Eulerian modelling of lung deposition with sectional representation of aerosol dynamics

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Abstract

A dynamical model of respiratory deposition is developed based on an Eulerian approach. The model simulates detailed lung deposition along all generations of the respiratory tract by solving numerically the aerosol general dynamics equation (GDE). All deposition mechanisms are described mechanistically, without using any empirical correlations. The GDE is solved in a one-dimensional form using a sectional method to describe the aerosol size distribution. To describe lung geometry the classical Weibel’s morphometric model is used, employing a time-varying alveolar geometry to accommodate inhalation dynamics. A computationally efficient methodology is implemented based on a time-step splitting and subcycling approach, combined with a moving grid method for the growth process. The model is validated by comparing extensively with experimental and numerical results. The simulation results show that aerosol dynamics, in particular condensational growth, significantly influence respiratory deposition of fine hygroscopic particles. Instead, the effect of coagulation was found to be negligible. Particle deposition in terms of number, surface, or mass is addressed, which is of interest to current inhalation toxicology studies.

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Keywords: Aerosol dynamics; Lung deposition; Inhalation dosimetry; Sectional method

1. Introduction

The estimation of the aerosol deposition and its distribution in the respiratory tract (RT) during breathing is of importance in environmental health and occupational hygiene assessments, providing valuable
## Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>(A_A)</td>
<td>cross-sectional area of all airways at distance (x)</td>
</tr>
<tr>
<td>(A_T)</td>
<td>cross-sectional area of all airways and alveoli at distance (x)</td>
</tr>
<tr>
<td>(C_c)</td>
<td>Cunningham slip correction factor</td>
</tr>
<tr>
<td>(D_B)</td>
<td>Brownian diffusion coefficient</td>
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<tr>
<td>(D_{\text{eff}})</td>
<td>effective diffusion coefficient</td>
</tr>
<tr>
<td>(D_v)</td>
<td>vapour diffusivity in air</td>
</tr>
<tr>
<td>(d)</td>
<td>particle diameter</td>
</tr>
<tr>
<td>(d_A)</td>
<td>airway diameter (constant)</td>
</tr>
<tr>
<td>(d_T)</td>
<td>airway diameter (time-dependent)</td>
</tr>
<tr>
<td>(g)</td>
<td>acceleration due to gravity, Fuch’s length</td>
</tr>
<tr>
<td>(K)</td>
<td>coagulation kernel</td>
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<tr>
<td>(K_B)</td>
<td>Brownian kernel</td>
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<tr>
<td>(K_G)</td>
<td>gravitational kernel</td>
</tr>
<tr>
<td>(k_g)</td>
<td>fluid (gas) thermal conductivity</td>
</tr>
<tr>
<td>(k_B)</td>
<td>Boltzmann’s constant</td>
</tr>
<tr>
<td>(L)</td>
<td>generation length</td>
</tr>
<tr>
<td>(L_H)</td>
<td>latent heat of condensation</td>
</tr>
<tr>
<td>(M_l)</td>
<td>water molecular weight</td>
</tr>
<tr>
<td>(M_s)</td>
<td>dry particle molecular weight</td>
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<tr>
<td>(m)</td>
<td>particle mass</td>
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<tr>
<td>(m_0)</td>
<td>dry particle mass</td>
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<tr>
<td>(N)</td>
<td>particle number concentration</td>
</tr>
<tr>
<td>(N_B)</td>
<td>total number of size bins</td>
</tr>
<tr>
<td>(n)</td>
<td>number of airways at a distance (x)</td>
</tr>
<tr>
<td>(n_s)</td>
<td>number of dissociated ions</td>
</tr>
<tr>
<td>(P_d)</td>
<td>deposition efficiency</td>
</tr>
<tr>
<td>(P_s)</td>
<td>saturation vapour pressure</td>
</tr>
<tr>
<td>(Re)</td>
<td>Reynolds number</td>
</tr>
<tr>
<td>(R_v)</td>
<td>gas constant for water vapour</td>
</tr>
<tr>
<td>(S)</td>
<td>saturation ratio</td>
</tr>
<tr>
<td>(S_{\text{cp}})</td>
<td>particle Schmidt number</td>
</tr>
<tr>
<td>(Sh)</td>
<td>Sherwood number</td>
</tr>
<tr>
<td>(Stk)</td>
<td>Stokes number based on airway diameter</td>
</tr>
<tr>
<td>(Stk')</td>
<td>Stokes number based on radius of circular motion</td>
</tr>
<tr>
<td>(s)</td>
<td>particle surface</td>
</tr>
<tr>
<td>(T)</td>
<td>period of the breathing cycle</td>
</tr>
<tr>
<td>(T_g)</td>
<td>fluid (gas) temperature</td>
</tr>
<tr>
<td>(t)</td>
<td>time</td>
</tr>
<tr>
<td>(u)</td>
<td>fluid velocity</td>
</tr>
<tr>
<td>(u_s)</td>
<td>terminal settling velocity</td>
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information on the complete exposure–dose–response relationship (EPA, 1996). Realistic inhalation dosimetry modelling is required in epidemiological, toxicological or pathological studies (Balashazy, Hofmann, & Heistracher, 2003). It is also important in the analysis of inhaled pharmaceutical aerosols, delivered for lung diseases or other therapeutic purposes.

In respiratory deposition modelling one may distinguish between two broad categories of models, namely, empirical and mechanistic models. The empirical models consider the human RT as a series of anatomical compartments through which the aerosol passes during a breath (Chan & Lippmann, 1980; Rudolf, Gebhart, Heyder, Schiller, & Stahlhofen, 1986; Chang, Griffith, Shyr, Yeh, Cuddihy, & Seiler, 1991; Phalen et al., 1991; ICRP, 1994). Each compartment is seen as a filter; hence, respiratory deposition is seen as a stationary filtering process. The expressions describing the filtering efficiencies derive from, and therefore fit on, experimental data. Such models are attractive because they are simple to use. In particular, the model recommended by the International Commission on Radiological Protection (ICRP, 1994) finds wide application, and is considered as a standard model for routine inhalation dosimetry assessments. Clearly, however, the application range of such models is strictly limited to the specific morphology, physiology and lung conditions for which the model parameters were adjusted, and, therefore it is not possible to investigate different conditions and exposure scenarios.
Mechanistic models calculate respiratory deposition on the basis of a more realistic description of lung structure and physiology, and as a result of physical processes. The essential benefit of mechanistic modelling is the ability to address a variety of conditions. For example, it is possible to investigate breathing pattern variations (important in the study of subjects with chronic obstructive pulmonary diseases—COPDs), or effects connected with the respiratory tract morphology (important in extrapolating from laboratory animal’s toxicological studies to humans). Mechanistic models can be classified in a number of ways. One may distinguish between Eulerian and Lagrangian models, depending on the frame considered in calculating the aerosol flow (stationary or moving with the flow, respectively). They can be classified as deterministic or stochastic, depending on the description of the flow pathway in the lung. Deterministic models employ a single predefined path representing average lung conditions, whereas stochastic models implement Monte Carlo techniques to account for lung asymmetry and path variations. One may also distinguish between models based on idealized descriptions of lung morphology and physiology (e.g. Weibel’s scheme) and computationally intensive models based on computational fluid dynamics (CFD). The former are able to analyse the whole RT, whereas the latter are limited in determining detailed deposition patterns in single elements of the RT in isolation from the rest of the system (e.g. a bifurcating airway, or a single alveolated duct). A detailed discussion on mechanistic respiratory deposition modelling can be found elsewhere (e.g. in Finlay, 2001).

Aerosol physical processes during breathing have been considered by several authors (Ferron, Kreyling, & Haider, 1988; Persons, Hess, & Scherer, 1987; Broday & Georgopoulos, 2001; Robinson & Yu, 2001). As a rule, condensational growth due to the hygroscopicity of inhaled particles is the only process considered. Very few studies exist in which more aerosol processes are incorporated. Such an example is the work of Robinson and Yu (2001) on cigarette smoke particles, where coagulation was also included, albeit in an approximate manner. Previous respiratory deposition models including aerosol dynamics use exclusively a Lagrangian approach: the sizes of the particles are tracked following an “aerosol bolus” that moves through the generations of the respiratory system. Indeed, the Lagrangian approach is more convenient for tracking hygroscopic growth in an aerosol flow. However, a Lagrangian scheme has serious limitations in describing the change in form of the aerosol bolus due to axial dispersion, or in describing time-varying flow rates and aerosol concentrations. These difficulties can be dealt with by employing an Eulerian approach. This, on the other hand, requires that appropriate numerical provisions be taken for the aerosol processes, especially growth, which is more complicated to calculate with an Eulerian description. It is not therefore surprising that the Eulerian respiratory deposition models that exist in the literature (e.g. Nixon & Egan, 1987; Taulbee & Yu, 1975) consider inert particles and deal primarily with effects connected with physiological and morphological attributes, rather than aerosol effects. Only recently researchers have included aerosol dynamical processes in Eulerian formulations of respiratory deposition, as for example in Lazaridis, Broday, Hov, and Georgopoulos (2001), who considered growth, coagulation and thermophoresis, ignoring, however, axial dispersion.

The purpose of the present work is to present an Eulerian, whole-RT deposition model with full aerosol dynamics effects, incorporating simultaneously hygroscopic growth and coagulation. The work is an extension and refinement of an Eulerian model developed recently by the authors (Mitsakou & Housiadas, 2003). The size distribution is described with a sectional method, which allows for arbitrary functional forms of the size distribution. In treating condensational growth one-way coupling is assumed, i.e. the particulate phase is assumed to exert negligible influence on the surrounding gas phase. This is the usual simplification made in respiratory deposition modelling. Finlay and Stapleton (1995) included heat and mass transfer coupling between particles and gas and demonstrated that in most cases two-way
coupling effects may be disregarded. To describe lung geometry the classical Weibel’s morphometric model is used. A time-varying alveolar geometry is employed to accommodate inhalation dynamics. Clearly, by employing deterministic typical-path lung geometry, the same deposition is predicted at all airways belonging to the same generation regardless of their position in the lung. Therefore, lobar or site-specific deposition cannot be obtained. Still, however, average deposition per generation can be satisfactorily predicted. To assess the accuracy obtained in terms of average deposition, comparisons with results from stochastic models are made.

Due to the idealized geometry used the model is computationally tractable and can deal with the whole airway tree structure. Our focus is on lung (i.e. thoracic) deposition and most cases considered are concerned with the aerosol entering the trachea. However, where necessary, the influence of the extrathoracic region is estimated with a simplified approach. Modelling of the thoracic region is based on a comprehensive description of aerosol processes along the human respiratory tract by employing generic theory for each process individually, without using adjustable parameters or lung deposition empirical correlations. The model is validated by comparing extensively with measurements and previous numerical results. Since the model is based on generic mechanistic principles, the favourable validation results provide confidence as to the ability of the model to apply over a variety of exposure scenarios and conditions. Hence, contrary to empirical models the present model may eventually be used for extrapolation beyond the range in which measurements are available. Moreover, the ability to predict detailed size-resolved deposition enables to assess lung deposition in terms of a variety of metrics, as number, mass or surface. This is of relevance to current toxicological and biological studies, as surface and number represent prominent parameters for describing the interactions between particles and biological fluids, cells and tissues (Kreyling, Semmler, Erbe, Mayer, Takenaka, & Schulz, 2002; Oberdörster et al., 2002; Wichmann et al., 2000).

2. Model description

2.1. Lung morphology—respiration physiology

The morphology of the lung is described with the help of the classical morphometric model “A” by Weibel (1963). The respiratory tract is an air conducting system in the form of an airway tree. The airways branch dichotomously beginning from generation 0, the trachea and ending to generation 23, which corresponds to the alveoli. The model is symmetric, and therefore the number of airways in every generation \( j \) is \( 2^j \). Generations 0–15 make up the so-called tracheobronchial region and generations 16–23 belong to the alveolar-interstitial or acinar region of the lung. Starting from generation 16, the airways become alveolated and the lung is expanded and contracted during respiration. The adopted single-path symmetric model has the advantage of being robust and simple, without requiring detailed knowledge of the branching structure of the lung. On the other hand, only average conditions can be simulated along the RT airway tree. However, this limitation does not seem to be stringent because there is evidence that the influence of the heterogeneity of lung structure on deposition calculations is not very large. Yu and Diu (1982) calculated total and regional deposition of inhaled particles in the lung based upon various lung models. They concluded that total deposition calculations for different lung models do not differ greatly. Regional and per generation deposition differences are somehow larger but within the scatter due to intersubject variability of the human lung morphology. Asgharian, Hofmann, and Bergmann (2001)
compared deposition predictions from 3 lung geometry models. Their results (which will be discussed below in more detail) show similar regional and per generation deposition for all lung models.

The flow path is described with the help of the so-called trumpet model of the lung, which is the most appropriate geometrical scheme for implementing a one-dimensional (1-D) modelling approach. Accordingly, the cross-sectional area of the flow path increases sharply with distance from the entrance of the trachea, because it is taken as the sum of the cross-sectional areas of all the individual airways belonging to the same generation. After generation 16, the airways become alveolated. The volume of the alveolated section of the lung is let to vary with time to accommodate effects due to breathing dynamics. The mean value of the lung volume during a breathing cycle is taken to be equal to the functional residual capacity plus one-half of the tidal volume. Hence, lung volume is considered to vary as

\[ V_L = \left( V_{\text{FRC}} + \frac{V_T}{2} \right) + \frac{V_T}{2} f(t), \]

where \( f(t) \) is a function of time that takes values between 1 (end of inspiration) and \(-1\) (end of expiration), i.e. \(-1 \leq f(t) \leq 1\). This function describes the breathing pattern during the cycle and can be specified arbitrarily. In the present study symmetric two-phase breathing is assumed; therefore, function \( f(t) \) is specified by a sinusoidal function. The diameters of the alveolated airways vary with time as

\[ \frac{d_T}{d_A} = \left( \frac{V_L}{V_{\text{FRC}}} \right)^{1/3} \quad \text{for generations} \geq 16. \]

The value \( d_T = d_A \) at \( V_L = V_{\text{FRC}} \) (beginning of the cycle) is determined by adjusting the original Weibel data, which correspond to a lung volume of 4.8 l, by a scaling factor of \( (V_{\text{FRC}}/4.8 \text{ l})^{1/3} \).

2.2. Aerosol dynamics

Different processes, acting simultaneously determine the transport and fate of the inhaled particulate matter. This is described with the aerosol general dynamic equation (GDE), which, here, is considered in a 1-D form along the flow direction. The size distribution is described with a sectional method, which allows for arbitrary functional forms of the size distribution. The considered GDE reads

\[
\frac{\partial}{\partial t} (A_T N_i) = - \frac{\partial}{\partial x} (A_A u N_i) + \frac{\partial}{\partial x} \left( A_T D_{\text{eff}} \frac{\partial N_i}{\partial x} \right) - V_{d_i} \Gamma N_i \\
+ \left( \frac{\partial}{\partial t} (A_T N_i) \right)_{\text{growth}} + \left( \frac{\partial}{\partial t} (A_T N_i) \right)_{\text{coagulation}}.
\]

If \( d_T \) is the diameter of an individual airway at distance \( x \) from the entrance of the trachea, then the cross-sectional area \( A_T \) is calculated as \( A_T = n \pi d_T^2 / 4 \), where \( n \) is the total number of airways in the respective generation. The corresponding wetted perimeter is taken as \( \Gamma = n \pi d_T \). Since \( d_T \) varies with time in the alveolated part of the lung by Eqs. (1) and (2), \( A_T \) and \( \Gamma \) are also functions of time, expanding and contracting during the cycle. The cross-sectional area \( A_A \) in the convective term [first term of the right-hand side of Eq. (3)] is taken constant during breathing, with the value corresponding at conditions at rest, \( A_A = n \pi d_A^2 / 4 \). Area \( A_A \) is taken to be constant because convective transport is assumed to occur through the cross-sectional area corresponding to the airways alone (conducting part), and not through
the part corresponding to the alveoli. This assumption is in agreement with previous analyses (Finlay, 2001; Egan & Nixon, 1985).

To solve Eq. (3) the air velocity \( u = u(x, t) \) along the airways of the respiratory tract is needed. It is determined by solving the equation of continuity, which is given below

\[
\frac{\partial A_T}{\partial t} = -\frac{\partial (A_A u)}{\partial x}. \tag{4}
\]

In the absence of convective flow, the axial transport of particles along the lung would be controlled by Brownian diffusion alone. Convective aerosol flow changes direction periodically during respiration (inspiration–expiration) and as a result, a complicated flow pattern is developed, accompanied by bulk irreversible mixing between tidal volume and reserved air. Scherer, Shendalman, Greene, and Bouhuys (1975) investigated experimentally these effects in the first generations of the Weibel geometry and proposed an effective axial diffusion coefficient to account for bulk mixing. Below are given, the effective diffusion coefficients, different in case of inspiration and expiration

\[
D_{\text{eff}} = \begin{cases} 
D_B + 1.08 \cdot u \cdot d_T & \text{for inspiration,} \\
D_B + 0.37 \cdot u \cdot d_T & \text{for inspiration.} 
\end{cases} \tag{5}
\]

Note that the above expression is empirical and that there is uncertainty as to its validity in different parts of the RT. It has been selected because it has the merits of simplicity, of being consistent with the used Weibel description, and of being the most frequently quoted formula for axial dispersion in the RT. In Eq. (5) the Brownian diffusion coefficient \( D_B \) is determined from the Stokes–Einstein equation

\[
D_B = \frac{k_B T g C_c}{3\pi \mu_g d^2}. \tag{6}
\]

Note that in the above expression the Cunningham slip correction factor has been included to account for the slip effects of the submicrometer particles.

The particle deposition is assumed to be the result of the combined effects of gravitational settling, Brownian diffusion and inertial impaction. The deposition velocity \( V_d \) is taken as the sum of the deposition velocities corresponding to each individual effect, namely \( V_d = V_{d(\text{sed})} + V_{d(\text{dif})} + V_{d(\text{imp})} \). Below an account is given on the way each individual component is determined.

The deposition velocity due to gravitational settling is written as

\[
V_{d(\text{sed})} = u_s \sin \theta, \tag{7}
\]

where \( u_s = \rho_d d^2 g C_c / 18 \mu_g \) is the terminal settling velocity as determined from the Stokes’ law for the drag force. Angle \( \theta \) the so-called gravity angle, which is the angle between the airway direction and the force of gravity. The gravity angle is taken from Weibel’s data. The term \( \sin \theta \) is included in Eq. (7) so that deposition flux is correctly attributed to a fraction of the inner airway surface, since sedimentation is a directional mechanism.

The deposition velocity due to Brownian diffusion is determined from mass transfer theory. It is expressed in terms of the concentration boundary-layer thickness, where according to the heat-mass transfer analogy the Nusselt number is replaced by the Sherwood number, \( Sh \)

\[
V_{d(\text{dif})} = \frac{D_B Sh}{d_T}. \tag{8}
\]
The local Sherwood number $Sh$ is specified as function of the distance from the beginning of the airway to properly account for entrance effects. The function $Sh = Sh(x)$ is given by an infinite series, whose accurate numerical evaluation requires considerable effort (Housiadas, Larrode, & Drossinos, 1999). For simplicity, the algebraic fittings of Shah and London (1978) are used, which provide the local Sherwood (Nusselt) number with accuracy better than 3% over the whole entrance length of the duct as function of the dimensionless length $x^+ = x/d_TReSc_p$:

$$Sh(x^+) = \begin{cases} 
1.077(x^+)^{-1/3} & \text{for } x^+ \leq 0.01, \\
3.657 + 6.874(10^3x^+)^{-0.488}\exp(-57.2x^+) & \text{for } x^+ > 0.01. 
\end{cases} \quad (9)$$

Deposition due to inertial effects (impaction) is determined on the basis of a simplified analysis of the curvilinear motion in the airway bifurcation region. Let $r_c$ be the radius of the curvature of the streamlines as flow is divided into the two daughter tubes. The centrifugal force acting on an aerosol particle will be $mu^2/r_c$ giving rise to a drift velocity equal to $u^2/r_c$. The latter makes particles escape the flow and impinge on the walls, and therefore, can approximate the deposition velocity of the process. It can be further expressed as $V_{d(imp)} = Stk'u$ with the Stokes number $Stk'$ defined on the basis of the radius of the circular motion ($Stk' = u/r_c = Stkd_T/r_c$). Simple geometrical considerations indicate that the radius $r_c$ can be written as $r_c = L_c/\phi$ where $\phi$ is the branching angle (in radians) between parent and daughter airway and $L_c$ the length of the curved branching zone. The length $L_c$ can be approximated as $L_c = 0.2L$, based on the physiologically realistic bifurcation (PRB) geometry proposed by Heistracher and Hofmann (1995). According to the PRB description 80% of the length of an airway is a straight tube and the last 20% constitutes the curved transition (branching) zone. On that basis, the deposition velocity is expressed as follows:

$$V_{d(imp)} = \begin{cases} 
0 & \text{over the first 80\% of the airway length),} \\
Stk' u = Stk u d_T / 0.2L & \text{over the last 20\% of the airway length).} 
\end{cases} \quad (10)$$

In the literature there are several empirical formulas for the impaction deposition efficiency in the lung airways. Finlay (2001) made an intercomparison of the various formulas and qualified the correlation of Chan and Lippmann (1980) as the most typical and representative one. The Chan and Lippmann correlation is given in terms of deposition efficiency as $P_{d(imp)} = 1.606Stk + 0.0023$. The predictions of this correlation are compared with the predictions of Eq. (10) in Fig. 1. To this end, the corresponding deposition efficiency has been determined from a simple mass balance over the airway tube as follows:

$$P_{d(imp)} = 1 - \exp(-4\phi Stk). \quad (11)$$

The measurement data of Chan and Lippmann (1980) are also shown in the figure. As can be seen there is a trend in the predictions of Eq. (11) towards higher values. Still, the predictions agree quite closely with the correlation of Chan and Lippmann, and pass satisfactorily through the experimental points. This comparison demonstrates the validity of the employed approach for the calculation of the impaction deposition [Eq. (10) and its counterpart, Eq. (11)]. Note also that the approach is based on a simplified, albeit formal analysis, without employing an empirical fitting procedure.

The growth term in Eq. (3) is written in terms of particle diameter increase is as follows:

$$\frac{\partial N_i}{\partial t} = -\frac{\partial}{\partial d_i} \left( \frac{d d_i}{d t} N_i \right). \quad (12)$$
The increase rate of particle diameter (growth law) is calculated according to the theory of Mason (1971), as follows:

$$\frac{d_d}{dt} = \frac{1}{d_i^3} \left( S - 1 - 4\sigma/d_i^3\rho_1 R_v T_g + 6n_s m_0 M / 2M_\rho d_i^2 \right) (2\lambda/d_i + 1)/(1 + 5.36(\lambda^2/d_i^2) + 3.42\lambda/d_i))$$

$$\rho_1 R_v T_g / 4D_v P_s + (L_H / R_v T_g - 1)L_H / 4k_g T_g$$

(13)

As can be noted, the Kelvin effect and the solute mass effect have been incorporated in the above equation, by introducing appropriate corrections to the term $S - 1$ (first and second term after term $S - 1$, respectively). Also, the Fuchs correction has been incorporated to account for diffusional growth in the whole range from continuum to free molecular regime (term in the second parenthesis of the nominator).

The coagulation term of Eq. (3) is given on the basis of a modified Smoluchowski equation, appropriate for a sectional representation of the particle size distribution. According to the theory of Jacobson, Turco, Jensen, and Toon (1994), the coagulation equation in the sectional approach can be approximated as follows:

$$\frac{dN_i}{dt} = \sum_{j=1}^{i} \sum_{k=1}^{i-1} f_{i,j,k} K(d_j, d_k) \frac{v_k}{v_i} N_j N_k - v_i N_i \sum_{j=1}^{N_B} (1 - f_{i,j,i}) K(d_i, d_j) N_j$$

(14)

The first term on the right-hand side of Eq. (14) accounts for appearance of particles in the $i$th size bin due to collisions of smaller particles and the second term accounts for depletion of particles in the $i$th size bin due to collisions with all other particles. The coefficients $f_{i,j,k}$ arise from the sectional representation of the size distribution, and represent the fraction of the new particles formed from collisions of sizes $j$ and $k$ that is partitioned into size bin $i$. These coefficients are given as follows (Jacobson et al., 1994):

$$f_{i,j,k} = \begin{cases} \frac{(v_{k+1} - v_i - v_j)}{(v_{k+1} - v_k)} \frac{v_k}{v_i + v_j}, & v_k \leq v_i + v_j < v_{k+1}, \ k < N_B, \\ 1 - f_{i,j,k-1}, & v_{k-1} < v_i + v_j < v_k, \ k > 1, \\ 1, & v_i + v_j \geq v_k, \ k = N_B, \\ 0, & \text{all other cases}. \end{cases}$$

(15)
The coagulation kernel \( K \) is taken as the linear addition of Brownian kernel \( K_B \) and gravitational kernel \( K_G \), namely \( K = K_B + K_G \). The Brownian kernel is determined from the standard Fuchs interpolation formula (Fuchs, 1964), which is valid over the entire size spectrum, from the continuum regime to the free molecular regime

\[
K_B(d_j, d_k) = 2\pi(d_j + d_k)(D_j + D_k) \left[ \frac{d_j + d_k}{d_j + d_k + 2(g_j^2 + g_k^2)^{1/2}} + \frac{8(D_j + D_k)}{(d_j + d_k)(c_j^2 + c_k^2)^{1/2}} \right]^{-1}.
\]

(16)

In the above equation the mean particle velocity is \( \bar{c}_i = \left( \frac{8k_B T_g}{\pi m_i} \right)^{1/2} \) and \( g_i \) is the so-called Fuch’s length

\[
g_i = \frac{1}{3d_i l_i} [(d_i + l_i)^3 - (d_i^3 + l_i^3)^{3/2}] - d_i
\]

(17)

with \( l_i = 8D_i / (\pi \bar{c}_i) \) the mean free path of the aerosol particle. The particle diffusion coefficients in Eq. (16) are determined from Eq. (6). The gravitational kernel is calculated as the product of the effective target area times the relative particle velocity

\[
K_G(d_j, d_k) = \frac{\pi(d_j + d_k)^2}{4} |u_{s_j} - u_{s_k}|.
\]

(18)

The solution of the system of Eqs. (3) and (4) subject to the boundary and initial conditions allows the determination of the number concentrations of each size section \( N_i \) as functions of time along the whole respiratory tract, i.e. \( N_i = N_i(x, t) \). Hence, the model permits to track the changes of the size distribution throughout the whole respiratory tract during the breathing cycle. The deposited fraction in a specific area of the lung with length \( L \) (for example, a generation) is determined as the fraction of the number of particles deposited in the area to the number of particles that are introduced in the RT, consequently

\[
\text{deposition fraction} = \frac{\sum_{i=1}^{N_B} \int_0^T \int_0^L N_i n V_d_i \Gamma \, dx \, dt}{\sum_{i=1}^{N_B} \int_0^T \int_0^{T/2} N_i A_{A_0} u_0 \, dt},
\]

(19)

where \( A_{A_0} \) is the cross-sectional area of the entrance and \( u_0 \) the air velocity at the entrance. The deposited fraction in terms of mass, or surface is determined by the same equation above, by using, respectively, \( N_i m_i \), or \( N_i s_i \) in place of \( N_i \).

The point \( x = 0 \) may represent the entrance of the trachea, or the mouth/nose inlet. In the former case thoracic deposition is calculated. In the latter case a fictitious generation is added before generation zero.
(trachea) simulating the extrathoracic region. In this fictitious generation deposition is no longer determined from the mechanistic models described above, but form the empirical correlations of ICRP (1994) that give the deposited fraction in the head airways during nasal or oral breathing. Instead, growth and coagulation are calculated as before. Eqs. (13) and (14) are integrated over a time interval equal to the flow transit time through the head airways. The transit time of each breathing phase (inspiration, expiration) is determined as 

\[ V_D(\text{ET}) \frac{\dot{V}}{V} \]

where \( V_D(\text{ET}) \) is the anatomical dead space of the extrathoracic region with \( \dot{V} = 2V_T/T \) being the volumetric flowrate. There is an effort underway to describe the extrathoracic region as a series of sequential cylindrical parts and calculate deposition with the same methodology as in the thoracic region. Satisfactory results have been obtained for mouth breathing (Mitsakou, Helmis, & Housiadas, 2004), by employing the simplified geometrical description of Stapleton, Guentsch, Hoskinson, and Finlay (2000).

2.3. Numerics

It is well-known that the GDE, Eq. (3), describes a complicated interaction of different physical processes giving rise to numerical difficulties and inaccuracies, because each process requires a different time step \( \Delta t \) to ensure the stability of the algorithm. An appropriate technique for improving accuracy and stability without using the most restrictive \( \Delta t \) for all of the processes is to subcycle the process integrations within the global time step \( \Delta t \) (Oran & Boris, 2001). This time-step splitting and subcycling procedure assumes that the process that requires a shorter time step than the global \( \Delta t \) can be decoupled from the other processes for the duration of \( \Delta t \). According to the above approach, Eq. (3) is solved first by neglecting the growth and coagulation terms. Thus, the particle deposition along the respiratory tract is determined for a stable aerosol. In this step the upwind scheme is applied for the first-order spatial derivative (convective term) and the Crank–Nicholson scheme for the second-order spatial derivative (diffusion term). Next, the growth process is computed through subcycling, by integrating Eq. (13) with an integrator for stiff equations. The integrator is based on a fourth-order Rosenbrock method with monitoring of local truncation error to adjust stepsize (Press, Teukolsky, Vetterling, & Flannery, 1994). Finally, the coagulation process is computed by integrating Eq. (14) with the semi-implicit scheme suggested by Jacobson et al. (1994). This scheme requires no iterations and is numerically stable regardless of the time step. The newly derived concentrations are then used as input for the next time step.

A major aspect of the employed algorithm is the use of two grids for the sectional description of the particle size distribution, one fixed and another one moving. As is well-known, the numerical solution of the growth process is characterized by intense numerical diffusion due to the hyperbolic nature of Eq. (12). To minimize numerical diffusion a moving grid method is used (Gelbard, 1990) in which the size sections are allowed to move along the particle size axis according to the growth law, Eq. (13). On the other hand, the solution of the other processes (convection, coagulation and diffusion) requires a stationary grid. Therefore, the concentrations obtained after the growth step are reallocated to the original (stationary) size bins. This reallocation is performed using a cubic spline fitting procedure, as suggested by Lurmann, Wexler, Pandis, Musarra, Kumar, and Seinfeld (1997).

The efficiency of the time-step splitting and subcycling procedure has been tested by calculating the concentration of a monodisperse aerosol along all generations as it evolves during the breathing cycle. Identical predictions have been obtained with or without time-step splitting and subcycling. On the other hand, the computing time was reduced significantly with time-step splitting and subcycling. For example, in a run with particles of diameter \( d = 0.5 \mu m \), period of respiration \( T = 4s \) and tidal volume \( V_T = 1000cm^3 \)
the required computing time on a usual personal computer was about 2 h without the time-step splitting and subcycling technique, whereas it dropped to 3 min when this technique was implemented.

Also, tests have been performed with respect to the grid sizes and time steps employed. Satisfactory convergence is achieved by employing 500 spatial nodes (for the whole RT) and a global time step $\Delta t = 0.01$ s. Regarding particle size distribution, the grid is defined so that the range of interest is logarithmically divided into $N_B$ size sections. Very good convergence is generally obtained with $N_B = 30$.

3. Results

The model has been used to simulate respiratory deposition for hygroscopic and inert (hydrophobic) particles. All the results presented below refer to total or per generation deposition as a function of particle size, in terms of deposited fraction of the amount entering either the trachea or the nose/mouth. Our calculations showed that stationary conditions are established after a number of breathing cycles (generally, between 5 and 10 cycles), depending on particle size. The presented results correspond to the stationary part of the simulations.

First, a series of sensitivity runs was performed to check the responsiveness of the model to parametric variations. The contribution of each deposition mechanism (sedimentation, diffusion, impaction) to lung deposition is shown in Fig. 2. Total deposition (in the thoracic region) is shown as a function of particle diameter, considering each deposition mechanism separately. As can be noticed, the deposition of ultrafine particles is undertaken exclusively by diffusion, whereas coarse particles are deposited predominantly by sedimentation and impaction. Deposition is minimum for fine particles, over the range of intermediate sizes. This result is expected and is in line with the characteristic behaviour of aerosol retention in filters, where also all deposition mechanisms act together.

The influence of the varying lung geometry (expanding and contracting alveolar section) is shown in Fig. 3, where the results obtained with a time-dependent and a fixed lung geometry are compared. The fixed-geometry solution is obtained by replacing $A_T$ with $A_A$ in Eqs. (3) and (4), and calculating the wetted perimeter $\Gamma$ in Eq. (3) as $\Gamma = n\pi d_A$. An inert monodisperse aerosol is considered with $d = 0.05 \mu$m. We
assume symmetric breathing over a period of respiration of $T = 4$ s, and with two different tidal volumes ($V_T = 1000$ or $2000$ cm$^3$). The lung volume at rest is taken $V_{FRC} = 3300$ cm$^3$. The results are shown in terms of normalized particle concentration (with respect to the concentration at the entrance of the trachea) at two moments of the respiratory cycle, one during inspiration ($0.5T$) and another during expiration ($0.8T$). We see that the effect of varying lung geometry, although not very large, is noticeable in the alveolar region (after generation 16). The effect becomes more pronounced with increasing tidal volume, as expected in view of Eqs. (1) and (2). The results indicate that suspended aerosol concentration is overestimated when the lung is taken with fixed geometry. Therefore, with fixed lung the deposited aerosol in the alveolar region tends to be underestimated in comparison with the amount calculated with an expanding/contracting lung.

The influence of the description of morphology has been investigated by comparing our predictions with the simulation results of Asgharian et al. (2001). This work examined the impact of morphometric model selection, by using the respiratory deposition model of Anjilvel and Asgharian (1995) and implementing three different morphological models, namely, a five-lobe symmetric, a typical-path symmetric (a variant of Weibel’s model, as proposed by Yeh, Schum, & Duggan, 1979) and a stochastic model (Koblinger & Hofmann, 1990). The deposition fractions of the amount entering the trachea were calculated for a tidal volume of $625$ cm$^3$ and a period of respiration equal to $5$ s. The same parameters have been also used in our simulations. The models are compared by considering particle sizes throughout the whole size range of interest. Figs. 4a and b show the deposited fractions per generation number for the case of ultrafine particles ($d = 0.01 \mu m$) and fine particles ($d = 1 \mu m$), respectively. In both cases, a satisfactory consistency among the various models (including the present one) can be observed. This result is in agreement with the findings of the inter-comparison study of Asgharian et al. (2001). For coarse particles ($d = 10 \mu m$) the comparison also indicated a similar consistency among models, except over the proximal tracheobronchial region, where, however, the stochastic calculations of Asgharian et al. (2001) are reported with very large uncertainties. On the basis of the above comparisons we may conclude that the obtained improvement when average lung deposition is predicted with detailed and complicated morphological schemes is rather minor and, hence, the employed symmetric model of Weibel is adequate for the purposes of the present study.
Fig. 4. Deposition fraction per generation as calculated with different morphological models for particles with diameter $d = 0.01 \mu m$ (A), $d = 1 \mu m$ (B).

Fig. 5. Total deposited fraction of inert and hygroscopic particles in terms of number for different physiological parameters, as a function of particle diameter.

The effect of growth on particle deposition has been also considered. Indeed, due to the high relative humidity ($\sim 99.5\%$) prevailing in the human lungs, hygroscopic particles are expected to grow significantly as they pass through the water-saturated airways during the respiration process. In Fig. 5 total deposition (extrathoracic and thoracic) of hydrophobic and hygroscopic particles in terms of number is presented as a function of the initial particle diameter. The considered hygroscopic aerosol consists of initially solid NaCl particles. The calculation in the extrathoracic region is done with the approach described at the end of Section 2.2. The spatial variation of temperature and humidity in the head airways and the first proximal generations is ignored. Temperature and humidity are taken as constants for the entire RT. With this simplification growth is enhanced. However, the effect is not large as the sensitivity analysis of Ferron et al. (1988) has indicated. The results of Fig. 5 show that deposition is significantly influenced by hygroscopic growth. The minimum deposition for hygroscopic aerosol shifts to smaller particle
diameters, compared to the deposition of hydrophobic (inert) particles. Indeed, the effect of hygroscopic growth makes the effective particle diameter to appear greater than the initial one. In the same figure, the influence of physiological parameters (tidal volume, period of respiration) is also shown. As can be seen, the greater the average airflow is (i.e. greater tidal volume with constant period of respiration) the deposition tends to increase. Deposition, mostly of coarse particles, increases with the average airflow rate because of the velocity-dependent mechanism of inertial impaction. Moreover, greater deposition is observed in Fig. 5 when the period of respiration increases. Indeed, as the period of respiration increases providing a longer residence time in the lung, the deposition of particles influenced by sedimentation and diffusion is enhanced.

A great deal of effort has been devoted to the validation of the developed model by comparing with available experimental and numerical results. Figs. 6a and b compare the experimental results of Lippmann (1977), Chan and Lippmann (1980) and Stahlhofen, Gebhart, and Heyder (1980) with the predictions of the present model. The data refer to deposited fractions of the aerosol entering the trachea. The predictions of the empirical inhalation dosimetry model recommended by the International Commission on Radiological Protection (ICRP, 1994) are also included. The experimental results have been obtained from in vivo measurements by non-smoker volunteers and from measurements in hollow casts of the human respiratory tree. The experimental measurements and model predictions shown in Figs. 6a and b refer to a tidal volume of 1000 cm$^3$ and a period of respiration of 4 s (with the exception of the data of Stahlhofen et al., which refer to a tidal volume of 1500 cm$^3$). The figures show deposition as a function of particle aerodynamic diameter in the tracheobronchial and alveolar regions, respectively. The agreement of the present model with the experimental data and the ICRP model is satisfactory, considering the scatter in the experimental data. In the tracheobronchial region the ICRP model gives generally lower values than the present model. This is due to the lower impaction deposition calculated by the ICRP model, which uses the Chan and Lippman correlation (see Fig. 1). The consistency between experiments and ICRP predictions is expected, since the ICRP model has been largely fitted against these data. On the other hand, the agreement between experimental data and the predictions of the present model can be considered as a major achievement of the model, because the model has been based on a mechanistic description of deposition without any reference or adjustment to inhalation dosimetry data.
Comparison between the present predictions and experimental results on deposition of hygroscopic particles is given in Fig. 7. For this comparison the experimental data of Tu and Knutson (1984) and Blanchard and Willeke (1984) have been used. Tu and Knutson (1984) studied the total deposition of monodisperse hydrophobic and hygroscopic aerosols, in the size range of 0.03–0.4 μm, for nasal and oral breathing. The hydrophobic aerosols tested are kerosene heater and aluminosilicate particles and the hygroscopic aerosols are sodium chloride. In the experiments of Blanchard and Willeke (1984) monodisperse hygroscopic sodium chloride particles were used. The data shown in Fig. 7 refer to a tidal volume equal to 1000 cm³ and a period of respiration equal to 4 s. The figure shows the experimental results alongside with the predictions of the present model, as a function of the initial particle diameter. The model reproduces satisfactorily the experimental data over the whole size range investigated, considering the uncertainties in the measurements. Furthermore, it is apparent in the experimental data of Tu and Knutson (1984) that the different types of breathing—nasal and oral—do not significantly influence the total deposition for either hydrophobic or hygroscopic particles. This is due to the small influence of the extrathoracic region because the considered particle sizes are the most penetrating in the extrathoracic (and tracheobronchial) region. Deposition mostly occurs in the alveolar region. Indeed, as can be seen in Fig. 7, the differences between oral and nasal breathing (if any) are well masked by experimental uncertainty, indicating that the influence of the extrathoracic deposition is minimal in the considered cases. This trend is also depicted in the simulation results, which change little with or without the extrathoracic region. Here again, the extrathoracic region is calculated with the simplified approach described before. The satisfactory predictions obtained provide evidence as to the ability of the model to calculate hygroscopic growth. Comparisons in terms of regional deposition would further consolidate this conclusion. Unfortunately, such detailed comparisons were not possible due to unavailability of measurements of regional deposition of hygroscopic particles in the human lung.
Fig. 8 shows the deposited fraction as a function of generation number in terms of number, surface, or mass. The shown results refer to monodisperse hydroscopic particles of sodium chloride. Obviously, for an inert monodisperse aerosol the three fractions would be identical. Instead, in the case of hygroscopic particles significant differences can be obtained, as clearly illustrated by the results of Fig. 8. In this simulation the initial particle diameter considered is 0.1 μm, the tidal volume is 1000 cm$^3$ and the period of respiration is 4 s. To investigate the influence of coagulation the simulation was performed by considering growth alone, or growth and coagulation acting together. The mass and the surface of the aerosol increase significantly inside the lung due to condensational growth. Instead, coagulation has negligible influence on the results. We see that while the deposited fraction [defined in Eq. (19)] in terms of number is always < 1, in terms of mass, for example, may well exceed unity. The effect was found to be more pronounced with larger initial particle diameters. This effect should be taken into consideration in the interpretation of toxicological results when surface or mass is used as a surrogate for the toxicologically effective lung dose.

4. Conclusions

An Eulerian model has been developed that enables the determination of detailed aerosol concentration and deposition along all generations of the respiratory tract, taking into account inhalation dynamics and physical aerosol processes. The description is fully dynamical and mechanistic, and is based on standard theory for the various aerosol processes avoiding the use of empirical correlations specific to inhalation dosimetry. In particular, a simple non-empirical approach for inertial deposition in the lung airways is proposed [Eqs. (10) and (11)], which has been satisfactorily implemented and tested. An advanced numerical scheme is employed, enabling the calculation throughout the whole respiratory tract with little computing effort. The scheme is based on the solution of the aerosol general dynamics equation (GDE) in a one-dimensional form using a sectional method to describe the aerosol size distribution. To deal with stiffness, a time-step splitting and subcycling approach is implemented, combined with a moving
grid method for the growth process to minimize numerical diffusion. A thorough validation exercise was carried out, based on extensive comparisons with available experimental data and previous numerical results. In all comparisons satisfactory agreement was obtained.

Since the model is built from first principles and without reference to inhalation dosimetry empirical correlations, the favourable validation results provide strong confidence as to the ability of the model to apply over a variety of exposure scenarios and lung morphological and physiological attributes. This is an important advancement with respect to the currently used empirical models, such as the model recommended by the International Commission on Radiological Protection (ICRP, 1994), which cannot be really applied outside the strict range in which their parameters have been adjusted. Also, due to its computational efficiency the present model can treat the respiratory tract as a whole and from this point of view offers an important advantage with respect to complicated CFD-based mechanistic models. The latter can deal only with isolated elements of the respiratory system and, as a consequence, are rarely validated against experimental data.

A sensitivity analysis was made which showed that the model responds to varied physiological parameters and different deposition mechanisms in a consistent way. The employed morphological model, although simple and symmetric, produced congruous results in terms of average deposition per generation. Therefore, the selection of the morphological scheme appears to be of secondary importance if average lung deposition is sought. Of course, more advanced morphological description would be required to predict lobar, or site-specific deposition. The model starts the calculations at the entrance of the trachea. The influence of the extrathoracic region can be accounted for with a simple semi-empirical approach, purposely developed. The predictions with or without the extrathoracic region compare favourably with experimental results of hydrophobic and hygroscopic total aerosol deposition of fine particles around 0.1 μm, both in cases of nasal and oral breathing, indicating that the influence of the extrathoracic flow path on total thoracic deposition is not very important for such particle sizes.

The importance of aerosol dynamics along the respiratory tract was clearly illustrated. More specifically, condensational growth of hygroscopic particles is found to influence respiratory deposition significantly. The influence of coagulation was found to be negligible. Inclusion of aerosol dynamics enables the knowledge of the size distribution and by that the calculation of deposition in terms of particle number, mass or surface. In particular, for hygroscopic particles the deposited fraction was found to depend critically on the metric used, and may exceed unity when the metric is mass or surface. This should be taken into account in addressing the exposure-to-dose relationship, depending on the parameter used to describe the toxicologically significant dose.

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