

Phenotype, endotype and patient-specific computational modelling for optimal treatment design in asthma

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Understanding and treatment of asthma is significantly complicated by the heterogeneous spectrum of phenotypes associated with the disease. Recent advances in phenotype classification promise more targeted therapies, but these categories are based on constellations of largely external measurements and are not necessarily indicative of underlying pathophysiology. We propose that computational modelling is a valuable tool that allows the disease spectrum to be decomposed not into phenotypes but rather into groups organized by underlying dysfunction, referred to by some authors as endotypes. By breaking down the asthmatic spectrum in this way, therapies can be targeted more directly to the underlying defects. This would be not only an important improvement in its own right, but also an important step towards the ultimate goal of patient-specific modelling.

Introduction

Asthma is a disease that is fundamentally defined by reversible airway constriction, but its treatment (and fundamental understanding) is significantly complicated by the

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heterogeneous spectrum of phenotypes which comprise the larger disease family. Clearly drug and treatment design could be improved by more specific targeting within this spectrum. Much recent work has focussed on decomposing the asthmatic population into phenotypes, in this context classified by constellations of external measurements (pulmonary function tests, such as forced expired volume in one second (FEV1), forced vital capacity (FVC), etc., atopy, and others – see e.g. [27]). These phenotypes may then be useful for treatment design for a more specific underlying condition, rather than general ‘asthma’. However, phenotype classification is necessarily a result of bulk measurements which do not necessarily tightly correspond to the underlying pathophysiology. Some authors refer to *endotype* as an alternate decomposition of the disease spectrum into subgroups based not on external measurement constellations, but rather by underlying cause (e.g. [21]). The crucial distinction is that while phenotype classification is driven by bulk observables, an endotype is defined by a distinct underlying mechanism. Of course one of the great challenges of asthma research is to isolate the underlying mechanism experimentally, and so

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endotype classification remains elusive. However, such classification has obvious benefits for optimal treatment design.

We propose that multiscale computational modelling is an ideal tool to help bridge the gap between phenotype and endotype classification, by helping to decompose external measurements into clusters of underlying, rather than external, behaviours. This is particularly important in asthma because of the myriad phenomena involved, and the (non-linear) interactions and synergies between these in determining the pulmonary function test response. In order to successfully classify by endotype, one must be able to distinguish the role of each underlying phenomenon, not just in isolation but also in terms of interplay with other effects. Such classification would be extremely valuable in allowing design of treatment strategies with a firmer understanding of the underlying defects.

To accomplish this we require a model which connects the essential spatial scales involved; in particular, phenomena which influence bulk behaviour occur at the cellular, molecular and tissue scales, and these must be coupled not just to one another, but also to the organ scale so that the outcome of external measurements can be determined. For example, how does a change in airway smooth muscle SERCA pump expression affect FEV1? Moreover, how does this change interact with other alterations to underlying behaviour? These are questions we can answer only with a model which encompasses *appropriate* phenomena at the relevant scales, and their interactions. As always, the key modelling decisions are which aspects to include and which to neglect; unnecessary complexity can make a model cumbersome and unworkable, while excessive simplification may render it useless (e.g. [14]). This is especially true in multiscale models, where only a small fraction of sub-scale phenomena is likely to be important [22].

Multiscale modelling

We have developed a multiscale computational model of the lung that encompasses behaviours at the molecular, cellular, tissue and organ scales [32]. This allows us to consider the effects of phenomena which occur at each of these scales, their interactions, and the resulting effects on bulk external measurements. Here we outline the essential features of the model, the phenomena considered at each scale, and the coupling between scales. For full details the reader is referred to [5,32,43,44].

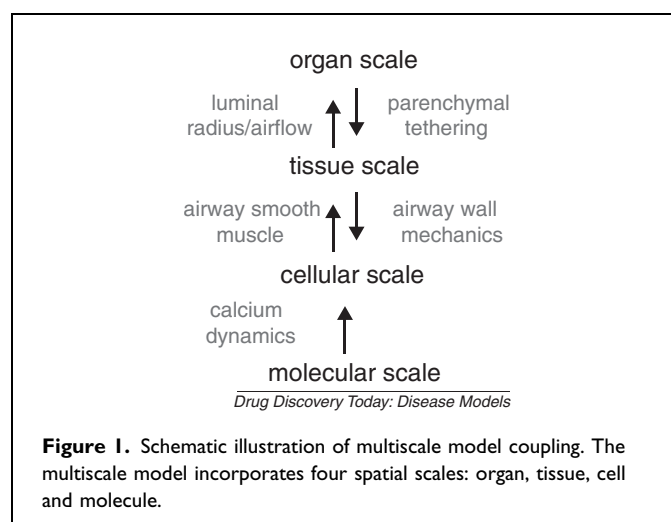
The organ scale takes account of tissue deformation due to breathing and gravity [38,39], with parenchymal mechanics described by a continuum mechanics model in a patient-specific geometry acquired from computed tomography (CT). The airway tree down to the segmental bronchi is extracted from CT data; below this the airway tree is generated algorithmically [4,37]. The organ scale is interconnected with the tissue scale by the calculation of local parenchymal material properties surrounding each airway [18,32].

At the tissue scale each airway is modelled mechanically (e.g. [19]) with inputs of parenchymal tethering pressure [18] and airway smooth muscle (ASM) tension, and the interrelated ASM length. It is in modelling the ASM that the cellular (and molecular scales) are introduced.

Airway smooth muscle cells are described by crossbridge mechanics [8,11,13,25,43], based on sliding filament theory which dynamically relates muscle length and tension. (Note that questions remain about possible underlying differences between asthmatics and normals in isolated ASM behaviour (e.g. [6]).) The muscle length is determined in balance with the airway radius and is thus connected with the tissue scale; the muscle tension contributes to the airway transmural pressure that manifests at the tissue scale.

Activation of ASM is controlled by intracellular calcium concentration, and calcium dynamics play an important role in determining ASM dynamics. The dynamics of calcium response to agonist stimulation in ASM cells is an important consideration in determining the overall response [44]. Here we use the physiological, dynamic model developed by [44] for agonist- and KCl-induced calcium oscillations in ASM. This compartmental model of an ASM cell takes account of the role of both inositol trisphosphate receptors (IPR) and ryanodine receptors (RyR), and is based on ASM experimental data from lung-slice preparations. The result is that cells subjected to agonist (MCh) stimulation display elevated calcium levels in the form of short-period [calcium] oscillations, which in turn activate crossbridge contraction at the cellular scale. The four spatial scales and their interconnections are shown schematically in Fig. 1.

Of course we must also accurately model experimental protocols for external measurement, as these provide the experimental data against which comparisons (and hence classification) must be made. The underlying multiscale computational model can be extended to simulate respiratory impedance [40], FEV1 [12,19], and multi-breath nitrogen



washout (MBNW) [26,41], among clinical measurements. These experimental mimics are crucial to allow model output pulmonary function test (PFT) constellations that map to underlying behaviours.

Similarly, the underlying model must be fit for purpose to consider an appropriate set of hypothesized underlying behaviours. Including too much detail yields an unwieldy and uninformative model; similarly, neglecting important phenomena precludes their association with altered outputs.

There are many possible effects which have been hypothesized as contributing to airway narrowing in asthma [23]. For example, airway wall thickening has been thought to play a role, both in terms of reduced luminal area [28,29] but also via wall stiffening or changes in compliance [7,30]. Airway smooth muscle is also an oft-cited culprit, in terms of thickening [15,16,34], or shortening velocity [3]; but also the so-called fluidization response [9,17], and in particular the response to deep inspirations [10,20]. SERCA pump expression has also been implicated [24]. Other hypothesized effects include the role of obesity and chest wall compliance [33], differences in agonist diffusion into the ASM [1,42], and disruption to parenchymal tethering [2].

The multiscale model is well suited to incorporate these hypothesized changes, with resulting changes to output measurements, and hence combinations of underlying effects can generate constellations of output measurements. Because these are generated directly by the model, and hence the underlying inputs are known, it may then be possible to classify not by phenotype but rather by endotype.

Endotype classification

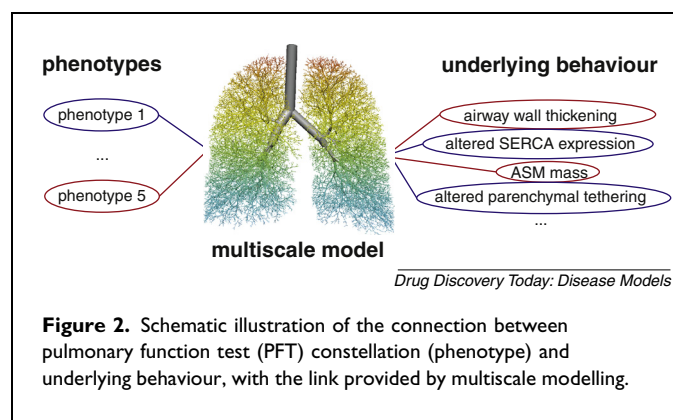
Untangling underlying phenomena is a complex process due to the interactions between them, as we will demonstrate shortly. The challenge is to establish a set of external measurements which can uniquely identify the underlying endotype (i.e. for any given set of external measurements there is no guarantee that this can uniquely identify the underlying endotype). Of course it might be useful, for purposes of designing treatment, just to narrow the choices of possible endotype, but unique identification is the goal.

In order to do this we must study the so-called *inverse problem* (e.g. [36]) – that is, to assign underlying behaviour to a given set of external measurements. The idea is to use this modelling study to determine the sets of external measurements which would be able to uniquely identify endotypes.

The basic idea is illustrated schematically in Fig. 2. That is, given an appropriate set of measurements, the multiscale model can be used to map underlying behaviours to existing phenotypes, allowing endotype classification.

Synergies

Classification into endotypes is a particularly challenging problem because of the synergies between physiological



mechanisms that contribute to asthma. Consider, as an illustration, the relative roles of airway wall thickening and increased ASM contractile force (as a proxy for ASM mass). Both are hypothesized to be involved in at least some asthma phenotypes. By inputting these altered parameters into the computational model, we can consider their effects in isolation, and together (see Fig. 3), on (e.g.) respiratory resistance and elastance. We can see immediately that while each phenomenon alone has a relatively modest effect on the observed resistance and elastance, the combined effect is much greater than the sum of its parts. We hypothesize that this nonlinear interaction is crucial to understanding asthma; hence it is not enough to consider involved phenomena in isolation. Though this only illustrates the interplay between two phenomena, similar issues exist with many effects that are associated with asthma, and disentangling them is crucial to making associations between pulmonary function test outcomes and underlying dysfunction.

Given these nonlinear interactions, one must be prepared for the possibility that the measurements currently used to classify by phenotype are insufficient to fully and uniquely identify endotypes – rather, that several combinations of underlying phenomena are equally capable of explaining the standard observation constellations. (I.e. the inverse problem is particularly ill-posed.)

This outcome would imply that the current phenotype classification scheme has already made good use of the available data, and computational modelling can offer two possible directions of improvement: first, even non-unique endotype classification might be of some use. For example, if an external measurement constellation can be explained by two, distinct underlying mechanisms, this might still be of use in treatment design. Second, the model can be used to predict which (plausible) additional measurements would be able to isolate endotypes. Some observations which might help disentangle seemingly overlapping endotypes might be, for example, differential response to intravenous versus inhaled agonist [35], or perhaps continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP) response (e.g. [31]).

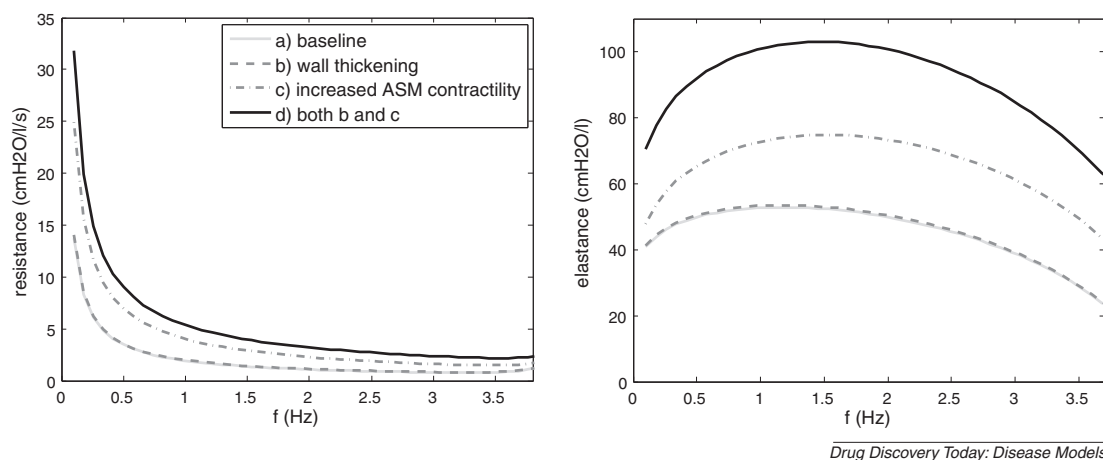


Figure 3. Demonstration of synergistic interaction between underlying airway dysfunction. Respiratory resistance and elastance are calculated at baseline, with airway wall thickening (alone), with increased ASM force (alone), and with both airway wall thickening and increased ASM force. The resulting increases in resistance and elastance clearly demonstrate a nonlinear interaction where the combined increase is much greater than the sum of its parts.

Other possible differentiating measurements include regional measurements (e.g. apical versus basal response), postural differences, response to deep inspiration, differences in agonist deposition, amongst many others.

In this case another possibility would of course be that one or more of the neglected effects plays an important role, requiring model extensions to capture phenomena not currently included.

Conclusions

Computational modelling is a valuable tool with the potential to decompose the spectrum of asthmatic behaviour into distinct endotypes, each defined by the underlying mechanism (as opposed to the current approach of phenotype classification, which does not necessarily implicate underlying cause). In particular, multiscale modelling is a valuable tool for exploring the interactions between effects which occur at distinct spatial scales.

Asthma is a particularly challenging case, not just because of the breadth of the disease spectrum (as evidenced by the number of phenotype classifications, and number of mooted underlying phenomena), but also the interaction between those underlying phenomena. We have illustrated the potential for these synergistic effects to severely compromise respiratory function through the nonlinear combination of effects which are relatively mild in isolation. Computational modelling has the potential to contribute to greater understanding and better treatment design by isolating the underlying behaviours that are associated with different parts of the asthmatic spectrum.

All of this is progress towards the ultimate goal of patient-specific modelling. However, endotype classification, with identification of underlying mechanisms allowing more precise treatment design, is an important step in this direction.

In order to do so we must have an appropriate model of phenomena of interest, and their interactions – this latter step is particularly important in asthma where so many hypothesized effects have such significant interactions.

Conflict of interest

The authors have no conflict of interest to declare.

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