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The role of anisotropic expansion for pulmonary acinar aerosol deposition

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Abstract

Lung deformations at the local pulmonary acinar scale are intrinsically anisotropic. Despite progress in imaging modalities, the true heterogeneous nature of acinar expansion during breathing remains controversial, where our understanding of inhaled aerosol deposition still widely emanates from studies under self-similar, isotropic wall motions. Building on recent 3D models of multi-generation acinar networks, we explore in numerical simulations how different hypothesized scenarios of anisotropic expansion influence deposition outcomes of inhaled aerosols in the acinar depths. While the broader range of particles acknowledged to reach the acinar region ($d_p = 0.005\text{--}5.0\text{ }\mu\text{m}$) are largely unaffected by the details of anisotropic expansion under tidal breathing, our results suggest nevertheless that anisotropy modulates the deposition sites and fractions for a narrow band of sub-micron particles ($d_p \sim 0.5\text{--}0.75\text{ }\mu\text{m}$), where the fate of aerosols is greatly intertwined with local convective flows. Our findings underscore how intrinsic aerosol motion (*i.e.* diffusion, sedimentation) undermines the role of anisotropic wall expansion that is often attributed in determining aerosol mixing and acinar deposition.

Keywords

Pulmonary acinus; Anisotropic expansion; Numerical simulations; CFD; Particle transport; Aerosol deposition

1 Background

The past two decades have witnessed important efforts to resolve respiratory flows in the acinar depths, motivated in part by the prospect of predicting the fate of inhaled aerosols for therapeutic delivery (Sznitman, 2013; Tsuda et al., 2013). Parallel to the emergence of true-scale experimental acinar platforms (Fishler et al., 2013, 2015), numerical simulations have served as a backbone to help advance our understanding of acinar aerosol transport given their appeal and versatility to model such 3D microscale transport phenomena (Kleinstreuer et al., 2008; Kleinstreuer and Zhang, 2010). In this context, parenchymal wall motions during breathing are recognized as paramount in giving rise to physiologically realistic

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Conflict of interest statement

None declared.

acinar airflows and ensuing aerosol transport dynamics (Tsuda et al., 2008); static conditions not only fail to capture authentic flow topologies in the acinus but also prohibit convective ventilation exchange between alveoli and the acinar ducts (Sznitman, 2013).

To date the vast majority of numerical studies addressing inhaled particle transport, including several of our own (Hofemeier and Sznitman, 2014, 2015; Tenenbaum et al., 2016), have relied on acinar models that mimic self-similar wall motion during lung expansion (Henry et al., 2002; Sera et al., 2014; Tsuda et al., 1995). Such isotropic distensions are widely acknowledged to capture the principal mode of lung motion at a macroscopic whole-lung level (Ardila et al., 1974; Gil et al., 1979). Yet, it has long been established that local anisotropy at the acinar scale lies at the origin of complex and heterogeneous deformations leading for example to geometrical hysteresis (Gil and Weibel, 1972; Kojic et al., 2011; Mead et al., 1957), a process observed amongst other in surface-to-volume loops during lung inflation–deflation maneuver (Miki et al., 1993).

With advances in imaging modalities, the anisotropic motion of the acinus has recently received accrued attention, spanning micro-computed tomography (μ CT) measurements *in situ* under quasi-static inflation (Kumar et al., 2013; Sera et al., 2013) to *in vivo* imaging of intact mice with synchrotron X-ray microscopy (Chang et al., 2015). By fitting imaging data to geometric models of the alveolar duct, these studies have inferred that alveoli and the underlying ducts expand differently as total acinar volume increases. In contrast, *in vivo* MRI-based studies in humans have advanced the idea of progressive alveolar recruitment along the acinar tree (Hajari et al., 2012); a concept initially brought forward in deposition studies of excised lungs by estimating settling rates of monodisperse aerosols (Smaldone et al., 1983). Despite the emergence of new acinar imaging data, the expansion of acinar structures during breathing remains controversial and continues to be a topic of debate, as highlighted in recent editorials (Nieman, 2012; Smaldone and Mitzner, 2012).

The question of anisotropic acinar expansion arose initially in physiology (Greaves et al., 2011; Mead et al., 1957; Radford, 1963). Yet its relevance for inhaled aerosols is potentially significant. In the realm of low-Reynolds-number acinar airflows, departure from self-similarity can lead to irreversible flows (Tsuda et al., 1999) that may affect particle mixing and deposition (Tsuda et al., 2011, 2013); a process we have quantified for example in simulations of passive tracers in alveolated ducts (Hofemeier and Sznitman, 2014). While a number of conceptual frameworks on the nature of acinar expansion have been formulated (Smaldone and Mitzner, 2012) (Fig. 1), our bulk understanding of deposition still emanates from studies under isotropic expansion (Hofemeier and Sznitman, 2015; Khajeh-Hosseini-Dalasm and Longest, 2015; Sznitman, 2013). Motivated by these ongoing questions, we explore in simulations how anisotropic scenarios of acinar expansion may ultimately influence the deposition of inhaled aerosols. Specifically, we investigate the transport of a wide range of aerosol sizes (0.005–5.0 μ m) acknowledged to reach the acinar regions (Hinds, 1999; ICRP, 1994).

2 Methods

Drawing on recent models of multi-generational acinar networks (Hofemeier and Sznitman, 2015; Sznitman et al., 2009; Tian et al., 2015), our airway trees feature an asymmetric bifurcating structure reaching up to 6 generations with a total of 277 polyhedral alveolar units (Fig. 2) that capture the space-filling acinar morphology (Fung, 1988). Despite their simplicity and limitations (*e.g.* see discussion in Hofemeier and Sznitman, 2015), these domains constitute a versatile computational platform to investigate a wide range of acinar flow phenomena including aerosol deposition in developing infant airways (Tenenbaum et al., 2016), diffusional screening of oxygen transport (Hofemeier et al., 2016) and modeling diseased emphysematous acini (Oakes et al., 2016). Here, the Navier–Stokes and continuity equations are solved using an arbitrary Lagrangian–Eulerian (ALE) framework in OpenFOAM (v.2.1.1), where oscillatory flows result from mesh motion during breathing. Details on the numerical solver, discretization schemes and mesh convergence are discussed at length in Hofemeier and Sznitman (2015).

Inspired by scenarios of hypothesized acinar motion (Greaves et al., 2011), we compare sinusoidal self-similar displacements to three distinct anisotropic expansion schemes whose conceptualization, and corresponding terminologies, are directly borrowed from recent discussions (Smaldone and Mitzner, 2012) and schematically illustrated in Fig. 1a–d. For a dynamic comparison of the respective domain motions during the expansion and contraction maneuver the reader is invited to consult SM Video 1. We recall that isotropic motions (Fig. 1a) are characterized by $\mathbf{L} \propto \mathbf{L}_0$, where $\mathbf{L}$ represents a time-dependent vector between a reference point and any location on the domain surface, and $\mathbf{L}_0$ is its initial length at the onset of inhalation ($t = 0$). First, we mimic the “cup to saucer” motion advanced by structural models of alveolar duct displacement (Denny and Schroter, 1997; Kojic et al., 2011); here, acinar motion is modeled by a hyperbolic-like radial expansion, where

$\mathbf{R} \propto \mathbf{R}_0^{-1/2}$ and $\mathbf{R}$ represents any radial vector orthogonal to the ductal centerline (Fig. 1b).

Alternatively, we implement a parabolic radial expansion with $\mathbf{R} \propto \mathbf{R}_0^2$ (Fig. 1c) to model a “saucer to cup” expansion (Smaldone and Mitzner, 2012), where alveolar volume changes dominate (*e.g.* more characteristic of large lung expansions, Sera et al., 2013). Lastly, we mimic an alveolar recruitment maneuver following previous conceptualizations (Hajari et al., 2012; Smaldone et al., 1983). Here, alveolar cavities positioned more proximally along the acinar tree expand earlier during the breathing cycle relative to those located more distally. In practice, alveoli are inflated sequentially with the progression of an advancing front that travels distally with speed $U_{AF}(t)$, as schematically shown in Fig. 1d (see also SM Video 1). Details on the analytical kinematic function for such expansion scenario as well as others (*i.e.* self-similar, cup-to-saucer, saucer-to-cup) are provided in the Supplementary Material (SM).

We investigate in a systematic fashion how specifically anisotropic motions (rather than inhaled volume or breathing frequency) influence the fate of inhaled aerosols relative to self-similar conditions by maintaining across all breathing scenarios a constant tidal breathing for an average human adult at rest (Hofemeier and Sznitman, 2015), with tidal volume $V_T = 0.5$ l, functional residual capacity $FRC = 3$ l and breathing period $\tau = 3$ s. We select this

breathing pattern as it remains to date the most prevalent in the current literature on flows and particle transport in the acinar region (Sznitman, 2013; Tsuda et al., 2008, 2013). To quantify the dynamic changes that thus occur under tidal breathing, we plot for each displacement scenario (Fig. 1e) the average ductal diameter across the acinar tree (normalized to its value at FRC, *i.e.* $t = 0$) during a complete breathing cycle. Notably, absolute differences of more than $30\text{ }\mu\text{m}$ (equivalent to relative changes of 15% in length) are observed when comparing self-similar conditions to the saucer-to-cup expansion. Correspondingly, Fig. 1f highlights the temporal differences that arise between the “alveolar recruitment” maneuver and the self-similar case by probing the length of ductal diameters at each individual acinar generation (rather than the average for all 6 generations as depicted in Fig. 1d). Such unsteady profiles highlight how during alveolar recruitment proximal acinar generations begin to expand sooner during the cycle whereas distal generations are seen to expand the most.

Finally, we consider spherical particles ($\rho_p = 1000\text{ kg/m}^3$) spanning $d_p = 0.005\text{--}5.0\text{ }\mu\text{m}$ in diameter; a size range widely acknowledged to reach the acinar region (Hinds, 1999; Sznitman, 2013). By accounting for the bolus transit time to cross over the anatomical dead space ($\sim 150\text{ ml}$), aerosols are injected continuously from $t = \tau \sim 0.2$ (a function of the expansion scenario) until the end of inhalation ($t = \tau \sim 0.5$) and proportionally to the local inlet velocity, thereby mimicking a constant aerosol concentration entering the acinar domain (Oakes et al., 2014; Tenenbaum et al., 2016). Depending on the expansion scenario, a total of $\sim 190,000\text{--}245,000$ particles are injected with a log-uniform size distribution and simulated until aerosols either deposit upon wall contact or exit the domain. Neglecting hygroscopic and electrostatic effects, the principal forces acting are thus gravitational sedimentation, viscous drag (convection) and Brownian diffusion. Note that across all simulations, the gravitational force is arbitrarily fixed and oriented along the negative y -direction (see Fig. 2). Here, our approach follows directly the recent work of Khajeh-Hosseini-Dalasm and Longest (2015) in space-filling models of asymmetrically bifurcating acinar airways, where a single gravity orientation is adequate to capture statistically both particle dynamics and deposition outcomes. As particle concentrations in the acinus are anticipated to be low (Sznitman, 2013), a one-way fluid-particle coupling is implemented. Details on the particle solver and validation are provided elsewhere (Hofemeier and Sznitman, 2014, 2015).

3 Results and discussion

Modulations in the acinar expansion kinematics are anticipated to give rise to changes in airflow characteristics across the acinar network. While the underlying parabolic-like velocity profiles in the ducts and recirculation zones in alveoli remain common features across breathing motions, Fig. 2 exemplifies differences in flow magnitudes along the acinar tree. Here, 1D velocity profiles are presented at peak inspiration ($t/\tau \sim 0.25$) across the acinar ducts and alveoli ($\parallel W$, see domain in Fig. 2), normalized against the mean flow entering the domain inlet under self-similar conditions. In proximal acinar generations (Fig. 2a), velocities are highest under the alveolar recruitment maneuver, both within the duct and the alveolar cavities where the moving front has already passed by. Flows are also locally altered in the alveoli where we note for example the absence of a zero velocity crossing for

the alveolar recruitment scenario (Fig. 2a, inset); this follows from the change in location of the vortex center during the passage of the moving front that gives rise to transient alveolar flow patterns in contrast to the quasi-steady nature for the other scenarios (Sznitman, 2013). In contrast, velocities are lowest under alveolar recruitment in the more distal generations (Fig. 2b, c), where the moving front has yet to cross. Lastly, we note that the “cup-to-saucer” consistently lags behind both the self-similar and “saucer-to-cup” expansions. This may be explained from the weaker flows arising in the ducts as a consequence of relatively less alveolar volume expansion (Sznitman et al., 2009; Sznitman, 2013).

Next, we explore whether the small yet significant changes in flow characteristics alter acinar aerosol deposition outcomes. To render a quantitative yet comprehensive snapshot, we examine deposition fractions as a function of particle size (Fig. 3a). We note that all deposition curves exhibit similar trends regardless of the expansion maneuver and are in alignment with established deposition guidelines (ICRP, 1994). These highlight characteristic “U-shaped” profiles with a minimum around $d_p \sim 0.5 \mu\text{m}$, *i.e.* a signature of the narrow band of sub-micron aerosols where transport is dominated by acinar convection (Hofemeier and Sznitman, 2015; Tenenbaum et al., 2016). Despite such strong similarities, we find that particles in the size range of $0.1\text{--}1.0 \mu\text{m}$ showcase slight differences in deposition efficiencies, as a result of the different modes of expansion. Most notably, the cup-to-saucer scenario exhibits the lowest deposition fractions, since ductal and alveolar flows are weaker (Fig. 2) and have thus less ability to draw aerosols deep into the acinar model. At the end of the first inhalation, the remaining airborne particles present within the domain represent a mere 2.1% of the initially injected ones in the size range $d_p = 0.1\text{--}1 \mu\text{m}$. Comparing between the different breathing motions, we find that in the case of alveolar recruitment 3% of particles ($d_p = 0.1\text{--}1 \mu\text{m}$) remain airborne while in the case of a cup-to-saucer and saucer-to-cup expansions, solely 1.5% ($d_p = 0.1\text{--}1 \mu\text{m}$) of the particles remain airborne. In other words, the statistics presented in Fig. 3a are anticipated to capture the overall deposition trend where the small population of remaining airborne particles is likely to deposit in subsequent breathing cycles.

We note that aerosols in the sub-micron range (most markedly for $d_p < 0.1 \mu\text{m}$) exhibit transport dynamics increasingly dominated by Brownian diffusion compared to the role of convective mechanisms (*i.e.* wall expansion). In turn, outcomes for deposition efficiency rapidly increase to unity as particle size decreases below 10 nm (Fig. 3a). Moreover, deposition sites are confined almost entirely within proximal acinar generations near the domain inlet (see SM, Fig. S1), as highlighted elsewhere (Hofemeier and Sznitman, 2015). This latter observation points to the fact that in reality few nanometer-sized particles ($< 10 \text{ nm}$) are anticipated to reach altogether the acinar region during inhalation. Instead such aerosols deposit in more proximal airway generations of the conductive region, as predicted by semi-empirical models for regional deposition (Hinds, 1999; ICRP, 1994). On the other side of the spectrum, heavier particles biased by gravity ($d_p > 2 \mu\text{m}$) yield high deposition fractions that quickly converge to unity as sedimentation overtakes as the prevalent deposition mechanism.

Turning our attention to Fig. 3b, we present the ratio of alveolar to ductal deposition as a function of particle size. This ratio discriminates between deposition within the alveolar

cavities compared to that in the alveolar ducts (including the alveolar rings) and is of physiological relevance when considering spatial deposition patterns (Tsuda et al., 2013). As shown in previous numerical simulations under self-similar conditions (Darquenne and Paiva, 1996; Hofemeier and Sznitman, 2015; Tsuda et al., 1994), aerosol deposition is typically biased towards the acinar ducts including importantly the alveolar rings; an observation in line with past *in vivo* animal studies (Zeltner et al., 1991). Our present findings suggest that the ratio of alveolar to ductal deposition does not change sensibly with anisotropic lung expansions. Namely, all curves virtually collapse on top of each other and values where the ratio remains typically < 0.5 across the wide majority of particle sizes ($d_p < 2 \mu\text{m}$). Such findings would suggest that this ratio is instead mainly affected by the underlying acinar topology, where alveolar cavities densely populate the acinar ducts and form a tightly packed concentric sleeve with adjacent alveoli separated by dividing septal walls (Gehr et al., 1978; Weibel, 2008).

Furthermore, we investigate the spatial distribution of deposited particles (relative to total injected) according to their penetration depth, *i.e.* acinar generation. For a fixed V_T and τ , the overall deposition distributions are rather insensitive to the local acinar expansion dynamics compared to the role of particle diameter. Therefore, self-similar motion captures well the overarching spatial deposition distributions (see SM Fig. S1 where data for isotropic motion are representative for all expansion scenarios). Finer subtleties nevertheless arise in the range $d_p \sim 0.1\text{--}1 \mu\text{m}$, where aerosol dynamics are significantly influenced by local ductal and alveolar convection. This difference is exemplified in the histograms of Fig. 4 for the particular case of $d_p = 0.5\text{--}0.75 \mu\text{m}$. Since deposition characteristics for such particle size range are sensitive to subtle changes in the convective fields (Fig. 2), the “alveolar recruitment” scenario has the ability to draw just slightly more aerosols into the deeper generations (*i.e.* generation 4) as the moving front progresses more distally. Yet, differences remain small compared to the self-similar case. In contrast, the “cup-to-saucer” scenario yields relatively more proximal deposition and overall lower deposition (recalling Fig. 3a), since aerosols are drawn less deeply into the acinar tree.

We briefly recall that our findings hold at best for particles that have effectively entered the acinar domain. Within the limitations of such bottom-up approaches (Tenenbaum et al., 2016), our simulations hence do not account for filtration or deposition mechanisms that occur in airways proximal to the acinar network as well as the re-entry of particles into the acinar space over multiple breathing cycles. Furthermore, we have confined our simulations to quiet breathing only, where inhalation and exhalation phases are symmetrical. Indeed, it has been recently shown that approximating such tidal breathing maneuvers using sinusoidal cycles is well suited to capture physiological breathing characteristics (Scheinerr et al., 2015). When considering alternate breathing patterns such as deep inhalation, recent numerical simulations in 3D acinar models have underlined how unsteady flow characteristics are strongly affected relative to those under tidal breathing (Hofemeier et al., 2016). Hence, we anticipate that for deep inhalation maneuvers pertinent to drug inhalation (Delvadia et al., 2015; Khajeh-Hosseini-Dalasm and Longest, 2015), when V_T and τ are increased, differences in the ensuing deposition outcomes could be exacerbated between the acinar expansion modes.

Recognizing such limitations, the present simulations suggest nevertheless that self-similar breathing motions have the ability to deliver presumably a reasonable, if not good, estimate of acinar deposition; the details of acinar expansion have generally lesser importance relative to intrinsic particle motion (Hofemeier and Sznitman, 2015). Moreover, implementing an injection delay to mimic the time for a continuously inhaled aerosol bolus to cross over the dead space (see Methods) has significant ramifications in predicting more physiologically realistic deposition characteristics compared to previous approaches relying on a fixed bolus injected at $t = 0$ (Hofemeier and Sznitman, 2015).

In the context of ongoing discussions in the field (Darquenne, 2001; Hofemeier and Sznitman, 2014; Hofemeier et al., 2014; Tsuda et al., 1999, 2011, 2013), it is often brought forward that heterogeneous wall expansions may significantly contribute to flow irreversibility; in turn, such mechanisms are anticipated to play an important if not determining role in the deposition of fine and ultrafine (nano) particles deep in the lung. These conclusions have been often based on the underlying assumption that inhaled sub-micrometer aerosols in the acinar region are mainly affected by convection in the absence of Brownian diffusion and as such, sub-micron particles act mainly as passive flow tracers (Darquenne, 2001; Heyder et al., 1988; Tsuda et al., 1999). Not only does the present work shed new light on such questions, but our findings underline how the net effects on particle transport arising from changes in wall motion are anticipated to be overestimated, once intrinsic transport mechanisms are accounted. Moreover, and to the best of our knowledge, we quantify for the first time which particle size range ($d_p \sim 0.5\text{--}0.75\ \mu\text{m}$) will experience modulations in transport and deposition characteristics due to anisotropic wall expansion, albeit not dramatic under tidal breathing conditions. These efforts continue to help consolidate our views and understanding of acinar aerosol transport.

Appendix A. Supplementary data

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Schematic illustrations of acinar expansion motions shown at two instances t_1 and t_2 : (a) self-similar expansion, (b) "cup to saucer" expansion, (c) "saucer to cup" and (d) alveolar recruitment. (e) Average ductal diameter across the entire acinar tree (normalized to its value at FRC, *i.e.* $t=0$) during a complete breathing cycle. (f) Corresponding normalized ductal diameters at each individual acinar generation for the alveolar recruitment scenario relative to self-similar motion. (see Supplementary Material for details on the kinematic

displacement functions for each wall expansion scenario as well as SM Video 1 for a dynamic visualization of each expansion mode).

Fig. 2.

Snapshots at peak inhalation ($t/\tau \sim 0.25$) of one-dimensional (1D) velocity profiles extracted across the width of acinar ducts and alveoli (see L/W in the acinar domain) for different acinar breathing motion in (a) generation 1, (b) generation 3 and (c) generation 6. Velocity magnitudes are normalized against the mean flow entering the domain inlet under self-similar conditions.

Fig. 3. Particle deposition characteristics in the acinar domain as a function of expansion maneuver. (a) Deposition fraction and (b) ratio of alveolar to ductal deposition as a function of particle diameter.

Fig. 4.

Spatial distribution of deposited particles (relative to total injected) according to their penetration depth (*i.e.* acinar generation). Shown here is the narrow range of sub-micron particles $d_p = 0.5\text{--}0.75\ \mu\text{m}$, influenced by local acinar convection. See SM for complete data for $d_p = 0.005\text{--}5.0\ \mu\text{m}$.