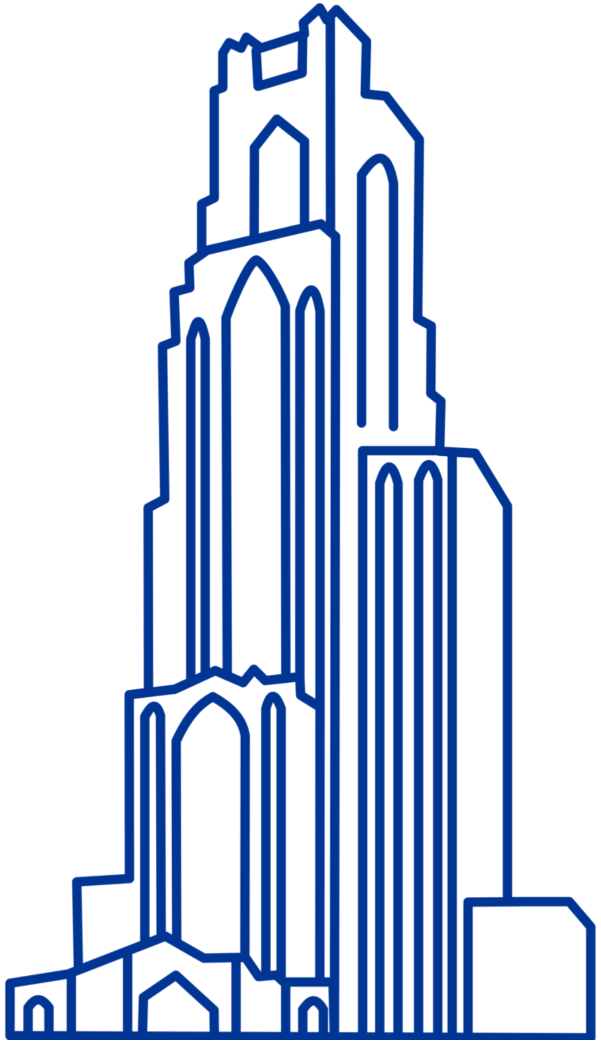


Computational Biology

(BIOSC 1540)

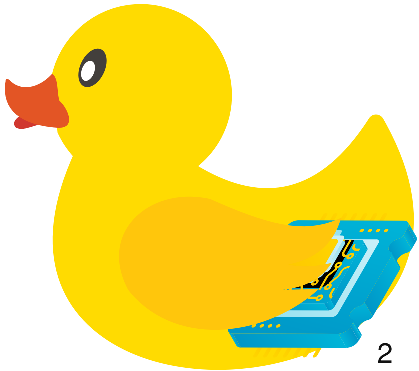
Lecture 17:
Docking and virtual screening

Oct 31, 2024

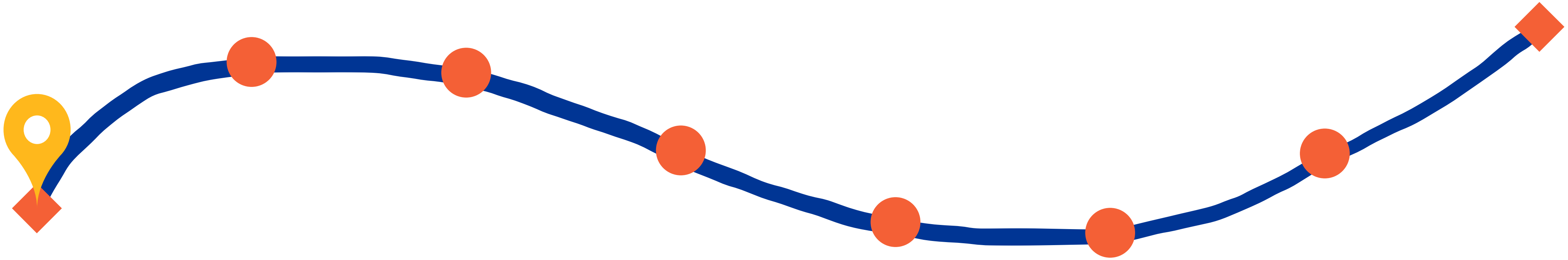
University of Pittsburgh

Announcements

- A06 is due tonight by 11:59 pm
  - **Reminder:** There is a (soft) limit of 100 words for each question
- A07 (final assignment) will be released tomorrow
- No class on Tuesday (Nov 5) for election day
- The next exam is on Nov 14
  - We will have a review session on Nov 12
  - Request DRS accommodations if needed
- Project will be released Nov 21 and is due Dec 10



After today, you should have a better understanding of

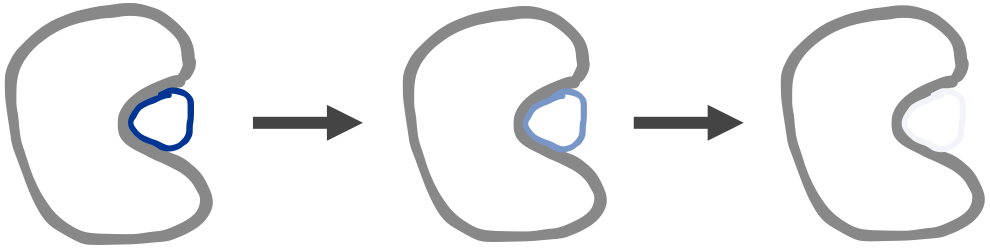


Need limitations of

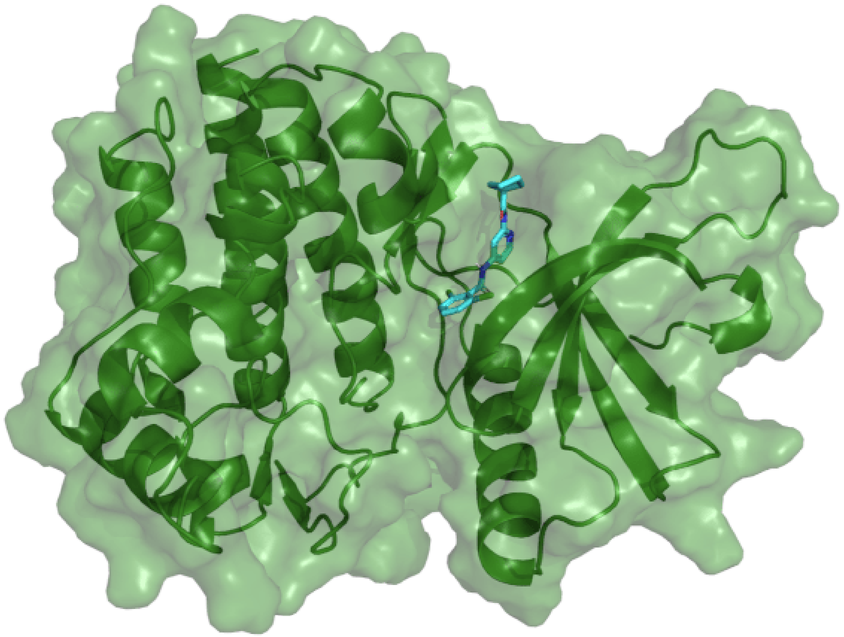
alchemical simulations

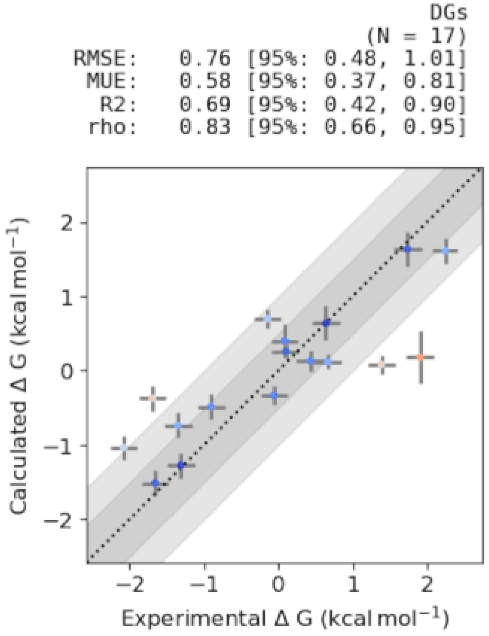
Alchemical simulations: Precise but expensive

Alchemical simulations compute free energy changes by gradually transforming one molecule into another



Importance in drug discovery: Highly precise, offering detailed insights into binding affinities essential for drug design





```
                                  DGs
                               (N = 17)
RMSE:    0.76 [95%: 0.48, 1.01]
 MUE:    0.58 [95%: 0.37, 0.81]
  R2:    0.69 [95%: 0.42, 0.90]
 rho:    0.83 [95%: 0.66, 0.95]
```

Calculated Δ G (kcal mol^{-1})
Experimental Δ G (kcal mol^{-1})
−2
−1
0
1
2
−2
−1
0
1
2

Why are alchemical simulations computationally expensive?

Atomistic forces: Computes forces for all atoms in proteins, ligands, cofactors, ions, solvents for millions of structures

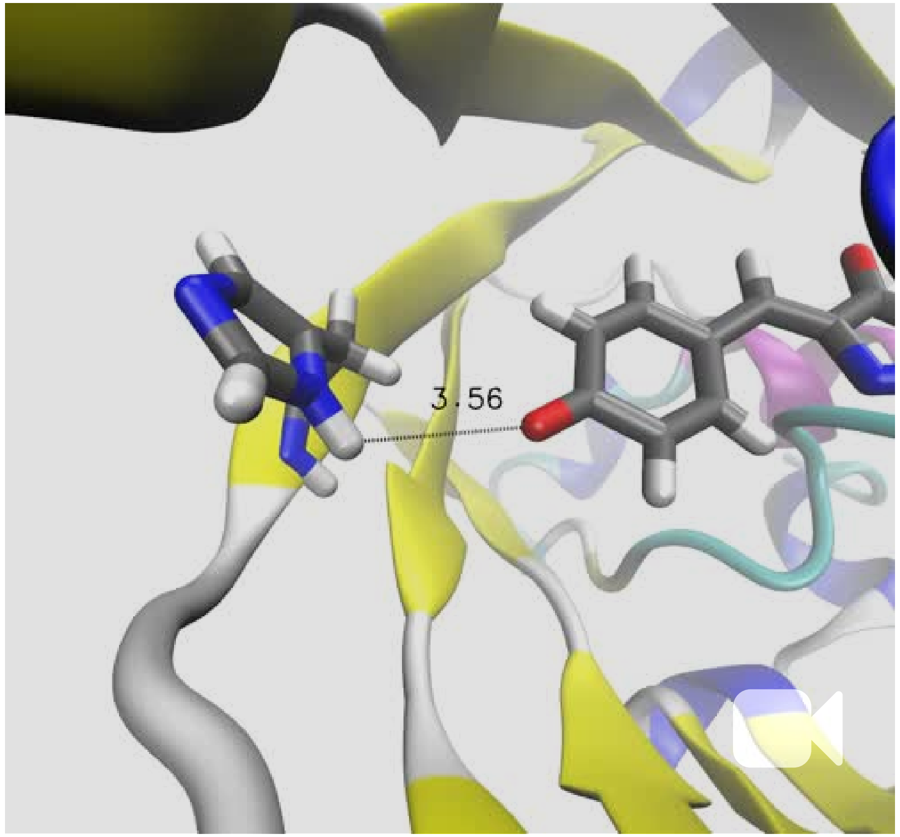
Detailed sampling: Captures a wide range of conformations, which adds more dimensions to the calculation

Alchemical parameters: Simulations must be performed at various alchemical parameters

Okay, so how long is this really?

~10,000 CPU hours

- ~417 days on a 1 core
- ~42 days on 10 cores
- ~4 days on 100 cores
- ~10 hours on 1,000 cores

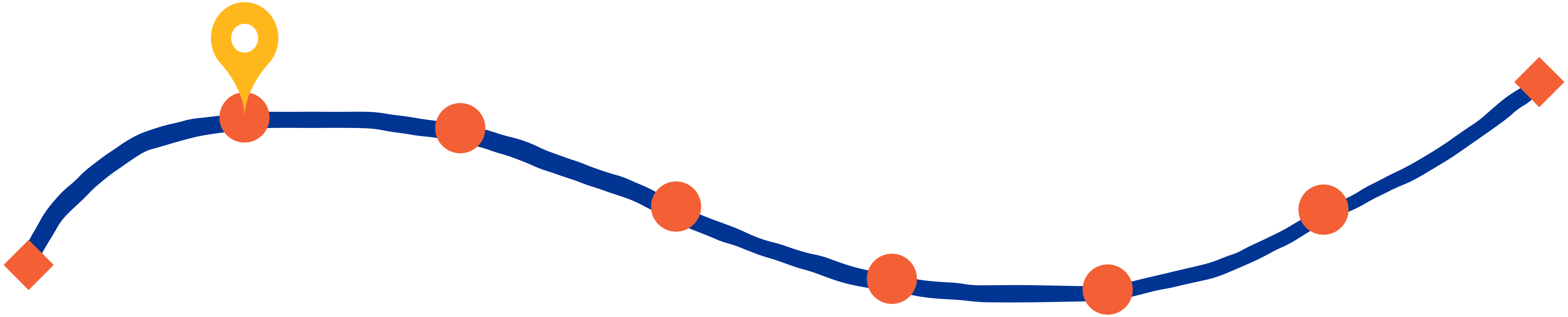


(For context, most supercomputers have ~24 cores per $30,000 node.)

Efficient methods are needed for virtual screening

Remember: Chemical space is unfathomably large and the role of computation is to virtually test as many compounds as possible

After today, you should have a better understanding of



Value of data-driven approaches

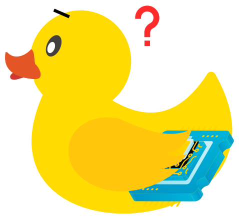
for drug discovery

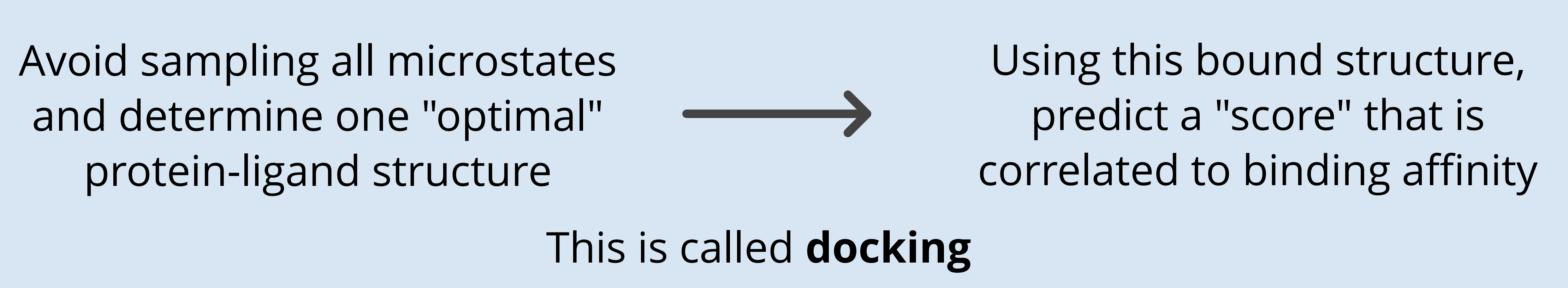
Accurate and efficient binding predictions are essential

Objective: Directly predict binding affinity from protein and ligand structures with high accuracy and minimal computational resources.

We can carefully simplify our methodology to improve speed with (hopefully) minimal impact to accuracy

What are some ideas?





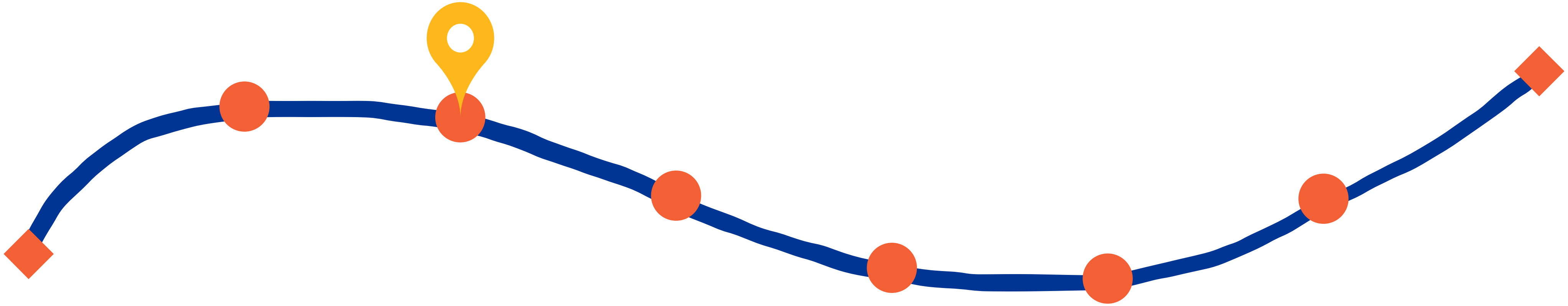
Avoid sampling all microstates and determine one "optimal" protein-ligand structure

Using this bound structure, predict a "score" that is correlated to binding affinity

This is called **docking**

Docking simplifies the binding free energy prediction problem to enhance speed

After today, you should have a better understanding of



Identifying relevant protein conformations

Accurate, reproducible docking requires a relevant protein conformation

Docking still considers the protein structure, but we only select one

Significance of Protein Conformation in Docking

- Protein-ligand interactions are highly dependent on the protein's 3D structure.
- Using an inappropriate protein conformation can lead to inaccurate docking results.

Challenge: Proteins Are Dynamic Molecules

- **Conformational Flexibility**: Proteins are not rigid structures; they exhibit movements ranging from side-chain rotations to large domain motions
- **Impact on Binding Sites**: The shape and properties of the binding site can change, affecting ligand binding affinity and specificity.
- **Limited Experimental Structures**: Crystallography and NMR provide snapshots of protein conformations but may not capture all relevant states.

Sources of Protein Conformational Data

Experimental Methods

- **X-ray Crystallography**: Provides high-resolution structures but may miss dynamic conformations.
- **NMR Spectroscopy**: Captures ensembles of conformations but is limited to smaller proteins.

Computational Techniques

- **Molecular Dynamics (MD) Simulations**: Explore the conformational space over time.
- **Normal Mode Analysis (NMA)**: Identifies collective motions in proteins.
- **Ensemble Generation Methods**: Generate multiple protein conformations for docking.

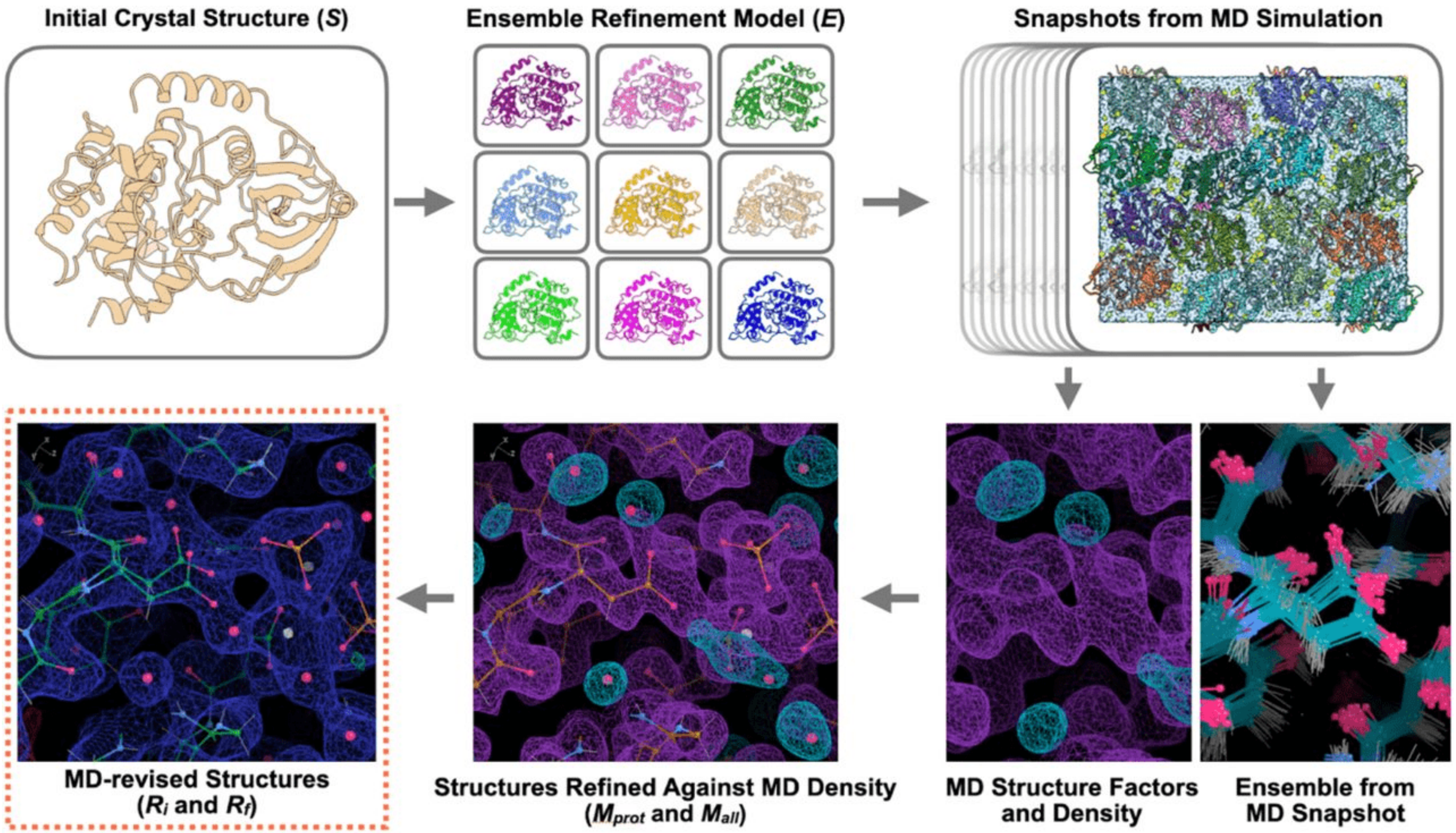
Experimental Structure Selection Criteria

- **Resolution and Quality**
  - Prefer structures with higher resolution (e.g., <2.5 Å).
  - Assess reliability using R-factors and validation reports.
- **Ligand-Bound vs. Apo Structures**
  - **Ligand-Bound (Holo) Structures**
    - Provide direct insight into binding site conformation.
  - **Apo Structures**
    - May reveal binding site flexibility in the absence of ligands.
- **Relevance to Target Ligand**
  - Choose structures co-crystallized with ligands similar to those of interest.

Molecular Dynamics Simulations for Conformational Sampling

Extract representative structures using clustering algorithms.

Identify conformations with open or closed binding sites.


Initial Crystal Structure (S)
Ensemble Refinement Model (E)
Snapshots from MD Simulation
MD-revised Structures (R_i and R_f)
Structures Refined Against MD Density (M_{prot} and M_{all})
MD Structure Factors and Density
Ensemble from MD Snapshot

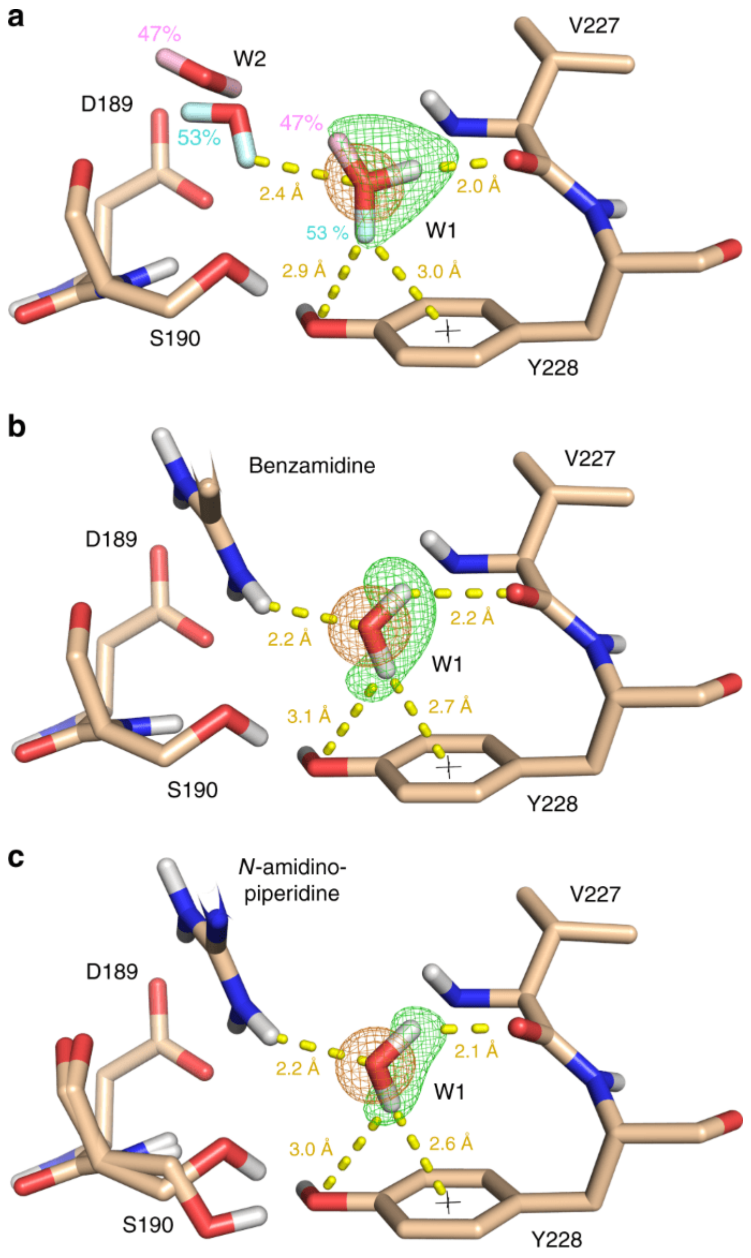
Importance of Water Molecules

Role in Binding: Structured water molecules can mediate interactions between the protein and ligand.

Inclusion Criteria: Retain water molecules that are conserved across multiple crystal structures.

Handling Water in Docking

- Some docking programs allow explicit water molecules in the binding site.
- Alternatively, consider their effect implicitly in scoring functions.



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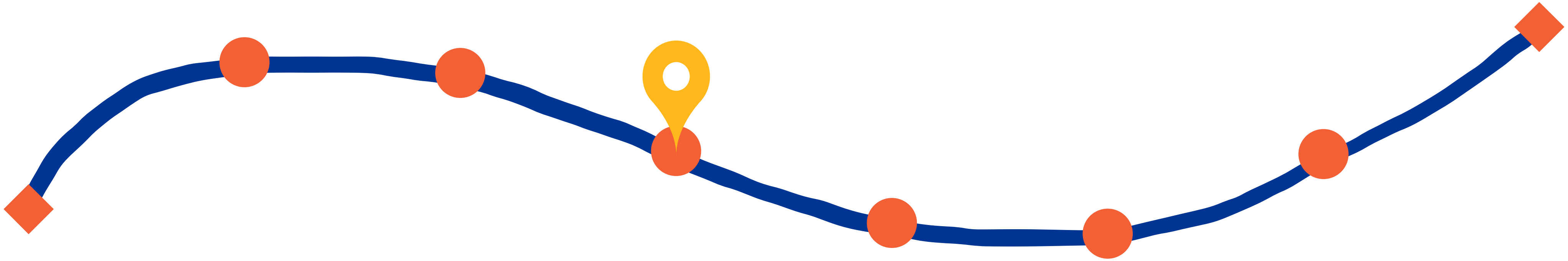
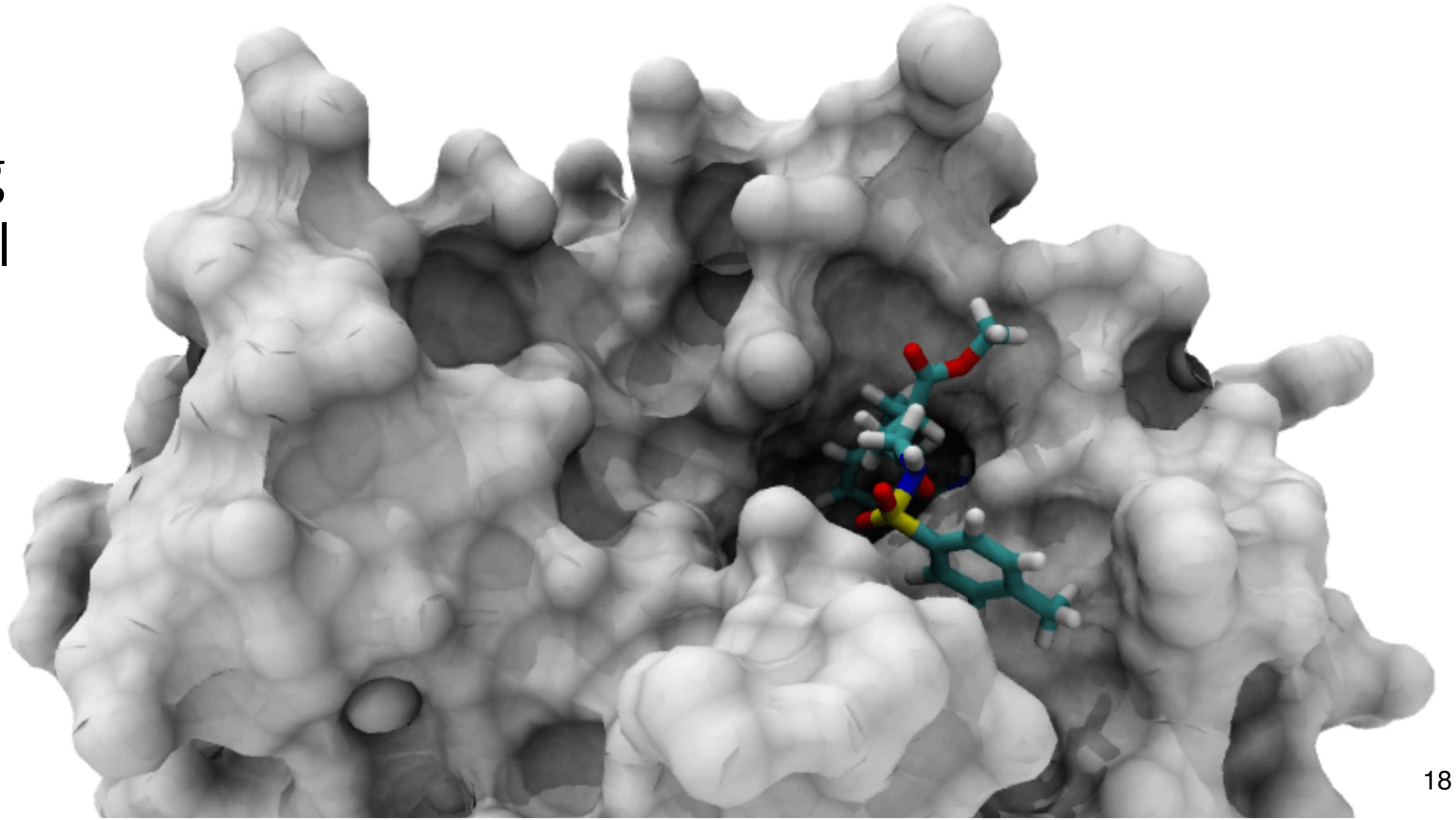


Detecting binding pockets

Accurate Binding Pocket Detection is Crucial for Docking

The binding pocket is the specific region where a ligand interacts with a protein

Accurate identification of binding pockets is essential for successful docking and virtual screening.



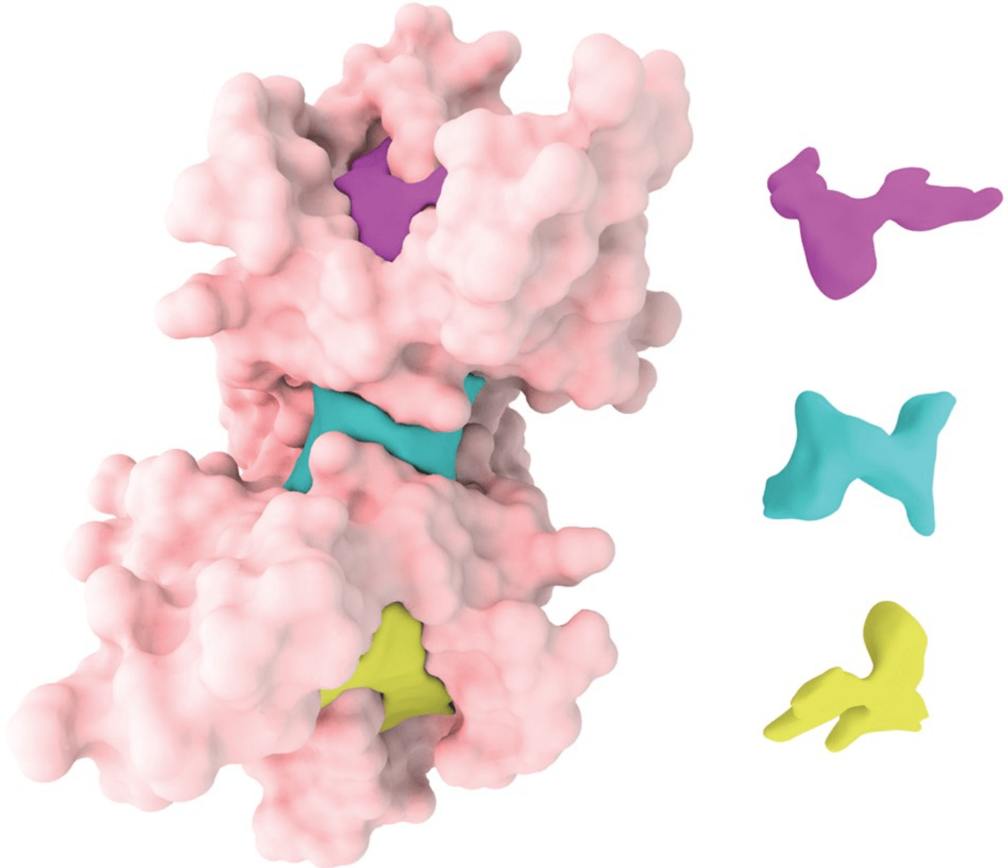
Understanding Protein Surface Topography

Terminology

- **Binding Pocket**: A cavity that can accommodate a ligand.
- **Active Site**: The functional region where biochemical reactions occur (often a binding pocket in enzymes).

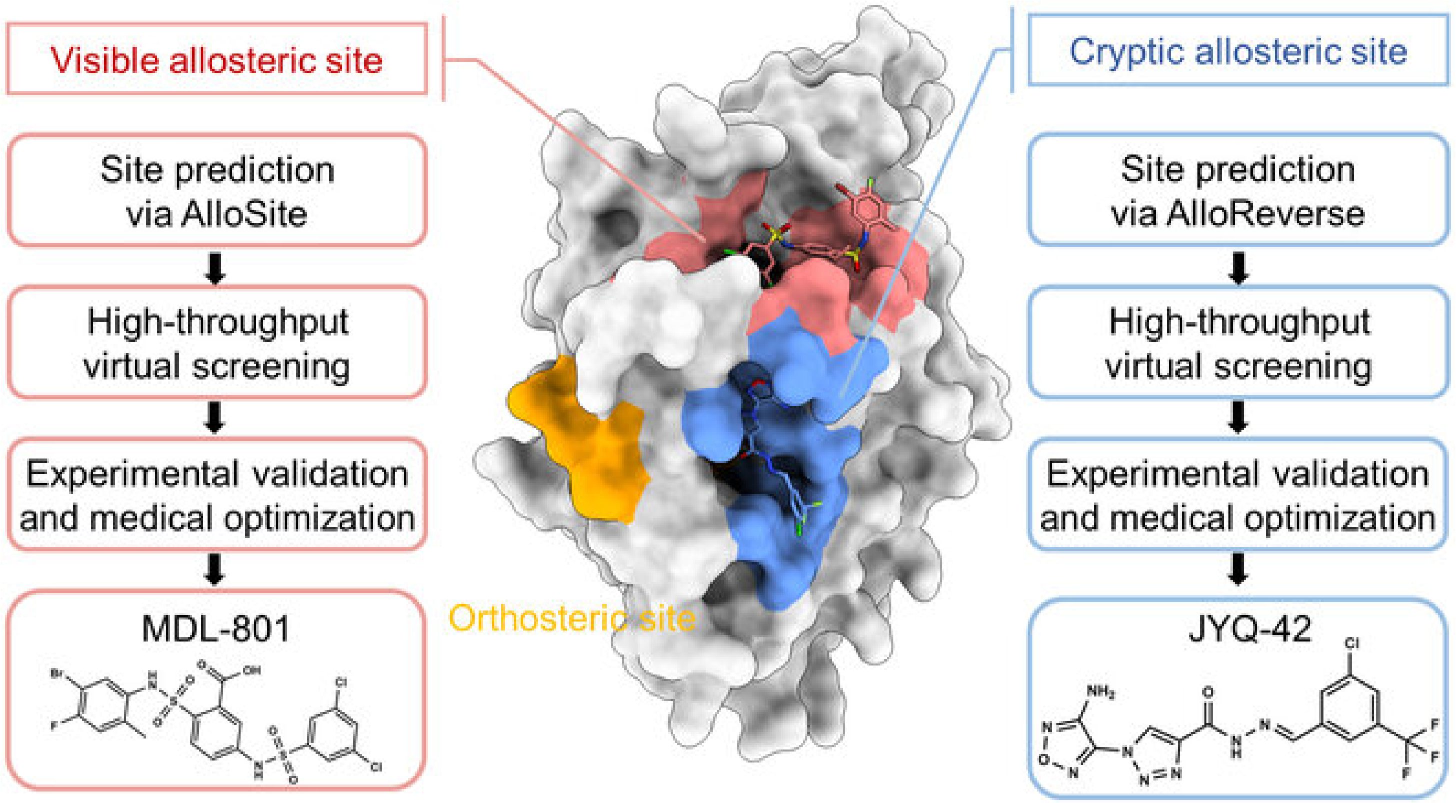
Protein Surface Characteristics

- **Convex Regions**: Typically inaccessible to ligands.
- **Concave Regions (Cavities)**: Potential binding sites.



Classification of Binding Pockets

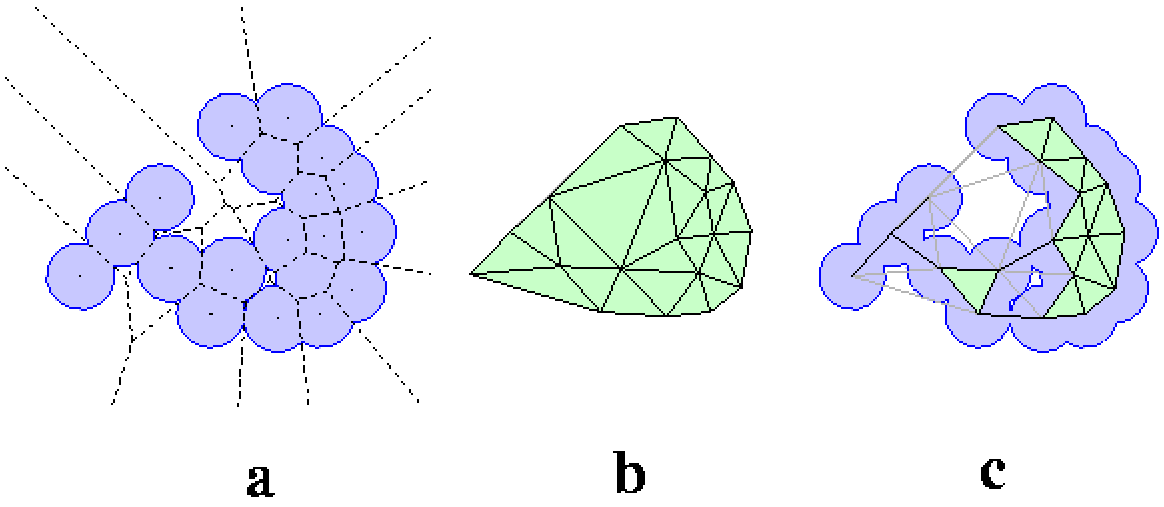
- **Orthosteric Sites**: The primary active site where endogenous ligands bind.
- **Allosteric Sites**: Secondary sites that modulate protein function upon ligand binding.

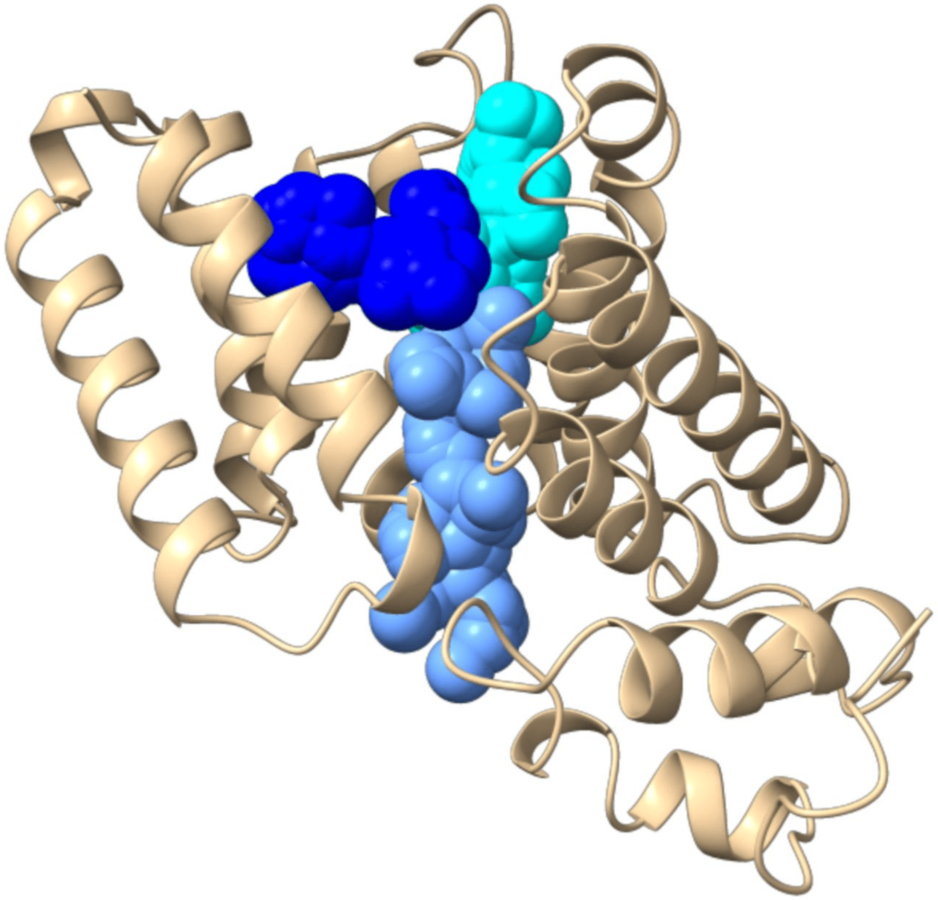

Visible allosteric site
Site prediction via AlloSite
High-throughput virtual screening
Experimental validation and medical optimization
MDL-801
Orthosteric site
Cryptic allosteric site
Site prediction via AlloReverse
High-throughput virtual screening
Experimental validation and medical optimization
JYQ-42

- **Cryptic Sites**: Binding pockets not apparent in the unbound protein structure but form upon ligand binding or conformational change.

Geometry-Based Pocket Detection Techniques

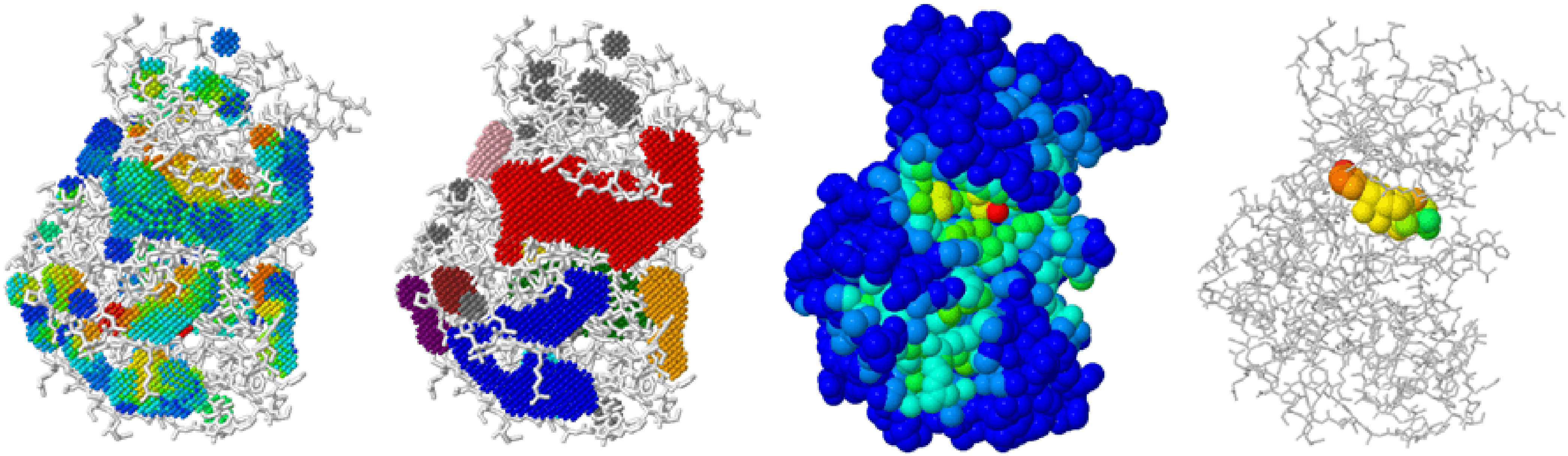
Alpha Shape Theory: Uses Delaunay triangulation and alpha complexes to define cavities.





Grid-Based Pocket Detection

- **Methodology**
  - Overlay a 3D grid on the protein structure.
  - Classify grid points as inside, outside, or on the surface.
- **Pocket Identification**
  - Clusters of surface grid points forming concave regions indicate potential pockets.



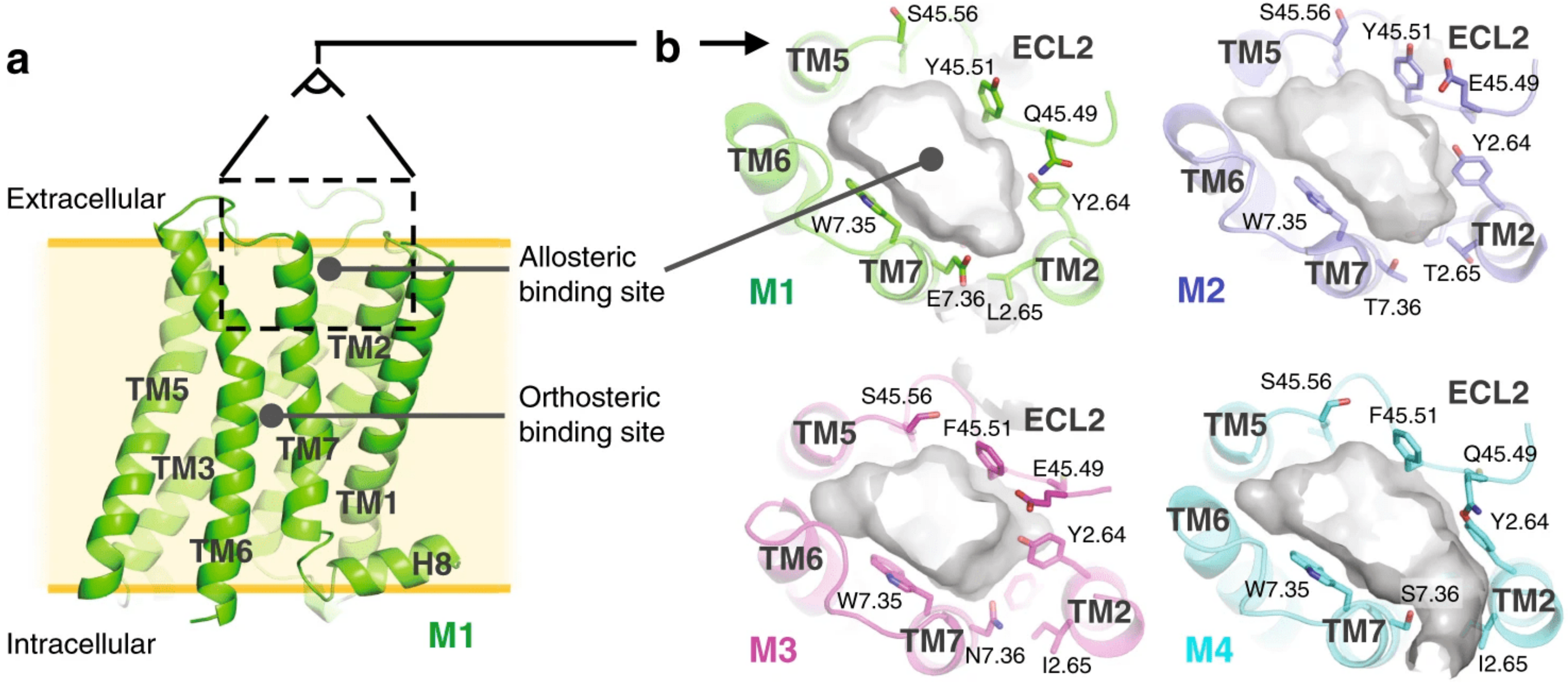
Detecting Cryptic Binding Sites

Cryptic sites are hidden in the unbound structure and require conformational changes to become apparent.

Strategies

- Use enhanced sampling MD methods like metadynamics.
- Apply pocket detection to multiple conformations.

Case Study: Identification of allosteric sites in Hsp90



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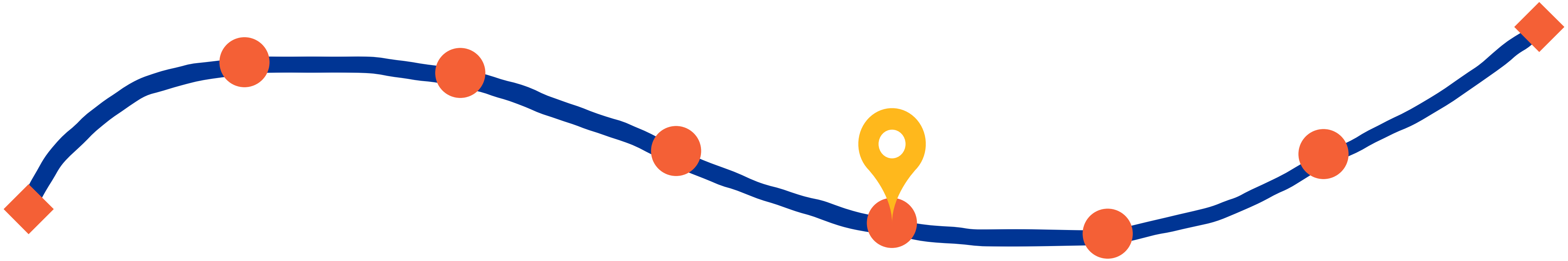
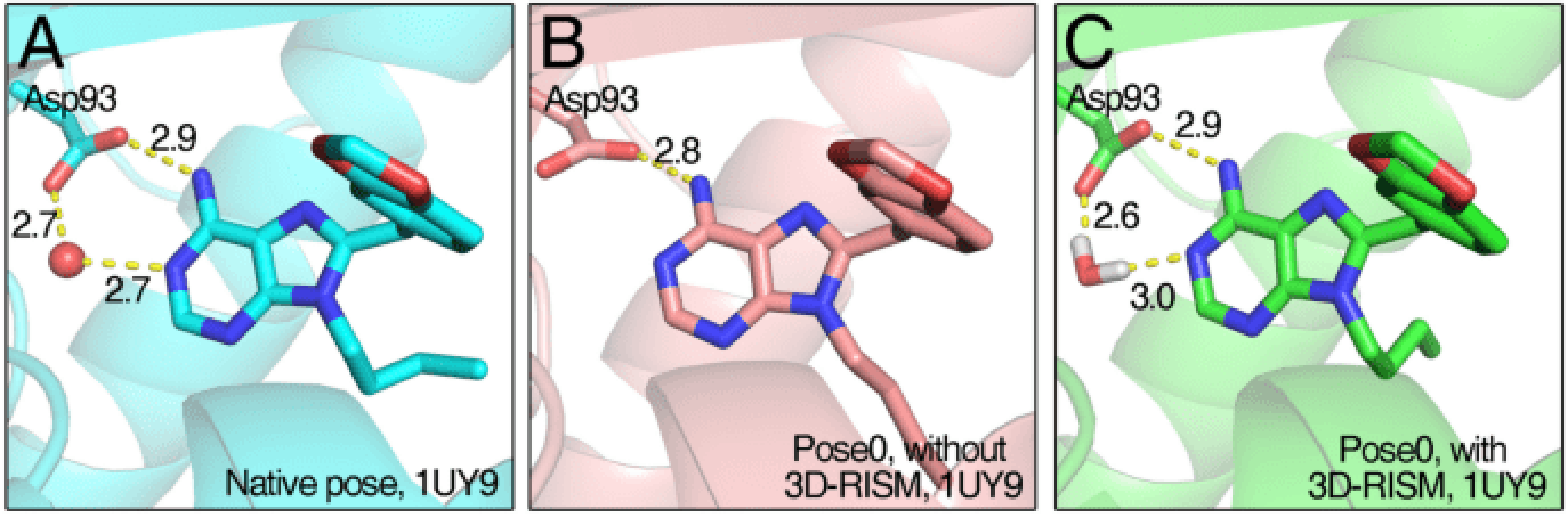


Ligand pose optimization

Accurate Docking Depends on Optimized Ligand Poses

- Precise ligand poses are crucial for reliable predictions of binding affinity and activity.
- Incorrect poses can lead to false negatives or positives, misguiding drug development efforts.



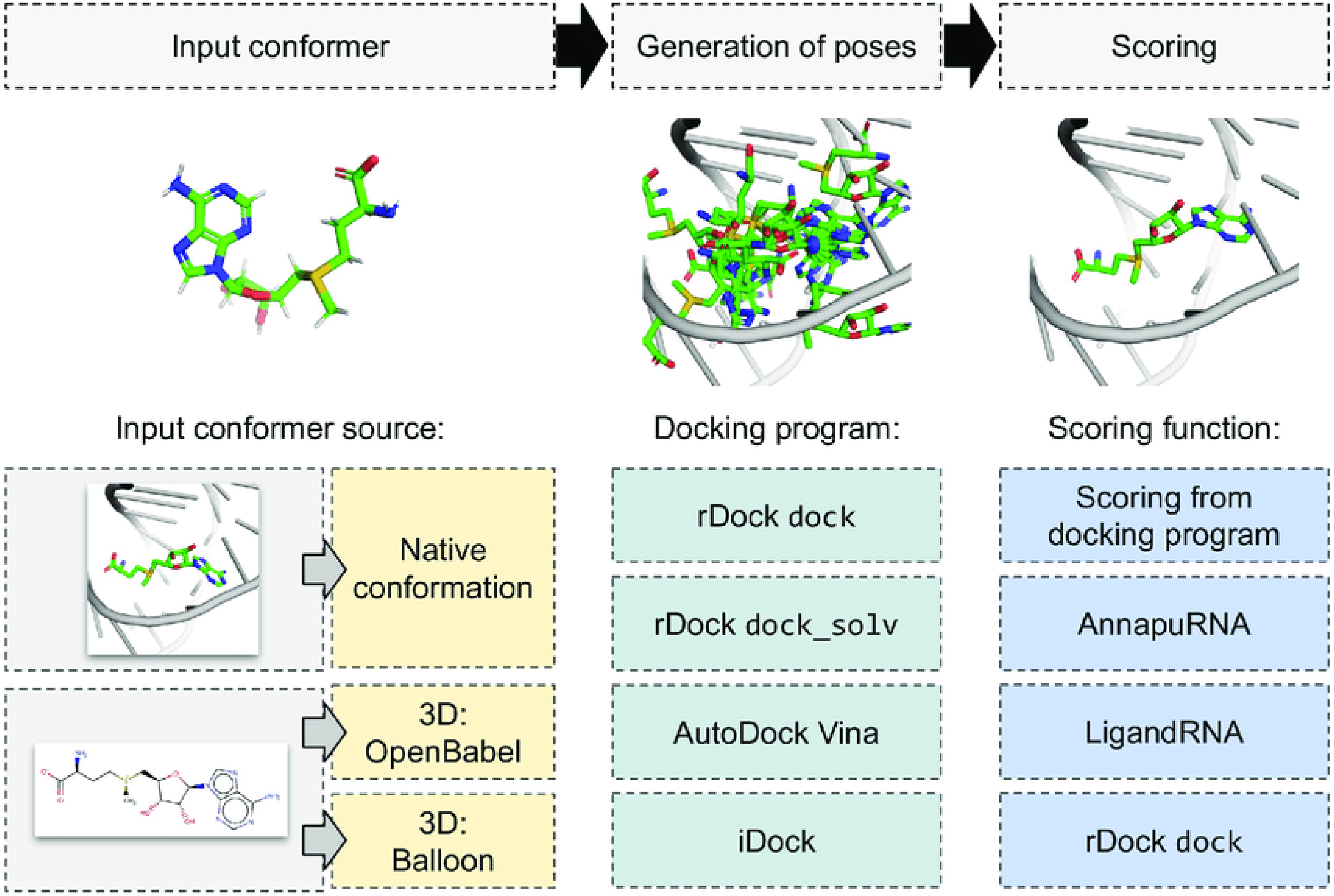
Fundamentals of Ligand Pose Optimization

- **Definition of Ligand Pose**
  - The specific orientation and conformation of a ligand within the binding site of a target protein.
- **Optimization Goal**
  - Identify the energetically most favorable pose that closely represents the true binding mode.
- **Key Components**
  - **Orientation**: Position and alignment within the binding pocket.
  - **Conformation**: Internal geometry, including bond angles, lengths, and torsions.

Docking needs to generate diverse conformations

Search strategies

- Systematic
- Stochastic
- Empirical
- Machine learning



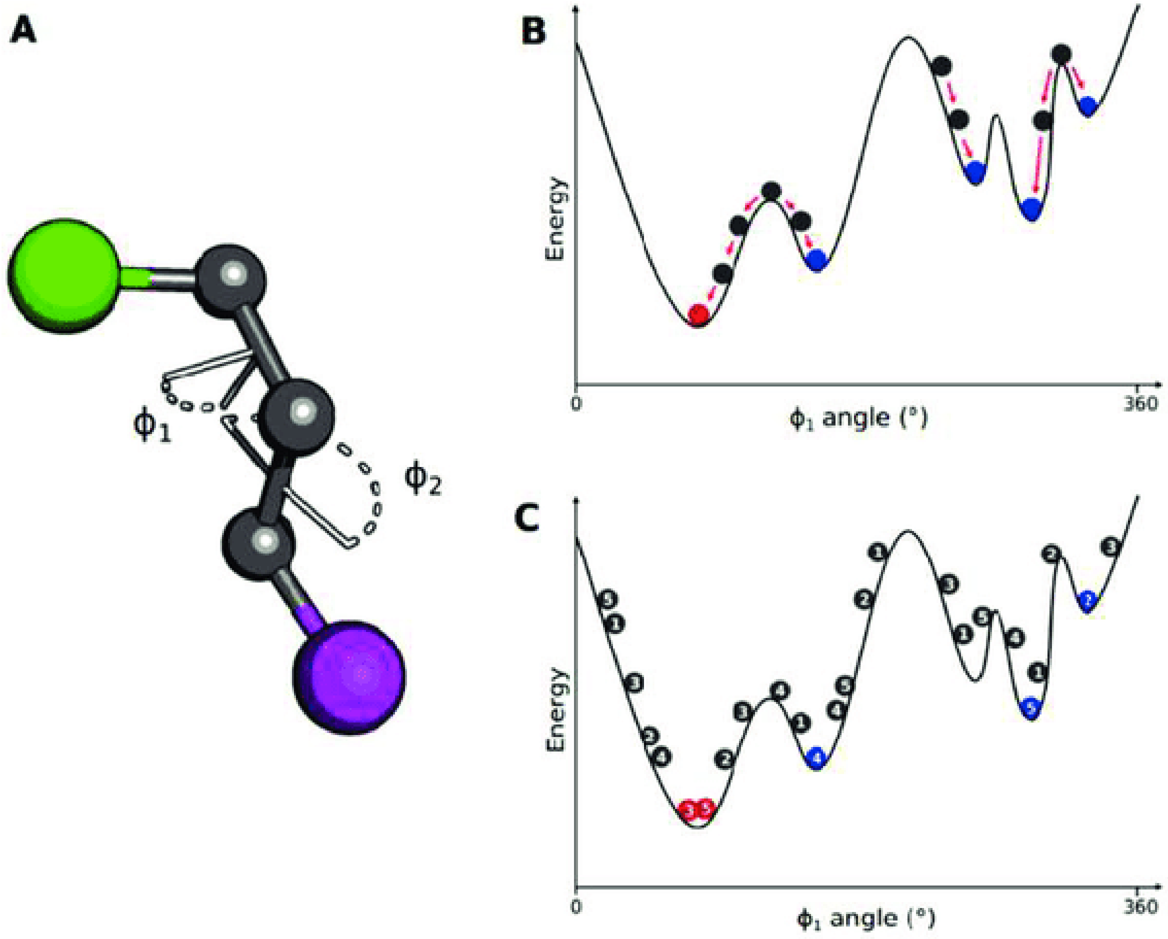
Systematic searches numerically iterate over all possible conformations

Identify important degrees of freedom

- Angles
- Dihedrals

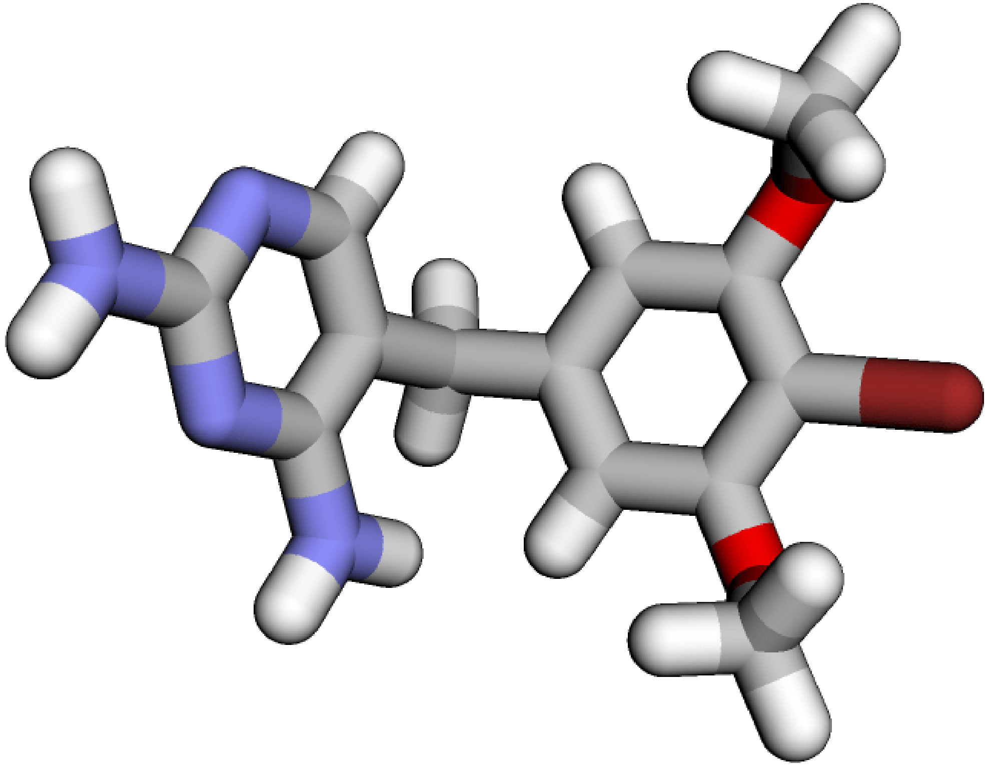
Scan along each angle with a step size of a *N* degrees

Remove structures with high strain



Systematic searches are only possible for very small molecules

How many different conformations would we have in this molecule if we scanned only dihedrals every 45 degrees?



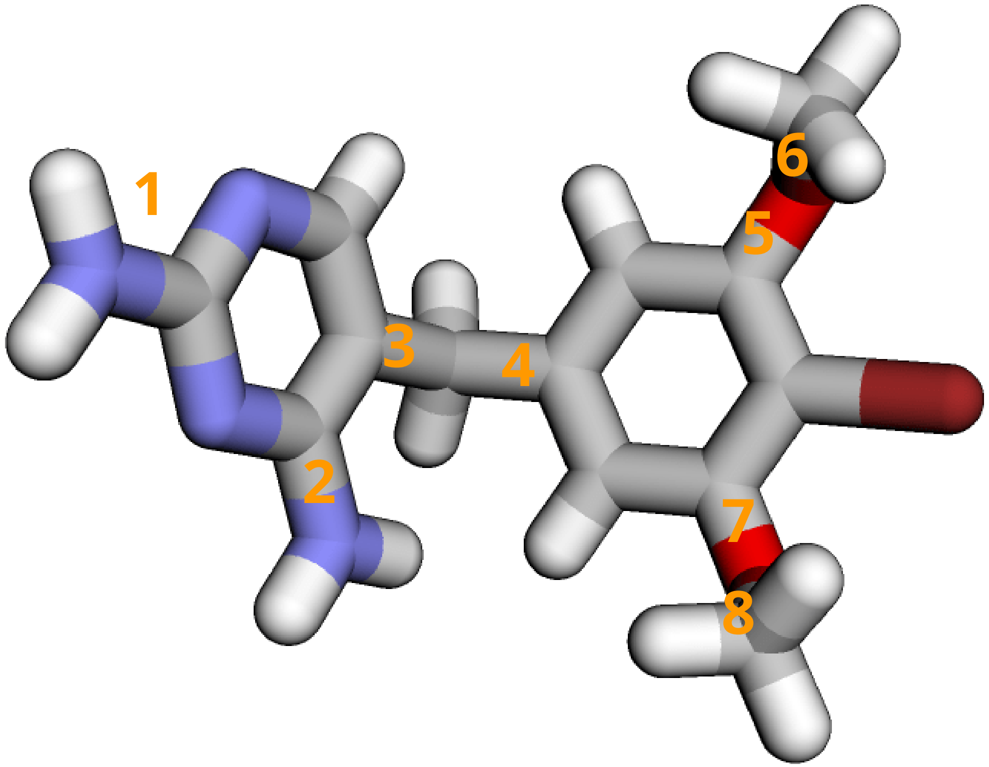
Systematic searches are only possible for very small molecules

8 × 8 × 8 × 8 × 8 × 8 × 8 × 8 = 16,777,216

That's a lot of structures, and many of them will clash!

We almost never do a systematic search in practice without some precautions to combinatorics

8 dihedrals 8 angles



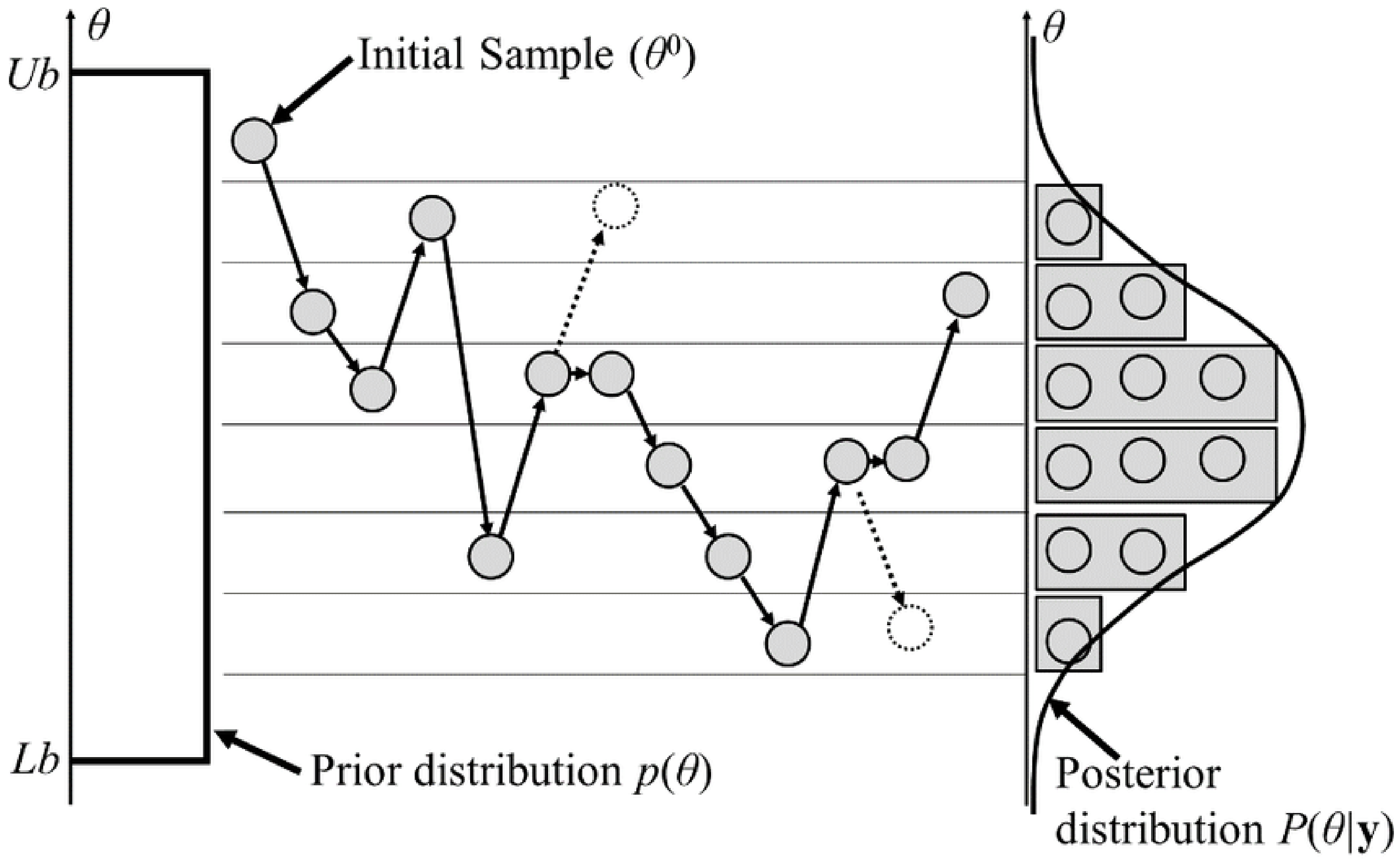
Stochastic algorithms provide better balance of sampling and cost

Monte Carlo

Steps:

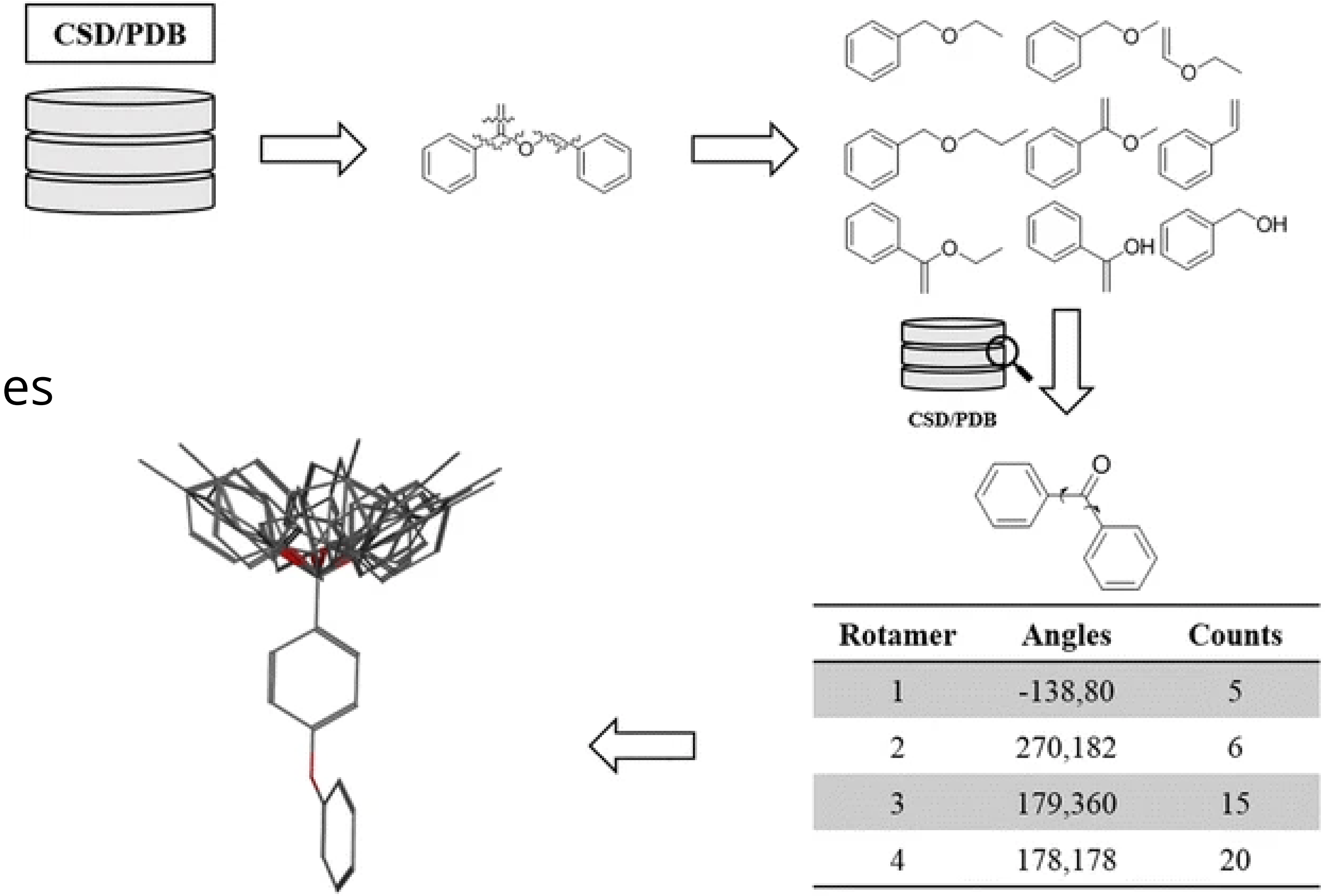
- Generate conformation
- Compute energy change
- If energy change less than a random sample: make move
- Repeat

Allows us to sample efficiently


θ
Ub
Lb
Initial Sample (θ^0)
Prior distribution $p(\theta)$
θ
Posterior distribution $P(\theta|\mathbf{y})$

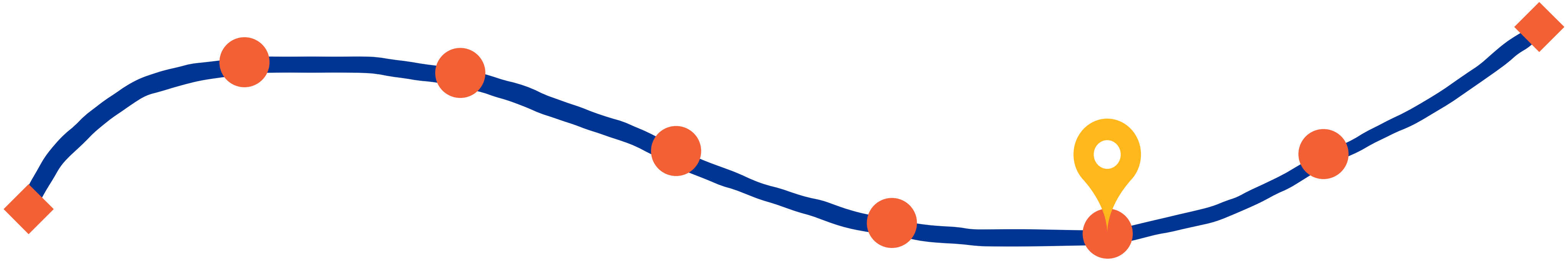
We also have conformer libraries

Use pre-generated libraries



Rotamer	Angles	Counts
1	-138,80	5
2	270,182	6
3	179,360	15
4	178,178	20

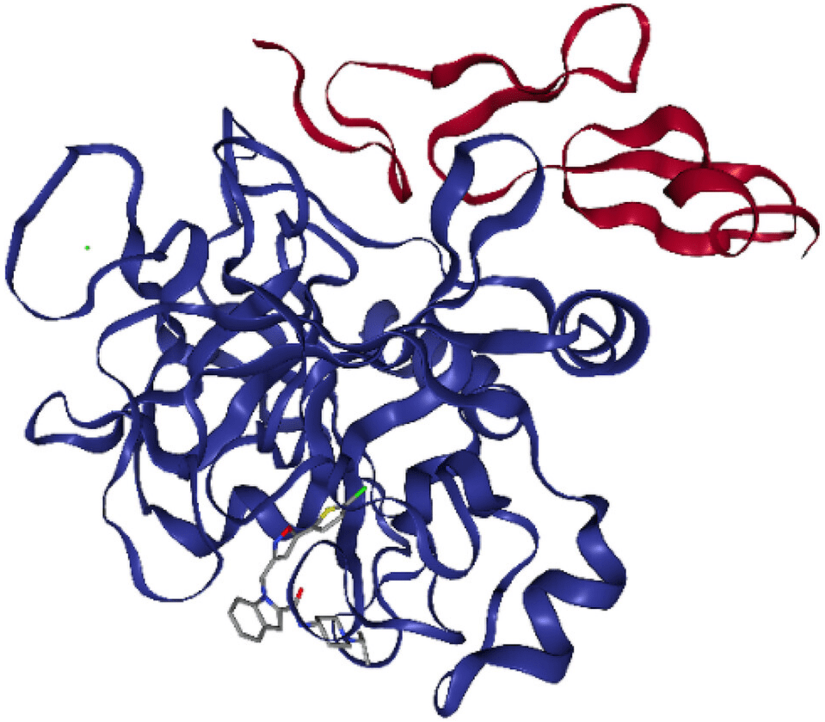
After today, you should have a better understanding of

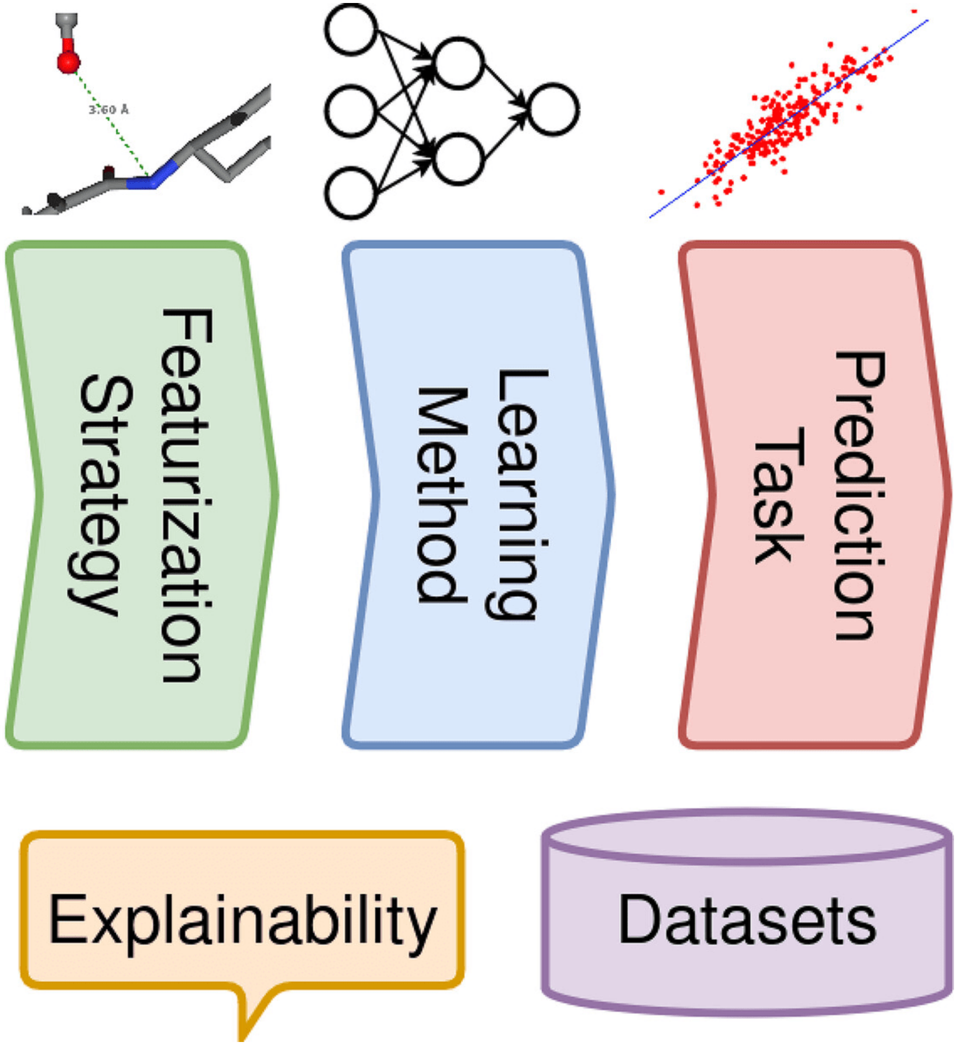


Scoring functions as

data-driven predictors

Scoring function are parameterized models to estimate binding affinity after docking





Featurization Strategy

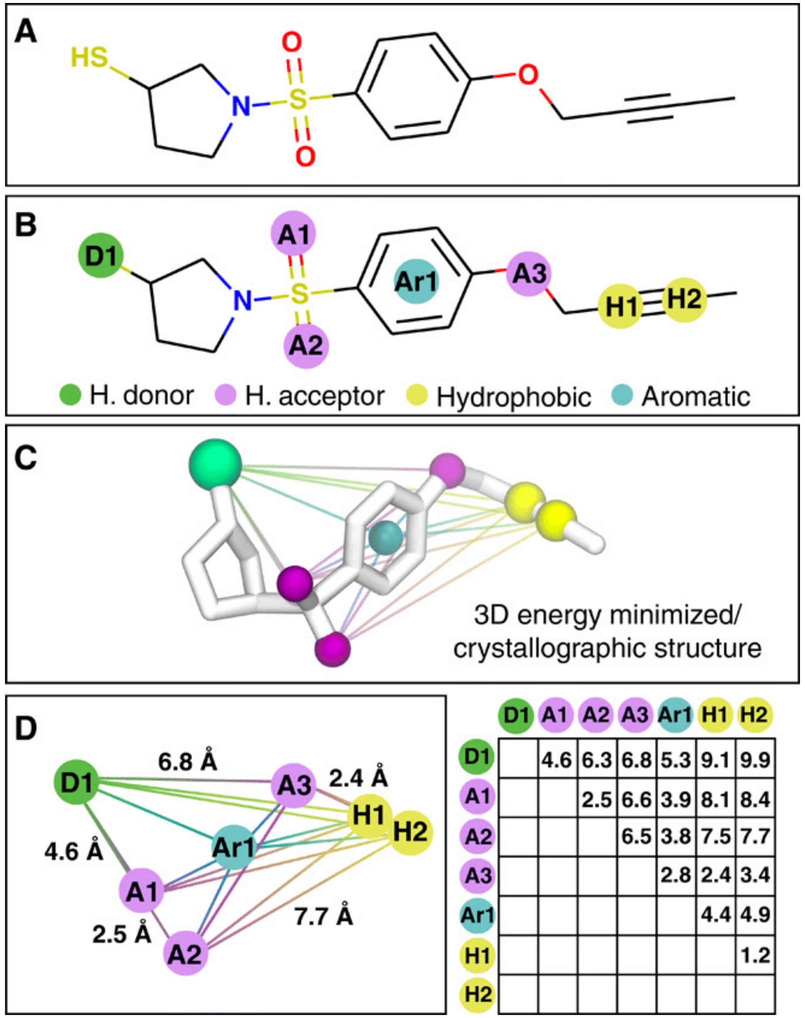
Learning Method

Prediction Task

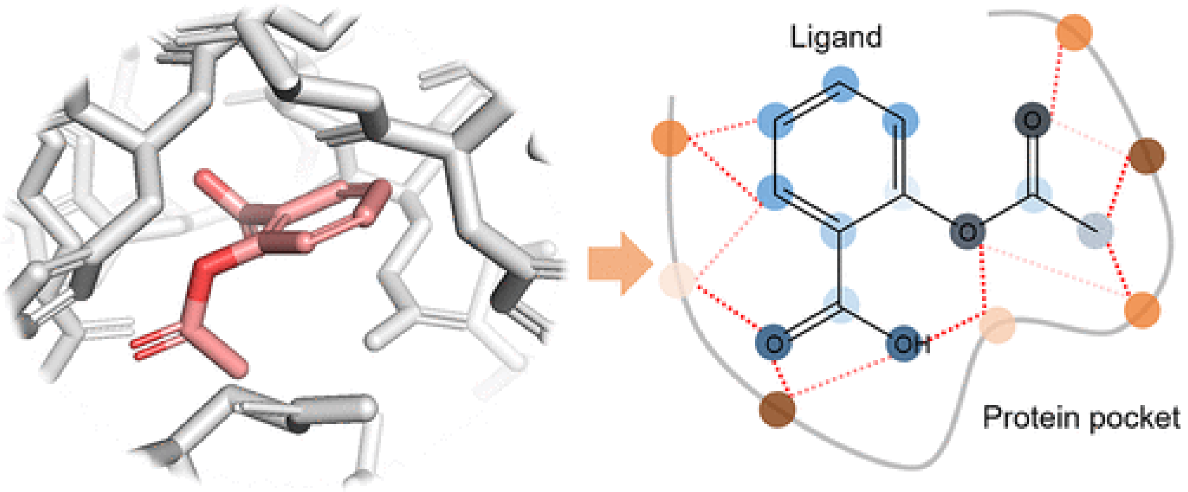
Explainability

Datasets

Physics-based methods using force-field like methods



	D1	A1	A2	A3	Ar1	H1	H2
D1		4.6	6.3	6.8	5.3	9.1	9.9
A1			2.5	6.6	3.9	8.1	8.4
A2				6.5	3.8	7.5	7.7
A3					2.8	2.4	3.4
Ar1						4.4	4.9
H1							1.2
H2							



Recently, machine learning (e.g., graph neural networks) have been gaining traction

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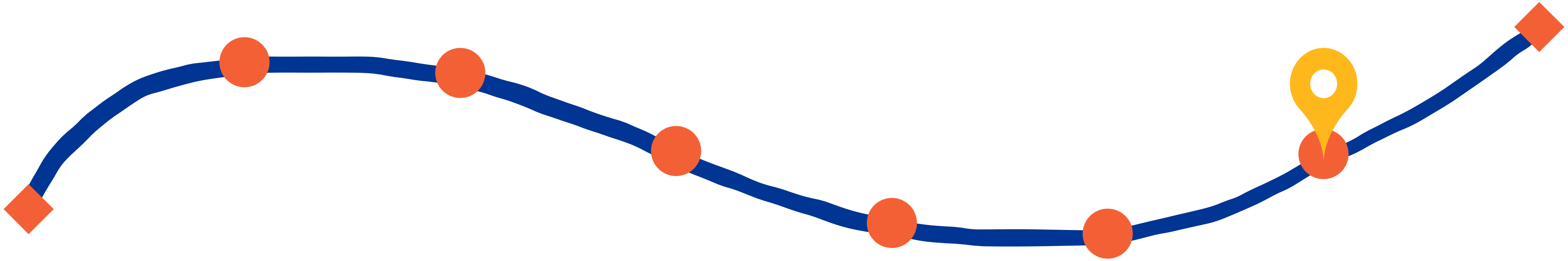


Interpretation of

docking results

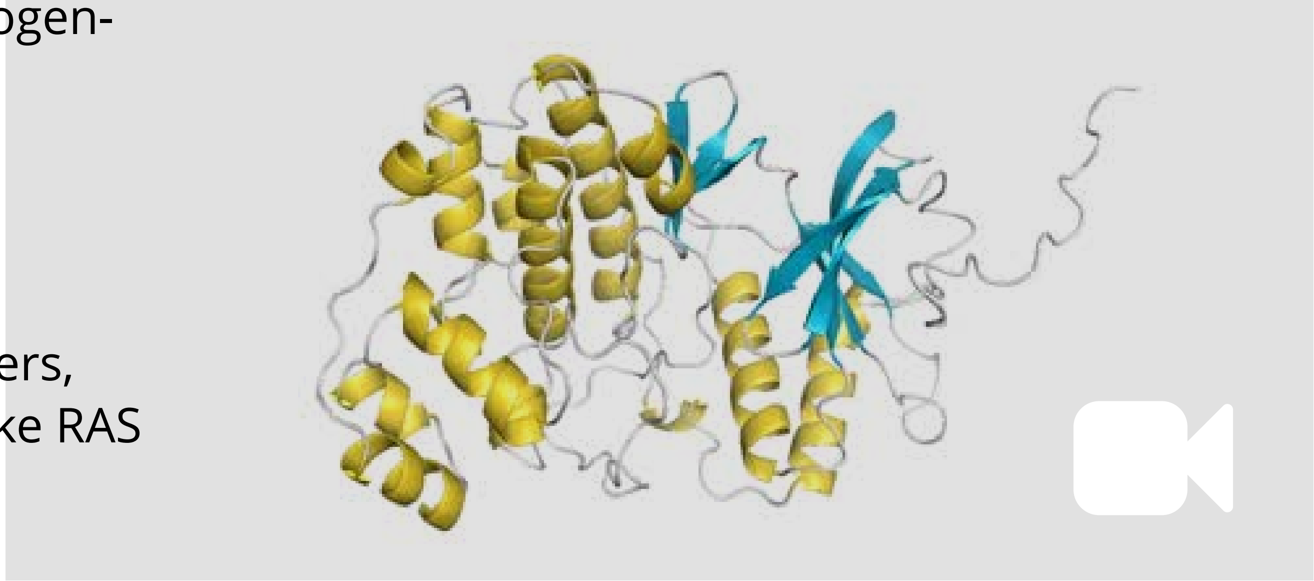
Case study: MAP kinase ERK2

Overview of ERK2:

- Extracellular signal-regulated kinase 2 (ERK2), encoded by the MAPK1 gene, is a crucial component of the mitogen-activated protein kinase (MAPK) signaling pathway.
- ERK2 regulates vital cellular processes, including proliferation, differentiation, and survival.

Role in Disease:

- Aberrant ERK2 activity is implicated in various cancers, often due to mutations in upstream components like RAS and RAF, leading to uncontrolled cell growth.
- ERK2 is also involved in inflammatory diseases and neurodegenerative disorders.



AlphaFold 2 Prediction

MolModa

Before the next class, you should

Lecture 17:
Docking and virtual screening

Lecture 18:
Ligand-based drug design

Today

Thursday

- Finish A06
- Work on A07
- Study for exam