Utilizing Bioinformatics for Ligand-Protein Interactions

By: Yogindra Raghav

Introduction

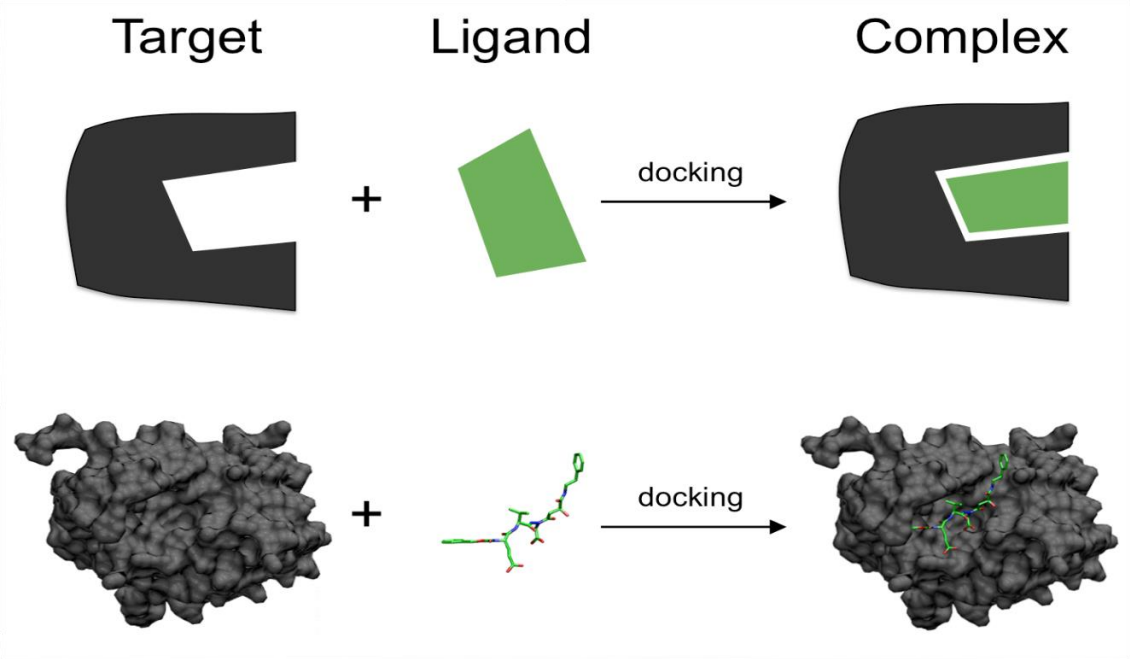
Bioinformatics software for *in silico* testing of ligand-protein interactions? Quite the word jumble. Let's break it down!

Bioinformatics: an inter-disciplinary field that develops computational methods to better understand biology. It's also a great major that's offered within the Department of Biological Sciences here at Pitt!

In silico: Performed on a computer (biological experiments).

Ligand-Protein Interactions: Quantifiable chemical interactions occurring between a small molecule (ligand) and larger complex (protein).

The idea, mentioned in the first sentence of this piece, is commonly referred to as Computational Docking and is used contemporarily in the field of drug discovery. A great visualization of this is provided below.

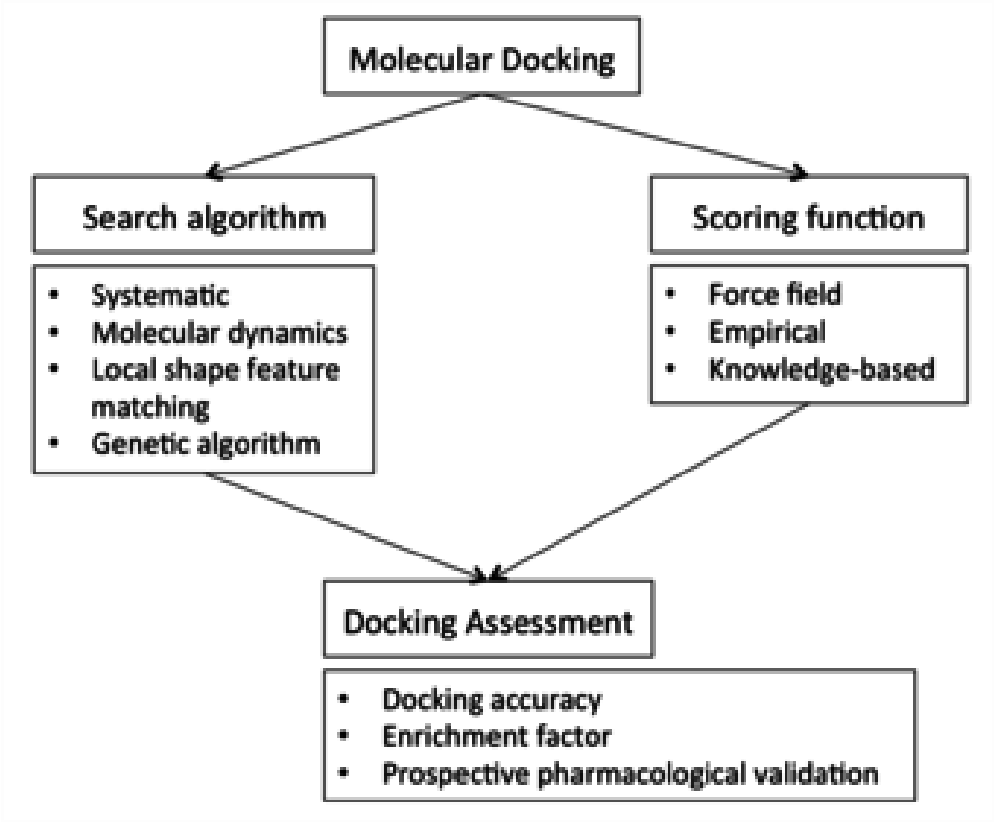


Foundations

The basis for how these programs work is provided in the figure below. Prediction of interactions between a ligand and target protein(s) is computationally non-trivial! There are an

unimaginable number of possible small molecules that each have multiple possible conformations. Consider that proteins themselves are not rigid and stationary, as they have multiple potential conformations in chemical space, and you have an exponential number of possibilities and calculations to run! An unreasonable task!

Docking programs use many shortcuts/heuristics to report results of interactions in a reasonable time frame (the details of which are too long for a post like this). Rest assured that most computation is related to the chemical-physics force-fields that surround molecules to predict favorable/unfavorable interactions.



Applications

Why might this be useful? Before the advent of Computational Docking software, the only way to test potential molecules against proteins was by brute-force screening done by engineering-intensive and expensive robots. Though these robots are still in use today, the ability to pre-screen compounds *in silico* has allowed for reductions in compound synthesis and time required to test molecules. Docking has been commonly used throughout the field of drug discovery as a high-throughput, lower cost means of screening large swathes of potential chemical compounds to change the activity of a target protein. The capability to

precisely find and optimize such interactions allows researchers to propose innovative manners of inhibiting disease processes that are caused by protein malfunction.

An example to motivate the usage of such software is as follows. Let's assume we aim to find a drug to cure Parkinson's disease. We recognize that this disease is caused by an aggregation of misfolded proteins. If we could find computationally find a small molecule to bind a reactive pocket or region of our protein(s), we may cause a conformational change in that protein to either prevent aggregation or to dilute aggregated proteins. If such an example were to ever come to fruition, the potential of Bioinformatics for ameliorating human health would be unquestionable.

Software Availability

Some famous freely available programs include Autodock, SwissDock and UCSF Chimera. For anyone interested in looking into these programs, there are many tutorials available online to teach yourself but be warned that the documentation may be spotty at best.