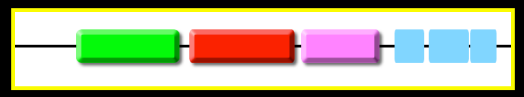
Protein Bioinformatics

Building Useful Relationships
Between Multiple Protein
Sequences and Structures

MSRKGPRAEVCADCSA
PDPGWASISRGVLVCDE
CCSVHRLGRHISIVKHLR
HSAWPPTLLQMVHTLA
SNGANSIWEHSLLDPA
QVQSGRRKAN



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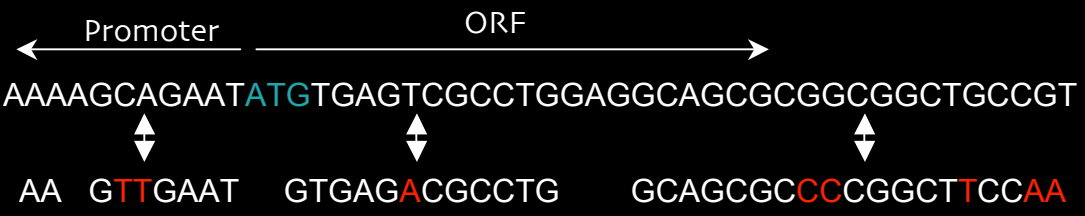
Overview

- Introduction
- Sequence Comparisons
  - Pairwise Letter by Letter vs. Word by Word
  - Multiple Sequence Alignments (MSA)
- Sequence Domains
  - Phylogenetic Trees and Multiple Sequence Alignments
  - Blocks, Patterns, and Profiles (Motifs)
- Structural Comparisons
  - Analyzing Protein Structures
  - Structure Prediction

Translated Transition

- DNA Bioinformatics
  - Sequence Comparison, Gene & Promoter ID



- Protein Bioinformatics
  - Sequence, Function, Structure ID & Comparison

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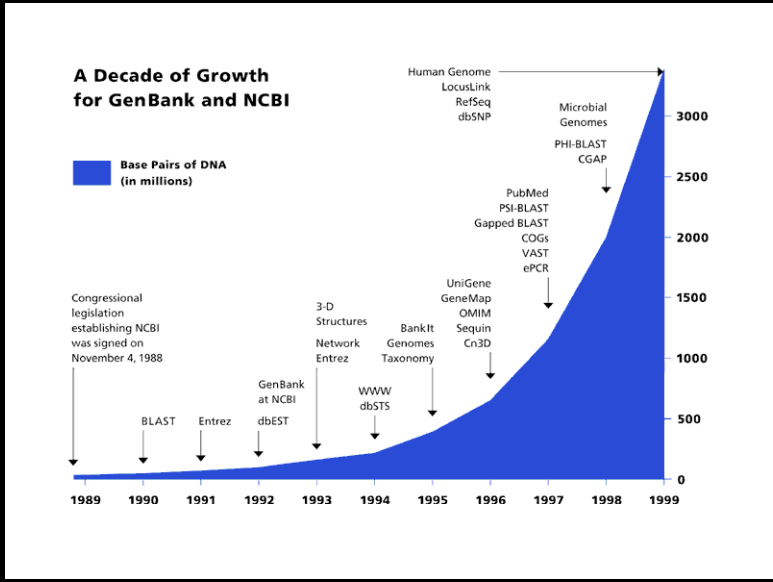
Bioinformatics Databases

Sequence Database Growth

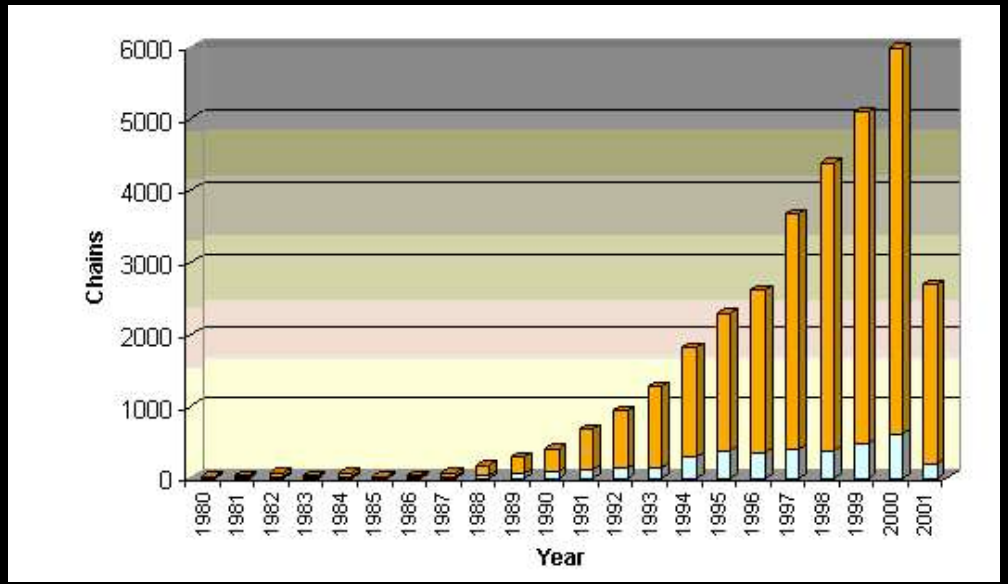
Sequences / NT ( )



(Cooper NCBI)

Protein Structure Database Expansion

Sequences / AA ( )



(PDB)

Bioinformatics Resources

aBi
Atelier BioInformatique
Université Aix-Marseille I

On line analysis tools

er for Biotechnology Information
f Medicine National Institutes of Health
PubMed Entrez BLAST OMIM Books TaxBrowser Structure
Search Nucleotide for Go

e! project Ensembl
The Wellcome Trust Sanger Institute EBI

SWISS-MODEL

ne Database

Pfam :: HMM Search
Analyze a query sequence using the Pfam HMM d

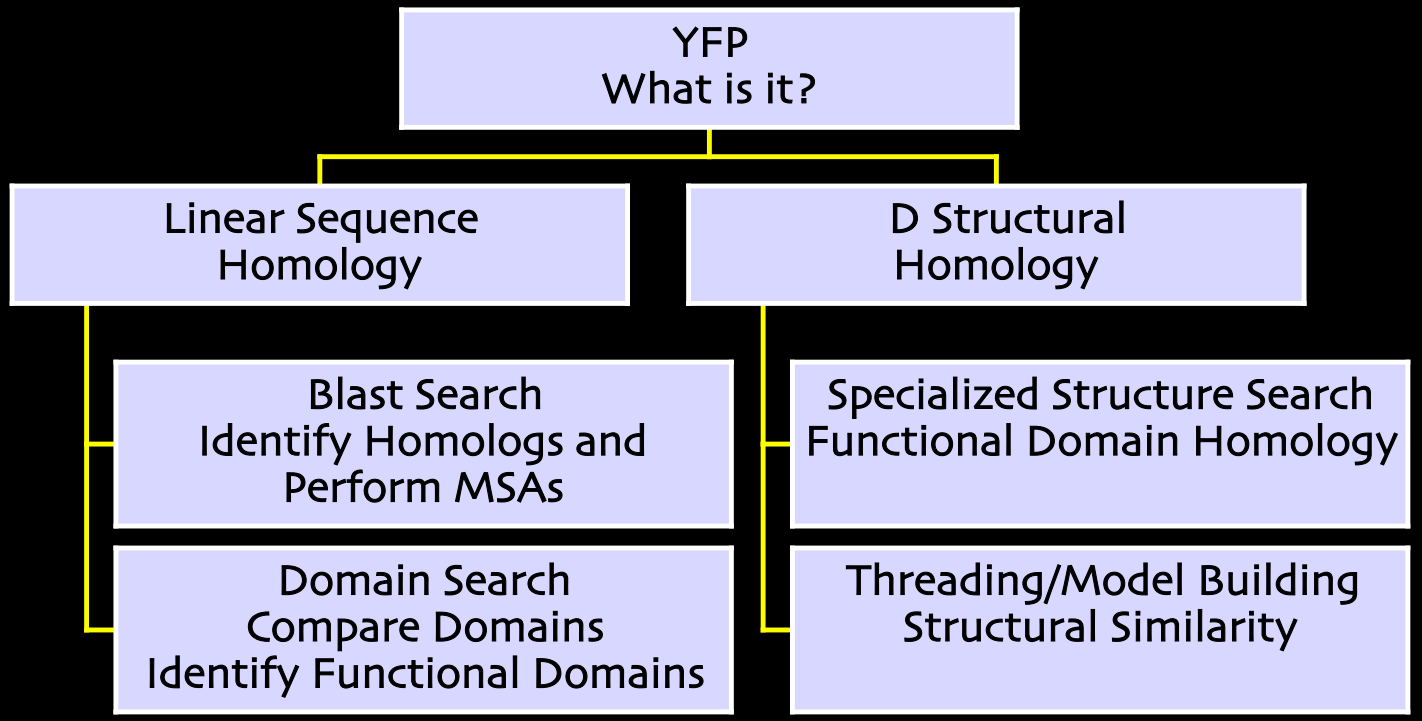
The Protein Domain Datab
ProDor

SWISS-PROT
Protein knowledgebase
TrEMBL
SIB swissprot

SS-PROT

Pole Bio-Informatique Lyonnais
Network Protein Sequence @nalysis
NPS@ is the IBCP contribution to PBIL in Lyon, France

Bioinformatics Approaches

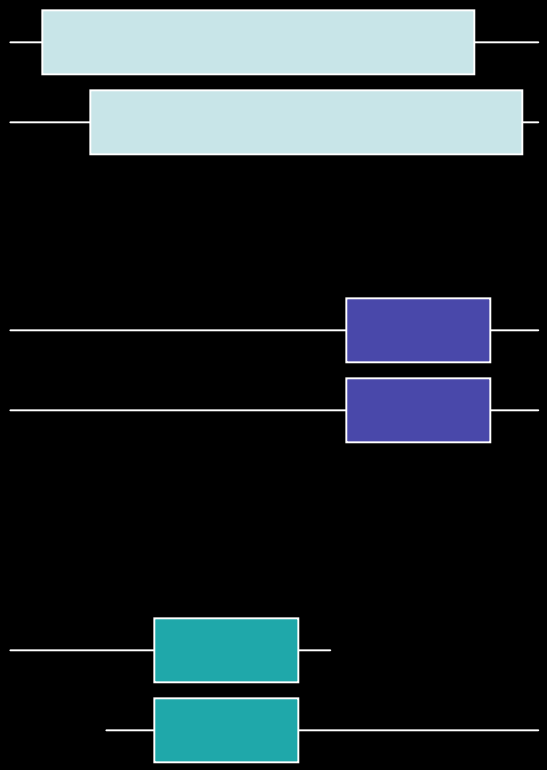


Overview

- Introduction
- Sequence Comparisons
  - Letter by Letter vs. Word by Word
  - Global Multiple Sequence Comparisons
- Local Sequence Domains
- Structural Domains

Protein Modules

- Proteins are derived from a limited number of basic building blocks (Domains)
- Evolution has shuffled these modules giving rise to a diverse repertoire of protein sequences
- As a result, proteins can share a global or local relationship



(Higgins)

Residue by Residue Comparisons

A: V R W A H S G C T R T

B: V R G A H K D R T

GUUAGAUGGGCUCAUAGUGGCUGCACUCGGACC
GUUAGAGGUGCUCATAAAGAUCGGACC

I. V R W A H S G C T R T

V R G A H – – K D R T

GUU AGA UGG GCU CAU AGU GGC UGC ACU CGG ACC
GUU AGA GGU GCU CAU AAA GAU CGG ACC

II. V R W A H S G C T R T

V R G A H – K D – R T

III. V R W A H S G C T R T

V R G A H – K – D R T

Word by Word Comparisons

Query: **GTQITVEDLFYNIATRRKALKN**

GTQ
Word Size = 3
TQI
QIT
ITV -> **LTV,MTV,ISV,LSV,MSV**
TVE **IAV,LAV,MAV,ITL,etc.**
VED
EDL
DLF

Adjustable

2 or 3 for protein (3 default)

> 7 for blastn searches (11 default)

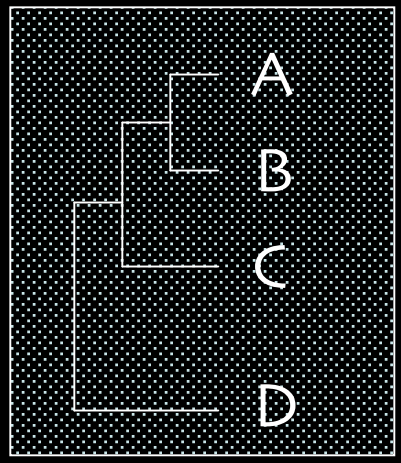
Neighborhood Words

Make table for both query and database

(Cooper NCBI)

Multiple Sequence Comparisons

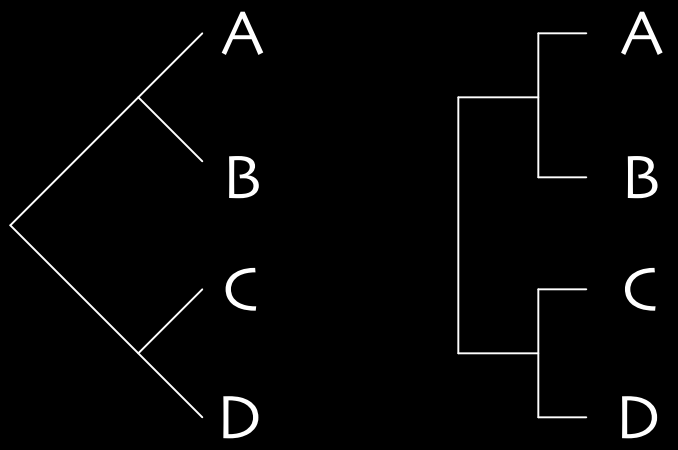
- Phylogenetic Trees
  - Graphs representing the evolutionary history of a gene
  - Relationship of one sequence to other sequences
  - Dissect the appearance order of insertions, deletions, and mutations
- Multiple Sequence Alignments
  - Place residues in columns that are derived from a common ancestral residue



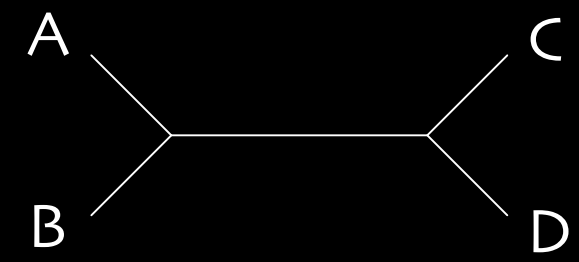

```
A:V W A H S C R
B:V G A H - K R
C:V G A H S K R
D:V G A H - C R
```

Phylogenetic Trees

Rooted



Unrooted



Branches intersect at Nodes

Predict function, observe epidemiology, analyzing changes in viral strains

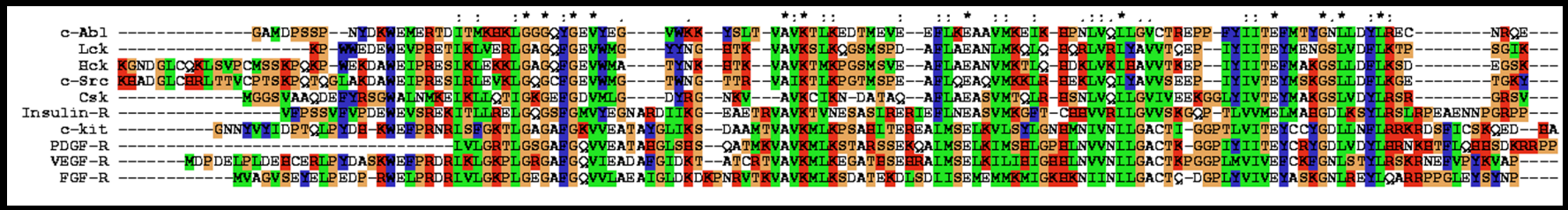
Tree Building

- Building and Drawing Trees

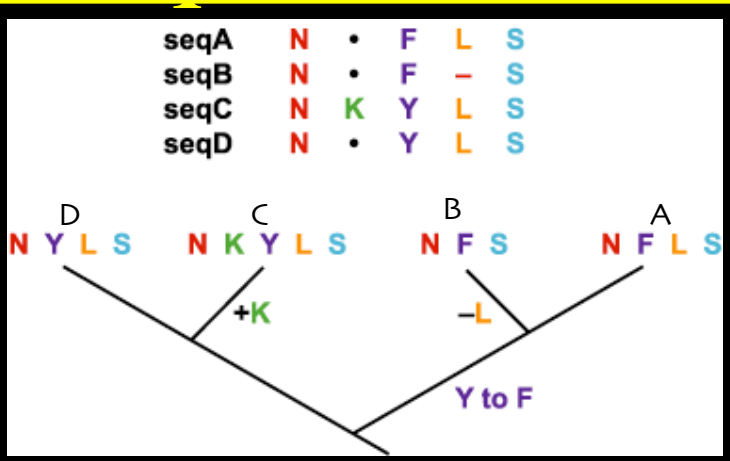
  http://bioweb.pasteur.fr/seqanal/phylogeny/phylip-uk.html

Multiple Sequence Alignments

- Global
  - Search for alignments, matching over entire sequences
- Local
  - Examine regions of sequence for conserved segments
- Matches, Mismatches, Gaps



Multiple Sequence Comparisons



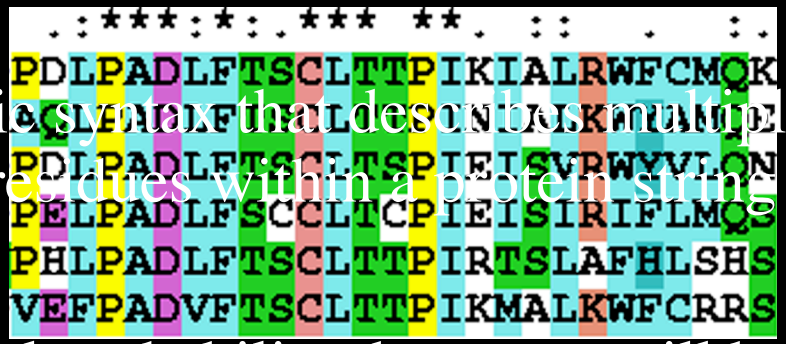
- MSCs Can Reveal Sequence Patterns
  - Demonstration of homology between >2 sequences
  - Identification of functionally important sites & structure prediction
- ClustalX
  - Web-based http://pir.georgetown.edu/pirwww/search/multaln.html
  - Stand-alone
- MSAs Are Related To Trees

Overview

- Introduction
- Sequence Comparisons
- Local Sequence Domains
- Structural Domains

Local Alignments: Domains of Conserved Sequence

- Blocks
  - Represent a conserved region within a MSA that contains matches & mismatches but no gaps
  - Serve as anchors to assist in aligning sequences
  - http://blocks.fhcrc.org/
- Patterns
  - Deterministic syntax that describes multiple combinations of possible residues within a protein string
- Profiles
  - Mathematical probability that an aa will be located at a given position



Pattern Matching

- Find patterns like aa1 xx aa2 xxxx aa3
  - Definition of a non-contiguous motif

```
C Y D     C A F T L R Q S A V M H K H A R E H
C A T Y   C R T A I D T V K N S L K H H S A H
C W D G G C G I S V E R M D T V H K H D T V H
C Y C     C S D H M K K D A V E R M H K K D H
C N M F   C M P I F R Q N S L A R E H E R M H
C L N N T C T A F W R Q K K D D T V H N S L H
```

C x(2,4) C x(3) [LIVMFW] x(8) H x(3,5) H

Define/Search A Motif http://us.expasy.org/tools/scanprosite/

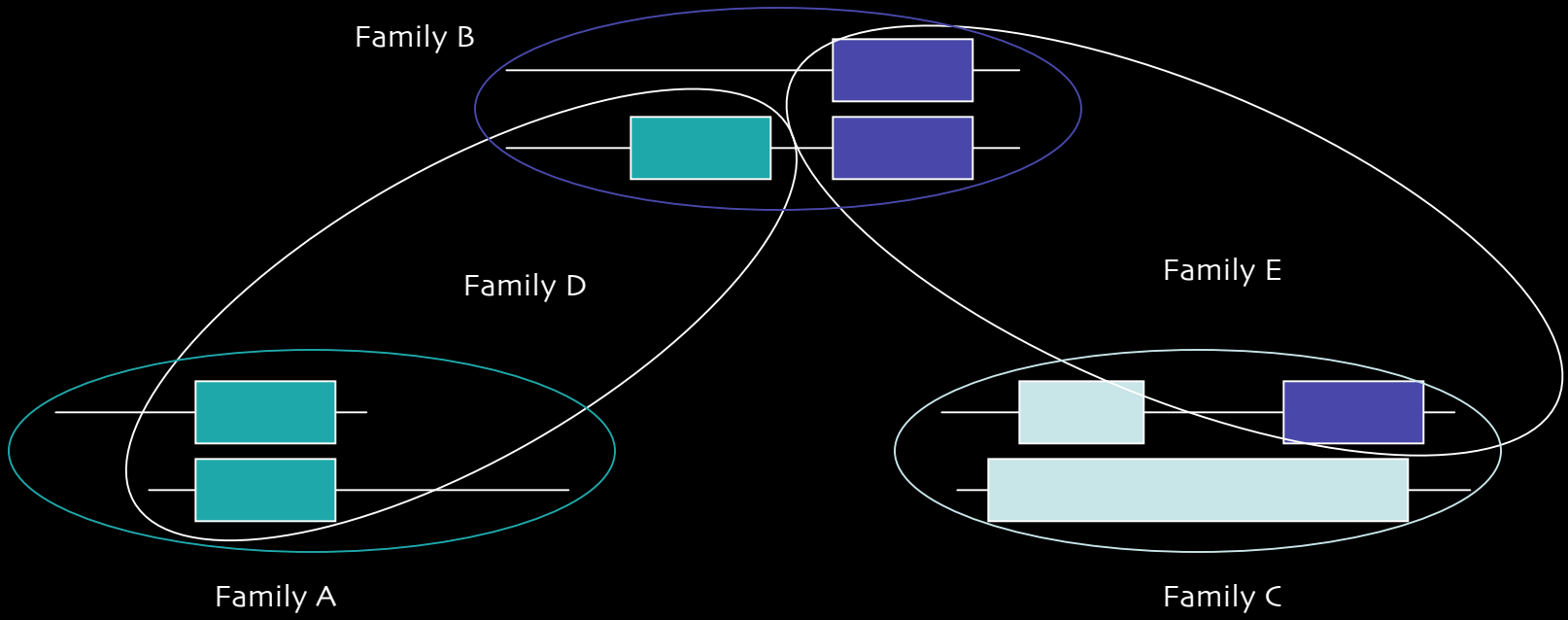
Profile Searching

- PSSM - Position Specific Scoring Matrix
  - –Columns of weights for every aa corresponding to each column of a MSA

http://www.ncbi.nlm.nih.gov/BLAST

CON	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
I	8	-2	5	4	5	5	-4	24	0	15	13	1	1	1	-7	2	22	21	-18	-6
T	13	-5	24	18	-18	19	7	1	7	E	-4	14	11	10	-1	9	29	3	-28	-14
L	5	-5	3	4	13	4	2	8	-4	14	12	8	-5	0	-10	0	10	10	-1	5
S	17	17	13	10	-12	29	-5	-5	6	-14	-9	12	10	0	-2	34	19	1	-8	-15

Protein Families



- Protein Family - a group of proteins that share a common function and/or structure, that are potentially derived from a common ancestor (set of homologous proteins)

Family Databases Resources

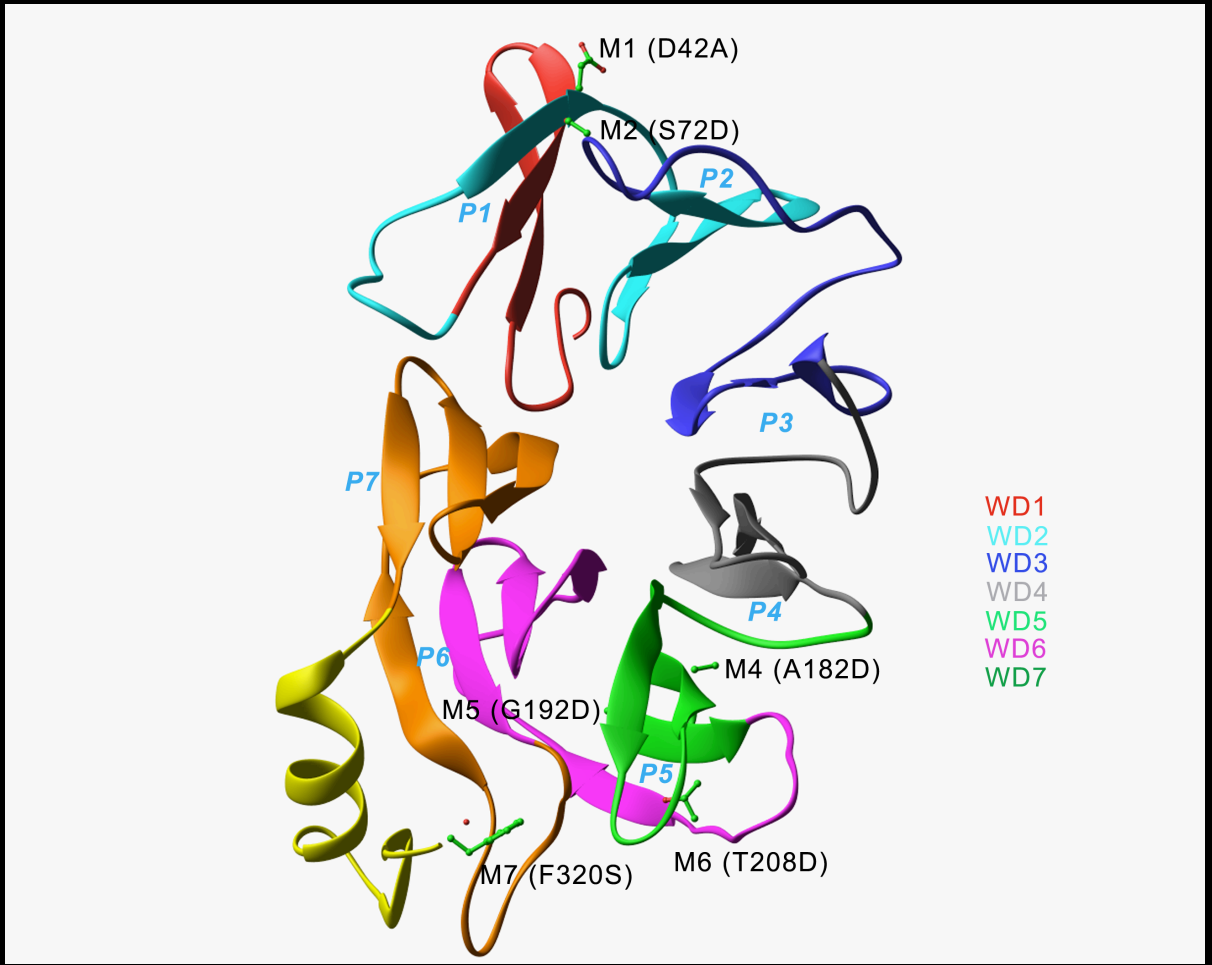
- Curated Databases
  - Proteins are placed into families with which they share a specific sequence pattern
  - Pfam http://pfam.wustl.edu/hmmsearch.shtml/
- Clustering Databases
  - Sequence similarity-based without the prior knowledge of a specific patterns by searching a database against itself
  - ProDom http://prodes.toulouse.inra.fr/prodom/doc/prodom.html
- Derived Databases
  - Pool other databases into one central resource
  - Blocks - Search and Make http://blocks.fhcrc.org/blocks/

Overview

- Introduction
- Sequence Comparisons
- Local Sequence Domains
- Structural Domains
  - Structural Comparisons (Alignment, Substitution Modeling, Domain Identification, Residue Mapping)
  - Structure Prediction

Protein Structure Classification

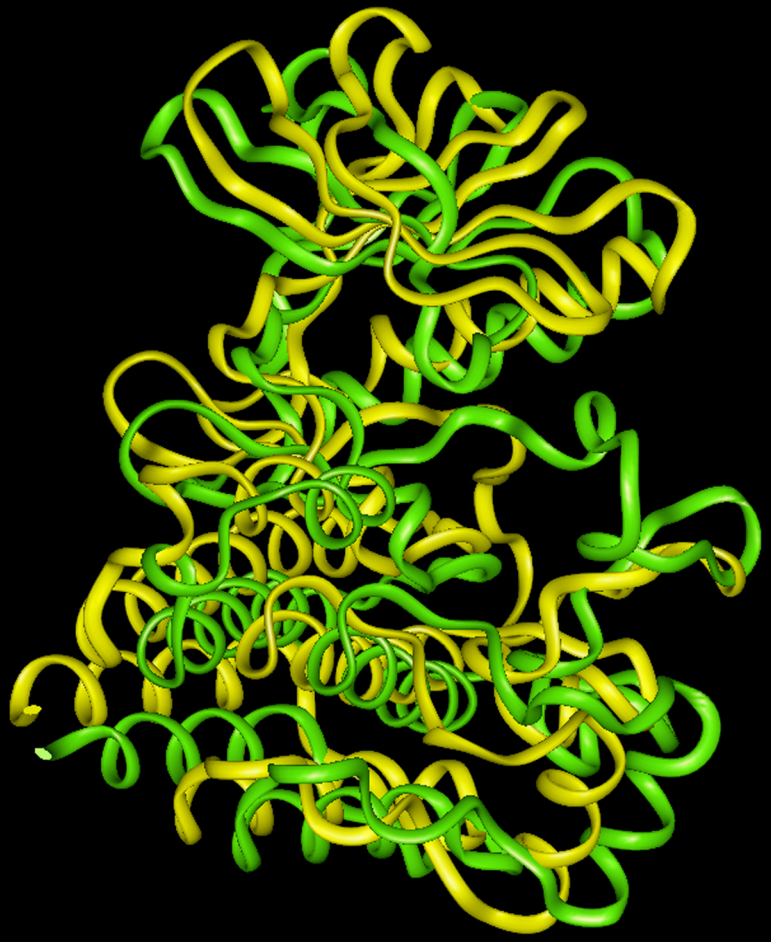
- Proteins can adopt only a limited number of possible 3D conformations
- Protein Structure Classes
- Completely different sequences can fold into similar shapes



Structure Family Databases

- SCOP: Structural Classification Of Proteins
  - Hierarchical levels to reflect evolutionary and structural relationships
  - http://scop.mrc-lmb.cam.ac.uk/scop
- CATH: Classification by Class, Architecture, Topology, and Homology
  - http://www.biochem.ucl.ac.uk/bsm/cath/
- FSSP: Fold classification based on Structure-Structure alignment of Proteins
  - DALI pair-wise alignments
  - http://www2.embl-ebi.ac.uk/dali/fssp/fssp.html
- SARF: Spatial Arrangement of Backbone Fragments
  - http://123d.ncifcrf.gov/

Structural Alignments



Superimpose Structures

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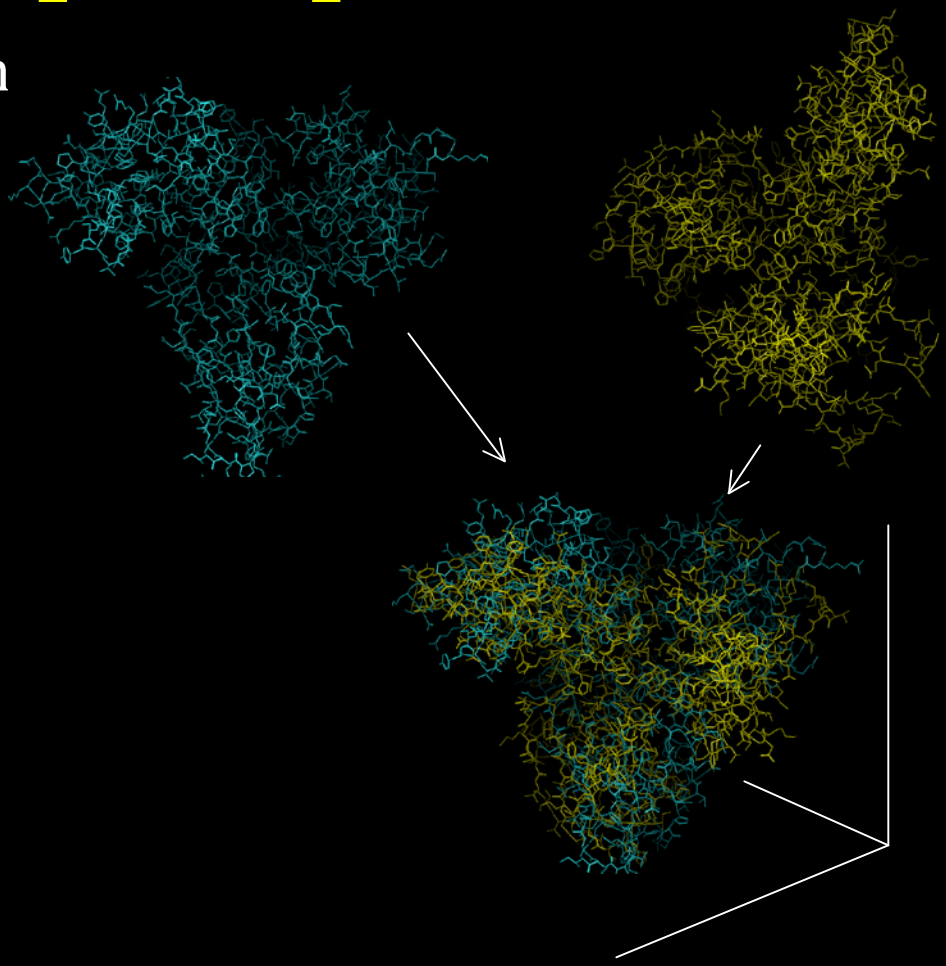
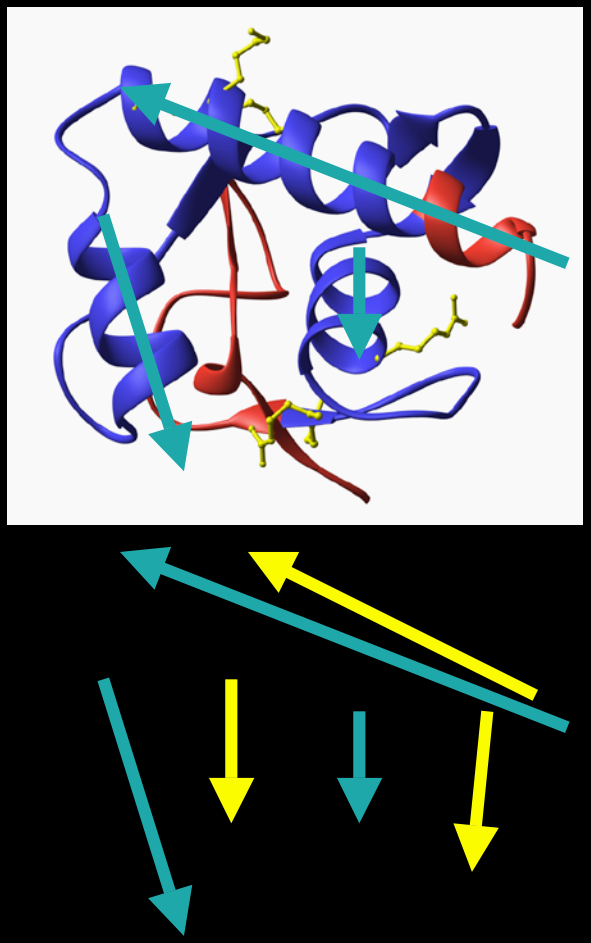
ligand

Structure Superimposition

- Sequence alignment based on LINEAR sequence similarity
- Structure alignment forms relationships in 3D space
  - similarity can be redundant for multiple sequences
- Alignment
  - Translate center of mass to a common origin
  - Rotate to find a suitable superposition
- Considerations
  - What to align and compare?



VAST and SARF



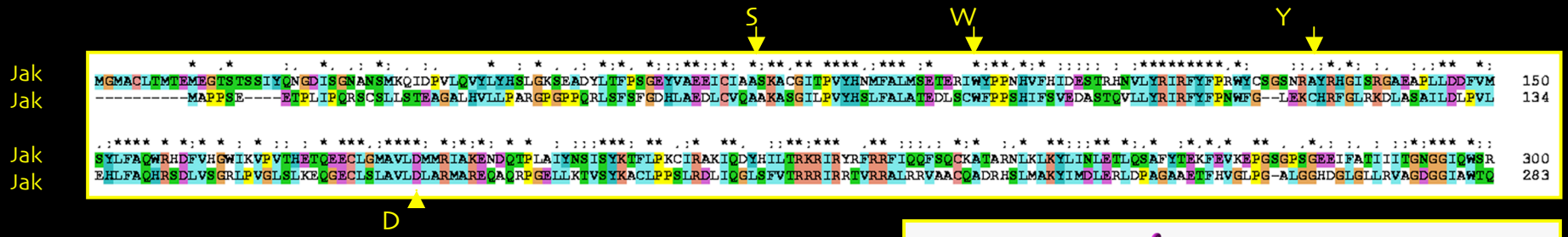
- Implement rapid methods to assign secondary structure
- VAST

http://www.ncbi.nlm.nih.gov:80/Structure/VAST/vastsearch.html

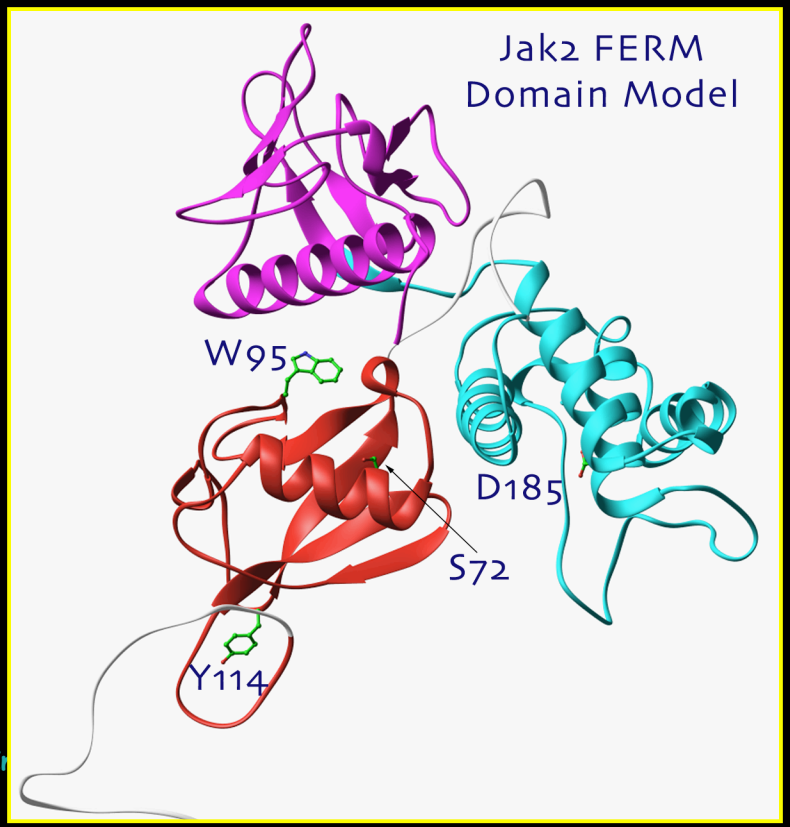
- SARF

http://123d.ncifcrf.gov/

Substitution Modeling



- Mapping Variants
- Construct Design
- Ligand Associations



(L Huang & R Latek)

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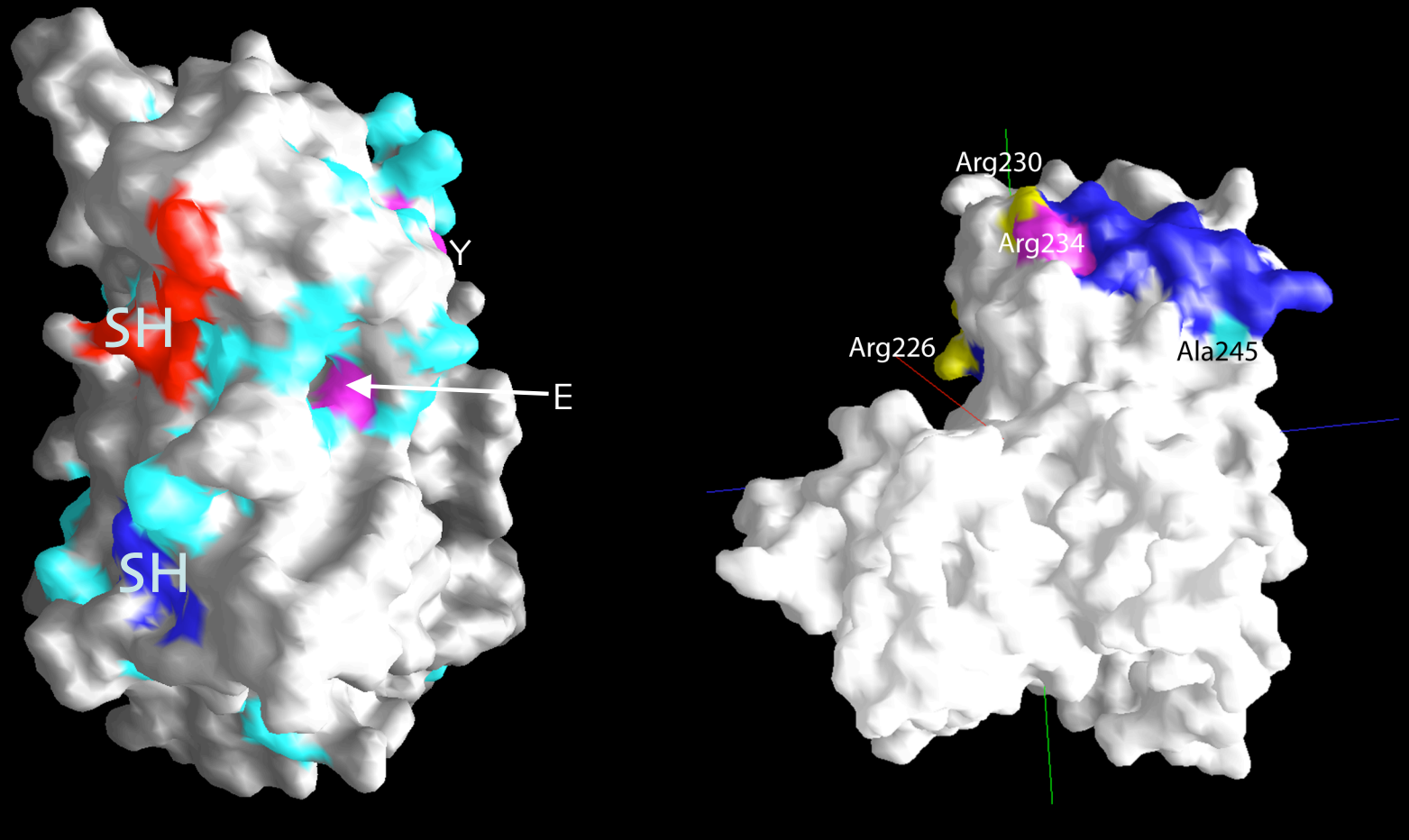
Surface Mapping



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Structure Prediction

- Secondary Structure Prediction
- Specialized Structures
- Tertiary Structural Modeling

Secondary Structure Prediction

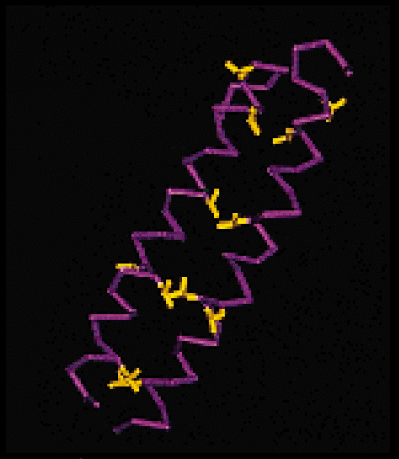
- Recognizing Potential Secondary Structure
  - 50% of a sequence is usually alpha helices and beta sheet structures
  - Helices: 3.6 residues/turn, N+4 bonding
  - Strands: extended conformation, interactions between strands, disrupted by beta bulges
  - Coils: A,G,S,T,P are predominant
  - Sequences with >45% sequence identity should have similar structures
- Databases of sequences and accompanying secondary structures

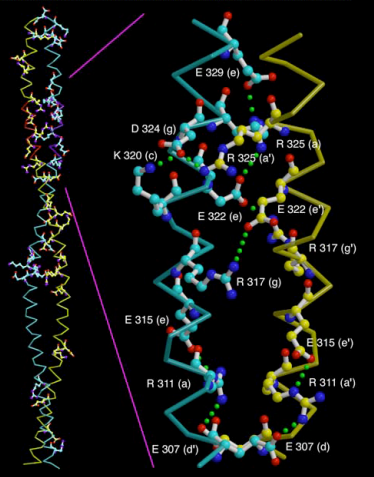
Secondary Structure Prediction Tools

- NNpredict - 65 % effective*, outputs H,E,-
  - http://www.cmpharm.ucsf.edu/~nomi/nnpredict.html
- PredictProtein - query sequence examined against SWISS-PROT to find homologous sequences
  - MSA of results given to PHD for prediction
  - 72% effective*
  - http://www.embl-heidelberg.de/predictprotein/submit_def.html
- Jpred - integrates multiple structure prediction applications and returns a consensus, 73% effective*
  - http://jura.ebi.ac.uk:8888/

Specialized Structures

- Leucine Zippers
  - □ helices held together by interactions between L residues spaced at ever 7th position
- Coiled Coils
  - 2 or three a helices coiled around each other in a left-handed supercoil
  - Multicoil http://gaiberg.wi.mit.edu/cgi-bin/multicoil.pl
- Transmembrane Regions
  - 20-30aa domains with strong hydrophobicity
  - PHDhtm, PHDtopology, TMpred (TMbase)
  - http://www.embl-heidelberg.de/predictprotein/predictprotein.html





Tertiary Structural Modeling

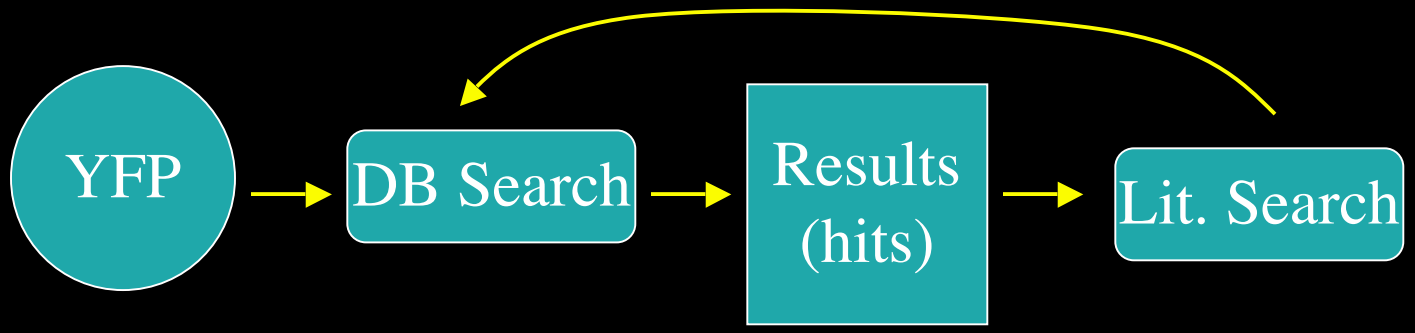
- Goal
  - Build a model to use for comparison with other structures, identify important residues/interactions, determine function
- Challenges
  - Reveal interactions that occur between residues that are distant from each other in a linear sequence
  - Slight changes in local structure can have large effects on global structure
- Methods
  - Sequence Homology - use a homologous sequence as a template
  - Threading - search for structures that have similar fold configurations without any obvious sequence similarity

Structural Modeling Tools

- Perform Automated Model Constructions
  - –SWISS-MODEL
    - •Compare sequence to ExPdb to find a homolog
    - •Define your own templates (from threading)
    - •http://www.expasy.ch/swissmod/SWISS-MODEL.html
  - –GENO3D
    - •PSI-BLAST to identify homologs possessing structures to be used as templates
    - •http://geno3d-pbil.ibcp.fr
- Threading

  123D http://123d.ncifcrf.gov/123D+.html

Post-Processing



- Literature Searches
- Do the Results Make Sense?
- Are the Results Consistent?
- Can the Results be Substantiated Biologically?

Questions?

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PDF Slides Available At:
http://staffa wi mit edu/bio/proteins pdf

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