Structure of the HIV-1 Capsid Assembly by a hybrid approach

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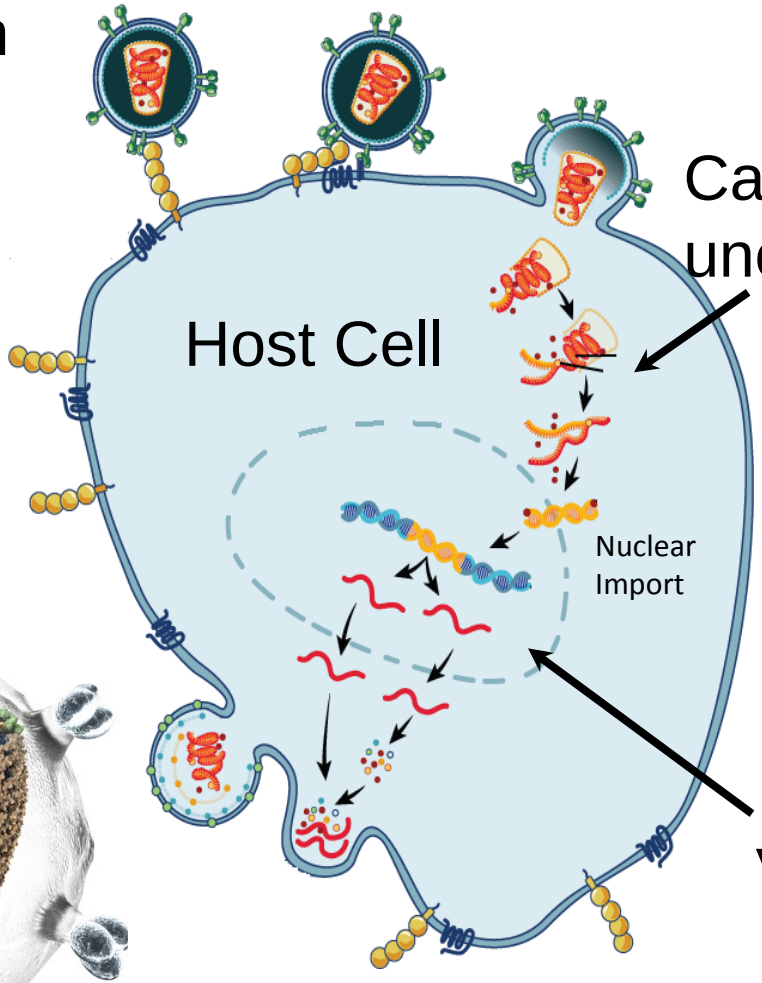
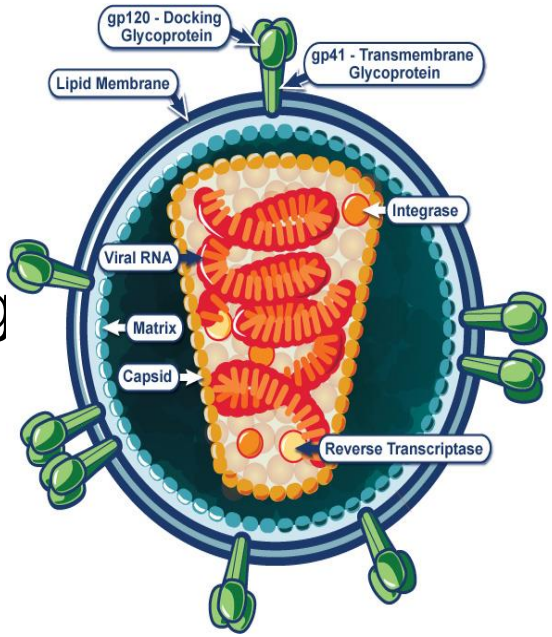
HIV infective cycle

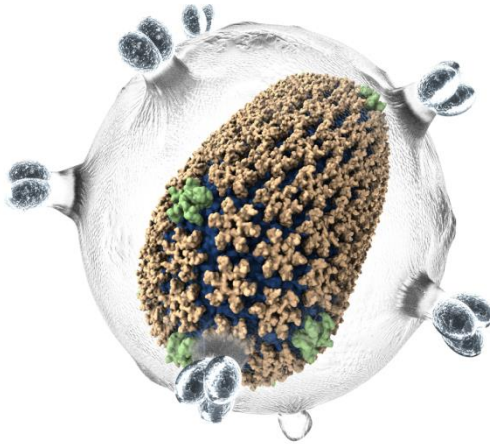
Virion



Capsid uncoating



Capsid restriction results in abortive infection

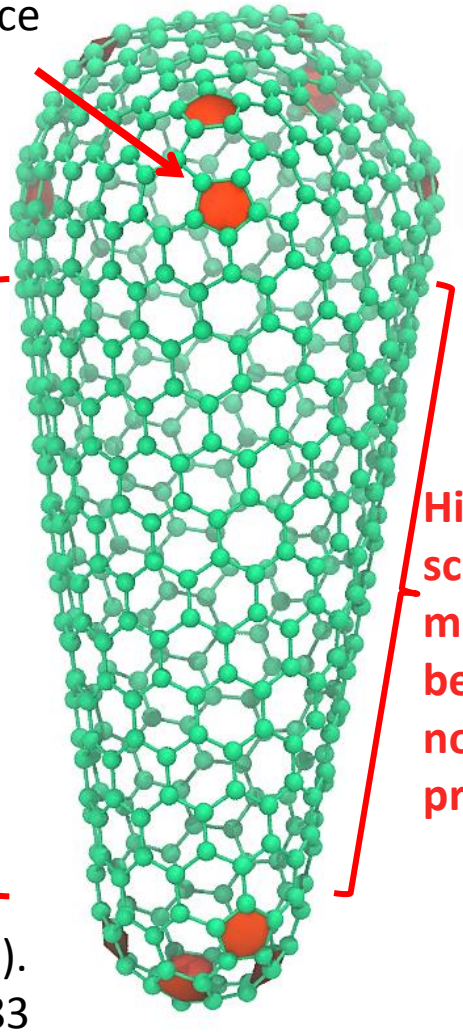


Viral DNA is integrated into host genome

Nature **497** (7451), 643-646

Structure of the HIV capsid

Pentamers introduce sharp declinations

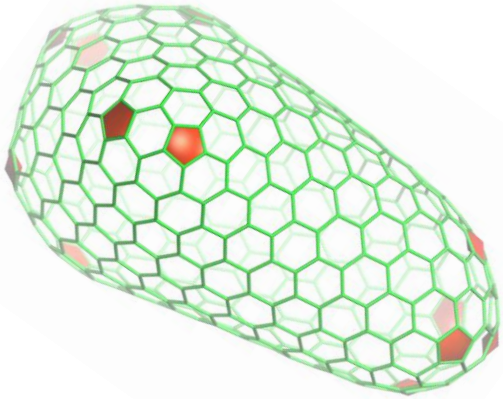


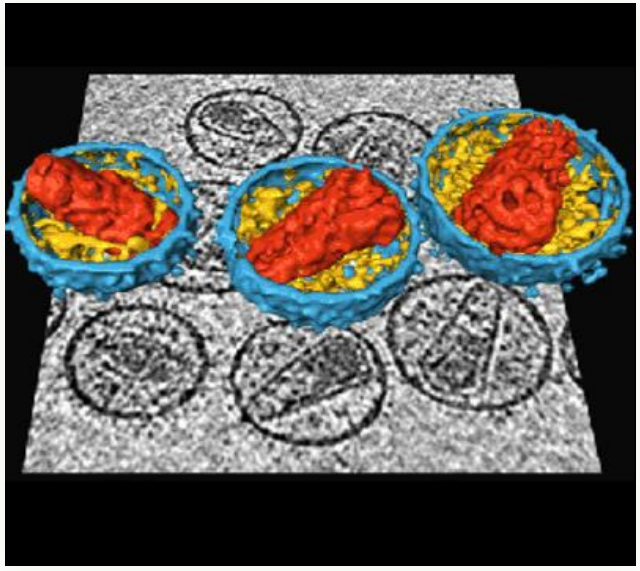
Continuously changing curvature in the hexagonal lattice

Highly schematic model; beads are not proteins!

Ganser, B. K. (1999). *Science*, *283*, 80–83

Capped fullerene cone



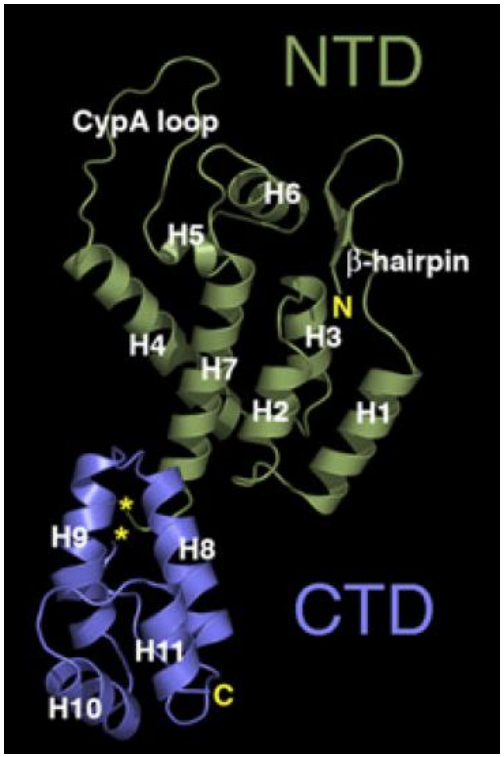


Briggs, J. et al. (2006). *Structure*, *14*, 15–20

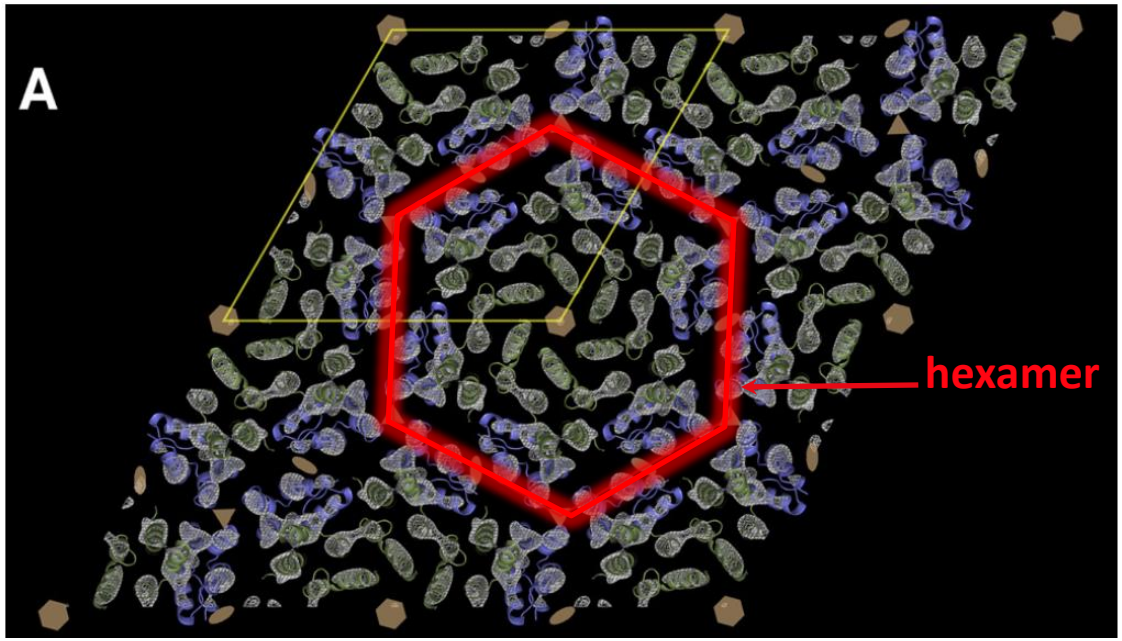
Structure of Full Length CA
NTDs and CTDs play different roles

hexameric center trimeric center

NTD = N-terminal domain There are also dimeric symetry centers!



CTD = C-terminal domain



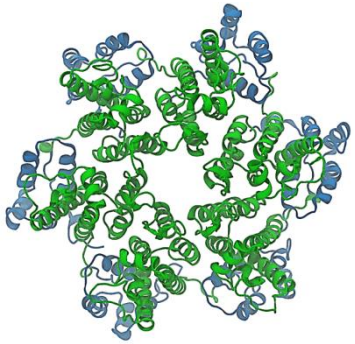
CA-hexameric **planar** lattice in crystal

NTD fills inside space of hexamers, CTD fills outside.

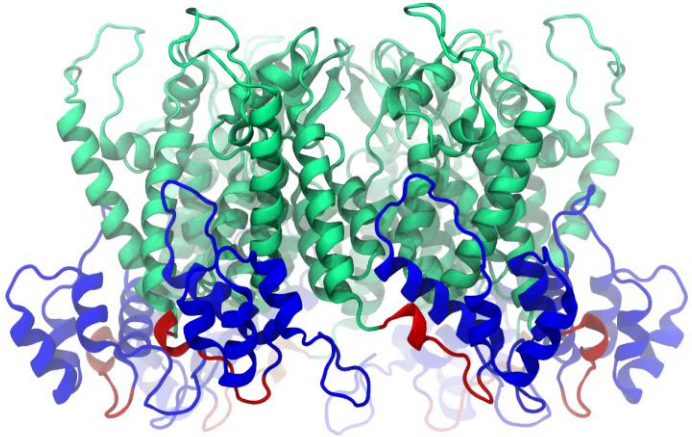
Ganser-Pornillos, B. K. et al. (2007). *Cell*, *131*(1), 70–9.

Structure of Full Length CA
NTDs and CTDs play different roles

C-terminal domain

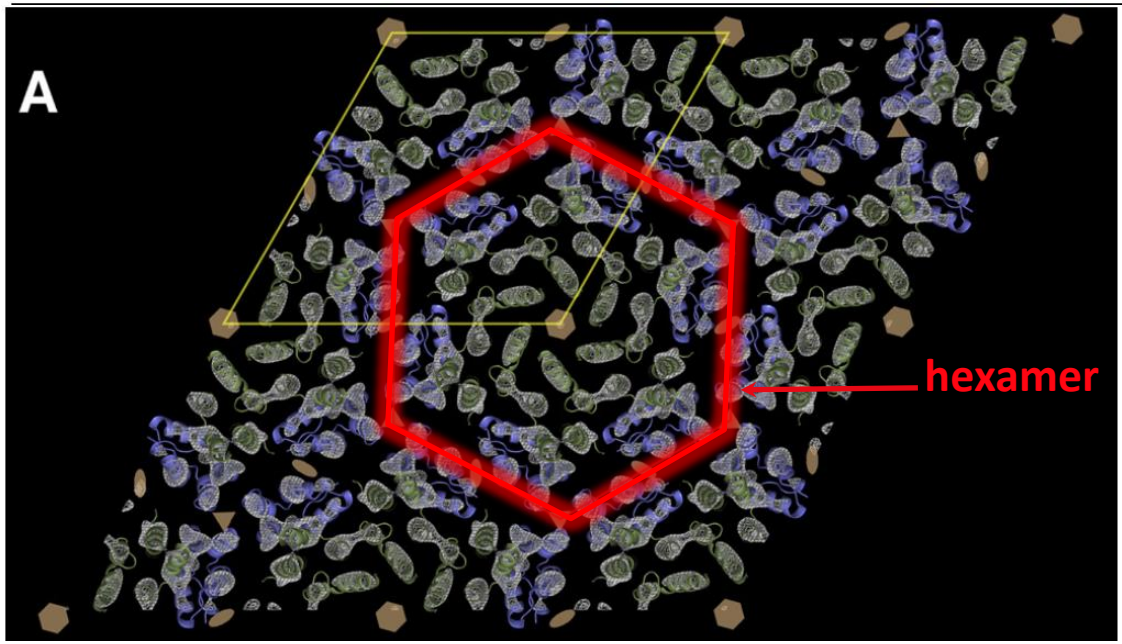


N-terminal domain



hexameric center trimeric center

There are also dimeric symmetry centers!



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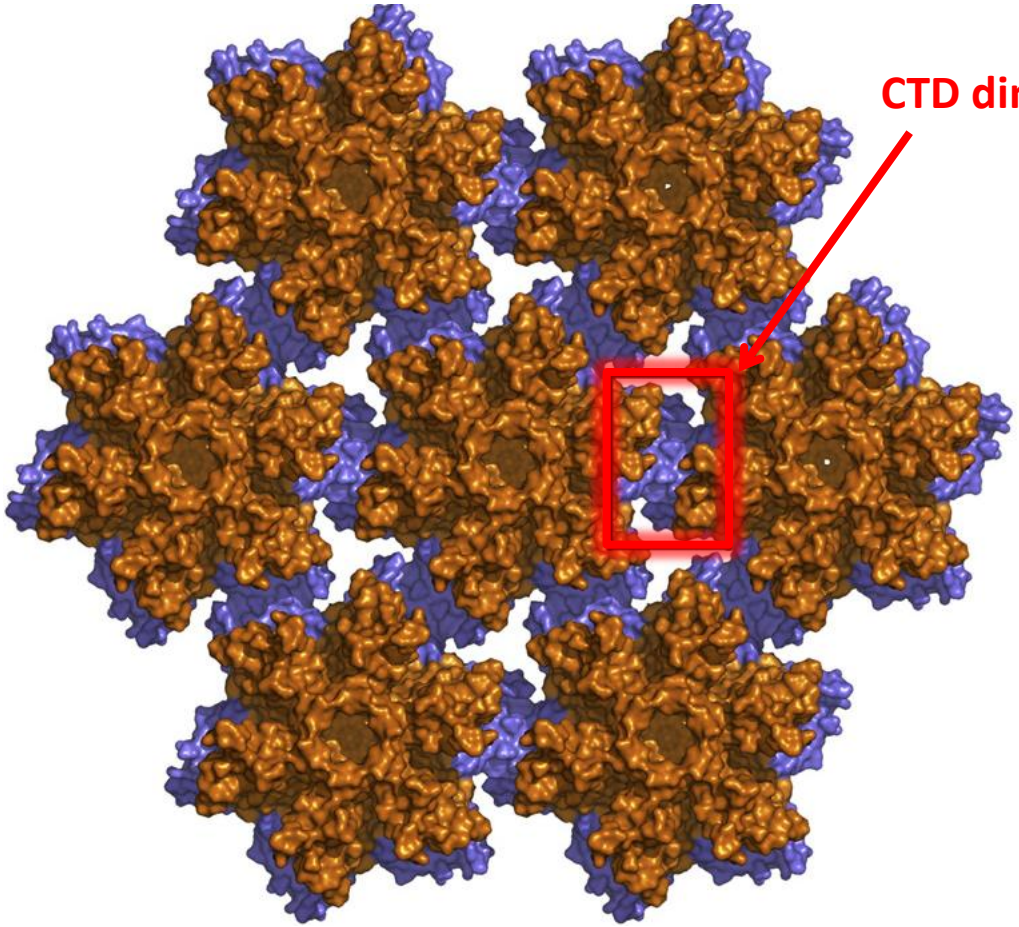
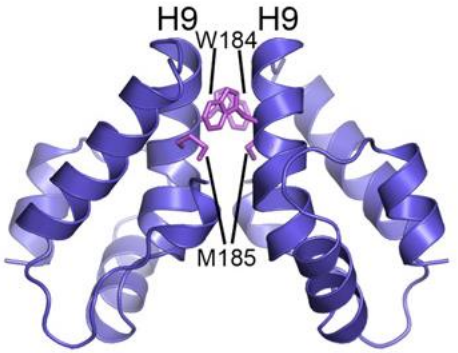
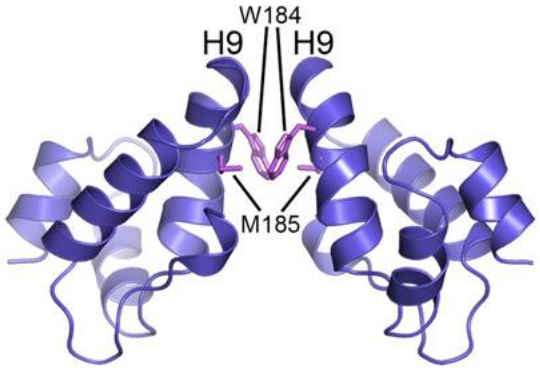
NMR structures for the CTD dimers



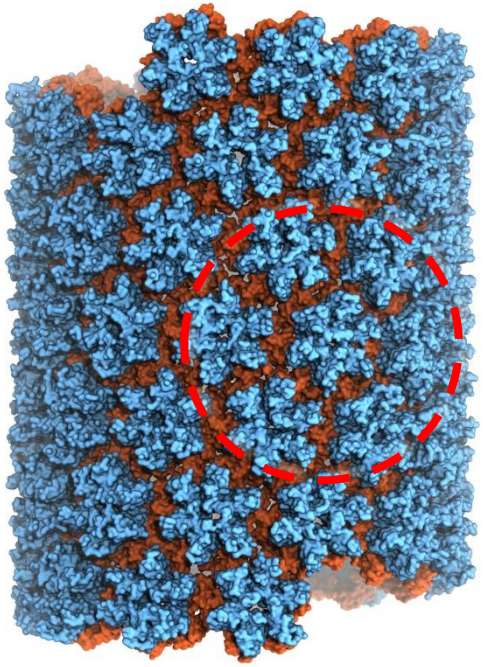


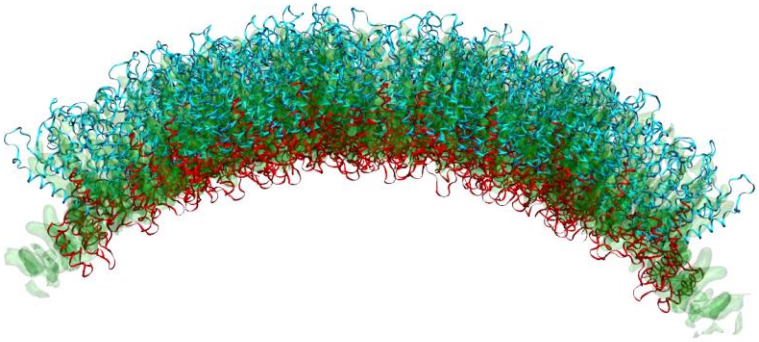


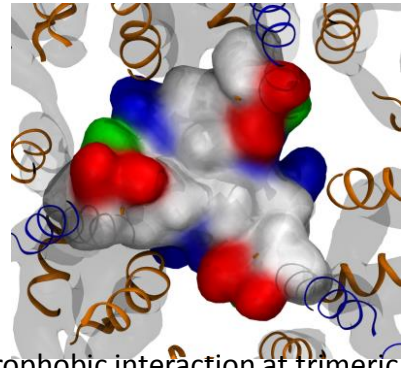
Helix 9s form angle

Byeon, I.-J., Gronenborn, et al. (2009). *Cell*, *139*(4), 780–790.

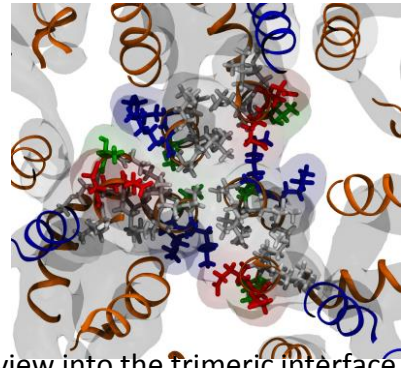
MDFF Structural Refinement



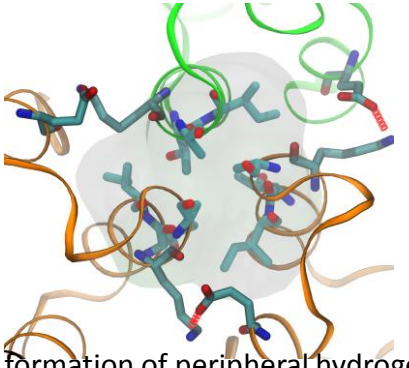




hydrophobic interaction at trimeric interface, surr. by polar residues

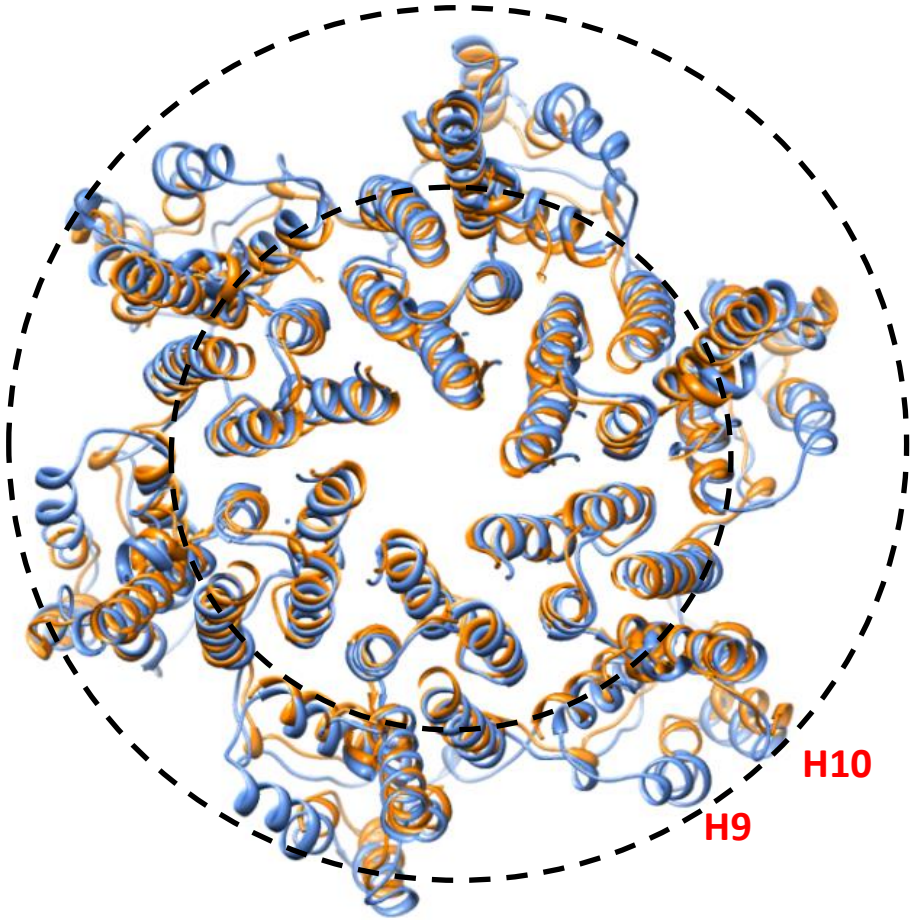


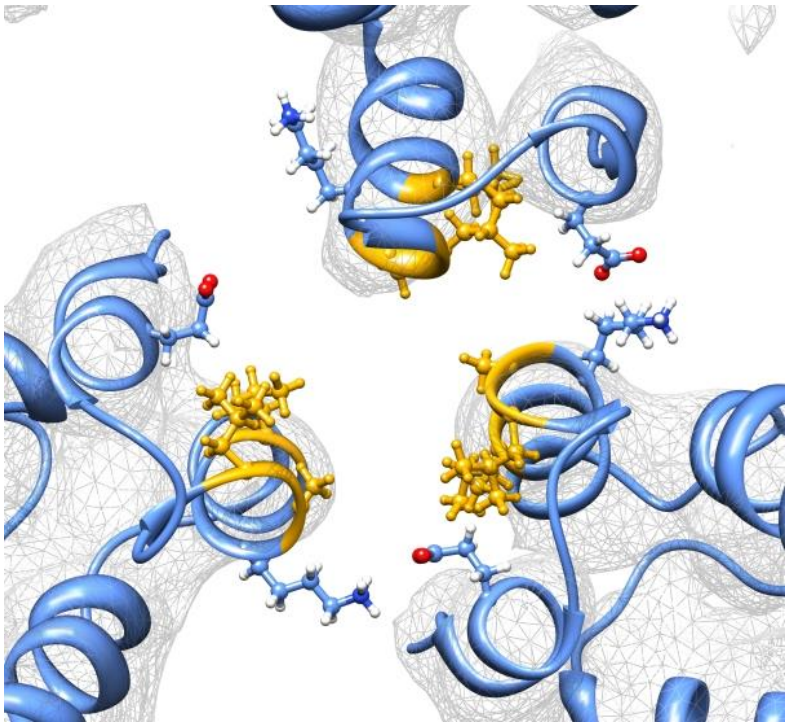
a view into the trimeric interface, contacts between three helices_10



formation of peripheral hydrogen bonds

MDFF reveals a different hexameric conformation and a novel trimeric interface





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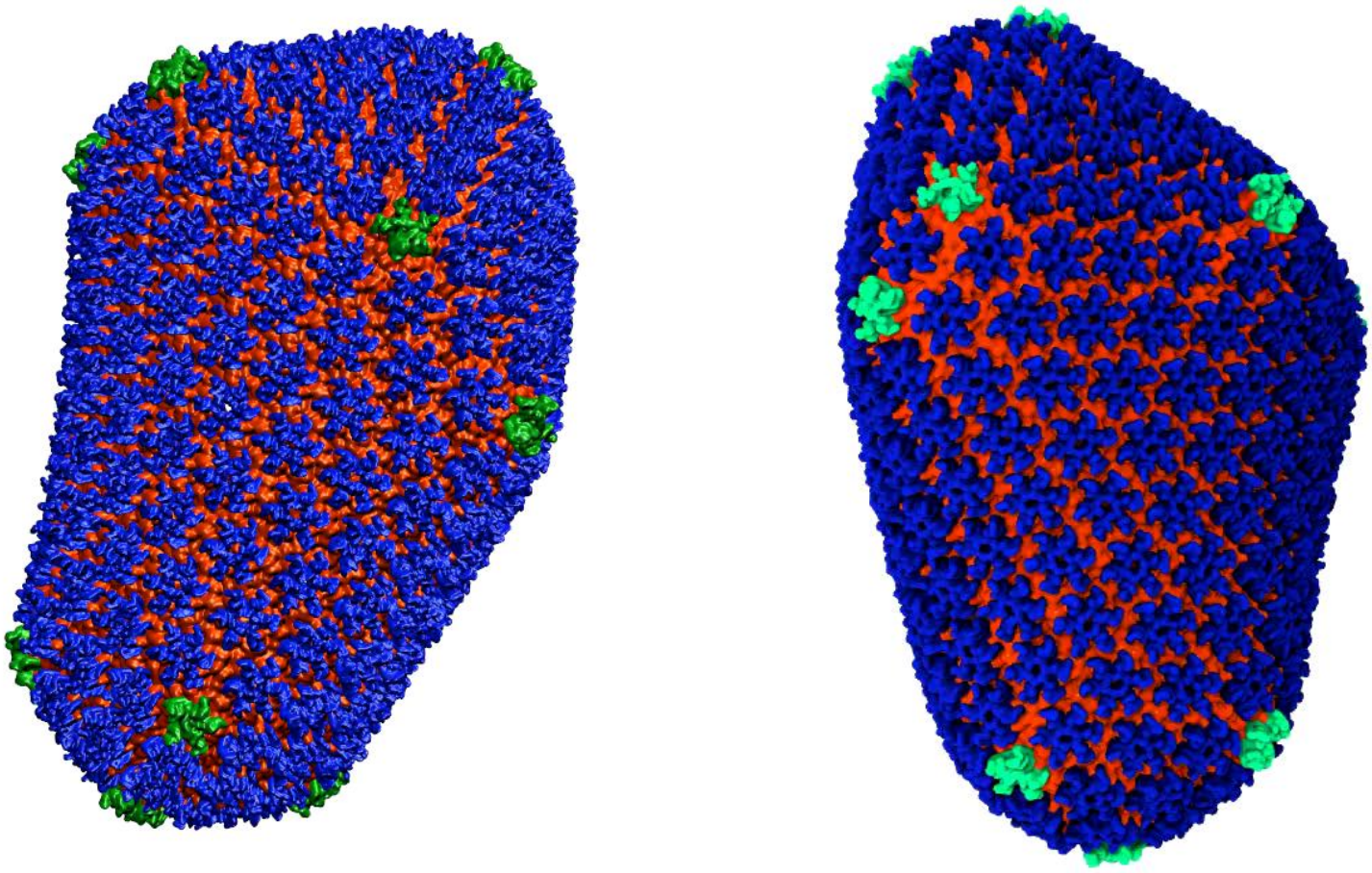
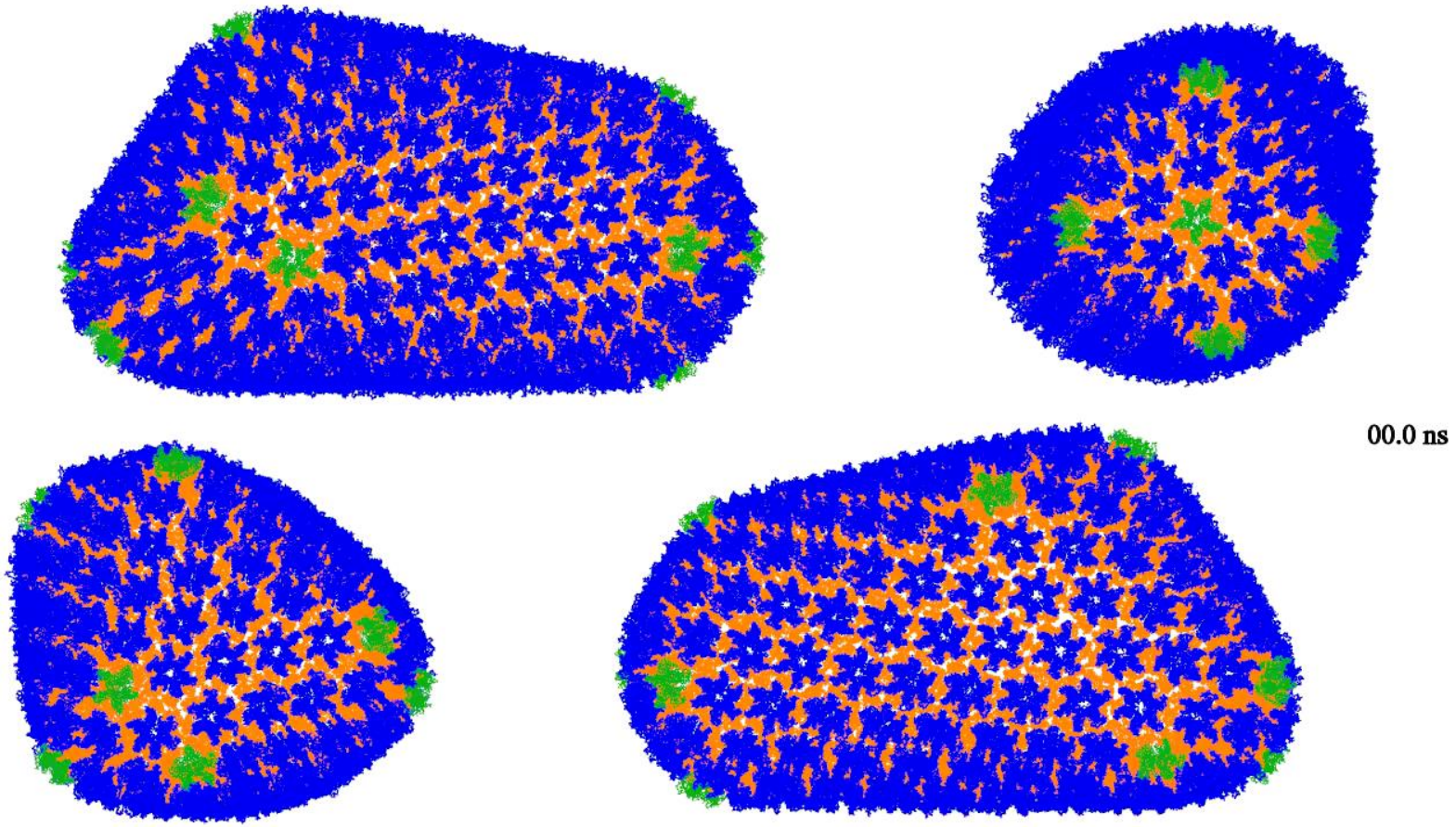
All-atom MD simulation of mature HIV-1 capsid



- **216 hexamers +12 pentamers (13.4 M),**
- **64 million atoms total including solvent**
- **100 ns running NAMD on 4000 Cray-XE nodes, 128000 cores**
- **6 ns/day**

BLUE WATERS
SUSTAINED PETASCALE COMPUTING

All-atom MD simulation of mature HIV-1 capsid



- **186 hexamers +12 pentamers (12 M),**
- **64 million atoms total**
- **500 ns running *NAMD* on NCSA Blue Waters**
  2000 to 3500 XK Nodes equipped with NVIDIA Tesla K20X
- **9 to 14 ns/day**

BLUE WATERS
SUSTAINED PETASCALE COMPUTING

Solvation of large systems

Avoid GUI altogether. Scripts offer more control over the modeling process.
Use JS file format. Available in all version of **psfgen** and **developmental versions of VMD**.

- **PROBLEM**:
  - Solvate GUI/script performs several atom selections that result in poor performance for large systems. Solvating a large structure can take **days**.

```
# Create an empty water box of 100nm x 100nm x 100nm
solvate -o solvent.js -minmax {{0 0 0} {1000 1000 1000}}

# Load solute and solvent and save as a single js file with clashes.
package require psfgen
readjs solute.js
readjs solvent.js
writejs clashes.js

# Save non clashing atoms
mol new clashes.js
set good [atomselect top  "not same residue as within 2.4 of not segname \”W.*\”"]

$good writejs final.js
$good writenamdbin final.coor
```

Ionization of large systems

Autoionize does NOT handle large structures properly.
Limited to one segment (9999 atoms).
Also a problem for high ionic concentrations in medium sized systems.
Default parameters for ions are CHARMM22 unless manually changed.

```
# Get water segments
set water [atomselect top "water"]
set segments [lsort -unique [$water get segnames]]

# Loop over water segments and ionize each segment independetly
foreach watseg $segments {
    #Select current water segment
    set atomsel [atomselect top "segname ${watseg}]
    #Write segment as a pdb
    $atomsel writepdb water/${watseg}.pdb
    #Create a psf for water segment
    segment ${watseg} {
      auto none
      pdb watert/${watseg}.pdb
    }  ; coordpdb water/${watseg}.pdb $watseg
   writepdb water/${watseg}.pdb
   writepsf watert/${watseg}.psf
```

Ionization of large systems

```
# Get new segment name for ionized water box

    set number [string trimleft ${watseg} W]
    set segment I${watseg}

# Ionize each water segment

    autoionize -psf water/${watseg}.psf  -pdb water/${watseg}.pdb -sc $sc
                -o ions/$segment -seg  $segment
}
# Load solute and ionized water box
resetpsf
readjs solute.js
foreach watseg $segments {
    set number [string trimleft ${watseg} W]
    set segment I${watseg}
    readpsf ions/$segment
    coordpdb ions/$segment
}
writejs ionized.js
writenamdbin ionized.coor
```

IMPORTANT: Make sure the system is neutralized, add more ions if necessary.

Special considerations for simulations of large systems

- Use the new minimizer. Older versions of NAMD require the use of velocity quenching.
- Make use of the multi-time stepping algorithm available in NAMD
  MTS 2-1-3 (2fs inner loop, 2 fs non-bonded, 6fs electrostatics)
  shake must be enabled.
- Set **PME** grid spacing to **2Å** and increase **interpolation order** to **8**.
- Make use of the **hybrid** load balancer
- Use the **memory optimized** version of NAMD.
  http://www.ks.uiuc.edu/Research/namd/wiki/?NamdMemoryReduction
  Different handling of fixed and restrained atoms.
  Supports TMD, TCL forces, and other features.
- Limit the number of I/O nodes. NAMD uses parallel I/O.
- If running in NPT, set the period of the barostat to a large value (e.g. ~ 15ps).
- Watch out for excluded volumes for the appearance of bubbles.