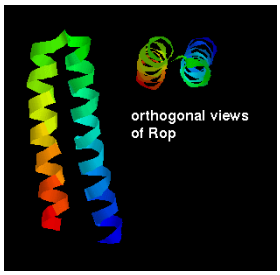
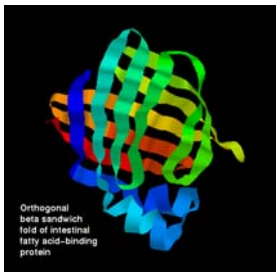
# Protein Structure Analysis & Protein-Protein Interactions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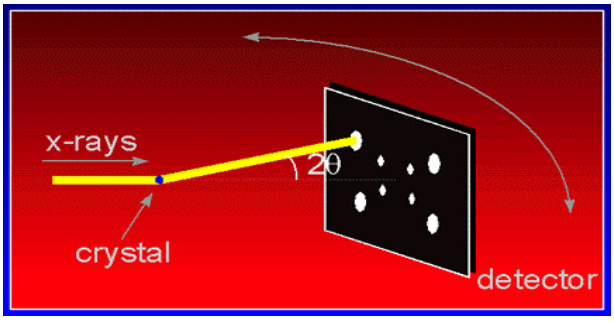
## Much Ado About Structure

- **Structure ⟷ Function**
- **Structure ⟷ Mechanism**
- **Structure ⟷ Origins/Evolution**
- **Structure-based Drug Design**
- **Solving the Protein Folding Problem**

## Routes to 3D Structure

- X-ray Crystallography (the best)
- NMR Spectroscopy (close second)
- Cryoelectron microsocopy (distant 3rd)
- Homology Modelling (sometimes VG)
- Threading (sometimes VG)

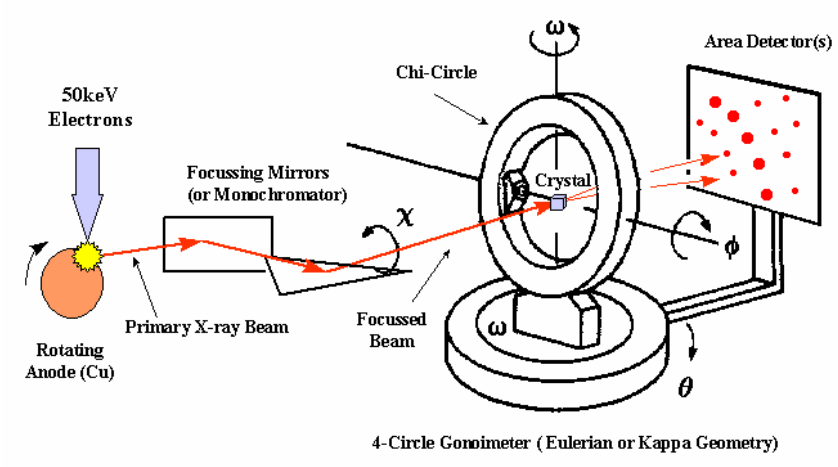
## X-ray Crystallography



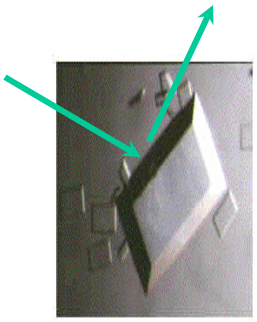
# X-ray Crystallography

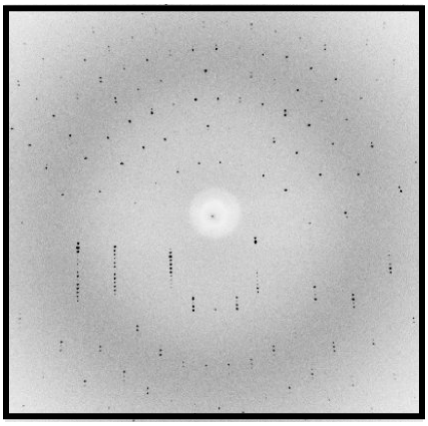
- Crystallization
- Diffraction Apparatus
- Diffraction Principles
- Conversion of Diffraction Data to Electron Density
- Resolution
- Chain Tracing

# Diffraction Apparatus



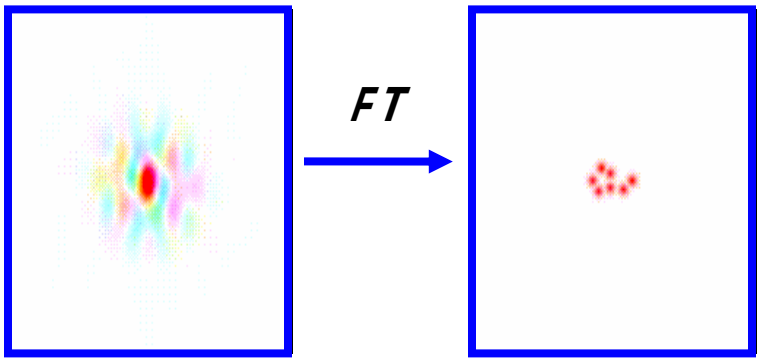
# Protein Crystal Diffraction



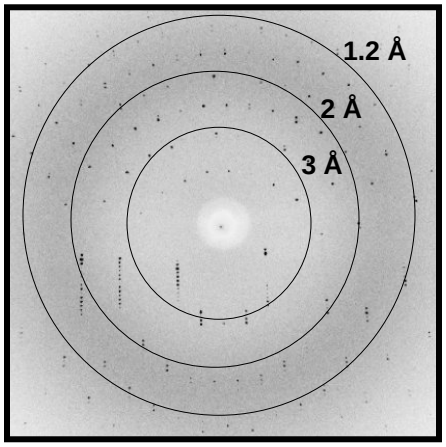


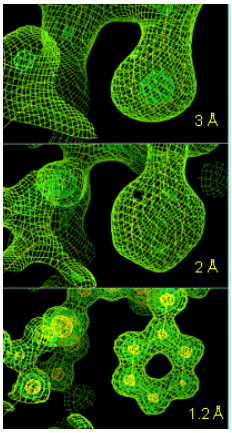
Diffraction Pattern

# Converting Diffraction Data to Electron Density



# Resolution




# The Final Result

```
ORIGX2      0.000000  1.000000  0.000000        0.00000                      2TRX 147
ORIGX3      0.000000  0.000000  1.000000        0.00000                      2TRX 148
SCALE1      0.011173  0.000000  0.004858        0.00000                      2TRX 149
SCALE2      0.000000  0.019585  0.000000        0.00000                      2TRX 150
SCALE3      0.000000  0.000000  0.018039        0.00000                      2TRX 151
ATOM      1  N   SER A   1      21.389  25.406  -4.628  1.00 23.22           2TRX 152
ATOM      2  CA  SER A   1      21.628  26.691  -3.983  1.00 24.42           2TRX 153
ATOM      3  C   SER A   1      20.937  26.944  -2.679  1.00 24.21           2TRX 154
ATOM      4  O   SER A   1      21.072  28.079  -2.093  1.00 24.97           2TRX 155
ATOM      5  CB  SER A   1      21.117  27.770  -5.002  1.00 28.27           2TRX 156
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ATOM     10  O   ASP A   2      19.760  26.575   1.371  1.00 21.49           2TRX 161
ATOM     11  CB  ASP A   2      18.439  24.914  -0.856  1.00 22.14           2TRX 162
```
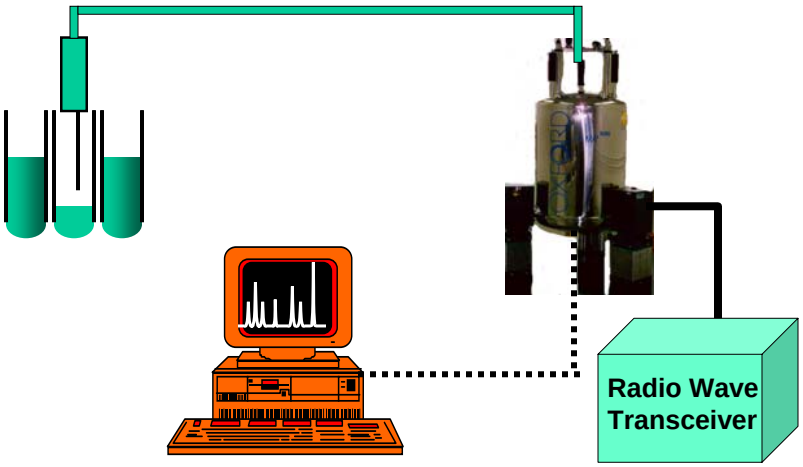
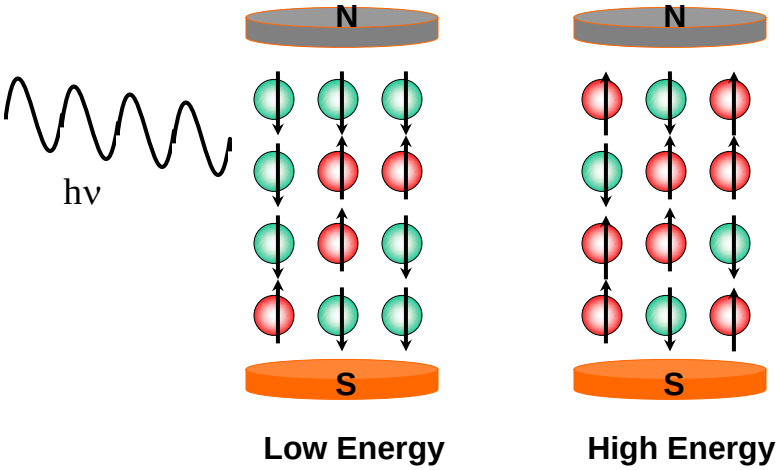

**http://www-structure.llnl.gov/Xray/101index.html**

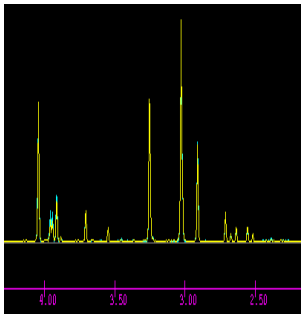
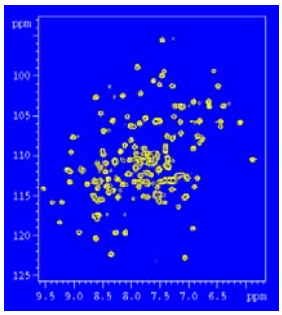
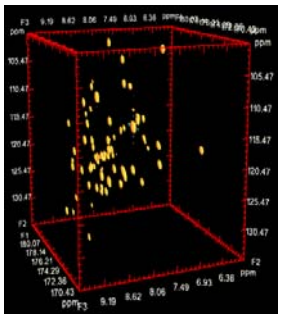
# NMR Spectroscopy




# Principles of NMR



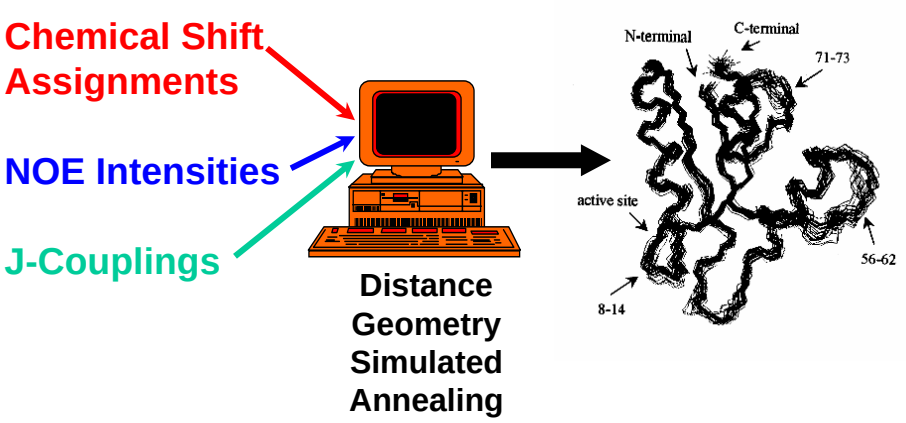
# Multidimensional NMR

| 1D | 2D | 3D |
|---|---|---|
|  |  |  |
| MW ~ 500 | MW ~ 10,000 | MW ~ 30,000 |

# The NMR Process

- Obtain protein sequence
- Collect TOCSY & NOESY data
- Use chemical shift tables and known sequence to assign TOCSY spectrum
- Use TOCSY to assign NOESY spectrum
- Obtain inter and intra-residue distance information from NOESY data
- Feed data to computer to solve structure

# NMR Spectroscopy




# The Final Result

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ATOM      1  N   SER A   1      21.389  25.406  -4.628  1.00 23.22           2TRX 152
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ATOM      3  C   SER A   1      20.937  26.944  -2.679  1.00 24.21           2TRX 154
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ATOM     10  O   ASP A   2      19.760  26.575   1.371  1.00 21.49           2TRX 161
ATOM     11  CB  ASP A   2      18.439  24.914  -0.856  1.00 22.14           2TRX 162
```

# X-ray Versus NMR

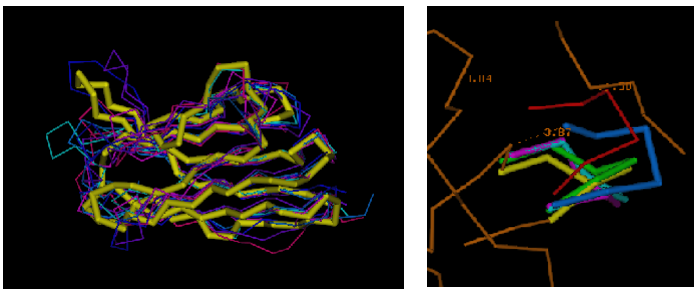
**X-ray**

- Producing enough protein for trials
- Crystallization time and effort
- Crystal quality, stability and size control
- Finding isomorphous derivatives
- Chain tracing & checking

**NMR**

- Producing enough labeled protein for collection
- Sample “conditioning”
- Size of protein
- Assignment process is slow and error prone
- Measuring NOE’s is slow and error prone

# Comparative (Homology) Modelling



```
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ASDEYAHLRILDPQRSTVAYAYE--KSFAPPGSFKWEYEAHADS
MCDEYAHIRLMNPERSTVAGGHQWERT----GSFKEWYAAHADD
```

## Homology Modelling

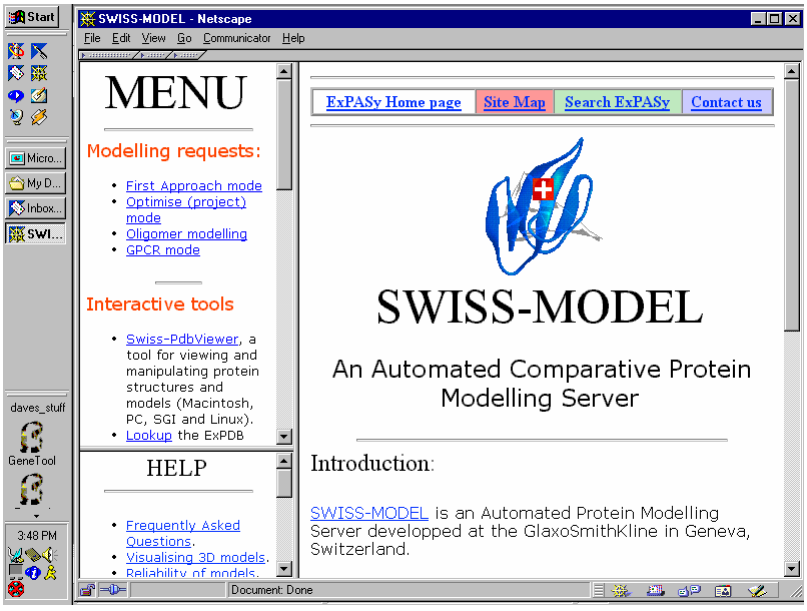
- Offers a method to “Predict” the 3D structure of proteins for which it is not possible to obtain X-ray or NMR data
- Can be used in understanding function, activity, specificity, etc.
- Of interest to drug companies wishing to do structure-aided drug design
- A keystone of Structural Proteomics

## Homology Modelling

- Identify homologous sequences in PDB
- Align query sequence with homologues
- Find Structurally Conserved Regions (SCRs)
- Identify Structurally Variable Regions (SVRs)
- Generate coordinates for core region
- Generate coordinates for loops
- Add side chains (Check rotamer library)
- Refine structure using energy minimization
- Validate structure

# Modelling on the Web

- Prior to 1998 homology modelling could only be done with commercial software or command-line freeware
- The process was time-consuming and labor-intensive
- The past few years has seen an explosion in automated web-based homology modelling servers
- Now anyone can homology model!




http://www.expasy.ch/swissmod/SWISS-MODEL.html

# The Final Result

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ATOM     11  CB  ASP A   2      18.439  24.914  -0.856  1.00 22.14           2TRX 162
```
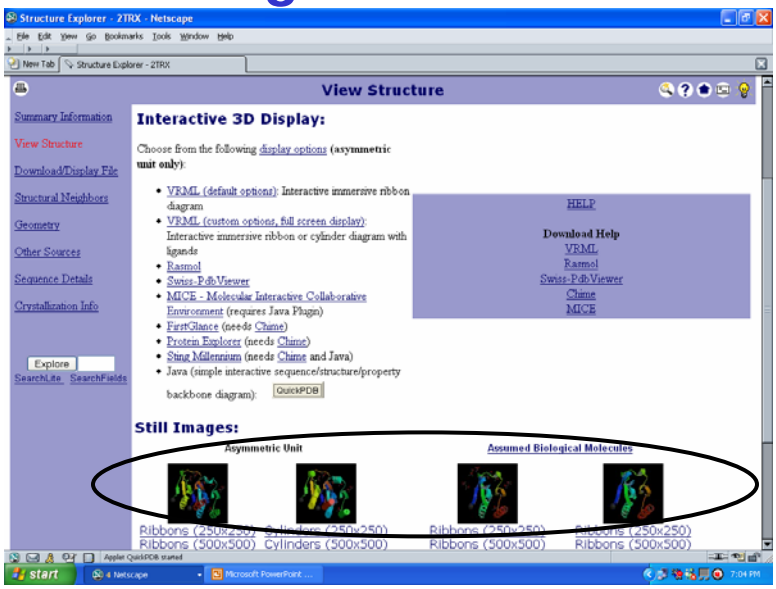

# The PDB

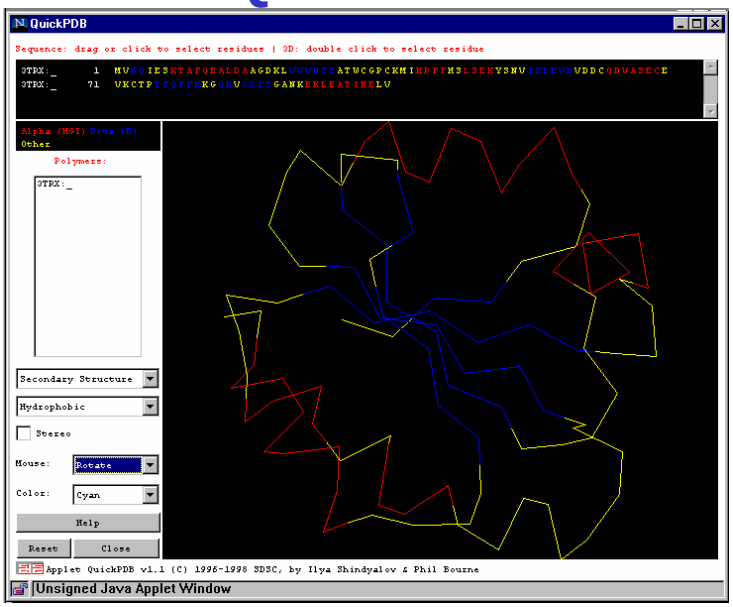
- **PDB - Protein Data Bank**
- **Established in 1971 at Brookhaven National Lab (7 structures)**
- **Primary archive for macromolecular structures (proteins, nucleic acids, carbohydrates – now 30,000 structrs)**
- **Moved from BNL to RCSB (Research Collaboratory for Structural Bioinformatics) in 1998**


http://www.rcsb.org/pdb/

# Viewing 3D Structures



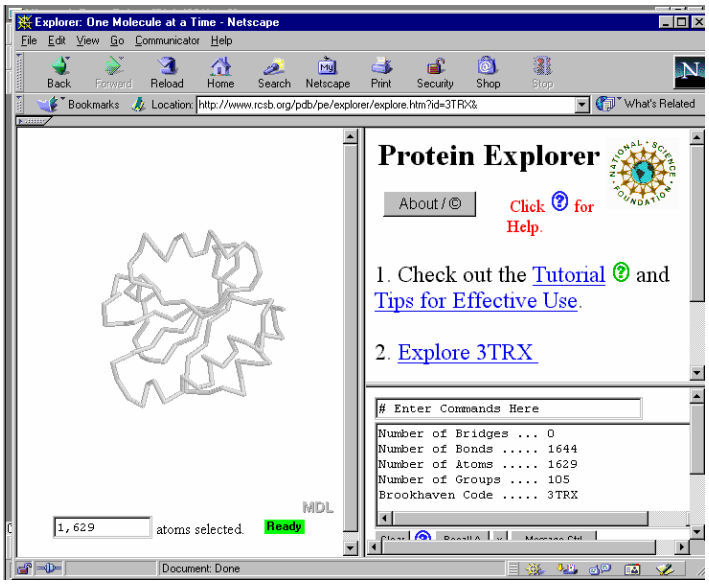
# QuickPDB




# Quick PDB

- http://www.sdsc.edu/pb/Software.html
- Very simple viewing program with limited manipulation and very limited rendering capacity -- Very fast
- Java Applet (Source code available)
- Compatible with most browsers and computer platforms

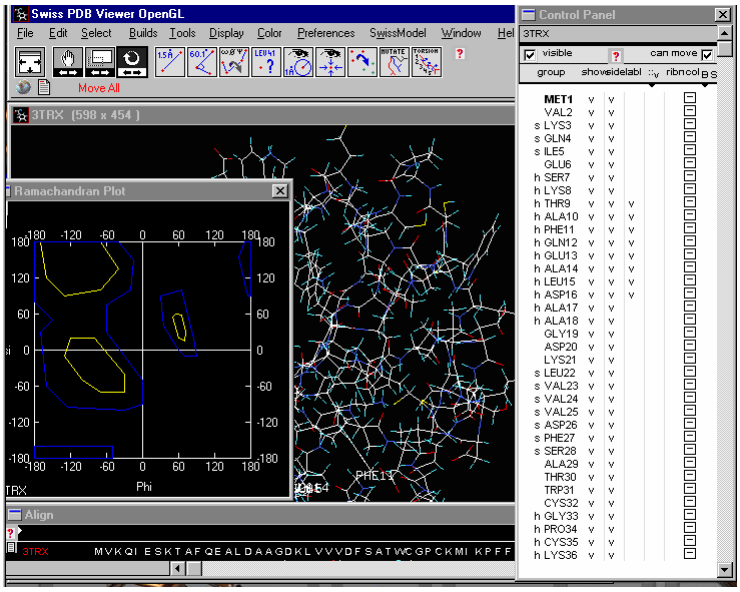
# Protein Explorer (Chime)




# Protein Explorer

- http://www.umass.edu/microbio/chime/explorer/
- **Uses Chime & Rasmol for its back-end**
- **Very flexible, user friendly, well documented, offers morphing, sequence structure interface, comparisons, context-dependent help, smart zooming, off-line**
- **Browser Plug-in (Like PDF reader)**
- **Compatible with Netscape (Mac & Win)**

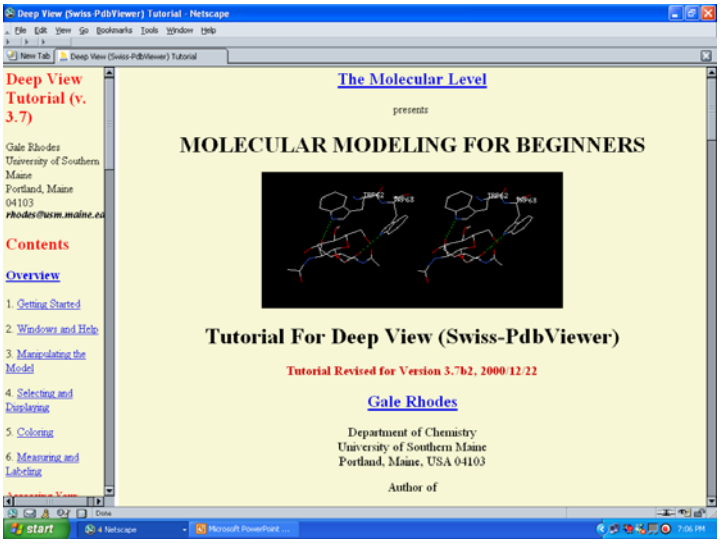
# Swiss PDB Viewer




# Swiss PDB Viewer

- http://www.expasy.ch/spdbv/
- Among most sophisticated molecular rendering, manipulation and modelling packages (commercial or freeware)
- Supports threading, hom. Modelling, energy minimization, seq/struc interface
- Stand-alone version only
- Compatible on Mac, Win, Linux, SGI

# Swiss PDB Tutorial

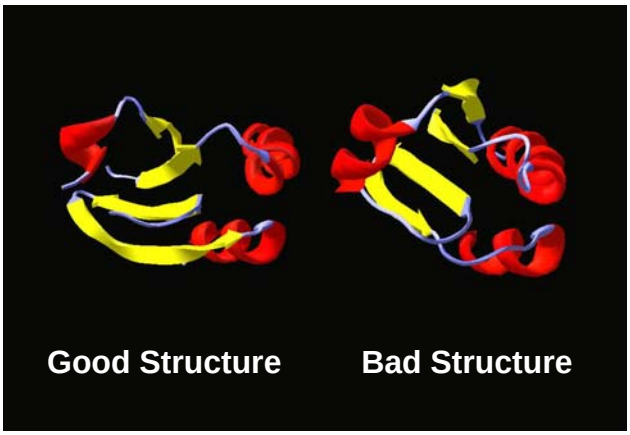



http://www.usm.maine.edu/~rhodes/SPVTut/

# Summary

| | Mac | Win | Unix | Rendr | SeqView | Super | E Min | Modeling |
|---|---|---|---|---|---|---|---|---|
| Rasmol | + | + | + | ++ | - | - | - | - |
| Chime | + | + | - | + | - | - | - | - |
| Prot. Expl. | + | + | - | ++ | + | + | - | - |
| Quick PDB | + | + | + | + | + | - | - | - |
| Biomer | + | + | + | ++ | - | + | + | + |
| SwP Viewer | + | + | + | +++ | + | + | + | + |
| MolMol | - | + | + | +++ | - | + | - | + |

# Analyzing and Assessing 3D Structures




# Why Assess Structure?

- A structure can (and often does) have mistakes
- A poor structure will lead to poor models of mechanism or relationship
- Unusual parts of a structure may indicate something important (or an error)

## Famous “bad” structures

- Azobacter ferredoxin (wrong space group)
- Zn-metallothionein (mistraced chain)
- Alpha bungarotoxin (poor stereochemistry)
- Yeast enolase (mistraced chain)
- Ras P21 oncogene (mistraced chain)
- Gene V protein (poor stereochemistry)

## How to Assess Structure?

- Assess experimental fit (look at R factor {X-ray} or rmsd {NMR})
- Assess correctness of overall fold (look at disposition of hydrophobes, location of charged residues)
- Assess structure quality (packing, stereochemistry, bad contacts, etc.)

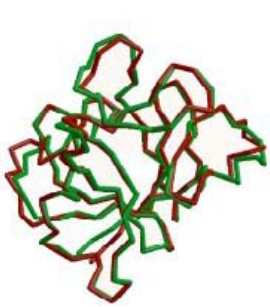
## A Good Protein Structure..

| X-ray structure | NMR structure |
|---|---|
| • R = 0.59 random chain | • rmsd = 4 Å random |
| • R = 0.45 initial structure | • rmsd = 2 Å initial fit |
| • R = 0.35 getting there | • rmsd = 1.5 Å OK |
| • R = 0.25 typical protein | • rmsd = 0.8 Å typical |
| • R = 0.15 best case | • rmsd = 0.4 Å best case |
| • R = 0.05 small molecule | • rmsd = 0.2 Å dream on |

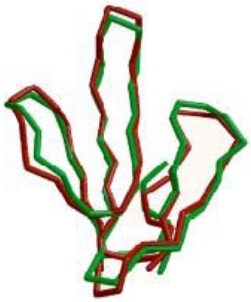
## Cautions...

- A low R factor or a good RMSD value does not guarantee that the structure is “right”
- Differences due to crystallization conditions, crystal packing, solvent conditions, concentration effects, etc. can perturb structures substantially
- Long recognized need to find other ways to ID good structures from bad (not just assessing experimental fit)

## Structure Variability



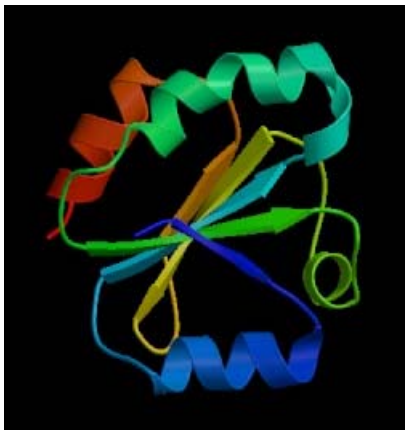
X-ray to X-ray
Interleukin 1β
(41bi vs 2mlb)



NMR to X-ray
Erabutoxin
(3ebx vs 1era)

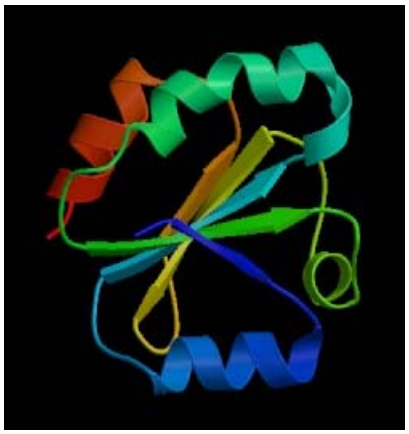
## A Good Protein Structure..

- Minimizes disallowed torsion angles
- Maximizes number of hydrogen bonds
- Maximizes buried hydrophobic ASA
- Maximizes exposed hydrophilic ASA
- Minimizes interstitial cavities or spaces



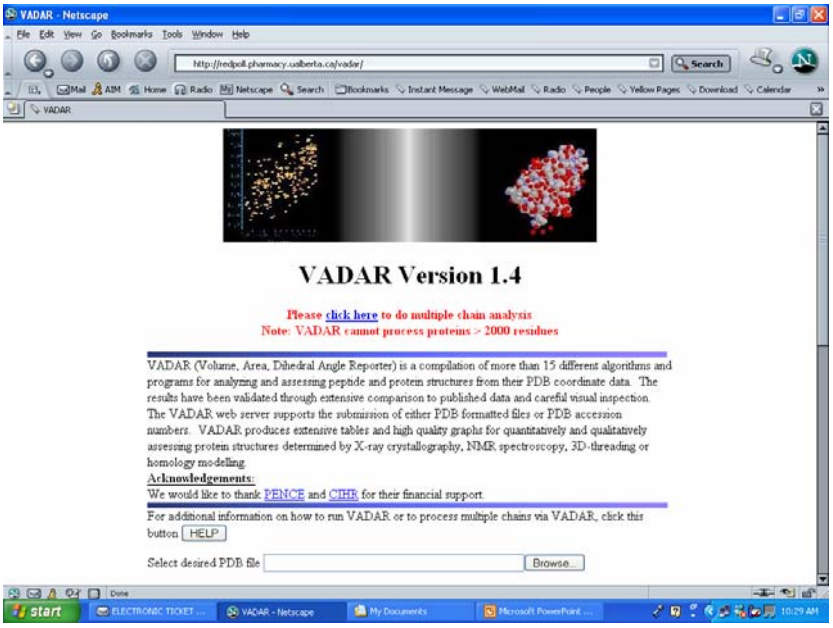
## A Good Protein Structure..

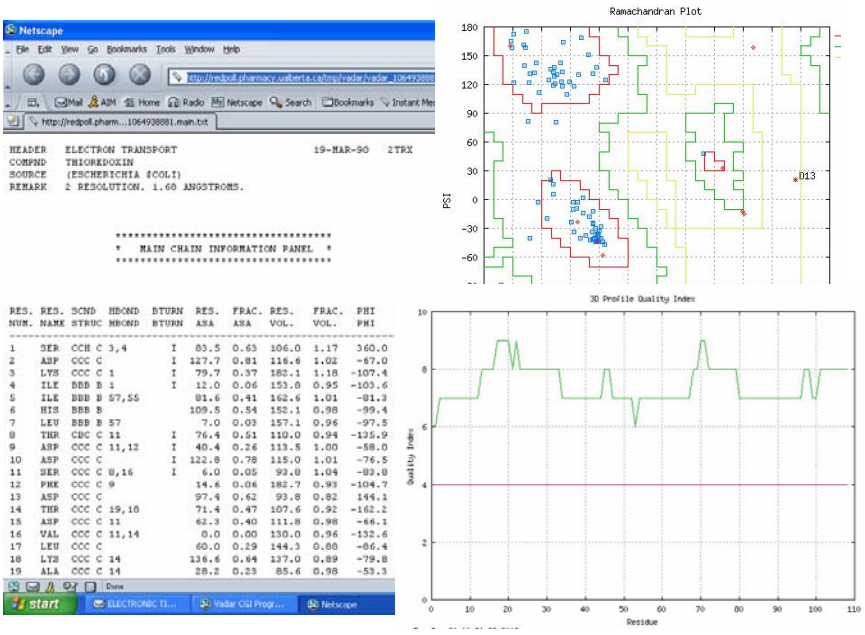
- Minimizes number of "bad" contacts
- Minimizes number of buried charges
- Minimizes radius of gyration
- Minimizes covalent and noncovalent (van der Waals and coulombic) energies



## Structure Validation Servers

- **WhatIf Web Server -** http://www.cmbi.kun.nl:1100/WIWWWI/
- **Biotech Validation Suite -** http://biotech.ebi.ac.uk:8400/cgi-bin/sendquery
- **Verify3D -** http://www.doe-mbi.ucla.edu/Services/Verify_3D/
- **VADAR -** http://redpoll.pharmacy.ualberta.ca

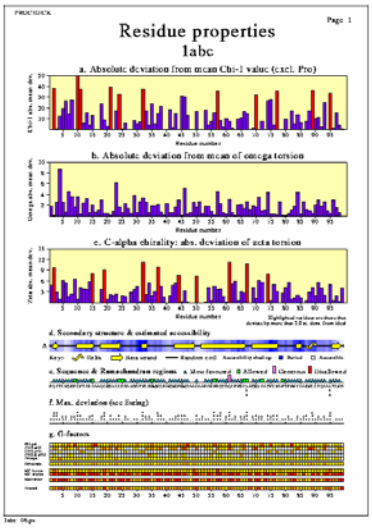

VADAR - Netscape
VADAR Version 1.4
Please click here to do multiple chain analysis
Note: VADAR cannot process proteins > 2000 residues
VADAR (Volume, Area, Dihedral Angle Reporter) is a compilation of more than 15 different algorithms and programs for analyzing and assessing peptide and protein structures from their PDB coordinate data. The results have been validated through extensive comparison to published data and careful visual inspection. The VADAR web server supports the submission of either PDB formatted files or PDB accession numbers. VADAR produces extensive tables and high quality graphs for quantitatively and qualitatively assessing protein structures determined by X-ray crystallography, NMR spectroscopy, 3D-threading or homology modelling.
Acknowledgements:
We would like to thank PENCE and CIHR for their financial support.
For additional information on how to run VADAR or to process multiple chains via VADAR, click this button HELP
Select desired PDB file
Browse...

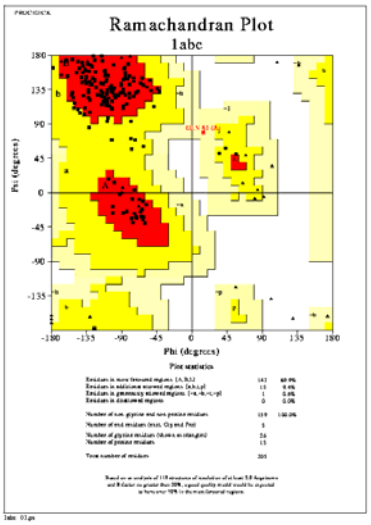

Netscape
HEADER ELECTRON TRANSPORT 19-MAR-90 2TRX
COMPND THIOREDOXIN
SOURCE (ESCHERICHIA COLI)
REMARK 2 RESOLUTION. 1.60 ANGSTROMS.
* MAIN CHAIN INFORMATION PANEL *
RES. NUM. RES. NAME SCND STRUC HBOND BTURN RES. ASA FRAC. ASA RES. VOL. FRAC. VOL. PHI
Ramachandran Plot
PSI
3D Profile Quality Index
Quality Index
Residue

# Structure Validation Programs

- **PROCHECK -**
  http://www.biochem.ucl.ac.uk/~roman/procheck/procheck.html
- **PROSA II -**
  http://lore.came.sbg.ac.at/People/mo/Prosa/prosa.html
- **VADAR -**
  http://www.pence.ualberta.ca/ftp/vadar/
- **DSSP -**
  http://www.embl-heidelberg.de/dssp/

# Procheck



## Comparing 3D Structures

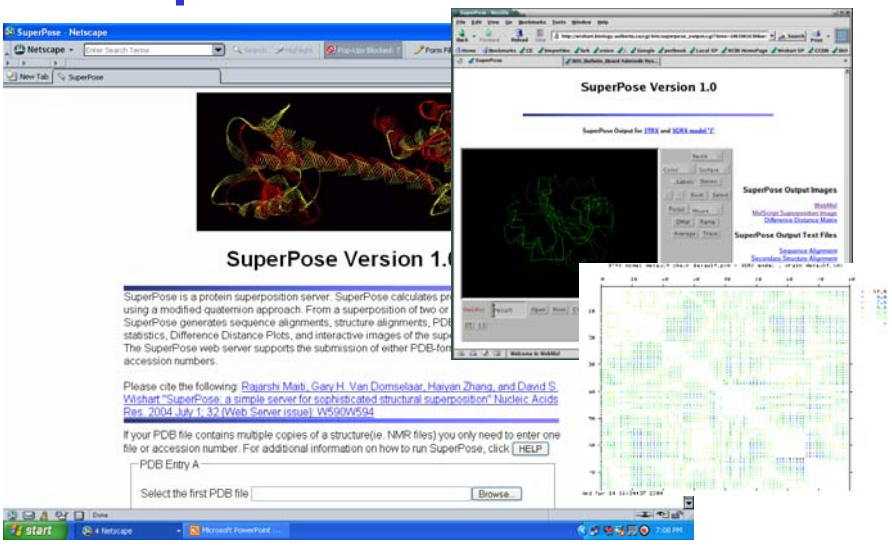

**Qualitative vs. Quantitative**

## Rigid Body Superposition

# Superposition

- Objective is to match or overlay 2 or more similar objects
- Requires use of translation and rotation operators (matrices/vectors)
- Least squares or conjugate gradient minimization (McLachlan/Kabsch)
- Lagrangian multipliers
- Quaternion-based methods (*fastest*)

# SuperPose Web Server

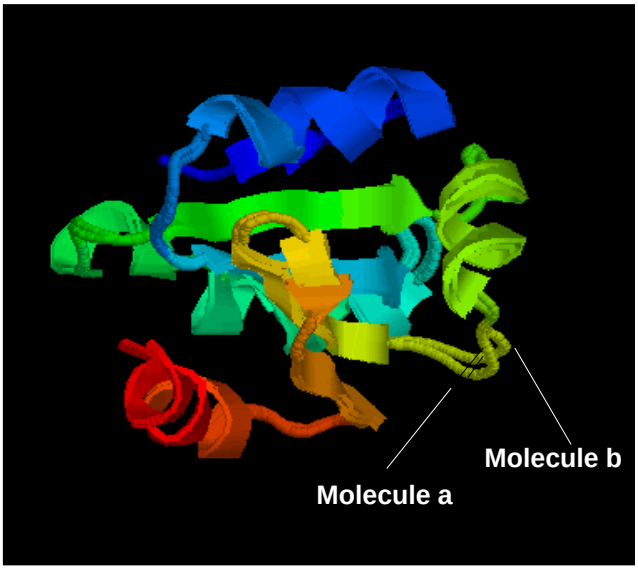



http://wishart.biology.ualberta.ca/SuperPose/

## Superposition - Applications

- Ideal for comparing or overlaying two or more protein structures
- Allows identification of structural homologues (CATH and SCOP)
- Allows loops to be inserted or replaced from loop libraries (comparative modelling)
- Allows side chains to be replaced or inserted with relative ease

## Measuring Superpositions



## RMSD - Root Mean Square Deviation

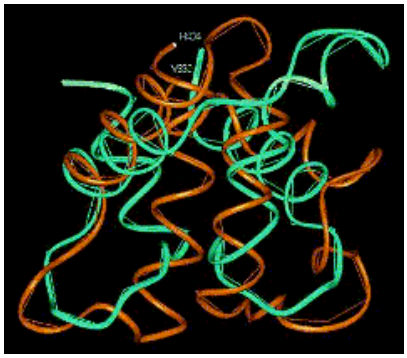
- Method to quantify structural similarity - same as standard deviation
- Requires 2 superimposed structures (designated here as “a” & “b”)
- N = number of atoms being compared

$$RMSD = \frac{\sqrt{\sum_i (x_{ai} - x_{bi})^2 + (y_{ai} - y_{bi})^2 + (z_{ai} - z_{bi})^2}}{\sqrt{N}}$$

## RMSD

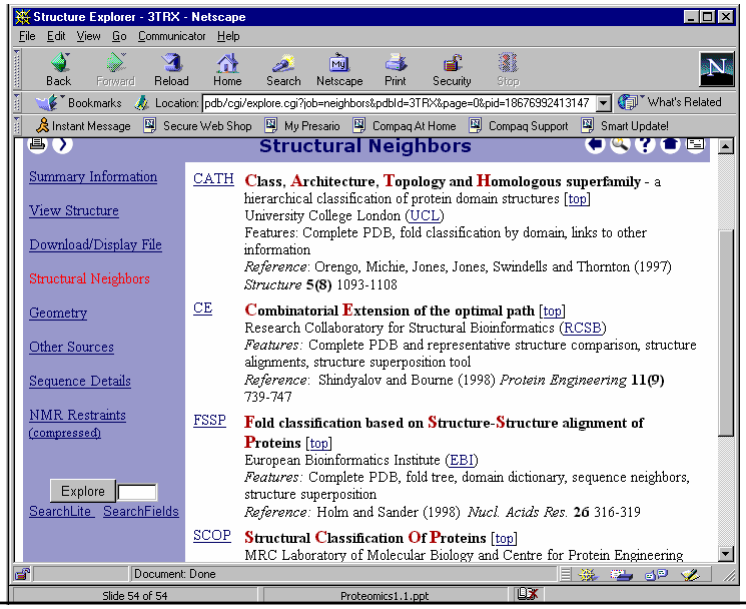
- 0.0-0.5 Å → Essentially Identical
- <1.5 Å → Very good fit
- < 5.0 Å → Moderately good fit
- 5.0-7.0 Å → Structurally related
- > 7.0 Å → Dubious relationship
- > 12.0 Å → Completely unrelated

# Detecting Unusual Relationships

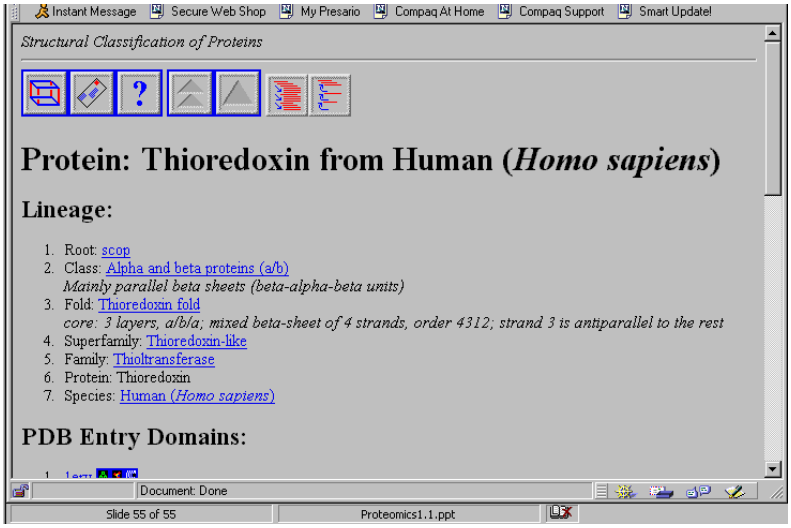


**Similarity between Calmodulin and Acetylcholinesterase**

# Classifying Protein Folds



# SCOP Database

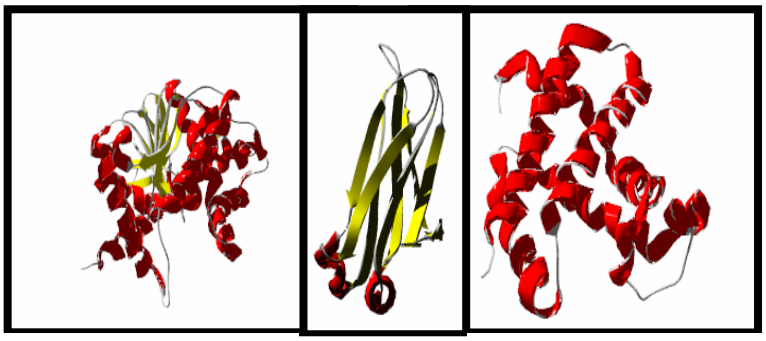



http://scop.mrc-lmb.cam.ac.uk/scop

# SCOP

- **Class** folding class derived from secondary structure content
- **Fold** derived from topological connection, orientation, arrangement and # 2º structures
- **Superfamily** clusters of low sequence ID but related structures & functions
- **Family** clusers of proteins with seq ID > 30% with v. similar struct. & function

# Different Folding Classes



Lactate Dehydrogenase: Mixed α / β

Immunoglobulin Fold: β

Hemoglobin B Chain: α

# CATH Database


http://www.biochem.ucl.ac.uk/bsm/cath/

## CATH

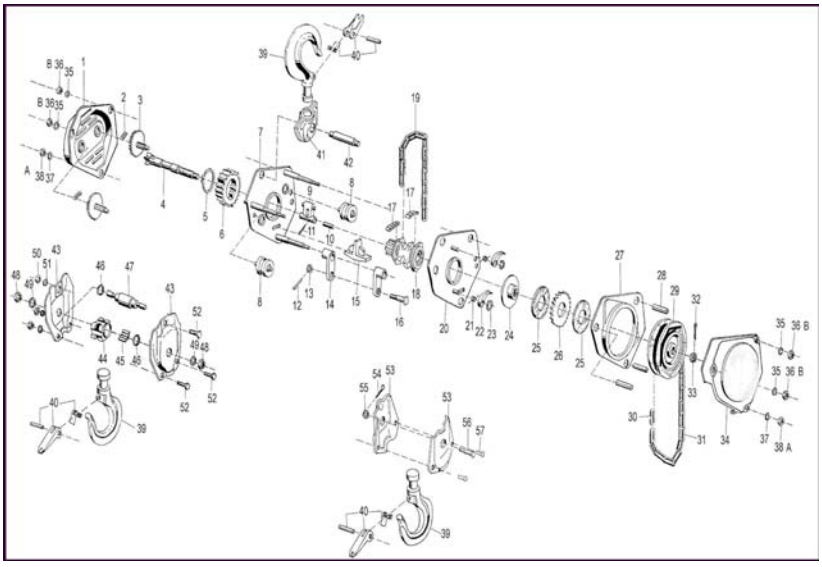
- **Class** [C] derived from secondary structure content (automatic)
- **Architecture** (A) derived from orientation of $2^o$ structures (manual)
- **Topology** (T) derived from topological connection and # $2^o$ structures
- **Homologous** Superfamily (H) clusters of similar structures & functions

## Other Servers/Databases

- **Dali -** http://www.ebi.ac.uk/dali/
- **VAST -** http://www.ncbi.nlm.nih.gov/Structure/VAST/vast.shtml
- **CE -** http://cl.sdsc.edu/ce.html
- **FSSP -** http://www.ebi.ac.uk/dali/fssp/fssp.html
- **PDBsum -** www.biochem.ucl.ac.uk/bsm/pdbsum/

# Protein Interactions

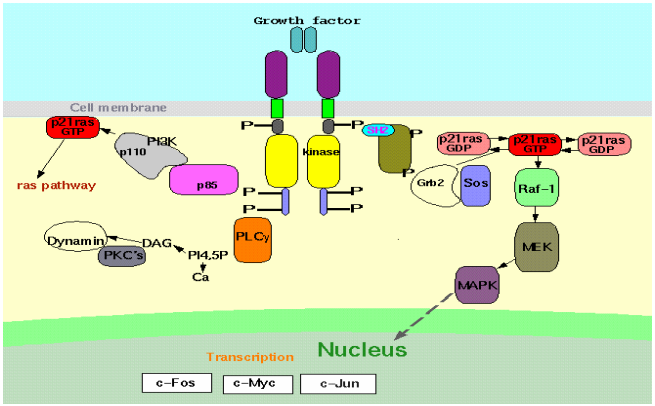
# The Protein Parts List



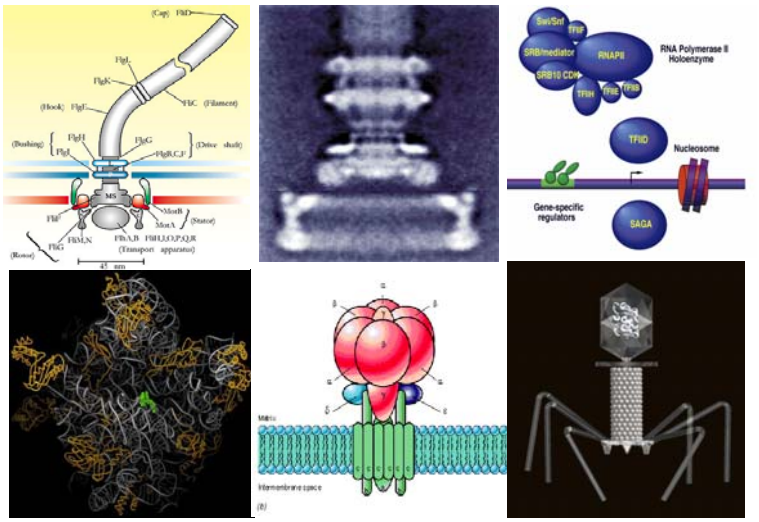
## The Parts List

- Sequencing gives “serial number”
- Sequence alignment gives a name
- Microarrays give # of parts
- X-ray and NMR give a picture
- However, having a collection of parts and names doesn’t tell you how to put something together or how things connect -- ***this is biology***

## Remember: *Proteins Interact*



## Proteins *Assemble*

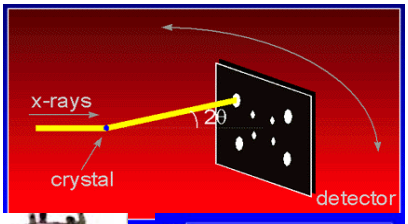


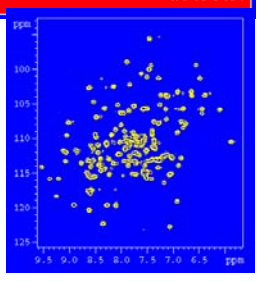

## Types of Interactions

- **Permanent (quaternary structure, formation of stable complexes)**
- **Transient (brief interactions, signaling events, pathways)**
- **About 1/4 to 1/3 of all proteins form complexes (dimers → multimers)**
- **Each protein may transiently interact with ~3 other proteins**

# Protein Interaction Tools and Techniques - Experimental Methods

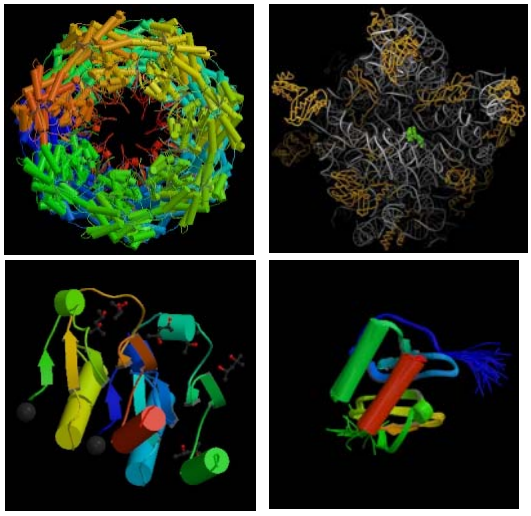
## 3D Structure Determination



- **X-ray crystallography**
  - grow crystal
  - collect diffract. data
  - calculate e- density
  - trace chain
- **NMR spectroscopy**
  - label protein
  - collect NMR spectra
  - assign spectra & NOEs
  - calculate structure using distance geom.

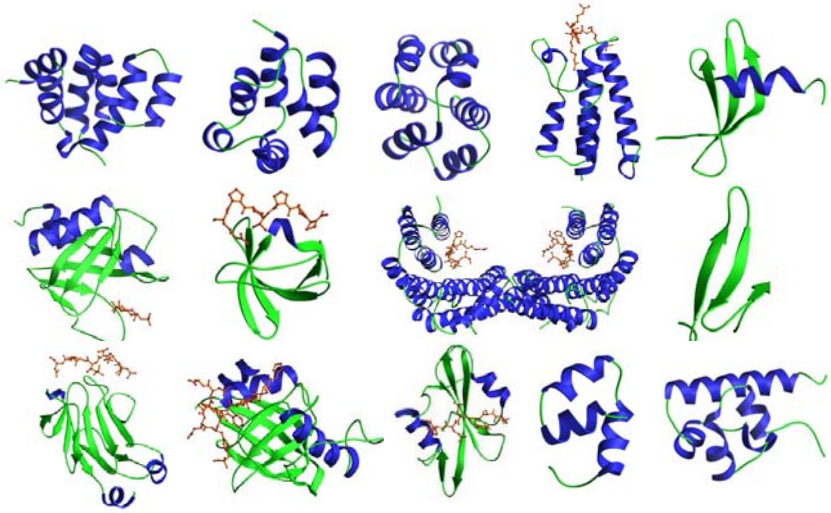
# Quaternary Structure



**Some interactions are real**

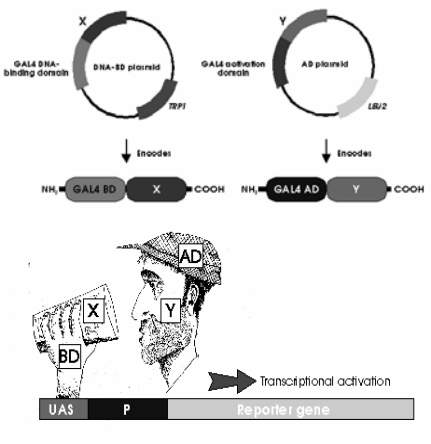
**Others are not**

# Protein Interaction Domains



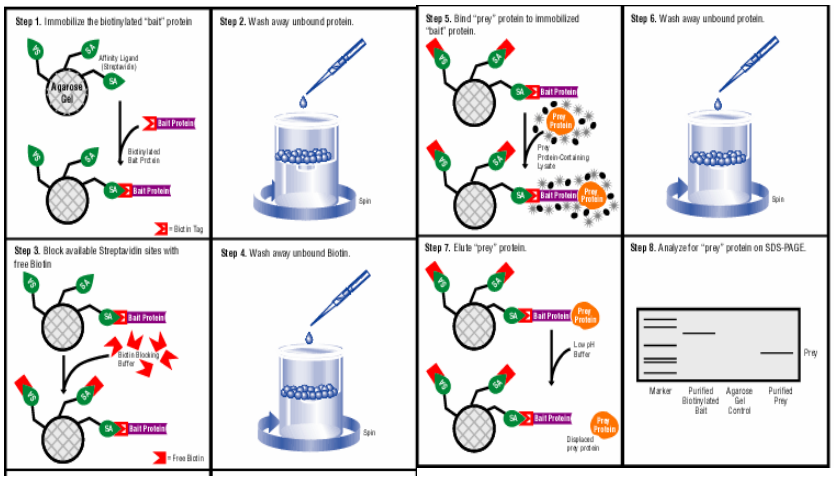
http://www.mshri.on.ca/pawson/domains.html

# Yeast Two-Hybrid Analysis

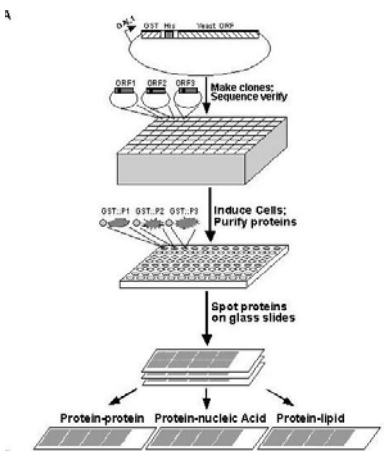


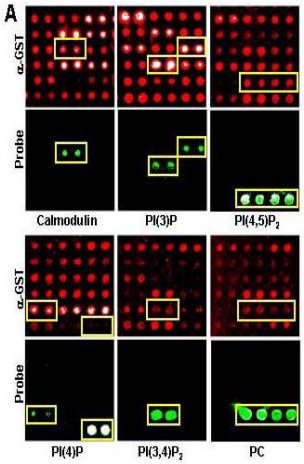

- Yeast two hybrid experiments yield information on protein protein interactions
- GAL4 Binding Domain
- GAL4 Activation Domain
- X and Y are two proteins of interest
- If X & Y interact then reporter gene is expressed

# Affinity Pull-down



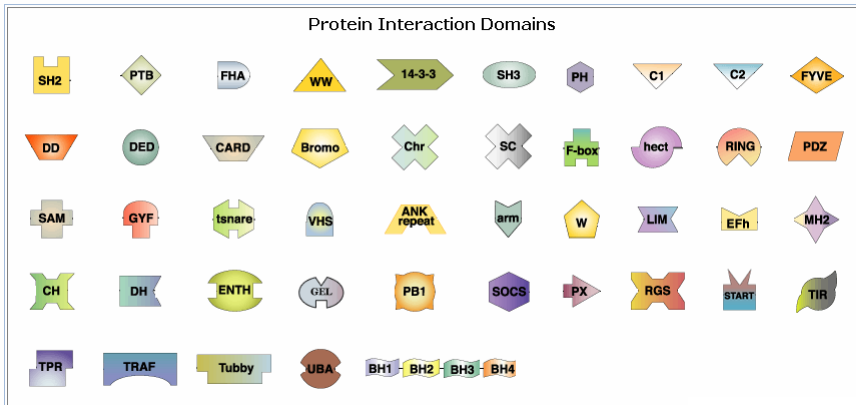
# Protein Arrays




# Protein Interaction Tools and Techniques - Computational Methods

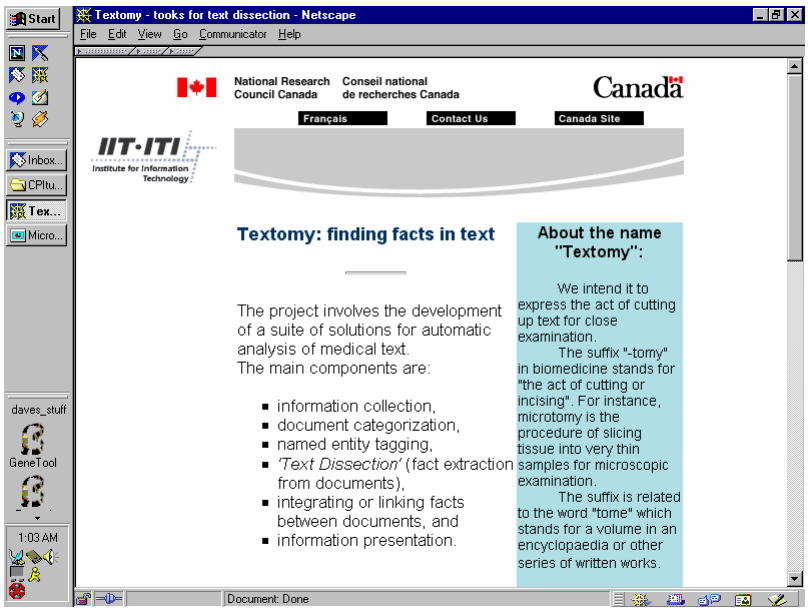
# Sequence Searching Against Known Domains




**http://www.mshri.on.ca/pawson/domains.html**

# Text Mining

- **Searching Medline or Pubmed for words or word combinations**
- **“X binds to Y”; “X interacts with Y”; “X associates with Y” etc. etc.**
- **Requires a list of known gene names or protein names for a given organism**
- **Sometimes called “Textomy”**




**http://textomy.iit.nrc.ca/**

# Pre-BIND

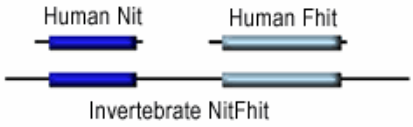
- *Donaldson et al. BMC Bioinformatics 2003 4:11*
- **Used Support Vector Machine (SVM) to scan literature for protein interactions**
- **Precision, accuracy and recall of 92% for correctly classifying PI abstracts**
- **Estimated to capture 60% of all abstracted protein interactions for a given organism**

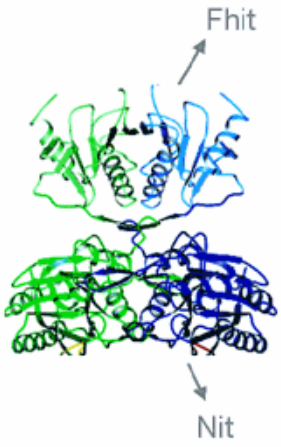
# Rosetta Stone Method

Monomeric proteins that are fused in other organisms tend to be functionally related and physically interacting.

For example, using the Rosetta Stone™ method, it was found that human Nit and Fhit proteins are:

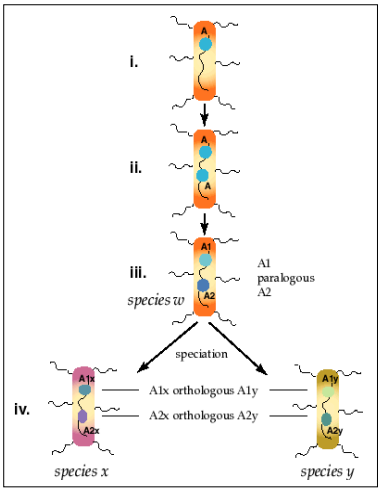
- fused in invertebrates
- form a heterocomplex in mammals




# Interologs, Homologs, Paralogs...

- **Homolog**
  - **Common Ancestors**
  - **Common 3D Structure**
  - **Common Active Sites**
- **Ortholog**
  - **Derived from Speciation**
- **Paralog**
  - **Derived from Duplication**
- **Interolog**
  - **Protein Protein Interaction**



## A Flood of Data

- High throughput techniques are leading to more and more data on protein interactions
- Very high level of false positives – need tools to sort and rationalize
- This is where bioinformatics can play a key role
- Some suggest that this is the "future" for bioinformatics

## Interaction Databases

- BIND
  - http://www.bind.ca/
- DIP
  - http://dip.doe-mbi.ucla.edu/
- MINT
  - http://160.80.34.4/mint/
- IntAct
  - http://www.ebi.ac.uk/intact/index.jsp

*More Protein Interaction Databases*
*http://www.hgmp.mrc.ac.uk/GenomeWeb/prot-interaction.html*

## The BIND Database

- BIND - Biomolecular Interaction Network Database
- Designed to capture almost all interactions between biomolecules (large and small)
- Largest database of its kind -- 135,000 interactions recorded to date

## BIND Can Encode...

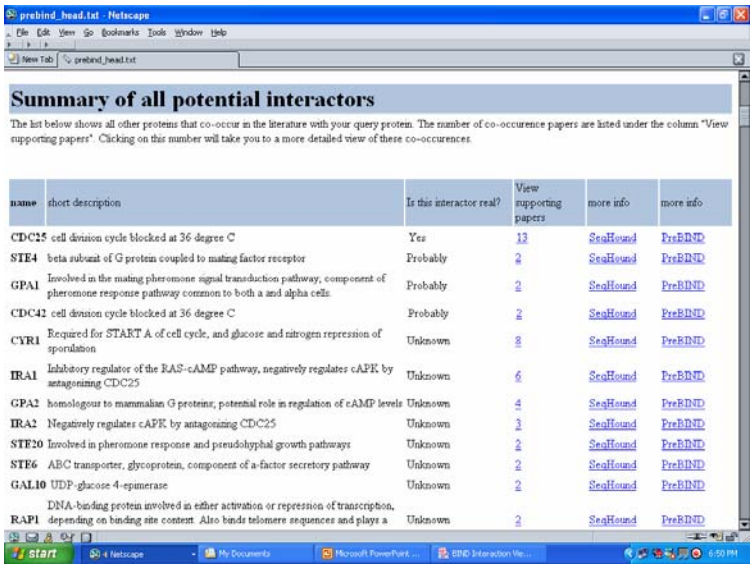
- Simple binary interactions
- Enzymes, substrates and conformational changes
- Restriction enzymes
- Limited proteolysis
- Phosphorylation (reversible)
- Glycosylation
- Intron splicing
- Transcriptional factors

# BIND


# BIND Queries

- **Users may search PreBIND by**
  - **Protein name, organism, protein accession # or PubMed ID**
- **Users may search BIND by**
  - **Accession or GI #, GO ID, PDB ID, PubMed ID, taxonomy, author, journal, Entrez GeneID, or more than 20 different database identifier tags**
  - **Sequence (via BINDBlast)**

# PreBIND Query (Ras1 & Yeast)



prebind_head.txt - Netscape

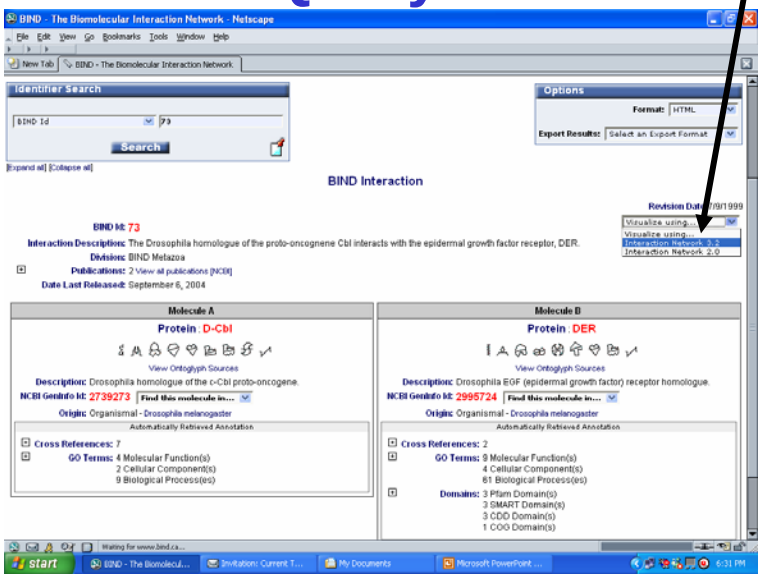
**Summary of all potential interactors**

The list below shows all other proteins that co-occur in the literature with your query protein. The number of co-occurence papers are listed under the column "View supporting papers". Clicking on this number will take you to a more detailed view of these co-occurences.

| name | short description | Is this interactor real? | View supporting papers | more info | more info |
|---|---|---|---|---|---|
| CDC25 | cell division cycle blocked at 36 degree C | Yes | 13 | SeqHound | PreBIND |
| STE4 | beta subunit of G protein coupled to mating factor receptor | Probably | 2 | SeqHound | PreBIND |
| GPA1 | Involved in the mating pheromone signal transduction pathway; component of pheromone response pathway common to both a and alpha cells. | Probably | 2 | SeqHound | PreBIND |
| CDC42 | cell division cycle blocked at 36 degree C | Probably | 2 | SeqHound | PreBIND |
| CYR1 | Required for START A of cell cycle, and glucose and nitrogen repression of sporulation | Unknown | 8 | SeqHound | PreBIND |
| IRA1 | Inhibitory regulator of the RAS-cAMP pathway, negatively regulates cAPK by antagonizing CDC25 | Unknown | 6 | SeqHound | PreBIND |
| GPA2 | homologous to mammalian G proteins; potential role in regulation of cAMP levels | Unknown | 4 | SeqHound | PreBIND |
| IRA2 | Negatively regulates cAPK by antagonizing CDC25 | Unknown | 3 | SeqHound | PreBIND |
| STE20 | Involved in pheromone response and pseudohyphal growth pathways | Unknown | 2 | SeqHound | PreBIND |
| STE6 | ABC transporter, glycoprotein, component of a-factor secretory pathway | Unknown | 2 | SeqHound | PreBIND |
| GAL10 | UDP-glucose 4-epimerase | Unknown | 2 | SeqHound | PreBIND |
| RAP1 | DNA-binding protein involved in either activation or repression of transcription, depending on binding site context. Also binds telomere sequences and plays a | Unknown | 2 | SeqHound | PreBIND |

# BIND Query Result

click



BIND - The Biomolecular Interaction Network - Netscape

Identifier Search — BIND Id: 73 — Search

Options — Format: HTML — Export Results: Select an Export Format

BIND Interaction

BIND Id: 73

Interaction Description: The Drosophila homologue of the proto-oncogene Cbl interacts with the epidermal growth factor receptor, DER.

Division: BIND Metazoa

Publications: 2 View all publications [NCBI]

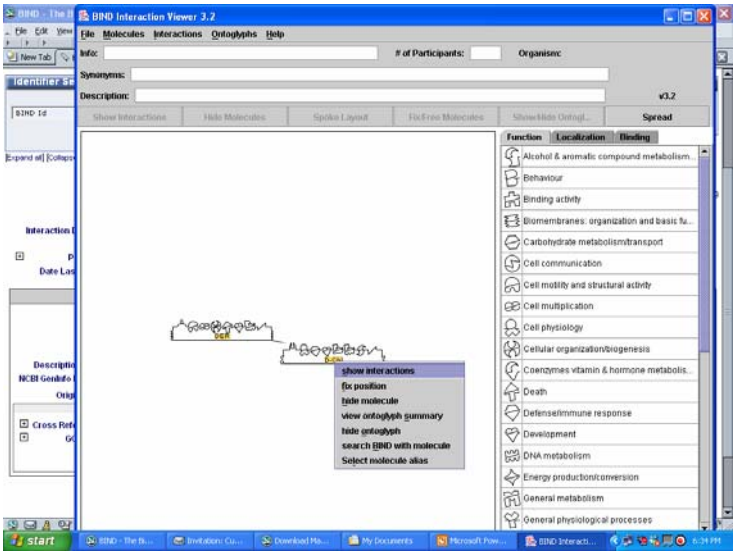
Date Last Released: September 6, 2004

Revision Date: 9/1/1999

Visualize using... Interaction Network 2.2 Interaction Network 2.0

| Molecule A | Molecule B |
|---|---|
| Protein: D-Cbl | Protein: DER |
| View Ontoglyph Sources | View Ontoglyph Sources |
| Description: Drosophila homologue of the c-Cbl proto-oncogene. | Description: Drosophila EGF (epidermal growth factor) receptor homologue. |
| NCBI GenInfo Id: 2739273 Find this molecule in... | NCBI GenInfo Id: 2995724 Find this molecule in... |
| Origin: Organismal - Drosophila melanogaster | Origin: Organismal - Drosophila melanogaster |
| Automatically Retrieved Annotation | Automatically Retrieved Annotation |
| Cross References: 7 | Cross References: 2 |
| GO Terms: 4 Molecular Function(s) 2 Cellular Component(s) 9 Biological Process(es) | GO Terms: 9 Molecular Function(s) 4 Cellular Component(s) 61 Biological Process(es) |
| | Domains: 3 Pfam Domain(s) 3 SMART Domain(s) 3 CDD Domain(s) 1 COG Domain(s) |

# BIND Details




# Ontoglyphs

| Function | Localization | Binding |
|---|---|---|
| Alcohol & aromatic compound metabolism | Actin cytoskeleton | Antigen binding |
| Behaviour | Axon or dendrite | ATP binding |
| Binding activity | Biological membrane | Coenzyme binding |
| Biomembranes: organization and basic fu... | Cell periphery | Calmodulin binding |
| Carbohydrate metabolism/transport | Cytoplasm | Carbohydrate binding |
| Cell communication | Cytoplasmic vesicle | Cytokine binding |
| Cell motility and structural activity | Endoplasmic reticulum | Cytoskeletal protein binding |
| Cell multiplication | Endosome | DNA binding |
| Cell physiology | Extracellular /cell surface | Double stranded DNA binding |
| Cellular organization/biogenesis | Flagellum /cilium | Guanyl nucleotide binding |
| Coenzymes vitamin & hormone metabolis... | Golgi apparatus | Lipid binding |
| Death | Lipid particle | Metal ion binding |
| Defense/immune response | Microtubule cytoskeleton | mRNA binding |
| Development | Mitochondrion | Nucleic acid binding |
| DNA metabolism | Nuclear periphery | Nucleotide binding |
| Energy production/conversion | Nucleolus | Oxygen binding |
| General metabolism | Nucleus | Protein binding |
| General physiological processes | Peroxisome | Adenyl nucleotide binding |

## Summary

- First application of bioinformatics was probably in protein structure (the PDB)
- Structural biology continues to be a rich source for bioinformatics innovation and bioinformaticians
- Next “big” step in bioinformatics is to go from the “parts list” to figuring out how to put it all together