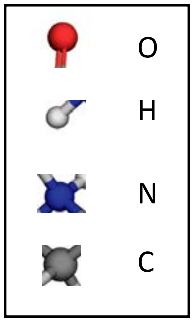
BMEG245 - Week 2-1
Dr. Nabi

Protein Structure and Function

Chapter 4
Essential Cell Biology, Alberts et al., 4th Edition, Garland Science.

Peptide bond



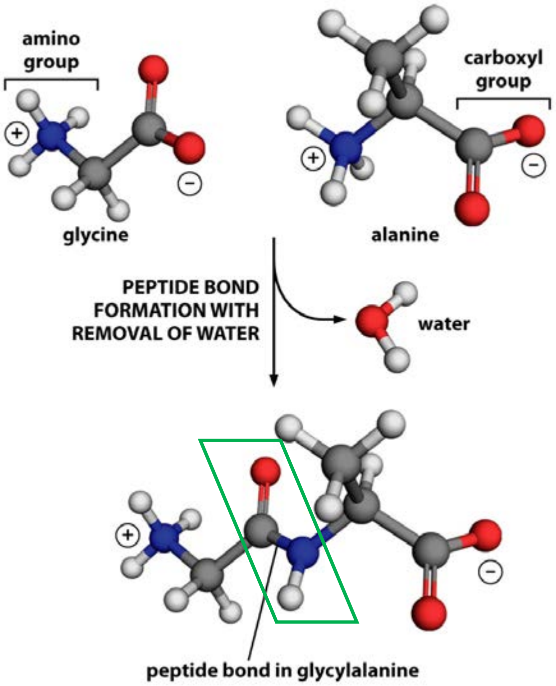


Figure 4-1 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Peptide bond

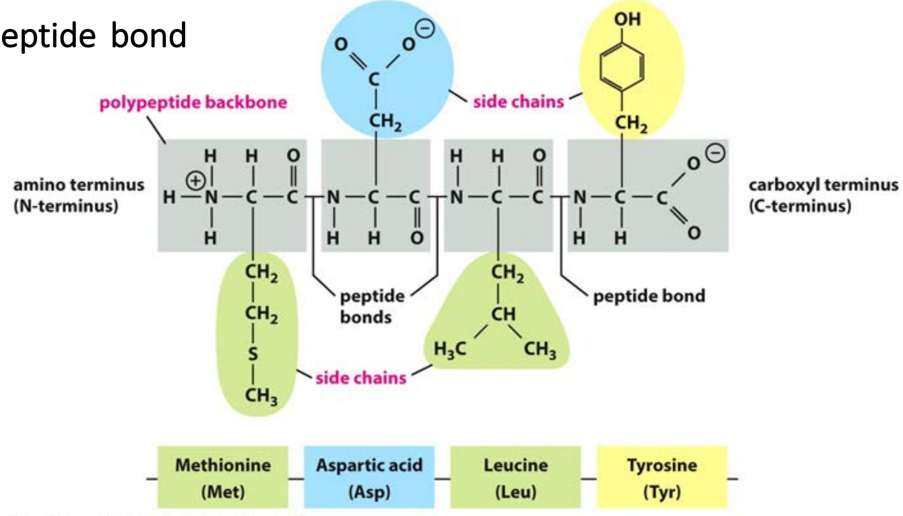
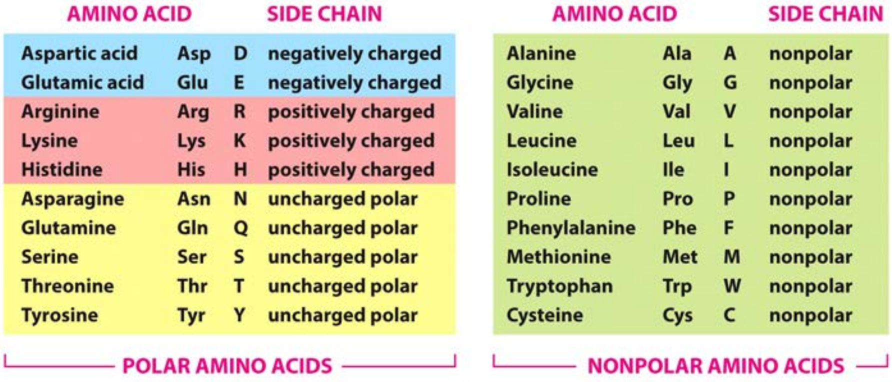


Figure 4-2 Essential Cell Biology, 4th ed. (© Garland Science 2014)

There are 20 possible amino acids at each site of this 4 amino acid long polypeptide so 20x20x20x20 = 160,000 different possible sequences

For a typical protein of 300 amino acids there are 20^{300} or **10^{390}** possible combinations!



AMINO ACID			SIDE CHAIN
Aspartic acid	Asp	D	negatively charged
Glutamic acid	Glu	E	negatively charged
Arginine	Arg	R	positively charged
Lysine	Lys	K	positively charged
Histidine	His	H	positively charged
Asparagine	Asn	N	uncharged polar
Glutamine	Gln	Q	uncharged polar
Serine	Ser	S	uncharged polar
Threonine	Thr	T	uncharged polar
Tyrosine	Tyr	Y	uncharged polar

POLAR AMINO ACIDS

AMINO ACID			SIDE CHAIN
Alanine	Ala	A	nonpolar
Glycine	Gly	G	nonpolar
Valine	Val	V	nonpolar
Leucine	Leu	L	nonpolar
Isoleucine	Ile	I	nonpolar
Proline	Pro	P	nonpolar
Phenylalanine	Phe	F	nonpolar
Methionine	Met	M	nonpolar
Tryptophan	Trp	W	nonpolar
Cysteine	Cys	C	nonpolar

NONPOLAR AMINO ACIDS

Figure 4-3 Essential Cell Biology, 4th ed. (© Garland Science 2014)

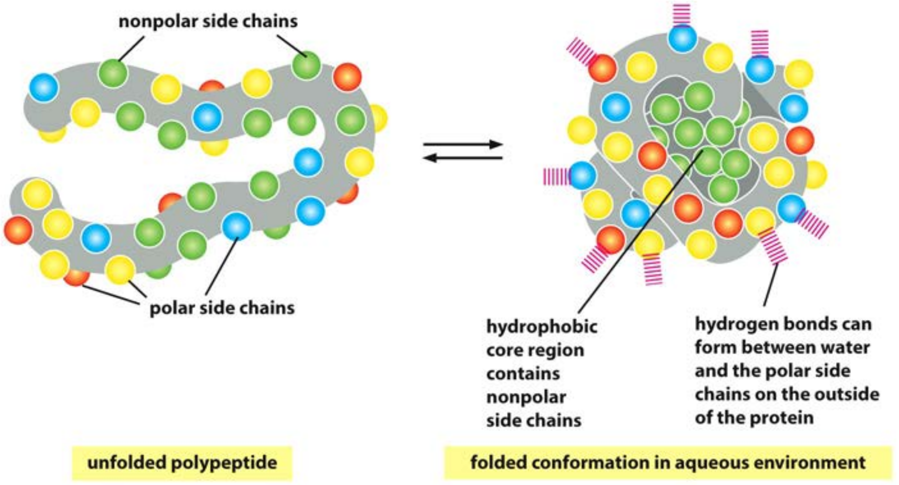
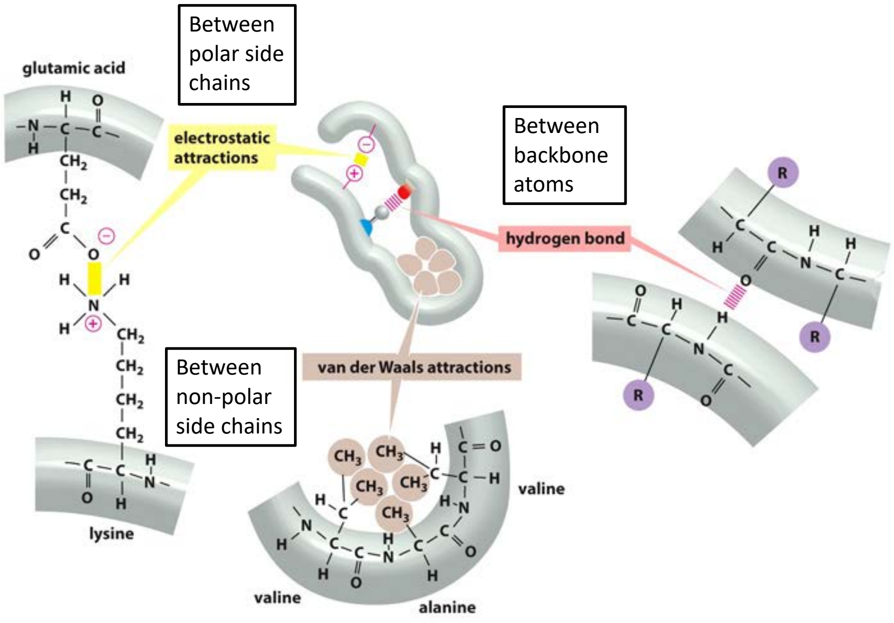


Figure 4-5 Essential Cell Biology, 4th ed. (© Garland Science 2014)

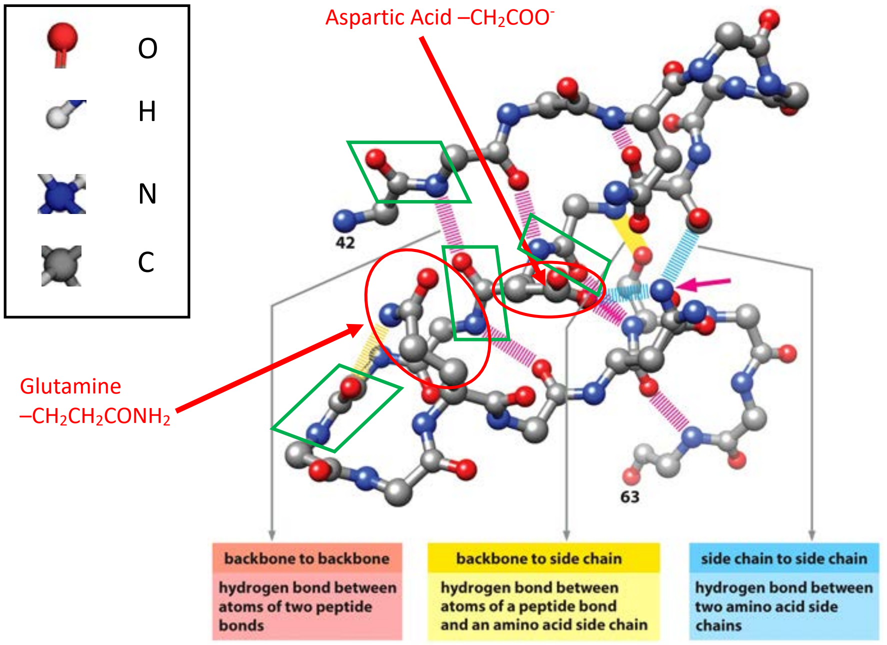


Between polar side chains

Between backbone atoms

Between non-polar side chains

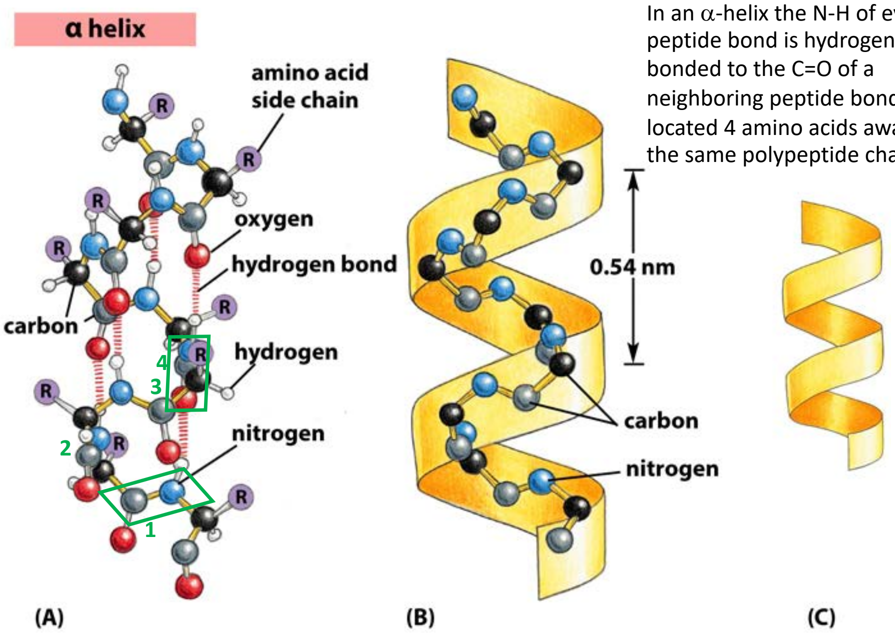
Figure 4-4 Essential Cell Biology, 4th ed. (© Garland Science 2014)



Aspartic Acid $-CH_2COO^-$

Glutamine $-CH_2CH_2CONH_2$

Figure 4-6 Essential Cell Biology, 4th ed. (© Garland Science 2014)



In an α-helix the N-H of every peptide bond is hydrogen bonded to the C=O of a neighboring peptide bond located 4 amino acids away on the same polypeptide chain

Figure 4-13 (part 1 of 2) Essential Cell Biology, 4th ed. (© Garland Science 2014)

https://vimeo.com/garlandscience30308032/review/188833213/4e486e1eb3

Transmembrane domains of proteins are often alpha helices that present their non-polar side chains to the outside of the helix.

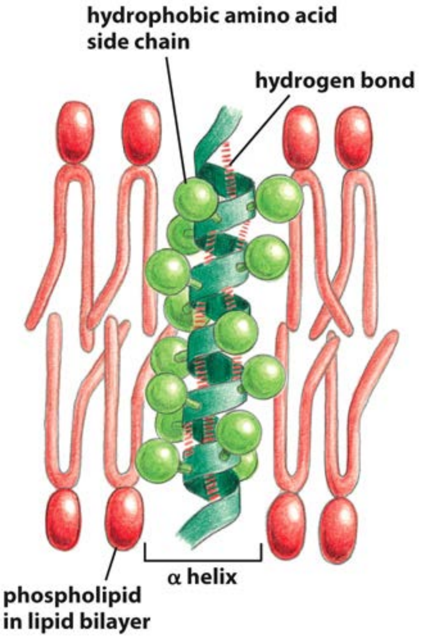


Figure 4-15 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Coiled-coils form when 2-3 alpha helices with most of their non-polar side chains to one side twist around each other forming stable rod-like structures.

An example is keratin

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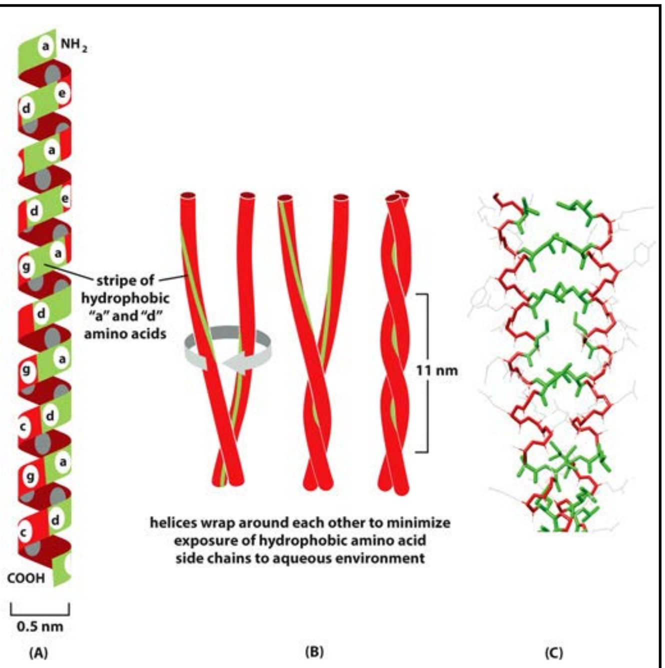


Figure 4-16 Essential Cell Biology, 4th ed. (© Garland Science 2014)

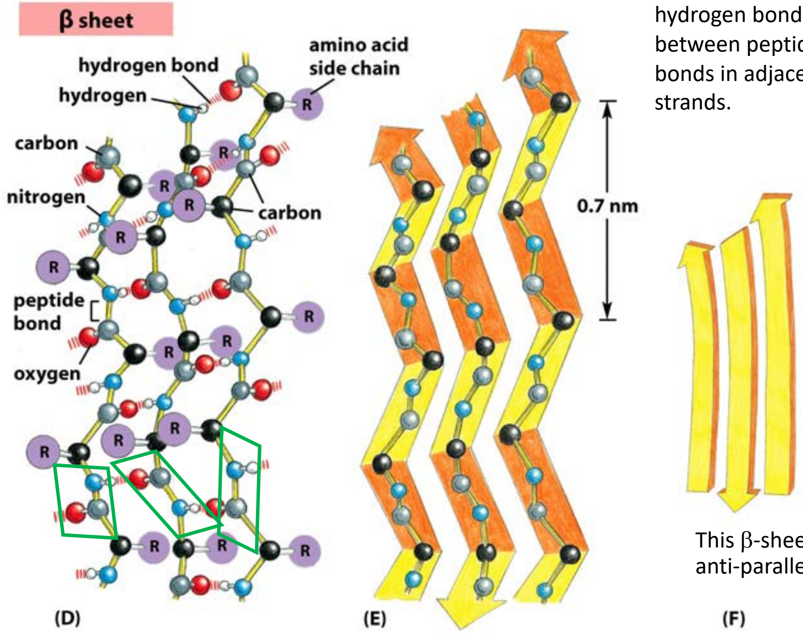
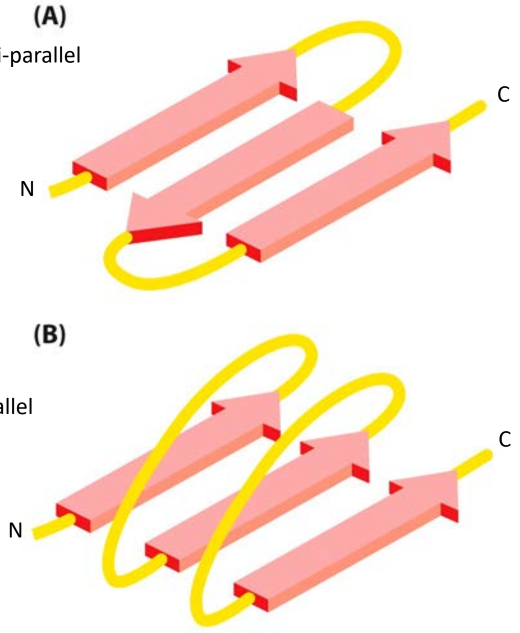


Figure 4-13 (part 2 of 2) Essential Cell Biology, 4th ed. (© Garland Science 2014)

A β-sheet forms when hydrogen bonds form between peptide bonds in adjacent strands.

This β-sheet is anti-parallel

β-sheets



Anti-parallel

Parallel

Figure 4-17 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Ribbon model:
Arrows point towards C-terminus of polypeptide chain
B-sheets are linked by unstructured "intrinsically disordered regions"

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Proteins can be composed of separate functional domains
In the same polypeptide

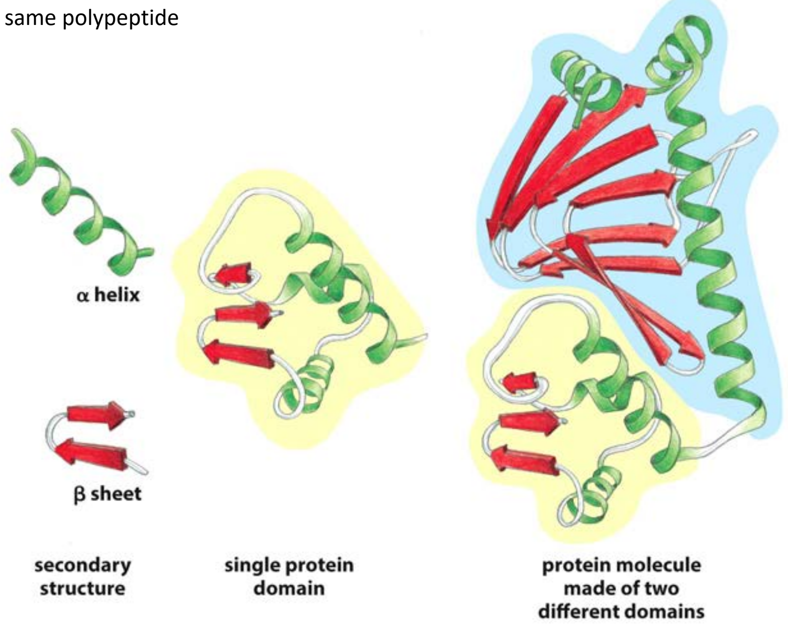


Figure 4-19 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Unstructured regions of polypeptides
can bind to protein domains and link
binding domains

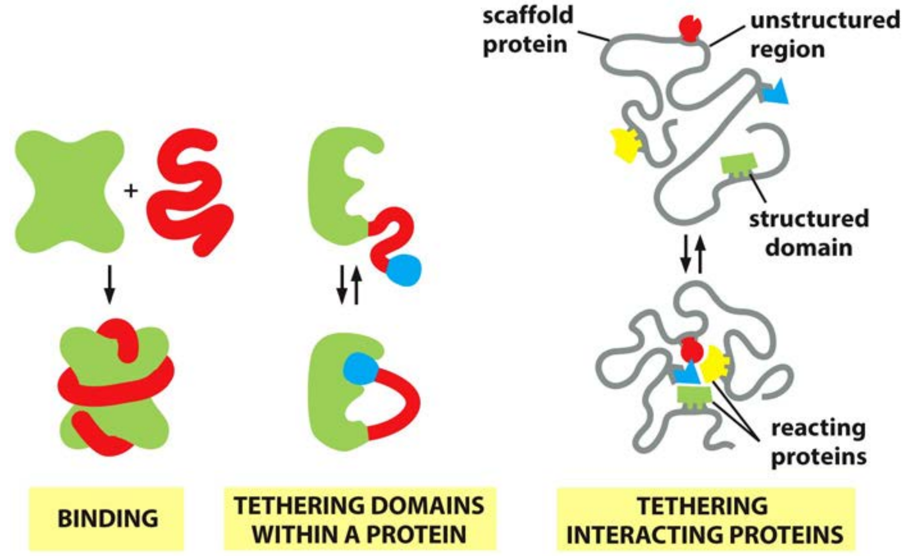


Figure 4-21 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Protein structure

Primary structure:	amino acid sequence
Secondary structure:	α-helices and β-sheets
Tertiary structure:	the full three dimensional conformation of the protein including random coils loops and folds…
Quarternary structure:	complete structure of a protein formed of more than one polypeptide chain.

But only a few of the **10^{390}** possible combinations of amino acids in polypeptides actually form stable well-defined three-dimensional conformations.

These are very highly conserved between species and form families of proteins with similar if distinct functions.

Serine proteases are a family of proteolytic enzymes.
While only the green highlighted regions are conserved the overall protein conformation is very similar but the two enzymes prefer different substrates (active site in red)

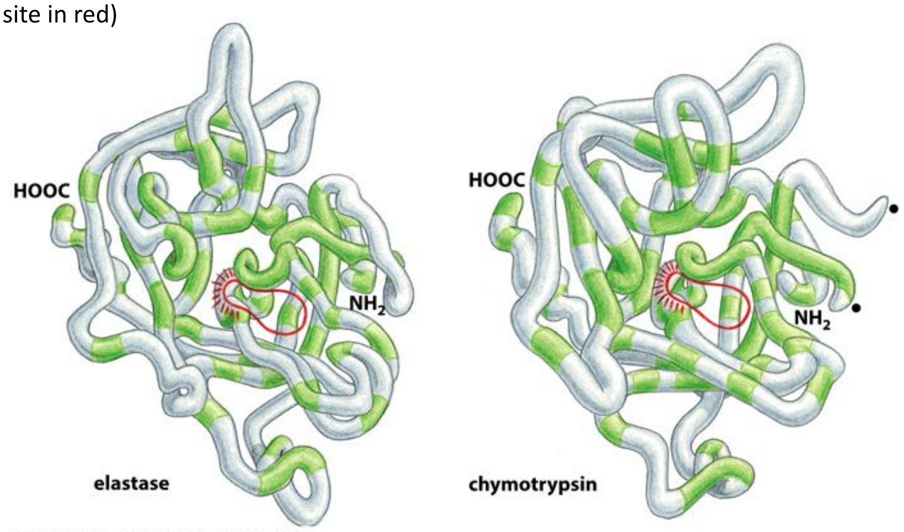
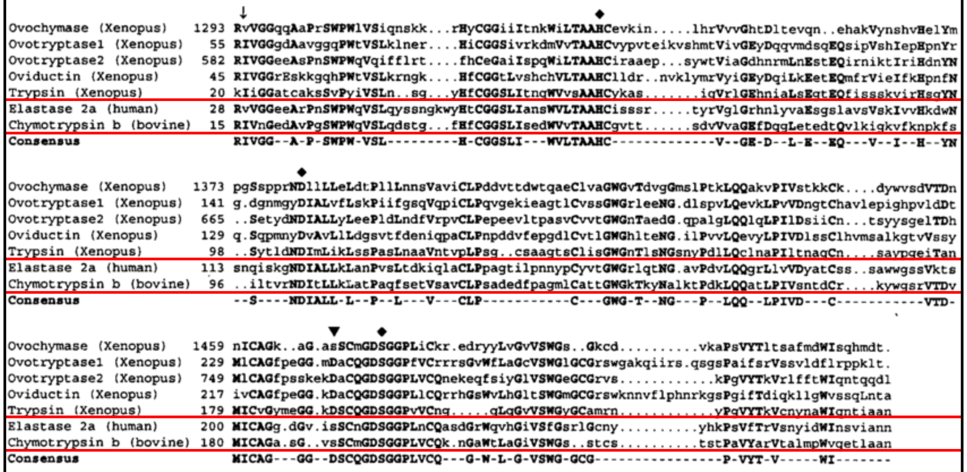


Figure 4-22 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Elastase: cleaves peptide bonds after small uncharged amino acids

Chymotrypsin: cleaves peptide bonds after aromatic or bulky side chains

Serine proteases are a family of proteolytic enzymes.
While only the green highlighted regions are conserved the overall protein conformation is very similar but the two enzymes prefer different substrates (active site in red)



```
                              ↓                                            ◆
Ovochymase (Xenopus)    1293 RvVGGqqAaPrSWPWlVSiqnskk...rHyCGGiiItnkWiLTAAHCevkin.....lhrVvvGhtDltevqn..ehakVynshvHelYm
Ovotryptase1 (Xenopus)    55 RIVGGgdAavggqPWtVSLklner....HiCGGSivrkdmVvTAAHCvypvteikvshmtVivGEyDqqvmdsqEQsipVshIepHpnYr
Ovotryptase2 (Xenopus)   582 RIVGGeeAsPnSWPWqVqifflrt....fhCeGaiIspqWiLTAAHCiraaep...sywtViaGdhnrmLnEstEQirniktIriHdnYN
Oviductin (Xenopus)       45 RIVGGrEskkgqhPWtVSLkrngk....HfCGGtLvshchVLTAAHClldr..nvklymrVyiGEyDqiLkEetEQmfrVieIfkHpnfN
Trypsin (Xenopus)         20 kIiGGatcaksSvPyiVSLn..sq...yHfCGGSLItnqWVvsAAHCykas.......iqVrlGEhniaLsEqtEQfissskvirHsqYN
Elastase 2a (human)       28 RvVGGeeArPnSWPWqVSLqyssngkwyHtCGGSLIansWVLTAAHCisssr.....tyrVglGrhnlyvaEsgslavsVskIvvHkdwN
Chymotrypsin b (bovine)   15 RIVnGedAvPgSWPWqVSLqdstg...fHfCGGSLIsedWVvTAAHCgvtt......sdvVvaGEfDqgLetedtQvlkiqkvfknpkfs
Consensus                    RIVGG--A-P-SWPW-VSL--------H-CGGSLI---WVLTAAHC------------V--GE-D--L-E--EQ---V--I--H--YN

                                     ◆
Ovochymase (Xenopus)    1373 pgSspprNDllLLeLdtPllLnnsVaviCLPddvttdwtqaeClvaGWGvTdvgGmslPtkLQQakvPIVstkkCk....dywvsdVTDn
Ovotryptase1 (Xenopus)   141 g.dgnmgyDIALvfLskPiifgsqVqpiCLPqvgekieagtlCvssGWGrleeNG.dlspvLQevkLPvVDngtChavlepighpvldDt
Ovotryptase2 (Xenopus)   665 ..SetydNDIALLyLeePldLndfVrpvCLPepeevltpasvCvvtGWGnTaedG.qpalgLQQlqLPIlDsiiCn...tsyysgelTDh
Oviductin (Xenopus)      129 q.SqpmnyDvAvLlLdgsvtfdeniqpaCLPnpddvfepgdlCvtlGWGhlteNG.ilPvvLQevyLPIVDlssClhvmsalkgtvVssy
Trypsin (Xenopus)         98 ..SytldNDImLikLssPasLnaaVntvpLPsg..csaagtsClisGWGnTlsNGsnyPdlLQclnaPIltnaqCn....saypgeiTan
Elastase 2a (human)      113 snqiskgNDIALLkLanPvsLtdkiqlaCLPpagtilpnnypCyvtGWGrlqtNG.avPdvLQQgrLlvVDyatCss..sawwgssVkts
Chymotrypsin b (bovine)   96 ..iltvrNDItLLkLatPaqfsetVsavCLPsadedfpagmlCattGWGkTkyNalktPdkLQQatLPIVsntdCr....kywgsrVTDv
Consensus                    --S----NDIALL-L--P--L---V---CLP-----------C---GWG-T--NG---P--LQQ--LPIVD---C-----------VTD-

                                         ▼     ◆
Ovochymase (Xenopus)    1459 nICAGk..aG.asSCmGDSGGPLiCkr.edryyLvGvVSWGs..Gkcd..........vkaPsVYTltsafmdWIsqhmdt.
Ovotryptase1 (Xenopus)   229 MlCAGfpeGG.mDaCQGDSGGPfVCrrrsGvWfLaGcVSWGlGCGrswgakqiirs.qsgsPaifsrVssvldflrppklt.
Ovotryptase2 (Xenopus)   749 MlCAGfpsskekDaCQGDSGGPLVCQnekeqfsiyGlVSWGeGCGrvs............kPgVYTkVrlfftWIqntqqdl
Oviductin (Xenopus)      217 ivCAGfpeGG.kDaCQGDSGGPLlCQrrhGsWvLhGltSWGmGCGrswknnvflphnrkgsPgifTdiqkllgWvssqLnta
Trypsin (Xenopus)        179 MICvGymeGG.kDSCQGDSGGPvVCnq.....qLqGvVSWGyGCamrn............yPgVYTkVcnynaWIqntiaan
Elastase 2a (human)      200 MICAGg.dGv.isSCnGDSGGPLnCQasdGrWqvhGiVSfGsrlGcny..........yhkPsVfTrVsnyidWInsviann
Chymotrypsin b (bovine)  180 MICAGa.sG..vsSCmGDSGGPLVCQk.nGaWtLaGiVSWGs..stcs..........tstPaVYarVtalmpWvqetlaan
Consensus                    MICAG---GG--DSCQGDSGGPLVCQ---G-W-L-G-VSWG-GCG---------------P-VYT-V-----WI-------
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Elastase: cleaves peptide bonds after small uncharged amino acids

Chymotrypsin: cleaves peptide bonds after aromatic or bulky side chains

Identical protein subunits can assemble into various complex structures

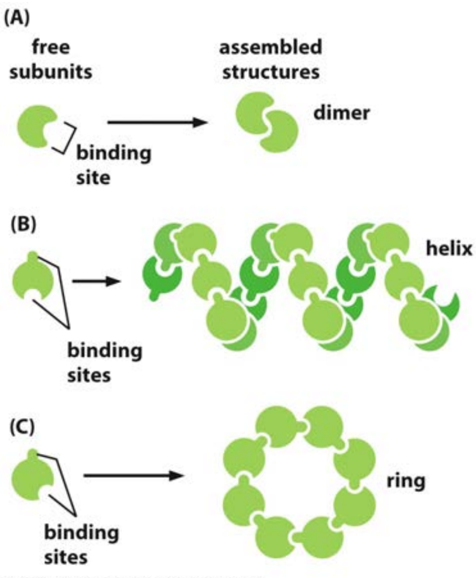
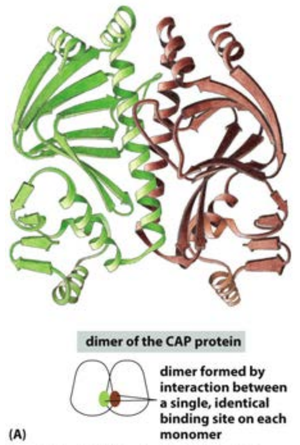


Figure 4-25 Essential Cell Biology, 4th ed. (© Garland Science 2014)



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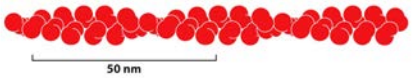
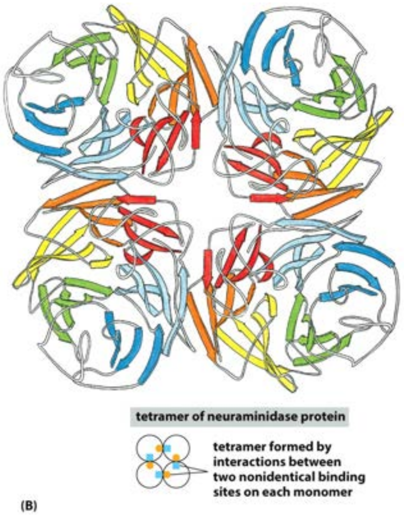


Figure 4-26 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Actin filaments are helical array of actin monomers

Protein oligomers can form from identical subunits or different subunits



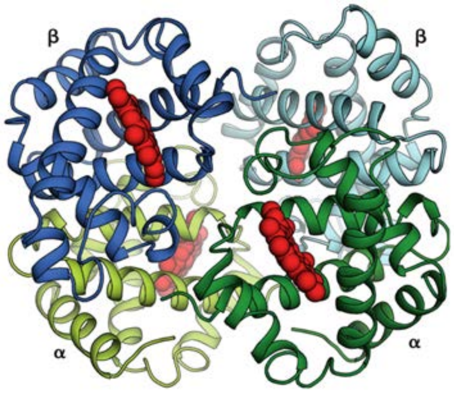


Figure 4-24 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Hemoglobin is a tetramer formed of two copies of α-globin and two copies of β-globin

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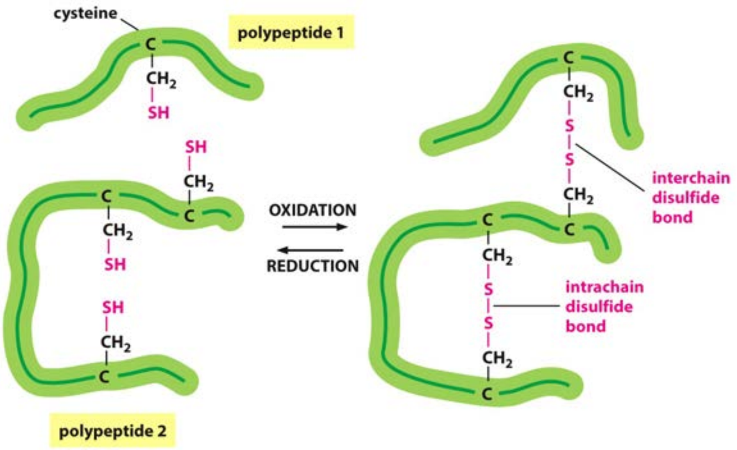
Disulfide bonds are covalent linkages between cysteine amino acid side chains on the same polypeptide or different polypeptides



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Fibrous proteins form from extended polypeptide chains (collagen)
or from disulfide crosslinking of smaller polypeptides (elastin)

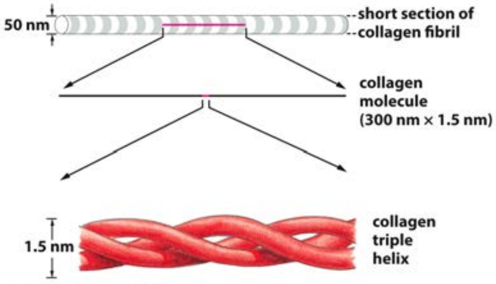


Figure 4-29a Essential Cell Biology, 4th ed. (© Garland Science 2014)

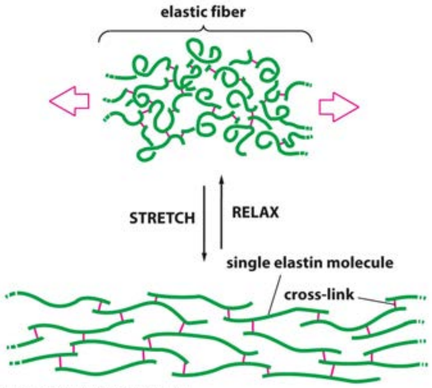


Figure 4-29b Essential Cell Biology, 4th ed. (© Garland Science 2014)

Protein-protein and protein-ligand interactions are highly specific and depend on the folding of a sequence of amino acid side chains in three-dimensional space to form a binding site into which the ligand or polypeptide chain will fit.

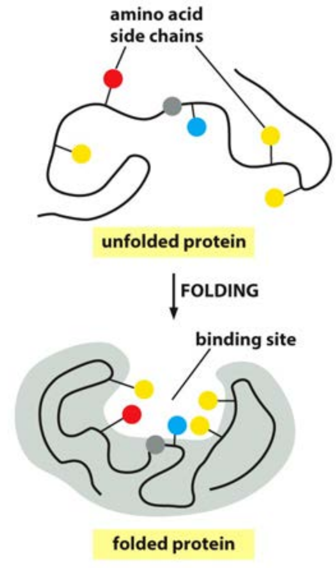


Figure 4-32a Essential Cell Biology, 4th ed. (© Garland Science 2014)

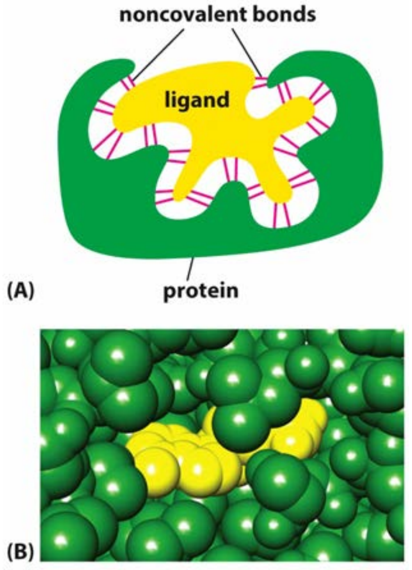


Figure 4-31 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Binding site
Polypeptide folding allows 5 amino acid side chains and one peptide bond amino group to form hydrogen bonds and electrostatic interactions with cAMP

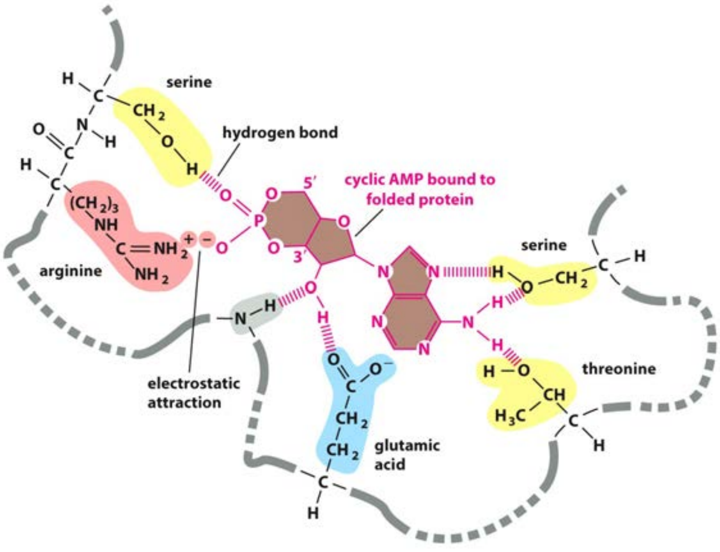
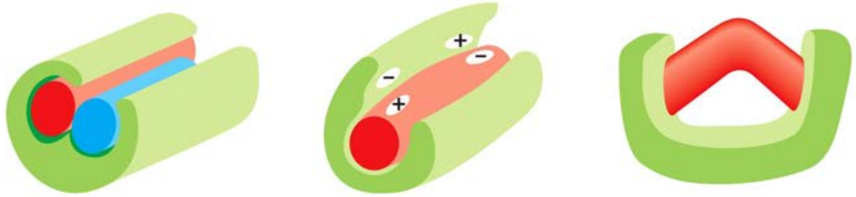


Figure 4-32b Essential Cell Biology, 4th ed. (© Garland Science 2014)

Enzymes are catalysts – speeding up reactions by a factor of 1,000,000 or more
See Table 4-1 for a list of common functional classes of enzymes

Enzymes promote a reaction in different ways



(A) enzyme binds to two substrate molecules and orients them precisely to encourage a reaction to occur between them

(B) binding of substrate to enzyme rearranges electrons in the substrate, creating partial negative and positive charges that favor a reaction

(C) enzyme strains the bound substrate molecule, forcing it toward a transition state to favor a reaction

Figure 4-36 Essential Cell Biology, 4th ed. (© Garland Science 2014)

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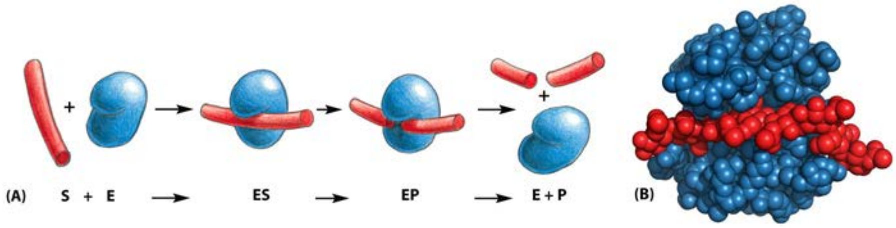
Lysosyme is an enzyme that cleaves a polysaccharide chain



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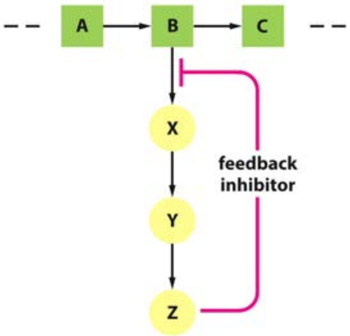
https://vimeo.com/garlandscience30308032/review/188833208/9d6dee2947

Feedback inhibition
A substrate of a biosynthetic or metabolic pathway inhibits an upstream enzyme



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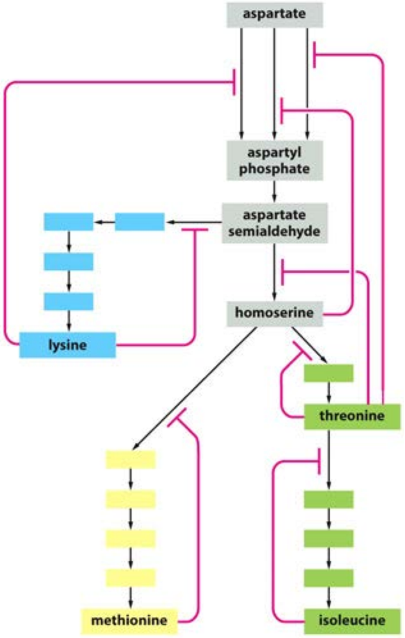


Figure 4-39 Essential Cell Biology, 4th ed. (© Garland Science 2014)

Protein phosphorylation covalently adds a charge phosphate group to **serine**, **threonine** and **tyrosine** side chains altering protein conformation and either increasing or decreasing protein activity.

Kinase – adds phosphate group
Phosphatase – removes phosphate group

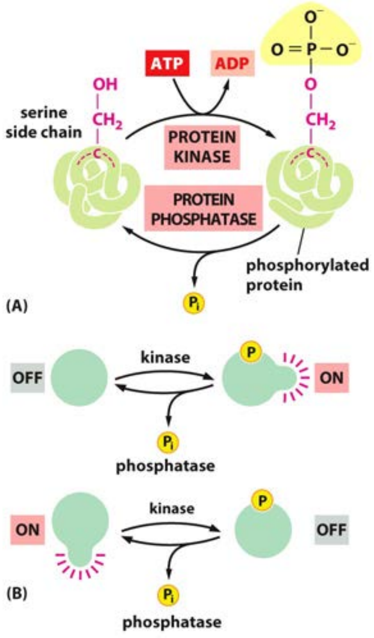


Figure 4-42 Essential Cell Biology, 4th ed. (© Garland Science 2014)

GTP binding proteins function as molecular switches

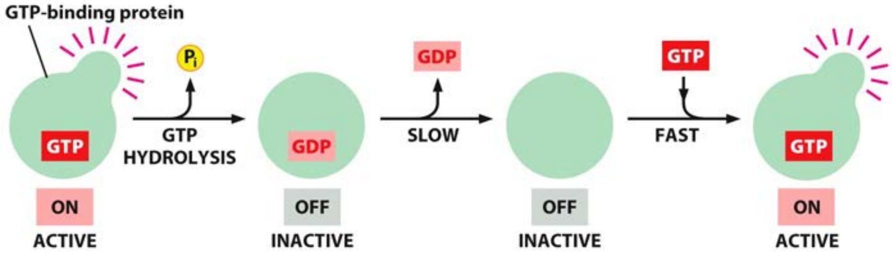


Figure 4-44 Essential Cell Biology, 4th ed. (© Garland Science 2014)

A motor protein uses ATP hydrolysis to transition between three conformations and move unidirectionally along a cytoskeletal filament

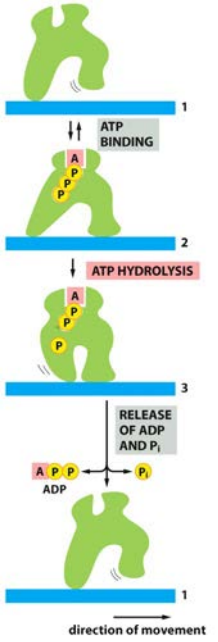
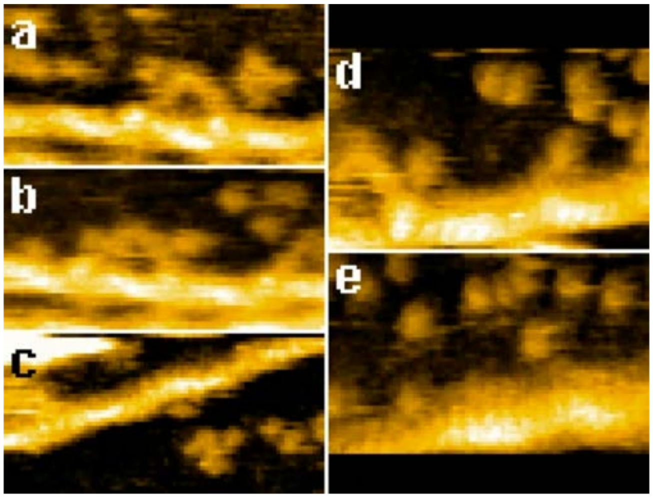
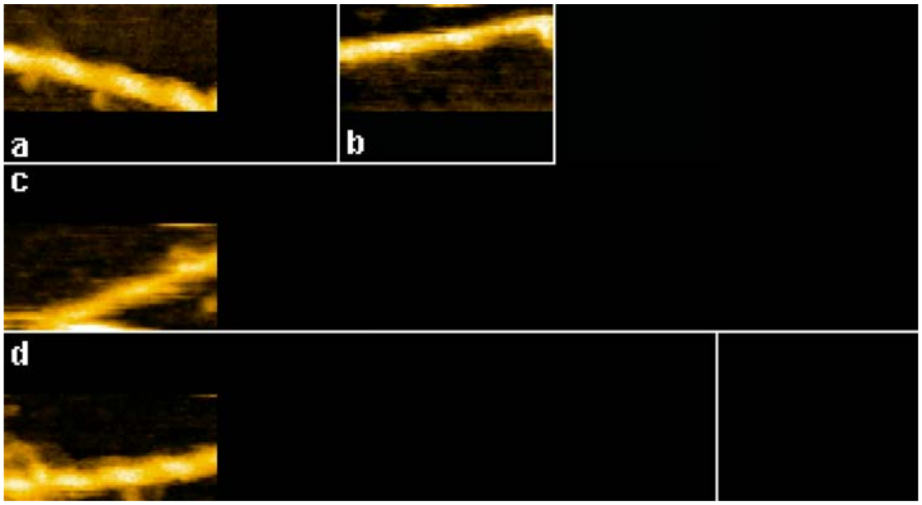


Figure 4-46 Essential Cell Biology, 4th ed. (© Garland Science 2014)

High speed atomic force microscopy shows myosin V molecules walking along actin tracks, using high-speed atomic force microscopy.



Video imaging of walking myosin V by high-speed atomic force microscopy
Noriyuki Kodera, **Daisuke Yamamoto**, **Ryoki Ishikawa** & **Toshio Ando**
Nature 468, 72–76 (04 November 2010) doi:10.1038/nature09450



Summary

Polypeptides:	protein folding
Secondary Structure:	alpha helix beta sheets
Tertiary structure:	proteins have multiple conserve functional domains
Quartenary structure:	proteins assemble into different complex structures

Protein interactions and enzymes