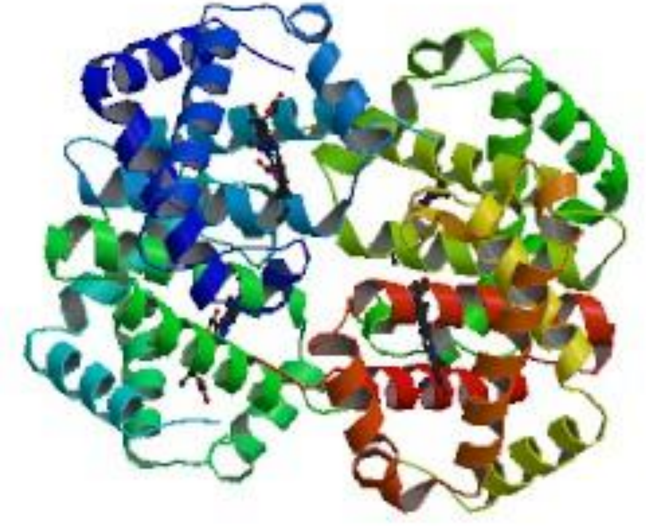
ME 411 / ME 511

Biological Frameworks for Engineers

UNIVERSITY OF
WASHINGTON

Class Organization

- HW1 due
- HW2 online
- Lab 1 – Protein Structure
  - MEB 231
  - Handouts provided

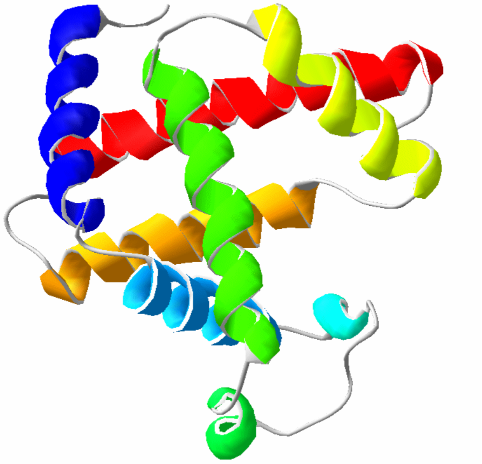


ME 411 / ME 511

Proteins

Protein

- Greek ‘protas’ (of primary importance)
- Proteins are essential to the structure and function of all living cells
- Human genome contains 25,000 genes that encode proteins*



**Alternative splicings and post-translational modifications can lead to 100,000 ‘distinct’ proteins*

Form is Function

- Folding and assembly define function
- 3-D shape has enzymatic nooks and structural parts
- Form determined by non-covalent bonds between AAs.
- Interactions between local and proximal regions in linear sequence of AAs

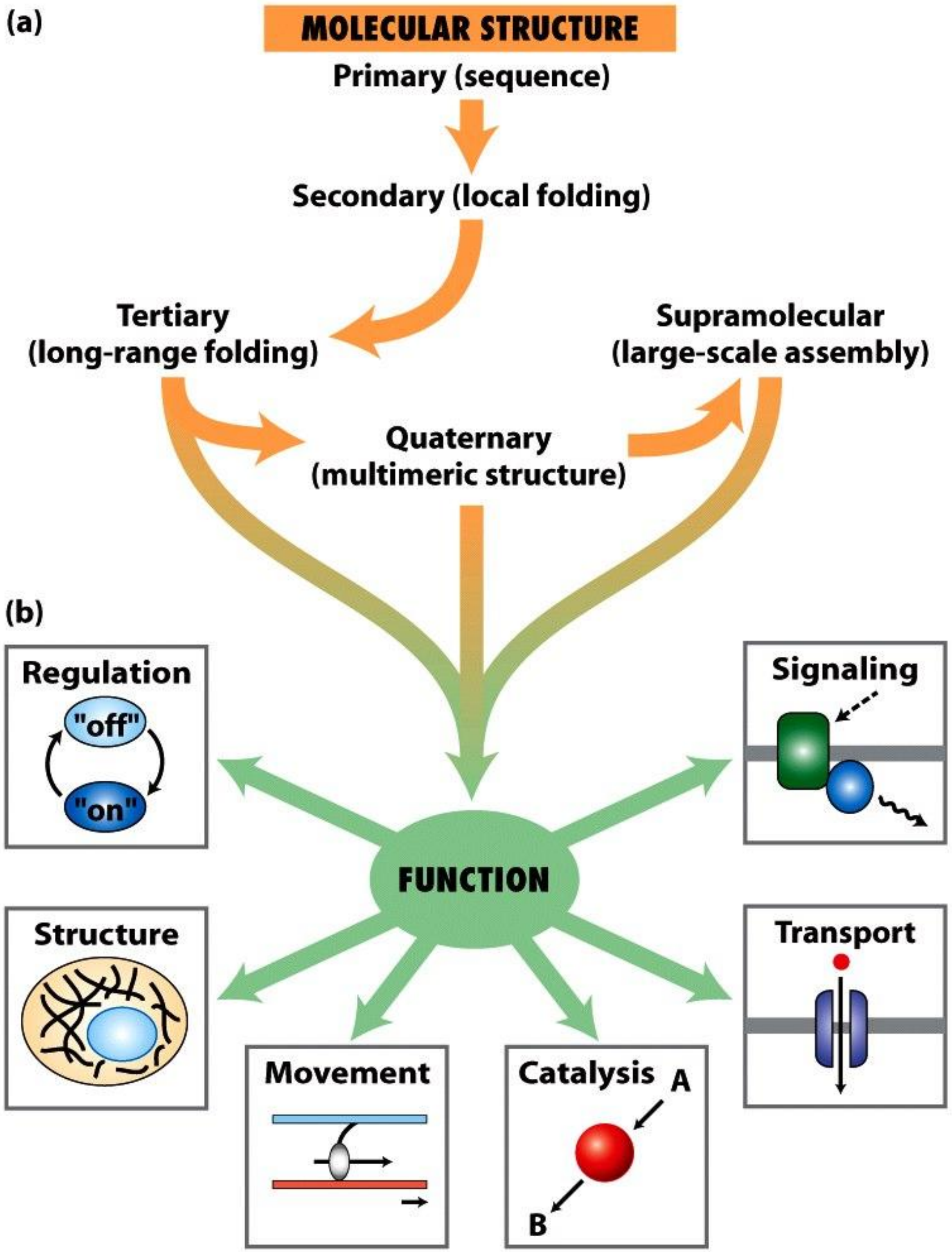


Figure 3-1
Molecular Cell Biology, Sixth Edition

Noncovalent interactions

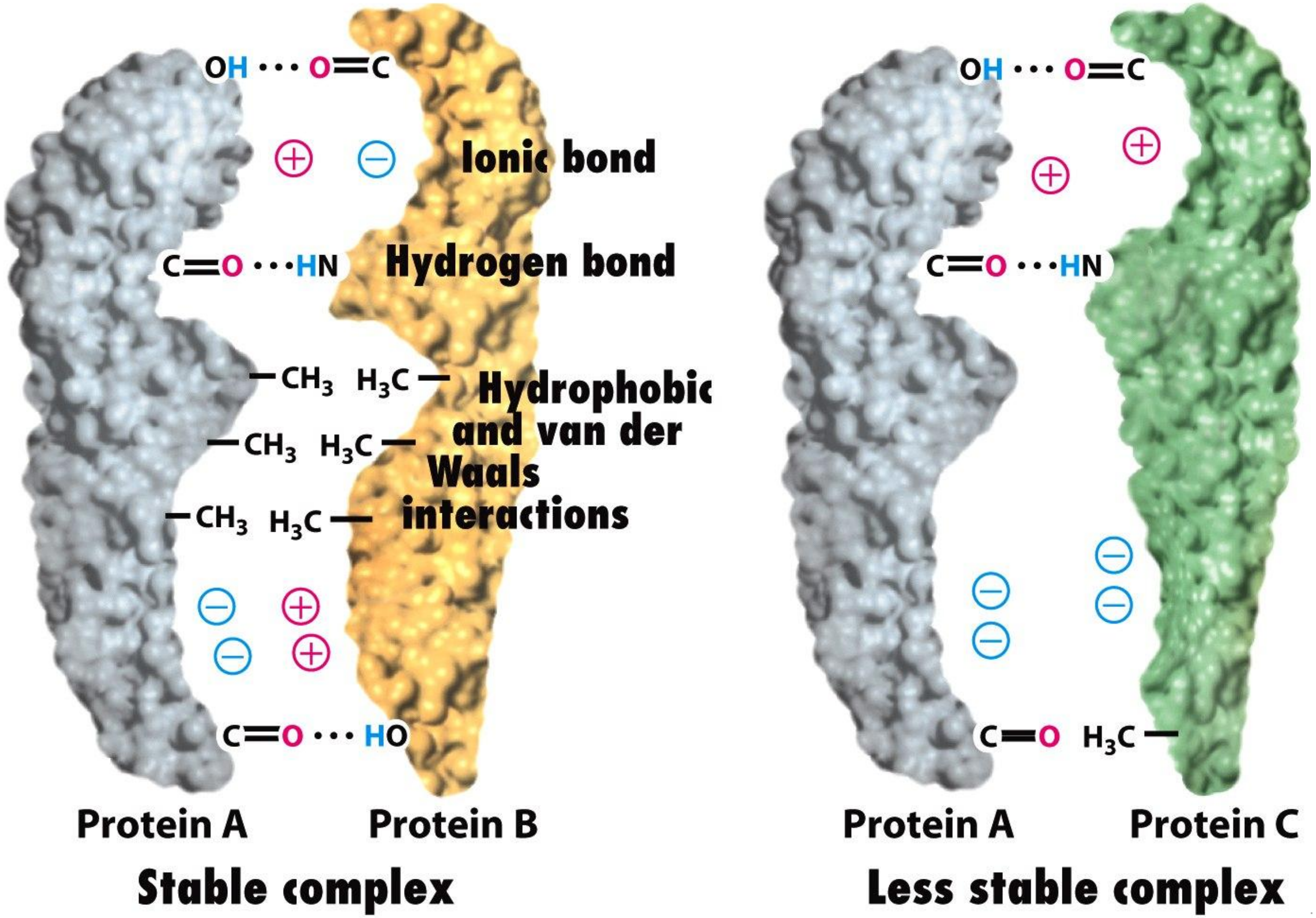


Figure 2-12
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Form-Function Example

Ras GTPase

GTP → GDP + P

GAP binding site

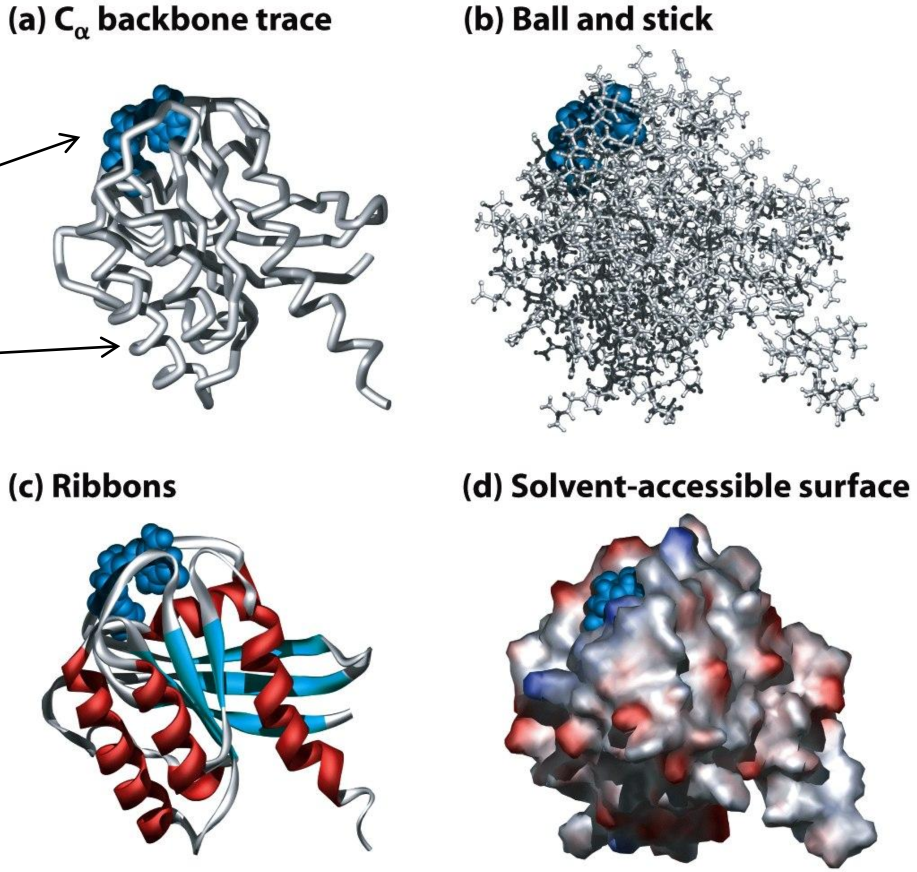


Figure 3-8
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

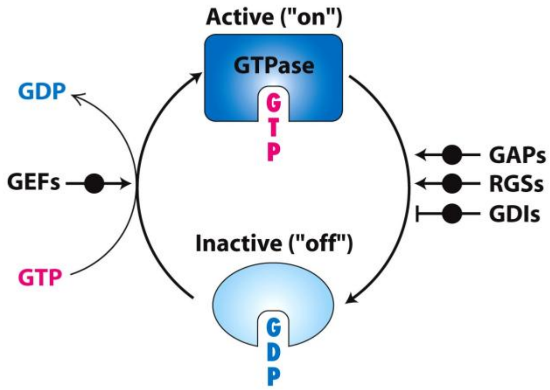
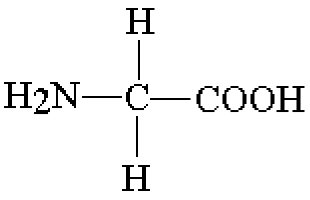


Figure 3-32
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Amino Acids

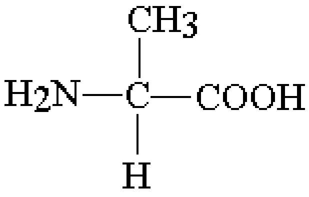
- Central alpha carbon atom (Cα)
  - Amino group (-NH_2)
  - Carboxyl group (-COOH)
  - Hydrogen atom (-H)
  - Unique side chain/residue (20 in total)



$H_2N-C(H)(H)-COOH$

glycine

Gly, G

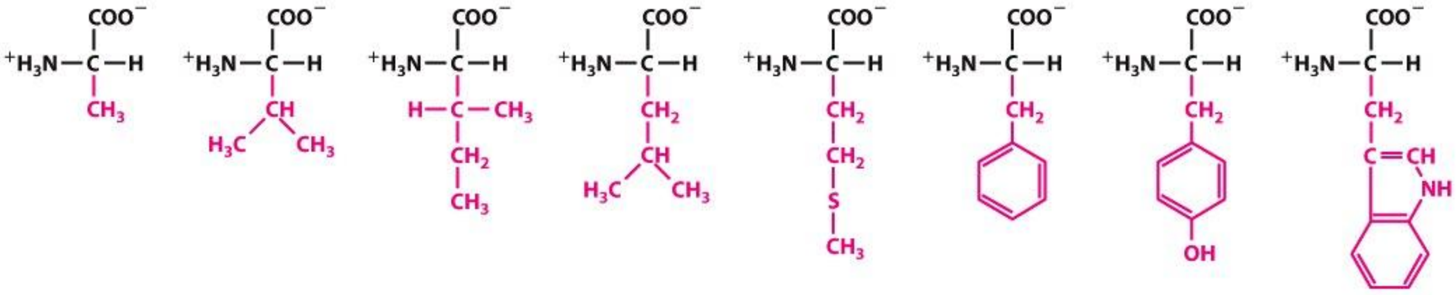


$H_2N-C(CH_3)(H)-COOH$

alanine

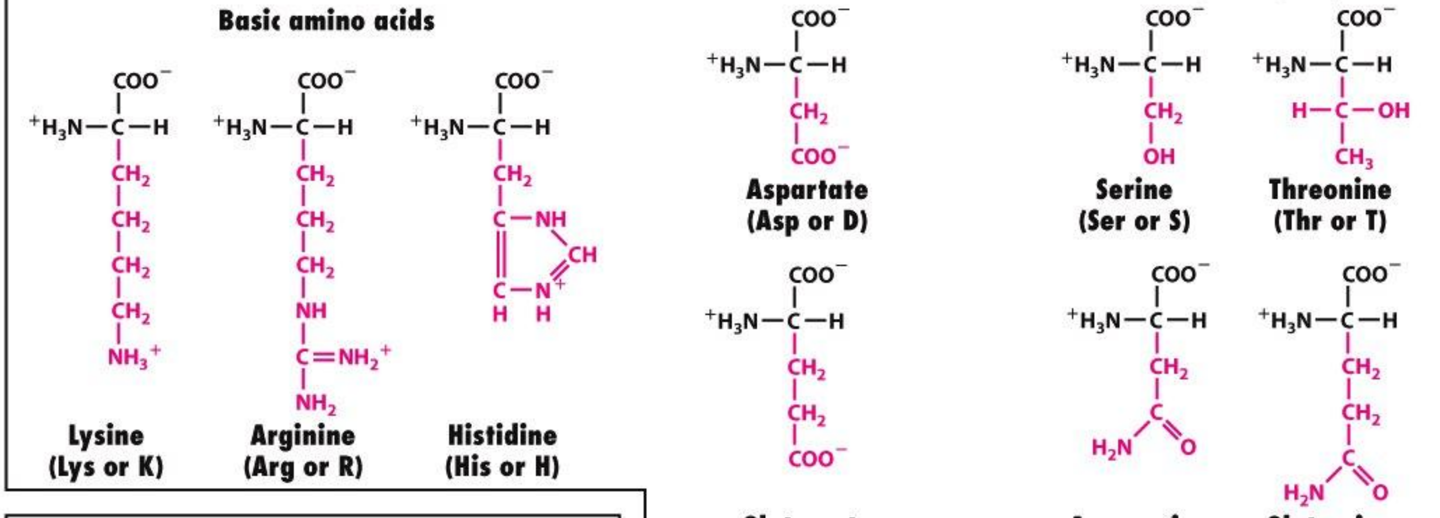
Ala, A

HYDROPHOBIC AMINO ACIDS



Alanine (Ala or A)
Valine (Val or V)
Isoleucine (Ile or I)
Leucine (Leu or L)
Methionine (Met or M)
Phenylalanine (Phe or F)
Tyrosine (Tyr or Y)
Tryptophan (Trp or W)

HYDROPHILIC AMINO ACIDS



Basic amino acids

Lysine (Lys or K)
Arginine (Arg or R)
Histidine (His or H)

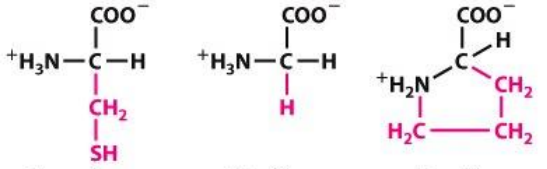
Acidic amino acids

Aspartate (Asp or D)
Glutamate (Glu or E)

Polar amino acids with uncharged R groups

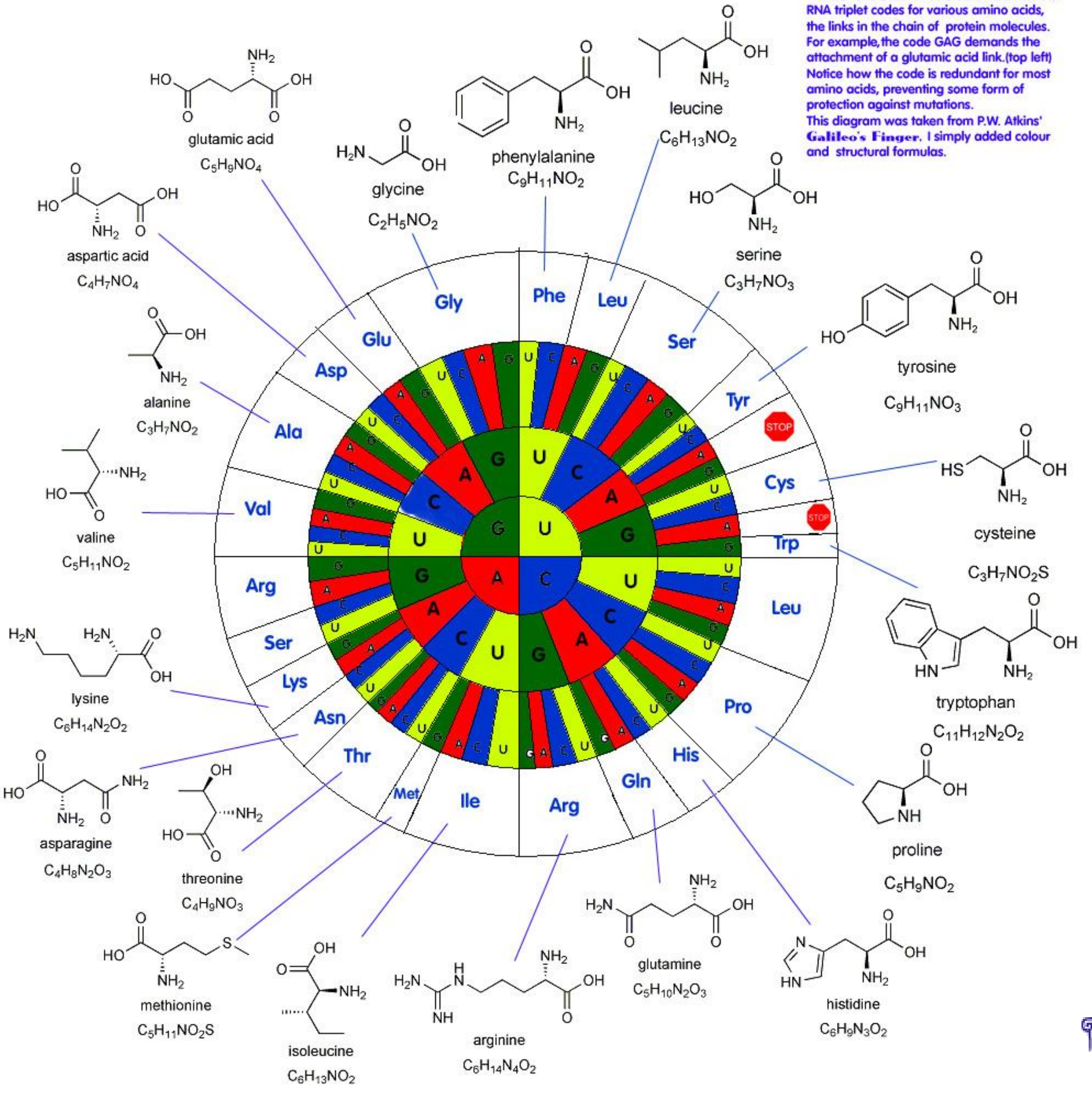
Serine (Ser or S)
Threonine (Thr or T)
Asparagine (Asn or N)
Glutamine (Gln or Q)

SPECIAL AMINO ACIDS



Cysteine (Cys or C)
Glycine (Gly or G)
Proline (Pro or P)

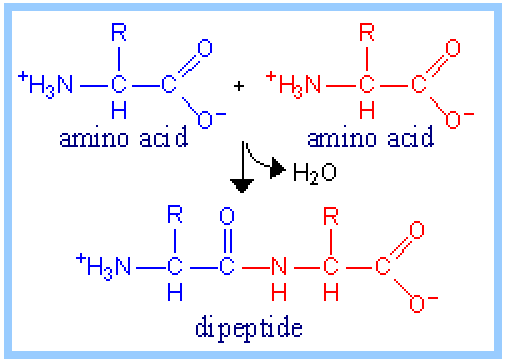
Recall: DNA → RNA → AA

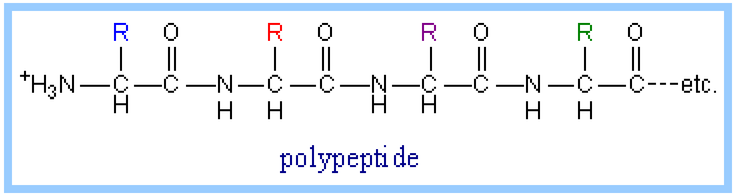


The Genetic Code: The colour wheel reveals RNA triplet codes for various amino acids, the links in the chain of protein molecules. For example, the code GAG demands the attachment of a glutamic acid link.(top left) Notice how the code is redundant for most amino acids, preventing some form of protection against mutations.
This diagram was taken from P.W. Atkins' **Galileo's Finger.** I simply added colour and structural formulas.

Amino Acids to Polypeptides

- Peptide bond – carboxyl reacting with an amino group: C – NO + H_2O

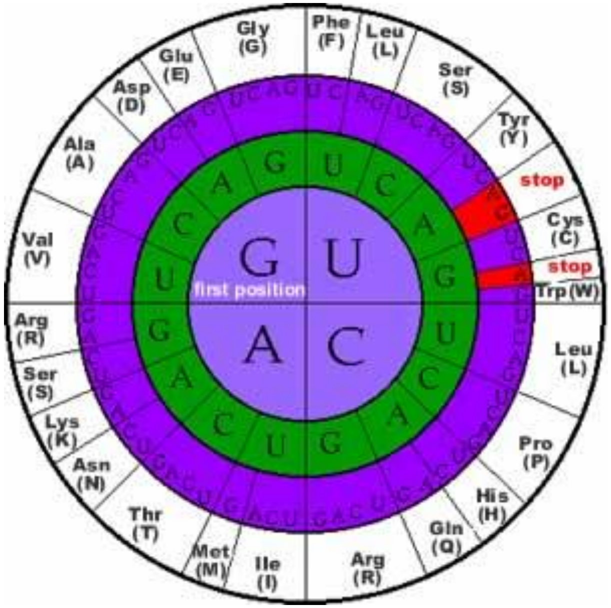




- Amino end is called N-terminus (starting end for translation)
- Carboxyl end is C-terminus

Residue Sequence for Actin

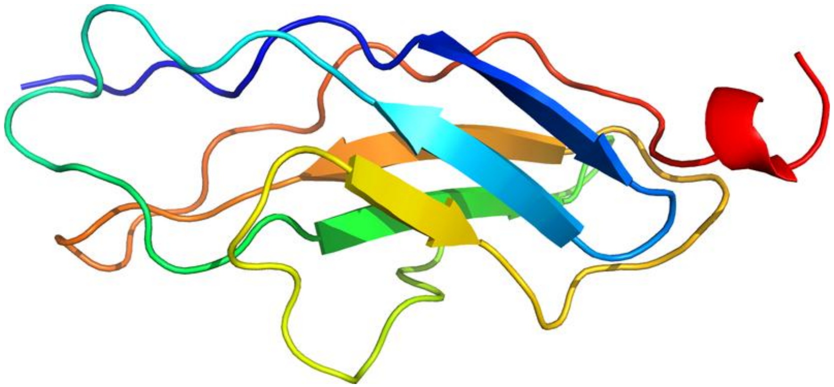
MCEEETTALV CDNGSGLCKA GFAGDDAPRA VFPSIVGRPR
HQGVMVGMGQ KDSYVGDEAQ SKRGILTLKY PIEHGIITNW
DDMEKIWHHS FYNELRVAPE EHPTLLTEAP INPKANREKM
TQIMFETFNV PAMYVAIQAV LSLYASGRTT GIVLDSGDGV
THNVPIYEGY ALPHAIMRLD LAGRDLTDYL MKILTERGYS
FVTTAEREIV RDIKEKLCYV ALDFENEMAT AASSSSLEKS
YELPDGQVIT IGNERFRCPE TLFQPSFIGM ESAGIHETTY
NSIMKCDIDI RKDLYANNVL SGGTTMYPGI ADRMQKEITA
LAPSTMKIKI IAPPERKYSV
WIGGSILASL STFQQMWISK
PEYDEAGPSI VHRKCF



Peptide Mass

- Protein weight is reported in Daltons
  - 1.66×10^{-24} Da = 1 gram
- Average amino acid is ~113 Da

Titin



Largest protein
3816 kDa
34,350 residues
(111 Da/AA)

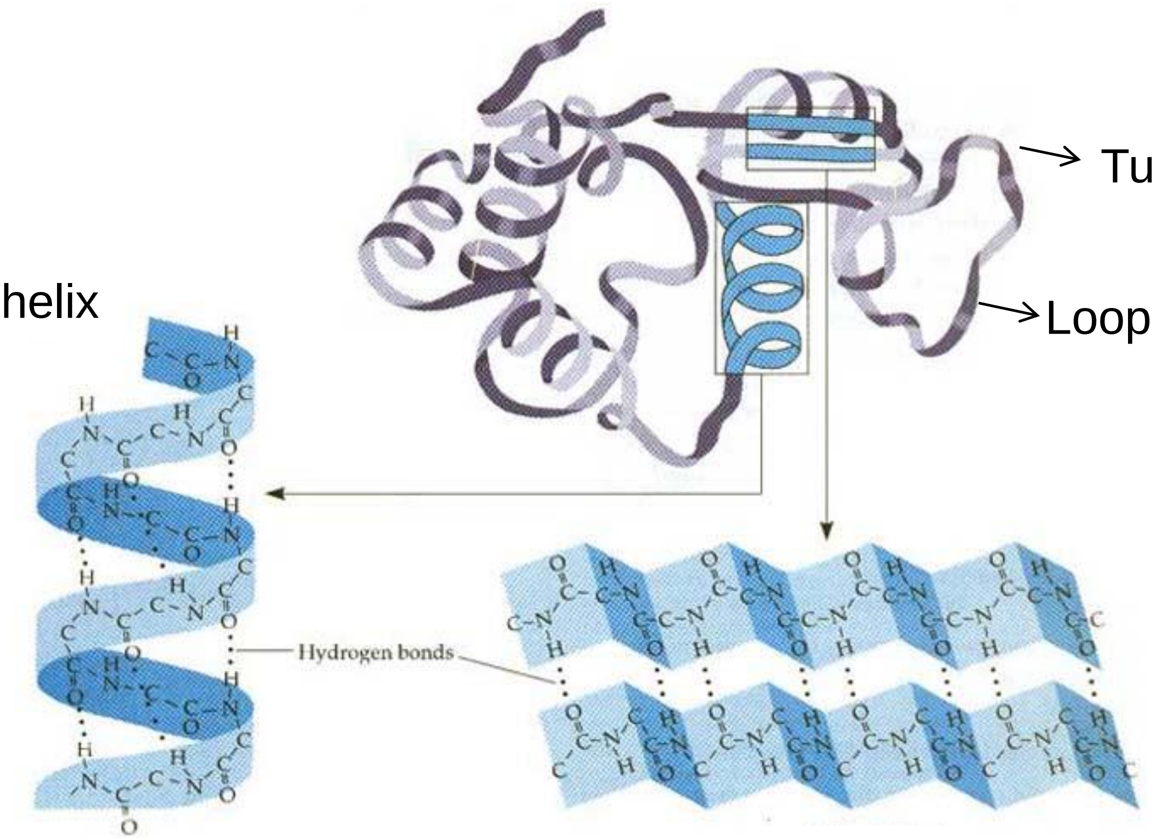
Protein Structure

- Primary – amino acid sequence
- Secondary – patterned sub-structures
- Tertiary – overall shape of a single protein molecule or unit
- Quaternary – union of more than one protein units

Primary Structure

MCEEETTALV CDNGSGLCKA GFAGDDAPRA VFPSIVGRPR
HQGVMVGMGQ KDSYVGDEAQ SKRGILTLKY PIEHGIITNW
DDMEKIWHHS FYNELRVAPE EHPTLLTEAP INPKANREKM
TQIMFETFNV PAMYVAIQAV LSLYASGRTT GIVLDSGDGV
THNVPIYEGY ALPHAIMRLD LAGRDLTDYL MKILTERGYS
FVTTAEREIV RDIKEKLCYV ALDFENEMAT AASSSSLEKS
YELPDGQVIT IGNERFRCPE TLFQPSFIGM ESAGIHETTY
NSIMKCDIDI RKDLYANNVL SGGTTMYPGI ADRMQKEITA
LAPSTMKIKI IAPPERKYSV WIGGSILASL STFQQMWISK
PEYDEAGPSI VHRKCF

Secondary Structure



Turn (γ, β, α, π)

Loop

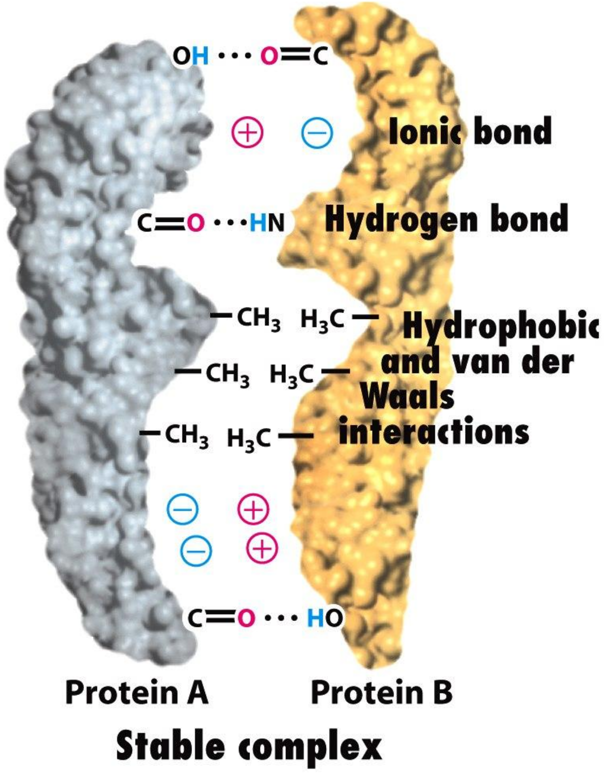
α-helix

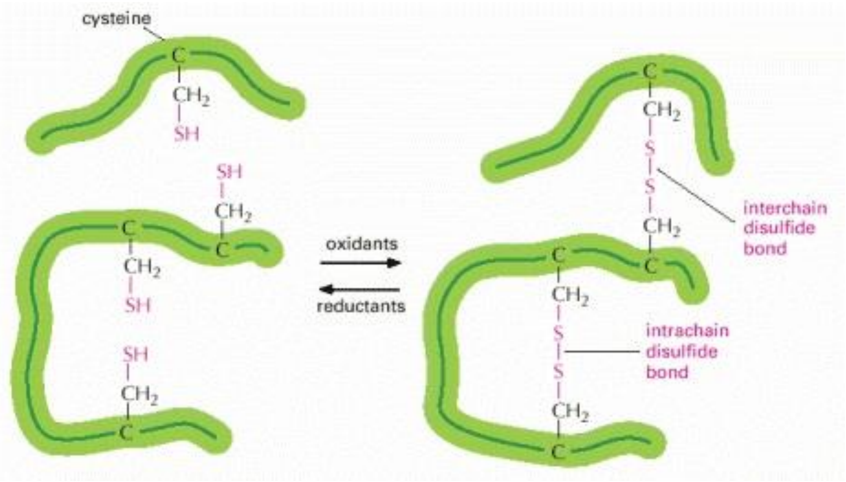
β-sheet

Tertiary Structure

- Hydrogen Bonds,
- Ionic Interactions

- Hydrophobic Bonds
- van der Waals
- Disulfide Bonds





Quaternary Structure

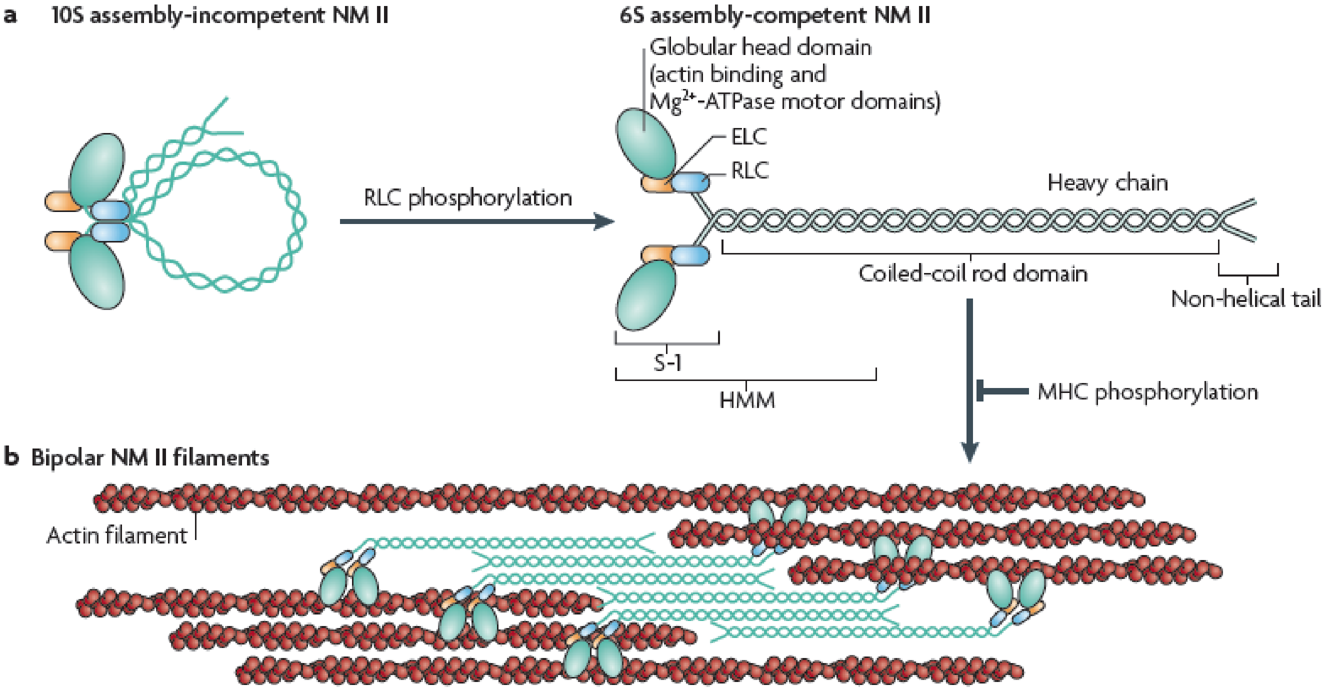


Figure 1 | **Domain structure of NM II. a** | The subunit and domain structure of non-muscle myosin II (NM II), which forms a dimer through interactions between the α-helical coiled-coil rod domains. The globular head domain contains the actin-binding regions and the enzymatic Mg^{2+}-ATPase motor domains. The essential light chains (ELCs) and the regulatory light chains (RLCs) bind to the heavy chains at the lever arms that link the head and rod domains. In the absence of RLC phosphorylation, NM II forms a compact molecule through a head to tail interaction. This results in an assembly-incompetent form (10S; left) that is unable to associate with other NM II dimers. On RLC phosphorylation, the 10S structure unfolds and becomes an assembly-competent form (6S). S-1 is a fragment of NM II that contains the motor domain and neck but lacks the rod domain and is unable to dimerize. Heavy meromyosin (HMM) is a fragment that contains the motor domain, neck and enough of the rod to effect dimerization. **b** | NM II molecules assemble into bipolar filaments through interactions between their rod domains. These filaments bind to actin through their head domains and the ATPase activity of the head enables a conformational change that moves actin filaments in an anti-parallel manner. Bipolar myosin filaments link actin filaments together in thick bundles that form cellular structures such as stress fibres.

Vincentes-Manzanares, M. *et al.* Nat Rev – Mol Cell Biol, 10, 779-90

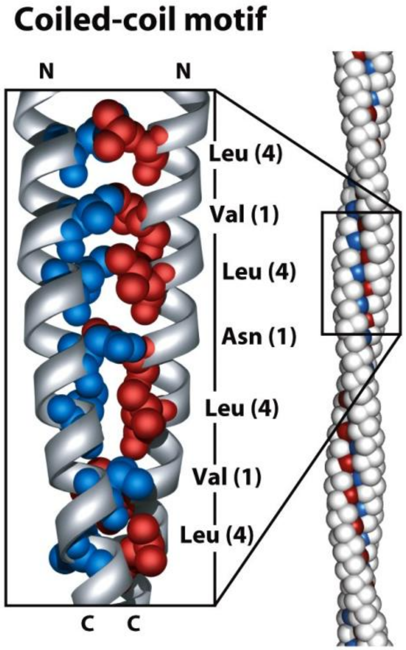
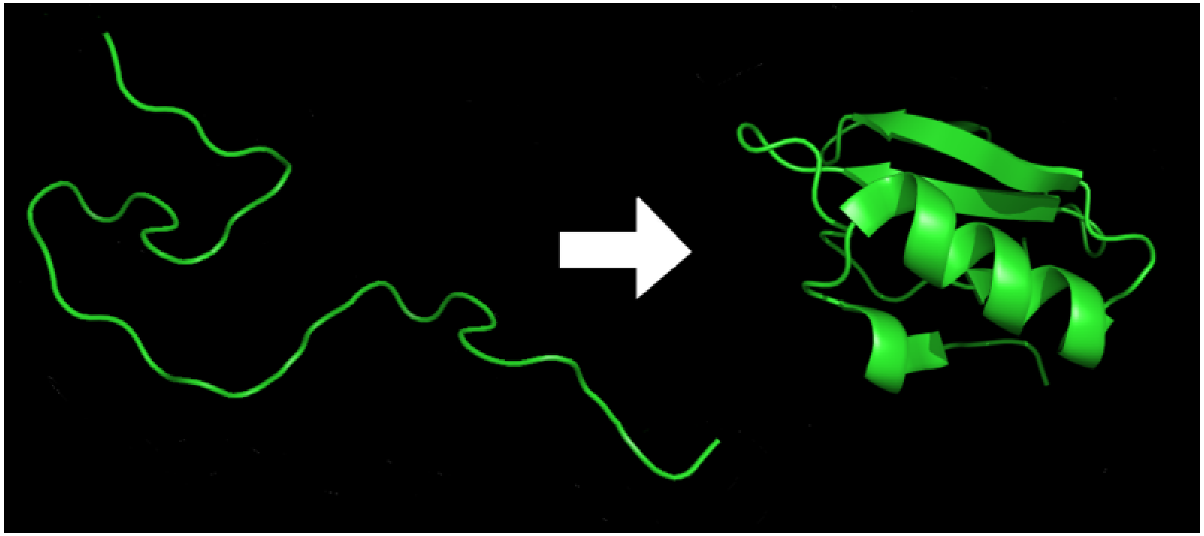
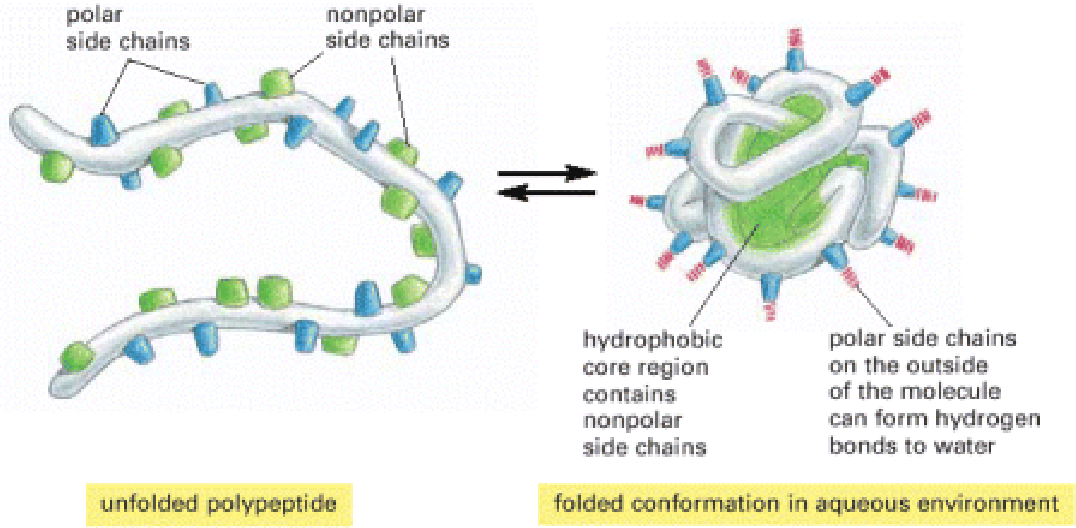


Figure 3-9a
Molecular Cell Biology, Sixth Edition

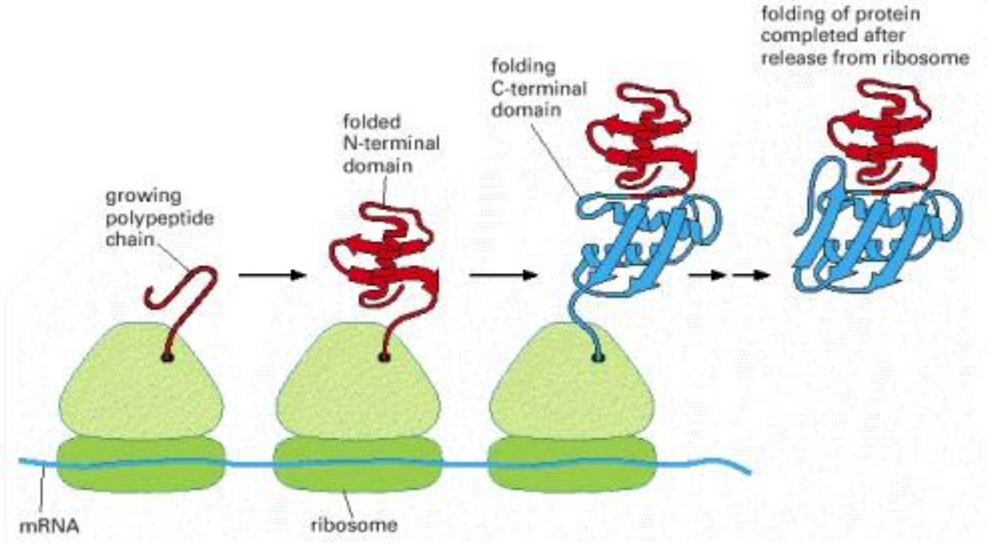
Protein Folding





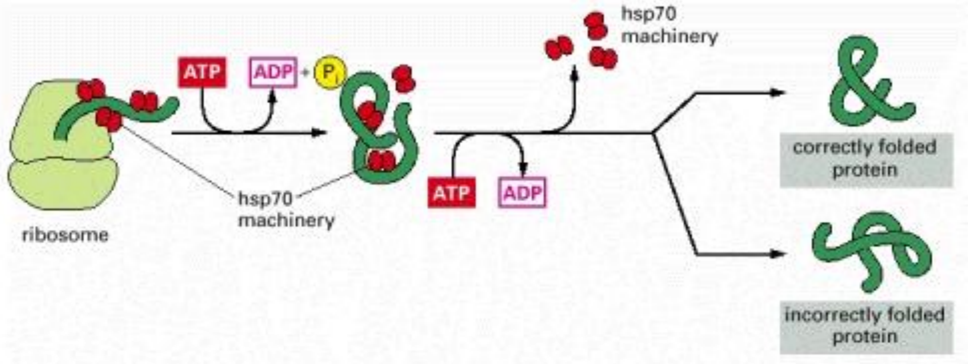
Co-translational Folding

- Polypeptide chain can acquire its secondary and tertiary structure as it emerges from a ribosome
- N-terminus folds first

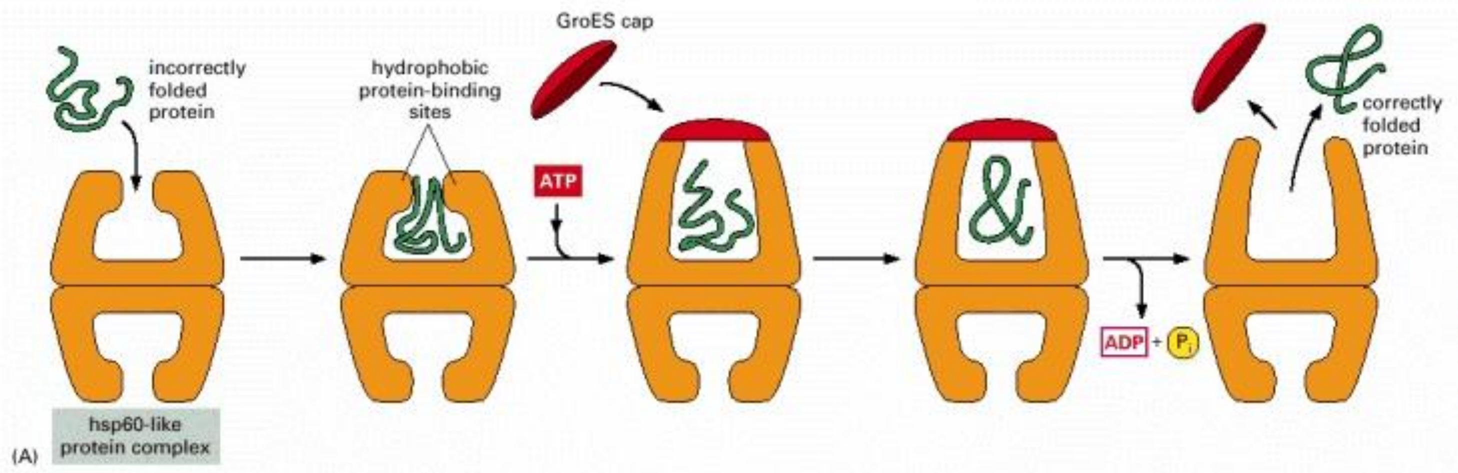


Molecular Chaperones

- Heat shock protein (hsp70)

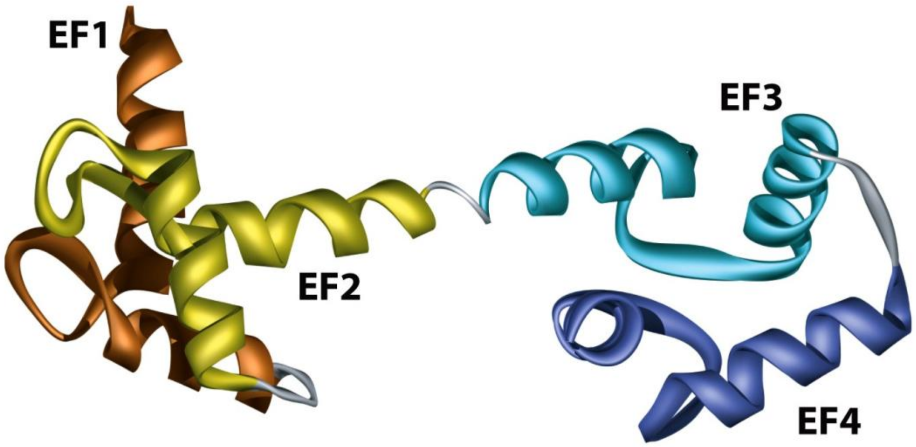


- Chaperonin



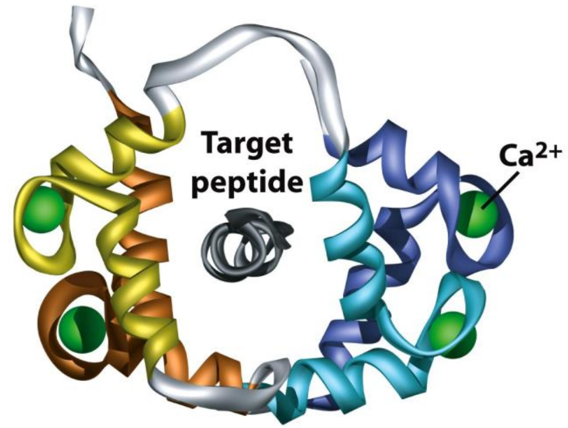
Functional Folding Domains

- e.g., EF hand is a helix-loop-helix domain in Ca^{2+} binding proteins
- Domains are similar amongst proteins



Calmodulin without calcium

Figure 3-31a
Molecular Cell Biology, Sixth Edition

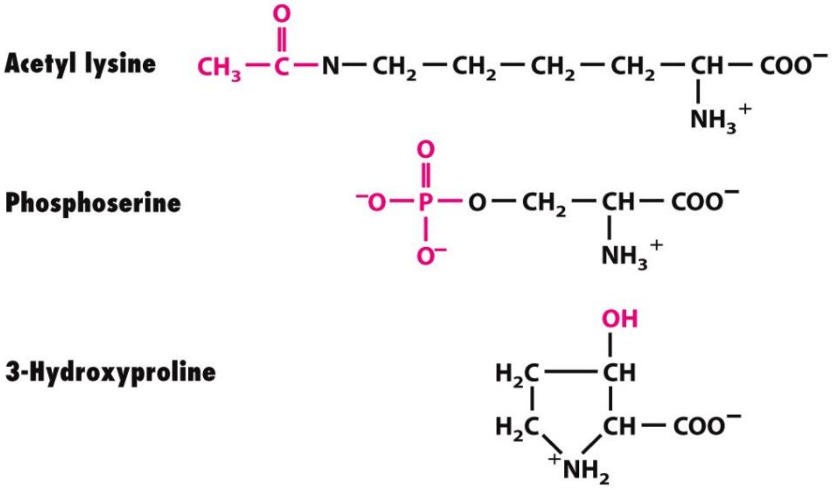


Ca^{2+}/ calmodulin bound to target peptide

Figure 3-31b
Molecular Cell Biology, Sixth Edition

Posttranslational Modifications

- Functional Groups
  - Phosphorylation
  - Acetylation
  - Hydroxylation
- Proteins
  - Ubiquitination
  - Sumoylation
- Glycans
- Lipids
- Disulfide bonds



Worksheet

- Identify the Dictator
  a. DNA sequence in a gene and amino acid sequence?
  b. amino acid sequence and structure?
  c. protein structure and protein function?
  d. DNA sequence in a gene and protein function?

Worksheet

- Identify the Dictator
  a. DNA sequence in a gene and amino acid sequence?
  b. amino acid sequence and structure?
  c. protein structure and protein function?
  d. DNA sequence in a gene and protein function?

Worksheet

- Identify the Dictator
  a. DNA sequence in a gene and amino acid sequence?
  b. amino acid sequence and structure?
  c. protein structure and protein function?
  d. DNA sequence in a gene and protein function?

Worksheet

- Identify the Dictator
  a. DNA sequence in a gene and amino acid sequence?
  b. amino acid sequence and structure?
  c. protein structure and protein function?
  d. DNA sequence in a gene and protein function?

Worksheet

- Identify the Dictator
  a. DNA sequence in a gene and amino acid sequence?
  b. amino acid sequence and structure?
  c. protein structure and protein function?
  d. DNA sequence in a gene and protein function?

Questions ?