Center for **V**irtu**A**l mo**D**elling of r**E**spi**R**ation - **VADER center**

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Academies: 2 (principal), 4 and 5
Objectives. We propose to create an UCA JEDI interdisciplinary center on the topic of respiration modelling by federating respiration' strengths in UCA and in Nice industrial tissue. With the support of the "Maison de la Simulation", we will more particularly focus on *in silico* models. The center will promote respiration's modelling for original, striking and valuable applications such as artistic expression (i.e. dance and music), environmental, health, industrial (i.e perfumery) or sports activities. The center also aims to create a dynamic by developing new specific actions of training, not only towards students, academics and private companies, but also towards the general public through popularization actions. The interdisciplinary range of the center would be the first of its kind in the world with the aims to become a national and international reference.

Background

Rationale of the project. The word "respiration" covers different, though related, meanings depending on the context in which it is used. In common usage, respiration refers to the phenomenon of back and forth motion of air in the lungs, also called lung ventilation. In physiology, respiration corresponds to the integrated systems for oxygen transport and transfer from outside air towards the cells, and for carbon dioxide removal from the cells and transport to the outside air, typically involving organs such as lungs, heart and vessels, physical interfaces such as air/blood and blood/tissue exchanges surface. In biochemistry, respiration corresponds to the set of chemical reactions occurring in the cells and mitochondria. These reactions produce ATP from oxidative phosphorylation. This produces carbon dioxide, whose hydration leads to the formation of bicarbonate and acidic ions (H+). These metabolic by-products are constantly removed, being extracted in part from blood by the lungs where they recombine to form the exhaled carbon dioxide and water. As a consequence, oxygen, carbon dioxide, H+ and bicarbonate concentrations are strongly regulated by numerous chemoreceptors spread throughout the body. In the frame of this project, we will speak of respiration as the set of all the phenomena described above.
Respiration is constantly adjusted to the needs of the organisms. Not only respiration participate to homeostasis, it also participates to important communication functions -such as speaking, singing- and to adaption to exercise, diving or to compensatory functions in some diseases. Respiration is also plastic and specific trainings are developed to optimize respiration efficiency to reach higher demanding capabilities in sports, arts or mental performances. On the pathology side, respiration's diseases (such as sleep apnea syndromes) have high prevalence in the population like lung's cancer, asthma, chronic obstructive pulmonary diseases (COPD), diabetes, atherosclerosis, etc.
UCA strengths in the field of Respiration. We identified UCA members who work on topics related to respiration and who are interested into the center development. The projects developed by these teams involve national and international collaborations, and are often internationally renowned. They can be regrouped into four main axes:
1- Respiration and Health. Nice CHU and Lenval hospital both have research and clinical teams working on respiratory diseases. Researches range from lung's cancer (e.g. CHU, IRCAN), cardio-respiratory diseases in children and adults (CHU, Lenval, LP2M), pulmonary fibrosis and ciliated cells (CHU, IPMC), modeling of pH regulation (INLN, LP2M, LPMC, Axe Physique du Vivant), modeling of chest physiotherapy in the frame of cystic fibrosis (LJAD, INLN, Lenval hospital) or modeling of the fluid mechanics in the sinuses (LJAD). Moreover, we are in contact with several private biomedical companies (RespInnovation, IMape, Percussionaire).
2- Respiration and body performances. UCA hosts various researches and interests in human performances where respiration plays a crucial role: athletes' performance (LAMHESS), dancer's performance with artistic constraints on ventilation and metabolism (Ecole de Danse Rosella Hightower), performance of singers and of wind instruments' players (CIRM, CNRR, LPMC), Darwinian evolution of the respiratory system (LJAD).
3- Functions of respiration. Respiration is linked to the ***olfactory sense:*** olfactory cells are located in the nasal cavities and play a key role in many life functions ranging from sexual to metabolic rate. Molecular and psychophysiology of olfactory chemistry are investigated in ICN, in collaboration with Grasse perfumeries. ***Transport functions:*** the respiration system is a transportation system for the above mentioned gases but also for a large set of other compounds. UCA hosts research projects on allergen's concentration in air (IMREDD), on the modeling and optimization of oxygen and carbon dioxide transport in lung and blood (LJAD) and on the modelling of medicine delivery through blood (LJAD). Finally, a team in LPMC has developed a unique microfluidic experimental device that can be used to model experimentally transport within the vascular network.
4- Data for respiratory modelling. Real data are crucial for models' validation. The center will setup an exhaustive database from various patient's data collected in Nice centers (i.e CHU and Lenval hospitals), including non-respiratory data

(cardiovascular, life style, etc…). We also plan to develop data banks' sharing with other national and international partners, beginning with Paris Diderot and Auckland Universities. LAMHESS, Nice CHU, IM2S (Monaco) and other national and international partners have a long standing experience of data acquisition in sports. UCA also hosts I3S experts in signal processing for the cardiorespiratory coupling analysis and in image reconstructions. Also, a team in LJAD is specialist in fitting and validating models with high numbers of parameters. Finally, INRIA team AROMATH works on geometric modeling of complex shapes to support numerical simulations (shape extraction and optimization, image processing, etc.), with an application to the study of shapes of branching tubular structures such as blood vessels or the throat's trachea.

Hence, UCA hosts a rich pool of respiration's related researches, with a strong component in term of respiration's modelling through its informatics, mathematics and physics laboratories. In addition, the structure of UCA naturally supports *in silico* modeling with the "maison de la simulation". As a consequence, UCA exhibits a big potential for the development of a federative center focusing on the modeling of respiration, with original applications extracted from UCA members' diversity and from local industrial tissue.

Center's goals

Research program. The center will be based on the community created by the emergence of UCA JEDI, and begin with regrouping the strengths of UCA researchers on respiration within the frame of the 4 axes presented above. The center will also be associated with private companies interested in respiration modelling, and with whom we are in contact. Based on this configuration, the center will thus promote three main goals.

First, it aims at developing interdisciplinary researches to answer today's challenges in respiration modelling: a/ to develop sufficiently detailed biophysics-based integrative models that are able to bring quantitative predictions in respiratory physiology and diseases. b/ to develop very detailed models of respiration subsystems with "boundary" conditions to mimic correctly the effects of parts that are not included. c/ to gather and make easily available complete datasets in order to fit and validate the models.

Second, the center aims at promoting very original applications for the models, supported by center's members or private companies whose activity involves understanding or optimizing any or all of the respiratory processes.

Third, the center will create and maintain a dynamic about respiration's modeling: funding, thematic workshops, internationally renowned researchers' invitations, young researchers' promotion (dedicated workshop, prices, etc.), setup between researchers, clinicians, artists and private companies, proposal of thematic topics to international journals or conferences, website, Facebook, Twitter, etc.

These goals will be developed to answer important original questions about respiration, with a specific focus on the interests and strengths of VADER center's partners: biology, dance, diseases, music, physiology and sports.

Teaching and training. In a general frame, we plan to develop interdisciplinary training both towards students, researchers and private companies' employees. These trainings will ease exchanges between partners from different disciplines, prepare students to understand and manipulate interdisciplinary knowledge and vocabulary, and extend the competence of private companies' employees.

1/ The center will propose conferences and mini-courses performed by international renowned researchers (from UCA or abroad) on specific topics. Each of the mini-courses will cover a whole topic, starting from its basics in order to be accessible to a wide range of researchers.

2/ Interdisciplinary MOOCs on Respiration will be specifically developed with the aim to reach a large audience.

3/ More specifically, the center will aim to develop innovative teaching tools for students (STAPS, medical school, nurse and physiotherapy, …) and professionals (health, vendors, …) training. The tools will be based on the development of web-based softwares based on the *in silico* models developed by the research program. The aim is to improve, by an original interdisciplinary approach (simulators, serious games, etc.) training on respiratory physiology and pathologies. This approach is fully complementary to the research approach with potential pedagogic and economic developments. The project is fully transversal and will involves all partners of the center for the developments. Once developed and validated in the frame of medicine, we plan to extend the tools' application to other disciplines.

Popularization & communication. One of the main goal of the center will be to develop original, transdisciplinary communications' actions, not only towards researchers and students, but also towards general public. Communications about the topic of Respiration will be performed through the actual channels (UNS Pod, website, twitter and Facebook accounts, etc.). In collaboration with UCA communication services, the center will organize regularly general public interdisciplinary conferences on hot topics and societal questions linked to Respiration. Major topics will cover sports, arts or respiratory in health and diseases. Importantly, speakers will be from different university's disciplines and cultural backgrounds. These conferences could be forwarded on the center YouTube channel. We are also considering developing and organizing yearly sportive and/or artistic events. We plan to get support from a wide diversity of sponsors for these events, thus increasing the center visibility. The center will also cover national events such as "la fête de la science".

APPENDIX

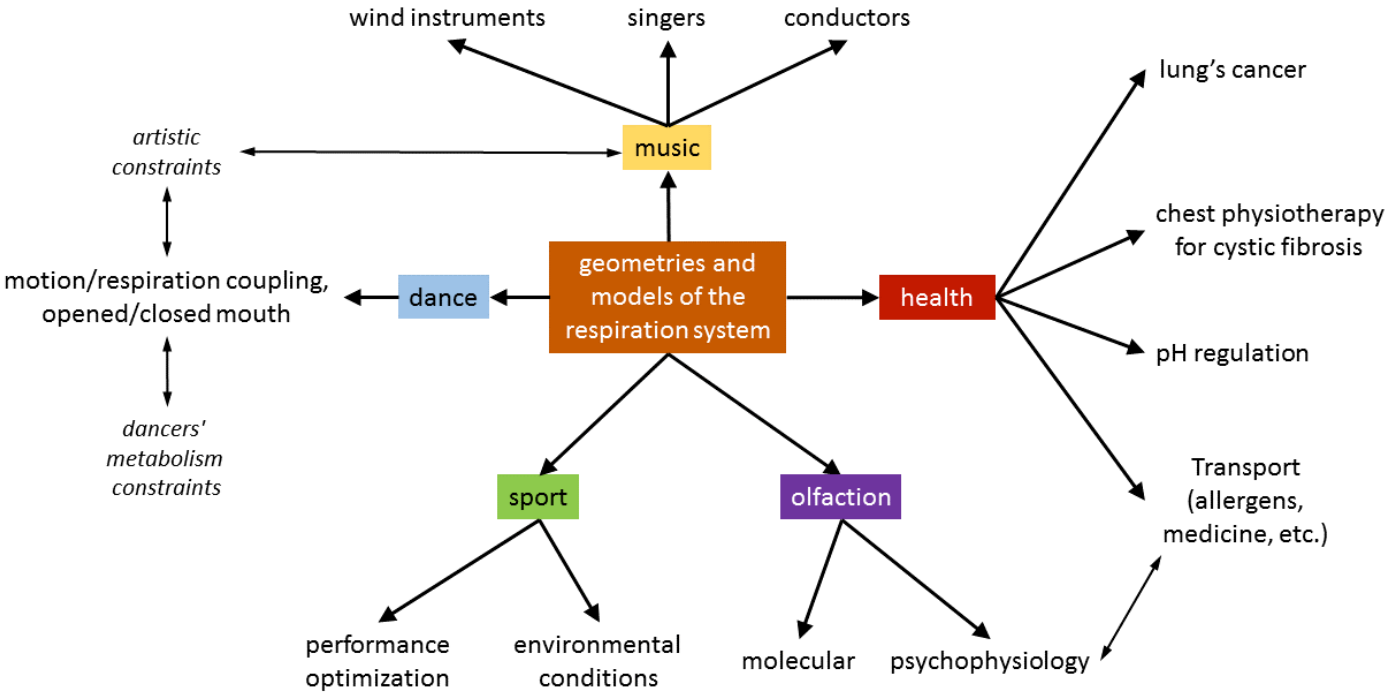
VADER center's partners

The table reflects the people contacted in the frame of this intention's letter who have agreed at this stage to be partners to VADER center.

Laboratory	Discipline	# of people involved	Contact
CHU Nice	Medicine	2+1	P. Hofman HOFMAN.P@chu-nice.fr
CIRM	Music	2	F. Paris paris@cirm-manca.org
CNRR	Music	1	B. Pasquier bruno.pasquier@ville-nice.fr
Ecole de danse Rosella Hightower	Dance	2	P. Lewton Brain peterlewton@gmail.com
I3S	Informatic	3	O. Meste meste@i3s.unice.fr
ICN	Chemistry	3	S. Antonczak Serge.ANTONCZAK@unice.fr
IMREDD	Environment and Durable Development	1	E. Dumetz Eric.DUMETZ@unice.fr
INLN	Physics	1	M. Argentina mederic.argentina@unice.fr
INRIA (équipe AROMATH)	Geometric modelling	4	Andre Galligo andre.galligo@unice.fr
IPMC	Pharmacology	2	P. Barbry barbry@ipmc.cnrs.fr
LAMHESS	STAPS	3	J. Brisswalter Jeanick.Brisswalter@unice.fr
Lenval hospital	Medicine	2	G. Leftheriotis georges.leftheriotis@unice.fr
LJAD	Mathematics	6	B. Mauroy benjamin.mauroy@unice.fr
LP2M	Biology	1 (+1 Lenval)	L. Counillon Laurent.COUNILLON@unice.fr
LPMC	Physics	3	O. Legrand Olivier.Legrand@unice.fr
		TOTAL : ≈ 36	

Example of synergies within the center

The goal of the center is to promote the development of original dedicated respiration's models in the frame of dance, health, music, sports and transport within the respiration system. The following organigram shows the interdisciplinary and federative research projects considered by the projects' partners. All these projects are based on biophysical, mathematical and numerical models of respiration (integrative or local) and on data acquisition and analysis.



The following projects are either **running projects (RP)** or **potential projects (PP)** that have emerged from the discussion between partner's member. These projects would benefit from UCA support to VADER center. This list is not at all exhaustive and other projects are still discussed or will emerge in the future. A workshop between VADER center's partners will be organized in late 2016.

Example of transverse projects: models

Here we describe typical examples of projects that would be supported by VADER center, and whose goals are to develop original powerful tools for the study of respiration.

Geometrical modeling of organs (RP+PP)

Oxygen and carbon dioxide are carried through a pathway with complex geometries, built from associations of tubular shapes: the mouth, the throat, the trachea, lungs' bronchia, acini, and blood vessels. Precise geometric representations are needed both for 2D or 3D image processing, and for computer modelling of fluid flows or chemical exchanges. UCA hosts the project team Aromath at INRIA specialized in this field, its members will develop and implement adapted curved meshes and efficient tubular representation using skeletal and radial distance functions. Such detailed and smooth representations for respiratory organs will be a huge step forward for many projects of center's partners, to model accurate geometries from patient's data, and/or to perform high-end fluid dynamics computations in realistic and robust geometries.

Integrative models of respiration for human performance studies and optimizations (PP)

Through the association of UCA's modelling strengths about respiration, we will be able to develop integrative models of respiration, with the aim to understand and to optimize high-level human performances. Models will be built

using a common basis, and adapted to each application by including specific constraints and conditions. Integrative models will be developed thanks to collaborations between teams in CHU, I3S, INLN, LAMHESS, LJAD, LPMC. The following projects are based on the development of integrative models of respiration.

Examples of respirations' projects based on integrative models.

The following projects will be based on the modeling tools developed by the center's partners working on respiration's modeling.

Athletes performance (RP+PP)

We are the second region in France concerning high level sports and there is a strong interest in understanding and optimizing athletes' performances. One of the main condition for athletes to reach high endurance performances is to optimize glycolysis pathway. This pathway is limited by the amount of H+ it produces which are regulated by a sufficient inflow of oxygen and a sufficient outflow of carbon dioxide. In this process, lung and cardiovascular functions are associated together in order to regulate these flows. Fine neural processes are in operation, with selective blood perfusion in the lung depending on the ventilation phase. Performance in high level sports is thus crucially dependent on an optimal functioning of this system. This is all the more critical if the organism lacks oxygen (hypoxia), as in diving or in altitude, or has too much oxygen (hyperoxia) as for military swimmers. We aim to develop synthetic models of respiration based on reliable hypotheses built from the expertise of the center's partners. We aim to get qualitative and quantitative predictions, and to extract which factors are essentials for optimizing performance of athletes. This project will be principally investigated in LAMHESS.

Controlled respiration and artistic constraints effects on dancers' metabolism (PP)

Dancers are athletic artists and dance practice raises several major constraints for athletic skills: physical conditioning to stay in lean condition and artistic expression. Dancer's metabolism function is not well understood, they have been shown to have surprisingly low levels of both physical condition and breathing capacity. Closed mouth breathing for example influences strongly expressive transmission in performing artists but also seems to improve their metabolism, by thus facilitating weight control. In addition to the teams involved in the model development, this project will involve the Ecole de danse Rosella Hightower and the Pole santé danse.

Circular breathing in wind instruments' performance (PP)

Circular breathing is a technique that allows to expulse air from the mouth continuously and independently on the lung's ventilation phase. This technique is used by wind instruments players who are able to perform for hours without stopping playing. We will study how the technique might affect blood gas concentrations and search how to optimize circular breathing. Data will be acquired in wind instruments' performers from CIRM and CNRR, using data acquisition experiences from CHU and LAMHESS. In parallel a dedicated model of respiration will be developed to study circular ventilation. The model will then be confronted to data for qualitative and, if possible, quantitative fitting. Then we will use the model to search for optimal techniques. Circular breathing is also used by glass blowers, and we consider contacting glass blowers in the *Verrerie de Biot* to compare their techniques with those of musicians.

Example of partial modeling of the respiration's system.

Modeling of chest physiotherapy effects for cystic fibrosis patients (RP+PP).

Chest physiotherapy is used when secretions are stuck in the lungs, either because of non-mature natural mechanism for expectoration or because of a pathology, such as cystic fibrosis. However, no scientific studies on the mechanisms of chest physiotherapy exists as of today. We plan to develop a numerical model of chest physiotherapy effects in cystic fibrosis. Our goal is to build a patient dependent model able to give more insights to the physiotherapists concerning their manipulations. This project decomposes is a collaboration between LJAD, INLN, Lenval Hospital, MSC (biophysics, Paris 7), Robert Debré Hospital (Paris), SYMME (mecatronics, Chambery) and the Auckland Bioengineering Institute (New-Zealand).

At the end of the project, a detailed model of lung's mechanics will be available and will be adapted and used to study other applications.

Training and teaching respiration.

An interactive Web-based platform to teach respiratory physiology (RP+PP)

As part of the IDEX project VADER, we propose the creation of a Web-based platform to teach respiratory physiology for students of the Health cursus (i.e. medicine, pharmacy, dental, midwifery and kinesiology) and the Sport sciences as well as those in the scientific cursus (i.e. biology). The platform will be accessible via the Internet and will gather interactive and dynamic teaching tools (e.g. simulators, serious games ...) jointly developed with partners of the VADER project.

Specifically, the project will address the initial training (licence level) as well as post-university training, especially in the Health career. The numerical modules, which are the core of the simulation system, will be developed from experimental research and modeling works conducted by the laboratories involved in the project VADER (e.g. Laboratoire JA Dieudonné, LP2M, LAMHESS, ..). National external partners will also be involved in the project (e.g. ESAIP and University of Angers, Interaction HealthCare society).

Beside the educational goal of the interactive program developed with the plateform, the project aims to monitor the progression the learner by a return of results and behaviors (i.e. debriefing) to the teacher about the different steps of the program. This method will help for personalized educational program by detecting and orienting the learner according to its abilities as well as giving a feedback for the teacher.

This project is in accordance with the national development of simulation as a tool to teach Health professional, as defined by the HAS and will also contribute to suppress the use of laboraty animals (e.g. rats) for teaching. For health professional, it will advantageously contribute to the preparatory phases (refresher's courses) before professional scenario-based tests could be conducted. The opportunity to develop applications useful for the general public will also be considered, particularly for patients (e.g. asthma,…).

The project will involve national experts to evaluate and validate the educational content (i.e. french Physiology Society and National College of Teachers in Health and Physiology). Later, the platform will be accessible to other universities and could be run through agreement. The respiratory module is part of a larger project aiming at developing various simulation tools for teaching and other modules can be progressively added to complete the offer.

This innovative and original project, based on a "web" approach, aims to solve the growing problem of managing large flux of students in the initial stages of training in Biology and Health. In addition to MOOCS and other large scale teaching that give theoretical and basic knowledge, it will offer the opportunity to consolidate and evaluate the reasoning performances of the students in a simulated environment of experimentation. The project is also an excellent opportunity to valorize the results of the research program conducted with the different partners involved in the project VADER.

Economic benefits should be expected at the end of the development process.

Building respiration's data banks (PP)

One of the challenge for modeling studies is to gather data, either by new measure campaigns or, if data is already available, by getting access to this data. This remains a difficult and time-consuming task in general. One of the goal of the center will be to centralize respiration's based data in order to ease data access to VADER's center partners and to scientists in general. The new head of Lenval's functional exploration center plans to develop data banks in Lenval hospital that will gather all medical data of patients in a centralized file, amongst which respiration's data. The center plans to support the development of data centralization in Lenval's hospital, to support its extension to Nice CHU and then to develop a collaborative exchange with national and international partners. Typically, partner's members have contact with other institutions which are interested in developing these banks: Robert Debré hospital and Auckland University (New-Zealand). New contacts will be made when a first version of the bank has been successfully setup.