

DEVELOPMENT AND APPLICATION OF
COARSE-GRAINED FORCE FIELDS FOR
SIMULATION OF LIPID MEMBRANES AND
VESICLES IN THE PRESENCE AMPHIPHILIC
SOLVENTS AND BIOCOMPATIBLE IONIC
LIQUIDS

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY DELHI

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by

SHOBHNA

DEPARTMENT OF CHEMISTRY

Submitted

in fulfillment of the requirement of the degree of doctor of philosophy

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

November 2023

*Dedicated to
My Mother*

Certificate

This is to certify that the thesis titled "**Development and Application of Coarse-grained Force-fields for Simulation of Lipid Membranes and Vesicles in the Presence of Amphiphilic Solvents and Biocompatible Ionic Liquids**" is being submitted by **Ms. Shobhna** to the Department of Chemistry, Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**. This thesis is a record of bonafide research work carried out by her under my supervision. In my opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree. The results contained in this thesis have not been submitted to any other University or Institute for the award of any degree or diploma.

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Contents

Certificate	i
Acknowledgements	iii
Table of Contents	ix
List of Figures	xi
List of Tables	xxiii
1 Introduction	5
1.1 General Introduction	5
1.1.1 Cell Membranes	6
1.1.2 Modulation of Lipid Membrane Properties by Small Amphiphilic Molecules	8
1.1.3 Molecular Dynamics Simulations in Studying Membrane Prop- erties	11
1.1.4 Simplifying the Complexity of Lipid Membranes: Coarse- Grained Simulations	12
1.1.5 Coarse-Graining Methods in Biomolecular Modeling: From Atomistic to Macroscopic Scales	13
1.2 Biocompatible Ionic Liquids and their Interactions with Lipid Membrane	14
1.3 Molecular Simulations and Force-fields	17
1.3.1 Exploring Interaction Potentials and Force-fields	18
1.3.2 Integration of Equations of Motion	21
1.3.3 Periodic Boundary Conditions and Minimum Image Convention	23
1.3.4 Calculation of Long-Rang Electrostatic interactions using Ewald Summation Method	23

1.3.5	Exploring the Phase Space in Canonical, Grand Canonical and Microcanonical Ensembles	25
1.3.6	Thermostats and Barostats	27
1.4	Computation and Analysis of Properties	29
1.4.1	Lipid Tail Order Parameter	29
1.4.2	Metadynamics Method in Free Energy Calculations for Biomolecular Systems.	30
1.4.3	Area per Lipid, Electron and Number Density Profiles and Bilayer Thickness	31
1.5	Hydrogen Bonding Analysis	32
1.6	Two-dimensional (2D) Radial Distribution Function	33
1.7	Motivation and Organization of the Thesis	34
2	Coarse-grained Modeling of Dimethyl Sulfoxide Solvent for Elucidating its Impact on Biomimetic Lipid Membranes	37
2.1	Introduction	37
2.2	Simulation Details	40
2.2.1	All-atom Molecular Dynamics (AA-MD)	40
2.2.2	Coarse-grained Molecular Dynamics (CG-MD)	41
2.2.3	The CG Model and Parametrization	42
2.2.4	Transfer Free Energy of DMSO	44
2.3	Results and Discussions	45
2.3.1	CG Force-field for DMSO	45
2.3.2	CG Force-field for DMSO-water Interactions	47
2.3.3	DMSO Interaction with Phospholipid Bilayers	49
2.4	Conclusion	52
3	Ethanol-driven Swelling, Rupturing, Aggregation and Fusion of Lipid Vesicles: Development and Applications of a Novel Coarse-grained Model for Ethanol and Ethanol-membrane Interactions	53
3.1	Introduction	53
3.2	Molecular Dynamics Simulation Details	58
3.2.1	Coarse-grained Simulations	60

3.2.2	CG Modeling	60
3.2.3	Free Energy of Ethanol Insertion	61
3.3	Results and Discussion	61
3.3.1	Optimization of Ethanol Parameters	61
3.3.2	Optimization of Ethanol-water Interactions	64
3.3.3	Optimization of Ethanol-lipid Interactions	65
3.3.4	Ethanol Interaction with Phospholipid Bilayers	66
3.4	Application Studies	69
3.4.1	Vesicle Swelling at Lower Concentrations of Ethanol	70
3.4.2	Vesicle Rupturing at Higher Concentrations of Ethanol	74
3.4.3	Vesicle Aggregation and Rupturing in Multivesicle Systems	76
3.4.4	Vesicle-vesicle Fusion	77
3.5	Conclusion	80
4	Understanding the Impact of Ethanol on Biomimetic Lipid Membrane and Vesicle in Presence of Cholesterol Using Coarse-grained Molecular Dynamics	81
4.1	Introduction	81
4.2	Molecular Dynamics Simulation Details	83
4.2.1	Atomistic Simulations	83
4.2.2	Coarse-grained Simulations	84
4.2.3	CG Modeling	85
4.2.4	Free Energy of Ethanol Insertion	86
4.3	Results and Discussion	87
4.3.1	Deriving the CG parameters for the interactions of Ethanol and Cholesterol CG Molecules	87
4.3.2	Impact of Ethanol Concentration on the Structure of POPC-CHOL Bilayer	90
4.3.3	Effect of Ethanol on Lateral Structure of Lipid Bilayer	91
4.3.4	Changes in Cholesterol Tilt Angle	92
4.3.5	Swelling of Hydrated POPC-CHOL Vesicle in Presence of Ethanol	92
4.3.6	Rupturing of POPC-CHOL Vesicles at Higher Ethanol Concentrations	98

4.4	Conclusions	98
5	Development and Applications of a New Coarse-grained Force-field for <i>Escherichia coli</i> Bacterial Membrane in the Presence and Absence of Ethanol	101
5.1	Introduction	101
5.2	Molecular Dynamics Simulations Details	103
5.2.1	Atomistic Simulations	103
5.2.2	Simulations of Coarse-grained system	104
5.2.3	CG Model of <i>E. coli</i> Bacterial Membrane	105
5.2.4	Transfer Free Energy of Ethanol insertion	105
5.3	Results and Discussion	107
5.3.1	Deriving the Coarse-grained force field for pure POPG lipid bilayer.	107
5.3.2	Deducing the Coarse-grained Force field for <i>E. coli</i> Bacterial Membrane	109
5.3.3	Deteriorating Effect of Ethanol on <i>E. coli</i> Bacterial Membrane .	109
5.4	Application Studies	112
5.4.1	Swelling in <i>E. coli</i> Vesicles at Lower Concentration of Ethanol. .	112
5.4.2	Rupturing of <i>E. coli</i> Vesicle at Higher EtOH Concentrations . .	116
5.4.3	Multi Vesicle Rupturing and Shrinking in at Higher Ethanol Concentrations	117
5.5	Conclusions	119
6	Mechanistic Insight on Biocompatible Ionic Liquids Driven Alterations in the Structure of Biomimetic Lipid Bilayers	121
6.1	Introduction	121
6.2	Molecular Dynamics Simulation Details	124
6.3	Results and Discussion	128
6.3.1	Variation in Area per Lipid and Bilayer Thickness	128
6.3.2	Density Distribution along Bilayer Normal	131
6.3.3	Transfer Free Energy Landscape of [Phe] ⁻	134
6.3.4	Variation in Lipid Tail Order	136
6.3.5	Impact on Interdigitation of Membrane Leaflets	137

6.3.6	Hydrogen Bonding	138
6.3.7	Lateral Membrane Structure	138
6.4	Conclusions	139
7	Summary, Implications, and Future Research Prospects	141
	Appendix	146
	Bibliography	151
	Biodata	177

List of Figures

1.1	CG mapping of <i>E.coli</i> bacterial membrane.	13
1.2	Applications of BioIL in drug formulation and delivery systems. Reproduced from ref.[71] Copyright (2023), with permission from MDPI.	15
1.3	(a) Chemical structures of BioIL and ionic species and (b) DMPC lipid molecule.	15
2.1	Mapping of atomistic DMSO into CG model. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	39
2.2	Schematic mapping of atomistic POPC and POPE molecules into corresponding CG model. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	40
2.3	Comparison of radial distribution functions between beads (a) B1-B1, (b) B2-B2, and (c) B1-B2 of DMSO computed from AA and CG models. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	43
2.4	(a) Temperature-dependent density variation (298 to 323 K) of pure DMSO computed from CG simulations and from experiment.[129] (b) Concentration-dependent density variation comparison of DMSO computed from CG simulations with experimental[129] data at 298 K. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	44
2.5	Potentials of mean force (PMF) for the transfer of DMSO from water to (a) POPC and (b) POPE bilayer. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	46

2.6	Change in the orientational ordering of palmitoyl tail (sn1) of (a) POPC and (b) POPE lipid molecules at different concentration of DMSO from 0 to 15 mol%. Solid and dashed lines represent results from simulations of AA and CG models, respectively. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	48
2.7	Electron density profiles of (a) POPC, (b) DMSO, and (c) water molecules in homogeneous POPC bilayer system, and electron density profiles of (d) POPE, (e) DMSO, and (f) water molecules in homogeneous POPE bilayer system and at different concentration of DMSO (0 to 15 mol%). Solid and dashed lines represent results from simulations of AA and CG models, respectively. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	48
2.8	2-D RDFs for (a) NC-NC and (b) PH-PH head group beads of POPC, and (c) NH-NH and (d) PHE-PHE head group beads of POPE bilayer systems at different concentration of DMSO (5 to 15 mol%). Solid and dashed lines represents results from simulations of AA and CG model, respectively. Color coding representing each mole fraction is same as used in Figures 2.7. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	50
2.9	Equilibrium snapshots of the CG phospholipid bilayers systems having 5 and 15 mol% of CG DMSO. In the snapshots, NC and PH beads of POPC lipid heads are rendered in blue and tan colors, respectively while the bead NH and PHE of POPE lipid heads are rendered in cyan and pink colors, respectively. The common interfacial region of POPC and POPE lipid molecules contains beads GL rendered in orange along with the ester group and lipid tails rendered in grey color. DMSO molecules are represented by red (B1) and green (B2) beads. Water beads are shown in transparent white. Reproduced from ref.[4] Copyright (2021), with permission from American Institute of Physics.	51
3.1	Schematic mapping of atomistic POPC, POPE, water and ethanol molecules into corresponding CG model. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	56

3.2	Comparison of radial distribution functions for (a) E1-E1, (b) E2-E2, and (c) E1-E2 pairs of beads of ethanol computed from AA (cyan) and CG (orange) simulations. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	62
3.3	Comparison of concentration-dependent densities as a function of ethanol mol% computed from CG simulations with experimental data at 298 K[165].	62
3.4	Potentials of mean force (PMF) for the transfer of an ethanol molecule from bulk water to hydrophobic core region of (a) POPC and (b) POPE bilayer. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	62
3.5	Equilibrium snapshots of CG bilayer comprising POPC (a, b) and POPE (c, d) lipids containing 5 and 10 mol% of ethanol. E1 and E2 beads of ethanol are rendered in blue and orange colors, respectively, lipid tails of POPC and POPE are rendered in silver and cyan colors, respectively. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	63
3.6	Electron density profiles of (a) EtOH, (b) water, and (c) POPC molecules in POPC bilayer system. EDPs of (d) EtOH, (e) water, and (f) POPE molecules in POPE bilayer system. Solid and dashed lines are for AA and CG simulations, respectively. Solid indigo lines in (c) and (f) represent the electron density profiles from pure water atomistic simulations. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	63
3.7	Changes in the orientational ordering of palmitoyl tail (sn1) of (a) POPC and (b) POPE lipids at different concentrations of ethanol. Solid and dashed lines represent results from AA and CG simulations, respectively. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	63

3.8	Variation in the lateral RDFs for (a) NC-NC and (b) PH-PH pairs of POPC lipid head groups and for (c) NH-NH and (d) PHE-PHE pairs of POPE lipid head groups in Ethanol-water-membrane system containing different concentrations of ethanol. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	64
3.9	Equilibrium snapshots representing the concentration-dependent (0-30 mol% of ethanol) effect of ethanol on POPC lipid vesicles. Lipid tails are rendered in silver, head groups are rendered in cyan, water bead and ethanol molecules are rendered in blue and orange colors, respectively. Water and ethanol are not shown outside the vesicles for clarity. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	69
3.10	Variation in the (a) bilayer thickness and (b) surface area of POPC single spherical as a function of ethanol mol%. (c) Variation in the surface area of fused vesicles at different mol% of ethanol. The thickness of the vesicle bilayer was computed by considering the distance between the NC head groups of two opposing leaflets. The surface area of the single vesicles was computed by considering it as a perfect sphere and by computing the average radius between the center of vesicle to the middle of vesicle bilayer. For fused vesicle, the surface area was computed by considering it as a perfect ellipsoid. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	71
3.11	Variation in the (a) number densities and (b) mole-fractions of ethanol and water beads as a function of radial distance from the center of the lipid vesicle to the bulk solvent region at different mol% of EtOH (0-30 mol%). Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	71
3.12	Time-dependent effect of higher mol% of ethanol (40 mol% (a) and 70 mol% (b)) on single vesicle systems. Only lipid molecules are shown for clarity. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	72

3.13	Concentration-dependent effect on multiple POPC lipid vesicles with (a) 0, (b) 20, (c) 25 and (d) 30 mol% of EtOH. Water and ethanol are not shown for clarity. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	75
3.14	Time-dependent effect of higher mol% of EtOH (40 mol% (a) and 70 mol% (b)) on multiple POPC vesicles. Only lipid molecules are shown for clarity. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	75
3.15	Ethanol mediated fusion of POPC vesicles at 20, 25 and 30 mol% of Ethanol. Only lipid molecules are shown. Here, in all the rows, the first pair of vesicles are in water, the second and third pairs are in Ethanol in absence and presence of the adhesive force. The final image is of the fused state of the vesicles. Reproduced from ref.[5] Copyright (2022), with permission from American Chemical Society.	78
4.1	Pictorial representation of CG models of (a) POPC, (b) CHOL, (c) EtOH, and (d) water molecules.	83
4.2	PMFs for the insertion of an ethanol molecule from the hydrophilic water phase to the hydrophobic center of the POPC-CHOL lipid membrane from both the AA and CG simulations. Each error bar in the PMF profiles represent one standard deviation.	87
4.3	Variation in (a) surface area per lipid and (b) bilayer thickness of POPC-CHOL lipid membrane as a function of mol% of ethanol. For more details on APL and bilayer thickness calculations refer to 1.	88
4.4	Ethanol concentration-dependent variation in the EDPs of (a) POPC, (b) water, and (c) EtOH, in POPC lipid bilayer systems at 30% CHOL concentration. Solid and dashed lines represent simulations from atomistic and CG MD simulations, respectively.	88
4.5	Variation in the segmental order parameter of the palmitoyl tail of POPC lipids in POPC-CHOL membrane at various mol% of EtOH. Solid and dashed lines represent results from atomistic and CG MD simulations, respectively.	89

4.6	Equilibrium snapshots representing the effect of ethanol on POPC-CHOL binary lipid CG membrane systems at (a) 0% , (b) 10% and (c) 20% of ethanol. Equilibrium snapshots showing the lateral distributions (top view) of CHOL and POPC molecules at (d) 0%, (e) 10% and (f) 20% of ethanol.	89
4.7	Concentration-dependent variation in the probability distribution of cholesterol tilt angle in AA and CG simulations. Here, the tilt angle is defined as the angle between the vector parallel to cholesterol axis (vector computed between C3 and C17 atom of AA cholesterol and OAB and CTBB beads of CG cholesterol, see Figure A.1 in the Appendix and Figure 4.1.) and the bilayer normal.	93
4.8	Images of equilibrated vesicles demonstrating the concentration-dependent (0-30 mol%) effect of ethanol on POPC-CHOL lipid vesicles. Acyl chains of POPC lipid molecules are rendered in lime, lipid head groups are rendered in iceblue, respectively. Cholesterol molecules are rendered in red color. For clarity, solvent molecules are not shown outside the vesicles. The first and second rows depict ethanol mol% dependent variation in the vesicles. Solvent molecules are not shown. The third row represents the increasing presence of ethanol within the in vesicle with its increasing mol%. At different concentrations of ethanol, the surface area of POPC-CHOL lipid vesicles was calculated by assuming they were perfect spheres and finding the average distance between the center of the vesicle (the origin) and the middle of the vesicle lipid membrane. The bilayer thickness of the lipid vesicle was calculated by taking the distance between the NC beads of two opposing leaflets. . . .	94
4.9	Changes in (a) surface area and (b) bilayer thickness of POPC-CHOL vesicles as a function of mol% of ethanol.	95
4.10	Variation in the (a) number densities and the (b) mole-fractions of ethanol and water as a function of radial distance from the center of the POPC-CHOL lipid vesicle to the bulk solvent region at various mol% of ethanol (0-30 mol%).	96

4.11	Vesicle images demonstrating the ethanol higher mol% repercussions on POPC-CHOL lipid vesicles. POPC lipid tails are rendered in lime, lipid head groups are rendered in iceblue respectively. Cholesterol molecules are rendered in red. Water and ethanol are not shown for clarity. . . .	97
5.1	Pictorial representation of CG models of (a) POPG, (b) POPE, (c) Ethanol, and (d) water molecules.	103
5.2	Variance in the EDPs of (a) <i>E. coli</i> , (b) POPG, (c) POPE, and (d) water in fully hydrated lipid bilayer systems of <i>E. coli</i>	110
5.3	Segmental order parameter of the palmitoyl tail of (a) POPG and (b) POPE lipids in pure <i>E. coli</i> bacterial membrane. The color scheme used in representing the segmental order parameter is same as used in Figure 5.2.	110
5.4	Equilibrium images showing the impact of EtOH at (a) 0%, (b) 5%, and (C) 10% on the lipid CG membrane systems of <i>E. coli</i> . The rest of the POPG and POPE lipid molecules are represented by the purple and silver colors, respectively, the head groups of POPG and POPE are represented by green (OAL), silver (PH), ice blue (NH) and silver (PHE) colors, respectively.	111
5.5	Variation in the EDPs of (a) <i>E. coli</i> , (b) EtOH, and (c) water in <i>E. coli</i> lipid bilayer systems at different EtOH concentration. Simulations from AA and CG MD simulations are shown as solid and dotted lines, respectively.	112
5.6	Alteration in the segmental order parameter of the (a) POPG and (b) POPE palmitoyl tails in the <i>E. coli</i> bacterial membrane at various mole per percent of EtOH. Results from atomistic and CG MD simulations are represented by solid and dotted lines, respectively.	113

5.7	Images displaying the influence of ethanol molecules on the lipid vesicles of <i>E. coli</i> , which is concentration-dependent (0–30 mol%). The acyl chains of <i>E. coli</i> membrane composed of POPE and POPG lipid molecules, along with their lipid head groups, are shown in silver and purple colors, respectively. For the sake of clarity, the solvent molecules are not shown outside of the vesicles. The first and second columns represent whole and half-chopped vesicles, respectively, show EtOH mol% dependent variation.	114
5.8	(a) Surface area and (b) bilayer thickness of <i>E. coli</i> vesicles as a function of ethanol concentration.	115
5.9	Change in the number densities and mole-fractions of (a) ethanol and (b) water as a function of the radial distance from the middle of the <i>E. coli</i> vesicle to the bulk solvent area.	116
5.10	<i>E. coli</i> vesicle rupturing at higher EtOH concentrations. EtOH and water molecules are not shown.	117
5.11	Time-dependent effect of higher mol% of EtOH (40 mol % (a) and 70 mol % (b)) on multiple <i>E. coli</i> vesicles. Only lipid molecules are shown for clarity.	118
6.1	The chemical structures of DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine) lipid and ions of the BioILs studied. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	123
6.2	[Ch][Gly] and [Ch][Phe] concentration-dependent variations in (a) APL and (b) D_{pp} of DMPC lipid bilayer. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	126
6.3	Atomic Number density distributions of (a) lipid, (b) water, (c) [Ch] ⁺ , and (d) [Gly] ⁻ molecules in DMPC-[Ch][Gly] systems. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	128
6.4	Atomic Number density distributions of (a) lipid, (b) water, (c) [Ch] ⁺ and (d) [Phe] ⁻ molecules in DMPC-[Ch][Phe] systems. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	128

6.5	Equilibrium snapshots representing the concentration-dependent impact of (a-e) [Ch][Gly] (0-30 mol%) BioIL on DMPC lipid bilayer. P atoms of DMPC head groups are shown in pink color, and lipids are rendered in cyan. [Ch] ⁺ , and [Gly] ⁻ ions are rendered in lime and purple color, respectively. Waters molecules are not shown for clarity. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	130
6.6	Equilibrium snapshots representing the concentration dependent impact of [Ch][Phe] for (a) pure, (b) 5 mol%, and (c) 10 mol% BioIL on DMPC lipid bilayers. Color scheme used for lipid molecules and cholinium cation is kept same as in Figure 6.5. [Phe] ⁻ side chain and polar backbone are rendered in blue and orange colors, respectively. Waters molecules are not shown for clarity. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	130
6.7	Atomic number density distributions of N and O atoms of [Ch] ⁺ , [Gly] ⁻ and [Phe] ⁻ ions in (a) DMPC-[Ch][Gly] and (b) DMPC-[Ch][Phe] systems at different concentrations of the BioIL. (c) Number density distributions of the side chain and backbone components of [Phe] ⁻ at 5 and 10% of [Ch][Phe] BioIL. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	131
6.8	PMF profiles for the transfer of (a) [Phe] ⁻ and (b) [Gly] ⁻ ions from aqueous phase to lipid bilayer interior. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	132
6.9	Deuterium order parameter of tails of DMPC lipids at different concentration of (a) [Ch][Gly] and (b) [Ch][Phe] BioILs. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	133
6.10	Concentration dependence of interleaflet overlap parameter for DMPC lipid membrane with (a) [Ch][Gly] and (b) [Ch][Phe] BioILs. The leaflet-wise NDPs are plotted with respect to the density scale shown on left y-axis and the overlap parameter (ρ_{ov}) colored in magenta is plotted with respect to the right y-axis scale. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	134

6.11	Distribution of H-bonds for (a) DMPC-Water, (b) DMPC-[Ch] ⁺ , and (c) DMPC-[Gly] ⁻ in DMPC-[Ch][Gly] systems. For color coding of different concentration refer to Figure 6.3. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	135
6.12	Distribution of H-bonds for (a) DMPC-water, (b) DMPC-[Ch] ⁺ , and (c) DMPC-[Phe] ⁻ in DMPC-[Ch][Phe] systems. For color coding of different concentration refer to Figure 6.4. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	135
6.13	2D RDFs for (a) P-P and (b) N-N correlations of DMPC lipids in DMPC-[Ch][Gly] systems and (c) P-P and (d) N-N atom correlations of DMPC lipids in DMPC-[Ch][Phe]. Reproduced from ref.[6] Copyright (2021), with permission from American Chemical Society.	136
A.1	Pictorial representation of atomistic models of (a) POPC, (b) CHOL, (c) EtOH, and (d) water molecules respectively, with their corresponding CG mapping.	146
A.2	Time evolution of APL for POPC-CHOL lipid membrane system at different concentrations of ethanol for AA and CG systems.	146
A.3	2D center of mass radial distribution functions for (a) CHOL-CHOL, (b) POPC-POPC, and (c) CHOL-POPC at different mol% of ethanol. The solid lines are 2D RDF calculated from AA simulations and dashed lines are the 2D RDF calculated from the CG-MD simulation.	147
A.4	Time evolution of surface area for POPC-CHOL lipid vesicles at different concentration of ethanol for CG systems.	147
A.5	EDPs of (a) pure POPG, (b) beads wise distributions of POPG lipids, and (c) water in aqueous POPG lipid bilayer. (d) Variation in the palmitoyl tail segmental order parameter of POPG lipids in pure POPG lipid bilayer. Atomistic and CG MD simulations are represented by solid and dotted lines respectively.	148
A.6	PMFs for the insertion of an ethanol molecule from the hydrophilic water phase to the hydrophobic core of a POPG lipid bilayer from both the AA and CG simulations. In the PMF profiles, each error bar indicates one standard deviation.	148

A.7	Variation in the (a) POPG, (b) ethanol, and (c) water EDPs in the pure POPG lipid bilayer with respect to different EtOH concentrations. (d) The palmitoyl tail segmental order parameter for POPG lipids. Results from atomistic and CG MD simulations are represented by solid and dotted lines, respectively.	149
A.8	Equilibrium snapshots representing the effect of EtOH on CG POPG lipid membrane systems at (a) 0% , (b) 5% and (C) 10% EtOH. Lipid head group beads are rendered in green (OAL) and silver (PH), and the rest of the lipid molecules in rendered in purple color.	149
A.9	Time evolution of APL for (a) DMPC-[Ch][Gly] and (b) DMPC-[Ch][Phe] systems with varying concentration of BioILs.	150

List of Tables

2.1	Summary of the simulated bilayer systems.	41
2.2	Bond stretching parameters.	41
2.3	Nonbonded interaction parameters	42
2.4	Comparison between simulated and experimental densities (in g cm^{-3}) of pure and aqueous mixtures of DMSO.	45
2.5	Average APL (in \AA^2) and bilayer thickness (in \AA) of homogeneous POPC and POPE bilayers from atomistic and CG simulations.	47
3.1	Summary of the simulated bilayer systems	57
3.2	Bond stretching parameters for ethanol beads	57
3.3	Nonbonded interaction parameters involving ethanol	58
3.4	Comparison of simulated and experimental densities (in g cm^{-3}) of pure and aqueous mixtures of ethanol	59
3.5	Average APL (in \AA^2) and bilayer thickness (in \AA) of homogeneous POPC and POPE bilayer from AA and CG simulations.	59
3.6	Summary of simulated POPC lipid vesicle systems	65
3.7	Concentration-dependent variation in surface area (in nm^2) and bilayer thickness (in nm) for single spherical and fused POPC vesicles in pres- ence of ethanol.	65
4.1	Outline of the simulated POPC-CHOL bilayer systems	85
4.2	Nonbonded interaction parameters involving ethanol and cholesterol. ϵ (kcal mol^{-1}) and σ (\AA)	88
4.3	Variation in the APL (in \AA^2) and membrane thickness (D_{HH} , in \AA) of POPC-CHOL membrane from atomistic and CG MD simulations	90
4.4	Summary of simulated POPC-CHOL lipid vesicle system at different concentrations of ethanol	93

4.5	Ethanol concentration-dependent variation in surface area and bilayer thickness for single spherical POPC-CHOL vesicles comprising 30 mol% of cholesterol	93
5.1	Brief description of the simulated bilayer systems	105
5.2	Comparison of APL (in \AA^2) and membrane thickness (D_{HH} , in \AA) of the POPG and <i>E. coli</i> membranes from atomistic and CG MD simulations	106
5.3	Non-bonding parameters for interactions involving POPG lipid bilayer .	106
5.4	Non-bonding parameters for interactions involving ethanol and <i>E. coli</i> lipid bilayer	106
5.5	Bond stretching parameters for POPG lipid	106
5.6	Angle bending parameters for POPG lipid	107
5.7	Summary of simulated <i>E. coli</i> vesicle systems	111
6.1	Summary of the simulated bilayer systems	125
6.2	Variation in APL and bilayer thickness of DMPC lipid bilayer	126
6.3	Concentration-dependent average number of H-bonds per lipid molecule between different pairs of DMPC-[Ch][Gly] and DMPC-[Ch][Phe] systems.	137

Abstract

In this thesis, we report development and application of coarse-grained (CG) force-field for simulation of lipid membranes and vesicles in the presence of amphiphilic solvents and also studied the effect of biocompatible ionic liquids (BioILs) on biomimetic DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine) lipid membrane. Motivation behind this work originates from the fact that lipid membranes play important roles in various biological processes, including cell signaling, transport, and division. To understand these processes at the molecular level, computer simulations have been proven to be important technique to study how lipid membranes and vesicles behave in different environments, such as in the presence of pharmacologically active amphiphiles, which are used to move drugs across cell membranes[1, 2]. However, simulating these systems at an atomistic (AA) level is computationally expensive, limiting the size and timescale of simulations that can be accessed. Coarse-grained simulations, which reduce the number of particles by grouping them into larger entities, are an effective way to overcome these limitations[3]. In this thesis, we aim to develop and apply CG force-fields for simulating lipid membranes and vesicles in the presence of amphiphilic solvents and also studied the impact of BioILs on the structure of lipid membranes. We have first developed a CG model for DMSO for molecular dynamics (MD) simulations with the lipid membrane[4]. The proposed DMSO model successfully mimics the structural variation in biomimetic phospholipid bilayer systems comprised of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE) lipids, including alteration in bilayer thickness, lipid tail ordering, lipid lateral packing, and electron density profiles, when compared to results obtained from atomistic simulations. This model helps us appreciate the details on how the membrane physical properties such as fluidity and thickness are modulated by amphiphile-lipid interactions. Further, we develop a CG model for liquid ethanol (EtOH) and its aqueous mixture with lipid membranes for MD simulations[5]. The employment of the proposed ethanol model reveals ethanol-induced swelling, aggregation, and fusion of POPC lipid vesicles at different concentration of ethanol. Our study is further extended to observed the effect of ethanol molecules on more realistic vesicle membrane comprising POPC and cholesterol molecules. With CG MD simulations, it was found that ethanol had a detrimental effect on the biomimetic bilayers

and vesicle membranes, in presence of 30% cholesterol. Further we have broaden our study to develop the CG model for pathogenic membranes such as *Escherichia coli* (*E. coli*) under ethanolic stress. This study demonstrates the effect of ethanol on the structural alteration of membrane bilayers and vesicles using CG MD simulations. The study presents how a CG SPICA force-field was used to model the membrane of Gram-negative *E. coli* and how it interacts with amphiphilic ethanol. In the last core chapter, impact of two popular choline-amino acid-based ILs, cholinium glycinate ([Ch][Gly]) and cholinium phenylalaninate ([Ch][Phe]), which have previously been utilized as an alternative media for diverse applications, have been investigated on the structural organization and phase behavior of biomimetic bilayers at different concentrations[6] using MD simulations.

अमूर्त

इस थीसिस में, हम मोटे अनाज वाले (सीजी) बल-क्षेत्र के विकास और अनुप्रयोग की रिपोर्ट करते हैं एम्फीफिलिक सॉल्वेंट्स की उपस्थिति में लिपिड झिल्ली और पुटिकाओं के अनुकरण के लिए और बायोमिमेटिक डीएमपीसी पर बायोकम्पैटिबल आयनिक तरल पदार्थ (बीओआईएल) के प्रभाव का भी अध्ययन किया (1,2-डिमिरिस्टॉयल-एसएन-ग्लिसरो-3-फॉस्फोकोलिन) लिपिड झिल्ली। इसके पीछे प्रेरणा कार्य इस तथ्य से उत्पन्न होता है कि लिपिड झिल्ली विभिन्न द्वि-क्रियाओं में महत्वपूर्ण भूमिका निभाती है। सेल सिग्नलिंग, परिवहन और विभाजन सहित तार्किक प्रक्रियाएं। समझ में आणविक स्तर पर ये प्रक्रियाएँ, कंप्यूटर सिमुलेशन सिद्ध हो चुकी हैं यह अध्ययन करने के लिए महत्वपूर्ण तकनीक है कि लिपिड झिल्ली और पुटिकाएं अलग-अलग तरीके से कैसे व्यवहार करती हैं वातावरण, जैसे कि औषधीय रूप से सक्रिय उभयचरों की उपस्थिति में, जो कोशिका झिल्लियों में दवाओं को स्थानांतरित करने के लिए उपयोग किया जाता है [1, 2]। हालाँकि, इन प्रणालियों का अनुकरण-परमाणु (एए) स्तर पर तापमान कम्प्यूटेशनल रूप से महंगा है, जिससे आकार सीमित हो जाता है सिमुलेशन का टाइमस्केल जिसे एक्सेस किया जा सकता है। मोटे दाने वाले सिमुलेशन, जो पुनः-करणों को बड़ी इकाइयों में समूहित करके उनकी संख्या बढ़ाना प्रभावी है इन सीमाओं को पार करने का तरीका[3]। इस थीसिस में, हमारा लक्ष्य सीजी को विकसित करना और लागू करना है एम्फीफिलिक की उपस्थिति में लिपिड झिल्ली और पुटिकाओं का अनुकरण करने के लिए बल-क्षेत्र सॉल्वेंट्स और लिपिड झिल्ली की संरचना पर बायोआईएल के प्रभाव का भी अध्ययन किया।

हमने सबसे पहले आणविक गतिशीलता (एमडी) सिम के लिए डीएमएसओ के लिए एक सीजी मॉडल विकसित किया है। लिपिड झिल्ली के साथ उत्सर्जन[4]। प्रस्तावित डीएमएसओ मॉडल सफलतापूर्वक नकल- बायोमिमेटिक फॉस्फोलिपिड बाइलेयर प्रणालियों में संरचनात्मक भिन्नता शामिल है 1-पामिटॉयल-2-ओलेयोल-एसएन-ग्लिसरो-3-फॉस्फोकोलीन (पीओपीसी) और 1-पामिटॉयल-2-ओलेयोल-एसएन-ग्लिसरो-3-फॉस्फोएथेनॉलमाइन (पीओपीई) लिपिड, जिसमें बाइलेयर मोटाई में परिवर्तन शामिल है- नेस, लिपिड टेल ऑर्डरिंग, लिपिड लेटरल पैकिंग, और इलेक्ट्रॉन घनत्व प्रोफाइल, जब कॉम-परमाणु सिमुलेशन से प्राप्त परिणामों के अनुरूप। यह मॉडल हमें सराहना करने में मदद करता है झिल्ली की भौतिक संपत्ति कैसे होती है, यह मॉडल हमें इस बारे में विवरण समझने में मदद करता है कि झिल्ली के भौतिक गुण जैसे तरलता और मोटाई कैसे हैं एम्फीफाइल-लिपिड इंटरैक्शन द्वारा संशोधित। इसके अलावा, हम एमडी सिमुलेशन के लिए तरल इथेनॉल (ईटीओएच) और लिपिड झिल्ली के साथ इसके जलीय मिश्रण के लिए एक सीजी मॉडल विकसित करते हैं। प्रस्तावित इथेनॉल मॉडल के प्रयोग से इथेनॉल-प्रेरित सूजन, एग- का पता चलता है। इथेनॉल की विभिन्न सांद्रता पर पीओपीसी लिपिड पुटिकाओं का एकत्रीकरण और संलयन। पीओपीसी और कोलेस्ट्रॉल अणुओं से युक्त अधिक यथार्थवादी पुटिका झिल्ली पर इथेनॉल अणुओं के प्रभाव को देखने के लिए हमारा अध्ययन आगे बढ़ाया गया है। सीजी एमडी सिमु के साथ-अध्ययन में पाया गया कि 30% कोलेस्ट्रॉल की उपस्थिति में इथेनॉल का बायोमिमेटिक बाइलेयर्स और वेसिकल झिल्लियों पर हानिकारक प्रभाव पड़ता है। इसके अलावा हमने एस्चेरिचिया कोली जैसी रोगजनक झिल्लियों के लिए सीजी मॉडल विकसित करने के लिए अपने अध्ययन का विस्तार किया है

(ई. कोलाई) इथेनॉलिक तनाव के तहत। यह अध्ययन सीजी एमडी सिमुलेशन का उपयोग करके झिल्ली बाइलेयर्स और वेसिकल्स के संरचनात्मक परिवर्तन पर इथेनॉल के प्रभाव को प्रदर्शित करता है। अध्ययन प्रस्तुत करता है कि ग्राम-की झिल्ली को मॉडल करने के लिए सीजी स्पिका बल-क्षेत्र का उपयोग कैसे किया गया था नकारात्मक ई. कोलाई और यह एम्फीफिलिक इथेनॉल के साथ कैसे इंटरैक्ट करता है। अंतिम मुख्य अध्याय में, दो लोकप्रिय कोलीन-अमीनो एसिड-आधारित आईएल, कोलिनियम ग्लाइसीनेट ([Ch][Gly]) का प्रभाव और कोलिनियम फेनिलएलिनेट ([Ch][Phe]), जिसका उपयोग पहले भी किया जा चुका है विविध अनुप्रयोगों के लिए वैकल्पिक मीडिया की संरचनात्मक जांच की गई है विभिन्न सांद्रता पर बायोमिमेटिक बाइलेयर्स का संगठन और चरण व्यवहार एमडी सिमुलेशन का उपयोग करना।

Permissions

Permissions have been taken from the respective journals to reprint the publications related to the work presented in this thesis.

List of Publications Related to Work Presented in this Thesis

1. **Shobhna**, Monika Kumari, and Hemant K. Kashyap, Mechanistic Insight on BioIL-Induced Structural Alterations in DMPC Lipid Bilayer. *J. Chem. Phys.* **2020** 153, 035104.
2. **Shobhna** and Hemant K. Kashyap, Deciphering Ethanol-Driven Swelling, Rupturing, Aggregation, and Fusion of Lipid Vesicles Using Coarse-Grained Molecular Dynamics Simulations. *Langmuir* **2022** 38, 2445.
3. **Shobhna**, Monika Kumari, and Hemant K. Kashyap, Mechanistic Insight on BioIL-Induced Structural Alterations in DMPC Lipid Bilayer, *J. Phys. Chem. B* **2021**, 125, 11955.