An Initial Study: Coarse Grained Molecular Dynamic Simulations of nAChR Within Model Native Membranes

Brannigan Lab Coarse Grained Research

nAChR and a Historical Perspective

- nAChR is functionally dependent on cholesterol
- Cholesterol tends to partition into domains rich in saturated lipids and sphingomyelin
    - These domains are highly ordered, rigid, high melting point
- nAchR has been historically described to partition into this ordered domain

nAChR and a Historical Perspective

Correlation between Acetylcholine Receptor Function and Structural Properties of Membranes†

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Anionic Lipid and Cholesterol Interactions with α4β2 nAChR: Insights from MD Simulations

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Transbilayer asymmetry and sphingomyelin composition modulate the preferential membrane partitioning of the nicotinic acetylcholine receptor in lo domains

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nAChR and a Historical Perspective

- These experiments tend to take place in model membranes or oocytes
- Native membranes are not often used

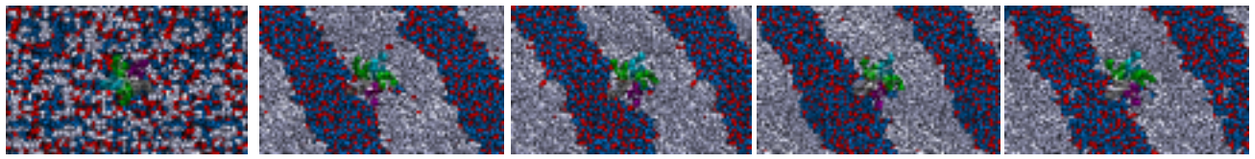
Membrane Comparisons

Saturation/Head Group	*Torpedo*	*Synapse*	*Xenopus Oocyte*	*Mammal*
n-0	59	52	46	53
n-9	14	15	22	20
n-7	< 1	< 1	14	13
PUFA	28	33	17	14
— n-3	— 19	— 18	— 6	— 4
— n-6	— 9	— 15	— 11	— 10
PC	43	43	36	27
PE	32	36	22	16
PS	13	12	5	5
SM	8	4	26	14
PI	4	3	7	2
PA	< 1	0	0	1
Other	6	2	4	5
Chol Mol Frac	32	39	21	30

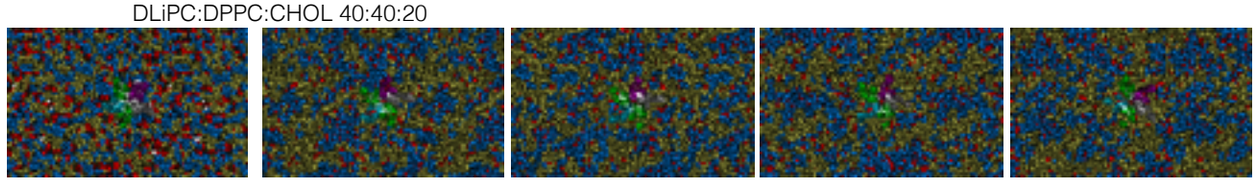
Fig1

These will be movies! They are in the works

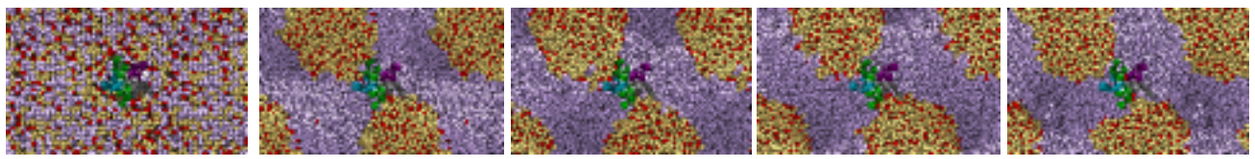
DHA-PE:DPPC:CHOL 40:40:20



DLiPC:DPPC:CHOL 40:40:20



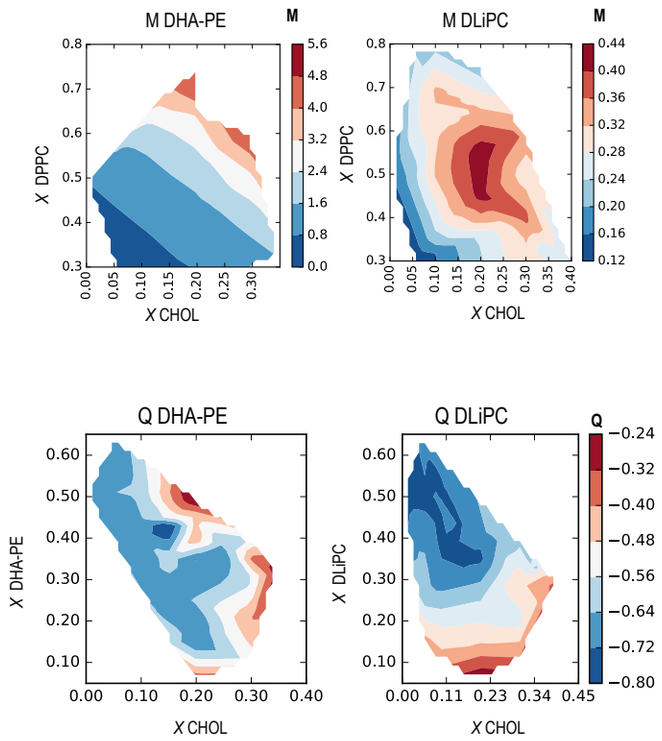
DHA-PC:DPPE:CHOL 40:40:20



nAChR does not influence the formation of domains, it may influence the geometry of domains.

nAChR does not seem to have a preference zwiterionic head groups, it seems to prefer PUFAs.

Fig2

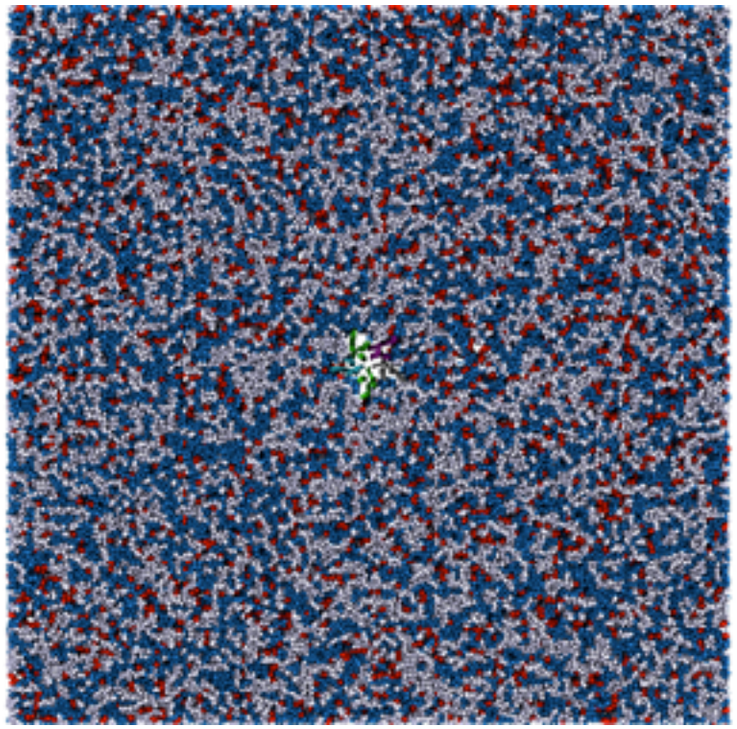


Top: Concentration space of ternary membranes. Systems including DHA-PE show significant demixing (blue) when lipids which for lo phases are absent, but tend to mix when membranes are enriched with lo lipids. DLiPC remains mixed-like. DLiPC prefers to remain near like lipids, but easily interacts with DPPC and cholesterol. There is a mixing sweet spot ~ DPPC:DLiPC:CHOL 50:20:30.

Bottom: Boundary lipid DPPC. Q represents 1: boundary domain is enriched, 0: boundary domain is mixed, -1: boundary domain is depleted. DHA-PE shows complex mixing. DPPC is not found as a linear gradient this is most likely due to the applied box sizes and stringent domain formation. DLiPC has a less defined domain; while nAChR tends to be surrounded by DLiPC, both DPPC and cholesterol can come and go. It becomes easier for lo lipids to surround nAChR at lower concentrations of DLiPC

Fig2

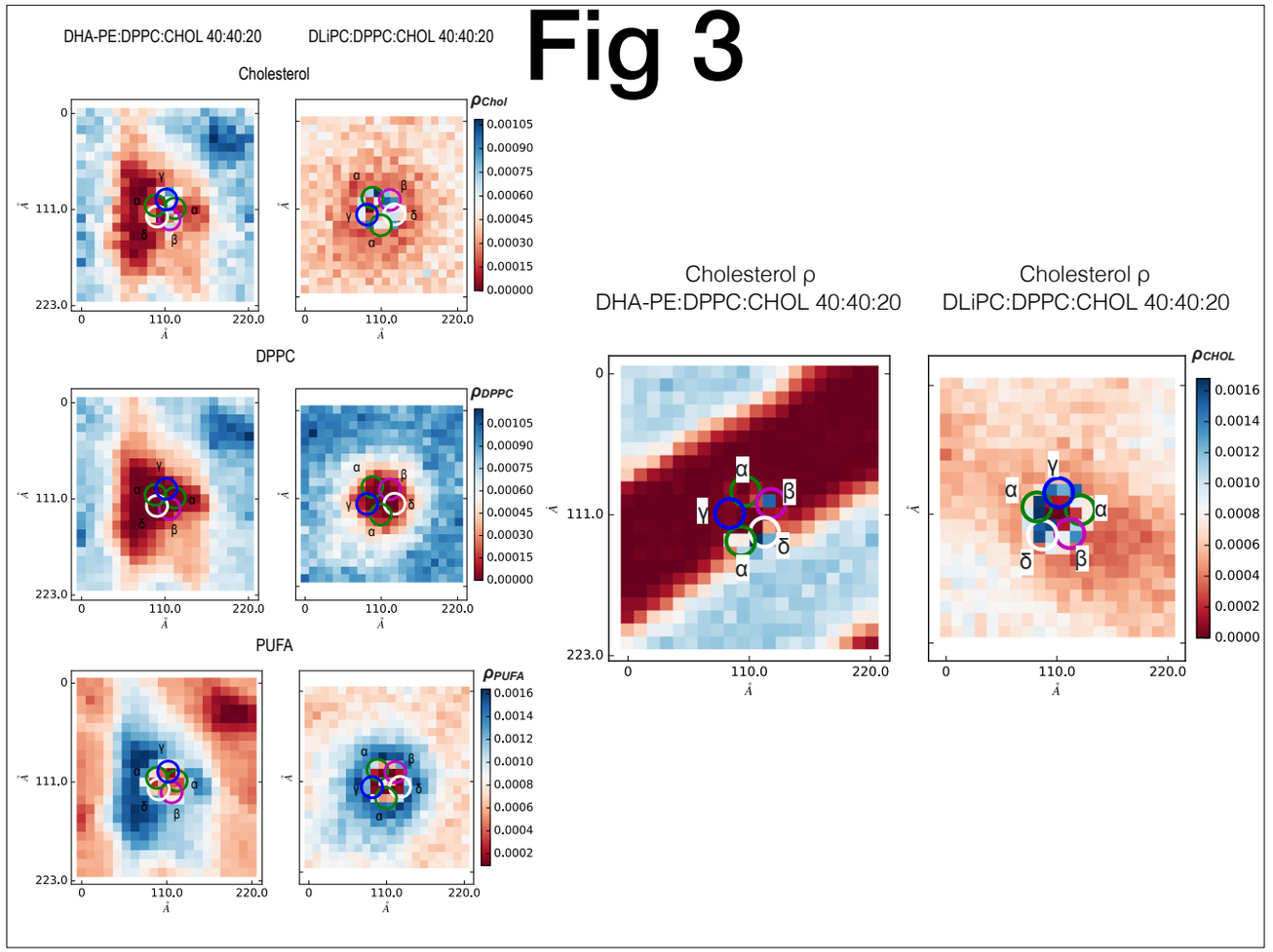
DHA-PE:DPPC:CHOL 40:40:20



What where nAChR sits

We should see it remain in the ld, but bounce between the lo’s. To me, it looks like it consistently tries to point the alpha subunits to be near the lo.

Fig 3



left: We can more clearly visualize lipid-subunit preference using the above heat map. Analyzing the average distribution of specific lipid species of replicated systems, there is a clear trend. nAChR surrounds itself with a PUFA. It does not like being near DPPC, but, it will allows cholesterol to be near by

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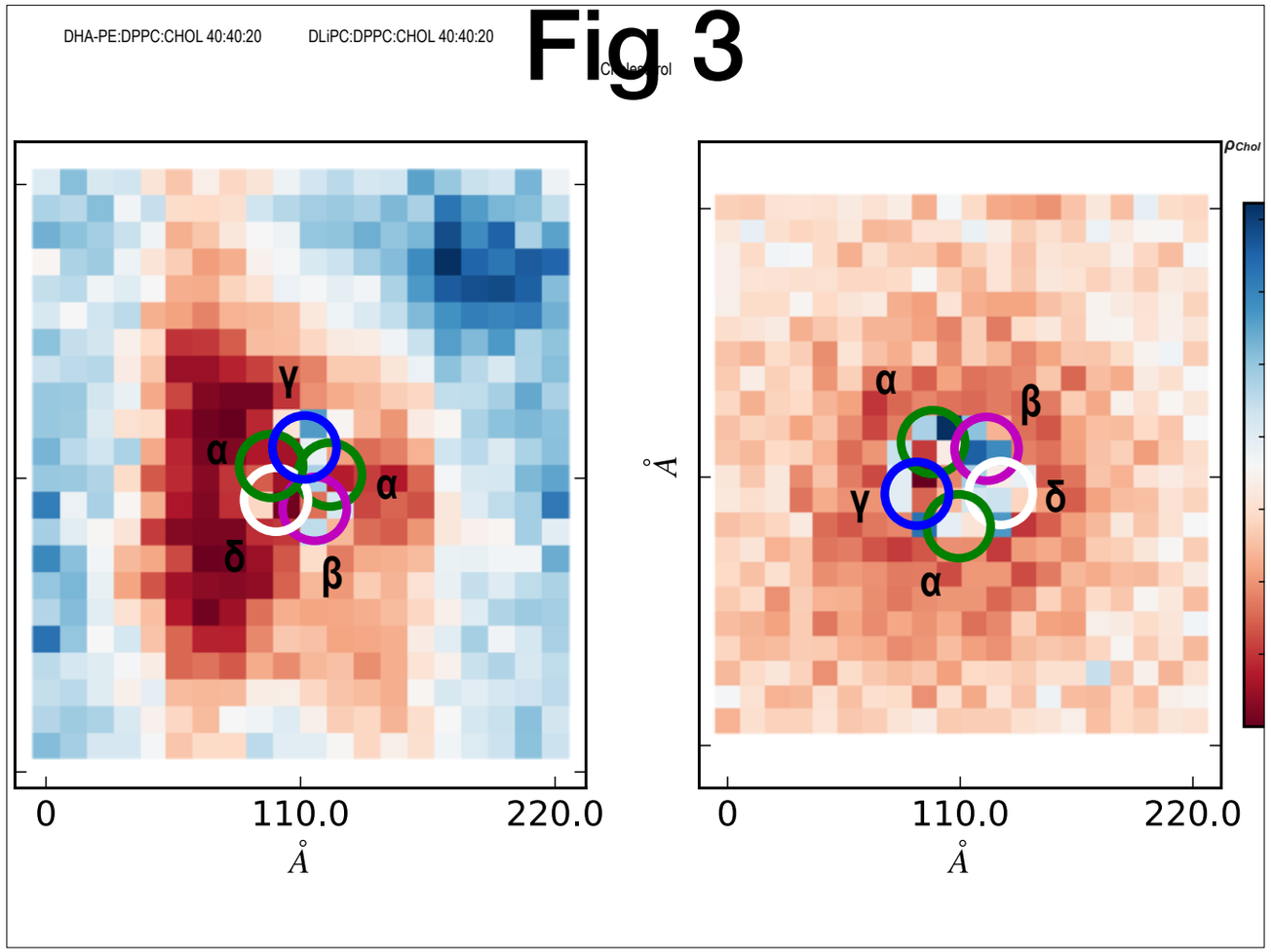

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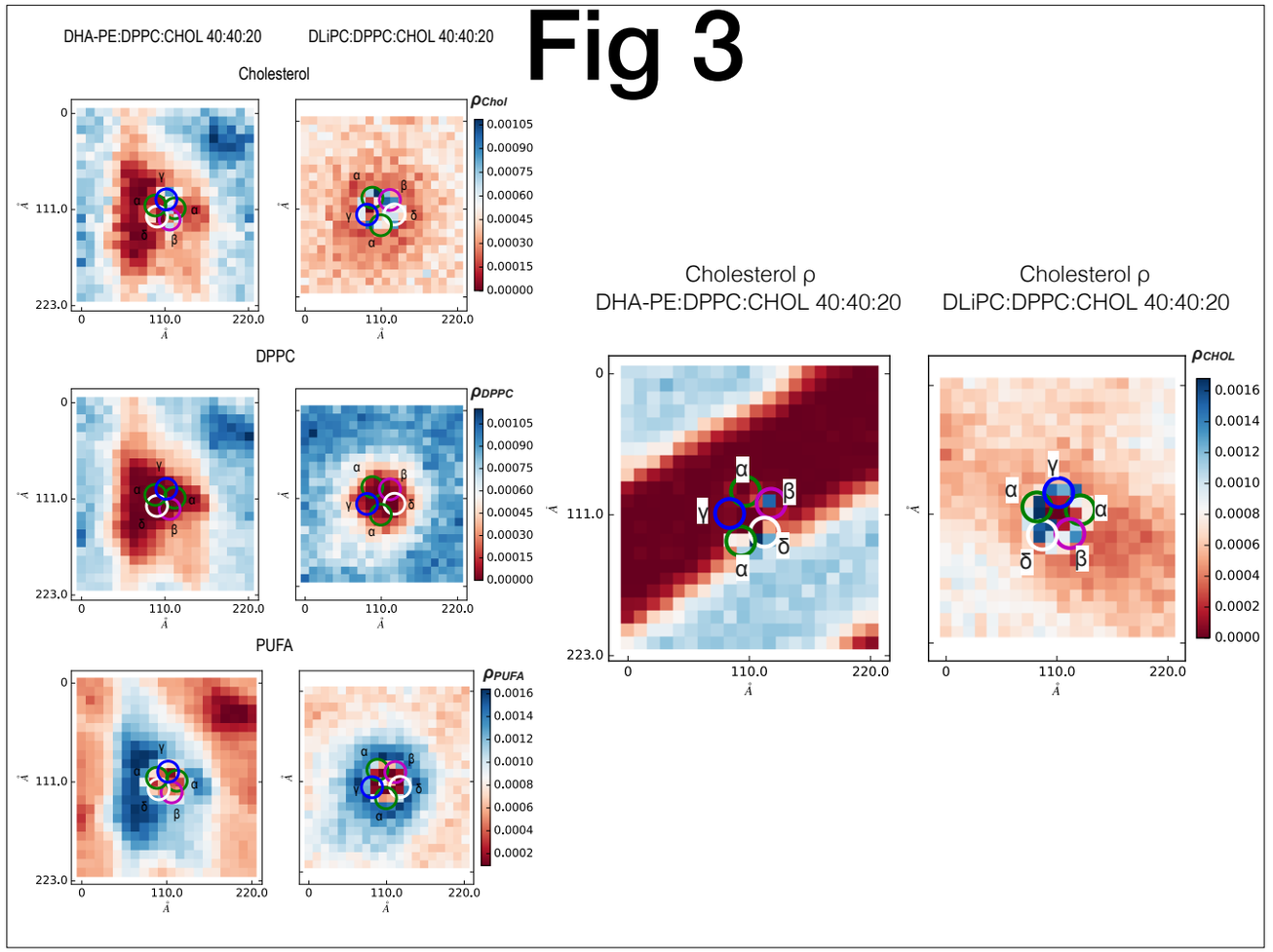

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right: More so, cholesterol can be seen embedding within subunits! This is observed for PUFAs too, though cholesterol's small size does make it easy.

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Segregation of lipids near acetylcholine-receptor channels imaged by cryo-EM

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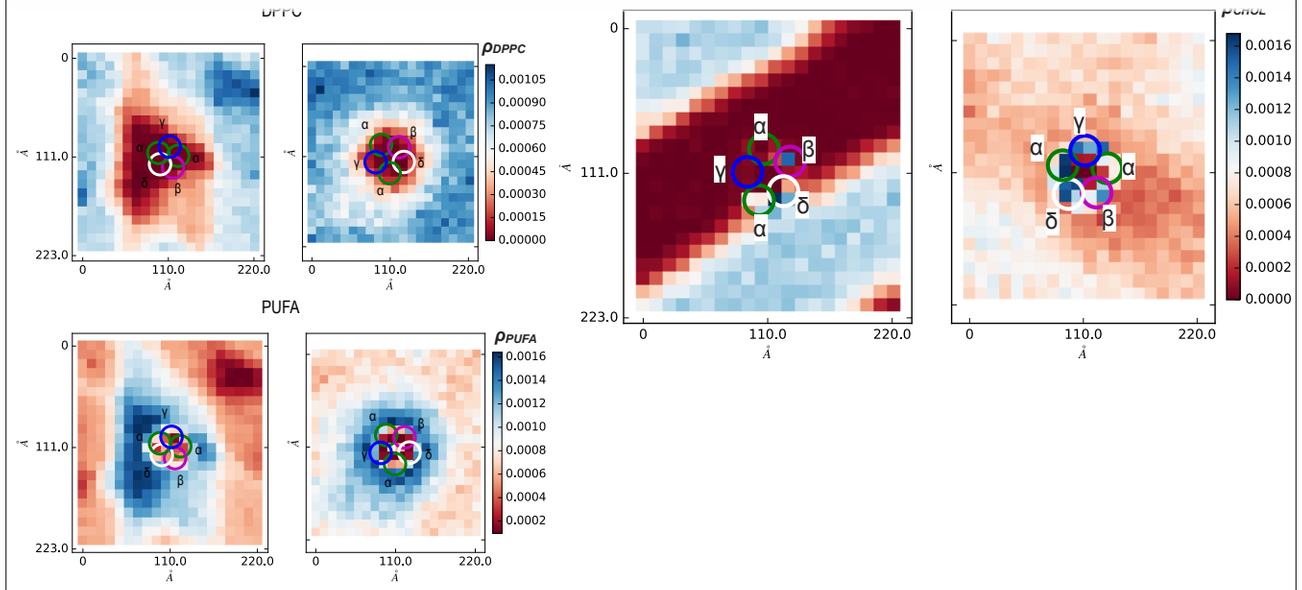

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Embedded Lipids
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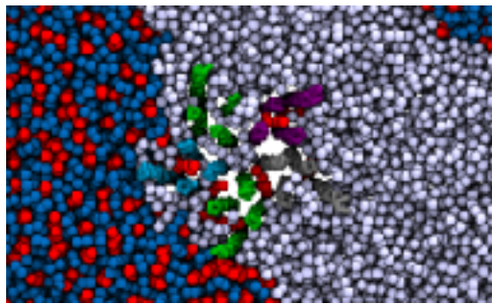
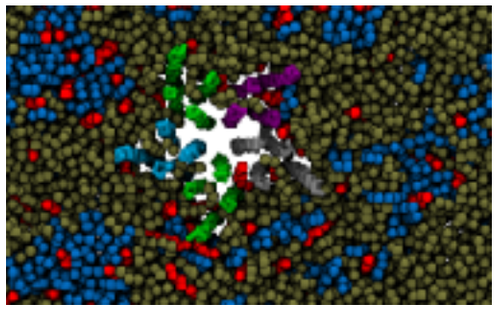


Embedded Lipids
DLiPC:DPPC:CHOL 40:40:20



Embedded Lipids: Cholesterol is a prime candidate, but so are highly unsaturated lipids. DHA is observed having both acyl chains and head groups embed as deep as the pore. Binding as deep as the pore may be an issue. DLiPC, while binding is not as intensive, is still seen to embed between subunits.

Conclusion

- Still much work to do
- nAChR appears to like the cholesterol depleted domains
- nAChR has the potential for lipid embedding
- Domains form with or without nAChR
- Potential something to help anger experimentalists

Future Project

- Comparative simulations of native nAChR membranes and Oocytes