# Proteínas

- Al estudiar la actividad bioquímica o eléctrica de la célula, o al mirar a través del microscopio estamos en esencia observando proteínas,

- Constituyen la mayoría del peso seco de la célula
- No sólo son Bloques de construcción importantes de la célula sino que,
- Llevan a cabo casi todas las funciones celulares
  - Enzimas proveen las superficies moleculares en la célula que promueven muchas reacciones químicas
  - Las proteínas embebidas en la membrana celular forman canales y bombas que controlan el pasaje de moléculas pequeñas fuera y dentro de esta.

- Llevan mensajes de una célula a otra
- Máquinas moleculares pequeñas con partes movibles:
  - Kinesina: empuja organelos a través del citoplasma
  - Topoisimerasa: desenreda nudos en la molécula de DNA
- Proteínas especializadas
  - Anticuerpos, toxinas, hormonas, fibras elásticas

- Para entender como los genes trabajan, como el músculo se contrae y como los nervios conducen electricidad hay que tener un profundo entendimiento de las **Proteínas**

## Forma y estructura de las proteínas

- Moléculas mas complejas estructuralmente y funcionalmente
- La estructura y función de cada proteína ha sido desarrollada y afinada a través de millones de años de evolución

## La forma de la proteína es especificada por su secuencia de aminoácidos

- Una proteína es hecha de una larga cadena de aminoácidos unidos por medio de enlaces covalentes, enlace peptídico
- También conocidas como polipéptidos
- Miles de proteínas son conocidas cada una con su secuencia única de aminoácidos

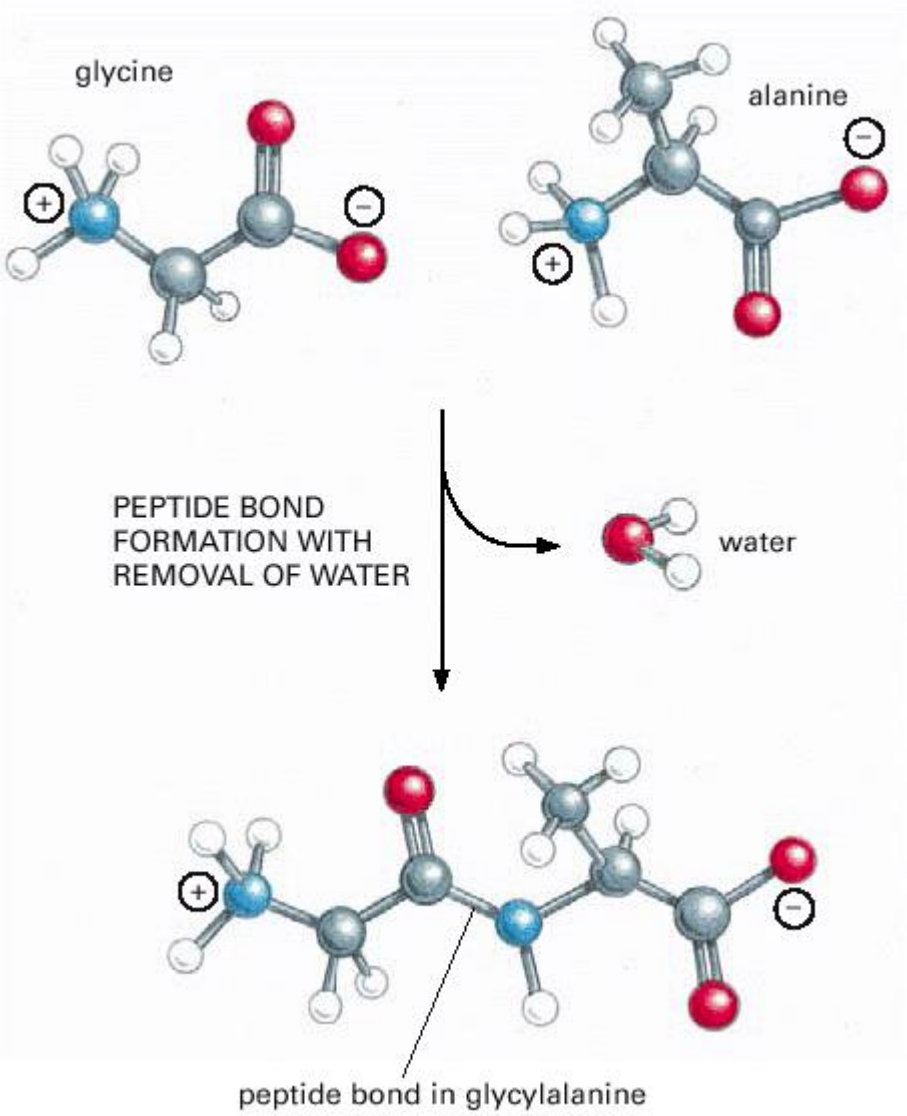



**Figure 3-1. A peptide bond.** This covalent bond forms when the carbon atom from the carboxyl group of one amino acid shares electrons with the nitrogen atom *(blue)* from the amino group of a second amino acid. As indicated, a molecule of water is lost in this condensation reaction.

- La *secuencia repetitiva* de átomos a lo largo de la cadena de aminoácidos se conoce como: esqueleto del polipéptido (polypeptide backbone)
- Adherida a esta secuencia repetitiva que no forman parte en la formación del enlace peptídico y que proveen de las propiedades únicas de cada aminoácido están: las cadenas laterales o funcionales
- De acuerdo a su cadena lateral hay diferentes tipos aminoácidos
  - Ácidos
  - Básicos
  - Polares sin carga
  - No polares

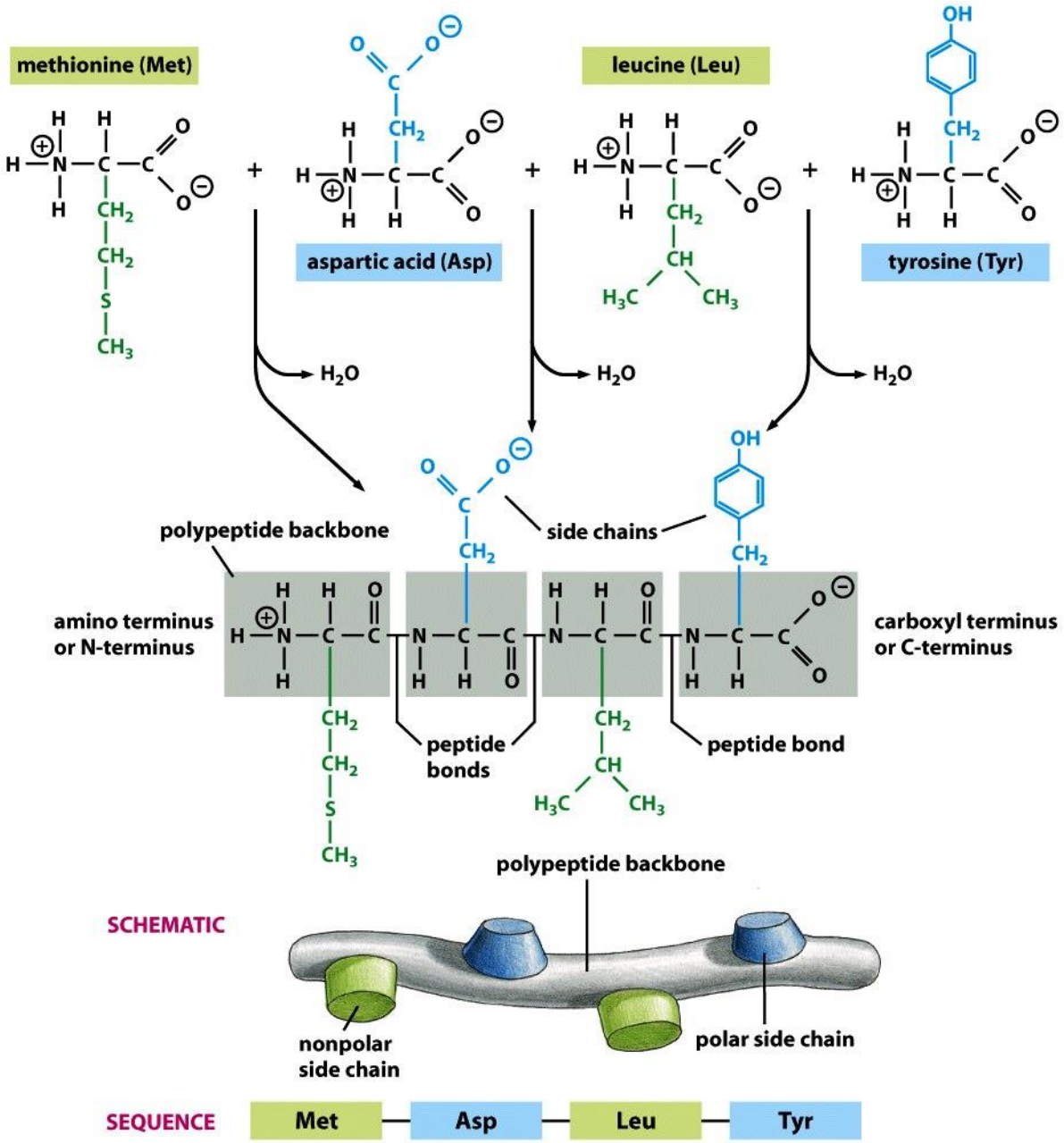



**Figure 3-2. The structural components of a protein.** A protein consists of a polypeptide backbone with attached side chains. Each type of protein differs in its sequence and number of amino acids; therefore, it is the sequence of the chemically different side chains that makes each protein distinct. The two ends of a polypeptide chain are chemically different: the end carrying the free amino group ($NH_3^+$, also written $NH_2$) is the amino terminus, or N-terminus, and that carrying the free carboxyl group (COO , also written COOH) is the carboxyl terminus or C-terminus. The amino acid sequence of a protein is always presented in the N-to-C direction, reading from left to right

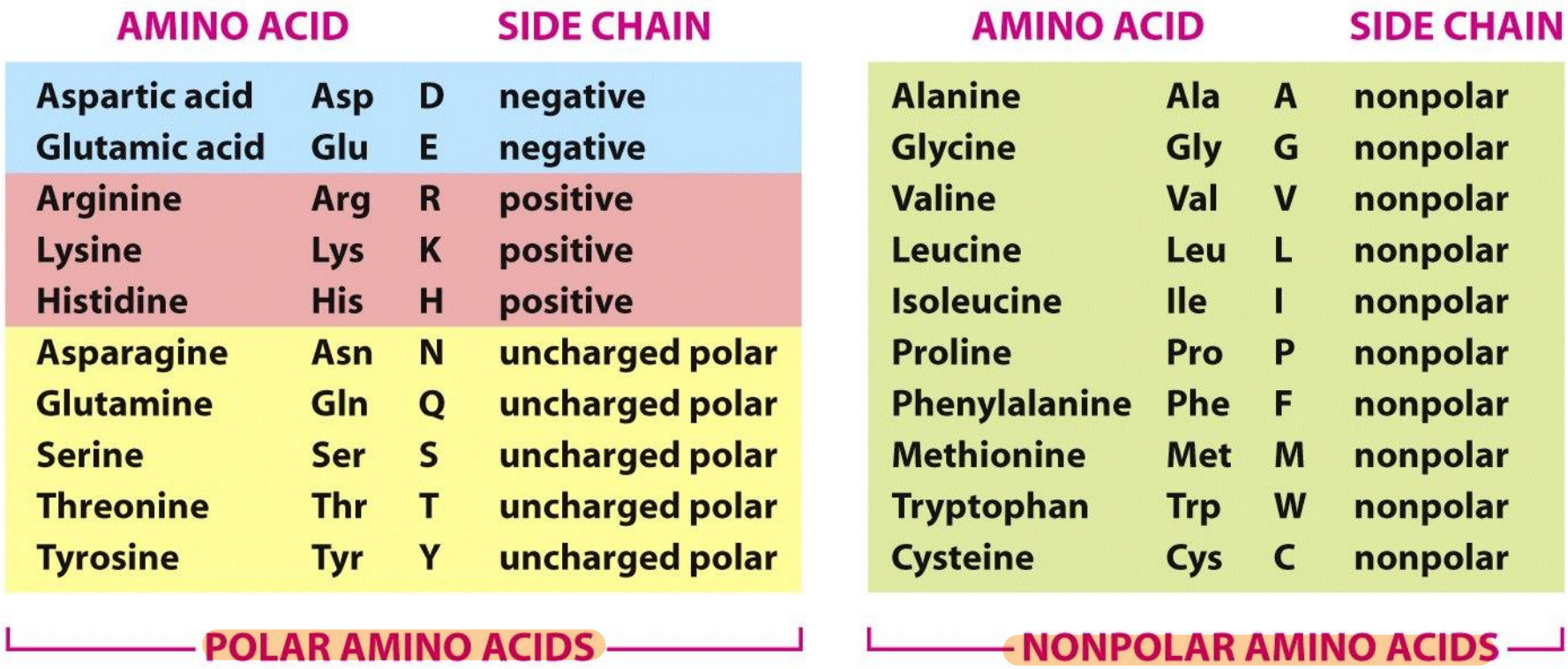
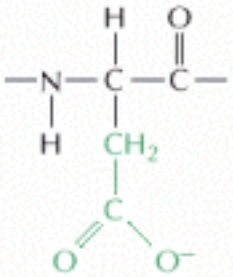



**Figure 3-3. The 20 amino acids found in proteins.** Both three-letter and one-letter abbreviations are listed. As shown, there are equal numbers of polar and nonpolar side chains. For their atomic structures

## ACIDIC SIDE CHAINS

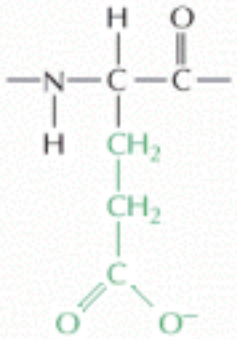
**aspartic acid**

(Asp, or D)



**glutamic acid**

(Glu, or E)



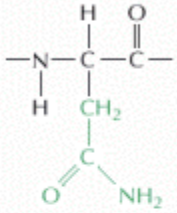
carga -

carga -

## UNCHARGED POLAR SIDE CHAINS

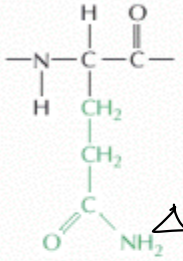
**asparagine**

(Asn, or N)



**glutamine**

(Gln, or Q)

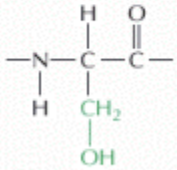


polar sin carga.

Although the amide N is not charged at neutral pH, it is polar.

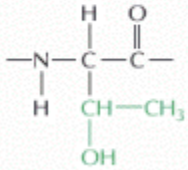
**serine**

(Ser, or S)



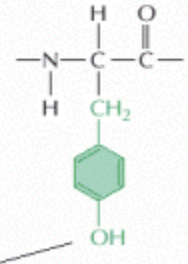
**threonine**

(Thr, or T)



**tyrosine**

(Tyr, or Y)



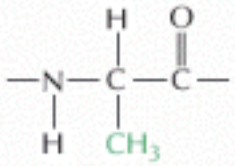
The –OH group is polar.

## NONPOLAR SIDE CHAINS

C.A.A. apolar, no polar)

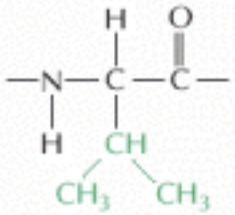
**alanine**

(Ala, or A)



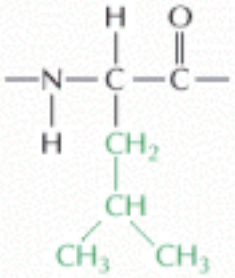
**valine**

(Val, or V)



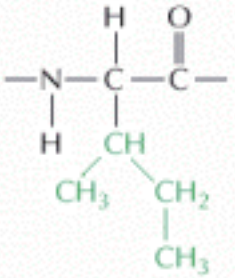
**leucine**

(Leu, or L)



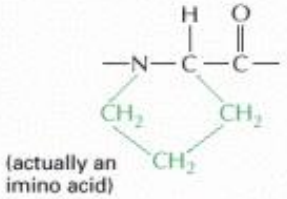
**isoleucine**

(Ile, or I)



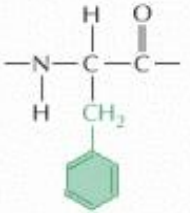
**proline**

(Pro, or P)



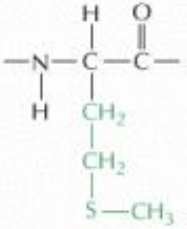

**phenylalanine**

(Phe, or F)



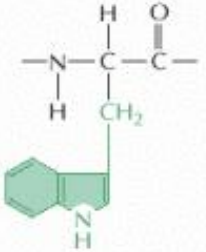
**methionine**

(Met, or M)



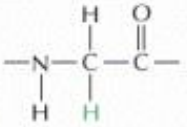
**tryptophan**

(Trp, or W)



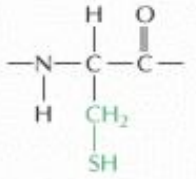
**glycine**

(Gly, or G)



**cysteine**

(Cys, or C)



Disulfide bonds can form between two cysteine side chains in proteins.

La conformación de una proteína puede estar limitada por:

- Atomos se comportan como si fueran esferas de un radio definido (van der Waals radius). La limitación de que dos átomos no se superpongan limita los posibles ángulos de enlace en una cadena polipeptídica
- Además otras interacciones estéricas (relacionado al arreglo espacial de átomos en la mol) limitan la variedad de los arreglos tridimensionales de los átomos que son posibles: Conformación.
- Sin embargo la cadena flexible de una proteína todavía se puede plegar en una variedad enorme de formas

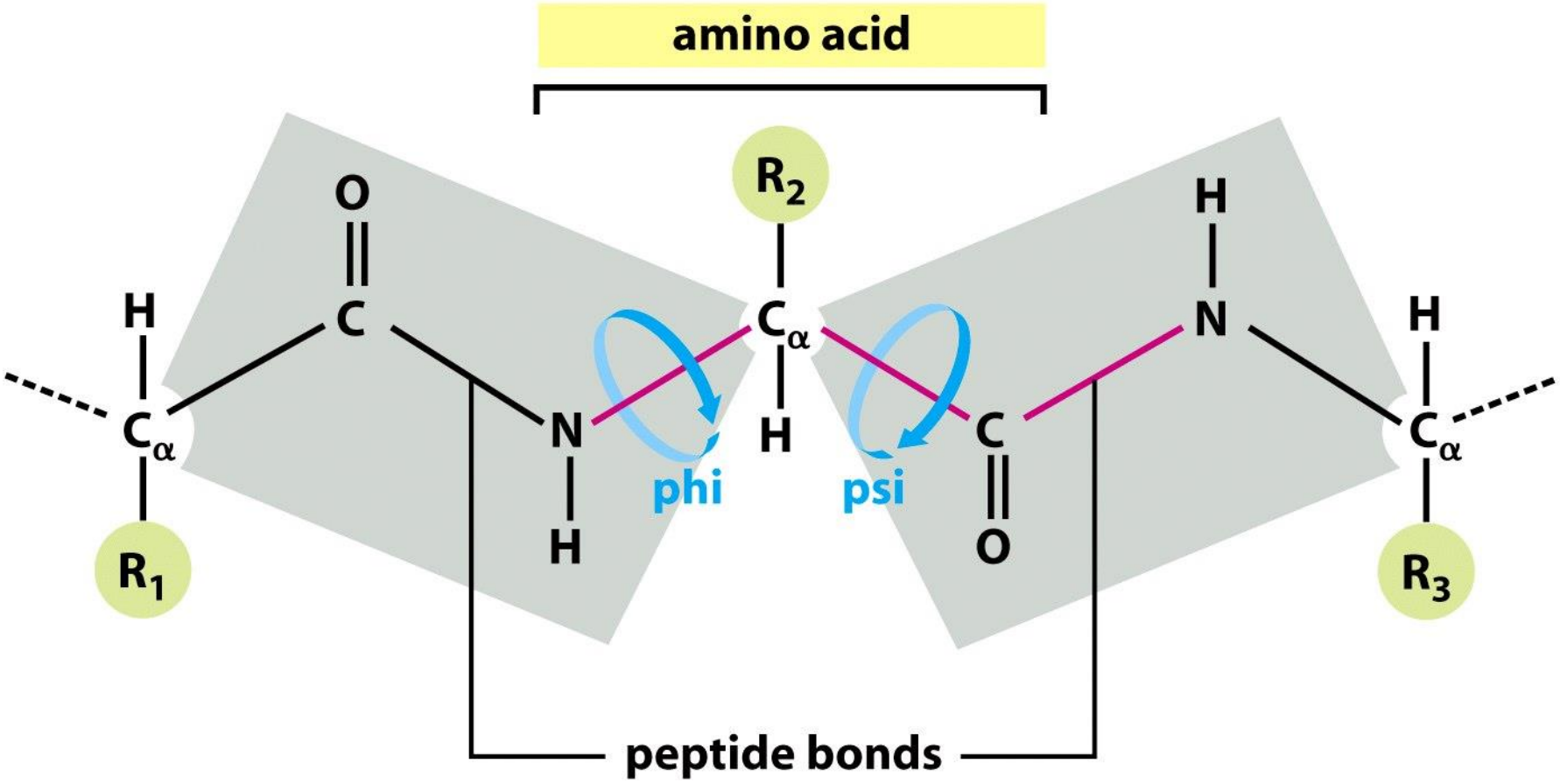
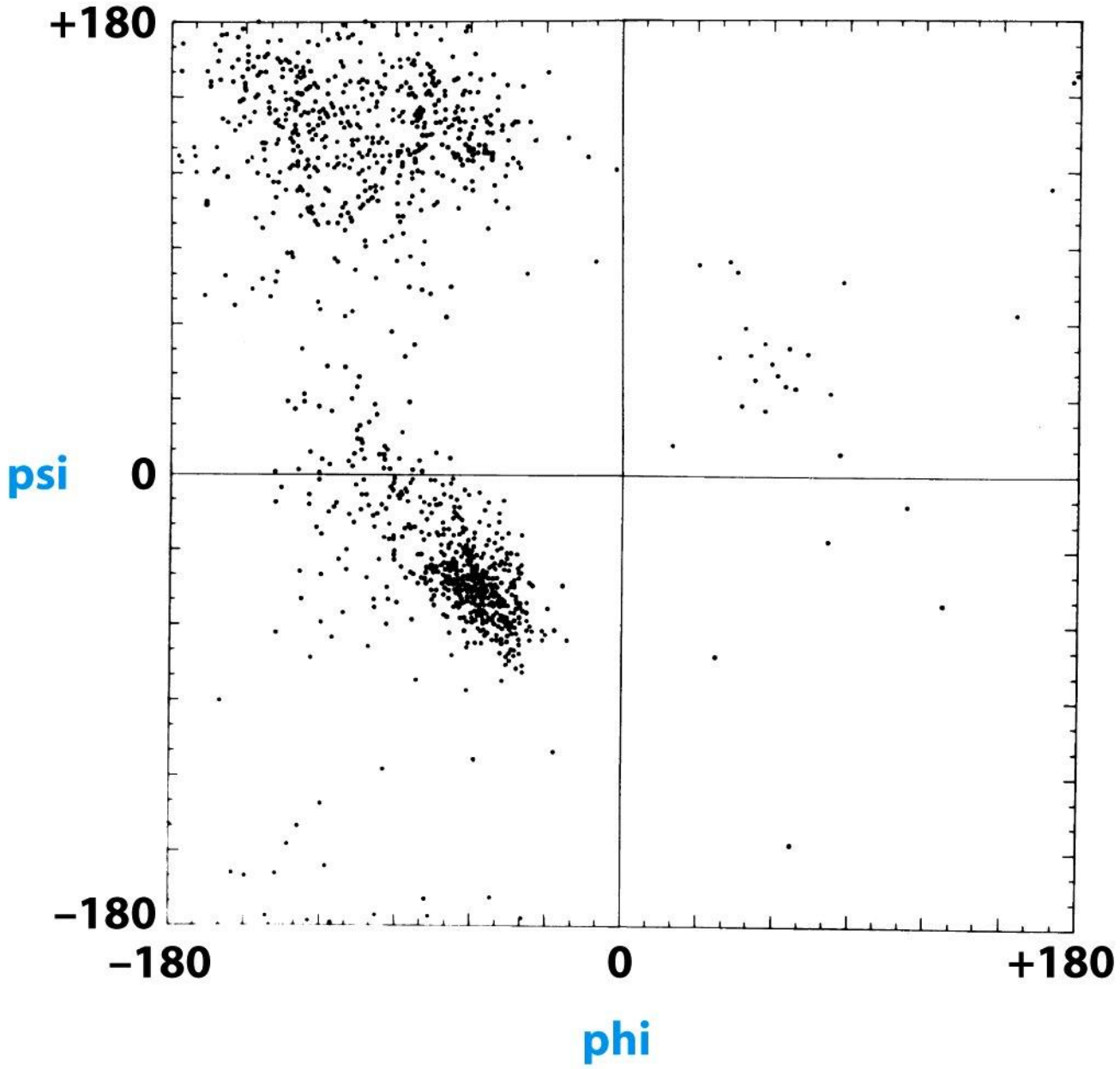



**Figure 3-4. Steric limitations on the bond angles in a polypeptide chain.** (A) Each amino acid contributes three bonds *(red)* to the backbone of the chain. The peptide bond is planar *(gray shading)* and does not permit rotation. By contrast, rotation can occur about the $C_\alpha$ C bond, whose angle of rotation is called psi ($\psi$), and about the N $C_\alpha$ bond, whose angle of rotation is called phi ($\phi$). By convention, an R group is often used to denote an amino acid side chain *(green circles).* (B) The conformation of the main-chain atoms in a protein is determined by one pair of $\phi$ and $\psi$ angles for each amino acid; because of steric collisions between atoms within each amino acid, most pairs of $\phi$ and $\psi$ angles do not occur. In this so-called Ramachandran plot, each dot represents an observed pair of angles in a protein. (B, from J. Richardson, *Adv*. *Prot*. *Chem*. 34:174 175, 1981. © Academic Press.)


+180
psi
0
−180
−180
0
+180
phi

- Además la conformación de una proteína es limitada por interacciones débiles
  - Puentes de hidrogeno
  - Enlaces iónicos
  - Fuerzas de van der Waals
  - Interacciones hidrofóbicas (fuerza a las cadenas laterales no polares hacia el interior de la cadena en un ambiente acuoso en contraste con las cadenas polares que se encuentran en el exterior de la cadena polipeptídica donde pueden formar puentes de hidrógeno con agua o otras moléculas polares. Los a.a. polares en el interior de la proteína forman puentes de hidrogeno con otros a.a. polares)
- Individualmente estos enlaces son 30-300 veces más débiles que un enlace covalente. Pero muchos de ellos pueden actuar en paralelo para mantener dos regiones de un polipéptido juntas.
- La estabilidad de cada conformación es determinada entonces por la fuerza combinada de un gran número de enlaces **no** covalentes

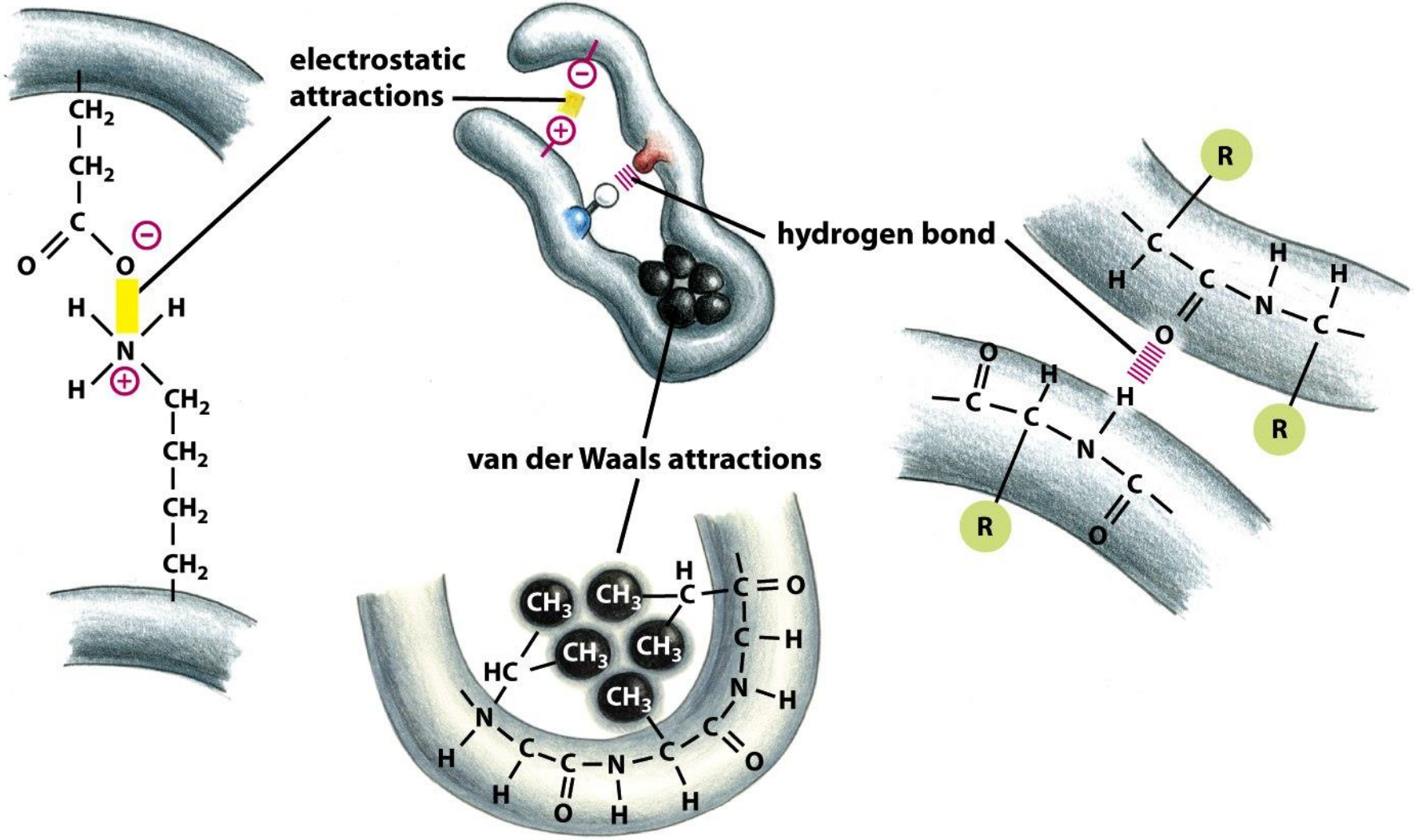



**Figure 3-5. Three types of noncovalent bonds that help proteins fold.** Although a single one of these bonds is quite weak, many of them often form together to create a strong bonding arrangement, as in the example shown. As in the previous figure, R is used as a general designation for an amino acid side chain.

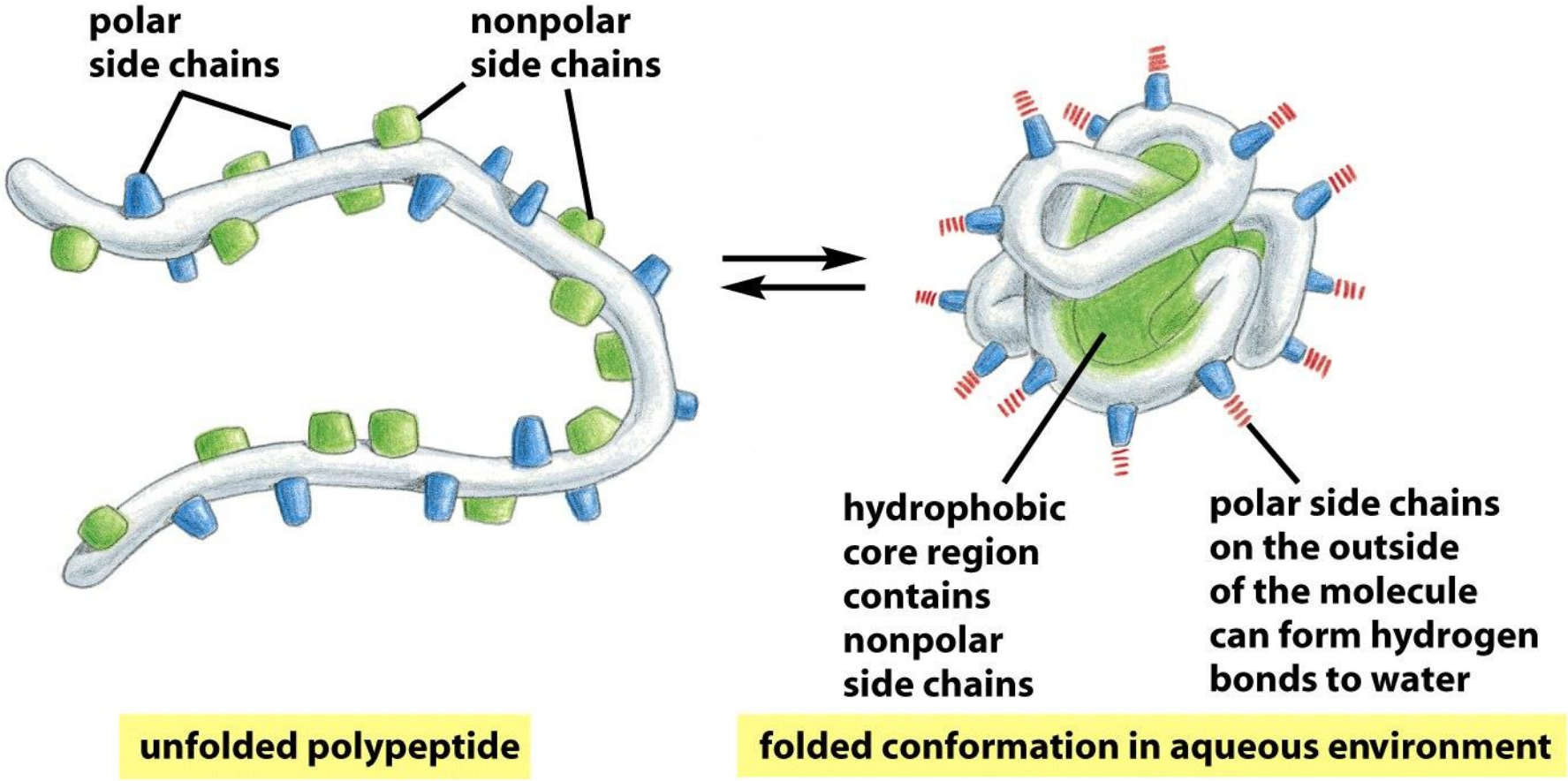



**Figure 3-6. How a protein folds into a compact conformation.** The polar amino acid side chains tend to gather on the outside of the protein, where they can interact with water; the nonpolar amino acid side chains are buried on the inside to form a tightly packed hydrophobic core of atoms that are hidden from water. In this schematic drawing, the protein contains only about 30 amino acids.

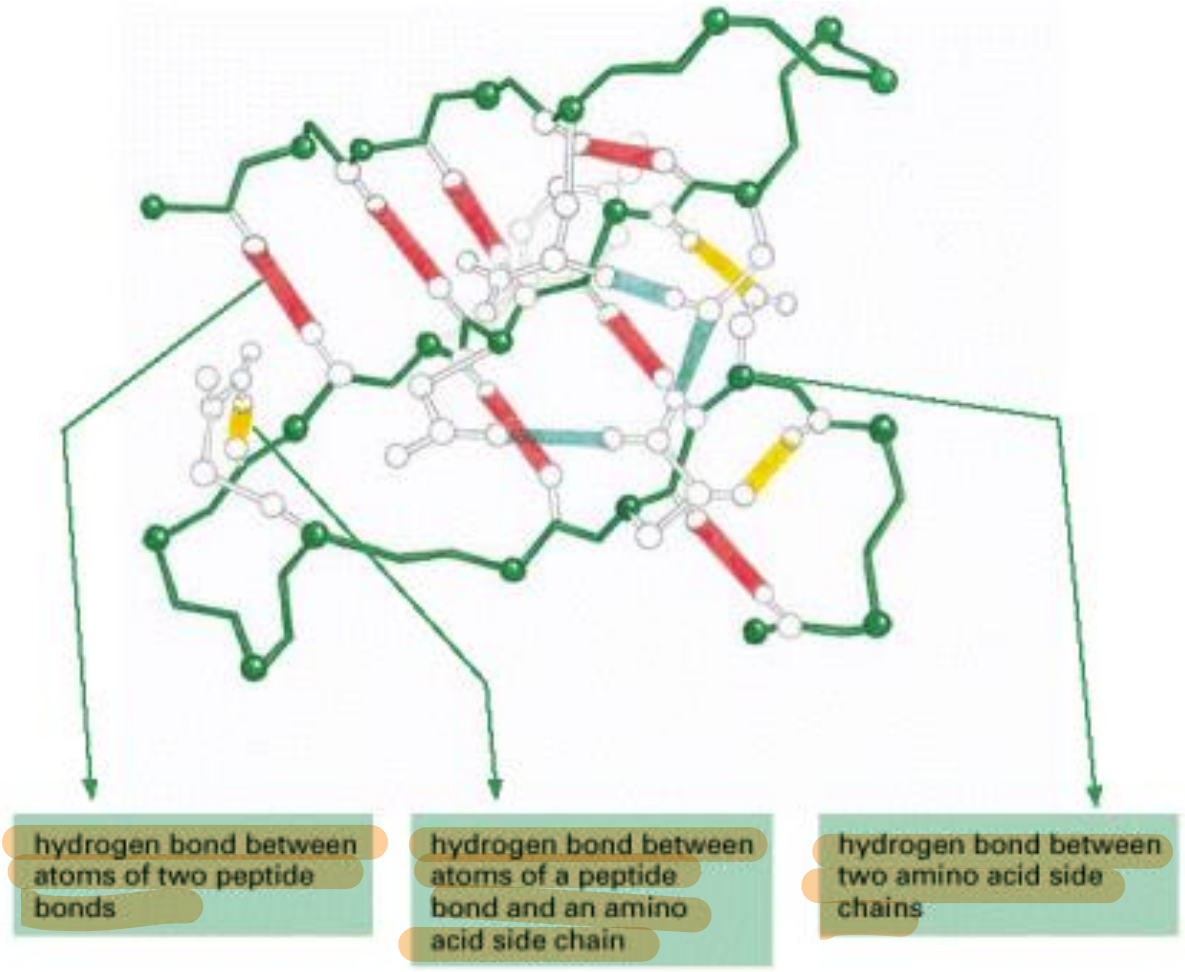



**Figure 3-7. Hydrogen bonds in a protein molecule.** Large numbers of hydrogen bonds form between adjacent regions of the folded polypeptide chain and help stabilize its three-dimensional shape. The protein depicted is a portion of the enzyme lysozyme, and the hydrogen bonds between the three possible pairs of partners have been differently colored, as indicated.

## La proteínas se pliegan en una conformación de baja energía

- Como resultado de estas interacciones débiles cada proteína tiene una conformación particular (estructura tridimensional) determinada por *el orden de los aminoácidos en la cadena*.
- Esta conformación corresponde al estado más bajo de energía libre
- Experimentos pueden ser llevados a cabo donde se añaden solventes que desnaturalizan las proteínas (en una cadena larga y flexible) que rompen las interacciones no covalentes.
- La eliminación de los solventes permite la renaturalizacion de las proteínas indicando que la única información necesaria para especificar la estructura tridimensional es de una proteína esta contenida en su secuencia de aminoácidos

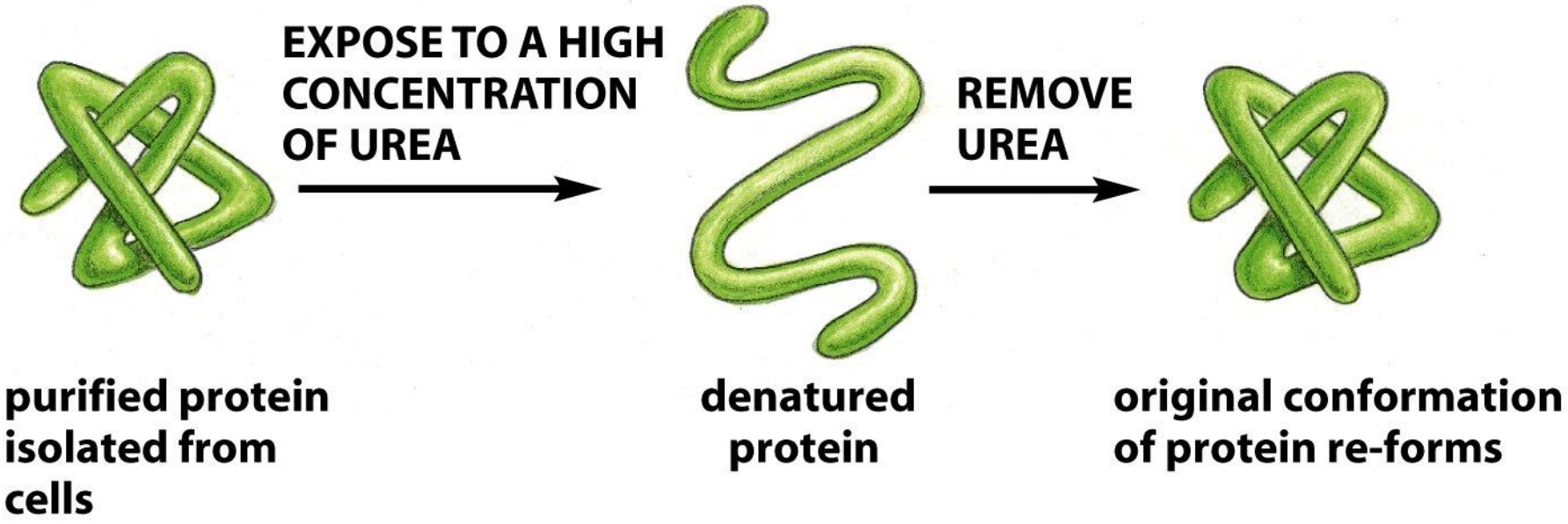
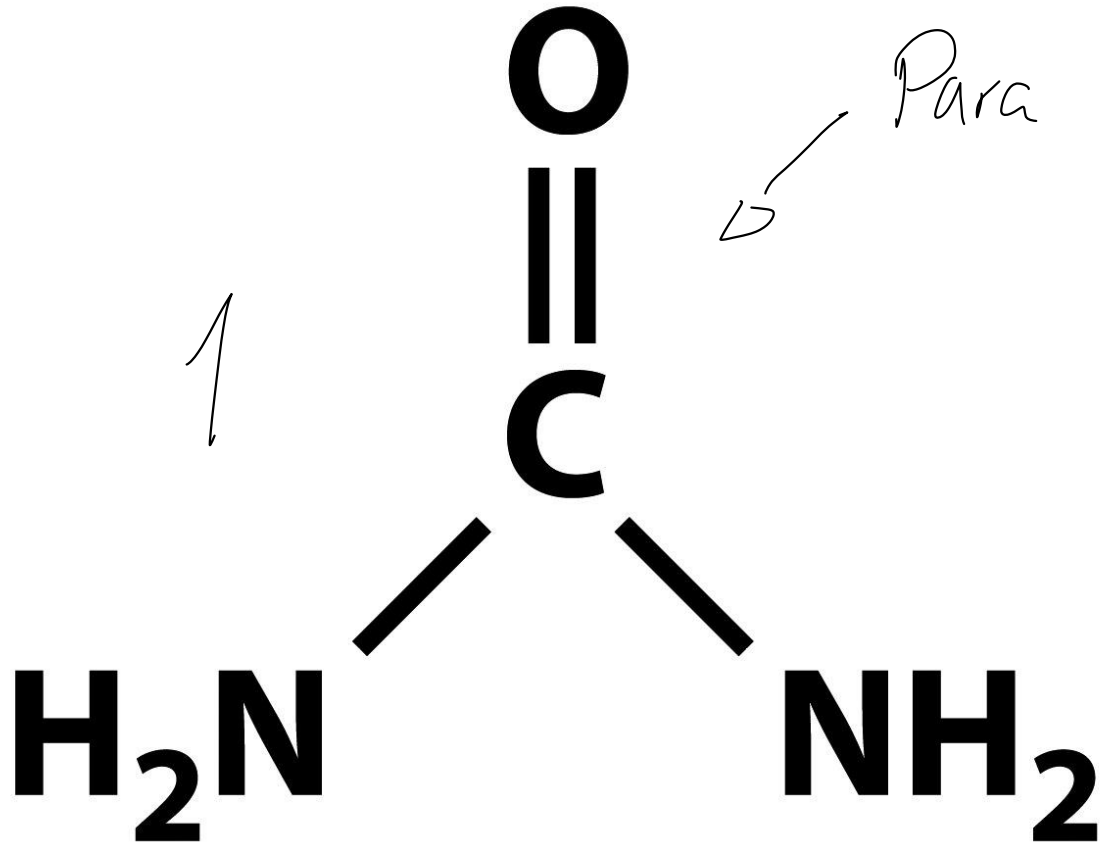
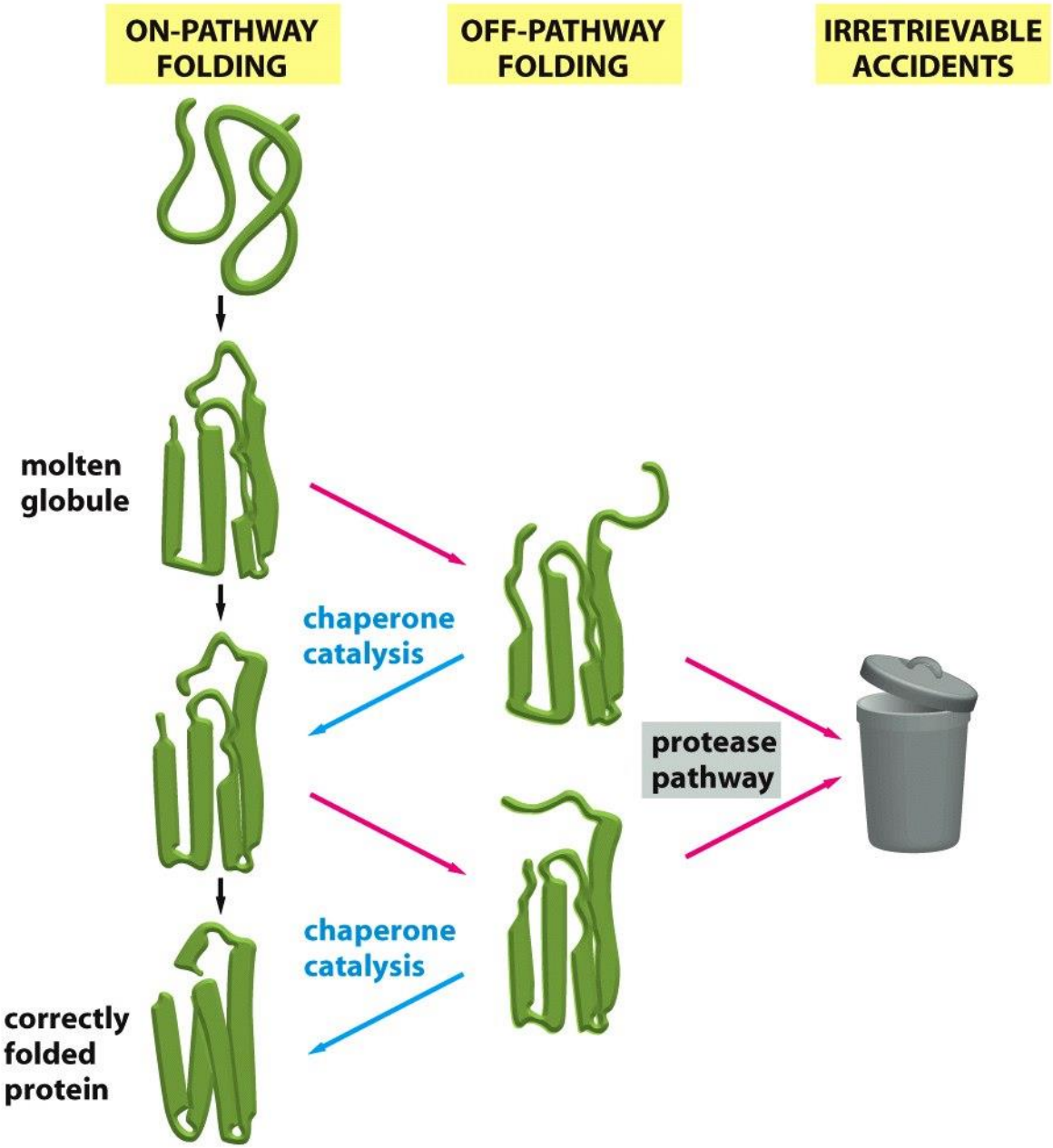



**Figure 3-8. The refolding of a denatured protein.** (A) This experiment demonstrates that the conformation of a protein is determined solely by its amino acid sequence. (




B) The structure of urea. Urea is very soluble in water and unfolds proteins at high concentrations, where there is about one urea molecule for every six water molecules

- Cada proteína tiene una sola conformación. Sin embargo esta frecuentemente cambia ligeramente cuando interactúa con otras moléculas en la célula. Este cambio es crucial para la función de la proteína.
- Aunque una proteína puede adquirir su conformación sin ayuda, en la célula hay proteínas especiales que asisten a una proteína a adquirir su estructura tridimensional: Chaperonas: Previenen regiones hidrofóbicas del polipéptido recién sintetizado a asociarse, lo que conllevaría a la formación de agregados, haciendo el plegado de la proteína más confiable aunque este finalmente es específicado por la secuencia de sus a.a.
- Las proteínas varían en la forma, y están formadas generalmente de 50-2000 a.a.
- Las proteínas grandes generalmente consisten de Dominios: unidades estructurales que se pliegan independientemente de cada una.


ON-PATHWAY FOLDING
OFF-PATHWAY FOLDING
IRRETRIEVABLE ACCIDENTS
molten globule
chaperone catalysis
protease pathway
chaperone catalysis
correctly folded protein

# Patrones de plegamiento:

- Aunque la conformación de una proteína es única, dos patrones regulares de plegamiento se repiten en esta
- De estudios tempranos (al comienzo de los 60) de estructura de proteínas estos dos patrones son
  - $\alpha$ hélice: en $\alpha$keratina, abundante en piel, uñas y cabello
  - Laminas $\beta$: fibroina mayor componente de la seda
  - Ambos resultan de **puentes de hidrógeno entre el N-H y C=O** del esqueleto del polipéptido **sin participación de las cadenas laterales**

- En las alpha hélices los puentes de hidrógeno se forman entre aminoácidos que están separados por 4 enlaces peptídicos. Con un giro completo de la hélice cada 3.6 aminoácidos
- Regiones cortas de $\alpha$-hélice (compuestos de cadenas laterales no polares) son comunes en proteínas transmembranosas, el esqueleto hidrofílico de la cadena polipeptídica es así escudado por estos a.a. no polares
- En otras proteínas las $\alpha$-helices (de nuevo compuestas de cadenas laterales no polares) se enrollan una sobre otra para formar una espiral enrollada

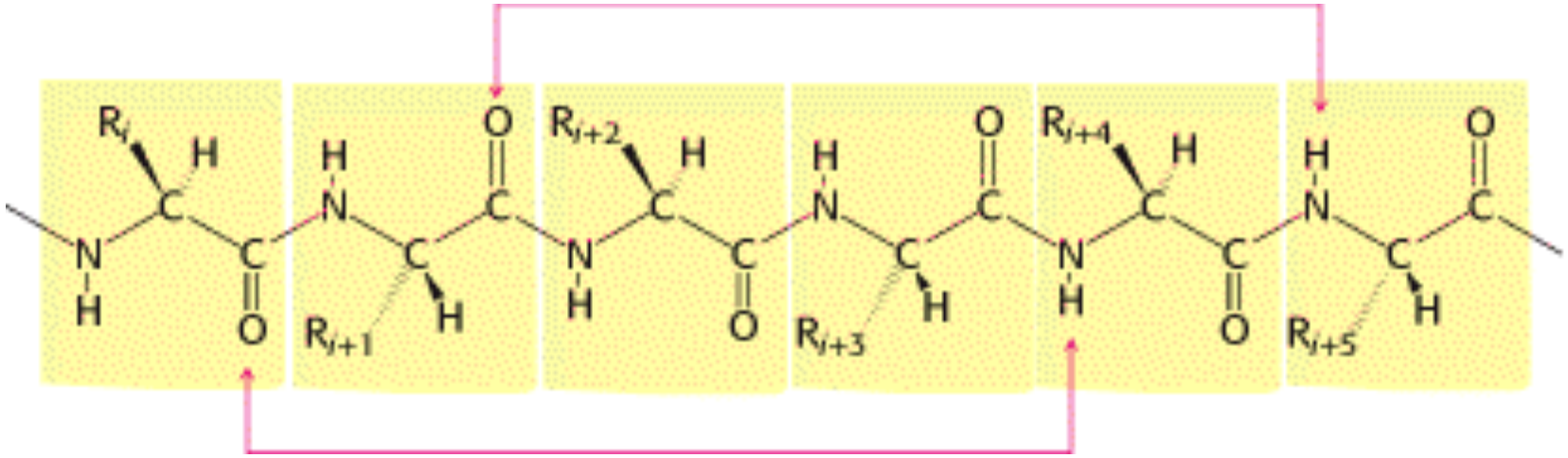
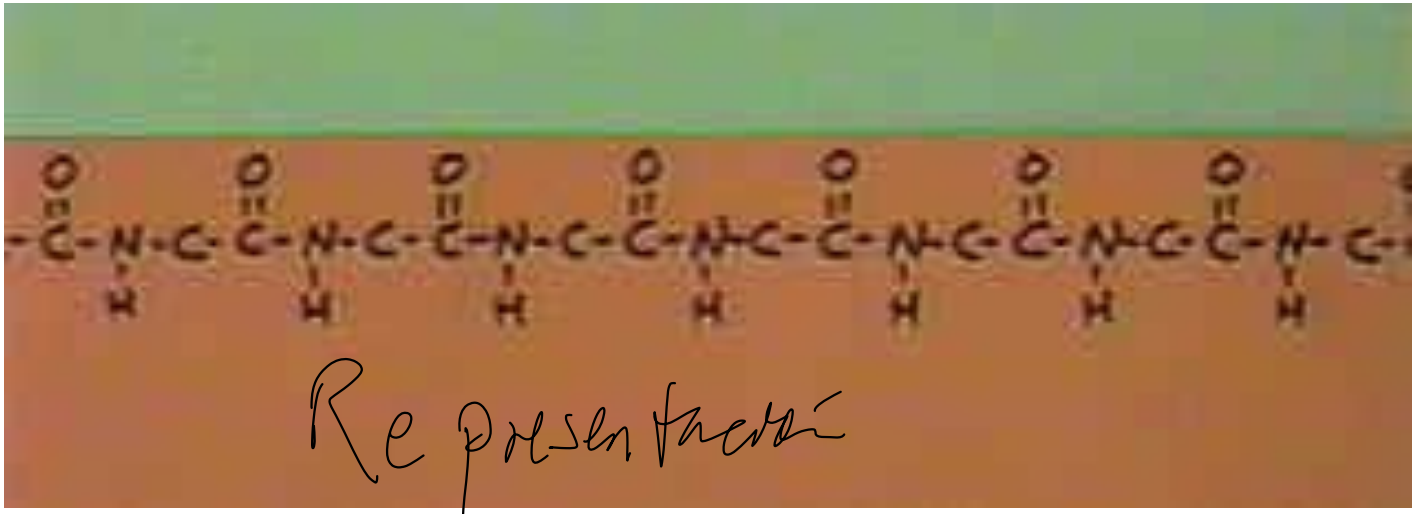


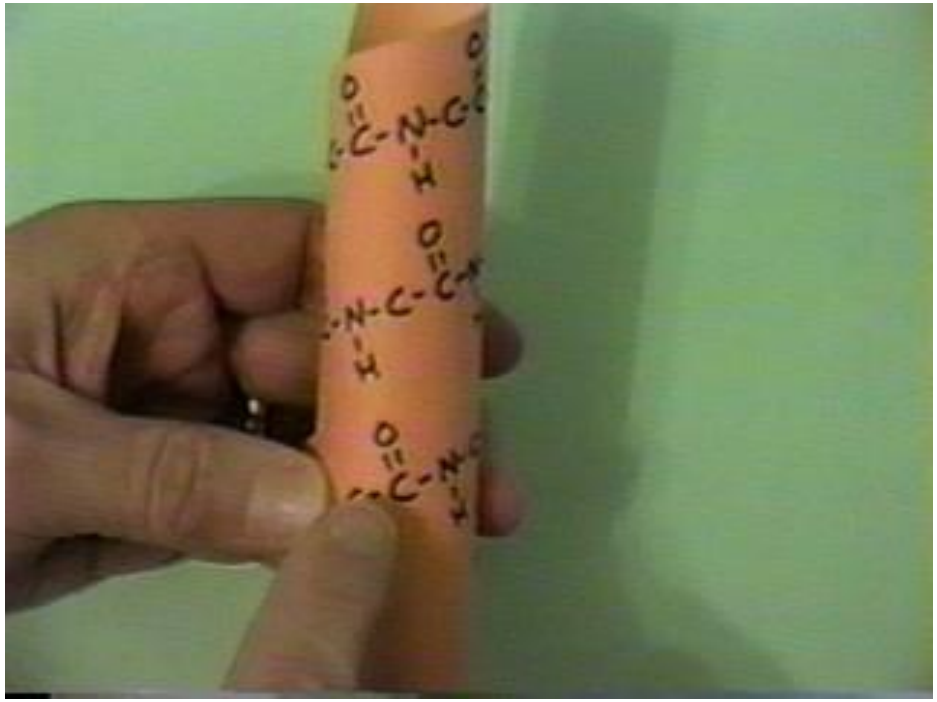

**Figure 3.30. Hydrogen-Bonding Scheme For an a helix.** In the a helix, the CO group of residue *n* forms a hydrogen bond with the NH group of residue *n*+ 4.




**Alpha Helix**

Here we have representation of a **primary structure**. It consists of a sequence of amino acid residues. In this case I have left out the hydrogen and the side group from the alpha carbon. I just want to ignore those for a moment.


One of the most common types of secondary structure is referred to as an **alpha helix**. Essentially what is involved in an alpha helix is that the primary structure of the protein twists around upon itself in such a way, somewhat like rolling up this paper model, to form a recurring pattern that is very important

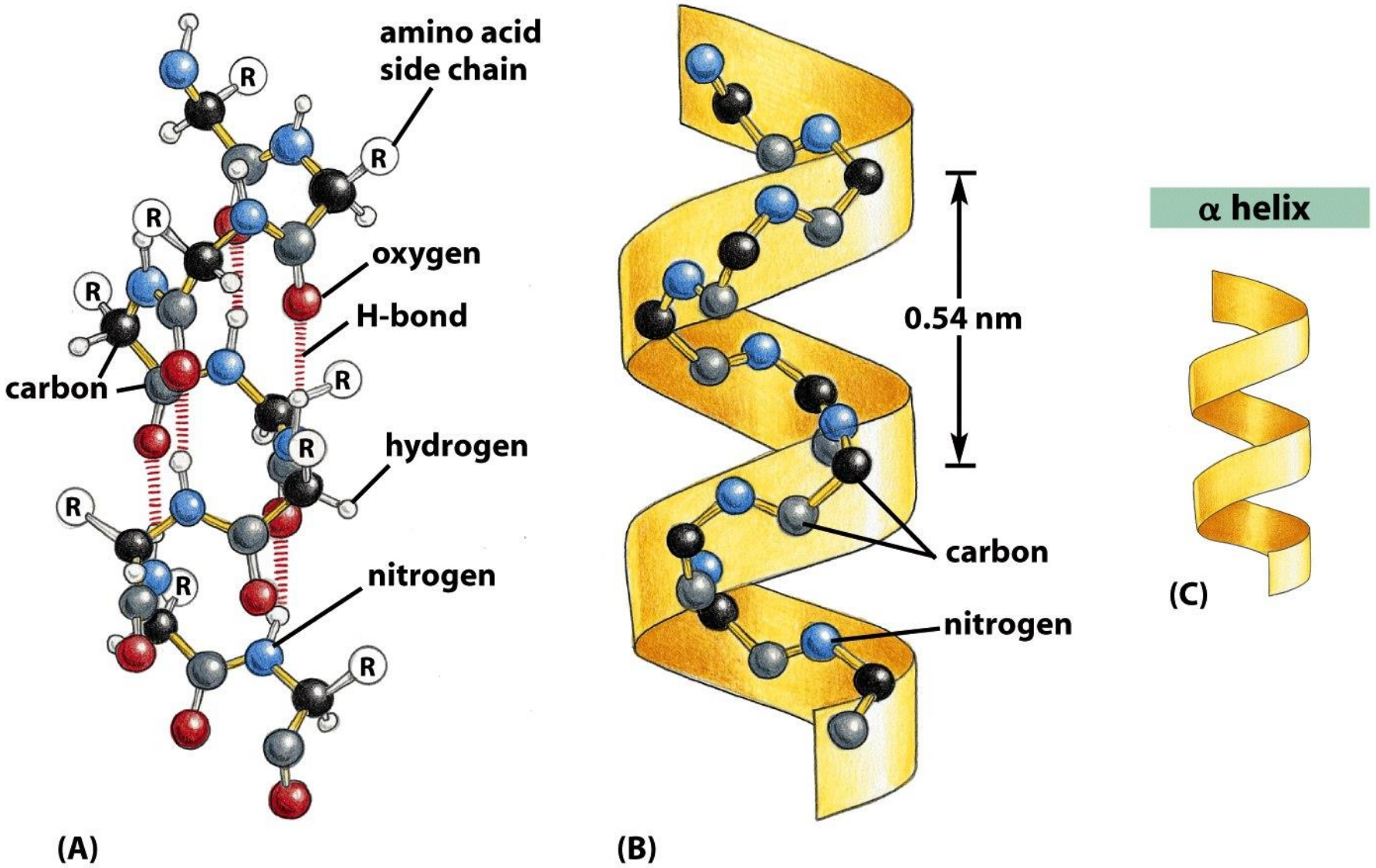


The hydrogen from the amino group lines up with the oxygen from a carbonyl group. That happens over and over again in this structure. So you can see that **hydrogen bonding** can occur with this arrangement of amino acids in an alpha helix


If we were to build a model of this alpha helix and consider bond angles, you would find that it doesn't work out quite as smoothly as what is shown here (talking in gng(e))

Also, if you consider the **side chains** that I originally chose to ignore, you would see that they tend to stick out on the outsides of the helix.


The type and location of these side groups is very important in determining the **ultimate structure** and also the **function** of a particular protein


amino acid
side chain
R
oxygen
H-bond
carbon
hydrogen
nitrogen
(A)
0.54 nm
carbon
nitrogen
(B)
α helix
(C)

- Regiones cortas de alpha hélices son especialmente abundantes en las proteínas de la membrana celular como proteínas de transporte y receptores
- En otras proteínas las alpha hélices se enrollan una sobre otra para formar una estructura estable conocida como: espiral enrollada (coiled coil). Esta estructura se forma cuando dos alpha hélices tienen la mayoría de sus aminoácidos no polares en un lado , de manera que pueden girar una alrededor de la otra con estas cadenas laterales hacia el interior.
  - Ej. αKeratina que forma fibras intracelulares que refuerza la capa externa de la piel y la miosina responsable de la contracción muscular

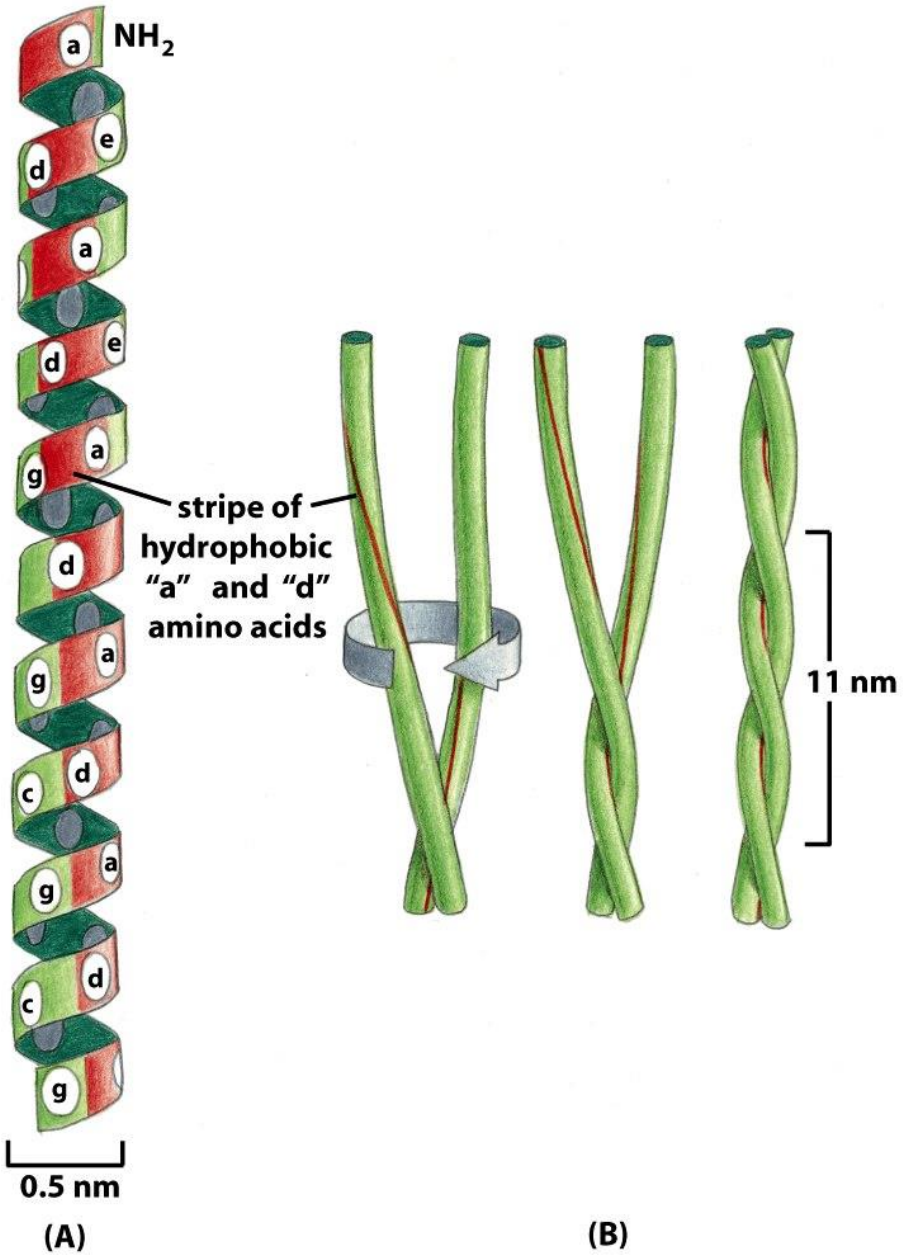
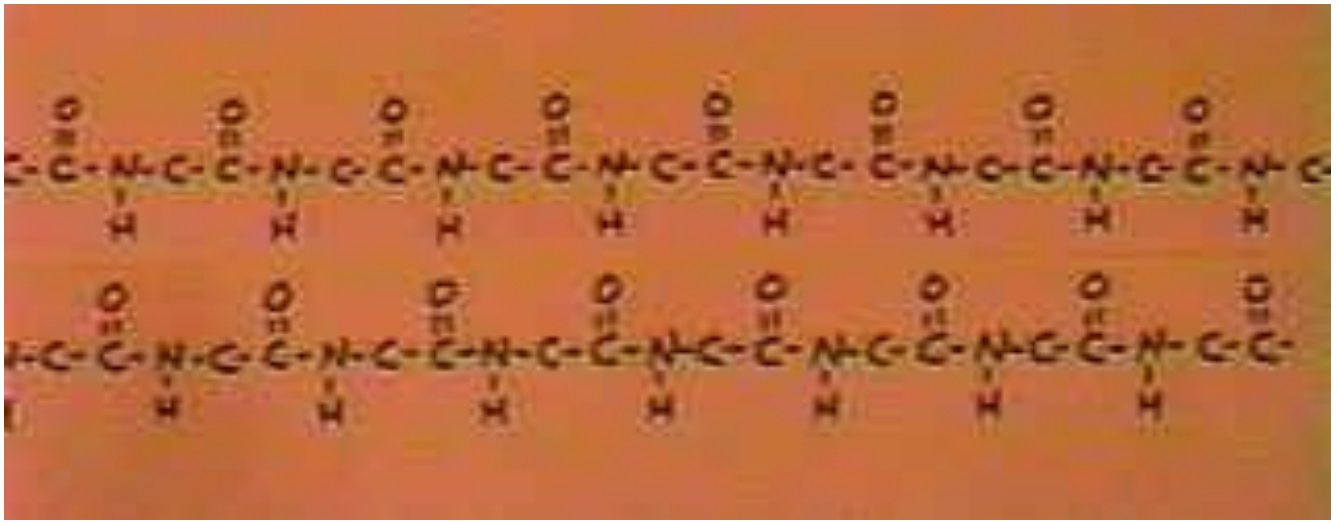
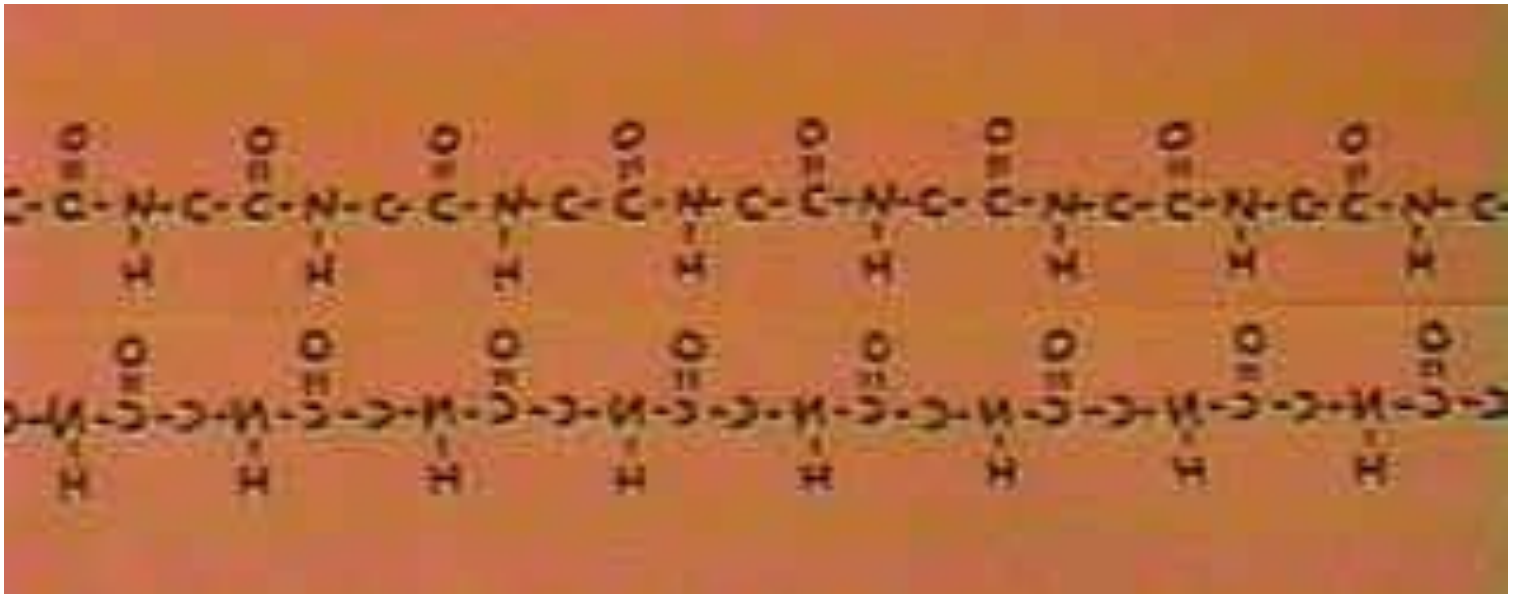



**Figure 3-11. The structure of a coiled-coil.** (A) A single α helix, with successive amino acid side chains labeled in a sevenfold sequence, "abcdefg" (from bottom to top). Amino acids "a" and "d" in such a sequence lie close together on the cylinder surface, forming a "stripe" (*red*) that winds slowly around the α helix. Proteins that form coiled-coils typically have nonpolar amino acids at positions "a" and "d." Consequently, as shown in (B), the two α helices can wrap around each other with the nonpolar side chains of one α helix interacting with the nonpolar side chains of the other, while the more hydrophilic amino acid side chains are left exposed to the aqueous environment. (C) The atomic structure of a coiled-coil determined by x-ray crystallography. The *red* side chains are nonpolar.



Beta Sheet

It is also possible for the protein's strands to line up side by side with one another and form hydrogen bonds in this way. When that happens with the strands both running in the **same direction** it is called **parallel**



When that happens with the strands running in the **opposite direction** it's called **antiparallel**

Parallel or antiparallel, this particular kind of secondary structure is referred to as **beta sheet** structure. These strands, of course, are not completely flat as shown on this screen. The amide bond portion is flat but the molecules bend on both sides of the alpha-carbon with tetrahedral angles. Consequently they fold up and down and these structures are quite often called **beta pleated sheets**

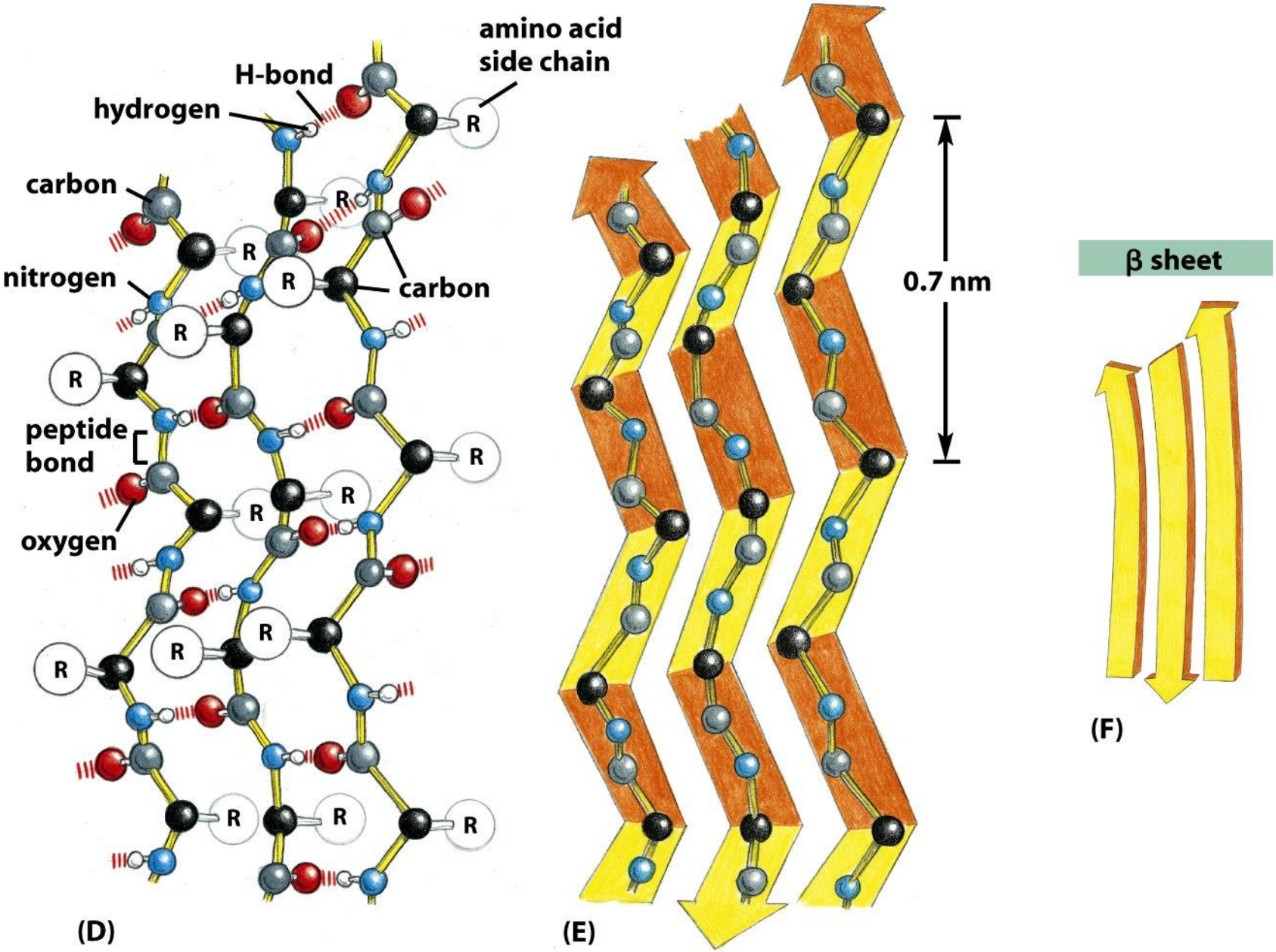

amino acid
side chain
H-bond
hydrogen
carbon
nitrogen
carbon
peptide
bond
oxygen
R
(D)
0.7 nm
(E)
β sheet
(F)

**Figure 3-9. The regular conformation of the polypeptide backbone observed in the α helix and the β sheet.** (A, B, and C) The α helix. The N  H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. The individual polypeptide chains (strands) in a β sheet are held together by hydrogen-bonding between peptide bonds in different strands, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins

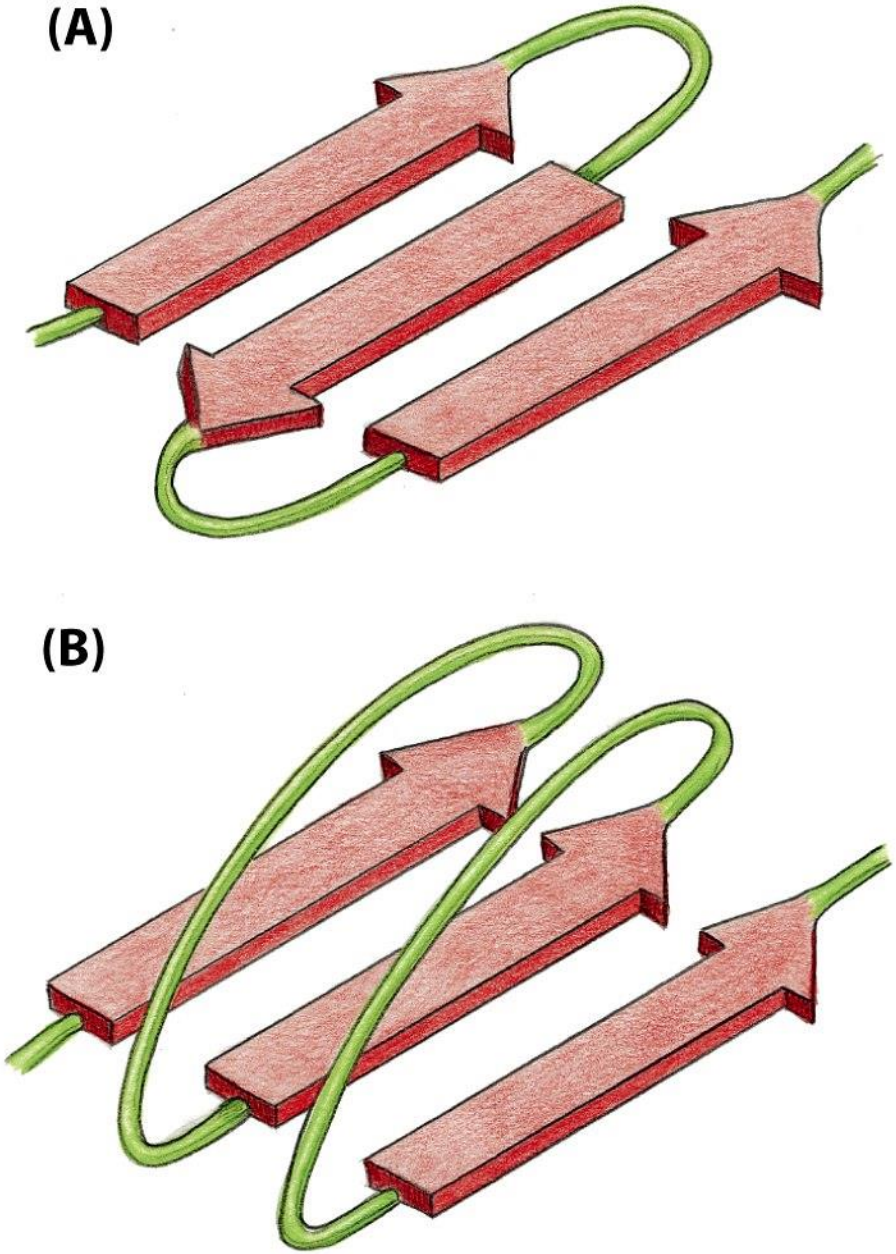
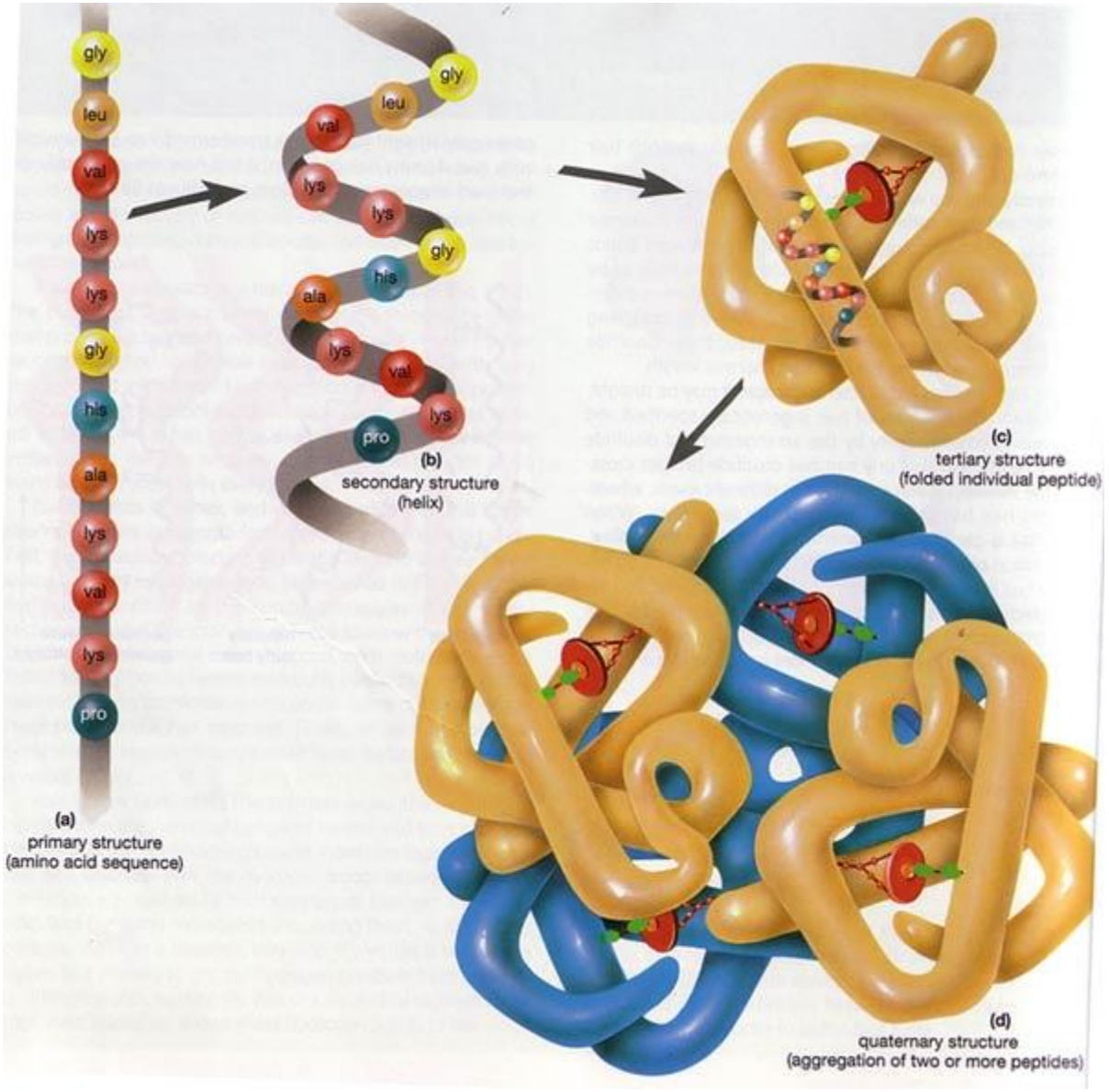



**Figure 3-10. Two types of b sheet structures.** (A) An antiparallel b sheet (see Figure 3-9D). (B) A parallel b sheet. Both of these structures are common in proteins


molymod™

El dominio de una proteína es la unidad fundamental de su organización:

- Se distinguen 4 níveles de organización en la estructura de una proteína
  - Primaria: Secuencia de aminoácidos unidos por enlaces peptídicos
  - Secundaria: segmentos del polipéptido que forman $\alpha$ hélices y laminas $\beta$ unidos por puentes de hidrogeno
  - Terciaria: forma tridimensional, organización tridimensional de la cadena polipeptídica por medio de puentes de hidrógeno, interacciones hidrofóbicas, enlaces disulfido, puentes de sales
  - Cuaternaria: Interacciones entre dos o mas cadenas polipeptídicas (las mismas interacciones de la estructura terciaria)


gly
leu
val
lys
lys
gly
his
ala
lys
val
pro
(a)
primary structure
(amino acid sequence)
(b)
secondary structure
(helix)
(c)
tertiary structure
(folded individual peptide)
(d)
quaternary structure
(aggregation of two or more peptides)

- Además de estos niveles de organización, también se puede discutir una proteína en términos de dominios:
  - Subestructura producida por cualquier parte de la cadena polipeptídica que se pliega independientemente del resto de la proteína en una estructura compacta y estable
  - El dominio consiste de una combinación particular de hélices y laminas conocido como: pliegue o doblez de la proteína (protein fold)
  - Están compuestos típicamente de 40-350 aminoácidos y es la unidad modular a partir de la cual muchas proteínas están construidas
  - Tienen funciones especificas dentro de la proteína
    - Ej. Roles de regulación o catalíticos
  - De las miles de proteínas cuyas conformaciones son conocidas más de mil diferentes dominios son conocidos

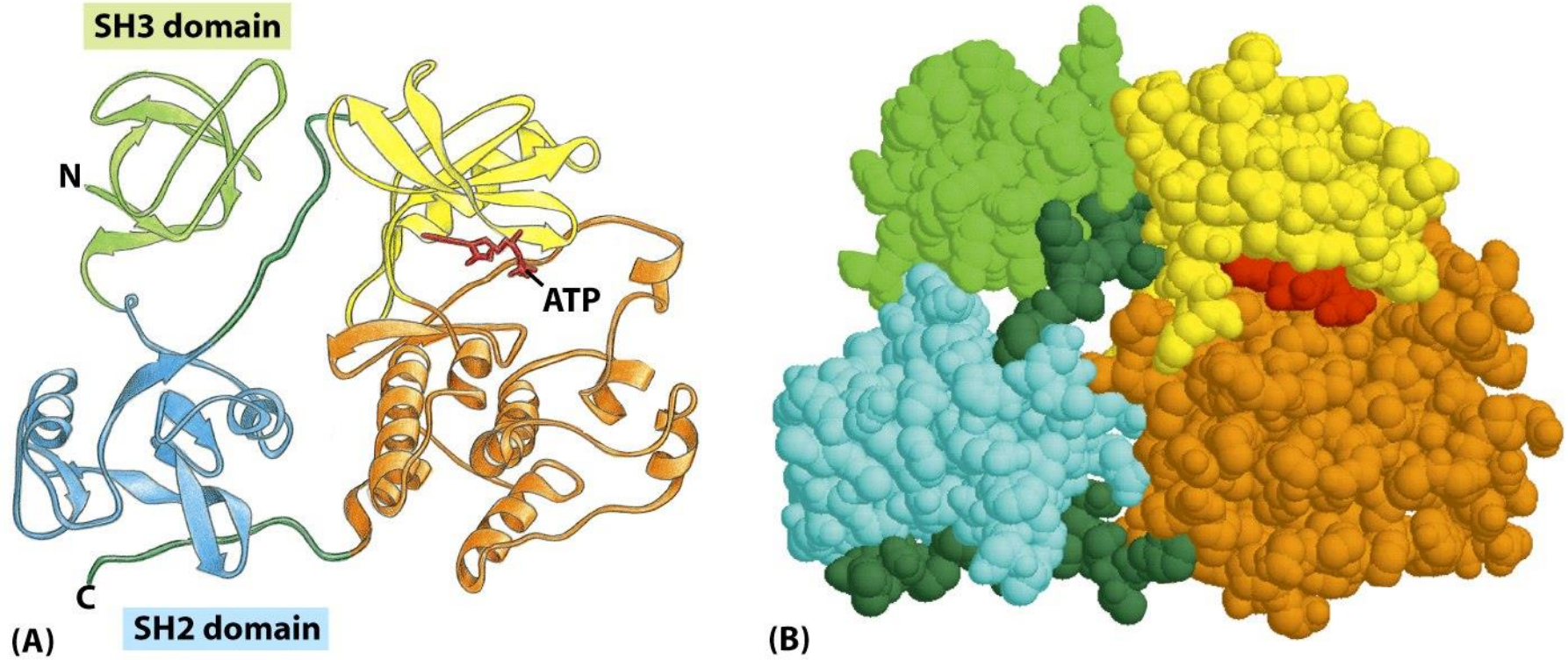



**Figure 3-12. A protein formed from four domains.** In the Src protein shown, two of the domains form a protein kinase enzyme, while the SH2 and SH3 domains perform regulatory functions. (A) A ribbon model, with ATP substrate in *red*. (B) A spacing-filling model, with ATP substrate in *red*. Note that the site that binds ATP is positioned at the interface of the two domains that form the kinase

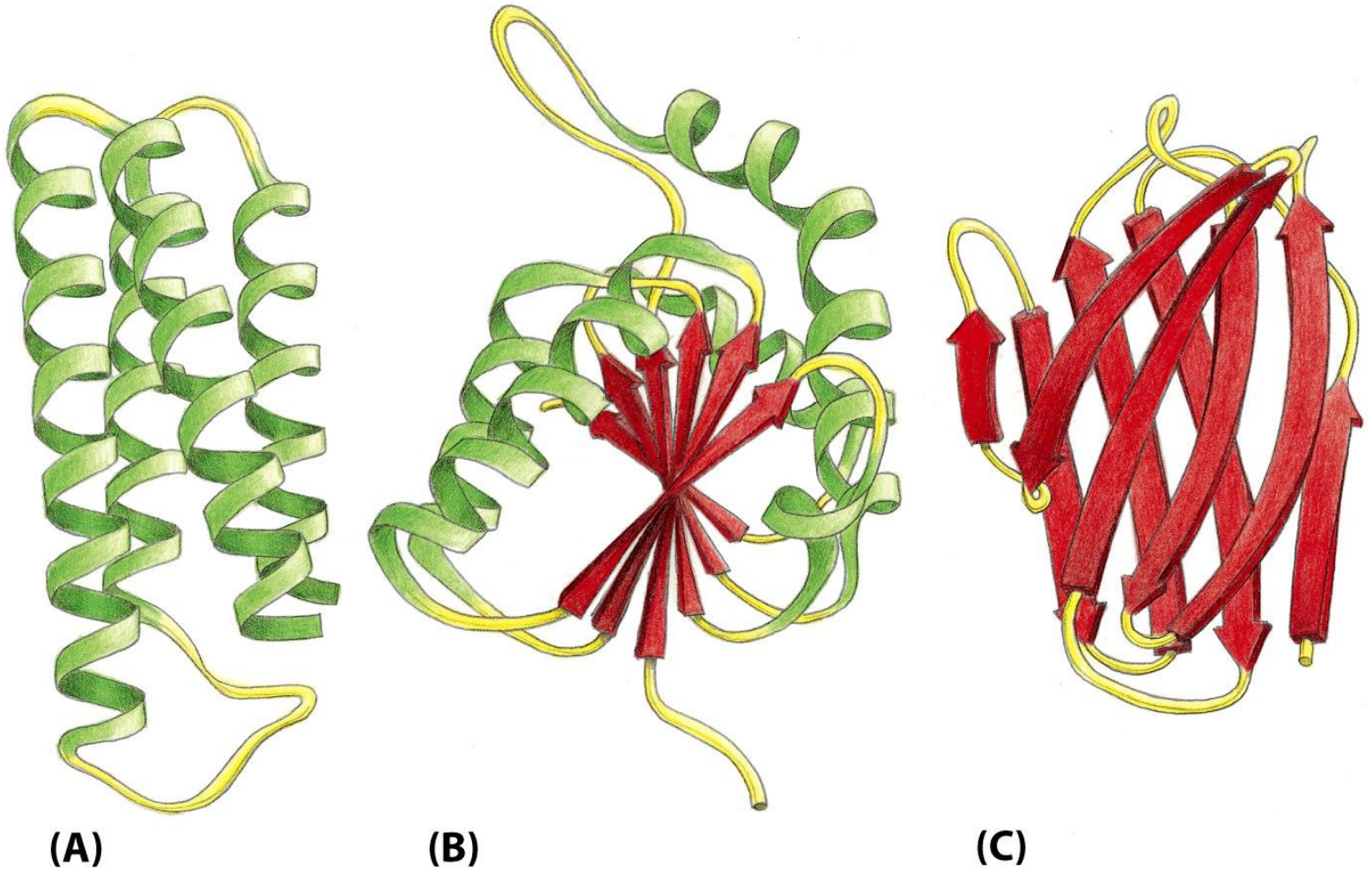



**Figure 3-13. Ribbon models of three different protein domains.** (A) Cytochrome *b*562, a single-domain protein involved in electron transport in mitochondria. This protein is composed almost entirely of a helices. (B) The NAD-binding domain of the enzyme lactic dehydrogenase, which is composed of a mixture of a helices and b sheets. (C) The variable domain of an immunoglobulin (antibody) light chain, composed of a sandwich of two b sheets. In these examples, the a helices are shown in *green*, while strands organized as b sheets are denoted by *red arrows*. Note that the polypeptide chain generally traverses back and forth across the entire domain, making sharp turns only at the protein surface. It is the protruding loop regions *(yellow)* that often form the binding sites for other molecules. (Adapted from drawings courtesy of Jane Richardson.)

De las posibles cadenas polipeptídicas solo unas pocas serán útiles.

- Cada a.a. es químicamente distinto y pueden en principio ocurrir en cualquier posición de la cadena polipeptídica: 20x20x20x20=160,000 posibles polipéptidos si esta fuera de 4 a.a de largo.
- Para n a.a. entonces $20^n$ en teoría
- Solo una fracción pequeña de estos posibles polipéptidos adoptaran una sola conformación tridimensional estable (1 en 1 billón)
- Selección natural: Una proteína con una conformación y actividad bioquímica variable es improbable que ayude a la sobrevivencia de la célula y será eliminada por selección natural durante el proceso evolutivo

- Las proteínas también pueden ser agrupadas en familias (similitud entre ciertas proteínas es probablemente resultado de la evolución):
  - Una vez la proteína ha evolucionado en una conformación estable con funciones útiles esta puede ser modificada durante la evolución para llevar a cabo nuevas funciones
    - Proceso acelerado por mecanismos genéticos que producen duplicaciones de los genes, permitiendo a una de las copias del gen evolucionar independientemente para llevar a cabo una nueva función o los cambios son neutrales sin dañar o beneficiar la estructura básica o función de la proteína
  - Ej. Proteasas de serina: Un grupo grande de enzimas segmentadoras (proteolíticas)
    - Quimiotripsina, elastasa, tripsina envueltas en la coagulación de la sangre
    - Los miembros de esta familia son específicas en el enlace peptídico a cortar
    - Pero comparten similitudes (se asemejan) estructurales (conformación) y de secuencias de aminoácidos (ciertas partes de la cadena polipeptídica)

Se duplica su gen produce la proteína y mutan.

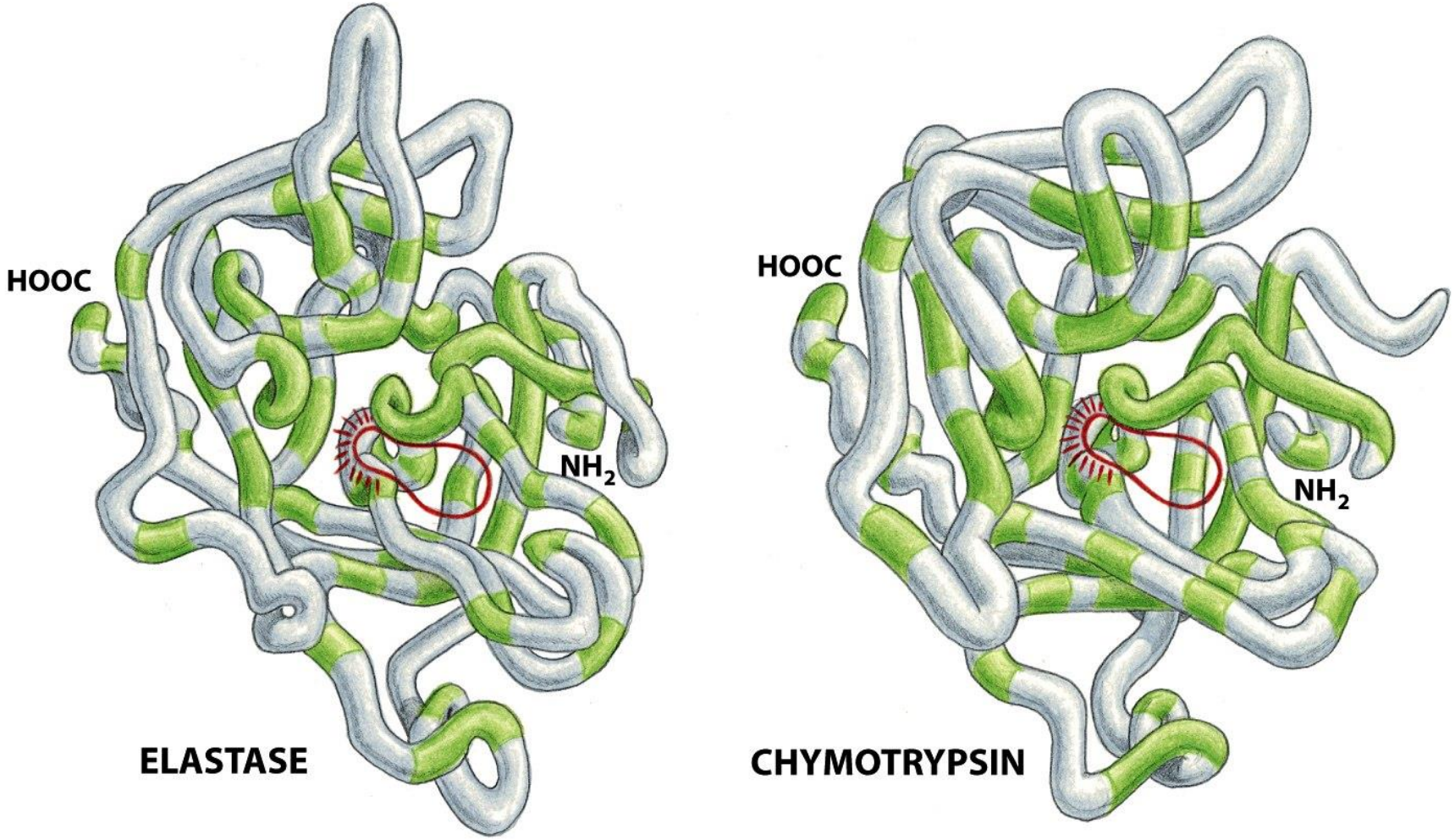



**Figure 3-14. The conformations of two serine proteases compared.** The backbone conformations of elastase and chymotrypsin. Although only those amino acids in the polypeptide chain shaded in *green* are the same in the two proteins, the two conformations are very similar nearly everywhere. The active site of each enzyme is circled in *red;* this is where the peptide bonds of the proteins that serve as substrates are bound and cleaved by hydrolysis. The serine proteases derive their name from the amino acid serine, whose side chain is part of the active site of each enzyme and directly participates in the cleavage reaction.

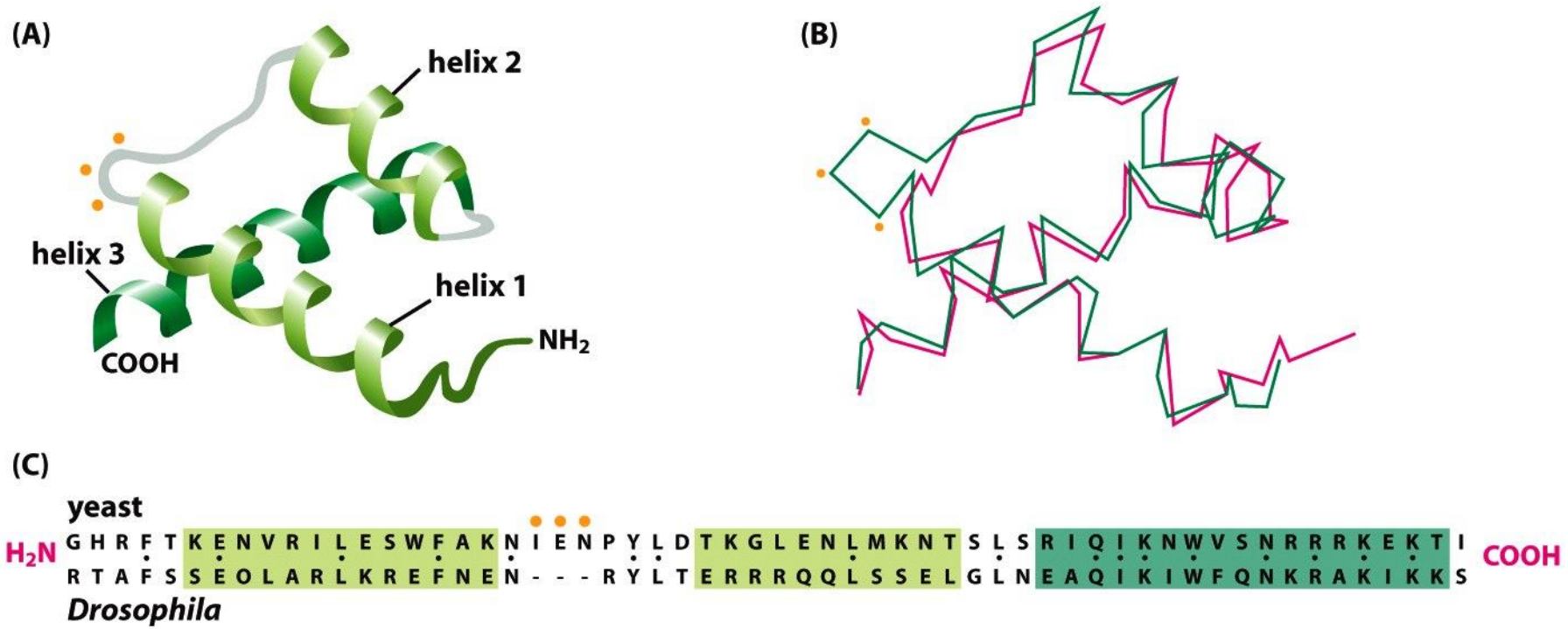



**Figure 3-15. A comparison of a class of DNA-binding domains, called homeodomains, in a pair of proteins from two organisms separated by more than a billion years of evolution.** (A) A ribbon model of the structure common to both proteins. (B) A trace of the a-carbon positions. The three-dimensional structures shown were determined by x-ray crystallography for the yeast a2 protein *(green)* and the *Drosophila* engrailed protein *(red).* (C) A comparison of amino acid sequences for the region of the proteins shown in (A) and (B). *Black dots* mark sites with identical amino acids. *Orange dots* indicate the position of a three amino acid insert in the a2 protein.

- En muchos casos la secuencia de aminoácidos ha divergido mucho que no se puede estar seguro de la relación familiar entre proteínas sin obtener la estructura tridimensional
  - Ej. Familia de homeodominios (enlazan DNA)
    - $\alpha$2 en levadura
    - Drosophila engrailed protein

- Las familias de proteínas son fácilmente reconocidas cuando el genoma de un organismo es secuenciado.

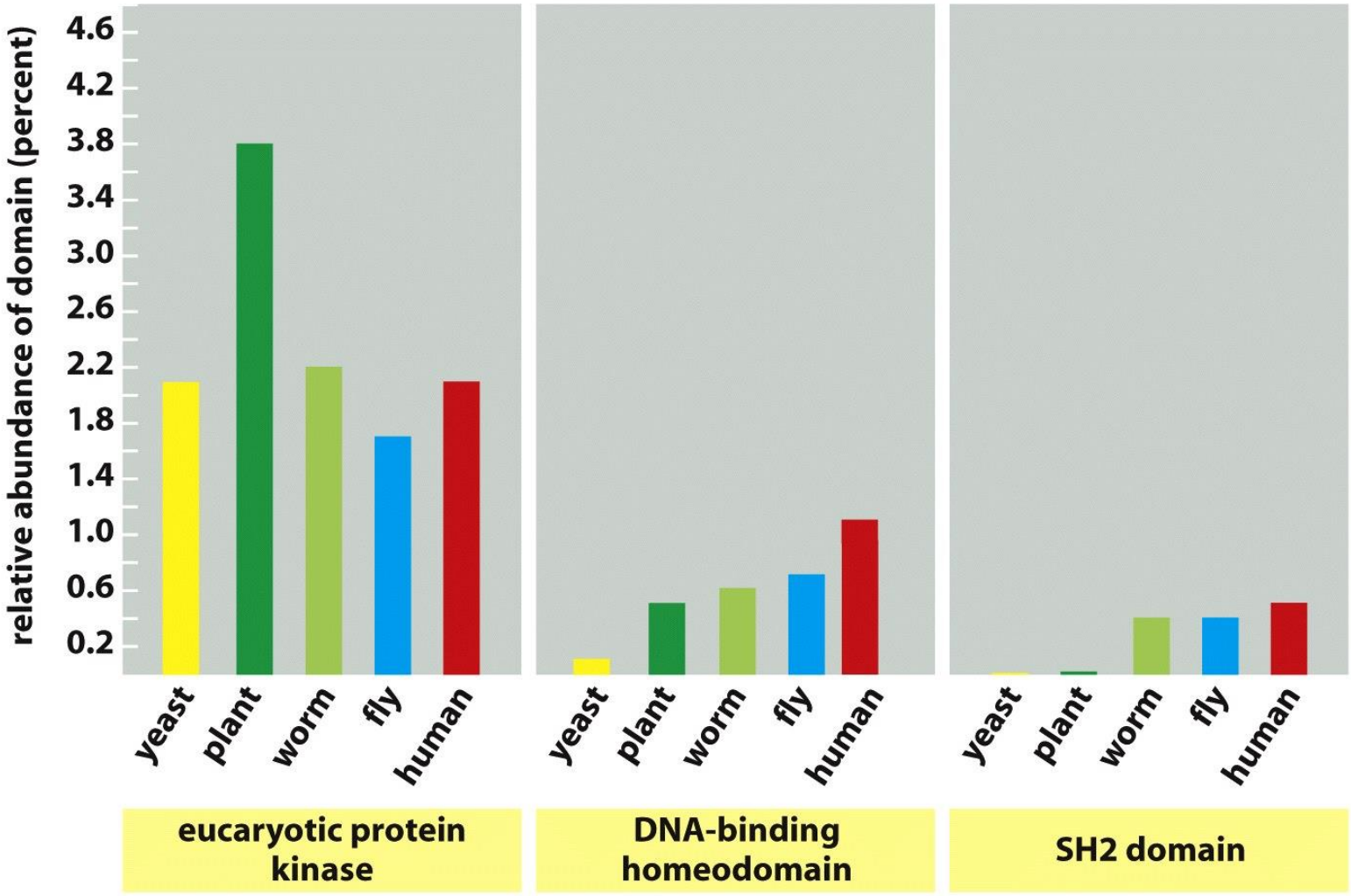



**Figure 3-16. Percentage of total genes containing one or more copies of the indicated protein domain, as derived from complete genome sequences.** Note that one of the three domains selected, the immunoglobulin domain, has been a relatively late addition, and its relative abundance has increased in the vertebrate lineage. The estimates of human gene numbers are approximate.

## Algunos dominios de proteínas llamados Módulos forman parte de muchas proteínas diferentes

- Las proteínas con multidominios se piensa que se originan cuando la secuencia de DNA que codifica dicho dominio accidentalmente se une creando un nuevo gen.
- Noveles Superficies de enlaces han sido creadas por yuxtaposición de dominios y muchas proteínas grandes han evolucionado mediante el enlace de dominios preexistentes, proceso evolutivo conocido como domain Shuffling

- Los módulos son mas pequeños que un dominio promedio(40-200a.a), bloques de construcción particularmente móviles
- Estos módulos consisten de un centro formado de laminas beta rodeado de lazos polipeptídicos flexibles
  - Contienen sus términos N y C periferalmente localizado lo que permite su fácil integración a polipéptidos existentes
- Los genomas de vertebrados no son más grandes que los de insectos, lombrices o plantas simples
  - Pero las proteínas codificadas son mas complejas, es decir contienen mas dominios
  - Esta extra sofisticación en las proteínas de vertebrados implica una mayor interacción entre proteínas

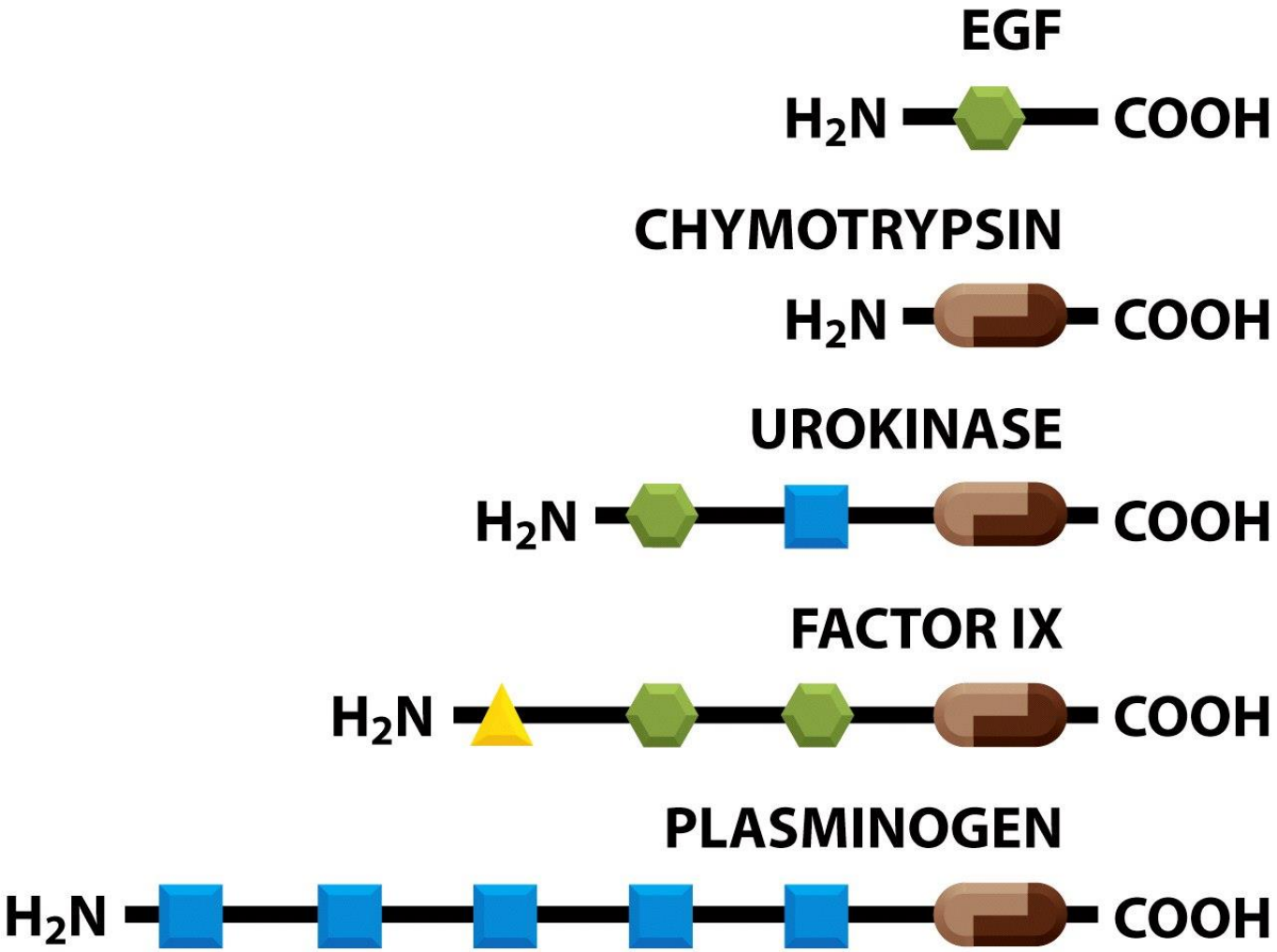



**Figure 3-18. Domain shuffling.** An extensive shuffling of blocks of protein sequence (protein domains) has occurred during protein evolution. Those portions of a protein denoted by the same shape and color in this diagram are evolutionarily related. Serine proteases like chymotrypsin are formed from two domains *(brown).* In the three other proteases shown, which are highly regulated and more specialized, these two protease domains are connected to one or more domains homologous to domains found in epidermal growth factor (EGF; *green),* to a calcium-binding protein *(yellow),* or to a "kringle" domain *(blue)* that contains three internal disulfide bridges. Chymotrypsin

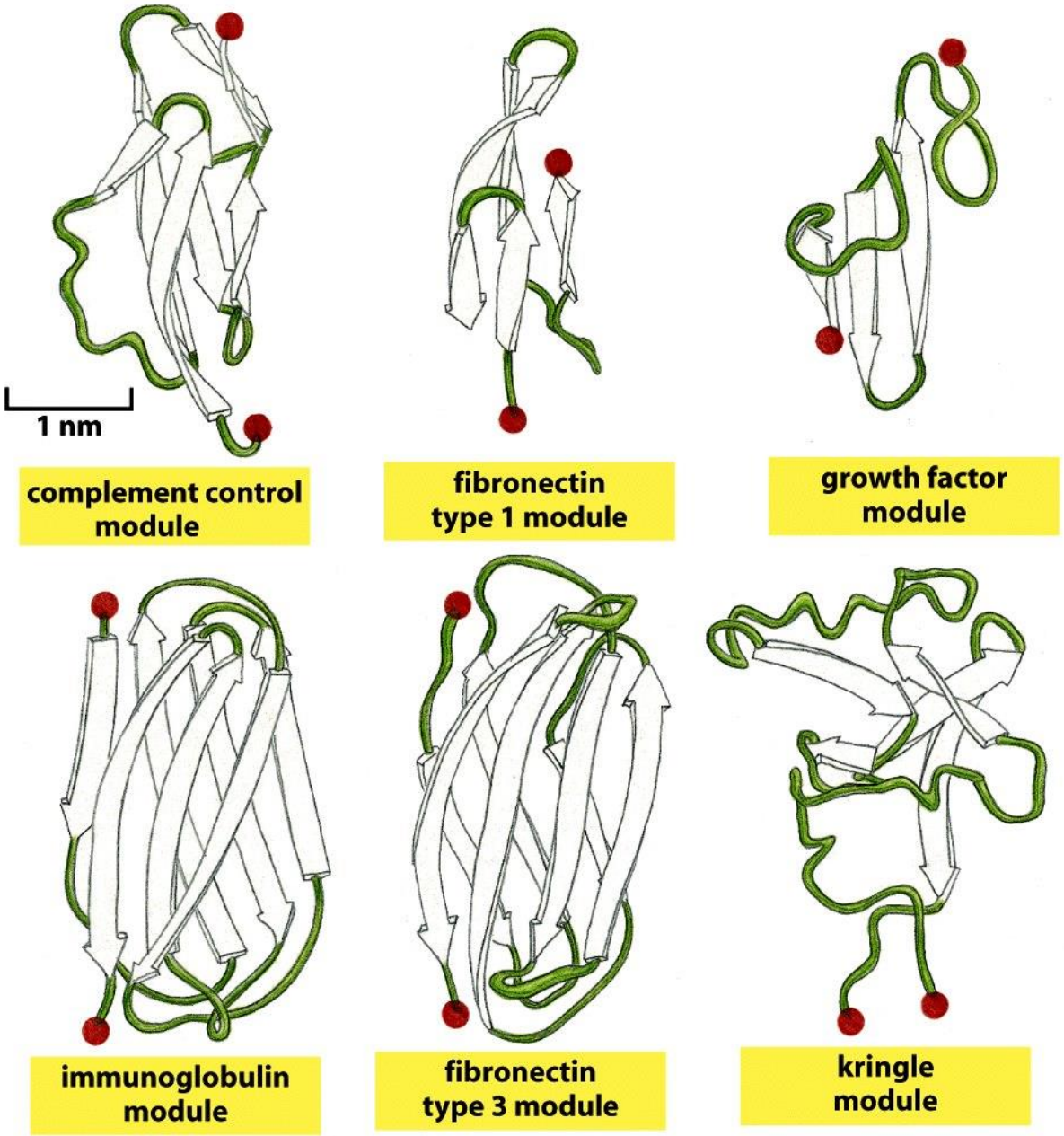



**Figure 3-19. The three-dimensional structures of some protein modules.** In these ribbon diagrams, β-sheet strands are shown as *arrows,* and the N- and C-termini are indicated by *red spheres.* (Adapted from M. Baron, D.G. Norman, and I.D. Campbell, *Trends Biochem. Sci.* 16:13 17, 1991, and D.J. Leahy et al., *Science* 258:987 991, 1992.)

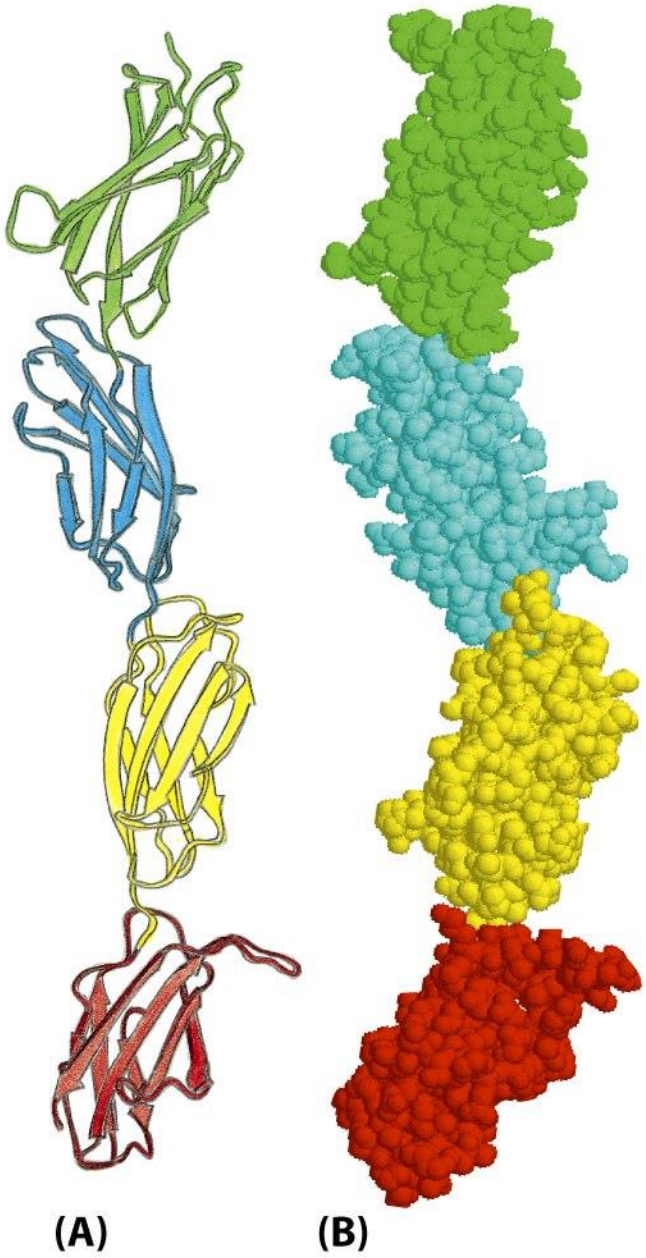



**Figure 3-20. An extended structure formed from a series of in-line protein modules.** Four fibronectin type 3 modules (see Figure 3-19) from the extracellular matrix molecule fibronectin are illustrated in (A) ribbon and (B) space-filling models. (Adapted from D.J. Leahy, I. Aukhil, and H.P. Erickson, *Cell* 84:155 164, 1996.)

## Proteínas Grandes

- Las proteínas tienen regiones particulares que permiten el enlace no covalente
  - Estos sitios se llaman **sitios de enlace**
- Dos cadenas polipeptídicas plegadas pueden enlazarse para formar una proteína mas grande
  - Las cadenas polipeptídicas se llaman **subunidades** proteínicas
- Un ejemplo simple es un dímero compuesto de dos subunidades idénticas
  - Ej. Represor Cro (desactiva genes virales)
- Un ejemplo de tetrámero es la neuraminidasa que forma un anillo
- Un ejemplo mas complejo es la hemoglobina, compuestas de 4 subunidades
  - Dos subunidades alpha globinas y dos beta globinas

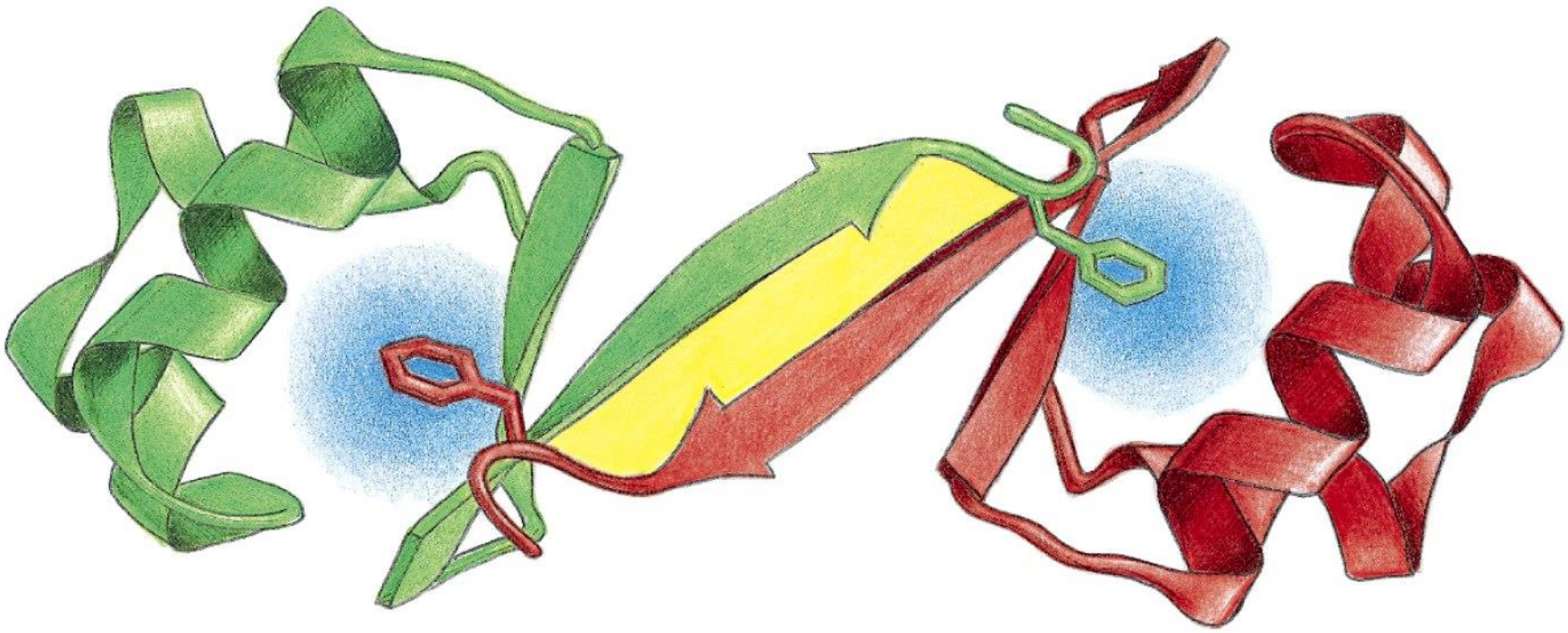


**Figure 3-21. Two identical protein subunits binding together to form a symmetric protein dimer.** The Cro repressor protein from bacteriophage lambda binds to DNA to turn off viral genes. Its two identical subunits bind head-to-head, held together by a combination of hydrophobic forces *(blue)* and a set of hydrogen bonds *(yellow* region).

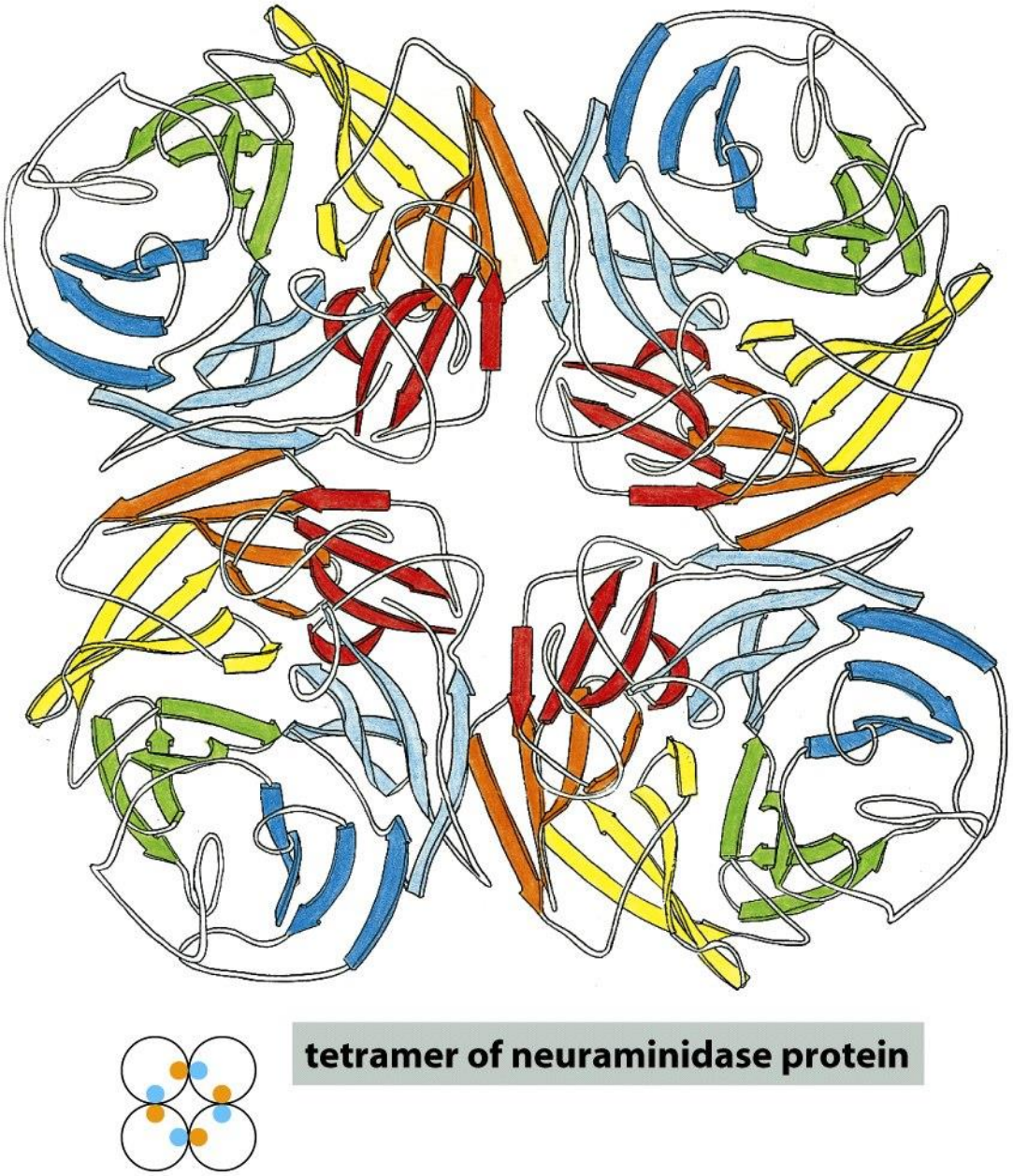



**Figure 3-22. A protein molecule containing multiple copies of a single protein subunit.** The enzyme neuraminidase exists as a **ring of four identical polypeptide chains**. The small diagram shows how the repeated use of the same binding interaction forms the structure.

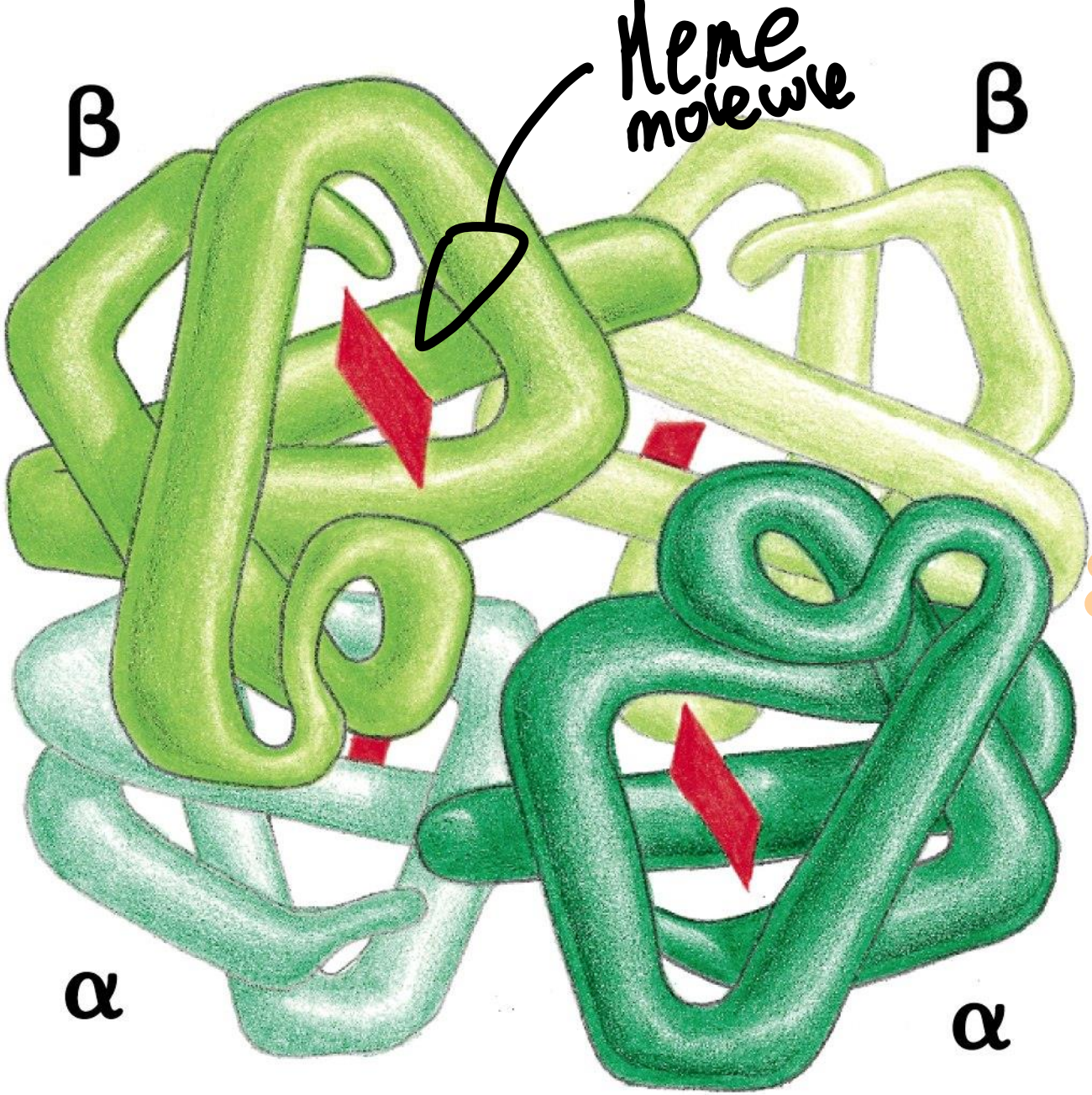



**Figure 3-23. A protein formed as a symmetric assembly of two different subunits.** Hemoglobin is an abundant protein in red blood cells that contains **two copies of a globin and two copies of b globin (polypeptides**. Each of these four polypeptide chains contains a heme molecule *(red),* which is the site where oxygen (O2) is bound. Thus, each molecule of hemoglobin in the blood carries four molecules of oxygen.

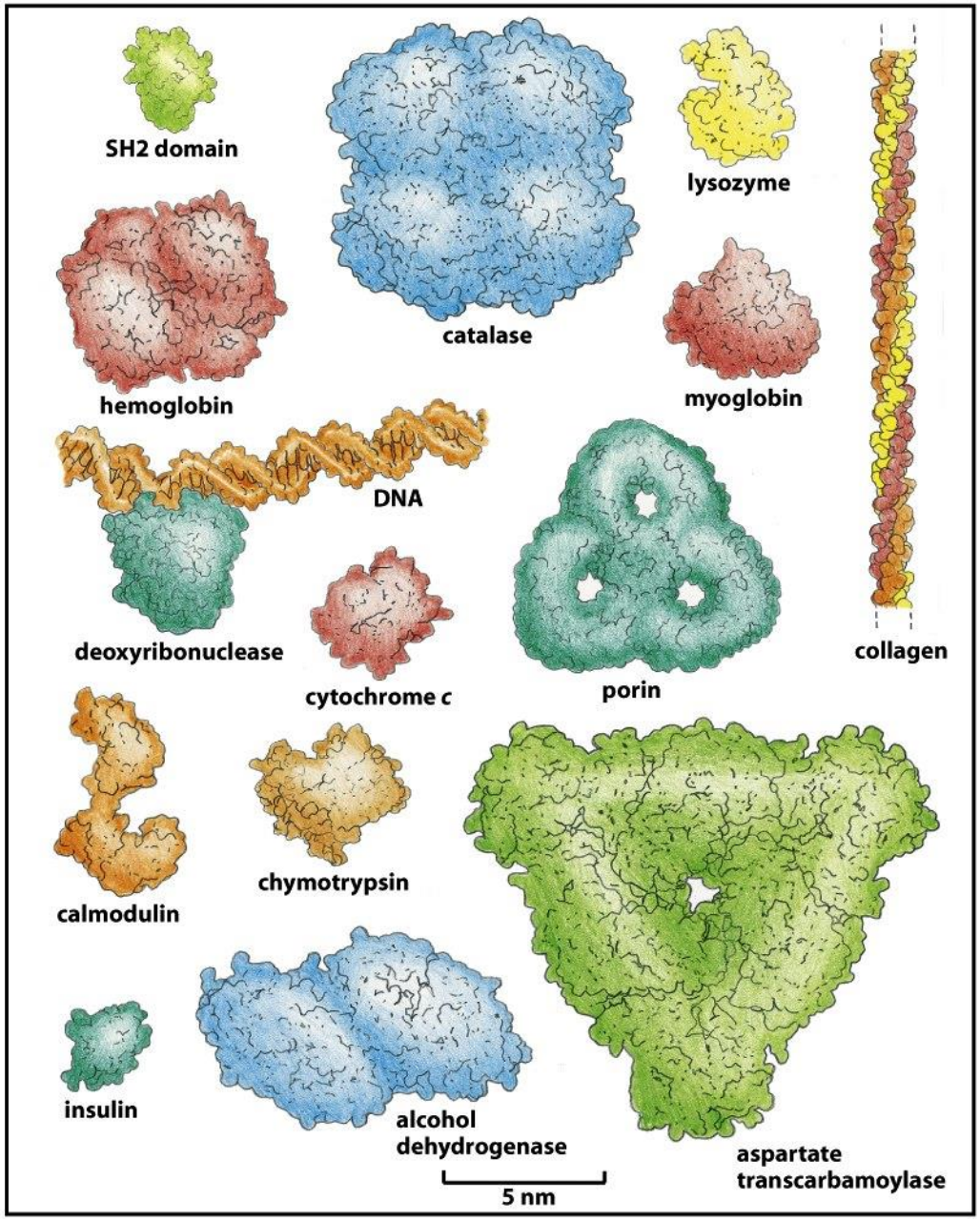
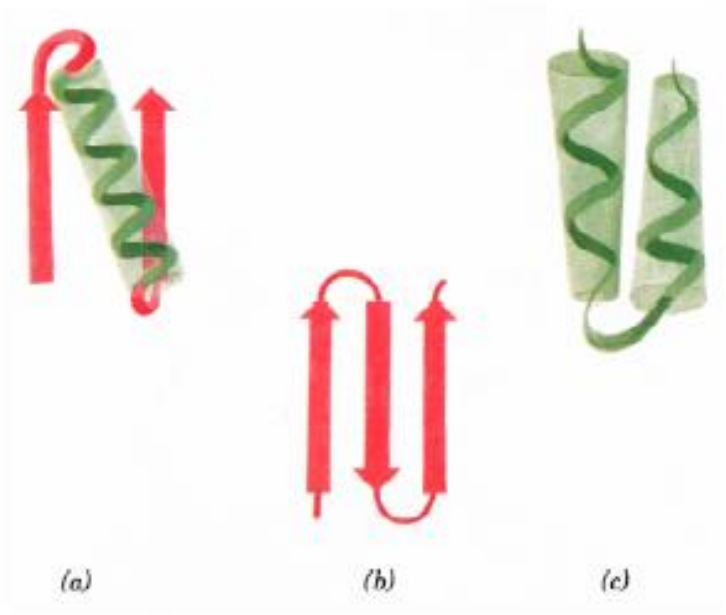



**Figure 3-24. A collection of protein molecules, shown at the same scale.** For comparison, a DNA molecule bound to a protein is also illustrated. These space-filling models represent a range of sizes and shapes. Hemoglobin, catalase, porin, alcohol dehydrogenase, and aspartate transcarbamoylase are formed from multiple copies of subunits. The SH2 domain *(top left)* is presented in detail in Panel 3-2 (pp. 138 139). (After David S. Goodsell, Our Molecular Nature. New York: Springer-Verlag, 1996




**βαβ motif** **β hairpin** **αα motif**

## Supersecondary Structure

- Simple assemblies of 2–3 secondary structure elements
- Often include turns (to re-orient the chain)
- Modules – used to build up the 3° level folds
- Generally not stable on their own

| | Used to build … | Specialized function? |
|---|---|---|
| β–hairpin | antiparallel sheets | |
| α –hairpin | helix bundles | |
| β – α – β | parallel sheets, TIM | |
| greek key | | |
| helix–turn–helix | | DNA binding |
| EF hand | | Ca++ binding |

Algunas proteínas forman largos **filamentos** helicales

- Si dos subunidades proteínicas tienen dos sitios de enlace complementarios es posible crear cadenas de tales subunidades

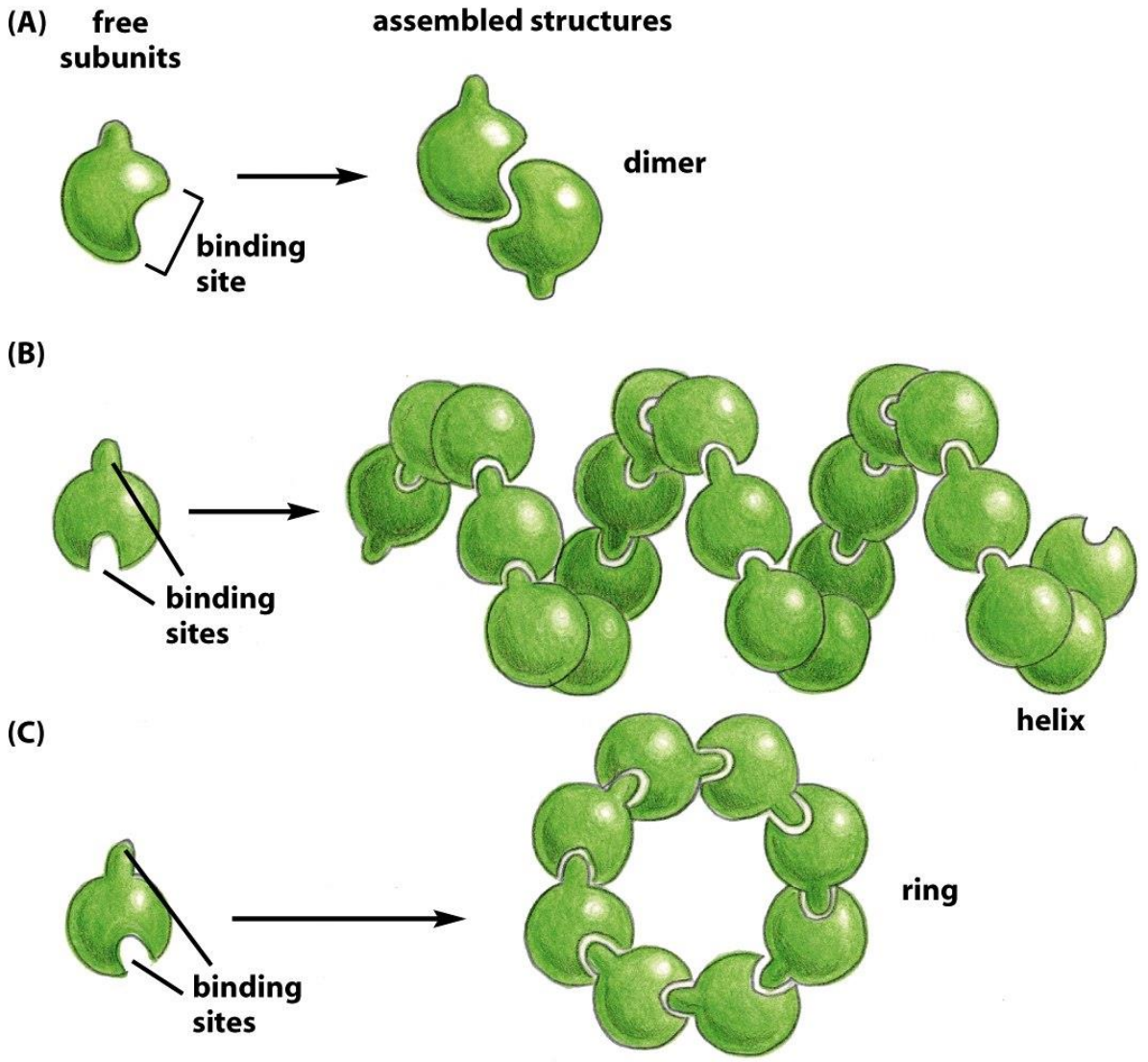



**Figure 3-25. Protein assemblies.** (A) A protein with just one binding site can form a dimer with another identical protein. (B) Identical proteins with two different binding sites often form a long helical filament. (C) If the two binding sites are disposed appropriately in relation to each other, the protein subunits may form a closed ring instead of a helix. (For an example of A, see Figure 3-21; for an example of C, see Figure 3-22.)

- Ej. Subunidades actina forman el filamento helical de actina.
  - Abundante en células eucariotas donde esta constituye uno de los mayores sistemas de filamento del citoesqueleto
- La mayoría de las proteínas son **globulares: ej. enzimas**

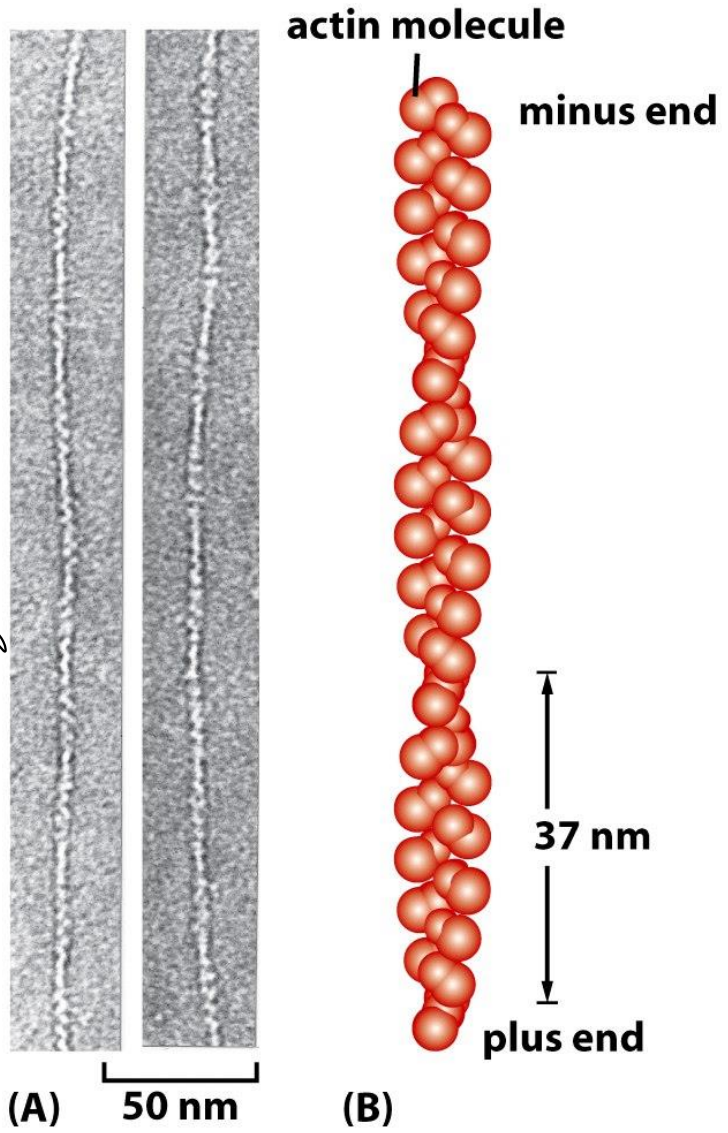



**Figure 3-26. Actin filaments.** (A) Transmission electron micrographs of negatively stained actin filaments. (B) The helical arrangement of actin molecules in an actin filament. (A, courtesy of Roger Craig.)

- Este mecanismo de enlazar subunidades con sitios de enlace complementarios generalmente lleva a la ***formación de estructuras helicales***
  - Son comunes en biología, las biomoléculas generalmente resultan de la unión repetitiva de subunidades idénticas en una cadena que frecuentemente solo se puede orientar de una manera.
  - Es muy raro que formen una línea recta generalmente resulta una hélice
  - Son comunes ya sea que las subunidades son moléculas pequeñas unidas por enlaces covalentes (ej. Proteínas, alfa hélices) o por nocovalentes (actina, subunidades proteìnicas)

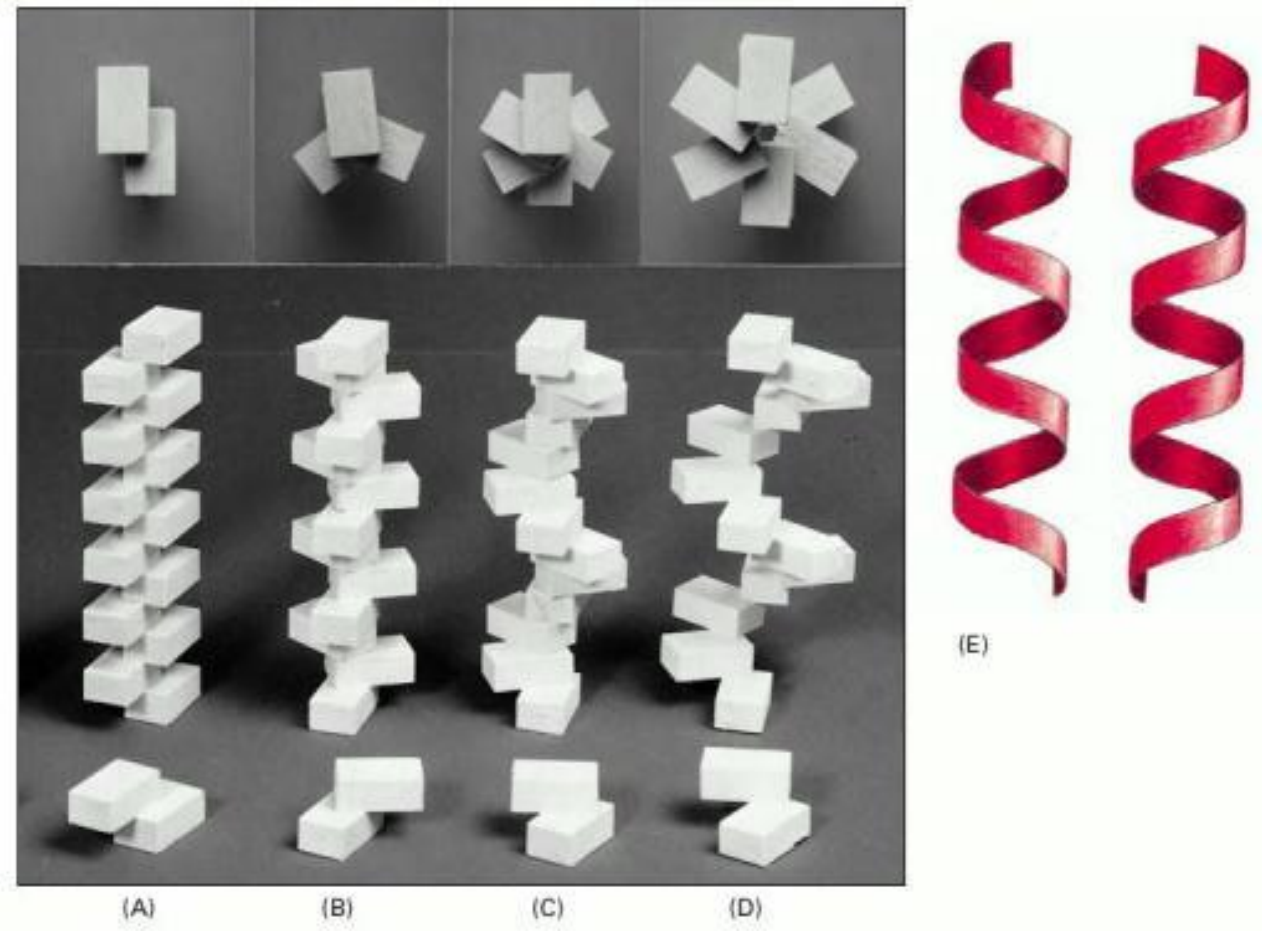
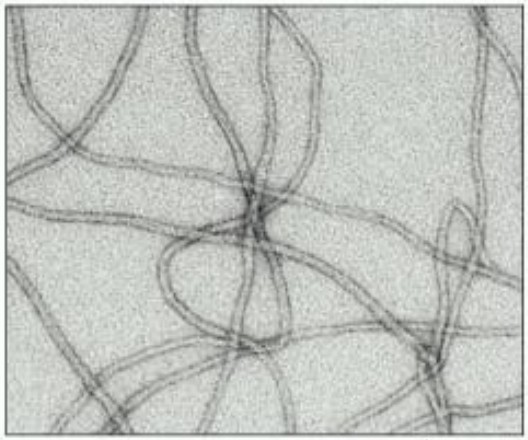
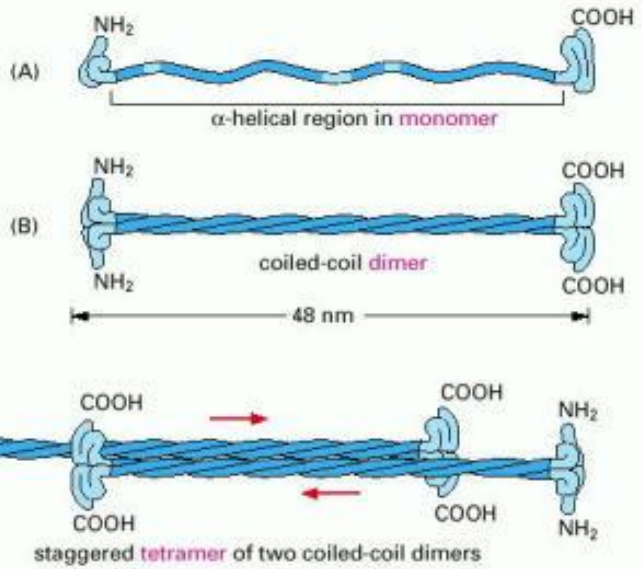



**Figure 3-27. Some properties of a helix.** (A D) A helix forms when a series of subunits bind to each other in a regular way. At the bottom, the interaction between two subunits is shown; behind them are the helices that result. These helices have two (A), three (B), and six (C and D) subunits per helical turn. At the top, the arrangement of subunits has been photographed from directly above the helix. Note that the helix in (D) has a wider path than that in (C), but the same number of subunits per turn. (E) A helix can be either right-handed or left-handed. As a reference, it is useful to remember that standard metal screws, which insert when turned clockwise, are right-handed. Note that a helix retains the same handedness when it is turned upside down.

Algunas **proteínas** pueden tener una forma **fibrosa** y alongada

- Proteínas en la célula que tienen como rol expandir grandes distancias
- $\alpha$ keratinas, componentes del cabello, pesuñas y uñas
  - Formada de filamentos helicales enrollados (coil-coiled), estas regiones helicales que en sus terminaciones tienen dominios globulares que contienen sitios de enlaces.
- Lo que permite a esta clase de proteína ensamblarse en una estructura a manera de soga, *los filamentos intermedios,* un componente importante del citoesqueleto


0.1 μm


(A)
NH2
COOH
α-helical region in monomer
(B)
NH2
COOH
coiled-coil dimer
NH2
COOH
48 nm
(C)
NH2
COOH
COOH
NH2
NH2
COOH
COOH
NH2
staggered tetramer of two coiled-coil dimers


(D)
two tetramers packed together

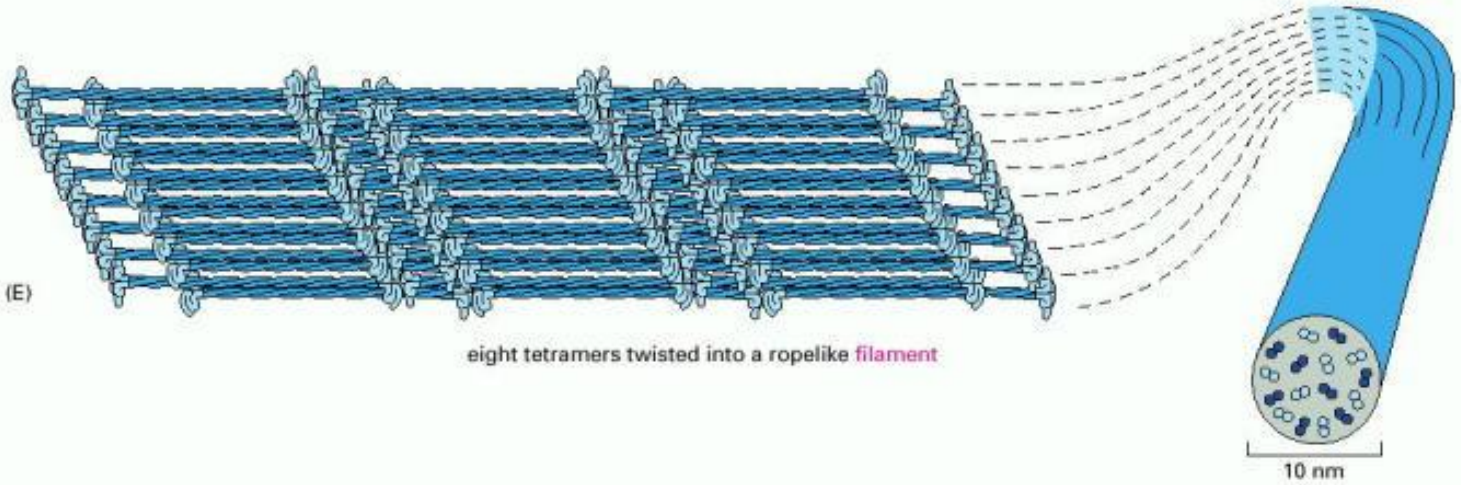

(E)
eight tetramers twisted into a ropelike filament
10 nm

**Figure 16-16. A model of intermediate filament construction.** The monomer shown in (A) pairs with an identical monomer to form a dimer (B), in which the conserved central rod domains are aligned in parallel and wound together into a coiled coil. (C) Two dimers then line up side by side to form an antiparallel tetramer of four polypeptide chains. The tetramer is the soluble subunit of intermediate filaments. (D) Within each tetramer, the two dimers are offset with respect to one another, thereby allowing it to associate with another tetramer. (E) In the final 10-nm rope-like filament, tetramers are packed together in a helical array, which has 16 dimers in cross-section. Half of these dimers are pointing in each direction. An electron micrograph of intermediate filaments are shown on the upper left. (Electron micrograph courtesy of Roy Quinlan.)

- Las proteínas fibrosas son de importancia especial fuera de la célula donde son componentes principales de la ***matriz extracelular*** que ayuda a mantener las células juntas para la formación de tejidos
  - Es secretada por la célula donde se ensamblan como sabanas de fibrillas
  - Colágeno es la mas abundante, formada de tres cadenas polipeptídicas que se enlazan unas con otras lado a lado para crear arreglos que dan al tejido conectivo su fuerza de tensión
  - En contraste la elastina formada de cadenas polipeptídicas no estructuradas que están enlazadas covalentemente (entrecruzadas) para formar una red que no tiene una estructura estable y puede cambiar de conformación

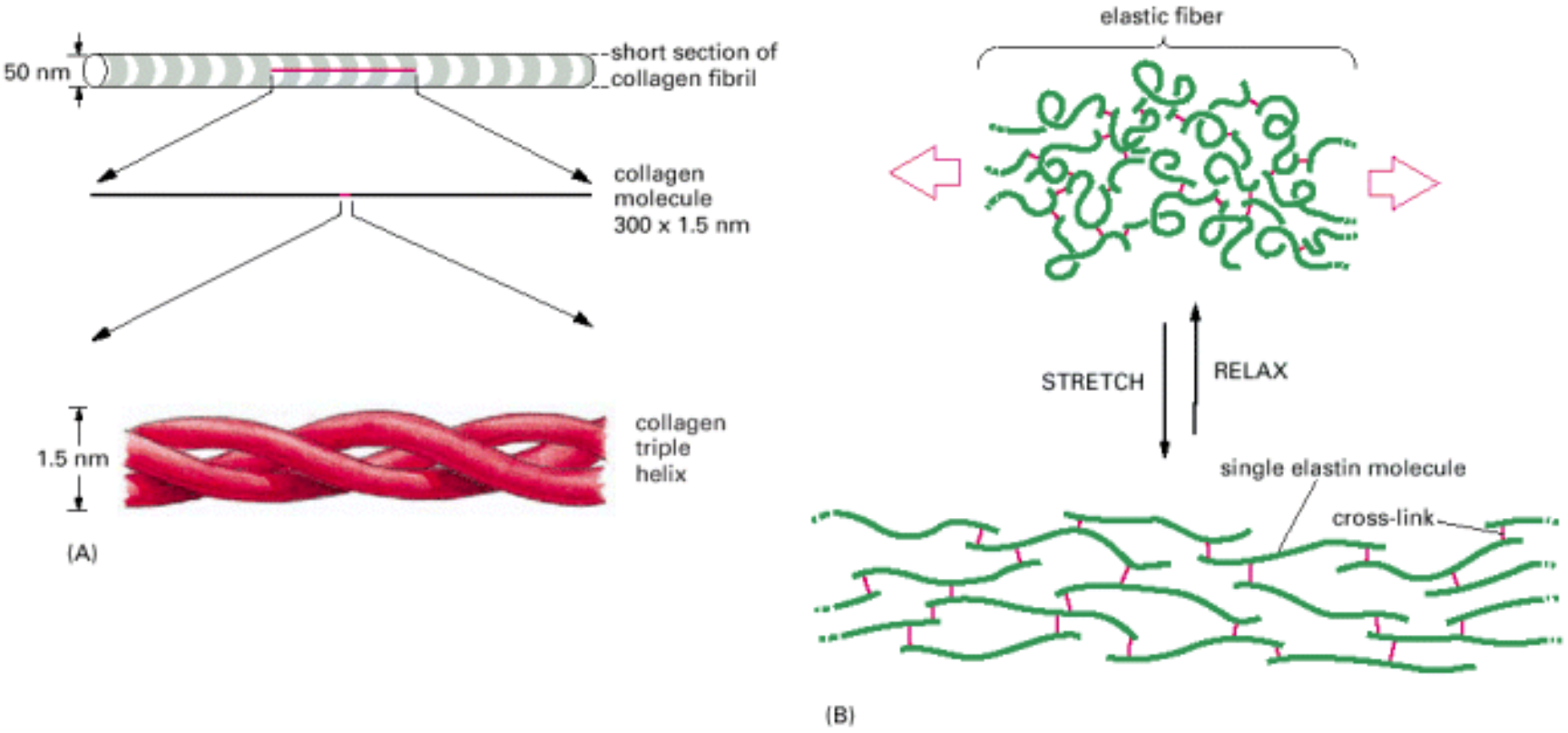



**Figure 3-28. Collagen and elastin.** (A) Collagen is a triple helix formed by three extended protein chains that wrap around one another *(bottom).* Many rodlike collagen molecules are cross-linked together in the extracellular space to form unextendable collagen fibrils *(top)* that have the tensile strength of steel. The striping on the collagen fibril is caused by the regular repeating arrangement of the collagen molecules within the fibril. (B) Elastin polypeptide chains are cross-linked together to form rubberlike, elastic fibers. Each elastin molecule uncoils into a more extended conformation when the fiber is stretched and recoils spontaneously as soon as the stretching force is relaxed.

- Las proteínas extracelulares existen en ambientes mas severos que las proteínas intracelulares.
  - Por esta razón deben incrementar su rigidez estructural por medios de enlaces disulfidos (S-S)
  - Estos enlaces son rápidamente separados por agente reductores en el citoplasma de la célula

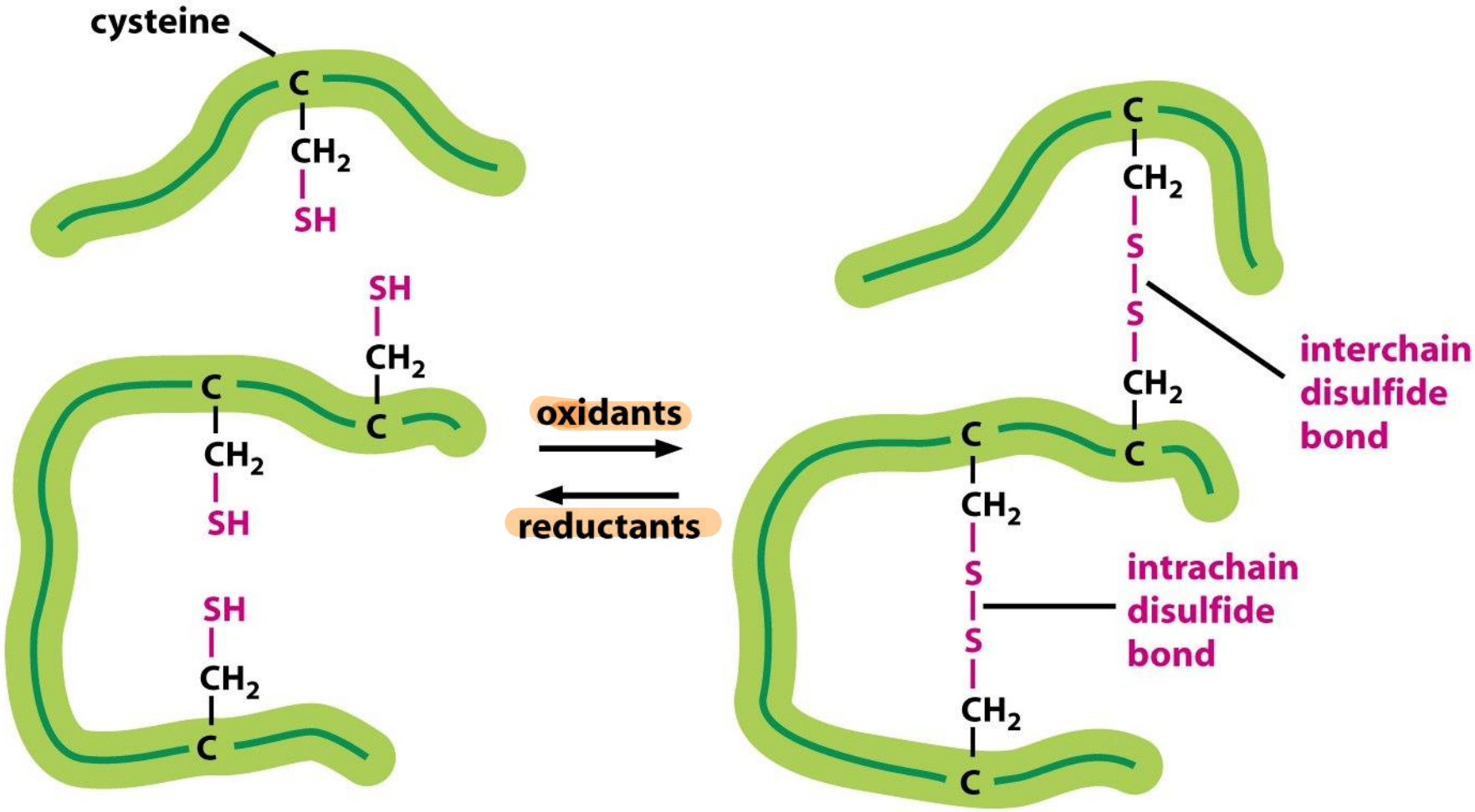



**Figure 3-29. Disulfide bonds.** This diagram illustrates how covalent disulfide bonds form between adjacent cysteine side chains. As indicated, these cross-linkages can join either two parts of the same polypeptide chain or two different polypeptide chains. Since the energy required to break one covalent bond is much larger than the energy required to break even a whole set of noncovalent bonds (see Table 2-2, p. 57), a disulfide bond can have a major stabilizing effect on a protein.

Estructuras mayores:

- Estructuras supramoleculares como
  - Complejos enzimáticos
  - Ribosomas
  - Filamentos de proteínas
  - Virus
  - Membranas
  - Creadas de un gran número de proteínas unidas *no covalentemente* que sirven como subunidades del ensamblaje final y no una sola estructura gigante de moléculas unidas covalentemente

## Ventajas de usar subunidades pequeñas

- Subunidades pequeñas menor información genética
- Ensamblaje y desensamblaje puede ser fácilmente controlado ya que las subunidades están unidos por enlaces débiles
- Errores en la síntesis pueden ser evitados ya que mecanismos de corrección pueden operar durante el ensamblaje o se excluyen subunidades malformadas
- Tales ensamblajes están construidas como sabanas que pueden ser convertidas en tubos o esferas que incrementan su estabilidad ya que poseen un mayor numero de interacciones débiles

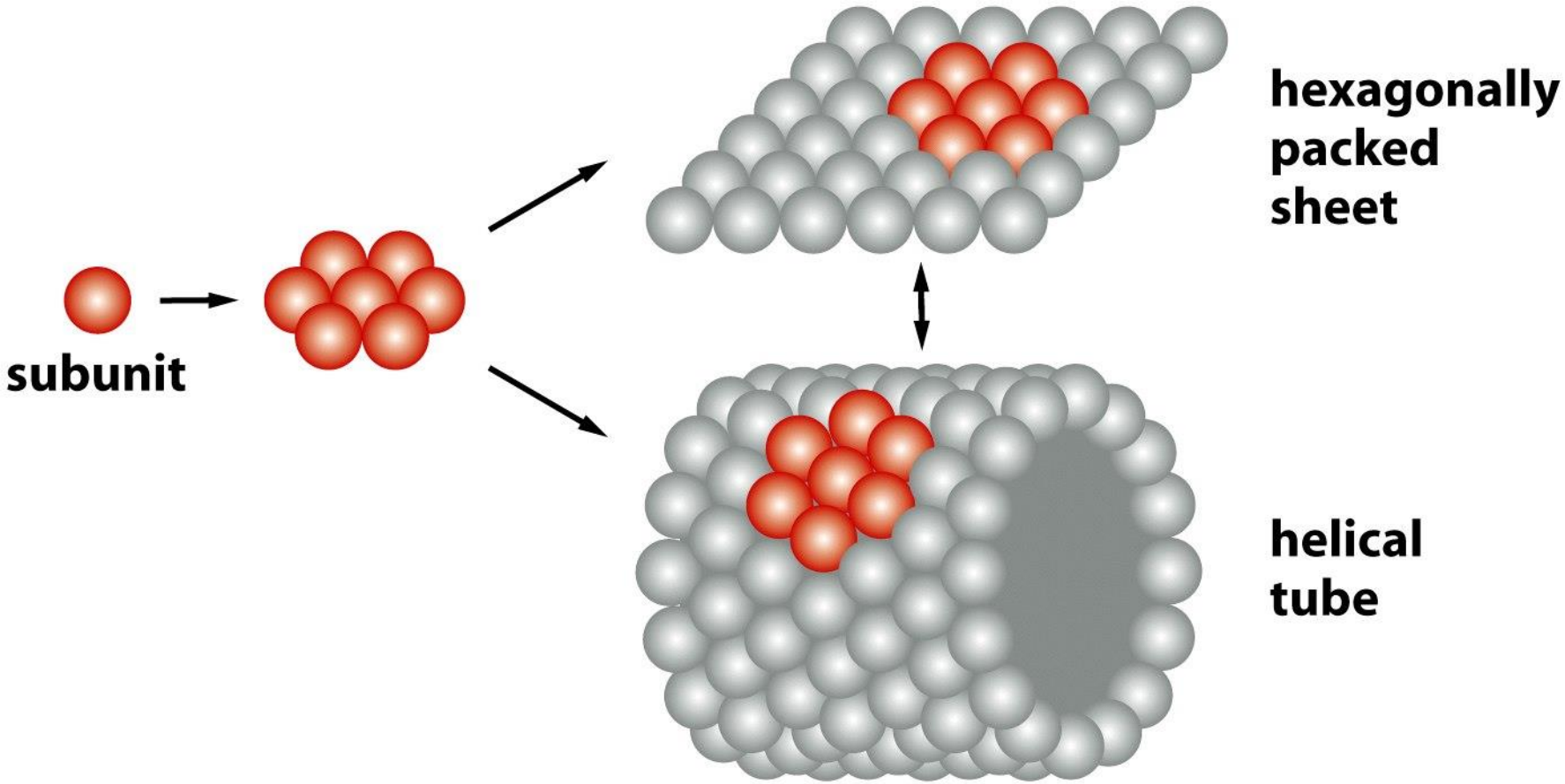



**Figure 3-30. An example of single protein subunit assembly requiring multiple protein  protein contacts.** Hexagonally packed globular protein subunits can form either a flat sheet or a tube.

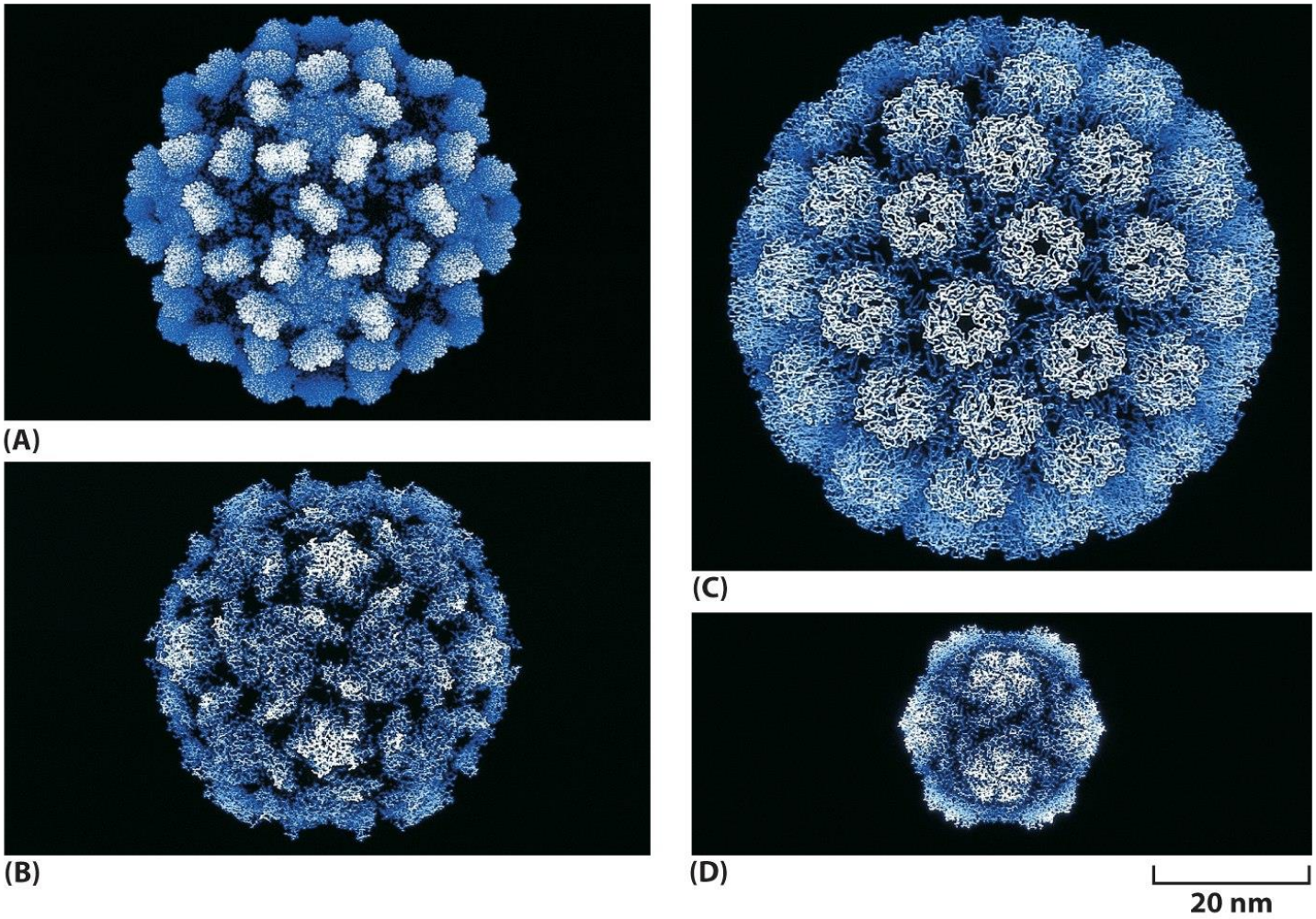



**Figure 3-31. The capsids of some viruses, all shown at the same scale.** (A) Tomato bushy stunt virus; (B) poliovirus; (C) simian virus 40 (SV40); (D) satellite tobacco necrosis virus. The structures of all of these capsids have been determined by x-ray crystallography and are known in atomic detail. (Courtesy of Robert Grant, Stephan Crainic, and James M. Hogle.)

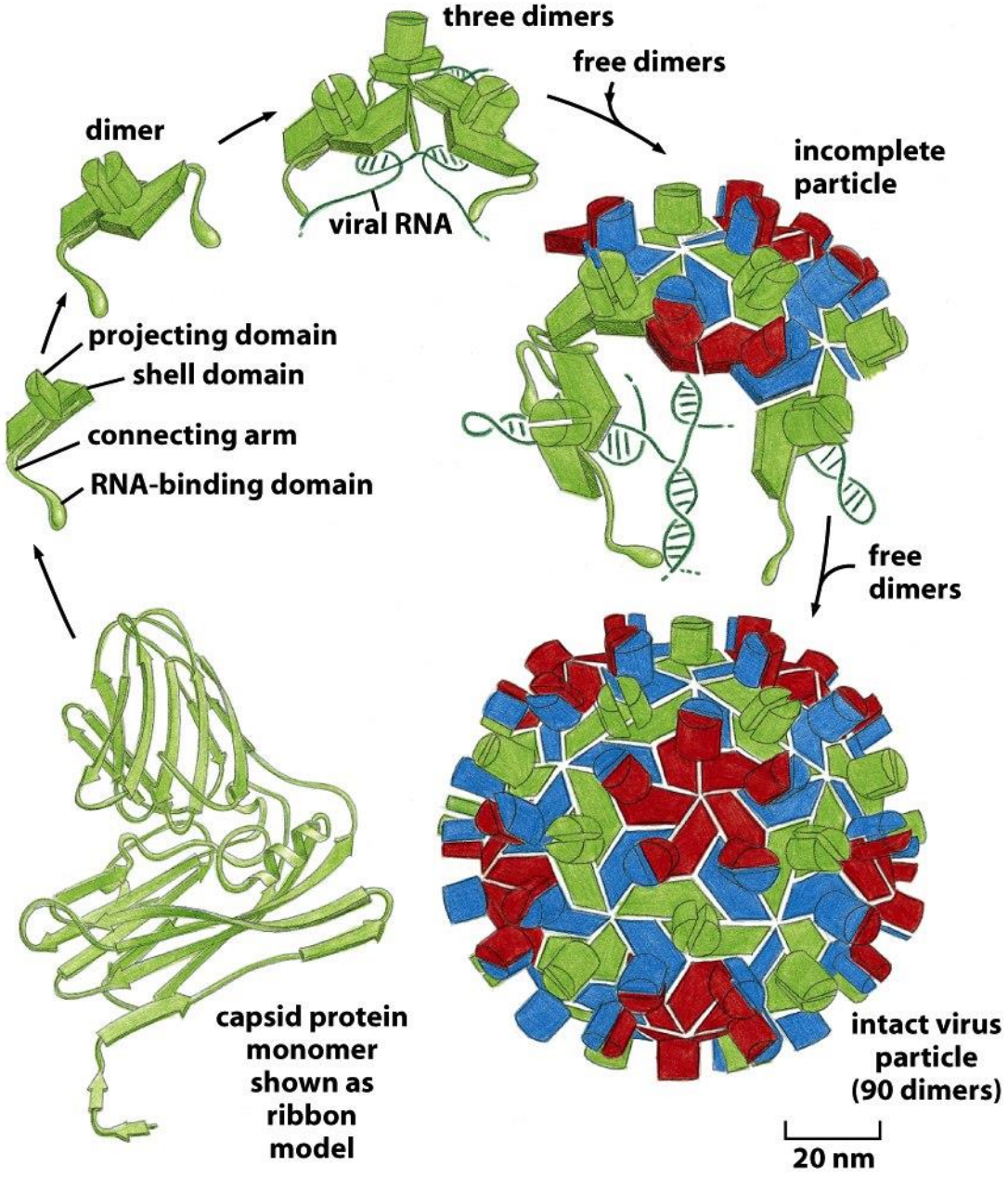



**Figure 3-32. The structure of a spherical virus.** In many viruses, identical protein subunits pack together to create a spherical shell (a capsid) that encloses the viral genome, composed of either RNA or DNA (see also Figure 3-31). For geometric reasons, no more than 60 identical subunits can pack together in a precisely symmetric way. If slight irregularities are allowed, however, more subunits can be used to produce a larger capsid. The tomato bushy stunt virus (TBSV) shown here, for example, is a spherical virus about 33 nm in diameter formed from 180 identical copies of a 386 amino acid capsid protein plus an RNA genome of 4500 nucleotides. To construct such a large capsid, the protein must be able to fit into three somewhat different environments, each of which is differently colored in the virus particle shown here. The postulated pathway of assembly is shown; the precise three-dimensional structure has been determined by x-ray diffraction. (Courtesy of Steve Harrison.)

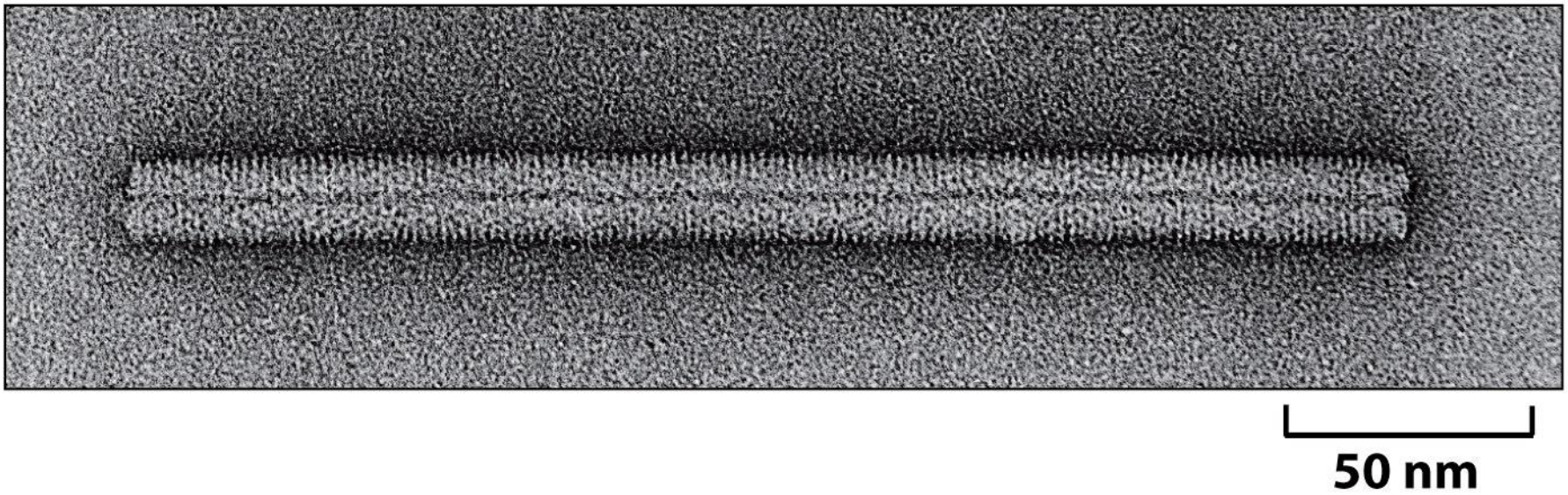



**Figure 3-33**.**The structure of tobacco mosaic virus (TMV)**(A) An electron micrograph of the viral particle, which consists of a single long RNA molecule enclosed in a cylindrical protein coat composed of identical protein subunits. (B) A model showing part of the structure of TMV. A single-stranded RNA molecule of 6000 nucleotides is packaged in a helical coat constructed from 2130 copies of a coat protein 158 amino acids long. Fully infective viral particles can self-assemble in a test tube from purified RNA and protein molecules. (A, courtesy of Robley Williams; B, courtesy of Richard J. Feldmann.)