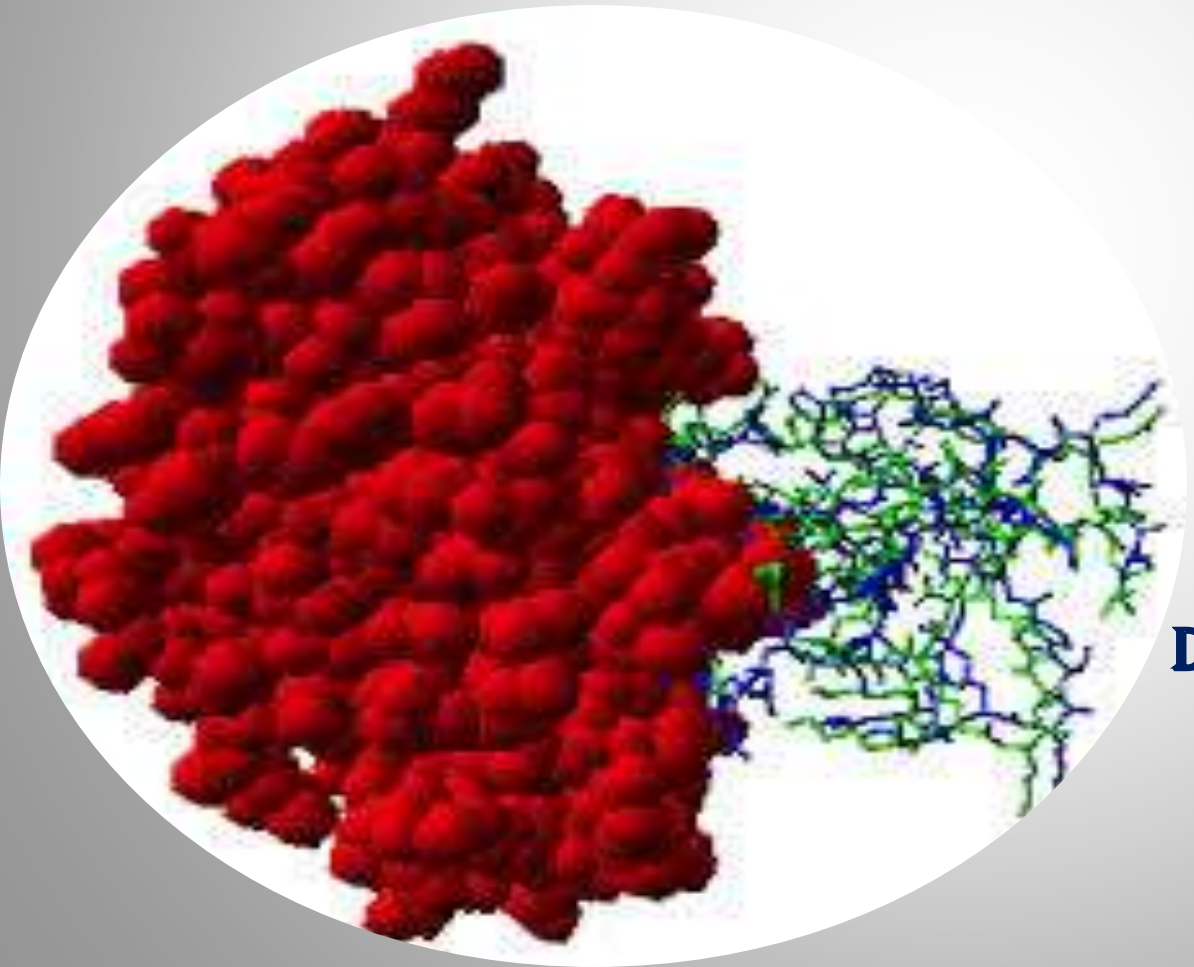
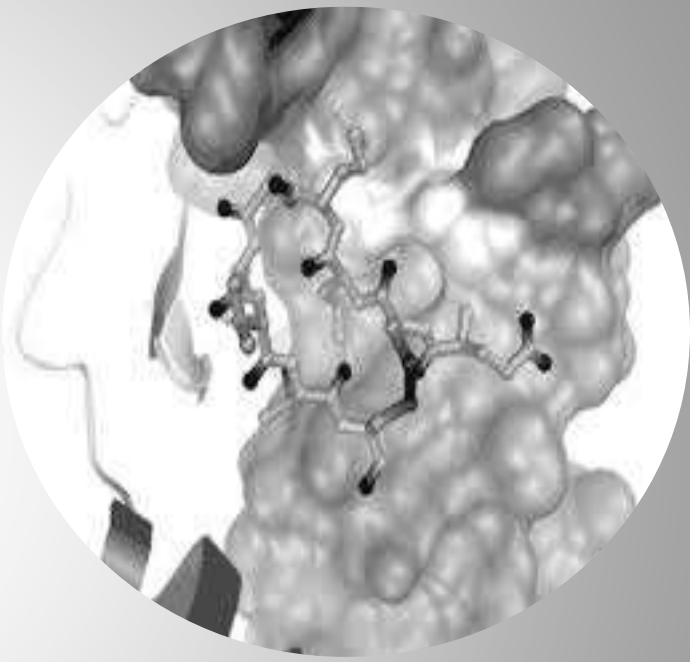
MOLECULAR DOCKING





DHANASREE PALLIYATH

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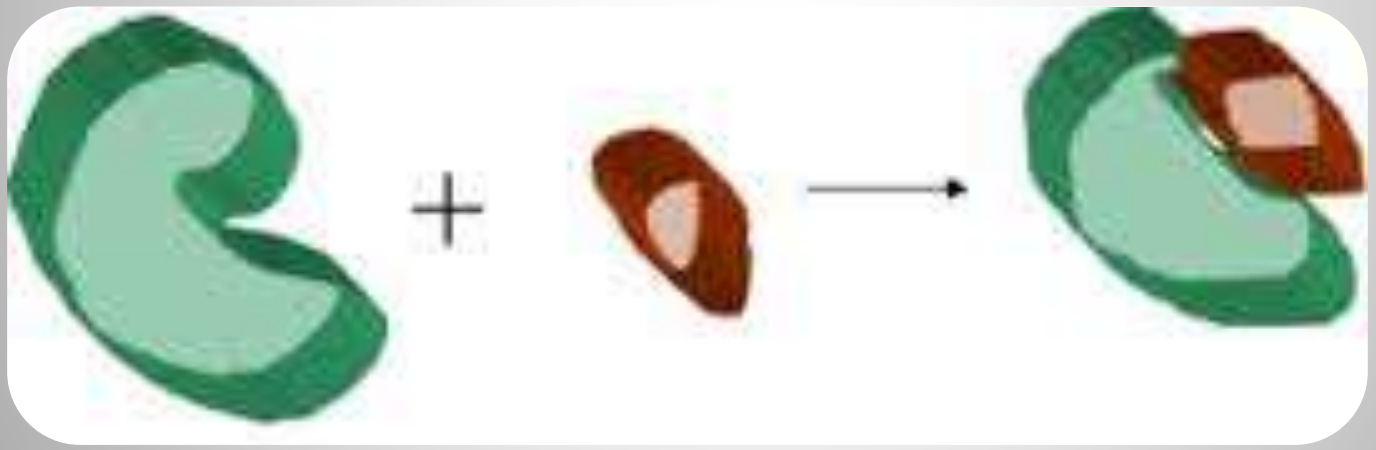
SoLS,MANIPAL

INTRODUCTION

- Docking is an attempt to find the best matching between two molecules.
- A more serious definition….

  Docking is a method which predicts the preferred orientation of one ligand when bound in an active site to form a stable complex.



Docking of small molecule ligand (brown) with a protein receptor (green) to produce a complex.

LOCK AND KEY

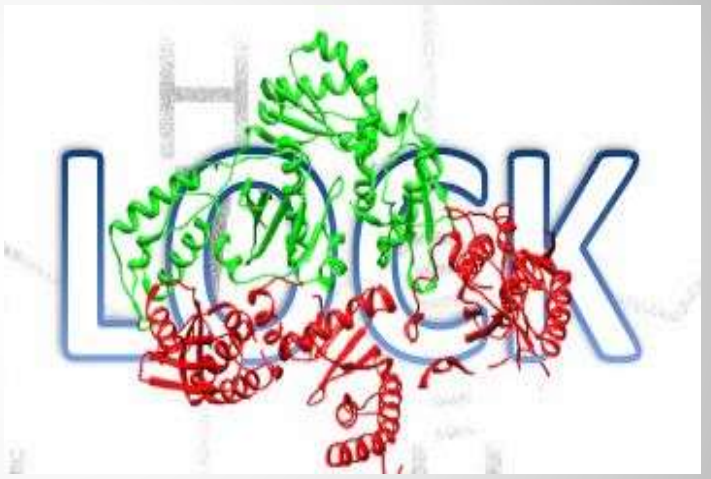
- Finding the correct relative orientation of the "key" which will open up the "lock".

- On the surface of the lock is the key hole…

- In which direction to turn the key after it is inserted …

- The protein can be thought of as the “lock” and the ligand can be thought of as a “key”.

NVP: Nevirapine



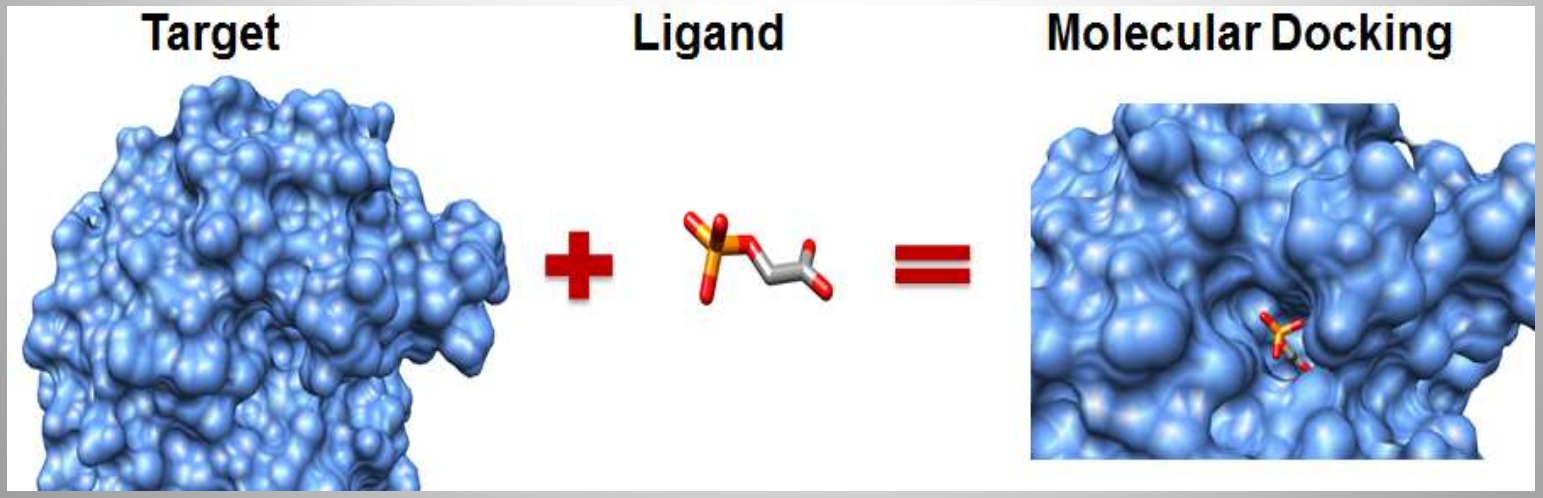
Crystallographic structure of HIV-1 reverse transcriptase:
green coloured P51 subunit & red coloured P66 subunit

MOLECULAR DOCKING

- Aim:

  To achieve an optimized conformation for both receptor and ligand & the relative orientation between protein and ligand such that the free energy of the overall system is minimized

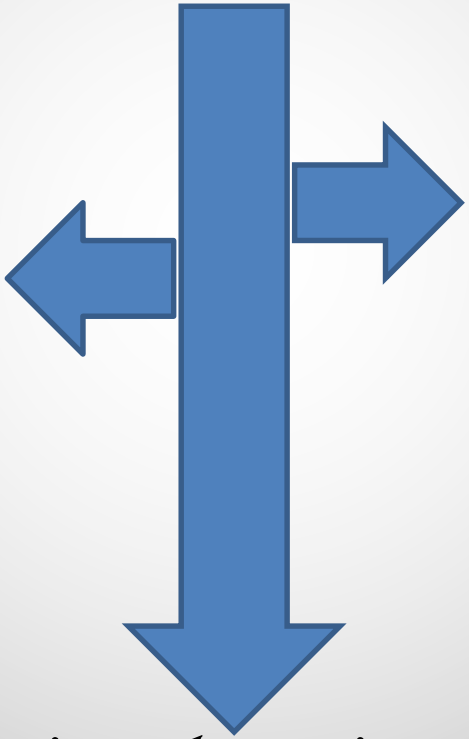
- Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings.



IMPORTANCE

Molecular Docking

Identification of the ligand's correct binding geometry (pose) in the binding site (Binding Mode)



Prediction of the binding affinity (Scoring Function)

Rational Design Of Drugs

TYPES OF DOCKING

Rigid Docking (Lock and Key)

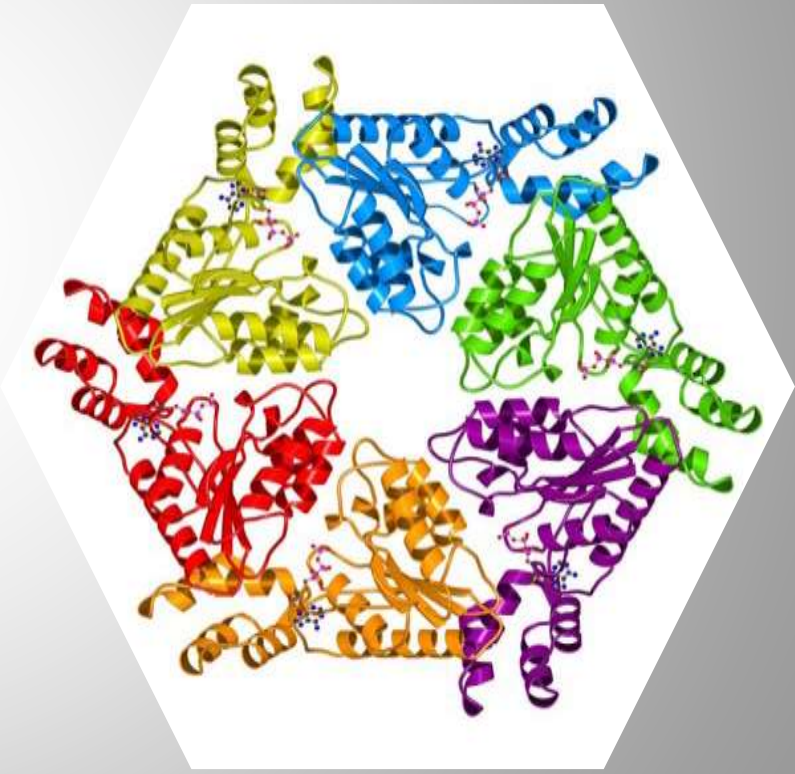
In rigid docking, the internal geometry of both the receptor and ligand are treated as rigid.

Flexible Docking (**Induced fit**)

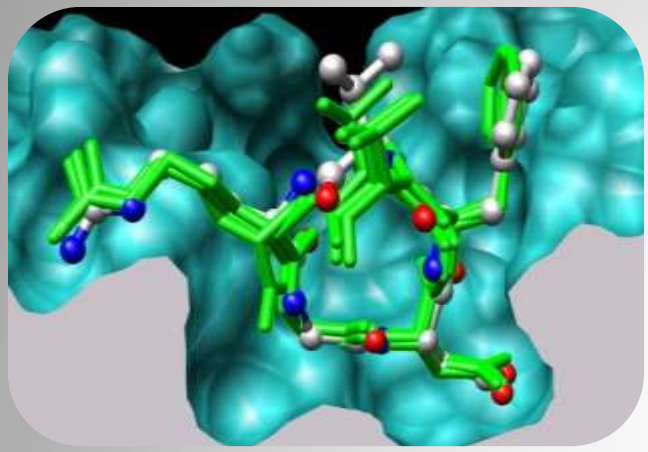
An enumeration on the rotations of one of the molecules (usually smaller one) is performed. Every rotation the energy is calculated; later the most optimum pose is selected.

Docking can be between….

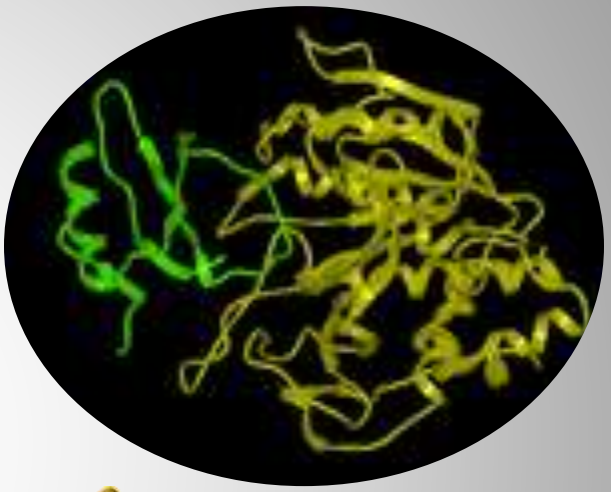
- Protein - Ligand
- Protein – Protein
- Protein – Nucleotide

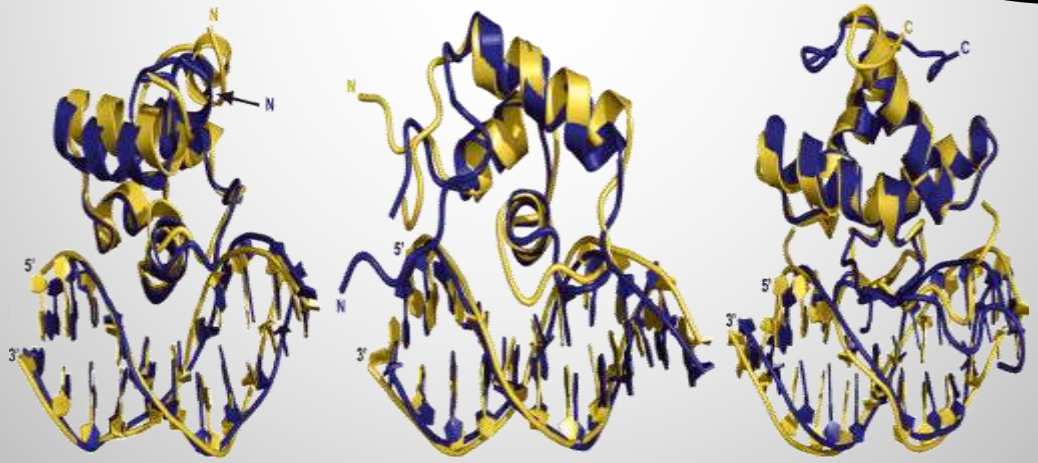


Protein - Ligand



Protein - Protein





Protein - Nucleotide

TYPES OF INTERACTIONS

- **Electrostatic forces** - Forces with electrostatic origin are due to the charges residing in the matter.

- **Electrodynamics forces** - The most widely known is probably the van der Waals interaction.

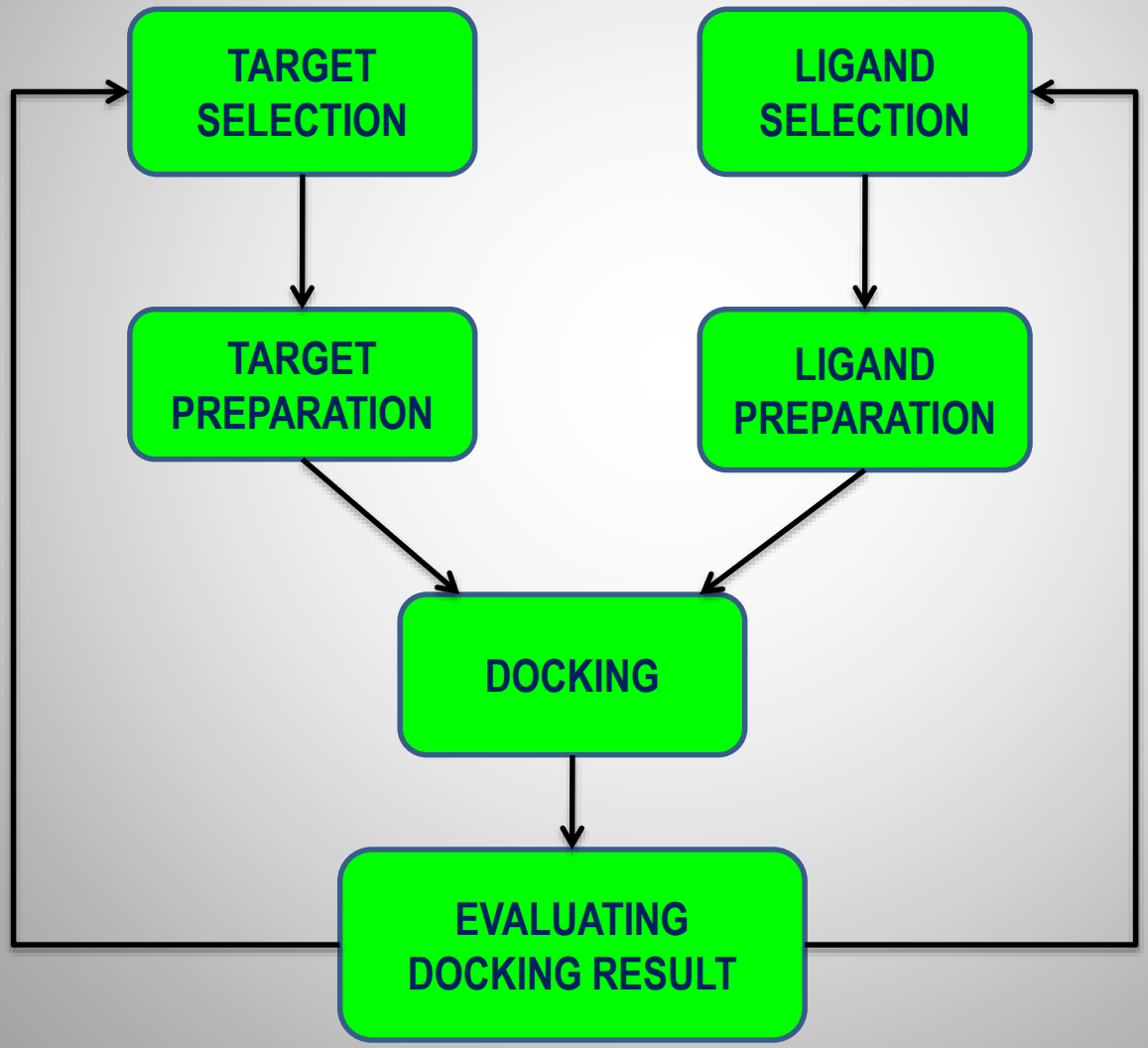
- **Steric forces** - These are caused by entropy. For example, in cases where entropy is limited, there may be forces to minimize the free energy of the system.

- **Solvent-related forces** – These are due to the structural changes of the solvent. These structural changes are generated, when ions, colloids, proteins etc, are added into the structure of solvent. The most commonly are Hydrogen bond and hydrophobic interactions

KEY STAGES IN DOCKING

- Target/Receptor selection and preparation
- Ligand selection and preparation
- Docking
- Evaluating docking results

A typical docking workflow



Receptor selection and preparation

Building the Receptor

The 3D structure of the receptor should be considered which can be downloaded from PDB.

The available structure should be processed.

The receptor should be biologically active and stable.

Identification of the Active Site

The active site within the receptor should be identified.

The receptor may have many active sites but the one of the interest should be selected.

Ligand selection and preparation

Ligands can be obtained from various databases like ZINC, PubChem or can be sketched using tools like Chemsketch.

Docking

The ligand is docked onto the receptor and the interactions are checked. The scoring function generates score, depending on which the best fit ligand is selected.

SOFTWARES

- **SANJEEVINI** – IIT Delhi (www.scfbio-iitd.res.in/sanjeevini/sanjeevini.jsp)
- **GOLD** – University of Cambridge ,UK (www.ccdc.cam.ac.uk/Solutions/GoldSuite/Pages/GOLD.aspx)
- **AUTODOCK** - Scripps Research Institute,USA (autodock.scripps.edu/)
- **GemDock(Generic Evolutionary Method for Molecular Docking)** - A tool, developed by Jinn-Moon Yang, a professor of the Institute of Bioinformatics, National Chiao Tung University, Taiwan (gemdock.life.nctu.edu.tw/dock/)
- **Hex Protein Docking** - University of Aberdeen, UK (hex.loria.fr/)
- **GRAMM (Global Range Molecular Matching) Protein docking** - A Center for Bioinformatics, University of Kansas, USA (www.bioinformatics.ku.edu/files/vakser/gramm/)

APPLICATIONS

- **Virtual screening (hit identification)**

  docking with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest.

- **Drug Discovery (lead optimization)**

  docking can be used to predict in where and in which relative orientation a ligand binds to a protein (binding mode or pose). This information may in turn be used to design more potent and selective analogs.

- **Bioremediation**

  Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes.

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Manipal

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THANK YOU