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BILLY AND THE TIME-A-SAURUS

BY

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ABSTRACT OF THE DISSERTATION

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Pentameric ligand-gated ion channels (pLGIC) are a family of channels essential in synaptic function. pLGICs are shown to be functionally dependent on their environment's lipid composition. The local interactions and direct lipids-proteins contacts are poorly understood.

While the role of lipids is essential to pLGIC, the accessible boundary lipids have not been identified. Experimental studies have provided mixed results determining boundary lipids in model membranes, and have largely ignored native membranes. We simulate the pLGIC the nicotinic acetylcholine receptor (nAChR) in neuronal membranes (membranes nAChR resides in), and Xenopus oocyte membranes (a membrane used in experimental studies). nAChR native membranes have approximately 3x the -3's polyunsaturated fatty acids (PUFAs) and 1.5x the cholesterol compared to Xenopus oocytes; yet, -3 PUFAs are infrequently used in pLGIC experimental studies.

pLGIC are conserved across structures and have been observed to function in similar lipid compositions. To better understand the interplay between pLGICs and -3 PUFAs we simulate a series of ternary membranes using saturated fatty acids, -6 PUFAs, and -3 PUFAs using various pLGICs with existing crystal or cryo-EM structures. We hypothesize one of two outcomes: 1) all pLGICs form a similar boundary distribution of PUFAs, suggesting lipid organization is a result

of a shared structure. 2) Lipid distributions are dissimilar, and lipid organization is driven by protein sequence over the structure.

CG-MD simulations play the role of a "computational microscope" to visualize lipid diffusion and various feasible lipid-protein arrangements in thermodynamically equilibrated systems over microseconds, allowing observations not readily seen experimentally.

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While there are still more to thank, I have a finite number of pages. To both friends and family not mentioned, your support has ment the world to me. I would like to leave you with a quote by Sir Terry Pratchett.

“But then science is nothing but a series of questions that lead to more questions.”— Terry Pratchett, The Long Earth

Dedication

The body of the dedication

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0.1 Introduction

Ion channels are transmembrane proteins that transport ions outside of the cell to the inside of the cell. Pentameric ligand gated ion channels (pLGICs) are ion channels made of 5 subunits and gated by various ligands such as neurotransmitters, drugs, and modulated by lipids. pLGICs are divided into three major segments: the extra-cellular domain (ECD), the transmembrane domain (TMD), and the poorly understood inter-cellular domain (ICD), see Figure 1. The ECD is composed of beta-sheets, with ligand binding pockets usually at inter-subunit regions. The TMD spans the membrane. Each subunit is made of 4 alpha-helices, M1 to M4. Alpha-helices M1 and M3 form the 'body' of the TMD, M2 makes up the channel's pore, and M4 protrude into the membrane, and are in constant direct contact with lipids.

pLGICs are essential proteins dedicated to neuronal function. In mammals pLGICs are found in both the central and peripheral nervous system. pLGICs play various roles in neurological diseases related to inflammation Taly et al. (2009); Cornelison et al. (2016); Patel et al. (2017b); Yocum et al. (2017); Egea et al. (2015), addiction Cornelison et al. (2016), chronic pain Xiong et al. (2012), Alzheimer's Disease Walstab et al. (2010); Picciotto & Zoli (2008); CM et al. (1999); Kalamida et al. (2007b), spinal muscular atrophy Arnold et al. (2004), schizophrenia Haydar & Dunlop (2010); Kalamida et al. (2007b) and neurological autoimmune diseases Lennon et al. (2003); Kumari et al. (2008).

There are 4? species of eukaryotic pLGICs: cationic and anionic. Cationic pLGICs, such as nicotinic acetylcholine receptors (nAChRs) and serotonin receptors (5-HT₃R) are responsible for stimulating action potential along axons. Anionic pLGICs, such as γ -aminobutyric acid type A (GABA_AR) and glycine receptors (GlyR), are responsible for inhibiting action potentials.

pLGICs are sensitive to their local lipid composition, especially nAChR.

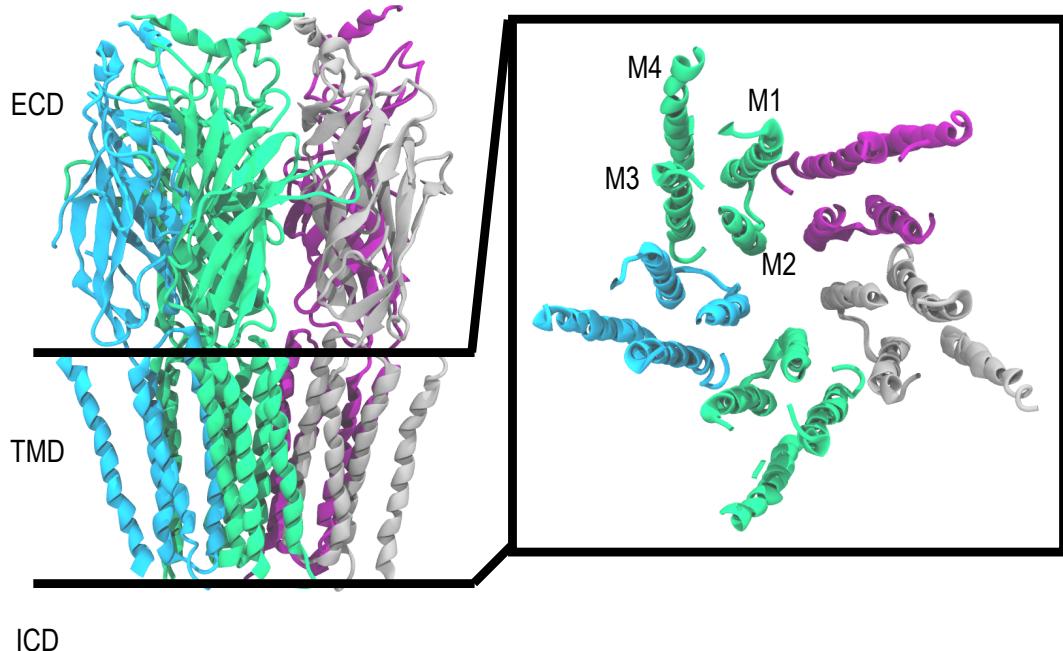


Figure 1: The pLGIC structure nAChR. Structure shown from a side view on the left. ECD is comprised of beta sheets. TMD are alpha helices. The ICD is disordered and not show. The TMD looking down from the ECD. M1 and M3 make up a cylindrical "body" of the channel. M2 makes up the central pore. M4 directly interact with lipids, and provide the conical/star shape. α : green, γ : blue, δ : grey, β : purple.

Experimental approaches to analyze pLGIC membrane domain and boundary lipid composition have relied heavily on model membranes. Model membranes are man made membranes usually consisting of 1 to 3 lipids. Cholesterol and anionic lipids are frequently used and are important for modulating **nAChRfunction**. Cholesterol in particular plays a number of roles in membranes beyond binding to pLGICs. **Cholesterol decreases** membrane permeability and the average area per lipid, and adds order to the **bulk** membrane Yeagle (2016b). The ordering effect of cholesterol on membranes can result in membrane domain formation, if other **domain forming lipids are present**. Domain formation is the de-mixing of ordered

saturated lipids and cholesterol from less ordered unsaturated lipids, forming liquid ordered (l_o) and liquid disordered (l_{do}) domains respectively. These domains can form a lipid reservoir of favorable boundary lipids.

Model membranes are useful tools for developing predictive ~~boundary lipid~~ models, but they lack the lipid diversity of a plasma membrane. Model organisms, such as *Xenopus* oocyte may have more than thirty phospholipid species Gamba et al. (2005); Ferreira et al. (2010). pLGIC native membranes, such as neuronal membranes or *Torpedo* electric organs have more than 30 species of phospholipid ?Taguchi & Ishikawa (2010); ?); Ingólfsson et al. (2017); ?); Quesada et al. (2016). Lipid diversity is not enough though, nAChR when placed in *Xenopus* oocyte have poor function and require lipid additives to conduct ions. This suggests there are specific lipids required for nAChR function not found in *Xenopus* oocyte or not enough of these specific lipids to play a boundary role. A hypothesized essential boundary lipid acyl-species are n-3 polyunsaturated fatty acids (PUFAs).n-3 PUFAs compose $\sim 15 - 20\%$ of phospholipids found in pLGICnative membranes, but only $\leq 10\%$ in *Xenopus* oocytes.

Missing parts still Bullet 3

pLGICs are modulated by their boundary lipid composition. Cholesterol, saturated, and monounsaturated lipids, with neutral or anionic head groups, have been studied the most. how do lipids modulate function??? Cholesterol has been a key lipid of study. In model membranes a minimum of 10 – 20% cholesterol was required to return function to nAChR.

Bullet 4, kind of 5 too...

The structure and sequence of pLGICs dictates where specific lipids will bind. The M4 alpha-helices have the highest probability to interact with unsaturated lipids and cholesterol. It is hypothesized that PUFAs minimize the membrane deformation caused by the M4 alpha-helices' conical-star shape need pic, and cholesterol helps stabilize the structure. Inter-subunit sites have the

highest probability to interact with saturated lipids, n-3 PUFAs, and cholesterol. We hypothesize n-3 PUFAs and cholesterol stabilize the protein's structure, and saturated lipid's low flexibility ~~fit~~ interact favorably with pLGIC's cylindrical inter-subunit sites. The sequence of the pLGIC's structure dictates the location of anionic lipid binding. The prokaryotic pLGICELIC's inner inter-subunit sites tend to be occupied by anionic lipids, however nAChR's inner M4 sites tend to be occupied by anionic lipids.

pLGICs reconstituted or ~~grown/injected~~ into model membranes, or model organisms, have boundary lipid compositions not optimized for function. The model organism, *Xenopus* oocyte, has more n-6 and fewer n-3 PUFAs than neuronal membranes. A result of this is n-6 PUFAs tend occupy the M4 region in greater numbers than n-3 PUFAs. *Xenopus* oocyte also have $\sim 21\%$ cholesterol versus $\sim 40\%$ cholesterol in neuronal membranes. The difference in cholesterol results in a drop in boundary cholesterol density. These composition changes may be the cause of the decrease in function, and increased membrane deformation.

It is experimentally challenging to capture the boundary lipid composition of pLGICs, as well as other membrane channels. Functional experiments, such as electrophysiology and florence quenching, demonstrated anionic lipids and cholesterol as lipid modulated pLGIC's function Ellena et al. (1983); Fong & McNamee (1986b); ?); Jones & Mcnamee (1988); Sunshine & McNamee (1994); DaCosta et al. (2009), but pLGICs are functional dependent on boundary cholesterol Dalziel et al. (1980); Addona et al. (1998); Criado et al. (1983). Structural biology such as cryo-EM, x-ray crystallography, and mass spectrometry, has found potential cholesterol sites at the subunit interface Laverty et al. (2017); Budelier et al. (2019), potential specific phospholipid sites in the inter-subunit site Hénault et al. (2019); Basak et al. (2017) and inter-subunit sites sites Kim et al. (2020), and anionic lipids binding to inner inter-subunit sites Tong et al. (2019). MD simulations are used as a computational tool to visualize below the diffraction

limit and visualize and predict, protein-lipid interactions. MD simulation has identified cholesterol Brannigan et al. (2008a); Woods et al. (2019) interaction at inter-subunit sites and PUFA sites at M4 sites Woods et al. (2019), as well as anionic lipids binding at inner inter-subunit sites Tong et al. (2019).

Predicting boundary pLGIC boundary lipid and specific sites of protein occupancy has been exhaustedly done in model membranes or model organism. These model membranes have provided invaluable predictive models, however pLGIC native boundary lipids are unknown. This thesis is the accumulation for four projects predict pLGIC boundary lipids in coarse-grained model and quasi-realistic membranes. Chapter 1 looks at where nAChR resides in domain forming membranes. Chapter 2 compares domain and non-domain forming membranes for multiple nAChR and predicts locations for lipid occupancy. Chapter 3 is computational work from a collaborative project, predicting anionic occupancy sites for the pLGIC ELIC. Chapter 4 embeds nAChR in a quasi-native membrane, and tests the predicted occupancy sites from chapters 2 and 3 by calculating the binding affinity of acyl-chain saturation and head group charge.

Chapter 1

Boundary lipids of the nicotinic acetylcholine receptor: spontaneous partitioning via coarse-grained molecular dynamics simulation

1.0.1 Introduction

The nicotinic acetylcholine receptor (nAChR) is an excitatory pentameric ligand gated ion channel (pLGIC) commonly found in the neuronal post synaptic membrane and neuromuscular junction (NMJ) in mammals as well as the electric organs of the *Torpedo* electric ray. nAChRs play a fundamental role in rapid excitation within the central and peripheral nervous system, and neuronal nAChRs are also critical for cognition and memory Dani (2001); Changeux et al. (2015). Acetylcholine is the orthosteric nAChR ligand, but numerous other exogenous and endogenous small molecules modulate nAChRs, including nicotine, general anesthetics, the tipped-arrow poison curare, phospholipids, cholesterol, and cholesterol-derived hormones.Klaassen & Watkins (2015); Taly et al. (2009) The larger pLGIC super family that includes nAChRs has been shown to play roles in numerous diseases related to inflammation, Patel et al. (2017b); Yocum et al. (2017); Cornelison et al. (2016), addiction Cornelison et al. (2016), chronic pain Xiong et al. (2012), Alzheimer's Disease Walstab et al. (2010); Picciotto & Zoli (2008); CM et al. (1999), spinal muscular atrophy Arnold et al. (2004), schizophrenia Haydar & Dunlop (2010) and neurological autoimmune diseases Lennon et al. (2003).

nAChRs are highly sensitive to the surrounding lipid environmentHamouda et al. (2006b); Baenziger et al. (2017); Padilla-Morales et al. (2016); Barrantes

(2007) for reasons that remain poorly understood. In the late 1970s it was observed that reconstituted nAChRs only exhibit native conductance if model phospholipid membranes contained at least 10-20% cholesterol Dalziel et al. (1980); Criado et al. (1982); Ochoa et al. (1983). Three generations of investigation into the mechanism have followed, with the first generation of studies Marsh & Barrantes (1978); Dalziel et al. (1980); Marsh et al. (1981a); Criado et al. (1982); Gonzalez-Ros et al. (1982); McNamee et al. (1982); Ellena et al. (1983); Ochoa et al. (1983); Zabrecky & Raftery (1985); Bristow & Martin (1987); Leibel et al. (1987); Middlemas & Raftery (1987); Jones et al. (1988); Jones & McNamee (1988); Fong & McNamee (1986b); ?); McNamee & Fong (1988a); ?); Sunshine & McNamee (1992, 1994); Narayanaswami & McNamee (1993); Addona et al. (1998); Corbin et al. (1998); Barrantes et al. (2000) aiming to differentiate between the role of bulk, annular, and non-annular cholesterol. The second generation Baenziger et al. (2015); Brusés et al. (2001); Marchand et al. (2002); Oshikawa et al. (2003); Pato et al. (2008); ?); Baenziger et al. (2017); Barrantes (2007); Barrantes et al. (2000, 2010); Bermudez et al. (2010); Perillo et al. (2016); Wenz & Barrantes (2005); Borroni et al. (2016); Unwin (2017a) of studies probed membrane-mediated effects on organization of multiple nAChRs, while the third generation Basak et al. (2017); Althoff et al. (2014); Laverty et al. (2017); Zhu et al. (2018) has applied x-ray crystallography and high-resolution cryo electron microscopy to directly observe lipid binding modes.

Members of the pLGIC family other than nAChR are also lipid-sensitive, Dunn et al. (1989a); Sookswate & Simmonds (2001); Baenziger & Corringer (2011); Dostalova et al. (2014) and lipids other than cholesterol can also modulate function Bhushan & McNamee (1993); Cheng et al. (2007); ?); Rankin et al. (1997); Wenz & Barrantes (2005); Hamouda et al. (2006b), but these mechanisms have not been as extensively studied. The recent publication of several crystal and cryo-EM structures Basak et al. (2017); Althoff et al. (2014); Laverty et al. (2017);

Zhu et al. (2018) has confirmed that specific lipid-pLGIC interactions extend beyond cholesterol and nAChR. Such interactions are also well-established in other transmembrane proteins, including G-protein coupled receptors (GPCRs) and other ion channels, as reviewed in Burger et al. (2000); Lee (2004a); Pucadyil & Chattopadhyay (2006); ?; Smithers et al. (2012).

Even in the specific case of cholesterol-nAChR interactions, results from different approaches have suggested complex behavior and even contradictory interpretations. Results have indicated that both cholesterol enrichmentDalziel et al. (1980); Criado et al. (1982); Ochoa et al. (1983) and cholesterol depletionSantiago et al. (2001) cause gain of function, that anionic phospholipids are unnecessary for native functionDalziel et al. (1980); Criado et al. (1982); Ochoa et al. (1983) or must be?? included in a reconstitution mixture, that cholesterol increases nAChR clusteringPato et al. (2008); ?); Barrantes (2007) and directly interacts with nAChR Leibel et al. (1987); Jones & Mcnamee (1988), but nAChR does not consistently partition into cholesterol-rich domainsBermúdez et al. (2010). We suggest here that some of these apparent contradictions may be explained by competition between cholesterol and other lipids found in native membranes, primarily lipids with polyunsaturated fatty acyl chains (PUFAs).

Interactions of nAChR with PUFAs have not been systematically investigated experimentally, but a large amount of circumstantial experimental evidence suggests an important role for PUFAs in nAChR function. Clinically, long-chain $n - 3$ (commonly called “Omega-3” or $\omega - 3$) lipids have a neuroprotective rolePiomelli et al. (2007), and nAChR-associated pathologies can arise for patients with low levels of $n - 3$ PUFAs. $\alpha 7$ nAChRs are implicated in schizophreniaHaydar & Dunlop (2010), and dietary supplementation with $n - 3$ fatty acids (usually through fish oil) can reduce the likelihood of psychosis, with dramatic effects in some individual cases.Amminger et al. (2010)

In vitro, PUFA-rich asolectinRegost et al. (2003); Olsen et al. (2003) is one of

the most robust additivesCriado et al. (1982) for obtaining native nAChR function: restoration of native function by cholestryl hemisuccinate (CHS) is observed only over a narrow CHS concentration range in monounsaturated PE/PS membranes, but a much wider concentration range in asolectinCriado et al. (1982). The specific component(s) of asolectin that complement cholesterol in improving nAChR function have not been isolated. Long chained $n - 3$ PUFA lipids are abundant in two seemingly disparate nAChR native membranes: mammalian neuronal membranesBreckenridge et al. (1973); Cotman et al. (1969) and those of the *Torpedo* electric organ,?Quesada et al. (2016). Both such membranes also have an abundance of phosphoethanolamine (PE) headgroups and saturated glycerophospholipids, and a scarcity of monounsaturated acyl chains and sphingomyelin compared to thhe *Xenopus* oocyte membranes ? common in functional studies, or a “generalized” mammalian cell membrane ?.

Membranes composed of ternary mixtures of saturated lipids, unsaturated lipids, and cholesterol tend to demix into separate domains. Saturated lipids and cholesterol constitute a rigid liquid ordered phase (l_o) in which acyl chains remain relatively straight. Feller (2008); Yeagle (2016a); Cicuta et al. (2007); Bleecker et al. (2016) Unsaturated lipids form a more flexible liquid disordered phase (l_{do}) in which the chains remain fully melted. l_o domains are often visualized as signaling “platforms”, restricting membrane proteins into high density “rafts” that diffuse within a fluid membrane Simons & Ikonen (1997); ?. This conceptualization requires that l_o domains have a much smaller area than l_{do} domains, and does not well-represent membranes that are over 30% cholesterol, such as neuronal membranes.

The first generation of studies into the mechanism underlying cholesterol-modulation of nAChR were conducted and interpreted in an era preceding the discovery of lipid-induced domain formation in membranes. The second generation explicitly considered potential interactions of nAChR with lipid domains,

in part to determine the requirements for the extremely high density ($\sim 10^4 \mu^{-2}$) of nAChRs at the neuromuscular junction ?. Since direct interaction between nAChR and cholesterol had been demonstrated in the first generation of studies, a sensible initial hypothesis was that nAChR persistently partitioned to l_o domains, retaining little contact with unsaturated chains. Tests of this hypothesis have yielded results that are inconclusive, contradictory, or highly sensitive to lipid composition.

Barrantes and colleagues Wenz & Barrantes (2005) found that the addition of nAChRs to a domain-forming lipid mixture increased the size of Dipalmitoylphosphatidylcholine/Cholesterol (DPPC/Chol) lipid-ordered domains, which (combined with additional FRET data) was interpreted as indicating nAChR was embedded in liquid-ordered domains. Some studies Marchand et al. (2002); Stetzkowski-Marden et al. (2006); Willmann et al. (2006) suggest that nAChRs are associated with microdomains independently of stimulation by other proteins associated with the neuromuscular junction. Other studies?Campagna & Fallon (2006) suggested that nAChRs require stimulation by a protein such as agrin to partition into microdomains. Formation and disassembly of the nAChR-rich microdomains is highly sensitive to cholesterol concentration. Barrantes (2007); Brusés et al. (2001); Marchand et al. (2002); ?; Pun et al. (2002)

These studies suggested a role for cholesterol-induced phase separation, but did not confirm that nAChR partitions to the cholesterol-rich phase. To test for an intrinsic nAChR domain preference, Barrantes and co-workers checked for enrichment of nAChRs in the detergent resistant membrane (DRM). nAChRs were not enriched in the DRM of a model, domain-forming mixture (1:1:1 Chol: palmitoyloleoylphosphatidylcholine(POPC): sphingomyelin) Bermúdez et al. (2010) but inducing compositional asymmetry across leaflets did yield nAChR enrichment in the DRM fraction ?. While more precise and robust experimental methods for determining partitioning preference and specific boundary lipids such as mass

spectrometry have been applied for other transmembrane proteins Gupta et al. (2018); Chorev et al. (2018), they have not been applied to complex heteromers like nAChR.

Fully atomistic molecular dynamics (MD) simulations? Cheng et al. (2009); Hénin et al. (2014); Carswell et al. (2015a) have served as a natural complement to the third-generation structural biology approach, but are limited in their ability to resolve contradictions between first and second generation studies, because lipids are unable to diffuse over simulation time scales. Ingólfsson et al. (2014); Bond & Sansom (2006); Parton et al. (2013); Goose & Sansom (2013); Scott et al. (2008). Efficient lipid diffusion is a requirement for equilibrating domains or detecting protein-induced lipid sorting. Coarse-grained MD (CG-MD) has been used to great success in a number of simulations for both lipid-protein binding and membrane organization Bond & Sansom (2006); Scott et al. (2008); Parton et al. (2013); Goose & Sansom (2013); Iyer et al. (2018); Sodt et al. (2014). Here we use CG-MD as a “computational microscope” to observe the equilibrium distribution of lipids local to the nAChR in a range of binary and ternary lipid mixtures inspired by native membranes. We observe a remarkable enrichment of polyunsaturated lipids among nAChR boundary lipids. To our knowledge, these are the first molecular simulations of the nAChR in non-randomly mixed membranes, and the first study to systematically investigate the likelihood of polyunsaturated lipids as nAChR boundary lipids.

1.1 Methods

System Composition

All simulations reported here used the coarse-grained MARTINI 2.2 Marrink et al. (2007a) topology and forcefield. nAChR coordinates were based on a cryo-EM structure of the $\alpha\beta\gamma\delta$ muscle-type receptor in native torpedo membrane (PDB

2BG9?). This is a medium resolution structure (4\AA) and was further coarse-grained using the martinize.py script; medium resolution is sufficient for use in coarse-grained simulation, and the native lipid environment of the proteins used to construct 2BG9 is critical for the present study. The secondary, tertiary and quaternary structure in 2BG9 was preserved via soft backbone restraints during simulation as described below, so any inaccuracies in local residue-residue interactions would not cause instability in the global conformation.

Coarse-grained membranes were built using the Martini script insane.py, which was also used to embed the coarse-grained nAChR within the membrane. The insane.py script randomly places lipids throughout the inter- and extra-cellular leaflets, and each simulation presented in this manuscript was built separately. Binary mixed membranes were composed of one saturated lipid species (Dipalmitoylphosphatidylcholine-DPPC or Dipalmitoylphosphatidylethanolamine-DPPE) and cholesterol (CHOL), while ternary mixed membranes also included either two $n-6$ PUFA acyl chains : Dilinoleoylphosphatidylcholine (dLA-PC) or Dilinoleoylphosphatidylethanolamine (dLA-PE) or two $n-3$ PUFA acyl chains : Didocosahexaenoylphosphatidylethanolamine (dDHA-PE) or Didocosahexaenoylphosphatidylcholine (dDHA-PC). DHA-PC is not distributed with the MARTINI lipidome, but was constructed in-house using MARTINI DHA tails and PC headgroups). Multiple box sizes were used depending on the goal; “small” boxes were between $22x22x20 \text{ nm}^3$ and $25x25x25 \text{ nm}^3$, with about ~ 1400 total lipids and ~ 80000 total beads, and were used primarily to investigate composition trends, “large” boxes were about $45x45x40 \text{ nm}^3$ with about $\sim 8,300$ total lipids and $\sim 820,000$ total beads, and were used primarily to investigate subunit specificity and long-range sorting, and “very large” boxes were $\sim 75x75x40 \text{ nm}^3$ with about $\sim 19,000$ total lipids and ~ 1.8 million total beads, and were used to verify that partitioning in the l_{do} phase did not reflect finite size effects.

Simulations

Molecular dynamics simulations were carried out using GROMACS Berendsen et al. (1995); small boxes used GROMACS 5.0.6 and large and very large boxes used GROMACS 5.1.2 or 5.1.4. All systems were run using van der Waals (vdW) and Electrostatics in shifted form with a dielectric constant of $\epsilon_r=15$. vdW cutoff lengths were between 0.9 and 1.2 nm, with electrostatic cutoff length at 1.2 nm.

Energy minimization was performed over 10000 to 21000 steps. Molecular dynamics were run using a time step of 25 fs, as recommended by MARTINI, for 2 μ s for small membranes, and 10 μ s for large and very large membranes. Simulations were conducted in the isothermal-isobaric (NPT) ensemble, by using a Berendsen thermostat set to 323 K with temperature coupling constant set to 1 ps, as well as isotropic pressure coupling with compressibility set to 3×10^{-5} bar $^{-1}$ and a pressure coupling constant set to 3.0 ps.

Secondary structures restraints consistent with MARTINI recommendations were constructed by the martinize.py Marrink et al. (2007a) script and imposed by Gromacs Berendsen et al. (1995). Protein conformation was maintained in small systems via harmonic restraint (with a spring constant of 1000 kJ· mol $^{-1}$) on the position of backbone beads. nAChR conformation in large systems was preserved via harmonic bonds between backbone beads separated by less than 0.5 nm, calculated using the ElNeDyn algorithm Periole et al. (2009) associated with MARTINI Marrink et al. (2007a) with a coefficient of 900 kJ· mol $^{-1}$. These restraints limited the root-mean-squared-displacement (RMSD) of the backbone to less than 2.5 Å throughout the simulation.

The minimum equilibration time depended on the system size. Small systems typically began domain formation by 500 ns, with domains fully formed by 1000 ns. Large systems and very large simulations required about 5 μ s of equilibration for stabilization of metrics described below.

Analysis

Extent of domain formation within the membrane was tracked by

$$\begin{aligned} M_{A,B} &\equiv \frac{\langle n_{A,B} \rangle}{6x_B} - 1 \\ M_A &\equiv \frac{\langle n_{A,A} \rangle}{6x_A} - 1 \end{aligned} \quad (1.1)$$

where $n_{A,B}$ is the number of type B molecules among the 6 nearest neighbors for a given type A molecule, the average is over time and all molecules of type A, and the self-association metric is notated $M_A \equiv M_{A,A}$ for brevity. For a random mixture, $\langle n_{A,B} \rangle = 6x_B$, where x_B is the fraction of overall bulk lipids that are of type B. $M_A = 0$ indicates random mixing while $M_A > 0$ and $M_A < 0$ indicate demixing and excessive mixing respectively.

Extent of receptor partitioning within the l_o or l_{do} domain was tracked by counting the number b_{sat} of saturated annular boundary lipids and comparing with the expectation for a random mixture, via the order parameter Q_{sat} :

$$Q_{\text{sat}} \equiv \frac{1}{x_{\text{sat}}} \left\langle \frac{b_{\text{sat}}}{b_{\text{tot}}} \right\rangle - 1, \quad (1.2)$$

where b_{tot} is the total number of lipids in the annular boundary region and x_{sat} is the fraction of overall bulk lipids that are saturated phospholipids. $Q_{\text{sat}} < 0$ indicates depletion of saturated lipids among boundary lipids, as expected for partitioning into an l_{do} phase, while $Q_{\text{sat}} > 0$ indicates enrichment and likely partitioning into an l_o phase. Each frame, b_{tot} and b_{sat} were calculated by counting the number of total and saturated lipids, respectively, for which the phosphate bead fell within a distance of 1.0 nm to 3.5 nm from the M2 helices, projected onto the membrane plane.

Two-dimensional density distribution of the beads within a given lipid species B around the protein was calculated on a polar grid:

$$\rho_B(r_i, \theta_j) = \frac{\langle n_B(r_i, \theta_j) \rangle}{r_i \Delta r \Delta \theta} \quad (1.3)$$

where $r_i = i\Delta r$ is the projected distance of the bin center from the protein center, $\theta_j = j\Delta\theta$ is the polar angle associated with bin j , $\Delta r = 10\text{\AA}$ and $\Delta\theta = \frac{\pi}{15}$ radians are the bin widths in the radial and angular direction respectively, and $\langle n_B(r_i, \theta_j) \rangle$ is the time-averaged number of beads of lipid species B found within the bin centered around radius r_i and polar angle θ_j . In order to determine enrichment or depletion, the normalized density $\tilde{\rho}_B(r_i, \theta_j)$ is calculated by dividing by the approximate expected density of beads of lipid type B in a random mixture, $x_B s_B N_L / \langle L^2 \rangle$, where s_B is the number of beads in one lipid of species B , N_L is the total number of lipids in the system, and $\langle L^2 \rangle$ is the average projected box area:

$$\tilde{\rho}_B(r_i, \theta_j) = \frac{\rho_B(r_i, \theta_j)}{x_B s_B N_L / \langle L^2 \rangle} \quad (1.4)$$

This expression is approximate because it does not correct for the protein footprint or any undulation-induced deviations of the membrane area. The associated corrections are small compared to the membrane area and would shift the expected density for all species equally, without affecting the comparisons we perform here.

1.1.1 Results

Spontaneous association with cholesterol in binary membranes

Lipid sorting was characterized for nAChRs in binary DPPC:CHOL membranes (Figure 1.1A) using several metrics. Non-random lipid mixing (including domain formation) was quantified using the self-association metric M_A as defined in Equation 1.1. As expected, in simulated binary membranes containing only DPPC and 0-40% cholesterol, minimal demixing was observed, with values of M_{DPPC} (Fig 1.1B) rising slightly for higher cholesterol concentrations but remaining persistently below 0.05.

Depletion of saturated lipids among nAChR boundary lipids (relative to those expected for a random mixture) was quantified using the metric Q_{sat} defined in

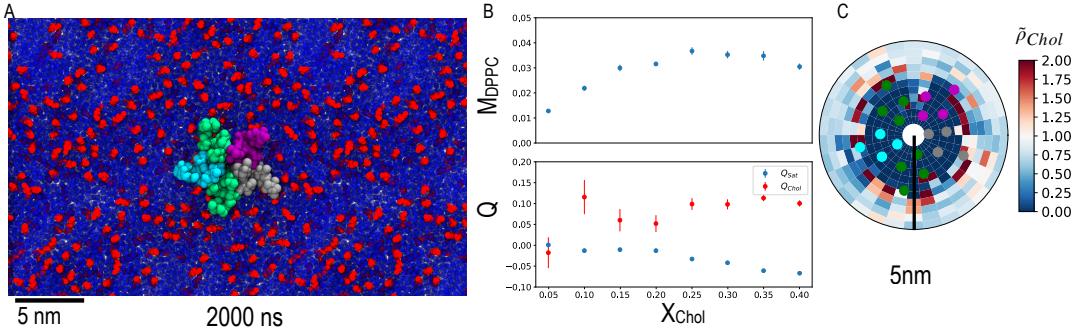


Figure 1.1: nAChR boundary lipids in binary mixtures of DPPC and CHOL. A: Representative frame from a simulated trajectory of a single nAChR embedded in a small membrane, colored by subunit (α :green, β :purple, δ :gray, γ :cyan) in a 4:1 DPPC (blue):Chol (red) mixture. B: Extent of demixing (M_{DPPC} defined in Eq. 1.1) and depletion of saturated lipids from the boundary (Q_{sat} defined in Eq.1.2) in small binary membranes. In this binary system, cholesterol depletion/enrichment is directly related to the saturated lipid depletion/enrichment: $Q_{\text{chol}} = -x_{\text{sat}}Q_{\text{sat}}/x_{\text{Chol}}$. Error bars represent standard error for a blocking average over 50 ns. C: Average normalized density (Eq. 4.2) of cholesterol for the system in A. Data is equivalent to that in Figure 1.5: Binary Mixture “Chol” row.

equation 1.2. Negative and positive values of Q_{sat} reflect depletion or enrichment of saturated lipids in the nAChR boundary, respectively. In binary systems containing cholesterol and saturated lipids, depletion of saturated lipids corresponds directly to enrichment of cholesterol: $Q_{\text{chol}} = -Q_{\text{sat}}x_{\text{sat}}/x_{\text{Chol}}$.

In binary DPPC:CHOL mixtures, Q_{sat} was very slightly negative for $x_{\text{Chol}} < 20\%$, but decreased steadily for higher concentrations. This trend indicates some depletion of DPPC (and enrichment of cholesterol) among nAChR boundary lipids (Figure 1.1B). Typically, between 10 and 20% cholesterol has been required in reconstitution mixtures to restore native function Fong & McNamee (1986a); Dalziel et al. (1980); Criado et al. (1982) and a phase transition at about 20%

cholesterol in binary DPPC:CHOL model membranes is indicated by differential scanning calorimetry. Marsh (2010)

Spontaneous binding of cholesterol to non-annular or “embedded” sites, similar to what we previously proposed?, was observed in these CG-simulations, and penetration of the TMD bundle by DPPC acyl chains was also observed at lower cholesterol concentrations (Fig 1.1A). Distribution of density for embedded lipids is further discussed in Section 3.4.

Annular cholesterol (enrichment of cholesterol at the protein-lipid interface), is visible for the binary systems via a ring of high (red) cholesterol density just around the protein in Figure 1.1C. Enrichment of cholesterol near the protein is highly localized with a ring that is less than 5Å wide. This is in general agreement with evidence for annular cholesterol in randomly-mixed binary membranes. Barrantes et al. (2010)

Domains formed in PUFA-containing ternary membranes are not affected by introduction of an nAChR

In order to test whether nAChR affected domain formation in domain-forming membranes, we characterized M_{PUFA} for systems containing DPPC, Cholesterol, and PE or PC with either n-3 (DHA) or n-6 (LA) acyl chains. Addition of phospholipids with unsaturated acyl chains to systems containing a saturated lipid and cholesterol is well-established to induce domain formation, and polyunsaturated phospholipids make these domains more well-definedLevental et al. (2016). As expected, we observed that addition of PUFAs to DPPC/CHOL bilayers did induce domain formation over a range of compositions, and values for M_{PUFA} are shown as filled symbols in Figure 1.2 A.

Introducing a single nAChR to these same systems did not significantly affect domain formation. M_{DHA} was determined for an isolated nAChR in ternary mixed membranes with over 40 different combinations of DHA, DPPC, and Cholesterol

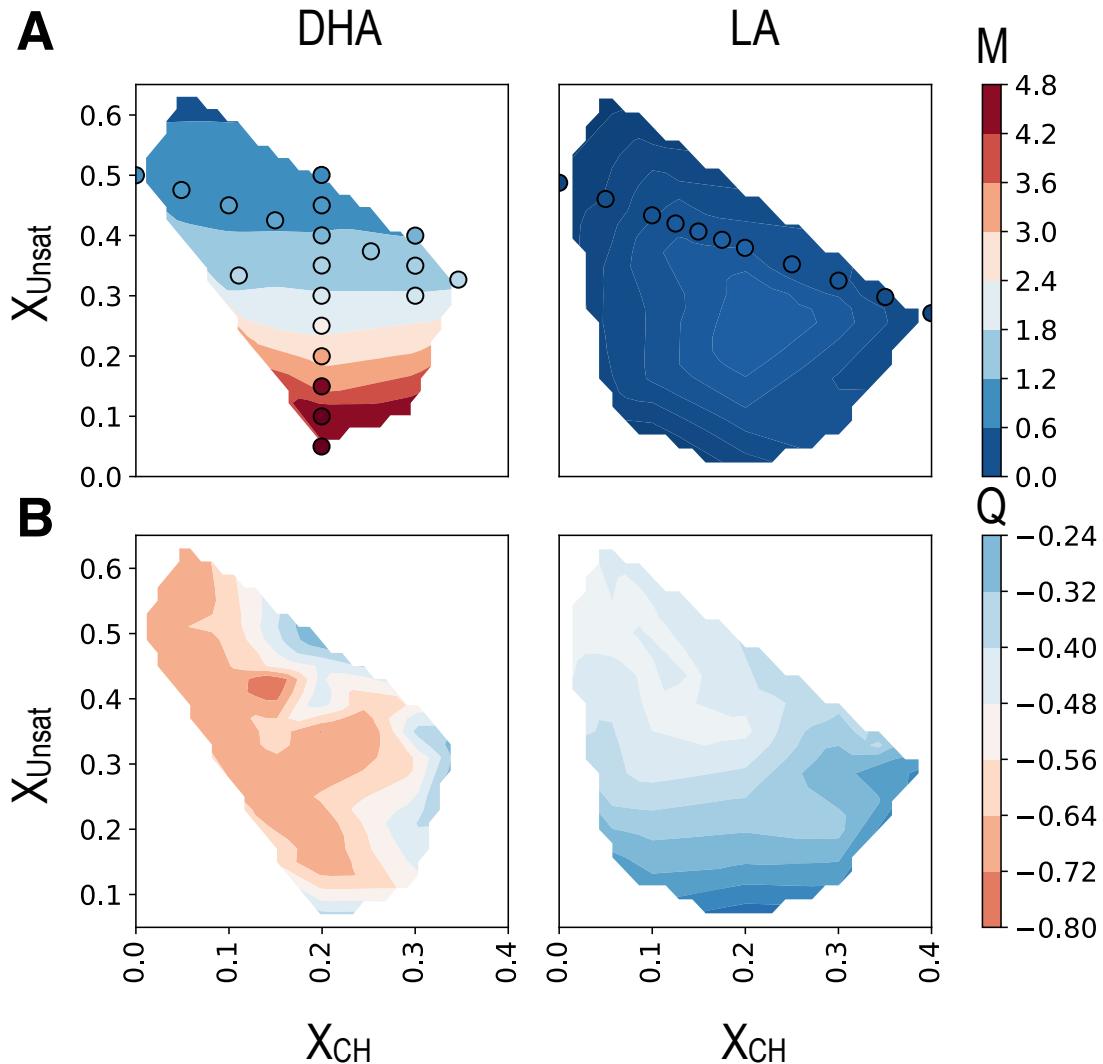


Figure 1.2: Quantitative analysis of bulk membrane mixing and nAChR boundary lipid composition across small membranes containing DPPC, Cholesterol, and either dDHA-PE or dLA-PC. Shaded contours were constructed based on 40 individual simulations with dDHA-PE and 30 with dLA-PC. A: M_{PUFA} , defined in eq 1.1. Circles represent mixing of systems with the same lipid composition but no nAChR. B: Q_{sat} , defined in Eq 1.2.

(Figure 1.2A, shaded contours). Its effect on membrane organization is represented by the difference in color of the circular symbol and the shaded contour

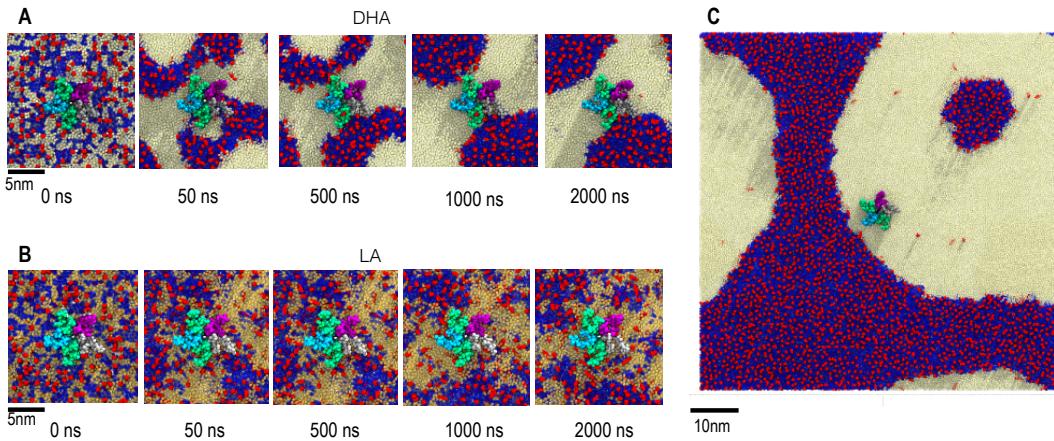


Figure 1.3: Trajectories of ternary mixtures at ratios of 2:2:1 DPPC:PUFA:Chol. A and B: Trajectories of simulation systems with a single nAChR embedded within small membranes, using lipids containing DHA acyl chains or LA acyl chains. Both simulations were run for 2 μ s. C: Final snapshot of 4 μ s trajectory of a system within a large $\sim 75 \times 75$ nm 2 membrane with the same composition as in A. Subunits are colored: α : green, β : purple, δ : gray, γ : cyan. Lipids are colored: Chol: red, DPPC: blue, dDHA-PE: white, dLA-PC: tan.

at the same composition. Introducing a single nAChR into the DHA-containing systems does slightly reduce the amount of DHA required to obtain a given value of M_{DHA} . This subtle trend may reflect increased likelihood of DHA-DHA interactions due to nucleation of DHA-containing lipids around the protein (Figure 1.3).

Across ternary mixtures with two long $n - 3$ PUFA chains (DHA) and a PE headgroup, maximum values of M_{DHA} approached 5 (Figure 1.2A), and were significantly reduced (to less than 0.5) when DHA chains were replaced with linoleic acyl (LA) chains. This result is consistent with a previously-observed significant increase in miscibility temperature upon supplementation of plasma membranes with $n - 3$ lipids. Levental et al. (2016)

Substantial lipid demixing in DHA-containing mixtures was observed even at

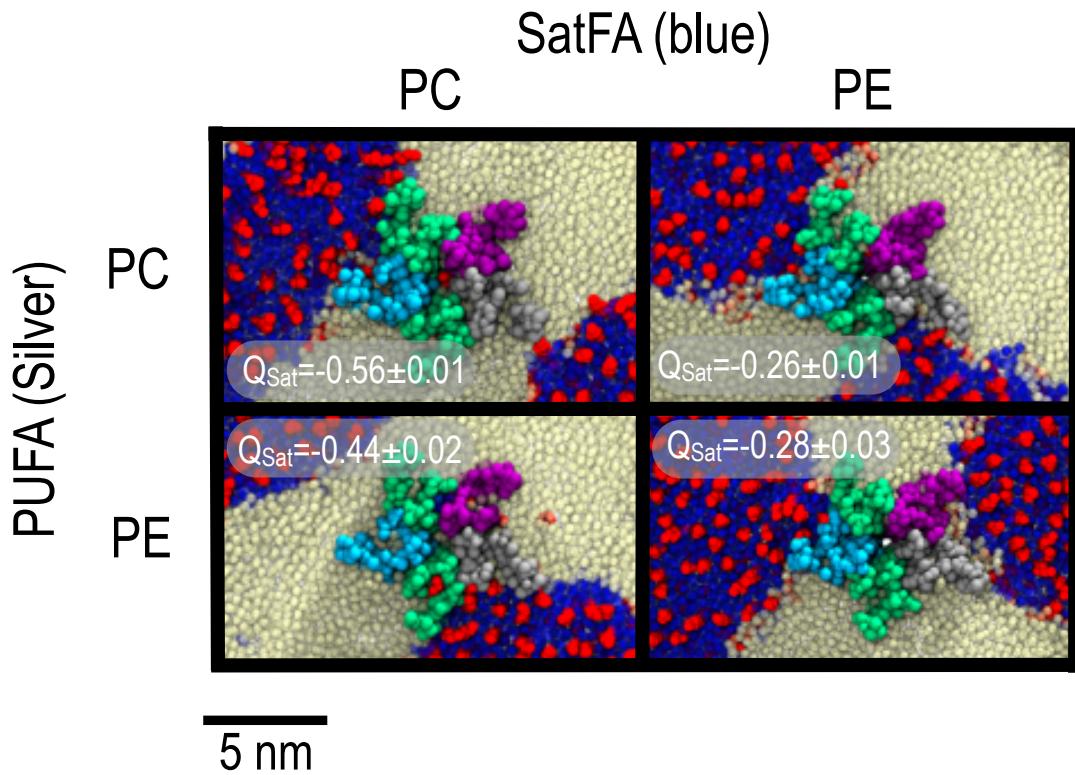


Figure 1.4: Comparison of nAChR partitioning based on lipid headgroups (PC and PE). All images represent last frame of $2\mu\text{s}$ simulations of small membranes with composition 2:2:1 Sat:PUFA:Cholesterol. Rows represent the head-group for the PUFA-containing lipid, while columns represent the head-group of the saturate lipid. Each image includes Q_{sat} values related to individual systems with errors across averaging 50 ns blocks.

low cholesterol concentrations. Over the range we tested, M_{DHA} was not sensitive to cholesterol concentration x_{Chol} , as shown by the horizontal contours for DHA in Figure 1.2A.

1.1.2 nAChR consistently partitions to the liquid disordered domain

For more than 70 lipid compositions tested, nAChR always partitioned into a PUFA-rich l_{do} phase if such a phase was present. We never observed nAChR partitioning to an l_{o} phase. Representative frames from trajectories of domain formation in the presence of nAChR are shown in Figure 1.3. This observation includes all tested concentrations of the ternary mixtures, regardless of whether the zwitterionic headgroup was PC or PE (Figure 1.4), or whether DPPC was replaced by dioleoylphosphatidylcholine (DOPC) (di-18:1), Palmitoyloleoylphosphatidylcholine (POPC) (16:0,18:1), or dilauroylphosphatidylcholine (DLPC) (di-14:0), as shown in Figure S1.

These results are quantified for nAChR embedded in ternary membranes containing DPPC, CHOL, and either dDHA-PE or dLA-PC in Figure 1.2 B, using the metric Q_{sat} defined in equation 1.2. In all systems studied here, $Q_{\text{sat}} < 0$, indicating depletion of saturated lipids as boundary lipids, consistent with observed partitioning to the l_{do} domain in Figure 1.3. Furthermore, depletion was much stronger in systems containing DHA ($Q_{\text{sat}}^{\text{DHA}} \ll Q_{\text{sat}}^{\text{LA}}$), consistent with the more well-defined DHA domains ($M_{\text{DHA}} \gg M_{\text{LA}}$).

The nAChR annulus is highly enriched in DHA: DHA-PE constitute nearly 100% of the local lipids even in membranes with very low DHA concentrations. This strong signal could indicate multiple high affinity sites for DHA chains across the transmembrane protein surface. At another extreme, DHA enrichment could be driven by a very slight preference for DHA in a highly non-ideal bulk: since DHA is found in well-defined domains without protein, even one DHA molecule that binds to the protein surface could stabilize the rest of the l_{do} domain nearby. Comparing boundary lipid and domain formation trends can help distinguish between these two scenarios. If boundary lipid enrichment is determined purely by

how well-defined domains are (the latter scenario), we would expect similar trends for M_{DHA} and Q_{sat} in the DHA column of Figure 1.2. In contrast, Figure 1.2 shows that while domain formation in DHA-containing systems is only weakly sensitive to cholesterol content (horizontal contours), composition of boundary lipids is highly sensitive to cholesterol content (diagonal contours). These results suggest that direct interactions between multiple favorable sites on nAChR and DHA-containing lipids dominate the observed enrichment of DHA among boundary lipids.

The simulations represented in Figure 1.2 do compare the effects of two unsaturated lipids that also have different headgroups. DHA is far more commonly paired with PE in native membranes, while LA is more commonly found with PC. We found no qualitative differences in nAChR domain partitioning or significant quantitative effect on Q_{sat} upon switching PC and PE headgroups on the PUFA lipid. We did observe a quantitative effect of *saturated* lipid headgroup on boundary lipid composition: Q_{sat} was reduced by half when saturated PE was used instead of saturated PC. (Figure 1.4). As shown in Figure 1.4, nAChR is bordered by l_o domains on two opposing faces when saturated PE is used, compared to only one face if PC is used. The particular domain topology shown in Figure 1.4 is an artifact of the periodic boundary conditions, but still indicates more favorable interactions of nAChR with an l_o domain composed of DPPE vs DPPC. This may reflect a difference in the lipid shape (wedge-shaped DPPE vs cylindrical-shaped DPPC) and the associated monolayer spontaneous curvature. For PUFA lipids in flexible l_{do} domains, lipid shape is less likely to play a significant role in determining partitioning. The dramatic difference in domain flexibility is apparent in Figure S2.

1.1.3 Spontaneous integration of lipids into nAChR TMD bundle

The nAChR structure used for these simulations was determined in a native membrane with a high fraction of polyunsaturated lipids. While we previously ? proposed that unresolved density in this structure could be embedded cholesterol, the possibility of occupation by phospholipids other than POPC was not investigated. Furthermore, we did not consider possible asymmetry across subunits in binding previously. Here we do observe penetration of both the intersubunit (“type B”) and the intrasubunit (“type A/C”) sites previously proposed?, by both phospholipids and cholesterol, but with a high degree of subunit specificity.

Two dimensional density distributions of DPPC, PUFAs, and cholesterol over short and long length scales were measured for two ternary mixtures and one binary mixture (Figure 1.5). In binary DPPC/cholesterol membranes, DPPC was more likely than cholesterol to occupy intrasubunit sites. DPPC binds shallowly in the α subunit and more deeply in the β subunit. Introducing PUFAs resulted in displacement of both cholesterol and DPPC from intrasubunit sites, except for the β intrasubunit site, which became more likely to be occupied by cholesterol. The interior of the β subunit TMD has the largest amount of available volume, could sequester cholesterol (but not DPPC) from the PUFA lipids in the annulus, and filling the interior with a PUFA chain may be entropically costly. PUFA chains did occupy other intrasubunit sites, but remained fluid, as shown in Figure 4.7.

Intersubunit sites were rarely occupied by DPPC, with the exception of the $\beta+$
 $/\alpha-$ site in the binary system (Figure 1.5). Intersubunit sites were more likely to bind cholesterol, particularly the $\beta+/ \alpha-$, $\alpha+/ \gamma-$, and $\alpha+/ \delta-$ subunit interfaces. Occupation of the $\alpha+/ \delta-$ interface is consistent with cryo-EM observationsUnwin (2017b) of enhanced cholesterol density around the $\alpha+/ \delta-$ site. Intersubunit sites that were not significantly occupied by cholesterol ($\delta+/ \beta-$ and $\gamma-/ \alpha+$) did show

significant and deep occupation by DHA, which tended to enter from the adjacent intrasubunit site rather than from the membrane. Even those intersubunit sites with significant cholesterol occupancy can simultaneously bind part of a DHA chain, yielding non-vanishing DHA density.

Lipid sorting over the 5-20 nm range is associated with larger domains

We also calculated density distributions of each lipid species at distances beyond the “annular” ring, over the 5-20 nm range. As shown in Figure 1.5 (left column), observed sorting of lipids within 5-20 nm of the nAChR is dependent on the overall composition of the membrane. For all compositions shown, cholesterol is depleted within 5-20 nm and enriched even farther from the protein. Within the binary systems this effect is minor ($\tilde{\rho}_{CHOL} \sim 1$), but it becomes stronger in the moderately demixed LA systems ($\tilde{\rho}_{CHOL} \sim 0.5$) and substantial ($\tilde{\rho}_{CHOL} \sim 0.25$) for the highly-segregated DHA containing systems. A similar pattern is observed for DPPC, which suggests that “sorting” over the 5-20 nm range is primarily driven by intrinsic differences in membrane organization that would be observed without the receptor. PUFAs are also most highly enriched at intermediate distances : the deepest red band is found at about 5 nm in LA-containing systems and about 8 nm in DHA-containing systems. This would be expected when nAChR partitions near a curved domain boundary, as in Figure 1.4.

1.1.4 Discussion

In this work we used coarse-grained simulations to predict the local lipid composition around the nicotinic acetylcholine receptor, in a range of domain forming membranes. We observed nAChR partitioning to the liquid-disordered phase in all systems for which such a phase was present. This is inconsistent with the model of lipid rafts as platforms that contain a high density of nAChRs, and unexpected in light of the established cholesterol dependence of nAChR. As shown

in these simulations, partitioning to the l_{do} phase does not prevent nAChR from accessing cholesterol.

The simulations presented here involve only one receptor per system. Using the present results only, the simplest extrapolation to multiple receptors would assume that receptors are simply distributed randomly across the l_{do} domain. The local receptor area density would be the number of receptors divided by the total area of l_{do} domains.

In the model membranes used here, as well as in native nAChR membranes, the lipid composition would be expected to yield l_{do} phases that were about the same size as l_{o} phases. The l_{o} “raft” in an l_{do} “sea” analogy is not representative when over 50% of the membrane is in the “raft” phase. A more representative analogy would be receptors as boats, floating on an l_{do} lake within an l_{o} rigid land mass. Filling in the lake by adding to the coastline would force any boats in the lake closer together. Similarly, any process that decreased total l_{do} area while keeping the number of receptors constant would increase the local receptor density. In this model, observing increased nAChR density by adding membrane cholesterol (as in Barrantes et al. (2000); Barrantes (2014); Brusés et al. (2001); Marchand et al. (2002); Oshikawa et al. (2003); Pato et al. (2008); ?); Barrantes (2007); Wenz & Barrantes (2005); Borroni et al. (2016)) would be consistent with nAChR partitioning to the cholesterol-poor phase rather than the cholesterol-rich phase.

This extrapolation from a single receptor assumes that introduction of additional receptors does not change partitioning behavior. We do still find reliable partitioning to the l_{do} phase upon adding more receptors, and we will characterize systems with multiple receptors in a future publication. Due to receptor dimerization and trimerization, distribution of individual receptors within the l_{do} phase will not be random. This would not change the expected trend of density increasing with added cholesterol, however. This interpretation also assumes that

cholesterol is randomly mixed within the l_o phase, while results from atomistic simulations Sodt et al. (2014); Iyer et al. (2018) have suggested that cholesterol may preferentially partition to the boundary between l_o phases and l_{do} phases composed of monounsaturated lipids. Similar studies in which the l_{do} domain is composed of PUFAAs and the interface is much more compact have not been reported. In the present coarse-grained simulations, we did observe random mixing of cholesterol within l_o phases, rather than at the boundary with the PUFA-rich l_{do} phase.

Observed partitioning into the l_{do} phase could be considered inconsistent with interpretations of some experiments, Bermúdez et al. (2010); ? which suggest minimal nAChR partitioning preference in symmetric model membranes or an actual preference for an l_o phase in asymmetric model membranes. These experiments used only monounsaturated acyl chains, and may have had less well-defined domains. They further relied on detergent resistant membrane (DRM) methods, which are sensitive to the choice of detergent Brown (2007) and could be unable to distinguish between proteins with no partitioning preference vs proteins that persistently partition to one side of a boundary.

The origin of preferential partitioning observed in these simulations for the l_{do} domain is still unclear, but may reflect different elastic properties of the l_{do} and l_o domains. In general, proteins embedded in membranes will introduce a boundary condition on the membrane shape, such that (1) the thickness of the membrane matches the thickness of the transmembrane domain Aranda-Espinoza et al. (1996); Jensen & Mouritsen (2004); ? and (2) interfacial lipids are parallel to the protein surface Goulian et al. (1993). Transmembrane proteins with hydrophobic mismatch with the surrounding membrane may deform the membrane thickness to satisfy constraint (1), while cone-shaped proteins like pLGICs must also introduce a “tilt” deformation to satisfy (2). Each leaflet of the membrane has an elastic resistance to bending away from its spontaneous curvature, and

satisfying these constraints is energetically costly.

Continuum theories based on the Helfrich Hamiltonian have been used to predict shape deformations around protein inclusions in homogeneous membranes. Goulian et al. (1993); Aranda-Espinoza et al. (1996); ? In mixed membranes, minimization of the protein-deformation free energy may also induce lipid sorting. Two distinct sorting mechanisms could minimize the bending free energy: sorting that A) reduces the required bending deformation, by selecting boundary lipids with a specific thickness, leaflet asymmetry, or shape or B) reduces the free energy cost of the bending deformation, by selecting for flexible boundary lipids. Mechanism (B) is the most generally applicable approach, and would stabilize partitioning to the most flexible domains, consistent with our observations (Figure S2). In some cases, mechanism (A) may also contribute to partitioning or lipid-sorting, and could explain why nAChR tends to attract saturated PE over saturated PC, or how leaflet asymmetry can promote partitioning to more rigid phases as observed in ? .

We previously ? proposed unresolved density in the cryo-EM structure of nAChR in the *Torpedo* membrane could be embedded cholesterol, based on gain of function caused by cholesterol in reconstitution mixtures Fong & McNamee (1986a); Sunshine & MG (1992); ?; Butler & McNamee (1993); ?; Fong & McNamee (1987); Bednarczyk et al. (2002a); daCosta et al. (2001), but we did not consider the possibility of occupation by polyunsaturated chains. Here we observe spontaneous binding of cholesterol to coarse-grained embedded sites, but long-chain PUFA tails displace cholesterol in some binding sites. Long acyl chains may penetrate far into the TMD bundle without requiring the entire head group also be incorporated, and long-chain PUFAs may do so without as substantial an entropic penalty as long saturated chains. Cholesterol (like phosphatidic acid, another lipid known to cause gain of function under some preparations Butler &

McNamee (1993); ?); Fong & McNamee (1987); Bednarczyk et al. (2002a); da-Costa et al. (2001)) has a much smaller headgroup than PC or PE. It can become fully incorporated into the TMD without the TMD needing to accommodate the bulky headgroup. These complex associations underlie the challenges of predicting local lipid environment in heterogeneous, highly non-ideal mixtures.

All simulations reported here contain lipids with di-saturated tails or di-PUFA tails. While lipid species with two identical acyl chains do exist in the native membrane, they are far less common than hybrid lipids with heterogeneous acyl chains. Including hybrid lipids would reduce the potential for formation of large domains, while increasing the length of the domain interface. Incorporation of hybrid lipids would also reduce the nAChR-local concentration of PUFA chains. Even 5-10% DHA is a saturating concentration for nAChR cavities, however, so we expect occupation of cavities to be minimally affected by replacement of di-DHA lipids with twice the number of hybrid lipids.

None of the three generations of experimental studies into the effects of cholesterol and lipid headgroup on nAChR function have systematically considered the effects of lipid polyunsaturation. We predict that first-generation-style functional studies would find that nAChRs reconstituted in model membranes are sensitive to replacement of even a small fraction of saturated or mono/diunsaturated acyl chains with $n - 6$ and (especially) $n - 3$ PUFAs. Within domain forming membranes common to second-generation studies, systematically varying polyunsaturation and phospholipid topology could help untangle the effect of direct interactions vs organization, as we discussed in Brannigan (2017). Third-generation structural biology techniques are the most promising approaches for detecting subunit-specific interactions. While it is unlikely that polyunsaturated acyl chains could be resolved, lipids could be chosen such that particular chains also had a unique and resolvable headgroups. In general, modular lipid topology allows for numerous strategically-designed experiments to isolate the role of head-group

versus acyl chain in determining boundary lipids.

1.2 Acknowledgment

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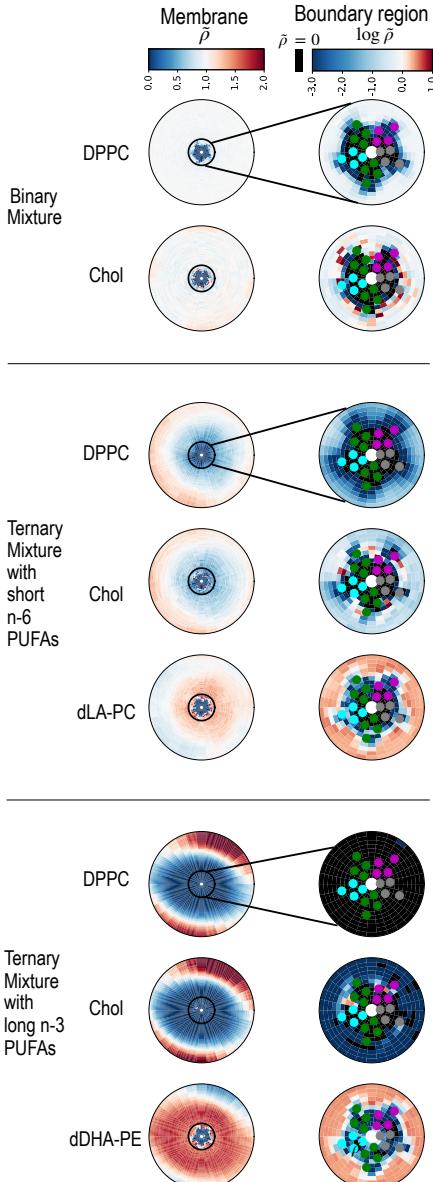


Figure 1.5: Lipid density enrichment or depletion around a single central nAChR. Heatmaps are colored according to the normalized density $\tilde{\rho}_a$ (left, defined in eq 4.2) or $\ln \tilde{\rho}_a$ (right), averaged over the final $5\mu s$ of a $10\mu s$ simulation. Membrane column (left) depicts density across the simulated membrane; $\tilde{\rho}_a < 1$ indicates depletion compared to a random mixture, while $\tilde{\rho}_a > 1$ indicates enrichment. Boundary column (right) shows a zoomed-in region around the protein, with circles corresponding to average position of the protein helices, colored as in Figure 1, and black indicating no detected lipid density. If no non-annular or embedded lipid binding was observed, the entire protein footprint would be black for all lipids. Binary mixture contains 4:1 DPPC:CHOL as in Figure 1, while both ternary mixtures contain 2:2:1 DPPC:PUFA:Chol.

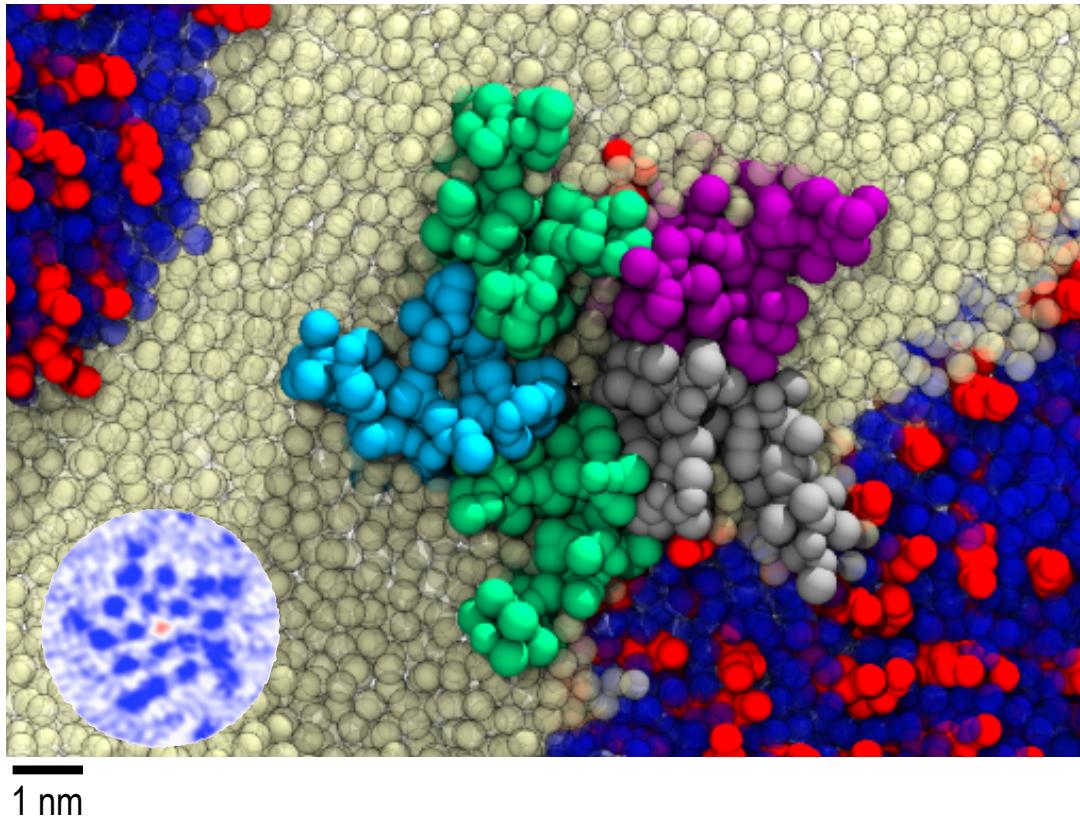


Figure 1.6: Embedded lipids in the nAChR. Main image: Representative frame from equilibrated small membrane simulation of nAChR in 2:2:1 DPPC:DHA-PE:CHOL. Backbone beads of the TMD helices are colored by subunit as in Figure 1.2; side-chain beads are not shown. Both DHA-PE (white) and cholesterol (red) equilibrate to embedded sites in the subunit center and subunit interfaces, although most cholesterol is found in the l_o phase with DPPC (blue). Inset : Cryo-EM density of nAChR from Miyazawa et al. (2003) as rendered in ?; dark blue indicates high density, white is medium density, and red is low density.

Chapter 2

Untangling direct and domain-mediated interactions between nicotinic acetylcholine receptors in DHA-rich membranes

2.0.1 Introduction

The muscle-derived nicotinic acetylcholine receptor (nAChR) (PDB 2BG9) (Unwin 2005) is the most abundant neurotransmitter receptor at the neuromuscular junction (NMJ) in most vertebrates, including humans (Albuquerque et al. 2009). Within the postsynaptic membrane, nAChRs cluster in high densities (10,000 per μm^2) to properly activate the skeletal muscle (Ramaraao & Cohen 1998; Breckenridge et al. 1972). As a major transmembrane protein, nAChR depends upon a highly specific lipid environment to maintain functionality. Lipids influence nAChR activity by affecting both function and organization. It is essential to understand how changes in lipid environment impact nAChR's structure and activity, given that lipids can change in response to aging and disease (Yadav & Tiwari 2014), and also vary across tissue and organism.

Over the past few decades, considerable progress has been made in uncovering lipid sensitivities associated with nAChR (Criado et al. 1982). In a majority of experiments, researchers have prioritized studying cholesterol over other membrane lipids. Early studies revealed that, when reconstituted into membrane mixtures, nAChR failed to conduct cations across the lipid bilayer unless cholesterol was present (Fong & McNamee 1986a; Sunshine & MG 1992; Butler & McNamee 1993; Fong & McNamee 1987; daCosta et al. 2001). More recently, researchers

have examined the effects of membrane dynamics on nAChR organization (Baenziger et al. 2015; Brusés et al. 2001; ?; Oshikawa et al. 2003; Pato et al. 2008; Zhu et al. 2006; Baenziger et al. 2017; Barrantes 2007; Barrantes et al. 2000; Bermudez et al. 2010; Barrantes et al. 2010; Perillo et al. 2016; Wenz & Barrantes 2005; Borroni et al. 2016; Unwin 2017a). In-vitro studies (Barrantes 2007; Barrantes et al. 2010) indicate that nAChRs form larger aggregates upon cholesterol depletion. Experimental evidence suggest that cholesterol-rich lipid domains, known as lipid rafts, facilitate clustering of nAChRs (Campagna & Fallon 2006; ?; Pato et al. 2008). More specifically, after disrupting lipid raft formation, Zhu et al. observed a significant loss of nAChR clusters in-vitro (Zhu et al. 2006). In the mature neuromuscular membrane, nAChRs are linked by the intracellular anchoring protein, rapsyn, which bridges receptors together at their bases (Zuber & Unwin 2013a). According to fluorescent studies (?), lipid rafts mediate the association between rapsyn and neighboring nAChR molecules. In the mid-2000's, Willmann et al. and Stetzkowski-Marden et al. proposed that lipid rafts can stabilize receptor networks and may even provide a localized environment for nAChR (Willmann et al. 2006; Stetzkowski-Marden et al. 2006).

Domain formation occurs when a membrane is comprised of at least three lipid types: cholesterol, unsaturated fatty acids, and a molecule that interacts closely with cholesterol such as saturated fatty acids or sphingomyelin (Feller 2008; Yeagle 2016a). The membrane separates into at least two domains, a liquid-ordered or “raft” phase containing cholesterol and saturated lipids/sphingomyelin, and a liquid-disordered phase containing unsaturated lipids. Polyunsaturated phospholipids make these domains more well-defined (Levental et al. 2016). Some results from atomistic simulations (Sodt et al. 2014; Iyer et al. 2018) indicate that cholesterol may preferentially partition to the boundary between liquid-ordered phases and liquid-disordered phases composed of monounsaturated lipids. In neuromuscular membranes, intrinsic domain formation is dependent upon several lipid

species, including the widely influential omega-3 (ω -3) fatty acids. One ω -3 in particular, Docosahexaenoic acid (DHA), is prevalent in the native neuromuscular membrane and is strongly associated with flexible and well-defined domains (Turk & Chapkin 2013; ?). Additionally, DHA is a major contributor to brain functioning, motor activity, and cardiac health; however, its specific effects on neuromuscular health are poorly understood (Lavandera et al. 2017; Wassall & Stillwell 2008; Georgieva et al. 2015).

Characterizing such complex lipid-protein interactions requires detailed information on each molecular structure. The nAChR is a member of a family of ion channels, known as pentameric ligand-gated ion channels (pLGICs), which has a number of recent structures (Laverty et al. 2019, 2017; Masiulis et al. 2019; Althoff et al. 2014; Hibbs & Gouaux 2011; Morales-Perez et al. 2016; Baenziger & Corringer 2011; Corringer et al. 2012; Nemecz et al. 2016; Prevost et al. 2012b; Sauguet et al. 2014); however, only single structures have been determined, rather than dimers. pLGICs are composed of five subunits; each subunit is composed of an extracellular domain for ligand binding, a transmembrane domain (TMD), and an intracellular domain (ICD) (Figure 1A). The TMD is the embedded portion of pLGICs that interacts most often with surrounding membrane lipids; this region of pLGICs is composed of four alpha-helices, M1-M4, with the innermost, M2 helices forming the ion pore. The ICD, or cytoplasmic domain, is highly disordered, making it challenging to obtain information on its structure. Currently, there are two structures of nAChR pentamers resolved from x-ray crystallography (neuronal type) and cryo-electron microscopy (muscle-type) (?Unwin 2005).

Other closely related channels have been resolved with bound lipids. In 2017, the inhibitory neurotransmitter receptor, the gamma-aminobutyric acid ($GABA_A$) receptor, was crystallized with a cholesterol molecule protruding between its M1 and M3 helices (Laverty et al. 2017), similar to our previous prediction (?). Interestingly, x-ray structures of the glutamate-gated chloride channel

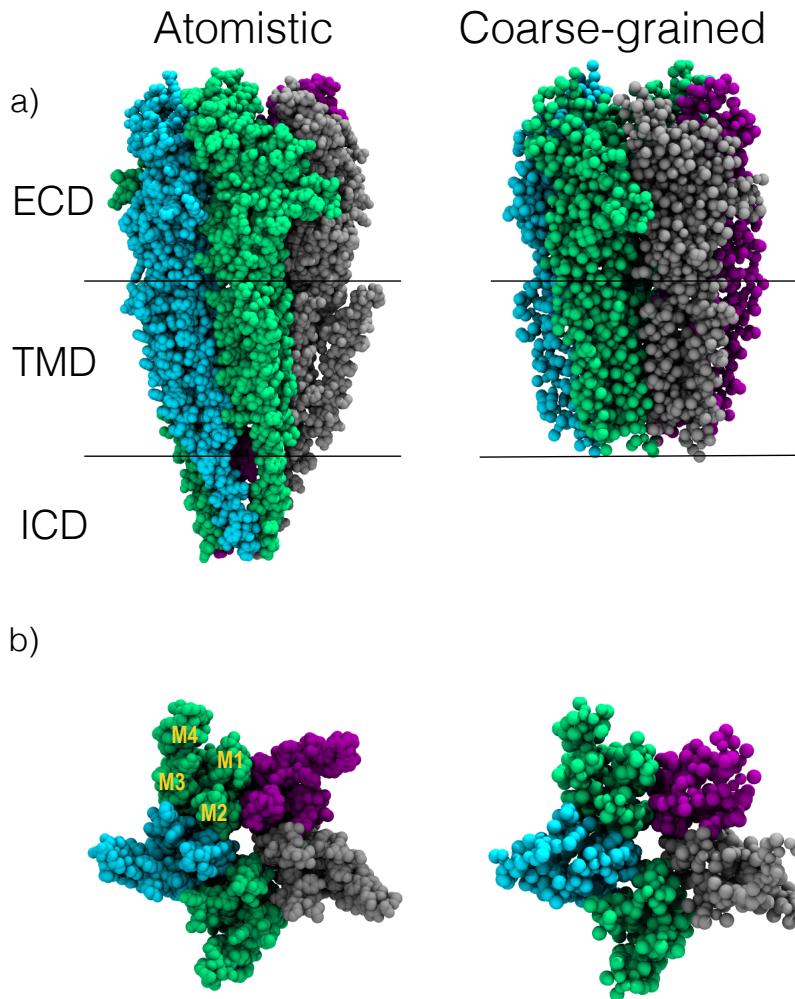


Figure 2.1: Nicotinic acetylcholine receptor (nAChR) structure. a) Atomistic and coarse-grained representations of Unwin et al's cryo-EM structure, PDB 2BG9. The nAChR is colored by subunit (α : green, β : purple, δ : gray, γ : cyan) and labeled by structure. The extracellular domain (ECD) is located above the bilayer and is critical for ligand-binding. The transmembrane domain (TMD) is positioned within the lipid bilayer, and the intracellular domain (ICD) is located in the cytoplasm. The coarse-grained model omits the ICD since it is poorly resolved and not necessary for this study. b) TMD from the extracellular perspective, with its four alpha helices labelled in a single α subunit. The outermost M4 helices closely interact with surrounding membrane lipids, while the M2 helices outline the ion pore; the M1 and M3 helices make up the body of the transmembrane domain (Unwin 2005).

(GluCl) revealed embedded POPC phospholipids in the same location (Althoff et al. 2014). Together, these data provide evidence for lipid-based modulation of pLGICs, which can potentially be applied to the gating of nAChR.

Structural information alone, however, is insufficient for answering questions about native cell membranes. For one, most structures are obtained under artificial conditions, using detergents or nanodisks with non-native lipid composition. Additionally, current structures do not represent oligomers, particularly in a liquid state. Fully atomistic molecular dynamics (MD) simulations Brannigan et al. (2008b); Cheng et al. (2009); Hénin et al. (2014); Carswell et al. (2015a) have complemented experimental investigations of pLGICs interacting with lipids, but they are limited in their ability to capture domain formation since atomistic lipids cannot diffuse over typical simulation microsecond time scales (Ingólfsson et al. 2014; Bond & Sansom 2006; Parton et al. 2013; Goose & Sansom 2013; Scott et al. 2008). Furthermore, it is unfeasible to incorporate multiple nAChRs in simulations with atomistic resolution. Coarse-grained MD (CG-MD) simulations are run over longer length and time scales, making them suitable for exploring complex model membranes. CG-MD is widely applied in simulations of both lipid-protein binding and domain formation (Bond & Sansom 2006; Scott et al. 2008; Parton et al. 2013; Goose & Sansom 2013). Additionally, CG-MD can capture large-scale membrane phenomenon such as protein self-assembly and lipid-mediated oligomerization (Gahbauer & Böckmann 2016; Baaden & Marrink 2013).

Recently, we (Sharp et al. 2019) conducted CG-MD simulations of a single nAChR from the electric ray *Torpedo* in mixed membranes. Contrary to expectations, nAChR consistently preferred a local lipid environment rich in PUFAs rather than cholesterol, especially long-chained ω -3s, such as DHA. While cholesterol occupied the transmembrane gaps of nAChR, PUFAs were even more likely to be embedded, regardless of their phospholipid headgroup.

The present study adopts a similar approach, with a particular focus on

nAChR-associated clustering. Through molecular dynamics simulations, we investigate nAChR lipid preferences and clustering behavior in membranes with and without domains. For this study, we tested three major hypotheses: 1) Membrane organization affects nAChR boundary lipid specificity: when PUFA chains are prevented from forming PUFA rich domains, their prevalence among nAChR boundary lipids will be significantly reduced. 2) Domain formation will indirectly facilitate the clustering of nAChRs, by inducing partitioning preferences and restricting diffusion within the membrane. 3) Within a dimer, we will observe sequence preferences in facing subunits.

2.0.2 Methods

System setup

In order to isolate the role of lipid domain formation on nAChR-based lipid sorting and clustering, our simulations compared two different membranes with distinct phospholipid topology. Each membrane had 30% cholesterol and 70% phospholipids. The phospholipids all had phosphatidylcholine (PC) headgroups, and half the total number of acyl chains were saturated (16:0) chains, while the other half were polyunsaturated (22:6) chains. For homoacid membranes, all phospholipids had either two polyunsaturated acyl chains (didocosahexaenoylphosphatidylcholine or dDHA-PC) or two saturated chains (dipalmitoylphosphatidylcholine or DPPC), facilitating domain-formation. In the heteroacid membranes, all phospholipids were hybrid lipids with one polyunsaturated acyl chain and one saturated chain (1-palmitoyl- 2-docosahexaenoyl- phosphatidylcholine or PDPC), which are topologically unable to separate into PUFA-rich and PUFA-poor domains.

Lipids and proteins were modeled using the coarse-grained (CG) Martini 2.2 force field (Marrink et al. 2007a). Systems included between 1-4 nAChR

molecules, derived from the Torpedo electric organ (Unwin 2005) (PDB 2BG9). This structure is the only pLGIC structure obtained in a native membrane.

We converted protein structures into CG models using the Martini script "martinize.py", mapping four non-hydrogen atoms to one CG interaction. We constructed and assembled our protein-bilayer systems using the Martini script, "insane.py", using a box sizes of 29x29x21 nm³ for one-to-two proteins, 40x40x20 nm³ for three proteins, and 44x44x22 nm³ for four protein systems, respectively (Marrink et al. 2007b). Initially, the proteins were in a circle of about 13 nm. The receptors were evenly spaced, and their δ subunits were facing the same direction. Once simulations started, nAChRs shifted from their initial orientations. We ran 24 CG-MD simulations containing 1-4 nAChRs (3 replicas per system).

Simulation details

Simulations were run using the Martini 2.2 force field parameters and the Gromacs 5.1.2 simulation package, (Marrink et al. 2007b; Pronk et al. 2013) as in our previous work, (Sharp et al. 2019). Each simulation consisted of two steps: energy minimization and molecular dynamics. For each system, we ran two consecutive energy minimizations for 10,000 steps. Harmonic restraints between backbone atoms were imposed to preserve nAChR conformation. More specifically, we applied an elastic force constant of 750 kJ/mol and set lower and upper bounds on the bond with using a bond length of 0.7 nm (Marrink et al. 2007b; Pronk et al. 2013). The molecular dynamics simulations ran for 10-20 μ s at a 0.025 ps time-step. Simulation temperature and pressure were kept constant at values of 323 K and a reference pressure of 1 bar. The isotropic pressure coupling compressibility constant was maintained at 3.0×10^{-5} bar⁻¹.

Analysis

For a given nAChR, n_{emb}^{α} is the total number of embedded lipids of lipid species α , where embedded lipids satisfy the following criteria: the headgroup (in the case of cholesterol) or the terminal bead on the acyl chains (in the case of phospholipids) are within 10 Å of the M2 helices. Visual inspection indicated any lipids outside of this range were also outside of the TMD bundle.

Similarly, n_{ann}^{α} is the total number of annular lipids of lipid species α , where annular lipids satisfy the following criteria: headgroup or the terminal bead on the acyl chains is between 10 Å and 35 Å of the M2 helices. This range of lipids corresponded to the third lipidation shell around nAChR.

(For phospholipids, each acyl chain was counted separately as a half-lipid, so it was possible for e.g. the sn-1 chain to be embedded and the sn-2 chain to be annular.)

Boundary lipid fractions for a given species α are defined as

$$f_{\text{emb}}^{\alpha} \equiv \frac{n_{\text{emb}}^{\alpha}}{n_{\text{emb}}}, \quad (2.1)$$

$$f_{\text{ann}}^{\alpha} \equiv \frac{n_{\text{ann}}^{\alpha}}{n_{\text{ann}}} \quad (2.2)$$

where n_{emb} and n_{ann} are the total number of embedded and annular lipids, respectively.

Two dimensional density distributions of boundary acyl chain species (B), $\tilde{\rho}_B(r_i, \theta_j)$ were calculated, as a function of radius, r_i , and angle θ_j projected onto the membrane.

$$\rho_B(r_i, \theta_j) = \frac{\langle n_B(r_i, \theta_j) \rangle}{r_i \Delta r \Delta \theta} \quad (2.3)$$

where $r_i = i\Delta r$ is the distance from the origin to the center of bin i, Δr is the radial bin width, and $\Delta\theta$ is the angular bin width. $\langle n_B(r_i, \theta_j) \rangle$ is the time-averaged number of acyl chain beads of species B within bin i.

To quantify enrichment or depletion of a given acyl chain with respect to random distribution, the normalized density, $\tilde{\rho}_B(r_i, \theta_j)$, was calculated.

$$\tilde{\rho}_B(r_i, \theta_j) = \frac{\rho_B(r_i, \theta_j)}{x_B s_B N_L / \langle L^2 \rangle} \quad (2.4)$$

where s_B is the number of beads of lipid species B, N_L is total number of lipids in a system, and $\langle L^2 \rangle$ is the average projected box area, and x_B is lipid B concentration. The expression does not take into consideration the protein footprint or undulations present within the system, and as such is an approximation.

The radial distribution function $g(r)$ of multiple nAChRs was calculated using the three dimensional distance r between the centers of mass of the receptors for each of the 8000 frames, evenly distributed through the simulation. It was derived from the distribution of pairwise separations, $P(r)$, by dividing by the expected separations in a random distribution : $g(r) = \frac{P(r)}{r} \frac{dr}{\int_0^R r dr} \times \int_0^R r dr$. The height of the $g(r)$ peak corresponds to the amount of enrichment in probability for a given distance; for example, if $g(10 \text{ nm}) = 50$, it is 50 times more probable that two monomers will be 10 nm apart than expected in a random distribution.

The total number of observed dimers n_d is given by the number of pairs (across all analyzed proteins) where $r < 100 \text{ \AA}$. For each observed dimer, the closest subunit pair was determined, and the enrichment calculated as $F_{x,y}$:

$$F_{x,y} = \frac{25}{n_d} (n_{x,y} + n_{y,x}), \quad (2.5)$$

where $n_{x,y}$ represents the number of dimers in which subunits x and y form the closest pair, and 1/25 is the expectation for a random distribution.

We visualized and imaged all simulation results using Visual Molecular Dynamics (VMD) (Humphrey et al. 1996).

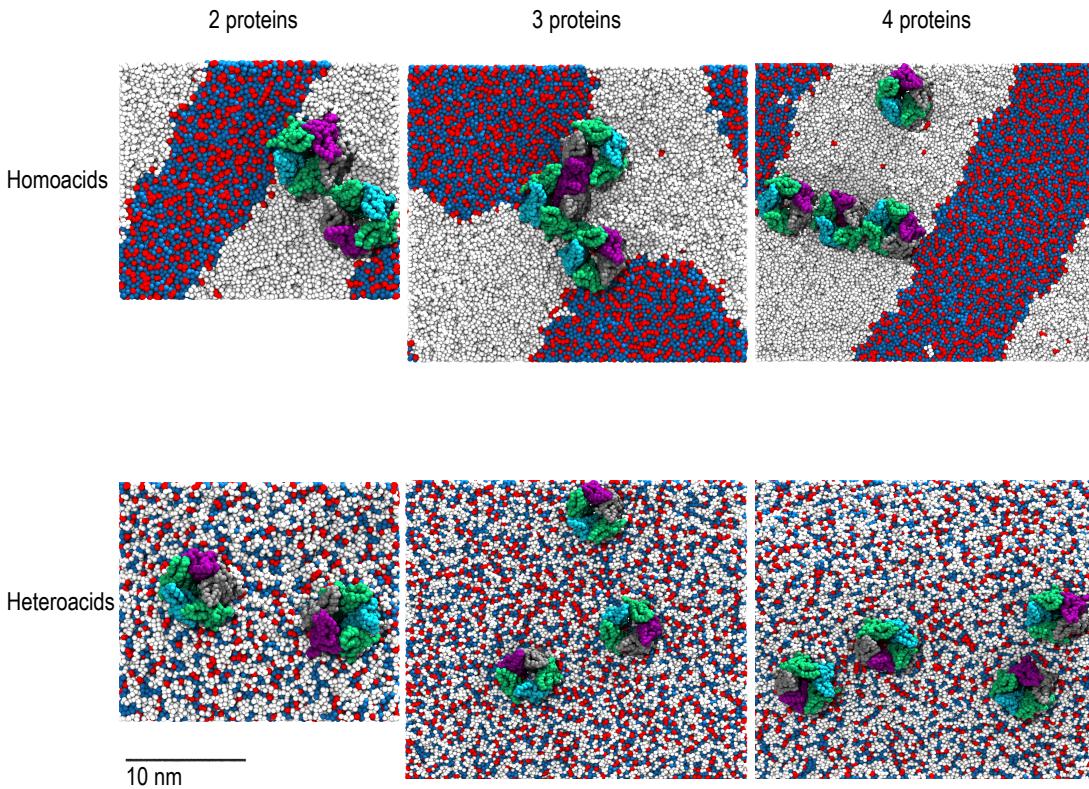


Figure 2.2: Protein clustering in domain-forming (top row) and hybrid (bottom row) membranes. View of the membrane from the extracellular region at the final frame of $10 \mu\text{s}$ simulations. nAChRs were colored by subunit (α : green, β : purple, δ : gray, γ : cyan), and lipids by acyl chain (DHA: white, saturated: blue, and cholesterol: red). Clustering of nAChRs on the borders of lipid rafts is visible in the domain-forming membranes.

2.1 Results

nAChR boundary lipid preferences

In order to determine the significance of domain formation on enrichment of polyunsaturated acyl chains among boundary lipids, we calculated the fraction of embedded and annular boundary lipids in two types of membranes with equal amounts of cholesterol and saturated and polyunsaturated acyl chains. In the domain-forming membranes, all phospholipids had either two polyunsaturated

	mean embedded fraction		mean annular fraction		bulk
	homoacid	heteroacid	homoacid	heteroacid	
cholesterol	0.29 (0.02)	0.42 (0.04)	0.23 (0.02)	0.31 (0.01)	0.30
PUFA	0.61 (0.01)	0.39 (0.04)	0.52 (0.02)	0.32 (0.01)	0.35
saturated	0.10 (0.05)	0.19 (0.01)	0.25 (0.02)	0.37 (0.01)	0.35

Table 2.1: Composition of nAChR Boundary Lipid chains in domain forming (homoacidic) and non-domain forming (heteroacidic) membranes. Embedded and Annular chains are determined as described in Methods. Averages are across systems, and across proteins in multi-protein systems. Each protein is treated as a separate replica ($n=30$) and standard errors are shown in parentheses.

acyl chains or two saturated chains (homoacids), while in the non-domain forming membranes, all phospholipids had one polyunsaturated acyl chain and one saturated chain (heteroacids).

Distributions for f_{emb} and f_{ann} are shown in Figure 2.3 in heteroacids compositions without domains and in Figure 2.4 for homoacids compositions with domains, while mean values are given in Table 2.1. For heteroacids, PUFA chains are slightly enriched among embedded chains and slightly depleted among annular chains, while the reverse trend is observed for saturated lipids. Saturated chains are significantly depleted from the embedded lipids, but due to the topology of these lipids, a fully embedded polyunsaturated acyl chain must also contribute a saturated chain to the protein annulus. Distributions were remarkably consistent across simulations containing 1,2,3, or 4 proteins.

Figure 2.4 shows the results of the same analysis for homoacidic membranes. Replacing heteroacids with homoacids substantially increases the fraction of polyunsaturated chains among both embedded and annular lipids, with the peak of the distribution shifting further to the right as more proteins are included (Figure 2.4).

Together, these results are consistent with our previous (Sharp et al. 2019) observation that polyunsaturated chains can displace cholesterol from embedded sites. For heteroacids, embedding a PUFA constrained the linked saturated chain to the nAChR annulus. In this case, cholesterol (which introduces no such constraint) was enriched among embedded lipids. For homoacids, embedded PUFAs constrained a corresponding PUFA chain to the nAChR annulus, and here cholesterol was not enriched among embedded lipids.

The fraction of embedded chains that were polyunsaturated increased as more proteins were added to the homoacidic membrane. This could be consistent with each nAChR monomer in an oligomer blocking access to embedded lipid binding sites in the other monomers: flexible PUFA chains have multiple routes to access an embedded site, and rigid lipids have only one or two.

The two dimensional density distribution of each lipid species from the center of a single nAChR is shown in Figure 2.5. For all three lipids, there was a five-fold symmetry of densities surrounding nAChR, with lipid preferences determined by transmembrane helix, rather than by subunit. In heteroacid mixtures, cholesterol is enriched near the subunit interfaces, and even buried more deeply within the γ/α interface, with saturated acyl chains packed just outside cholesterol. The outermost M4 helices, however, were packed with PUFAs; PUFA chains also diffused throughout the TMD bundle. In homoacid membranes, saturated lipids and cholesterol were depleted among embedded lipids, but they maintained the same helix association observed in heteroacid membranes. PUFAs were especially enriched in domain-forming membranes, with high densities around all four transmembrane helices.

nAChR clustering in the presence and absence of lipid domains

Here, we repeatedly observed spontaneous formation of receptor dimers in the simulations containing multiple proteins (Figure 2.2). To investigate the role

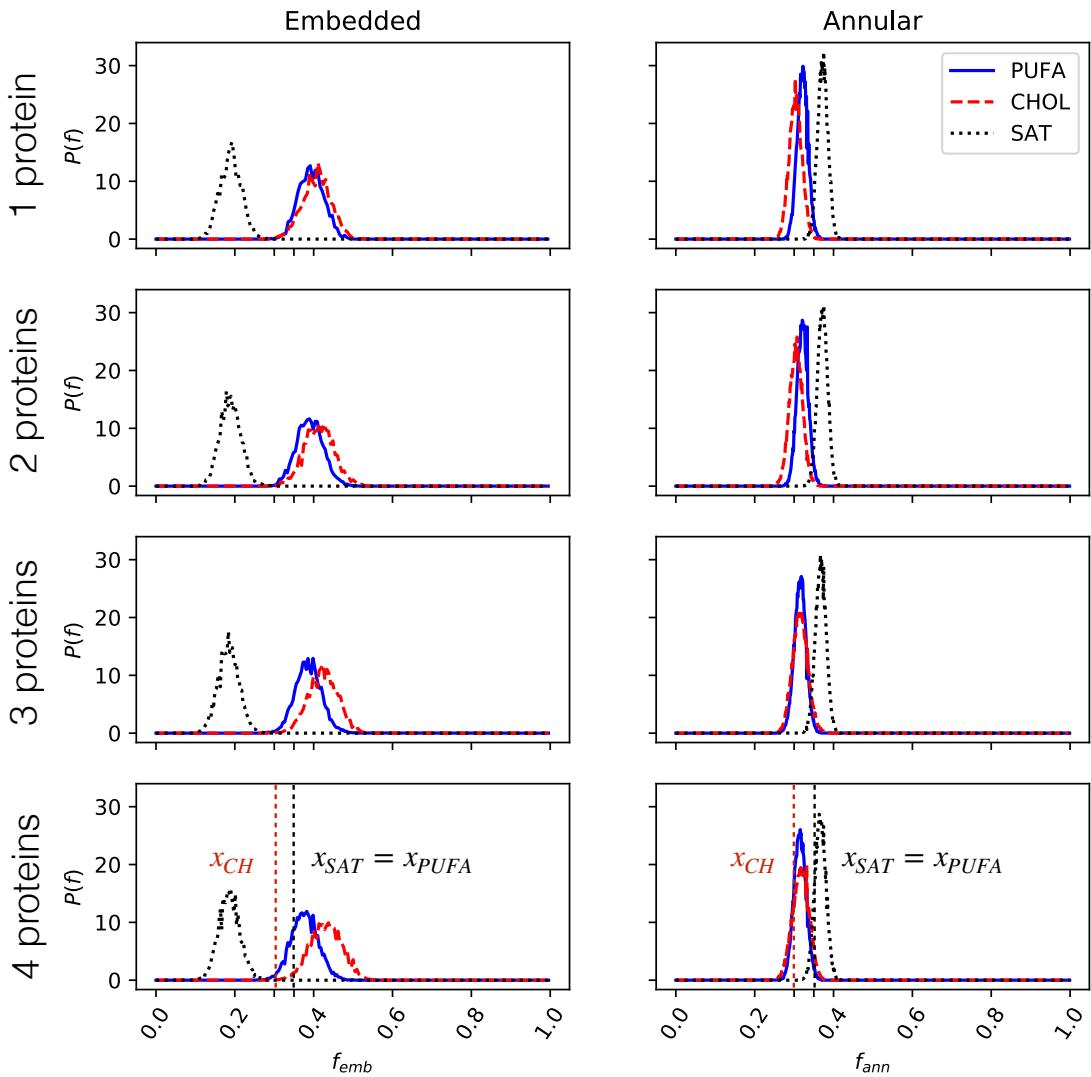


Figure 2.3: Distribution of nAChR boundary cholesterol or acyl chain fractions in mixed membranes containing heteroacidic phospholipids.
 Probability density distribution of fraction of embedded (f_{emb}) or annular lipids (f_{ann}) as defined in Eq. 2.2 are shown for 1 to 4 proteins. Dashed lines represent expected boundary ratios for a randomly-mixed membrane, based on bulk lipid composition ($x_{CH} = 0.3$, $x_{SAT} = x_{PUFA} = 0.35$)

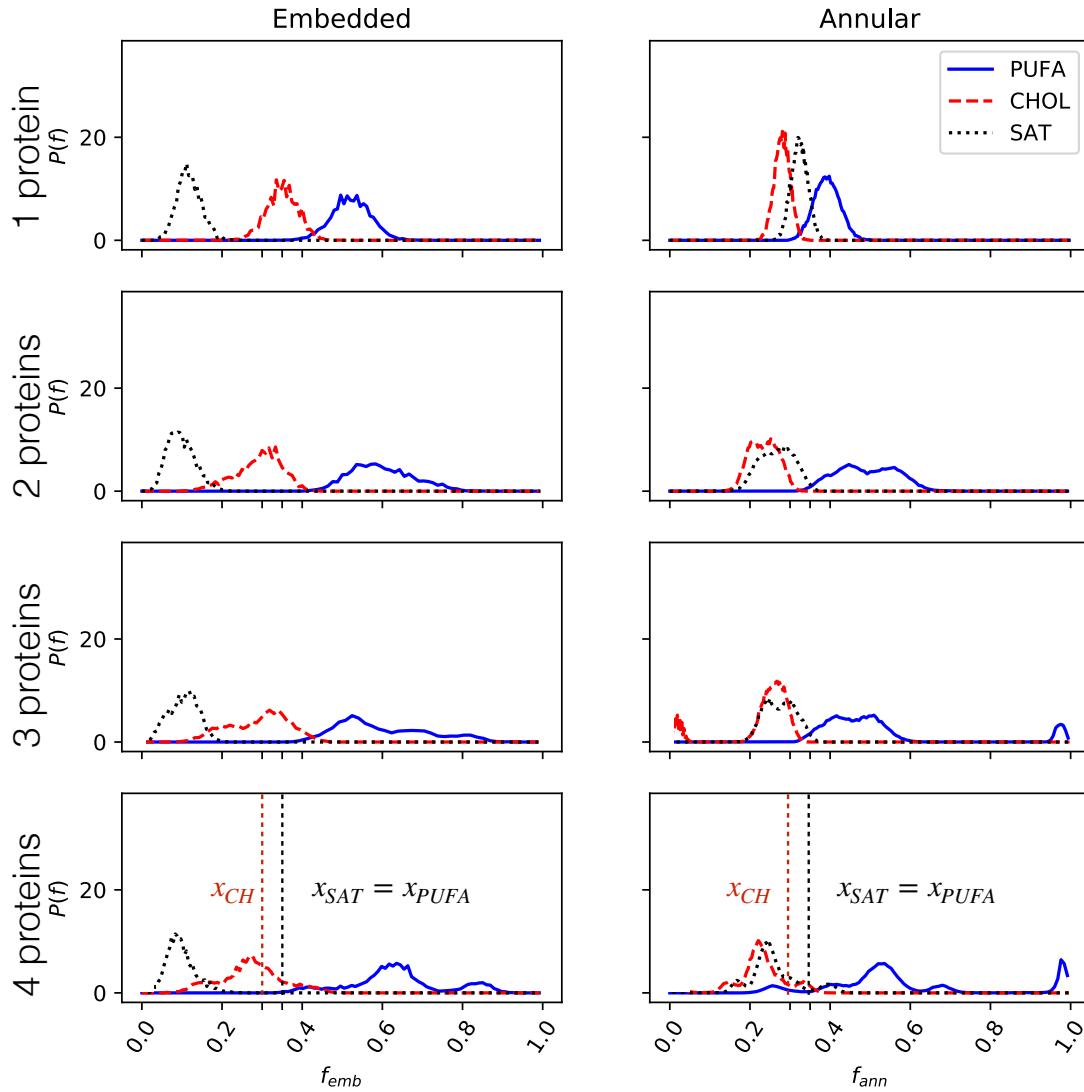


Figure 2.4: Distribution of nAChR boundary cholesterol or acyl chain fractions in mixed membranes containing homoacidic phospholipids. Probability density distribution of fraction of embedded (f_{emb}) or annular lipids (f_{ann}) as defined in Eq. 2.2 are shown for 1 to 4 proteins. Dashed lines represent expected boundary ratios for a randomly-mixed membrane, based on bulk lipid composition ($x_{CH} = 0.3$, $x_{SAT} = x_{PUFA} = 0.35$).

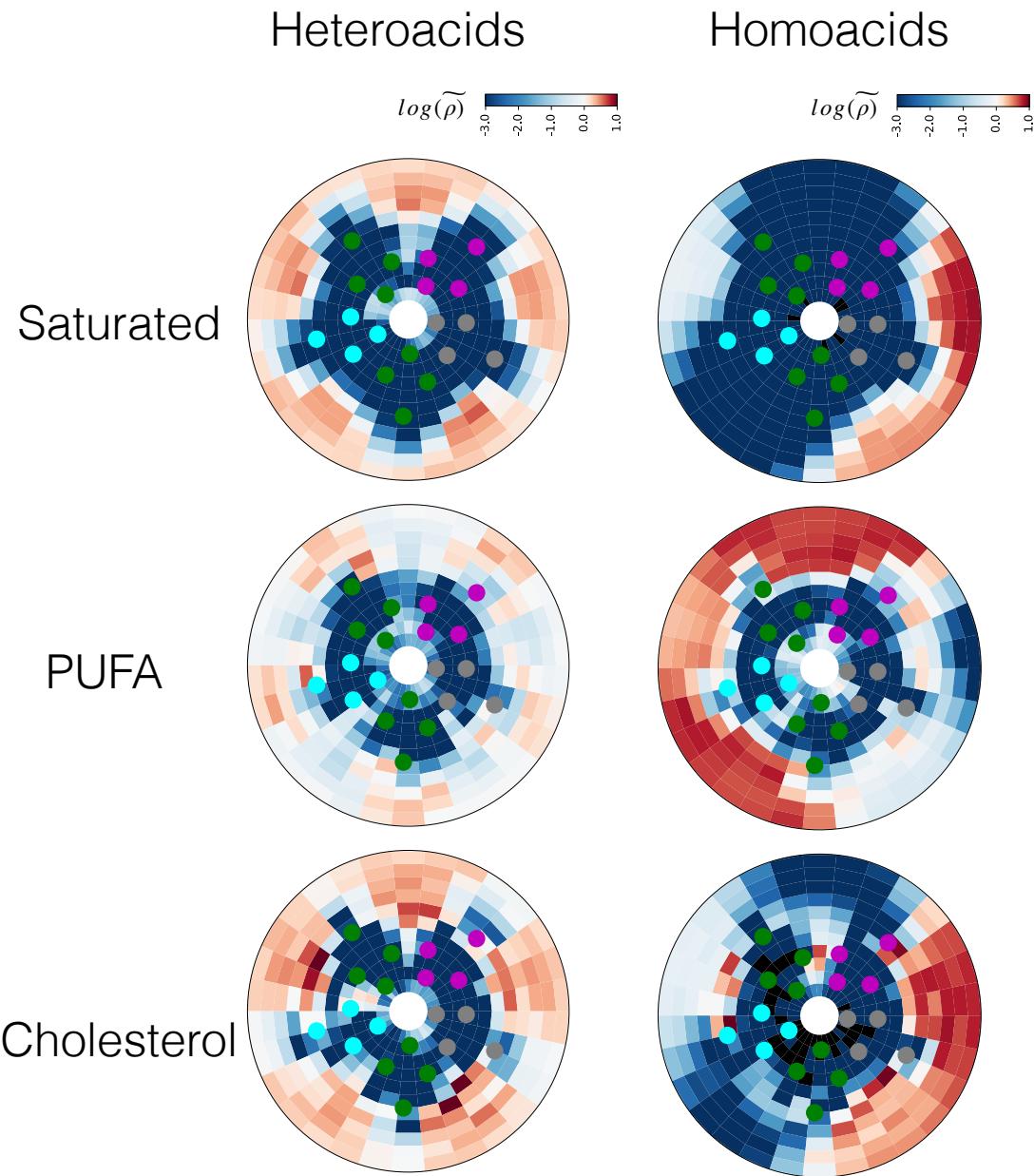


Figure 2.5: Enrichment or depletion of lipid species surrounding a single nAChR. Heatmaps represent normalized lipid densities ($\tilde{\rho}_B(r_i, \theta_j)$) as defined in Eq. 4.2, on a scale of -3 (blue, indicating depletion) to 1 (red, indicating enrichment). Densities were averaged over the last 8 μs of the 10 μs simulations and across three replicas.

of lipid domain formation in driving nAChR oligomerization, we calculated the radial distribution function for the pairwise distances between centers of mass, as shown in Figure 2.6. For both heteroacid and homoacid membranes, we observed a peak at $r \sim 7.5$ nm, corresponding to dimerization. The differences in profiles between domain and non-domain forming membranes were primarily quantitative: most significantly, the peak corresponding to dimers was substantially higher for 2 and 3 proteins in homoacids than in heteroacids. For two proteins, the distribution for homoacids was shifted to the left, relative to the distribution for heteroacids, indicating that the peak for dimerization was at a shorter distance in domain-forming membranes. This difference is consistent with results indicating a role for domain formation in aggregation and clustering of nAChRs (Barrantes 2007; Oshikawa et al. 2003; Pato et al. 2008). The simplest explanation of this difference is the higher effective concentration of proteins when domains are present: all nAChRs are corralled in a single liquid-disordered domain, with approximately half the area of the overall membrane.

Closest subunits across dimerizing proteins

In order to determine whether nAChR dimers were more likely to form with specific subunit interactions, we determined the closest interacting subunit pair for nAChR dimers within each frame. To ensure that dimers, rather than larger oligomers, were being analyzed, we excluded trimers and tetramers from the analysis and only considered two protein systems, with increased sampling. Figure 2.7 shows the amount of enrichment for each possible subunit pairing, relative to an expected random distribution. Results were very sensitive to the use of domain-forming compositions. In heteroacidic membranes, the α_δ subunit formed a monomer-monomer interaction with the β subunit, while the α_γ most favorably interacted with the δ subunit. In domain-forming membranes, the $\delta - \alpha_\delta - \gamma$ interface was two to five times as likely to pair with a α_δ subunit compared to a

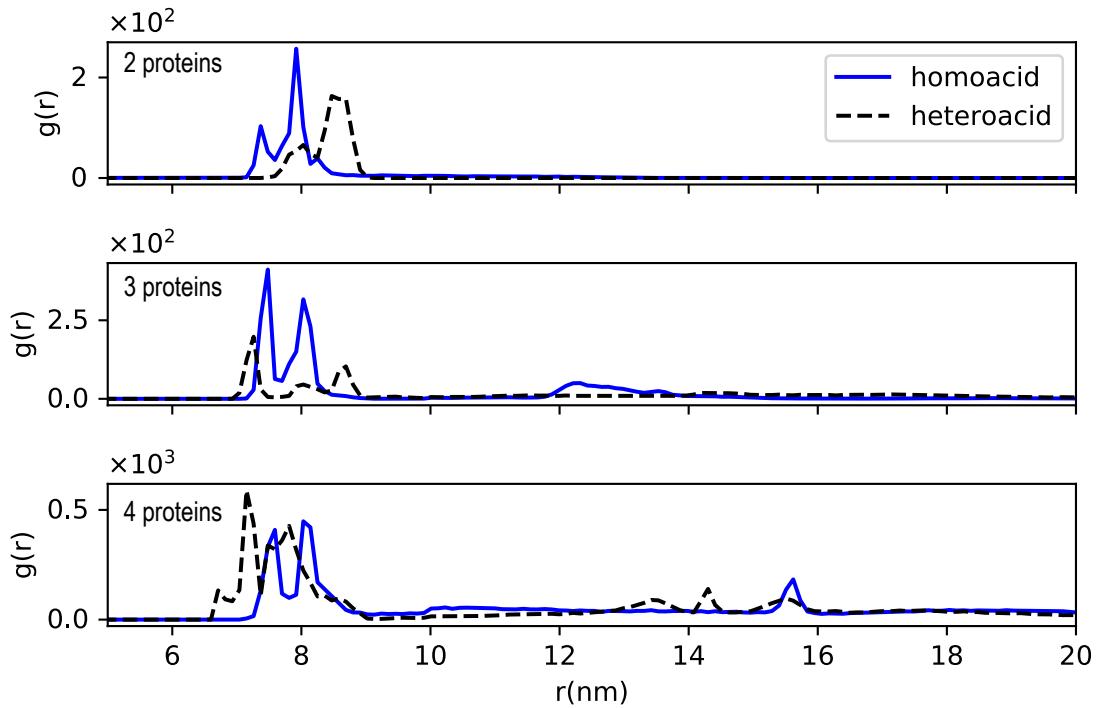


Figure 2.6: Radial distribution function $g(r)$ of pairwise protein center-of-mass distances, across multi-protein systems. Data collection began at $2 \mu s$ into each trajectory and ended at $10 \mu s$, respectively. The peak between 7-10 nm corresponds to dimer formation.

random distribution, but substantially more dispersion was detected than in non-domain forming membranes. This difference suggests that nAChRs have preferred dimerization orientations, but membrane organization can reorient receptors. Although δ subunits are linked by a disulfide bond at the NMJ (Chang & Bock 1977), our simulations suggest that without this link, δ subunits do not form the closest pair among dimerizing proteins.

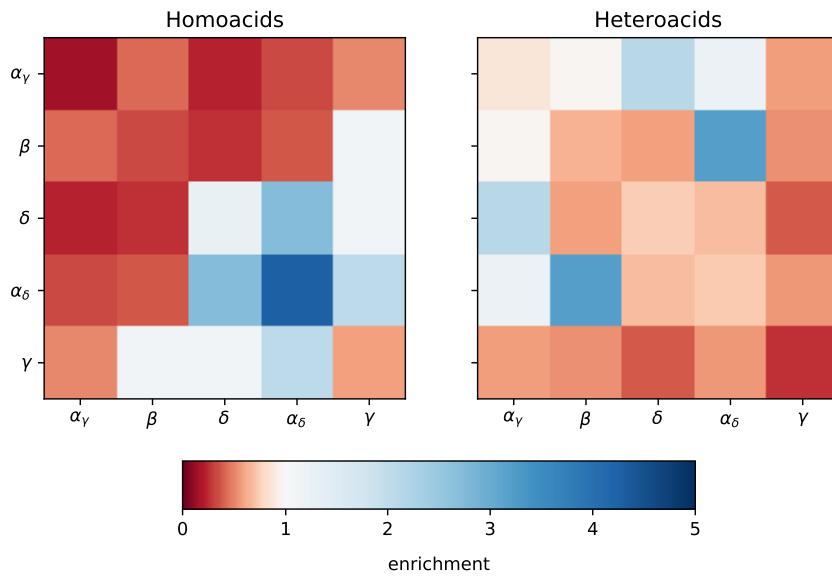


Figure 2.7: Most probable subunit pairs among dimerizing proteins.
 Heat-map showing the likelihood that two subunits were closest together among dimerizing proteins (100 Å threshold). Distinct subunits are each expected to form the closest pair 8 % of the time, while identical subunits are each expected to dimerize only 4 % of the time. Each color on the heatmap represents multiplicative depletion or enrichment relative to the pair’s expectation value, ranging from complete depletion (red) to no enrichment (white) to five-fold enrichment (blue).

2.1.1 Discussion

The nAChR is one of the most well-studied, fundamental pLGICs for understanding human cognition, memory, and muscle contraction (Gotti et al. 1997).

As an integral membrane protein, the function and organization of nAChR is strongly dictated by its surrounding lipid environment. DHA is an ω -3 polyunsaturated fatty acid abundant in synaptic membranes and the Torpedo electric organs, which are both native nAChR membranes. With its six double bonds, DHA is considered highly disordered and can induce domain formation in membranes (Wassall & Stillwell 2008). We previously observed (Sharp et al. 2019) favorable interactions between a single nAChR and DHA-rich, cholesterol-poor domains using coarse-grained simulations. Here, we have extended this approach to investigate the role of lipid topology and domain-formation on boundary lipids of individual nAChRs. We have also conducted the first simulations containing multiple nAChRs, which has allowed us to observe spontaneous dimerization.

While DHA is implicated in human health and disease, (Lavandera et al. 2017) experimental studies considering its interactions with nAChR have exclusively considered its free-fatty acid form (FFA), (Antollini & Barrantes 2016) rather than as an acyl chain component of a phospholipid. Application of $\omega - 3$ FFAs causes a significant reduction in open times observed through single-channel recordings (Bouzat & Barrantes 1993). Here, we observe a substantial effect of lipid topology on both embedded and annular lipids: DHA chains in homoacidic phospholipids are far more likely to be found as either annular or embedded boundary lipids. We previously observed only quantitative effects of swapping PE with PC on partitioning, but the headgroup does serve to anchor the lipid at the membrane/protein interface (Sharp et al. 2019). DHA in its FFA form (without a headgroup) may diffuse into an open nAChR pore, blocking the channel.

We find that, consistent with coarse-grained MD simulations using one nAChR (Sharp et al. 2019), multiple nAChRs continue to prefer the liquid-disordered phase containing long-chain ω -3 fatty acids. While the number of nAChRs in the system did not affect the partitioning profile in these simulations, it did affect the composition of embedded lipids. Our results are consistent with each nAChR

monomer in an oligomer blocking access to embedded lipid binding sites in the other monomers, suggesting an intriguing coupling between specific binding and membrane organization.

Interestingly, upon removing membrane organization, embedded lipids cluster around specific transmembrane helices in a five-fold symmetry around nAChR. This finding suggests that intrinsic lipid preferences are primarily helix dependent, rather than subunit dependent. In homoacid membranes, a lipid preference for DHA was observed across all transmembrane helices, with shells of PUFAs found even at the border of the liquid-ordered phase. Although saturated acyl chains and cholesterol were generally depleted around nAChR, the highest densities for both lipids were found around the M1 and M3 helices, as seen in heteroacid membranes.

In native membranes, nAChR dimers can be stabilized by a disulfide bond between δ subunits (Chang & Bock 1977). An early controversy (Anholt et al. 1980; Rüchel et al. 1981; Zingsheim et al. 1982; Schindler et al. 1984) concerned whether the disulfide bond was necessary for dimer formation. There is no mechanism for covalent bonds between monomers in these coarse-grained simulations. All dimers were stabilized by non-covalent interactions, consistent with the results of (Rüchel et al. 1981; Schindler et al. 1984). We observed far more stable dimers in the homoacid mixtures than the heteroacid mixtures, which would be consistent with high sensitivity to experimental conditions. We did not observe a consistent $\delta - \delta$ preference for interfacing subunits in either homoacid or heteroacid mixtures. Schindler *et al* (1984) observed an apparent gain-of-function for single-channels within dimers relative to monomers, regardless of disulfide linking (Schindler et al. 1984), suggesting that lipid modulation of oligomerization could also provide a pathway for modulating single channel function.

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Chapter 3

Computational approaches in Direct binding of phosphatidylglycerol at specific sites modulates desensitization of a ligand-gated ion channel

3.0.1 Introduction

pLGICs are a family of essential proteins evolved for neuronal function. pLGICs are gated by various neurotransmitters, but are functionally modulated by their boundary lipid composition. The well studied pLGIC nAChR conducts cations across the membrane to stimulate an action potential, and is functionally dependent on cholesterol and anionic lipids Dalziel et al. (1980); Ellena et al. (1983); Criado et al. (1983); Fong & McNamee (1986b); ?); Jones & McNamee (1988); Sunshine & McNamee (1994); DaCosta et al. (2009). Lipid binding sites for pLGICs are still relatively unknown.

Structural biology has predicted cholesterol and fatty acid binding sites in pLGICs Laverty et al. (2017); Basak et al. (2017). Coarse grained molecular dynamics (CGMD) work by SharpSharp et al. (2019) and WoodsWoods et al. (2019) predicted cholesterol binding sites around nAChR. pLGIC-anionic lipid binding sites are still unknown. This work is the computational portion of a collaborative project predicting anionic binding site for the pLGIC *Erwinia* ligand-gated ion channel (ELIC). Using CGMD as a computational microscope and simulating ELIC in membranes comprised of neutral and anionic lipids we visualize and test potential anionic-ELIC binding distributions from native mass spectrometry studies performed by Tong et al. (2019).

3.0.2 Computational Methods

All simulations reported here used the MARTINI 2.2 Marrink et al. (2007a) coarse-grained topology and force field. The crystal structure of ELIC (PDB 3RQW) (62) was coarse-grained using MARTINI martinize.py script. Secondary structural restraints were constructed using martinize.py while imposed through Gromacs (63). Conformational restraints were preserved through harmonic bonds between backbone beads less than 0.5 nm apart with a coefficient of 900 kJ mol⁻¹. Pairs were determined using the ElNeDyn algorithm (64). Membranes were constructed using the MARTINI script insane.py (61). The insane.py script randomly places lipids throughout both inner and outer membranes and embeds selected proteins into the membrane. Two series of simulations were developed, the first using POPE and POPG, and the second POPC and POPG. Box sizes were about 30 x 30 x 25 nm³ and each simulation box contained about 3000 lipids.

Molecular dynamics simulations were carried out using GROMACS 5.1.4 Berendsen et al. (1995). All systems were run using van der Waals (vdW) and electrostatics in cutoff and reaction-field, respectively, with a dielectric constant of $\varepsilon = 15$. vdW and electrostatics used a cutoff length of 1.1 nm as defined in current MARTINI build specifications. Energy minimizations were performed for about 30,000 steps. All systems were run for short equilibration steps. Canonical ensembles (NVT) were run for 100 ps using Berendsen thermostat set to 323 K with the temperature coupling constant set to 1 ps. Isothermal-Isobaric ensemble (NPT) equilibration was run for 5000 ps using Berendsen thermostat and barostat. The thermostat was set to 323 K with the temperature coupling constant set to 1 ps, and the barostat was set to a pressure coupling constant of 3 ps with a compressibility of 3×10^{-5} bar⁻¹ holding at 1 bar. Molecular dynamics were carried out using NPT ensemble and were simulated for 15 μ s with a time step of 0.015 ps using v-rescale thermostat set to 323 K and a temperature coupling constant of 1 ps. Membranes consisting of POPE used the Parrinello-Rahman barostat, and

membranes consisting of POPC used the Berendsen barostat, both under semi-isotropic coupling. The reference pressure was set to 1 bar, the compressibility $3 \times 10^{-4} \text{ bar}^{-1}$, and the pressure coupling constant 1 ps.

Annular lipids were determined using the annular lipid metric B:

$$B_i = \left\langle \frac{b_i}{b_{\text{tot}}} \right\rangle \frac{1}{x_i} - 1 \quad (3)$$

where b_i is the instantaneous number of boundary lipids of species i , b_{tot} is the instantaneous total number of boundary lipids, x_i is the overall (bulk) fraction of species i and the brackets represent an average over time and replicas. $B_i < 0$ and $B_i > 0$ indicate enrichment and depletion of species i , respectively, relative to the abundance in the bulk membrane. A given lipid was counted as a boundary lipid if it was within 6 Å of the ELIC transmembrane domain.

Two dimensional lipid density distributions around a central ELIC pentamer were calculated for each leaflet using polar coordinates (28). For every sampled frame, all lipids of species i were separated into leaflets. For all i lipids in a given leaflet, the vector separating the phosphate beads from ELIC center was calculated and projected onto the membrane plane. The two-dimensional separation vector was then used to assign the lipid to the appropriate polar bin of radial bin width 4 Å and angular bin width $\frac{\pi}{15}$. The area density in each bin was averaged over time and replicas.

3.0.3 Computational Results

To further examine phospholipid interactions with ELIC using a molecular model, coarse-grained MD simulations were performed on binary POPG/POPC and POPG/POPE model membranes containing a single ELIC pentamer (Fig. 2A). Unlike fully-atomistic simulations, coarse-grained simulations permit significant diffusion of lipids over simulation time scales. The boundary lipid composition can thus equilibrate over the simulation time, even if it varies significantly from the bulk membrane composition. The POPG fraction was varied between 0 and 70%.

Enrichment or depletion of POPG among boundary lipids for each concentration was quantified using the boundary lipid metric B (Equation 3, see Methods). For a given lipid species, $B > 0$ reflects enrichment, $B < 0$ reflects depletion, and $B = 0$ reflects random mixing. For POPG, $B > 0$ for all compositions tested (Fig. 2B). This result indicates that if POPG is present in the membrane, it is enriched among boundary lipids. This enrichment is strongest for lower amounts of POPG (i.e. lower x_{POPG}), consistent with specific binding of POPG to ELIC.

We further examined these sites of interaction using our coarse-grained MD simulations. To identify whether boundary POPG were localized around specific helices or residues, two-dimensional densities of the negatively-charged headgroup bead were calculated. The distributions are separated by leaflet where each leaflet contained 10% POPG. As shown in Figure 5A, POPG was more likely to interact with ELIC in the inner leaflet than the outer leaflet, consistent with three out of five interfacial arginines residues being located on the intracellular interface of the ELIC TMD. These three arginines are located on TM3 (R286) and TM4 (R299 and R301). Contacts between POPG and all three of these residues are also visible in individual frames of the simulation (Fig. 5B). Moreover, POPG is more likely to be contacting the interfacial residues in TM4 (such as R299 and R301) than accessible interfacial residues in any other helices (Fig. 5A). The remaining two arginine residues are located at the TMD-ECD interface (R117 and R123). POPG density in the outer leaflet localized to these residues at intrasubunit sites between TM4 and TM1 or TM4 and TM3 (Fig. 5A), and contacts between these residues and POPG headgroups in the outer leaflet were also observed in snapshots from the MD simulations (Fig. 5B). In summary, the native MS data and coarse-grained MD simulations demonstrate that five interfacial arginines contribute to specific POPG binding sites in the inner and outer leaflets adjacent to TM4.

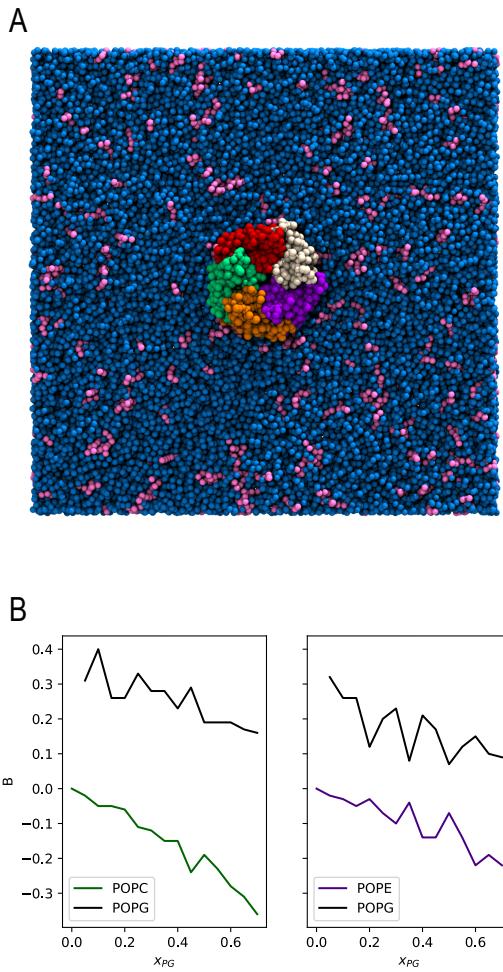


Figure 3.1: Enrichment of POPG among ELIC boundary phospholipids from coarse-grained simulations. (A) Image of the simulation model of ELIC embedded in a membrane consisting of 10% POPG (pink) and % POPC (blue). The view is from the extracellular side of ELIC perpendicular to the membrane. (B) The boundary enrichment metric, B , is shown for phospholipid species in POPC/POPG membranes (left) or POPE/POPG membranes (right) over a range of POPG mole fractions (x_{PG}). B is defined in Equation 3 (see Methods) and reflects the fractional difference between the amount of a lipid species found in the boundary and the bulk membrane: $B > 0$ indicates enrichment, $B < 0$ indicates depletion, and $B = 0$ indicates no difference in mole fraction between the bulk and the boundary.

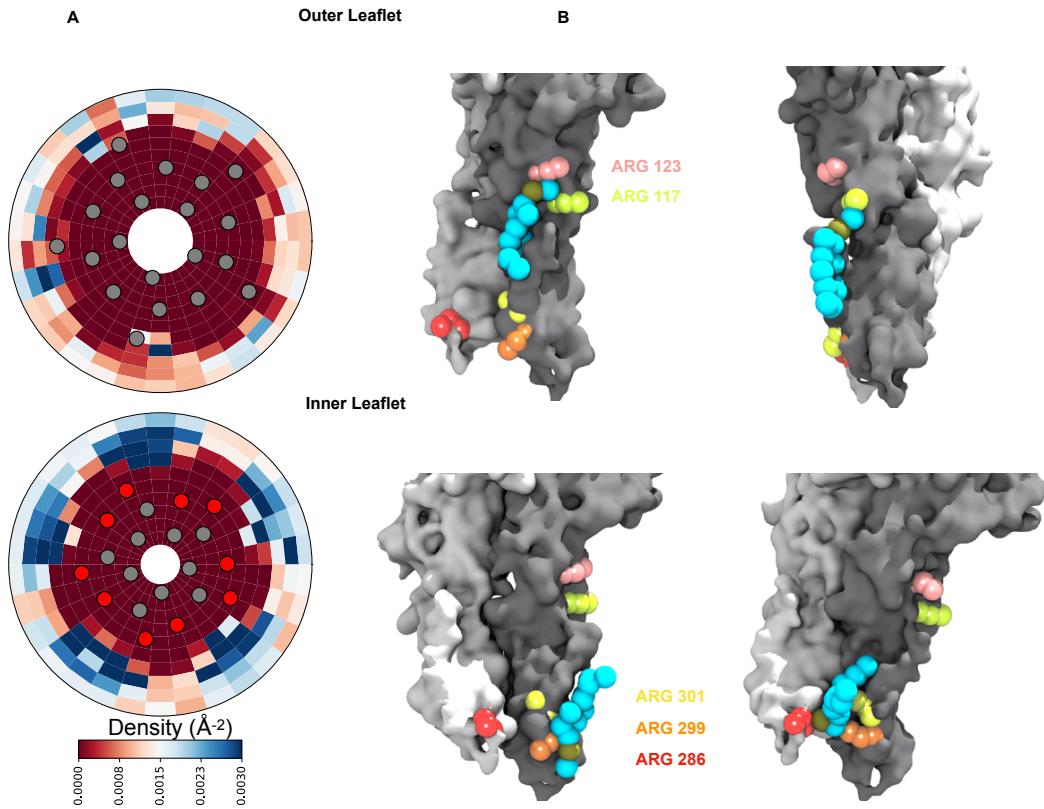


Figure 3.2: Density calculations of lipids in binary membranes and visualization of direct POPG-ELIC interactions at 10% POPG. (A) Distribution of POPG density in a POPG-POPC membrane, within 40 Å from the ELIC pore over the last half of a 15 μ s simulation, for both the outer leaflet (top) and the inner leaflet (bottom). Density is colored according to the color bar, where red and blue represent low and high POPG density, respectively. Circles represent the ELIC transmembrane backbone center of mass, with the helices containing the interfacial arginines colored in red (B) Representative frames after 9 μ s of simulation, showing multiple POPG binding modes associated with high density areas in (A). Two adjacent subunits of ELIC are shown in grey and white, while arginine side chains of interest are colored in peach, lime-yellow, orange, yellow, and red. POPG phosphate is colored in tan with the rest of the lipid in cyan.

Chapter 4

Nicotinic Acetylcholine Receptor Boundary Lipid Characterization Within Native and Experimental Membranes

4.1 Introduction

The nicotinic acetylcholine receptor (nAChR) is a well studied excitatory pentameric ligand gated ion channel (pLGICs). nAChRs are found at high density in post-synaptic membranes and the neuromuscular junction in mammals, and the electric organ in *Torpedo* electric rays. nAChR is activated by binding nicotine or acetylcholine in specific binding pockets in the extra cellular domain. When nAChRs are activated en-mass they stimulate an action potential. nAChRs play a critical role in both cognition and memory Hénault et al. (2015) and neuromuscular function Mukhtasimova et al. (2016); Kalamida et al. (2007b). nAChR and the greater pLGIC superfamily, play various roles in neurological diseases related to inflammation Taly et al. (2009); Cornelison et al. (2016); Patel et al. (2017b); Yocum et al. (2017); Egea et al. (2015), addiction Cornelison et al. (2016), chronic pain Xiong et al. (2012), Alzheimer's Disease Walstab et al. (2010); Picciotto & Zoli (2008); CM et al. (1999); Kalamida et al. (2007b), spinal muscular atrophy Arnold et al. (2004), schizophrenia Haydar & Dunlop (2010); Kalamida et al. (2007b) and neurological autoimmune diseases Lennon et al. (2003); Kumari et al. (2008).

nAChRs are highly sensitive to their local lipid environment. Previous studies using model membranes suggest cholesterol and anionic lipids Dalziel et al. (1980); Ellena et al. (1983); Criado et al. (1983); Fong & McNamee (1986b); ?); Jones &

McNamee (1988); Sunshine & McNamee (1994); DaCosta et al. (2009) are required for nAChR function. Functional studies using Zhou et al. (2003); Gamba et al. (2005); Chen et al. (2015); Kouvatsos et al. (2016); Nys et al. (2016); Polovinkin et al. (2018); Moffett et al. (2019); Kumar et al. (2020) require lipid additives such as asolectin Criado et al. (1983); Zhou et al. (2003); Gamba et al. (2005); Chen et al. (2015); Kouvatsos et al. (2016); Nys et al. (2016); Polovinkin et al. (2018); Moffett et al. (2019); Kumar et al. (2020) or synaptic membranes Conti et al. (2013) to return native ion flux to nAChR. It is unclear what nAChR's boundary lipid composition is in neuronal membranes.

Mammalian neuronal membranes ?Taguchi & Ishikawa (2010); ?); Ingólfsson et al. (2017) have unique compositions compared to other mammalian membranesMcEvoy et al. (2000); Kim et al. (2001); van Meer & de Kroon (2010); Lorent et al. (2020); Ingólfsson et al. (2014). Neuronal membranes are more similar to *Torpedo* electric ray's electric organ ?Quesada et al. (2016) than the average mammalian membraneIngólfsson et al. (2014). Neuronal membrane ?Taguchi & Ishikawa (2010); ?); Ingólfsson et al. (2017) composition consists of a number of essential PUFAs, more specifically the *n* – 6 PUFA arachidonic acid (AA), and the *n* – 3 PUFAs Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA). These three PUFA's comprise a sizable fraction of neuronal phospholipids, and are involved in secondary signaling McNamara et al. (2008); Hamazaki et al. (2015) and neuronal development Maekawa et al. (2017). PUFAs are linked to a number of neurological diseases and disorders that overlap nAChR related diseases. PUFAs play a roll in major depressive and bipolar disorder ?McNamara et al. (2008); Schneider et al. (2017); Koga et al. (2019); Hamazaki et al. (2015), schizophrenia Peet (2003); Bushe & Paton (2005); Berger et al. (2006); Schneider et al. (2017); Maekawa et al. (2017); Hamazaki et al. (2015), and Alzheimer's Disease Conquer et al. (2000); Di Paolo & Kim (2011); Bennett et al. (2013); ?); ?); Escribá (2017).

It is experimentally challenging to capture the boundary lipid composition of

pLGICs, as well as other membrane channels. Functional experiments demonstrated anionic lipids and cholesterol as lipid modulated pLGIC's function Ellena et al. (1983); Fong & McNamee (1986b); ?); Jones & Mcnamee (1988); Sunshine & McNamee (1994); DaCosta et al. (2009), but pLGICs are functional dependent on boundary cholesterol Dalziel et al. (1980); Addona et al. (1998); Criado et al. (1983). Structural biology has found potential cholesterol sites at the subunit interface Laverty et al. (2017); Budelier et al. (2019), potential specific phospholipid sites in the inter-subunit site Hénault et al. (2019); Basak et al. (2017) and inter-subunit sites Kim et al. (2020), and anionic lipids binding to inner inter-subunit sites Tong et al. (2019). MD simulations are used as a computational tool to visualize below the diffraction limit and visualize or predict, protein-lipid interactions. MD simulation has identified cholesterol Brannigan et al. (2008a) interaction at inter-subunit sites and PUFA sites at M4 sites Woods et al. (2019), as well as anionic lipids binding at inner inter-subunit sites Tong et al. (2019).

With the growing use of coarse-grained molecular dynamics (CGMD) simulations, complex quasi-realistic membranes are becoming more practicle. Ingólfsson et al. (2014) simulated and analyzed an "average mammalian" membrane. In 2017, Ingólfsson compared a coarse-grained neuronal membrane Ingólfsson et al. (2017) to the average mammalian membrane. To our knowledge this begins the first generation of realistic simulated membranes. Accessible and simulatable realistic membranes are being expanded on, comparing the difference between model and quasi-realistic membranes and their protein interactions Marrink et al. (2019); Wilson et al. (2020a); Ingólfsson et al. (2020); Carpenter et al. (2018); Lorent et al. (2019).

Work by Sharp Sharp et al. (2019), Woods Woods et al. (2019), and Tong Tong et al. (2019) predict lipid distributions around pLGICs using model membranes. These membranes are significantly simplified compared to realistic membranes, i.e. 2-3 lipid species versus 10 or more. However the model membranes used

are useful in predicting how lipid species may occupy sites. Model membranes do not consider how multiple lipids of similar acyl-chain saturation compete to bind to a pLGIC (i.e. EPA compared to DHA, or DHA and ALA). Nor do model membranes consider how various like charged lipid head groups interact at the boundary region (i.e. which binds more PE or PC, PS or PI). Determining nAChR's boundary lipid composition in native membranes is critical to understanding the receptor's function, or what lipid additives are required to prevent a lack of function.

For this work, we embed the neuromuscular nAChRUnwin (2005) in a coarse-grained neuronal membrane Ingólfsson et al. (2017). Based on our previous work Sharp et al. (2019); Woods et al. (2019); Tong et al. (2019), we hypothesize a series of lipid occupancy sites for nAChR based on acyl-chain saturation and head group charge, see figure 4.1a. We predict PUFAs will occupy regions around the M4 alpha helices, and raft forming lipids will occupy inter-subunit sites. Neutral lipids are predicted to occupy any site in the outer leaflet and inner leaflet M4 sites, but anionic lipids will predominately occupy only the inner leaflet inter-subunit sites. To test this hypothesis we use polar enrichment density plots and occupancy affinity free energy calculations. We find our hypothesis, based on model membranes, does not hold. In the outer leaflet neutral lipids are more favorable in the outer leaflet, but n-3 PUFAs and cholesterol tend to occupy nAChR sites indiscriminately. Unsaturated lipids tended to have stronger affinities for M4 and saturated lipids had stronger affinity for inter-subunit sites. In the inner leaflet neutral n-3 PUFAs and cholesterol tend to compete with anionic n-3 PUFAs and cholesterol tend to occupy inter-subunit sites, however anionic lipids occupy M4 regardless of acyl-chain saturation.

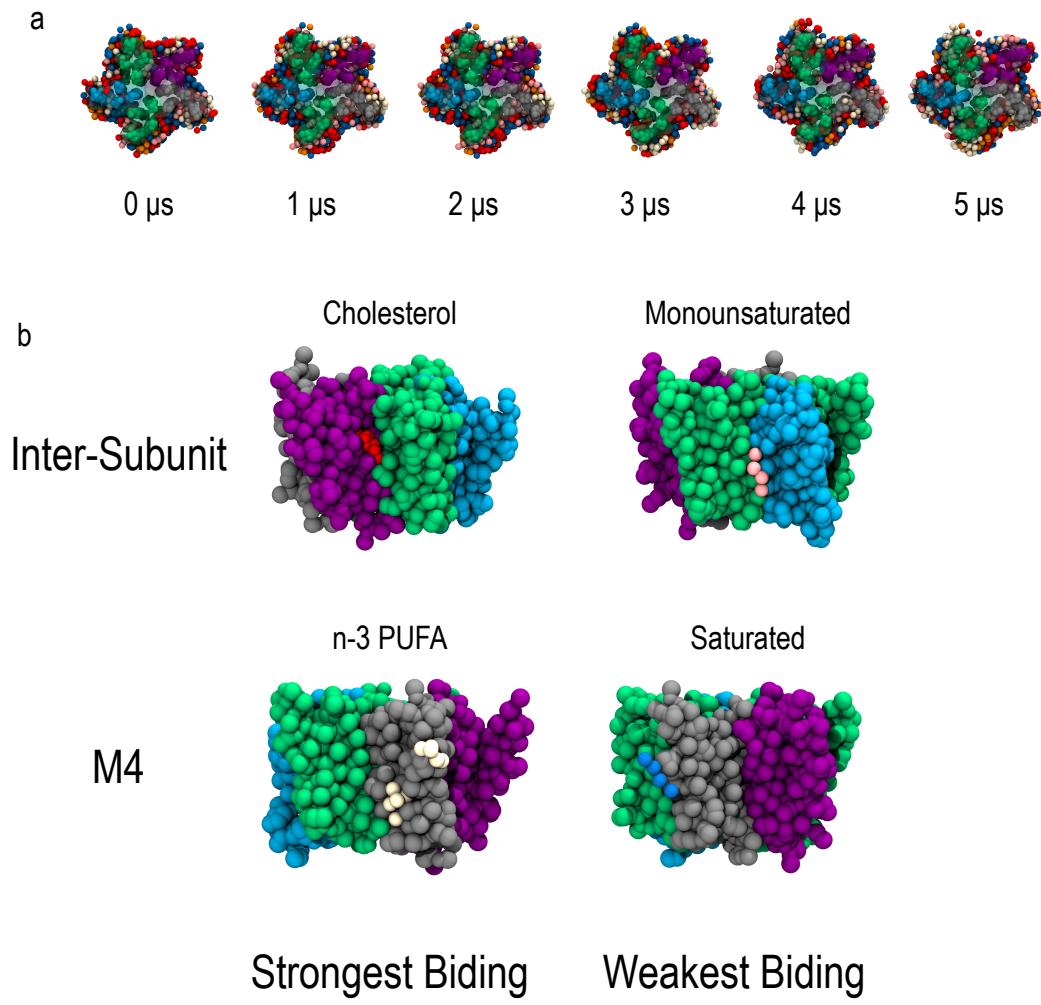


Figure 4.1: Visualization of boundary lipids surrounding nAChR and most favorable and least favorable at inter-subunit and M4 sites. Colors for all VMD images are: α -subunits:green, γ -subunits cyan, δ -subunits:grey, *beta*-subunits:purple, saturated lipids: blue, monounsaturated lipids:orange, n-6 PUFAs:pink, n-3 PUFAs:beige, and cholesterol:red. a) Frames from neuronal membrane trajectory over 5 μ s. nAChR is depicted using van der Waals beads and transparent quicksurf. Only lipid acyl chains are shown using van der Waals. Lipids are shown within 15 Å of nAChR. b) Inter-subunit and M4 sites and lipids with the strongest and weakest binding affinities.

4.2 Methods

4.2.1 Simulation Composition

All simulations used the coarse-grained MARTINI 2.2De Jong et al. (2012) topology and forcefield. nAChR coordinates were based on a cryo-EM structure of the $\alpha\beta\gamma\delta$ muscle-type receptor in native torpedo membrane (PDB 2BG9Unwin (2005)). This is a medium resolution structure (4Å) and was further coarse-grained using the martinize.py script; medium resolution is sufficient for use in coarse-grained simulation, and the native lipid environment of the proteins used to construct 2BG9 is critical for the present study. The secondary, tertiary and quaternary structure in 2BG9 was preserved via soft backbone restraints during simulation as described below, so any inaccuracies in local residue-residue interactions would not cause instability in the global conformation.

nAChR was embedded in a coarse-grained neuronal membrane based on Ingólfsson Ingólfsson et al. (2017). The neuronal membrane from described by Ingólfsson contains phospholipids, sterols, diacylglycerol, and ceramide. Membranes presented in this paper only consider phospholipids and cholesterol, for a total of 36 unique lipid species.

Coarse-grained membranes were built using the MARTINI script insane.py, which was also used to embed the coarse-grained nAChR within the membrane. The insane.py script randomly places lipids throughout the inter- and extra-cellular leaflets, and each simulation presented in this manuscript was built separately. Head-group and acyl-chain compositions were dictated by Ingolfsson 2017 Ingólfsson et al. (2017). All simulation box sizes were $40 \times 40 \times 35$ nm³ with $\sim 4,500 - 5,000$ lipids and total $\sim 450,000$ beads.

4.2.2 Simulations

Molecular dynamics simulations run using the MARTINI 2.2De Jong et al. (2012) forcefield and GROMACS?Abraham et al. (2015) 2019.2 . All systems used van der Waals (vdW) and Electrostatics with reaction-field and a dielectric constant of $\epsilon_r=15$ and electrostatic cutoff length at 1.1 nm. Energy minimization was performed for 1000000 steps, but energy minimization tended to concluded after $\sim 5000 - 10000$ steps.

Volume and pressure equilibrations were run with isothermal-isochoric (NVT) and isothermal-isobaric (NPT) ensembles respectively. NVT and NPT simulations used a time step of 15 fs and run for 0.3 ns using Berendsen thermostat held at a temperature of 323 K, and Berendsen pressure coupling with compressibility set to 3×10^{-5} bar $^{-1}$ and a pressure coupling constant set to 3.0 ps for the NPT ensemble.

Molecular dynamics simulation were run using a time step of 20 fs for 5 μ s and replicated ten times. Simulations were conducted in the NPT ensemble, by using the V-Rescale thermostat set to 323 K with temperature and a coupling constant set to 1 ps. Semi-isotropic pressure coupling was set to Parrinello-Rahman with compressibility at 3×10^{-5} bar $^{-1}$ and pressure coupling constant set to 3.0 ps.

Secondary structures restraints consistent with MARTINI recommendations were constructed by the martinize.py De Jong et al. (2012); ? script and imposed by GROMACS ?Abraham et al. (2015). nAChR conformation was preserved by harmonic bonds between backbone beads separated by less than 0.5 nm and calculated using the ElNeDyn algorithm ? associated with MARTINI De Jong et al. (2012) with a coefficient of 900 kJ·mol $^{-1}$.

4.2.3 Analysis

Two-dimensional density distribution of the beads within a given lipid species l around the protein was calculated on a polar grid:

$$\rho_B(r_i, \theta_j) = \frac{\langle n_B(r_i, \theta_j) \rangle}{r_i \Delta r \Delta \theta} \quad (4.1)$$

where $r_i = i\Delta r$ is the projected distance of the bin center from the protein center, $\theta_j = j\Delta\theta$ is the polar angle associated with bin j , $\Delta r = 10\text{\AA}$ and $\Delta\theta = \frac{\pi}{15}$ radians are the bin widths in the radial and angular direction respectively, and $\langle n_B(r_i, \theta_j) \rangle$ is the time-averaged number of beads of lipid species B found within the bin centered around radius r_i and polar angle θ_j . In order to determine enrichment or depletion, the normalized density $\tilde{\rho}_B(r_i, \theta_j)$ is calculated by dividing by the approximate expected density of beads of lipid type B in a random mixture, $x_B s_B N_L / \langle L^2 \rangle$, where s_B is the number of beads in one lipid of species B , N_L is the total number of lipids in the system, and $\langle L^2 \rangle$ is the average projected box area:

$$\tilde{\rho}_B(r_i, \theta_j) = \frac{\rho_B(r_i, \theta_j)}{x_B s_B N_L / \langle L^2 \rangle} \quad (4.2)$$

where the expected density is derived at the first frame of the simulation.

This expression is approximate because it does not correct for the protein footprint or any undulation-induced deviations of the membrane area. The associated corrections are small compared to the membrane area and would shift the expected density for all species equally, without affecting the comparisons we perform here.

We hypothesized 20 occupancy around nAChR's TMD: 5 inter-subunit sites and 5 M4 sites in both outer and inner leaflets. These sites are predicted in Woods et al 2019 Woods et al. (2019) and Tong et al 2019 Tong et al. (2019). Site occupation does not follow the standard "a ligand is occupied or unoccupied" model. Instead we consider partial occupation. Partial occupancy ranges from fully occupied, partially occupied, or unoccupied. We demonstrate a model of

partial occupancy in figure 4.2 a. An occupancy site is fully occupied if a single lipid species (A) is the only lipid species occupying a site. Like the small molecule displaced by water, a portion of lipid A may be partially or fully displaced by a second lipid (B). We use this partial occupancy approach to define affinities.

Affinity is defined as the change in the Gibbs' free energy (ΔG). ΔG is calculated using two probability distributions, P_{occ} and P_{bulk} , see figure 4.2 b. Both distributions are calculated from the time averaged number of lipid beads within the area of an occupancy site (P_{occ}) or an identical area in the bulk membrane (P_{bulk}). The area of an occupancy site (A_s) is the sum of the area accessible to the lipids (A_{acc_s}) and the area restricted to the lipids by the protein (A_{rest_s}):

$$A_s = A_{acc_s} + A_{rest_s}.$$

A_s values are calculated on a polar plane, see figure 4.3 a. A_s for inter-subunit and M4 sites are determined by non-overlapping angular and radial bin densities. Inter-subunit sites are determined by the angular component of bins between two adjacent subunits' M1 and M3 α -helices and the radial component is $\{r|10 < r \leq 32 \text{ \AA}\}$. M4 sites are determined by the angular component given by the set of bins within one subunit using M1 and M3 α -helices and the radial component is $\{r|10 < r \leq 44 \text{ \AA}\}$. The area for each site is calculated by:

$$A_s = \frac{\langle n_s(r, \theta) \rangle}{\rho_s(r, \theta)} \quad (4.3)$$

Where $\langle n_s(r, \theta) \rangle$ is the associated time averaged number of beads within a polar bin and ρ_s is the time averaged numeric bin density, see eq 4.1. Only values of $\langle n_s(r, \theta) \rangle$ and ρ_s within the range of angular and radial bins described above are used. For the affinity calculation described below the bin radial and angular widths are $\Delta r = 4 \text{ \AA}$ and $\Delta \theta = \frac{\pi}{25}$. Using the values calculated for A_s , we calculate A_{acc} to determine accurate bulk areas for P_{bulk} .

$$A_{acc_s} \equiv \frac{\langle n_{occ_s} \rangle A_s}{\langle n_s \rangle} \quad (4.4)$$

$\langle n_{occ_s} \rangle$ and $\langle n_s \rangle$ are the average number of lipid beads for a specific occupancy site and the average number of lipid beads in the bulk membrane within a given area A_s . The values for A_{acc_s} are then used to calculate P_{bulk} , see figure 4.2 b.

To calculate the affinity, we define $P_<$ and $P_>$

$$P_< \equiv \sum P_{occ} \leq \langle P_{bulk} \rangle \quad (4.5a)$$

$$P_> \equiv \sum P_{occ} > \langle P_{bulk} \rangle \quad (4.5b)$$

Using the mean value of P_{bulk} as a reference, the sum of overlapping P_{occ} less than or equal to P_{bulk} are defined as $P_<$. The sum of P_{occ} greater than P_{bulk} are defined as $P_>$. The affinity is then defined as the overlap between $P_<$ and $P_>$.

$$\Delta G = -RT \ln \frac{P_>}{P_<} \quad (4.6)$$

Where RT is the gas constant R and the temperature of the simulation.

4.3 Results and Discussion

4.3.1 Effect of Acyl-Chain on Neutral Lipid Affinities

Results from Woods et al 2019 Woods et al. (2019) predict lipid occupancy sites for PUFAs and raft forming lipids at M4 and inter-subunit sites respectively. We hypothesize PUFAs will tend to occupy the M4 alpha helices for both leaflets and raft forming lipids will occupy inter-subunit sites for both leaflets. To test these occupancy sites for specific lipid interaction, we use radial enrichment densities (see equation 4.2) and a histogram method for calculating affinity as ΔG values, (described in methods and equations 4.3-4.6).

In order to compare the lipid distributions for the native system to our previous model system, we plotted enrichment density plots for acyl-chains based

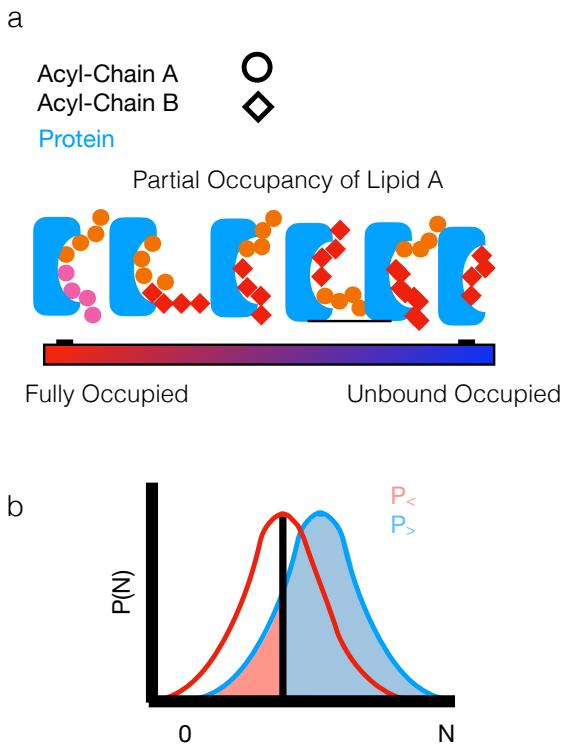


Figure 4.2: a) Model of partial occupancy of lipid species "A" to a protein. Proteins models are blue with an occupancy region carved out. Lipid species A is represented by circles and lipid species B by diamonds. A protein's occupancy of lipid species A is demonstrated by the color bar, where red is lipid A is fully bound and blue is lipid A is fully unbound. The region in between represents possible partial occupancy conformation. b) Toy P_{occ} and P_{unocc} distributions in red and blue curves respectively. Black line shows mean value of P_{unocc} . $P_{<}$ (pink) is the sum of P_{occ} less than and equal to P_{unocc} 's mean value. $P_{>}$ (light blue) is the sum of P_{occ} greater than P_{unocc} 's mean value.

on degree of saturation, and cholesterol, see figure 4.3. Saturated and monounsaturated fatty acids are approximately random. Cholesterol, with the exception of highly specific peaks at the protein's annulus, are depleted in both leaflets. Both n-6 and n-3 PUFAs are symmetrically enriched around the M4 α -helices, but also have non-uniform enrichment around the inter-subunit regions in the

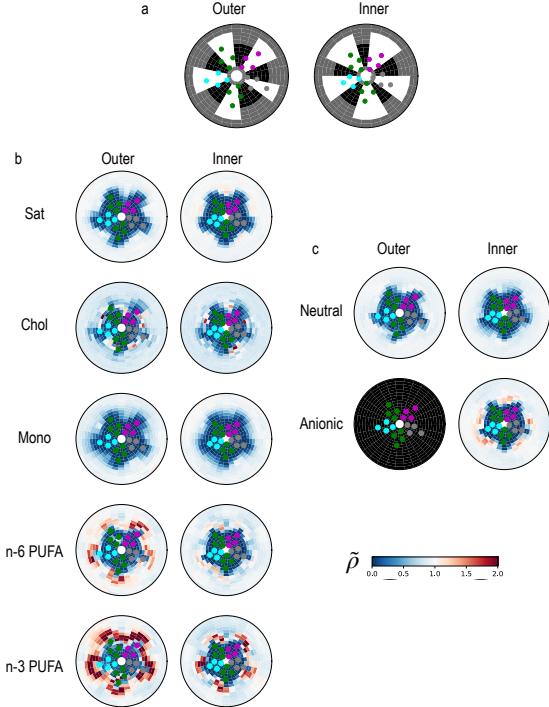


Figure 4.3: Model binding areas and acyl-chain density enrichment or depletion around a central singular nAChR. a) Binding site area's. Black and white represent areas for inter-subunit and M4 occupancy sites. Grey show sites not considered for occupancy areas. Density enrichment is calculate using eq 4.2 for both outer and inner leaflet columns, averaged over 10 replicas for $2.5 \mu\text{s}$ each. The maximum radius from pore of nAChR is 60\AA . $\tilde{\rho}_a < 1$ describes acyl-chain depletion compared to a random bulk mixture, $\tilde{\rho}_a = 0$ describes the expected mixture, and $\tilde{\rho}_a > 1$ describes acyl-chain enrichment compared to a random mixture. b) Density enrichment based on acyl-chains, c) density enrichment based on head group charge.

outer leaflet. The PUFA area of enrichment decrease in the inner leaflet, where n-3 PUFAs show strong enrichment around the annulus of the protein and n-6 enrichment values approach weak to expected levels. These results diverge from what we saw in Woods et alWoods et al. (2019). In our previous model membranes, we had clear five fold enrichment for n-3 PUFAs, however in the native

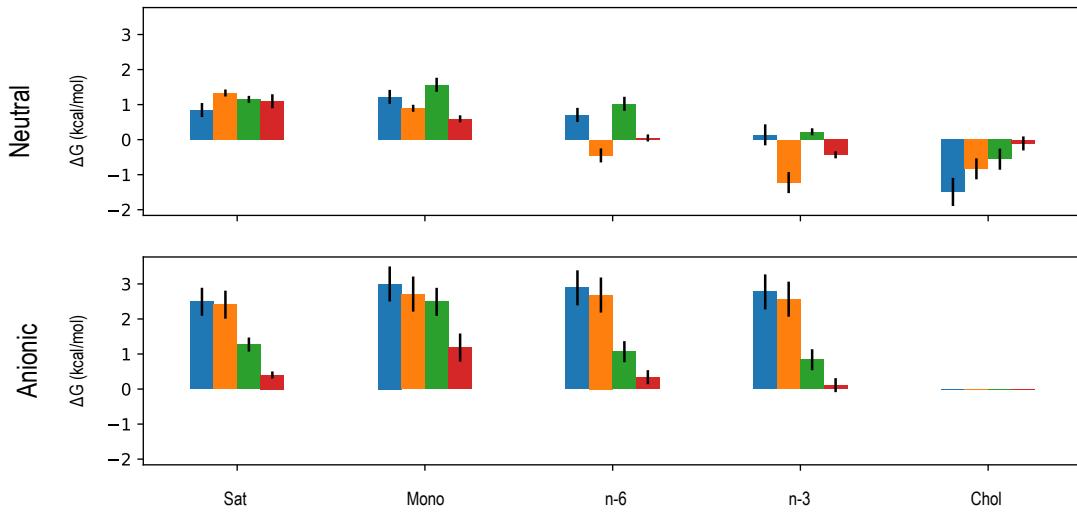


Figure 4.4: Affinity calculation ranking for neutral and anionic lipid saturation species averaged over last half of 10 $5\mu s$ replicas. Occupancy sites are averaged over each site type. Columns are lipid saturation, rows are charge, and colors represent a lipid occupancy site.

membranes, the exact boundary becomes blurred.

We compare inter-subunit and M4 site occupation affinities across neutral lipid acyl-chain saturations, and cholesterol, see figure 4.4. Saturated and monounsaturated lipids generally have the weakest affinities. Neutral PUFAs and cholesterol have the strongest affinities across all sites. At the M4 site, n-6 PUFAs have the weakest affinity of the PUFAs and cholesterol, at ≤ 0 kcal/mol values for M4 sites. n-3 PUFAs have stronger affinities for M4 sites when compared to n-6 PUFAs. The weakest n-3 affinity value is approximately equal to the strongest n-6 affinity value at M4. n-3 PUFAs also have affinity values approximately 0.2 kcal/mol for inter-subunit sites for both leaflets, 0.5 kcal/mol or smaller than saturated lipid affinity values. Unlike phospholipids, cholesterol has strong affinity values for all sites. Per leaflet, cholesterol has stronger affinities for inter-subunit than the M4 sites, but we report solely negative affinity values.

Figure 4.5 analyzes occupancy site affinity for acyl-species, charge, and leaflet.

Cholesterol has the strongest affinity of the neutral lipids at inter-subunit sites. Phospholipids have affinity values > 0 kcal/mol at inter-subunit sites, where cholesterol affinity values are < 0 . This trend is also observed in the inner leaflet, though the affinity for cholesterol is weakened by $\sim 50\%$. Neutral phospholipids at inter-subunit sites show highly conserved affinity values between leaflets, with n-3 having the strongest and monounsaturated with the weakest affinities. Phospholipids affinities at M4 also show a conserved trend between leaflets where affinity is correlated with acyl-chain flexibility, such that the less saturated an acyl-chain is the greater affinity it has for M4. The affinity results we observe, reinforce what is shown in figure 4.3, where n-3 PUFAs can occupy most regions of the TMD. Cholesterol's strong affinity for most sites have been averaged out in enrichment density plots but can be seen in Figure 4.8, which provides lipid bead distributions.

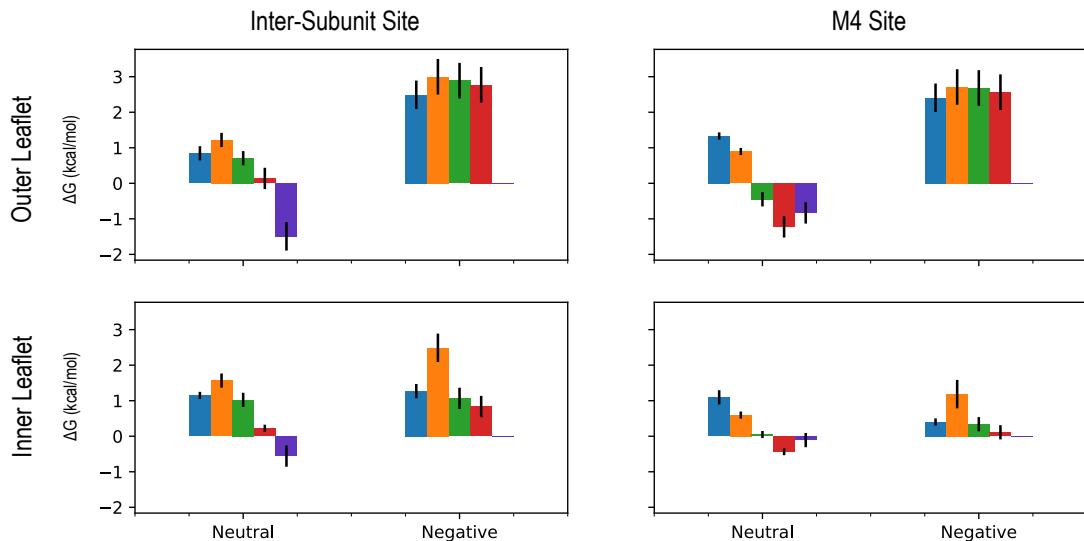


Figure 4.5: Affinity calculation ranking for neutral and anionic lipid saturation species averaged over last half of 10 replicas. Occupancy sites are averaged from 20 sites. Row one is the outer leaflet and row two is the inner leaflet. Columns are charge, each subplot is a difference occupancy site.

4.3.2 Effect of Head Group Charge on Affinity Depends on Leaflet and Binding Site

Research by Tong et al 2019 Tong et al. (2019) showed anionic lipids favorably occupied around ELIC’s inter-subunit sites in the inner leaflet. ELIC inner inter-subunit sites have multiple arginines, promoting anionic lipid occupancy. Based on this work, we hypothesize nAChR’s outer TMD and inner M4 sites will have a strong affinity for neutral phospholipids but nAChR’s inner inter-subunit sites will have a strong affinity for anionic phospholipids. We test the proposed lipid distributions using both enrichment density analysis and affinity calculations, as we did in *Effect of Acyl-Chain on Neutral Lipid Affinities*.

We analyze the distribution for both neutral and anionic lipids using polar enrichment density plots, see figure 4.3. Neutral lipids in the outer leaflet have weak enrichment around the M4 subunits and are approximately randomly distributed around the rest of the protein. Anionic lipids are not present in the outer leaflet at the start of simulations. With minimal anionic lipid-flipping their contribution is negligible (to be updated). Neutral lipids in the lower leaflet have an approximately random distribution. Anionic lipids in the lower leaflet are enriched at inter-subunit sites and non-uniformly around non- α -subunit M4 sites. Anionic lipids are generally enriched around the M3/M4 helices, see in figure 4.3 for α_γ , γ , δ , and β . The distribution of anionic lipids differs from work by Tong et al 2019Tong et al. (2019).

We hypothesize the difference in our result is from the number and placement of charged amino acids in ELIC’s (TMD PDB:3RQWPan et al. (2012)) versus that of neuromuscular nAChR. We use VMD Humphrey et al. (1996) to visualize the difference between nAChR and ELIC’s inner leaflet TMD, see figure 4.6. Both pLGICs have a number of cationic amino acids around their annulus. ELIC has more cationic amino acids embedded in the protein density than at

the annulus. Cationic amino acids found in the nAChR structure tend to be more outward facing than cationic amino acids in the ELIC structure. Non- α nAChR subunits have cationic amino acids closer to M4 α -helices. ELIC has cationic amino acids closer to the inter-subunit sites. Anionic amino acids are found at nAChRM4 α -helices, with the exception of the β subunit. Anionic amino acids are found closer to the M1/M4 α -helices interfaces in ELIC, or embedded within the **inner/non-annular/bulk of protein**.

We compare the relative affinities for neutral and anionic lipids in the outer leaflet, see figure 4.5. Neutral lipids have a stronger affinity compared to anionic lipids for both inter-subunit and M4 sites. All anionic lipids have affinity values \geq 2.0 kcal/mol. There is weak variation between acyl-chain saturation. The general trend we observe in both outer neutral and anionic phospholipids at inter-subunit sites, from weakest to strongest is monounsaturated, saturated, n-6 PUFA, and n-3 PUFA. The outer leaflet phospholipid-protein interactions appear consistent with Tong et all 2019Tong et al. (2019).

We compare the relative affinities for neutral and anionic lipids in the lower inter-subunit sites, see figure 4.5. Neutral and anionic lipids have similar affinity values for saturated and n-6 PUFAs. The similar affinity values between neutral and anionic saturated and n-6 PUFAs suggest potential lipid competition for this site. Neutral n-3 PUFAs have a stronger affinity than anionic n-3 PUFAs, -0.4 and 0.1 kcal/mol respectively. We observe a small change in neutral lipid affinities between inner and outer inter-subunit sites. Anionic lipids, with the exception of monounsaturated lipids, have stronger affinities for inner inter-subunit sites than outer inter-subunit sites.

We compare the relative affinities for neutral and anionic lipids in the lower M4 sites, see figure 4.5. Neutral and anionic lipids have different affinity distributions at M4 compared to inter-subunit sites. Neutral lipid affinities are related to the acyl-chain flexibility. Anionic lipids have the ranking we previously discussed

(weakest to strongest: monounsaturated, saturated, n-6 PUFA, and n-3 PUFA). Neutral PUFAs and cholesterol have the strongest affinity values, ≤ 0 kcal/mol. Both neutral PUFAs have weaker affinities at inner M4 compared to outer M4. Neutral saturated and monounsaturated lipids have stronger affinities in lower M4 than outer M4. Anionic lipids are generally < 0.6 kcal/mol, but monounsaturated lipids are an exception. The average affinity difference between anionic inter-subunit and M4 sites is ~ -1.0 kcal/mol. Anionic lipids have a stronger affinity for the inner M4 than inner inter-subunit sites, see figures 4.4 and 4.5.

4.3.3 Effect of Head Group Details on Lipid Affinities

Neutral lipids have a higher affinity in the outer leaflet. Neutral and anionic lipids show a level of competition at inner inter-subunit sites. Anionic lipids have an acutely stronger affinity at inner M4 sites compared to neutral lipids. Neutral and anionic are bulk terms that categorize numerous lipid head-groups by charge. Frequently head group charge and size play a factor in direct protein-lipid interactions. Here we look at head groups species with the strongest affinities for occupying nAChR by leaflet and site.

We measure head group affinities by outer leaflet site, see table 4.1. Anionic lipid affinity values for PS and PI are both above 2 kcal/mol, and PIPS and PA above 3.5 kcal/mol. Neutral and small PE lipids have the highest affinity in both inter-subunit and M4 sites, -0.2 ± 0.3 and -1.1 ± 0.2 kcal/mol respectively). The bulkier PC and SM are weaker to PE by $\sim > 0.5$ kcal/mol. Sharp et al 2019Sharp et al. (2019) and Tong et al 2019Tong et al. (2019) observed slightly more enrichment of PE than PC around pLGICs. In living cells PUFAs are frequently associated with PE more than PC or SM ?Taguchi & Ishikawa (2010); ?); Ingólfsson et al. (2017); Gamba et al. (2005); Lorent et al. (2020).

We measure head group affinities by site for the lower leaflet, see table 4.2. Anionic lipids have a substantial increase in affinity interacting with nAChR in

the inner leaflet compared to the outer leaflet, specifically at the M4 sites. PE still has a stronger affinity compared to the anionic lipids PI and PS. Both PI and PS are ~ 0.6 and ~ 0.4 kcal/mol weaker than PE at inter-subunit and M4 sites respectively. It is unclear why PE is more favorable at this time. It may be due to the frequency which PE are attached to lipids with PUFAs or the size of the head group. However, many of the the anionic lipid head groups are attached to PUFAs. If head group size were the leading factor, PS would be expected to have a greater occupancy affinity than PI lipids, as PS is smaller.

Table 4.1: Outer Leaflet ΔG affinities for lipids based on head groups. Head groups are sorted by inter-subunit.

	Outer Inter Sites kcal/mol	Outer M4 Sites kcal/mol
PE	-0.2 \pm 0.3	-1.1 \pm 0.2
PC	0.8 \pm 0.3	0.5 \pm 0.2
SM	1.9 \pm 0.3	1.7 \pm 0.1
PS	2.5 \pm 0.4	2.4 \pm 0.4
PI	2.8 \pm 0.5	2.6 \pm 0.4
PIP3	4.1 \pm 0.5	3.8 \pm 0.6
PIP1	4.1 \pm 0.5	4.0 \pm 0.5
PA	4.3 \pm 0.4	4.1 \pm 0.5
PIP2	4.6 \pm 0.3	4.5 \pm 0.4

4.4 Conclusions

We used a neuronal lipid compositions modified from Ingólfsson et al. (2017) to analyze nAChR within a neuronal membrane. We hypothesized lipid-protein occupancy sites based off the results from work by SharpSharp et al. (2019), WoodsWoods et al. (2019), and TongTong et al. (2019). We hypothesized PUFAs

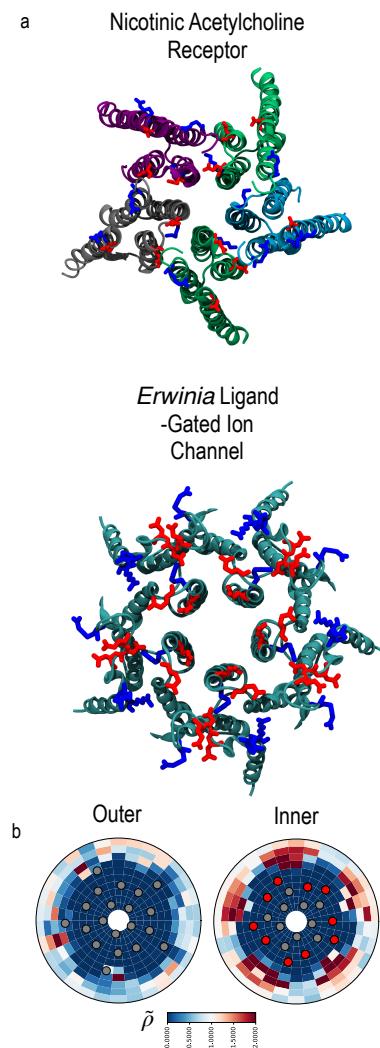


Figure 4.6: Charged amino acid representation in the TMD/ECD interface and expected anionic enrichment. a) Inner cellular view up of nAChR (top) and ELIC (bottom). nAChR is color coded by subunit (α :green, β : purple, δ : grey, γ : cyan), ELIC is cyan. Cationic amino acids are colored in blue while anionic lipids are colored in red for both structures. b) Anionic polar density enrichment observed in ELIC, derived from Tong et al. (2019). Grey circles represent center of mass of alpha helices, red circles represent center of mass of alpha helices with cationic amino acids.

Table 4.2: Inner Leaflet ΔG affinities for lipids based on head groups. Head groups are sorted by inter-subunit.

	Inner Inter Sites kcal/mol	Inner M4 Sites kcal/mol
PE	0.3±0.2	-0.1±0.1
PI	0.9±0.3	0.2±0.1
PS	1.0 ±0.2	0.4±0.1
PC	1.2 ±0.2	0.7±0.1
SM	2.2 ±0.4	1.4 ±0.1
PIP3	2.6±0.4	1.8 ±0.4
PIP2	2.8 ±0.2	2.1±0.4
PIP1	2.4 ±0.3	2.1±0.4
PA	3.0 ±0.3	2.2±0.4

and raft forming lipids would occupy the M4 and inter-subunit sites respectively, while anionic lipids would occupy inner inter-subunit region of nAChR. Our results show lipid distributions among occupancy sites differ from our hypothesis.

Of the phospholipids analyzed, n-3 PUFAs have the strongest affinities across all sites, with affinities values of $\sim < 0$ kcal/mol for M4 sites and $\sim <.5$ kcal/mol for inter-subunit sites. We predict the relative high affinity for n-3 PUFAs are a result of their flexibility. The n-3 PUFA, DHA, has a number of unique membrane properties Stillwell & Wassall (2003); Gawrisch et al. (2003), and is observed to consistently interact with non-annular sites in and around pLGICs Sharp et al. (2019); Woods et al. (2019). The inherent disorder in PUFAs and the strong affinity they have for M4 sites suggests PUFAs may minimize unfavorable membrane deformation?Brannigan & Brown (2007); Hu et al. (2012b); ?); Buganza Tepole (2017); Dan et al. (1993); Fournier & Galatola (2015) around pLGIC's conical-star shape provided by M4.

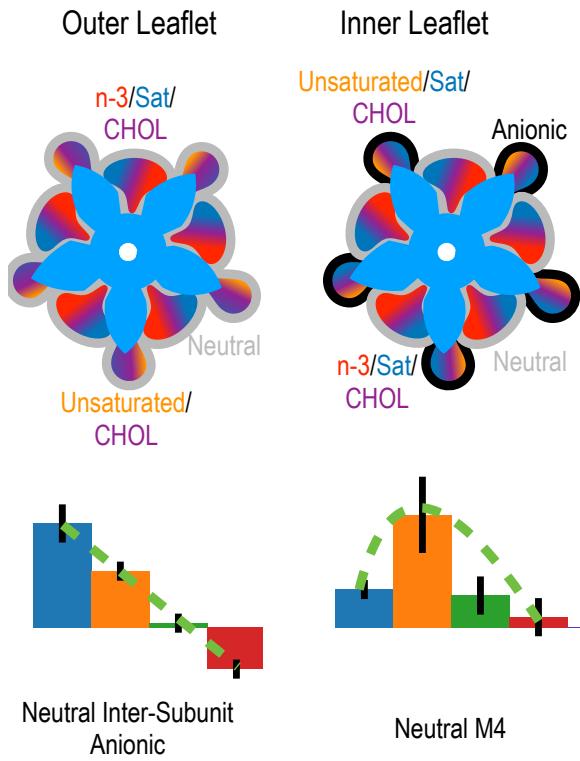


Figure 4.7: A cartoon depicting lipid-protein occupancy of nAChR in a native membrane for both leaflets. Protein is shown in the center of both leaflets a cyan floral shape. Grey and black outlines depict occupancy sites for neutral and anionic lipids respectively. Filled colors represent most likely lipids to occupy inter-subunit or M4 sites. Red: n-3 PUFAs, blue: saturated, purple: cholesterol, orange: generally unsaturated.

Similar to n-3 PUFAs cholesterol occupies sites nearly indiscriminately. For each leaflet cholesterol has the strongest affinity for the inter-subunit site. Cholesterol's affinity for the M4, compared to inter-subunit sites, is reduced by about 50% and 80% for the outer and inner leaflets respectively. However, unlike the phospholipids cholesterol's affinity for each site is consistently $< 0\text{kcal/mol}$. Brannigan et al 2008 Brannigan et al. (2008a) hypothesized 15 non-annular cholesterol binding sites for nAChR. Sharp et al 2019 Sharp et al. (2019) observed cholesterol embedded in β subunits of nAChR. It could be cholesterol's favorability for M4

is a result of having an even stronger affinity for within a subunit of nAChR, or more straight forwardly its relative small size makes it ideal for packing between alpha helices.

For most sites monounsaturated lipids have the weakest affinities. We hypothesize this is due to packing limitation from monounsaturated lipids single acyl-chain kink. Cholesterol and PUFAs are small or highly flexible and readily fit at various sites in pLGIC's topology. Saturated lipids, which lack any kinks and are more rigid than unsaturated lipids, may pack around inter-subunit site's "flat" topology. We argue the single acyl-chain kink found in monounsaturated lipids may prevent packing of itself around inter-subunit sites, and is not flexibility to compete with PUFA's occupying M4 sites.

Neutral lipids that occupy M4 have an unique trend in affinity. The affinity strength increase as a relation to acyl-chain flexibility, initially state in section *Effect of Acyl-Chain on Neutral Lipid Affinities*. Neutral lipids at inter-subunit sites and all anionic lipids share a non-monotonic affinity trend where it is more akin to a concave function. [all here. I have a figure that I want to tie in though](#)

Neutral lipids have a stronger affinity for the outer leaflet compared to anionic lipids. Neutral lipids found at the inner inter-subunit sites have slightly weaker affinities compared to the same lipids in the outer inter-subunit site. Anionic lipids deviate from our hypothesis. Anionic lipids have stronger affinity for inner M4 than inner inter-subunit sites. Inner anionic saturated, n-6 and n-3 PUFAs have significantly greater affinities than outer anionic lipids of the same saturation types. Inner monounsaturated lipids affinity values do not change much from outer anionic monounsaturated lipid values ($\sim 0.5\text{kcal/mol}$). We hypothesize anionic lipids have stronger affinity for M4 in nAChR compared to ELIC due to cationic amino acid distribution. nAChR has cationic amino acids at both inter-subunit and M4 sites, while ELIC only has them at inter-subunit sites.

For both outer and inner leaflets neutral lipids with smaller head groups (PE)

have stronger affinity than the larger PC or SM. Anionic lipids in the lower leaflet have some what of an inverse relationship, where the bulkier PI has greater affinity than the smaller PS. PA has the weakest affinity of the anionic lipids, though it has the smallest head group, and PIPS which are much bulkier than all the other head groups are comparable to PA. PI, PS share the same charge: -1.0 C. It is unclear why neutral and anionic head group affinities are uncorrelated, though it may be a product of head group to acyl-chain combination, evolution, or the coarse grained model. The PE head group bead types are Qd and Qa, which are attracted to most of the other bead types. PS has P5 which is attractive to about half the bead types and repulsive to the other half. PI has coarse-grained ring of P5 and P1s, and Qa, all of which tend to be attractive to other beads.

Closer, but the last possibility is not necessarily different from the drivers

nAChR lipid occupancy appears to be driven in two steps. First a "coarse-sorting" by head groups, and second "fine-sorting" by acyl-chains. In the outer leaflet anionic lipids are clearly unfavorable, coarse-sorting. A neutral lipid will occupy nAChR's boundary region and then there is "fine-sorting" by acyl-chain saturation. Inner Inter subunit sites have competition between lipid head group charge, but have specific acyl-chain affinity. The inner M4 site has the strongest affinity for anionic lipids regardless of saturation type, which diverges from the proposed occupancy driver. However inner anionic lipid occupancy could be driven by another mechanism: anionic lipids occupy M4 due to the number of positively charged amino acids until the site is saturated with anionic lipids, similar to Tong et al Tong et al. (2019). The remainder anionic lipids do not defusing back to the bulk membrane, they weakly interact with the inner inter-subunit site as a local anionic lipid pool for M4.

These results show a significant divergence from our proposed hypothesis and are depicted in figure 4.7. In the outer leaflet neutral have a strong affinity to

occupy sites. Unsaturated lipids and cholesterol occupy the M4 site, while n-3 PUFAs, cholesterol, and saturated lipids occupy inter-subunit sites. Neutral and anionic lipids occupy inner inter-subunit sites with similar lipid composition compared to the outer leaflet. Inner M4 sites have a strong affinity for anionic lipids regardless of acyl chain.

Table 4.3: Affinity values averaged over 10 replicas. ΔG values for averaged occupancy sites.

	Outer Inter Sites kcal/mol	Outer M4 Sites kcal/mol	Inner Inter Sites kcal/mol	Inner M4 Sites kcal/mol
CHOL	-1.5 ±0.4	-0.8±0.3	-0.6±0.3	-0.1±0.2
Sat	0.7 ±0.3	1.3 ±0.2	1.0 ± 0.2	1.1 ±0.2
Mono	1.2 ±0.2	0.8± 0.2	1.4 ±0.1	0.7 ±0.2
n-6	0.6 ±0.2	-0.5 ±0.1	0.3 ±0.2	-0.3 ±0.2
n-3	-0.0 ±0.4	-1.3 ±0.3	-0.20.2±	-0.9±0.2
Neutral	0.4 ±0.3	-0.4±0.2	0.5 ±0.2	0.5±0.2
Anionic	2.4 ±0.4	2.4 ±0.4	0.3 ±0.2	-0.3 ±0.1
Sat Neutral	0.8 ±0.2	1.3 ±0.1	1.1±0.1	1.1 ±0.2
Mono Neutral	1.2±0.2	0.9 ±0.1	1.6 ±0.2	0.6 ±0.1
n-6 Neutral	0.7 ±0.2	-0.5 ±0.2	1.0 ±0.2	0.0 ±0.1
n-3 Neutral	0.1 ±0.3	-1.2±0.3	0.2 ±0.1	-0.4 ±0.1
Sat Anionic	2.5 ±0.4	2.4±0.4	1.3±0.2	0.4±0.1
Mono Anionic	3.0±0.5	2.7 ±0.5	2.5 ±0.4	1.2 ±0.4
n-6 Anionic	2.9 ±0.5	2.7 ±0.5	1.1 ±0.3	0.3±0.2
n-3 Anionic	2.8 ±0.5	2.6 ±0.5	0.8 ±0.3	0.1 ±0.2

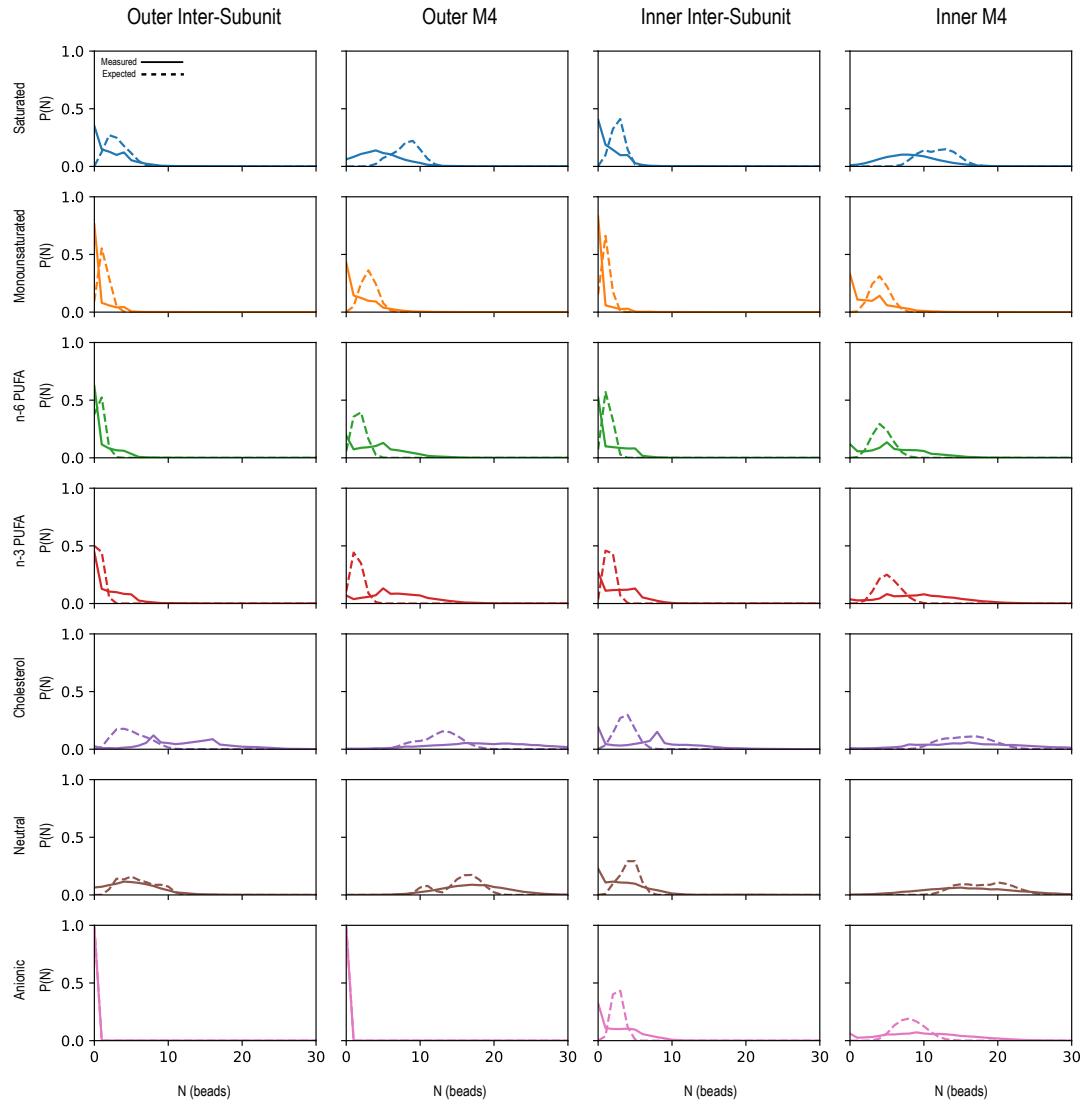


Figure 4.8: SI:Probability distributions of acyl-chain saturations, including cholesterol, and head group charge. Solid lines are probability of a given number of beads found at occupancy site, averaged over both the course of the simulation and subunit sites. Dashed lines represent the probability of a given number of beads in the bulk averaged over time. Bulk areas are square areas of equal area of occupancy sites.

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Vita

Education

Academics

- 2016-Expected Winter 2020 Computational and Integrative Biology Rutgers University Camden, NJ *PhD*
- 2014-2016 Computational and Integrative Biology Rutgers University Camden, NJ *MS*
- 2008–2012 Physics Juniata College Huntingdon, PA *B.S.*

Certificates

- **2019 Software Carpentry** Software Carpentries Instructor
- **2015 Rutgers University Camden** Level I Tutor
- **2012 Pennsylvania State University** Nanofabrication Manufacturing Technology (NMT) Capstone Semester

Publications

- **2019:** Liam Sharp, Reza Salari, Grace Brannigan, *Boundary lipids of the nicotinic acetylcholine receptor: Spontaneous partitioning via coarse-grained molecular dynamics simulation*, Biochimica et Biophysica Acta (BBA) - Biomembranes, ISSN 0005-2736, <https://doi.org/10.1016/j.bbamem.2019.01.005>.
- **2019:** Kristen Woods*, Liam Sharp*, Grace Brannigan, *Untangling direct and domain-mediated interactions between nicotinic acetylcholine receptors in dha-rich membranes*, The Journal of membrane biology, ISSN 0022-2631, <https://doi.org/10.1007/s00232-019-00079-0>.

*Joint first author.

- **2019:** Ailing Tong, John T. Petroff II, Fong-Fu Hsu, Philipp A. M. Schmid-peter, Crina M. Nimigean, Liam Sharp, Grace Brannigan, Wayland W. L. Cheng, *Direct Binding of Phosphatidylglycerol at Specific Sites Modulates Desensitization of a Pentameric Ligand-Gated Ion Channel*, eLife, doi: 10.7554/eLife.50766.

I ran coarse-grained simulations of ELIC in membranes containing PG, which were validated by our experimental collaborators.

In Preparation

- *Coarse-grained simulations of multiple subtypes of mammalian pLGICs in quasi-physiological membranes* : Pentameric ligand gated ion channels are frequently used in functional studies embedded in *Xenopus* oocytes, but are native to membranes similar to synapses. I run simulations in neuronal and *Xenopus* oocytes to determine nAChR's boundary lipid composition to predict lipid additives for functional experiments in *Xenopus* oocytes.
- *Investigation of the relative importance of pLGIC sequence versus shape in determining preferred lipid domain* : pLGICs sequence vary across species and even within individual species, despite all pLGICs sharing a common structure. It is unclear whether boundary lipids composition is driven by a protein's sequence or its structure. I have run multiple pLGICs in model native membranes to compare boundary lipid composition to better understand the effect these receptors' shape and sequence play on boundary lipid sorting.

Leadership Experience

Leadership Roles

- Co-Computational Chair for Center for Computational and Integrative Biology's student run organization. This position is shared with an Experimental Chair and a Sitting President. Assists with:
 - * Planning student social and student informational events.
 - * Leading journal readings and discussions.
 - * Communicating student issues with the Director and Graduate Director.
 - * Welcoming and guiding prospective and new students.
 - * Presenting at undergraduate open houses.
- CCIB Graduate Student Liaison with the Graduate Student Union Representative. I am in charge of keeping in contact with the union, bringing up issues students have with university related concerns, and setting up meeting with our center's students and the union representative.
- Senior graduate student within the Brannigan Lab.
 - * Helped train and mentor two undergraduate and four graduate students.
 - * Assisted with keeping computers and users up to date with IT.
 - * On occasion, led lab group meetings.
 - * Discussed approaches and concerns dealing with peers research.
 - * Assisted with daily lab maintenance and reporting lab issues.
 - * Assisted with benchmarking molecular dynamic simulations for various allocation grants.

Teaching

- Developed, adapted, and maintained curriculums for algebra and mathematical physics courses.
- Participated in approximately 10 educational training sessions through Rutgers Camden Learning Center and the Biophysics Society Annual Conference.
- Taken part in Software Carpentry Instructor reviews and updates three times a year .
- Taught classes as small as three students and as large as thirty-five.
- Tutored one-on-one in math and physics during my MS.

Courses Taught

- **Spring Semester 2019:**
Mathematical Physics (3 credits)
- **Fall Semester 2018:**
Introductory Physics Lab (1 credits)
- **2017-2018:**
Advanced Algebra (4 credits)
- **2016-2017:**
Introductory Algebra (3 credits)

Additional Teaching Experience

- **Fall 2019:** Guided Data Organization in Spreadsheets and Introduction to R in Data Carpentry Workshop.
- **Summer 2019:** Guided Programming with Python in Software Carpentry Workshop.
- **Spring 2019:** Guided Programming with Python in Software Carpentry Workshop.
- **Fall 2014-Spring 2016** Tutor at Rutgers University Camden Learning Center.

Additional Experiences

- **Internship Summer 2011** University of Pennsylvania, High Energy Physics Laboratory: Developed code to track annealing rate of irradiated transistors.

Presentations

- **2020 Seminar:** Nicotinic Acetylcholine Receptors Lipid Preferences Within Complex Quasi-Native Membranes, Center for Computational and Integrative Biology, Rutgers University Camden, NJ 2020.
- **2020 Poster:** Nicotinic Acetylcholine Receptors Lipid Preferences Within Complex Quasi-Native Membranes, Biophysical Society Annual Meeting, San Diego, CA 2020.
- **2019 Demonstrations:** Science Carnival, Science on the Parkway, Science Week, Philadelphia, PA 2019.

- **2019 Seminar:** Boundary Lipids Of The Nicotinic Acetylcholine Receptor In Quasi-Native Membranes, Q-Step, Rutgers University Camden, NJ 2019.
- **2019 Poster:** Boundary Lipids Of The Nicotinic Acetylcholine Receptor In Quasi-Native Membranes, Biophysical Society Annual Meeting, Baltimore, MD 2019.
- **2018 Seminar:** Boundary Lipids of the Nicotinic Acetylcholine Receptor in Quasi-Native Membranes, Center For Computational and Integrative Biology, Rutgers University, Camden, NJ. 2018.
- **2018 Poster:** Interactions of nicotinic acetylcholine receptors with cholesterol and polyunsaturated fatty acids in model, native-like, and oocyte membranes. Biophysical Society Annual Meeting, San Francisco, CA. 2018.
- **2017 Seminar:** A Coarse Grained Study of Nicotinic Acetylcholine Receptor-Lipid Interactions, Center For Computational and Integrative Biology, Rutgers University, Camden, NJ. 2017.
- **2017 Poster:** Interactions of nicotinic acetylcholine receptors with liquid-disordered domains rich in n-3 polyunsaturated fatty acids. Biophysical Society Annual Meeting, New Orleans, LA. 2017.
- **2016 Poster:** Effects of quasi-native lipid composition on membrane domain formation induced by nicotinic acetylcholine receptors. Biophysical Society Annual Meeting, Los Angeles, CA. 2016.

Awards and Allocations:

- **2019 CCIB Best Paper Award (3rd Place)**
- **2019** The Rutgers Office of Advanced Research Computing Allocation; ~30000000 Service Units Allotted
- **2018 CCIB Best Poster Award (3rd Place)**

Technical skills

- **Programming Languages:** Proficient in: Python, TCL, Bash, git, and TeX.
- **Industry Software Skills:** GROMACS, VMD, Slurm, Spyder, MATLAB.

Bibliography

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Adibhatla, R. M., & Hatcher, J. F. 2007, Future lipidology, 2, 403

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