Modeling airflow and particle transport/deposition in pulmonary airways

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A review of research papers is presented, pertinent to computer modeling of airflow as well as nano- and micron-size particle deposition in pulmonary airway replicas. The key modeling steps are outlined, including construction of suitable airway geometries, mathematical description of the air-particle transport phenomena and computer simulation of micron and nanoparticle depositions. Specifically, diffusion-dominated nanomaterial deposits on airway surfaces much more uniformly than micron particles of the same material. This may imply different toxicity effects. Due to impaction and secondary flows, micron particles tend to accumulate around the carinal ridges and to form “hot spots”, i.e., locally high concentrations which may lead to tumor developments. Inhaled particles in the size range of \(20 \text{ nm} \leq d_p \leq 3 \mu \text{m} \) may readily reach the deeper lung region. Concerning inhaled therapeutic particles, optimal parameters for mechanical drug-aerosol targeting of predetermined lung areas can be computed, given representative pulmonary airways.

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1. Introduction and overview

Experimental and computational modeling of biomechanics of the human respiratory system is quite challenging because of the complex airway geometries, three-phase flow phenomena, fluid-structure interactions, and species mass transfer. Of basic concern is the understanding and achievement of \(O_2-CO_2\) gas exchange under normal and pathological conditions. Modeling applications include: (i) dosimetry-and-health effects of inhaled toxic particulate matter, of interest to toxicologists, health-care providers and regulators and (ii) optimal drug-aerosol targeting to predetermined sites to combat lung and systemic diseases. Clearly, the biomechanics phenomena occurring in a complete set of realistic pulmonary airways cannot yet be simulated alone for every patient. However, based on CT-scans and MRI as well as benchmark experimental data sets, detailed computer simulations can be performed at least for representative airway segments. In addition, “global lung” models in terms of simple semi-empirical correlations have provided surprisingly accurate deposition efficiencies for a wide range of (spherical) particle diameters.

With the advent of petascale (10\(^{15}\) calculations/s) computing, future simulation results will cover the most important biomechanics phenomena in actual human airways and provide solutions to the patient-specific drug-aerosol targeting problem.

1.1. Toxic particulate matter inhalation

Toxic material in vapor, liquid droplet and solid particle forms is being inhaled, as it appears indoors or outdoors in all shapes and sizes, typically ranging from nanometers (10\(^{-9}\) m) to micrometers (10\(^{-6}\) m). Most severely affected by polluted air may be the children and the elderly. Given any set of ambient conditions in terms of pollutant concentration, temperature and humidity, it is of interest to predict how much deposits where in the human respiratory tract under realistic breathing conditions. Such results, usually obtained via experimentally validated computer simulations, are of great interest to toxicologists, epidemiologists, health-care providers, and regulators of air pollution standards. Toxic material dynamics is described in two size-dependent categories; because the transport mechanism for nanomaterial is diffusion dominant while micron particles are impaction and possibly gravitation dominant. Hence, nanoparticles, which include some vapors, are modeled with a mass transfer equation and micron particles with Newton’s second law of motion (Kleinstreuer, 2006).
1.1. Toxic nanomaterial

Nanotechnology and related manufacture of nano-scale materials are major growth industries (Roco, 2006). Clearly at the stages of nanomaterial production, handling and use, nanoparticles become airborne and inhaled (Service, 2003; Theodore and Kunz, 2005; among others). Hence, the specter of serious health problems arise from inhalation of such (toxic) metal, metal-oxide, carbon-based and synthetic nanomaterials (Oberdörster et al., 2005; Kumar, 2006; among others). After nanoparticle inhalation, tissue absorption and transport to extra-pulmonary organs, nanomaterial may target the central nervous system and immune system (Bang and Murr, 2002; Oberdörster et al., 2005). It is not just the level of toxicity of some nanomaterials which poses potential respiratory and other health risks; but, also their size, shape and surface distribution which turns out to be even more toxic than inhaled micron particles of the same material. Also, other toxins could bind with nanoparticles and piggyback their way into the body. In summary, the enhanced toxicity of nanomaterial can be attributed to (i) the greater surface reactivity of nanoparticles due to high curvatures as well as the larger surface area relative to the nanoparticle mass; (ii) the prolonged retention time and decreasing fraction of clearance for ultrafine particles; (iii) an almost uniform coating of the airway surfaces by nanoparticles; (iv) larger deposition fractions (DF) of nanomaterial in deeper parts of the lung, including the alveolar region.

So far, there are relatively few investigations of (spherical) nanoparticle deposition in the human airways, primarily because of the difficulty of nanoparticle generation for experimental measurements and accurate predictions with computational fluid-particle dynamics (CFPD) simulations. In a series of papers, Cheng et al. (1988, 1995, 1996, 1997a,b) and Smith et al. (2001) published their measurements of mass transfer and deposition of nanoparticles (3.6 nm < \( d_p < 150 \) nm) in casts of human nasal, oral and upper tracheobronchial (TB) airways; Cohen et al. (1990) reported their experimental work on nanoparticle deposition in an upper tracheobronchial airway cast; (Kelly et al., 2004b) measured the nasal deposition efficiencies of nanoparticles with diameter between 5 and 150 nm; Daigle et al. (2003) and Kim and Jaques (2004) measured total respiratory tract deposition fraction of nanoparticles (8–100 nm) in healthy adults. Examples of numerical simulations for nanoparticle deposition include Asgharian and Anjilvel (1995), Balashazy and Hofmann (1993, 1995), Yu et al. (1996, 1998), Moskal and Gradon (2002), Hofmann et al. (2003), Kelly et al. (2004b), Zhang and Kleinstreuer (2004), Shi et al. (2006), Zamankhan et al. (2006), and Longest and Xi (2007b).

Almost all theoretical as well as experimental studies describing the diffusional deposition in the tracheobronchial airways assumed uniform or parabolic inlet velocity profiles and particle distributions. However, the actual velocity profiles and particle distributions are quite different from those axisymmetric profiles and distributions due to flow development, secondary flows, and non-uniform particle transport in the upstream airway sections (Kleinstreuer and Zhang, 2003a). In addition, many published numerical simulations were lacking detailed model validations. Recently, the Euler–Euler approach has been validated as an accurate and effective modeling technique for spherical nanoparticle deposition in idealized airway segments (Shi et al., 2004; Zhang and Kleinstreuer, 2004; Zhang et al., 2005). So far, little information is available about modeling of nanoparticle (>100 nm) deposition in the alveolar region. In fact, major nanoparticle deposition may occur in the pulmonary region (e.g., about 20–35% of 40–100 nm particles, see Kim and Jaques, 2004). The low surface tension produced by a surfactant film in the deeper parts of the lung, including the alveolar region, may aid the transfer of nanoparticles through the liquid wall layer (Geiser et al., 2000) so that the toxicity effect of deposited particles in these regions is enhanced. Furthermore, the coupling of fluid flow and alveolar wall movement during expansion/contraction (i.e., fluid–structure interactions) and its effects on particle transport/deposition have rarely been analyzed (Tsuda et al., 1994; Haber et al., 2003; Darquenne and Prisk, 2003; Haber and Tsuda, 2006). Reliable studies of transport and deposition of non-spherical nanoparticles are even less available. Non-spherical particle motion, say, of carbon nanotubes, is much more complicated than that of spherical particles because these particles undergo simultaneous translation, rotation and re-orientation when traveling in shear flow (Brenner and Condiffe, 1972; Bernstein and Shapiro, 1994). Due to the complicated motion of non-spherical particles, most of the existing models for non-spherical particles, such as fiber deposition in human airways, focus on deposition of fibers with diameters in the micro-size range in single airway bifurcation models assuming simple shear flow or simple fiber transport (e.g., Cai and Yu, 1988; Asgharian and Anjilvel, 1995; Zhang et al., 1996; Balashazy et al., 2005).

1.1.2. Toxic micron particles

While the potential health hazards of nanomaterials has only been very recently acknowledged, inhaled micron-particle deposits for dosimetry–and-health-risk assessments have been studied for decades (Heyder, 2004). Clearly, the experimental and computational contributions reviewed deal with spherical micron particles that are completely neutral concerning toxic or therapeutic effects.

For example, Schlesinger et al. (1982), Gurman et al. (1984), and Kim and Garcia (1991) showed that cyclic inhalation generates higher particle deposition efficiencies than steady inhalation at the mean Reynolds number of the inlet flow waveform. Specifically, Gurman et al. (1984) have estimated a 15% increase in inertial impaction with cyclic flows. Kim and Garcia (1991) calculated that the deposition efficiency (DE) should increase by about 23% with sine-wave type flows regardless of the cyclic frequency. Cheng and Wang (1976) measured the deposition of 0.58–2.05 \( \mu \)m aerosols along the airway walls of a second generation under condition of constant and cyclic inspiratory flows for a single mean inspiratory flow rate. Overall deposition was found to be greater under cyclic flow. The maximum increase was 26% above that observed when constant flow at the mean Reynolds number was assumed. Schlesinger et al. (1982) and Gurman et al. (1984) measured the deposition of 3 and 8 \( \mu \)m monodispersed aerosols in replicate casts of the human tracheobronchial tree under conditions of constant and cyclic “inspiratory flows”. Their results also showed that the deposition efficiencies within hollowed airway casts under cyclic flow were greater than those under constant flow assuming the mean flow rate. For a high flow rate (60 L/min), the deposition efficiencies (DEs) increase by about 100% for 8 \( \mu \)m particle and up to 600% for 3 \( \mu \)m particles. However, this marked increase in DE may be attributed to turbulence effects under cyclic flow conditions in their experiments. Kim and Garcia (1991) measured the deposition of micron-sized particles in a single bifurcation model approximately representing generations G3–G4 for cyclic flow at mean Reynolds numbers of 679–5547 and Stokes numbers of 0.028–0.25. Their results showed that the DE with cyclic flow was also higher than that obtained with constant flow. More in vitro experimental studies of micron–particle deposition in tracheobronchial airways focused on steady inhalation in glass or metal casts of the TB tree from one to several bifurcations (see Ferron, 1977; Kim and Iglesias, 1989; Oldham et al., 1997, 2000; Kim and Fisher, 1999; Zhang and Finlay, 2005; among others), or realistic airway replica based on cadavers representing trachea (G0) to generations G3, G4 or G5 (see Schlesinger and Lippmann, 1972; Schlesinger et al., 1977; Zhou and Cheng, 2005; among others).
The deposition efficiencies at each generation were usually measured in these studies for different combinations of particle size and inspiratory flow rate. However, detailed air/particle transport phenomena as well as local deposition patterns and surface densities of deposited particle in bifurcating airways are difficult to obtain experimentally.

Clearly, computational fluid dynamics (CFD) simulation is an effective way to gain such information. Examples of such contributions focusing on tracheobronchial trees, include Comer et al. (2001), Zhang et al. (2002a,2005), Nowak et al. (2003), van Erbruggen et al. (2005), Li et al. (2007a), and Longest and Xi (2007a). So far, most of these studies concentrated on one to several bifurcations of the TB tree. Some of these studies lacked sufficient model validations (e.g., Nowak et al., 2003). Considering the large amount of branches in the lower airways (say, 2^15 for the 16th generation in Weibel's lung model), the direct simulation of particles in the entire tracheononchial airways (say, from G0 to G16) is still impossible. However, petascale computing may allow for rather accurate patient-specific lung modeling in the near future.

1.2. Mechanical drug-aerosol targeting

Inhalation of drug aerosols, typically in the effective diameter range of 3–10 μm, is a standard procedure for treating respiratory ailments, especially chronic obstructive pulmonary diseases (COPD) and asthma. The nasal and oral pathways are now also being used as portals to deliver medicine for pain management and to combat systemic diseases, respectively, where oral inhalation of insulin for diabetes patients is one modern example. However, to be successful and cost-effective, drug-aerosol delivery has to be targeted. Obviously, maximum deposition of suitable therapeutic solid particles (or droplets or vapor) at predetermined sites, which are related to specific diseases, minimizes potential side-effects in case of aggressive drugs and reduces health-care cost with the increased efficacy. “Targeting” is here understood as a mechanical goal to bring drug aerosols from their release points (i.e., the inhaler exit) to a desired landing area in the respiratory system for maximum medical effectiveness. In order to achieve that goal, future inhaler devices have to operate based on a targeting methodology featuring optimal: (i) particle characteristics, (ii) inhalation waveform, (iii) particle-release positions, and (iv) concentration range. This mechanistic approach differs from drug targeting via special design as Cebral and Summers (2004) used CT-scans to construct central airways. Others, mainly focusing on the human upper airways for meshing and subsequently computer simulations, constructed rigid 3D configurations which somewhat represent actual airways for meshing and subsequently computer simulations, constructed rigid 3D configurations which somewhat represent actual airways.

Several aspects of drug-aerosol delivery have been recently reviewed in the books edited by Gradon and Marijnissen (2003) as well as Hickey (2004). The book by Finlay (2001) and the volume edited by Bissgard et al. (2002) also discuss pertinent elements of drug delivery to the lungs. Experimentally validated computer simulations of micron-particle transport and deposition, employing pressurized metered dose inhalers (pMDIs) and a new delivery methodology for optimal drug-aerosol targeting, are discussed by Kleinstreuer et al. (2007a).

2. Geometric models of the oral and pulmonary airways

Accurate and realistic airway models are the necessary pre-cursor for experimental or computational airflow and particle transport/deposition analyses. Once a comprehensive, flexible and experimentally validated computer simulation model has been developed, local and Segmentally averaged concentrations of toxic particles as well as operational parameters for optimal drug-aerosol targeting can be determined. Ultimately, such tasks can be accomplished for individual patients, eliminating the present problem of inter-subject variability.

In any case, the nasal plus oral airways are labeled the extrathoracic region which forms with the tracheobronchial and alveolar regions the respiratory system. From a functional viewpoint, the respiratory tract is divided into the conducting zone (i.e., Generations 0–16) and the respiratory zone (Generations 17–23) where the O2–CO2 gas exchange takes place. An alternative geometric division would include the extrathoracic, upper bronchial, lower bronchial, and alveolar region (see Fig. 1). There are two basic approaches for generating geometric lung models, i.e., either via algorithms which specify inhibited-volume-based rules for the relationships between parent and daughter airways (e.g., Kitaoka et al., 1999 and Tawhai et al., 2000) or lung replicas digitally reconstructed from CT-scan or MRI data (e.g., van Erbruggen et al., 2005). Using the first approach, Tebockhorst et al. (2007) also included in their computer model lung-airway morphogenesis, due to development in children or triggered by lung diseases.

Finlay (2001) in his Chapter 5 summarized human lung geometric and breathing data, while Hickey and Thompson (2004) focused more on the structure and function of the human airways. For experimental studies and computational analyses the respiratory tract has been traditionally segmented into the nasal cavities, oral airway (i.e., mouth to trachea), the tracheobronchial tree (typically Generations 0–3 or 6) and part of the alveolar region ranging from single alveolar cells to alveolated ducts. Historically, Weibel (1963) was the first to provide idealized geometric data, i.e., tube diameter and length, of symmetrically bifurcating lung airways, known world-wide as the Weibel Type A model. In contrast, Horsfield et al. (1971) and Raabe et al. (1976) published geometry information on asymmetric airways obtained from human lung resin casts, while Hammersley and Olson (1992) focused on small airway bifurcations. Phalen et al. (1985) published measurements of the right upper lobe airways taken from 20 replica casts of people aged 11 days to 21 years. Morphometric data of the human pulmonary acinus, i.e., all the daughter generations of a single terminal bronchiolus, was collected by Haefeli-Bleuer and Weibel (1988). Modern imaging techniques allow for an even more detailed mapping of the human respiratory tract. For example, Ley et al. (2002) obtained from CT-scan data a semi-automatically generated tracheobronchial tree, while Tawhai et al. (2004) as well as Cebral and Summers (2004) used CT-scans to construct central airways. Others, mainly focusing on the human upper airways for meshing and subsequently computer simulations, constructed rigid 3D configurations which somewhat represent actual airways (see Kleinstreuer and Zhang, 2003a; Matida et al., 2004; Farkas et al., 2006; Jin et al., 2007; Xi and Longest, 2007; among others). Dynamic effects of finer geometric aspects of the upper respiratory tract were also investigated, such as local area changes during inhalation (Ehtezazi et al., 2004; Zhang and Finlay, 2005), cartilaginous rings in the trachea (Zhang and Finlay, 2005), and different static glottis openings (Brouns et al., 2007). Rather faithful replicas of the upper respiratory tract for experimental studies were employed by Cheng et al. (1999) and Gracic et al. (2004), among others. Transient geometric changes have to be considered in the throat while speaking, swallowing or switching breathing modes and in the alveolar region during inhalation/exhalation (Ehtezazi et al., 2004; Haber and Tsuda, 2006). Transport phenomena and certain airway diseases may also be coupled to temporary changes in local airway geometry and hence should be considered as well. Examples include mucus-layer flow (Kim et al., 1987) and clearance (Grotberg, 2001) as well as patients with asthma, COPD, cystic fibroses, tumors, etc., as reviewed by Meyer et al. (2003), Brown and Bennett (2004), and Yang et al. (2006).
3. Computational aspects of airflow and particle transport simulations

As alluded to in Section 1.1, “lung aerosol dynamics” investigations were historically mainly concerned with toxic particulate matter deposition and subsequently with the implications of dosimetry-and-health effects. Especially maturing CFD techniques allowed for non-invasive, high-resolution, cost-effective and safe simulations of airflow pattern, particle transport and particle deposition as well as particle mass transfer into the lung tissue. Major simplifications made include somewhat idealized rigid airways with smooth (sticky) surfaces, spherical non-interacting fine or ultrafine particles, and constant inhalation flow rates.

Clearly, the geometry of an actual respiratory system is very complex, augmented by changing wall boundaries, rough surfaces, and moving mucus layers. Nevertheless, the goal is patient-specific modeling, and the generic step-by-step procedure for generating airway geometry data is as follows:

- CT-scan images of a subject’s respiratory tract (i.e., DiCom files), enhanced with a contrasting agent, are obtained from a radiologist or surgeon. It should be noted that the determination of airway or vessel wall thicknesses is still rather difficult. Magnetic resonance imaging (MRI) is good for distinguishing different tissues; thus, may help to estimate variable wall thickness. The time between contrast agent intake and scanning is crucial because the chemical should only change the apparent blood density before migrating into the tissue and by then greatly diminishing contrasts between blood and tissue.
- The DiCom files are loaded into geometry-file-conversion software, such as Mimics/Geomagic (Materialise, Belgium) or Simpleware (Simpleware Ltd., Exeter, UK), it enables the modeler to edit the images, isolate the structures of interest, and generate 3D geometry models.
- The CAD-like geometry files are then exported in suitable formats, typically to CFD software, for numerical fluid flow and solid structure analysis (see, for example, Wolters et al., 2005, Li and Kleinstreuer, 2005, and Shi et al., 2006, among many others).
- Alternatively, the 3D finite element computer model can be exported as an STL-file (stereolithography) to a rapid prototyping machine to build a physical model for laboratory studies (e.g., Kratzberg et al., 2005).

The condition of deposition is usually fulfilled when a particle is one radius away from the wall, i.e., it touches an airway surface. The assumption of dilute micron-particle suspensions allows for separate computations of the airflow (Eulerian approach solving the Navier–Stokes equations) and the particle dynamics (Lagrangian approach solving Newton’s second law of motion). The same holds for the analysis of submicron particles; however, in that case an Euler–Euler approach is recommended, i.e., the nanoparticle (or vapor) phase is described with the mass transfer equation containing an appropriate diffusion term (Crowe et al., 1998; Kleinstreuer, 2003; Zhang et al., 2005). For dense suspension flows, e.g., nasal droplet sprays, both phases are coupled and hence fluid–particle interactions have to be modeled, typically via a “momentum source term” (Kleinstreuer, 2003; Shi and Kleinstreuer, 2007). Most naturally occurring and man-made particles, including most drug aerosols, are non-spherical and hence require special mathematical description for accurate trajectory and deposition simulations (see, for example, Shenoy and Kleinstreuer, 2008). Droplets as well as thermal and humidity effects in the respiratory environment require also special considerations (Zhang and Kleinstreuer, 2003b; Zhang et al., 2006). The assumption of quasi-steady inhalation is justifiable for micron-particle deposition modeling, when an equivalent inlet Reynolds number is selected. Specifically, Zhang et al. (2002a) showed that such an equivalent dimensionless group is the arithmetic mean of
the maximum and mean Reynolds numbers of the given inhalation waveform. For elevated inhalation flow rates, i.e., $Q_{in} > 12$ L/min during exercise, transition to turbulent airflow after the larynx (see Fig. 1) may occur with relaminarization further downstream. It was shown that the low Reynolds number $k-\omega$ turbulence model of Wilcox (1998) adequately describes these changing flow regimes (Kleinstreuer and Zhang, 2003a; Varghese and Frankel, 2003; Zhang and Kleinstreuer, 2003a; Ryval et al., 2004).

The rapidly growing interest in using the mouth/nose as portals for the delivery of medicine caused a shift in the application and interpretation of computational/experimental inhalation studies, i.e., “toxic particle deposition” results appeared as “therapeutic drug-aerosol targeting” outcome. One early example is the determination of a critical tumor radius for which drug-aerosol deposition was at a maximum for all inlet Reynolds and Stokes number combinations (Kleinstreuer and Zhang, 2003b).

### 3.1. Inhaled air flow fields

The understanding of airflow structures in the human airways underlies the basis for analyzing particle transport and deposition. Steady and transient inspired air flows in the human nasal/oral and bronchial airways have been reviewed by Pedley (1977) and Grotberg (1994, 2001). Detailed investigations, both experimentally and theoretically, were recently provided by Lieber and Zhao (1998), Fujioka et al. (2001), Caro et al. (2002), Gemci et al. (2002), Zhang and Kleinstreuer (2002, 2004), Kleinstreuer and Zhang (2003a), Liu et al. (2003), Nowak et al. (2003), Horschler et al. (2003, 2006), Johnstone et al. (2004), van Ertbruggen et al. (2005), Shi et al. (2006), Adler and Brucker (2007), and Grosse et al. (2007), among others. Effects of geometric airway changes are most pronounced during inhalation. So far, experimental and computational analyses focused mainly on isolated sections of the human airways and only for laminar airflows. However, at moderate to high breathing rates the air flow from the larynx to generation G3 is transitional-to-turbulent which may complicate flow structures as well as aerosol transport and deposition (Kleinstreuer and Zhang, 2003a; Zhang and Kleinstreuer, 2004). Usually, the turbulent intensity in the oral airway rises rapidly after the constriction caused by the soft palate, and then decreases until the disturbance is activated again by the throat (glottis) (Zhang and Kleinstreuer, 2003a; Lin et al., 2007). Turbulence levels, in terms of kinetic energy $k$, seem to increase quickly through the strong varying diameter-zone after the glottis, and then decay approaching an asymptotic level of approximately 0.2–0.3 ($k/\mu u^2$) at six-diameter station from the throat (Corcoran and Chigier, 2000). The flow instabilities may be induced again at the bifurcation region due to the great geometric transition from the parent tube to two daughter tubes, while the strongest turbulence fluctuations occur just around the flow dividers due to the contraction of top and bottom surfaces in the carinal ridges (Zhang and Kleinstreuer, 2004). Then, turbulence decays rapidly in the straight segments of the bifurcating tubes. Generally, turbulence which occurs after the throat can propagate to at least a few generations even at a low local Reynolds number (say, $Re = 700$) because of the enhancement of flow instabilities just upstream of the flow divider (Olson et al., 1973; Zhang and Kleinstreuer, 2004).

Typical inspiratory airflow patterns in bifurcating airways are shown in Fig. 2. The essential flow characteristics includes: (i) the air stream splits at the flow dividers and new boundary layers are generated at the inner walls of daughter tubes; (ii) the velocity patterns vary with the development of upstream flows and the generation of the new boundary layers near the inner walls at the dividers; (iii) the skewed profile with a maximum axial velocity near the inner wall may be observed just after the flow divider so that different tubes may experience different air flow rates; (iv) strong secondary vortices appear inside the branch.

![Fig. 2. Velocity profiles in the bifurcation airway model at steady inhalation with $Q_{in} = 30$ L/min. The left panel exhibits mid-plane speed contours. The right panel shows the axial velocity contours and secondary velocity vectors at different cross sections (see Zhang and Kleinstreuer, 2004).](image-url)
tubes. The upstream flow fields (i.e., flow history), and realistic airway geometry features (e.g., asymmetric bifurcations, non-planar branches, cartilaginous rings and local obstructions) will influence the specific airflow characteristics, including patterns of skewed axial velocity profiles, axial velocity magnitude, as well as locations and intensities of secondary vortices (see Zhang et al., 2002d; Nowak et al., 2003; Yang et al., 2006; Li et al., 2007b; Lin et al., 2007).

3.2. Particle deposition

3.2.1. Micron vs. nano-size particles

In general, both transport and deposition of inhaled particulate matter are definitely size-dependent. Typically, nanomaterial dispersion is due to diffusion and convection, while micron particles are transported via convection and/or sedimentation. Specifically, micron-particle deposition in the lung occurs mainly by impaction, including secondary airflow convecting particles to the airway walls, as well as diffusional or gravitational effects. Clearly, inertial impaction (IP) is proportional to the air flow rate \( Q \) and the (aerodynamic) particle diameter \( d \)

\[
\text{IP} = Qd^2
\]  

Concerning particle deposition mechanisms, diffusional and gravitational phenomena are measurable at very low flow rates, i.e., typically in the lower lung regions, where diffusion is dominant for ultrafine particles in areas of high concentration gradients and gravity effects significant for relatively large/heavy particles (Heyder, 2004). Key in diffusional transport of spherical nanomaterial due to the Brownian motion effect is the diffusion coefficient given by the Stokes–Einstein equation:

\[
D_{\text{nano}} = \frac{k_B T C_{\text{slip}}}{3\pi \mu d_p}
\]  

where \( k_B \) is the Boltzmann constant \((1.38 \times 10^{-23} \, \text{JK}^{-1})\), \( T \) is the temperature, \( \mu \) is the fluid viscosity, and \( C_{\text{slip}} \) is the Cunningham slip correction factor (Clift et al., 1978).

For particle deposition studies the Stokes number (St) is generally being used in the form

\[
St = \frac{\rho_p d_p^2 U}{18 \mu D}
\]  

which can be also interpreted as the ratio of particle relaxation and flow characteristic times. In Eq. (3), \( \rho_p \) is the particle density. Thus, the Stokes number, being mainly a function of particle-diameter squared as well as the characteristic air velocity \( U \) and length scale \( D \), is a measure of the influence of the inertial effects during a particle’s trajectory. However, in the (human) respiratory system the local airway geometries are rather complex or exhibit sudden changes, while the airflow velocities are rapidly changing as well. Thus, Stokes numbers as well as Reynolds numbers have to be defined locally to capture more accurately the underlying physics of micron-particle deposition.

3.2.2. Micron-particle deposition

Assuming non-interacting spherical micron particles, a Lagrangian frame of reference can be employed and in light of the large particle-to-air density ratio, dilute particle suspensions and negligible particle rotation, drag is the dominant force with additional forces relevant near the airway walls. Thus, Newton’s second law of motion can be written for laminar and turbulent micron-particle transport as:

\[
\frac{d}{dt}(m_p u_p) = F_D + F_{\text{gravity}} + F_{\text{lubrication}} + F_{\text{interact}}
\]  

where \( u_p \) and \( m_p \) are the velocity and mass of the particle, respectively, \( F_D \) is the drag force, \( F_{\text{gravity}} \) is gravity, and the underlined force terms (lubrication and interaction forces) are activated near the airway wall (Longest et al., 2004). For high aerosol loadings, a particle-particle interaction (or collision) force has to be added. When non-isothermal effects have to be considered, including particle growth (i.e., hygroscopicity), modeling details are given by Zhang and Kleinstreuer (2003b) and Broday and Georgopoulos (2001), among others.

The regional deposition of micron particles in human airways can be quantified in terms of the deposition fraction or deposition efficiency in a specific region (e.g. oral airway, first, second and third bifurcation, etc.). They are defined as:

\[
\text{DF}_{\text{particle}} = \frac{\text{number of deposited particles in a specific region}}{\text{number of particles entering the mouth and/or nose}}
\]  

\[
\text{DE}_{\text{particle}} = \frac{\text{number of deposited particles in a specific region}}{\text{number of particles entering this region}}
\]  

The regional deposition efficiency is mainly used to develop the deposition equation for algebraic (total) lung modeling.

The local deposition patterns of micron particles can be quantified in terms of a deposition enhancement factor (DEF). The particle deposition enhancement factor is defined as the ratio of local to average deposition densities, where deposition densities are computed as the number of deposited particles in a surface area divided by the size of that surface area (Balashazy et al., 1999, 2003; Zhang et al., 2005). Clearly, if the overall and maximum DEF-values in one airway region are close to one, the distribution of deposited particles tends to be uniform. In contrast, the presence of high DEF-values indicates non-uniform deposition patterns, including “hot spots”. Some “hot spots” of toxic particulate matter are related to the induction of certain lung diseases, e.g., cancer.

Focusing mainly on the oral and bronchial airways, micron-particle transport and deposition has been extensively investigated by Stahlhofen et al. (1989), Katz and Martonen (1996), Li et al. (1998), Balashazy et al. (1999, 2003), Cheng et al. (1999), Katz et al. (1999), Kim and Fisher (1999), Corcoran and Chigier (2000), Stapleton et al. (2000), Gemi et al. (2002), Zhang et al. (2002a,b,c, 2005), Kleinstreuer and Zhang (2003a, 2003b), Grgic et al. (2004), Heyder (2004), Matida et al. (2004), van Erbruggen et al. (2005), Zhang and Finlay (2005), Zhou and Cheng (2005), Longest et al. (2006), Kleinstreuer et al. (2007b), and Xi and Longest (2007), among others. Recently, micron-particle transport and deposition in the human nasal airways have gained attention due to the advancements in new nasal drug delivery technologies and computer simulations (Cheng, 2003; Kelly et al., 2004a; Su and Cheng, 2005; Inthavong et al., 2006; Shi et al., 2007). However, very little information is available regarding transport and deposition of vaporizing droplet in the human nasal airways (Shi et al., 2007).

As shown in Fig. 3, micron-particle deposition during inhalation is mainly due to impaction, secondary flow convection, and turbulent dispersion (Li et al., 2007a). Thus, they largely deposit at stagnation points for axial particle motion, such as the tongue portion in the oral cavity, the outer bend of the pharynx/larynx, and the regions just upstream of the glottis and the straight tracheal tube. As expected, for micron particles the high DEF-values appear...
mainly around the carinal ridges due to inertial impaction, but the specific distribution of DEFs at each carina is different and varies with the inhalation flow rate as well. Some micron particles also land outside the vicinities of the cranial ridges due to secondary flows and turbulent dispersion.

The local particle deposition patterns can be further quantitatively described by 3D surface distributions of DEF results. As shown in Fig. 4 (Zhang et al., 2005), the maximum DEF-value is about 1400 for $d_p = 10 \mu m$. This implies that the deposition patterns of micron particles in the upper airways are highly non-uniform, and hence a small surface area where the maximum DEF occurs, may receive hundred times higher dosages when compared to the average value for the whole airway. Such a site of massive particle deposition is usually located around the carinal ridges in the bronchial airways. Recent CFD studies have also shown that more realistic models, e.g., asymmetric and non-planar geometries, may result in some different local deposition rates (Nowak et al., 2003; Li et al., 2007a,c; Xi and Longest, 2007).

3.3. Nanomaterial transport and deposition

The appropriate modeling approach for ultrafine particle transport is the mass transfer equation with the Stokes–Einstein equation for the Brownian motion type nanoparticle diffusivity ($D_{nano}$) (see Eq. (2)); although, a few researchers adopted the Euler–Lagrangian approach when simulating nanoparticle transport (Hofmann et al., 2003; Zamankhan et al., 2006; Longest and Xi, 2007). Thus, the proper convection–diffusion equation for laminar and turbulent transport reads:

$$\frac{\partial Y}{\partial t} + \frac{\partial}{\partial x_j} (u_j Y) = \frac{\partial}{\partial x_j} \left[ \left( D_{nano} + \frac{\nu_l}{\sigma_Y} \right) \frac{\partial Y}{\partial x_j} \right]$$

(7)

where $Y$ is the mass fraction and $\sigma_Y$ is the turbulence Schmidt number for $Y$.

The regional deposition fraction can be determined according to Fick’s law (Zhang and Kleinstreuer, 2004), i.e.,

$$DF_{region} = \sum_{i=1}^{n} \frac{A_i (D + (\nu_l/\sigma_Y)) (\partial Y/\partial n)}{Q_{in} Y_m}$$

(8)

where $A_i$ is the area of the local wall cell ($i$), and $n$ is the number of wall cells in one certain airway region, e.g., oral airway, first airway bifurcation, etc. The local deposition patterns of nanoparticles can again be quantified in terms of a deposition enhancement factor (Balashazy et al., 1999, 2003; Zhang et al., 2005), which is defined as the ratio of local to average deposition densities, i.e.,

$$DF = \frac{\sum_{i=1}^{n} A_i (D + (\nu_l/\sigma_Y)) (\partial Y/\partial n)|_{i}}{\sum_{i=1}^{n} A_i}$$

(9)

Assuming that the airway wall is a perfect sink for aerosols upon touch, the boundary condition at the wall is $Y_w = 0$. This assumption is reasonable for fast aerosol–wall reaction kinetics (Fan et al., 1996) and also suitable for estimating conservatively the maximum deposition of particles or toxic vapors in airways.

A typical nanoparticle deposition pattern is shown in Fig. 5 in terms of DEF-distributions in a bifurcation airway model (Zhang et al., 2005). Again, the enhanced deposition mainly occurs at the carinal ridges and the inside walls around the carinal ridges due to the complicated air flows and large particle concentration gradients in these regions. As the particle size increases, wall depositions
A summary graph of regional particle deposition fraction in human upper airways is given in Fig. 6 (see Shi et al., 2007 and Zhang et al., 2005, for details). It shows that inhaled particles in the diameter range of 0.01 to about 1 μm are difficult to be captured by the upper respiratory tract, i.e., they may reach the deeper lung region if not exhaled (Heyder, 2004). Both inspiratory flow rate and particle size play a significant role in the particle deposition process. Specifically, with an increasing particle diameter the DFs decrease for nanoparticles because of the decrease in diffusive capacity while they may increase for micron particles due to increasing impaction. Similarly, the higher the inhalation flow rate, the lower the deposition of nanoparticles and the higher the deposition of micron particles (Zhang et al., 2005). Furthermore, the location of bifurcation airways and airway geometry features (e.g., asymmetry, non-planar, obstruction) may influence inhaled particle deposition as well, as numerically confirmed by Zhang et al. (2002d), Nowak et al. (2003), Farkas and Balashazy (2007), Li et al. (2007c), and Luo et al. (2007).

4. Conclusions and future work

A review of research papers is presented, pertinent to computer modeling of airflow as well as nano- and micron-size particle deposition in mainly pulmonary airway replicas. The key modeling steps are outlined, including construction of suitable airway geometries, mathematical description of the air–particle transport phenomena and computer simulation of micron and nano-particle depositions. Specifically, diffusion-dominated nanomaterial deposits on airway surfaces much more uniformly than micron particles of the same material. This may imply different toxicity effects. Due to impaction and secondary flows, micron particles tend to accumulate around the carinal ridges and to form “hot spots”, i.e., locally high concentrations which may lead to tumor developments. Inhaled particles in the size range of 20 nm ≤ dp ≤ 3 μm may readily reach the deeper lung region. Concerning inhaled therapeutic particles, optimal parameters for mechanical drug-aerosol targeting of predetermined lung areas can be computed, given representative pulmonary airways.

Future computational work will center around simulation realism and accuracy in order to understand and predict dosimetry-and-health-risk effects in case of inhaled toxins and optimal operational conditions of smart inhaler systems in case of drug-aerosol targeting. New hardware and software developments in the petascale computing environment will allow for patient-specific solutions to these problems.

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References


