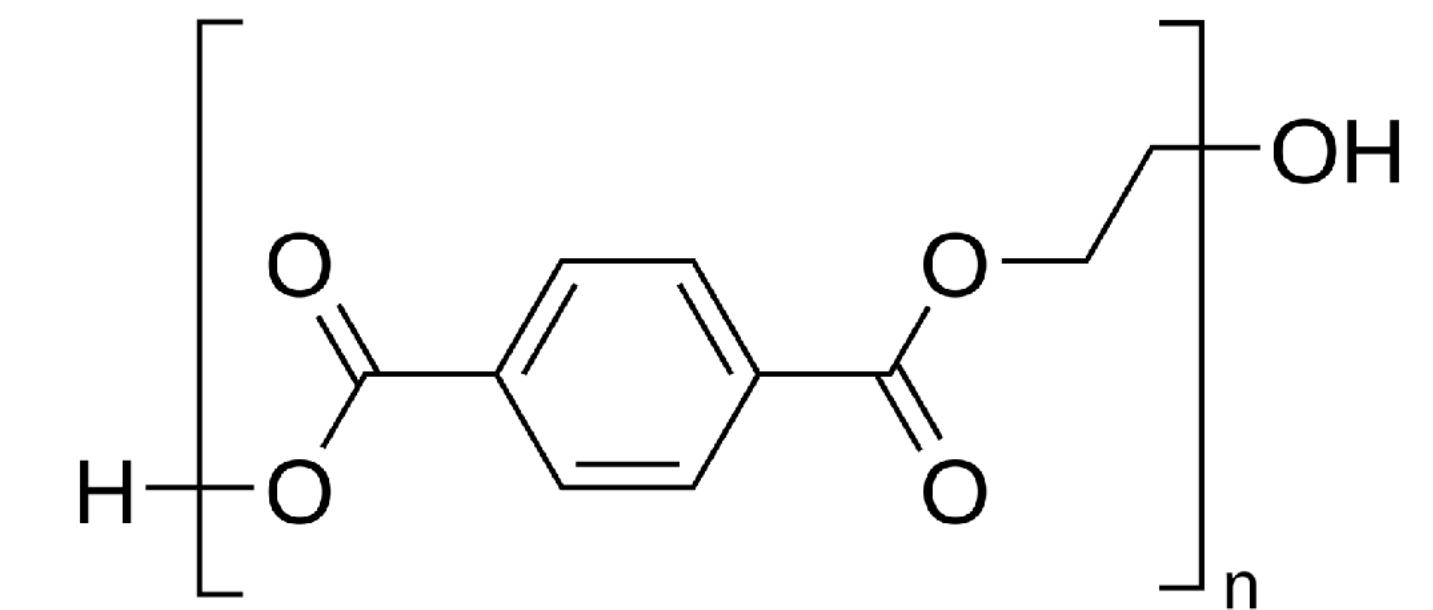


Biological Macromolecules

- This mini-lecture will be about how biological macromolecules
 - are heteropolymers
 - are folded
 - have noncovalent interactions with many drugs
- At the end of this mini-lecture, you should be able to answer the following questions:
 - What are biological macromolecules made of?
 - What does it mean for a biological macromolecule to be folded?
 - How do most drugs interact with their targets?

Biological macromolecules are heteropolymers

- Polymers - made of smaller building blocks - monomers - that are covalently joined together
 - Homopolymers - monomers repeat, e.g. in a plastic
 - Heteropolymers - monomers do not exactly repeat
- Different types of macromolecules are made of different types of building blocks

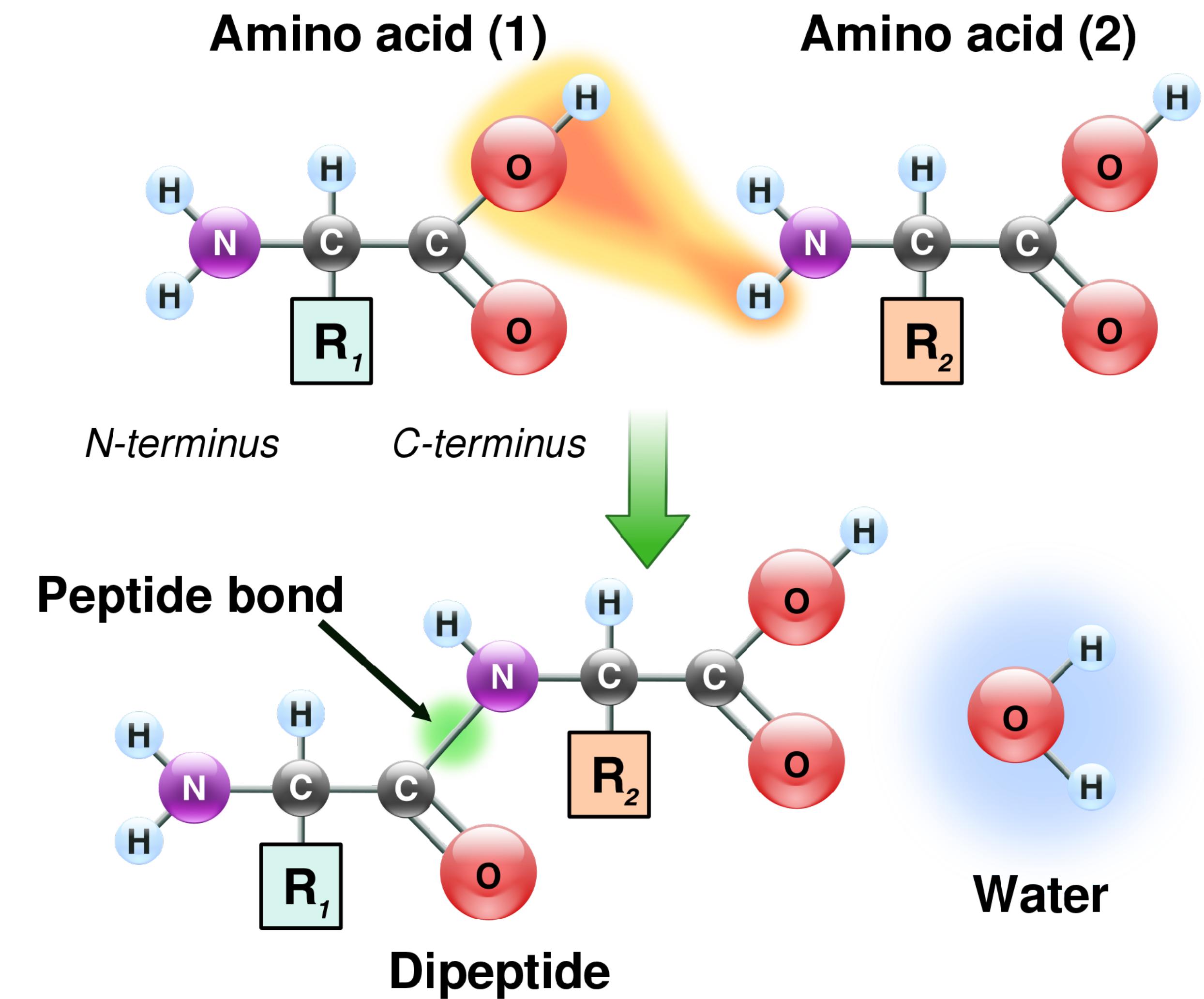


Polyethylene terephthalate, a homopolymer

<https://commons.wikimedia.org/wiki/File:Polyethyleneterephthalate.svg>

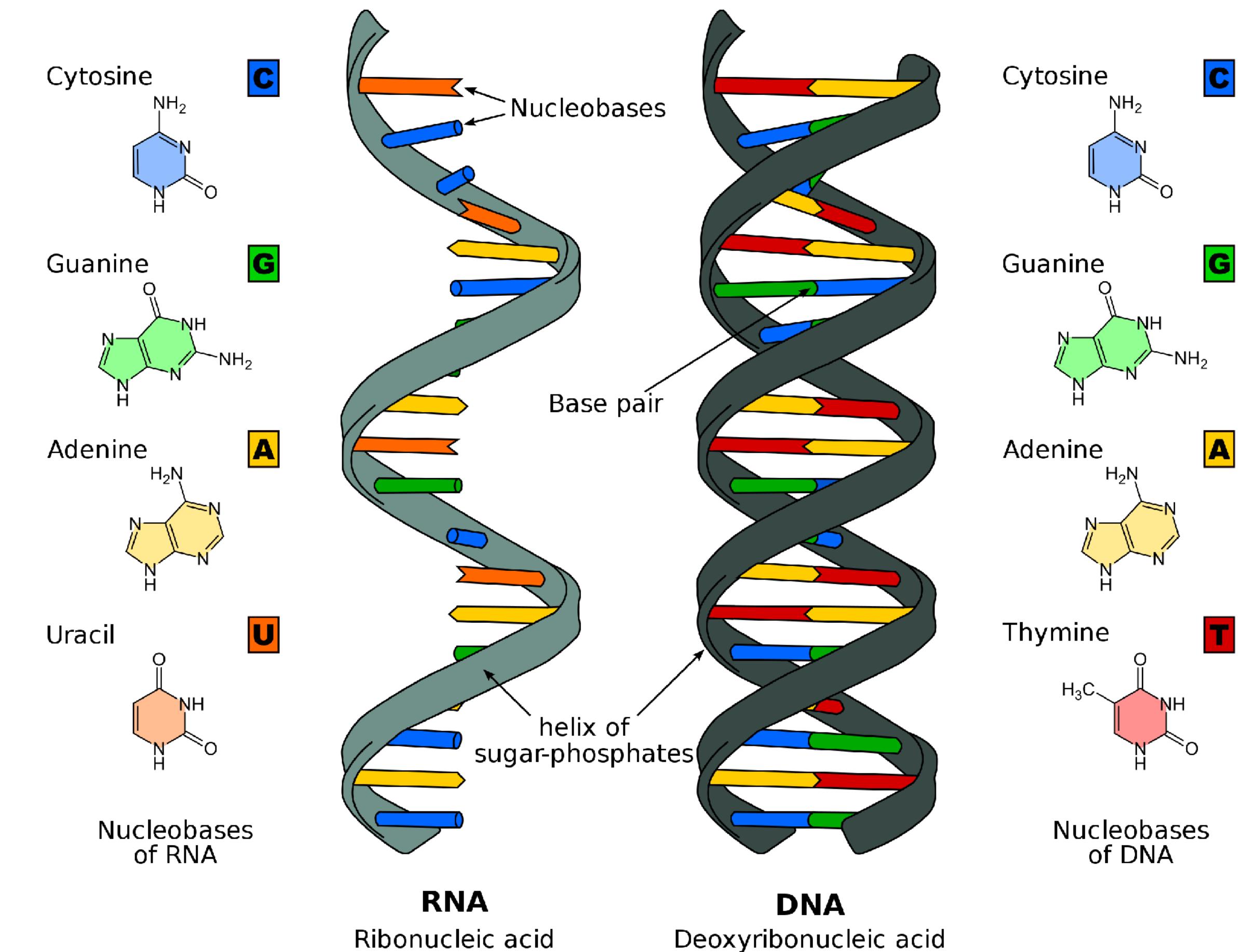
The monomers are small organic molecules

- Proteins are made of
 - 20 standard amino acids
 - linked by peptide bonds
 - modifications, e.g.
 - post-translational modification
 - disulfide bonds
 - cofactors and prosthetic groups



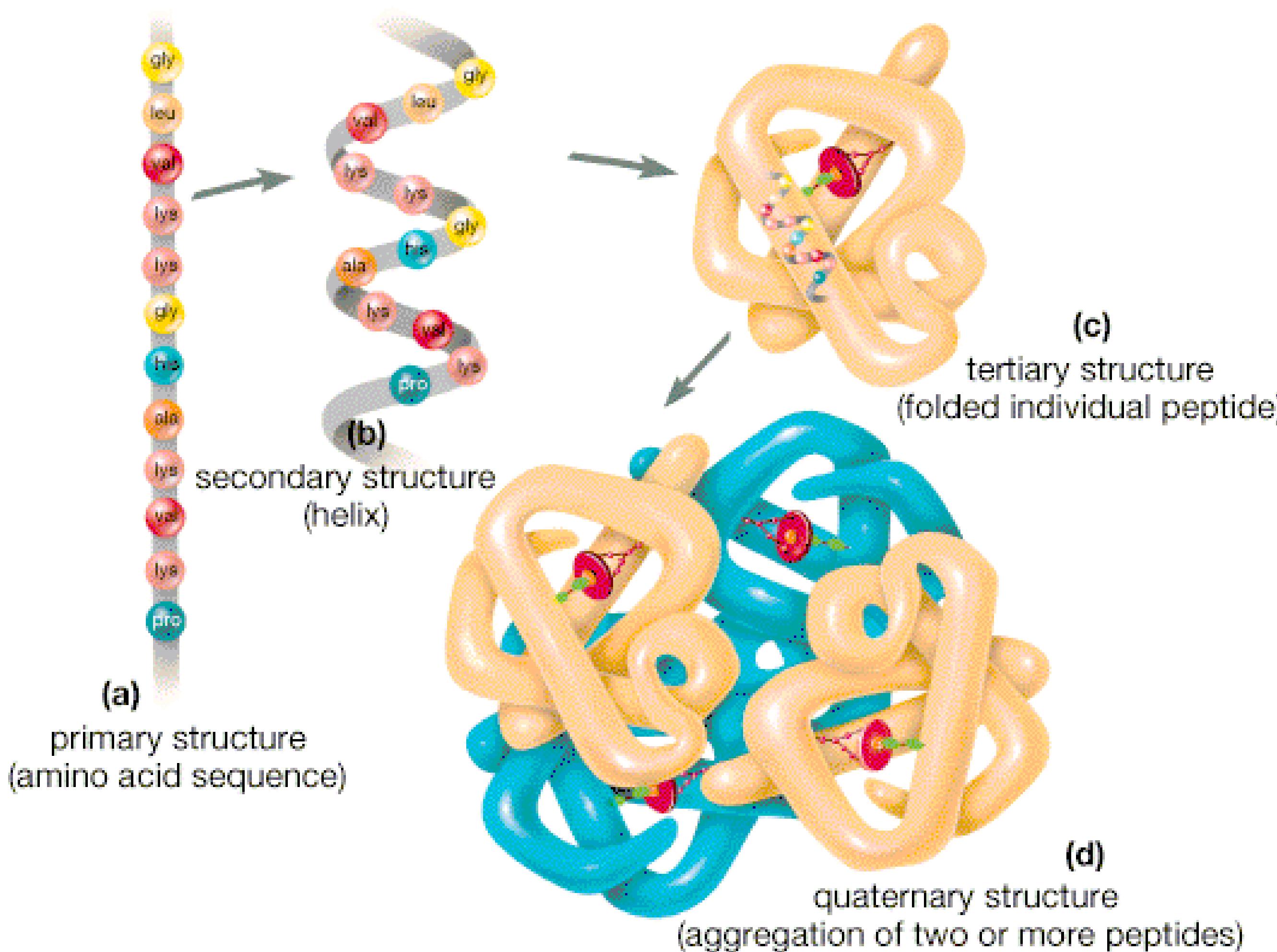
The monomers are small organic molecules

- DNA and RNA are made of nucleic acids
- DNA usually forms a double helix
- RNA is more flexible and can have complex structure
- Which can have catalytic activity? DNA or RNA?



https://en.wikipedia.org/wiki/Nucleic_acid#/media/File:Difference_DNA_RNA-EN.svg

There are four levels of protein structure



The primary structure is the monomer sequence

Primary Structure = sequence
of amino acids

3-letter code

Lys-Thr-Tyr-Phe-Pro-His-
Phe-Asp-Leu-Ser-His-**Gly**...

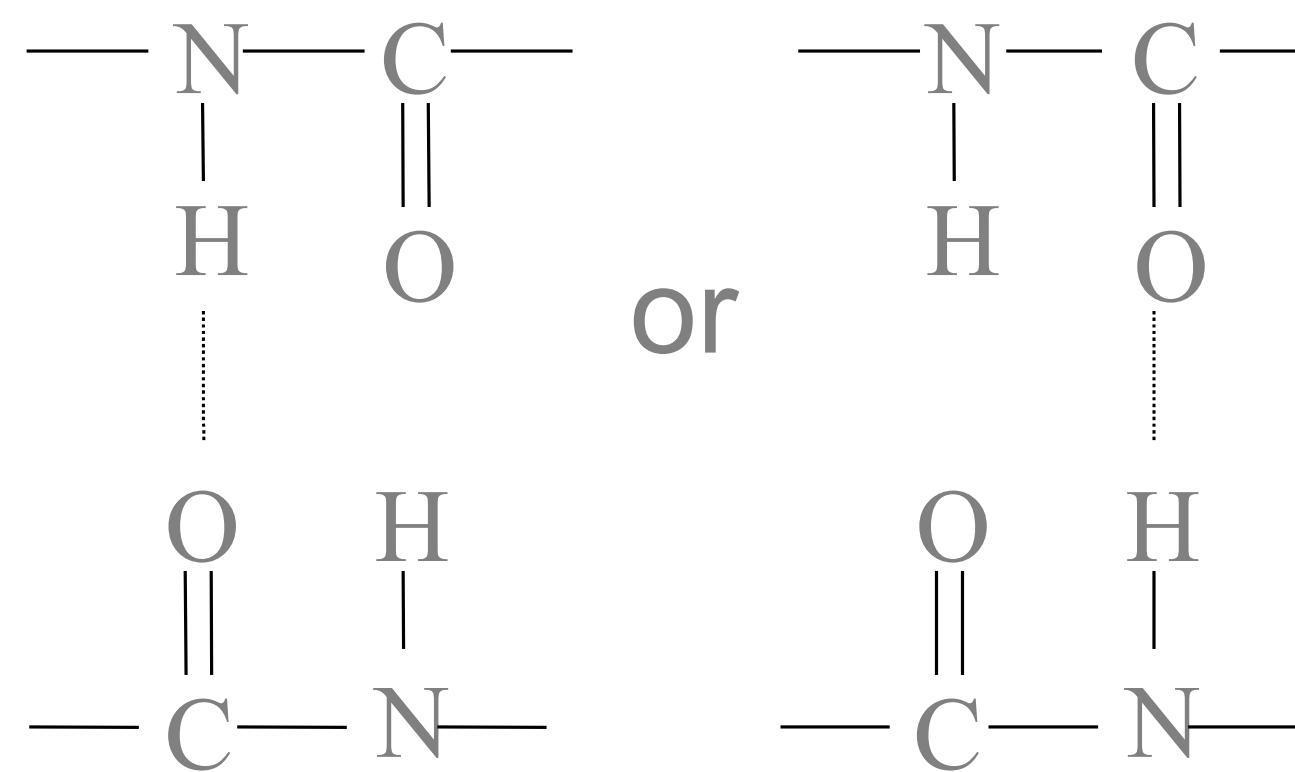
1-letter code

KTYFPHFDLSH**G**...

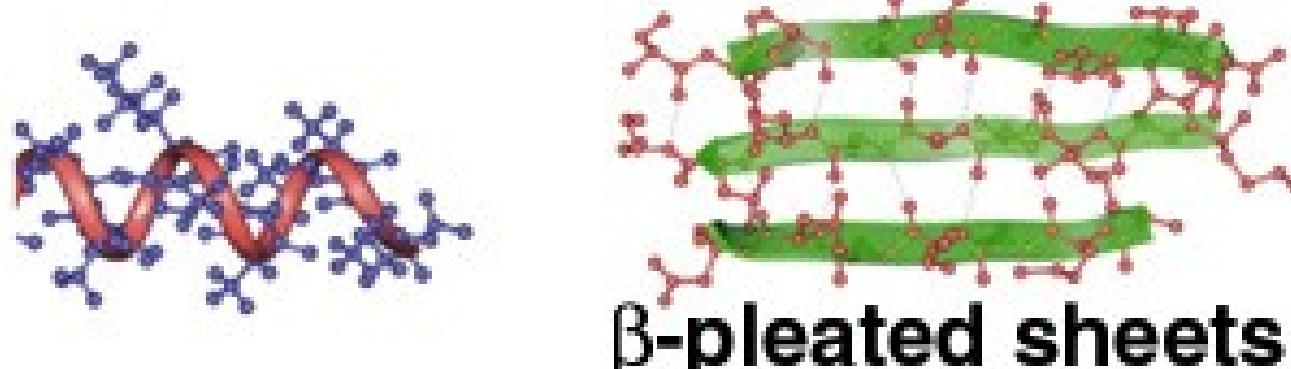
A **chain** is a sequence of amino acids connected by covalent peptide bonds. Chains are synthesized from the **amino terminus**, with new amino acids being added at the **carboxy terminus**.

Many sequences have secondary structure

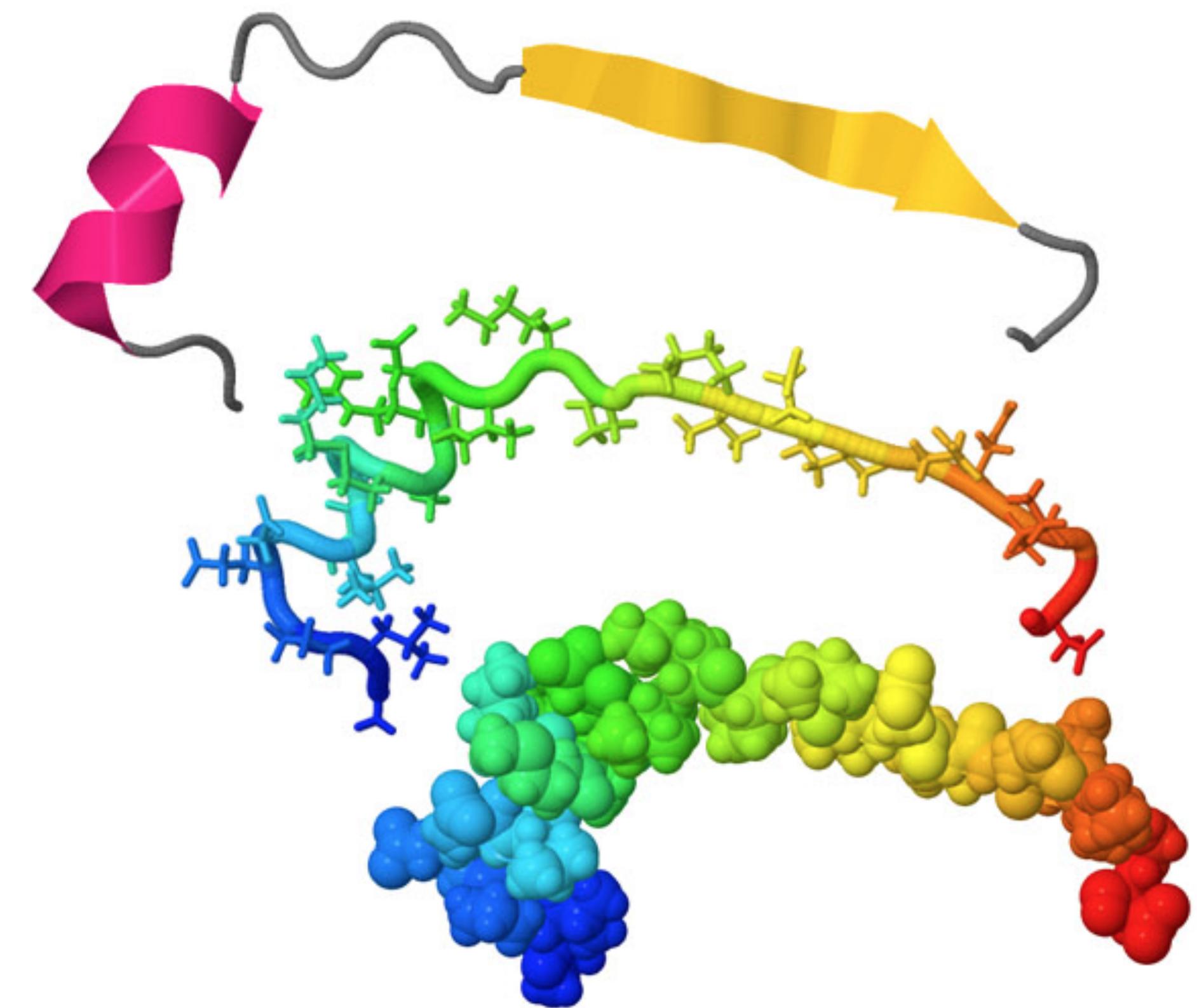
Folded structure due to hydrogen bonds between the amino and acid groups of amino acids



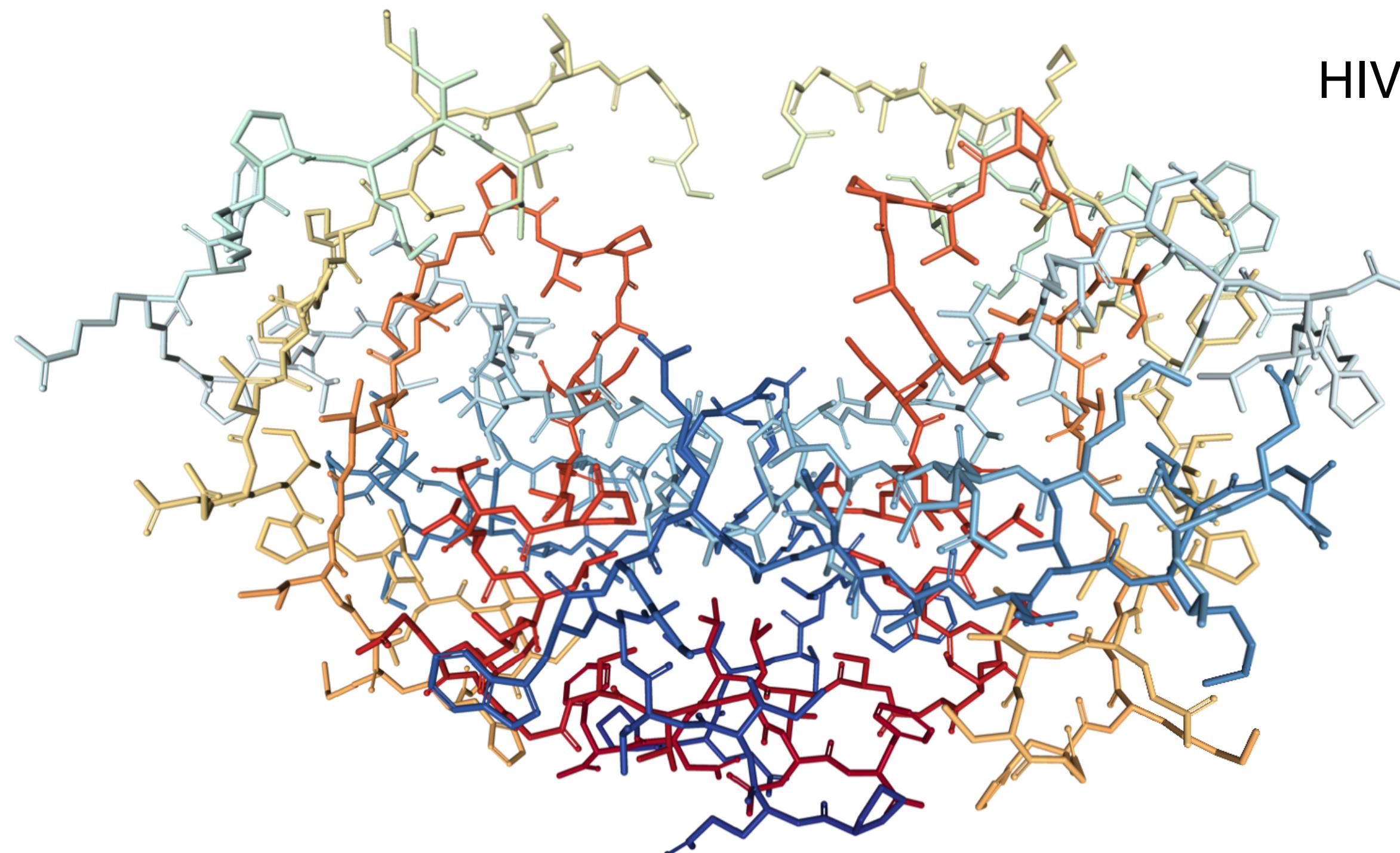
(c) 2° structures



Secondary Structure =
alpha helices, beta strands



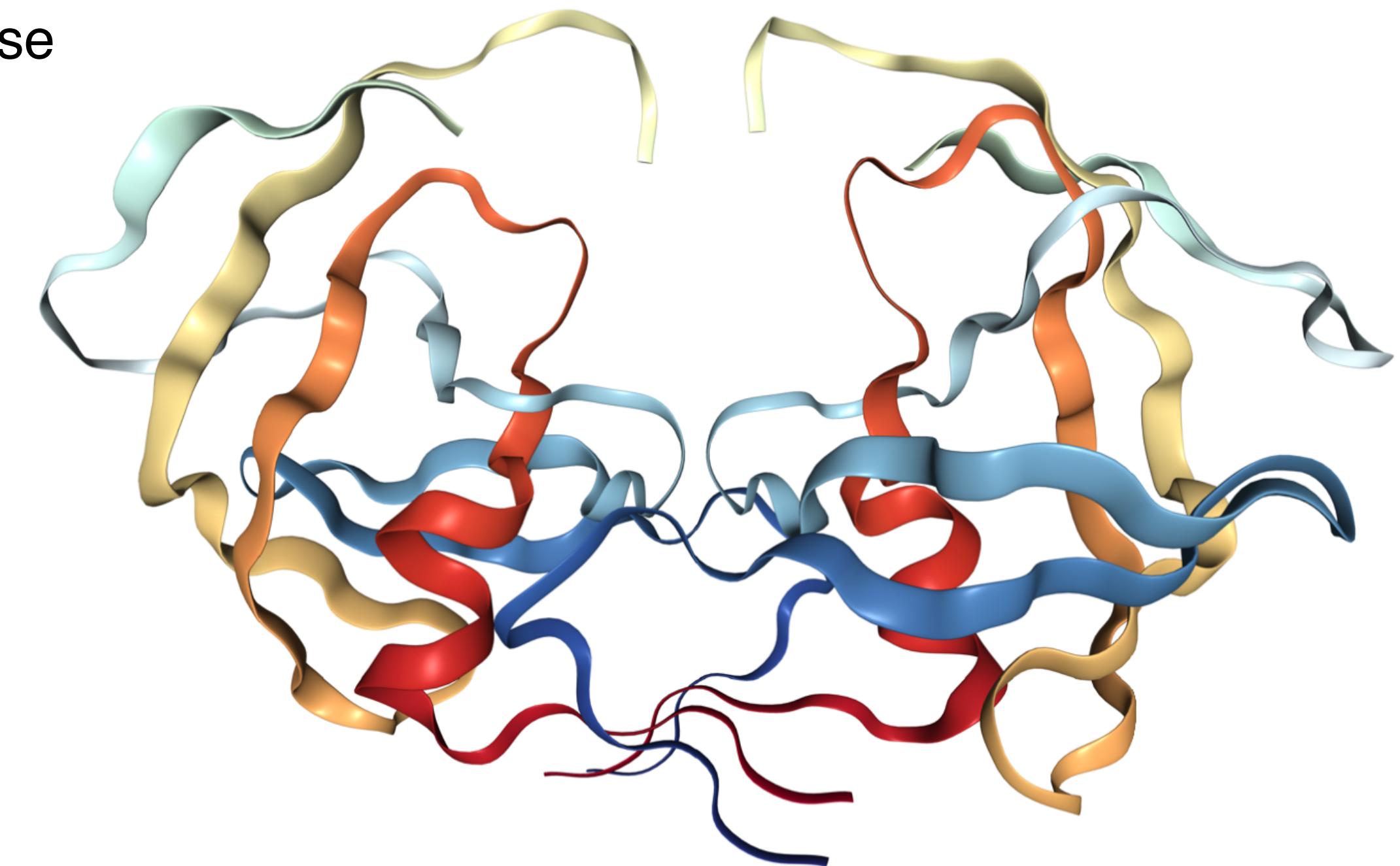
Proteins often form folded tertiary structures



“Licorice” view showing all heavy atoms

HIV protease

<http://www.rcsb.org/3d-view/2HB2>



“Ribbon” view showing backbone, emphasizing α helices and β sheets

“Folded” does not mean that they are completely rigid, but they are *fairly* well-defined.

Primary Structure = sequence
of amino acids

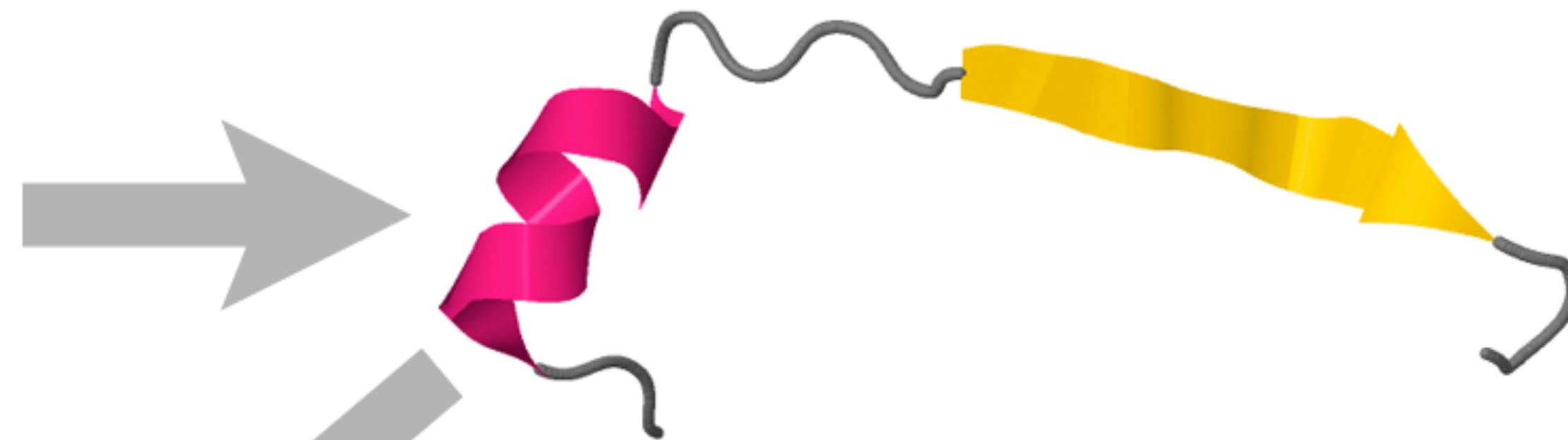
3-letter code

Lys-Thr-Tyr-Phe-Pro-His-
Phe-Asp-Leu-Ser-His-**Gly** ...

1-letter code

KTYFPHFDLSH**G**

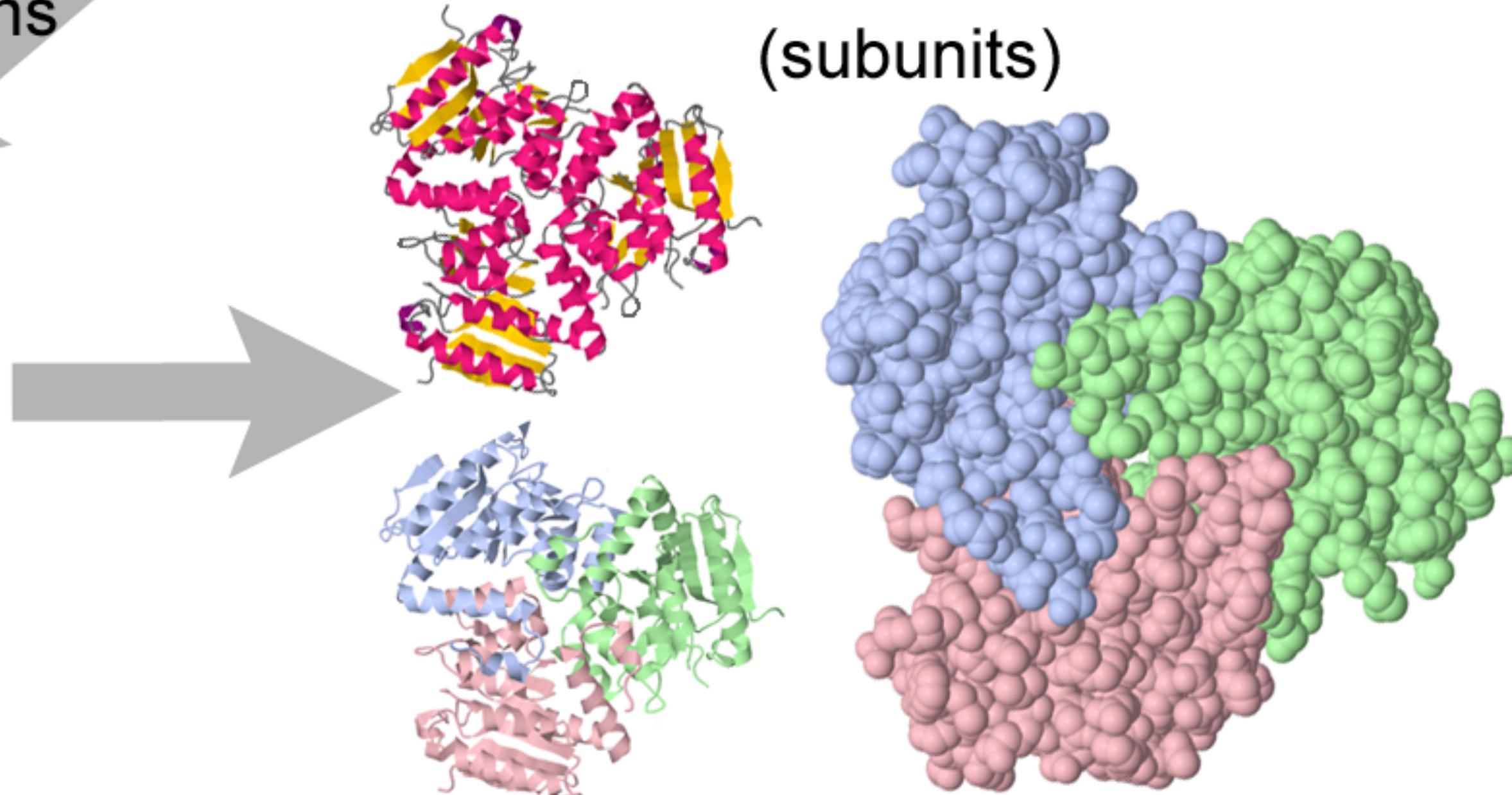
Secondary Structure =
alpha helices, **beta strands**



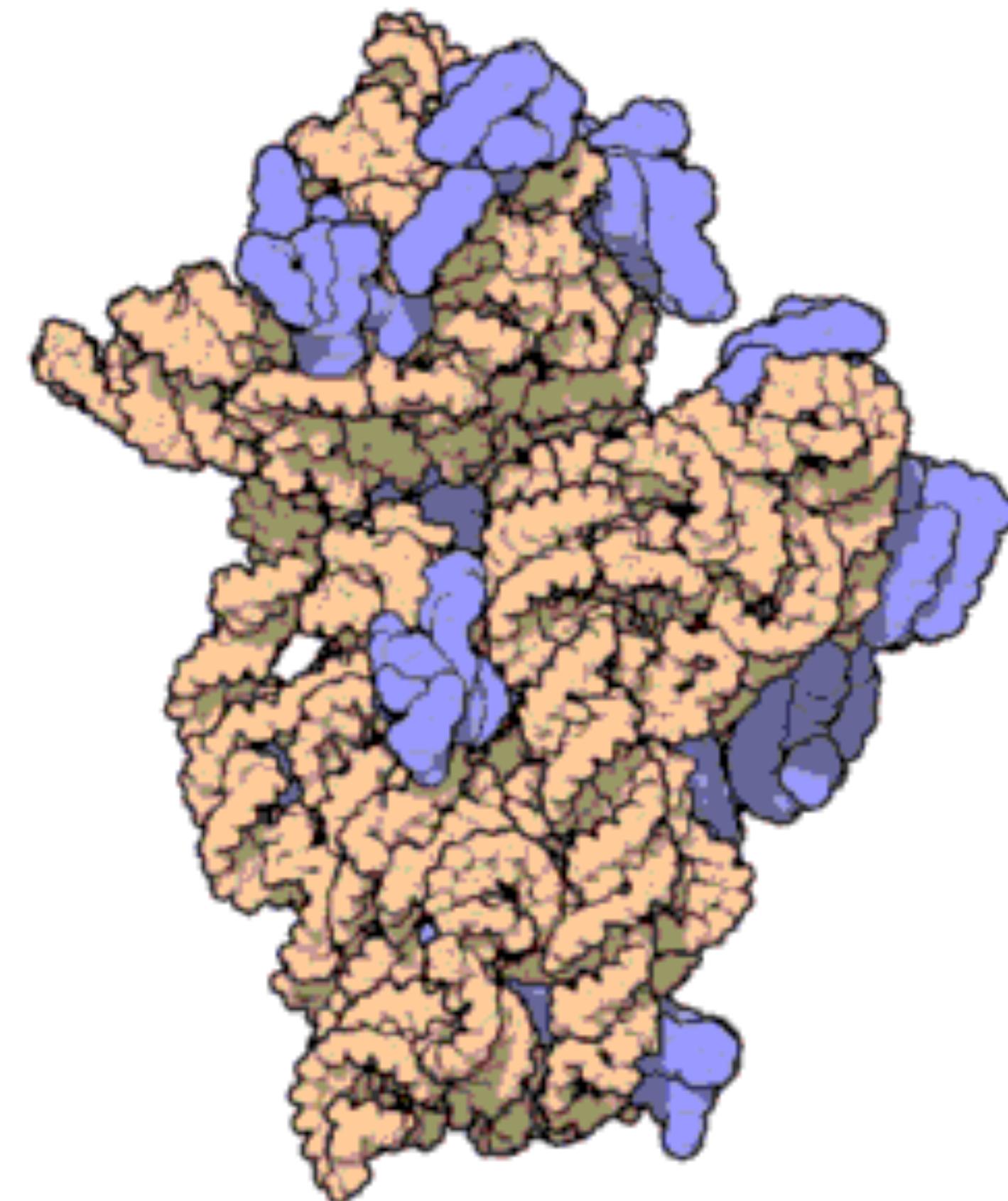
Tertiary Structure = fold
helices and strands into domains



Quaternary Structure (Biological Units)
= functional assemblies of chains
(subunits)



Complexes can include protein + nucleic acids



30S subunit from a bacterial ribosome,
which is made of both protein and RNA

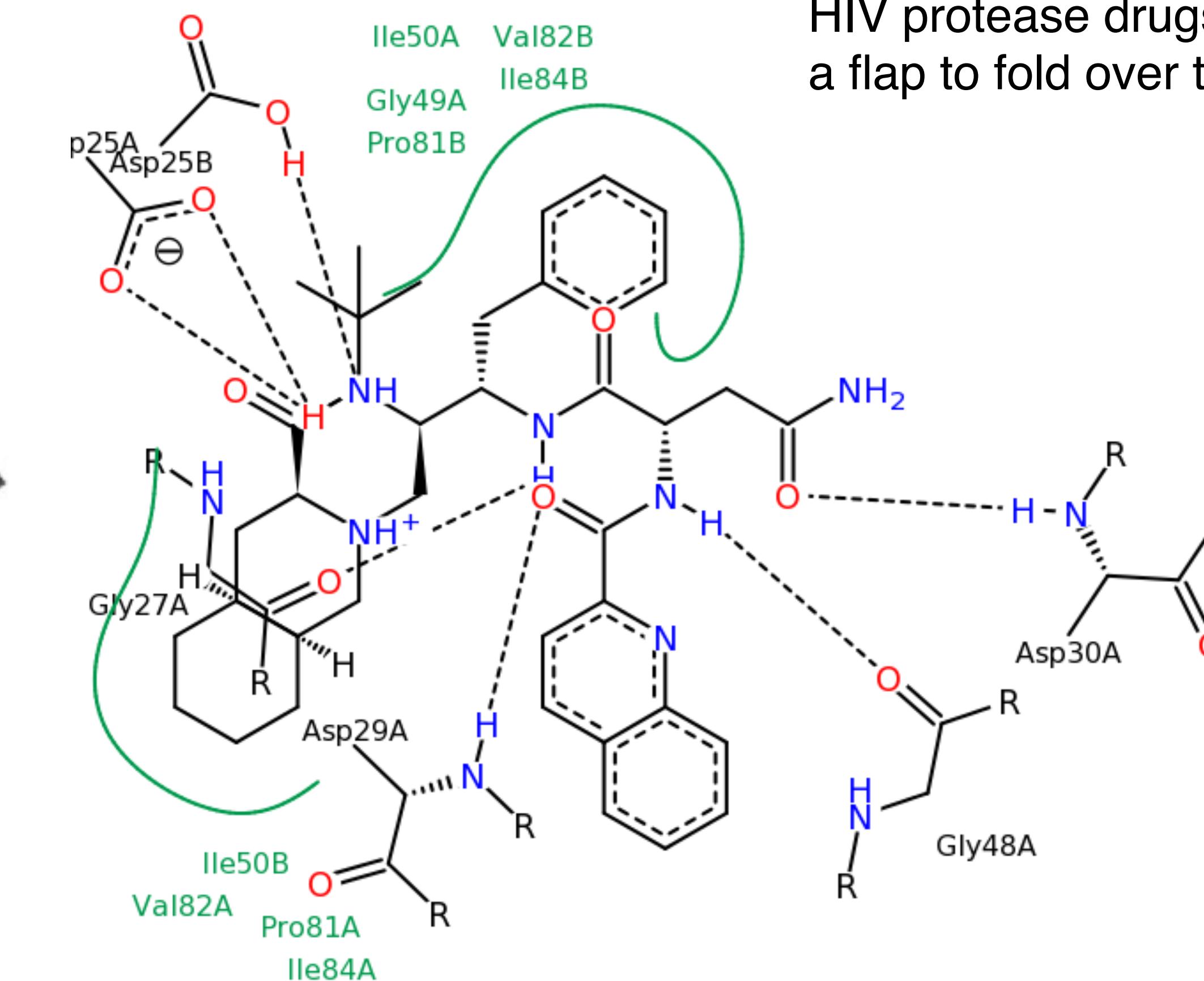
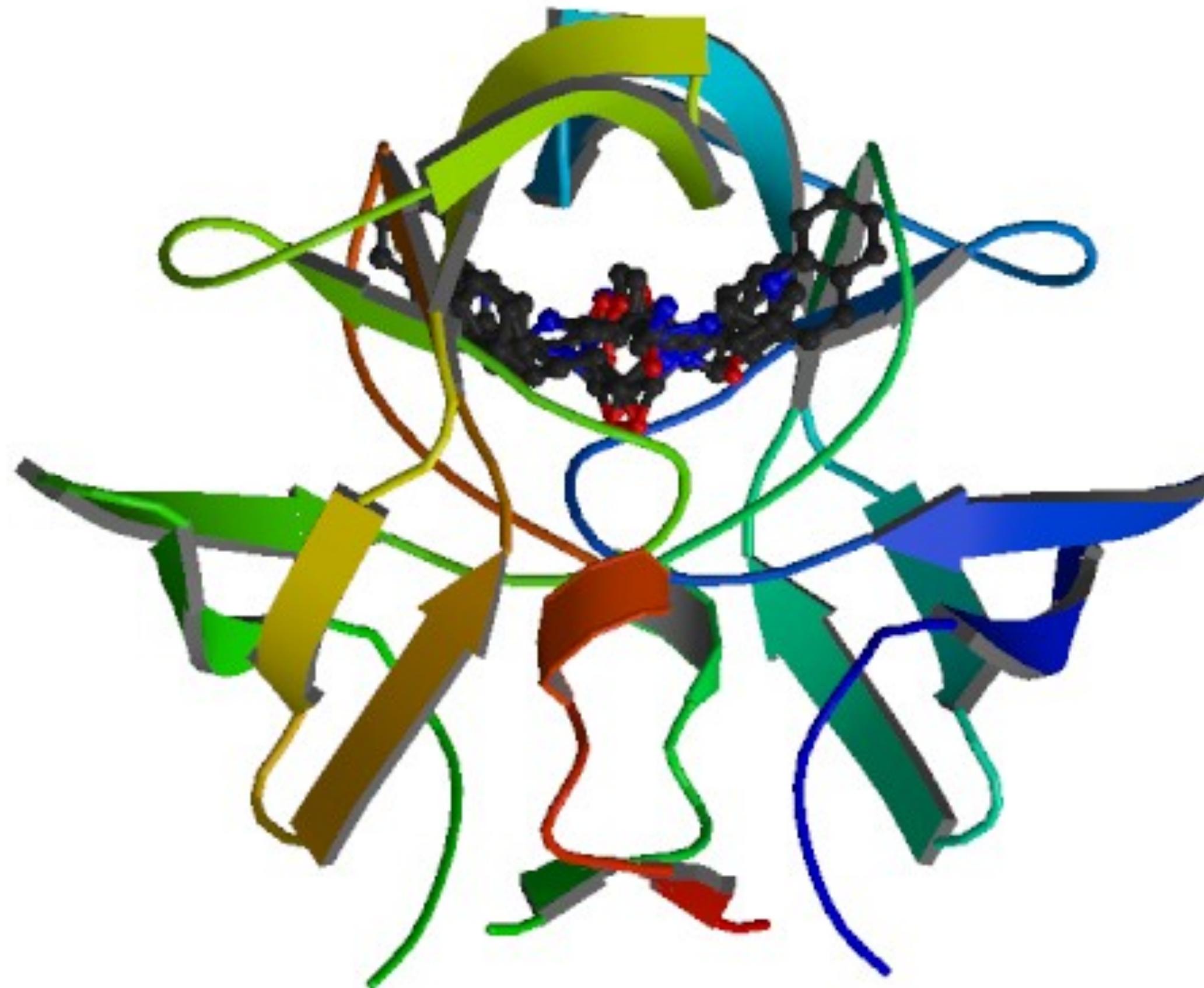
Review Questions

- 1. Primary
- 2. Secondary
- 3. Tertiary
- 4. Quaternary

- A. Which structure results exclusively from hydrogen bonding?
- B. Which structure involves an association of two or more protein chains?
- C. Which structure describes the linear sequence of amino acids?
- D. Which structure depends upon interactions between the R groups of the amino acids?

Most drugs are small molecules that specifically interact with the folded structures

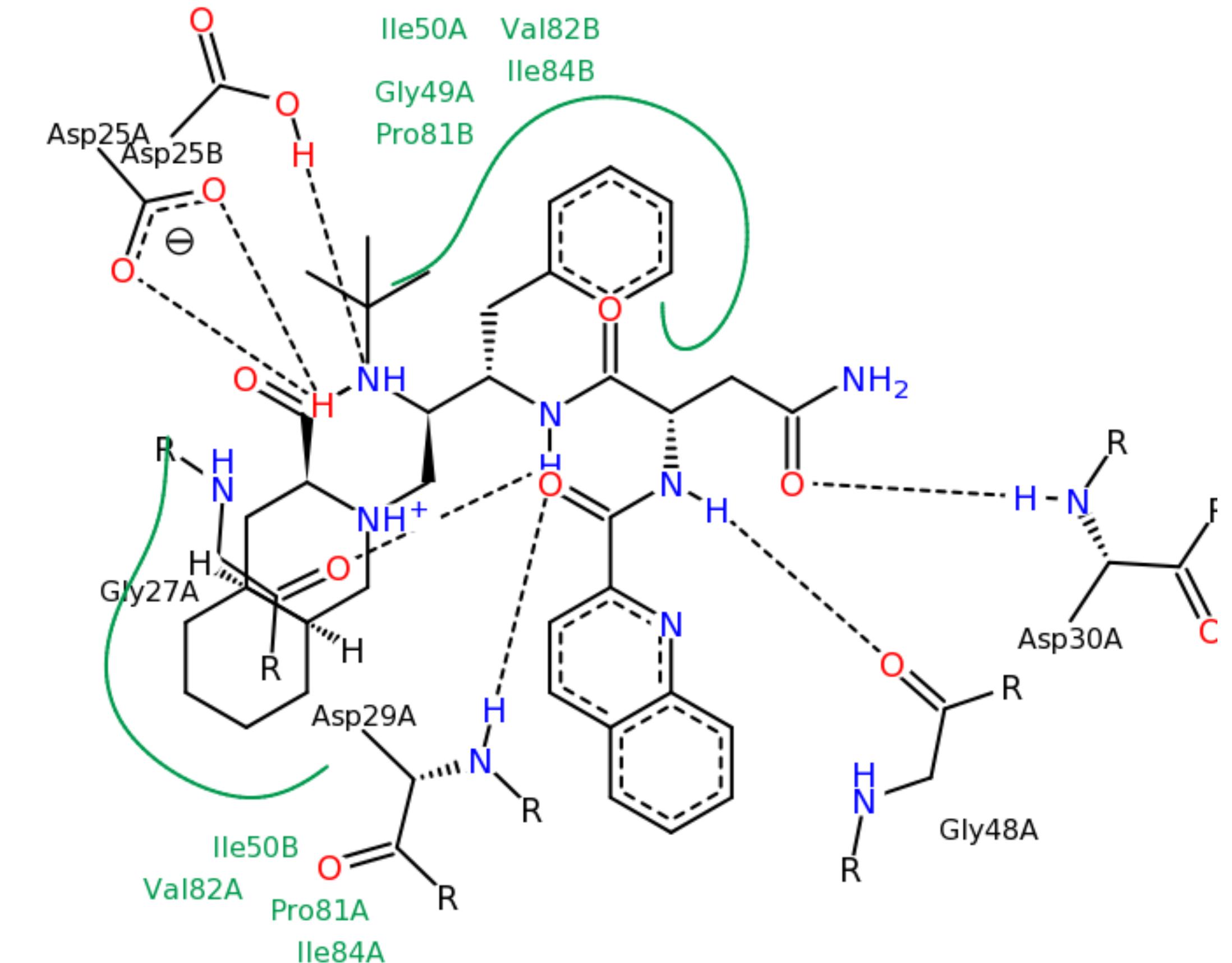
HIV protease with saquinavir



HIV protease drugs often cause a flap to fold over the active site

Most drug-target interactions are noncovalent

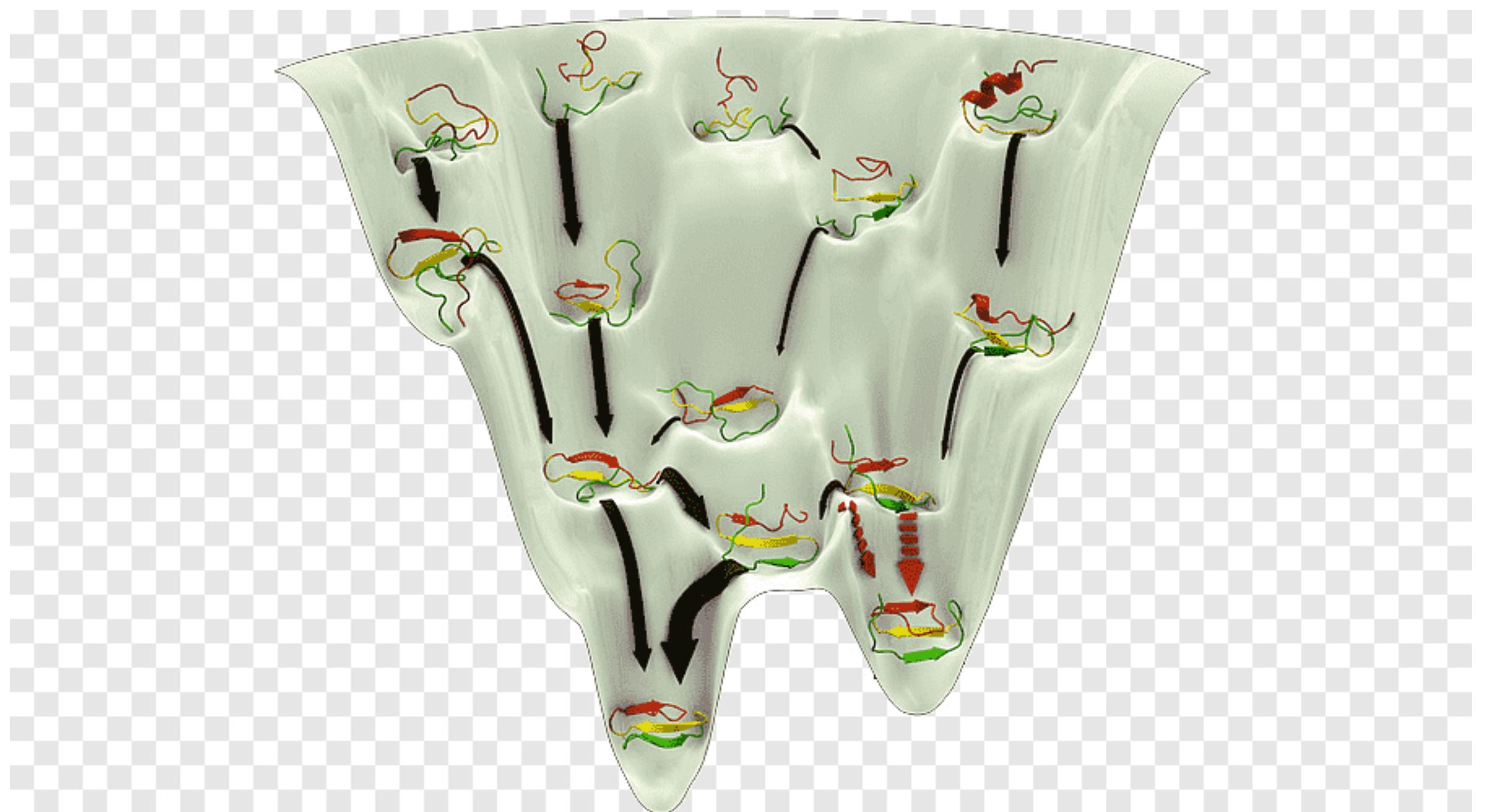
- The interactions driving drug binding are primarily
 - steric - van der Waals. atoms like to be close but not *too* close.
 - electrostatic - like charges repel and opposite charges attract. H bonding often treated as electrostatic.
- Water can play an important role.
- Some drugs (like penicillin) bind to their targets covalently.



http://www.rcsb.org/pdb/101/motm_discussed_entry.do?id=1hxb

Folding and binding processes are described by energy landscapes

- Many configurations are possible
- There are many pathways between unfolded configurations
- Packing of hydrophobic side chains is a key driver of folding



Review Questions

- What are biological macromolecules made of?
- What does it mean for a biological macromolecule to be folded?
- How do most drugs interact with their targets?

Misc

- A beautiful short video on “A basic introduction to drugs, drug targets, and molecular interactions”: <https://www.youtube.com/watch?v=u49k72rUdyC>