Class 010 - Structural Biology pt. I

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1 - Introduction to the RCSB ProteinData Bank (PDB)

```
#Note: this is how we create hyperlinks within our HTML.
```

PDB is the main repository of bio-molecular structure data. Let;s see what is in it:

```
stats <- read.csv("pdb_stats (1).csv")
head(stats)
```

```
           Molecular.Type  X.ray    EM   NMR Integrative Multiple.methods
1          Protein (only) 178795 21825 12773         343              226
2 Protein/Oligosaccharide  10363  3564    34           8               11
3              Protein/NA   9106  6335   287          24                7
4     Nucleic acid (only)   3132   221  1566           3               15
5                   Other    175    25    33           4                0
6  Oligosaccharide (only)     11     0     6           0                1
  Neutron Other  Total
1      84    32 214078
2       1     0  13981
```

```
3       0     0  15759
4       3     1   4941
5       0     0    237
6       0     4     22
```

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

```
n.sums <- colSums(stats[ , -1]) # compute column totals after dropping the first (non-numeric
n <- n.sums / n.sums["Total"]
round(n, 3)
```

```
          X.ray              EM             NMR     Integrative
          0.810           0.128           0.059           0.002
Multiple.methods         Neutron           Other           Total
          0.001           0.000           0.000           1.000
```

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

nsums[“Total”]

```
n.sums["Total"]
```

```
 Total
249018
```

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?

~1,173 as of 2/9/26.

```
#Note: I don't think this is correct, too tired to care.
```

Using Molstar

We can use the main Molstar viewer online

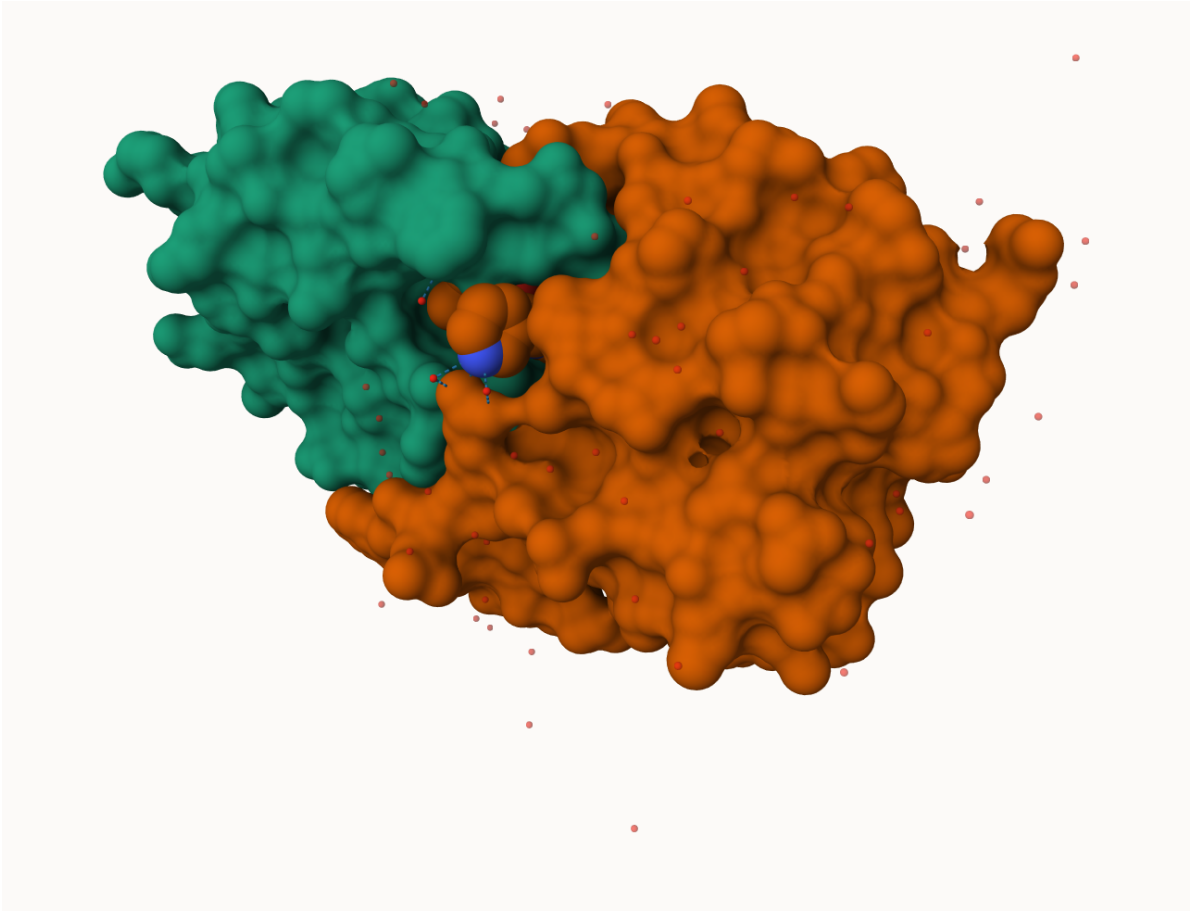


Figure 1: **Figure Caption Goes Here** and appears below image. **Ex:** First view of HIV-Pr Dimer with ligand in active site.

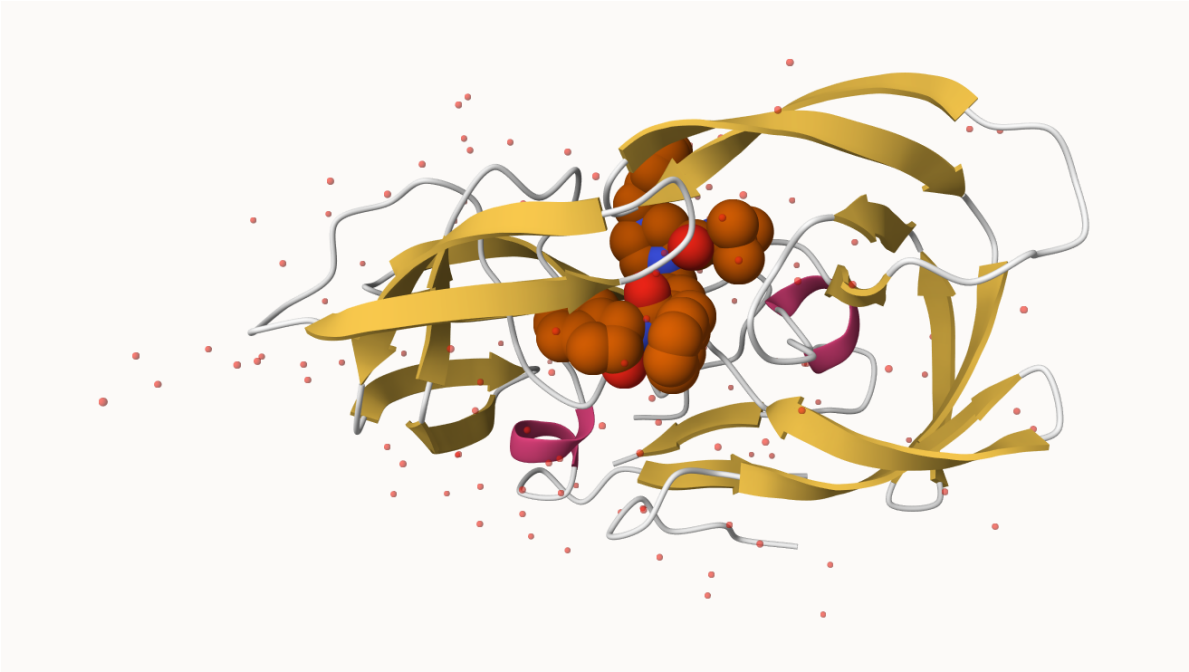
Q4: Water molecules normally have 3 atoms. Why do we see just one atom per water molecule in this structure?

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

2 - Visualizing the HIV-1 protease structure

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. Discussion Topic:

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



Q7 (optional) Generate and save a figure clearly showing the two HIV-1 protease chains, the bound inhibitor, the catalytic ASP25 residues from each chain, and the conserved active-site water molecule.

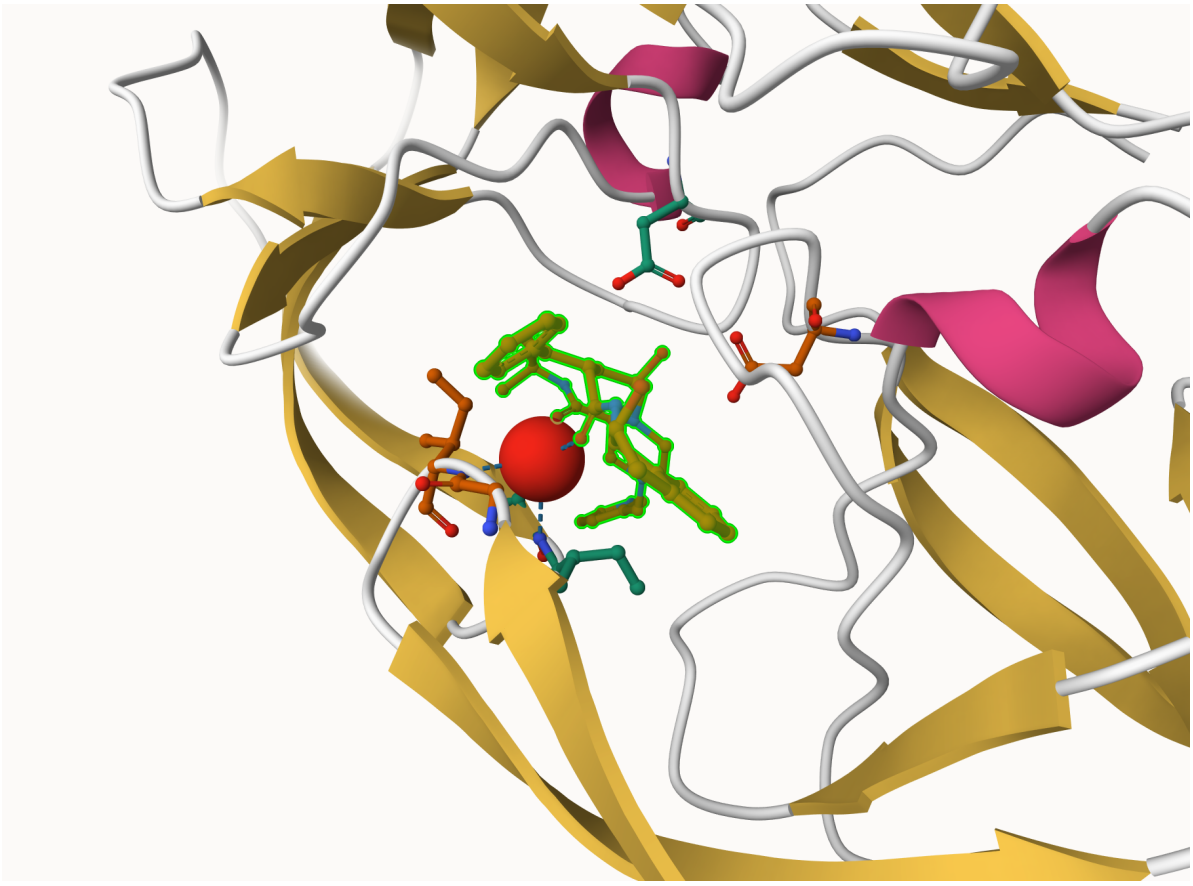


Figure 2: Ligand is highlighted green, residues ASP25 for both chains shown along with H2O molecule as red space fill sphere.

3 - Introduction to Bio3D in R

`Bio3D` is an R package for structural bioinformatics. Features include the ability to read, write and analyze biomolecular structure, sequence and dynamic trajectory data.

```
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
```

```
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>
```

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

There are 198 AA residues. This can be identifed by: '(residues/Calpha atoms#: 198)'.

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

MK1 is one of the two non-protein residues.

Q9: How many protein chains are in this structure?

This structure has 2 protein chains, identified by A and B.

Quick PDB Visualization in R

```
#library(bio3dview)library(NGLVieweR)view.pdb(pdb) |>setSpin()


# Select the important ASP 25 residue sele <- atom.select(pdb, resno=25)

# and highlight them in spacefill representation view.pdb(pdb, cols=c("navy","teal"),highligh


#Adjusted this code to keep it here silently.
```

Reading in Adenylate Kinase

```
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
```

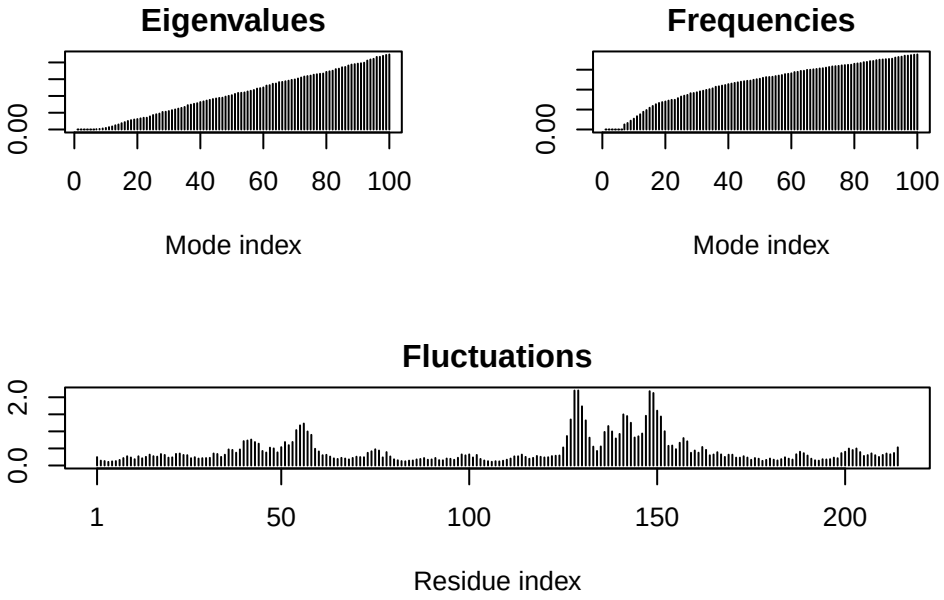
```
      VGRRVHAPSGRVYHVKFNPPKVEGKDDVTGEELTTRKDDQEETVRKRLVEYHQMTAPLIG
      YYSKEAEAGNTKYAKVDGTKPVAEVRADLEKILG

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

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

```
 Building Hessian...        Done in 0.029 seconds.
 Diagonalizing Hessian...   Done in 0.587 seconds.
```

```
plot(m)
```



Movie - Visual :

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

4 - Comparative structure analysis of Andenylate Kinase

```
#Notes (From instructions) : The install.packages() function is used to install packages fro
```

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

`msa` is only available through BioConductor and not CRAN.

Q11. Which of the above packages is not found on BioConductor or CRAN?: `bio3dview` is on neither.

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

TRUE

Search and Retrieve

```
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?

Out shows that this contains 214 AAs in this sequence.

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

```
# 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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  |======================================================================| 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
```

Annotate Collected PDB Structures

```
# Vector containing PDB database codes
ids <- basename.pdb(pdbs$id)

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"
```

```
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
1E4Y_A        1E4Y       A           Protein         214                X-
ray
3X2S_A        3X2S       A           Protein         214                X-
ray
6HAP_A        6HAP       A           Protein         214                X-
ray
6HAM_A        6HAM       A           Protein         214                X-
ray
4K46_A        4K46       A           Protein         214                X-
ray
3GMT_A        3GMT       A           Protein         230                X-
ray
4PZL_A        4PZL       A           Protein         242                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 (ADK)
3HPR_A       2.00             <NA> Adenylate kinase, active site lid (ADK_lid)
1E4V_A       1.85 Adenylate kinase                    Adenylate kinase (ADK)
5EJE_A       1.90             <NA> Adenylate kinase, active site lid (ADK_lid)
1E4Y_A       1.85 Adenylate kinase Adenylate kinase, active site lid (ADK_lid)
3X2S_A       2.80             <NA>                                      <NA>
6HAP_A       2.70             <NA>                    Adenylate kinase (ADK)
6HAM_A       2.55             <NA> Adenylate kinase, active site lid (ADK_lid)
4K46_A       2.01             <NA> Adenylate kinase, active site lid (ADK_lid)
3GMT_A       2.10             <NA>                                      <NA>
4PZL_A       2.10             <NA>                    Adenylate kinase (ADK)
              ligandId
1AKE_A             AP5
6S36_A CL (3),NA,MG (2)
6RZE_A    NA (3),CL (2)
3HPR_A             AP5
1E4V_A             AP5
5EJE_A          AP5,CO
1E4Y_A             AP5
3X2S_A   JPY (2),AP5,MG
6HAP_A             AP5
6HAM_A             AP5
```

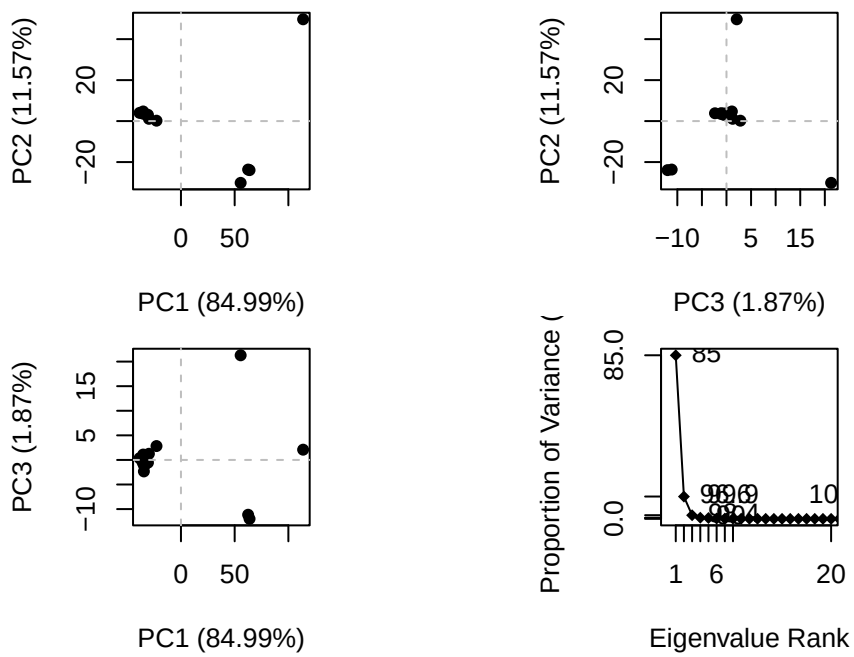
```
4K46_A      ADP,AMP,PO4
3GMT_A          SO4 (2)
4PZL_A       CA,FMT,GOL
                                                                                ligandName
1AKE_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
6S36_A                                    CHLORIDE ION (3),SODIUM ION,MAGNESIUM ION (2)
6RZE_A                                                   SODIUM ION (3),CHLORIDE ION (2)
3HPR_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
1E4V_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
5EJE_A                                 BIS(ADENOSINE)-5'-PENTAPHOSPHATE,COBALT (II) ION
1E4Y_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
3X2S_A N-(pyren-1-ylmethyl)acetamide (2),BIS(ADENOSINE)-5'-PENTAPHOSPHATE,MAGNESIUM ION
6HAP_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
6HAM_A                                                  BIS(ADENOSINE)-5'-
PENTAPHOSPHATE
4K46_A                    ADENOSINE-5'-DIPHOSPHATE,ADENOSINE MONOPHOSPHATE,PHOSPHATE ION
3GMT_A                                                                    SULFATE ION (2)
4PZL_A                                                  CALCIUM ION,FORMIC ACID,GLYCEROL
                                                 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
1E4Y_A                                Escherichia coli
3X2S_A         Escherichia coli str. K-12 substr. MDS42
6HAP_A           Escherichia coli O139:H28 str. E24377A
6HAM_A                             Escherichia coli K-12
4K46_A                         Photobacterium profundum
3GMT_A                   Burkholderia pseudomallei 1710b
4PZL_A Francisella tularensis subsp. tularensis SCHU S4

1AKE_A STRUCTURE OF THE COMPLEX BETWEEN ADENYLATE KINASE FROM ESCHERICHIA COLI AND THE INHIBI
6S36_A
6RZE_A
3HPR_A
1E4V_A
```

```
loop
5EJE_A                                                                    Cryst
1E4Y_A
loop
3X2S_A
conjugated adenylate kinase
6HAP_A
6HAM_A
4K46_A
3GMT_A
4PZL_A                                                                    The cryst
                                                      citation rObserved   rFree
1AKE_A              Muller, C.W., et al. J Mol Biology (1992)   0.19600      NA
6S36_A                  Rogne, P., et al. Biochemistry (2019)   0.16320 0.23560
6RZE_A                  Rogne, P., et al. Biochemistry (2019)   0.18650 0.23500
3HPR_A  Schrank, T.P., et al. Proc Natl Acad Sci U S A (2009)   0.21000 0.24320
1E4V_A                   Muller, C.W., et al. Proteins (1993)   0.19600      NA
5EJE_A  Kovermann, M., et al. Proc Natl Acad Sci U S A (2017)   0.18890 0.23580
1E4Y_A                   Muller, C.W., et al. Proteins (1993)   0.17800      NA
3X2S_A                Fujii, A., et al. Bioconjug Chem (2015)   0.20700 0.25600
6HAP_A               Kantaev, R., et al. J Phys Chem B (2018)   0.22630 0.27760
6HAM_A               Kantaev, R., et al. J Phys Chem B (2018)   0.20511 0.24325
4K46_A                    Cho, Y.-J., et al. To be published    0.17000 0.22290
3GMT_A Buchko, G.W., et al. Biochem Biophys Res Commun (2010)   0.23800 0.29500
4PZL_A                       Tan, K., et al. To be published    0.19360 0.23680
         rWork spaceGroup
1AKE_A 0.19600  P 21 2 21
6S36_A 0.15940    C 1 2 1
6RZE_A 0.18190    C 1 2 1
3HPR_A 0.20620  P 21 21 2
1E4V_A 0.19600  P 21 2 21
5EJE_A 0.18630  P 21 2 21
1E4Y_A 0.17800   P 1 21 1
3X2S_A 0.20700 P 21 21 21
6HAP_A 0.22370    I 2 2 2
6HAM_A 0.20311       P 43
4K46_A 0.16730 P 21 21 21
3GMT_A 0.23500   P 1 21 1
4PZL_A 0.19130       P 32
```

Perform PCA

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



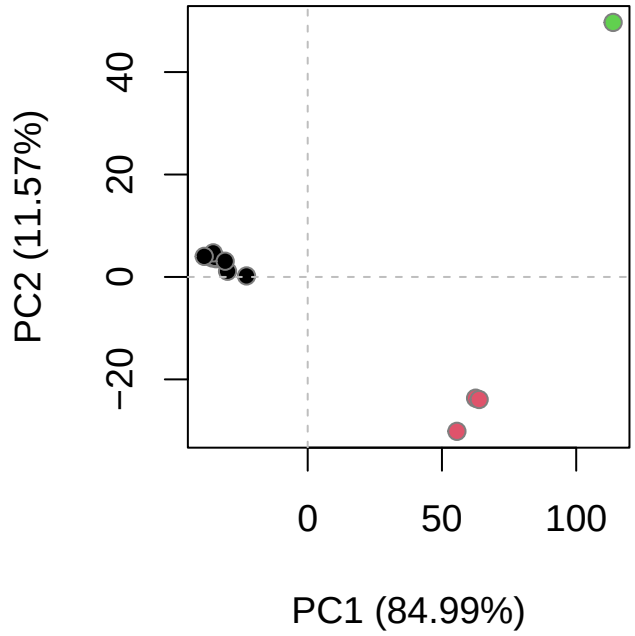

```
#Note: Function rmsd() will calculate all pairwise RMSD values of the structural ensemble. Th
```

```
# 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)
```




```
#Notes (From Instructions): The plot shows a conformer plot - a low-dimensional representatio
```

5 - Optional

6 - Normal mode analysis

(Says optional but has question so do it anyways)

```
# NMA of all structures
modes <- nma(pdbs)
```

```
Details of Scheduled Calculation:
  ... 13 input structures
  ... storing 606 eigenvectors for each structure
  ... dimension of x$U.subspace: ( 612x606x13 )
  ... coordinate superposition prior to NM calculation
  ... aligned eigenvectors (gap containing positions removed)
  ... estimated memory usage of final 'eNMA' object: 36.9 Mb
```

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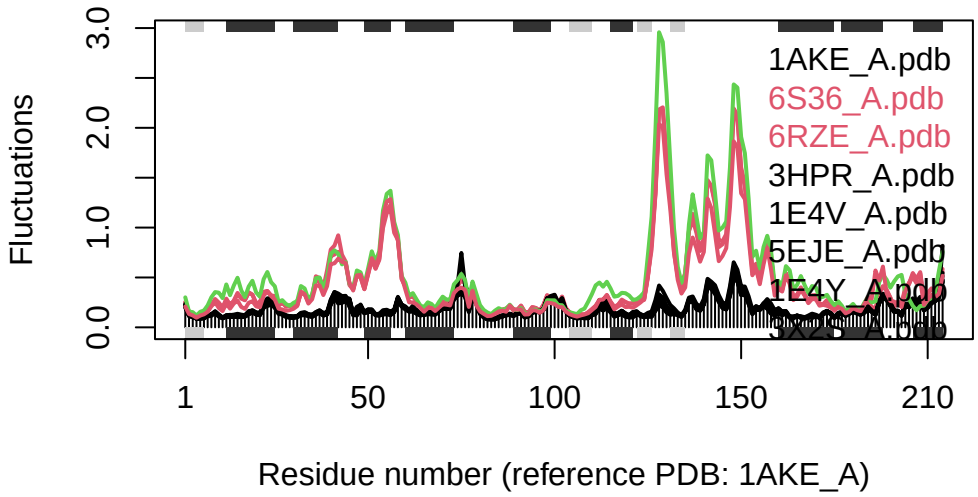
```

```
plot(modes, pdbs, col=grps.rd)
```

```
Extracting SSE from pdbs$sse attribute
```



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?

The black and colored lines are similar in general shape which is indicative of their spatial similarity. This shared flexibility indicates conserved motion across proteins. They differ the most in the region from ~ 110-170. Within this region we can see much higher amplitude for the two hits indicated, 6S36_A and 6RZE_A, can correspond to a few characteristics. Namely, changes in conformational states, seqeunce variation, ligands etc.