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Multiscale mathematical models of airway constriction and disease

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ABSTRACT

Loss of lung function in airway disease frequently involves many complex phenomena and interconnected underlying causes. In many conditions, such as asthmatic airway hyper-responsiveness, hypothesised underlying causes span multiple spatial scales. In cases like this, it is insufficient to take a reductionist approach, wherein each subsystem (at a given spatial scale) is considered in isolation and then the whole is taken to be merely the sum of the parts; this is because there can be significant and important interactions and synergies between spatial scales. Experimentally this can manifest as, for example, significant differences between behaviour in isolated tissue and that seen in vivo, while from a modelling perspective, it necessitates multiscale modelling approaches. Because it is precisely in these complex environs that models have the greatest potential to improve understanding of underlying behaviours, these multiscale models are of particular importance. This paper reviews several examples of multiscale models from the most important models in the literature, with a particular emphasis on those concerned with airway hyper-responsiveness and airway constriction.

1. Introduction

Attempting to understand the mechanisms underlying lung function, both in health and disease, presents a host of challenges. The structure and geometry are clearly daunting, with the bifurcating airway tree beginning at the trachea and descending through 28 airway orders to more than 30,000 distal terminal bronchioles [1] and even more numerous alveoli, wherein gas exchange takes place. In addition the pulmonary circulation is an equally imposing parallel system, and combined this complex structure fills the volume of the lungs. Not only is the scale imposing, but underlying function is further complicated by interactions between tissues which may be coupled in different ways: by airway, by vasculature, or between multiple spatial scales. All the while this must be sufficiently compliant to undergo large deformations, even during normal breathing [2]. Efforts to observe the underlying processes at work are often complicated by potentially significant differences between behaviour observed in vitro and that which occurs in vivo [3,4], as well as inter-species differences (i.e. [5]).

Moreover, many observed phenomena are complex behaviours, such as “patchy” ventilation (i.e. [6]) and strain-induced fluidisation (e.g. [7–9]) which elude simple explanation. This complex environment is an excellent opportunity for mathematical models to complement experimental and clinical evidence in order to enhance our fundamental understanding of the underlying biological mechanisms at work. Improved models lead to improved understanding, and improved understanding leads to improved therapies.

Consider, for example, asthma and airway constriction, which will be the focus of this review. Despite the prevalence of asthma and its widespread study, there are still many hypothesised mechanisms at work and widespread uncertainty as to which, if any, are the most important, and as to how they interact. We hope that mathematical models can help answer these questions by suggesting answers that can then be verified, or disproved, by testable predictions.

2. Multiscale models

In complex systems involving multiple scales, function occurring at an isolated scale does not necessarily extend to the coupled, multiscale system. It has been thought for some time that understanding lung function requires taking account of a range of spatial scales [10]. In such systems it is generally insufficient to take a reductionist approach, in which each subsystem is considered only in isolation and the whole is then thought to be the sum of the parts. For example, significant loss of function in asthma may indeed be due in part to negative synergies between impairments which are significantly less severe when taken individually [11].

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In fact, this has a particular relevance to a recent debate with regard to the role of tidal stretches in modulating asthmatic airway hyper-responsiveness (AHR). It has been a widely held view, based primarily on in vitro studies, that dynamic stretches due to tidal breathing and deep inspirations are responsible for a reduction in airway narrowing capacity, especially in healthy subjects, which has important implications for loss of function in asthmatics (i.e. [12,13]). Recently new in vitro evidence demonstrated little to no effect [14], while attributing this to the interactions between scales which occur in intact airways but not in isolated tissue; this has ignited a spirited debate about the potential factors at work [5,15,11]. While this issue is far from settled, it highlights the potential importance of multiscale interactions in understanding the complex behaviour of the lung.

Likewise, there are many hypothesised factors at work in asthma and AHR, and determining their relative impact and interactions cannot be obtained by studying a single scale alone. For example, much effort has focused on the role of airway smooth muscle (ASM) dynamics or function (i.e. [16–21])[1] and airway remodelling (e.g. [22–28]), though certainly other theories abound (i.e. [29–33]). Many of these are thought not only to work in isolation, but also to have potential synergies between them. As such, it becomes fundamentally necessary to link events at the smallest scales with those at the largest, to determine the integrative behaviour and overall function and outcome.

There are several important modelling studies considering these types of multiscale interactions. In the following sections we review the purpose, scope, and important findings of several of these studies.

2.1. Heterogeneity and patchiness in interdependent terminal airways

One of the best-known models in the literature is that of Venegas et al. [6], which is a network-based extension of the work of the model of Anafi and Wilson [34,35]. Because of the intimate connection between these two works we shall discuss them here together.

Anafi and Wilson [34,35] consider primarily the relationship between pressure and flow due to airway constriction at maximal ASM activation in a single, terminal airway. Importantly the model includes a positive feedback loop between flow and resistance, by way of parenchymal interdependence. This is the salient feature of this model; that a terminal airway is surrounded by the parenchyma it serves. This can be seen by examining the model equations. Airway entrance pressure (P_{aw}) and pressure in the acinus (P_A) are related by

$$P_A(t) = \overline{P} + ||P_A||\sin(\omega t - \alpha)$$

where

$$||P_A|| = ||P_{aw}||\frac{E}{\sqrt{E^2 + (\omega R_{aw})^2}} \quad (1)$$

and E is the elastance, while P_{aw} is sinusoidally oscillatory with mean $\overline{P}$, frequency ω and amplitude $||P_{aw}||$, and α is a phase lag. Thus an increase in airway entrance pressure drives increased alveolar pressure. Parenchymal tethering stress τ is handled using the model of Lai-Fook [36] such that

$$\tau = P_A\left(1 + 1.4y + 2.1y^2\right)$$

where y is a measure of parenchymal distortion. Thus increased alveolar pressure leads to increased tethering stress. An increase in tethering stress is then connected with an increase in transmural pressure and thus airway radius; this leads to increased airway calibre and hence decreased resistance R_{aw} ; and thus to increased alveolar pressure via Eq. (1). This completes the feedback loop. As such, an increase in flow drives an increase in alveolar pressure, which in turn increases tethering stress and hence increases airway calibre and further increases flow. The equivalent feedback loop in the opposite direction is that a decrease in flow reduces alveolar pressure, and hence reduces parenchymal tethering stress leading to further airway constriction and reduction in flow. Thus very small initial differences between airways can be magnified by this feedback mechanism into significant heterogeneity. It is important to note that this mechanism requires flow driven *at the entrance*, generally by volume (but also more recently by pressure [37]), as in mechanical ventilation. The feedback mechanism does not function under flow driven by negative pressure at the periphery, such as spontaneous breathing.

This basic model of Anafi and Wilson for a single terminal airway is put to use by Venegas et al. [6] who distribute the basic model across a Mandelbrot-like, symmetric-bifurcating airway network connected by airflow, and iterate the entire system to steady state. Pressure (P), resistance (R) and flow ($\dot{V}$) are related for a single order-n terminal airway at time t by

$$P(t,n) = R(n)\dot{V}(t,n) + \frac{2^n}{C_L}\int_0^t \dot{V}(t',n)dt' + \frac{1}{C_{cw}}\int_0^t \dot{V}(t',0)dt'$$

where C_L and C_{cw} are the compliances of the lung parenchyma and chest wall, respectively, and $\dot{V}(t,0)$ is the flow through the single generation-zero airway. Pressures and flows for connected airways in the network are related in the intuitive way: pressures are equal and volumes must sum at bifurcations, and the pressure drop down a segment is equal to the product of resistance and flow. Then from the resulting volume and pressure for each segment, resulting airway calibre is calculated using the nonlinear model of Anafi and Wilson [34].

This distributed and interconnected network representation then makes plain the predicted heterogeneity driven by the feedback mechanism described above. This is illustrated in Fig. 1 plotting relative airway calibre versus ASM activation for large airways (upper panel) and small airways (lower panel). As ASM activation is increased from a low level, there is initially a slow and gradual decrease in radius for all airways in an approximately uniform fashion. However, at a critical transition value (here between 0.85 and 0.9) the feedback mechanisms take over and drive a portion of the airways towards closure while triggering an offsetting dilation in other airways (tidal volume is assumed to remain constant). Thus the expected heterogeneity occurs across the airway tree, along with a range of interesting complex behaviours [38].

2.2. Parenchymal tethering and general airway bistability

The model of Affonce and Lutchen [39] is a static model focussing on asthma, AHR and airway hyper-sensitivity, and airway constriction. It is an extension of the work of Lambert et al. [16] taking account of the behaviour of not only the airway wall, but also increased parenchymal tethering due to constriction, elastic lung recoil, and ASM stress. While each of these elements are included in fairly simple and largely empirical ways, the assembled model has very important behaviour in terms of bistability in the

[1] It is impractical to cite here every relevant paper in the vast literature of hypothesised causes and associated discussion. Instead we refer only to a few representative works and reviews.

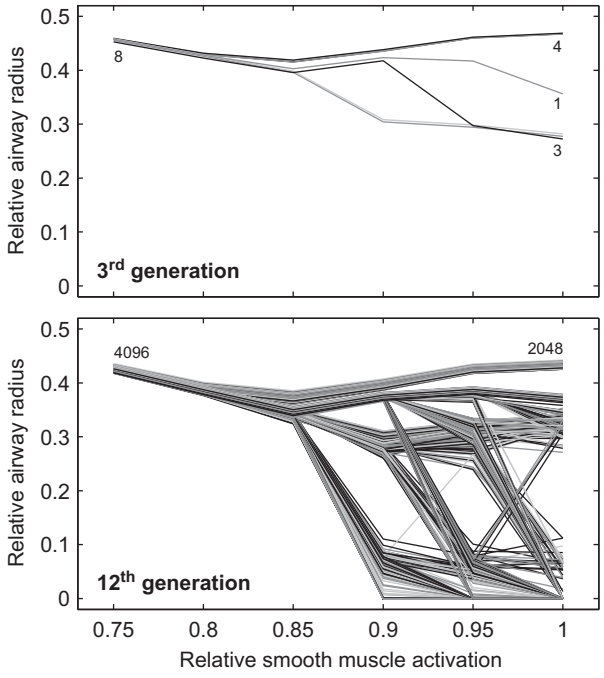

Fig. 1. From the model of Winkler and Venegas: airway radii at increasing levels of smooth muscle activation. The characteristic behaviour of airways at the 3rd generation is representative for central airways, while the 12th generation shows the behaviour of peripheral airways. Above the critical level of smooth muscle activation (>0.85) emerged a combination of constriction and dilation, showing evidence of parallel airway interdependence between dilating airways located outside of ventilation defects and constricting airways located within ventilation defects. The number of airways in groups of similar size visualises the contribution of different airway behaviours to the heterogeneous response within a generation. Reproduced from Winkler and Venegas, J Appl Physiol 2007 [38] Am Physiol Soc, used with permission.

airway calibre-ASM tension relationship which has important implications for observed heterogeneity in the lung. Many of the subsequent works discussed above have been heavily influenced by these ideas.

Consider the relationship between airway calibre and ASM tension; the model equations in [39] yield several interesting features. We reproduce in Fig. 2 the relationship between airway calibre (here constricted diameter D_c normalised by baseline diameter D_b) and ASM tension T (also normalised), for a central airway in the top panel and a peripheral airway in the bottom panel. There are several important results which can be extracted from this figure. First, note that the relationships are generally multivalued for some values of normalised tension. That is, for a particular ASM tension in otherwise identical airways, it is possible for the state of airway constriction to be different; this is an important theoretical driver of heterogeneity. Moreover, for increasing severity of asthma, this effect becomes more pronounced and the onset occurs at lower levels of ASM tension. For example, in the most extreme case, that of severe asthma without tethering in a peripheral airway, for $T/T_{\mathrm{Max-C}} \approx 0.25$ the airway diameter ratio can take values ranging from around 0.8 down to near closure with minimal change in ASM tension. Thus very subtle differences in airway state can have a very large influence on calibre and hence drive both significant heterogeneity and loss of lung function.

2.3. Airway constriction dynamics and agonist binding kinetics

A recent dynamic, multiscale model focussing on the role of aerosol challenge and airway constriction is the work of Amin et al. [40]. Importantly, this model takes account of the kinetics of

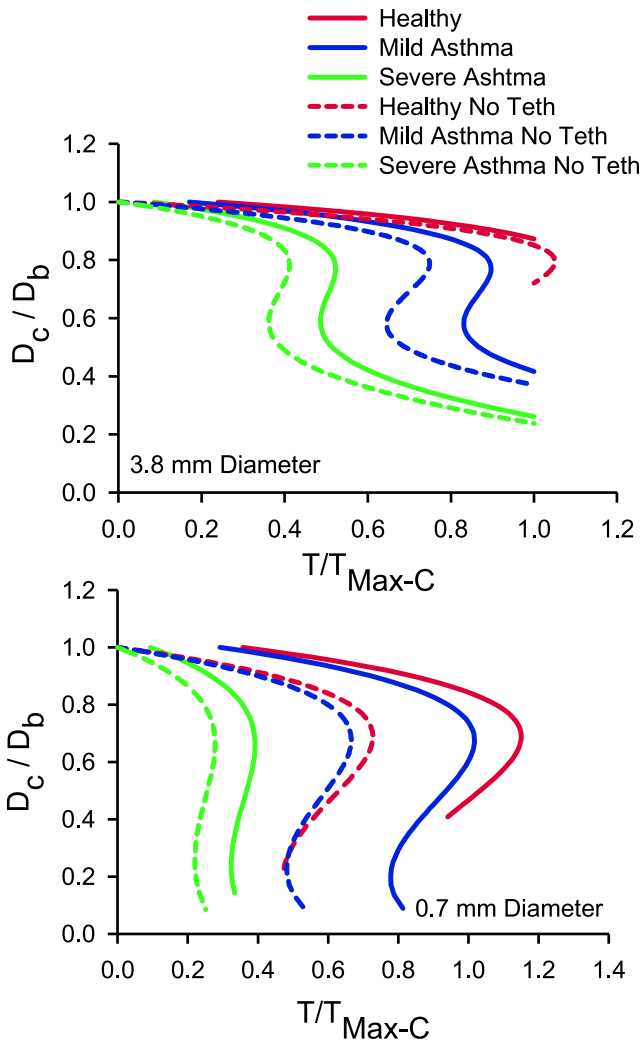

Fig. 2. From the model of Affonce and Lutchen: Effects of removing coupling effects between the airway wall and lung parenchyma. Top: central airway. Bottom: peripheral airway. Healthy airways are shown in red, mild to moderate asthmatic airways in blue, and severe asthmatics in green. Solid lines represent the baseline cases with the shearing forces in play, whereas dashed lines represent the case where shearing of local parenchyma is set to zero to represent the decoupling of the lung parenchyma and airway adventitia. Reproduced from Affonce and Lutchen, J Appl Physiol 2006 [39] Am Physiol Soc, used with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

agonist-receptor binding and the resulting multiscale interactions with airway wall mechanics and pressure-driven flow. The authors use a simple, two-state dynamic pharmacokinetic model for agonist binding and unbinding, where S_B and S_U represent bound and unbound populations respectively. Then

$$\frac{dS_U}{dt} = -\alpha S_U + \beta S_B - \gamma S_U + S'_{dep} \tag{2}$$

$$\frac{dS_B}{dt} = \alpha S_U - \beta S_B, \tag{3}$$

where unbound agonist binds to receptors at rate α, bound agonist unbinds at rate β, unbound agonist is removed by diffusion and circulation at rate γ, and unbound agonist continually added at the deposition rate S'_{dep}. Bound receptors then trigger ASM tension by way of a sigmoidal ASM response. Airway wall mechanics are due to Lambert et al. [41], determining airway calibre given imposed ASM stress. Airway radii determined in this fashion are coupled

with airflow and agonist deposition, creating a feedback mechanism as detailed below.

Each airway is part of a 10-generation symmetric-bifurcating airway tree, and within this structure global agonist transport and deposition are taken account of by pressure-driven flow, modelled as Poiseuille flow. This flow model is importantly coupled to the agonist kinetics as airway constriction alters the flow pattern, and hence influences agonist deposition and thus agonist binding and ASM response. An important consequence of the cross-scale interaction is the formation of a negative feedback loop wherein increased constriction leads to decreased flow and hence decreased deposition and decreased constriction. Likewise, a decrease in airway constriction leads to increased flow and deposition, and thus increased constriction. The authors postulate that this negative feedback loop is a protective mechanism operating within the lung, with potentially important consequences.

Interestingly, this *protective* feedback mechanism operates in the opposite direction as the positive feedback mechanism described by Anafi and Wilson [34] (see Sec. 2.1). In that model small differences between airways are exaggerated by airflow-influenced parenchymal tethering forces; here the protective mechanism reduces differences by control of airflow-controlled agonist deposition.

A second important result is that airway diameters during aerosol challenge cannot be adequately predicted by the corresponding initial diameter, despite this protective feedback mechanism. We reproduce the model results of Amin et al. for the relationship between baseline diameter and constricted diameter ratio at peak constriction in Fig. 3 for each airway in the tree. While for the larger airways the predictive relationship is good, clearly significant heterogeneity emerges amongst the smaller airways constricted diameter ratios for the smallest airways ranging from approximately 0.4–0.9 with almost negligible variation in baseline diameter. Again, the model results highlight the potential importance of interplay between multiple spatial scales.

2.4. Multiscale pathways from molecule to organ

The multiscale, spatially-distributed model of Politi et al. [42] is focussed on asthmatic AHR and considers models at four different spatial scales: molecular, cellular, tissue and organ. Here the molecular scale is taken to mean intracellular Ca^{2+} dynamics due to agonist (MCh) stimulation; the cellular scale concerns ASM dynamics and force generation; the tissue scale takes account of airway wall mechanics and parenchymal tethering; and the organ scale includes mechanical deformation of the lung due to breathing and gravity.

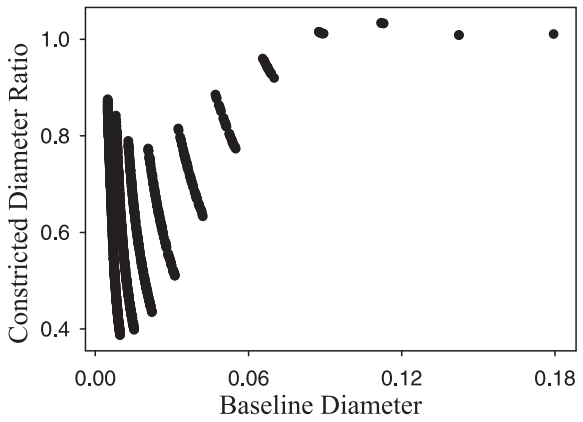

Fig. 3. From the model of Amin et al.: normalised airway diameters at peak constriction after challenge plotted against their initial diameters. Reproduced from Amin et al., J Appl Physiol 2010 [40] Am Physiol Soc, used with permission.

At the smallest, molecular, scale, an imposed agonist concentration (simulating bronchial challenge) triggers an increased Ca^{2+} response. That is, applied agonist concentration a is a function of both space and time, depending on the mode of application, so that

$$a = a(\vec{x}, t)$$

where the spatial dependence $\vec{x}$ indicates the position of each individual airway within the lung. Applied agonist triggers a time-dependent Ca^{2+} response, which is then in general

$$c = c(a, t).$$

While in [42] a simple, linear relationship is used, a more sophisticated dynamic model would be, for example, that of Wang et al. [43] for ASM.

Both applied agonist and induced Ca^{2+} concentrations are then coupled to a sliding filament (actin/myosin) ASM model, wherein Ca^{2+} release activates myosin light-chain kinase (MLCK) which enables phosphorylation of myosin and hence binding to actin and thus ASM stress. Generated force is determined by number of bound binding sites at any given time, which is dependent both on Ca^{2+} and agonist concentrations as well as physical displacement of the filaments due to physical interaction with larger spatial scales. Specifically the model employed is a modified Huxley/Hai/Murphy–type crossbridge model [44–46] calibrated to ASM behaviour in tissue slice preparations. The model thus considers four populations of myosin, distinguished by binding and phosphorylation: unbound, unphosphorylated myosin M; unbound, phosphorylated myosin M_p; bound, unphosphorylated myosin AM; and bound, phosphorylated myosin AM_p. Each population is then evolved in time by solving the governing partial differential equations [46], which depend both on a and c as well ASM velocity. Then ASM force depends on the bound states

$$f(t) = \kappa \int_{-\infty}^{\infty} x\left[AM(x,t) + AM_p(x,t)\right] dx$$

where the constant parameter κ characterises the stiffness of the muscle.

ASM force and velocity are then coupled to the tissue-level model of each individual airway. Each airway incorporates an (incompressible) airway wall which relates transmural pressure P_{tm} and airway inner radius r_i with a relationship due to Lambert et al. [41]. Simple geometrical constraints impose an incompressible smooth muscle layer (with ASM force and velocity from the cellular-level model). Parenchymal tethering is accounted for using a compressible local parenchymal layer which creates a pressure increase in response to airway constriction

$$\Delta P = 2\mu\left(\Delta R + \nu(\Delta R)^2\right),$$

which is due to Lai-Fook [36] where ν is an empirical parameter. The material shear modulus μ depends on both on space and time, as determined by the organ-level model. Thus

$$\mu = \mu(\vec{x}, t)$$

as determined by linearising the organ-level model at each desired location in both space and time.

At the largest, organ-level spatial scale, the global lung parenchyma is modelled as a 3D hyperelastic continuum with (optionally) a computational geometry taken directly from patient-specific CT-images [47]. The strain-energy function used

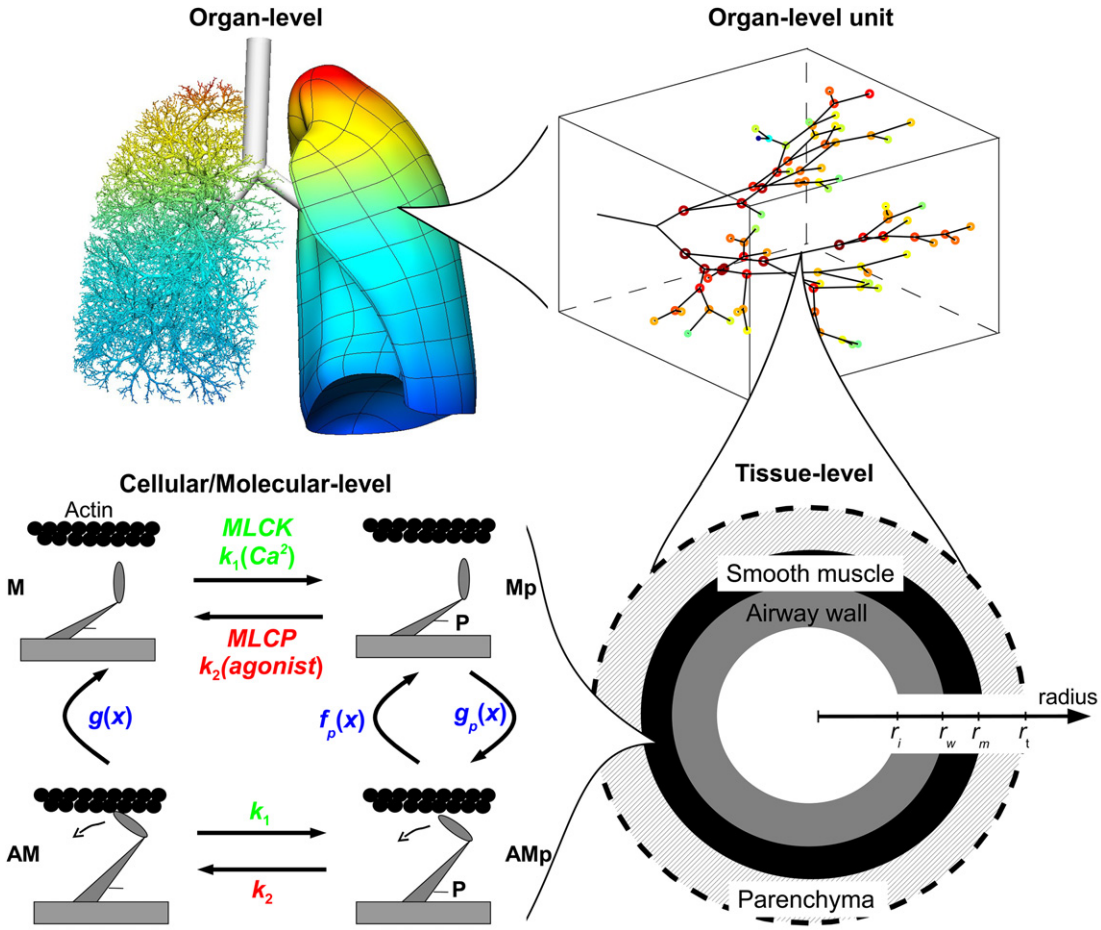

Fig. 4. For the model of Politi et al.: schematic of multiscale interactions. Upper left panel: complete anatomically-accurate organ-level model, with parenchymal tissue elements displayed in the left lung and the embedded airway tree in the right. Upper right panel: organ-level tissue unit with 90 embedded airway segments. The circles at the airway tree bifurcations represent the radii computed at the tissue level. Lower right panel: in the tissue level, each airway segment is modelled as a cylinder. We consider three layers: airway wall, smooth muscle cells, and a parenchymal layer. Lower left panel: cellular/molecular level. Phosphorylation of myosin (M to Mp) enables binding to actin (A). Force is generated by the attached populations, AM and AMp. Phosphorylation is controlled by several stimuli that increase Ca^{2+} release which in turn activates MLCK, whereas dephosphorylation is controlled by MLCP, which itself can be regulated by agonists. Reprinted from [42] with permission from Elsevier.

$$W(E) = \frac{C}{2}\exp\left(\alpha J_1^2 + \beta J_2\right)$$

is due to Fung [48] with parameters from Tawhai et al. [47] and where J_1 and J_2 are the first and second invariants of the Green strain tensor E. The conducting airway tree is embedded in this global parenchyma, with the largest airways taken from imaging up to the imaging resolution restrictions, and representative, asymmetric-bifurcating smaller airways constructed numerically [49].

Each airway in this embedded tree is connected with its own tissue-level cylindrical model, which is in turn coupled with individual crossbridge mechanics and Ca^{2+} dynamics. At each time, and for each airway, the resulting airway radius is determined by force balance across all of these scales. The multiscale coupling arrangement is represented schematically in Fig. 4, reproduced from [42].

This model has several important outcomes which feature prominently in the discussion here on the importance of multiscale considerations. The first is emergent heterogeneity, as in the previously discussed models, wherein significant spatial heterogeneity arises as a result of relatively small differences in organ-level tissue deformation, for airways otherwise identical at the smaller scales.

The second important outcome is the relatively small degree of airway dilation resulting from tidal oscillations, as compared with the static case without oscillations. As previously discussed, controversy now surrounds the extent to which dynamic stretches due to tidal breathing and oscillations are bronchoprotective, due to a reduction in generated ASM force. While the model predictions are qualitatively in agreement that tidal oscillations do cause reduction in generated crossbridge force and thus less airway constriction, quantitatively the effect is very small in the multiscale, coupled case, in agreement with the hypothesis put forward in [14] that interactions between spatial scales must be taken into account. Here we again see the potential importance of multiscale interactions and limitations of the reductionist approach, wherein behaviour seen at one scale in isolation does not necessarily extend to the full system.

3. Summary

Of course, there are many important aspects of AHR and airway constriction which are not considered by these models. For example, none of the models discussed explicitly take account of bronchial mucosal folding, a potentially important effect (well-reviewed by Kamm [50], plus several more recent efforts [51–53]), or mechanotransduction (i.e. [54,55]), among many possibly important effects. Likewise there are modelling studies with multiscale features which have not been discussed at length here, such as the acute respiratory distress syndrome (ARDS)-focused model

of Wall et al. [56], which divides the respiratory system into a "conducting zone" and a "respiratory zone" and explicitly resolves the former whilst employing an impedance-based alveolar ensemble for the latter; the model of Ma and Lutchen [57] which incorporates airflow dynamics through the airway tree, reaching down to alveolar tissue units using the constant phase viscoelastic model; the efforts of Latourelle et al. [58], which emphasised the importance of dynamic equilibration of ASM; the more sophisticated airway constriction model of Brook et al. [59] taking account of local stress and cellular-level responses; the seminal early works of Lambert and coworkers [41] on which nearly all of these later models depend; as well as the Physiome Project [60].

Nonetheless, the models and effects considered here illustrate an important point: multiscale mathematical models are a valuable tool for furthering understanding of complex phenomena where a reductionist approach is insufficient. We have reviewed brief details of a number of important models which consider multiscale interactions and synergies which lead to overall behaviours which are potentially different from that predicted by considering the subscales only in isolation. While the contributions of these works are significant, there still remains much to do. Many of these models have raised questions rather than answering them. However, this is part of the important, iterative process between theory and experiment, taking account of the unique capabilities of each, which will ultimately yield greater understanding of the complex phenomena at work and thus improved therapies and treatments.

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