Coarse-grained Molecular Dynamics Simulations with Membrane Proteins

Marc Gómez Autet
(mgautet@gmail.com)

Universitat Autònoma de Barcelona

MSc in Bioinformatics

Molecular Dynamics Simulations

- Molecular dynamics **(MD) simulations** as ‘computational microscopes’.
- When computationally modeling biomolecular systems, the **molecular model** (degrees of freedom) can be either:
    - Atomic model (All Atom MD)
    - Models grouping atoms (Coarse-Grained MD)
- The molecular model will depend on the type of properties of interest of the system under study.

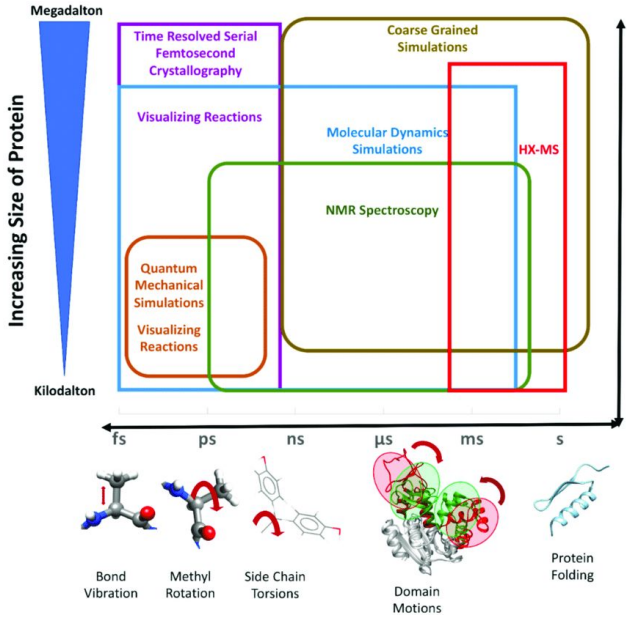
Coarse-Grained MD Simulations

- **Coarse-grained models reduce the level of description by grouping all atom types in larger particles.**

- The lack of resolution confers **unique properties** to the MD simulations. This comes with advantages and limitations of this type of models.
- Depending on the particular parameters we need to analyse for our study: only AA or CG (usually); or both type of models can be suitable.

Coarse-Grained MD Simulations

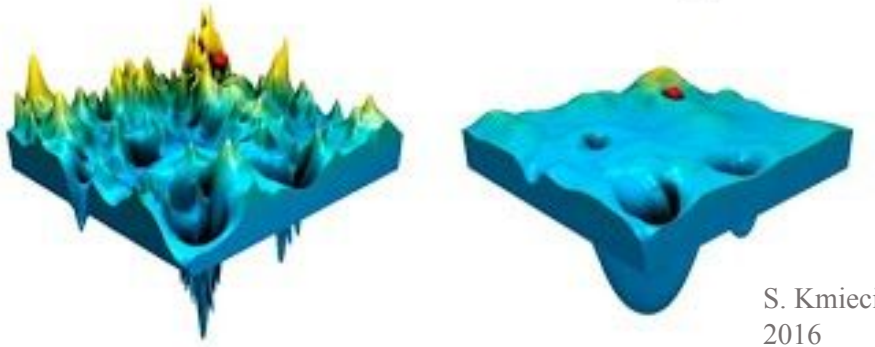
- **Simulation of large systems and long timescales** which are inaccessible to traditional AA simulations.



Srivastava et al., 2018

Coarse-Grained MD Simulations

- **Simulation of large systems and long timescales** which are inaccessible to traditional AA simulations.
- CG simulations show a smoothened potential energy landscape (reduced friction) → In the same simulation time, a CG system can therefore sample more of that energy landscape in a given time of period. → Speed up of the system kinetics. → **The event of study usually occurs in less simulation time** (not well defined).



S. Kmiecik et al., 2016

Coarse-Grained MD Simulations

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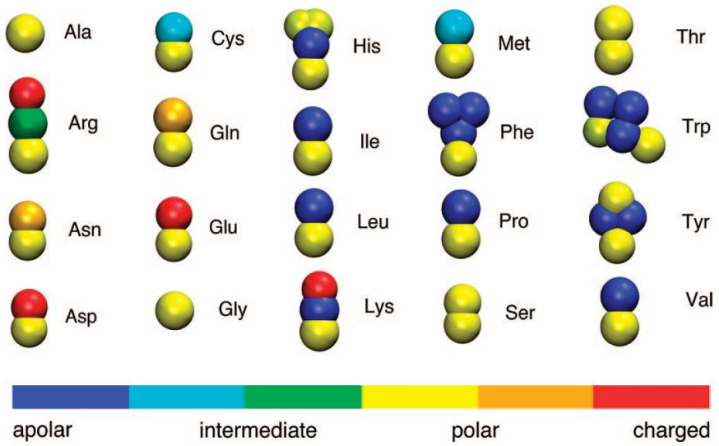
- This advantages come from a **lack of resolution** → The questions under investigation cannot strongly depend on the lost degrees of freedom.
    - Increase resolution, hybrid systems, backmapping?

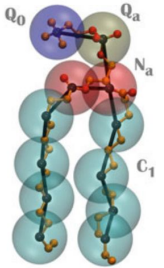
The MARTINI Forcefield

- 4 to 1 mapping.
  - *4 main types of particle (charged (Q), polar (P), non-polar (N) and apolar (C)).*
  - *18 final bead types or 'building blocks'*
- Realistic structural information.
  - *Preferred interaction modes*
  - *Aggregation patterns*
  - *Lipid-mediated effects*
- Speed up of the system kinetics (time scale)
- **Limitations**
  - Resolution
  - Elastic Network
  - Excessive aggregation



Periole and Marrink, 2013

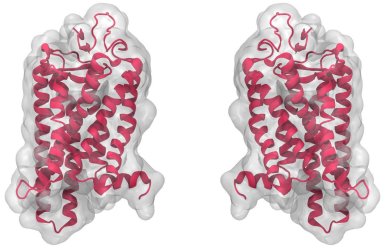
DPPC



Water

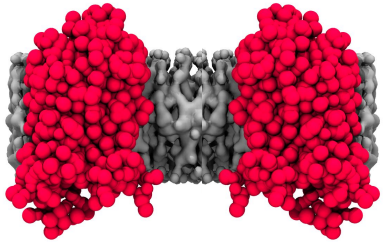
Monticelli et al., 2013

Today's Protocol



PDB (4dkl)

CHARMM-GUI
(MARTINI MAKER module)



GROMACS + MARTINI FF
(MD simulation package)

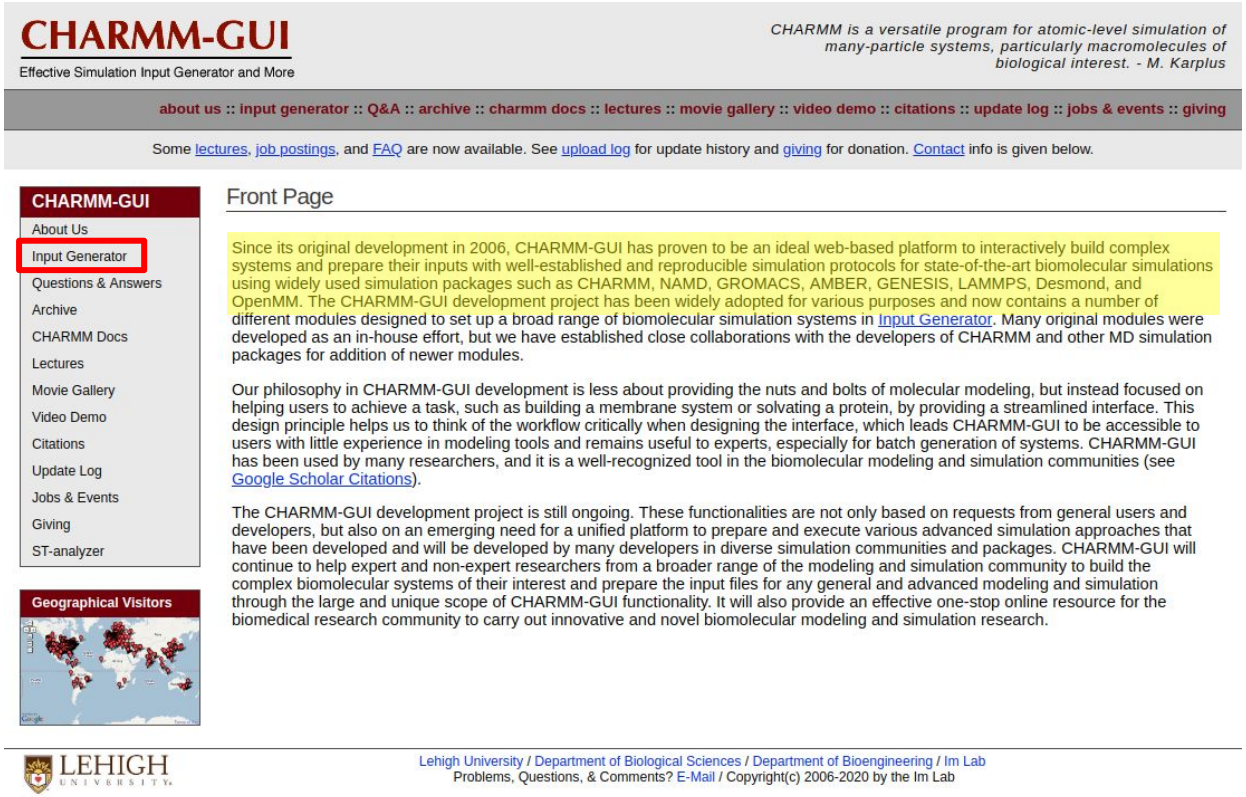
EM → Equilibration → **Production (30ns)**

Python
(Jupyter notebooks + MD Analysis)

Analysis

http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



http://www.charmm-gui.org/

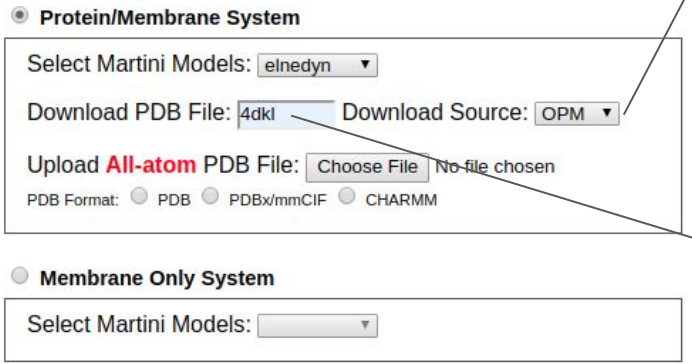
Generating a CG system using CHARMM-GUI

all atom

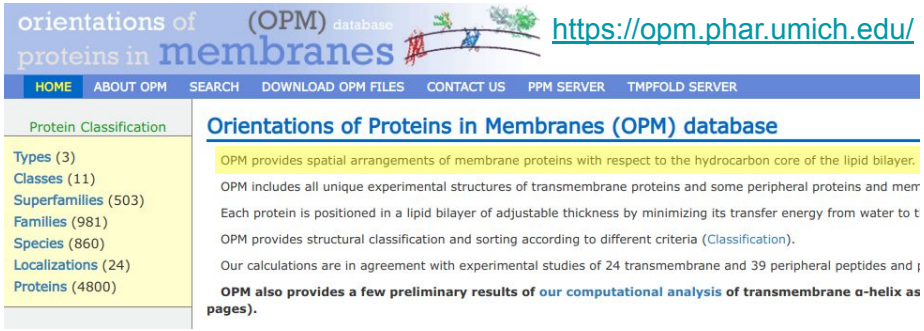
coarse-grained

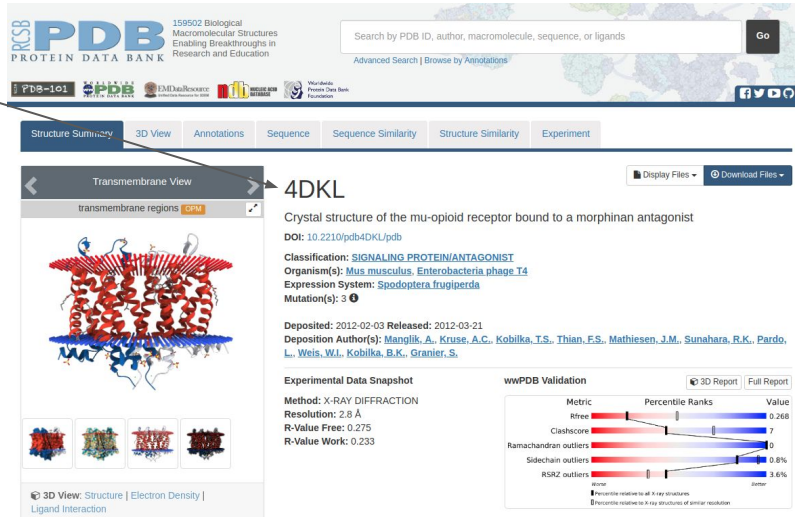
http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



https://opm.phar.umich.edu/

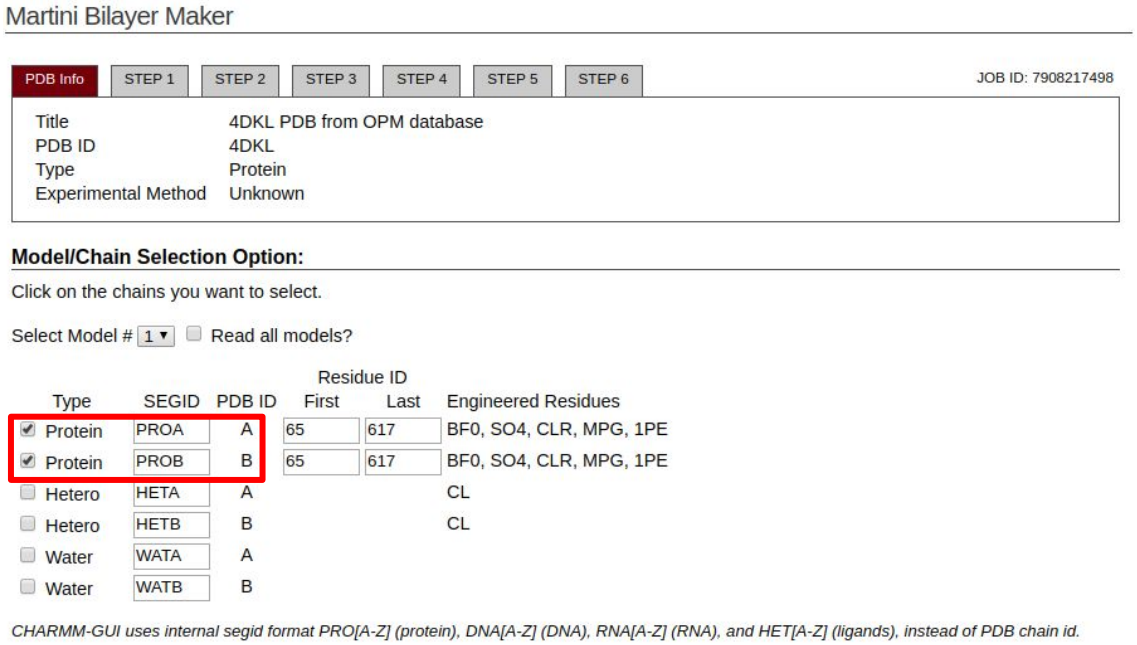




https://www.rcsb.org/structure/4dkl

http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



http://www.charmm-gui.org/

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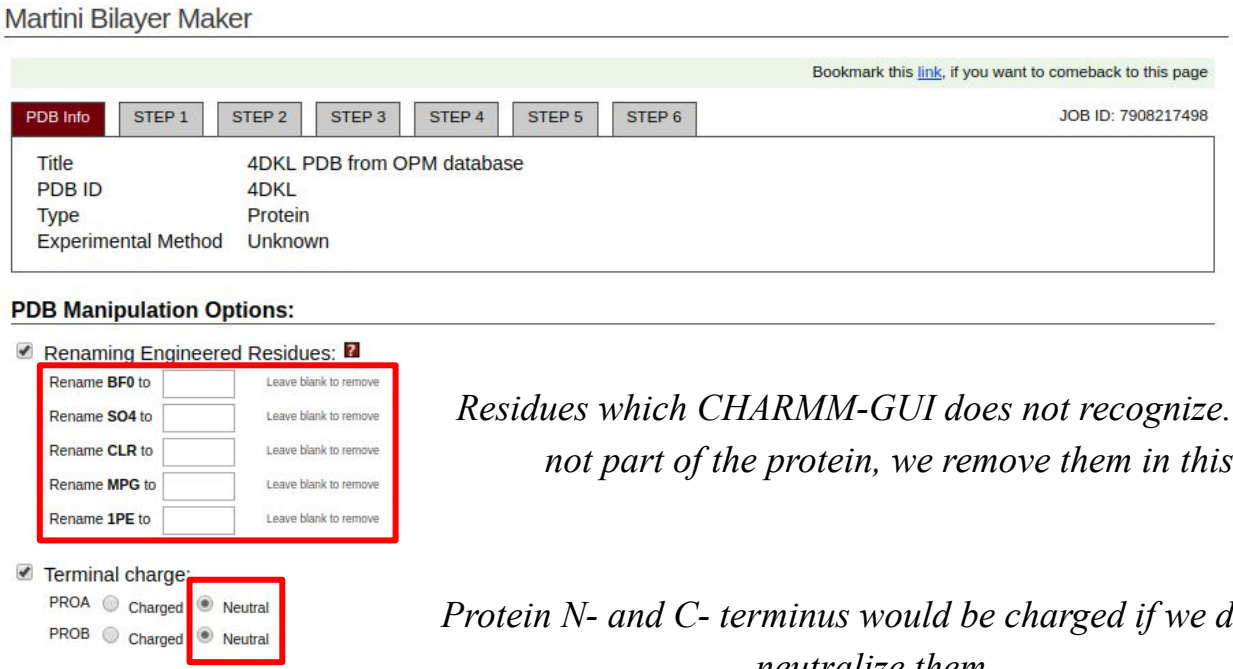
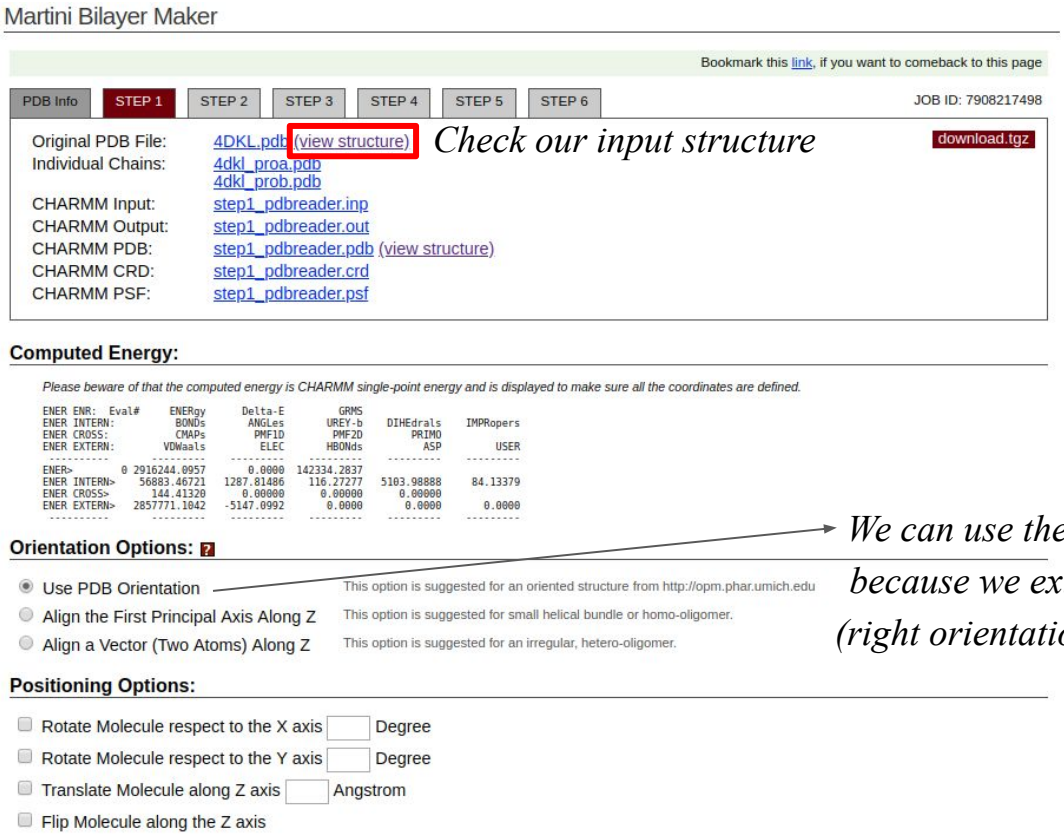


Residues which CHARMM-GUI does not recognize. As they are not part of the protein, we remove them in this case.

Protein N- and C- terminus would be charged if we do not neutralize them.

http://www.charmm-gui.org/

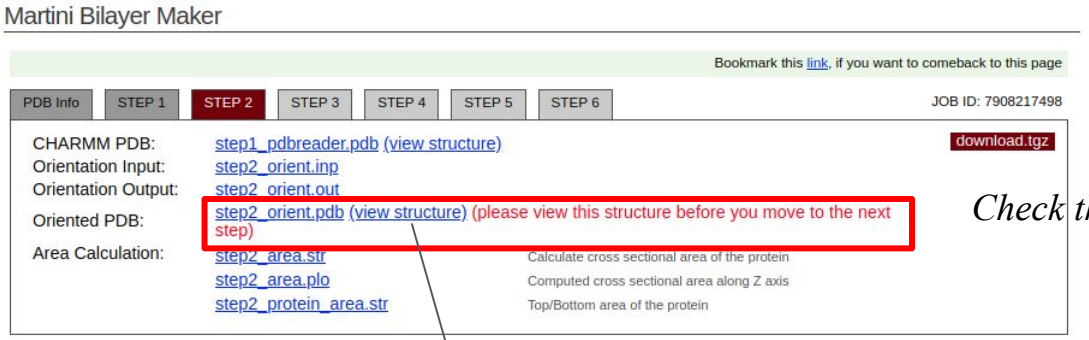
Generating a CG system using CHARMM-GUI



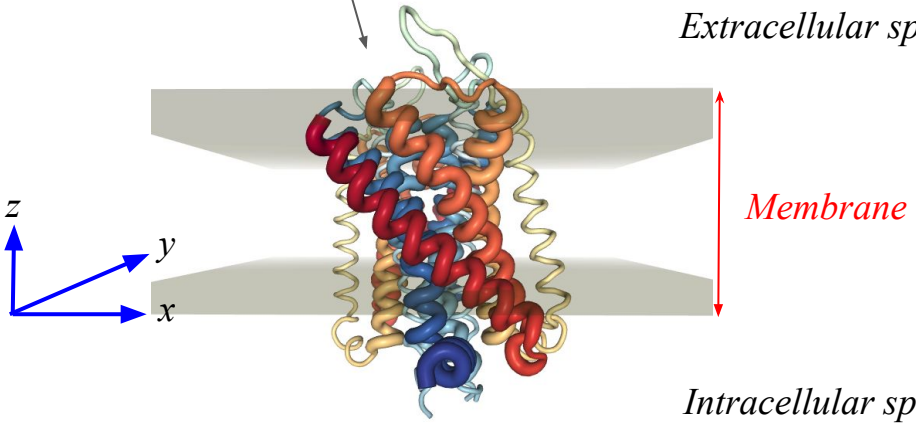
We can use the orientation of our PDB because we extracted it from the OPM (right orientation inside the membrane).

http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



Check the orientation in the membrane



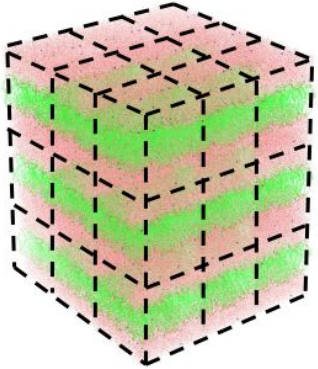
Extracellular space

Intracellular space

http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI

In no case, the protein should be able to interact herself with any of the images in the periodic boundary conditions.



System Size Determination Options:

Homogeneous Lipid "Homogeneous Lipid" option is no longer supported. You can use "Heterogeneous Lipid" option even for homogeneous lipid bilayer building.

Heterogeneous Lipid

1. Box Type: Rectangular

2. Length of Z based on:
   Water thickness 15 (Minimum water height on top and bottom of the system)

3. Length of XY based on:
   Ratios of lipid components
   Numbers of lipid components

Length of X and Y: 120 (initial guess)
(The system size along the X and Y must be the same)

Show the system info click this once you fill the following table:

Lipid Type	Charge [e]	Tail Info. [sn1/sn2]	Images	Upperleaflet Ratio (Integer)	Lowerleaflet Ratio (Integer)	Surface Area
▸ Sterols						
▸ PA (phosphatidic acid) Lipids						
▾ PC (phosphatidylcholine) Lipids						
DAPC	0	20:4-22:5 / 20:4-22:5	[Image]	0	0	76.1
DBPC	0	20:0-22:0 / 20:0-22:0	[Image]	0	0	65.4
DFPC	0	18:3 / 18:3	[Image]	0	0	77.9
DGPC	0	20:1-22:1 / 20:1-22:1	[Image]	0	0	68.5
DIPC	0	18:2 / 18:2	[Image]	0	0	76.5
DLPC	0	12:0-14:0 / 12:0-14:0	[Image]	0	0	64.1
DNPC	0	24:1-26:1 / 24:1-26:1	[Image]	0	0	68.2
DOPC	0	16:1-18:1 / 16:1-18:1	[Image]	0	0	69.7
DPPC	0	16:0-18:0 / 16:0-18:0	[Image]	0	0	63.0
DRPC	0	22:6-24:6 / 22:6-24:6	[Image]	0	0	95.7
DTPC	0	08:0-10:0 / 08:0-10:0	[Image]	0	0	60.5
DVPC	0	16:1-18:1 / 16:1-18:1	[Image]	0	0	65.6
DXPC	0	24:0-26:0 / 24:0-26:0	[Image]	0	0	62.3
DYPC	0	12:1-14:1 / 12:1-14:1	[Image]	0	0	61.6
LPPC	0	12:0-14:0 / 16:0-18:0	[Image]	0	0	61.4
PAPC	0	16:0-18:0 / 20:4-22:5	[Image]	0	0	71.5
PEPC	0	16:0-18:0 / 20:2	[Image]	0	0	68.3
PGPC	0	16:0-18:0 / 20:1-22:1	[Image]	0	0	65.5
PIPC	0	16:0-18:0 / 18:2	[Image]	0	0	67.8
POPC	0	16:0-18:0 / 16:1-18:1	[Image]	1	1	68.3

Calculated Number of Lipids:

Lipid Type	Upperleaflet Number	Lowerleaflet Number
POPC	179	178

Calculated XY System Size:

	Upperleaflet	Lowerleaflet
Protein Area	2196.35966	2295.08284
Lipid Area	12225.7	12157.4
# of Lipids	179	178
Total Area	14422.05966	14452.48284
Protein X Extent	38.26	
Protein Y Extent	28.25	
Average Area	14437.27	
A	120.16	
B	120.16	

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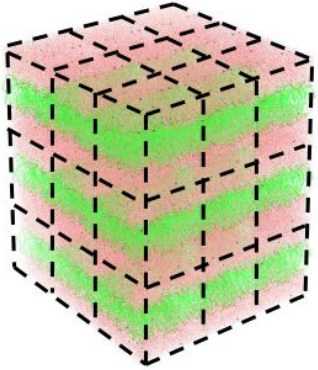

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If we give a X and Y length (in Å) which would generate a system too small for our protein...

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POPC	5	4

Calculated XY System Size:

	Upperleaflet	Lowerleaflet
Protein Area	2196.35966	2295.08284
Lipid Area	341.5	273.2
# of Lipids	5	4
Total Area	2537.85966	2568.28284
Protein X Extent	38.26	
Protein Y Extent	28.25	
Average Area	2553.07	
A	50.53	
B	50.53	

The system is smaller than the protein extent.

Information about the system that will be generated

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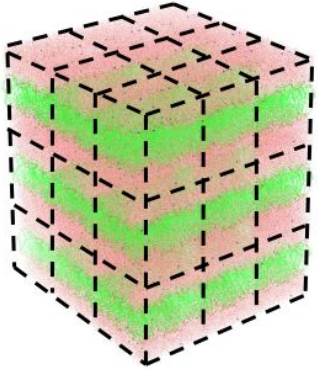

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A	120.16	
B	120.16	

Information about the system that will be generated

In this case we'll use a 100% POPC membrane, but more complex and realistic membranes can be created by combination of lipid ratios.

http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI

Martini Bilayer Maker

Bookmark this link, if you want to comeback to this page

PDB Info | STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 | STEP 6 — JOB ID: 7908217498

download.tgz

Oriented PDB:	step2_orient.pdb (view structure)	
System Size Input:	step3_size.inp	
System Size Output:	step3_size.out	
System Size:	step3_size.str	
Packing Simulation:	step3_packing.inp	Packing Simulation Input
	step3_packing.out	Packing Simulation Output
	crystal_image.str	Crystal Image
	step3_packing_pol.str	Topology File of Pseudo Lipid Spheres
	step3_packing.pdb (view structure)	Generated Packed System (please view this structure before you move to the next step)

Determined System Size:

Box Type	Rectangle		
Crystal Type	TETRAGONAL		
System Size	A	120.15518	Dimension along the A (X) axis
	B	120.15518	Dimension along the B (Y) axis
	C	100.178	Dimension along the C (Z) axis
Crystal Angle	Alpha	90.0	Angle between the axis B and C
	Beta	90.0	Angle between the axis A and C
	Gamma	90.0	Angle between the axis A and B
# of Lipids	on Top	179	
	on Bottom	178	
Z Center	-3.196		Center of the system along the Z axis

System Building Options:

- Insertion method — Build system using insertion method
- Replacement method — Build system using replacement method
- Check lipid ring (and protein surface) penetration

For this system, insertion method can not be used. Replacement method will be used instead.

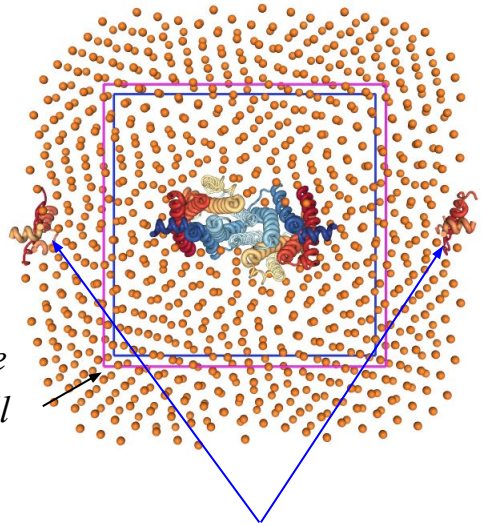
Component Building Options:

- Include Ions
  - 0.15 M NaCl (ion concentration) Calculate number of ions
  - Add neutralizing ions

78 positive ions and 102 negative ions will be generated. Note that this is the estimated ion numbers, so the actual ion numbers may differ.

Ion Placing Method: Distance

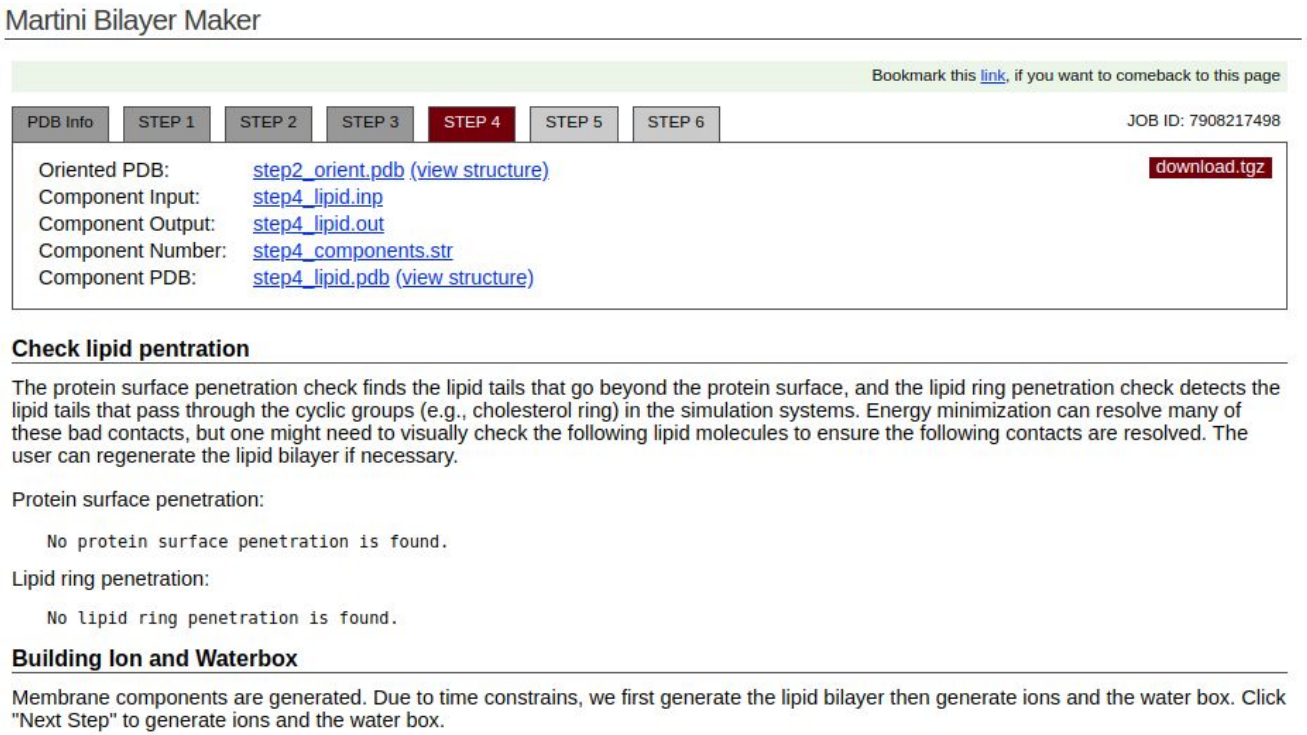
The squares define the system that will be generated.



Periodic boundary images

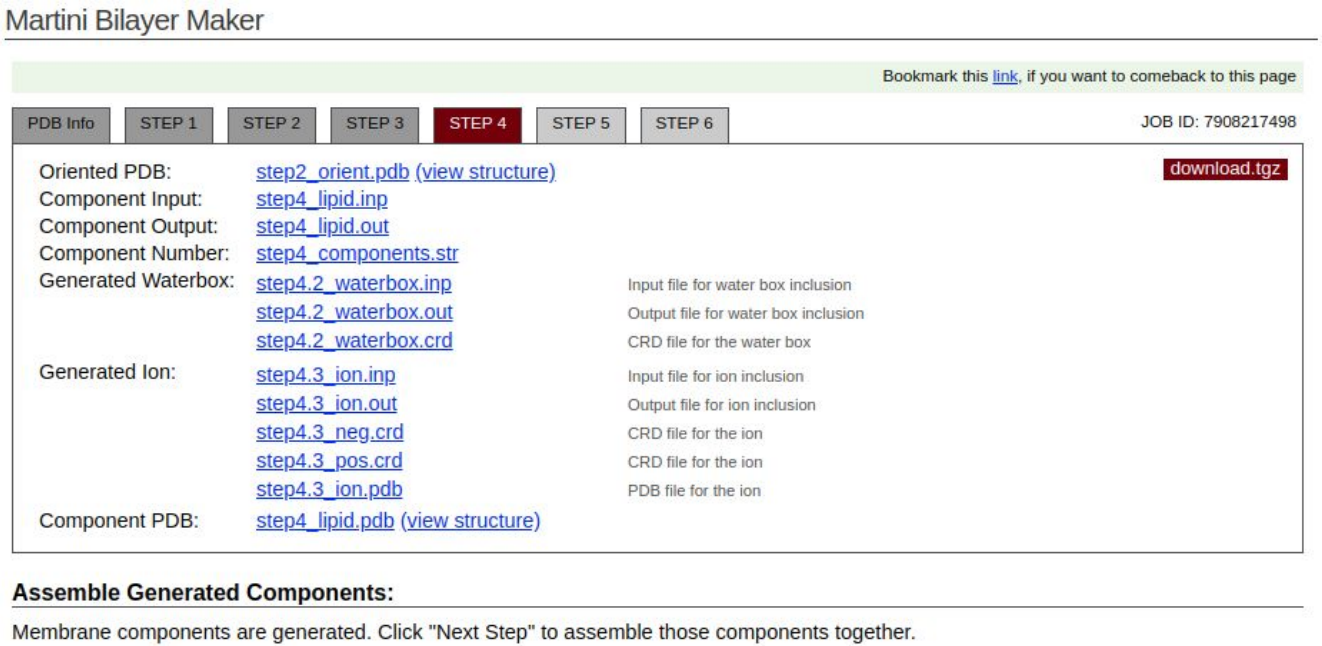
http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



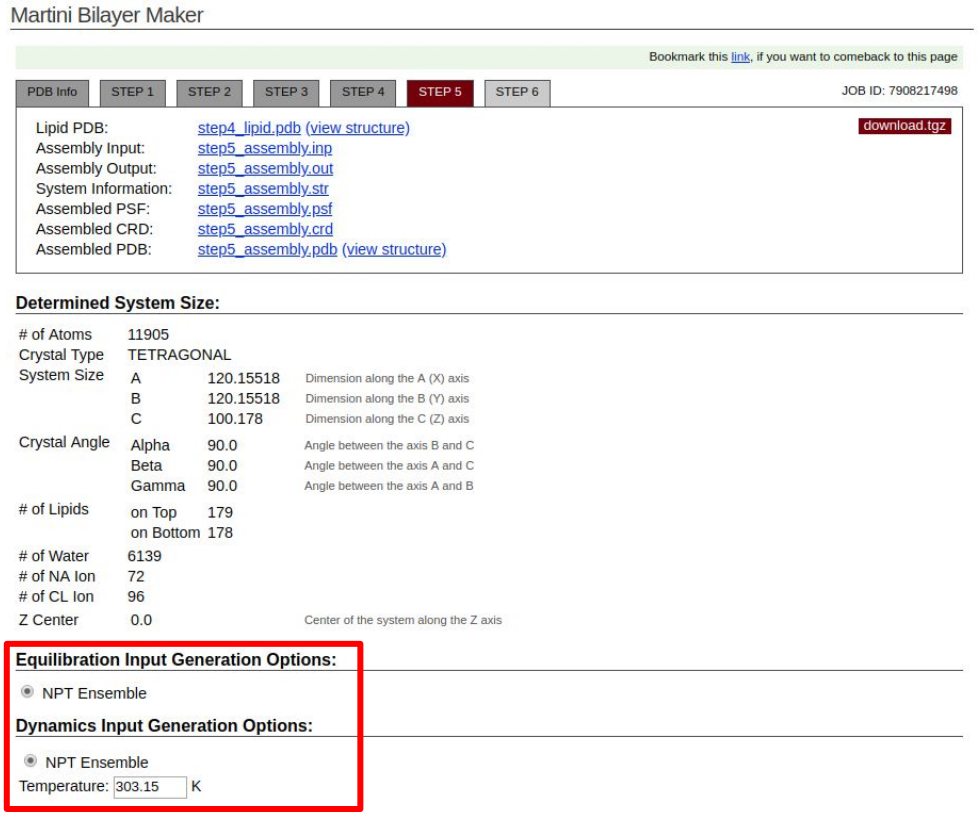
http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



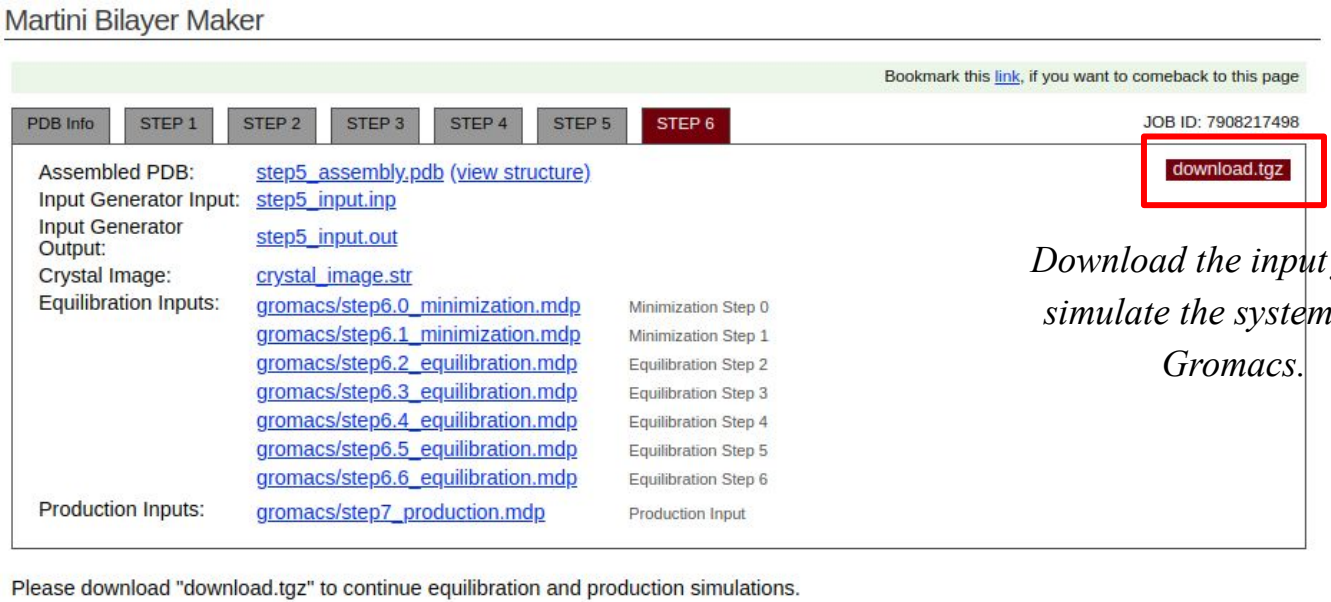
http://www.charmm-gui.org/

Generating a CG system using CHARMM-GUI



http://www.charmm-gui.org/

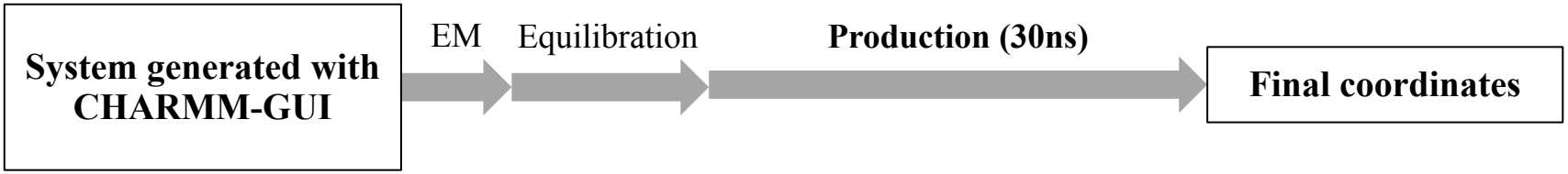
Generating a CG system using CHARMM-GUI



Download the input files to simulate the system using Gromacs.

CG MD Protocol

GROMACS + MARTINI FF




```
index.ndx                step6.0_minimization.mdp   step6.5_equilibration.mdp
PROA_P.itp               step6.1_minimization.mdp   step6.6_equilibration.mdp
PROB_P.itp               step6.2_equilibration.mdp  step7_production.mdp
README                   step6.3_equilibration.mdp  system.top
step5_charmm2gmx.pdb     step6.4_equilibration.mdp  toppar
```

To simulate with GROMACS we need:

Coordinates (.gro/.pdb) | **FF + Topologies (.top/.itp)** | **Simulation options (.mdp)**