Class9: Structural Bioinformatics

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This main database for structural data is called the PDB (protein data bank). Let's see what it contains:

Data from:https://www.rcsb.org/stats/

Read this into R

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

```
                         X.ray     EM    NMR Multiple.methods Neutron Other
Protein (only)         167,192 15,572 12,529              208      77    32
Protein/Oligosaccharide  9,639  2,635     34                8       2     0
Protein/NA               8,730  4,697    286                7       0     0
Nucleic acid (only)      2,869    137  1,507               14       3     1
Other                      170     10     33                0       0     0
Oligosaccharide (only)      11      0      6                1       0     4
                         Total
Protein (only)         195,610
Protein/Oligosaccharide  12,318
Protein/NA               13,720
Nucleic acid (only)       4,531
Other                       213
Oligosaccharide (only)       22
```

and answer the following questions:

```
pdbdb$Total
```

```
[1] "195,610" "12,318"  "13,720"  "4,531"   "213"     "22"
```

I need to remove the comma and convert to numeric to do math:

```
as.numeric(sub(",","",pdbdb$Total))
```

```
[1] 195610  12318  13720   4531    213     22
```

I could turn this into a function to fix the whole table or any future table I read like this:

```
x <- pdbdb$Total
as.numeric(sub(",","",x))
```

```
[1] 195610  12318  13720   4531    213     22
```

```
comma2numeric <- function(x){
  as.numeric(sub(",","",x))
}
```

Test it

```
comma2numeric(pdbdb$X.ray)
```

```
[1] 167192   9639   8730   2869    170     11
```

```
apply(pdbdb,2, comma2numeric)
```

```
      X.ray    EM   NMR Multiple.methods Neutron Other  Total
[1,] 167192 15572 12529               208      77    32 195610
[2,]   9639  2635    34                 8       2     0  12318
[3,]   8730  4697   286                 7       0     0  13720
[4,]   2869   137  1507                14       3     1   4531
[5,]    170    10    33                 0       0     0    213
[6,]     11     0     6                 1       0     4     22
```

##Or try a different read/import function:

```
library(readr)
pdbdb <- read_csv("Data Export Summary.csv")
```

```
Rows: 6 Columns: 8
-- Column specification --------------------------------------------------------
Delimiter: ","
chr (1): Molecular Type
dbl (3): 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.
```

```
sum(pdbdb$Total)
```

```
[1] 226414
```

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

```
(sum(pdbdb$`X-ray`)+sum(pdbdb$EM))/sum(pdbdb$Total)*100
```

```
[1] 93.4845
```

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

```
pdbdb$Total[1]/sum(pdbdb$Total)
```

```
[1] 0.8639483
```

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?

226,414

##Mol *Mol* (pronounced "molstar") is a new web-based molecular viewer that we will need to learn the basics of here.

https://molstar.org/viewer/

We will use PDB code: 1HSG

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

The water molecules are in ball & stick representation, where H atoms are not displayed.

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

HOH 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 1: A first image from molstar

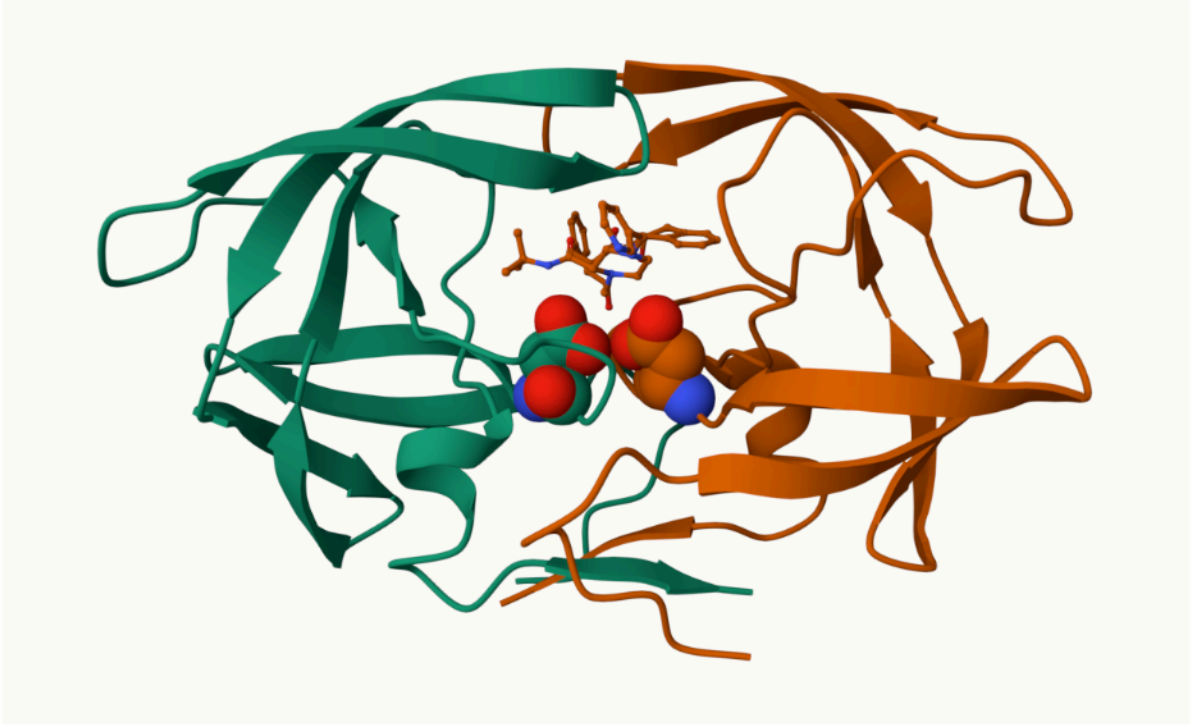


Figure 2: The all important catlytic ASP25 amino acids

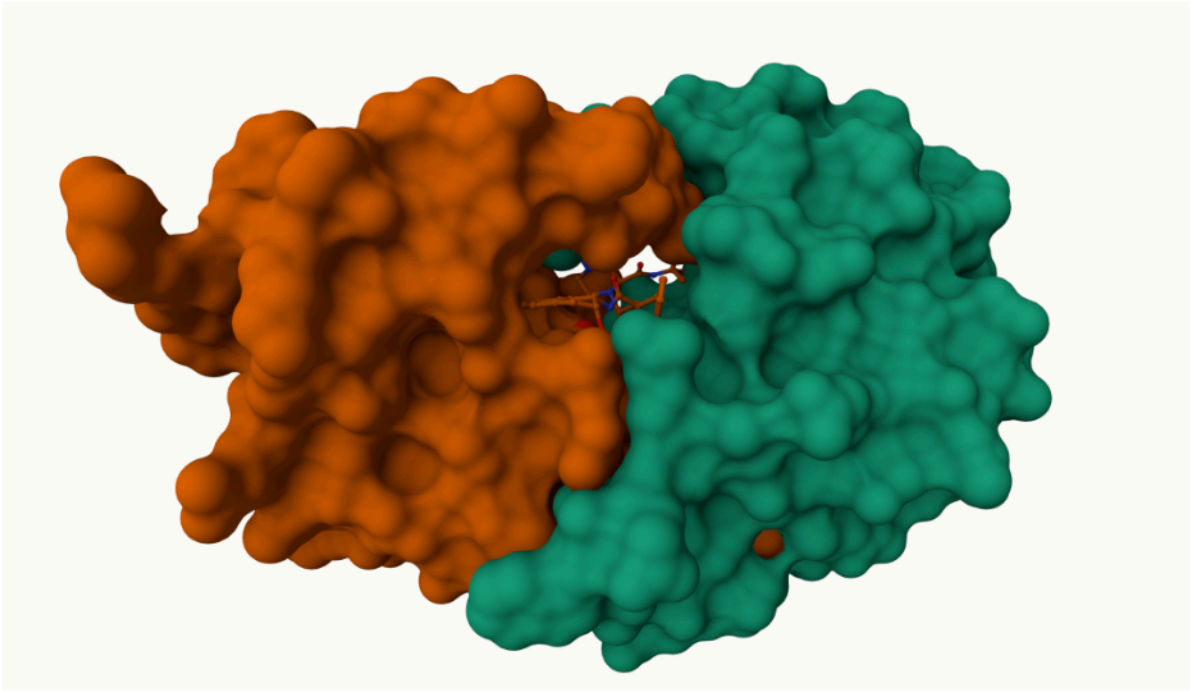


Figure 3: Surface display showing Merk compound in the peptide binding pocket

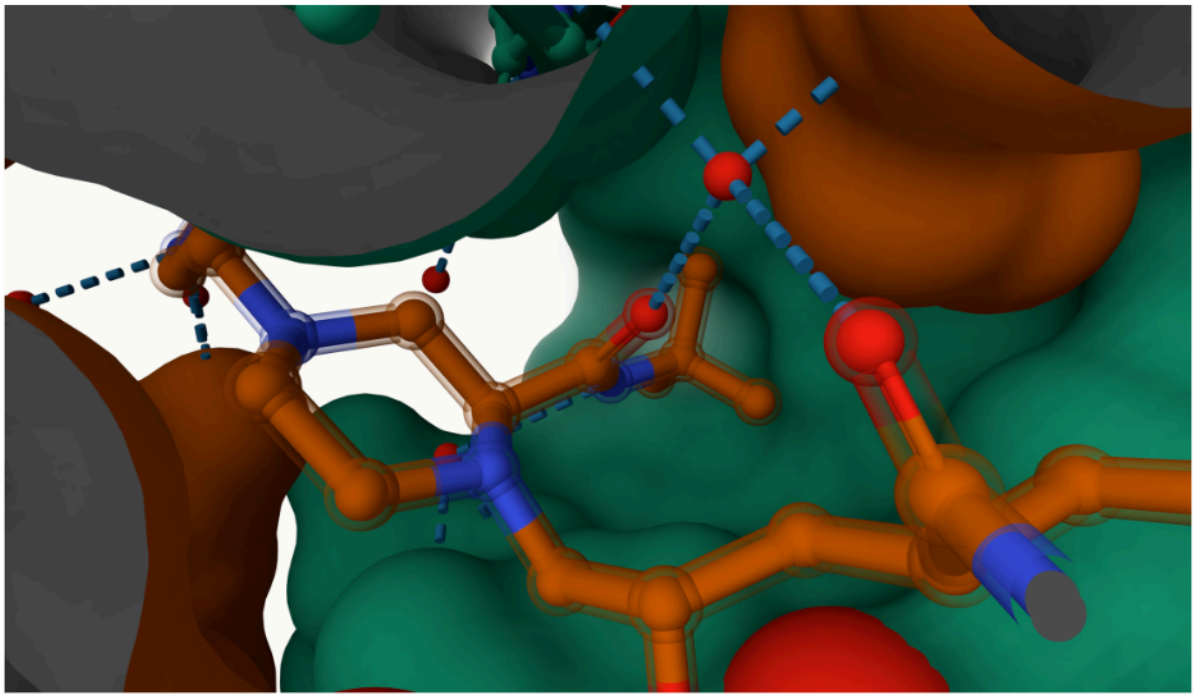


Figure 4: HOH 308 in the peptide binding pocket

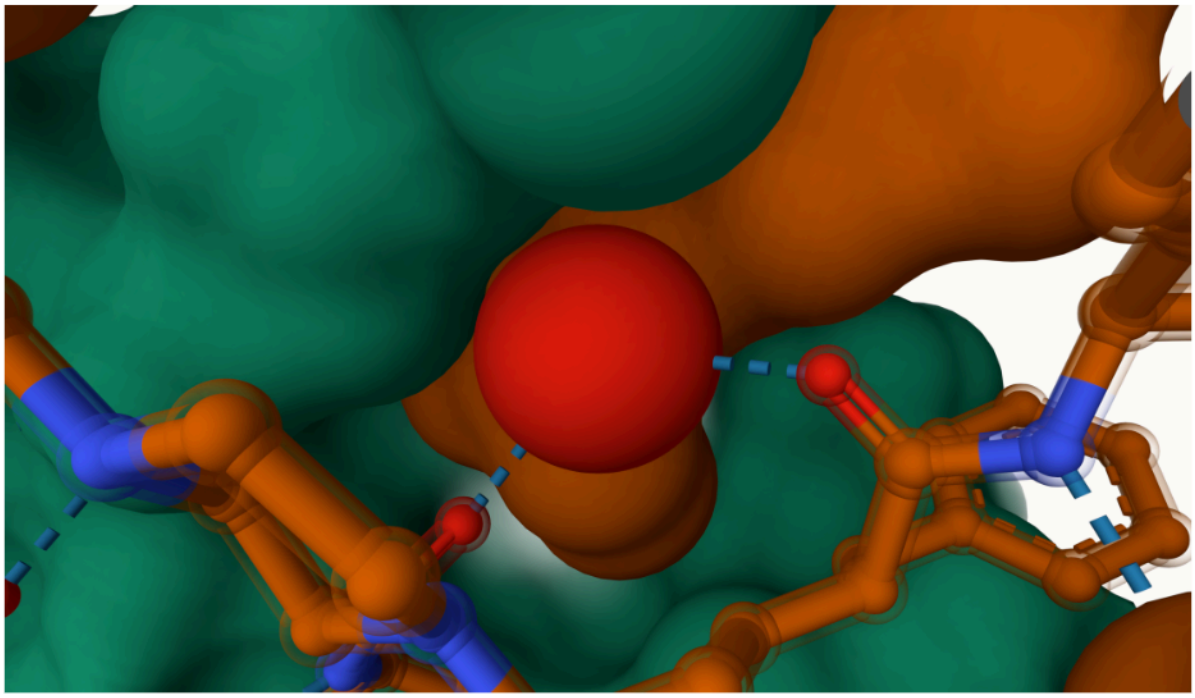


Figure 5: Another picture of HOH 308 as spacefill

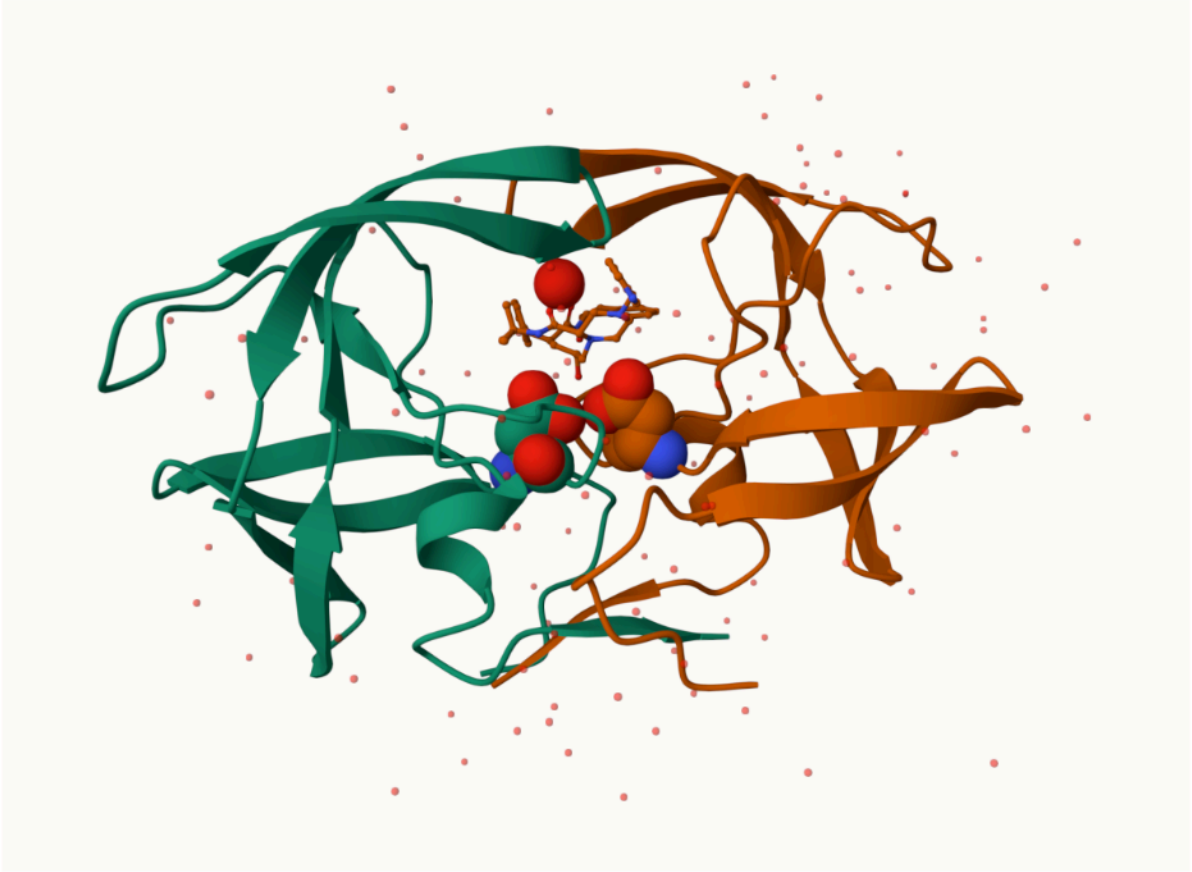


Figure 6: Another picture with HOH 308 and ASP25 as spacefill

##The Bio3D package

The bio3d package allows us to do all sorts of strucutral bioinformatics work in R.

Let's start with how it cna read these PDB ifles:

```
library(bio3d)
pdb <- read.pdb("1hsg")
```

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

```
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
```

```
attributes(pdb)
```

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

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

```
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>
```

```
pdbseq(pdb)[25]
```

```
 25
"D"
```

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

```
sum(pdb$calpha)
```

```
[1] 198
```

```
length(pdbseq(pdb))
```

```
[1] 198
```

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

HOH and MK1

Q9: How many protein chains are in this structure?

2

```
unique(pdb$atom$chain)
```

```
[1] "A" "B"
```

##Predicting functional motions of a single structure

Let's do a bioinformatics prediction of functional motions-i.e. the movements that one of these molecules needs to make to do its stuff.

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

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

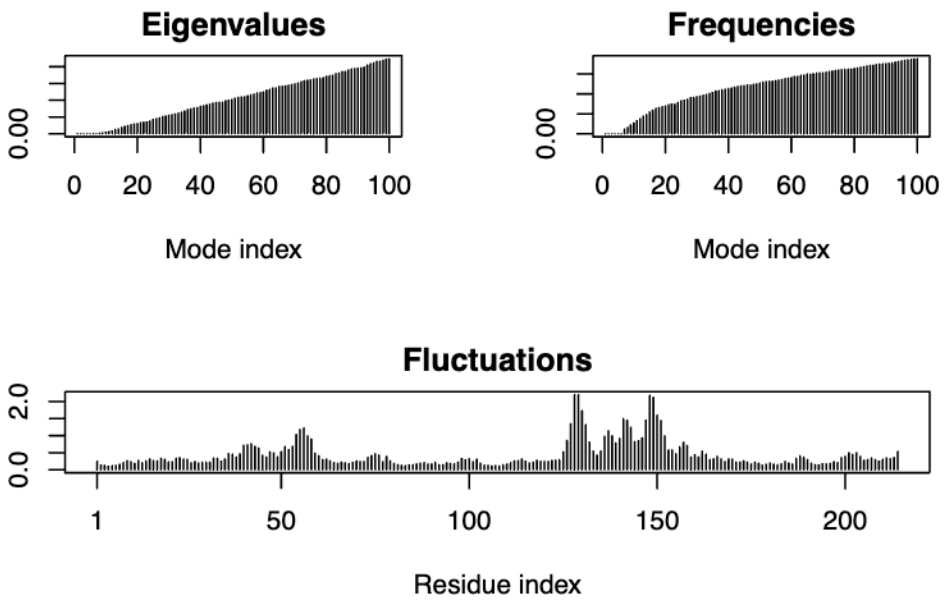
```
adk
```

```
 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
```

```
# Perform flexiblity prediction
m <- nma(adk)
```

```
 Building Hessian...        Done in 0.013 seconds.
 Diagonalizing Hessian...   Done in 0.278 seconds.
```

```
plot(m)
```



Write out multi-model PDB file (trajectory) that we can use to make an animation of the predicted motion.

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

I can open this in Mol* to play the trajectory...

install.packages("bio3d") install.packages("devtools") install.packages("BiocManager")

BiocManager::install("msa") devtools::install_bitbucket("Grantlab/bio3d-view")

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

msa

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

bio3d-view

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

True

```
library(bio3d)
aa <- get.seq("1ake_A")
```

```
Warning in get.seq("1ake_A"): Removing existing file: seqs.fasta

Fetching... Please wait. Done.
```

```
aa
```

```
              1        .         .         .         .         .         60
pdb|1AKE|A    MRIILLGAPGAGKGTQAQFIMEKYGIPQISTGDMLRAAVKSGSELGKQAKDIMDAGKLVT
              1        .         .         .         .         .         60

             61        .         .         .         .         .         120
pdb|1AKE|A    DELVIALVKERIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFDVPDELIVDRI
             61        .         .         .         .         .         120

            121        .         .         .         .         .         180
pdb|1AKE|A    VGRRVHAPSGRVYHVKFNPPKVEGKDDVTGEELTTRKDDQEETVRKRLVEYHQMTAPLIG
            121        .         .         .         .         .         180

            181        .         .         .   214
pdb|1AKE|A    YYSKEAEAGNTKYAKVDGTKPVAEVRADLEKILG
            181        .         .         .   214

Call:
  read.fasta(file = outfile)

Class:
  fasta

Alignment dimensions:
  1 sequence rows; 214 position columns (214 non-gap, 0 gap)

+ attr: id, ali, call
```

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

214

```
# Blast or hmmer search
#b <- blast.pdb(aa)
#hits <- plot(b)
#head(hits$pdb.id)
hits <- NULL
hits$pdb.id <- c('1AKE_A','6S36_A','6RZE_A','3HPR_A','1E4V_A','5EJE_A','1E4Y_A','3X2S_A','6HA
```

```
# 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/1AKE.pdb.gz exists. Skipping download

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

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

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

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

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

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

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

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

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

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

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

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


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  |================================================================      |  85%
  |
  |====================================================================  |  92%
  |
  |======================================================================| 100%
```
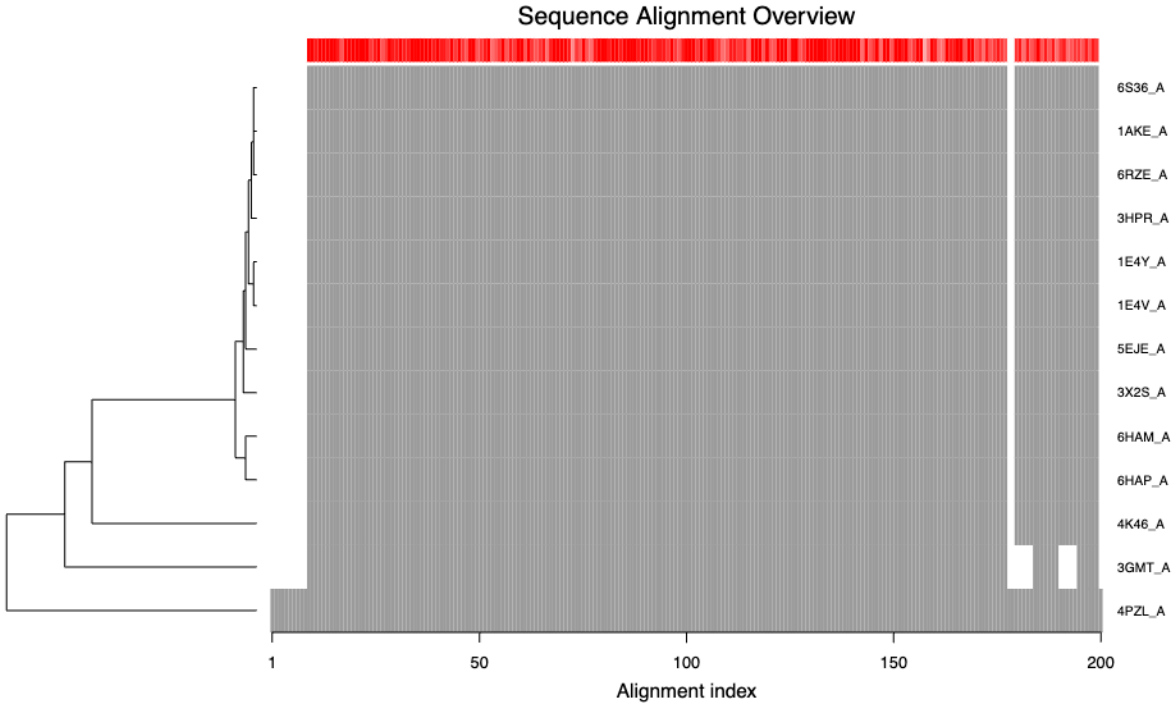

```
# Align releated PDBs
pdbs <- pdbaln(files, fit = TRUE, exefile="msa")
```

```
Reading PDB files:
pdbs/split_chain/1AKE_A.pdb
pdbs/split_chain/6S36_A.pdb
pdbs/split_chain/6RZE_A.pdb
pdbs/split_chain/3HPR_A.pdb
pdbs/split_chain/1E4V_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/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
...

Extracting sequences

pdb/seq: 1   name: pdbs/split_chain/1AKE_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 2   name: pdbs/split_chain/6S36_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 3   name: pdbs/split_chain/6RZE_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 4   name: pdbs/split_chain/3HPR_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 5   name: pdbs/split_chain/1E4V_A.pdb
pdb/seq: 6   name: pdbs/split_chain/5EJE_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 7   name: pdbs/split_chain/1E4Y_A.pdb
pdb/seq: 8   name: pdbs/split_chain/3X2S_A.pdb
pdb/seq: 9   name: pdbs/split_chain/6HAP_A.pdb
pdb/seq: 10   name: pdbs/split_chain/6HAM_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
pdb/seq: 11   name: pdbs/split_chain/4K46_A.pdb
   PDB has ALT records, taking A only, rm.alt=TRUE
```

```
pdb/seq: 12   name: pdbs/split_chain/3GMT_A.pdb
pdb/seq: 13   name: pdbs/split_chain/4PZL_A.pdb
```

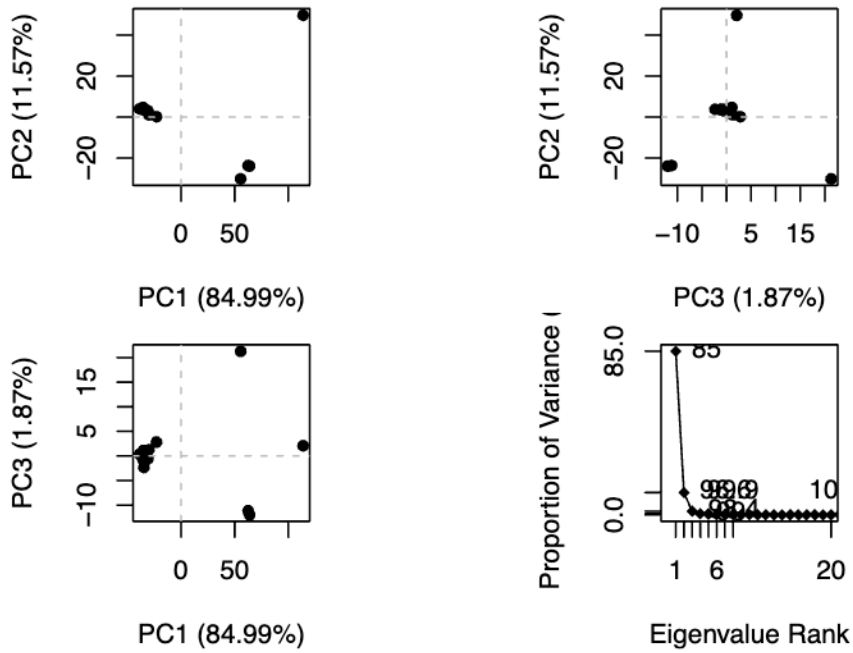
```
# Vector containing PDB codes for figure axis

ids <- basename.pdb(pdbs$id)

# Draw schematic alignment
plot(pdbs, labels = ids)
```




```
anno <- pdb.annotate(ids)
unique(anno$source)
```

```
[1] "Escherichia coli"
[2] "Escherichia coli K-12"
[3] "Escherichia coli O139:H28 str. E24377A"
[4] "Escherichia coli str. K-12 substr. MDS42"
[5] "Photobacterium profundum"
[6] "Burkholderia pseudomallei 1710b"
[7] "Francisella tularensis subsp. tularensis SCHU S4"
```

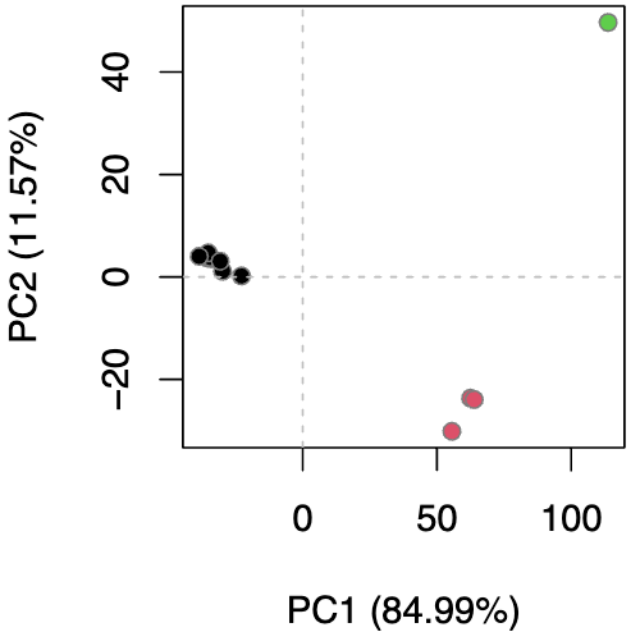
```
# Perform PCA
pc.xray <- pca(pdbs)
plot(pc.xray)
```




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

```
Warning in rmsd(pdbs): No indices provided, using the 204 non NA positions
```

```
# 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)
```


PC2 (11.57%)
40
20
0
−20
0
50
100
PC1 (84.99%)