Journal of Biomechanics 49 (2016) 3543–3548

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Short communication

The role of anisotropic expansion for pulmonary acinar aerosol deposition

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ARTICLE INFO

Article history:
Accepted 16 August 2016

Keywords:
Pulmonary acinus
Anisotropic expansion
Numerical simulations
CFD
Particle transport
Aerosol deposition

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 ($d_p = 0.005–5.0$ μm) 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 ($d_p \sim 0.5–0.75$ μm), 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.

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 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 is 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 (μCT) 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).

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http://dx.doi.org/10.1016/j.jbiomech.2016.08.025
0021-9290/

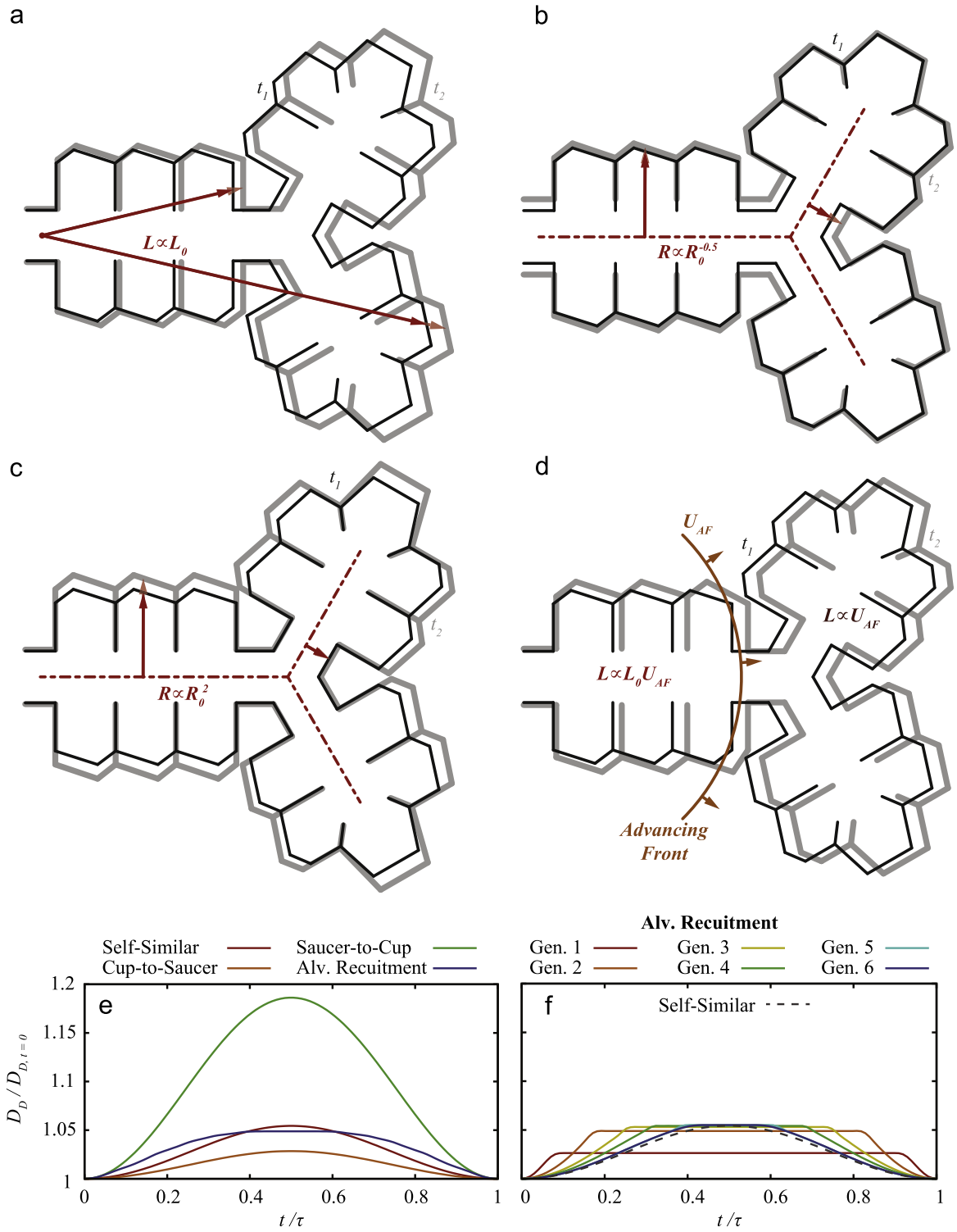

Fig. 1. Schematic illustrations of acinar expansion motions shown at two instances t_1 and t_2: (a) self-similar expansion, (b) "cup to saucer" expansion, (c) "saucer to cup" and (d) alveolar recruitment. (e) Average ductal diameter across the entire acinar tree (normalized to its value at FRC, *i.e.* $t=0$) 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).

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