# Computational models of the airways to unravel the pathophysiological mechanisms in asthma and COPD (AirPROM)

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## Introduction

Respiratory disease presents a huge health and economic burden. The diseases asthma and chronic obstructive pulmonary disease (COPD) together affect over 500 million people world-wide (1) and cost the European Union in excess of €56 billion per year. Asthma and COPD are complex airway diseases encompassing several underlying pathological conditions that develop as a consequence of a variety of gene-environment interactions giving rise to various clinical phenotypes. The diseases are characterised by an underlying inflammatory response that induces airway remodelling, airflow limitation, ventilation-perfusion (V/Q) mismatch and diminished lung function. Current therapies are inadequate due to our incomplete understanding of the pathophysiology of these diseases and our lack of recognition of the enormous disease heterogeneity: we need to characterise this heterogeneity on a patient-specific basis to advance healthcare. In an effort to achieve this goal our consortium, Airway Disease Predicting Outcomes through Patient Specific Computational Modelling (AirPROM) brings together existing clinical consortia with expertise in physiology, radiology, image analysis, bioengineering, data harmonisation, data security and ethics, computational modelling and systems biology. Together we are developing an integrated multi-scale model of the airways in order to unravel the complex pathophysiological mechanisms occurring in the diseases asthma and COPD.

## Methods

The key components of research within the AirPROM consortium include collection and analysis of patient data, extraction of structural information from medical imaging and the construction of computational meshes, 3D Computational Fluid Dynamics (CFD) and the development of a multi-scale model – capturing information from the genetic-cell-tissue level - that predicts clinically-relevant outcomes. Models are being developed from data of normal, asthmatic and COPD patients.

### Patient data

We are working towards integrating and extending existing patient-specific data from 3 clinical consortia (U-BIOPRED, EvA, and BTS severe asthma). These data include extensive genomic, transcriptomic, and proteomic profiles, detailed lung function with novel small airway physiological measures, bronchial challenge studies, computed tomography (CT) imaging and cutting-edge hyperpolarised gas magnetic resonance imaging (HP MRI), and patient reported outcomes. The clinical measurements provide both cross-sectional and longitudinal follow-up data. Proof-of-concept clinical trials with standard and novel interventions will also contribute to the huge patient dataset available. These patient-specific data together with known biological pathway data from public databases are being integrated into a 'Knowledge Management' platform supported by 'Cloud' computing and cognisant of ethico-legal, security and harmonisation issues.

### Image segmentation and meshing

State-of-the-art software is being developed to enable automatic extraction of morphological properties of the large airways (to the level of the proximal conducting airways with a diameter of >2 mm or approximately 6-8 generations) and lobar geometries from patient CT data. These procedures will form part of a high-throughput semi-automated framework for modelling the structure and

function within the large airways. High-resolution computational meshes of the central airways and lung surface are generated for use in 3D CFD simulations studies using the ANSYS software.

**3D Computational Fluid Dynamic (CFD) Simulations and Validation**

Predictions of the flow characteristics within the central airways are obtained via 3D CFD using the patient specific geometries created. Realistic boundary conditions (change in lobar volumes during a breath or distal 1D tree information) are applied. Previous modelling outcomes using this technique have been validated against functional imaging measurements (2). HP MRI has also been shown to provide insight into ventilation dynamics in human lungs. We will build on the extensive experience with HP MRI at the University of Sheffield to develop quantitative time resolved methods for measuring gas flow velocity to provide additional CFD validation. Pioneering multi-material additive layer manufacturing (ALM) will be used to produce CT-based models that are not only anatomically realistic, but also mimic the mechanical behaviour of the different airway tissues enabling CFD validation as well as investigation of airway dynamics. These combined techniques will be used to attempt to find new biomarkers of disease and changes during current or new therapies.

**The multi-scale model**

Building upon existing mathematical and computational techniques, we are developing 'micro-scale' (gene-cell) and 'macro-scale' (tissue-whole organ) models of the lungs in order to understand the mechanisms linking from gene to whole organ outcomes. The framework for a multi-scale model has been established at the outset of the project and incorporates models developed at the micro and macro scales as outlined in Figure 1. The 'micro-scale' model simulates cells as discrete entities (agent-based modelling) and is being developed and validated with *ex vivo* tissue models. A continuum approach is being used to link cell level dynamics to airway tissue-level properties that will be integrated within the whole organ level computational model. In addition, a combined HP MRI and modelling approach (3) are being used to measure the function of small airways in asthma and COPD and to validate both imaging and modelling techniques.

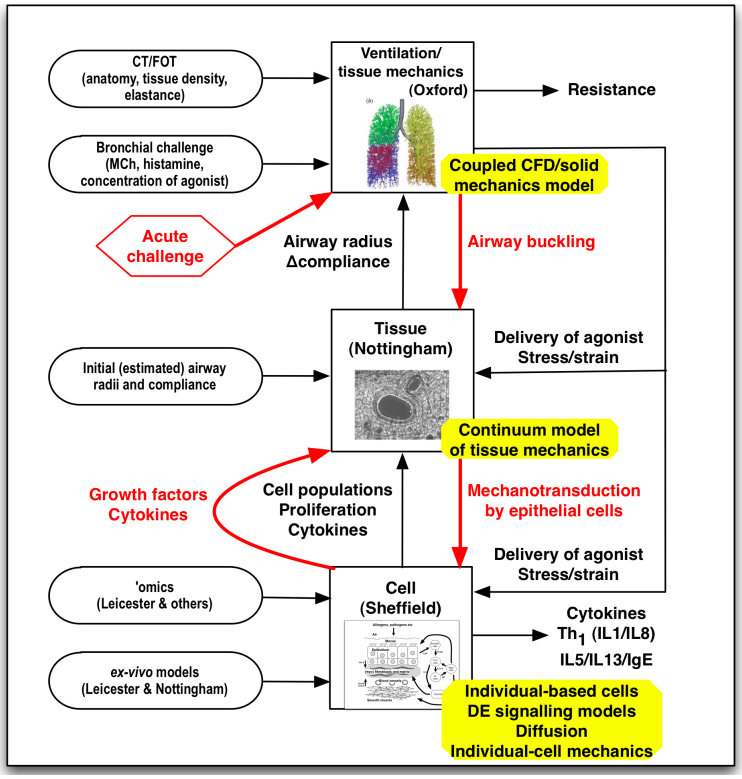


Figure 1: Schematic of the multi-scale model being developed within the AirPROM project.

Patient-specific data will both inform and validate the models. The model verification, clinical validation and development will occur in multiple iterative cycles each with increasing throughput and

automation working towards a 'turn-key' platform. AirPROM will thus develop a validated patient-specific multi-scale predictive computational airway model underpinned by extensive clinical data.

## Results and conclusions

Development of high-throughput meshing techniques is well underway. These techniques have been applied to high resolution CT data for 20 asthmatic subjects and 9 normals so far with more subjects planned. This analysis provides airway and lobar structure as well as tissue density information. The lobes and the central airways for a single subject were segmented using Mimics® (Materialise NV, Leuven, Belgium) and are demonstrated in Figure 2.

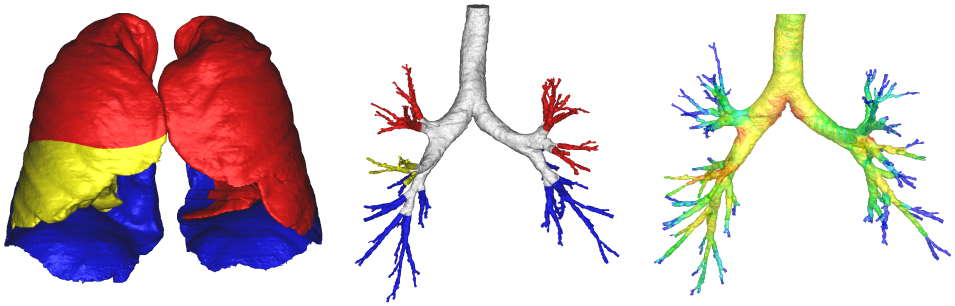

Figure 2: Computational meshes of the central airways and lung surface for a single asthmatic subject.

Figure 2C illustrates the pressure solution within the central airways (red = high pressure, dark blue = lowest pressure) obtained via 3D CFD. The boundary conditions applied for this solution were derived from the volume change of each lobe from functional residual (FRC) to total lung capacity (TLC). A larger pressure gradient was observed in the airways towards the upper lobes indicative of elevated resistance levels in these regions. This increased resistance correlated with signs of hyperinflation as described by the upper lobar volumes (right upper and right mid lobes were ~123 and 128% of predicted normal and left upper lobar volume was 137% of predicted). This example illustrates the added value that can be created through a combined approach using imaging and CFD. The image-based outcome parameters can complement existing clinical tools such as spirometry that often lack the sensitivity to accurately explain the patients' symptoms. Even though in the abovementioned patient, the imaging and the clinical assessment (GINA V) showed abnormalities the FEV1 remained in the normal range (2.14 L, 94.1% predicted).

One of the many strengths of AirPROM is the close interaction between clinicians, patients and pharmaceutical companies so that the project from its outset – and through its development – will be aware of the needs of the patients, as well as the practicality of the application of models in the clinic, drug discovery and development. Through our exploitation and dissemination plan we have already engaged the prospective 'users' and 'providers' and therefore are uniquely positioned to translate the platforms into usable applications. Indeed this has already been realised: collaborations with pharmaceutical companies are already developing into joint projects. AirPROM will bridge the critical gaps in our clinical management of airways disease, by providing validated models to predict disease progression and response to treatment and the platform to translate these patient-specific tools, so as to pave the way to improved, personalised management of airways disease.

## Acknowledgements

This work is funded by the European Union Seventh Framework Programme FP7/2007-2013 under grant agreement n° 270194. For additional details on the AirPROM project see www.airprom.eu.

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