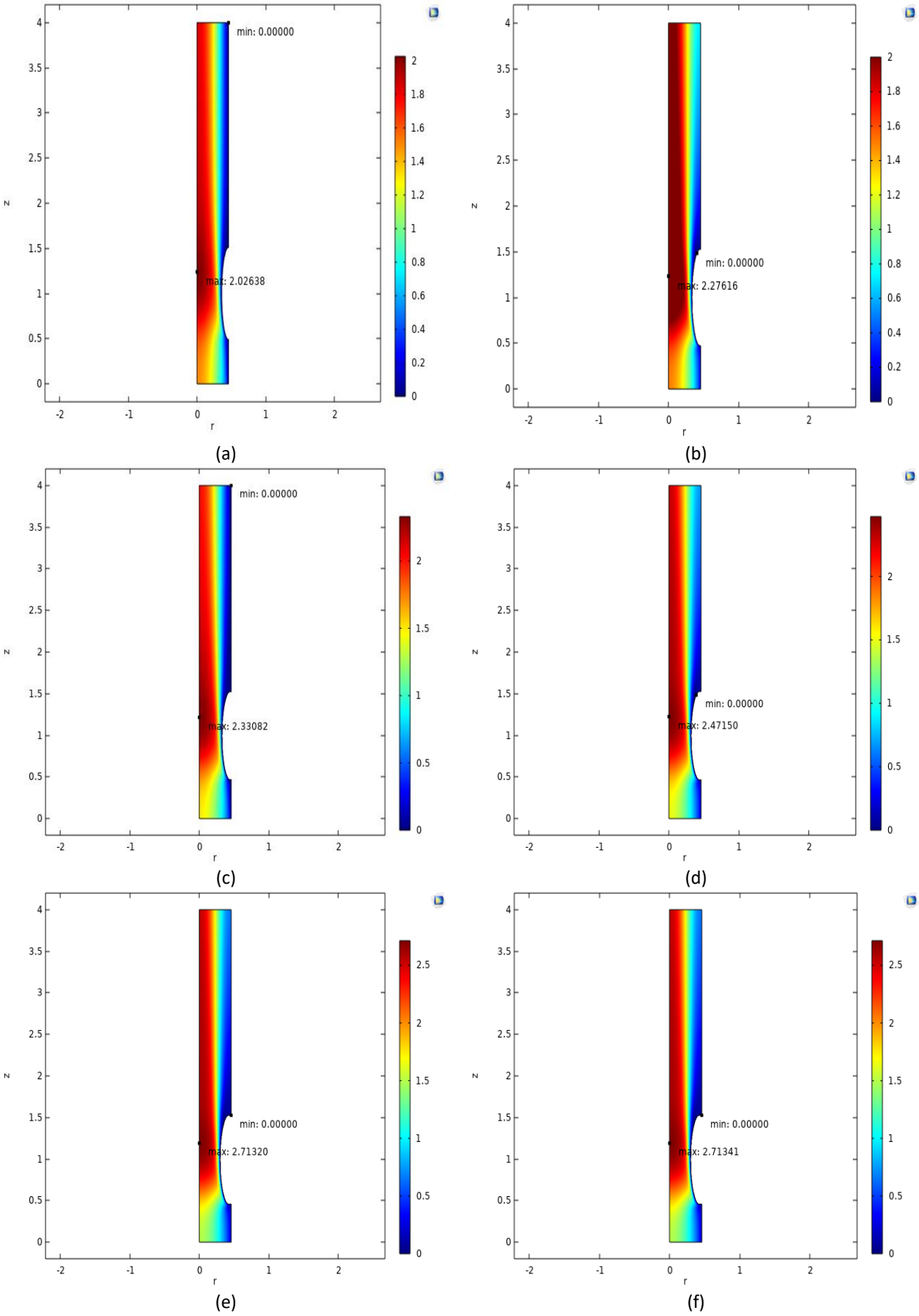
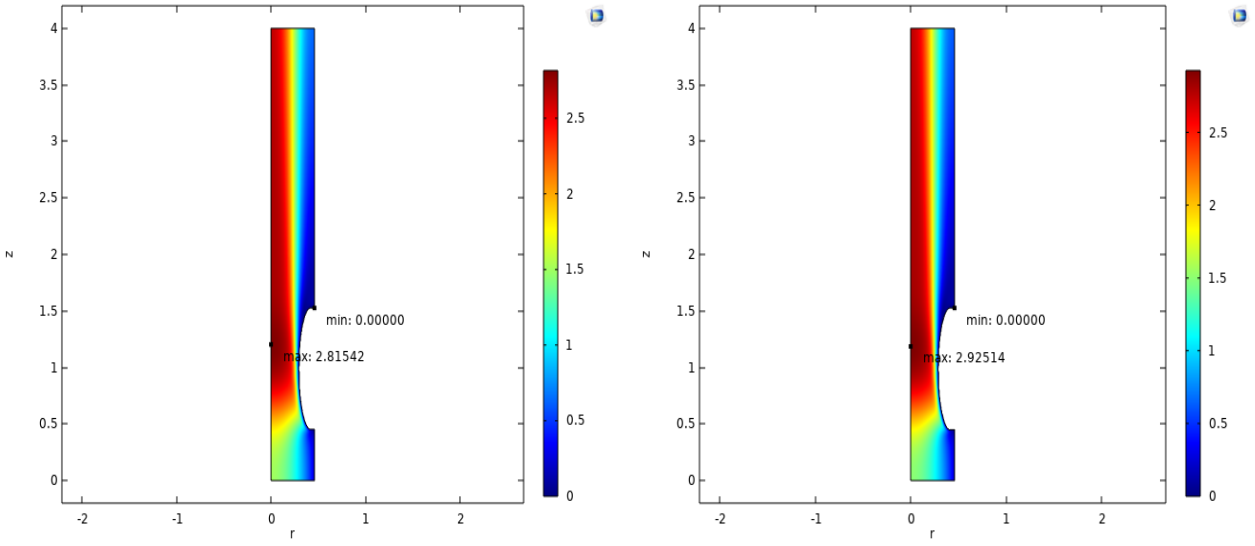


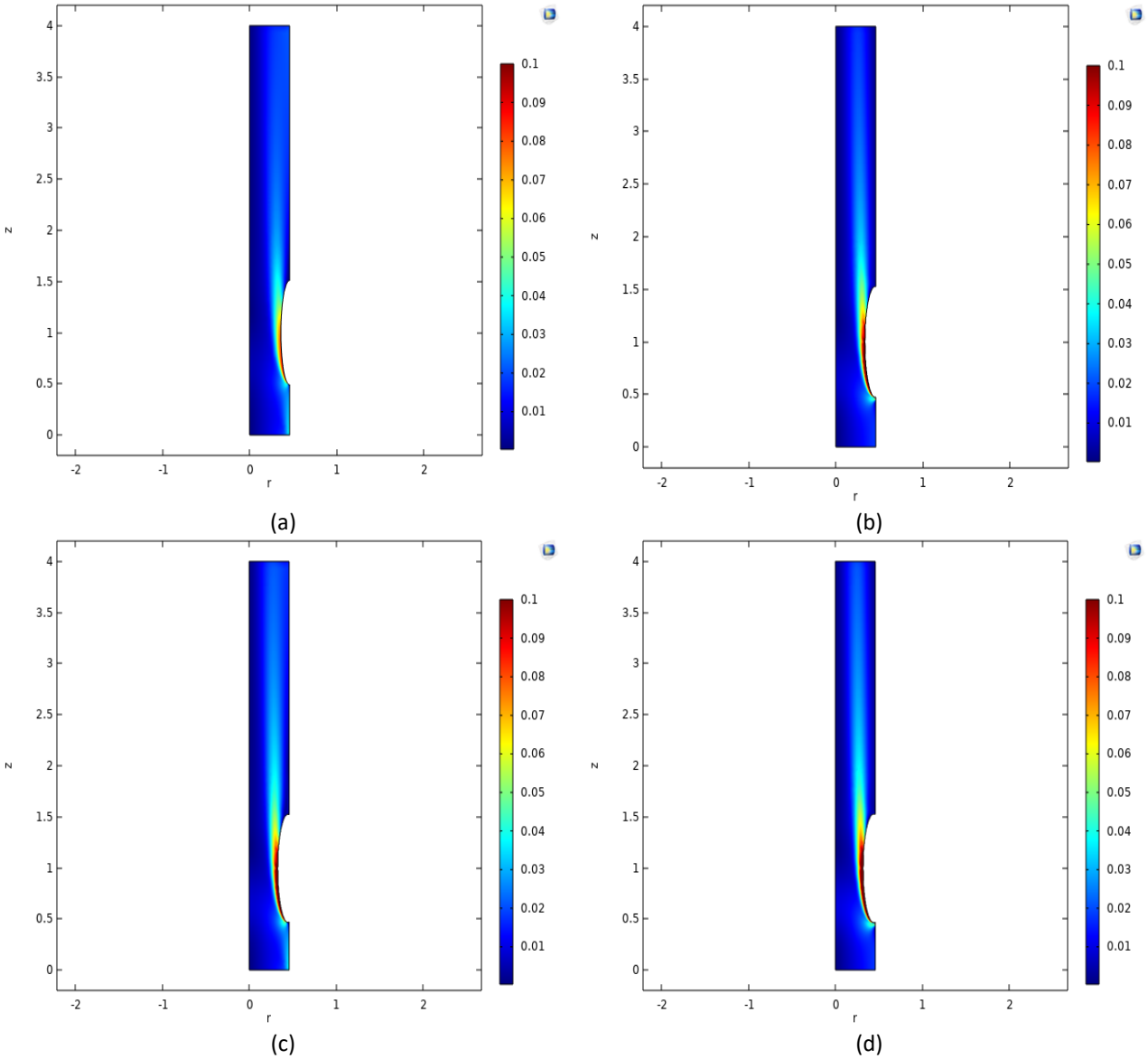
Fig. 5. Progress deformation of the stenosis


min: 0.00000
max: 2.02638
(a)
min: 0.00000
max: 2.27616
(b)
min: 0.00000
max: 2.33082
(c)
min: 0.00000
max: 2.47150
(d)
min: 0.00000
max: 2.71320
(e)
min: 0.00000
max: 2.71341
(f)



(g) (h)

Fig. 6. Velocity profile of the blood flow



(a) (b)

(c) (d)

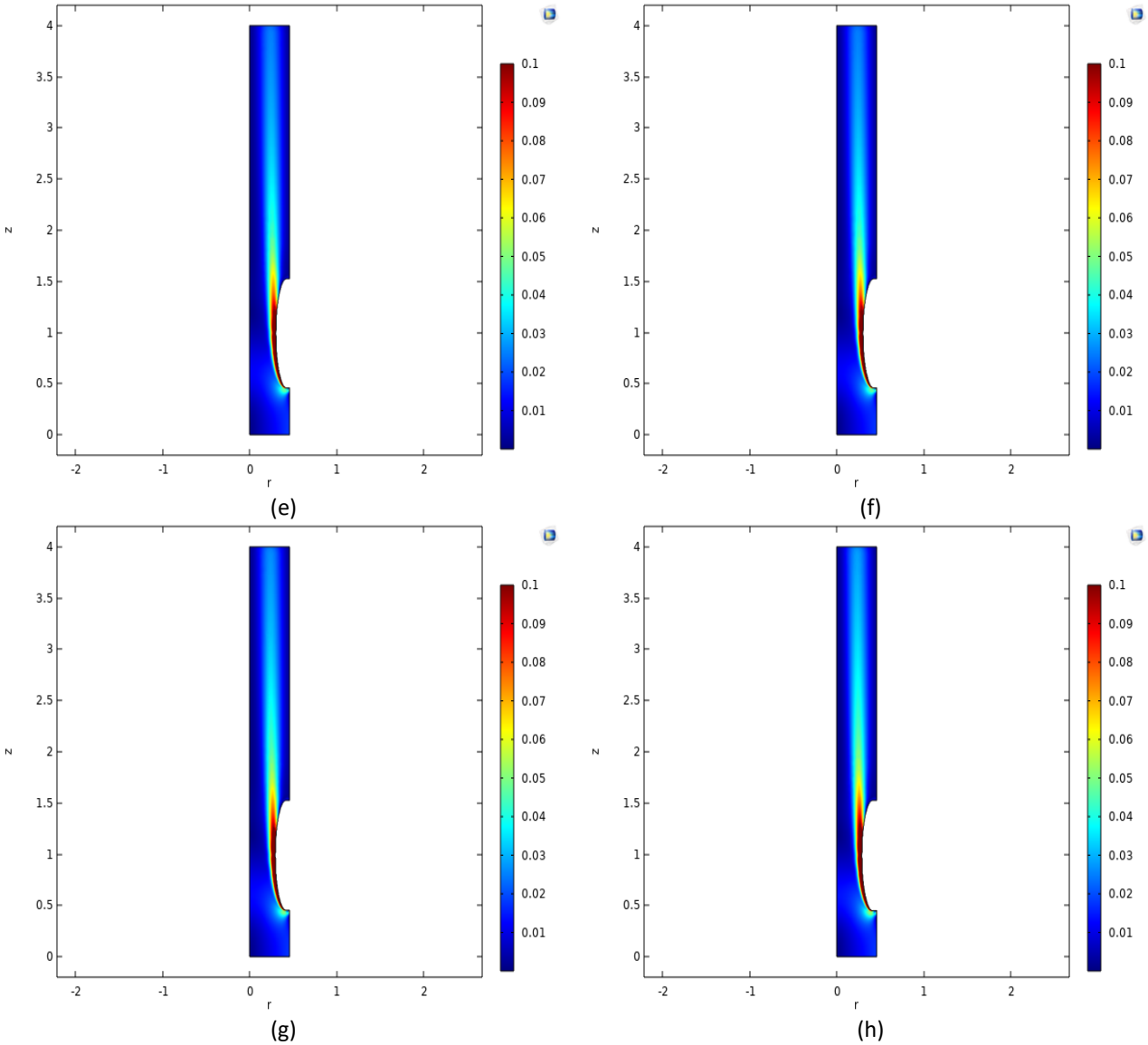
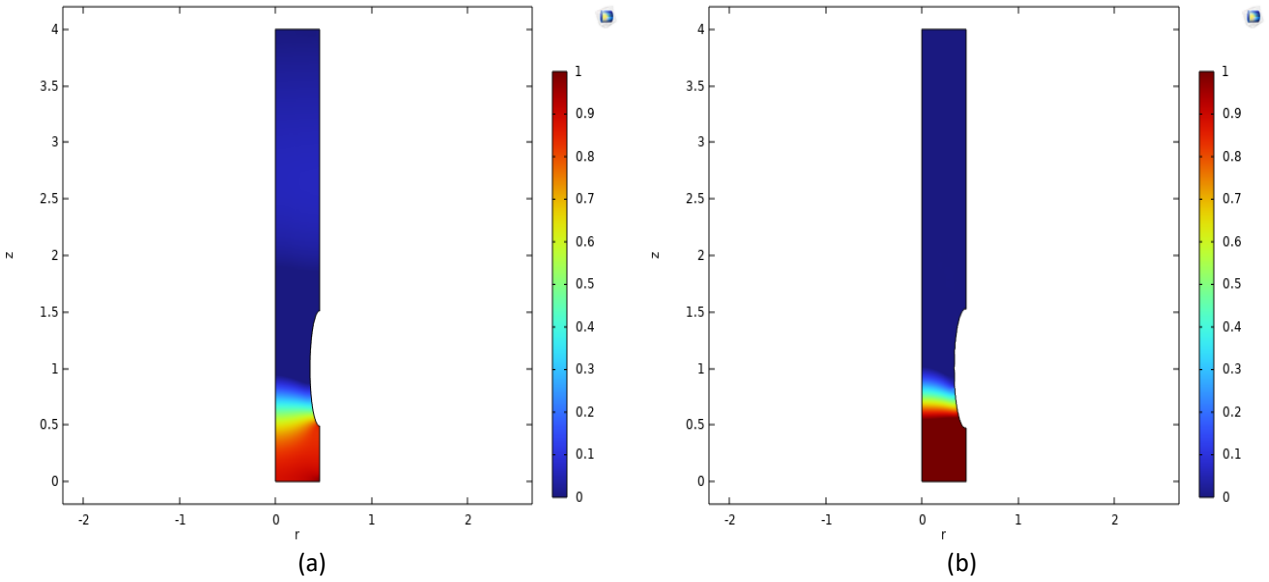


Fig. 7. Wall shear stress profile of the blood flow



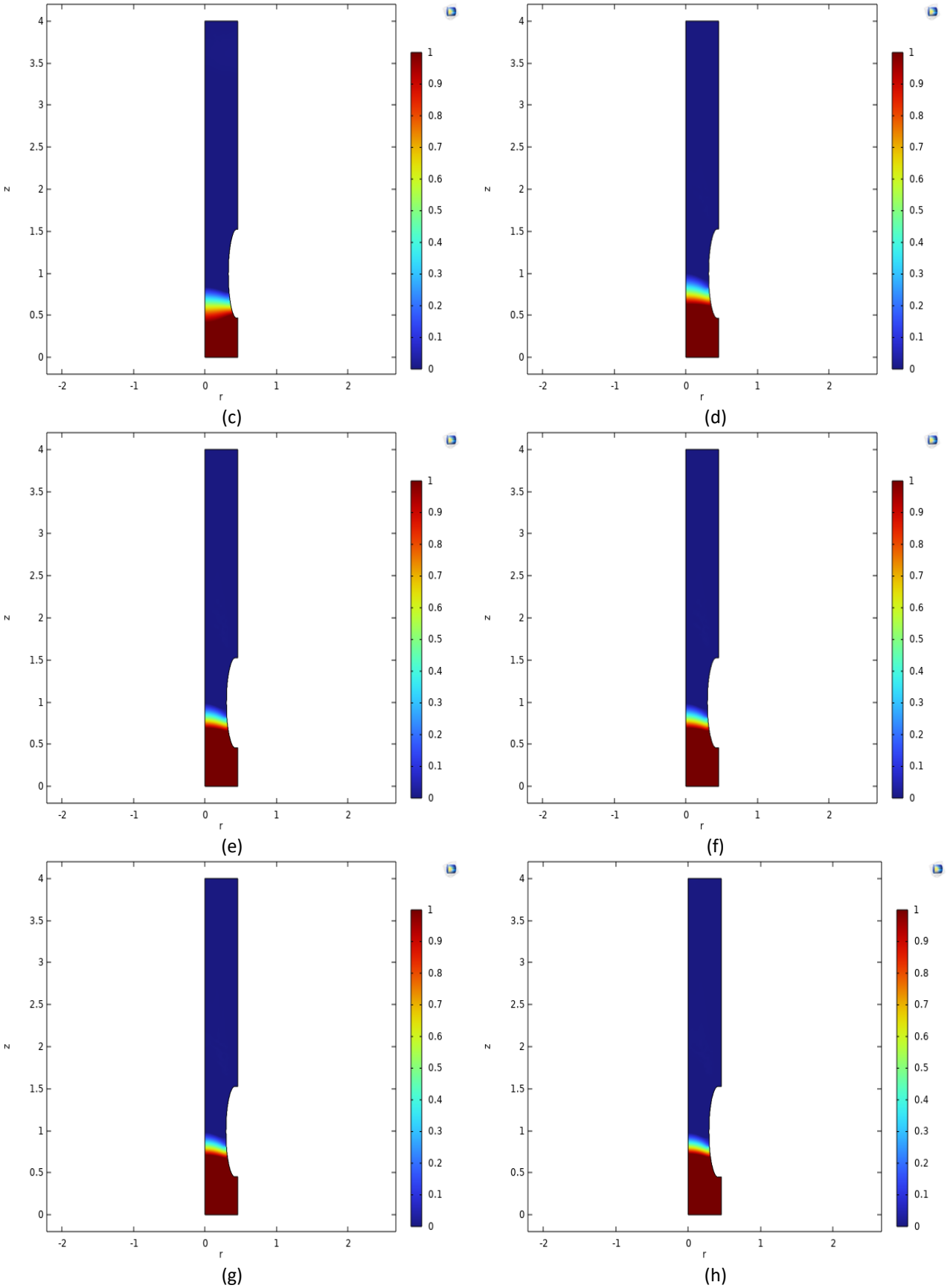
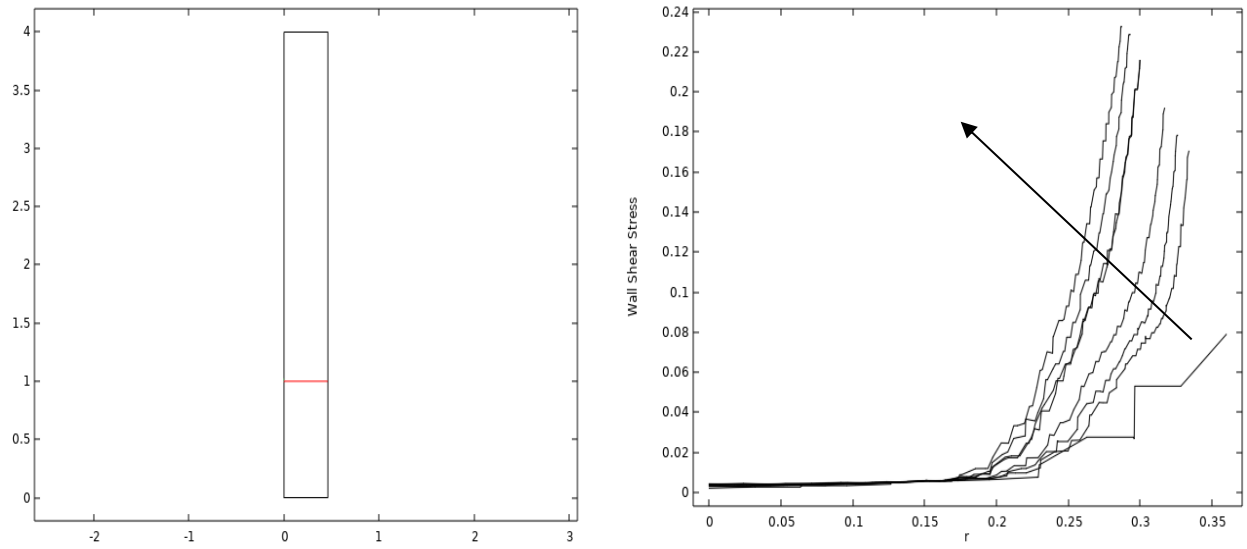


Fig. 8. Pressure profile of the blood flow



(a) (b)

Fig. 9. Wall shear stress (b) at the line cut (a) for the various progression of the stenosis

4. Conclusions

The present study emphasizes the role of Agent-Based Modelling (ABM) in predictive biological modelling, particularly for tissue engineering applications. This study aims to leverage ABM's capabilities to simulate the interplay between blood flow and stenosis progression, ultimately aiming to enhance our understanding of arterial disease development by combining ABM from MATLAB and Finite Element Analysis (FEA) from COMSOL Multiphysics. In conclusion, the study effectively demonstrates how ABM can comprehensively depict stenosis progression and its impact on artery blood flow dynamics. The outcomes of the current study can be summarized as follows:

i. The ABM shows stenosis progression and its artery blood flow impact effectively,
ii. Altered stenosis structure affects blood flow behavior; maximum velocity rises with stenosis development,
iii. Increasing stenosis size raises WSS near its surface, altering blood flow characteristics,
iv. Insight into stenosis progression through blood flow inspires advanced treatments and early coronary artery disease detection alternatives.

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