class 10: Structural Bioinformatics (part 1)

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What is in the PDB?

Downloaded a CSV file with current composition data form: https://www.rcsb.org/stats/summary

```r
pdbstats <- read.csv("Data Export Summary.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
```

```r
pdbstats$X.ray
```

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

```r
x <- "2,2222"
as.numeric(x)
```

```
Warning:                              NA
```

```
[1] NA
```

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

```
Warning:                              NA
```

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

`gsub()` function is used to remove comma in numbers, because it can not read as a number by program.

```
x <- "2,222"
as.numeric(gsub(",", "",x))
```

```
[1] 2222
```

```
commasum <- function(x) {
  #Remove comma, convert to numeric and sum
  sum(as.numeric(gsub(",","",x)))
}
```

```
#Code -> Extract function and here we can use it as a function
commasum(pdbstats$X.ray)
```

```
[1] 182348
```

`apply()` can use this function to my wee tablet to get all the number i get

```
round(apply(pdbstats, 2, commasum) /
  commasum(pdbstats$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 
```

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

X.ray: 84.54 %;
EM: 8.72 %.

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

According to PDB data, the Total count of "protein only" structures is 186898, and the sum of all elements is 215684. To calculate proportion of structures with only proteins, we divide and multiply to 100: 86.69 %

```
186989/215684 * 100
```

```
[1] 86.69581
```

> Q. How does the total number of protein strutures in the PDB relate to the toral number of protein sequences in UniProt?

```
186898 / 250322721 * 100
```

```
[1] 0.07466282
```

> 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?

26,204 Structures

Visualizing the HIV-1 protease structure

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

Just like amino acids, water molecules usually have 3 atoms—2 hydrogen and 1 oxygen. But when we look at pictures of proteins, we often see water represented by just one dot. This is to make things easier to understand and not make the picture too crowded.

> 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

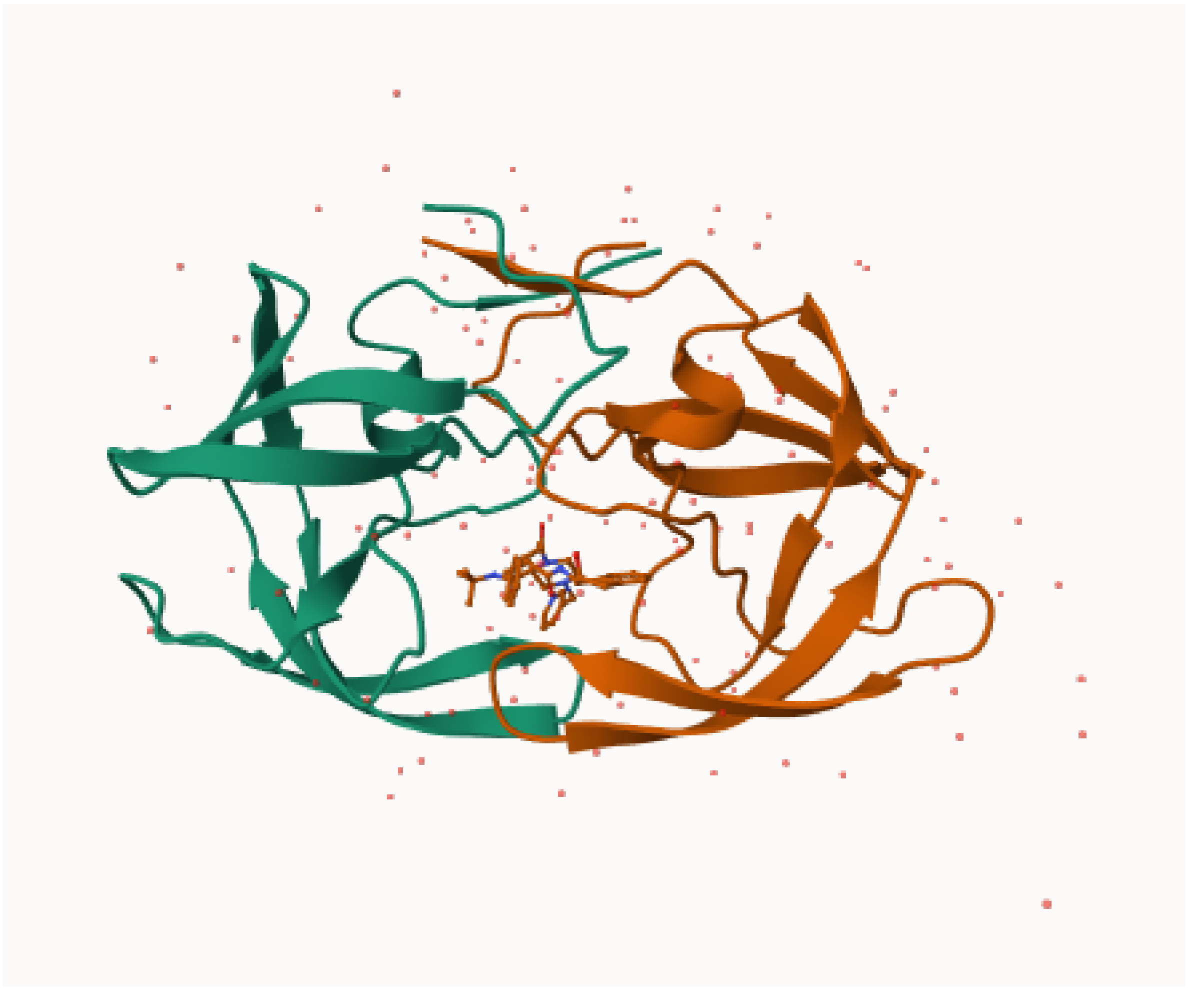


Figure 1: First image

Conserved water molecules in protein binding sites can play critical roles in maintaining the structural integrity and function of the protein. In this case it is ASP 25.

#We will use the Mol* (mol-star) viewer at: https://molstar.org/viewer/

A first image

> 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.

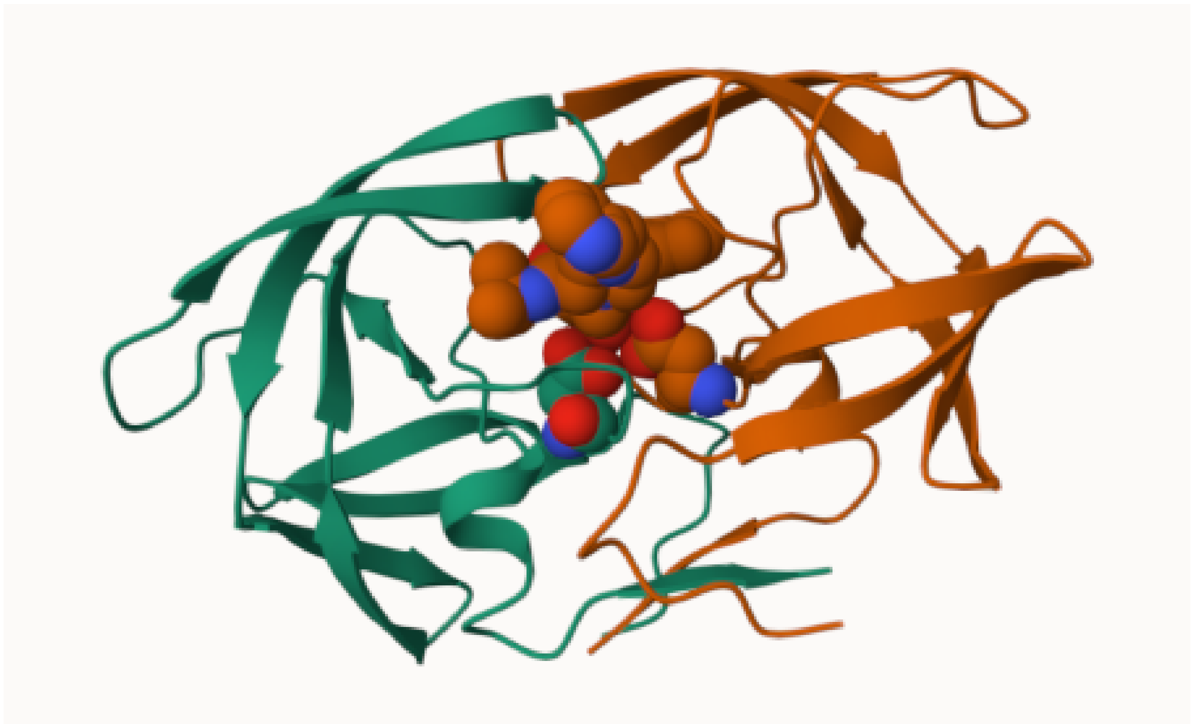


Figure 2: A nice display showing the MK1 ligand and all important ASP 25

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

Indinavir is a protease inhibitor used in the treatment of HIV. Probably because of Water molecules that can act as mediators for ligand entry. When there are water filled channels, ligands may enter and displace water molecules.

Working with structures in R

We will use the bio3d package for structural bioinformatics

```r
library(bio3d)

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

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

```r
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?

residues/Calpha atoms#: 198

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

Water H2O

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

2: A, B.

```
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>
```

```
aa123(pdbseq(hiv)[25])
```

```
[1] "ASP"
```

#Predicting functional motions of a single structure

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

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

```
adk
```

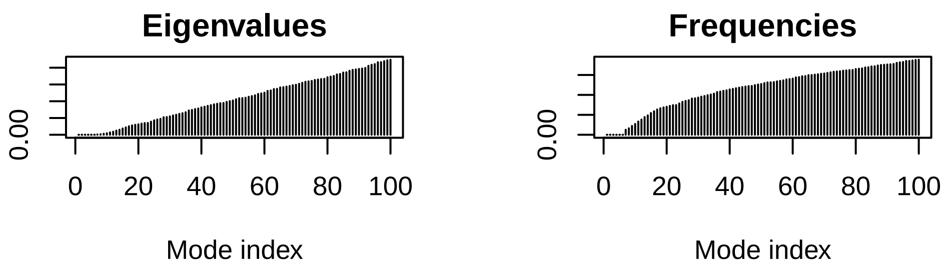
```

 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
```

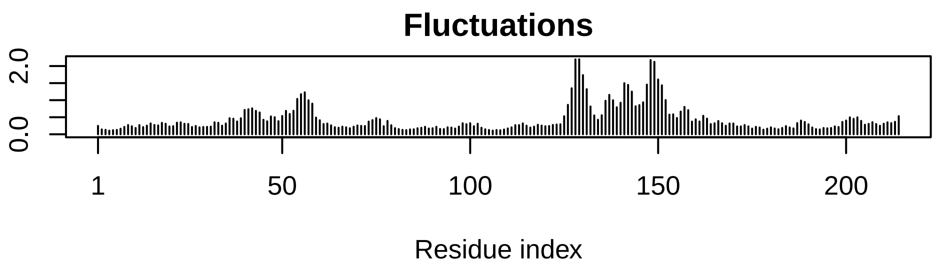
Normal mode analysis (NMA) a bioinformatics method to predict functional motions and large scale changes.

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

```
 Building Hessian...        Done in 0.08 seconds.
 Diagonalizing Hessian...   Done in 1.16 seconds.
```

```r
plot(m)
```





Make a wee movie (aka "trajectory") of these predicted motions

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

#Quick comparitive

Extract sequence and run a BLAST search

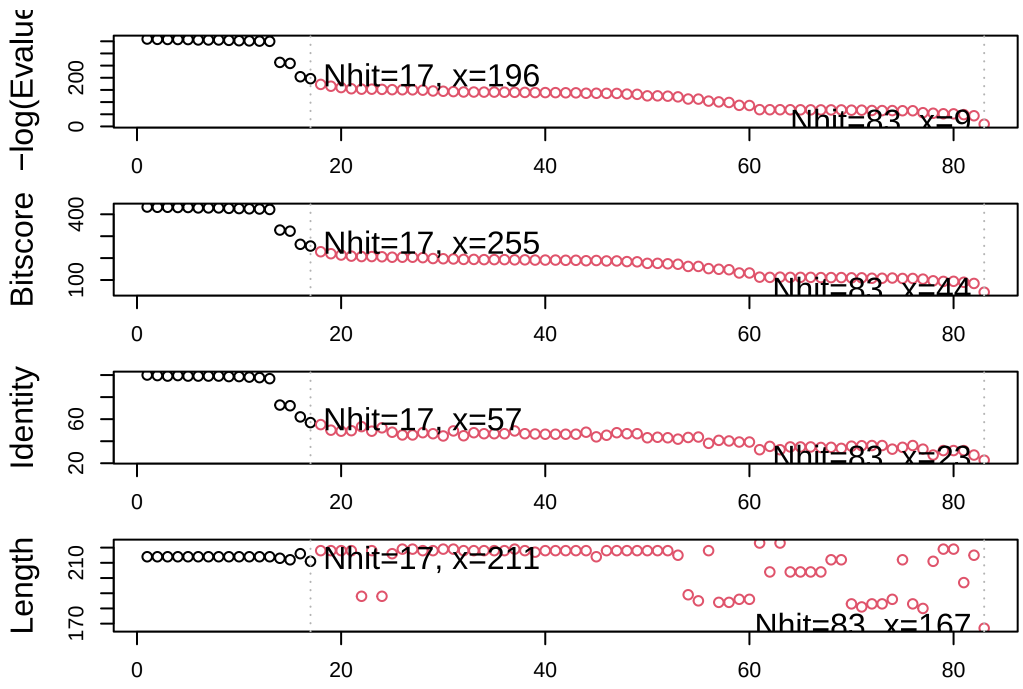
```
s <- pdbseq(adk)
blast <- blast.pdb(s)
```

```
Searching ... please wait (updates every 5 seconds) RID = WJRRW84W013
.......
Reporting 83 hits
```

```
plot(blast)
```

```
  * Possible cutoff values:    196 9
            Yielding Nhits:    17 83

  * Chosen cutoff value of:    196
```

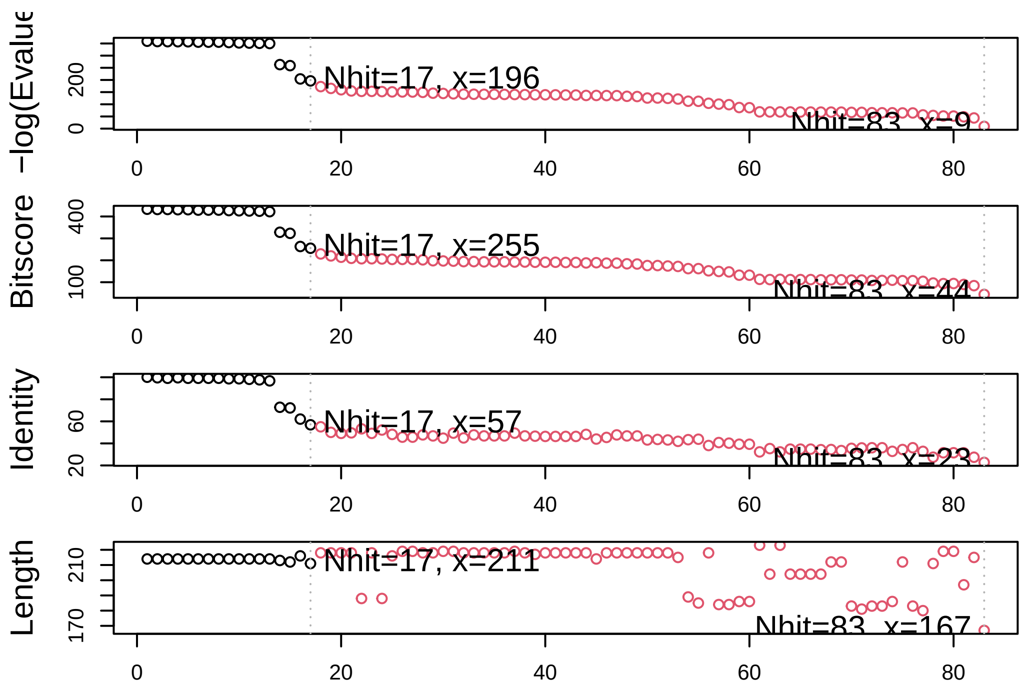
```
          Yielding Nhits:    17
```



Get the results from BLAST and download all the top hits.

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

```
* Possible cutoff values:    196 9
          Yielding Nhits:    17 83

* Chosen cutoff value of:    196
          Yielding Nhits:    17
```



```
hits$pdb.id
```

```
 [1] "6S36_A" "1AKE_A" "8BQF_A" "6RZE_A" "4X8M_A" "4X8H_A" "1E4V_A" "3HPR_A"
 [9] "5EJE_A" "1E4Y_A" "3X2S_A" "6HAP_A" "6HAM_A" "4K46_A" "4NP6_A" "3GMT_A"
[17] "4PZL_A"
```

```
# Download releated PDB files
files <- get.pdb(hits$pdb.id, path="pdbs", split=TRUE, gzip=TRUE)
```

```
Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/6S36.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/1AKE.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/8BQF.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/6RZE.pdb exists. Skipping download
```

```
Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/4X8M.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/4X8H.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/1E4V.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/3HPR.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/5EJE.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/1E4Y.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/3X2S.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/6HAP.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/6HAM.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/4K46.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/4NP6.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/3GMT.pdb exists. Skipping download

Warning in get.pdb(hits$pdb.id, path = "pdbs", split = TRUE, gzip = TRUE):
pdbs/4PZL.pdb exists. Skipping download
```

```
  |
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  |
  |==============================================================        |  88%
  |
  |==================================================================    |  94%
  |
  |======================================================================| 100%
```

```r
# Align releated PDBs
pdbs <- pdbaln(files, fit = TRUE, exefile="msa")
```

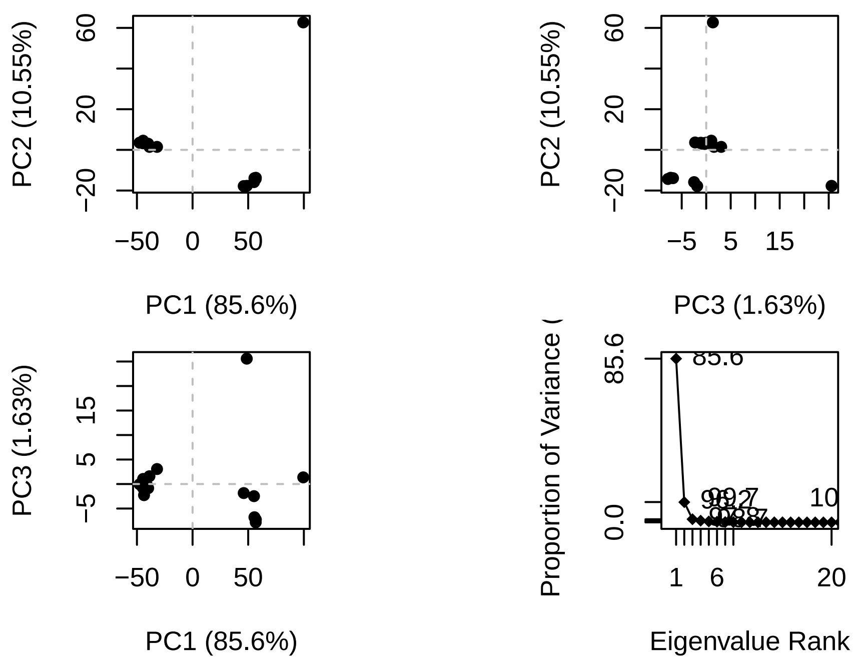
```
Reading PDB files:
```

```
pdbs/split_chain/6S36_A.pdb
pdbs/split_chain/1AKE_A.pdb
pdbs/split_chain/8BQF_A.pdb
pdbs/split_chain/6RZE_A.pdb
pdbs/split_chain/4X8M_A.pdb
pdbs/split_chain/4X8H_A.pdb
pdbs/split_chain/1E4V_A.pdb
pdbs/split_chain/3HPR_A.pdb
pdbs/split_chain/5EJE_A.pdb
pdbs/split_chain/1E4Y_A.pdb
pdbs/split_chain/3X2S_A.pdb
pdbs/split_chain/6HAP_A.pdb
pdbs/split_chain/6HAM_A.pdb
pdbs/split_chain/4K46_A.pdb
pdbs/split_chain/4NP6_A.pdb
pdbs/split_chain/3GMT_A.pdb
pdbs/split_chain/4PZL_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
.   PDB has ALT records, taking A only, rm.alt=TRUE
.   PDB has ALT records, taking A only, rm.alt=TRUE
.   PDB has ALT records, taking A only, rm.alt=TRUE
....   PDB has ALT records, taking A only, rm.alt=TRUE
.   PDB has ALT records, taking A only, rm.alt=TRUE
....   PDB has ALT records, taking A only, rm.alt=TRUE
.   PDB has ALT records, taking A only, rm.alt=TRUE
....

Extracting sequences

pdb/seq: 1   name: pdbs/split_chain/6S36_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 2   name: pdbs/split_chain/1AKE_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 3   name: pdbs/split_chain/8BQF_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 4   name: pdbs/split_chain/6RZE_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 5   name: pdbs/split_chain/4X8M_A.pdb
pdb/seq: 6   name: pdbs/split_chain/4X8H_A.pdb
pdb/seq: 7   name: pdbs/split_chain/1E4V_A.pdb
pdb/seq: 8   name: pdbs/split_chain/3HPR_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 9   name: pdbs/split_chain/5EJE_A.pdb
```

```
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 10   name: pdbs/split_chain/1E4Y_A.pdb
pdb/seq: 11   name: pdbs/split_chain/3X2S_A.pdb
pdb/seq: 12   name: pdbs/split_chain/6HAP_A.pdb
pdb/seq: 13   name: pdbs/split_chain/6HAM_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 14   name: pdbs/split_chain/4K46_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 15   name: pdbs/split_chain/4NP6_A.pdb
pdb/seq: 16   name: pdbs/split_chain/3GMT_A.pdb
pdb/seq: 17   name: pdbs/split_chain/4PZL_A.pdb
```

##Principal component analysis With these all PDB files

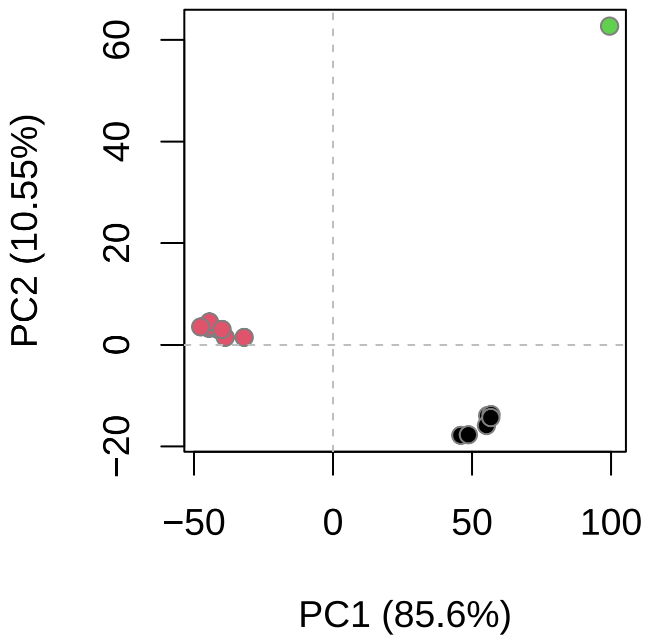
```
# Perform PCA
pc.xray <- pca(pdbs)
plot(pc.xray)
```



```
# Calculate RMSD
rd <- rmsd(pdbs)
```

```
Warning in rmsd(pdbs): No indices provided, using the 199 non NA positions
```

```r
# Structure-based clustering
hc.rd <- hclust(dist(rd))
grps.rd <- cutree(hc.rd, k=3)

plot(pc.xray, 1:2, col="grey50", bg=grps.rd, pch=21, cex=1)
```



```r
mktrj(pc.xray)
```

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

BiocManager::install("msa")

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

"devtools" package itself is not hosted on CRAN or Bioconductor, it is available on GitHub, and can be installed like: install.packages("devtools")

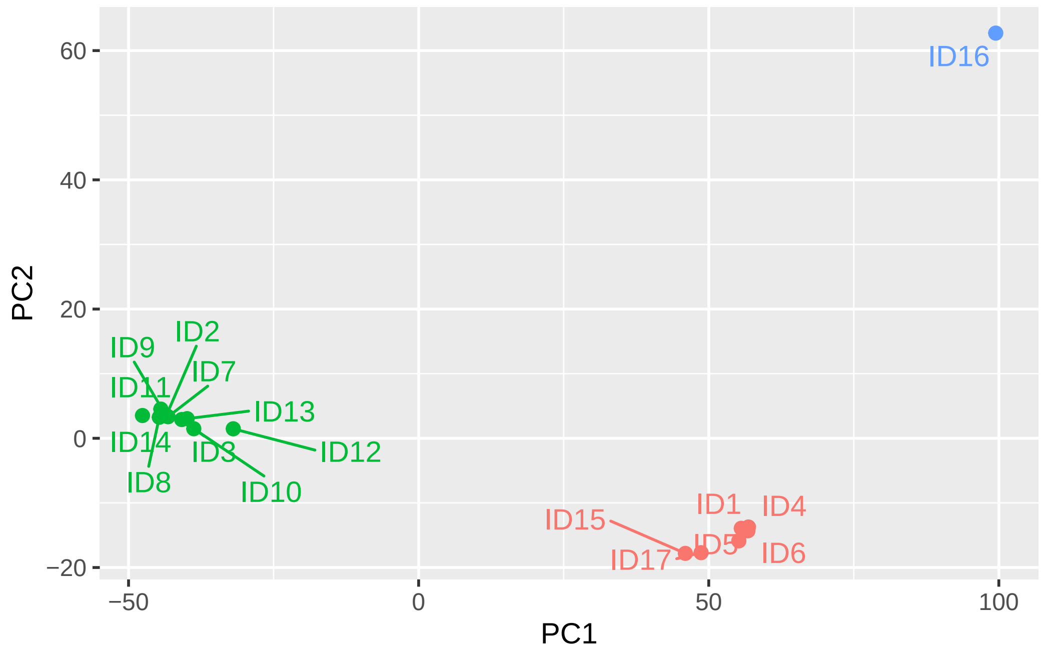
> Q12. True or False? Functions from the devtools package can be used to install packages from GitHub and BitBucket?

TRUE

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

```r
ids <- paste("ID", 1:17, sep = "")
```

```r
#Plotting results with ggplot2
library(ggplot2)
library(ggrepel)

df <- data.frame(PC1=pc.xray$z[,1],
                 PC2=pc.xray$z[,2],
                 col=as.factor(grps.rd),
                 ids=ids)

p <- ggplot(df) +
  aes(PC1, PC2, col=col, label=ids) +
  geom_point(size=2) +
  geom_text_repel(max.overlaps = 20) +
  theme(legend.position = "none")
p
```


PC2
PC1
ID16
ID9
ID2
ID7
ID11
ID13
ID14
ID3
ID12
ID8
ID10
ID15
ID1
ID4
ID5
ID6
ID17