Introduction:
Discovering cryptic binding sites
Computational drug design usually targets binding pockets found in experimental structures

Example: ligand docking

- Predicts...
  - The **pose** of the molecule in the binding site
  - The binding affinity or a **score** representing the strength of binding
Problem: some drug targets don’t have appropriate binding pockets

• That is, in available experimental structures, either:
  – The drug target has no pockets with properties that would allow a drug-like molecule to bind
  – Binding of a drug to the available pockets wouldn’t have the desired effect (e.g., preventing a particular molecule from binding to that target in the cell)

• These targets are sometimes called “undruggable”
Cryptic binding pockets to the rescue

- Experimental structures show that binding pockets often “open up” in the presence of an appropriate ligand
  - These are called “cryptic” binding pockets/sites
- If we could discover more such sites, then more targets might become druggable

![Diagram of binding site with residues and ligands](image-url)
How can we discover unknown cryptic binding pockets?

• The papers we’ll cover on Thursday present several computational approaches to this problem:
  – Molecular dynamics (MD) simulations
    • With a generic “probe” ligand present OR
    • Without a “probe” ligand but using Markov State Models to probe longer timescales
  – A machine learning approach based on analysis of known cryptic binding sites
Background material

• Ligand docking slides from CS/CME/BioE/Biophys/BMI 279: