class10

#Comparitive Analysis of ADK

ADK is an important drug target and we would love to know how it works- i.e. molecular mechanism.

There has been lots of work done on this protein due to it's importance inclusing lots of crystal structures.

We will begin with getting an example ADK sequence from the database

```
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
```

We can now run BLAST with this sequence

```
#b<-blast.pdb(aa)
```

We can run `hits`

```
#hits <- plot(b)
```

```
#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','
```

Now we can download all these PDB strcture files:

```
# 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


  |
  |                                                                      |   0%
  |
  |=====                                                                 |   8%
  |
  |===========                                                           |  15%
  |
  |================                                                      |  23%
```

```
  |
  |======================                                                |  31%
  |
  |=========================                                             |  38%
  |
  |===============================                                       |  46%
  |
  |====================================                                  |  54%
  |
  |==========================================                            |  62%
  |
  |================================================                      |  69%
  |
  |======================================================                |  77%
  |
  |============================================================          |  85%
  |
  |==================================================================    |  92%
  |
  |======================================================================| 100%
```

Now I want to align and supperpose these structures which are all over the place.

```
# 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
```

Let's have a look at out **pdbs** object.

```
pdbs
```

```
                                1        .        .        .         40
[Truncated_Name:1]1AKE_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:2]6S36_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:3]6RZE_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:4]3HPR_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:5]1E4V_A.pdb    ----------MRIILLGAPVAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:6]5EJE_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:7]1E4Y_A.pdb    ----------MRIILLGALVAGKGTQAQFIMEKYGIPQIS
```

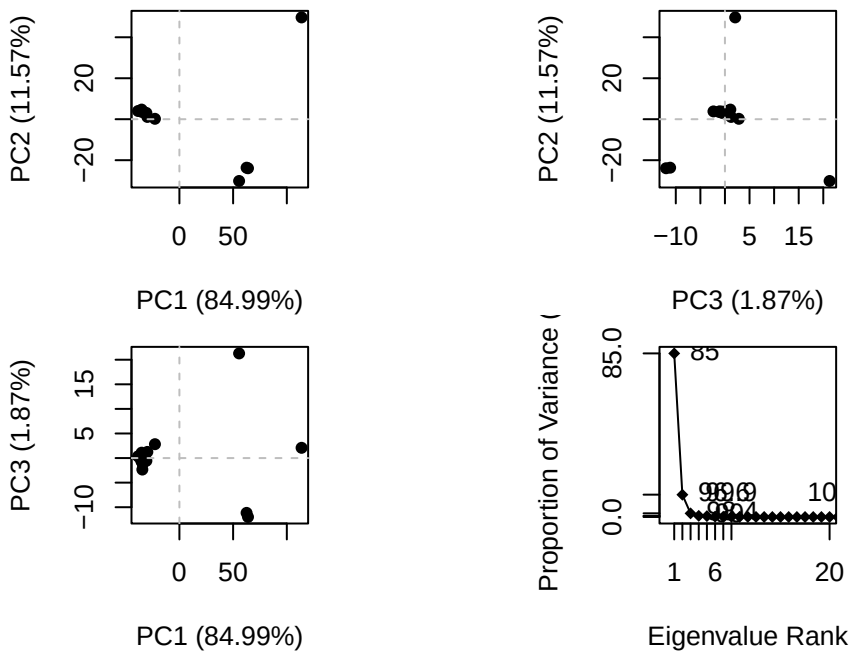
```
[Truncated_Name:8]3X2S_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:9]6HAP_A.pdb    ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:10]6HAM_A.pdb   ----------MRIILLGAPGAGKGTQAQFIMEKYGIPQIS
[Truncated_Name:11]4K46_A.pdb   ----------MRIILLGAPGAGKGTQAQFIMAKFGIPQIS
[Truncated_Name:12]3GMT_A.pdb   ----------MRLILLGAPGAGKGTQANFIKEKFGIPQIS
[Truncated_Name:13]4PZL_A.pdb   TENLYFQSNAMRIILLGAPGAGKGTQAKIIEQKYNIAHIS
                                          **^*****  *******  *  *^ *  **
                                1         .         .         .         40

                                41        .         .         .         80
[Truncated_Name:1]1AKE_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:2]6S36_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:3]6RZE_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:4]3HPR_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:5]1E4V_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:6]5EJE_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDACKLVTDELVIALVKE
[Truncated_Name:7]1E4Y_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVKE
[Truncated_Name:8]3X2S_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDCGKLVTDELVIALVKE
[Truncated_Name:9]6HAP_A.pdb    TGDMLRAAVKSGSELGKQAKDIMDAGKLVTDELVIALVRE
[Truncated_Name:10]6HAM_A.pdb   TGDMLRAAIKSGSELGKQAKDIMDAGKLVTDEIIIALVKE
[Truncated_Name:11]4K46_A.pdb   TGDMLRAAIKAGTELGKQAKSVIDAGQLVSDDIILGLVKE
[Truncated_Name:12]3GMT_A.pdb   TGDMLRAAVKAGTPLGVEAKTYMDEGKLVPDSLIIGLVKE
[Truncated_Name:13]4PZL_A.pdb   TGDMIRETIKSGSALGQELKKVLDAGELVSDEFIIKIVKD
                                ****^*  ^* *^ **   *  ^*   ** *  ^^ ^*^^
                                41        .         .         .         80

                                81        .         .         .         120
[Truncated_Name:1]1AKE_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:2]6S36_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:3]6RZE_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:4]3HPR_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:5]1E4V_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:6]5EJE_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:7]1E4Y_A.pdb    RIAQEDCRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:8]3X2S_A.pdb    RIAQEDSRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:9]6HAP_A.pdb    RICQEDSRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:10]6HAM_A.pdb   RICQEDSRNGFLLDGFPRTIPQADAMKEAGINVDYVLEFD
[Truncated_Name:11]4K46_A.pdb   RIAQDDCAKGFLLDGFPRTIPQADGLKEVGVVVDYVIEFD
[Truncated_Name:12]3GMT_A.pdb   RLKEADCANGYLFDGFPRTIAQADAMKEAGVAIDYVLEID
[Truncated_Name:13]4PZL_A.pdb   RISKNDCNNGFLLDGVPRTIPQAQELDKLGVNIDYIVEVD
                                *^   *   *^* ** **** **  ^   *^ ^**^^* *
                                81        .         .         .         120
```

```
                                121        .         .         .         160
[Truncated_Name:1]1AKE_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:2]6S36_A.pdb      VPDELIVDKIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:3]6RZE_A.pdb      VPDELIVDAIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:4]3HPR_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDGTG
[Truncated_Name:5]1E4V_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:6]5EJE_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:7]1E4Y_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:8]3X2S_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:9]6HAP_A.pdb      VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:10]6HAM_A.pdb     VPDELIVDRIVGRRVHAPSGRVYHVKFNPPKVEGKDDVTG
[Truncated_Name:11]4K46_A.pdb     VADSVIVERMAGRRAHLASGRTYHNVYNPPKVEGKDDVTG
[Truncated_Name:12]3GMT_A.pdb     VPFSEIIERMSGRRTHPASGRTYHVKFNPPKVEGKDDVTG
[Truncated_Name:13]4PZL_A.pdb     VADNLLIERITGRRIHPASGRTYHTKFNPPKVADKDDVTG
                                  *    ^^^ ^ *** *  *** **  ^*****  *** **
                                121        .         .         .         160

                                161        .         .         .         200
[Truncated_Name:1]1AKE_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:2]6S36_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:3]6RZE_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:4]3HPR_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:5]1E4V_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:6]5EJE_A.pdb      EELTTRKDDQEECVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:7]1E4Y_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:8]3X2S_A.pdb      EELTTRKDDQEETVRKRLCEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:9]6HAP_A.pdb      EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:10]6HAM_A.pdb     EELTTRKDDQEETVRKRLVEYHQMTAPLIGYYSKEAEAGN
[Truncated_Name:11]4K46_A.pdb     EDLVIREDDKEETVLARLGVYHNQTAPLIAYYGKEAEAGN
[Truncated_Name:12]3GMT_A.pdb     EPLVQRDDDKEETVKKRLDVYEAQTKPLITYYGDWARRGA
[Truncated_Name:13]4PZL_A.pdb     EPLITRTDDNEDTVKQRLSVYHAQTAKLIDFYRNFSSTNT
                                  * *  * ** *^ *  **  *   *  ** ^*
                                161        .         .         .         200

                                201        .         .      227
[Truncated_Name:1]1AKE_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:2]6S36_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:3]6RZE_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:4]3HPR_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:5]1E4V_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:6]5EJE_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:7]1E4Y_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
[Truncated_Name:8]3X2S_A.pdb      T--KYAKVDGTKPVAEVRADLEKILG-
```

```
[Truncated_Name:9]6HAP_A.pdb    T--KYAKVDGTKPVCEVRADLEKILG-
[Truncated_Name:10]6HAM_A.pdb   T--KYAKVDGTKPVCEVRADLEKILG-
[Truncated_Name:11]4K46_A.pdb   T--QYLKFDGTKAVAEVSAELEKALA-
[Truncated_Name:12]3GMT_A.pdb   E-------NGLKAPA-----YRKISG-
[Truncated_Name:13]4PZL_A.pdb   KIPKYIKINGDQAVEKVSQDIFDQLNK
                                         *
                              201        .         .      227

Call:
  pdbaln(files = files, fit = TRUE, exefile = "msa")

Class:
  pdbs, fasta

Alignment dimensions:
  13 sequence rows; 227 position columns (204 non-gap, 23 gap)

+ attr: xyz, resno, b, chain, id, ali, resid, sse, call
```

Now we have our aligned and superposed structures we can perform all sorts of analysis on them. Let's do PCA…

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



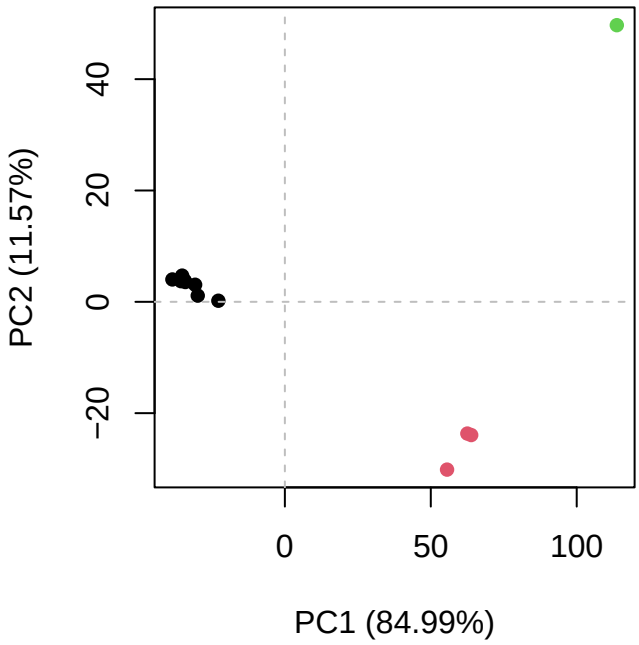
Results of PCA on Adenylate kinase X-ray structures. Each dot represents one PDB structure.

We can cluster the structures by RMSD (or any other method).

```
rd<-rmsd(pdbs)
```

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

```
hc.rd <- hclust(dist(rd))
grps<- cutree(hc.rd, k=3)

plot(pc.xray,1:2, col=grps)
```



We can make a wee movie- also called a trajectory of the major differences (i.e. structural displacements) of ADK

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