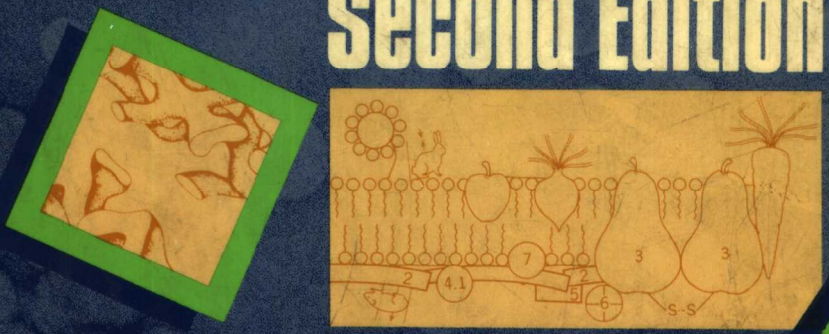
INTRODUCTION TO BIOLOGICAL MEMBRANES

Second Edition



Mahendra Jain

Introduction to Biological Membranes

SECOND EDITION

Mahendra Kumar Jain
Department of Chemistry
University of Delaware
Newark, Delaware

A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS
NEW YORK CHICHESTER BRISBANE TORONTO SINGAPORE

To My Mother
who once wondered
why the evening news always
lasts thirty minutes

Library of Congress Cataloging-in-Publication Data:

Jain, Mahendra K., 1938–
Introduction to biological membranes / Mahendra Kumar Jain.—2nd ed.

p. cm.
"A Wiley-Interscience publication."
Bibliography: p.
Includes index.
ISBN 0-471-84471-3: $39.95 (est.)
1. Membranes (Biology) I. Title.
QH601.J36 1988
574.87'5—dc19 87-18914
CIP

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Preface

Experts do not give objective opinion, they give their opinion.

Morarji Desai

Considerable progress has been made during the last two decades toward a molecular description of membrane processes. The study of membranes has the distinction of not being part of any one of the classical disciplines; therefore, an introductory text on membranes must transcend the boundaries of most classical disciplines while permitting the reader to draw information and inspiration from diverse areas of investigation. Although the perspectives from the various disciplines are neither unified nor always coincident, the sophistication of techniques and articulation of models have reached a stage at which, with modest imagination, we can begin to appreciate the functional complexity of membranes in the form of an organizational hierarchy. We have reached a descriptive level at which we can write schemes and often dissect the rate constants, and the stage is set to elaborate on the molecular dynamics and the underlying mechanisms.

In the hierarchy of biological organization, the structure and function of membranes lies somewhere between macromolecules and cells. As noncovalently aggregated macroscopic structures arising from amphipathic molecules, membranes in general have their unique characteristics that are not shared by other biomolecules and their aggregates. This book is an attempt to capture at present a theme that underlies the phenomenon of biological membranes, to provide a conceptual context, and to guide the novice to the specialized literature. Whenever possible, along with the phenomenology, a qualitative description of the underlying biophysical concepts is presented. This is not an authoritative treatise nor a critical review, although I have

tried to approximate the general consensus on the state-of-the-art. Since this book is intended for a wide variety of readers, primary and secondary key references leading to the various levels of complexity are included. No attempt has been made to provide an extensive bibliography, although references as a general guide for the background material are also given.

I have greatly benefited from the thoughtful comments and reprints provided by a large number of membranologists. In the light of such suggestions I have tried to strike a balance while maintaining a conceptual continuity. I have refrained from summaries that require oversimplifications and unwarranted generalizations. I deeply appreciate informal comments from friends and strangers, and I look forward to suggestions from novices as well as experts, which I hope to incorporate in future versions.

MAHENDRA KUMAR JAIN

Newark, Delaware

Contents

1 Introduction

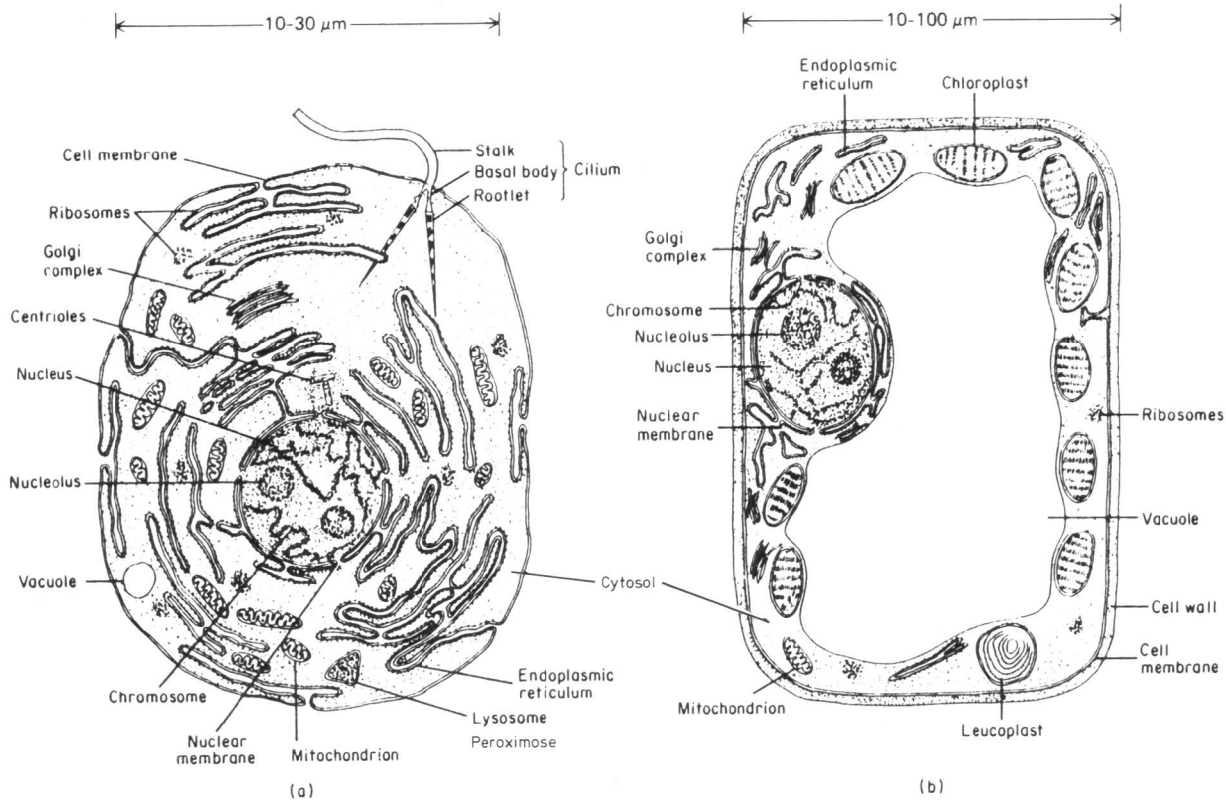
. . . liquids pose a great problem of packaging, which every experienced chemist knows. And it was well known to God Almighty, who solved it brilliantly, as he is wont to, with cellular membranes, egg shells, the multiple peels of oranges, and our own skins, because after all we too are liquids. Now at that time, there did not exist polyethylene, which would have suited me perfectly since it is flexible, light, and splendidly impermeable: but it is also a bit too incorruptible, and not by chance God Almighty himself, although he is a master of polymerization, abstained from patenting it: He does not like incorruptible things.

PRIMO LEVI
The Periodic Table*

Containing, compartmentalizing, and regulating the transfer of metabolites and macromolecules in a living organism are the primary functions of membranes. In nucleated cells, for example, plasma membranes surround an impressive array of cytoplasmic organelles, each with its own membrane as shown schematically in Fig. 1-1. The identity and the very existence of a cell and its organelles are not possible without membranes which separate the internal *milieu* from the surrounding environment. Functional specialization of structures enclosed with membranes, like organelles, is due to certain distinctive characteristics of their membranes.

Membranes provide a biophysical basis for the very concept of the cell (for an introductory text, see Alberts et al., 1983) as a unifying theme in the biosphere. It is not easy to conceive how life in all its manifestations, as we know it, could have evolved without a membrane-like structure that isolates the internal microenvironment from the variability and fluctuations of its surroundings. The problem of the evolution of membrane is multifaceted. The concept of a two-dimensional continuous molecular matrix is intrinsic to the concept of membrane-enclosed structures and it is necessary for compartmentalization. However, compared with the behavior of linear biological polymeric macromolecules like proteins and nucleic acids, the noncovalent supramolecular organization of biomembranes poses unique questions about

* This dilemma was encountered by the author, while in a German concentration camp, trying to steal in order to stave off starvation


10-30 μm
Cell membrane
Stalk
Basal body
Cilium
Rootlet
Ribosomes
Golgi complex
Centrioles
Nucleus
Nucleolus
Vacuole
Cytosol
Chromosome
Nuclear membrane
Mitochondrion
Endoplasmic reticulum
Lysosome
Peroximose
(a)
10-100 μm
Endoplasmic reticulum
Chloroplast
Golgi complex
Chromosome
Nucleolus
Nucleus
Nuclear membrane
Ribosomes
Vacuole
Cell wall
Cell membrane
Mitochondrion
Leucoplast
(b)

thermodynamics and kinetics of assembly, organization, repair, material balance, cooperative interactions, asymmetry, and degrees of motional freedom.

The ubiquity of membranes in living systems implies their antiquity and functional diversity in the evolutionary sense. Our concept of evolution depends upon the spontaneous evolution of a cell. This cannot be achieved without membranes, although genes and proteins are also necessary, but not sufficient. As one would also expect from the diversity of life forms, membranes have evolved to perform diverse tasks (Fig. 1-2). For example, simple membranes such as those of the egg yolk sac essentially act as barriers; the plant cell membranes permit passage of certain solutes but not others; bacterial membranes tend to accumulate nutrients from the surroundings against concentration gradients; chloroplast membranes convert light energy into the energy of the proton gradient; and nerve cell membranes transmit coded electrical signals in response to specific stimuli. The underlying biophysical processes, which range from osmosis, to gated channels ultimately form the molecular basis for understanding such complex organismic functions as blood-brain-barrier (BBB), respiration, motility, and memory. Thus, for example, the BBB is made up of epithelial cells, and the passage of solutes through this complex barrier could occur via intercellular channels, through solubility-diffusion or facilitated transport mechanism, by transbilayer *flip-flop*, or by endocytosis.

Fig. 1-1. Caricature of the thin section of a generalized animal (a) and of a higher plant cell (b) illustrating relationships between different compartments created by the plasma membrane and the membranes of organelles. Membranes are shown as a pair of lines separated by a light interzone. The invaginations of the cell surface (especially in the animal cell) are indicated in several areas; some of these endoplasmic reticular structures extend for a considerable distance into the cell. The nuclear membrane is composed of flattened sacs of the endoplasmic reticulum (ER), and the enclosed space is in continuity with the cytoplasm. Golgi complex is shown here as modified ER but separated from cellular membrane. Mitochondria are shown with their cristae formed by invagination of their inner membrane. Chloroplasts have a similar, but not identical, structure. Lysosomes represent a class of organelles whose condition within a tissue varies under different stimuli. Organelles in general vary in form, size, and location within the cell. Also the number of organelles in a given type of cell may vary several hundredfold. Extracellular matrix (a "fuzz" always seen on the outer surface of a cell) and filamentous cytoskeleton are not shown. In animal cells the cytoskeleton is often organized in areas near the nucleus that contain the cell's pair of centrioles. The cytoskeletal filaments are made up of arrays of proteins that seem to hold organelles in the cytosol, give membrane its shape, and anchor certain membrane proteins. Three kinds of filaments that are often found are microtubules (diameter 25 nm), actin filaments (7 nm), and intermediate filaments (10 nm). For further details of the various organelles and morphological compartments see Fig. 2-1.

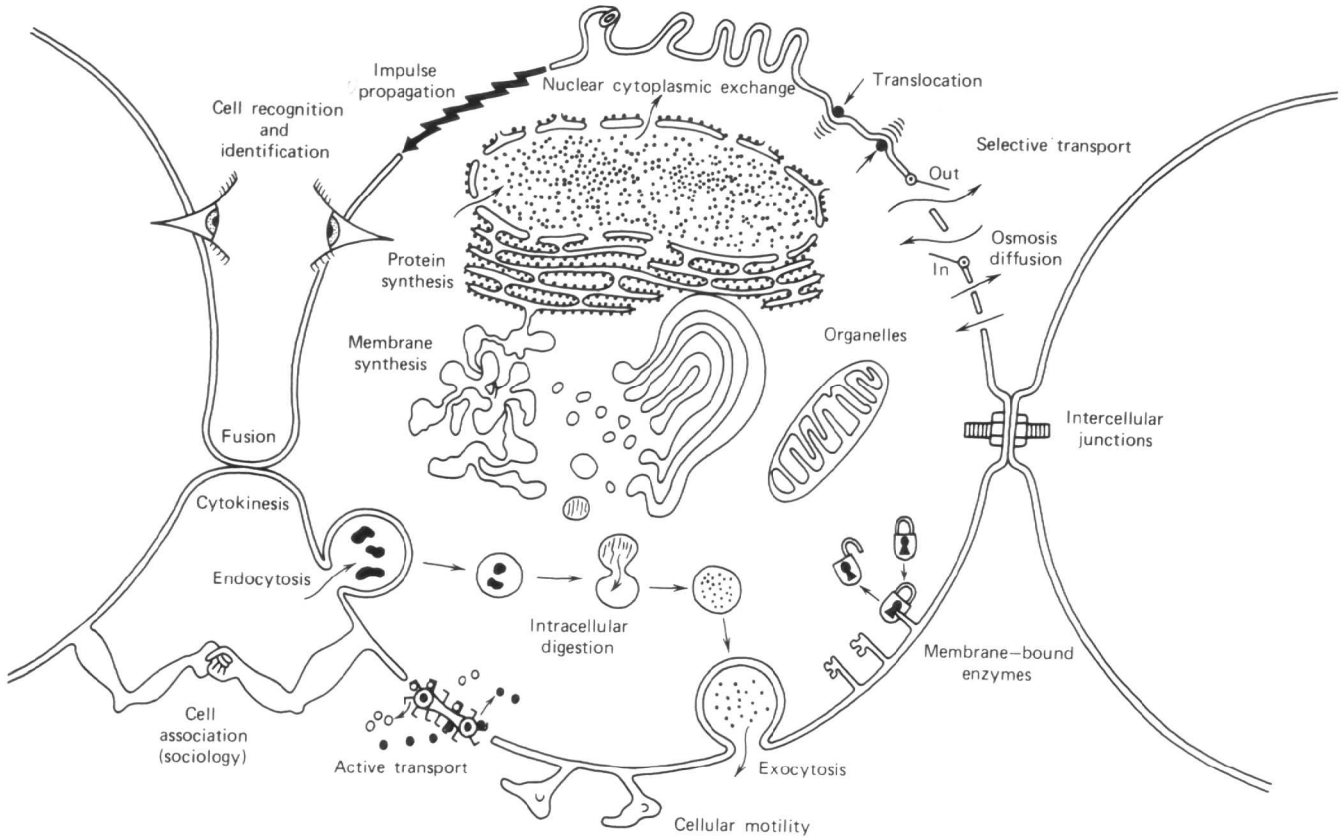


Fig. 1-2. A cartoon of a cell, emphasizing the various processes and functions (individual and social) mediated and modulated by the plasma membrane. (Courtesy of R. Wagner.)

In spite of the staggering diversity of form and function of organelles and cells, some first-order generalizations can be outlined as a basis for a discussion of the general functions of membranes. These include:

Compartmentalization provides morphological identity to the cell and organelles.

Selective barrier properties ultimately control the internal milieu.

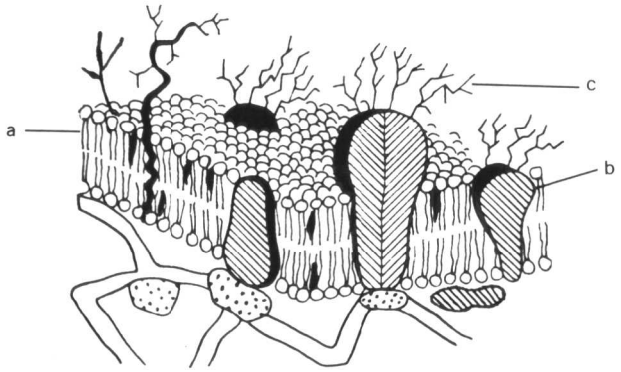
The bilayer matrix provides a surface for specific distribution, orientation, and sidedness for a variety of functional molecules.

Communication and stimulus–response coupling across and along the membrane provide a basis for functions such as excitability, adhesion, immune response, and hormone action.

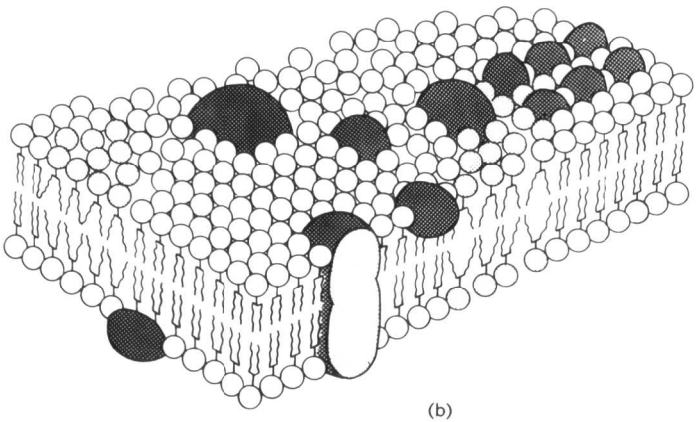
To mediate such functions, lipids act as barriers, solvents, anchors, activators, and conformational stabilizers for proteins that carry out specific catalytic and translocation functions. How such apparently diverse functions are mediated and regulated by and through membranes is an area of active investigation. To a first approximation, the diversity of functions arises from qualitative and quantitative differences in their composition that ultimately give rise to heterogeneity in lateral and transbilayer organization. Therefore, it is not very meaningful to surmise about the general structure and organization of membranes as they relate to specific functions. The underlying diversity of composition and organization must be kept in perspective as one often does, albeit more so, while talking about the structure of proteins and nucleic acids.

The following heuristic conceptual generalizations have been useful in stimulating thinking about membrane structure and organization (Overton, 1899; Gorter and Grendel, 1925; Danielli and Davson, 1935; Singer and Nicholson, 1972; Jain and White, 1977):

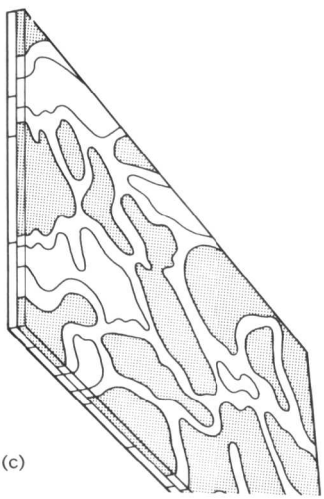
1. Biological membranes essentially consist of a two-dimensional matrix made up of a phospholipid bilayer interrupted and coated by proteins (Fig. 1-3). Thus, the interior of the membrane is much less polar than the interfacial region. Such an organization is a direct consequence of the **hydrophobic effect**, whereby the apolar acyl chains of lipids and the side-chains of the nonpolar amino acid residues in proteins tend to be *squeezed away* from the aqueous phase.
2. The components in a bilayer matrix are held together largely by noncovalent forces. The hydrophobic effect accounts for most of the interaction energy that stabilizes the bilayer organization; however, hydro-



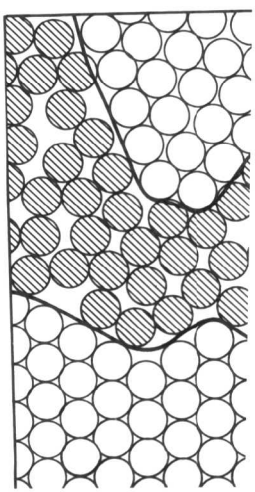
(a)



(b)



(c)



(d)

gen bonding and electrostatic interactions are significant in the polar group region.

3. The uncatalyzed exchange of components from one interface of the bilayer to the other is very slow for lipids and probably nonexistent for proteins. **Transbilayer movement** of amphipathic solutes is energetically unfavorable because it requires insertion of the polar groups into nonpolar regions and exposure of the apolar groups to the polar regions. Compositional **asymmetry** gives rise to morphological and functional asymmetry. The composition of the aqueous environment at the two interfaces is also always asymmetrical. A loss of such asymmetries is lethal to cells.
4. Specific interactions between the membrane components lead to **selective orientation** and **segregation** of the components in the plane of the membrane.
5. Several types of molecular motions are experienced by the components within the constraints of the bilayer organization (Fig. 1-4). **Rotation** of molecules along their axes perpendicular to the plane of the membrane occurs every 0.1–100 nsec for lipids and 0.01–100 msec for proteins; **segmental** motion of acyl chains (0.01–1 nsec) gives rise to an increased disorder toward the center of the membrane; **translational** motion of molecules in the plane of the membrane occurs with a **lateral diffusion** coefficient of 10^{-13} to 10^{-8} $cm^2 \cdot sec^{-1}$. These orientational and motional parameters for the components in the membrane differ more than what would be expected only on the basis of the size of these components. It should be emphasized that not all the molecules of the same type in the same membrane necessarily have the same motional properties.
6. The two-dimensional matrix of a biomembrane probably consists of patches of phospholipid molecules in different degrees of conformational disorder. Under certain conditions, the bilayer organization can

Fig. 1-3. Organizational and structural framework of biomembranes in various degrees of schematization. (A) A general patchwork representation of the organization of the components emphasizing lipids (a), proteins (b), carbohydrates (c), bilayer organization, asymmetry, channel, orientation, and anchoring of proteins. Additional points to be emphasized are long-range order and defects. As shown in B, both lipids and proteins may form distinct patches due to specific intermolecular interactions within the plane of the membrane. A nonrandom topological view of the membrane is exaggerated in C, where regions of differing composition and organization may coexist along with the intervening regions of relative disorder. Such regions of relative disorder are emphasized in D, where only the top view of the lipid molecules in a bilayer is shown.

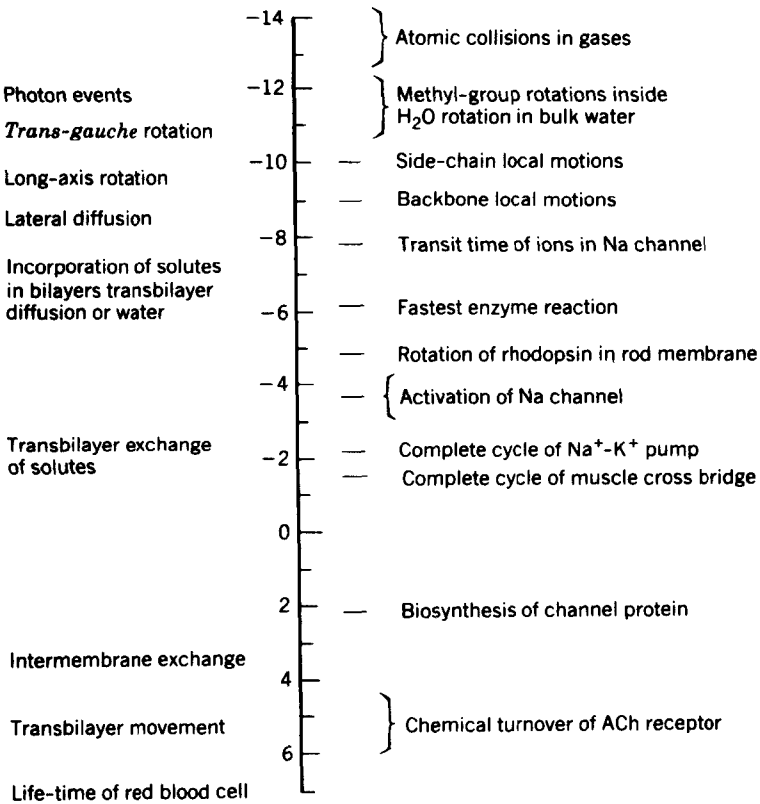


Fig. 1-4. The time-scale of events in membranes. The vertical axis is logarithmic in seconds (i.e., 1 ns = −9).

be interrupted by nonbilayer phases as well as by bilayer phases of differing compositions, and by the regions of mismatch between coexisting phases. Such features within the gross organization of a membrane can have different life-times, and may be induced in response to environmental and metabolic perturbations. Such organizational defects probably act as sites for a variety of functions that require topological discontinuities in the plane of the bilayer.

A description of biological membranes that emerges from these generalizations also has some broad consequences. The functional consequences of the organizational and motional constraints imposed upon the matrix of a biomembrane by virtue of its constituents and environment are elaborated in the following chapters. The hydrophobic forces lead to energetically favor-

able conformations and self-aggregation of phospholipid molecules in a bilayer matrix. This matrix can accommodate the wide range of constraints required for an interface between the relatively stable internal *milleu* of a cell and its changing external environment. This is accomplished with relatively few types of molecules, whose self-assembly is a spontaneous process not directly requiring genetic information. However, the overall process does make an economical use of the genetic information, in the sense that the properties of the membrane are modulated generally by altering the lipid composition rather than the structure of specific lipid components. Similarly, the ability of a large variety of relatively simple molecules to form bilayer organization is consistent with the suggestion that the spontaneous formation of a membranous structure from the primordial soup did not require any elaborate mechanism at a stage of evolution where the very identity of living forms was yet to be established.