Class09: Structural Bioinformatics pt1.

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##The PDB database

The main repository for biomolecular structure data is the Protein Data Bank (PDB) https://www.rcsb.org/

Let's have a quick look at the composition of this database:

```r
# Save your input data file into your Project directory
# Complete the following code to input the data and store as wisc.df
stats <- read.csv("PDB.csv", row.names=1)

stats
```

```
                          X.ray     EM    NMR Integrative Multiple.methods
Protein (only)          176,378 20,438 12,709         342              221
Protein/Oligosaccharide  10,284  3,396     34           8               11
Protein/NA                9,007  5,931    287          24                7
Nucleic acid (only)       3,077    200  1,554           2               15
Other                       174     13     33           3                0
Oligosaccharide (only)       11      0      6           0                1
                        Neutron Other   Total
Protein (only)               83    32 210,203
Protein/Oligosaccharide       1     0  13,734
Protein/NA                    0     0  15,256
Nucleic acid (only)           3     1   4,852
Other                         0     0     223
Oligosaccharide (only)        0     4      22
```

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

```r
X.ray <- as.numeric(sub(",","",stats$X.ray))
EM <- as.numeric(sub(",","",stats$EM))
Total <- as.numeric(sub(",","",stats$Total))
```

This is annoying, let’s try another import function from the **readr** package.

```r
library(readr)

stats <- read_csv("PDB.csv")
```

```
Rows: 6 Columns: 9
-- Column specification --------------------------------------------------------
Delimiter: ","
chr (1): Molecular Type
dbl (4): Integrative, Multiple methods, Neutron, Other
num (4): X-ray, EM, NMR, Total

i Use `spec()` to retrieve the full column specification for this data.
i Specify the column types or set `show_col_types = FALSE` to quiet this message.
```

```r
stats
```

```
# A tibble: 6 x 9
  `Molecular Type`    `X-ray`    EM   NMR Integrative `Multiple methods` Neutron
  <chr>                 <dbl> <dbl> <dbl>       <dbl>              <dbl>   <dbl>
1 Protein (only)       176378 20438 12709         342                221      83
2 Protein/Oligosacch~   10284  3396    34           8                 11       1
3 Protein/NA             9007  5931   287          24                  7       0
4 Nucleic acid (only)    3077   200  1554           2                 15       3
5 Other                   174    13    33           3                  0       0
6 Oligosaccharide (o~      11     0     6           0                  1       0
# i 2 more variables: Other <dbl>, Total <dbl>
```

Percent Xray

```r
n.total <-sum(stats$Total)
n.xray <- sum(stats$'X-ray')
n.em <- sum(stats$EM)

round(n.xray/n.total * 100, 2)
```

```
[1] 81.43
```

```r
round(n.em/n.total * 100, 2)
```

```
[1] 12.27
```

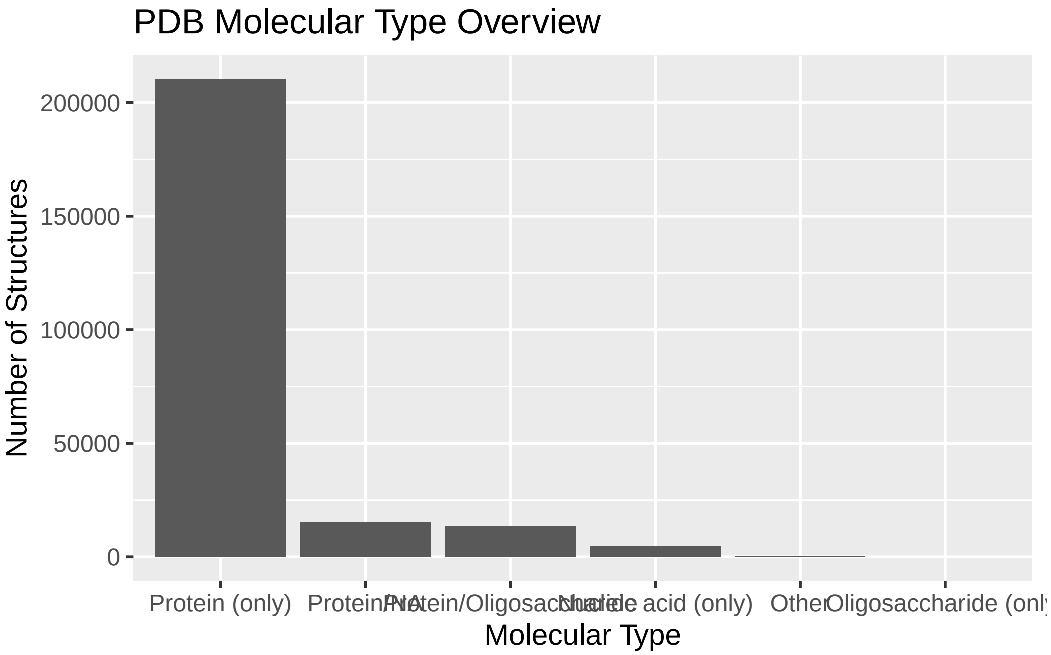
Q2: What proportion of structures in the PDB are protein only?

```r
stats$Total[1]/sum(stats$Total) * 100
```

```
[1] 86.0465
```

Q2b: Make a bar plot overview of Molecular type composition using ggplot2.

```r
library(ggplot2)

ggplot(stats, aes(x=reorder(`Molecular Type`,-Total), Total)) +
  geom_bar(stat="identity") +
  labs(title="PDB Molecular Type Overview",
       x="Molecular Type",
       y="Number of Structures")
```



##Visualizing structure data

The Mol* viewer is embedded in many bioinformatics websites. https://molstar.org/viewer/

PDB ID: 1HSG

I can insert any figure or image file using markdown format

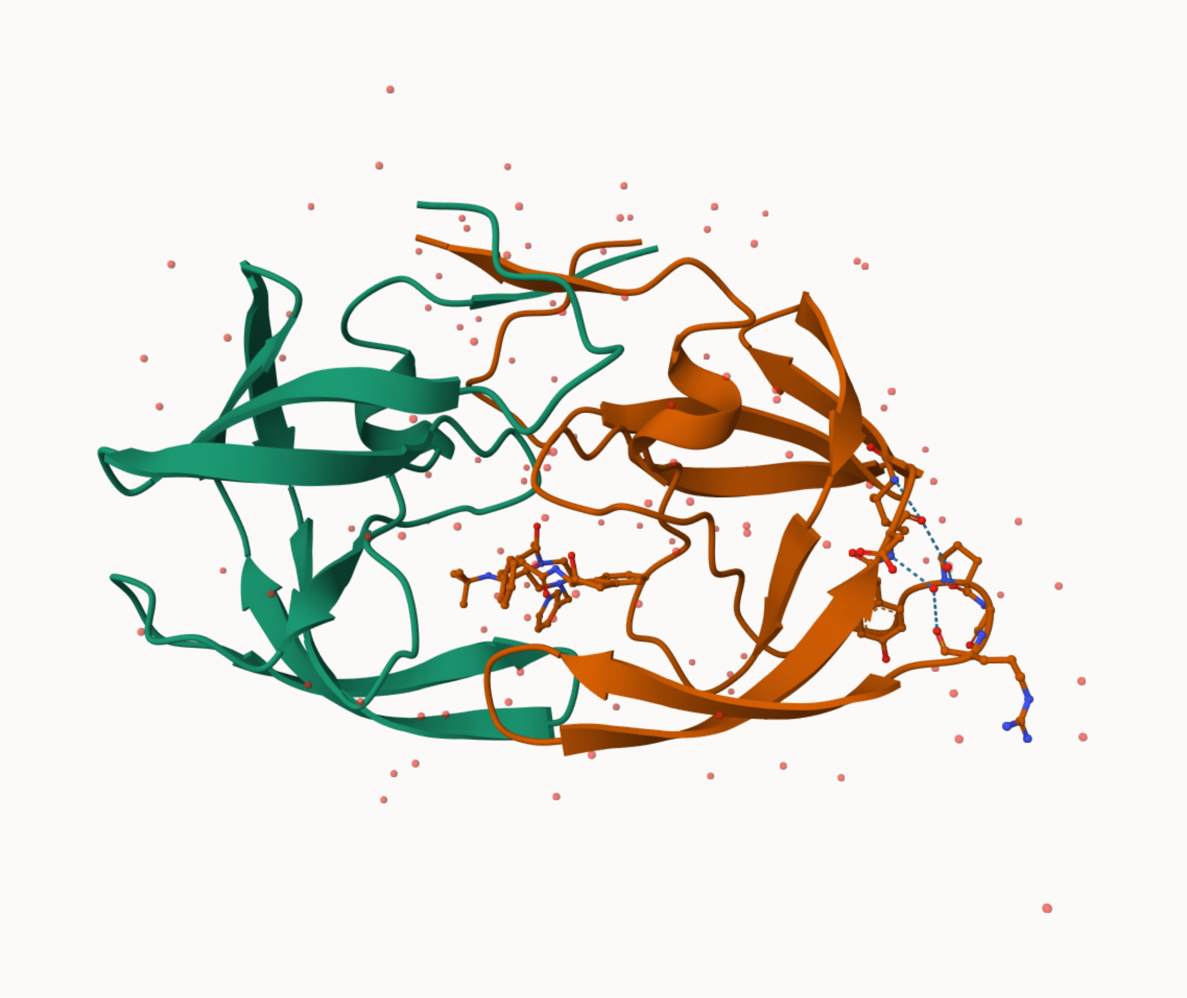


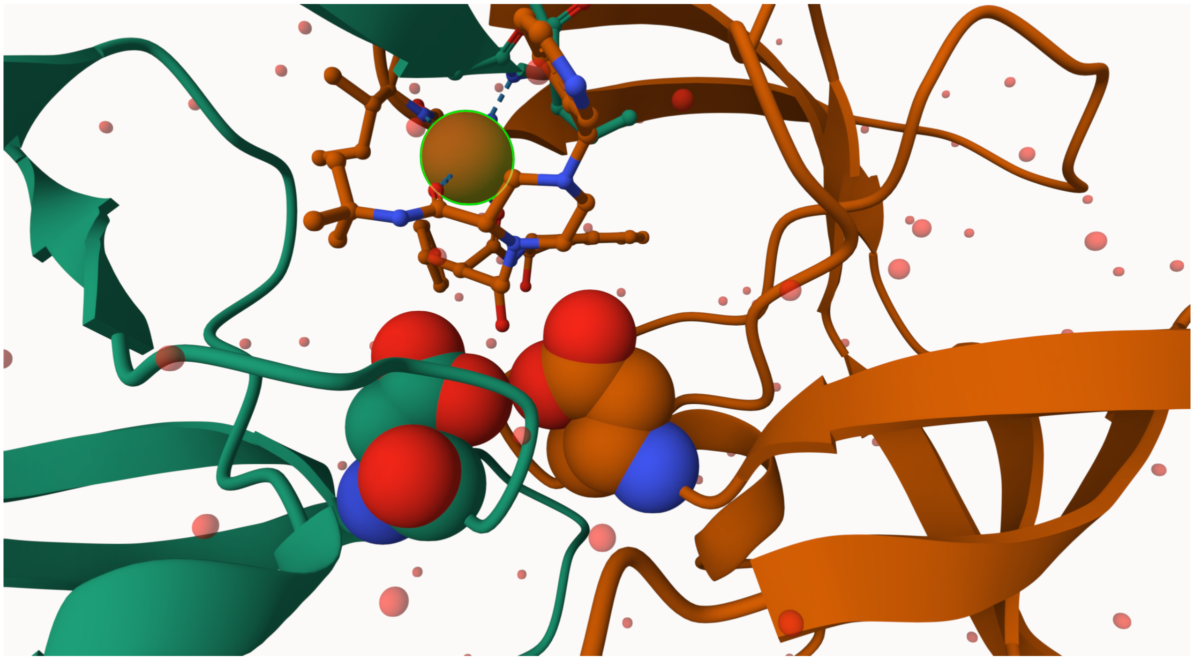
Figure 1: The HIV-Pr dimer with bound inhibitor

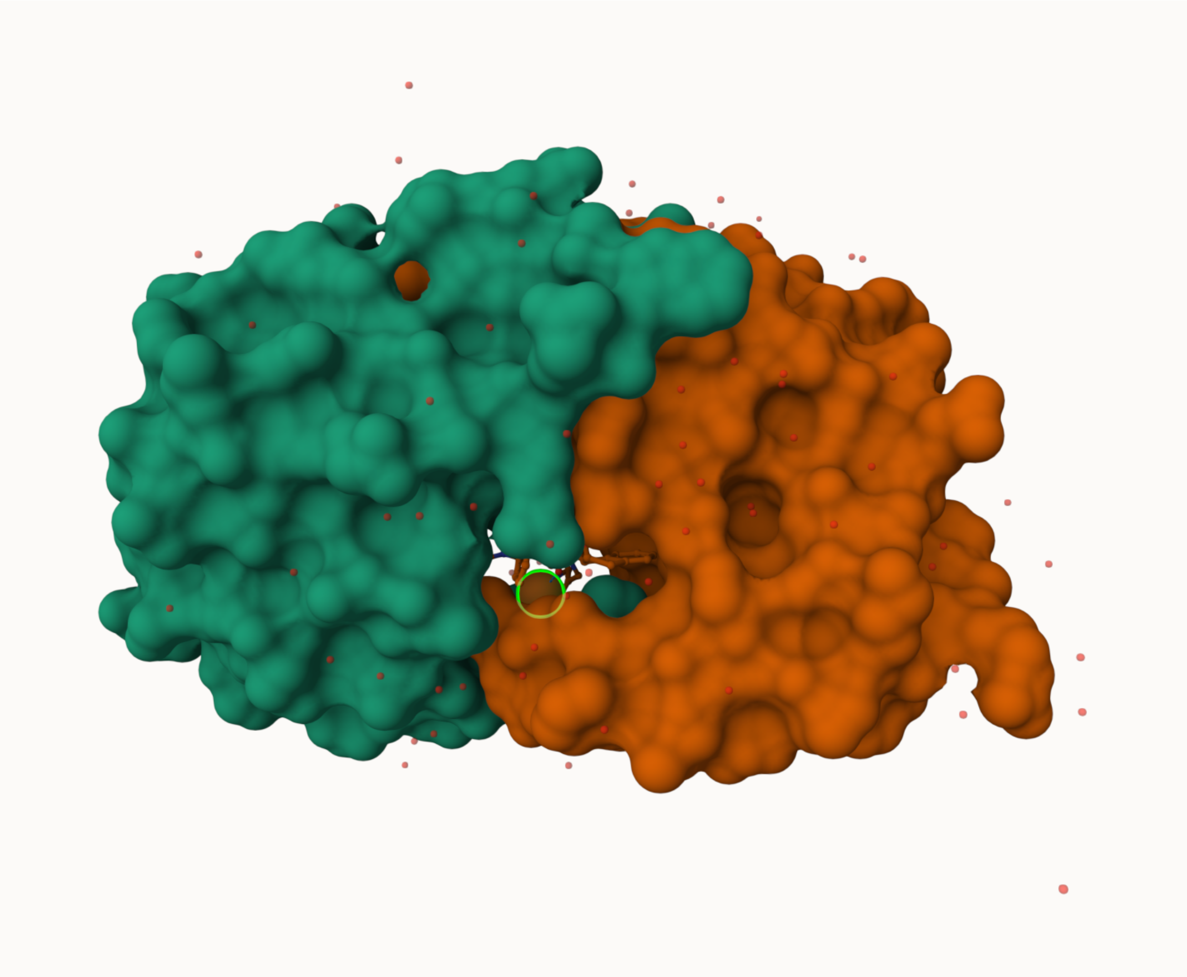
> Q3: Type HIV in the PDB website search box on the home page and determine how many HIV-1 protease structures are in the current PDB?

According to the websites, there are 4,866 structures found for “HIV-1 protease”.

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

Why not presenting H atoms but only O atom. Because only the oxygen is experimentally located — the two hydrogens are implied, not directly observed.





##Bio3D package for structural bioinformatics

We can use the Bio3D package to read and analyze biomolecular data in R:

```
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
```

```
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>
```

Let's get the sequence

```
pdbseq(hiv) #for both chaim A and B
```

```
  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"
```

Let’s trim it to chain A and get just it’s sequence.

```r
chainA<-trim.pdb(hiv, chain="A")
chainA.seq <- pdbseq(chainA)
```

Let’s blast

```r
blast <- blast.pdb(chainA.seq)
```

```
 Searching ... please wait (updates every 5 seconds) RID = G5TDCA3T014
 .
 Reporting 249 hits
```

```r
head(blast$hit.tbl)
```

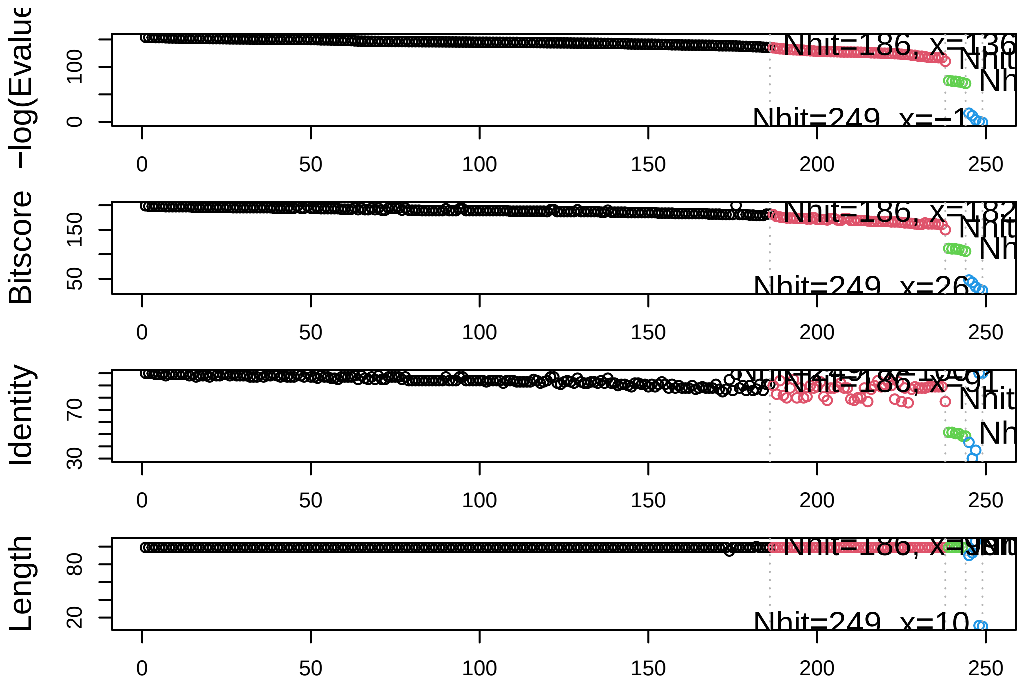
```
        queryid subjectids identity alignmentlength mismatches gapopens q.start
1 Query_8208195     1W5V_A   100.00              99          0        0       1
2 Query_8208195     2FDE_A   100.00              99          0        0       1
3 Query_8208195     1AJV_A   100.00              99          0        0       1
4 Query_8208195     2R38_A    98.99              99          1        0       1
5 Query_8208195     2R3T_A    98.99              99          1        0       1
```

```
6 Query_8208195     1HXB_A    98.99              99          1        0       1
  q.end s.start s.end   evalue bitscore positives mlog.evalue pdb.id    acc
1    99      12   110 1.38e-67      199       100    153.9511 1W5V_A 1W5V_A
2    99       2   100 1.70e-67      198       100    153.7426 2FDE_A 2FDE_A
3    99       1    99 1.99e-67      198       100    153.5851 1AJV_A 1AJV_A
4    99       1    99 2.50e-67      198       100    153.3569 2R38_A 2R38_A
5    99       1    99 2.50e-67      198       100    153.3569 2R3T_A 2R3T_A
6    99       1    99 2.50e-67      198       100    153.3569 1HXB_A 1HXB_A
```

Plot a quick overview of the blast results

```
hits <- plot(blast)
```

```
  * Possible cutoff values:    135 110 69 -2 
            Yielding Nhits:    186 238 244 249 

  * Chosen cutoff value of:    69 
            Yielding Nhits:    244 
```



```
hits$pdb.id #accession number from the results
```

```
  [1] "1W5V_A" "2FDE_A" "1AJV_A" "2R38_A" "2R3T_A" "1HXB_A" "1BV9_A" "1AAQ_A"
  [9] "1AXA_A" "1HVS_A" "1ZP8_A" "2QHC_A" "1A8G_A" "2O4L_A" "5COK_A" "1TCX_A"
 [17] "2Z54_A" "1D4S_A" "1BV7_A" "1BWA_A" "1A9M_A" "2FLE_A" "1ODY_A" "1GNN_A"
 [25] "1GNM_A" "5YRS_B" "1HEF_E" "1ODX_A" "4QGI_A" "1BVE_A" "2AZ8_A" "1A30_A"
 [33] "6DH6_A" "6DH0_A" "2I4D_A" "6OOS_A" "1RL8_A" "5YRS_A" "1ZSF_A" "2Q64_A"
 [41] "6DH3_A" "2NPH_A" "2Q63_A" "1LZQ_A" "1FB7_A" "1G6L_A" "1HIV_A" "6OOU_A"
 [49] "1HVC_A" "2I4V_A" "2AZ9_A" "6OOT_A" "2P3B_B" "5KAO_A" "2WL0_A" "6OPT_A"
 [57] "1IZI_A" "1MRX_A" "2PYM_A" "2PYN_A" "1DMP_A" "4K4P_A" "1LV1_A" "1AID_A"
 [65] "1LV1_A" "1ZBG_A" "3TKG_A" "1HVC_A" "5YOK_A" "1G6L_A" "1FGC_C" "3K4V_A"
 [73] "3KT5_A" "3KT5_A" "4QLH_A" "4QLH_A" "2F3K_A" "4Q5M_A" "2AOC_A" "3B80_A"
 [81] "3VF5_A" "2AVQ_A" "1DW6_C" "1KZK_A" "2HS1_A" "1K6C_A" "1MTB_A" "4Q1X_A"
 [89] "4Q1W_A" "4Q5M_A" "3D1X_A" "2AVM_A" "3PWM_A" "3KT2_A" "3KT2_A" "1SDV_A"
 [97] "3JVW_A" "3OY4_A" "1A94_A" "2HS2_A" "4EJ8_A" "2FGU_A" "2AVV_A" "3JW2_A"
[105] "3BVA_A" "1FFF_C" "3S43_B" "2NXD_A" "1FG6_C" "1EBK_C" "4Q1Y_A" "3EL4_A"
[113] "1F7A_A" "1K2B_A" "2FGV_A" "1Z8C_A" "2G69_A" "3EL9_A" "3OXV_A" "1BDR_A"
[121] "3N3I_A" "3N3I_A" "3OXW_A" "3S43_A" "3EM3_A" "3CYW_A" "5KQX_A" "2B60_A"
[129] "7DOZ_A" "1K2C_A" "1MT7_A" "3EM4_A" "4QJ9_A" "1BDL_A" "3LZS_A" "5T84_A"
[137] "4DQB_A" "7DOZ_A" "4QJ2_A" "3LZV_A" "1SGU_A" "2FXE_A" "1BDQ_A" "3U71_A"
[145] "2R5P_A" "4OBD_A" "7MAS_A" "3IXO_A" "3D3T_A" "5YOJ_A" "3LZU_A" "4NJS_A"
[153] "3EKP_A" "1B6J_A" "3EKQ_A" "2RKF_A" "1C6X_A" "7MAR_A" "4DQF_A" "1RPI_A"
[161] "3OU1_B" "3PJ6_A" "2P3A_A" "6OGQ_A" "3OQ7_A" "5KR1_A" "3OQD_A" "4RVI_A"
[169] "3OQA_A" "1B6K_A" "3OUD_B" "6MK9_A" "3SO9_A" "1Q9P_A" "6I45_A" "7SEP_A"
[177] "4NJT_A" "3BXR_A" "4YOA_A" "4DQC_A" "2FDD_A" "2RKG_A" "4DQH_A" "2P3C_A"
[185] "4EP2_A" "4EP2_A" "4EQ0_A" "4NPT_A" "6OPU_A" "4NPU_A" "3U7S_A" "3HAW_A"
[193] "2AZB_A" "3TTP_A" "3HBO_A" "3GGU_A" "7N6T_A" "6OPV_A" "4EQ0_A" "6OPX_A"
[201] "2O4N_A" "5T2E_A" "3UCB_A" "3KA2_A" "3FSM_A" "6OPW_A" "2AZC_A" "3FSM_A"
[209] "3HLO_A" "2P3D_A" "3T3C_A" "7MYP_A" "6O54_X" "6OPY_A" "4Z4X_A" "6OPZ_A"
[217] "2JE4_A" "1DAZ_C" "7MAP_A" "7MAQ_A" "1K1U_A" "2B7Z_A" "3MWS_A" "1K1T_A"
[225] "8DCH_A" "3I2L_A" "6P9A_A" "2FXD_A" "2J9J_A" "3DCK_A" "2J9J_B" "3NXE_A"
[233] "2O40_A" "2O40_A" "3NXE_A" "3KA2_A" "3HLO_A" "5B18_A" "1SIP_A" "2SAM_A"
[241] "1AZ5_A" "1SIV_A" "1HII_A" "1IVP_A"
```

##Prediction of funtional motions

We can ran on Normal Mode Analysis (NMA)to predict large scale motions/flexibility/dynamics of any biomolecule that we can read into R.

Let’s look at ADK chain A only!

```
adk <- read.pdb("1ake")
```

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

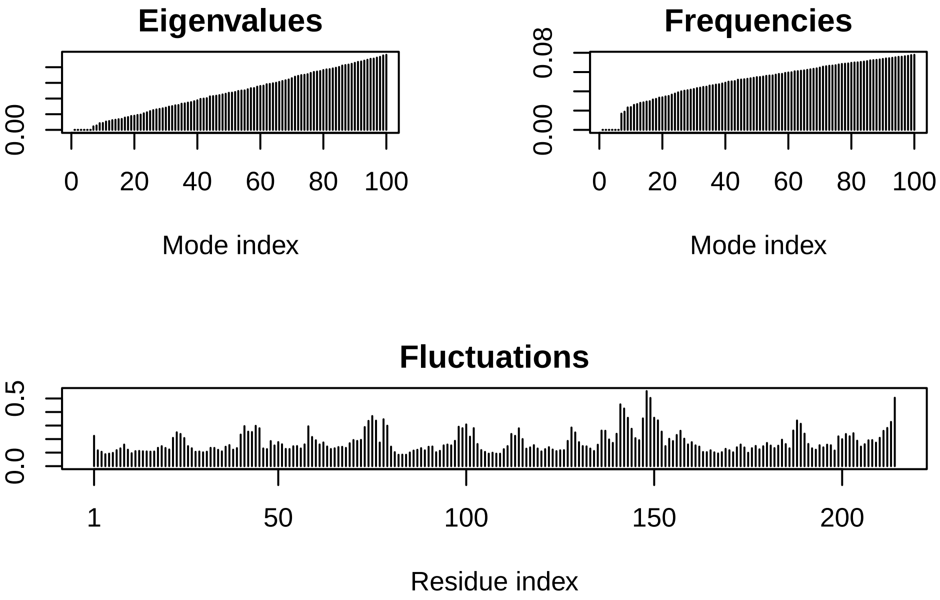
```r
adk_A <- trim.pdb(adk, chain="A")
adk_A
```

```
 Call:  trim.pdb(pdb = adk, chain = "A")

   Total Models#: 1
     Total Atoms#: 1954,  XYZs#: 5862  Chains#: 1  (values: A)

     Protein Atoms#: 1656  (residues/Calpha atoms#: 214)
     Nucleic acid Atoms#: 0  (residues/phosphate atoms#: 0)

     Non-protein/nucleic Atoms#: 298  (residues: 242)
     Non-protein/nucleic resid values: [ AP5 (1), HOH (241) ]

   Protein sequence:
      MRIILLGAPGAGKGTQAQFIMEKYGIPQISTGDMLRAAVKSGSELGKQAKDIMDAGKLVT
      DELVIALVKERIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFDVPDELIVDRI
      VGRRVHAPSGRVYHVKFNPPKVEGKDDVTGEELTTRKDDQEETVRKRLVEYHQMTAPLIG
      YYSKEAEAGNTKYAKVDGTKPVAEVRADLEKILG

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

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

```
 Building Hessian...        Done in 0.02 seconds.
 Diagonalizing Hessian...    Done in 0.446 seconds.
```

```r
plot(m)
```



Let’s write out a “trajectory” of predicted motion

```r
mktrj(m, file="adk_nma.pdb")
```

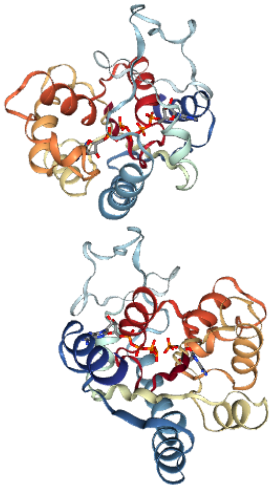
Play with 3D viewing in R

We can use the new **bio3dview** package, which is not yet on CRAN, to render interacting 3D views in R and HTML quanto output reports.

To install from GitHub we can use the **pak** package.

```r
library(bio3dview)

view.pdb(adk)
```

```
file:////private/var/folders/j2/s2jtkphj3dz36gjxv0jybzk00000gn/T/RtmpnL3QIe/filecfc518ea6621/
```



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?

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.

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

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

Q9: How many protein chains are in this structure?

Q10. Which of the packages above is found only on BioConductor and not CRAN?

Q11. Which of the above packages is not found on BioConductor or CRAN?:

Q12. True or False? Functions from the devtools package can be used to install packages from GitHub and BitBucket?

Q13. How many amino acids are in this sequence, i.e. how long is this sequence?

Q14. What do you note about this plot? Are the black and colored lines similar or different? Where do you think they differ most and why?