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Current Opinion in Physiology

Mathematical modelling of lung function — what have we learnt and where to next?

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Mathematical modelling has been used in airway and lung physiology with varying degrees of successes. We review recent progress including patient-specific and multi-scale models, ranging from the cellular scale through to tissue and organ scale. We focus on progress in the last three years, but also place that works in a broader historical context. We further comment on the ways in which modelling and experiment interact, and how that might serve the field going forward.

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Current Opinion in Physiology 2021, **21**:17–22

This review comes from a themed issue on **Physiology of the diseased lung**

Edited by **Alexander Larcombe** and **Peter Noble**

For a complete overview see the Issue

Available online 20th March 2021

https://doi.org/10.1016/j.cophys.2021.03.004

Introduction

Our understanding of the underlying mechanisms of lung function and the pathophysiology of respiratory diseases such as asthma is often limited by gaps left by the available experimental approaches. Although functional measurements (e.g. FEV1,[1] spirometry) assess overall lung function, they are necessarily integrated measurements with limited scope for assessing fine structure. Medical imaging (e.g. magnetic resonance imaging (MRI) and computed tomography (CT)) may provide more detail, but is generally limited by resolution and/or radiation exposure [1,2••]. Availability of human tissue for *ex vivo* use is severely restricted and compromises exist with the use of animal models; furthermore, it can be unclear to what extent an ex vivo experimental environment is representative of *in vivo* conditions.

[1] Forced expiratory volume in one second.

There are many additional factors that amplify the uncertainty of our understanding of lung function. Tens of thousands of potentially mutually dependent airways pose a challenge in fully investigating the full scale and interaction of the lung. Many airway/lung diseases, such as asthma, are highly heterogeneous in presentation, and consist of distinct subtypes (endotypes and phenotypes) [3]. Finally, many observed behaviours, for example clustered ventilation defects [4–10], are rich and complex; results from investigations are often difficult to stitch together with available data, in order to coherently understand airway behaviour.

This complex environment thus provides an opportunity for mathematical and computational modelling to contribute to integrating the available data into a coherent understanding of behaviour. Predictive modelling can be used to complement experimental and clinical evidence, and help fill in the gaps of our understanding of the underlying biological mechanisms at work, both in health and disease.

In this article, we highlight the rationale used in developing theoretical models investigating lung function and airway behaviour. Specifically, we describe the mechanical and macroscopic aspects which drive the development of studies and discuss how these attempts has helped shaped our understanding of lung physiology and the pathophysiology of respiratory disease. We then look to the future of lung function modelling and describe possible areas for further study.

Mathematical modelling of lung function

Airways, parenchymal tethering and airway smooth muscle (ASM) interactions

During the breathing process, numerous mechanical and physical forces act both externally and internally on the organ at every scale. At the organ level, the lung undergoes mechanical deformation due to breathing and gravity. At the tissue level, local elastic properties of the parenchyma, as well as boundary pressures, are present, and these directly affect the behaviour of individual airways. Additionally, calcium activated airway smooth muscle (ASM) cells generate contractile forces, altering the airway lumen and thus affecting airflow. At each of these scales, mathematical and computational models have been developed to qualitatively and quantitatively reproduce behaviour seen *in vivo* and *in vitro*. These models range in complexity from simple compartmental models to complex

Figure 1

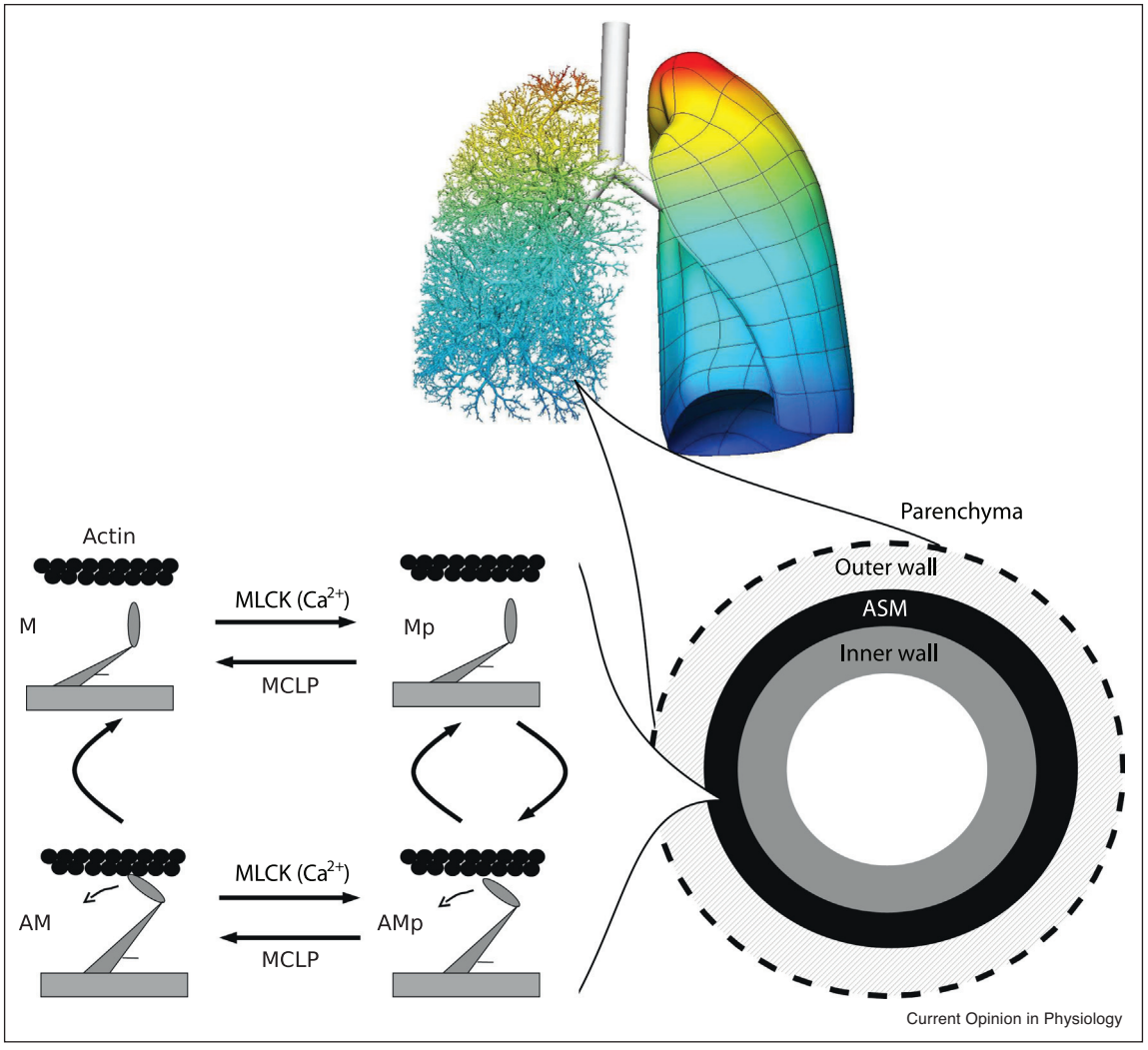

Illustration of relationship between scales. Abbreviations: A, actin; M, myosin; p, phosphorylation; MLCK, myosin light-chain kinase; MLCP, myosin light chain phosphatase.

multiscale models[2] which span cellular, tissue and organ levels (see Figure 1).

Many of the theoretical and *in silico* models that have been developed over the years are a direct result of interest sparked by experimental findings during the study of respiratory diseases. These *in vitro* experiments and *in vivo* imaging provides the necessary foundation of data for which mathematical models can be built, validated and used to further understand the complex interactions between the airways, ASM and the parenchyma (alveoli and connecting tissues) in which they are embedded.

Isolated airway behaviour is in general neither linear nor elastic, but instead characterized by a sigmoidal shape and hysteresis, particularly in smaller airways [11–13]. This behaviour has proven to be a key feature in the derivation of computational models of asthma and other airway diseases. Additionally, histological and experimental studies of lung tissue suggests that ASM dynamics play a vital role in the structure and function of airways [14]. As a result, many theoretical and computational models have been developed to capture the rich ASM dynamics observed experimentally, for example in the response

[2] It is important to avoid the temptation to conclude that more complex models are intrinsically superior to their 'simple' cousins. To paraphrase Einstein: 'Everything should be as simple as possible, but no simpler'; and this is just as relevant to biological modelling as to physics.

of ASM to oscillatory behaviours of various kinds (e.g. [15–17]). The interactions between ASM and airway wall behaviours thus are not simple to understand, even at the level of the individual airway; several groups investigating respiratory diseases have included these dynamics in primarily isolated airways with non-linear airway wall compliance [18–21]. Biomechanical models of intact airways have also been developed considering lung tissue as a continuous material with a defined rest shape (elastic continuum models) with ASM cells embedded in parenchyma [19,20,22]. Central to these models is the ability to model the force generated by individual cells, as a contractile force distributed across the muscle layer. This approach aims to develop very detailed mathematical models which can be used to shed light on events occurring within the ASM at the molecular level to tissue-level behaviour. Similar models help to shed light on airway remodeling [23] (changes to airway structure in disease), the behaviour of airway slices embedded in parenchyma [24], and the interactions between ASM and the extracellular matrix (ECM) [25], which modulates the force transmission of the ASM.

Although some understanding of lung function can be extrapolated from these studies, other work suggests that whole-lung behaviour often cannot be easily inferred from isolated airways, and suggest that inter-airway interactions, via both branched airflow coupling and the interdependence between the airways and lung parenchyma, must be considered [2••,26••]. From a modelling perspective, this leads to a dichotomy of choices: either include computationally expensive ASM dynamics and elastic deformation airway models for quantitative and qualitative agreement with experiments on isolated airways, or include computationally reduced models to investigate coupled airways and whole lung function.

Whole lung modelling

There are many challenges inherent to whole lung modelling efforts. A human lung consists of approximately 30,000 conducting airways whose mechanical properties dynamically change with airflow. Thus, regulation of airflow naturally leads to modelling lung function via a fluid dynamics approach (e.g. [27–32]). Airflow may be modelled via the well-studied incompressible Navier–Stokes equations where the structure of the lung are treated as pressure boundary conditions to represent compliance at each airway outlet. These fully resolved fluid models are often used for investigating flow patterns in the lung such as vortices or jets, and for quantifying particle deposition or drug delivery in the upper and lower airways [30,33–35]. However the scale of these models are generally limited only to parts of the respiratory system (perhaps a few coupled airways), again due to the computational effort required to solve these systems of equations. In order to investigate larger scale lung models, simplifying assumptions often must be made.

One tempting simplification is to effectively treat the conducting airways in isolation, that is, that the behaviour of one airway does not depend upon another. This certainly reduces the computational complexity to tractable levels. However, in many situations it is not sufficient, particularly when considering ASM activation and airway constriction. In general it is exceedingly difficult to measure *in vivo* constriction of the individual small airways, but two groups have demonstrated this capability in animal models (using techniques which are not viable in humans): Dubsky *et al.* [26••] using synchrotron CT in mice, and Phung *et al.* [2••] via tantalum dust and microfocal X-ray in rats. Both demonstrate that the constriction response to agonist *in vivo* is complex, with individual airways exhibiting a mixture of constriction, dilation, and no change, and that the distribution of the response depends upon the airway size. The nature of such behaviour is that it is essentially impossible to predict by considering airways in isolation, but instead arises from the interactions between airways.

From a modelling perspective this has been suggested going back to the work of Anafi and Wilson [36] proposing a dynamic instability at the level of the single terminal airway which exhibits a bistability between states which may be thought of as effectively open and closed, for the same effective airway pressure. The Anafi–Wilson mechanism was subsequently extended to a symmetric, homogeneous airway tree in the well-known work of Venegas *et al.* [7], and together these provided a potential explanation for spatial heterogeneity and clustered ventilation defects observed at the level of the whole lung. Furthermore, later work demonstrated that isolated airway closures were not sufficient to explain *in vivo* observations [10] but instead require collective, emergent behaviours. These ideas have subsequently been further extended to asymmetric branching airway trees with detailed airway structure [9,37] and have begun to yield insights into disease and therapy, for example bronchial thermoplasty [38]. Broadly these rely upon simplification of the airflow equations to steady state, for example assuming Poiseuille flow, possibly with an empirical correction [39]. This allows model resolution of individual conducting airways coupled at the whole lung scale. Alternative approaches include homogenizing the peripheral airways, rather than treating them individually, while resolving the central airways [27,29,30,40]; or empirical circuit-analogue approaches [41,42,43•].

Multiscale models

Macroscopic behaviour emerges from group dynamics of components when they are sufficiently numerous to act as an ensemble. Multi-scale modelling aims, ideally, not to include every biological detail into each model, but instead to include that which is necessary to obtain physiologically important emergent behaviour at scales being investigated [44]. Multi-scale modelling have been

successfully used when investigating airflow through the airway tree [28], deposition of aerosols in the lung [35,45,46], and the recruitment and de-recruitment of airways in acute lung injury [47,48,49•].

Multi-scale airway models such as [19,20] coupled subcellular ASM interactions with the airway wall and investigated the role of geometry and biochemical structure in the response to transmural pressure perturbations. These models aim to extend previous models developed to perform experiments comparing applied fluctuations to intact airways with length or force fluctuations to a strip of ASM isolated from the same airway [50,51]. Multiscale modelling efforts have also helped to understand the effects of heat distribution in bronchial thermoplasty [52].

Outlook

One major impact of the mathematical modelling of lung function lies in the potential development of patient-specific diagnosis and treatment of respiratory illnesses. For example, the AIRPROM project developed patient-specific, multiscale computational models specifically for asthma and COPD [53]. The lung Physiome/Virtual Physiological Human initiative is a cross-disciplinary initiative that aims to build a complete picture of lung structure and its interaction with function across multiple spatial scales, physical functions, and their integration [54]. By doing so, a modelling framework that is applicable across any number of physiological and pathophysiological investigations of the lung can be developed with the ultimate goal to enrich and interpret information for clinical decision-making; as with any model, care must be taken that the model and its underlying assumptions are appropriate to the problem at hand.

As a general modelling philosophy, we favour simplicity where possible and complexity only where necessary. That something is merely present in the true system does not mean it should be included in the model — an element of the 'true' system which is not contributing to the specific question at hand should in general be excluded, by assumption, from the model system. The ideal theoretical model then consists only of those elements which contribute to the specific research question. This can be challenging because it limits model re-use: a model which is designed for a specific research question is likely not appropriate for a related question, at least without careful reassessment of the assumptions for the new situation.

Achieving these goals would be furthered by greater collaboration and willingness to collaborate between mathematical modellers and experimentalists, particularly at early stages of both experimental design and model development. Ideally models are not constructed for post hoc data interpretation but rather as an integrated process. By creating constructive, collaborative relationships between physiologists and mathematicians, we can envisage a more effective investigative process. One barrier is that some investigators view theoretical results with a suspicion that the theoretical is somehow intrinsically inferior to the physical [55••]. We argue instead that all models have assumptions which can limit the applicability of their results from the model system to the 'true' system. While this is evidently true for theoretical models, with assumptions that tend to be explicit, it is also true for physical models (e.g. animal models, cell-line, *in vitro*, etc.), even if the assumptions of those models are more often implicit. On the other side of the coin, modellers do themselves no favours when they fail to distinguish between results which are principally interesting for their biological or physiological insights, and those which are inspired by biological problems but which are fundamentally mathematical results. Both kinds can fall broadly under the heading of 'mathematical biology', but only the former is of genuine interest to experimental scientists, and attempting to represent the latter as the former only feeds distrust of theoretical results. However, there certainly are areas of physiology where experimental/theoretical collaboration works well, for example (computational) neuroscience and cardiac electrophysiology, and indeed the more-familiar example of the success of the sliding-filament model of muscle mechanics arising from the seminal work of Huxley [56,57]. As a community we should aspire to such standards.

Conclusion

Mathematical modelling has been widely used, both in isolation and in collaboration with experimental data to analyze, investigate and discover varying aspects of respiratory physiology. Guided by biology, these models serve not to replace experimental procedures, but to help fill gaps that may arise from such procedures. Specifically, modelling can be used to explore lung function in areas and conditions that may be infeasible to do so in a clinical or laboratory setting.

Conflict of interest statement

Nothing declared.

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