Reconstruction of the airway tree and airflow and drug delivery calculations in the lungs of children with disease

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Motivation

- Explore novel airway modeling techniques to help detect disease stage early before airway destruction, and potentially identify “windows” for therapeutic interventions

- Use airway modeling techniques to explore new ways to target drugs to affected sites in the lung at the desired dose while avoiding delivery to other sites to minimize possible side effects

- 3D modeling of children’s lungs requires high-resolution imaging. Leverage image sets already obtained in other studies
  - Diseased Lungs
  - Normal Lungs

Knowledge Gaps

- Physiological identification of sources of within-subject variability
- Leveraging model complexity and model performance
- Model validation due to lack of actual data
  - Building confidence in reliability and performance of complicated mechanism based models
- Understanding physiology and pathology in sub populations, and drug effect on disease progression and its feedback on PK
- Developing in vivo relevant in vitro testing

Example: Cystic Fibrosis

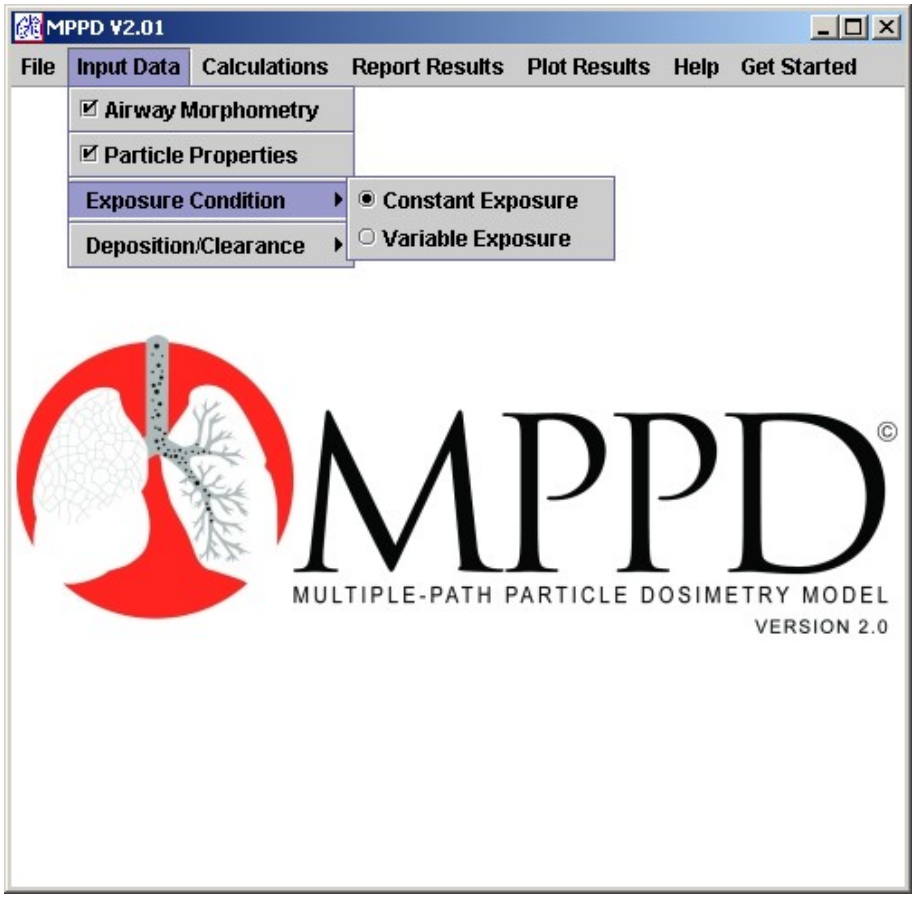
- Cystic fibrosis (CF) is a hereditary chronic disease, which mainly targets the lungs.
- Structural and physiologic abnormalities associated with CF begin early in life.
  - CT scans obtained for diagnosis.
- Treatment is aimed to ease severity of the child's symptoms and slow the progression of the disease.
- Early intervention is key to effective treatment
- The development of endpoints that detect CF airway disease before "irreversible" damage has proven challenging, especially during infancy.

Objectives

- Explore novel airway modeling techniques
  - 3D lung reconstruction
  - Computational fluid dynamics studies
- Determine quantifiable variables associated with respiratory diseases such as CF
  - Bronchial cross-sectional area
  - Airflow partitioning (right-left allocation)
  - Airway resistance, impedance, etc.
- Conduct computational studies
  - Airflow distribution in patient lungs → Lung function to detect early stage
  - Study drug delivery to the diseased lungs
- Develop multiple-path dosimetry models for diseased lungs to allow patient-specific, bench top calculations

Multiple-Path Dosimetry Model

- Develop diseased models as different stages
- Include in multiple-path dosimetry model



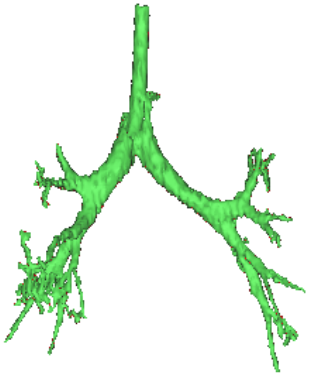
Preliminary studies

- Chest CT scans were obtained in 8 CF subjects (ages 3 months to 5 years: 4 males, 4 females):

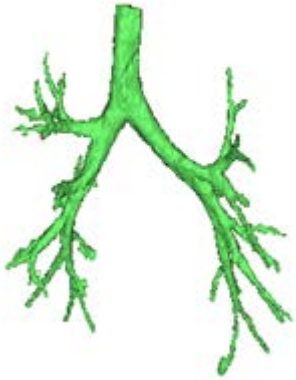
R01 HL116211 (Principal Investigator: Stephanie D. Davis, MD, Pediatric Pulmonology, Indiana University and Riley Hospital for Children, Indianapolis, IN), Co-Investigator: Julia Kimbell UNC Chapel Hill, NC.
NIH/NHLBI
Viral Pathogenesis of Early Cystic Fibrosis Lung Disease
The objective of this project is to examine the role of viral infections in the pathogenesis of CF lung disease using information from bronchoalveolar lavage combined with computerized x-ray tomographic (CT) imaging, infant pulmonary function (iPFT) measurements, and airway and vascular modeling techniques.

3D Lung Reconstructions

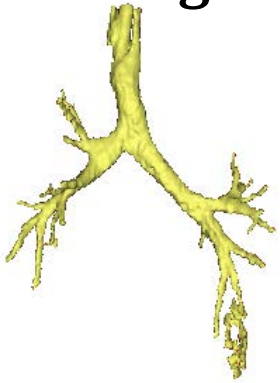
3 month old girl



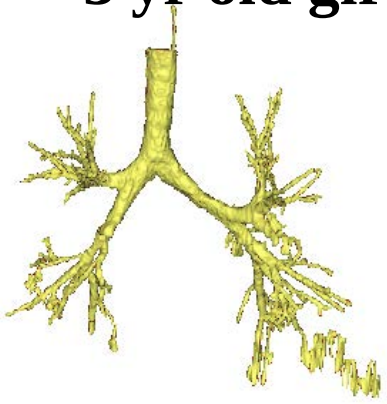
10 month old girl



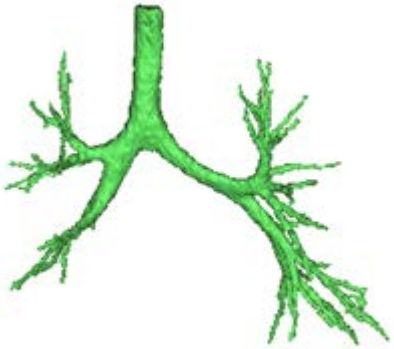
12 month old girl



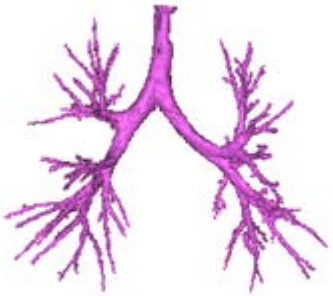
3 yr old girl



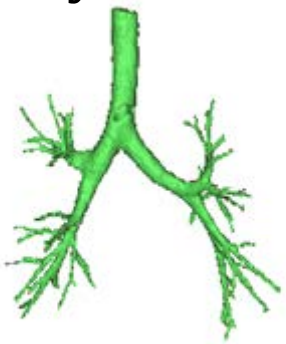
3 yr old boy



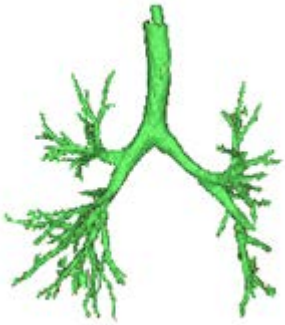
5 yr old boy



5 yr old boy



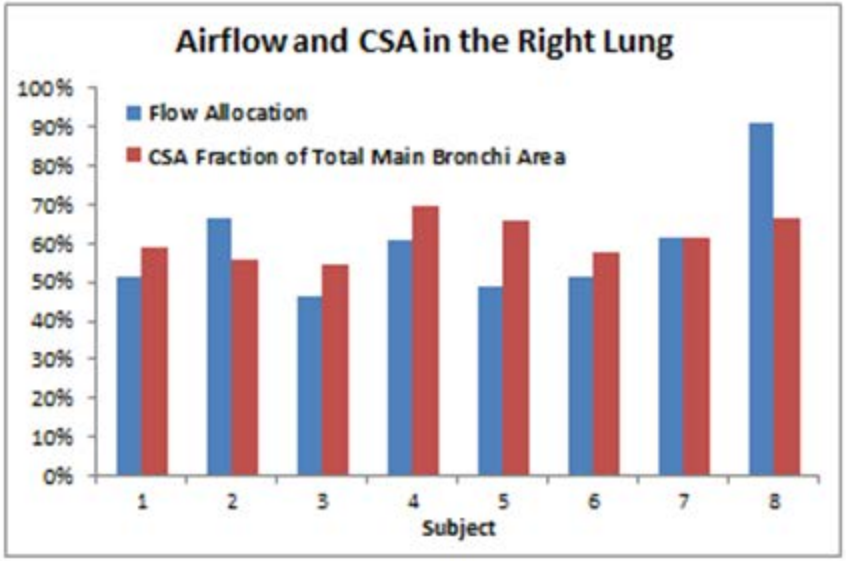
5 yr old boy

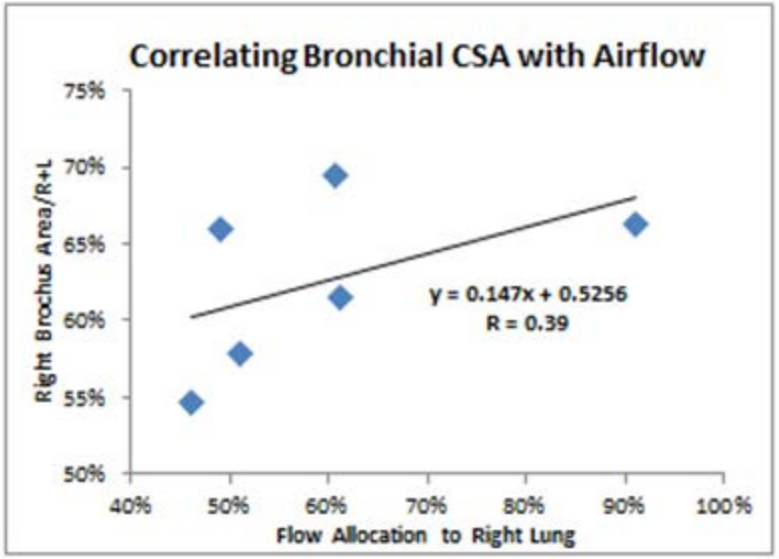


Preliminary Studies

- Cross-sectional areas (CSA) of right and left main bronchi were estimated from three-dimensional (3D) reconstructions of at least 3 generations of the upper airways from each scan, and expressed as percentages of the combined right and left CSAs
- Preliminary estimates of ventilation distribution were obtained from CFD simulations of steady-state, inspiratory airflow at resting breathing rates
- Right and left ventilation distribution was expressed as the percent of total inspiratory flow exiting right or left lung outlets, respectively

CSA & Airflow Distribution





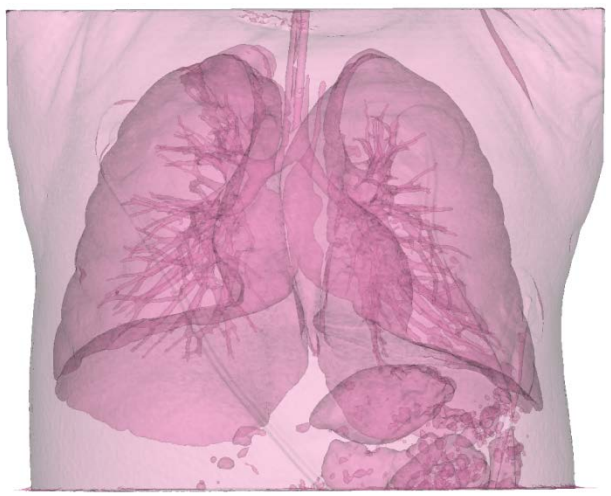
Findings/Future Direction

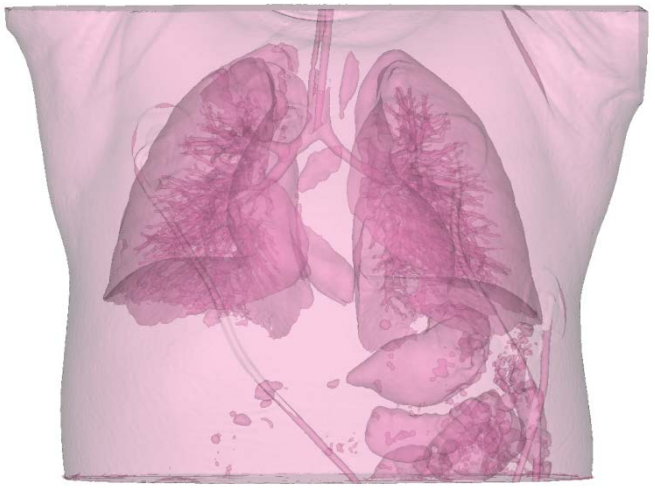
- Preliminary estimates of airflow distribution to right and left lungs in pediatric CF subjects are generally similar to the CSA distribution between the two main bronchi.
- Work is in progress to create models for 12-mon-old CF subjects.
- Further work is needed to assess 3D lung reconstruction accuracy and explore other functional variables such as airway resistance.
- These modeling tools have the potential to quantify early-age, CF effects on lung structure, growth, and function for development and evaluation of therapeutic treatment.

Preliminary Studies

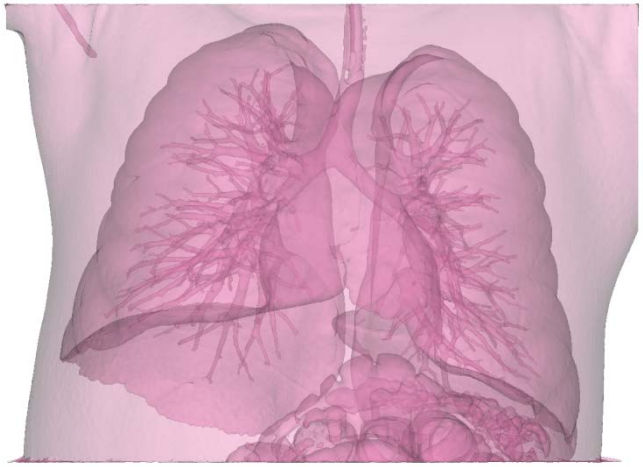
Comparison of reconstructions for two 12 mon-old CF subjects

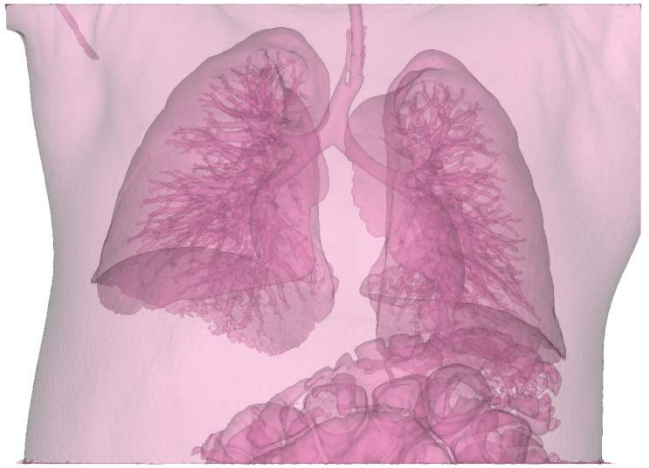
Subject 1





Subject 2



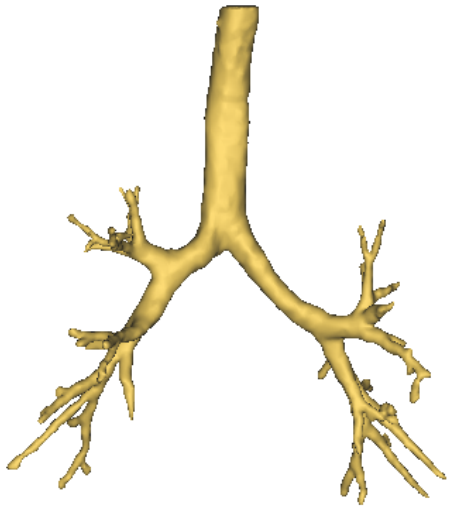


Inspiratory

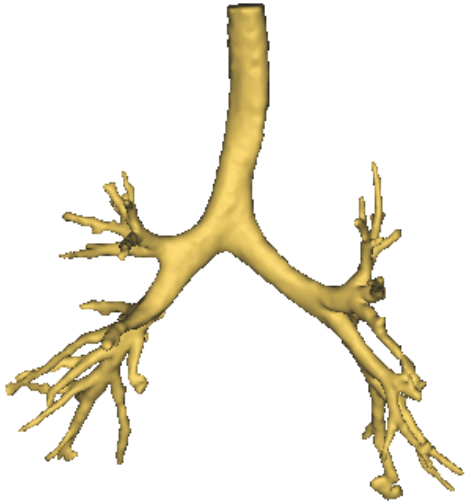
Expiratory

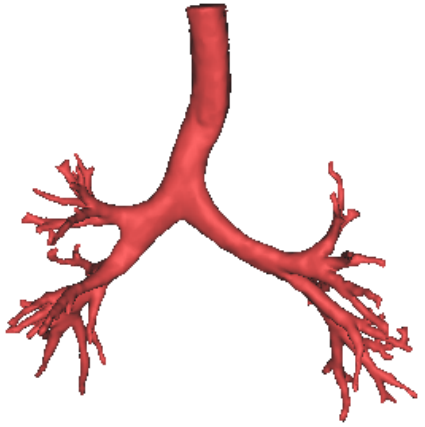
Upper Airway Reconstructions

Subject 1



Subject 2





Inspiratory

Expiratory

Additional Datasets Are Available

- Lung CT scans have been made for a large number (> 50) CF children at 12-months of age
- CT images were also collected retrospectively for healthy children from birth to 17 years old
  - R01 HL105241 "*Predictive Modeling for Treatment of Upper Airway Obstruction in Young Children*"
- Databases such as these can be used to
  - Study drug delivery to diseased lungs
  - Understand dosing in healthy and diseased states

Research Needs for FDA to Consider

Use 3D reconstructions of readily available CT scan images of the lungs of children with disease to:

- Compare them with lung reconstructions of healthy children for which scan images are also available to study disease biomarkers
- Conduct computational fluid dynamics studies of the airflow in the lungs of healthy and diseased children to:
  - Examine possible ways to maximize airflow and drug delivery to diseased lobes.
  - Minimize side effects resulting from the drug reaching undesired sites.
- Develop dosimetry model for diseased lungs to allow patient – specific dose predictions on desk-top computer.
- Validate simulation predictions by comparing with available data.