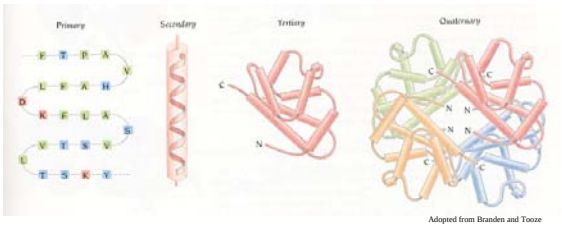
Introduction to Bioinformatics

Iosif Vaisman

Email: ivaisman@gmu.edu

Protein Structure Hierarchy



Adopted from Branden and Tooze

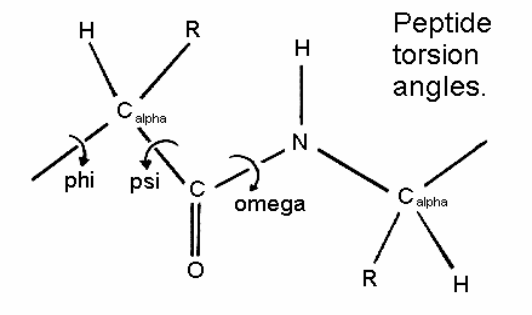
- Primary - the sequence of amino acid residues
- Secondary - ordered regions of primary sequence (helices, beta-sheets, turns)
- Tertiary - the three-dimensional fold of a protein subunit
- Quaternary - the arrangement of subunits in oligomers.

Anfinsen's Dogma

Three-dimensional structure of a protein is determined solely by its amino-acid sequence.

Native conformation of the protein is the global-minimum free energy conformation.

Levinthal paradox



3 conformations per residue is a very conservative estimate

Complexity of protein structure (Levinthal paradox)

100 residue protein
3 conformations per residue

number of distinct conformations:
$3^{100} \cong 10^{48}$

sampling time $\cong 10^{30}$ years

Complexity

P (Polynomial)
complexity class of decision problems for which execution time of a computation is no more than a polynomial function of the problem size

NP (Nondeterministic Polynomial)
complexity class of decision problems for which answers can be checked by an algorithm whose run time is polynomial in the size of the input

Protein Folding Problem

Given: sequence
Find: structure

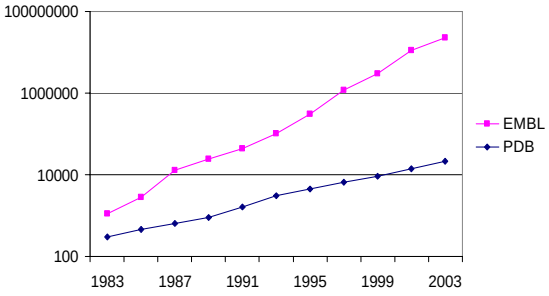
The problem is NP-complete

Protein Folding Problem

Problem for us, not for proteins.
They just fold...

(Ken Dill)

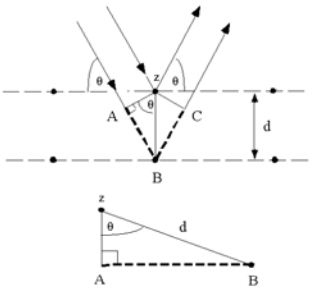
Dynamics of Database Growth



Protein Structure Determination

X-ray crystallography
NMR spectroscopy
Neutron diffraction
Electron microscopy
Atomic force microscopy

X-ray crystallography

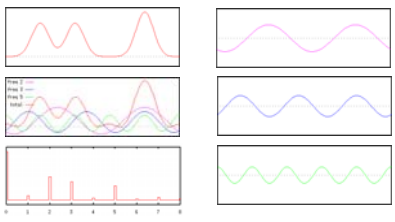


Bragg's Law

$n\lambda = 2d \sin\theta$

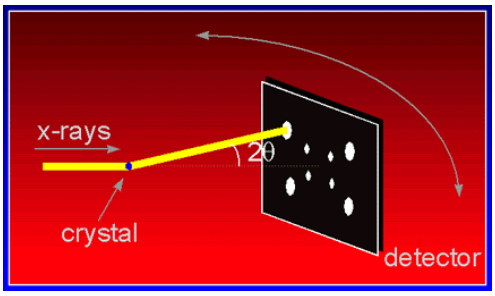
X-ray crystallography

Phase determination: MIR and MAD
(Multiple Isomorphous Replacement and Multiwavelength Anomalous Diffraction)

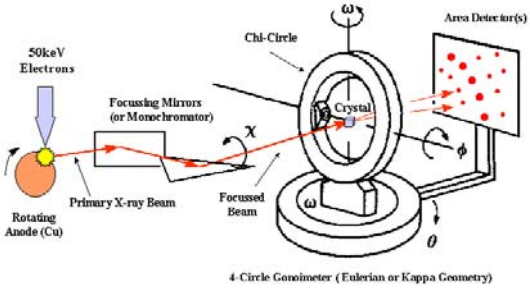


Fourier Transforms

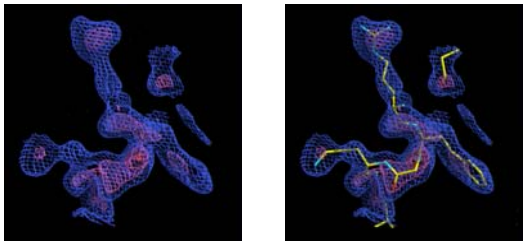
X-ray crystallography



X-ray crystallography

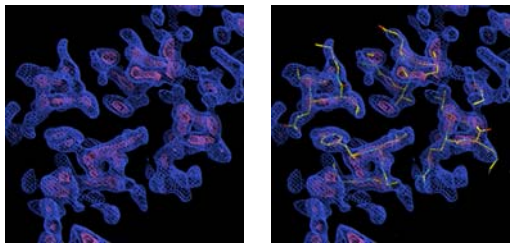


X-ray crystallography



Electron density map created from multi-wavelength data (Arg)

X-ray crystallography



Experimental electron density map and model fitting
(apoE four helix bundle)

X-ray crystallography

Confidence in structural features of proteins determined by X-ray crystallography

(These are *rough* estimates, and depend strongly on the quality of the data.)

Structural feature	Resolution				
	5 Å	3 Å	2.5 Å	2.0 Å	1.5 Å
Chain tracing	—	Fair	Good	Good	Good
Secondary structure	Helices fair	Fair	Good	Good	Good
Sidechain conformations	—	—	Fair	Good	Good
Orientation of peptide planes	—	—	Fair	Good	Good
Protein hydrogen atoms visible	—	—	—	—	Good

Structure verification and validation

Biotech Validation Suite
ERRAT
Verify3D
Procheck

Procheck programs

CLEAN - cleaning PDF file

SECSTR - assigning secondary structure

NB - identifying non-bonded interactions

ANGLEN - calculating bond lengths and bond angles

TPLOT, PPLOT, BPLOT - graphical output

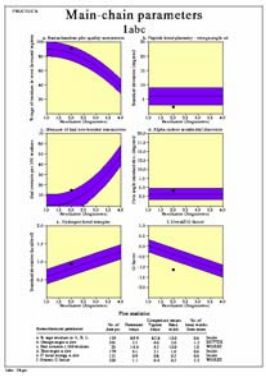
Bond lengths (Procheck)

Bond	labeling		Value	sigma
C-N	C-NH1	(except Pro)	1.329	0.014
	C-N	(Pro)	1.341	0.016
C-O	C-O		1.231	0.020
Calpha-C	CH1E-C	(except Gly)	1.525	0.021
	CH2G*-C	(Gly)	1.516	0.018
Calpha-Cbeta	CH1E-CH3E	(Ala)	1.521	0.033
	CH1E-CH1E	(Ile,Thr,Val)	1.540	0.027
	CH1E-CH2E	(the rest)	1.530	0.020
N-Calpha	NH1-CH1E	(except Gly,Pro)	1.458	0.019
	NH1-CH2G*	(Gly)	1.451	0.016
	N-CH1E	(Pro)	1.466	0.015

Bond angles (Procheck)

Angle	labeling		Value	sigma
C-N-Calpha	C-NH1-CH1E	(except Gly,Pro)	121.7	1.8
	C-NH1-CH2G*	(Gly)	120.6	1.7
	C-N-CH1E	(Pro)	122.6	5.0
Calpha-C-N	CH1E-C-NH1	(except Gly,Pro)	116.2	2.0
	CH2G*-C-NH1	(Gly)	116.4	2.1
	CH1E-C-N	(Pro)	116.9	1.5
Calpha-C-O	CH1E-C-O	(except Gly)	120.8	1.7
	CH2G*-C-O	(Gly)	120.8	2.1

Procheck output



a. Ramachandran plot quality - percentage of the protein's residues that are in the core regions of the Ramachandran plot.

b. Peptide bond planarity - standard deviation of the protein structure's omega torsion angles.

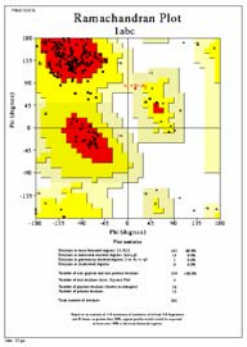
c. Bad non-bonded interactions - number of bad contacts per 100 residues.

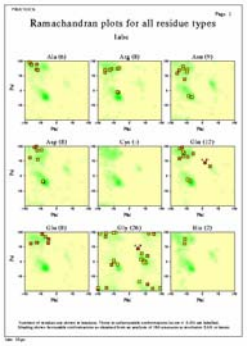
d. Cα tetrahedral distortion - standard deviation of the ζ torsion angle (Cα, N, C, and Cβ).

e. Main-chain hydrogen bond energy - standard deviation of the hydrogen bond energies for main-chain hydrogen bonds.

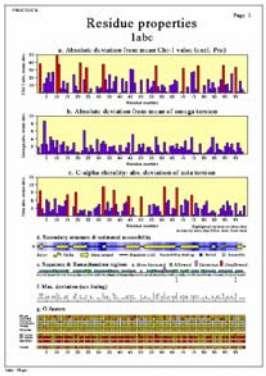
f. Overall G-factor - average of different G-factors for each residue in the structure.

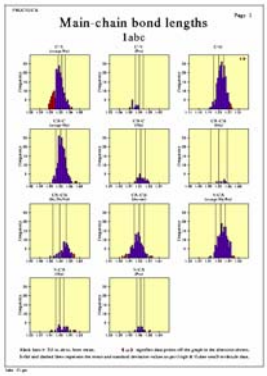
Procheck output



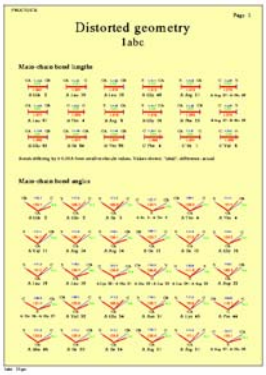


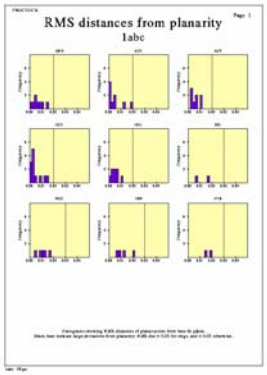
Procheck output



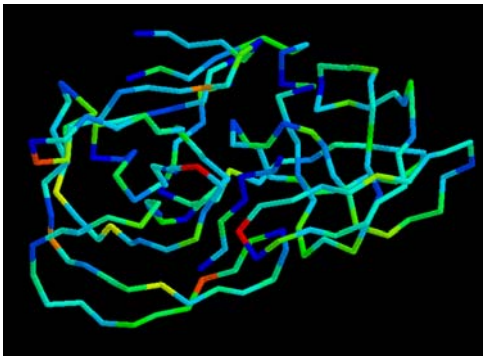


Procheck output

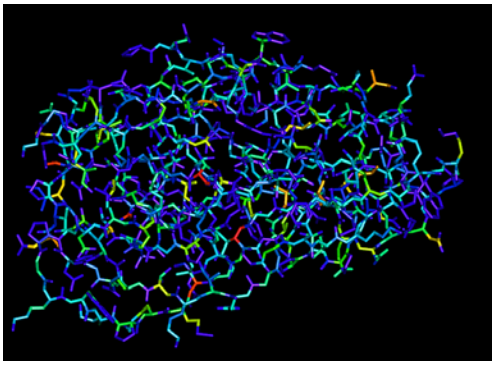




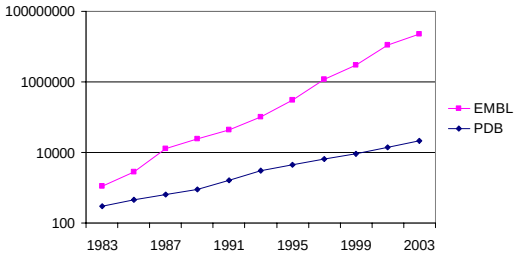
Procheck output - backbone G factors



Procheck output - all atom G factors



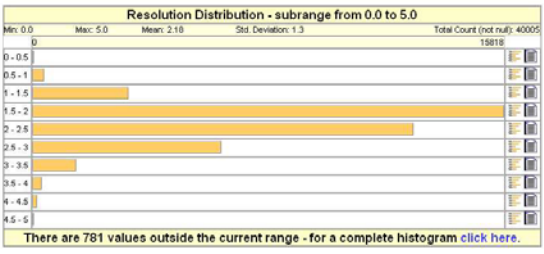
Dynamics of Database Growth



PDB Current Holdings (11/07/07)

		Molecule Type				
		Proteins	Nucleic Acids	Protein/ NA Compl	Other	**Total**
Exp. Meth.	X-ray	37254	1000	1726	24	**40004**
	NMR	5948	789	136	7	**6880**
	EM	109	11	40	0	**160**
	Other	83	4	4	2	**93**
	Total	**43394**	**1804**	**1906**	**33**	**47137**

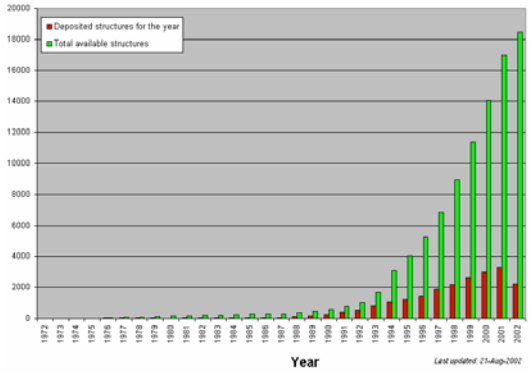
PDB Structures by Resolution



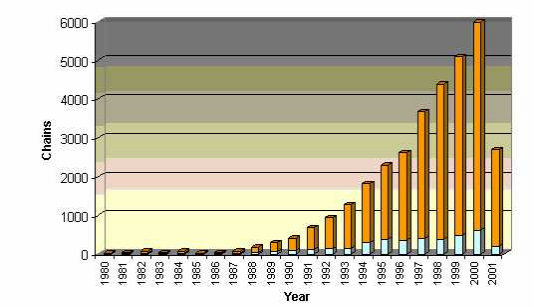
PDB Redundancy

Method	Description	# of Clusters
blast	95% identity (one chain)	18106
blast	90% identity (one chain)	17367
blast	70% identity (one chain)	15507
blast	50% identity (one chain)	13201
blast	40% identity (one chain)	11457
blast	30% identity (one chain)	9458

PDB Growth



Growth of New Folds in PDB



"new folds" (blue) and "old folds" (orange)

Growth of New Folds in PDB