Class 10: Structural Bioinformatics (Pt 1)

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1. The PDB Database

The main repository of biomolecular structure data is called the Protein Data Bank (PDB for short). It is the second oldest database (after Genbank).

What is currently in the PDB? We can access the current composition stats here

```r
stats <- read.csv("Data Export Summary.csv", row.names=1)
stats
```

```
                          X.ray     EM    NMR Multiple.methods Neutron Other
Protein (only)          171,959 18,083 12,622              210      84    32
Protein/Oligosaccharide  10,018  2,968     34               10       2     0
Protein/NA                8,847  5,376    286                7       0     0
Nucleic acid (only)       2,947    185  1,535               14       3     1
Other                       170     10     33                0       0     0
Oligosaccharide (only)       11      0      6                1       0     4
                          Total
Protein (only)          202,990
Protein/Oligosaccharide  13,032
Protein/NA               14,516
Nucleic acid (only)       4,685
Other                       213
```

```
Oligosaccharide (only)       22
```

> Q1: What percentage of structures in the PDB are solved by X-Ray and Electron Microscopy.

```r
# Substitute commas for nothing then convert to numeric

y <- as.numeric(gsub(",", "", stats$X.ray))
sum(y)
```

```
[1] 193952
```

Turn this snippet into a function so I can use it any time I have this comma problem (i.e. the other columns of this `stats` table)

```r
comma.rm <- function(x) {
  remove_comma <- gsub(",", "", x)
  convert_numeric <- as.numeric(remove_comma)
  return(sum(convert_numeric))
}
```

```r
x.ray_sum <- comma.rm(stats$X.ray)
em_sum <- comma.rm(stats$EM)
total.sum <- comma.rm(stats$Total)
```

Percentage of structures solved by X-ray

```r
(x.ray_sum/total.sum)*100
```

```
[1] 82.37223
```

Percentage of structures solved by EM

```r
(em_sum/total.sum)*100
```

```
[1] 11.30648
```

> Q2: What proportion of structures in the PDB are protein?

```
protein_total <- comma.rm(stats["Protein (only)","Total"])
(protein_total/total.sum)*100
```

```
[1] 86.2107
```

> Q3: Type HIV in the PDB website search box on the home page and determine how many HIV-1 protease structures are in the current PDB?

1,149 structures of HIV-1 protease.

2. Visualizing with Mol-star

Explore the HIV-1 protease structure with PDB code: `1HSG` Mol-star homepage at: https://molstar.org/viewer/

> Q4: Water molecules normally have 3 atoms. Why do we see just one atom per water molecule in this structure?

Because the resolution of the camera is higher than the size of the hydrogen atoms, so the hydrogen atoms will not appear.

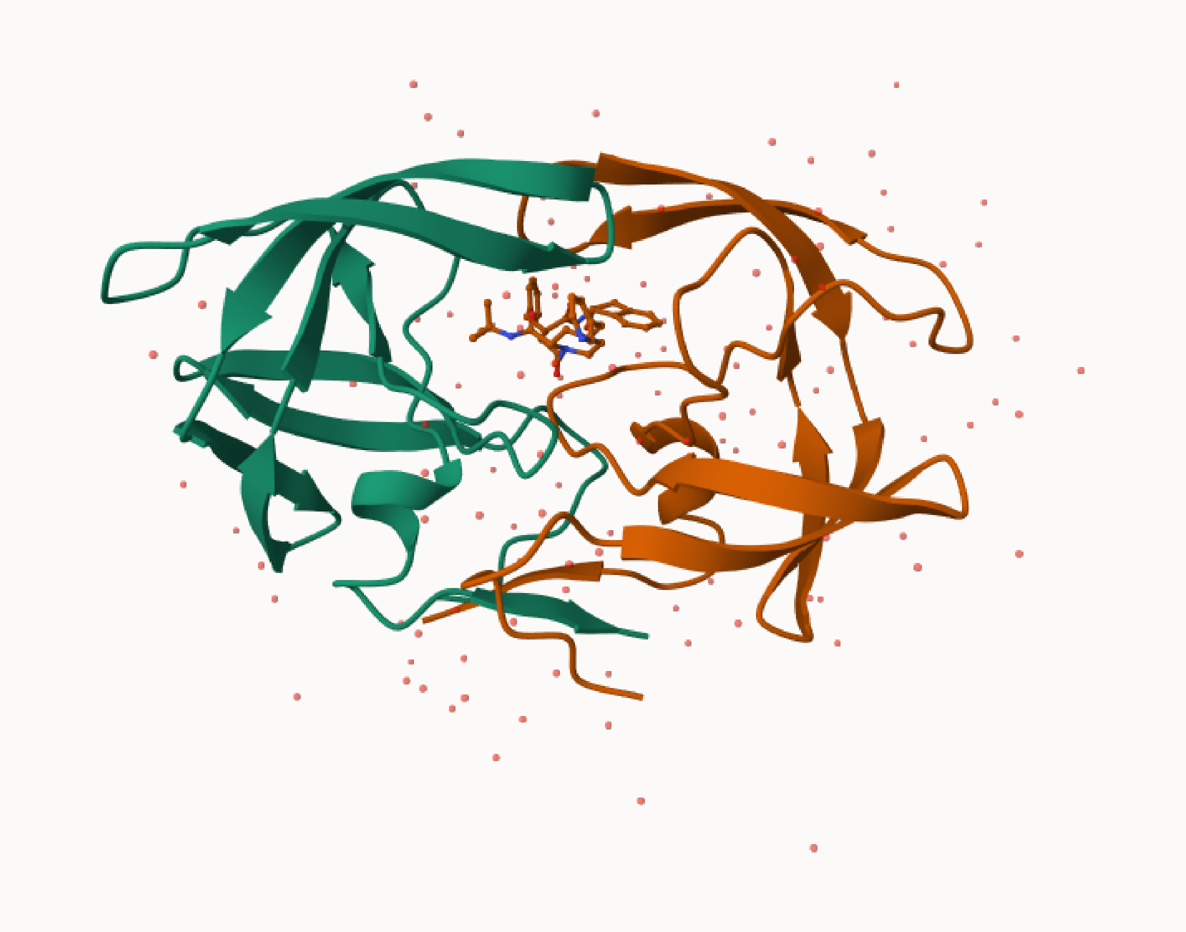


Figure 1: Figure 1. A first view of HIV-Pr

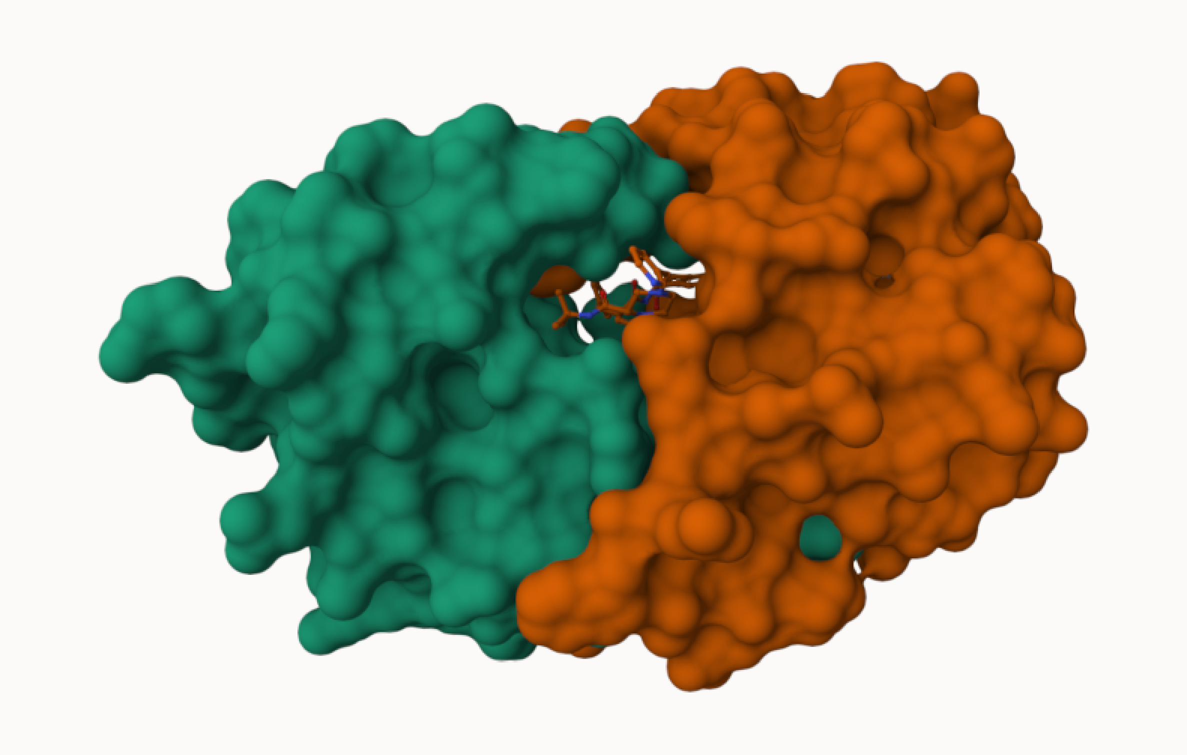


Figure 2: Figure 2. Molecular surface showing binding cavity

Q5: There is a critical “conserved” water molecule in the binding site. Can you identify this water molecule? What residue number does this water molecule have

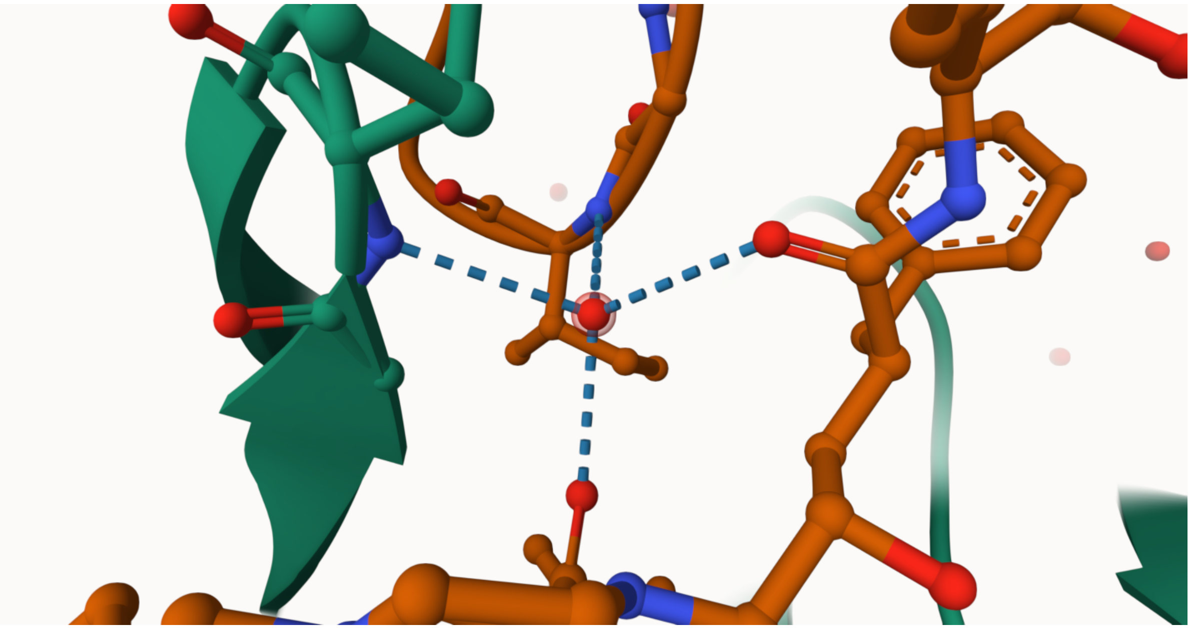


Figure 3: Figure 3. Water molecule found inside of the cavity

The water molecule has residue number 308.

> Q6: Generate and save a figure clearly showing the two distinct chains of HIV-protease along with the ligand. You might also consider showing the catalytic residues ASP 25 in each chain and the critical water (we recommend "Ball & Stick" for these side-chains). Add this figure to your Quarto document.

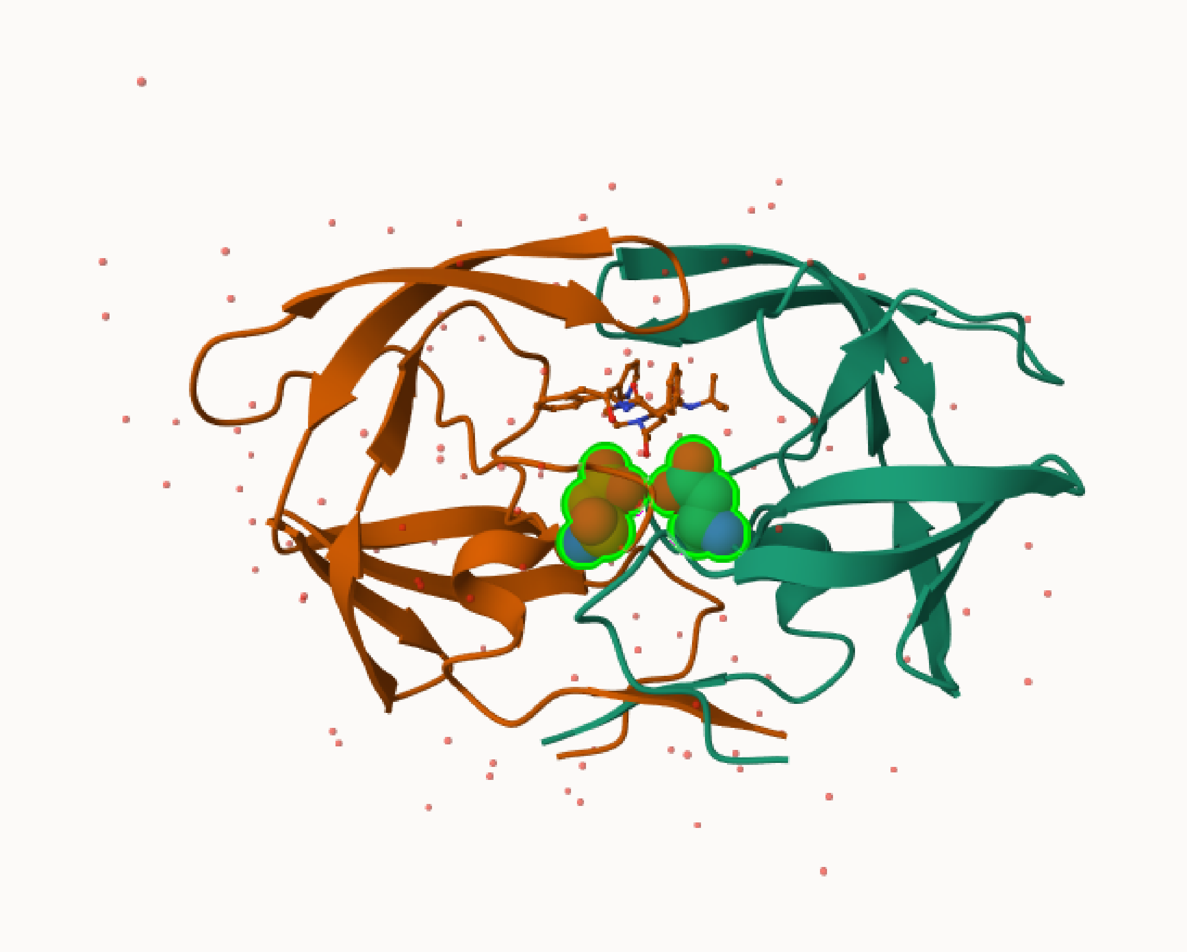


Figure 4: Figure 4. The catalytically important ASP25 amino acids and drug interacting HOH 308 water molecule

3. Using the bio3D package in R

The Bio3D package is focused on structural bioinformatics analysis and allows us to read and analyze PDB (and related) data.

```
library(bio3d)
```

```
pdb <- read.pdb("1hsg")
```

```
  Note: Accessing on-line PDB file
```

```r
pdb
```

```

 Call:  read.pdb(file = "1hsg")

   Total Models#: 1
     Total Atoms#: 1686,  XYZs#: 5058  Chains#: 2  (values: A B)

     Protein Atoms#: 1514  (residues/Calpha atoms#: 198)
     Nucleic acid Atoms#: 0  (residues/phosphate atoms#: 0)

     Non-protein/nucleic Atoms#: 172  (residues: 128)
     Non-protein/nucleic resid values: [ HOH (127), MK1 (1) ]

   Protein sequence:
      PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYD
      QILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNFPQITLWQRPLVTIKIGGQLKE
      ALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTP
      VNIIGRNLLTQIGCTLNF

+ attr: atom, xyz, seqres, helix, sheet,
        calpha, remark, call
```

```r
attributes(pdb)
```

```
$names
[1] "atom"   "xyz"    "seqres" "helix"  "sheet"  "calpha" "remark" "call"  

$class
[1] "pdb" "sse"
```

> Q7: How many amino acid residues are there in this pdb object?

198

> Q8: Name one of the two non-protein residues?

HOH 127 and MK1

> Q9: How many protein chains are in this structure?

2 chains

We can see atom data with `pdb$atom`:

```
head(pdb$atom)
```

```
  type eleno elety  alt resid chain resno insert      x      y     z o     b
1 ATOM     1     N <NA>   PRO     A     1   <NA> 29.361 39.686 5.862 1 38.10
2 ATOM     2    CA <NA>   PRO     A     1   <NA> 30.307 38.663 5.319 1 40.62
3 ATOM     3     C <NA>   PRO     A     1   <NA> 29.760 38.071 4.022 1 42.64
4 ATOM     4     O <NA>   PRO     A     1   <NA> 28.600 38.302 3.676 1 43.40
5 ATOM     5    CB <NA>   PRO     A     1   <NA> 30.508 37.541 6.342 1 37.87
6 ATOM     6    CG <NA>   PRO     A     1   <NA> 29.296 37.591 7.162 1 38.40
  segid elesy charge
1  <NA>     N   <NA>
2  <NA>     C   <NA>
3  <NA>     C   <NA>
4  <NA>     O   <NA>
5  <NA>     C   <NA>
6  <NA>     C   <NA>
```

```
head(pdbseq(pdb))
```

```
  1   2   3   4   5   6 
"P" "Q" "I" "T" "L" "W" 
```

Molecular Visualization in R

We can make a quick 3D viz with the `view.pdb()`

```
library(bio3dview)
library(NGLVieweR)

# view.pdb(pdb, backgroundColor = "pink", colorScheme = "sse")
```

```
sel <- atom.select(pdb, resno=25)

# view.pdb(pdb, cols=c("green", "orange"),
         # highlight=sel,
         # highlight.style="spacefill") |>
  # setRock()
```

Predicting functional motions of a single structure

We can finish off today with a bioinformatics prediction of the functional motions of a protein.

We will run a Normal Mode Analysis (NMA)

```r
adk <- read.pdb("6s36")
```

```
  Note: Accessing on-line PDB file
   PDB has ALT records, taking A only, rm.alt=TRUE
```

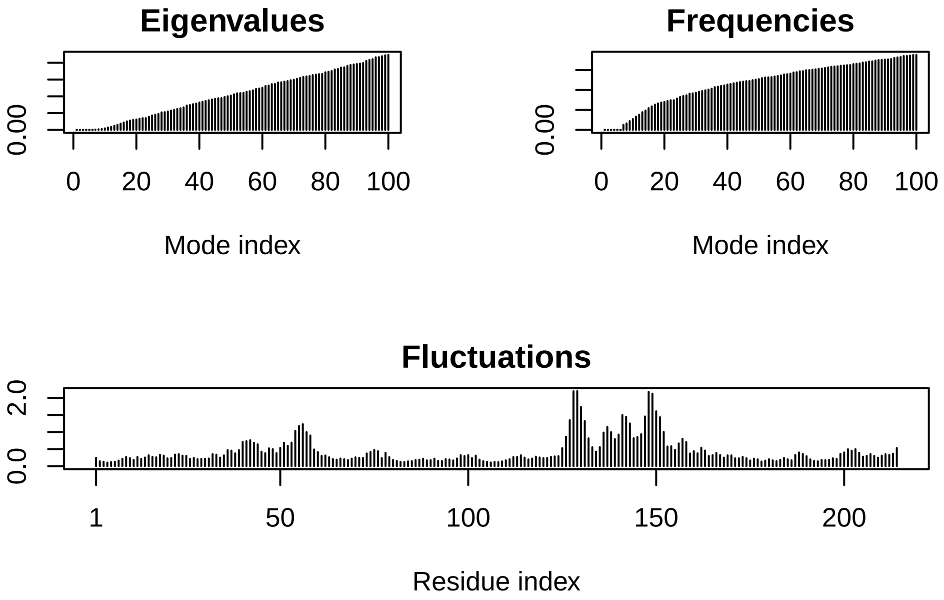
```r
adk
```

```

 Call:  read.pdb(file = "6s36")

   Total Models#: 1
     Total Atoms#: 1898,  XYZs#: 5694  Chains#: 1  (values: A)

     Protein Atoms#: 1654  (residues/Calpha atoms#: 214)
     Nucleic acid Atoms#: 0  (residues/phosphate atoms#: 0)

     Non-protein/nucleic Atoms#: 244  (residues: 244)
     Non-protein/nucleic resid values: [ CL (3), HOH (238), MG (2), NA (1) ]

   Protein sequence:
      MRIILLGAPGAGKGTQAQFIMEKYGIPQISTGDMLRAAVKSGSELGKQAKDIMDAGKLVT
      DELVIALVKERIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFDVPDELIVDKI
      VGRRVHAPSGRVYHVKFNPPKVEGKDDVTGEELTTRKDDQEETVRKRLVEYHQMTAPLIG
      YYSKEAEAGNTKYAKVDGTKPVAEVRADLEKILG

+ attr: atom, xyz, seqres, helix, sheet,
        calpha, remark, call
```

```r
m <- nma(adk)
```

```
 Building Hessian...        Done in 0.03 seconds.
 Diagonalizing Hessian...   Done in 0.3 seconds.
```

```
plot(m)
```



```
# view.nma(m)
```

We can write out a trajectory of the predicted dynamics and view this in Mol-star

```
mktrj(m, file="nma.pdb")
```

```
# view.nma(m, pdb=adk)
```