BC530

Protein Structure I

"Seven Levels – part I"

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PROTEINS

Proteins are wonderful molecules of life which perform an enormous number of different functions in each organism.

They are complicated, dynamic and gregarious

In order to understand them, it is crucial to realize that:

- Most, but not all, proteins assume at least one well defined "native state"

- Many proteins adopt several quite different states while performing their function

- Many proteins form multimeric assemblies, or protein-nucleic acid complexes

- About 20-30% of all proteins are, at least partially, embedded in a lipid bilayer

- Many proteins have covalently modified side chains, or even modified main chains

- Many proteins bind metal ions or organic molecules ("cofactors")

The complexity of functions performed by proteins is unbelievable

Proteins:

- carry out the most wonderful chemistry as enzymes
- perform exquisite feats of recognition in:
  - signal transduction,
  - immune recognition, etc.
- capture and emit light
- pump small and large molecules, and protons, across membranes
- form cellular scaffolds, like microtubules and actin fibers
- run along highways, usually burning ATP as fuel
- pamper, regulate, repair, chop up and copy RNA and DNA
- form hair, nail, cartilage, and silk
- etc.

Several proteins perform multiple, totally unrelated, functions.

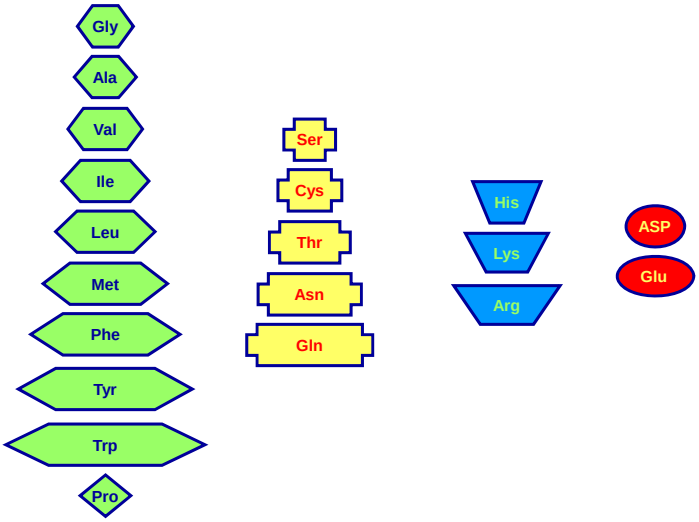
For instance, aldolase in the malaria parasite is:

1. a key glycolytic enzyme
2. a component of the host cell invasion machinery

Proteins

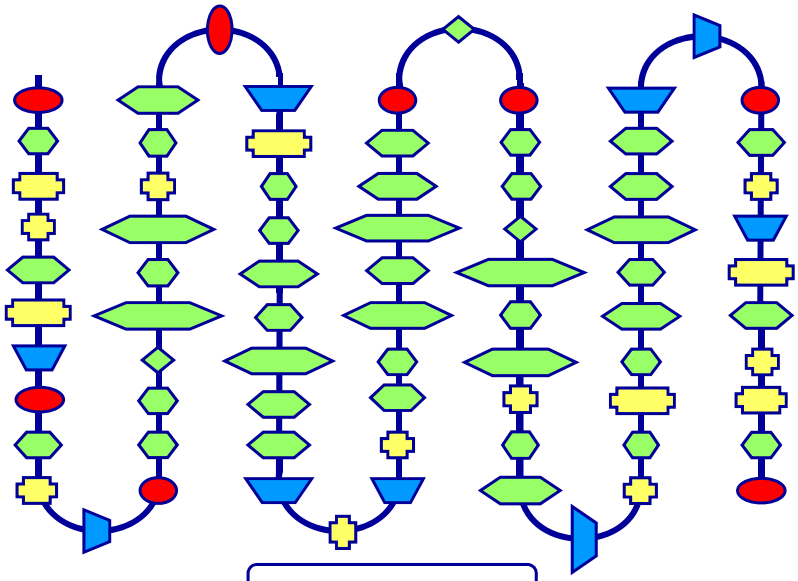
A Very Quick Initial View

Twenty Amino Acids



The Building Blocks of Proteins

Link Amino Acids Together

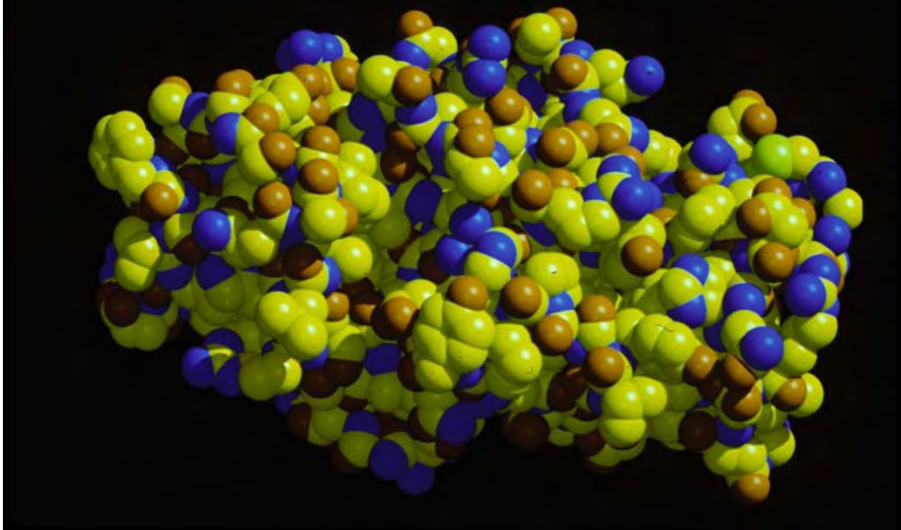


A Polypeptide Chain

The Chain Adopts a “Fold”

The B-subunit of Cholera Toxin

Proteins adopt usually a (quite) compact structure



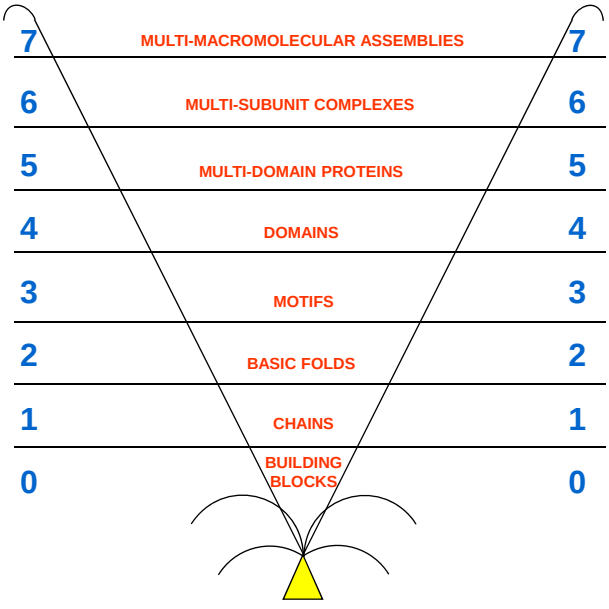
The A-subunit of Cholera Toxin

Basic Principles of Protein Structure

Thou shalt:

1. **Bury (sufficient) hydrophobics**
2. **Not create (too) many cavities**
3. **Satisfy (most) hydrogen bond donors and acceptors**
4. **Pamper thy buried charges**
5. **Avoid (most) side chain and main chain strain**

PROTEIN STRUCTURE HIERARCHY



THE SEVEN LEVELS

Proteins

Level 1:

“Building Blocks”

PROTEIN BUILDING BLOCKS

Proteins are made of:

- **20 natural amino acids**
- ***Trans*-peptide units**
- ***Cis*-peptide units - quite rare**
- **Numerous, often complex, inorganic and organic co-factors**
- **Many, many, many covalent modifications of sidechains, and sometimes even the main chain.**
  - **These modifications are often, but not always, made by other proteins.**
  - **Many of these modifications are permanent, others are transient.**

Peptide units, side chains and dihedral angles

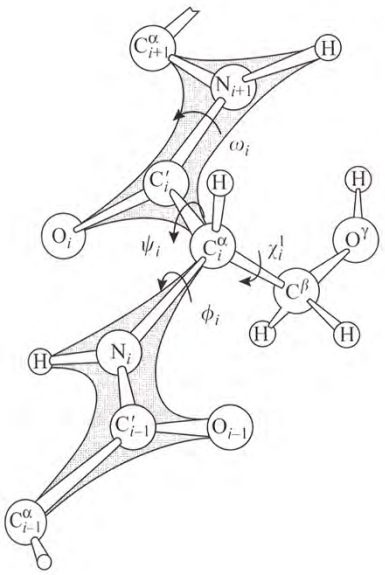


Diagram showing a polypeptide chain with a side group (Ser;'i' is its number in the chain).

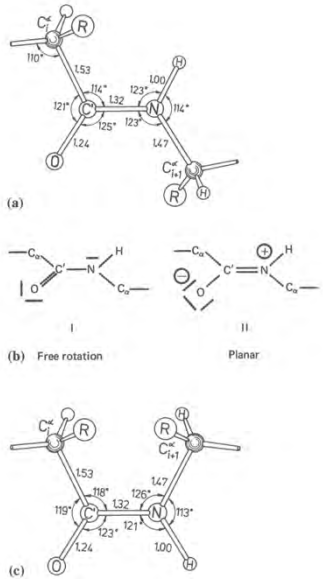
The peptide units are outlined.

The main-chain angles of rotation (Φ,Ψ,ω) and that of the side chain (χ^1) are presented.

Arrows show the direction of rotation of the part of the chain closest to the viewer about its remote part that increases the rotation angle.

(From Finkelstein and Ptitsyn - "Protein Physics")

Two variants of the Peptide Unit



The *trans* peptide unit

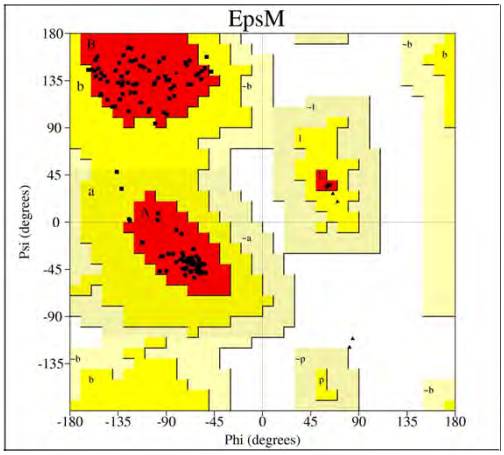
The partial double bond character of the C-N peptide bond makes the peptide unit quite planar

The *cis* peptide unit

G.E. Schulz & R.H. Schirmer. Principles of Protein Structure.. 1979: Figure 2.1

The Ramachandran plot

(for *trans* peptides only)



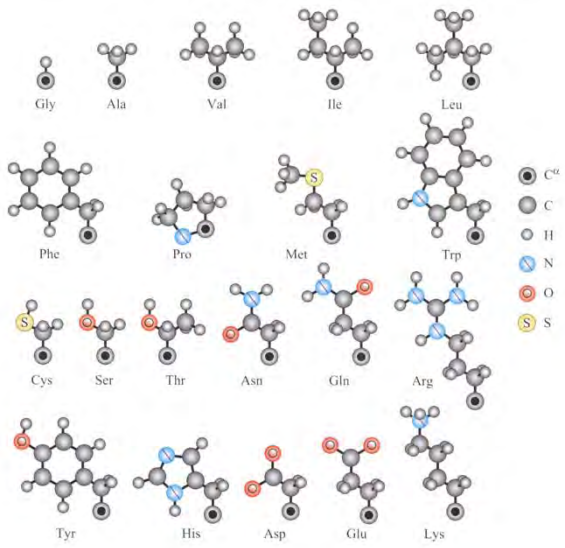
For non-Gly and non-Pro only: Red and Yellow :OK Pale Yellow : "Generously Allowed" White : Special or Problem

Rama: for Pro much more restricted; for Gly much less restricted; for *cis-trans* and for *trans-cis* –peptides: a nice exercise

For recent fine tuning of peptide group geometry as function of phi-psi combination see:

Berkholz, Structure 17:1316 (2009)

The Amino Acid Side Chains

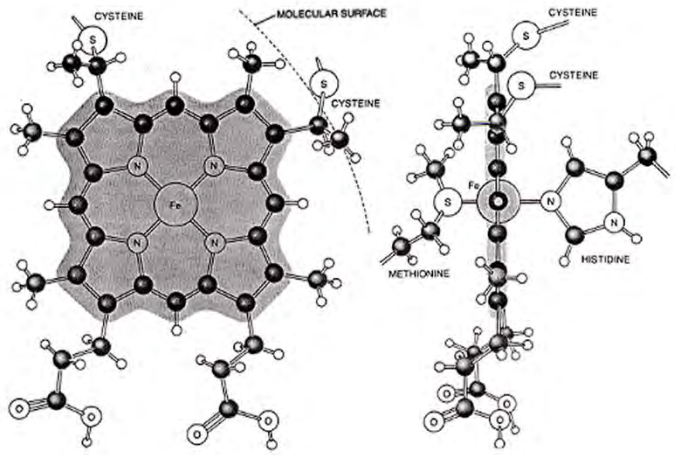


The side chains of twenty standard amino acid residues (projecting from the main-chain C^{α} atoms).

Atoms forming the amino acids are shown on the right

(From Finkelstein and Ptitsyn - "Protein Physics")

A Complex Co-factor..



…and also a post-translational modification!

STRUCTURE OF HEME and its attachments to the protein chain of cytochrome c. The face view (left) shows how the central iron atom is attached to four nitrogen atoms within the planar heme ring: as is shown in the edge view (right), the iron also has bonds to the sulfur atom of a methionine side chain on the protein and to the nitrogen atom of a histidine. The heme is also attached to the protein chain covalently through the sulfur atoms of two cysteines, electrons are "delocalized" within the porphyrin skeleton (colored region of left).

Dickerson, (March 1980) *Scient. American*, **242** 2:137

Proteins

Level 2:

"Secondary Structure Elements"

SECONDARY STRUCTURE ELEMENTS : α and ß

1. The *right*-handed α-helix

2. The ß-sheet:

of which there are three types:

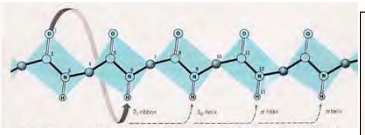
- **anti-parallel**
- **parallel**
- **mixed**

Almost all ß-sheets have a *left*-handed twist when viewed *in* the plane of the sheet *perpendicular* to the strand direction. The twist is due to a preference for a small *right*-handed twist of the individual ß-strands.

[The right-handedness of the α-helix and the left-handed twist of the ß-sheets are the consequence of interatomic contacts of the chain made up of L-amino acids.]

Different Types of Helices

3_{10} – helix: rare; α–helix: very common; π – helix: "never"



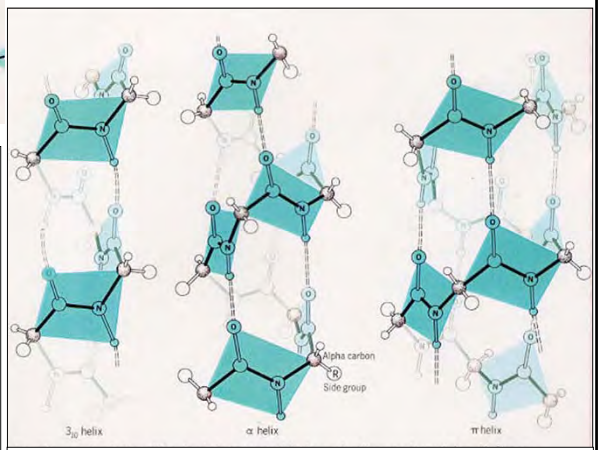
Theoretically, a polypeptide chain can be folded into several different regular helices without serious steric clashes around the helix axis.

One nomenclature is based on (i) the number of residues per turn; and (ii) the number of atoms in the ring formed by closing the hydrogen bond.

The 3_{10}-helix, with 3 residues per turn, and 10 atoms in the H-bonded ring, is pretty tight around the helix axis. Hence it does not occur often. It forms an H-bond between the C=O of residue n, and the N-H of residue (n+3);

The α-helix, a 3.6_{13}-helix, has 3.6 residues per turn, and 13 atoms in the H-bonded ring, is just right around the helix axis. Hence it does occur often. It forms an H-bond between the C=O of residue n, and the N-H of residue (n+4);

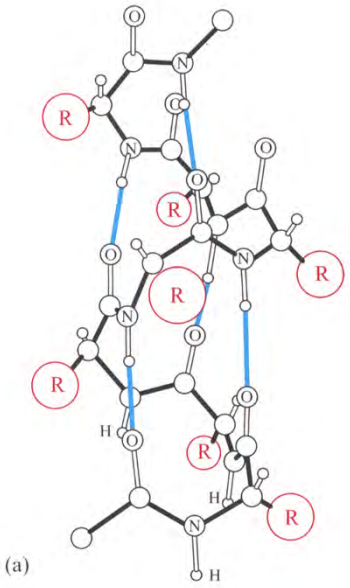
The π-helix, a 4.4_{16}-helix, has 4.4 residues per turn, and 16 atoms in the H-bonded ring, leaves empty space around the helix axis. Hence it does essentially not occur at all. It forms an H-bond between the C=O of residue n, and the N-H of residue (n+5).

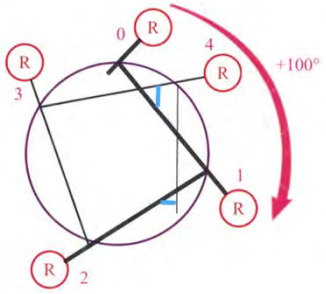


The 3_{10}-helix, α-helix, and π-helix differ in their pattern of hydrogen bonding as shown on the left. Hydrogen Bonds in the α-helix are particularly unrestrained, making the α-helix especially stable.

After Dickerson & Geiss, "Structure and Function of Proteins" (1969)

The α-Helix





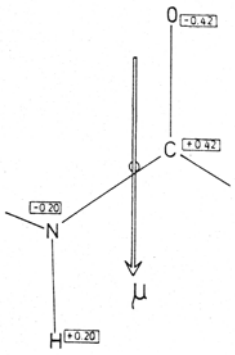
Helix characteristics:

- **100° rotation per residue**
- **3.6 residues per turn**
- **1.5 Å shift parallel to helix axis per residue**
- **5.4 Å shift parallel to helix axis per turn**

(Adapted from Finkelstein and Ptitsyn - "Protein Physics")

The Dipole of the Peptide Unit

- **An approximate charge distribution of a peptide unit**
- **The actual charge distribution is different since:**
  - **there is some charge on the C^{α}**
  - **every peptide unit is in a different environment**
  - **hydrogen bonding changes charge distribution**
  - **electric fields change charge distribution**
  - **atomic polarizibility**
- **The canonical value of μ_{pep} = 3.5 Debye = 0.728 e.Å**
  (For comparison μ_{H20} = 1.85 Debye)

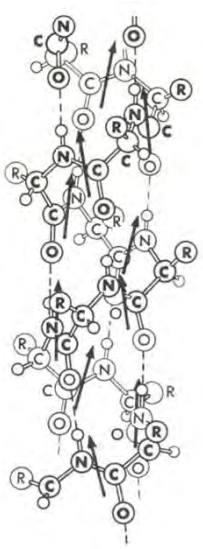


The key point for what follows is that the peptide dipole moment can be approximated as a positive point charge of 0.728 elementary units and a negative point charge of -0.728 units, separated by 1 Å;

AND ALSO by two half elementary charges of opposite sign separated by 1.5 Å.

After all, the dipole moment remains the same: 0.728x1.0 ≈ 0.5x1.5 ≈ 0.73 e.Å

The α–helix dipole



1. In an α-helix the peptide dipole moments are essentially parallel to the helix axis;

2. The positive end of each peptide unit's dipole is near the N-terminus of the helix;

3. Each peptide unit is shifted by 1.5 Å parallel to the helix axis;

4. Each peptide dipole can be projected onto the helix axis as two half charges of opposite sign, separated by 1.5 Å;

5. Hence all half charges cancel out EXCEPT:

- one positive half charge near the N-terminus, and

- one negative half charge near the C-terminus.

The α-helix dipole and the properties of proteins. *Nature* **273**, 443-446. Hol, W. G. J., van Duijnen, P. T. & Berendsen, H. J. C. (1978).

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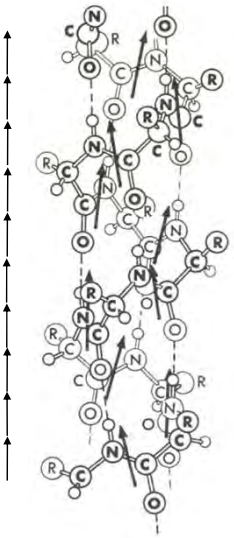
The α–helix dipole



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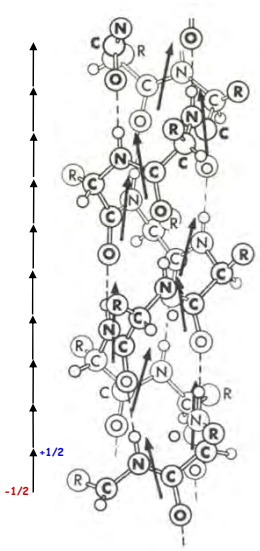

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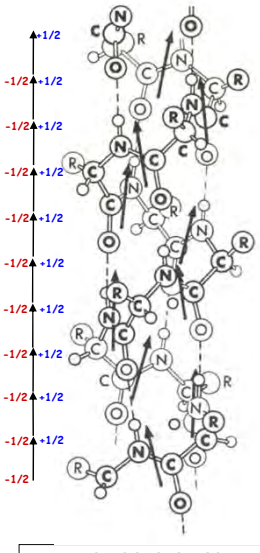

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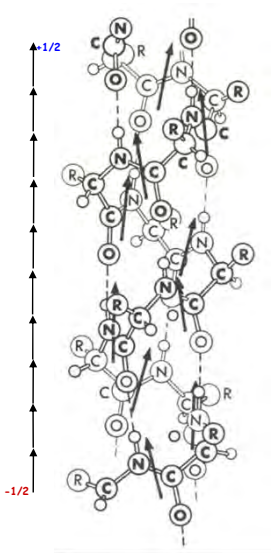

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Electrostatic energy and the α–helix dipole

(1) $1\ \text{eV} = 23.06\ \text{kcal mol}^{-1}$

(2) $U_{el} = q \times \Phi$ = charge x potential (in eV)

For Helix Dipole:

At 5 Å from N-term of a 2-turn helix and assuming ε = 2: Φ ≈ 0.5 Volts

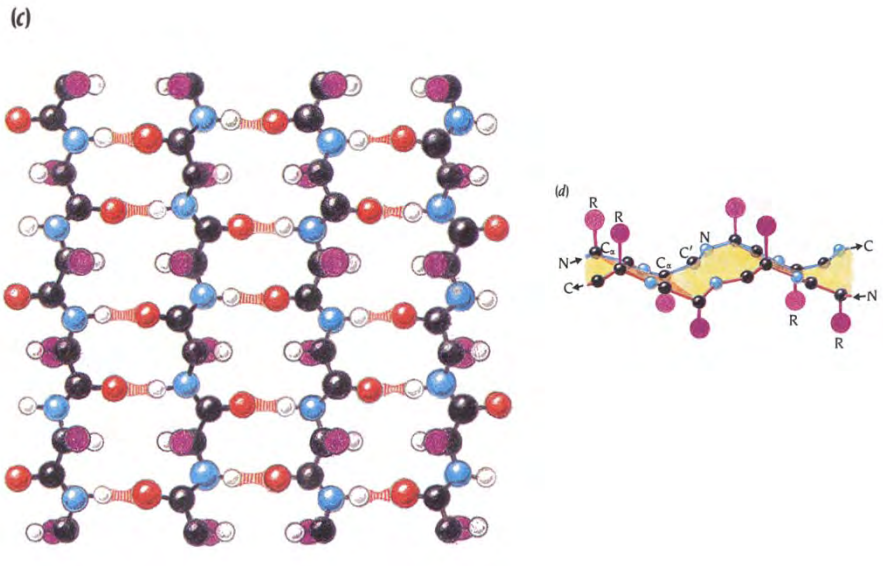
Then the energy after bringing a negative point charge from infinity through a medium of constant dielectric properties to the point with potential Φ is:

For ε = 2: $U_{el} = -1 \times 0.5 = -0.5\ \text{eV} \cong -12$ **kcal mol^{-1}**

For ε = 80: $U_{el} = -1 \times \frac{0.5}{40} = -\frac{0.5}{40}\ \text{eV} \cong -\frac{12}{40} \approx -0.3$ **kcal mol^{-1}**

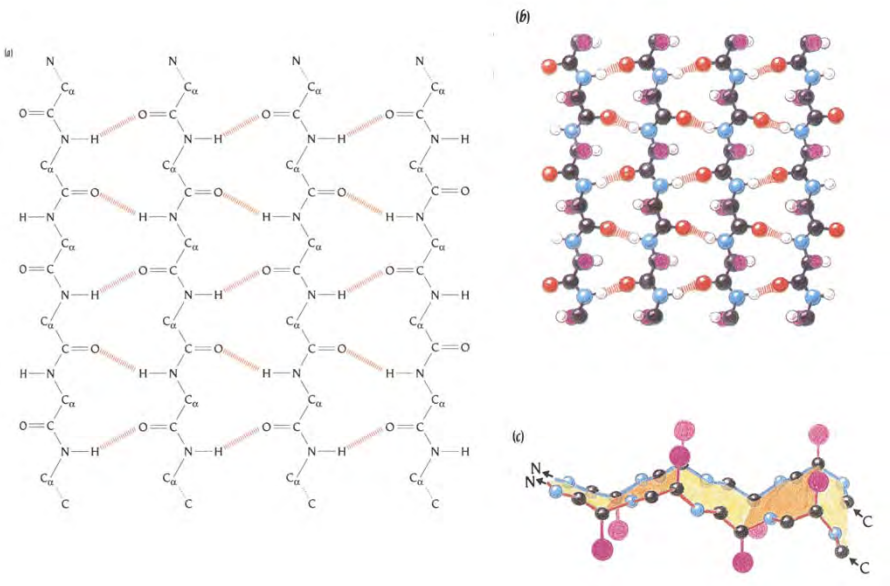
Hence, bringing a doubly charged negative ion from infinity to 5 Å from the N-terminus of an α-helix: $U_{el} \approx$ - 0.6 kcal mol^{-1} (assuming ε = 80)

The anti-parallel beta-sheet



(From Branden and Tooze - "Introduction to Protein Structure, 1st ed.")

The parallel beta-sheet



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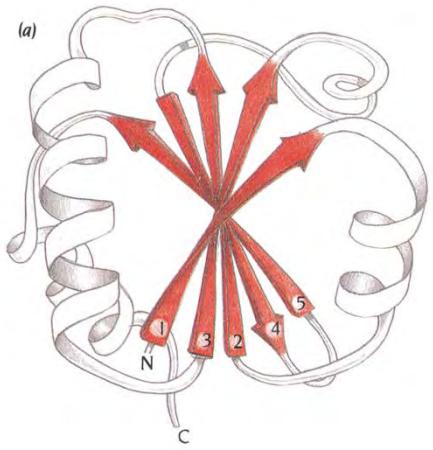
The twist of the β-sheet



A mixed β-sheet with the typical *left*-handed twist of the SHEET,

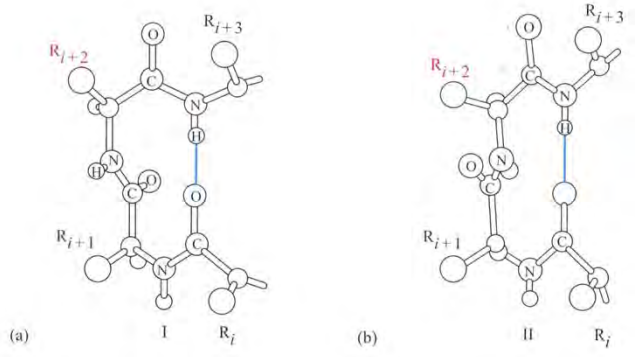
(When viewed perpendicular to the β-strands in the plane of the sheet)

A result of the typical *right*-handed twist of each individual β-STRAND.

(When viewed along each individual β-strand)

From Branden and Tooze - "Introduction to Protein Structure, 1st ed."

Tight Turns



***β*-turns.**

(a=left) The Type I *β*-turn. (Type III looks very similar and therefore is not depicted here).

(b=right)) The Type II *β*-turn. It differs from the *β*-turn I mainly by the inverted peptide group between the residues I + 1 and I + 2.

Secondary structure elements are connected by turns and loops of different types and lengths

(From Finkelstein and Ptitsyn - "Protein Physics")

Proteins

Level 3:

“Motifs”

MOTIFS

Structural motifs, also called "folding units" or "supersecondary structure elements", are compact entities composed of only a few secondary structure elements.

The most elemental structural motifs are:

1. The αα unit - two anti-parallel helices linked by a shorn turn

2. The ßß unit - two anti-parallel ß strands linked by a short turn

3. The ßαß unit - Note that the "right handed ßαß unit" is much more common than the "left handed ßαß unit" for reasons which are not entirely clear.

With these elemental structural motifs, larger modules can easily be formed. For instance:

1. two ßαß units, with a share middle ß strand → "ßαßαß"

2. two ßß units → "W" or "ß propeller" motif

3. one ßß unit and an α-helix → Zn-finger

4. and many more

Supersecondary structure elements

Greek Key motif
Formed by folding over two β-hairpins

βαβ-motif ββββ-motif αα-motif

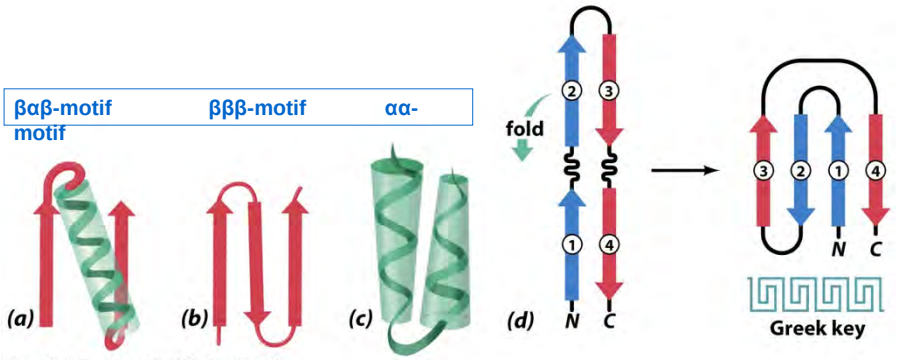


Figure 6-29 Fundamentals of Biochemistry, 2/e
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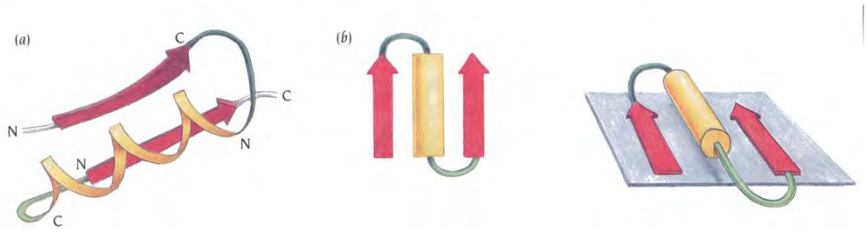
Looks all simple but…

35

…the β-α-β unit has a surprise



Two adjacent parallel β strands are usually connected by an α helix from three C-terminus of strand 1 to the N-terminus of strand 2. Most protein structures that contain parallel β sheets are built up from combinations of such β-α-β motifs. Beta strands are red, and α helices are yellow. Arrows represent β strands, and cylinders represent helices.

(a) Schematic diagram of the path of the main chain.

(b) Topological diagrams of the β-α-β motif.

…in actual proteins the β-α-β unit is *right*-handed (!)
(When looking perpendicular to the β-strands in the plane of the β-sheet)

(From Branden and Tooze - "Introduction to Protein Structure, 1st ed.")

Proteins

Level 4:

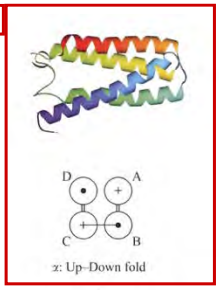
“Domains”

DOMAINS

- **Domains can be defined as compact folded units of contiguous polypeptide chain.**
- **They are quite fundamental units of protein structure.**
- **Nature "juggles" with domains.**
- **But plenty proteins are not easily assembled from domains, and are more complex.**

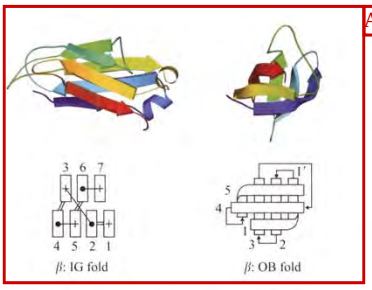
The main classes of Domains: all-α, all-*β*, α/*β* and α+*β*

All-α

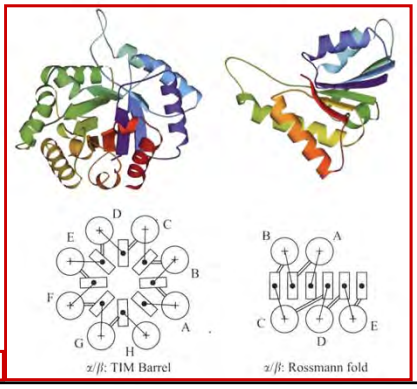


α: Up–Down fold

All- β



β: IG fold *β*: OB fold



α/*β*: TIM Barrel α/*β*: Rossmann fold

α+*β*: α/*β*-plait

α+β

Topology diagrams are shown below each Ribbon diagram.

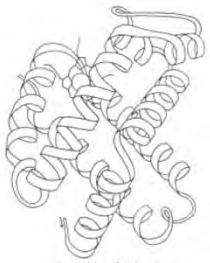
With some simplification, these structures can be considered to be layered, with each layer composed of either α-helices or *β*-strands but not both secondary structure elements.

(From Finkelstein and Ptitsyn - "Protein Physics")

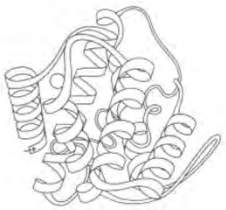
All-α Domains

Myohemerythrin

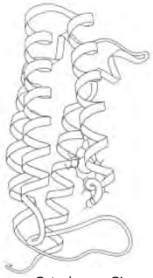
Cytochrome b_{562}



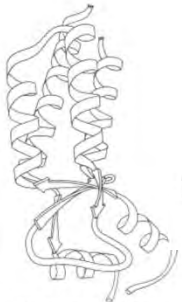
Hemoglobin β subunit



Thermolysin domain 2



Cytochrome C'



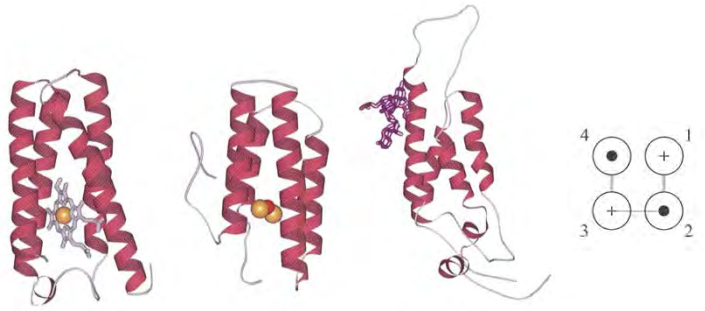
Tobacco Mosaic Virus Protein

Phage T4 Lysosome domain 2

Papain domain 1

The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

SAME FOLD YET ENTIRELY DIFFERENT FUNCTIONS



Cytocrome c' **Hemerythrin** **TMV Coat protein**
(TMV=Tobacco Mosaic Virus)

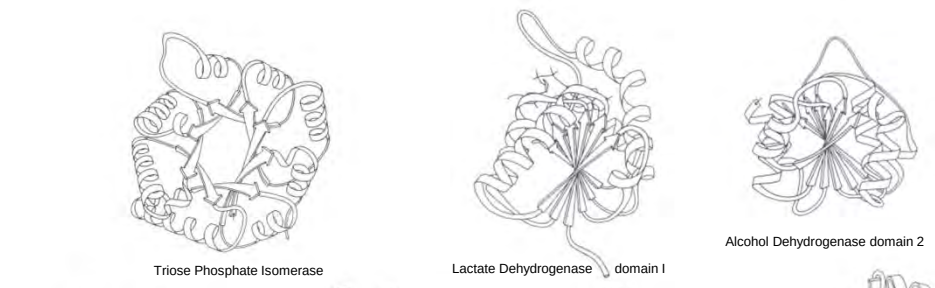
Three all α-proteins that are similar in architecture ("four-helix bundle") but entirely different in function.

Both the protein chain and co-factors are shown: wire models represent the heme (in cytochrome) and an RNA fragment (in virus coat protein), orange spheres are for iron ions (in the cytochrome heme and in hemerythrin), and the red sphere is for iron-bound oxygen (in hemerythrin). The overall architecture of such "bundles" resembles the co-linear packing of β-sheets.

The topological diagram (right) shows all these proteins as viewed (in the same orientation) from their lower butt-ends. The circles represent the ends of α-helices. The cross corresponds to the N-end of the segment (i.e., the segment goes away for the view); the dot corresponds to its C-end (i.e., the segment comes towards the viewer).

Finkelstein and Ptitsyn - "Protein Physics"

α/β domains



Triose Phosphate Isomerase

Lactate Dehydrogenase domain I

Alcohol Dehydrogenase domain 2

Pyruvate Kinase domain I

KDPG Aldolase (?)

Aspartate Transcarbamylase catalytic domain 2

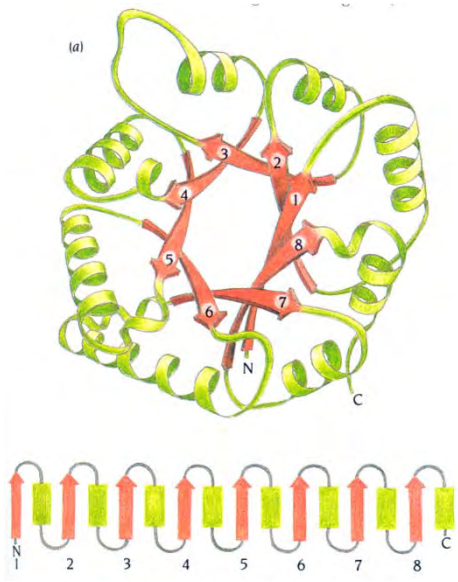
Phosphoglycerate Kinase domain 2

Parallel β-barrels

Parallel/ Mixed β-sheets

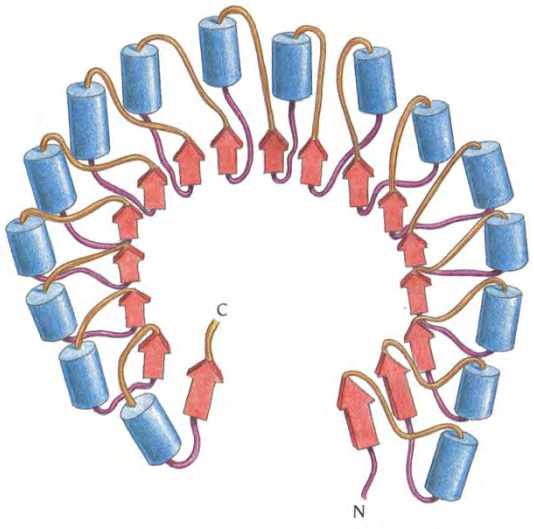
The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

The common "TIM-barrel" – a famous α/β protein fold



Branden, C. & Tooze, J. (1991). *Introduction to Protein Science.*

A quite different α/β protein with a "β-loop-α" motif repeated



Schematic diagram of the structure of the ribonuclease inhibitor.

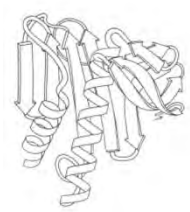
The molecule, which is built up by **repetitive β-loop-α motifs**, resembles a horseshoe with a 17-stranded parallel β sheet on the inside and 16 α helices on the outside.

The β sheet is light red, α - helices are blue, and loops that are part of the β-loop-α motifs are orange.

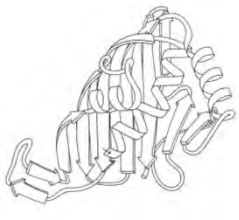
(Adapted from B. Kobe et al., *Nature* 366: 751-756, 1993)

Branden, C. & Tooze, J. *Introduction to Protein Science.*

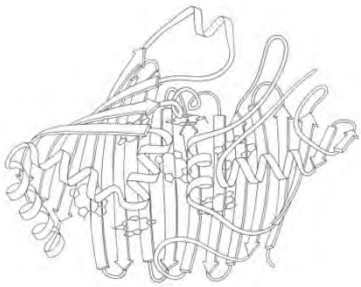
α+β domains



Thermolysin domain 1



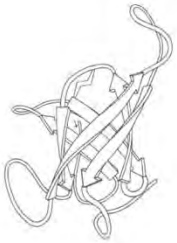
Glyceraldehyde P Dehydrogenase domain 2



Bacteriochlorophyll Protein

The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

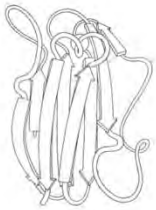
All-β domains



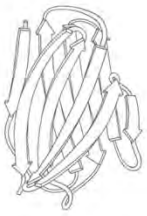
Trypsin domain 1

Pyruvate Kinase domain 2

Prealbumin

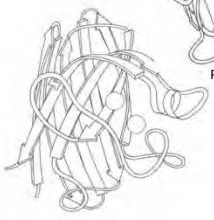


Plastocyanin



Immunoglobulin V_L domain

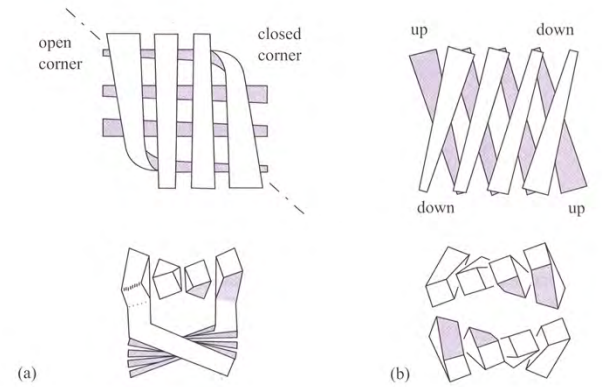
Staphylococcal Nuclease



Cu, Zn Superoxide Dismutase

The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

Packing of β-sheets in simple all-β proteins

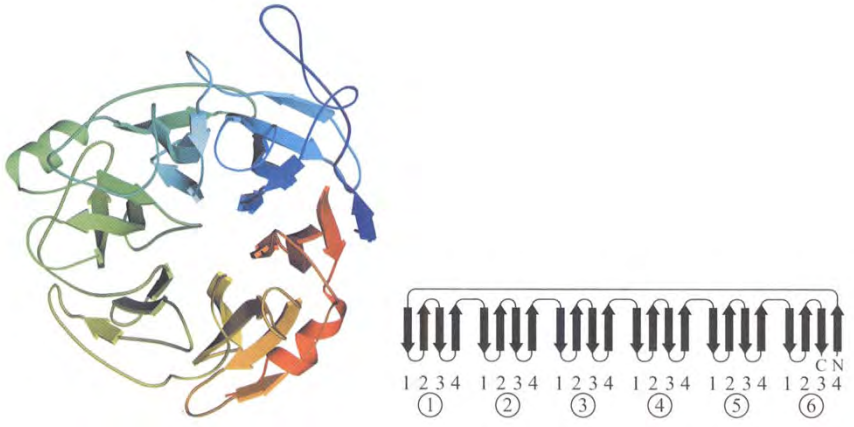


The orthogonal (a) and aligned (b) packing of *β*-sheets viewed face on (top) and from their lower end (bottom). In the face view, the *β*-strands are wider as they approach the viewer. The dashed line shows the axis of the orthogonal *β*-barrel to which both "open" corners belong. Here the two *β*-sheets are most splayed. At the two "closed" corners the sheets are extremely close together; here the chain bends and passes from one layer to the next. In the orthogonal packing the hydrophobic core is almost cylindrical. In contrast, in the aligned packing, the core is flat, the distance between the twisted sheets remains virtually unchanged, and the relative arrangement of the sheets allows the hydrophobic faces of twisted *β*-strands to make contact over a great length.

Adapted from Chothia C., Finkelstein A.V. *Annu. Rev. Biochem*. (1990) 59: 1007-1039

From Finkelstein and Ptitsyn - "Protein Physics"

Six anti-parallel β_4-motifs in a circular arrangement

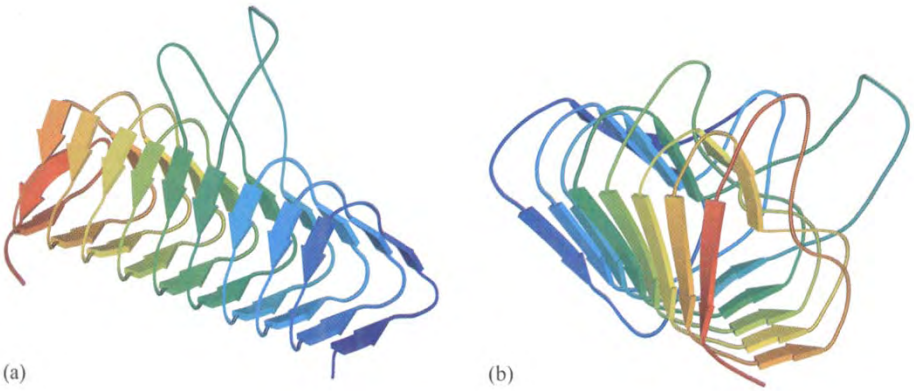


Left: *β*-structures forming a "six-blade propeller" in influenza virus neuraminidase

Right: topological diagram of this protein

From Finkelstein and Ptitsyn - "Protein Physics"

All-ß proteins: Parallel ß-helices



The *β*-prism in acyl transferase (a) and in pectate lyase (b).

Notice the handedness of the chain's coiling around the axis of the prism: (a) *left-handed*, which is unusual, (b) *right-handed*, which is common. (Ignore the N-to-C-direction of the chain!)

Also note that when the chain's coiling is left-handed, as in (a), the common twist of the *β*-sheet is absent.

This common twist, i.e., the left-handed twist, (viewed *perpendicular* to the β-strands *in* the plane of the sheet) is seen in (b).

From Finkelstein and Ptitsyn - "Protein Physics"

Proteins

Level 5:
"Multi-domain proteins"

Multi-Domain Proteins

Single-Domain Proteins **obviously coincide with Level 4: "Domains"**

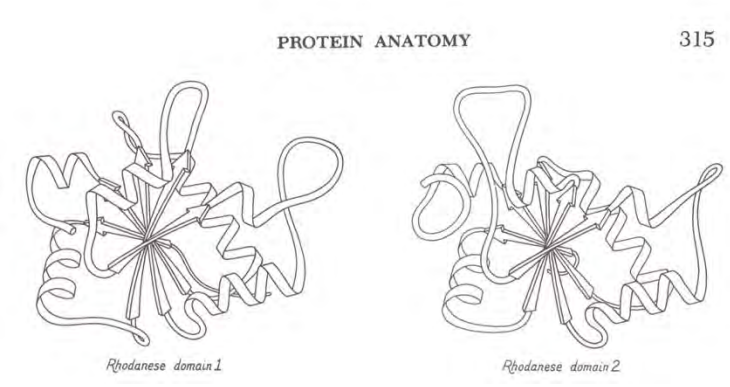
Multi-Domain Proteins **can be classified as Proteins with:**

- **Multiple copies of *similar* domains**
  - **As seen in:**
    - **rhodanese: sequence similarity lost, folds of the two domains very similar**
    - **immunoglobulins: a true multidomain game**
- **Multiple *dissimilar* domains**
  - **As seen in many proteins, for instance:**
    - **tyrosine kinases**
    - **pyruvate kinase**
    - **phosphoglycerate kinase**

And of course also:
Multiple copies of similar domains plus multiple dissimilar domains, etc.

Multi-domain proteins with domains of similar fold

Yet the sequences in the domains can be very different

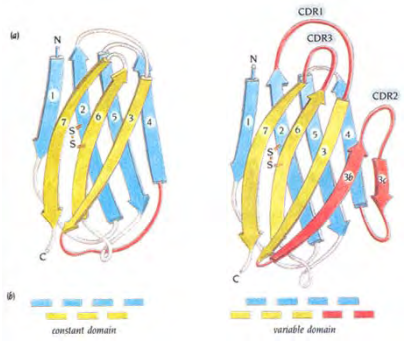


The two domains of rhodanese resemble each other very much in structure
But are quite different in sequence
A theme seen many times since 1978…

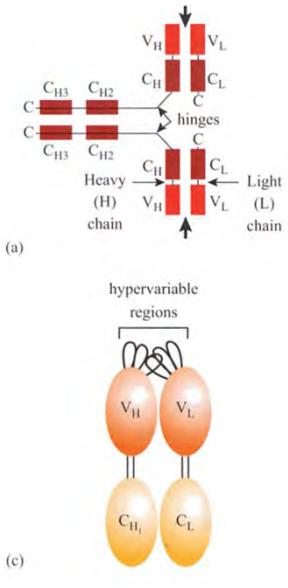
The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

Immunoglobulins G (IgG)

Combinatorial juggle of V and C domains



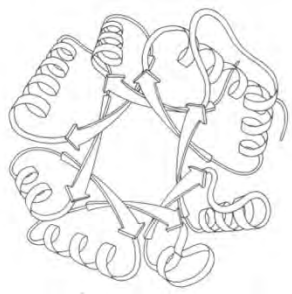
"C-domains" "V-domains"



Branden, C. & Tooze, J. (1991). *Introduction to Protein Science*

(From Finkelstein and Ptitsyn - "Protein Physics")

Multi-domain proteins with dissimilar domains



Pyruvate Kinase domain 1

Pyruvate Kinase domain 2

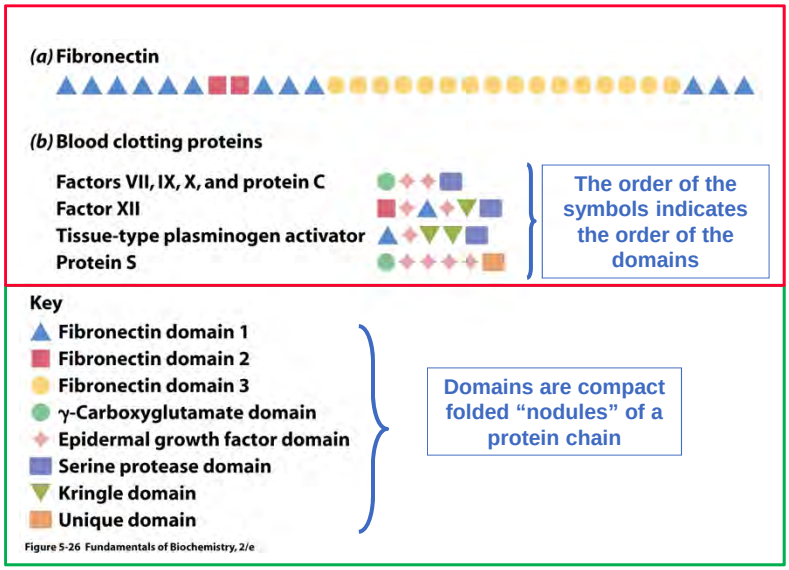
Pyruvate Kinase domain 3

Pyruvate kinase domains 1, 2, and 3 as an example of a protein whose domains show no structural resemblance whatsoever.

The anatomy and taxonomy of protein structure, J.S Richardson Adv, Protein Chem. 34, 167- 339 (1981)

The Multi-domain Game

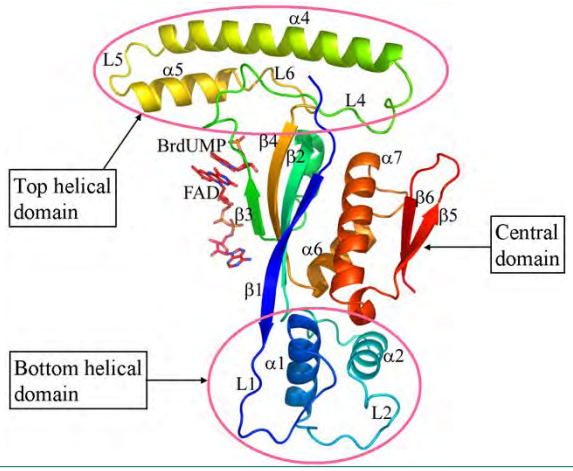
(Combining domains is e.g. a rapid way to combine functions in a single chain protein)



55

Do NOT forget: Many proteins have a complex fold

(A "novel" Thymidylate Synthase - *not* simply "Domains-on-a-string"



ThyX from *Mycobacterium tuberculosis* has a complex fold:

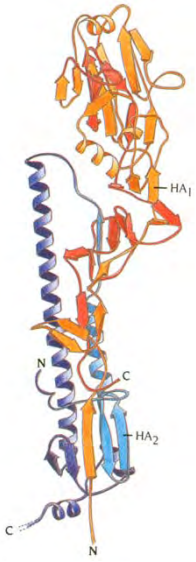
The Top and Bottom Domains are made up of a "contiguous piece of polypeptide chain.

But look at the Central Domain: the stretch α6-α7-β5-β6 is contiguous, but strands β1-β2-β3-β4 of the central β-sheet are very non-contiguous.

Parthasarathy Sampathkumar.

Influenza Virus Haemagglutinin

(i. e. again *not* simply "Domains-on-a-string"



Just following the chain in this structure is quite a challenge….

Branden, C. & Tooze, J. (1991). *Introduction to Protein Science*.

Proteins

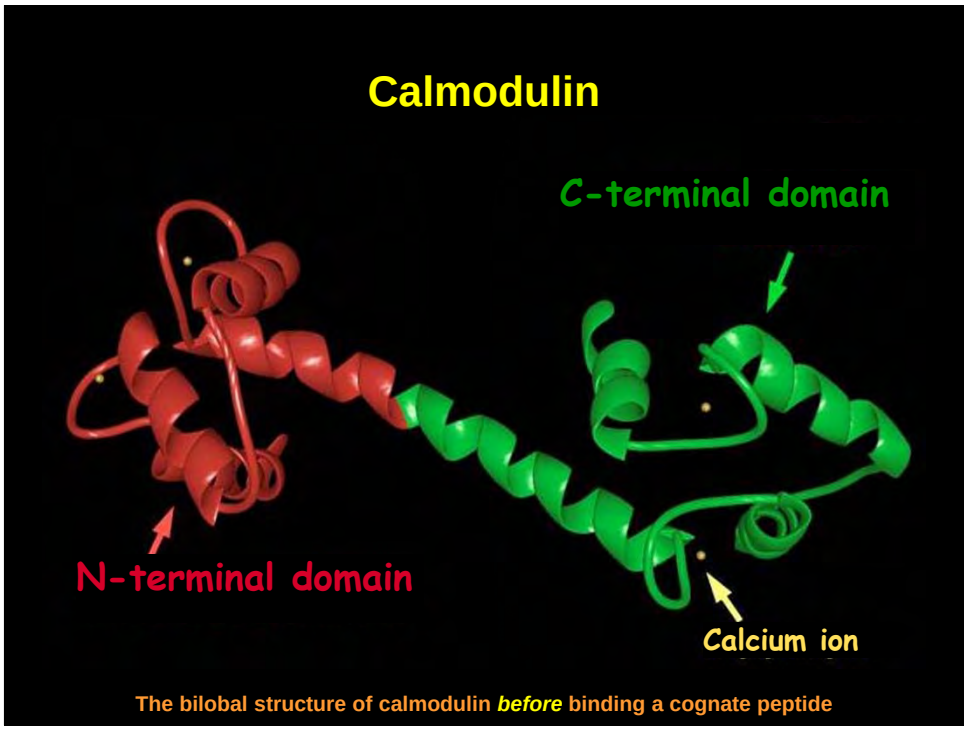
"The Conformational Change"

CONFORMATIONAL CHANGES

A crucial property of biomacromolecules

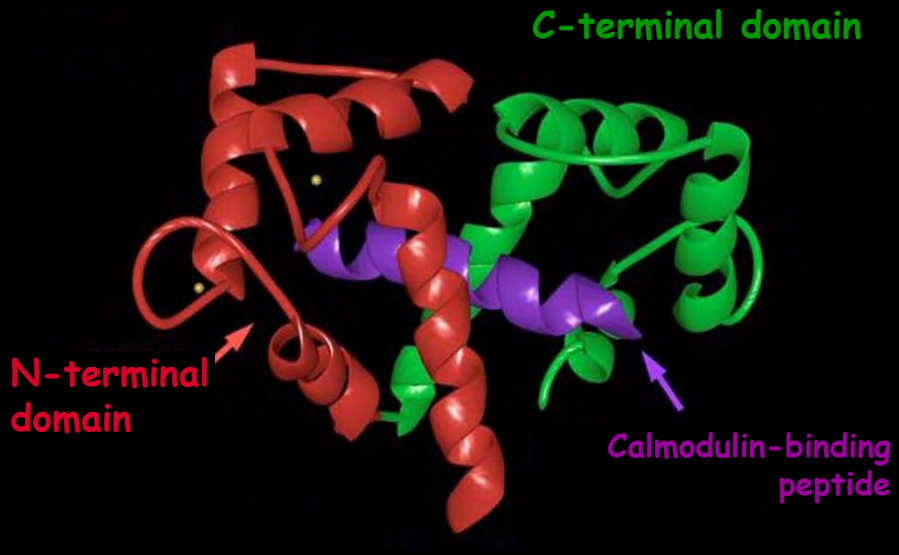
- **Proteins, e.g.:**
  - **phosphoglycerate kinase**
  - **adenylate kinase**
  - **GTPases like Elongation Factor Tu**
  - **Influenza virus haemagglutinin**
  - **Oxy vs deoxy hemoglobin**
  - **F_1 ATPase**
  - **Protein kinases**
- **DNA, e.g.**
  - **as bound, in a very kinked manner, to TATA-box binding protein**
- **RNA**
  - **where the same RNA molecule can choose different base-pairing schemes to end up with *very* different structures.**

An interesting database on Protein Motions is: http://molmovdb.mbb.yale.edu/MolMovDB/



The bilobal structure of calmodulin *before* binding a cognate peptide

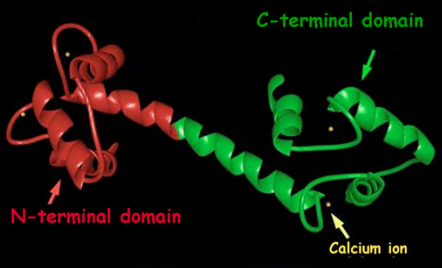
A Calmodulin/ Peptide complex



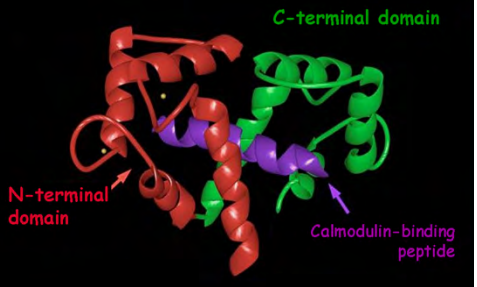
The compact structure of calmodulin *after* binding a cognate peptide

The Conformation Change of Calmodulin

Before peptide binding



After peptide binding



Protein structure is important.
Yet, without functional conformational changes of proteins life would be pretty miserable.

LITERATURE

The newest book on protein structure is:
"Text book of Strutural Biology"
by Liljas, Liljas, Piskur, Lindblom, Nissen and Kjelgaard
World Scientific 2009

An excellent book on protein structure is:
"Introduction to Protein Structure"
by C. Branden and John Tooze
New York: Garland Publishing, 1st Ed 1991, 2nd Ed 1999

Another book is:
"Protein Structure and Function"
By G Petsko and Dagmar Ringe
New Science Press 2004

A beautiful much older book is:
"The Structure and Action of Proteins"
by Richard E. Dickerson & Irving Geiss
New York: Harper & Row, 1969

Physical principles are emphasized in:
"Biophysical Chemistry"
by Charles R. Cantor & Paul R. Schimmel
San Francisco: W.H. Freeman, 1980

`"Proteins, Structure and Molecular Properties"
by Thomas E. Creighton
Oxford; Boston: Blackwell Scientific Publications, 1993

A older review on protein domains, a true classic, is:
"The anatomy and taxonomy of protein structure"
by Jane S. Richardson
Adv. Prot. Chemistry 34:167-339 (1981)
Now also on the web: http://kinemage.biochem.duke.edu/teaching/anatax/index.html

LITERATURE (Ctd)

A good book with emphasis on biophysics:
"Protein Physics"
Alexei Finkelstein and Oleg B Ptitsyn
Academic Press (2002)

A book giving a broad perspective:
"From Cells to Atoms"
by Rees and Sternberg
Blackwell Scientific Publications, 1984

An award winning website on Principles of Protein Structure:
http://www.cryst.bbk.ac.uk/PPS2/
(But this site does not appear to have been updated since mid-1996…)

Structural Classifications of Proteins SCOP and CATH:
http://scop.mrc-lmb.cam.ac.uk/scop/
http://www.cathdb.info/

Proteopedia:
http://www.proteopedia.org

Protein motion:
http://molmovdb.org/

The End
of
Seven Levels Part I