Computational modeling of lung deposition of inhaled particles in chronic obstructive pulmonary disease (COPD) patients: identification of gaps in knowledge and data

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Computational modeling of lung deposition of inhaled particles in chronic obstructive pulmonary disease (COPD) patients: identification of gaps in knowledge and data

Koustav Gangulya, Ulrika Carlanderb, Estella DG Garessusc, Markus Fridénc, Ulf G Erikssonbd, Ulrika Tehlerce and Gunnar Johansone

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ABSTRACT
Computational modeling together with experimental data are essential to assess the risk for particulate matter mediated lung toxicity and to predict the efficacy, safety and fate of aerosolized drug molecules used in inhalation therapy. In silico models are widely used to understand the deposition, distribution, and clearance of inhaled particles and aerosols in the human lung. Exacerbations of chronic obstructive pulmonary disease (COPD) have been reported due to increased particulate matter related air pollution episodes. Considering the profound functional, anatomical and structural changes occurring in COPD lungs, the relevance of the existing in silico models for mimicking diseased lungs warrants reevaluation. Currently available computational modeling tools were developed for the healthy adult (male) lung. Here, we analyze the major alterations occurring in the airway structure, anatomy and pulmonary function in the COPD lung, as compared to the healthy lung. We also scrutinize the various physiological and particle characteristics that influence particle deposition, distribution and clearance in the lung. The aim of this review is to evaluate the availability of the fundamental knowledge and data required for modeling particle deposition in a COPD lung departing from the existing healthy lung models. The extent to which COPD pathophysiology may affect aerosol deposition depends on the relative contribution of several factors such as altered lung structure and function, bronchoconstriction, emphysema, loss of elastic recoil, altered breathing pattern and altered liquid volumes that warrant consideration while developing physiologically relevant in silico models.

Abbreviations: CLE: centrilobular emphysema; COPD: chronic obstructive pulmonary disease; CFPD: computational fluid and particle dynamics; CSA: cross sectional area; CT: computed tomography; FEV1: forced expiratory volume in 1 second; FRC: functional residual capacity; FOT: forced oscillations single frequency sound waves; FVC: forced vital capacity; GOLD: global initiative for chronic obstructive lung disease; HPLDB: hygroscopic particle lung deposition model B; HRCT: high resolution CT; IOS: impulses of multiple frequency sound waves; LAA: Low attenuation area; Lm: mean linear intercept; MEF: maximal expiratory flow; MPPD: multiple path particle dosimetry model; PET: positron emission tomography; PLE: panlobular emphysema; RV: reserve volume; SPECT: single photon emission computed tomography; TEF: tidal expiratory flow; TLC: total lung capacity; VC: vital capacity

Table of contents

Introduction ............................................................................................................... 161
COPD, chronic bronchitis, and emphysema ............................................................ 161
Normal lung structure ............................................................................................ 162
Factors influencing lung particle deposition ......................................................... 163
Functional changes of COPD lungs ....................................................................... 163
  Pulmonary function .............................................................................................. 163
  Hyperinflation ...................................................................................................... 163
  Breathing pattern ................................................................................................ 163
  Airway wall .......................................................................................................... 164
Structural changes in COPD lungs ......................................................................... 164
  Alveolar parenchyma .......................................................................................... 164
  Small airways ...................................................................................................... 164
  Vascularity .......................................................................................................... 164
  Relationship between airway obstruction and emphysema ............................... 164
In silico lung models .............................................................................................. 165
Modeling COPD lungs with particle lung deposition models ............................... 166
  Lung structure .................................................................................................... 167

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Introduction

Chronic obstructive pulmonary disease (COPD) accounts for more than 3 million deaths every year (http://www.who.int/mediacentre/factsheets/fs315/en/). COPD is the 3rd leading cause of death globally and has enormous impact on the society, patients and their families in terms of cost and quality of life (Ferkol and Schraufnagel 2014; https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death).

Tobacco smoking is the main cause for the development of COPD, but non-tobacco related causes like biomass smoke exposure, air pollution, exposure to occupational dusts and chemicals, genetic pre-disposition, impaired lung development and accelerated aging also predispose individuals to COPD (Vogelmeier et al. 2017). COPD is diagnosed based on persistent airflow obstruction measured by spirometry. However, spirometry measurements reflect the sum of all the different complex and heterogenous COPD pathologies. Agusti (2014) explained the "complexity of COPD" as the non-linear dynamic interaction of intra-pulmonary and extra-pulmonary components with time. "Heterogeneity" of COPD has been explained as the fact that not all the complexities are present among all COPD patients at any given point of time (Agusti 2014). Thus, in terms of causality and pathophysiology, COPD represents an extremely heterogeneous condition.

Exposure to particulate matter from sources such as indoor (e.g. biomass smoke) and outdoor air pollution can not only initiate and promote the development of COPD but can also trigger exacerbation of respiratory symptoms among COPD patients (Dockery et al. 1993; Pope 2000; Samet et al. 2000). In order to better understand the pathophysiology of COPD development and COPD exacerbations, a good understanding of particle deposition is warranted. In addition, knowledge of particle deposition in diseased lungs is useful for optimization of therapeutic inhalation strategies that involve delivery and targeted deposition of aerosolized drug to the diseased part of the lung (Schulz 1998; Bäckman et al. 2018). By tuning particle properties and breathing conditions, distribution to different parts of the lung can be adjusted. Information on particle deposition can be generated from computational particle deposition models. Different types of particle deposition models are available (Hofmann 2011). However, most, if not all, models are built on data from healthy adult (male) lungs (ICRP 1994). Moreover, most models are based on ideal aerosols (spherical particles), which is far from the real scenario.

COPD, chronic bronchitis, and emphysema

COPD is diagnosed as a persistent airflow obstruction determined by the ratio of post-bronchodilator forced expiratory volume in 1 s/forced expiratory volume (FEV1/FVC) of <70% (http://goldcopd.org/; Vogelmeier et al. 2017). The severity staging (stages I-IV) of COPD is based on the percentage decrease of FEV1 from predicted values (Figure 1; http://goldcopd.org/; Vogelmeier et al. 2017). Diagnosis of COPD is difficult during the initial stages of the disease due to the lack of corresponding reflection in pulmonary function tests (Niewoehner et al. 1974; Brusasco and Martinez 2014). However, as a result of the profound anatomical and structural alterations occurring in the lung already during early stages of COPD, it is likely that the particle deposition and distribution in the different regions of lung may also be affected. Thus, a severity stage based model of the COPD lung would provide deeper understanding of particle deposition and distribution along with the disease progression.

Chronic bronchitis and emphysema are the two common COPD associated phenotypes (http://www.who.int/respiratory/copd/en/). Although chronic bronchitis and emphysema are not included in the definition of COPD *per se* (Vogelmeier et al. 2017), their characterization is essential for understanding the disease pathogenesis and defining the therapeutic strategies (Brusasco and Martinez 2014). In chronic bronchitis, obstruction of small airways, inflammation, mucus gland enlargement, excess mucus production, and goblet cell hyperplasia (Saetta et al. 2000; Hogg et al. 2004; Willems et al. 2004) is accompanied with continuous cough (> 3 months duration per year) (Fabbri et al. 2003, 2004; Vestbo et al. 2013). Emphysema on the other hand involves enlargement of lower airspaces, destruction of lung parenchyma, loss of lung elasticity, and closure of small airways (Macnee 2005; Timmins et al. 2011). Therefore, in order to model particle deposition in the COPD lung, consideration of chronic bronchitis and emphysema is essential.
Normal lung structure

Lungs are composed of about half a liter of tissue, similar volume of blood and ~4.3 liters of air in a healthy "standard" man (30 y, 1.75 m, 70 kg) consisting of the trachea, two main bronchi, bronchioles, alveolar ducts and alveolar sacs. (Murray 2010). The classical Weibel's model (Weibel 1963) described 23 generations of branching airways in the human respiratory tract that is classified into two zones: (a) Conducting zone (generations 0–16) and (b) Respiratory zone (generations 17–23) (ICRP 1994). The Conducting zone (100–150 ml) comprises of the trachea, bronchi, bronchioles and terminal bronchioles and delivers air to the respiratory zone (West 2007; Wang et al. 2014). It has a thick airway wall and is devoid of any alveoli, thereby not participating in the process of gas exchange (Weibel 1963). The respiratory zone (2.5–3 ml) comprises of the respiratory bronchioles, alveolar ducts and alveolar sacs and facilitates the process of gas exchange at the blood-air barrier. Alveolar ducts and alveolar sacs are covered by alveoli, the gas exchange units of the lung (alveolar surface area: 70–80 m²) (Weibel 1963; West 2007; Wang et al. 2014). Mucociliary clearance is the process of mucus transport towards the throat by the coordinated ciliary beating (20 mm/min in trachea to 1 mm/min in small peripheral airways) and expiratory airflow to clear foreign objects out of the lung (West 1992; Wang et al. 2014). This process is an essential mechanism to clear respirable particulate matter from the respiratory tract. On the other hand, macrophagic phagocytosis is the main particle clearance mechanism within alveoli. Adult human lung consists of about 500 million alveoli with about 12–14 resident macrophages in each alveoli. Resident alveolar macrophages contribute to approximately 1% of the total alveolar surface area (Patton and Byron 2007; Geiser 2010; Geiser and Kreyling 2010; Wang et al. 2014). Particles that are small enough to penetrate into the alveolar tissue may also be cleared via translocation to lung-associated lymph nodes as shown in several animal species including humans (Snipes et al. 1983; Kitamura et al. 2007; Choi et al. 2010; Nakane 2012). The translocation appear to be small (<0.1% of the deposited dose) but can increase due to disease and inflammation in the lung (Nakane 2012; Keller et al. 2014; Bevan et al. 2018). Translocation of various types of fine and ultrafine particles

<table>
<thead>
<tr>
<th>GOLD criteria (<a href="http://www.goldcopd.org">www.goldcopd.org</a>)</th>
<th>COPD severity staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FEV1/FVC &lt; 0.7</td>
<td>Mild (stage I): FEV1 &gt;80% pred.</td>
</tr>
<tr>
<td>- Mild (stage II): FEV1 &gt;70% pred.</td>
<td>Moderate (stage III): FEV1 &gt;50% pred.</td>
</tr>
<tr>
<td>- Severe (stage IV): FEV1 &lt;50%</td>
<td>Very Severe (stage V): FEV1 &lt;30% pred.</td>
</tr>
<tr>
<td></td>
<td>or FEV1 &lt;30% and chronic respiratory failure</td>
</tr>
</tbody>
</table>

Two most common phenotypes associated with COPD:

- Chronic bronchitis: Obstruction of small airways, inflammation, mucous gland enlargement, excess mucus production, gullet cell hyperplasia, continuous cough>3 months in a year, dyspepsia.
- Emphysema: Enlargement of airspace, destruction of parenchyma, loss of lung elasticity, closure of small airways, dyspepsia.

**Figure 1.** An integrated view on the various factors for consideration to model a chronic obstructive pulmonary disease (COPD) lung in a physiologically relevant manner for particle deposition, distribution and clearance studies. % FEV1 pred.: percent of predicted forced expiratory volume in 1 second; FVC: forced expiratory volume.
have also been detected in the mediastinal and/or hilar lymph nodes in mice and rats, following inhalation, intranasal and/or intra-tracheal instillation (Shwe et al. 2005; van Ravenzwaay et al 2009; Pauluhn 2012; Nakane 2012). Another clearance mechanism, of importance particularly for soluble particles and small nanoparticles, is absorption into the systemic circulation (Kermanizadeh et al. 2015).

**Factors influencing lung particle deposition**

A certain fraction of inhaled particles is deposited in the respiratory system following contact with the lining fluid of the airways (Edsbäcker et al. 2008). Particle deposition is influenced by several factors related to the particle properties as well as physiological and anatomical features of the subject inhaling those particles (Schulz 1998; Schulz and Muhle 2000). The main physical processes determining pulmonary particle deposition are (i) impaction, (ii) sedimentation and (iii) diffusion (Tena and Clara 2012). The extent and pattern of particle deposition are driven by: (i) particle size, shape and density, (ii) physicochemical properties of the inhaled aerosol, (iii) airflow velocity, (iv) breathing patterns, (v) lung geometry (e.g. airway diameter and number of alveoli) and structure, (vi) anatomy of the nasal, oral and pharyngeal areas, and (vii) temperature and humidity (Tena and Clara 2012; Jinxiang et al. 2014; Borghardt et al. 2015). COPD associated changes in the airway dimensions (bronchoconstriction and hyperinflation), lung structure (emphysema) (Wagner 2003), altered airflows and breathing patterns (Löning et al. 2009) and reduced lung elasticity (Wagner 2003) may affect particle deposition. Thus, modeling of a COPD lung warrants consideration of the associated structural, dimensional and functional changes.

**Functional changes of COPD lungs**

**Pulmonary function**

Spirometry measurement to demonstrate irreversible airflow obstruction (FEV1/FVC < 0.70) is essential for the clinical diagnosis of COPD (Rabe et al. 2007; Vogelmeier et al. 2017). However, a decreased FEV1/FVC does not always indicate airflow obstruction particularly when the FEV1 and FVC values are within or above the normal range (Brusasco and Martinez 2014). Moreover, in the early stages of COPD, FEV1 and airway conductance are not affected as the structural changes of lung are mainly localized in the small airways (Brusasco and Martinez 2014). However, changes in lung function parameters other than FEV1 may as well impact the disease severity. For example, in the case of obstructive disorders, the maximal expiratory flow (MEF) is limited at lower values than normal. During early stages of COPD, MEF remains much larger than tidal expiratory flows (TEF) resulting in availability of a sufficient “flow reserve” for increasing minute ventilation at rest or normal daily activities. At later stages of the disease when airflow limitation is increased, the “flow reserve” is decreased (Eltyara et al. 1996; Brusasco and Martinez 2014). Thus, apart from FEV1 and FVC values, MEF and TEF may also serve as important data sets for modeling purposes.

**Hyperinflation**

Lung hyperinflation is a major functional consequence of altered lung mechanics in COPD (Pride and Peter 2011; Brusasco and Martinez 2014). It affects total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC). Increased RV in COPD occurs due to reduced lung elastic recoil or airway narrowing or combination of both (Bates et al. 1962, 1966; Brusasco and Martinez 2014). Increased TLC in COPD patients have been reported in emphysematous lungs (Berend et al. 1980; Loyd et al. 1966; Naunheim et al. 2006; Simon et al. 1973; Brusasco and Martinez 2014). Changes in RV and TLC determine changes in vital capacity (VC) and also in FEV1. VC may be normal or increased during early phases of emphysema because the increase in RV is compensated by an increase in the TLC. With advanced stages of the disease, the RV increases more than the TLC, thus reducing the VC and also contributing to the FEV1 decrease (Brusasco and Martinez 2014). Increased FRC in COPD is attributed to the COPD-associated emphysema and hyperinflation (Akimoto 2003; Halbert et al. 2006). FRC increase in COPD may be due to static or dynamic or both mechanisms (Sharp 1968; Brusasco and Martinez 2014). FRC values in COPD patients have been shown to vary from 2.11 to 12.51 (Jamaati et al. 2013). Other studies reported average FRC values in COPD patients to be 7.21 and that of healthy individuals to be 3.71 (Gorman et al. 2002). Lung dimensions and lung geometry are affected not only by COPD severity but also by age and gender (US-EPA 2004). Thus, it is important to correct for these factors in order to predict the effect of COPD on the particle deposition.

**Breathing pattern**

Another characteristic observation among COPD patients is shallow and altered breathing pattern. The mechanism behind the altered breathing pattern is not completely understood, but weakness of the respiratory muscles has been suggested as one of the main factors. Comparison of breathing pattern revealed decreased inspiratory time and reduced expiratory airflow among COPD patients compared to healthy individuals (Löning 2009; Wilkens et al. 2010; Vestbo et al. 2013; Motamedi-Fakhri et al. 2016). However, effects on other breathing parameters like tidal breathing, exhalation time and breathing frequency were more heterogeneous among COPD patients (Löning 2009; Wilkens et al. 2010; Yamauchi et al. 2012; Motamedi-Fakhri et al. 2016). However, measuring techniques (eg. use of nose-clips, mouth pieces or masks) may significantly influence the breathing pattern by increasing the breathing frequency (Askanazi et al. 1980).

**Airway wall**

The physical properties of the airway wall layer (mucosa, submucosa and adventitia) can influence the airflow (Brusasco
and Martinez 2014). Computational modeling studies suggest that the airway smooth muscle tone in the cartilaginous airways is associated with airflow obstruction in COPD (Lambert et al. 1993; Brusasco and Martinez 2014). Thickening of the mucosal layer of the airway wall is regarded as the primary mechanism for increased airflow resistance and airway closure (Moreno et al. 1986; Wiggs et al. 1992). Presence of mucus within the airway lumen (Yager et al. 1989) and increased surface tension due to altered surfactant integrity (Enhorning et al. 1995) also contributes to the airway narrowing. Furthermore, loss of lung elastic recoil contributes to airflow resistance among long term smokers without COPD and nonsmokers (Enhorning et al. 1995; Brusasco and Martinez 2014). Thickening of airway wall also contributes to airway obstruction (Landser et al. 1982; Moreno et al. 1986; Wiggs et al. 1992).

Vascularity
Reduced vascularity within alveolar septa in emphysema due to endothelial dysfunction is a well-recognized phenomenon (Liebow 1959; Brusasco and Martinez 2014). However, the corresponding impact of vascular changes on lung mechanics and pathology is poorly understood. Quantitative CT measurements of the total cross-sectional area (CSA) of small pulmonary blood vessels (<5 mm²) at sub-segmental levels strongly correlate with the extent of emphysema (Matsuoka et al. 2010). In the study by Matsuoka et al. (2010), a strong negative correlation (r = −0.83; p < 0.0001) between % CSA of pulmonary vessels (<5 mm²) and % low attenuation area (LAA, less than 950 Hounsfield units is defined as emphysema) have been reported. Percent CSA of pulmonary vessels (5–10 mm²) was weakly (r = −0.25; p = 0.0004) correlated to emphysematous change (Matsuoka et al. 2010). Incorporation of vascular changes in COPD modeling studies may be important, as reduced vascularity may impair particle clearance. However, quantitative data on the vascularity of healthy and diseased lung are lacking.

Relationship between airway obstruction and emphysema
Very few studies have addressed the relationship between small airway obstruction and emphysematous destruction of the lung. McDonough and colleagues used multi-detector computed tomography (micro-CT) to compare the number of airways (2.0–2.5 mm) among 78 patients with various stages of COPD (with CLE and PLE) judged according to the GOLD guidelines. Micro-CT was used to measure the mean linear intercept (Lₘ, i.e. the distance between alveolar walls), terminal bronchioles per milliliter (ml) of lung volume, along with the minimum diameters and CSA of the terminal bronchioles. The morphometric data were represented as: (i) number of small airways (2.0–2.5 mm diameter) per pair of lungs in COPD patients compared to healthy lung have been reported (McDonough et al. 2011; Hogg et al. 2013). Airways smaller than 2 mm in diameter account for ~20% of the total lower airway resistance and are also the major site of airflow obstruction in COPD (Hogg 2012; Hogg et al. 2013). Loss and narrowing of small conductive airways precede the development of emphysema which in turn explains the increase in resistance among COPD patients. Long term smokers exhibit a higher degree of inflammation and more bronchioles (diameter < 0.4 mm) compared to nonsmokers. The number of airways with diameter < 2.0 mm are however similar among long term smokers without COPD and nonsmokers (Cosio et al. 1980). In clinically established COPD subjects, a reduced number of airways with diameter 2.5–2.0 mm are detected (Matsuba and Thurlbeck 1972; McDonough et al. 2011). Reduced number of terminal bronchioles in patients with mild COPD prior to the occurrence of CLE have been also reported through micro-computed tomography (CT) based stereological studies (McDonough et al. 2011). The findings of McDonough et al. (2011), suggest a 4–40 fold increase in peripheral resistance in COPD lungs. The corresponding total number of terminal bronchioles in

Structural changes in COPD lungs
The airflow obstruction in COPD patients is primarily due to changes in the peripheral conducting airways (chronic bronchitis) (Hogg et al. 1968) and destructive changes in bronchioles, alveolar ducts and alveoli (emphysema) (Thurlbeck 1976; Brusasco and Martinez 2014).

Alveolar parenchyma
 Destruction of the alveolar parenchyma is the main feature of an emphysematous lung. Centrilobular emphysema (CLE) is also associated with thickening of small airways and generally affects upper lung regions. On the other hand, panlobular emphysema (PLE) exhibits uniform dilatation and destruction of the entire secondary lobule (Thurlbeck 1963). Emphysematous destruction of the lung affects the expiratory flow rate due to loss of lung elastic recoil and destruction of alveolar attachments to peripheral airway walls (Nagai et al. 1976; Brusasco and Martinez 2014).

Small airways
Airways with a diameter below 2 mm are the main sites of airway narrowing in COPD (Hogg et al. 1968; Hogg 2012). A four to forty-fold increase in the small airway resistance among COPD patients compared to healthy lung have been reported (McDonough et al. 2011; Hogg et al. 2013). Airways smaller than 2 mm in diameter account for ~20% of the total lower airway resistance and are also the major site of airway obstruction in COPD (Hogg 2012; Hogg et al. 2013). Loss and narrowing of small conductive airways precede the development of emphysema which in turn explains the increase in resistance among COPD patients. Long term smokers exhibit a higher degree of inflammation and more bronchioles (diameter < 0.4 mm) compared to nonsmokers. The number of airways with diameter < 2.0 mm are however similar among long term smokers without COPD and nonsmokers (Cosio et al. 1980). In clinically established COPD subjects, a reduced number of airways with diameter 2.5–2.0 mm are detected (Matsuba and Thurlbeck 1972; McDonough et al. 2011). Reduced number of terminal bronchioles in patients with mild COPD prior to the occurrence of CLE have been also reported through micro-computed tomography (CT) based stereological studies (McDonough et al. 2011). Thickening of airway wall also contributes to airway obstruction (Landser et al. 1982; Moreno et al. 1986; Wiggs et al. 1992).
CLE and PLE patients was 2400 ± 600 per ml and 6200 ± 2100 per ml, respectively, compared to 22,300 ± 3900 per ml in control subjects.

From the above reviewed information it is apparent that small airways (<2 mm in diameter) are the major site of COPD pathology and that they are involved during the early course of the disease when spirometry or imaging tools do not provide adequate information for clinical diagnosis (McNulty and Usmani 2014). However, studies on small airways in COPD are limited mainly due to the small size and inaccessibility for biopsies (McNulty and Usmani 2014). Impulse oscillometry is a more sensitive technique in detecting small airway obstruction compared to spirometry. Forced oscillations of single frequency sound waves (FOT) or impulses of multiple frequency sound waves (IOS) are pushed into the lungs as pressure waves to measure respiratory resistance (frequency independent under healthy condition but frequency dependent under airway obstruction) and reactance (elastic and inertial lung properties; frequency independent). Importantly, impulse oscillometry is easy to use and effort independent technique therefore suitable for children and patients with severe lung diseases who cannot efficiently perform forced maneuvers required for spirometry (McNulty and Usmani 2014; Salvi 2015). Thus, assessment of pulmonary mechanics (reactance) through FOT/IOS may provide deeper insights of airflow obstruction in COPD. Recent developments of imaging technologies like high resolution computed tomography (HRCT), hyperpolarized magnetic resonance imaging, scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET) that may provide resolution capabilities beyond computer tomography to visualize airways as small as 2.0 mm to describe quantitative changes in the small airways, drug deposition, inflammation, and ventilation-perfusion relationships can be useful (McNulty and Usmani 2014). Table 1 summarizes the functional and structural parameters that warrant consideration for physiologically relevant in silico modeling of particle deposition in the COPD lung.

### In silico lung models

Different types of in silico models have been successfully used to predict deposition of particles in healthy human lungs (Hofmann 2011; Isaacs et al. 2012; Longest and Holbrook 2012; Darquenne et al. 2016). Currently, available lung models can be grouped into: (a) site-specific lung models and (b) whole lung models depending on the application and region of interest in the respiratory system.

Site-specific models typically provide information about local deposition and three-dimensional localization within targeted sites of the lung such as bronchial bifurcations, larynx, nose, mouth, and throat (Longest and Holbrook 2012; McNulty and Usmani 2014). However, studies on small airways in COPD are limited mainly due to the small size and inaccessibility for biopsies (McNulty and Usmani 2014). Importantly, impulse oscillometry is easy to use and effort independent technique therefore suitable for children and patients with severe lung diseases who cannot efficiently perform forced maneuvers required for spirometry (McNulty and Usmani 2014; Salvi 2015). Thus, assessment of pulmonary mechanics (reactance) through FOT/IOS may provide deeper insights of airflow obstruction in COPD. Recent developments of imaging technologies like high resolution computed tomography (HRCT), hyperpolarized magnetic resonance imaging, scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET) that may provide resolution capabilities beyond computer tomography to visualize airways as small as 2.0 mm to describe quantitative changes in the small airways, drug deposition, inflammation, and ventilation-perfusion relationships can be useful (McNulty and Usmani 2014). Table 1 summarizes the functional and structural parameters that warrant consideration for physiologically relevant in silico modeling of particle deposition in the COPD lung.

### Table 1. Summary of functional and structural parameters of the normal and chronic obstructive pulmonary disease (COPD) lung that warrant consideration for incorporation in the in silico particle deposition models.

<table>
<thead>
<tr>
<th>Functional and structural parameters</th>
<th>Healthy</th>
<th>COPD</th>
<th>Comments for in silico modeling purposes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC</td>
<td>&gt;0.70</td>
<td>&lt;0.70</td>
<td>Based on FEV1, models can be used for severity staging</td>
</tr>
<tr>
<td>FRC</td>
<td>3.71</td>
<td>2.14–12.51</td>
<td>Compliance is the corresponding lung function parameter; not evidently possible to accommodate in current modeling frameworks.</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>Not included in models</td>
<td>Loss of elastic recoil increases with COPD severity</td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>Not applicable</td>
<td>CLE: centrilobular emphysema</td>
<td>Reducing respiratory airway generations (17–23) and increasing alveolar volume to mimic hyperinflation</td>
</tr>
<tr>
<td>Breathing pattern</td>
<td>Inhalation time: 2.5 s Exhalation time: 2.5 s</td>
<td>Inhalation time: 1.0 s Exhalation time: 4.5 s</td>
<td>Shallow, prolonged or shortened or not affected</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>Not applicable</td>
<td>Airway diameter reduction: Generations 3–9: 6–90%</td>
<td>Gradient reduction of airway diameter to mimic severity levels</td>
</tr>
<tr>
<td>Inflammometry</td>
<td>Not applicable</td>
<td>Increased inflammation with recruitment of inflammatory cells (e.g. PMNs, macrophages)</td>
<td>Modeling approaches not available</td>
</tr>
<tr>
<td>Vascularity</td>
<td>50–100 m² in the alveolar surface</td>
<td>Reduction of small pulmonary vessels (&lt;5 m²)</td>
<td>Modeling approaches limited</td>
</tr>
<tr>
<td>Terminal bronchioles</td>
<td>22300 ± 3900</td>
<td>CLE: 2400 ± 600 PLE: 6200 ± 2100</td>
<td>Modeling approaches not available</td>
</tr>
<tr>
<td>Mucociliary beating</td>
<td>20 mm/min (trachea) 1 mm/min (small peripheral airways)</td>
<td>Slower but precise data not available</td>
<td>Modeling approaches not available</td>
</tr>
<tr>
<td>Macrophagic clearance</td>
<td>500 million alveoli 12–14 resident macrophages occupying 1% of total alveolar surface area</td>
<td>Macrophage recruitment; Very limited quantitative data available</td>
<td>Modeling approaches not available</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity.
Kolanjiyil et al (2017). These types of models are useful in the design of dry powder inhalers and also to identify areas with high local concentrations, the so-called “hot spots” in bifurcations. Site-specific lung models address particle transport and deposition by computational fluid and particle dynamics (CFPD) where concepts of complex airway geometry and flow physics are utilized. CFPD modeling is typically advanced and computationally intensive, requiring trained interdisciplinary scientists and high-performance hardware with adequate processing and extensive capacity. Site-specific clinical data are difficult to obtain and have restrained the validation of models.

The currently available whole lung models mainly differ in two aspects: (i) lung morphometry and (ii) computational technique (Hofmann 2011; Ruzer and Harley 2013). The choice of lung structure can range from simplified regional compartment models to detailed bronchial and acinar airway structures. Among the simplified lung structures, the resemblance with real human lungs varies considerably. Some describe the lung as regional compartments (Koblinger and Hofmann 1985) whereas others define the entire lung either as a single trumpet-shaped entity with a summed airway cross-sectional area that increases with the distance from the mouth (‘trumpet’ models) (Taulbee and Yu 1975), or as a continuum of airway branches that branch symmetrically (single path models) (Yeh and Schum 1980) or asymmetrically (deterministic or stochastic multiple path models) (Yeh and Schum 1980; Asgharian et al. 2001) into daughter branches.

The applied computational techniques used in the whole lung models are thus either empirical, deterministic or stochastic. A major advantage of the empirical and semi-empirical models is that deposition is calculated by fitting algebraic relationships to experimental human data. These models are also simple to use and do not require sophisticated computer programs. However, the experimental data sets on deposition have low resolution as they are limited to regions, making extrapolation to new scenarios, such as COPD, unreliable.

Deterministic modeling techniques use simplified assumptions about airway geometries and airflow conditions to derive analytical solutions of air and particle motion. The model tracks the path of a population of particles within the lung tree (Eulerian) utilizing analytical solutions based on mechanistic understanding of physiological and physical mechanisms. The models can be used on personal computers using freely available and user-friendly dedicated software.

In the stochastic approach, the morphology of the lung (airway diameter, airway length, and bifurcation angles) is considered to vary in a random manner within predefined limits. The particle path down the lung tree is tracked by following either a single particle (Lagrangian approach) or a particle population (Eulerian). A major advantage of the stochastic models is that they allow simulation of biological variability within the lungs of an individual as well as the variability between subjects. The model complexity requires trained user and access to specialized programs.

Two widely used freely available models describing lung deposition in a healthy person are: the Multiple-Path Particle Dosimetry Model (MPPD) (ARA 2017), and the Hygroscopic Particle Lung Deposition model B (HPLDB) (Ferron et al. 1988). Both models are based on a symmetrical lung structure and a deterministic approach. The MPPD model uses the Yeh and Schum (1980) model as default, whereas the HPLDB model uses Weibel’s (1963) symmetrical lung as default. The Weibel (1963) model describes the lung as a continuum of (airway) ducts, each of which branch into two smaller airways.

**Modeling COPD lungs with particle lung deposition models**

The heterogeneity of COPD combined with the lack of morphological data makes lung modeling of particle deposition challenging. Several experimental studies on particle deposition in COPD patients have been carried out; however, we found only four clinical studies where COPD patients versus healthy individuals were compared. The results from these four studies were inconclusive and the patient groups were small (n = 4–23 patients) (de Backer et al. 2010; Fazzi et al. 2009; Scheuch et al. 2009; Häusserman et al. 2007). In some, the total deposition was not significantly (p > 0.05) affected, whereas in others increased peripheral deposition in COPD was observed. It is plausible that the altered deposition pattern of aerosol reported in case of COPD lungs is disease severity driven. The extent to which COPD pathophysiology may affect aerosol deposition depends on the relative contribution of several factors such as altered lung structure and function, bronchoconstriction, emphysema, loss of elastic recoil, and altered breathing pattern. These COPD related physiological factors require integration into in silico lung models by modification of model parameters, equations, and structures to address the complexity and heterogeneity of a COPD lung.

As end users, researchers are limited to tune most of the predefined parameters in the freely available in silico lung models discussed above (HPLD and MPPD). These predefined parameters do not include for example airway diameters and alveolar volume. Tunable parameters are limited to changes in particle properties, tidal volume, FRC, breathing pattern and to symmetric or asymmetric lung structure. This significantly limits the usefulness of these in silico lung models when moving from the healthy to the COPD lung.

On the other hand, other investigators have integrated disease related physiological factors into their models to study the effect of COPD on particle deposition. These modeling efforts address bronchoconstriction, emphysema or both (Tables 2 and 3). In some, alterations in lung structure, breathing pattern and elastic recoil have also been incorporated. Local deposition in the diseased lung has typically been studied using CFPD (Zhang et al. 2018; Chen et al. 2012; Luo et al. 2007) whereas modeling efforts of particle deposition in the whole lung has usually used stochastic or deterministic approaches (Sturm and Hofmann 2004; Svartengren et al. 2004; Segal et al. 2008; Sturm 2013). Table 2 summarizes the characteristics of the common used whole lung particle deposition models.
### Table 2. A brief summary of commonly used models for estimating lung particle deposition.

<table>
<thead>
<tr>
<th>Whole lung model</th>
<th>Semi-empirical</th>
<th>Stochastic</th>
<th>Deterministic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modeling approach</td>
<td>Resolution of particle deposition</td>
<td>Particle tracking approach</td>
<td>Lung structure</td>
</tr>
<tr>
<td>Regions</td>
<td>N/A</td>
<td>Single airway generations</td>
<td>Regional compartments</td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td>Eulerian</td>
<td>Idealized, simplified continuous branching - symmetric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eulerian</td>
<td>Idealized, simplified continuous branching - asymmetric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lagrangian</td>
<td>Asymmetrical models (Asgharian et al. 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial differential equations</td>
<td>Further, asymmetrical as well as symmetrical models accurately describe total particle deposition in vivo (Anjilvel and Asgharian 1995) and in humans (Segal et al. 2000).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-linear ordinary differential equations</td>
<td>Nevertheless, similar regional and generation-by-generation deposition predictions have been obtained with symmetrical and asymmetrical models (Asgharian et al. 2001).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eulerian or Lagrangian</td>
<td>Recently, such CFPD models have been restricted to local parts of the lung due to computational restrictions (Burrowes 2014; Nowak et al. 2003).</td>
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<tr>
<td></td>
<td></td>
<td>Eulerian</td>
<td>Asymmetrical lung structures are closer to reality than symmetrical ones. It has been shown that asymmetry in branching results in a high variability in deposition within airways of the same generation (Hofmann et al. 2000).</td>
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<tr>
<td></td>
<td></td>
<td>Lagrangian</td>
<td>Furthermore, it has been demonstrated that the choice of lung structure, in particular, airway dimensions and number of airway generations (Yu and Diu 1982), and the volume of the dead space (Rissler et al. 2017) significantly influence the prediction of particle deposition.</td>
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<tr>
<td></td>
<td></td>
<td>Partial differential equations</td>
<td>Bronchoconstriction results in narrowing of the airways due to shrinkage of the diameter, locally or throughout the lung branch generations. This heterogeneity changes the airflow dynamics in the lung. In modeling efforts of COPD conditions, correlations between severity of COPD and reduced airway diameters and numbers of airways were identified.</td>
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<tr>
<td></td>
<td></td>
<td>Eulerian</td>
<td>Reduction of airway diameters with up to 40% and number of airways with up to 80% were observed. (Kurashima et al. 2007; Segal et al. 2000; Sturm and Hofmann 2004; Farkhadnia et al. 2016; Sturm 2013; Svartengren et al. 2004; Strum 2013; Williamson et al. 2011; McDonough et al. 2011). Due to limitations of CT resolution, data on airway dimensions beyond generation 6 (&lt;2.0 mm) is difficult to obtain. As a result of airway narrowing, the aerodynamics of airflow and the airway resistance are altered. Airway resistance is mainly affected by changes in airway diameter in the conducting zone (generations 0–16). Airflow becomes with generation number, starting as turbulent with plug flow profile and ends as non-turbulent with parabolic flow characteristics.</td>
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<tr>
<td></td>
<td></td>
<td>Eulerian</td>
<td>Narrowing of airways becomes critical when bronchioles are blocked resulting into cutting off the distal airways. The higher up in the branching airway blockage takes place, the more the distal airways are affected. Reduction of airway diameter locally is a feasible approach to mimic bronchoconstriction. This might require changes in the model to address aerodynamic alterations compatible with large and local narrowing of sections of the lung i.e. border effects (Szoke et al. 2007; Segal et al. 2008; Sturm 2013; Svartengren et al. 2004; Sturm and Hofmann 2004; Farkhadnia et al. 2016; Sturm 2017). However, freely available lung models do not offer the possibility to include bronchoconstriction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eulerian</td>
<td>Modeling of</td>
</tr>
</tbody>
</table>
Emphysema

Lung hyperinflation, due to destruction of the alveolar parenchyma, in emphysema results in increased alveolar volume and fewer alveoli. In the freely available tools, effects of emphysema cannot be simulated. In other models, different approaches have been used to integrate emphysema into whole lung models. The common theme is to increase volume of the alveoli. In the deterministic symmetric model, alveolar degeneration in COPD patients was described by increasing the alveolar volume by 10 to 30% (Segal et al. 2008). No major effect compared with healthy lung was observed. In the stochastic asymmetrical model applied by Sturm and coworkers, four different types of emphysema were simulated; (1) centriacinar, (2) paraseptal, (3) panacinar, and (4) bullous. The differences between these four types are related to the alveoli structure. Alveoli are connected to the conducting airways from generation 12 to 21 and after that on the alveolar duct. The volume of the alveoli increases and distributes further down along the airway generation when the emphysema goes from centriacinar to bullous. For all four types of emphysema, the calculated fraction of particles deposited in the entire lung as well as in the alveolar region decreased compared to the healthy lung (Sturm and Hofmann 2004; Sturm 2017).

Elastic recoil

During breathing the lung rhythmically expands and contracts. Since bronchioles are relatively stiff, the major parts of these movements take place in the alveolar region. Expansion and contraction of the alveoli have been included in CFPD simulations of the healthy lung (Kolanjiyil et al. 2017). So far, the loss of elastic recoil (increased compliance) has not been included in whole lung particle deposition models.

Breathing pattern

The existing models do not adequately address the dynamics of breathing i.e. how the lung is filled with air, an especially important for COPD patients compared with healthy subjects. The breathing pattern, and in particular the inhalation time have been shown to influence the deposition of particles in the lung (Falk et al. 1999; Rissler et al. 2017; Jakobsson et al.

| Table 3. The various lung structural and functional properties relevant to chronic obstructive pulmonary disease (COPD) that have been addressed in the existing in silico models. |
|---|---|---|---|---|---|
| **Reference** | Segal 2002 | Sturm and Hofmann 2004 | Sturm 2013 | Sturm 2017 | Svartengren et al. 2004 |
| **Modeling approach** | Deterministic | Stochastic | Stochastic | Stochastic | Deterministic |
| **Particle tracking approach** | Eulerian | Lagrangian | Lagrangian | Lagrangian | Eulerian |
| **Lung structure (simplified)** | Symmetric | Asymmetric | Asymmetric | Asymmetric | Symmetric |
| **Experimental data** | Airway resistance, FRC | No | No | No | No |
| **Reported particle deposition in the lung** | 0–23 airway generations | ALV | ET, TUB, ALV | Total lung | BB, bb, ALV |
| **Modeling addresses** | Bronchoconstriction | Yes | Yes | Yes | No | Yes |
| **Emphysema** | Yes | Yes | No | Yes | No |
| **Elastic recoil** | No | No | No | No | No |
| **Breathing conditions** | No | No | Yes | No | Yes |
| **Lung clearance** | No | No | Yes | No | Yes |
| **Mucus clearance** | No | No | Yes | No | No |
| **Modeling parameter values** | Particle size | 1 μm | 1 nm–10 μm | 10 nm–10 μm | 0.84 μm | 6 μm |
| **Particle density** | 0.91 g/cm³ | * | * | 1 g/cm³ | * |
| **Inspiratory flow (l/s)** | 0.5 | 0.25–0.5 | * | 0.25 | 0.05 |
| **Inhalation time (s)** | 1 | 2 | * | 4 | 20 |
| **Duty cycle (Ti/Ttot)** | 0.5 | * | 0.5 | 1000 | 1000 |
| **Tidal volume (TV, ml)** | 500 | 500–1000 | * | 3300 | 3300 |
| **Functional residual capacity (FRC, ml)** | 1850–6820 | 3300–5000 | * | 3300 | 3400–5400 |
| **Other comments** | Compared parabolic and plug flow. | Compared different mixing factors in alveolar sac | Addresses clearance and compared sitting to light-work breathing conditions | Injection of bolus doses at different time points during inhalation | Slow inspiration flow for target deposition |

ALV: alveolar region, BB: bronchial region, bb: bronchiolar region, ET: extra-thoracic region, FEV1%: percent predicted forced expiratory volume in 1 s, FRC: functional residual capacity, Raw: total airway resistance, TUB: tubular compartment containing the entire bronchial network, *: not reported.
To some extent, alteration of breathing pattern can be addressed in the existing models, including the freely available models, by changing the relevant parameters, namely inhalation time, exhalation time and/or breath holding time. The common approach in the modeling of particle deposition in COPD patients is to set inhalation and exhalation times equal with no breath holding (Sturm and Hofmann 2004; Sturm 2013, 2017 and Segal et al. 2008). However, there seems to be substantial disagreement and contradictory data regarding the effect of COPD on the modeling parameters related to airflows and breathing pattern. Clinical measurements on COPD patients indicate that these parameter values can vary. Overall, it appears that the inhalation time is shorter than the exhalation time and that the difference increases with disease severity and with physical exercise (Löring et al. 2009; Wilkens et al. 2010; Vestbo et al. 2013; Motamedi-Fakhr et al. 2016). Low inhalation airflow has been shown to increase the particle delivery to the small conductive airways. Slow inhalation was applied in modeling and experimental validation of particle deposition in patients with chronic bronchitis (Svartengren et al. 2004). In another model simulating bronchoconstriction, the breathing conditions under sitting and light exercise showed similar particle deposition patterns (Sturm 2013). Table 3 summarizes the various structural and functional properties relevant to COPD that have been addressed in the existing in silico lung models.

**Physiologically relevant modeling of the COPD lung**

Based on the reviewed information it seems that in order to mimic physiologically relevant COPD lung for modeling of particle deposition the deposition in COPD lungs needs to be better understood and existing models have to be modified and validated against experimental data. Factors that require further attention are: (i) heterogeneity and reduced airway diameters (to mimic bronchoconstriction), (ii) reduced number of alveoli and increased volume per alveolus (to mimic emphysema), (iii) increased inspiratory airflow (i.e. shortened inhalation time) and reduced expiratory airflow (i.e. prolonged exhalation time) (to mimic altered breathing, particularly expiratory airflow limitation), (iv) inability of the lung to inflate upon inhalation and deflate upon exhalation (to mimic lung tissue fibrosis, loss of lung elasticity, and abnormal air-filled spaces), (v) slower mucociliary clearance, (vi) increased tidal volume, and (vii) site-specific deposition modeling. We are unaware of any existing computational lung model that allows for adjustment of all these factors. Modeling of particle deposition in COPD is highly complex and requires close interdisciplinary collaboration. Figure 1 provides a summarized view of various factors for considerations to model a COPD lung. Currently, there are limitations regarding biological data for input as model parameters as well as experimental data on particle deposition for model validation. Both types of data are required for better understanding of the deposition pattern, especially in the COPD lung.

**Perspective**

Clinically potential domains currently considered for future management of COPD include: systemic and pulmonary inflammation, lung microbiome, disease activity as well as imaging for emphysema, lung cancer, bronchiectasis and molecular imaging (Agusti 2014). Thus, to achieve physiologically relevant in silico modeling of the COPD lung, “inflammometry” (e.g. quantitative representation of inflammatory cell recruitment) as well as data obtained from rapidly evolving thoracic imaging techniques including low-dose CT scanners, SPECT, PET, and magnetic resonance imaging (MRI) as well as pulmonary mechanics data generated with the FOT/IOS technique need to be considered. In this context, several large COPD cohort studies may be useful. The COPDGene study (Regan et al. 2010) currently has an enrollment of over 10000 individuals and uses chest CT phenotypes including assessment of emphysema, gas trapping, and airway wall thickening for disease classification. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) COPD subjects (GOLD categories II–IV): 2180, smoking control: 343, and nonsmoking control: 223) study also uses chest CT scans for disease classification (Vestbo et al. 2008). Subpopulations and intermediate outcomes in COPD study (SPIROMICS; 3200 participants) aimed to provide robust criteria for sub-classifying COPD consists of participants in four strata: severe COPD, mild/moderate COPD, smokers without airflow obstruction and nonsmoking controls with expiratory chest CT assessments (Couper et al. 2014). Therefore, quantitative imaging data generated COPDGene, ECLIPSE, and SPIROMICS studies may provide important information for COPD-lung modeling purposes (Agusti 2014; Sheikh et al. 2016). Access to quantitative information on small airway morphometry and damage at different COPD stages will greatly enhance the usefulness of computational modeling to predict particle deposition in the diseased lung. We hope that, in the near future, well-characterized studies for bronchiolar remodeling using quantitative histology and micro-computed tomography, measurement of bronchiolar tissue volume, alveolar space, airways per generation, thickness of epithelial lining fluid, airway wall thickness and vasculature apart from detailed spirometry will become available. Such data will greatly enhance the possibilities to use and develop models that can describe and predict particle deposition, distribution, and clearance of particles in the COPD lung. Still, additional knowledge is needed to fully understand the pathophysiology of COPD in relation to particle deposition. Such areas include regional alterations in morphology resulting in regional differences in ventilation and particle deposition, as well as changes in breathing pattern, epithelial integrity, clearance capacity (mucociliary, macrophagic) and inflammatory cell recruitment. Therefore, it is also essential to generate experimental data in parallel with model development. To conclude, the field requires close interdisciplinary collaborative work amongst experimental, clinical, and computational fields to understand particle deposition in COPD by addressing stage-specific disease heterogeneity.
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Declaration of interest

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The authors’ affiliations are as shown on the cover page. The authors participated in the development of the paper as individual professionals and not as representative of their employers. None of the authors have been involved in the last five years with regulatory or legal proceedings related to the contents of the paper.

Prior to submission, the manuscript was submitted to AZ for internal review for the sole purpose to check that the paper did not violate AZ’s proprietary rights or business secrets. The internal review was not intended to, and did not, result in any changes to the manuscript. The contents of the paper, including the conclusions drawn, are exclusively the views of the authors and not necessarily those of their employers.

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