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HOMOLOGY MODELING OF ALPHA-SYNUCLEIN (SNCA) PROTEIN OF HUMAN

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Abstract: Homology modeling [4] aims to build three-dimensional protein structure [2] models using experimentally determined structures of related family members as templates. SWISS-MODEL [13] workspace is an integrated Web-based modeling [11] expert system. For a given target protein, a library of experimental protein structures is searched to identify suitable templates. On the basis of a sequence alignment [23][24] between the target protein and the template structure, a three-dimensional model for the target protein is generated. Model quality assessment tools are used to estimate the reliability of the resulting models. Homology modeling [4] is currently the most accurate computational method [3] to generate reliable structural models and is routinely used in many biological applications.

I. BACKGROUND

Alpha-synuclein(SNCA)[31] is a protein that, is encoded by the SNCA gene in human. An alpha-synuclein fragment, known as the non-A beta component (NAC) of Alzheimer's disease amyloid, found in an amyloid-enriched fraction, is shown to be a fragment of its precursor protein, NACP, by cloning of the full-length CDNA.Alpha-synuclein is specifically upregulated in a discrete population of presynaptic terminals of the brain during a period of acquisition-related synaptic rearrangement. It has been shown that alpha-synuclein significant interacts with tubulin Alpha-synuclein[32] is specifically upregulated in a discrete population of presynaptic and that alpha-synuclein may have an activity as potential microtubule-associated protein like tau.Recent evidence suggests that alpha-synuclein functions as a molecular chaperone in the formation of SNARE complexes. Indeed, there is growing evidence that alpha-synuclein is involved in the functioning of the neuronal Golgi apparatus and vesicle trafficking [35].

Alpha-synuclein [33]primary structure[1] is usually divided in three distinct domains:

1) Residues 1-60: An amphipathic N-terminal region dominated by four 11-residue repeats including the consensus sequence KTKEGV. This sequence has a structural alpha helix propensity similar to apolipoproteins-binding domains. 2)Residues 61-95: A central hydrophobic region which includes the non-amyloid component (NAC) region, involved in protein aggregation. 3)Residues 96-140: an highly acidic and proline-rich region which has no distinct Structural propensity.

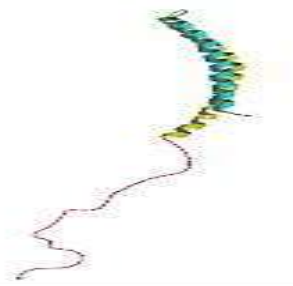

Fig.1 Synuclein, alpha (non-Abeta component of Alzheimer's disease amyloid precursor protein: NACP)

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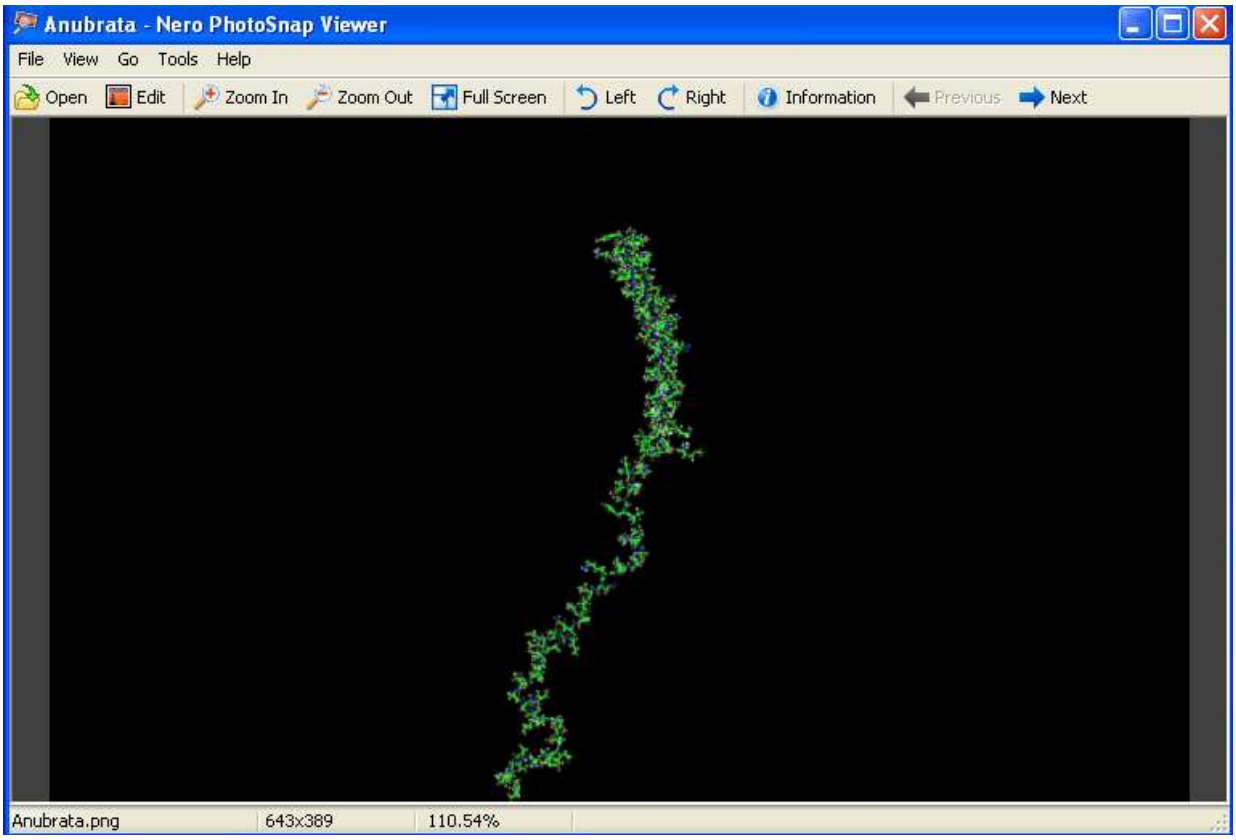

Fig. 2 PDB Resourse Information

```
 PyMOL(TM) Incentive Product - Copyright (C) 2006 DeLano Scientific LLC.

 A current PyMOL Maintenance and/or Support Subscription may be required
 for legal use of this Build beyond a finite honor-system evaluation period.
 Please visit http://www.pymol.org/funding.html for more information.

 This PyMOL Executable Build incorporates Open-Source PyMOL 0.99rc6.
HEADER    LIPID BINDING PROTEIN                   11-OCT-04   1XQ8
TITLE     HUMAN MICELLE-BOUND ALPHA-SYNUCLEIN
COMPND    MOL_ID: 1;
COMPND   2 MOLECULE: ALPHA-SYNUCLEIN;
COMPND   3 CHAIN: A;
COMPND   4 SYNONYM: NON-A BETA COMPONENT OF AD AMYLOID, NON-A4
COMPND   5 COMPONENT OF AMYLOID, NACP;
COMPND   6 ENGINEERED: YES
 ObjectMolecule: Read secondary structure assignments.
 ObjectMolecule: Read crystal symmetry information.
 Symmetry: Found 1 symmetry operators.
 CmdLoad: "D:\anubrata 1\exam.1\1XQ8.pdb.pdb" loaded as "1XQ8.pdb".
 ScenePNG: wrote 643x389 pixel image to file "C:/Documents and Settings/Administrator/Desktop/Anubrata.png".
```

Fig. 3 Protein Data Base File Information

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II. MATERIALS

Equipment:

1) Amino-acid sequence of the protein to be modeled.

2) A computer with access to the Internet and a Web browse.

3) A multiple protein sequence alignment[23][24], including at least the sequences of the target protein and the template structure (optional; see Step 6B in PROCEDURE for information on sequence alignment formats).

4) DeepView for protein structure analysis and visualization (optional software). DeepView can be freely downloaded from the ExPASy website (http://www.expasy.org/spdbv/).

Server &Software: SWISS-MODEL (www): http://swissmodel.expasy.org/*;* http://ncbi.org; http://pdb.org; http://blast. ncbi.nlm .nih.gov/Blast.cgi.

SWISS-MODEL [13] is accessible via a web interface at http://swissmodel.expasy.org, or directly as a link from SWISS-PROT entries on the ExPASy server. The program DeepView (Swiss-PdbViewer) can be downloaded for free athttp://www.expasy.org/spdbv/. Depending on the complexity of the modeling task and server workload, it may take a few minutes to several hours for the server to build a model, including energy minimization. The model coordinates and log-files are returned to the user by email. The computational resources for the SWISS-MODEL server are provided by collaboration between the Swiss Institute of Bioinformatics at the Biozentrum Basel (University of Basel, Switzerland) and the Advanced Biomedical Computing Center (NCIFCRF Frederick, MD, USA).

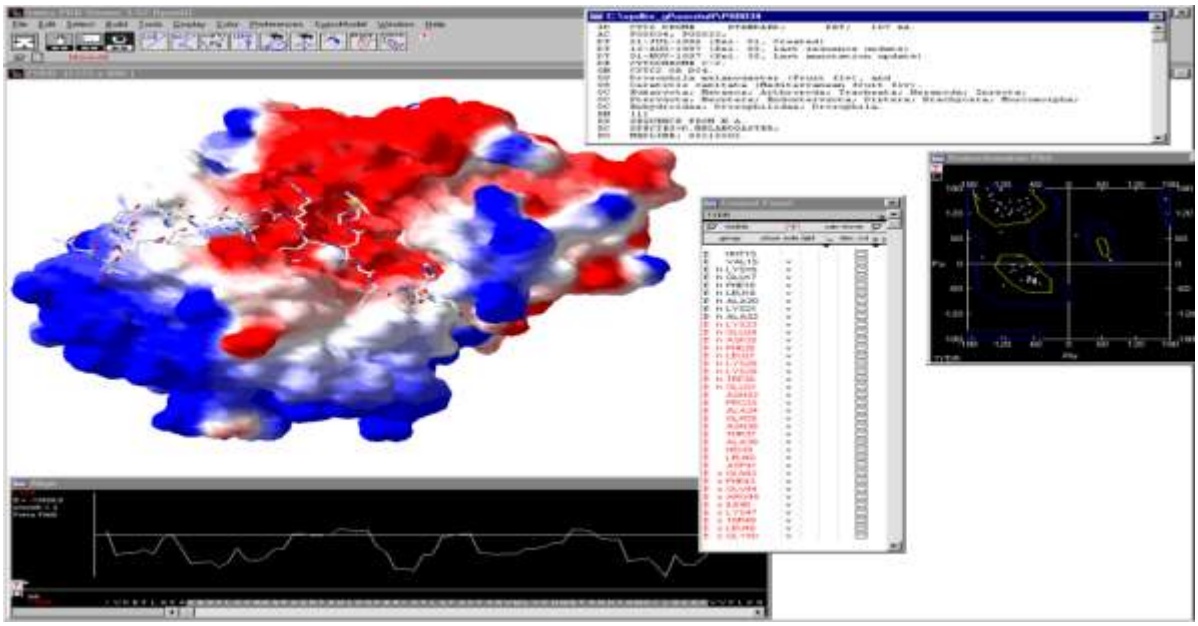

Fig. 4 Tools: - Swiss-PdbViewer – DeepView

Analysis tools:

1) Protein sequence and structure analysis tools (primary, secondary, tertiary structure).

2) protein Function assignment.Database: - Generalized (DNA,proteins and carbohydrates, 3D-structures)[2][5].

3) Protein sequence databases: SWISS-PROT (Swiss Institute of Bioinformatics, SIB, Geneva, CH).

4) Primary sequence databases:NCBI (NATIONAL CENTRE OF BIOTECHNOLOGY INFORMATICS),GenBank (at National Center for Biotechnology information, NCBI, Bethesda, MD, USA).

5) Protein sequence databases,SWISS-PROT (Swiss Institute of Bioinformatics, SIB, Geneva, CH).

6) 3D structure database:SPDV (SWSS-PDB VIEWER),PDB.

III. METHODS

STEP 1: Species: - Homosapiens

Identity of FASTA format : -

>gi|49456267|emb|CAG46454.1| SNCA

MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVGSKTKEGVVHGVATVAEKTKEQVTNVGGAV

VTGVTAVAQKTVEGAGSIAAATGFVKKDQLGKNEEGAPQEGILEDMPVDPDNEAYEMPSEEGYQDYEPEA

Procedure: I have taken the accession number (CAG46454) from NCBI of Homo sapiens.

SEARCHING FOR TARGET SEQUENCE:

1) Go to NCBI.

2) Click on All Databases and Select Raw protein.

3) Searching For "SNCA protein For Homo sapiens.

4) Get the Sequence in FASTA Format.

5) Copy it and Paste it in a Notepad in .txt Format.

STEPS 2: Species: - Homosapiens

Protein I.D. : 1XQ8, 2Z2D

SEARCHING FOR THE TEMPLATE SEQUENCE:

1) Go to NCBI.

2) Go to BLAST [25] Menu.

3) Select BLASTp.

4) Paste the Target Sequence.

5) Choose Database PDB Options for Advance BLASTING.

6) Select from Homo sapiens (ORGN) and go to BLAST FORMAT.

7) Choose Template and Go to PDB.

8) Paste 1XQ8 in PDB ID. Search.

9) Download and Save 1XQ8 PDB File.

10) Again Download and Save 2Z2D PDB File.

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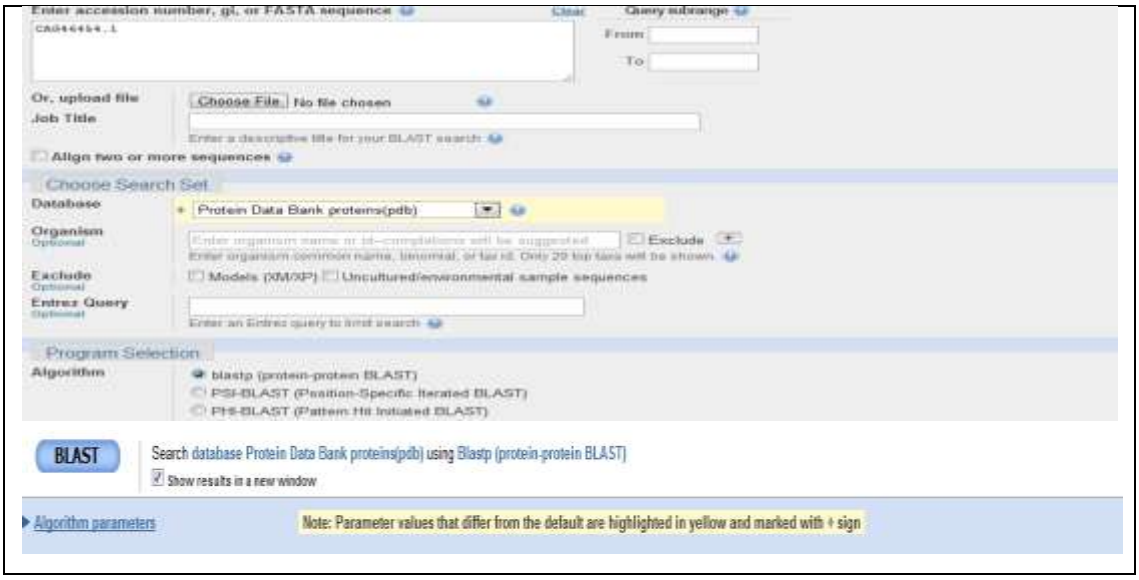

STEPS 3:

MODELLING WITH THE HELP OF SWISS PDB VIEWER:

1) Go to the SWISS-PDB Viewer.

2) Open the SWISS-PDB Viewer.

3) Go to the SWISS MODEL[30] Menu.

4) Choose LOAD RAW SEQUENCE TO MOEL.

5) Load the target sequence in .txt format.

6) Go to FILE Menu and Open PDB File.

7) Click 1XQ8 and Open.

8) Back to Open PDB File.

9) Click 2Z2D and Open.

10) Press Ctrl+L to Open ALLINGNMENT WINDOW.

11) Click 1XQ8 Go to Fit Menu and Open Magic Fit (All Atom) and press Ok.

12) Go to Iterative Magic Fit Menu and Press Ok (All Atom)Twice times.

13) Click on Target Sequence and Active it.

14) Go to the Magic Fit Menu and select (All Atom) and press Ok.

15) Click Iterative Magic Fit Menu and Press Ok (All Atom) Twice times.

16) Go to Tool Menu and Click Fix and Select Side Chain Quick and dirty.

17) Save Project in .PDB File Format.

18) Go to SWISS Model and Submit the Modeling[3] request.

19) Browse the Save File and Send to SWISS-MODEL Server.

20) Receive the correct Project from corresponding Mial.

21) Go to the SWISS-PDB Viewer.

22) Upload the corrected Project File.

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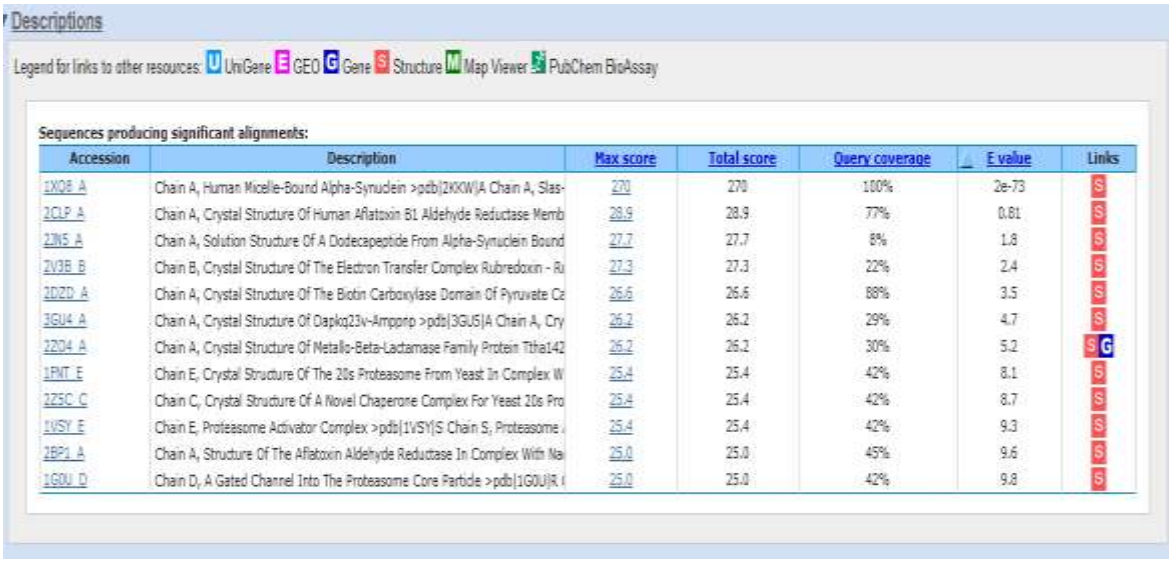
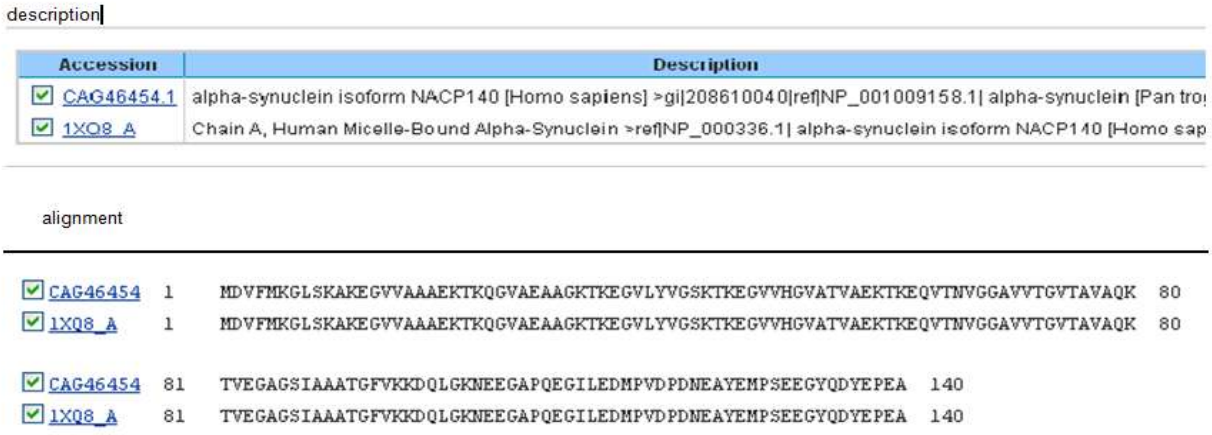
STEPS 4:

PreparationAutomated mode[22][11]:Select a template structure with high 99-77 % identity and average resolution, or let SwissModel choose best one.



Alignment mode:Obtain multiple alignment between possible templates and your query sequence.



Check alignment[23][24] – Manually adjust as necessary, using Jalview.

Upload alignment, select template, and submit.

STEP 5:

Energy Minimization:

1)Go to the Preference Menu.

2)Click Energy Minimization.

3)Go to Energy Minimization Preference.

4)Go to Tool Menu.

5)Click Energy Minimization.

6)See the Results.

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IV. RESULTS

Output:

1) Within a few minutes of submission, your results are returned to the Workspace.

2) Output Page:

a) Your model in pdb format (plus simple viewer).

b) Query to template alignment.c)Simple assessment graphs.d)Logging data of the modeling process.

3) Save the model [29] in Swiss-Pdb Viewer (DeepView) Project format, then open in Swiss-Pdb Viewer, and color by B-factor.

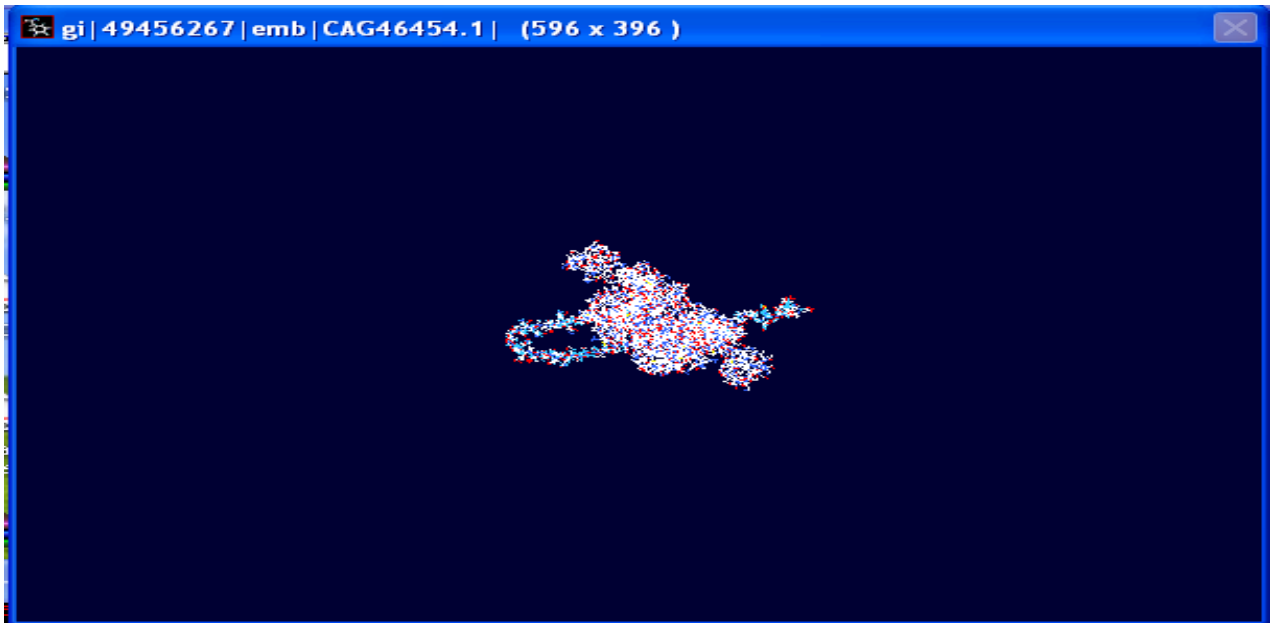
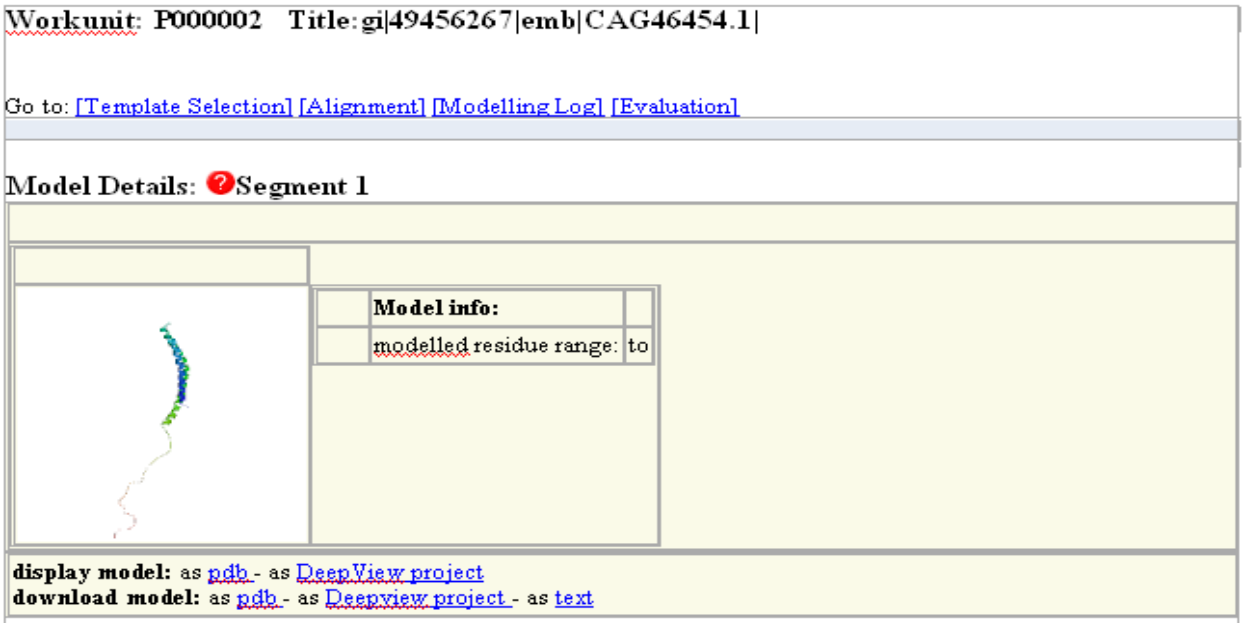


Fig. 5 Output



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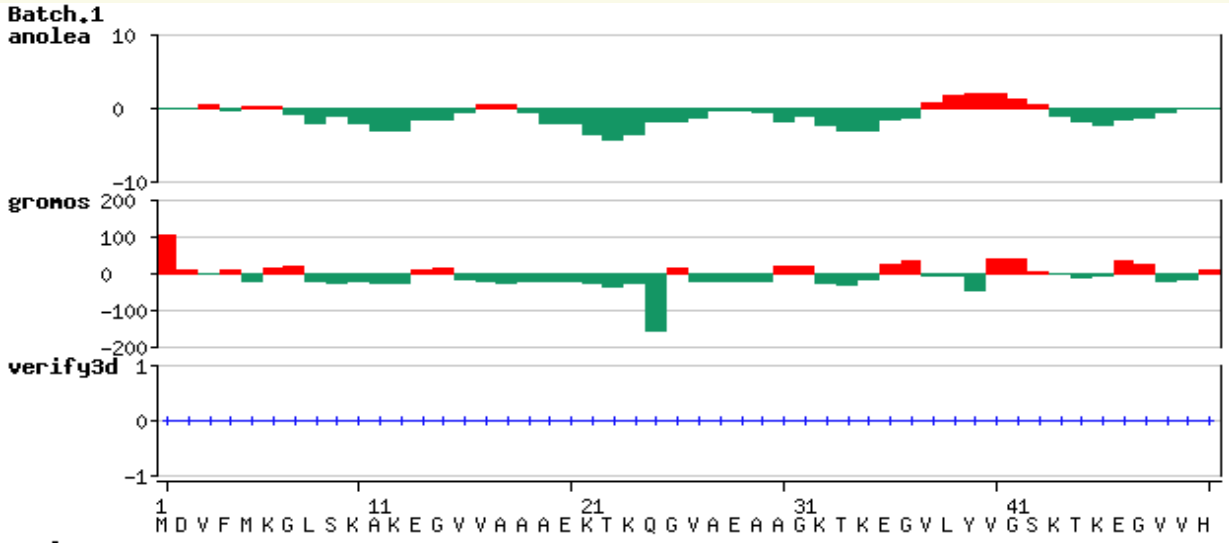
```
gi|49456  1MDVF
1XQ8.pdb  1                                   mdvf

gi|49456                                      h
1XQ8.pdb                                        h

gi|49456  5     MKGLSKAKEG VVAAAEKTKQ GVAEAAGKTK EGVLYVGSKT KE--------
1XQ8.pdb  5     mkglskakegvvaaaektkqgvaeaagktkegvlyvgsktke--------
                                      ********
gi|49456        hhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhh
1XQ8.pdb          hhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhh

gi|49456  47    ---------- ---------- ---------- ---------- ----GVVHGV
1XQ8.pdb  47    ---------- ---------- ---------- ---------- ----gvvhgv
          ********** ********** ********** ********** ****
gi|49456                                    hhhhhh
1XQ8.pdb                                      hhhhhh

gi|49456  53    ATVAEKTKEQ VTNVGGAVVT GVTAVAQKTV EGAGSIAAAT GFVKKDQLGK
1XQ8.pdb  53    atvaektkeqvtnvggavvtgvtavaqktvegagsiaaatgfvkkdqlgk

gi|49456        hhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhh
1XQ8.pdb          hhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhh

gi|49456  103   NEEGAPQEGI LEDMPVDPDN EAYEMPSEEG YQDYEPEA
1XQ8.pdb  103   neegapqegiledmpvdpdneayempseegyqdyepea-

gi|49456
1XQ8.pdb
```

Anolea / Gromos / Verify3D [top]

anolea: on off 40rooms: on off verify3d: on off show



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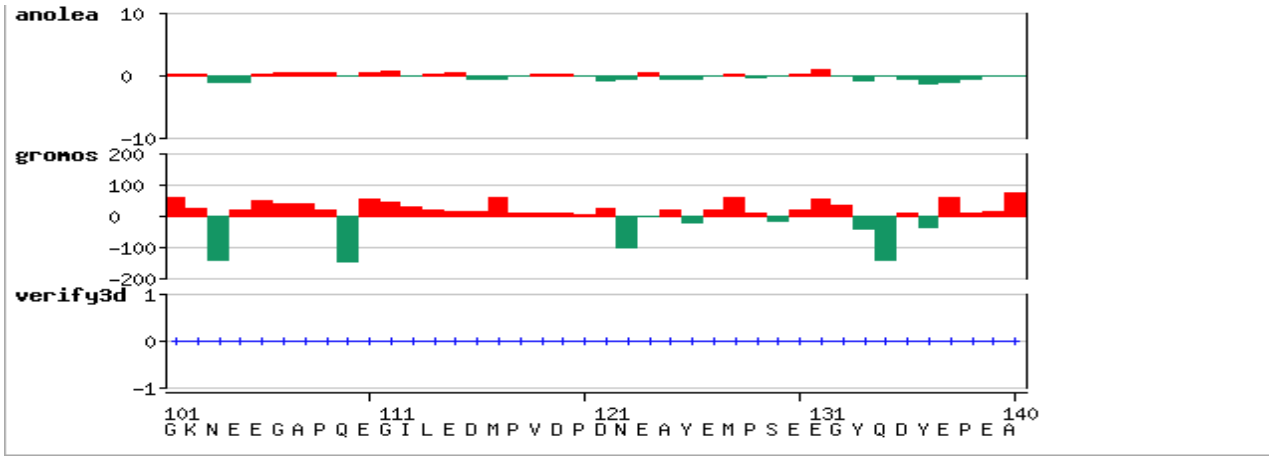
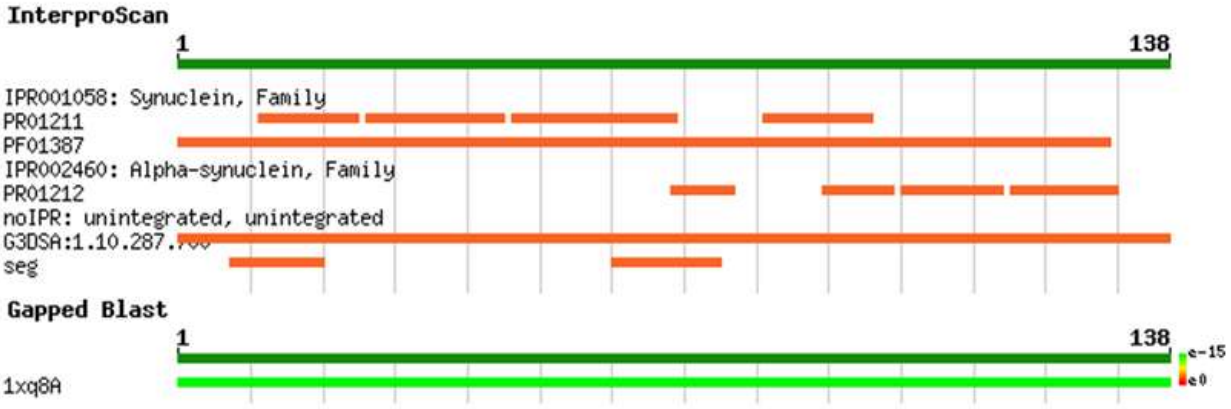


Workunit: P000003
Title: gi|49456267|emb|CAG46454.1|



Interpro: top

Interpro Scan has finished. Here are the results:

IPR001058: Synuclein, Family
PR01211: 12 - 26 SYNUCLEIN
PR01211: 27 - 46 SYNUCLEIN
PR01211: 47 - 70 SYNUCLEIN
PR01211: 82 - 97 SYNUCLEIN

IPR001058: Synuclein, Family
PF01387: 1 - 130 Synuclein

IPR002460: Alpha-synuclein, Family
PR01212: 69 - 78 ASYNUCLEIN
PR01212: 90 - 100 ASYNUCLEIN
PR01212: 101 - 115 ASYNUCLEIN
PR01212: 116 - 131 ASYNUCLEIN

noIPR: unintegrated, unintegrated
G3DSA:1.10.287.700: 1 - 138 no description

noIPR: unintegrated, unintegrated
seg: 8 - 21 seg
seg: 61 - 76 seg

```
Reference for composition-based statistics:
Schaffer, Alejandro A., L. Aravind, Thomas L. Madden,
Sergei Shavirin, John L. Spouge, Yuri I. Wolf,
Eugene V. Koonin, and Stephen F. Altschul (2001),
"Improving the accuracy of PSI-BLAST protein database searches with
composition-based statistics and other refinements",  Nucleic Acids Res. 29:2994-3005.

Query= gi|49456267|emb|CAG46454.1|, 138 bases, 750EB2B7 checksum.
         (138 letters)

Database: SMTL100
           54,676 sequences; 13,842,974 total letters

Searching.....................................................done


                                                                  Score     E
Sequences producing significant alignments:                       (bits) Value

ExPDB|1xq8A|99|none                                                185    6e-48
```

[top]

```
>[Template]|1xq8A|99|none
          Length = 140
```

[Display Alignment in DeepView]

```
 Score =  185 bits (470), Expect = 6e-48,   Method: Composition-based stats.
 Identities = 138/138 (100%), Positives = 138/138 (100%)

Query: 1   VFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVGSKTKEGVVHGVATVAEKTKEQ 60
           VFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVGSKTKEGVVHGVATVAEKTKEQ
Sbjct: 3   VFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVGSKTKEGVVHGVATVAEKTKEQ 62

Query: 61  VTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFVKKDQLGKNEEGAPQEGILEDMPVDPDN 120
           VTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFVKKDQLGKNEEGAPQEGILEDMPVDPDN
Sbjct: 63  VTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFVKKDQLGKNEEGAPQEGILEDMPVDPDN 122

Query: 121 EAYEMPSEEGYQDYEPEA 138
           EAYEMPSEEGYQDYEPEA
Sbjct: 123 EAYEMPSEEGYQDYEPEA 140


  Database: SMTL100
    Posted date:  Jul 14, 2010  1:59 PM
  Number of letters in database: 13,842,974
  Number of sequences in database:  54,676

Lambda      K       H
   0.303     0.124     0.330

   Lambda      K       H
      0.267    0.0410     0.140


   Matrix: BLOSUM62
   Gap Penalties: Existence: 11, Extension: 1



  Number of Hits to DB: 3,786,446
  Number of Sequences: 54676
  Number of extensions: 151714
  Number of successful extensions: 401
  Number of sequences better than 1.0e-01: 1
  Number of HSP's better than  0.1 without gapping: 1
  Number of HSP's successfully gapped in prelim test: 0
  Number of HSP's that attempted gapping in prelim test: 392
  Number of HSP's gapped (non-prelim): 1
  length of query: 138
  length of database: 13,842,974
  effective HSP length: 88
  effective length of query: 50
  effective length of database: 9,031,486
  effective search space: 451574300
  effective search space used: 451574300
  T: 11
  A: 40
  X1: 17 ( 7.4 bits)
  X2: 38 (14.6 bits)
  X3: 64 (24.7 bits)
  S1: 43 (21.8 bits)
  S2: 72 (32.3 bits)
```

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ENERGY MINIMIZATION:

The energy of the point of threading:-

E= -1420.616 KJ/mol

Final energy minimization result

E= -1789.273 KJ/mol

V. DISCUSSION

The study of the species (Homosapiens) of Alpha-Sycuclein protein of Homo sapiensis conclusive in respect; especially that it satisfies the aims and objectives of the study.

With the help of computational technique and different Biological databases and biotools, can find out easily the target and the template sequence.

Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK., want to state that the two developments have imparted a new direction to research on the aetiology and pathogenesis of Parkinson's disease. First, the discovery that a missense mutation in the α-synuclein[31] gene is a rare genetic cause of Parkinson's disease. Second, the identification of the α-synuclein protein as the main component of Lewy bodies and Lewyneurites, the defining neuropathological characteristics of all cases of Parkinson's[33] and several other diseases. The filamentous inclusions of multiple system atrophy are also made of α-synuclein. These findings have placed α-synuclein dysfunction at the centre of several common neurodegenerative diseases. Here, I review the molecular properties of the synucleins, the different diseases characterized by the accumulation of α-synuclein, and the possible mechanisms by which dysfunction of α-synuclein might lead to neurodegeneration.

The table in the result section shows significant minimization of energy (range) which shows that Final energy minimization result (E= -1789.273 KJ/mol) range is the lowest range of minimization of energy which is possible with the help of Swiss PDB deep viewer[13]. All the cases were studied according to the algorithm of respective database, biotools and the article of relevant molecular modeling of Alpha- Synuclein protein[32] of Homosapiens. On analyzing the result of the newly formed template of *Homo-sapiens* it was founded that it might be possible to build a PDB file of Alpha-Syclein protein of Homosapiens.

VI. CONCLUSIONS

Several genes have been identified for monogenic disorders that variably resemble Parkinson's disease. Dominant mutations in the gene encoding α-synuclein[31] enhance the propensity of this protein to aggregate. As a consequence, these patients have a widespread disease with protein inclusion bodies in several brain areas. In contrast, mutations in several recessive genes (parkin, DJ-1, and PINK1) produce neuronal cell loss but generally without protein aggregation pathology. Progress has been made in understanding some of the mechanisms of toxicity: Parkin[35]is an E3 ubiquitin ligase and DJ-1 and PINK1 appear to protect against mitochondrial damage. However, we have not yet fully resolved how the recessive genes relate to α-synuclein, or whether they represent different ways to induce a similar phenotype.

ACKNOWLEDGEMENTS

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