

Ph.D. at the National Center for Scientific Research
Adaptation of the Brain to Hypoxia in the Southern Elephant Seal

Advisors:

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Scientific context and hypothesis:

The mammalian brain is the organ with the highest basal energy demand. It is therefore extremely vulnerable 1) to sudden interruptions in the blood's oxygen supply, which can cause neuronal death within minutes with devastating consequences, or 2) to chronic cerebral hypoperfusion or hypoxia (oxygen deprivation), which lead to neurodegeneration and cognitive decline (vascular dementias, etc.).

In this context, IMFT has recently shown that the intrinsic heterogeneity of the cerebral microvascular system, and of the associated blood flow and transport processes, causes the emergence of microregions with low oxygen levels in brain tissue, primarily located in subcortical areas, even when perfusion is normal [1]. The greater this heterogeneity, the less the vascular system can withstand additional stress (e.g., capillary occlusions, vascular rarefaction, and/or hypoperfusion, which are typically observed in aging and many pathologies).

This finding suggests that, under stress, the microvascular system may activate compensatory mechanisms (e.g., short-term vasoreactivity and/or chronic remodeling of cerebral vessels) that allow it to reduce this heterogeneity.

To explore this hypothesis, we will use a marine mammal model that has developed exceptional evolutionary capabilities for resistance to hypoxia: the southern elephant seals (EM), *Mirounga leonina*, which dive to depths of 400 to 1,000 m for durations ranging from 30 minutes to 2 hours (vs. the common seal (PC), *Phoca vitulina*, 20 m, 10 to 20 minutes) [2,3], whose cerebrovascular system the CEBC has begun to study under natural conditions (field campaigns in Kerguelen), revealing an increase in the density and tortuosity of cerebral capillaries with age, linked to a shift in lifestyle: terrestrial (juveniles) to marine (adults) [3]. We therefore hypothesize that this phenotypic change in cerebral vessels is sufficient to reduce the intrinsic heterogeneity of blood flow and microvascular transport processes, thereby enabling the maintenance of neuronal oxygenation during phases of diving-associated hypoxia.

Objectives:

The first objective is therefore to quantitatively explore the variability in the architectural properties of microvascular networks across brain regions (cortex, cerebellum, and hypothalamus) and over the course of a lifetime in EM and PC, as well as the correlations between this variability and the level of exposure to hypoxia. In fact, the EM lives on land for up to 8 weeks after birth, and then goes on to make a series of dives (averaging 30 minutes), with severe arterial hypoxia in experienced adults at the end of a dive ($PAO_2 \sim 3$ mmHg), which still maintain their cognitive functions.

The second objective is to use theoretical and numerical modeling approaches of microvascular blood flow and oxygen transport to study the impact of this variability on the heterogeneity of blood flow and transport. If the above hypothesis is valid, we can indeed expect: 1) an initial phase during which morphological and topological changes in the vascular system would lead to a decrease in this heterogeneity during development in EM, much more markedly than in PC; and 2) by analogy with clinical knowledge in humans [4], beyond a certain level of accumulated stress, a collapse of these adaptive capacities, leading to premature aging, which may explain the particularly short life expectancy of EM (15 years on average) compared to PC (30–40 years on average).

Methodology:

The necessary EM tissues, which have already been collected, are housed at the CEBC (26 brains, 20 from juveniles and 6 from adults) and include various regions (neocortex, cerebellum, hypothalamus, and hippocampus). The CEBC will have access to brains from juvenile and adult PC via PELAGIS (CNRS-UAR3462, La Rochelle). The tissues will be cleared, and the blood vessels will be visualized using immunolabeling to enable imaging of the entire vasculature via light-sheet microscopy (Bordeaux Imaging Center), in 10 mm³ volumes for the various brain regions (EM and PC, young and adults). Concurrently, the functionality of the neurovascular unit in relation to brain aging will be studied using histology.

The IMFT has expertise in tools for the architectural analysis of microvascular networks based on imaging data (e.g., [5,6]) and has developed the multiscale simulation approaches necessary for studying the coupled transport/reaction phenomena for oxygen in blood and brain tissue [7,8,9]. Data from the CEBC will enable the use of these tools to gain a better understanding of the underlying mechanisms.

Impact:

This work will shed entirely new light on the mechanisms of adaptation to hypoxia throughout the lifespan and from an evolutionary perspective. In particular, it will help us understand the interactions between vasoreactivity (how to rapidly improve oxygenation by adjusting only the vascular diameters for a given morphology) and remodeling (how architectural changes in the vascular network over the course of a lifetime influence oxygenation).

Research Context:

This thesis project is part of a collaboration between two teams developing complementary approaches. The “Porous and Biological Media” group at the Toulouse Institute of Fluid Mechanics is a pioneer in multiscale modeling of cerebral blood microcirculation and its role in neurodegenerative diseases. The Chizé Center for Biological Studies possesses world-class expertise in the adaptation of marine mammals to environmental stressors (ecophysiology), particularly thanks to its privileged access to the Dumont-d’Urville Antarctic station. The position will be based for 18 months at the CEBC (Chizé) and then for 18 months at the IMFT (Toulouse), with regular assignments between the two laboratories.

Candidate Profile:

Strong background in Fluid Mechanics or Physics. Demonstrated motivation to work at the interface with life sciences. Experience in biophysics, biomechanics, biomedical engineering, and/or imaging/image processing is welcome. A Master’s degree (M2R) in Fluid Mechanics or related disciplines is required, as well as fluency in English.

Administrative aspects:

The employer is the National Center for Scientific Research (CNRS, www.cnrs.fr), Europe’s leading organization for basic research. The doctoral school of affiliation is Mécanique Énergétique Génie des Procédés (MEGEP) in Toulouse. Funding has been secured for 3 years, with a start date scheduled for fall 2026.

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