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# Morphogenetic implications of peristaltic fluid–tissue dynamics in the embryonic lung

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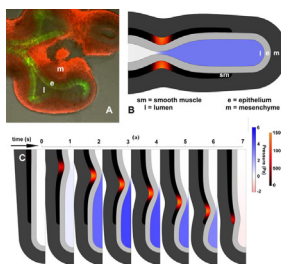
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## HIGHLIGHTS

- Peristalsis in the prenatal airway critically modulates development.
- We developed a model of peristaltic fluid–tissue interactions in embryonic lung.
- Peristalsis flattens cells in the airway tip and elongates cells in the tubule stalk.
- Occlusion and most measures of stretch depend linearly on smooth muscle force.

## GRAPHICAL ABSTRACT



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## ABSTRACT

Peristalsis begins in the lung as soon as the smooth muscle forms, and persists until birth. Since the prenatal lung is liquid-filled, smooth muscle action can deform tissues and transport fluid far from the immediately adjacent tissues. Stretching of embryonic tissues and sensation of internal fluid flows have been shown to have potent morphogenetic effects. We hypothesize that these effects are at work in lung morphogenesis. To place that hypothesis in a quantitative framework, we analyze a model of the fluid–structure interactions between embryonic tissues and lumen fluid resulting from peristaltic waves that partially occlude the airway. We find that if the airway is closed, deformations are synchronized; by contrast, if the trachea is open, maximal occlusion precedes maximal pressure. We perform a parametric analysis of how occlusion, stretch, and flow depend on tissue stiffnesses, smooth muscle force, tissue shape and size, and fluid viscosity. We find that most of these relationships are governed by simple ratios.

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## 1. Introduction

Q2 Airway peristalsis (AP) produces spontaneous phasic airway contractions and transient, reversible airway occlusions throughout normal lung development (Jesudason et al., 2005; Pandya et al., 2006; Parvez et al., 2006; Schittny et al., 2000). AP begins as

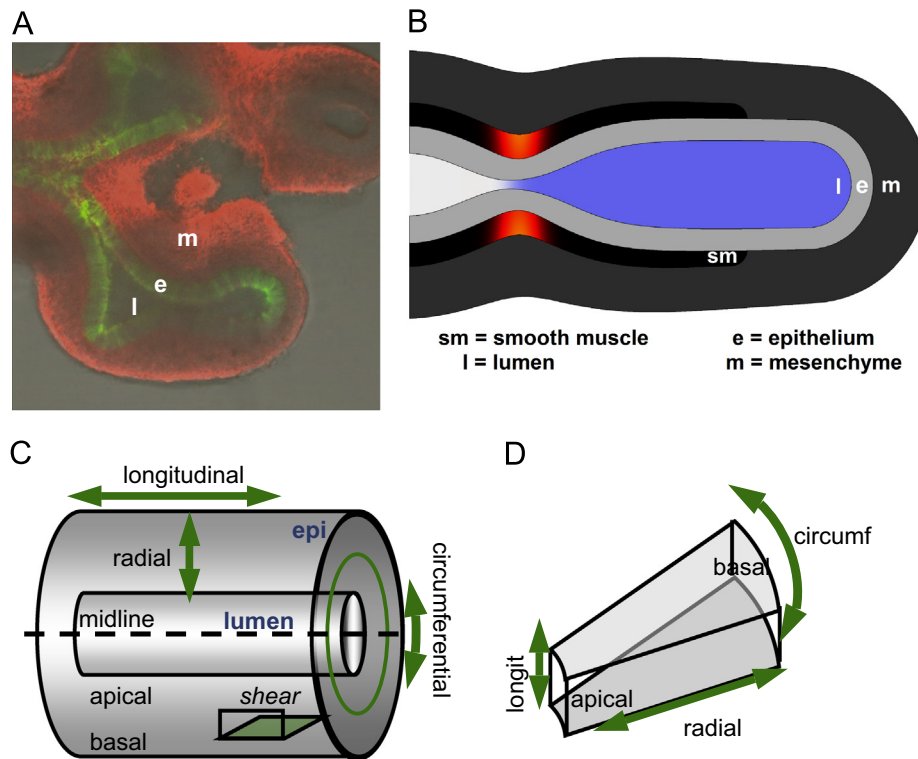
soon as the smooth muscle (SM) develops, concurrently with pseudoglandular branching (Fig. 1A), and becomes more robust towards later stages of development. AP has been shown to influence lung development and blockage of AP interferes with lung development (reviewed in Jesudason (2009)), but the mechanisms remain unclear. We hypothesize (Jesudason, 2009) that AP critically modulates physical forces on airway cells, influencing the patterning of branching morphogenesis and, ultimately, the overall growth of the lung (Jesudason, 2006; Warburton and Olver, 1997). A more specific hypothesis would

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**Fig. 1.** Geometry of embryonic lung and model. (A) Explanted E11.5 mouse lung showing lumen (l), epithelium (e, green), and mesenchyme (m, red). Smooth muscle (sm) not visible. (B) Embryonic lung idealized as unbranched tubule, with three uniform tissue layers plus lumen. Smooth muscle undergoes active circumferential contraction wave. Lumen color indicates pressure; smooth muscle color indicates contractile stress. (C) Orientation in a tubule. Tissue can be stretched or compressed in radial, circumferential, and/or longitudinal directions, and can be sheared in radial–longitudinal interaction. (D) Idealized epithelial cell from stalk region of a tubule. What deforms a tissue in a specific direction deforms its cells in the same direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

consider that AP involves fluid flow and multiple tissues; mechanosensing operates very differently in these different contexts. In further specificity, the physical inputs to the cells are not simply distinguished by on/off presence or absence, but by magnitude and timing, and also by orientation. With the aim of clarifying and refining our mechanobiological hypothesis, to more richly characterize these physical forces, we developed and analyzed a computational mechanical model of AP in the embryonic airway.

Peristaltic pumping, for bulk transport, is widespread not just biologically, but also in industrial and medical applications. There are decades of research on the fluid–structure interactions of peristalsis. A comprehensive review of peristalsis modeling is outside the scope of this article, but we briefly outline here the geometric classifications and their significance. The physics and engineering of open-ended peristalsis are, by now, well understood. Peristalsis has been abundantly modeled as in an infinitely long tube (Burns and Parkes, 1967; Carew and Pedley, 1997; Fung and Yih, 1968; Grotberg and Jensen, 2004; Jaffrin and Shapiro, 1971; Pozrikidis, 1987; Shapiro et al., 1969; Yin and Fung, 1971) or in a finite-length tube open at both ends (Li and Brasseur, 1993), exhibiting richly varied behaviors including stalling and reflux. There are a few studies of blind-ended peristalsis in a channel of fixed length (Yaniv et al., 2012, 2009). However, to our knowledge, the mechanics of blind-ended peristalsis in a tube has until very recently (Aranda et al., 2015) not been studied.

In a concurrent paper (Bokka et al., in preparation), we examine the case of complete occlusion, estimating the deformations of individual cells in the epithelium with a purely geometric model, accounting for conservation of lumen and cell volume. In another concurrent paper (Bokka et al., in press), we analyze the effect of AP on transport of solutes, and discuss the morphogenetic implications of this modification of transport.

In this paper, we determine mechanical stresses on tissues and cells involved in AP, and some flow characteristics in the lumen. We quantitatively identify how the physical characteristics of lumen fluid, tissue stiffness, and SM contraction determine these outcomes. Because we hypothesize that mechanical stimulation alters branching morphogenesis, and want to clarify the mechanisms associated with that, we focus on the early development of the lung as the branches form, in the pseudoglandular period. Our mechanical model tracks the fluid–structure interactions of a tubule with three tissue layers and a liquid-filled lumen (Fig. 1A). In the interest of parsimony, we omit other tissues such as blood vessels.

By the end of the pseudoglandular period, the lung is richly branched. In order to focus on the fundamental aspects of embryonic AP, we model the embryonic lung as an unbranched, radially symmetric tube, with a liquid-filled lumen (Fig. 1B–D). This idealized shape corresponds to the beginning of the pseudoglandular period, before branching, but can also serve as a model of the immediate vicinity of a distal tip of a later branched embryonic stage. A wave of AP propagates from trachea to tip (Fig. 1B).

Because AP is present in prenatal lungs of different species, at very different stages of development, and of very different sizes, we want to develop an understanding of the mechanics of AP in all these variations. Fortunately, what would be an enormous study in vivo becomes a relatively simple study in silico. We test the model on the full range of biologically plausible parameter values, and determine the importance and influence of tissue stiffness, lumen fluid viscosity, and smooth muscle force on measurable quantities such as deformations (strain, in several different orientations), fluid flow, pressure, and occlusion, as well as on less measurable quantities such as stress.

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