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"What is personalized lung poromechanical modeling and how can it improve the understanding and management of fibrotic interstitial lung diseases?"

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1. Why develop biomechanical models to evaluate pulmonary fibrotic diseases?

Interstitial lung diseases (ILDs) leading to pulmonary fibrosis have a wide spectrum of etiologies and clinical presentations, of which idiopathic pulmonary fibrosis (IPF) is the archetypal fibrotic disease [1]. Progressive pulmonary fibrosis is a severe and often fatal disease, characterized by the replacement of normal gas-exchanging tissue [2] by inflammatory and fibrotic cells within an abnormal extracellular matrix) resulting in loss of elasticity and increased lung stiffness [3,4]. High-resolution computed tomography (CTscan) plays a central role in the assessment of ILDs, providing detailed imaging of the lung parenchyma and helping to differentiate between different ILDs [5]. Fibrosis is assessed by characteristic patterns observed on CT scans, with increasing use of machine learning models used for quantification in clinical research [6,7].

We hypothesized that by combining images from the inspiration and expiration phases of breathing, mathematical modelling could help to elucidate the pathophysiology of ILDs at different anatomical scales and during simulated breathing. A dynamic approach, as opposed to static imaging, by assessing the deformation, stress and stiffness of the different parenchymal areas, could improve understanding of the correlations between pathology and equivocal imaging findings. In addition, it could shed light on the local mechanical stresses generated and experienced as a result of structural changes secondary to fibrosis. This is crucial, as increasing evidence points to the role of mechanotransduction in disease progression [4,8,9]

Therefore, we developed a poromechanical dynamic model capable of assessing the heterogeneous regional lung compliance and mechanical stresses in a patient specific manner based on CT scans for diagnosis and follow-up of ILD (10,11). To the best of our knowledge, the only published results are those obtained by registering the inhalation and exhalation images of a CT scan to calculate the Jacobian determinant, which characterizes local volume changes [12]. This measure has been used in ILD to assess the progression of fibrosis between two inspiratory CT scans [13], but it does not provide an estimate of the induced mechanical forces that can be derived from the changes in the images. A major drawback of this approach is the variation in lung volume between each CT scan acquisition as the reproducibility of inspiration and expiration is poor, especially as the disease progresses. Another line of work has been proposed that aims at modelling the fibrosis processes at the alveolar scale [14], allowing to reveal mechanotransduction mechanisms at play in pulmonary fibrosis [14], but cannot integrate directly organ-scale clinical data. In our efforts, we assumed that mathematical models would allow the integration of real data from patient images, integrate lung fluctuations over time and provide an estimate of the mechanical stress induced by fibrosis, making it a valuable tool for understanding the pathophysiology of ILDs and the management of ILD patients [15].

2. What is a personalized lung poromechanical modeling?

Let us now focus on the questions of "what exactly is personalized poromechanical modeling?" and "why is it relevant to fibrosis diagnosis and treatment?". One might first ask what a model is. To make it simple, let us consider that they are mathematical relations that mimic a phenomenon (e.g., the law of gravitation) or an object (e.g., the lung), and can be used to describe (i.e., physics/biology) or predict/control (i.e., engineering/medicine). It is important to remind the classical aphorism "all models are wrong, some can be useful", and emphasize that the art of modeling does not consist in

building the "perfect" model, but rather a model with the right amount of ingredients described with the right level of detail to address a given question. Thus, to derive useful biomarkers from clinical images, pure image analysis based on physics-agnostic statistical models trained on available data might be "enough"; however, for some questions, introducing kinematics/motion information (which requires multiple images) might prove critical; similarly, the introduction of forces, stresses, and other mechanical concepts may prove extremely useful, as we will now discuss.

However, before diving into poromechanics, let us discuss the notion of model personalization. Basically, most mathematical relations that form models contain parameters that must be assigned numerical values for the model to be evaluated. If a physics-based model involves drastically less parameters (most of which being fully interpretable) than machine learning models (whose parameters are often hard to interpret), and if some of these parameters (e.g., gravity, mass density of water, etc.) have known values, multiple parameters (e.g. lung geometry, local parenchymal compliance, etc.) must be estimated based on patient data. This is usually done by finding the parameter values that somehow minimize the distance between the model response and the data; for instance, one can find tissue stiffness/compliance values that make a lung model produce a breathing motion that corresponds to the one observed in clinical images. And once the parameters are personalized for a given patient, the model becomes a digital twin of the organ of the patient, and can potentially be used (i) to estimate various biomarkers that cannot be measured directly (e.g., the mechanical forces within the lung), thus augmenting the data and providing diagnostic capabilities, as well as (ii) to predict the evolution of the organ or its response to various drugs or procedures, thus providing prognostic or therapeutic capabilities [15]. Note that techniques at the interface between modeling and data processing are currently a very active field of research and are evolving fast [15].

We can now focus on mechanics. Generally speaking, it is the science of motion (notably deformation, strain) and forces (notably pressure, stresses). Mechanics is important for the lung not only because it is essential to its function, but also because it could be a driving force for diseases such as IPF [4,8,9]. More generally, biomechanics and mechanobiology, two fields at the interface between mechanics and biology, are nowadays extremely active. A mechanical model describes the temporal and spatial evolution of strains (notably the change of volume characterized by the so-called Jacobian, and shearing) and stresses (similarly, the internal pressure and shear forces within the tissue), both being related by the stiffness (the inverse of the compliance). The ingredients of the model are the geometry (which can be generic or personalized), equilibrium (derived from the Newton's third law, it is a fundamental equation that holds for any material), behavior (relationship between stress and strain) and boundary conditions (coupling between the organ and its environment), the latter two offering many choices in terms of level of details.

If a basic mechanical model would describe the lung as a simple continuum deforming under the action of breathing forces, without taking into account its various constituents, poromechanics allows for a more detailed description. It is a branch of mechanics that describes the combined deformation of a solid "matrix" (here, the lung parenchyma) and the flow of fluids (here, air, blood, etc.) within its conduits and pores through a mixture (i.e., without explicitly representing the microstructure) approach. It was originally developed for geological formations, notably by [16]. Several attempts have been made to apply it to the lung [17,18]. It allows notably to integrate the porosity field that can be extracted from clinical images. As a consequence, the local effective compliance becomes a product of the solid compliance and volume fraction—in other words, the mixture can be stiffer in some regions than in others because it is less porous or because the matrix is stiffer.

3. How can personalized lung poromechanical modeling improve the understanding and management of fibrotic interstitial lung disease?

Back to organ-scale poromechanical models, once personalized to a given patient by identifying model parameters such that the model response matches the patient data as much as possible, they potentially offer multiple possibilities beside purely kinematical or even basic mechanical approaches. For instance, as discussed in Patte et al. [10] and in Laville et al. [11], when used in clinical trials, they could be used to estimate regional tissue compliance, which could represent an important biomarker for early and non-invasive differentiation between various types of fibrosis. Such biomarkers could also be used to monitor the affected areas during disease progression, allowing a quantitative evaluation of patient response to existing and new potential treatments. It is with this hypothesis that we began the “Quantitative Multi-compartment Study by Thoracic CT Scanning in Progressive Pulmonary Fibrosis (MLQ-CT study, ClinicalTrials.gov ID NCT06618924, founded in 2023 by the French National Research Agency) and aiming to evaluate a set of imaging biomarkers to identify patients at risk of progressive and irreversible fibrosis and those who could respond to antifibrotic treatments, from the numerical modeling of routine thoracic CT scans [15].

In summary, the synergy between radiologists, pulmonologists, and mathematicians/mechanicians in the field of ILDs is evident in our research endeavors. By combining our respective expertise, we are able to conduct cutting-edge studies that push the boundaries of our understanding of ILDs. Poromechanics modeling allows to see beyond images, transforming X-ray densities into functional characteristics, complementary to pulmonary function tests.

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- **The boundary conditions of our lung model have been improved, to take into account gravity and heterogeneous pleural pressure fields.**

Figure legend

Personalized lung model: Summary of the biomarker extraction method using a personalized poromechanical lung model applied to a patient with mild pulmonary fibrosis. The input images are inspiration and expiration CT images presented sagittally along the midclavicular line (top row). The different steps of the process can be schematically divided into: (i) "mesh reconstruction" (geometry) from medical images using segmentation, (ii) displacement field extraction between end-exhalation and end-inhalation using motion tracking, (iii) "model parameter estimation" using optimization, (iv) biomarker calculation using the personalized model for specific disease investigation ("digital twin"). The biomarker shown in this figure represents the deviatoric stress value (i.e. shear stress, from 0.1 to 2 MPa), which is one of the candidate biomarkers along with strain invariants (the third being the Jacobian) and hydrostatic stress. In this example, increased deviatoric stress values related to shear stress are shown (ultramarine to red areas) in fibrotic regions that are localized in the lung periphery.

