gregates can form. Tubulin consists of two subunits, and they come together to form a dimer. The dimers are thought to form small aggregates, the "nuclei," during the *nucleation period*. When a sufficient number of nuclei are present, they come together to form large aggregates at a rapid rate during the *elongation period*. At equilibrium, large microtubules shed and regain tubulin dimers at the same rate.

Not all protein aggregates are beneficial. In patients afflicted with sickle-cell anemia, hemoglobin molecules aggregate into rods, rendering the red blood cell unable to transport O_2 efficiently. Also, the presence of aggregates of proteins in the brain appears to be associated with several serious conditions. For example, the *amyloid plaques* found in postmortem analysis of the brains of patients with Alzheimer's disease are a mixture of damaged neurons and aggregates of the β amyloid protein, which is an extended antiparallel β sheet. In solution, the mechanism of aggregation also shows that nucleation is the rate-determining step, and curves of aggregate concentration against time are similar to those shown in Fig. 11.49.

11.15 Interactions between proteins and biological membranes

Because the proteins embedded in cell membranes are responsible for many important biological processes, such as the conduction of nerve impulses and the synthesis of ATP, we need to understand the factors that optimize the self-assembly of proteins with lipid bilayers.

In Chapter 2 we saw that cell membranes are sheetlike lipid bilayers, with hydrophilic groups pointing outward and hydrophobic groups aggregating in the interior of the layered structure (Fig. 2.17). The aggregate is held together by hydrophobic interactions between the long hydrocarbon chains of lipid molecules. Experimental evidence suggests that the bilayer is a highly mobile structure (see Section 2.12). Not only are the hydrocarbon chains ceaselessly twisting and turning in the region between the polar groups, but phospholipid and cholesterol molecules migrate over the surface. It is better to think of the membrane as a viscous fluid rather than a permanent structure, with a viscosity about 100 times that of water. In common with diffusional behavior in general (see Section 8.1), the average distance a phospholipid molecule diffuses is proportional to the square root of the time. Typically, a phospholipid molecule migrates through about 1 μm (the diameter of a cell) in about 1 min.

Peripheral proteins are proteins attached to the bilayer. **Integral proteins** are proteins immersed in the mobile but viscous bilayer. Examples include complexes I–IV of oxidative phosphorylation (Section 5.11), ion channels, and ion pumps (Section 5.3). Integral proteins may span the depth of the bilayer and consist of tightly packed α helices or, in some cases, β sheets containing hydrophobic residues that sit comfortably within the hydrocarbon region of the bilayer. The hydrophobicity of a residue can be assessed by measuring the Gibbs energy of transfer of the corresponding amino acid from an aqueous solution to the interior of a membrane (Table 11.7). Amino acids with negative values of the Gibbs energy of transfer are likely to be found in the membrane-spanning regions of integral proteins.

There are two views of the motion of integral proteins in the bilayer. In the **fluid mosaic model** shown in Fig. 11.50, the proteins are mobile, but their diffusion coefficients are much smaller than those of the lipids. In the **lipid raft model**, a number of lipid and cholesterol molecules form ordered structures, or "rafts," that envelope proteins and help carry them to specific parts of the cell.

COMMENT 11.7 For a molecule confined to a two-dimensional plane, the average distance traveled in a time t is equal to $(4Dt)^{1/2}$, where D is the diffusion coefficient. ■

Table 11.7 Gibbs energies of transfer of amino acid residues in an α helix from the interior of a membrane to water

Amino acid	$\Delta_{transfer}G$/(kJ mol^{-1})
Phenylalanine	15.5
Methionine	14.3
Isoleucine	13.0
Leucine	11.8
Valine	10.9
Cysteine	8.4
Tryptophan	8.0
Alanine	6.7
Threonine	5.0
Glycine	4.2
Serine	2.5
Proline	−0.8
Tyrosine	−2.9
Histidine	−12.6
Glutamine	−17.2
Asparagine	−20.2
Glutamic acid	−34.4
Lysine	−37.0
Aspartic acid	−38.6
Arginine	−51.7

Data from D.M. Engelman, T.A. Steitz, and A. Goldman, *Ann. Rev. Biophys. Biophys. Chem.* **15**, 330 (1986).

The mobility of the bilayer enables it to flow around a molecule close to the outer surface, to engulf it, and to incorporate it into the cell by the process of *endocytosis*. Alternatively, material from the cell interior wrapped in cell membrane may coalesce with the cell membrane itself, which then withdraws and ejects the material in the process of *exocytosis*. An important function of the proteins embedded in the bilayer, though, is to act as devices for transporting matter into and out of the cell in a more subtle manner, as discussed in Section 8.2.

11.16 Nucleic acids

Of crucial biological importance are the conformations adopted by nucleic acids, the key components of the mechanism of storage and transfer of genetic information in biological cells.

Deoxyribonucleic acid (DNA) contains the instructions for protein synthesis, which is carried out by different forms of ribonucleic acid (RNA). They are polynucleotides, polymers of base-sugar-phosphate units linked by phosphodiester bonds (Section 3.5), that self-assemble into complex three-dimensional structures.

An example of secondary structure in nucleic acids is the winding of two polynucleotide chains around each other to form a DNA double helix, as shown in Figs. 3.15 and 11.51. Figure 11.51 also shows that different forms of the double