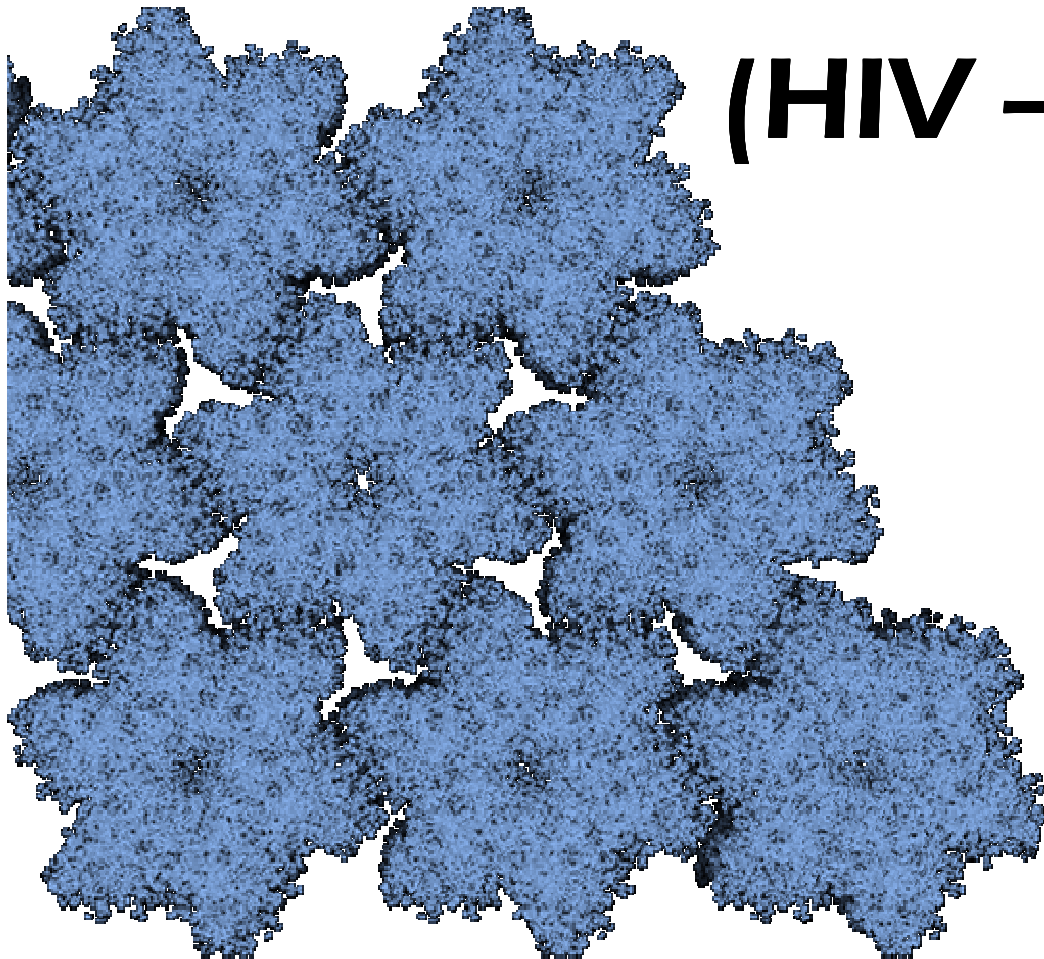


CAPSIDS OF VIRUSES

Human immunodeficiency virus 1 (HIV – 1)



Irene Durán
Laura Gaspa
Alba Paula Navarro
Josep M^a Agustín

INDEX

1. Introduction

2. CA - monomer

2.1. NTD

2.2. CTD

3. CA - subunits

3.1. Hexamers

- NTD-NTD
- NTD-CTD
- CTD-CTD

3.2. Pentamers

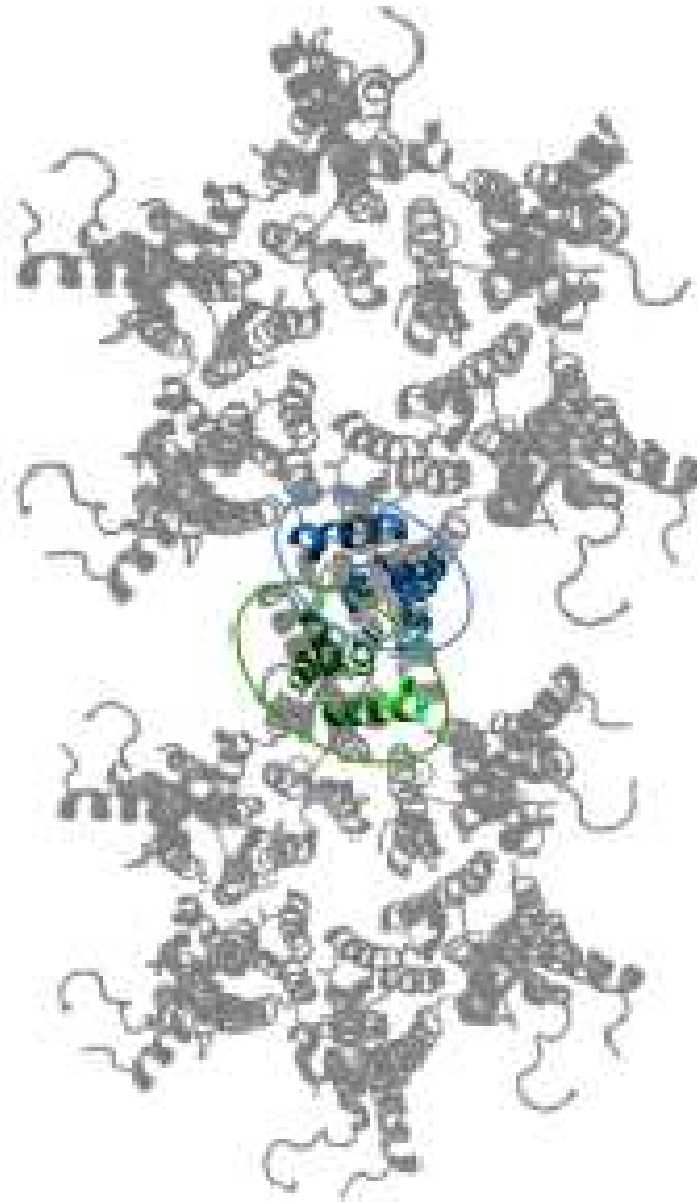
- NTD-NTD
- NTD-CTD

4. Capsid curvature

4.1. Rigid-body motions

4.2. CTD flexibility

5. Current situation



1.INTRODUCTION

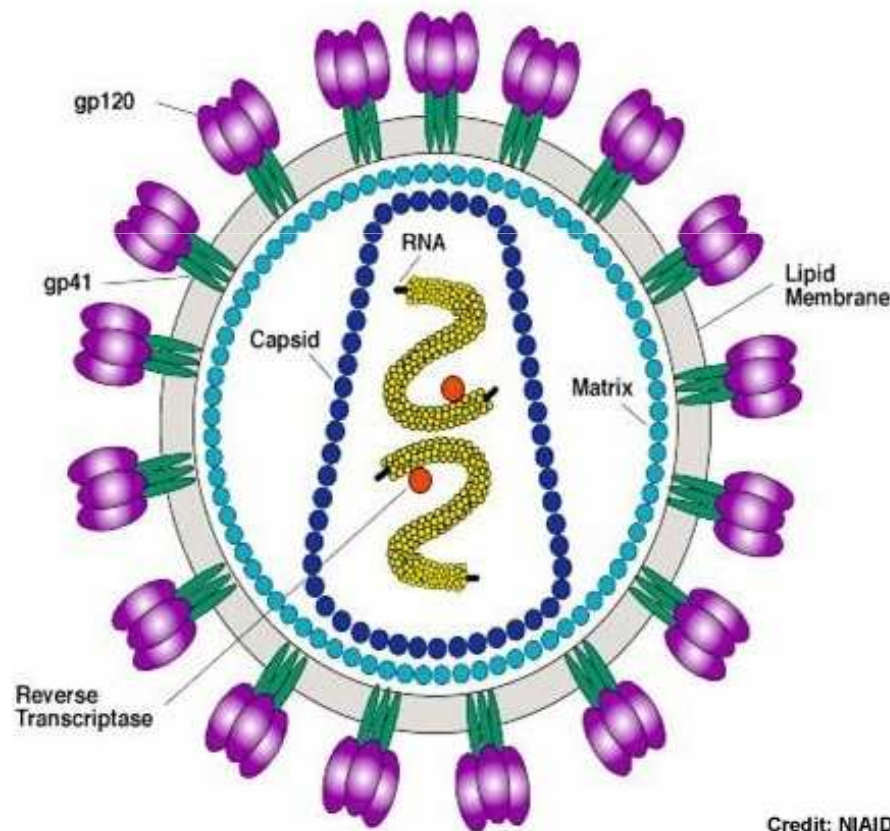
Human Immunodeficiency virus -1 (HIV-1)

Family: Retroviridae

Genus: Lentivirus

Structure

- ssRNA
- Nucleocapsid (p7)
- Capsid (p24)
- Matrix (p17)
- Envelope
 - Gp 120
 - Gp 41



Credit: NIAID

Infected cells

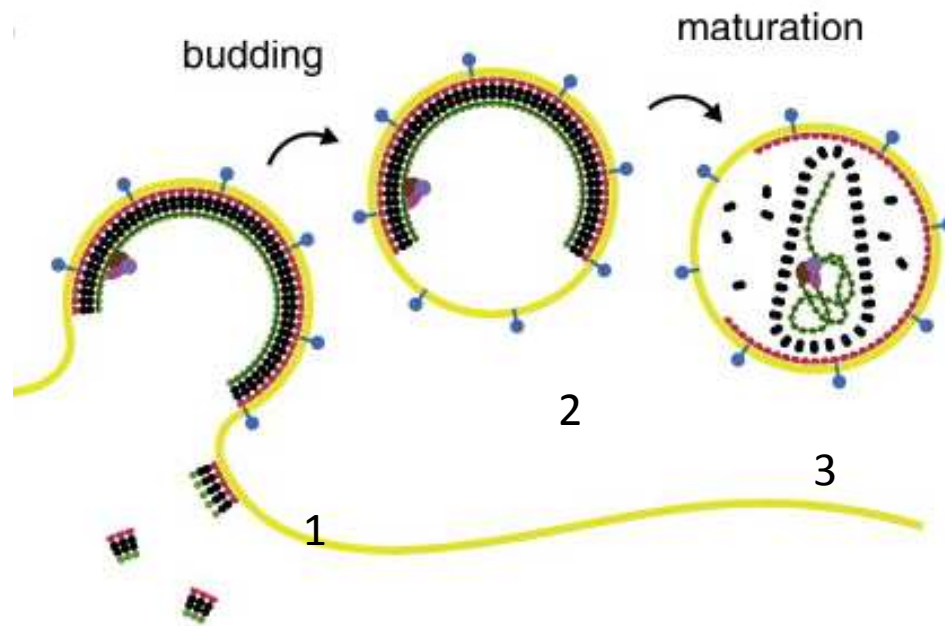
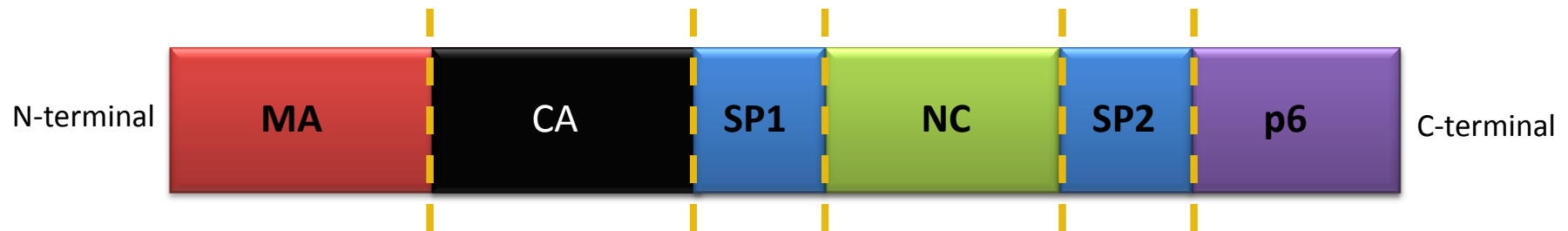
CD4+ T cells

Macrophages

Microglial cells

1.INTRODUCTION

GAG POLYPROTEIN



MA: Matrix
CA: Capsid
NC: Nucleocapsid

- 1 - budding
- 2 - proteolytic maturation
- 3 - Mature CA formed



1.INTRODUCTION

“Protein structure prediction programs suggest that the last 7 residues of the CA domain and the first 7 residues of SP1 might form an α -helix”



```
# PSIPRED HFORMAT (PSIPRED V2.3 by David Jones)
```

Conf: 667765454217888766788778887634777532277403421457602478999999
Pred: HHHHHHHHHHCCCCCHHHHHHHHHHHHHHHHHHHHHCCCCCEEECCCCCHHHHHHHHHHH
AA: STLQEQIAWMTNPPPIPVGEIYKRWIILGLNKIVRMYSPTSILDIKQGPKEPFRDYVDRE
250 260 270 280 290 300

Conf: 997423344478885422103530799867889974274246899998850478841567
 Pred: HHHHHHHHHHHHHHHHHHHHHHEEEEECCCCCHHHHHHHHCCCHHHHHHHHHHHHHHHHHHHCCCCHHHH
 AA: YKTLRAEQASQEVKNWMTETLLVQNSNPDKTILKALGPAATLEEMMTACQGVGGPSHKA
 310 320 330 340 350 360

Conf: 889999876200002333157520112641121047766320014576100112304477
Pred: HHHHHHHHHHHHCCCEEEECCHHCCCEEECCCCCCCCCCCCCHHCHHHHCCCC
AA: RILAEAMSQVTNSAAIMMQKGNFRKQRNSVKCFNCGKEGHVARNCRAPRKKGCKGKEG
370 380 390 400 410 420

Confidence level	
Secondary structure	
CTD	SP1

INDEX

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2. CA - monomer

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3. CA - subunits

3.1. Hexamers

- NTD-NTD
- NTD-CTD
- CTD-CTD

3.2. Pentamers

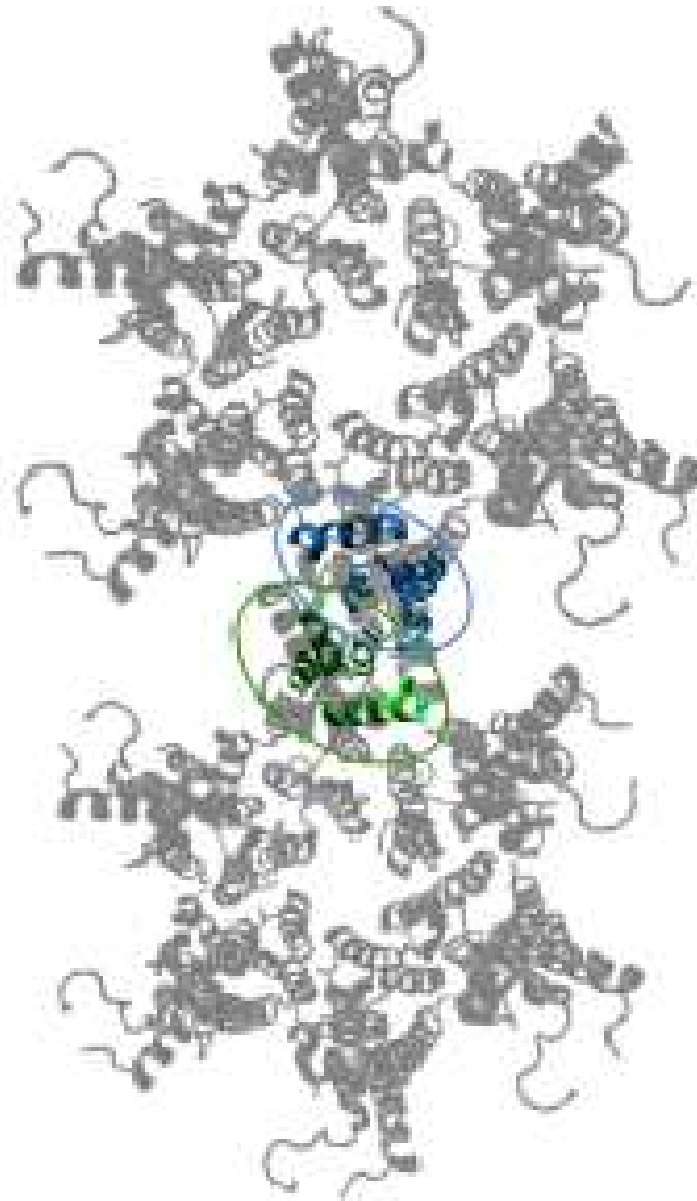
- NTD-NTD
- NTD-CTD

4. Capsid curvature

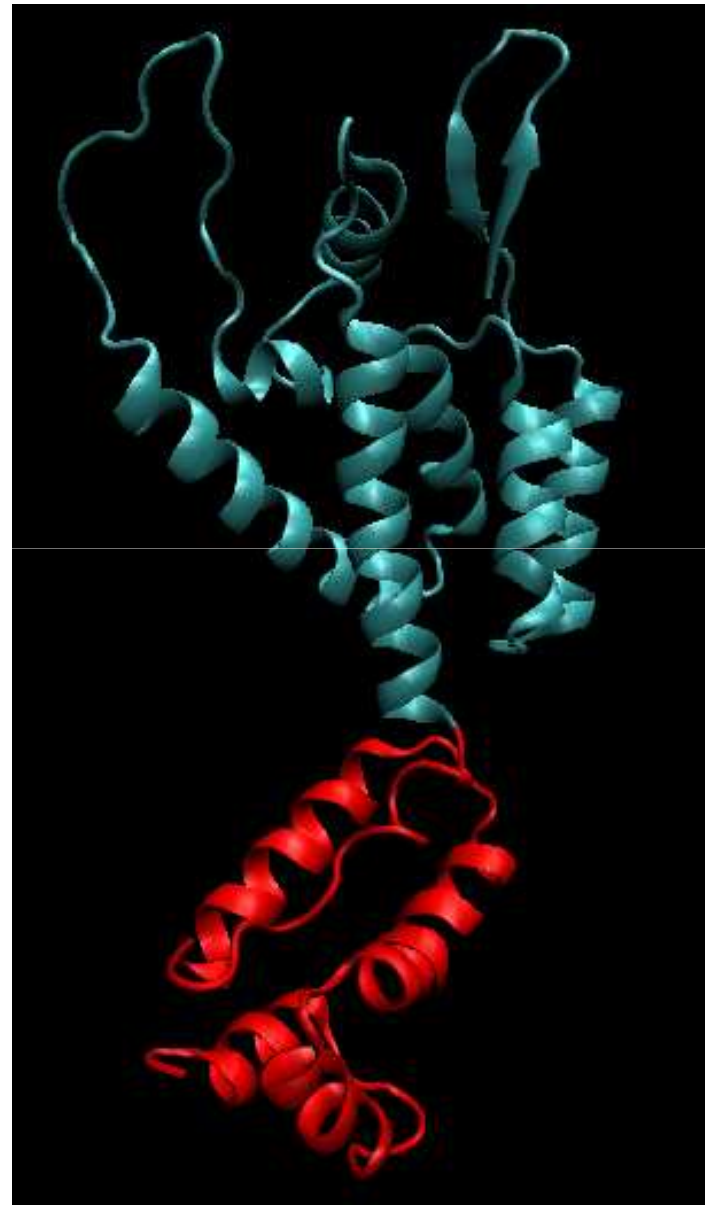
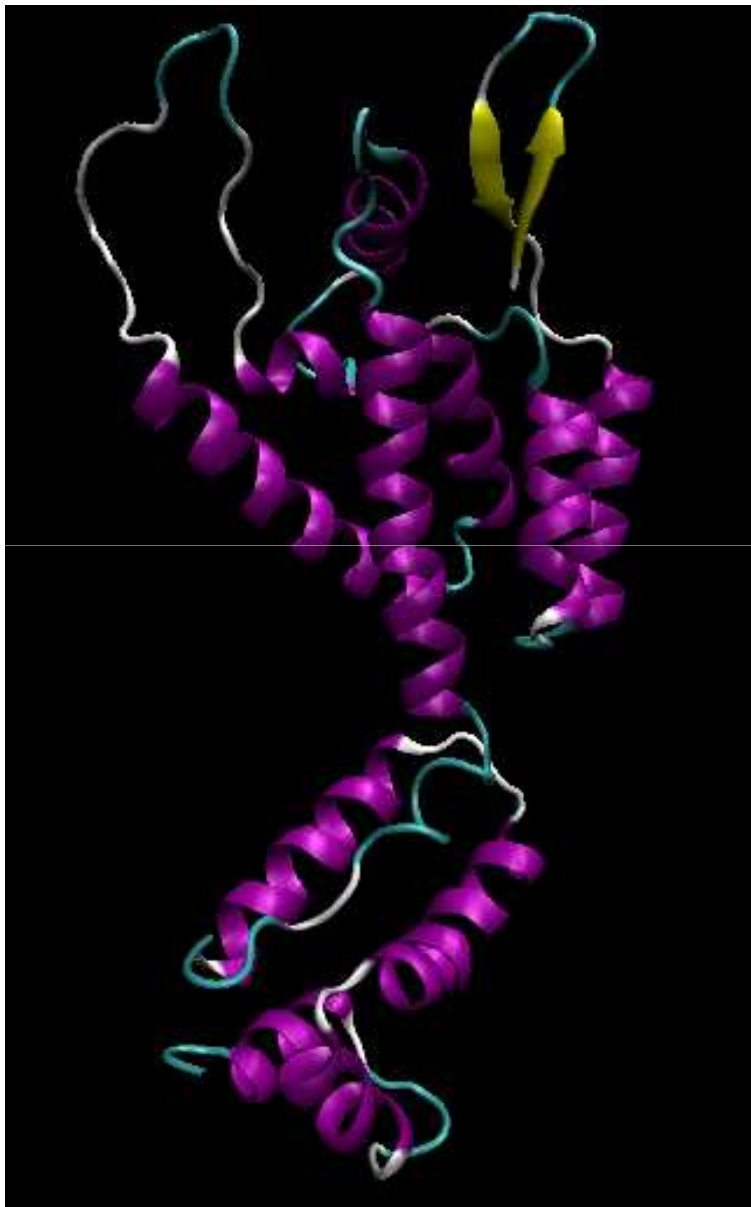
4.1. Rigid-body motions

4.2. CTD flexibility

5. Current situation



2.CA-MONOMER



2. CA-MONOMER

The two domains of CA belong to different superfamilies

NTD domain Superfamily: Retrovirus capsid protein, N-terminal core domain

1. Root: [scop](#)
2. Class: [All alpha proteins](#) [46456]
3. Fold: [Retrovirus capsid protein, N-terminal core domain](#) [47942]
core: 5 helices; bundle
4. Superfamily: [Retrovirus capsid protein, N-terminal core domain](#) [47943]
Superfamily
5. Family: [Retrovirus capsid protein, N-terminal core domain](#) [47944]

Protein Domains:

1. HIV-1 capsid protein [47945]
 1. [Human immunodeficiency virus type 1 \[TaxId: 11676\]](#) [47946] (16)
2. EIAV capsid protein p26 [47947]
 1. [Equine infectious anemia virus \[TaxId: 11665\]](#) [47948] (2)
3. HTLV-I capsid protein [47949]
 1. [Human T-cell leukemia virus type 1 \[TaxId: 11908\]](#) [47950] (2)
4. RSV capsid protein [47951]
 1. [Rous sarcoma virus \[TaxId: 11886\]](#) [47952] (3)
5. AKV capsid [116949]
 1. [AKV murine leukemia virus \[TaxId: 11791\]](#) [116950] (1)

SQ P03336 215-345 # fragment of the core shell protein p30 (215-477)

CTD domain Superfamily: Retrovirus capsid dimerization domain-like

1. Root: [scop](#)
2. Class: [All alpha proteins](#) [46456]
3. Fold: [Acyl carrier protein-like](#) [47335]
4 helices, bundle; helix 3 is shorter than others; up-and-down
4. Superfamily: [Retrovirus capsid dimerization domain-like](#) [47353]
Superfamily
5. Family: [Retrovirus capsid protein C-terminal domain](#) [47354]

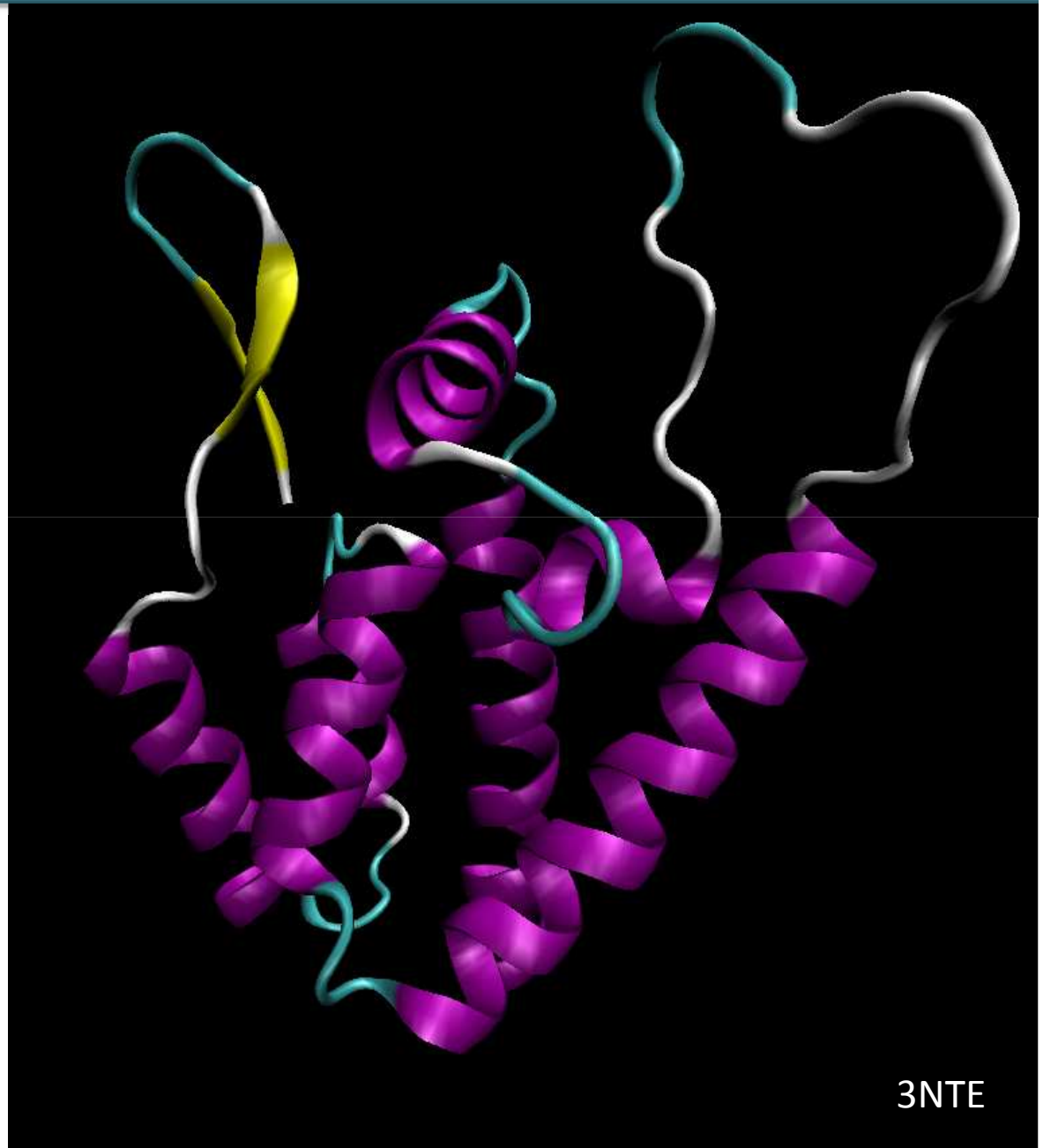
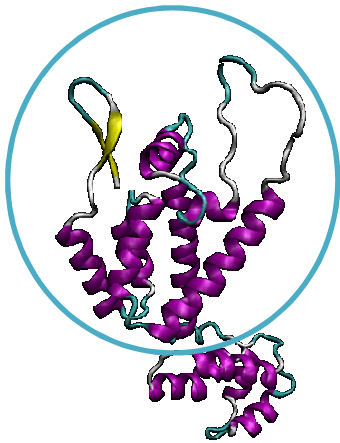
Protein Domains:

1. EIAV capsid protein p26 [47355]
 1. [Equine infectious anemia virus \[TaxId: 11665\]](#) [47356] (2)
2. HTLV-I capsid protein [47357]
 1. [Human T-cell leukemia virus type 1 \[TaxId: 11908\]](#) [47358] (1)
3. HIV capsid protein, dimerisation domain [47359]
 1. [Human immunodeficiency virus type 1 \[TaxId: 11676\]](#) [47360] (7)
4. RSV capsid protein [47361]
 1. [Rous sarcoma virus \[TaxId: 11886\]](#) [47362] (2)

2.1. NTD

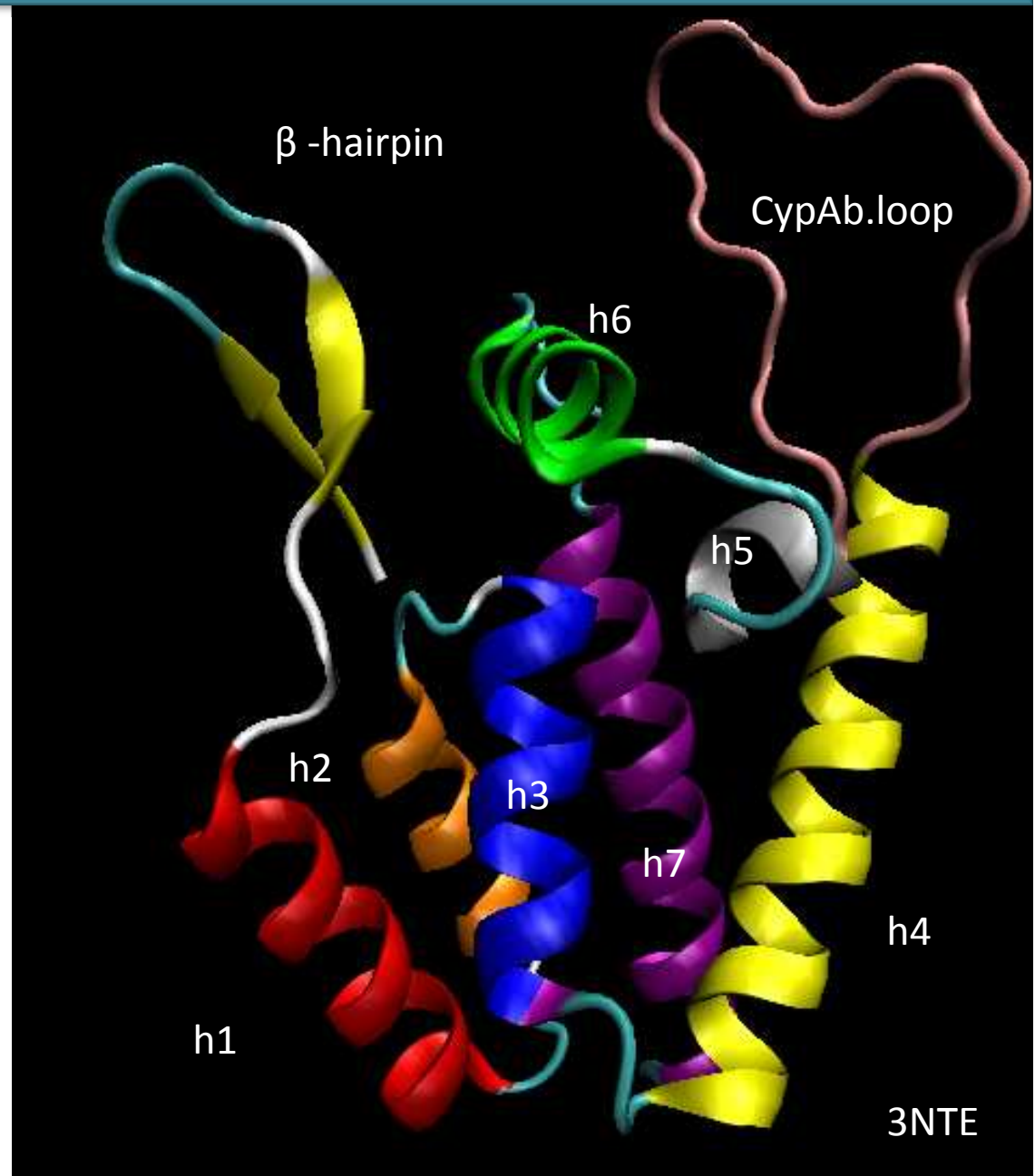
Residues: 1-146

Dimensions: 18x35x45 Å



2.1. NTD

β -hairpin	(1-13)
Helix 1	(17-29)
Helix2	(36-43)
Helix3	(49-58)
Helix4	(63-83)
CypAb.l.	(85-99)
Helix5	(101-104)
Helix6	(111-118)
Helix7	(126-145)



2.1. NTD



2Y4Z, 1G03, 1EM9, 1GWP

STAMP NTD superfamily

```
./1EM9.pdb 1EM9 ( ALL
  0.12363   -0.84230    0.52464    40.67896
 -0.95800    0.03656    0.28444    19.58468
 -0.25876   -0.53777   -0.80240    34.43766  )
./1G03.pdb 1G03 ( ALL
  0.84367   -0.50092    0.19312    22.12993
 -0.50440   -0.61644    0.60464     9.44606
 -0.18383   -0.60752   -0.77274    11.85248  )
./2Y4Z.pdb 2Y4Z ( ALL
  0.99515   -0.03853   -0.09047    -1.50927
  0.07430    0.89727    0.43520    -4.91943
  0.06441   -0.43981    0.89578     3.27455  )
./1GWP.pdb 1GWP ( ALL
 -0.61849   -0.72056   -0.31346    22.55360
 -0.76571    0.46303    0.44642    -0.78172
 -0.17653    0.51613   -0.83812    11.56435  )
```

Alignment score $S_c = 5.178694$

Alignment length $L_p = 335$

RMS deviation after fitting on 86 atoms = 2.209671

Secondary structures are from DSSP

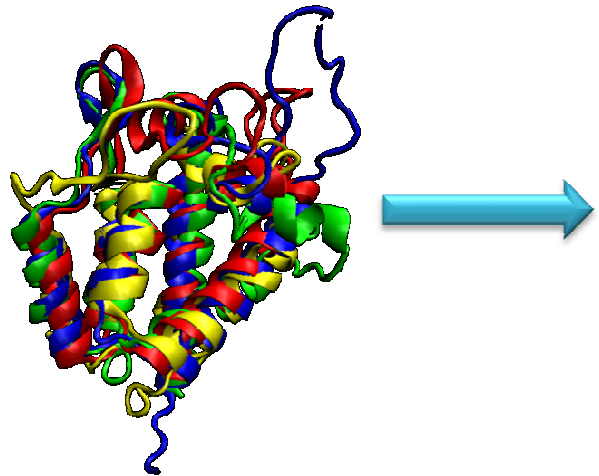
Blue: HIV-1

Green: MLV

Yellow: HTLV-1

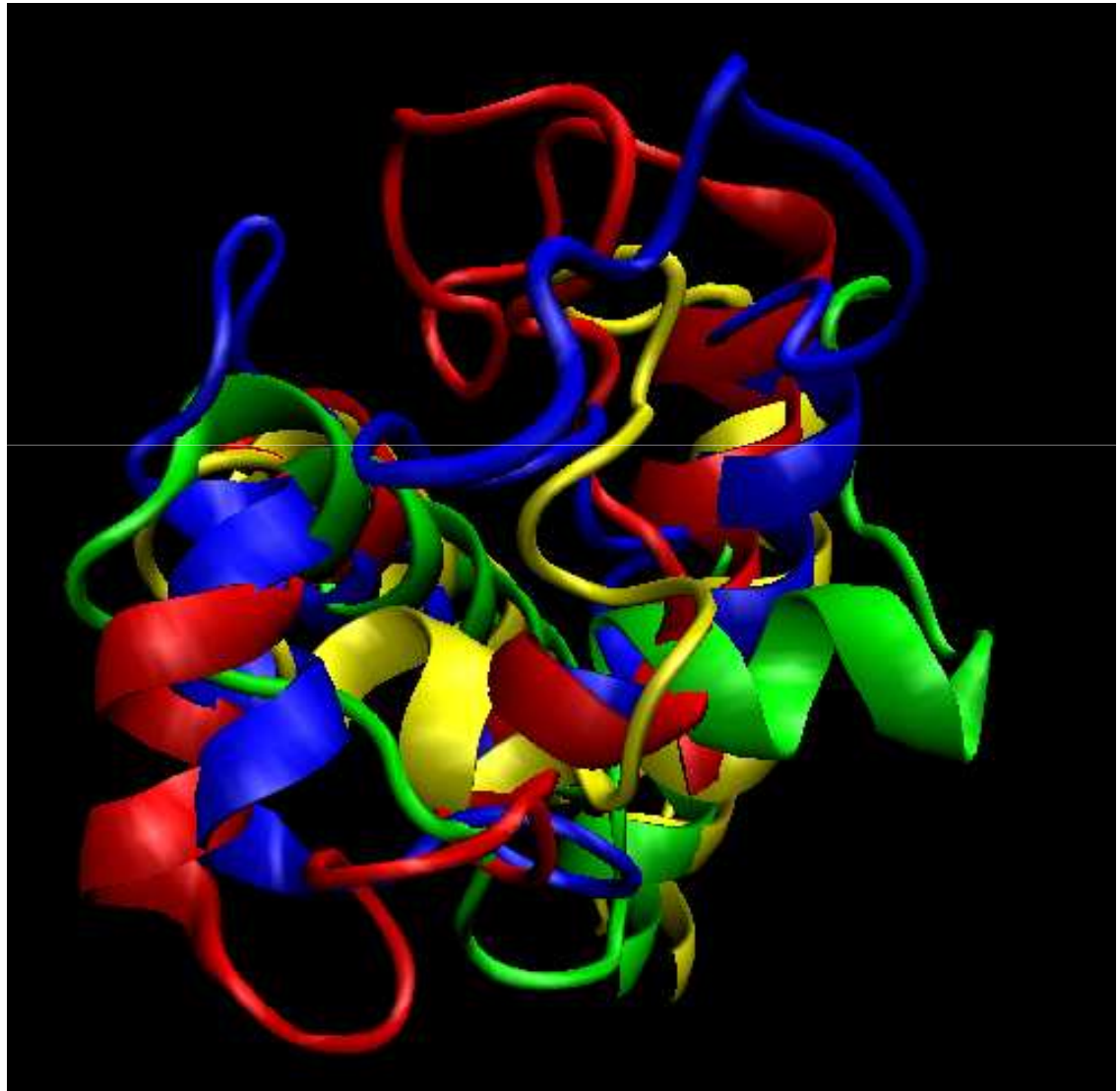
Red: RSV

2.1. NTD



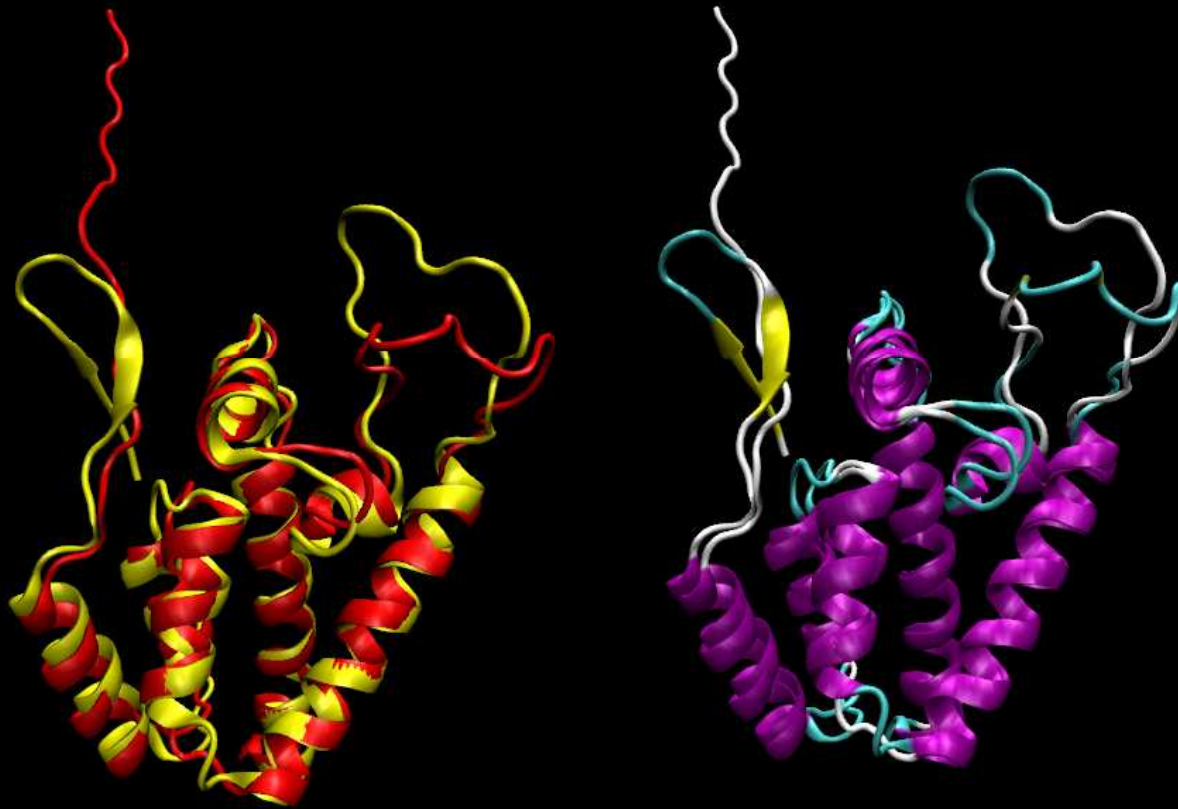
Why the region h4 to h6 is more flexible than the others?

No assembly interactions!!!!



2.1. NTD

STAMP MATURE vs
IMMATURE NTD



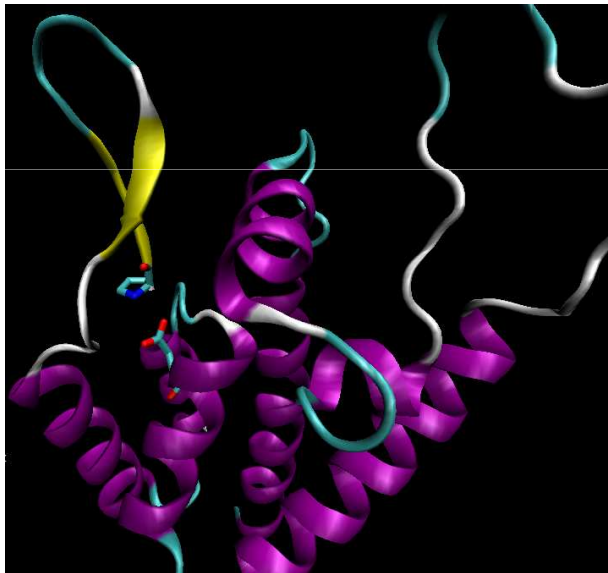
1L6N, 3NTE

Red: immature
Yellow: mature

2.1. NTD

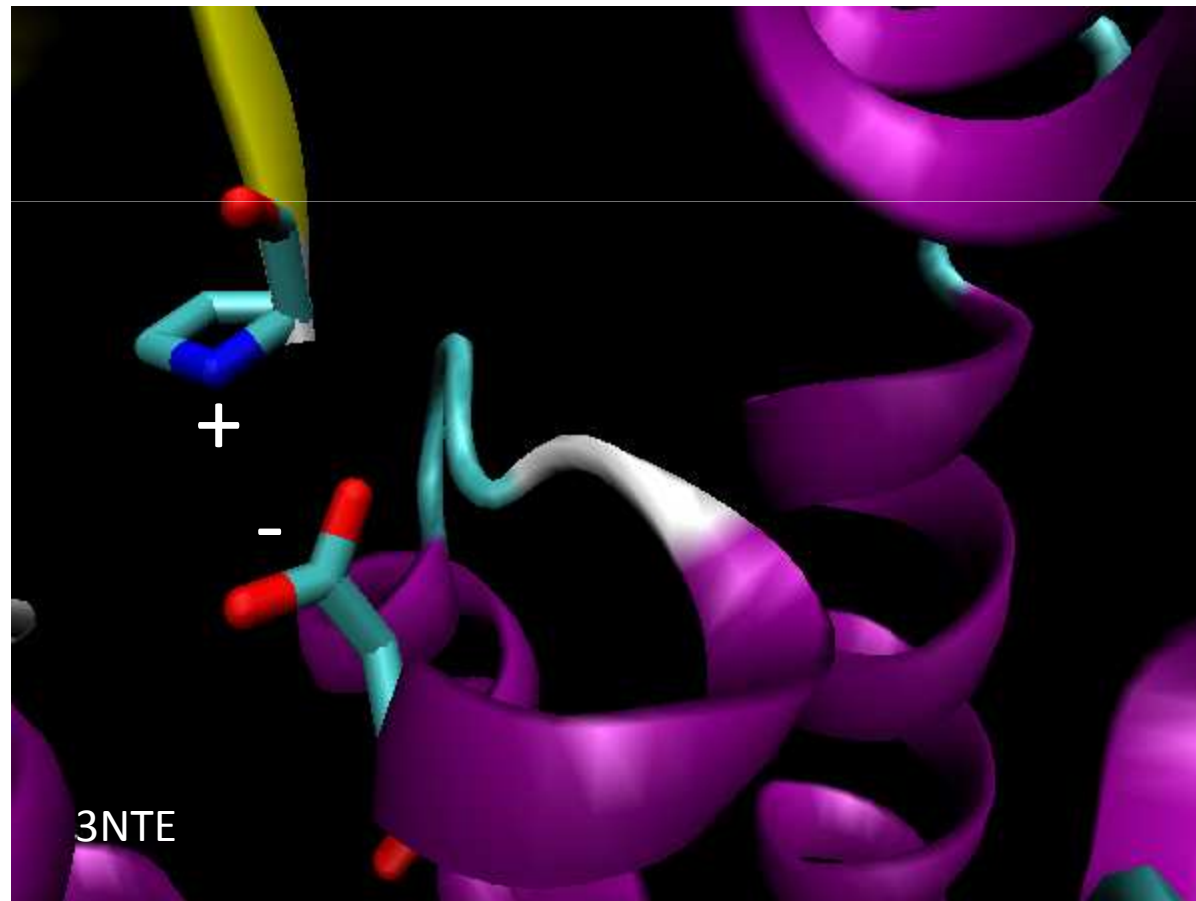
β -hairpin

1. Salt bridge P1 – D51



Three types of interactions:

1. Salt bridge P1 – D51
2. Inter B-hairpin H-bonds
3. Interactions with surrounding structures



2.1. NTD

β -hairpin

Highlight conserved P1 and D51 in the members of the superfamily

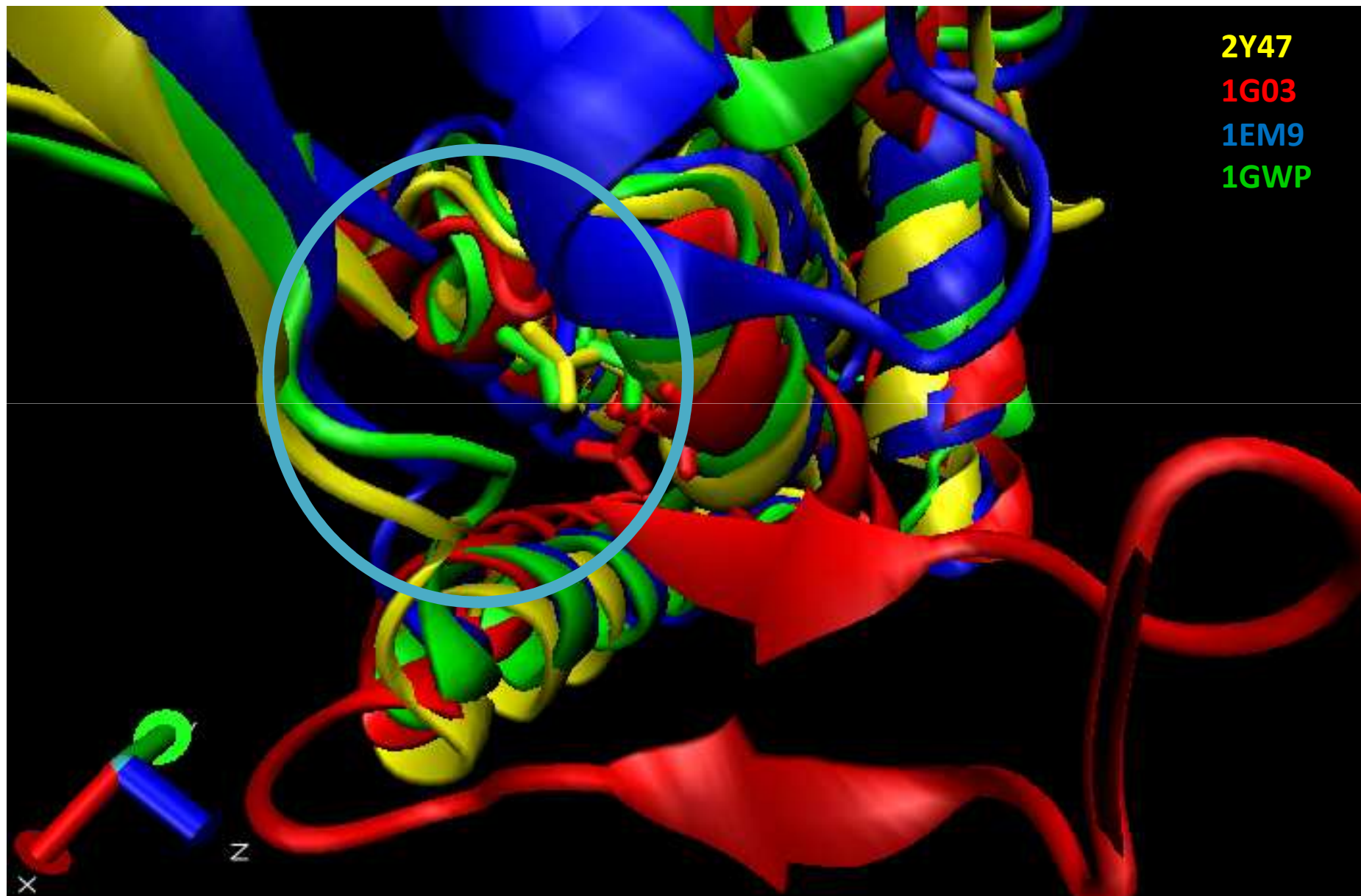
Structural alignment

```
1EM9    PVVI-KTEGPAW-----T-PLPKLITRLADTVR-TK---GLRSPITMAEVEA
1G03    -----PVMHPHGAPPNHRPWQMKDLQAIKQEVSA--PG-SPQFMQTIRL
2Y4Z    PLRLGGNGQWQY-----P-FSSSDLYNWKN--NN-PSFSED-PGKLTALIES
1GWP    PIVQNLQGQMVHQ-----A-ISPRTLNAWVKVVEE-KA---F-SPEVIPMFSA

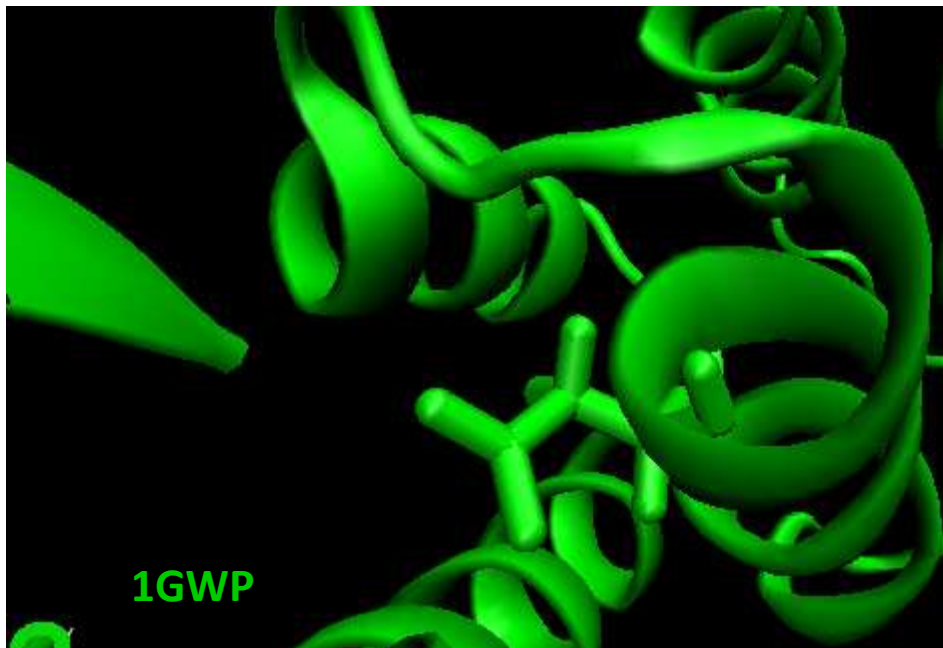
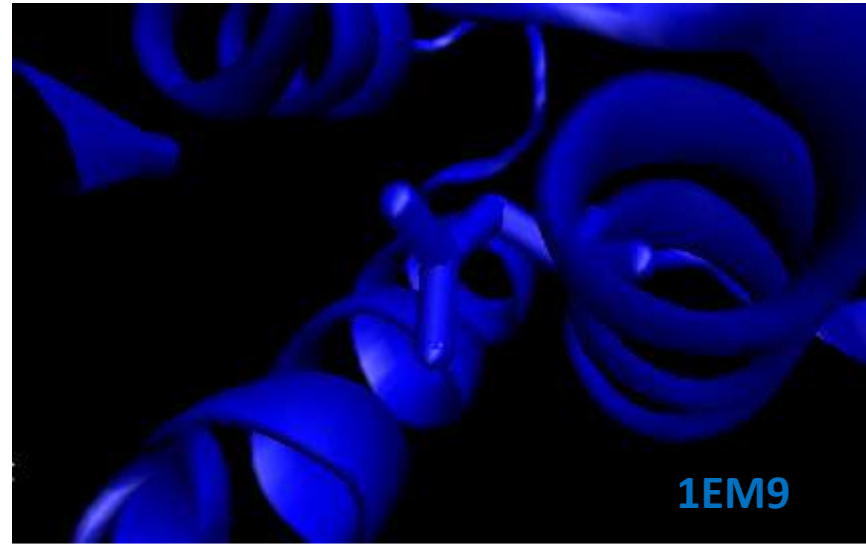
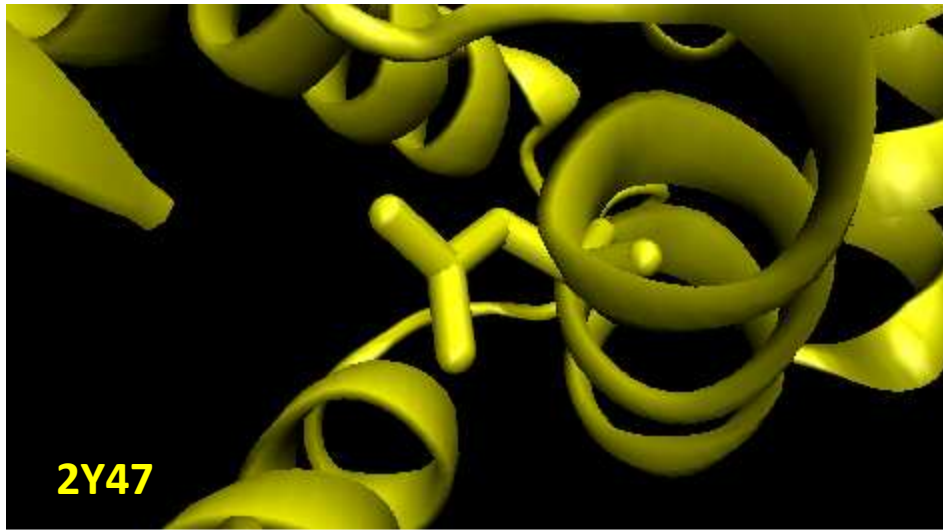
1EM9    LM-SSPLLFDYTNLMRVIL-GPAPYALWMDAWGVQLQTVI-----AAATRDPRHPA
1G03    AVQQFDPTAKDQDLLQYLC-SSLVASLHHQQQLDSLISEAE-----TRGIT-----S
2Y4Z    VLTTHQPTWDDQQLLGTLT-GEEKQRVLLEARKA-VRGNDGRPTQL-----
1GWP    LS--EGATFDNTMLNTVGGHQAAMQMLKETINEEAAEWDR-----LH-----P

1EM9    NGQ-----G---RGERTNLNRLK--GLADGMVGNPQ-GQAAL-----LRPGELVAITASA
1G03    ---Y-----NPL-AGP-L-----RVQA-N-N-P-Q-QQGLRREYQQLW
2Y4Z    -----PNEVDAAFLER--P-----D-W--DYT-TQRGRNHLVLYRQLL
1GWP    ---VHAGPIAPGQMREPRGSDIAG--T--TS--TLQE-QIGWMTHNPP-IPVGEIYKRWI
```


2.1. NTD



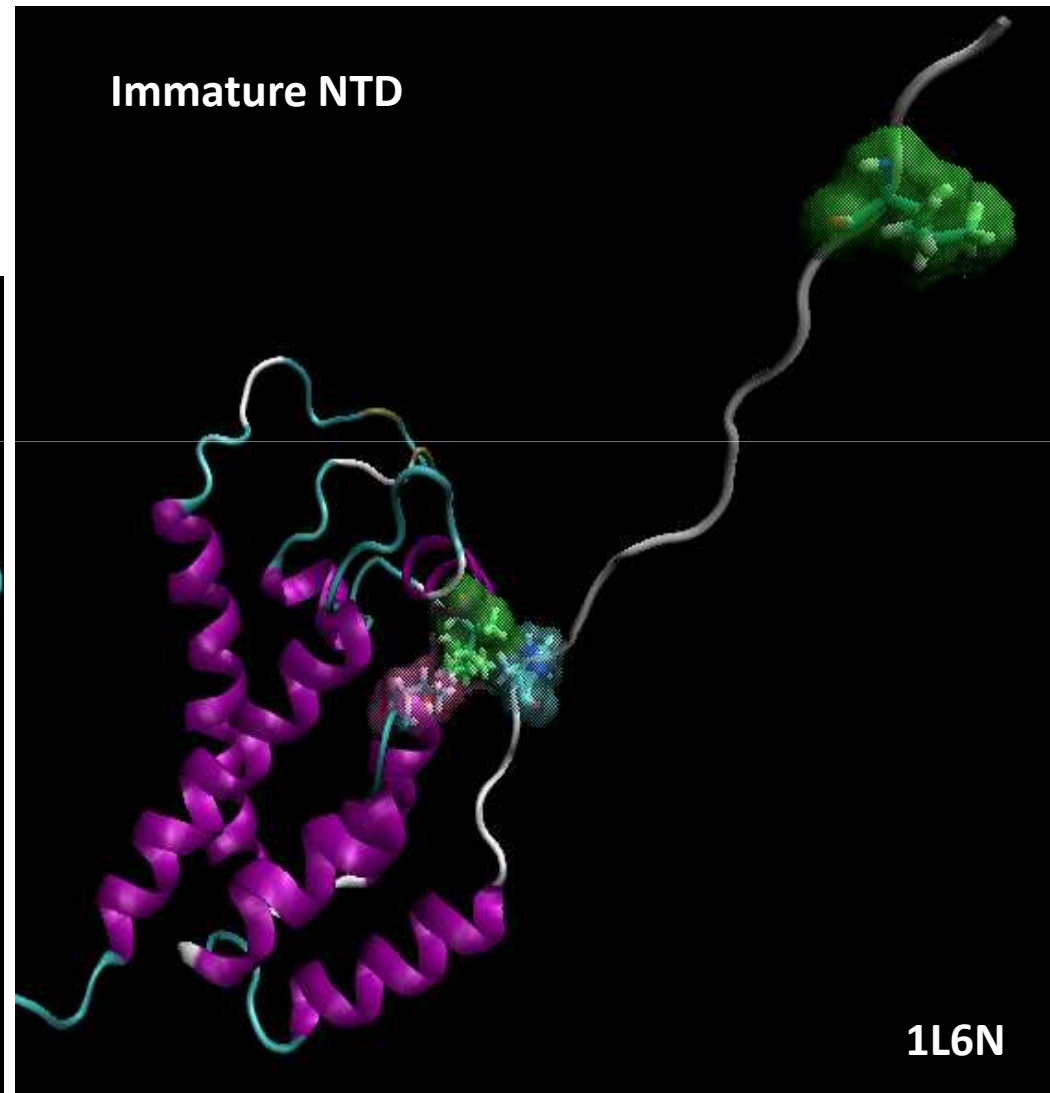
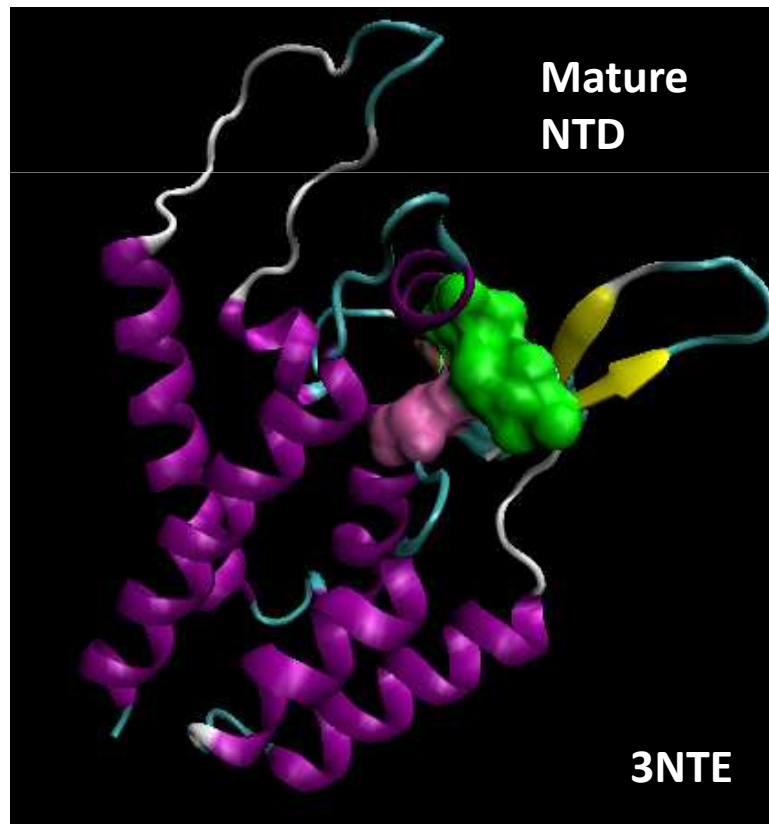
2.1. NTD



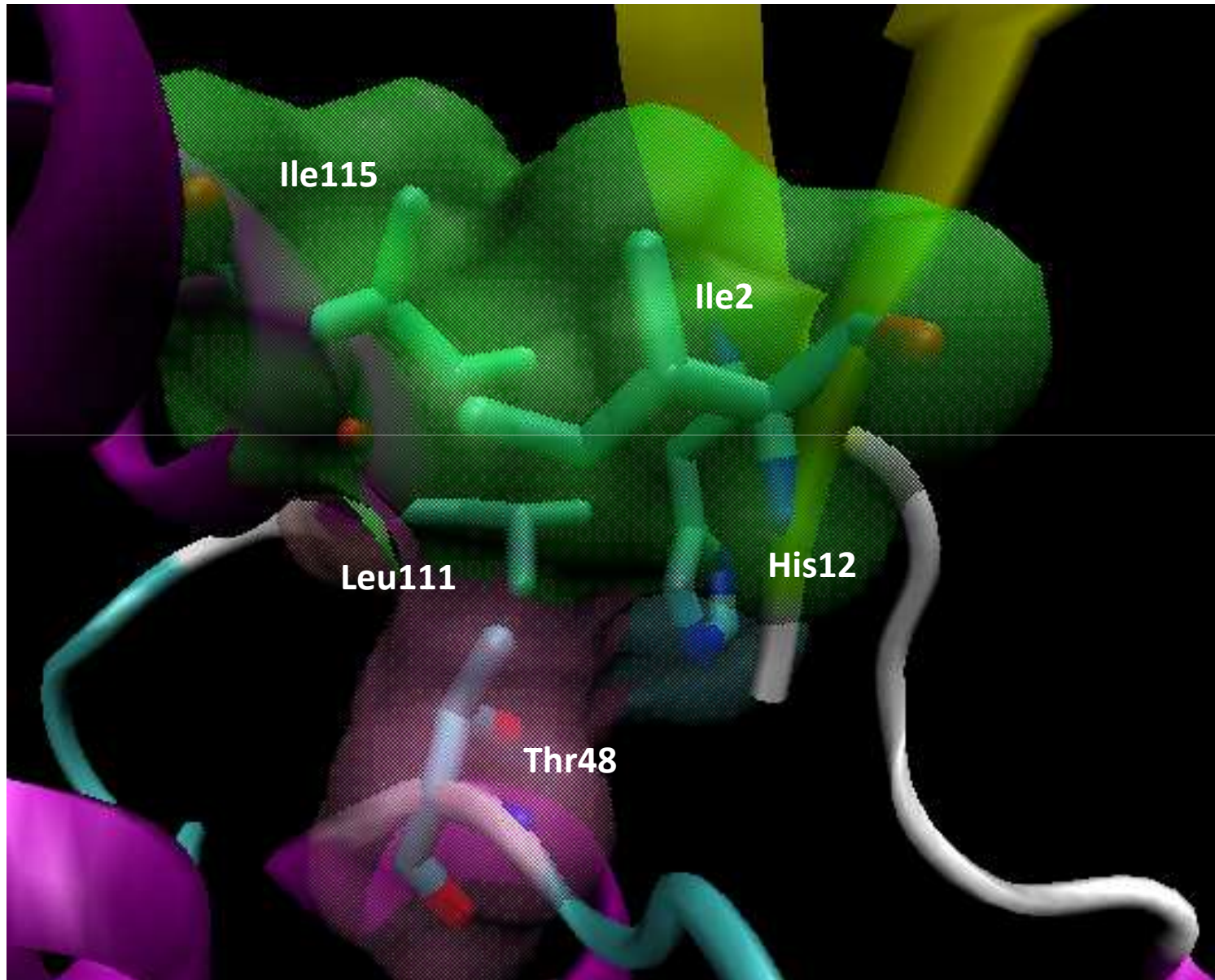
2.1. NTD

β -hairpin

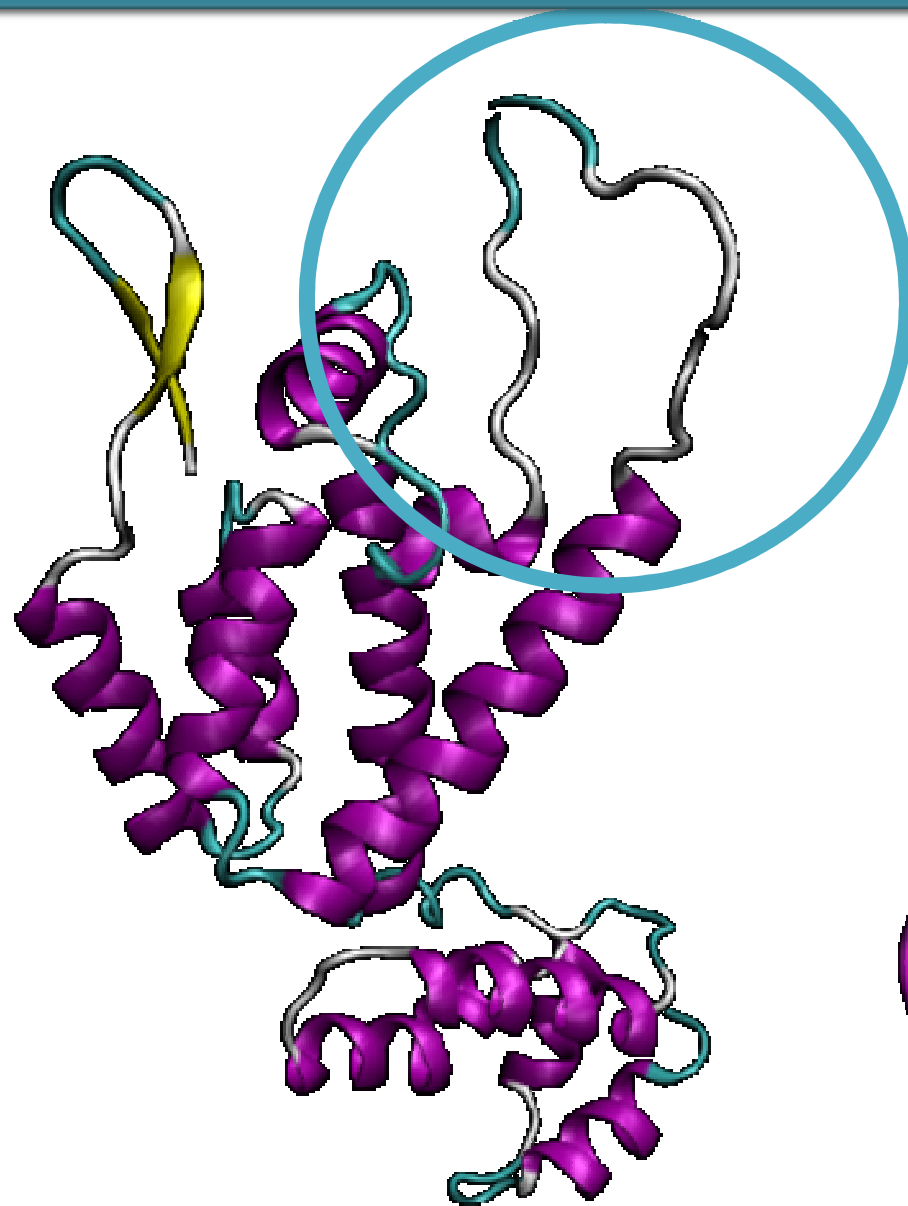
2. Hidrophobic interactions



2.1. NTD

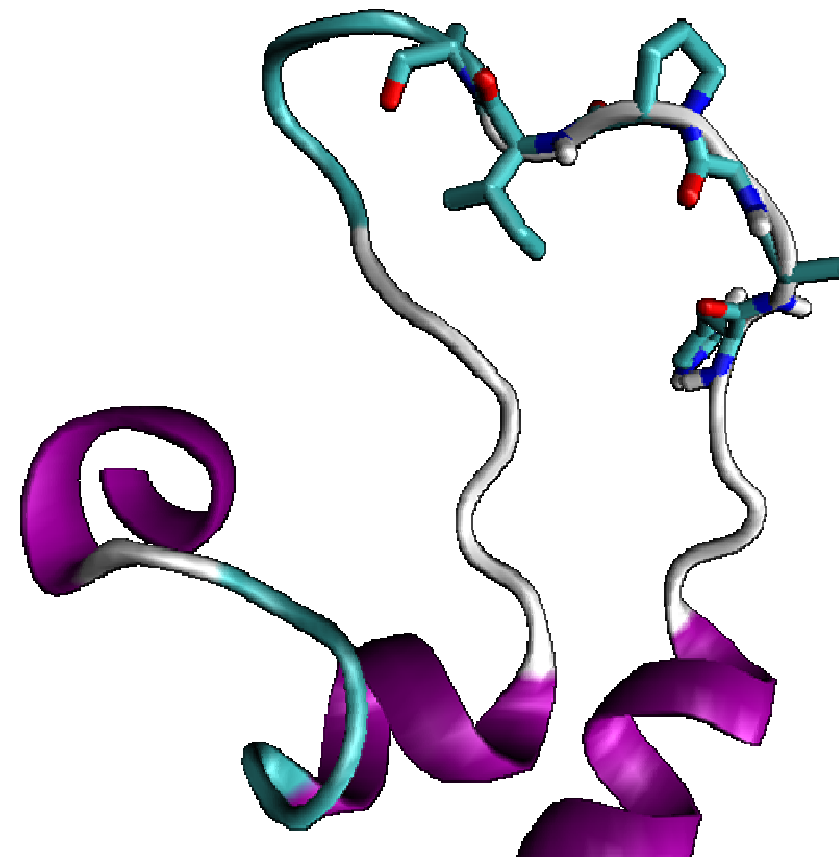


2.1. NTD

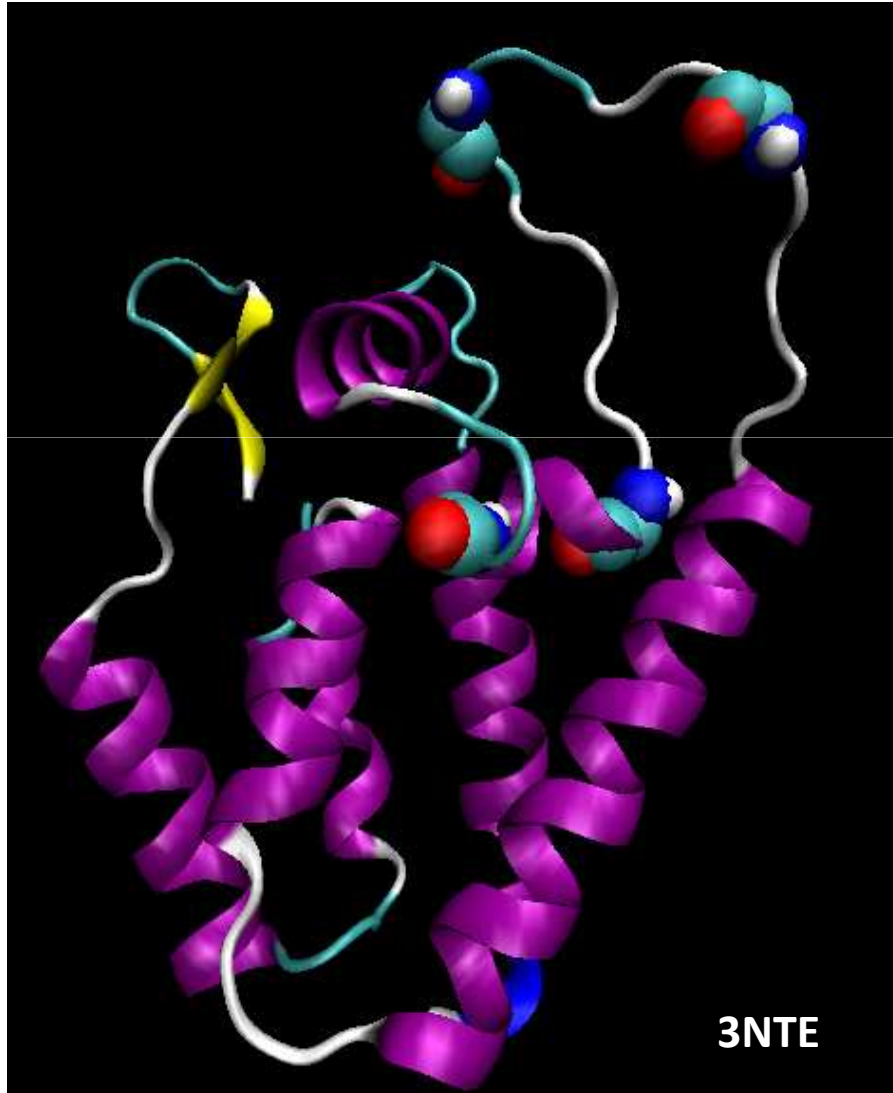


CyPA-bindingloop

⁸⁷HAGPIA⁹²



2.1. NTD

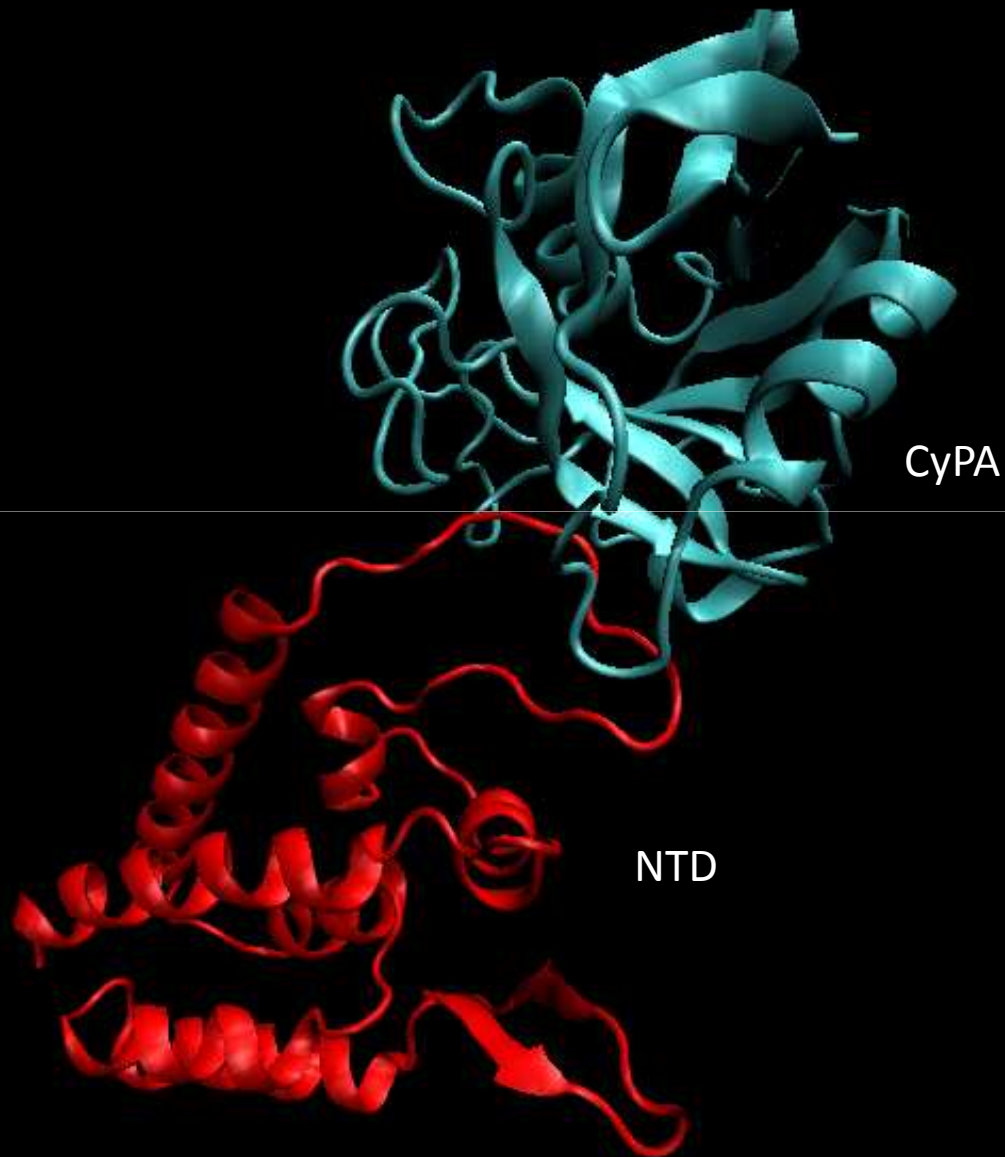


The high flexibility of the loop between alpha helices 4 and 5 is consistent with its:

1. Gly-rich composition
2. High degree of solvent accessibility
3. Lack of tertiary contacts with the protein core

2.1. NTD

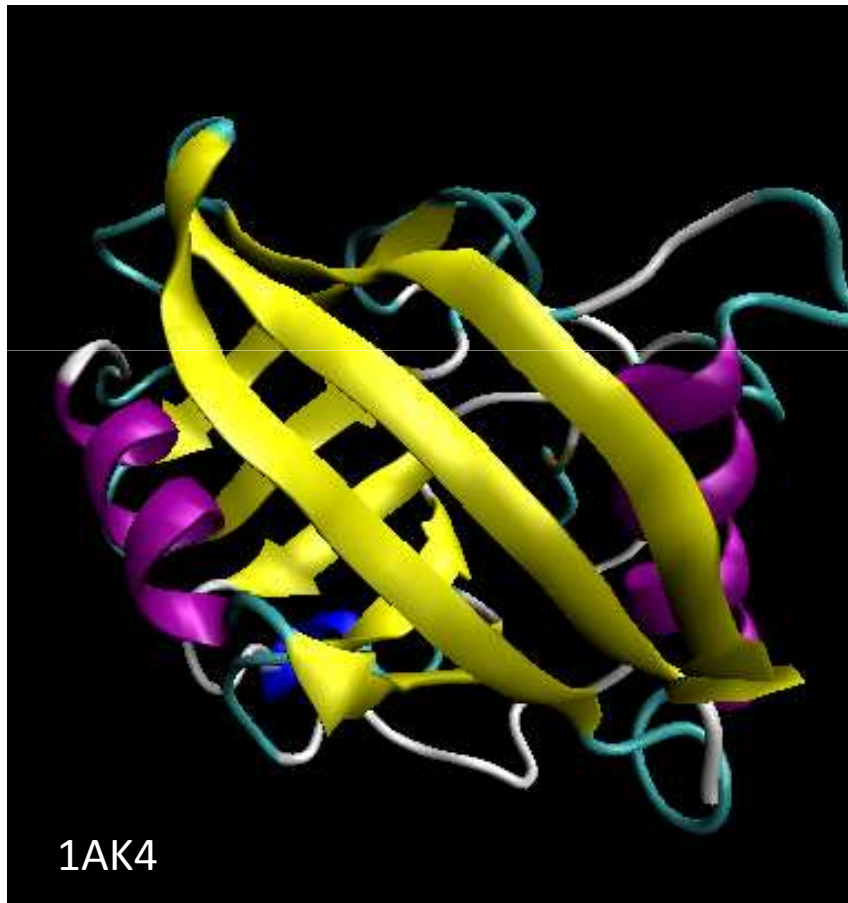
Interaction
CyPA-NTD



1AK4

2.1. NTD

CyPA



165 residues

B-barrel Structure

{ 8 antiparallel beta chains
2 helix alfa

Hydrophobic pocket on the surface

Therapeutic target: Ciclosporina A

IMPORTANCE



**peptidyl-prolyl-cis-trans
isomerization**

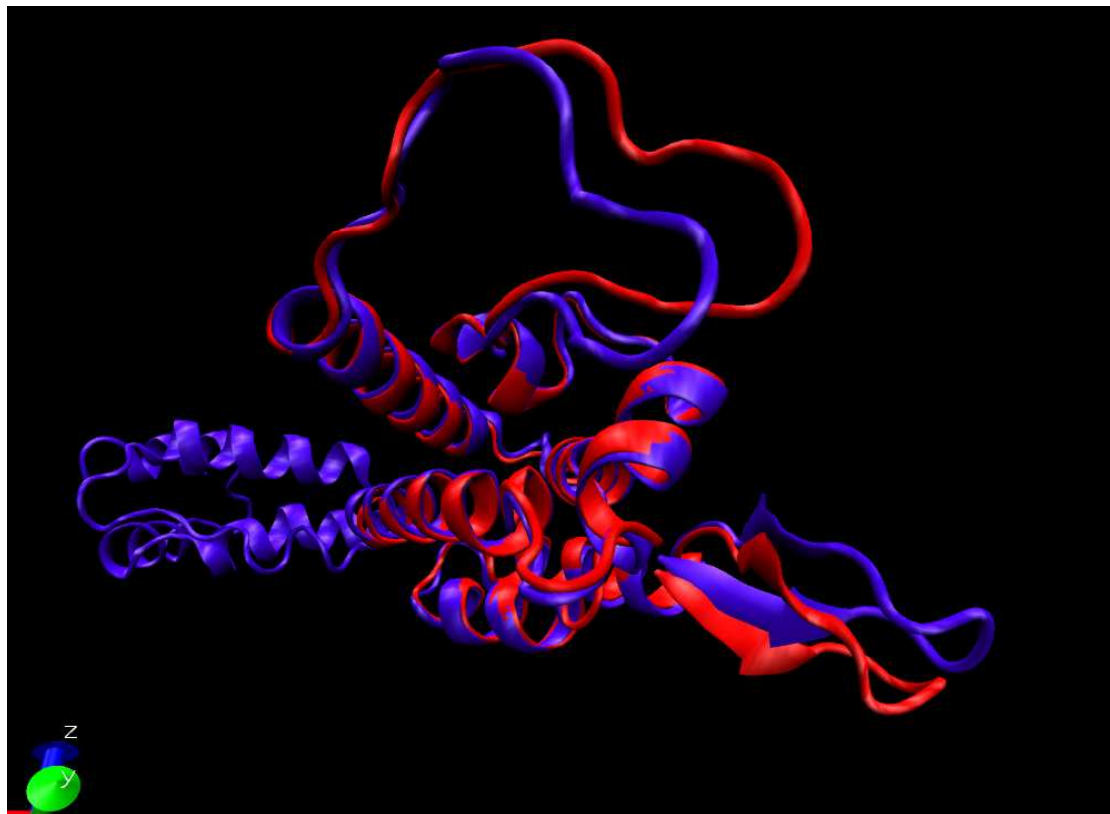


Unknown Function – correct folding of p24

2.1. NTD

Relevant conformational changes in beta hairpin and Cyclophilin bindingloop

STAMP NTD
CyPA/no-CyPA



STAMP Structural Alignment of Multiple Proteins
by Robert B. Russell & Geoffrey J. Barton
Please cite PROTEINS, v14, 309-323, 1992

Running roughfit.

Sc = STAMP score, RMS = RMS deviation, Align = alignment length
Len1, Len2 = length of domain, Nfit = residues fitted
Secs = no. equivalent sec. strucs. Eq = no. equivalent residues
%I = seq. identity, %S = sec. str. identity
P(m) = P value (p=1/10) calculated after Murzin (1993), JMB, 230, 689-694

No.	Domain1	Domain2	Sc	RMS	Len1	Len2	Align	NFit	Eq.	Seq
%I	%S	P(m)								
Pair	1	NTD1								
		NTD2	5.70	0.97	145	221	145	133	132	(
98.48 100.00 0.00e+00										
Reading in matrix file NTD.mat...										
Doing cluster analysis...										
Cluster: 1 (NTD1 & NTD2) Sc 5.70 RMS 0.96 Len 145 nfit 132										
See file NTD.1 for the alignment and transformations										

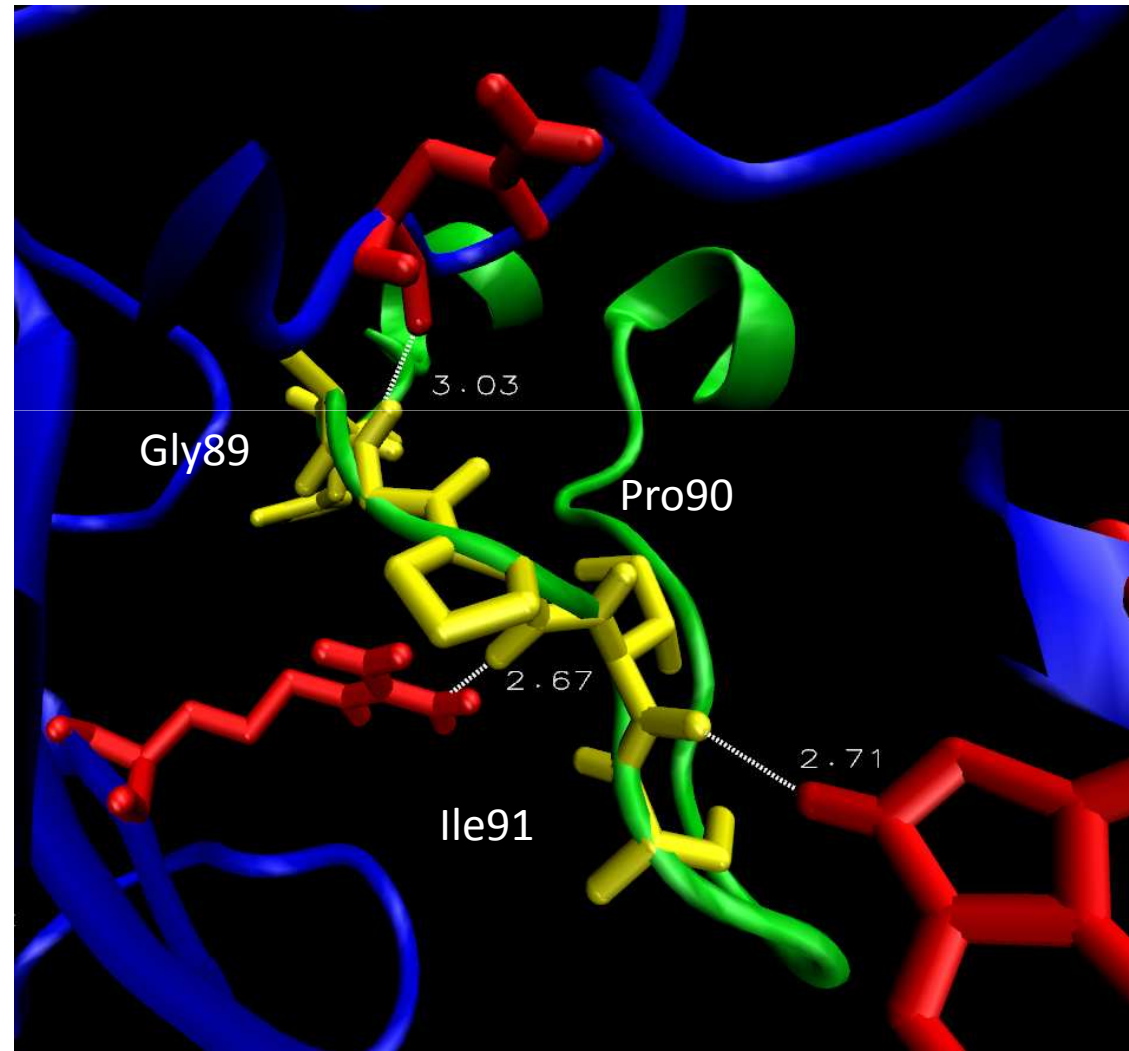
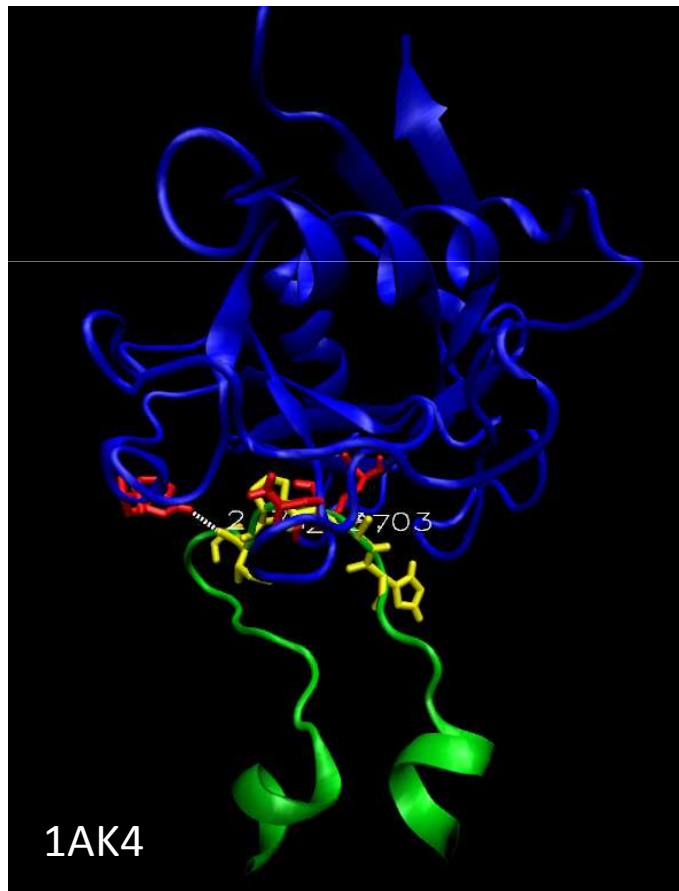
Blue: NTD not bound to CyPA
Red: NTD bound to CyPA

2.1. NTD

Interaction Cyclophilin-
binding loop and CyPA

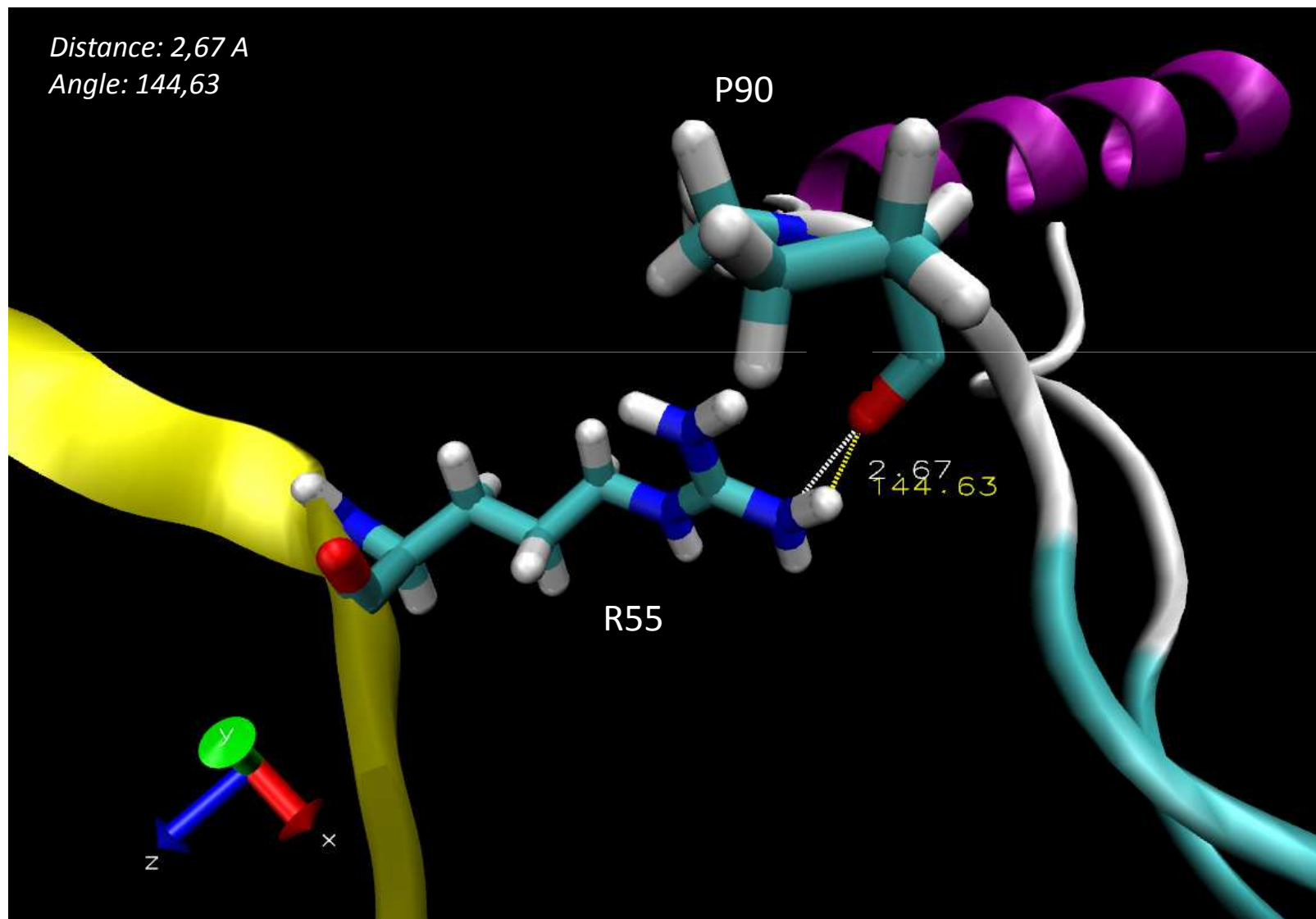


HBONDS
HBONDS



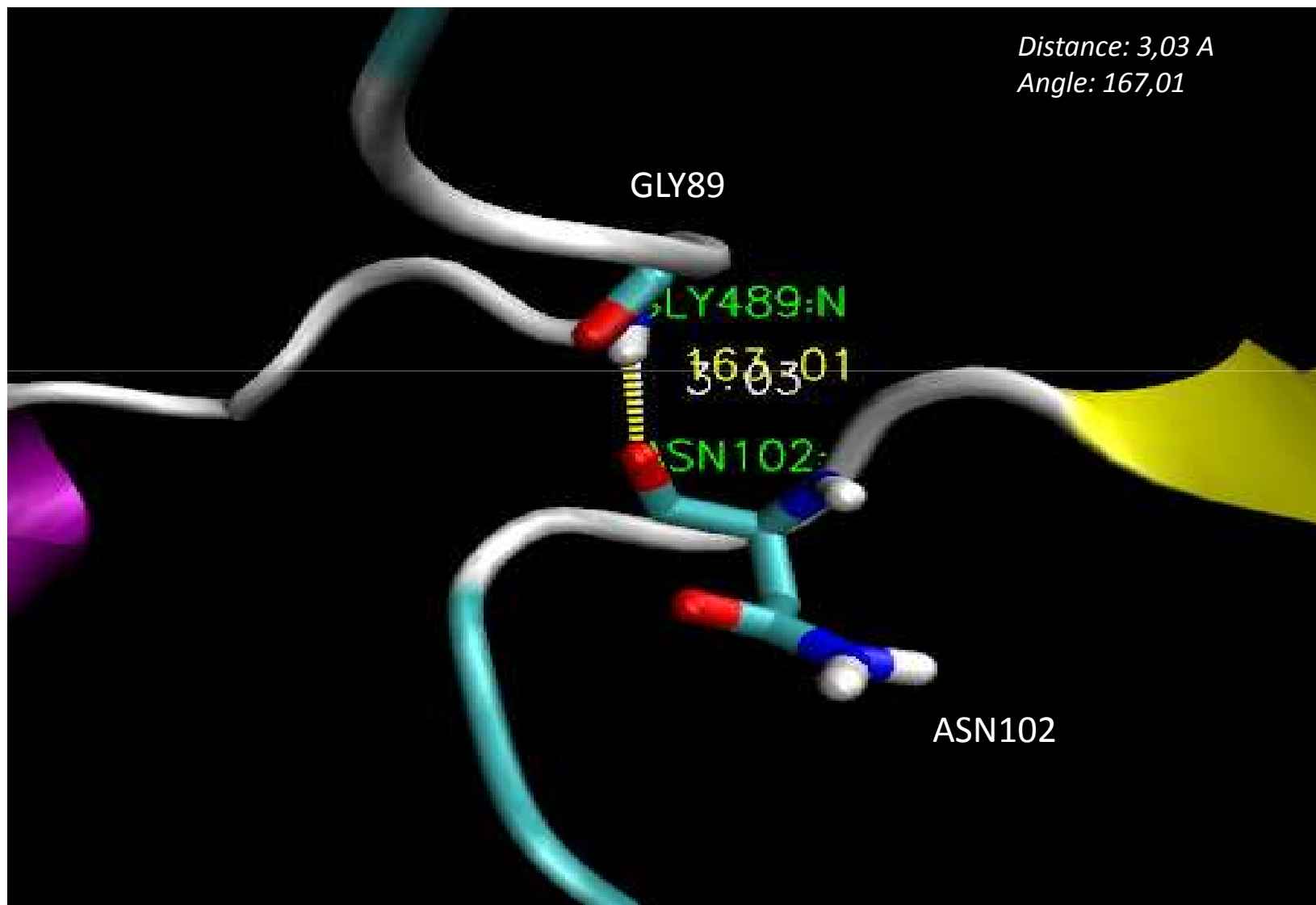
2.1. NTD

Hydrogen bond R55 of CyPA and P90 of CA



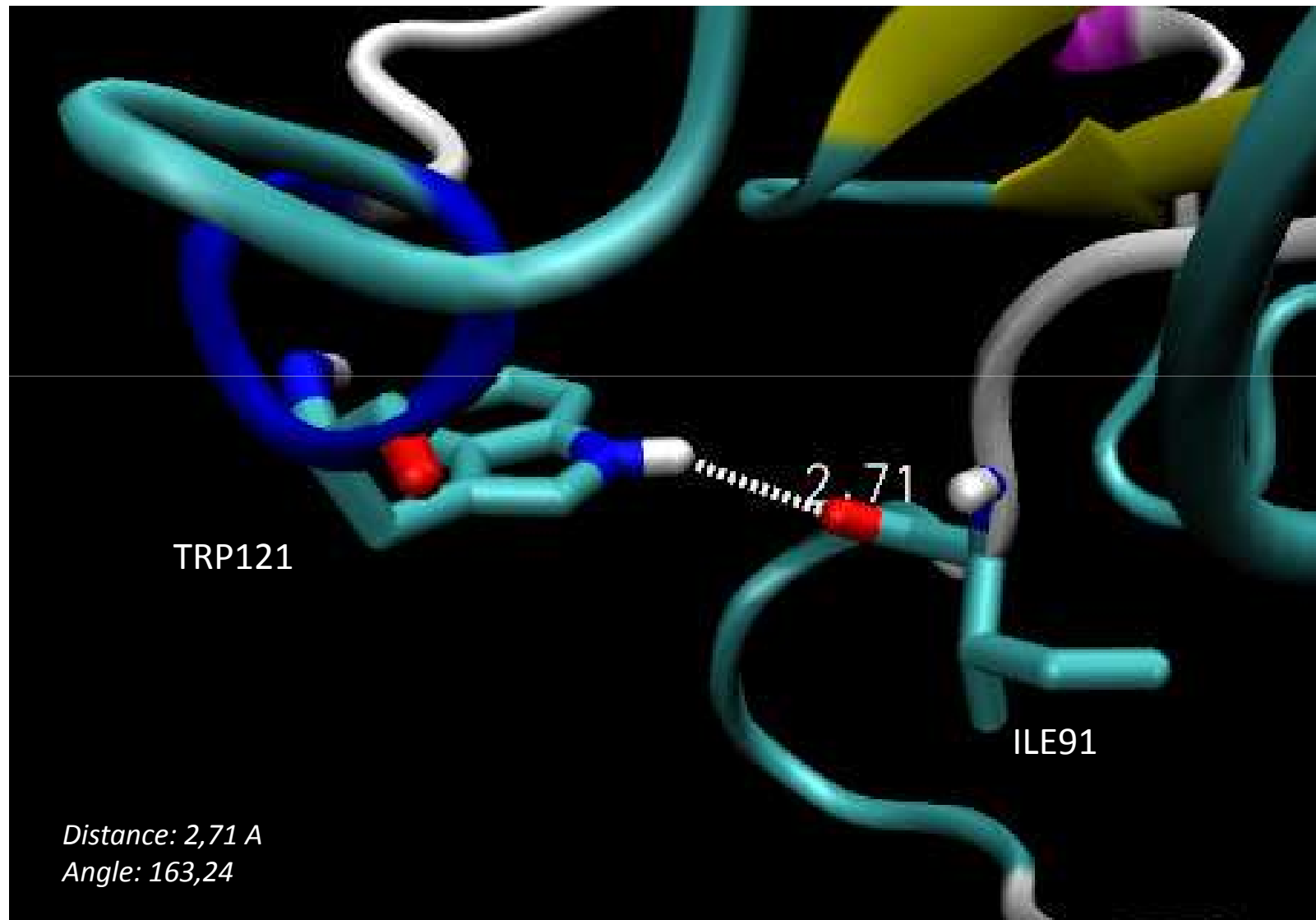
2.1. NTD

Hydrogen bond ASN102 of CyPA and GLY of CA



2.1. NTD

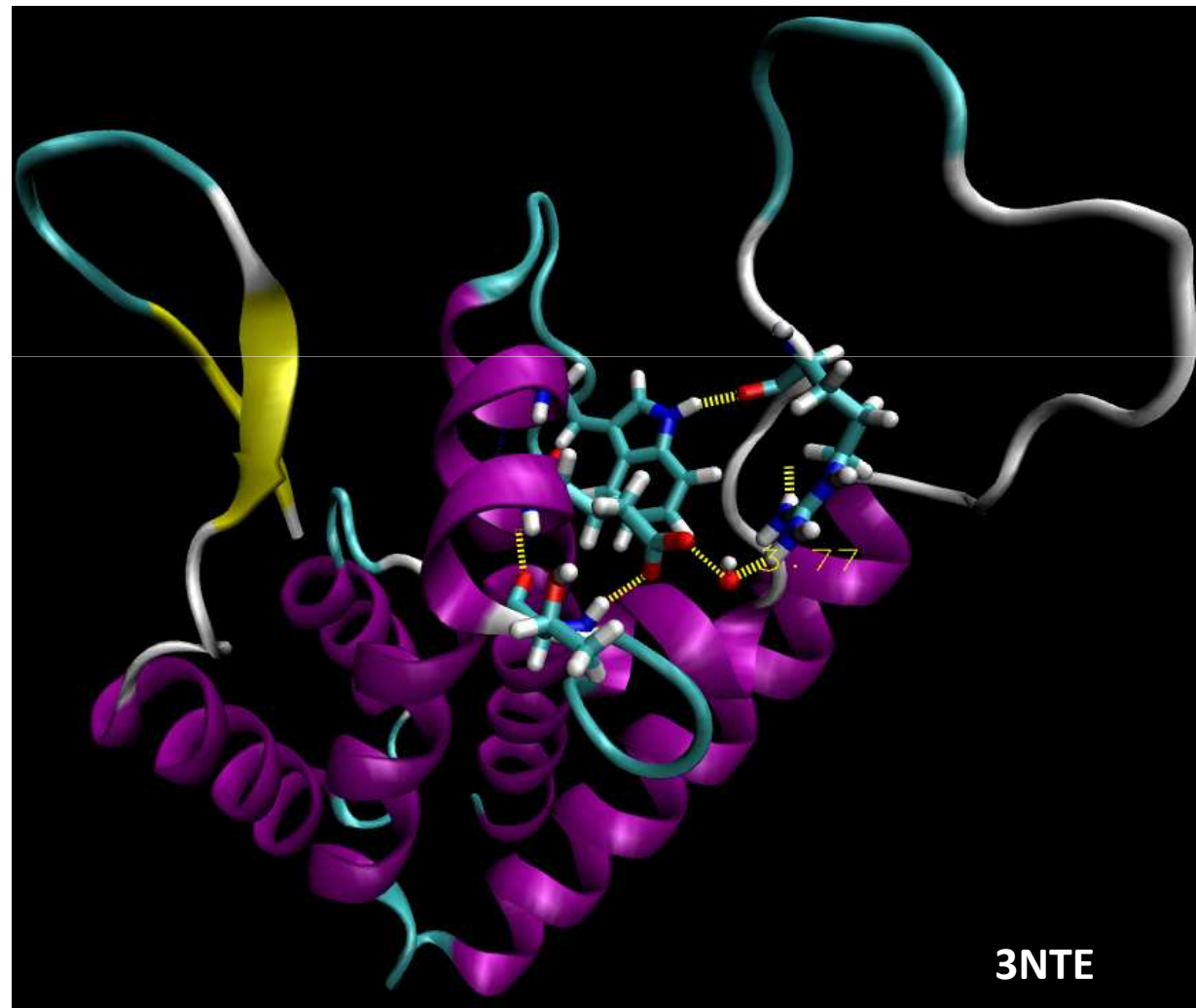
Hydrogenbond TRP121 of CyPA and ILE91 of CA



2.1. NTD

Helix6- CyPA binding loop

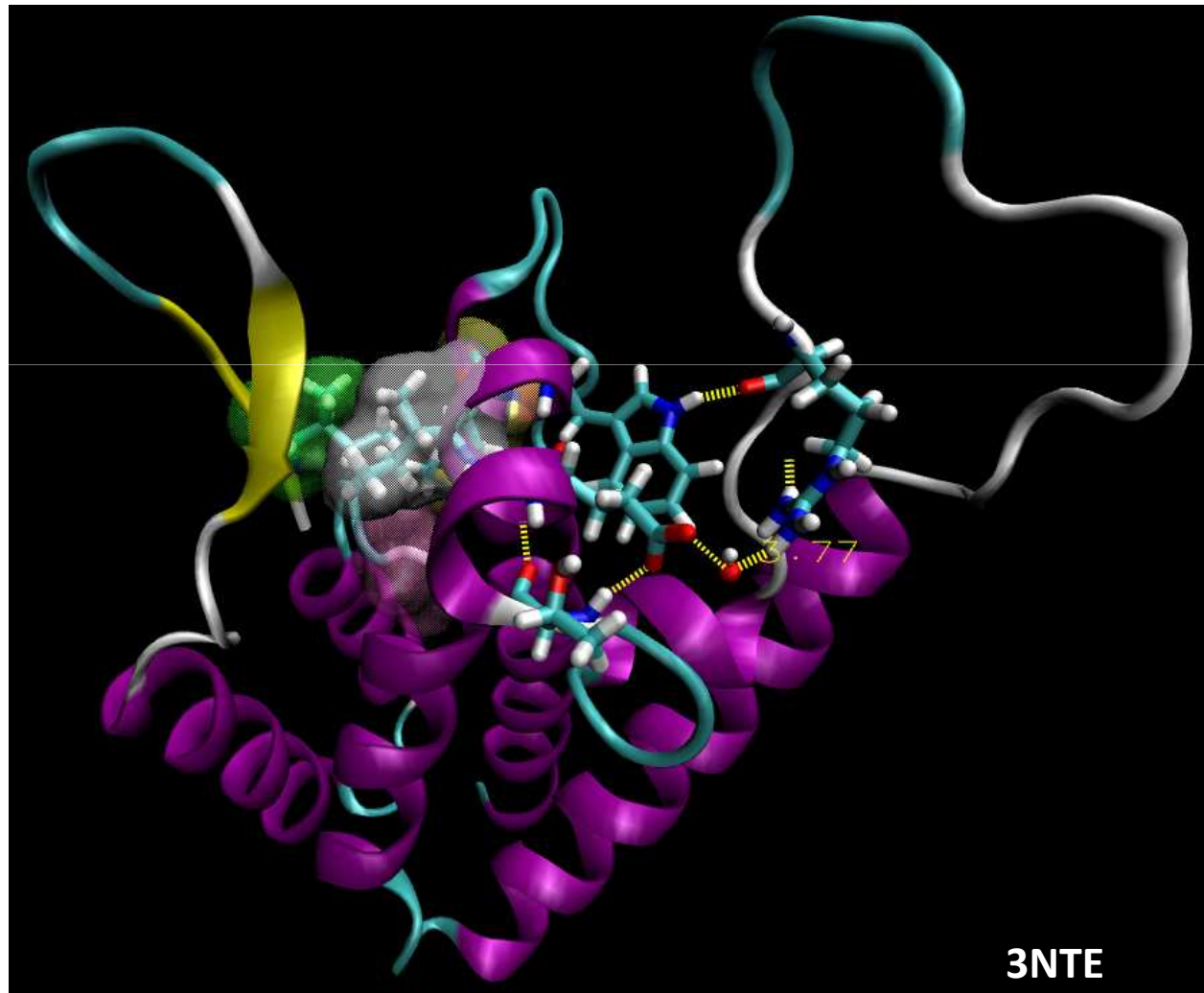
Hydrogen bonds
between H6 and
CypA binding loop



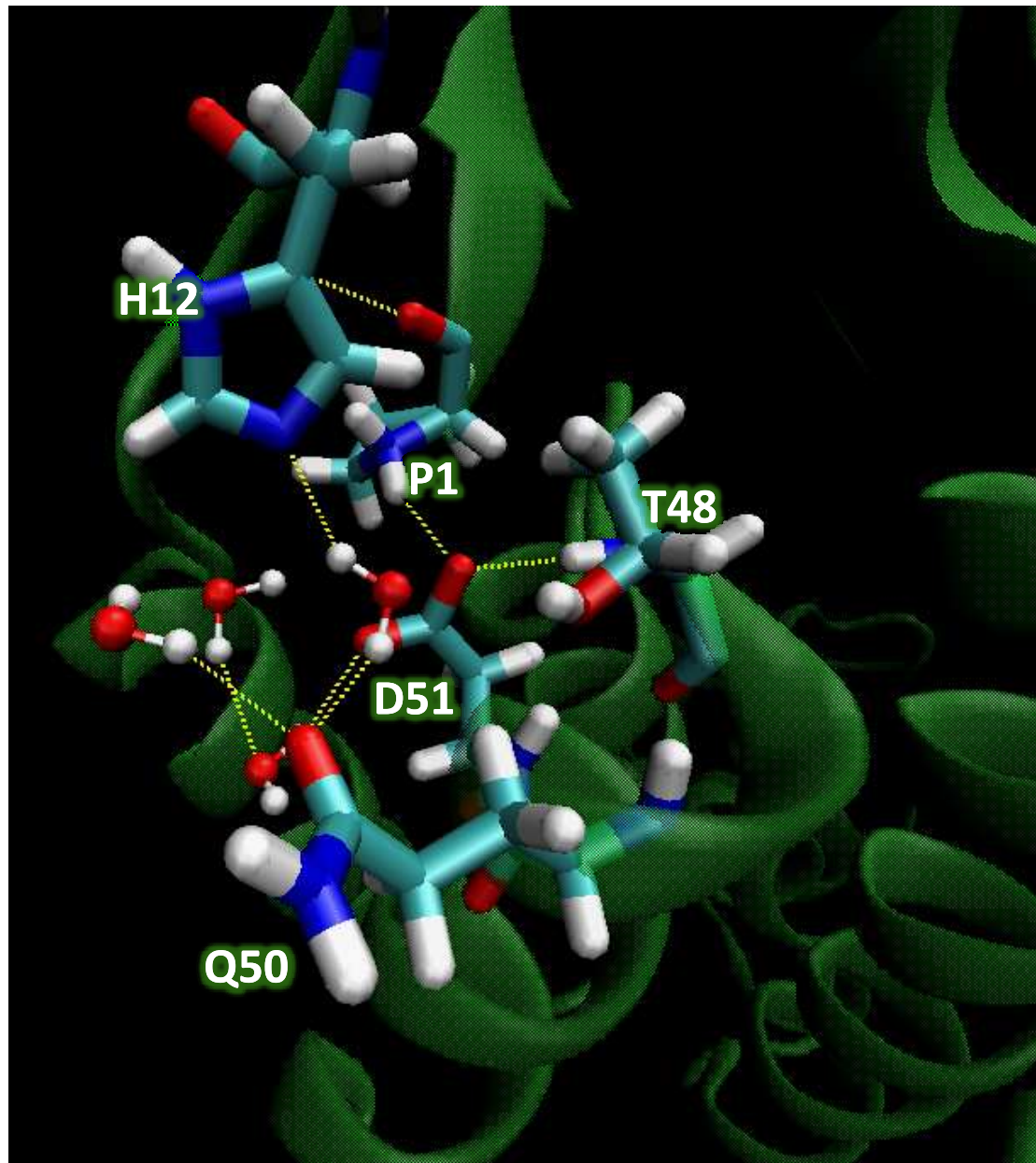
2.1. NTD

B-hairpin-Helix6- CyPA binding loop

Hydrogen bonds between
B-hairpin - H6 and
CypA binding loop



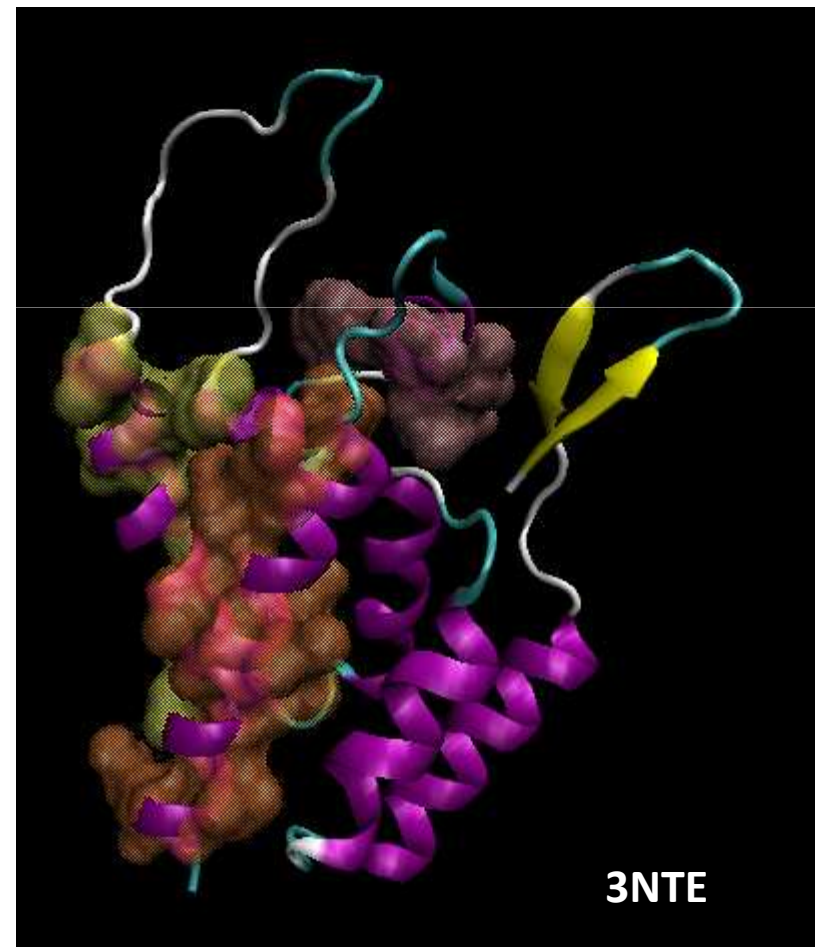
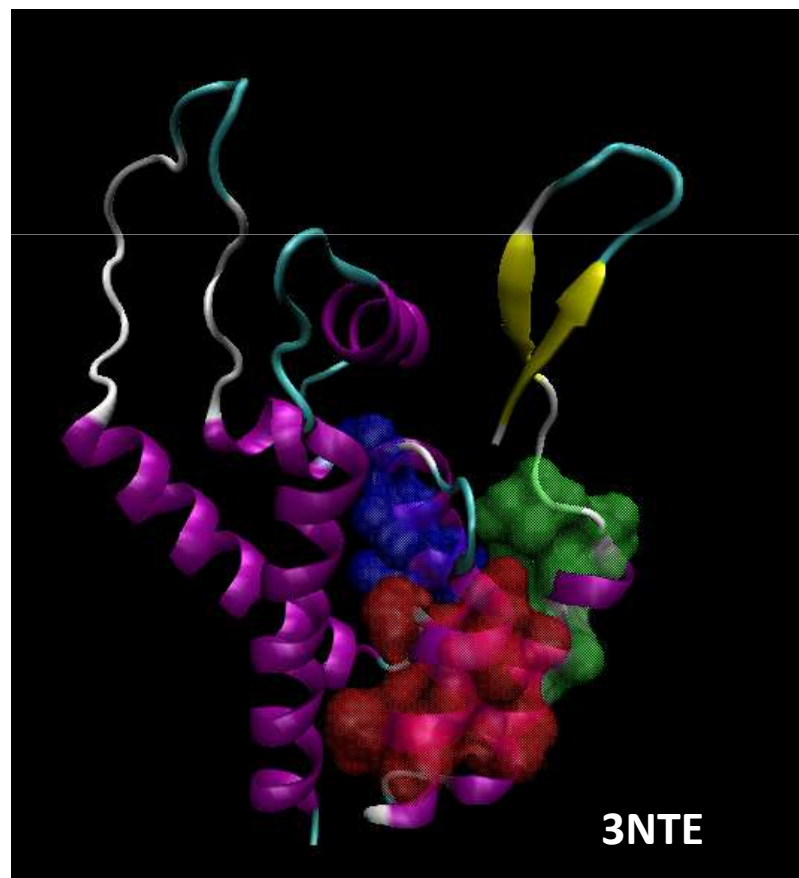
2.1. NTD



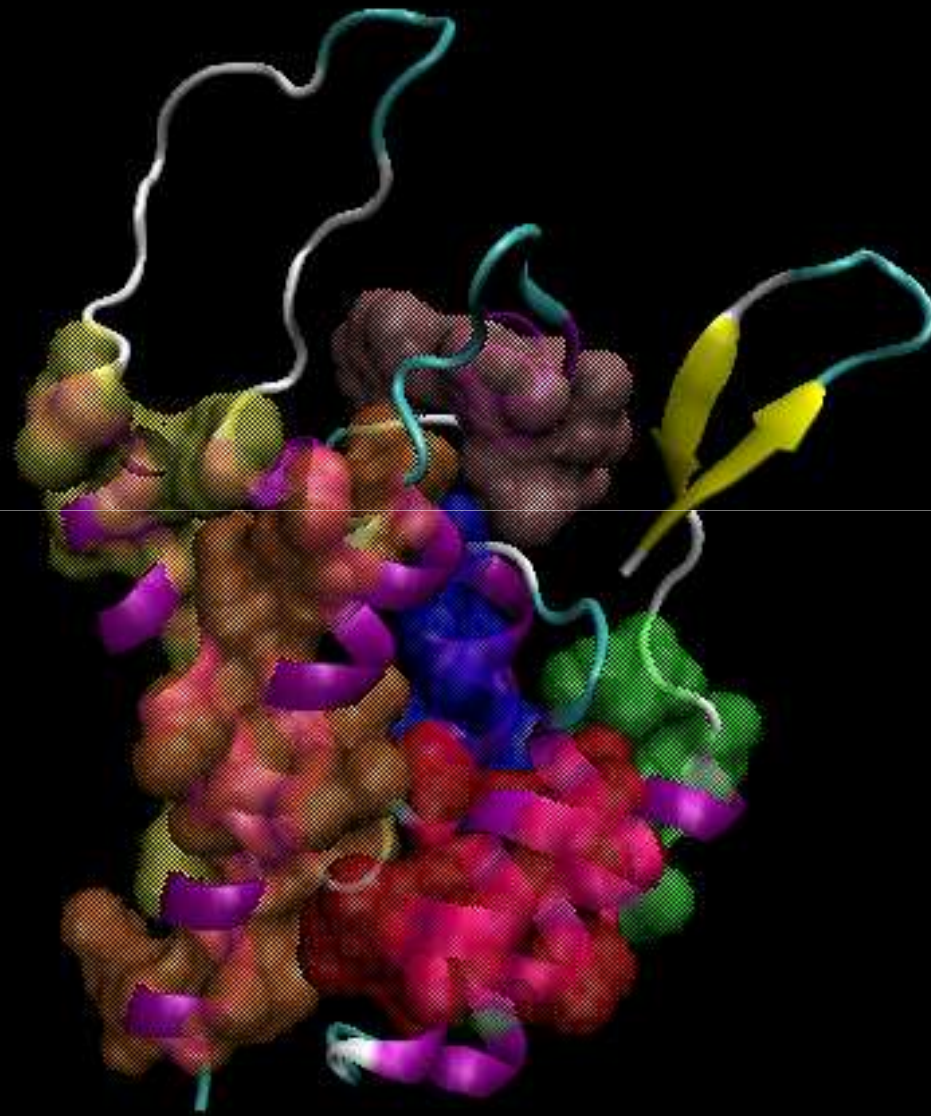
Hbonds mediated by water molecules.

2.1 NTD

Hydrophobic
interactions



Domini NTD



3NTE

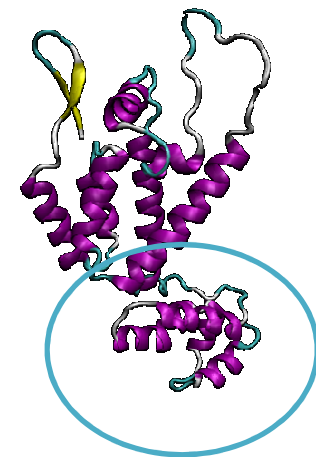
Index

- Introduction
- CA (monomer)
 - NTD
 - CTD
- Capsid subunit (hexamer)
 - Oligomerization interfaces
 - Assembly interactions
 - Flexibility
- Lattice model

2.2.Domini CTD

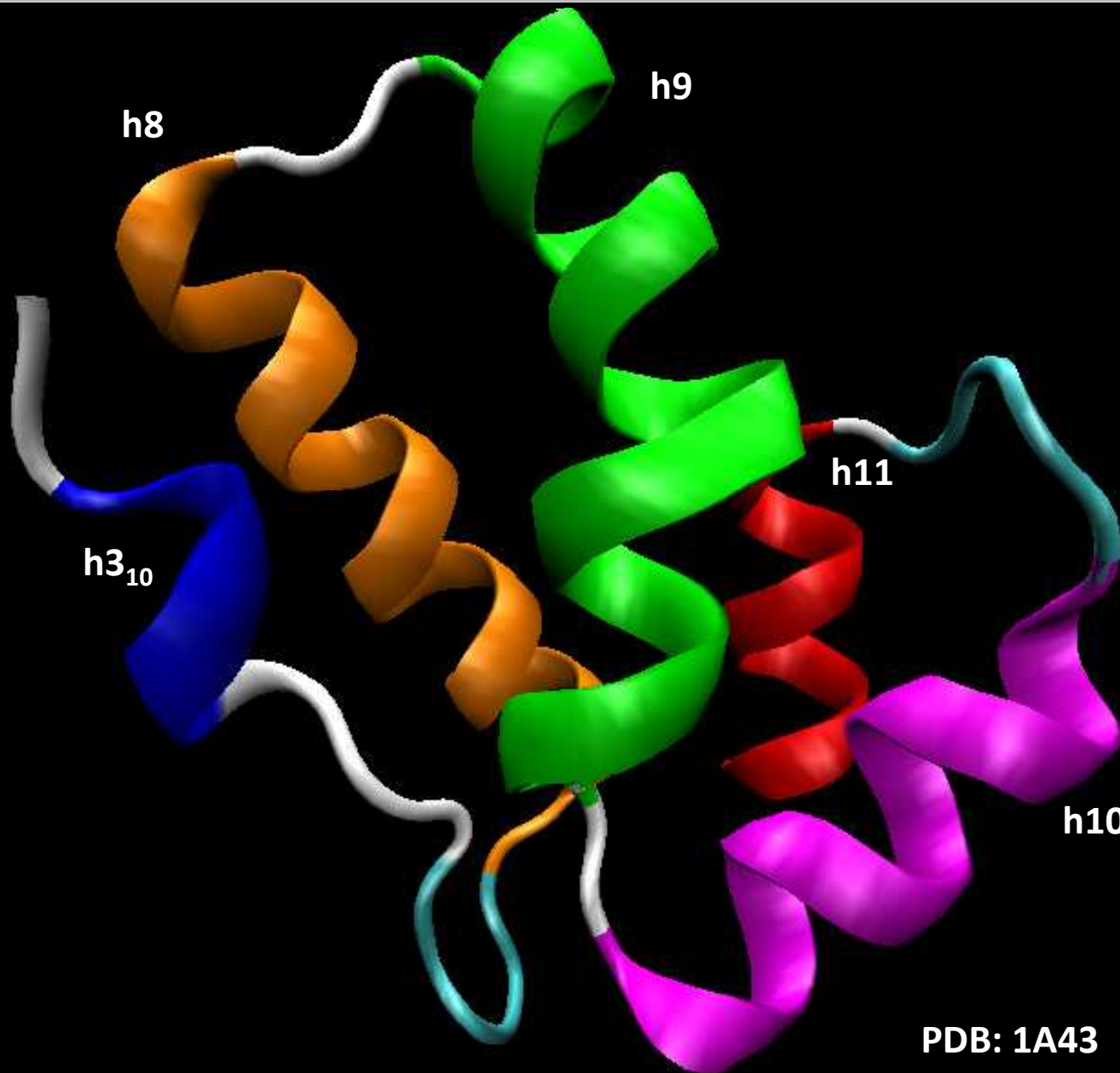
Residues: 150-231

Dimensions: 29x36x28 Å



PDB: 1A43

2.2.Domini CTD



3₁₀-helix (150-152)
α-helix 8 (160-176)
α-helix 9 (179-195)
α-helix 10 (196-206)
α-helix 11 (211-219)
220-231 disordered

Glycine –rich
motif
“GVGGP”

2.2.Domini CTD

The two domains of CA belong to different superfamilies

CTD domain Superfamily: Retrovirus capsid dimerization domain-like

- 4. Superfamily: [Retrovirus capsid dimerization domain-like](#) [47353]
Superfamily
- 5. Family: [Retrovirus capsid protein C-terminal domain](#) [47354]

Protein Domains:

- 1. EIAV capsid protein p26 [47355]
 - 1. [Equine infectious anemia virus](#) [TaxId: 11665] [47356] (2) 
- 2. HTLV-I capsid protein [47357]
 - 1. [Human T-cell leukemia virus type 1](#) [TaxId: 11908] [47358] (1) 
- 3. HIV capsid protein, dimerisation domain [47359]
 - 1. [Human immunodeficiency virus type 1](#) [TaxId: 11676] [47360] (7) 
- 4. RSV capsid protein [47361]
 - 1. [Rous sarcoma virus](#) [TaxId: 11886] [47362] (2) 

NTD domain Superfamily: Retrovirus capsid protein, N-terminal core domain

- 4. Superfamily: [Retrovirus capsid protein, N-terminal core domain](#) [47943]
Superfamily
- 5. Family: [Retrovirus capsid protein, N-terminal core domain](#) [47944]

Protein Domains:

- 1. HIV-1 capsid protein [47945]
 - 1. [Human immunodeficiency virus type 1](#) [TaxId: 11676] [47946] (16) 
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- 3. HTLV-I capsid protein [47949]
 - 1. [Human T-cell leukemia virus type 1](#) [TaxId: 11908] [47950] (2) 
- 4. RSV capsid protein [47951]
 - 1. [Rous sarcoma virus](#) [TaxId: 11886] [47952] (3) 
- 5. AKV capsid [116949]
 - 1. [AKV murine leukemia virus](#) [TaxId: 11791] [116950] (1) 
SQ [P03336](#) 215-345 # fragment of the core shell protein p30 (215-477)

2.2.Domini CTD

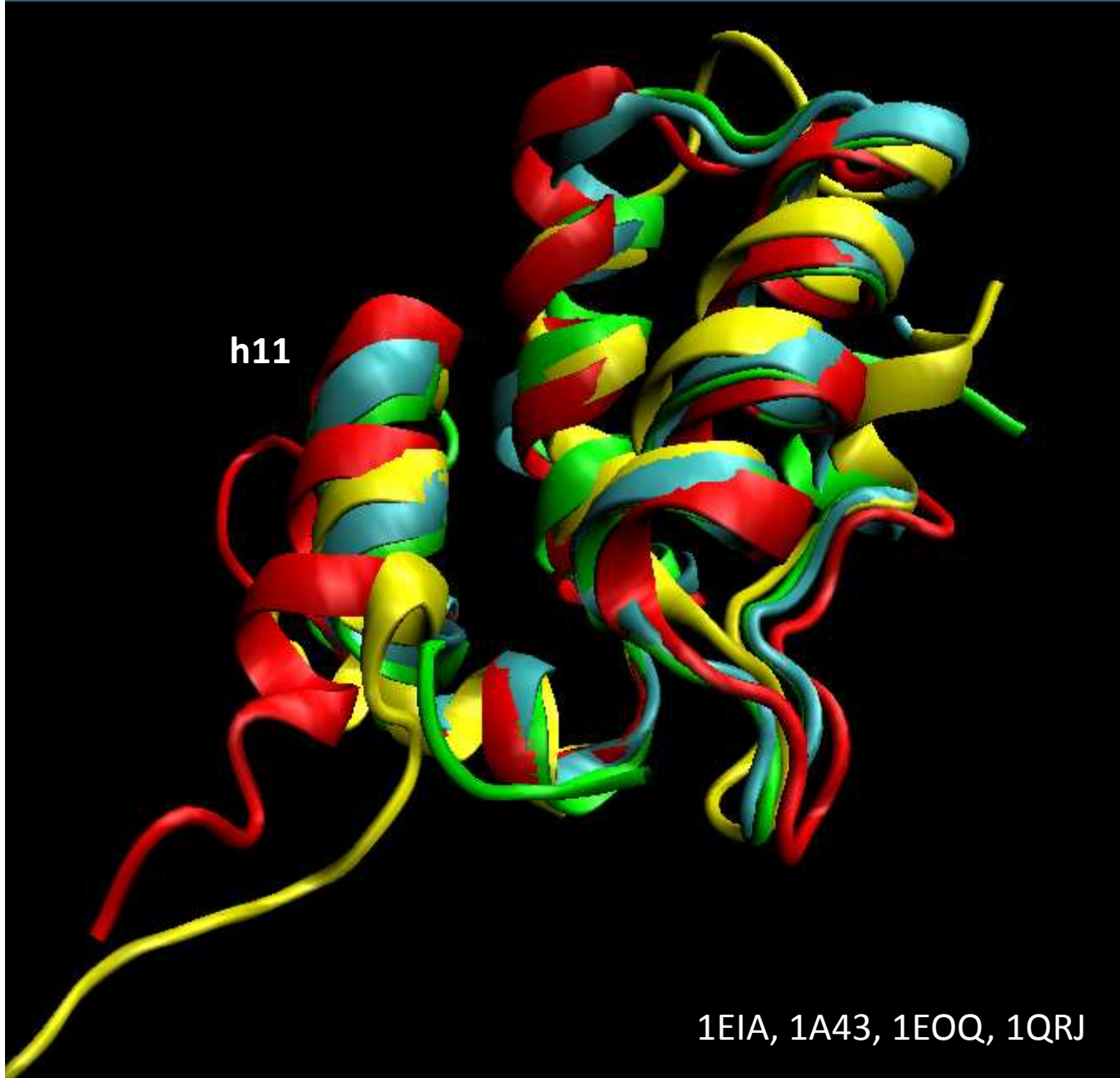
Superfamily

STAMP CTD of
members of the
superfamily

h11

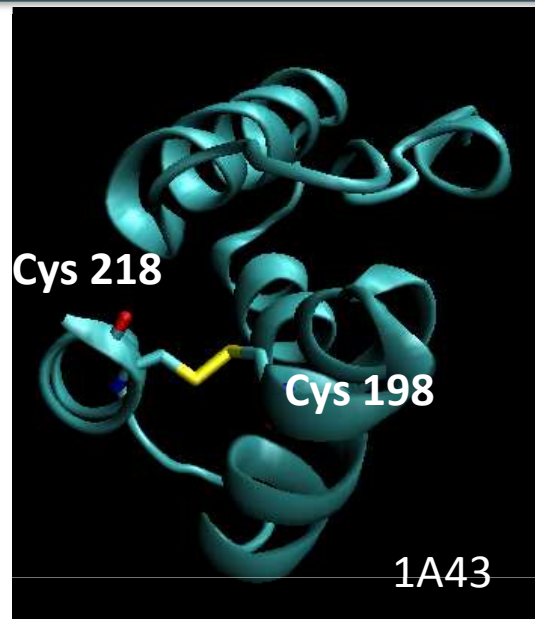
Blue: HIV-1
Green: EIAV
Yellow: HTLV-1
Red: RSV

1EIA, 1A43, 1EOQ, 1QRJ

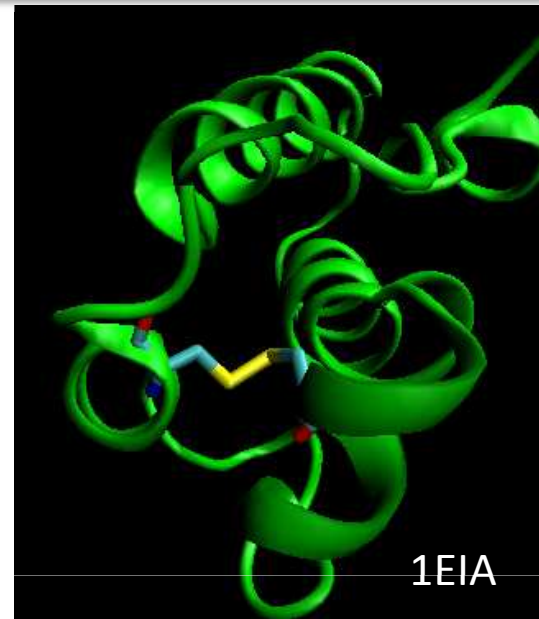


2.2.Domini CTD

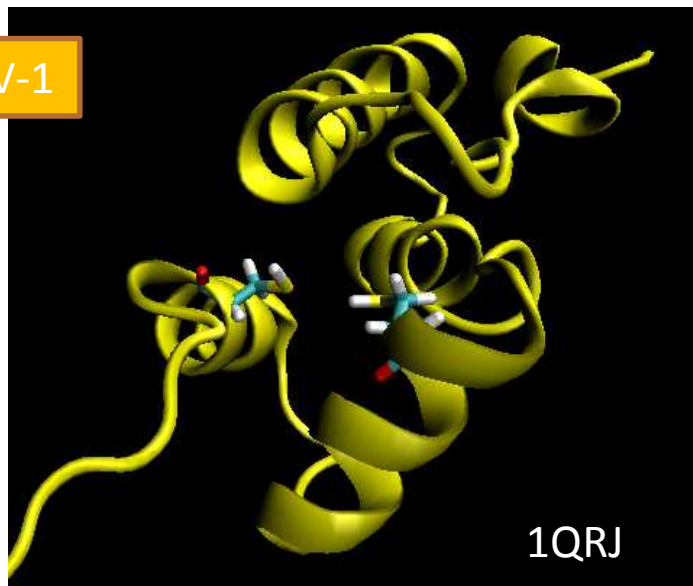
HIV-1



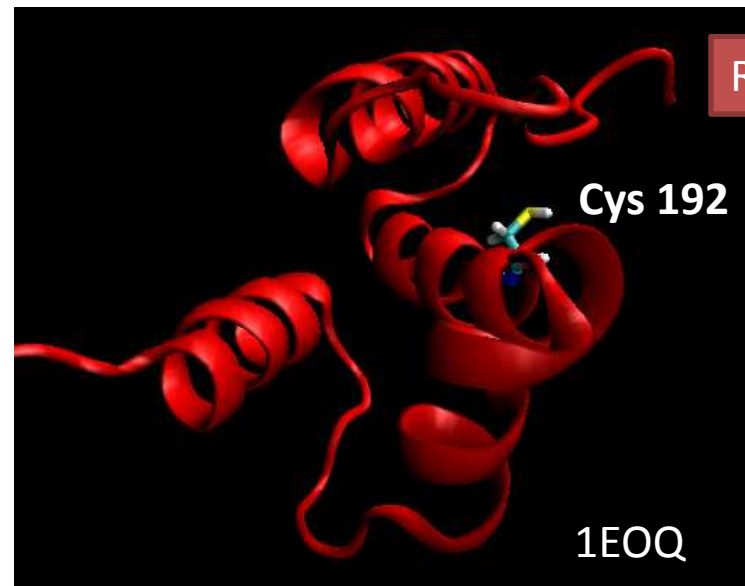
EIAV



HTLV-1



RSV



2.2.Domini CTD

Superfamily-Sequence alignment with HHM

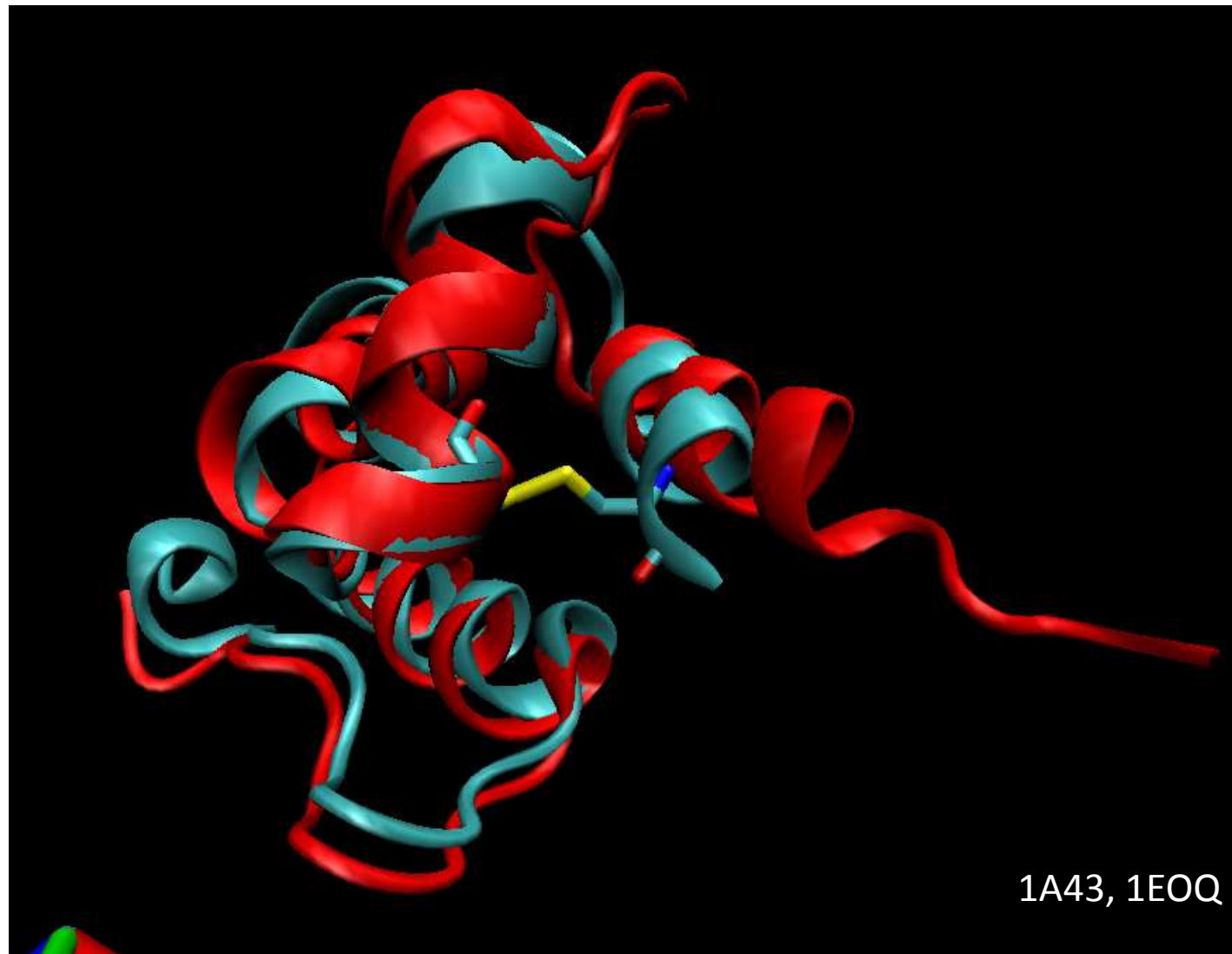
```
1A43      mspt-SILDIRQGPKEPFRDYVDRFYKTLRAEQ--ASQEVKNWMTETLLV
1EIA      ....PKAQNIRQGAKEPYPEFVDRLLSQIKSEG--HPQEISKFLTDTLTI
1EOQ      ....---MDIMQGPSESFVDFANRLIKAVEGSD--LPPSARAPVIIDCFR
1QRJ      ..kdPSWASILQGLEEPYHAFVERLNIALDNGLPEG--TPKDPILRSLAY
#=GC RF    ....XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
```

```
1A43      QNANPDCKTILKA--LPGGATLEEMMTAC-QG-VGGPghkarvl.....
1EIA      QNANEECRNAMRH--LRPEDTLEEKMYAC-RD-IG--.....
1EOQ      QKSQPDIIQLIRT-APSTLTTPGEIIKVLDRQ-KTAPltdqgiaaamss
1QRJ      SNANKECQKLLQARGHT-NSPLGDMLRAC-QTWT PKDktkvl.....
#=GC RF    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.....
```

```
1A43      .....
1EIA      .....
1EOQ      aiqplim
1QRJ      .....
#=GC RF    .....
//
```

1A43: HIV-1
1EIA: EIAV
1EOQ: RSV
1QRJ: HTLV-1

2.2.Domini CTD



Superfamily

STAMP CTD of
HIV and RSV

Blue: HIV-1

Red: RSV

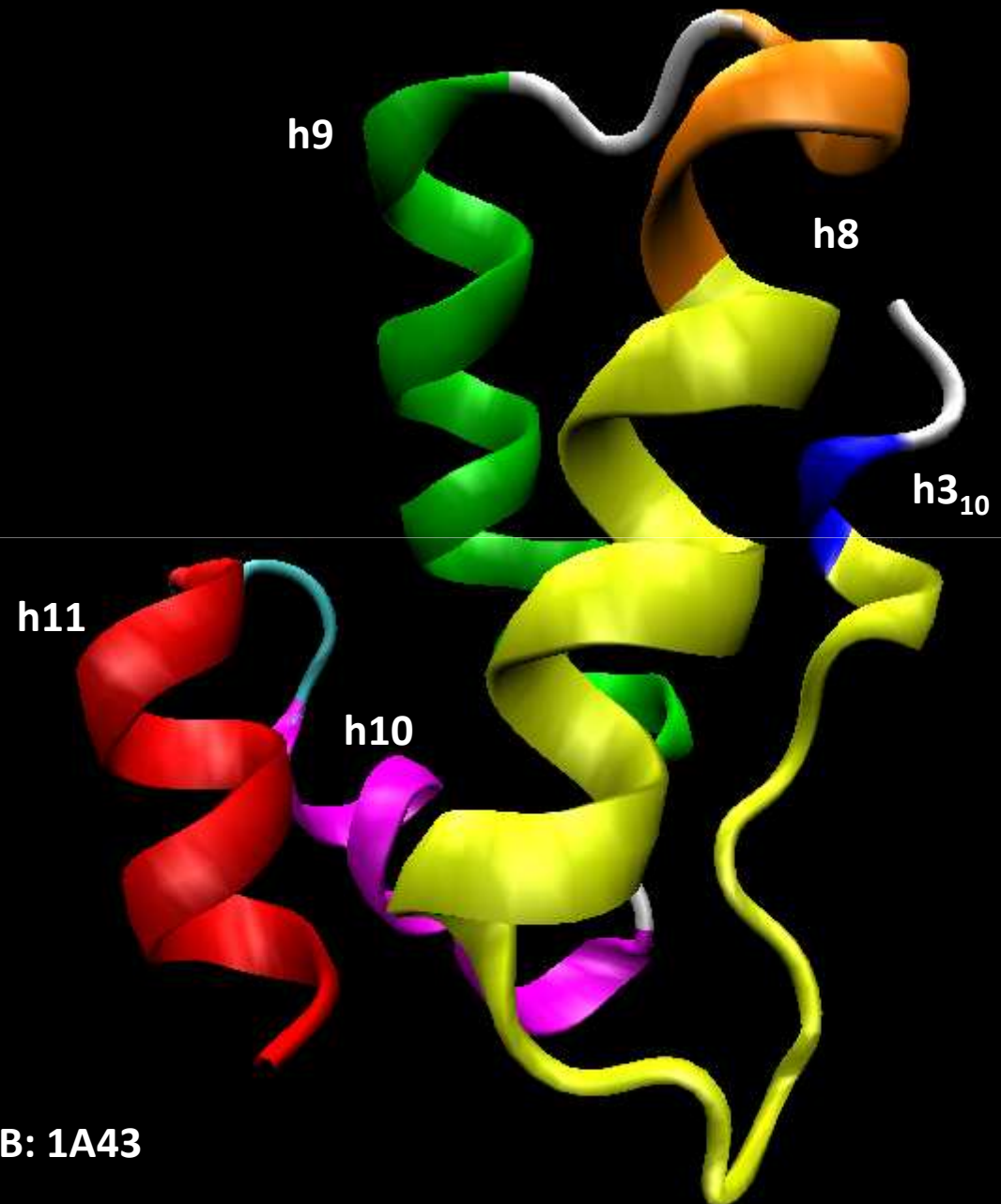
2.2.Domini CTD

The Major Homology Region

MHR

Residus: 152 to 172
Strand-turn-helix motif

This region is highly
conserved among the
Retroviridae family



PDB: 1A43

2.2.Domini CTD

```

HIV-1  PIVQNIQ G --- QMVH QAI SPRTLNAWVKVVEEKAFS FEVIPM
SIV     PLVONAO G --- QMVH QAI SPRTLNAWVKVVEEKAFS FEVIPM
BIV     PAITQD G --- TPRF DPDLMKQLKIWSDATEKRGVD LHAVNI
EIAV    ----- TPRGYTTWNTTQTNGLLNEASQNL
VISNA   PIVNLQA G --- GRSW KAVESVVPQOLQTVAMOHGLVSEDFERQ
FIV     PIQTV N G --- APQY VALDPKMVSIFMEKARE GLGGEVQLW
MTTV    PVVFMGE S DDDDTTPVW EPLPLKTLKELQSAVRTMGPSAPYTLQV
RSV     PVVIKTE G --- PAW TPLEPKLITRLADTVRTKGLRSPITMAE
HTLV1   PVMHPHG A --- PPNH RPWQMKDLQAIKQEVSAAPGSPQMOT
FeLV    PLREGPN N --- RPQY WPFSSADLYNWKSHNPFSSQDPVALTNL
BLV     PIISEGN --- RNRH RAWALRELQDIKKEIENKAPGSQVWIOT
Mo-MuLV PLRAGGN G --- QLQY WPFSSADLYNWKSHNPFSSQDPGKLTAL
GaLV    PLRAIGP AEPNGLVPLQY WPFSSADLYNWKSHNPFSENPAGLTGL
M-PMV   PVTETVD G --- QGQAWRHNGGDFFAVIKELKTAASQYGATAPYTLAI

```

cons

```

HIV-1  F--SALSEGATPDQNTMLNTVGGHQAA--MQ--MLKETINEEA--A
SIV     F--SALSEGALPODVNTMLNAVGGHQA--MQ--VLKEVINEEA--A
BIV     L--GVITANLVQEEIKLLNSTPKWRLLD--VQ--LIESKVRKENAHR
EIAV    F--GILSVDCSTEEMNAFLDVVPQAGQ--KQ--ILLDAIDKIA--D
VISNA   LAY--YATTWTSKDILEVLAAMPGNRAQ--KE--LIOGKLINEEA--E
FIV     F--TAFSANLTPDMDATLMAAPGCAAD--KE--ILDESILKQLT--A
MTTV    VDM-VASQWLTPSDWHQTARATLSPGDYVLWRTYE--KSKE--TVQ
RSV     VE-ALMSSPLLPHDVTNLMRVILGPAPYALWMDANGVOLOTVIAA--ATR
HTLV1   IRLAVQQFDPPTAKDLQDLQLCYLSSSLVASLHHQ--QLDSLISE--AET
FeLV    IESILVTHQPTWDDCQQLQALLTGEE--QR--VLLEARKQVP--G
BLV     LRLAILQADPTPADLEQLCOYIASPVDOTAHMT--SLTAAIAA--AEA
Mo-MuLV IESVLITHQPTWDDCQQLGTLTGEEK--QR--VLLEARKAVR--G
GaLV    LESLMSHQPOTWDDCQQLQILFTTEER--ER--ILLEARKNVL--G
M-PMV   VES-VADNWLTPDWTNLTVRVAVLSGGDHLLWSEFFE--NCRD--TAK

```

cons

```

HIV-1  F--SALSEGATPDQNTMLNTVGGHQAA--MQ--MLKETINEEA--A
SIV     F--SALSEGALPODVNTMLNAVGGHQA--MQ--VLKEVINEEA--A
BIV     L--GVITANLVQEEIKLLNSTPKWRLLD--VQ--LIESKVRKENAHR
EIAV    F--GILSVDCSTEEMNAFLDVVPQAGQ--KQ--ILLDAIDKIA--D
VISNA   LAY--YATTWTSKDILEVLAAMPGNRAQ--KE--LIOGKLINEEA--E
FIV     F--TAFSANLTPDMDATLMAAPGCAAD--KE--ILDESILKQLT--A
MTTV    VDM-VASQWLTPSDWHQTARATLSPGDYVLWRTYE--KSKE--TVQ
RSV     VE-ALMSSPLLPHDVTNLMRVILGPAPYALWMDANGVOLOTVIAA--ATR
HTLV1   IRLAVQQFDPPTAKDLQDLQLCYLSSSLVASLHHQ--QLDSLISE--AET
FeLV    IESILVTHQPTWDDCQQLQALLTGEE--QR--VLLEARKQVP--G
BLV     LRLAILQADPTPADLEQLCOYIASPVDOTAHMT--SLTAAIAA--AEA
Mo-MuLV IESVLITHQPTWDDCQQLGTLTGEEK--QR--VLLEARKAVR--G
GaLV    LESLMSHQPOTWDDCQQLQILFTTEER--ER--ILLEARKNVL--G
M-PMV   VES-VADNWLTPDWTNLTVRVAVLSGGDHLLWSEFFE--NCRD--TAK

```

cons

```

HIV-1  EWDRVHPVHAGFI--APGQMRSE--RGSDIAG--TTSTL--QEQIGWMINNF
SIV     EWDRLHPHAGFI--APGQMRSE--RGSDIAG--TTSTL--QEQIGWTTANF
BIV     TWKQHHP--AP--KTDEIIG--KGLSS--AQATL--I
EIAV    DWDNRHPLNAPLVA--PAPQGFIPMTARFIRG--LGVP--ERQMEP--A
VISNA   RWVRQNP--GF--N--V--LTVDQIMG--VGOTN--QOASOA--N
FIV     EYDRTNPP--GF--RPLPY--FTAAEIMG--IGLTQ--EQQARA--R
MTTV    --KT--A--GK--RKG--K--VSLDMLLG--TGQFLSPS--SQI--K
RSV     --DPRHPAN--GQ--GRGER--TNLNRKGLADGMVGNPQGOAALI--R
HTLV1   --RG--I--TGYNPLA--GPLR--VQANNE--Q
FeLV    EDG--RPTQ--LE--N--V--IDETFE--LTRPN--WDFATP--A
BLV     --ATP--S--RVLTPTK--GTLT--QOASAP--N
Mo-MuLV DDG--RPTQ--LE--N--E--VDAAPP--LERPD--WDYTTQ--A
GaLV    DNG--APTQ--LE--N--L--INEAPP--LNRPH--WDYNTA--A
M-PMV   --RN--Q--QA--GN--G--WDFDMLTG--SGNYSSTT--AQM--Q

```

cons

```

HIV-1  PI--PVGEIYKRWIILGLNKIVRMYSPTSLIRQGPKEPFRDYVDRFYKT
SIV     PIVGDIVRRWVILGLNKIVRMYCPVSLIRQGPKEPFRDYVDRFYKT
BIV     SV--ECRETRFRQVVLQAAMEVAQAKHATPGPIIRQGPKEPYTDFINRLVAA
EIAV    PD--QFRQYTRQWIIEAMSEGIKVMIGKPKAQIRQGAKEPYPEFVDRLLSQ
VISNA   MD--QARQICLOWVITALRSVVRHMSHRPGNPMVKOKNTESYEDFIARLLA
FIV     FA--PARMQCRAWYLEALGKLAIAKASPRAVLRQGAKEYSSFIDRLFAQ
MTTV    LSKDVLKDVTTNAVLAWRRAIPPGVKKTVLAIRKQGNESYETFISRLA
RSV     PG--E--LVAITASALOAFREVARLAEPAGPWAIMOGPSESFVDFANRLIKA
HTLV1   QQ--GLRREYQQLWLAAFAALP--GSANDPSWAILQGLEEYPYHAFVERLNLIA
FeLV    GR--EHLRLYRQLLLAGLGAARRPTNLAQVKVVOGKEETPAAPFLERLKEA
BLV     AG--DLRSOYONLWLOAGKISL--LVLOLOPWSIIVOGPAESSVEFVNRLQIS
Mo-MuLV GR--NHLVHYRQLLLAGLQAGRSPTNLAQVKITQGPNESSPSAFLERLKEA
GaLV    GR--ERLLVYRRTLVAGLKGAAARRPTNLAQVSVLQGAEPSPSVFLERLMEA
M-PMV   YDPLGFAQIQAAATKAWRKLVPKGDPGASLTVKQGPDEPFADFVHRLITT

```

cons

```

HIV-1  LR--EQASQEVKN--W--MTETLLVQNANPDCKTILK--ALGPA--ATLEEM
SIV     LR--EQASQEVKN--W--MTDTLVONANPDCKQILK--ALGPG--ATLEEM
BIV     LE--MAAPETTK--Y--LLQHLSDIHANEDCQSILR--PLGPN--TMEJK
EIAV    IR--EGHPQEKISK--F--LTDTLTIQANEECRNAMR--HLRPE--DTLEEK
VISNA   ID--EPVTDPIKT--Y--LKVTLSYTNASTDCOKOMDRTLGTTRVQOATVEEK
FIV     ID--EQNTAEVKL--Y--LKQSLSIANANAECCKAMS--HLKPE--STLEEK
MTTV    VY--VMPRGEESD--I--LIKQLAWENANSLCQDLIR--PMRKT--GTMQDY
RSV     VE--SDLPSSARA--P--VIIDCFROKSQPDIOQLIR--TAPST--LTPGEI
HTLV1   LD--GLPEGTPKD--P--ILRSLAYSNANKECQKLLQ--ARGHT--NSPLGDM
FeLV    YR--YTPYDFEDFGQAASVILSF--IQSSPDIRNKLQRLGL--QGFTLSDL
BLV     LA--NLDPGVLRN--P--LLTPLVMQMLTESVSKFCR--GEAS--GR--GGAK
Mo-MuLV YR--YTPYDFEDFGQETNVSMSEF--IQSAPDIGHKLERLEDL--KNKTLGDL
GaLV    YR--YTPYDFPSSEGQQAAMAF--IQSAPDIKKKLQRLGL--QDYSLQDL
M-PMV   AG--RIFGSAEAGV--D--YVKQLAYENANPACQAAIR--PYRKK--TDLTGY

```

cons

```

HIV-1  MTA--CQG
SIV     MTA--COGV
BIV     LEA--CRVV
EIAV    MYA--CRDI
VISNA   MOA--CRD
FIV     LRA--CQEI
MTTV    IRA--CLDA
RSV     IKYVLDROKT
HTLV1   LRA--CQAW
FeLV    LKE--AEKIYKRETPEREERLWQR--QEERDKKRH
BLV     TAG--LRTI
Mo-MuLV VRE--AEKIYKRETPEREERIRRETEEEKERRTEDEQ--KEKERDRRH
GaLV    VKE--AEKVYKRETEERQEREKKEAE--KERRDRPKK
M-PMV   IRL--CSDI

```

cons

```

HIV-1  -----V
SIV     --HKARVL
BIV     --KSKMQF
EIAV    -----G
VISNA   --VGSEGF
FIV     --GYKMQL
MTTV    --VQGMAY
RSV     --QGIAAM
HTLV1   --PKDK
FeLV    --KEMTKVL
BLV     --MKQPALL
Mo-MuLV --REMSKLL
GaLV    --KNLTKIL
M-PMV   --QQGLAMA

```

cons

Multiple sequence
alignment (t_coffee)

2.2.Domini CTD

Multiple sequence alignment (t_coffee)

Lentivirus	HIV-1	TSILDIRQGPKEPFRDYVDRFYKTLFAEQASQEVKN---W-MTETLLVQNANPDCKTILK
	SIV	VSILDIRQGPKEPFRDYVDRFYKTLFAEQASQEVKN---W-MTDTLLVQNANPDCKQILK
	BIV	PGPINIHQGPKEPYTDFINRLVAALEGMAAPETTKE---Y-LLQHLSIDHANEDCQSILR
	EIAV	PKAQWIRQGAKEPYPEFVDRLLSQIFSEGHPQEISK---F-LTDTLTIQNANEECRNAMR
	VISNA	GNPMLVKQKNTESYEDFIARLLEAIIAEPVTDPIKT---Y-LKVTLSTYTNASTDCQKQMD
	FIV	PRAVQLRQAKEDYSSFIDRLFAQIIDQEQNTAEVKL---Y-LKQSLSIANANAECCKAMS
B type	MMTV	TVLASLKGNEESYETFISRLEEAVYRVMPRGEESD---I-LIKQLAWENANSLCQDLIR
	RSV	GPWADIMQGPSESFVDFANRLIKAVEGSDLPPSARA---P-VIIDCFRQKSQPDIIQQLIR
C type	HTLV1	PSWASILQGLEEPYHAFVERLNIALINGLPEGTPKD---P-ILRSLAYSANANKECQKLLQ
	FeLV	AQVKQVVGKEETPAAFLERLKEAYEMYTPYDPEDPGQAASVILSF-IYQSSPDIRNKLQ
	BLV	QPWSTIVQGPAESSVEFVNRLQISLADNLPDGVLRN---P-LLTPLVMQMLTESVSKFCR
	Mo-MuLV	AKVKGITQGPNESPSAFLERLKEAYERYTPYDPEDPGQETNVSMSF-IWQSAPDIGRKLE
D type	GaLV	AKVREVLQGPAEPPSVFELERLMEAYERYTPFDPSSEGQQAAMAF-IGQSAPDIKKKLQ
	M-PMV	ASLTGVKQGPDEPFADFVHRLITTAGRIFGSAEAGV---D-YVKQLAYENANPACQAAIR
		: * * : * :

Absolutely conserved

Conservative mutation

Hydrophobic

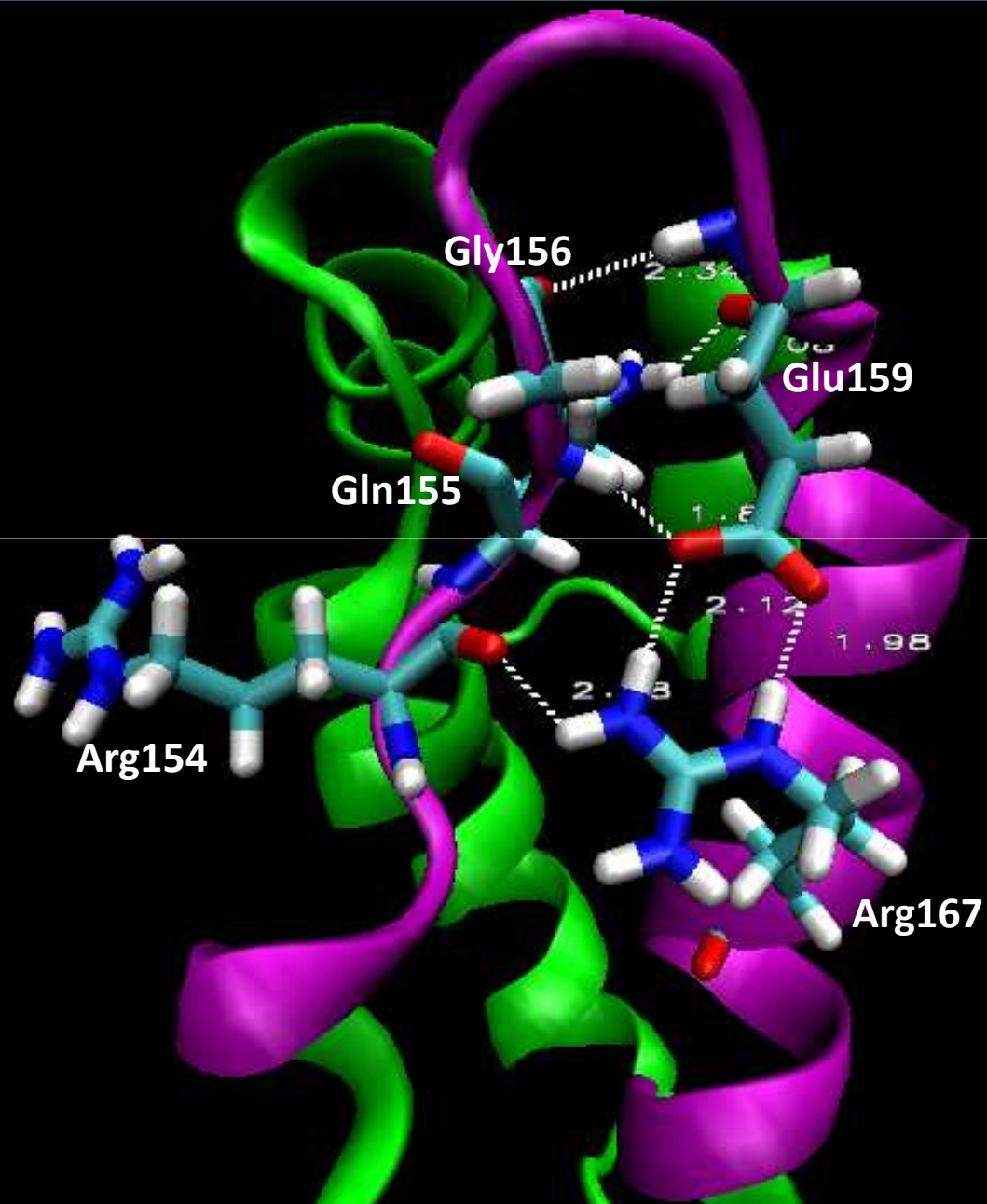
HYDROGEN NETWORK (Q155,E159, R167 and G156)
HYDROPHOBIC INTERACTIONS

2.2.Domini CTD

Major Homology
Region

HYDROGEN NETWORK

Glu159...Gly156
Gln155...Glu159
Arg167...Glu159
Arg167...Glu159
Arg167...Arg154



PDB: 1A43

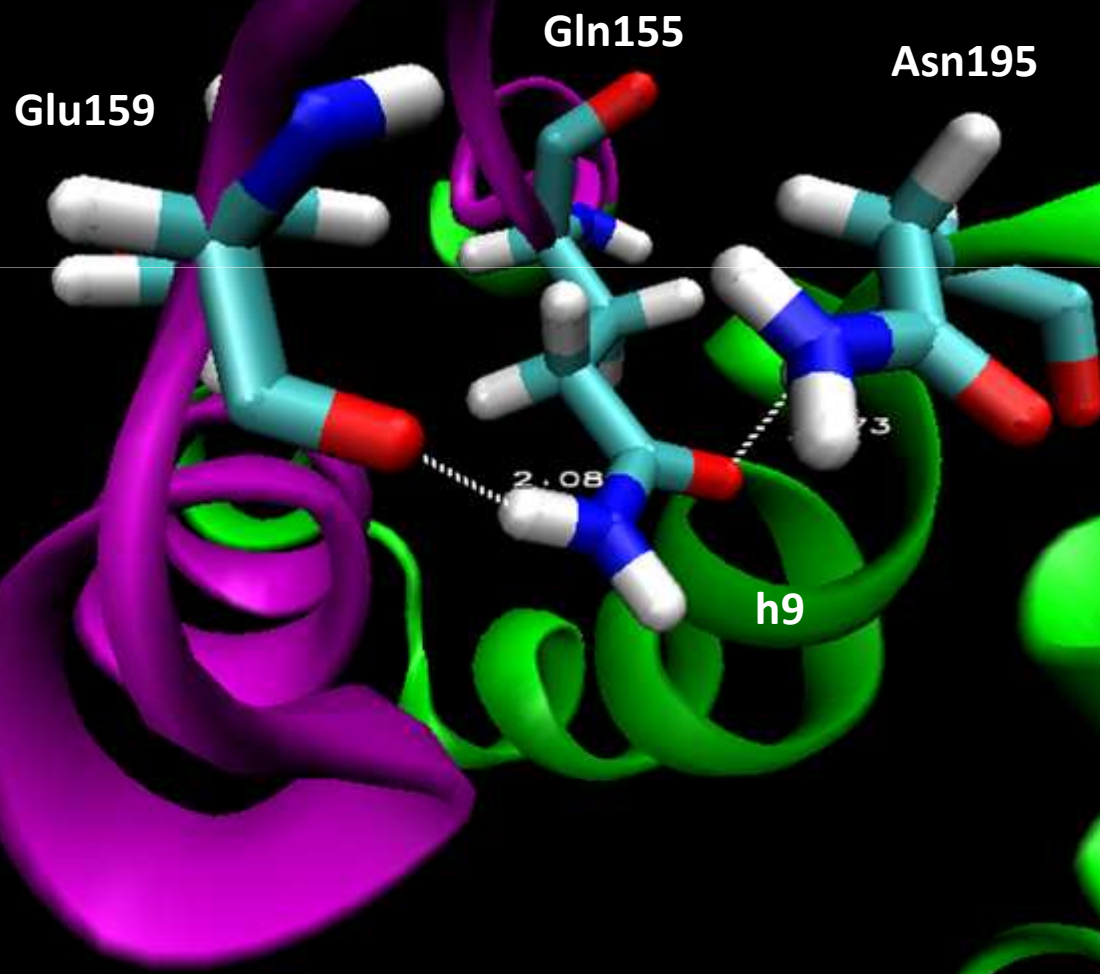
2.2.Domini CTD

Major
Homology
Region

PDB: 1A43

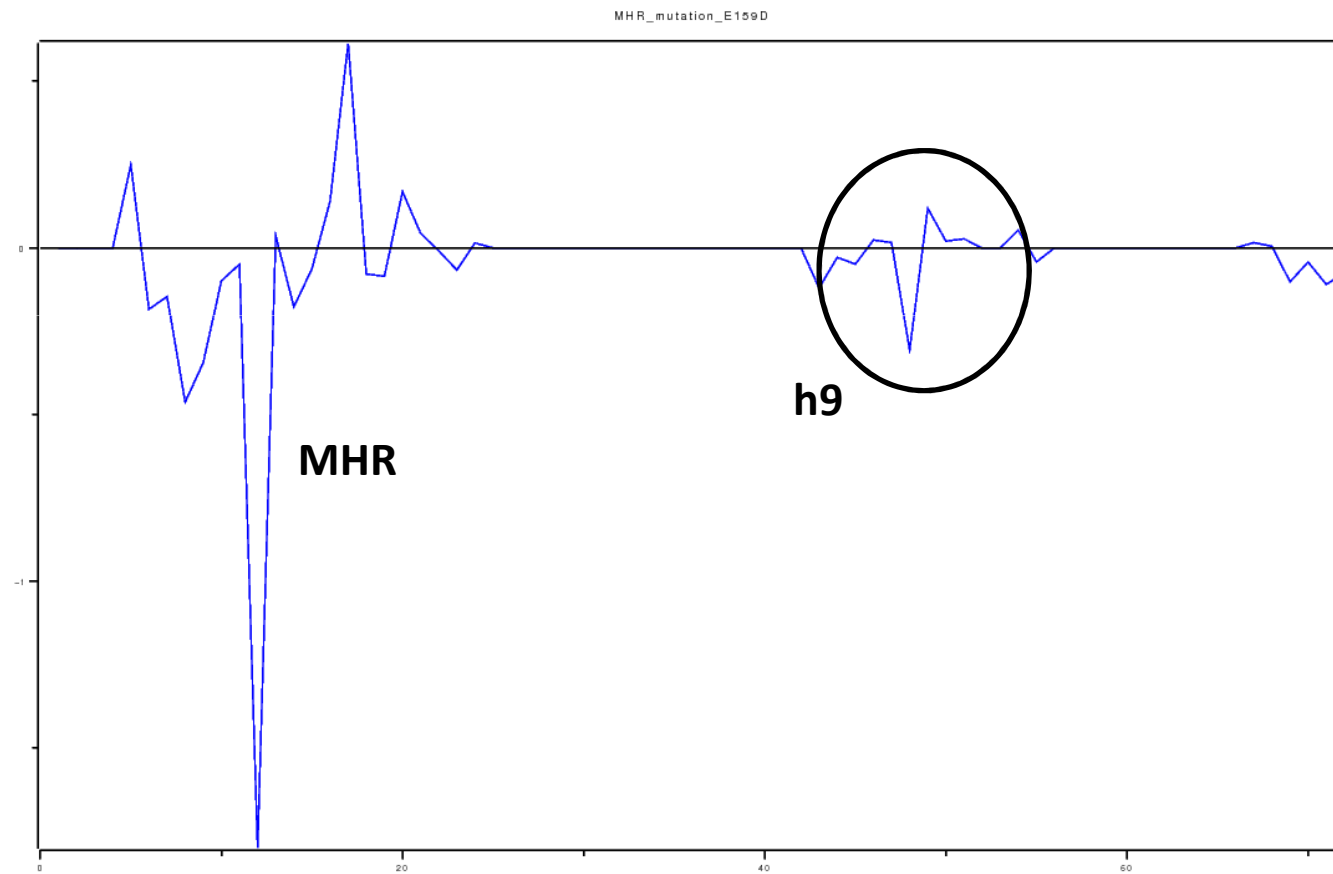
HYDROGEN NETWORK

Asn195...Gln155



2.2.Domini CTD

Mutació E159A

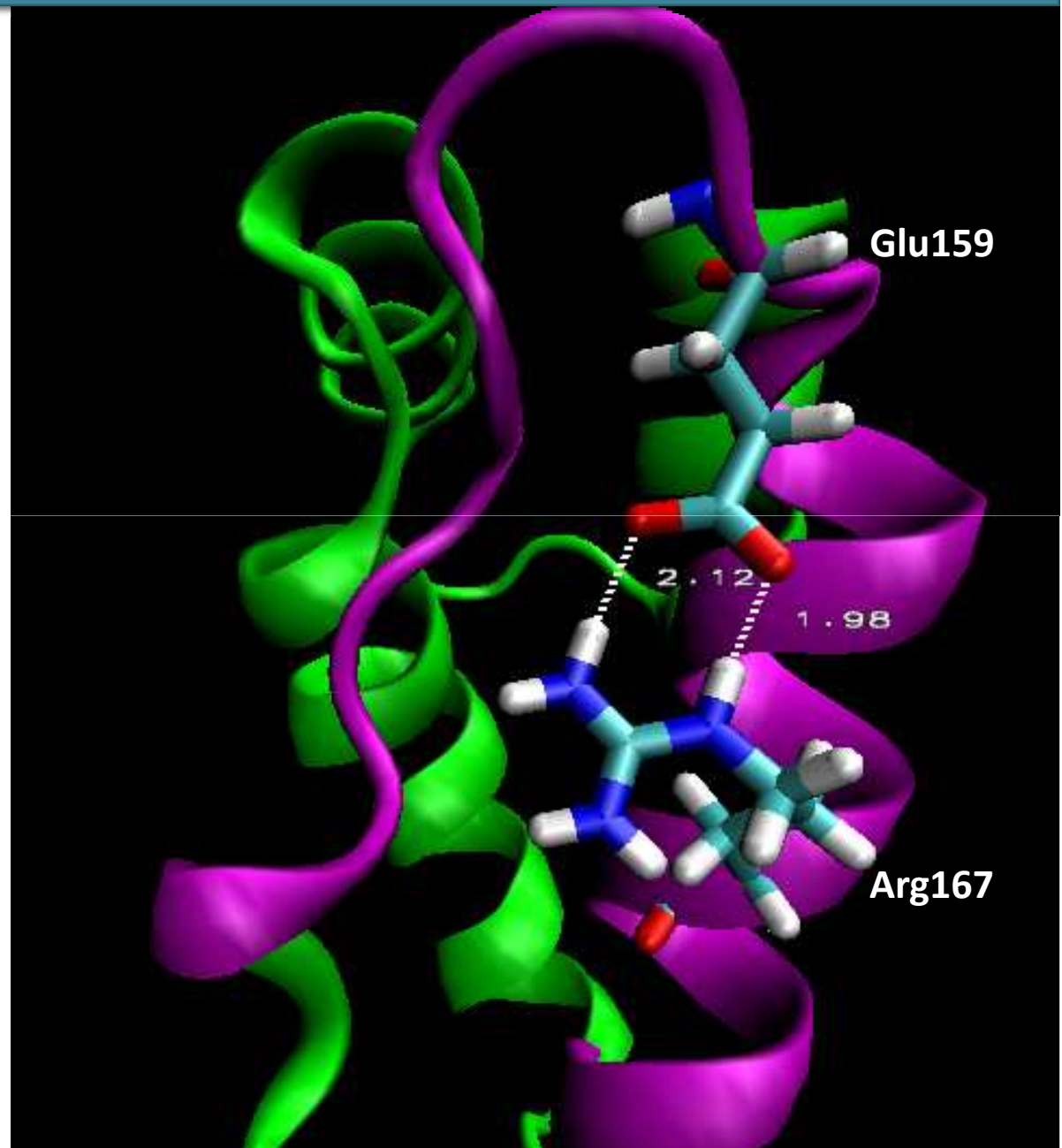


2.2.Domini CTD

Major Homology Region

SALT BRIDGE

Arg167...Glu159

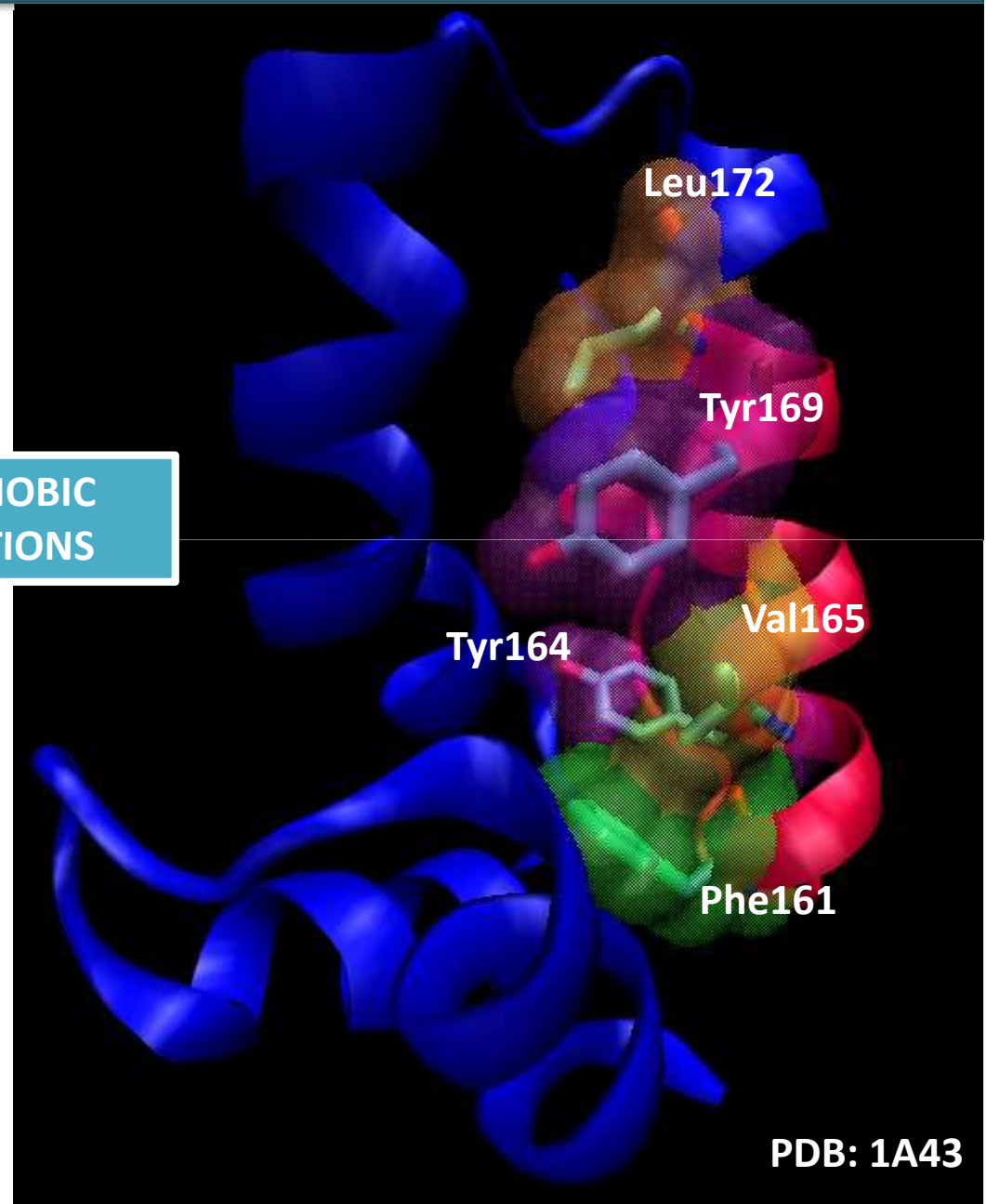
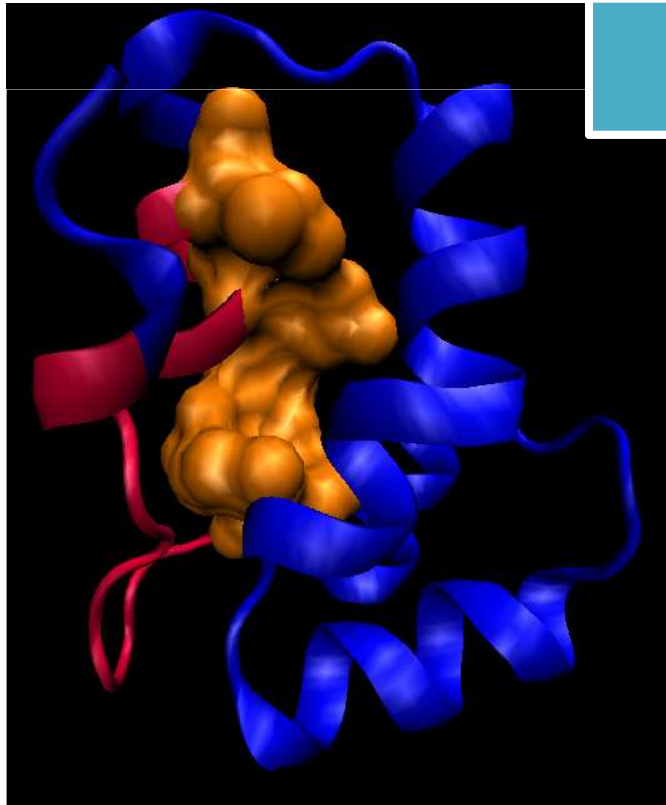


2.2.Domini CTD

Major Homology Region

Phe 161
Tyr 164/169
Val 165
Leu 172

HYDROPHOBIC
INTERACTIONS



2.2.Domini CTD

Major Homology Region

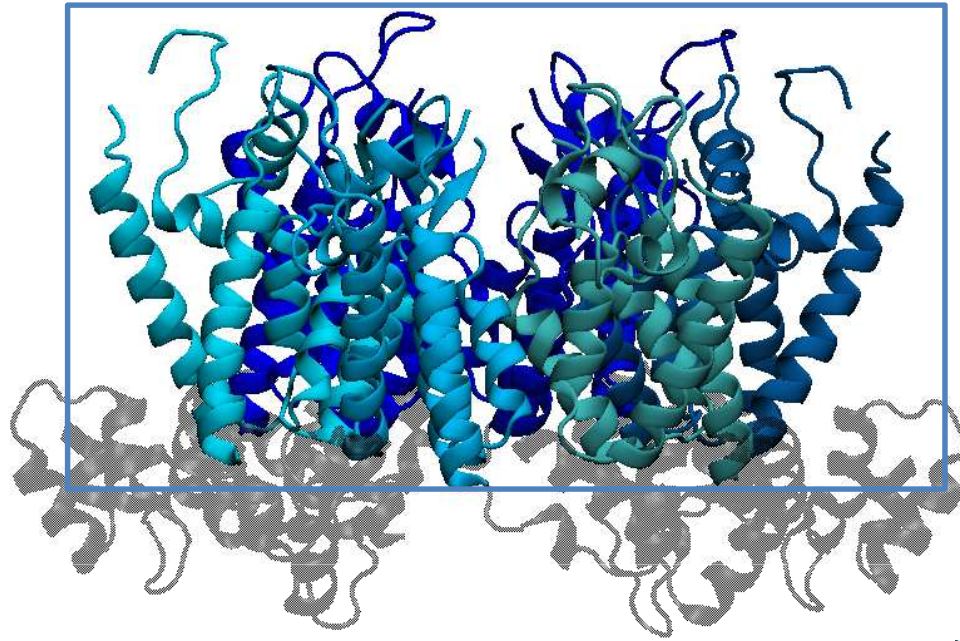
Why is this region so conserved among retrovirus?

- The contribution of the **hydrogen network** to the dimerization between CTDs
- The participation of some of the residues to **NTD-CTD interactions**
- The hydrophobic residues of this region mediates the contacts in the **domain-swapped dimer** of the CTDs protein

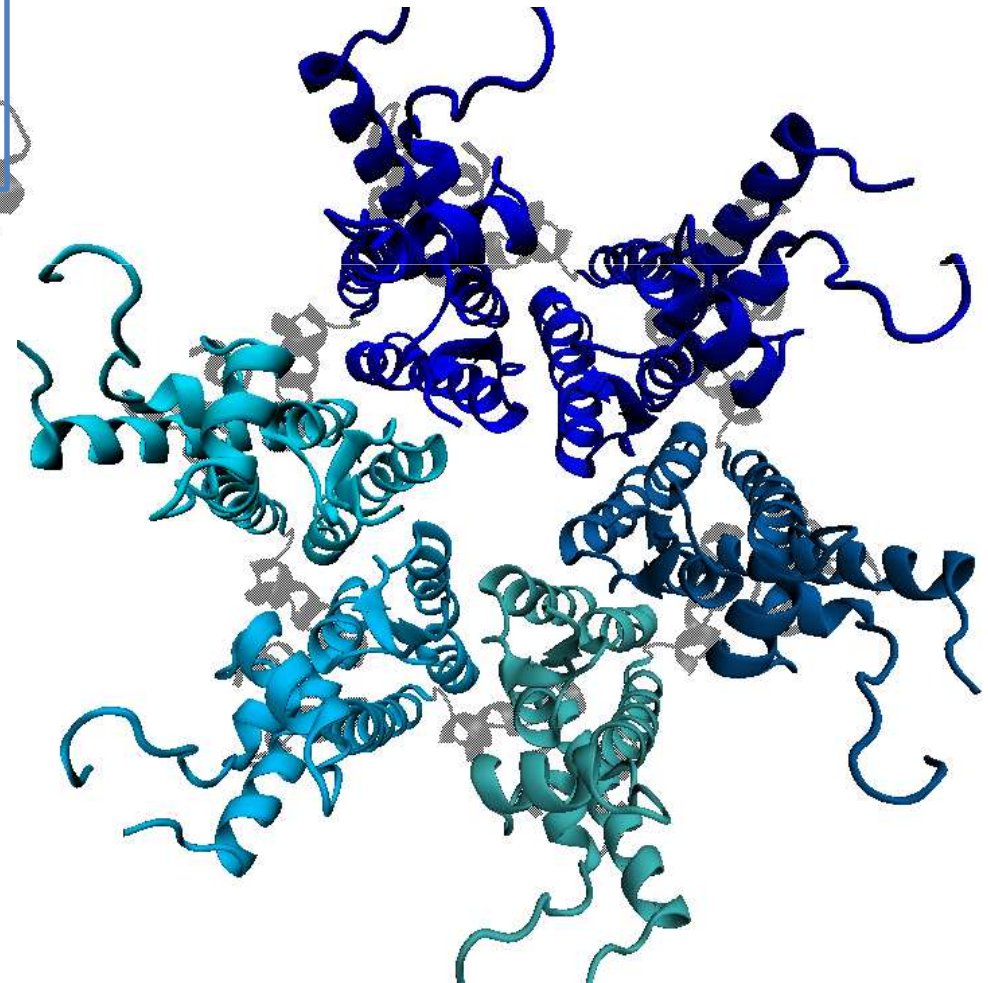
Index

- Introduction
- CA (monomer)
 - NTD
 - CTD
- Capsid subunit (hexamer)
 - Oligomerization interfaces
 - Assembly interactions
 - Flexibility
- Lattice model

Capsid subunit



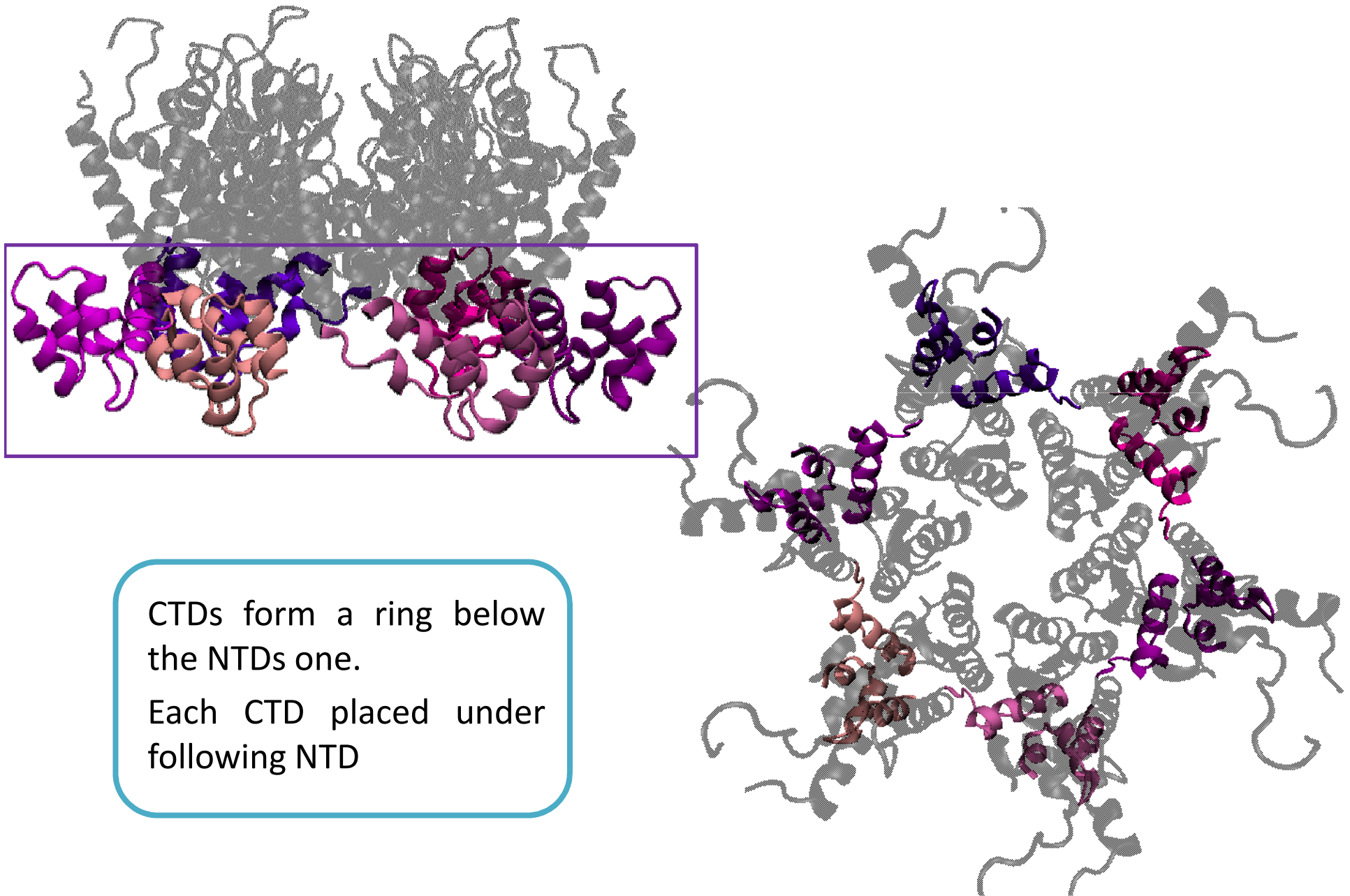
HEXAMERS:



Hexamers are formed by six monomers such that form two rings.

NTDs domains form a ring on the top of hexamer

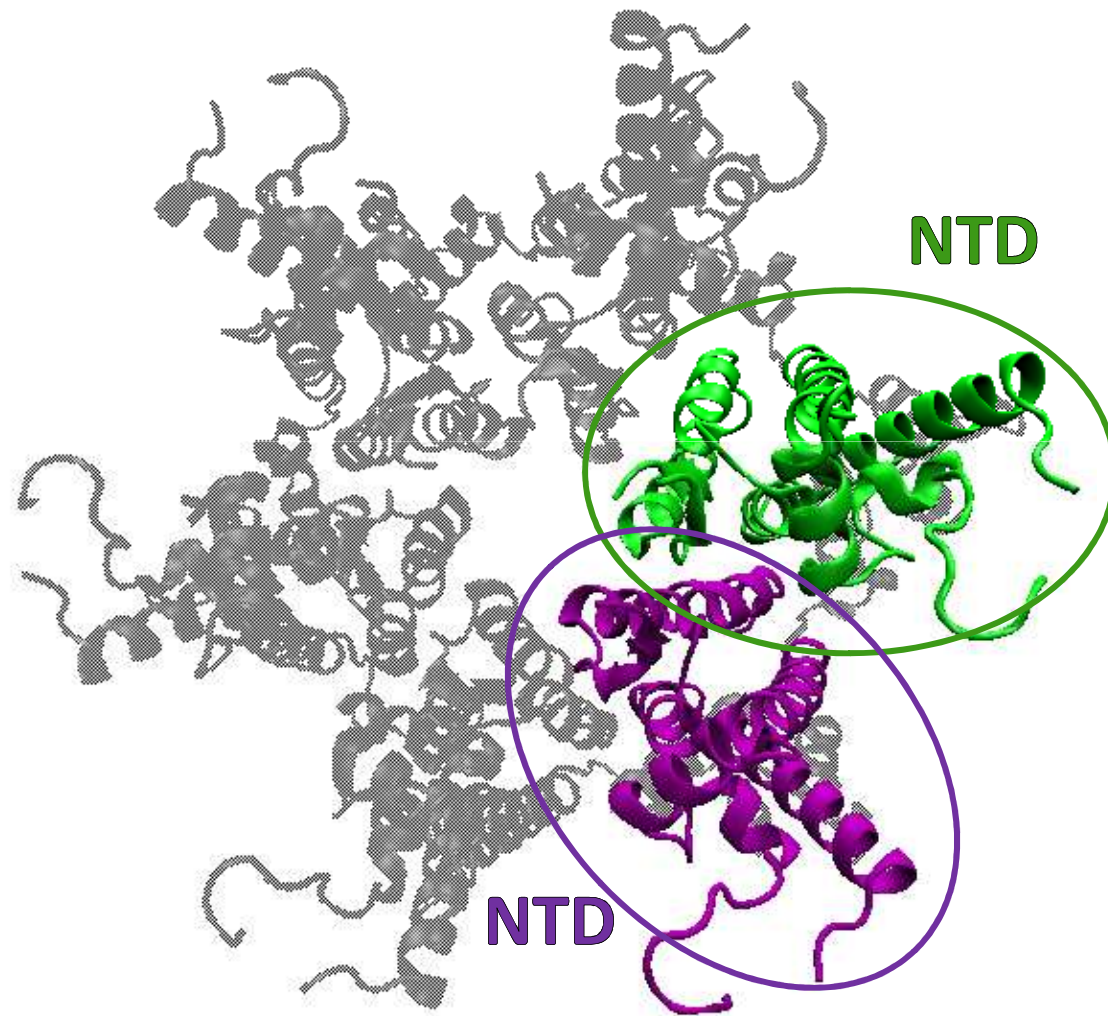
Capsid subunit



CTDs form a ring below
the NTDs one.

Each CTD placed under
following NTD

Capsid subunit



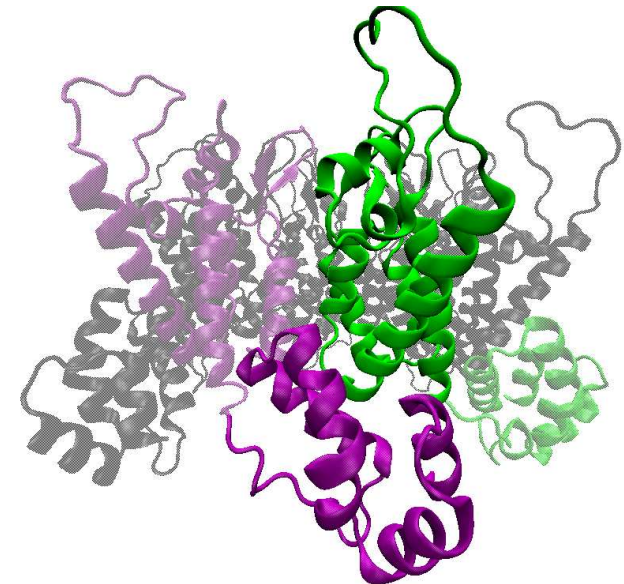
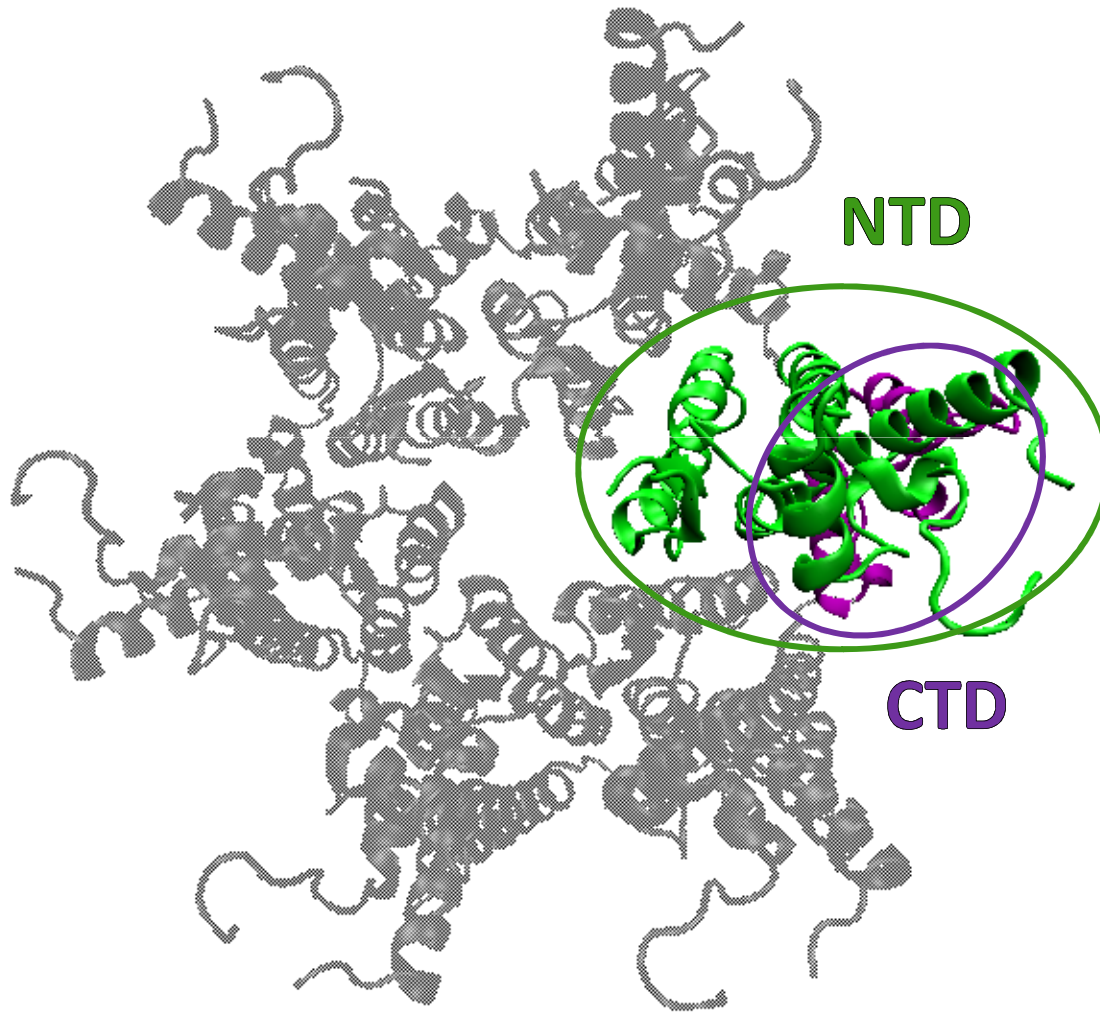
Capsid can be formed by three different types of interfaces:

- NTD – NTD
- NTD – CTD
- CTD - CTD

Capsid subunit

Capsid can be formed by three different types of interfaces:

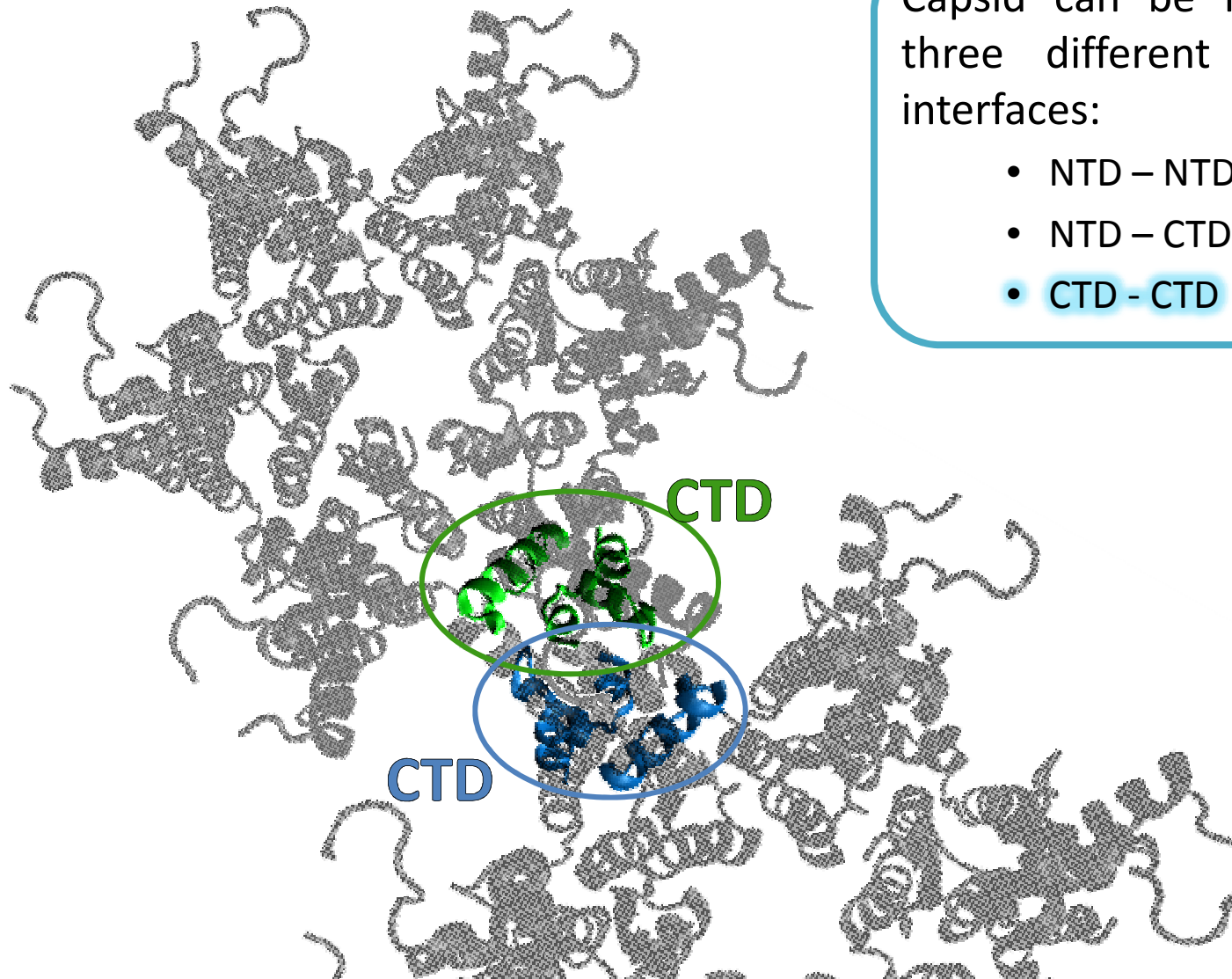
- NTD – NTD
- NTD – CTD
- CTD – CTD



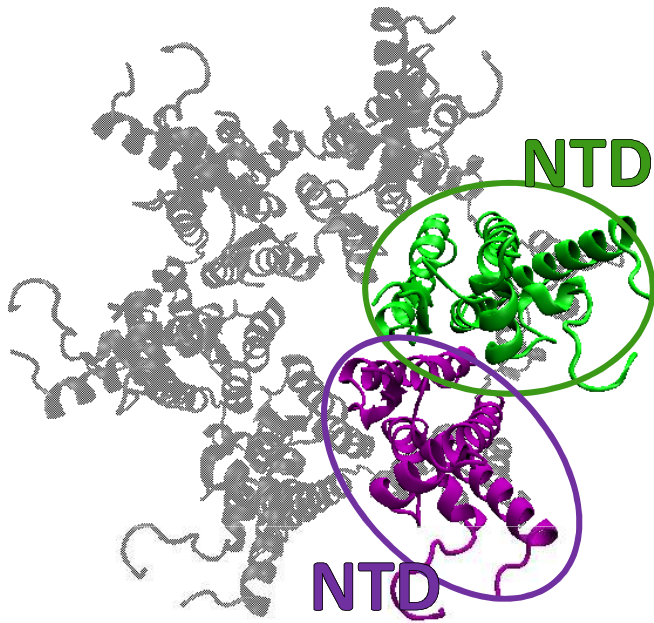
Capsid subunit

Capsid can be formed by three different types of interfaces:

- NTD – NTD
- NTD – CTD
- CTD - CTD

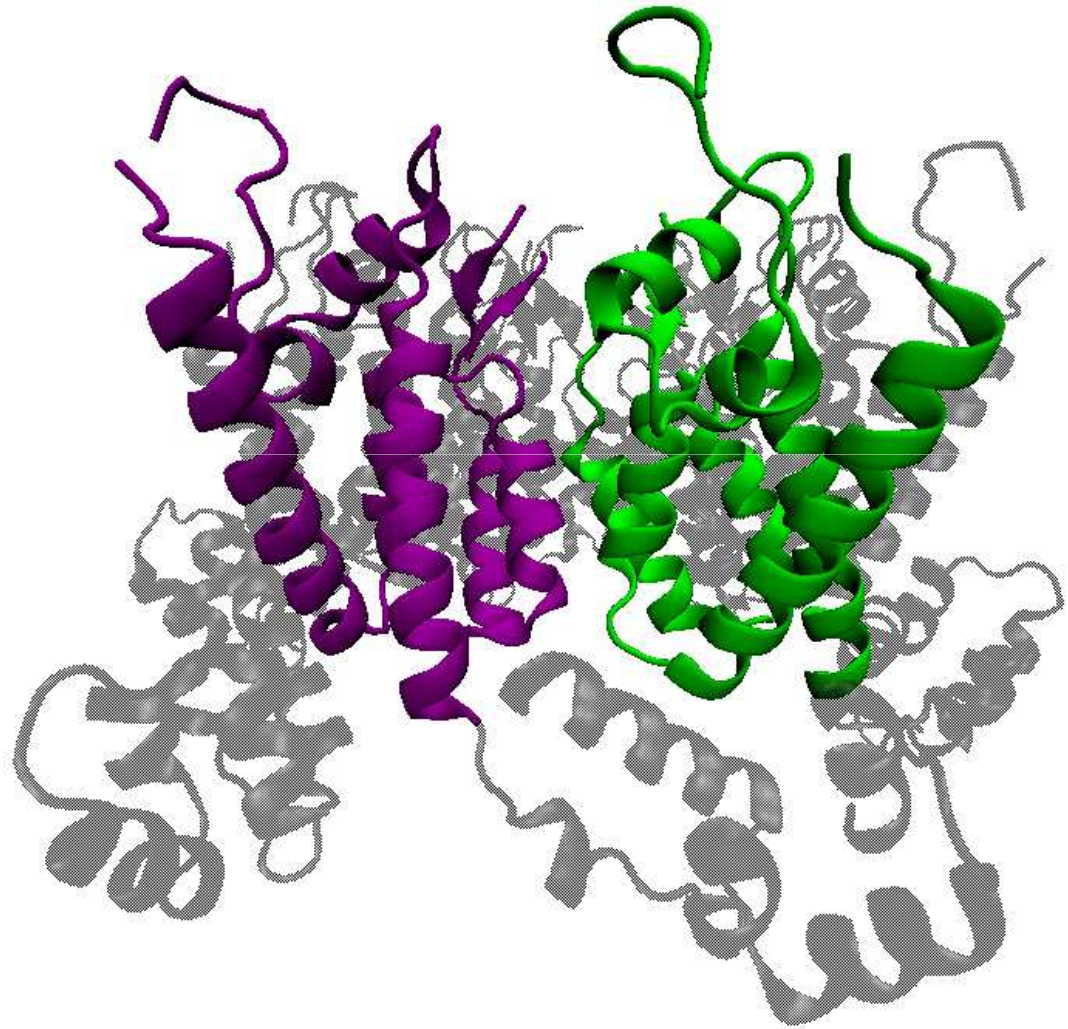


NTD-NTD interface

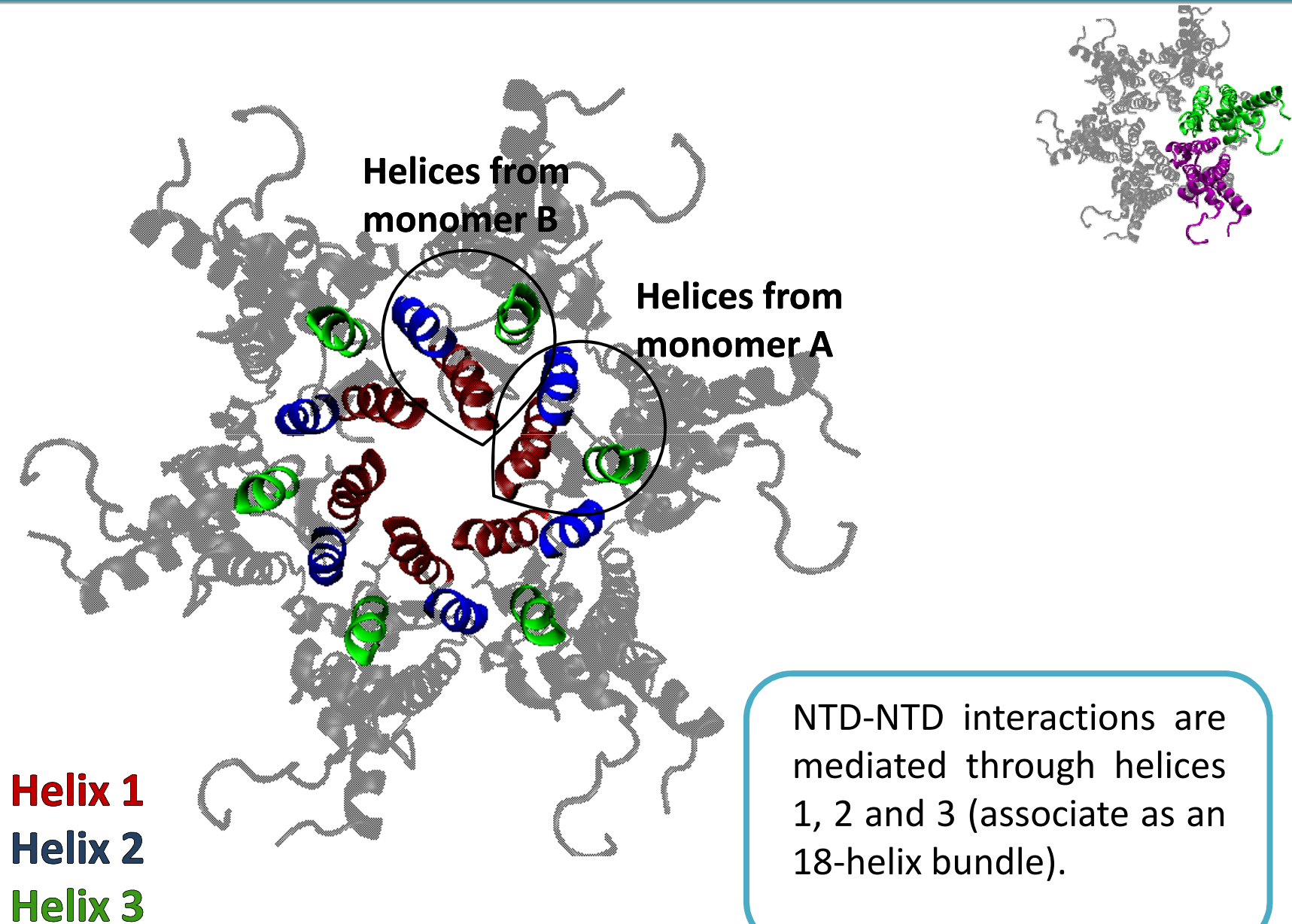


There are two kind of interactions:

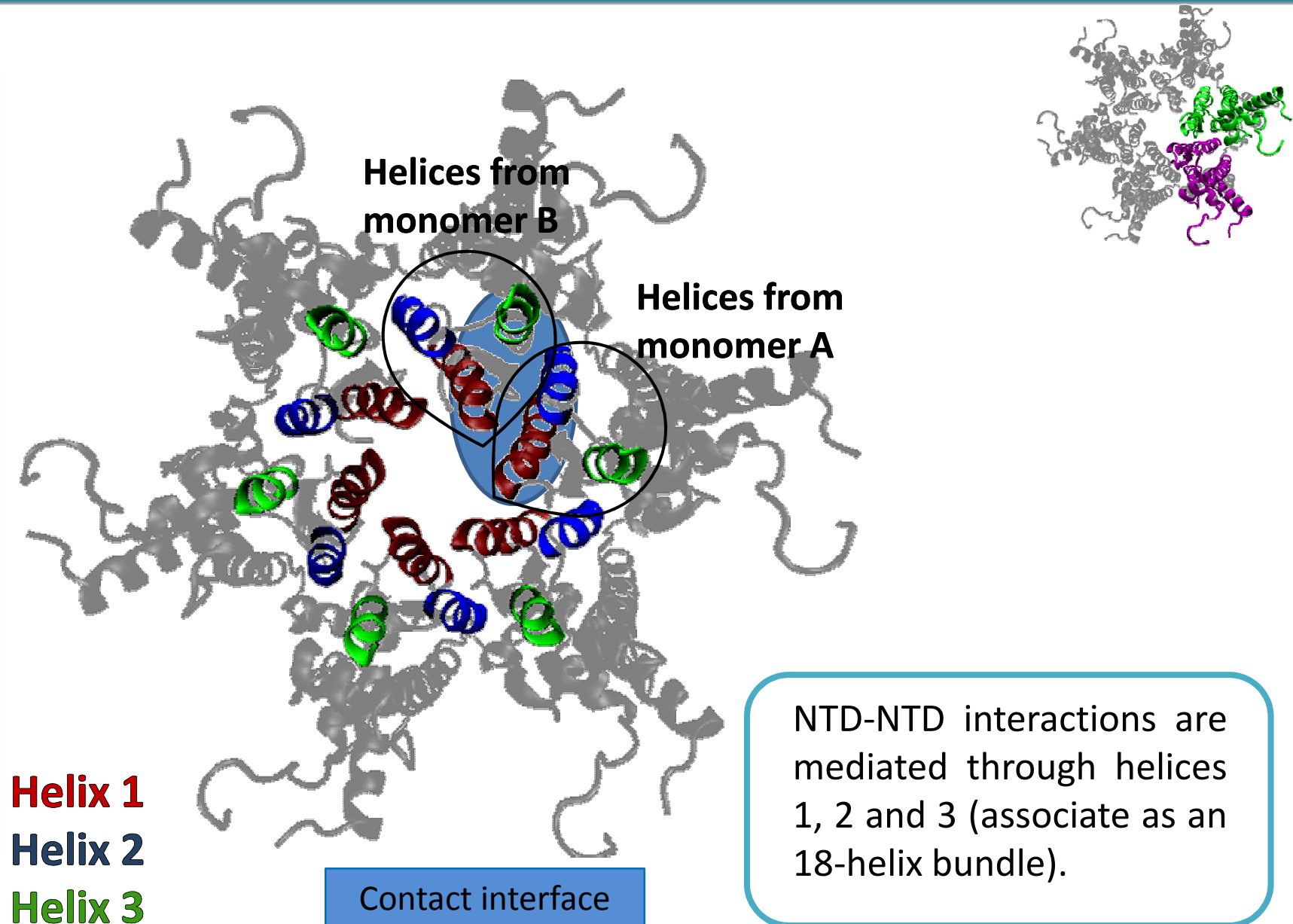
- Hydrophobic contacts
- Polar (water mediated) contacts



NTD-NTD interface

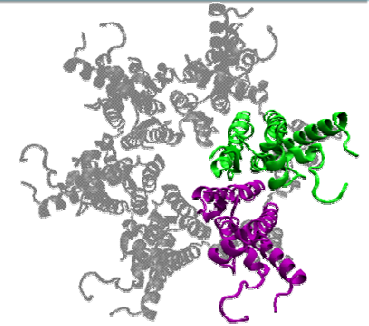
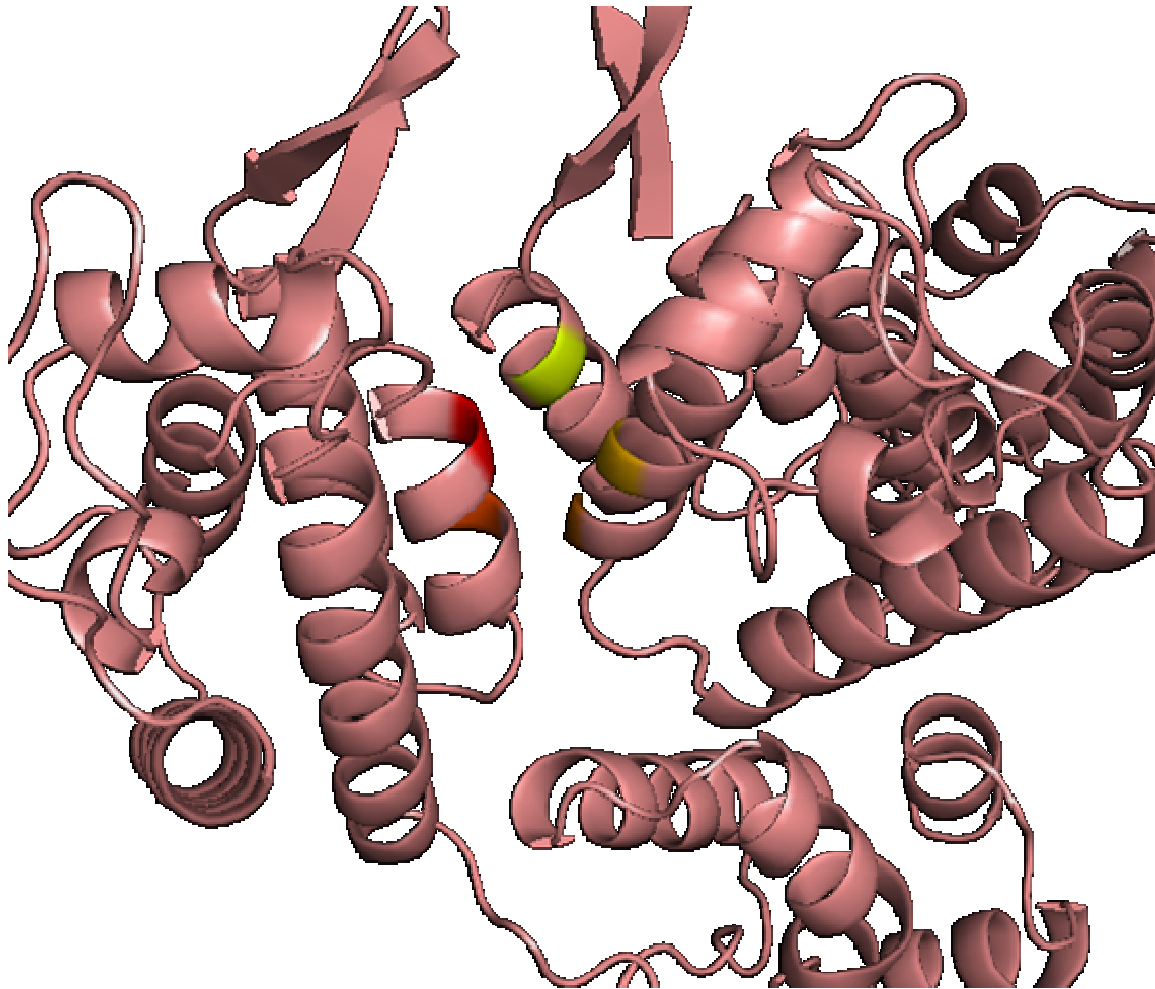


NTD-NTD interface



NTD-NTD interface

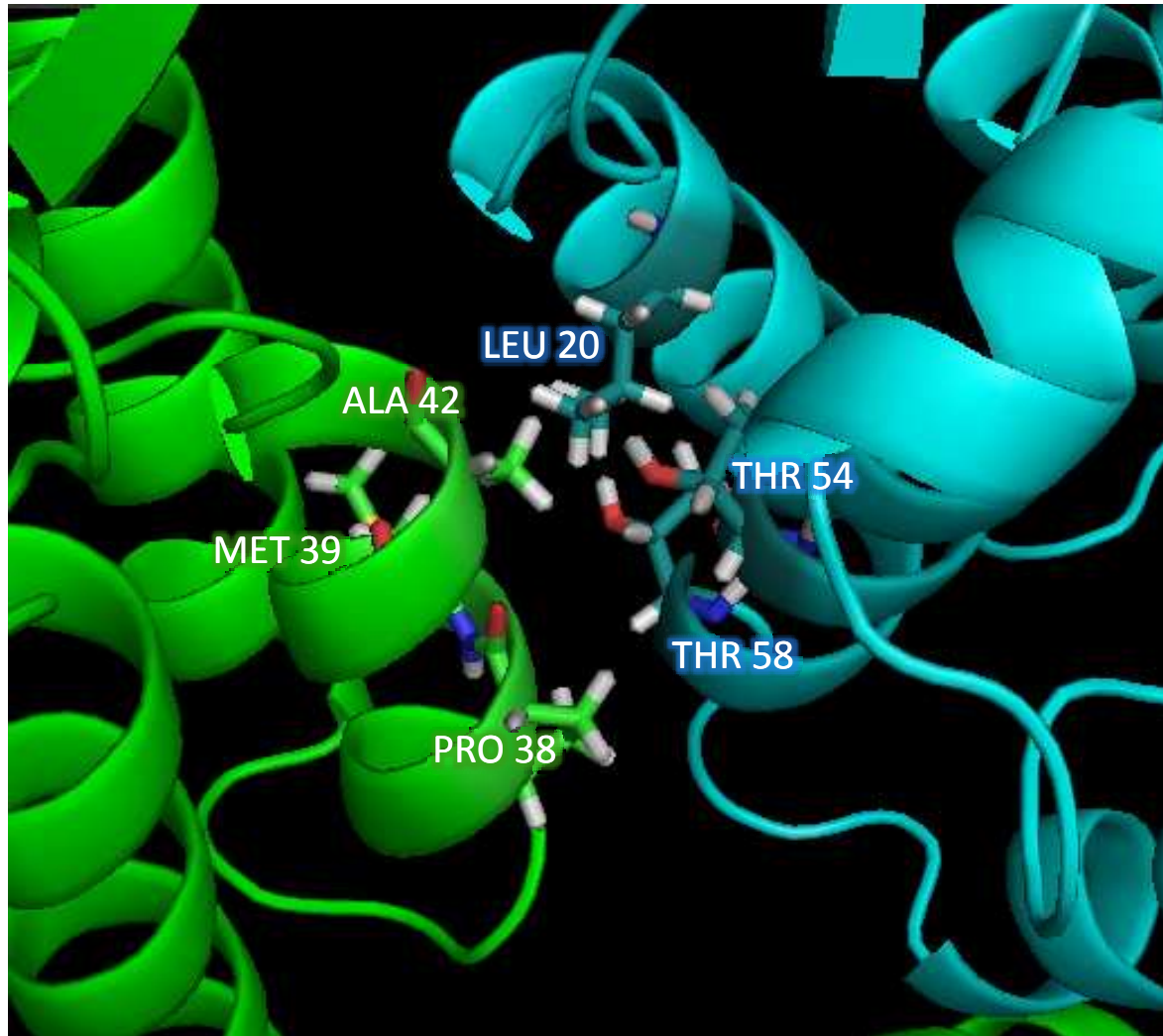
HYDROPHOBIC CONTACTS:



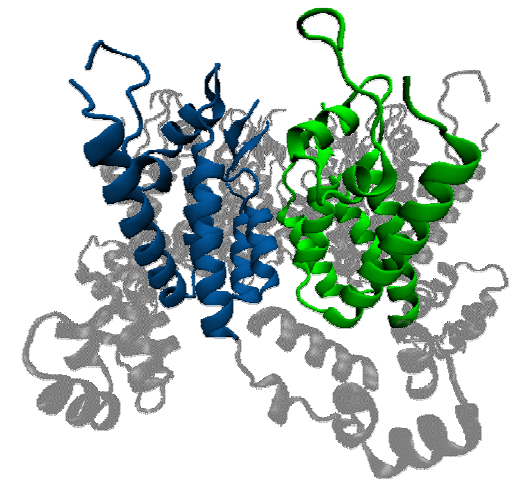
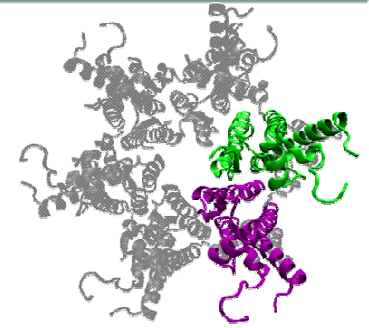
Residues in helix 2 and helices 1 and 3 form a hydrophobic core with aliphatic side chains.

NTD-NTD interface

HYDROPHOBIC CONTACTS:

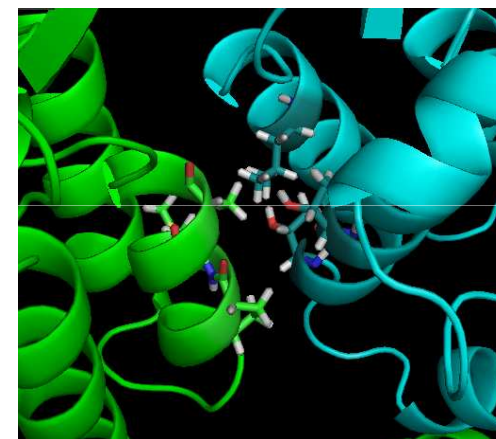
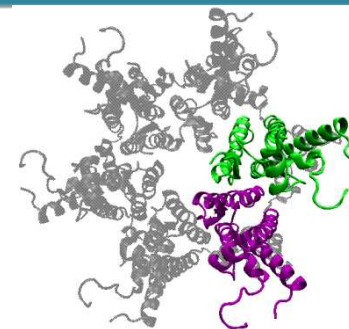
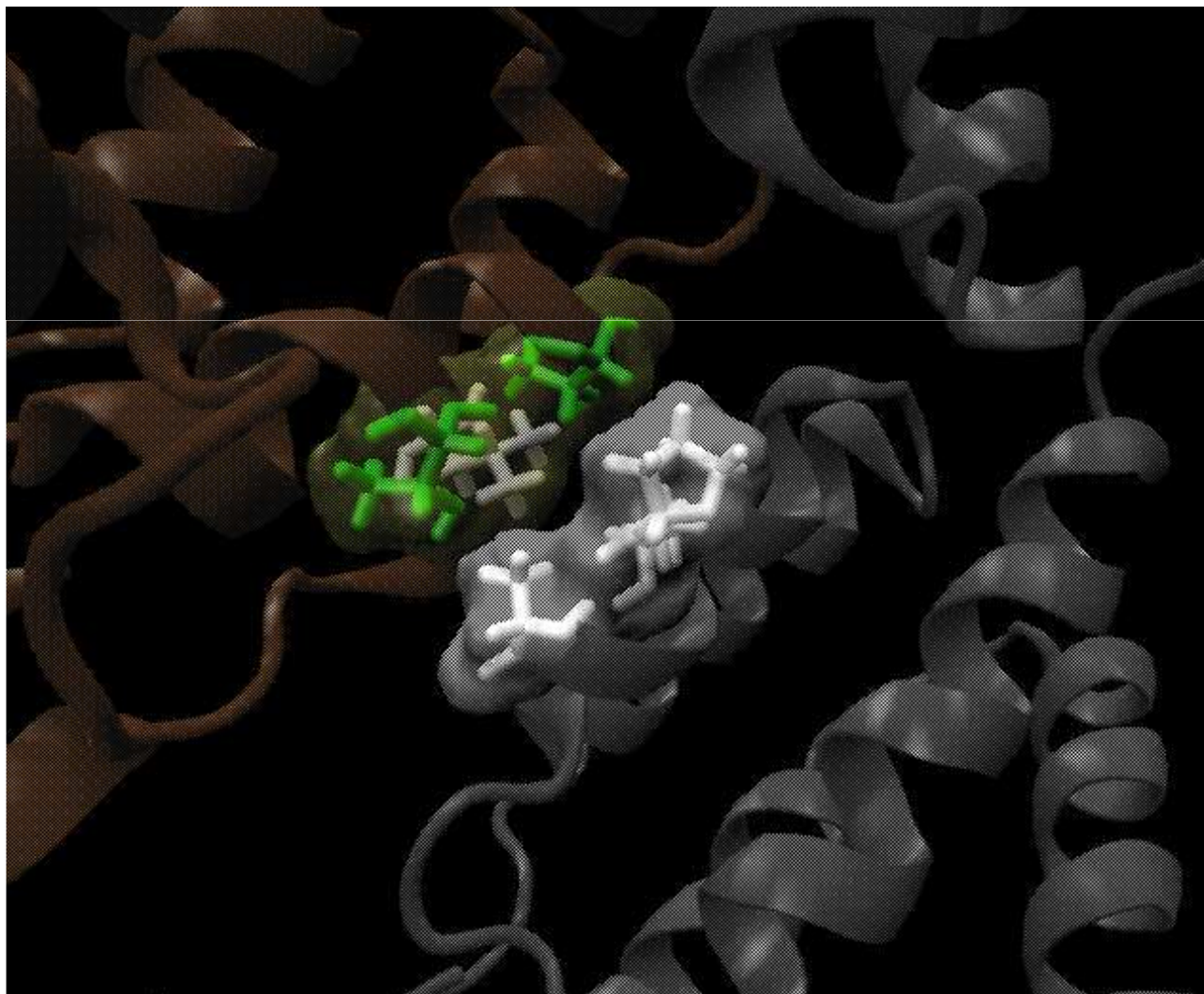


- A42, M39, P38
(helix 2)
- L20 (helix 1)
- T54 and T58 (helix 3)



NTD-NTD interface

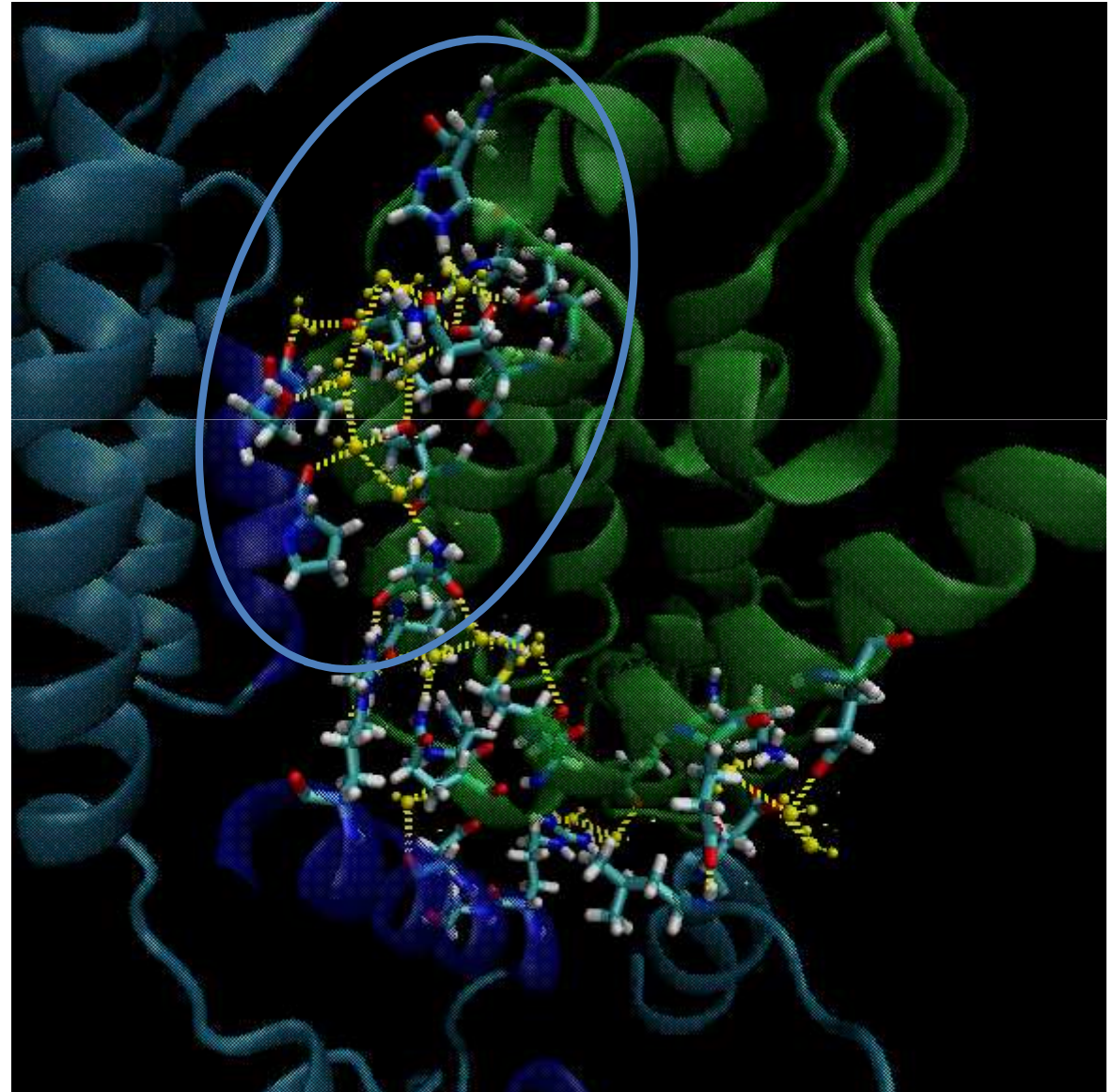
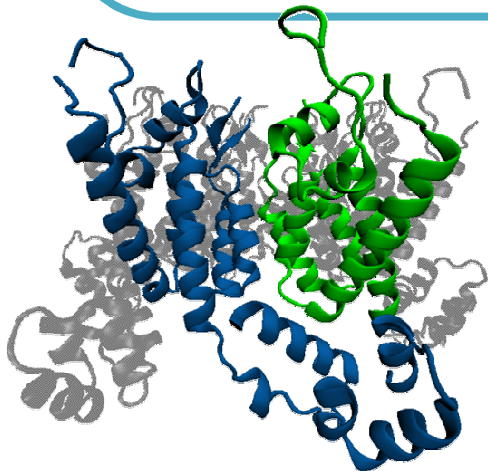
HYDROPHOBIC CONTACTS:



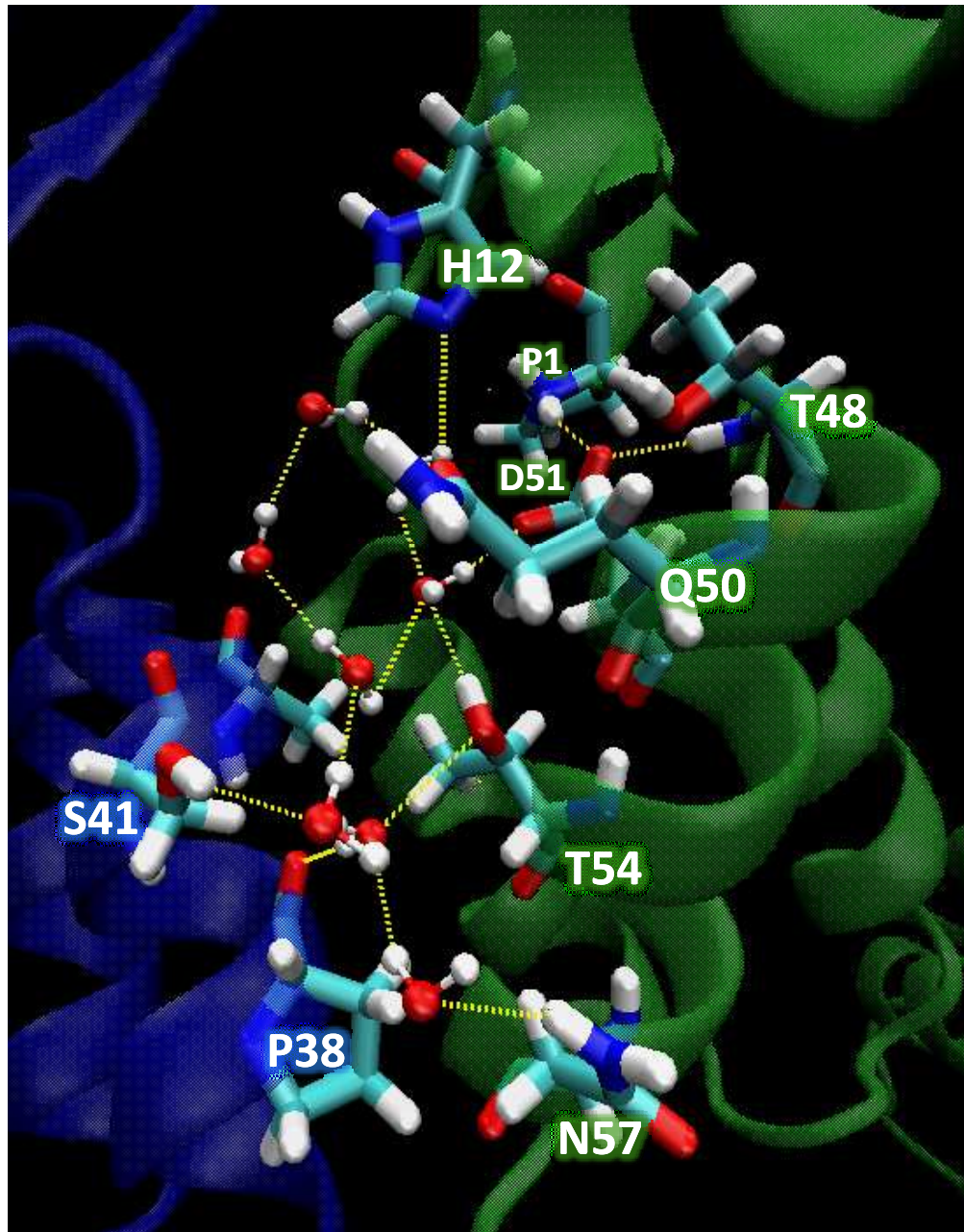
NTD-NTD interface

POLAR CONTACTS: **Water mediated.**

The most relevant interactions are polar contacts. Most of them are water mediated. We would find them both in NTD – NTD as CTD – NTD interfaces.



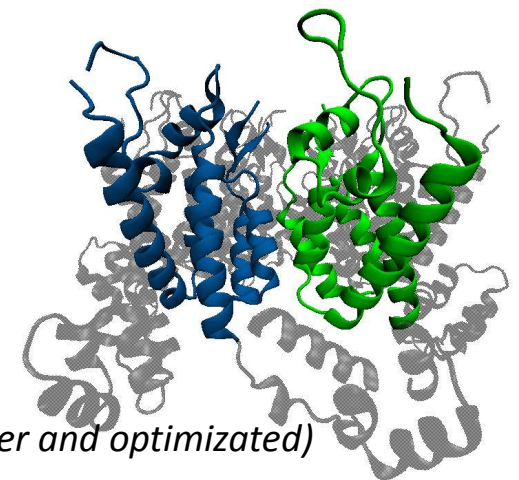
NTD-NTD interface



POLAR CONTACTS: Water mediated.

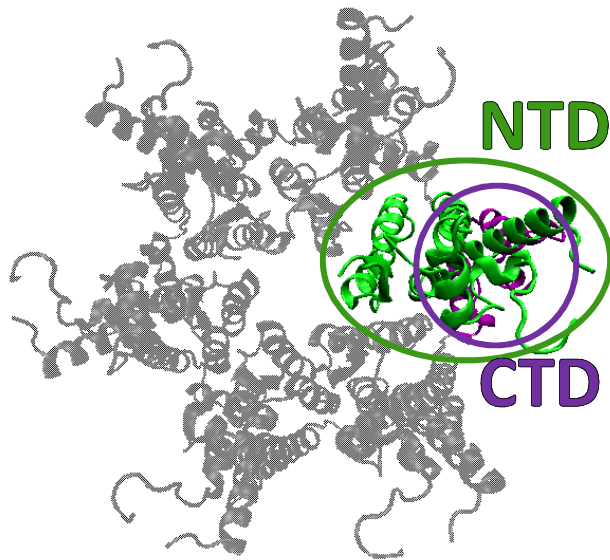
- Residues that are involved in water mediated contacts:

- P1
- H12
- P38
- S41
- T48
- Q50
- D51
- T54
- N57



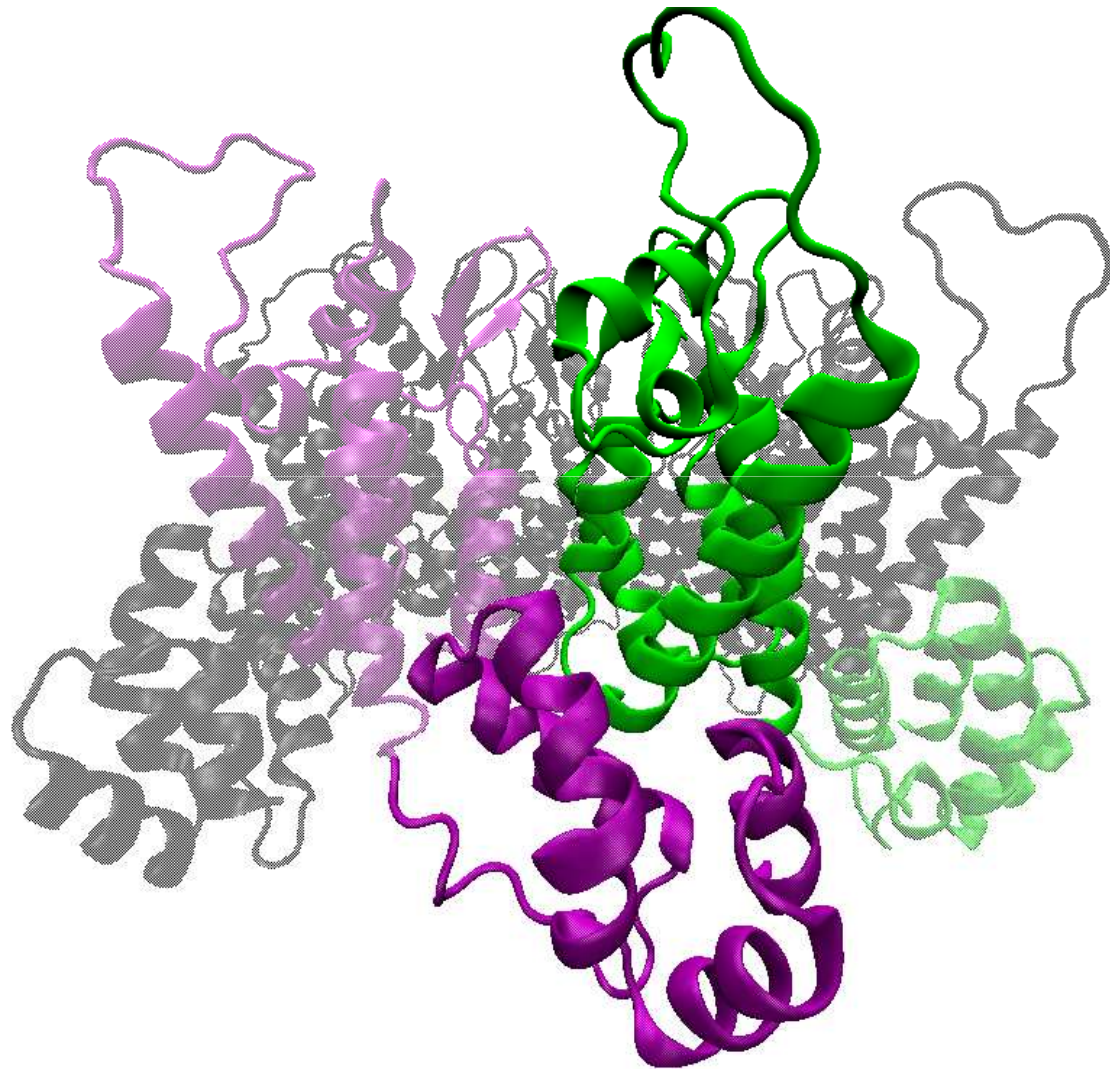
Pdb: 3H47 (added water and optimized)

NTD-CTD interface



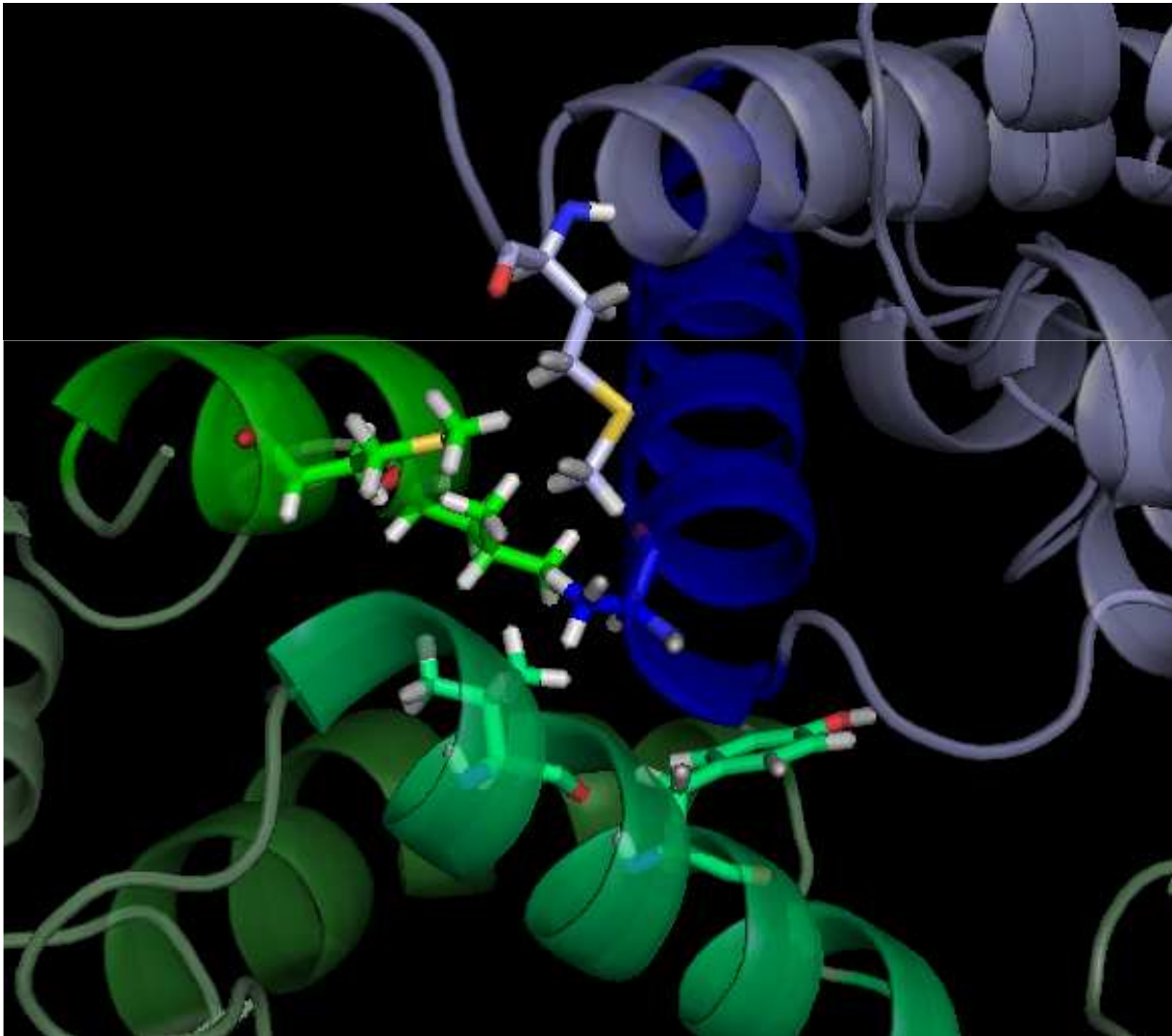
There are three kind of interactions:

- Hydrophobic
- Polar (water mediated)
- Helix capping

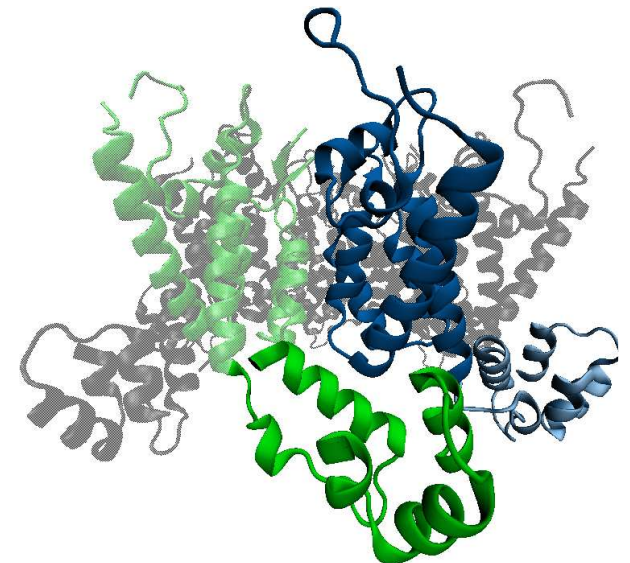


NTD-CTD interface

HYDROPHOBIC CONTACTS:

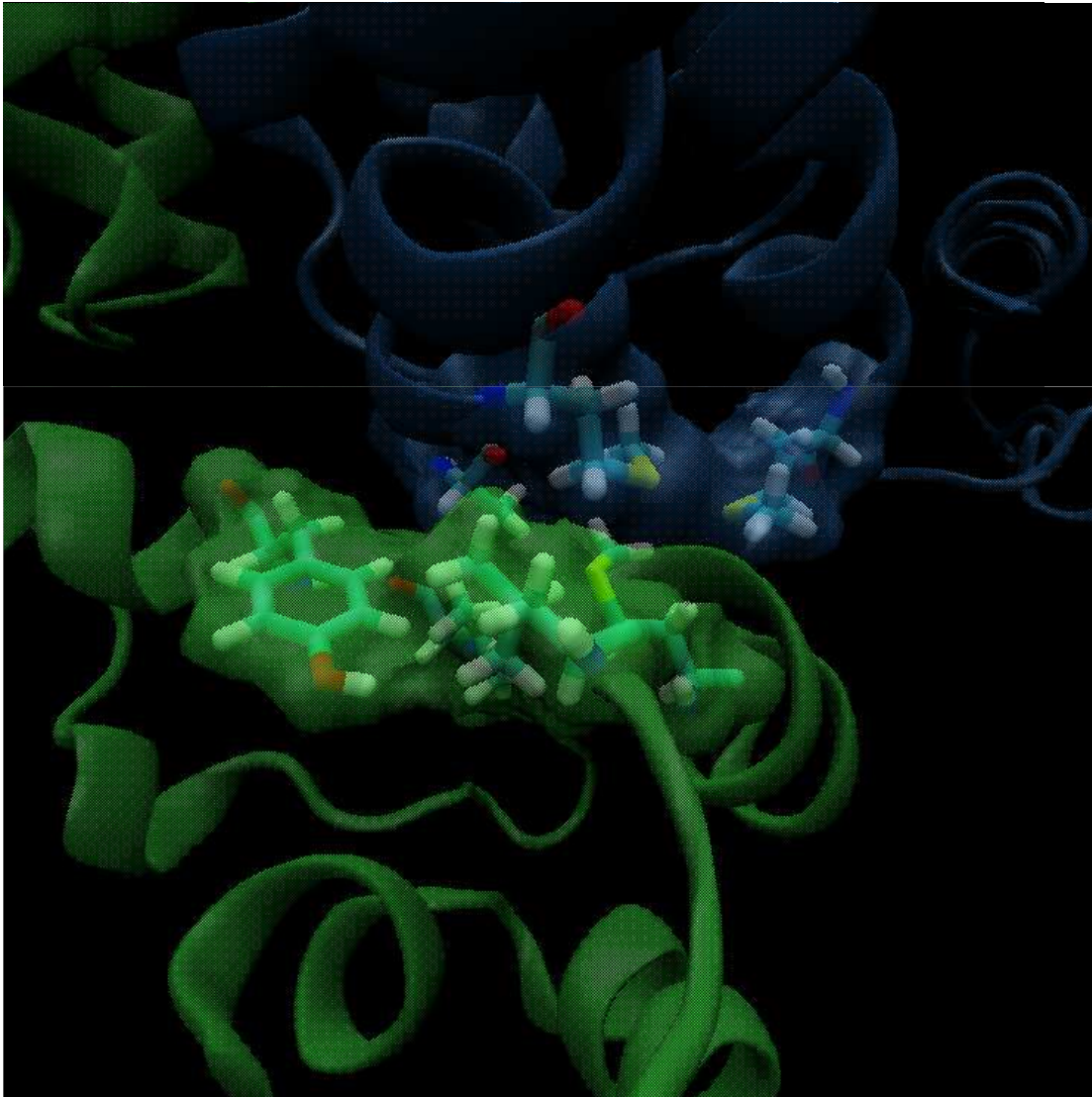


Residues on helix 4 (blue) and helices 8 and 11 (green) are involved in hydrophobic core formation.



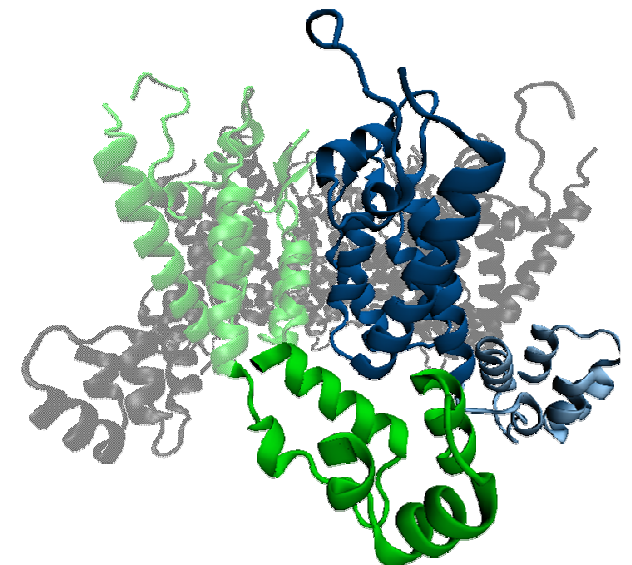
NTD-CTD interface

HYDROPHOBIC CONTACTS:



Residues that are involved:

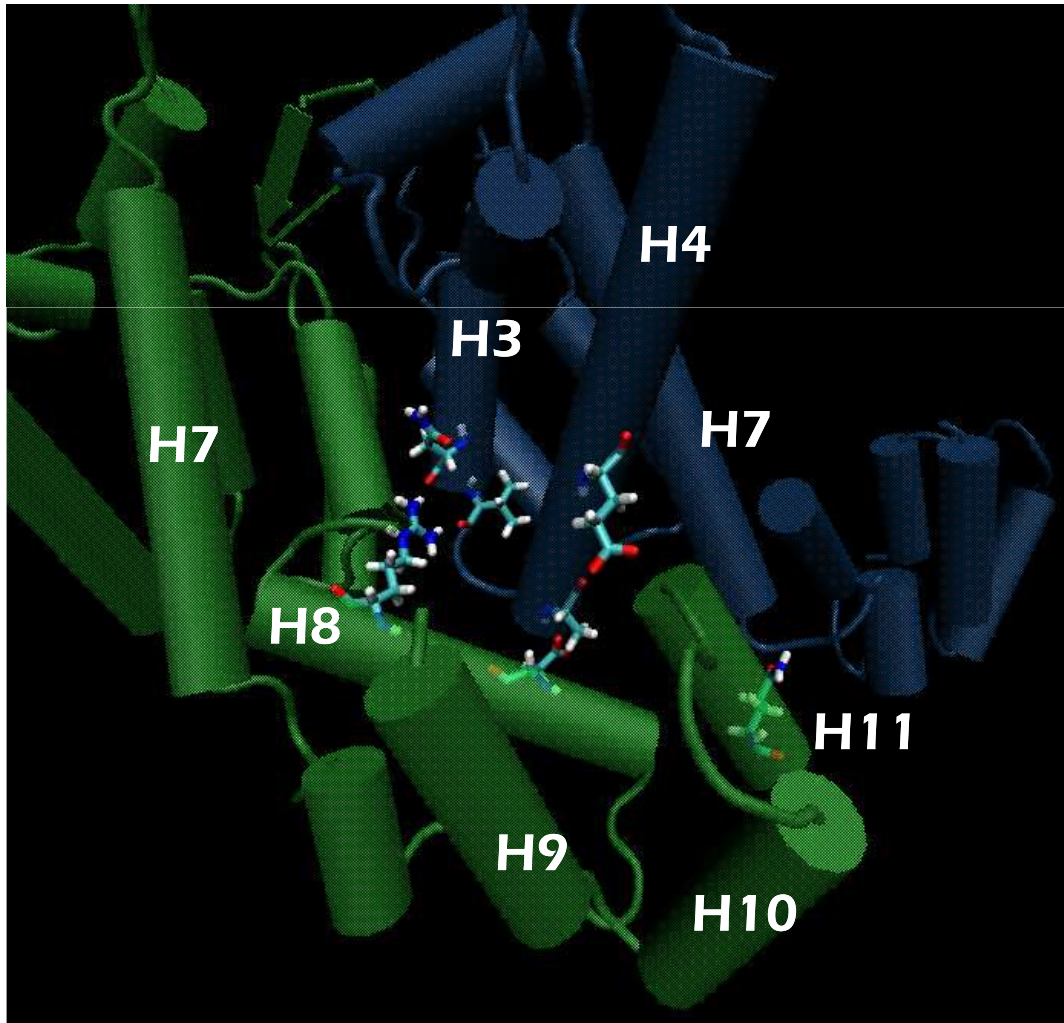
Y169	A64
V165	M68
M215	M144
L211	



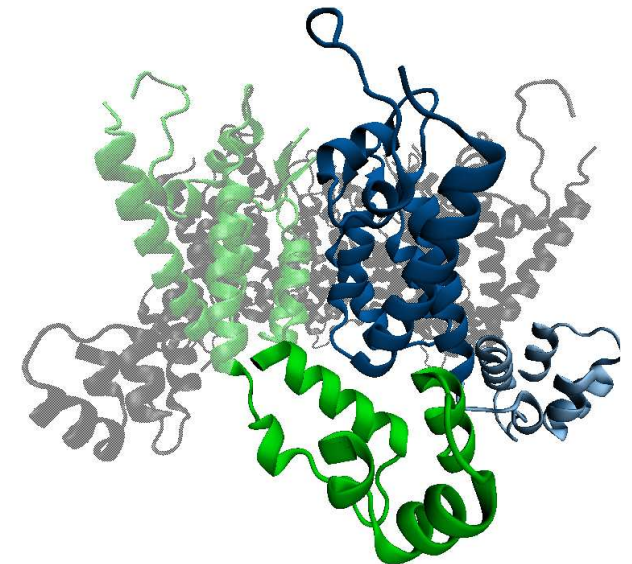
NTD-CTD interface

POLAR AND WATER MEDIATED CONTACTS:

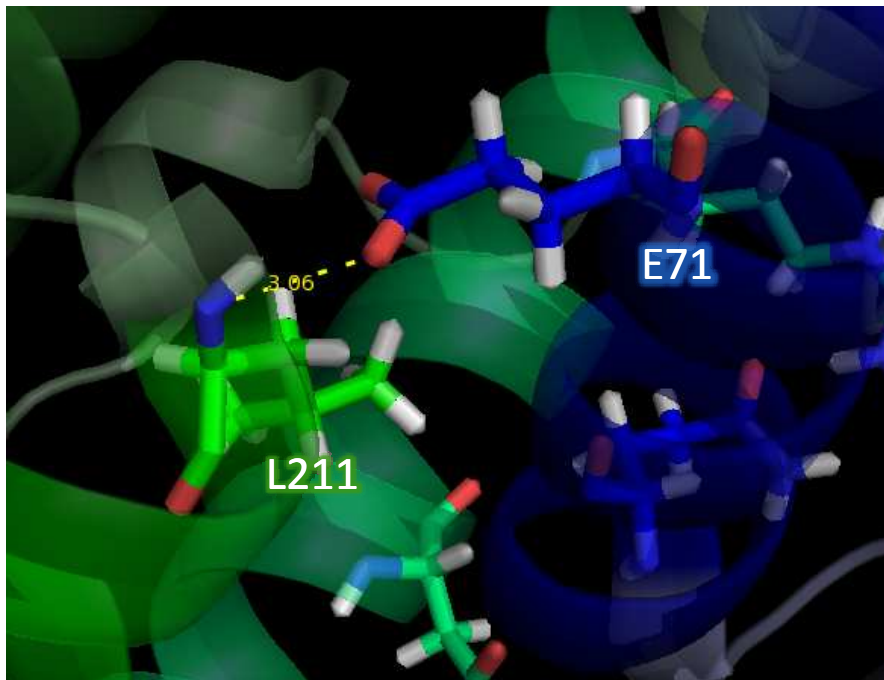
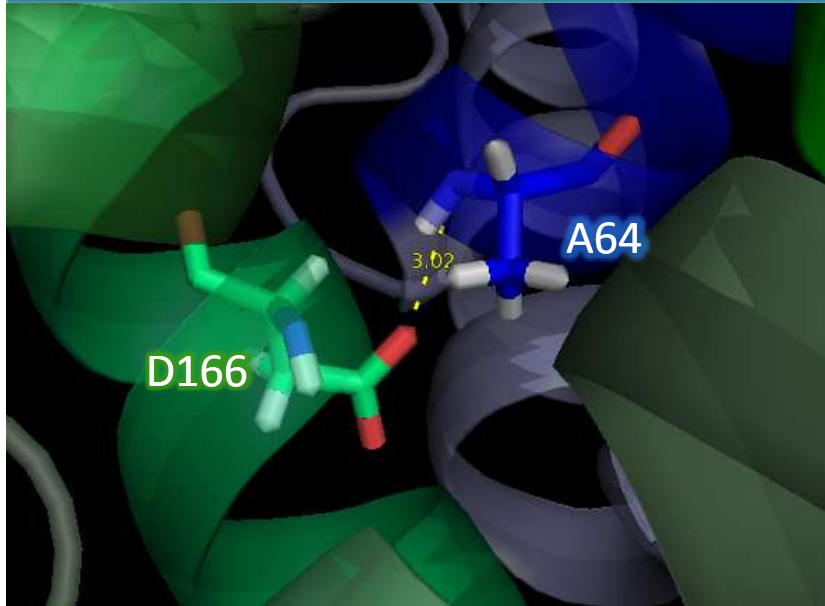
- Capping interactions



Capping interactions are the most important ones. A side chain from a residue interact with the last residue from a helix (cap residue).

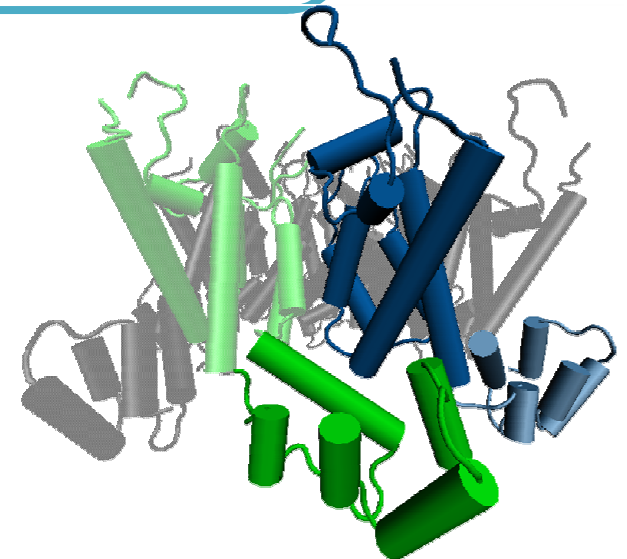


NTD-CTD interface



**POLAR AND WATER
MEDIATED CONTACTS:**
- Capping interactions

- E71 – L211
- A64 – D166
- N57 + V59 – R173

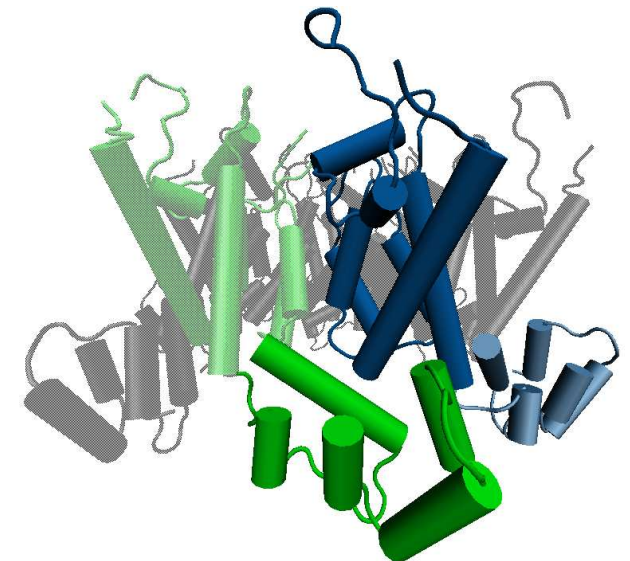
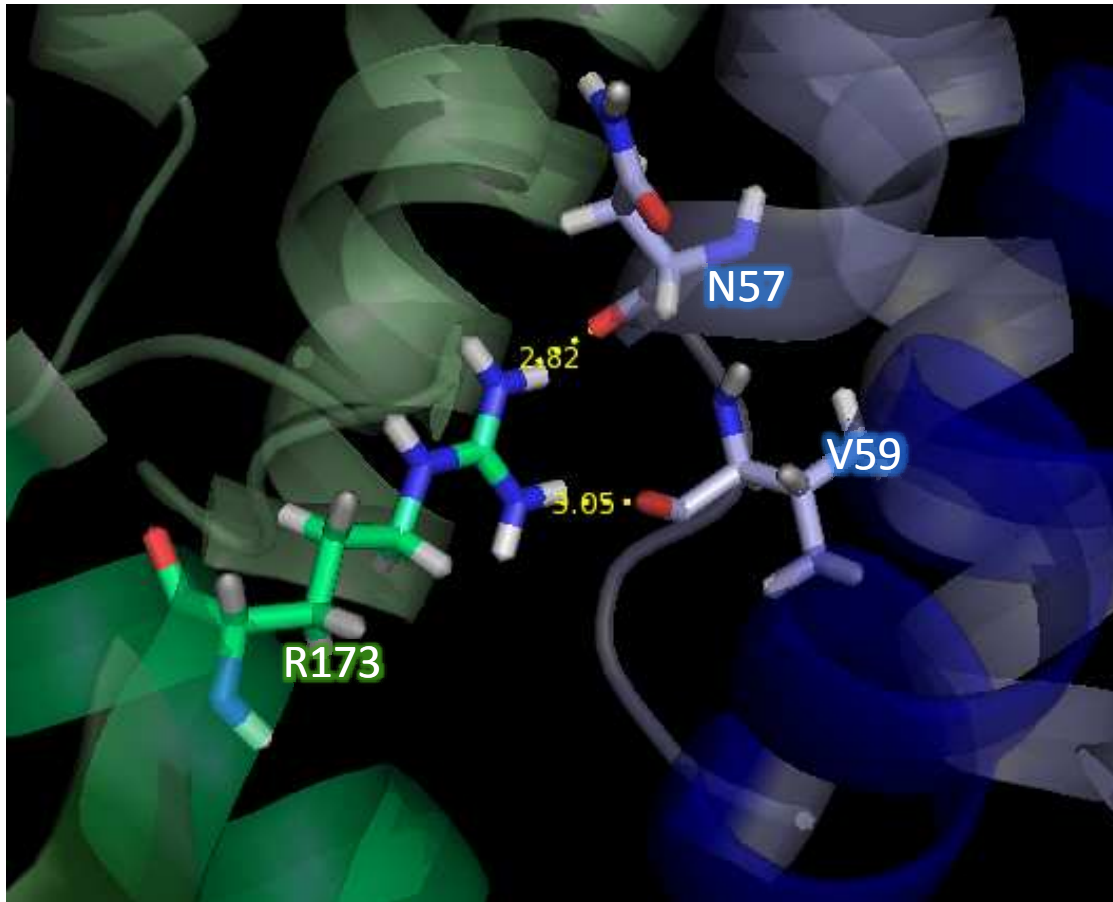


NTD-CTD interface

POLAR AND WATER MEDIATED CONTACTS:

- Capping interactions

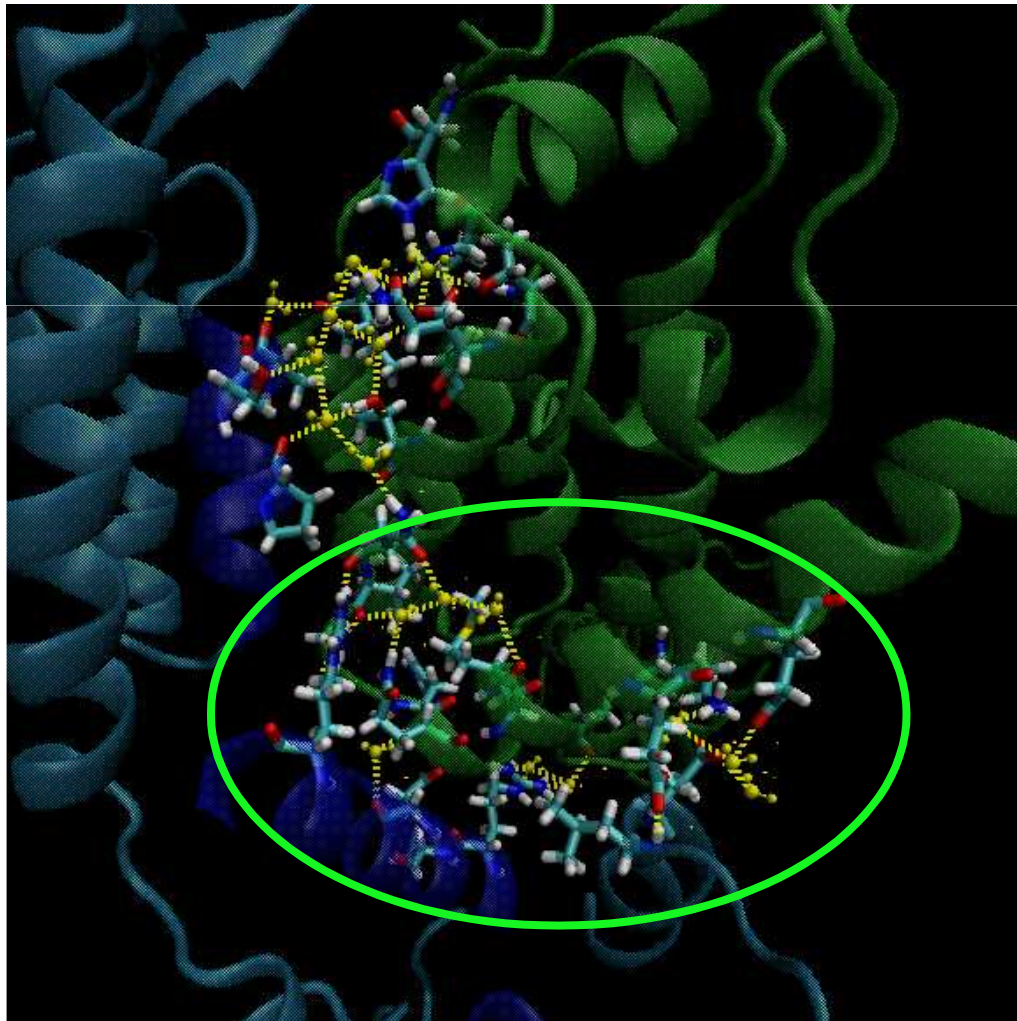
- E71 – L211
- D166 – A64
- R173 – N57 + V59



NTD-CTD interface

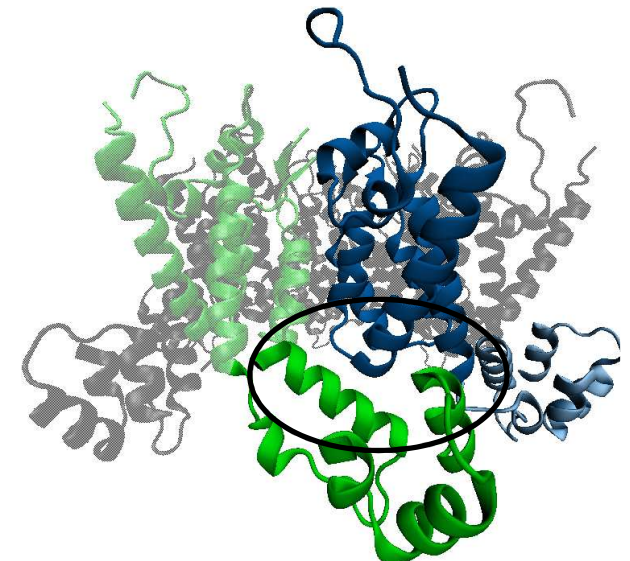
POLAR AND WATER MEDIATED CONTACTS:

- Water mediated contacts:



There are also water mediated contacts.

They involved helices 8, 11 (blue) and 4 and 7 (green).



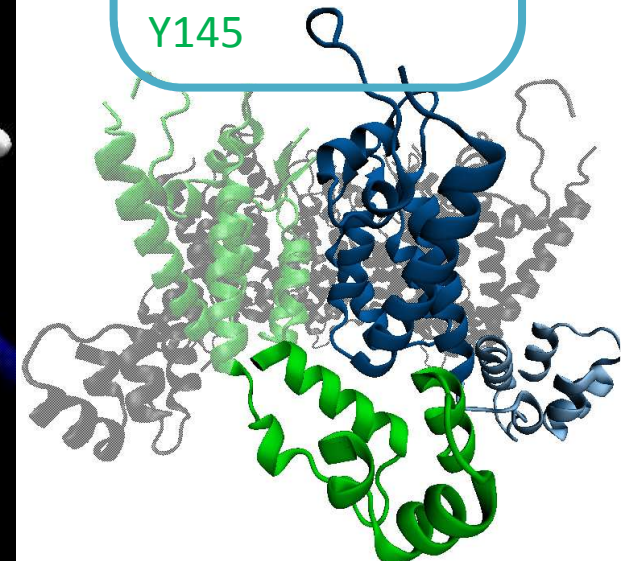
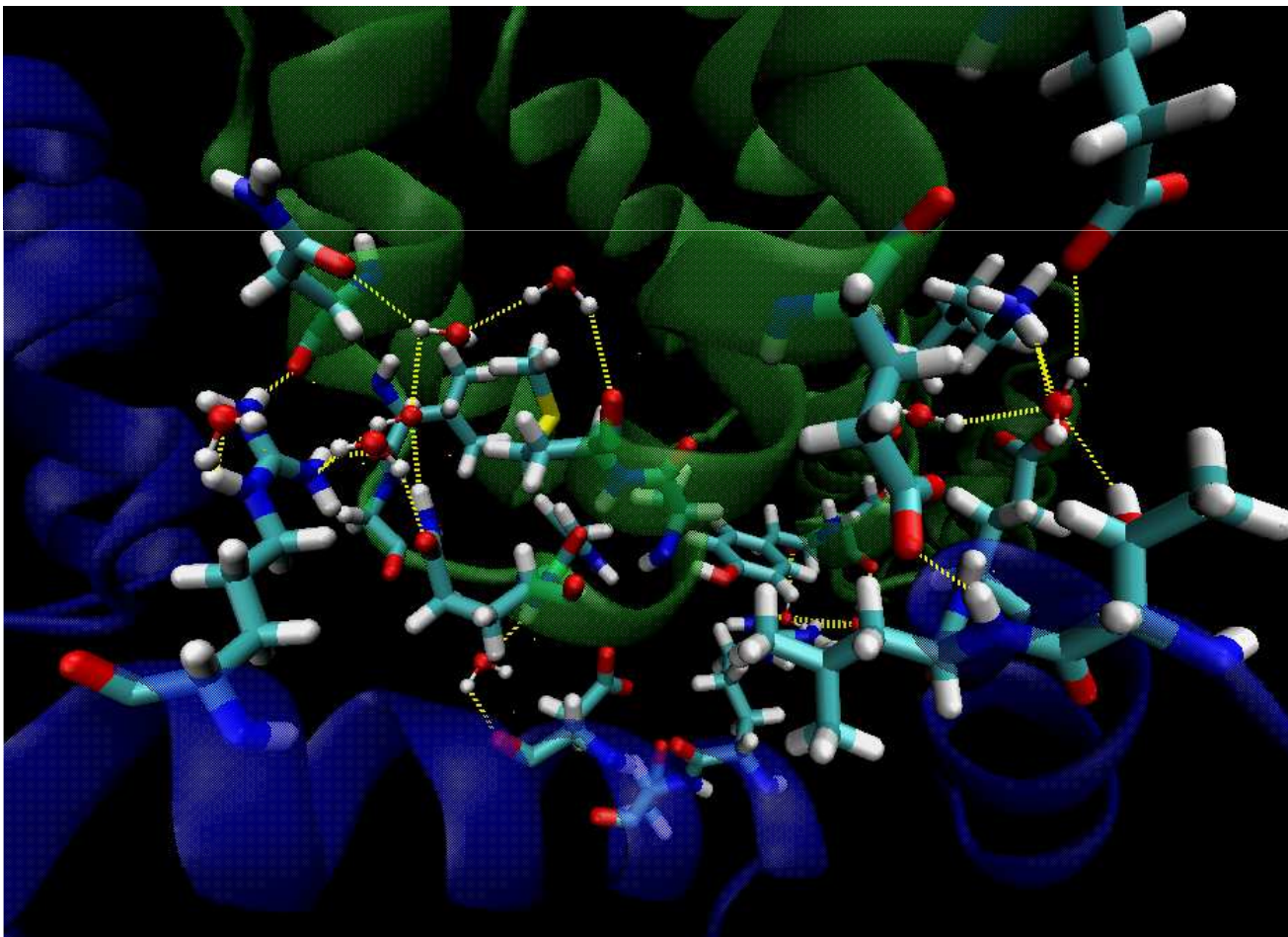
NTD-CTD interface

POLAR AND WATER MEDIATED CONTACTS:

- Water mediated contacts:

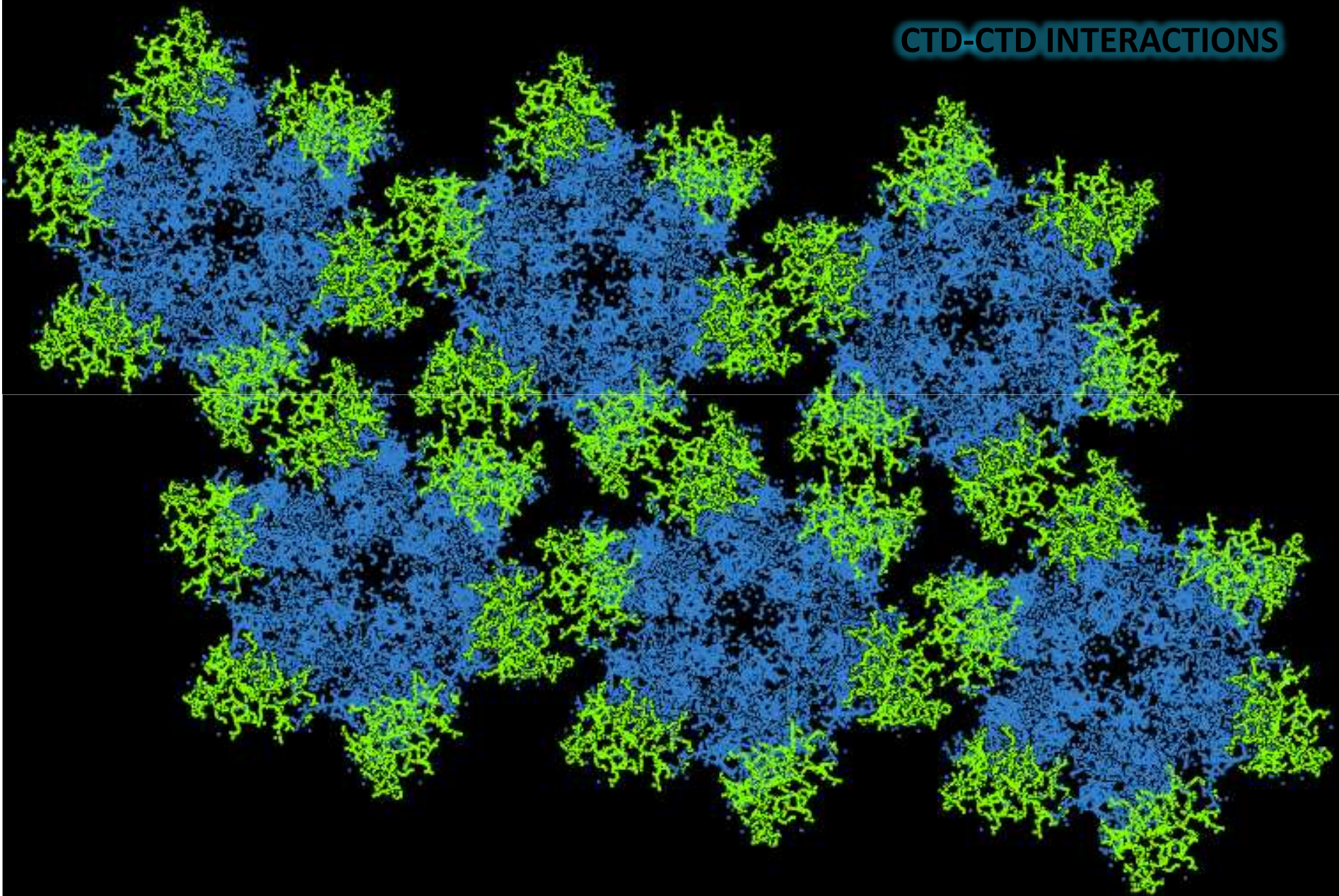
Residues involved:

G60	R173
H62	D166
Q63	R162
A65	D163
M66	T210
N57	L211
V59	E212
K140	
E71	
E75	
P146	
Y145	

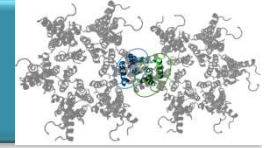


3.1. HEXAMERS

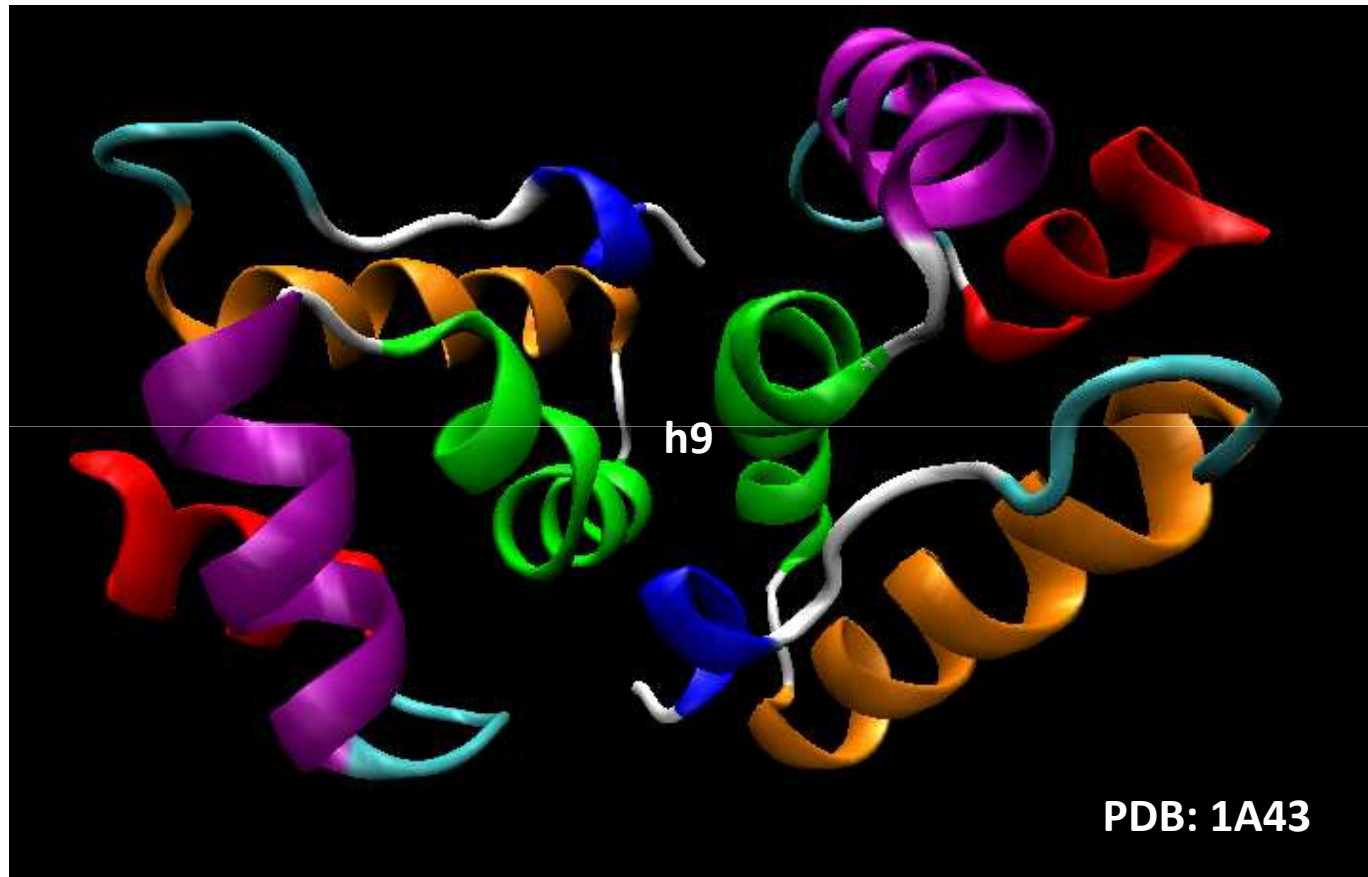
CTD-CTD INTERACTIONS



3.1. HEXAMERS



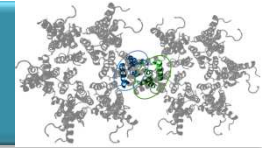
CTD-CTD INTERACTIONS



HYDROPHOBIC INTERACTIONS

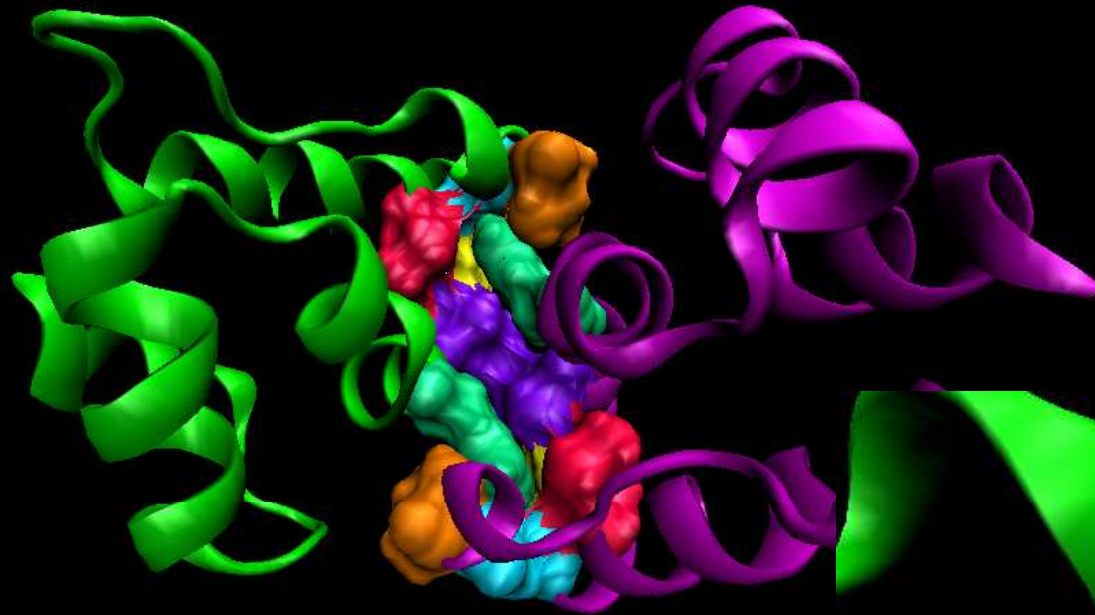
POLAR INTERACTIONS: 4 hydrogen bonds and 2 salt bridges

3.1.HEXAMERS



CTD-CTD INTERACTIONS

HYDROPHOBIC INTERACTIONS



PDB: 1A43

Trp 184 helix 9' against:

Thr 148

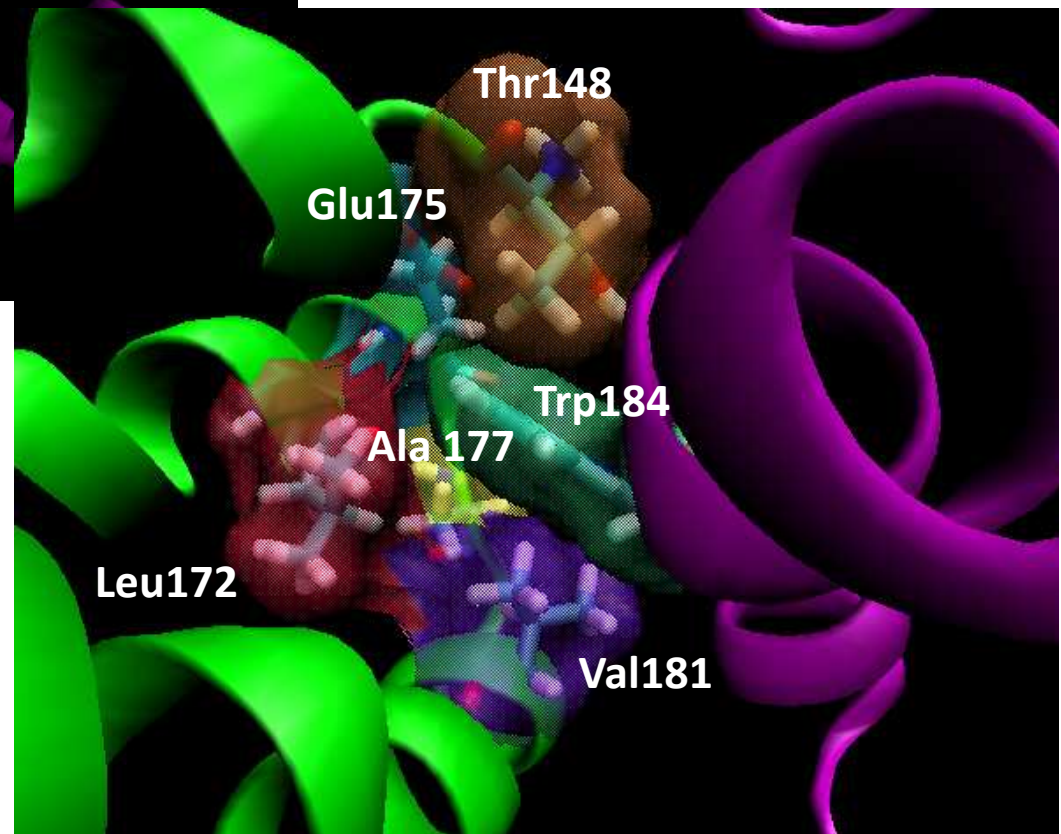
Leu 172

Glu 175

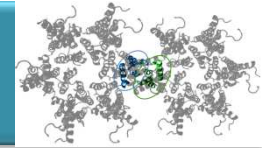
Ala 177

Val 181

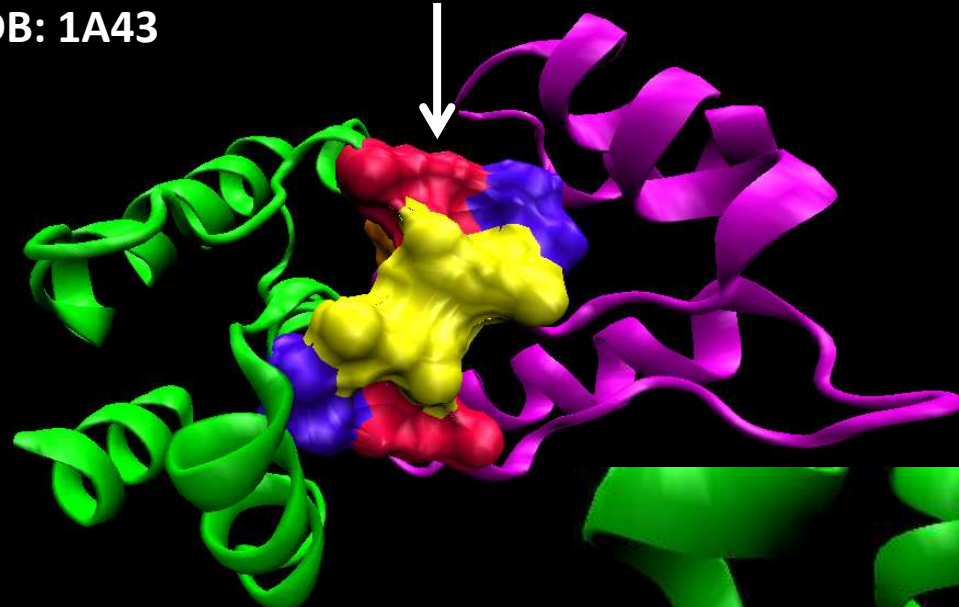
From helix 9"



3.1.HEXAMERS



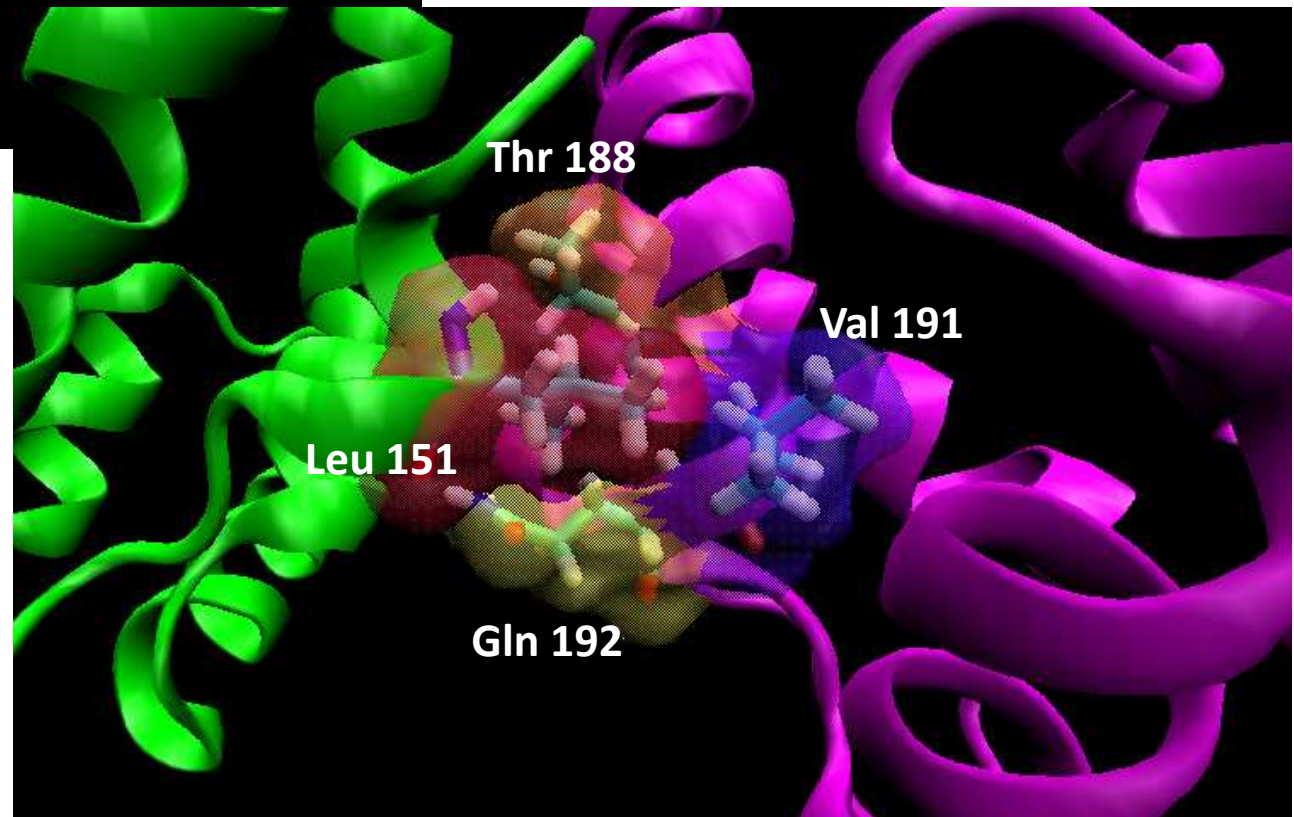
PDB: 1A43



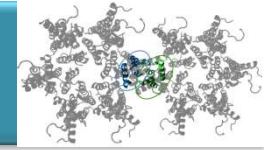
CTD-CTD INTERACTIONS

HYDROPHOBIC INTERACTIONS

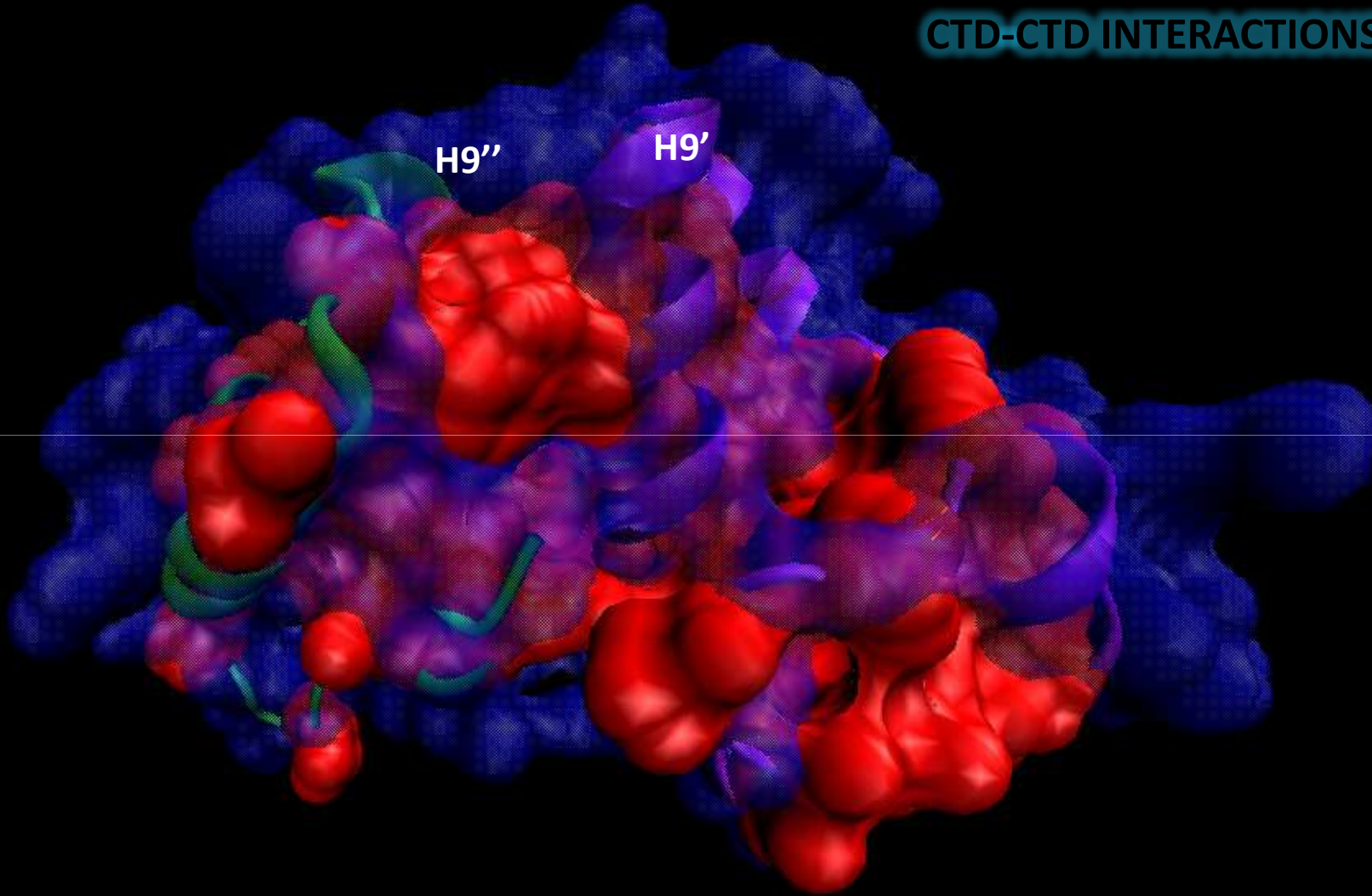
Leu 151 from 3₁₀
helix against:
Thr 188
Val 191
Gln 192
Met 185
from helix 9''



3.1. HEXAMERS

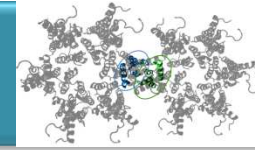


CTD-CTD INTERACTIONS



PDB: 1A43

3.1.HEXAMERS

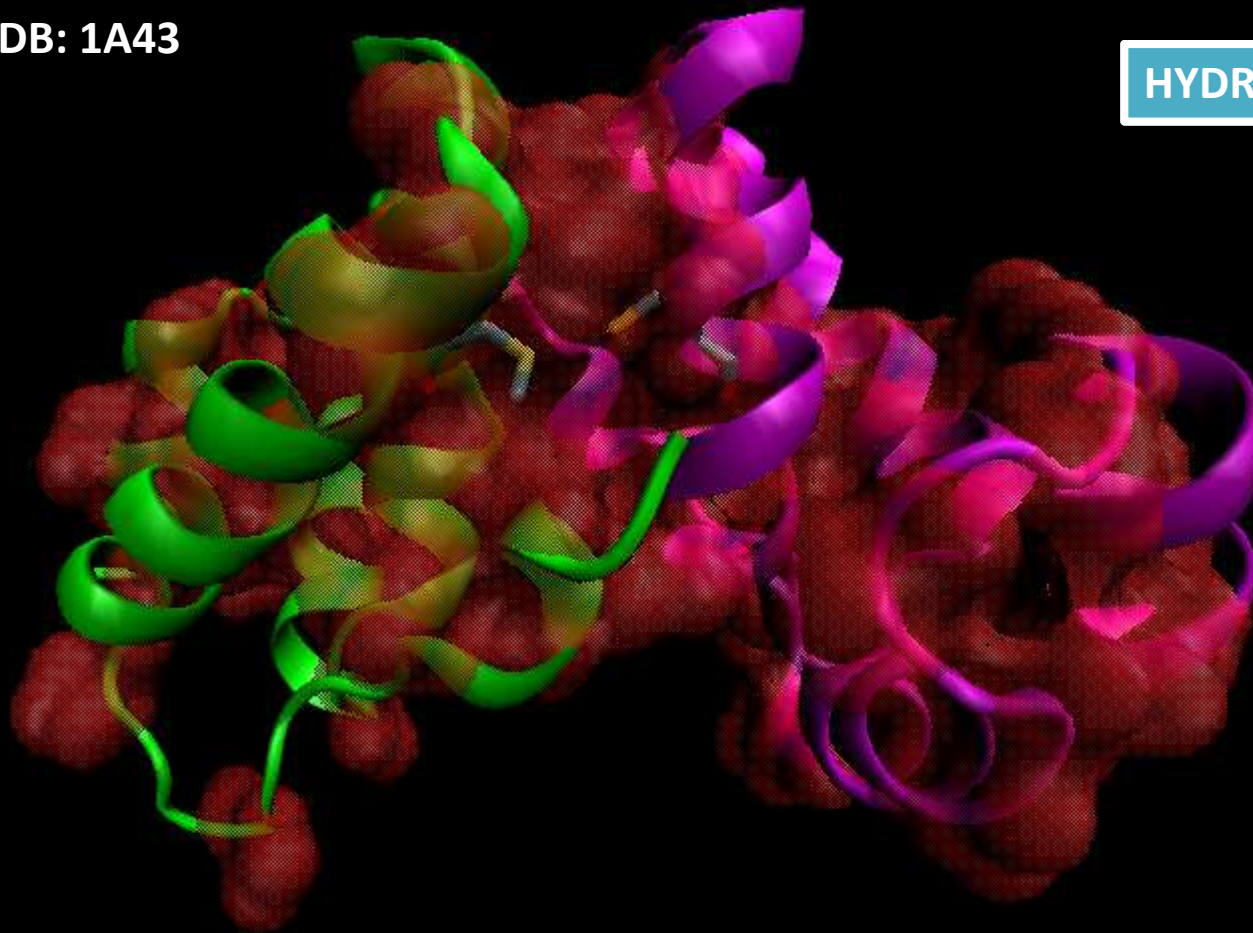


CTD-CTD INTERACTIONS

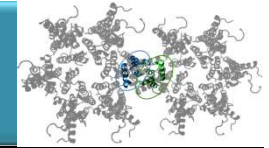
PDB: 1A43

HYDROPHOBIC INTERACTIONS

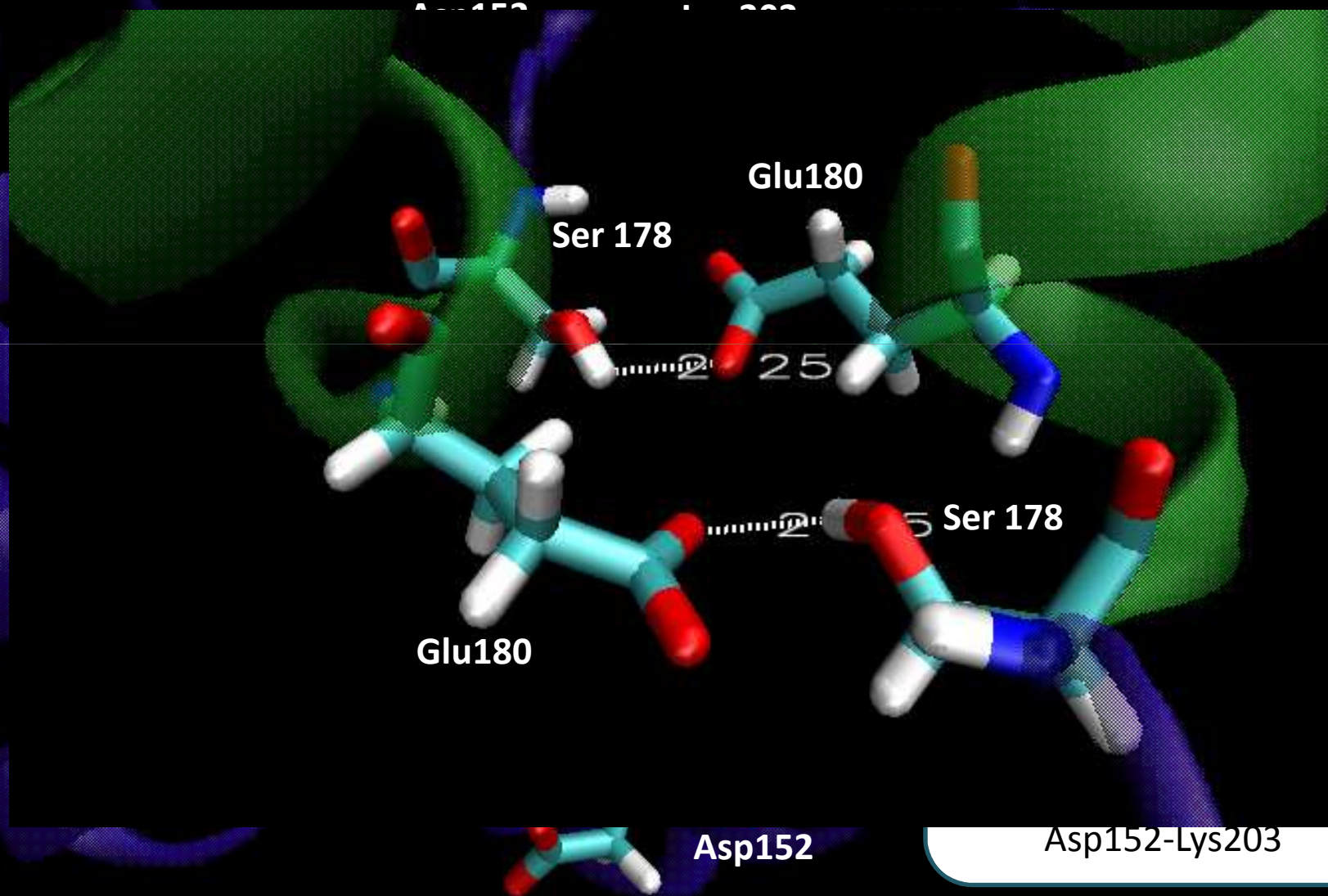
Met 185



3.1. HEXAMERS



CTD-CTD INTERACTIONS



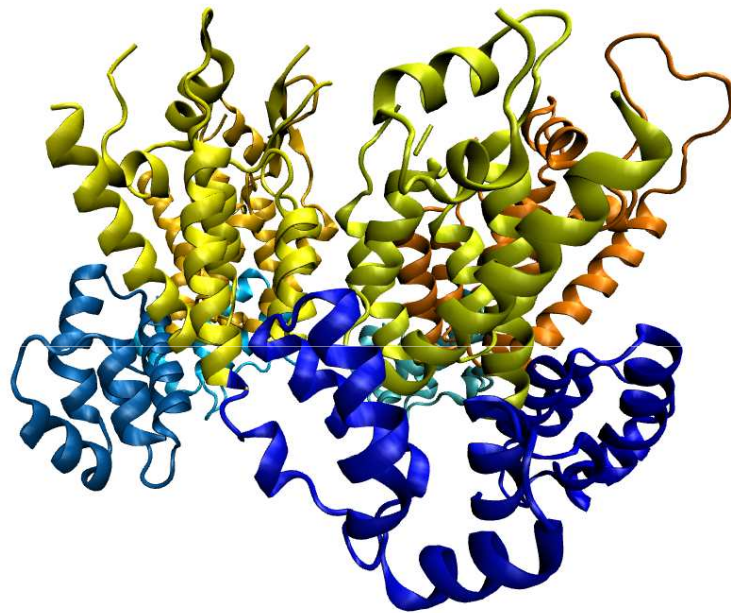
Index

- Introduction
- CA (monomer)
 - NTD
 - CTD
- Capsid subunits
 - Hexamers
 - Pentamers
- Capsid curvature
- Current situation

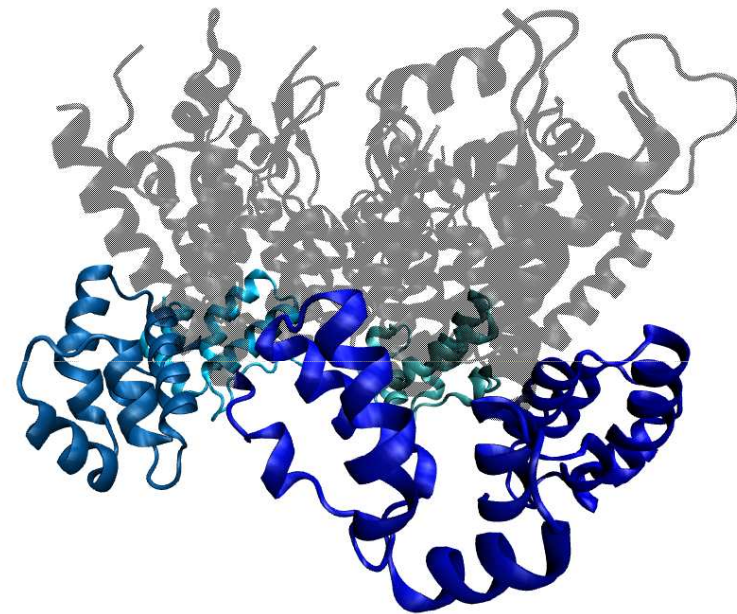
Index

- Introduction
- CA (monomer)
 - NTD
 - CTD
- Capsid subunits
 - Hexamers
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3.2. PENTAMERS



CA is packed in the same way

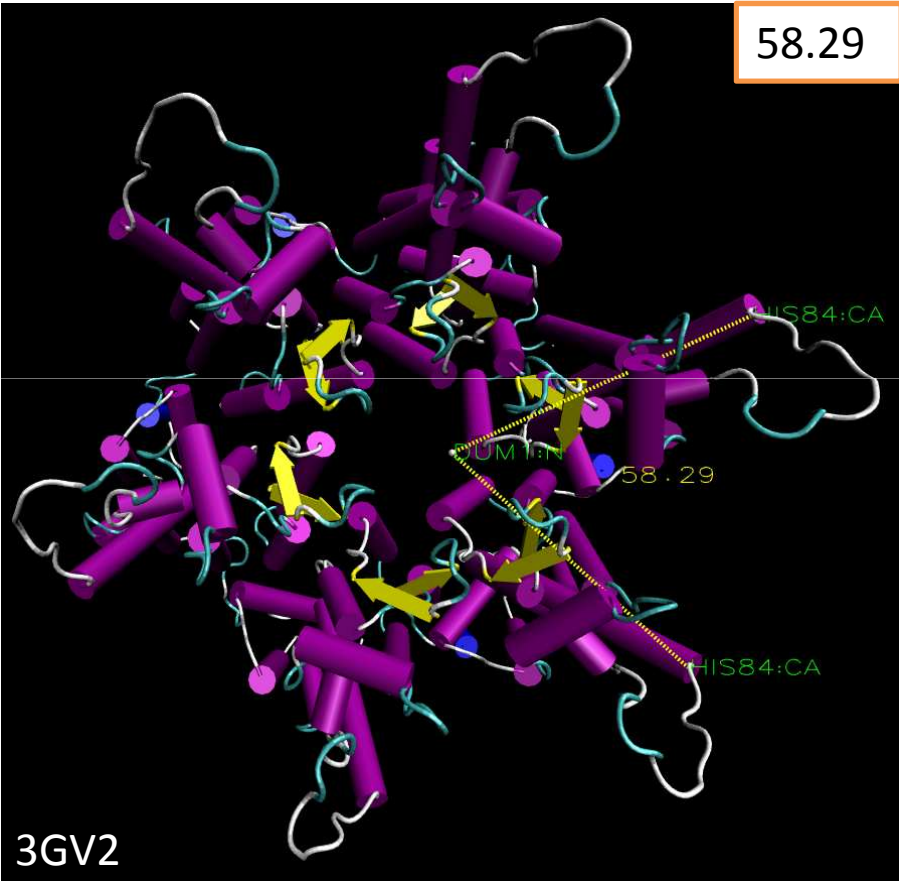


NTD inner ring, CTD outer ring

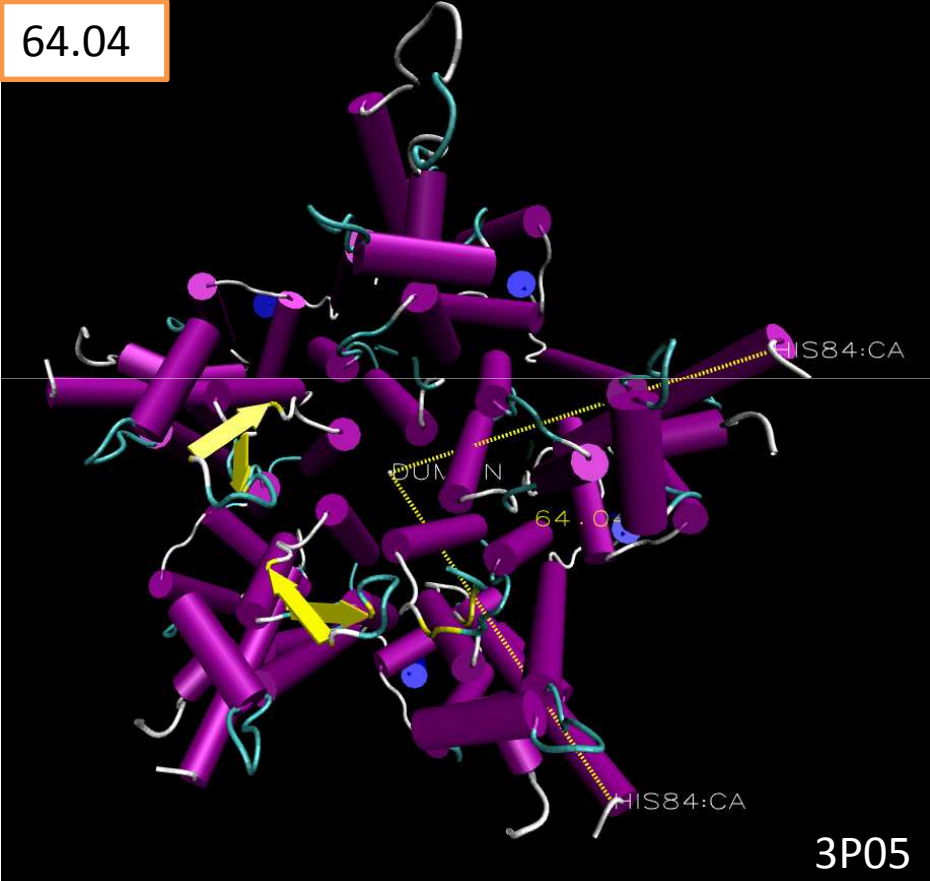
NTD: yellow
CTD: blue

3.2. PENTAMERS

HEXAMER



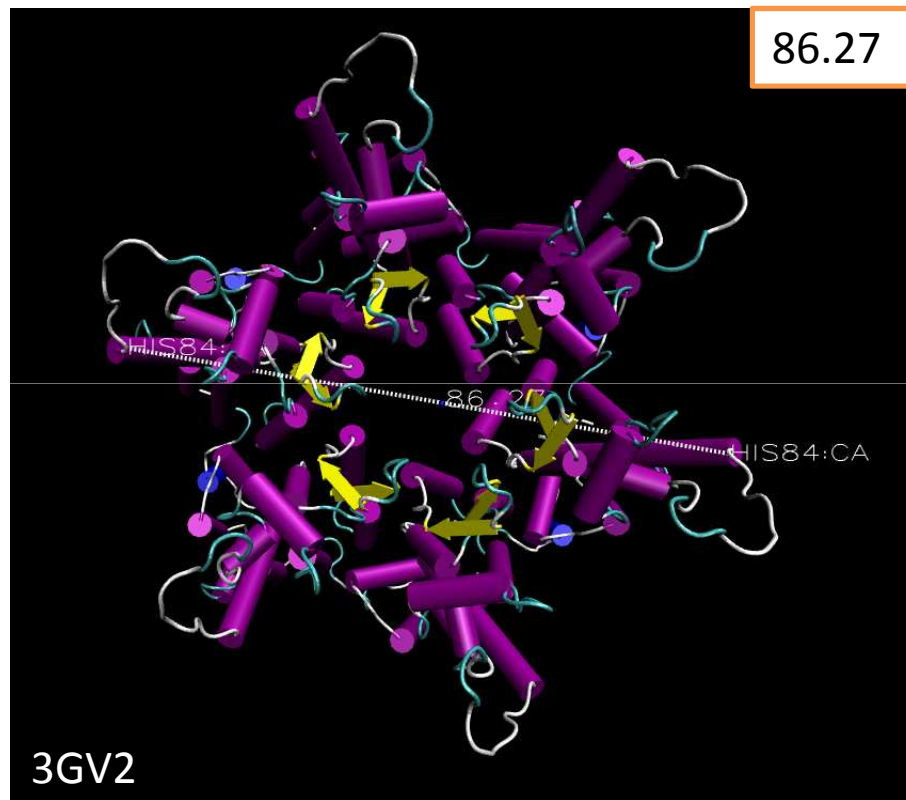
PENTAMER



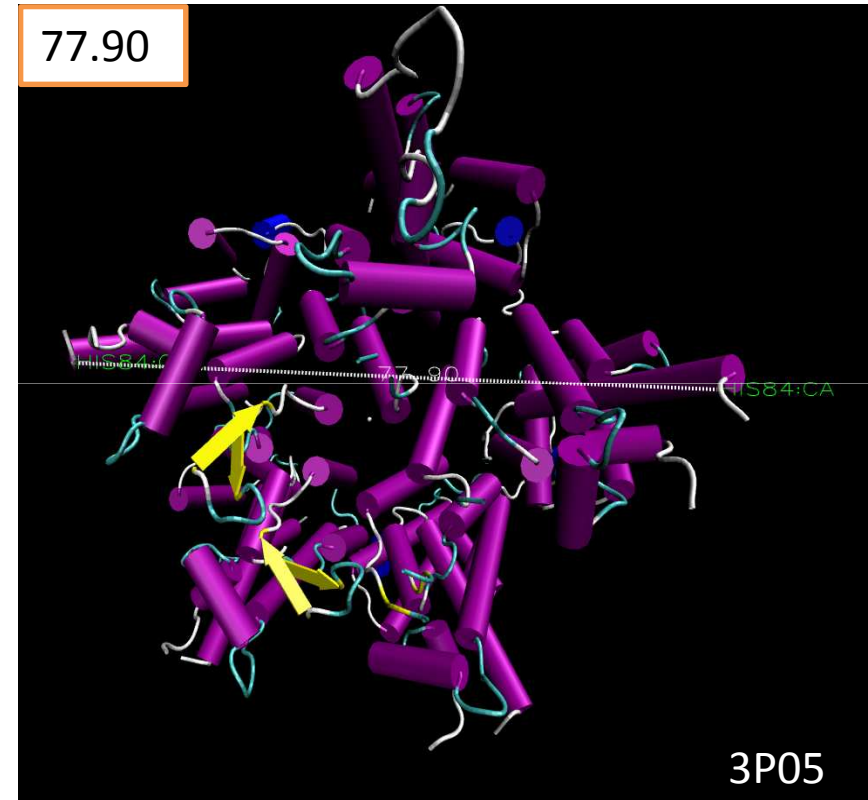
Differences in the angle between monomers

3.2. PENTAMERS

HEXAMER



PENTAMER

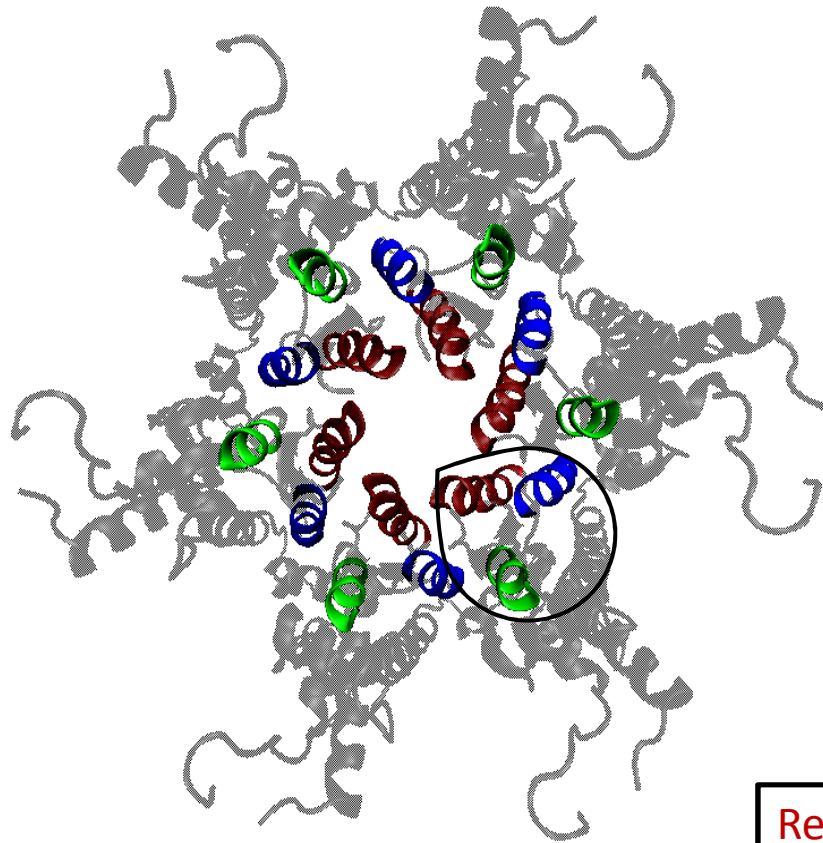


Differences in the diameter

3.2. PENTAMERS

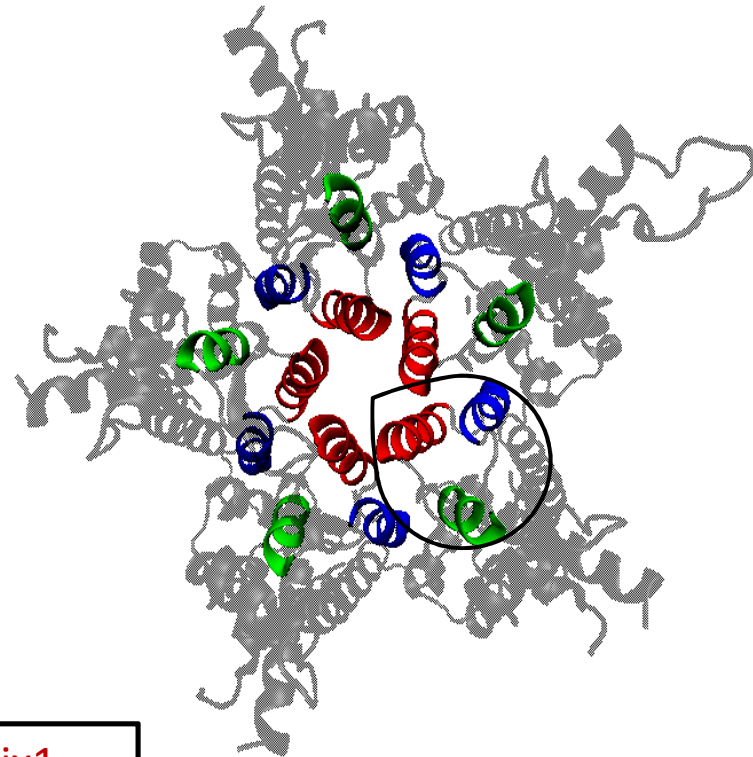
NTD-NTD interface

18-helix bundle



HEXAMER

15-helix bundle

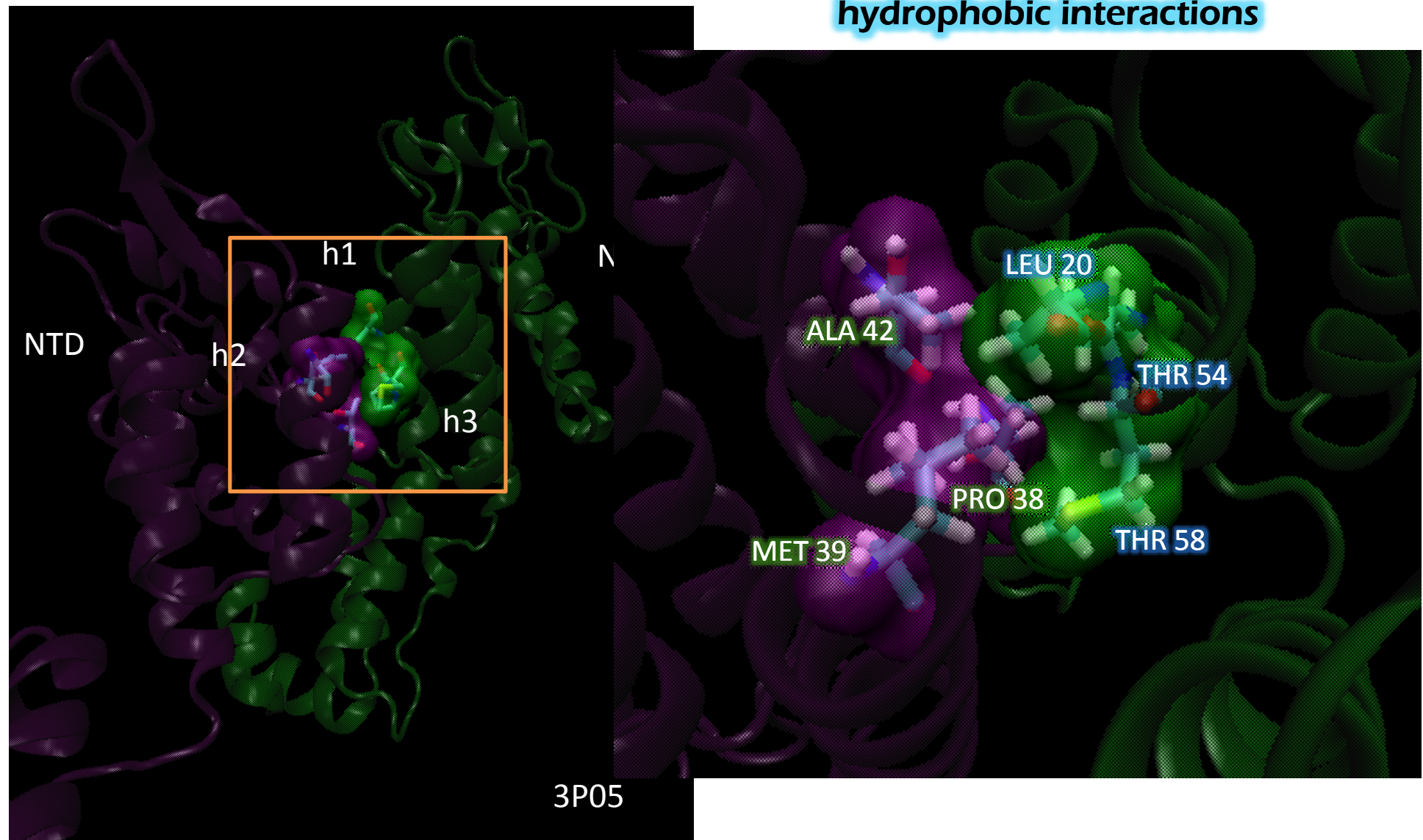


PENTAMER

Red: helix1
Blue: helix2
Green: helix3

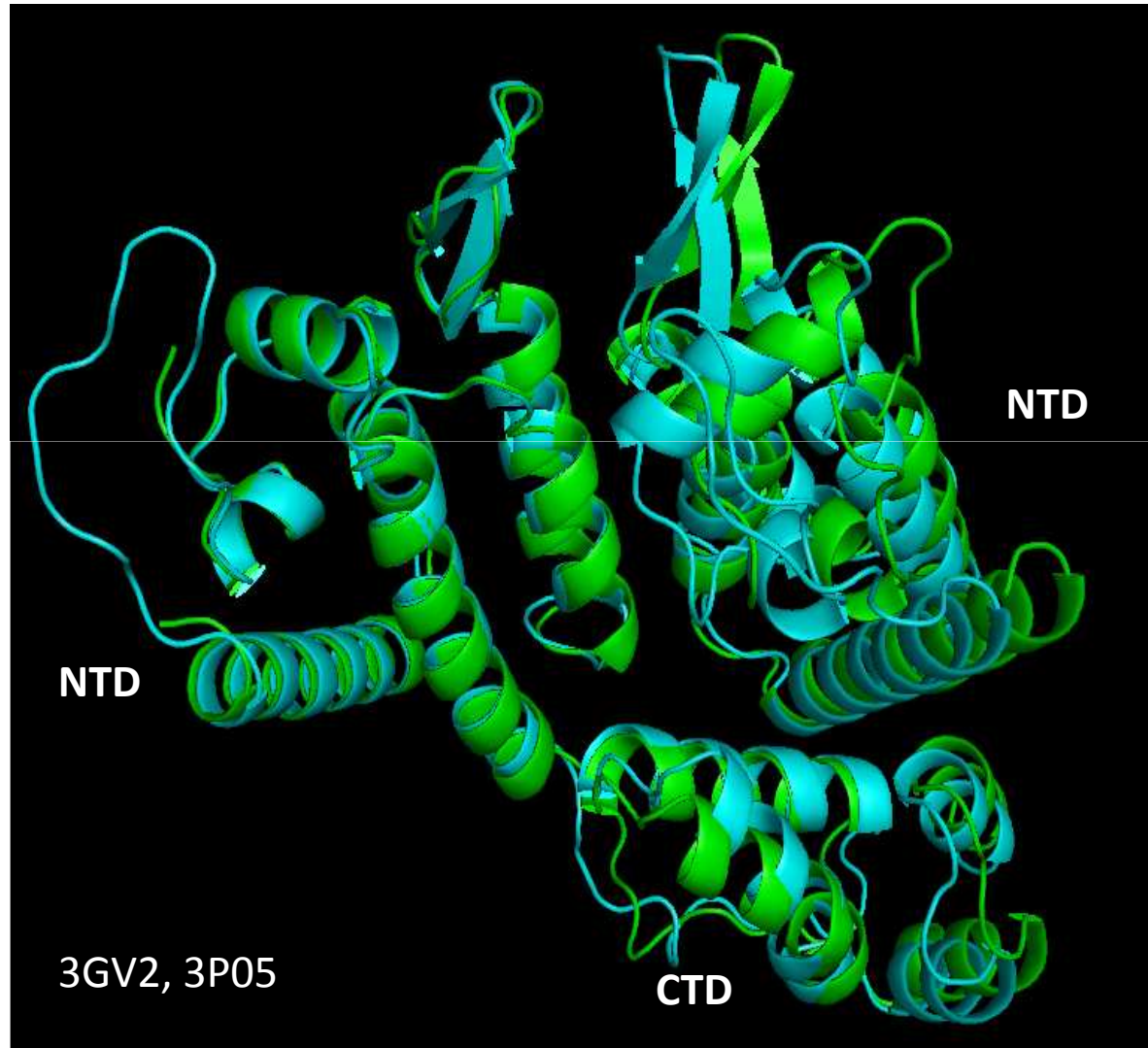
3.2. PENTAMERS

NTD-NTD interface



3.2. PENTAMERS

NTD-NTD interface



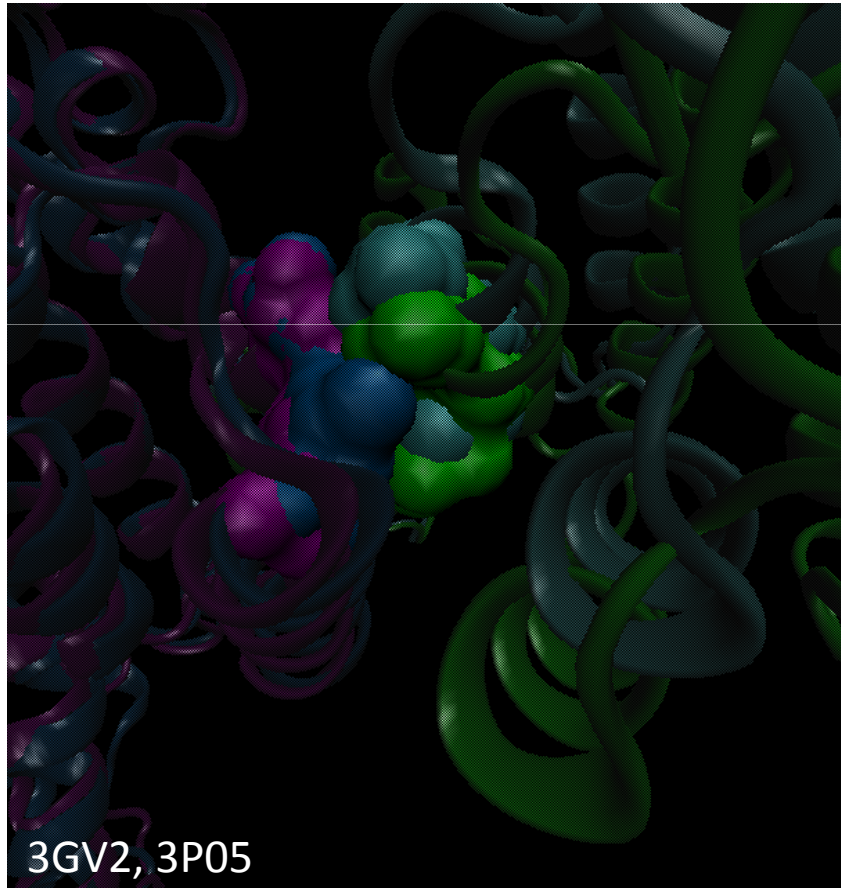
STAMP Hexamer
and Pentamer

Blue: hexamer
Green: pentamer

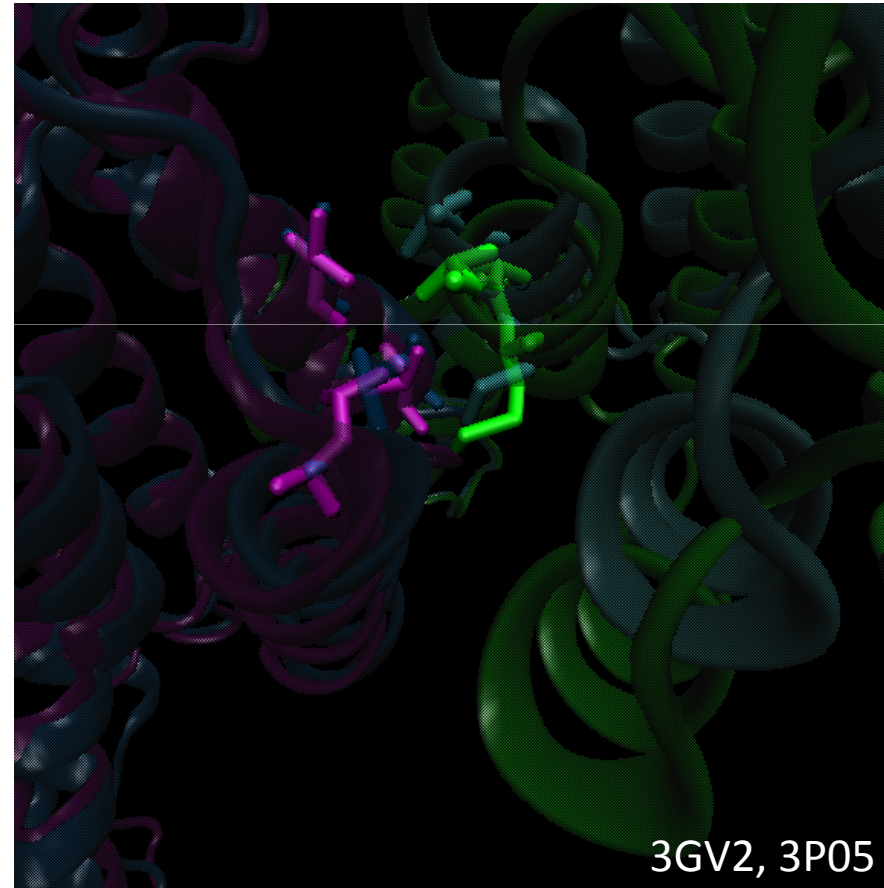
3.2. PENTAMERS

NTD-NTD interface

hydrophobic interactions



STAMP Hexamer
and Pentamer

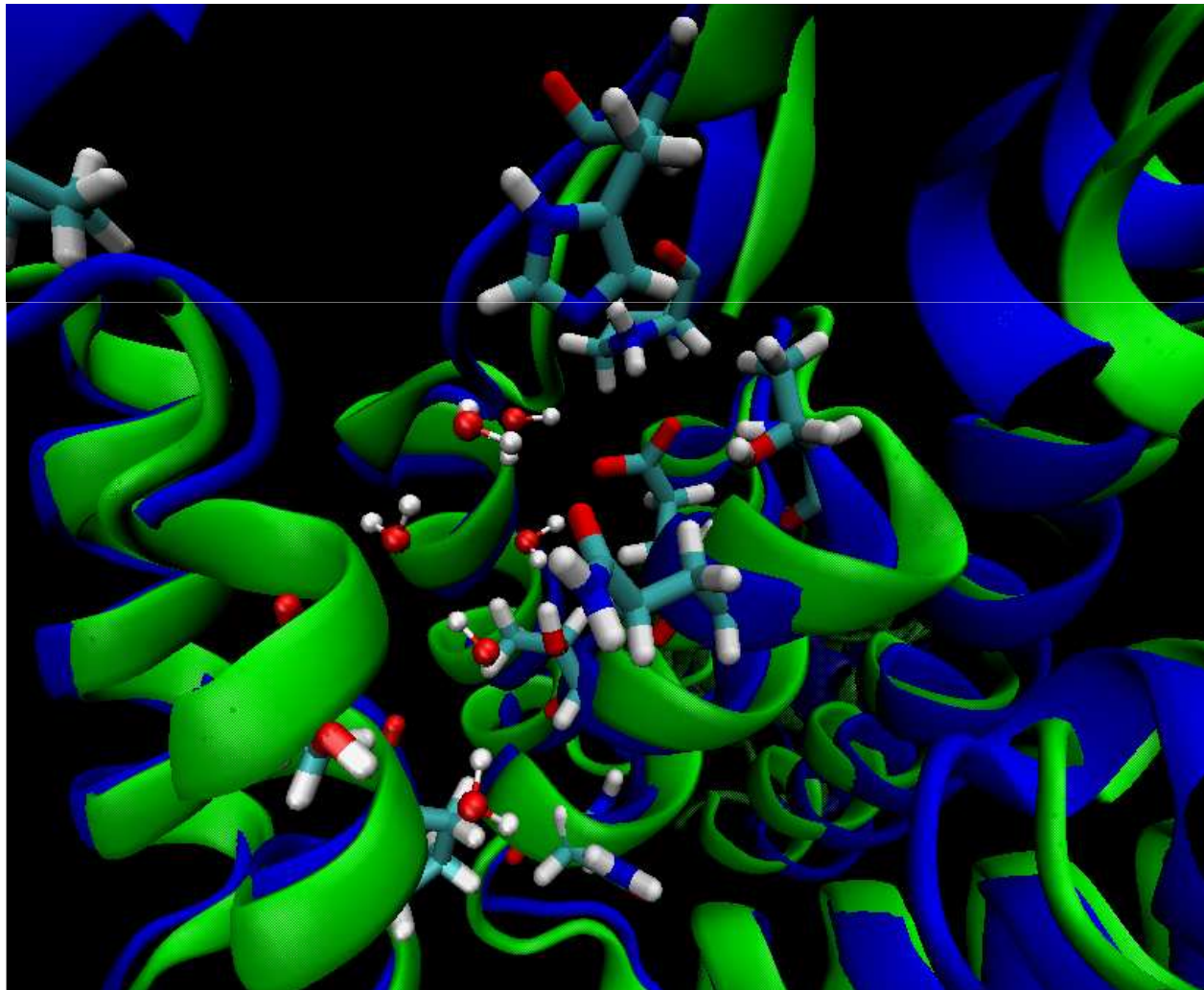


Hydrophobic interactions are conserved

3.2. PENTAMERS

NTD-NTD interface

polar interactions – water mediated



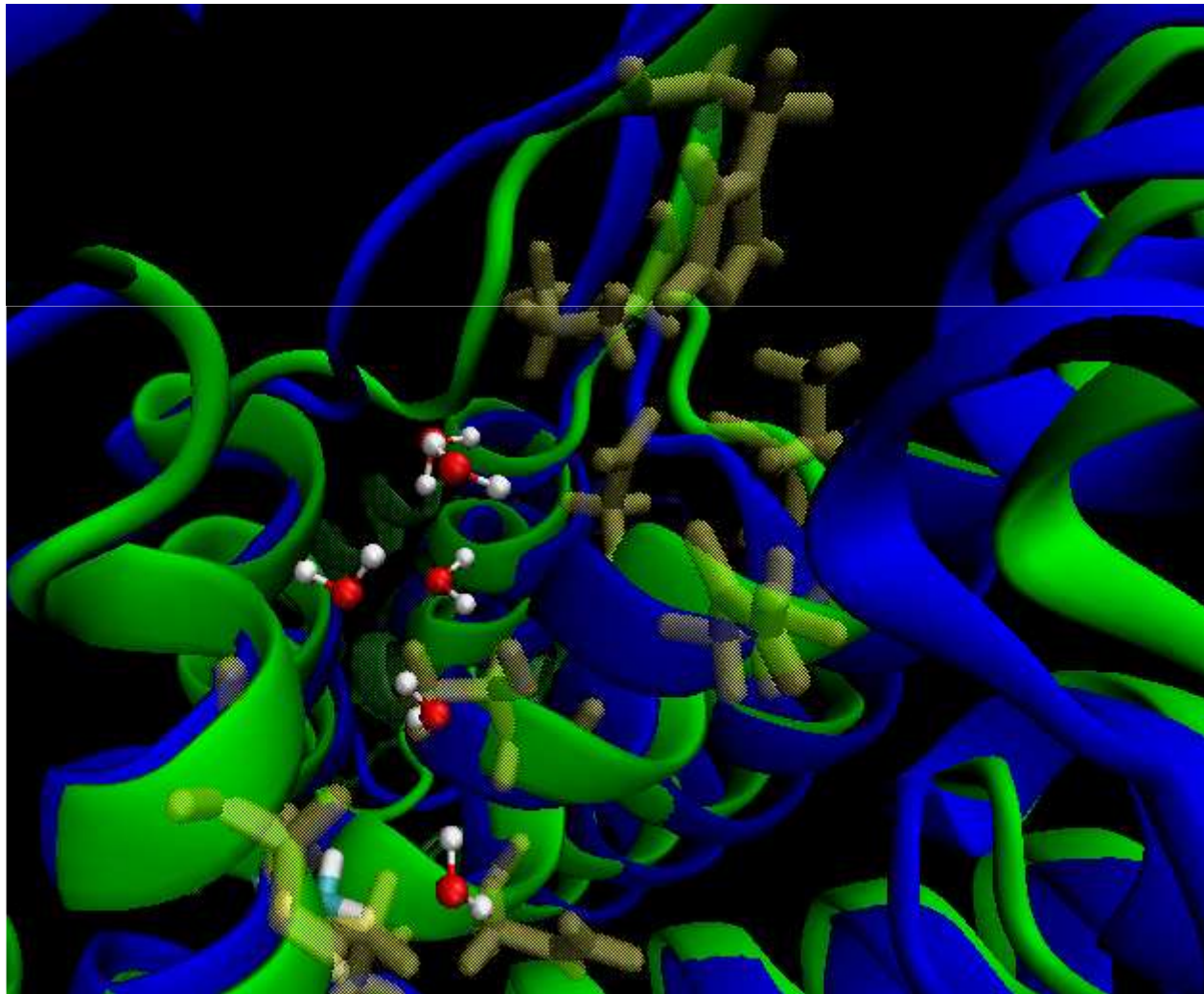
STAMP Hexamer
and Pentamer

Blue: hexamer
Green: pentamer

3.2. PENTAMERS

NTD-NTD interface

polar interactions – water mediated



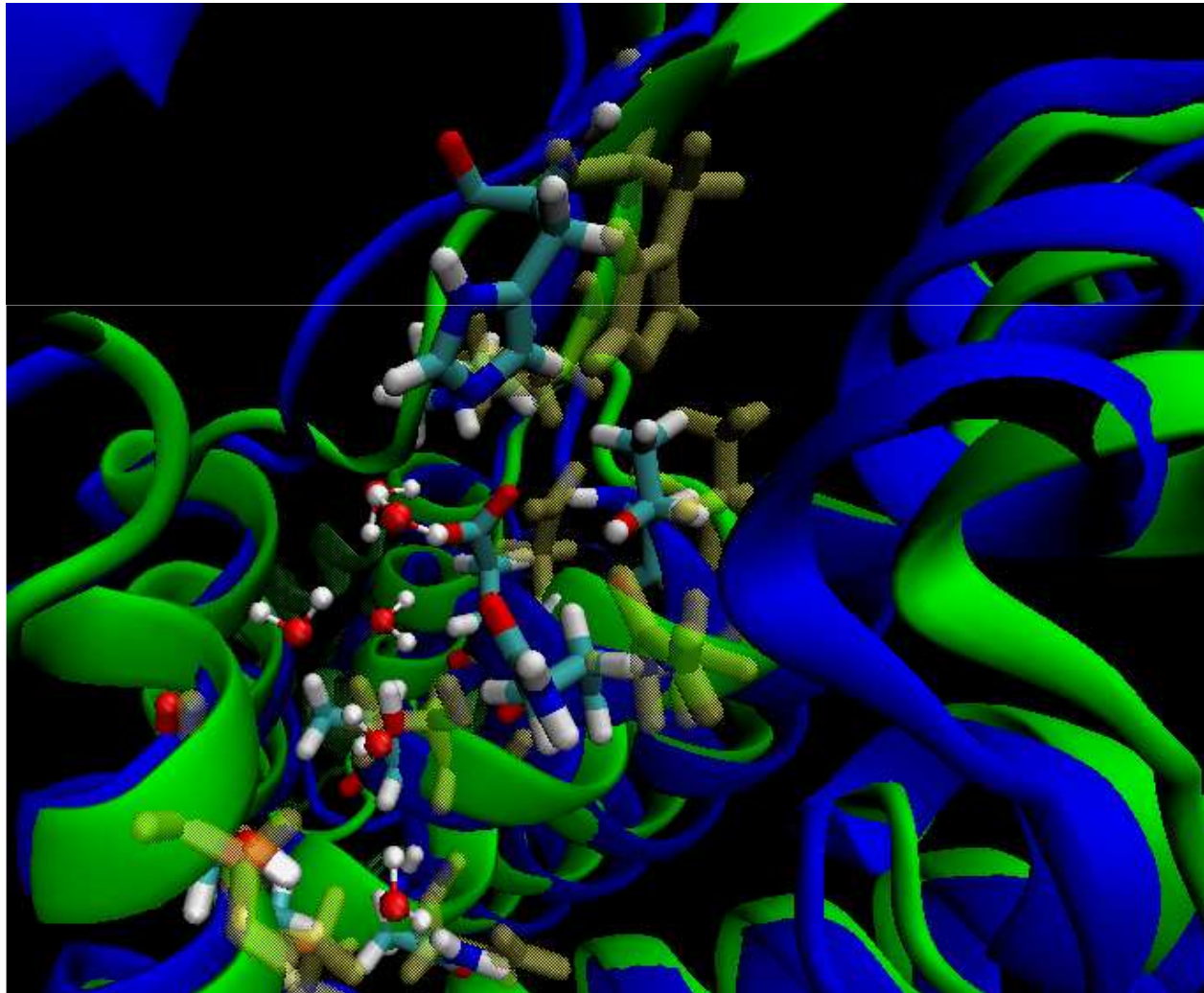
STAMP Hexamer
and Pentamer

Blue: hexamer
Green: pentamer

3.2. PENTAMERS

NTD-NTD interface

polar interactions – water mediated



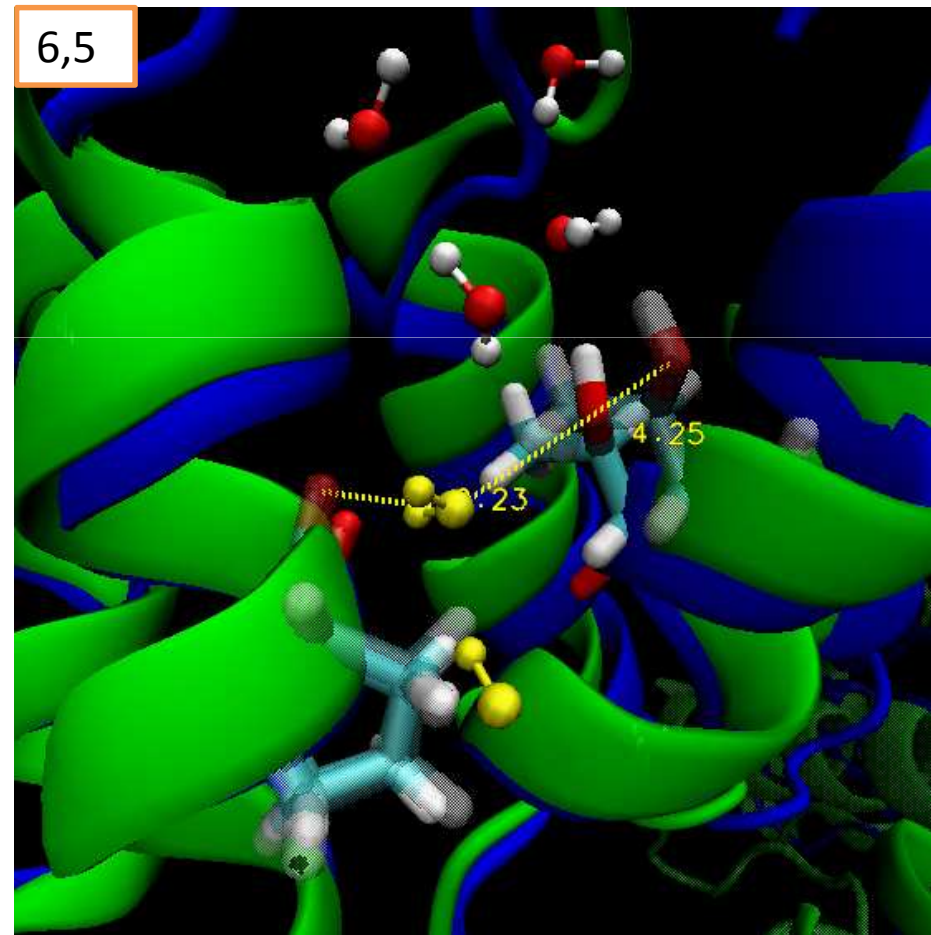
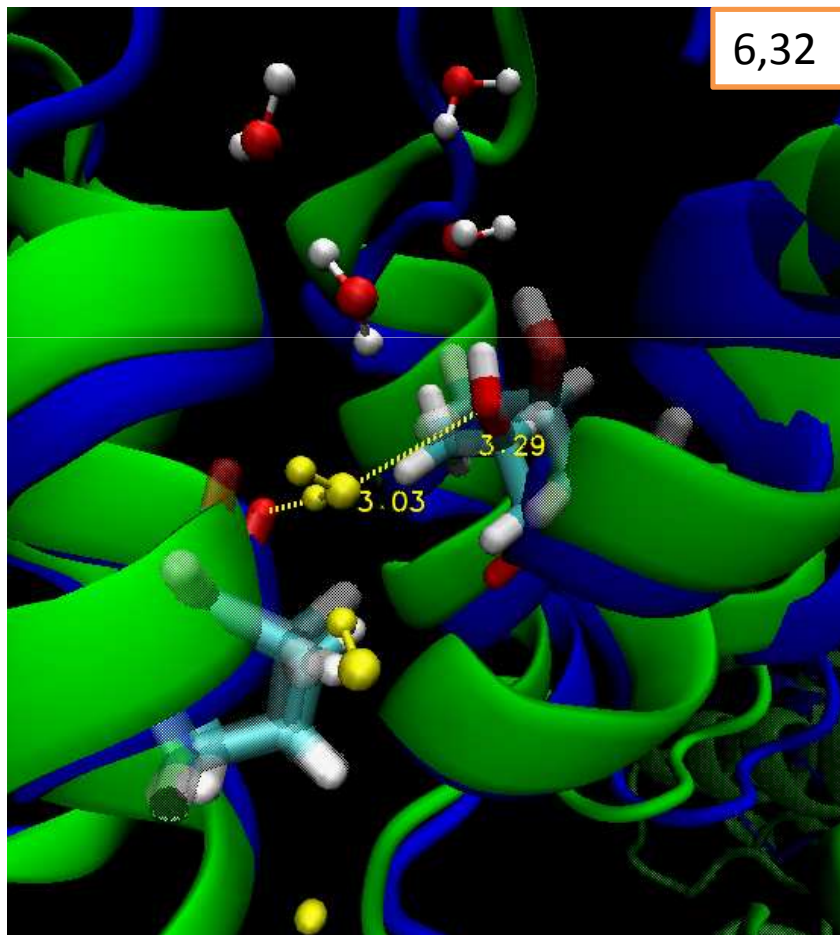
STAMP Hexamer
and Pentamer

Blue: hexamer
Green: pentamer

3.2. PENTAMERS

NTD-NTD interface

polar interactions – water mediated



3.2. PENTAMERS

NTD-CTD INTERFACE:

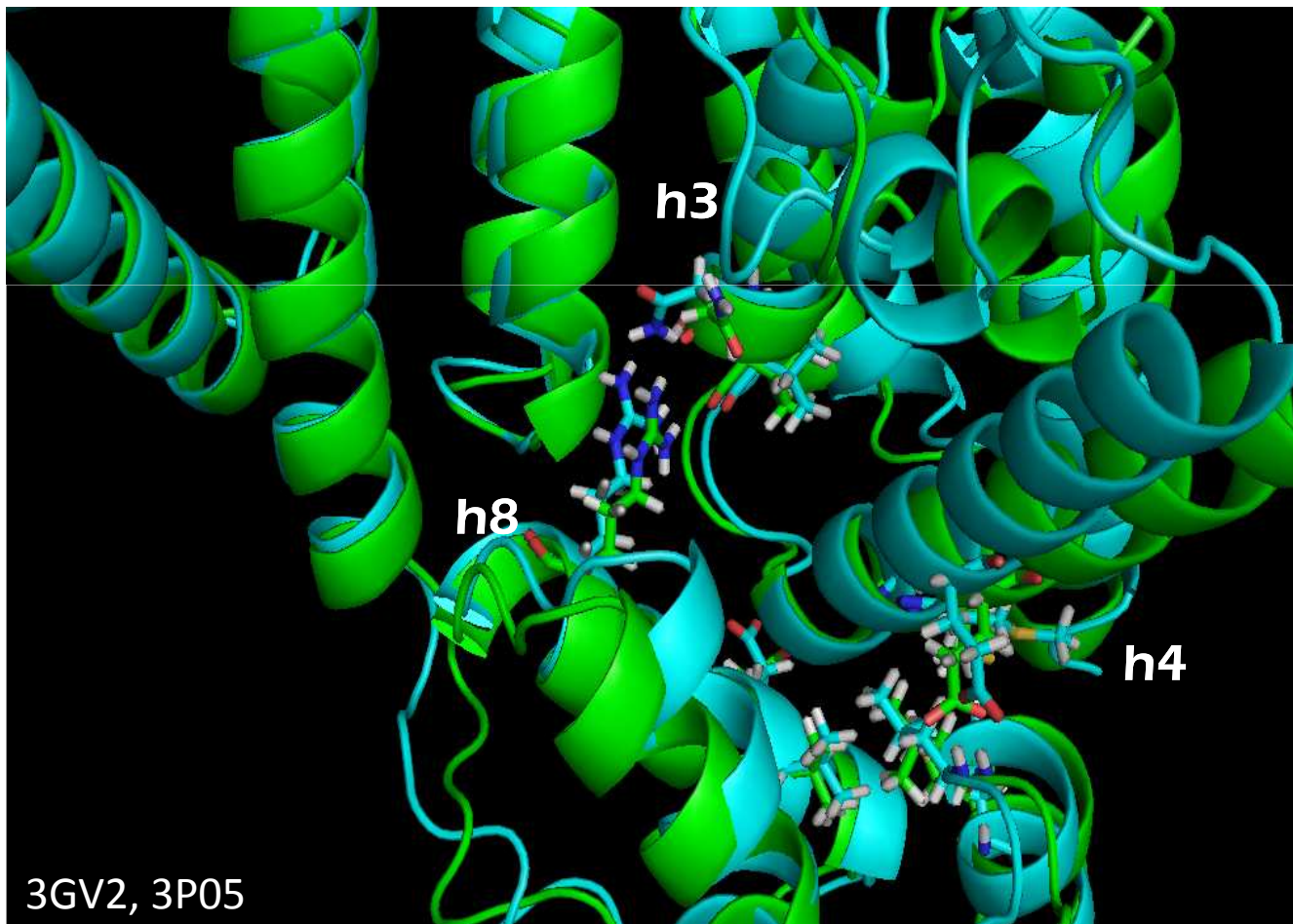
POLAR CONTACTS:

- Capping interactions

STAMP Hexamer and Pentamer

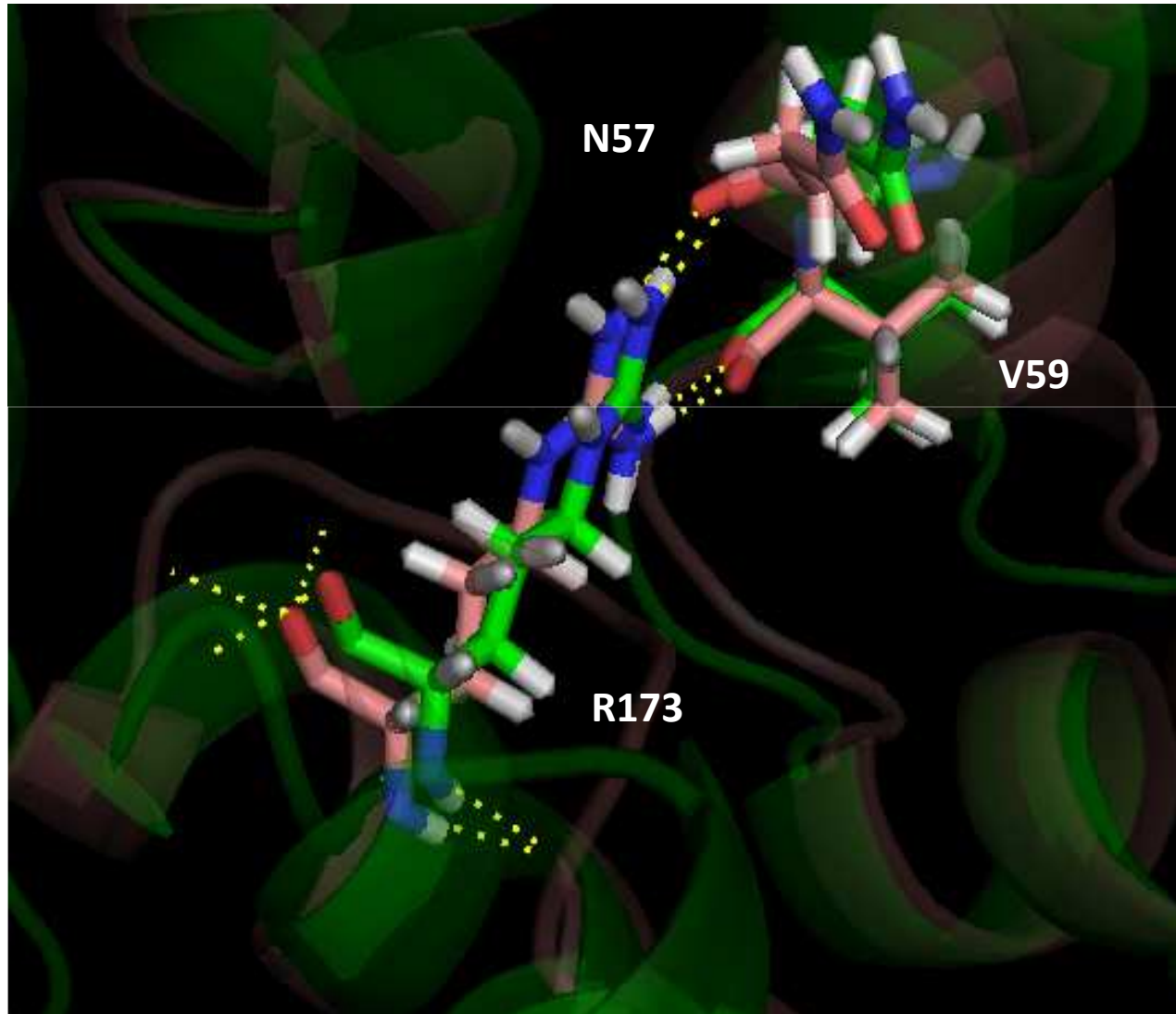
- E71 – L211
- A64 – D166
- N57 + V59 – R173

Blue: hexamer
Green: pentamer



3.2. PENTAMERS

NTD-CTD INTERFACE:



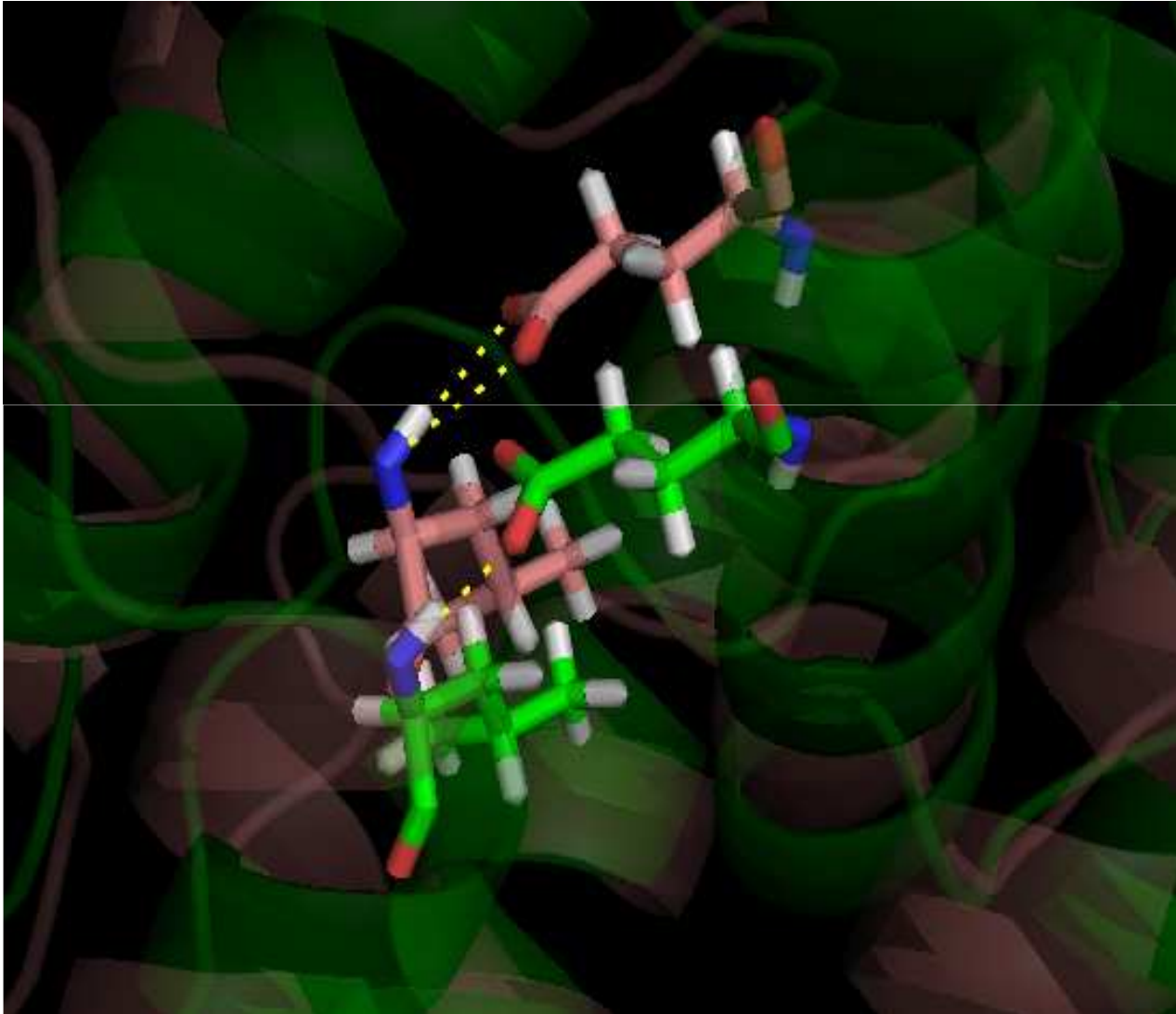
POLAR CONTACTS:

- Capping interactions

H-bonds interactions
are conserved

3.2. PENTAMERS

NTD-CTD INTERFACE:



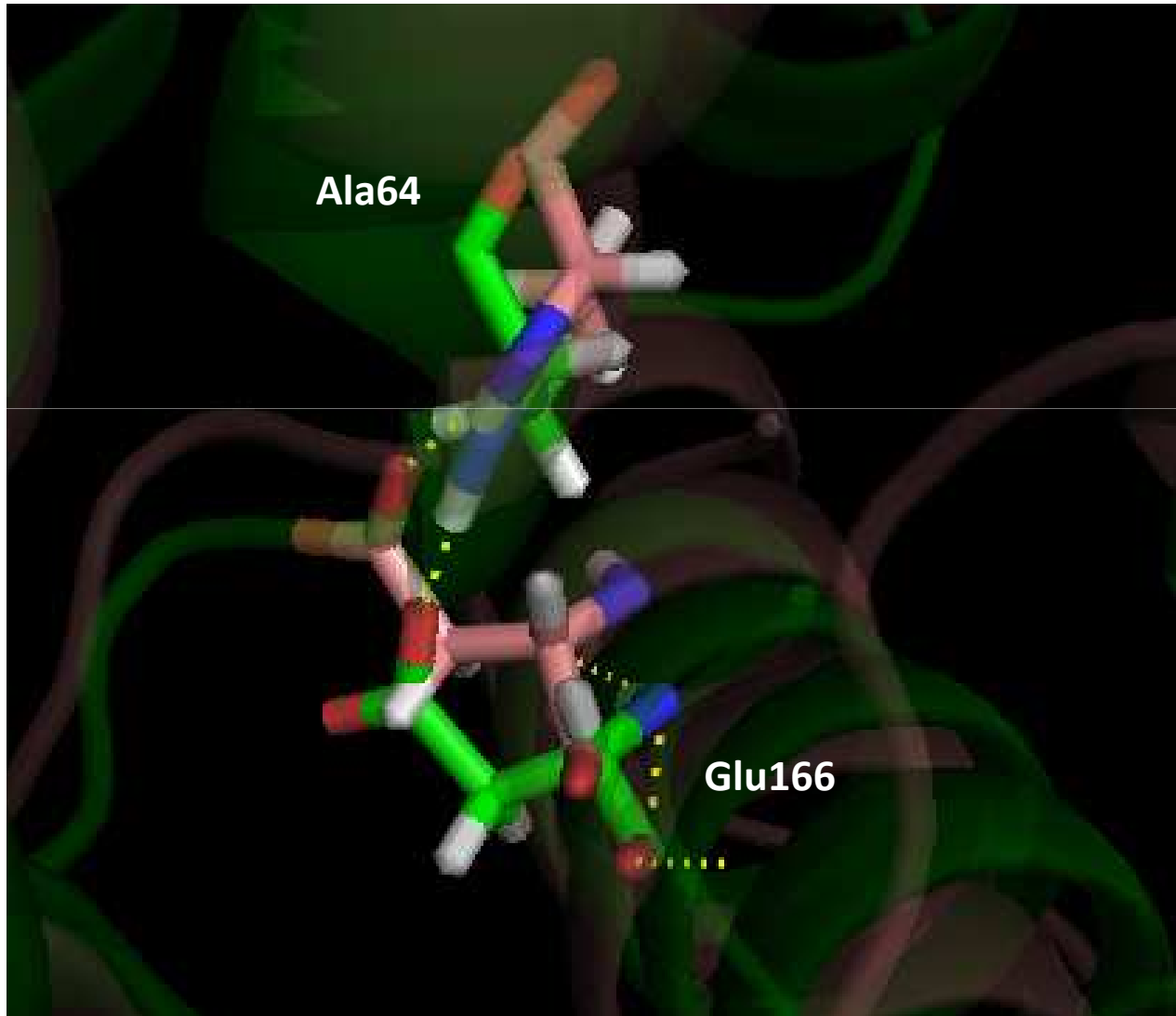
POLAR CONTACTS:

- Capping interactions

H-bonds interactions
are conserved

3.2. PENTAMERS

NTD-CTD INTERFACE:

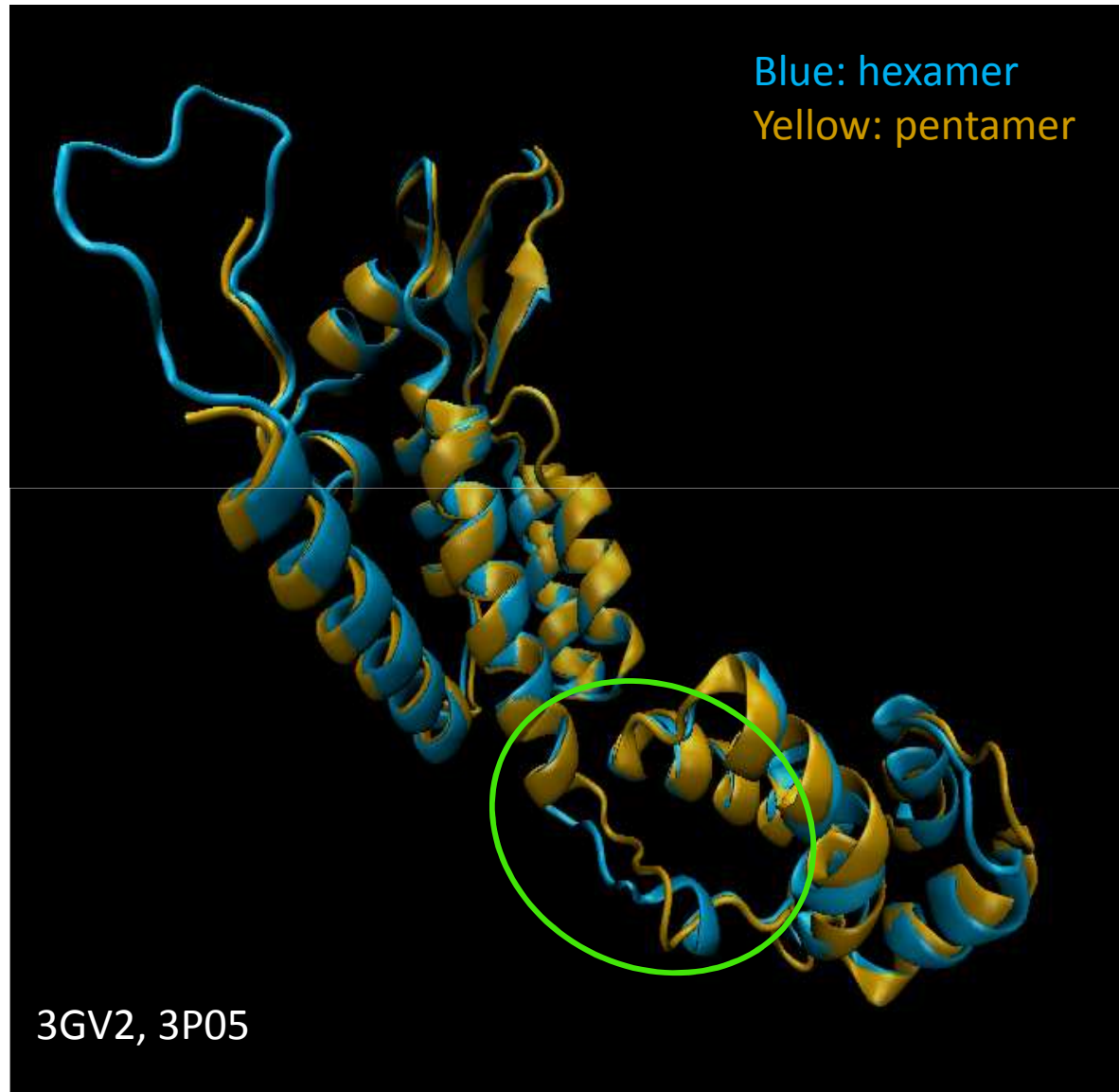


POLAR CONTACTS:

- Capping interactions

H-bonds interactions
are conserved

3.2. PENTAMERS



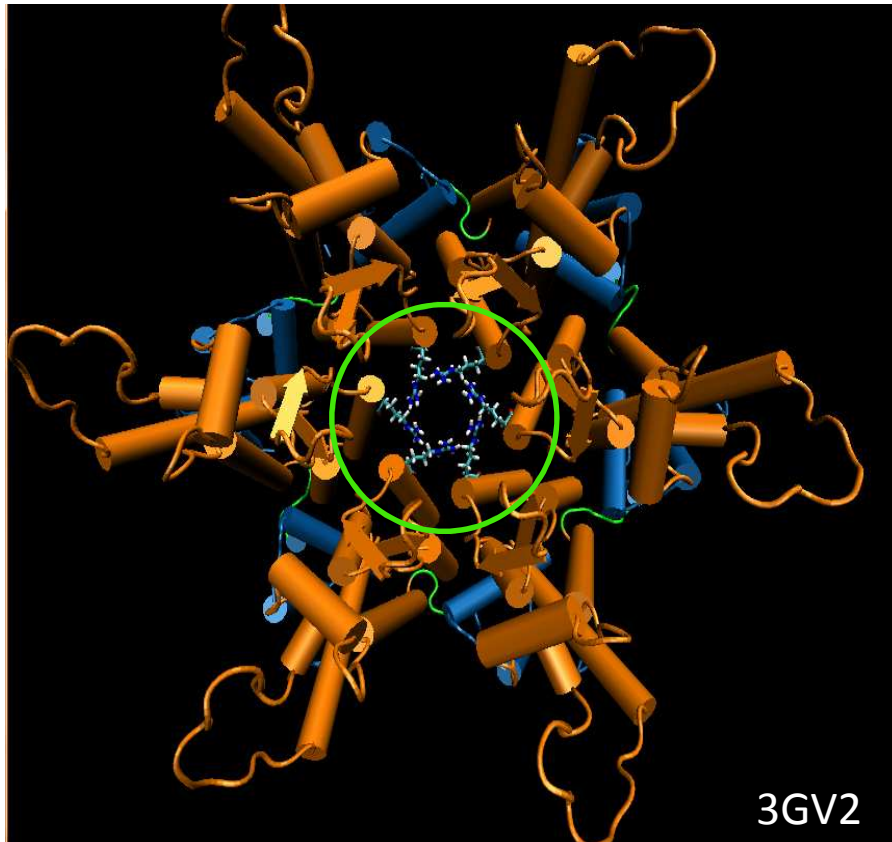
Flexible linker

STAMP Hexamer
and Pentamer

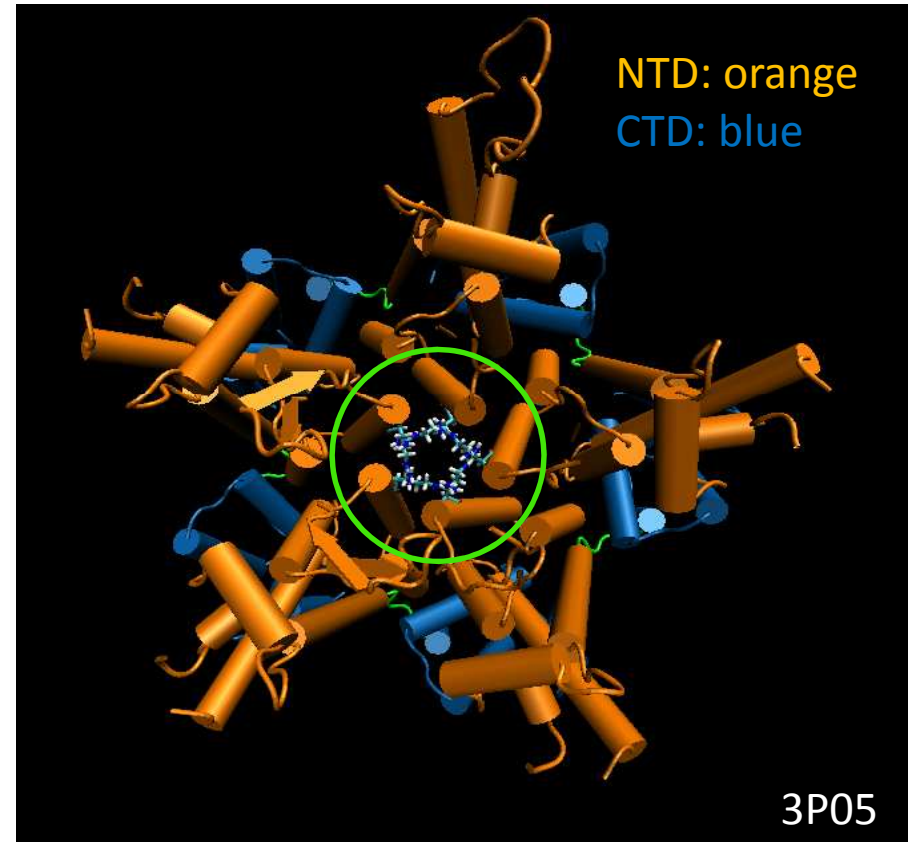
**Allows movement of the
CTD relative to the NTD**

3.2. PENTAMERS

ELECTROSTATIC SWITCH – Arg18

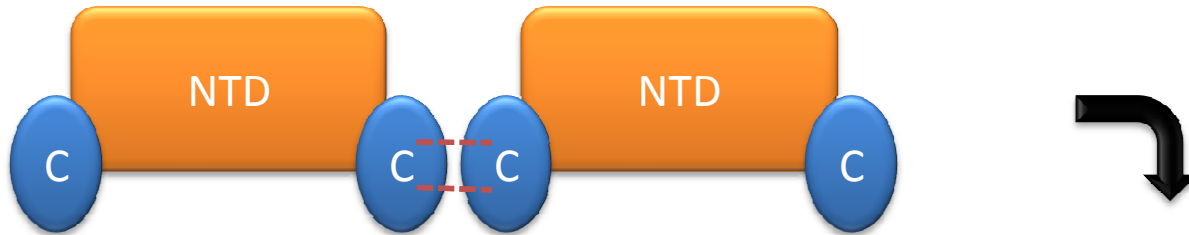


HEXAMER

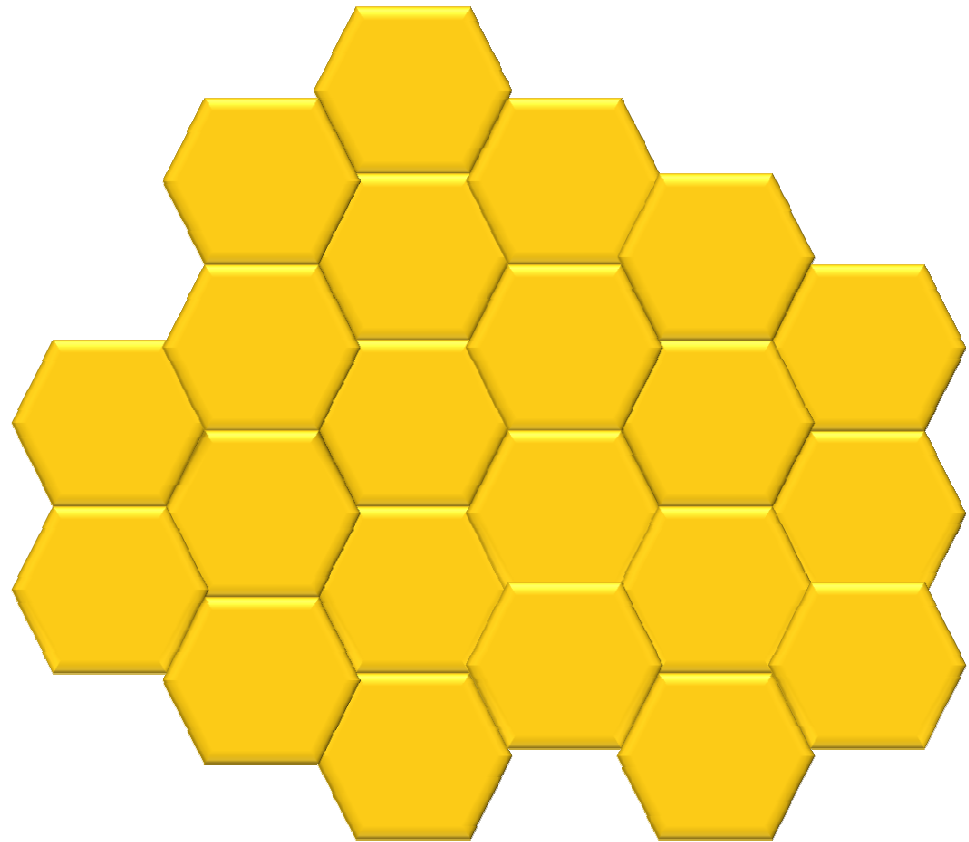


PENTAMER

4. CAPSID CURVATURE

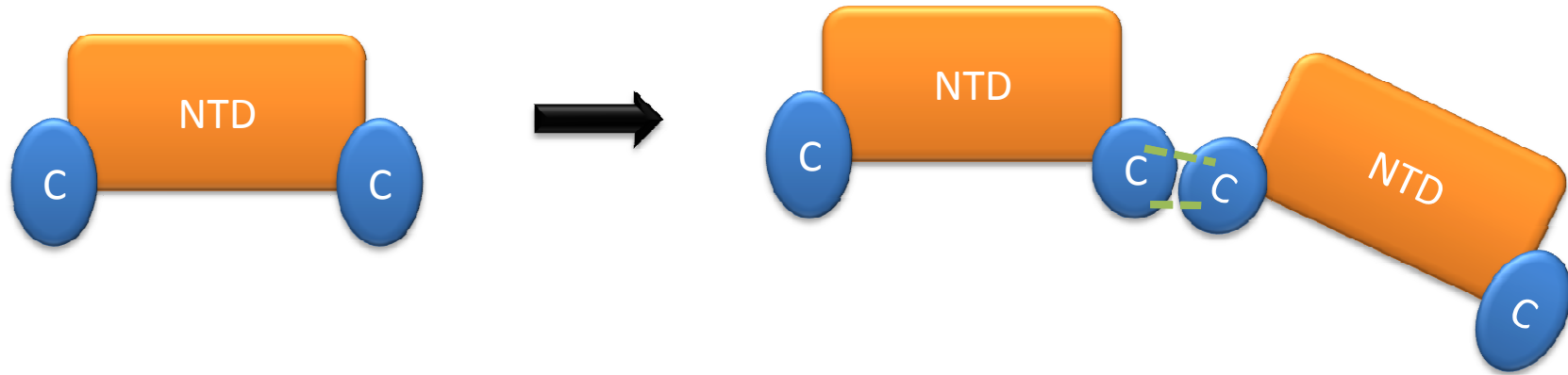


BUT, HOW A
LATTICE OF
HEXAMERS
CAN FORM
A CONICAL
SHAPE?

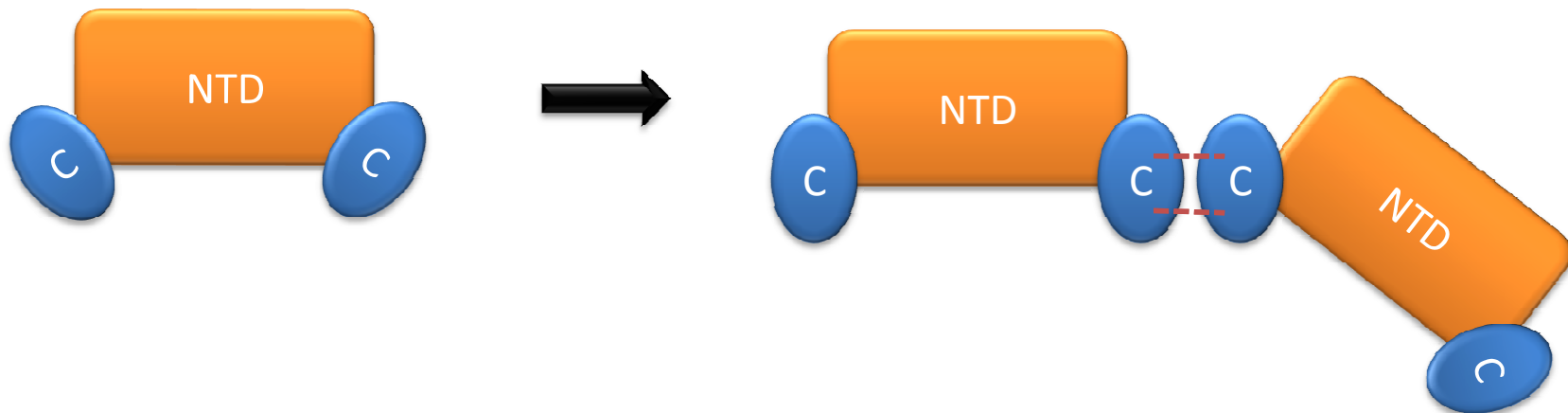


4. CAPSID CURVATURE

1. CTD flexibility

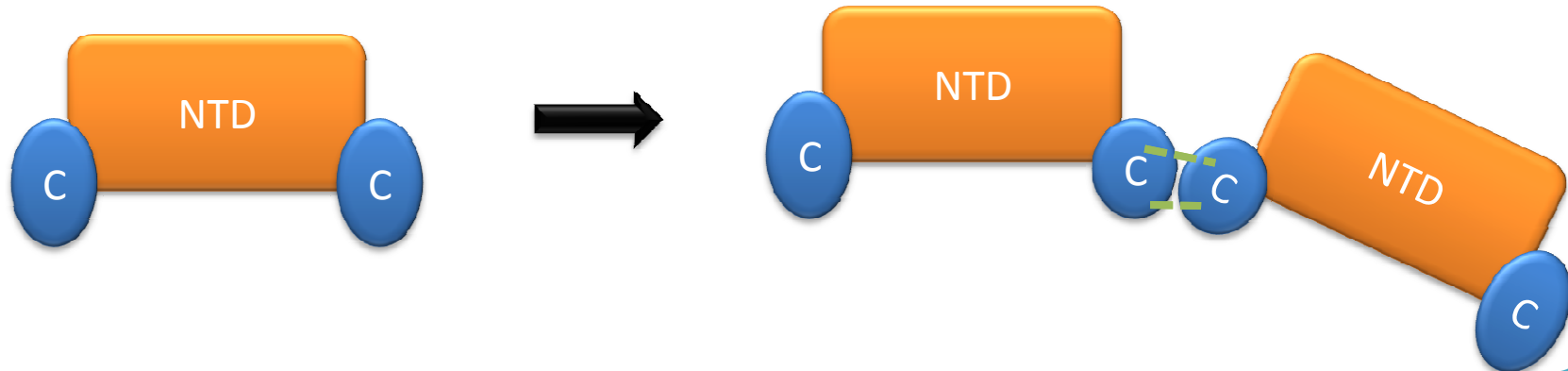


2. Rigid-body motions

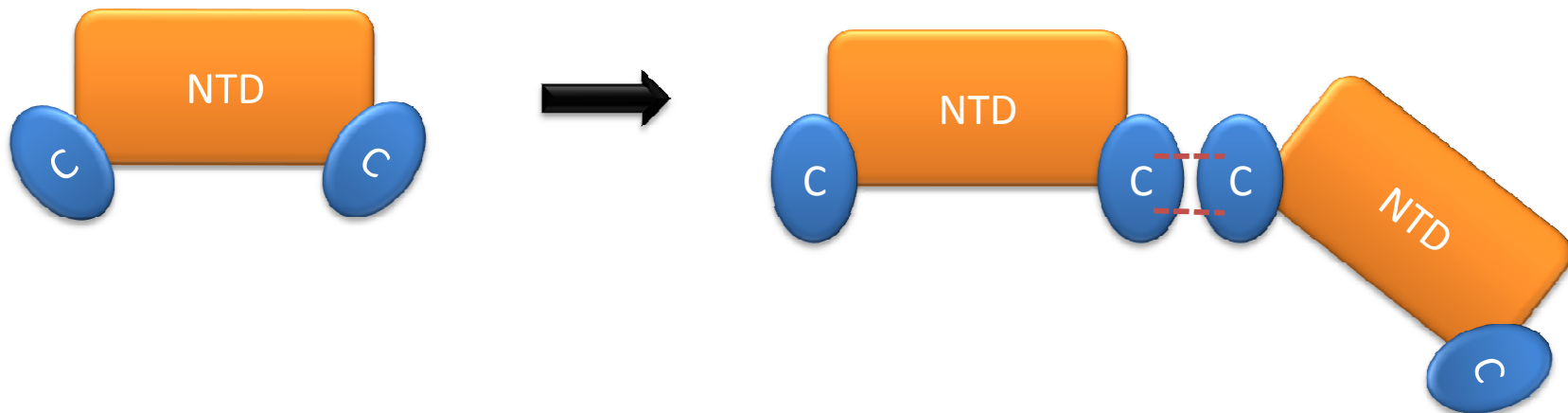


4. CAPSID CURVATURE

1. CTD flexibility

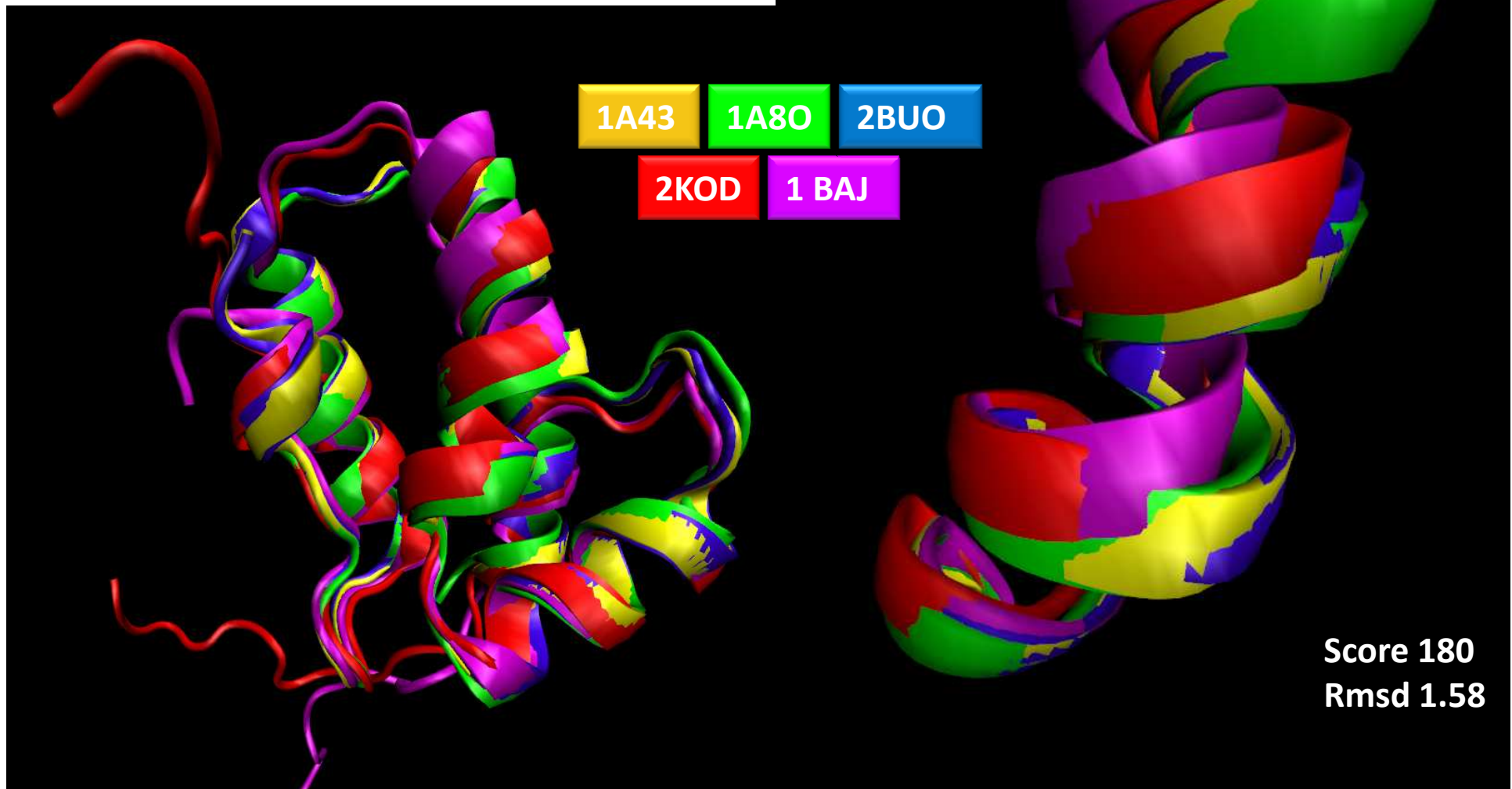


2. Rigid-body motions



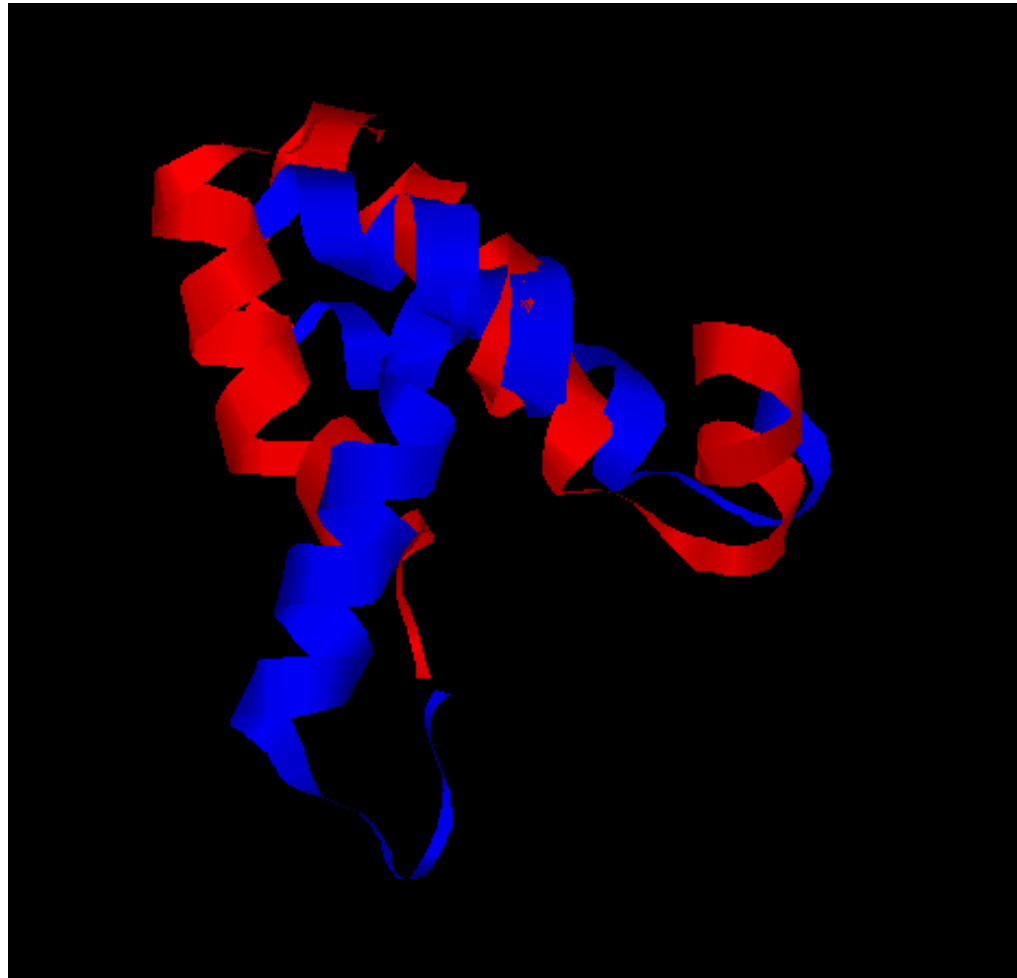
4.1. CTD FLEXIBILITY

There are variations between the available structures of the dimerization domain at tertiary level



4.1. CTD FLEXIBILITY

There are also variations between the structure at quaternary level

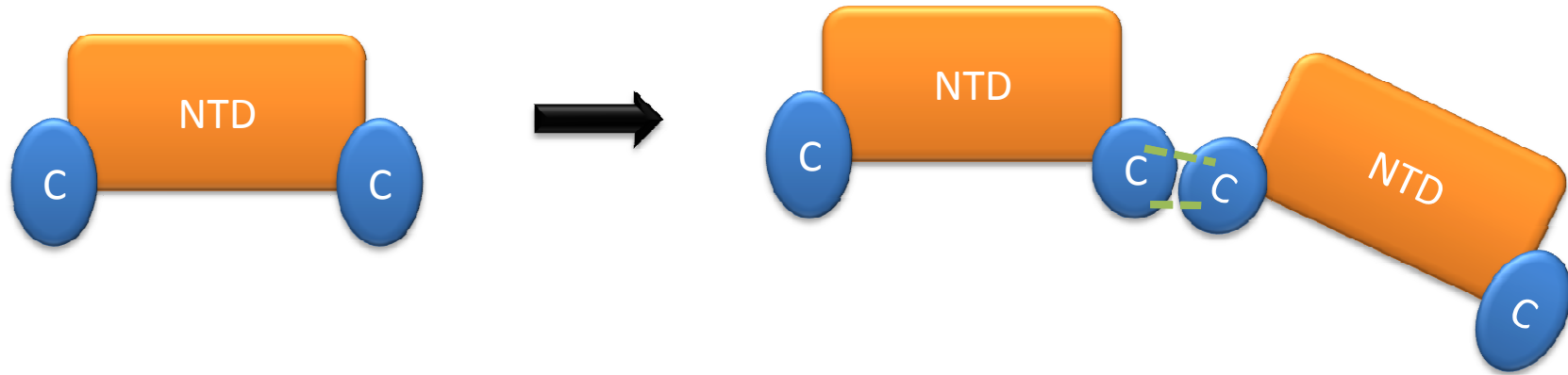


1A43

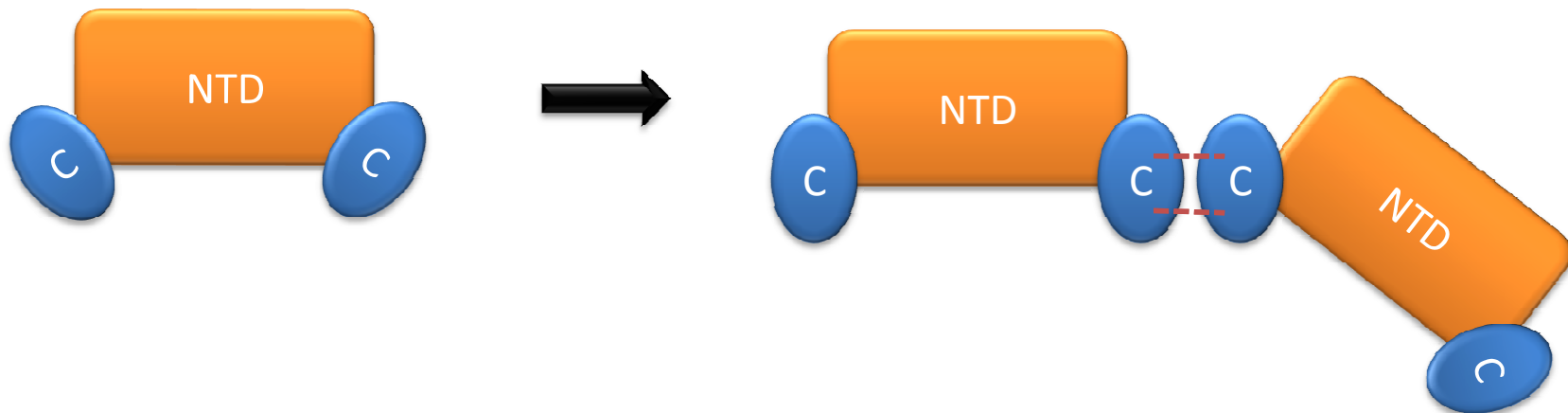
2KOD

4. CAPSID CURVATURE

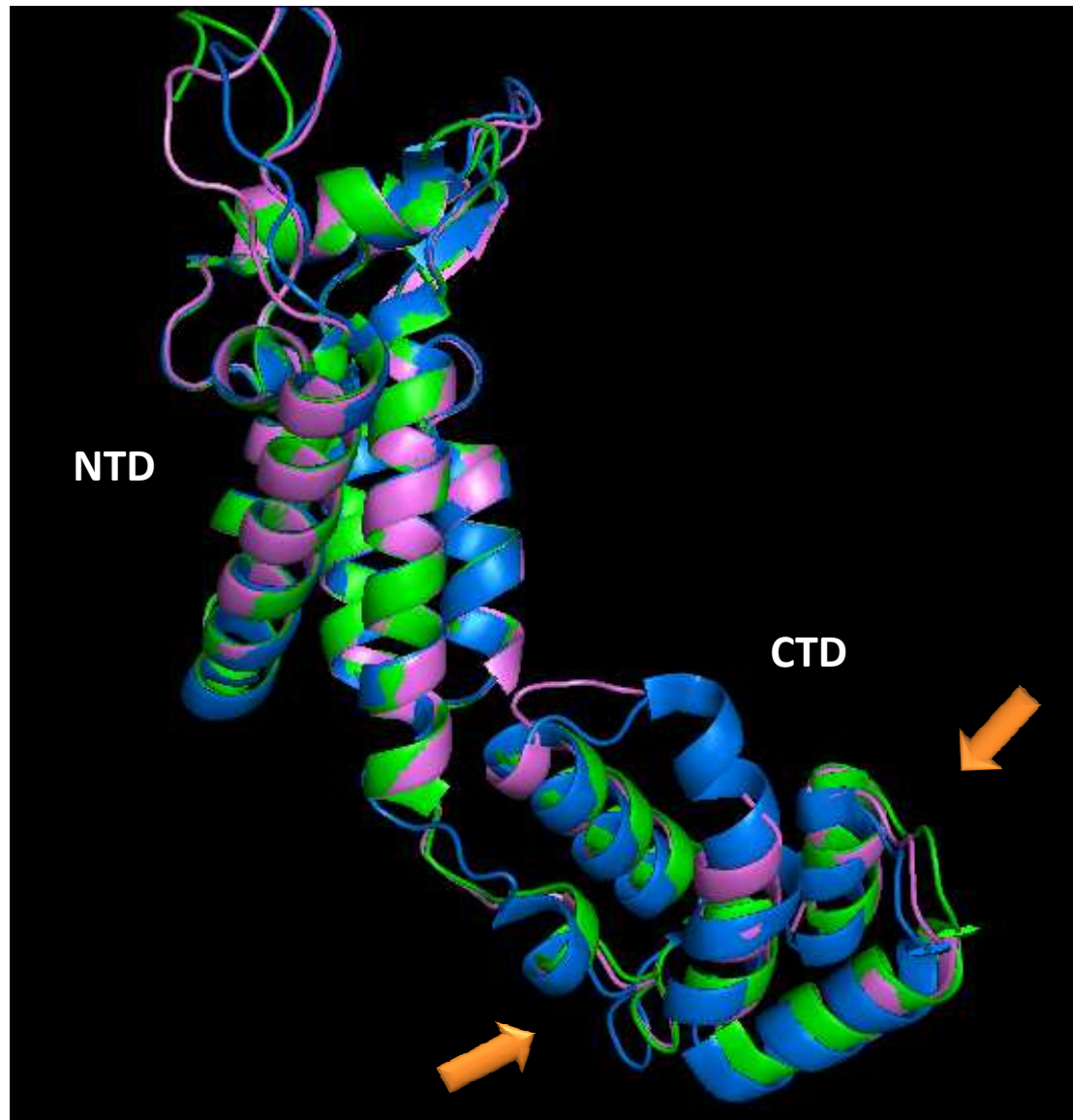
1. CTD flexibility



2. Rigid-body motions

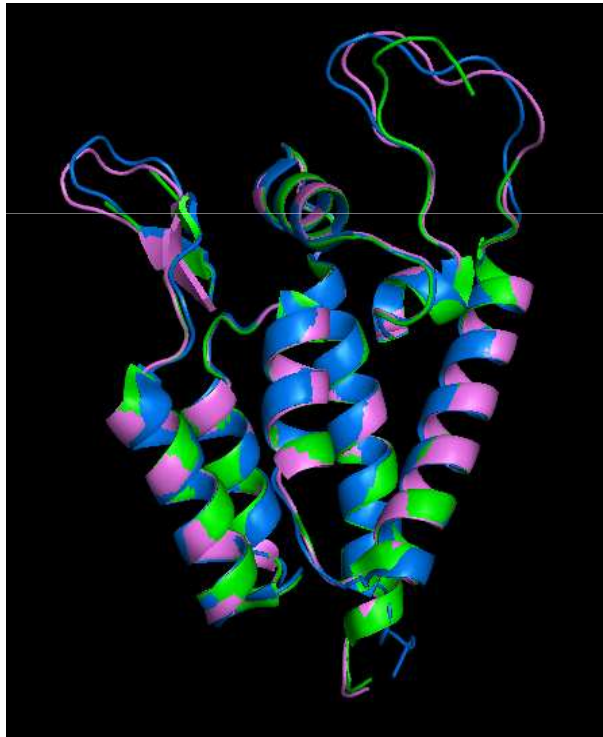


4.2. RIGID-BODY MOTIONS



STAMP
3 Hexamers

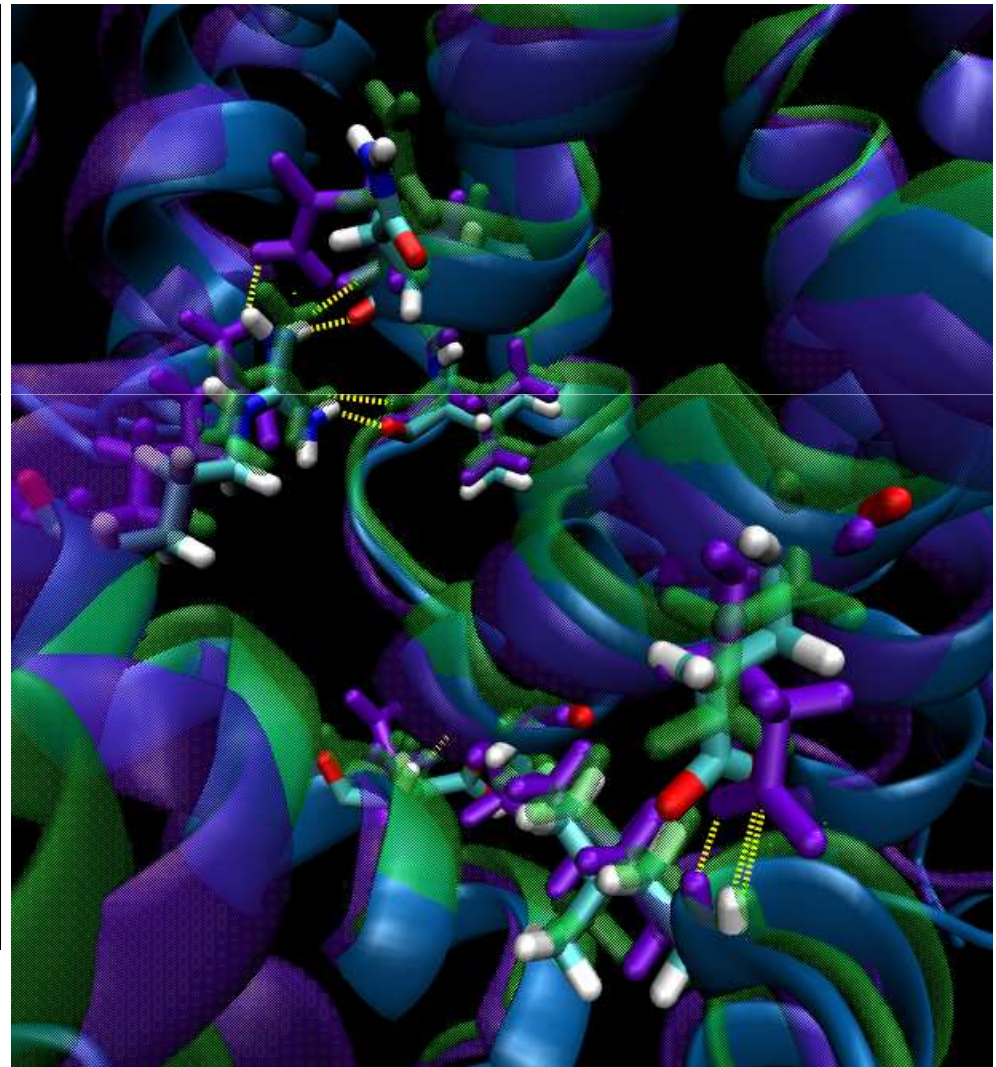
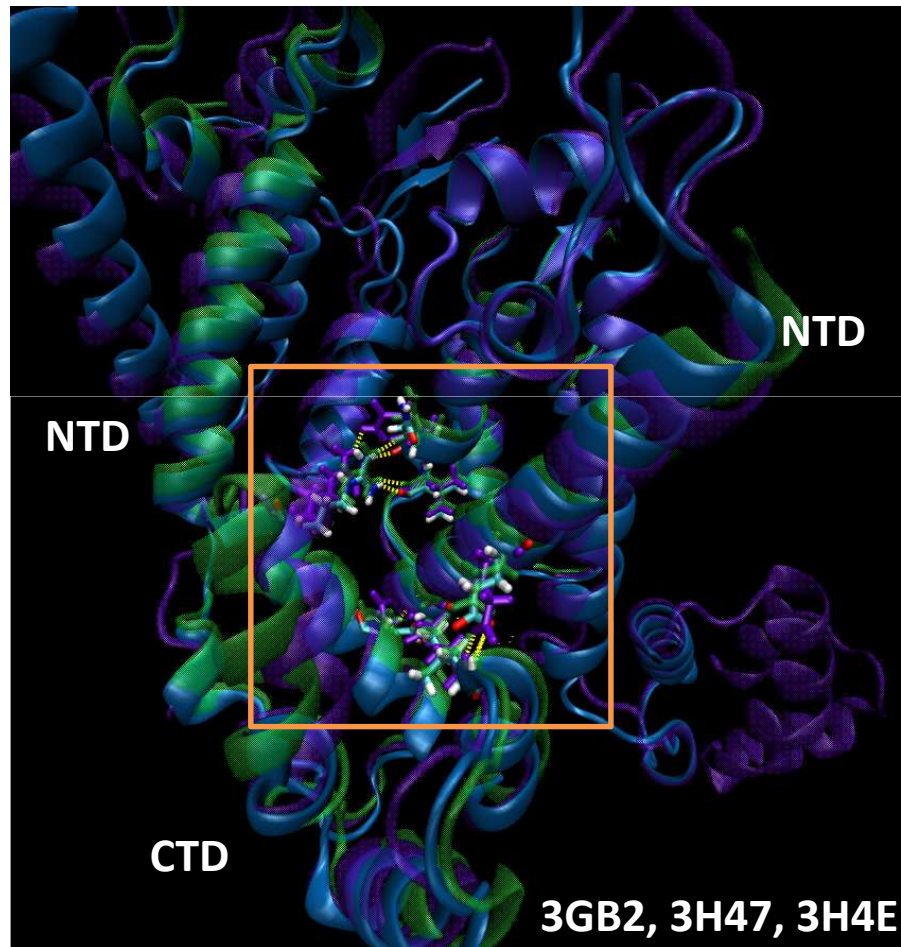
Pdb 3h47
Pdb 3GV2
Pdb 3H4E



- NTD
 - Helix 1, 2, 3, 4
 - Cyp binding loop
 - Helix 5, 6
- **Pdb 3h47**: resolution: 1,90 Å
- **Pdb 3GV2**: resolution 7 Å (some variability)
- **Pdb 3H4E**: resolutin: 2,70 Å

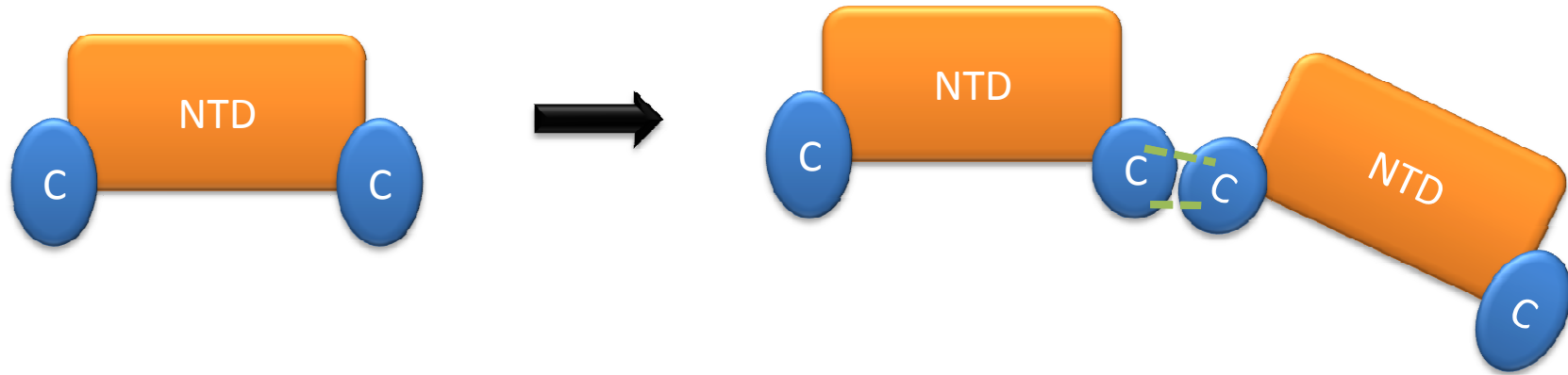
4.2. RIGID-BODY MOTIONS

STAMP 3Hexamer

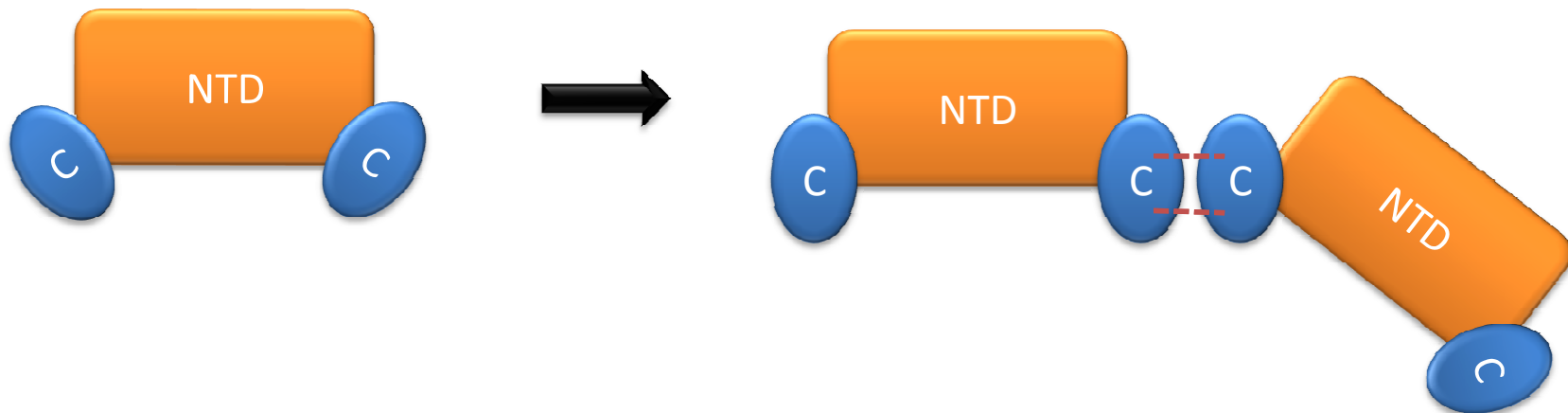


4. CAPSID CURVATURE

1. CTD flexibility



2. Rigid-body motions



Index

- Introduction
- CA (monomer)
 - NTD
 - CTD
- Capsid subunits
 - Hexamers
 - Pentamers
- Capsid curvature
- Current situation

5. Current situation

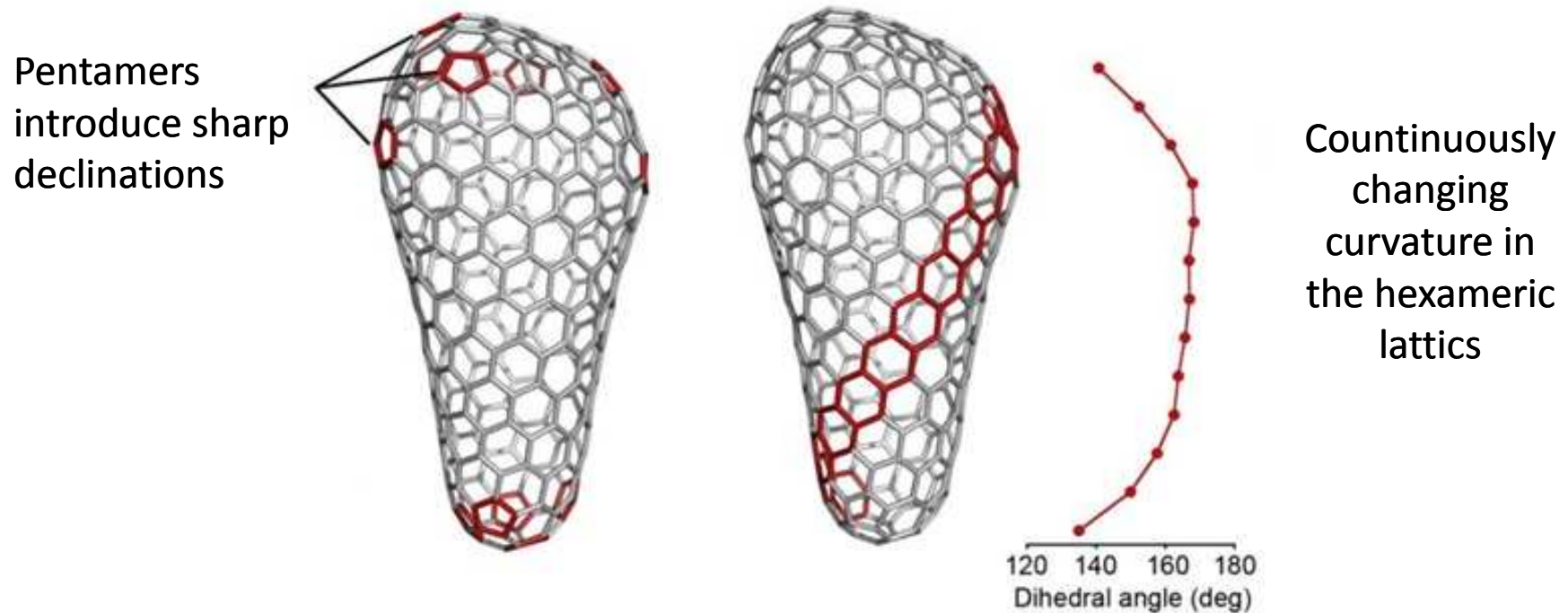


Figure from: Pornillos et al, 2011

5. Current situation

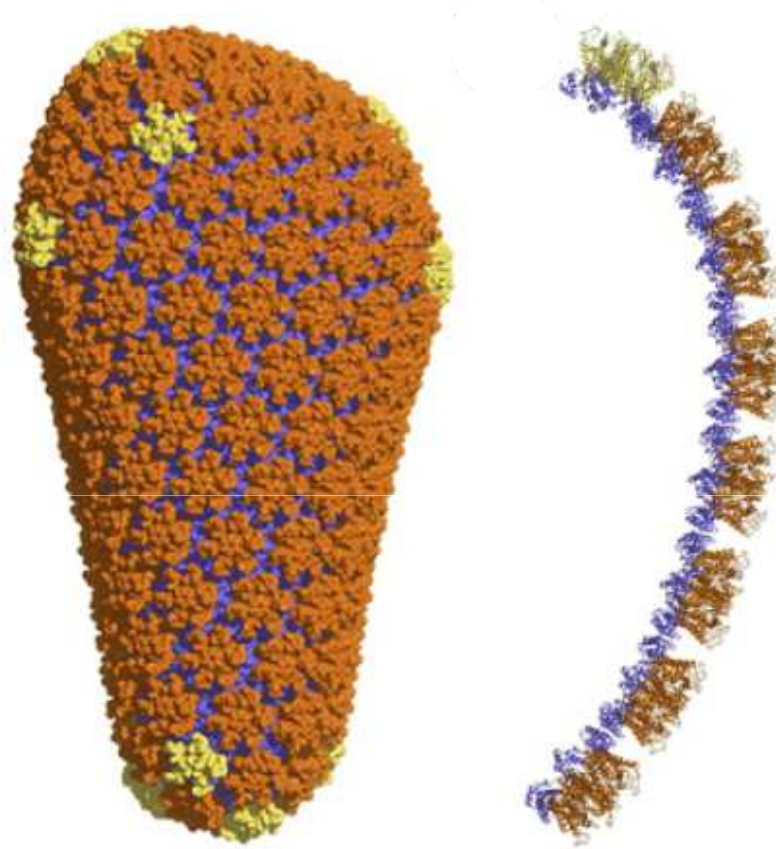
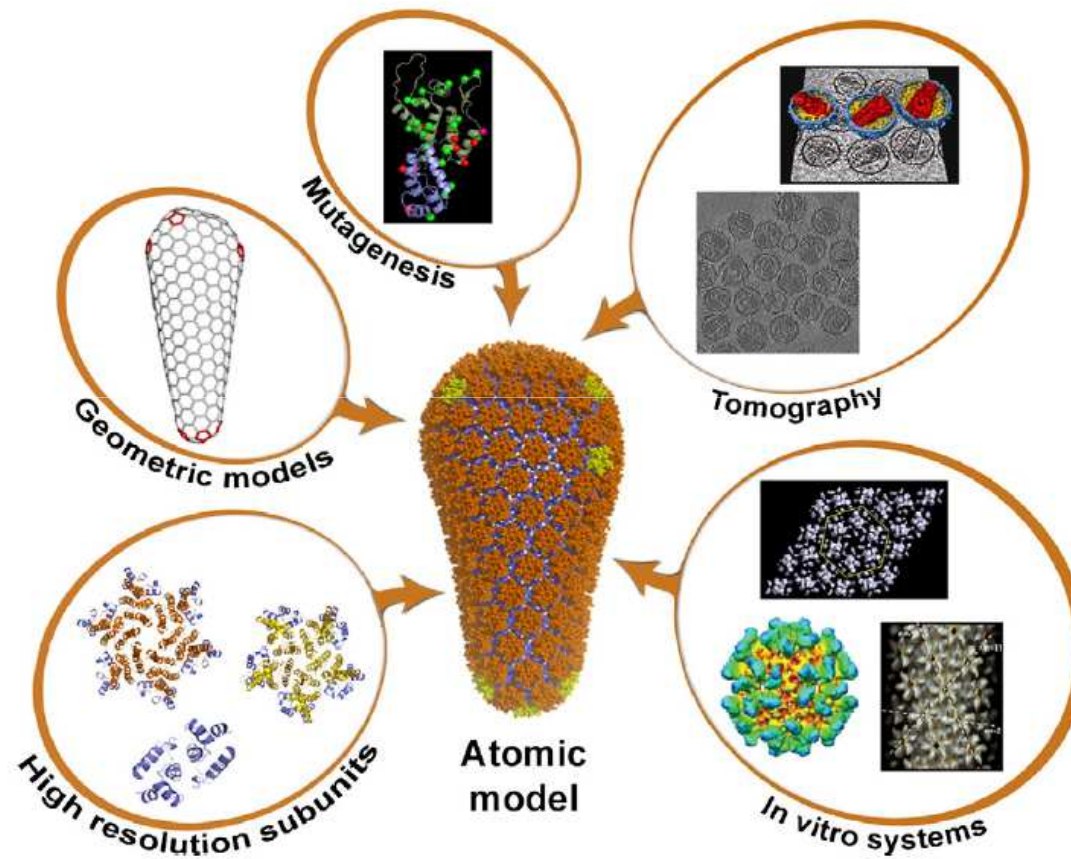


Figure from: Pornillos et al, 2011

Capsid – model



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**THANK YOU FOR YOUR
ATTENTION!**

