

MSc Thesis

Dissertation Project – 2nd Cycle

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Título/Title: Study of O₂ diffusion in Cytochrome c Oxidases

Sumário do Plano de Trabalho/ Project Summary

Cytochrome c oxidases (Ccoxs) are the terminal enzymes of the respiratory chain in mitochondria and most bacteria. They are membrane-bound multi-subunit complexes that catalyze dioxygen reduction to water and simultaneously promote proton translocation across membranes. Over the last 20 years, most of the Ccoxs research focused on the mechanisms and energetics of reduction and/or proton pumping and little emphasis has been given to the pathway(s) used by dioxygen to travel from the exterior to the catalytic binuclear center (BNC). Furthermore, the identification of alternative putative gas pathways in Ccoxs as well as the atomic details of O₂ diffusion is an essential step towards understanding the working mechanisms of these proteins. Recently, we have already performed an exhaustive study of the channels used by O₂ to reach the catalytic center of an A-type bacterial Ccox from *R. sphaeroides* in the fully reduced state and found evidence for two alternative channels, besides the previously X-ray inferred channel.

During this project, we want to extend the O₂ diffusion studies to other Ccox members (such as the *P. denitrificans* and the Mitochondrial enzymes) in order to clarify if the gas channels are conserved among the family.

The main objectives of this work are:

- 1- Understand, at the molecular level, the mechanisms of O₂ diffusion in Ccoxs using computational theoretical approaches, such as Molecular dynamics simulations.**

Molecular dynamics simulations is, nowadays, one of the major theoretical tools used to study biological molecules and it is routinely used to investigate the structure, dynamics and thermodynamics properties of proteins.

- 2- Identification of the putative gas channels used to reach the BNC in different Ccox members.**