Class10: Structural Bioinformatics (Part 1)

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The PDB database

Here we examine the size and composition of the main database of biomolecular structures - the PDB.

Get a CSV file from the PDB database and read it into R.

```
pdbstats <- read.csv("pdb_stats.csv", row.names=1)
head(pdbstats)
```

	X.ray	EM	NMR	Multiple.methods	Neutron	Other
Protein (only)	161,663	12,592	12,337	200	74	32
Protein/Oligosaccharide	9,348	2,167	34	8	2	0
Protein/NA	8,404	3,924	286	7	0	0
Nucleic acid (only)	2,758	125	1,477	14	3	1
Other	164	9	33	0	0	0
Oligosaccharide (only)	11	0	6	1	0	4

	Total
Protein (only)	186,898
Protein/Oligosaccharide	11,559
Protein/NA	12,621
Nucleic acid (only)	4,378
Other	206
Oligosaccharide (only)	22

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

My pdbstats data frame has numbers with commas in them. This may cause us problems. Let's see:

```
pdbstats$X.ray
```

```
[1] "161,663" "9,348"   "8,404"   "2,758"   "164"     "11"
```

```
as.numeric(pdbstats$X.ray)
```

```
Warning: NAs introduced by coercion
```

```
[1]  NA  NA  NA  NA 164  11
```

```
x <- "22,200"
as.numeric(x) + 1
```

```
Warning: NAs introduced by coercion
```

```
[1] NA
```

We found a function called `gsub()` now we can figure out how it works.

```
x <- "22,200"
as.numeric(gsub(",", "", x))
```

```
[1] 22200
```

I can turn this snipet into a function that I can use for every column in the table.

```
commasum <- function(x) {
  sum(as.numeric(gsub(",", "", x)))
}

commasum(pdbstats$X.ray)
```

```
[1] 182348
```

Apply across all columns.

```
totals <- apply(pdbstats, 2, commasum)
totals
```

```
        X.ray            EM           NMR Multiple.methods
       182348         18817         14173           230
      Neutron         Other         Total
           79            37        215684
```

```
View(totals)
```

```
round(totals / totals["Total"] * 100, 2)
```

```
        X.ray            EM           NMR Multiple.methods
        84.54          8.72          6.57          0.11
      Neutron         Other         Total
         0.04          0.02        100.00
```

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

```
totalPro <- commasum(pdbstats[1,7])
totalPro
```

```
[1] 186898
```

```
round(totalPro / totals["Total"] * 100, 2)
```

```
Total
86.65
```

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?

```
(215684/249751891 * 100)
```

```
[1] 0.08635931
```

2. Visualizing Protein Structure

We will learn the basics of Mol* (mol-star) homepage: https://molstar.org/viewer/

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

Hydrogen atoms are too small for the scale.

> 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

H308

> 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.

We will play with PDB code 1HSG

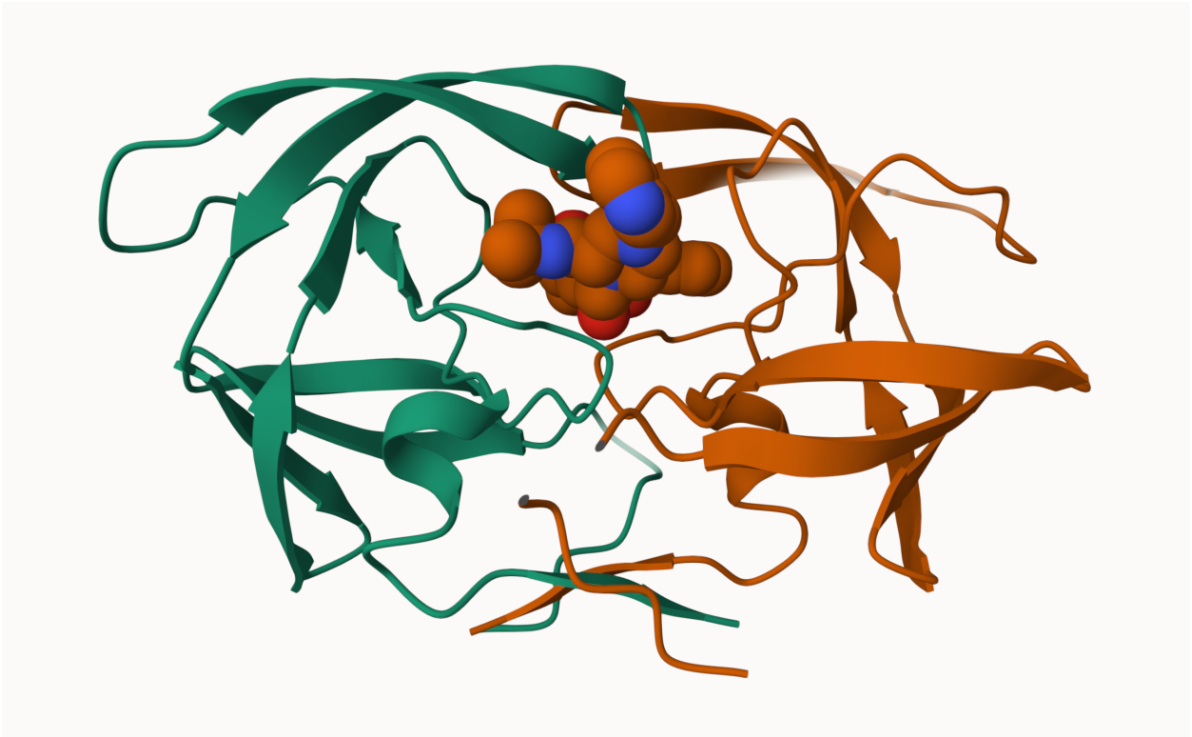


Figure 1: HIV

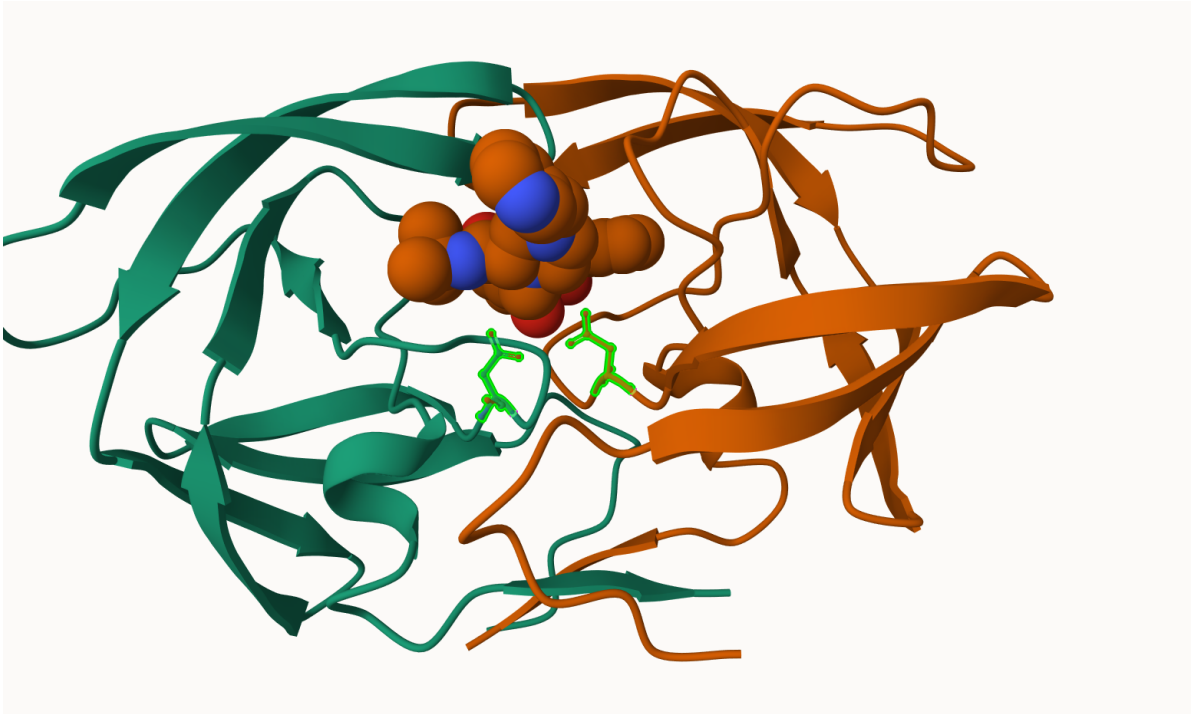


Figure 2: HIV-Pr with a bound inhibitor showing the two important ASP 25 amino acids

Show the ASP 25 amino acids:

Show the ASP 25 amino acids with the stabilizing water molecule:

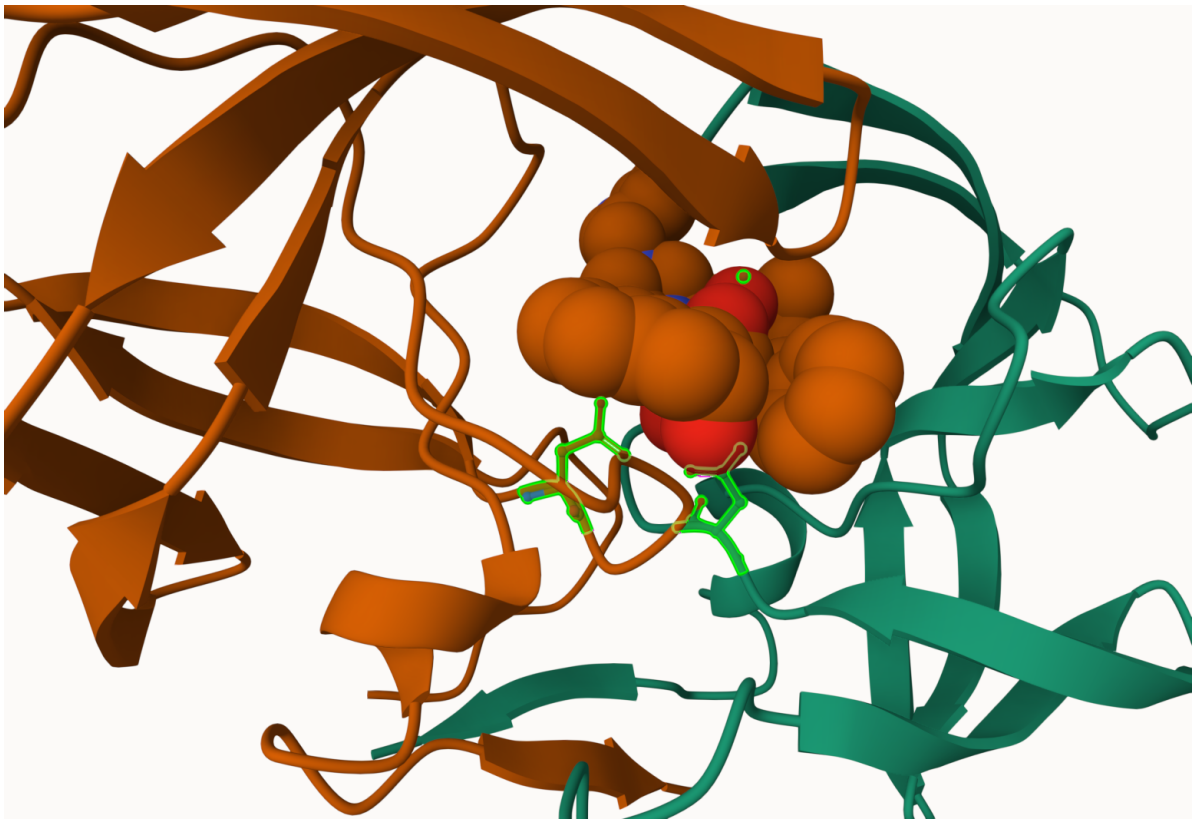


Figure 3: HIV-Pr with a bound inhibitor showing the two important ASP 25 amino acids and water

> Discussion Topic: Can you think of a way in which indinavir, or even larger ligands and substrates, could enter the binding site?

If the enzyme's active site can open up at the regions in contact with the water molecule (the flaps) in order for the substrate to access the active ASPs.

Back to R and working with PDB structures

Predict the dynamics (flexibility) of an imporant protein:

```
library(bio3d)
```

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

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

```
hiv
```

```
 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
```

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

198

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

HOH

Q9: How many protein chains are in this structure?

2

```
head(hiv$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>
```

```
pdbseq(hiv)
```

```
  1   2   3   4   5   6   7   8   9  10  11  12  13  14  15  16  17  18  19  20
"P" "Q" "I" "T" "L" "W" "Q" "R" "P" "L" "V" "T" "I" "K" "I" "G" "G" "Q" "L" "K"
 21  22  23  24  25  26  27  28  29  30  31  32  33  34  35  36  37  38  39  40
"E" "A" "L" "L" "D" "T" "G" "A" "D" "D" "T" "V" "L" "E" "E" "M" "S" "L" "P" "G"
 41  42  43  44  45  46  47  48  49  50  51  52  53  54  55  56  57  58  59  60
"R" "W" "K" "P" "K" "M" "I" "G" "G" "I" "G" "G" "F" "I" "K" "V" "R" "Q" "Y" "D"
 61  62  63  64  65  66  67  68  69  70  71  72  73  74  75  76  77  78  79  80
"Q" "I" "L" "I" "E" "I" "C" "G" "H" "K" "A" "I" "G" "T" "V" "L" "V" "G" "P" "T"
 81  82  83  84  85  86  87  88  89  90  91  92  93  94  95  96  97  98  99   1
"P" "V" "N" "I" "I" "G" "R" "N" "L" "L" "T" "Q" "I" "G" "C" "T" "L" "N" "F" "P"
  2   3   4   5   6   7   8   9  10  11  12  13  14  15  16  17  18  19  20  21
"Q" "I" "T" "L" "W" "Q" "R" "P" "L" "V" "T" "I" "K" "I" "G" "G" "Q" "L" "K" "E"
 22  23  24  25  26  27  28  29  30  31  32  33  34  35  36  37  38  39  40  41
"A" "L" "L" "D" "T" "G" "A" "D" "D" "T" "V" "L" "E" "E" "M" "S" "L" "P" "G" "R"
 42  43  44  45  46  47  48  49  50  51  52  53  54  55  56  57  58  59  60  61
"W" "K" "P" "K" "M" "I" "G" "G" "I" "G" "G" "F" "I" "K" "V" "R" "Q" "Y" "D" "Q"
 62  63  64  65  66  67  68  69  70  71  72  73  74  75  76  77  78  79  80  81
"I" "L" "I" "E" "I" "C" "G" "H" "K" "A" "I" "G" "T" "V" "L" "V" "G" "P" "T" "P"
 82  83  84  85  86  87  88  89  90  91  92  93  94  95  96  97  98  99
"V" "N" "I" "I" "G" "R" "N" "L" "L" "T" "Q" "I" "G" "C" "T" "L" "N" "F"
```

Here we will do a Normal Mode Analysis (NMA) to predict functional motions of a kinase protein.

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

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

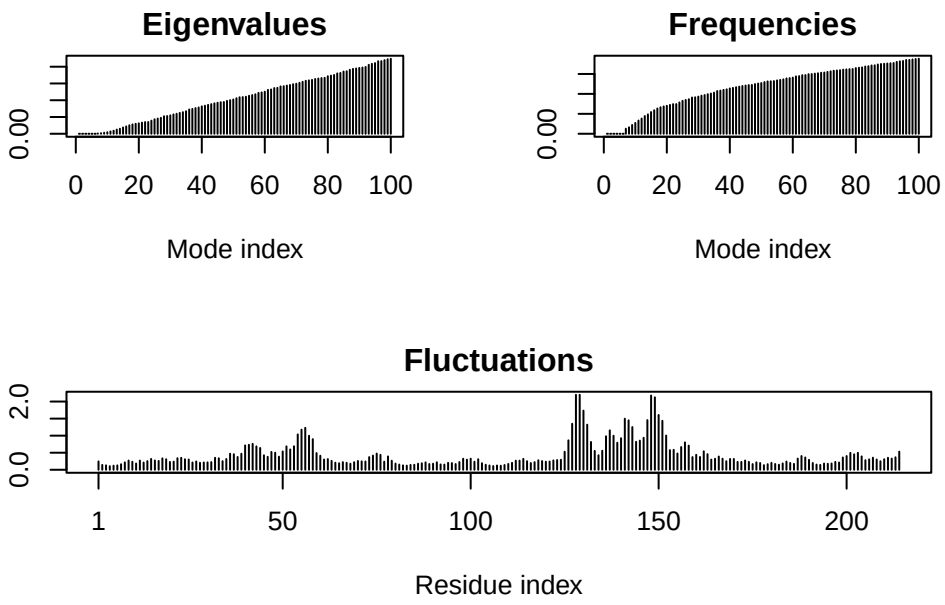
```
adk
```

```
 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
```

```
modes <- nma(adk)
```

```
 Building Hessian...        Done in 0.015 seconds.
 Diagonalizing Hessian...   Done in 0.287 seconds.
```

```
plot(modes)
```



Make a "move" called a trajectory of the predicted motion:

```
mktrj(modes, file = "adk_m7.pdb")
```