INSTITUTO DE TECNOLOGIA QUÍMICA E BIOLÓGICA /UNL

Knowledge Creation

MSc Thesis

Dissertation Project – 2nd Cycle

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TITLE: Proton pumping mechanisms of the M2 protein from influenza virus

BACKGROUND

The influenza virus is one of the most devastating human pathogens. One of the most promising drug and vaccine targets of this virus is the M2 protein, a transmembrane protein that translocates protons in the direction of the gradient. The functional unit of the M2 protein is a tetramer and each monomer is composed by 97 amino acid residues. The protein contains 3 distinct segments, a N-terminal segment of 25 residues in the viral exterior, a single transmembrane (TM) helix of 21 residues, and a C-terminal segment in the viral interior. Several NMR and X-ray crystallography structures of the M2 protein, obtained in different conditions, have shown that the TM domain is arranged as a four-helix bundle. It has also been shown that the four H37 residues (one from each monomer) play a crucial role in the proton translocation process. Although this protein has been extensively studied, the mechanism by which it translocates protons remains unknown

OBJECTIVES

The main goal of this project is to shed light into the proton translocation mechanism of M2 by using molecular simulation techniques. In particular, we want to address the following questions:

- What is the appropriate simulation setup to study this protein?
- Are there significant differences in the structure and dynamics of the protein at different pH values?
- Are the protons translocated directly by the H37 residues or through a water-wire mechanism?

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PROJECT DESCRIPTION

In order to provide molecular insights into the proton conductance mechanisms of the M2 protein, we will use a computational approach. The student will learn and apply molecular simulation techniques to address the questions described in the objectives. Below we describe the main tasks of the project.

Task 1. Bibliographic research

The student will search and read the most relevant papers focusing on the subject addressed by this project.

Task 2. Learning the basics of molecular simulation

The student will get familiarized with the basic concepts of molecular simulation and learn how to use the techniques that will be applied during the project

Task 3. Standard molecular dynamics (MD) simulations of the M2 protein

One of the questions that we need to address is to design the appropriate simulation setup for this system: choice of force field and simulation conditions. After that the student will compare the behaviour of M2 in simulations considering different protonation states.

Task 4. Constant-pH MD simulations of the M2 protein

Constant-pH MD simulations of the M2 protein inserted into a lipid membrane will be performed in order to study the protonation–conformation coupling and understand how proton transfer occurs in this enzyme.

TIMELINE (use fill tool for the cells)

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Task 4										
Thesis										