Abstract

Worldwide, more than 6000 rare diseases have been identified, affecting an estimated total of 350 million people. *Rare diseases* are highly heterogeneous presenting a high level of complexity. Most rare diseases are genetic pathological mutations, often related to the absence of expression or improper behaviour of the protein associated with the affected gene. The immense variety and complexity in the field of rare diseases require methodologies that can contribute to reducing costs and optimising resources in the understanding of the disease and the search for treatment. The rise in computational power has advanced computational molecular modelling to a cutting-edge method for studying protein behaviour and designing drugs. This PhD research explores the application of molecular modelling in the study of structured proteins associated with rare diseases.

Molecular modelling can be a support tool to other experts for many areas such as the understanding of proteins physiological behaviour, aberrant comportment related to pathological mutations, understanding and rationalization of experiments and design of treatments.

This PhD work has faced some of these aspects, exploiting molecular modelling techniques and in particular molecular dynamics to investigate two proteins related to rare neurodegenerative pathologies. The investigation of structure to function relationship and how this can be altered by a mutation has been performed on the alsin protein. Alsin is a multidomain protein whose mutation has been linked to a group of recessive early-onset rare diseases, namely Infantile-onset ascending hereditary spastic paralysis, Juvenile Primary Lateral Sclerosis, and Juvenile Amyotrophic Lateral Sclerosis. Alsin molecular structure is nowadays experimentally unknown making difficult the investigation of the related diseases. In this thesis, in silico structure, prediction has been used to predict the molecular structure of alsin. Subsequently, molecular dynamics has been employed to investigate the structure-to-function relationship of alsin in a domain-focused manner. Then, in collaboration with an experimental group, the optimization of a construct for the structural experimental determination of one domain of the alsin has been carried out. Moreover, the local effect on alsin structure of a pathological mutation was investigated. Understanding the molecular basis of the disease could serve as a starting point for therapeutic design. However, the heterogeneity of rare diseases and their low prevalence necessitate strategies that optimize and rationalize resources for treatment design. In this thesis, the case study of Spinocerebellar Ataxia related to Ataxin-1 protein has been explored for the preliminary design of a therapeutic strategy.

To conclude, this thesis has provided evidence, through two case studies concerning rare neurodegenerative diseases currently without cures, of how molecular modelling possesses the necessary characteristics to be a preferred tool in aiding the comprehension and development of strategies to address the challenge of understanding and treating rare neurodegenerative diseases.