Handbook of Modern Biophysics

Series Editor
Thomas Jue
University of California Davis
Davis, California

For other titles published in this series, go to
www.springer.com/series/7845

Roland Faller • Thomas Jue
Marjorie L. Longo • Subhash H. Risbud
Editors

Biomembrane Frontiers

Nanostructures, Models, and the Design of Life

Volume 2

Humana Press

Editors
Roland Faller
Department of Chemical Engineering
and Materials Science
University of California, Davis
One Shields Avenue
Davis, CA 95616
USA
rfaller@ucdavis.edu

Thomas Jue
Department of Biochemistry and Molecular Medicine
University of California, Davis
4418 Tupper Hall
One Shields Avenue
Davis, CA 95616
USA
tjue@ucdavis.com

Marjorie L. Longo
Department of Chemical Engineering
and Materials Science
University of California, Davis
One Shields Avenue
Davis, CA 95616
USA
mllongo@ucdavis.edu

Subhash H. Risbud
Department of Chemical Engineering
and Materials Science
University of California, Davis
One Shields Avenue
Davis, CA 95616
USA
shrisbud@ucdavis.edu

ISBN 978-1-60761-313-8 e-ISBN 978-1-60761-314-5
DOI 10.1007/978-1-60761-314-5
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009927494

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

PREFACE

The book, *Biomembrane Frontiers: Nanostructures, Models, and the Design of Life*, a volume in the *Handbook of Modern Biophysics* series, is based on a workshop held on the 20th and 21st of March 2008 at the University of California Davis. Unlike other meeting monographs, the book presents the exciting frontiers of biomembrane research for both expert and student colleagues interested in research at the interface of biology and physics.

The idea of the workshop originated from discussions about how to create an effective outreach for the NSF-NIRT joint project "Aerogel and Nanoporous Materials for Biomolecular Applications" between the Longo, Faller, and Risbud groups at UC Davis and the groups of Curt Frank at Stanford and Joe Satcher at Lawrence Livermore National Laboratory. In the project we interacted with researchers from diverse backgrounds and hoped to create an opportunity to foster a multi- and interdisciplinary exchange of ideas. Thus, the workshop idea was conceived.

The workshop brought together experts working on many different aspects of biological membranes: from theory and simulation, to supported model bilayers, and to clinical applications. Several material scientists working on the interactions of biological membranes with biological or nonbiological materials also participated. Such a diverse set of experts in one meeting is unusual, as the different communities of theorists and experimentalists working on model membranes and real biological systems are typically quite distinct and do not often interact. Very few, if any, conferences take up the challenge of embracing a broad range of research interests. The chapters of the volume reflect the dynamic synergism of the diverse research interests in biomembrane research and present invaluable, leading ideas to a broad community of researchers and students.

At the workshop, the lively discussion made clear that everybody learned from this unique interaction with colleagues from several disciplines. It was obvious that many aspects of membranes cut across a variety of disciplines and that only research using a combination of ideas and techniques can facilitate real progress.

Several of the speakers invited their graduate students to the workshop. A large number of local graduate students and faculty also participated. Indeed, the graduate students benefited from examining the common theme of membranes from many different perspectives. These students also presented impressive work during poster sessions. The workshop had more than 70 participants.

The book is arranged topically. It leads from theory to applications. After an introduction by Harden McConnell on the history of lipid complexes over the last century, several chapters on theoretical and computational descriptions of membranes follow. Even within this subgroup there is already great diversity. Studying membranes at many different time and length scales is important and requires a wide variety of theoretical approaches to address them. The next block of chapters deals with techniques and applications in model membranes of increasing complexity. In this area there is always the compromise between the simplicity necessary to understand the system in as much detail as possible and the complexity to mimic real biological membranes as realistically as possible. The final chapters address questions of biological and clinical importance involving real membranes.

The workshop and ultimately this book would not have been possible without the dedicated support of a number of people: these are, of course, first and foremost, the speakers and graduate student poster presenters at the workshop and the authors of the chapters. They volunteered their time and effort to make this workshop a success. Specifically, we would like to thank our graduate students Allison Dickey, Emel Goksu, Clark Henderson, Matthew Hoopes, Monica Lozano, Barbie Nellis, Mike Skaug, Juan Vanegas, and Chenyue Xing for their help in organizing and running the workshop. In particular, we would like to acknowledge the organizational talent of Jenny McDonald. Finally, we would like to thank the NSF-NIRT program and the Graduate Group in Biophysics at UC Davis for their financial support, and Springer Science+Business Media for the opportunity to publish this book.

Roland Faller, Thomas Jue, Marjorie Longo, and Subhash Risbud

CONTENTS

3 Structure and Dynamics of Lipid Monolayers: Theory and Applications

Svetlana Baoukina, Siewert J. Marrink, and D. Peter Tieleman

4 Multiscale Modeling of Supported Lipid Bilayers

Matthew I. Hoopes, Chenyue Xing, and Roland Faller

5 Collective Dynamics in Lipid Membranes: From Pore Formation to Flip-Flops

Andrey A. Gurtovenko and Ilpo Vattulainen

6 Spatiotemporal Organization of Spin-Coated Supported Model Membranes

Adam Cohen Simonsen

7 Nanopore Analysis of Nucleic Acids: Single-Molecule Studies of Molecular Dynamics, Structure, and Base Sequence

Felix Olasagasti and David W. Deamer

8 Complex Applications of Simple FRAP on Membranes

Minchul Kang and Anne K. Kenworthy

9 Punching Holes in Membranes: How Oligomeric Pore-Forming Proteins and Lipids Cooperate to Form Aqueous Channels in Membranes

Cécile Fradin, Dmitri Satsoura, and David W. Andrews

10 Morphogens, Membranes and Mechanotransduction in Articular Cartilage

Shirley Motaung, Stephanie Chan, and A. Hari Reddi

11 Lifecycle of a Lipoprotein from a Biophysical Perspective

John C. Rutledge, Thomas Huser, John Voss, James Chan, and Atul Parikh

12 Targeting Apolipoproteins in Magnetic Resonance Imaging

Renuka Sriram, Jens O. Lagerstedt, Haris Samardzic, Ulrike Kreutzer, Jitka Petrolova, Hongtao Xie, George A. Kaysen, John C. Voss, Jean F. Desreux, and Thomas Jue

CONTRIBUTORS

David W. Andrews (chap. 9)
Department of Biochemistry
& Biomedical Sciences
McMaster University
1280 Main Street W
Hamilton, Ontario, L8S4M1, Canada

Svetlana Baoukina (chap. 3)
Department of Biological Sciences
University of Calgary
2500 University Drive NW
Calgary AB T2N1N4, Canada

James Chan (chap. 11)
Center for Biophotonics Science
& Technology
University of California Davis
2700 Stockton Boulevard
Sacramento, CA 95817, USA

Stephanie Chan (chap. 10)
Department of Orthopaedic Surgery
Lawrence Ellison Center for Tissue Regeneration
University of California Davis,
School of Medicine
Research Building 1, Room 2000
4635 Second Avenue
Sacramento, CA 95817, USA

David W. Deamer (chap. 7)
University of California Santa Cruz
1156 High Street
Santa Cruz, CA 95064-1077, USA
deamer@chemistry.ucsc.edu

Markus Deserno (chap. 2)
Department of Physics
Carnegie Mellon University
5000 Forbes Avenue
Pittsburgh, PA 15213, USA
deserno@andrew.cmu.edu

Jean-François Desreux (chap. 12)
Coordination and Radiochemistry
Sart Tilman-B16
University of Liège
Liège 4000, Belgium
jf.desreux@ulg.ac.be

Roland Faller (chap. 4)
Graduate Group in Biophysics
University of California Davis
Bainer Hall, One Shields Avenue
Davis, CA 95616, USA
rfaller@ucdavis.edu

Cécile Fradin (chap. 9)
Department of Physics & Astronomy
McMaster University
1280 Main Street W
Hamilton, Ontario, L8S4M1, Canada
fradin@physics.mcmaster.ca

Laura J. D. Frink (chap. 1)
Colder Insights
Saint Paul, MN 55126, USA
ljfrink@coldersinsights.com

Amalie L. Frischknecht (chap. 1)
Sandia National Laboratories
P.O. Box 5800 MS 1411
Albuquerque, NM 87185, USA
alfrisc@sandia.gov

Andrey A. Gurtovenko (chap. 5)
Computational Biophysics Laboratory
Institute of Pharmaceutical Innovation
University of Bradford
Bradford, West Yorkshire, BD7 1, UK
A.Gurtovenko@gmail.com

Matthew I. Hoopes (chap. 4)
Graduate Group in Biophysics
University of California Davis
Bainer Hall, One Shields Avenue
Davis, CA 95616, USA

Thomas Huser (chap. 11)
Department of Medicine
School of Medicine
University of California Davis
5404 GBSF
Davis, CA 95618, USA

Thomas Jue (chap. 12)
Department of Biochemistry & Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
tjue@ucdavis.edu

Minchul Kang (chap. 8)
Department of Molecular Physiology & Biophysics
Vanderbilt University School of Medicine
718 Light Hall
Nashville, TN 37232, USA
minchul.kang@vanderbilt.edu

George A. Kaysen (chap. 12)
Department of Biochemistry & Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
gakaysen@ucdavis.edu

Anne K. Kenworthy (chap. 8)
Department of Molecular Physiology & Biophysics
Vanderbilt University School of Medicine
718 Light Hall
Nashville, TN 37232, USA
anne.kenworthy@vanderbilt.edu

Ulrike Kreutzer (chap. 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
umkreutzer@ucdavis.edu

Jens O. Lagerstedt (chap. 12)
Department of Biochemistry & Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
jlagerstedt@ucdavis.edu

Siewert J. Marrink (chap. 3)
Groningen Biomolecular Sciences
& Biotechnology Institute
University of Groningen, Nijenborgh 4
9747 AG Groningen, The Netherlands

Harden McConnell (intro)
Department of Chemistry
Stanford University
Stanford, CA 94305-5080, USA
harden@leland.stanford.edu

Shirley Motaung (chap. 10)
Faculty of Science
Department of Biomedical Sciences
Tshwane University of Technology
Private Bag X680
Pretoria, South Africa, 0001
smotaung@gmail.com

Felix Olasagasti (chap. 7)
Department of Chemistry & Biochemistry
University of California Santa Cruz
1156 High Street
Santa Cruz, CA 95064-1077, USA
olasagas@chemistry.ucsc.edu

Atul Parikh (chap. 11)
Department of Medicine
School of Medicine
University of California Davis
5404 GBSF
Davis, CA 95618, USA

Jitka Petrolova (chap. 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
jpetrolova@ucdavis.edu

A. Hari Reddi (chap. 10)
Department of Orthopaedic Surgery
Lawrence Ellison Center for Tissue Regeneration
University of California Davis,
School of Medicine
Research Building 1, Room 2000
4635 Second Avenue
Sacramento, CA 95817, USA
ahreddi@ucdavis.edu

John C. Rutledge (chap. 11)
Department of Medicine
School of Medicine
University of California Davis
5404 GBSF
Davis, CA 95618, USA
jcrutledge@ucdavis.edu
jcrutledge@gmail.com

Haris Samardzic (chap. 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
hsamardzic@ucdavis.edu

Dmitri Satsoura (chap. 9)
Department of Biochemistry
& Biomedical Sciences
McMaster University
1280 Main Street W
Hamilton, Ontario, L8S4M1, Canada

Adam Cohen Simonsen (chap. 6)
MEMPHYS —Center for Biomembrane Physics
Department of Physics and Chemistry (IFK)
University of Southern Denmark
Campusvej 55
DK-5230 Odense M, Denmark
http://memphys.sdu.dk/~adam
e-mail:adam@memphys.sdu.dk

Renuka Sriram (chap. 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
rsriram@ucdavis.edu

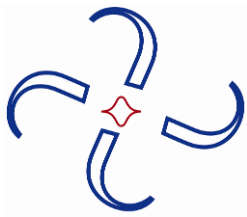
D. Peter Tieleman (chap. 3)
Department of Biological Sciences
University of Calgary
2500 University Drive NW
Calgary AB T2N1N4, Canada
http://moose.bio.ucalgary.ca
tieleman@ucalgary.ca

Ilpo Vattulainen (chap. 5)
Department of Physics
Tampere University of Technology
P.O. Box 692
FI-33101 Tampere, Finland
Ilpo.Vattulainen@tut.fi

John C. Voss (chaps. 11, 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
jcvoss@ucdavis.edu

Hongtao Xie (chap. 12)
Department of Biochemistry
& Molecular Medicine
University of California Davis
One Shields Avenue
Davis, CA 95616 USA
hxie@ucdavis.edu

Chenyue Xing (chap. 4)
Department of Chemical Engineering
& Materials Science
University of California Davis
Bainer Hall, One Shields Avenue
Davis, CA 95616, USA
Cxing@ucdavis.edu



PERSPECTIVES: COMPLEXES IN LIQUIDS, 1900–2008

Harden McConnell
Department of Chemistry, Stanford University, Stanford, California

INTRODUCTION

The interplay of chemical and phase equilibria is one of the classical problems in physical chemistry, having literature citations as far back as the early 1900s. Phase diagrams of particular interest have been those for ternary liquid mixtures (and alloys) that form closed loops. These loops correspond to composition regions in which two liquids are formed. These diagrams were sometimes interpreted in terms of the reversible formation of compounds, or complexes between components of the mixtures. This subject is now of renewed interest in connection with the discovery of liquid–liquid immiscibility in monolayer and bilayer membranes composed of phospholipids and cholesterol. Specific ternary mixtures of phospholipids and cholesterol in bilayers have closed-loop phase diagrams, and have also been interpreted in terms of the formation of complexes. Immiscibility is found in model mixtures of defined composition, and also in lipids extracted from cell membranes and in lipid blebs from animal cells. The observed consolute critical temperatures of some of these mixtures are not far from temperatures characteristic of animal cells, raising the possibility of biophysical significance.

The purpose of this discussion will be to describe simple models of intermolecular interactions that have been used to model liquid–liquid immiscibility in monolayers and bilayers.

COMPLEXES AND THE ORIGIN OF LIQUID–LIQUID IMMISCIBILITY

Our interest in complex formation between cholesterol and phospholipids originated with attempts to model phase diagrams observed for monolayer mixtures at the air–water interface

Address correspondence to Harden McConnell, Department of Chemistry, Stanford University, Stanford, CA 94305-5080, USA, 650 723-4571, <harden@leland.stanford.edu>.

[1,2]. In our calculations we followed the earlier general theoretical studies of Corrales and Wheeler [3]. Much earlier investigators were also interested in nonideal concentrated liquid mixtures [4]. Of particular interest were closed-loop phase diagrams that describe liquid–liquid immiscibility in ternary mixtures [5]. One example is the phase diagram for a ternary mixture of phenol, acetone, and water. At temperatures between 65 and 92°C any pair of these substances is completely miscible, but mixtures containing all three components simultaneously give rise to two liquid phases. An explanation, doubtless oversimplified, is that (a) acetone and phenol form a complex, and (b) this complex is immiscible with water.

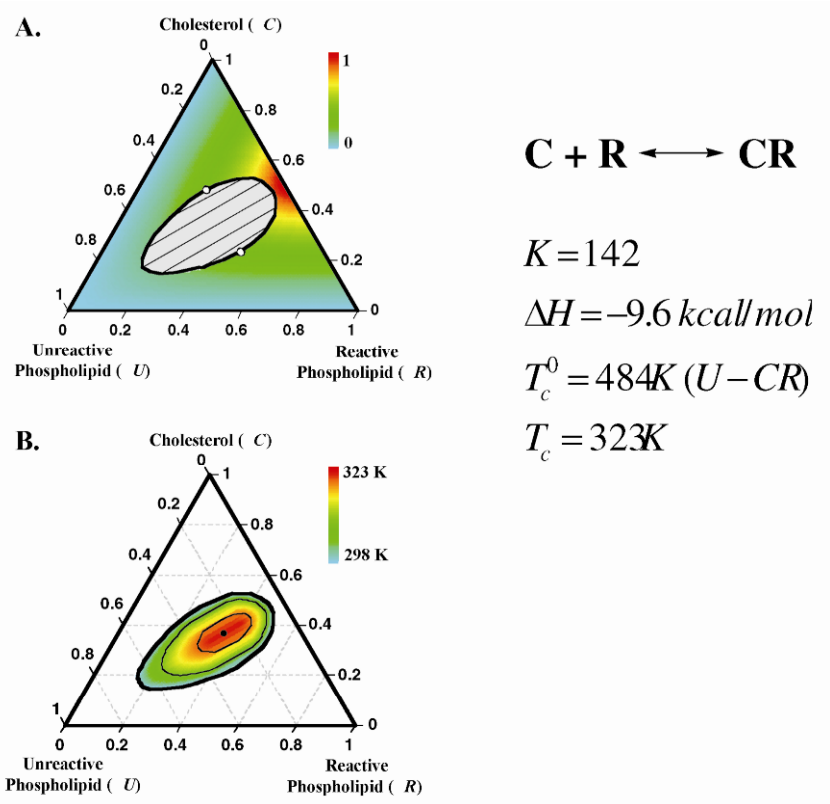


Figure 1. Calculated phase diagram for a ternary lipid mixture in which two components — C (cholesterol) and R (saturated phospholipid) — react reversibly to form a 1:1 molecular complex, and in which this complex undergoes repulsive interactions with the third component, U (dioleoylphosphatidylcholine). Please visit http://www.springer.com/series/7845 to view a high-resolution full-color version of this illustration.

A number of ternary lipid mixtures in bilayers also show closed-loop phase diagrams, as shown in the work of Veatch and Keller [6]. The ternary lipids usually consist of cholesterol, a saturated phospholipid, and an unsaturated phospholipid. We proposed that this immiscibility is related to the formation of "condensed complexes" between cholesterol and the saturated phospholipid [7], by analogy with the model used earlier for monolayers [1,2]. Figure 1 gives the result of a theoretical calculation of the phase diagram of a ternary lipid mixture: cholesterol

(C), dipalmitoylphosphatidylcholine (DPPC, or "reactive" phospholipid (R)), and dioleoylphosphatidylcholine (DOPC, or "unreactive" phospholipid (U)) [8]. In constructing this diagram it was assumed that cholesterol and DPPC form a complex, and that this complex tends to be immiscible with DOPC. The diagram in Figure 1 seeks to model the experimental results of Veatch and Keller for the phase diagrams of ternary lipid mixtures containing cholesterol and phospholipids [6]. Of course, over the years there have been many earlier qualitative proposals for the formation of cholesterol–phospholipid complexes, but there have been very few attempts at quantitative studies. (See [2] for extensive references to these earlier proposals.)

One can summarize some of the theoretical methods that can be used to calculate the thermodynamic phase diagrams yielding liquid–liquid immiscibility with the following formulas.

Two components, mean field repulsion:

$$F = -TS + |a| X_A X_B . \tag{1}$$

Three components, mean field attraction:

$$F = -TS - |a| X_A X_B , \tag{2}$$

Two, three, or more components, mean field plus complexes:

$$F = -TS - kTX_{\text{cpx}} \ln K + |a| X_{\text{cpx}} X_{\text{DOPC}} . \tag{3}$$

Ising lattice model:

$$E = -\Sigma_{i<j} J_{ij} (s_i s_j - 1) . \tag{4}$$

In Eqs. (1)–(3), $-TS$ gives the contribution of the entropy of mixing to the free energy, and $|a|$ is a parameter that represents a mean-field repulsion (Eqs. (1) and (3)) or attraction (Eq. (2)) between molecules. Equation (3) was used in constructing the phase diagram in Figure1; here K is the equilibrium constant describing the formation of a complex between cholesterol and DPPC, and the parameter $|a|$ describes the putative repulsion between the complex and DOPC. The quantities X represent the mole fractions of components.

Equation (1) is the most elementary equation that can be used to model liquid–liquid immiscibility, in this case between two components A and B. In this model there is a competition between the entropy that favors random mixing and the energy term proportional to $|a|$ that favors a separation of the A and B molecules. The mean field term $|a| X_A X_B$ has the form of a long-range interaction between A and B molecules. There are usually no long-range interactions in bilayers. The Ising model, described in Eq. (4), can also be discussed in terms of A and B molecules, and does not involve a mean-field free energy.

In the Ising model, spins with possible values of $S_i = \pm 1$ are placed on a square lattice, where the nearest neighbor interactions are repulsive when neighboring spins have opposite values, $S_i = -S_j$. Otherwise, there is no interaction. One can also describe this Ising problem in terms of the interactions between molecules A and B. That is, equal numbers of molecules A and B are placed on a square lattice. Molecules A and B repel one another. This gives rise to the temperature-dependent "liquid–liquid" phase separation sketched in Figure 2, for which the critical transition temperature is T_C.

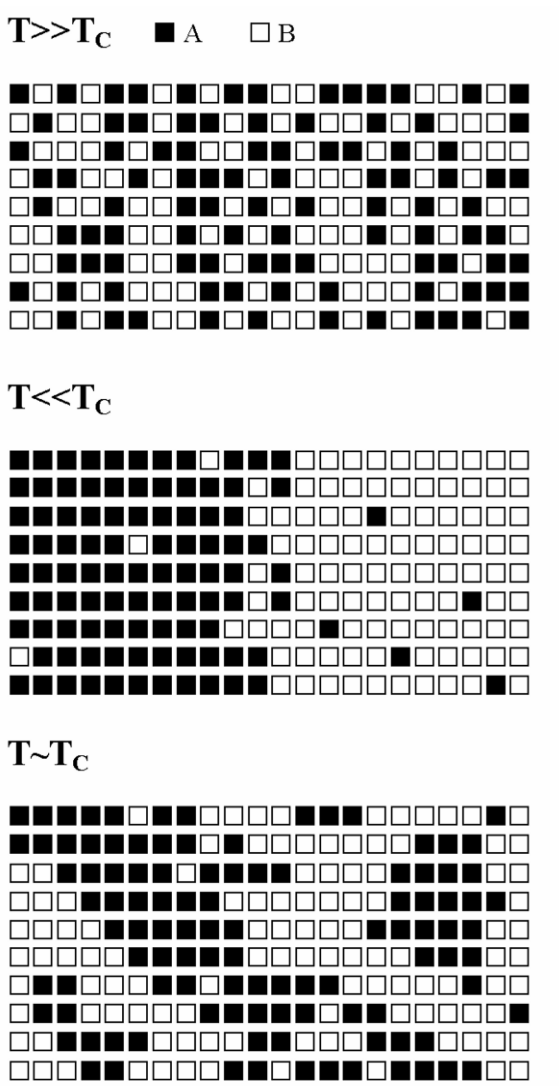


Figure 2. Schematic representation of the Ising problem in terms of molecules A and B where A and B repel one another. At high temperatures the distribution of molecules is dominated by the entropy of mixing, whereas at lower temperatures the phase separation into a liquid rich in A and a liquid rich in B is dominated by the repulsive AB interaction. At the critical transition temperature, T_c, there is long-range composition correlation in the sense that molecules of one type are most likely to be surrounded by molecules of the same type, that is, A (B) molecules are most likely to be surrounded by A (B) molecules.

It has recently been shown that ternary lipids mixtures containing cholesterol, as well as animal cell lipids, have properties (critical exponents) that conform to this 2D Ising model [9,10]. A lattice model can also be used in describing complex formation, as illustrated in Figure 3. Here molecules A and B react reversibly to form a complex C, and this complex undergoes repulsions with both A and B. Some models, termed "decorated lattice models," can describe complex formation and can be mapped mathematically on the Ising model [3].

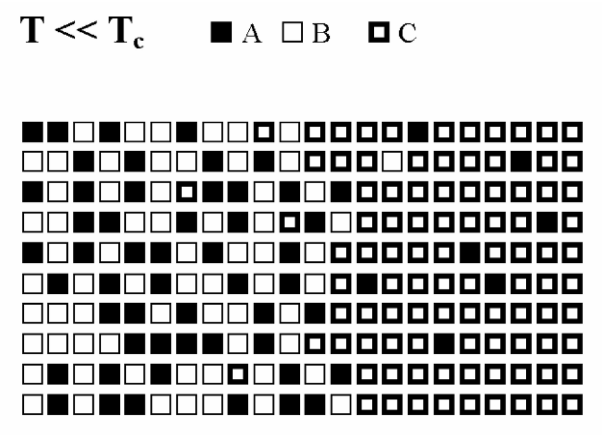


Figure 3. Phase separation can also be described by means of a lattice model, including complex formation. Here phase separation is brought about by the reaction of A and B to form a complex C, where C undergoes a repulsive interaction with A and B.

Clearly, a number of thermodynamic models can be used to describe liquid–liquid immiscibility in membranes containing phospholipids and cholesterol. Some of these models explicitly postulate the formation of molecular complexes. In these concentrated, condensed liquids molecular pairs may preferentially associate with one another due to repulsive interactions among other molecules. (Note the preferred association of the A molecules with one another in Fig. 2 due to the repulsion between the A and B molecules.) In general we use the term "complex" formation between molecules X and Y to describe molecular liquids in which the probability of finding neighboring XY molecules exceeds that expected for random mixing, irrespective of whether or not isolated pairs of X and Y "attract" one another.

We find the idea of complexes to be chemically intuitive, and to facilitate the calculations of the shapes of phase diagrams, chemical activities, heat capacities, and NMR spectra. The NMR spectra of bilayers containing cholesterol and phospholipids may reflect the kinetics of formation and dissociation of complexes (for leading references, see [11]).

OUTLOOK

Our objective in using complexes to interpret the physical chemical properties of phospholipid-cholesterol mixtures is twofold. First, as briefly summarized above, this is a convenient intuitive first-approximation. Second, the idea of complex formation is likely to be appropriate to other weak but relatively specific reversible lipid–protein and protein–protein interactions in cell membranes. References [1,2,6–11] provide many references to earlier as well as more recent work in this field.

REFERENCES

1. Radhakrishnan A, McConnell HM. 1999. Condensed complexes of cholesterol and phospholipids. *Biophys J* **77:**1507–1517.
2. McConnell HM, Radhakrishnan A. 2003. Condensed complexes of cholesterol and phospholipids. *Biochim Biophys Acta* **1610**:159–173.
3. Corrales LR, Wheeler JC. 1989. Chemical reaction-driven phase transitions and critical points. *J. Chem. Phys.* **91:**7097–7112.
4. Dolezalek F. 1908. Zur theorie binaren gemische und konzentrieten losungen. *Phys Chem* **64:**727–747.
5. Schreinemakers FAH. 1900. *Z Phys Chem* **33:**78–79; **39**:489 (1902).
6. Veatch SL, Keller SL. 2003. Separation of liquid phases in giant vesicles of ternary mixtures of phospholipids and cholesterol. *Biophys J* **85**:3074–3083.
7. McConnell H. 2005. Complexes in ternary cholesterol-phospholipid mixtures. *Biophys J* **88**: L23–L25.
8. Radhakrishnan A, McConnell HM. 2002. Critical points in charged membranes containing cholesterol. *Proc Nat Acad Sci USA* **102**:13391–13396.
9. Honerkamp-Smith AR, Cicuta P, Collins MD, Veatch SL, den Nijs M, Schick M, Keller SL. 2008. Line tensions, correlation lengths, and critical exponents in lipid membranes near critical points. *Biophys J* 95(1):236–246.
10. Veatch SL, Cicuta P, Sengupta P, Honerkamp-Smith A, Holowka D, Baird B. 2008. Critical fluctuations in plasma membrane vesicles. *ACS Chem Biol* **3**:287–293.
11. McConnell H, Radhakrishnan A. 2008. Molecular motion at the critical point in lipid membranes. *Biophys J* **95**(2):L22–L24.