(a) Conventional Drug Delivery Method

Drug Particle Release Map
Q_{in}=1 L/min d_p= 1 micron

⊕ Drug Release Position

Drug Delivery Efficiency <25%

Uncontrolled Drug Deposition In the Whole Lung

(b) "Controlled Air-Drug Stream" Targeting Method

Drug Particle Release Map
Q_{in}=1 L/min d_p= 1 micron

⊕ Drug Release Position

Drug Delivery Efficiency >90%

100% Delivery Efficiency to the Right Upper Lobe
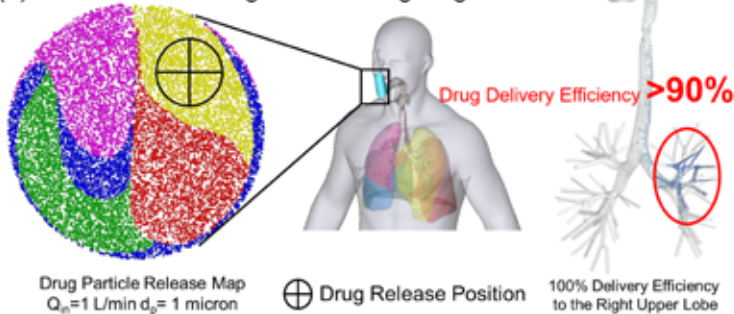
‹ Targeting the upper right lobe of the lung using the human digital twin prototype:
(a) conventional drug inhalation therapy (efficiency less than 25 percent)
(b) the controlled air-drug stream delivery method (efficiency greater than 90 percent)

TARGETING A TUMOR

By devising a new computational method that tracks the flow of therapeutic drug particles in an aerosol from the lips to the lungs, researchers can deposit a drug on a targeted lung tumor with 90 percent efficiency. This is a major improvement over the 20 percent efficiency of conventional aerosol treatment methods. One key to the success of this new computational method is the development of a human digital twin that can be made patient-specific using the real geometry of the patient's lungs.

By **Yu Feng**, Assistant Professor
School of Chemical Engineering
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Personalized medicine is starting to replace the current "one size fits all" approach to medical treatment. One goal is to deliver the right dose of the right drug, at the right time and location, to the specified patient. Researchers at Oklahoma State University used ANSYS computational fluid dynamics (CFD) simulations to devise a computational fluid–particle dynamics (CFPD) method for comprehensive analysis of inhaled drug particulate matter dynamics. CFPD is designed to answer the questions: "How can we determine where a given drug particle in an inhaled aerosol stream ends up in the lung," and "How can we change the properties of the aerosol to target a specific location in the lung?"

Through an academic partnership with ANSYS, university researchers at the Computational Biofluidics and Biomechanics Laboratory (CBBL) apply ANSYS CFD to study the precision delivery by an inhaler device of cancer-destroying drugs to tumor-only locations in the lungs (healthy tissue is not exposed). CFPD is also capable of subject-specific health risk assessment for in silico occupational exposure studies,

> **"By increasing the *accuracy* of delivering a chemotherapeutic drug to a lung tumor to *90 percent*, versus 20 percent by conventional aerosol methods, they have *potentially improved* the prognosis for many cancer patients."**
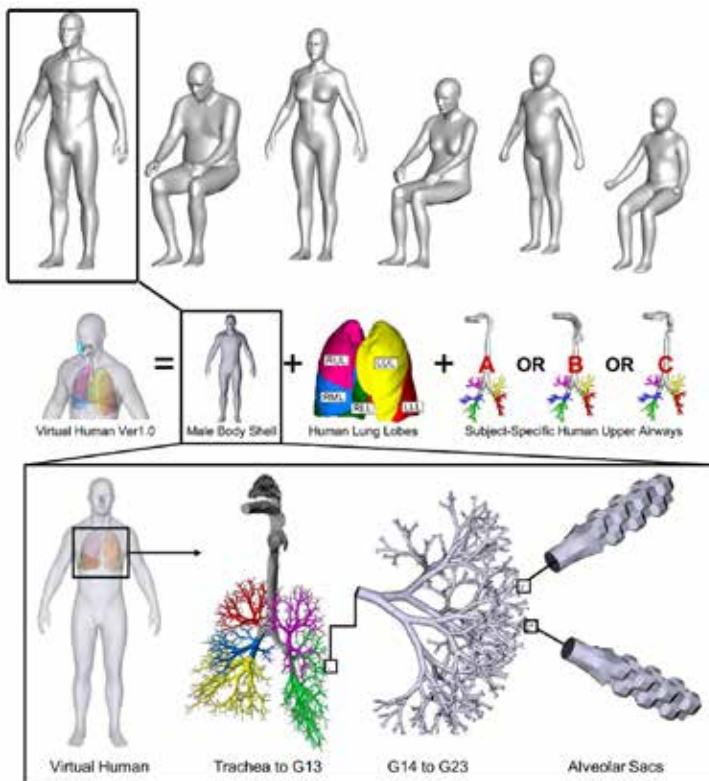
including simulations of real-time ventilation, skin absorption and lung deposition.

COMPUTATIONAL FLUID PARTICLE DYNAMICS

In the conventional drug delivery method for inhaled aerosol medications, the drug is distributed evenly throughout the volume of the aerosol. Upon reaching the lungs, the drug reaches its target — for example, a tumor in the upper lobe of the right lung — with 20 percent accuracy. The remaining drug falls on healthy tissue. In addition to drug loss, side effects can occur and healthy lung tissue can be damaged.

To improve on this result, CBBL researchers ran CFPD simulations to provide comprehensive analysis of the flow path of particulate matter in inhaled drugs. The goal was to determine whether 100 percent of the nano-in-micro drug particles can be directed to the localized lung tumor sites by restricting the injection area of the active drug particles to a smaller region during inhalation. By varying the drug particle diameters, particle density inhalation flow rate and the initial location of the drug particles in the aerosol stream, the researchers were able to simulate drug particle movement in the aerosol

through an adult upper airway configuration from mouth to the lungs. The final mesh contained approximately 10 million dense, hybrid tetrahedral/pentahedral elements. Using Euler-Euler and Euler-Lagrange models, as well as the dense discrete phase model (DDPM) with discrete element method (DEM), the researchers confirmed that, when the drug is restricted to a smaller region of the aerosol at the point of inhalation, the delivery efficiency can reach values greater than 90 percent. This controlled-air drug stream method is clearly more efficient than the conventional aerosol delivery method.

HUMAN DIGITAL TWINS

A key to the success of these simulations is the development of a "virtual human system" — an individualized digital twin. Version 2.0 of the human digital twin comprises six models: an adult male, female and child, each in sitting and standing positions. Each digital twin models a high-resolution human respiratory system covering the entire conducting and respiratory zones, lung lobes and body shell. The CBBL virtual humans are CFPD-ready. The human digital twins can be made patient-specific by performing a CT/MRI scan of the patient and importing the geometry of the lungs into the shell of the digital twin.

THE CBBL VIRTUAL POPULATION GROUP

Taking the simulations a step further, the CBBL researchers have created a large group of human
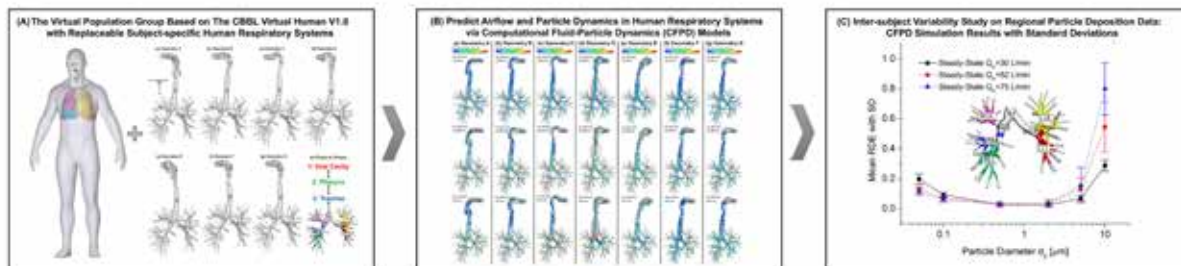

The CBBL virtual human system version 2.0 with a representative human respiratory system for computational fluid-particle dynamics (CFPD) simulations covering the entire conducting and respiratory zones

The CBBL virtual population group version 1.0 and the in-silico intersubject variability investigation framework

Flowchart of the personalized targeted pulmonary drug delivery planner

digital twins for better statistical analysis — the researchers refer to this as "CFPD simulation results with error bars." The virtual population group (VPG) is a set of detailed, high-resolution anatomical models created from CT/MRI data of human subjects. The VPG makes it newly possible to analyze variations in the general population or within specific subpopulation groups, increasing the statistical robustness of numerical studies.

However, as these analyses consider individual anatomical differences, they are computationally expensive. Using a reduced-order model (ROM) to accelerate the computation, future work will include the compilation of precomputed lung aerosol dynamics libraries to train the ROM and simplify in silico personalized, pulmonary drug delivery planning process.

THE MULTISCALE CFPD-PBPK/TK MODELING FRAMEWORK

The deposition of drugs in the lung is not the endpoint of the cancer treatment. Toxicologists, pharmacists and clinicians are more interested in the after-deposition dynamics, i.e., the time course of therapeutic or toxic species in plasma and different organs throughout the whole human body. CBBL has combined the CFPD model with a physiology-based pharmacokinetic/toxicokinetic (PBPK/TK) model to predict the systemic translocation of nicotine and acrolein (initial examples) in the human body after the deposition in the respiratory system. With this multiscale CFPD-PBPK/TK modeling framework, it is now possible to run simulations of extremely complex, lung–aerosol dynamics phenomena and whole-body translocation mechanisms at unprecedented levels of detail. This method can

be easily modified to fit in other pulmonary research areas, such as drug delivery and occupational exposure risk assessment.

THE FUTURE: PERSONALIZED PULMONARY HEALTHCARE PLANNER APP

CBBL researchers are now working on an app using ANSYS ACT that would automate patient-specific analyses, as shown in the flowchart of personalized lung disease treatment. Clinicians could use the app to design a treatment plan. With a few morphological parameters based on the patient-specific CT/MRI data of the human respiratory system, as well as the coordinates of known lesions, the personalized, pulmonary healthcare planner could provide an integrated solution to target localized lung sites based on a pre-computed database connected with a reliable machine-learning model. This fast, noninvasive, reliable, easy-to-use app is also patient-specific, and would prescribe treatment based on a personal digital twin.

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> **"The human *digital twin* can be made patient-specific by *performing* a CT/MRI scan of the patient and importing the geometry of the lungs into the shell of the *digital twin*."**

Researchers at the Computational Biofluidics and Biomechanics Laboratory at Oklahoma State University used ANSYS CFD to develop a unique simulation method that will advance the field of personalized medicine. By increasing the accuracy of delivering a chemotherapeutic drug to a lung tumor to 90 percent, versus 20 percent by conventional aerosol methods, they have potentially improved the prognosis for many cancer patients. The advancement of patient-specific, or personalized, medicine will continue to be dependent on the work of innovative researchers and the development of new simulation techniques to eradicate disease. ∧

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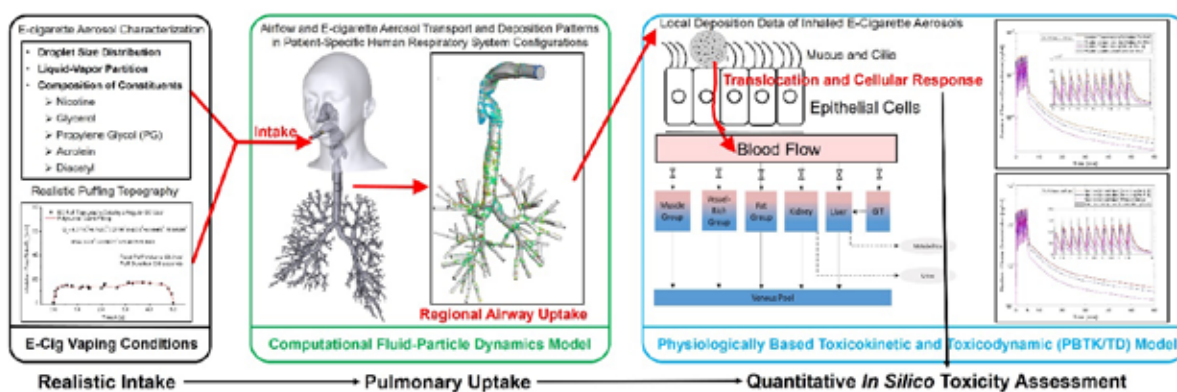
The multiscale computational fluid-particle dynamics (CFPD) plus physiological-based toxicokinetic (PBTK) modeling framework

ABOUT DR. YU FENG

Dr. Yu Feng is an assistant professor in the School of Chemical Engineering at Oklahoma State University, and a center investigator in the Oklahoma Center for Respiratory and Infectious Diseases (OCRID). He founded the Computational Biofluidics and Biomechanics Laboratory (CBBL) at Oklahoma State University, which focuses on developing and applying advanced CFPD models toward multiple applications associated with pulmonary healthcare. He has over 10 years of experience in modeling lung-aerosol dynamics on ANSYS CFX and Fluent platforms, and is published in more than 20 top-ranked journals of fluid dynamics and aerosol science.