Dynamics of Engineered Artificial Membranes and Biosensors

This state-of-the-art guide provides a powerful toolkit for building artificial membranes, combining techniques for synthesis with mathematical modeling.

- Drawing on the most recent advances in bioengineering, biochemistry, and computational biology, it describes how to precisely construct synthetic lipid bilayer membranes to mimic the remarkable properties of biological membranes, and shows how they can be used to develop biosensors and diagnostic devices.
- Experimental and modeling case studies provide insight into how artificial cell membranes actually operate at the molecular level, and molecular dynamics simulation code accompanying the book online enables readers to reproduce the key experimental results presented throughout.
- Multi-physics models for predicting membrane performance and improving design are developed, with coverage including molecular dynamics, coarse-grained molecular dynamics, Brownian dynamics, continuum theory, and reaction-rate theory.

This book is essential reading for researchers, students and professionals in bioengineering, biophysics, and electrical engineering.

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Preface

Biological membranes such as the cell membrane play an essential and ubiquitous role in cellular communication, energy storage, structural support, and protecting the contents of living cells. Biological membranes are dynamic structures with remarkable properties: they have moving parts, they act as electrical circuits with long-range memory, they contain protein macromolecules (ion channels) that selectively open and close to admit ions, thereby regulating the electrical activities of cells, and they spontaneously form pores (electroporation) which is crucial for the operation of antimicrobial drugs.

This book focuses on building and mathematically modeling artificial membranes that mimic biological membranes. Recent advances in bioengineering and biochemistry allow us to build artificial membranes precisely to mimic the remarkable properties of biological membranes and also to build synthetic biological devices out of these membranes. Also advances in computational molecular biology allow us to construct large-scale computer simulation models at the atomic-spatial scale to gain deep insight into the dynamic properties and structure-function relationship of such artificial membranes and devices. This dual approach of synthesis (building membranes and novel devices) and analysis (mathematical modeling) is vital for the future development of sensing devices, drug delivery mechanisms, and synthetic biological devices.

Summary. This book provides a comprehensive description of artificial membranes aimed at advanced undergraduate and graduate students, and researchers in electrical engineering, biological and chemical engineering, biophysics, and applied mathematics. Construction of artificial membranes and devices is intimately linked with careful mathematical modeling so as to predict the performance and improve the design. As a result this book is organized into three interrelated parts:

Part I gives an overview of the book along with an elementary primer on biochemistry for engineers and applied mathematicians.

Part II deals precisely with engineering and building artificial membranes, building novel synthetic biological devices out of these artificial membranes, and evaluating how such devices perform in experimental and clinical studies. The devices studied include a super-resolution biosensor (which can be viewed as a fully operational nanomachine), an electroporation platform (for studying how membranes spontaneously form water-filled pores), and an electrophysiological platform (for noninvasive measurements of cells).

Part III develops mathematical models that operate at multiple spatial and temporal scales to capture the dynamics of artificial membranes and devices, starting from

atoms and ending in the macroscopic device. Several levels of modeling abstractions are studied: molecular dynamics (at the atomic scale resolution), mesoscopic models (Poisson–Nernst–Planck models and generalizations) that take into account fluid flow dynamics, and reaction-rate models at the macroscopic device level.

The combination of engineered membranes (synthetic biology hardware discussed in Part II) together with mathematical models (software discussed in Part III) yields a powerful set of engineering tools to go from structure to function. The hardware allows us to consider various components in their natural state (as they interact with other components), whereas the software then zooms into specific subparts in isolation. This combination of hardware (ex vivo and in vitro) and software (in silico) is a unique feature of our book.

A challenge encountered with synthetic biological devices such as artificial cell membranes is the bioelectronic interface: charged ions carry information in biological membranes, while electrons carry information in electrical devices. Several sections of this book are devoted to building and detailed mathematical modeling of the bioelectronic interface at several levels of abstraction.

Readership. This book is written for advanced undergraduate students, graduate students, and researchers in electrical engineering, biological and chemical engineering, biophysics, and applied mathematics. The prerequisites are modest. A student or researcher with an applied mathematics, physics, bioengineering, or electrical engineering background (signal processing, circuits and systems, control theory) can follow the material in this book without a detailed knowledge of membrane biology and biochemistry. An undergraduate knowledge of cellular biology, signals and systems, and physics involving diffusion-type partial differential equations is adequate to understand the material. Also, the mathematical models proposed in this book for the dynamics of artificial membranes involve computer simulations using molecular dynamics, finite element, boundary element, and finite difference numerical methods. These are typically covered in computational physics and engineering mathematics undergraduate courses. Parts of this book have been class-tested in graduate and senior-level undergraduate courses at the University of British Columbia and the University of Technology Sydney.

This is not a book on the biology of membranes; instead we are interested in engineering membranes, namely, synthesizing (building membranes and devices) and analyzing (mathematically modeling) them. Given the multidisciplinary nature of this book, it is natural that several topics have been omitted which some readers might deem as being important. We do not cover molecular pumps, ionophores, or endocytosis/exocytosis. Also our discussion of ion channels focuses on engineering – how to use them to design and build synthetic biological devices and how to model these devices; we do not present detailed discussions on ion channel experiments (patch clamping) or modeling (Hodgkin-Huxley models, permeation).

Appendices and Internet supplement. The appendices discuss elementary partial differential equations and nondimensionalization, how to perform both coarse-grained molecular dynamics and all-atom molecular dynamics simulations, and the typical parameter values used in the mathematical models of engineered artificial membranes. Using the molecular dynamics simulation code provided, the reader can repeat the

computer simulation results documented in this book. Actual engineered membrane devices can be obtained by contacting the authors. Using these devices, the reader can repeat the experiments documented in this book.

To keep the cost manageable, all figures are printed in black and white. Color figures can be downloaded for free from the website of the book hosted at www.cambridge.org/engineered-artificial-membranes. The website also contains molecular dynamics simulation code and other pedagogical material.

Context. This book is truly a multidisciplinary effort between academia and industry. In the 1990s, Cornell (a biochemist) invented a remarkable biosensor built out of ion channels and synthetic membranes. In 2005, Krishnamurthy (with a background in electrical engineering and applied mathematics) and Cornell started collaborating on modeling the dynamics of this biosensor. The aim was to understand how a biosensor device comprising moving ion channels and complex structural components embedded in the membrane together with electrochemical reactions could be mathematically modeled to explain its remarkable sensitivity. In 2012, Hoiles (with an engineering physics background) joined Krishnamurthy's group as a PhD student and worked on molecular dynamics interpretations of various aspects of engineered membranes and devices. With more than a decade of fruitful collaboration, the three authors now have a useful understanding of artificial membranes and novel devices built out of these membranes – from a physics, biochemistry, engineering and applied mathematics viewpoint. We hope that this book conveys our multifaceted understanding of this fascinating area.

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Abbreviations

AMBER	assisted model building and energy refinement.
BCC	body-centered cubic.
BLM	bilayer lipid membrane.
CGMD	coarse-grained molecular dynamics.
CHARMM	Chemistry at Harvard Molecular Mechanics.
CM	cushioned membrane.
CPE	constant-phase element.
DLP	half-membrane-spanning tethered lipid.
DMPC	1,2-dimyristoyl-sn-glycero-3-phosphocholine.
DMPG	1,2-dimyristoyl-sn-glycero-3-phosphorylglycerol.
DOPC	1,2-dioleoyl-sn-glycero-3-phosphocholine.
DphPC	zwittrionic C20 diphytanyl-ether-glycero-phosphatidylcholine.
DPPC	1,2-dipalmitoyl-sn-glycero-3-phosphocholine.
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine.
EMP	electroporation measurement platform.
ERP	electrophysiological response platform.
FCC	face-centered cubic.
FEA	finite-element analysis.
FLB	freestanding lipid layer.
FRAP	fluorescence recovery after photobleaching.
gA	Gramicidin.
gA-dig	Gramicidin digoxin.
GDPE	C20 diphytanyl-diglyceride ether.
GPNP	generalized Poisson–Nernst–Planck.
GROMOS	Groningen Molecular Simulation.
HBL	hybrid bilayer lipid membranes.
hCG	human Chorionic Gonadotrophin.
HMM	hidden Markov model.
ICS	ion-channel switch biosensor.
IVDs	in vitro medical diagnostics.
MARTINI	A coarse-grained molecular dynamics force field.
MCT	mode-coupling theory.
MD	molecular dynamics.
MRD	molecular reaction dynamics.

MRSA	methicillin-resistant *Staphylococcus aureus*.
MSD	mean-square displacement.
MSE	mean-squared error.
MSL	membrane-spanning lipid.
MSLOH	synthetic archaebacterial membrane-spanning lipid.
MTOP	monoterpene oxidation product.
NMR	nuclear magnetic resonance.
NPV	negative predictive value.
NR	neutron reflectometry.
ODE	ordinary differential equation.
PBS	phosphate-buffered saline.
PDE	partial differential equation.
PEG	Polyethylene Glycol.
PFMP	pore formation measurement platform.
PFNP	Poisson–Fermi–Nernst–Planck.
PGLa	peptidyl-glycyl-leucine-carboxyamide.
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.
POPG	palmitoyloleoyl-phosphatidylglycerol.
PPV	positive predictive value.
SAPC	1-stearoyl-2-arachidonoyl-sn-glycero-3-phosphocholine.
SDPC	1-stearoyl-2-docosahexaenoyl-sn-glyerco-3-phosphocholine.
SLB	supported lipid bilayer.
SLPC	1-stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine.
SOPC	1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine.
SP	spacer.
tBLM	tethered bilayer lipid membrane.
TRP	transient receptor potential.
TSH	thyroid stimulating hormone.
VDAC	voltage-dependent anion channel.