

El titulo de la tesi: In-silico methods to
drug discovery

El subtítulo de la tesi: Cancer

Autor: Francisco Martínez Jiménez

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DIRECTOR DE LA TESI

Director: Marc A. Martí-Renom Departament Departament:
Biomedicine



A mi madre.

Agradecimientos Agraexio....

Abstract

This is the abstract of the thesis in English. Please, use less than 150 words.

Resum

Vet aqui el resum de la tesi en catala.

Prefaci

Sumari

Index of figures	xiii
List of tables	xv
CHAPTER 1 INTRODUCTION	3
1.1 Overview: Protein structure	3
1.1.1 Protein function	5
1.1.2 Protein-small molecule interaction	6
1.1.3 Protein modelling	6
1.1.4 Protein-ligand prediction	6
1.1.5 Drug discovery	6
1.1.6 subsection	6
1.2 Drug discovery	6
1.2.1 In-silico methods in drug-discovery	6
1.3 Mycobacterium tuberculosis	7
1.3.1 Tuberculosis treatments and PPcs	7
1.4 Drug resistance in cancer	7
1.4.1 Cancer Treatment and drugs	7
CHAPTER 2 OBJECTIVES	9
CHAPTER 3 NANNOLYZE	11
CHAPTER 4 PREDICTING TARGETS IN MTB	13
CHAPTER 5 DRUG RESISTANCE IN CANCER	15

Índex de figures

1.1	Hierarchical distribution of layers in protein structure	5
5.1	Example	15

Índex de taules

1.1	Prova de taula	6
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Summary

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Preamblel

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Index

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CAPÍTOL 1

INTRODUCTION

1.1 Overview: Protein structure

Proteins are essential *macromolecules* that play critical roles in the cell. They are not only the cell's building blocks, but also they perform nearly all the cell's functions. A protein is a molecule made from a long chain of amino acids linked thorough a covalent peptide bond. Proteins are therefore also known as *polypeptides*. Attached to this repetitive chain are those portions of the amino acids that are not involved in the covalent bond, the **side chains**. Side chains confer the different physico-chemical properties of each of the 20 types of amino acids [1]. The composition of the amino acid sequence determines the function and the structure of a protein. That is because the unique sequence creates a specific pattern of attractive and repulsive forces between amino acids along the polypeptide that leads to a folding process resulting in a specific three-dimensional structure. These forces are usually non-covalent interactions between the side chains of the amino acids. Non-covalent interactions are weaker than covalent ones, allowing the folded structure to certain degree of conformation mobility i.e: to be dynamic. This phenomenon is really important to facilitate the interaction with other molecules as we will explore further in [section protein-ligand interaction].

Protein structures are complex conformation of atoms organized in a hierarchical manner 1.1. The first level of this hierarchy, referred to as the **primary structure**, is the ordered sequence of amino acids of the polypeptide. Certain segments of these chains, tend to form simple shapes such as helices, strands, turns or loops. These folding patterns are referred to as secondary elements and collectively constitute the **secondary structure** of the protein. The two most frequent type of secondary elements are the α -helices and the β -strands [REF]. The overall chain tends to fold further into a three-dimensional **tertiary structure**. Contrary to the secondary structure, the tertiary structure folding is driven by interactions from amino acids far apart in the sequence. The tertiary structure, is generally

the most stable form of the protein, that is, the one that minimizes its free energy [REF]. Furthermore, the tertiary structure is also the biologically active form of the protein, and its unfolding usually leads towards partial or total inactivation of the protein. Finally, some proteins are composed by multiple folded chains. In such cases, each folded subunit folds independently and then joins the others forming a biologically active complex. This type of organization is considered as the **quaternary structure**.

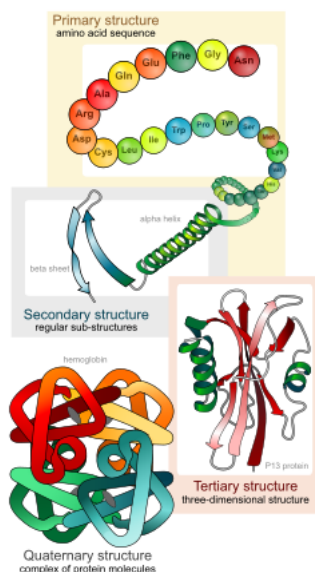


Figura 1.1: Hierarchical distribution of layers in protein structure

1.1.1 Protein function

The structure of a protein determines its biological function. However, different *regions* of the structure can perform semi-independent functions from each other. These regions are referred to as **protein domains** [REFS!!!!]. A domain is sub-structure produced by any part of polypeptide chain that can fold independently into a compact and stable structure. Domains on average contain 80-250 residues [REF]. Estimates of the number of domains per protein say that 67% of prokaryotic proteins and 80% of eukaryotic proteins include more than one domain [REF 259,260 libro protein]. Domains are not only the basic functional units of proteins, but also the evolutionary units of protein evolution [REF]. As proteins have evolved, domains have been modified and combined to build new proteins [REF]. The study of protein domains have become such an important topic in biology that several databases of protein domains are available. Some of them such as SCOP or CATH are purely based on the structure, while others such as PFAM or INTERPRO include information about the function in their classification.

Domains, and subsequently proteins; perform its biological activity by interacting with other molecules. Proteins can interact with other proteins, constructing a protein-protein complex, with ions or with small-molecules. The substance that is bound to the *target* protein is called the **ligand**, while the region of the protein where the ligand is binding is called ligand's *binding site*. In the thesis, I will use ligand only for small-molecule compounds while proteins will be considered as

equals and will be explicit named as protein-protein interaction[PIE DE NOTA]. The roles played by the ligands are diverse. Table X shows an example of the different functions that a small-molecule ligands can perform in a protein.

1.1.2 Protein-small molecule interaction

Binding constants, allosteric and binding-site, induced fit model. Expandir. Im-
poratante.

1.1.3 Protein modelling

3D-Structure modelling.

1.1.4 Protein-ligand prediction

1.1.5 Drug discovery

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Taula 1.1: Prova de taula

1.1.6 subsection

Subsection

1.2 Drug discovery

Second

1.2.1 In-silico methods in drug-discovery

Subsection

1.3 Mycobacterium tuberculosis

1.3.1 Tuberculosis treatments and PPcs

1.4 Drug resistance in cancer

1.4.1 Cancer Treatment and drugs

CAPÍTOL 2

OBJECTIVES

CAPÍTOL 3

NANNOLYZE

CAPÍTOL 4

PREDICTING TARGETS IN MTB

CAPÍTOL 5

DRUG RESISTANCE IN CANCER



Figura 5.1: Example

Bibliografia

- [1] B. Alberts. *Molecular Biology of the Cell: Reference edition*. Molecular Biology of the Cell: Reference Edition v. 1. Garland Science, 2008. ISBN: 9780815341116. URL: <https://books.google.es/books?id=iepqmRfP3ZoC> (v. la pàg. 3).