A Multi-scale Image-based Lung Model and a Statistics-based Strategy for a Population-level Analysis

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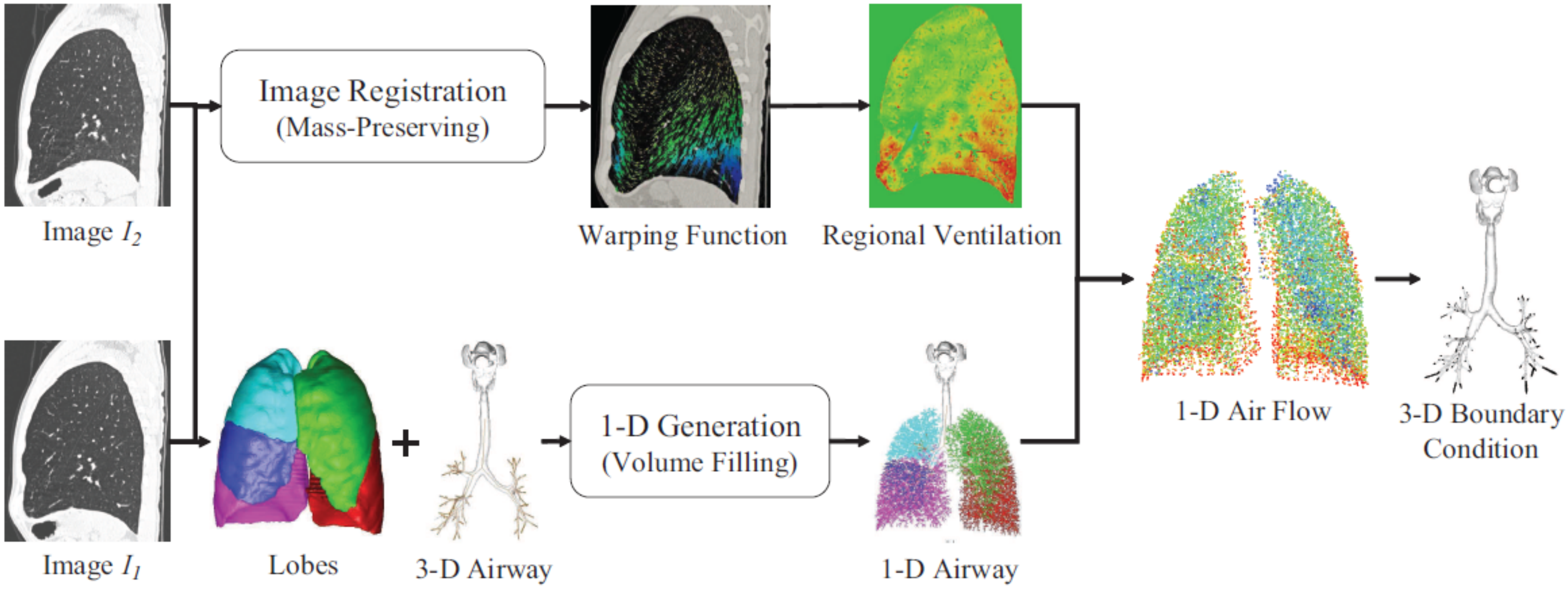
Rationale

- Build a multi-scale lung model for prediction of individual lung function.
- Due to the large number of structural and functional variables in the lung, application of such a lung model is often limited to a few random subjects and its interpretation can barely be generalized to a greater population.
- Cluster statistically large data sets into sub-populations and extract significant variables from sub-populations for analysis.

Outline

- Phase I – Digital Lung model for airflow and particle transport in the the human lungs:
    - Multi-scale: airway models, turbulent-transitional-laminar airflows, regional ventilation at organ level
    - Image-based models and registration-driven conditions
    - High-fidelity parallel computational fluid dynamics (CFD)
- Phase II – Airway defense system: flow/tissue induced stresses, cell response to predict periciliary layer water homeostasis for mucociliary clearance
- Phase III – Integrative deterministic & stochastic approaches for population-level analysis.

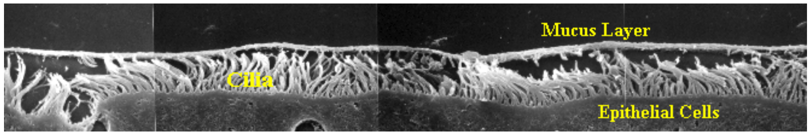
Phase I – Digital Lung



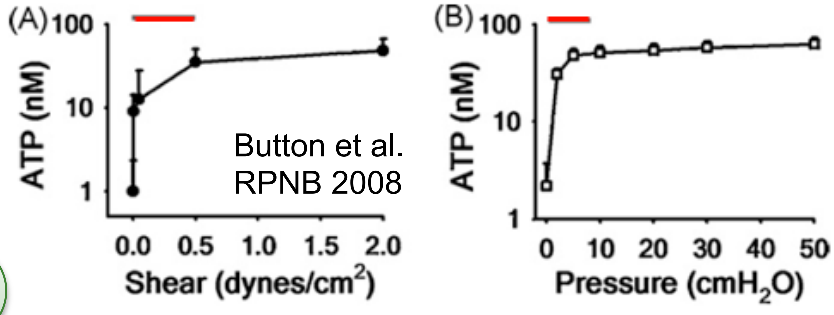
Yin, Y., J. Choi, E.A. Hoffman, M.H. Tawhai, & C.-L. Lin, *J. Biomechanics*, 43(11): 2159-2163, 2010.
Yin, Y., E. A. Hoffman, & C.-L. Lin, *Medical Physics*, 36(9): 4213-4222, 2009.

Phase II- Airway Defense

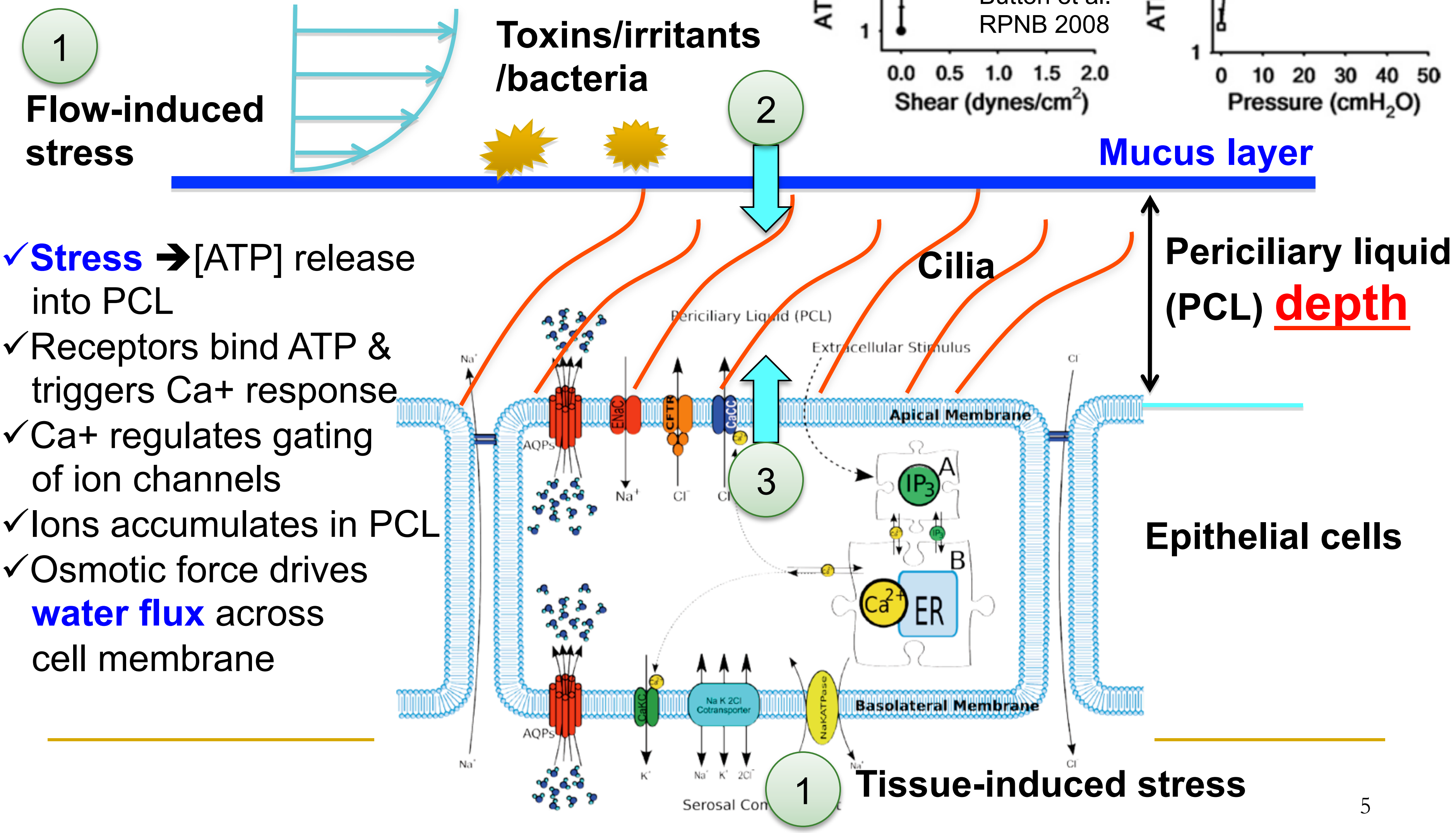
Adenosine triphosphate nucleotide (ATP)



M. Sanderson



Button et al. RPNB 2008



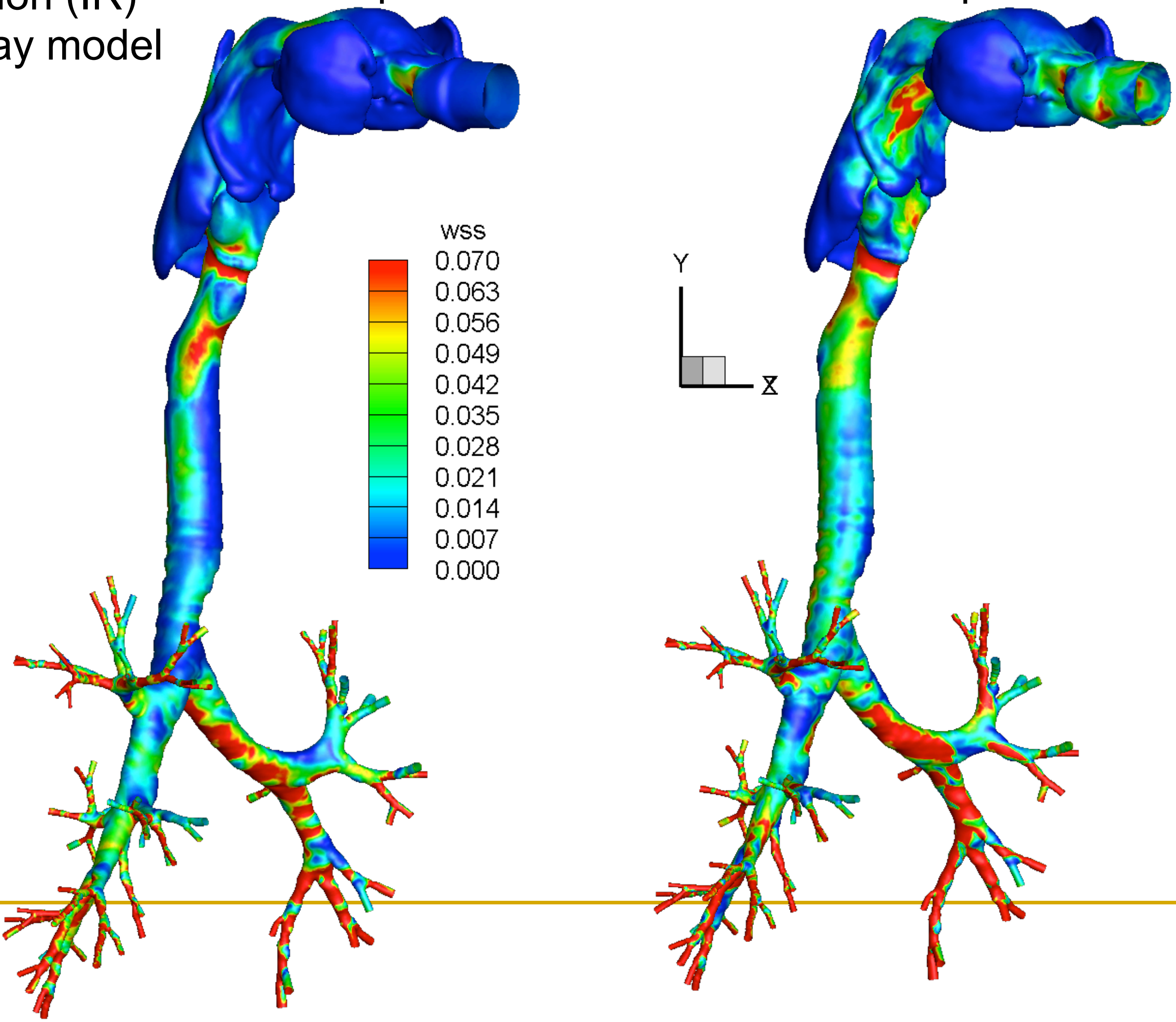
- ✓**Stress** ➔[ATP] release into PCL
- ✓Receptors bind ATP & triggers Ca+ response
- ✓Ca+ regulates gating of ion channels
- ✓Ions accumulates in PCL
- ✓Osmotic force drives **water flux** across cell membrane

Airway Defense Model

- Breathing Lungs –predict flow- and tissue-induced stresses in a breathing lung
  - Image-registration-based approach for the whole lung
  - Fluid structure interaction at a regional scale
- Thermodynamics model – predict water vapor concentration in the air and its condensation/ evaporation on the periciliary liquid (PCL) layer
- Airway epithelial cell model – model cell response to stress, which regulates transport of intracellular water flux into PCL

IR-Flow-induced Wall Shear Stress

Image-registration (IR) deforming airway model

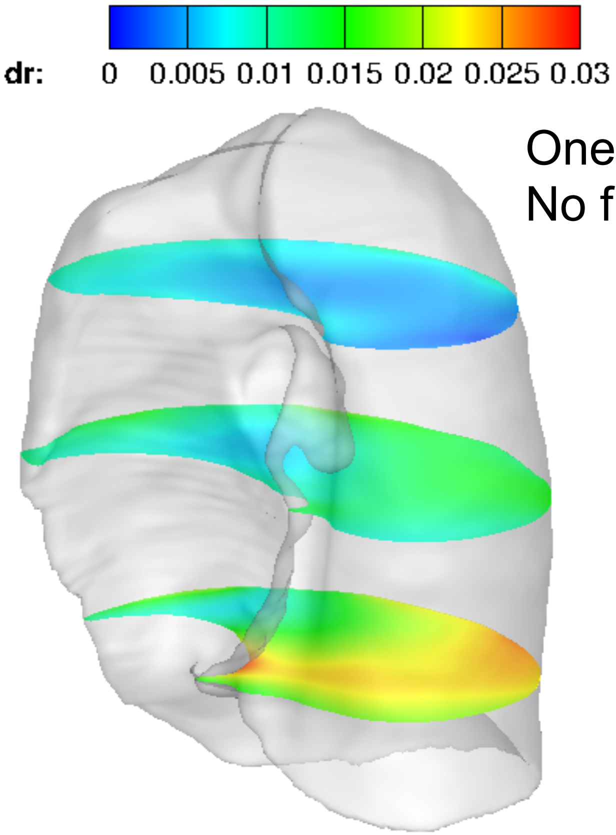


Peak inspiration

Peak expiration

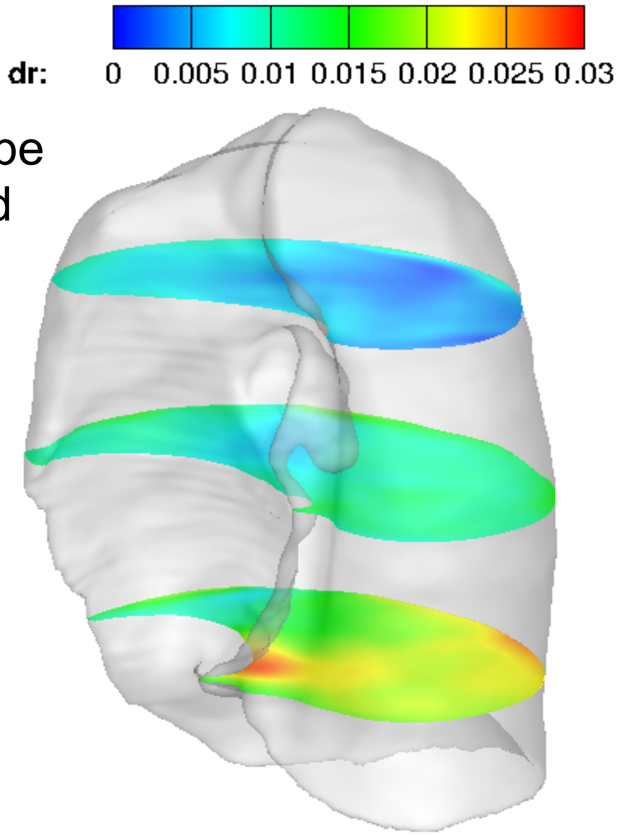
Displacement via CSM/IR & FSI

CSM lung mechanics



One lobe
No fluid

Image registration



Fluid-structure interaction

Material properties of E=5kPa and v=0.4

(FSI) Xia,Tawhai, Hoffman, **Lin**, Annals of Biomedical Engineering, 38(5), 2010.

Thermodynamics Model

Governing Equations

$$c_p\rho\frac{\partial T}{\partial t}+c_p\rho u_i\frac{\partial T}{\partial x_i}=\frac{\partial}{\partial x_i}\left(k\frac{\partial T}{\partial x_i}\right)$$

$$\frac{\partial C}{\partial t}+u_i\frac{\partial C}{\partial x_i}=\frac{\partial}{\partial x_i}\left(D\frac{\partial C}{\partial x_i}\right)$$

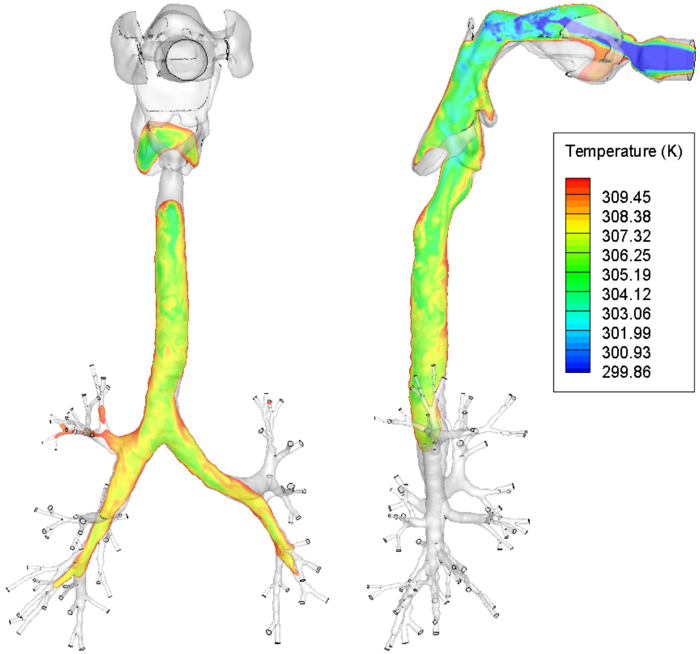
Airway Wall Models

1. At interface of airway surface liquid (ASL) and airway lumen, energy balance is enforced:

$$K_{asl}\frac{\partial T}{\partial r}\Big|_{R^+}=K_{air}\frac{\partial T}{\partial r}\Big|_{R^-}+D\Delta H\frac{\partial C}{\partial r}\Big|_{R^-}$$

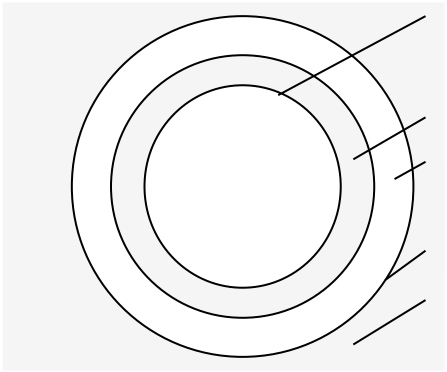
2. To model the heat conduction at different layers of airway wall, unsteady conduction equation is solved.

3. Temperature of interface of mucosa-submucosa layer and surrounding tissue must be modeled.



Temperature contour at end expiration, flow rate 15 l/min, inlet T=299.86 K

ASL=mucus+PCL



ASL & lumen interface

ASL

Mucosa-submucosa

Tw

Surrounding tissue

Cell Model

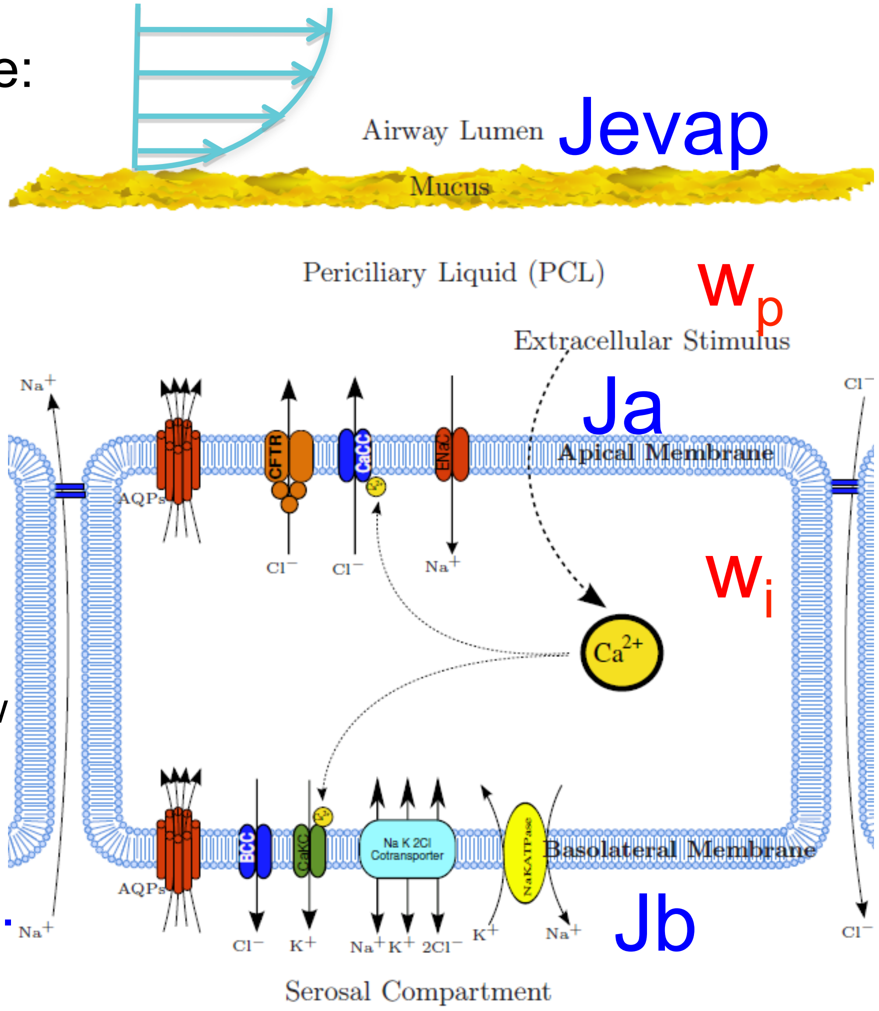
The rates of change of PCL & cell volume:

$$\frac{dw_p}{dt} = A_a J_a^w - A_a J_{evap} \qquad \frac{dw_i}{dt} = A_b J_b^w - A_a J_a^w$$

1. **Ja**, flux across the apical membrane
   Jb, flux across the basolateral membrane
   Jevap, evaporative flux predicted by the thermodynamics model.

> Ja and Jb, are controlled by osmotic gradient, depending on ionic concentrations.

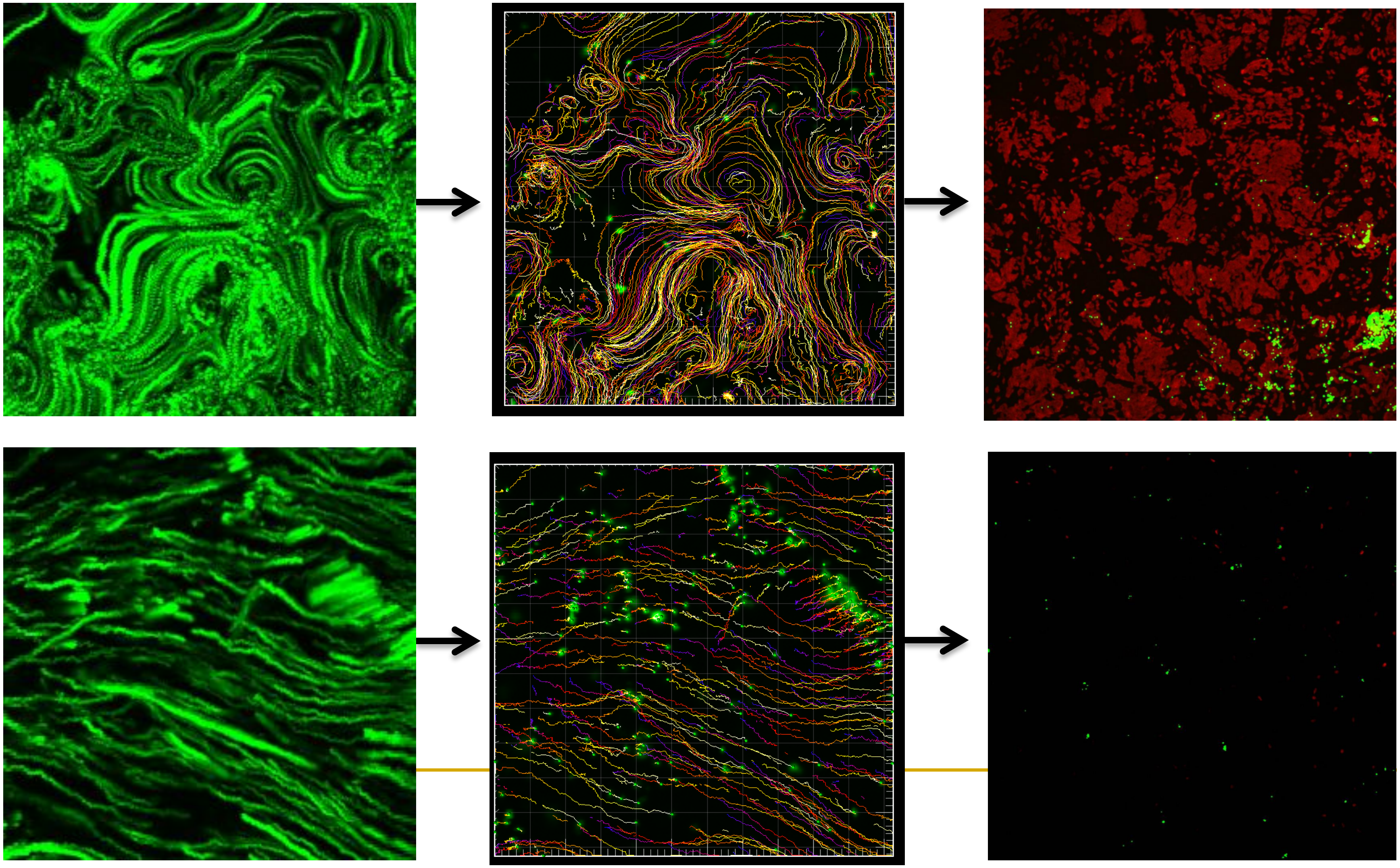
2. Ionic concentrations of [n] in each compartment w are regulated by **open probabilities** of ion channels and co-transporters.
3. The open probabilities are determined by **[Ca+].**
4. [Ca+] ➔IP3 messenger ➔P2Y receptor ➔ **[ATP].**
5. [ATP] is determined in part by **stress**.



Warren, Tawhai, Crampin,
J Theor Biol, 2009, 2010

Particle Clearance in Piglet Cell Cultures

Images of confocal microscope



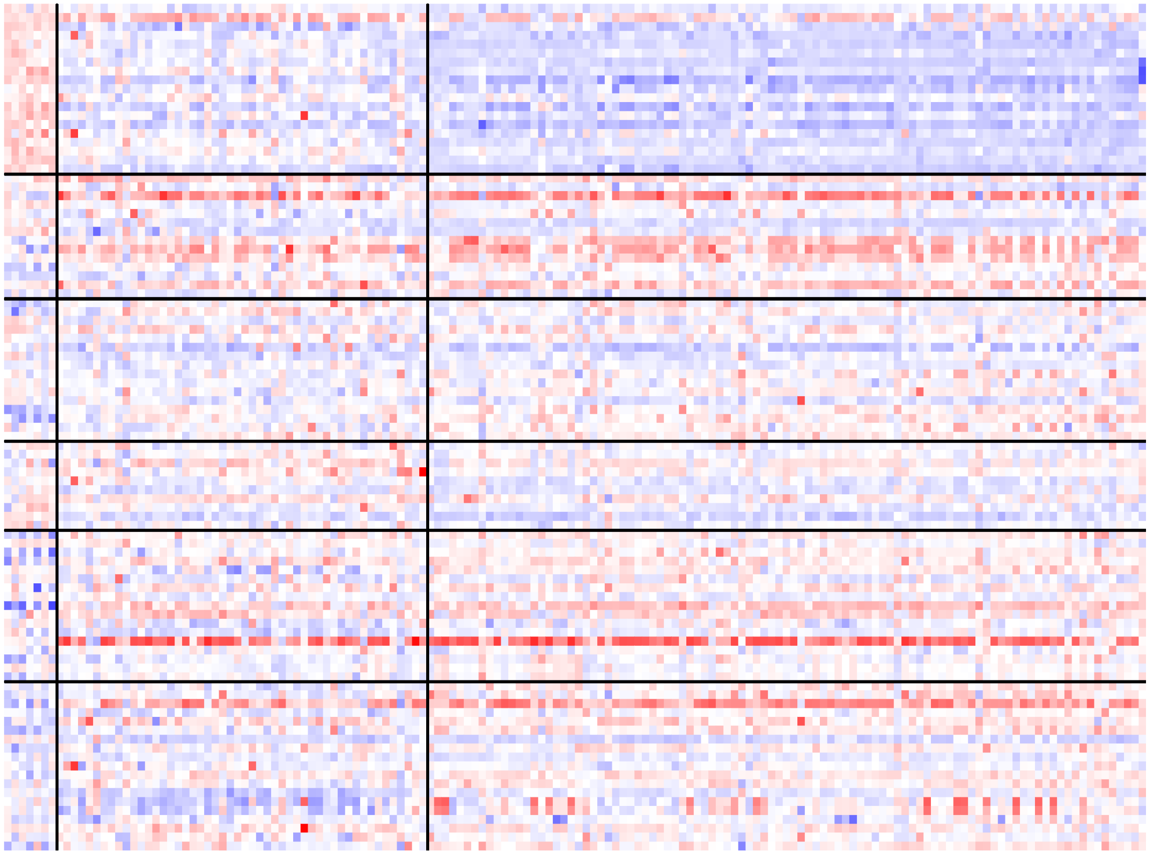
Phase III- NIH Multi-center Trials

- Severe Asthma Research Program (SARP): study adults and children with asthma.
- COPDGene: establish a racially diverse cohort to study the underlying genetic factors of chronic obstructive pulmonary disease (COPD)
- The SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS): identify and validate biomarkers of disease severity for intermediate outcome measures
- Phenotype and genotype relationships

Cluster Analysis of Normal & Asthma

CT-measured variables; red (blue) higher (lower) than mean

subjects



Normal lung

Mild asthma

Moderate asthma

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Very severe asthma

Selected Un-selected Selected variables

Chen K, et al. Reduced-rank stochastic regression with a sparse SVD. 2011, J. Royal Stat. Soc., Series B.

Summary

- We presented a multi-scale image-based lung model and its integration with statistical methods for population-level analysis.

Acknowledgements

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