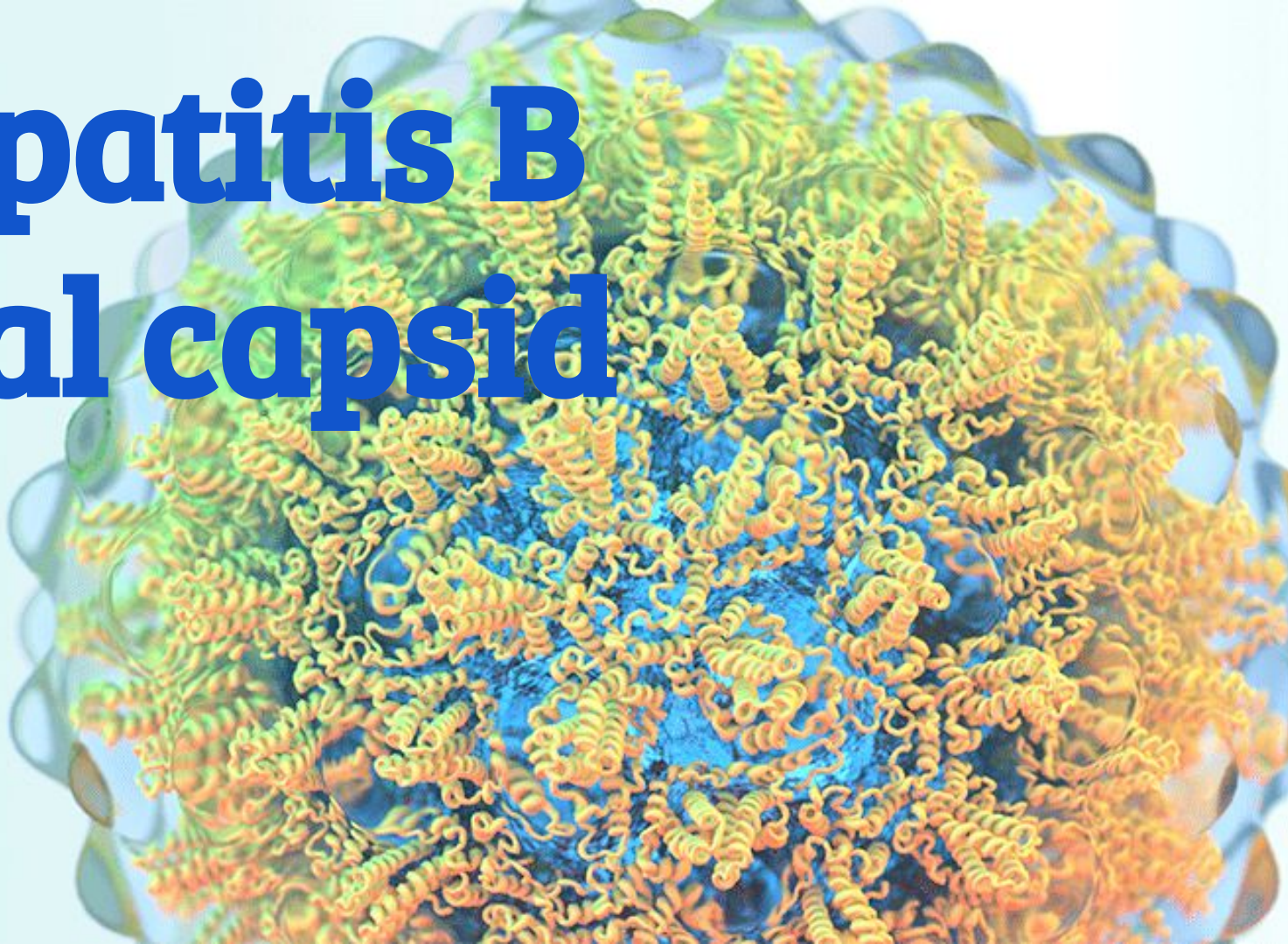
Hepatitis B viral capsid



Gemma Algaba
Martí Boltà
Júlia Coll
Cèlia Ventura

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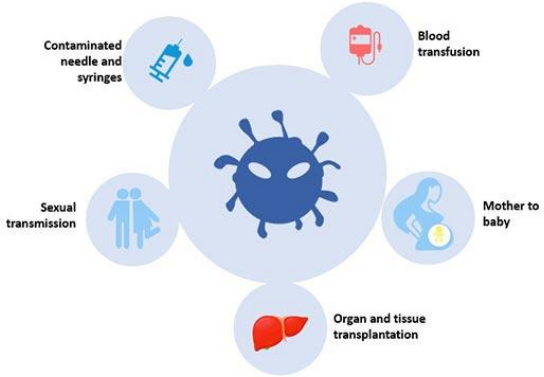
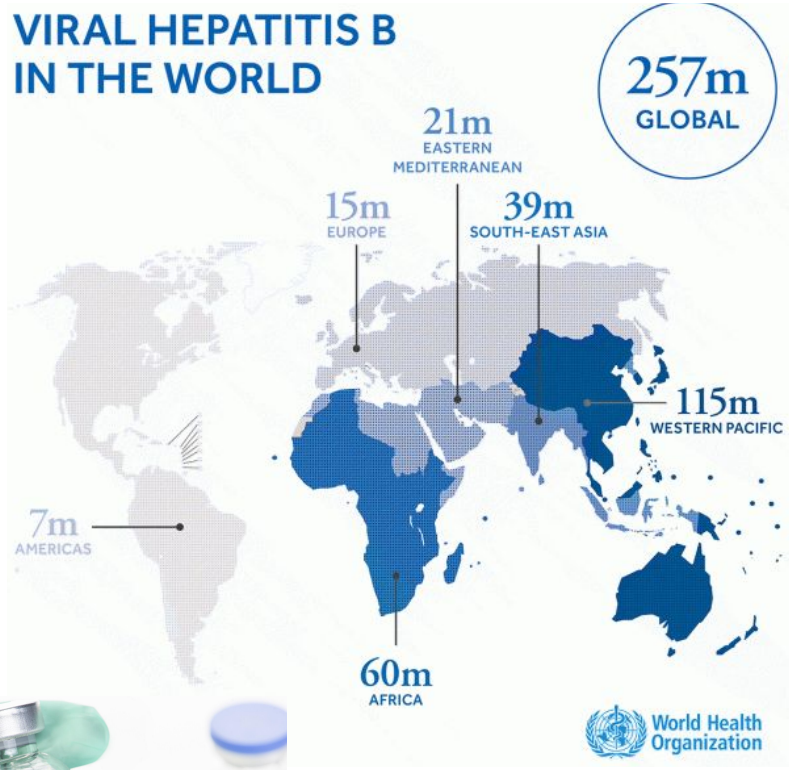
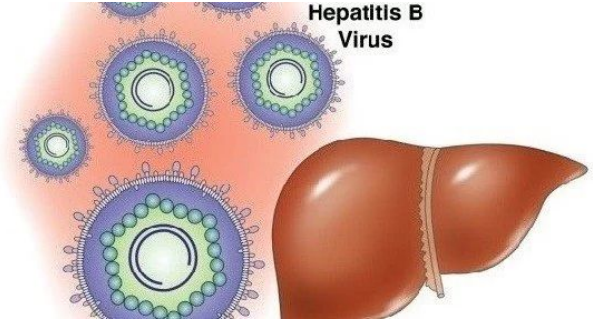
Introduction

Description and relevance

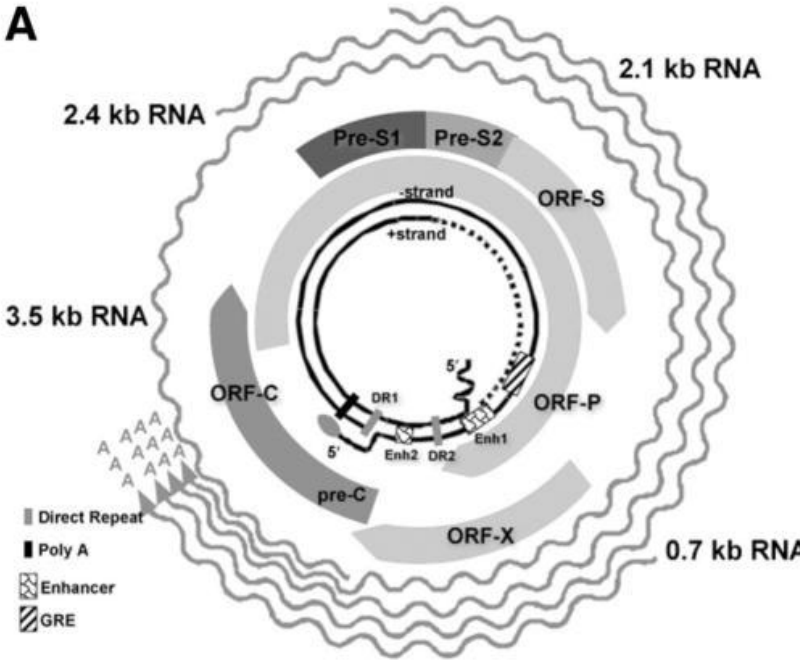


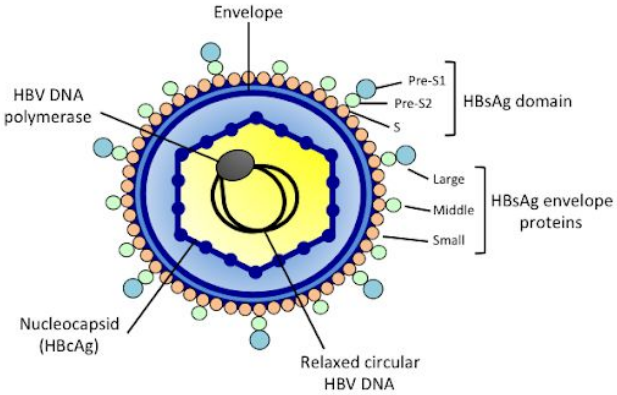


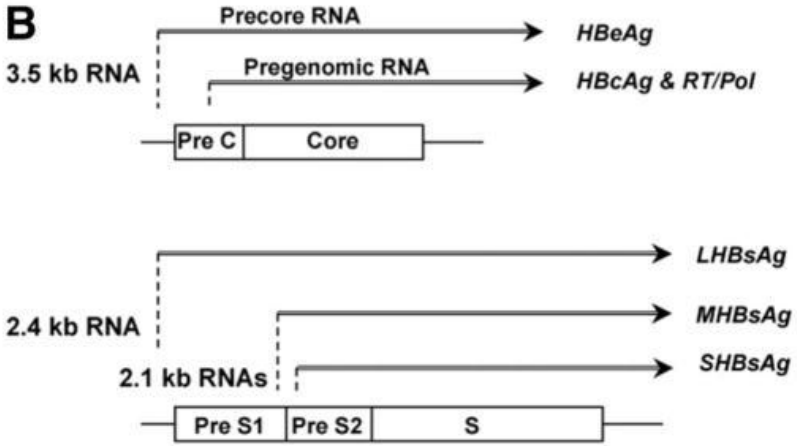


Introduction

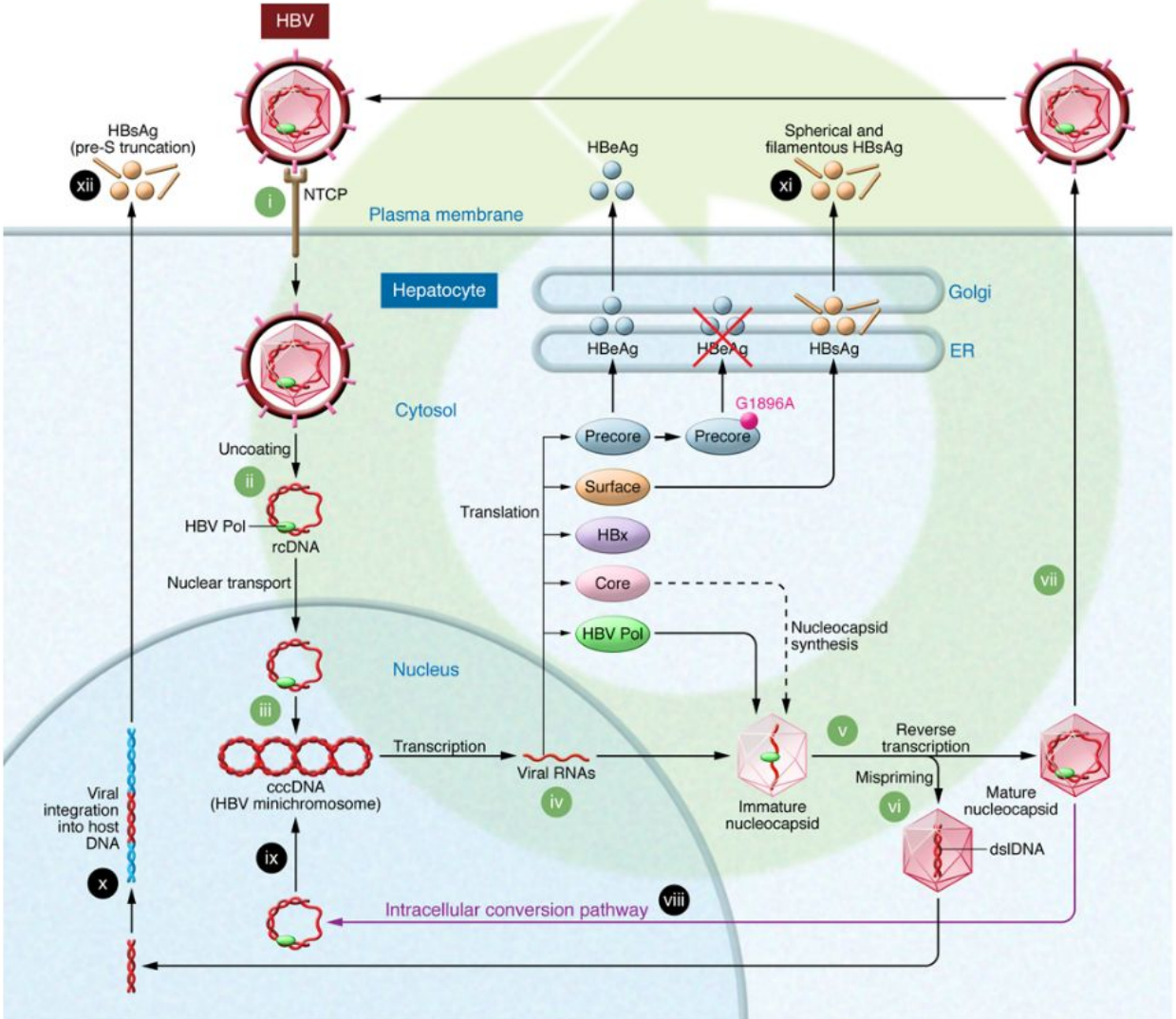
Structure and genes





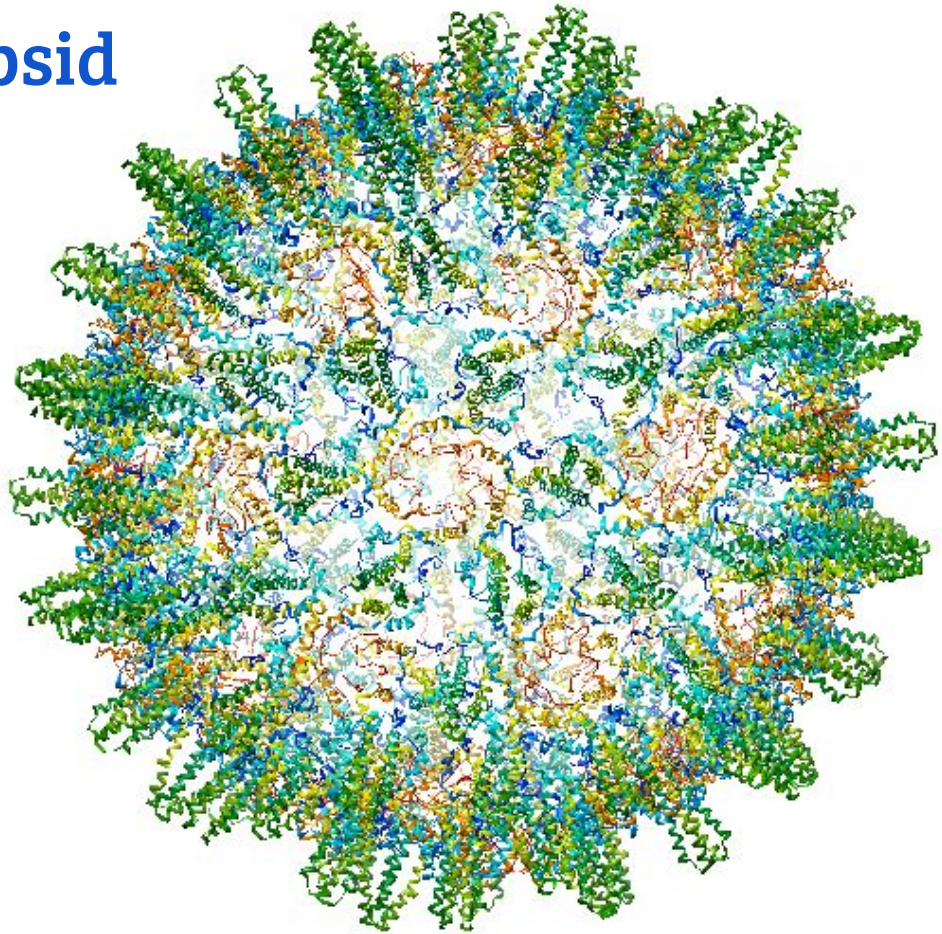


Life cycle



Revill PA, Locarnini SA. New perspectives on the hepatitis B virus life cycle in the human liver. *J Clin Invest* 2016; 126 (3): 833-836.

Hepatitis B capsid



SCOP Classification

Class: All alpha protein

Fold: Hepatitis B viral capsid (HBcAg)

Superfamily: Hepatitis B viral capsid (HBcAg)

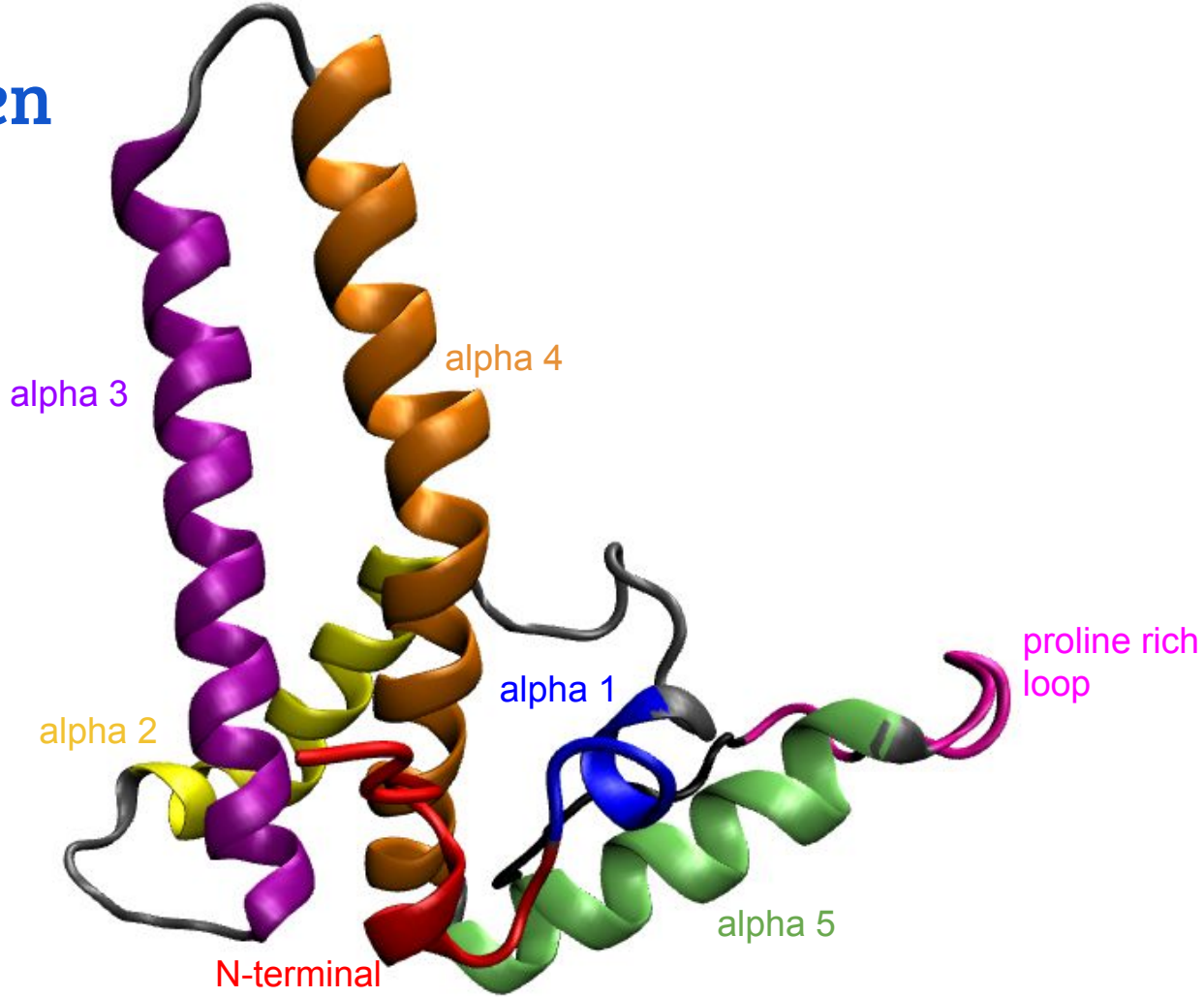
Family: Hepatitis B viral capsid (HBcAg)

Protein: Hepatitis B viral capsid (HBcAg)

5 helices; array; two long helices form a hairpin that dimerizes into a 4-helical bundle

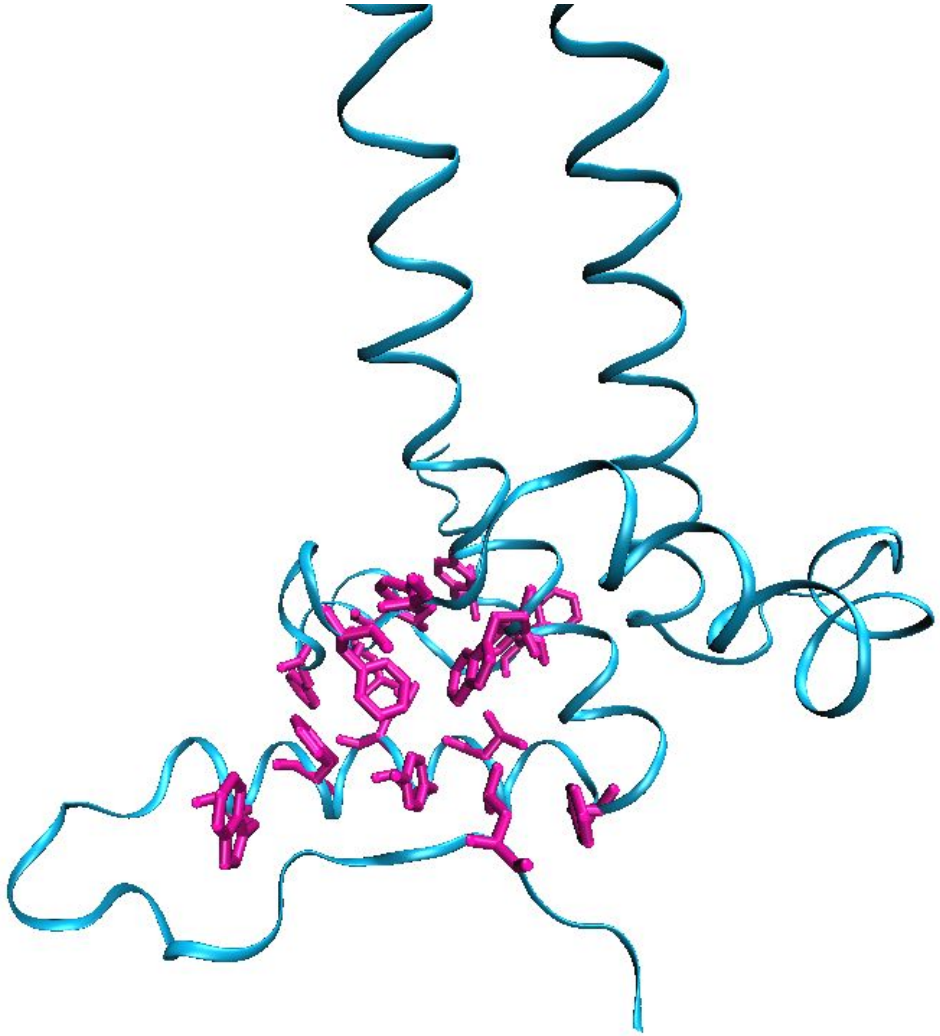
Core antigen

Monomere



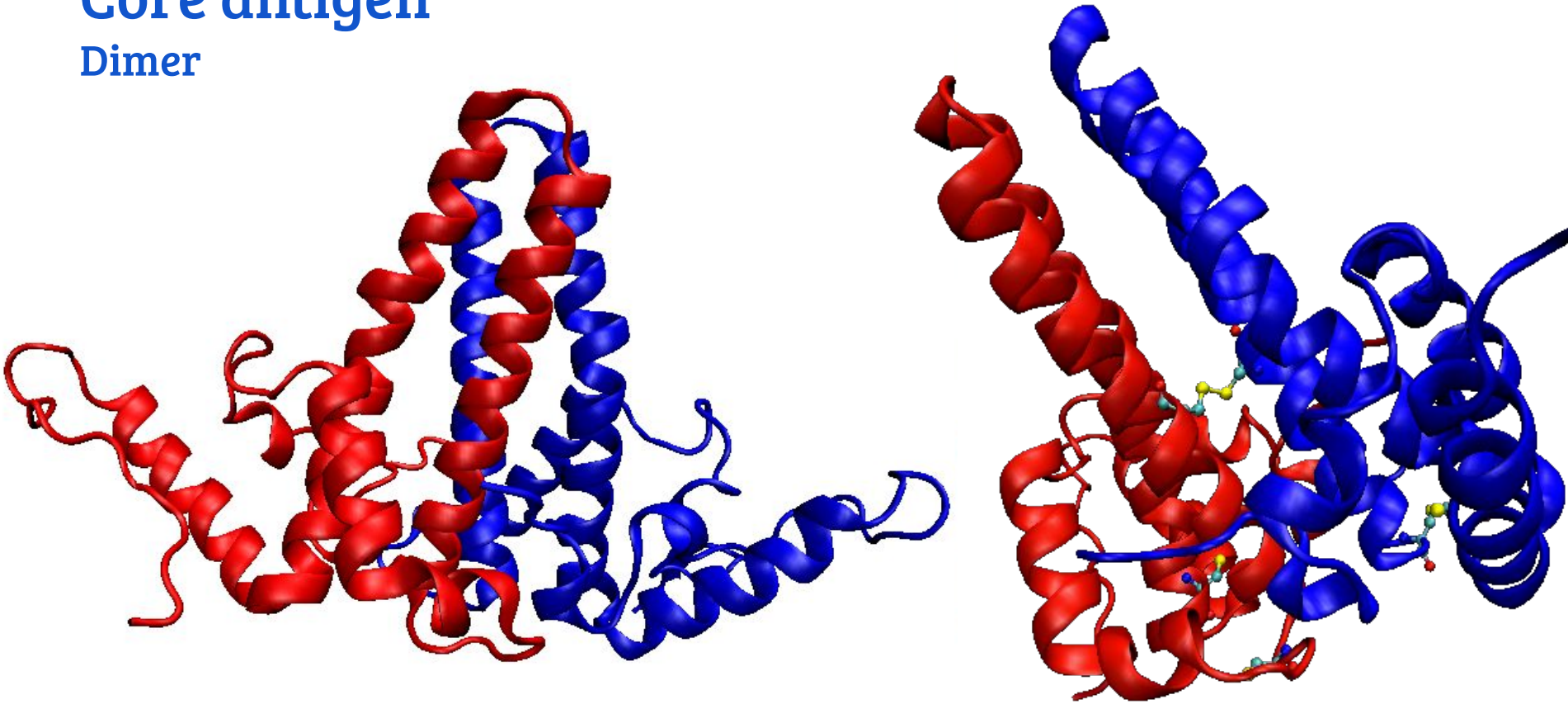
Core antigen

Hydrophobic core



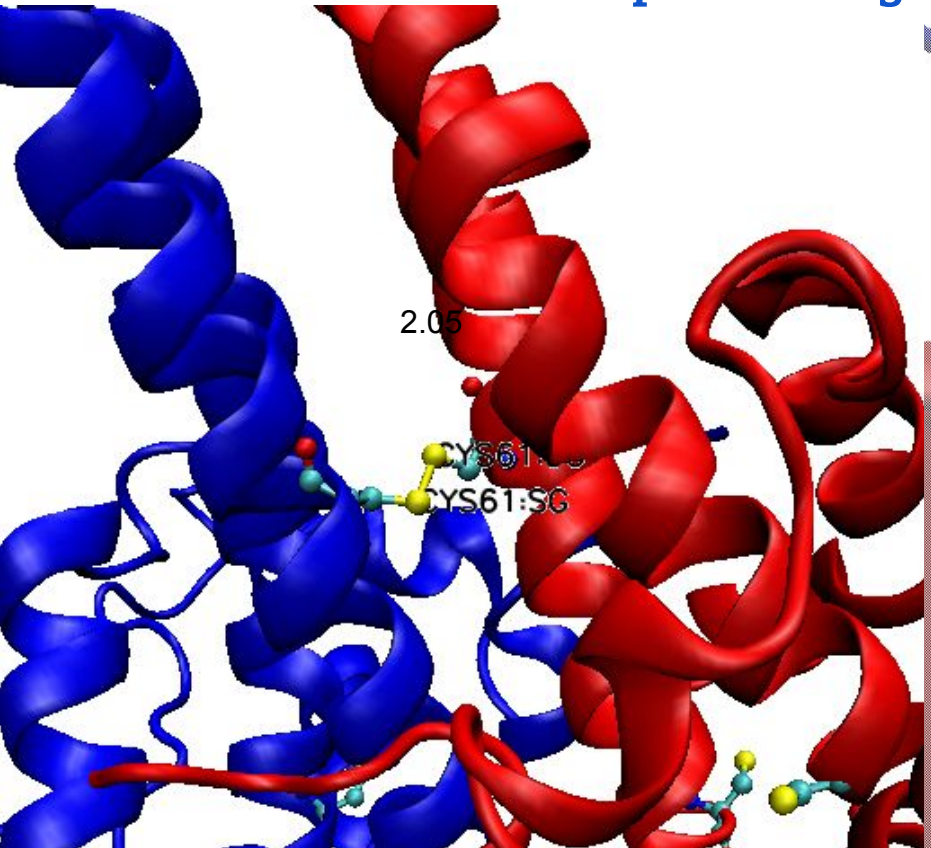
Core antigen

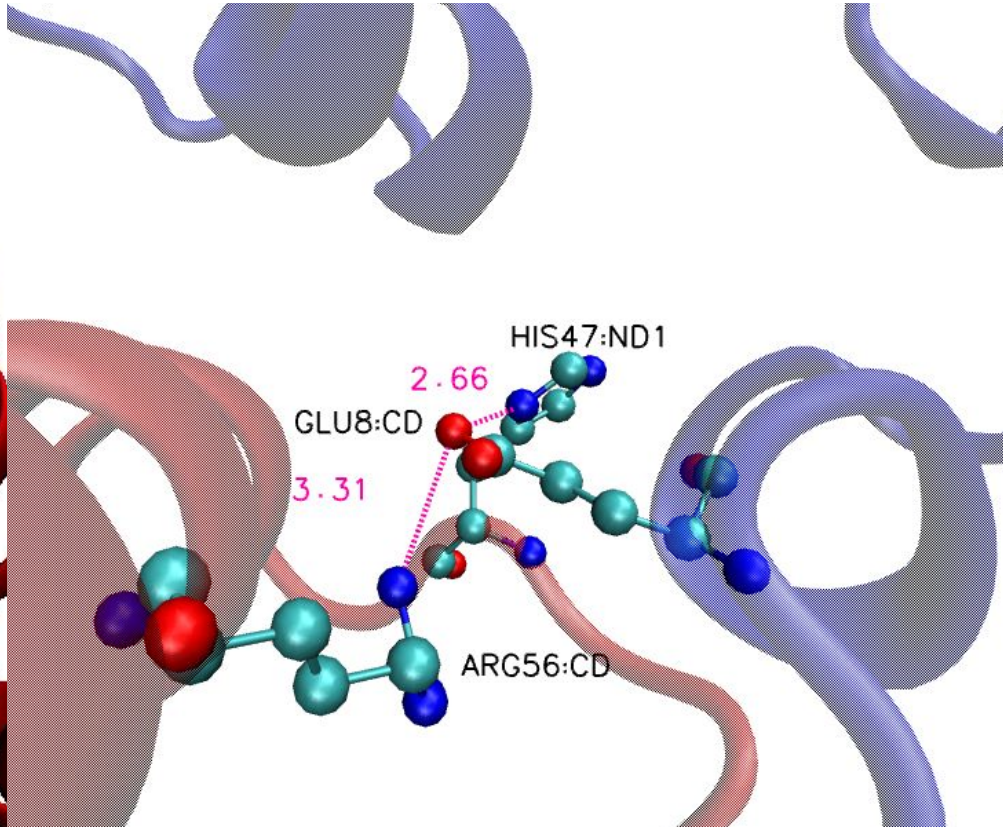
Dimer



Core antigen

Intermonomeric disulphide bridge

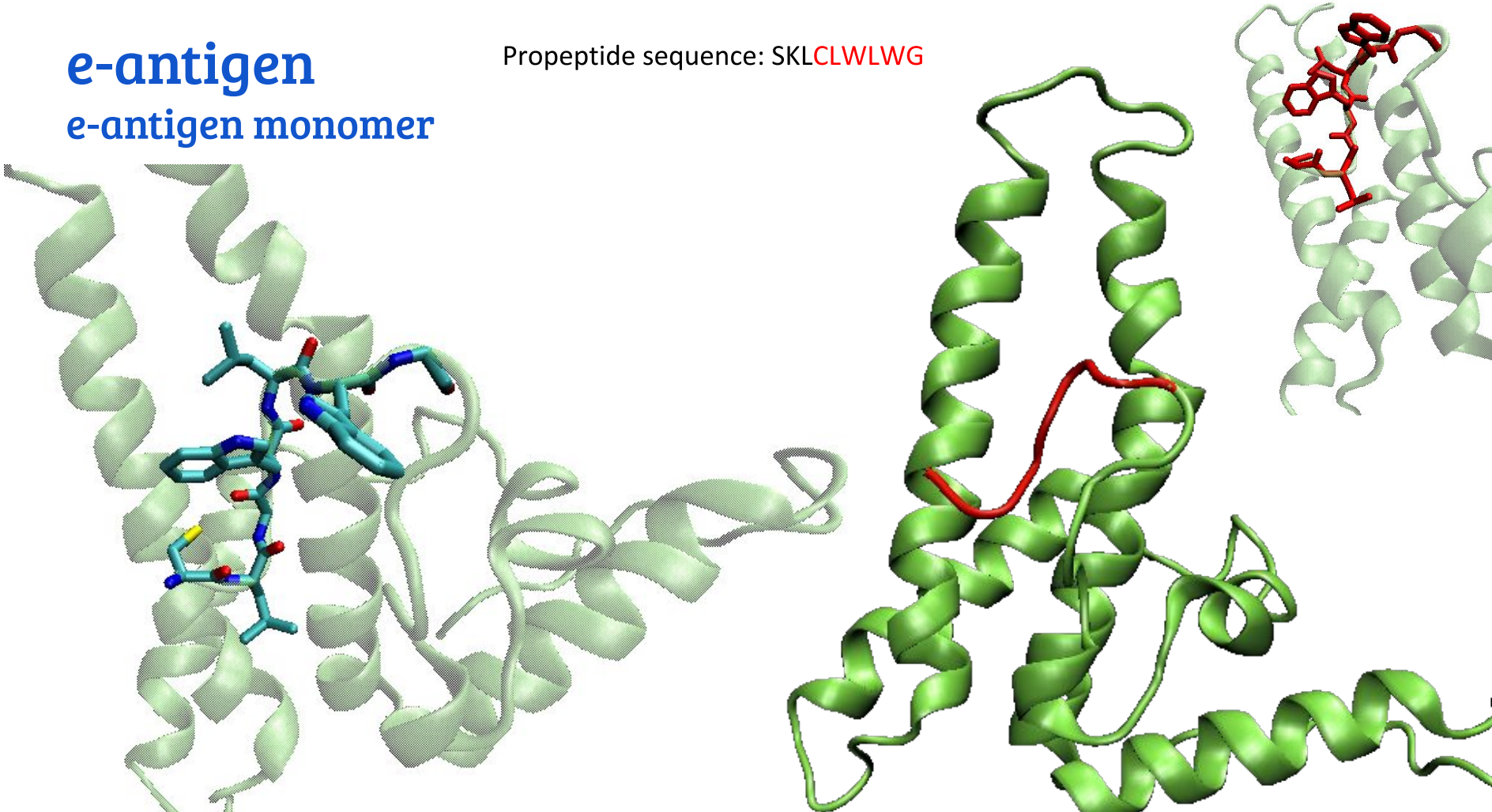




e-antigen

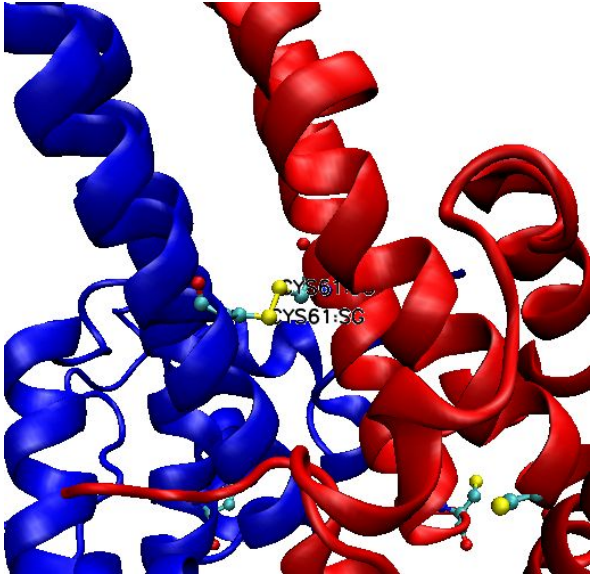
e-antigen monomer

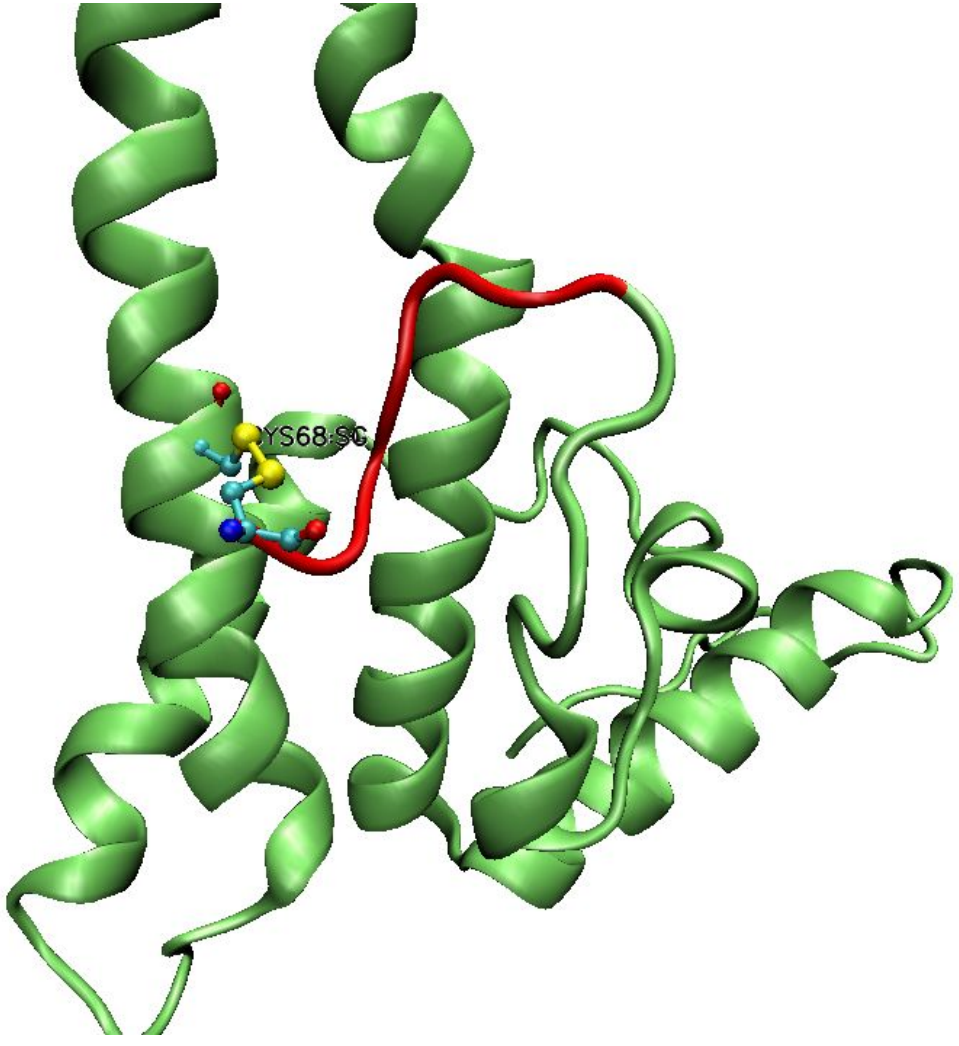
Propeptide sequence: SKLCLWLWG



e-antigen

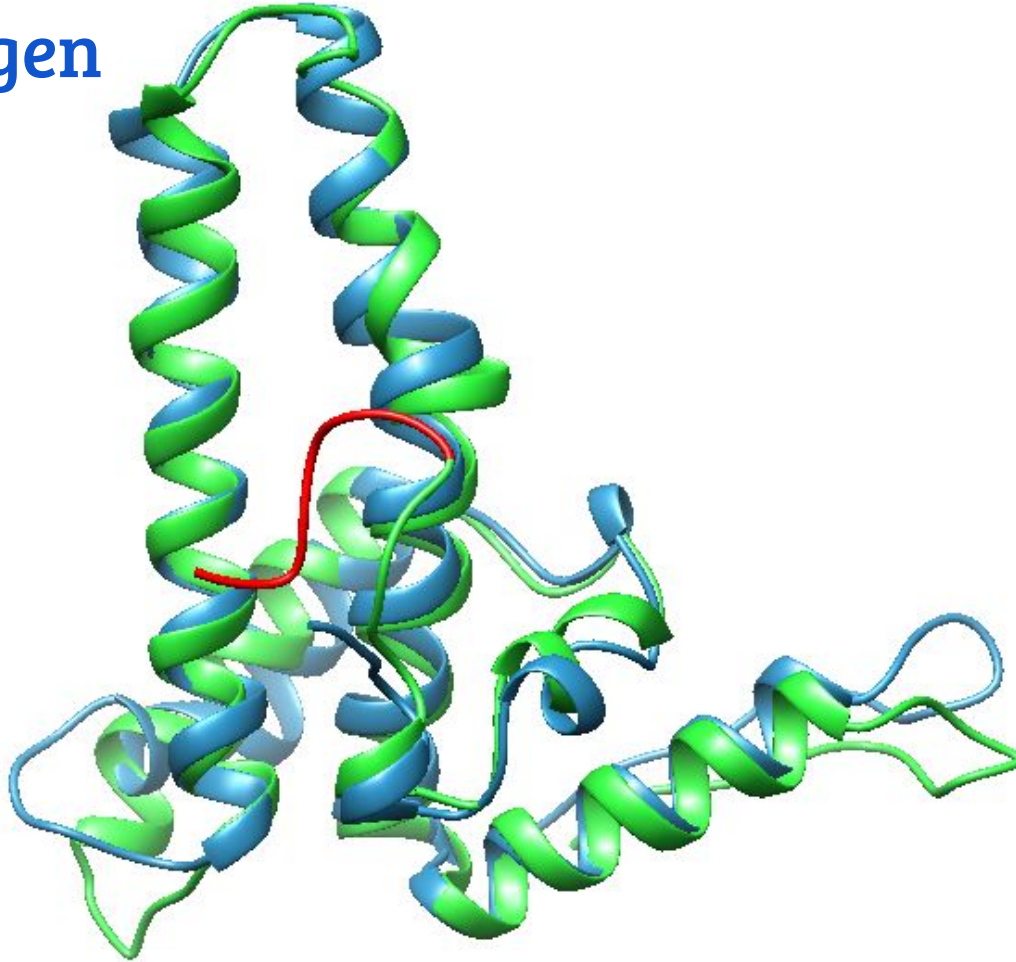
Intramonomeric disulfide bridge





core antigen and e-antigen

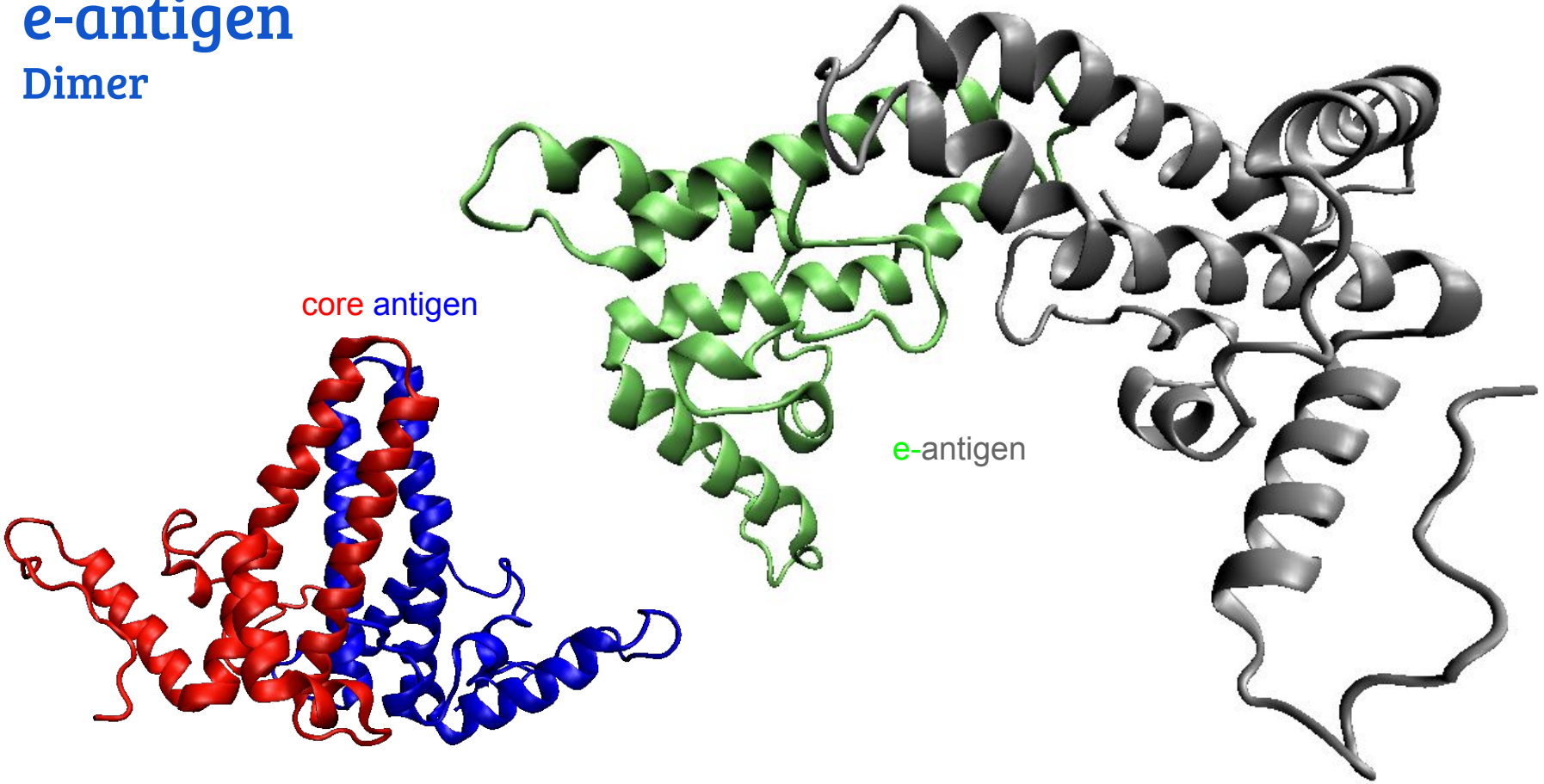
Superimposition



RMS 2.03

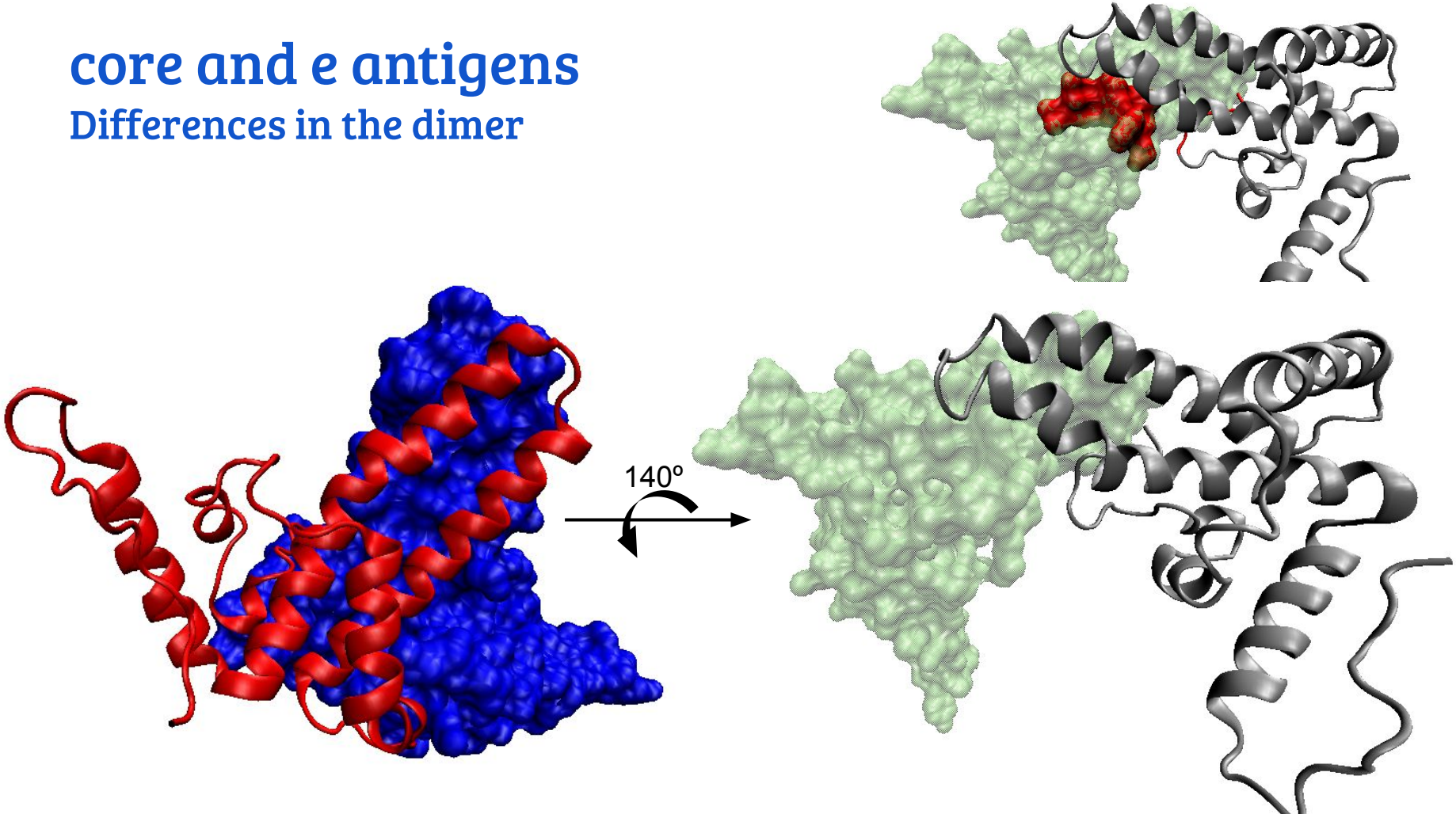
e-antigen

Dimer



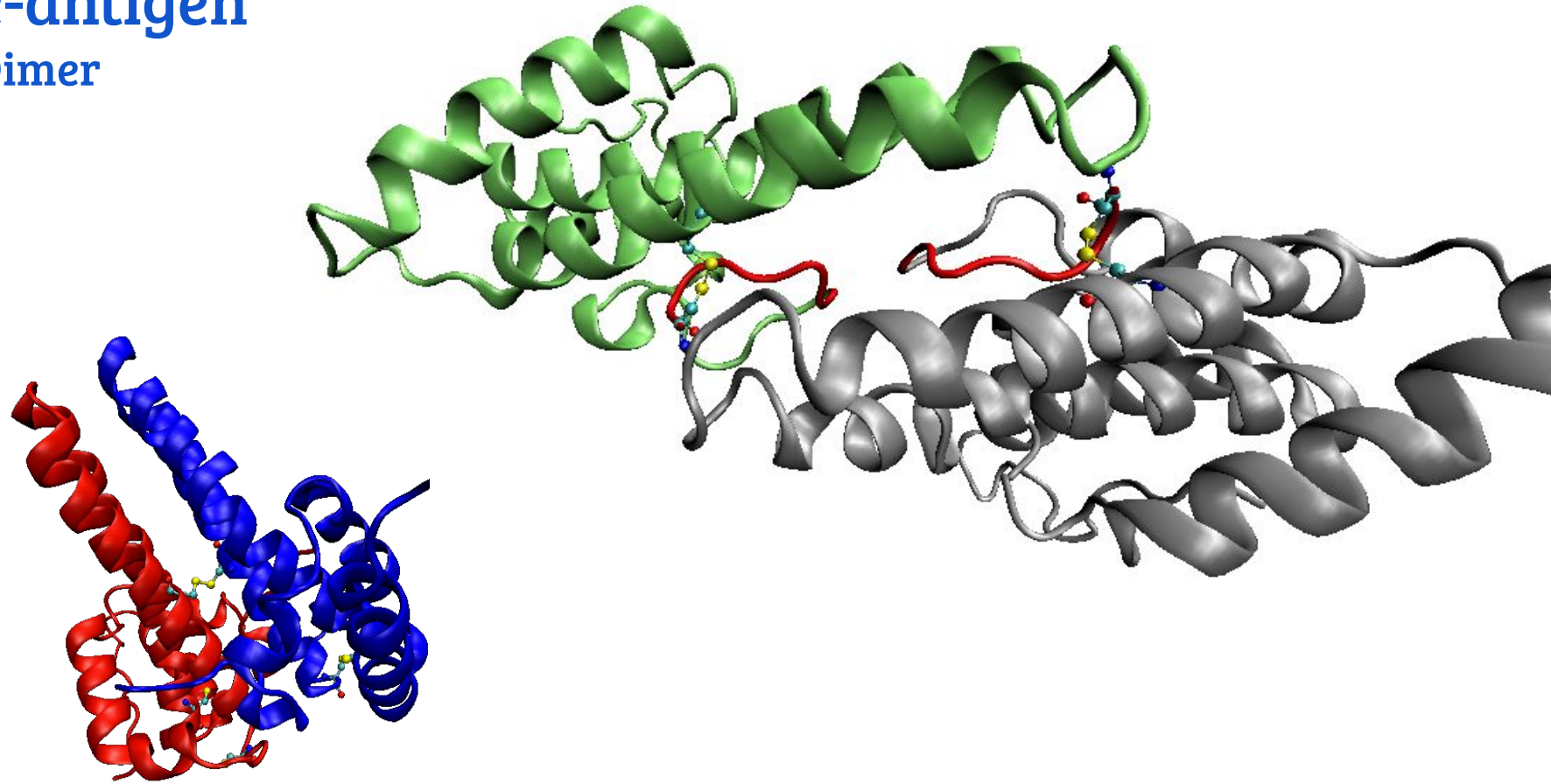
core and e antigens

Differences in the dimer



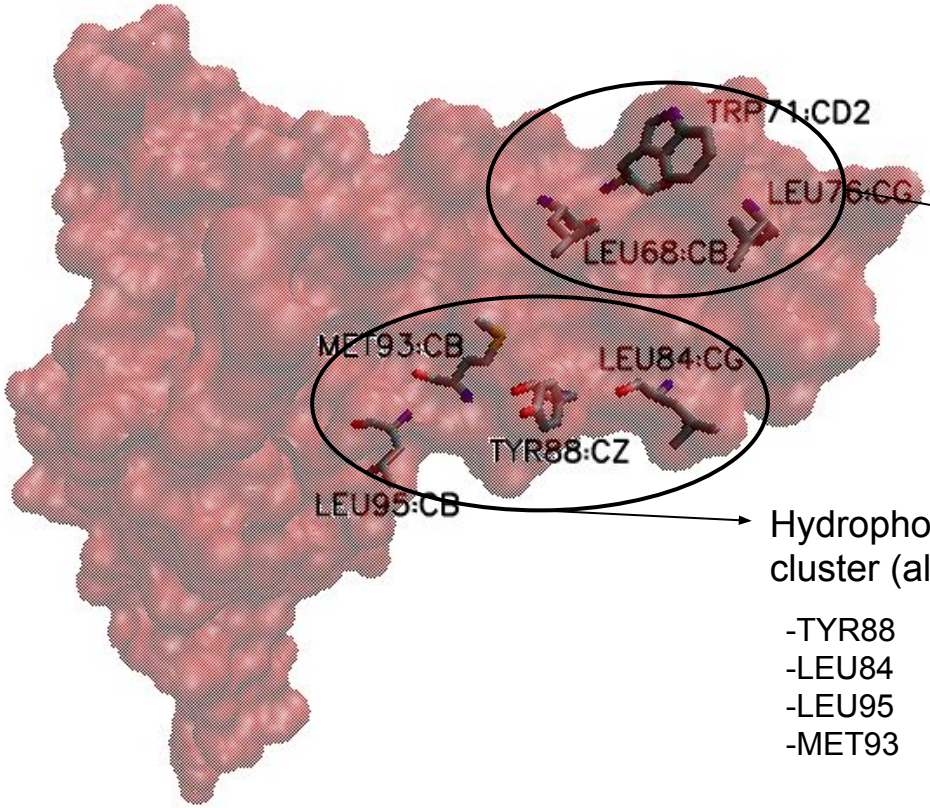
e-antigen

Dimer



core antigen

Hydrophobic dimer contacts

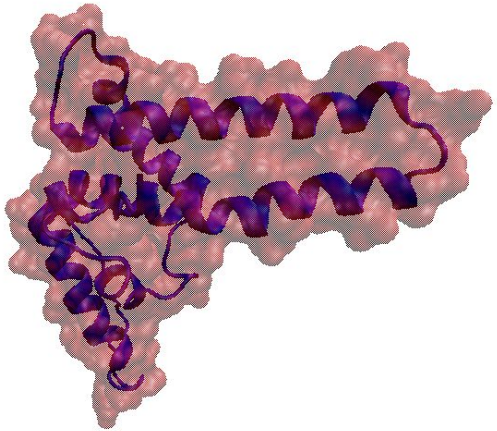


Hydrophobic patch (alpha3)

-TRP71
-LEU76
-LEU68

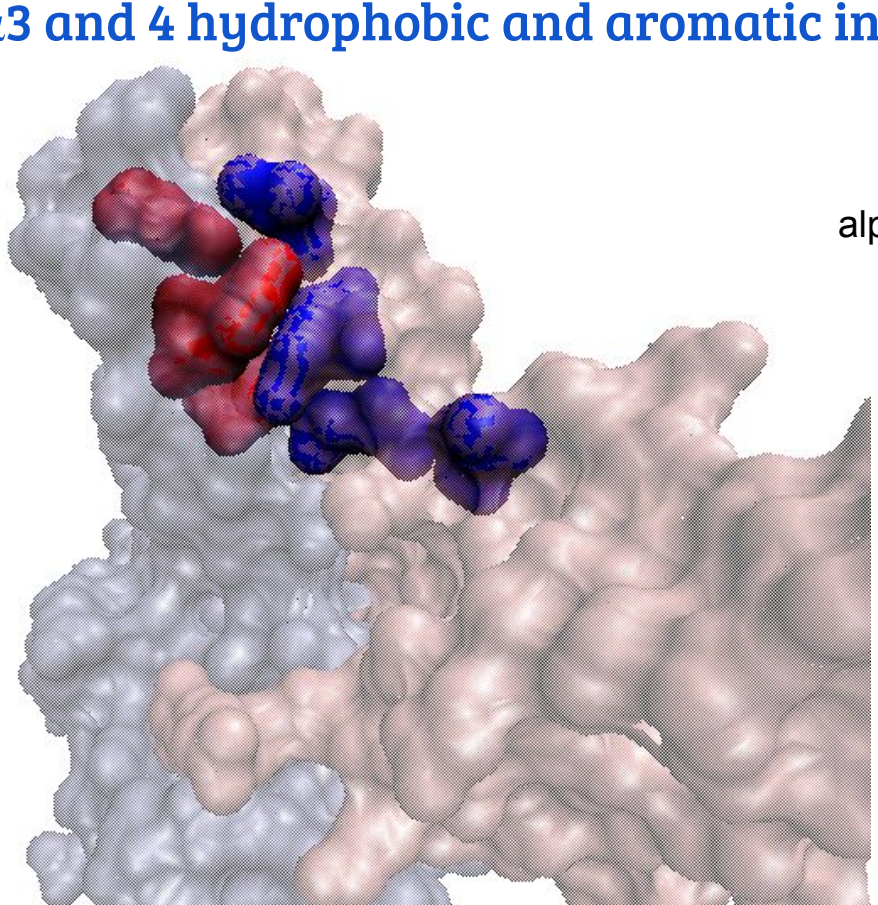
Hydrophobic cluster (alpha4)

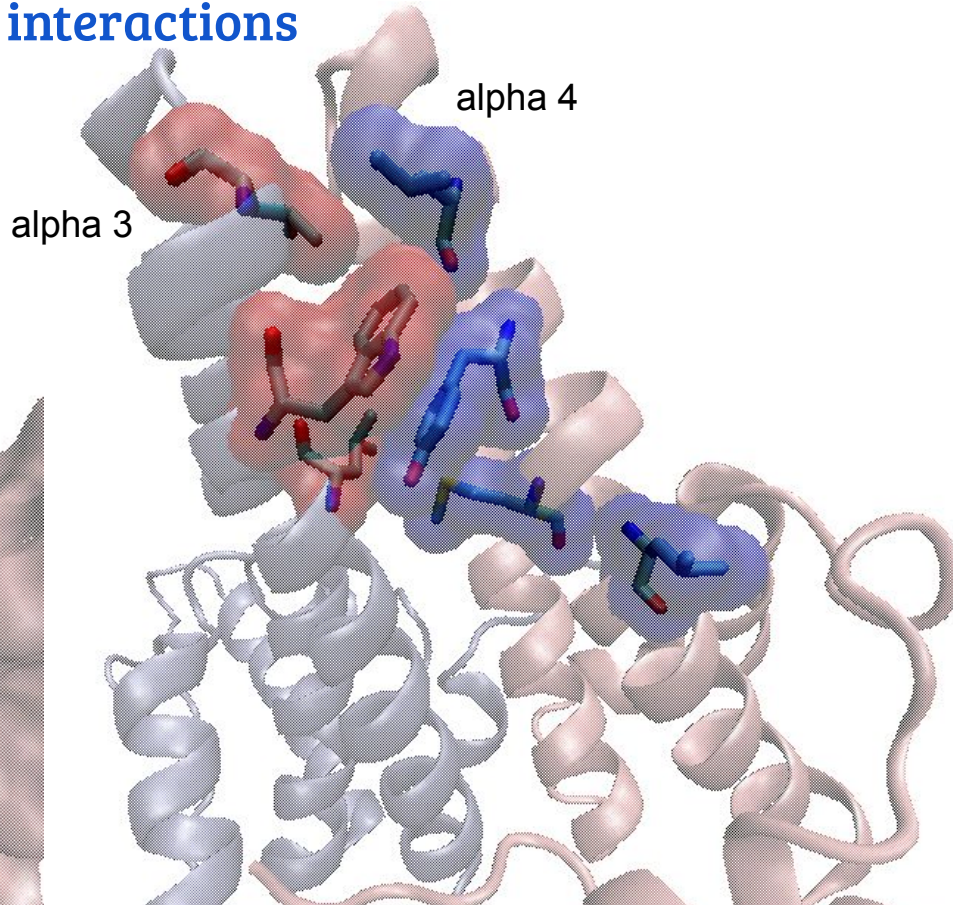
-TYR88
-LEU84
-LEU95
-MET93



core antigen

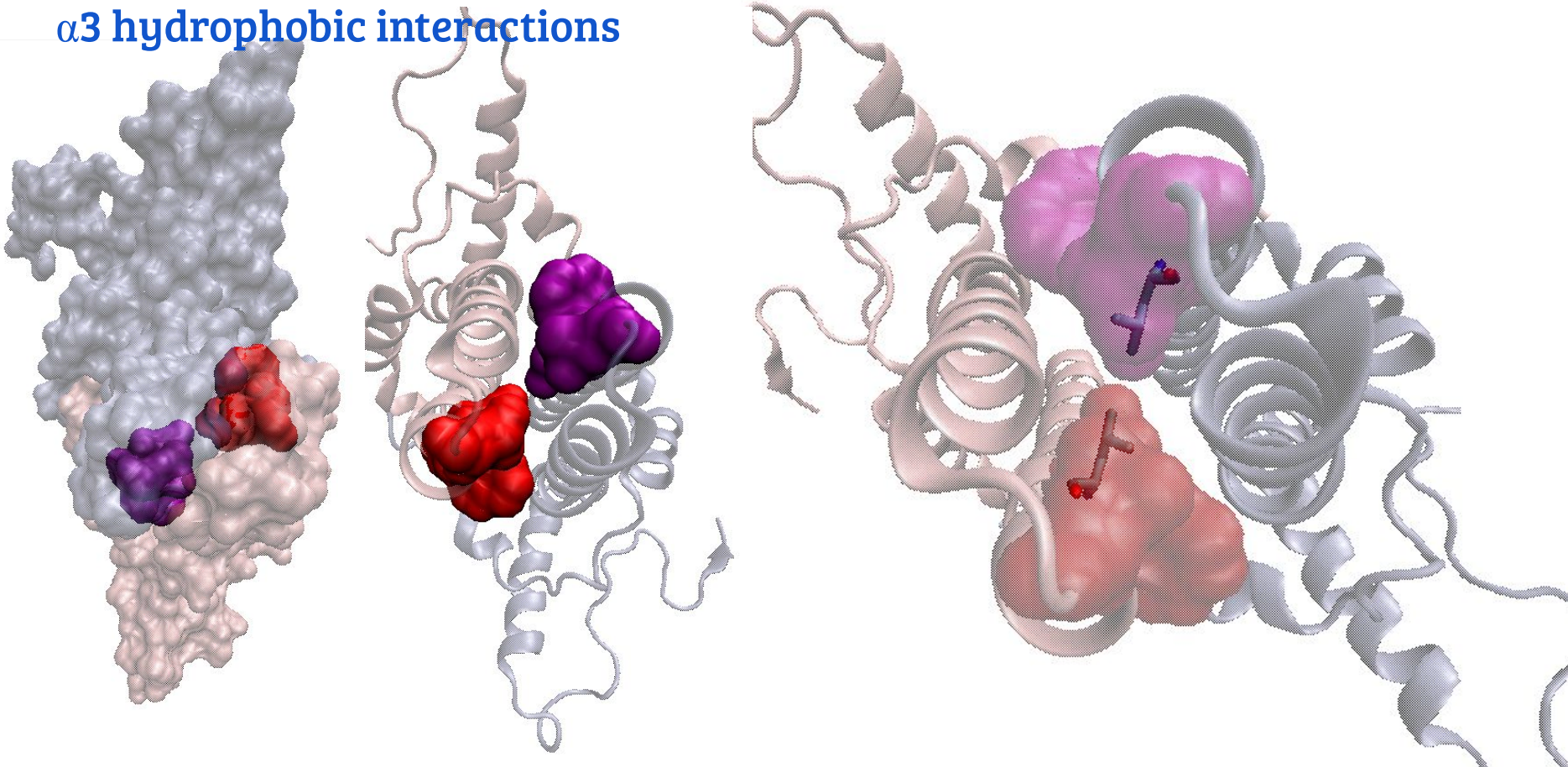
α3 and 4 hydrophobic and aromatic interactions





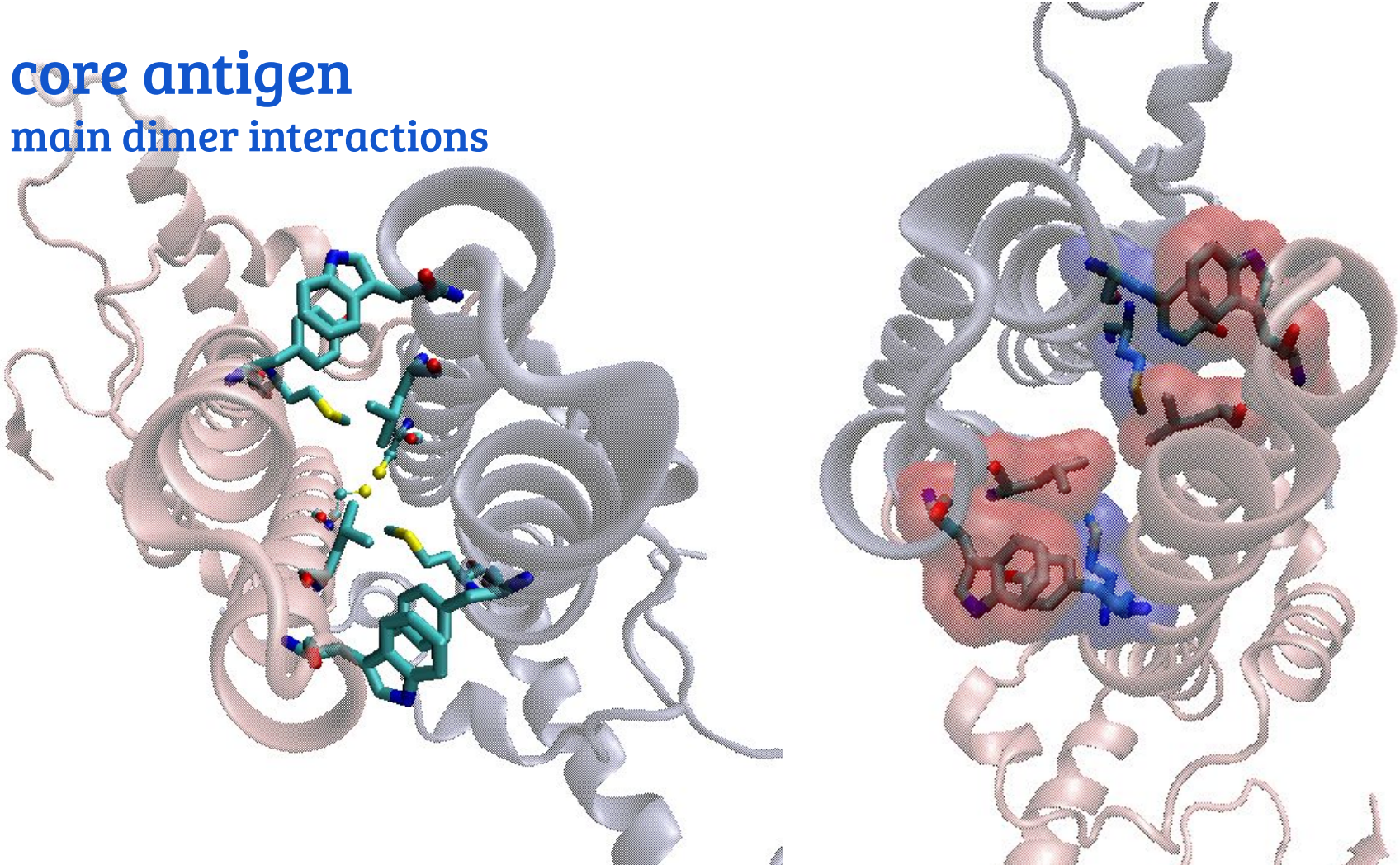
core antigen

α3 hydrophobic interactions



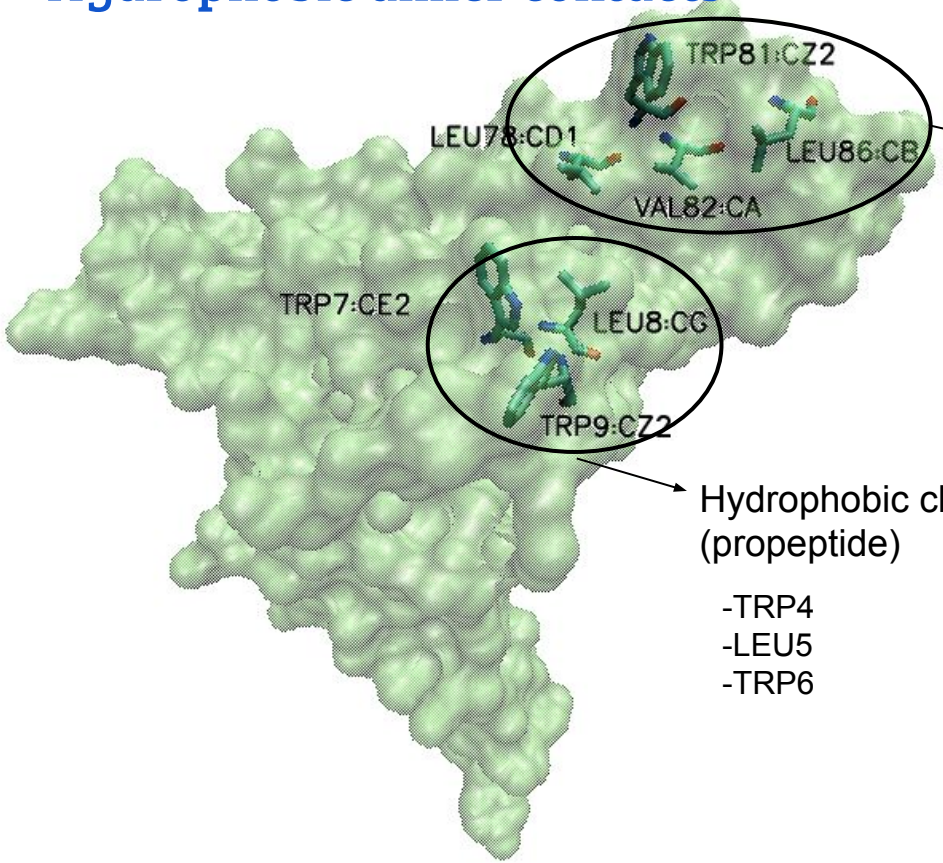
core antigen

main dimer interactions



e-antigen

Hydrophobic dimer contacts

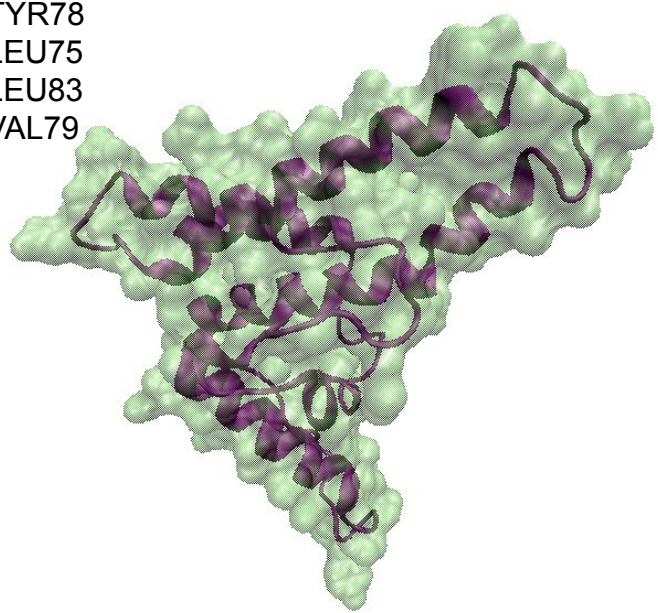


Hydrophobic patch
(alpha3)

-TYR78
-LEU75
-LEU83
-VAL79

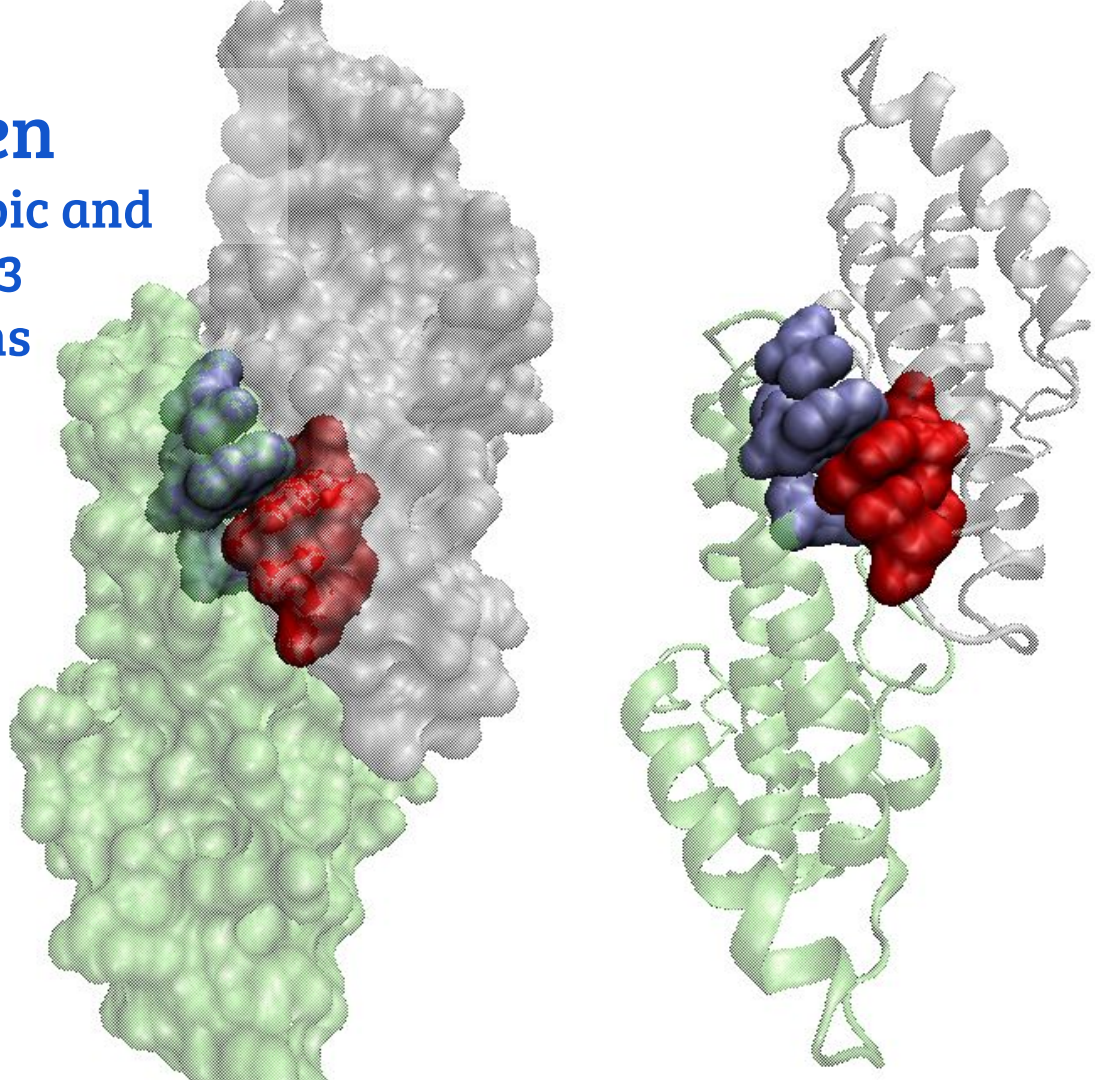
Hydrophobic cluster
(propeptide)

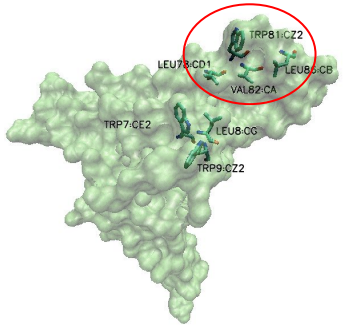
-TRP4
-LEU5
-TRP6



e-antigen

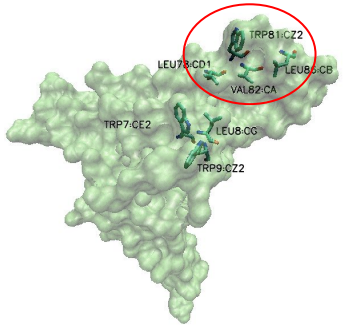
Hydrophobic and aromatic α3 interactions

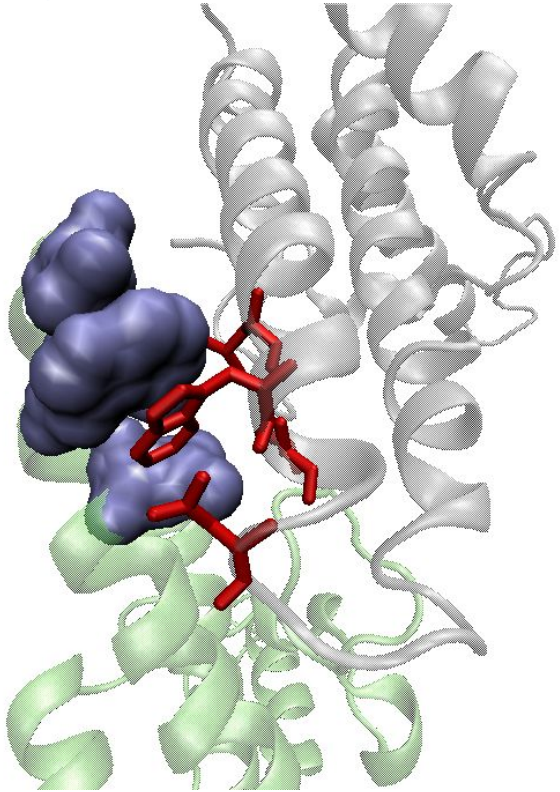


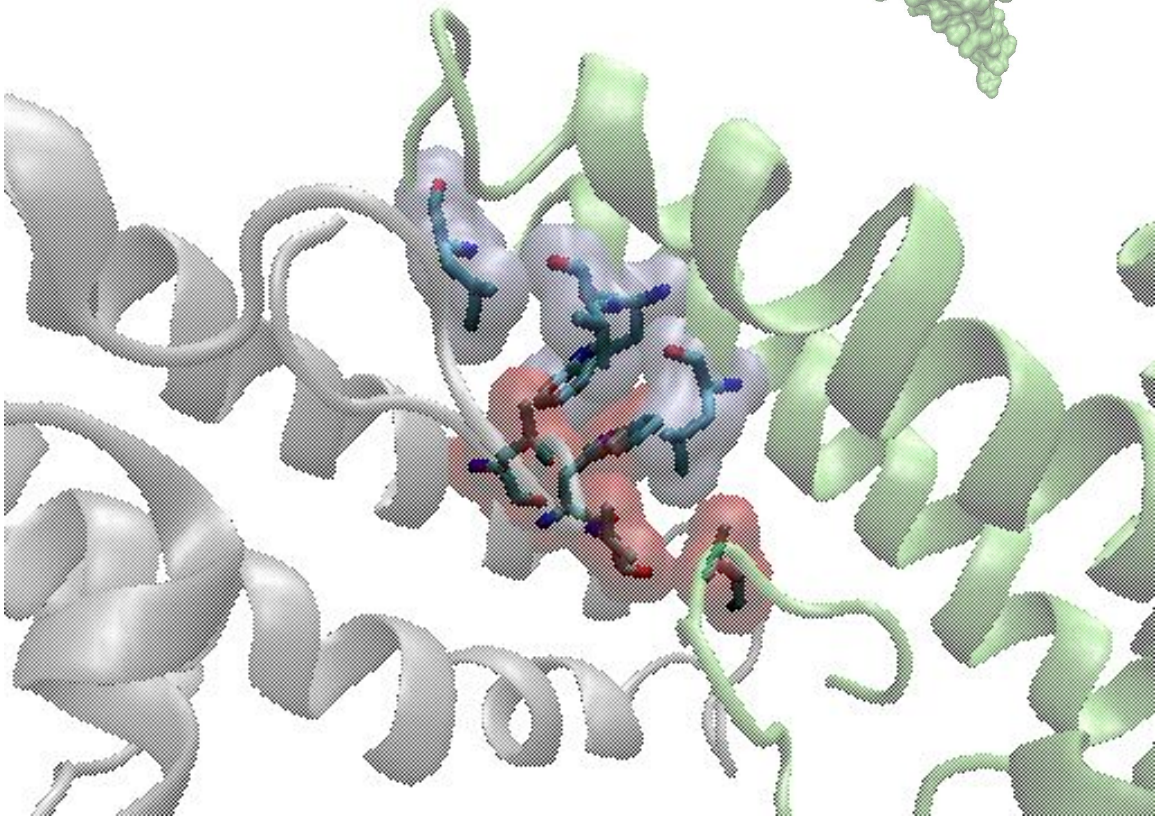


e-antigen

Hydrophobic α3 interactions

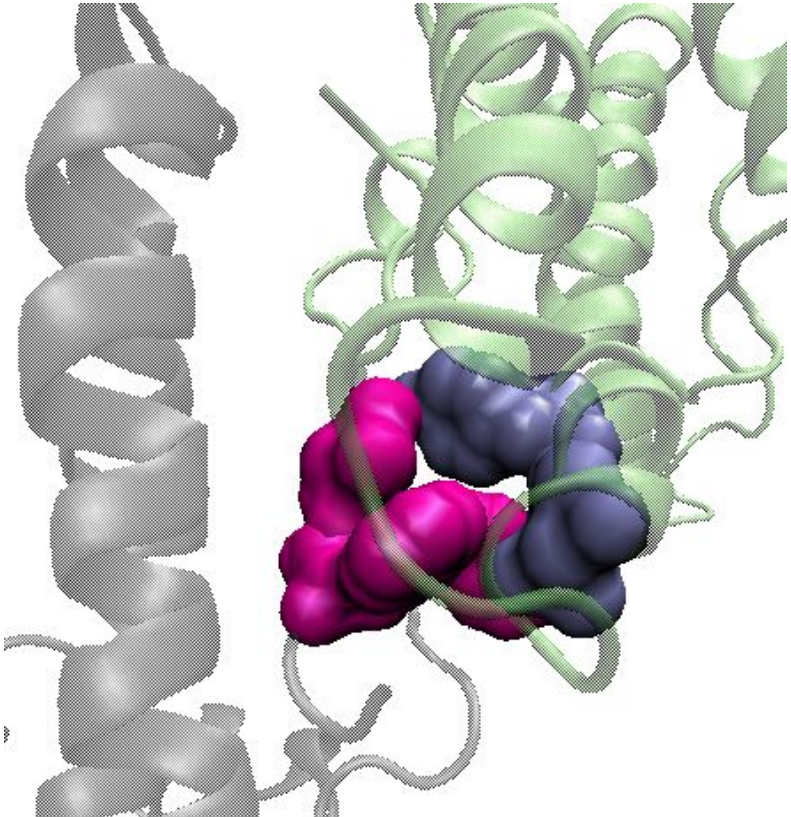


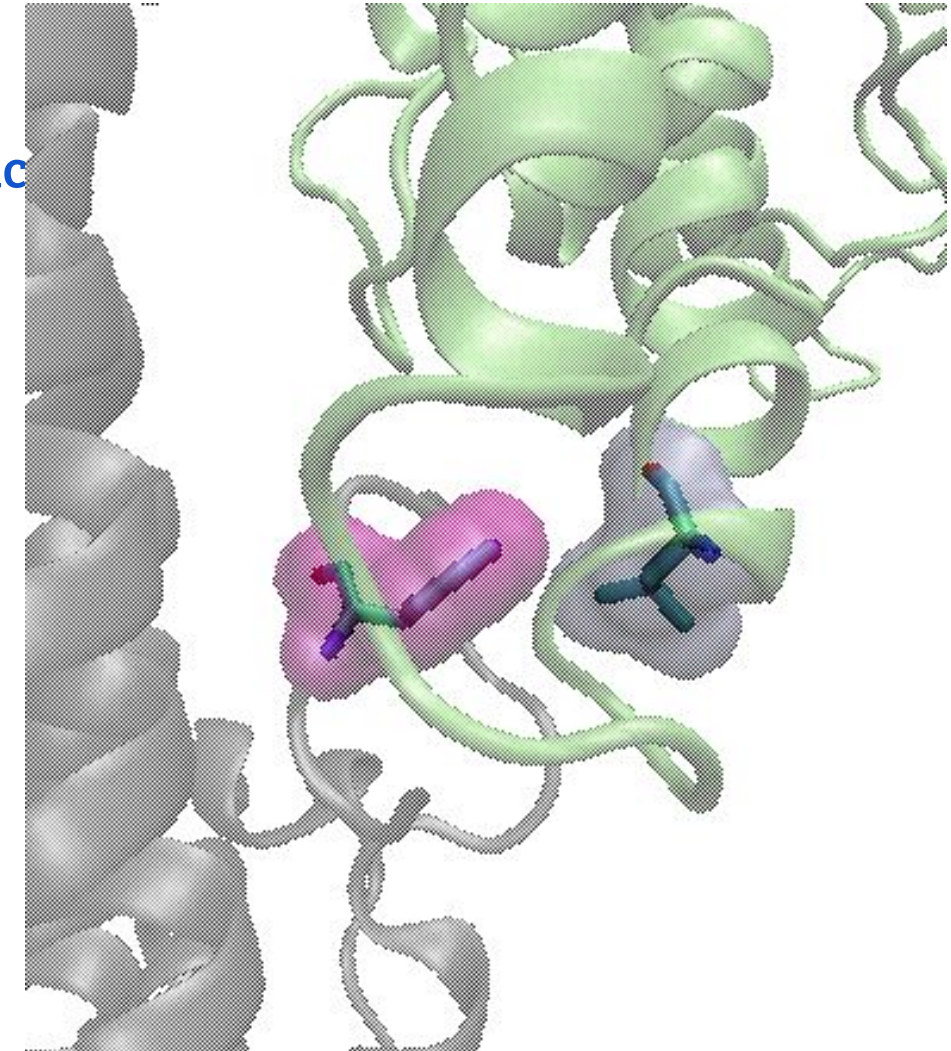




e-antigen

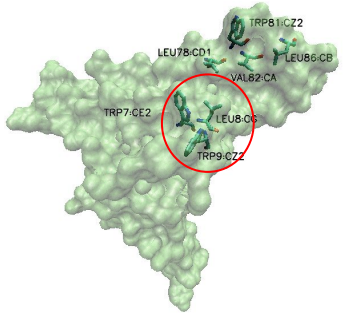
Hydrophobic propeptide and α4 interac

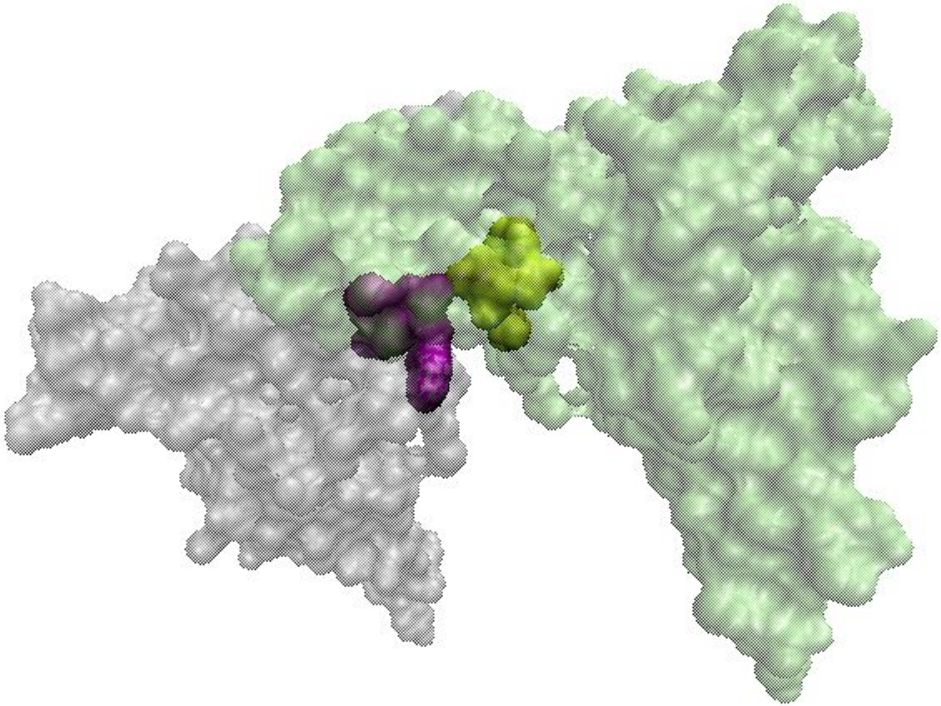


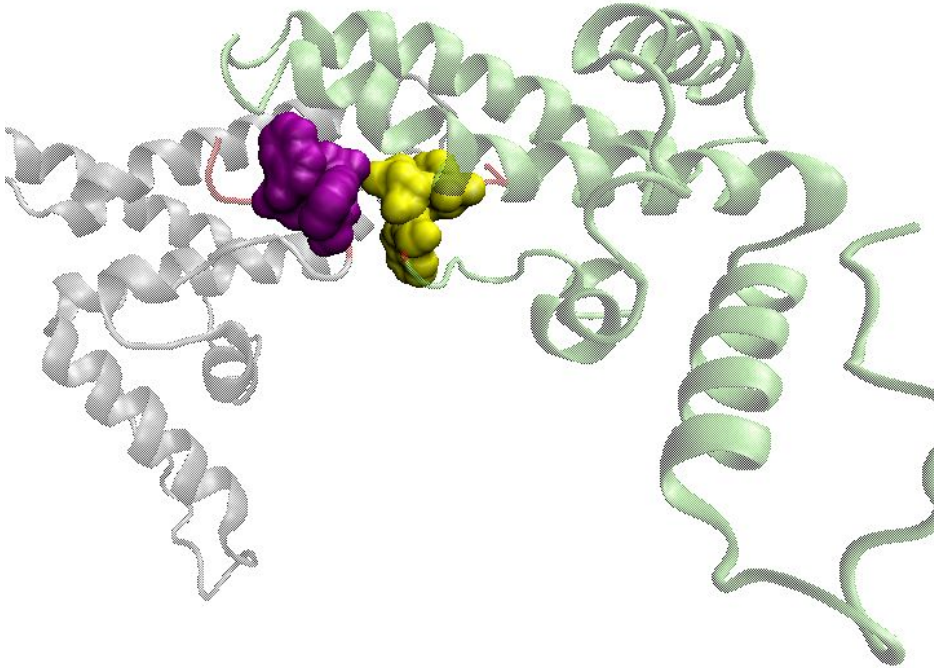


e-antigen

Hydrophobic propeptide interactions

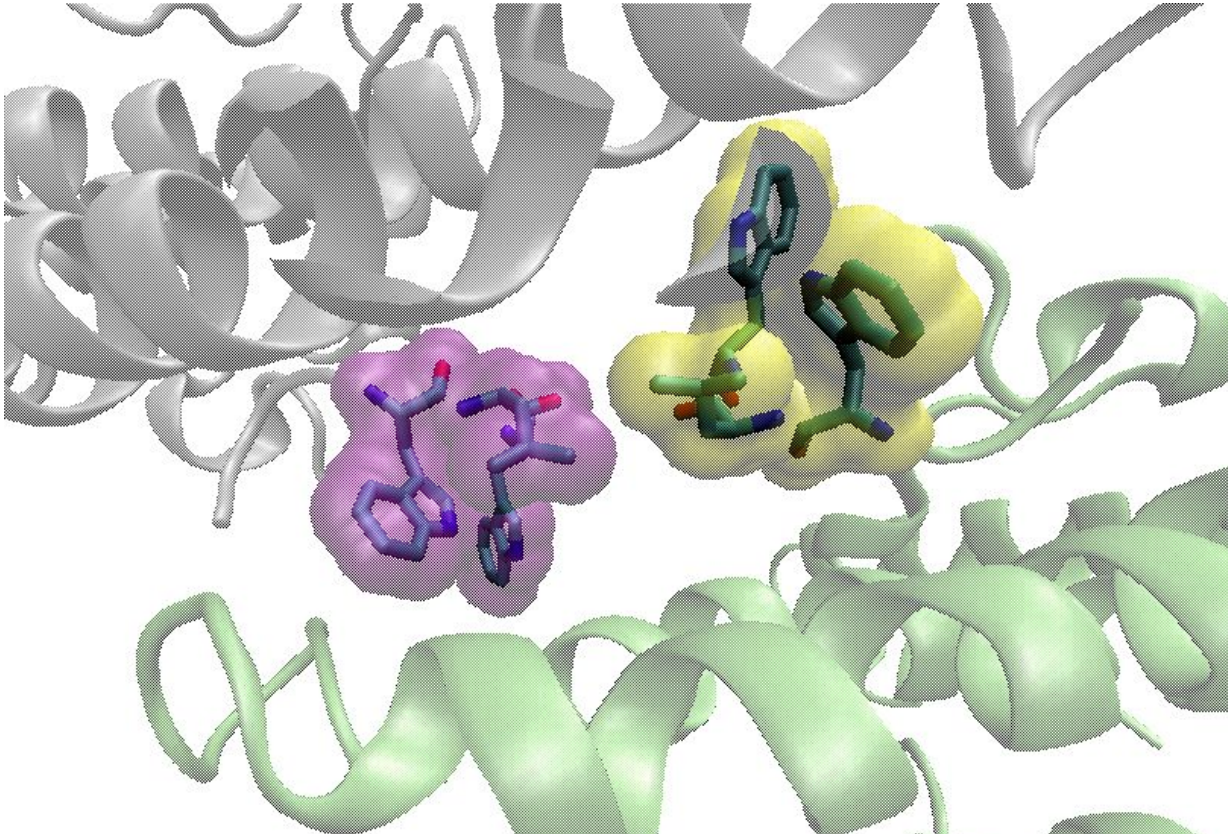






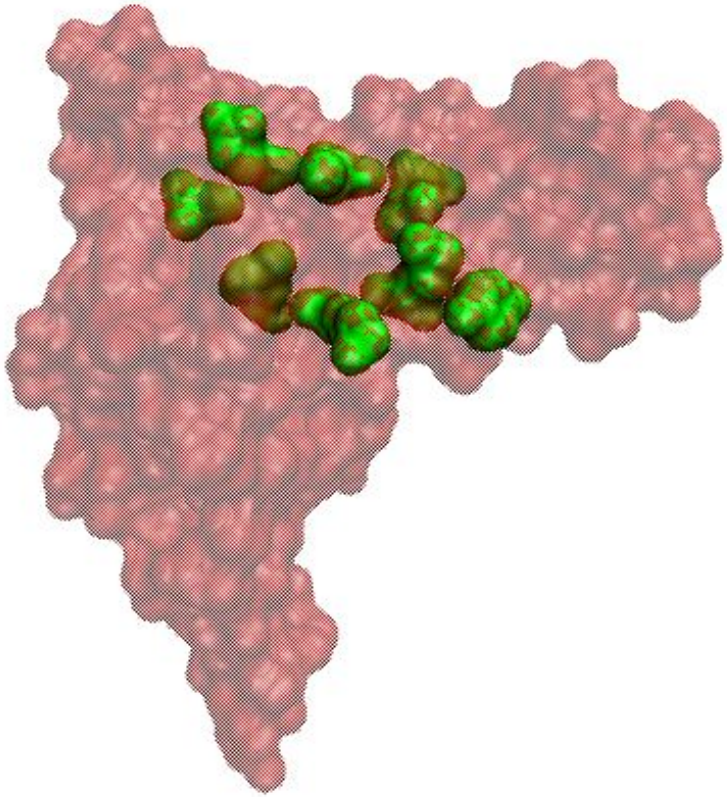
e-antigen

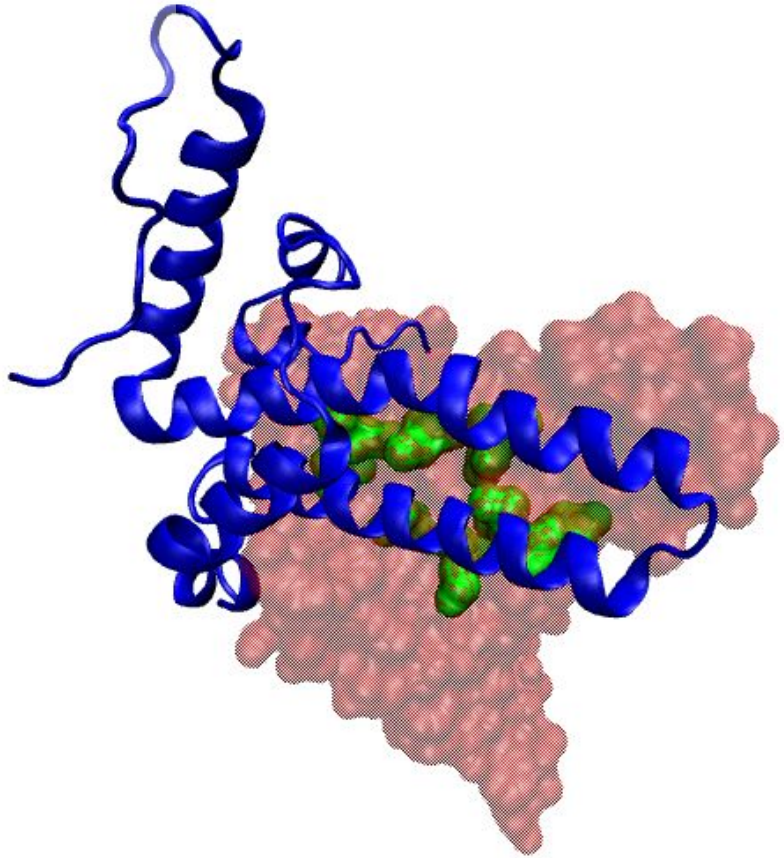
Hydrophobic propeptide interactions



core antigen

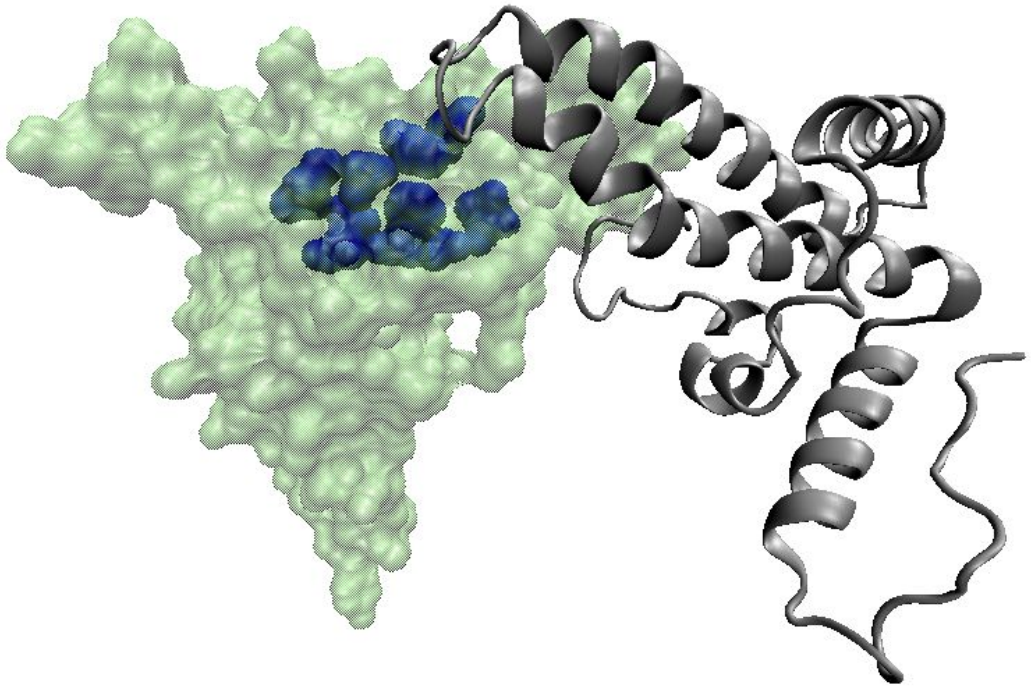
Hydrophobic interface in a dimer





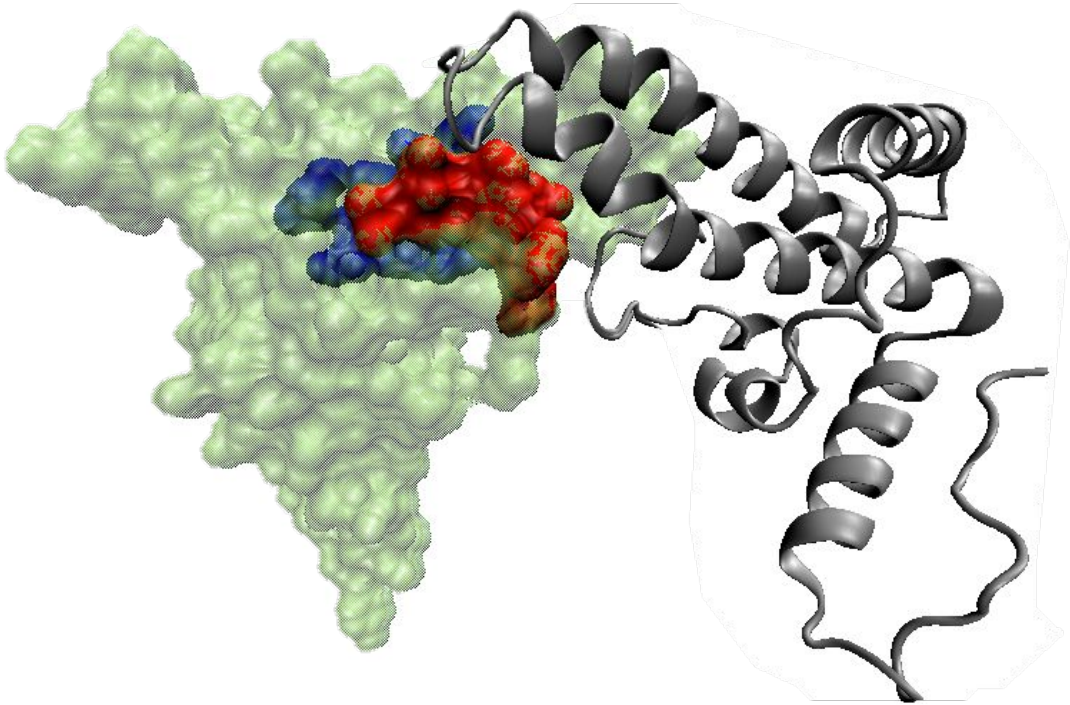
e-antigen

Hydrophobic interface is shielded by the propeptide



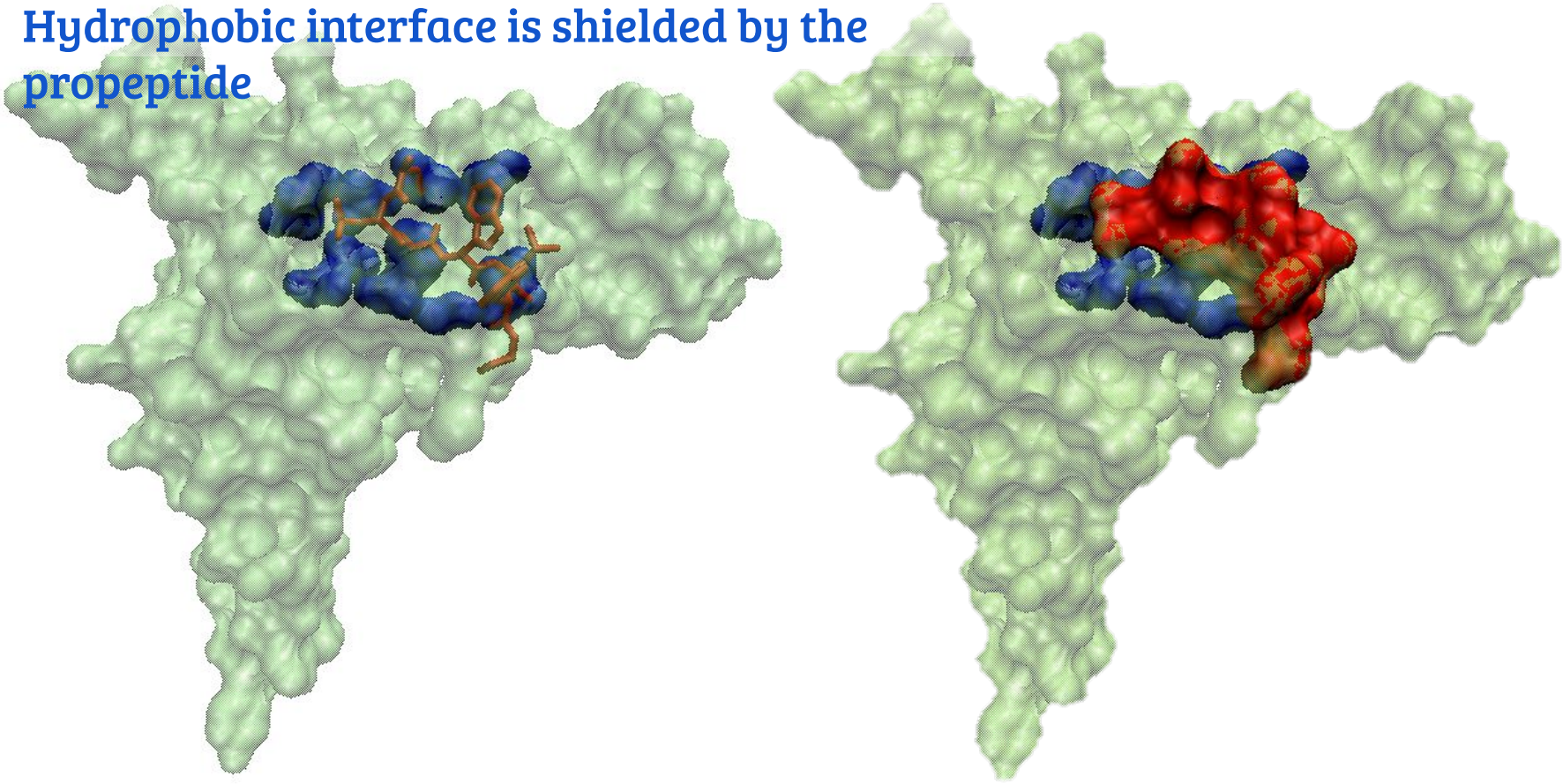
e-antigen

Hydrophobic interface is shielded by the propeptide

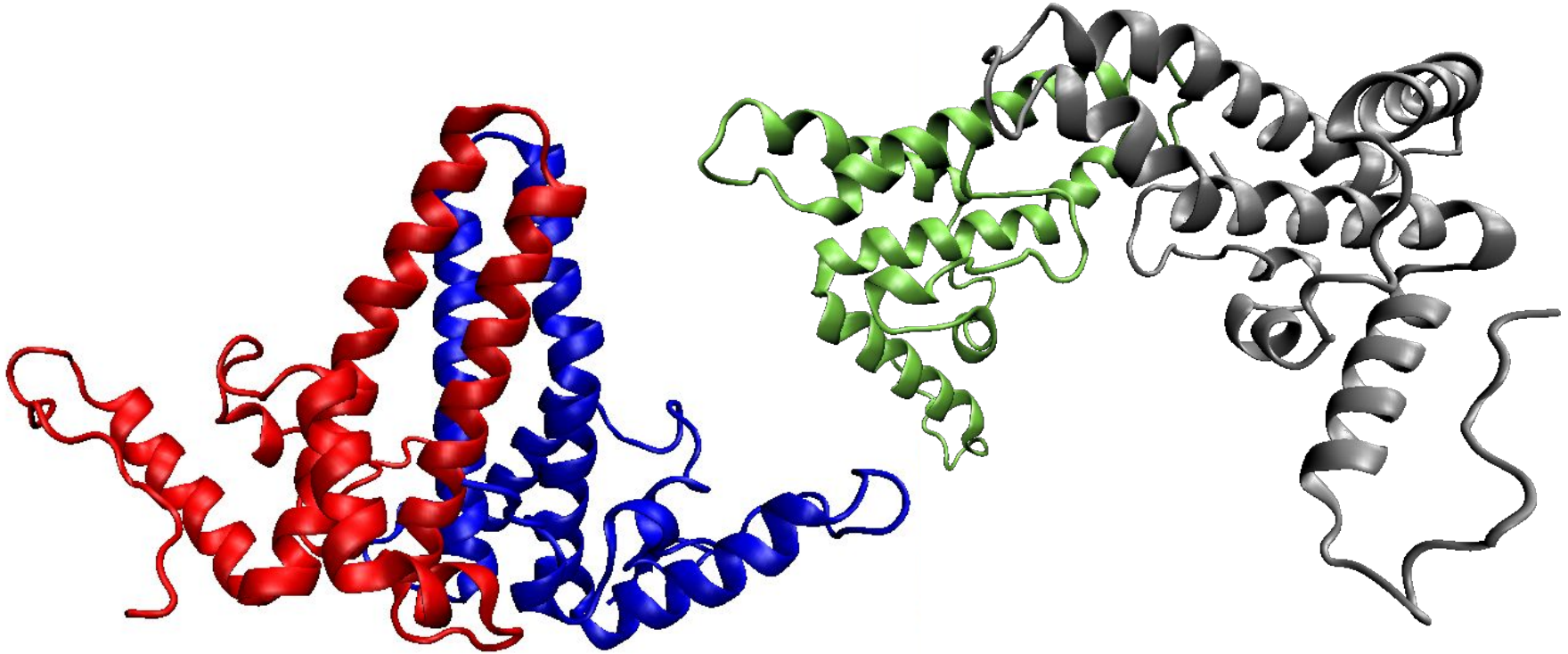


e-antigen

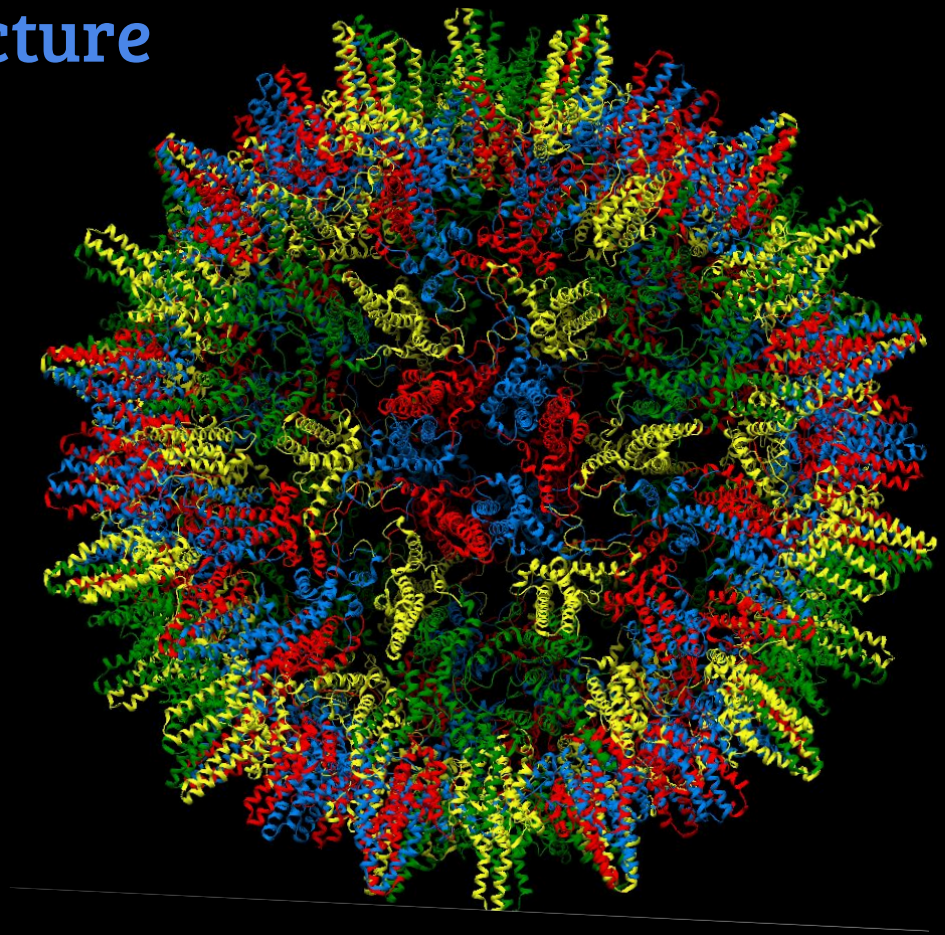
Hydrophobic interface is shielded by the propeptide



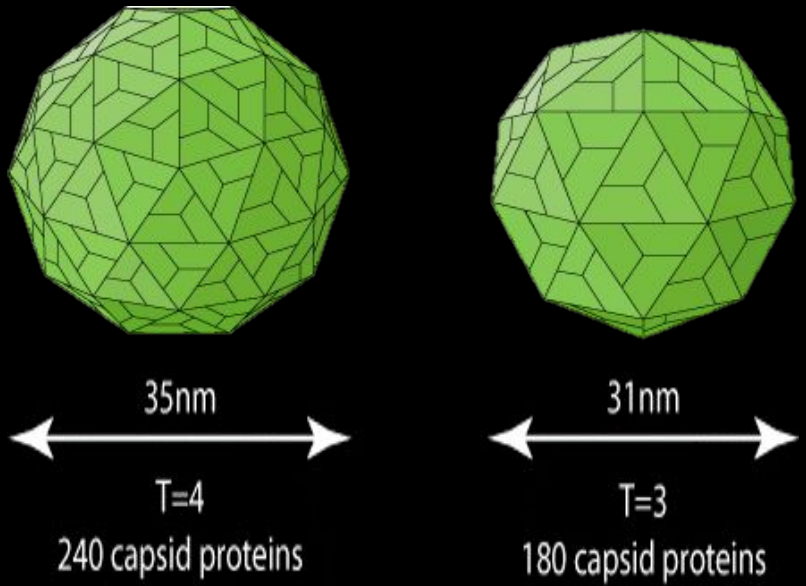
Different structures lead to a different function

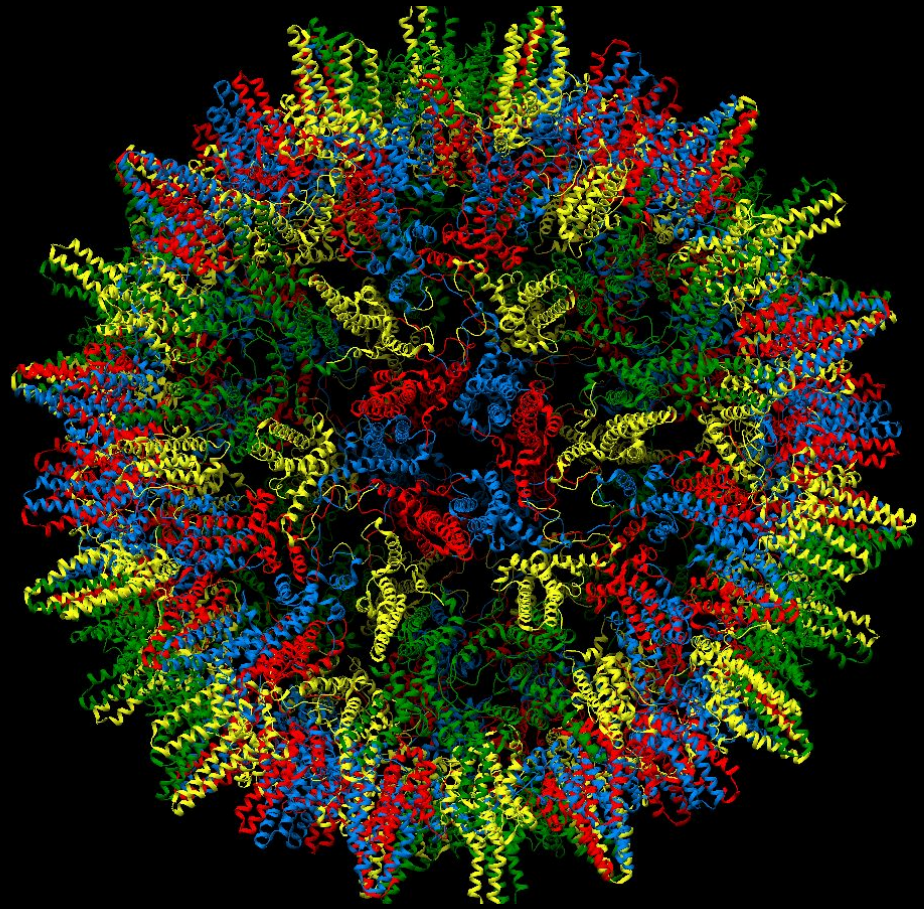


Capsid structure



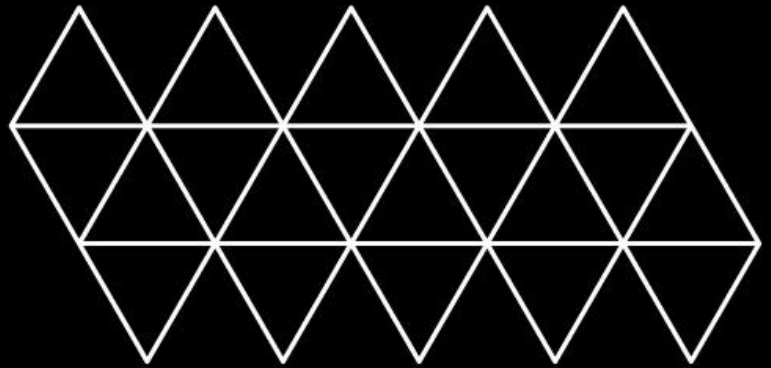
Capsid structure

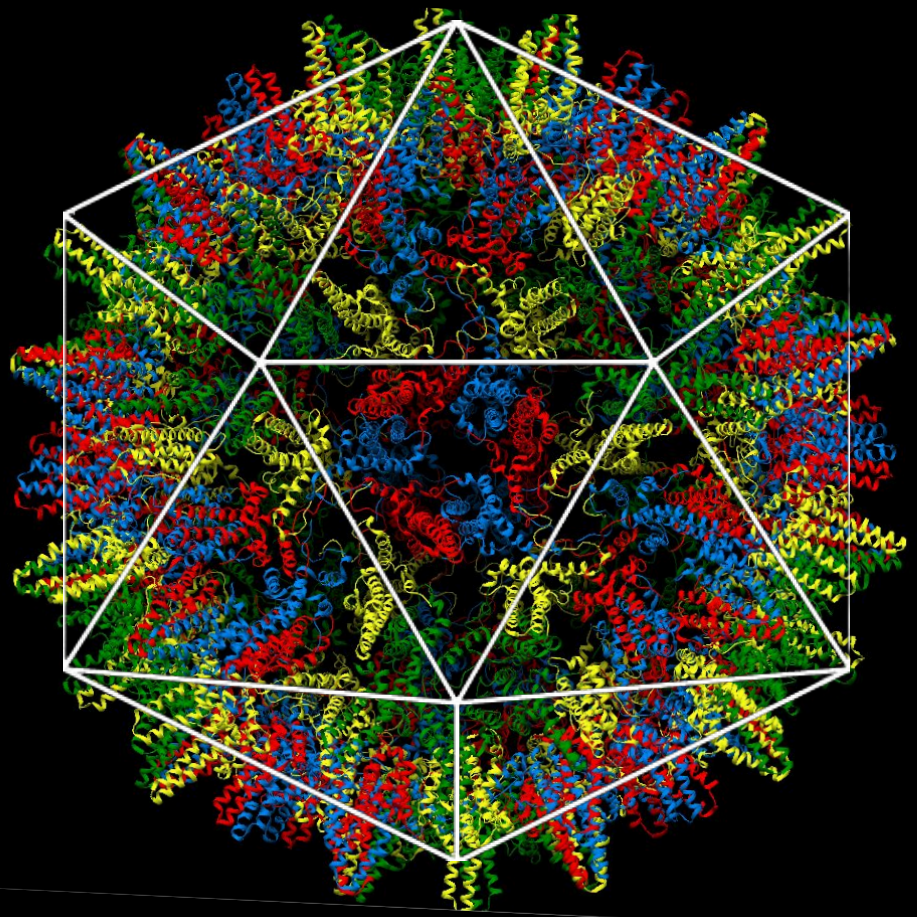




Capsid structure

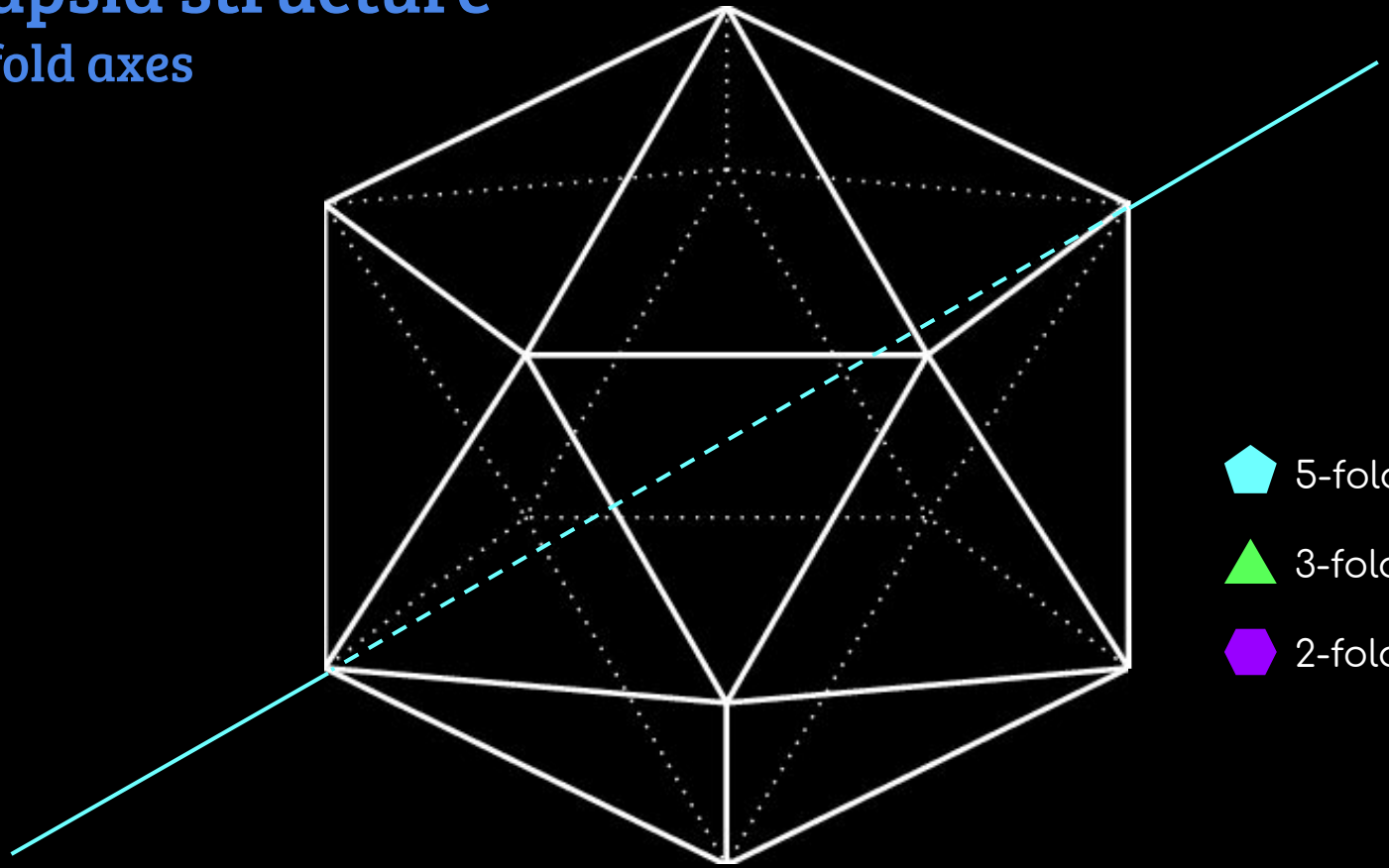
Symmetry

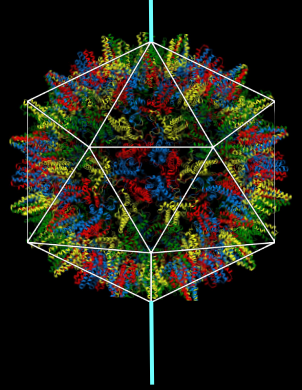




Capsid structure

5-fold axes





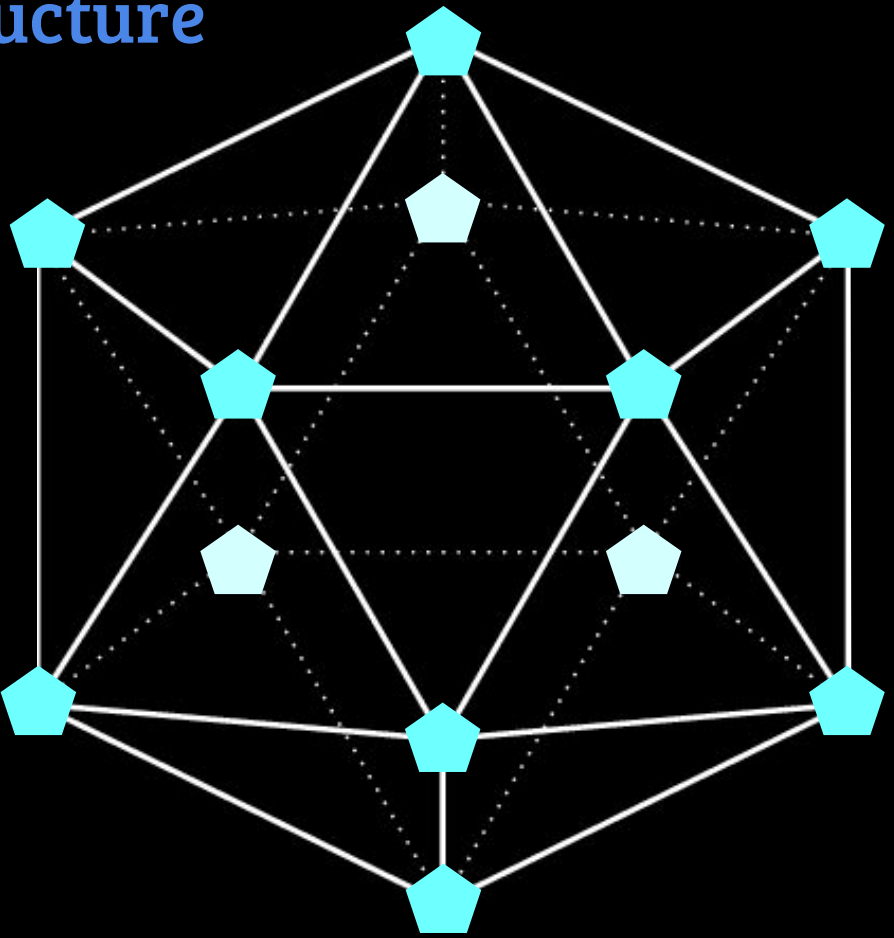
5-fold axis

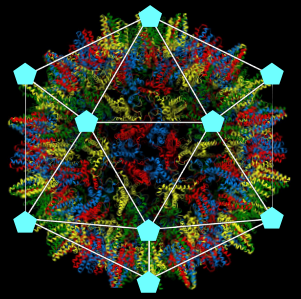
3-fold axis

2-fold axis

Capsid structure

5-fold axes





5-fold axis

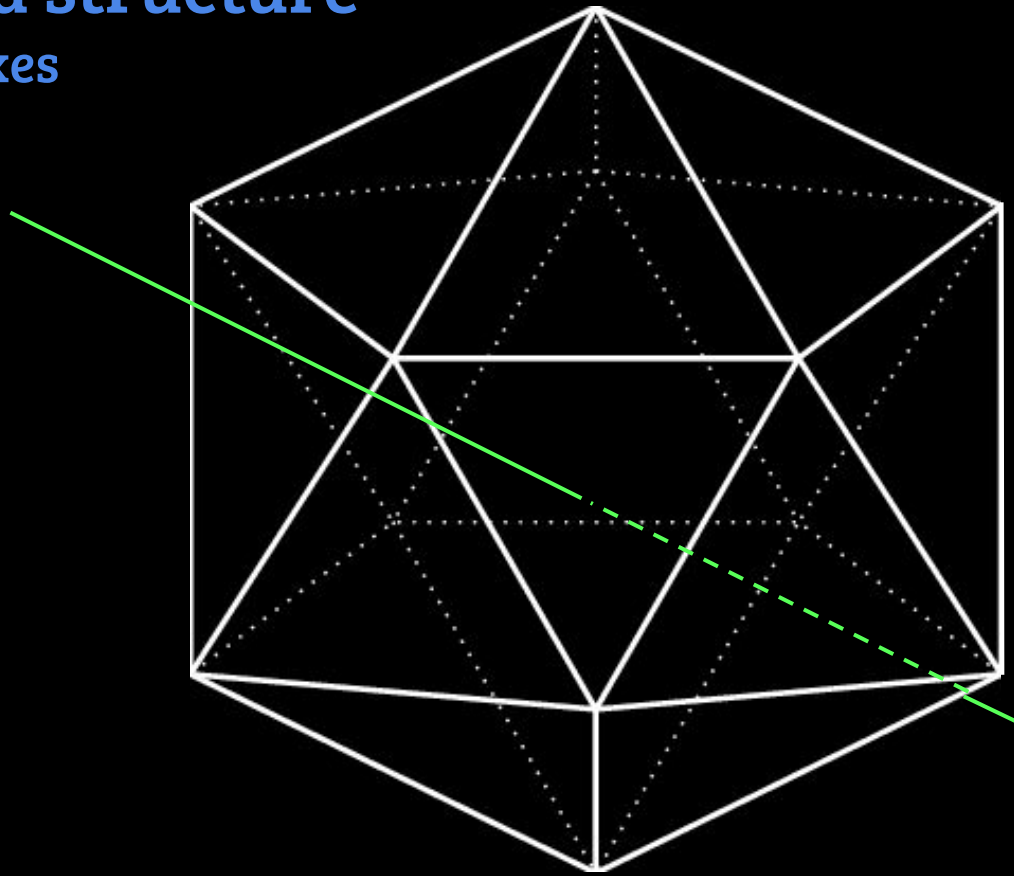
- 12 vertices
- 6 axes

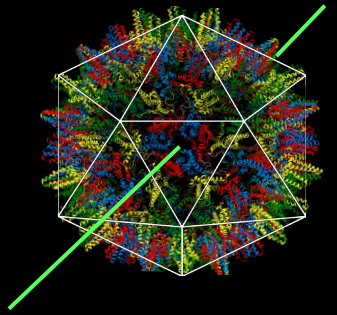
3-fold axis

2-fold axis

Capsid structure

3-fold axes





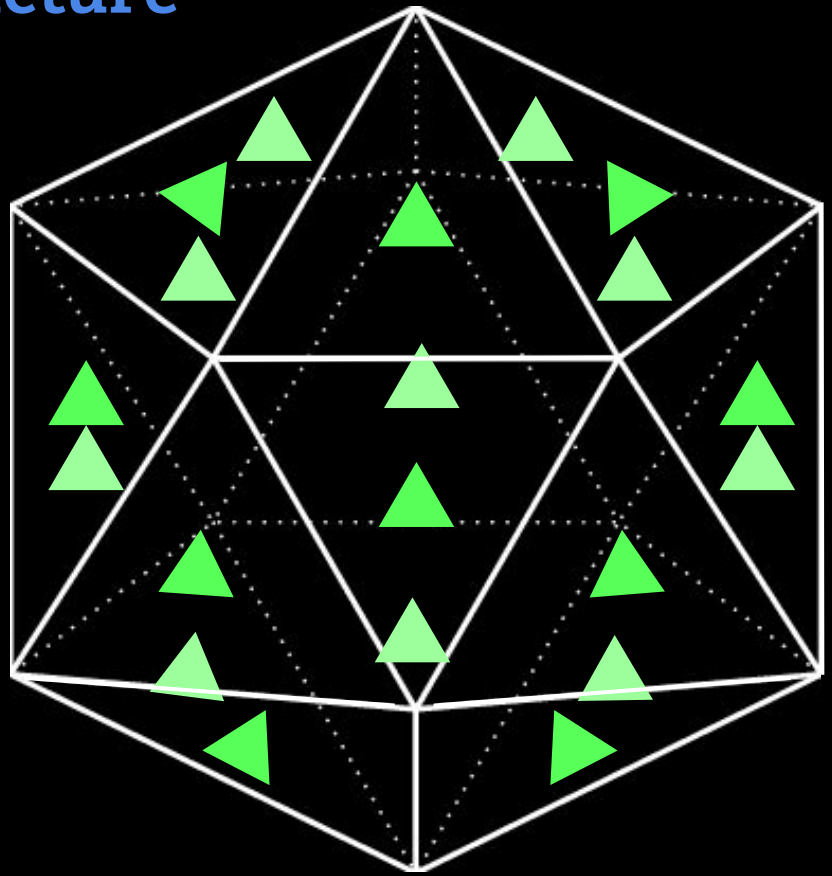
5-fold axis

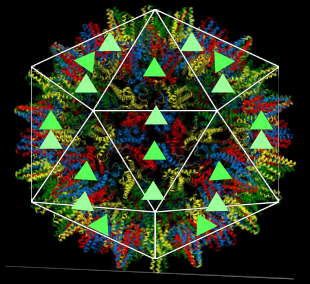
3-fold axis

2-fold axis

Capsid structure

3-fold axes





5-fold axis

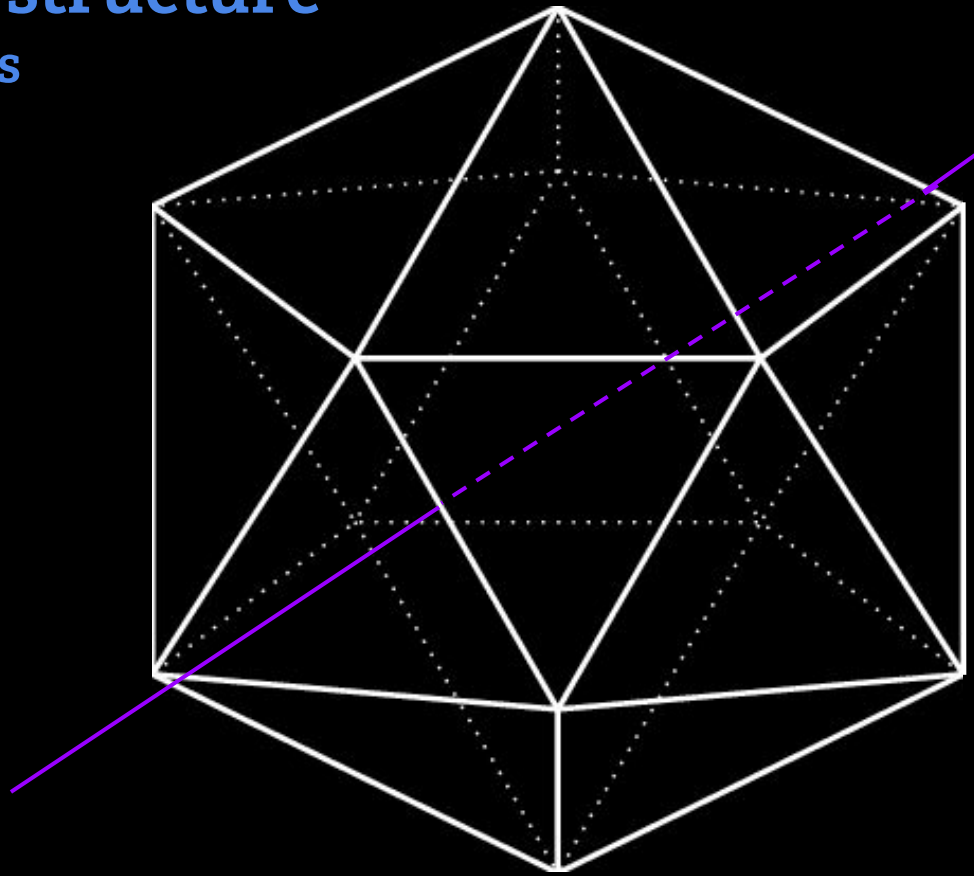
3-fold axis

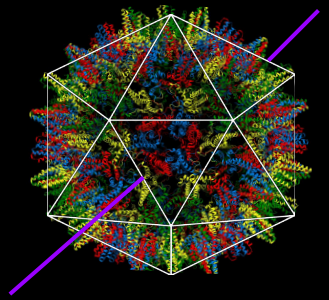
- 20 faces
- 10 axes

2-fold axis

Capsid structure

2-fold axes





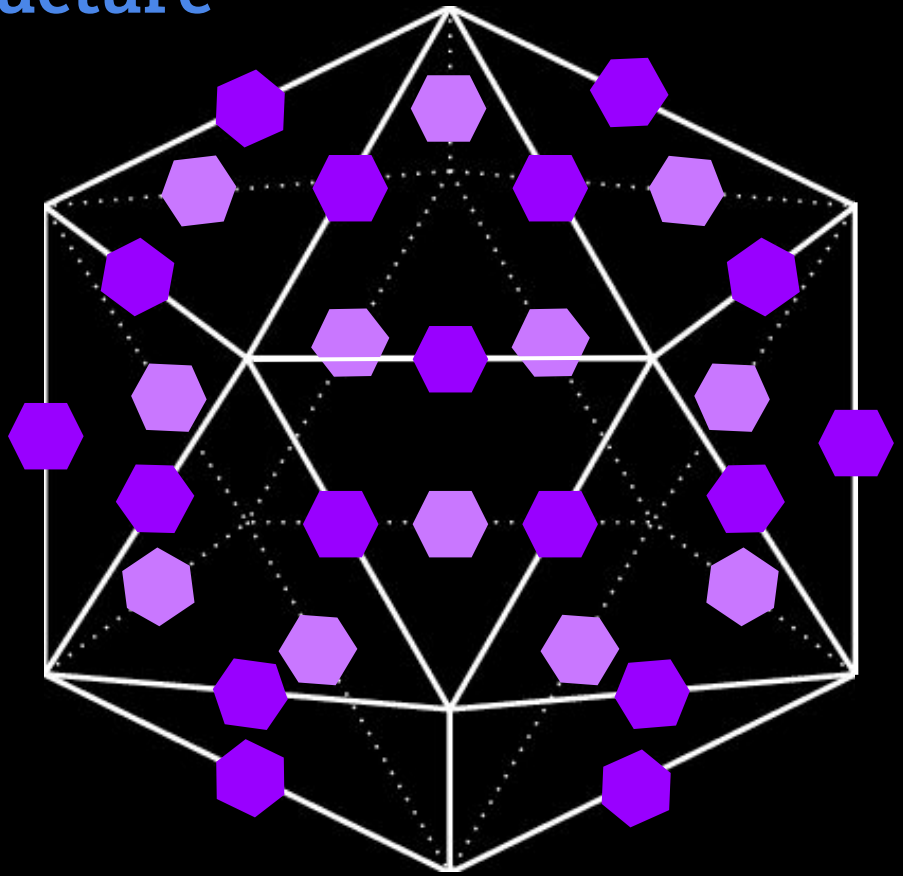
5-fold axis

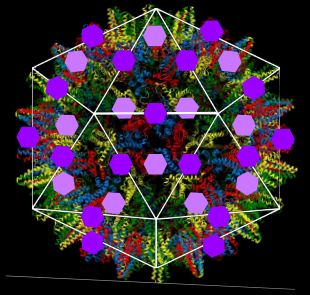
3-fold axis

2-fold axis

Capsid structure

2-fold axes





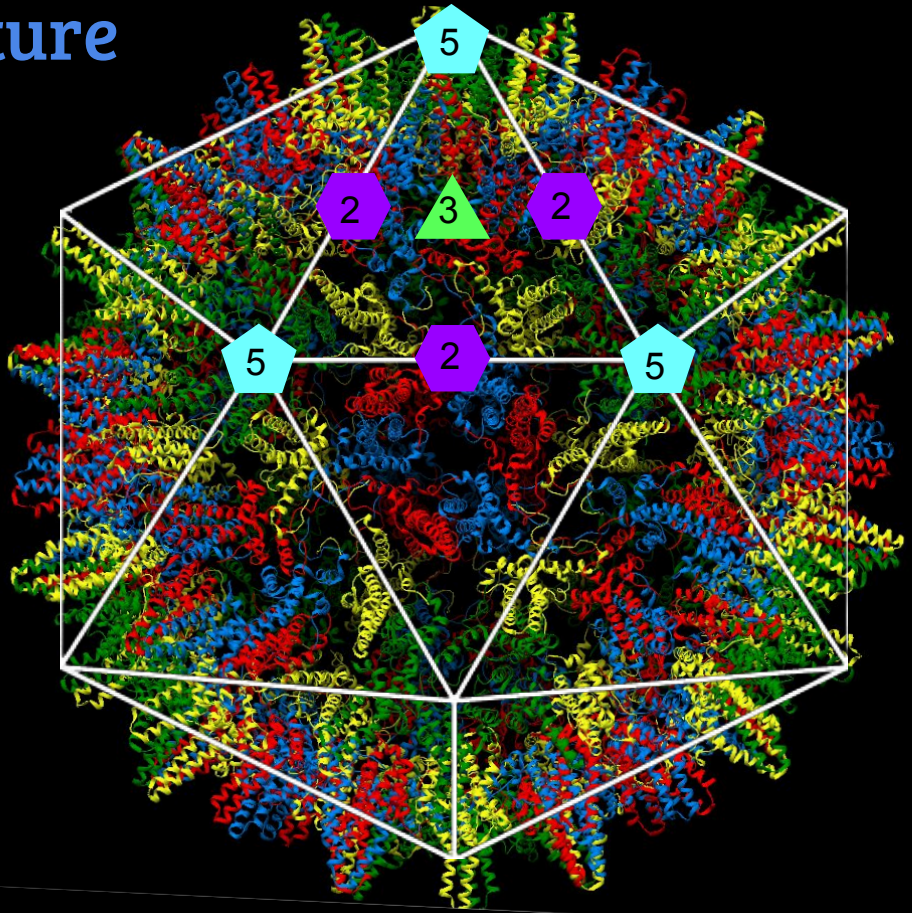
5-fold axis

3-fold axis

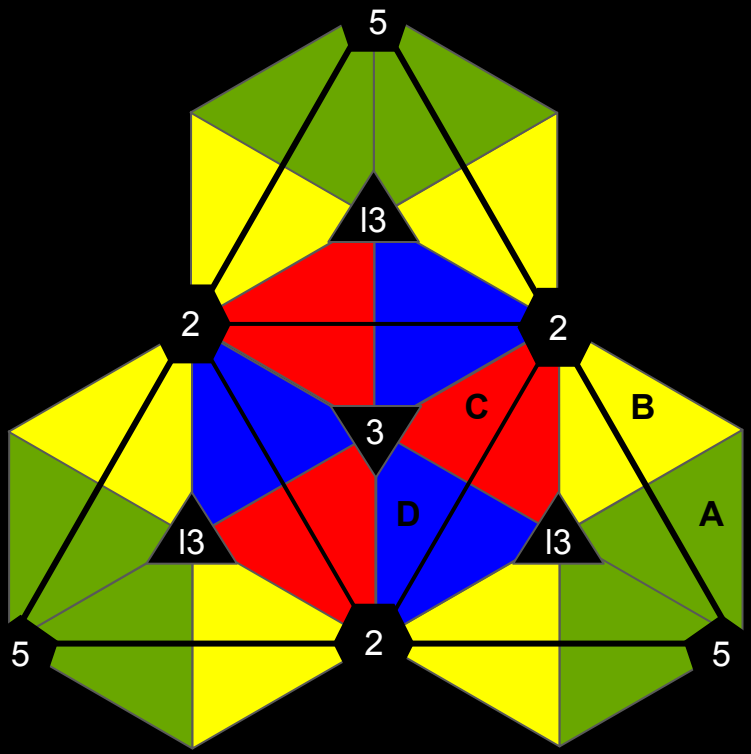
2-fold axis

- 30 edges
- 15 axes

Capsid structure

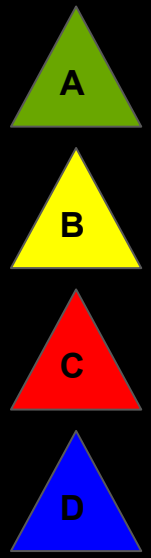


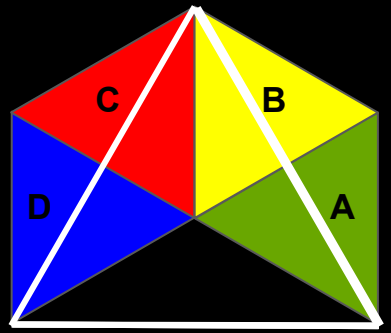
Capsid structure



Capsid structure

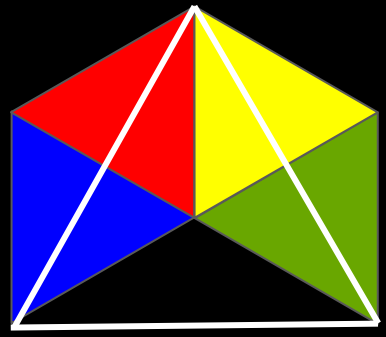
Asymmetric unit assembly

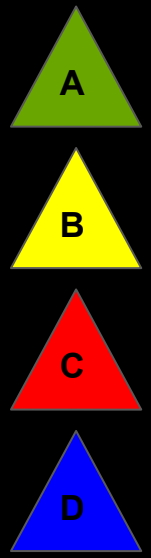




Capsid structure

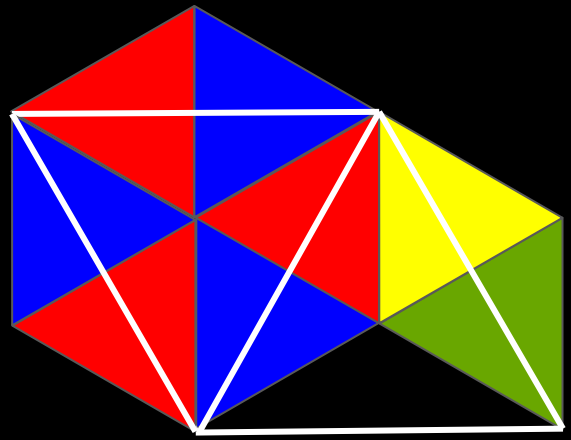
Asymmetric unit assembly

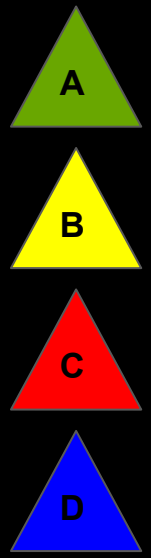




Capsid structure

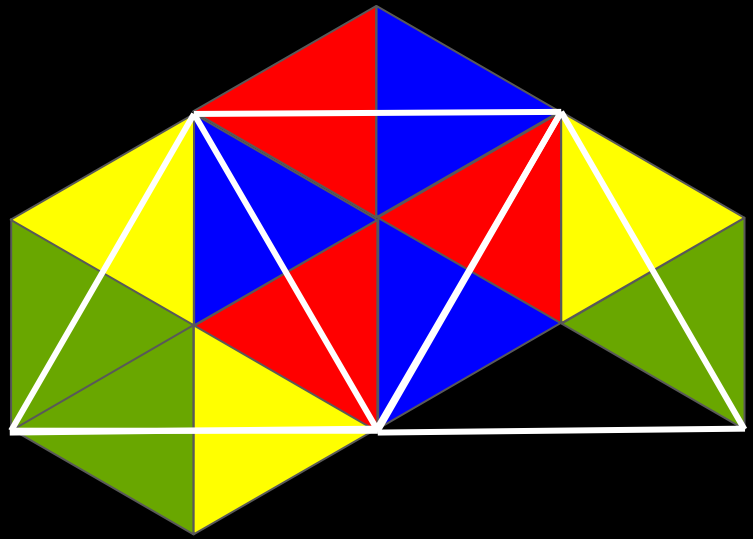
Asymmetric unit assembly

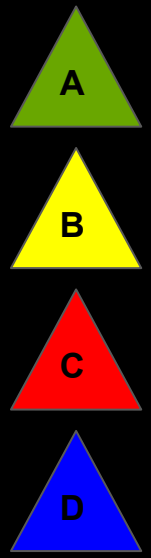




Capsid structure

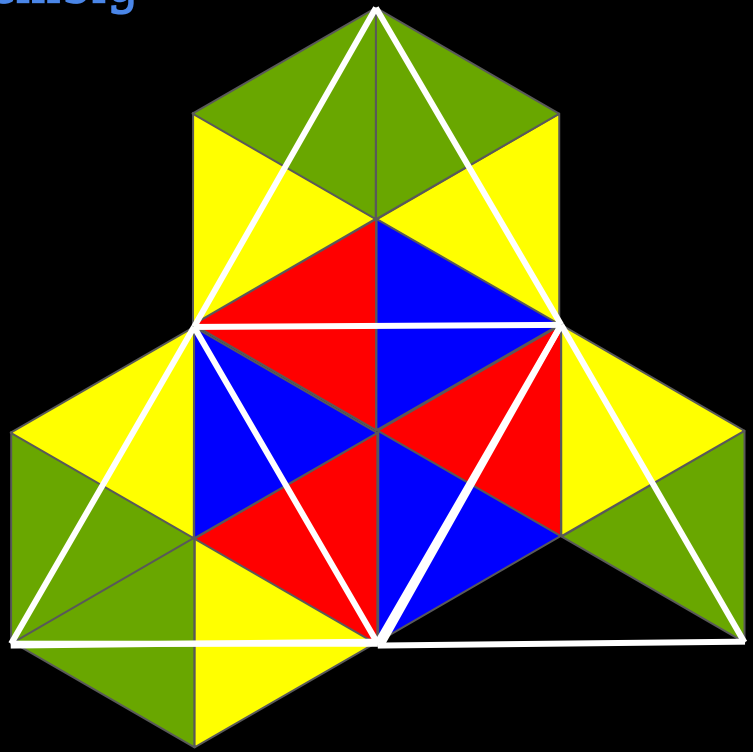
Asymmetric unit assembly

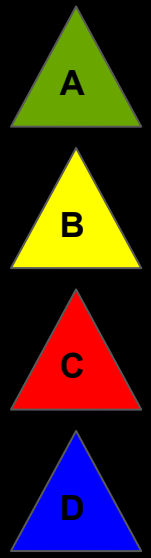




Capsid structure

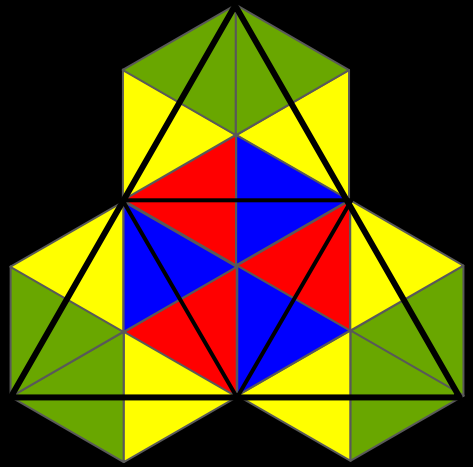
Asymmetric unit assembly





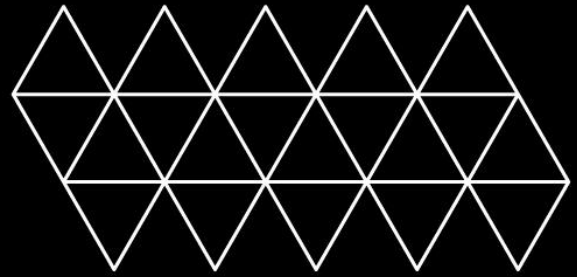
Capsid structure

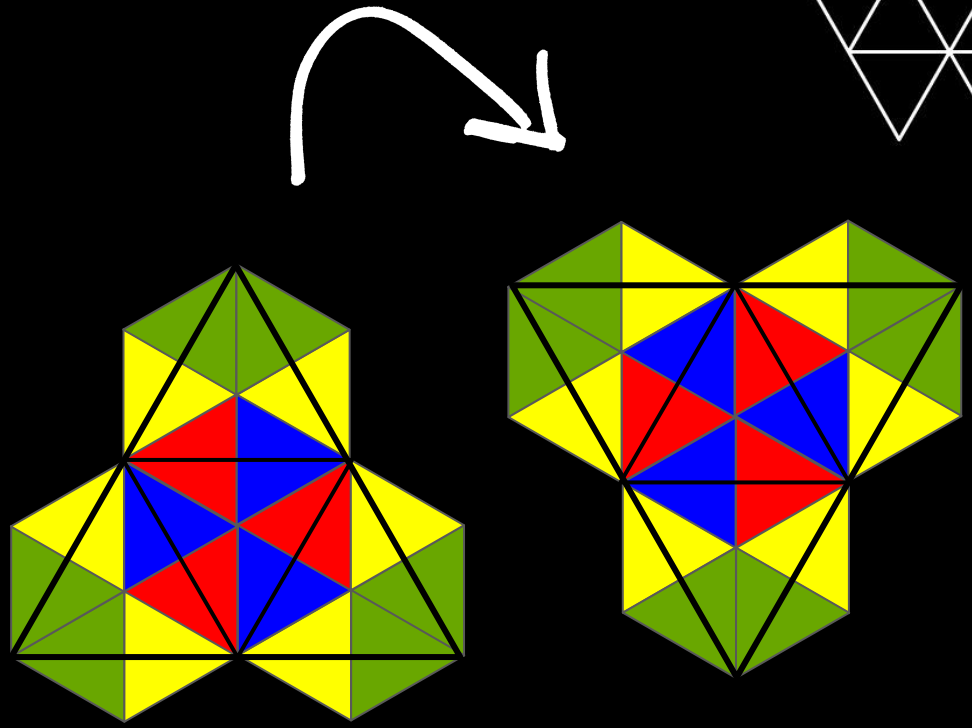
Asymmetric unit assembly



Capsid structure

Capsid assembly





Capsid structure

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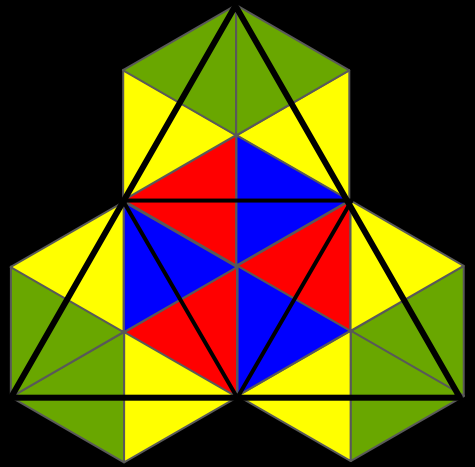

Capsid structure

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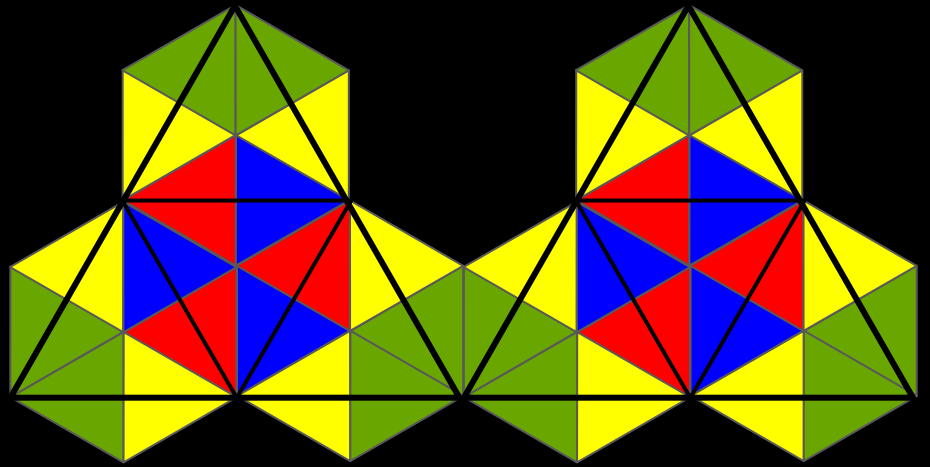

Capsid structure

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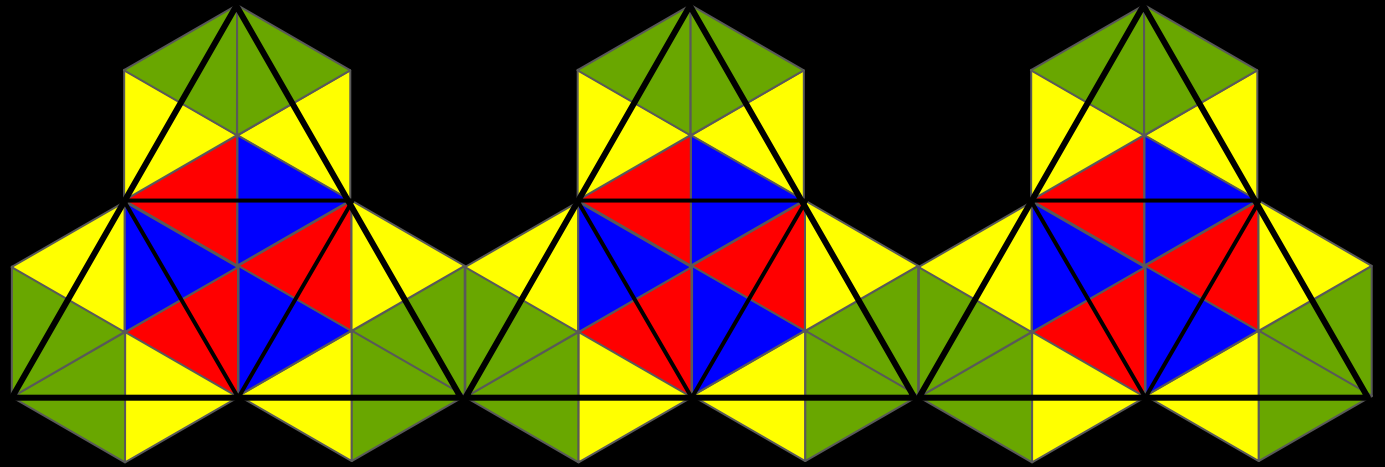

Capsid structure

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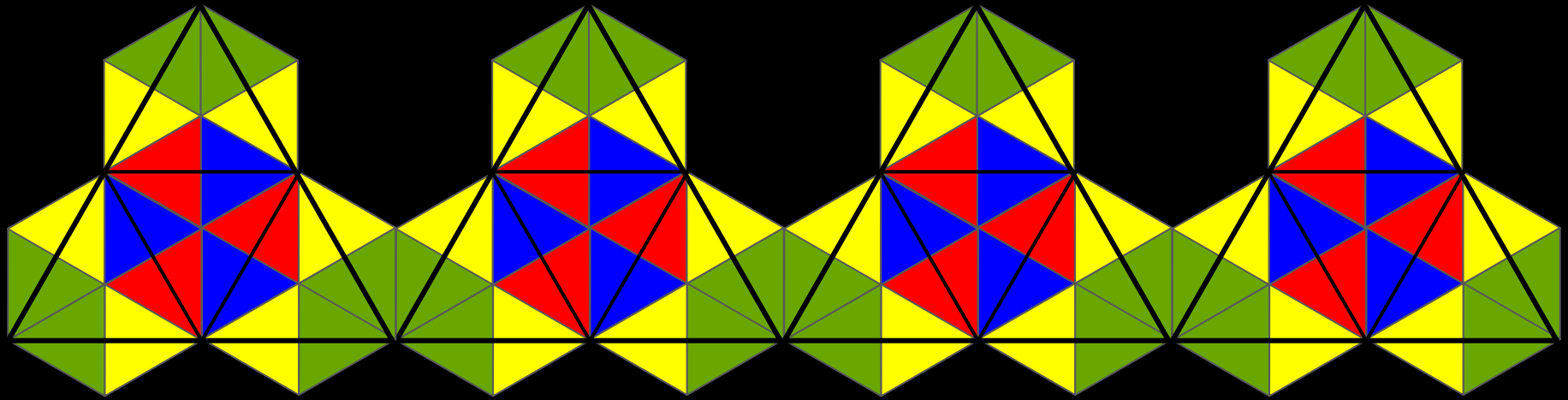

Capsid structure

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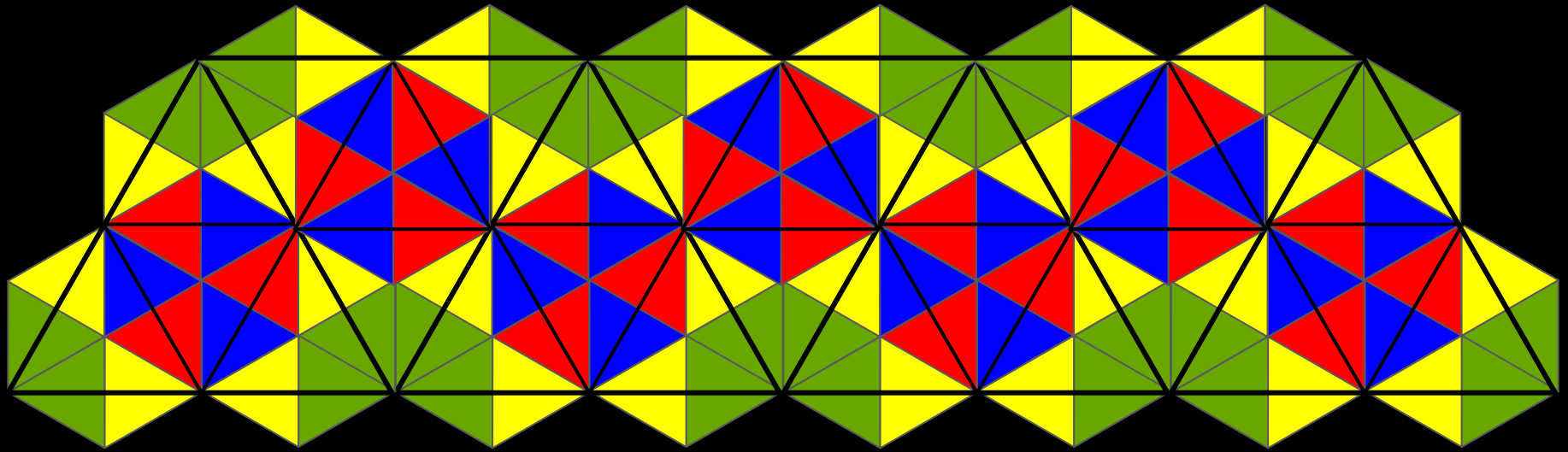
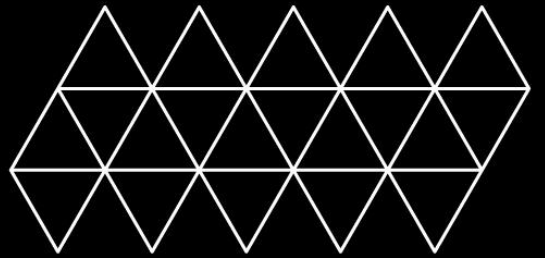
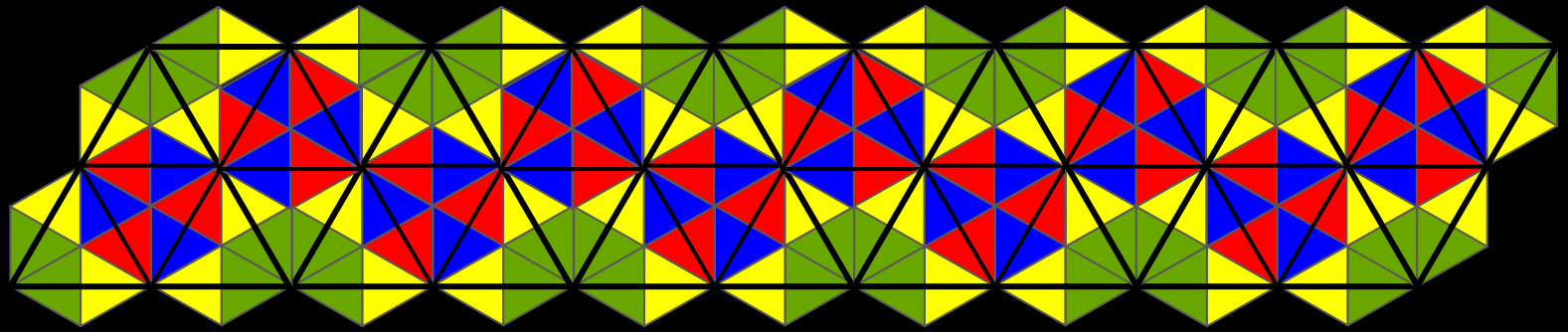


Capsid structure

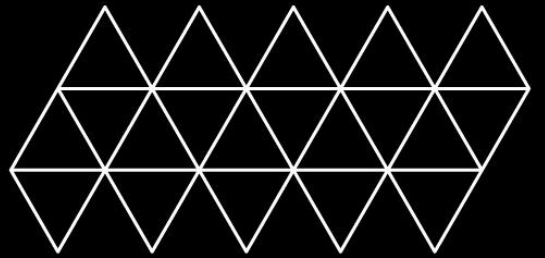
Capsid assembly

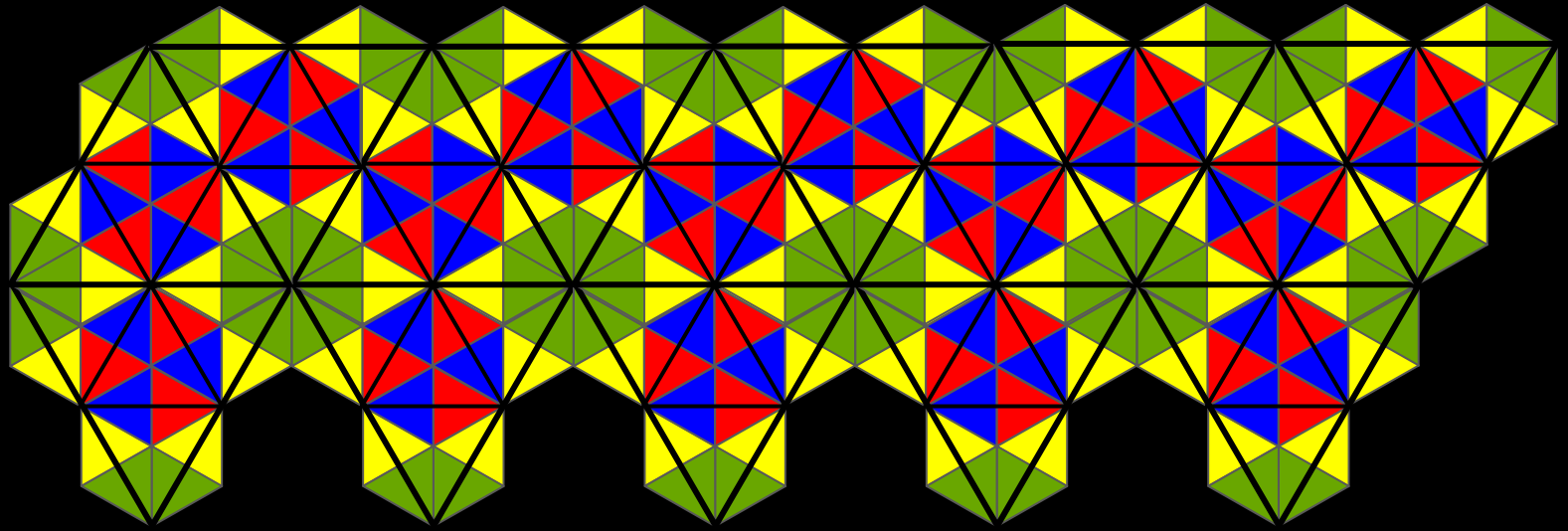




Capsid structure

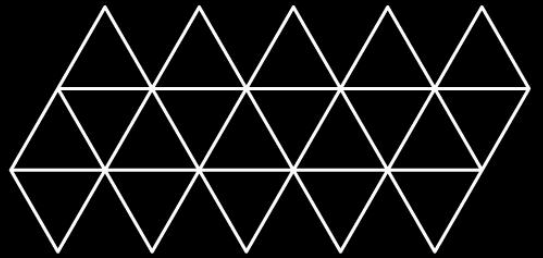
Capsid assembly

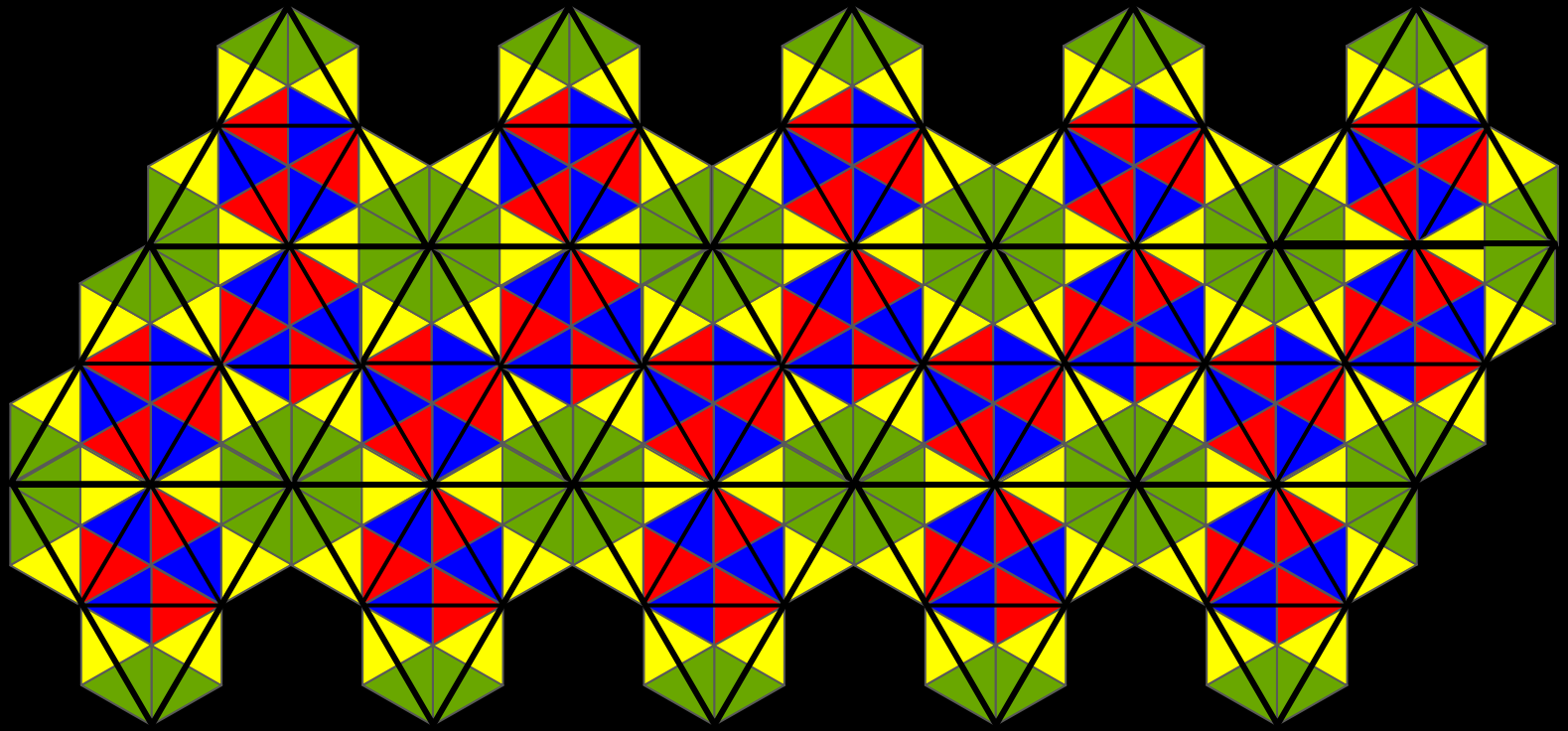




Capsid structure

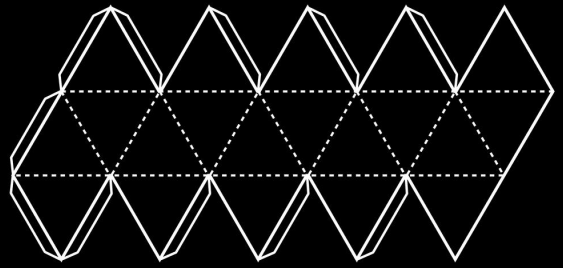
Capsid assembly

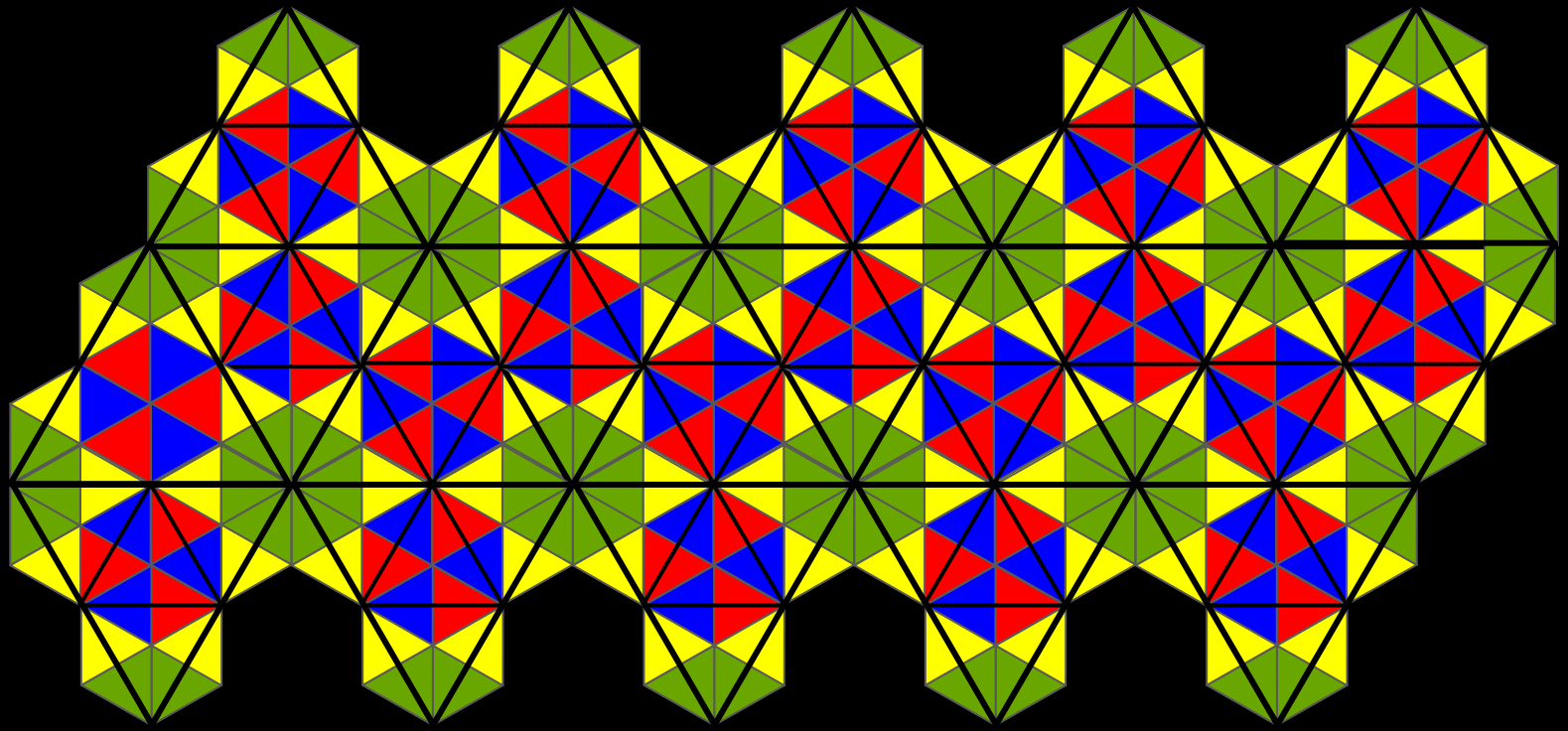




Capsid structure

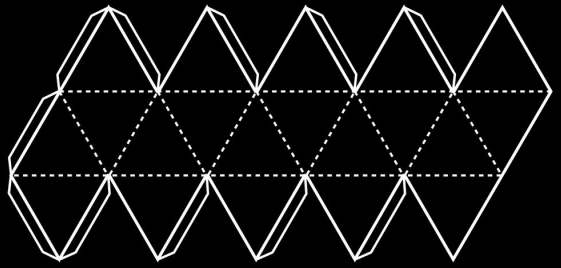
Capsid assembly

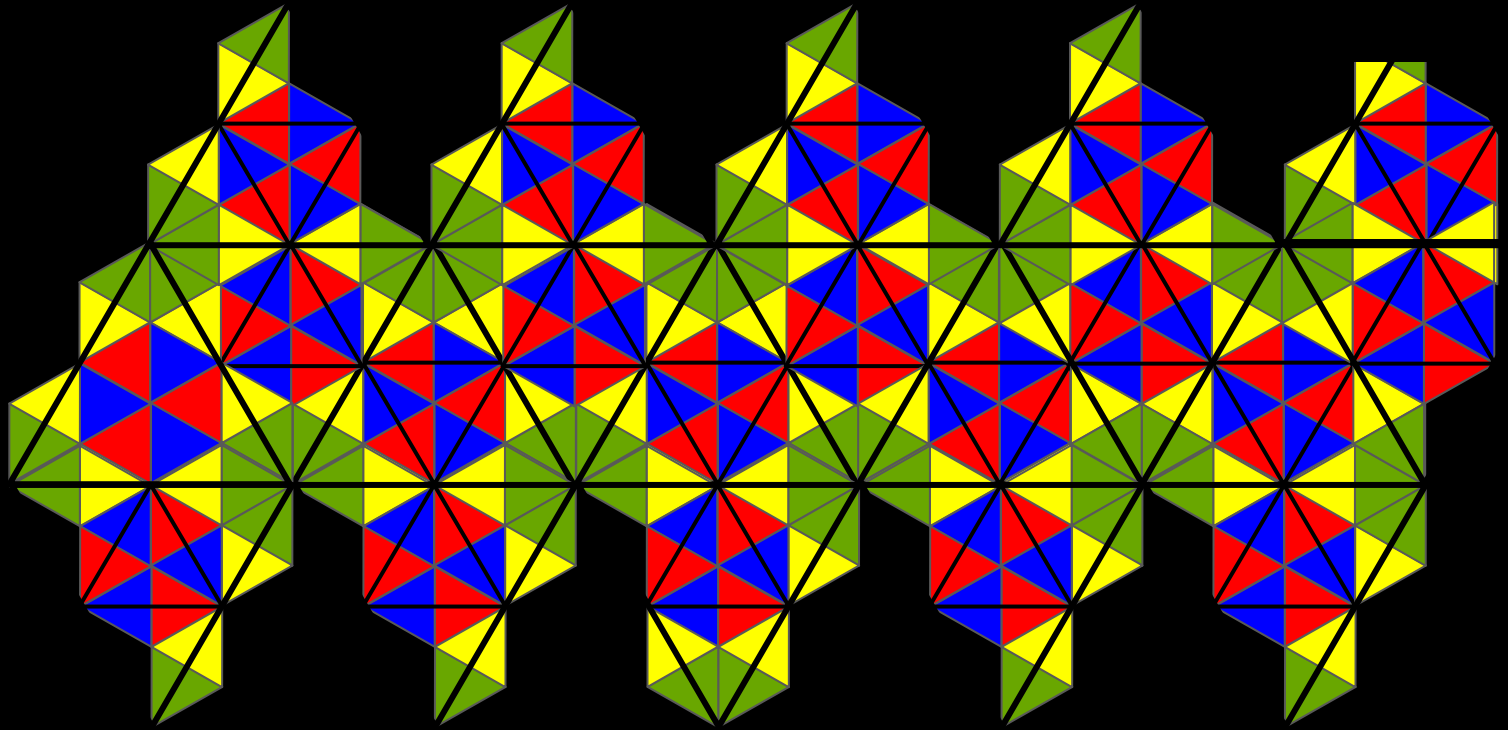




Capsid structure

Capsid assembly





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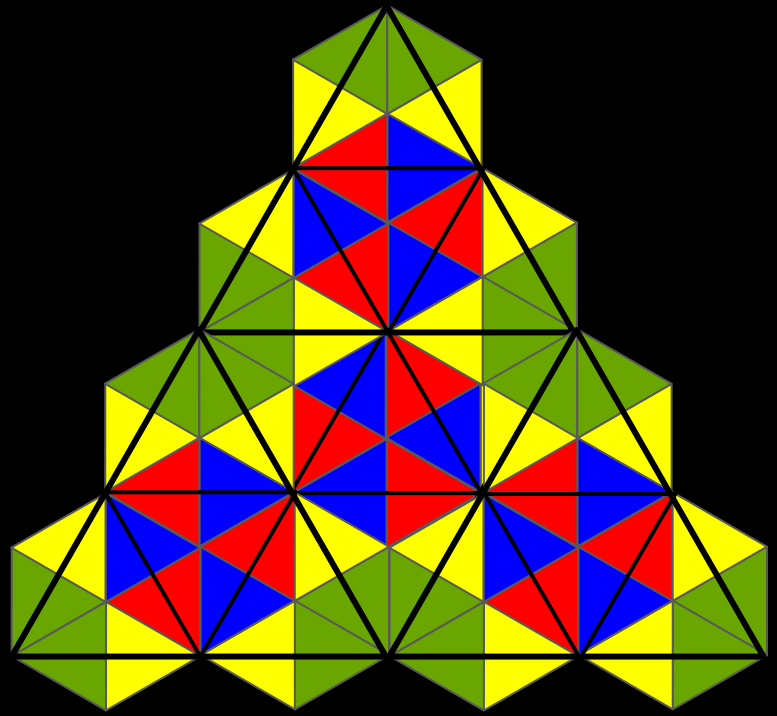

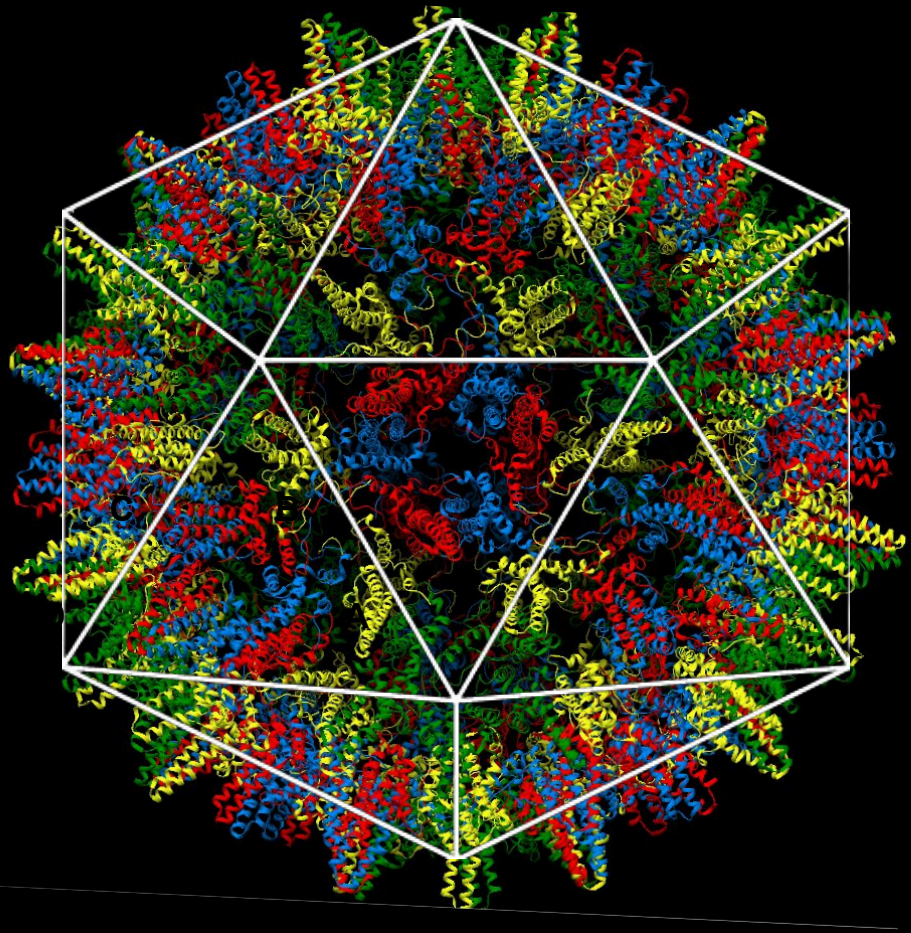

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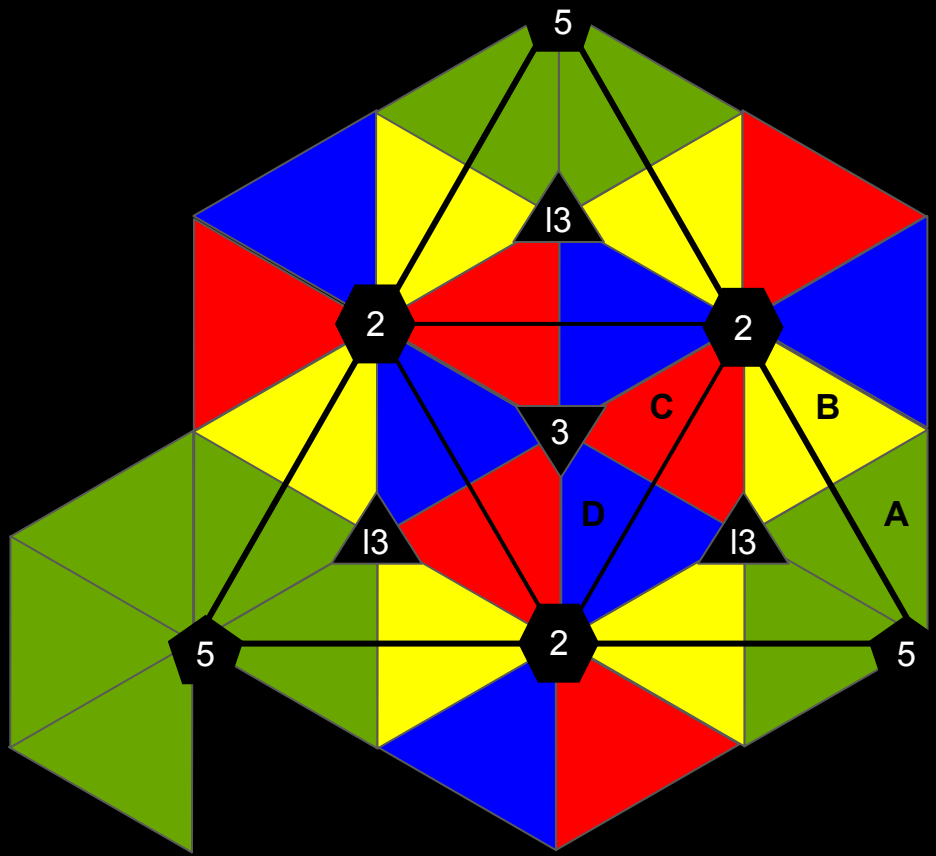

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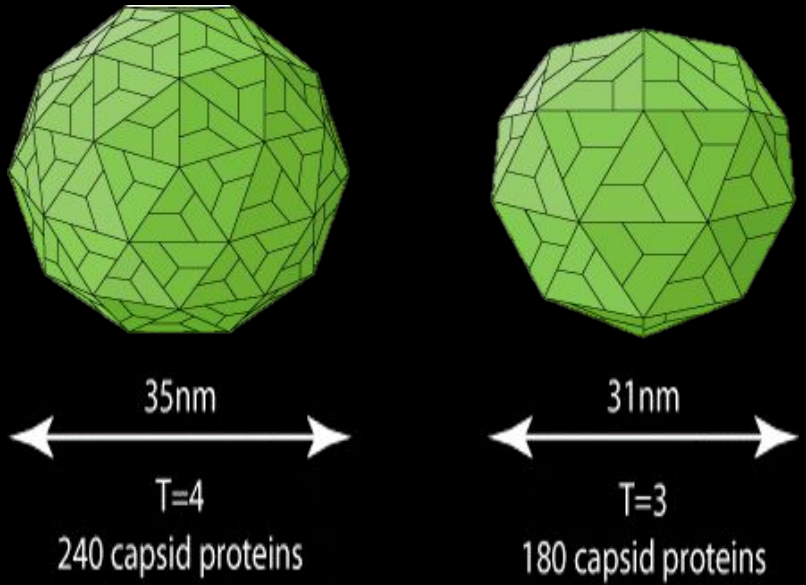
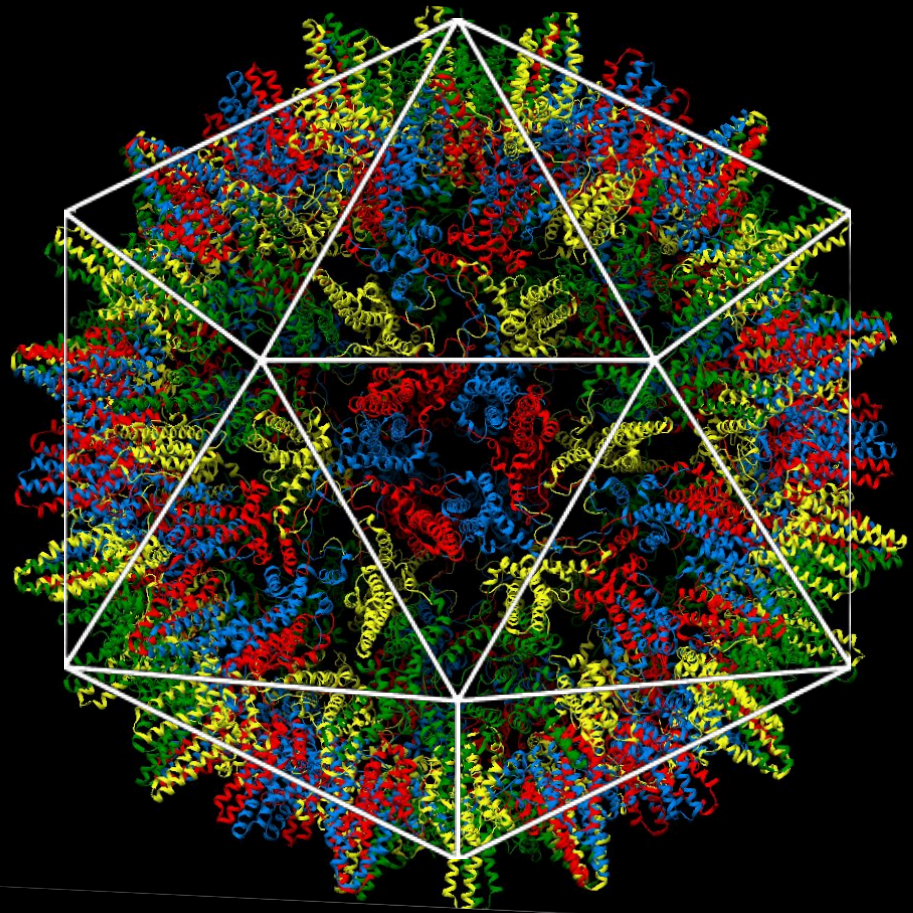
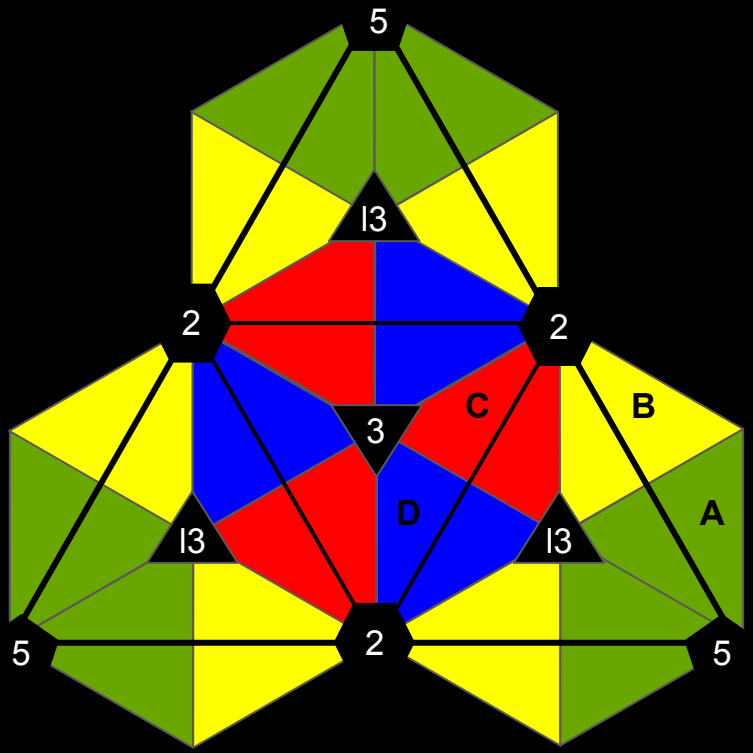




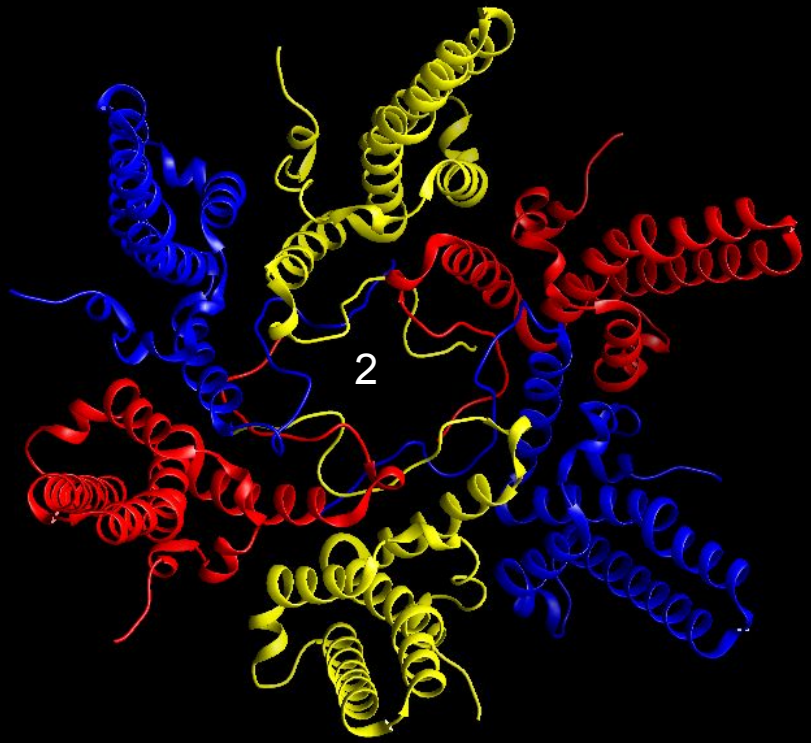
Capsid structure

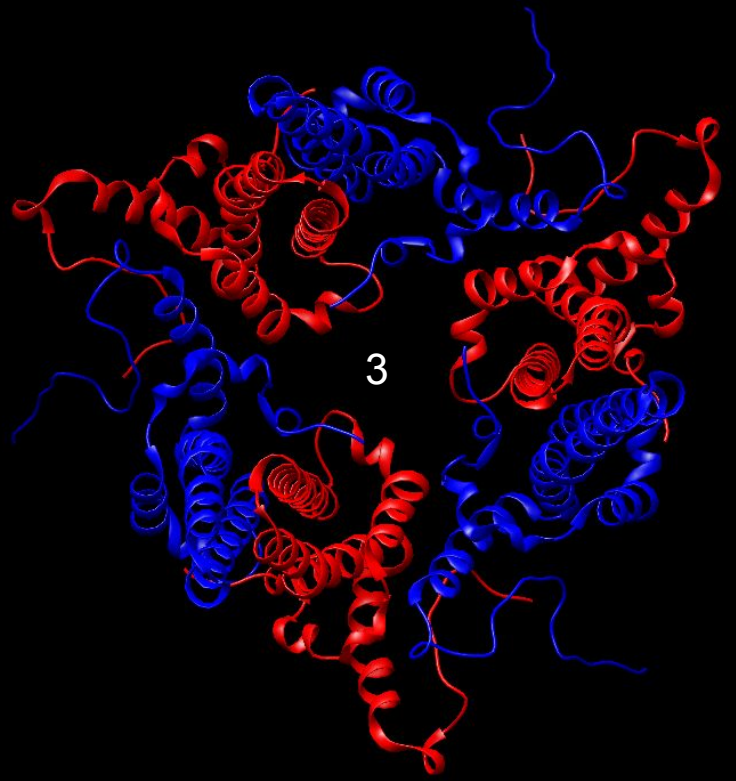
Fenestrations



Capsid structure

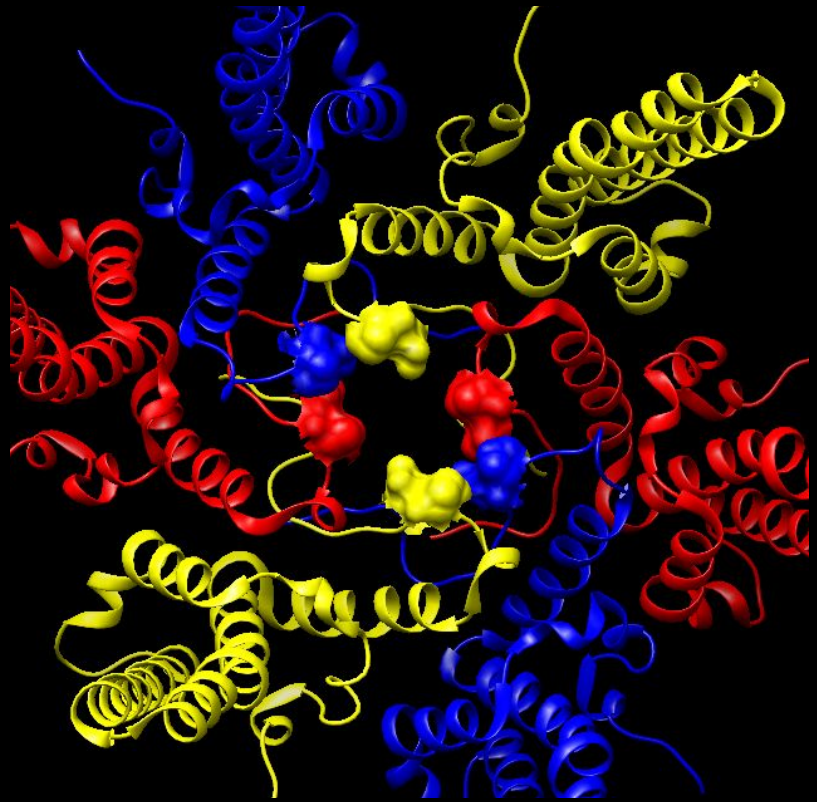
Fenestrations





Capsid structure

Fenestrations



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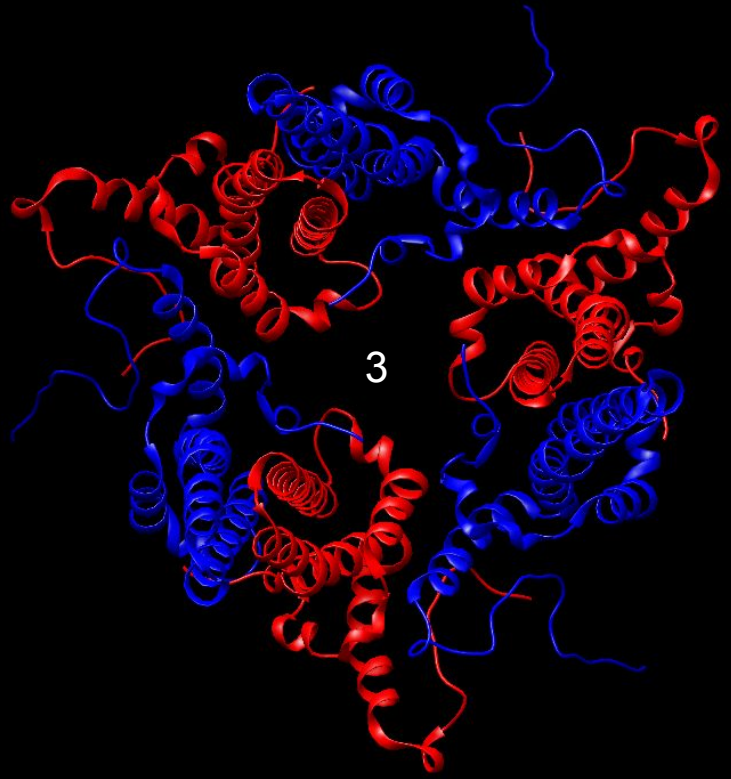
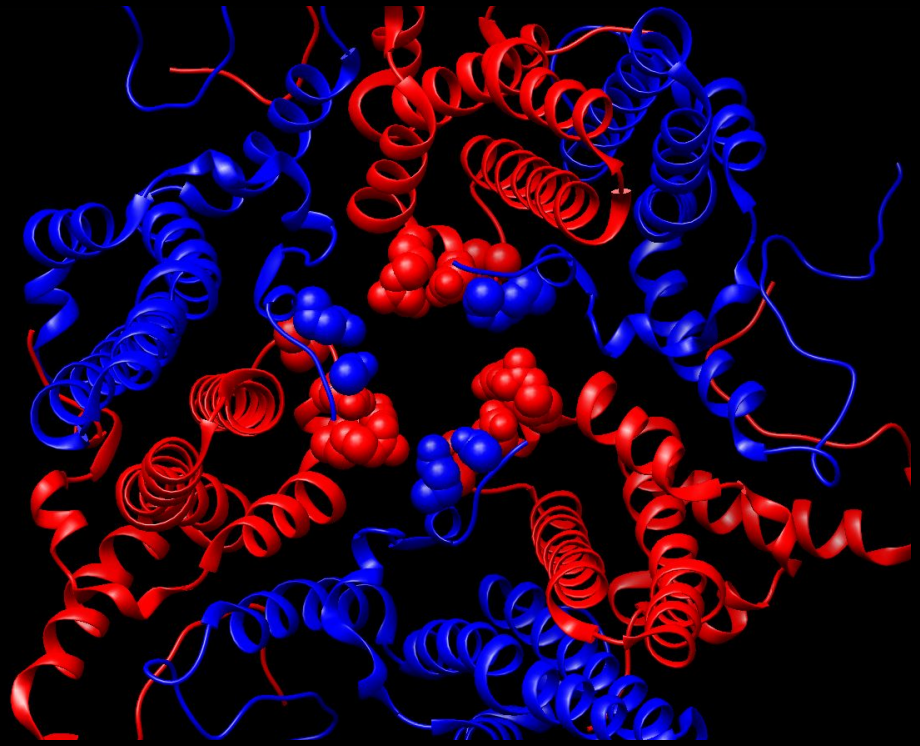
Fenestrations





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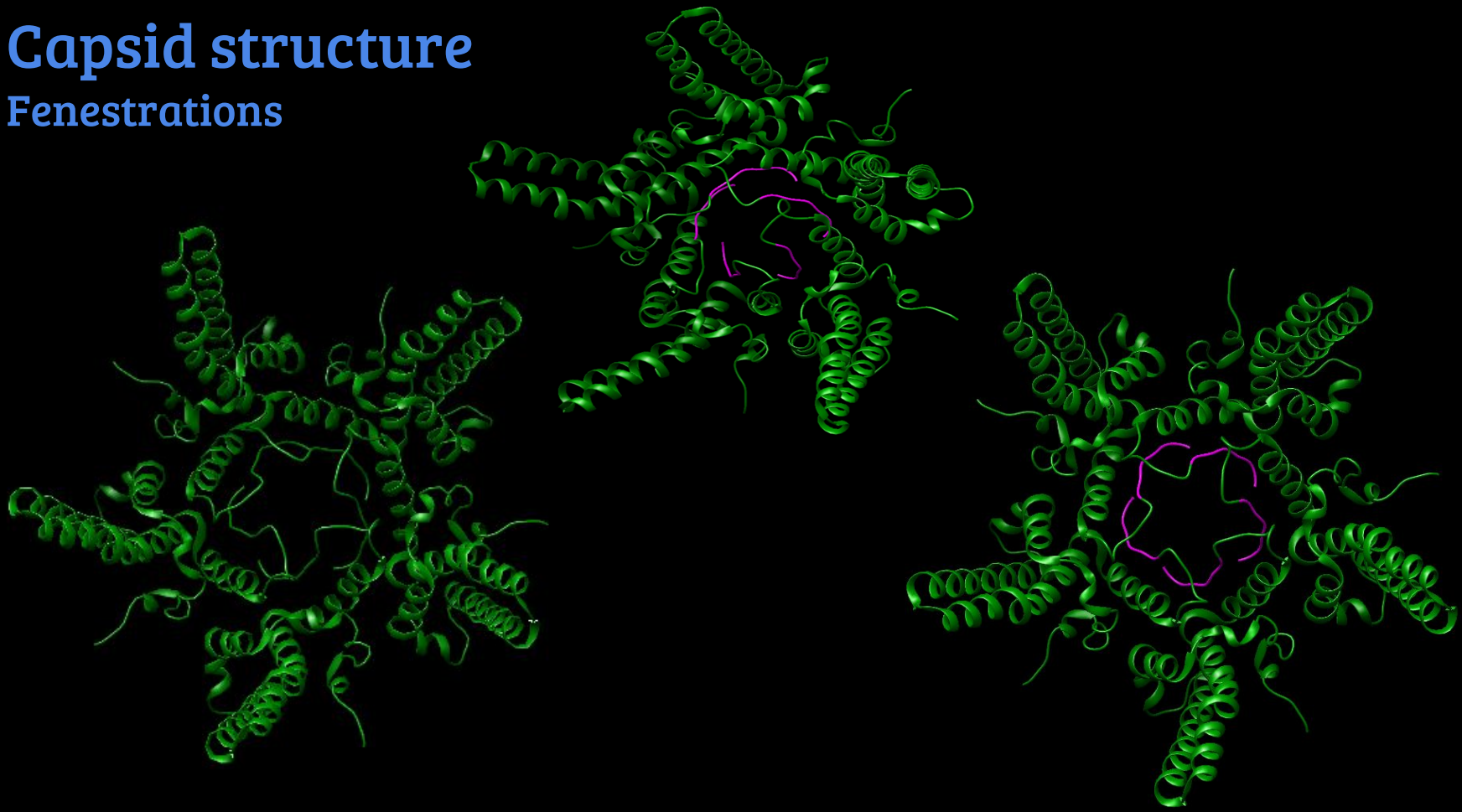
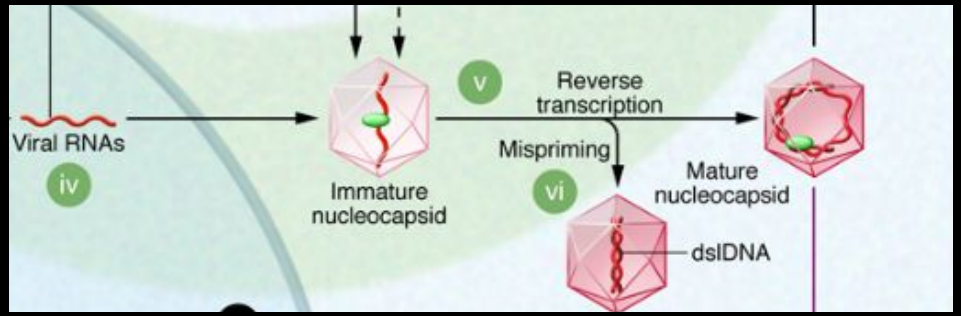
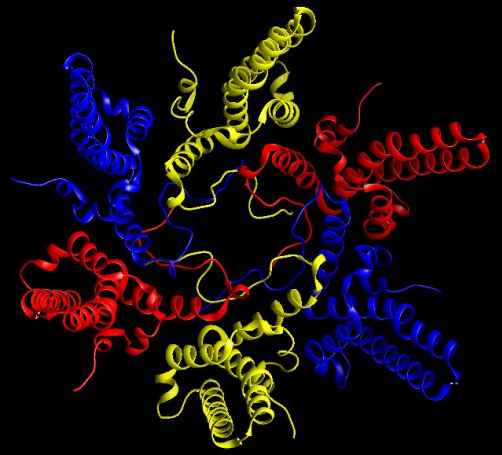
Fenestrations

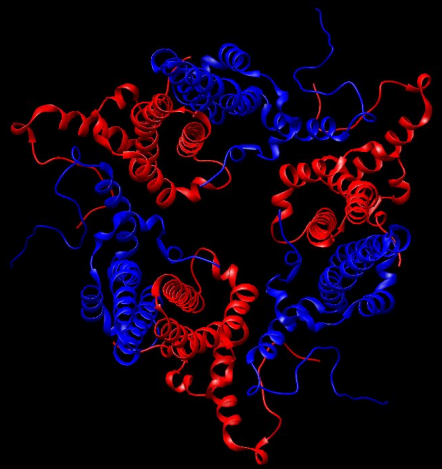


Capsid structure

Fenestrations

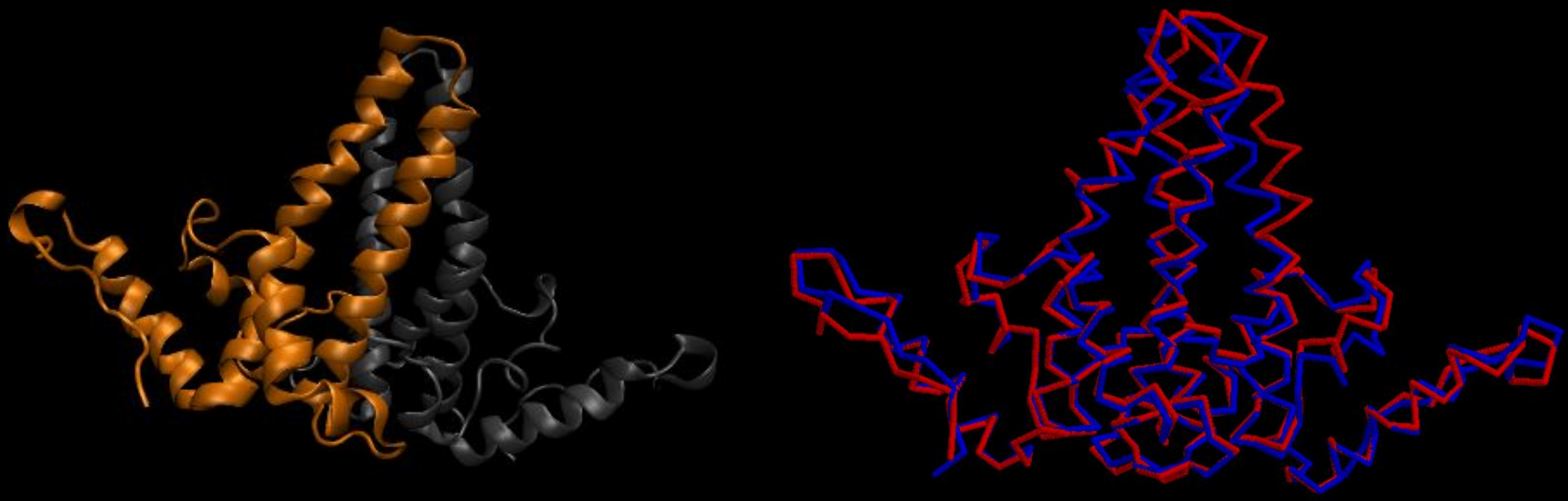






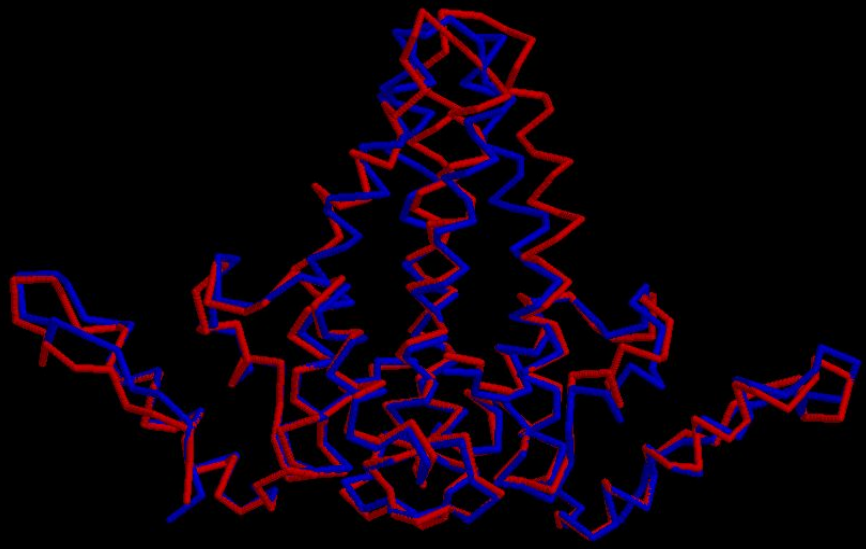
Capsid structure

Dimer conformation, free vs capsid form



Capsid structure

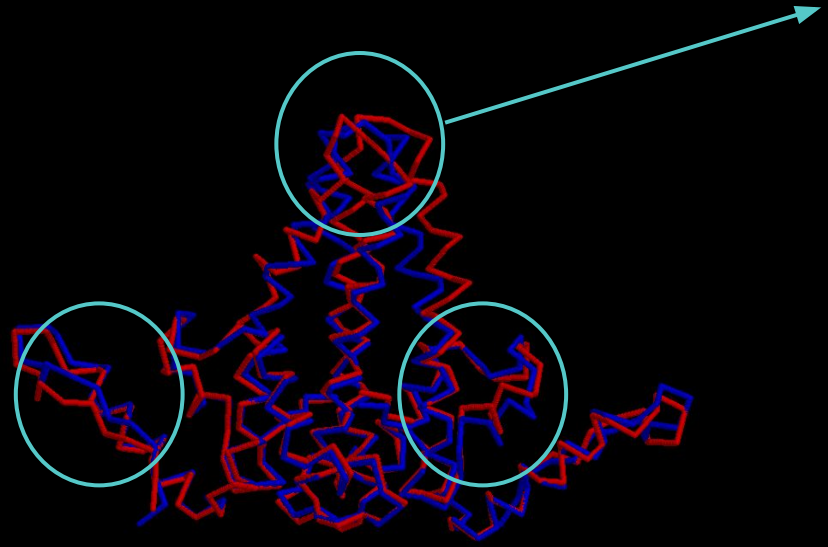
Dimer conformation, free vs capsid form



RMSD value = 1.41

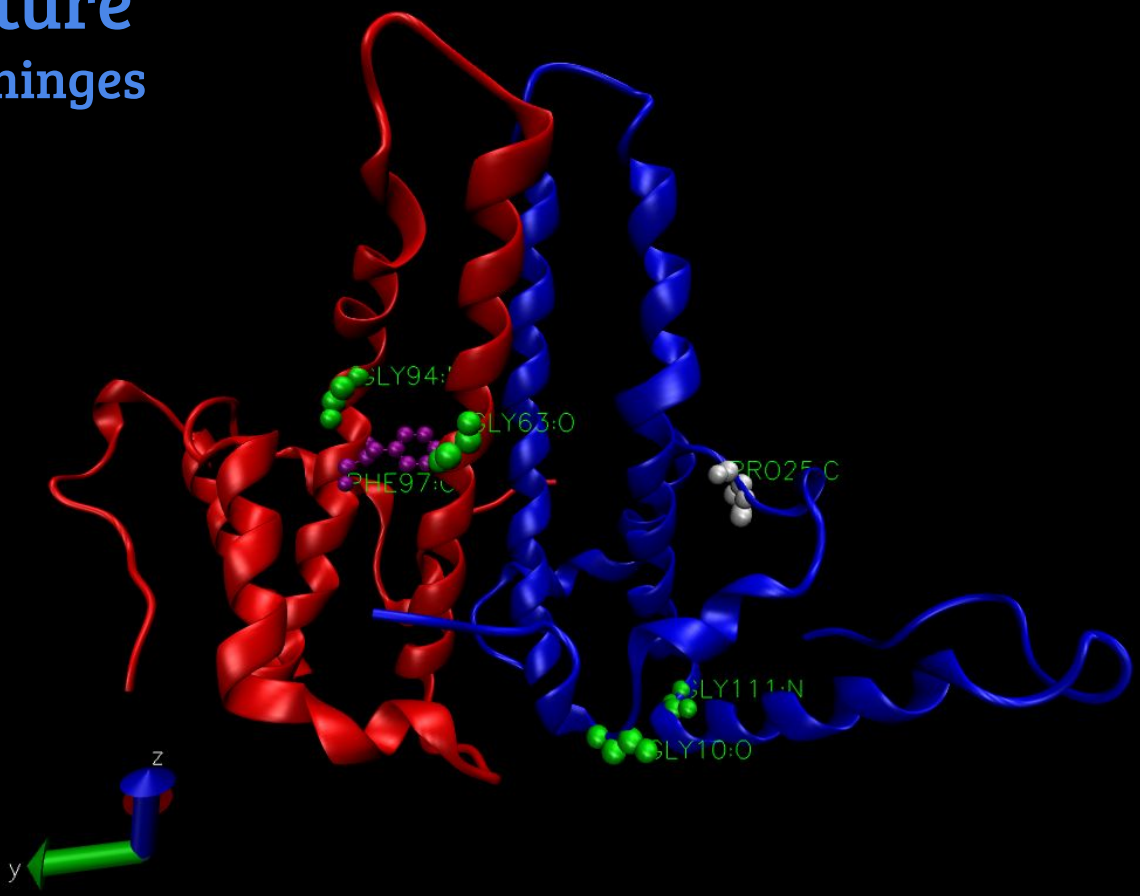
Capsid structure

Distances at the top of the spike



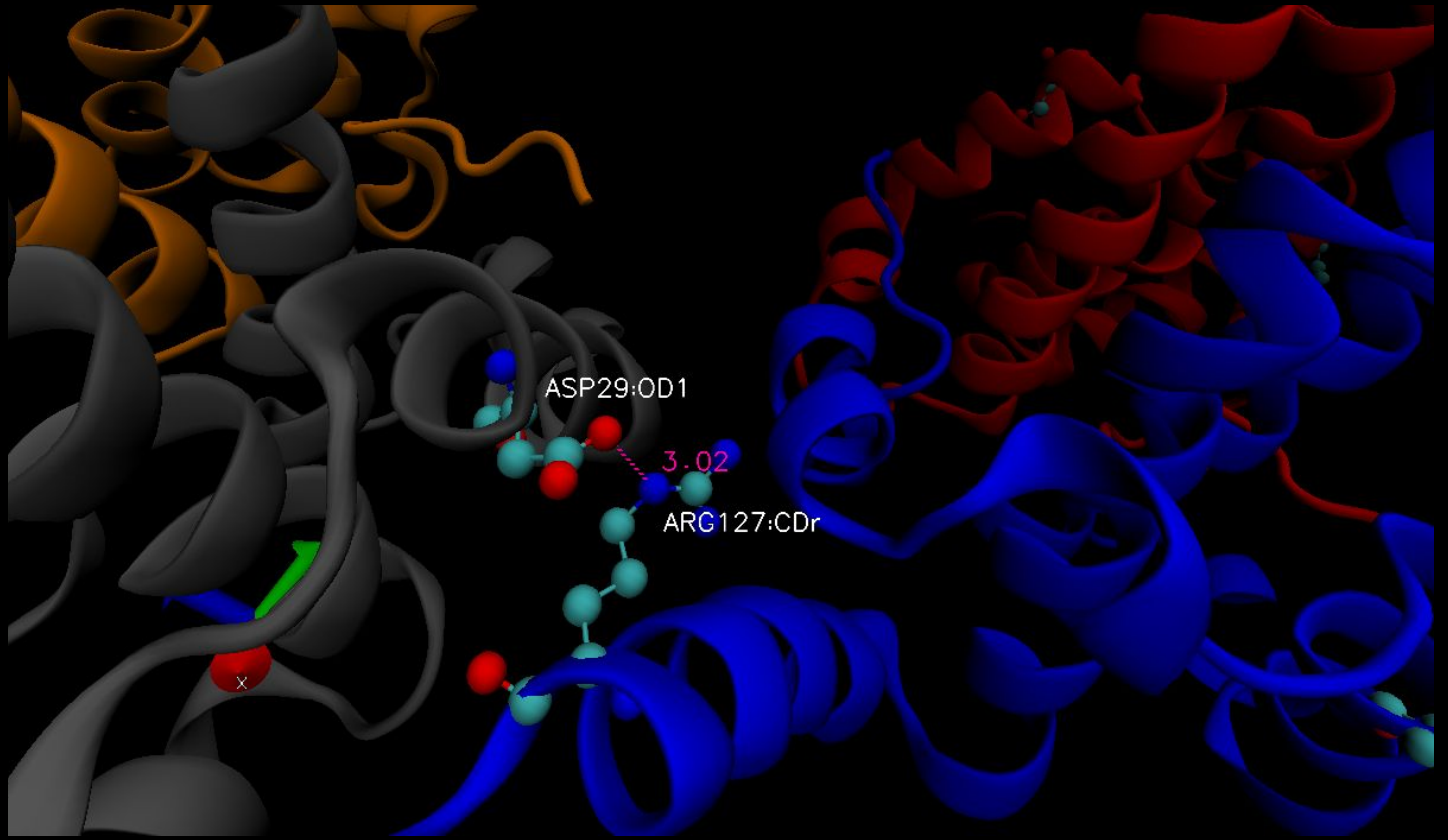
Capsid structure

Dimer molecular hinges



Capsid structure

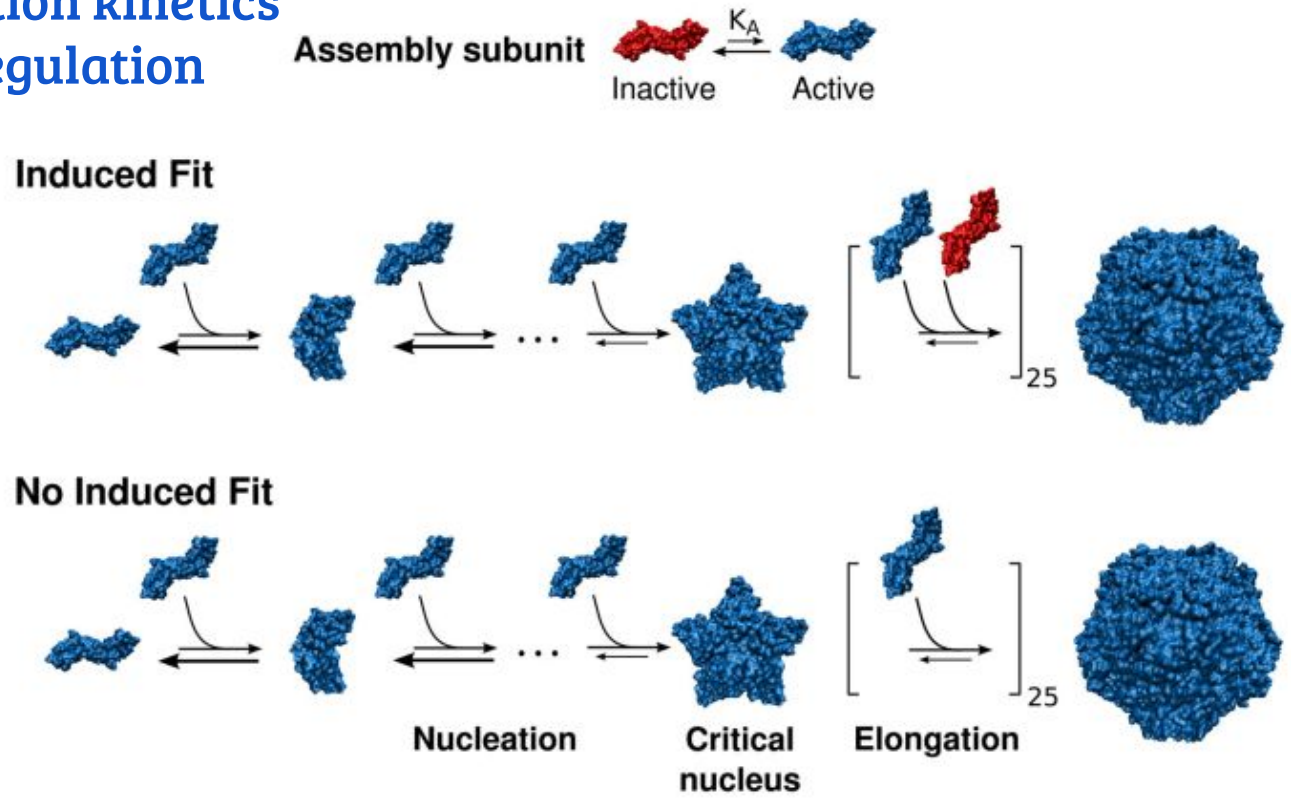
Key interactions between dimers



Capsid formation

Polymerization kinetics

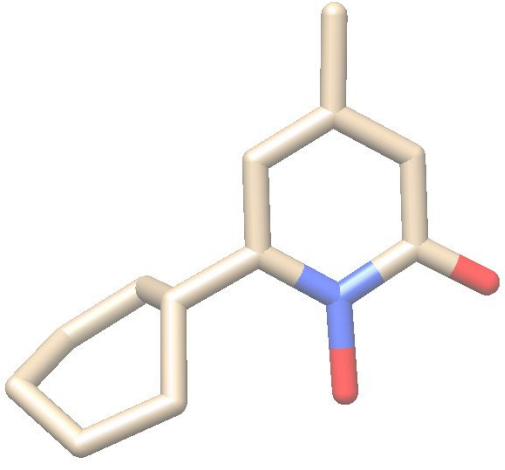
Allosteric regulation

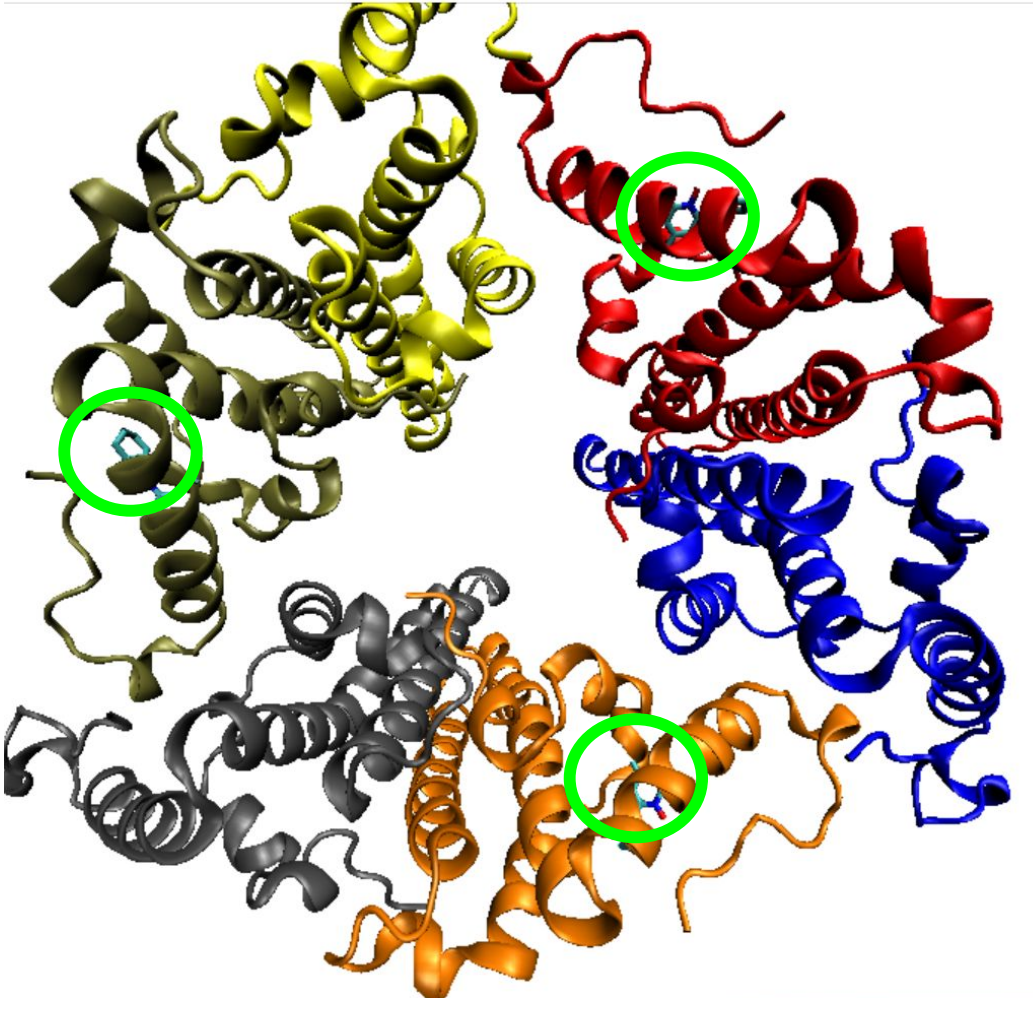


Lazaro GR, Hagan MF. Allosteric control of icosahedral capsid assembly. *J Phys Chem B* 2016; 120 (26); 6306-6318.

Developing treatment

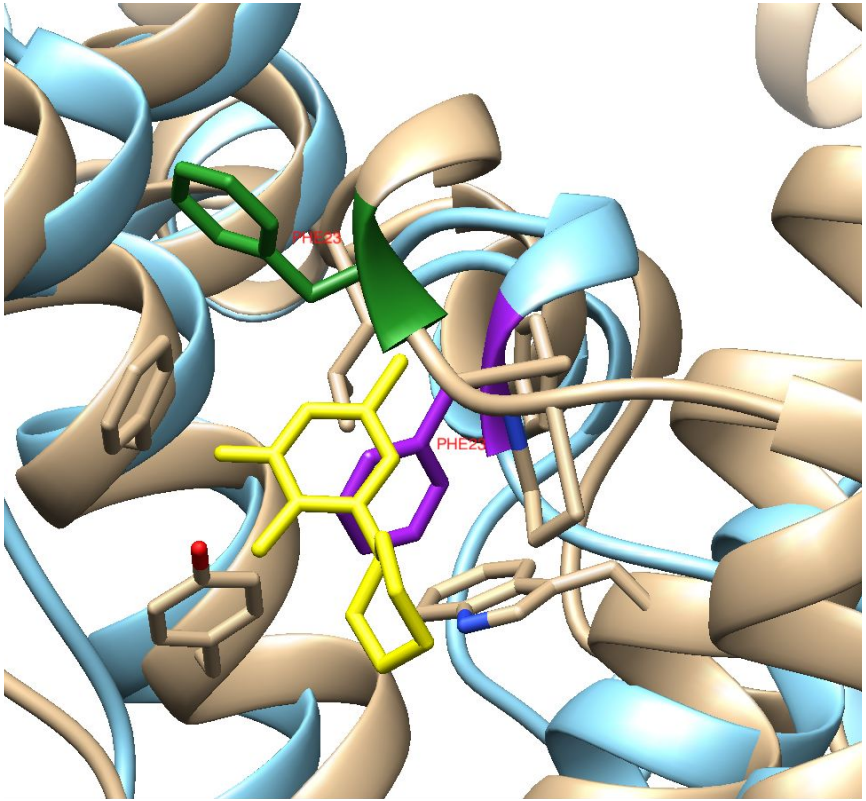
Ciclopirox

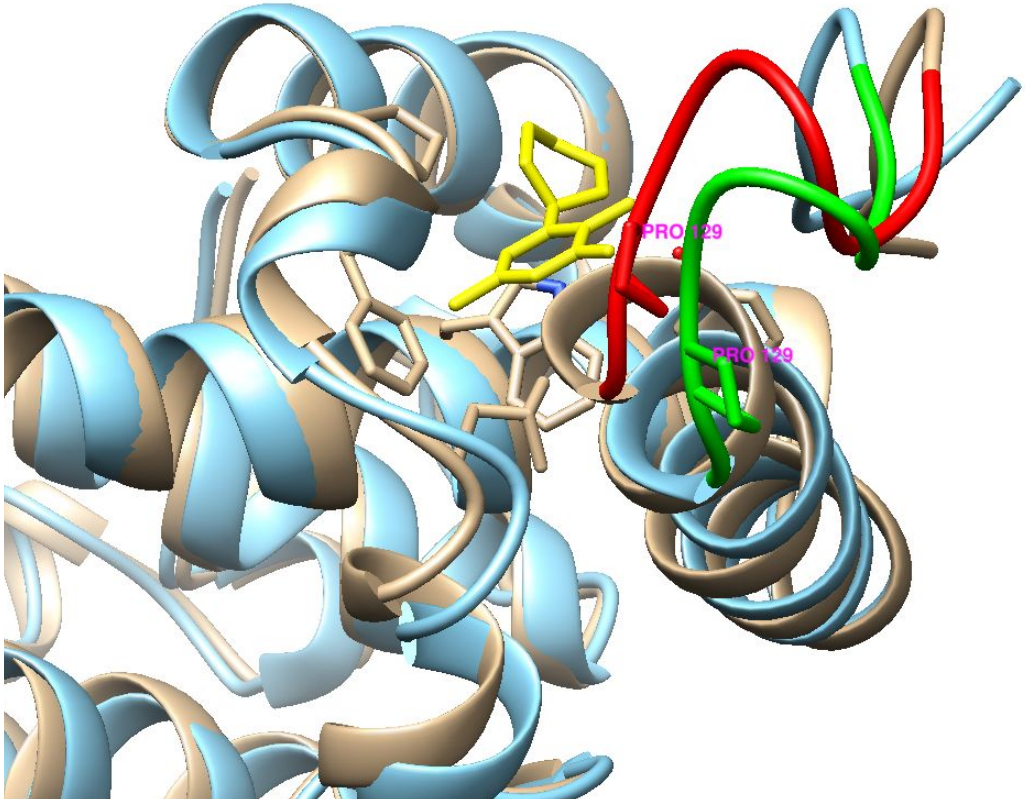




Ciclopirox

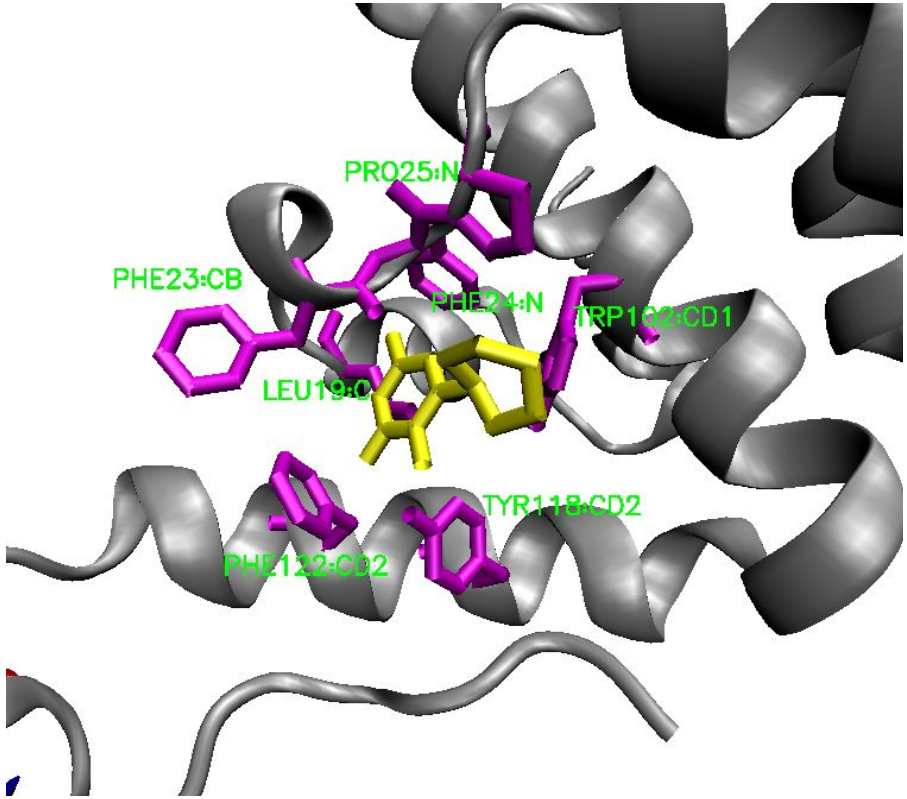
F23 and proline rich loop 6 rearrangement

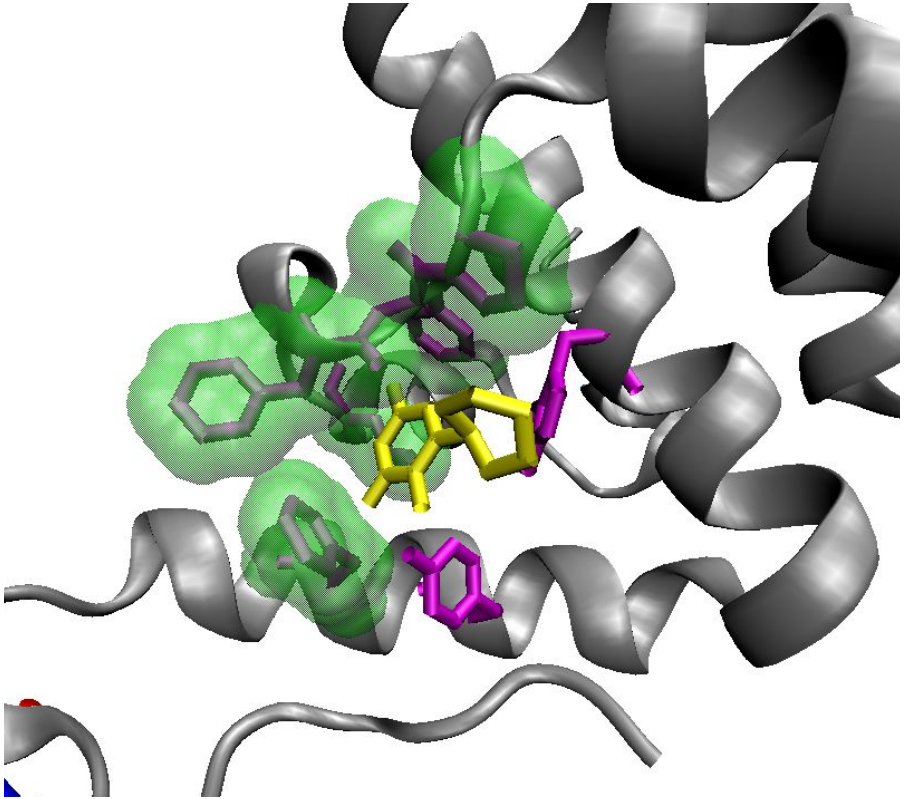




Ciclopirox

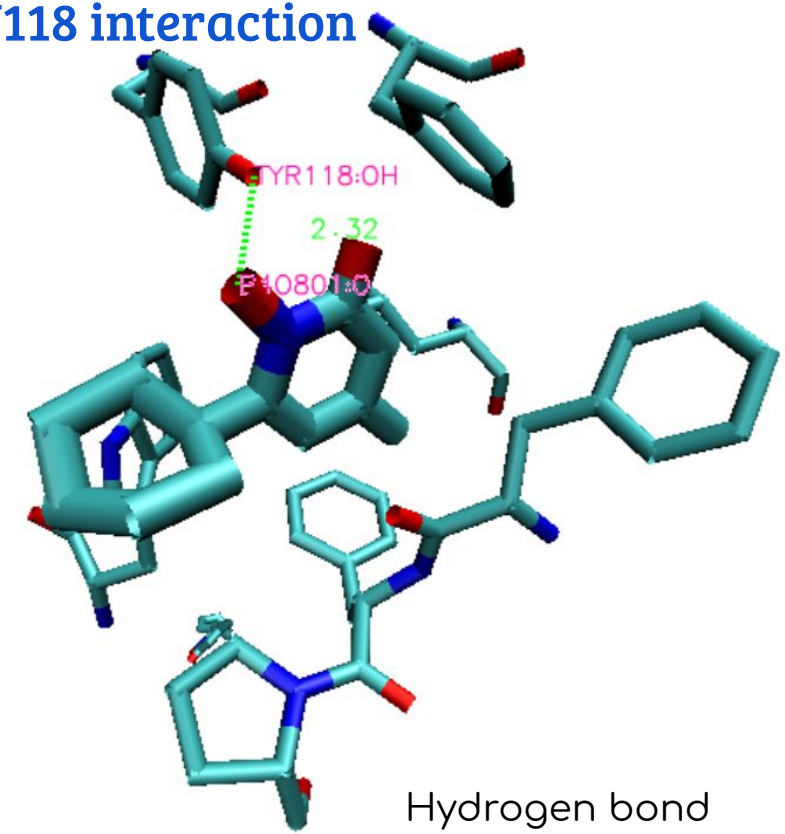
Binding pocket



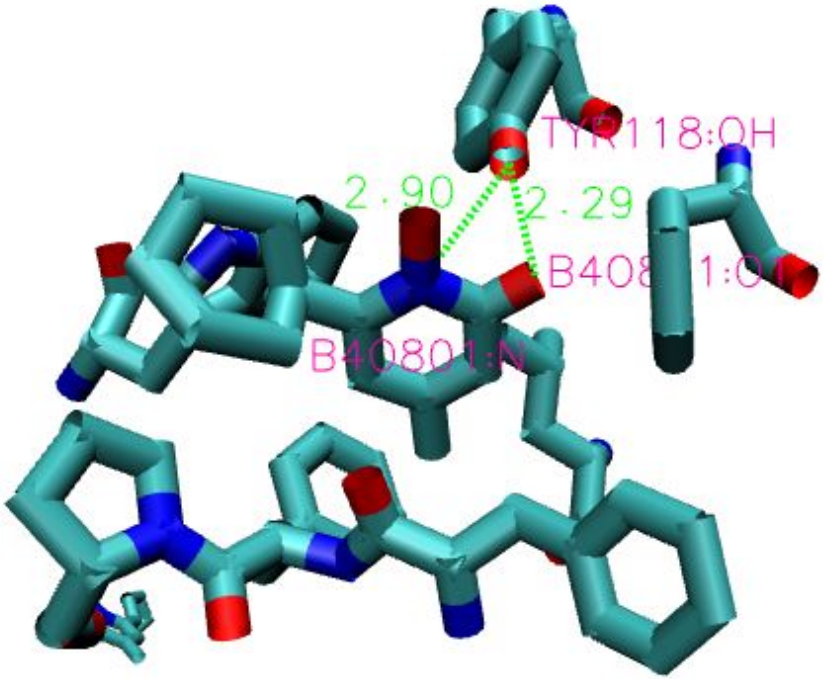


Ciclopirox

Y118 interaction



Hydrogen bond



Salt bridges

Conclusions

The capsid of Hepatitis B is very unique and different to other viruses

It is formed by a monomer that has 5 alpha helices

HBeAg is an alternative monomer that doesn’t allow for the capsid to assembly

The HBcAg dimer is the most stable structure in the capsid

The capsid has an icosahedron shape formed by the repetition of dimers

New drugs are being developed and more studies need to be done

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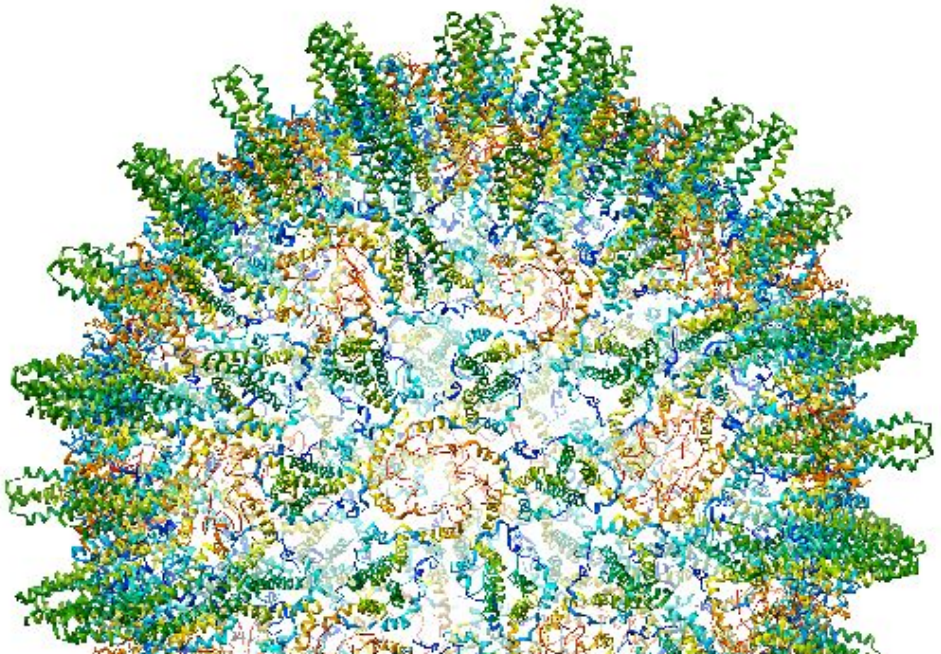
Thanks for your attention!



Questions

1. Select the correct sentences
   1. The hepatitis B virus capsid is formed by a single polypeptide that is classificated as all alpha protein
   2. In the formation of hepatitis B dimers the disulfide bridge formed between Cys61 of both monomers is very important to stabilize the dimer structure.
   3. Hepatitis B virus infection attacks the liver.
   4. The four chains that make the capsid of Hepatitis B are different both at an structural and sequence level.

a) 1,2,3
b) 1,3
c) 2,4
d) 4
e) 1,2,3,4

2. Which of these interactions was produced between Y118 residue of the hydrophobic pocket of the HBcAg protein and ciclopirox?

a) hydrogen bond
b) salt bridges
c) a and b are correct
d) metal interactions
e) they are all correct

Questions

3. Select the correct sentences
   1. There are two different sizes of hepatitis B capsid: T=4, that has 240 capsid proteins and T=3, which has only 180.
   2. The five-fold axis goes through the vertex of the icosahedron
   3. There are 3 different axes to explain the symmetry of the hepatitis b viral capsid
   4. The capsid of hepatitis B has an ichosaedrical shape.

a) 1,2,3
b) 1,3
c) 2,4
d) 4
e) 1,2,3,4

4. Which one of this fold axis has a big enough fenestration in the capsid for nucleotides to go in?
a) 2-fold axis
b) 3-fold axis
c) a and b are correct
d) 5-fold axis
e) They are all correct

Questions

5. How is HBeAg created?

a) Splicing
b) Mutation
c) There is an alternative upstream start codon
d) Fusion between the host and the virus DNA
e) HBeAg doesn't exist

6. About the disulphide bridges in HBV dimers:

1. In the core antigen dimer the disulphide bridge is intermonomeric
2. In the core antigen dimer there aren't disulphide bridges.
3. In the e-antigen dimer the disulphide bridges are intramonomeric
4. In the e-antigen dimer aren't disulphide bridges.

a) 1, 2, 3
b) 1, 3
c) 2, 4
d) 4
e) 1, 2, 3, 4

Questions

7. What is the current assembly model that explains the formation of the Hepatitis B viral capsid?

a) Random
b) Controlled by plasma proteins
c) a and b are correct
d) Allosteric regulation
e) They are all correct

8. What is the genetic material form of Hepatitis B virus?

a) ssRNA
b) dsRNA
c) ssDNA
d) dsDNA
e) dUTP

Questions

9. In order to assembly the hepatitis B capsid, the structure of the dimer core protein…
   a) Changes all its conformation
   b) Does not undergo conformational changes
   c) Undergoes conformational changes on the protein periphery
   d) Binds to host ribosomes
   e) All of the above are false

10. In order to assembly the hepatitis B capsid, the core protein dimers interact through...
   a) N-terminal helices
   b) C-terminal helices
   c) Hydrophobic cores
   d) The top of the 4-helix bundle
   e) All of the above are false

Capsid structure

Interactions

- Arg 127 133
- Thr 128 142
- Pro 129 130 134 135 138
- Ala 131 137
- Tyr 132
- Asn 136
- Ile 139
- Leu 140 143
- Ser 141