

CHEM 498Q / 630Q

Molecular modelling of proteins

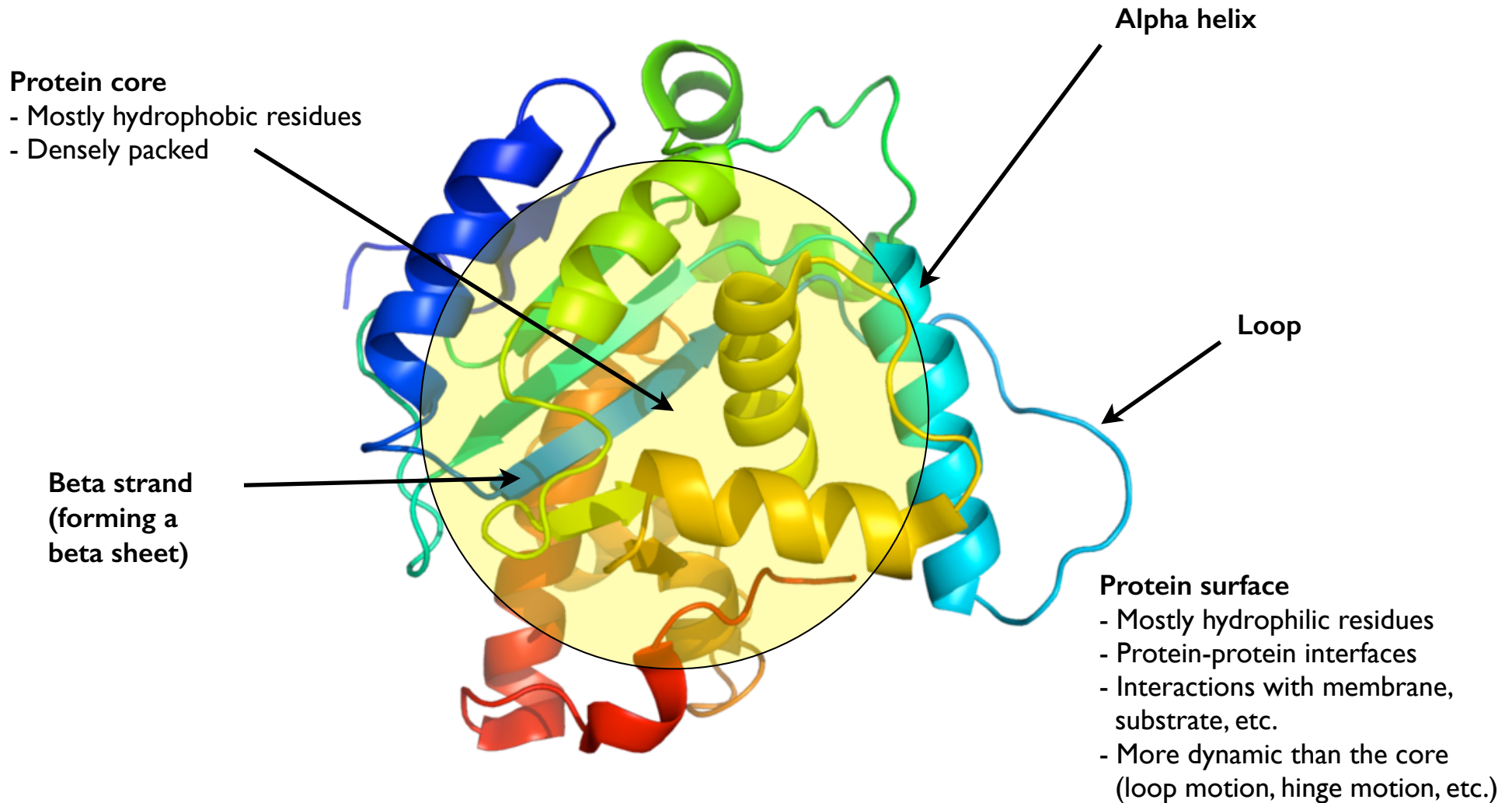
Fall 2015 Term

Instructor:

Guillaume Lamoureux

Concordia University, Montréal, Canada

Protein structure



Source: **Wikipedia**

http://upload.wikimedia.org/wikipedia/commons/e/e6/Spombe_Pop2p_protein_structure_rainbow.png

Finding the structure of a protein from its sequence

Levinthal's Paradox

(Why do proteins fold at all?)

Let's say that each amino acid of a 100-residue long protein can be in one of three conformations: extended, helical, or loop.

100 AAs
3 conformations each

If each AA adopts one of those conformations independently of its neighbors, the whole protein has 3^{100} possible conformations.

$3^{100} \approx 5 \times 10^{47}$ conformations

Let's presume that each conformation converts into any other one at the rate of 10^{14} s^{-1} (one isomerization every 0.01 ps).

$5 \times 10^{47} / (10^{14} \text{ s}^{-1}) = 5 \times 10^{33} \text{ s}$
to visit all conformations

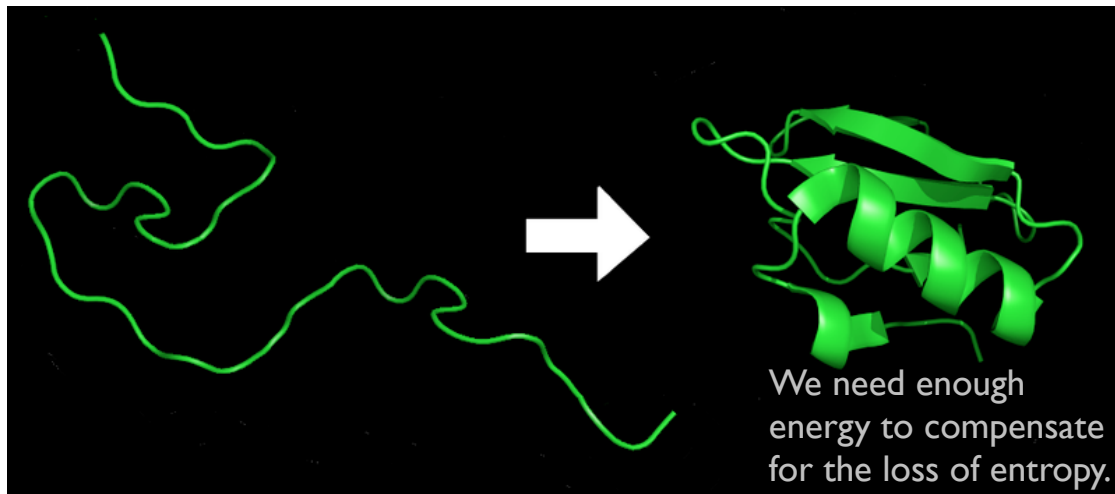
Age of the universe : $1.4 \times 10^{17} \text{ s}$

Proteins usually fold in a few milliseconds or microseconds.

Small segments of the sequence rapidly “nucleate” a specific secondary structure. Once these segments are “done”, there is not much “random exploration” left to do.

Why are protein folding?

What make proteins “collapse” in a given 3D structure?



- Hydrophobic effect
- Hydrogen bonds
- Salt bridges
- Metal ions (Ca^{2+} , Mg^{2+} , Zn^{2+} , etc.)
- etc.

Summary 3D View Sequence Annotations Seq. Similarity 3D Similarity Literature Biol. & Chem. Methods Links





A structural analysis of metal substitutions in thermolysin

DOI:10.2210/pdb1lnf/pdb


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Primary Citation


Structural analysis of zinc substitutions in the active site of thermolysin.


Holland, D.R. , Hausrath, A.C. , Juers, D. , Matthews, B.W. 

Journal: (1995) Protein Sci. 4: 1955-1965

PubMed: 8535232 

PubMedCentral: PMC2142975 

DOI: 10.1002/pro.5560041001 


Search Related Articles in PubMed 

PubMed Abstract:

Native thermolysin binds a single catalytically essential zinc ion that is tetrahedrally coordinated by three protein ligands and a water molecule. During catalysis the zinc ligation is thought to change from fourfold to fivefold. Substitution of the active-site zinc with... [Read More & Search PubMed Abstracts]

† Molecular Description

Hide

Classification: Hydrolase (metalloprotease) 

Structure Weight: 34930.77 

Molecule: THERMOLYSIN

Polymer: 1 **Type:** protein **Length:** 316

Chains: E

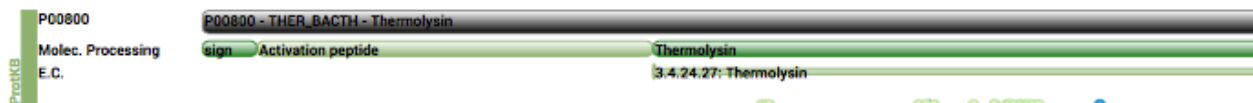
EC#: 3.4.24.27  

Organism: Bacillus thermoproteolyticus 

Gene Name: npr

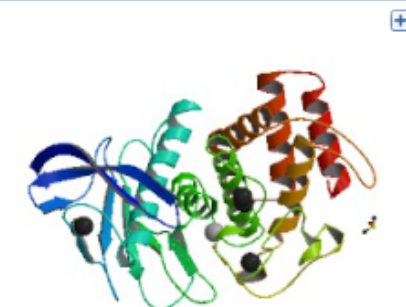
UniProtKB: Search PDB  | P00800 


 Protein Feature View



1LNF

Biological Assembly



 3D View: JSmol or PV [More Images](#)

Stoichiometry: Monomer

Biological assembly 1 assigned by authors and generated by PISA (software)


Downloadable viewers:

[Simple Viewer](#) [Protein Workshop](#)
[Kiosk Viewer](#)

† MyPDB Personal Annotations

To save personal annotations, please login to your MyPDB account.

† Deposition Summary

Authors: Holland, D.R. , Matthews,

PDB file format

(details at <http://www.wwpdb.org/documentation/file-format>)

```
HEADER      HYDROLASE (METALLOPROTEASE)                13-MAY-94    1LNF
TITLE       A STRUCTURAL ANALYSIS OF METAL SUBSTITUTIONS IN THERMOLYSIN
COMPND      MOL_ID: 1;
COMPND      2 MOLECULE: THERMOLYSIN;
COMPND      3 CHAIN: E;
COMPND      4 EC: 3.4.24.27;
COMPND      5 ENGINEERED: YES
SOURCE      MOL_ID: 1;
SOURCE      2 ORGANISM_SCIENTIFIC: BACILLUS THERMOPROTEOLYTICUS;
SOURCE      3 ORGANISM_TAXID: 1427
KEYWDS      HYDROLASE (METALLOPROTEASE)
EXPDTA      X-RAY DIFFRACTION
AUTHOR      D.R.HOLLAND,B.W.MATTHEWS
REVDAT      4    25-AUG-09 1LNF    1          SOURCE
REVDAT      3    14-JUL-09 1LNF    1          REMARK
REVDAT      2    24-FEB-09 1LNF    1          VERSN
REVDAT      1    08-MAY-95 1LNF    0
JRNL        AUTH    D.R.HOLLAND,A.C.HAUSRATH,D.JUERS,B.W.MATTHEWS
JRNL        TITL    STRUCTURAL ANALYSIS OF ZINC SUBSTITUTIONS IN THE
JRNL        TITL 2  ACTIVE SITE OF THERMOLYSIN.
JRNL        REF     PROTEIN SCI.                      V.    4    1955 1995
JRNL        REFN                      ISSN 0961-8368
JRNL        PMID    8535232
REMARK      1
REMARK      1 REFERENCE 1
REMARK      1 AUTH    D.R.HOLLAND,D.E.TRONRUD,H.W.PLEY,K.M.FLAHERTY,
REMARK      1 AUTH 2  W.STARK,J.N.JANSONIUS,D.B.MCKAY,B.W.MATTHEWS
REMARK      1 TITL    STRUCTURAL COMPARISON SUGGESTS THAT THERMOLYSIN AND
```

PDB file format

(details at <http://www.wwpdb.org/documentation/file-format>)

atom name ("name")										occupancy		element symbol ("symbol")
residue name ("resn")					chain identifier ("chain")					temperature factor ("b")		
residue number ("resi")												
ATOM	1	N	ILE	E	1	9.198	51.923	-1.205	1.00	56.09	N	
ATOM	2	CA	ILE	E	1	8.244	52.190	-0.120	1.00	34.74	C	
ATOM	3	C	ILE	E	1	7.870	53.687	0.082	1.00	41.10	C	
ATOM	4	O	ILE	E	1	8.699	54.583	-0.005	1.00	37.75	O	
ATOM	5	CB	ILE	E	1	8.733	51.578	1.191	1.00	39.04	C	
ATOM	6	CG1	ILE	E	1	8.149	50.191	1.418	1.00	26.23	C	
ATOM	7	CG2	ILE	E	1	8.402	52.483	2.377	1.00	61.96	C	
ATOM	8	CD1	ILE	E	1	8.191	49.808	2.899	1.00	100.00	C	
ATOM	9	N	THR	E	2	6.618	53.984	0.430	1.00	35.26	N	
ATOM	10	CA	THR	E	2	6.254	55.377	0.695	1.00	34.94	C	
ATOM	11	C	THR	E	2	5.978	55.528	2.171	1.00	35.54	C	
ATOM	12	O	THR	E	2	5.159	54.798	2.727	1.00	43.29	O	
ATOM	13	CB	THR	E	2	5.025	55.832	-0.111	1.00	44.88	C	
ATOM	14	OG1	THR	E	2	5.277	55.636	-1.477	1.00	44.03	O	
ATOM	15	CG2	THR	E	2	4.750	57.309	0.150	1.00	48.14	C	
ATOM	16	N	GLY	E	3	6.669	56.455	2.825	1.00	19.43	N	
ATOM	17	CA	GLY	E	3	6.467	56.590	4.234	1.00	12.80	C	
ATOM	18	C	GLY	E	3	7.170	57.813	4.752	1.00	22.88	C	
ATOM	19	O	GLY	E	3	7.464	58.772	4.026	1.00	29.00	O	
ATOM	20	N	THR	E	4	7.338	57.812	6.033	1.00	14.24	N	
ATOM	21	CA	THR	E	4	7.906	58.949	6.694	1.00	11.42	C	

Resolution (Å)	Meaning
> 4.0	Individual coordinates meaningless
3.0 – 4.0	Fold possibly correct, but errors are very likely. Many sidechains placed with wrong rotamer.
2.5 – 3.0	Fold likely correct except that some surface loops might be mismodelled. Several long, thin sidechains (Lys, Glu, Gln, etc.) and small sidechains (Ser, Val, Thr, etc.) likely to have wrong rotamers.
2.0 – 2.5	As 2.5–3.0, but number of sidechains in wrong rotamer is considerably less. Many small errors can normally be detected. Fold normally correct and number of errors in surface loops is small. Water molecules and small ligands become visible.
1.5 – 2.0	Few residues have wrong rotamer. Many small errors can normally be detected. Folds are extremely rarely incorrect, even in surface loops.
0.5 – 1.5	In general, structures have almost no errors at this resolution. Rotamer libraries and geometry studies are made from these structures.

Protein structure

Hydrogen bonds

Don't trust the positions of the hydrogen atoms in the PDB. Except for very high resolution structures ($< 1.0 \text{ \AA}$), they are put in automatically—and often incorrectly.

Structural metals (Ca^{2+} , Mg^{2+} , Zn^{2+} , etc.)

Stabilize loops, enhance protein-protein (or domain-domain) interactions.

Catalytic metals

At or near the active site. Usually coordinated by Asp, Glu, His, or Cys.

Disulfide bonds

Between two Cys. Enhance the stability of proteins in oxidative environment.

Cofactors

Ligands

Water molecules

etc.