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Title	Studies on Tetrahedral Diagram Analysis on Interfacial Properties of the Quaternary Lipid System Related to the Brain Cell Membrane
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Citation	大阪大学, 2026, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/105518
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Form 3

Abstract of Thesis

Name （Ajaikumar Arun）	
Title	Studies on Tetrahedral Diagram Analysis on Interfacial Properties of the Quaternary Lipid System Related to the Brain Cell Membrane (脳細胞膜に関連する四成分脂質系界面特性の四面体図解析に関する研究)

Abstract of Thesis

Various membrane properties are impacted by the specific composition of the lipid bilayer, and these properties are worth analyzing for their connection and implication in different pathologies. Particularly, the brain is an integral part of the central nervous system and thereby changes to any aspect of its anatomy, including lipid membrane properties, has the possibility of causing systemwide consequences. Liposomes are commonly used as a biomimetic environment that allows research to focus exclusively on the lipid membrane with minimal other molecular interference, thus liposomes made from brain lipids or their analogs were the primary platform of analysis in this work.

In chapter 1, a general introduction was provided about the relevance of lipid bilayer properties and its significant connection to the brain. An overview of the brain lipid membrane and relevant pathologies was discussed. Analytical techniques used in this thesis were introduced and their benefits were further discussed. Assessment on the limitations in current tools for interpretation and analysis of complex membrane properties was discussed. Finally, the overarching philosophy of this work was briefly introduced.

In chapter 2, emphasis was placed on how inter-lipid interactions with different ratios of lipids in the bilayer may impact the overall properties and functionality of a simple unary or binary membrane system. Brain sphingomyelin (bSM) and cholesterol (Chol) of different ratios were made into liposomes, and their polarity and fluidity were analyzed. Fluorescence spectroscopy and deconvolution analysis were both used for characterization and revealed a high possibility of heterogeneity in liposomes with 30% or more Chol content as temperature increased. Qualities that possibly act as precursors to lipid raft phenomena were briefly discussed.

In chapter 3, phosphatidylcholine (PC) and phosphatidylethanolamine (PE) lipids were introduced as brain lipid analogs for further adding complex variation to liposome compositions. Liposomes of ternary lipid compositions of varying ratios were constructed and a ternary phase diagram for characterizing fluorescence spectroscopy results was briefly introduced. Both the significance of the properties of these ternary membrane systems and the necessity of expanding the concept of ternary phase diagrams was discussed and a 2D “flattened tetrahedron phase diagram” was introduced as a tool for comparing multiple ternary phase diagrams with correlated lipid species. This flattened tetrahedron phase diagram was shown to show smooth transition in displaying the membrane polarity and relevant boundaries across the component ternary phase diagrams and was finally folded to propose the next step in data interpretation of increasingly complex membranes.

In chapter 4, the concept of the 2D “flattened tetrahedron phase diagram” was expanded into a more complex 3D tetrahedron phase diagram to analyze more complex quaternary lipid membrane compositions. Liposomes consisting of 4 lipid species were constructed and further analyzed with previously used fluorescence techniques. Phase states were discussed in the context of quaternary membrane compositions and depicted via the tetrahedron phase diagram. Quaternary membranes revealed more robustness in phase with temperature change. Insight was obtained into the interior of the tetrahedron diagram at specific temperatures. Ultimately, with the tetrahedron diagram, there was set a future goal of tetrahedron mapping of the brain lipid membrane as well as other important membranes in anatomy.

In chapter 5, we first examined how the composition of the lipid bilayer of brain lipids or their analogs impacted the aggregation of amyloid-β (Aβ) peptide on the liposome membrane. Temporal kinetic aspects of Aβ aggregation were analyzed and correlated to different membrane compositions. It was found that fluid membranes generally acted to enhance the speed of fibrillation kinetics of Aβ. Next, to conversely analyze how the Aβ impacted membrane properties, the membrane polarity at different stages of Aβ aggregation was both quantified and qualified with Laurdan fluorescence spectroscopy and deconvolution analysis. It was found that during the lag phase (tlag) of Aβ aggregation, there was slight hydration behavior of the membrane, followed by dehydration behavior as the aggregation progressed to its completion. This dehydration behavior revealed that surface level aggregation also impacts the solvent environment at the membrane’s interfacial region.

In chapter 6, we draw general conclusions from this work and how it is relevant to future research in both the microscopic/mesoscopic realm of lipid membrane research and the macroscopic realm of the biomedical field. Significance in the necessity for further development of the tetrahedron diagram for complex membrane composition analysis and tetrahedral diagram mapping of complex systems was discussed. Suggestions for future works were also proposed to further examine properties of increasingly complex lipid membrane compositions.

様式７

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

脂質二重膜の組成は膜の極性・流動性・相状態など多様な物性に影響を与え，これらの変化は脳をはじめとする中枢神経系の病態とも密接に関連することが知られている。本学位論文では，脳脂質またはその類縁体から調製したリポソームを生体膜模倣モデルとして用い，複雑な脂質膜物性の体系的理解と解析手法の高度化を目的とした研究を行っている。第1章では，脳脂質膜の構造と病態との関連性，および本研究で用いた蛍光分光法を中心とする解析手法の有用性と現状の課題を概説し，本研究の基本理念を提示している。第2章では，脳スフィンゴミエリンとコレステロールの二成分膜を対象として脂質間相互作用と膜物性の関係を検討し，高コレステロール条件における膜不均一性の発現とラフト様挙動の可能性を示している。第3章では，ホスファチジルコリンおよびホスファチジルエタノールアミンを加えた三成分膜へと系を拡張し，複数の三元相図を統合的に比較するための「 flattened tetrahedron phase diagram（平坦化四面体相図）」を提案し，膜極性変化の連続的可視化を可能とした。第4章では，四成分膜系に対して3D tetrahedron phase diagram（三次元四面体相図）を導入し，複雑な膜組成における相状態の温度依存性と膜内部の特性解析を行い，将来的な脳脂質膜マッピングの基盤を提示している。第5章では，アミロイドβペプチドの膜上での凝集挙動と膜物性変化の相互作用を検討し，流動性の高い膜が凝集速度を促進すること，さらに凝集過程に伴う膜界面の水和状態変化を明らかにしている。第6章では，本研究成果を総括するとともに，複雑脂質膜解析に向けた tetrahedron phase diagram の発展と今後の研究展望について述べている。以上より，本研究は複雑な脳脂質膜物性の体系的理解と病態関連研究への応用に資する新たな解析基盤を提示するものである。以上の記述のとおり、博士（工学）の学位論文として価値のあるものと認める。