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Pillars of Theoretical Biology: Airway stability and heterogeneity in the constricted lung

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1. Introduction

In this issue's *Pillars of Theoretical Biology* we consider Anafi & Wilson's terminal airway model (Anafi and Wilson, 2001) which paved the way for subsequent study of self-organization and pattern formation in the constricted lung. This has influenced thinking about the pathophysiology of asthma for 20 years, and will continue to do so going forward.

2. Anafi & Wilson's contribution

Asthma, despite being extremely widespread, is surprisingly poorly understood in terms of its underlying mechanisms. It is characterized by reversible airway constriction, driven by the airway smooth muscle surrounding the airways, but how and why this process becomes uncontrolled has been an open question for decades.

By the 1990's, it had become clear (by high-resolution CT (Amirav et al., 1993; Brown et al., 1993) and other means) that airway constriction *in vivo* was heterogeneous. What was less clear, however, was why this occurred. One hypothesis was that functional heterogeneity (heterogeneous airway constriction) was induced by structural heterogeneity (differences in the tissue or airways themselves). Anafi & Wilson introduced a new paradigm by proposing a model of a single terminal airway[1] describing a feedback mechanism between airflow, airway constriction, and so-called *parencyhmal interdependence*.[2] This model, based on relatively simple empirical descriptions of these processes, nonetheless describes an instability in which "terminal airways are predicted to have two stable states: one effectively open and one nearly closed" (under constrictive stimulus) and they further suggest that "the heterogeneity of whole lung constriction is a consequence of this behavior".

Anafi & Wilson depicted this bistability with the figure recreated in Fig. 1(a), illustrating how airflow volume relates to the pressure for a variety of conditions. Although they described this figure in terms of the slope of each region (I, II, III) in another context we recognize a fold (or saddle–node) bifurcation.[3] The corresponding inner airway radius (as related to airway entrance pressure) is shown in Fig. 1(b).

3. Subsequent and continuing developments

A range of developments have occurred and are ongoing, and published in journals including the *Journal of Theoretical Biology* and elsewhere. The most obvious subsequent question is how such an instability at the level of the individual (terminal) airway would manifest at the scale of the whole lung. In 2005 Venegas, Winkler and colleagues (Venegas et al., 2005) extended Anafi & Wilson's terminal unit model to a symmetric binary tree in an effort to answer this question. In this symmetric geometry, inter-airway coupling gives rise to self-organized pattern formation phenomena (often "clustered ventilation defects" in the physiology literature) which have generated much interest in airway phenomena as critical transitions or tipping points in a complex system (Petrovskii et al., 2017; Booton et al., 2017; Scheff et al., 2013; Scheffer et al., 2009).

This gave rise to a new way of thinking about airway constriction *in vivo*: if clustered ventilation defects emerge dynamically (rather than arise structurally), then maneuvers, such as a deep inspiration, might allow transitions between multiple states within the 'energy landscape' (Winkler and Venegas, 2007, 2011; Tgavalekos et al., 2007). Such hysteresis is an appealing explanation for the surprising effectiveness of deep inspiration (e.g. Golnabi et al., 2014).

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[1] Terminal bronchioles (airways) are the smallest conducting airways, which then lead to the gas exchange portion of the lung.

[2] The parenchyma is the gas exchange tissue in which the airway is embedded and tethered; when the airway constricts, these attachments (parenchymal tethering) oppose the narrowing – think of a hole in a sponge – and the degree to which this happens depends on the inflation of the parenchyma. Because the inflation of the parenchyma is determined by the flow through the airway(s), this parenchymal tethering is dependent upon flow, and the coupling is known as *airway-parenchymal interdependence*.

[3] The term 'bifurcation' does double duty in this context: both mathematical bifurcations in the sense familiar to most JTB readers, but also airway bifurcations as the airway tree branches.

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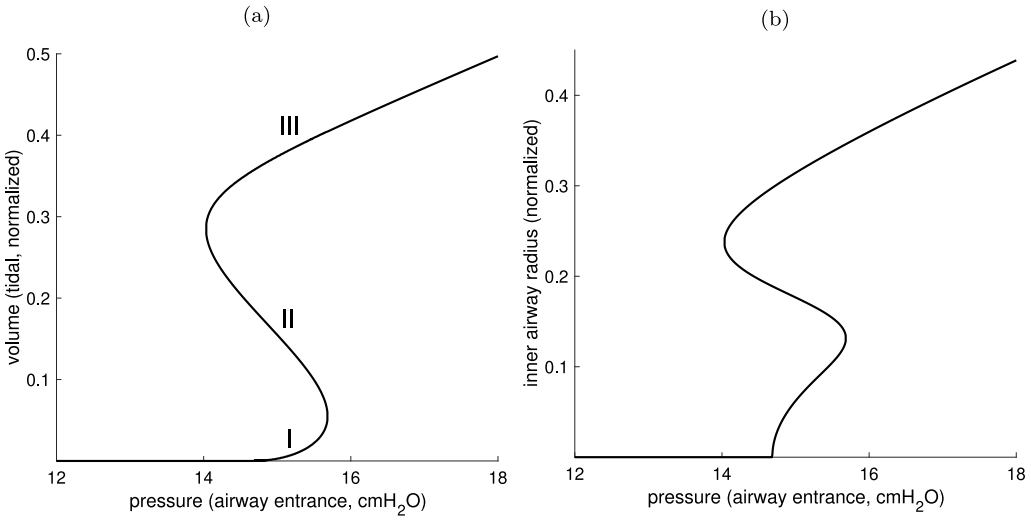

Fig. 1. Anafi & Wilson's terminal airway model: a fold by any other name. Panel (a): relationship between airway entrance pressure and tidal volume. Original caption: "Acinar tidal volume vs. peak airway entrance pressure. Acinar tidal volume is nondimensionalized by the volume of an acinus at TLC (VTLC). The curve can be divided into 3 regions according to the sign of its slope. In the regions with positive slope, regions I and III, the airway is nearly closed and well open, respectively. In the transition region (region II), the slope is negative, and the solution to the flow equations is unstable". Figure recreated by the author. Panel (b): corresponding inner airway radius as a function of airway entrance pressure; the same three regions are apparent.

However, the human bronchial tree is neither symmetric nor homogeneous. Other investigators extended these concepts to asymmetric-branching trees and CT-derived geometries (Leary et al., 2014; Donovan, 2016, 2017; Donovan et al., 2020). Study of these models, and comparison with imaging, raises an intriguing question: how are the formation and location of ventilation defects controlled?

At one logical extreme, we have what might be called the 'bad airway' hypothesis: functional defects are determined completely by structural abnormalities (Politi et al., 2010; Svenningsen et al., 2014b). Defect formation would be fully repeatable and persistent. At the other end of the spectrum, the Anafi–Wilson instability in a homogeneous, symmetric domain predicts the opposite: all regions are equally likely to constrict.

Imaging studies suggest however, that the truth lies somewhere in between: defect locations are neither fully random nor fully repeatable, but intermittent (e.g. Svenningsen et al., 2014a), as is perhaps unsurprising for a complex system near a tipping point. The question remains unanswered, but when we have done so we will have found another piece of the puzzle that is asthma, and we will probably have Anafi & Wilson to thank for it.

Declaration of competing interest

No conflicts of interest to declare.

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