UNIVERSITÉ CÔTE D'AZUR

Vader Center

- Center for VIRTUAL MODELING of RESPIRATION -

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Why modelling the pulmonary ventilation? Music, exercise and medicine.

VentiCorse 2019

IESC Cargèse, 18th to 22nd November 2019

Organization committee:
Grégory Blain (LAMHESS), Valérie Bougault (LAMHESS),
Olivier Legrand (INΦNI), Benjamin Mauroy (LJAD).

	Monday 18th	Tuesday 19th	Wednesday 20th	Thursday 21st	Friday 22nd
Morning	**9h00-12h15** **Respiratory physiology: Basic Concepts** Pr Dempsey (USA) **with a 10h00-10h15** Coffee break	**9h00-12h15** **Respiratory physiology and physics applied to wind instruments** Pr Cossette (Can) Pr Fabre (Fra) **with a 10h00-10h15** Coffee break	**Mathematical modeling of ventilation: from 0d to 3d models** **9h00-10h30** Pr Martin (Fra) **10h30-10h45** Coffee break **10h45-12h15** Dr Grandmont (Fra)	**9h00-12h15** Pr Dempsey (USA) **Respiratory System Response to Exercise** **10h00-10h15** Coffee break	**9h00-10h30** **Building an atlas of the human airways at the single-cell level: From cell droplets to oceans of data** Dr Zaragosi (Fra) **10h30-11h00** Coffee break **11h15** Departure for airport (flights at 14hXX) + take away lunch
12h15-13h15	**Lunch**	**Lunch**	**Lunch**	**Lunch**	**Lunch**
Afternoon	**13h30-15h30** **Respiratory Measurements** Pr Aliverti (Ita) **with a 15h30-16h00** Coffee break **16h00-17h30** **Modeling of forced expiration maneuver** Pr Filoche (Fra) **19h00-20h00** Poster session	**14h-17h** **Music workshop** **with a 15h15-15h30** Coffee break **18h45-20h00** Poster session	Free or Hiking in the callanques (transport by bus, schedule: 14h-18h, register to the organisers!)	**13h30-15h30** **Respiratory System Responses to Special Stressors/Circumstances** Pr Dempsey (USA) **15h30-15h45** Coffee break **15h45-16h45** **Exercise-induced asthma** Dr Bougault (Fra) **17h00-18h30** **Modeling of ventilation and aerosol in the healthy and emphysematous lung: can we understand experimental results?** Dr Vignon-Clémentel (Fra)	**13h30** Departure for airport (flights after 15h30)
Evening	**20h00**: Dinner in IESC	**20h00**: Dinner in IESC	**19h30**: Dinner in Cargèse	**19h30**: Corsican dinner in IESC	

ABSTRACTS – VentiCorse 2019

Monday 18th of November 2019

9h00-12h15 Pr Dempsey (USA) - **Respiratory physiology: Basic Concepts**

Recommended material for following this lecture is available here:
https://wetransfer.com/downloads/d813a49b8c77e20ae30444f47be3aeb920191113090908/d0c47aabfbad6d045c8ffd5ac57f264820191113090908/930c4d

13h30-15h30 Pr Aliverti (Ita) - **Respiratory Measurements**

This lecture will provide an overview of the main measurements methods and instruments which allow the development of studies regarding respiratory mechanics and modeling. After an introduction dealing with the basic measurements (i.e., volume, flow, pressure), plethysmographic methods, including total body plethysmography and measurement of ventilation from body surface measurements will be described. Successively, the lecture will describe the main methods for assessing both active (respiratory muscle function) and passive (mechanical properties) components of the respiratory system. Finally, imaging techniques based on CT, MRI and ultrasounds will be shown as the modern approach to assess pulmonary regional ventilation.

16h00-17h30 Pr Filoche[1,2] (Fra) - **Modeling of forced expiration maneuver**

Flow-volume loops (FVL) recorded during a forced expiration maneuver performed are one of the clinical gold standards tools of Pulmonary Function Tests (PFT). By imposing a mechanical challenge on the pulmonary airway system, the forced expiration maneuver allows physicians assessing the mechanical properties of the lung and possibly detecting alterations or diseases affecting the lung structure or mechanics. However, the information extracted from FVL is the result of a “black box” measurement which by definition is global and may hide local or deep modifications of the bronchi and parenchyma properties.

Is it possible to accurately reproduce these FVL through numerical simulations of the dynamics of gas transport in the airways? Such simulation would require in general computing fluid transport and fluid-structure interaction in the entire tracheobronchial tree, i.e., about 30,000 to 60,000 individual bronchi, all individual bronchial flows being coupled through Kirchhoff’s laws. We will present how FVL can be theoretically and numerically modeled in an efficient way. We will show how this approach is backed by experimental results, and will finally provide quantitative predictions about the alteration of the flow-volume curves in various scenarios such as COPD.

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References

[1] D.P. Schilder, A. Roberts, D.L. Fry, “Effect of gas density and viscosity on the maximal expiratory flow-volume relationship”, J. Clin. Invest. 42(11):1705-1713, 1963.
[2] M. Florens, B. Sapoval, M. Filoche, “The optimal branching asymmetry of a bidirectional distribution tree”, Comput. Phys. Commun. 182:1932-1936, 2011.
[3] M. Filoche and M. Florens, “The stationary flow in a heterogeneous compliant vessel network”, J. Phys.: Conf. Ser. 319:012008, 2011.
[4] Florens, B. Sapoval, M. Filoche, “An anatomical and functional model of the tracheobronchial tree”, J. Appl. Physiol., 110:756-763 (2011).

19h00-20h00 Poster session

Antoine Galco, *Pulsated forcing of a 2D idealized bronchus filled with non-Newtonian fluid.*
Cyril Karamaoun, *The lung: a heat and water exchanger?*
Alireza Kazemi, *Transport of complex fluids in the human pulmonary airway system.*
Frédérique Noël, *Optimal ventilation in a model of the lung.*

Tuesday 19th of November 2019

9h00-12h15 Pr Cossette (Can) and Pr Fabre (Fra) **Respiratory physiology and physics applied to wind instruments**

The morning session will be dedicated to foundational principles about sound production of wind instruments as well as a description of the respiratory parameters associated to sound production. We'll give an overview of the air pressure and flow requirements across different families of instruments and will demonstrate how these influence sound control. We'll then provide general principles on how the respiratory system adapts between different musical tasks and requirements as well as for different position or individuals.

14h00-17h00 Music workshop

Through the day, but mainly during the afternoon, we'll explore the principles into practical demonstrations such as the pressure-volume curve of the respiratory system, measurements of flow, etc. We'll use Hexoskin shirts to measure chest wall and abdominal displacements and will look at Konno-Mead diagrams for different musical tasks.

18h45-20h00 Poster session

Olivier Legrand, *Variations on Respiratory Inductive Plethysmography: from wind instruments to speakers & an artist book entitled Souffle.*

Vincent Fréour, *On the control of respiratory muscles in trombone performance.*

Michaël Brunengo, *Modelling the effects of respiratory physiotherapy on human lungs,* and *Deformation of an elastic material paired with a tree structure.*

Thomas Laporte, *An end-to-end algorithm for creating 3D and customized models of the respiratory system.*

Jonathan Stéphano, *Lung volume vs airflow: a match for shear stresses distribution in the bronchial tree.*

Wednesday 19th of November 2019

9h00-12h15 Dr Grandmont (Fra) and Pr Martin (Fra) - **Mathematical modeling of ventilation: from 0d to 3d models**

9h00-10h30 Pr. Martin,
In this talk, simple models of respiratory ventilation are considered. 1) Mechanical ventilation: basic properties of mechanical ventilation are presented. In particular, the derivation of the resistance of the bronchial tree is discussed, starting from the definition of the resistance of a simple tube to the equivalent resistance of the whole bronchial network. Model values and experimental values are then compared and discussed, highlighting the limitations of these simple models and leading to the consideration of nonlinear phenomena and subsequent nonlinear models (lumped 0d models, 3d models, 3d-0d models...). 2) Gas exchange: a lumped model of oxygen diffusion through the alveolar-capillary membrane is presented in a simple framework, including hemoglobin saturation and possible kinetic limitation. Comparison with data from the literature is discussed. Enriched models will be introduced in order to focus on different specific subjects of interest (heterogeneity of the gas exchange, helium-oxygen mixtures...).

10h45-12h15 Dr Grandmont,
In this lecture we will present some mathematical models developed to describe the ventilation at rest or for forced respiration. Motivation is getting a hierarchy of representative but easily parameterizable mathematical models to describe the mechanical phenomena related to human breathing. The difficulties associated with the study of such physiological systems lie in their complexity, in the different scales at play, in the multiphysic aspect of the phenomena but also in the few measures available. The choice of the level of description depends on the goal and on the available data. It may

be used to understand a global mechanism and the effect of pathologies on this mechanism as shown in the lecture of S. Martin, or to obtain, for instance, a three-dimensional description of the flow to further predict, for instance, in which areas of the tree will be deposited curative or polluting particles. We shall present several types of tridimensional models according to which phenomena one wants to focus on: do we want to have a precise description of the air flow or a precise description of the lung parenchyma motion (or both). We shall also investigate wether these models are able to represent reality, can be used as a prediction tool or to help the identification of pathologies.

Thursday 20th of November 2019

9h00-12h15 Pr Dempsey (USA) - **Respiratory System Responses to Special Stressors/Circumstances**

Recommended material for following this lecture is available here:
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13h30-15h30 Pr Dempsey (USA) - **Respiratory System Response to Exercise**

Recommended material for following this lecture is available here:
https://wetransfer.com/downloads/d813a49b8c77e20ae30444f47be3aeb920191113090908/d0c47aabfbad6d045c8ffd5ac57f264820191113090908/930c4d

15h45-16h45 Dr Bougault (Fra) - **Respiratory Health of elite athletes**

The percentage of athletes having exercise-induced bronchoconstriction (EIB) is very high, especially endurance sport athletes, making it one of the most common comorbidities in this group. Sustained high minute ventilation in conditions with dry air, high pollen or pollutants, and irritants are factors thought to increase the prevalence of EIB. There is a connection between the incidence and the number of training years and intensity of the sport suggesting that repetitive epithelial injury may play a role, maybe through a remodeling of the airway smooth muscle. After the characterization of airway disease and EIB in athletes, further research questions will be raised to elicit new multidisciplinary collaborations.

17h00-18h30 Pr Vignon-Clémentel (Fra) - **Modeling of ventilation and aerosol in the healthy and emphysematous lung: can we understand experimental results?**

Computational modeling has become a powerful tool to investigate ventilation and aerosol spread in the lung in health and disease, such asthma or emphysema. For respiration, our simulations range from global 0D (zero-dimensional) models for parameter estimation from data, and 3D models for more regional representation for the airways. The selection of one or the other, or their coupling, depend on the biomedical question to be addressed, the heterogeneity of the disease, and the available data. Moreover, aerosol spread in the lung cannot be currently imaged in a dynamic way. Simulations can provide insights about such dynamics in health versus disease (here emphysema). We have coupled 3D transport and deposition models to their 1D counter-part models of the distal lungs to study differences between lobes, and inspiration versus expiration. We will see how far these different models can help understanding experimental in-vivo data and why the apical lobe is called the 'dirty lobe'.

Friday 21th of November 2019

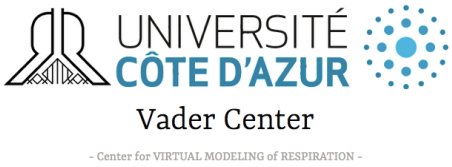
9h00-10h30 Dr Zaragosi (Fra) - **Building an atlas of the human airways at the single-cell level: From cell droplets to oceans of data**

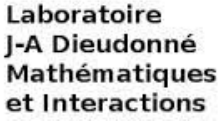
To understand the preservation of homeostasis in the human airway epithelium, it is crucial to identify drivers of differentiation dynamics and cell fate. In chronic airway diseases, the injured

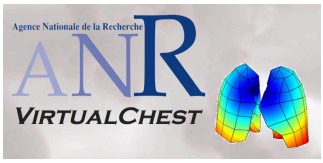
epithelium frequently displays defective regeneration leading to tissue remodeling, characterized by a loss of multiciliated cells and mucus hyper-secretion. We have used single cell transcriptomics (1) to characterize the sequence of cellular and molecular processes taking place during human airway epithelium regeneration in vitro and (2) to explore cellular heterogeneity of human airways by building an atlas from 12 healthy volunteers. From our single-cell data obtained from air-liquid interface primary cell cultures and lineage inference algorithms, we have unraveled cell trajectories from basal to multiciliated cells, providing markers for specific cell populations, such as deuterosomal cells, i.e. precursors of multiciliated cells. We report that goblet cells, like club/secretory cells, can act as precursors of multiciliated cells. We have extensively characterized epithelial cell populations at the molecular level and have confirmed our findings by collecting about 80 000 cells of healthy volunteers, by bronchoscopy at 35 distinct locations, from the nose to the 12th division of the airway tree, either by forceps, or brush biopsies. This atlas has revealed a strong gradient of gene expression in suprabasal, secretory, or multiciliated cells between nose and bronchial airways. By contrast, a much smaller gradient was detected between proximal, intermediate, and distal bronchial airway samples. Our atlas has also improved the description of 244 rare cells (0.3% of total), detecting ionocytes, pulmonary neuro-endocrine and brush cells, which likely derive from a unique population of precursor cells.

Altogether, the combination of in vitro data with the robust annotation of an unprecedented large single-cell cohort of 12 well-characterized human healthy volunteers establishes an important resource for future single cell investigations.

Acknowledgements





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