<table>
<thead>
<tr>
<th>Monomer/ Oligomere</th>
<th>Polymer/Aggregat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zucker</td>
<td>Glucose,</td>
</tr>
<tr>
<td></td>
<td>Energie, Zellmarker</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fettsäuren</td>
<td>Lipide, Fett</td>
</tr>
<tr>
<td></td>
<td>Energiespeicher</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nukleinsäuren</td>
<td>ATP, cAMP</td>
</tr>
<tr>
<td></td>
<td>Energie, Signalsubstanzen</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosäuren</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Hormone</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ribosomale Proteinsynthese

- mehrere rRNA Stränge
- > 50 Proteine
- Durchmesser ~21nm
in vitro:

Aktivierung und Schutzgruppentechnik erforderlich:

- Aufbau einer Aminosäuresequenz
- Primärstruktur
<table>
<thead>
<tr>
<th>Length</th>
<th>Coupling Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.995 0.99 0.98 0.97 0.96</td>
</tr>
<tr>
<td>5</td>
<td>0.98 0.95 0.92 0.89 0.85</td>
</tr>
<tr>
<td>10</td>
<td>0.96 0.91 0.83 0.76 0.69</td>
</tr>
<tr>
<td>15</td>
<td>0.93 0.87 0.75 0.65 0.56</td>
</tr>
<tr>
<td>20</td>
<td>0.91 0.83 0.68 0.56 0.46</td>
</tr>
<tr>
<td>25</td>
<td>0.89 0.79 0.62 0.48 0.38</td>
</tr>
<tr>
<td>30</td>
<td>0.86 0.75 0.56 0.41 0.31</td>
</tr>
<tr>
<td>35</td>
<td>0.84 0.71 0.50 0.36 0.25</td>
</tr>
<tr>
<td>40</td>
<td>0.82 0.67 0.45 0.30 0.20</td>
</tr>
<tr>
<td>45</td>
<td>0.80 0.63 0.41 0.26 0.17</td>
</tr>
<tr>
<td>50</td>
<td>0.78 0.60 0.37 0.22 0.14</td>
</tr>
<tr>
<td>55</td>
<td>0.76 0.58 0.34 0.19 0.11</td>
</tr>
<tr>
<td>60</td>
<td>0.74 0.55 0.30 0.17 0.09</td>
</tr>
<tr>
<td>65</td>
<td>0.73 0.53 0.27 0.14 0.07</td>
</tr>
<tr>
<td>70</td>
<td>0.71 0.50 0.25 0.12 0.06</td>
</tr>
</tbody>
</table>
Die räumliche Struktur von Peptiden und Proteinen

Peptide, vor allem jedoch Proteine zeichnen sich durch hochgeordnete, räumliche Struktur aus, die von grundlegender Bedeutung für alle biologischen Aufgaben eines Proteins ist.

- Primärstruktur
- Sekundärstruktur
- Tertiärstruktur
- Quartärstruktur

Verlieren Proteine diese hochgeordnete Struktur, können sie ihre Aufgaben nicht mehr erfüllen. Man spricht von der Denaturierung des Proteins.
Primärstruktur, Sekundärstruktur, Tertiärstruktur, Quartärstruktur

- Primärstruktur
  - Asp - Pro - Ala - Arg - Ser - Tyr - Val - His - Glu - Phe - Lys - Gly - Gly - Asn - Ile...

- Sekundärstrukturen
  - Faltblattstruktur

- Tertiärstruktur
  - globuläres Protein

- Quartärstruktur
Different graphical representations of the same protein
Faltungsproblem

Konformation eines Proteins als Random Walk:

Gitter-Modell:

Kleines Protein mit 100 Aminosäuren

=> Mögliche Konformationen: $3^{100} \approx 10^{30}$

Interne Dynamik typ ns

⇒ Zeit, um alle möglichen Kombinationen durchzuspielen \( \approx 10^{21} \)

Vergleiche: Alter des Universums \( \approx 10^{20} \) s!

Mother nature has no folding problem, but we do!
Flat landscape (Levinthal paradox)  
Tunnel landscape (discrete pathways)  
Realistic landscape ("folding funnel")
# Protein Folding Related Diseases

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Fibril Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Aβ peptide, 1-42, 1-43</td>
</tr>
<tr>
<td>Spongiform encephalopathies</td>
<td>Full-length prion or fragments</td>
</tr>
<tr>
<td>Primary systemic amyloidosis</td>
<td>Intact light chain or fragments</td>
</tr>
<tr>
<td>Secondary systemic amyloidosis</td>
<td>76-residue fragment of amyloid A protein</td>
</tr>
<tr>
<td>Familial amyloidosic polyneuropathy I</td>
<td>Transthyretin variants and fragments</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Wild-type transthyretin and fragments</td>
</tr>
<tr>
<td>Hereditary cerebral amyloid angiopathy</td>
<td>Fragment of cystatin-C</td>
</tr>
<tr>
<td>Haemodialysis-related amyloidosis</td>
<td>β₂-microglobulin</td>
</tr>
<tr>
<td>Familial amyloidosic polyneuropathy II</td>
<td>Fragments of apolipoprotein A-1</td>
</tr>
<tr>
<td>Finnish hereditary amyloidosis</td>
<td>71-residue fragment of gelsolin</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Fragment of islet-associated polypeptide</td>
</tr>
<tr>
<td>Medullary carcinoma of the thyroid</td>
<td>Fragments of calcitonin</td>
</tr>
<tr>
<td>Atrial amyloidosis</td>
<td>Atrial natriuretic factor</td>
</tr>
<tr>
<td>Lysozyme amyloidosis</td>
<td>Full-length lysozyme variants</td>
</tr>
<tr>
<td>Insulin-related amyloid</td>
<td>Full-length insulin</td>
</tr>
<tr>
<td>Fibrinogen α-chain amyloidosis</td>
<td>Fibrinogen α-chain variants</td>
</tr>
</tbody>
</table>
**Thermodynamics of Protein Folding**

Free Energy; $\Delta G = \Delta H - T\Delta S$ (-$\Delta G$ favors folding)

<table>
<thead>
<tr>
<th>Protein</th>
<th>$\Delta G$</th>
<th>$\Delta H$</th>
<th>$\Delta S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribonuclease</td>
<td>-46</td>
<td>-280</td>
<td>-0.790</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>-62</td>
<td>-220</td>
<td>-0.530</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>-50</td>
<td>0</td>
<td>+0.170</td>
</tr>
</tbody>
</table>

(@ 25 °C and pH of maximum stability)

Figure 6.22, p. 186: Biochemistry; Mathews, Van Holde, Ahern

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Proteinfunktionen

- Zellgerüst
- Motoren
- Sensoren
- Photosynthese
- Enzymatische Katalyse
- Ionenkanäle
- ....
Beispiel: Die Sehkaskade

Stäbchenzelle
**dark state (11-cis 15-anti)**

**Meta II (all-trans 15-anti)**

**Meta III (all-trans 15-syn)**
Photozyklus
Sehkaskade

Photons Rhodopsin Transduzin

GC 

Phosphodiesterase

PDE

GC

GC

GTP

CaM

Ionpumpe

Kationen-Kanal

offen im Dunkeln

geschlossen im Licht

Diskmembran

Cytoplasma

Außensegment-Membran

Rädler / Mathias

SS2011
Aminosäuren, Peptide, Proteine

α-Aminocarbonsäuren

Natürliche Aminosäuren sind chiral und besitzen S-Konfiguration

Beispiele für proteinogene Aminosäuren

<table>
<thead>
<tr>
<th>R</th>
<th>Trivialname</th>
<th>Abkürzung</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>Glycin</td>
<td>Gly</td>
</tr>
<tr>
<td>-CH₃</td>
<td>Alanin</td>
<td>Ala</td>
</tr>
<tr>
<td>-CH(CH₃)₂</td>
<td>Valin</td>
<td>Val</td>
</tr>
<tr>
<td>-CH₂-OH</td>
<td>Serin</td>
<td>Ser</td>
</tr>
<tr>
<td>-CH₂-C₆H₄-OH</td>
<td>Tyrosin</td>
<td>Tyr</td>
</tr>
<tr>
<td>-CH₂-CO-NH₂</td>
<td>Asparagin</td>
<td>Asn</td>
</tr>
<tr>
<td>-(CH₂)₄-NH₂</td>
<td>Lysin</td>
<td>Lys</td>
</tr>
<tr>
<td>-CH₂-SH</td>
<td>Cystein</td>
<td>Cys</td>
</tr>
<tr>
<td>-CH₂-COOH</td>
<td>Asparaginsäure</td>
<td>Asp</td>
</tr>
<tr>
<td>-CH₂-CH₂-COOH</td>
<td>Glutaminsäure</td>
<td>Glu</td>
</tr>
</tbody>
</table>

20 proteinogene Aminosäuren, natürlich vorkommende Aminosäuren, die zum Aufbau von Peptiden und Proteinen dienen
Chemical modifications and processing alter the biological activity of proteins

3-Hydroxyproline (mainly in collagen)

4-Hydroxyproline (mainly in collagen)

3-Methylhistidine (mainly in actin)

5-Hydroxylysine (mainly in collagen)

γ-Carboxyglutamate (mainly in prothrombin, an essential blood-clotting factor)
THE AMINO ACID

The general formula of an amino acid is

\[ \text{H}_2\text{N} - \text{COOH} \]

amino
group
\[ \alpha\text{-carbon atom} \]
carboxyl
group
side chain
group

R is commonly one of 20 different side chains. At pH 7 both the amino and carboxyl groups are ionized.

\[ \text{H}_2\text{N} - \text{C} - \text{COO}^- \]

Lö 27, 28, 31M 567/568

OPTICAL ISOMERS

The \(\alpha\)-carbon atom is asymmetric, which allows for two mirror image (or stereo-) isomers, \(L\) and \(D\).

Proteins consist exclusively of \(L\)-amino acids.

PEPTIDE BONDS

Amino acids are commonly joined together by an amide linkage, called a peptide bond.

\[ \text{H} - \text{N} - \text{C} - \text{C} - \text{O} - \text{H} \]

\[ \text{H} - \text{N} - \text{C} - \text{C} - \text{O} - \text{H} \]

peptide bond: The four atoms in each gray box form a rigid planar unit. There is no freedom of rotation about the C—N bond.

Proteins are long polymers of amino acids linked by peptide bonds, and they are always written with the N-terminus toward the left. The sequence of this tripeptide is His Cys Val.
FAMILIES OF AMINO ACIDS

The common amino acids are grouped according to whether their side chains are
- acidic
- basic
- uncharged polar
- nonpolar

These 20 amino acids are given both three-letter and one-letter abbreviations.
Thus: alanine = Ala = A

BASIC SIDE CHAINS

Lysine (Lys, or K)
\[
\begin{array}{c}
\text{N} \quad \text{C} \\
\text{H} \quad \text{C} \\
\text{CH}_3 \\
\text{CH}_2 \\
\end{array}
\]
This group is very basic because its positive charge is stabilized by resonance.

Arginine (Arg, or R)
\[
\begin{array}{c}
\text{N} \quad \text{C} \\
\text{H} \quad \text{C} \\
\text{CH}_2 \\
\text{CH}_2 \\
\text{NH}_3 \quad +
\end{array}
\]
These nitrogens have a relatively weak affinity for an H\(^+\) and are only partly positive at neutral pH.

Histidine (His, or H)
\[
\begin{array}{c}
\text{N} \quad \text{C} \\
\text{H} \quad \text{C} \\
\text{CH}_2 \\
\text{CH}_2 \\
\end{array}
\]

Amino acids with uncharged polar side chains are relatively hydrophilic and are usually on the outside of proteins, while the side chains on nonpolar amino acids tend to cluster together on the inside. Amino acids with basic or acidic side chains are very polar, and they are nearly always found on the outside of protein molecules.

The one-letter code in alphabetical order:

A = Ala  G = Gly  M = Met  S = Ser
C = Cys  H = His  N = Asn  T = Thr
D = Asp  I = Ileu  P = Pro  V = Val
E = Glu  K = Lys  Q = Gin  W = Trp
F = Phe  L = Leu  R = Arg  Y = Tyr

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

The —OH group is polar.
Disulfidbrücken stabilisieren Proteine
(können in seltenen Fällen auch Knoten bilden)

HUMAN AGOUTI RELATED PROTEIN
WEAK CHEMICAL BONDS

Organic molecules can interact with other molecules through short-range noncovalent forces.

Weak chemical bonds have less than 1/20 the strength of a strong covalent bond. They are strong enough to provide tight binding only when many of them are formed simultaneously.
VAN DER WAALS FORCES

At very short distances any two atoms show a weak bonding interaction due to their fluctuating electrical charges. This force is known as van der Waals attraction. However, two atoms will very strongly repel each other if they are brought too close together. This van der Waals repulsion plays a major part in limiting the possible conformations of a molecule.

ENERGY

attraction repulsion

van der Waals force equilibrium at this point

each type of atom has a radius, known as its van der Waals radius, at which van der Waals forces are in equilibrium.

H

1.2 Å (0.12 nm)

C

2.6 Å (0.2 nm)

N

1.5 Å (0.15 nm)

O

1.4 Å (0.14 nm)

Two atoms will be attracted to each other by van der Waals forces until the distance between them equals the sum of their van der Waals radii. Although they are individually very weak, these van der Waals attractions can become important when two macromolecular surfaces fit very close together.

WEAK CHEMICAL BONDS

Organic molecules can interact with other molecules through short-range noncovalent forces.

Weak chemical bonds have less than 1/20 the strength of a strong covalent bond. They are strong enough to provide tight binding only when many of them are formed simultaneously.
HYDROGEN BONDS

A hydrogen atom is shared between two other atoms (both electronegative, such as O and N) to give a hydrogen bond.

\[
\text{N} - \text{H} \quad \text{H} \quad \text{O}
\]

Covalent bond $\approx 0.1 \text{ nm long}$
Hydrogen bond $\approx 0.2 \text{ nm long}$

Hydrogen bonds are strongest when the three atoms are in a straight line:

\[
\text{O} - \text{H} - \text{O}
\]

Examples in macromolecules:

- Amino acids in polypeptide chains hydrogen-bonded together.

\[
\begin{align*}
\text{R} - \text{C} &= \text{H} \\
\text{C} &= \text{O} \quad \text{H} \\
\text{N} &= \text{H} \\
\text{R} &= \text{C}
\end{align*}
\]

- Two bases, G and C, hydrogen-bonded in DNA or RNA.

\[
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\]

HYDROGEN BONDS IN WATER

Any molecules that can form hydrogen bonds to each other can alternatively form hydrogen bonds to water molecules. Because of this competition with water molecules, the hydrogen bonds formed between two molecules dissolved in water are relatively weak.

\[
\begin{align*}
\text{C} - \text{C} - \text{N} - \text{C} &= \text{H} \quad \text{H} \\
\text{H} &= \text{O} \\
\text{H} &= \text{O} \\
\text{H} &= \text{O} \\
\text{H} &= \text{O}
\end{align*}
\]
Water forces hydrophobic groups together in order to minimize their disruptive effects on the hydrogen-bonded water network. Hydrophobic groups held together in this way are sometimes said to be held together by “hydrophobic bonds,” even though the attraction is actually caused by a repulsion from the water.
IONIC BONDS

Ionic bonds occur either between fully charged groups (ionic bond) or between partially charged groups.

The force of attraction between the two charges $\delta^+$ and $\delta^-$ is

$$\text{force} = \frac{\delta^+ \delta^-}{r^2 D}$$

(Coulomb's law)

where $D =$ dielectric constant

- (1 for vacuum; 80 for water)

$r =$ distance of separation

In the absence of water, ionic forces are very strong. They are responsible for the strength of such minerals as marble and agate.

IONIC BONDS IN AQUEOUS SOLUTIONS

Charged groups are shielded by their interactions with water molecules. Ionic bonds are therefore quite weak in aqueous solution.

Ionic bonds are further weakened by the presence of salts, whose atoms form the counterions that cluster around ions of opposite charge.

Measurement of the extent of destabilization of an interaction by salt provides a quantitative estimate of the total number of ionic bonds involved.

Despite being weakened by water and salt, ionic bonds are very important in biological systems; an enzyme that binds a positively charged substrate will often have a negatively charged amino acid side chain at the appropriate place.
Table 3-2. Covalent and Noncovalent Chemical Bonds

<table>
<thead>
<tr>
<th>Bond Type</th>
<th>Length (nm)</th>
<th>In Vacuum</th>
<th>In Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent</td>
<td>0.15</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Ionic</td>
<td>0.25</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>0.30</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>van der Waals attraction</td>
<td>0.35</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* The strength of a bond can be measured by the energy required to break it, here given in kilocalories per mole (kcal/mole). (One kilocalorie is the quantity of energy needed to raise the temperature of 1000 g of water by 1°C. An alternative unit in wide use is the kilojoule, kJ, equal to 0.24 kcal.) Individual bonds vary a great deal in strength, depending on the atoms involved and their precise environment, so that the above values are only a rough guide. Note that the aqueous environment in a cell will greatly weaken both the ionic and the hydrogen bonds between nonwater molecules (Panel 3-1, pp. 92-93). The bond length is the center-to-center distance between the two interacting atoms; the length given here for a hydrogen bond is that between its two nonhydrogen atoms.
Steric limitations on the bond angles in a polypeptide chain.

(A) Each amino acid contributes three bonds (colored red) to its polypeptide chain. The peptide bond is planar (gray shading) and does not permit rotation. By contrast, rotation can occur about the C–C bond, whose angle of rotation is called psi (ψ), and about the N–C (C–N) bond, whose angle of rotation is called phi (φ). The R group denotes an amino acid side chain. (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 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.)
Glyzin, Pre-Prolin, Prolin

A

B

Proline

Rädler / Mathias
SS2011

A β−sheet is a common structure formed by parts of the polypeptide chain in globular proteins. At the top, a domain of 115 amino acids from an immunoglobulin molecule is shown; it consists of a sandwich-like structure of two β−sheets, one of which is drawn in color. At the bottom, a perfect antiparallel β−sheet is shown in detail, with the amino acid side chains denoted R. Note that every peptide bond is hydrogen-bonded to a neighboring peptide bond. The actual sheet structures in globular proteins are usually less regular than the β−sheet shown here, and most sheets are slightly twisted.
An α-helix is another common structure formed by parts of the polypeptide chain in proteins. (A) The oxygen-carrying molecule myoglobin (153 amino acids long) is shown, with one region of α-helix outlined in color. (B) A perfect α-helix is shown in outline. (C) As in the β-sheet, every peptide bond in an α-helix is hydrogen-bonded to a neighboring peptide bond. Note that for clarity in (B) both the side chains [which protrude radially along the outside of the helix and are denoted by R in (C)] and the hydrogen atom are omitted on the α-carbon atom of each amino acid.
Motifs are regular combinations of secondary structures

A coiled coil motif is formed by two or more helices wound around one another e.g. Collagen
Three levels of organization of a protein. The three-dimensional structure of a protein can be described in terms of different levels of folding, each of which is constructed from the preceding one in hierarchical fashion. These levels are illustrated here using the catabolite activator protein (CAP), a bacterial gene regulatory protein with two domains. When the large domain binds cyclic AMP, it causes a conformational change in the protein that enables the small domain to bind to a specific DNA sequence. The amino acid sequence is termed the primary structure and the first folding level the secondary structure. As indicated under the brackets at the bottom of this figure, the combination of the second and third folding levels shown here is commonly termed the tertiary structure, and the fourth level (the assembly of subunits) the quaternary structure of a protein.
The information for protein folding is encoded in the sequence. The amino acid sequence of a polypeptide chain contains all the information required to fold the chain into its native, 3D structure.
Primary and secondary structure in hemagglutinin
Tertiary and quaternary structure in hemagglutinin
Up To Date No Unified Folding Theory

Molten globules, hydrophobic collapse

Framework model

Anfinsen
Spontaneous refolding

Nucleation growth

Jigsaw model

Rädler / Mathias
SS2011
Folding Funnel
Folding of proteins in vivo is promoted by chaperones