

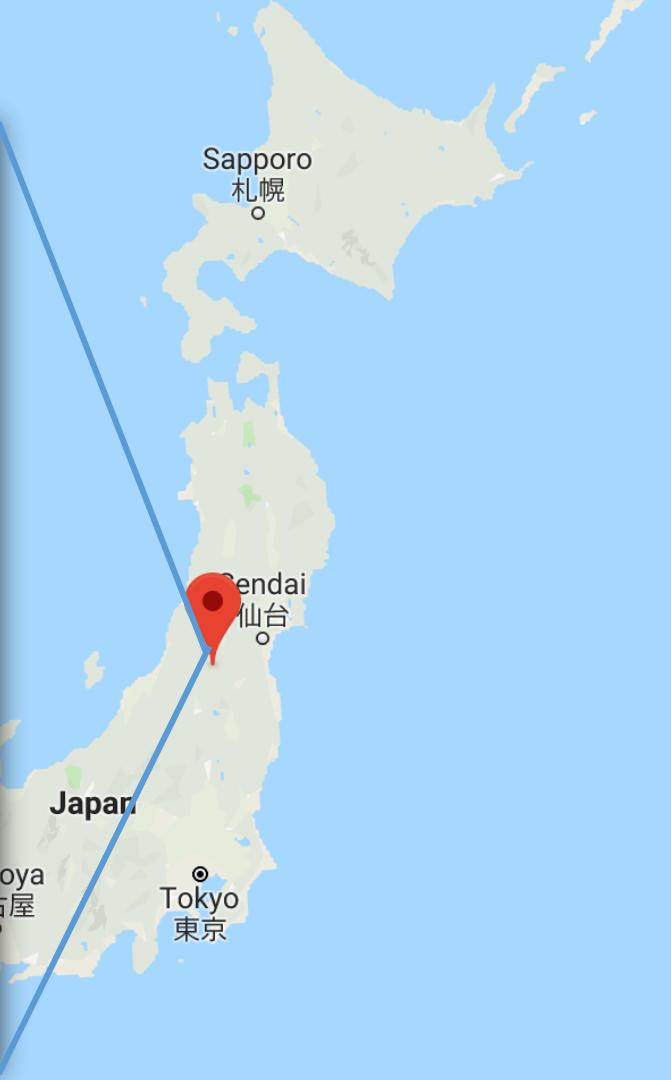
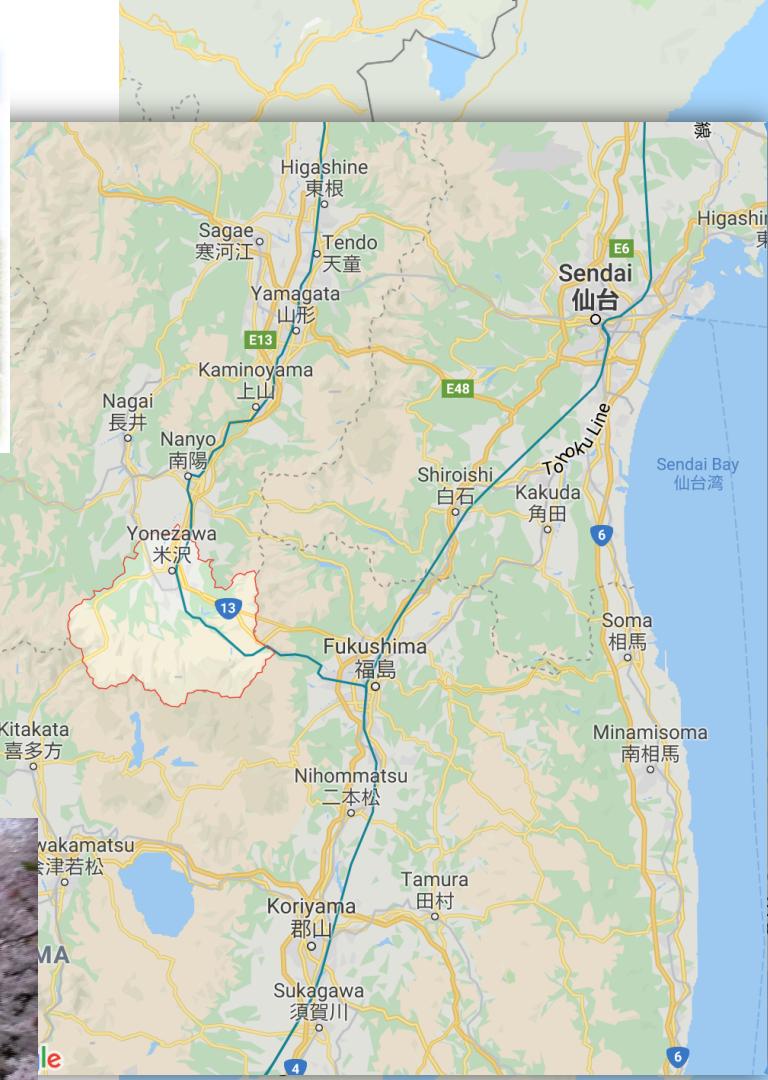


A Lipid Membrane Simulation Using the Hybrid PF-MD Approach

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Winter School on the Physics of the Cell, January 20th-31th, 2020, Trento



Google

Outlook

- ❑ Introduction
- ❑ Hybrid Particle-Field Technique Capability
- ❑ OCCAM MD Code
- ❑ Simulation of Self-Assembly of a phospholipid bilayer (tutorial)

Introduction

- Membranes are essential components of every cell, providing the cell's identity as well as defining a large variety of internal compartments. Typical cell membranes may contain hundreds of different lipids, asymmetrically distributed between the two bilayer leaflets and are crowded with proteins covering an estimated membrane area as large as 30%.
- Experimental techniques (as example: NMR, Fluorescent correlation Spectroscopy, solid-state NMR) are getting more and more sophisticated to reveal lateral membrane organization. However, the detailed membrane organization proves difficult to probe at molecular level, despite progress in experimental techniques that can directly probe living cells.

Yang, Y.; Lee, M.; Fairn, G. D. Phospholipid Subcellular Localization And Dynamics. *J. Biol. Chem.* 2018, 293, 6230–6240.

Harayama, T.; Riezman, H. Understanding The Diversity Of Membrane Lipid Composition. *Nat. Rev. Mol. Cell Biol.* 2018, 19, 281–296.

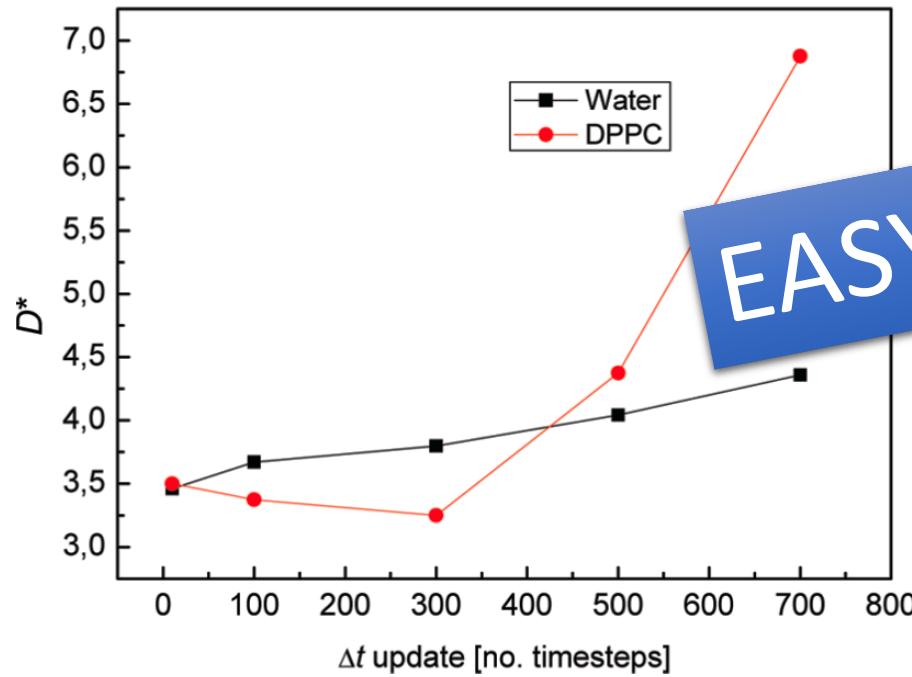
Van Meer, G.; Voelker, D. R.; Feigenson, G. V. Membrane Lipids: Where They Are And How They Behave. *Nat. Rev. Mol. Cell Biol.* 2008, 9, 112–24.

Lyman, E.; Hsieh, C. L.; Eggeling, C. From Dynamics to Membrane Organization: Experimental Breakthroughs Occasion a "Modeling Manifesto. *Biophys. J.* 2018, 115, 595–604.

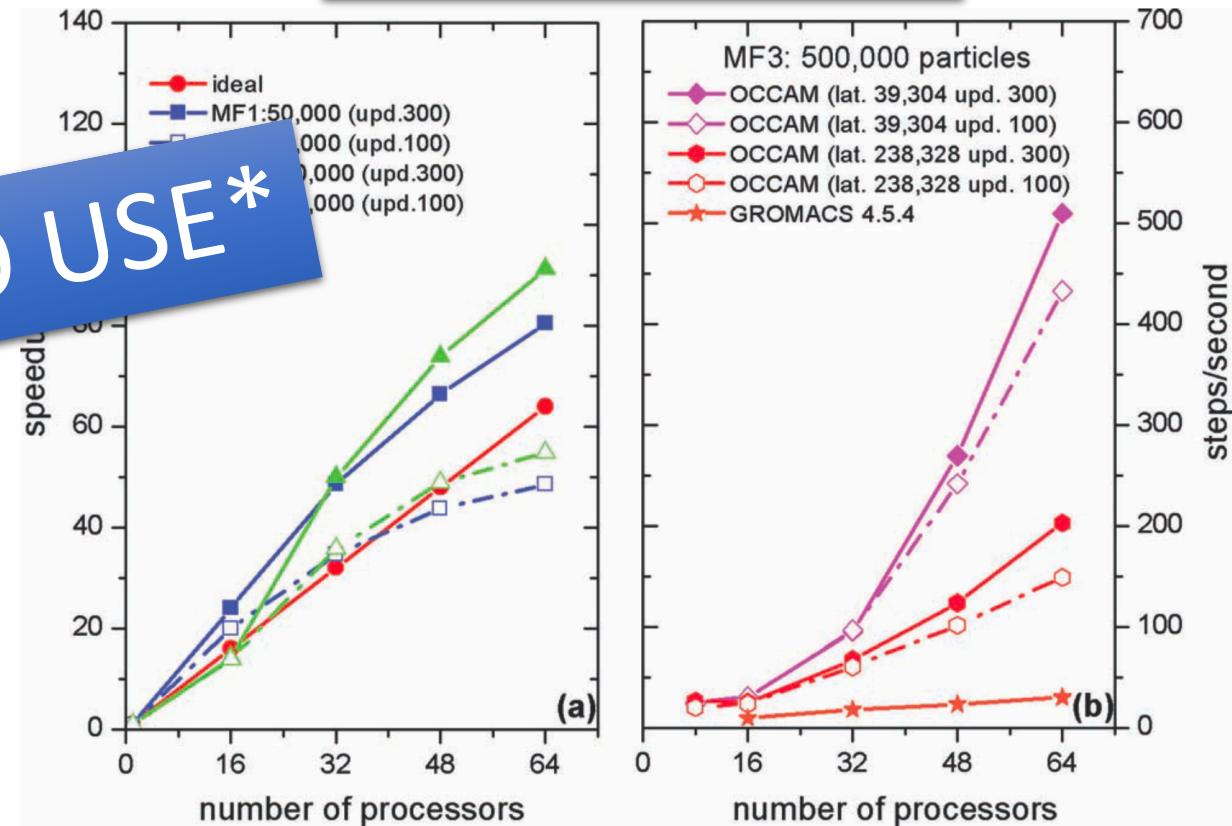
Maity, P. C.; Yang, J.; Klaesener, K.; Reth, M. The Nanoscale Organization Of The B Lymphocyte Membrane. *Biochim. Biophys. Acta, Mol. Cell Res.* 2015, 1853, 830–840.

Introduction: Hybrid Particle-Field Approach (OCCAM* MD CODE)

FASTER DYNAMICS



COMPUTATIONAL EFFICIENCY



Ratio between the diffusion coefficient of Martini CG model and Hybrid PF-MD model for a DPPC/Water system(1).

Benchmarks of parallel MD-SCF program with speedup for the monoatomic fluid (MF) systems a) MF1 (blue curves with squares) and MF2 (green) (2).

(1) De Nicola, A.; Zhao, Y.; Kawakatsu, T.; Roccatano, D.; Milano, G. Hybrid Particle-Field Coarse-Grained Models for Biological Phospholipids. *J. Chem. Theory Comput.* **2011**, 7 (9), 2947–2962.
(2) Zhao, Y.; De Nicola, A.; Kawakatsu, T.; Milano, G. Hybrid Particle-Field Molecular Dynamics Simulations: Parallelization and Benchmarks. *J. Comput. Chem.* **2012**, 33 (8), 868–880.

Hybrid Particle Field Coarse-Grained Model

JCTC
Journal of Chemical Theory and Computation

ARTICLE

pubs.acs.org/JCTC

Hybrid Particle-Field Coarse-Grained Models for Biological Phospholipids

Antonio De Nicola,^{†,‡} Ying Zhao,[†] Toshihiro Kawakatsu,[§] Danilo Roccatano,^{||} and Giuseppe Milano^{†,‡,*}

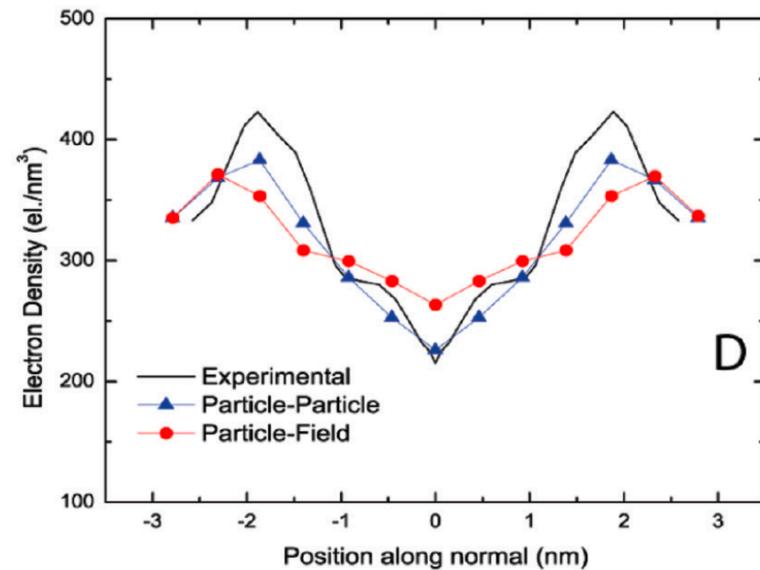
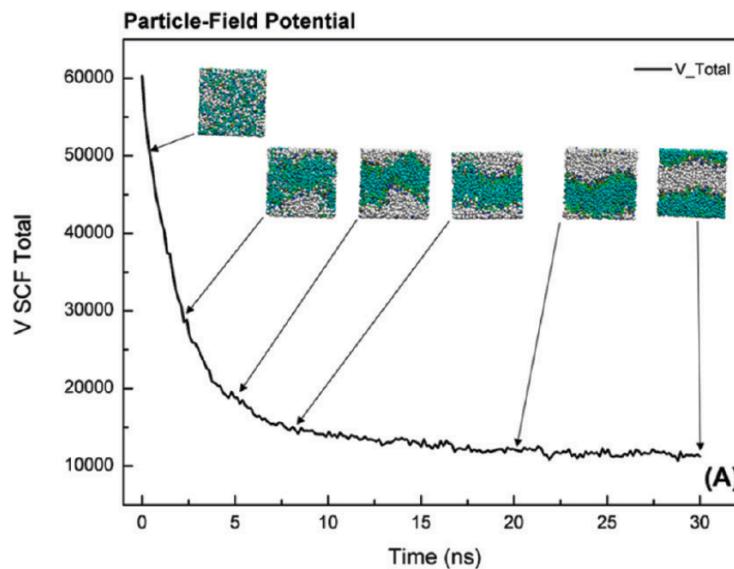
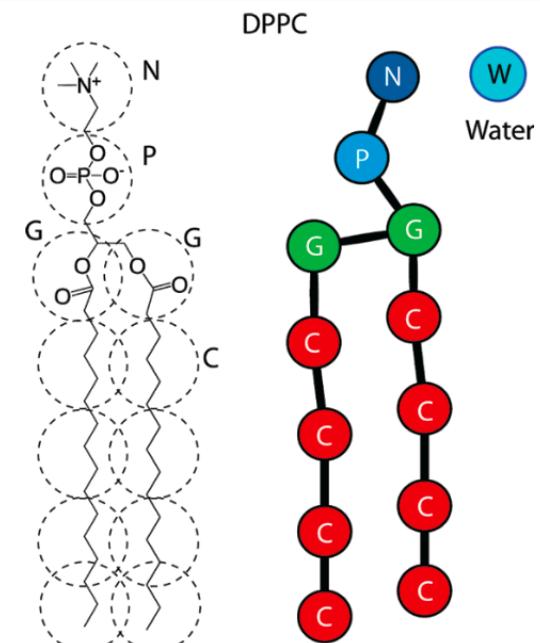
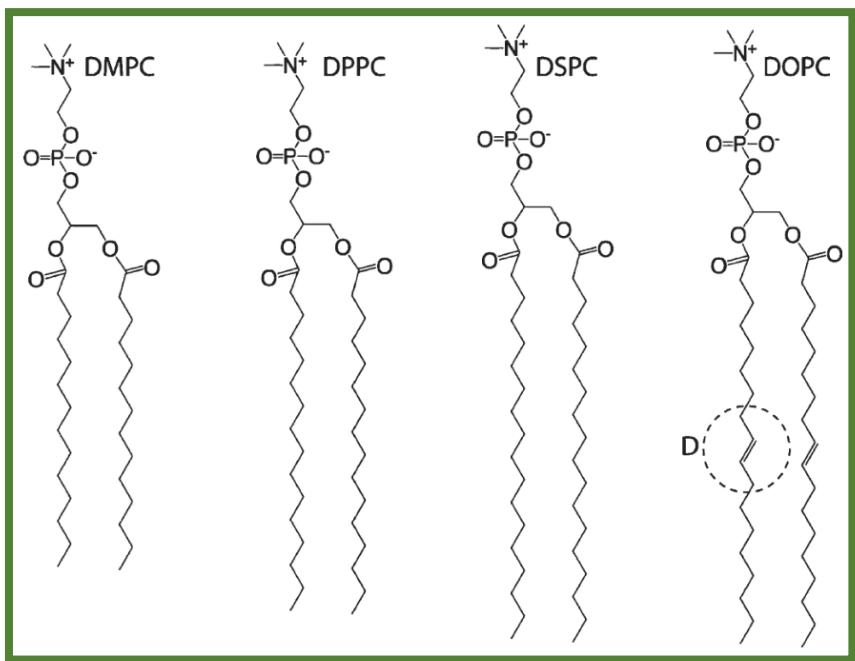


Table 6. Calculated Bilayer Thickness^a

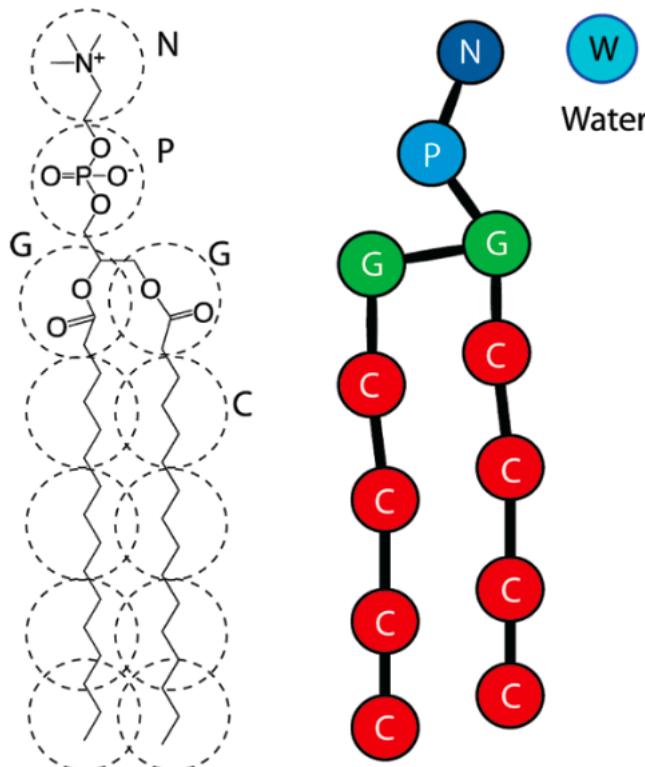
phospholipid	D_{HH} particle-particle (nm)	D_{HH} particle-field (nm)	D_{HH} experimental (nm)
DMPC	3.7 (30 °C)	3.7 (30 °C)	3.8 ^b –3.5 ^e (30 °C)
DPPC	3.5 (50 °C)	3.5 (50 °C)	3.6 ^b (50 °C)
DOPC	4.1 (30 °C)	4.0 (30 °C)	3.7 ^b –3.6 ^d (30 °C)
DSPC	4.1 (60 °C)	4.4 (60 °C)	4.0 ^b –4.1 ^c (60 °C)

^a Simulations have been performed at temperatures corresponding to the available experimental data. ^b From ref 48. ^c From ref 52. ^d From ref 53. ^e From ref 54.



Hybrid Particle Field Coarse-Grained Model: Intramolecular Parameters

Dipalmitoylphosphatidylcholine
(DPPC)



Bond

$$V_{bond}(R) = \frac{1}{2} K_{bond} (R - R_{bond})^2$$

bonds	R_{bond} (nm)	K_{bond} (kJ mol ⁻¹ nm ⁻²)
N-P	0.470	1250
P-G	0.470	1250
G-G	0.370	1250
G-C	0.470	1250
C-C	0.470	1250
D-C	0.470	1250

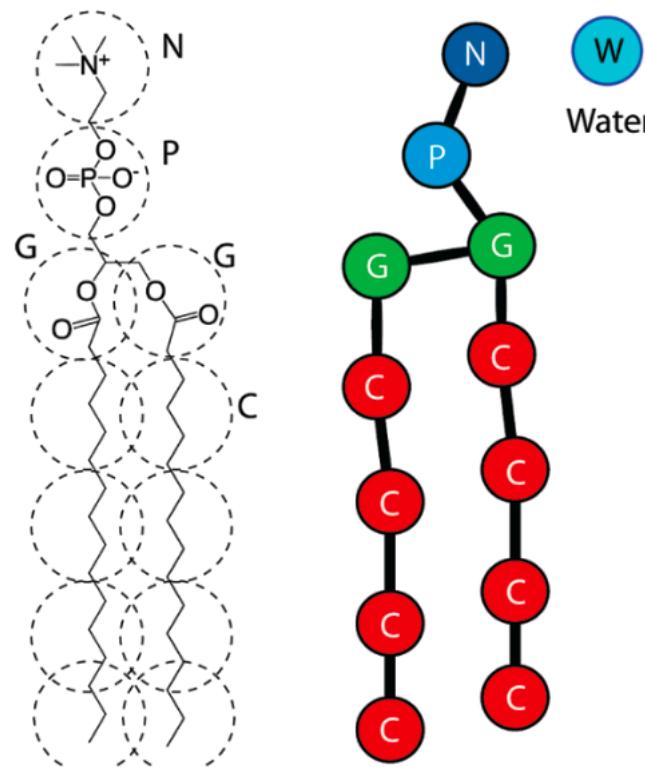
Angle

$$V_{angle}(\theta) = \frac{1}{2} K_{angle} \{ \cos(\theta) - \cos(\theta_0) \}^2$$

angle	θ_0 (deg)	K_{angle} (kJ mol ⁻¹)
P-G-G	120	25.0
P-G-C	180	25.0
G-C-C	180	25.0
C-C-C	180	25.0
C-D-C	120	45.0
D-C-C	180	25.0

Hybrid Particle Field Coarse-Grained Model: Intermolecular Parameters

Dipalmitoylphosphatidylcholine
(DPPC)



Mapping Scheme

$$V_K(\mathbf{r}) = \frac{\delta W[\{\phi_K(\mathbf{r})\}]}{\delta \phi_K(\mathbf{r})} = k_B T \sum_{K'} \chi_{KK'} \phi_{K'}(\mathbf{r}) + \frac{1}{\kappa} (\sum_K \phi_K(\mathbf{r}) - \phi_0)$$

Particle-Field Interaction Matrix χ

$\chi_{KK'}$	N	P	G	C	D	W
N	0.00	-1.50	6.30	9.00	7.20	-8.10
P	-1.50	0.00	4.50	13.50	11.70	-3.60
G	6.30	4.50	0.00	6.30	6.30	4.50
C	9.00	13.50	6.30	0.00	0.00	33.75
D	7.20	11.70	6.30	0.00	0.00	23.25
W	-8.10	-3.60	4.50	33.75	23.25	0.00

$\chi_{KK'} \times RT$ (kJ/mol) for particle of type K interacting with the field due to the particle K' .



Spontaneous formation of DPPC bilayer starting from a random initial configuration (DPPC and water molecules are randomly placed in the box) by using the Hybrid Particle-Field Approach.

To this aim you will use the code **OCCAM MD*** in which the hybrid Particle-Field is implemented. OCCAM code is a MPI parallel code with a user friendly interface. Moreover, interface ancillary codes interfacing OCCAM MD with Gromacs are available. Code web site can be found at address: www.occammd.org.

- short introduction to the usage of OCCAM MD.





The **fort.1** contains the general parameters for the simulations (*time step, thermodynamic conditions, ecc...*).

title: Title of simulation

atoms: 200 (number of atoms in the system)

nl_cutoff: 1.20 (the cutoff distance for non-bonded interaction in nm)

nl_size: 1.60 (Size of list of particles included in cutoff)

time_step: 0.03

number_of_steps: 1000 (number of steps)

velocity_read: (yes/no) (read the velocity from the **input.cor** file)

simulated_ensemble: NVT (type of ensemble that you want use for simulations)

target_temperature: 325 (temperature K)

collision_frequency: 7.00 (The collision frequency for the thermostat)

angle_funcion: 2 (type of function for the angle potential calculation)

mean_field: SCF (The self consistent field method is used in the simulation)

SCF_lattice_update: 100 (update frequency for the density field)

num_config_acc: 10 (accumulated num. of config. between two consecutive density update)

trj_print: 100 (output frequency for the trajectory file **out.xyz**)

OCCAM MD: Model Parameters (Fort.3)



OCCAM
Molecular Dynamics

***** model file *****

5 different atom types

*label mass charge

1 N 72.0000 1.0000

2 P 72.0000 -1.0000

3 G 72.0000 0.0000

4 C 72.0000 0.0000

5 W 72.0000 0.0000

5 different bond types

*atom 1 atom2 bond_length force_constant

1 2 0.47 1250.00

2 3 0.47 1250.00

3 3 0.37 1250.00

3 4 0.47 1250.00

4 4 0.47 1250.00

4 different bond angles

*atom1 atom2 atom3 theta0(deg) force_constant

2 3 3 120.00 25.000

2 3 4 180.00 25.000

3 4 4 180.00 25.000

4 4 4 180.00 25.000

0 different torsions

*atom1***atom2*** atom3***atom4***

5 different non-bonded interactions

*type 1 ** type 2 sigma epsilon

1 2 0.47 4.5

2 3 0.47 4.0

3 3 0.47 3.5

3 4 0.47 2.7

4 4 0.47 3.5

***** SCF settings *****

* mx my mz cells in X Y Z directions

14 14 12 (resolution)

* compressibility

0.1

*chi matrix

0.00 -1.50 6.30 9.00 -8.13

-1.50 0.00 4.50 13.50 -3.60

6.30 4.50 0.00 6.30 4.50

9.00 13.50 6.30 0.00 40.50

-8.13 -3.60 4.50 40.50 0.00

OCCAM MD: Coordinates (fort.5)



OCCAM
Molecular Dynamics

box:

8.176050 8.176050 6.949820 0.0000

Number of total molecules:

1808

molecule nr. 1

12

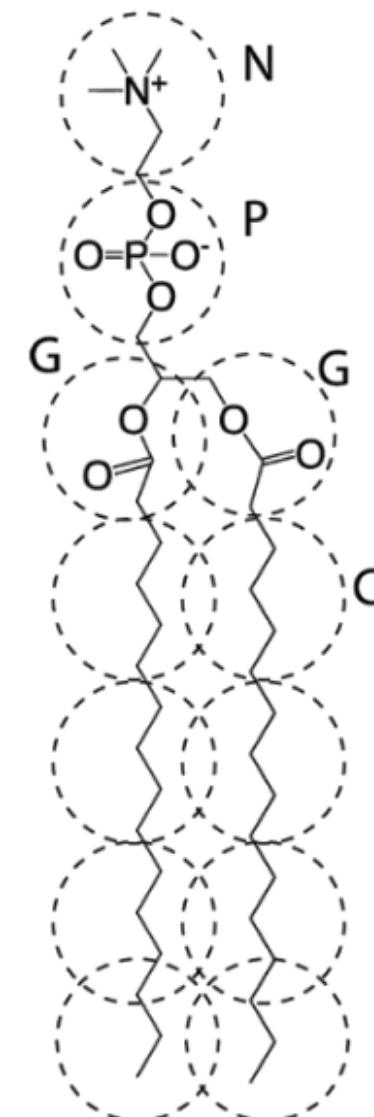
1	N	1	1	4.616	7.945	2.432	2	0	0	0
2	P	2	2	4.239	8.160	2.593	1	3	0	0
3	G	3	3	4.120	7.952	2.980	2	4	5	0
4	G	3	2	4.337	8.039	3.204	3	9	0	0
5	C	4	2	3.968	7.830	3.438	3	6	0	0
6	C	4	2	4.012	7.679	3.888	5	7	0	0
7	C	4	2	4.020	7.491	4.361	6	8	0	0
8	C	4	1	3.756	7.506	4.722	7	0	0	0
9	C	4	2	4.427	8.340	3.521	4	10	0	0
10	C	4	2	4.472	8.355	3.889	9	11	0	0
11	C	4	2	4.278	8.244	4.302	10	12	0	0
12	C	4	1	3.991	7.937	4.396	11	0	0	0

molecule nr. 2

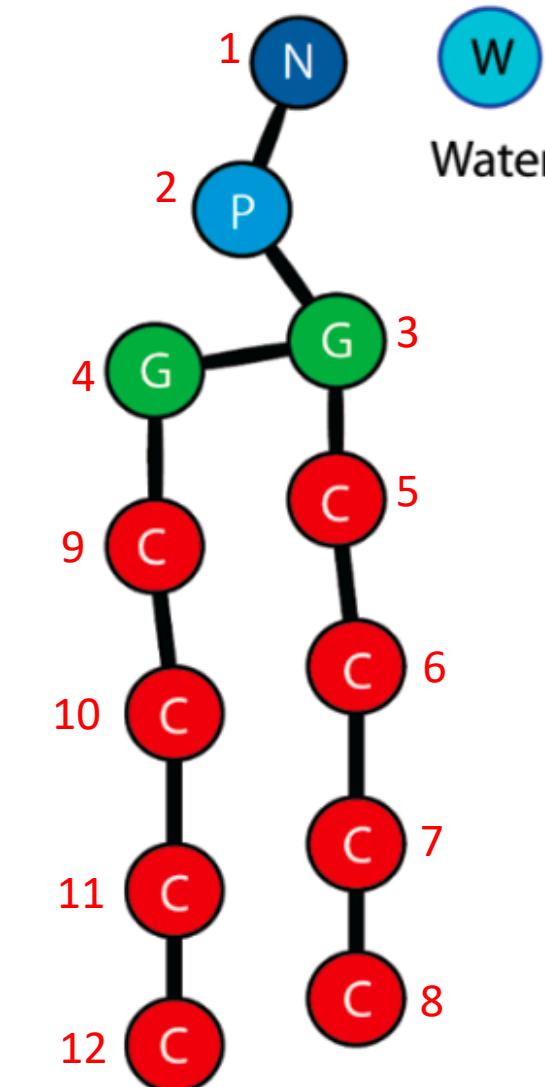
12

13	N	1	1	2.032	0.932	6.459	14	0	0	0
14	P	2	2	2.275	0.537	6.319	13	15	0	0

.....
.....
.....
.....
.....



DPPC



Tutorial: System Composition



OCCAM
Molecular Dynamics

System size:

128 DPPC lipid

1400 CG Water beads

Simulation Set-up:

$T = 325 \text{ K}$

Andersen Thermostat

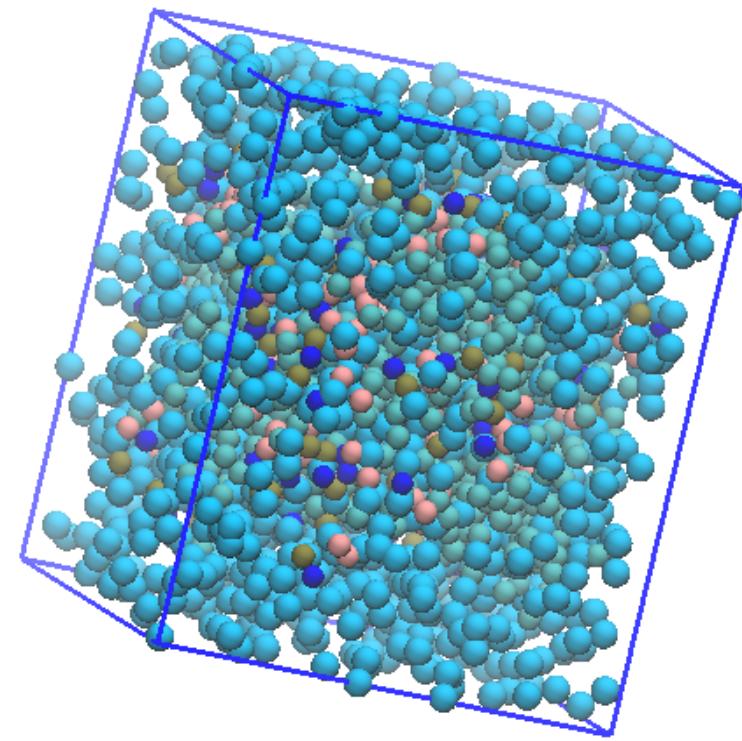
NVT ensemble

Self-Consistent Field Update Density = 100

Objectives:

Self-Assembly of the DPPC lipid bilayer

Tuning the Resolution of the Hybrid Particle-Field CG model

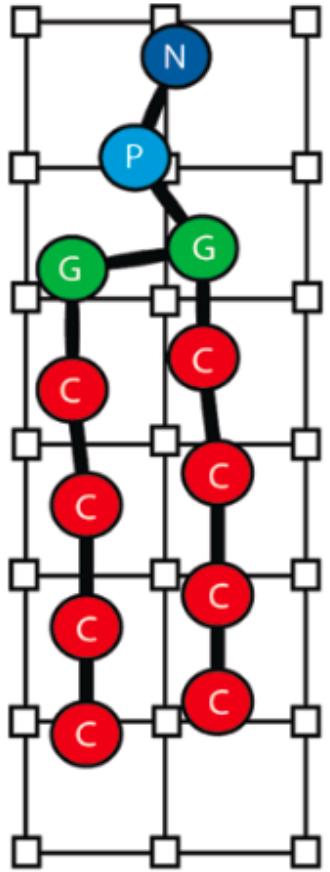


Tutorial: Grid Resolution

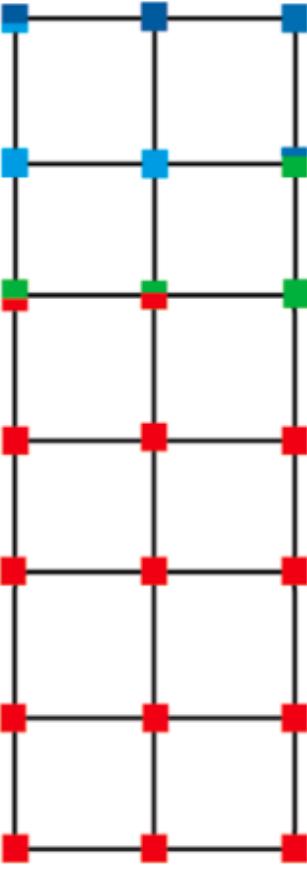


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Particle Sorting



Density Field



density field resolution

$l = 3.2 \text{ nm}$
(R_g of the chain)



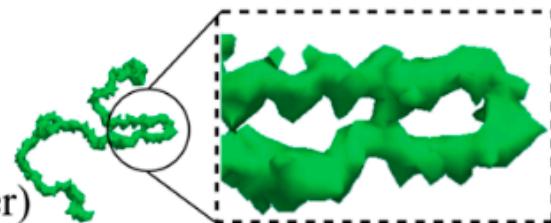
$l = 0.8 \text{ nm}$
(decamers)



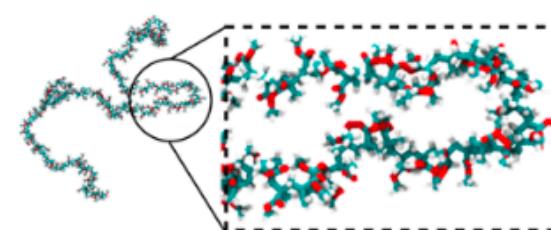
$l = 0.4 \text{ nm}$
(pentamers)



$l = 0.2 \text{ nm}$
(less than monomer)



Particle



Grid size:
0.5, 1.5, 3 nm

Tutorial: Sequence of Instructions



OCCAM
Molecular Dynamics

1. Start the OCCAMCG simulation:

```
>User$ cd grid_05
```

1. Start the OCCAMCG simulation:

```
>User$ chmod 777 occamcg  
>User$ ./occamcg &
```

2. After OCCAMCG simulation you can check the SCF potential and Temperature by the command:

```
User$ sh properties.sh
```

3. Compile the tools to convert the OCCAMCG trajectory (xyz format) into gromacs format:

```
>User$ gfortran -o xyz2gro.x xyz2gro_1.2.f
```

4. Use the code to convert the OCCAMCG traj into gromacs trajectory:

```
>User$ ./xyz2gro.x < to_gro
```

5. Visualize the trajectory by using vmd, and check the perpendicular direction of lipid bilayer. If the direction is different to Z go to step 6.

6. If the normal direction is different from Z, open by text editor (**vim**, **emacs**, **nano**) the file `dens_profile.sh` and modify the variable value `dir`.

7. Calculate the density profiles and visualize the results:

```
>User$ sh dens_profile.sh
```

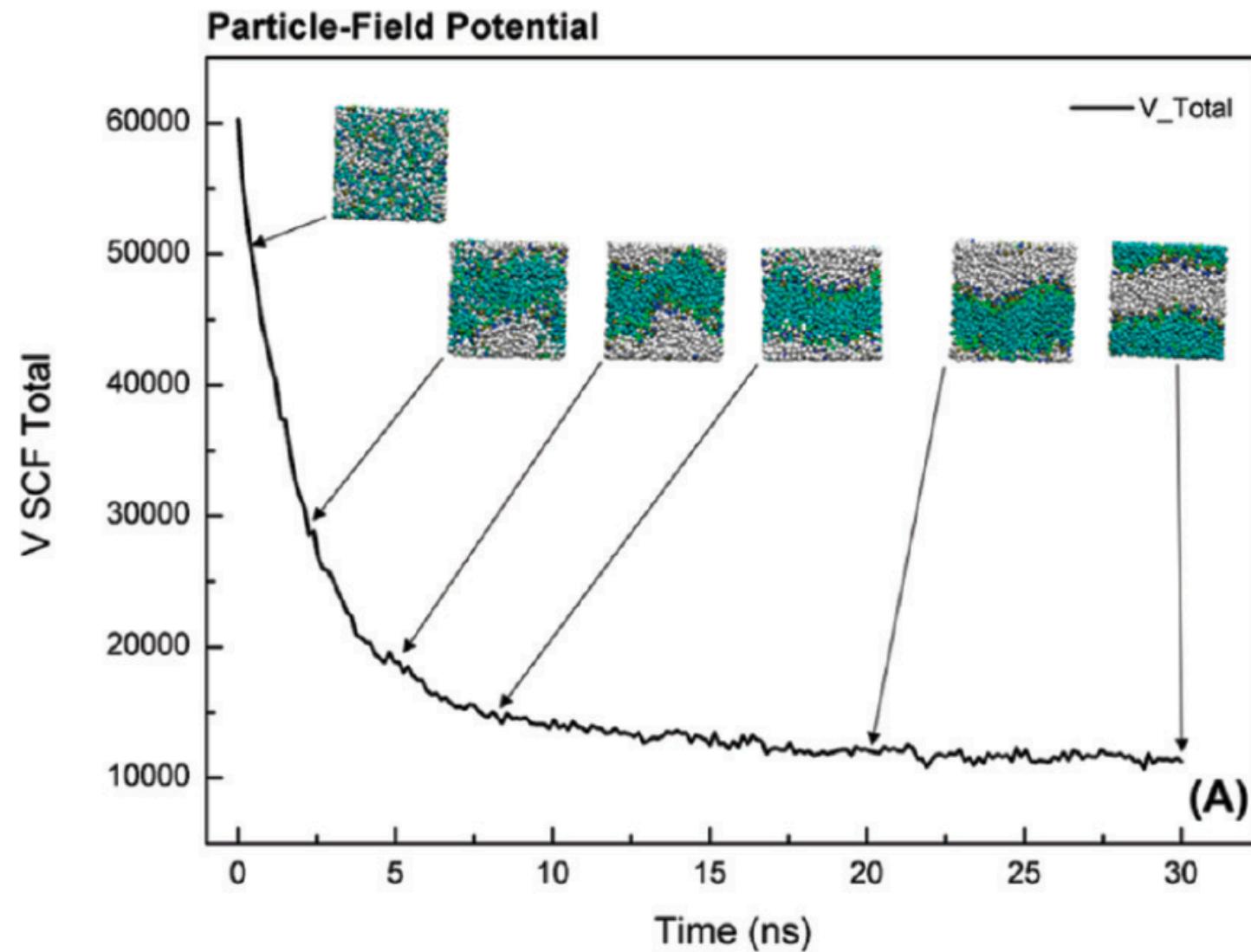


Repeat the same commands for the grid size 1.5 and 3 nm

Tutorial: Properties



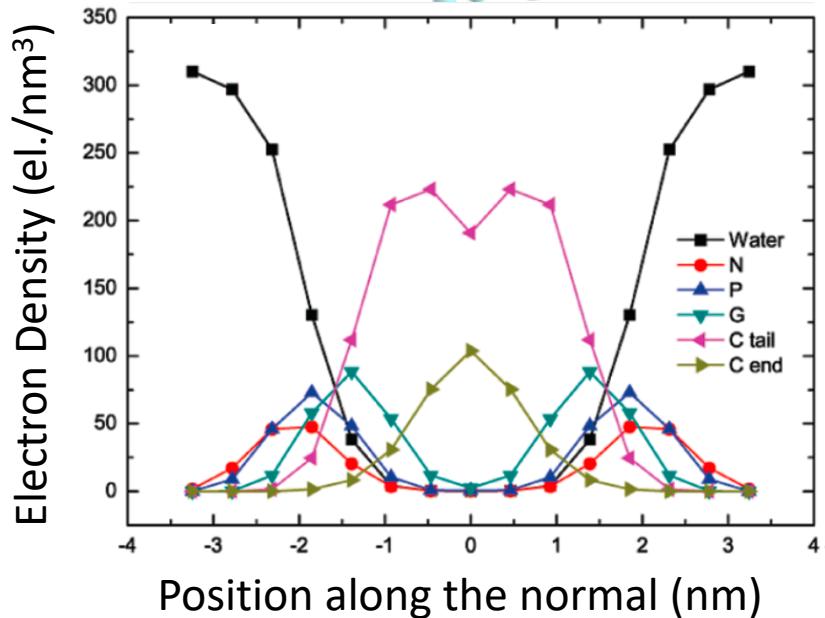
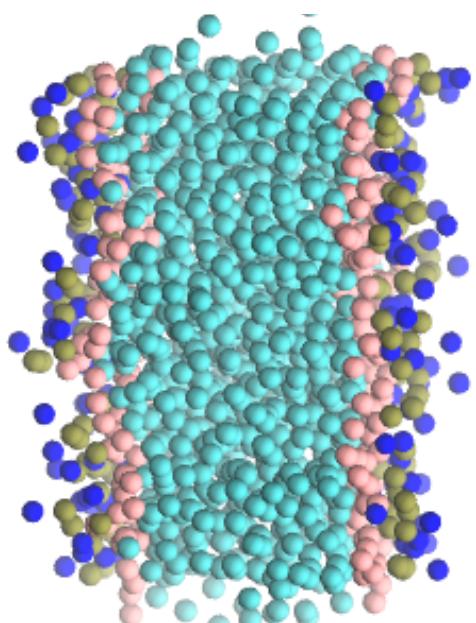
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Molecular Dynamics



Tutorial: Partial Density Profile



OCCAM
Molecular Dynamics



6. If the normal direction is different from Z, open by text editor (**vim**, **emacs**, **nano**) the file `dens_profile.sh` and modify the lines by replacing the Z (default) with the correct direction:

```
g_density -f trj.gro -s topol.tpr -sl 25 -d Z -n index.ndx -dens number -b 10000 -o W.xvg < opt
```

7. Calculate the density profiles and visualize the results:

```
>User$ sh dens_profile.sh
```

8. Calculate the thickness of bilayer. Compute the difference between the two maximum values of P type particle profile. $D_{HH} = |P_1 - P_2|$

```
>User$ less P.xvg
```



Compare the results between different resolutions (grid size)

Tutorial: Partial Density Profile



OCCAM
Molecular Dynamics

END