Journal of Theoretical Biology 266 (2010) 614–624

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

A multiscale, spatially distributed model of asthmatic airway hyper-responsiveness

Antonio Z. Politi [a,1], Graham M. Donovan [b,*,1], Merryn H. Tawhai [b], Michael J. Sanderson [c], Anne-Marie Lauzon [d], Jason H.T. Bates [e], James Sneyd [a]

[a] Department of Mathematics, University of Auckland, Private Bag 92019, Auckland Mail Centre, Auckland 1142, New Zealand
[b] Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland Mail Centre, Auckland 1142, New Zealand
[c] Department of Physiology, University of Massachusetts Medical School, Worcester, MA 01655, USA
[d] Department of Medicine, Meakins-Christie Laboratories, McGill University, Montreal, Canada
[e] Vermont Lung Center, Fletcher Allen Health Care, Department of Medicine, University of Vermont, Burlington, VT 05405, USA

ARTICLE INFO

Article history:
Received 1 February 2010
Received in revised form
26 July 2010
Accepted 26 July 2010
Available online 4 August 2010

Keywords:
Crossbridge
Calcium
Tethering
Smooth muscle cells
Actin–myosin

ABSTRACT

We present a multiscale, spatially distributed model of lung and airway behaviour with the goal of furthering the understanding of airway hyper-responsiveness and asthma. The model provides an initial computational framework for linking events at the cellular and molecular levels, such as Ca^{2+} and crossbridge dynamics, to events at the level of the entire organ. At the organ level, parenchymal tissue is modelled using a continuum approach as a compressible, hyperelastic material in three dimensions, with expansion and recoil of lung tissue due to tidal breathing. The governing equations of finite elasticity deformation are solved using a finite element method. The airway tree is embedded in this tissue, where each airway is modelled with its own airway wall, smooth muscle and surrounding parenchyma. The tissue model is then linked to models of the crossbridge mechanics and their control by Ca^{2+} dynamics, thus providing a link to molecular and cellular mechanisms in airway smooth muscle cells. By incorporating and coupling the models at these scales, we obtain a detailed, computational multiscale model incorporating important physiological phenomena associated with asthma.

1. Introduction

It is estimated that 300 million people worldwide suffer from asthma (Braman, 2006), a disease characterised by the emergent phenomena of airway hyper-responsiveness (AHR) and airway hyper-sensitivity. In AHR, the airways contract too severely; in airway hyper-sensitivity, they contract too readily. In particular, AHR is of primary interest because it is associated with the majority of asthmatic mortality and morbidity (Sterk and Bel, 1989). While the exact mechanisms involved are still an area of active research, it is believed that the role of airway smooth muscle contraction is critical in this excessive airway narrowing (Krishnan et al., 2008).

This work is part of a larger effort to create a comprehensive multiscale model of asthmatic AHR. The ultimate goal of the project is to develop a model encompassing and linking the molecular, cellular, tissue and organ scales. In this work, we present an initial computational framework for this multiscale model, focusing on how the organ level model can be linked to the tissue level model, and also on how molecular and cellular models can be included, resulting in a multiscale model that spans the entire range of spatial scales.

2. Multiscale model

Our approach to creating a multiscale model of asthmatic AHR involves joining models at four spatial scales: organ, tissue, molecule and cell. At the organ level, a continuum mechanics approach is employed to solve the mechanical deformations of the lung due to breathing and gravity (Section 2.1). The organ-level model provides the boundary pressures and local elastic properties of the parenchyma used as model inputs in the tissue-level model (Section 2.2), describing the behaviour of individual airways. The airway lumen radii computed at the tissue-level depend on the coupling with the organ level model, the nonlinear properties of the airway wall, and the active force generated by the airway *smooth muscle cells* (SMC) at the cellular level. The active force is modelled according to sliding filament theory, and controlled by intracellular Ca^{2+} dynamics, which is determined by the degree of external stimulation (Section 2.3). The stimulation is provided by an introduced agonist, triggering Ca^{2+} release

* Corresponding author.
E-mail address: g.donovan@auckland.ac.nz (G.M. Donovan).
[1] Contributed equally to this work.

0022-5193/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2010.07.032

at the molecular level and thus airway contraction. This introduced agonist mimics bronchial challenge, a standard clinical practice in the study of asthma (Cockcroft et al., 2001). The crossbridge model has already been treated in detail by Wang et al. (2008), while, for simplicity, we shall assume a piecewise constant Ca^{2+} concentration. We are currently developing a detailed model of Ca^{2+} dynamics in SMC, accounting for Ca^{2+} oscillations and frequency encoding of the stimulus (Perez and Sanderson, 2005), and this model can be easily incorporated into the framework described here.

2.1. Organ-level model

The human lung contains a bronchial airway tree with an asymmetric branching structure beginning at the trachea and descending to more than 30,000 distal terminal bronchioles no more than 0.6 mm in diameter, with a total of 27 airway orders, on average (Horsfield et al., 1971). The bronchial airways do not take part in gas exchange. The airway wall consists of a layer of airway smooth muscle, as well as an inner layer of mucosal and epithelial cells, all surrounding the airway lumen. The terminal bronchioles, the smallest and most peripheral conducting airways, connect with respiratory bronchioles, alveolar ducts, and alveolar sacs, each of which has walls fully or partially comprising alveoli. The alveoli are the site of respiratory gas exchange. Along with the corresponding pulmonary vasculature, this complex structure fills the volume of the lungs.

We begin by considering an arbitrary three-dimensional unit of lung tissue. While the methods we employ are agnostic to the tissue geometry, and can in fact be applied to anatomically-correct, patient-specific geometries (Tawhai et al., 2006, 2009), for simplicity at this stage we consider a smaller tissue unit which can be thought of as a spatial segment of the larger problem; see Fig. 1. The location of the tissue unit is not explicitly anatomically defined, but may be thought of as being away from the surface of the lung, in the centre of the gravitational field, and away from inter-lobar fissures. This tissue unit is initially uniform pulmonary parenchyma, within which the conducting bronchial tree is embedded. All structures aside from the conducting bronchial tree, including the acini and vasculature, are included in the parenchymal continuum. The conducting airway tree can thus be thought of as being embedded, or, alternately, as being suspended in a fibre network (Weibel, 1984). The conducting bronchial tree in the tissue unit may also be considered as a terminal subtree of the entire lung tree: it contains 90 airways ranging from distal terminal bronchioles at order 1 up to order 8, but no higher-order airways.

The airway tree geometry is generated throughout the tissue unit by a morphometrically-accurate, asymmetric-branching, 3D tree-generating algorithm (Tawhai et al., 2004). Because of the number of airways involved in computing a complete lung, we make several simplifying assumptions with regard to the airway tree in order to achieve computational feasibility. While perhaps not strictly necessary for simulating the smaller tissue unit, the computational complexity concerns are essential for scaling up to the complete lung geometry. For each airway segment, we assume that the airway is radially symmetric and longitudinally stiff. Thus, while they are distributed in a 3D tissue unit, each airway segment is essentially 1D. The change in length of the airway is computed during simulated breathing, however, the radial airway mechanics are assumed to be independent of changes in airway length during tidal breathing.

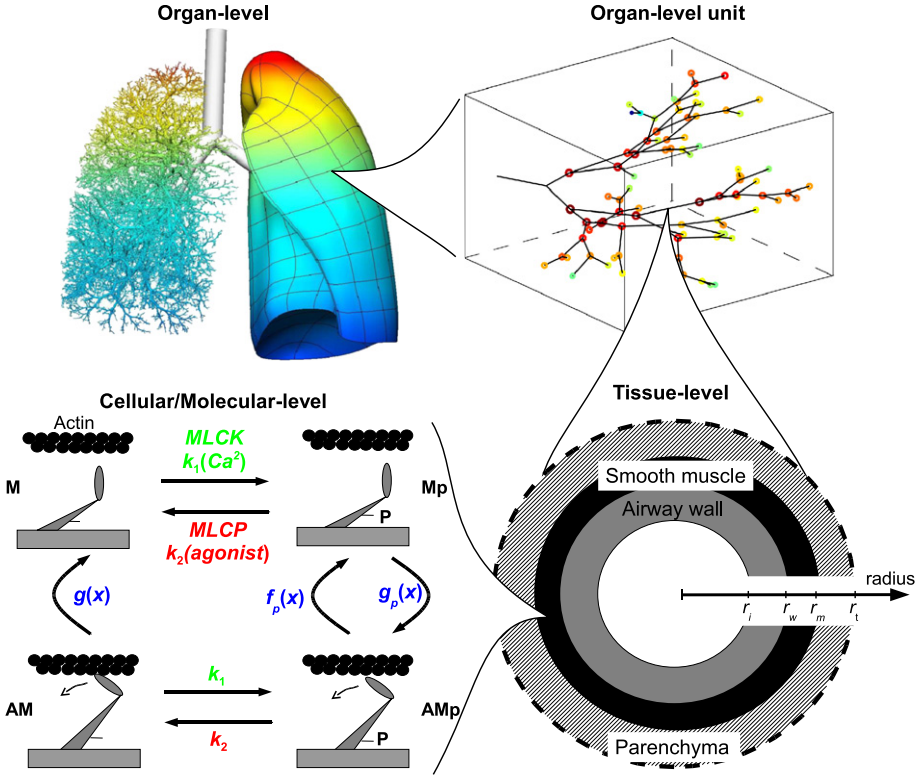

Fig. 1. Schematic of multiscale interactions. Upper left panel: complete anatomically-accurate organ-level model, with parenchymal tissue elements displayed in the left lung and the embedded airway tree in the right. Upper right panel: organ-level tissue unit with 90 embedded airway segments. The circles 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.