The MARTINI 3.0 CG Force Field: Open beta (version 3.0.b.3.2)

Since its release in 2007 (1), the MARTINI 2 coarse-grain force field have been expanded and tested with a great variety of systems, including many lipids (2), sterols (3), proteins (4–6), sugars (7), polymers, etc. Despite the huge success of the MARTINI model, certain problems have been reported as excessive protein and sugar aggregation (8, 9) and water freezing (10). Along with the modeling demand of new and challenging systems, these limitations pushed the MD group of Groningen, headed by Prof. S.J. Marrink, to improve the CG beads - the fundamental building blocks of MARTINI - until now largely untouched since 2007. The main features of this new version of MARTINI are:

- **New parametrization of small (S) and tiny (T) beads**, designed to be fully balanced with the normal (N) size beads. Now, you can have CG models of your aromatic rings reproducing realistic stacking distances (with better densities and oil-water partitioning). You also can try to build models in 4-1, 3-1 and 2-1 resolution.

- **New chemical-type beads tuned to model systems not included in the current version 2**. For instance, we now have more beads with hydrogen-bonding capabilities (all polar and non-polar beads) and Q-beads dedicated for modeling divalent ions (Q2). Water has also its own special bead, parametrized to improve its miscibility with other beads and also avoid freezing problems.

- **Improvements in the interaction matrix, including more interaction levels and smoother transitions between the beads**. Interaction matrix is now divided in three blocks: organic, water and ions. Each block has independent parametrization (based in experimental data as oil-water partitioning, miscibility, densities, trends in salvation free energies, etc), which leads to different definition for interactions levels. Different blocks have different properties regarding bead size.

- **Reformulation of charged (Q) bead:** Trends in solvent polarization and ion-pi interaction were implicitly included in the Lennard-Jones potential with neutral (water and organic) beads. Together with new Q-Q interaction levels, this approach turned possible the usage of Q-beads in small and tiny sizes. Divalent Q beads (Q2) were also developed following the same principle. The definition of chemical types for Q-beads is not only based in hydrogen-bonding capabilities, but includes hard-soft concepts and the Hofmeister series.

- **Quality control tests:** besides the experimental data of small (from 1 to 3 bead) molecules, a big collection of tests were included in the parametrization protocol, what we called “quality control tests”. Formulate as yes/no questions, these benchmark simulations have as goal to look fundamental aspects of the systems, that could easily indicate clear problems of the force field. For example, some monosaccharides in water should be soluble, even in relative high concentrations. So, if a short simulation of a low concentration sugar solution show all monosaccharides collapsing in one aggregate, there are something fundamentally wrong with the parameters and the parametrization should come back one step to improve this aspect.

- **New CG models with MARTINI 3:** the current list includes all the main biomolecules (lipids, nucleic acids, proteins ans sugars), organic solvents, (poly)aliphatic and (poly)aromatic rings, polymers, ionic liquids and other material-science related systems. Collaborations to expand the list are welcome.

--- **Protein CG models built with MARTINI 3**, with changes in the backbone and side chains. Backbone beads does not depend of secondary structure anymore while extensive use of small and tiny beads in the side chains guarantees better packing and modeling of pockets and cavities. Your soluble proteins should be much less sticky, with solubility dependent of salt concentration. Modeling of protein flexibility will improve with the usage of Go Models.

Quick start with MARTINI 3

Here you can find some tips and tricks about how to run simulations with MARTINI 3. Familiarity with the current MARTINI 2 version and GROMACS is assumed. If this previous knowledge is not your case, please first consult the GROMACS user manual and web-pages (www.gromacs.org). There are also excellent GROMACS and MARTINI tutorials. Here are the tips and tricks:

- **mdp files, input parameters and GROMACS VERSION:** We recommend the use of molecular dynamic parameters suggested by de Jong et al (11) together with the latest versions of GROMACS (2016.x or 2018.x). An example of general input parameter (new-rf.mdp) can be found here: http://cgmartini.nl/index.php/force-field-parameters/input-parameters With appropriate models (including the usage of constraints and virtual particles), all systems should be stable in MD simulations with a **time step of 20 fs**.

- **Building your simulation box with a bilayer:** As the mapping (and number of beads) of the main lipids did not change from version 2 to 3, you can continue using your favorite programs to build bilayers. We recommend Insane (12) or CHARMM-GUI (13, 14). Only remember to change the name of your water (from W to **WN**) and ions (from NA and CL to **TNA** and **TCL**, respectively) in your top file. PS: new cholesterol and glycolipid models for MARTINI 3 are not available yet.

- **Creating the itps for proteins:** for now, you can use an adapted version of MARTINIZE (4) distributed together with the itp files of MARTINI 3 to create the CG models of your protein. You can run the following command to generate the necessary gro and itp files.

/martinize -f protein.pdb -ff martini303v.partition -x CG.pdb -o CG.top -dssp dssp -elastic

Besides, we recommend the addition of side chain dihedral corrections to the model based in the crystallographic structure. You can do it using VMD (15), an adapted addDihedral.tcl (16)and bbsc.sh scripts.

./bbsc.sh Protein.itp protein.pdb

These temporary solutions (adapted MARTINIZE and addDihedral.tcl) will be replaced by MARTINIZE 2 in the near future. Be aware that protein bonded parameters are still under development, which includes the values for force constant and cut-off of your elastic network. You should check if the default values are good enough to capture the necessary flexibility of your protein. Pay also attention to proper protonation state and ion concentration. They really could affect the aggregation propensity in the current model. As protein solubility is still being calibrated, you may have some issues with dimeric/multimeric proteins. In case you have problems, report it in the forum.

- **Parametrization of new molecules:** as in the previous version, in MARTINI 3 we follow a systematic way for parametrization of new molecules, combining top-down (for choice of bead types) and bottom-up (for bonded parameters) strategies. The main differences in the approaches are regarding the use of small and tiny beads, that **are not exclusive for rings in MARTINI 3 (with a few expections for S-beads in MARTINI 2)**. Besides, the parametrization of the bond lengths between beads is based in molecular volume/surface area of the molecules. The appendices of this document should be enough information for advanced user or developers of MARTINI that would like to initiate your own parametrization using the new version. Anyway, in case of doubts, please send a message in our forum.

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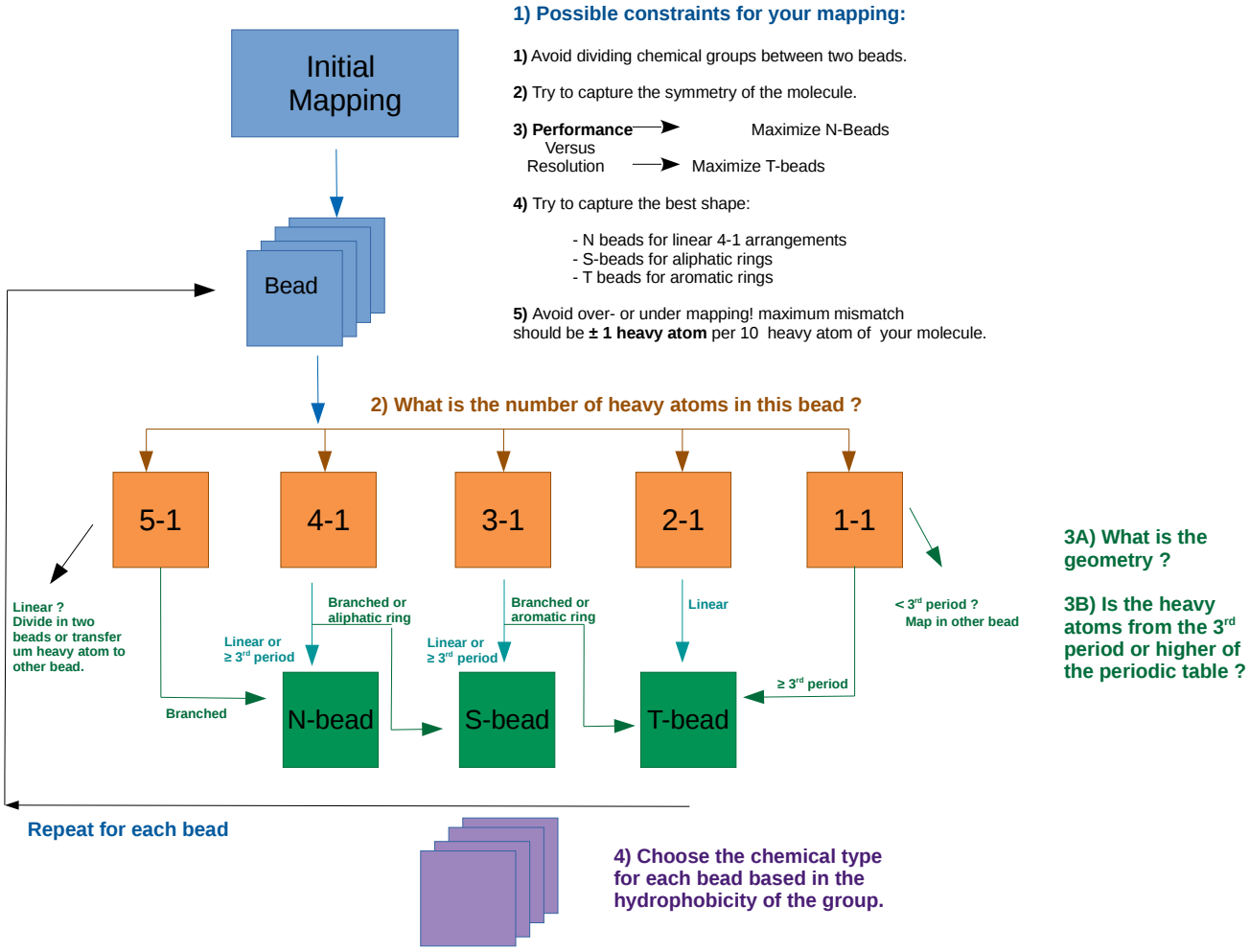
APPENDIX 1: Rules for parametrization of new molecules



APPENDIX 2: Interaction Matrix

-Blocks with different interaction levels

organic
water
ion
ion-organic/water

-Rules for donor/acceptor labels ("d" and "a") involving: N0 to P5 beads:

	NN/NS/NT	SS/ST	TT
d-d/a-a*	2	2	1
d-a	0	-1	-3
W-d/a	1	1	1
Qp-d/Qn-a*	1	1	1
Qp-a/Qn-p*	-1	-2	-3

* new level cannot be higher then 12

	Q2	Q1	Qn	Qp	Q0	P5	P4	P3	P2	P1	N3	N2	N1	N0	C6	C5	C4	C3	C2	C1	W	
Q2	13	12	12	12	12	1	2	3	3	4	4	5	6	7	14	16	18	20	21	21	0	**Q2**
Q1	12	0	1	1	10	2	3	4	4	4	5	6	7	8	13	15	17	18	21	21	1	**Q1**
Qn	12	1	8	4	10	4	5	5	5	5	6	7	8	9	12	14	16	17	20	20	2	**Qn**
Qp	12	1	4	8	10	4	5	5	5	5	6	7	8	9	11	12	14	15	20	20	2	**Qp**
Q0	12	10	10	10	9	5	5	5	5	5	6	7	8	9	9	10	12	14	19	19	3	**Q0**
P5	1	2	4	4	5	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	4	**P5**
P4	2	3	5	5	5	5	5	6	7	8	9	10	11	12	12	13	14	15	16	17	5	**P4**
P3	3	4	5	5	5	6	6	7	7	8	9	10	11	12	12	13	14	15	16	17	6	**P3**
P2	3	4	5	5	5	7	7	7	7	8	8	9	10	11	11	12	13	14	15	16	6	**P2**
P1	4	4	5	5	5	8	8	8	8	8	8	9	10	10	11	12	13	14	15	16	7	**P1**
N3	4	5	6	6	6	9	9	9	8	8	8	9	10	10	11	11	12	13	14	15	7	**N3**
N2	5	6	7	7	7	10	10	10	9	9	9	9	10	10	11	11	12	13	14	15	8	**N2**
N1	6	7	8	8	8	11	11	11	10	10	10	10	10	10	11	11	12	12	13	14	9	**N1**
N0	7	8	9	9	9	12	12	12	11	10	10	10	10	10	11	11	12	12	13	13	10	**N0**
C6	14	13	12	11	9	13	12	12	11	11	11	11	11	11	10	10	11	12	13	13	12	**C6**
C5	16	15	14	12	10	14	13	13	12	12	11	11	11	11	10	10	11	11	13	13	13	**C5**
C4	18	17	16	14	12	15	14	14	13	13	12	12	12	12	11	11	11	11	13	13	15	**C4**
C3	20	18	17	15	14	16	15	15	14	14	13	13	12	12	12	11	11	11	12	12	16	**C3**
C2	21	21	20	20	19	17	16	16	15	15	14	14	13	13	13	13	13	12	11	11	17	**C2**
C1	21	21	20	20	19	18	17	17	16	16	15	15	14	13	13	13	13	12	11	11	18	**C1**
W	0	1	2	2	3	4	5	6	6	7	7	8	9	10	12	13	15	16	17	18	-	**W**
	Q2	**Q1**	**Qn**	**Qp**	**Q0**	**P5**	**P4**	**P3**	**P2**	**P1**	**N3**	**N2**	**N1**	**N0**	**C6**	**C5**	**C4**	**C3**	**C2**	**C1**	**W**	

v2.2 levels	**0**		**1**		**2**		**3**		**4**			**5**		**6**		**7**	**8**	**9**		
v3.0 levels	0	1	**2**	3	**4**	5	**6**	7	**8**	**9**	10	**11**	12	**13**	14	**15**	16	**17**	**18**	19	20	**21**
	hyper attractive		**supra attractive**		**attractive**		**almost attractive**		**semi attractive**		**intermediate**			**almost intermediate**		**semi repulsive**		**almost repulsive**	**repulsive**	**super repulsive**		

APPENDIX 3: hexadecane/water and octanol/water partitioning and examples of possible usage of the bead

Oil-water partitions - kJ/mol			Examples of possible usage							
Normal	**HD-->WN**	**OCOS-->WN**	**name**	**structure**	**name**	**structure**	**name**	**structure**	**name**	**structure**
C1	18.2	18.3	butane	C-C-C-C	neopentane	C-(CH3)4 *	2-methyl-butane	C-C-(CH3)-C-C *	2-methyl-butane	C-C-(CH3)-C-C *
C2	16.5	17.5								
C3	12.8	15.2	butene	C-C=C-C						
C4	8.9	12.8	chloro propane	C-C-C-Cl	propanethiol	C-C-C-SH	buta-1,3-diene	C=C-C=C	ethyl methyl sulfide	C-C-S-C
C5	5.2	10.1	butyne	C-C≡C-C						
C6	3.5	9.1	imine	C-C=N(CH3)-C *						
N0	-0.2	6.2	diethyl ether	C-C-O-C-C						
N1	-4.7	4.0								
N2	-8.3	1.9	ethylmethylamine	C-NH-C-C						
N3	-10.5	1.0	propanol	C-C-C-OH	2-methyl-propanol	C-C(CH3)-C-OH				
P1	-12.7	-1.1	prop-2-en-1-ol	-C=C-C-OH						
P2	-14.7	-2.6	propanoic acid	-C-C-COOH	N-methylacetamide					
P3	-16.9	-4.2	propylene glycol	-C(OH)-C(OH)-C						
P4	-19.4	-6.4	propanamide	-C-C-CONH2						
P5	-23.9	-10.6	amino acid	NH3+-C-COO-						
Q0	-34.5	-12.4	choline	C-C-N-(C)3						
Qp	-46.5	-15.5	propianate	-C-C-COO(-)						
Qn	-46.4	-14.7	propyl-ammonium	-C-C-C-NH2(+)						
Q1	-60.6	-16.5	phosphate -1	-PO4(-1)-						
Q2	-63.2	-16.9	phosphate -2	-PO4(-2)	sulfate	-SO4(-2)				
N0d/a	1.4	7.8					diethyl ether	C-C-O-C-C		
N1d/a	-2.1	6.4	butanone (a)	-C-C(=O)-C-C-			ethyl methyl ether	C-O-C-C		
N2d/a	-6.3	3.4	propanal (a)	-C-C-C=O	n-propylamine (d)	-C-C-C-NH2	methyl acetate (a)	-C-O-C(=O)-		
N3d/a	-8.2	2.5								
P1d/a	-10.6	1.0								
P2d/a	-12.8	-0.9	1,3-dicarbonyl	-C(=O)-C-C(=O)-						
P3d/a	-14.7	-2.0	n,n-dimethylformamide (a)	C(=O)-N-(CH3)2						
P4d/a	-16.4	-3.7								
P5d/a	-21.0	-7.5								
Small	**HD-->WN**	**OCOS-->WN**	**name**	**structure**	**name**	**structure**	**name**	**structure**	**name**	**structure**
SC1	16.2	14.0	2-methyl-propane	C-C(CH3)-C*						
SC2	14.5	13.0	propane	C-C-C	cyclohexane ?	(-C-C-C)-				
SC3	10.7	10.3	propene	C=C-C	cyclopropane	C-C-C	cyclohexane ?	(-C-C-C)-		
SC4	6.8	8.0	chloro ethane	C-C-Cl	ethane-thiol	C-C-SH	3-1 - conjugated	--(C=C-C)=C	dimethyl sulfide	C-S-C
SC5	3.4	5.3	propyne	C-C≡C						
SC6	1.5	4.4	imine - conjugated	C-C-N-C *						
SN0	-2.0	1.4	dimethyl ether?	-C-O-C-						
SN1	-5.7	0.2								
SN2	-9.9	-2.2	dimethylamine	C-NH-C						
SN3	-12.2	-3.2	2-propanol	C-C(CH3)-C-OH*						
SP1	-14.0	-4.2	ethanol	C-C-OH						
SP2	-16.0	-6.1	acetic acid	C-C-COOH*						
SP3	-17.7	-6.8	ethylene glycol	-C(OH)-C(OH)-*						
SP4	-20.5	-9.2	acetamide	-C-CONH2						
SP5	-24.5	-12.5								
SQ0	-47.1	-18.8	trimethyl amonium							
SQp	-58.0	-21.8	acetate	-C-COO(-)						
SQn	-58.7	-21.8	ethyl-ammonium	-C-C-NH2(+)						
SQ1	-70.8	-21.9	hydrated chloride	Cl(-) (H2O)2	hydrated sodium	Na(+) (H2O)2				
SQ2	-112.4	-33.7	hydrated calcium	Ca(2+) (H2O)2						
SN0d/a	-0.3	3.3							dimethyl ether in polyethers?	-C-O-C-
SN1d/a	-4.2	1.4	propanone (a)	-C-C(=O)-C-		-O-C(=O)-	dimethyl ether in polyethers?	-C-O-C-		
SN2d/a	-7.9	-0.3	ethanal (a)	-C-C=O	methyl formate (a)		dimethyl ether in rings	-C-O-C-		
SN3d/a	-9.9	-1.3	ethyl amine (d)	-C-C-NH2						
SP1d/a	-12.0	-2.5								
SP2d/a	-13.9	-4.1								
SP3d/a	-15.9	-5.1								
SP4d/a	-18.1	-7.1								
SP5d/a	-21.9	-9.7								
Tiny	**HD-->WN**	**OCOS-->WN**	**name**	**structure**	**name**	**structure**	**name**	**structure**	**name**	**structure**
TC1	14.4	12.3	isopropyl group	-C(CH3)-CH3						
TC2	11.9	10.5	ethane	-C-C-						
TC3	8.2	8.0	ethene	-C=C-	ethyl near to polar group	-C-C-				
TC4	4.3	6.2	chloromethane	-C-Cl	thiol- group	-C-SH	2-1 - conjugated/aromatic	--(C=C-)C=C	sulfide group	-C-S-
TC5	1.2	3.7	ethyne	-C≡C-	thiol- comjugated/aromatic	-C-SH				
TC6	-0.5	2.8	imine - conjugated	C-N-C *						
TN0	-3.5	0.5	ether group	-C-O-						
TN1	-7.4	-1.5								
TN2	-10.9	-3.8								
TN3	-13.2	-5.1								
TP1	-15.7	-5.9	methanol	C-OH						
TP2	-17.7	-7.6								
TP3	-19.4	-8.3								
TP4	-22.3	-10.8								
TP5	-26.6	-13.4								
TQ0	-62.2	-17.4	heavy metals complexes	M(+)						
TQp	-76.4	-18.8	methylammonium	-C-NH2(+)						
TQn	-76.5	-18.5								
TQ1	-93.5	-22.5	dehydrated chloride	Cl(-)	dehydrated sodium	Na(+)				
TQ2	-198.5	-29.1	dehydrated calcium	Ca(2+)						
TN0d/a	-1.7	2.0								
TN1d/a	-5.6	0.2	ether -conjugated -aromatic	-C-O-						
TN2d/a	-8.9	-1.8	carbonyl group	-C=O						
TN3d/a	-11.2	-3.4	methyl-amine	C-NH2						
TP1d/a	-13.5	-3.9	carbonyl group in nucleot.	-C=O						
TP2d/a	-15.6	-5.8								
TP3d/a	-17.2	-6.4								
TP4d/a	-19.5	-8.4								
TP5d/a	-23.9	-10.9								

* overmapping but branched or part of ring

(a) and (d) indicate that you should use an acceptor or a donor version of the bead, respectively.

OBS: Most of the examples correspond to chemical groups attached to aliphatic molecules.

The bead types can change depeding of the situation (for example, chemical groups attached to aromatic rings).