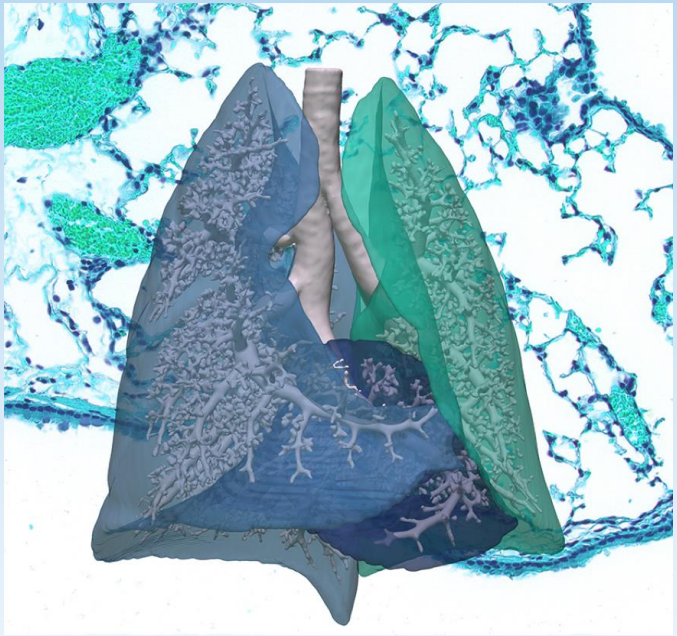
Computational Fluid Dynamics (CFD)-Based Dosimetry Modeling of the Respiratory System

Development, Application & Future Directions



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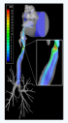
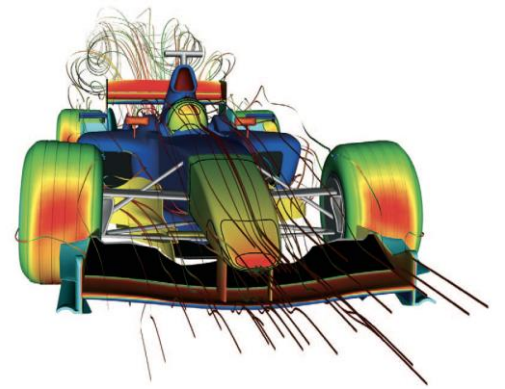
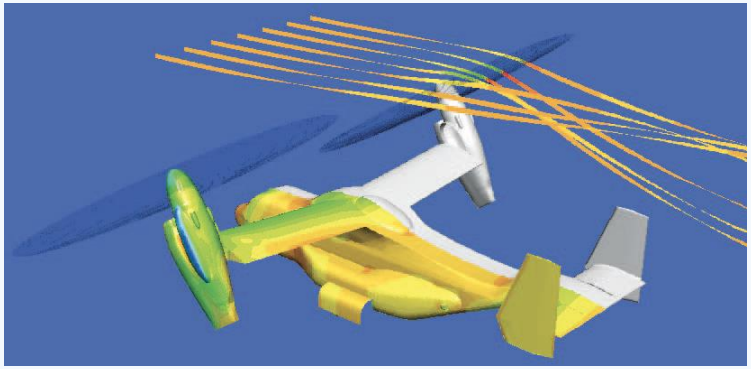
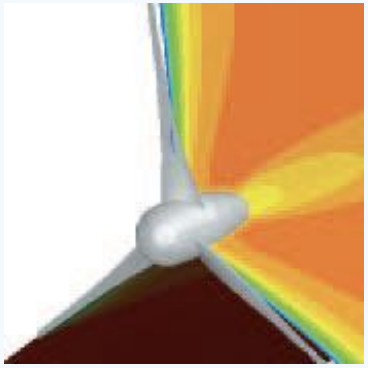
Modeling Approaches

- ✓**Whole-lung modeling**
  - MPPD for aerosol dosimetry
  - Other examples
    - ICRP (1994, 2015)
    - NCRP (1997)
    - Trumpet model (Yu, 1978; Robinson and Yu, 2001)
- **Site-specific modeling**
  - Imaging-based CFD modeling for gases, vapors and aerosols
- **Hybrid/multi-scale modeling**
  - Combining whole-lung with site-specific modeling
    - Combining CFD with stochastic and idealized airway approximations
    - Combining CFD with individualized MPPD, airway/tissue mechanics, PBPK modeling



What is Computational Fluid Dynamics or CFD?
In a nutshell…

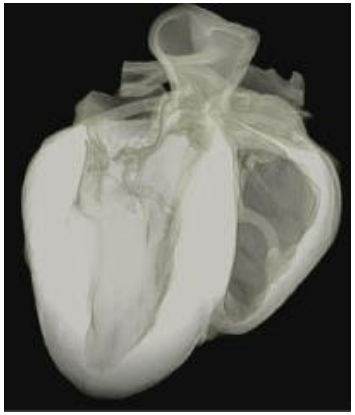
- **Numerical method for describing fluid flows**
  - Navier-Stokes Equations that describe the flow of a viscous fluid
  - The solution is a flow velocity field over space and time
  - Solved using a 3D computational mesh with appropriate boundary conditions (e.g. shape, mechanical properties, fluid characteristics, pressure, etc.)
- **Methods widely used in aerospace, automotive, energy, building HVAC, etc. industries to improve design, trouble-shooting, and decrease costs in product development**

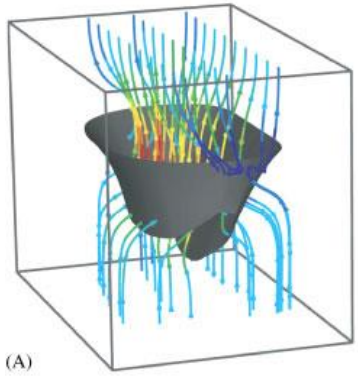




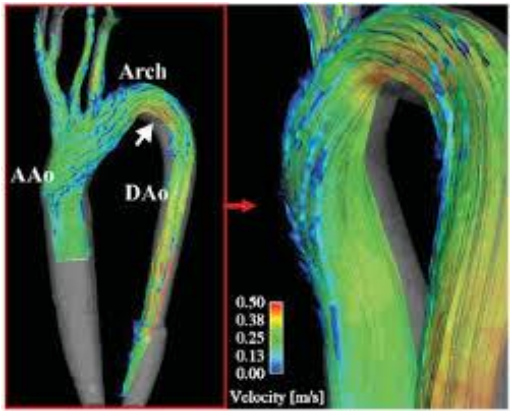
Source: Fluent News, 2005

What is CFD?

- **Biological applications are a comparatively recent development**
  - Heart function, blood flow, fluid-structure interactions





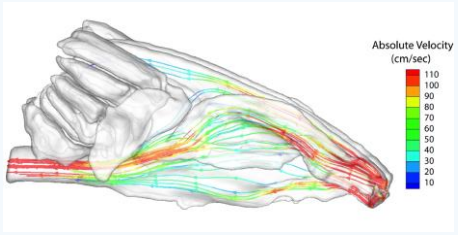


- **Why so few biological applications?**
  - Can be significantly more difficult to obtain 3D (and 4D) structures and boundary conditions than the physical sciences
  - Math phobes still exist in biology
    - Generally requires inter-disciplinary teams
- **Respiratory and Cardiovascular CFD are a rapidly growing area with the advent of new imaging, image analysis, and computational capabilities**

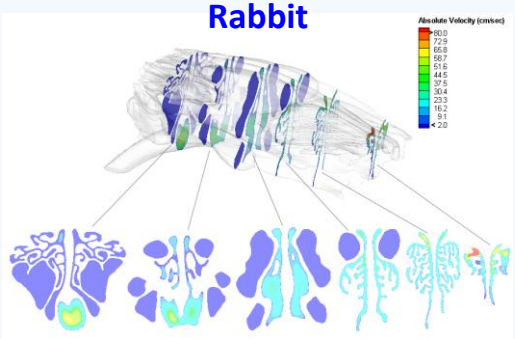
Imaging-Based Anatomy

CT Scans: Airways → Black; Bone/Pulmonary Vasculature → White; Tissues → Gray

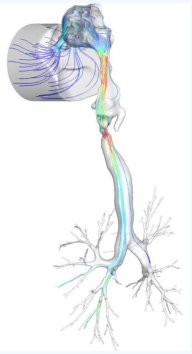
Rat

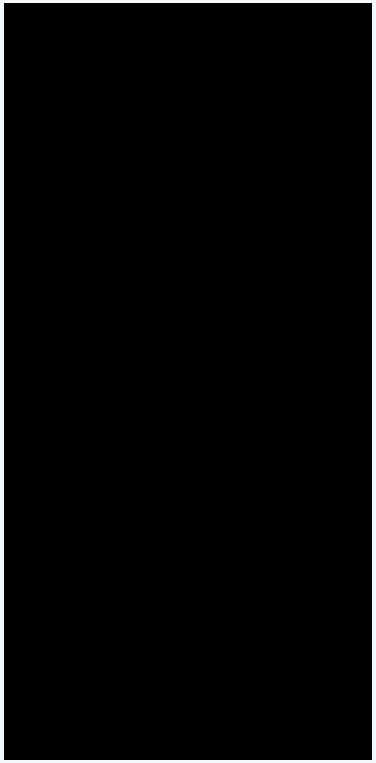


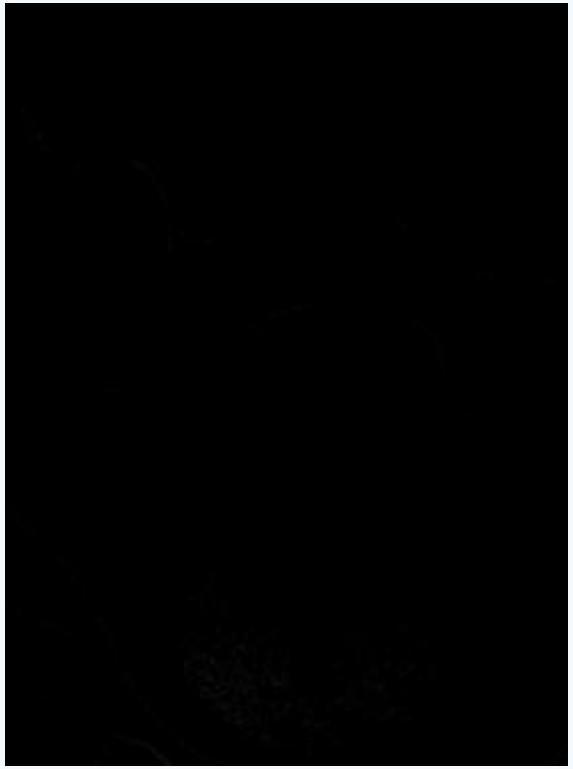
Rabbit

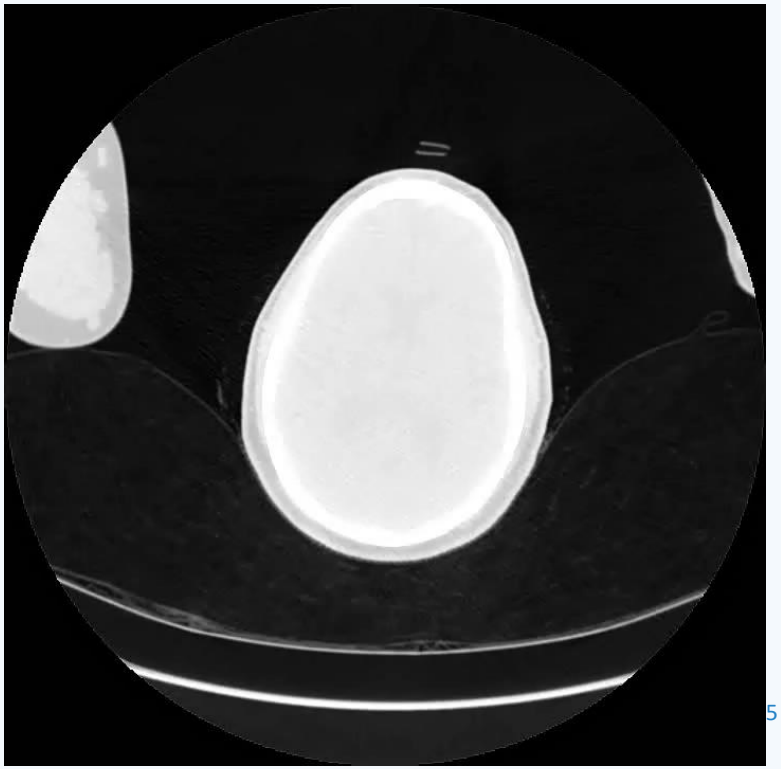


Human



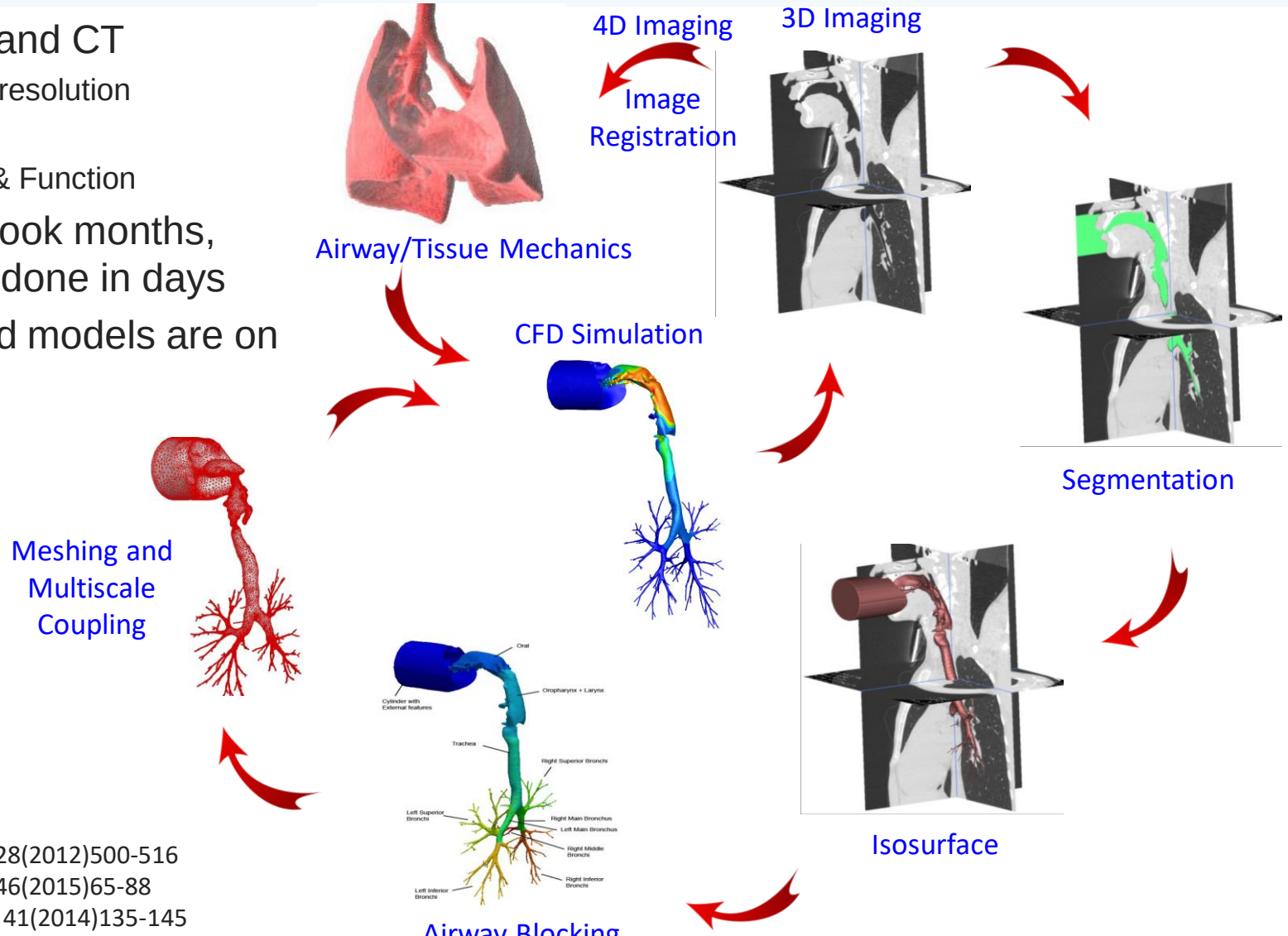






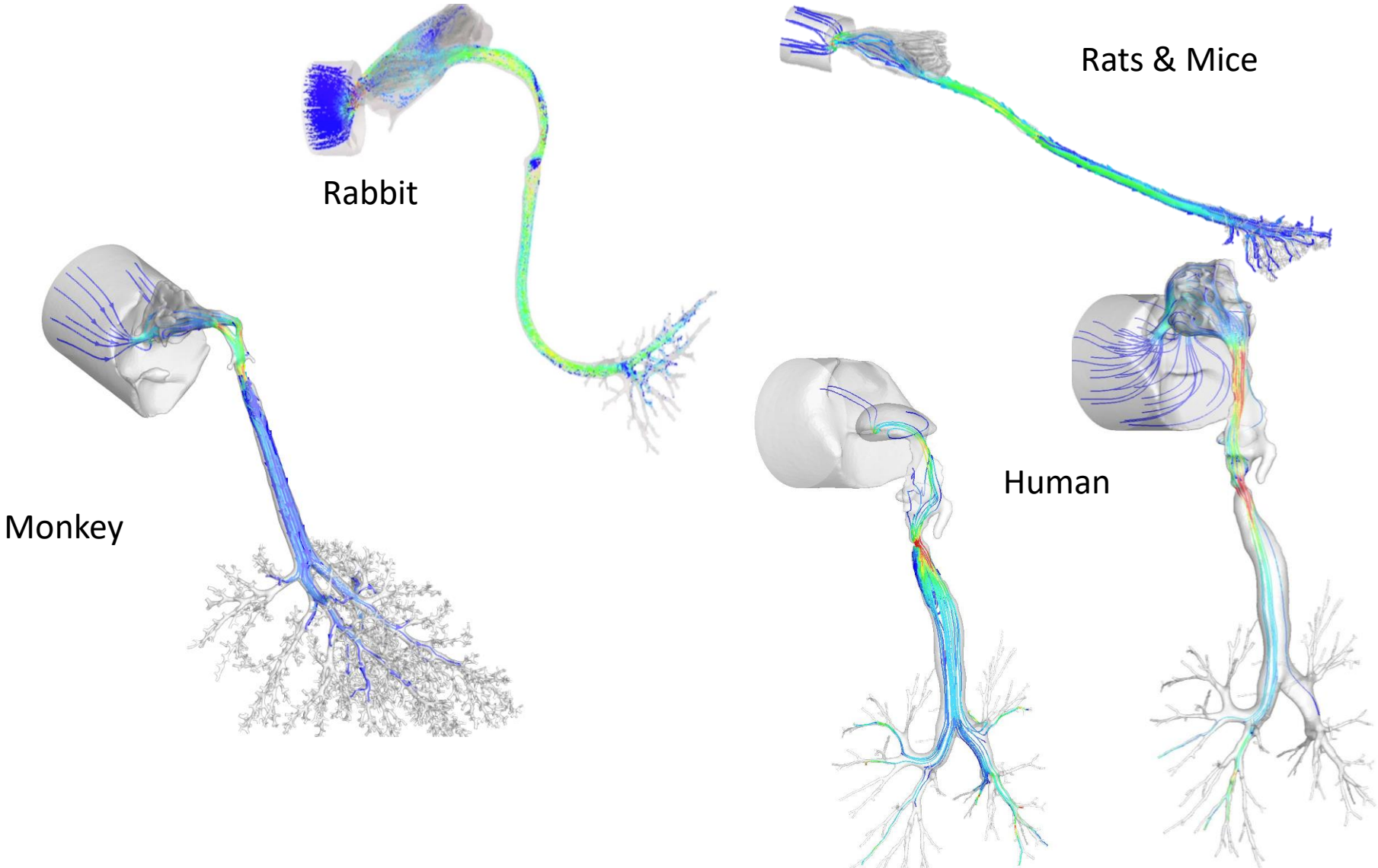
Imaging Based CFD Model Development is Now Routine

- 3D/4D MRI and CT
  - Mod-High resolution
  - Dynamic
  - Structure & Function
- What once took months, can now be done in days
- Personalized models are on the horizon



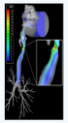
Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88
Jacob et al. Exp. Lung Res. 41(2014)135-145

Suite of Imaging-Based CFD Models & Data Sets for Model Performance Evaluation

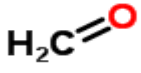
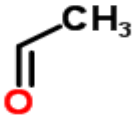
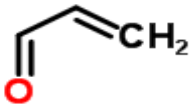


Example Applications of CFD-Based Approaches

- **Ex 1: Multi-scale CFD/PBPK for reactive aldehydes**
- **Ex 2: CFD/aerosol dosimetry for cross-species and IVIVE**
- **Ongoing/future directions: Multi-scale CFD/Whole Lung/Aerosol dosimetry including disease influences**



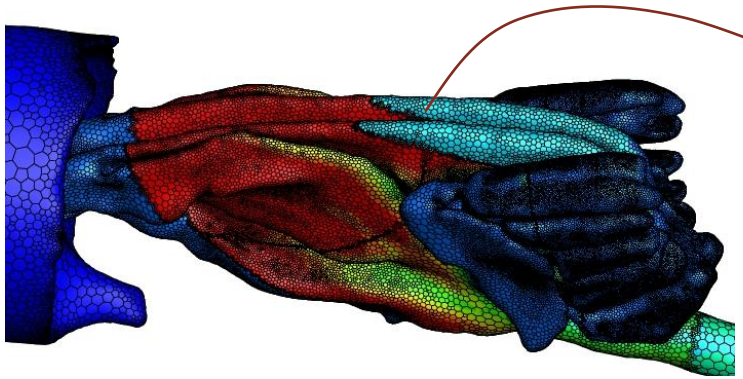
Ex 1: Multi-Scale CFD/PBPK for Reactive Aldehydes

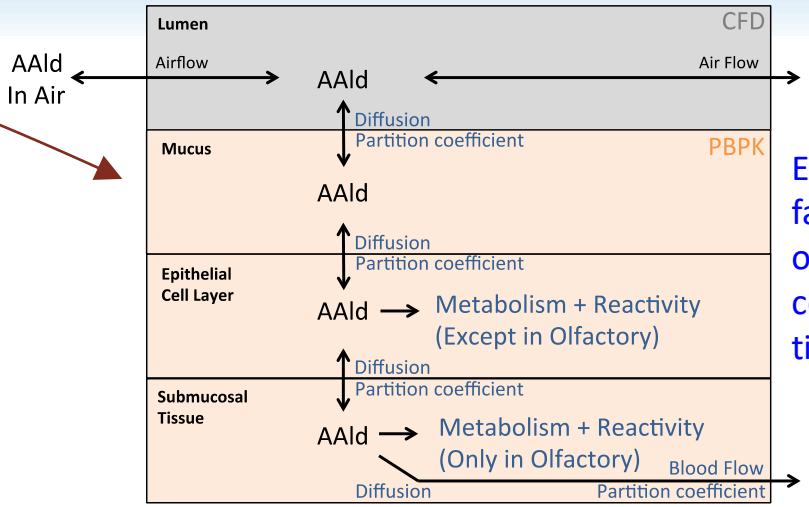
Formaldehyde  Acetaldehyde  Acrolein 

- **Important industrial chemical intermediates, by-products of combustion, endogenously produced, or dietary sources**
- **Highly reactive, water-soluble vapors, difficult to directly measure in tissues**
- **Contact site irritation, inflammation, cytoxicity/degeneration, compensatory tissue remodeling, mutations**
- **Cytotoxicity & tumors in nasal and upper respiratory tissues of rodents drive many human health risk assessments**
  - Systemic effects (e.g. leukemia, neurotoxicity, etc.) following inhalation exposures controversial
- **Smoking is a major source for human exposures**
  - Published constituent risk comparisons lack species-specific dosimetry considerations
    - Obligate nose breathers vs. human nasal/oral breathing

Ex 1: CFD/PBPK for Reactive Aldehydes

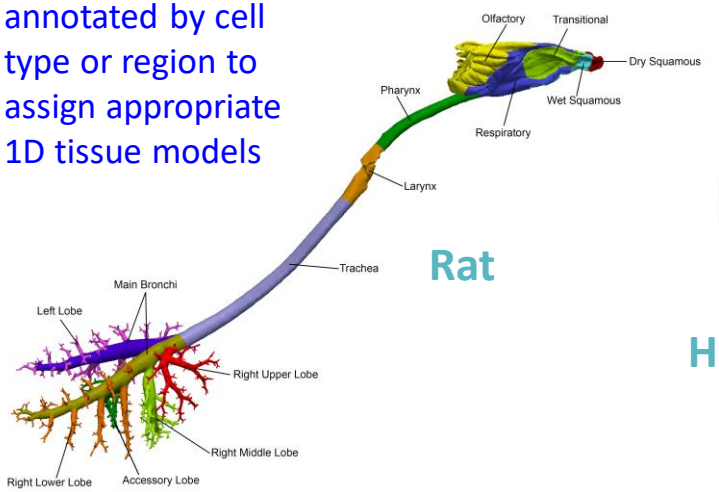
Model Structure



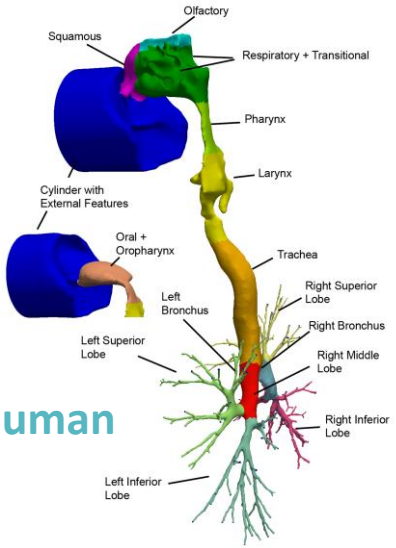


Each surface facet has it's own 2-way coupled PBPK tissue model

Airway surface is annotated by cell type or region to assign appropriate 1D tissue models



Rat



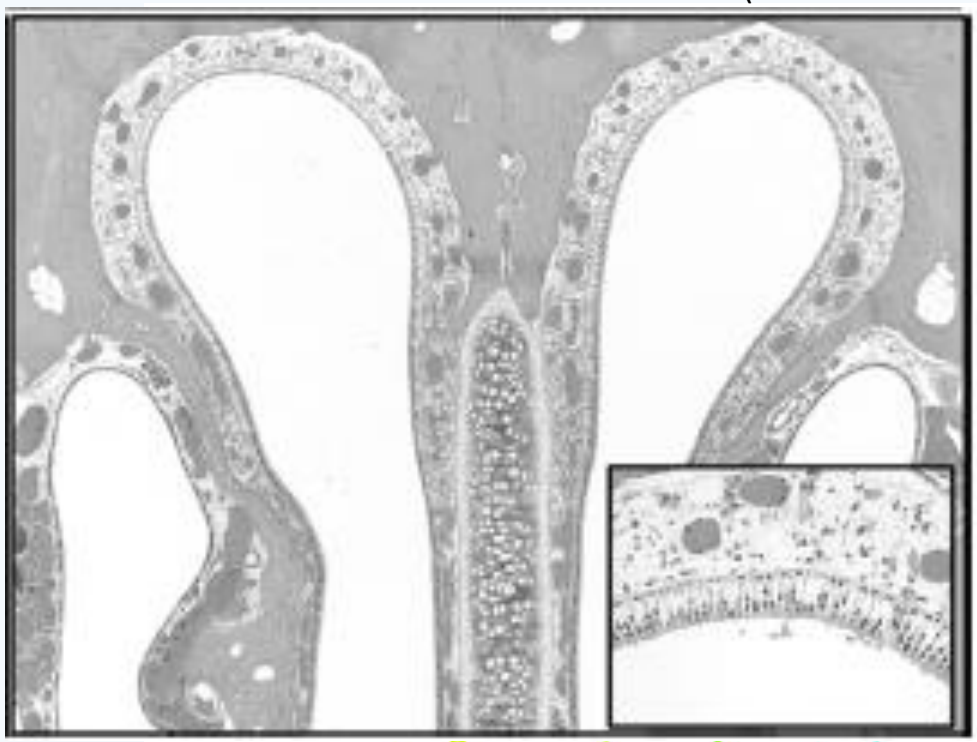
Human

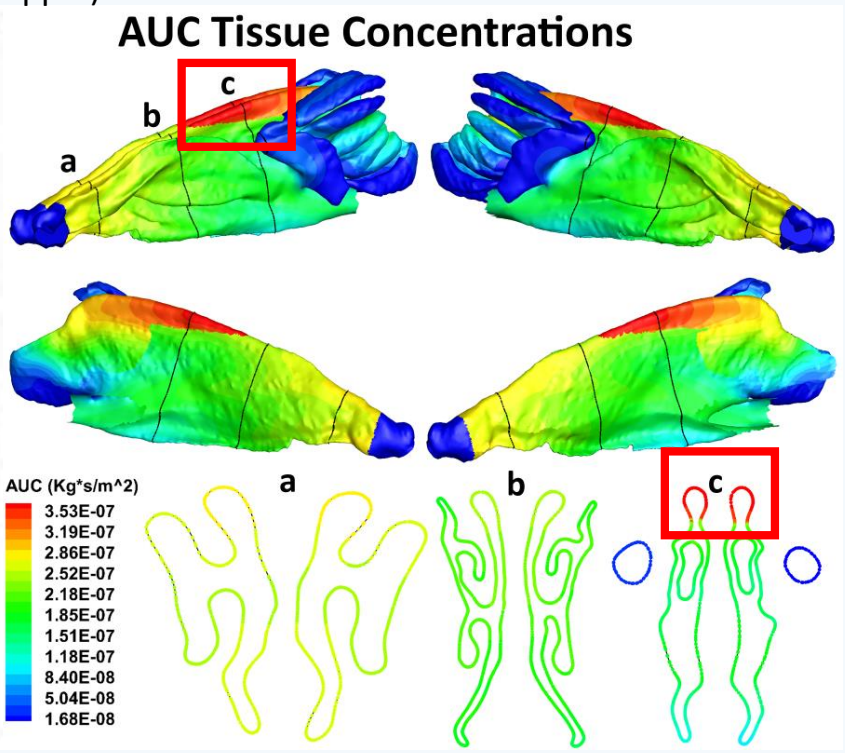
Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88

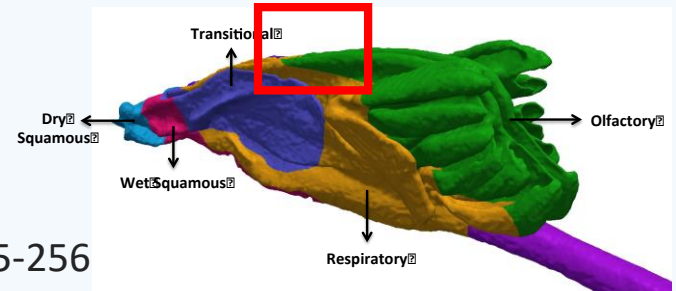
Ex 1: CFD/PBPK for Reactive Aldehydes
Surface Flux vs. AUC Tissue Concentrations

Acetaldehyde

(Rat NOAEL = 50 ppm)



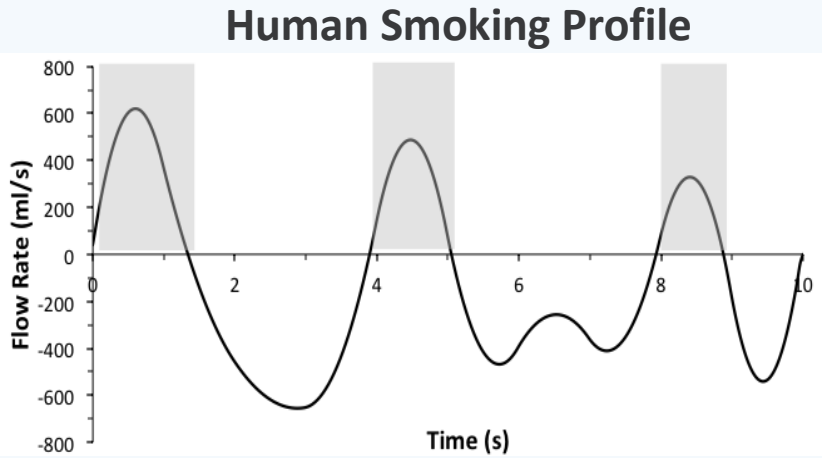




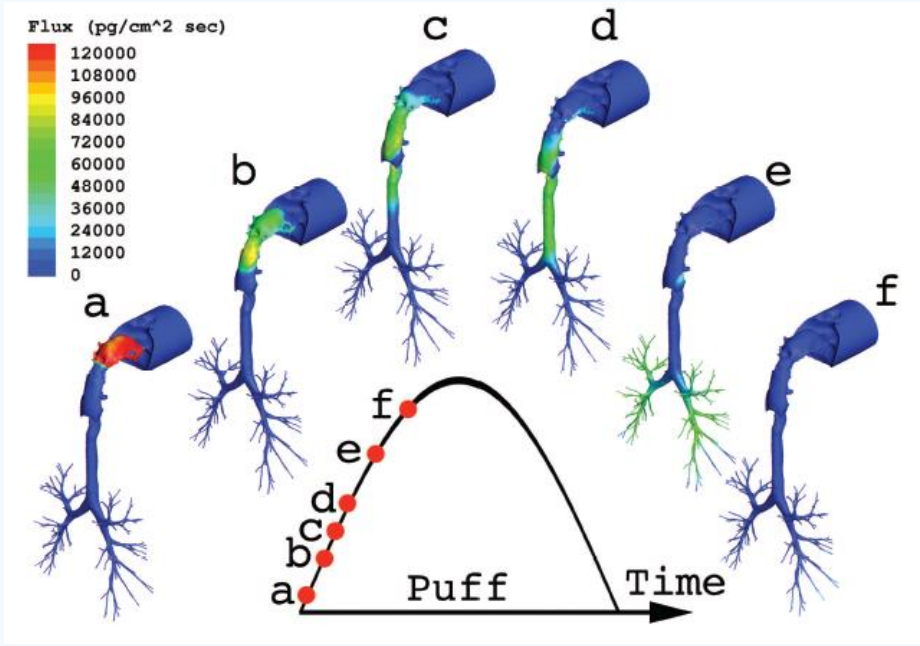
Corley et al. Toxicol. Sci. 146(2015)65-88

Dorman et al. Inhal. Toxicol. 20(2008)245-256

Ex 1: CFD/PBPK for Reactive Aldehydes
Comparisons to Human Exposure via Cigarette Smoking



- **Measured human puff profile (St. Charles et al. Inhal. Toxicol. 21(2009)712-718)**
- **Measured smoke compositions (Counts et al. Reg. Toxicol. Pharmacol. 41(2005)185-227) for representative puff concentrations**
  - Acetaldehyde – 1028 ppm (857 µg/cig)
  - Acrolein – 94 ppm (100 µg/cig)
  - Formaldehyde – 108 ppm (61 µg/cig)



Rat - Human comparisons based upon 'Hot Spot' AUCs and Exposure-Duration/#cigs per day Adjustments

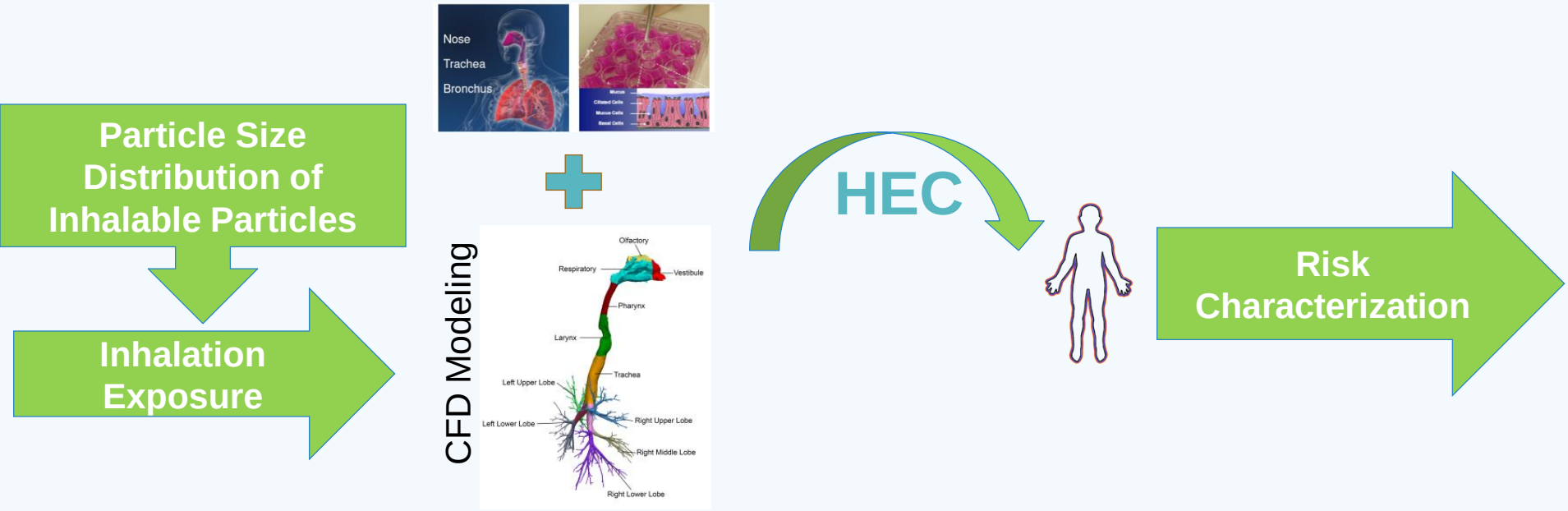
Corley et al. Toxicol. Sci. 146(2015)65-88

Ex 2: CFD/Particle Dosimetry for Cross-Species & IVIVE

Syngenta's Source-to-Outcome Approach for Pesticide Re-Registration

- **Replace requirement for 90-day rat inhalation toxicity study with *in vitro* studies in human cells coupled to enhanced characterization of exposure and target dose relevant to risk characterization (consistent with vision of NAS 2007 and 2012)**

In vitro Testing Based Point of Departure using MucilAir™ from Epithelix

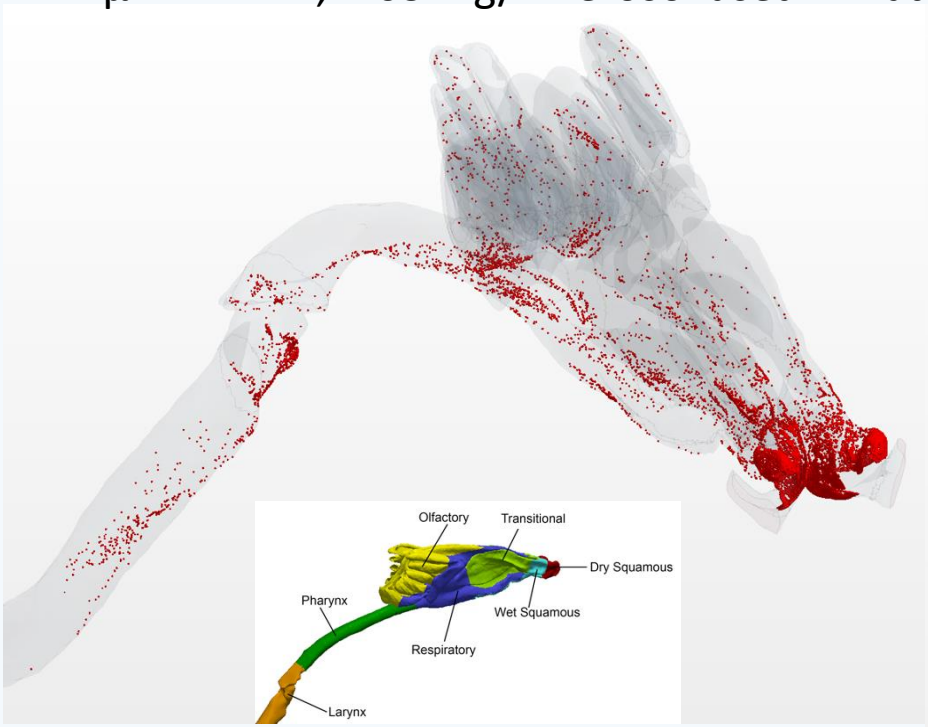


- **EPA FIFRA SAP Review Meeting Dec. 4-7, 2018**

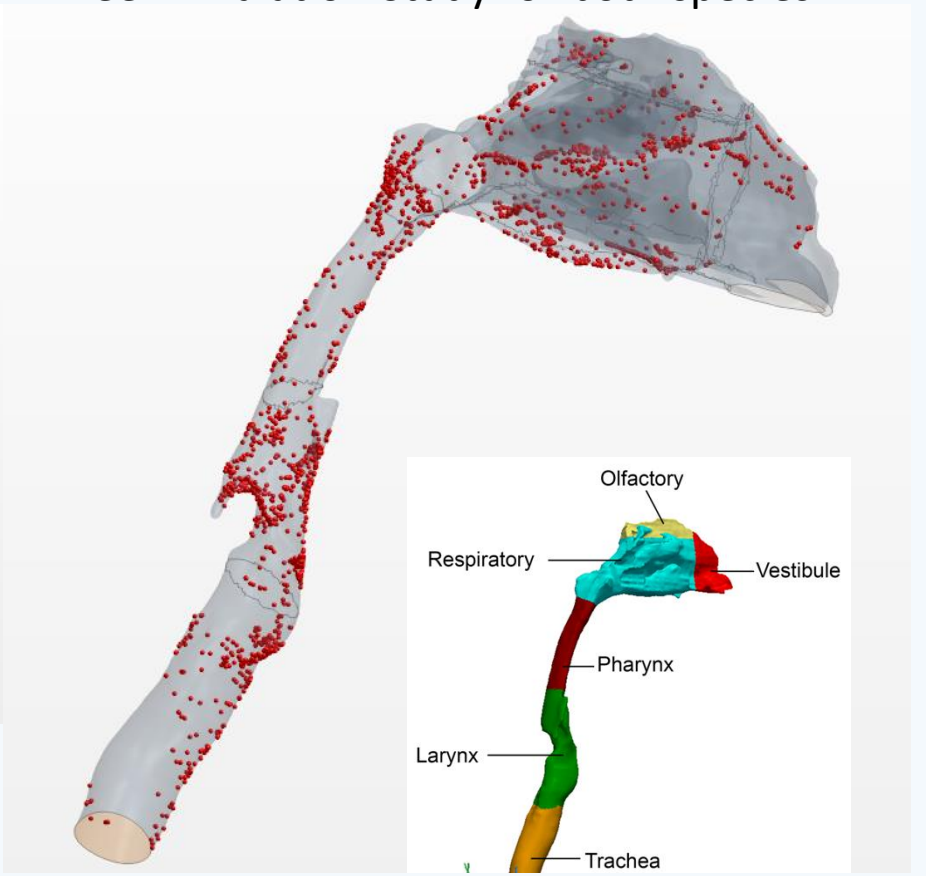
Ex 2: CFD/Particle Dosimetry for Cross-Species and IVIVE

Syngenta's Source-to-Outcome Approach for Pesticide Re-Registration

2.7 µm MMAD, 4.03 mg/L Aerosol used in Rat 2-Week Inhalation Study for both species



58.2% inhaled deposited in nose



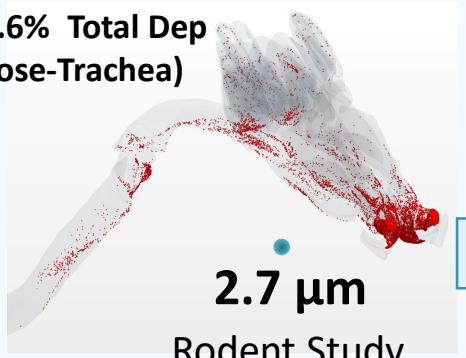
<1% inhaled deposited in nose

RA Corley, PhD
GCTC, LLC

Ex 2: CFD/Particle Dosimetry for Cross-Species and IVIVE

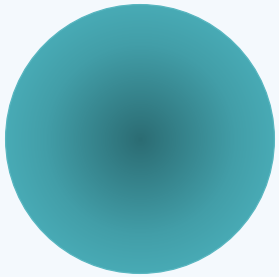
Syngenta's Source-to-Outcome Approach for Pesticide Re-Registration

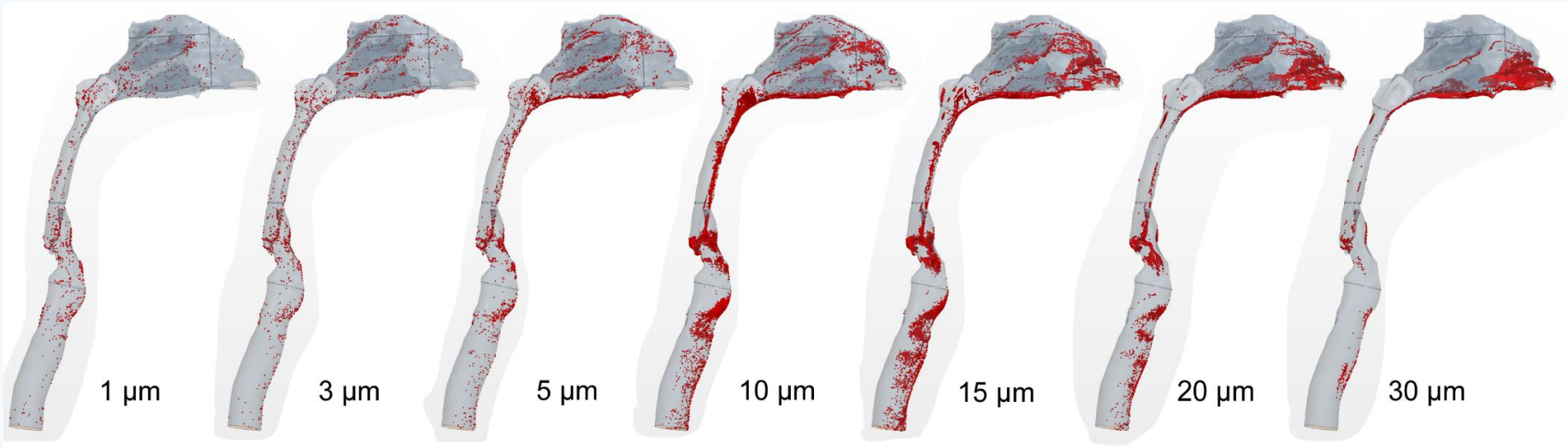
58.6% Total Dep (Nose-Trachea)



2.7 µm
Rodent Study MMAD

35 µm
Agricultural Exposure MMAD





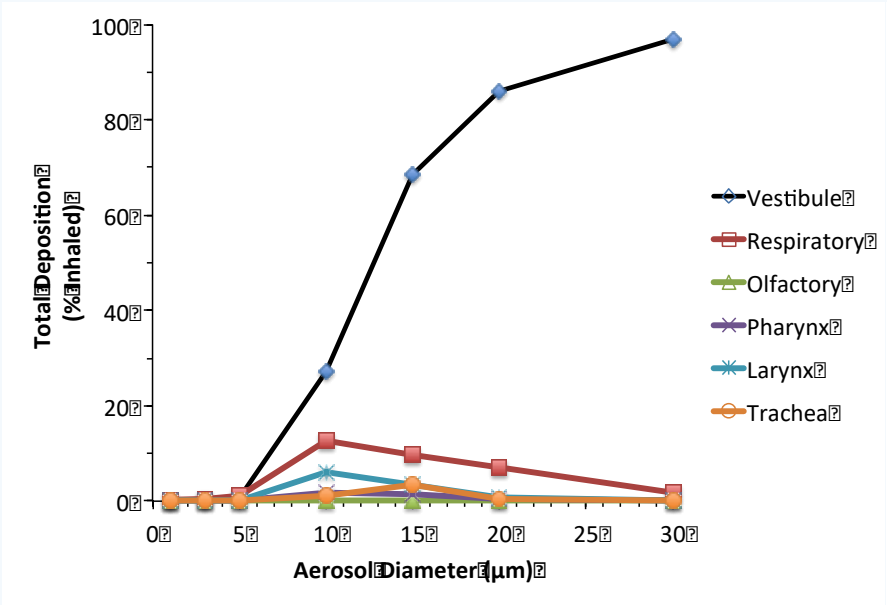
% Total Deposited (Nose – Trachea)

0.6	0.7	2.4	48.8	86.9	95.1	98.9

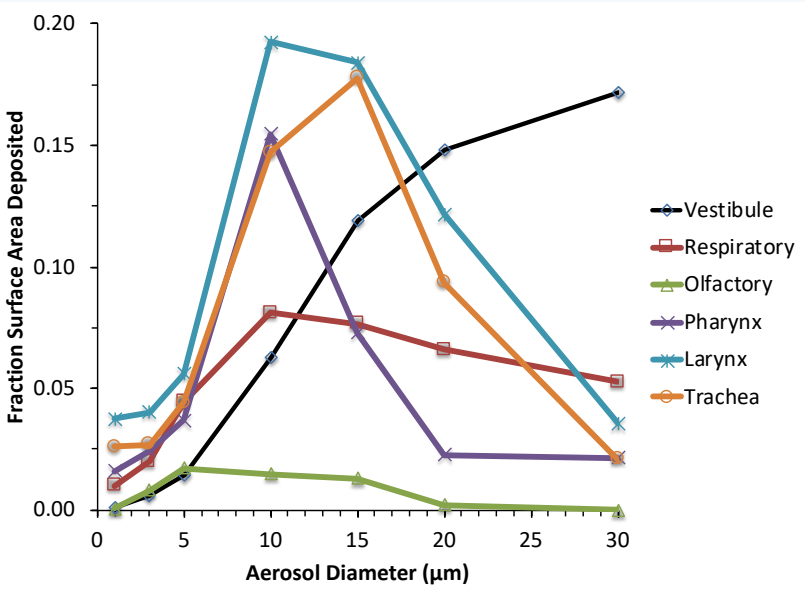
Ex 2: CFD/Particle Dosimetry for Cross-Species and IVIVE

Syngenta's Source-to-Outcome Approach for Pesticide Re-Registration

Total Deposition (% Inhaled)



Fraction of Surface Area With Deposition

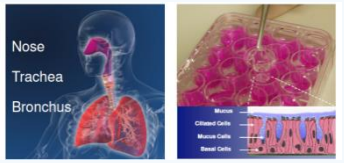


- **Aerosols associated with worker exposures largely deposit in nasal vestibule**
  - Peak regional airway exposures at 10-15 µm sized aerosols (excluding vestibule)
- **<20% of regional airway surfaces receive any aerosol deposition at high, 1 mg/L exposure**

Ex 2: CFD/Particle Dosimetry for Cross-Species and IVIVE

Syngenta's Source-to-Outcome Approach for Pesticide Re-Registration

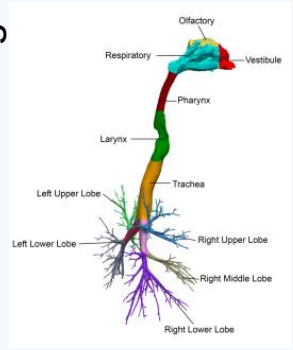
In vitro Testing Based Point of Departure using MucilAir™ from Epithelix



Particle Size Distribution of Inhalable Particles

Inhalation Exposure

CFD Modeling



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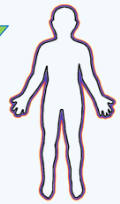


Risk Characterization

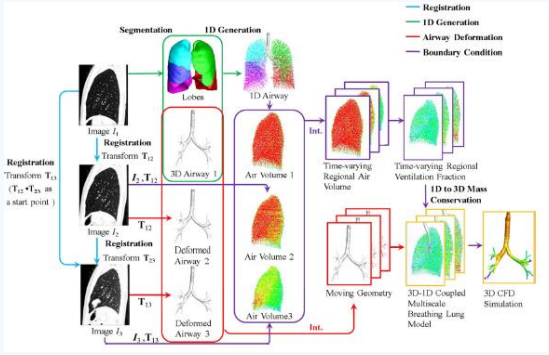
EPA FIFRA SAP Review Meeting Dec. 4-7, 2018

Public Docket: https://www.regulations.gov/docket?D=EPA-HQ-OPP-2018-0517

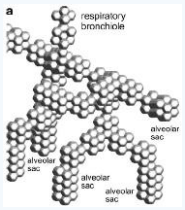
Ex 3: Hybrid/Multiscale Models beyond CFD/PBPPK

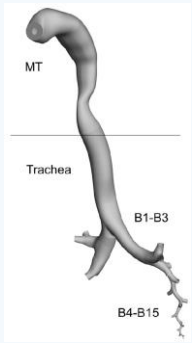
Current State-of-the-Art for CFD/Whole lung Models

- **Yin et al. (2010, 2013)**
  - Moving 4D CFD plus 1D volume-filling airway skeleton

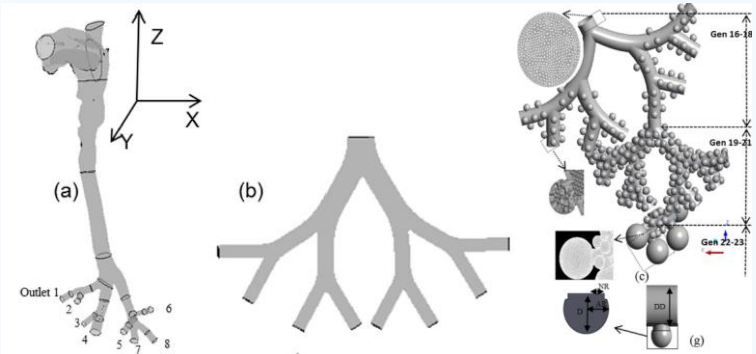


- **Longest et al. (2012, 2016)**
  - CFD airways to lobar bronchi coupled with Stochastic Individual Path (SIP) approximations of bronchioles plus acinar moving wall models





- **Kolanjiyil and Kleinstreuer (2017)**
  - Whole-lung airway model (WLAM) using CFD upper airways to lobar bronchi coupled to adjustable triple bifurcation units (TBUs)



Ex 3: Hybrid/Multiscale Models beyond CFD/PBPK

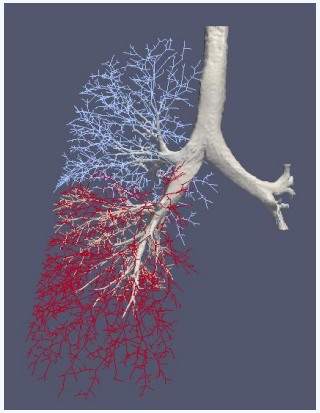
Current State-of-the-Art for CFD/Whole lung Models

- **Our current approach (personalized vs. idealized airways; NIEHS MSM U01 ES028669)**
  - Takes advantage of our unique imaging and aerosol database
    - Experimental data on aerosol deposition and 4D imaging in same subjects (rat and human)
    - Included disease and healthy conditions (rat and human)
  - Link CFD/Particle transport models with MPPD, 1D tissue mechanics and viscoelastic acinar ODE models for each individual
    - Incorporate imaging-based tissue mechanics
    - Utilize vasculature for personalized deep lung airway geometries for both CFD *and* MPPD configurations
    - Moving airways may be evaluated (if possible due to funding limits) but are actively pursued in other laboratories (i.e. Mullins, Perth; Feng, OSU; Lin, UI)

Ex 3: Hybrid/Multiscale Models

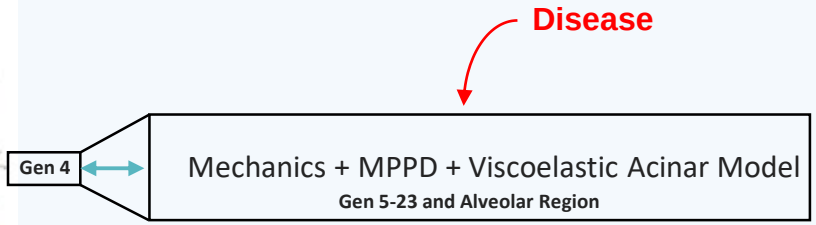
Personalized Aerosol Models & Influence of Disease

(1 µm Deposition (Darquenne et al. J. Aerosol Sci. 99(2016)27-39)



Vasculature-guided airways for personalized CFD/MPPD

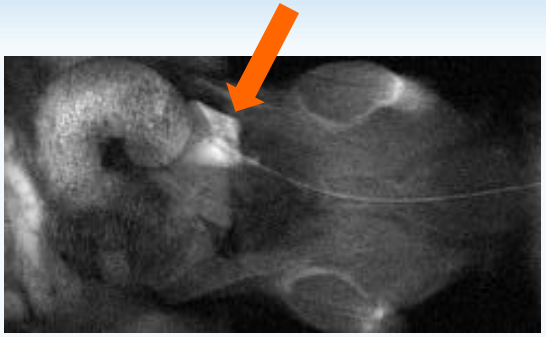
45-65% Particles Deposit in All Airways During Full Breathing Cycle



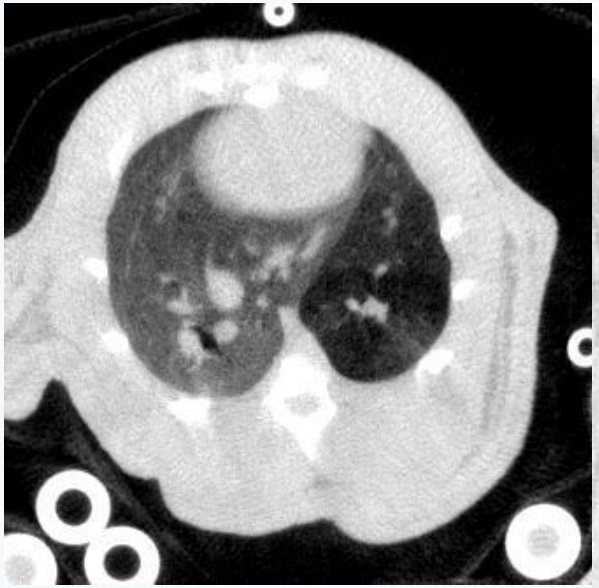
Replaces standard assumption of uniform, zero-pressure outlets with individual airway resistance, compliance, pleural pressure, etc. based upon 3D and 4D imaging and measured physiology

Ex 3: Hybrid/Multiscale Models

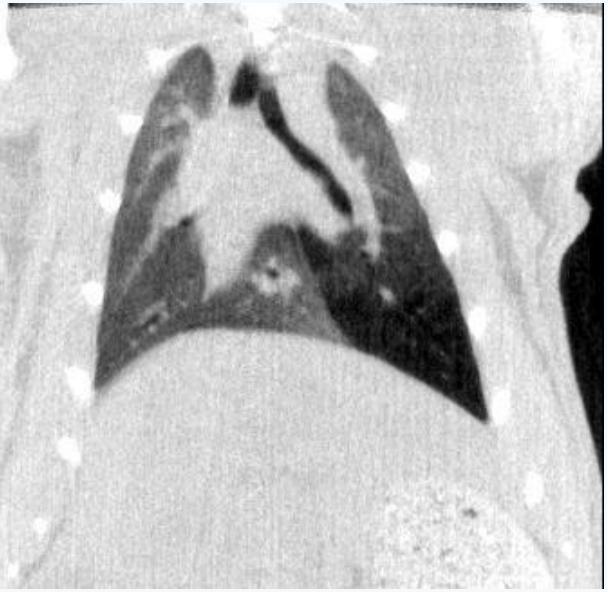
Personalized Aerosol Models & Influence of Disease



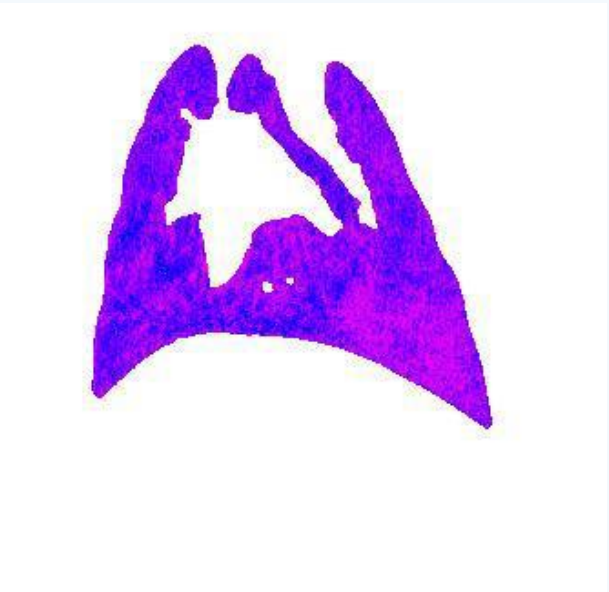
- **Mechanics of the lung is implicit in its motion**
- **Rat model of COPD**
  - Elastase-dosed rat (left lobe only)
  - CT images 11 times over 1-sec breathing cycle
  - Develop maps of ventilation and stress/strain relationships



CT (axial)



CT (coronal)



Ventilation

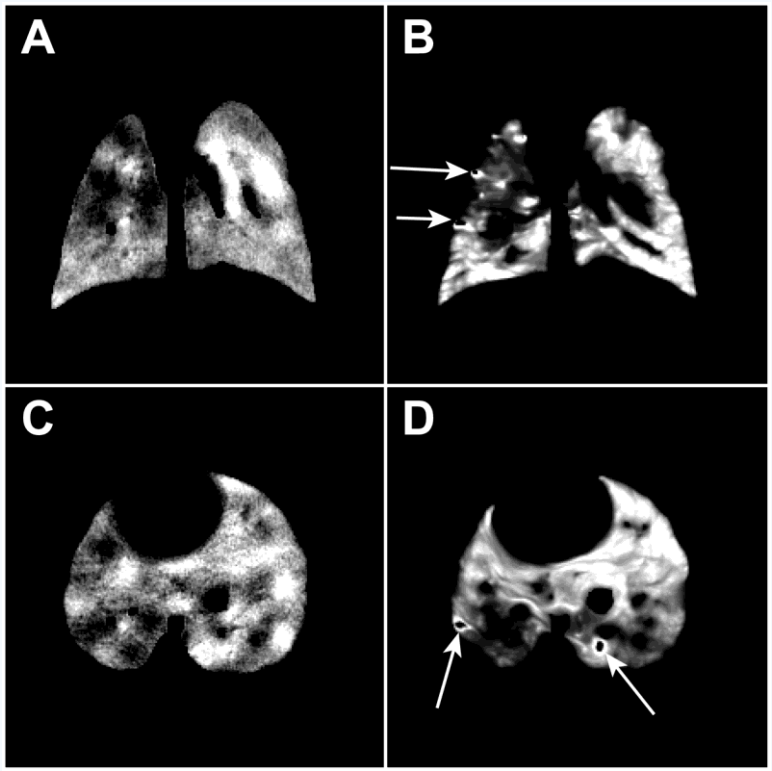
Ex 3: Hybrid/Multiscale Models

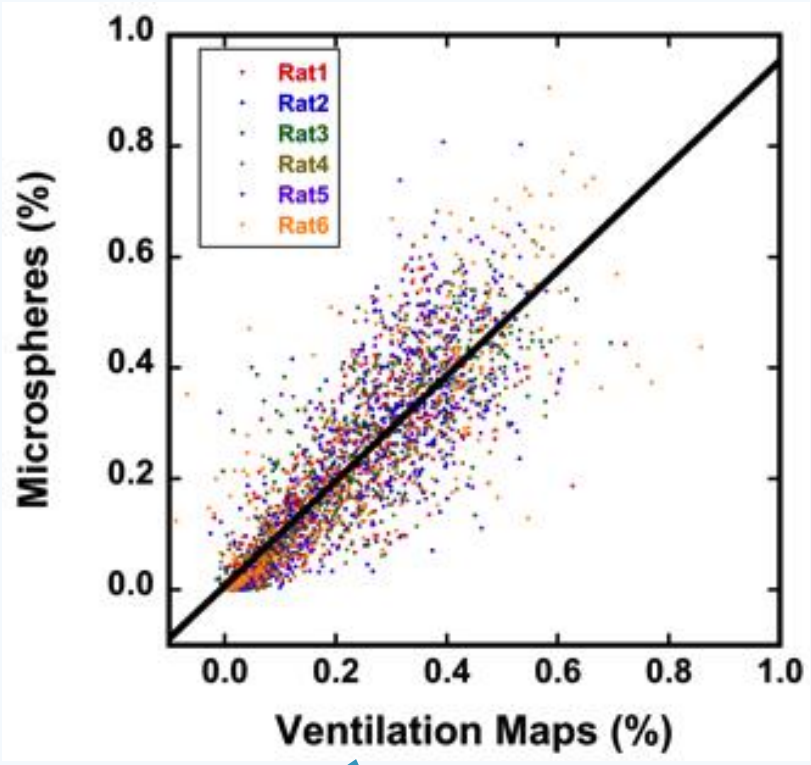
Personalized Aerosol Models & Influence of Disease

Aerosol Exposure + 4D/CT + FMS Cryomicrotome

CT-Based Ventilation Maps

FMS Cryomicrotome Images



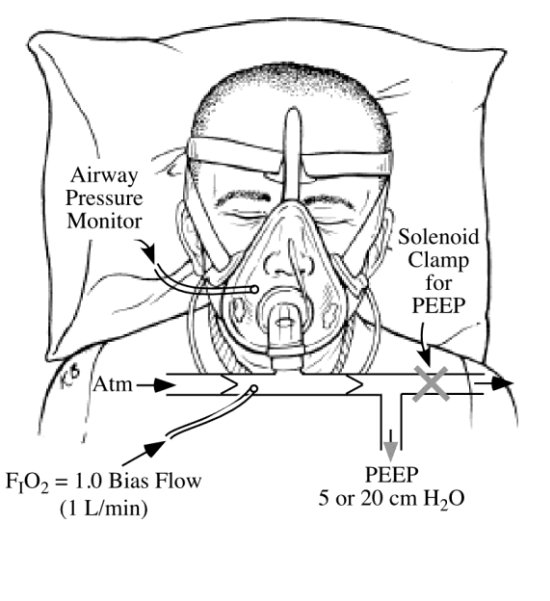


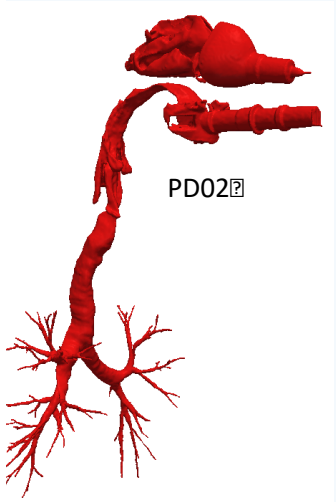
Non-linear Image Registration

Jacob et al. Exp. Lung Res. 41(2014)135-145

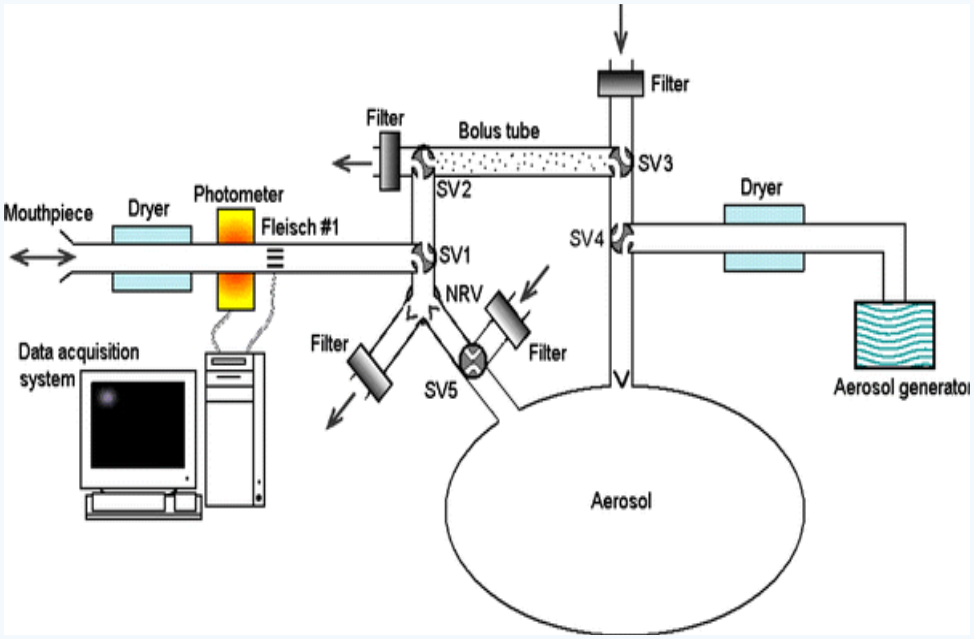
Ex 3: Hybrid/Multiscale Models

Personalized Aerosol Models & Influence of Disease





CT Scans Each Volunteer @ FRC and FRC + 1 L fitted with mask used in studies



Regional (bolus) vs total (continuous) & nasal vs. oral deposition with measured ventilation and +/- Heliox in same position (supine) as CT scans

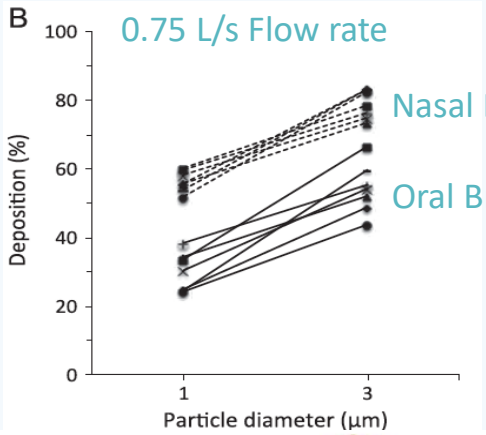
Darquenne et al. J. Aerosol Sci. 99(2016)27-39

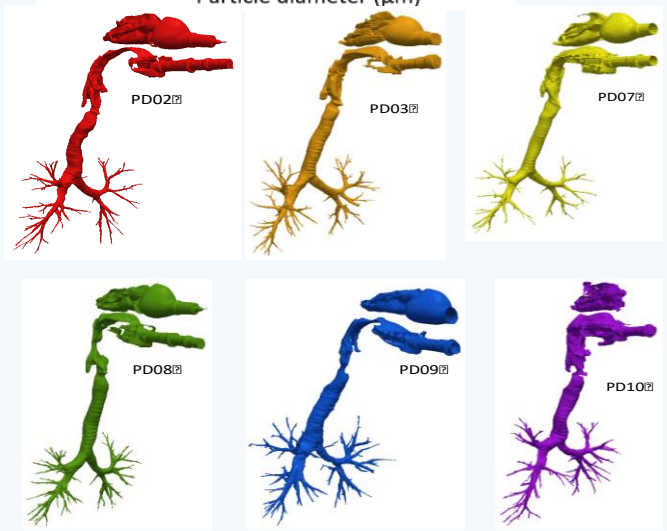
Ex 3: Hybrid/Multiscale Models

Personalized Aerosol Models & Influence of Disease

Continuous Exposure

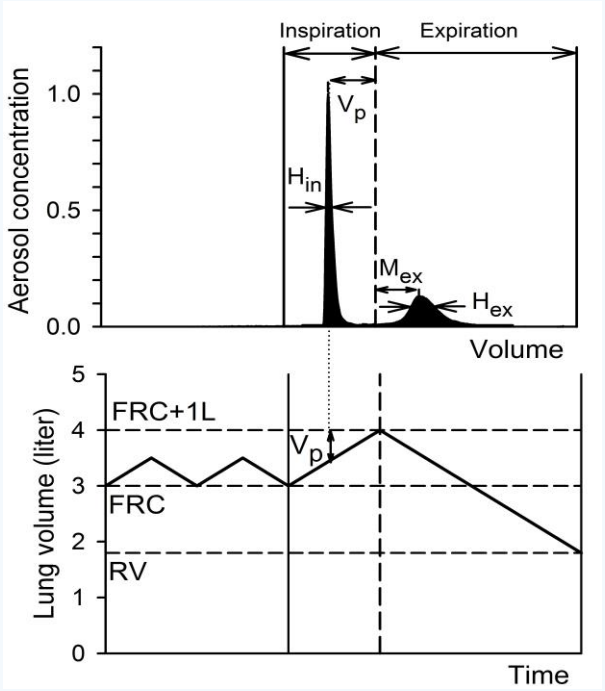
No Differences in Total Deposition with COPD





Aerosol Bolus Test

↑Heterogeneities (Dispersion) and Flow Sequences (Mode Shift) with COPD

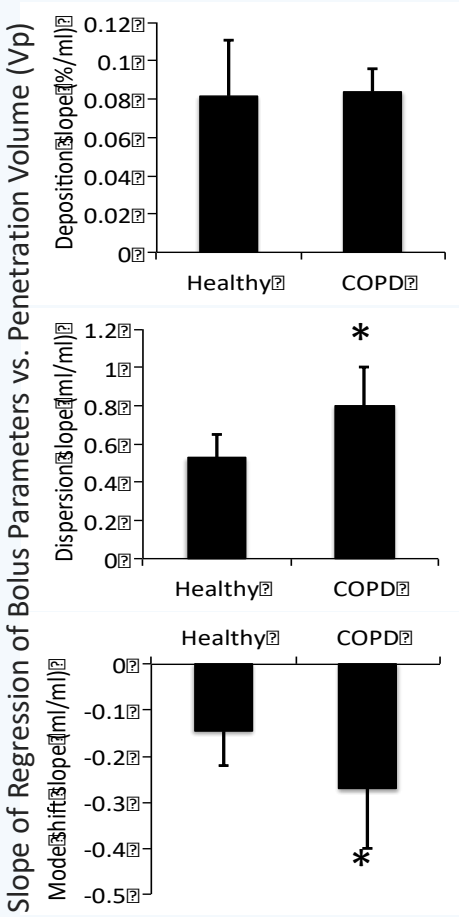


Bolus Parameters:

Deposition = $(1\text{-}AUC_{ex}/AUC_{in})$

Dispersion = $(H_{ex}^2 - H_{in}^2)^{0.5}$

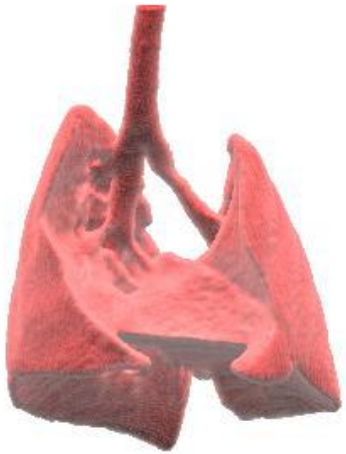
Mode Shift = $M_{ex} - V$



Darquenne et al. J. Aerosol Sci. 99(2016)27-39

Summary of Key Concepts

- **Time to develop 3D CFD-based models greatly reduced**
  - Imaging and new high-resolution ‘omics are key enabling technologies
  - Software and hardware infrastructure vastly improved over past decade
- **Models based upon realistic anatomy, physiology, physics of airflow, and material transport**
  - Minimizes assumptions and extrapolations
  - Significantly improves resolution in exposure-dose-response assessments
  - May be individualized to evaluate factors controlling variability
- **Animal use can be significantly reduced**
  - A variety of exposure conditions can be simulated across species
    - Exposures can be tested *in silico* before conducting experiments
    - Experimental design can be significantly improved
- **Human equivalent concentrations (HEC) can be determined for points of departure (POD) in both *in vivo* and *in vitro* studies**
- **All models are available**
  - Existing templates enhance new model applications



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