Structural Bioinformatics

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Introduction to the RCSB Protein Data Bank (PDB)

First, let's see what is in the PDB database, the main repository of protein structures.

Downloaded composition stats from: "https://www.rcsb.org/stats/summary"

For context:

```
Release 2023_04 of 13-Sep-2023 of UniProtKB/TrEMBL contains 251600768 sequence entries
```

The PDB only contains 183,201. (Structure determination takes a very long time and is very expensive) Sequencing is a lot easier and inexpensive.

```
stats <- read.csv("https://tinyurl.com/statspdb",row.names=1)
stats
```

```
                         X.ray     EM    NMR Multiple.methods Neutron Other
Protein (only)         158,844 11,759 12,296              197      73    32
Protein/Oligosaccharide  9,260  2,054     34                8       1     0
Protein/NA               8,307  3,667    284                7       0     0
Nucleic acid (only)      2,730    113  1,467               13       3     1
Other                      164      9     32                0       0     0
Oligosaccharide (only)      11      0      6                1       0     4
                         Total
Protein (only)         183,201
Protein/Oligosaccharide 11,357
Protein/NA              12,265
Nucleic acid (only)      4,327
Other                      205
Oligosaccharide (only)      22
```

We need to get rid of commas in the numbers because R is treating this dataframe as a characters instead of numericals.

```
x <- stats$X.ray
x
```

```
[1] "158,844" "9,260"   "8,307"   "2,730"   "164"     "11"
```

```
#gsub will (globally) substitute the commas with nothing on the column from x
# as.numeric will then convert x into a numeric
as.numeric(gsub(",", "", x))
```

```
[1] 158844   9260   8307   2730    164     11
```

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

```
rm.comma(stats$EM)
```

```
[1] 11759  2054  3667   113     9     0
```

I can use 'apply()' to fix the whole table...

```
# apply(df, row(1) or column(2), function to apply)
pbdstats <- apply(stats,2, rm.comma)
rownames(pbdstats) <- rownames(stats)
head(pbdstats)
```

```
                         X.ray    EM   NMR Multiple.methods Neutron Other
Protein (only)          158844 11759 12296              197      73    32
Protein/Oligosaccharide   9260  2054    34                8       1     0
Protein/NA                8307  3667   284                7       0     0
Nucleic acid (only)       2730   113  1467               13       3     1
Other                      164     9    32                0       0     0
Oligosaccharide (only)      11     0     6                1       0     4
                         Total
Protein (only)          183201
```

```
Protein/Oligosaccharide  11357
Protein/NA               12265
Nucleic acid (only)       4327
Other                      205
Oligosaccharide (only)      22
```

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

```
#long way to answer
(sum(pbdstats[,1])+sum(pbdstats[,2]))/(sum(pbdstats[,"Total"]))
```

```
[1] 0.9315962
```

```
#OR make a function with all column totals
totals <- apply(pbdstats, 2, sum)
round(totals/totals["Total"]*100,2)
```

```
         X.ray             EM            NMR Multiple.methods
         84.83           8.33           6.68           0.11
       Neutron          Other          Total
          0.04           0.02         100.00
```

```
84.83 +8.33
```

```
[1] 93.16
```

93.16% of the structures in the PDB are solved by X-Ray and Electron Microcopy

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

```
ptn_total <- pbdstats[1, "Total"]

ptn_total/sum(pbdstats[, "Total"])
```

```
[1] 0.8667026
```

86.67% of the structures in the PDB are protein.

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?

Skipped for time!

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?

This is a 2 angstrom structure.Hydrogen is smaller than the resolution of the program so it can't be seen in the 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

HOH 308; the water molecule is hydrogen bonded to the protein and the ligand; it stabilizes the binding between the two.

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.

Here is a lovely figure of HIP-Pr with the catalytic ASP residues, the MK1 compound and the all important water 308.

Introduction to Bio3D in R

The bio3d package for structural bioinformatics

```
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
```

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

There are 198 amino acid residues in this PDB object

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

HOH and MK1 (the drug/ligand)

Q9: How many protein chains are in this structure?

There are 2 protein chains in this structure.

```
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>
```

Look at Adenylate Kinase!

Let's finish today with a bioinformatics calculation to predict the functional motions of a PDB 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
```

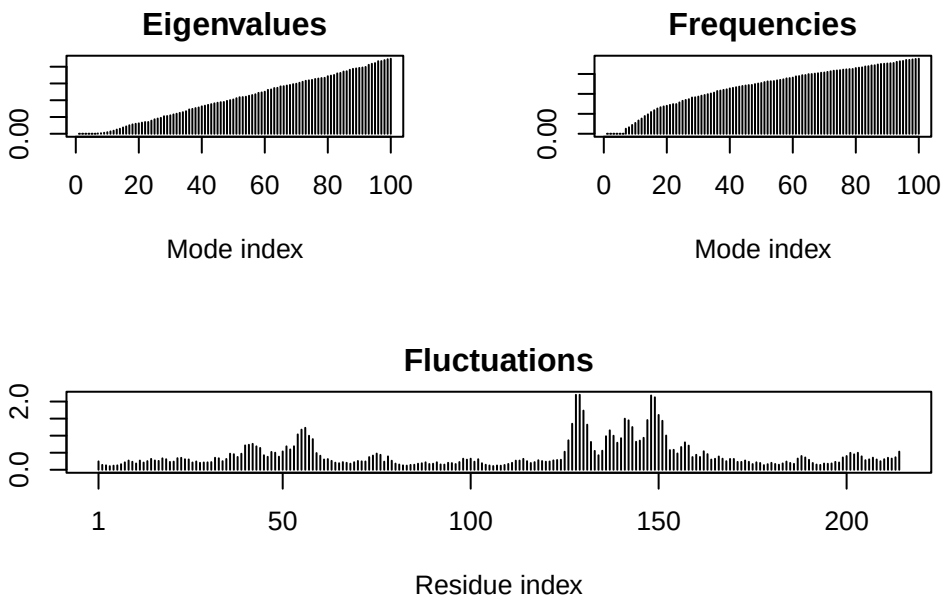
```
     Total Atoms#: 1898,  XYZs#: 5694  Chains#: 1  (values: A)

     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 is used predict protein flexibility and possible conformational changes in structural bioinformatics.

```
#Perform a NMA for adk
m <- nma (adk)
```

```
 Building Hessian...        Done in 0.044 seconds.
 Diagonalizing Hessian...   Done in 0.643 seconds.
```

```
plot(m)
```




```
# look at a "movie" of those possible motions by load the resulting "adk_m7.pdb" into Mol
mktrj(m, file="adk_m7.pdb")
```