2022 Proposition de Sujet de Stage de Master 2

- **Laboratoire d'accueil** : Synchrotron Radiation for Biomedicine (STROBE) Inserm UA07 ; Dir. Sam Bayat.

- **Intitulé du sujet :** A Patient-Specific *Digital Twin* for Personalized Assessment of Mechanical Ventilation in Patients with ARDS.

- **Nom, prénom, qualité du Directeur de thèse et laboratoire :** Sam BAYAT PUPH UGA HDR (2009), Laboratoire STROBE Inserm UA07

- **Noms des doctorants actuellement sous la responsabilité du Directeur de thèse (toutes ED confondues):** Mehdi Shekarnabi, Julien Cohen.

- **Codirection éventuelle (Nom, Prénom, laboratoire, préciser si HDR) :** Sjeng Quicken, Eindhoven University of Technology (TUE); Maciej ORKISZ PU UCBL HDR (2003) Laboratoire CREATIS, équipe MYRIAD.

- **Composition de l'équipe d'encadrement :** Sam Bayat (PUPH, STROBE), Sjeng Quicken (TUE), Maciej ORKISZ (PU, CREATIS).

- **Liste de 5 publications récentes de l'équipe d'encadrement :**

1. Cohen J, Shekarnabi M, Destors M, Tamisier R, Bouzon S, Orkisz M, Ferretti GR, Pepin JL, and Bayat S. Computed Tomography Registration-Derived Regional Ventilation Indices Compared to Global Lung Function Parameters in Patients With COPD. ***Frontiers in physiology*** 13: 862186, 2022.10.3389/fphys.2022.862186

2. Richard JC, Sigaud F, Gaillet M, Orkisz M, Bayat S, Roux E, Ahaouari T, Davila E, Boussel L, Ferretti G, Yonis H, Mezidi M, Danjou W, Bazzani A, Dhelft F, Folliet L, Girard M, Pozzi M, Terzi N, and Bitker L. Response to PEEP in COVID-19 ARDS patients with and without extracorporeal membrane oxygenation. A multicenter case-control computed tomography study. ***Crit Care*** 26: 195, 2022.10.1186/s13054-022-04076-z

3. Quicken S, Mees B, Zonnebeld N, Tordoir J, Huberts W, and Delhaas T. A realistic arteriovenous dialysis graft model for hemodynamic simulations. PLoS One 17: e0269825, 2022.10.1371/journal.pone.0269825.

4. L. Porra, L. Broche, L. Dégrugilliers, G. Albu, I. Malaspinas, C. Doras, M. Wallin, M. Hallbäck, W. Habre and S. Bayat. Synchrotron imaging shows effect of ventilator settings on intra-breath cyclic changes in pulmonary blood volume. **Am. J. Resp. Cell Molec. Biol.** 2017;57(4):459-467 doi: 10.1165/rcmb.2017-0007OC.

5. L. Broche, G. Perchiazzi, L. Porra, A. Tannoia, M. Pellegrini, S. Derosa, A. Sindaco, J.B. Borges, L. Dégrugilliers, A. Larsson, G. Hedenstierna, A. Wexler, A. Bravin, S. Verbanck, B.J. Smith, J.H.T. Bates and S. Bayat. Role of Parenchymal Interdependence in the Dynamics of Recruitment/Derecruitment in Injured Lung. **Crit. Care Med.** 2017; 45(4):687-694 doi: 10.1097/CCM.0000000000002234.

- **Description détaillée du projet :**

1. ***Positionnement médical/Contexte***

Many patients in the intensive care unit require mechanical ventilation (MV) to take over the work of breathing. Although MV is vital for patient survival, it can induce potentially life-threatening ventilator-induced lung injury (VILI) (1). This development is primarily caused by exaggerated and highly heterogenous mechanical loading of the lung during MV, which can lead to lung tissue damage due to local overdistention (*i.e.* volutrauma or barotrauma) or due to repeated opening and closing of the alveoli (*i.e.* atelectrauma) (2). The highly inhomogeneous loading of the lung can be attributed mainly to the derecruitment of lung tissue, gravity effects or to local variation in mechanical properties of the lung due to inflammation (2,3).

Mathematical models of the respiratory system can give local insight into lung mechanics and mechanical loading during MV (4,5). As such, when properly tuned, these models may provide new insight in VILI development. Currently however, most respiratory mechanics models assume homogeneous lung behavior. This assumption conceivably results from the fact that local lung properties are difficult to assess *in vivo*. However, since lung properties can vary considerably within the lung, the applicability of such models to investigate VILI development may be limited. Some methodologies have been described in the literature to implement more realistic compliance distributions in respiratory modelling. For instance, Roth *et al.* assumed a linear relation between CT image intensity (*i.e.* Hounsfield units) and local lung compliance (5). Unfortunately, the general validity of such assumptions is difficult to verify.

Recently, methods have been developed at STROBE (Grenoble) and CREATIS (Lyon) laboratories in collaboration with CHU Lyon & Grenoble to track local lung deformation using CT image registration (6). These methods have been applied to a dataset of almost 100 mechanically ventilated patients (Figure 1), who were all imaged at two known airway pressures. Since in this approach pressure increments and resulting local lung tissue deformation are known, it may be possible to use these analyses to derive realistic patient-specific distributions of lung material properties. Subsequently, these patient-specific distributions can be used to create more realistic models of respiratory mechanics during MV, paving the way for a "*Digital Twin"* that could ultimately allow *in silico* personalized optimization of the mechanical ventilator settings in order to minimize the risk of VILI.

2. Méthodologie envisagée

To estimate local lung mechanical parameters, several approaches can be taken. First, a purely data driven forward modelling approach can be used to directly derive local mechanical metrics from the deformation field. An initial approach to achieve this could be to simply compute local lung compliance using $C = \Delta V / \Delta P$, where ΔV represents the registration based local lung deformation and ΔP the pressure increment between the two images. Note however that in this approach, amongst others, mechanical interactions between neighboring regions are difficult to account for, which may limit the general applicability of this method.

Alternatively, inverse modelling techniques may be considered to estimate local lung mechanical parameters. Here, a mechanical model of the lungs is first created. Subsequently, local material properties in the model are fitted such that at equal pressure loading, simulated deformations match those observed in the CT image registration. When the observed and simulated deformation fields

match, it can be assumed that the fitted local material parameters are similar to the real values. A possible methodology that may be interesting in this context is presented in Poree *et al.* (7).

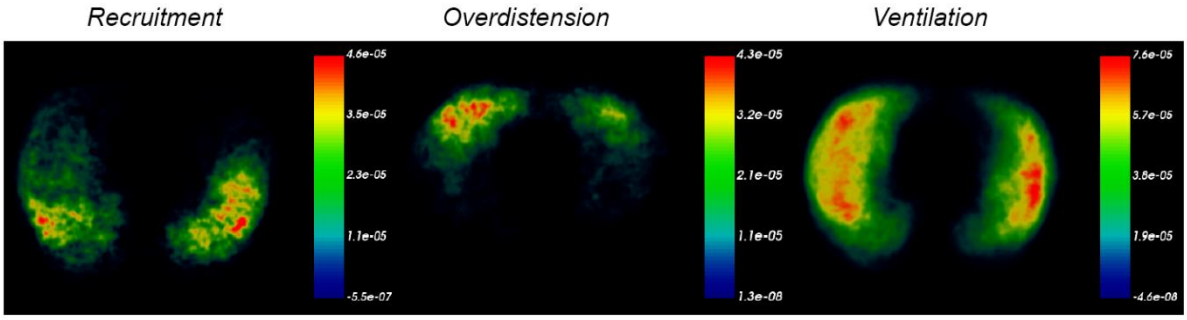

Figure 1. Axial views of a 3D atlas based on image-registration analysis between respiratory pressures of 5 – 15 cmH_2O, in 91 patients with ARDS due to COVID-19, under mechanical ventilation. *Unpublished data*.

3. *Objectifs du stage*

In this 6-month project you will perform your work at STROBE, Grenoble, France, in collaboration with CREATIS, Lyon, and the Department of Biomedical Engineering, Eindhoven University of Technology (TUE). You will develop methods to derive local lung material properties from registration-based deformation maps. Subsequently, the derived local mechanical parameters may be implemented in a 0D modelling framework of respiratory mechanics developed at the Eindhoven University of Technology to investigate patient-specific lung mechanics during MV.

1. *Bibliographie du sujet*

1. Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. N Engl J Med. 2013 Nov 28;369(22):2126–36.
2. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med. 2020;46(12):2385–96.
3. Cressoni M, Cadringher P, Chiurazzi C, Amini M, Gallazzi E, Marino A, et al. Lung Inhomogeneity in Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2014 Jan 15;189(2):149–58.
4. Roth CJ, Ismail M, Yoshihara L, Wall WA. A comprehensive computational human lung model incorporating inter-acinar dependencies: Application to spontaneous breathing and mechanical ventilation. Int J Numer Methods Biomed Eng. 2017;33(1):1–24.
5. Roth CJ, Becher T, Frerichs I, Weiler N, Wall WA. Coupling of EIT with computational lung modeling for predicting patient-specific ventilatory responses. J Appl Physiol. 2017;122(4):855–67.
6. Cohen J, Shekarnabi M, Destors M, Tamisier R, Bouzon S, Orkisz M, et al. Computed Tomography Registration-Derived Regional Ventilation Indices Compared to Global Lung Function Parameters in Patients With COPD. Front Physiol. 2022 May 26;13:862186.
7. Poree J, Chayer B, Soulez G, Ohayon J, Cloutier G. Noninvasive Vascular Modulography Method for Imaging the Local Elasticity of Atherosclerotic Plaques: Simulation and *In Vitro* Vessel Phantom Study. IEEE Trans Ultrason Ferroelectr Freq Control. 2017 Dec;64(12):1805–17.