

# 8/28/2024

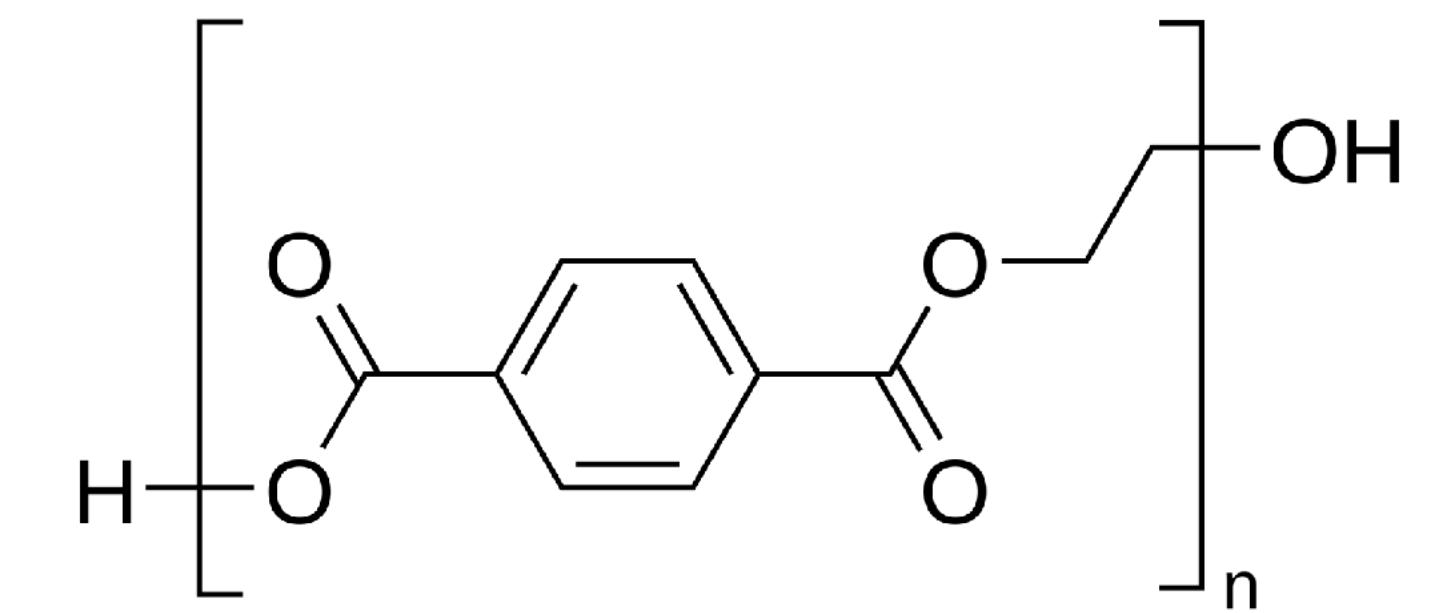
- Introduction to biological macromolecules
- Exercise 2: Structural visualization with py3DMol

# Biological Macromolecules

- This lecture is intended to help you achieve the following learning objectives:
  - Recall the main types of biological macromolecules, identify their monomers, and describe their levels of structure.
  - Describe the types of forces that maintain the structure of biological macromolecules and stabilize their interactions with small organic molecules.
- It 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

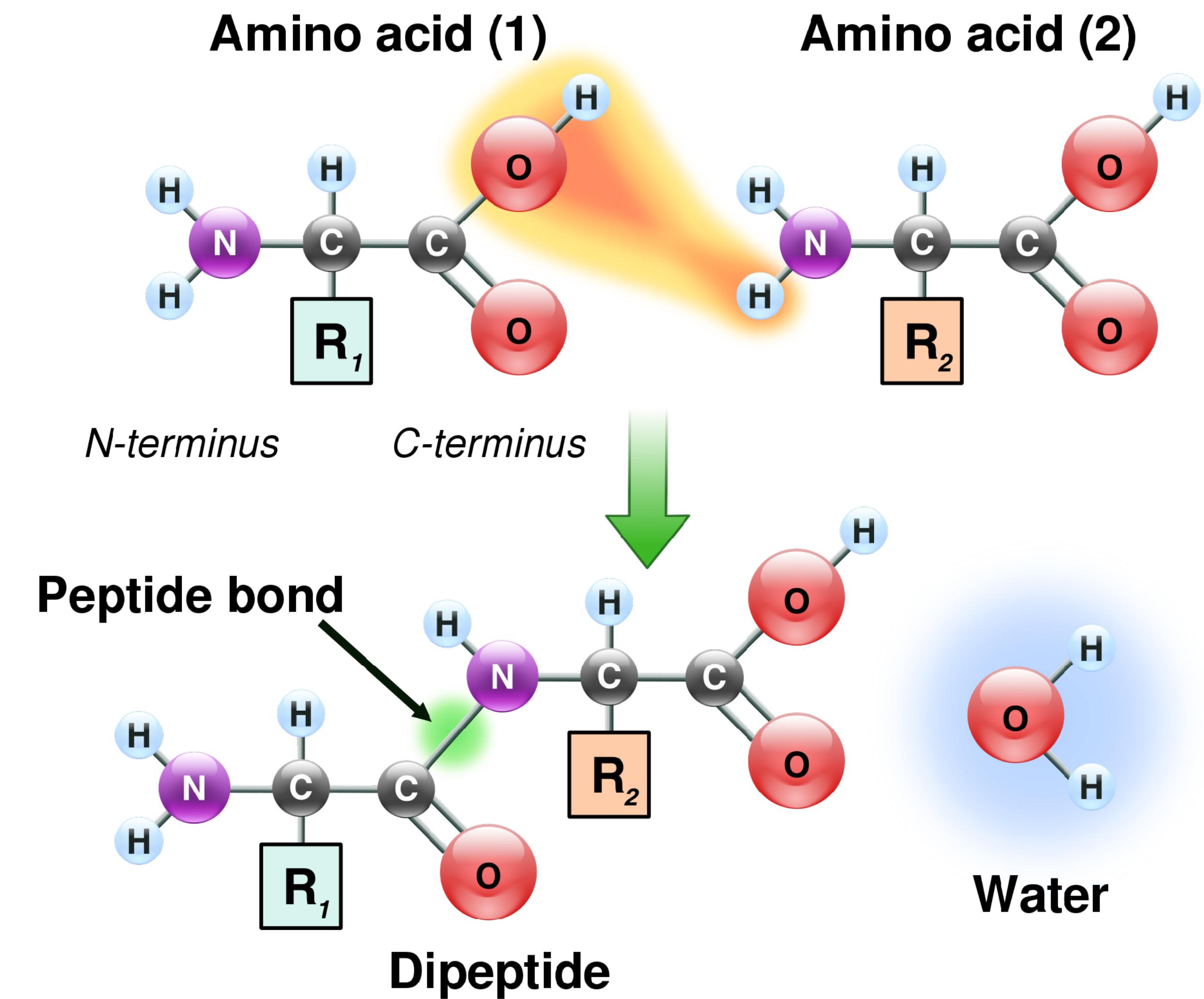


Polyethylene terephthalate, a homopolymer

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

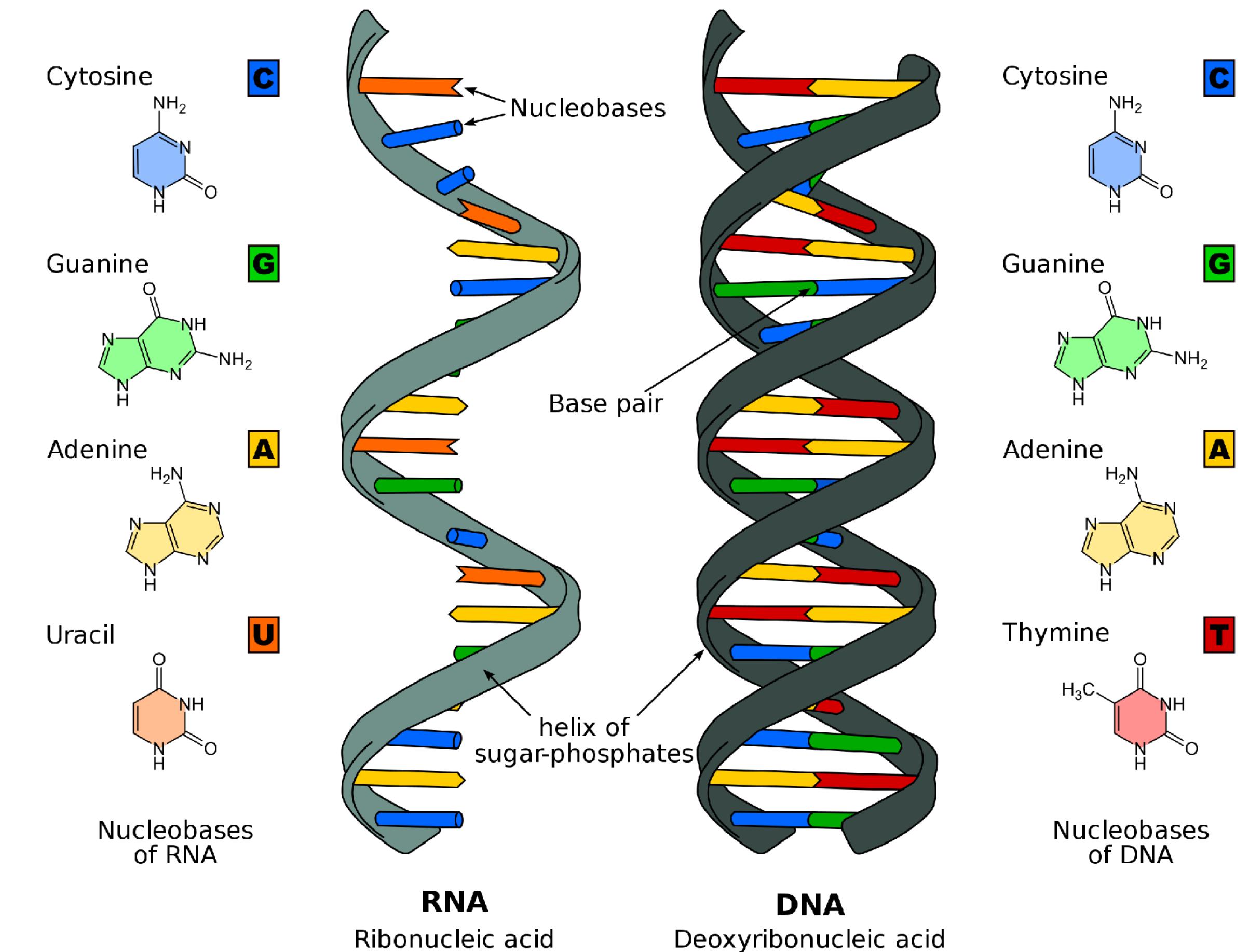
# The monomers are small organic molecules

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



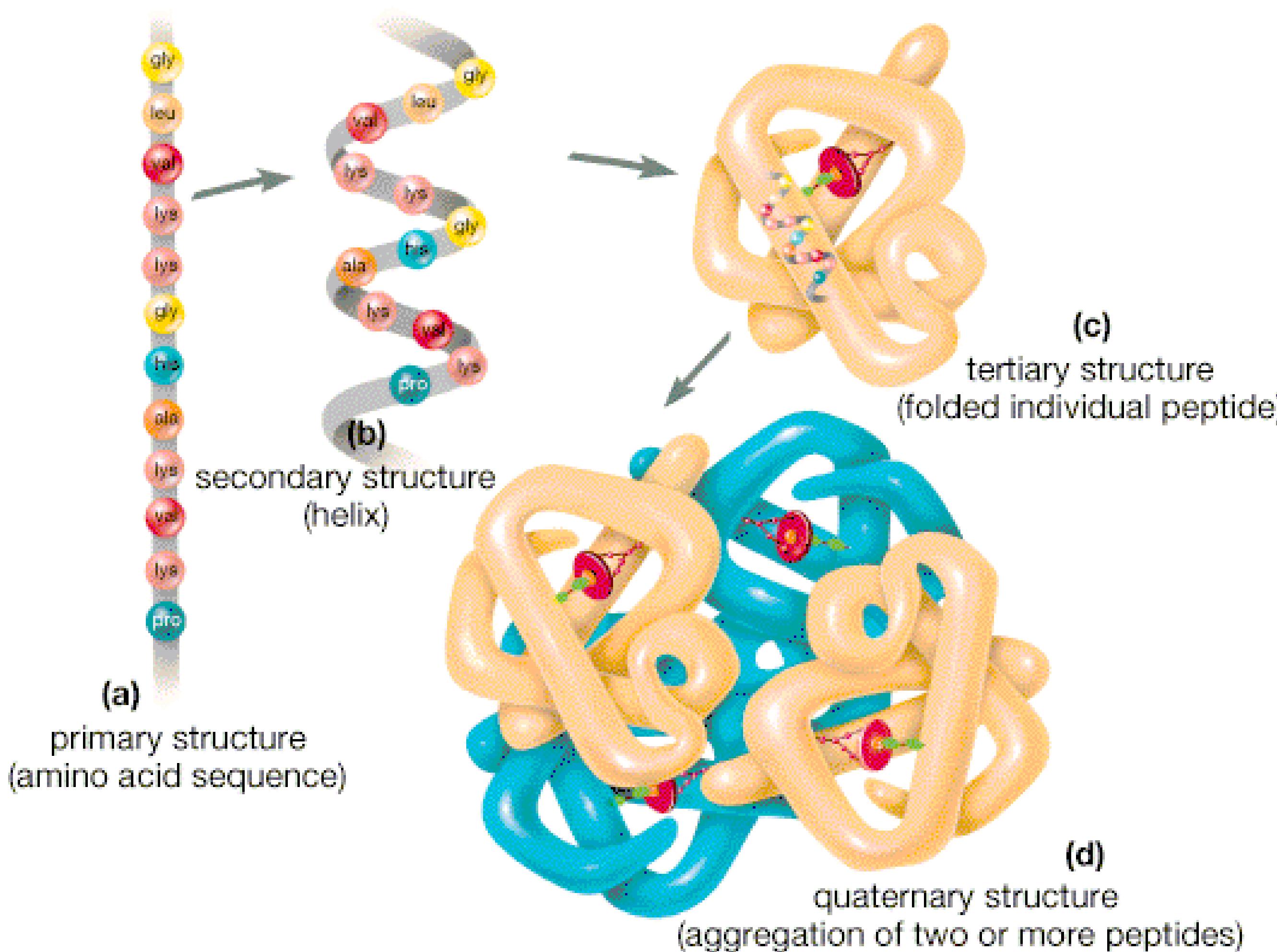
# The monomers are small organic molecules

- 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](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**...

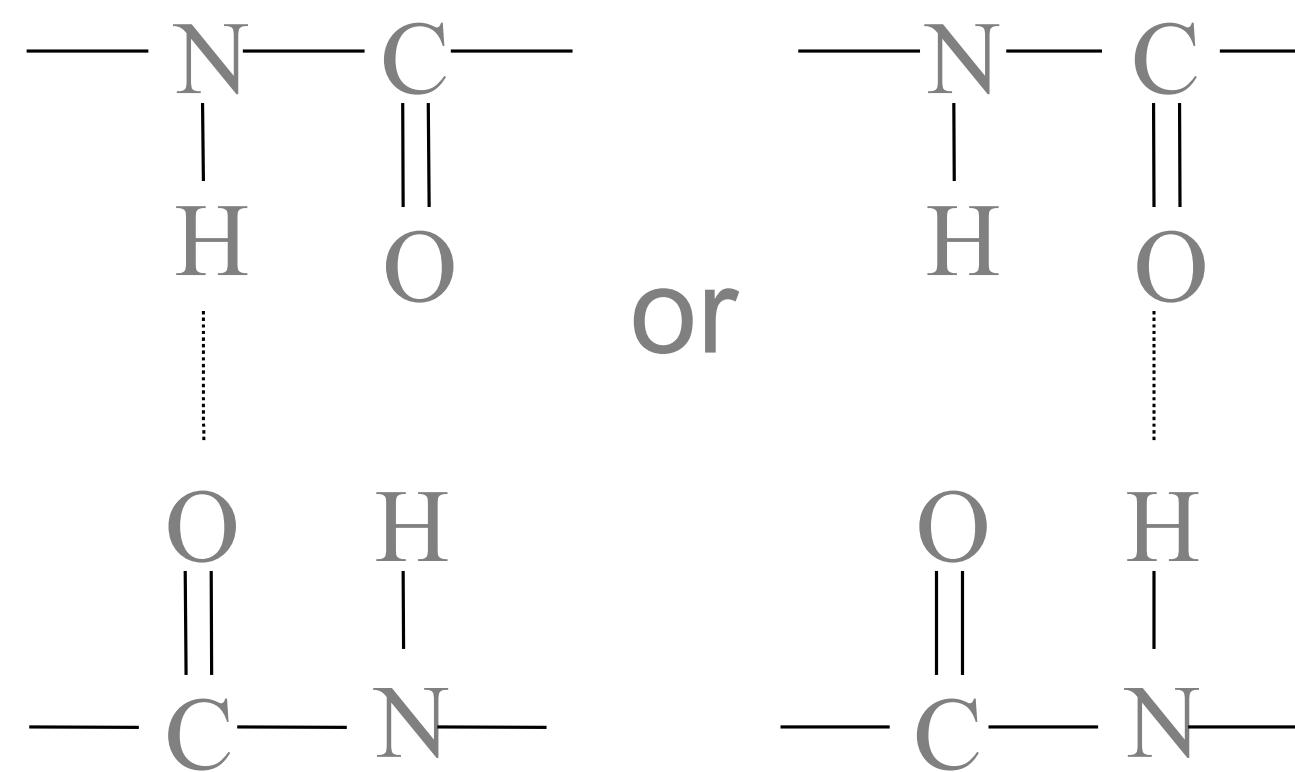
1-letter code

**K**TYFPHFDLSH**G**...

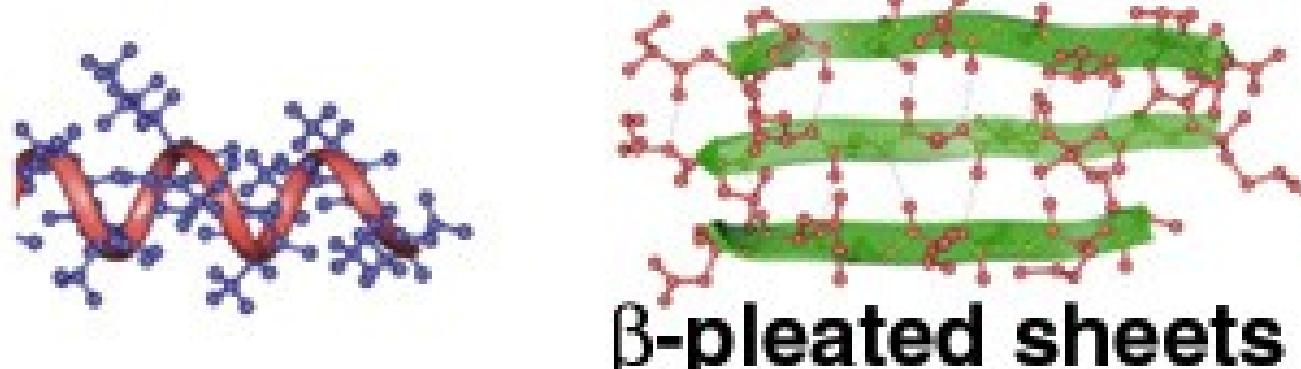
A **chain** is a sequence of amino acids connected by covalent peptide bonds. Chains are synthesized from the **amino terminus**, with new amino acids being added at the **carboxy terminus**.

# Many sequences have secondary structure

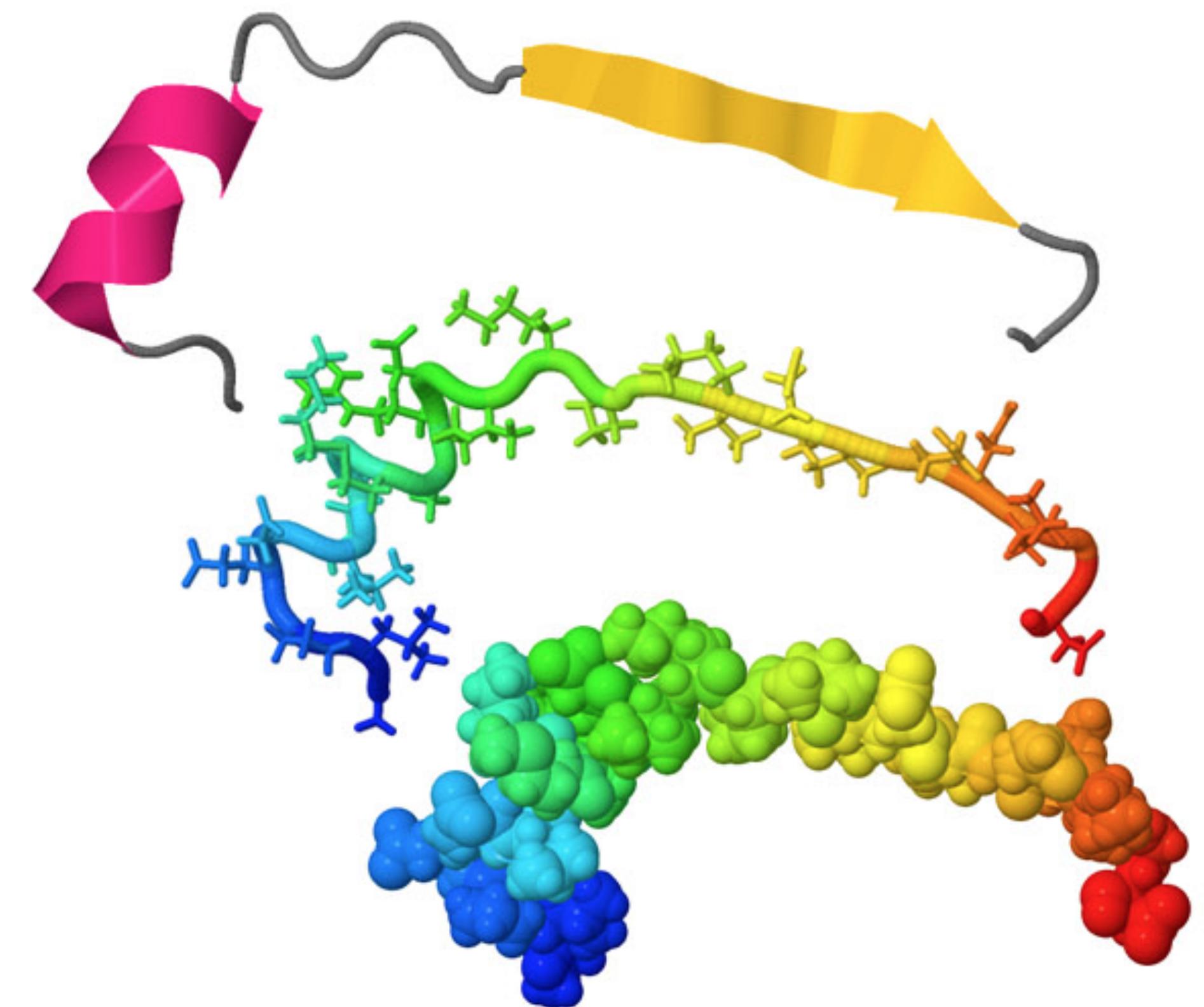
Folded structure due to hydrogen bonds between the amino and acid groups of amino acids



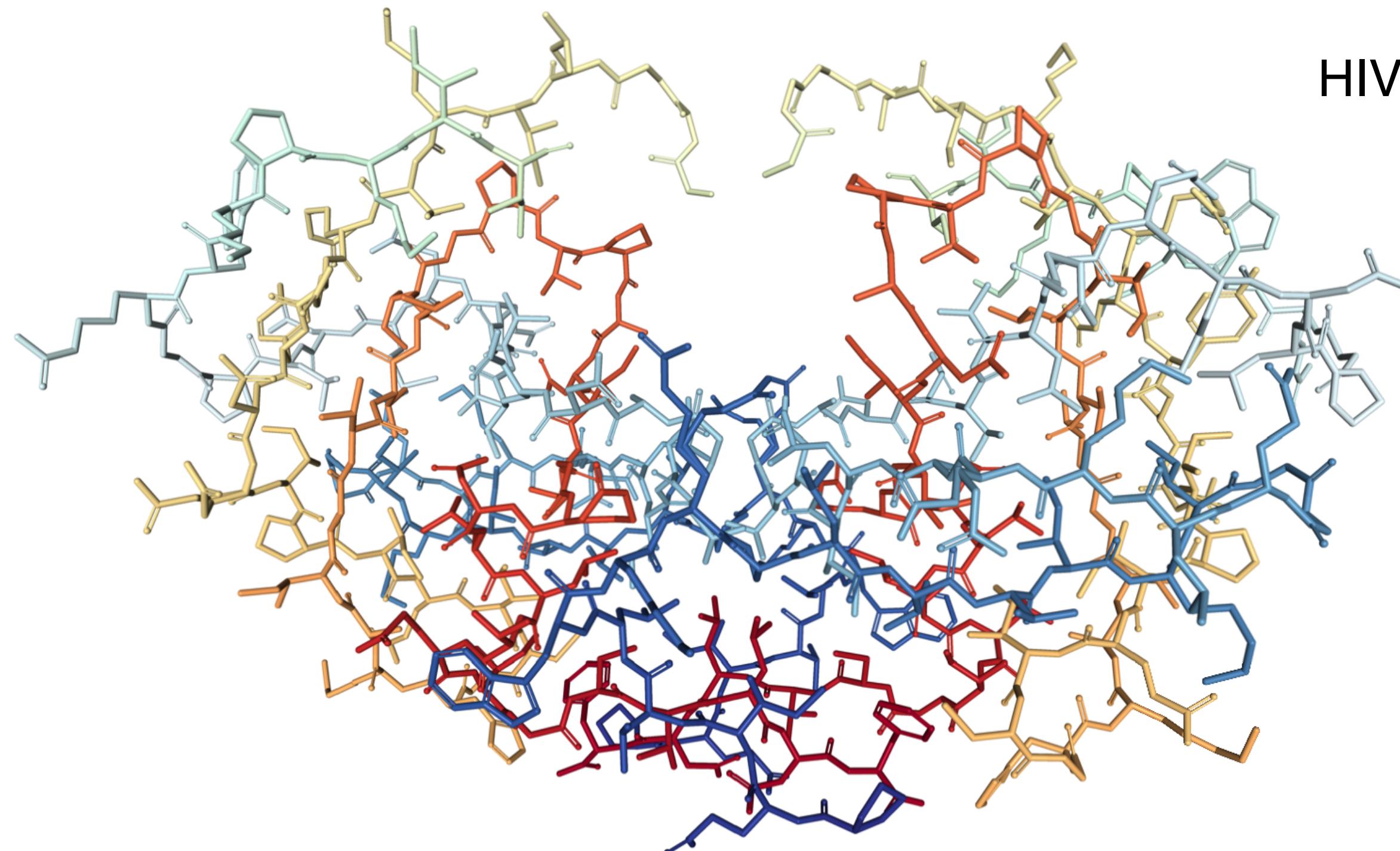
(c) 2° structures



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



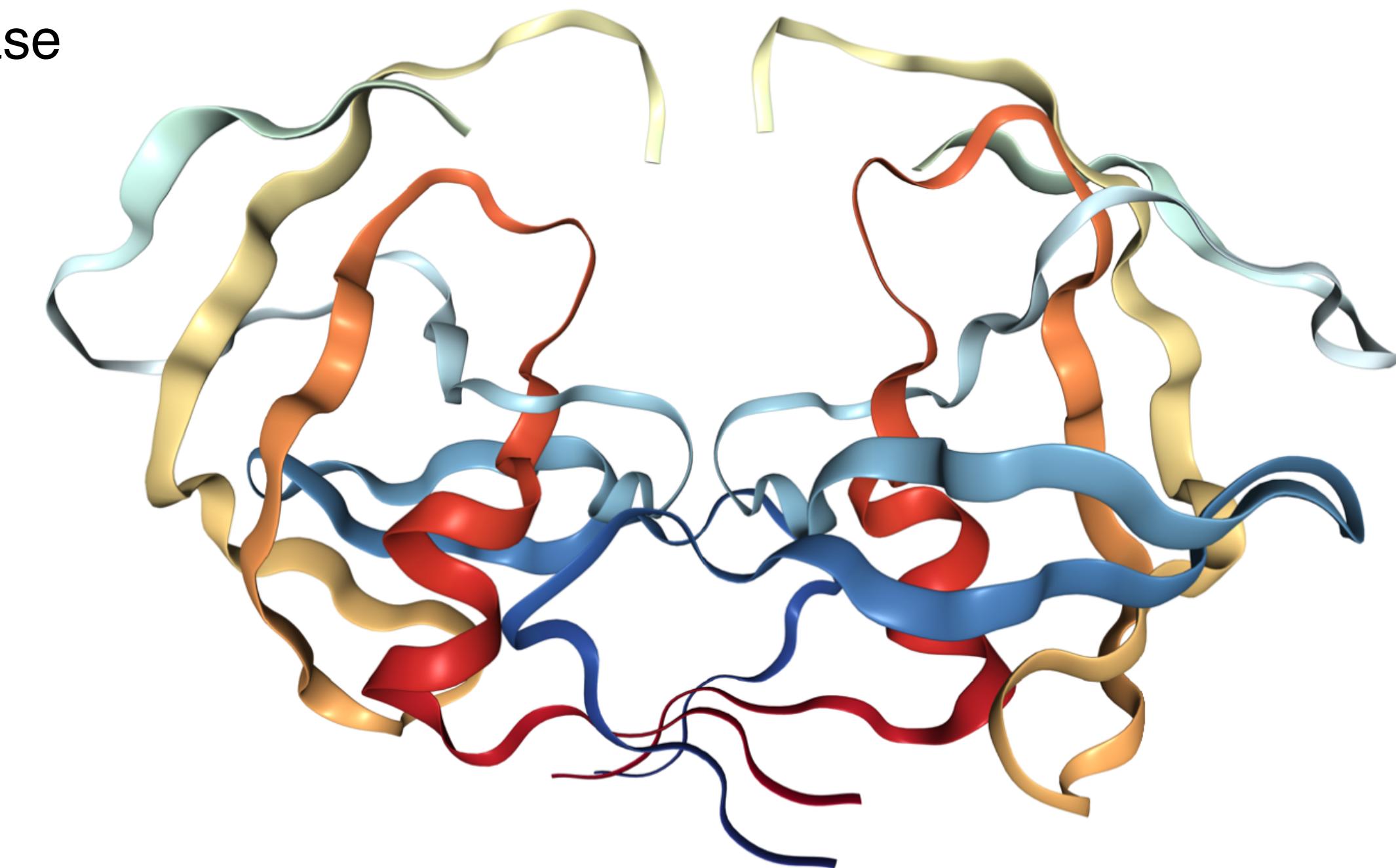
# Proteins often form folded tertiary structures



“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

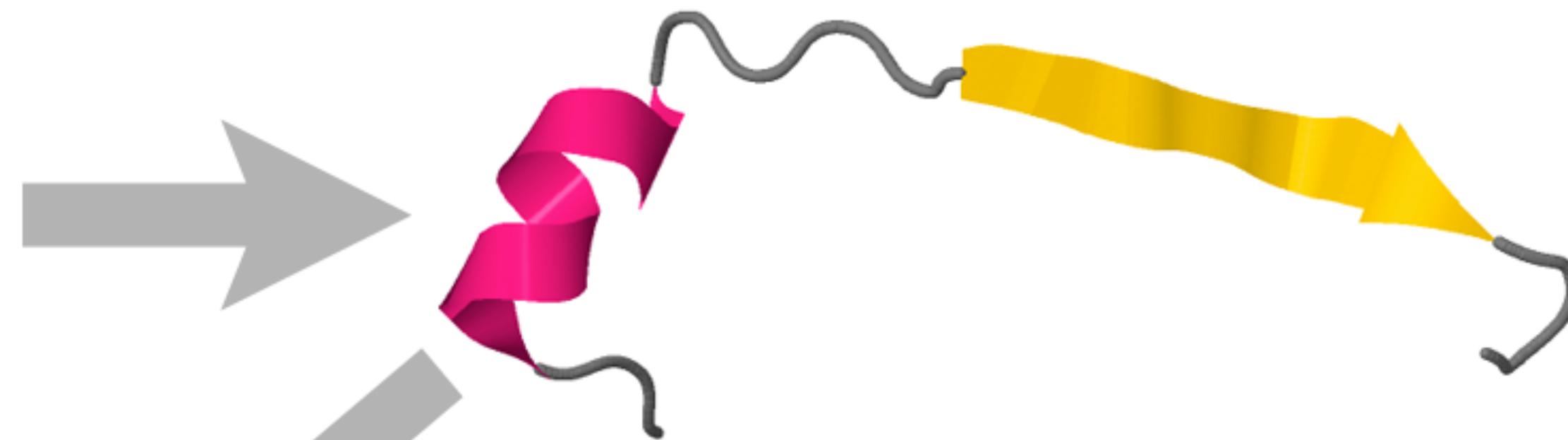
3-letter code

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

1-letter code

**K**TYFPHFDLSH**G**

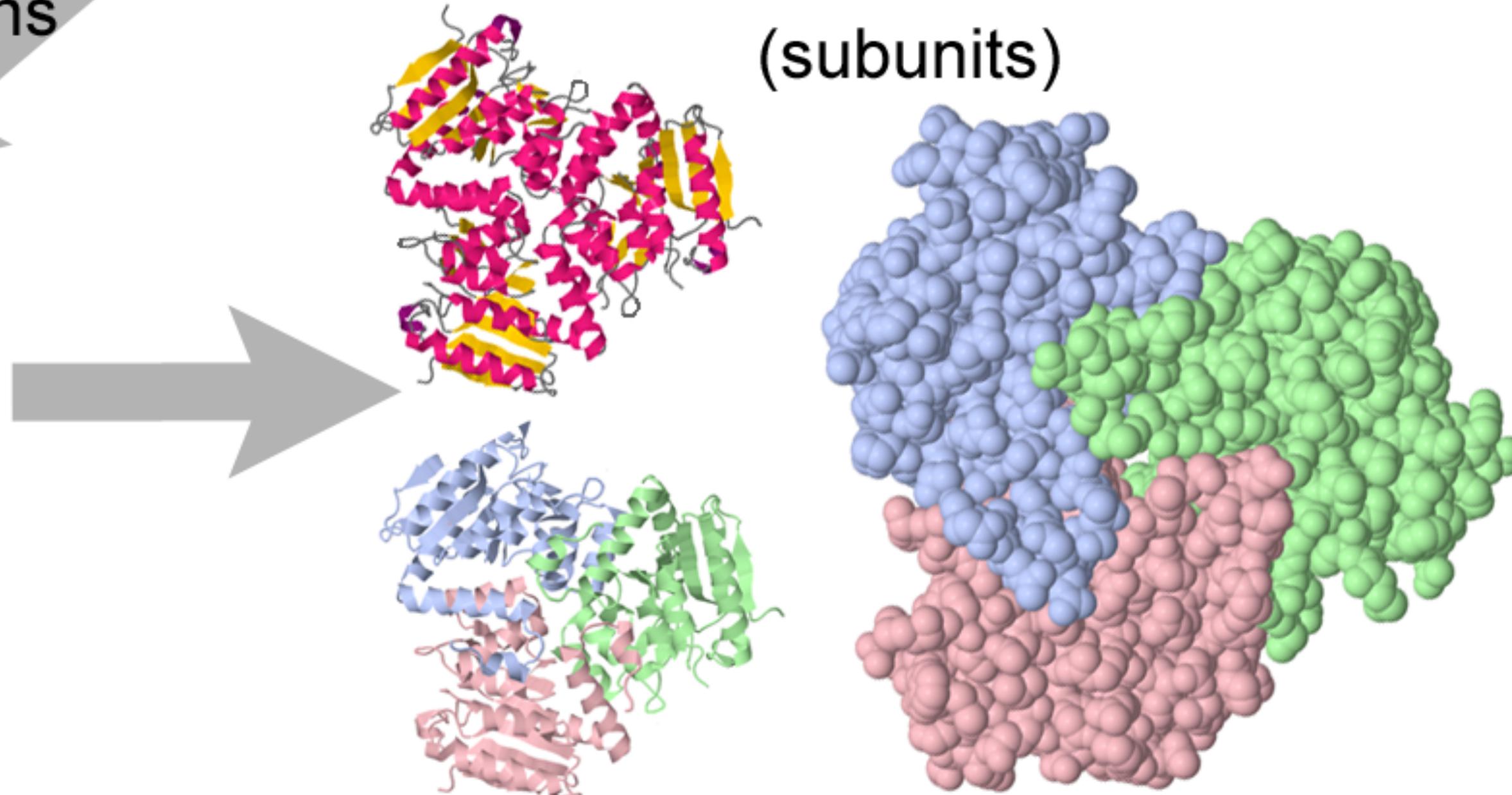
**Secondary Structure** =  
**alpha helices**, **beta strands**



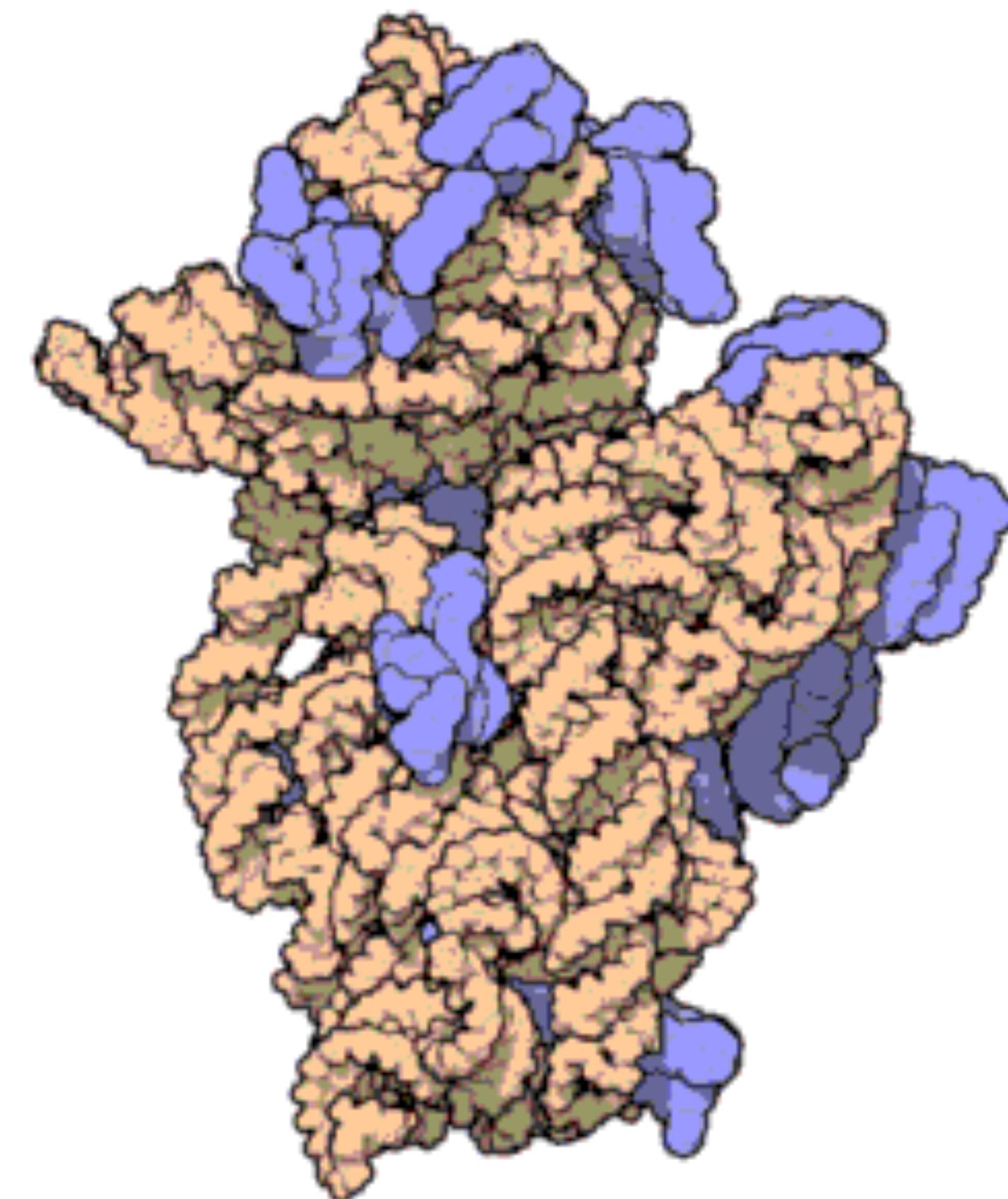
**Tertiary Structure** = fold  
helices and strands into domains



**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

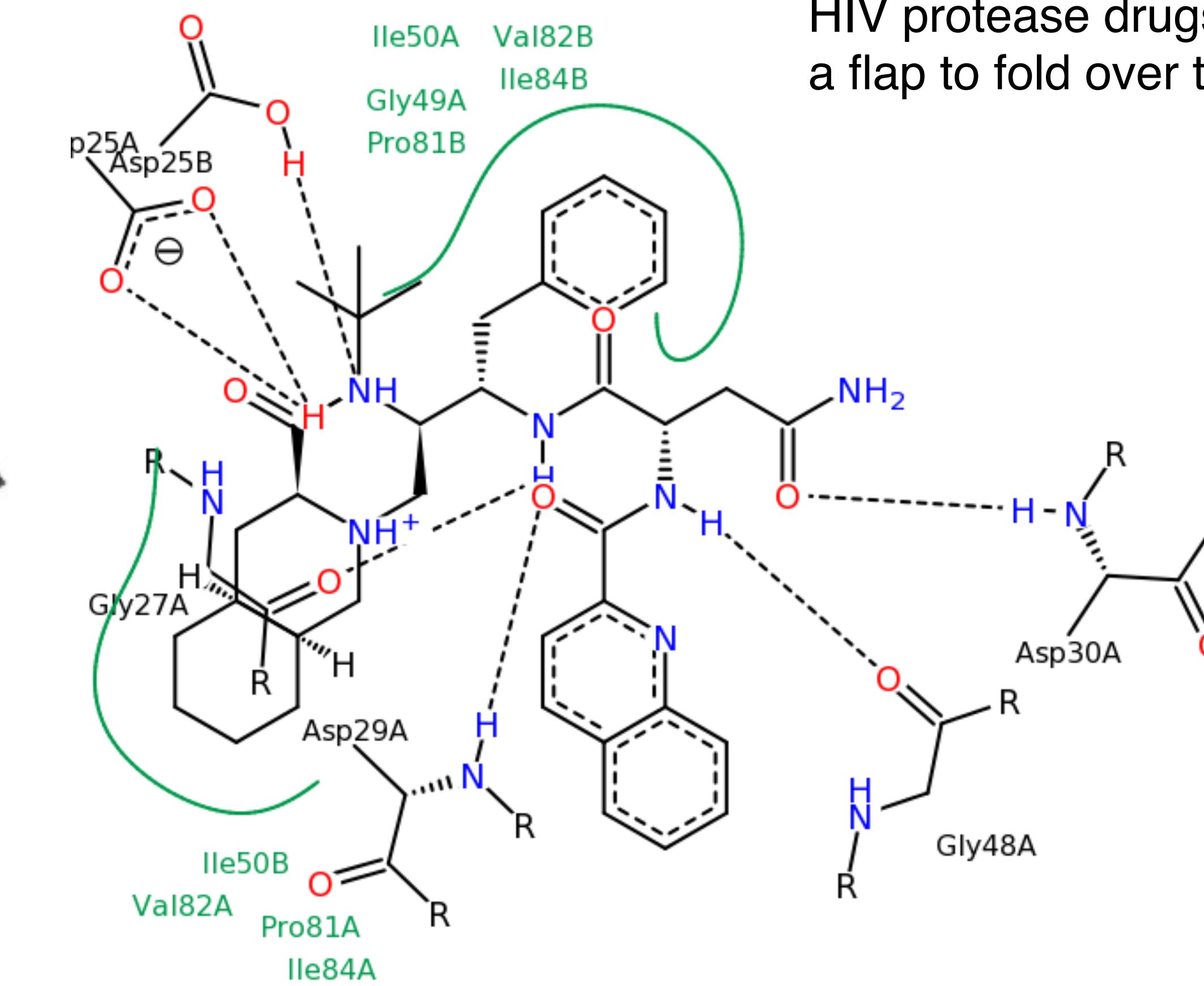
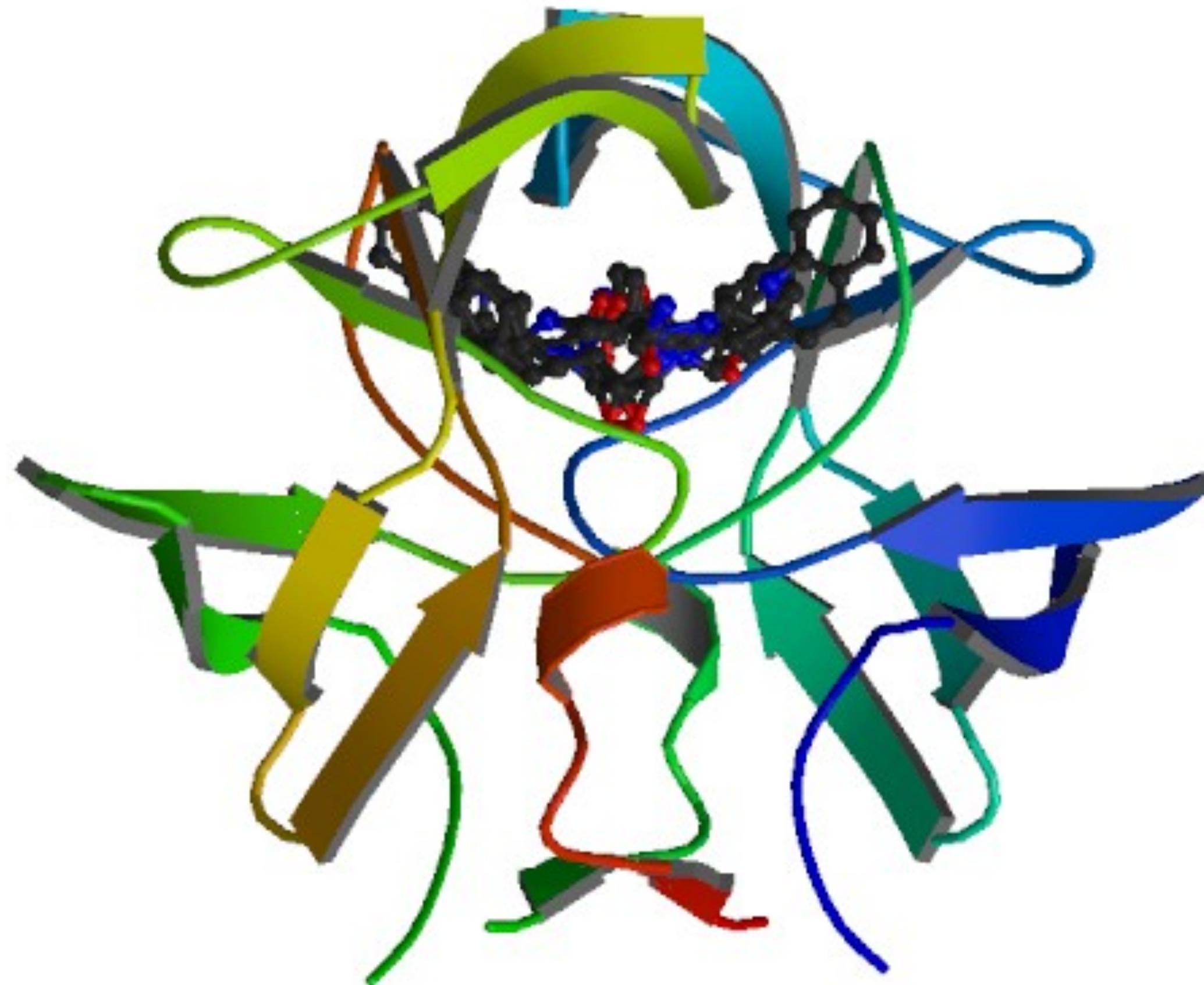
# Review Questions

- 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

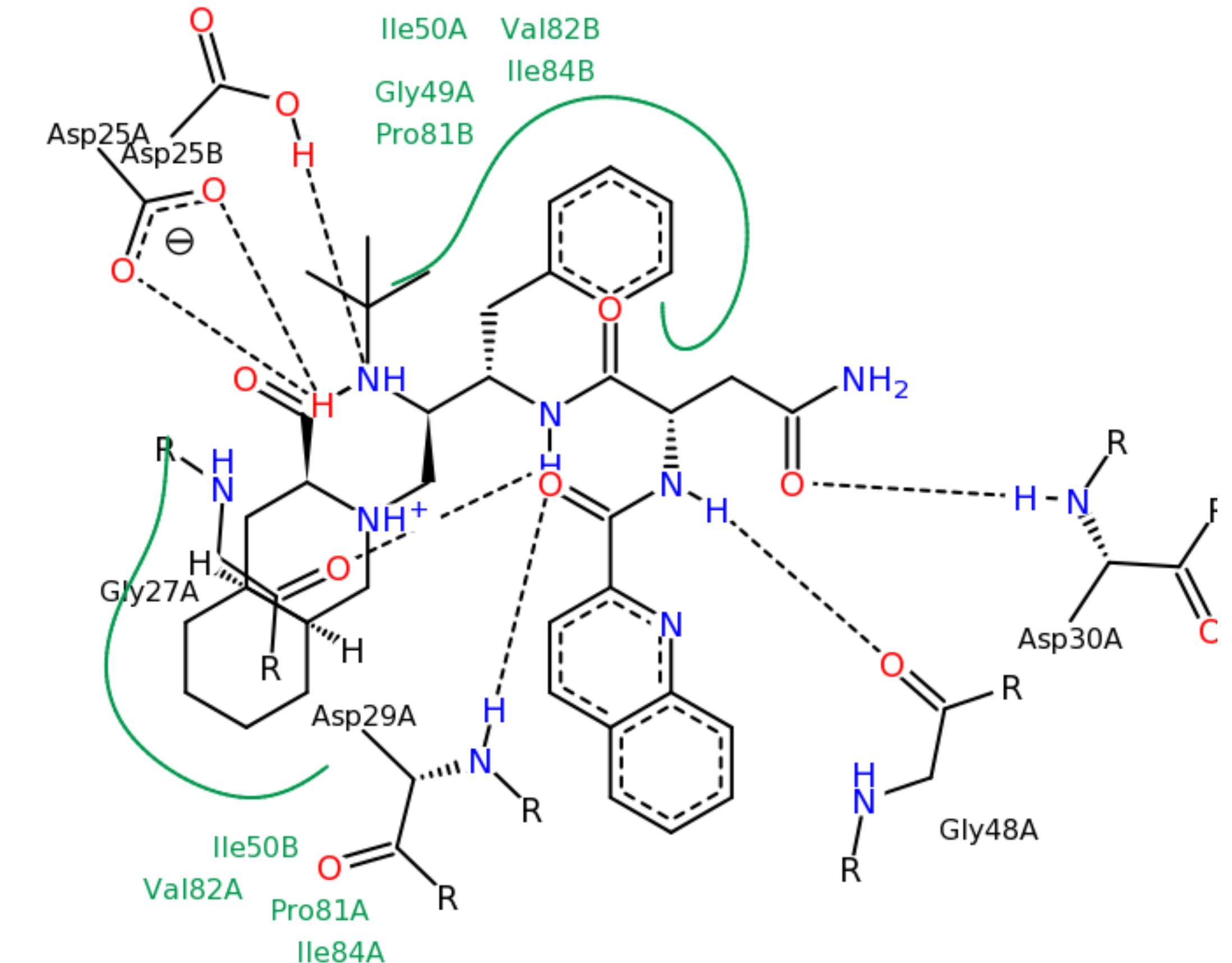


HIV protease drugs often cause a flap to fold over the active site

[http://www.rcsb.org/pdb/101/motm\\_discussed\\_entry.do?id=1hxh](http://www.rcsb.org/pdb/101/motm_discussed_entry.do?id=1hxh)

# 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](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>

# **Exercise 2: Structural visualization and alignment**

[https://colab.research.google.com/github/daveminh/Chem456-2024F/blob/main/  
exercises/02-Structural\\_Visualization.ipynb](https://colab.research.google.com/github/daveminh/Chem456-2024F/blob/main/exercises/02-Structural_Visualization.ipynb)