High Performance Computing for Sustainable Development

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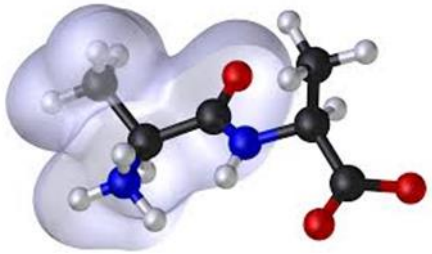
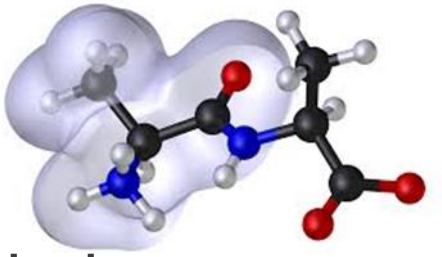
1 NO POVERTY
2 ZERO HUNGER
3 GOOD HEALTH AND WELL-BEING
4 QUALITY EDUCATION
5 GENDER EQUALITY
6 CLEAN WATER AND SANITATION
7 AFFORDABLE AND CLEAN ENERGY
8 DECENT WORK AND ECONOMIC GROWTH
9 INDUSTRY, INNOVATION AND INFRASTRUCTURE
10 REDUCED INEQUALITIES
11 SUSTAINABLE CITIES AND COMMUNITIES
THE GLOBAL GOALS
For Sustainable Development
12 RESPONSIBLE CONSUMPTION AND PRODUCTION
13 CLIMATE ACTION
14 LIFE BELOW WATER
15 LIFE ON LAND
16 PEACE AND JUSTICE STRONG INSTITUTIONS
17 PARTNERSHIPS FOR THE GOALS



How?

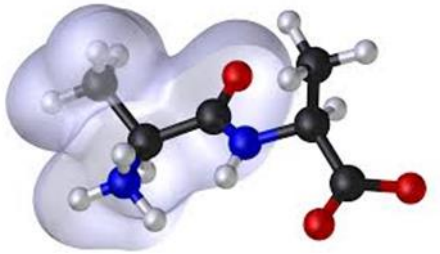


- Having lived through COVID-19 and various lockdown situations during the pandemic we have come to realise that there is a new way of collaborating and achieving goals such as vaccination development

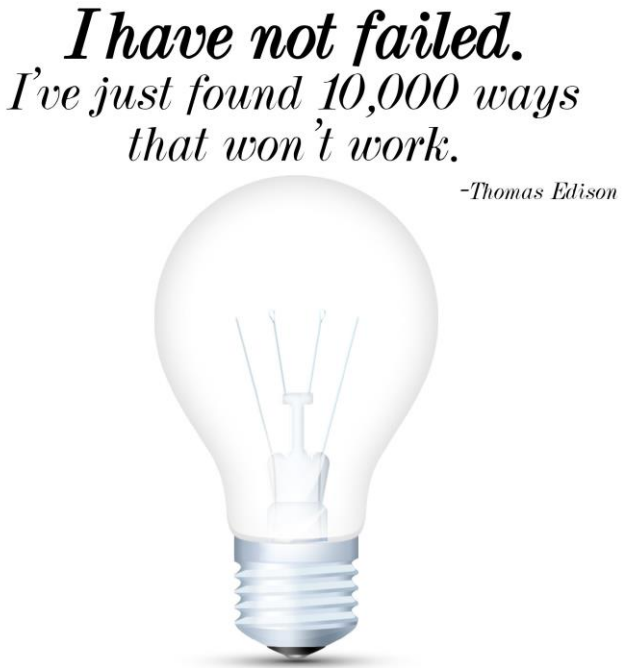
- We have proven that the conventional face-to-face method of conducting meaningful and life altering science is not needed

- One of the key role players in the fight against COVID-19 was high performance computing

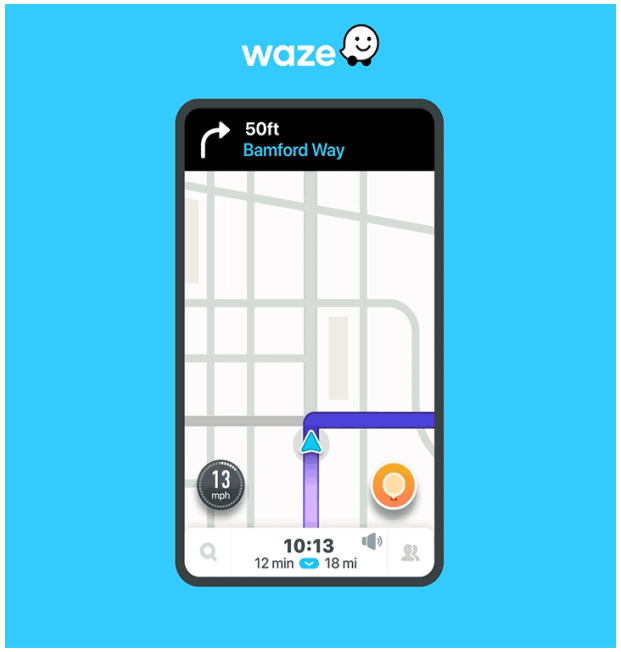
Why use molecular modelling?



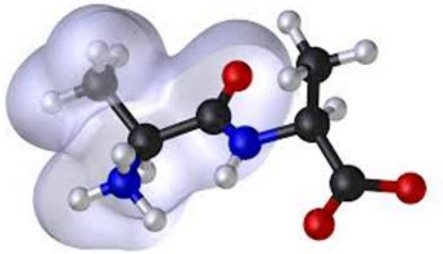
Old



Modern

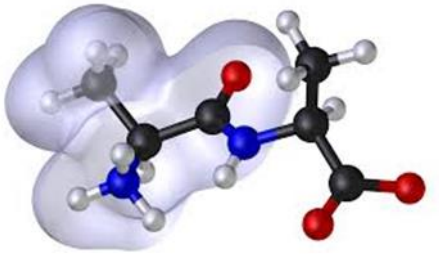


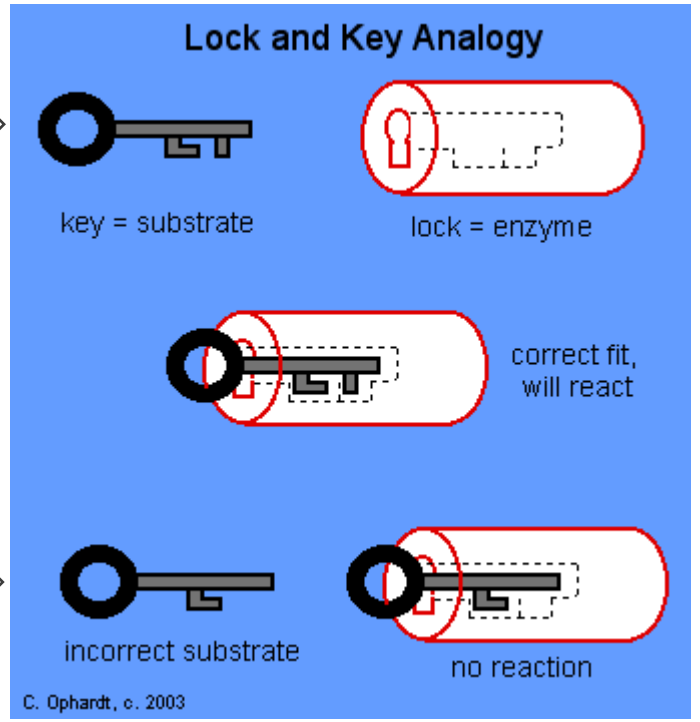
What is a drug?



- A drug is a small molecule (key) that binds to a target such as a large protein or enzyme (lock) and as a result it turns on or off specific biochemical/physiological processes in the body

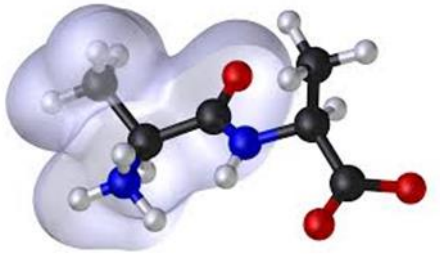
What is a drug?





[4] http://chemistry.elmhurst.edu/vchembook/571lockkey.html, accessed 05 Mar 2023

How do we find the key to our lock?



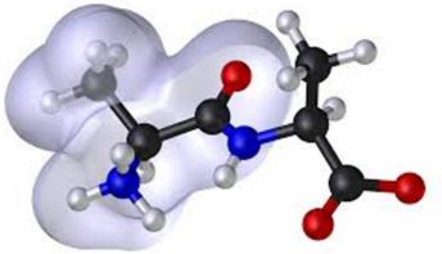
High-Throughput Screening (HTS)

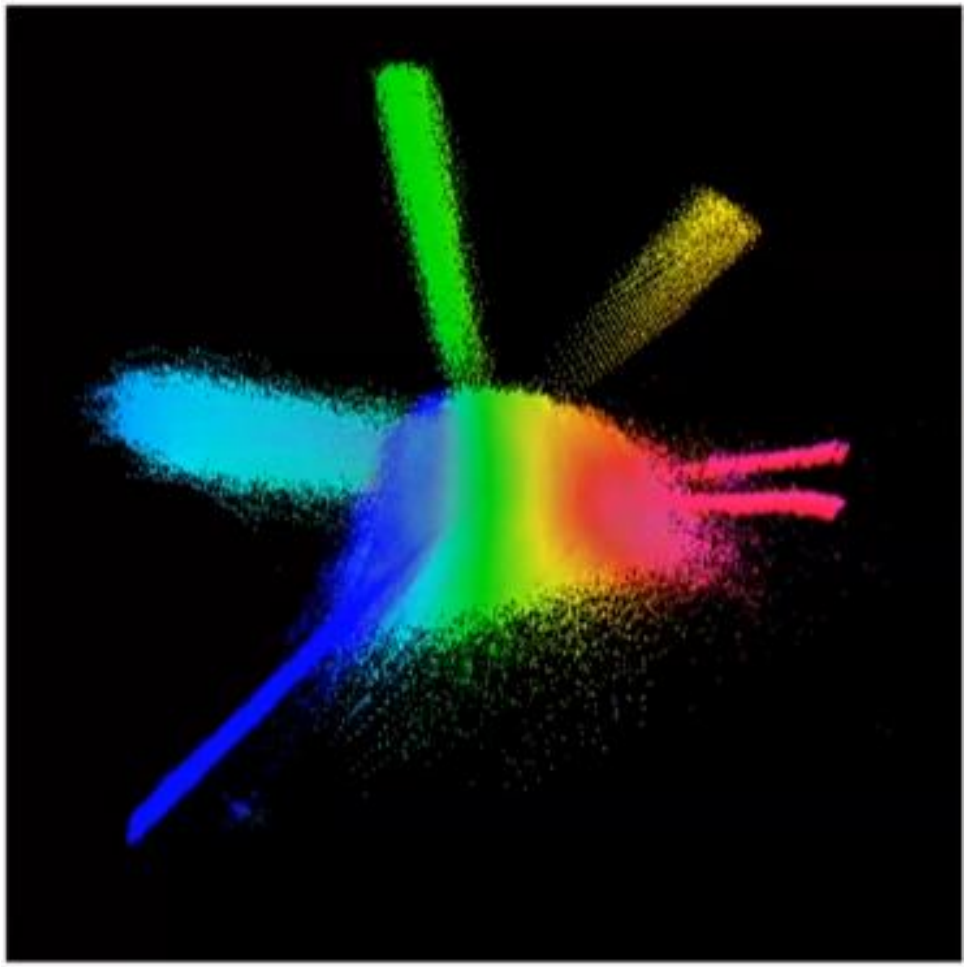
This is a method for scientific experimentation especially used in drug discovery and is relevant in biology and chemistry. It combines robotics, data processing and control software, liquid handling devices and sensitive detectors allowing researchers to conduct numerous chemical, genetic or pharmacological tests.

Virtual Screening (VS)

Is a computational technique used to search libraries of small molecules in order to identify those structures which are most likely to bind to a drug target, such as a large protein.

How do we find the key to our lock?

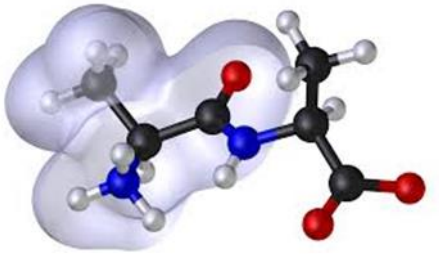




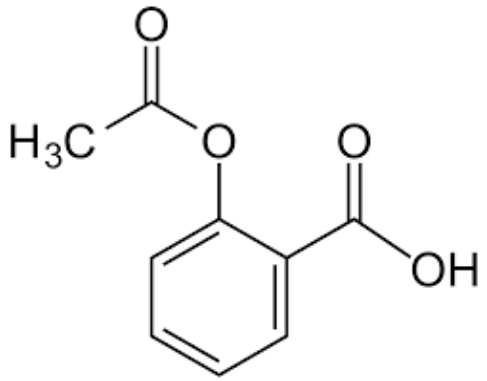
Database	Description	Size	Web address
PubChem	Known molecules from various public sources	32.5 M	http://pubchem.ncbi.nlm.nih.gov
Chemspider	Online resource from the Royal Society of Chemistry	26.0 M	http://www.chemspider.com
ZINC	Commercially available small molecules	21.0 M	http://zinc.docking.org
NCI Open	Anticancer and AIDS compounds with screening data	0.25 M	http://cactus.nci.nih.gov/ncidb2.1
ChemDB	Commercially available small molecules	4.1 M	http://cdb.ics.uci.edu
BindingDB	Bioactive molecules with binding affinity data	0.36 M	http://www.bindingdb.org
ChemBank	Small molecules annotated with screening data	1.2 M	http://chembank.broadinstitute.org
ChEMBL	Small molecules annotated with experimental data	1.1 M	https://www.ebi.ac.uk/chembldb
CTD	Comparative toxicogenomics database	0.17 M	http://ctdbase.org
HMDB	Human metabolome database	0.0085 M	http://www.hmdb.ca
SMPDB	Small molecule pathway database	0.001 M	http://www.smpdb.ca
DrugBank	Experimental and approved small molecule drugs	0.0065 M	http://www.drugbank.ca

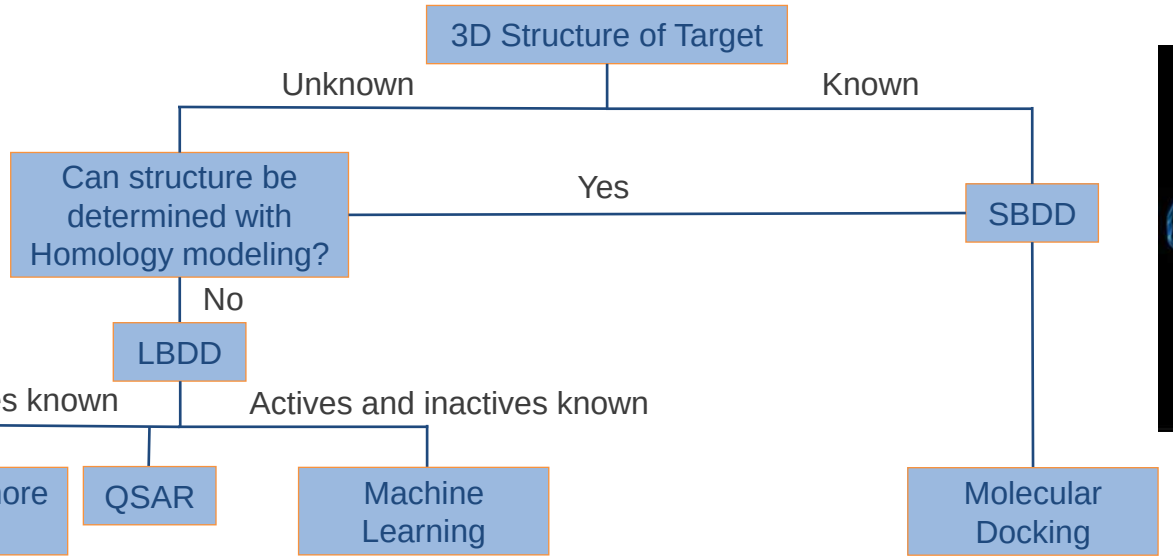
[5] Reymond, J-L and Awale, M. ACS Chem. Neurosci. 2012, 3, 649 – 657.

Computer aided drug design (CADD)

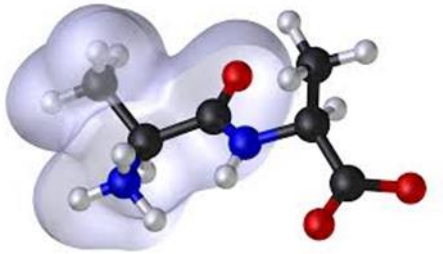


- There are two general types of CADD namely structure-based drug design (SBDD) and ligand-based drug design (LBDD)

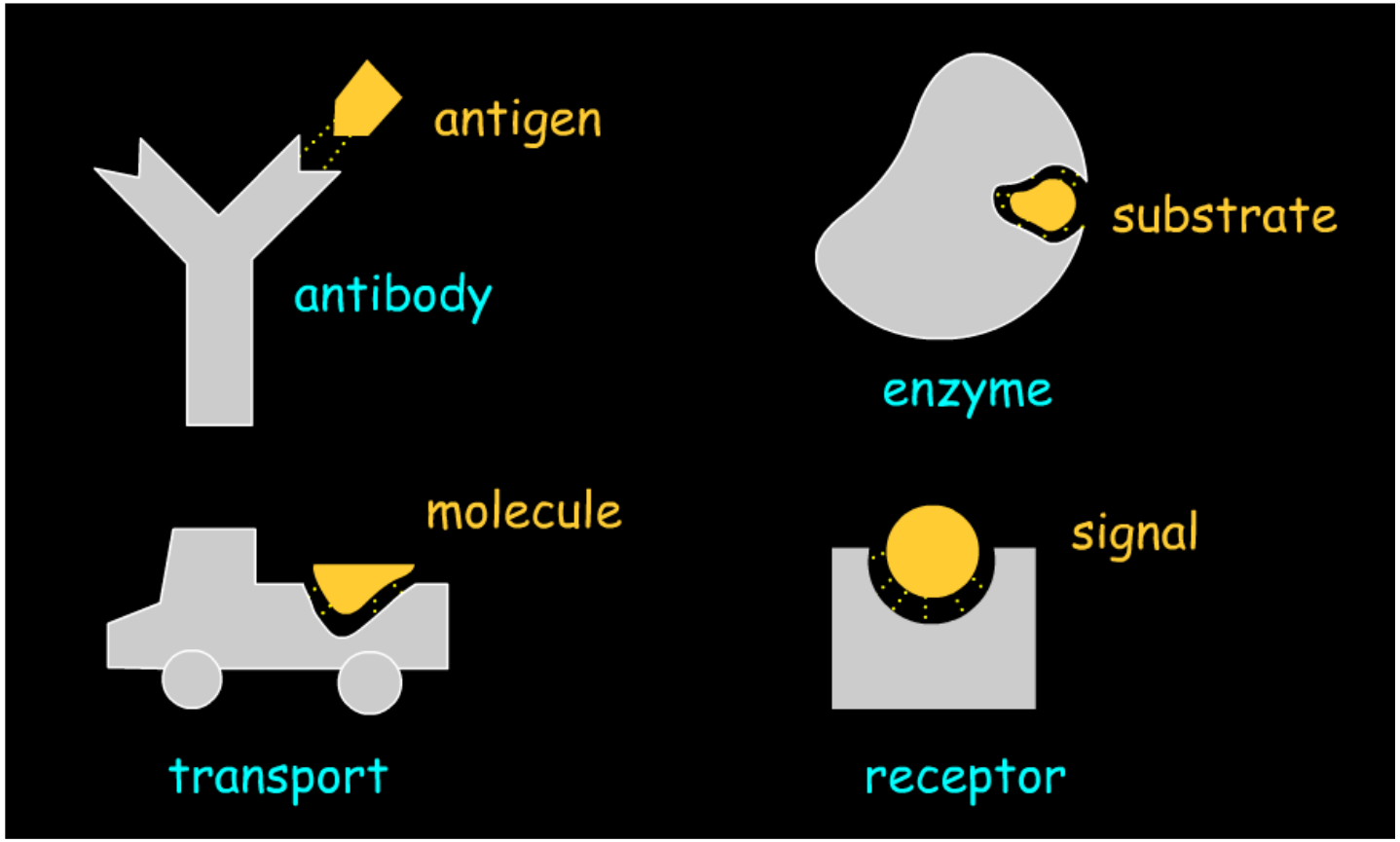




Molecular Docking



- Predicts the optimal orientation and conformation of interacting molecules in space and estimates the stability of the complex formed



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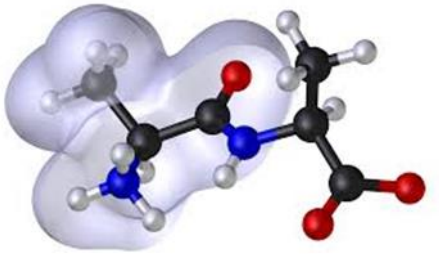
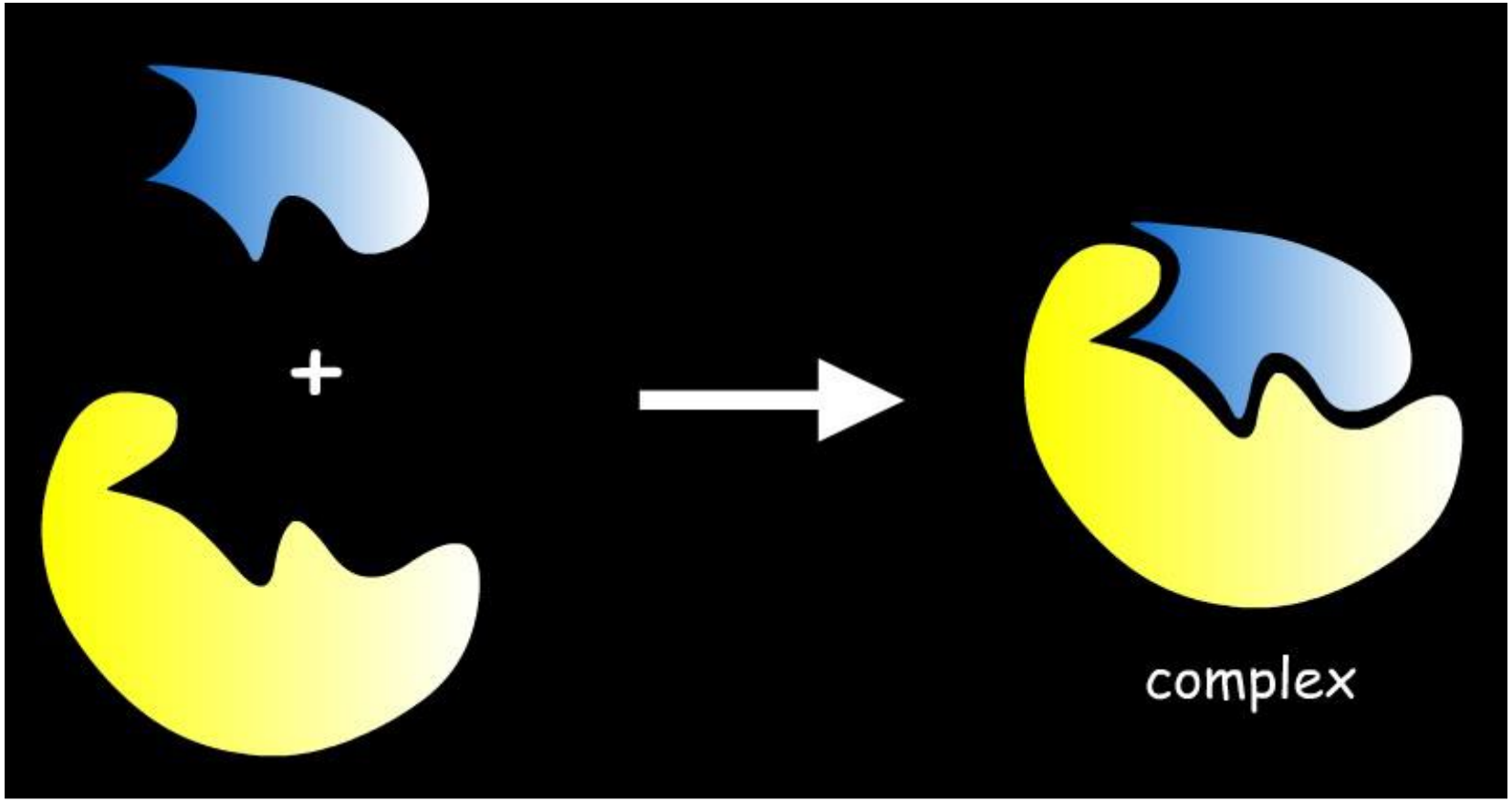
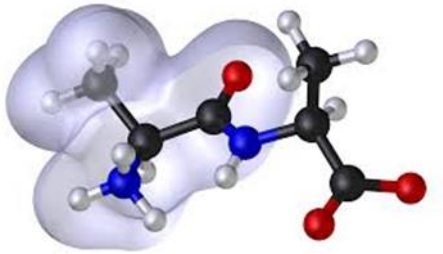


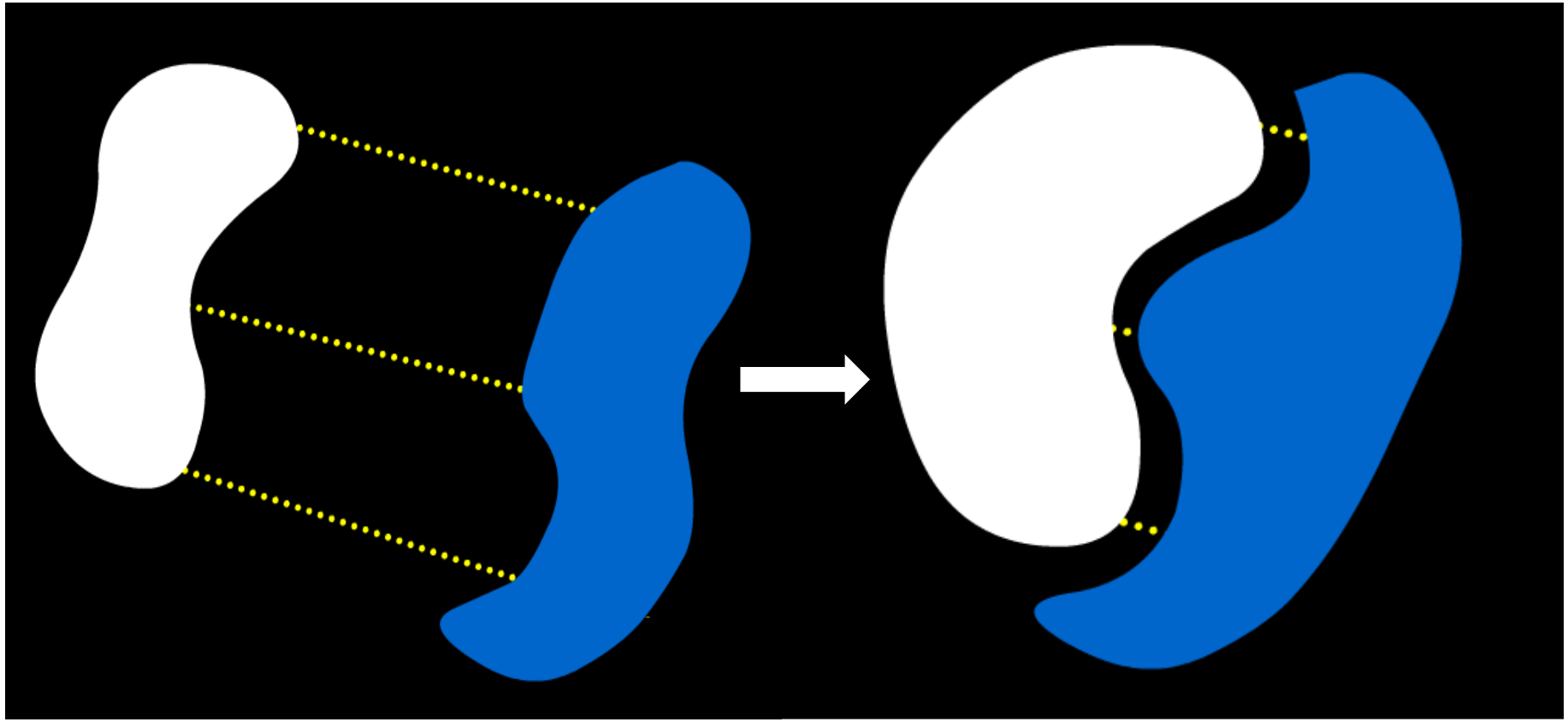
- **Lock-and-key**
  - A drug/ligand fits into the active site of a macromolecule, just like the key fits into a lock



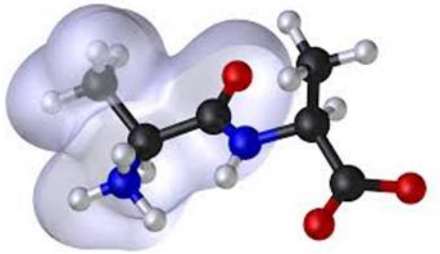
Molecular Docking



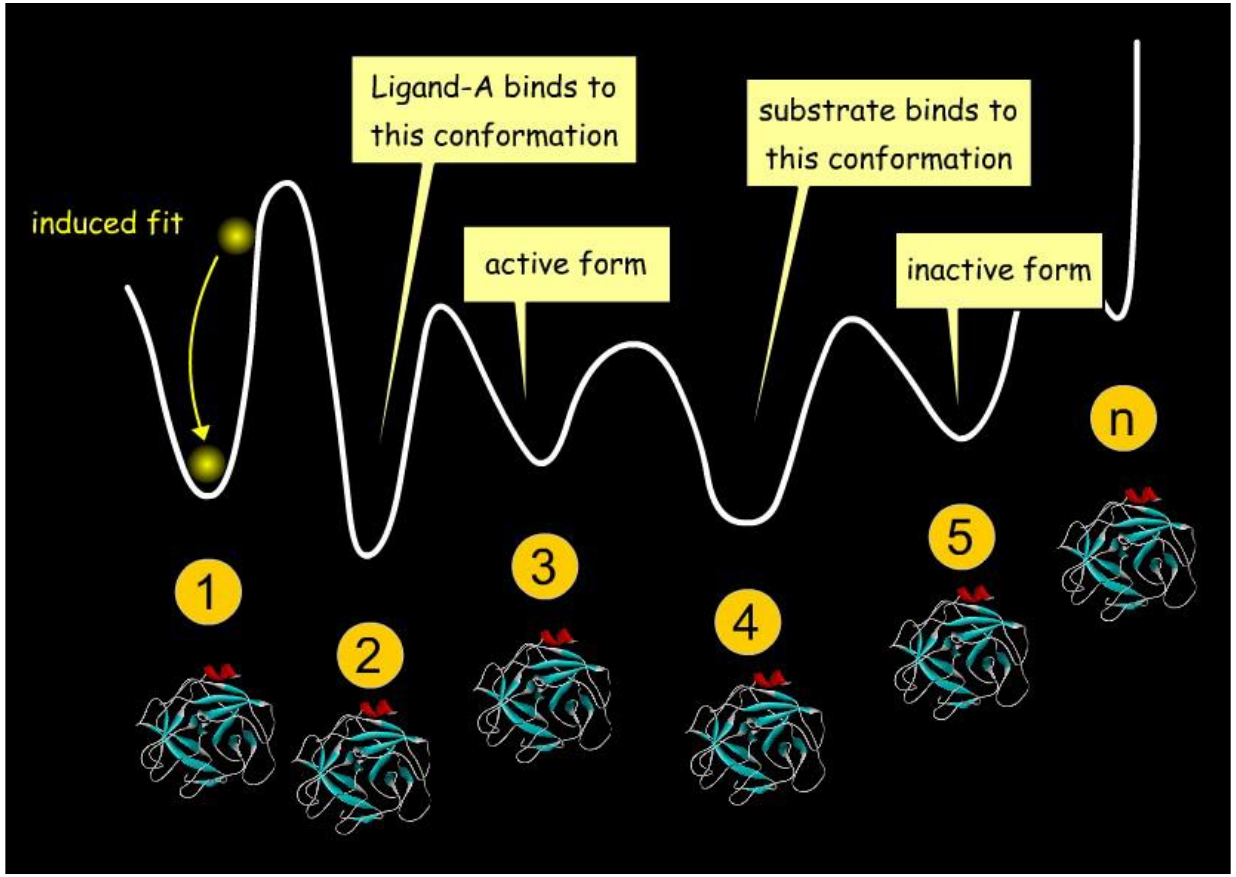
- **Induced fit**
  - Both drug/ligand and target protein mutually adapt to each other through small conformational changes until optimal fit is achieved



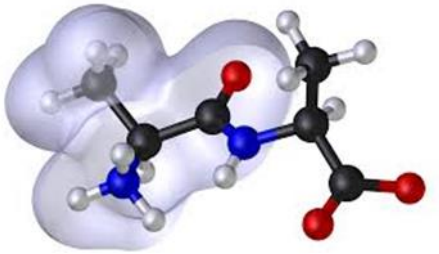
Molecular Docking

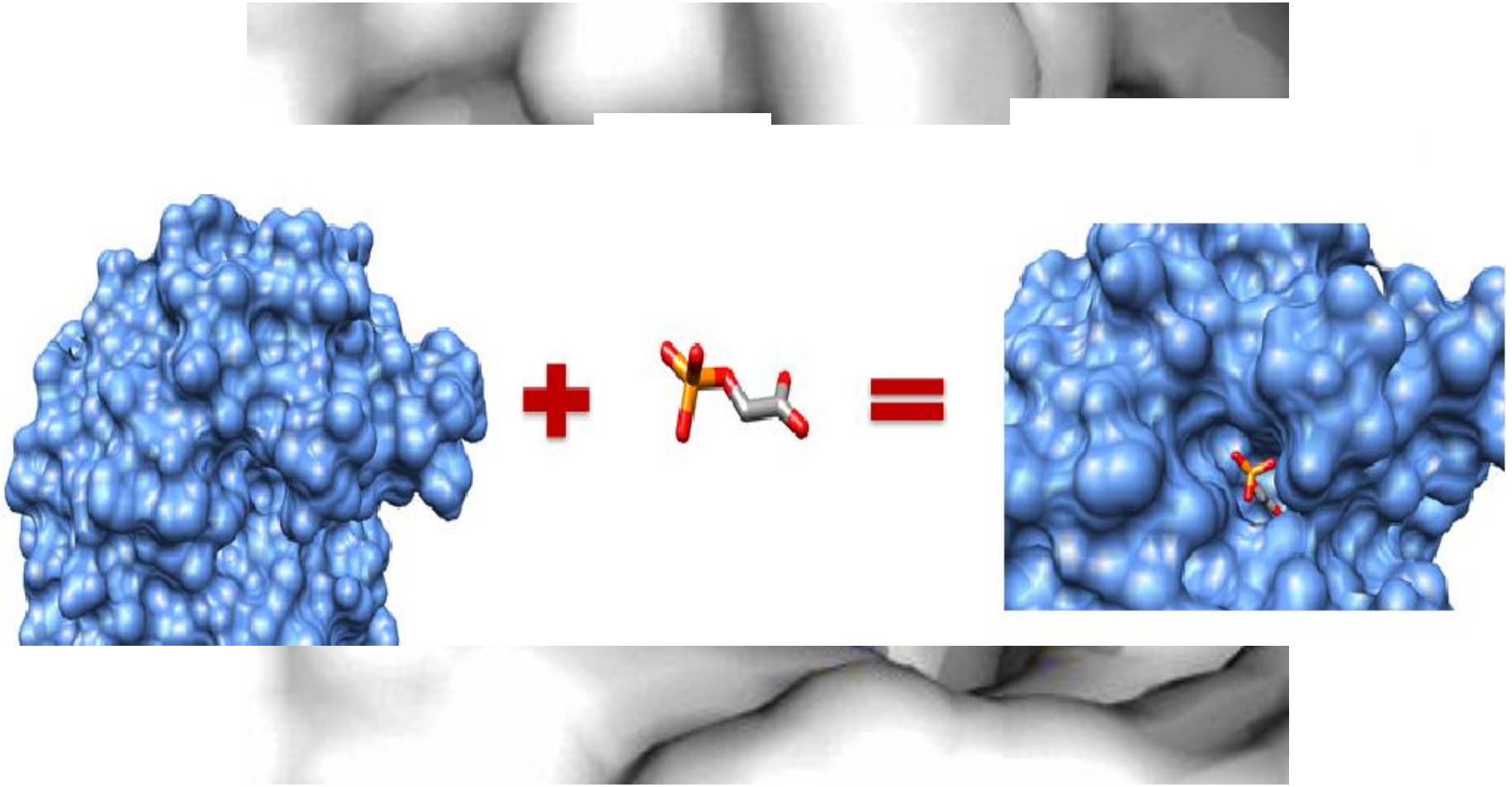


- **Conformational Ensemble**
  - Just like drugs/ligands can undergo conformational changes there are proteins that undergo large conformational changes.

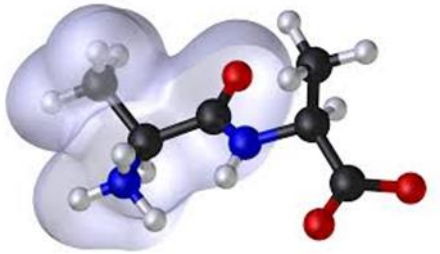


Molecular Docking

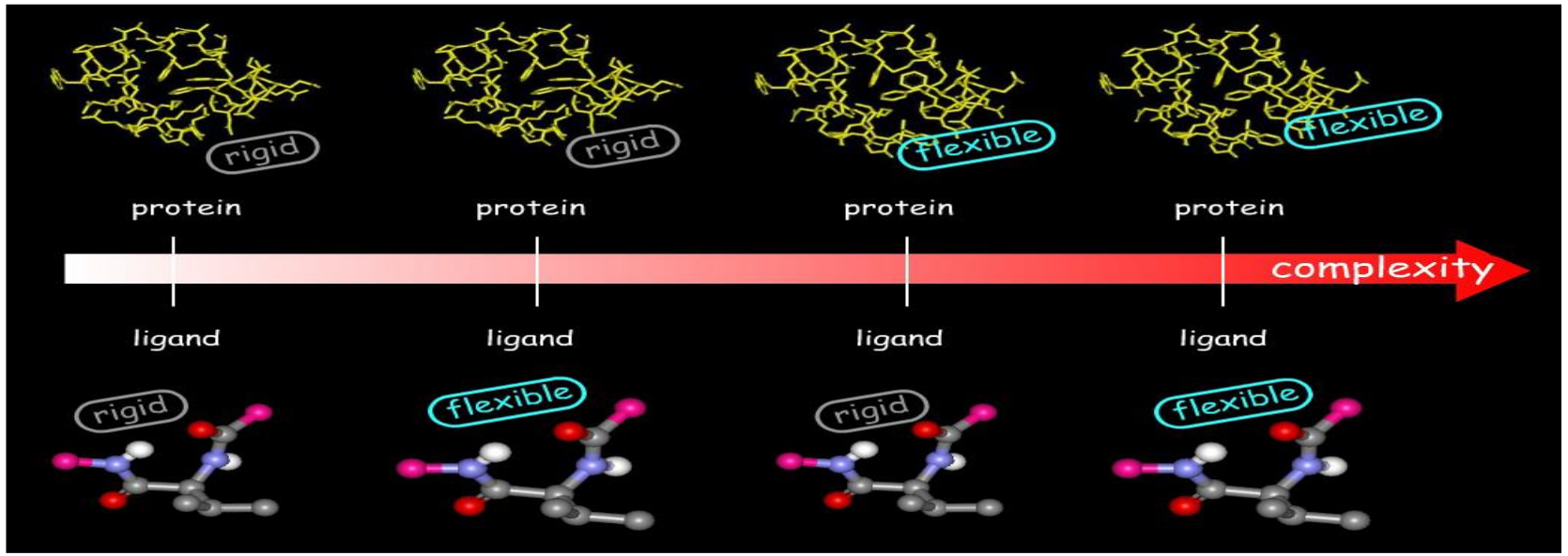




Molecular Docking

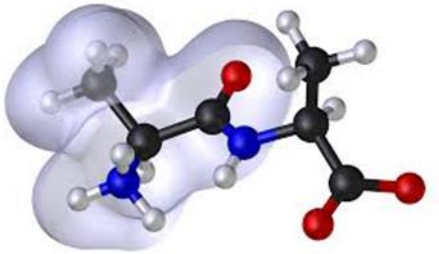


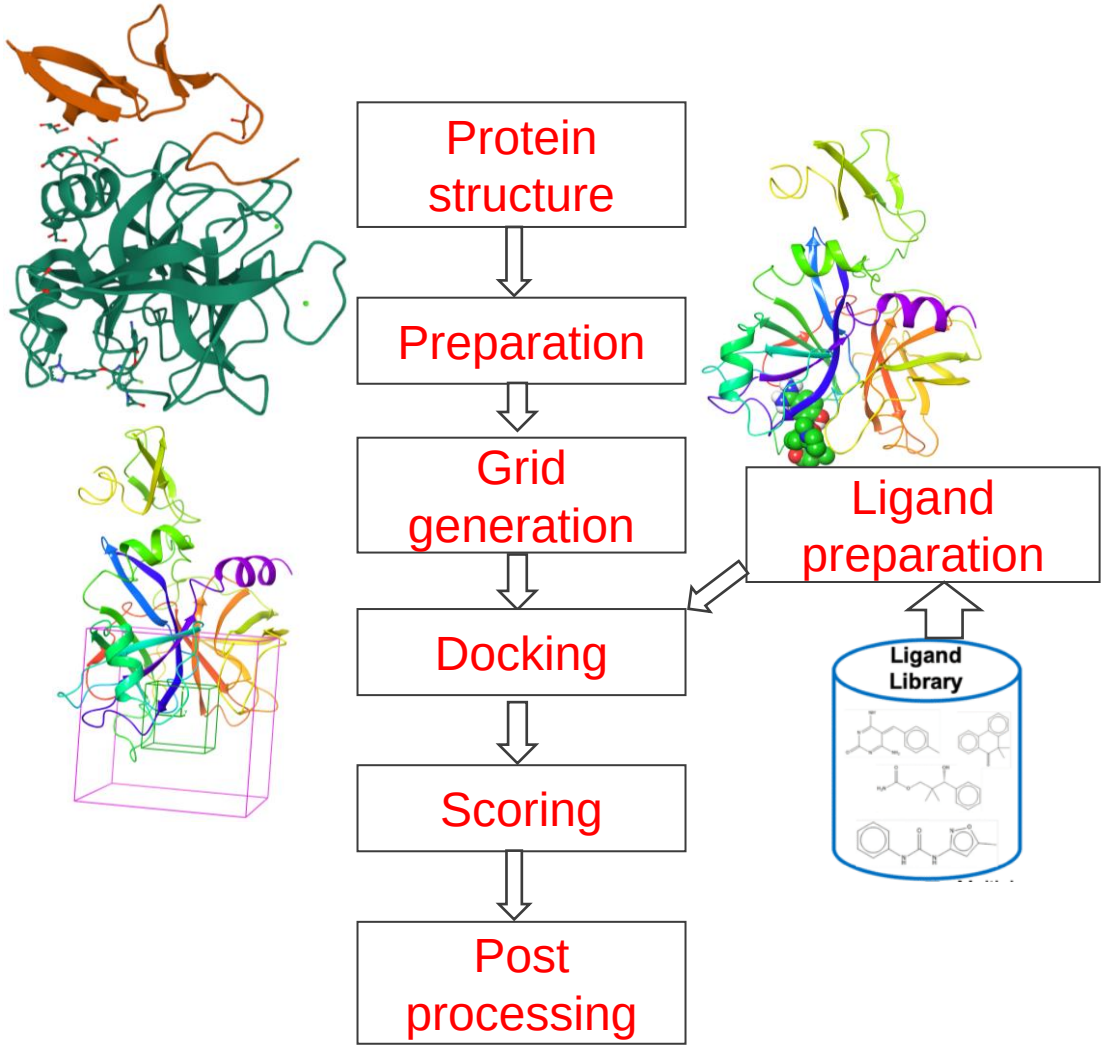
- **Different docking categories:**
  - Protein-ligand
  - Protein-protein
  - Protein-nucleic acid
  - Enzyme-substrate
  - Ligand-nucleic acid



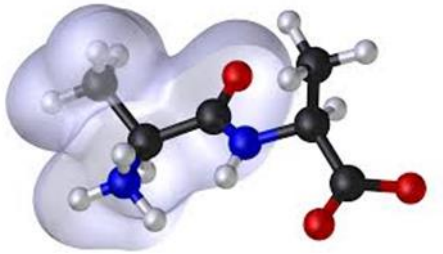
- The interactions between protein and ligand are by far much better understood compared to those between protein-protein or protein-nucleic acid

Molecular Docking



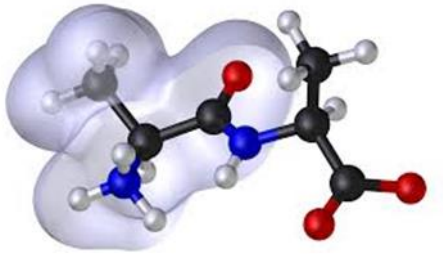


Molecular Docking



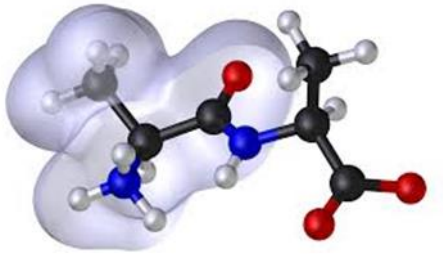
- Say we have 1 million ligand candidates that we wish to use for docking
- How do we get the ligands that are to be included in the ligand library?
- Do we download these 1 million entries individually?
- If not, what would be a faster way to obtain the ligands?
- Python
- Let’s look at an example

Molecular Docking



Number of ligands	Time per ligand (s)	Number of cores	Total Time (s)	Grand Total
2 million	2	1	4 million	≈ 46 days
2 million	2	8	500 000	≈ 6 days
2 million	2	24	≈ 166 666	≈ 2 days
2 million	2	5120	≈ 781	≈ 13 minutes

Molecular Docking

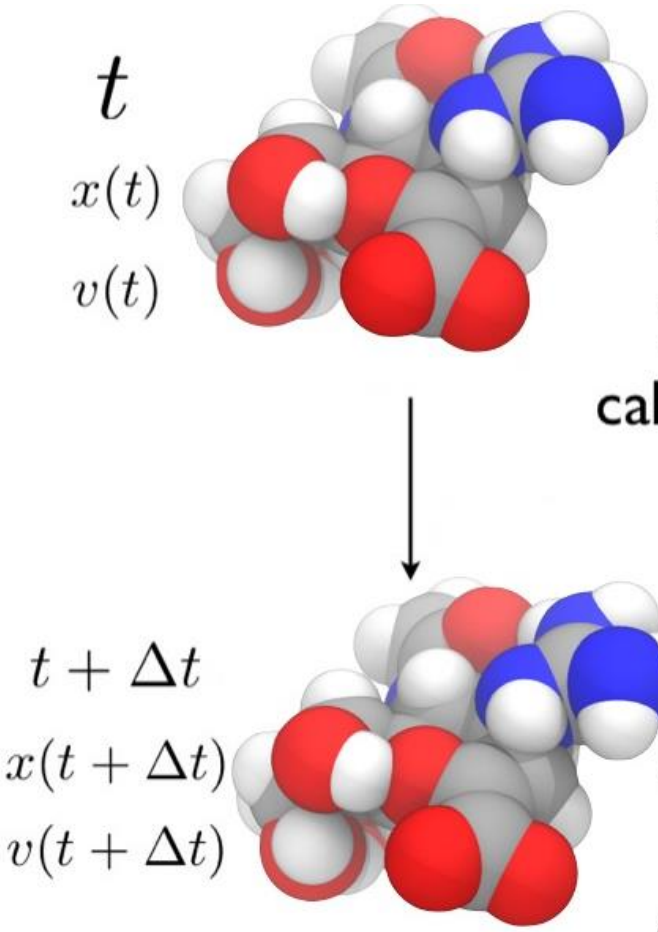


Software available for protein-ligand docking

Name	Type	Website
AutoDock	Academic	Download AutoDock4 – AutoDock (scripps.edu)
DOCK	Academic	UCSF DOCK
OEDOCKING	Academic	Molecular Docking Software for Virtual Screening (eyesopen.com)
SwissDock	Academic	http://www.swissdock.ch/
GOLD	Commercial	GOLD | CCDC (cam.ac.uk)
Glide	Commercial	Glide | Schrödinger (schrodinger.com)
VINA	Academic	AutoDock Vina (scripps.edu)
RDOCK	Academic	https://rdock.sourceforge.net/
HADDOCK	Academic	Bonvin Lab
LEDOCK	Academic	Software | Computational Insights into Drug Discovery (lephar.com)
FLEXX	Commercial	Products • BioSolveIT

Molecular Dynamics

Makes use of domain decomposition to assign different MPI processors

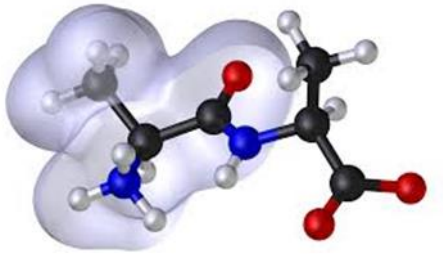


1. Assign velocities to all atoms
2. Calculate forces on all atoms
3. Use Newton's second law to calculate acceleration on each atom

$$F = ma$$

4. Calculate velocities for the next timestep
5. Use change of velocities to get coordinates for next timestep
6. Go to step 2.

Molecular Dynamics

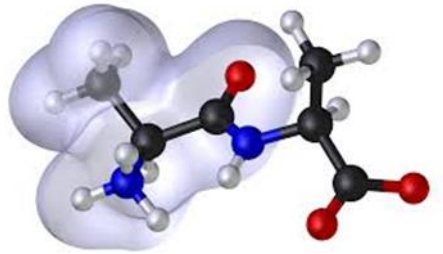


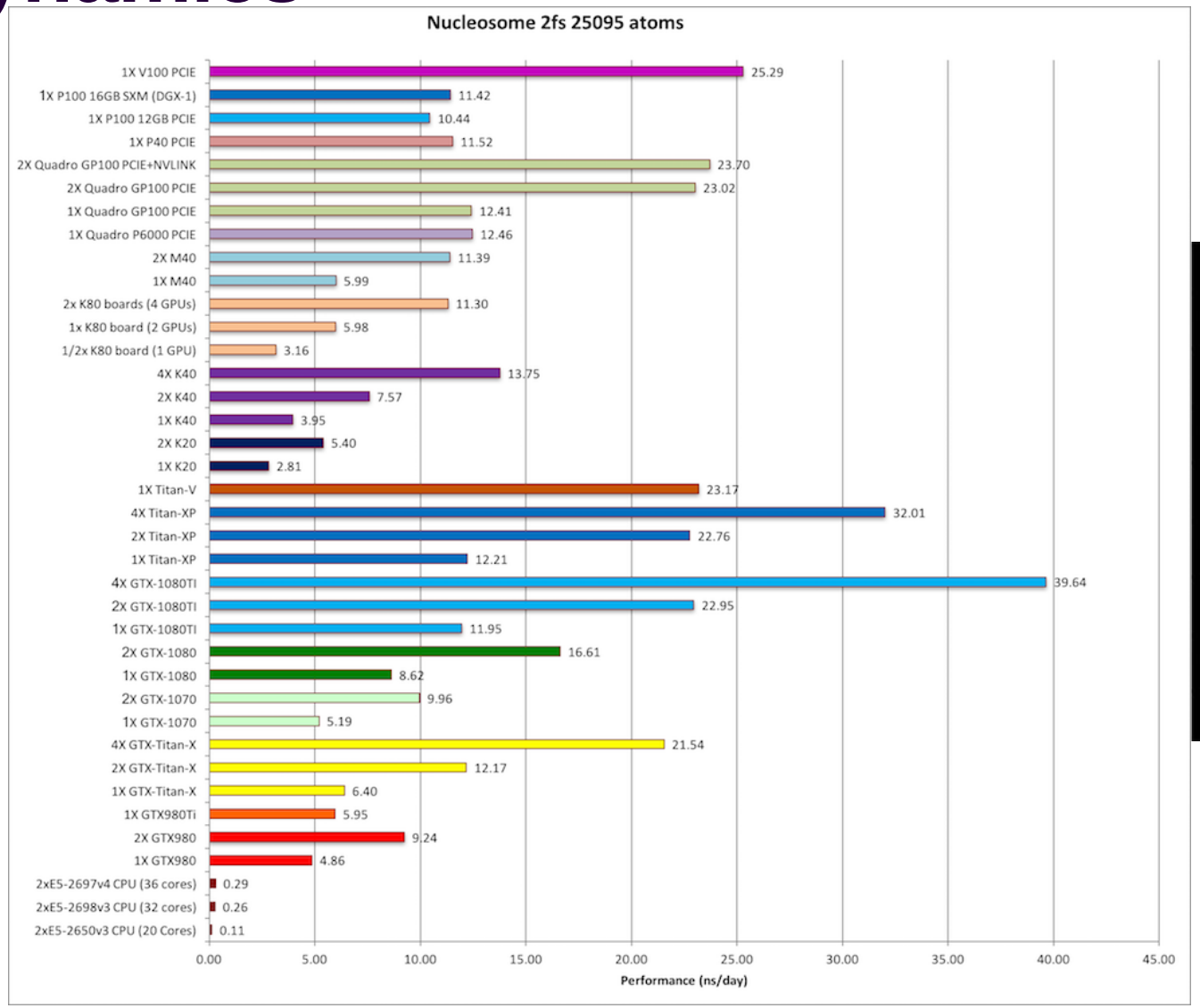
Software available for molecular dynamics simulations

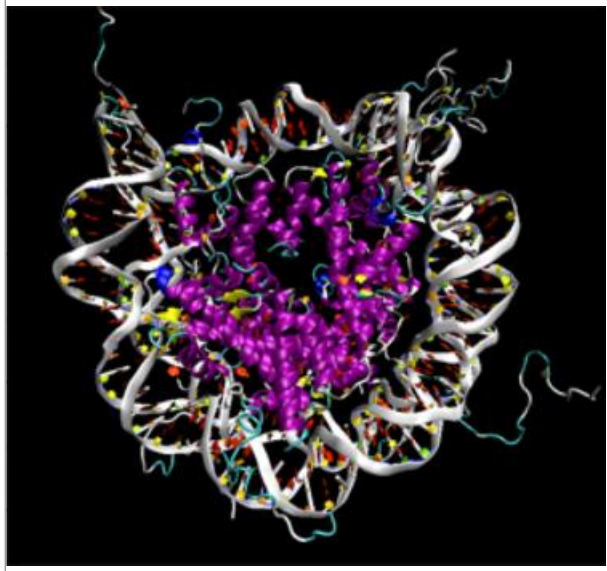
Name	Type	Website
AMBER	Academic/Commercial	The Amber Molecular Dynamics Package (ambermd.org)
GROMACS	Academic	Welcome to GROMACS — GROMACS webpage https://www.gromacs.org documentation
NAMD	Academic	NAMD - Scalable Molecular Dynamics (uiuc.edu)
DESMOND	Commercial	Desmond | Schrödinger (schrodinger.com)
CHARMM	Commercial	CHARMM: Home

Molecular Dynamics

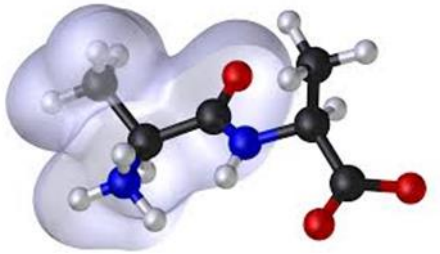
AMBER





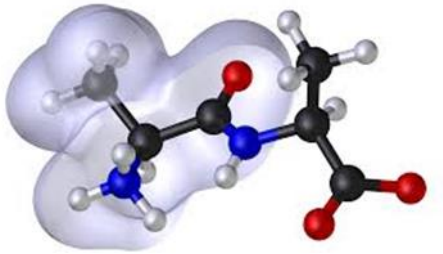


Conclusion



- Molecular docking can be used to identify potential drug candidates
- Molecular dynamics can be used to determine the stability of a protein and protein-ligand complexes
- The combination can be used to assist with developing new innovative drug candidates that can be used for various diseases
- These harness the power of HPC in pursuit of good health and well-being of humankind

Acknowledgements

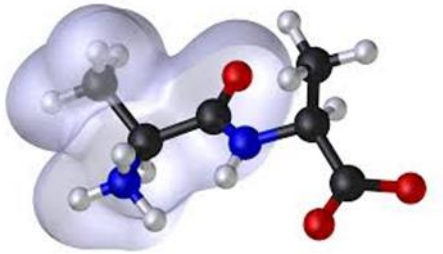


UNIVERSITY OF JOHANNESBURG

NICIS
NATIONAL INTEGRATED CYBERINFRASTRUCTURE SYSTEM
CHPC

NITheCS
National Institute for Theoretical and Computational Sciences

ICTP
The Abdus Salam International Centre for Theoretical Physics



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