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Essentials of Molecular Modelling for Drug Discovery

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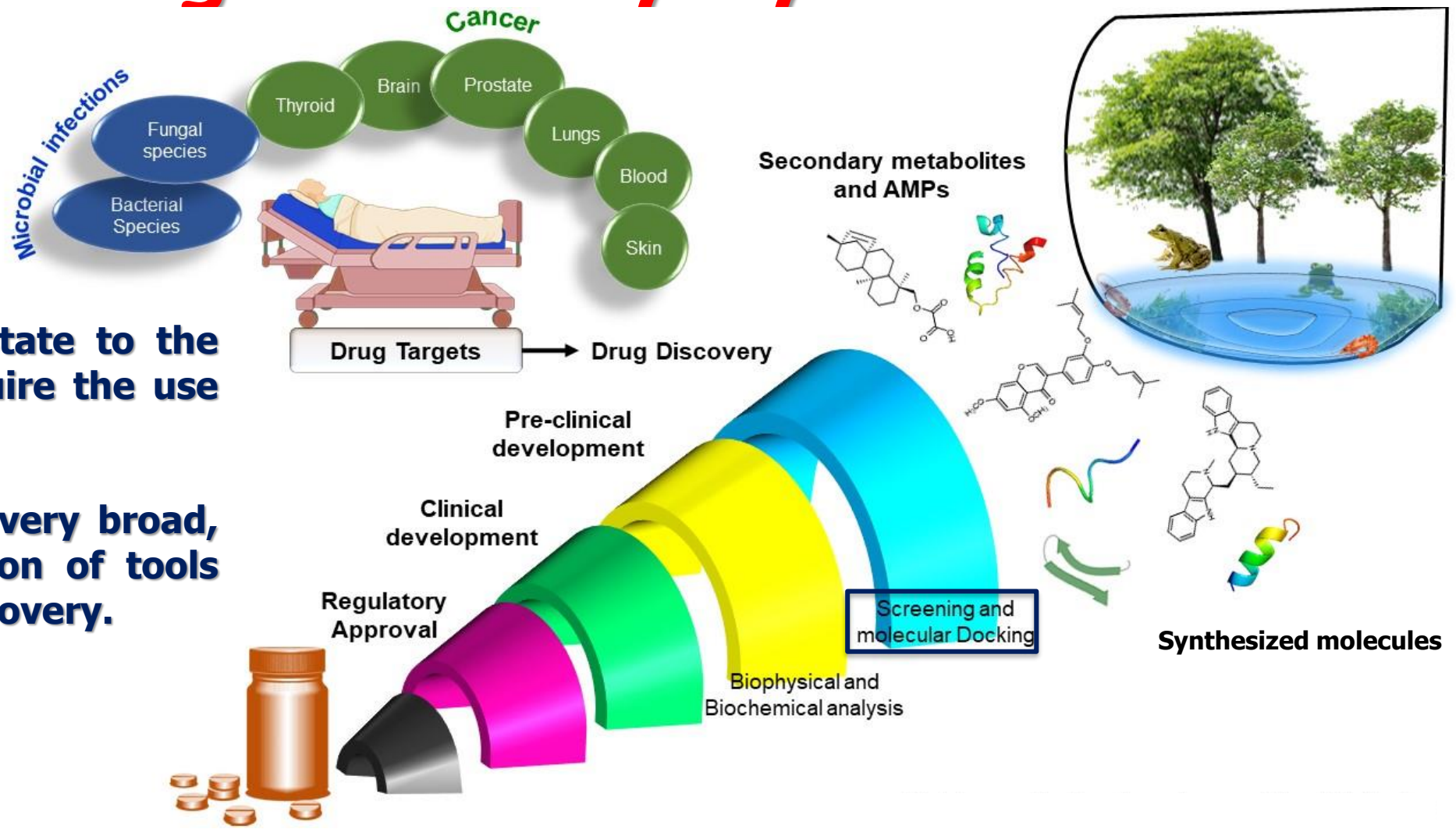
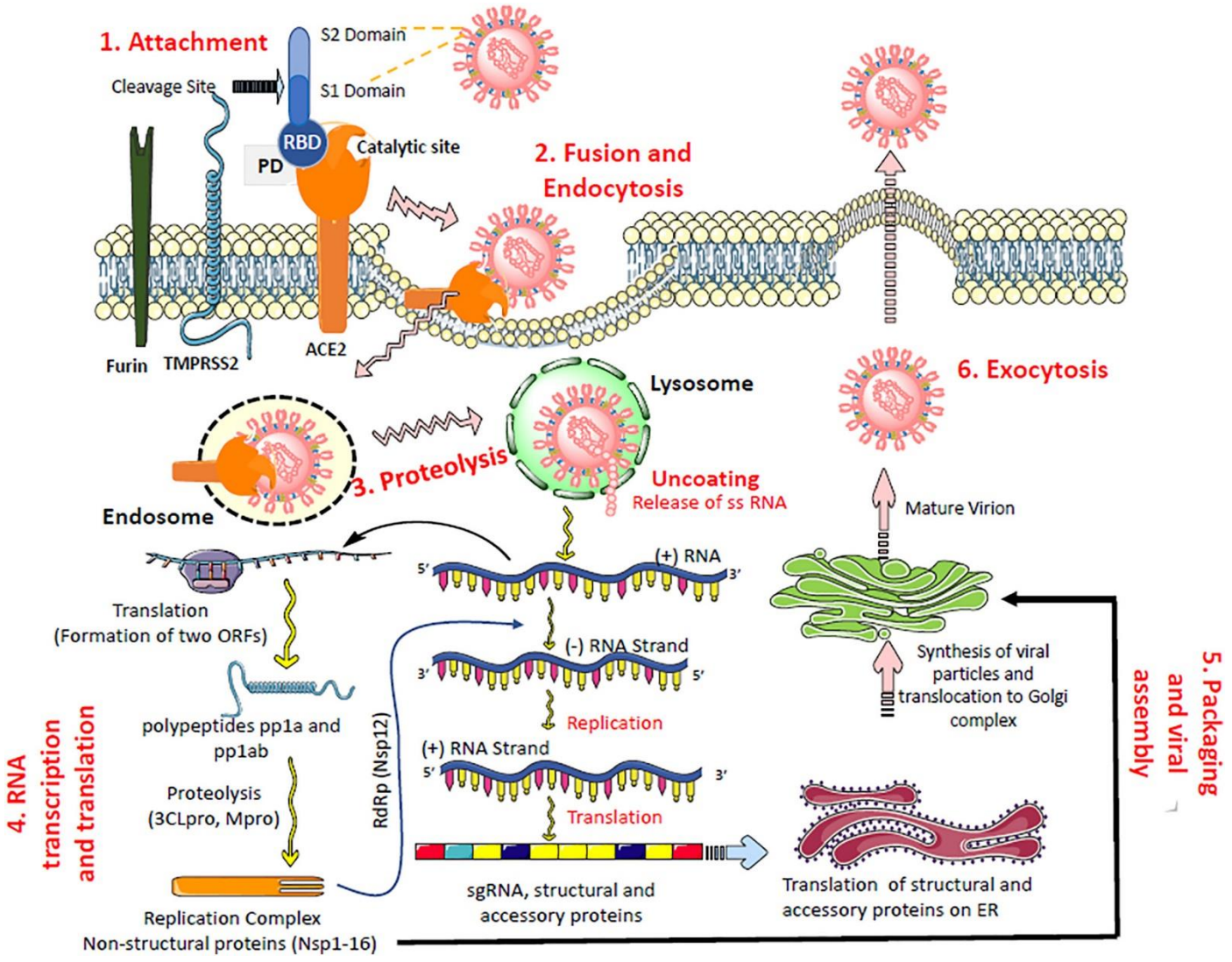
Drug discovery cycle



- **Identifying a disease state to the discovery of drugs require the use of models.**
- **Modeling concepts are very broad, hence a careful selection of tools could enhance drug discovery.**

Disease states and targets



What is identifiable in this chart/illustration ?

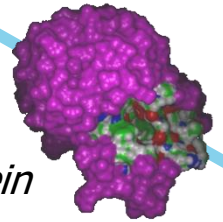
What could inform disease aetiology?

What are the available therapies for this disease?

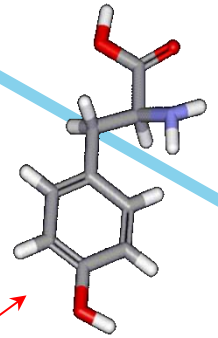
What can small molecules (secondary metabolites or natural products) do to help us?

Quite a journey

Identify disease



Isolate protein involved in disease (2-5 years)



Find a drug effective against disease protein (2-5 years)

Drug Design
- Molecular Modeling
- Virtual Screening

Preclinical testing (1-3 years)

Scale-up

Formulation

File IND

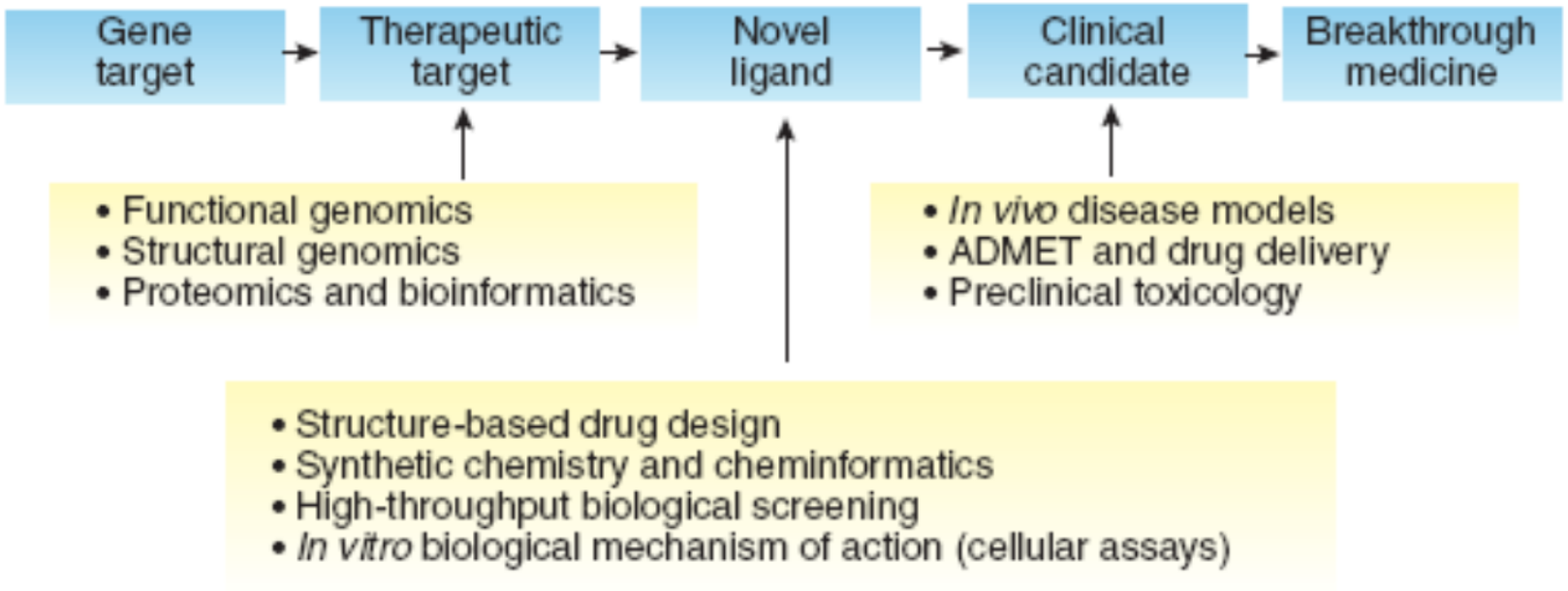
Human clinical trials (2-10 years)

File NDA

FDA approval (2-3 years)

IND: Investigational New Drug
NDA: New Drug Application

Smart drug discovery

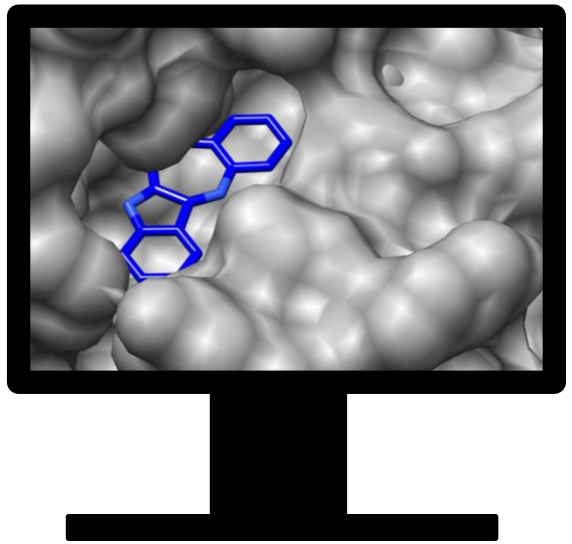


A view of Drug Discovery road map illustrating some key multidisciplinary technologies that enable the development of:

(a) Breakthrough medicines from promising candidates

(b) LO & generation processes that are relative to novel ligands.

What we do



Molecular modelling

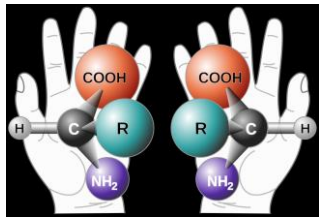
Molecular modelling:

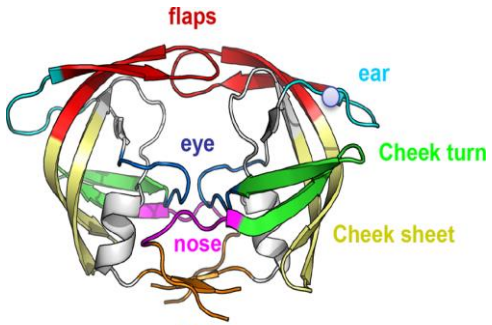
- ✓ Molecular modeling encompasses **all theoretical methods that allows science to describe macroscopic observations with the use of microscopic description of matter**
- ✓ Helps us to answer the two important questions; does the molecule work, and how does it work?
- ✓ Two useful tools are employed; molecular docking and molecular dynamics simulations

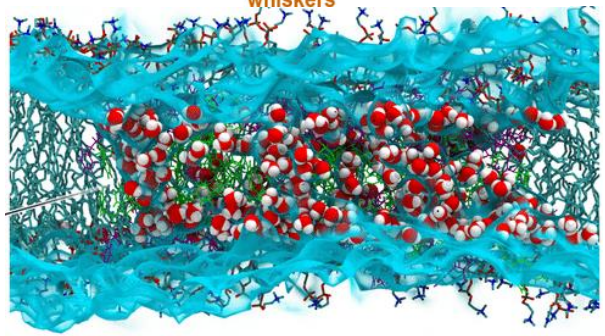
Conceptual framework of MM

Objects

Molecular systems







Tools

Models

$F = ma$

Physical laws

Atomic and molecular interactions

Mathematical models

$i\hbar\frac{\partial}{\partial t}\Psi = \hat{H}\Psi$

Goals

Properties
Comparison
Theory/Experience

Spectra

Geometries

Kinetics

Thermodynamics

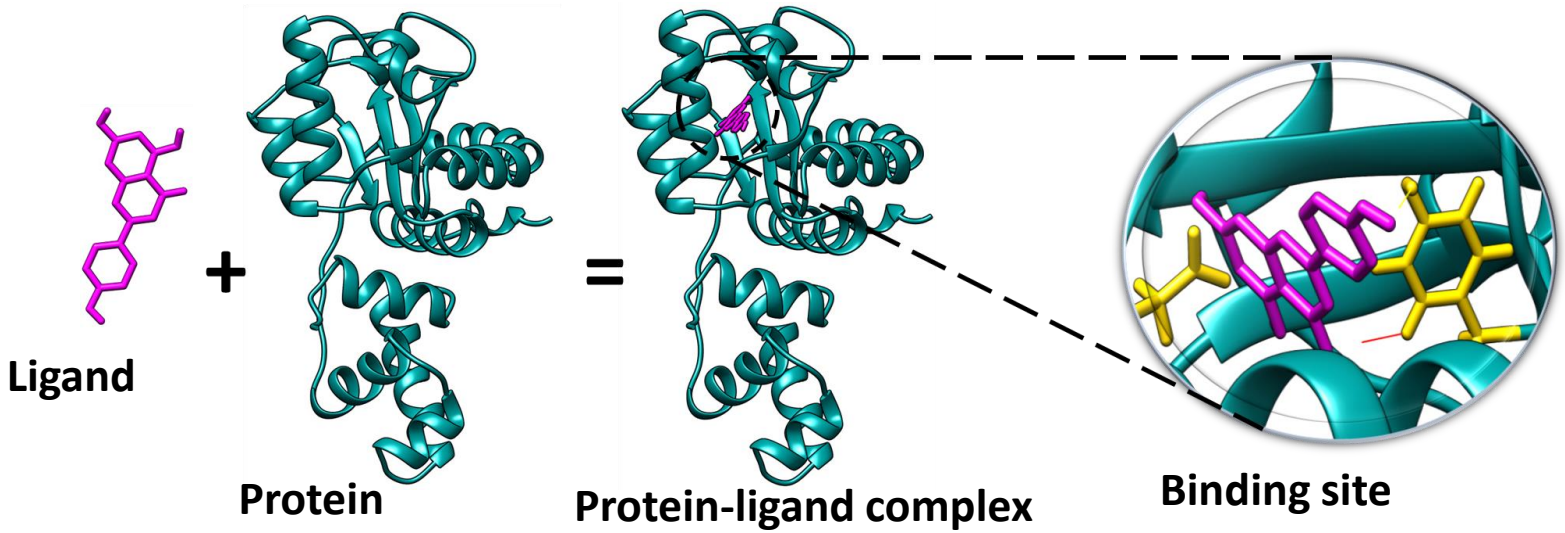
Understanding
Rationalization
Predictive power

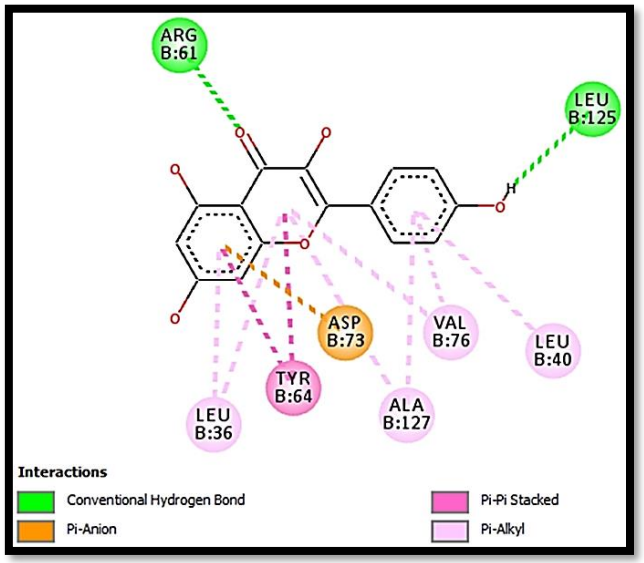
Molecular docking

Molecular docking – Computational method that mimics the binding of a ligand to a protein

Predicts

- The **pose** of the molecule in the binding site
- The **binding affinity** representing the strength of binding of the molecule to the protein





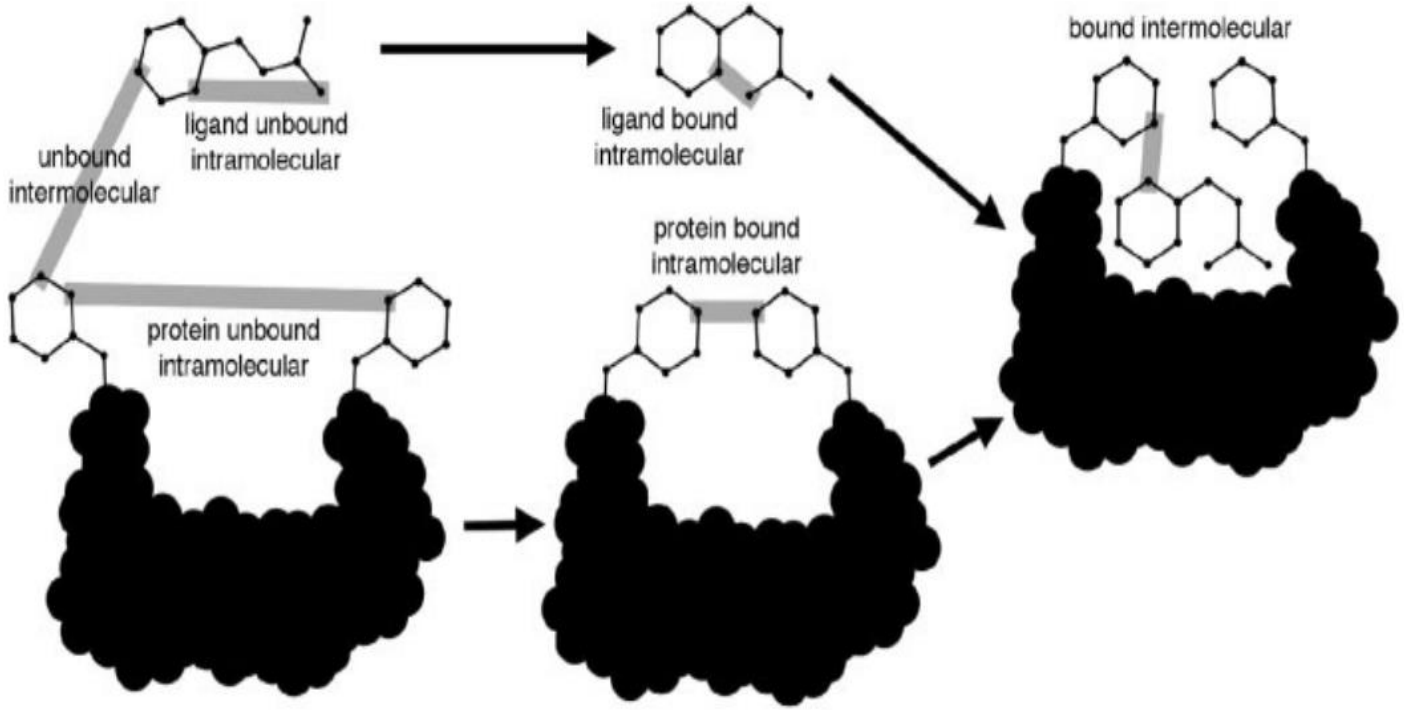
Protein-ligand interactions

Molecular docking

- Docking is ultimately interested in reproducing chemical potentials, which **determine the preferred pose** and **the free energy of binding**

- Calculates the **energy** of ligand and protein in the **unbound state** and of the **protein-ligand complex**

- Energy = sum of
  - Van der waals energy
  - Hydrogen bonds
  - Coulomb energy



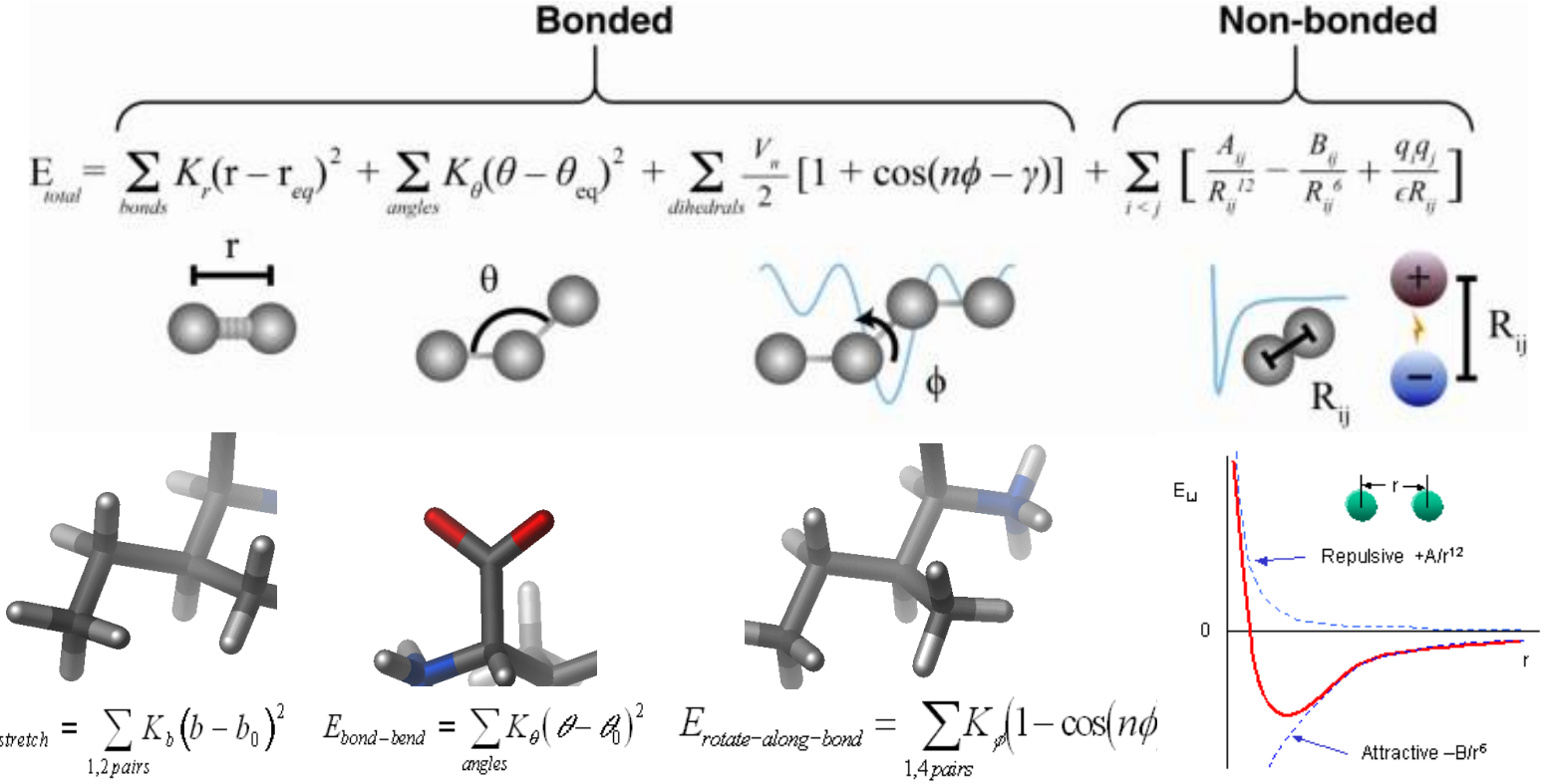
$$\Delta G = \left(V^{\text{L-L}}_{\text{bound}} - V^{\text{L-L}}_{\text{unbound}}\right) + \left(V^{\text{P-P}}_{\text{bound}} - V^{\text{P-P}}_{\text{unbound}}\right) + \left(V^{\text{P-L}}_{\text{bound}} - V^{\text{P-L}}_{\text{unbound}} + \Delta S_{\text{conf}}\right)$$

$$V = W_{vdw}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{\text{hbound}}\sum_{i,j}E(t)\left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{\text{elec}}\sum_{i,j}\frac{q_i q_j}{\varepsilon(r_{ij})r_{ij}} + W_{\text{sol}}\sum_{i,j}\left(S_i V_j + S_j V_i\right)e^{(-r_{ij}^2/2\sigma^2)}$$

Free energy = Contrib_(Product – Reactants)

Force field

The empirical potential energy function is differentiable with respect to the atomic coordinates; this gives the value and the direction of the force acting on an atom and thus it can be used in a **molecular simulation** – the study of conformational dynamics or the "scoring" of the events contributing to molecular recognition.



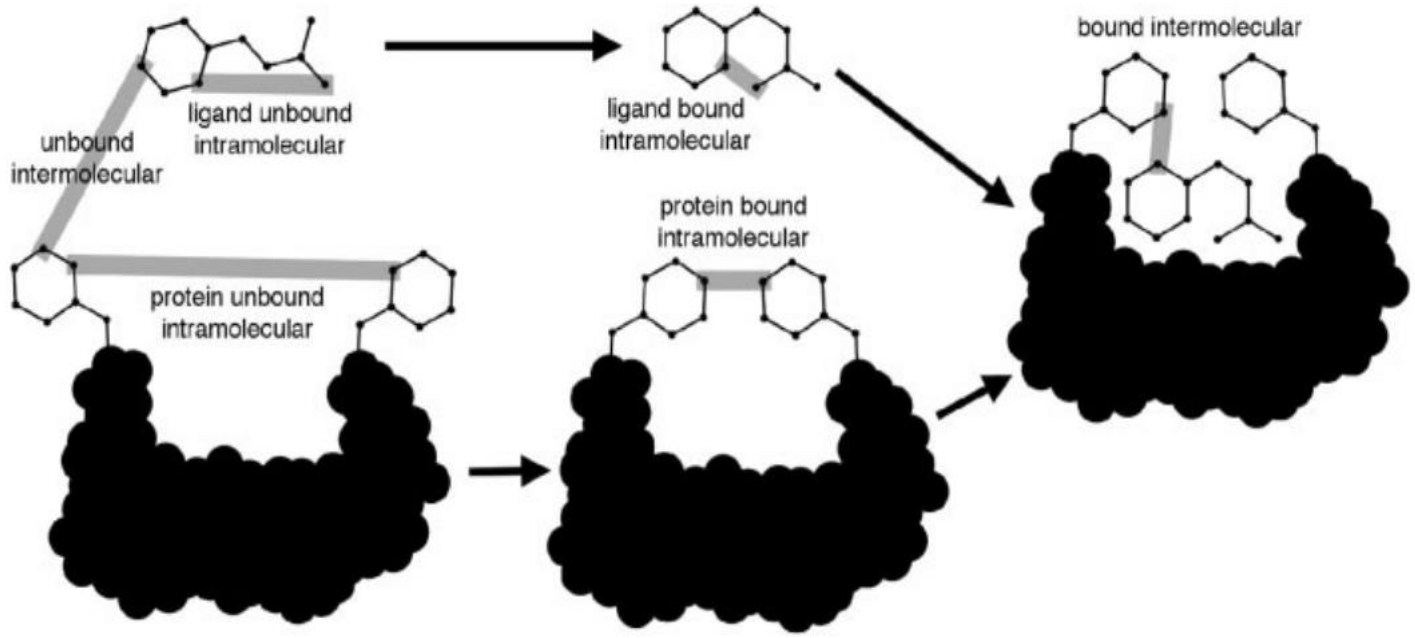
Scoring functions

Scoring function, can be seen as **an attempt to approximate the standard chemical potentials** of the system

Docking is ultimately interested in reproducing chemical potentials, which **determine the preferred pose** and **the free energy of binding**

Calculates the energy of ligand and protein in the unbound state and of the protein-ligand complex

They need to be **significantly empirically weighted**, in part, to account for this difference between energies and free energies



$$\Delta G = (V^{\text{L-L}}_{\text{bound}} - V^{\text{L-L}}_{\text{unbound}}) + (V^{\text{P-P}}_{\text{bound}} - V^{\text{P-P}}_{\text{unbound}}) + (V^{\text{P-L}}_{\text{bound}} - V^{\text{P-L}}_{\text{unbound}} + \Delta S_{\text{conf}})$$

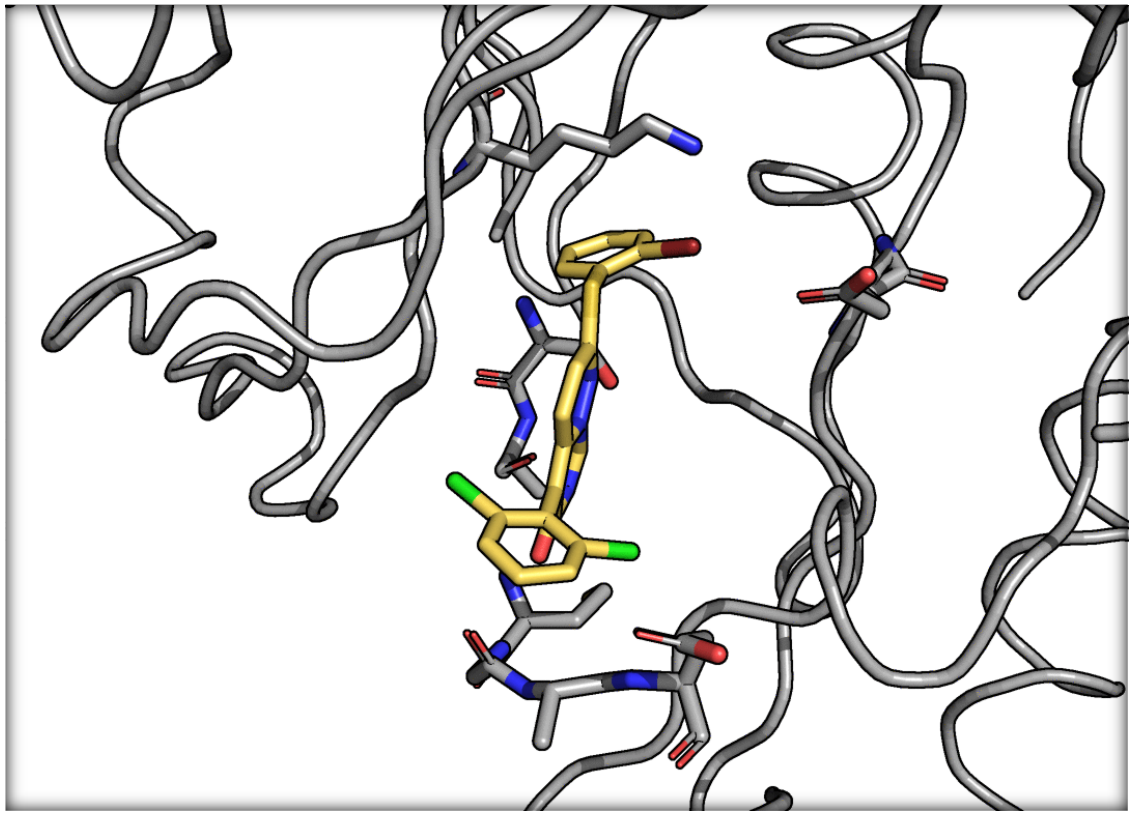
$$V = W_{vdw}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{\text{hbound}}\sum_{i,j}E(t)\left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{\text{elec}}\sum_{i,j}\frac{q_i q_j}{\varepsilon(r_{ij})r_{ij}} + W_{\text{sol}}\sum_{i,j}(S_i V_j + S_j V_i)e^{(-r_{ij}^2/2\sigma^2)}$$

Free energy = Contrib_(Product – Reactants)

Molecular dynamics

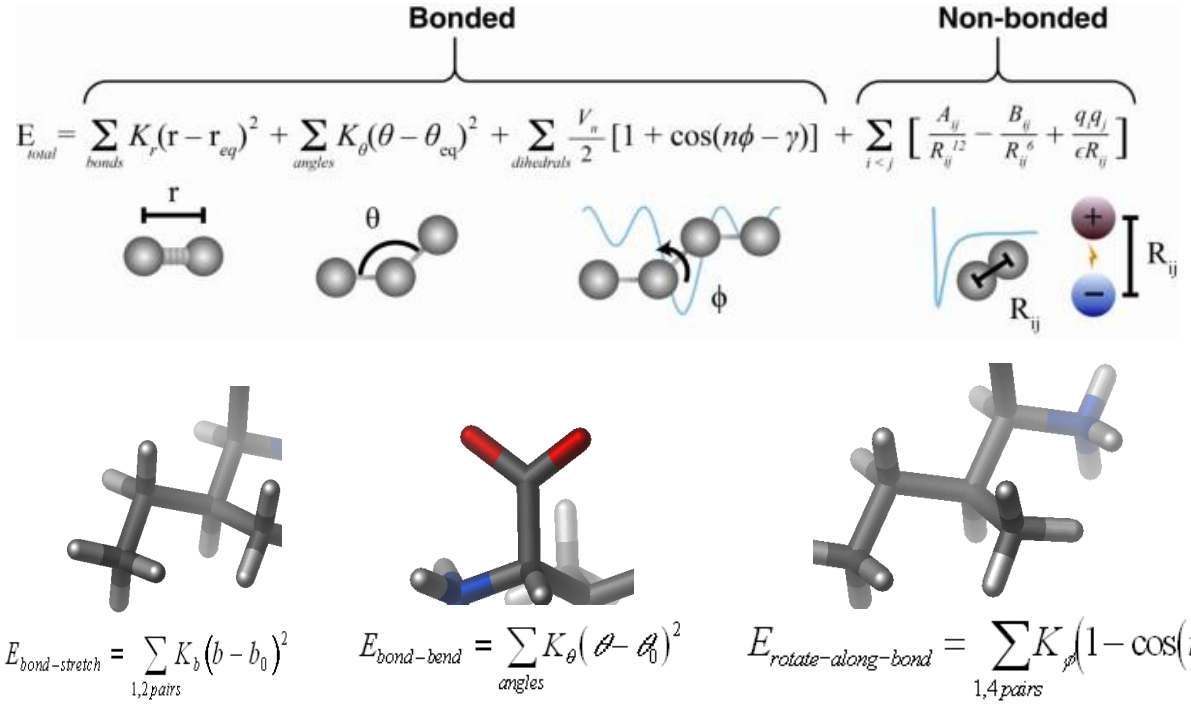
Molecular dynamics – Computational technique which simulates the dynamic behavior of molecular systems as a function of time

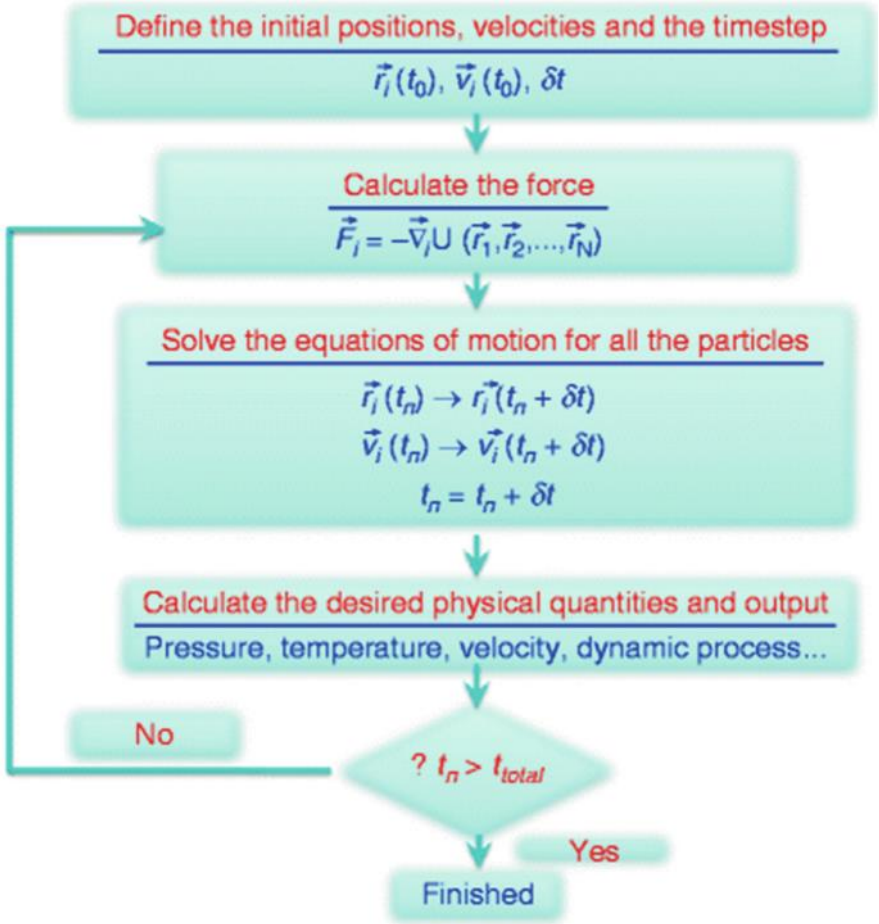
- Helps to determine the **stability** of molecules at the binding site of a protein
- Study structural properties of biomolecules
- Study the mechanism of action of molecules



❑ **The function of biological molecules rely largely on their dynamic motion**

Molecular dynamics





The motions of molecules can be predicted by analyzing the **position** of atoms, **forces** acting on the atoms, **interactions** between them, and the **velocities** with respect to **time**

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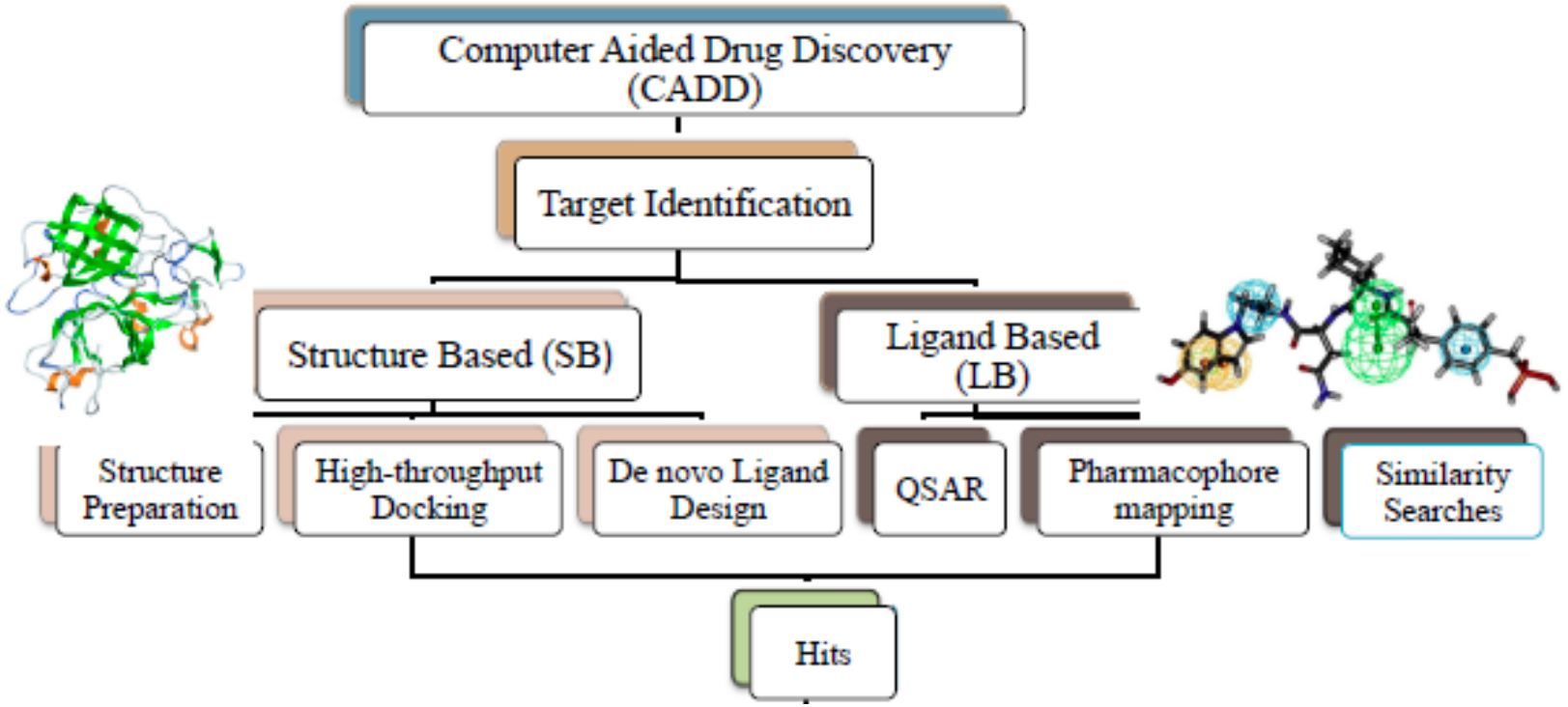
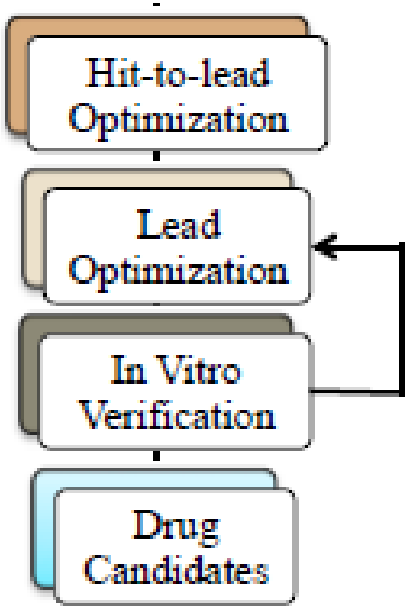
Role of CADD





- Target/disease pathway validation,
- Virtual screening,
- ADME-Tox,
- Small molecule multi-parameter optimizations…

ADME-Tox

- **Absorption**

For efficient absorption, there must be a balance between hydrophobicity and hydrophilicity.

Highly polar drugs will fail to cross membranes and highly non-polar ones will be poorly absorbed.

✓ Lipinski's rule for bioavailable drugs:

A molecular weight less than 500;

Not more than 5 hydrogen bond donors and 10 hydrogen bond acceptors;

Calculated logP less than +5

✓ Veber's parameters:

Polar surface area ≤ 140Å and ≤10 rotatable bonds.

For a drug to reach its molecular target with ease, it needs to be properly absorbed and this requires a good balance between hydrophobicity and hydrophilicity.

ADME-Tox

- **Distribution**

Blood carries drugs to their molecular targets

The percentage reaching circulation is termed the bioavailable dose

Volume of distribution (Vd):

$Vd = Dose/C_o$, where C_o is the bioavailable dose

Most drugs bind to serum proteins such as albumin

Only free or unbound drugs can reach and bind their molecular targets to elicit biological effects

Unbound volume of distribution:

$Vdu = Vd/fu$, where fu is the fraction unbound

The distribution of drugs through the blood to their molecular targets is complex. As a result, the dosage of a drug reaching the target is always lesser than the administered dose.

ADME-Tox

- **Metabolism**

Also known as biotransformation, metabolism happens primarily in the liver and less often in the gut walls

The purpose is for drugs to be easily excreted

Metabolites are mostly inactive, some retain similar activity, and some are active (prodrug strategy) than parent drug

Cytochrome P450 superfamily of enzymes; CYP3A4, CYP2D6, CYP2C9 and CYP2C19

Phase I and phase II

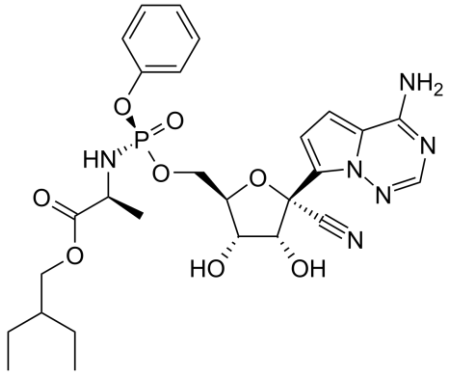


Figure 1. Remdesivir, a drug that relies on the prodrug strategy

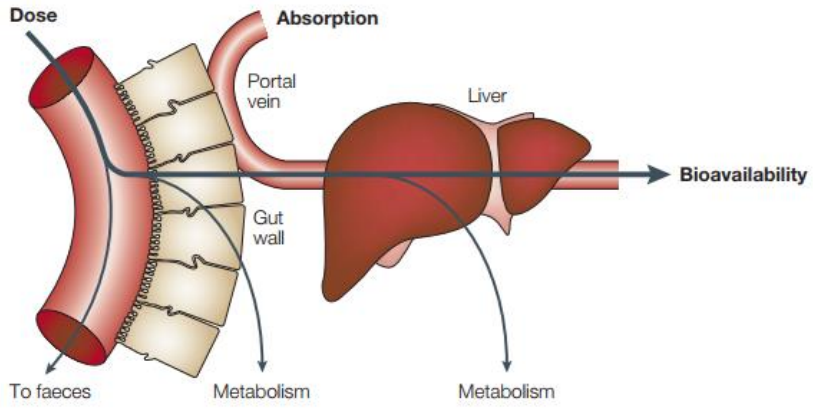


Figure 2. Drug metabolism

ADME-Tox

- **Phase I metabolism**

Focuses on making the drug more polar. Generally involve hydrolysis, oxidation, and reduction

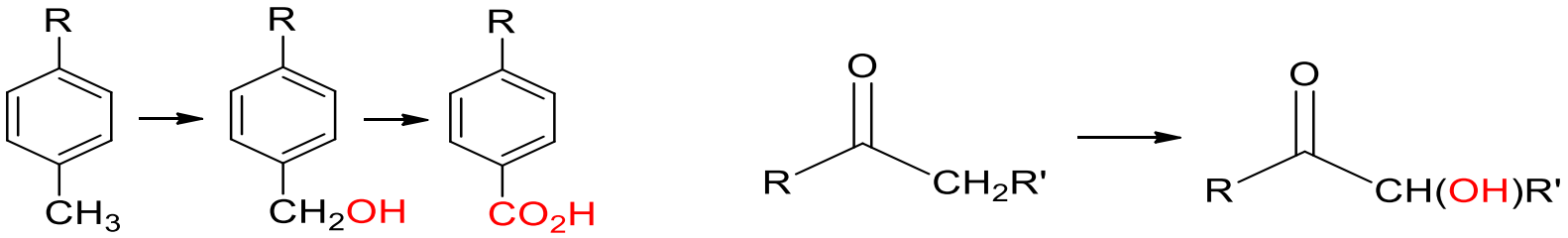


Figure 3. Some Phase I metabolic transformations

- **Phase II metabolism**

They are mostly conjugation reactions. The most common is the formation of glucuronic acid conjugates.

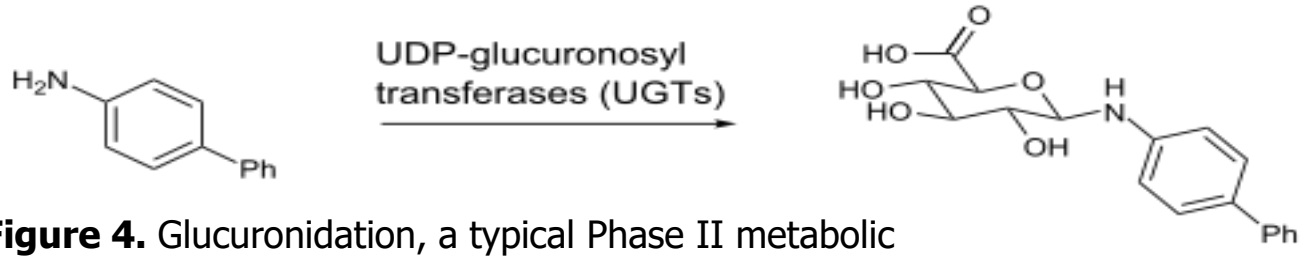


Figure 4. Glucuronidation, a typical Phase II metabolic transformation

ADME-Tox

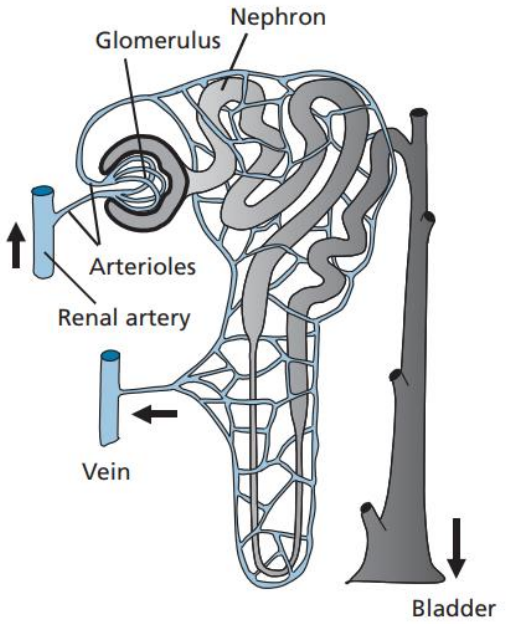
- **Excretion**

Excretion can take place through sweat, or bile but the kidney is the main organ

Kidney filter blood such that drugs and their metabolites enter the nephron

Non-polar compounds are reabsorbed into the blood

Polar compounds are retained and excreted

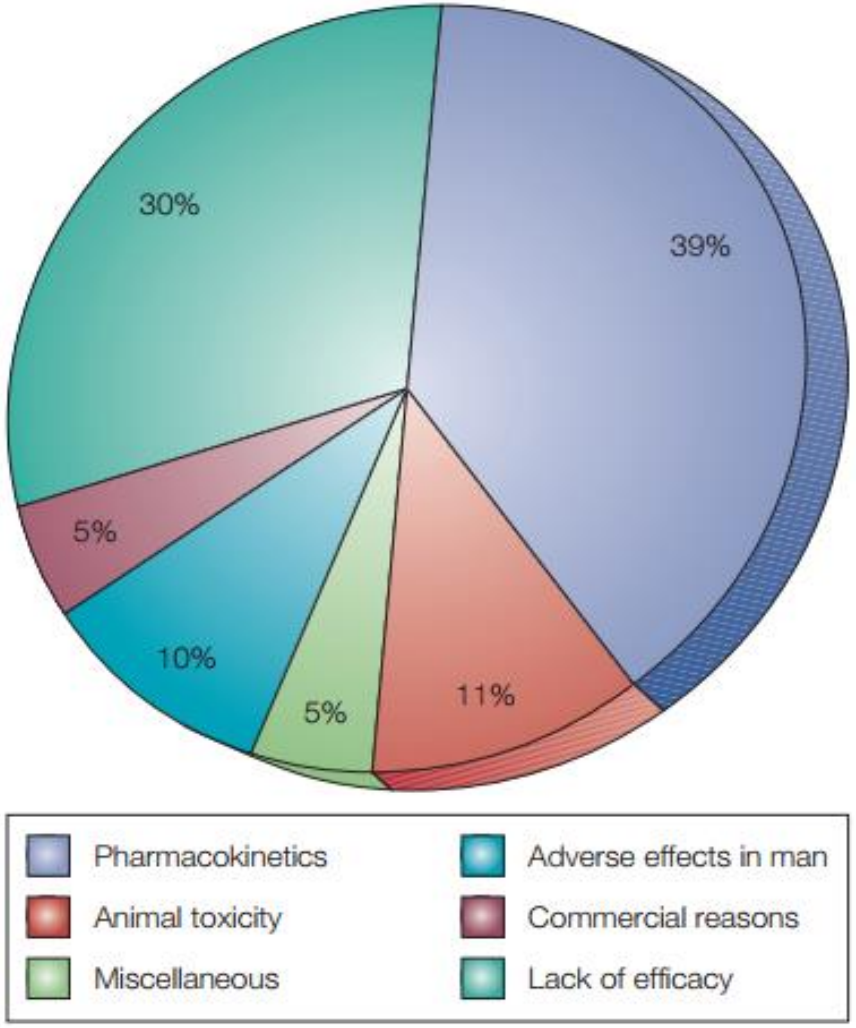


Metabolism, therefore, is very important for drug excretion

ADME-Tox: why should it be predicted?

- Large number of active compounds as a result of combinatorial chemistry and ultra-high throughput screening
- Number of approved drugs have not increased
- Majority of clinical failures are due to ADMET issues, not efficacy
- Addressing ADMET issues earlier in the drug discovery timeline

Predicting ADMET properties of ligands earlier decreases the attrition rate and increases the chances of a drug successfully entering the market



Thank You!