Septal destruction enhances chaotic mixing and increases cellular doses of nanoparticles in emphysematous acinus

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Abstract

One hallmark of emphysema is the breakdown of inter-alveolar septal walls in pulmonary acini. How the acinar dosimetry of environmental aerosols varies at different stages of emphysema remains unclear; this is specifically pertinent to users of tobacco products, which is the leading cause of emphysema. The objective of this study is to systematically assess the impacts of septal destruction on the behavior and fate of nanoparticles (1–800 nm) in a pyramid-shaped sub-acinar model consisting of 496 alveoli. Four diseased geometry variants were created by gradually removing the septal walls from the base model. Particle motions within the acinar region were tracked for particles raging 1–800 nm at four emphysema stages using a well-tested Lagrangian tracking model. Both spatial profile and temporal variation of particle deposition were predicted in healthy and diseased sub-acinar geometries on both a total and regional basis. Results show large differences in airflow and particle dynamics among different emphysema stages. Large differences in particle dynamics are also observed among different particle sizes, with one order of magnitude’s variation in the speeds of particles of 1, 10, and 200 nm. The destruction of septal walls also changed the deposition mechanisms, shifting from connective diffusion to chaotic mixing with emphysema progression. The sub-acinar dosimetry became less sensitive to particle size variation with more septal destructions. The lowest retention rate was found at 200–500 nm in the healthy sub-acinar geometry, but at 800 nm in all emphysematous models considered. The acinus-averaged dose for nanoparticles (1–800 nm) increases with aggravating septal destructions, indicating an even higher risk to the acinus at later emphysema stages.

1. Introduction

Emphysema is a chronic obstructive pulmonary disease (COPD) that is often caused by constant exposures to toxic agents such as cigarette smoke, chemical fumes, dust, or air pollution [1, 2]. In 2018, there are 3.8 million people (1.7 million female, 2.1 million male) in the US were diagnosed with emphysema [3] and 328 million people have COPD worldwide [4]. In fact, COPD is the third leading cause of death in the US and is projected to become the leading cause of mortality worldwide in 15 years [4]. Recent studies also show that the risk of COVID-19-related death in patients with emphysema or other COPD diseases can be 1.5 times higher [5]. Progressive septa destruction often occurs in emphysema, which further leads to less elastin, weak expiration, and more trapped air in the acini [6, 7]. Techniques to diagnose emphysema include stethoscopes for trapped air (hollow sound), oxygen saturation test (finger, earlobe, or forehead), x-rays, and spirometry [8]. Common symptoms include chronic cough, short breath, wheezing, fatigue, and excess mucus secretion [9]. Emphysema is an irreversible disease and medical interventions can only curb its exacerbation, not cure it. Besides quit smoking, emphysema management includes medications (e.g., antibiotics to reduce bacterial infection, steroids to relieve inflammation, or bronchodilators to clear obstruction), surgical intervention (volume reduction,
thermal ablation, or transplant or), and rehabilitation (oxygen supplement or respiration exercise) [10]. It is not yet clear how the inhaled airflow and aerosols differ in their behavior in emphysematous lungs, especially their temporal variations with emphysema progression; however, accurate knowledge of these variations, as well as the mechanisms underlying these variations, is crucial to develop more effective treatment plans for either inhalation drug delivery or respiration rehabilitation. It is also helpful to diagnose the development stages of emphysema.

Contrary to extensive studies of the upper respiratory tract, investigations into airflow and particle behaviors in the pulmonary acini are rare because of their secluded locations and tiny sizes that pose paramount challenges to measure their morphology, motion, ventilation, or particle dynamics. There are 3,000–4,000 alveoli in one pulmonary acinar unit [11], which form a complex network of air pockets supported by inter-alveolar septa [12]. In emphysematous acini, these septal walls rupture partially or entirely, producing large air space and decreased tissue elasticity [13, 14]. Considering the large variations in both anatomy and physiology, it is not clear whether the predominating mechanisms of particle deposition in emphysematous acini are still the same as those in healthy lungs [15]. It is well accepted that gravitational sedimentation dictates the deposition of large particles (>2.5 μm), chaotic mixing dominates the dosimetry of fine aerosols (0.1–2.5 μm) and Brownian motion prevails in ultrafine particles (<0.1 μm) [16, 17]. Also, note that it is often not one individual mechanism that governs, but the interactions (and transient balance) among these mechanisms determine the behaviors and fates of the inhaled particles. As a result, highly heterogeneous deposition distributions can occur within the pulmonary acini despite their tiny size, as demonstrated recently in both in vivo imaging [18] and numerical modeling [19]. This deposition heterogeneity has long been neglected in empirical dosimetry models, such as the trumpet model [20] and the ICRP compartment model [21], both of which assume uniform dose distributions.

Several studies have numerically examined the ventilation and aerosol dosimetry in acinar geometries of varying complexities and physical realism. It is now clear that the acinar dosimetry prediction with rigid walls and steady respirations can lead to a significant underestimation [22–24], and that alveolar wall motions are essential for predicted acinar dosimetry to match in vivo measurements [25, 26]. Because the terminal acinus is a dead-end space and the tidal volume is often very low (e.g., 23% of the functional residual capacity, or FRC), particle deposition often takes multiple respiratory cycles to complete [27, 28]. The physical realism of the acinar geometry is another critical factor determining the accuracy of predicted acinar dosimetry. Remarkable discrepancies have been reported in the aerodynamics and particle behaviors between alveolated bronchioles and terminal alveolar sacs [29, 30], as well as among acinar model geometries with different levels of physical realism [22, 31–35].

The space-filling acinar model has gained popularity since it was first introduced by Fung [36] and has been used in several studies to simulate the 3D network of alveoli [34, 37–42]. Notably, Oakes et al [39] investigated the differences in particle transport and deposition between normal and emphysematous acini in rats by retaining versus deleting intra-alveolar septal walls within individual alveolar ducts. Septal destruction was found to lead to a higher level of particle dispersion; also, a lower deposition was predicted in the emphysematous acinus than the in vivo dosimetry in rats (ref), which the authors have attributed to lower penetration depths of inhaled particles in the diseased models [39]. However, one important anatomical feature has been constantly neglected in previous studies: the alveolar duct units that branch from their parent alveolar duct can also share common septal walls [43, 44], like between adjacent seeds in a pomegranate [45] or cells in a honeybee comb [46]. Most space-filling models contained alveolar ducts that were only connected to their parent alveolar ducts and were separated from other alveolar ducts (i.e., without shared walls among them). In this way, emphysema-induced septal destructions will only affect the geometrical integrity of individual alveolar ducts, not their neighbors. In life conditions, however, the alveolar ducts and their alveoli are densely packed to fill the lung lobes, and tissue inflammation can damage both septal walls within an alveolus (i.e., intra-alveolar septa) and those shared by adjacent alveolar ducts (i.e., inter-alveolar septa). In this study, we aimed to understand the airflow and deposition of nanoparticles in emphysematous models with progressive destruction of both intra-alveolar and inter-alveolar septal walls. Specific aims included:

1. Develop a normal sub-acinar model (M0) retaining 62 alveolar duct units (496 alveoli) that are organized in a cascade-branching pattern but are separated from other units by inter-alveolar septal walls.
2. Gradually remove inter-alveolar septal walls from the normal model, M0 to develop emphysematous acinar models (M1–M4) at four stages.
3. Characterize the effect of septal destruction on the dynamics of nanoparticles of different sizes.
4. Understand the differences in deposition mechanisms between healthy and emphysematous acini.
5. Quantify the acinar dosimetry of nanoparticles on a total and regional basis at different emphysema stages.
2. Methods

2.1. Acinar models and wall kinematics

A sub-acinar model that consisted of 496 alveoli and 62 alveolar ducts was generated using an in-house module Lung4Cer [47, 48]. Each alveolus was represented by a polygon (figure 1(a)). The inset of figure 1(b) illustrated an alveolus that is connected to the main alveolar duct via an octagonal mouth (red). There are septal walls shared by the alveolus and the duct (cyan color, between the outer wall edges (blue) and the boundary of the alveolar mouth (red, inset of figure 1(b))). One major feature of the sub-acinar model is its branching structure where the children alveolar ducts bifurcate from the main (parent) alveolar duct form a complex network of inter-alveolar septal walls organized in pyramid-shaped space (figure 1(b)). In other words, the 496 alveolar units are not simply clustered around the main duct; instead, they belong to 62 different children alveolar ducts, whose position and orientation are determined based on the space-filling algorithm developed by Kitaoka et al [49, 50].

Figure 1. Normal (M0) and emphysematous sub-acinar models (M1–4) at four stages of septal destructions: (a) surface model that consists of 62 alveolar duct units (496 alveoli) with each alveolus represented by a polygon, (b) inner septal walls, which were divided into 4 sections (red: proximal, green: less proximal, blue: moderately distal, and cyan: distal), (c) a cut-view showing the four sections that represent four stages of the septal wall destruction due to emphysema, and (d) the surface area of the normal (M0) and emphysematous models with different degrees of septal wall destruction.

Figure 2. Sub-acinar wall kinematics and computational mesh: (a) the rhythmic wall expansion and contraction following sinusoidal waveforms with an I:E = 1:2 and respiration period of 4.5 s; (b) ICEM-generated computational mesh with very fine body-fitted elements near both the inner and outer walls, (c) grid sensitivity analysis in M0 by varying mesh size from 0.83 million to 4.91 million, and particle sensitivity study by varying the number of tracked particles from 10,000 to 100,000 for a given mesh of 3.79 million in M0. All tested meshes had a 5-layer prismatic mesh with a height of x mm in the first layer. The particle size used is 200 nm.
To generate the emphysematous models at four different stages, the inner septal walls were gradually removed. In doing so, the septal walls were divided into four sections depending on their odds to develop emphysema, which further developed due to the deposition distribution of inhaled toxins. This division is overall correlated with the distances from the main alveolar duct, with some exceptions of the alveoli near the acinar entrance; they are close to the main alveolar duct but may receive lower doses than alveoli inside the overall correlated with the distances from the main alveolar duct, with some exceptions of the alveoli near the acinus where interalveolar septa prevail. As shown in figures 1(b) and (c), the septa to be removed at different stages are visualized as follows: red: stage 1; green: stage 2, blue: stage 3, and cyan: stage 4. The alveoli near the outer wall were categorized into the last stage of the emphysema, as illustrated by Septa-4 (cyan color, figure 1(c)). Figure 1(d) shows the surface area of the inner, outer, and bottom in the five sub-acinar geometries, which are also listed in table 1.

Idealized kinematics of the sub-acinar wall motion was adopted in this study, with both expansion (inhalation) and contraction (exhalation) following sinusoidal waveforms, but with different amplitudes and periods. As shown in figure 2(a), the expansion phase has a half-period of 1.5 s and the contraction has a half-period of 3, resulting in a respiration cycle of 4.5 s with an I:E = 1:2. The amplitude ratio of expansion and contraction was determined so that the inhaled and exhaled volumes were identical. The rhythmic expansion and contraction of the acinar walls were implemented using a user-defined C-module [30].

### 2.2. Flow-particle simulations

Isothermal (37 °C) and incompressible (\( \rho = 1.139 \text{ kg m}^{-3} \)) airflows were assumed. Based on a flow velocity of 1 mm s \(^{-1} \) and an alveolar diameter (characteristic length) of 0.2 mm, the flow Reynolds number was estimated at 1.2 \( \times 10^5 \), suggesting a predominantly laminar flow regime of the transient acinar flows. Particles were tracked 3–6 respiration cycles till all particles deposit in or escape from the geometry. One cycle was computed to establish the transient flow field within the acinar space before tracking the particles, which were released into the main alveolar duct entrance at the beginning of the second cycle. A well-tested Lagrangian-tracking model was used to simulate the particle motion and deposition in the expanding/contracting acinar geometry. This discrete-phase Lagrangian model, which was enhanced with near-wall velocity interpolations for both airflow and particles [51, 52], has been proved to provide accurate predictions of the measured dosimetry for aerosols at both nano- [53, 54] and micro-scales [55, 56].

### 2.3. Numerical methods

ANSYS Fluent 19.1 (Canonsburg, PA) was used to resolve cyclic acinar flows and track particle trajectories. In-house programs were written to control the cyclic wall motions and calculate the temporal-spatial variations in particle deposition [57]. One-way fluid-structure interaction was assumed, i.e., from the moving wall to airflow. Likewise, one-way fluid-particle coupling was adopted, i.e., from the airflow to aerosols. ANSYS ICEM CFD (Canonsburg, PA) was utilized to generate the computational mesh inside the sub-acinar model. The prismatic mesh was applied to both one-side boundary walls and two-side septal walls, with four layers of body-fitted cells and a height of 0.25 \( \mu \text{m} \) in the first layer cell. The insets of figure 2(b) shows the prismatic mesh zoomed at different scales, which clearly show the high-resolution mesh near the wall and the relatively coarse mesh in the flow domain (figure 2(b)). Our previous studies have demonstrated that a prismatic mesh in the near-wall region is essential to obtain accurate inhalation dosimetry in comparison to experimental inhalation dosimetry for both submicron [58–60] and micrometer [54, 61] aerosols.

To secure accurate inhalation dosimetry predictions, sensitivity analyses were performed in two steps (figure 2(c)). First, the grid-independent study was conducted in the normal sub-acinar model (M0) by comparing six meshes from very coarse (0.83 million) to very fine (4.91 million), all with a four-layer prismatic mesh and a 0.25 \( \mu \text{m} \) height at the first layer. The deposition fractions (DF) of 200-nm particles in sub-acinar geometry, as well as the regional DF on the septal walls, were compared, as shown in the upper panel of figure 2(c). It is observed that a coarse mesh gave rise to a higher value for both total and regional DFs. Both DFs became stable at the mesh size of 3.79 million, with negligible variation (<1%) when further refining the mesh to 4.91 million. Thus, the computational mesh that comprises 3.79 million cells was adopted for all subsequent test

### Table 1. The morphological dimension of the normal and emphysematous acinar models.

| Area (mm\(^2\)) | Septa-1 | Septa-2 |Septa-3 | Septa-4 | Inner wall | Outer wall | Bottom | All     |
|-----------------|---------|---------|---------|---------|------------|-----------|---------|---------|
| M0(normal)      | 13.1    | 20.3    | 23.0    | 24.7    | 81.1       | 32.3      | 8.7     | 122.0   |
| M1(stage 1)     | NA      | 20.3    | 23.0    | 24.7    | 68.0       | 32.3      | 8.7     | 109.0   |
| M2(stage 2)     | NA      | NA      | 23.0    | 24.7    | 47.7       | 32.3      | 8.7     | 88.7    |
| M3(stage 3)     | NA      | NA      | NA      | 24.7    | 24.7       | 32.3      | 8.7     | 65.6    |
| M4(stage 4)     | NA      | NA      | NA      | NA      | 0.0        | 32.3      | 8.7     | 40.9    |
cases. In the second step, the number of particles necessary to obtain stable dosimetry results was determined by testing 7 groups of aerosols that consisted of 10k, 20k, 30k, 45k, 60k, 75k, and 100k of 200-nm particles, respectively (lower panel of figure 2(c)). Considering that the Brownian motions of nanoparticles can cause fluctuations in the predicted dosimetry, five runs were conducted for each test case to quantify this variance. With an insufficient amount of seed particles (e.g., 10,000), both higher doses and larger variance were predicted in comparison to the cases with more seed particles. The DF reached a stable value at 60k and beyond. An amount of 75k seed particles were used in this study so that the DF variance can also be minimized as possible.

3. Results

3.1. Acinar airflow dynamics

The airflow in the normal sun-acinar model (M0) is shown in figures 3(a) and (b) during inhalation (T = 1.0 s) and exhalation (T = 3.0 s), respectively. The first panel displays the iso-surface of the airflow at 0.4 mm s⁻¹ moving through the labyrinths of the inter-alveolar septal walls. For comparison purposes, the septal walls were hidden in the second panel to provide an unobstructed view of flow morphologies (figures 3(a) and (b)). One salient feature here is the branching and space-filling patterns in both inspiratory and expiratory flows. As alluded to previously, the 496 alveoli are not randomly clustered together but belong to different alveolar duct units that bifurcate from the main (parent) alveolar duct. The velocity iso-surface patterns in figure 3(a) clearly illustrated how the inhaled air stream branches into several daughter streams, each of which branches further and eventually fill the entire sub-acinar airspace. Likewise, a cascade-branching pattern is maintained during exhalation (at T = 3.0 s, figure 3(b)). Due to a prolonged expiratory phase (3 s versus 1.5 s for inhalation), the iso-surface region at 0.4 mm s⁻¹ is smaller than that at T = 1.0 s during inhalation (figure 3(b) versus Figure 3(a)). The flow streamlines were also plotted in the second panel of figure 3, showing the inward and outward directions of the inspiratory and expiratory flows.

The third panel compares the iso-surfaces at 0.8 mm s⁻¹ (light green color) during inhalation and exhalation in figures 3(a) and (b), respectively. As expected, a reduced size than the iso-surface of 0.4 mm s⁻¹ is observed during both inspiratory and expiratory phases. However, a more dramatic reduction occurs during inhalation. This is presumably due to the flow inertia, which needs energy input to acquire but no energy input maintain, as illustrated by the vortex structures (or energy carriers identified using the Q-criterion) in the fourth panel of figures 3(a) and (b). The instantaneous positions of 200-nm particles that enter the geometry at the beginning of inhalation are also superimposed with the flow pattern at 0.8 mm s⁻¹, which exhibits a highly heterogeneous distribution in space. The same particle distributions are also plotted in the last panel of figures 3(a) and (b), together with the particle velocity vectors. Marked differences are observed between inhalation and exhalation in both the particle distribution and particle velocities (note the densely packed velocity vectors in figure 3(a) versus the barely noticed vectors in figure 3(b), both plotted at the same scale). The counterclockwise recirculation...
Figure 4. Instantaneous snapshots of 1-nm particle positions in the normal (M0) and four emphysematous sub-acinar models at different instants after release: (a) 0.4 s, (b) 1.0 s, (c) 1.6 s, and (d) 2.2 s.

Figure 5. Comparison of instantaneous snapshots of 10-nm particle positions at different instants in the first two cycles between the normal (a) and emphysematous models (b) M1, (c) M2, (d) M3, and (e) M4.
inside the alveolus close to the entrance during inhalation, as well as the clockwise recirculation during exhalation, were also vividly captured.

### 3.2. Particle dynamics

#### 3.2.1. 1-nm particles

A comparison of the instantaneous positions of 1-nm particles between the healthy (M0) and diseased models (M1-4) is shown in figure 4 at different points of one breathing cycle. Considering M0, a small fraction of 1-nm particles reached the outer wall at 0.4 s due to their high diffusivity, even though the majority of particles, which were transported by the core flow convection, barely filled the main alveolar duct. Note the high speeds of the particles in the peripheral region (∼60 mm s⁻¹, red color), which is one order of magnitude higher than the airflow speed. More 1-nm particles diffused to the peripheral region in M1 and M2 due to less severe structural obstructions, where the inner wall Septa-1 and Septa-2 were progressively removed. Interestingly, further removing the septal walls didn’t lead more particles to the peripheral walls at T = 0.4 s. Rather, a reverse trend was observed, with very few particles reaching the peripheral region in the model with complete inner septal destruction (M4). This might result from the slower core-flow convection and that particles did not have sufficient time to diffuse away from the main flow (the rightmost panel, figure 4).

Considering all figure panels together in figure 4, it appears that the first three models (M0, M1, and M2, i.e., normal and moderately emphysematous) share more similarities than the last two models (M3 & M4, severely emphysematous). The differences between these two cohorts became more obvious at T = 0.1 s (figure 4(b)). In the first cohort (M0-2), the majority of particles were confined in the axial direction; in contrast, particles filled the entire sub-acinar space in the second cohort (M3-4). In our previous study, a flow recirculation zone was predicted in M3 and M4 due to the airspace expansion, which in turn facilitated the particle dispersion within the unobstructed space. This recirculation pattern in M3 and M4 persisted throughout the expiratory phase (T = 1.6 s and 2.2 s, the last two panels in figures 4(c) and (d)). Instead, the majority of particles in the first cohort (M0-M2) were only seen in the axial direction, with much fewer particles in the peripheral region during the expiratory phase (T = 1.6 s and 2.2 s, the first three panels in figures 4(c) and (d)). A further examination among M0-M2 revealed a more confined, faster-moving aerosol in M0 in comparison to a more dispersed, slower-moving aerosol in M2.
3.2.2. 10-nm particles
Figure 5 compares the dynamics of 10-nm particles among the five models at different points of the first and second breathing cycles. Compared to 1-nm particles in figure 4, a less amount of 10-nm particles in M0-2 reach the peripheral regions at T = 0.4 s due to reduced diffusivity. It is noted that a velocity scale of 0–12 mm s⁻¹ was used in figure 5, as opposed to the scale of 0–60 mm s⁻¹ in figure 4. Similar to figure 4, the first cohort (M0-2) has the majority of 10-nm particles in the axial direction with an only insignificant number of particles in the distal region, while the second cohort (M3-4) is dominated by a more dispersed distribution filling the entire sub-acinar airspace. As a result, more particles are expected to deposit at the bottom of M0-2, while elevated deposition is expected on the peripheral boundary walls of M3-4. During exhalation at T = 3.4, a high-speed particle plume (red) is detected in M0 and M1, which are absent in the three models with more septa destructions (M2–4). Also, the duration for 10-nm particles to complete deposition decreases with the emphysema severity. While there are still an appreciable amount of particles in M0 remaining at T = 7.5 s, nearly all particles have deposited in M4.

3.2.3. 200 nm particles
The instantaneous snapshots of 200-nm particles are presented in figure 6 at different points of the first and second breathing cycles in M0 and M4. In contrast to the relatively rounded profiles of 1-nm and 10-nm aerosols at T = 0.4 s in M0, the distribution of 200-nm particles appears much more irregular, indicating the decreasing effect of particle diffusivity versus convection, the latter of which is highly dependent on structural details. Also, note that the velocity scale used herein is 0–2.4 mm s⁻¹; by comparison, the velocity scale is 0–12 mm s⁻¹ for 10-nm particles (figure 5) and 0–60 mm s⁻¹ for 1-nm particles (figure 4). The differences between the two cohorts (M0-2 versus M3-4) observed for 1-nm and 10-nm particles (figures 4 and 5) are more pronounced in figure 6, with the majority of particles in the axial direction in M0 and highly dispersed particles filling the entire airspace in M4. Moreover, a higher concentration of 200-nm particles is observed near the peripheral walls than 1-nm and 10-nm particles, which is presumably attributed to the flow recirculation within the septa-derived airspace in M4. Again, more particles appear to remain in M0 than M4 at t = 8.5 s (close to the end of the second breathing cycle). Considering the particle size effects, the larger the particle size, the longer duration is needed to deposit (figures 4–6).

3.3. Nanoparticle deposition distribution
3.3.1. Effects of the particle size in M0
Figure 7 shows the particle deposition in the healthy sub-acinar geometry (M0) at different particle sizes (1–800 nm). The upper row shows deposited particles in the entire model, with all the walls visualized as transparent. Apparent disparities in deposition distribution exist between 1 nm and 800 nm, with gradual transitions between. Compared to 1 nm particles, the deposition pattern of 800 nm particles are more concentrated and localized. The radiating strips (arrows) parallel to the outer walls are reminiscent of the fact that particles deposit during the rhythmic expansion and contraction; in our current numerical model, particles are frozen wherever they deposit, even though in reality deposited particles will move with the dynamic wall. Due to different diffusivities, these particle strips are absent for 1-nm particles, discernible for 10-nm particles, and very obvious for 100-nm particles and above.
Figure 8. Comparison of particle deposition distributions among emphysematous models (M0-4) for different particle sizes: (a) 1 nm, (b) 20 nm, and (c) 200 nm.

Figure 9. Temporal evolution of particle deposition in different regions (blue dashed: inner wall, black solid: outer wall, green dash-dotted: bottom) of the five sub-acinar models for aerosols of (a) 1 nm, (b) 10 nm, (c) 100 μm, and (d) 800 nm. There is no inner wall deposition in M4 because all septal walls were removed. Particles that cross the alveolar duct opening (i.e., inlet, red solid line) will escape the sub-acinar geometry.
For all particle sizes considered in figure 7, elevated deposition is observed in the axial-central region of the sub-acinar geometry, which is consistent with the low resistance in the main alveolar duct versus the increased resistance and decreased ventilation in the lateral directions. The lower row of figure 7 shows particles that deposited on the inner septal wall only for 1, 100, and 800 nm particles. Considering that there are two faces onto which particles can deposit, particles deposited on Face1 and Face2 are also visualized separately, which exhibit a similar pattern between each pair. Again, axial-central deposition is found on the septal walls for all particle sizes considered, justifying our assumption to remove Septa-1 (as depicted in figure 1c) to represent the initial stage of septal destruction during emphysema. There is a clear branching pattern of deposition on Face 2 for 800-nm particles (due to bifurcating gas ventilation or convection) in contrast to a highly dispersed deposition pattern for 1 nm particles (due to high diffusion), with that for 100-nm particles falling midway between.

3.3.2. Effects of septal destruction

The effects of septal destruction on the deposition distribution of submicron particles are shown in figure 8. In comparison to the axial-central deposition pattern in M0, progressively removing the inner septal walls increases deposition in the lateral, peripheral region and decreases deposition at the bottom. At the same time, the particle distribution becomes increasingly scattered in the emphysematous acinus. In M3 and M4, high levels of particle accumulations are observed close to the bottom (dotted rectangle) and on the outer walls (hollow arrow) for the three particle sizes (1 nm, 10 nm, and 200 nm) considered.

3.4. Deposition quantification

3.4.1. Temporal deposition fraction

The temporal evaluation of the deposition fractions (DF) in different regions of the sub-acinar geometry is compared among different emphysematous models (in one column) and for different particle sizes (along one row), as shown in figure 9. Plotting the regional DF in the format of a matrix provides a systemic view of the particle behavior and fate in the sub-acinar model with deteriorating septal walls. From this matrix, the variation in both temporal response and spatial distribution of the sub-acinar dosimetry to progressive septal destructions, as well as to different nanoparticle sizes, can be visualized.

For a given particle size, the inner-wall DF (blue dashed line) constantly decreases from M0 to M4, which is expected in light of the decreasing septal area. Note that in M4 there is no inner-wall deposition because all septal walls were removed. By contrast, the inner-wall DF shows mixed responses to the particle size among the five models. In M0 and M1, larger particles give rise to slightly lower inner-wall DF and take longer times to deposit completely (dashed blue lines in the first and second rows, figure 9). In more severe emphysematous models
(M2 and M3), the inner-wall DF appears to be insensitive to the particle size (dashed blue lines in the third and fourth rows, figure 9).

The outer-wall DF (solid black line) increases with emphysema severity and decreases with particle size. As the result, the highest outer-wall DF in this study occurs in M4 for 1 nm particles (86%, figure 9(a)) and the lowest in M0 for 800 nm particles (32%, figure 9(d)). Striking differences exist between the bottom DF responses (dash-dotted green lines) in different emphysematous models. There are negligible DFs on the bottom wall in the first cohort (M0-2) for particles of 1–800 nm (dash-dotted green lines in the top three rows, figure 9). On the contrary, the bottom DF becomes increasingly significant in the second cohort (M3 and M4) with increasing emphysema severity and particle size (dash-dotted green lines in the fourth and fifth rows, figure 9). On the contrary, the bottom DF becomes increasingly significant in the second cohort (M3 and M4) with increasing emphysema severity and particle size (dash-dotted green lines in the fourth and fifth rows, figure 9).

The red solid line represents the fraction of particles escaping from the alveolar duct opening (i.e., inlet). Particles start leaving the sub-acinar geometry from around 3 s (the inhalation phase being 1.5 s) and constantly increase till 4.5 s (the period of on breathing cycle). A negligible amount of particles leave the geometry in subsequent cycles; however, particles remaining within the sub-acinar airspace may still need several more cycles to complete deposition. It is observed that the highest escaping fraction from the inlet occurs in M1 for 800 nm particles (i.e., lowest sub-acinar dose). It increases constantly with particle size in the range of 1–800 nm but exhibits a bell-shaped response to increasing septal destructions (from M0 to M4, with the peak in M1). We currently have no clear explanation for why the peak happens in M1 but speculates that it results from the balance between the axial main-flow convection versus increasing lateral ventilations from septal ruptures. As the escaping fraction from the inlet (sub-acinar opening) is directly associated with the retention rate of inhaled particles, the mechanisms (the critical balance point, in particular) underlying this observation needs to be examined in future studies.

**3.4.2. Total and regional deposition fractions**

More DF results from a wide range of test cases are summarized in figure 10 by including particles of 2, 3, 20, 50, 200, 500, 600 nm for M0 and 50, 200, and 500 nm for other models (M1–4). As discussed in figure 9, M1 has the lowest total DF among the five models for any given particle size (figure 10(b) versus 10a and 10c–e). Considering the particle size effect, the minimal total DF in M0 happens at 200–500 nm, which is consistent with the previous

**Figure 11.** Comparison of the regional DF normalized by the tissue area [(% / mm² × 100)] between different stages of emphysema for different particle sizes: (a) 1 nm, (b) 10 nm, and (c) 200 nm. Note that there is no inner wall and thus no inner-wall DF in M4.
in vivo dosimetry studies [21, 62]. However, the minimal total DF happens at 800 nm for all emphysematous models considered herein (M1-4, figure 10). The DF sensitivity to particle size variation decreases with the level of septal destruction. In M3 and M4 where most or all septal walls are absent, the total DF appears to be independent of the particle size in the range of 1–800 nm. Again, M3 and M4 have significantly higher DFs than M0-2 at the bottom wall, which increases with the particle size and the level of septal rupture (figures 10(d) and (e)).

3.4.3. Normalized DF per unit area
Considering that the surface area of inner septal walls varies in the five models, it is more appropriate to characterize the dosimetry as DF per unit area for risk assessments of the acinar tissues. Figure 11 shows the normalized DF by the tissue area on which particles deposited [%/mm² × 100] in the five models for 1, 10, and 200 nm, respectively. With adjustment of wall area, the average dose (i.e., total deposition per unit area) in the sub-acinus constantly increases from M0 to M4, indicating an increasingly higher risk of septal breakdown after the onset of the emphysema. Similarly, the normalized DF on the outer and bottom walls also constantly increases with emphysema severity, except M1 that has the minimal bottom DF among the five models. The normalized DFs on the inner wall, however, are lower than those on the outer walls and appear relatively insensitive to the emphysema stage.

To improve the risk assessment of inhaled particles on different parts of the inner septal walls, deposition distribution among the four septa (i.e., Septa-1: red, Septa-2: green, Speta-3: blue, and Speta-4: cyan, as originally delineated in figure 1(c)) were further explored (figure 12). As aforementioned, the normal sub-acinar model M0 has intact walls (Septa-1, 2, 3, 4), while the emphysematous model M1 comprises Septa-2, 3, and 4 only (by losing Septa-1). Similarly, M2 comprises Septa-3 and 4, M3 comprises Speta-4, whereas M4 has no septal wall. Figure 12(a) displays the deposition of 1-nm particles on each of the septa components in M0, M1, M2, and M3, respectively in the first, second, third, and fourth rows. The sub-regional DFs on each septa component are shown in the left lower corner. For a given model geometry, particle deposition can differ markedly among the septal components in both particle distribution and DF magnitude. For instance, the 1-nm dose in Septa-1 (red, 1.308%/mm²) is more than five times that in Septa-3 (blue, 0.238%/mm², figure 12(a)). It is also observed that this deposition heterogeneity decreases with particle size: for 10-nm particles, the DF ratio of Septa-1 to Septa-3 is 2.7 (i.e., 0.977 versus 0.360%/mm², figure 12(b)); and for 200-nm particles, it reduces to 1.7 (0.557 versus 0.333%/mm², figure 12(b)).
4. Discussion and summary

The effects of both the particle size and emphysema stage on the acinar deposition of nanoparticles were systematically investigated in a sub-acinar model comprising 496 alveoli using numerical simulations. Large differences exist in the dynamics of particles of different sizes in the sub-acinar geometry, with a peak speed of 60 mm s\(^{-1}\) for 1 nm, 12 mm s\(^{-1}\) for 10 nm, and 2.4 mm s\(^{-1}\) for 200 nm at a tidal volume ratio of 0.23 (figure 3). It takes one cycle for most 1-nm particles to complete the deposition but five cycles for 800-nm particles to complete (figure 9). The retention rates of particles entering the acinus are generally high (65.0%–97.4%), with the minimal DF 65% for 800 nm particles in M1 and 66% for 200–500 nm particles in M0. The DF sensitivity to particle size is the highest in M0 and decreases with the emphysema stage. For the particles typical for tobacco smoking aerosols ranging from 100–500 nm [63, 64], the total DF persistently increases with the emphysema stage, indicating an ever-increasing risk of continuous septal breakdown for cigarette smokers if not quitting or reducing smoking.

In this study, we observed that the total acinar dose per unit area constantly increases with the emphysema stage for all nanoparticles considered (1–800 nm, figure 11). This finding implies a higher risk of tissue inflammation and a potentially accelerating breakdown of epithelial walls once the process is started. The dose increase with septal destruction is especially large at the peripheral boundaries of the acinus (both outer wall and bottom in this study, figure 11). Tissue breakdown of the acinar boundaries can generate or enlarge pores between adjacent alveolar ducts or even different acini, leading to collateral ventilation among adjacent alveolar duct units [65], which has been observed in a significant proportion of patients with emphysema [66, 67].

To our initial surprise, the normalized DF per unit area on the inner septal wall is much lower (i.e., 3–5 times) than that on the outer walls, which may give an inaccurate impression that the inner septa have a lower risk than the outer wall. To avoid such potential misinterpretations, two points are clarified. First, the inner wall has two sides facing the airflow and the areas of both sides are counted in this study. However, the alveolar septal wall may contain only one layer of cells [68] and in this case, the DF should be doubled because deposited toxins can act from both sides of the septal cell. Second, particle deposition on the inner septal walls can be highly localized. Even though the averaged inner-wall dose appears moderate, the local or sub-regional dose can be much higher, and thus are more likely to activate tissue cellular responses. It is noted that significant accumulations of nanoparticles in local areas of the acinus are possible. Li et al [18] visualized the deposition pattern of PM\(_{0.2}\) in a mouse lung using the fluorescent intensity and reported highly localized deposition at the edge of the lungs (i.e., the outer wall of the acinus).

The acinus is unique in geometry in comparison to other regions of the respiratory tract in that it is a dead-end (cul-de-sac) structure, with the same opening for both inspiratory and expiratory flows. For a given tidal volume of 23%, only up to 23% of the air within the acinus will be replaced, leaving 77% or more old air remained. Particles that enter the geometry disperse into, and mix with, the residual air through both convection and diffusion. During the inhalation, particles are transported to the peripheral acinar regions by the bifurcating flow streams (figure 3(a)) and fill the acinar airspace (figures 4–6) to varying degrees at the end of the first cycle. Particles escaping the geometry during exhalation are carried by the expiratory airflow that only comprises 18.7% (i.e., 0.23/1.23) of the air in the acinus. To exit the geometry, exhaled particles need to avoid contacting the inner septal walls and travel far back enough to reach the alveolar duct opening. This may explain why the majority of exhaled particles exit the acinus only during the exhalation phase of the first cycle, as illustrated by the asymptotic profile of the escaping DF (red solid lines) after \(T = 4.5\) s in figure 9. The same mechanism also underlies the decreasing sensitivity of total DF to particle size at later stages of emphysema, a trend observed in figure 10, because of the increased particle mixing in septa-deprived airspaces. Similarly, Tsuda [16, 17] has demonstrated that chaotic mixing is the major mechanism determining the acinar deposition of fine aerosols (0.1–2.5 \(\mu\)m). Due to the intact inter-alveolar septal walls in M0, particle mixing is minimized within the daughter alveolar ducts (as displayed in figure 3), leaving the convection and diffusion being the major deposition mechanisms. As a result, the lowest total DF was found in M0 for 200–500 nm particles where neither the inertial impaction nor diffusion is significant. With progressive destructions of the septal wall, chaotic mixing intensifies and gradually becomes the predominant deposition mechanism over both the impaction and diffusion.

The transition of deposition mechanism from convection–diffusion to chaotic mixing with deteriorating emphysema, as well as the associated decreasing DF sensitivity to particle size, has the potential to estimate the severity of emphysema by measuring the DF differences between two particle sizes (e.g., 200 versus 800 nm). From figure 10, we also observed abnormally high deposition on the bottom wall at the late stages of emphysema (M3 and M4); moreover, it exhibits a high sensitivity to both particle size and emphysema stage, an index that can potentially be exploited to diagnose emphysema or estimate the stage of the disease.

Several assumptions in this study need to be clarified that could limit the results’ applicability, which includes a sub-acinar model instead of a whole acinar model, idealized wall kinematics, and predefined septal

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**References:**

[63, 64]"..."
destructions. First, an acinar unit contains 3,000–4,000 alveoli [11]; the sub-acinar model hereof retains 496 alveoli and thus cannot fully capture the physical realism of an acinar unit. The wall expansion and contraction follow sinusoidal waveforms with different periods (I:E = 1.5:3 s), while the breathing waveforms in emphysema patients can be different in both profile, magnitude, and period [69]. Also, the diseased models M1-4 were made by progressively deleting the septa walls close to the alveolar duct. However, the process of septal destruction can be more complicated in life conditions [6, 70, 71]. Furthermore, hyperinflation can happen due to the loss of elastin and associated prolonged expiration, while in our previous studies [30, 72], the alveolar size has been demonstrated to an important factor in dictating the alveolar dosimetry. Other limitations, including idealized particle properties (monodisperse, no electrostatic charge, no hygroscopic growth), releasing a bolus of aerosols at the beginning of inhalation, and excluding the conducting airways (mouth-G18) can also affect the applicability of the results to certain degrees. Previous studies have evaluated the effects of particle size distribution [73, 74], electrostatic charge [75, 76], and droplet evaporation/condensation [77] on particle deposition in the upper airways. Dense aerosol effects such as particle agglomeration and collision were also excluded [78]. After saying this, fundamental features of an emphysematous acinus were captured and systemically investigated in this study, which includes an anatomically realistic sub-acinar geometry with a branching network of alveolar duct units, progressive destruction of both intra-alveolar and inter-alveolar septal walls in exacerbating emphysema, and respiration driven by rhythmic expanding/contracting wall motions. Furthermore, with the aforementioned simplifications, the impact from the septal rupture on acinar flow, as well as the particle behavior and fate, could be isolated to be systematically examined by neglecting secondary, compounding factors. Specific findings of this study include:

1. Particle behaviors in the sub-acinus differ significantly among 1 nm, 10 nm, and 200 nm aerosols, with the peak speed being 60 m m/s, 1.2 mm s$^{-1}$, and 2.4 mm s$^{-1}$, respectively.

2. In the healthy model, particles penetrate deeper in the axial (main alveolar duct) direction but not in the lateral directions; particle dispersion increases with septal destruction with more particles dispensing to the outer walls of the pyramid-shape geometry.

3. For a given tidal volume ratio of 0.23, the retention rates of nanoparticles entering the acinus are 65.0%–97.4%. The deposition sensitivity to particle size decreases with the emphysema stage.

4. Increased total and peripheral wall deposition are predicted with aggravating emphysema, which can be attributed to the intensifying chaotic mixing (or particle dispersion) relative to the convective-diffusion mechanism.

5. The minimal deposition occurs at 200–500 nm in the healthy sub-acinar geometry, but at 800 nm in emphysematous models considered in this study.

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Conflict of interest

The authors report no conflicts of interest in this work.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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