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
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

- 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, cytotoxicity/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

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

Each surface facet has its own 2-way coupled PBPK tissue model.

Corley et al. Toxicol. Sci. 128(2012)500-516
Ex 1: CFD/PBPK for Reactive Aldehydes
Surface Flux vs. AUC Tissue Concentrations

Acetaldehyde
(Rat NOAEL = 50 ppm)

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

  - 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
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

- CFD Modeling
- Particle Size Distribution of Inhalable Particles
- Inhalation Exposure

• 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
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

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<th>Diameter (µm)</th>
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</table>
• 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

HEC

Risk Characterization

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

~35-55% Particles Exhaled

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

Disease

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
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

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

Continuous Exposure

No Differences in Total Deposition with COPD

0.75 L/s Flow rate

Nasal Breathing

Oral Breathing

Aerosol Bolus Test

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

Bolus Parameters:
Deposition = \(1-\frac{AUC_{\text{ex}}}{AUC_{\text{in}}}\)
Dispersion = \(\left(\frac{H_{\text{ex}}^2 - H_{\text{in}}^2}{0.5}\right)\)
Mode Shift = \(M_{\text{ex}} - V\)

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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