Protein Binding:
Ligands, Affinity and Specificity

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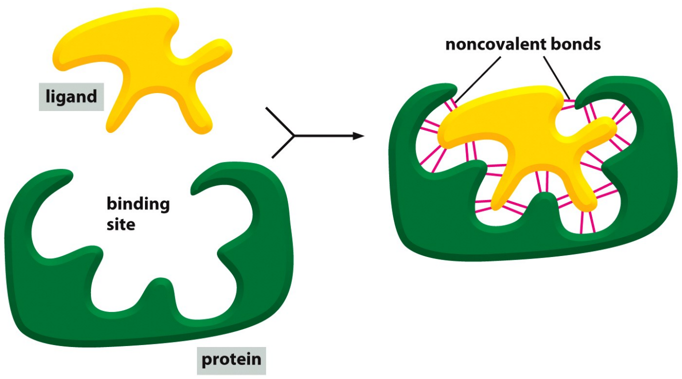
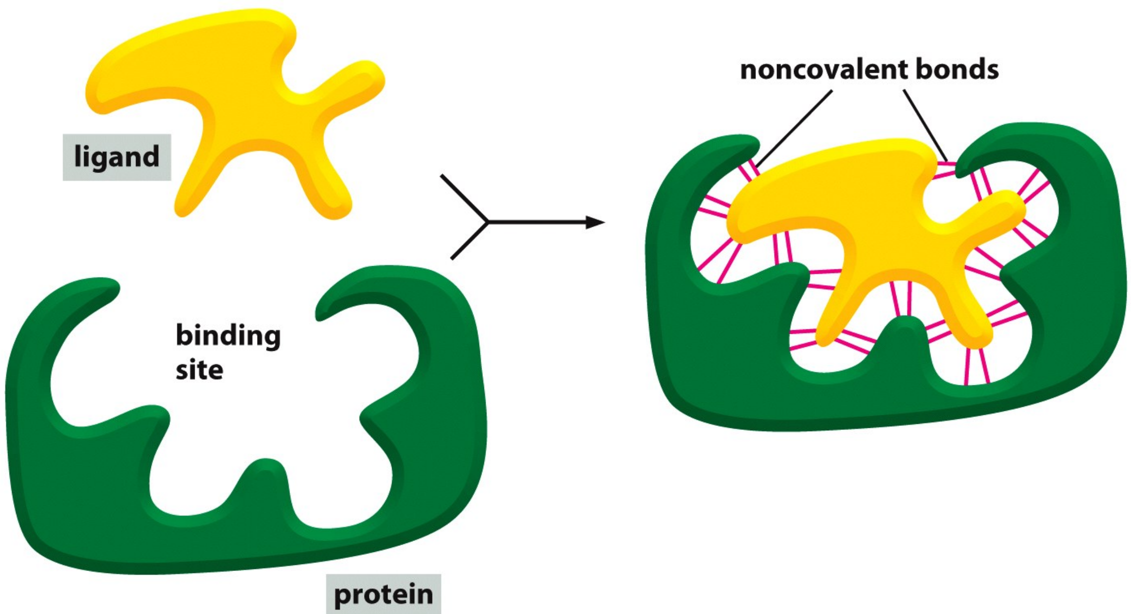
9/30/11



Key terms

- Ligand
- Affinity
- Specificity



Proteins don’t act alone

- Myglobin binds Heme and O_2

- Hemoglobin?

- Proteins act on things
  - transport and catalysis
- Or work together to make things
  - Structural proteins like microtubules and collagen

What can be a protein's ligand?

- Small molecules
  - For example O_2 in Hb and Mb
- Larger molecules
  - Complex sugar
- Other proteins or even more copies of itself

What governs protein-ligand interaction?

- What types of bonds determine the final structure of a protein?

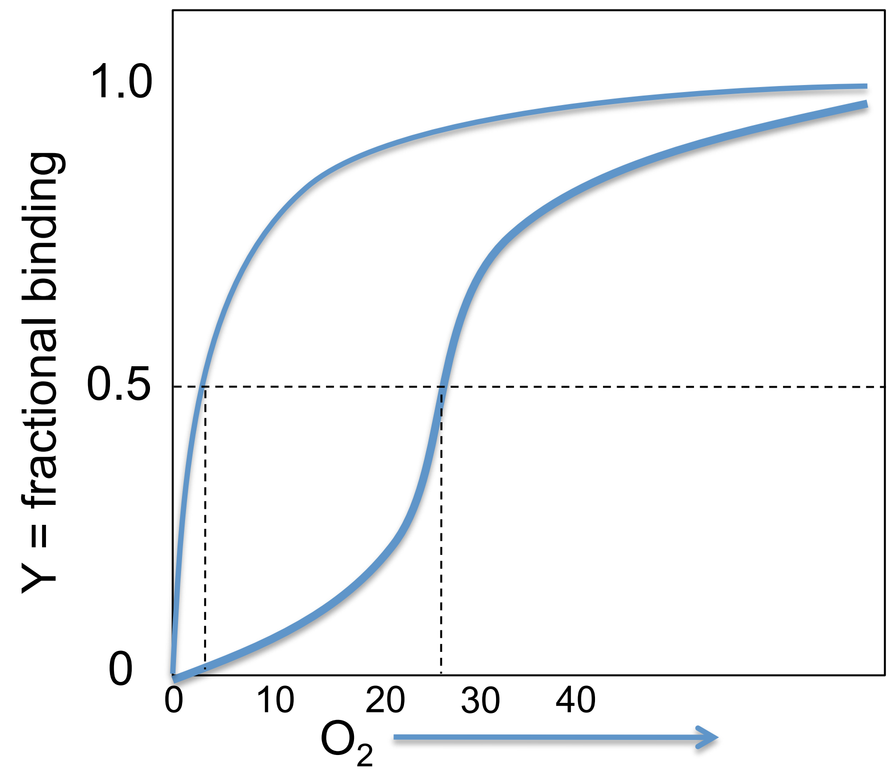
- These same interactions determine how strongly a protein can hold onto its ligand.

- The number and specific location of interactions

Mb and Hb

- Ligand: 0_2

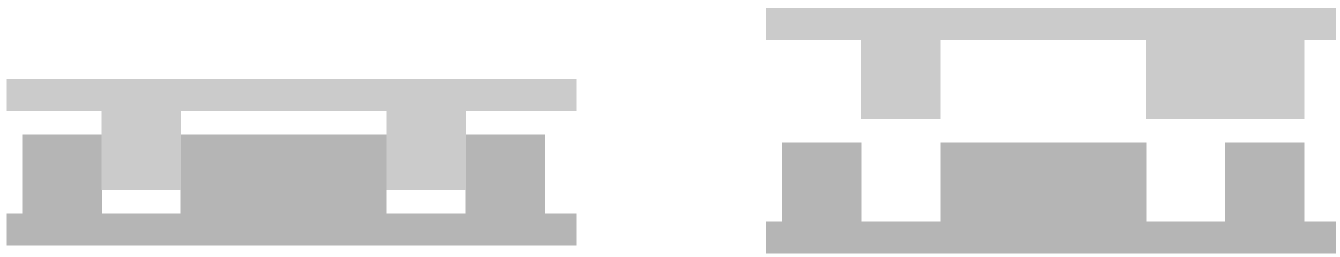
- Affinity: Kd
  - Low Kd, high affinity
  - High Kd, low affinity



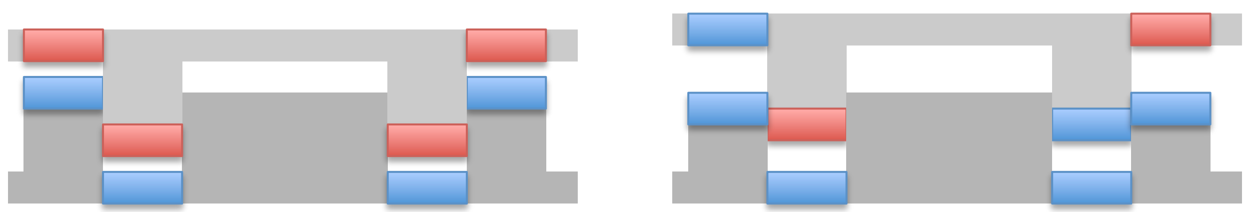
- Specificity: The distal histidine helps select for O_2 over CO

Strong binding when…

- The protein and ligand fit together



- The chemical contacts are right



Good contacts high affinity

“Fits” but poor contacts: low affinity

High selectivity!

Covalent vs Noncovalent bonds

		STRENGTH IN kcal/mole	
BOND TYPE	**LENGTH (nm)**	**IN VACUUM**	**IN WATER**
Covalent	0.15	90 (377)**	90 (377)
Noncovalent: ionic bond*	0.25	80 (335)	3 (12.6)
hydrogen bond	0.30	4 (16.7)	1 (4.2)
van der Waals attraction (per atom)	0.35	0.1 (0.4)	0.1 (0.4)

*An ionic bond is an electrostatic attraction between two fully charged atoms.
**Values in parentheses are kJ/mole. 1 calorie = 4.184 joules.

Can you draw an example of each of these?

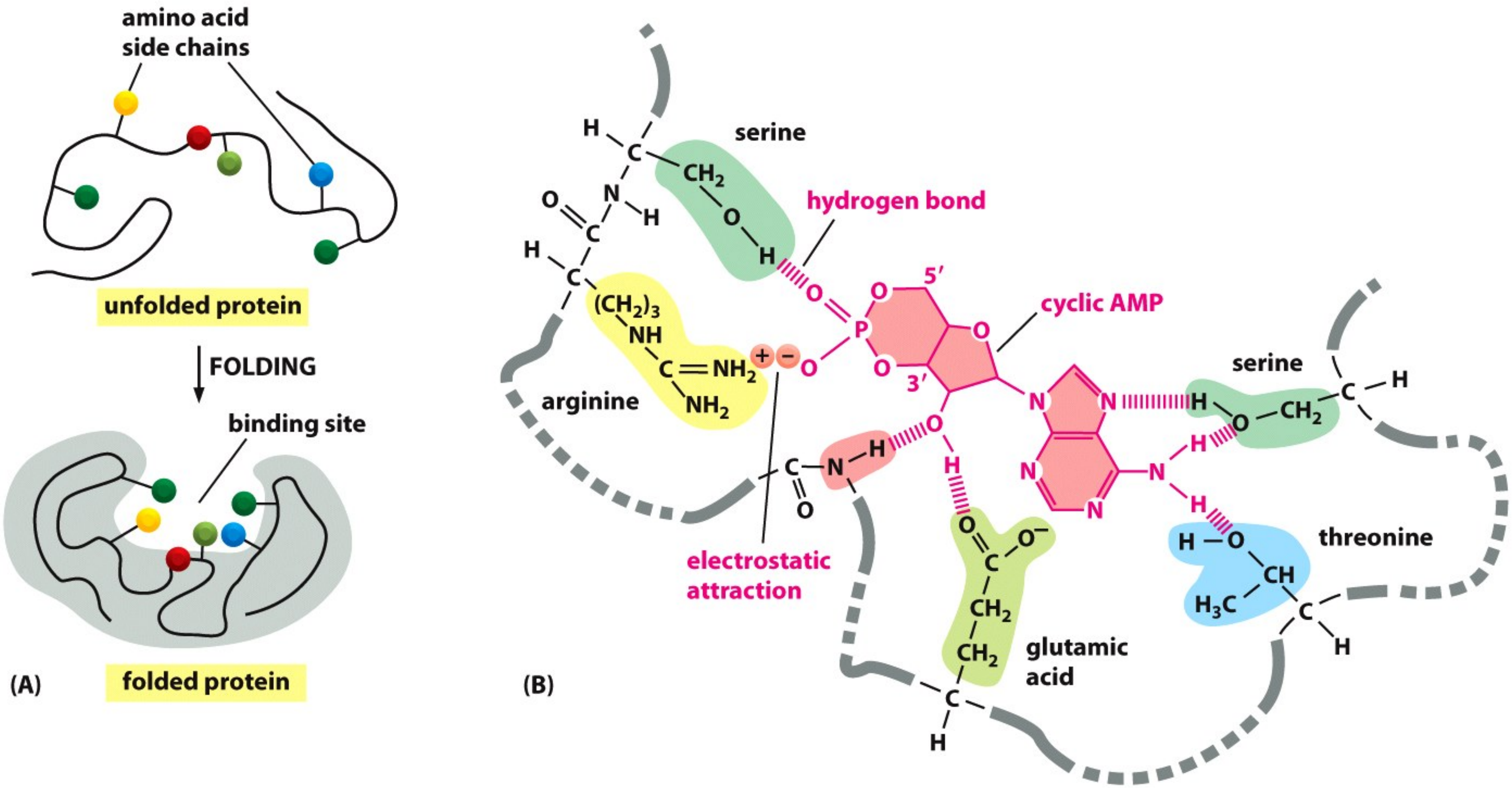
Can you easily recognize them in a figure?

Binding affinity vs specificity

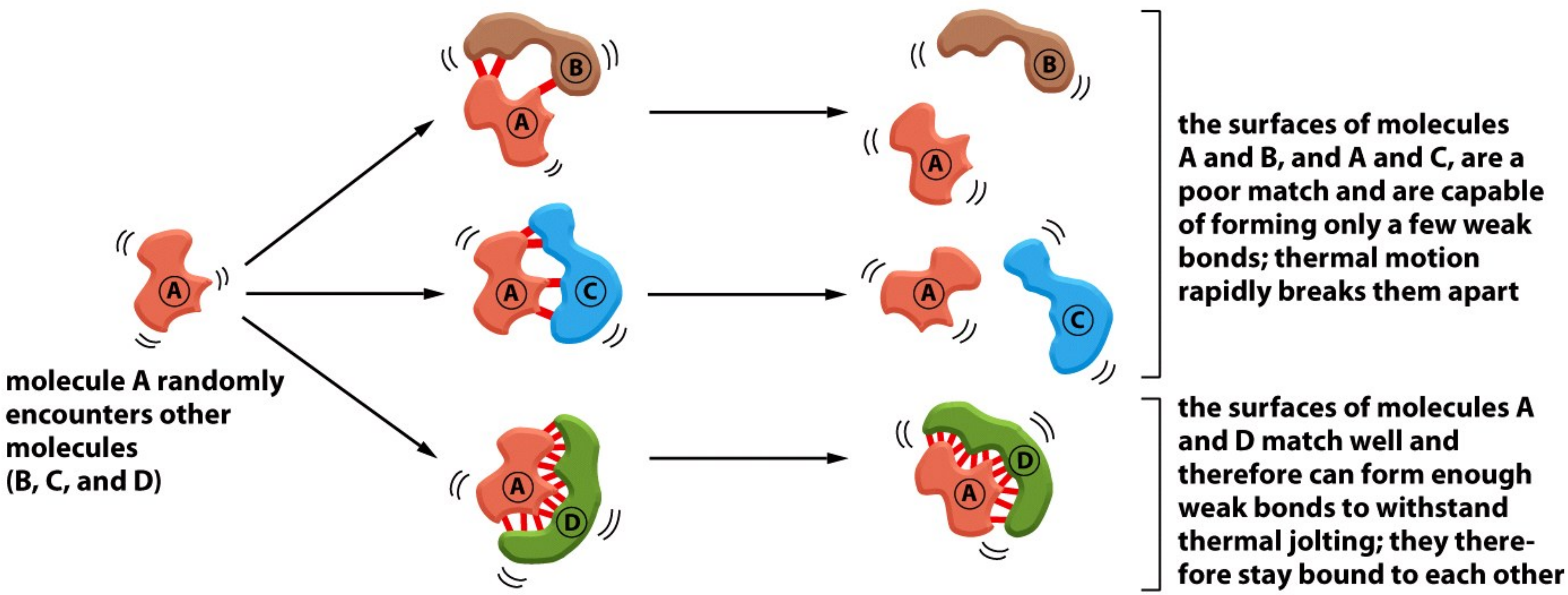
- The strength of each bond adds to the binding affinity
  - Many noncovalent bonds can result in “tight binding”

- The more bonds formed the more specific the protein is to for ligand
  - Especially true for ionic interactions

Visualizing specificity



Specificity and Function



What you already know, and why.

- Each protein can bind more than one different ligand at a time
- Binding of a ligand can change protein structure
- A change in protein structure can be passed along by non-covalent bonds

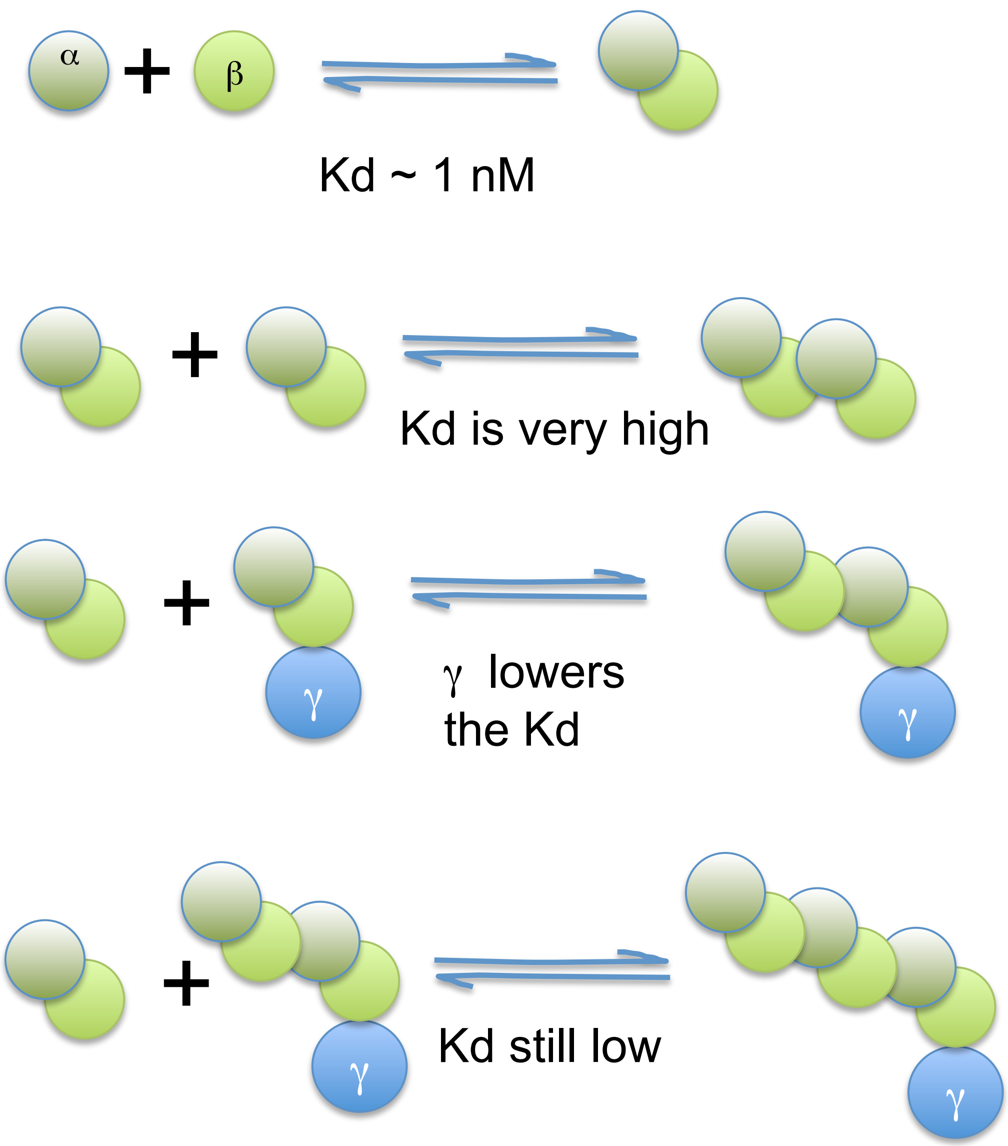
What would happen?

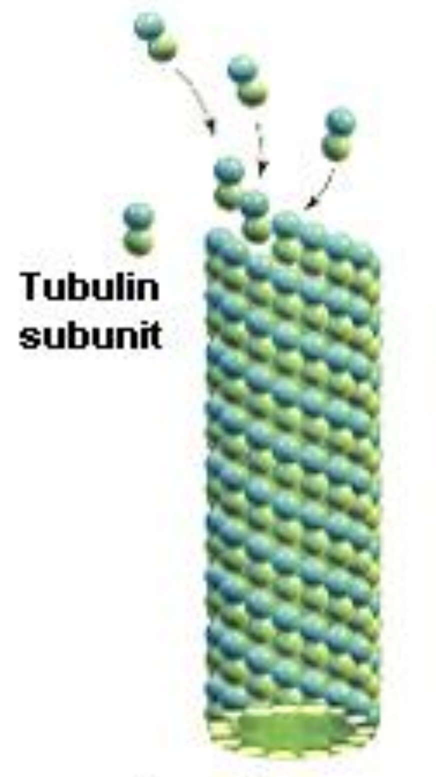
- If a lysozyme increased sugar affinity at the cost of specificity?
  - Lysozyme breaks down complex sugars that make up bacterial cell walls.

A fun example

- Microtubules
- Part of the cytoskeletal network
- Divide chromosomes during mitosis
- Large fibers made up of dimers of two related proteins

A fun example

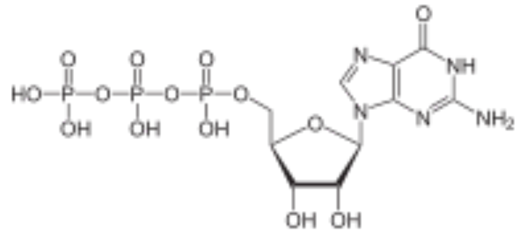




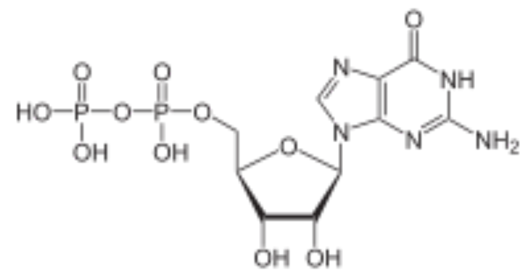
Gartner and Hiatt, 1994

Dynamic Instability

- Tubulin monomers have a ligand
  - GTP



- Over time, Tubulin in the microtubules hydrolyze GTP
  - GTP → H_2PO_4 +



- This causes a structural rearrangement that lowers the stability of dimer-dimer contacts

What happens?

- To the board.

- Inner Life of the Cell
  - Worth watching in total, but just a quick clip of microtubule polymerization and depolymerization for now

Summary

- Proteins interact with many things
- Which protein interacts with what?
  - The shape and chemical nature of each protein's surface determines specificity
- A protein's affinity for a ligand is based on the summation of non-covalent bonds
  - Low Kd, High affinity