# Introduction:
# Discovering cryptic binding sites

CS/CME/Biophys/BMI 371

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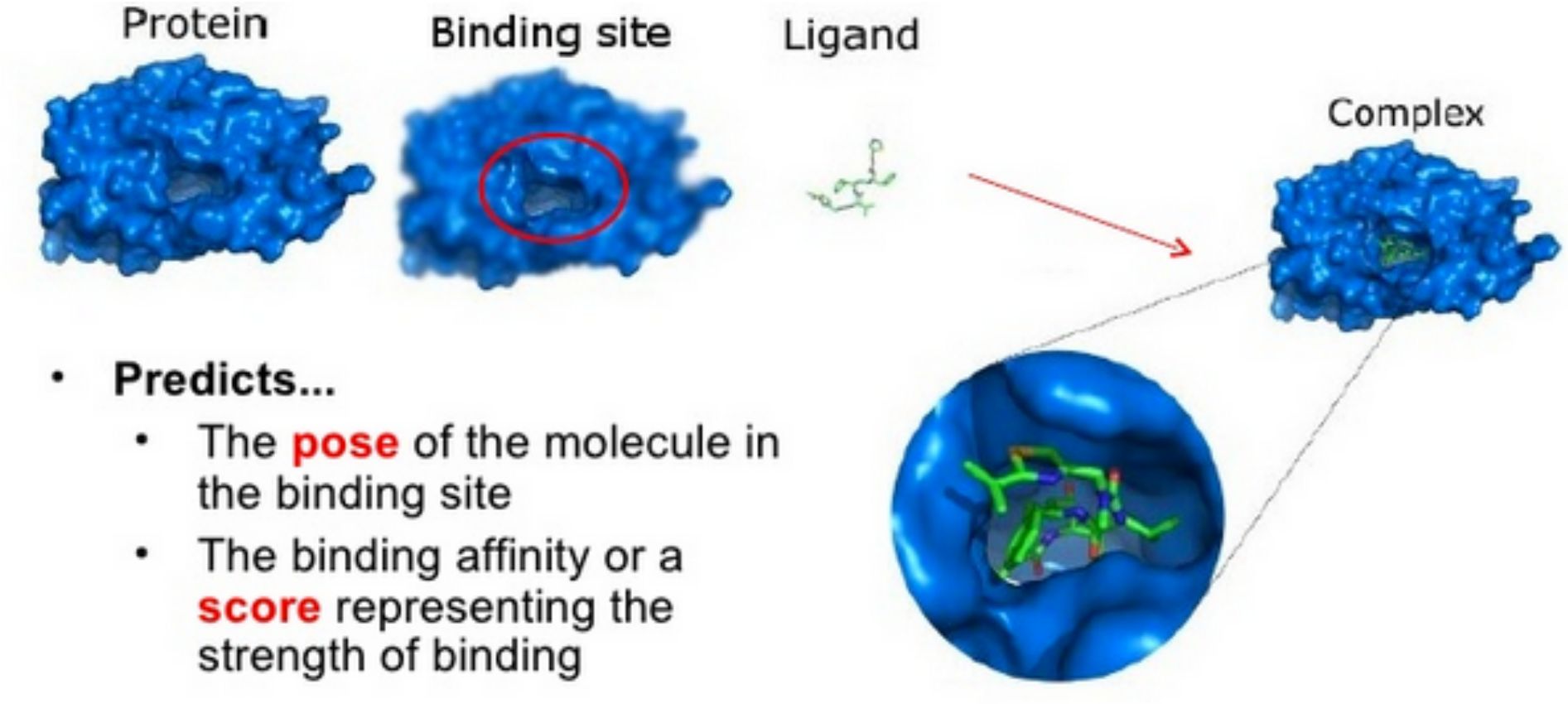
# Computational drug design usually targets binding pockets found in experimental structures

## Example: ligand docking



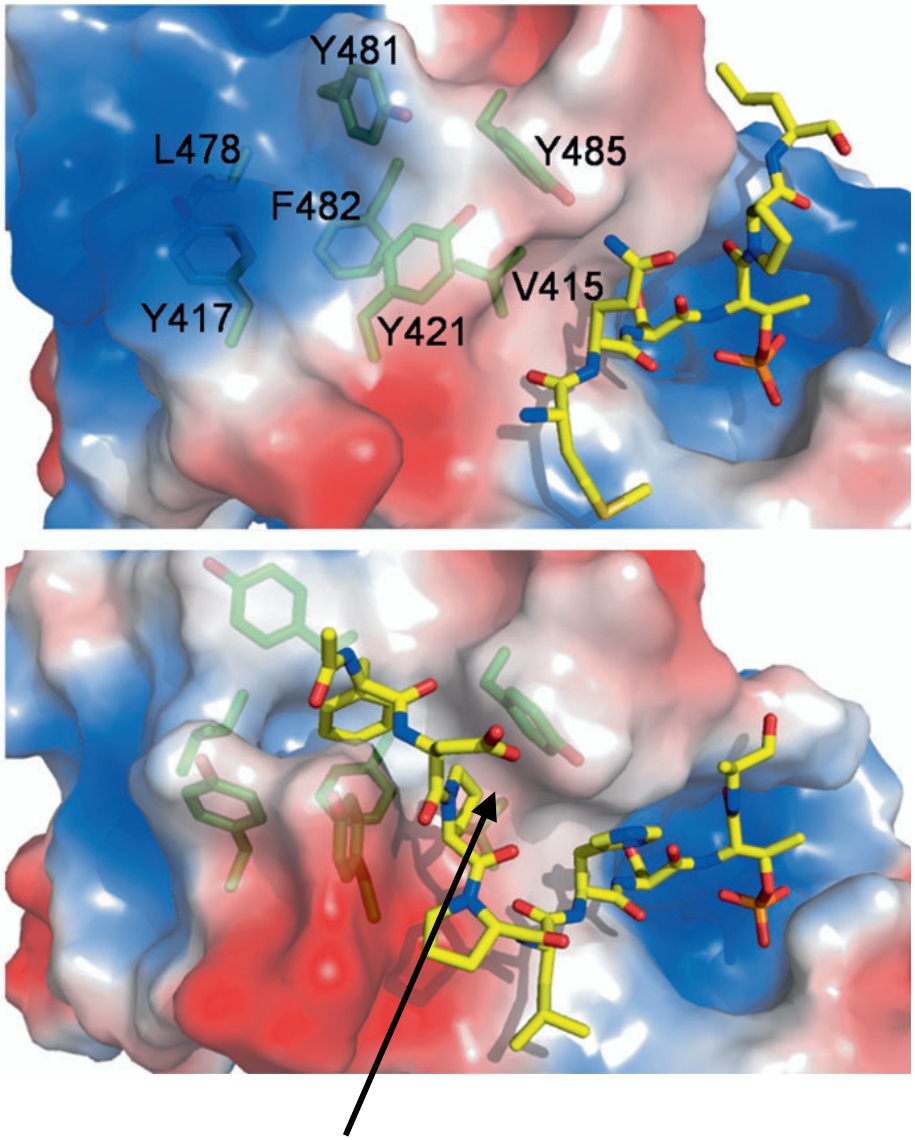

http://www.slideshare.net/baoilleach/proteinligand-docking-13581869

# 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




Tan et al., Angew. Chem. 2012 51:10078-81

# 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:
  - http://web.stanford.edu/class/cs279/lectures/lecture13.pdf

https://en.wikipedia.org/wiki/Crypt