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Numerical Simulation of Particle Transport and Deposition in the Pulmonary Vasculature

To quantify the transport and adhesion of drug particles in a complex vascular environment, computational fluid particle dynamics (CFPD) simulations of blood flow and drug particulate were conducted in three different geometries representing the human lung vasculature for steady and pulsatile flow conditions. A fully developed flow profile was assumed as the inlet velocity, and a lumped mathematical model was used for the calculation of the outlet pressure boundary condition. A receptor–ligand model was used to simulate the particle binding probability. The results indicate that bigger particles have lower deposition fraction due to less chance of successful binding. Realistic unsteady flow significantly accelerates the binding activity over a wide range of particle sizes and also improves the particle deposition fraction in bifurcation regions when comparing with steady flow condition. Furthermore, surface imperfections and geometrical complexity coupled with the pulsatility effect can enhance fluid mixing and accordingly particle binding efficiency. The particle binding density at bifurcation regions increases with generation order and drug carriers are washed away faster in steady flow. Thus, when studying drug delivery mechanism in vitro and in vivo, it is important to take into account blood flow pulsatility in realistic geometry. Moreover, tissues close to bifurcations are more susceptible to deterioration due to higher uptake.

[DOI: 10.1115/1.4028800]

Keywords: computational fluid particle dynamics, human lung vasculature, drug delivery, particle deposition

1 Introduction

Targeted drug delivery, as a method of delivering medication to patients in a manner which can increase the concentration of medication in the diseased tissues of the body, has acquired intense interest in pharmaceutical research and development. The goal of targeted drug delivery is to prolong, localize, target, and have a controllable drug interaction with the diseased tissue. Thus, the frequency of the dosages taken by patients, drug side-effects, and the fluctuation in circulating drug levels can be minimized. Nano/micro particles have been studied as potential multifunctional carriers for drug delivery [1,2]. They can encapsulate drug into their core or coat drug into their surface to fight against cardiovascular disease and various cancers [3]. Their half time in circulation and deposition distribution can be modulated by their shape and size. Thus, by using nanoparticles in medicine, the absorption rate, distribution, metabolism, and excretion of drugs can be significantly enhanced [4].

Size, as a key characteristic of nanoparticles (NPs), directly influences the mechanism of deposition [5]. For large particle, such as micron size particles in airway, the main deposition mechanism is inertia. For submicron particles, Brownian motion is more influential. Furthermore, other factors, including particle shape, fluid viscosity, fluid velocity, heart rate, and vascular geometry, should be considered as well. Many studies have been conducted on how particle size, shape, and velocity influence its transport and delivery [6–10]. They did numerical calculation using simple bifurcated branch and symmetric simulated ideal model to characterize the effects of NPs properties. Liu et al. [11] reported that smaller nanoparticles bind faster than bigger ones,

because diffusion coefficient is inversely proportional to the particle size. In that paper, only 10 nm and 100 nm particles have been studied in capillary vessel with diameter of 10 μm and 20 μm . The author did not give out a method to link the microscale particulate model with multiscale model of organ level, which is more beneficial to nanoparticle distribution prediction and drug dosage administration.

It is not trivial to reconstruct a large scale vasculature network. The geometry of the model has significant influence on the fluid velocity field, and accordingly the particle transport and deposition. Some results are even contradictory in realistic model and simulated model, as reported by Nowak et al. [12]. Previous researchers simulated the micro-particles delivery and deposition in human lung airway and compared the results of simulated Weibel model and real human trachea model [12–14]. It shows more particles bind at straight vessel in real trachea model. But in a simulated Weibel model, because of the relatively smoother and more symmetric geometry, almost no particle sticks at straight section. Thus a real 3D vascular model is necessary for a more realistic modeling of particle transport and binding process [15,16].

CFPD simulation provides an attractive way to study the particle delivery in a complex geometry model [11,17,18]. Some examples are presented by Schroeter et al. [19], Chern et al. [20,21], and Zhang et al. [22,23]. Most current numerical simulations for vascular network adopt realistic geometry with less than four generations in order to make computational costs affordable.

In this paper, a simulated Weibel model and a realistic subunit of pulmonary vascular model reconstructed from the left lung magnetic resonance imaging (MRI) image are considered. Blood flow is treated as Newtonian and laminar fluid flow [24]. Particles are tracked by integrating the force balance on them using discrete phase model. A fully developed physiological velocity profile is used at the inlet. To overcome the incompleteness of vascular

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Manuscript received April 21, 2014; final manuscript received October 6, 2014; accepted manuscript posted October 15, 2014; published online November 7, 2014. Assoc. Editor: Naomi Chesler.

system, a lumped mathematical model is derived to calculate the overall resistance at each outlet. Moreover, a shear rate and particle size dependent ligand–receptor model [25] is utilized to define the particles binding probability.

Using a realistic truncated model of pulmonary vasculature, we aim to 1. Study the influence of particle size on drug carrier transport and deposition; 2. Characterize the importance of pulsatile flow and surface smoothness on particle binding; and 3. Understand particle spatial distribution as well as the instantaneous binding patterns in a complex lung vasculature.

2 Numerical Modeling

To study the influence of vascular geometry on particles binding, three different lung models were used: 1. Simulated artificial model; 2. A realistic lung model with the original processed surface obtained from MR images; 3. The same realistic lung geometry with an oversmoothed surface. Different software applications, such as Vascular Modeling Toolkit (VMTK), Geomagic Studio, and Inventor, are used to reconstruct and process model structures. Moreover, Integrated Computer Engineering and Manufacturing-computational fluid dynamics (ICEM-CFD) is utilized for mesh generation. Fluid flow and particle tracking formulations used in this study are explained in the Appendix.

2.1 Reconstruction of pulmonary geometry

Artificial Geometry. Two assumptions are made for constructing the artificial model [12]: (1) the branching angel at each bifurcation is 60 deg and (2) the rotation angel of bifurcation plane originating from each daughter branch is 90 deg. Here, a four generations subunit model is constructed in Inventor as shown in Fig. 1(a). Its geometrical specifications are listed in Table 1.

Realistic Geometry. An MRI based digital imaging and communications in medicine (DICOM) image of a healthy, adult human lung vasculature was obtained retrospectively from an on-going clinical research study at University of Pittsburgh Medical Center (UPMC), following Institutional Review Board approval at UPMC and University of Texas at San Antonio (UTSA). Deidentified digital files of the DICOM images were saved on optical media and converted to Visualization Toolkit (VTK) format.

For 3D flow analysis, semiautomatic segmentation methods are used here which appear to be the most practical approach [26].

Fig. 1 (a) Artificial ideal Weibel model and (b) lung vasculature geometry reconstructed from a CT image dataset; a four-generation original (c) and oversmoothed (d) subunit of pulmonary vasculature

Table 1 Length and diameter of each branch

Generation No.	Length (cm)	Diameter (cm)
1	0.76	0.56
2	1.27	0.45
3	1.07	0.35
4	0.9	0.28

Then, a surface was extracted according to the image data, as shown in Fig. 1(b). It is a whole lung vascular model, which includes up to six generations.

Some outlets are closed with a blobby appearance. Therefore, it is important to clip the blobby endcaps manually. Moreover, it should be noted that some surface imperfections are resulting from branching regions of much smaller vessels which cannot be captured due to MRI resolution limitations. It is worthy to mention that flow extensions at the inlet regions have also been added to realistic geometry in order to reduce entrance effects on particle deposition results.

It is extremely challenging to model particle delivery in such a complex vascular system. Developing proper boundary conditions for realistic geometry is also nontrivial because it has over 200 outlets and is highly asymmetric. To model particle delivery in lung vasculature, we select a typical portion of the lung vasculature consisting of four generations, as shown in Fig. 1(c). Moreover, to investigate the effects of vascular surface imperfections on particle deposition patterns, another oversmoothed model was utilized as shown in Fig. 1(d). Using Relax tool in Geomagic Studio, the polygon surface mesh of realistic geometry is significantly smoothed by minimizing angles between individual polygons. Then, triangles are made more uniform in size by QuickSmooth tool. Geomagic just have maximum and minimum level for smoothing and it has the limitation of proper quantification of smoothing procedure. Thus, the oversmoothed model is processed under maximum available options in order to acquire better comparison. Moreover, it is also noteworthy that both realistic geometries have undergone spike removal and noise reduction procedures using the aforementioned software.

2.2 Particles Binding Probability Function. In this study, a receptor–ligand model proposed by Decuzzi and Ferrari [25] is adopted to calculate the particle deposition probability. The adhesive strength of particles depends on the selective binding of the molecules expressed over the target surface and their counter-molecules conjugated at the particle surface. The dislodge forces

Fig. 2 Illustration of a spherical particle in contact with vascular wall. δ_{eq} is the separation distance between the spheroidal particle and the substrate; h_0 is the maximum distance of the spheroid from the substrate at which a specific bond can occur; d is the diameter of the particle.

are influenced by the physiological factors such as wall shear stress, particle shape and size, as sketched in Fig. 2.

Dislodging forces, the drag force F along the flow direction and the torque T , are affected by the particle size d , separation distance from the substrate l and the shear stress μS at the wall. Their explicit expressions are shown as

$$F = 6\pi l \mu S F^S \quad (1)$$

$$T = 0.5\pi d^3 \mu S T^S \quad (2)$$

where the coefficients, F^S and T^S depend on aspect ratio. Here, $F^S = 1.668$ and $T^S = 0.944$ are for spherical particles [27]. When the particle surface and the substrate are close enough, the ligands with surface density m_l on the particle and the receptors with surface density m_r on the substrate can form bonds stochastically. A probability of adhesion P_a is defined as the probability of having at least one bond formed between the particle and substrate surface.

$$P_a = m_l m_r K_a^0 A_c \exp\left[-\frac{\lambda f}{k_B T}\right] \quad (3)$$

where K_a^0 is the association constant at zero load of the ligand–receptor pair; A_c is the interaction area between the particle and the substrate; f is the force per unit of ligand–receptor; λ is a characteristic length of the ligand–receptor bond; and $k_B T$ is the Boltzman thermal energy. A_c can be derived as

$$A_c = 0.25\pi d^2 \left(1 - \left(1 - \frac{2(h_0 - \delta_{eq})}{d}\right)^2\right) \quad (4)$$

f is expressed as the ratio of total dislodging force F_{dis} and the area of interaction A_c multiplied by the surface density of the receptors, that is $f = F_{dis}/(m_r A_c)$. Usually, it is assumed that the force F is uniformly shared among the bonds; whereas the torque T is only shared uniformly within the bonds which are stretched.

$$\frac{F_{dis}}{A_c} = \frac{F}{A_c} + \frac{2T}{A_c r_0} = \frac{3\pi d(d/2 + \delta_{eq})\mu S F^S}{A_c} + \pi d^3 \mu S T^S / A_c r_0 \quad (5)$$

Combining Eqs. (3), (4), and (5), P_a can be expressed as

$$P_a = m_l m_r K_a^0 \pi r_0^2 \exp\left[-\frac{\lambda d \mu S}{2k_B T r_0^2 m_r} \left[6(d/2 + \delta_{eq})F^S + 2\frac{d^2}{r_0}T^S\right]\right] \quad (6)$$

where r_0 is the radius of the interaction surface. The parameters are listed in Table 2. Binding probability decreases with wall shear stress, which is proven by Haun and Hammer [28,29]. The proper values of K_a^0 and m_l depend on particle type of ligand–receptor used and local chemical conditions, and usually require complex experimental tests on particle binding dynamics. To simplify and make our results applicable to delivery of general types of particles, we normalized the particle binding probability with respect to zero shear stress condition. In another word, the

binding probability is assumed to be one at zero shear stress, which is reasonable according to experimental observations [28,29].

2.3 Boundary Conditions

Inlet Flow Boundary Condition. The blood flow in pulmonary arteries is pulsatile. As shown in (Fig. 2 of Ref. [30]), the flow pattern in the pulmonary vasculature of normal subjects showed no retrograde flow during diastole. Furthermore, there was no apparent difference between the flow profiles of right and left pulmonary arteries in these subjects which can be interpreted into more or less equal perfusion for both vascular beds. As mentioned before, just a small truncated portion of real human left pulmonary vasculature has been used for modeling particle transport and deposition. Thus, the appropriate inlet velocity is carefully calculated using experimentally measured cardiac flow to left pulmonary artery and morphometric data of human pulmonary vasculature [30]. The approximate diameter and the number of vessels in every generation can be extracted from this data set. Based on inlet surface area, the appropriate number of vessels in the first generation of our model structure can be interpolated. Subsequently, the inlet flow rate into our reference geometry can be calculated. In order to utilize experimentally measured flow rate data points in our simulation, least square method is utilized to determine the coefficients of Fourier series expansion. Moreover, the fully developed flow assumption is used for the inlet velocity in order to eradicate unrealistic effect of developing region on simulation results. Thus, inlet profile has a parabolic outline which its amplitude changes with time during cardiac cycle as shown in Fig. 3.

Outlet Boundary Condition. Using Strahler's ordering system [31], Kassab et al. [32] defined every vessel between two successive bifurcation points as a segment. Moreover, they identified vascular element as a set of segments of the same order connected in series from the inlet to the outlet of the arterial tree. The segment length is the distance between bifurcation points. The diameter of an element was computed as the average of the diameters of the segments that make up the element. Similarly, the length of an element was obtained by adding up the lengths of the segments within that specific element. Moreover, Huang et al. [33], in their morphometric study of human pulmonary arteries, introduced a matrix that characterizes the connectivity of lung arteries. In this matrix, $C(m,n)$ is the ratio of the number of order m elements, evolving directly from order n elements, to the total number of order n elements. This connectivity matrix and statistical data set were derived for a human left pulmonary vasculature.

Fig. 3 Instantaneous inlet velocity profile estimated from experimentally measured data [30] for left and right pulmonary arteries (LPA and RPA). 0.1 m/s is approximately the average of LPA flow which occurs at 0.1 s and 0.45 s during cardiac cycle.

Table 2 Binding probability parameters

Parameters	Value
m_r	$10^{14}/\text{m}^2$
λ	10^{-10} m
k_B	$1.38 \times 10^{-23} \text{ m}^2 \text{ kg/s}^2 \text{ K}$
T	300 K
h_0	10^{-8}
δ_{eq}	5×10^{-9}

Furthermore, flow circuits can be built of elements because segments are already connected in series. Thus, we can develop a code to generate a tree of pulmonary elements using connectivity information of pulmonary elements for deriving the overall resistance at each outlet of our image-based model structure. The smallest vessels in this data set have a diameter of $20\ \mu\text{m}$, slightly larger than capillaries. It should also be mentioned that the outlets of this morphometry-based tree, the order one elements, were modeled as emptying into a reservoir with zero relative pressure. Furthermore, the dynamic viscosity was set to 0.04 poise except in vessels of order 1, 2, and 3, where the values were assumed to be 0.025, 0.03, and 0.035 poise, respectively, to account for the reduced apparent viscosity in lumens with small diameters [34]. Finally, the overall resistances at the beginning of every generation have been calculated. Thus, during CFD solving procedure, the outlet pressure will be updated every iteration using volumetric outflow and downstream calculated resistance, following a similar methodology as described in Ref. [26]. Here, in our model, generation orders of downstream vessels may vary from 8 to 12. Readers can find more details about CFD and particle tracking equations and methods in the Appendix.

3 Results and Discussion

In the following, the fluid field and its main features in original geometry are illustrated at first. Then, the results of CFPD simulation for steady and unsteady state flow rates in lung vasculature are discussed in details. Furthermore, an extensive mesh study is performed to investigate the independency of results with respect to mesh size. The results of this part are presented in the Appendix. The significance of surface imperfections is also studied using original, oversmoothed and artificial geometries, as shown Figs. 1(a), 1(c), and 1(d). It should also be mentioned that the entrance effect was carefully minimized by making use of flow extensions and fully developed inlet flow profile. Furthermore, all deposition fraction data have been normalized with respect to their target surface area.

3.1 Velocity Field. To visualize the flow field in this subunit of lung vasculature, velocity contour alongside some of its streamlines are demonstrated in an arbitrary cross section of truncated model in Fig. 4. Moreover, shear stress on vessel wall, which is a good measure of dislodging force exerted on the bound particles, is also shown in Fig. 5. These figures are plotted out for steady flow condition and at two different times of pulsatile flow case. The flow rate of pulsatile case at 0.1 s is increasing in the medium and reversely it is decreasing at 0.45 s, as shown in Figs. 4(b) and 4(c), respectively. Comparing steady and unsteady case, it can be concluded that fluid mixing is considerably enhanced due to presence of stronger vortices in pulsatile flow. The streamlines in Fig. 4 can give a qualitative presentation of vortices exist in the cross section of realistic geometry. Furthermore, it is observed that the shear stress distribution varies with flow regimes. But generally, shear stress is lowest in surface imperfections. Some of these imperfections are branching out sites of vessels with some order of generation lower than their parents and exist due to resolution limitation of imaging devices in capturing these small vessels. Neglecting them will pose a practical problem since smoothing them out can change flow pattern and accordingly it can affect deposition pattern in our patient-specific vasculature model [26]. Flow stream at 0.1 s with instantaneous 0.1 m/s inlet flow generally has higher shear stress than its equivalent steady case. On the contrary, for pulsatile flow case at $t = 0.45\ \text{s}$, the shear stress is considerably higher in bifurcation regions, but it is lower in other locations in comparison with steady condition case due to presence of vortices after bifurcating regions, refer to Figs. 4 and 5. It is expected that such nonuniform shear force distribution will likely influence particle binding pattern.

Fig. 4 Velocity contours and selected streamlines in a planar slice of original geometry in (a) steady flow case with 0.1 m/s inlet velocity and in (b), and (c) pulsatile flow case at $t = 0.1\ \text{s}$ and $t = 0.45\ \text{s}$ with 0.1 m/s instantaneous inlet velocity (refer to Fig. 6), respectively

3.2 Particle Transport and Deposition

Constant Flow Rate. Two million particles with different sizes have been injected into original geometry. The steady inlet velocities are chosen within physiological range of 0.05–0.2 m/s. Deposition fraction profiles versus particle diameter are demonstrated in Figs. 6(a) and 6(b) in two different ranges of particle diameters. As observed in Fig. 6(a), under inlet velocity of 0.15 m/s, particles have slightly higher deposition fraction in majority of sizes comparing. Under higher flow rates, particles will not have enough time to bind and may dislodge more easily. Under lower inlet velocities, fluid mixing and accordingly particle dispersion is poor for particle bigger than 30 nm. Thus, particle dispersion and accordingly binding rate is optimum at 0.15 m/s in this truncated model. Furthermore, since diffusion is the dominant driving force for small size particles in low flow rate regimes, particles with diameters less than 20 nm have the highest deposition percentage for 0.05 m/s inlet velocity case, as shown in Fig. 6(a). As mentioned before, the particle binding probability decreases by increasing shear stress and particle size. As expected, it is

Fig. 5 Demonstration of shear stress on the vessel wall in (a) steady flow case with 0.1 m/s inlet velocity and pulsatile flow case at $t = 0.1$ s, (b) and $t = 0.45$ s, and (c) with 0.1 m/s instantaneous inlet velocity

observed from Fig. 6(b) that the binding fraction gradually decreases as particle diameter increases. Furthermore, this decrease is also intensified by increasing luminal flow rate due to exponential reduction rate of binding probability by shear rate.

To investigate the effect of fluid flow field on particle binding pattern, particle deposition fraction has been studied in original, oversmoothed and artificial Weibel geometry under a steady state flow velocity of 0.15 m/s. As shown in Fig. 7, the percentage of bound particles is lowest for Weibel geometry and highest for original geometry. Due to better fluid mixing in truncated model, streamlines that start at the central regions of the inlet surface (accordingly particles carried by them) have a higher chance to get closer to the vessel's wall and deposit. In other words, streamlines are more disturbed and particle dispersion rate is higher in realistic vasculature. Thus, the deposition fraction is also influenced by surface smoothness.

Pulsatile Flow Rate. In reality, the cardiac flow in human lung vasculature is pulsatile. Thus, to have a more realistic CFPD modeling, ten million particles with diameters ranging from 1 nm to $3\ \mu\text{m}$ with uniform distribution are released into the original geometry under realistic flow rate described in Fig. 3. The result of the deposition fraction of particles in various diameters is depicted in the Figs. 8(a) and 8(b) in two distinct extents of particle size. Moreover, binding profiles of particles under steady flow condition is also added for comparison purposes. It should be noted that the average inlet velocity during cardiac cycle is approximately 0.1 m/s, which is chosen for the steady case. As shown in Fig. 8(a), for smaller particles, binding percentage is significantly higher when particles are released in pulsatile flow stream because the fluid mixing can be considerably enhanced by unsteady flows. However, as diameter increases, particles deposition fraction significantly decreases. Bigger particles experience larger detachment force during peak velocity time period and

Fig. 6 Particle deposition fraction at two different ranges of particle sizes under various steady flow rates (a) 1 to 100 nm and (b) 1 nm to $3\ \mu\text{m}$

accordingly can be easily dislodged from vessel's wall. Consequently, they will have lower chance of binding successfully.

Previously, it has been shown that the artificial geometry has the lowest binding fraction in steady flow condition. But it changes when pulsatile inlet flow condition is applied. It can be observed from Fig. 9 that original geometry has the higher deposition rate than oversmoothed and artificial geometries. Furthermore, deposition fraction of particles with diameter less than 20 nm is higher for oversmoothed geometry in comparison with artificial geometry results. But for bigger particles, artificial geometry has slightly higher binding rate.

Cumulative profiles of particle deposition with respect to time are demonstrated in Fig. 10(a) for different simulations in which two million particles with diameters ranging from 1 nm to $0.5\ \mu\text{m}$ are released in original geometry. It is worthy to mention that particles are injected at 0.2 s, peak of cardiac inlet velocity, for all pulsatile cases in order to make sure the numerical solution for fluid field is converged and stable. All profiles are normalized with respect to the total number of deposited particles. Comparing

Fig. 7 Study of streamline disturbance effect on particle deposition fraction using original, oversmoothed and artificial geometry with the same inlet flow rate

Fig. 8 Particle deposition fraction for particles of different sizes under steady and pulsatile blood flow. It is demonstrated at two different particle diameter ranges (a) 1 to 100 nm and (b) 1 nm to 3 μm .

Fig. 9 Effect of vessel surface smoothness on particle deposition fraction under pulsatile flow condition

results of steady cases, the deposition process finishes faster under higher inlet velocities. The reason is that particles would leave the lung vasculature sooner in higher velocities. Thus, there will not be any particle depositing on vessel wall after a certain period of time, see Fig. 10(a).

The blood traveling time through truncated model is approximately same for pulsatile flow and 0.1 m/s steady velocity. But as depicted in Fig. 10(a), particles bind much faster in pulsatile flow even though they have 0.2 s lag in their injection time. Moreover, it is observed that particles deposit faster in artificial geometry since there does not exist many vortices to trap drug carriers [35].

Furthermore, the instantaneous binding pattern of deposited particles is analyzed, see Fig. 10(b). The instantaneous number of particles deposited in each time interval for realistic cardiac flow in different geometries is derived and shown in Fig. 10(b). By over smoothing luminal surface imperfections, we will not be able to observe periodic particle binding pattern anymore. This feature is amplified for artificial model structure in which a peak of

Fig. 10 Illustrations of deposition profile versus time for various simulation parameters. (a) Accumulative profiles of particle binding under different flow conditions and geometries (b) instantaneous deposition profile of cardiac flow in geometries with different surface smoothness.

instantaneous deposition just happens at the second pulsatile cycle.

Deposition Pattern. To better understand the particle deposition pattern, the deposited location of particles is shown in three dimensions for original and artificial geometries in Fig. 11. It is observed that the particle deposition density is higher near bifurcation sections of the vasculature network which is also reported by Nowak et al. for lung airway [12]. It should be noted that faulty entrance effect was carefully treated for both cases. Returning to Fig. 4, streamlines in the cross section of the truncated model shows that vortices are the prominent feature of unsteady flow and it is an influential factor in increasing the number of wall-particle contacts. In the original model, more particles will deposit at the entrance region because small particles with much higher diffusivity rapidly trap on the wall. As it can be seen from Fig. 11(b), the bifurcation regions of artificial geometry are also have higher deposition density, but not as significant as the ones in the original geometry.

For studying whether particle sizes will influence topographical distribution pattern, the number of deposited particles have been normalized with respect to their target vasculature surface area as well as total number of deposited particles within that diameter

Fig. 11 3D demonstration of deposition pattern when releasing two million particles with diameters ranging from 1 nm to $0.5\mu\text{m}$ under pulsatile inlet flow in (a) original lung vascular geometry and (b) artificial Weibel geometry

Fig. 12 Normalized deposited number of particles with different diameter ranges deposited on various regions of the original geometry

range, see Fig. 12. Large number of particles especially smaller ones deposit in the first generation. This happens because particles released close to wall, rapidly diffuse and deposit on wall. In general, normalized binding is higher in bifurcation regions in comparison with luminal sections. Moreover, deposition density at branching sites also increases with generation order. But in contrast to particle deposition in respiratory system [7] in which a specific correlation can be found between the size of particle and the generation order, no clear correlation is observed in lung vasculature using our truncated realistic model.

Particle distribution pattern over time is also shown in Fig. 13. At early stages of particle injection into blood stream, majority of particles are first trapped at bifurcation sites. As time goes by, those particles trapped in vortices and subsequently are close to vessel wall would also have the chance to diffuse and deposit on

Fig. 13 3D representation for trapped location of injected particles at different times (a) 1 s, (b) 2 s, and (c) 8 s after starting the simulation with cardiac inlet flow

Fig. 14 Normalized deposited number on a bifurcating region of vasculature coated with different anti-ICAM densities for different particle sizes

the luminal sections as well. In these regions, the shear rate is also much lower which also act in favor of particles entrapment.

Changes in particle and vascular wall's physical properties largely influences total deposition fraction. Thus, a simple

sensitivity analysis to model parameter is carried out in this study. For instance, the effect of vascular receptor density on total binding density for various particle sizes is studied and accordingly demonstrated in Fig. 14. Increased Anti-InterCellular Adhesion Molecule (ICAM) density enhances probability of particle adhesion which ultimately lead to higher binding density. It is observed that the binding density of bigger particles increases much more when m_r rise.

4 Conclusion

The flow field was solved in a realistic subunit of the pulmonary vasculature with a fully developed physiological profile as the inlet velocity. Subsequently, particles were tracked in a discrete phase by integrating the force balance on them. Moreover, a resistance based formulation for outlet boundary condition and a ligand–receptor model for particle binding probability were integrated in our simulations. Utilizing a developed multiscale approach, particle delivery to the lung vasculature was studied in detail.

The following conclusions can be drawn from our CFPD simulations:

- (1) Using realistic cardiac flow and studying particle binding patterns in unsteady flow, it was found that pulsatility enhances the deposition rate. Moreover, larger particles have lower deposition fraction because of more dominant effect of the dislodging force on them.
- (2) Cumulative and instantaneous deposition profiles show how binding pattern is influenced by pulsatility. In the original geometry, the deposition rate is higher when the flow rate is maximum during the cardiac cycle but such patterns are not found in other geometries.
- (3) Regional deposition patterns demonstrated that bifurcations are the critical sites for particle binding and as blood flows into lower generations, the deposition density increases.
- (4) It was shown that in unsteady flow, the particles bind sooner at bifurcations in comparison with the luminal sections on which particles needs more time to deposit. Moreover, no clear correlation was found between the generation order and particle size.

The effect of blood flow pulsatility on particle transport and deposition is the most important outcome of the current study. Cardiac flow is significantly influential in drug delivery for the vessels in the proximal generations of the hierarchical vascular tree. Moreover, it was illustrated that using the original geometry in numerical modeling leads to results with improved physiological relevance. It should be pointed out that our numerical setup to-date cannot actually simulate drug particle entrapment at the capillary level. Since larger particles have lower deposition fraction on the larger vessel walls, it might be consistent with this known challenge that larger particles travel downstream might have an increased chance of lodging in the capillaries.

In summary, this original research represents a better understanding of drug delivery in the human lung vasculature and paves the way toward prediction of particle delivery efficacy and distribution in the lung vasculature. In future studies, after simulating deposition efficiency of particles in a geometry reconstructed from clinical image segmentation, it will be valuable to track drug agents in distal generations down to the capillary level. If a full scale model of the lung vasculature can be built, the full process of pulmonary injection can be modeled and drug delivery efficiency can be predicted.

Acknowledgment

The authors acknowledge the supports of this work from National Science Foundation (NSF) CAREER grant CBET-1113040, NSF CBET-1067502, and National Institutes of Health (NIH) grant EB015105.

Appendix

1.1 Governing Equations

1.1.1 Fluid Flow. In general, blood flow in tapered elastic vessels which connected in a branching network is a pulsatile flow. The fluid is non-Newtonian. Computational fluid dynamics, which requires solving the Navier–Stokes equation, together with appropriate non-Newtonian constitutive relations for blood should be used. It also needs to be coupled with the dynamics of the compliant vessels through which blood flows. But for large arteries, blood can usually be modeled as incompressible and Newtonian [36].

In this study, blood flow is assumed to be laminar and Newtonian. The maximum Re number in our numerical setup is 400 assuming maximum diameter and velocity of 0.6 cm and 0.2 m/s, respectively. A commercial finite-volume-based CFD solve, FLUENT 14.5.0 (ANSYS Inc.) was used for flow and particle tracking simulation. The blood flow is governed by the momentum conservation equation and mass conservation equation.

$$\frac{\partial}{\partial t}(\rho \mathbf{v}) + \nabla \cdot (\rho \mathbf{v} \mathbf{v}) = -\nabla p + \nabla \cdot (\boldsymbol{\tau}) + \rho \mathbf{g} + \mathbf{F} \quad (\text{A1})$$

where p is the static pressure, $\boldsymbol{\tau}$ is the stress tensor (described below), $\mathbf{g}$ and $\mathbf{F}$ are the gravitational body force and external force, respectively.

The stress tensor $\boldsymbol{\tau}$ is given by

$$\boldsymbol{\tau} = \mu \left[(\nabla \mathbf{v} + \nabla \mathbf{v}^T) - \frac{2}{3} \nabla \cdot \mathbf{v} \mathbf{I} \right] \quad (\text{A2})$$

where μ is the molecular viscosity, $\mathbf{I}$ is the unit tensor, and the second term on the right hand side is the effect of volume dilation.

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0 \quad (\text{A3})$$

Equation (A3) is the general form of the continuity equation which is valid for incompressible as well as compressible flows. All the blood properties used in this study are summarized in Table 3.

1.1.2 Particle Transport. Trajectories of discrete phase particles are predicted by integrating the force balance on the particle, which is written in a Lagrangian reference frame. This force balance equates the particle inertia with the forces acting on the particle, and can be expressed as

$$\frac{d\mathbf{u}_p}{dt} = F_D(\mathbf{u} - \mathbf{u}_p) + \frac{\mathbf{g}(\rho_p - \rho)}{\rho_p} + \mathbf{F} \quad (\text{A4})$$

where $\mathbf{u}$ is the fluid phase velocity, $\mathbf{u}_p$ is the particle velocity, ρ is the fluid density, ρ_p is the density of the particle, $\mathbf{F}$ is an additional acceleration term, $F_D(\mathbf{u} - \mathbf{u}_p)$ is the drag force per unit particle mass and

$$F_D = \frac{18\mu}{\rho_p d_p^2 C_c} \quad (\text{A5})$$

Table 3 Blood properties

Properties	Value
Density	1060 kg/m ³
Viscosity	0.003 Pas
Thermal conductivity	0.52 W/m deg C

Here, d_p is the particle diameter, μ is the molecular viscosity of the fluid, C_c is the Cunningham correction factor, which will be mentioned later.

For submicron or smaller particles, the effects of Brownian motion should be considered. In FLUENT, this effect can be expressed in the additional force term and modeled as a Gaussian white noise process with spectral intensity $S_{n,ij}$ given by

$$S_{n,ij} = S_0 \delta_{ij} \quad (A6)$$

where δ_{ij} is the Kronecker delta function, and

$$S_0 = \frac{216\nu k_B T}{\pi^2 \rho d_p^5 \left(\frac{\rho_p}{\rho}\right)^2 C_c} \quad (A7)$$

where T is the absolute temperature of the fluid, ν is the kinematic viscosity, C_c is the Cunningham correction (defined in Eq. (A8)), and k_B is the Boltzmann constant.

$$C_c = 1 + \frac{2\lambda}{d_p} (1.257 + 0.4e^{-(1.1d_p/2\lambda)}) \quad (A8)$$

For water and ethylene glycol, the values of molecular mean free path is 0.278 and 0.26 nm, respectively. Therefore, for the nanoparticles in range of interest (1–100 nm), the Knudsen number is relatively small compared to water and similar fluids ($Kn < 0.3$); thus, the assumption of continuum for blood surrounding the particles is reasonable. Accordingly, the C_c is set to be one in this study [37].

Amplitudes of the Brownian force components are of the form

$$F_{b_i} = \zeta_i \sqrt{\frac{\pi S_0}{\Delta t}} \quad (A9)$$

where ζ_i are zero-mean, unit-variance-independent Gaussian random number, and Δt is the calculation time step. The amplitudes of the Brownian force components are evaluated at each time step of simulation.

Also, for submicron particles, the Saffman's lift force is recommended to be included in the addition force term. The generalized expression of Saffman's lift force is

$$\mathbf{F} = \frac{2K\nu^{1/2}\rho d_{ij}}{\rho_p d_p (d_{ik}d_{kl})} (\mathbf{v} - \mathbf{v}_p) \quad (A10)$$

where $K = 2.594$ and d_{ij} is the deformation tensor.

In this study, it is assumed that the density of particle (ρ_p) is the same as density of blood (ρ). Particles are injected with the same time step as the calculation time step of flow from the inlet. The particle initial position is also random allocated at the inlet. Trapezoidal and implicit tracking schemes are chosen for higher and lower order numerical tracking schemes, respectively. Tolerance of relative error is set to 10^{-5} , and the maximum number of integration step is 10^6 .

2.1 Mesh Study. In this study, the fluid mesh was generated with ICEM-CFD. In order to get a better numerical solution of flow field near vessel wall and accordingly track particles more accurately, a very fine mesh is employed near vessel boundaries. To reduce the computation cost, a nonuniform mesh is applied as shown in Fig. 15. In this mesh model, element size at center is larger than that near the boundary. Delaunay mesh method is adopted and two prism layers are created near the boundary. The prism layer's initial height is 0.02 mm, following an exponential

Fig. 15 Mesh models over a cross section of a lung geometry. Mesh size is large in the middle and small near boundary. The minimum mesh size limits are 0.2, 0.15, 0.125, and 0.1 mm for (a), (b), (c), and (d) cases, respectively.

growth with a height ratio of 1.2. The final mesh features about nine million elements. Typical run times for the fluid flow and particles delivery simulation on a 20 processors workstation with parallel algorithm was approximately 10–20 h.

To study the independency of results with respect to mesh size, models with different mesh sizes have been used under the same flow and binding boundary conditions. Mesh elements in an arbitrary cross section of model structure is demonstrated for four different element sizes as shown in Fig. 15.

Our investigation shows that using the fourth mesh size, fluid field results are independent of elements size (data not shown for brevity). The number of deposited particle versus the number of mesh elements is plotted out in Fig. 16 and it shows that particle tracking in the original geometry are reasonably independent of mesh size after decreasing element size near wall by twice. Furthermore, deposition fractions for particles of various diameters

Fig. 16 Total number of deposited particle versus number of elements in different mesh models

Fig. 17 Mesh analysis using elements of four different sizes for (a) steady inlet flow and (b) unsteady inlet flow

Fig. 18 Mesh model of lung vasculature has been split into different regions. Gen: generation; Bif: bifurcation.

for steady and unsteady cases are also shown in Figs. 17(a) and 17(b), respectively. It is observed that under the realistic inflow condition, the particle deposition fraction basically does not significantly change for particles bigger than 125 nm.

Moreover, to examine deposition fractions of particles in different sections, the vascular network is divided into different regions, as shown in Fig. 18. Each color represents different regions of the lung vasculature, as labeled in Fig. 18.

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