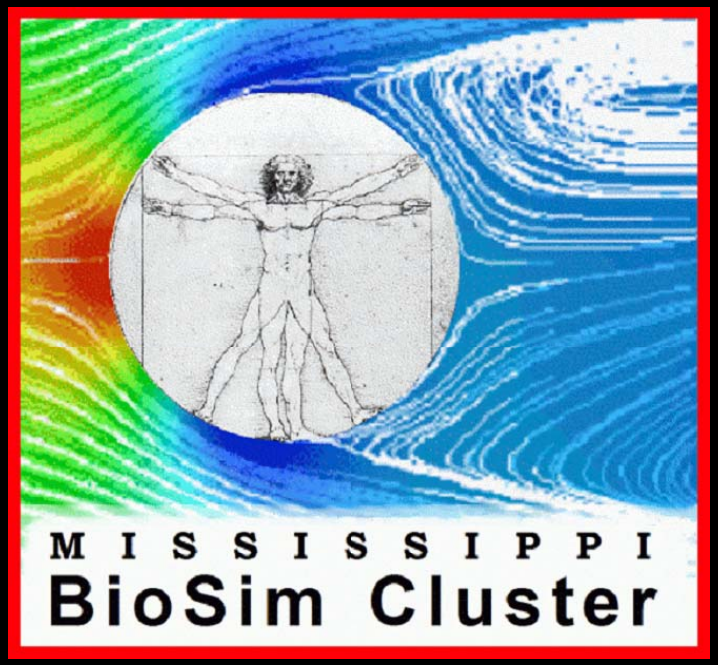
Research Area: Computational BioSimulation

Multi-Scale Biosystem Simulation/Modeling



Participants:

Mississippi State University

Jackson State University

University of Mississippi Medical Center

Senior Personnel

Greg Burgreen, MSU
David Thompson, MSU
Keisha Walters, MSU
Keith Walters, MSU

Thomas Coleman, UMC
Robert Hester, UMC
Richard Summers, UMC

Shahrouz Aliabadi, JSU

BioSim Cluster Long-Term Goals

1. Develop nationally recognized and respected multi-institutional programs of excellence in biosystem simulation.
2. Develop national expertise in multi-scale modeling for biological simulations.
3. Develop accurate models of physiological behavior and apply those models to realistic biosystem problems having clinical significance.

Objectives of Current RII

1. Establish an intra- and inter-institutional teaming arrangement among investigators from multiple disciplines, with a focus on computational modeling and biological systems.
2. Develop new and innovative modeling/simulation technologies needed to address multidisciplinary problems of significant scientific and societal impact.
3. Identify opportunities for the synthesis and integration of different (and often disparate) simulation techniques and tools to create next-generation multi-scale, multi-architecture simulation tools.
4. Provide educational and research opportunities for students (grad/undergrad/K-12) and others (K-12 teachers) to enhance the development of future computational science researchers.

Technical Approach

1. Driven by directed research

   - Real-world applications should actively drive our basic research.

2. Focus on interdisciplinary research

   - Combine High Performance Computing (HPC) results with desktop-based results (multi-architectural)

   - Combine high-fidelity simulations at *structure to organ* level with macro-scale models at *system to organism* level (multi-scale)

3. Three driving research projects:

   - Multilevel Integrative Model of Human Physiology

   - Fluid Dynamics of Lung Respiration and Meso-Scale Aerosol Deposition

   - Multi-Scale Simulation of Bioartificial Liver Device

Technical Organization

Integrative Model of Human Physiology

UMC, MSU

System/Organism Level Simulation

Desktop Architectures

Lung Fluid Dynamics and Aerosol Deposition

MSU, JSU, UMC

Multi-Scale Simulation of Bioartificial Liver

MSU, UMC

Structure/Organ Level Simulation

High Performance Computing

Surface Property Modeling for Lung Deposition

MSU

Advanced Algorithm Development

JSU, MSU

Support Activities

Summary of 2008 Accomplishments

1. Seven (7) archival journal publications arising directly out of the EPSCoR project
2. Four (4) conference proceedings papers and/or posters arising directly out of the EPSCoR project
3. Twenty-nine (29) proposals submitted totaling $15.5 M
4. Fifteen (15) proposals awarded totaling $2.2M
5. Six (6) graduate students and research associates supported
6. Eight (8) undergraduate researchers supported
7. Fifteen (15) undergraduate students, ten (10) K-12 teachers, and twelve (12) high-school students directly impacted by outreach activities.

Research Area Highlights

Integrative Model of Human Physiology

Fluid Dynamics of Lung Respiration and Meso-Scale Aerosol Deposition

Large-Scale Simulations of Airflow in the Bronchopulmonary Tree

Physicochemical Modeling of Lung Surface/Particle Interactions

Efficient Parallel Algorithms for Large-Scale CFD Simulations

Modeling of a Bioartificial Liver (BAL) Device

Advanced Numerical Methods for Multi-Phase Flows

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Integrative Model of Human Physiology (UMC, MSU)

Key Senior Personnel:
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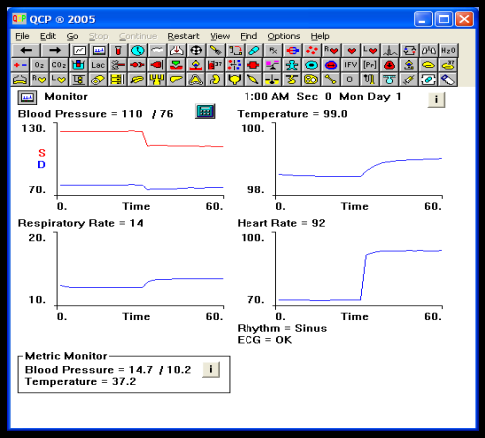


Objective/Overview:
Develop web-based, highly-accessible software and a component-based modeling library, Quantitative Human Physiology—QHP, such that scientists are enabled to build specialized physiological models in their area of interest.

QHP is a dynamic mathematical macro-scale model of over 20 organ and organ systems describing circulation, respiration, metabolism, hormones, neural control, body fluids, and kidney and temperature regulation.

Technical Collaboration:
The QCP modeling software was originally developed at UMC, and is being enhanced as part of this effort by UMC researchers. Ongoing technical discussion between UMC and MSU researchers is being used to guide the development so that future integration of the QHP model with HPC simulations will be seamless.

Evolution of Integrative Model

QCP (Quantitative Circulatory Physiology)

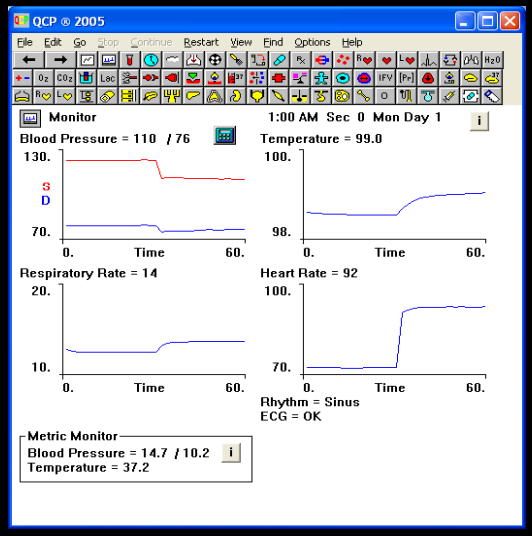
- Desktop (PC-based) application
- 4000 variables & equations
- Time-dependent simulations

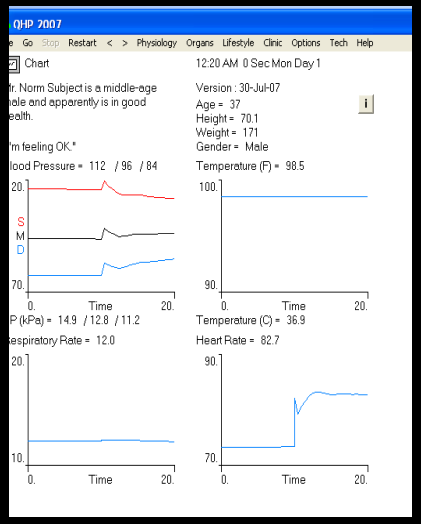
QHP (Quantitative Human Physiology)

- XML-based model descriptions
- XML allows passing of parameter
- Interaction with HPC simulations

Development of Physiological Responses

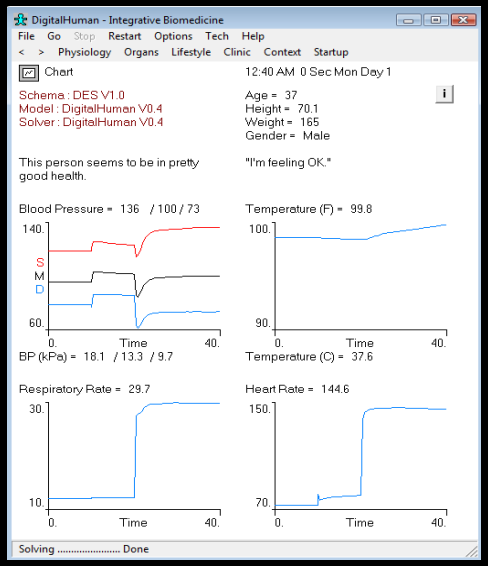
- Weightlessness and bone density (NASA)
- Regulation of human metabolism





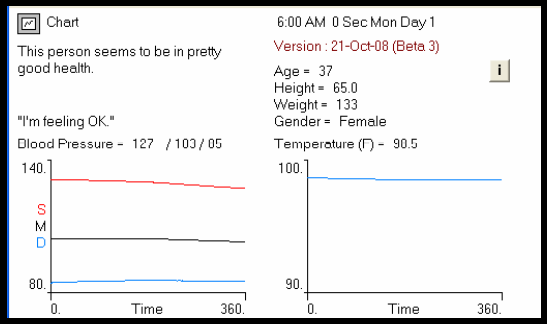
Current QHP Version—DigitalHuman

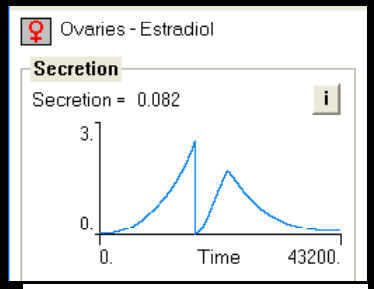
Currently DigitalHuman (DH) has over 5000 equations describing a variety of physiological responses

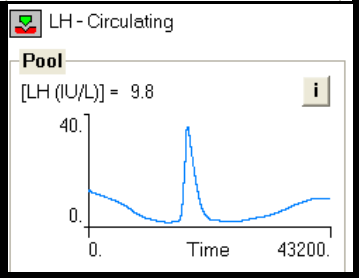


Gender Specific Modeling

- Original QHP based on male physiology
- Detail and scaling has been added to provide basis for simulating both sexes
- Example: ovarian secretion of estradiol, under cyclic LH control for one month







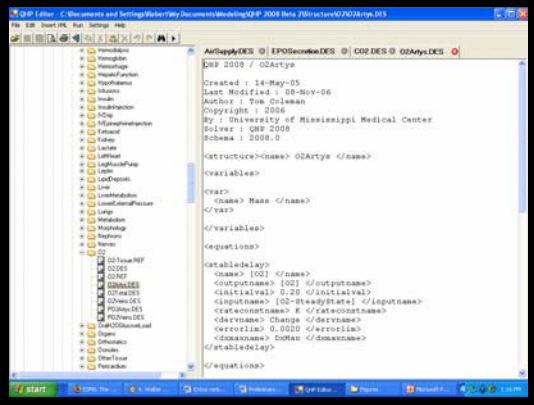
Current QHP Version—DigitalHuman

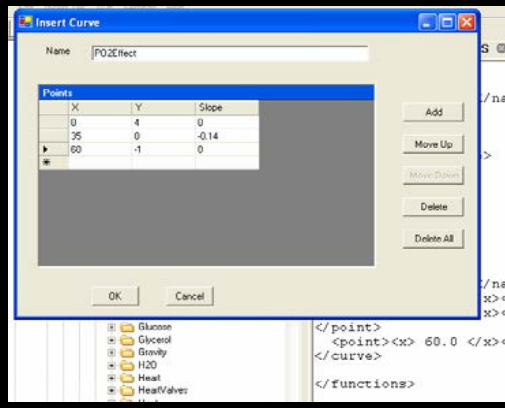
DigitalHuman Editor

XML model files can be written with any text editor

An editor specific to the needs of DH has been developed

File functions similar to most editors

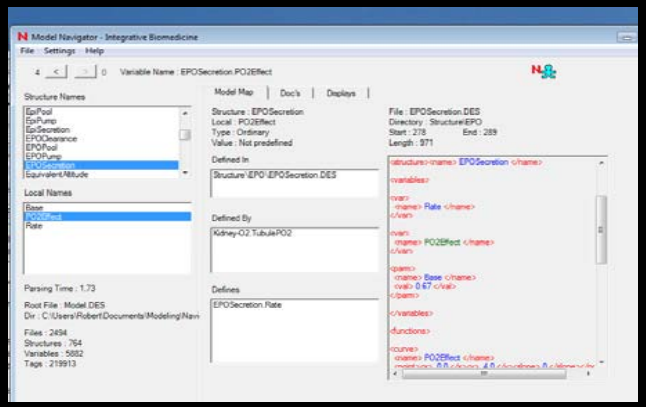




DigitalHuman Model Navigator

Facilitates understanding of DH structure

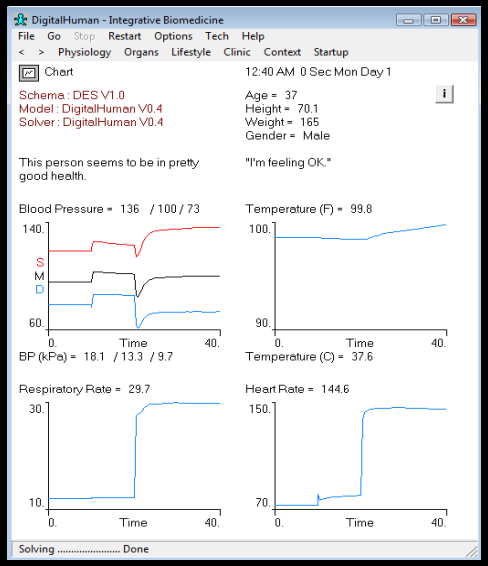
Allows user to clearly see all relationships among variables



Example DigitalHuman Simulation

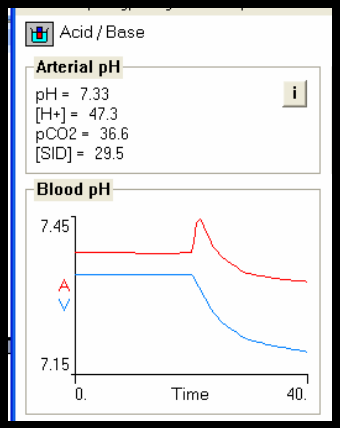
Response of Healthy Individual to:

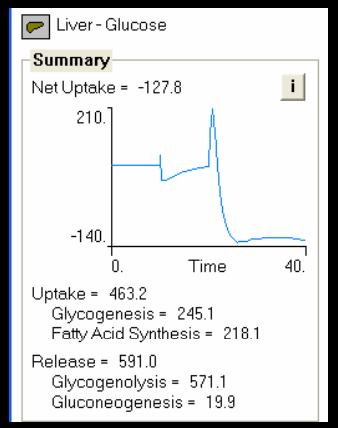
- 10 minutes lying down
- 10 minutes standing
- 20 minutes exercise—200 watts on an exercise bike

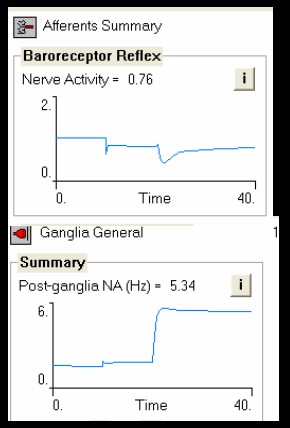


Figures at right show:

- Cardiovascular response
- Acid-base balance
- Liver metabolism
- Neural activity







Fluid Dynamics of Lung Respiration and Meso-Scale Aerosol Deposition (MSU, JSU, UMC)

Key Senior Personnel:
David Thompson, MSU
Keith Walters, MSU
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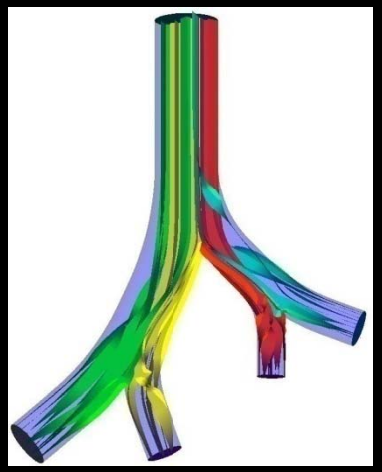
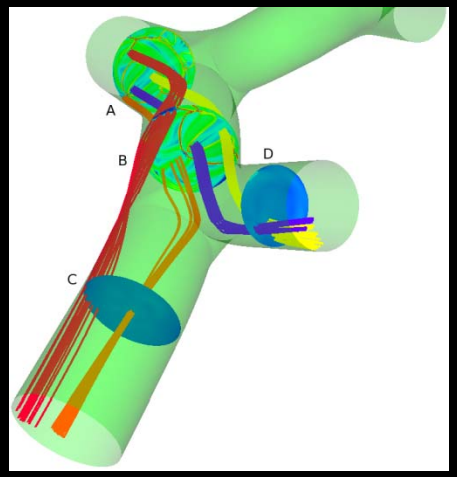




Objective/Overview:
Develop models and tools that facilitate simulation of aerosol deposition dynamics in the meso-scale structures of the human lungs.

Overall simulation methodology employs computational representation of complex geometry, high resolution unstructured mesh capability, state-of-the art high-resolution computational flow solvers, coupled flow and particle motion (multi-phase) simulation.

Technical Collaboration:
The simulation techniques and modeling methodologies used in this project are being jointly developed by researchers at MSU and JSU. Key input and output parameters have been determined to facilitate future integration into the QCP macro-scale model.

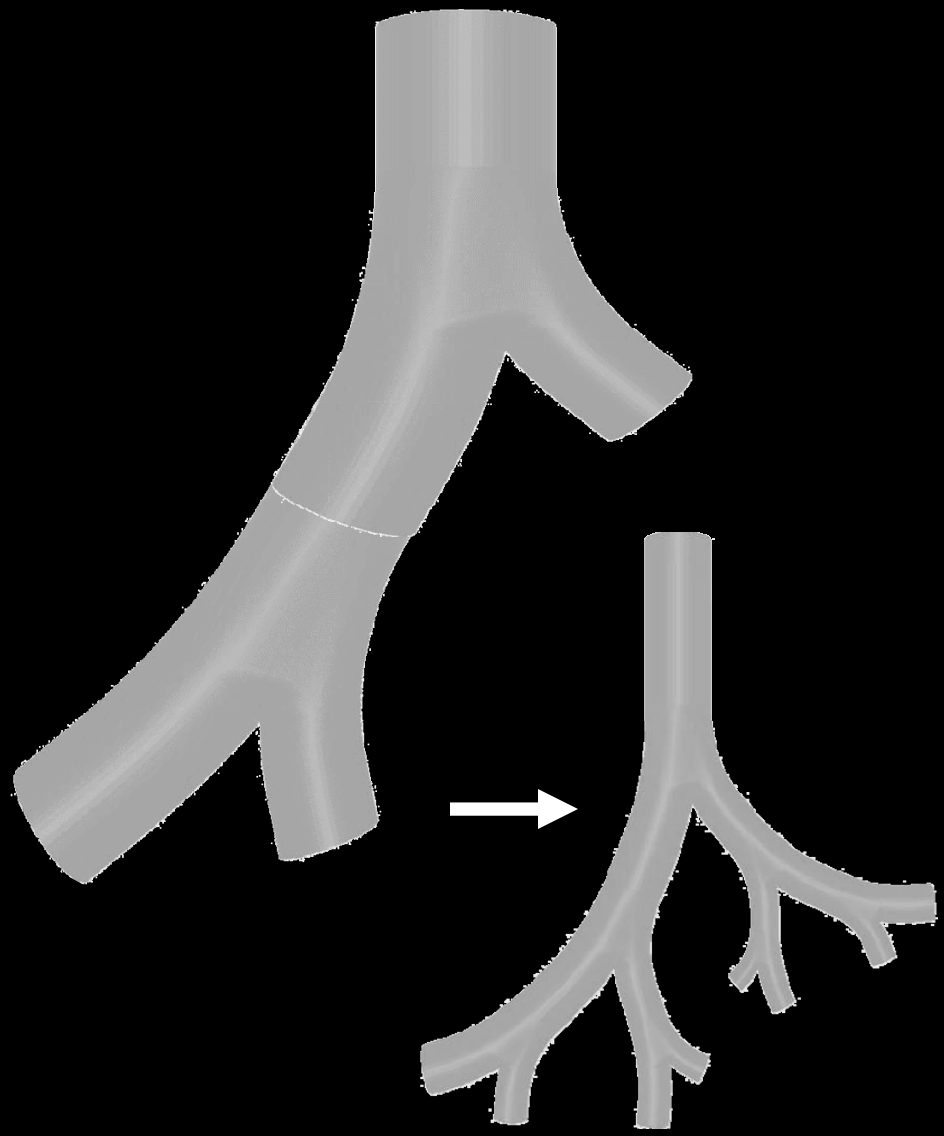
Computational Model for Small Bronchial Tubes

Fundamental unit of Hammersly and Olson – two generations: parent and two daughter tubes

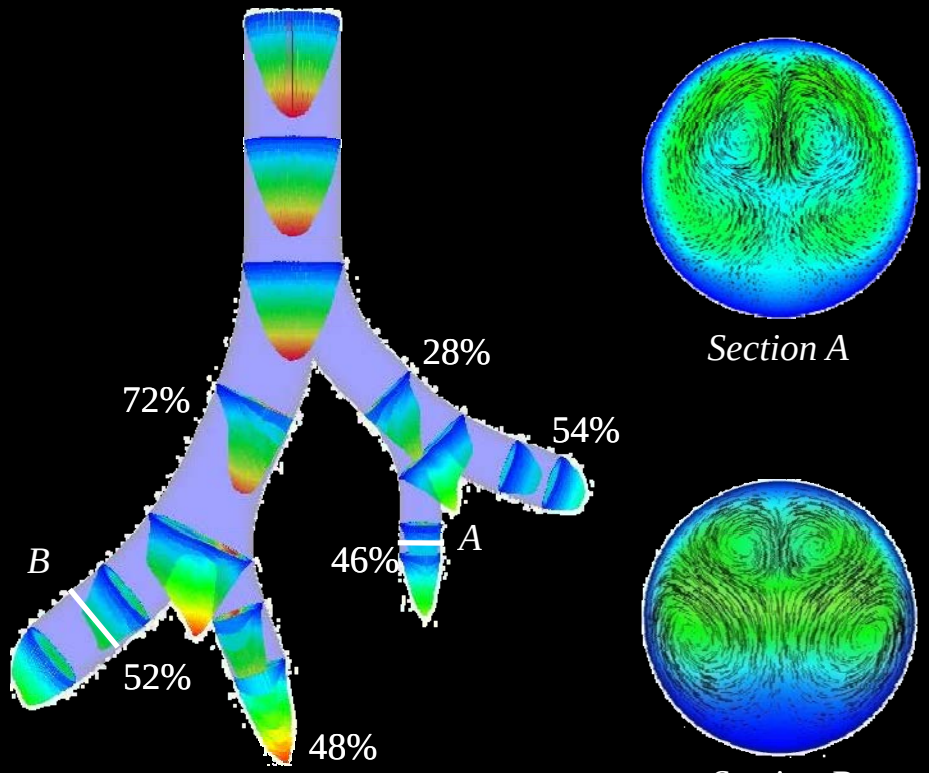
Synthetic multi-generation bronchial tube models can be constructed by adding appropriately scaled fundamental units to the exits of a fundamental unit.

How important are the simultaneous effects of asymmetric and nonplanar branching on the resulting flow fields and on particle deposition?

What are the implications for modeling?



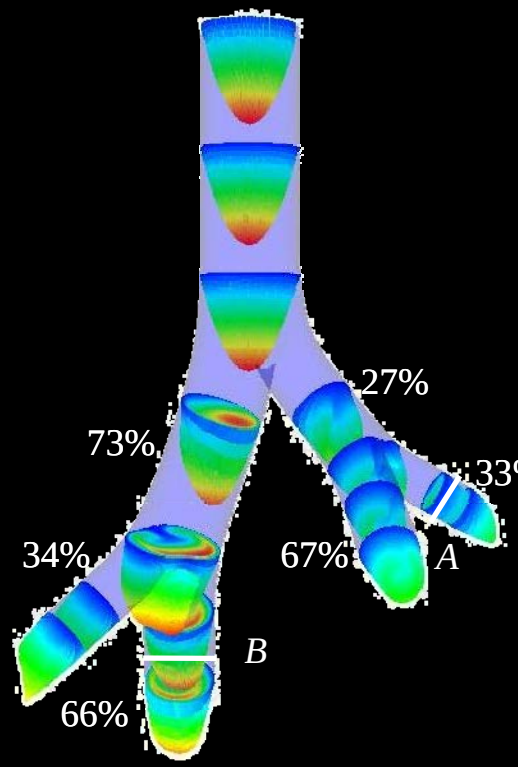
Flow Field Simulation – Primary and Secondary Flows

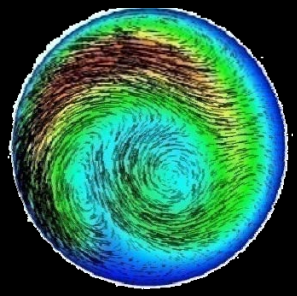


Section A

Section B

Planar





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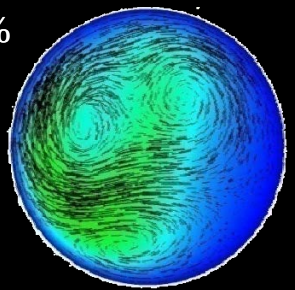
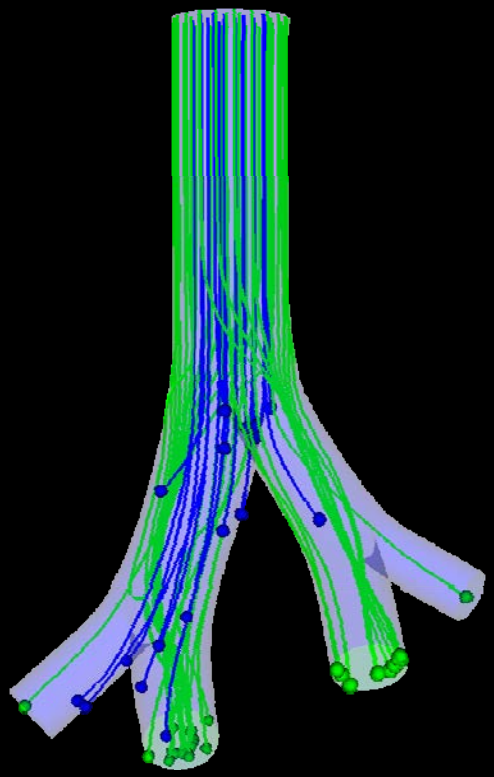


Section B

Non-Planar

Particle Trajectories – 10μ Water Droplets

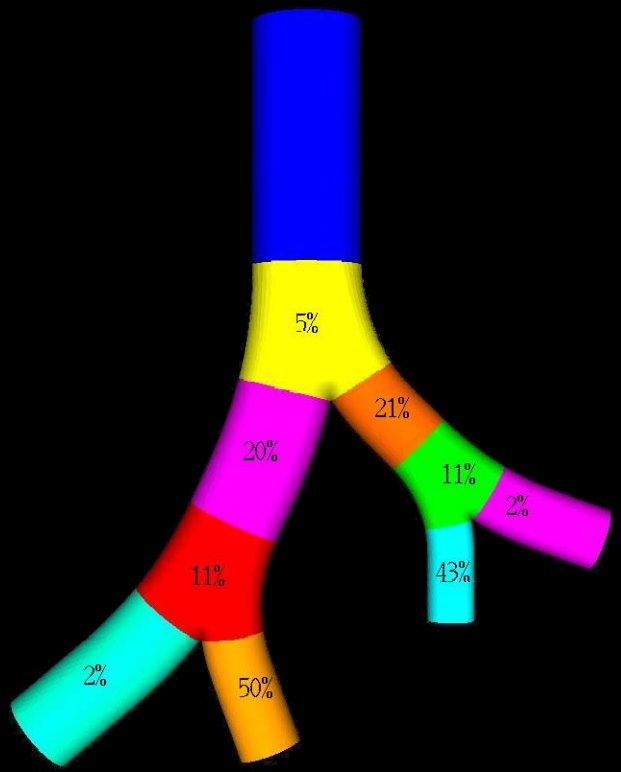
Planar



Non-planar

Green trajectories exit domain
Blue trajectories impact wall

Particle Deposition Efficiency – 10μ Water Droplets



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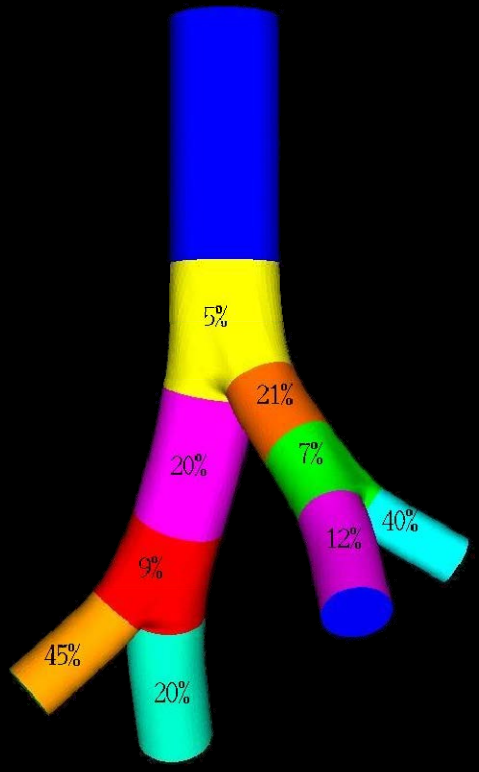
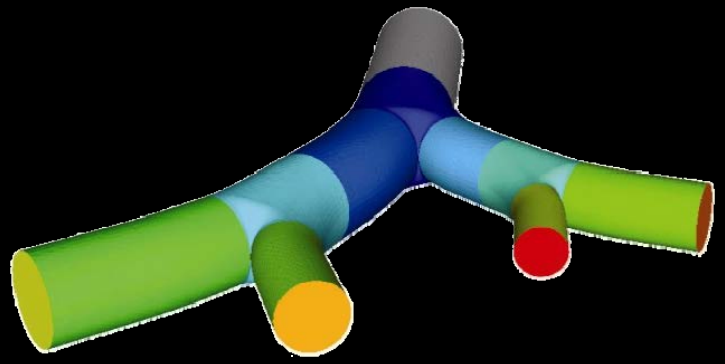


Non-planar

Percentage of particles entering a region that are deposited in the region.

Destination Maps and FTLE Maps – 10μ Water Droplets



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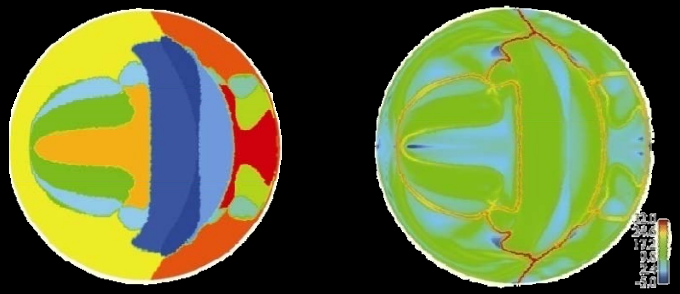
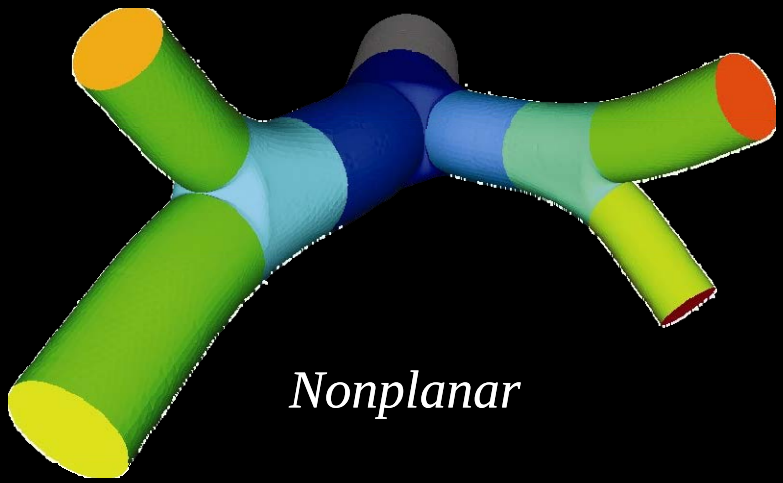
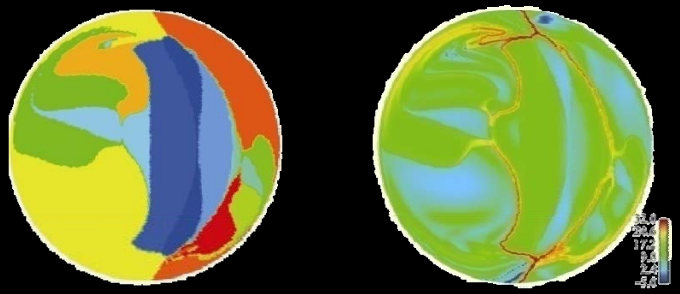


Destination map (left) and FTLE map (right) at inlet

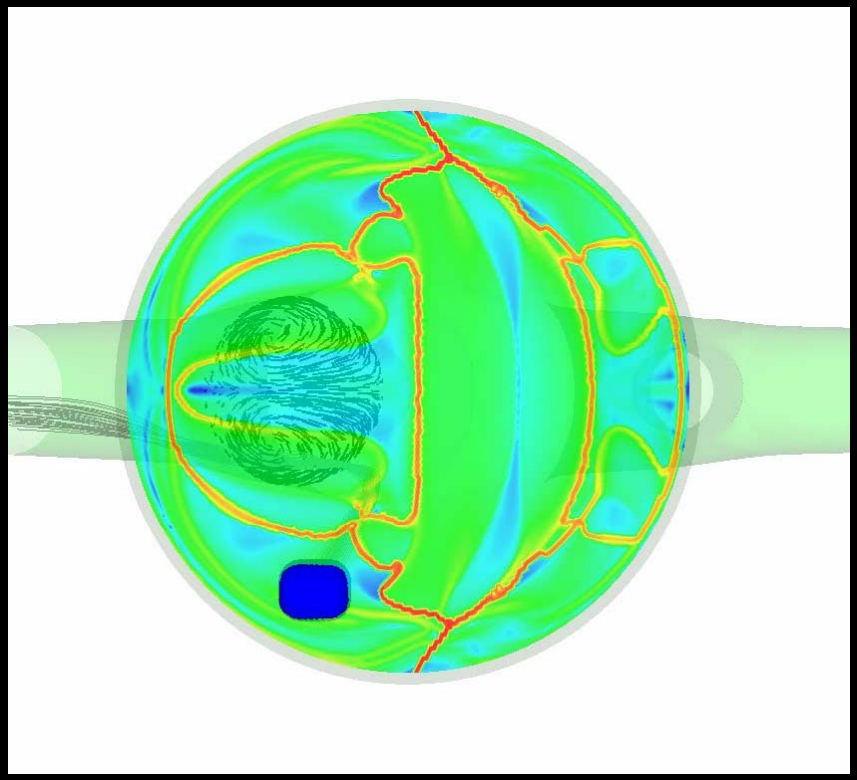


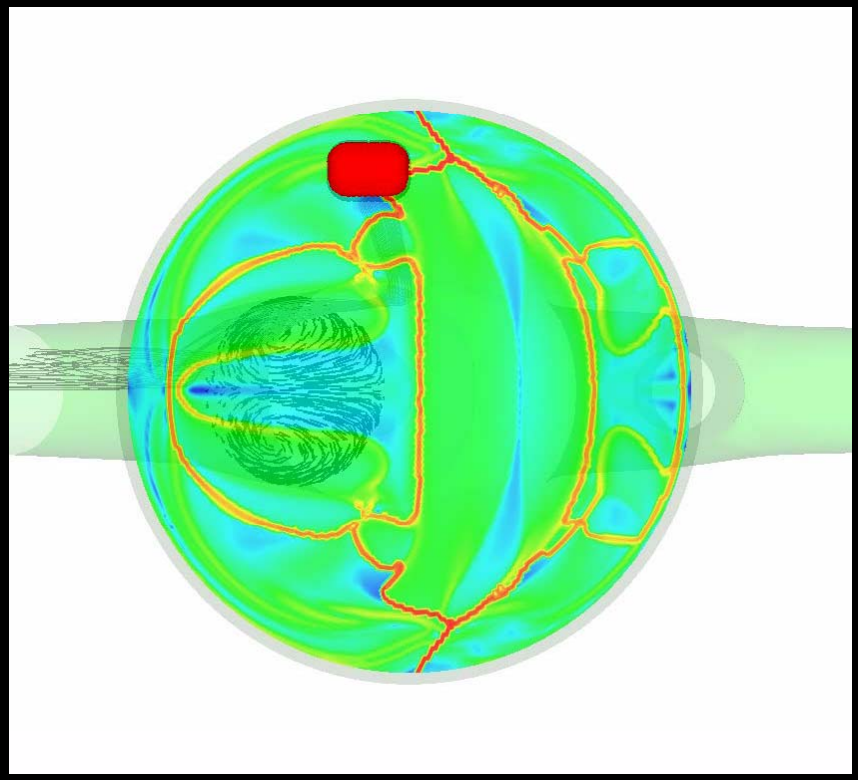
Nonplanar



Destination map shows region where particles are deposited and FTLE map shows particle dispersion (high values) or coherence (low values). See poster for more details.

Interactions of Particles with Vortices

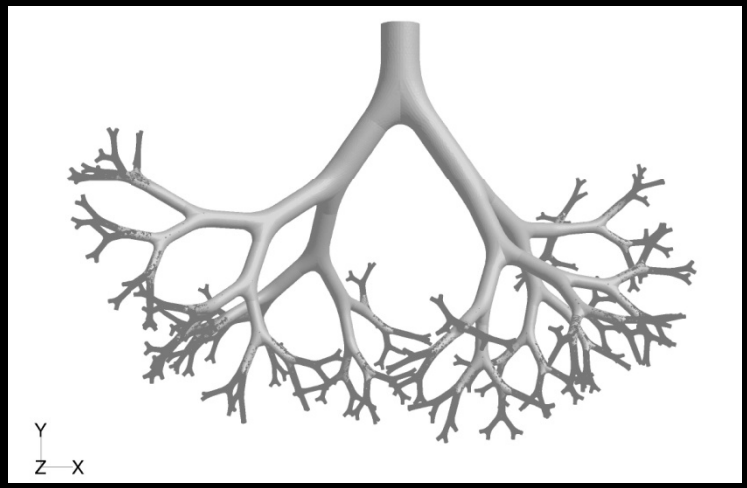




Particles that pass through core region of vortices are less dispersed because of reduced centripetal acceleration (blue region on left). Particles that pass outside of core region are more dispersed due to increased centripetal acceleration (red region on right).

Large-Scale CFD Simulations of Airflow in the Bronchopulmonary Tree (MSU, UMC)

Key Senior Personnel:
Keith Walters, MSU
David Thompson, MSU
Robert Hester, UMC



Objective/Overview:
Develop computational simulation methodologies that effectively model large-scale sections of the bronchopulmonary tree, up to and including simulations of the entire lung airway.

Current strategies in the literature use three-dimensional Navier-Stokes simulation of the larger airways coupled with simple empirical or one-dimensional models for the smaller (pulmonary) regions. The approach developed here utilizes a flow path ensemble (FPE) comprised of several distinct pathways, and stochastically coupled boundary conditions to accurately reproduce a virtual geometry for the large-scale system.

Technical Collaboration:
The flow in the lung airway is strongly coupled across all scales. Large-scale simulation techniques will allow the detailed, high-resolution particle deposition simulations to be effectively coupled with the high-level integrative model of human physiology.

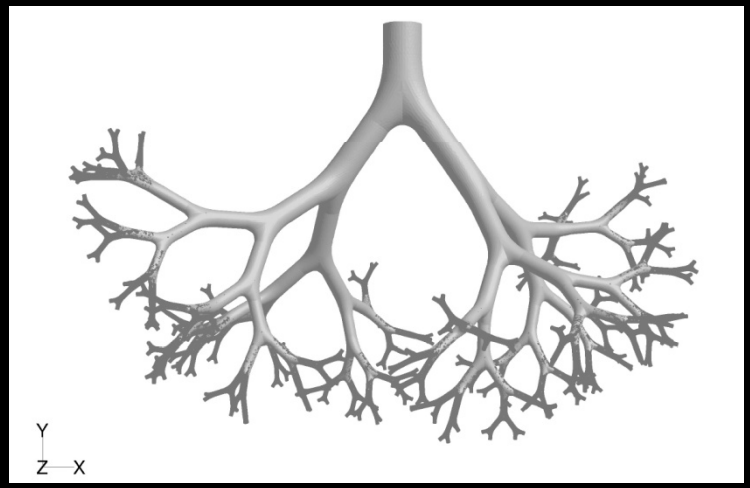
Flow Path Ensemble Method

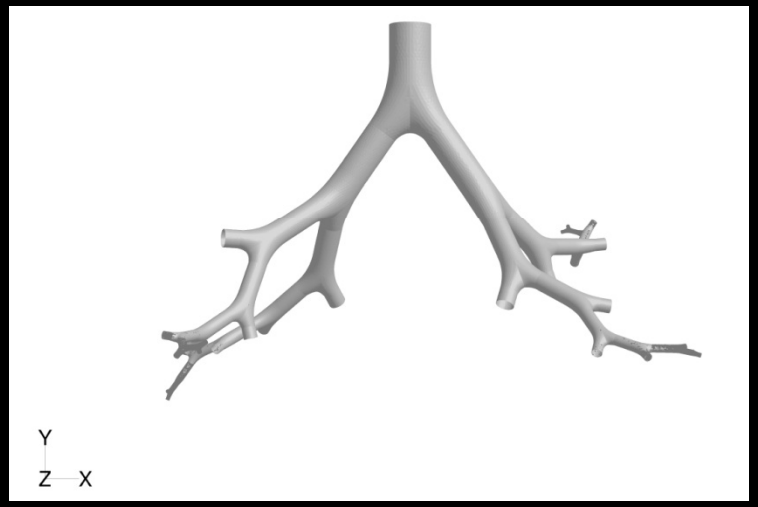
Finite number of distinct flow paths are retained in order to provide three-dimensional model representation at all scales

- Small airways represented using symmetric, non-planar branching generations

Boundary conditions at "cut segments" are obtained from equivalent locations in the resolved flowpaths and applied randomly

- Result is a "virtual geometry" in which the small scales are well represented provided a sufficient numbers of flow paths are retained

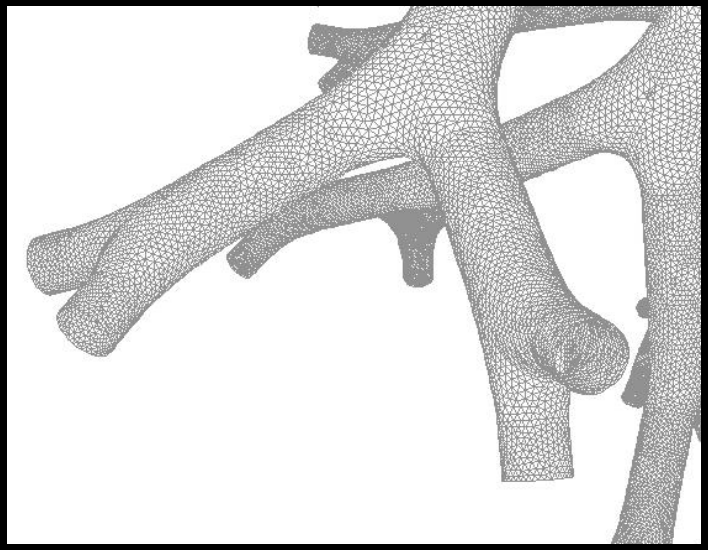




Flow Path Ensemble Method

Why not just simulate the entire lung airway geometry?

- 23-generation bronchopulmonary tree contains over 16 million branch segments
- Computational resources capable of simulations for research and clinical applications are estimated to be 30 years away



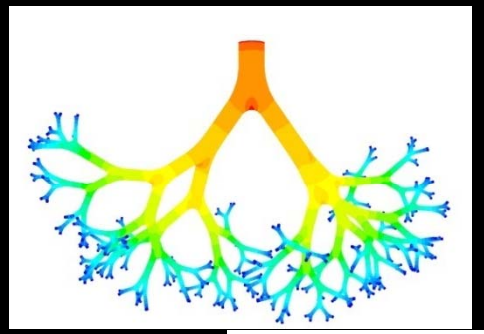
The FPE method allows a virtual geometry that provides accurate statistical information with a dramatic reduction in computational expense

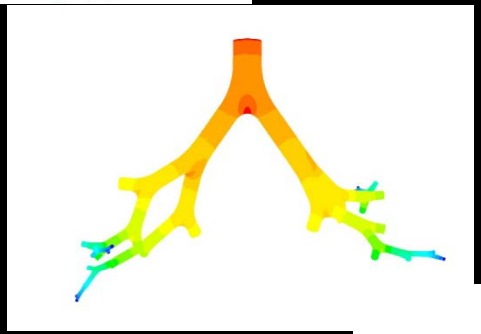
Model	Bifurcations	Mesh Size (Nodes)	% CPU / Memory
Full Geometry	8,388,607	3.6×10^{11}	100%
16 Path	319	14×10^{6}	0.004%
64 Path	1151	50×10^{6}	0.014%
256 Path	4095	176×10^{6}	0.049%

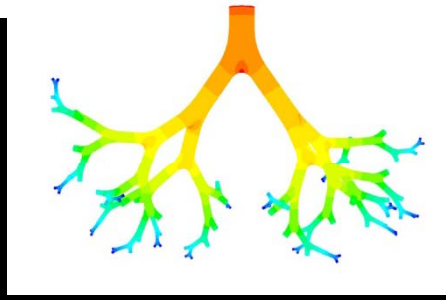
Test Case: Airflow in 8-Generation Section

Simulated steady inspiratory flow at 333 cm^3/s

- FPE models reduced computational expense between 81% and 94%
- Impedance (pressure drop) error for models with stochastic coupling range from 1.32% to 0.08%
- Comparable error for FPE with constant pressure boundary conditions ranges from 37.8% to 58.6%







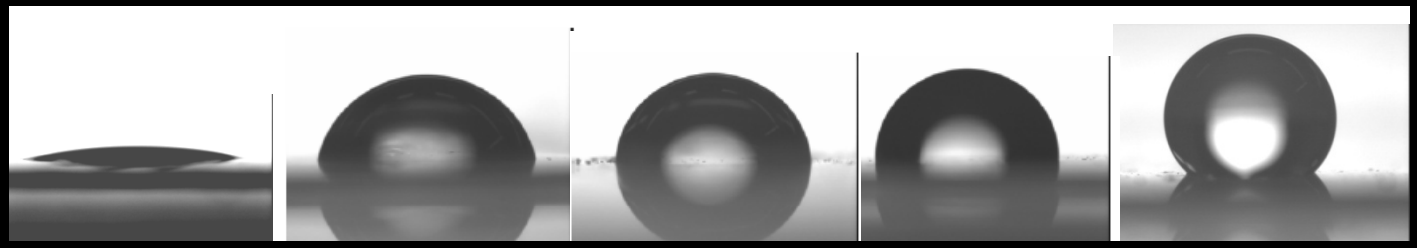
Pressure Contours (Red = High; Blue = Low)

The FPE results with stochastically coupled boundary conditions provide a high degree of accuracy at a fraction of the cost of fully resolved simulations

Model	% CPU / Memory	Impedance (%Error)	Outlet Flow Rate (% Error)
Full Geometry	100%	5.99 Pa (0%)	9.92×10^{-2} mg/s (0%)
4 Path	6%	6.07 Pa (1.32%)	10.12×10^{-2} mg/s (1.91%)
8 Path	11%	6.01 Pa (0.30%)	9.97×10^{-2} mg/s (0.40%)
16 Path	19%	5.99 Pa (0.08%)	9.93×10^{-2} mg/s (0.14%)

Aerosol Deposition Model Incorporating Lung Physiochemical Surface Properties

Key Senior Personnel:
Keisha Walters, MSU
David Thompson, MSU
Greg Burgreen, MSU
Robert Hester, UMC



Objective/Overview:

Develop empirical aerosol deposition models based on experimental measurements of the physical and chemical surface properties of lung tissues and lung-drug interactions.

These empirical models will then serve as boundary conditions in computational fluid dynamics (CFD) simulations being performed on aerosol deposition in human lung respiration and provide input parameters for QHP modeling.

Technical Collaboration:

This experimental effort will lead to improved computational modeling techniques. The experiments are being conducted with input from computational researchers, and the eventual CFD model development will require technical input from both experimentalists and modelers.

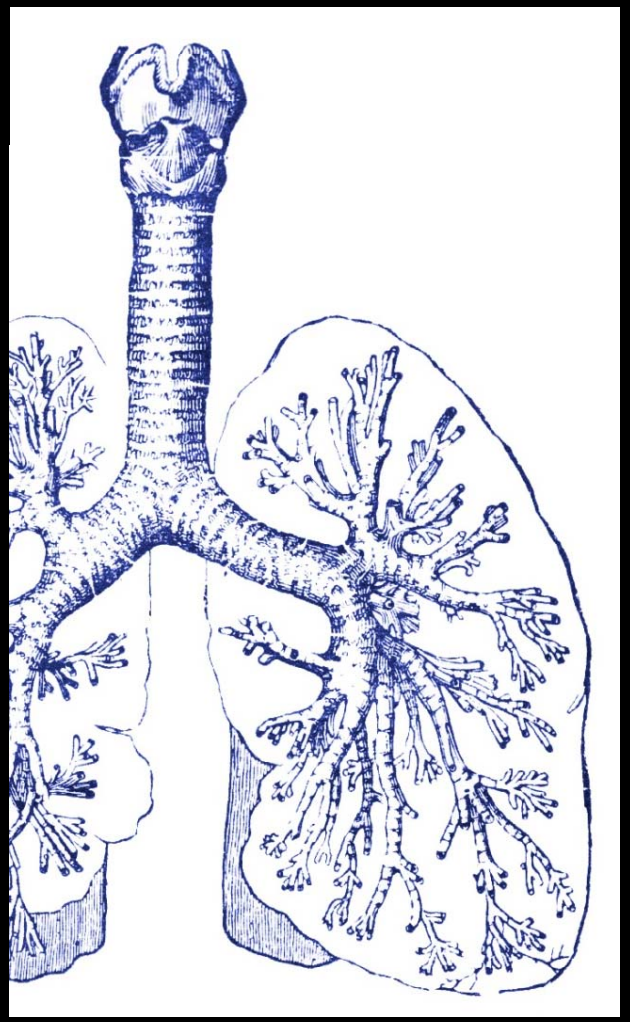
Motivation and Specific Objectives

Aerosol delivery has been found to be inefficient as only approximately 15-20% of the delivered medication is deposited in the lungs.

One tactic is to include mucoadhesive materials that bind to the mucin layer of a biological membrane

The specific objectives of this research are to:

- Experimentally investigate the physical and chemical surface properties of lung tissue
- Calculate the interfacial tension of drug-doped solutions using pendant and static contact angle measurements
- Model the interactions between lung tissue and drug-doped droplets traditionally used in aerosol inhalation medications



Experimental Methods

Materials

Substrates:

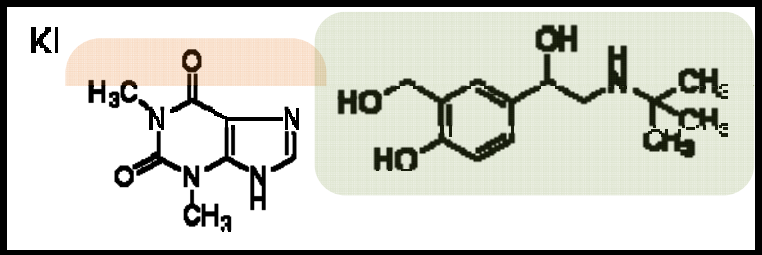
- Lung tissue (bovine and rabbit)
- PTFE control

Probe liquids:

- Controls: pH 7 phosphate buffer solution; HPLC water
- Artificial saliva solutions: Xialine 1 (X1); Xialine 2 (X2) ; Saliveze

Model Drugs:

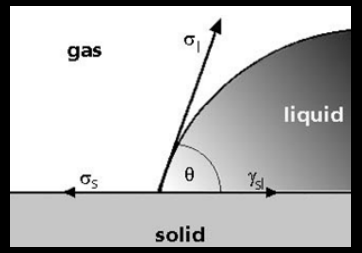
- Potassium iodide (KI)
- Theophylline (Theo)
- Salbutamol (Sal)



Contact Angle Techniques

Methods for Solids:

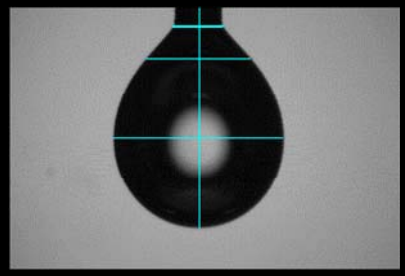
- Sessile drop (Static and Advancing/Receding)
- Dynamic Wilhelmy
- Single fiber
- Powder contact angle



Methods for Liquids:

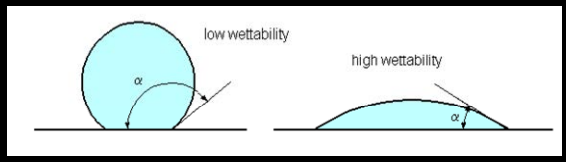
Static

- Du Nouy
- Wilhelmy Plate
- Spinning drop
- Pendant drop



Dynamic

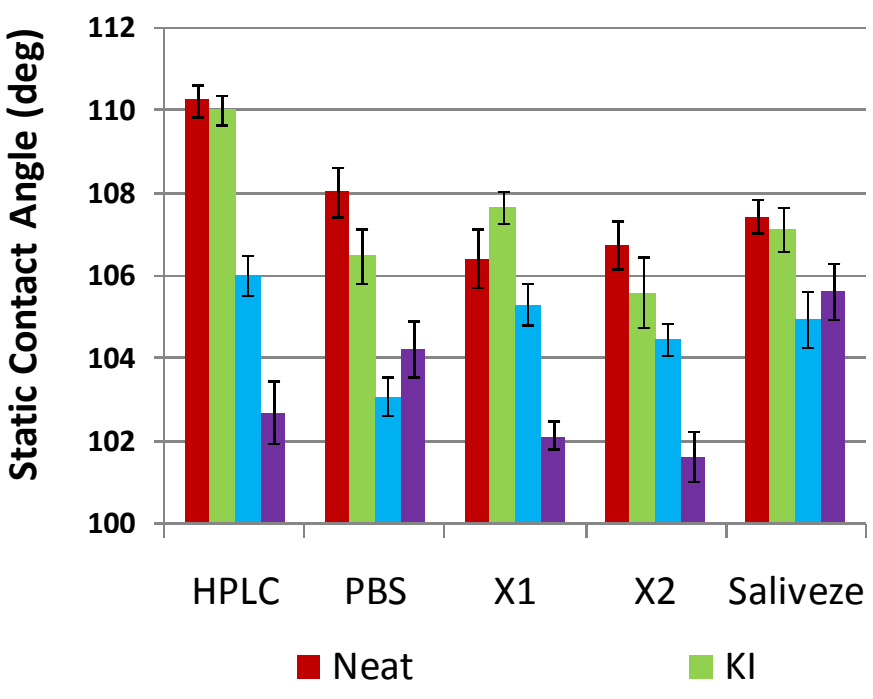
- Bubble pressure
- Drop volume

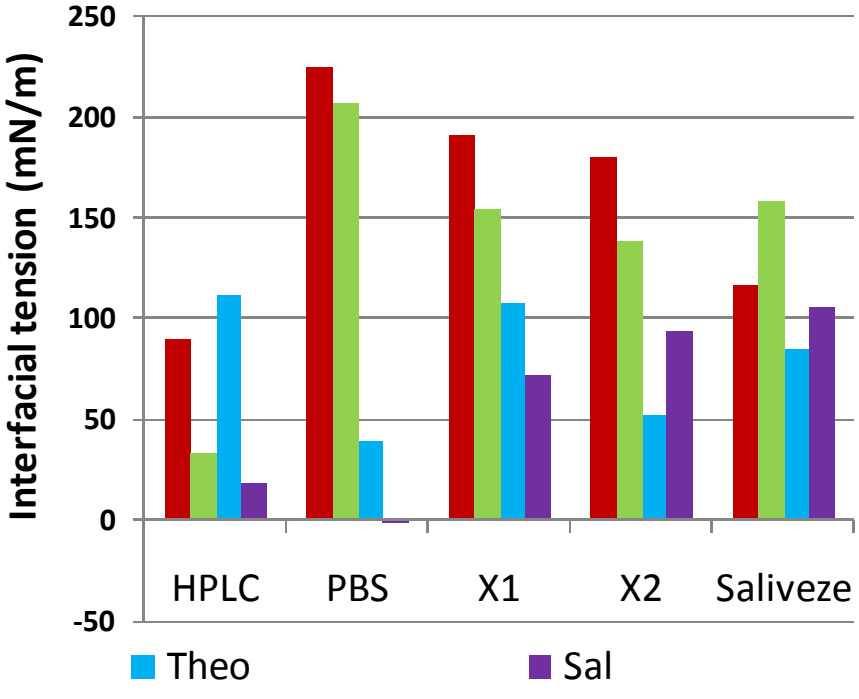


Interfacial Tensions

Static contact angles were measured on PTFE (control substrate) for neat (non-doped) and doped (0.1 g/L) probe liquids. Young's Equation was then used to calculate interfacial tension.

$$\gamma_{SL} + \gamma_{Lv}\cos(\theta) = \gamma_{SV}$$





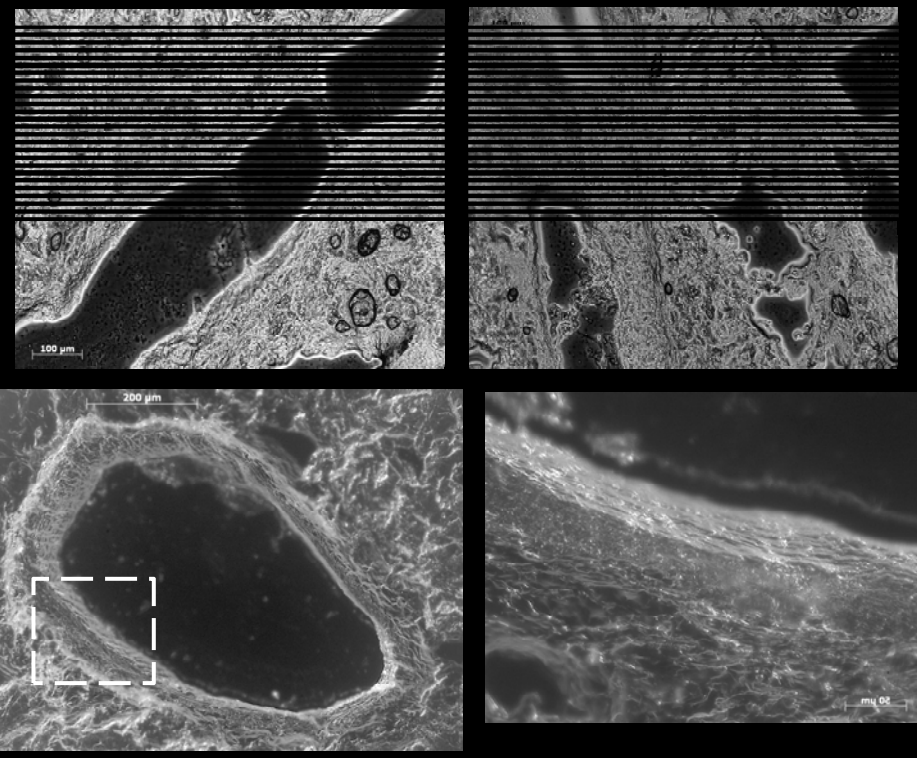
Light Microscopy

Bovine and rabbit lung tissue was cryotomed into 50 µm sections and stored in the freezer prior to characterization.

Bronchial tube diameter and density monitored as a function of position within the lobe.

Attempted to characterize mucosal lining.

Surface roughness of bronchioles evaluated.



Martonen Model

Model describes the cumulative deposition fraction of particles in the lung, P(c), which includes three deposition mechanisms: P(i) = inertial impaction; P(s) = sedimentation; and P(d) = diffusion. All parts of the model take into account whether the flow is turbulent or laminar.

$$P(c) = P(i) + P(s) + P(d) + P(i)P(s)P(d) - P(i)P(s) - P(i)P(d) - P(s)P(d)$$

$$P(i)_{Plug} - \frac{2}{\pi}[e(1-e^2)^{1/2} + \arcsin(e)]$$

$$P(i)_{Turblent} = 1 - \exp\left[\frac{-4e}{\pi}\right]$$

$$P(s)_{Plug} = \frac{2}{\pi}[e(1-e^2)^{1/2} + \arcsin(e)]$$

$$P(s)_{turblent} = 1 - \exp\left[\frac{-2g\pi(I)\cos\Phi(I)}{\pi R(I)}\right]$$

$$P(d)_{turblent} = 1 - \exp\left[\frac{-0.22 D^{*\frac{3}{4}} \mathrm{Re}(I)^{\frac{7}{8}} L(I)}{U(I)R(I)^2}\right]$$

$$P(d)_{plug} = 4\left[\frac{K}{\pi}\right]^{1/2} - K$$

$$P(d)_{parabolic} = 1 - 0.819\exp[-3.66K] - 0.0976\exp[-22.3K] - 0.0325\exp[-57K] - 0.0509\exp[-49.9K^{2/3}]$$

Deposition Model Development

Development of a model that is able to define the tendency for a given particle to deposit in the human lung is underway. Efforts by Martonen et al and others will be incorporated.

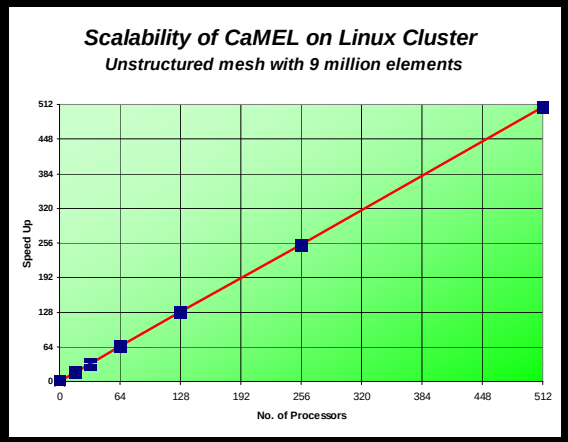
A unique feature of this model will be the ability to incorporate chemical properties for a given inhaled droplet in addition to physical characteristics, and so parameters such as surface tension (which can account for chemical composition, molecular weight and shape, and concentration), diameter, lung location, and velocity will be included.

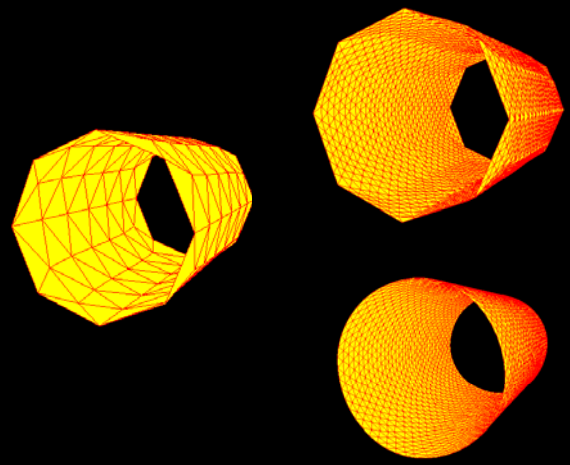
Future modeling efforts will incorporate experimental data collected as part of this project and from the literature.

Future modeling efforts will also extend the model to nanoparticle deposition.

Advanced Algorithm Development (JSU, MSU)

Key Senior Personnel:
Shahrouz Aliabadi, JSU
Keith Walters, MSU
Greg Burgreen, MSU





Objective/Overview:
Develop numerical algorithms and solver technology for next-generation HPC simulations of biological systems.

This effort addresses fundamental issues of computational simulation technology that are especially critical for biological systems, including advanced code development (CaMEL code, JSU), numerical schemes for multi-phase flows, and high-order representations of complex geometries.

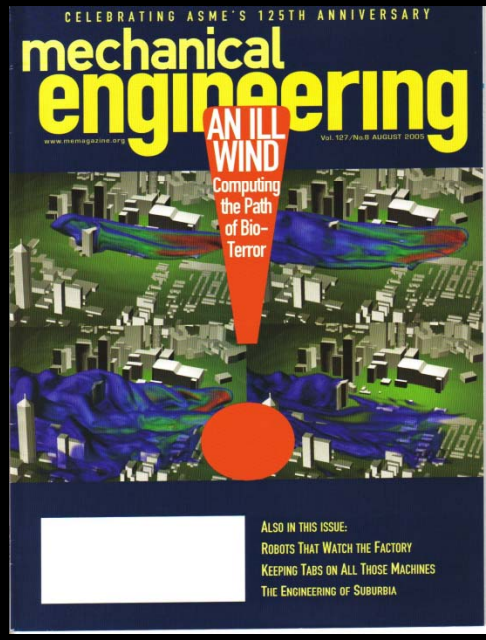
Technical Collaboration:
The algorithmic tools developed as part of this effort will be integrated into the HPC simulations of lung deposition and bioartificial liver device, providing improved accuracy and enhanced computational performance.

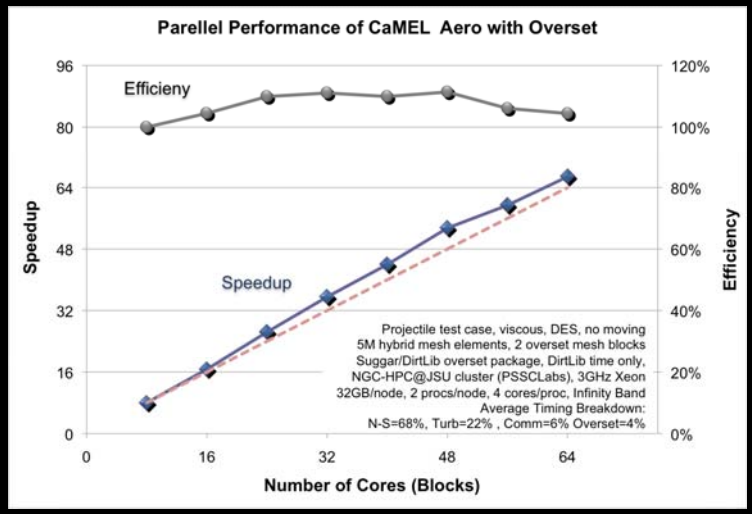
Core Technologies

CaMEL Flow Solvers

Finite element node-based and finite volume cell center hybrid flow solver. It solves fully incompressible and compressible Navier-Stokes equations coupled with the equations governing the heat and mass transfer in fluid. The fluid-structure interaction technology of the flow solver allows the simulations of problems with moving boundaries and interfaces.

CaMEL has been featured in Mechanical Engineering magazine. CaMEL was developed by Dr. Shahrouz Aliabadi's research team with support from Army Research Laboratory.

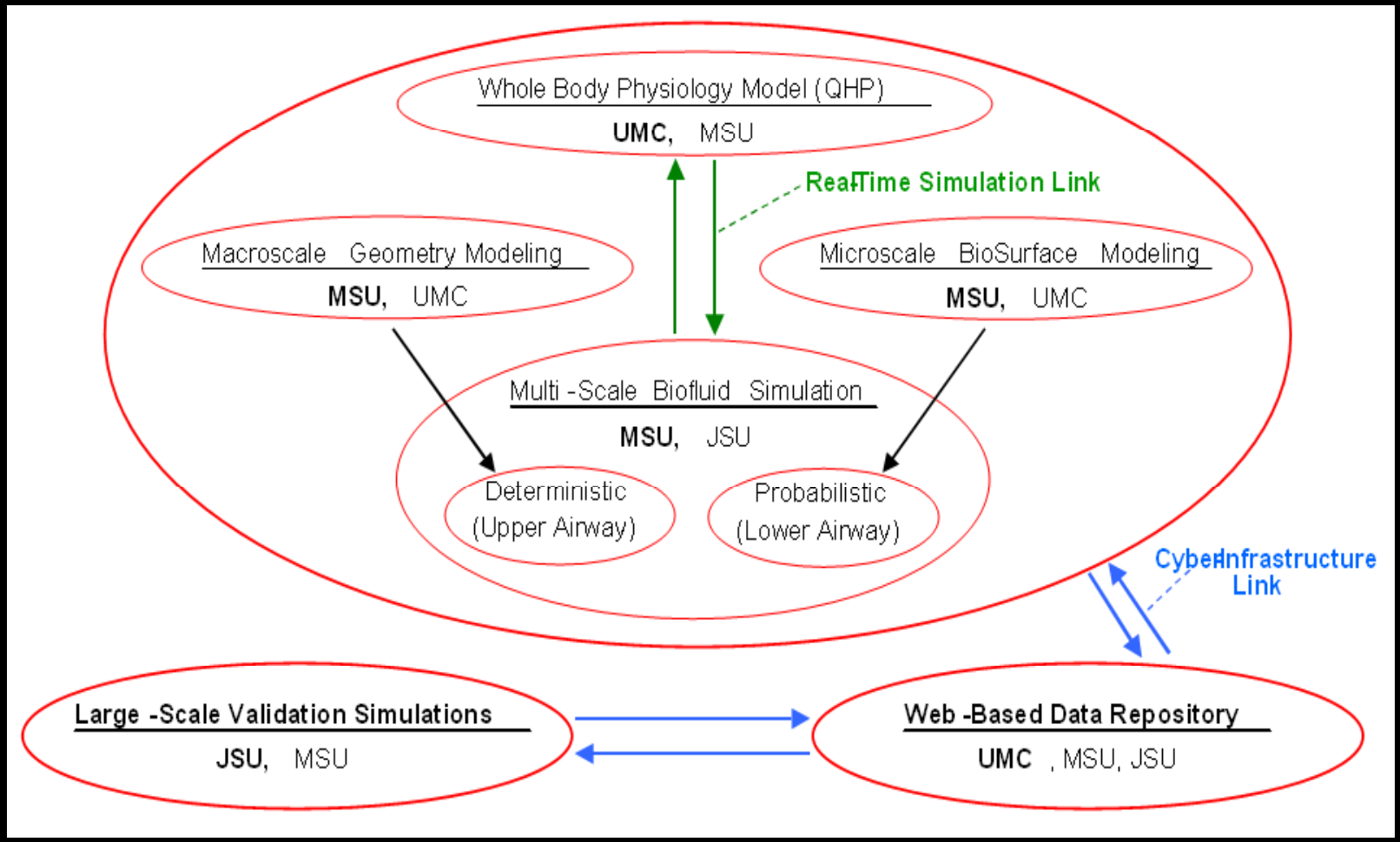




Objectives of Proposed RII

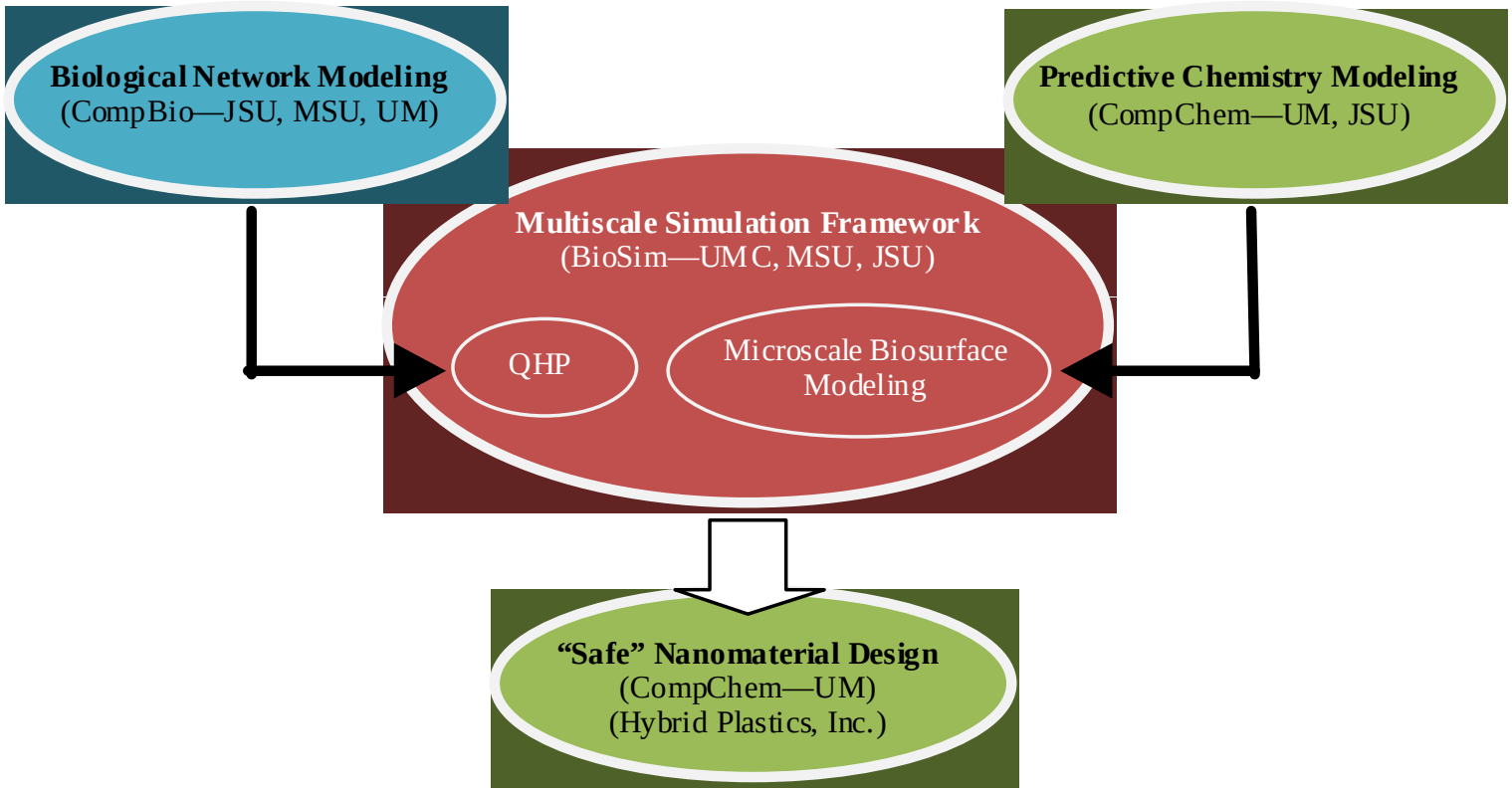
1. Develop a multi-scale simulation framework for investigation of human biological processes and to make this framework freely available via cyber-infrastructure for research, education, and training purposes.
2. Tightly integrate: 1) a macro-scale Quantitative Human Physiology (QHP) model of integrative human physiology; 2) meso-scale computational fluid dynamics (CFD) simulations of individual organs and organ systems; 3) reduced-geometry or probabilistic simulations of organ and organ system subcomponents; and 4) and micro-scale modeling and physiochemical characterization of inter-component interactions.
3. Demonstrate validity through a driving demonstration problem of practical value, specifically the simulation of inhalation exposure to nanoparticles and the resulting deleterious effects on respiratory and cardiovascular function.

Technical Organization of Proposed RII



BioSim Research Activities

Technical Organization of Proposed RII



Cross-Cutting Research Activities

Questions?