Computational Fluid Dynamics (CFD): Modeling the Respiratory System for Comparative Dosimetry

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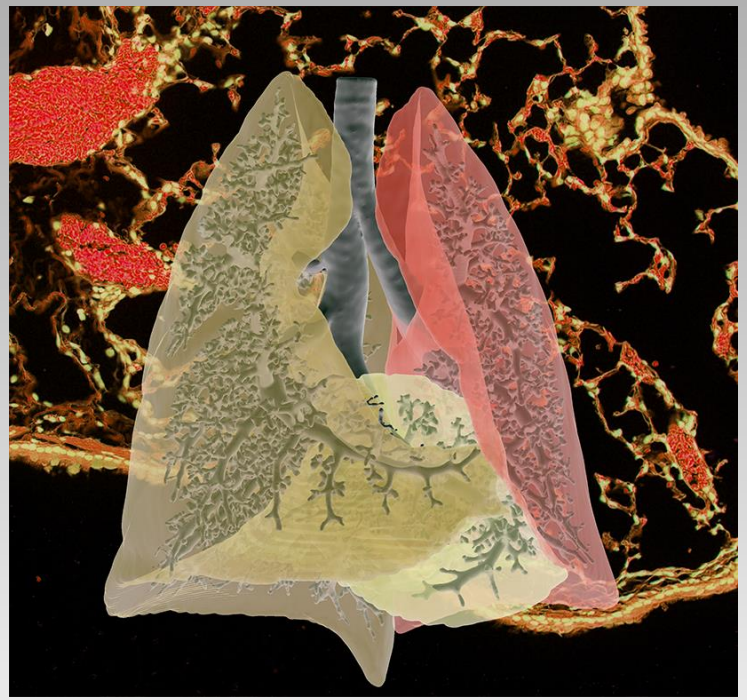


August 2, 2018

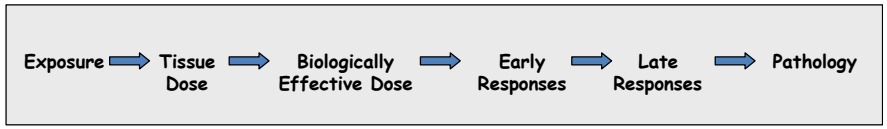
(R)Evolution (in)of Toxicology

Animal *In Vivo*

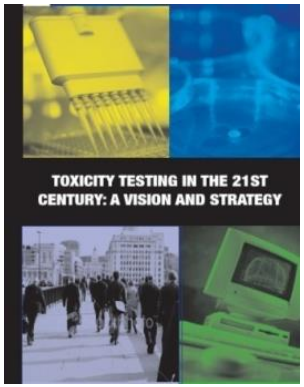
Scaling + Extrapolation

Human *In Vivo*

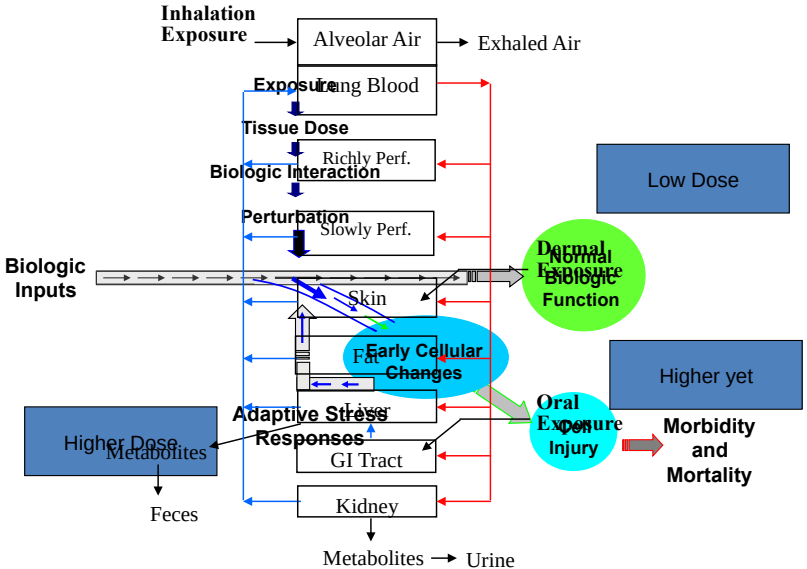
Early 2000's



2007



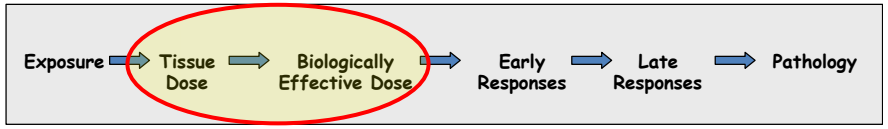
Physiologically Based Pharmacokinetic Models | Tissue Dose Metric | Mode of Action



Shift emphasis from apical endpoints in animals to pathway perturbations in human cells

(R)Evolution (in)of Toxicology

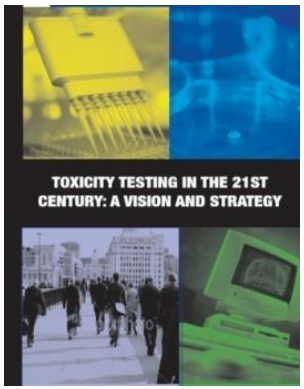
Early 2000's (to Present)



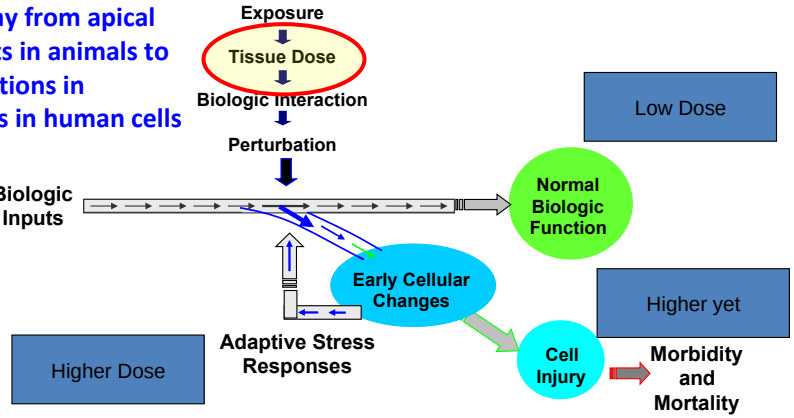
Physiologically Based Pharmacokinetic Models | Tissue Dose Metric | Mode of Action

Target tissue dose required to relate exposure to response, whether study is *in vivo* or *in vitro*

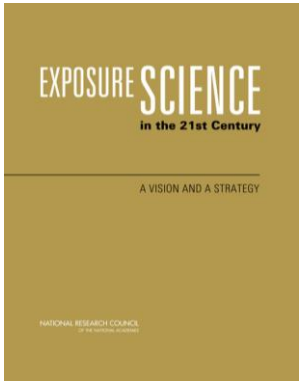
2007

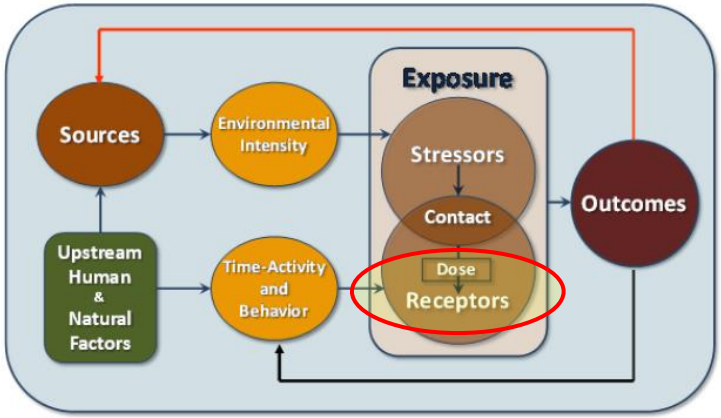


Shift away from apical endpoints in animals to perturbations in pathways in human cells



2012





Redefined "exposure" as dose to target receptor

(R)Evolution (in)of Toxicology

Shift in Focus for Computational Approaches to Extrapolation

Animal *In Vivo*

Human *In Vivo*

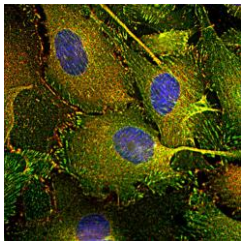
Scaling + Extrapolation

Current State of Art

Scaling

Predictive modeling still requires both *in vitro* and *in vivo* approaches and understanding of "target tissue dose" - response

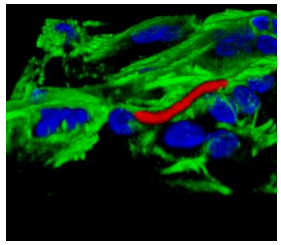
Scaling + Extrapolation



Animal *in vitro*

Scaling

Microphysiology/Organotypic/
Organ on a Chip



Human *in vitro*

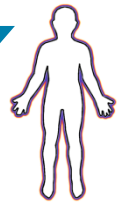
Aspirational State of Art

This is an exciting period of transition as new *in vitro* and computational tools are developed

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

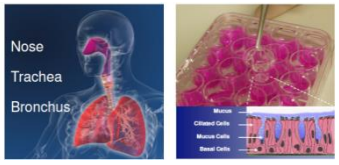
(see Webinar by Dr. Paul M. Hinderliter)

- 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)

Inhalation Exposure →  → **HEC** →  → **Risk Characterization**

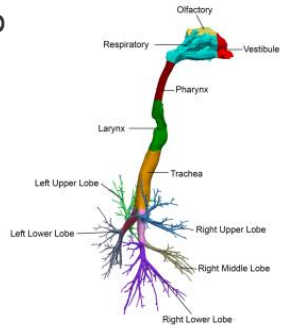
In vitro Testing Based Point of Departure using MucilAir™ from Epithelix

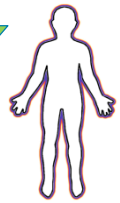
Particle Size Distribution of Inhalable Particles → **Inhalation Exposure**



+

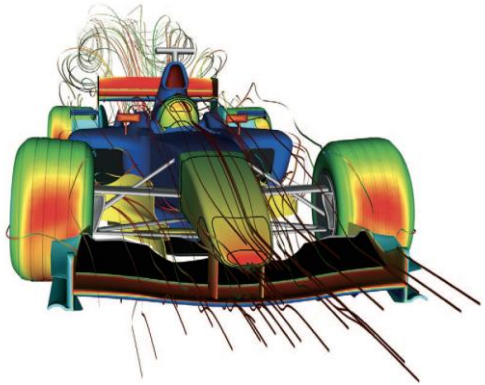
CFD Modeling

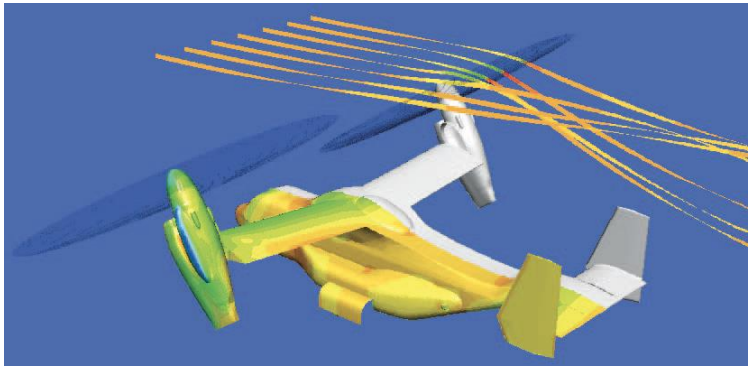


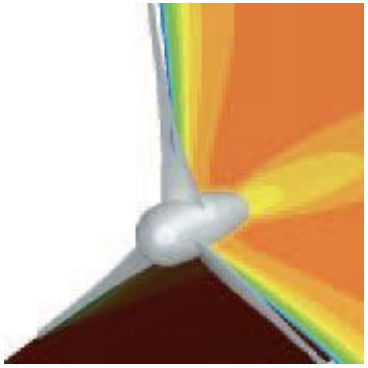
→ **HEC** →  → **Risk Characterization**

What is 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 (Fluent News, 2005)

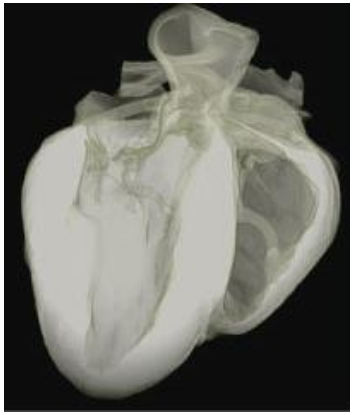


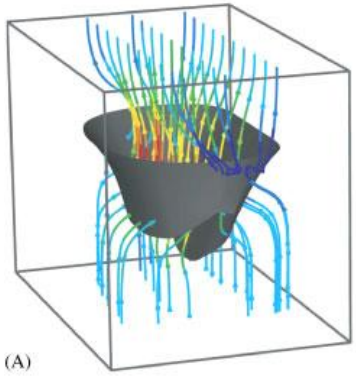


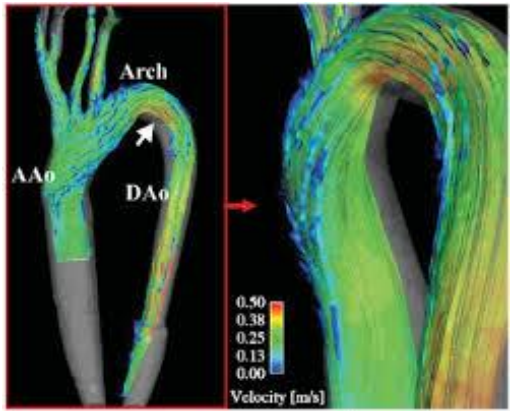


What is CFD?

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



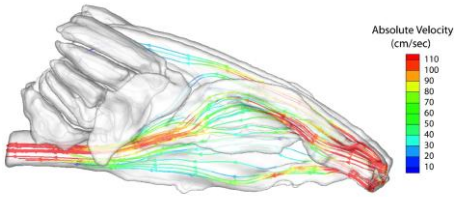




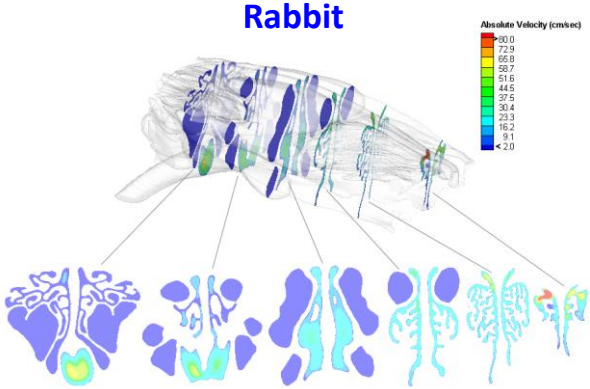
- Why so few biological applications?
  - Can be significantly more difficult to obtain 3D (and 4D) structures and boundary conditions than the physical sciences
  - Math phobes still exist in biology
    - Generally requires inter-disciplinary teams
- Respiratory and Cardiovascular CFD are a rapidly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

Imaging-Based Anatomy

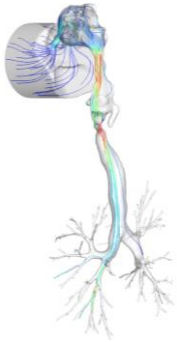
Rat

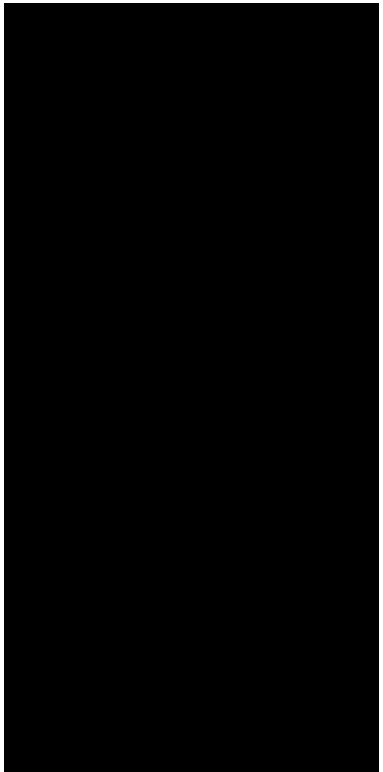


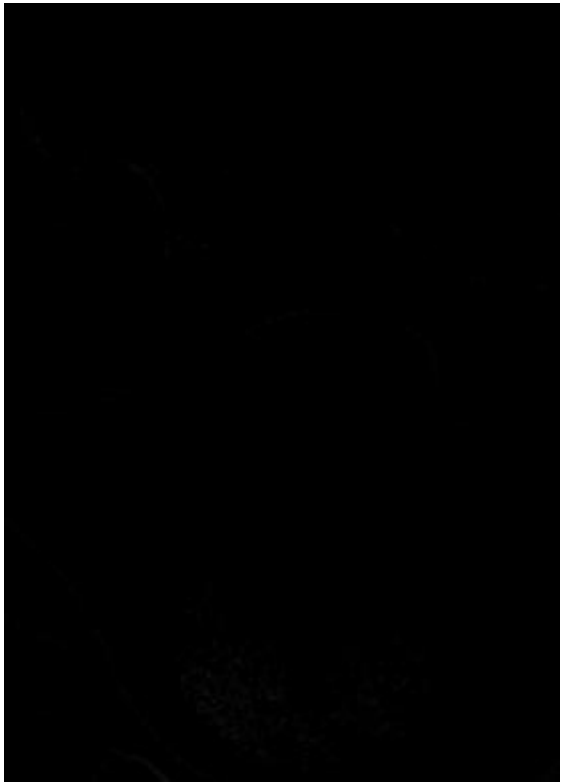
Rabbit

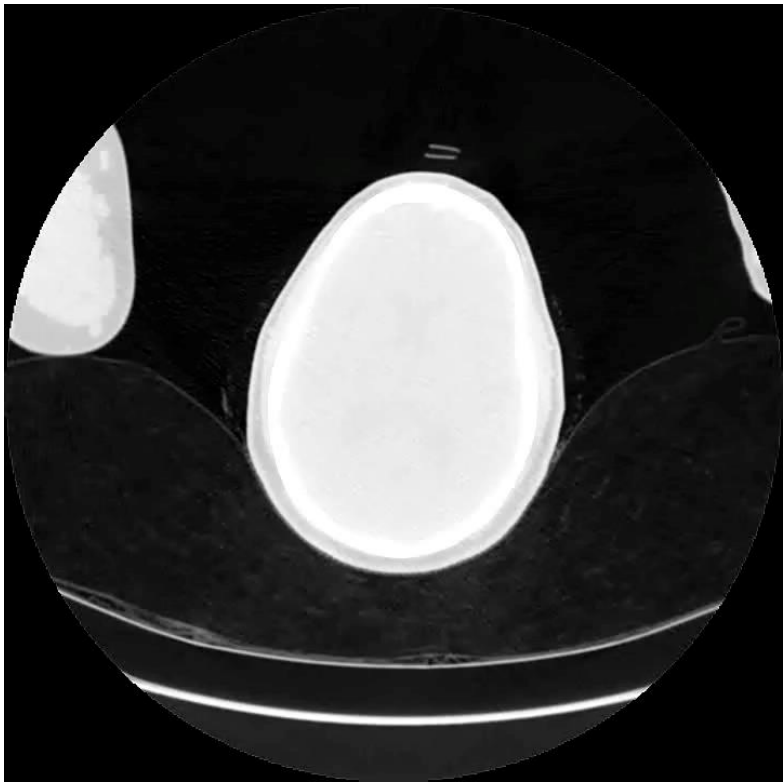


Human



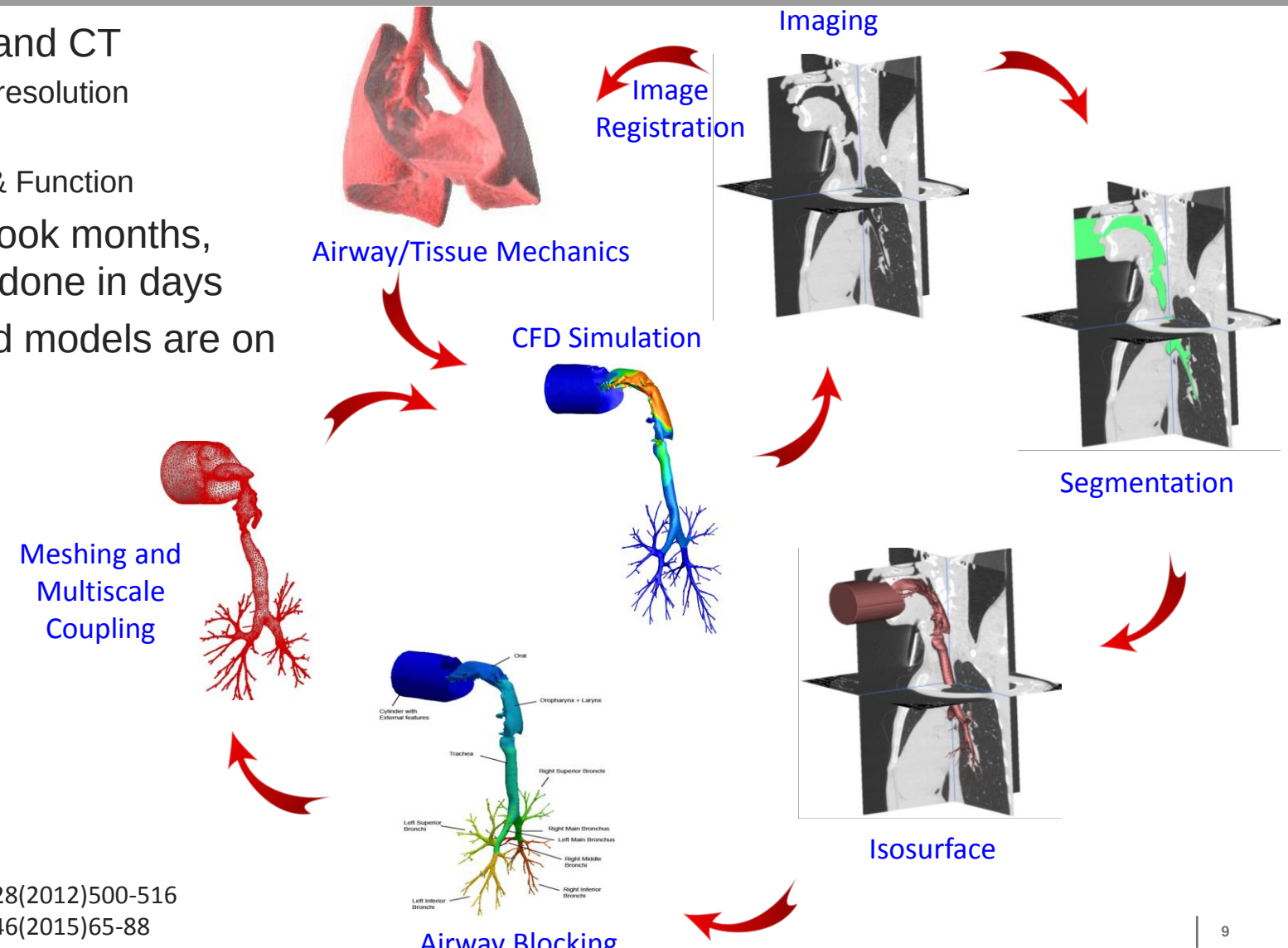






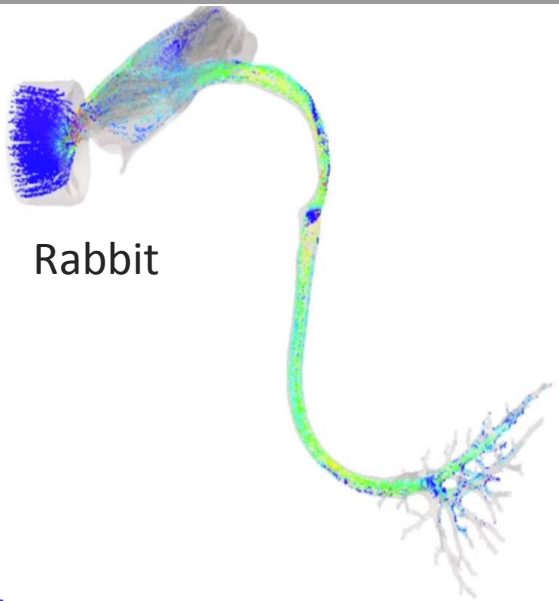
Imaging Based CFD Model Development is Now Routine

- 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

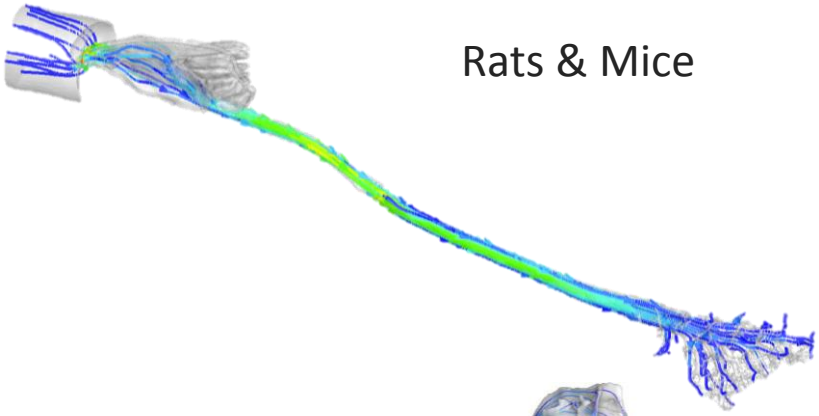


Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88
Jacob et al. Exp. Lung Res. 41(2014)135-145

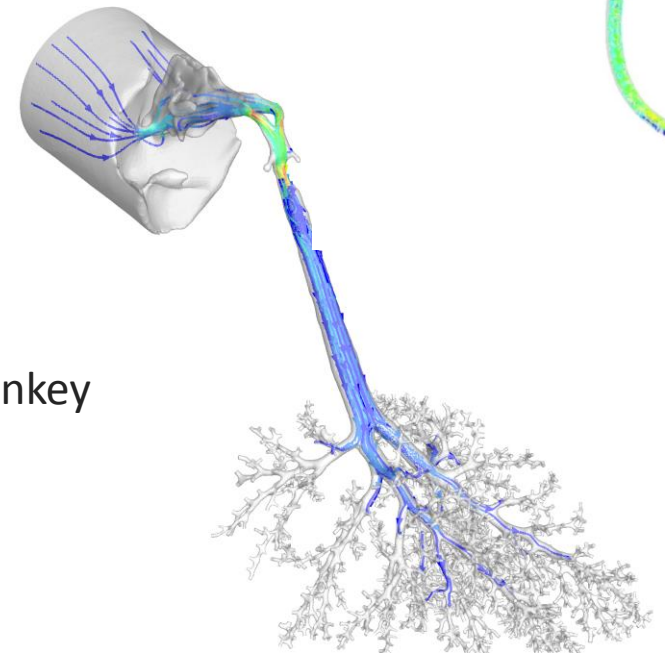
Suite of Imaging-Based CFD Models & Data Sets for Model Performance Evaluation



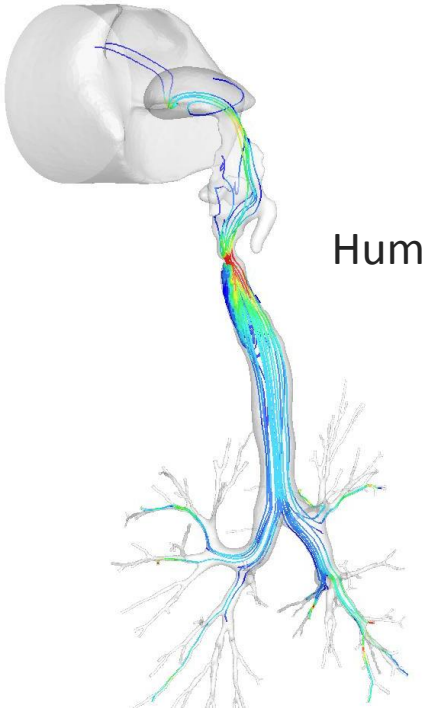
Rabbit

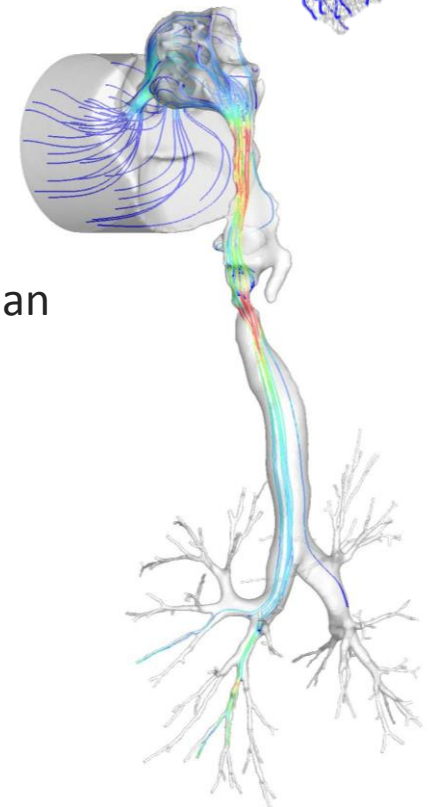


Rats & Mice



Monkey

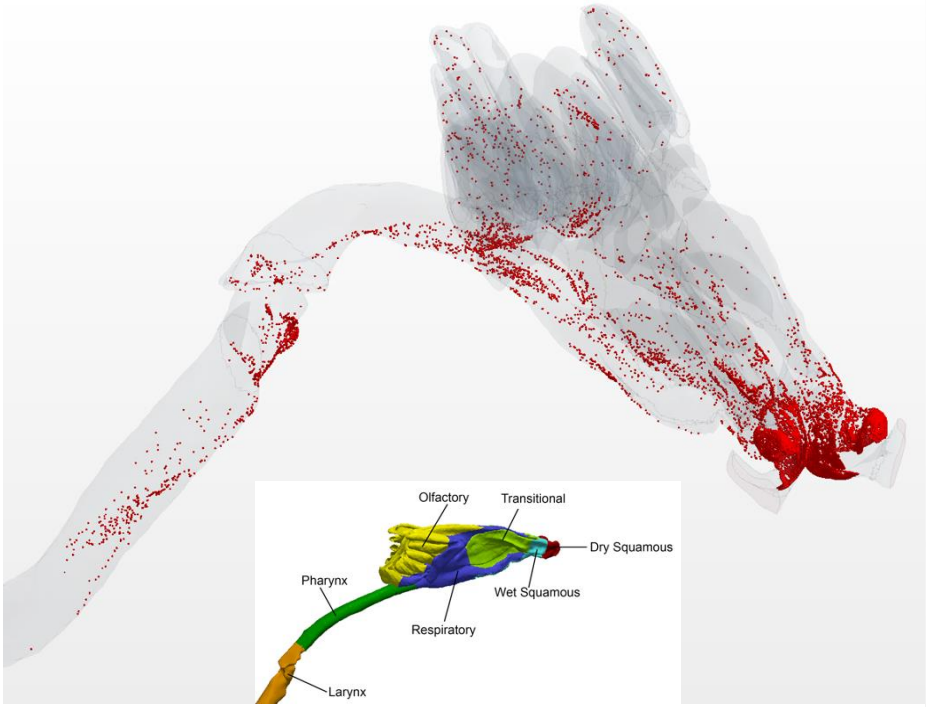




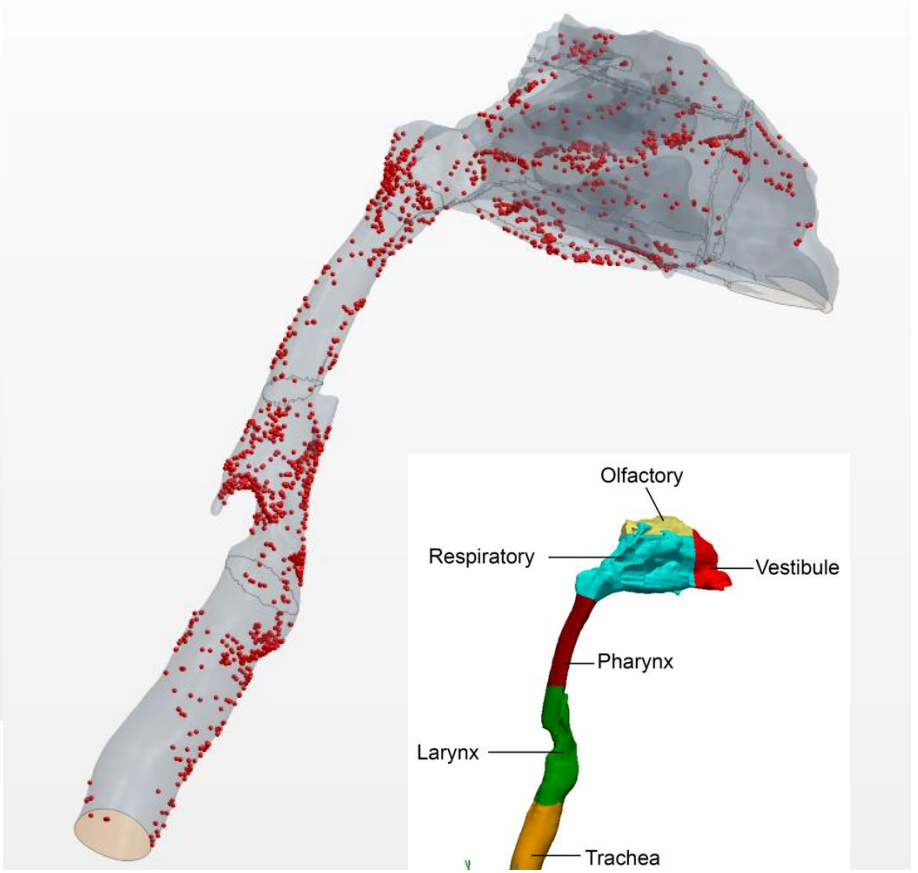
Human

Syngenta Rat vs. Human

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



58.2% inhaled deposited in nose



<1% inhaled deposited in nose

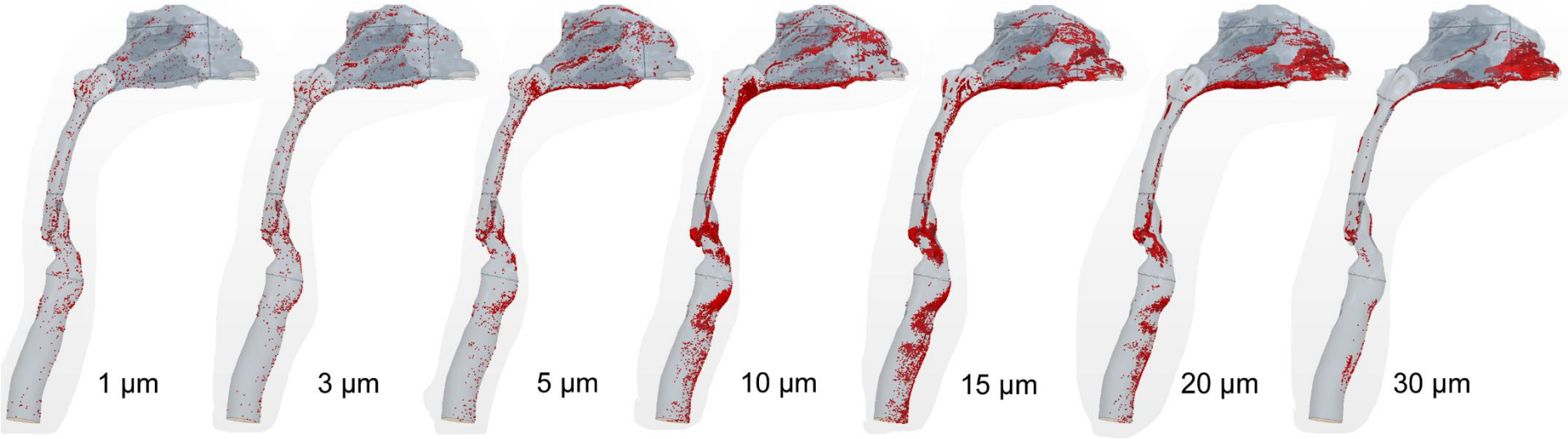
What is the Relevant Aerosol Droplet Size Distribution For Typical Agricultural Exposure?

See webinar by Dr. Paul Hinderliter for CFD-based HEC's for each aerosol size based upon human *in vitro* studies

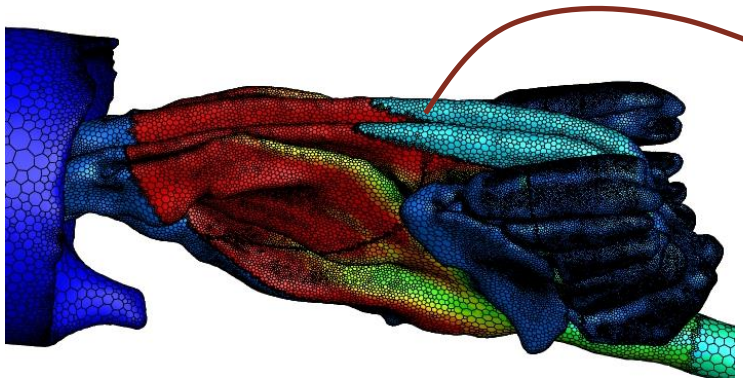
2.7 µm
Rodent Study MMAD

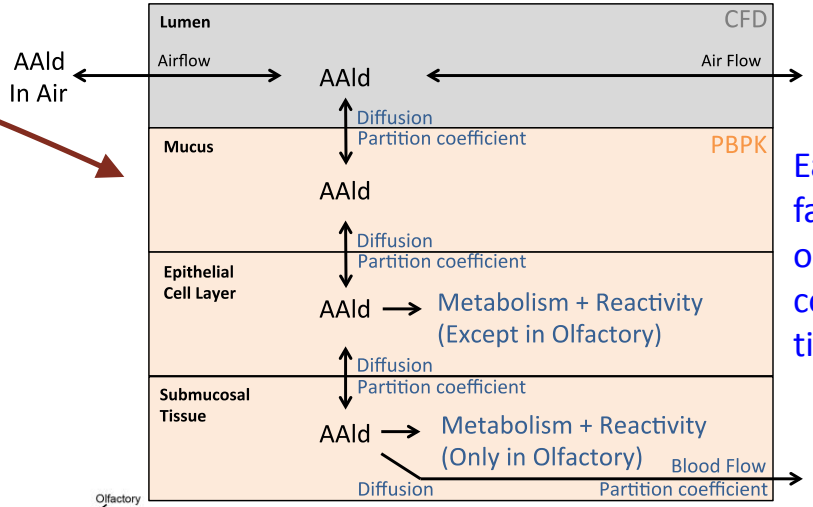
13 µm
Mixer/Loader Exposure MMAD

35 µm
Applicator Exposure MMAD



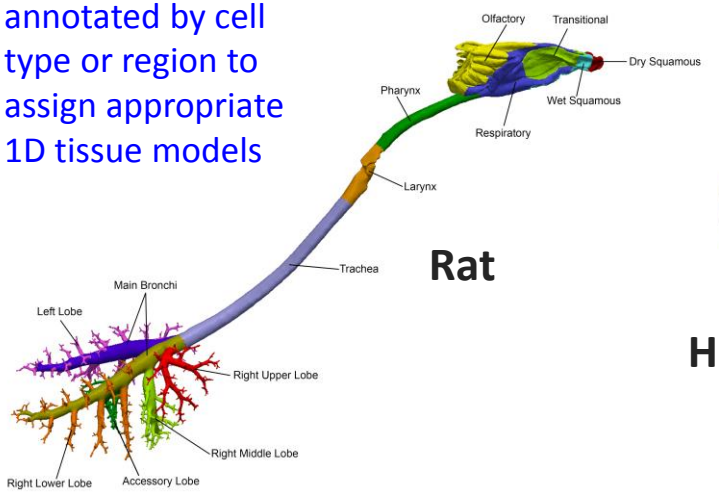
CFD/PBPK Examples for Reactive Aldehydes
(using existing models and data)

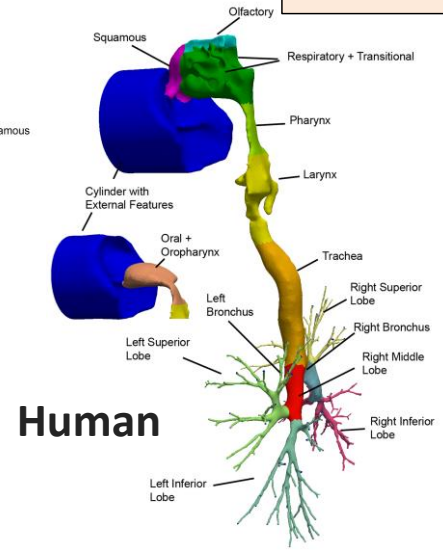


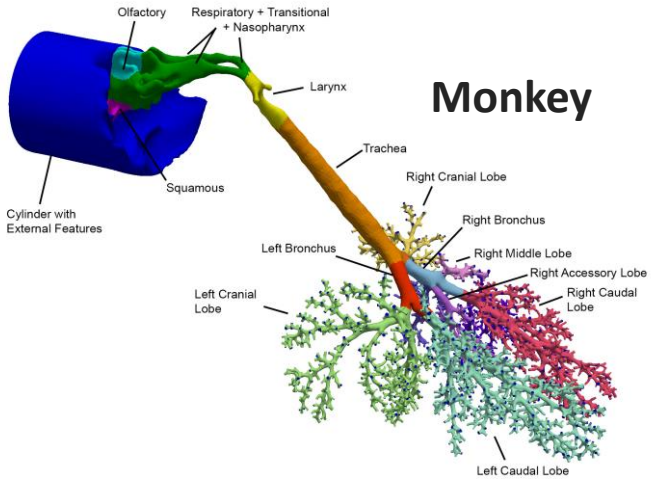


Each surface facet has it's own 2-way coupled PBPK tissue model

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



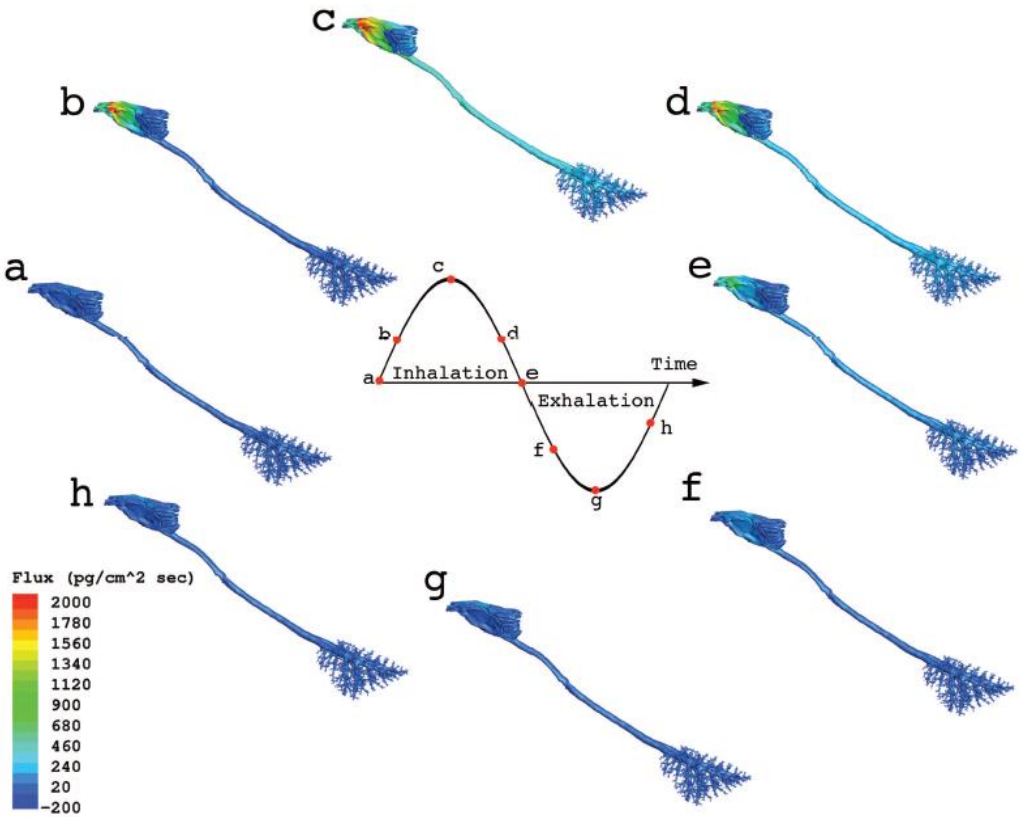


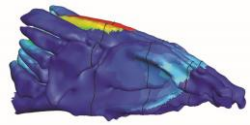


Carey et al. Toxicol. Pathol. 35(2007)27-40
Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88

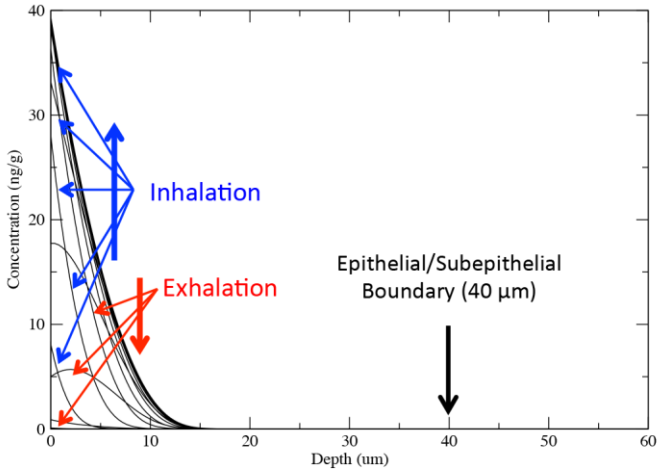
CFD/PBPK Examples for Reactive Aldehydes
CFD Simulations and Tissue Dose

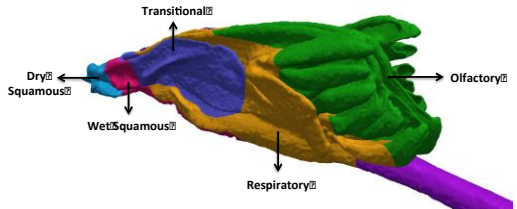
Acrolein (0.2 ppm, NOAEL)





Anterior Respiratory/Transitional

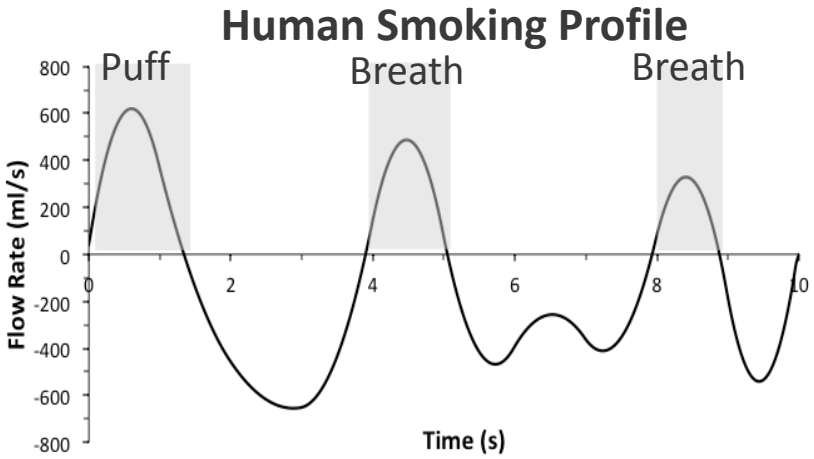




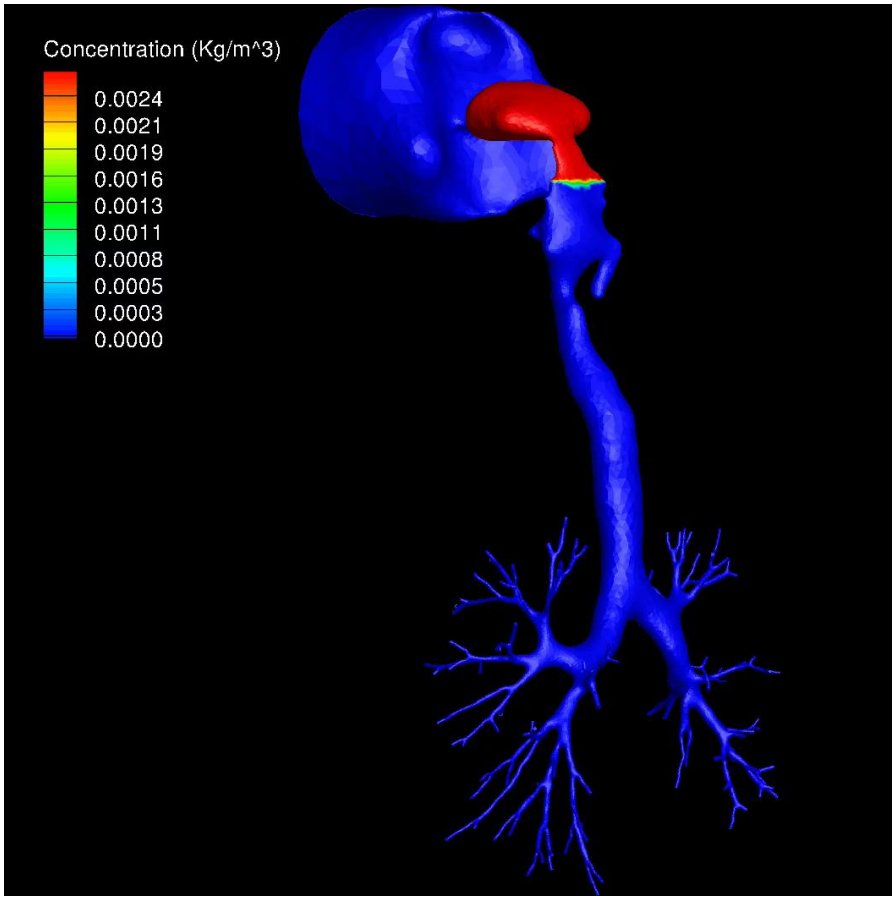
Simulation results shown for final breath once tissue dose reached periodicity (pseudo-steady-state)

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

CFD/PBPK Examples for Reactive Aldehydes
Simulation of Cigarette Puff (Oral Breathing)



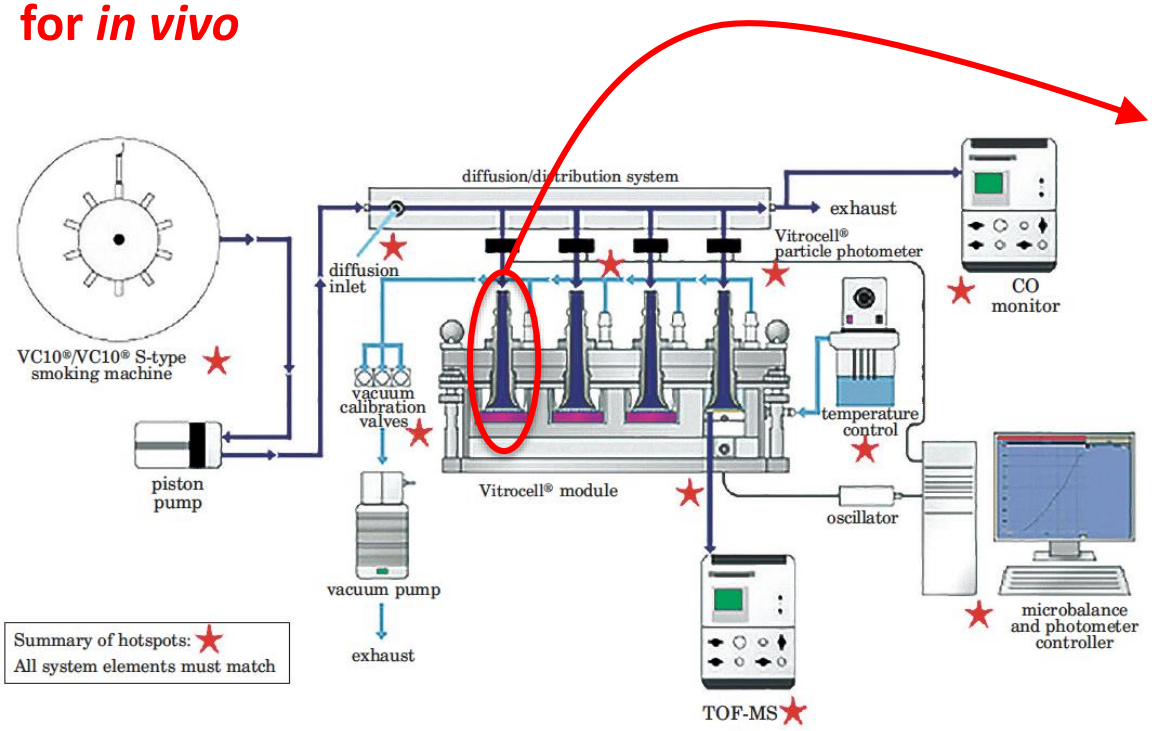
- Measured human puff profile (St. Charles et al. *Inhal. Toxicol.* 21(2009)712-718)
- Measured smoke compositions (Counts et al. *Reg. Toxicol. Pharmacol.* 41(2005)185-227) for representative puff concentrations
  - Acetaldehyde – 1028 ppm (857 µg/cig)
  - Acrolein – 94 ppm (100 µg/cig)
  - Formaldehyde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

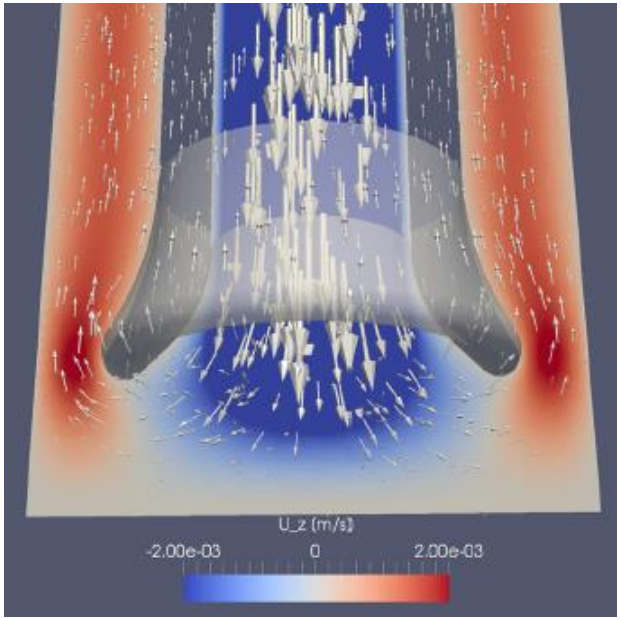


Corley et al. Toxicol. Sci. 146(2015)65-88

CFD Modeling of Vitrocell® Aerosol Exposure System (https://www.vitrocell.com)

Understanding "Delivered Dose" is just as critical for *in vitro* exposures as it is for *in vivo*





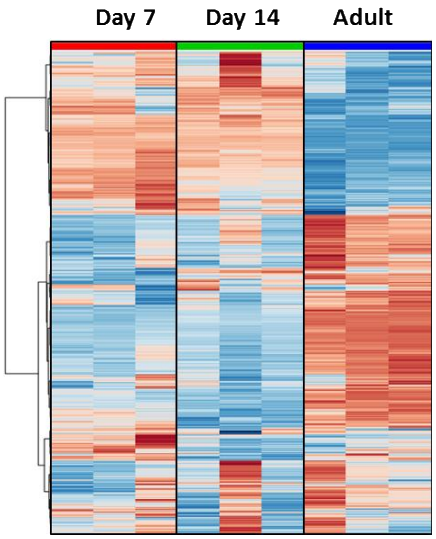
Behrsing et al. (2017) ATLA 45, 117-158

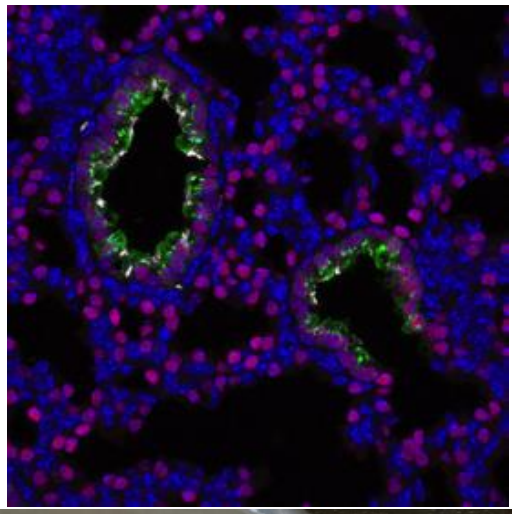
Lucci et al. (2018) J. Aerosol. Sci. 123, 141-160

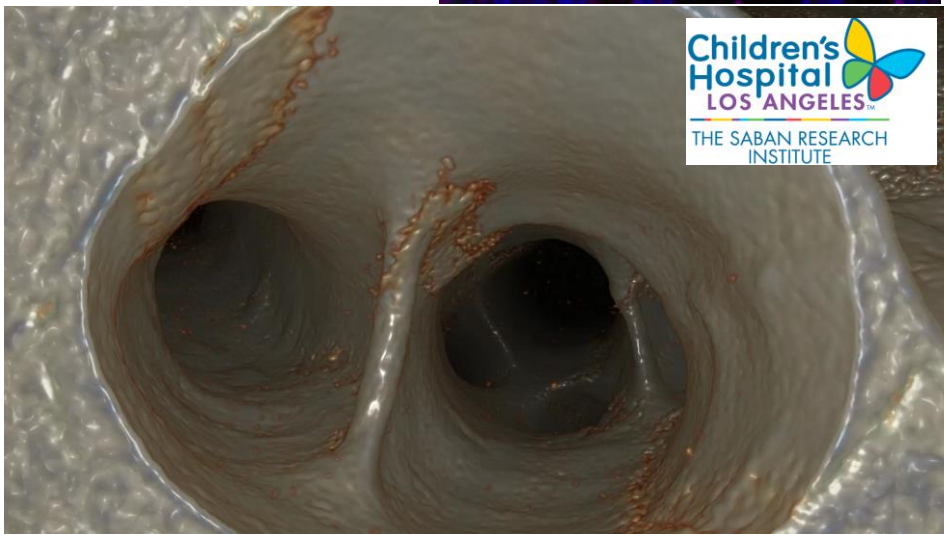
NHLBI LungMAP Consortium
www.lungmap.net

LungMAP
Molecular Atlas of Lung Development Program

- Create an open-access reference resource and comprehensive molecular atlas of the late-stage developing lung
  - Utilize state-of-the-art molecular and imaging technologies to **map and annotate the cell types of the developing mouse and human lung**
- Fill the knowledge gap in molecular/cellular events that drive lung development (**alveologenesis**) and cell function
- Provide tissues, reagents and data to the medical research community





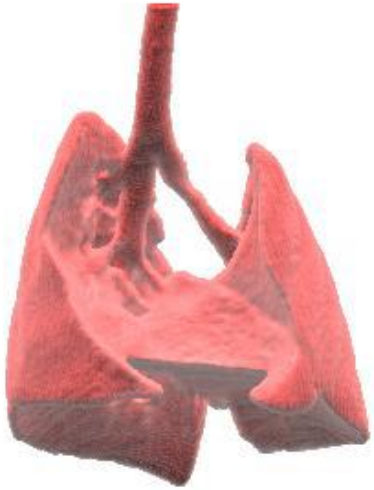


Children's Hospital LOS ANGELES
THE SABAN RESEARCH INSTITUTE

NIH National Heart, Lung, and Blood Institute

Summary of Key Concepts

- Time to develop 3D CFD 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
- 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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*Current Location

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