QUATERNARY STRUCTURE

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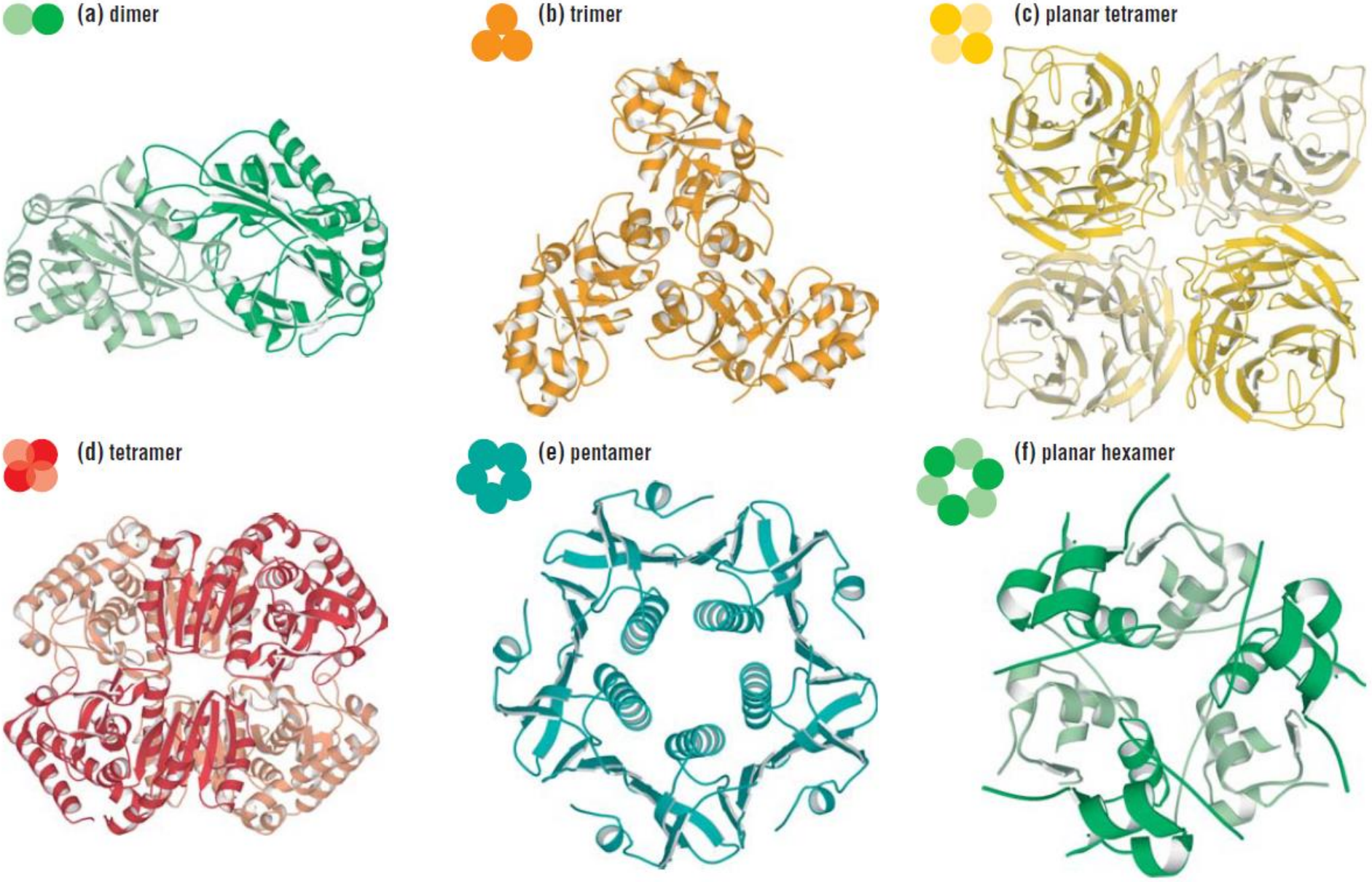
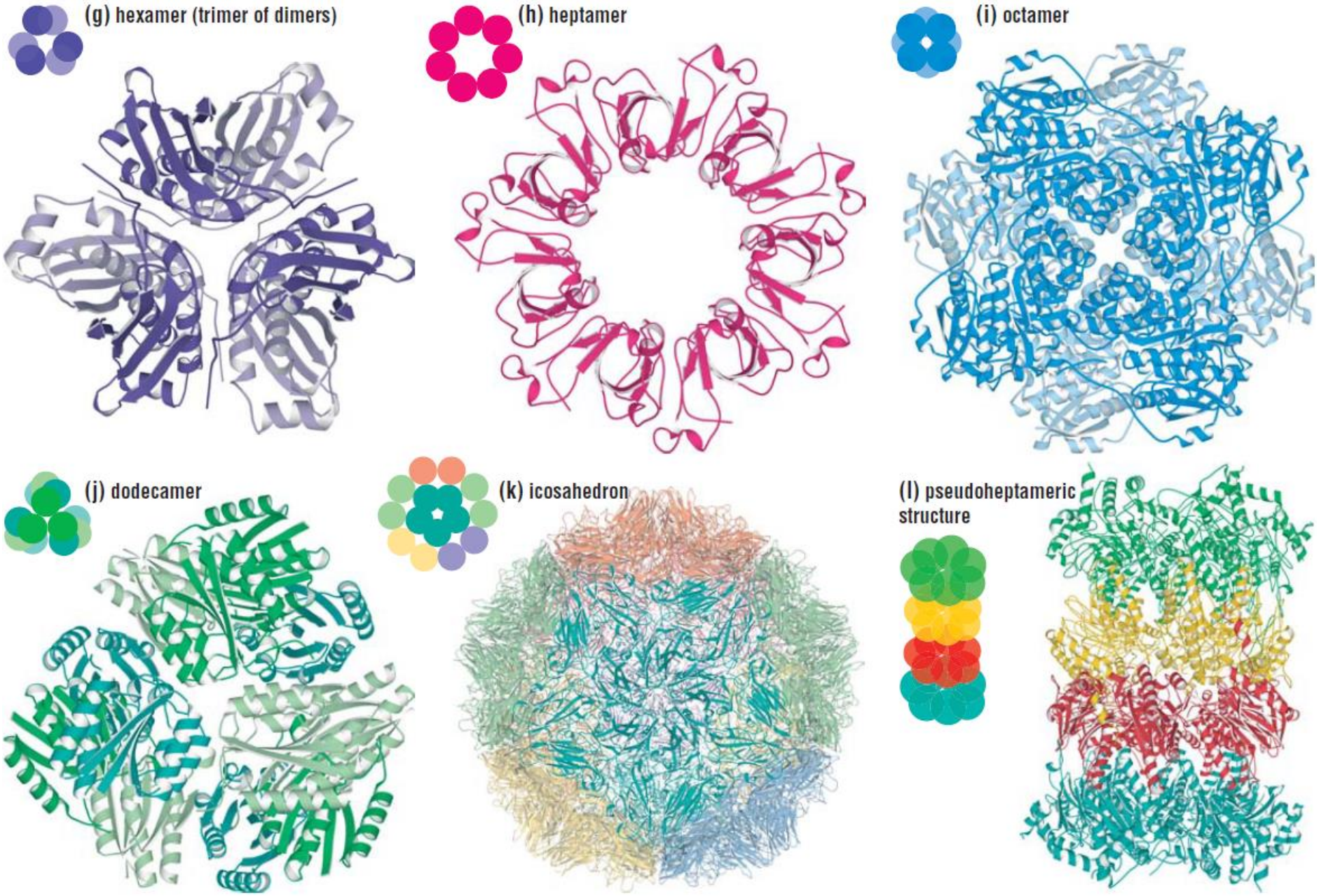
SUSTC

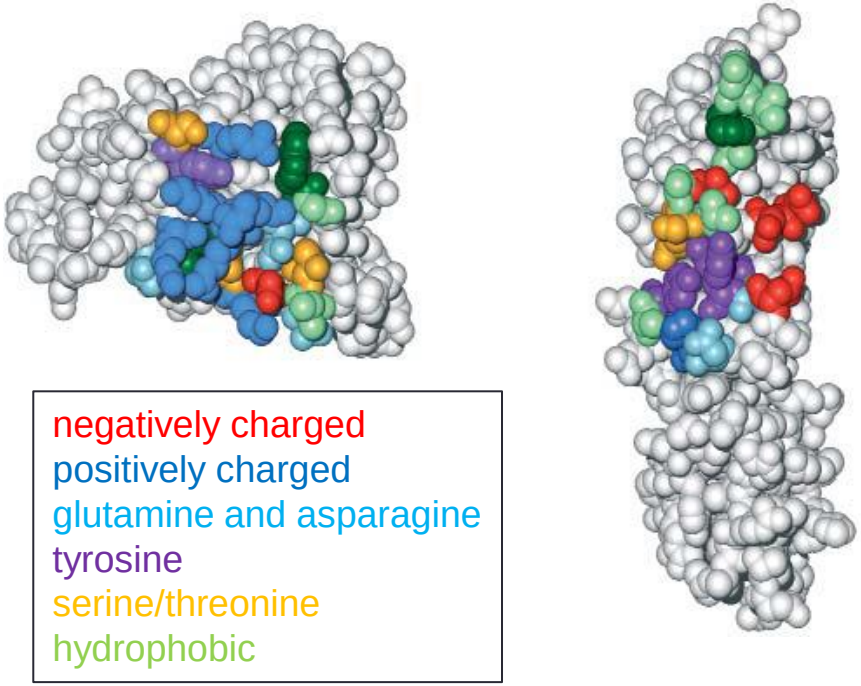
Multi-subunit Protein

- Functional protein often organized with multiple folded polypeptide chains (subunits)
  - Assembled via noncovalent forces
- Two types of quaternary organization
  - Homotypic – association between identical or nearly identical subunits
  - Heterotypic – association between very different subunits
- Numbers of subunits
  - Monomer
  - Oligomer
    - Dimer (2) \ Trimer (3) \ Tetramer (4) \ Pentamer (5) \ Hexamer (6) \ Heptamer (7) \ Octamer (8) \ nonamers (9) \ Dodecamer (12) \ eicosamer (20) …
  - Polymer


(a) dimer
(b) trimer
(c) planar tetramer
(d) tetramer
(e) pentamer
(f) planar hexamer


(g) hexamer (trimer of dimers)
(h) heptamer
(i) octamer
(j) dodecamer
(k) icosahedron
(l) pseudoheptameric structure

Surface Complementarity and interface



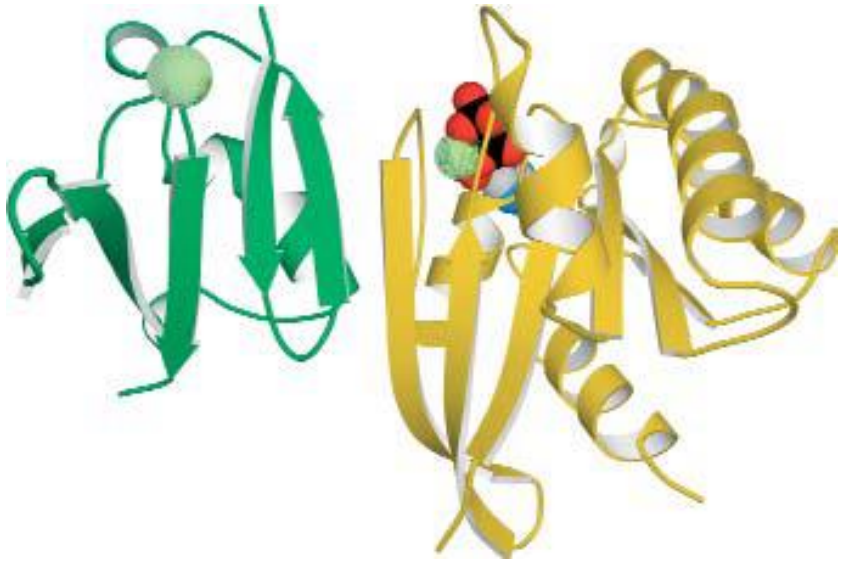
negatively charged
positively charged
glutamine and asparagine
tyrosine
serine/threonine
hydrophobic

“Open-book” view of the complementary structural surfaces that form the interface between interleukin-4 (left) and its receptor (right)

- Specific intermolecular interactions depend on complementarity
- Complementary shape
  - Protein surfaces are irregular
- Complementary weak interaction
  - Hydrogen-bond donors are opposite acceptors
  - Nonpolar groups are opposite other nonpolar groups
  - Positive charges are opposite negative charges
- Intermolecular interface
  - The surface portion that are buried by interacting molecule
  - Usually, larger buried surface area, higher binding strength
- For a complex to be stable long enough to function, the strength of binding must be greater than about 15–20 kJ/mol

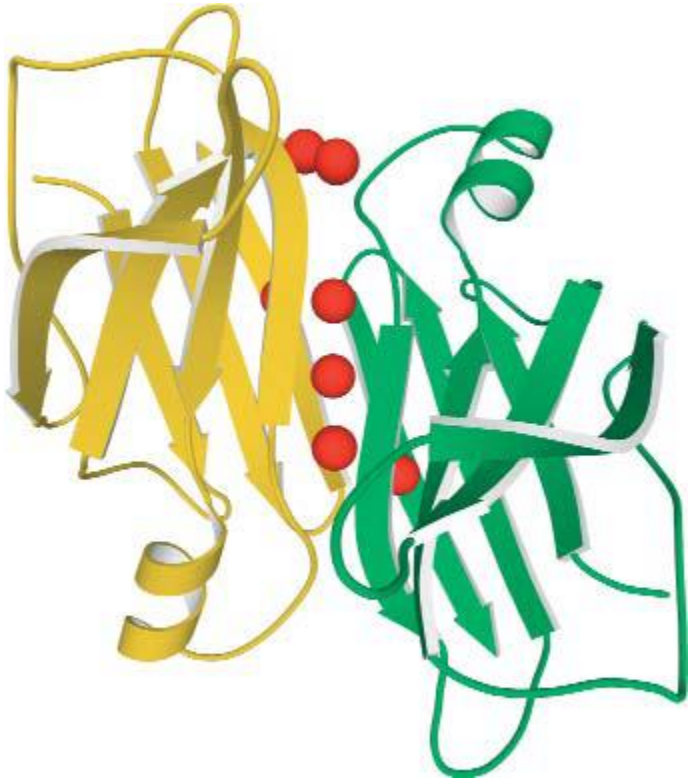
Interactions contribute to the formation of intermolecular interfaces

- Same as weak interactions for stabilizing tertiary structure
  - Hydrophobic interaction
  - Hydrogen bonding
  - Charge-charge interaction
  - Salt bridge
  - van der Waals interaction
- Very stable oligomers tend to bury a large hydrophobic surface area between subunits
- Easy assembly and dissembly employ more polar interactions
- Hydrogen bonds provide much of the specificity for complex oligomerizations
  - Hydrogen bonds are highly directional
  - They orient interactions between subunits



The signal transduction proteins Rap (left) and Raf (right) both contain β-sheets with exposed edge strands. These proteins form a heterodimer by using the edge strands to complete a continuous extended beta sheet that traverses both molecules. (PDB **1GUA**)

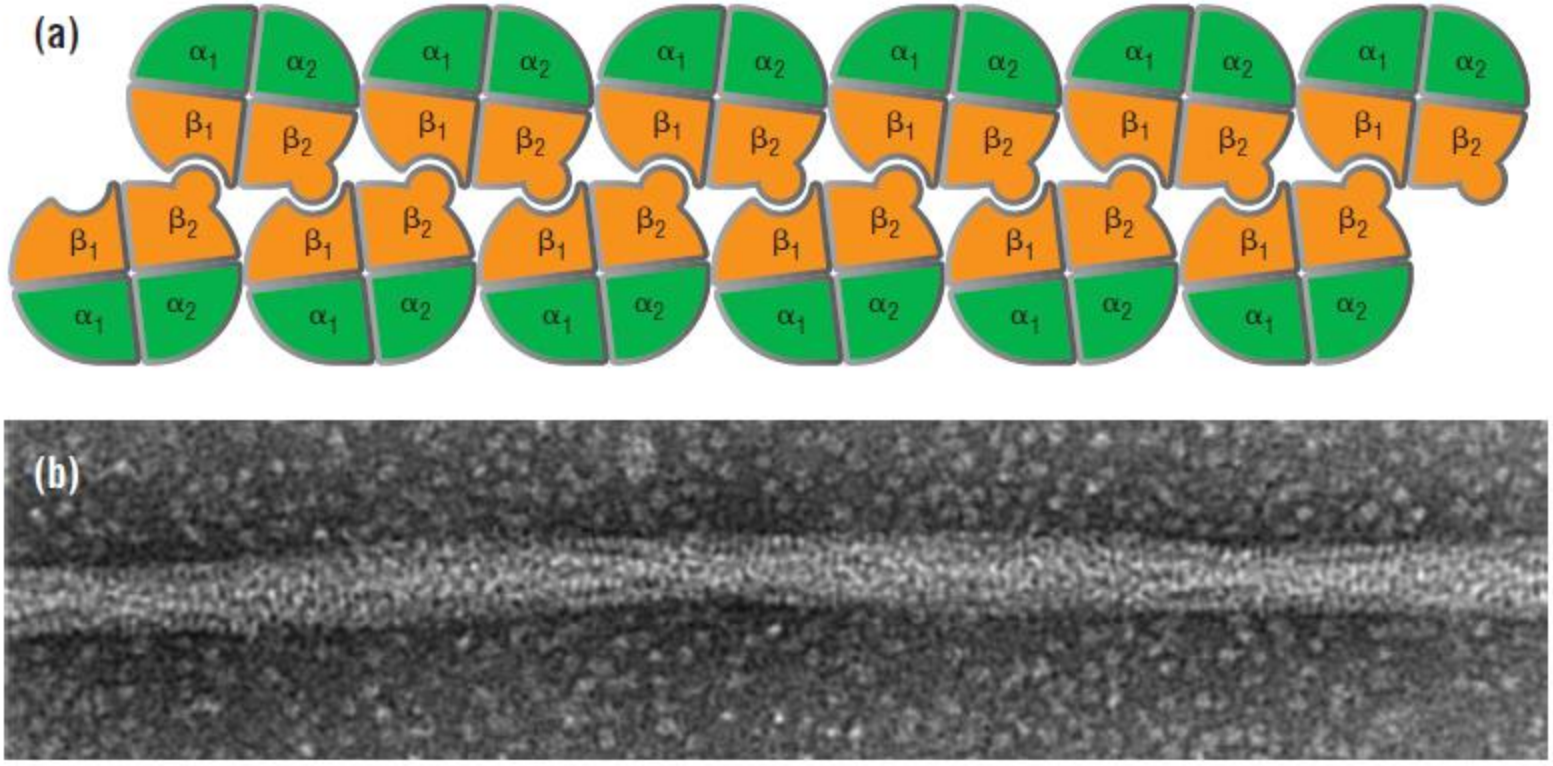
Water molecules may reside at interface



A network of water molecules trapped between the two subunits of a dimeric plasma protein, pre-albumin. (PDB **1BM7**)

- Forming a H-bond network to stabilize the interface

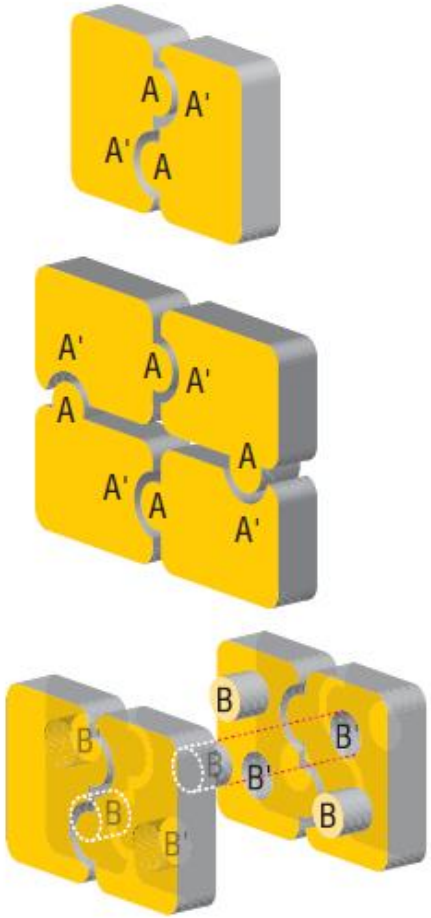
Inappropriate quaternary interaction

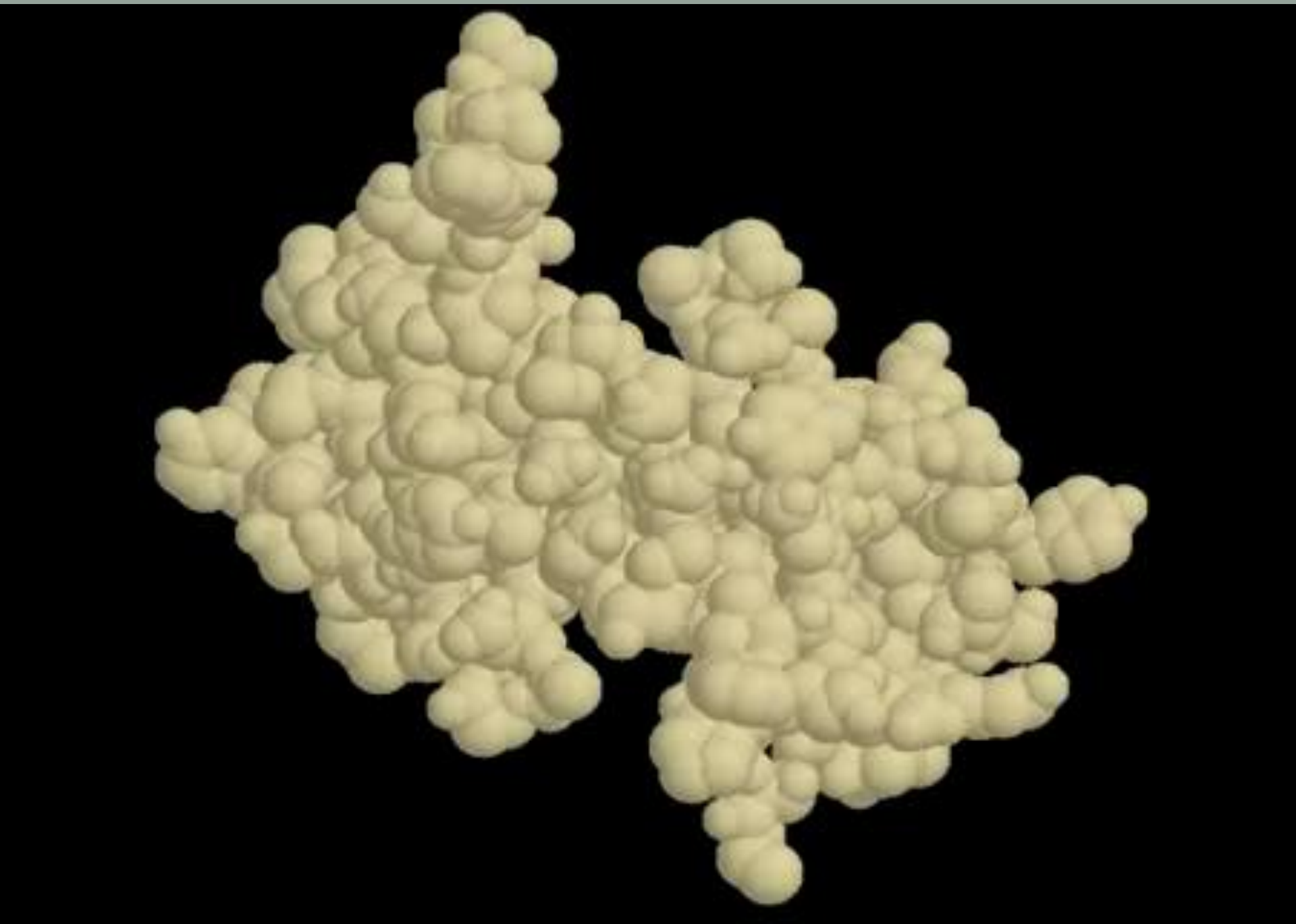


Sickle-cell hemoglobin

Symmetric protein assembly by identical subunits

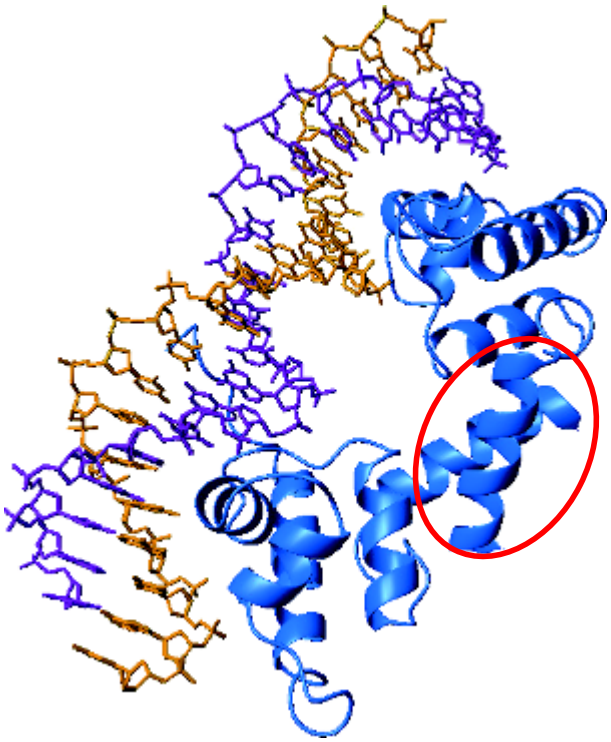
- Protein assemblies built of identical subunits are usually symmetric
- Protomer
  - The asymmetric unit from which a symmetric complex is built
- Pseudosymmetry
  - Nearly identical subunits





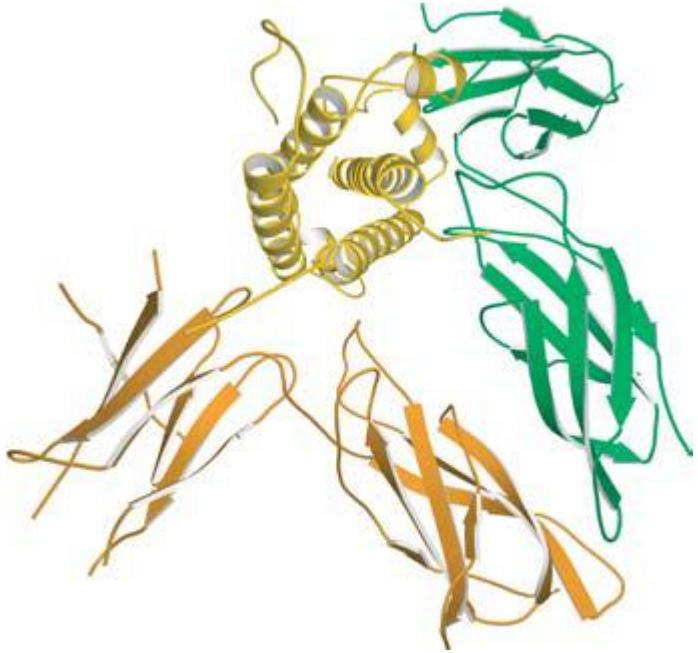
Dimeric DNA binding proteins

- TATA-binding protein
- λ repressor
  - Containing HTH motif
  - Dimerization allows the two HTH motifs to bind to two successive major grooves along a sequence of DNA
- Leucine zipper
  - Coiled-coil



The structure of the N terminal domain of the λ repressor in the presence of DNA. The fifth helix forms part of the dimerization domain that allows two monomer proteins to function as a homodimer. (PDB **1LMB**)

Asymmetric protein assembly by identical subunits



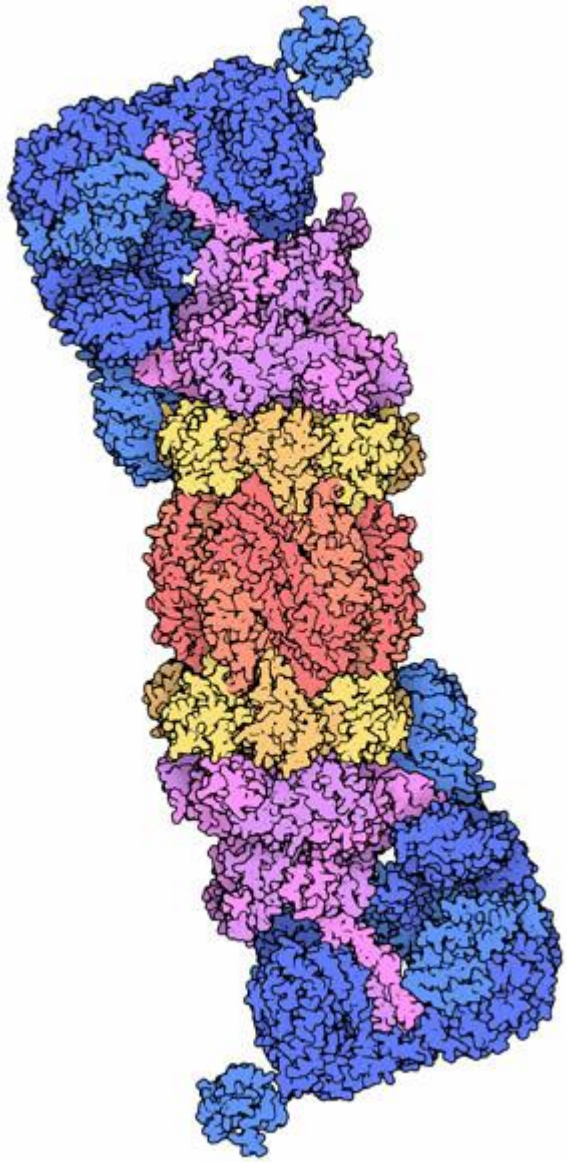
Human growth hormone (yellow) complexed with two identical molecules of its receptor (orange and green). The receptor is a membrane protein, but only the extracellular hormone-binding portion is shown. The plane of the membrane is indicated by the slanted line. A molecule of the monomeric hormone binds to two identical receptor molecules. Similar regions of the two receptor molecules are used to bind two distinct regions of the hormone; the conformational flexibility of these regions allows for this versatility. (PDB **3HHR**)

Why quaternary structure

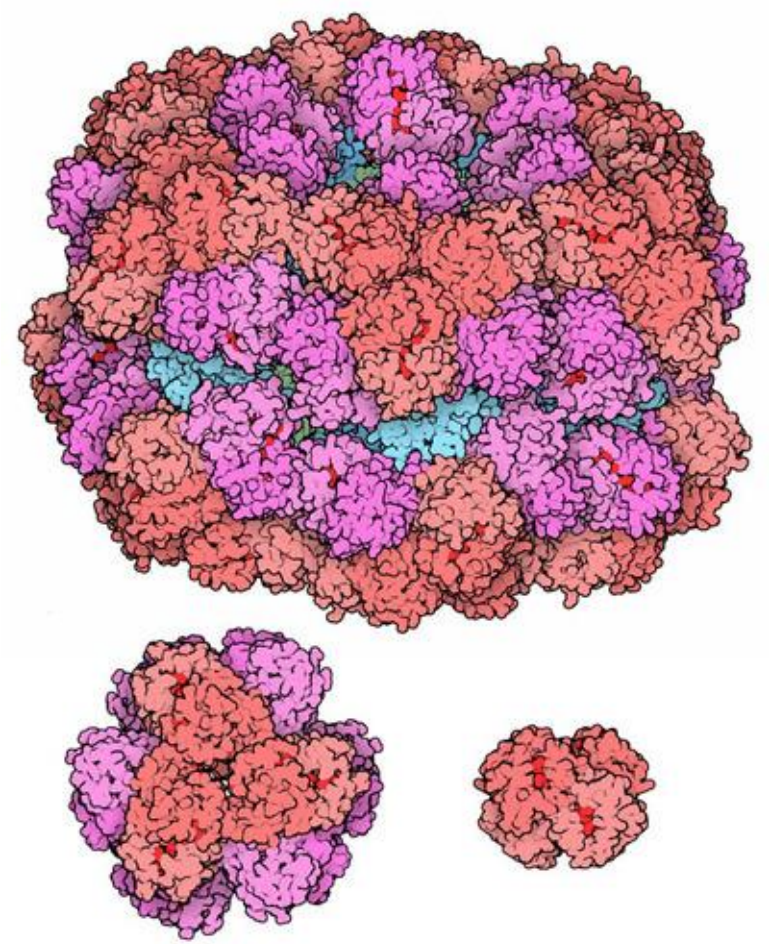
- More regulations, like allostery
  - Hemoglobin
- Enhanced specificity for recognition
  - Dimeric DNA binding protein
- For delicate and complicate work
  - Giant protein assembly
- Other reasons
  - Need to be investigated case by case

Huge protein assembly

- Huge enzymes
  - Fatty acid synthase: 12 chains
- Protein cages
  - Ferritin: 12-24 chains
  - Chaperonins
    - GroEL/ES: 21 chains
  - Proteasome: 42-46 chains
  - Clathrin cage: 28-36 chains
- Virus capsid
  - Icosahedral type: 60*T chains
- Structural proteins
  - F-actin
  - Microtubule



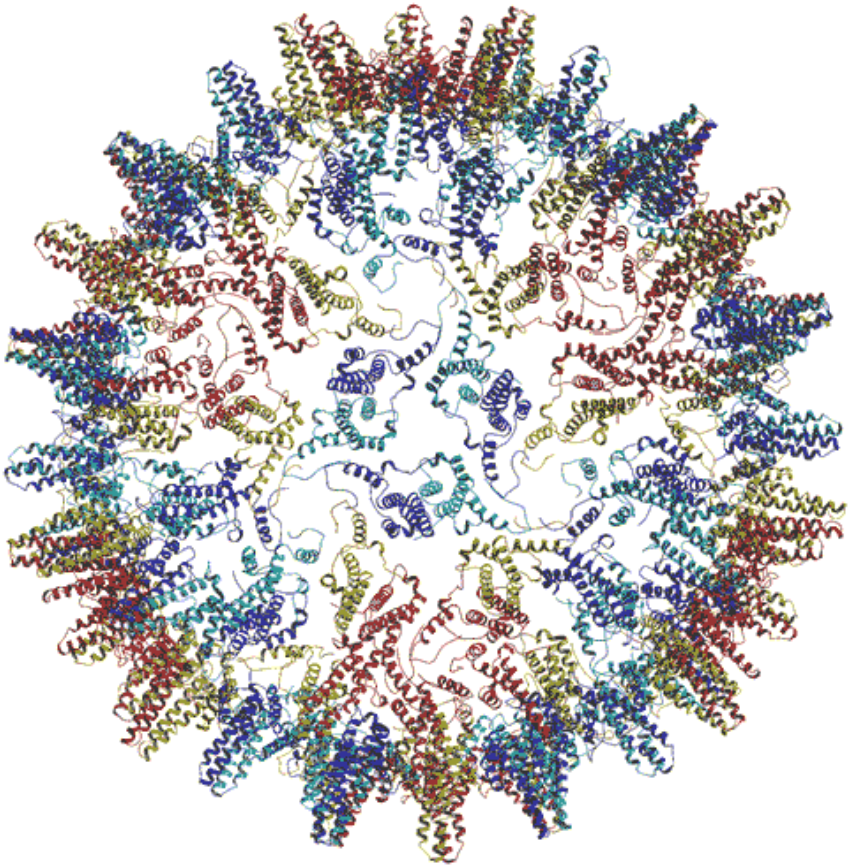
Erythrocruorin, a huge version of hemoglobin



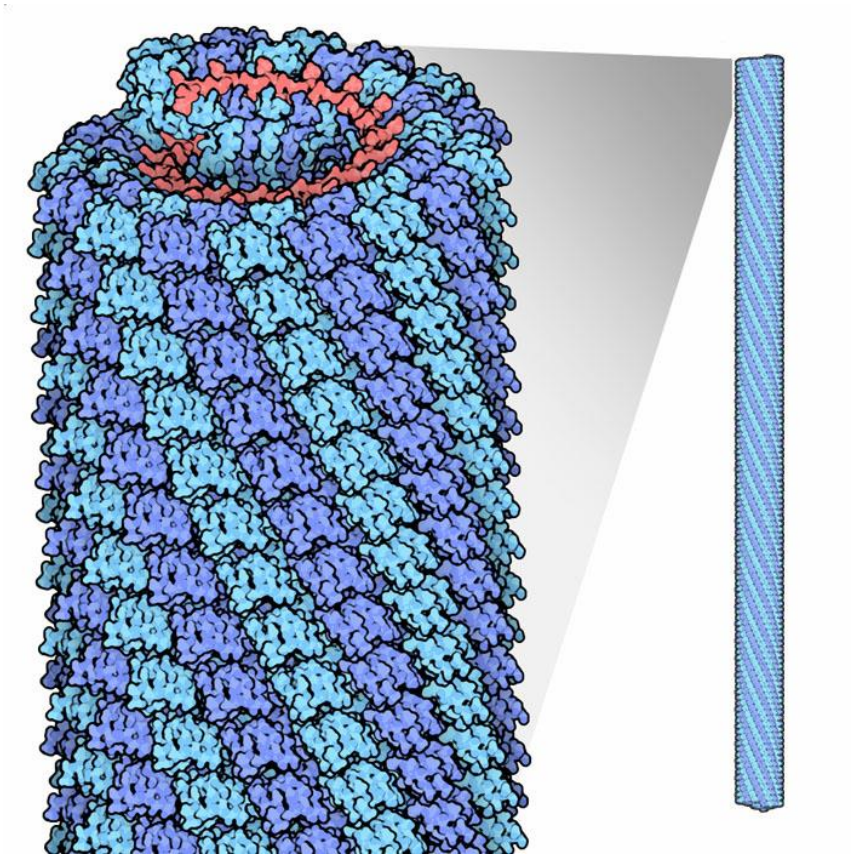
Hemoglobins from earthworm (top, PDB **2GTL**), tube worm (bottom left), and human (bottom)

- Earthworm's hemoglobin
  - 144 globin chains
  - 4 similar types (36 copies of each)
  - All have heme group to carry oxygen
- Why so big?
  - It floats freely in the liquid that flows through vascular system, and the large size may help reduce leakage of hemoglobin.
  - It allows lots of opportunities for interaction between subunits, and shows even more cooperativity in binding and release of oxygen.
  - It is a way to pack a lot of functional sites into one particle, which can help keep the viscosity of the solution manageable while having a high concentration of sites.

Virus capsid is a giant protein complex

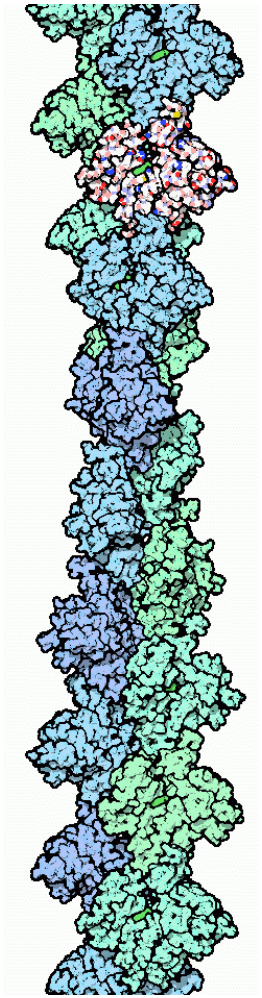


Hepatitis B capsid, T=4
(PDB **1QGT**)

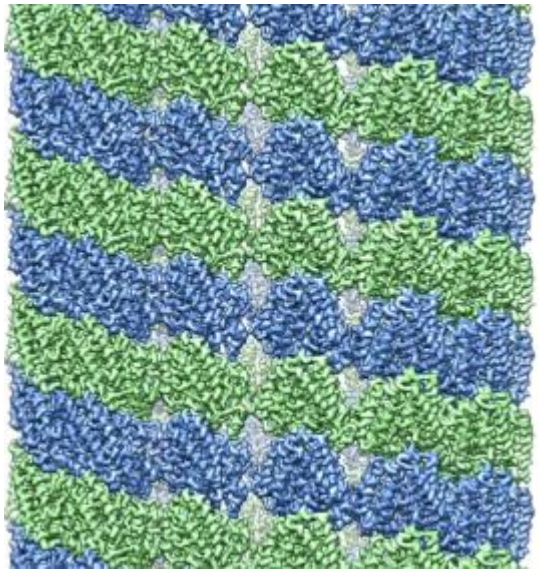


Tobacco mosaic virus, with the RNA genome in red (PDB **2OM3**)

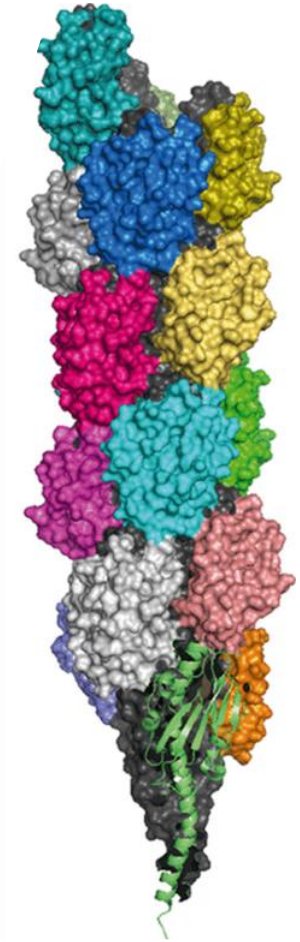
Helical symmetry is one of common types in huge protein complexes



F-actin



Microtubule



N. gonorrhoeae pilus (PDB **2HIL**)