# Molecular transport in the arterial wall with variation of shape and configuration of smooth muscle cells

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*Abstract*— **Molecular transport through the tunica media layer is influenced by the smooth muscle cells (SMCs). This study considers the media layer as a heterogeneous porous media composed of smooth muscle cells of elliptic and circular shapes distributed in ordered or disordered configurations. To study the role of SMCs on the transport of molecules in the media, we model the media layer as a two dimensional numerical simulation of interstitial flow through the media layer. The assumption of the elliptic shape resembles the spindled shape of SMCs. The molecular transport of ATP is considerably dependent of the shape of SMCs according to the results of our numerical model. More importantly, the ATP concentration was found to be extremely sensitive to the random configuration of SMCs, which is more close to the real arrangement of SMCs within the media layer**

*Keywords*— **Molecular Transport, Muscle cell, Computational Fluid Dynamics**

## I. Introduction

Atherosclerosis is a disease of the coronary, carotid, and other proximal arteries. The accumulation and the transportation of molecules in layers of the arterial wall play a major role in creation of atherosclerosis [1, 2]. Transportation of solutes from the bulk fluid (blood) to arterial wall considered in many studies and different mechanisms suggested for different solutes. However, the main parameters in transport through the arterial wall are so wide that makes it hard to specify the effect of each parameter [3-7].

Scientists have focused recently on tunica media layer, the middle layer of an arterial wall, as an important layer in molecular transportation. The media layer is modeled as a porous heterogeneous medium consisting of a continuous extracellular matrix phase with embedded smooth muscle cells (SMCs).The internal elastic lamina (IEL) separates the subendothelial intimal layer from the tunica medial layer and provides a complex entrance flow condition through fenestral pores[1, 3]. Molecules cross the endothelial cell layer and enter the media from fenestral pores in IEL.

Many analytical and numerical works have explored the mechanism of transport of molecules within the artery wall [1, 3, 8-10].Tada and Tarbell [11] studied the effects of fenestral pores on the fluid shear stress distribution on the superficial layer of SMC and observed a significant entrance effect. Tada and Tarbell [3] described fenestral pore entrance effects on the convective and diffusive mass transport processes in the media, which they modeled as a heterogeneous material consisting of a continuous interstitial porous media phase and an array of cylindrical SMCs embedded in the interstitial phase. They did not consider the configuration and shape of SMCs affects the distribution of species in the media.

In the present study, a mathematical model is developed to study the effects of configuration and shape of SMCs on diffusive mass transport processes in the media layer. The SMCs are assumed as cylindrical objects with elliptic cross sections. In earlier studies, the medial layer was considered as a heterogeneous medium composed of cylindrical SMCs with circular cross section [1, 3]. The assumption of elliptic shape resembles the spindled shape of SMCs. We consider ATP enters the medial layer of the artery through fenestral pores, which are uniformly distributed over the IEL. Driving forces for the diffusion of ATP molecules is associated with concentration gradient across the wall and degradation of ATP on SMCs surface. To obtain the effect of SMCs shape and configuration in transportation of ATP, we compare our results for elliptic SMCs with result for circular SMCs that were obtained by Tada and Tarbell [3].

## II. Methods

*Model description:* In the present study, two-dimensional (2D) numerical simulation of interstitial flow and transport in the tunica media were performed to investigate the influence of SMC configuration and shape on distribution of molecules across the media.

A schematic illustration of the media is shown in Fig.1. Similar to assumptions made in Ref. [3] this figure shows transverse sectional view of an artery wall. However, in the current geometry the media layer is modeled as a heterogeneous medium composed of SMCs with elliptic shapes distributed in disordered fashion. The left end in Fig.1 corresponds to the IEL, and the right end corresponds to the interface between the medial layer and adventitia. The medial layer of blood vessel wall is modeled as a heterogeneous medium composed of a periodic array of elliptic SMCs and a continuous interstitial fluid phase filled with protegly

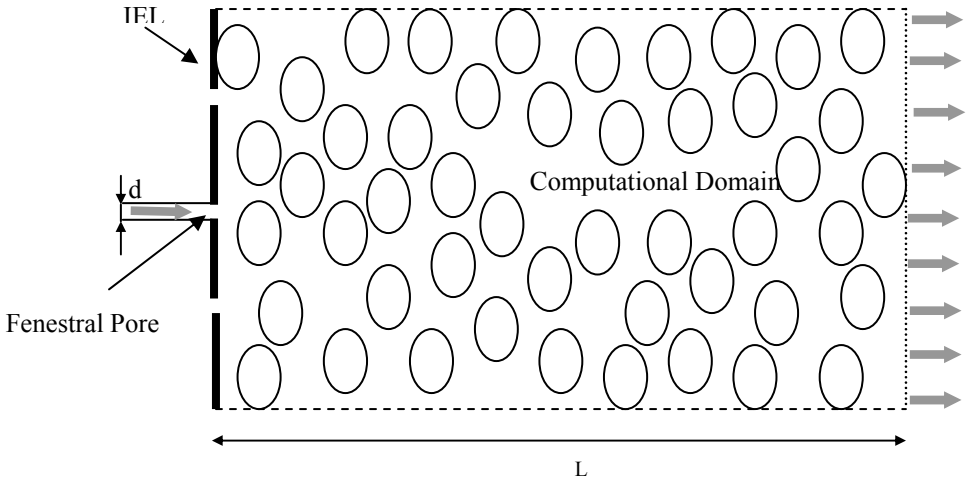


Fig. 1 Schematic illustration of the arterial wall. The IEL is an impermeable barrier to fluid flow except for the pores that were assumed to be uniformly distributed over this wall. Smooth muscle cells (SMCs) are modeled as elliptic cylinders in a disordered configuration.

can and collagen fibers as a uniform fiber matrix. Transmural flow is distributed into the medial layer from the intima by passing through fenestral pores of IEL. The IEL is assumed to be an impermeable barrier to fluid flow except for its pores that provide transport pathways for solutes and water [12]. SMCs are modeled as circular and elliptic particles [12]. Tada and Tarbell concluded in Ref. [3] that ATP fluid-phase transport is dominated by diffusion emanating from the fenestral pores. They modeled the degradation of ATP (hydrolysis of ATP to ADP) on SMCs surface using Michaelis-Menten kinetics.

*Mathematical formulation:* The governing equation for steady state diffusion of any solute in a fluid phase is

$$-D_f^* \nabla^2 C = Q \tag{1}$$

C is the interstitial molecule concentration, and $D_f^*$ is the dimensionless effective diffusivity of solutes in the fiber matrix normalized by $D_f$ of solute ( $D_f$ for ATP $= 2.36\times10^{-10}\ m^2/s$ ). In this equation Q represents a dimensionless volume source. Note that Eq.1 is given in dimensionless form. The boundary condition on the surface of an SMC is

$$L k_r C = D_f \frac{\partial C}{\partial n} \tag{2}$$

Which assumes that the rate of disappearance of solute by surface reaction is a first process with rate constant $k_r$ ( $k_r$ for ATP = $1.25\times10^{-6}\ m/s$ ). n is normal direction to the surface. The surface of the IEL was assumed to be impermeable and nonreactive to solutes except at the fenestral pores. Thus the boundary conditions for solute concentration on the IEL are

$$\frac{\partial C}{\partial n} = 0 \tag{3}$$

everywhere except at the fenestral pores where

$$C = 1 \tag{4}$$

Note that the ATP concentration is normalized by that at the fenestral pore entrance. On lateral surfaces of the rectangular computational domain, we apply a symmetry boundary condition because the fenestral pores and SMCs were assumed to be arranged in spatially periodic arrays for computational convenience even in disordered configuration of SMCs. The height of the rectangular computational domain is one-half of the distance between neighboring fenestral pores (3).

*Computational method:* From experimental resources in various animals, we find out the physiological parameters used in numerical simulation. The diameter (D) of circular SMCs is taken 4.0 μm based on data for the rabbit thoracic aorta [10, 12-15]. The eccentricity of elliptic SMC is con-

sidered as 0.66 (large diameter in vertical direction) which has larger exposed area of SMC. Note that the cross sectional area of elliptic SMC is equal to that of circular SMC. These data show the volume fraction of the SMCs (F) in the range 0.4-0.7, and the media layer thickness (L) calculated from SMC diameter and volume fraction in the range 120~150 μm. The present model considers the SMCs volume fraction (F) of 0.4 in the media layer and the media thickness is 120 μm.

Using these experimental data, we obtain the area fraction of fenestral pores (f) in the range 0.004-0.016 and the fenestral pore diameter (d) in the range 0.4-3.2 μm. The distance between the IEL and the upstream end of the most proximal SMCs (a) is estimated to be 0.36 μm [3, 11]. In our model, the area fraction is held constant at 0.004, and d is varied in the range 0.8-1.6 μm. The number of SMCs in one row in ordered distribution (in disordered part we use the same number of SMCs considered in ordered part) and width of computational domain( $l$ ) are dependent of the diameter of fenestral pore and the fenestral pore spacing because in fixed area fraction (f), the pores are spaced further apart as pore diameter (d) increases. For larger d then, there are more SMCs between neighboring pores. The relation between these parameters is available elsewhere[3] in greater detail and will not be repeated here. Briefly, the equation 5 describes this relation

$$l = \frac{d}{2}\sqrt{\frac{\pi}{f}} \tag{5}$$

We solve Eq.1 with the above-mentioned boundary conditions using the finite-element method (FEM) provided in the PDEToolbox of MATLAB [16].

It should be noted that the meshing of our model domain takes into account the border between the matrix and disks, i.e., the mesh is automatically adjusted to conform with substantial changes of the material parameters. The number of nodes used in the calculations depends on the surface fraction of disks, e.g., it is about 3000 for small surface fraction to about 10 000 for the highest surface fractions.

## III. Results and discussion

In this work, results show that the ATP concentration on the surface of SMC and within the bulk depend on the shape and configuration of SMCs and the diameter of fenestral pores.

Figure 2 shows the ATP concentration on the surface of SMCs with circular and elliptic shape for three different diameters of fenestral pore. In this part, SMCs are distributed in ordered configurations with a constant area fraction (f) of 0.004 through different diameters of fenestral pore (d). The value of the surface concentration represents an average with respect to all the cells in the same row. The ATP concentration is demonstrated for d=0.8 μm, 1.2 μm, and 1.6 μm in Figure 2. Figure 2A shows concentration profiles for circular SMCs and Figure 2B is for elliptic SMCs. Concentration profiles for only ten rows of the SMC array are displayed.

Results indicate that in the elliptic shape of SMCs the ATP concentration decreases. The eccentricity of elliptic SMC is considered as 0.66 (large diameter in vertical direction) which has larger exposed area of SMC to consume ATP. Note that the cross sectional area of elliptic SMC is equal to that of circular SMC.

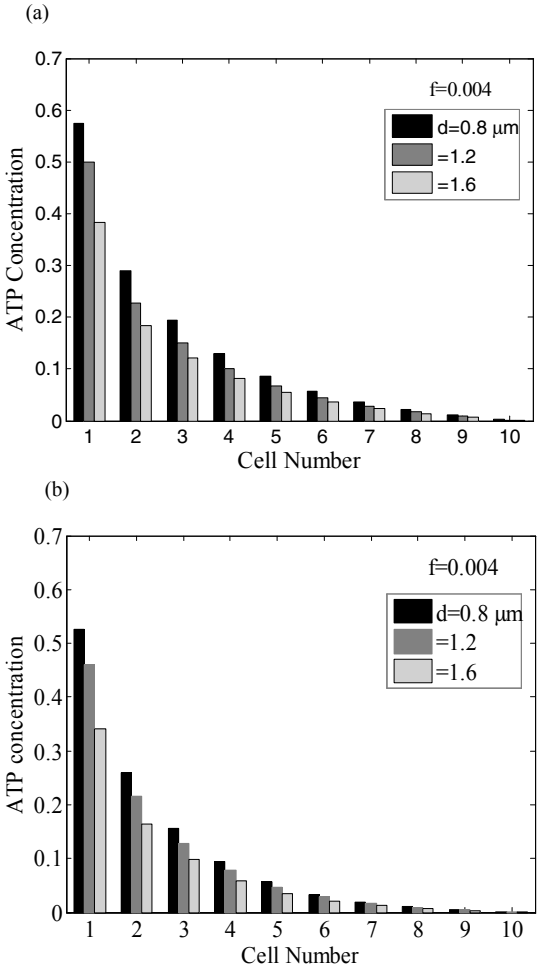


Fig. 2 Profiles of ATP concentration on the SMCs surface in the direction of the interstitial flow for three values of the fenestral pore diameter (d). (a): shows result for circular SMCs. (b): concentration profile for elliptic SMCs.

Another result obtained from Fig.2A and Fig.2B is that the surface ATP concentration for both circular and elliptic SMC drops as the size of fenestral pore increases. We can explain these changes if we note that fluid-phase transport for ATP is dominated by diffusion, not convection and fluid diffuses into the media from each fenestral pore. To keep the value of pore area fraction (f) constant when fenestarl pore diameter (d) increases, both the pore spacing ($l$) and number of SMCs between neighboring pores to consume ATP are increased. Therefore ATP concentration decreases as d increases.

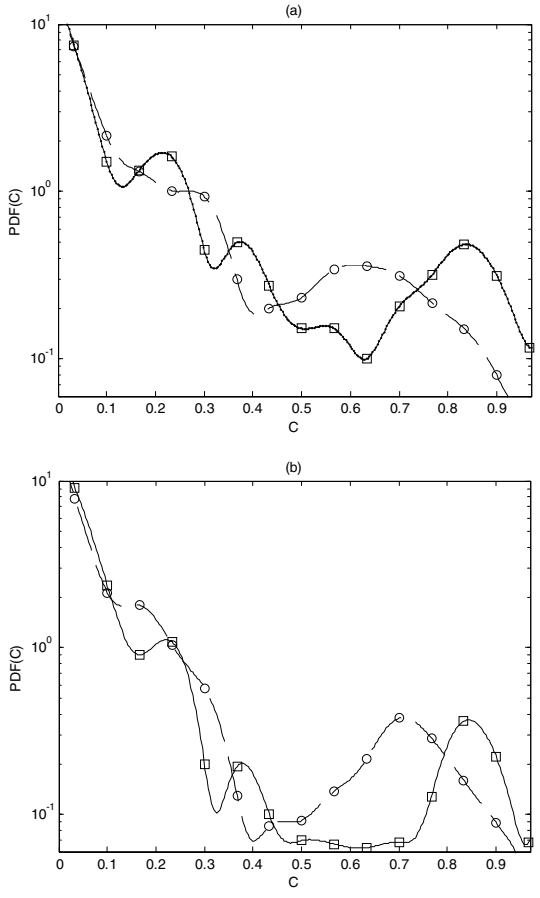


Fig. 3 Probability density function of ATP concentration field within the bulk for ordered and disordered configurations of SMCs for f=0.4 and d=1.6 μm. The dashed line presents disordered configuration. (a): PDF for circular SMCs, (b): PDF for elliptic SMCs.

Figure 3 displays the probability density function (PDF) of the entire concentration field for ordered and disordered configurations of SMCs. The same number of SMCs is considered in these cases and volume fraction of SMCs, the area fraction of fenestral pore, and the diameter of pores are 0.4, 0.004, and 1.6 respectively. Fig3 (a) is for circular SMCs and Fig3 (b) is for elliptic SMCs. Figure 3 shows the ATP concentration in the bulk fluid decreases in disordered configuration for both elliptic and circular SMCs as the concentration is greater than 0.8. In intermediate concentration, PDF for disordered cases are slightly higher than those of ordered cases. In concentrations less than 0.5, the distribution of ATP concentration for all cases is approximately the same.

These changes are related to the pore structure and the distribution of SMCs. In disordered distribution, random position of SMCs let the fluid pass through the media layer.

Therefore, the probability of points which have a large con centration is more than the ordered cases. It is worth mentioning that the given data in disordered cases represent an average between 3 different random configurations of SMCs.

## IV. Conclusions

In conclusion, this study explains the effect of SMC shape and configuration on mass transport in media layer for the first time. The media layer is modeled as a heterogeneous medium consisting an array of elliptic and circular SMCs embedded in a continuous, porous interstitial matrix phase. The realistic form of SMC based on microscopic images in the literature is spindled shape. Therefore, the elliptic shape resembles the spindled shape of SMCs. The results indicate the ATP concentration at the SMC surface decreases in elliptic SMCs because of larger exposed area. Moreover, the probability density function of ATP concentration in the bulk increases in disordered distribution for intermediate concentrations.

Three different values for diameter of fenestral pore (d) in IEL are considered. The results show concentration within media layer decreases for both elliptic and circular SMCs decrease with the size of fenestral pore. This work elucidates the role of SMC shape and configuration, and the size of fenestral pore in the transport of ATP through the media layer which has a significant impact on our knowledge about the atherosclerosis.

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