Modeling the particle deposition in the respiratory system during successive respiratory cycles

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Abstract

In this study, using a 5-lobe symmetric model, total, lobar and generational particle deposition in the lungs during successive cycles is investigated. It has been found that for the particle size between 0.05 and 2 \( \mu m \) and the tidal volumes greater than 1000 \( ml \), considering the effect of successive cycles predicted more deposition fraction per cycle compared to a single cycle up to about 16 percent. The mentioned range of tidal volume is related to light or heavy physical activities. So, it can be understood that people exposed to particulate matter within the mentioned size range, when acting physically, are at more health risk compared not only to the resting state, but also to the same state calculations based on a single cycle. Finally, total and generational remaining mass fraction suspended in the respiratory tract after the completion of each cycle is calculated. This remaining mass fraction turned out to be negligible except for particles between 0.05 and 2 \( \mu m \).

**Key words:** particle deposition, respiratory system, lung, lobe, successive respiratory cycles
1. Introduction

The investigation of the amount and the pattern of particle deposition in the human respiratory system, has drawn lots of researchers' attention during recent years. These studies are done pursuing two main goals: the first one is to study and control the adverse effects of the particulate matter air pollution on human health; and the second one is to investigate and increase the deposition rate of aerosolized drug particles in the respiratory system. For the treatment of some diseases, specifically pulmonary diseases, aerosolized drugs are prepared and inhaled. If the particles released from these equipment are in the proper amount and reach the proper spots, the treatment can occur effectively.

So far, a lot of modeling is done in the field of particle deposition in the respiratory system. Some researchers have studied this problem locally, for example in the oral or nasal cavity. On the other hand, some others have developed whole lung models or models representing the whole respiratory system. One of the first studies has been done by Yeh and Schum[1]. They calculated the particle deposition in a single path of the respiratory tract. Koblinger and Hofmann[2-6] in their research series, as well as introducing a novel statistical model, simulated the particle deposition in the respiratory tract using the empirical formulas according to Yeh and Schum[1]. Dastanpour et al.[7] modeled the whole lung particle deposition based on the statistical model and using a Monte-Carlo method. They presented a novel technique to calculate the air flow in each airway based on the position of the airway and the alveoli distal to it. Monjezi et al.[8] used a multi-scale method to develop a whole lung particle deposition model. They coupled a 3D model of the upper airways with an impedance model of the distal airways to calculate the flow in each airway. They also used the statistical model to build up the geometric structure of the lungs. Also, Georgakakou et al.[9] have recently developed a simplified model based on perfect alveolar mixing. The results they derived for the pulmonary deposition, were in good agreement with previous data for particles greater than 0.1 micrometers.

Asgharian et al.[10] used a multiple-path geometry based on the data presented by Raabe et al.[11] and Yeh et al.[1] and calculated the particle deposition using the concentration equation. Salma et al.[12] calculated the particle deposition under different physical activity conditions for the different regions of Budapest using the statistical geometric model. Their results showed that for the harder physical activities, the acinar deposition increases, while the tracheobronchial deposition fraction remains almost constant.

In the present study, the effect of successive respiratory cycles on the particle deposition is investigated as a more exact solution of the problem, instead of a single cycle that is studied widely so far. Total and generational deposition fraction and the
remaining mass fraction suspended in the respiratory tract after successive cycles until the quasi-steady state of breathing is also calculated and discussed.

2. Methodology

In order to simulate the particle deposition in the respiratory system, three major steps must be taken. The first step is the simulation of the geometry of the respiratory tract. Based on the challenge of each problem, the proper geometrical model, among the different presented geometrical models, should be chosen and one should build up the geometry of the respiratory tract. The second step is the calculation of the airflow in each of the airways. It can be done by using proper hydrodynamic boundary conditions. Finally, the third step is the calculation of the particle deposition fraction in each airway, based on the presented deposition formulas. Each of these major steps in this study, will be explained in the following sections.

2.1. Geometry

In the present study, Yeh and Shum’s 5-lobe geometric model[1] is used. In this model, the airways proximal to the starting point of the five lobes, are modeled as the asymmetric channels each of which having its own geometric data. On the other hand, within each of the five lobes, the bifurcations are considered to be symmetric and the airways in the same generation, have the same geometric data. Although the respiratory tract is supposed to be symmetric in each lobe, each of the five lobes have its own geometric data sheet. So, we can model each lobe separately and capture its own particle deposition pattern. In this model for each lobe, the generation after which the airways are in the alveolar region, is determined. Based on the research by Weibel et al.[13] for the first three generations of the alveolar region, it is supposed that 0.2, 0.4 and 0.7 of the lateral area of the airways is covered by the alveoli, respectively. For the next generations, this area fraction increases to unity. It means that for the generations distal to the third alveolar generation, the lateral area is totally covered by the alveoli. The FRC—which stands for “Functional residual capacity”- is considered equal to 2300 ml based on the physiologic data. After the mentioned modifications on the model according to Weibel et al.[13], the total number of alveoli is calculated to be about 450 millions. Ochs et al.[14] studied the lung of six adults and presented 480 million for the average number of alveoli for an adult. This shows that our modification on the original geometric model that presented 300 million for the number of alveoli, could make it closer to the real structure of the lung and so make it more accurate. Although among the geometric models, the statistical model can predict the uncertainties better than the other models, in this study, we used a 5-lobe
symmetric model. Considering that the challenge of the present study is the effect of successive respiratory cycles, using a statistical model during successive cycles can lead to an enormous computational cost that was out of our computational facilities.

2.2. Flow calculation

In order to simulate the airflow in the airways, at first we need to know the temporal breathing profile. In the primary researches, as the first approximation, the inhalation and exhalation flow was assumed to be constant with respect to time. Thereafter, based on the suggestion of other researchers [15, 16], the sinusoidal profile was used frequently. This profile is more similar to the real breathing flow profile and nevertheless has the simplicity needed for the calculation algorithm to be run with reasonable time and energy cost.

The other challenge in the simulation of the airflow, is the flow division between the airways. Considering this fact that the main reason of the flow creation is the expansion and contraction of the alveoli, we calculated the flow share of each airway based on the number of the alveoli distal to it. This technique was also used by Henry and Tsuda[17] in 2010 and reused by Dastanpour et al. [7] in 2014. In the alveolar airways, a fraction of the lateral area is covered by the alveoli, so a portion of flow goes into these alveoli, and in accordance, the output flow is somewhat less than the input flow.

In this study, based on the physiological data, the inhalation and exhalation time is considered to be 2 seconds, and the respiratory pause time (the time between the end of an exhalation and the start of the next inhalation) is considered to be 1 second. The calculation is done for three different values of the tidal volume. A tidal volume of 500 ml is considered for the simulation of breathing in the normal mode, 1000 ml for the state of light physical activity, and 1500 ml is considered for the state of heavy physical activity. The total air flow as a function of time, is depicted in Fig. 1 for three different values of tidal volume.

2.3. The calculation algorithm

In this study, it is supposed that the subject is continuously exposed to the particles. It means that the boundary condition at the inlet of the respiratory system, is the constant concentration of particles during the inhalation and the escape boundary condition for the exited particles during the exhalation. This state can be considered as the case of the air pollution calculation. In this problem, we need two types of numerical integrations. The first one is on the mass of the entered particles to the oral or nasal cavity and the second one is to track every group of particles in the respiratory tract. Each of these integrations has its own time step. For both of these numerical integrations, the time-step size study was done. For the integration on the entrance particles mass, three different time steps of 0.05, 0.02 and 0.01 s were used and the results were close. So, the problem was solved based on 0.05 s. For the integration to track every group of particles in the respiratory tract, a time-step
between 0.001 s and 0.0001 s was chosen based on the geometry of each lobe. So, each lobe has its own time-step. For each of the five lobes, the time-step was decreased until the results change negligibly after dividing the time-step by 2 and 4. Then, this time-step was considered for the corresponding lobe.

The general algorithm to solve the problem, has four main steps that is described below:

1) At the beginning, it is supposed that the whole respiratory system is empty of particles. At this time, breathing in the air containing particles begins. Unity is attributed to the total particle mass entered in the respiratory system during the inhalation.

2) In each time step, knowing the airflow versus time, the entered mass fraction into the respiratory system can be tracked in the respiratory tract and its deposition fraction in each airway is calculated. After exiting each airway, the remaining particles are divided into two parts and enter the distal airways based on the flow division between the daughter airways. This procedure continues until the first inhalation ends.

3) At the end of the first inhalation, part of total particle mass is deposited in the airways, part of it is entered into the alveoli and the rest is suspended in the airways. The mass entered into the alveoli is partly deposited and the rest is suspended in the alveoli. In the initial state before the inhalation begins, the alveoli contain a volume of air inside them. When the new particles containing air is sucked into the alveoli, this “polluted” air is partly mixed with the “clean” air that exists initially in the alveoli. This amount of mixture is introduced by “mixing factor”. Koblinger and Hofmann[2] suggested the amount of 0.25 for this parameter based on best fitting with the experimental results. In this study, this amount is considered for the mixing factor. During the exhalation, part of the suspended mass in the alveoli, exits the respiratory system. But the part that is determined by mixing factor is mixed with the initial air in the alveoli and exits the alveoli gradually and with a delay to the main wave of the exhalation air. It means that exactly after the unmixed part of air exits the alveoli, the exiting process of the mixed part of air begins and lasts until the exhalation ends. This time delay causes that at the end of the exhalation, the particles in the mixed part of the air cannot totally exit the respiratory system and part of it remains in the airways. This is the main mechanism that is responsible for the remaining mass in the respiratory tract at the end of the respiratory cycle. By integrating on the time-steps of the first respiratory cycle, we can calculate the deposited fraction and the remaining fraction of the particles mass after the first exhalation ends. During the pause time, part of the remaining mass is deposited and the remaining mass decreases slightly.

At this moment, modeling of the first respiratory cycle is completed and the deposition fraction and pattern, remaining mass fraction and pattern, and the exited mass fraction after the first respiratory cycle can be obtained.
4) When the second respiratory cycle begins, at first the location of the remaining mass fractions are tracked and their own deposition and remaining mass fraction is calculated. Then, the calculation related to the newly entered mass from oral or nasal cavity is done just like the first cycle algorithm. The computational algorithm for the next cycles is exactly like the second cycle.

Finally, after a few respiratory cycles, the deposited fraction during each cycle and the remaining mass fraction in the respiratory tract will be accessible. The above computational algorithm was run by a computational code and the results were extracted. The flowcharts of particle deposition algorithm in the tracheobronchial and alveolar regions in a typical lobe, is presented in the Appendix A.

For more clarification, mass balance equation is presented below. For every stage of the geometry, namely, a single alveolus, an airway, and the whole respiratory system, the mass is balanced based on the Eq. 1.

\[
\begin{align*}
m_{\text{rem}}^{\text{old}} + m_{\text{en}} &= m_{\text{dep}} + m_{\text{out}} + m_{\text{rem}}^{\text{new}} \\
\text{Eq. 1}
\end{align*}
\]

In the above equation, \(m_{\text{rem}}^{\text{old}}\) and \(m_{\text{rem}}^{\text{new}}\) are remaining mass fraction at the beginning and the end of a typical respiratory cycle, \(m_{\text{en}}\) is the entered mass fraction, \(m_{\text{out}}\) is the exited mass fraction and \(m_{\text{dep}}\) is the deposited mass fraction during the current cycle in each airway or alveolus. As the aim of this study is assessing the effect of successive cycles that is basically due to the alveolar mixing, the mass balance equations in a single alveolus are presented below, specifically.

\[
\begin{align*}
m_{\text{en}} &= m_{\text{m}} + m_{\text{u}} = m_{\text{en}} * mf + m_{\text{en}} * (1-mf) \\
\text{Eq. 2 (a)}
\end{align*}
\]

\[
\begin{align*}
m_{\text{dep}} &= (m_{\text{m}} + m_{\text{u}} + m_{\text{rem}}^{\text{old}}) * df \\
\text{Eq. 2 (b)}
\end{align*}
\]

\[
\begin{align*}
m_{\text{out}} &= m_{\text{u}} * (1-df) + m_{\text{m}} * \left(1 - \frac{v_{\text{min}}}{v_{\text{en}}} \right) * (1-df) \\
\text{Eq. 2 (c)}
\end{align*}
\]

\[
\begin{align*}
m_{\text{rem}}^{\text{new}} &= m_{\text{rem}}^{\text{old}} * (1-df) + m_{\text{m}} * \frac{v_{\text{min}}}{v_{\text{en}}} * (1-df) \\
\text{Eq. 2 (d)}
\end{align*}
\]

In the equations 2 (a) to 2 (d), \(mf\) and \(df\) are mixing factor and deposition fraction, respectively. Deposition fraction in each airway or alveolus is calculated based on formulas that will introduced in the following sections. \(m_{\text{m}}\) and \(m_{\text{u}}\) are mixed and unmixed parts of entered mass to the alveoli, respectively. Also, in these equations, \(v_{\text{min}}\) and \(v_{\text{en}}\) are the minimum volume and the volume of a typical alveolus at the moment that the particle containing air front enters to the alveolus, respectively. The total minimum volume of alveoli is calculated using FRC and the volume of respiratory dead space that are considered to be 2300ml and 150ml, respectively in this study. Minimum volume of each alveolus is calculated by dividing the total minimum volume of alveoli by their number (450 millions) that gives the amount of
4.78e-12 m$^3$. $V_{en}$ is different for each alveolus and its amount is calculated computationally by tracking the particle containing air front. Fig. 2 depicts a schematic view of the deflection of a typical alveolus and the entrance of the air front into it during a cycle. It may give a good conceptual sense of $v_{en}$. In the Fig. 2, the areas with higher concentration of particles are shown darker. This spectrum has no quantitative basis and is depicted merely to clarify the computational algorithm for the reader. In the Fig. 2, it is shown that the alveolar mixing increases the remaining mass fraction that exists from the previous cycle. When the respiration reaches the quasi-steady state, this increment decays and the remaining mass fraction experiences periodic variations along the respiratory cycles.

In the present study, deposition due to three major deposition mechanisms e.g. impaction, sedimentation and diffusion is calculated. In the oral and nasal cavities, best to our knowledge, no research is done to estimate the deposition fraction purely by sedimentation. Moreover, due to the small residence time of the particles in these cavities, we can neglect the deposition by sedimentation. So, for the oral and nasal cavities, the deposition is calculated based on impaction and diffusion. In the alveoli, due to the small velocity of the air flow and in turn, particles, the impaction is insignificant and the deposition is calculated based on diffusion and sedimentation.

2.4. Nasal and oral cavities deposition

To calculate the deposition fraction in the oral and nasal cavities, mainly the two mechanisms of impaction and diffusion are considered. Researchers have suggested different relations for the deposition fraction due to each of these mechanisms during the inhalation and exhalation. In this study, we have tried to apply the most recent and reliable relations to calculate the deposition fraction in each part of the respiratory system.

2.4.1. Nasal deposition during inhalation

To calculate the deposition fraction due to impaction in the nasal cavity during the inhalation, we used the results of the research by Shang et al.[18]. They investigated the regional deposition of micro-particles in the nasal cavity and derived a diagram for the impaction deposition versus the inertial parameter. The inertial parameter is defined as $I=d^2Q$, where $d$ is the particle aerodynamic diameter and $Q$ is the volumetric air flow rate. Their research is published in 2015 and is one of the most recent researches of its field.

To calculate the deposition fraction in the nasal cavity due to diffusion, we used the Eq. 3 that is suggested by Shi et al.[19]. This relation is based on the diffusion parameter and Schmidt number.
Schmidt number in the Eq. 3 represents the ratio of the momentum diffusivity in the fluid to the mass diffusivity of the particles. The diffusion parameter and Schmidt number are defined as \( \Delta = \pi \bar{D}L/4Q \) and \( Sc = \nu / \bar{D} \) respectively. \( \bar{D}, L, Q, \nu \) are the diffusion coefficient, the airway length, the air flow rate, and the kinetic viscosity of air, respectively.

2.4.2. Nasal deposition during exhalation

Compared to inhalation, little research has been done on the oral and nasal deposition during the exhalation. The most recent and reliable relations for the nasal deposition fraction during the exhalation are presented by NCRP[20] in 1997. These relations that are presented in Eq. 4 and Eq. 5 predict the particle deposition fraction in the nasal cavity during the exhalation due to impaction and diffusion, respectively. The subscript \( p \) refers to the particles properties.

\[
\eta_{\text{imp}} = \left(1 + \left(\rho_p d_p^3 Q / 2300\right)^{1.01}\right)^{1.01} \quad \text{Eq. 4}
\]

\[
\eta_{\text{diff}} = 1 - \exp\left(-15\bar{D}^{1/2}Q^{-1/8}\right) \quad \text{Eq. 5}
\]

We have used these relations for the exhalation particle deposition.

2.4.3. Oral deposition during inhalation

Golshahi et al. [21] in 2013 presented a new relation for the oral deposition fraction during the inhalation. In their experimental research, they made several replicas of the extrathoracic airways of a few adults and by releasing micro-particles at the flow inlet, they measured the deposition fraction. As their particle sizes were greater than 0.5 \( \mu m \), we considered their results as the impaction deposition. Their results represent the particle deposition fraction as a function of Reynolds number and Stokes number. In this study, we used their relation as follows.

\[
\eta = 1 - \left[ \frac{(1.5e5)}{\left(Stk^{3.03} Re^{0.25}\right) + 1} \right] \quad \text{Eq. 6}
\]

Reynolds and Stokes numbers are defined as \( Re = 4 \rho Q / (\pi \mu D) \) and
\[
Stk = 2 \rho_p d_p^2 QC / \left(9 \mu \pi D^3\right),\]
in which, \( \rho_p \) and \( d_p \) are particle density and diameter, \( Q \) is volumetric flow rate, and \( D \) is the airway diameter.

To calculate the \( C_c \), Cunningham slip correction factor, one may refer to ref.[22]. Xi and Longest[23] suggested a relation that predicts the oral deposition due to diffusion during the inhalation. Their research is done recently and is more
complete than the other related researches. It contains several geometric parameters of the oral cavity, for example total surface area and the hydraulic diameter of the inlet section are engaged. In this relation, like its counterpart for the nasal cavity, the deposition fraction is a function of Reynolds and Schmidt dimensionless numbers. This relation is presented in Eq. 7.

\[
\eta = 1 - \exp\left(-0.1654 \frac{A_{\text{sur}}}{A_{\text{en}}} Re^{-0.339} Sc^{-0.661}\right) \quad \text{Eq. 7}
\]

In the above relation, Reynolds number is calculated based on the hydraulic diameter of the inlet and is defined as \( Re = \frac{U_{\text{en}} D_h}{v} \). The subscripts \( \text{en} \) and \( h \) refer to “entrance” and “hydraulic”, respectively.

2.4.4. Oral deposition during exhalation

Yu et al. [24] predicted that the impaction deposition in the oral cavity during the exhalation is negligible, considering the oral cavity geometry and the flow pattern. So, in this study we neglected the oral deposition during the exhalation due to impaction. To calculate the oral deposition during the exhalation due to diffusion, the relation based on NCRP [20] is used as:

\[
\eta = 1 - \exp\left(-8.51 D^{1/2} Q^{-1/8}\right) \quad \text{Eq. 8}
\]

2.4.5. Total deposition in the oral and nasal cavities

Considering this fact that in the oral and nasal cavity both impaction and diffusion mechanisms take part in the deposition, we used the addition law of probability to obtain the overall deposition fraction as follows:

\[
\eta_{\text{tot}} = \eta_d + \eta_i - \eta_d \eta_i \quad \text{Eq. 9}
\]

2.5. Deposition in the tracheobronchial airways

Different researchers have studied the deposition in the tracheobronchial airways. Yeh and Schum[1] suggested the relations based on the experimental data for the deposition fraction in the tracheobronchial airways. These relations were used by Koblinger and Hofmann[2] and Salma et al.[25, 26]. The most comprehensive relation set to calculate the deposition fraction is suggested by NCRP[20] in 1997. However there is even newer relations presented by Zhang et al.[27] in 2008. These new relations are limited to certain range of some parameters like the particle size. So, in the present study, we used the newer relations in their own range of parameters, otherwise the NCRP[20] relations are used. In the tracheobronchial
airways three mechanisms of impaction, sedimentation and diffusion are considered to take part in the deposition.

2.5.1. Deposition due to diffusion

The diffusion phenomena is a result of the well-known Brownian motion of the particles. The diffusion coefficient represents the diffusivity of the particles. The deposition fraction of the particles in a typical volume is a fraction of the volume dimensions and the residence time of the particles, in addition to the particles diffusivity. The relation suggested by Zhang et al.[27] which is a function of the diffusion parameter is:

\[ p_d = \Delta^a \exp (b - c\Delta) \]  

Eq. 10

The diffusion parameter in the Eq. 10 is defined in 2.4.1, with the difference that the specific airway’s own length and air flow are used in the formula. In the Eq. 10, \(a\), \(b\) and \(c\) are constants that are determined based on the value of the diffusion parameter. For the details, refer to Zhang et al.[27]. To calculate the deposition fraction due to diffusion in the tracheobronchial airways, by default, the Eq. 10 is used, unless its limitations are not authenticated. In such situations, the NCRP[20] relation is used. This relation is represented in Eq. 11.

\[ p_d = 1 - 0.819e^{-14.63\Delta} - 0.0976e^{-89.22\Delta} - 0.0325e^{-228\Delta} - 0.0509e^{-125.9\Delta^{0.5}} \]  

Eq. 11

In the pause time, the deposition fraction is calculated by Eq. 12 that is also suggested by NCRP[20].

\[ p_d = 1 - \exp \left( -23.136 \frac{Dt_{rest}}{D^2} \right) \]  

Eq. 12

2.5.2. Deposition due to impaction

The impaction deposition is a result of the deviation of the particles from their initial streamline, due to the curvature of the flow pattern. Larger and heavier particles and sharper curvature of the flow path, result in more deviation and in consequence, more deposition fraction due to impaction. Eq. 13 that is presented by NCRP[20], shows the deposition fraction due to impaction as a function of Stokes number and the angle of bifurcation.

\[ p_i = 1 - \left( \frac{2}{\pi} \right) \cos^{-1} \left( \frac{\theta_{Stk}}{\theta_{Stk}} \right) + \left( \frac{1}{\pi} \right) \sin \left[ 2 \cos^{-1} \left( \frac{\theta_{Stk}}{\theta_{Stk}} \right) \right] \]  

Eq. 13

2.5.3. Deposition due to sedimentation
The deposition due to sedimentation is a result of the gravity. NCRP presented the relation in Eq. 14 for this part of deposition. This equation is a function of the settling velocity, flow velocity, the dimensions of the airway and the gravity angle.

\[
p_s = 1 - \exp \left( - \frac{4}{\pi} \frac{v_{\text{set}} L}{U} \cos(\omega) \right) \tag{Eq. 14}
\]

In Eq. 14, \( \omega \) is calculated as \( \omega = (\pi / 2) - \varphi \), in which \( \varphi \) is the angle between the axis of the channel and the direction of the gravity field. The settling velocity that is a function of the particle properties, the gravity acceleration, the viscosity of the fluid and Cunningham slip correction factor, is calculated as \( v_{\text{set}} = C_v \rho_p g d_p^2 / (18 \mu) \).

Knowing this fact that the sedimentation deposition happens because of the gravity and is not dependent on the air flow, we should calculate it also during the pause time. In Eq. 14 the \( L/U \) ratio represents the residence time of the particles in the airway. So, we can replace it by \( t_{\text{pause}} \) and use it to calculate the deposition during the respiratory pause time. The result is presented in Eq. 15.

\[
p_s = 1 - \exp \left( - \frac{4}{\pi} \frac{v_{\text{set}} t_{\text{pause}}}{D} \cos(\omega) \right) \tag{Eq. 15}
\]

2.5.4. Total deposition in the tracheobronchial airways

Koblinger and Hofmann[2] used the simple summation of the deposition fractions due to the different mechanisms to obtain the total deposition fraction in each airway. But, as the three mechanisms are not independent, Goo and Kim[28] suggested the addition law of probability to calculate the total deposition fraction due to all mechanisms, as presented in Eq. 16.

\[
p_{\text{tot}} = P_d + P_t + P_s - P_d P_t - P_d P_s - P_t P_s + P_d P_t P_s \tag{Eq. 16}
\]

In this study, total deposition in each airway is calculated based on Eq. 16.

2.6. Particles deposition in the alveolar ducts

As mentioned in the geometry section, the geometric data based on Weibel et al.[13] is used to simulate the structure of the alveolar ducts. The other parameter effective on the alveolar deposition is the mixing factor. The mixing of the “new” air and the “old” air in the alveoli, is responsible for the effect of the previous respiratory cycles on the next cycles. The mixing phenomena is basically dependent on the respiration conditions and the particle size; however, Hofmann and Koblinger[2] suggested the constant value of 0.25 for the mixing factor. They presented this value based on the best fitting of their simulation results with the experimental data. The method for the application of the mixing factor comes below in details. After the aerosol mass entered into the alveoli is partly deposited, 0.25 fraction of the undeposited particle mass is mixed with the air that existed initially in the alveoli before the beginning of
the inhalation; and the rest, totally exits the alveoli during the exhalation. The mass fraction that is mixed with the old air, exits the alveoli gradually until the exhalation ends. The alveolar deposition is calculated based on the proper relations and the remaining mass fraction in each alveoli is saved for the calculations of the exhalation. When the exhalation begins, the unmixed part of the particles mass, after calculating its deposition, exits the alveoli just like its entrance, and in the following, the mixed part exits the alveoli gradually until the exhalation ends. The unmixed part is tracked in the respiratory tract and its deposition during the exhalation is calculated and finally, its residual fraction totally exits the respiratory system. As the exit of the mixed part of the particles lasts until the end of the exhalation, a typical particle of this mass fraction may stop at any point of the respiratory tract at the end of the exhalation. For this part, the deposition fraction of the mass fraction is calculated to the stopping point of the particles and the remaining part of this mass fraction is saved at its geometric position for the calculations of the next respiratory cycle.

For the alveolar regions, the deposition fraction is calculated in two parts: the first one is the alveolar part of the duct and the second one is the cylindrical part of it. The total deposition in an alveolar airway is obtained by summation of these two deposition fractions. For this purpose, the presented relations by Koblinger and Hofmann[2] are used.

3. Results and discussion

In this study, the particle deposition in different regions of the respiratory system, in each of the five lobes and for different particle sizes is calculated. For each lobe, a symmetric pathway is considered based on the lobe-specific geometrical data, and the calculations were done for several successive respiratory cycles. The air flow in each airway is determined based on the alveoli number distal to it. So, the share of each lobe from the total air flow is considered proportional to the number of the lobe alveoli. Fig. 3 shows the share of each lobe from the total air flow. It can be observed that the left lower lobe and the right lower lobe draw the most share and the right middle lobe receives the least share of flow. In Fig. 3, the obtained flow division is also compared to the results of Cohen et al.[29]. As is shown, the trend is the same, but some difference can be detected. Cohen et al. used the pressure outlet boundary condition to calculate the flow division. So, the observed difference is due to the different methods. As the main reason of the air flow is expansion and suction of the alveoli, it is more reasonable to calculate the air flow based on the alveoli number, which is pursued in the present study.
To calculate the deposition of each particle group in each airway, the flow of the airway at that specific moment is used. This technique, results in more accurate computations compared to the most of the previous studies which used the average flow rate in the calculations. The particles density is considered to be the standard value of 1 g/ml. Calculations are done for 37 different particle sizes ranging from 1 nm to 10 μm. The total respiratory deposition of different particle sizes is shown in Fig. 4.

When breathing begins, theoretically, a few breathing cycles are needed for the total deposition per cycle to reach a quasi-steady amount. Depending on the particle size and the tidal volume, the number of cycles to reach the quasi-steady state can be different. To examine the validity of the results, the calculated total deposition in a single cycle, for the tidal volume of 500 ml, is compared to the other researchers’ results. This comparison that is shown in Fig. 4, shows a proper matching with other results that are based on the researches by Koblinger and Hofmann[2], Yeh and Schum[1], Asgharian et al.[30] and Choi and Kim[31].

The total deposition fraction during a single cycle, is compared with the total deposition fraction per cycle in the quasi-steady state. Fig. 5 show this comparison for the tidal volumes of 500, 1000 and 1500 ml. The variation of the total deposition fraction less than 1 percent is considered as the criterion of reaching the quasi-steady state.

In Fig. 5 it can be observed that for the particle size near 10 μm and 1 nm, total respiratory deposition is close to unity. It means that these particles are almost totally deposited in the respiratory tract. High deposition fraction of the particles near 10 μm is due to their huge inertia that increases the impaction and sedimentation deposition in the airways. For the small particles near 1 nm, due to their small size, the diffusion coefficient is so large that causes high diffusive deposition in the respiratory tract. For the particles between these two limit sizes, total deposition fraction decreases until it reaches its minimum for the particle size about 0.5 to 0.6 μm. The particles in this size range are not massive enough nor small enough to deposit totally in the respiratory tract. So, there will be a minimum for the total deposition fraction.

According to Fig. 5 increasing the tidal volume, total deposition increases for all particle sizes. It can be observed that for the tidal volume of 500, 1000 and 1500 ml, the minimum deposition fraction is about 0.1, 0.2 and 0.25, respectively. This increment is due to the increment of the flow velocity in the airways and more penetration of the particles into the depth of the respiratory system. Moreover, this is obvious that by increasing the tidal volume, the difference between total deposition in a single cycle and a cycle after reaching the quasi-steady state, increases. By increasing the tidal volume, the entered air to the alveoli increases and more particles enter the alveoli. Consequently, more particle mass fraction involves in the alveolar mixing. Knowing that the alveolar mixing is the main reason of the difference between a single cycle and the quasi-steady state, this is clear that by increasing the tidal volume and in turn, the increment of the alveolar mixing, this difference becomes greater.
The increment of deposition per cycle in the quasi-steady state compared to a single cycle is shown in Fig. 6 for three tidal volumes. The following facts can be inferred from the figure. For the tidal volume of 500 ml that corresponds to the breathing at rest, in the quasi-steady state, the deposition increment is obvious for the particles between 0.2 and 1 μm; and at the maximum, it reaches 5.7 % for the 0.5 μm particles. For tidal volumes of 1000 and 1500 ml, the maximum increment corresponds to the 0.5 μm particles, too; and equals to 12.4 % and 15.5 %, respectively. Also, it can be inferred that by increasing the tidal volume, from 500 to 1500 ml, the particle size range that shows the difference between the two mentioned states, expand from 0.2 to 1 μm, corresponding to 500 ml, to 0.07 to 2 μm, corresponding to 1500 ml. This happens because as the tidal volume increases, the alveolar mixing becomes more important and more particle sizes are engaged.

To evaluate the difference of the results between geometric models, a comparison is performed between the results of the present study –that is done based on a 5-lobe symmetric geometric model- and the results according to MPPD© v2.1 software. MPPD© v2.1 which its name is the acronym of the phrase “Multiple-Path Particle Dosimetry”, is developed by Applied Research Associates, Inc. (ARA) in 2009. This software has the capability for the calculation of total, lobar, regional and generational particle deposition in the different geometric models in the respiratory system during a respiratory cycle. For our purpose, this program is run based on two geometric models e.g. the used-by-us 5-lobe symmetric model and the stochastic geometric model. The results of total deposition in a single cycle for tidal volume of 1000 ml that is more close to the daily outdoor physical activity state, for the two models by MPPD and the present study based on the 5-lobe model is shown in Fig. 7. It can be observed that the results are well close to each other. The difference in the total deposition between the present study and the stochastic model by MPPD, at most reaches 16 percent and is pertaining to 0.6 μm particles. On the other hand, the difference between the present study and the 5-lobe model by MPPD has even less amount. So, it can be inferred that in this investigation, we could achieve a good estimate of the effect of successive respiratory cycles on the particle deposition based on a 5-lobe symmetric model, without any unacceptable deviation from the results of the more realistic stochastic geometric model.

In Fig. 8, the deposition versus the generation number is compared between a single cycle and for a cycle after reaching the quasi-steady state for three tidal volumes and 0.5 μm particles. It is obvious that the deposition per cycle in the quasi steady state is slightly more than the deposition in a single cycle. This difference is more sensible in the last generations. This happens because the alveolar mixing happens in the last generations that are connected to the alveoli. So, the effect of the successive cycles is more obvious in the last generations. Also, it can be seen that by increasing the tidal volume, the maximum deposition generation number increases; that is because of more penetration of particles into the respiratory tract. Besides, this can be observed that for the tidal volume of 500 ml, there is a little difference between a single cycle and the quasi-steady state; and by increasing the tidal
volume, this difference increases to more significant values due to more mass fraction of particles that reach the alveoli, where the alveolar mixing happens.

Besides the mixing factor, the other parameter that is effective on the difference between the quasi-steady state and a single cycle, is the remaining mass fraction of particles in the respiratory tract at the end of each respiratory cycle. Considering the whole particles mass entering the respiratory system, part of it deposits, part of it totally exits the respiratory system during the exhalation and finally, part of it remains suspended in the respiratory tract after the exhalation due to the delayed exit from the alveoli after the main wave of the particles, caused by the alveolar mixing. This remaining part increases the deposition per cycle in the next respiratory cycles. In the present study, as mentioned before, we supposed that at the beginning of the first respiratory cycle, the respiratory tract is totally empty of particles. After the first cycle ends, some particle mass fraction remains in the respiratory tract. At the end of the second cycle, this remaining mass amount, somewhat increases. After a few cycles, in the quasi-steady state, the remaining mass fraction after each cycle, reaches a constant value. Fig. 9 shows the total remaining mass fraction in the respiratory system for the tidal volume of 500 ml at the end of the successive respiratory cycles. It can be observed that for this tidal volume, at the end of the first respiratory cycle, the maximum remaining mass fraction corresponds to 0.5 μm particles and equals to 0.011 fraction of the total entered particle mass. As is depicted in the figure, this value increases after the successive cycles until reaching the quasi-steady state, in which, increases to about 0.022 of the total entered mass.

The variation of the tidal volume can also change the amount of the remaining mass fraction at the end of the cycles in the quasi-steady state. Fig. 10 shows the total remaining mass fraction at the end of the cycles in the quasi-steady state for three values of tidal volume. As is shown in the figure, the increment of the tidal volume can increase the remaining mass fraction. This is due to a stronger alveolar mixing. The maximum remaining mass fraction that increases from 0.02 for 500 ml tidal volume to 0.06 for 1500 ml tidal volume, corresponds to 0.5 μm particles. It shows that for this particle size, none of the deposition mechanisms is strong enough to avoid the particles to reach the alveolar region.

Besides the total remaining mass fraction, it can be meaningful to investigate the remaining mass fraction versus the generation number. Fig. 11 shows the generational remaining mass fraction after the successive cycles for tidal volume of 500 ml and the particle size of 0.5 μm. It can be seen that by passing the successive cycles and getting close to the quasi-steady state, the generational remaining mass fractions approaches a certain profile. A maximum can be detected in this graph for the quasi-steady state. This maximum happens at the 21st generation. As mentioned beforehand, the alveolar mixing that is responsible for the difference between a single cycle and the quasi-steady state happens in the last generations that are connected to the alveoli. So, this is due to the strong effect of the alveolar mixing in
this region. We can remember that for the generational deposition fraction, the maximum appeared at the 21st generation, too.

In Error! Reference source not found.1 the most cycle numbers needed to reach the quasi-steady state and their corresponding particle size are presented for three value of the tidal volume.

The criterion for reaching the quasi-steady state is considered when the total deposition fraction changes less than 1 percent during a respiratory cycle. For the middle particle sizes, a few respiratory cycles are needed to reach the quasi-steady state. According to Error! Reference source not found.1, by increasing the tidal volume, the number of needed cycles increases. This is due to the increment of the alveolar mixing. The most needed cycles number that correspond to the particles around 0.5 $\mu m$, are 2, 4 and 5 cycles for the tidal volume of 500, 1000 and 1500 ml, respectively.

According to the Fig. 10 it can be inferred that for particles greater than 2 $\mu m$ and particles smaller than 0.05 $\mu m$, we can always do our calculations based on a single cycle with a great precision, because the successive cycles effect is practically zero for these particles. This happens because for these particles, the deposition mechanisms are so strong that can avoid the particles to reach the alveolar region and take part in the alveolar mixing. Fortunately, the most of the aerosolized medications like the inhalers and the nebulizers mainly work in the particle size range of 1 $\mu m$ and larger. So, for the calculations corresponding to these medical equipment, we can safely use the results of a single cycle with enough precision and no excess computational cost is necessary.

For the assessment of the results sensitivity to the amount of mixing fraction, total deposition fraction per cycle in the quasi steady state is depicted in Fig. 12 for different values of mixing fraction. In this figure, total deposition fraction for the tidal volume of 1000 ml is assessed with different values of mixing factors varying from 0 (no mixing) to 1 (perfect mixing). For this amount of tidal volume, the variation of mixing factor from 0.25 to 1, at most, increases the deposition fraction 12% and 25%, respectively that is pertaining to 0.5 micrometer particles, and for the other amount of particle size, this increment is less. It is obvious that the amount of mixing factor is not so effective that its variation makes a significant difference in the deposition fraction of too large or too small particles. This is another confirmation for the claim that the effect of successive cycles is negligible for large and small particles, and is partly sensible for the middle size particles.

4. Conclusion

In this study, the particle deposition in the respiratory system during the successive respiratory cycles is modeled. We used a 5-lobe symmetric geometric model and used the deposition formulas according to different researchers to
calculate the deposition fraction in each airway. Although the model does not fundamentally capture the physics of particle deposition process, its results are in good agreement with the experimental data. For three tidal volumes of 500, 1000 and 1500 ml and for particle sizes ranging from 1 nm to 10 μm, the calculations were done and the results were extracted. The results of this work showed that for different particle sizes and different values of tidal volume, a few cycles are needed for deposition fraction to reach a quasi-steady state. Also, comparison of the results of the present study for total deposition fraction with the results of MPPD® v2.1 software showed that the difference between the 5-lobe model that we used and the more realistic stochastic model is not unacceptable. This difference for the typical tidal volume of 1000 ml turned out to be at most 16 percent. So, in this study, a model is developed that can make a good estimate of the effect of successive respiratory cycles on the total and generational particle deposition, though it uses a 5-lobe symmetric model. The difference between the quasi-steady state and a single respiratory cycle is due to the alveolar mixing and the remaining mass fraction at the end of each respiratory cycle. The results showed that for particles smaller than 0.05 μm and particles larger than 2 μm, for all values of the tidal volume, the remaining mass fraction is negligible due to the high deposition fraction and the results of successive respiratory cycles have no difference with the results of a single cycle. For particles between 0.05 and 2 μm, due to the high penetration of the particles into the alveolar region, there was a difference between a single cycle and the quasi-steady state. The maximum difference appeared at particle size of 0.5 μm as for this particle size, none of the deposition mechanisms is strong enough to avoid the particles to reach the alveolar region and get engaged to the alveolar mixing. For this particle size, the total deposition fraction in the quasi-steady state was about 6, 12 and 16 percent greater than a single cycle for the tidal volume of 500, 1000 and 1500 ml, respectively. On the other hand, for low values of the tidal volume, due to less fraction of the particles reaching the alveolar region and weak alveolar mixing, the calculations of the quasi-steady state had negligible difference with a single cycle; and at high tidal volumes, this difference becomes significant. So, it shows that for a wide range of applications, we can use the results based on a single cycle with reasonable accuracy to avoid the unnecessary computational cost.
5. References


**Appendix A: Flowcharts**

The flowcharts are presented in this section. Fig a 1. shows the deposition calculation flowchart in a tracheobronchial airway of a typical lobe and Fig a 2. shows the deposition calculation flowchart in an alveolar airway of a typical lobe. The details of them is presented in the main text.

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Fig a 1

Read SW(Lobe) & \( t_{ent}(Lobe) \)

Read Lobe geometry

\( \text{gen}=1 \)
\( X=0 \)
\( t=t_{ent}(Lobe) \)
\( SW(\text{gen})=SW(Lobe) \)

\( x=x+v\cdot dt \)
\( t=t+dt \)

\( \text{t}<t_{\text{inh}} \)

\( \text{y} \)

\( x<L_{\text{gen}} \)

\( \text{y} \)

\( \text{gen} = \text{gen} + 1 \)
\( x=0 \)

Other Lobes

\[ \text{dep}(\text{gen})=SW(\text{gen})\cdot\text{dep}\cdot x/L(\text{gen}) \]
\[ SW(\text{gen})=SW(\text{gen})^{(1-\text{dep}\cdot x/L(\text{gen}))} \]

Alveolar region

\[ \text{dep}(\text{gen})=SW(\text{gen})\cdot\text{dep}\]
\[ SW(\text{gen}+1)=SW(\text{gen})^{(1-\text{dep}\cdot q(\text{gen}+1)/q(\text{gen}))} \]

\( \text{gen}<\text{gen}_{\text{alv}}? \)

\( \text{y} \)

\( \text{n} \)
**Table 1**

<table>
<thead>
<tr>
<th>Tidal volume (ml)</th>
<th>The most needed cycles</th>
<th>Corresponding particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>2</td>
<td>0.4 - 0.9</td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>1500</td>
<td>5</td>
<td>0.5 - 0.6</td>
</tr>
</tbody>
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