

Structural Analysis Quick Start

An NCBI Mini-Course

A protein domain is considered to be a distinct functional and/or structural unit. A domain in a structural context refers to a segment of a polypeptide chain that can fold into an independent three dimensional structure. It may interact with other domains of the protein or may simply be joined to other domains by a polypeptide chain. A domain in a sequence context refers to a long sequence pattern that is shared by other proteins having a common evolutionary origin. A domain may include all of the protein sequence or a part of it. A conserved domain is a recurring unit in molecular evolution whose extents can be determined by sequence and structure analysis.

The Conserved Domain Database (CDD) contains domains derived from the Smart, Pfam and Clusters of Orthologous Groups (COGs) databases. Conserved domains can be represented as multiple sequence alignments. Source alignments are processed by NCBI as follows:

- Sequences in the alignment for which a link can not be provided to a protein in Entrez are removed.
- If possible, a closely related sequence with a known structure is substituted.
- A representative sequence, preferably with a structure link, is chosen from among those in the alignment.
- A consensus sequence is made.
- A position-specific scoring matrix (PSSM) is constructed.

The Conserved Domain search (CD-search) compares a protein sequence to the PSSMs in the CDD database to identify conserved domains within it and to identify a 3-D modeling template. Since the PSSMs are the "subject", instead of the query as in PSI-Blast, the CD-search is a form of Reverse Position-Specific Blast (RPS-Blast).

The Conserved Domain Architecture Retrieval Tool (CDART) can be used to identify proteins containing the domain(s) present in the query sequence. Conserved domain(s) present in all sequences within Entrez proteins are identified using CD-search during routine NCBI processing. These pre-computed results are accessed through CDART.

The Vector Alignment Search Tool (VAST) is a computer algorithm developed at NCBI to detect similar protein 3-dimensional structures. The "structure neighbors" for every structure in NCBI's Molecular Modeling DataBase (MMDB)

are pre-computed. These neighbors can be used to identify distant homologs that cannot be recognized by sequence comparison alone. A VAST-search can be used for determining the structure neighbors for recently solved structures not yet in MMDB.

Cn3D is a helper application for web browsers to view 3-dimensional structures from NCBI's Entrez retrieval service. Cn3D runs on Windows, Macintosh, and Unix. Cn3D simultaneously displays structure, sequence, and alignment, and now has powerful annotation and alignment editing features.

In this course, we will learn to

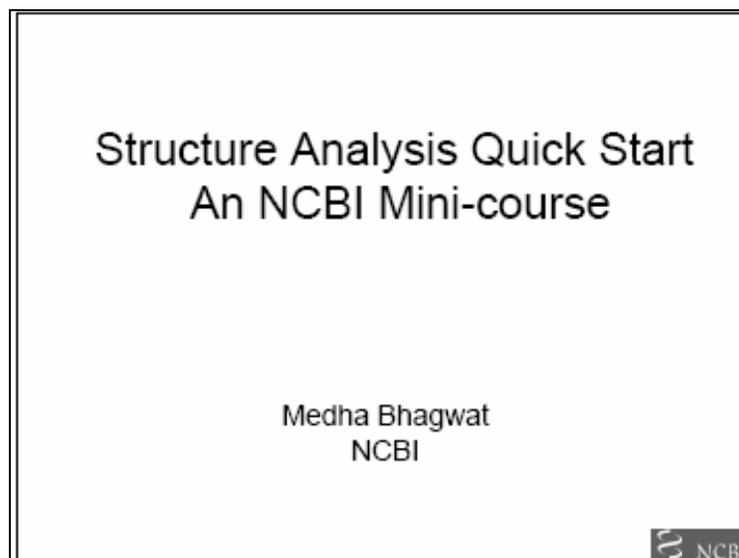
- Identify a conserved domain present in the query protein using **CDD**
- Search for other proteins containing similar domain(s) using **CDART**
- Explore a 3D modeling template for the query sequence using **CDD**
- Find similar structures using **VAST**
- Visualize and annotate the 3D protein structures using **Cn3D**

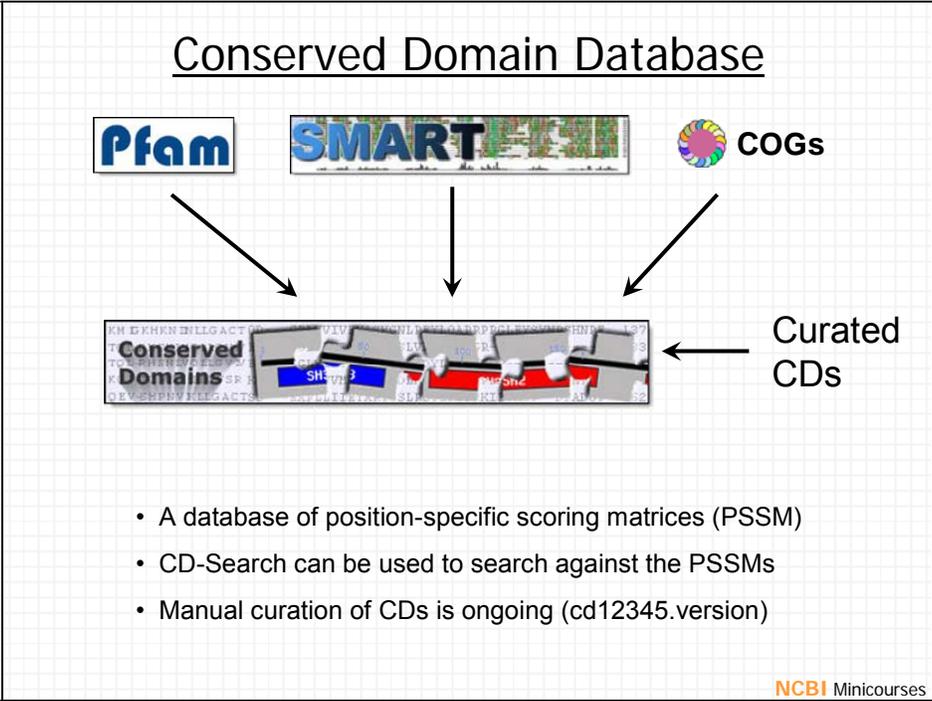
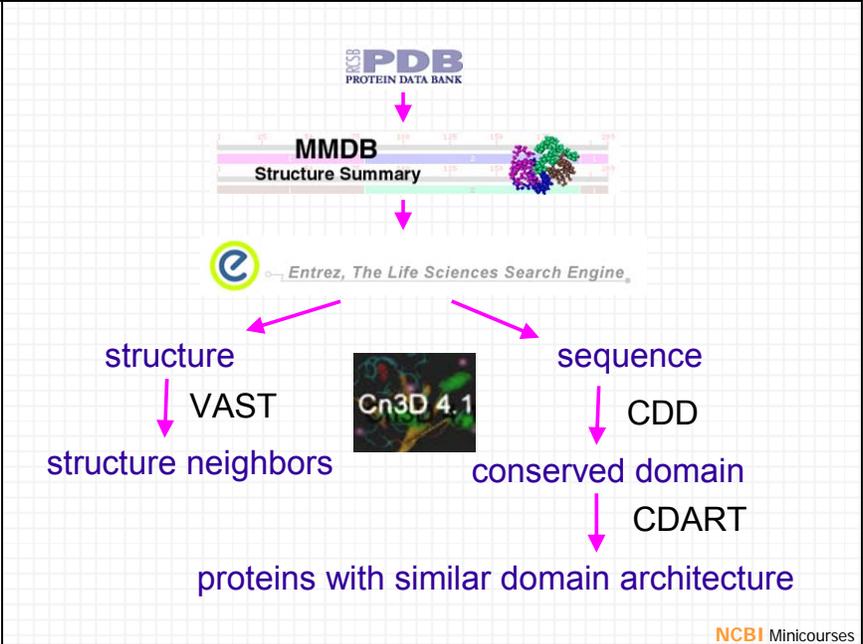
The remainder of the handout includes the introductory slides and the screen shots of the exercise demonstrated in Problem 1.

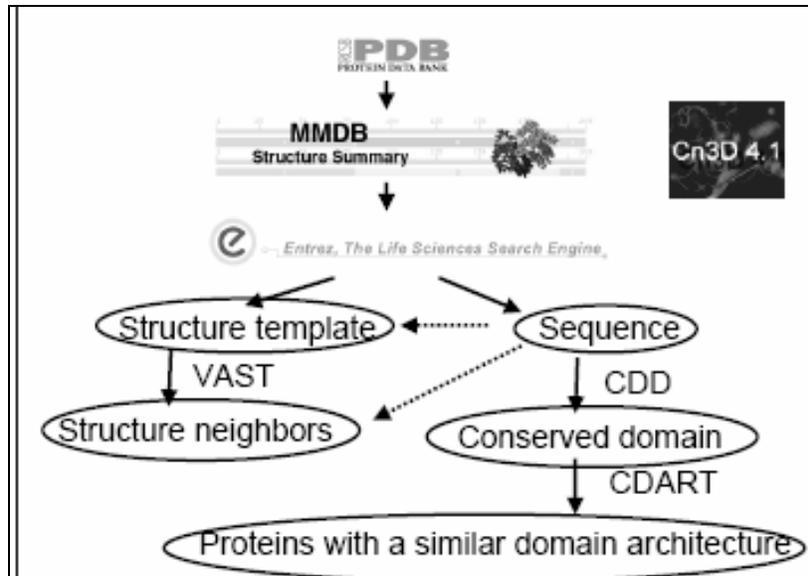
URL: <http://www.ncbi.nlm.nih.gov/Class/minicourses/quickstructure.html>

Course developed by: Dr. Medha Bhagwat (bhagwat@ncbi.nlm.nih.gov)

Slides







Outline

For a query protein:

1. Identify the conserved domain(s) present in it.
2. Search for other proteins containing similar domain(s).
3. Explore a 3D modeling template.
4. Find distant sequence homologs.

Problem 1

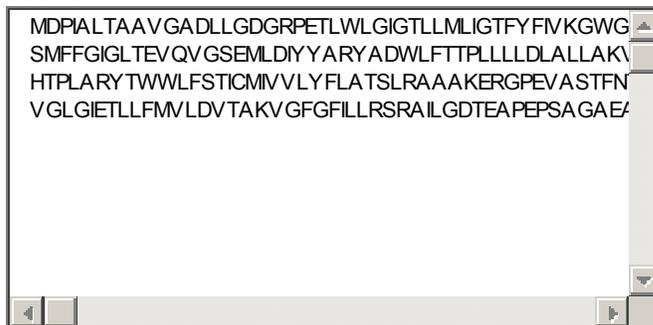
In this problem, we will follow these steps:

- A. Identify conserved domain(s) present in a protein.
- B. Search for other proteins containing similar domain(s).
- C. Explore a 3D modeling template for the query sequence.
- D. Find distant sequence homologs that may not be identified by BLAST.

NCBI's Conserved Domain Search allows you to match your protein sequence to a library of conserved protein domains, generate a multiple sequence alignment based on this match, and explore 3D modeling templates for your sequence. Click on the CDD link provided below,

CDD

Paste the following protein sequence in the CD-Search query box and run the search.



```
MDPIALTAAVGADLLGDGRPETLWLGIGTLLMLIGTFYFIVKGWG
SMFFGIGL TEVQV GSEMLDIYARYADWLFTPLLLLDLALLAKV
HTPLARYTWWLFFSTICMIVVLYFLATSLRAAAKERGPEVASTFN
VGLGIETLLFMVLDVTAKVGF G FILLRSRAILGDTEAPEPSAGAE/
```

- A. What is the domain present in this protein?
Obtain more information about the domain by searching in [NCBI's Bookshelf](#)
- B. Go back to the CD-Search results page. Obtain a list of proteins with similar domain architecture by clicking on the "Search for similar domain architectures" button. To display the records, click on the link to the sequences and from there on the "Look up Sequences in Entrez". Change the display from "Summary" to "FASTA".
- C. Go back to the CD-Search results page. Generate a multiple sequence alignment for the top 10 sequences representative of the conserved domain hit by clicking on the graphic of the domain. Use the "Row Display" list box pull down menu to specify "up to 5" sequences and reformat sequence alignment. Extend the "Structure" display and invoke Cn3D with a display of a 3D modeling template and a multiple sequence alignment including your query sequence by pressing the "Show Structure" button.

The structure of the *Halobacterium salinarum* halorhodopsin protein and its sequence alignment with our query protein are displayed. For a better view of the backbone, remove the side chains globally (Style--Edit global style--Protein side chains). The query protein contains a bacterial rhodopsin signature (FMVLDVTAKVGF) where K is the retinal binding site. Identify these residues in the query protein and highlight the corresponding lysine residue in the halorhodopsin protein sequence.

Display the side chains of this residue (Use Style--Annotate--New--Edit Style. Change the protein backbone Rendering to Tubes, Color Scheme to User Selection and User Color to choose the color for the highlighted residue, for example yellow. Repeat these steps for the Protein Side chains row and click the Protein Side chains on. Click on the "Done" button. To zoom in, press z on the keyboard. Identify the cofactor near the lysine residue.

D. To obtain the structural neighbors for the halorhodopsin protein, first click on the structure entry link, 1TNO_A, on the CD-Browser page. Then click Links → Structure on the top right, then on 1TNO again in the Entrez Structure page, and finally on the chain A graphic. To view neighbors with 1TNO_A, select one or more of the check boxes next to the structure neighbors and view by clicking on the "View 3D Structure" button.

Screenshots

The screenshot displays the NCBI Conserved Domain Database (CDD) search interface. At the top, there is a navigation bar with links for HOME, SEARCH, SITE MAP, PubMed, Entrez, CDD, Structure, Protein, Taxonomy, BLAST, and Help?. Below this is a search bar labeled "Search across Entrez databases" with GO and CLEAR buttons. The main content area is titled "A Conserved Domain Database and Search Service, v2.11". On the left, there is a sidebar with links for CDTree, CDD help, NCBI Handbook, CD-Search, CDART, Pfam, SMART, and COG. The main search form includes a "Submit Query" button, a "Search Database" dropdown menu set to "CDD v2.11 - 17402 PSSMs", and a text input field containing a protein sequence: "SMFFGIGLTEVQVGSSEMLDIYYARYADWLFITPLLLLDLALLAKVDRVSIIGTLVGVDMALMIVIGLVGALS HTPLARYTWNLFSTICMIVLVYFLATSLRAAAKERGPEVASTFNLTALVVLWTAVPILWIIGTEGAGV VGLGIETLLFMVLDVTAKVGFILLRSRAILGDTAPEFSGAGEASAAD". Below the input field is a "Find CDDs" button. At the top of the page, there is a 3D protein structure diagram with "Conserved Domains" labeled SH3 and SH2. A red arrow points to the "Submit Query" button.

NCBI

Conserved Domains

Query sequence: [(local sequence)|cl|Undefined_sequence]

Concise Result
 Full Result
 Show Search Information

Bac_rhodopsin

Title	Pssmid	Multi-Dom	E-value
pfam01036_Bac_rhodopsin_Bacteriorhodopsin..	64878	No	1e-50

Search for similar domain architectures

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 Alberts, Bruce; Johnson, Alexander, Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter.
 New York: [Garland Publishing](#); c2002.

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 Berg, Jeremy M.; Tymoczko, John L.; and Stryer, Lubert.
 New York: [W. H. Freeman and Co.](#); 2002.

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 Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E.
 New York: [W. H. Freeman & Co.](#); c2000.

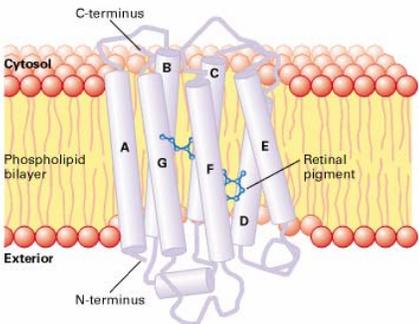
Many Integral Proteins Contain Multiple Transmembrane α Helices

Although [Figure 3-33](#) depicts glycophorin as a monomer with a single α helix spanning the bilayer, this protein is present in erythrocyte membranes as a dimer of two identical polypeptide chains. The two membrane-spanning α helices of glycophorin are thought to form a coiled-coil structure (see [Figure 3-9a](#)) stabilized by specific interactions between the amino acid side chains at the interface of the two helices. It is now known that many other transmembrane proteins contain two or more membrane-spanning α helices. For instance, the *bacterial photosynthetic reaction center (PRC)* comprises four subunits and several prosthetic groups, including four chlorophyll molecules. In this complex protein, three of the four subunits span the membrane; two of these subunits (L and M) each contain five membrane-spanning α helices (see [Figure 16-40](#)).

A large and important family of integral proteins is defined by the presence of seven membrane-spanning α helices. More than 150 such “seven-spanning” membrane proteins have been identified. This class of integral proteins is typified by *bacteriorhodopsin*, a protein found in a photosynthetic bacterium ([Figure 3-34](#)). Absorption of light by the retinal group attached to *bacteriorhodopsin* causes a conformational change in the protein that results in pumping of protons from the cytosol across the bacterial membrane to the extracellular space. The proton concentration gradient thus generated across the membrane is used to synthesize ATP, as discussed in [Chapter 16](#). Both the overall arrangement of the seven α helices in *bacteriorhodopsin* and the identity of most of the amino acids can be resolved by computer analysis of micrographs of two-dimensional crystals of the membrane-embedded protein taken at various angles to the electron beam.

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Molecular Cell Biology → **3. Protein Structure and Function** → 3.4. Membrane Proteins



The diagram illustrates the structure of bacteriorhodopsin embedded in a phospholipid bilayer. The bilayer is shown with a yellow lipid head group and a red tail group. The protein is depicted as a purple ribbon structure with seven transmembrane α helices labeled A through G. Helix A is the N-terminus, and helix G is the C-terminus. A retinal pigment is covalently attached to lysine 216 in helix G. The protein is oriented with the cytosol on the left and the exterior on the right.

Navigation

- [About this book](#)
- 3. Protein Structure and Function**
- 3.1. Hierarchical Structure of Proteins
- 3.2. Folding, Modification, and Degradation of Proteins
- 3.3. Functional Design of Proteins
- ➔ 3.4. Membrane Proteins
- 3.5. Purifying, Detecting, and Characterizing Proteins
- PERSPECTIVES for the Future
- PERSPECTIVES in the Literature
- Testing Yourself on the Concepts
- MCAT/GRE-Style Questions
- References

Figure 3-34. Overall structure of bacteriorhodopsin as deduced from electron diffraction analyses of two-dimensional crystals of the protein in the bacterial membrane. The seven membrane-spanning α helices are labeled A–G. The retinal pigment is covalently attached to lysine 216 in helix G. The approximate position of the protein in the phospholipid bilayer is indicated. [Adapted from R. Henderson et al., 1990, *J. Mol. Biol.* 213:899.]

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Conserved Domains

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Concise Result Full Result Show Search Information

Bac_rhodopsin

Title	Pssmid	Multi-Dom	E-value
[+]pfam01036, Bac_rhodopsin, Bacteriorhodopsin...	64878	No	1e-50

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CDART: Conserved Domain Architecture Retrieval Tool

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0 100 200 300

Query 

Similar domain architectures

YP_001277280 Roseiflexus sp. RS rhodopsin		more>
EDK94938 Methylobacterium s rhodopsin		more>
EDK43481 Lodderomyces elong conserved hypothet		more>
BAA75201 Haloterrigena sp. halorhodopsin		more>
XP_001395306 Aspergillus niger hypothetical prote		more>
XP_001395233 Aspergillus niger hypothetical prote		more>
AB088140 gamma proteobacter proteorhodopsin		more>
AB088139 gamma proteobacter proteorhodopsin		more>
AB088138 gamma proteobacter proteorhodopsin		more>

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Item 1 - 5 of 554 page 1 of 111 Previous Next

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Query sequence: [(local sequence)|c|] Undefined_sequence

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Descriptions

Title	Pssmid	Multi-Dom	E-value
[+]pfam01036, Bac_rhodopsin, Bacteriorhodopsin...	64878	No	1e-50

Search for similar domain architectures

NCBI Conserved Domains

pfam01036.13 Bac_rhodopsin, with user query added

Bacteriorhodopsin.

Other Related Conserved Domains: C069524

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NCBI Conserved Domains

pfam01036.13 Bac_rhodopsin, with user query added

Bacteriorhodopsin.

Show Structure

Program: Cn3D Drawing: All Atoms Aligned Rows: up to 5

[Download Cn3D]

Other Related Conserved Domains: C069524

Reformat Sequence Alignment Format: Compact Hypertext Row Display: up to 5 Color Bits: 2.0 bits

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CDD Descriptive Items

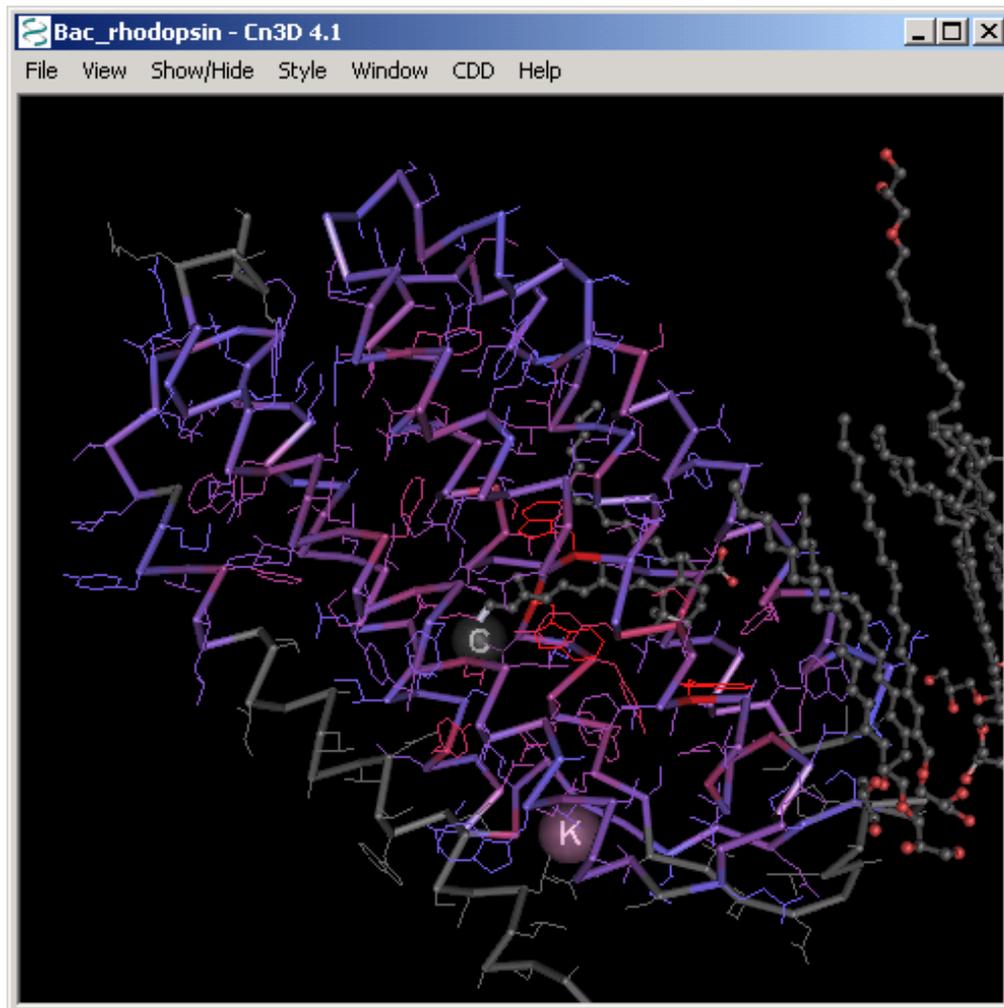
Name: Bac_rhodopsin

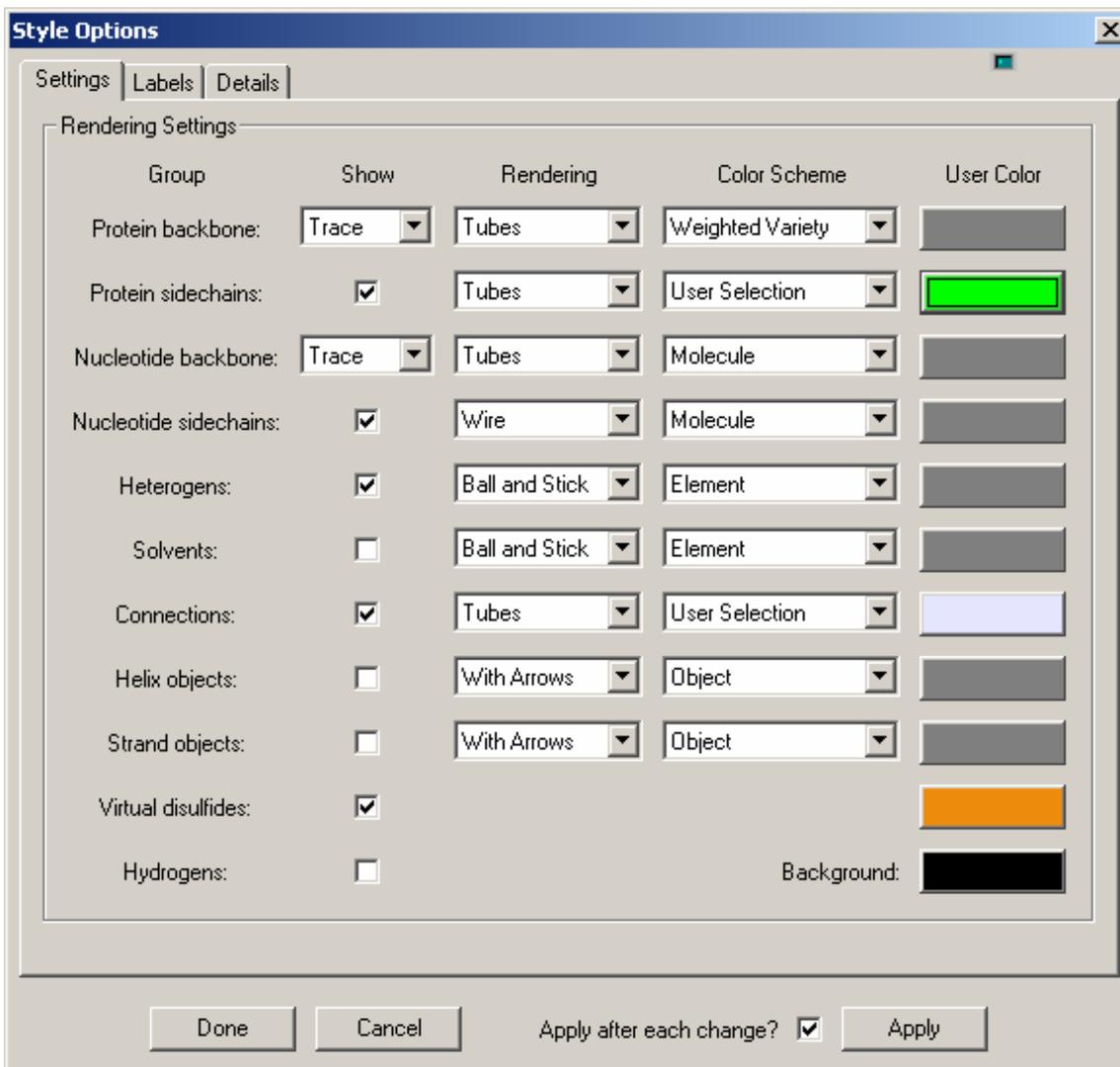
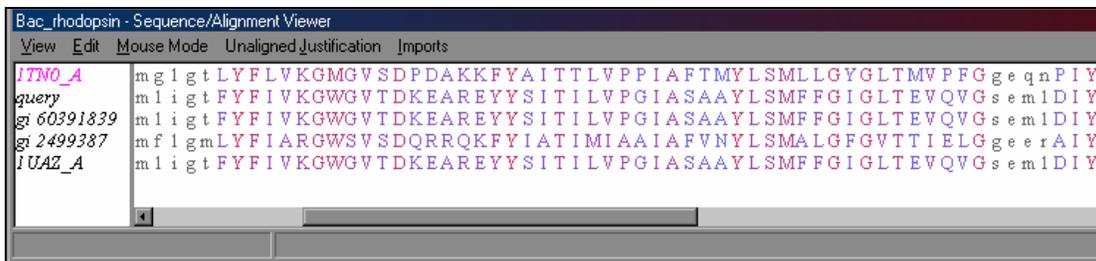
Bacteriorhodopsin.

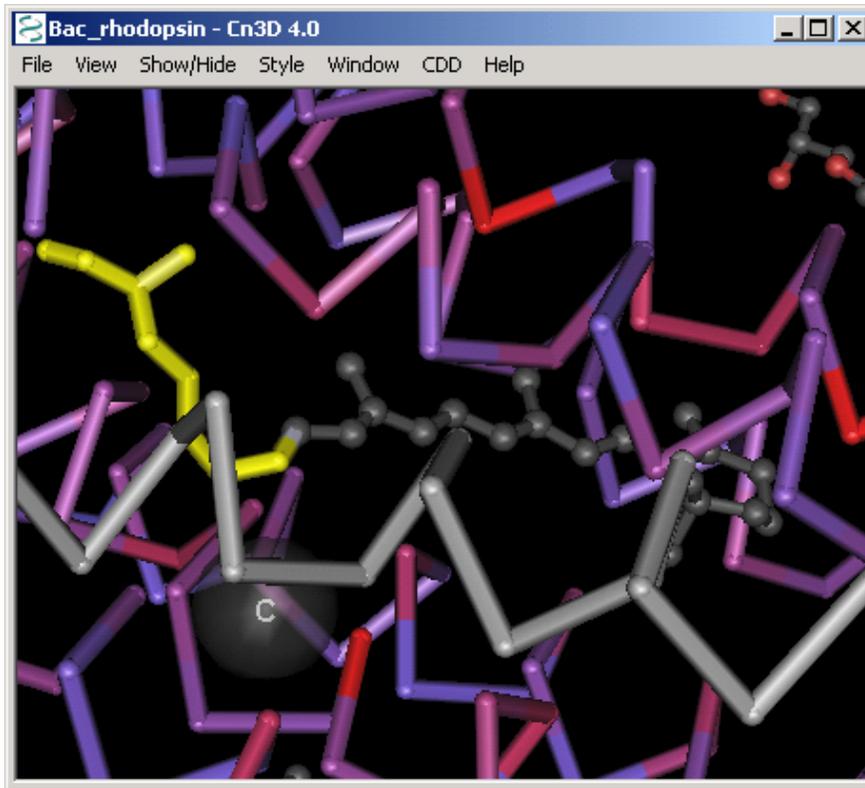
Structure summary:

PDB 1TN0 (MMDB 29943)
1TN0_A: gi 56553896 ([Halobacterium salinarum] Structure Of Bacteriorhodopsin Mutant A51p)

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NCBI

Conserved Domains

pfam01036.13 Bac_rhodopsin, with user query added

Bacteriorhodopsin.

Links: Statistics: Structure:

Show Structure

Program: Cn3D

Drawing: All Atoms

Aligned Rows: up to 5

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Other related Conserved Domains: CD05524

Reformat Sequence Alignment

Format: Compact Hypertext

Row Display: up to 5

Color Bits: 2.0bits

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1UAZ_A	15	[16]	.FYFIVKGGVTDKEAREYYSITLVPGIASAAVLSMFFGIGLTVQVG	[4]	.DIYYARYADWLFTTPLL	103

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Range: from begin to end Features: CDD

1: 1TN0A, Reports Chain A, Structur... [gi:56553896] [ELink](#) [Conserved Dom](#)

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LOCUS 1TN0_A 249 aa linear BCT 11-JUN-2004

DEFINITION Chain A, Structure Of Bacterorhodopsin Mutant A51p.

ACCESSION 1TN0_A

VERSION 1TN0_A GI:56553896

DBSOURCE pdb: molecule 1TN0, chain 6S, release Jun 11, 2004;

deposition: Jun 11, 2004;

class: Membrane Protein;

source: Mol_id: 1; Organism_scientific: Halobacterium Salinarium;

Organism_common: Halobacterium Halobium; Gene: Bop, Vng1467g;

Expression_system: Escherichia Coli; Expression_system_common:

Bacteria;

Exp. method: X-Ray Diffraction.

KEYWORDS .

SOURCE Halobacterium salinarum

ORGANISM [Halobacterium salinarum](#)

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- Domain Relatives
- PubMed
- Structure
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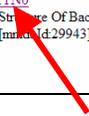
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All: 1 Bacterial: 1 Eukaryotic: 0 Ligand: 1 NMR: 0 X-ray: 1

1: 1TN0 [VAST](#) [Links](#)

Structure Of Bacterorhodopsin Mutant A51p
[mmdbId:29943]



NCBI **MMDB** Structure Summary

PubMed BLAST Structure Taxonomy OMIM Help? Cn3d

Reference: Yohannan S, Yang D, Faham S, Boulting G, Whitelegge J, Bowie JU [Proline substitutions are not easily accommodated in a membrane protein](#) *J. Mol. Biol.* v341, p.1-6

Description: Structure Of Bacterorhodopsin Mutant A51p.

Deposition: 2004/6/11

Taxonomy: [Halobacterium salinarum](#)

MMDB: [29943](#) **PDB:** [1TN0](#) **Structure Neighbors:** [VAST](#)

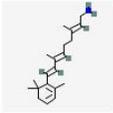
View 3D Structure of All Atom Model Cn3D Display Download Cn3D!

Molecular components in the MMDB structure are listed below. The icons indicate macromolecular chains, 3D domains, protein classifications and ligands. Please hold the mouse over each icon for more information on the component.

Protein Chain A
Domain Family Bac_rhodopsin

Protein Chain B
Domain Family Bac_rhodopsin

Ligand (x 2)



NCBI **VAST** Structure Neighbors

PubMed BLAST Structure Taxonomy OMIM Help? Cn3d

VAST neighbors for **MMDB 29943, 1TN0 A**

Overview: There are two main sections to this page. The first section consists of the alignment view controls, the list controls, and the advanced neighbor search controls. The second section is the VAST neighbor list itself.

View 3D Alignment of All Atoms with Cn3D Display Download Cn3D!

View Sequence Alignment using Hypertext for Selected VAST neighbors

List Medium redundancy subset, sorted by Aligned Length in Graphics

Advanced neighbor search

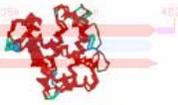
Move the mouse over the red alignment footprints in the graphics below and click you will obtain a structure-based sequence alignment.

Total neighbors: 177; 28 representatives from the Medium redundancy subset displayed.

Click to: [Check All](#) [Uncheck All](#)

1TN0 A Protein Family	Ali_len
<input type="checkbox"/> 2JRF A	225
<input type="checkbox"/> 1C3M A	222
<input type="checkbox"/> 1E12 A	220
<input type="checkbox"/> 1H2S A	216
<input type="checkbox"/> 2F93 A	214
<input type="checkbox"/> 1XT0 A	208





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VAST neighbors for: [MMDB 29943](#), [1TN0 A](#)

Overview: There are two main sections to this page. The first section consists of the alignment view controls, the list controls, and the advanced neighbor search controls. The second section is the VAST neighbor list itself.

of with [Download Cn3D!](#)

using for VAST neighbors

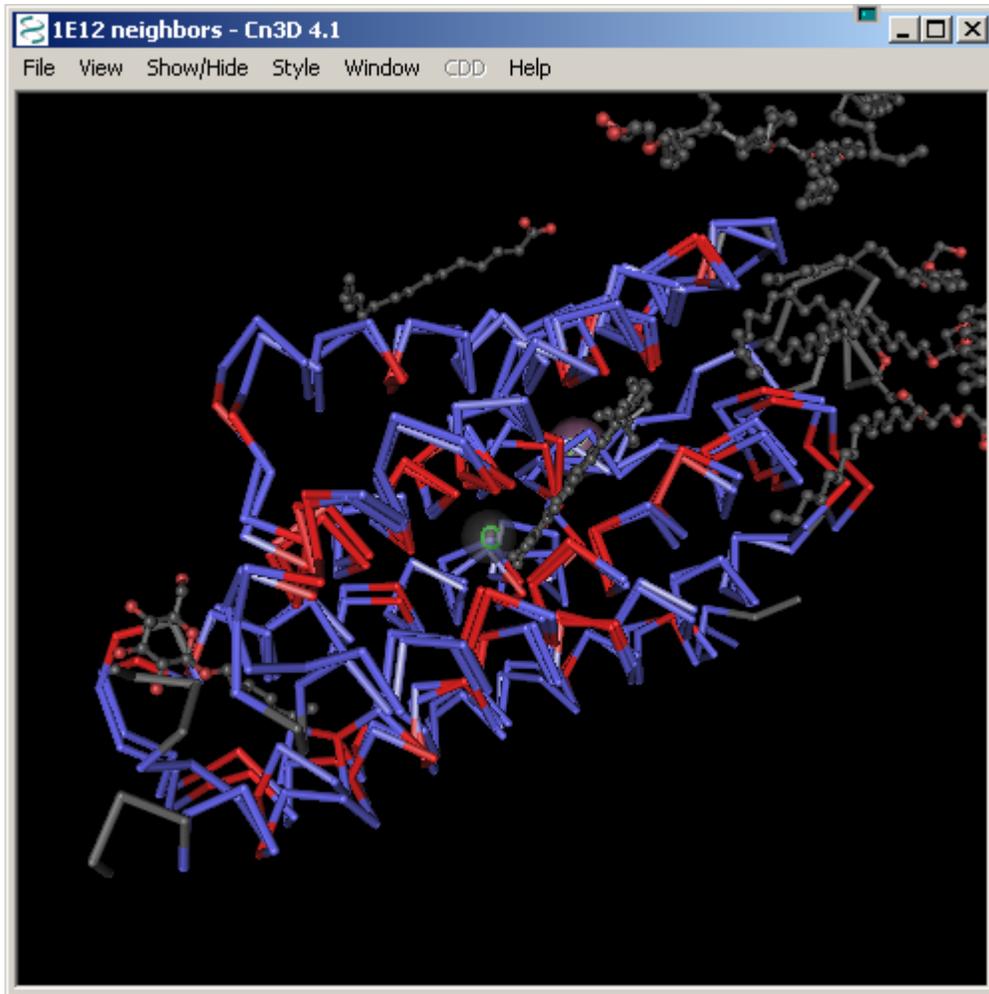
subset, sorted by in

Advanced neighbor search

Total neighbors: 177; 28 representatives from the [Medium redundancy](#) subset displayed.

Click to: [Check All](#) [Uncheck All](#)

	PDB	C	D	Ali. Len	Score	E_Val	Rmsd	%Id	MMDB Date	LHM	GSP	Description
<input type="checkbox"/>	2JAF	A		225	15.3	10e-14.9	1.7	33.3	01/2007	2.2	0.8	Ground State Of Halorhodopsin T203v
<input type="checkbox"/>	1C3W	A		222	16.0	10e-16.8	0.8	99.5	03/2001	0.8	0.4	BacteriorhodopsinLIPID COMPLEX AT 1.55 A RESOLUTION
<input type="checkbox"/>	1E12	A		220	15.5	10e-15.3	1.5	34.1	03/2001	2.1	0.7	Halorhodopsin, A Light-Driven Chloride Pump
<input checked="" type="checkbox"/>	1H2S	A		216	15.3	10e-14.8	1.1	29.2	11/2002	1.5	0.5	Molecular Basis Of Transmembrane Signalling By Sensory Rhodopsin li-Transducer Complex
<input type="checkbox"/>	2F93	A		214	15.5	10e-15.2	1.0	29.4	05/2006	1.4	0.5	K Intermediate Structure Of Sensory Rhodopsin liTRANSDUCER Complex In Combination With The Ground State Structure
<input type="checkbox"/>	1XIO	A		208	11.4	10e-8.9	1.6	29.3	11/2004	2.5	0.8	Anabaena Sensory Rhodopsin



1TNO neighbors - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

1TNO_A	q a q i t G R P E W I W L A L G T A L M G L G T L Y F L V K G M G V s D P D A K K F Y A I T T L V P P I A F T M Y L S M L L C
1H2S_A	~ ~ ~ ~ M V G L T T L F W L G A I G M L V G T L A F A W A G R D A ~ G S G E R R Y Y V T L V G I S G I A A V A Y V V M A L C

Problem 2

In this problem, we will follow these steps:

- Identify conserved domain(s) present in a protein.
- Search for other proteins containing similar domain(s).
- Explore a 3D modeling template for the query sequence.
- Find distant sequence homologs that may not be identified by BLAST.

NCBI's Conserved Domain Search allows you to match your protein sequence to a library of conserved protein domains, generate a multiple sequence alignment based on this match, and explore 3D modeling templates for your sequence. Click on the CDD link provided below,

[CDD](#)

paste the following protein sequence in the CD-Search query box and run the search.

```
>gij2851597|sp|P25848|PHY1_CERPU Light-sensor Protein kina:
MSATKKTY SSTTSAKSKHSVRVAQTTADAALAEVYEMSGDSC
QREGLIQNFGCMVAVEEPNFCVIA YSENA SEFLDLIPQAVPSMGE
AATQDISLLNPTVHCRRSGKPLYAJAHRIDIGVIDFEAVK MIDVPV
LPGGDIELLCDTVEEVRELTGYDRVMAFKFHEDEHGEVVAEIRR
KNRVRLIADCYASPVKLIQDPDIRQPVSLAGSTLRAPHGCHAYI
IQRGRKLWGLVV CQHTSPRTV PFPLRSVCEFLMQVFGMQLNLH
PIGVSQTPNIMDLVKCDGAALYYGKR V WLLGTTPTENQIKEADV
HLLGDAVCGMAAAKITAKDFLWFRSHTATEV KWGGAKHDPDE
EDVEMDAIHSLQLLRGSFRDIADSDTKTMIHARLNDLKLQGV EER
```

- What are the domains present in this protein?
(Select the "Full Result" radio button to display all of the domains.)

-Suppose, we are interested in the serine/threonine protein kinase domain. Obtain more information about it by searching in [NCBI's Bookshelf](#)

- Go back to the CD-Search results page. Obtain a list of proteins with similar domain architecture by clicking on the "Search for similar domains architectures" button. To display the records, click on the links to the subsets of sequences and from there on the "Look up Sequences in Entrez". Change the display from "Summary" to "FASTA".

- Go back to the CD-Search results page. Click on the "Full Report" radio button. Generate a multiple sequence alignment for the top 10 sequences representative of the conserved domain hit by clicking on the graphic representation of the serine/threonine kinase domain from CDD (CDD|00180). Use the "Aligned Rows" list box pull down menu to specify "up to 5" sequences

and invoke Cn3D with a display of a 3D modeling template and a multiple sequence alignment including your query sequence by pressing the "Show Structure" button.

To show only one top structure, click on the down arrow key. For better view of the backbone, remove the side chains globally (Style--Edit global style--Protein side chains). The query protein contains a serine/threonine protein kinase active-site signature (IIHRDLKSMNILV) where K is the ATP binding site. Identify these residues in the query protein and highlight the corresponding lysine residue in the first protein sequence.

Display the side chains of this residue (Use Style--Annotate--New--Edit Style. Change the protein backbone Rendering to Tubes, Color Scheme to User Selection and User Color to choose the color for the highlighted residue, for example yellow. Repeat these steps for the Protein Side chains row and click the Protein Side chains on. Click on the "Done" button. To zoom in, press z on the keyboard. Note the heterogen near the conserved lysine residue.

D. To obtain the structural neighbors for the serine/threonine protein kinase protein, first click on the structure entry link 1JNK of the similar protein from the CD-Browser page. Then click on the structure link on the top right side, then on 1JNK, and finally on the chain graphic. Select one or more of the check boxes next to the structure neighbors and download the structures by clicking on the "View 3D Alignment" button.