

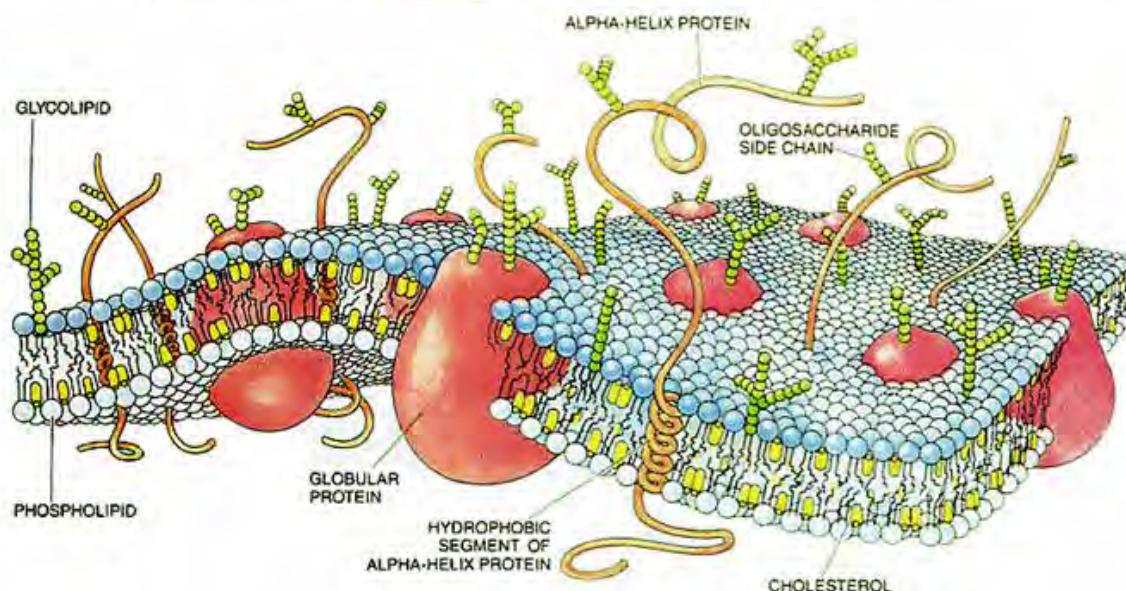
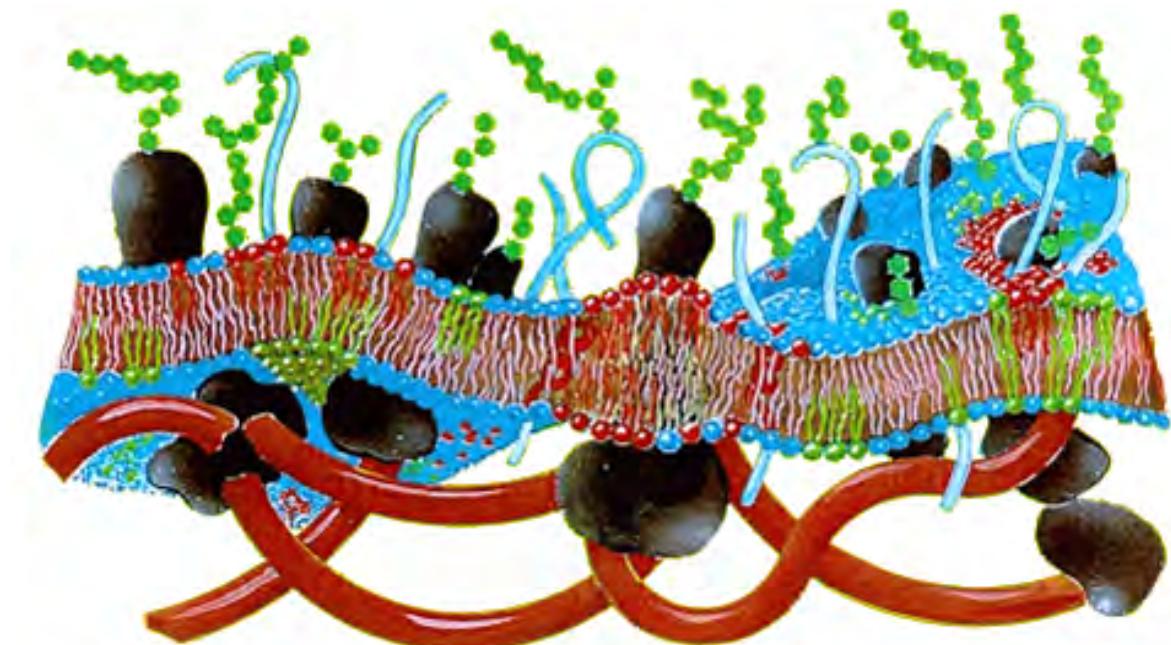
Increasing complexity in membrane simulations



Peter Tielemans

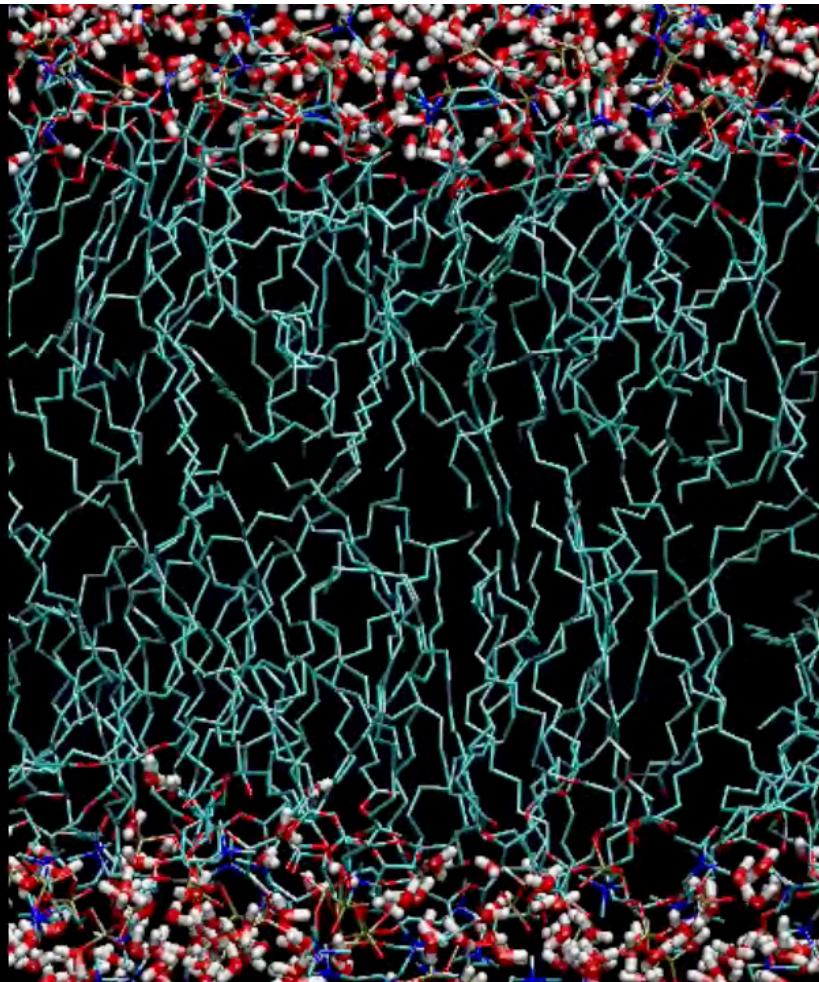
University of Calgary, Centre for Molecular Simulation
<http://science.ucalgary.ca/molsim>

Cell envelopes / plasma membranes



- Hundreds of different lipid species
- Asymmetric leaflet composition
- Lateral inhomogeneity
- Complex (non-equilibrium?) dynamics

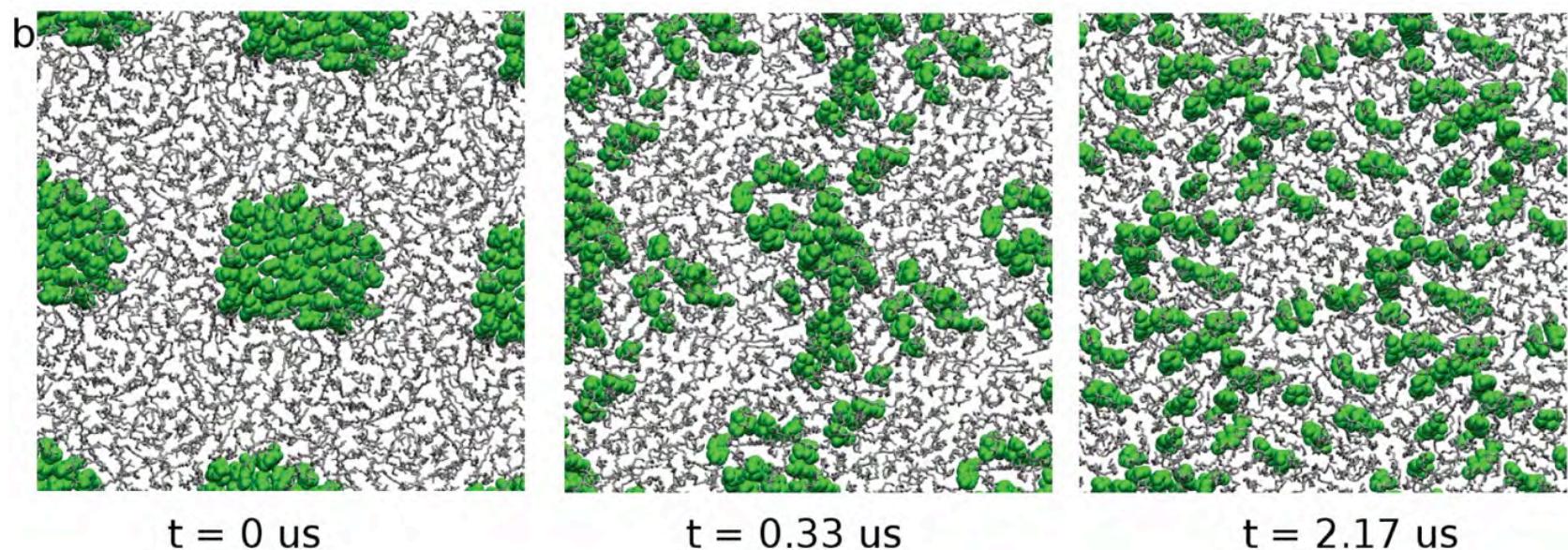
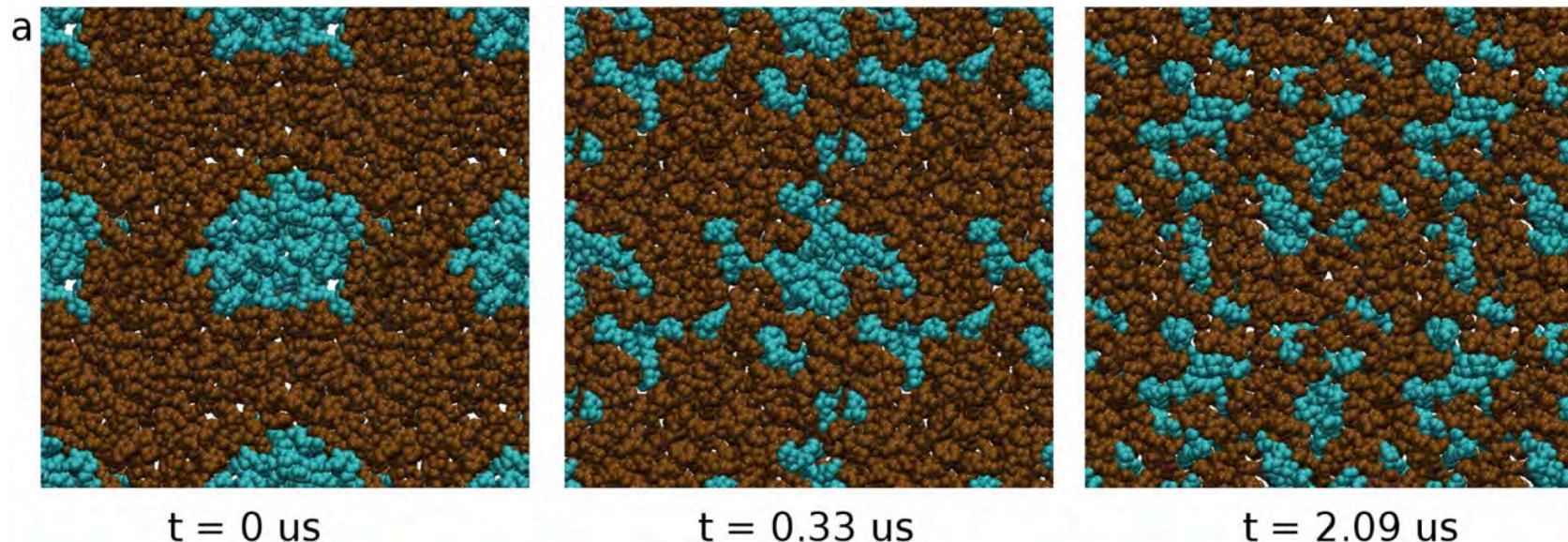
Molecular dynamics of one component



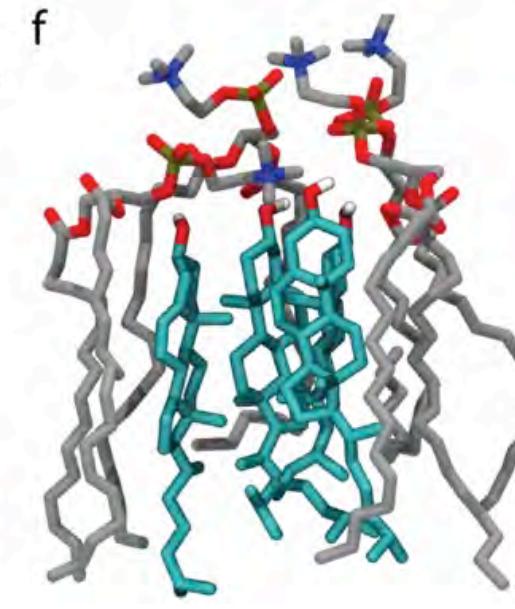
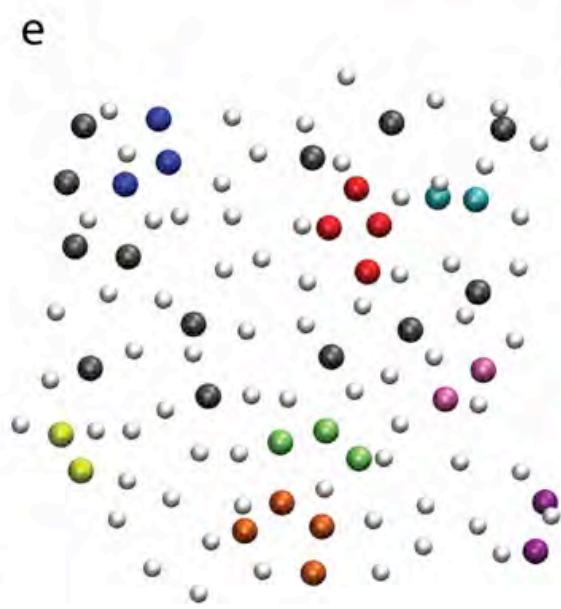
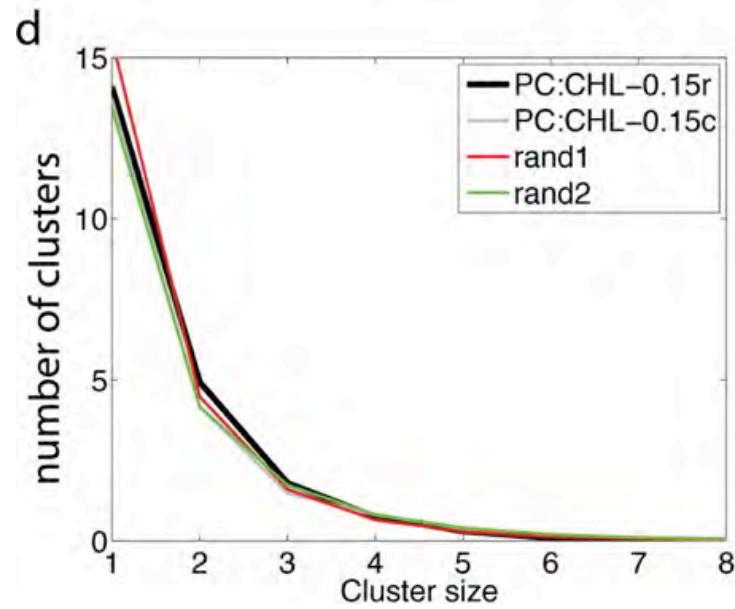
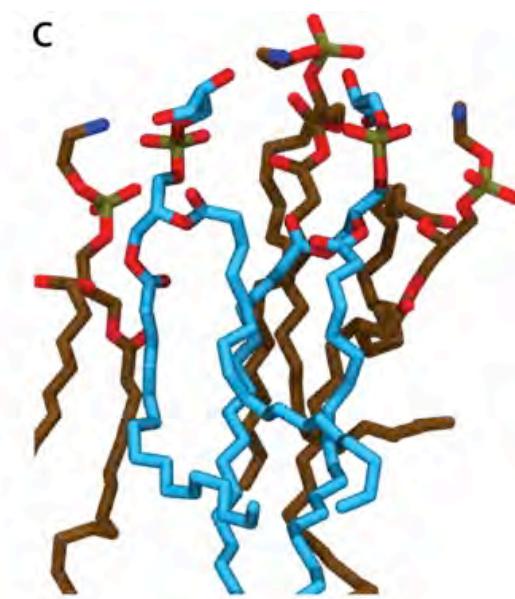
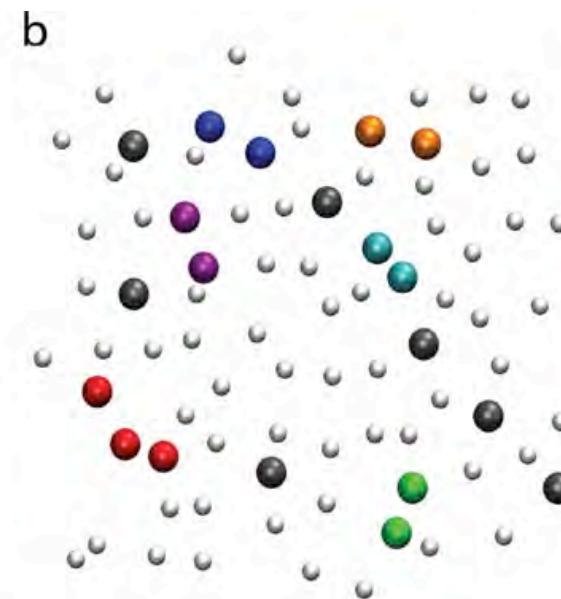
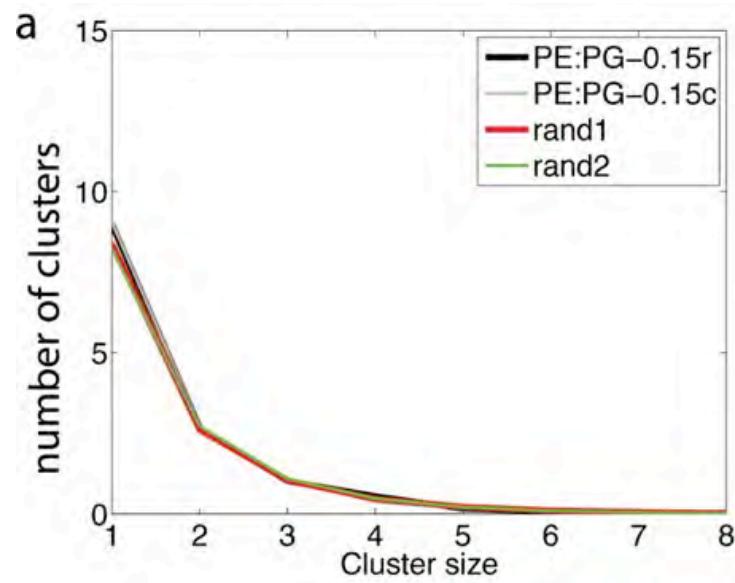
$$V(\mathbf{r}^N) = \sum_{bonds} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2} (\theta_i - \theta_{i,0})^2 + \sum_{torsions} \frac{V_n}{2} (1 + \cos(n\omega - \gamma)) + \\ \sum_{i=1}^N \sum_{j=i+1}^N \left(4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right) + \dots$$

- **Describe the forces on all atoms.**
 - Bonded (bonds, angles, dihedrals).
 - Non-bonded (van der Waals, electrostatic).
- **Describe the initial atom positions and momenta**
- **Integrate equations of motions**
- **Result:** the positions of all atoms during μs . In principle, all properties that depend on position, velocities and forces on atoms can be calculated
- **Movie: 100 ps lipid dynamics**

Two-component mixtures: POPG/POPE and POPC/cholesterol



Cluster size distribution: random



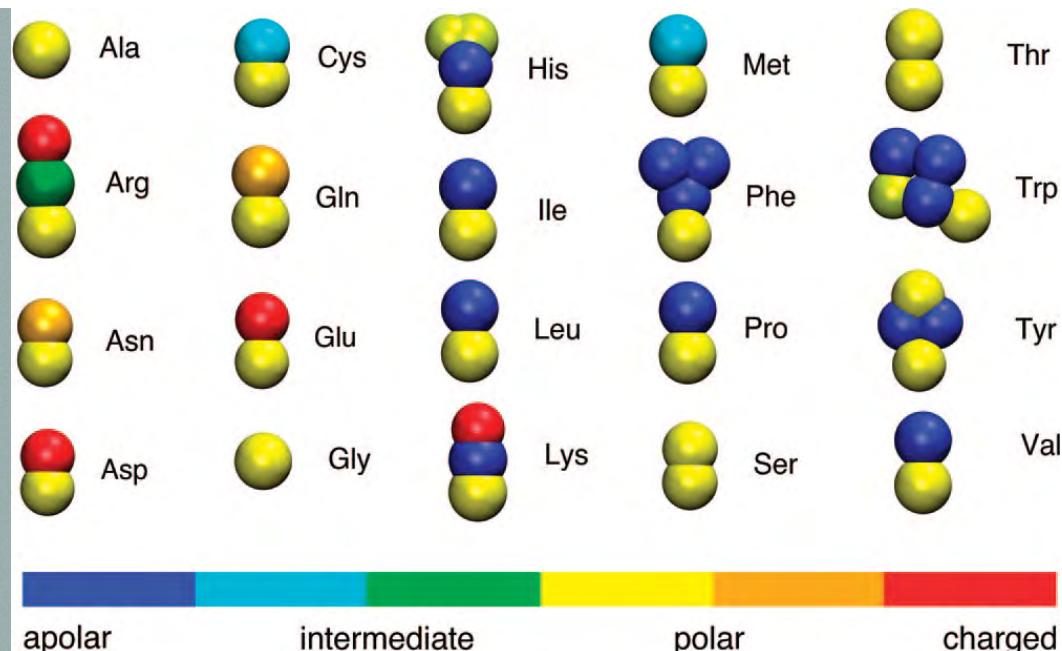
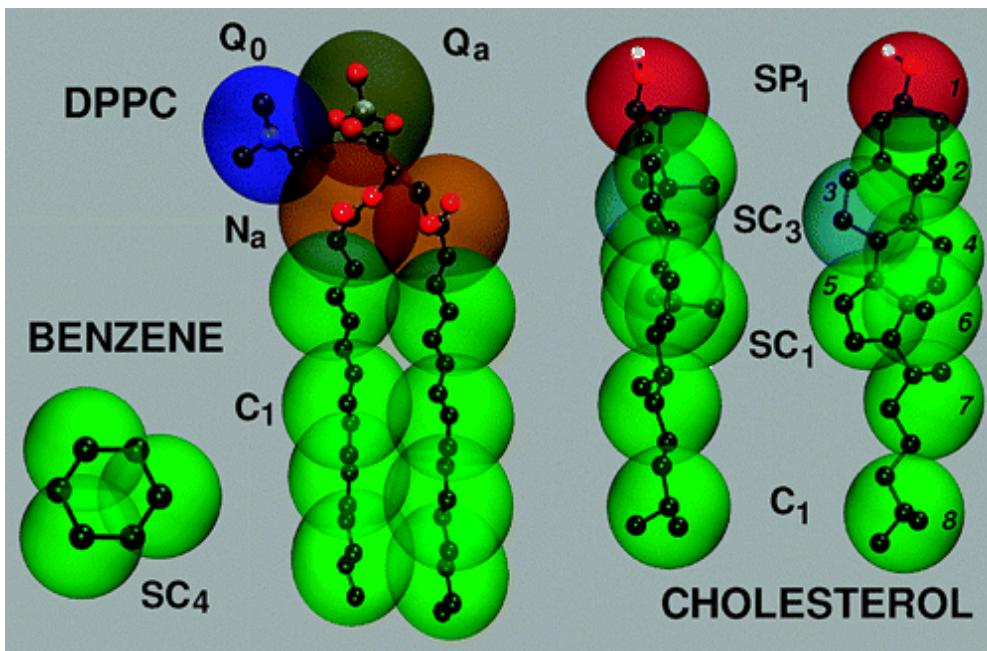
Coarse-grained (CG) simulations

Martini force field

(Marrink *et al.*, 2004, 2007;
Ingolfsson 2014)

Extended to proteins

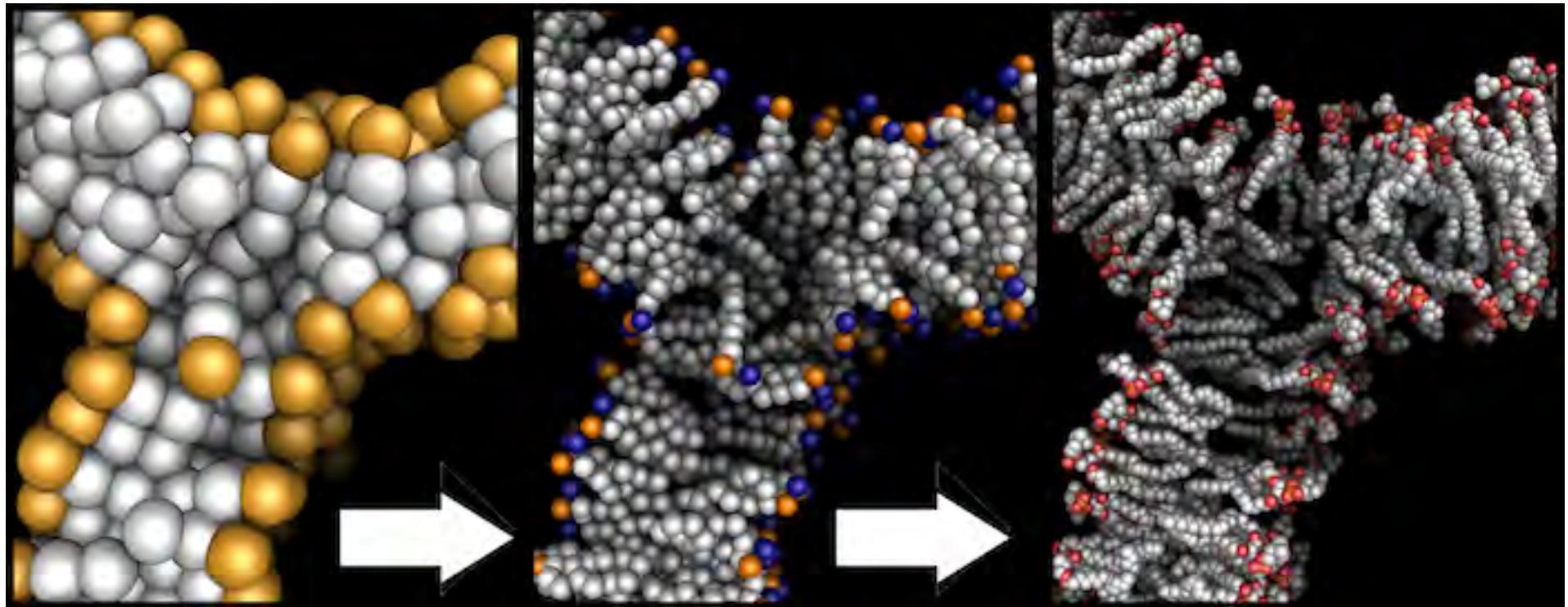
(Monticelli *et al.*, JCTC, 2008; De Jong *et al*, 2013;
Marrink and Tieleman, Chem. Soc. Rev. 2013)



- ca. 2-3 orders of magnitude faster than atomistic simulations
- loss of chemical specificity, detailed interactions, other stuff
- ca. 4 heavy atoms map to 1 bead
- MD potential with electrostatics shift function, dielectric constant of 15 (no long-range interactions, normally)
- Parameters for most biomolecules, polymers, surfactants

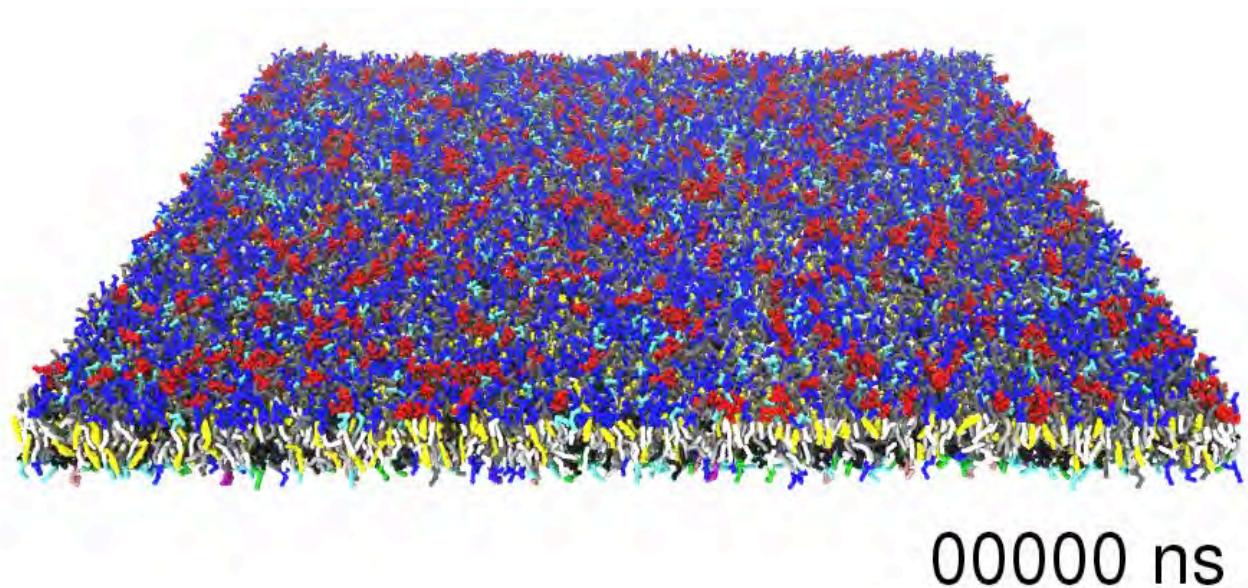
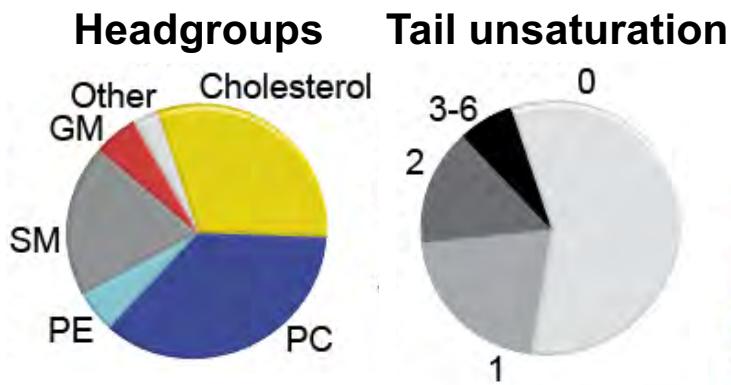
Backmapping: linking Martini and atomistic

- MARTINI strengths: sampling, ease of creating complex systems
- Atomistic strengths: accuracy, detail
- How can we combine these strengths?

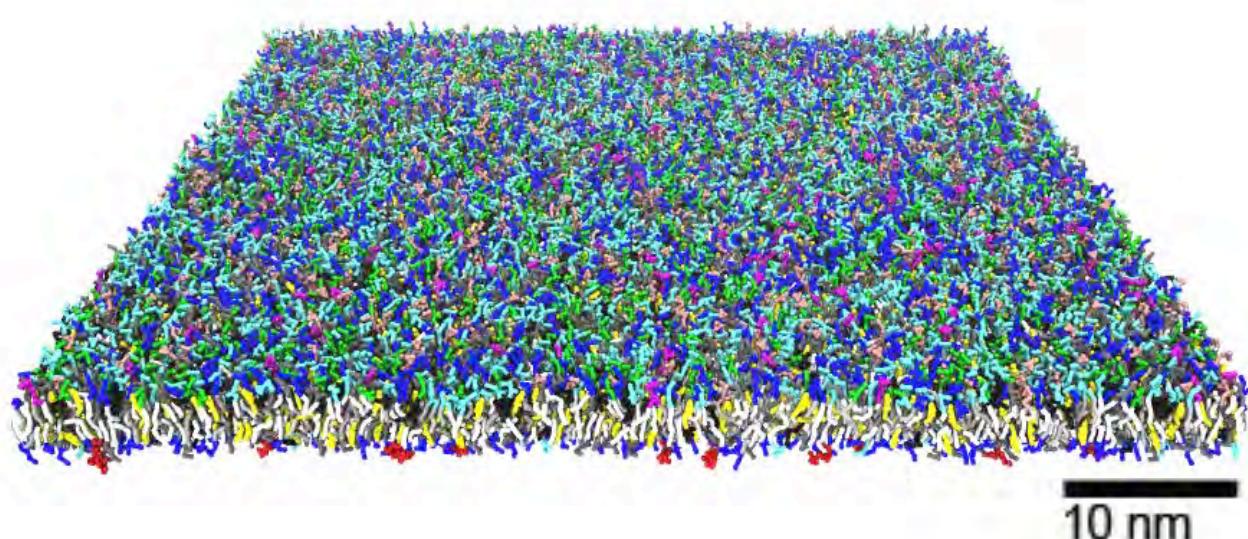
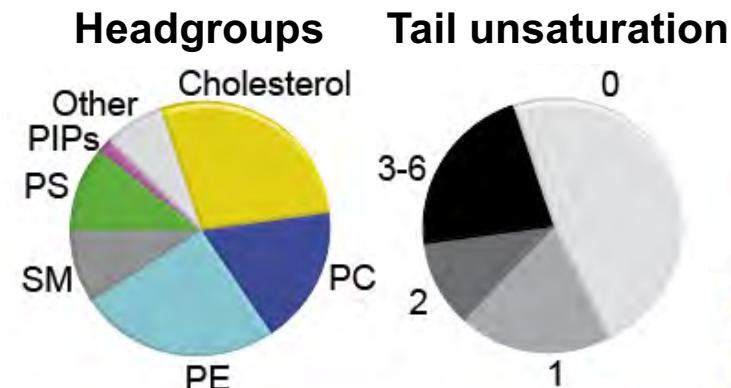


Idealized plasma membrane

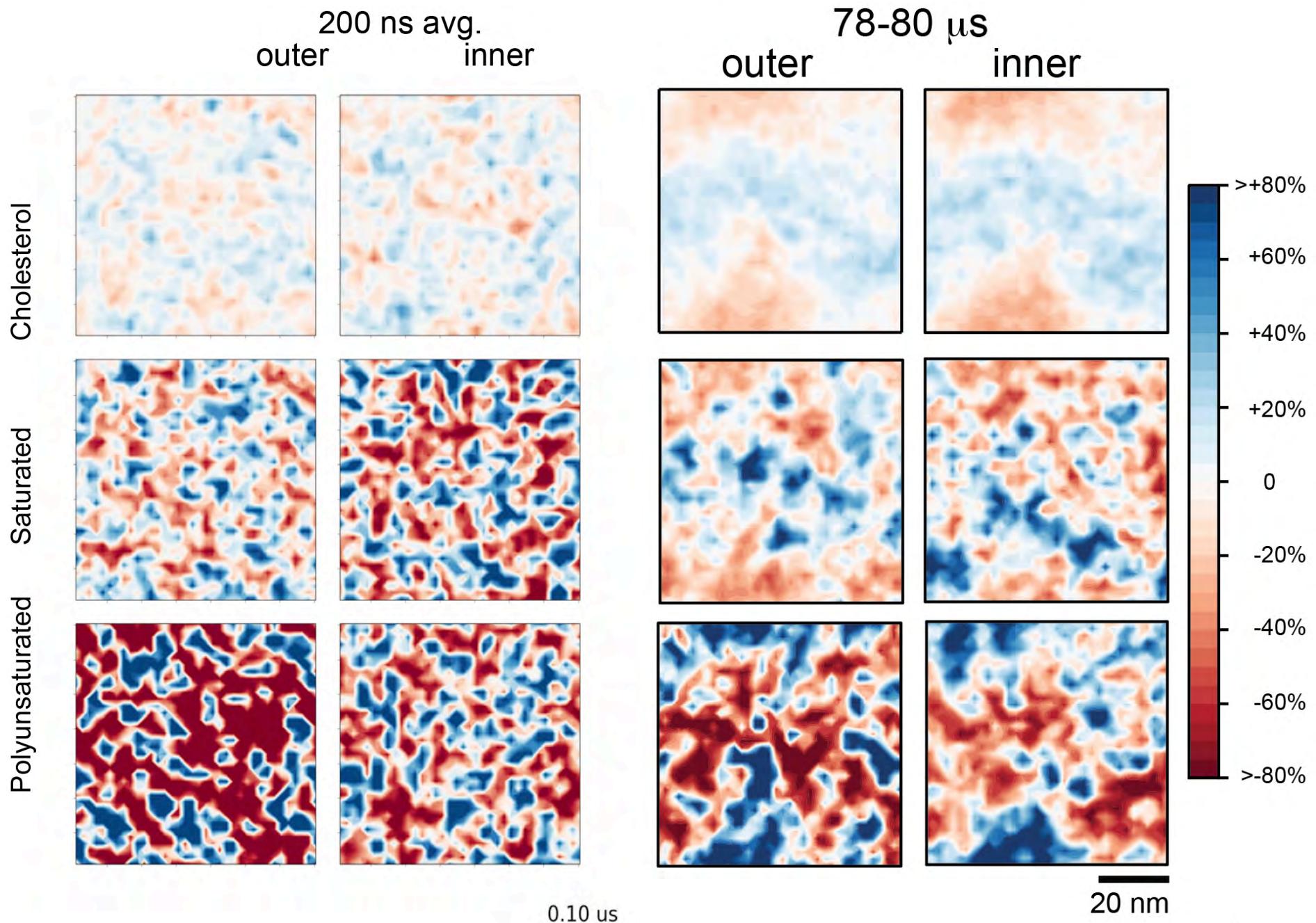
Outer leaflet:



Inner leaflet:

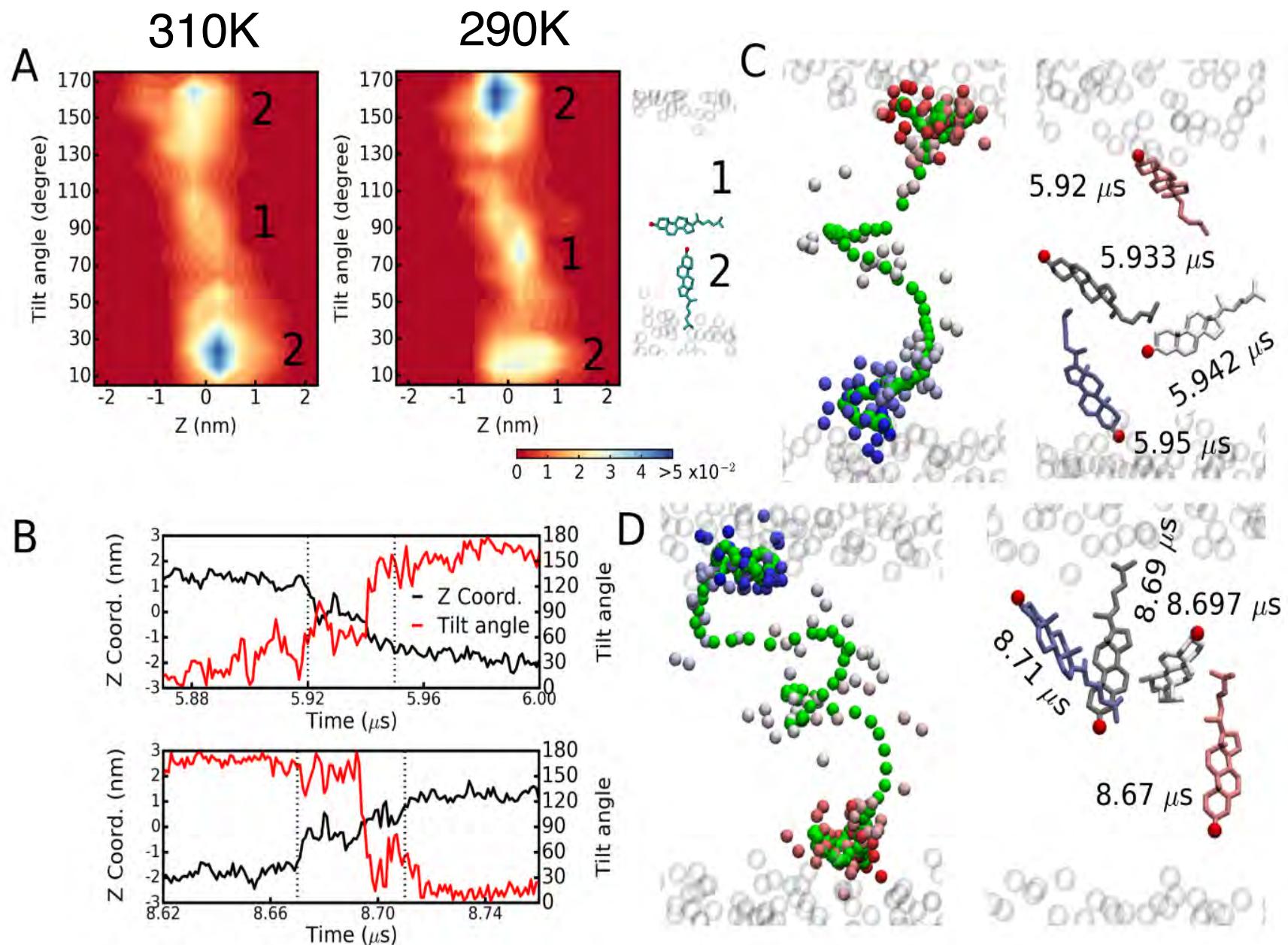


Plasma membrane – domains?

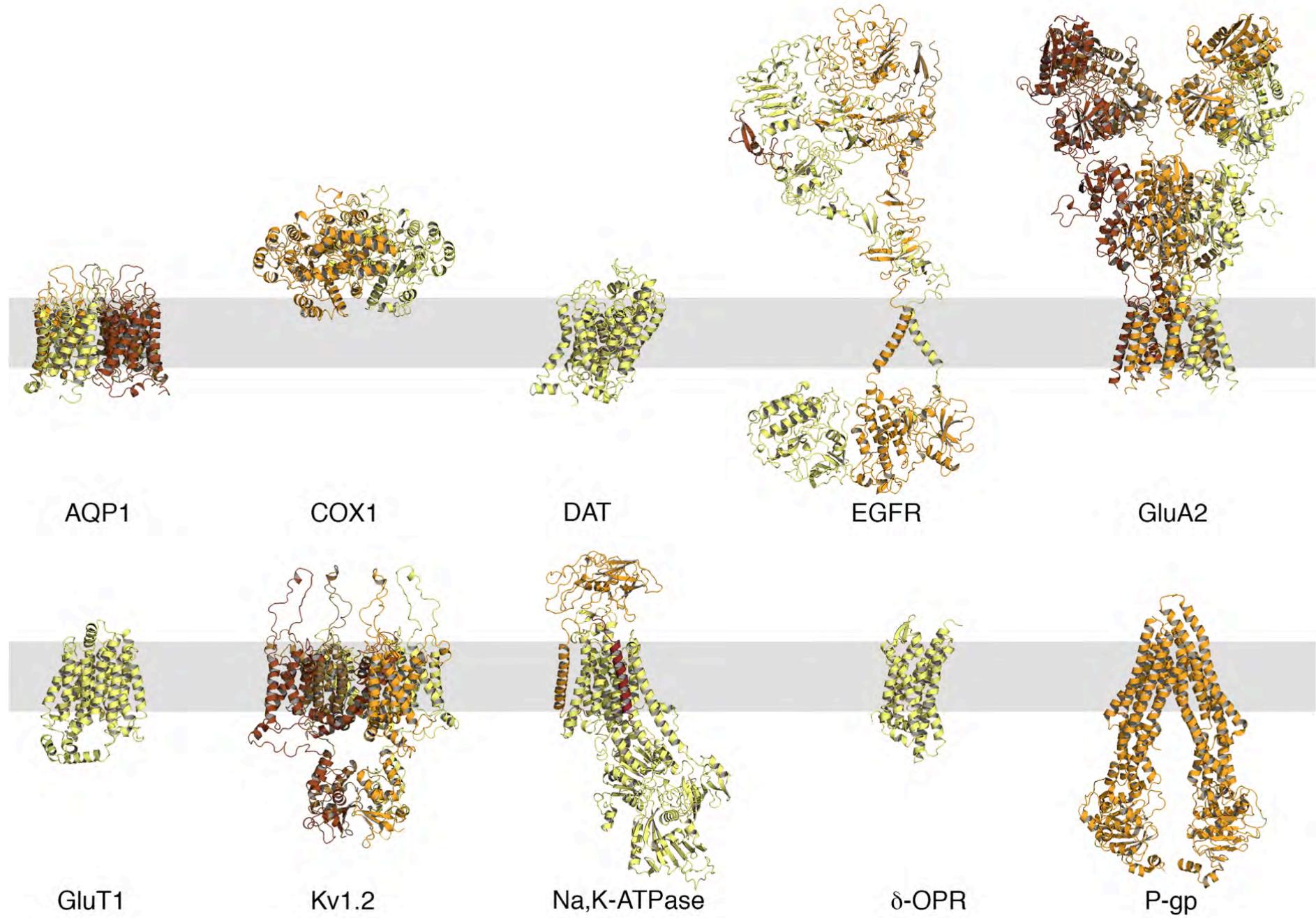


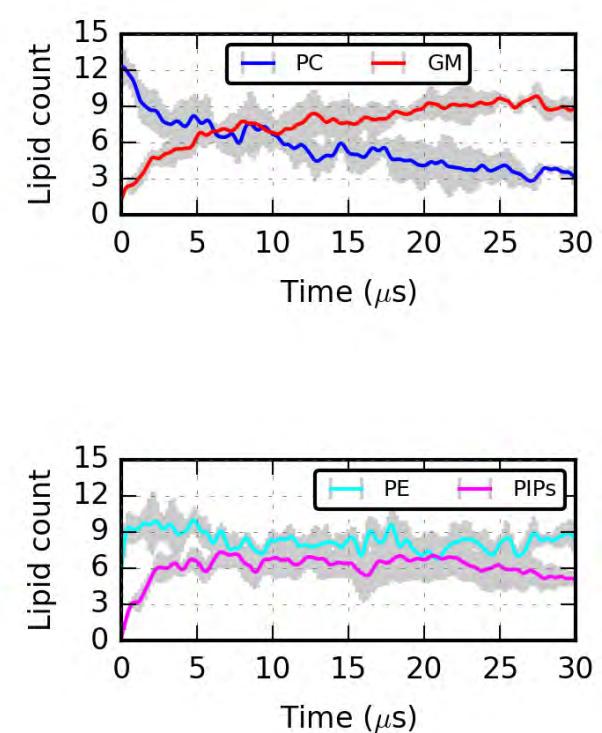
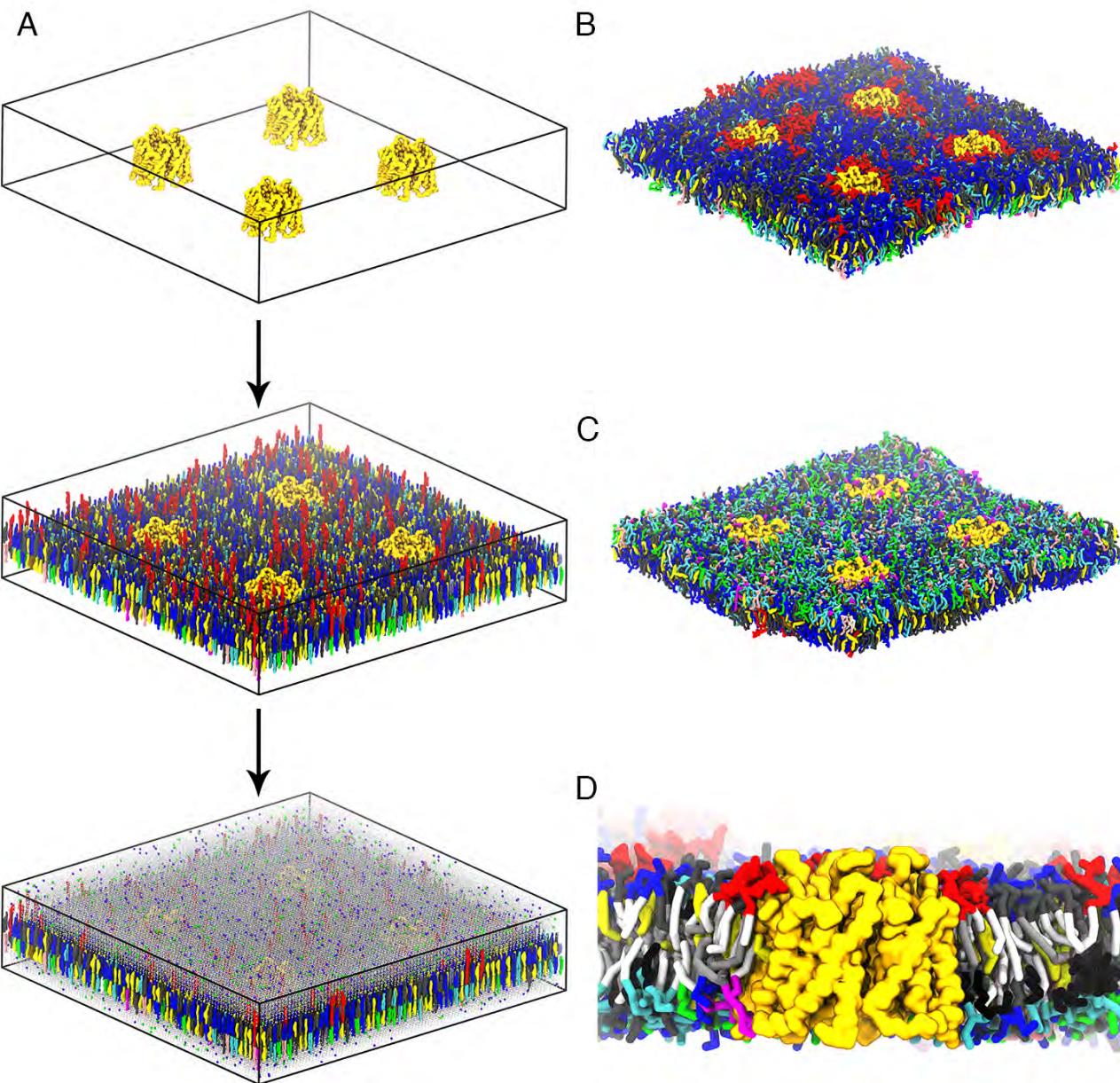
- Lateral structure depends on averaging time
- Almost all structure disappears averaging over microseconds
- No evidence for rafts or persistent domains
- Gangliosides and PIP lipids form small clusters (not shown)
- Cholesterol redistributes, with the majority in the outer leaflet of the plasma membrane, on sub-millisecond time scales (open question)

Cholesterol flip-flop atomistically

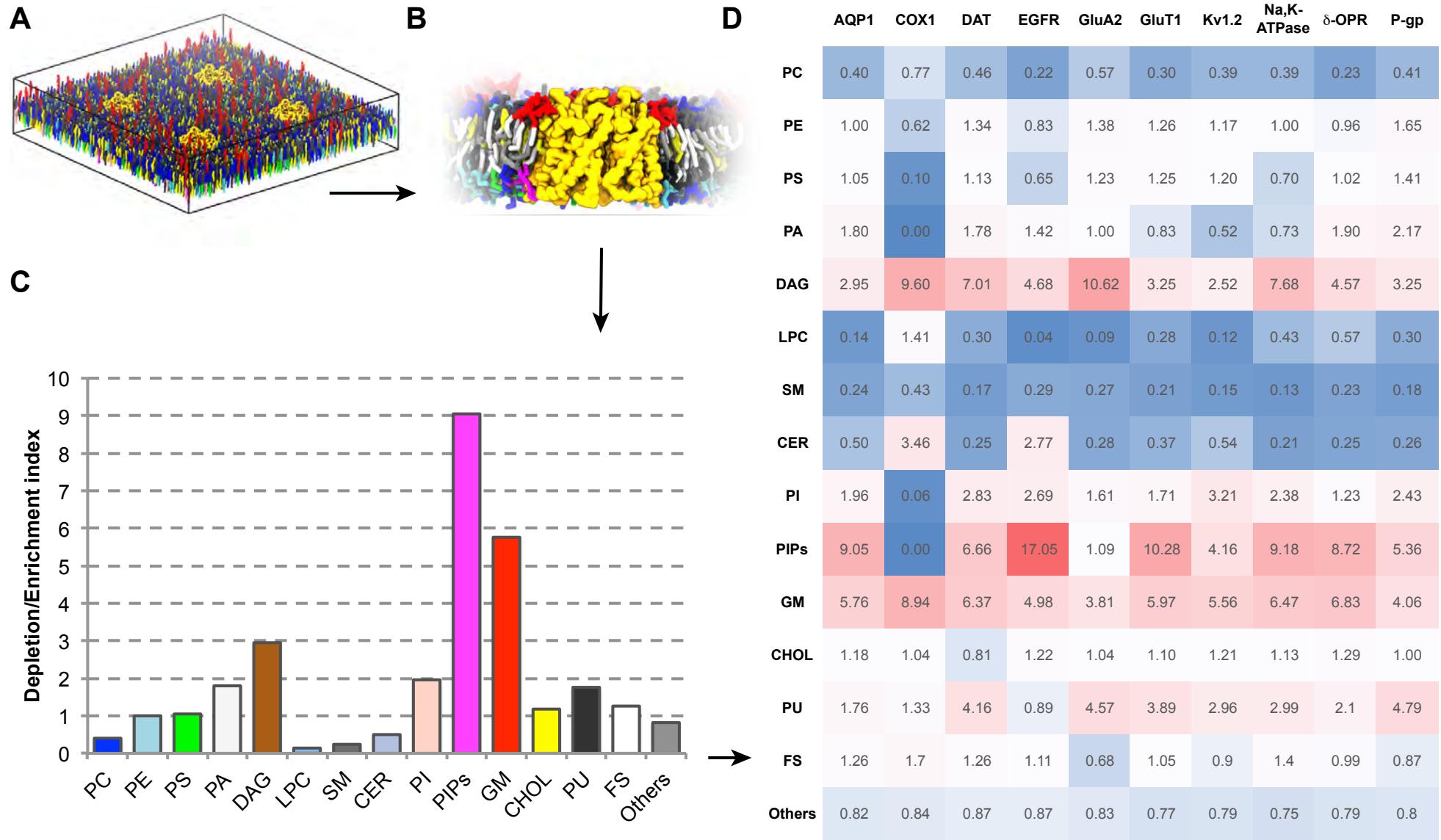


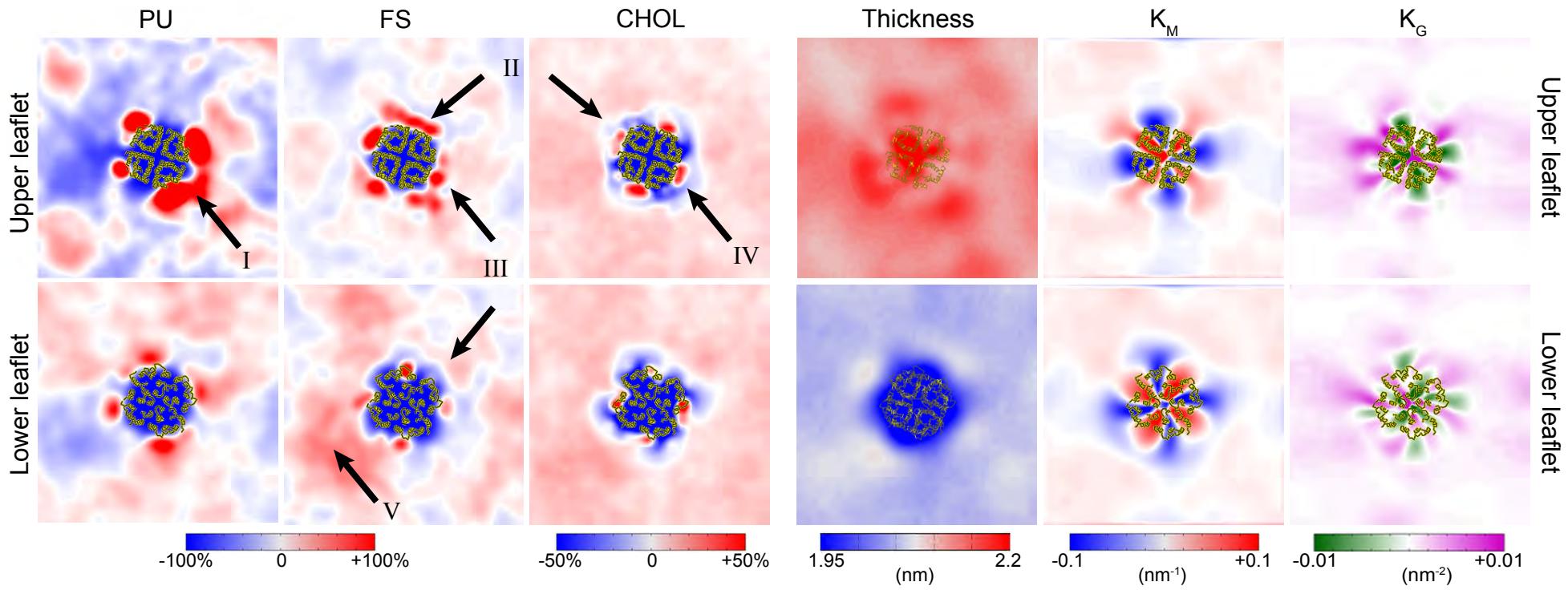
Next: lipid-protein interactions



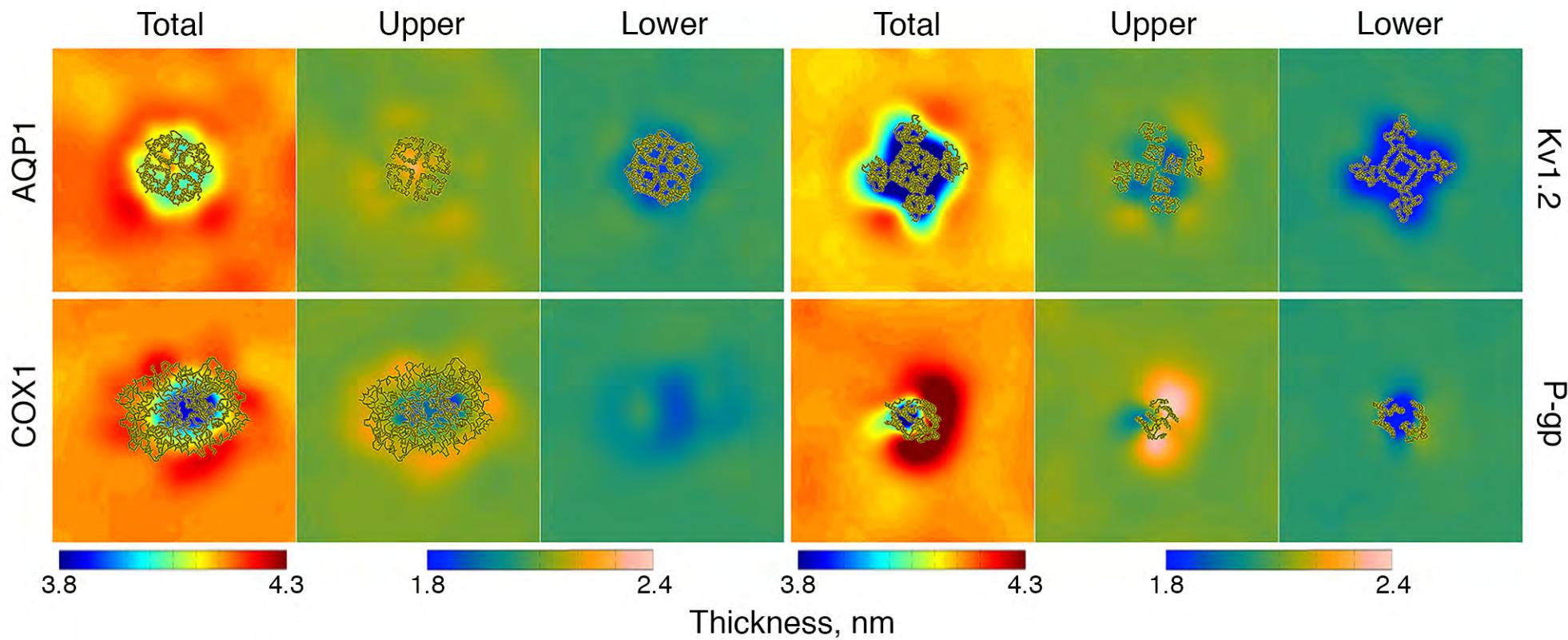


Lipid class	Distance cut-off (nm)		
	0.7	1.4	2.1
PU	1.8±0.6	1.5±0.5	1.4±0.4
FS	1.3±0.2	1.3±0.1	1.2±0.1
CHOL	1.2±0.0	1.1±0.0	1.0±0.0
Others	0.8±0.0	0.9±0.0	0.9±0.0



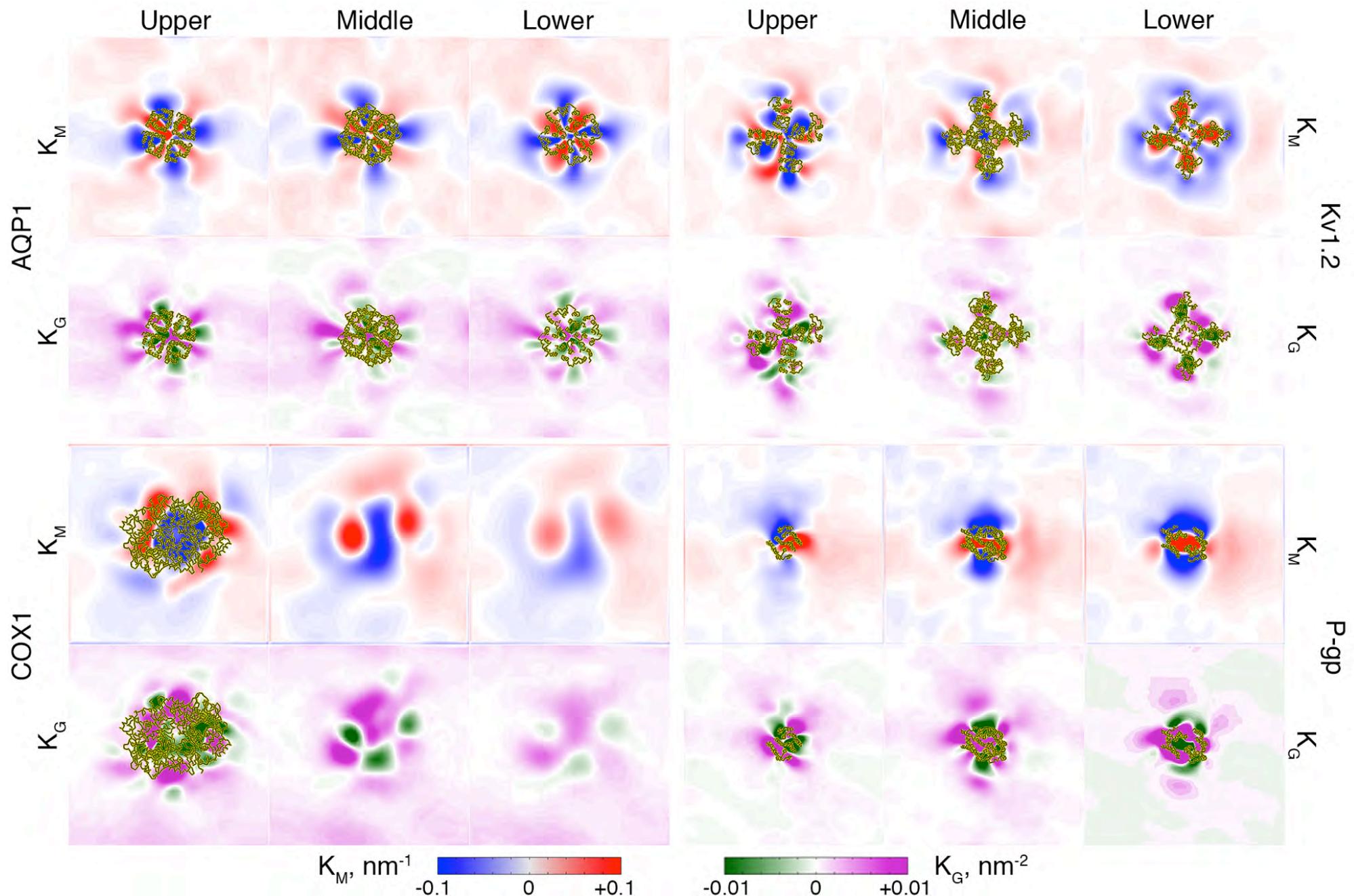


Membrane thickness

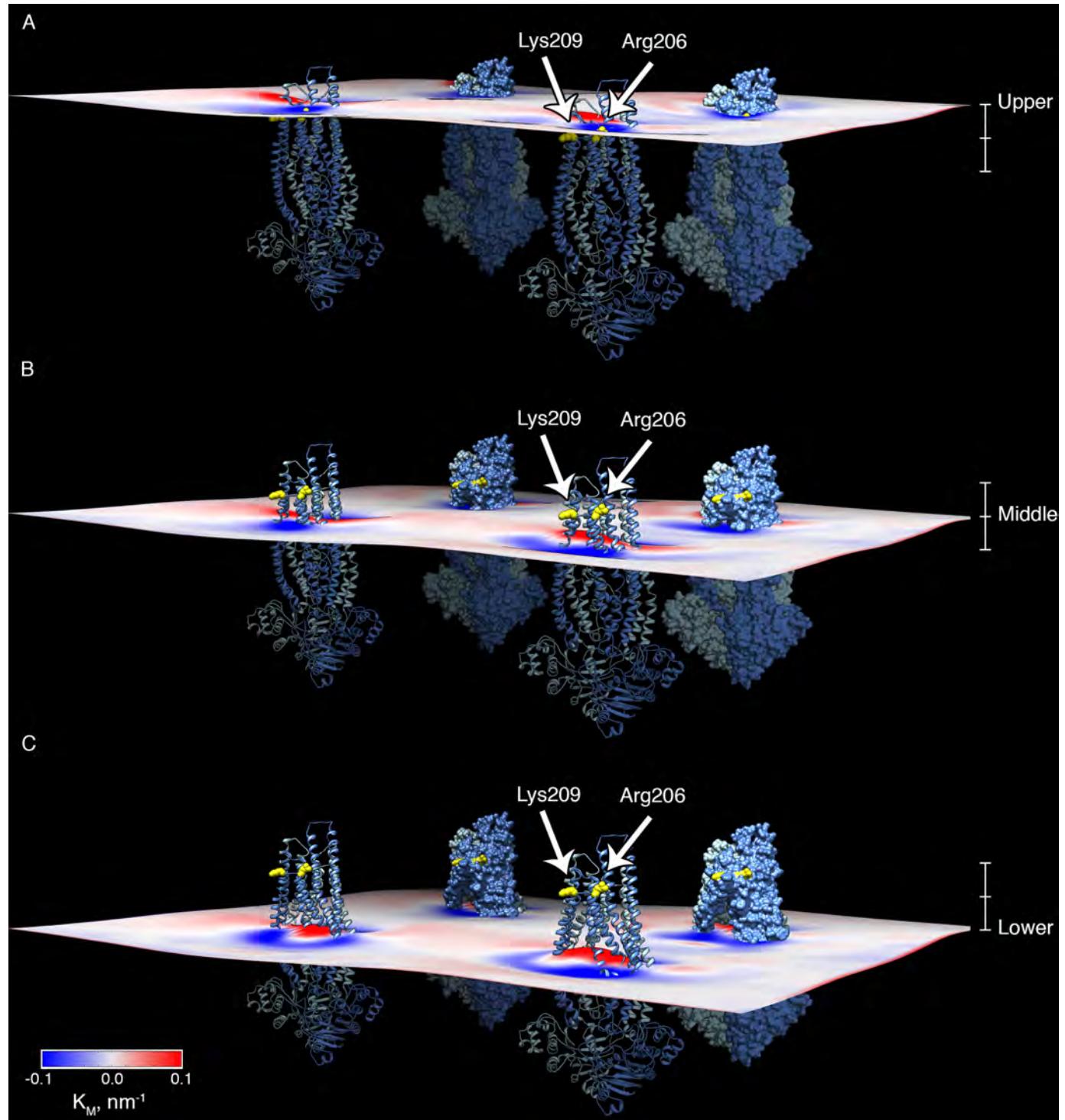


- Reflects the symmetry of the proteins
- Several Å deformation
- Some proteins more than others
- Leaflets affected differently
- COX1 is peripheral, but affects opposing leaflet too

Mean and Gaussian curvatures



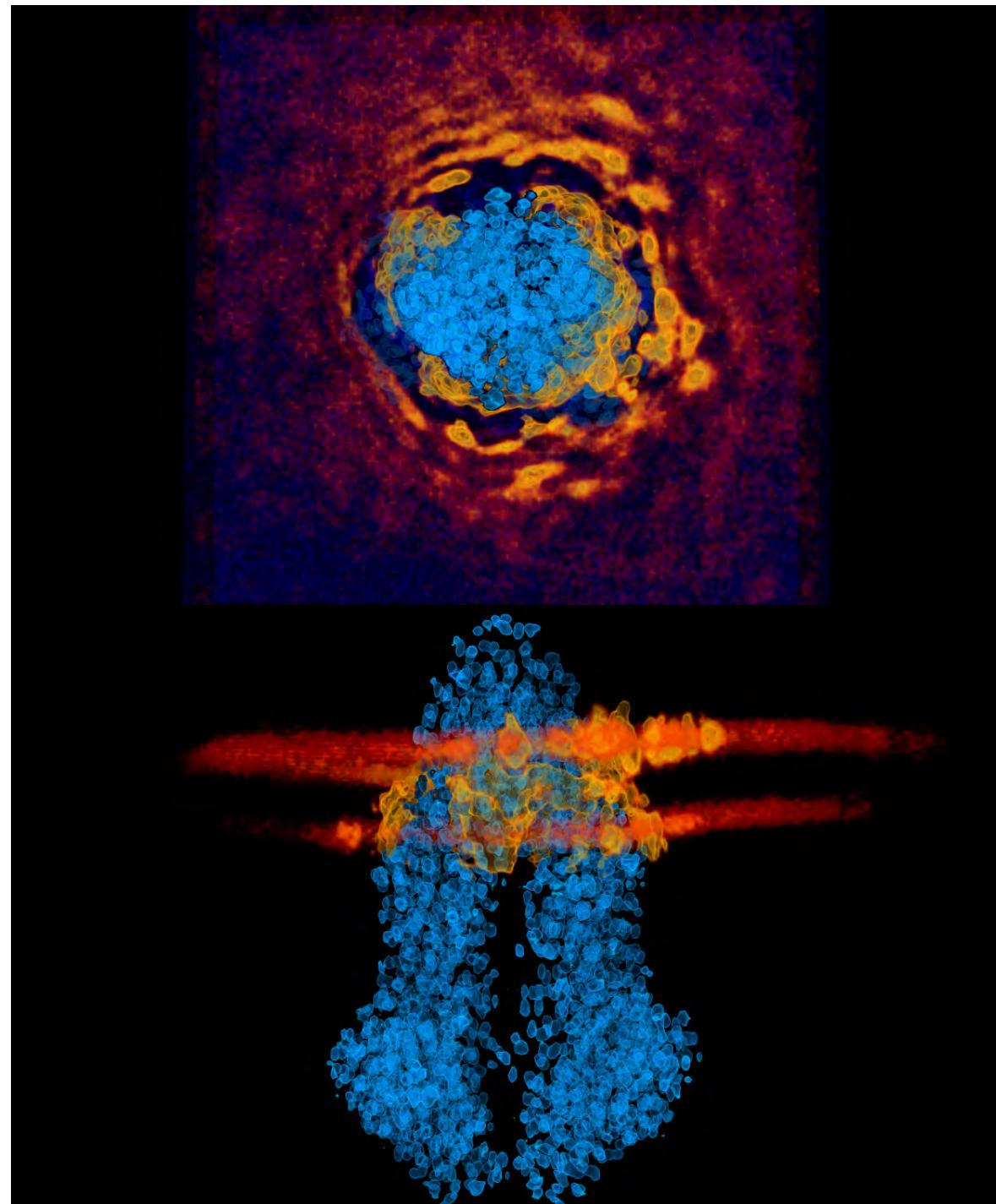
P-gp



Cholesterol in mouse P-glycoprotein

Avg. cholesterol
number density:
Blue = avg -1std
Red = avg +1std
Yellow = avg = 2std

Cyan = protein density



POPE in mouse P-glycoprotein

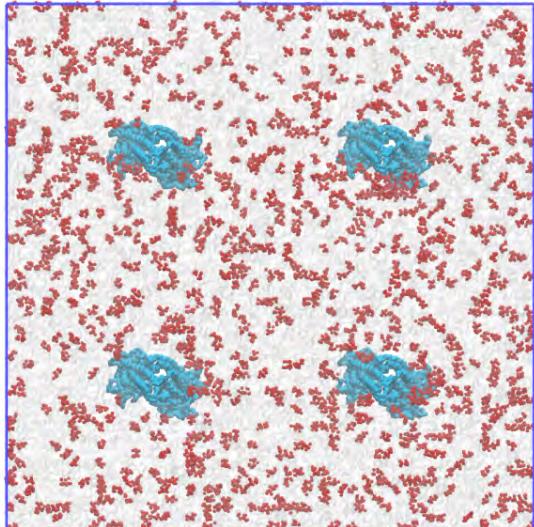
Avg. PE lipids number density

Blue = avg - 1std

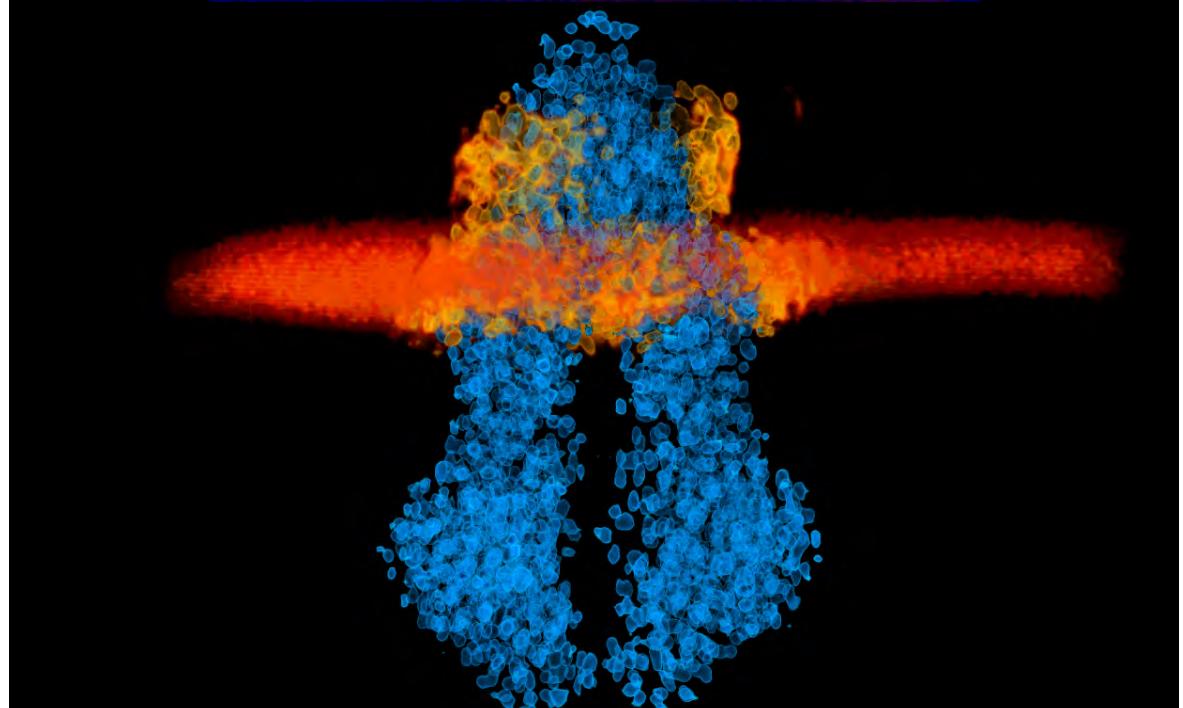
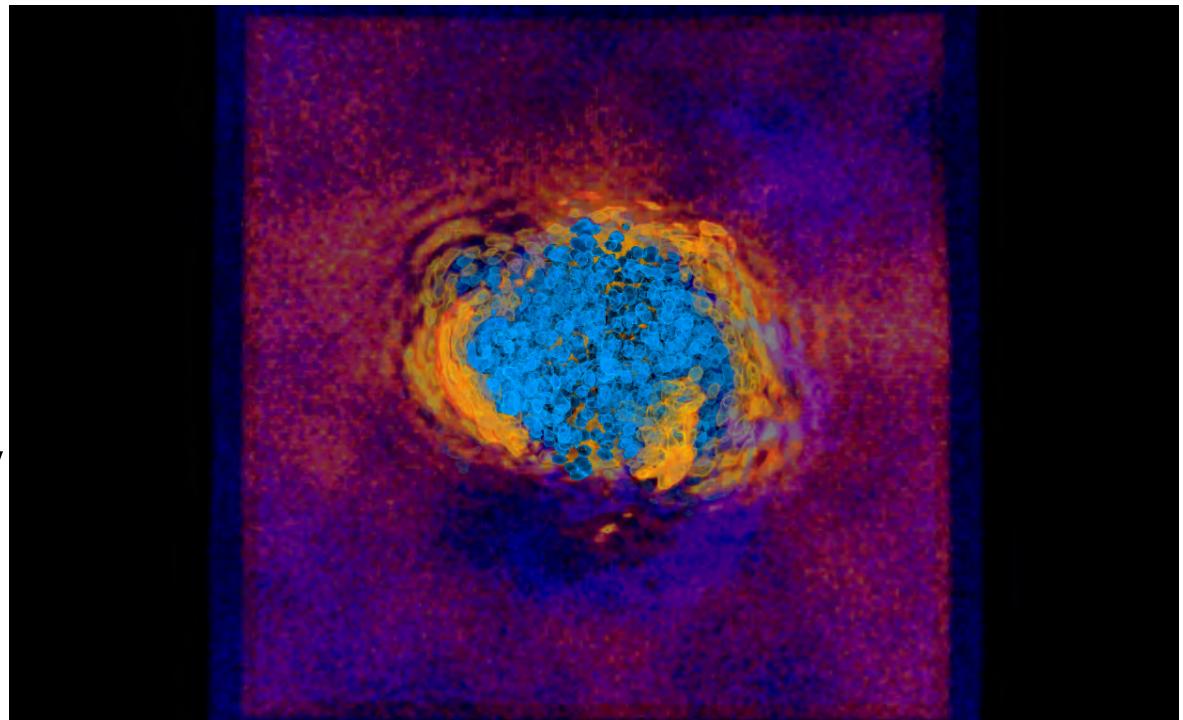
Red = avg + 1std

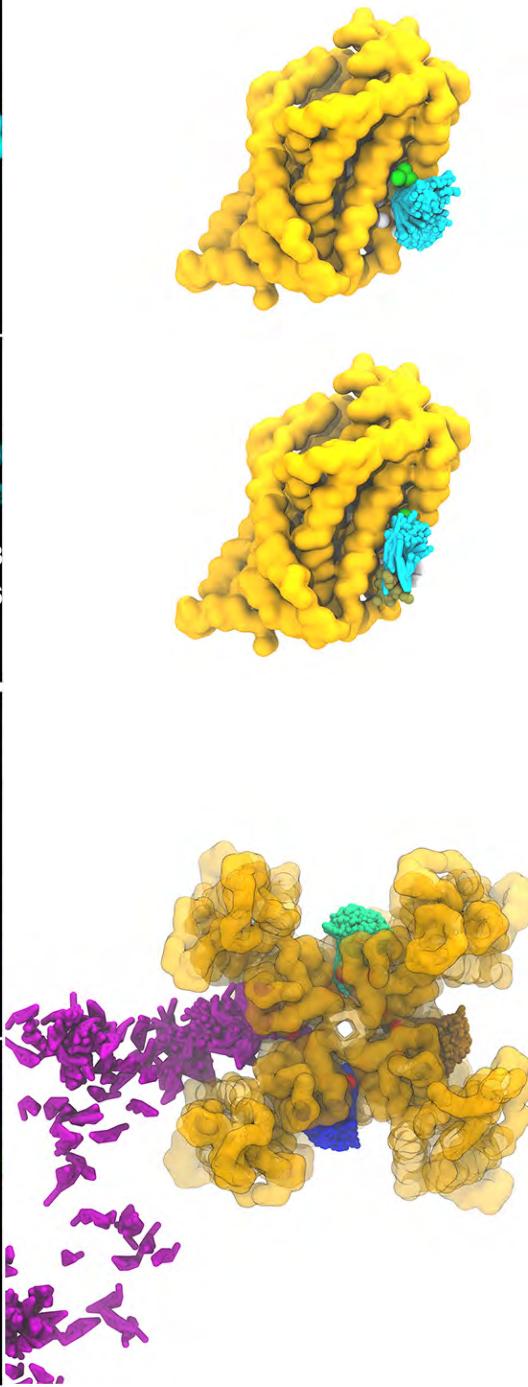
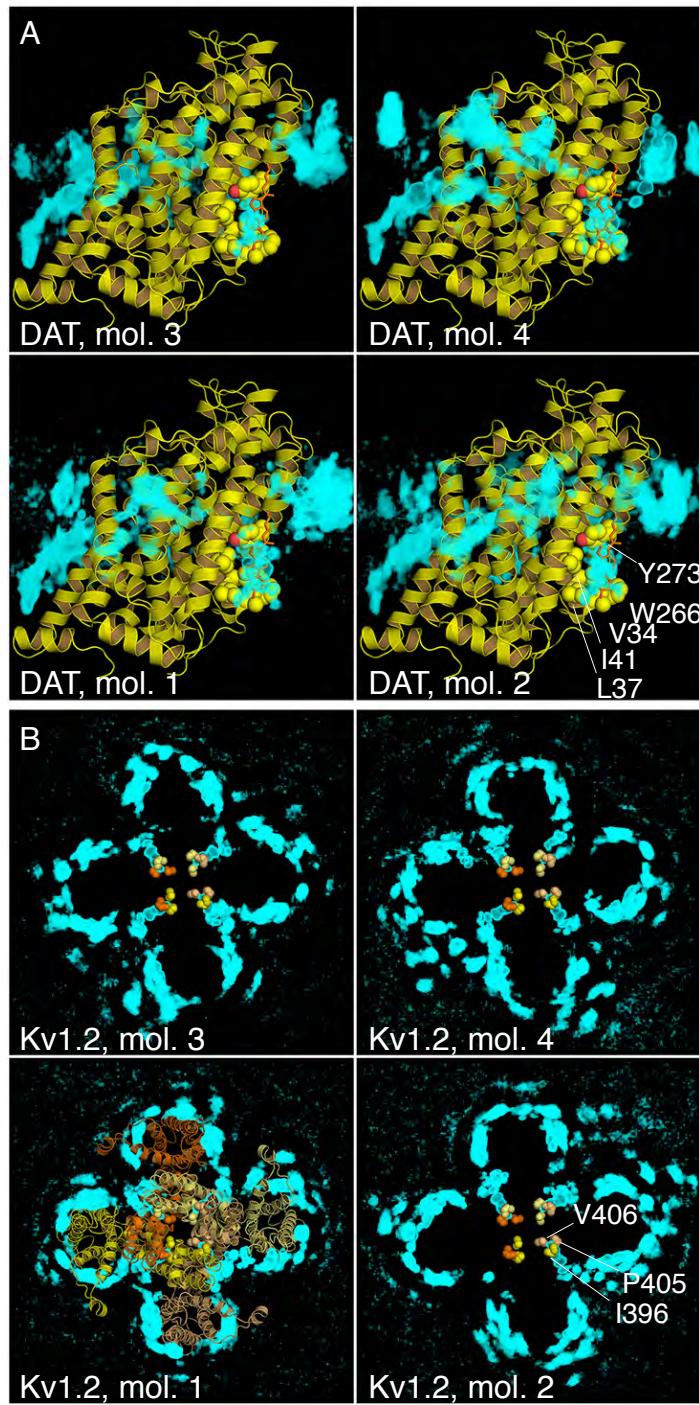
Yellow = avg = 2std

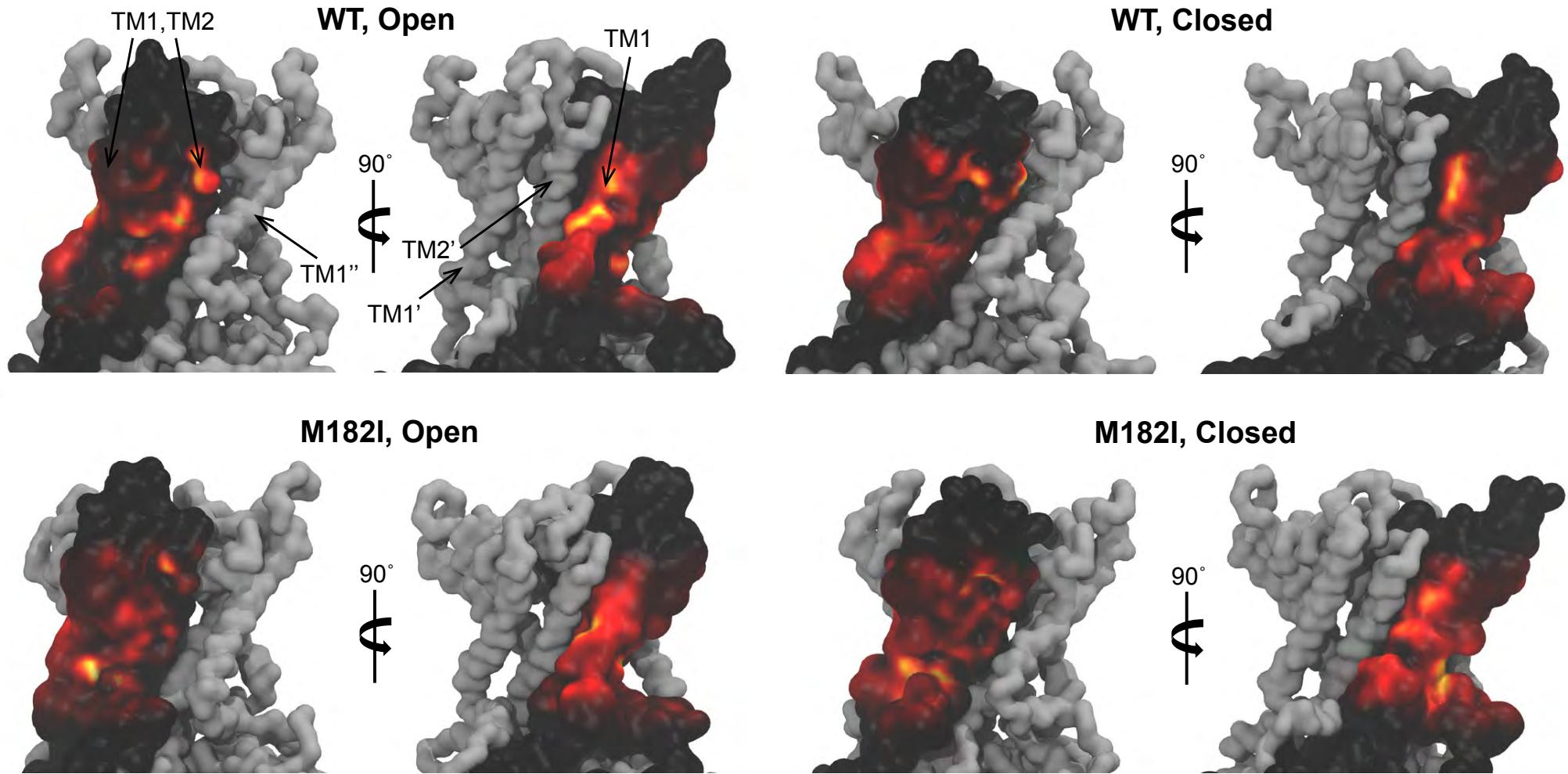
Cyan = Protein density



Initial system: no PE lipids in the cavity







Lipid-protein conclusions

- Each protein has a unique lipid-protein interaction finger print in a complex mixture
- Perhaps too much emphasis on specific lipid-protein interactions in the literature. Weaker interactions can cause a wide range of membrane modifications
- Simulations of tens of microseconds give detailed insight in lipid distributions and local membrane properties
- Membrane perturbation by proteins can be quite long-ranged

Future directions

- Improvements to Martini
- Looking for experimental validations of some lipid-protein simulation results.
Willing to do new simulations.
- Applications of similar methods to specific proteins, conformational change: ABC transporters, GPCRs
- Applications to simpler models where Martini and atomistic can be directly compared

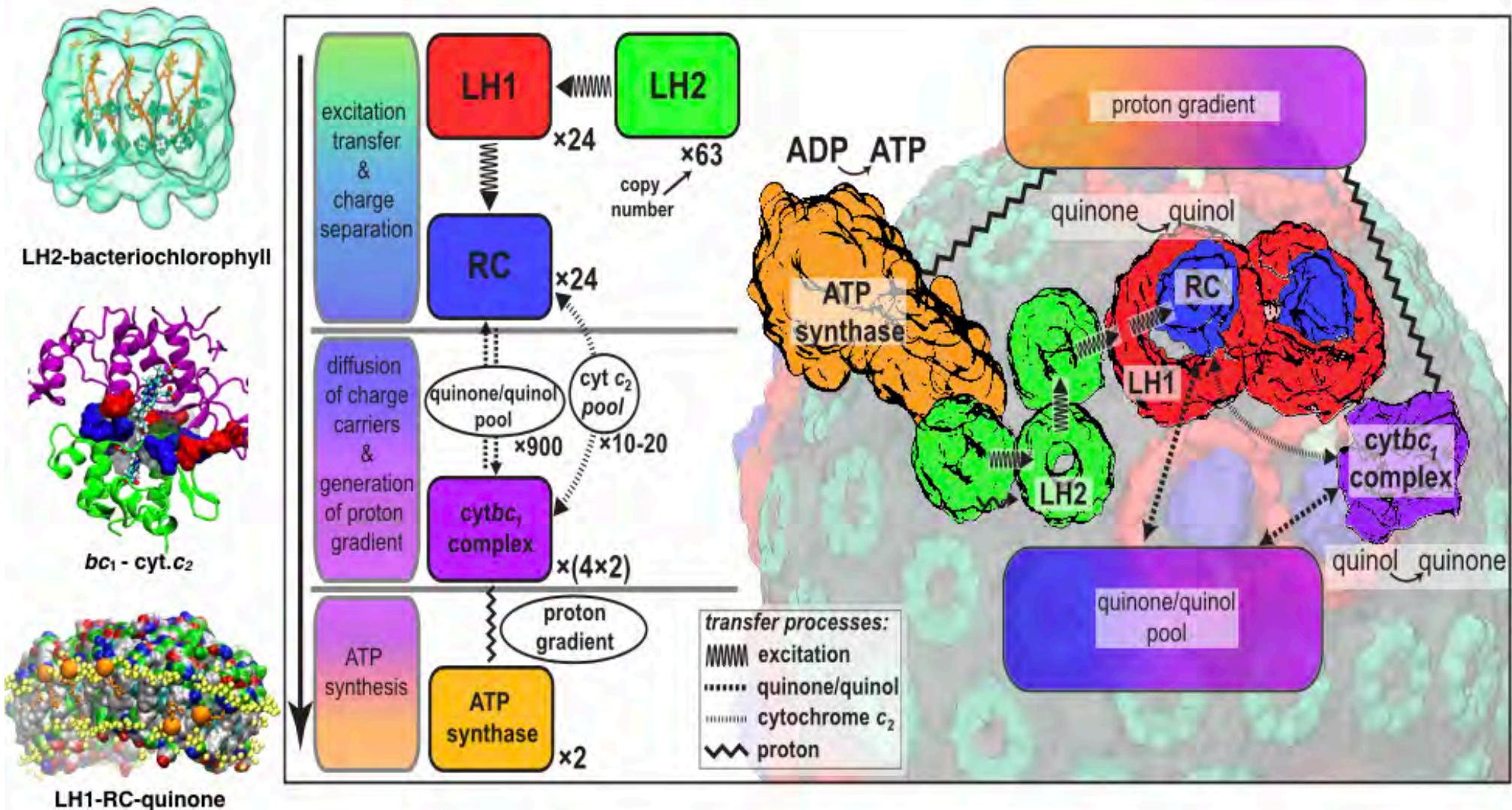


Reviews on complex
membranes, lipid
protein interactions

Atoms to Phenotypes: Molecular Design Principles of Cellular Energy Metabolism

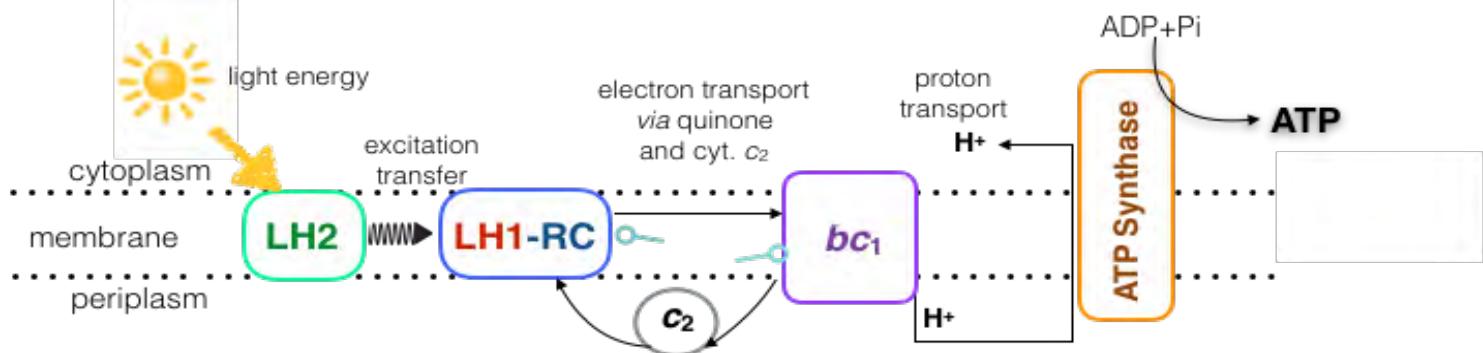
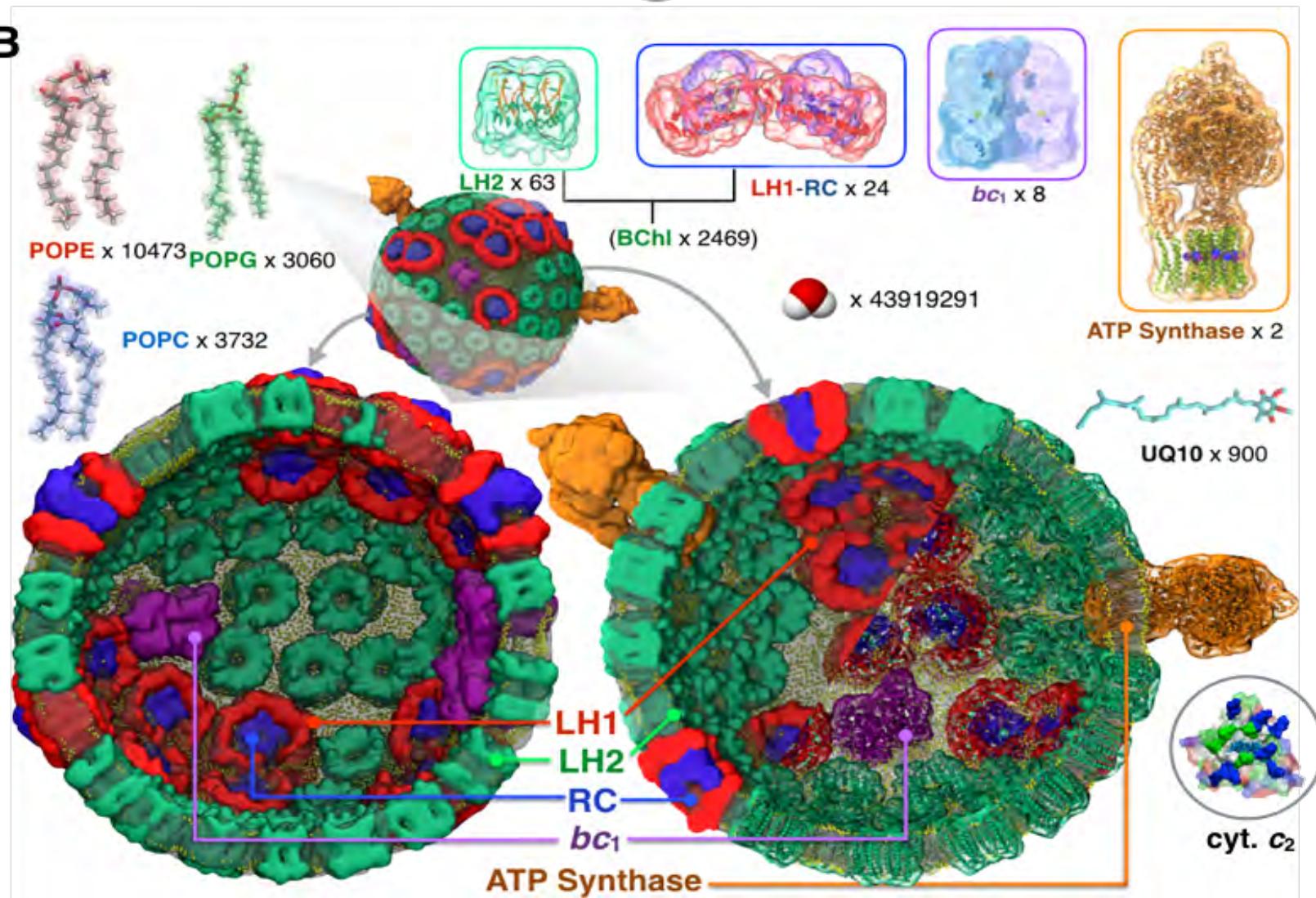
A. Singharoy¹, C. Maffeo^{2,5*}, K.H. Delgado-Magnero^{3,*}, D. J. K. Swainsbury^{4,*}, M. Sener^{5,*}, U. Kleinekathöfer^{6*}, B. Isralewitz,⁵ I. Teo,⁵ D. Chandler,⁵ J. W. Vant,¹ J. E. Stone,⁵ J. Phillips,⁵ T. V. Pogorelov,⁷ M. I. Mallus,⁶ C. Chipot,^{2,5} Z. Luthey-Schulten,^{2,7} D.P. Tielemans,³ C. N. Hunter,⁴ E. Tajkhorshid,^{5,8,9} A. Aksimentiev,^{2,5,9} K. Schulten^{2,5}

Chromatophore



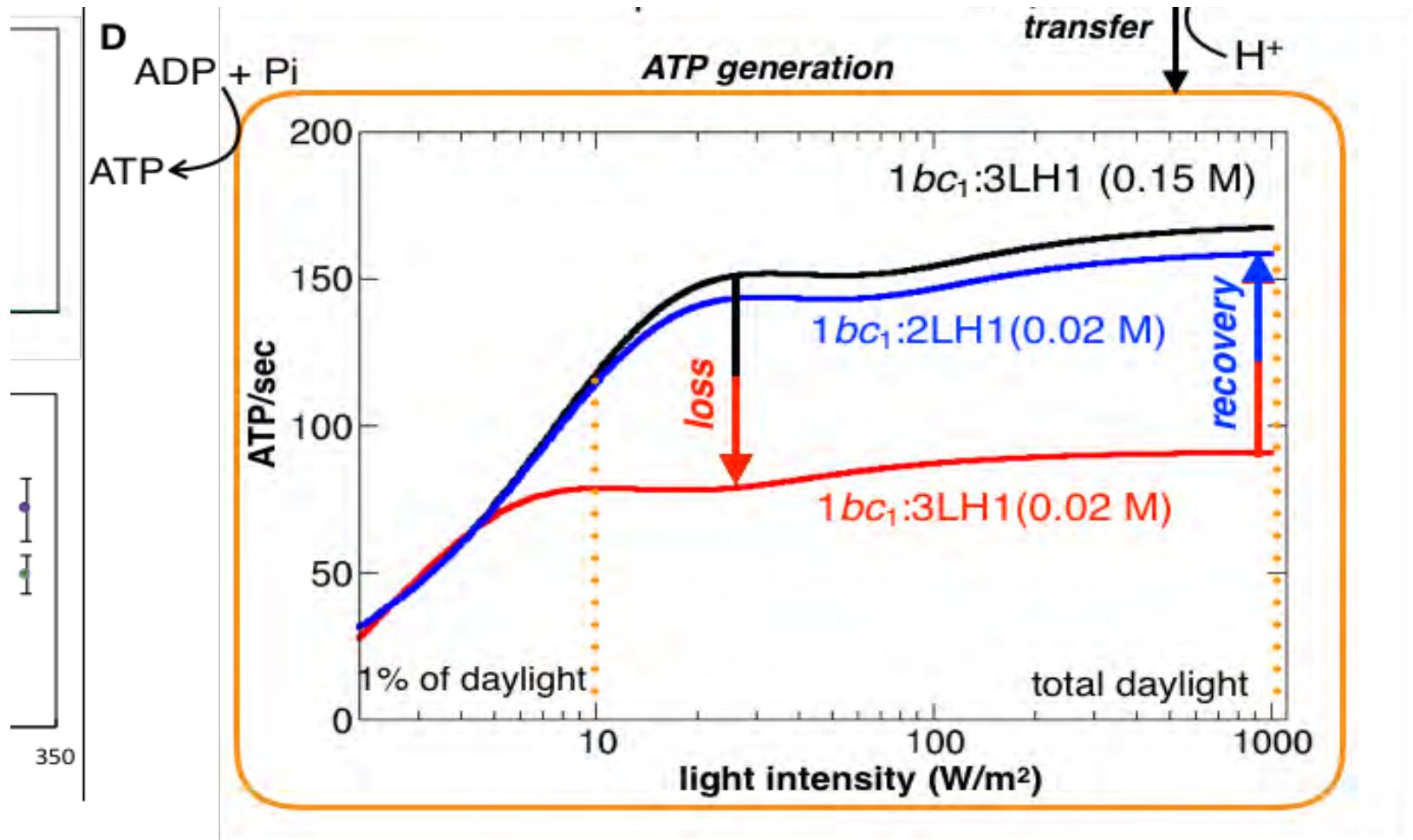
Logic

- How does energy flow from light harvesting to ATP, at the level of charge carriers/electrons/atoms/molecules?
- How efficient/optimized is the overall organization of the chromatophore?
- Macho multiscale problem: from electron capture to ATP synthesis efficiency
- Macho system: 130+ million atoms; entire organelle, not a part of it

A**B**

Methods

- MD simulation of 136 million atom chromatophore model
- QM/MM simulations based on MD snapshots for all 1701 BCIs within LH2 rings (ZINDO/S-CIS)
- Martini simulations to look at curvature
- Electrostatic calculations using ABPS
- BD simulations using ARBD for 2.8 ms of 5000 independent quinone molecules based on Boltzmann inversion of distribution functions from MD
- Umbrella sampling of cyt. c₂ dissociation from bc₁ and RC
- TLC for lipid content, spectroscopy for LH₁/LH₂ content
- Experiment from literature: EM and AFM imaging



Acknowledgments

Dr. Valentina Corradi

Dr. Eduardo Mendez-Villuendas

Besian Sejdiu

Mohsen Ramenzanpour

Karelia Delgado

Dr. Yoav Atsmon-Raz

Dr. Nandhitha Subramanian

Haydee Mesa Galloso

Yevhen Cherniavskyi

- NSERC
- CIHR
- Alberta Innovates Health
Alberta Innovates
Technology Futures
- Compute Canada
- Canada Research Chairs

(Calgary)

Dr. Sergei Noskov

(Groningen)

Dr. Siewert-Jan Marrink

Dr. Tsjerk Wassenaar

Dr. Helgi Ingolfsson (LLNL)