4°. Workshop de High Performance Computing – USP

Simulação Computacional usando Campo de Força Coarse-Grained: Desenvolvimento e Aplicação em Bicamadas Lipídicas

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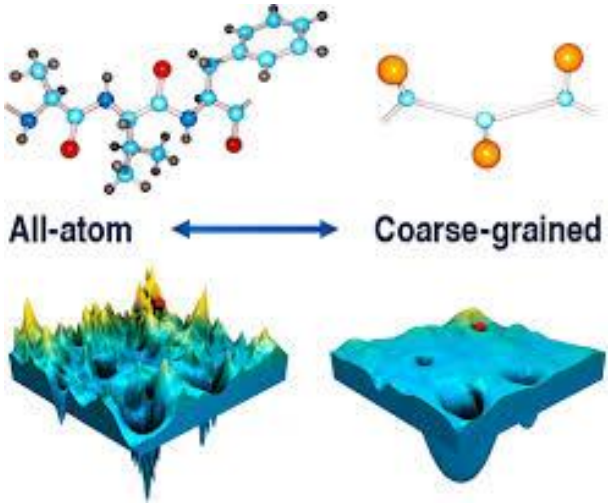
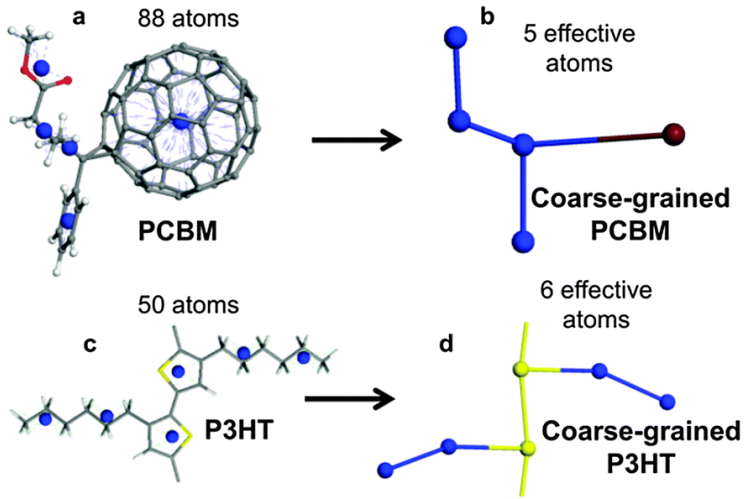
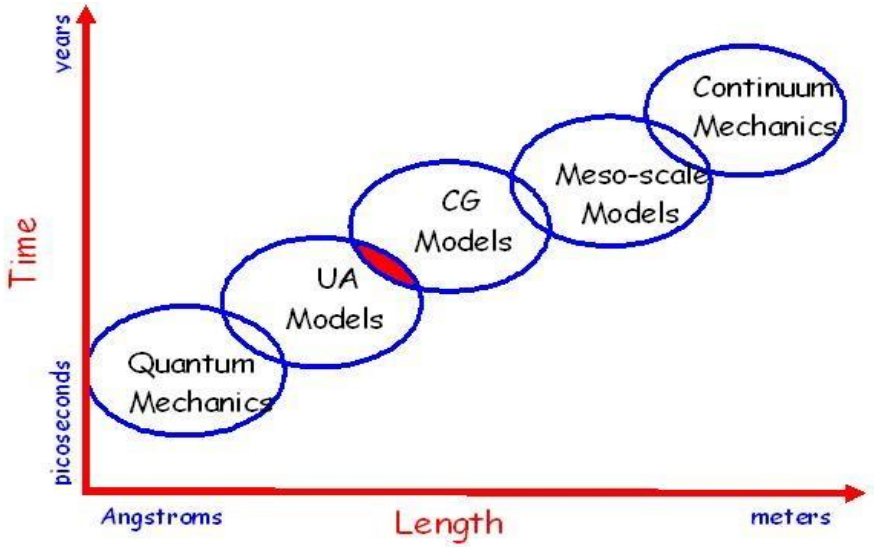
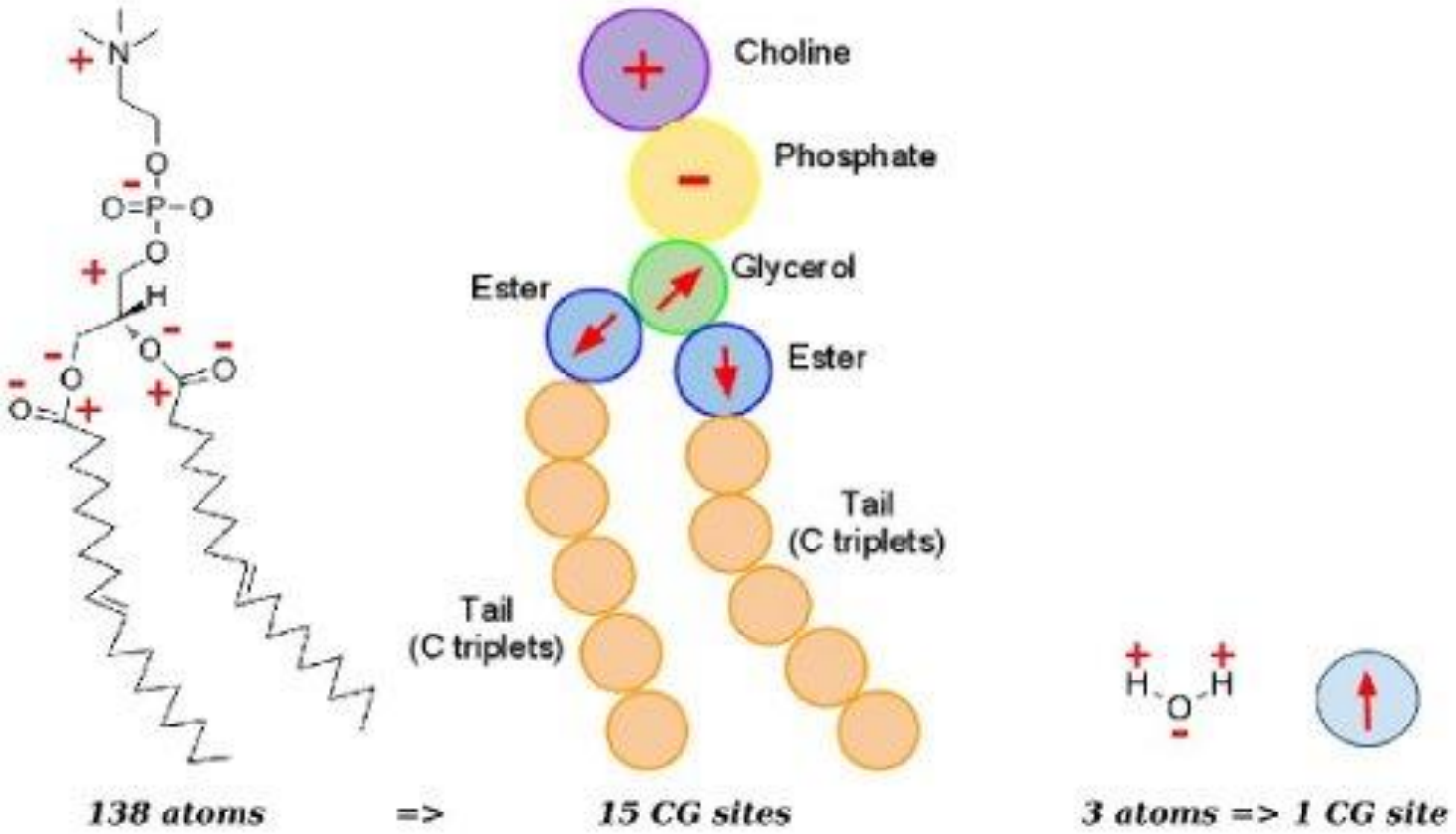
❑ *Coarse-Graining Modeling*







❑ *ELectrostatic BAsed force field (ELBA)*



M. Orsi and J.W. Essex

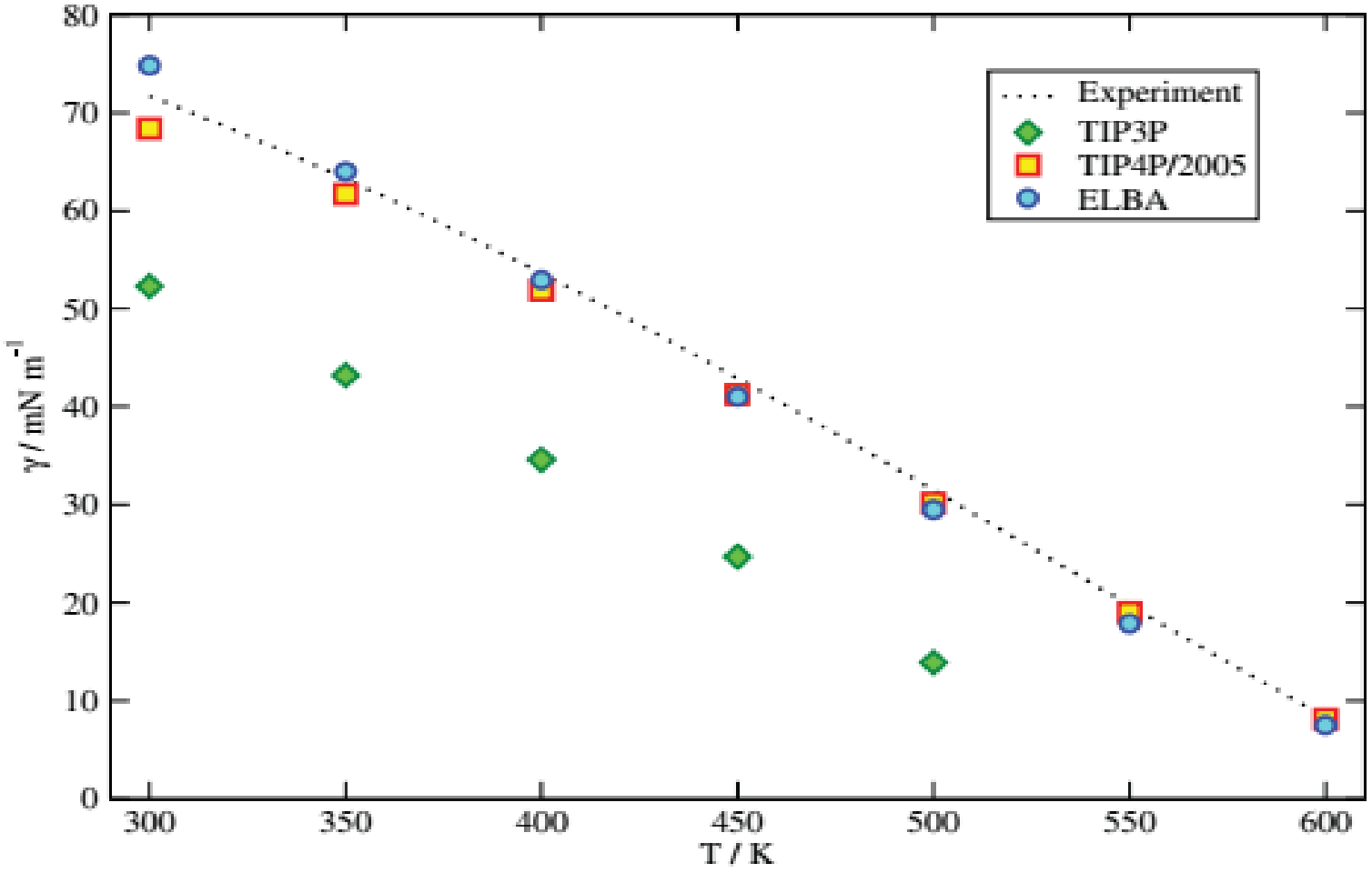
The ELBA force field for coarse-grain modeling of lipid membranes

PLoS ONE 2011, 6, e28637

- *ELBA force field incorporates electrostatic interactions through a relative dielectric constant of unity. No effective dielectric constant is necessary*
- *Beads are described as LJ + point dipole + point monopole particles. Electrostatic and LJ interactions are shifted&truncated*
- *ELBA water is a Stockmayer fluid having point dipole equals to 2.3-2.6 D, 40 amu (!), 1 amu nm²*

	ρ (g cm^{-3})	E_{pot} (kcal mol^{-1})	ΔH_{vap} (kcal mol^{-1} K^{-1})	D ($\times$ 10^{-9} m^2 s^{-1})
Experiment	0.997047[a]	−9.92[b]	10.52[c], 11.0[d]	2.3[e]
ELBA	0.99945(1)	−9.3145(1)	9.9068(1)	2.16(1)
SPC	0.97690(1)	−9.94832(7)	10.5404(1)	4.42(3)
SPC/E	0.99840(2)	−11.1562(1)	11.7484(1)	2.78(2)
TIP3P-Ew	0.99586(1)	−9.92777(8)	10.5199(1)	4.30(2)
TIP4P-Ew	0.99714(2)	−11.0877(2)	11.6798(2)	2.53(1)
TIP4P/2005	0.99846(4)	−11.4049(2)	11.9971(2)	2.28(2)

- *Interestingly, ELBA water model compares to TIP4P/2005 in surface tension prediction with temperature*

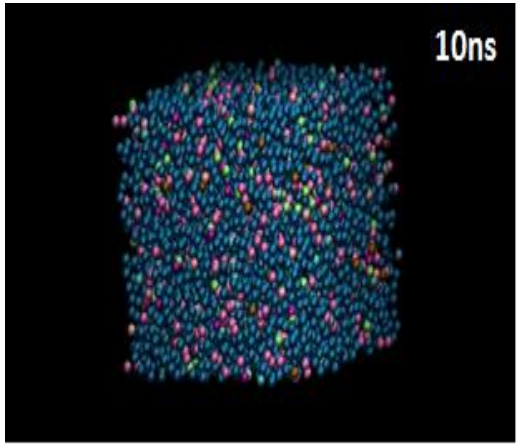


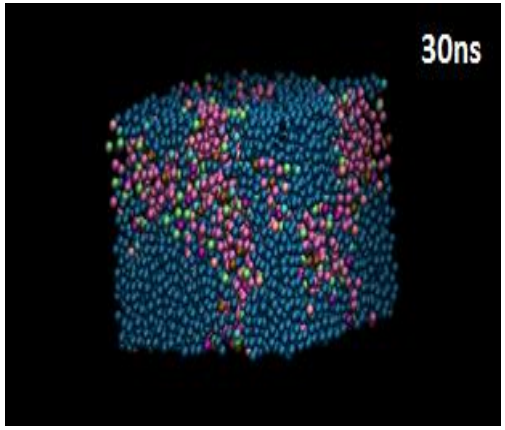
- *Comparison between the ELBA water with others coarse-grained models.*

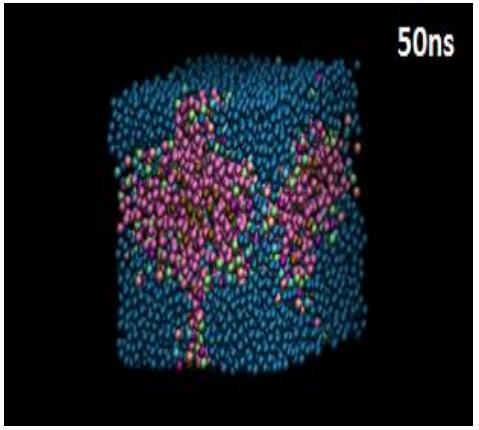
	Mapping[a]	ρ (g cm^{-3})	E_{pot} (kcal mol^{-1})	D ($\times$ 10^{-9} m^2 s^{-1})	γ (mN m^{-1})
Experiment	–	0.997047[b]	−9.92[c]	2.3[d]	71.7[e]
ELBA	1 → 1	0.99945(1)	−9.3145(1)	2.16(1)	74.8(1)
SSD[f]	1 → 1	0.972–0.999	−9.60	1.78–2.51	–
SSDQO[g]	1 → 1	0.999[h]	–	2.21–2.26	–
M3B[i]	1 → 1	0.97(2)	–	1.7	–
mW[j]	1 → 1	1.001	–	6.5	66.0
MARTINI[k]	4 → 1	0.900[l]	–	2	30–45
P-MARTINI[m]	4 → 3	1.043	–	2.5	30.5
BMW[n]	4 → 3	1.047	–	–	77
GROMOS[o]	5 → 2	0.995	−5.569	6.9	51.2
WT4[p]	11 → 4	1.0001	–	2.23	17

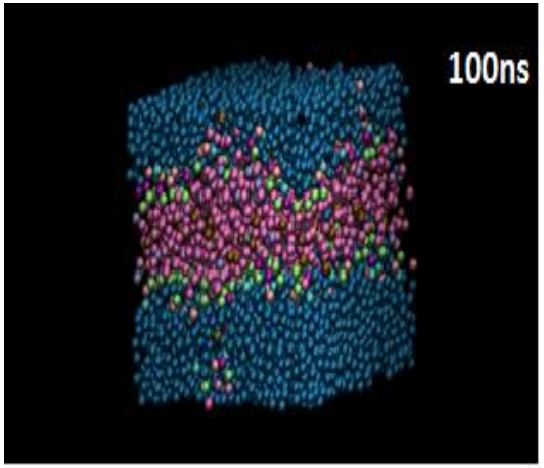
[a]The notation $m \rightarrow n$ indicates that m water molecules are mapped to n interaction sites.

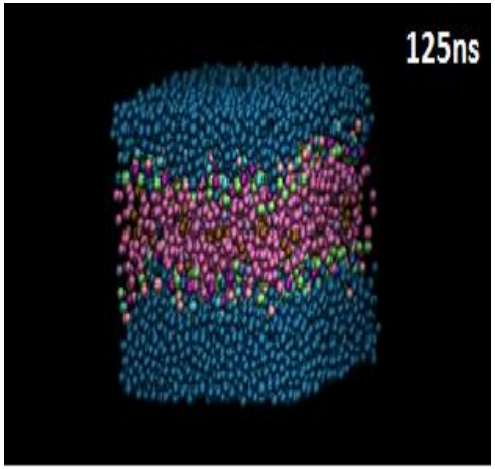
- *Self-assembling test:*



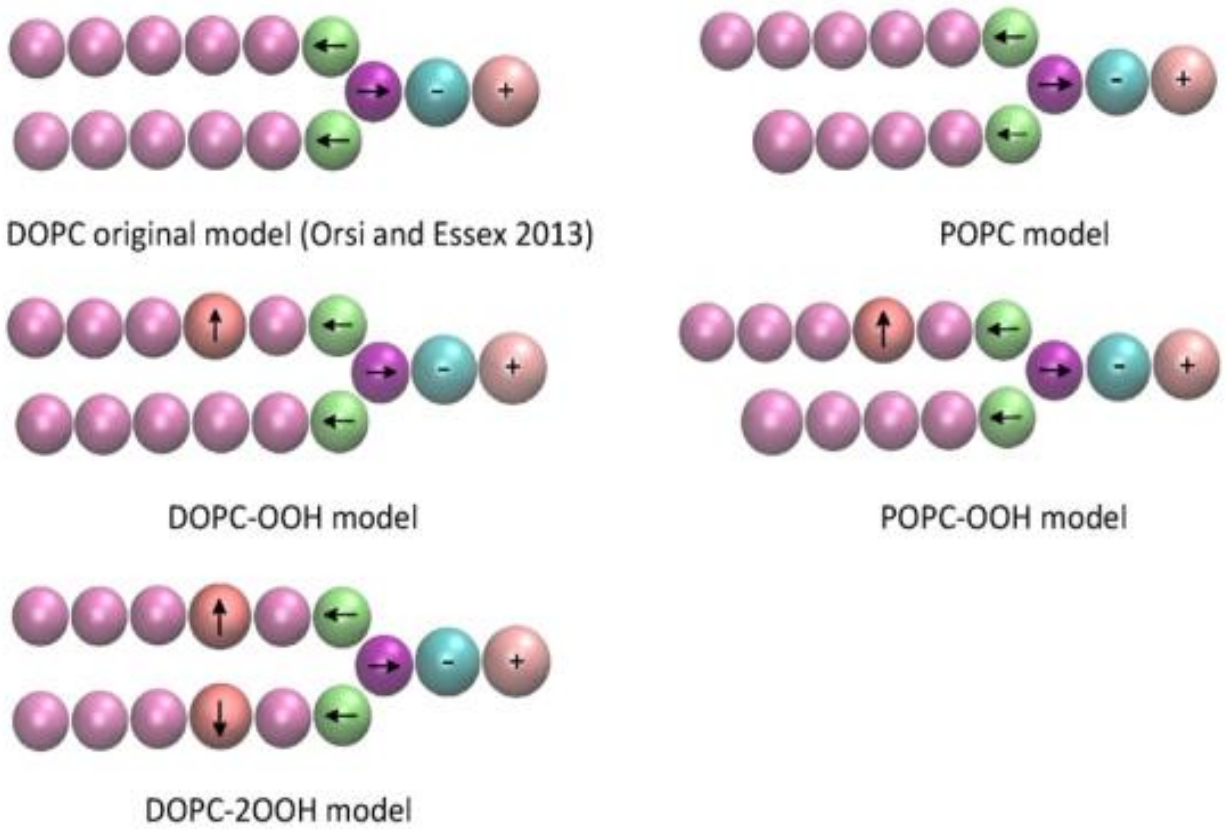








- ***ELBA models:*** *POPC, POPC-OOH, DOPC-OOH, DOPC-2OOH, DPPC*

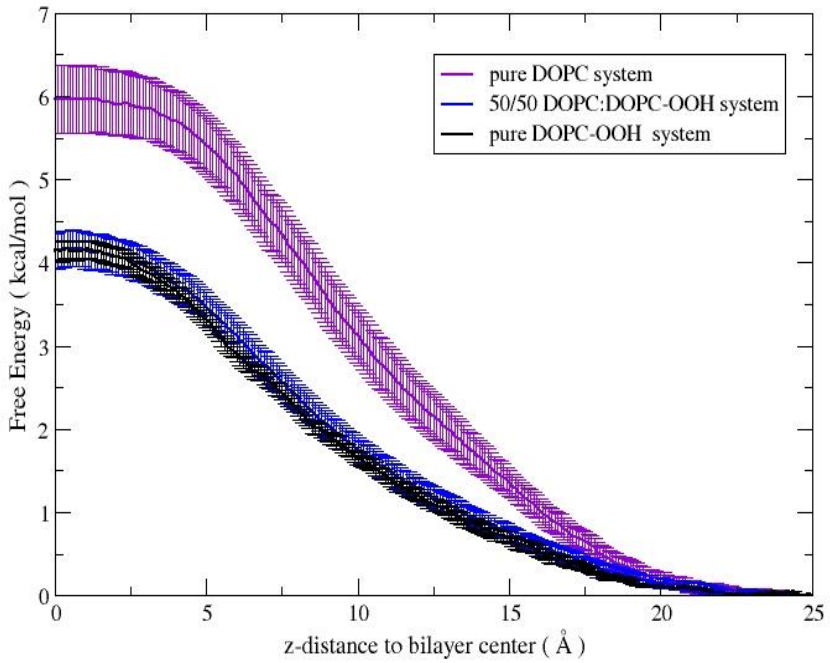


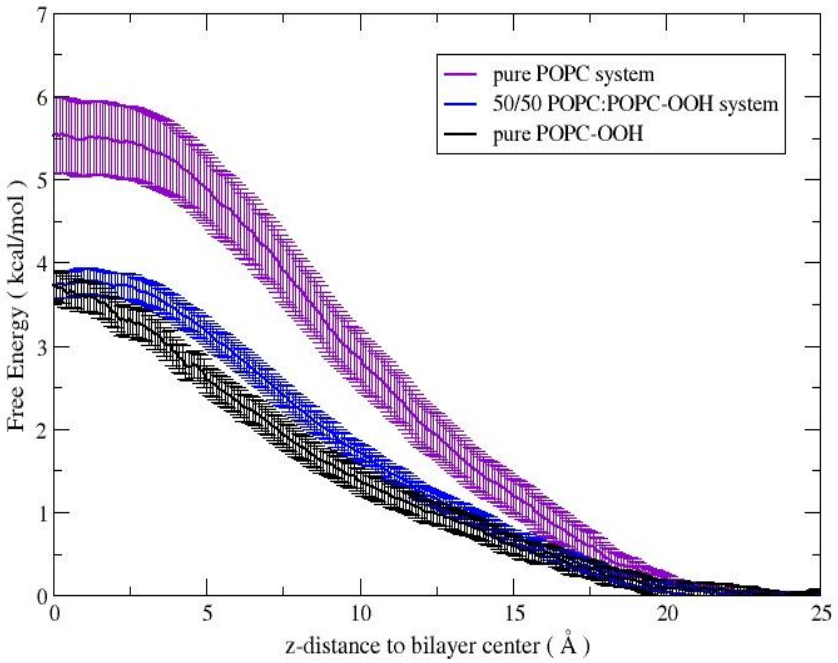
Siani et al.

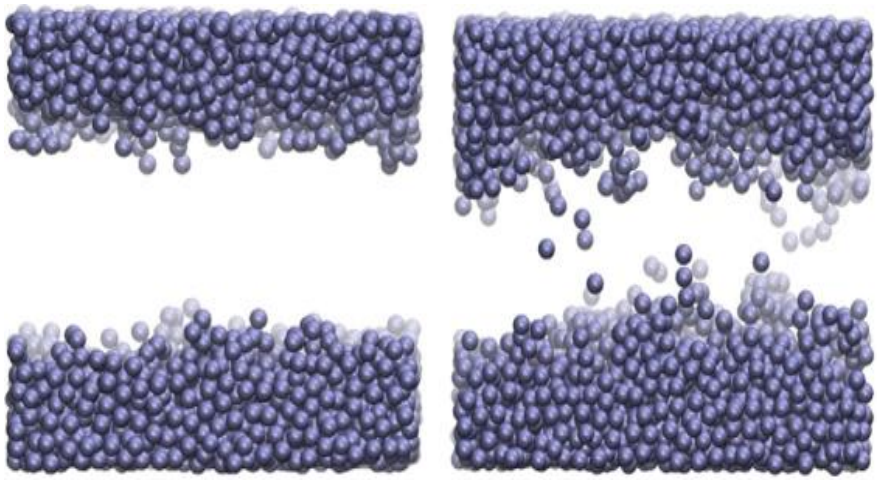
An overview of molecular dynamics simulations of oxidized lipid systems, with a comparison of ELBA and MARTINI force fields for coarse grained lipid simulations

Biochim. Biophys. Acta 2016, 1858, 2498

- *Water PMF in DOPC, DOPC-OOH, POPC, POPC-OOH:*







- *Comparison ELBA vs MARTINI: lateral self-diffusion coefficients*

Lateral diffusion coefficients for pure POPC, DOPC, POPC-OOH, DOPC-OOH, DOPC-2OOH and POPC:POPC-OOH (1:1) and DOPC:DOPC-OOH (1:1) mixtures (in $\mu m^2 s^{-1}$). ELBA simulations used 128 phospholipids. MARTINI simulations were carried out using 512 phospholipids.

System	ELBA force field	MARTINI force field[a]	Experimental data
POPC	2.57 ± 1.52	40.2 ± 2.6	7 ± 3[c]
POPC-OOH	7.29 ± 1.21	32.2 ± 2.2	-
POPC:POPC-POOH	8.65 ± 2.22	-	-
DOPC	3.19 ± 2.59	34.5 ± 1.5	4.2 ± 0.4[b]
DOPC-OOH	6.98 ± 1.45	-	-
DOPC:DOPC-OOH	9.02 ± 1.76	-	-
DOPC-2OOH	8.18 ± 1.25	24.4 ± 2.2	-

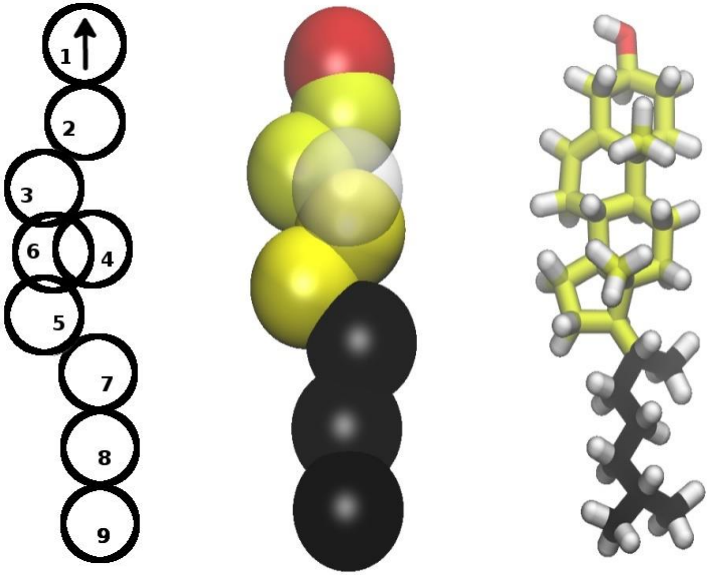
- *Comparison ELBA vs MARTINI: stretching modulus*

Comparison of the stretching modulus (K_a) and between ELBA FF and MARTINI FF.

	ELBA force field with 128 lipids	ELBA force field with 1058 lipids	MARTINI force field with 512 lipids	MARTINI force field with 8192 lipids
	Ka(mN/m)	Ka(mN/m)	Ka(mN/m)	Ka(mN/m)
POPC	403 ± 8	159 ± 12	379 ± 21	245 ± 42
POPC:POPC-OOH	229 ± 12	48 ± 2	–	–
POPC-OOH	209 ± 5	44.05 ± 4	211 ± 11	104 ± 25
DOPC	488 ± 7	302 ± 9	357 ± 19	230 ± 27
DOPC:DOPC-OOH	300 ± 10	138 ± 2	–	–
DOPC-OOH	275 ± 6	42 ± 10	–	–
DOPC-2OOH	232 ± 2	89 ± 44	103 ± 12	73 ± 7

- *ELBA and MARTINI are consistent with experimental data.*

❑ *ELBA force field for cholesterol*



- *Based on CT3-Me2b (3 bead tail + one bead methyl group), 2 to 5 beads are rigid, point dipole is a free rotor (small dihedral barrier for OH rotation), 7 to 9 beads are flexible*

Daily et al.

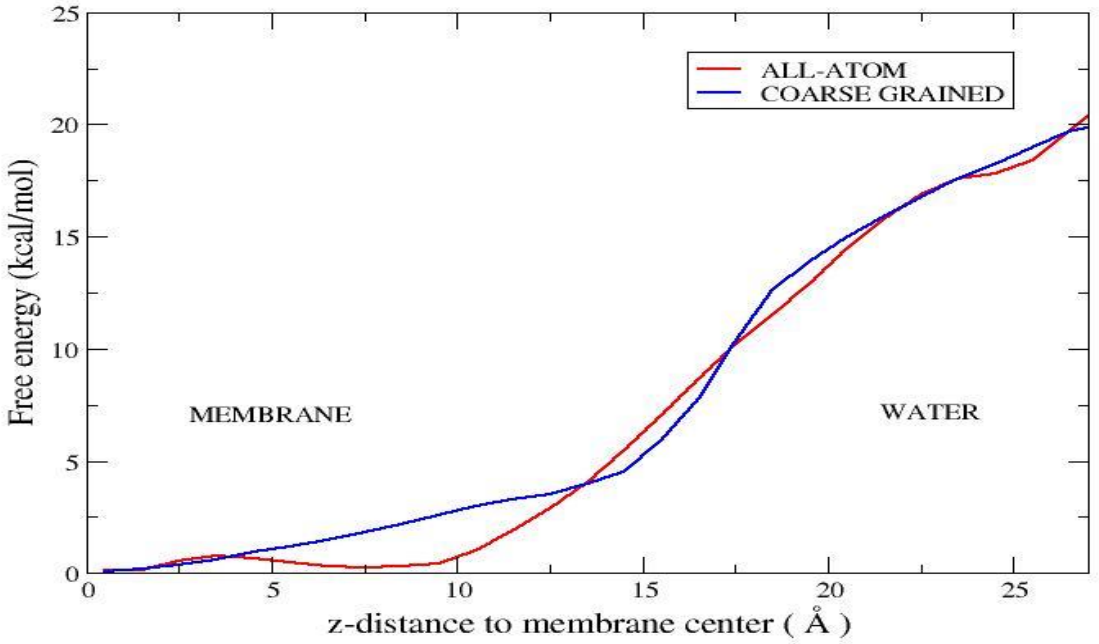
Improved Coarse-Grained Modeling of Cholesterol-Containing Lipid Bilayers

J. Chem. Theory Comput. 2014, 10, 2137

- *Dipole magnitude is being optimized using electrostatic free energy for charging process from all-atom simulations*

All atom CHARMM36	ΔG_{el}(kcal mol^{-1})	Coarse-grained ELBA	ΔG_{el}(kcal mol^{-1})
Water	-7.9 $\pm$ 0.2	Water	-7.4 $\pm$ 0.2
DPPC membrane center	-0.2 $\pm$ 0.2	DPPC membrane center	0.2 $\pm$ 0.4
Water -> DPPC	7.7 $\pm$ 0.2	Water -> DPPC	7.2 $\pm$ 0.4

- *LJ terms are being optimized using cavitation work as calculated by all-atom force field*

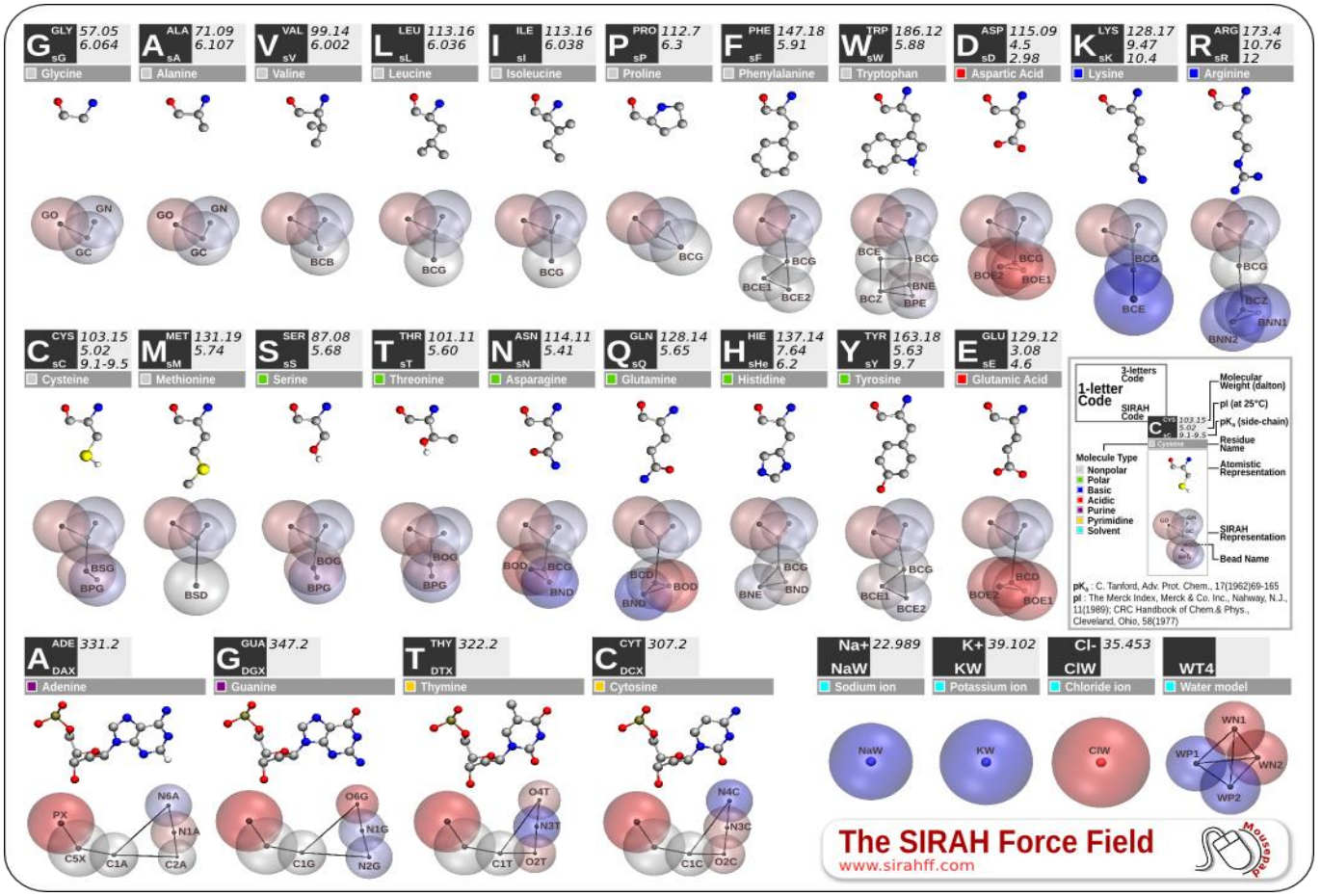


- *DPPC + CHOL mixtures: partial molecular volumes*

CHOL molar fraction	ELBA (Angs^3)		Experimental data (Angs^3)	
	DPPC	CHOL	DPPC	CHOL
0.50	1176 ± 3	647 ± 2	1158	647-652
0.40	1163 ± 2	660 ± 4	1158	647-652
0.30	1142 ± 2	696 ± 8	1147	716-723
0.25	1136 ± 2	708 ± 12	1147	716-723

- *Non-linear behavior for CHOL volume with molar fraction is predicted by ELBA force field with new parameters*
- *Room for improvements, study of ternaries mixtures (POPC-OOH/POPC/CHOL, POPC-OOH/DPPC/CHOL,...)*

❑ *ELBA + SIRAH force field*



Darré et al.

SIRAH: A Structurally Unbiased Coarse-Grained Force Field for Proteins with Aqueous Solvation and Long-Range Electrostatics

J. Chem. Theory Comput. 2015, 11, 723

❑ *Thanks*

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