# Modeling and simulation of the human respiratory system; Part 2: Inhaler design, *in vitro* experiments and imaging

## Second in a two-part series on state-of-the art models and future challenges in design

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*To address the challenges related to lung modeling and creation of digital twins of the human respiratory system, the first Lung Modeling Congress was held in November 2023. This article, together with a prior article published in the December 2024 issue of Inhalation, presents a summary of the current state-of-the-art and future challenges in various research areas and was written by the major experts who attended the Congress.*

The first article in this two-part series discusses strengths and limitations of computational fluid dynamics simulations (CFD) and discrete element methods (DEM) when applied to the human respiratory system and how these techniques can assist when designing orally inhaled drug products. The main disadvantage of these models is their inability to describe the whole bronchial tree, due to the excessive computational effort that would be required. Therefore, the first article also includes a review of whole lung models, which can provide high quality descriptions of air and aerosol behavior while keeping computational costs low. These models can describe the whole bronchial tree, as well as lung function, and generally are physiologically accurate.

In this second article, the first section considers inhaler devices. The design and optimization of such devices can benefit from the same coupled CFD-DEM techniques previously described to model and simulate the human respiratory system. All the models share a critical need for extensive validation by comparison with experimental measurements for airflow characteristics and airborne particle behavior.

The second section describes methodologies to characterize airflow behavior in the lungs, as well as aerosol transport and deposition. *In vitro* methods will be reviewed and *in vivo* imaging in patients will be discussed. Examples of machine learning will be presented, which can be used on images for a variety of applications, ranging from assisting in diagnosis to extraction of airway morphologies to be used in patient-specific simulations.

The last section is devoted to *in vivo* and *ex vivo* methods applied to animal models, which should be studied for several reasons. Experiments in animals can generate large datasets for the validation of CFD and whole lung simulations in a quick and low-cost manner. More information can be extracted from animals than humans, due to the use of invasive or terminal procedures. Once validated on a significant dataset from animals, simulations can easily be applied to the human respiratory system. Further, a reliable tool to simulate drug delivery in both humans and animals can be of great advantage in translating, to humans, information on pharmacological effectiveness and toxicology, acquired in animals during the early stage of drug development.

Table 1

**Test methods to characterize air flow, aerosol dynamics and properties**

| Test Technique | Type | Complexity/Cost | Output | Considerations |
|---|---|---|---|---|
| Device pressure drop | Quantitative | Low | Correlation of overall device pressure drop | Accuracy of 3D prints Defects in molded parts |
| High speed video analysis (e.g., plume geometry in optically clear induction port or mouth-throat models) | Qualitative | Medium | Visual correlation of plume output in any mouth-throat or United States Pharmacopeia induction port | Generation of optically clear mouth-throat models easily cleaned between runs currently not standardized process |
| Schlieren photography of plume geometry (pMDI) [6] | Qualitative and Quantitative | Medium | Correlation of plume velocities and shape in open atmosphere | Can be useful in pMDI development, especially in evaluating new vs. old propellant performance or device changes (Figure 1a) |
| Laser diffraction | Quantitative | High | Particle size distribution | Faster than impactor, useful for early prototype screening |
| Particle image velocimetry (PIV) | Qualitative and Quantitative | High | 2D flow field profile, spray pattern and geometry | Commonly used in pMDI/ DPI development [7] |
| Laser Doppler velocimetry [8] | Quantitative | Medium | Velocity at point in flow field | |
| X-ray imaging [6] | Qualitative and Quantitative | High | High speed video of particle and internal mechanism motion | Requires synchrotron facilities. However, ability to visualize widely diverse range of internal propellant or particle motion and device operation often worth effort involved (Figure 1b) |

## Design and optimization of inhalers through CFD simulations

At present, CFD and DEM are well-developed tools for analyzing and understanding internal flow fields in both dry powder inhaler (DPI) [1, 2] and pressurized metered dose inhaler (pMDI) [3-5] applications. Like all other modeling techniques, they offer the tantalizing prospect of performing multiple, rapid design iterations before making physical prototypes. Typical properties of interest to designers are inhaler resistance, occurrence of dose retention or leakage, shape and particle size of the generated aerosol cloud, and aerosol emission time and duration, all of which are strongly related to final inhaler performance. Simulation methods also can provide information about activities within devices to help gain detailed understanding of flow path and particle motion, from the drug receptacle (e.g., a dosing cup, capsule or pierced blister) to the device outlet and beyond for numerous inhalation profiles.

To give more than qualitative insights to designers, simulations must be validated against results of physical tests. Moreover, certain characteristics of the generated aerosol must be measured and provided as input parameters for simulations (e.g., aerosol particle size distribution, spray plume geometry and velocity). Most of the available measurement/testing methods can be divided into two categories:

1) **Imaging and measurements of air flow and aerosol plume characteristics.** Available techniques are summarized in Table 1. For these tests, a direct comparison with a simulation is usually possible. As many of these tests are expensive and cannot show what is happening inside an inhaler, they are usually performed at the outlet of a single prototype inhaler. Once the simulations are validated, they provide insight about activities inside the tested inhaler and can be used to study the impact of geometry/formulation variations, thereby reducing the amount of experimental testing.

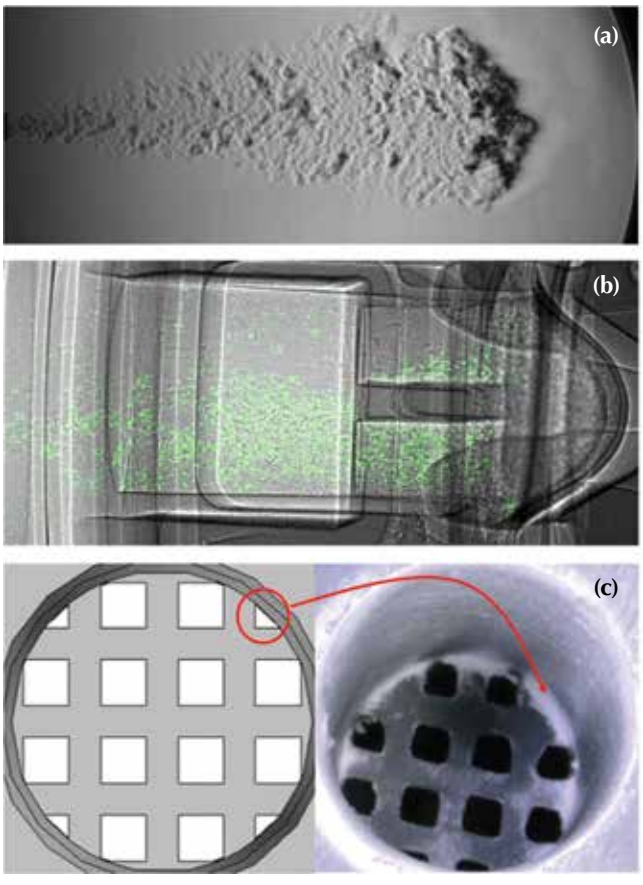
2) ***In vitro*** **quantification of inhalation performance**. Currently, cascade impactor (CI) assessments to determine aerodynamic particle size distribution (APSD) profiles and fine particle fraction (FPF) are the gold standard of inhaler testing but can be costly in early-stage development when many design variants are examined. However, efforts are being made to make these determinations faster and more clinically relevant [9-11]. A direct, quantitative comparison of inhaler performance to simulations has not been possible to date because it would require simulation of all the *in vitro* testing equipment downstream of the inhaler, with details including filtering stages, and a realistic drug dose mass (tens of billions of polydispersed aerosol particles) would need to be simulated.

However, in many cases, correlations can be found between certain physical quantities calculated in a simulation (on a small but representative sample of aerosol particles) and *in vitro* inhaler performance. For instance, in a DPI, intensity of the turbulence experienced by powder particles as they travel inside the inhaler, as well as the number of collisions they experience against the inhaler inner walls, have been shown to quantitatively correlate with the measured fine particle fraction [5]. After such correlations are established, simulations can be used to predict variations in inhaler performance due to the introduction of certain geometry/formulation modifications.

In a simulation-experiment comparison, a key concern is that simulations are often conducted with ideal inhaler geometry derived from technical drawings, whereas geometric differences or leak paths due to manufacturing tolerances are not accounted for (Figure 1c). In fact, a first step by many CFD practitioners is to "seal up" problematic gaps in CAD files to make meshing easier. However, those small leaks or physical differences can have major implications for the real inhaler flow field and estimation of inhaler resistance. Therefore, one must have a thorough understanding of the prototype/device manufacturing methods (usually 3D-printing in early design phases and injection molding in later phases).

Figure 1

**(a) Schlieren image of a DPI on Prior PLM's Schlieren photography rig. (b) High speed X-ray image of a DPI using Prior's PLM test fixturing at the European Synchrotron Radiation Foundation (ESRF). (c) Example of a mismatch between ideal inhaler geometry and corresponding 3D-printed prototype.**




Correct representation of both the inlet and outlet conditions in the test setup should also be reflected in the CFD model. For example, the initial stages of the test fixture to which the inhaler is connected (whether a dosage unit sampling apparatus (DUSA) tube, United States Pharmacopeia (USP) induction port or semi-anatomic mouth-throat), should be modeled, if computational resources permit. It also has been shown that the specific mouth-throat model used can be a potential source of influence on CI test results [12, 13]. Modeling the downstream test fixture also allows visualization of the aerosol plume in the CFD outputs, which can then be used for model validation [5, 14, 15].

DPIs and pMDIs present various practical difficulties and limitations when it comes to their CFD-DEM simulations. The main difficulty for DPIs is simulation of a powder dose of realistic mass, which is necessary to achieve a correct description of the early powder lift and disaggregation, as well as to match the particles' residence time and the plume emission time. If the mass of powder simulated is too small, effects of powder retention in the inhaler can be overestimated [5]. However, simulating even a few milligrams of micronized powder requires handling of billions of particles so an exact direct simulation would be unfeasible. In this respect, adopting a coarse-grained approach is certainly of value, although it comes with limitations [16].

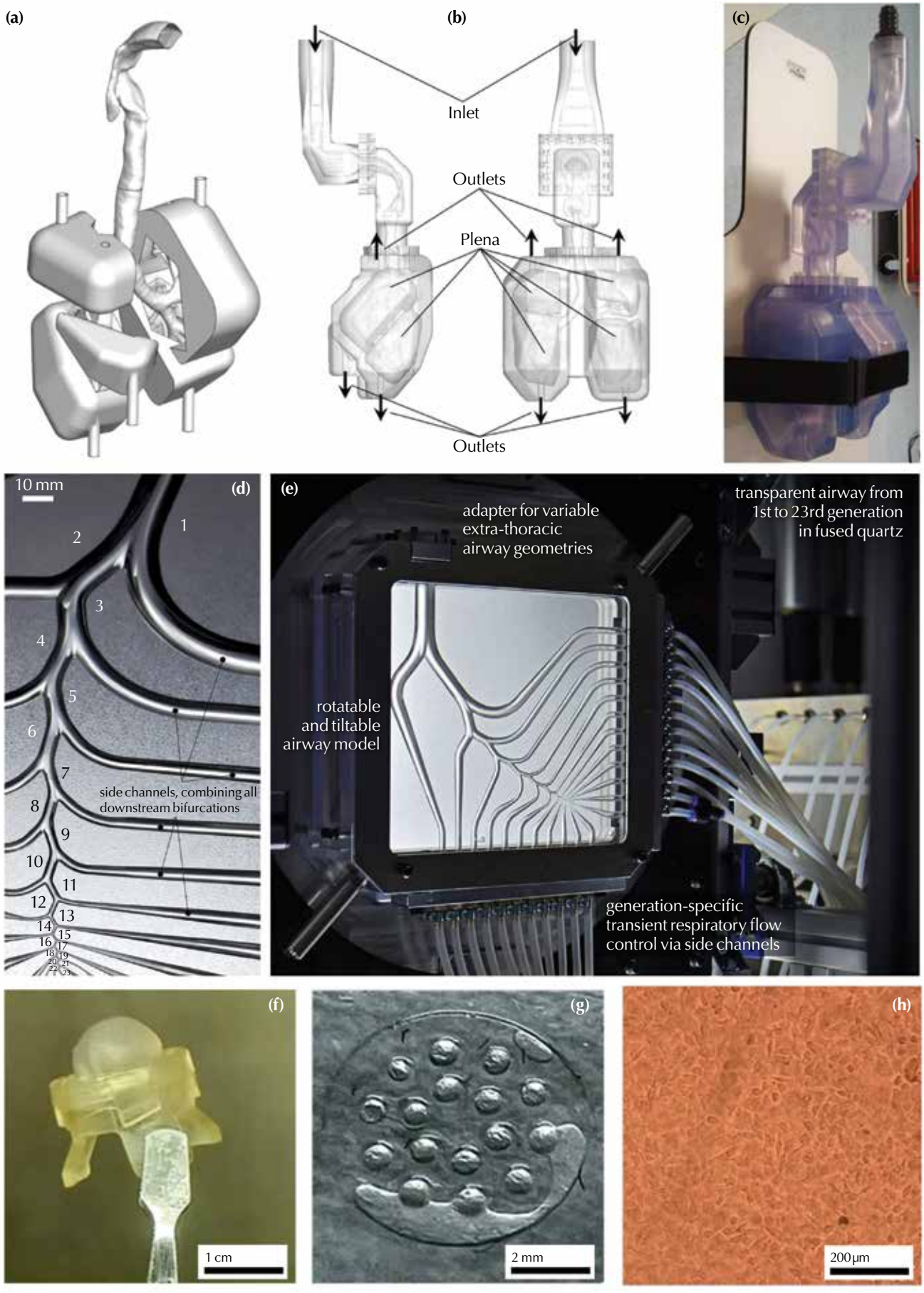
pMDIs present their own challenges. Simulating the propellant flash-boiling phase transition requires complex and time-consuming, multi-phase flow simulations involving latent heat exchange and strong temperature variations [17]. Moreover, although the mechanical instability leading to the liquid film breakage and droplet formation at the nozzle, in principle, could be simulated with interface-capturing methods [18], a direct simulation of the whole plume would be unaffordable due to computation costs. Therefore, the droplets in pMDI plumes are generally simulated using a Lagrangian approach, i.e., by assuming them to be particles [19] or by hybrid methods [20].

## *In vitro* studies and validation of models

*In vitro* experimental studies are of great value for understanding and quantifying airflow characteristics and aerosol behavior in human lungs. They can generate datasets in simplistic, standardized conditions for use by *in silico* modelers to design and validate computational tools. Once deemed fully reliable, computational models can be extensively applied, with considerably smaller costs and timeframes, to

## Figure 2

**(a-c) Upper airways cast of a healthy adult male. (d-e) Planar model of a single airway bifurcating 23 times, thereby covering all the generations down to the alveoli. (f-g) Spherical alveolar structure at macro- and micro-scale respectively, designed and fabricated at the Research Center "E. Piaggio" (University of Pisa). (h) Alveolar epithelial cells cultured on top of artificial alveoli membranes.**



breathing conditions, formulations and inhaler types to explore inter- and intra-population variabilities, as well as to study pathology-induced morphological modifications. In addition, cell-based *in vitro* studies may provide additional information regarding particle interaction with lung epithelia.

*In vitro* experiments can focus on specific portions or segments of the respiratory system such as extrathoracic and/or upper airways only; or models that have idealized geometry [21-23]; or are anatomically accurate [24-28] Figure 2a-c); or have a single pathway spanning all generations [29, 30] (Figure 2d-e); or have multi-scale alveoli and terminal bronchioles [31-33], (Figure 2f-g).

Rigid airway models are typically manufactured by casting or additive manufacturing, e.g., stereolithography [26, 34, 35]. Alternatively, transparent airway models in glass or sapphire can be realized using subtractive manufacturing, e.g., by combining micro-milling (with an accuracy of 20 µm) for the first 15 bifurcations and selective laser-induced etching (with an accuracy of 1 µm) for the following airway segments up to the 23rd generation [36].

In experiments that characterize air flow, air is usually replaced by a viscous liquid to facilitate various imaging techniques, such as matching the refractive index of the cast material to avoid optical distortions and aberrations. By properly re-scaling the liquid flow characteristics, dynamic similarity can be achieved and the measurements remain representative of an air flow in physiologically relevant regimens. For rigid airway casts, the primary dimensionless parameters are the Reynolds and Womersely numbers [37].

Among the many experimental methods used to characterize airflow and aerosol transport in the lungs [38], two are widely adopted imaging techniques for detailed velocimetry measurements: particle image velocimetry (PIV) [39, 40] and magnetic resonance velocimetry (MRV) [24, 41, 42]. Advantages and disadvantages of each technique lie in their dimensionality, ease of implementation, cost and ability to obtain turbulence statistics. Both methodologies obtain fields-of-view that are on the order of 10 cm in size at sub-millimeter spatial resolution.

PIV is most often implemented as a planar measurement technique, yielding two- or three-component instantaneous velocity data on two-dimensional image planes, depending on the number of cameras used [43, 44]. Therefore, turbulence statistics can be obtained. Additionally, recent algorithmic advancements have enabled 3D measurements at high tracer seeding densities, albeit at the expense of additional cameras [45]. As an optical technique, PIV requires at least two directions of optical access, which can be achieved using index refractive matching liquids but requires care in design of the experimental apparatus due to inlet and outlet ducting, fasteners and other components.

MRV is fundamentally different in its data acquisition. It measures the signal produced by hydrogen protons in aqueous solutions under the application of magnetic fields using radio frequency excitations. Measurements can be performed in optically opaque MRV compatible casts (e.g., plastic 3D-printed casts). This simplifies experimental design for complex geometries. Three-dimensional, three-component velocity data can be acquired using clinically available imaging sequences on 1.5 Tesla to 3 Tesla magnetic resonance imaging (MRI) scanners. However, MRV is not a time-resolved technique and therefore obtains time-averaged data (or phase-averaged data for periodic flows) [42]. Application of MRV for quantitative turbulence measurements is an active area of research [46]. Together, both PIV and MRV have provided significant insight into streamwise momentum distribution, secondary flows and turbulence intensity to inform observations of particle deposition and simulation validation.

Transported aerosol particles can be traced within the airflow by means of high-speed transmitted light microscopy [36]. For complementary aerosol characterization, phase Doppler or laser Doppler techniques can be used at the inlet of airway models [36] as well as inside for selected areas with suitable curvature and quality of the transparent airway surfaces [47]. Several measurement techniques have been applied and discussed in the literature for characterization of deposition in airway models [38]. The resulting deposition field along the airways usually cannot be resolved. Instead, deposition fractions or deposition efficiencies are determined integrally for selected airway segments as a function of airway generation. *Ex situ* gravimetry or fluorometry methods, including liquid chromatography [48] or gas chromatography-mass spectrometry [49], are suitable for this purpose.

To obtain more detailed information about local distribution and deposition along the airways, nuclear imaging methods such as positron emission tomography (PET) have been applied, providing local resolution in the range of a few millimetres on the basis of long-term images [50]. Recently, it was shown that an *in situ* analysis of the deposition field along a transparent airway model during respiratory cycles is possible at high spatial and temporal resolution using laser-induced fluorescence (LIF) [30,51]. This method allows a direct correlation of the measured deposition field with temporally and spatially variable local flow parameters and aerosol characteristics.

Alveolar geometry can be replicated over different length-scales (from centimeters to micrometers) combining biomaterials and biofabrication strategies to obtain spherical membranes [52]. Alveolar epithelial cells are typically seeded on these structures to mimic the air-liquid interface (ALI) on which airborne drug particles land and dissolve, thereby solubilizing the active molecule [53].

The newest advanced systems combine replication of the 3D spherical structure with mechanical stimuli from breathing dynamics. This approach, coupled with miniaturized fluid circuits replicating air and blood circulation, can potentially make pharmacology studies and lung-on-a-chip devices more relevant to humans [54]. Similar bioengineering strategies also can be implemented using tracheobronchial cells to replicate various lung districts. Moreover, the presence of other cell types, such as goblet cells and immune cells, may improve the biological complexity of the model [53].

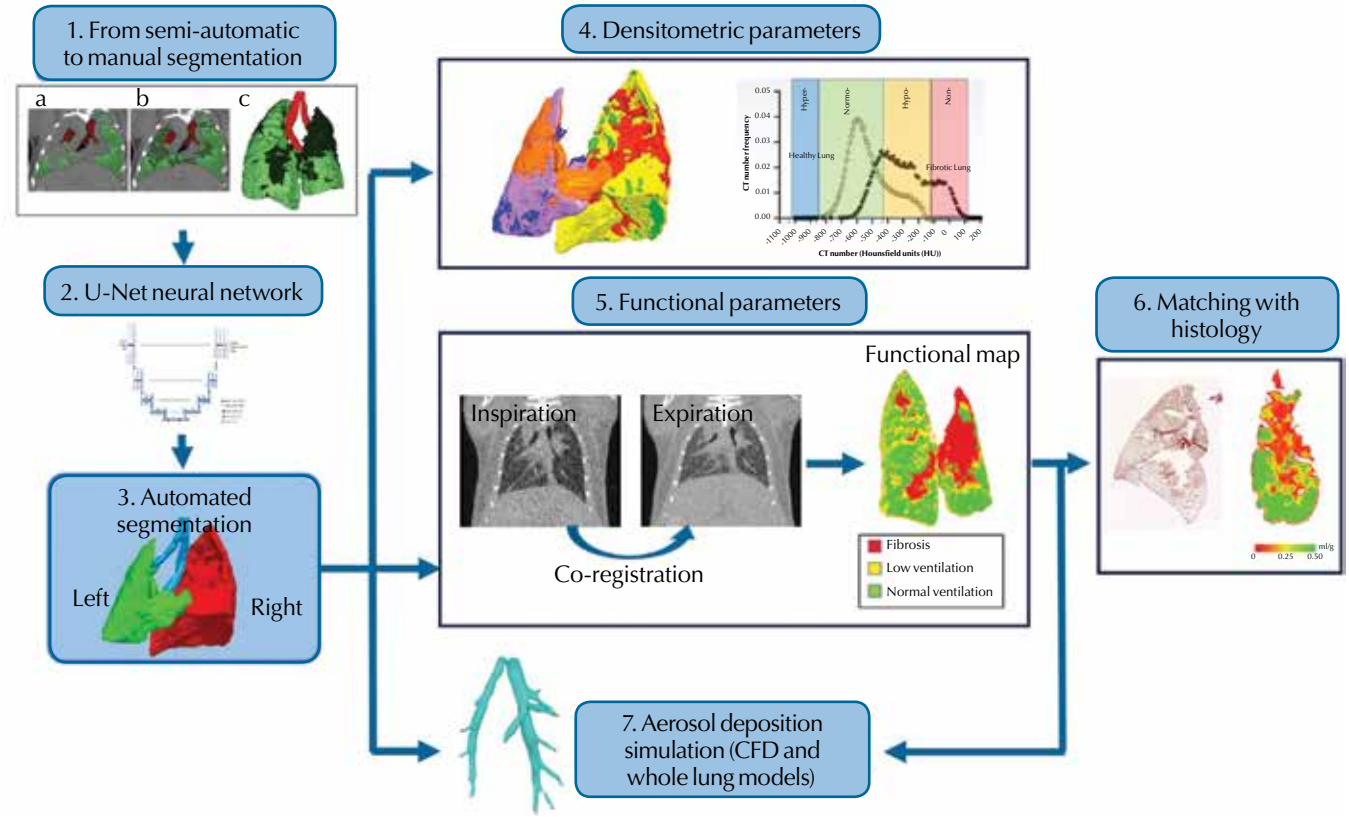
## Open-source medical imaging databases

In recent decades, the advent of artificial intelligence (AI) and deep learning techniques has contributed to the exploration of medical imaging and its potential role in helping shape clinical decision-making. Such techniques require large datasets to train and test algorithms so their success is closely related to the creation of large, accessible, curated databases of high-quality medical images. In the field of rare disease, an example is provided by the Open-Source Imaging Consortium (OSIC) [55]. The consortium was created in 2018 to build a collaborative alliance for fibrosing lung diseases and bring together orthogonally related experts in the fields of pulmonology, radiology and computational science. Its mission is to make radical progress by driving collaboration and progressing research via an open-source environment.

This unique global consortium was designed to combat the issues typically facing AI/medical image databases, which include quality, reliability, scarcity, diversity, transparency and patient privacy. The OSIC Cloud Data Repository was built on the premise that CT scans alone, while important, will grow exponentially in value when anonymized, curated clinical data is added. In addition to baseline and follow-up high resolution CT scans, the OSIC Cloud includes data on patient age, region of the world, smoking history, lung function measurements, familial history and more. The repository started with a minimal amount of clinical data but more pieces have been added as machine learning technology has evolved.

Figure 3

**Fully automated pipeline for analysis of mouse lung CT scans. 1. Semi-automatic segmentation of a fibrotic lung and manual reconstruction. 2. A U-Net neural network trained with 200 CT images to develop a deep-learning algorithm. 3. Representative 3D rendering of a lung automatically segmented and divided into left and right lobes. 4. Quantification of densitometric parameters (aeration compartments: hyper-, normo-, hypo- and non-aerated tissue). 5. Functional parameters (i.e., normal ventilation, low ventilation and fibrosis) derived by co-registration of both inspiration and expiration CT scans. 6. Representative 2D coronal histological slide from fibrotic mice and the corresponding functional map. 7. Bronchial tree geometries and functional maps used in CFD simulations and whole lung models.**



The other vital part of any image database is diversity of the data. This is even truer with diseases that are considered heterogeneous. It is unwise to attempt to create reliable algorithms for a heterogeneous disease based on a homogeneous database, as biases could be extreme. To date, the OSIC Cloud contains more than 5,000 fibrosing lung disease scans, with 20,000 committed from all over the world. While not extensive compared to a mainstream disease database, it is the largest repository of its kind for a rare lung disease. This anonymized database has also expanded to include a variety of machine modalities, multiple lung diseases and, most recently, routine lung-cancer screenings to search for the presence of interstitial lung abnormalities to drive early detection and understand potential progression. Because imaging plays a major role in assessing drug trial eligibility for fibrosing lung diseases, and with few approved drugs for this category of diseases, it is incumbent upon all of us to drive efficiency in finding successful therapeutic solutions for patients in need.

Currently, there are 35 companies and more than 60 computational scientists and researchers using the OSIC Cloud. Two companies have submitted for United States Food and Drug Administration (FDA) algorithmic approval and two more are close to submission [56, 57]. Companies have used the database for feature extraction to quantify disease severity [58-61]. Others have built a lung disease phenotype library [62, 63]. A postdoc working with OSIC has used the database to attempt to identify new disease patterns using unsupervised clustering. Further, OSIC's Ahmed Shahin has created a new progression and mortality prediction model named CenTime, which uses images and clinical data to give direct time to death estimates by using limited non-survivor cases [64]. Further, large image databases allow extraction of bronchial tree geometries and functional information to be used in CFD simulations and whole lung models. This is expected to enhance fidelity and realism of models and would enable customization of drug products for specific patient populations or severity of diseases.

## Integrating imaging techniques with experimental animals to facilitate pulmonary drug discovery

The use of animal models in research is an essential step in understanding the impacts on various stages of disease progression and developing new medications. One of the most significant barriers to drug discovery is the lack of accessible mouse models that replicate human pathophysiology and disease phenotypes.

A range of animal models for chronic lung disorders has been developed, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and idiopathic lung fibrosis (IPF). However, none of these models completely replicate the characteristics of the human disease. While numerous molecular pathways are implicated in the onset and progression of chronic lung diseases, understanding of their etiology remains limited. Only by gaining deeper knowledge of these processes will it be possible to identify more therapeutic targets and facilitate development of new therapies.

Clinical visualization of human lung diseases primarily relies on imaging methods such as high resolution computed tomography (HRCT), positron emission tomography, single photon emission computed tomography (SPECT) and magnetic resonance imaging. Although these technologies do not provide precise measurements, they have been used extensively for diagnosis to visualize mechanical and physiological responses such as diaphragmatic motion, pulmonary perfusion and ventilation, and airway remodeling, as well as to evaluate responses to pharmacological treatment [65, 66]. Until now, conventional assessments in preclinical studies typically have depended on invasive and terminal procedures, such as lung function evaluation, *ex vivo* assessment of pulmonary cellular infiltration and observations of anatomical changes like airway remodeling and collagen deposition [67-70]. However, while these methods can provide valuable insights, they are known to exhibit high variability among animals and merely capture a single moment in time within a significantly more intricate and dynamic biological process. Neither histology nor biochemical analysis provide information about a lesion's temporal and spatial distribution throughout a study and may limit following the pathogenesis of a disease in the same subjects.

Recently, medical imaging techniques with the prefix "micro," such as μCT, μPET and μMRI, have been developed and proven reliable in assessing lung diseases at various time points in living animals, allowing each subject to act as its own control. These technologies serve as a translational step between preclinical research and clinical practice [71-73]. In particular, *in vivo* lung μCT, which offers strong air-tissue contrast, is increasingly being employed in pulmonary research to investigate respiratory diseases in experimental animals [74]. Indeed, serial μCT-based analysis can provide excellent air-tissue contrast results, including quantitative information enabling longitudinal assessment, comparison between treatment groups and precise tomographic information in individual animals. Cross-talk between μCT and experimental animals could be exploited, specifically in the pulmonary fibrosis disease model. Bleomycin (BLM)-induced lung fibrosis is the most commonly used mouse model for studying disease pathogenesis and evaluating the efficacy of new potential antifibrotic drugs [75, 76].

However, lung segmentation is required for any quantitative analysis of chest CT scans, which is time-consuming and subject to inter- and intra-observer variability, if performed manually. This is a pertinent obstacle in fibrosis drug discovery, as a large

number of scans must be analyzed and trustworthy, quantitative data obtained in a very short period of time. Moreover, dynamic lung function biomarkers can only be derived by segmenting two reconstructed datasets, one for end-inspiration and the other for end-expiration [72, 77]. Without such information, only a static view of the intrapulmonary condition can be provided. However, these limitations have recently been addressed through development of a fully automated µCT deep learning approach for rapid quantitative analysis. The technique would be used for precise and dynamic preclinical investigation of lung fibrosis progression as well as evaluation of the response to antifibrotic therapy [72, 73, 78].

As described in the pipeline shown in Figure 3, µCT imaging can provide functionally relevant *in vivo* biomarkers that allow longitudinal, region-specific measurements of lung function, revealing a robust structure-function relationship, thereby facilitating translation of preclinical findings to the clinical setting. This work can make an essential contribution by analyzing the link between *in vivo* biomarkers and histological features. µCT imaging, coupled with histology, can be utilized to offer more accurate 3D information about individual animals as the disease progresses. Furthermore, the critical importance of µCT in decreasing the number of animals required per experiment has been proven. This is consistent with the 3R principles (Replace, Reduce, Refine) because each animal should be compared to its own baseline control, consequently minimizing variability. This approach can also decrease costs considerably and optimize efficiency of the drug discovery process.

The aerosol deposition studies mentioned earlier are conducted on portions of the respiratory system or on single branches of the bronchial tree. In addition, these studies can be extended to the whole tree by performing *ex vivo* deposition in fleshly, explanted animal lungs [79, 80] or by exposing animals to an aerosol in controlled conditions and imaging them post mortem [81].

Overall, the process of developing new drugs is expensive, time-consuming and risky; only a small number of medications are approved each year. To move more quickly and effectively into clinical trials, new approaches are needed to find novel drug candidates. It is recognized that animal models have drawbacks; their lung architecture differs from that of humans and DPIs designed for patients cannot be directly used with animals. However, to overcome the latter limitation, animals can be treated intratracheally to simulate DPI treatment [82] or by using inhalation towers that mimic aerosol administration [83]. To date, these methods are considered valuable for understanding the behavior of inhaled compounds and validating data from simulations.

It is possible to design preclinical experiments that not only can predict clinical imaging observations but offer a mechanistic understanding of the observed biological response, since the majority of molecular imaging techniques are standard procedures in clinical radiology departments and have equivalents in the experimental research setting. µCT imaging has been shown, in a number of animal models, to be an effective technique for accurately visualizing and measuring the dynamic progression and localized severity of lung disease. However, to maximize the benefits of this imaging approach, the post-processing analysis must be automated. On the computational side, deep learning is already being employed for extracting functionally important biomarkers, which allow longitudinal, region-specific measures of lung function, indicating a rather stable structure-function connection. Similar approaches could be extended and adapted to other animal models such as rabbits or rats by transfer learning.

The ability to analyze and quantify a specific molecular read-out in conjunction with anatomical alterations in the same animals at multiple time points marks a significant advancement in understanding disease development, with implications for functional and pharmacological studies. These studies can pave the way for a novel, more efficient drug discovery approach and shed new light on the necessity of examining clinical endpoints in preclinical trials, providing a better indication of new and more efficient therapies to advance to the clinic.

## Conclusions

The application of CFD and CFD-DEM simulation for inhaler design and optimization appears very promising. Air dynamics and inhaler resistance can be predicted quantitatively, even by simple Reynolds-averaged Navier-Stokes (RANS) calculations, when aerosol dynamics quantitative results are attainable only in limited cases. However, the use of particle coarse-graining and relative comparison among different inhalers can convey multiple, useful insights. A correlation between simulated quantities and *in vitro* inhalation performance can be established, in some cases, thereby paving the way for machine-learning-based geometry optimization. Meanwhile, the first attempts to simulate *in vitro* performance experiments are ongoing [84].

*In vitro* experiments could be significantly improved. To the best of our knowledge, a systematic study of the ways various materials or surface finishing for casts reflects on measured properties is not available. Rigid models of the upper airways could be complemented by compliant sections presenting distal airways. In fact, deformability seems to play a role, at least when studying the frequency response of high frequency oscillatory ventilation techniques [85]. Further, standardized databases can be created for *in vitro* patient-specific measurements. Phase-discriminated measurements could allow simultaneous measure-

ment and imaging of active pharmaceutical ingredients (APIs) and excipients.

The CFD and whole lung models discussed in the first part of our review also can be extended to animal models, where they easily could be tested and validated due to the increasing application of functional imaging to animals. Conversely, having reliable and robust computational techniques to simulate both animal and patient lungs could enable better translation of animal model results to patients [86, 87]. This could certainly improve the translation of preclinical data, generated in animal models, to humans for new inhaled drug products under development. Future developments for the medical imaging repositories include AI image generation methods using diffusion models, synthetic work focused on data enrichment and the improvement of specificity on quantitative biomarkers.

Greater collaboration among the communities of researchers studying medical imaging analysis, modeling and simulation, experimental measurements on airflow and aerosol transport, and toxicology/pharmacology could certainly help drive change toward data-driven and science-driven healthcare.

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