

# Symmetry in Protein Structures

## 1. Introduction

Proteins are fascinating molecules. They have been selected and made to perform so many tasks that one could possibly imagine such as collecting sun light, transporting materials, provide mechanical strength or even fighting with viruses or bacteria etc. Yet proteins are relatively simple molecules. A protein (or a subunit) consists of a number of amino acids (there are 20 types of them) connected into a linear chain. The sequence of amino acids specified a protein. For a protein to perform its function, it has to be folded into a three dimensional structure which then may be aggregated with other protein subunits to produce a bio-molecular machine or component.

With many protein structures (now over 16,000 proteins) solved and a lot of experiments done over the past decade, it has been found that most of the proteins form symmetrical oligomeric complexes consisting of two or more identical subunits. Symmetry seems to be a very important ingredient in understanding protein structures and functions.

## 2. Symmetry in Protein Structures

Protein structures can be classified using the crystallographic point groups, translational symmetry and the functions related to the symmetry. Figure 1 shows examples of proteins for each crystallographic point group symmetry. The **Cyclic Groups** have one rotational axis of symmetry, for example, C1 symmetry (monomeric protein), C2 symmetry (dimeric protein). The proteins in this group are specialized in functions that require directionality or sidedness such as a formation of a hollow tube or chamber or interaction with membranes. The **Dihedral Groups** has higher symmetry i.e. it contains an additional perpendicular axis of two-fold symmetry. This symmetry provides more variety of interfaces that leads to more stability and better allosteric control. The **Cubic Groups** consist of a three-fold symmetry combined with a non-perpendicular rotational axis. This group of protein structure plays an important role in storage and transport particularly the icosahedral symmetry. **Helical symmetry** is also employed by combining translation with rotation about the direction of translation to create extended filaments. The symmetry selected by proteins depends on their function, stability, the number of subunits and folding efficiency.

## 3. Why build Large Symmetrical Oligomeric Proteins?

If large oligomeric proteins are very common then there must be some selective advantage driving the evolution of monomeric species into **large** oligomers; and some driving forces making them symmetric. There are many reasons in making proteins large. Functional requirement such as having multiple binding sites could be one reason that causes protein to be big. Small solvent exposed surface area and high stability against denaturation could also be other reasons. By having protein consisting of many small subunits, it may be easier for the **oligomeric** protein to be made with high fidelity. It requires less information for coding the protein. Usually closed **symmetric** system tends to have lower energy than asymmetric one as the intersubunit interactions is maximized. So symmetry could make proteins more stable and could to the driving force that make proteins symmetric.

#### 4. Symmetry depends on Functions

The symmetry of a protein structure is limited by the required functions of the protein. For example membrane protein structures are very directional. They are oriented in a specific direction (usually with its axis perpendicular to the membrane) to indicate "inside" from "outside" of the cell or vice versa. This direction helps them to function correctly e.g. to transport ions or small molecules through cell membrane. Figure 2 shows ATP synthase which is a membrane protein that makes ATP from the energy of proton gradient across the mitochondrial membrane. Since the transmembrane part (cylinder part in the figure) of ATP synthase has cyclic symmetry, they are all oriented in the same direction perpendicular to the internal surface of the mitochondrial membrane. This makes sure that all the ATPs produced are on one side of the membrane.

#### 5. Symmetry Breaking in Oligomeric Proteins

Symmetry of oligomeric proteins is often broken for functional purposes. There are many ways in which this is accomplished. In some viruses (see Figure 3), **Quasisymmetry** is employed as a way to pack protein subunits onto icosahedral shells. For Clathrin (see Figure 4), **Pleomorphic Symmetry** (identical subunits that form many different structures) is used to pack its subunits onto Buckminstersfullerene structures. **Pseudosymmetry** is reflected strongly in the case of Hemoglobin (see Figure 5) as it forms tetrameric structure from two alpha and two beta subunits which have similar structure. **Symmetry Mismatch** due to the five fold symmetry of the icosahedral head and the six fold symmetry of the DNA connector (see Figure 6) and DNA has been proposed to explain the DNA injection mechanism ("vernier" mechanism) of bacteriophage.

#### 6. Conclusion

Both symmetry and symmetry breaking play important roles in shaping the structures of proteins under the constraints of required functions. More aspects of proteins structures and functions are still being explored. Little is known in detail about the dynamics of oligomeric proteins and its connection to its structure and function.

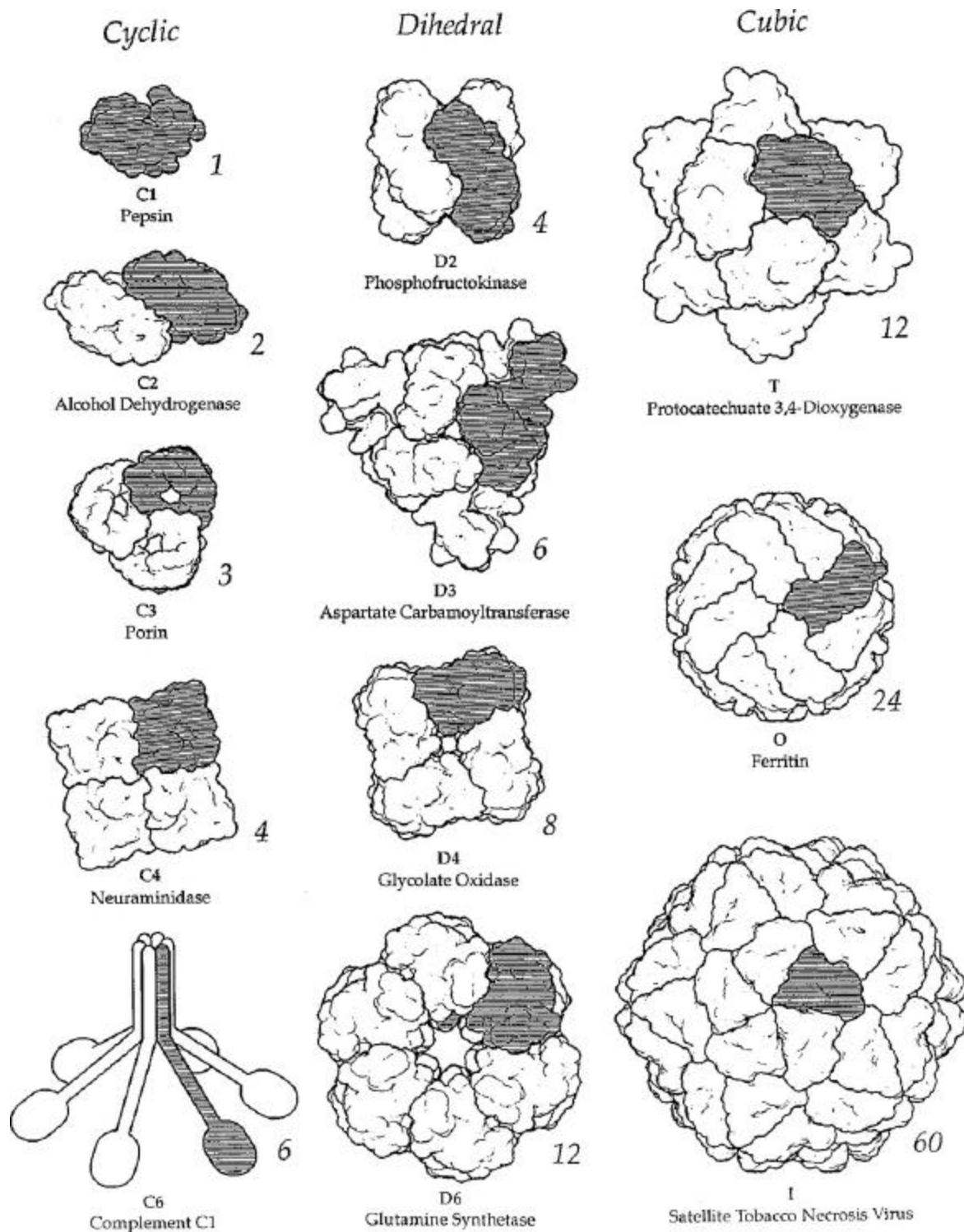
#### 7. References

Goodsell, D. S., Olson, A. J., Structural Symmetry and Protein Function, *Annu. Rev. Biophys. Biomol. Struct.* **29**, 105-153 (2000).

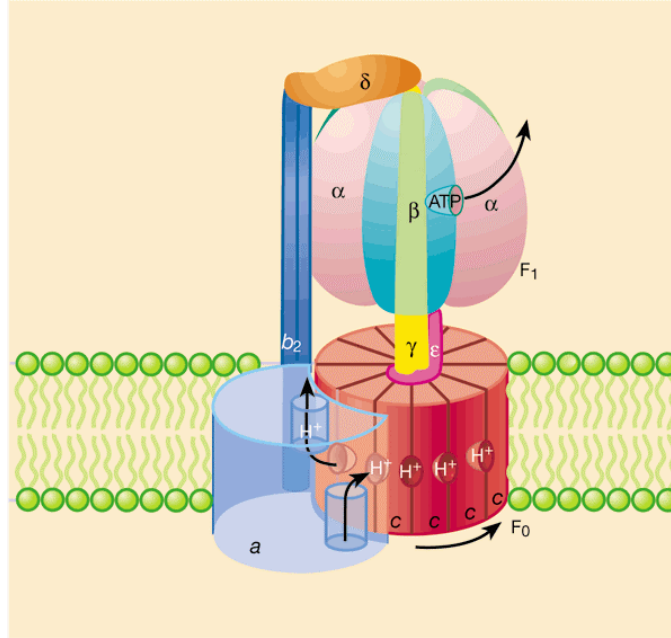
Boyer, P. D., Molecular motors: What makes ATP synthase spin?, *Nature* 402, 247-249 (1999)

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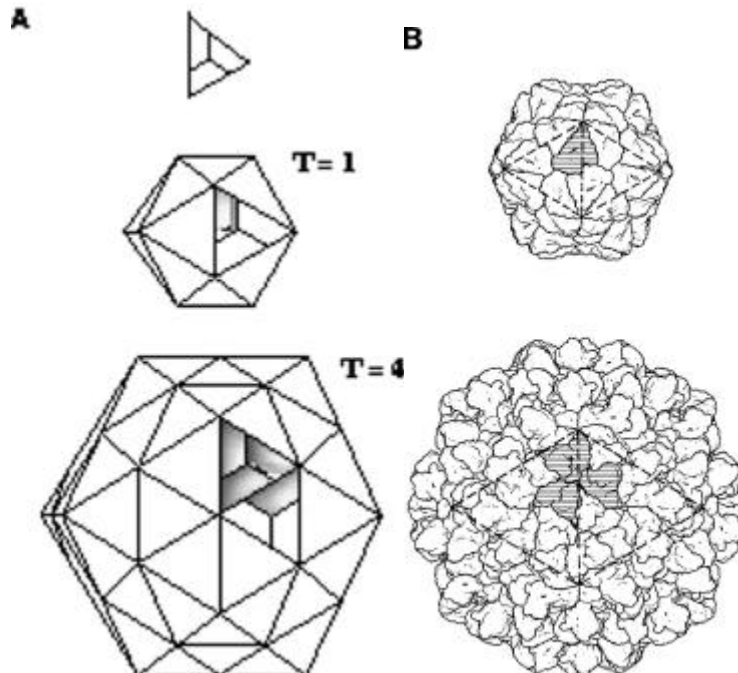
Protein Data Bank (<http://www.rcsb.org/pdb>).



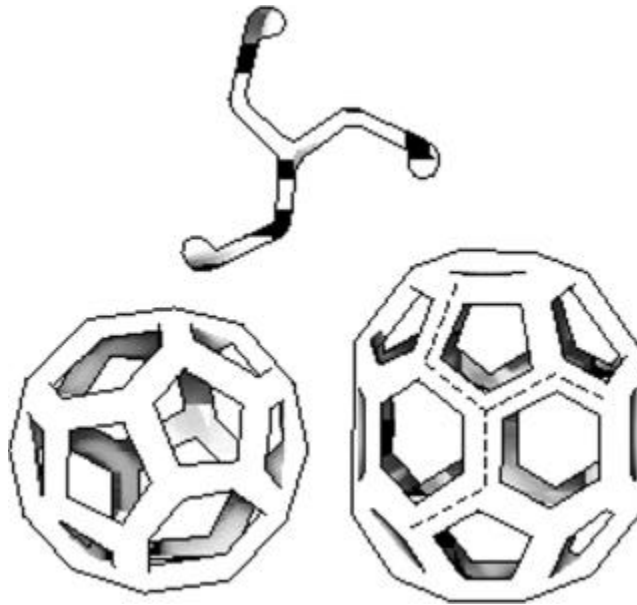
**Figure 1** Examples of proteins for each of the crystallographic point group symmetries. Point group symbols are included below each protein structure (e.g. C1 and D2). The number of identical subunits in each group is included to the right of the structure (e.g. 24 in octahedral group O). One subunit is shaded in each example. Protein Data Bank accession codes for all structures used in this figure are accessible via the Internet (<http://www.rcsb.org/pdb>).



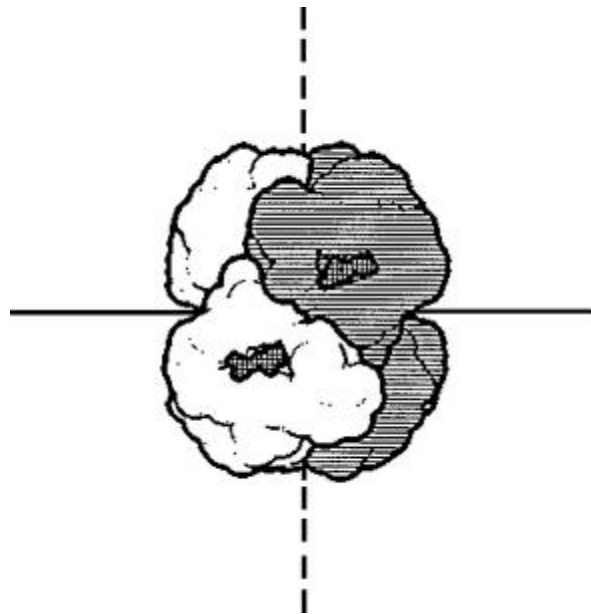
**Figure 2** Model of ATP synthase embedded in the lipid bilayer membrane. The top part of the ATP synthase always points towards the inside of the Mitochondria.



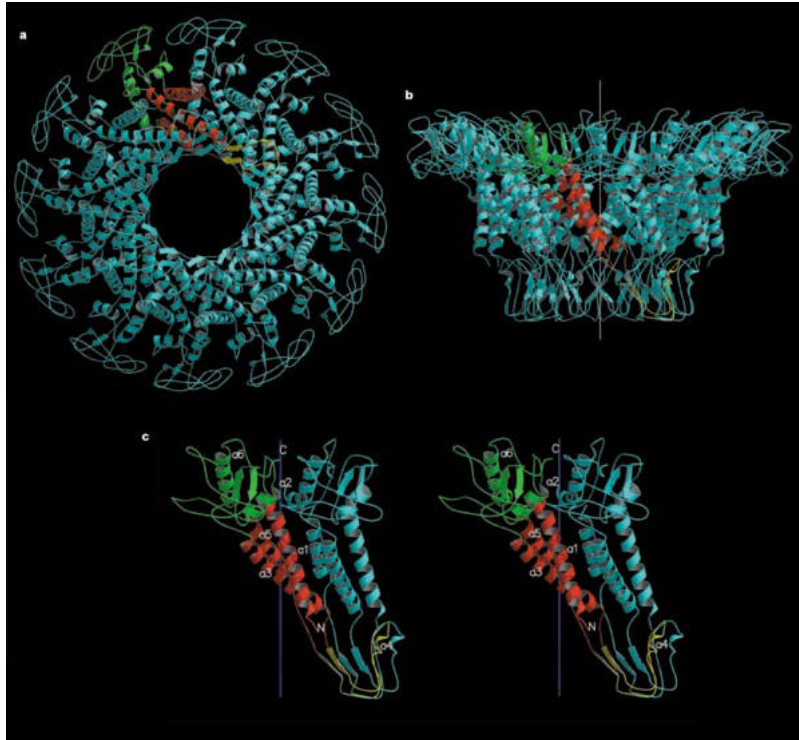
**Figure 3** A. Two Quasisymmetrical Icosahedral Shells and the basic triangular unit, B. (Top) Satellite Tobacco Necrosis Virus and a single subunit in the asymmetric unit; (bottom) Tomato Bushy Stunt Virus and three subunits



**Figure 4** (Top) Trimeric subunit of **Clathrin**. They arrange into a variety of geodesic structures. (Left) Soccer ball is rich in five-fold rings; (Right) larger structure add sixfold rings. The location of a subunit is shown in dotted lines in the right structure.



**Figure 5 Hemoglobin pseudosymmetry.** Hemoglobin is a heterotetramer of two  $\alpha$  subunits, shown in white, and two  $\beta$  subunits, shown shaded. The heme groups are shown in darker shading. A perfect two-fold axis relates the two  $\alpha$  and the two  $\beta$  subunits, shown as the horizontal line. Since the  $\alpha$  and  $\beta$  subunits are similar in sequence and structure, they may be related by pseudosymmetry, forming pseudo-two-fold axes vertically, shown with a dotted line, and perpendicular to the plane of the paper through the center of the tetramer.



**Figure 6 Connector structure.** It connects to a five fold vertex of icosahedral head of Bacteriophage. DNA is forced from the phage head to pass through the hole in the middle of the connector. **(Top Left)** The dodecameric connector seen from the tail looking towards the head; **(Top Right)** a side view with the pRNA-binding site at the bottom, showing the conical structure of the connector and the helical twist of each subunit around the 12-fold axis (white); **(Bottom)** a stereo diagram of a pair of monomers. One monomer is coloured red in the central domain, green in the wide-end domain that resides inside the capsid, and yellow at the narrow-end domain. The other monomers are all coloured blue.