Class10: Structural Bioinformatics (Pt. 1)

Yi-Hung Lee(PID: A16587141)

1: Introduction to the RCSB Protein Data Bank (PDB)

Import .csv file

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

```
                         X.ray     EM    NMR Multiple.methods Neutron Other
Protein (only)         163,468 13,582 12,390              204      74    32
Protein/Oligosaccharide  9,437  2,287     34                8       2     0
Protein/NA               8,482  4,181    286                7       0     0
Nucleic acid (only)      2,800    132  1,488               14       3     1
Other                      164      9     33                0       0     0
Oligosaccharide (only)      11      0      6                1       0     4
                         Total
Protein (only)         189,750
Protein/Oligosaccharide 11,768
Protein/NA              12,956
Nucleic acid (only)      4,438
Other                      206
Oligosaccharide (only)      22
```

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

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

data <- as.data.frame(apply(data, 2, sumcomma))
data
```

```
   X.ray    EM   NMR Multiple.methods Neutron Other  Total
1 163468 13582 12390              204      74    32 189750
2   9437  2287    34                8       2     0  11768
3   8482  4181   286                7       0     0  12956
4   2800   132  1488               14       3     1   4438
5    164     9    33                0       0     0    206
6     11     0     6                1       0     4     22
```

```
(data$X.ray[1] + data$EM[1]) / data$Total[1] * 100
```

```
[1] 93.30698
```

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

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

```
[1] 86.58848
```

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?

```
248805733 - 186898
```

```
[1] 248618835
```

Visualizing the HIV-1 protease structure

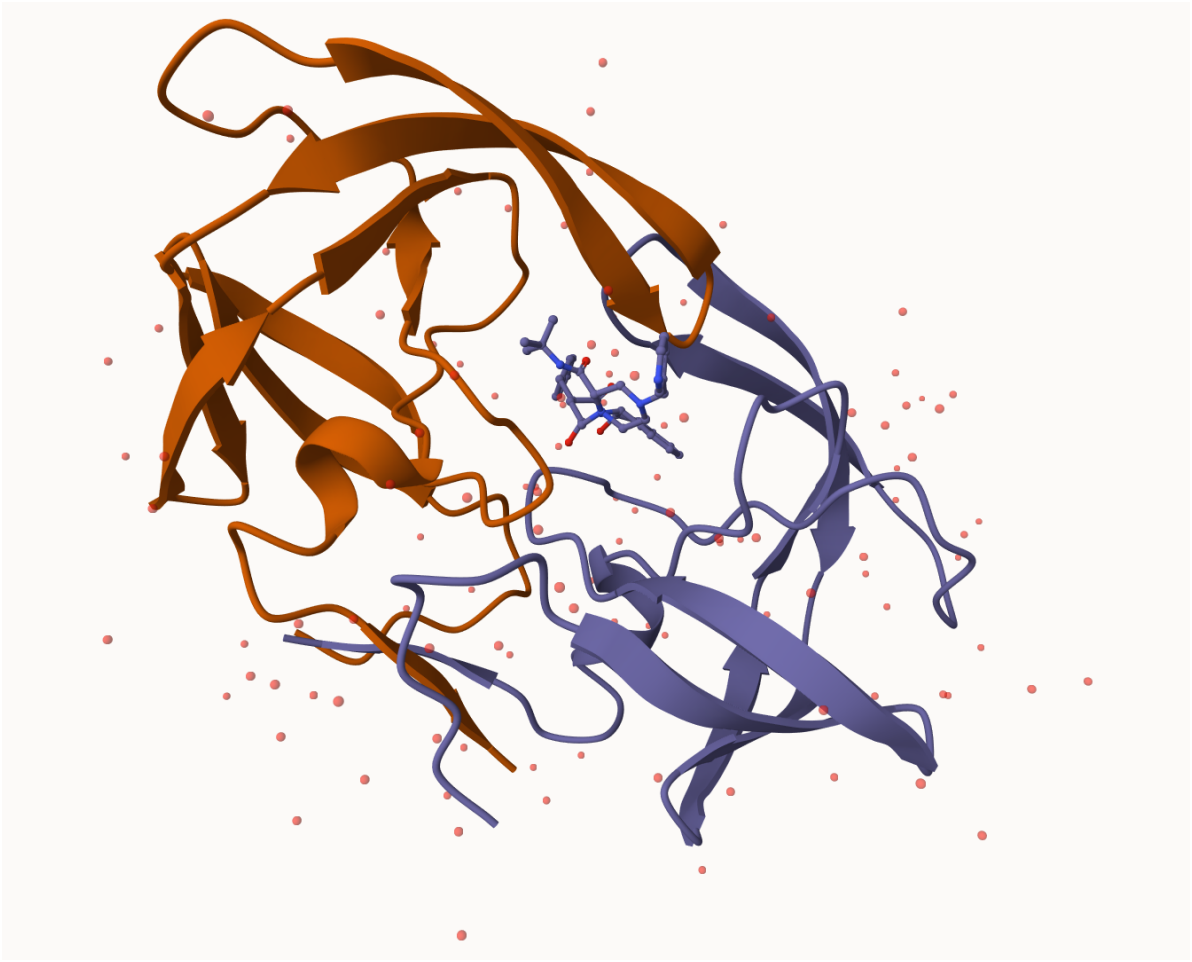
Mol* (Molstar) viewer is now everywhere

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

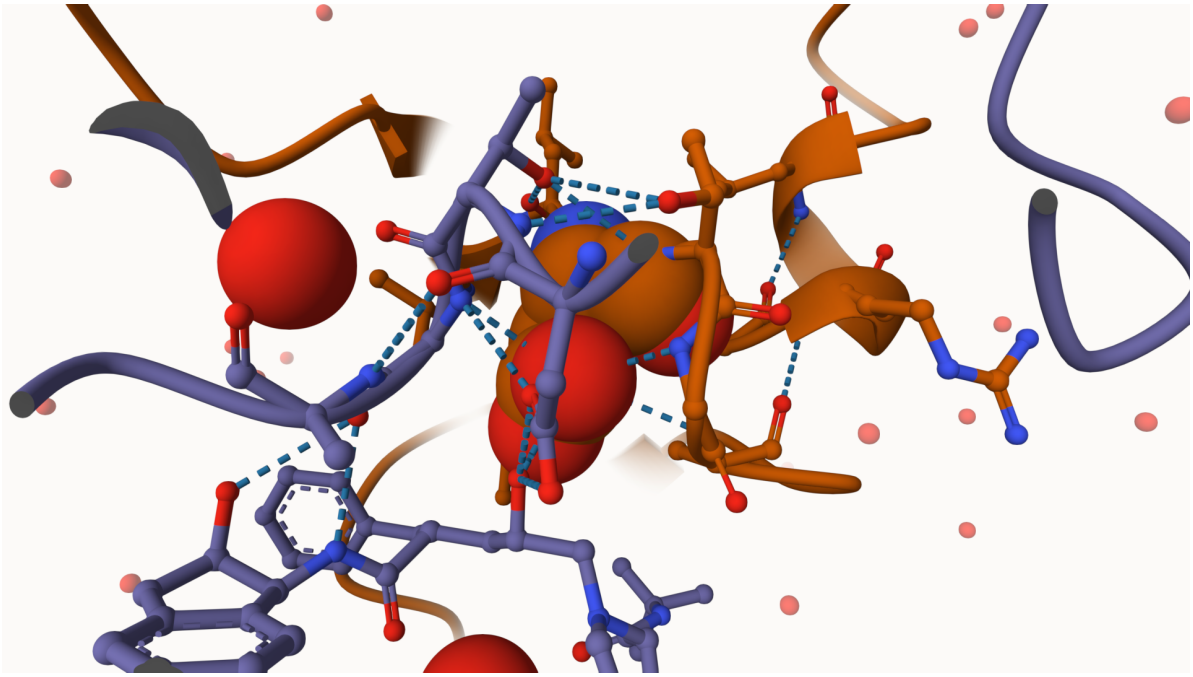
Hydrogen is too small

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

ASP 25 interact with 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.



```
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"
```

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

There are 198 amino acids in the pdb object

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

HOH (127), MK1 (1)

Q9: How many protein chains are in this structure?

```
length(pdb$helix$chain)
```

```
[1] 2
```

```
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>
```

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
```

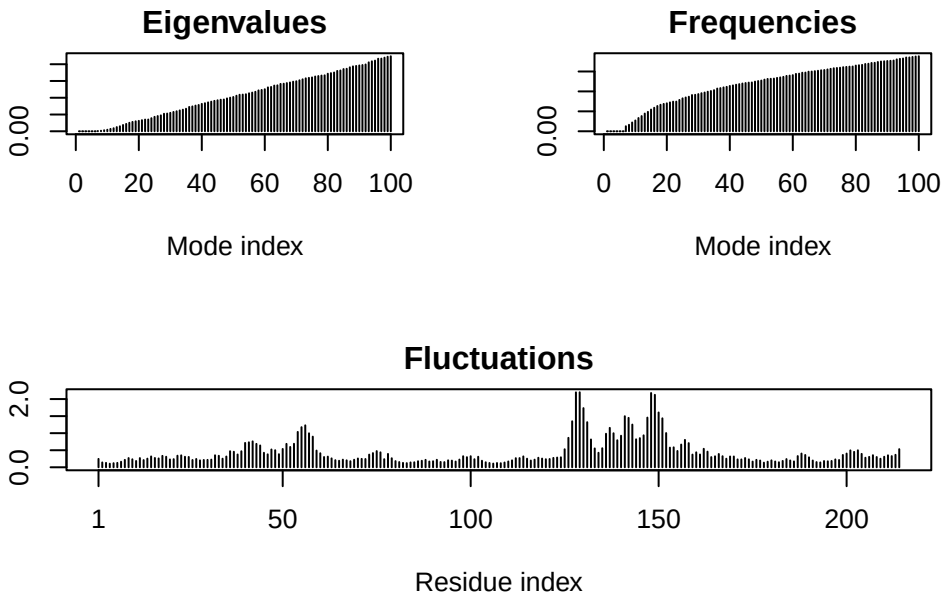
```
adk
```

```
 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
```

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

```
Building Hessian...        Done in 0.013 seconds.
Diagonalizing Hessian...   Done in 0.255 seconds.
```

```
plot(m)
```




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

4. Comparative structure analysis of Adenylate Kinase

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

msa package

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

devtools

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

True

```
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)
```

```
# Plot a summary of search results
# hits <- plot(b)
```

```
hits <- NULL
hits$pdb.id <- c('1AKE_A','6S36_A','6RZE_A','3HPR_A','1E4V_A','5EJE_A','1E4Y_A','3X2S_A','
```

```
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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  |======================================================================| 100%
```

Align and superpose structures

```
# 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
#par(mar = c(1, 1, 1, 1))
#plot(pdbs, labels=ids)
```

Annotate collected PDB structures

```
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"
```

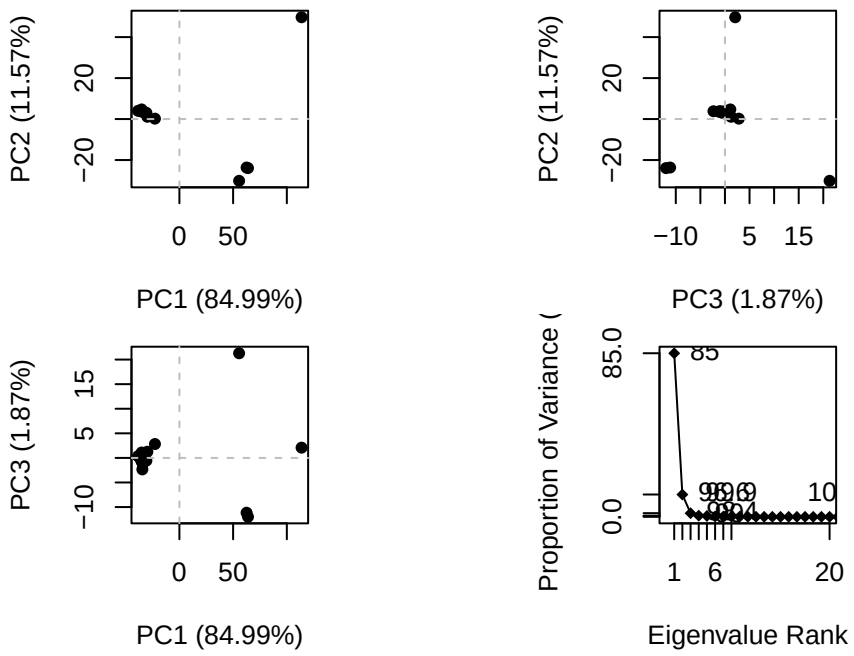
```
head(anno)
```

```
       structureId chainId macromoleculeType chainLength experimentalTechnique
1AKE_A        1AKE       A           Protein         214                X-ray
6S36_A        6S36       A           Protein         214                X-ray
6RZE_A        6RZE       A           Protein         214                X-ray
3HPR_A        3HPR       A           Protein         214                X-ray
1E4V_A        1E4V       A           Protein         214                X-ray
```

```
5EJE_A        5EJE       A           Protein         214                 X-ray
       resolution       scopDomain                                       pfam
1AKE_A       2.00 Adenylate kinase Adenylate kinase, active site lid (ADK_lid)
6S36_A       1.60             <NA>                      Adenylate kinase (ADK)
6RZE_A       1.69             <NA> Adenylate kinase, active site lid (ADK_lid)
3HPR_A       2.00             <NA>                      Adenylate kinase (ADK)
1E4V_A       1.85 Adenylate kinase                      Adenylate kinase (ADK)
5EJE_A       1.90             <NA>                      Adenylate kinase (ADK)
               ligandId                                      ligandName
1AKE_A              AP5                 BIS(ADENOSINE)-5'-PENTAPHOSPHATE
6S36_A CL (3),NA,MG (2)    CHLORIDE ION (3),SODIUM ION,MAGNESIUM ION (2)
6RZE_A    NA (3),CL (2)                  SODIUM ION (3),CHLORIDE ION (2)
3HPR_A              AP5                 BIS(ADENOSINE)-5'-PENTAPHOSPHATE
1E4V_A              AP5                 BIS(ADENOSINE)-5'-PENTAPHOSPHATE
5EJE_A           AP5,CO BIS(ADENOSINE)-5'-PENTAPHOSPHATE,COBALT (II) ION
                                  source
1AKE_A                      Escherichia coli
6S36_A                      Escherichia coli
6RZE_A                      Escherichia coli
3HPR_A                 Escherichia coli K-12
1E4V_A                      Escherichia coli
5EJE_A Escherichia coli O139:H28 str. E24377A

1AKE_A STRUCTURE OF THE COMPLEX BETWEEN ADENYLATE KINASE FROM ESCHERICHIA COLI AND THE INHIBI
6S36_A
6RZE_A
3HPR_A
1E4V_A
5EJE_A                                                                    Cryst
                                                 citation rObserved  rFree
1AKE_A               Muller, C.W., et al. J Mol Biol (1992)    0.1960     NA
6S36_A                Rogne, P., et al. Biochemistry (2019)    0.1632 0.2356
6RZE_A                Rogne, P., et al. Biochemistry (2019)    0.1865 0.2350
3HPR_A Schrank, T.P., et al. Proc Natl Acad Sci U S A (2009)    0.2100 0.2432
1E4V_A                 Muller, C.W., et al. Proteins (1993)    0.1960     NA
5EJE_A Kovermann, M., et al. Proc Natl Acad Sci U S A (2017)    0.1889 0.2358
       rWork spaceGroup
1AKE_A 0.1960  P 21 2 21
6S36_A 0.1594    C 1 2 1
6RZE_A 0.1819    C 1 2 1
3HPR_A 0.2062  P 21 21 2
1E4V_A 0.1960  P 21 2 21
5EJE_A 0.1863  P 21 2 21
```

```
pc.xray <- pca(pdbs)
plot(pc.xray)
```

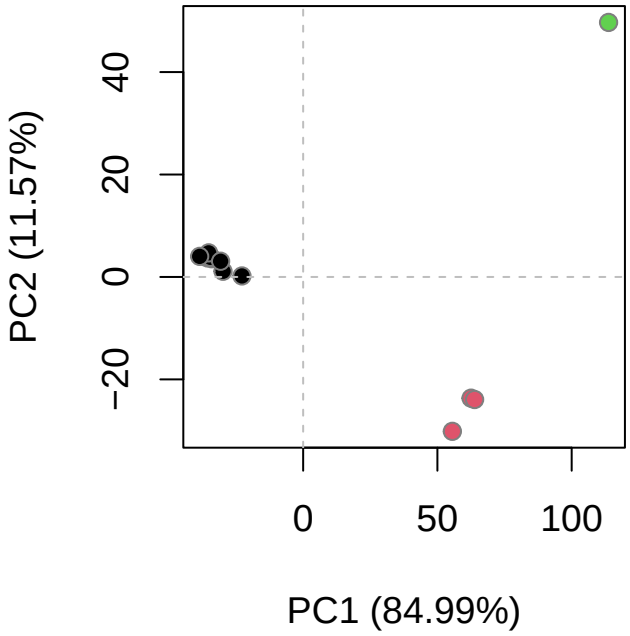



```
# Calculate RMSD
rd <- rmsd(pdbs)
```

```
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)
```



5. Optional further visualization

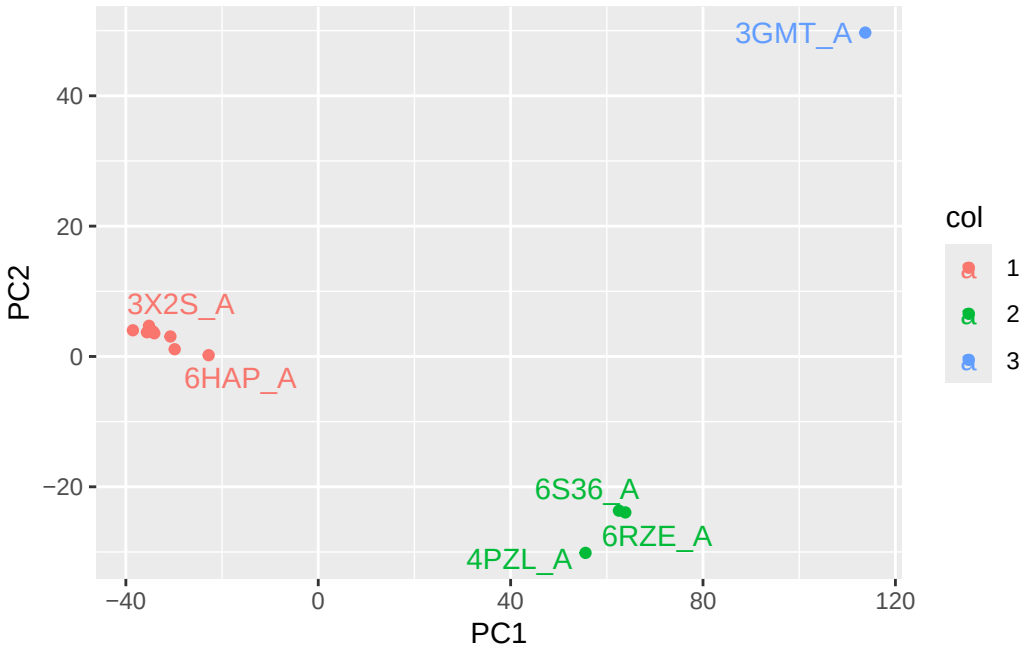
```
# Visualize first principal component
pc1 <- mktrj(pc.xray, pc=1, file="pc_1.pdb")
```

```
library(ggplot2)
library(ggrepel)

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

ggplot(df, aes(PC1, PC2, col = col, label = ids)) +
  geom_point() +
  geom_text_repel(max.overlaps = 15)
```

```
Warning: ggrepel: 7 unlabeled data points (too many overlaps). Consider
increasing max.overlaps
```


3GMT_A
3X2S_A
6HAP_A
6S36_A
6RZE_A
4PZL_A
40
20
0
−20
PC2
−40
0
40
80
120
PC1
col
1
2
3