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Nanoparticle transport and delivery in a heterogeneous pulmonary vasculature

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ABSTRACT

Quantitative understanding of nanoparticles delivery in a complex vascular networks is very challenging because it involves interplay of transport, hydrodynamic force, and multivalent interactions across different scales. Heterogeneous pulmonary network includes up to 16 generations of vessels in its arterial tree. Modeling the complete pulmonary vascular system in 3D is computationally unrealistic. To save computational cost, a model reconstructed from MRI scanned images is cut into an arbitrary pathway consisting of the upper 4-generations. The remaining generations are represented by an artificially rebuilt pathway. Physiological data such as branch information and connectivity matrix are used for geometry reconstruction. A lumped model is used to model the flow resistance of the branches that are cut off from the truncated pathway. Moreover, since the nanoparticle binding process is stochastic in nature, a binding probability function is used to simplify the carrier attachment and detachment processes. The stitched realistic and artificial geometries coupled with the lumped model at the unresolved outlets are used to resolve the flow field within the truncated arterial tree. Then, the biodistribution of 200 nm, 700 nm and 2 μm particles at different vessel generations is studied. At the end, 0.2–0.5% nanocarrier deposition is predicted during one time passage of drug carriers through pulmonary vascular tree. Our truncated approach enabled us to efficiently model hemodynamics and accordingly particle distribution in a complex 3D vasculature providing a simple, yet efficient predictive tool to study drug delivery at organ level.

1. Introduction

Nanoparticles have been widely studied as potential multifunctional carrier platforms for therapeutic drug delivery and imaging applications (Farokhzad and Langer, 2006; Roney et al., 2005; Zhou et al., 2016). Nanoparticles (NPs) need to be delivered directly to the desired tissues while minimizing deposition/uptake by other tissues. To evaluate delivery efficacy to target region and assess damage to healthy tissues, the distribution and concentration of deposited NPs along the vascular pathway is needed. Nanoparticle targeted delivery in a vascular system involves interplay of transport, hydrodynamic force, and multivalent interactions with targeted biosurfaces. The biodistribution of drug carriers in a vascular network depends on many parameters such as particle size, vascular geometry, and local flow conditions (Sohrabi et al., 2014). For instance, several studies have demonstrated that particle binding is inversely correlated with shear rates (Lin et al., 2010; Blackwell et al., 2001).

Various nanomedicine and drug administration methods have been developed for treating and diagnosing lung diseases such as lung cancer, tuberculosis, cystic fibrosis. Therapeutic or diagnostic compounds enter the lung mainly in two ways: intravenous injection and inhalational delivery (De Jong et al., 2008; Santra et al., 2005; Fabian et al., 2008; Videira et al., 2002; Pandey and Khuller, 2005). While there have been extensive studies on the NP transport during inhalational delivery (Schroeter et al., 2012; Zhang et al., 2005; Kleinstreuer and Zhang, 2003), little has been done on NP transport in pulmonary circulation. In fact, pulmonary circulation is involved in the distribution and uptake of not only intravenously injected but also inhaled drugs since pulmonary circulation could be one of the primary vascular targets of NPs that

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penetrate into the lungs after inhalation. It is thus important to develop a tool for evaluation of vascular NP delivery in lung, which has a high translational impact on pulmonary therapeutics.

Lung vasculature tree is highly branched and complex in morphometry (Tawhai et al., 2006). Some Vessels feed the lobes and others provide blood to the individual alveoli (Yang et al., 2010). The structure and function of lung are intimately related (Burrowes et al., 2008). Many mathematical models have been developed to incorporate actual branching pattern of pulmonary tree to better understand heterogeneous network hemodynamic (Karau et al., 2001; Molthen et al., 2004; Krenz and Dawson, 2003; Spilker et al., 2007). Studies focusing on pulmonary blood flow have emphasized the role of vessel branching pattern on flow and pressure distribution within the arterial tree (Burrowes et al., 2005a; Tawhai et al., 2011). Assuming rigid vessels, Burrowes et al. (2005a) used imaging data, volume-filling branching algorithm (VFB) (Burrowes et al., 2005b; Tawhai et al., 2000) and 1D linear finite element method to relate the structure to the function of left lung vasculature. Yang et al. (2010) compared individual representations of vascular trees to propose a statistically meaningful branching pattern for lung and placenta. Introducing tapering principal pathway as observed in rat tomography X-rays (Karau et al., 2001); Dawson et al. (1999) studied the heterogeneity of pulmonary blood flow using concepts related to fractal-like structures, e.g. self-consistency. In self-consistent tree (Boxt et al., 1994), the structure of all side branches off main pathway can be assumed to be statistically indistinguishable from their corresponding sub-regions in the principal trunk.

Numerical models have been extensively used to study drug particle behavior in blood flow. Computational fluid-particle dynamic (CFPD) simulation provides an attractive way to study the particle delivery in a complex geometry model (Marsden et al., 2007; Oakes et al., 2013; Liu et al., 2012; Wang et al., 2014). Gentile et al. (2008) investigated the effect of vessel permeability and blood rheology on the transport of nanoparticles. Longest and Kleinstreuer (2003) simulated the blood particle deposition process in a non-parallel flow. Sohrabi et al. (2014) quantified the transport and adhesion of drug particles in a 4 generation vascular model. However, there has been no attempt in literature to quantify distribution of drug particles at an organ level. To accomplish this task, a complete 3D model of vascular network is needed.

Due to the complexity of the lung vascular network, using a full scale model for the whole lung is computationally unrealistic (Zhang et al., 2008). In this study, we propose a novel approach for reconstruction of heterogeneous lung vascular tree from morphometric data. Using this model, we are able to solve blood flow in 3D. The objective is to develop a tool to study drug particle deposition in a whole vascular tree. First, the whole heterogeneous complex network is truncated into a sample pathway beginning from main pulmonary artery and emptying into capillaries. Lumped model (Zhang et al., 2008; Walters and Luke, 2010) at the unresolved boundaries yields a virtual flow geometry that allows acceptable statistical resolution of the flow at all scales for any set of flow conditions. This computationally efficient 3D model is then used to study the transport and adhesion of drug particles where we can quantify drug delivery in a heterogeneous lung vascular network. Since the nanoparticle binding process is stochastic in nature, we have used a binding probability function to account for ligand-receptor dynamics. In what follows, the geometry reconstruction process is explained first, then the model is carefully benchmarked and fluid flow results are discussed in detail. At the end, we showed distribution of drug carrier at various generations of vascular tree and evaluated the percentage of delivered drug load.

2. Method

2.1. Connectivity matrix

The asymmetry feature of vasculature considerably influences hemodynamics and subsequently stress distribution to which the vessel walls were exposed in reality (Huang et al., 1996). In lung vasculature, every vessel between two bifurcation points is described as a segment and the combination of those vessels with the same order connected in series are defined as an element. The statistical average length and diameter of elements are listed in Table 1 (Huang et al., 1996). In a heterogeneous tree, blood vessels of order n not only originate from vessels of order $n-1$ but also branch off vessels of order n, $n-2$ and $n-3$. Connectivity matrix (CM) proposed by Kassab et al. (1993) quantitatively describes the branching pattern of lung vasculature. Table 2 demonstrates the connectivity matrix of pulmonary arteries of a human left lung. Each entry indicates the ratio of the total number of elements of order m (which expands from a parent element of order n) divided by total number of elements of order n. CM can also be used to calculate the total number of elements of order m using $N_m = \sum_{n=m}^{k} C(m,n)N_n$ as shown in Table 1.

2.2. Realistic vessel geometry

A MRI[1] based DICOM[2] image of a healthy, adult human lung vasculature was obtained retrospectively from a clinical research study at UPMC[3]. Since modeling the blood flow in a full vasculature tree is extremely challenging, we propose to trim the network tree into an arbitrary pathway as shown in Fig. 1a. The cut realistic geometry comprises of upper four generations of arterial tree and 18 truncated daughter segments. The summation of entries in every column of connectivity matrix, shown in Table 2, can roughly represents the number of vessels originated from a parent element. In our case, the summation of CM entries within the grey region in Table 2 adds up ~17.4 which is approximately equal to 18, the number of daughter segments in our truncated realistic geometry, as shown in Fig. 1a.

2.3. Artificial vessel geometry

Examination of the MRI-images shows that the vessels smaller than generation 12 do not have an acceptable image precision. The inaccuracies are generally caused by scanning resolution limitations or patient's movement during the scanning procedure. To reconstruct a full scale model of lung vasculature, the truncated realistic pathway is extended by an artificial substitute model down to capillaries. Starting from generation 12, we have constructed a substitute pathway using the pulmonary morphometric data by Huang et al. (1996). Since the entries in CM are not integers, we need to round them up/down for geometry reconstruction. Moreover, segment-to-element ratio ($\alpha = N_S/N_E$) represents the number of daughter branching sites in parent elements which is also needed to be rounded.

In Table 2, the integer numbers in parentheses characterize the exact configuration of our substitute network as shown Fig. 1b. Every parent element is divided into segments separated by internal nodes. Generally, the two largest daughter vessels branch out from the last node of parent element. The rest were connected to the interior nodes such that the larger daughters were closer to the element inlet. The branching daughters that branch out from main truck are cut by their segment length. The reconstructed pathway has two triple bifurcations and all branching angles were assumed to be 60°. The smallest vessel is 20 μm in diameter, slightly larger than capillaries.

The artificial truncated model is reconstructed as shown in Fig. 1b. It should be noted that some elements even originate from the vessels with the same order, e.g. generations 8, 5 and 4. The total number of cut daughter vessels in the proposed pathway is approximately equal to the summation of all CM entries. Furthermore, we virtually expanded the truncated branches of our artificial model to calculate the total number of vessels in every generation. It is shown that it agrees well with listed morphometric data (Huang et al., 1996) in Table 1. At the end, stitching truncated realistic and artificial geometries, a sample pathway representing whole pulmonary arterial tree is reconstructed. Generations 15 and 1 have two orders of magnitude size difference. Dividing the whole geometry into separate sections, we are able to attribute different computational mesh settings to each region. More detail information about mesh generation can be found in Supplementary information.

2.4. Boundary condition

The average blood flow to main pulmonary artery (MPA) of a normal subject is 3.4 l/min (Henk et al., 1998). It corresponds to average inlet velocity of 0.135 m/s to

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